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Jutatip Boonsombat Date

Application of IMDAF and Rh(II)-Catalyzed Cascade Reactions for Total Synthesis of Natural Products

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Doctor of Philosophy

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Abstract

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There are two major themes to this thesis. In part A, an intramolecular [4 + 2]-cycloaddition/rearrangement cascade of an indolyl-substituted amidofuran (IMDAF) was utilized as a key strategy for the synthesis of various natural products containing the hydroindoline or hydroquinoline ring system. The total synthesis of several *Strychnos* alkaloids were developed. The central step consists of an IMDAF reaction that delivers an aza-tetracyclic ABCE-rings of the *Strychnos* alkaloid family. Closure of the remaining D-ring was carried out by an intramolecular palladium-catalyzed enolate-driven cross-coupling reaction. The IMDAF approach was successfully applied to the synthesis of (±)-strychnopivotine, (±)-tubifolidine, and (±)-valparicine. A variation of this tactic was utilized for a synthesis of the heptacyclic alkaloid (±)-strychnine. Another aspect of the thesis was to test the IMDAF strategy for an approach toward the fawcettimine alkaloid family. We were able to assemble the BCD core structure of the carbinolamine portion of fawcettimine. An efficient route for the construction of the methyl furanyl carbamate necessary for the alkaloids was also developed. However, attempts to cyclize the A-ring using an internal displacement reaction were unsuccessful. Further work is therefore necessary to determine the appropriate precursor for A-ring formation.

Part B of the thesis involves the application of Rh(II)-catalyzed cyclization/cycloaddition cascade for preparing natural products containing the oxabicyclo[3.2.1]octane ring system. The intramolecular Rh(II)-catalyzed reactions of an *ortho*-carbomethoxy aryl diazo dione was investigated as a potential route to the oxatricyclo[6.3.1.$0^{0,0}$]dodecane substructure found in komaroviquinone. Preparation of the hexa-substituted arene required for the natural product is also described. Part B also describes attempts to prepare a furan precursor for a synthesis of furanether B by a Rh(II)-catalyzed reaction. An efficient strategy to prepare the requisite 3,4-disubstituted furan is described. Further investigations dealing with the critical diazo furanyl ketone needed are underway. We have also investigated the Rh(II)-catalyzed reaction of the *Z*-isomer of 2-diazo-3,6-dioxo-6-phenyl-hex-4-enoic acid methyl ester and found that we were unable to trigger a [5+2]-cycloaddition. Instead, an unknown dimer was formed as the major product. The Rh(II)-catalyzed reaction of the *E*-isomer was carried out in the presence of various carbonyl compounds and was found to give 1,3-dioxoles as products.

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Part B

Table 1. Reaction of *E*-isomer of α-diazo compound (**24**) with various carbonyl compounds…….. 347

List of Abbreviations

μ	micro
[a]	specific rotation
Ac	acetyl
anal	analysis
Aq	aqueous
Ar	argon
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
^{o}C	degree Celsius
calcd	calculated
δ	chemical shift(s)
d	doublet
DIBAL-H	Diisobutylaluminum hydride
DMAP	demethylamino pyridine
Decomp	decomposition
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
E	entgegen
ee	enantiomeric excess
ESI	electrospray ionization
EDG	electron donating group(s)
EWG	electron withdrawing group(s)
Et	ethyl
FT	Fourier transform
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IBCF	Isobutylchloroformate
i-Pr	isopropyl
IR	Infrared Spectroscopy
J	coupling constant
LA	Lewis acid
LHMDS	lithium bis(trimethylsilyl)amide
mol	mole
m	multiplet
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram(s)

MHz	megahertz
min	minute(s)
mL	milliliter(s)
µL	microliter(s)
mmol	millimole(s)
mp	melting point
Ms	Methanesulfonyl
NMM	4-methylmorpholine
NMR	Nuclear Magnetic Resonance
q	quartet
rt	room temperature
s	singlet
SM	starting material
t	triplet
TBAF	Tetrabutylammonium fluoride
TBAHS	Tetrabutylammonium hydrogen sulfate
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
p-TsOH	*para*-toluenesulfonic acid

Part A

The IMDAF Reaction for the Construction of Natural Products Containing Hydroindole or Hydroquinoline System

Chapter A. 1

General Introduction

The hydroindole and hydroquinoline skeletons are very important components found in a variety of natural products that not only possess interesting biological properties but are also synthetically challenging structures. These two ring systems are widely distributed in many alkaloids such as the *amarylliaceace* (*i.e.* **1**),[1] *daphniphylum* (*i.e.* **2**),[2] *aspidosperma* (*i.e.* **3**),[3] *strychnos* (*i.e.* **4**),[4] and *lycopodium* (*i.e.* **5** and **6**)[5] family (Scheme 1).

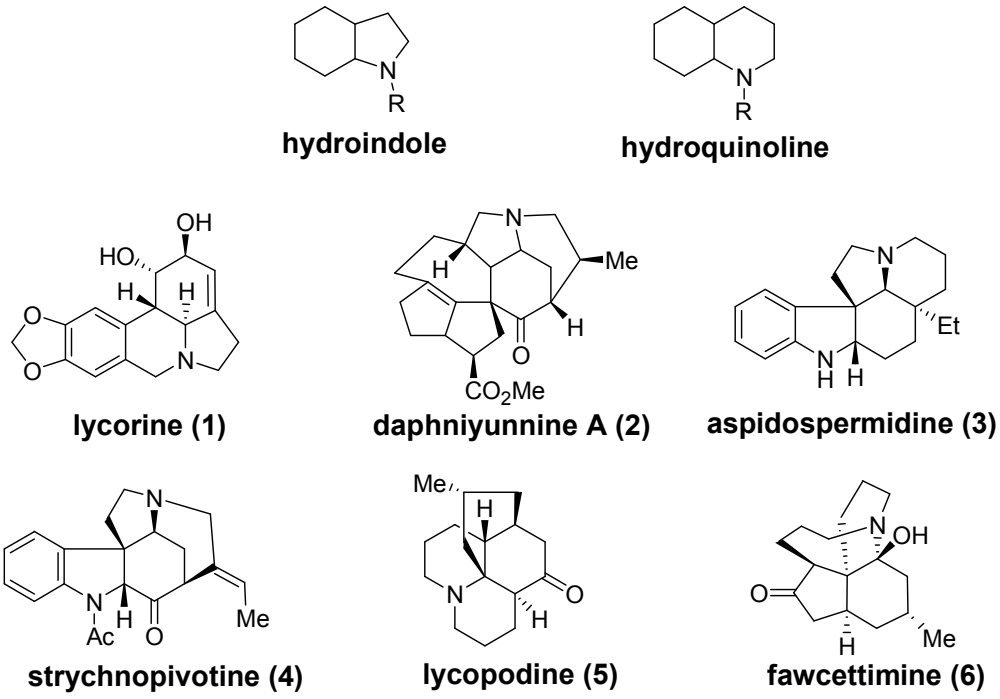


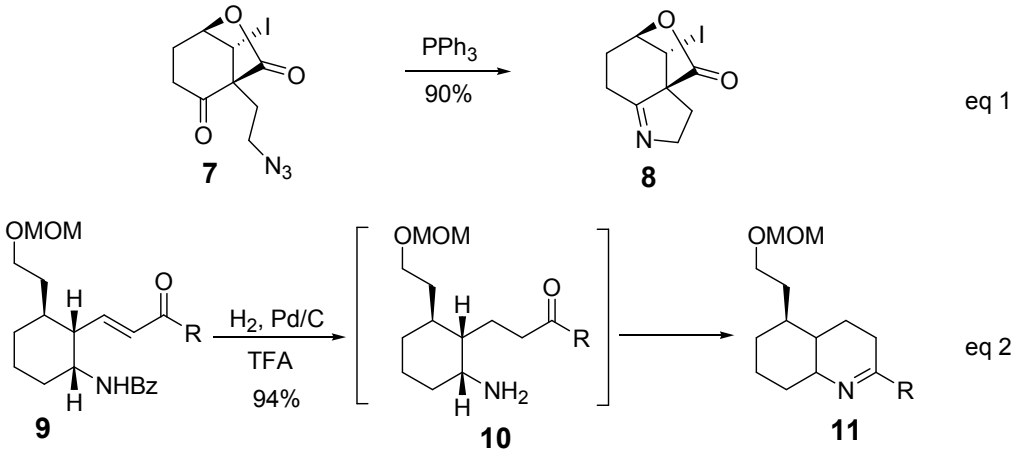
Figure 1. Representative examples of natural products containing hydroindole and hydroquinoline units

A number of synthetic entries to these two rings have been reported in the literature and can be categorized into two general approaches. One approach involes a stepwise process consisting of two independent transformations whereby an existing six-membered ring carbocycle or a five- or six-membered

ring cyclic amine is used to create the second ring. The second method involves a one step process in which both rings are constructed at the same time.

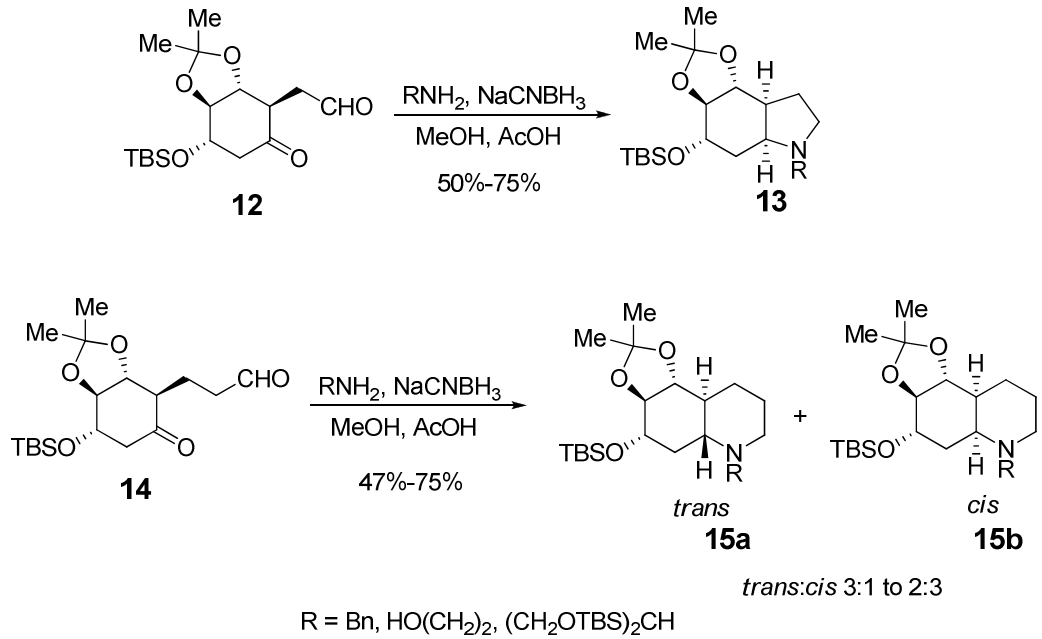
- **Stepwise process to construct hydroindoles and hydroquinolines**

The annealing of a cyclic amine ring onto an existing carbocyclic six-membered ring for the synthesis of hydroindole and hydroquinoline skeletons has already been carried out utilizing a wide range of chemistry. One straightforward method involves the condensation of an amine functionality onto a carbonyl unit, as shown in Scheme 1. Schultz has shown that the Staudinger reaction of azide **7** with triphenylphosphine first generates iminophosphorane which then undergoes an aza-Wittig reaction with the keto group to produce hydroindole **8** in 90% yield (eq 1, Scheme 1).[6] A second example involves a catalytic hydrogenation under acidic conditions, which causes the reduction of both the olefinic π-bond and the deprotection of the benzyl carbamate of cyclohexene **9**. The resulting intermediate **10** then spontaneously cyclizes onto the pendant keto group to generate hydroquinoline **11** (eq 2, Scheme 1).[7]



Scheme 1. Cyclization to a hydroindole core by amine with carbonyl tether

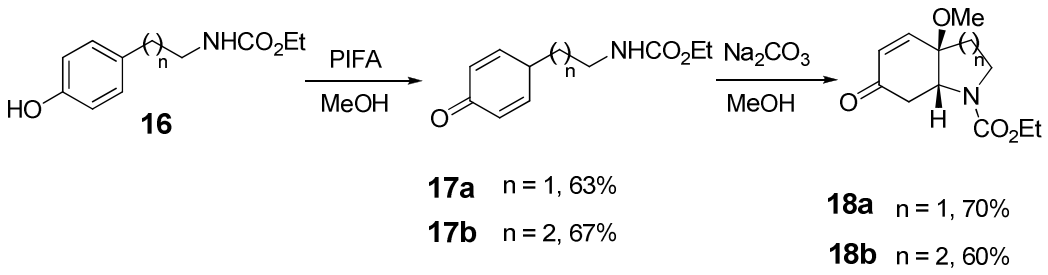
In a similar manner, a double reductive amination of the six-membered ring keto-aldehyde **12** or **14** with various primary amines followed by reaction with cyanoborohydride provided an expedient route to hydroindole **13** or hydroquinoline **15** as shown in Scheme 2.[8]



Scheme 2. Reductive amination approach to hydroindole and hydroquinoline

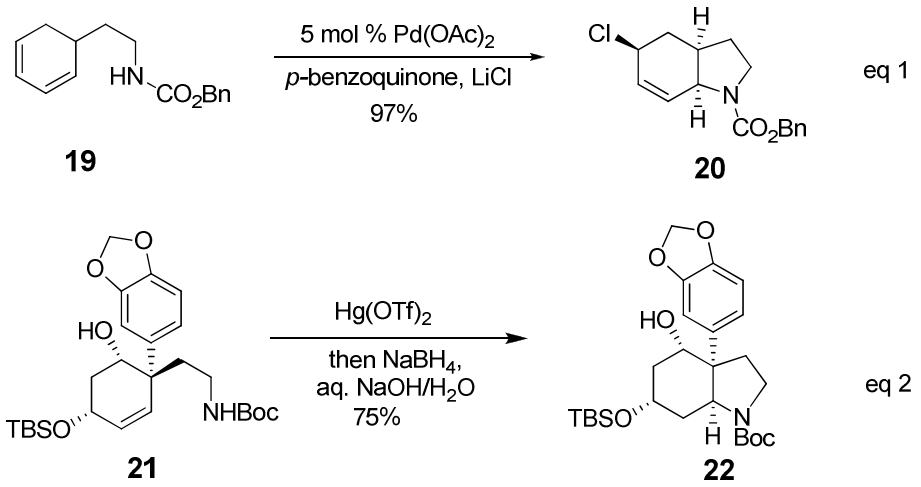
Another interesting approach involving cyclization of an amine is shown in Scheme 3 and consists of phenolic oxidation and subsequent 1,4-addition of the amine tether.[9] Thus, oxidation of phenol **16** with phenyliodine bis(trifluoroacetate) (PIFA) in MeOH produced cyclohexadienenone **17**. Subsequent treatment of **17** with base resulted in an intramolecular 1,4-addition of the tethered nitrogen onto the double bond of the cyclohexadienenone ring to give hydroindolenone **18a** and hydroquinolenone **18b** in 70% and 60% yield,

respectively. An asymmetric version of this methodology starting with tyrosine has been utilized by Wipf for the stereocontrolled synthesis of several alkaloids.[10]



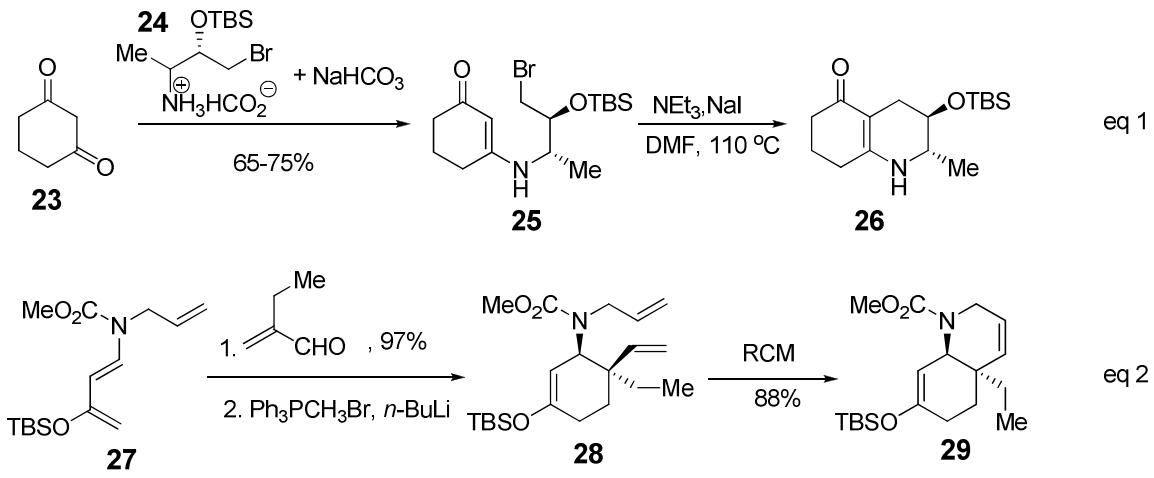
Scheme 3. 1,4-addition pathway *via* phenolic oxidation to hydroindole and hydroquinoline system

The addition of an amine tether onto a cyclohexene ring to generate a bicyclic system has also been utilized by several investigators. For example, Bäckvall and Anderson described an efficient palladium-catalyzed amination reaction. Amine **19** underwent nucleophilic addition onto a Pd-activated double bond of cyclohexadiene **19** to give hydroindole **20** in 97% yield (eq 1, Scheme 4).[11] Another example involves the use of the intramolecular aminomercuration reaction which proceeds by addition of the amine tether in **21** onto the olefinic π-bond. This was followed by reduction with $NaBH_4$ and $NaOH/H_2O$ which resulted in demercuration to afford hydroindole **22** in 75% yield (eq 2, Scheme 4).[12]



Scheme 4. Ring closure to hydroindole by cyclization of amine tether onto a cyclohexene ring

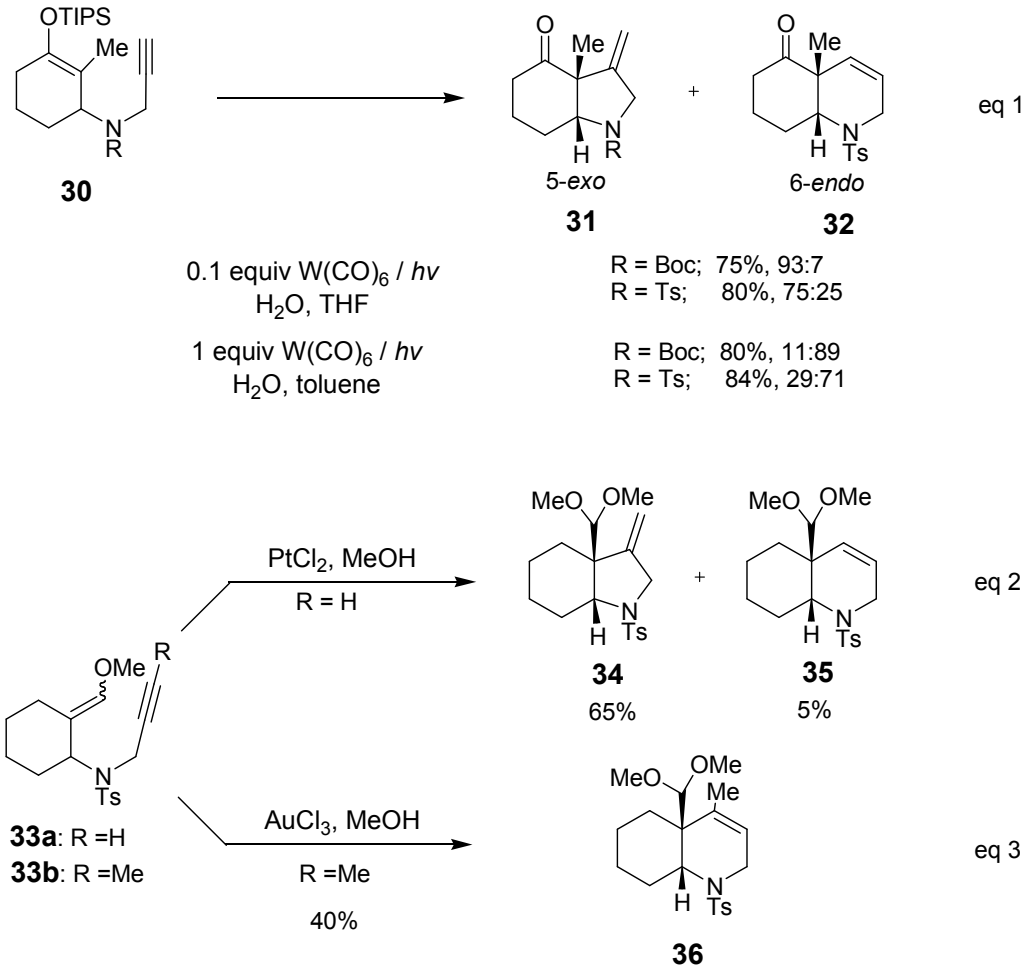
Generation of the hydroindole and hydroindoline framework can also be accomplished using various C-C bond forming reactions to anneal a cyclic amine onto an existing six-membered ring carbocycle. For example, Ma prepared hydroquinoline **26** by the initial generation of cyclohexenone **25** *via* condensation of chiral **24** with 1,3-cyclohexanedione. Further alkylative cyclization of **25** with base afforded **26** in 98% yield (eq 1, Scheme 5).[13] Rawal used a Diels-Alder reaction followed by a subsequent Wittig reaction to prepare cyclohexene **28** in which a *cis*-relationship of groups was found at the ring junction.[14] A subsequent ring closing metathesis of **28** then delivered the hydroindoline ring **29** in 73% yield over the three step sequence (eq 2, Scheme 5).



Scheme 5. Synthesis of hydroquinoline by cyclization of amine tether

Transition metal catalyzed cyclizations have also been extensively utilized in recent years. The reaction of a cyclic amine onto an existing six-membered carbocycle *via* nucleophilic addition to a transition metal activated alkyne has been used to generate both the hydroindole and hydroindoline skeleton. In the $W(CO)_6$-catalyzed cyclization of ω-acetylenic silyl enol ether **30** reported by Iwasawa,[15] either the 5-*exo* or 6-*endo*-dig cyclization product could be obtained by changing the reaction solvent and catalyst stoichiometry (eq 1, Scheme 6). Use of 10% $W(CO)_6$ in THF/H_2O gave hydroindole **31** a *via* 5-*exo* dig cyclization as the major product. On the other hand, using 1 equivalent of $W(CO)_6$ in toluene/H_2O gave hydroquinoline **32** *via* a 6-*endo* dig cyclization. Echavarren showed that the intramolecular reaction of enol ether **33a** which contains a terminal alkyne can be catalyzed by $PtCl_2$ and produced hydroindole **34** (65%) and hydroquinoline **35** (5%) (eq 2, Scheme 6). Interestingly, when a methyl substituent was present on the alkyne (**33b**), the reaction led to selective 6-*endo*-dig cyclization. The $AuCl_3$ catalyst gave the most reproducible result and

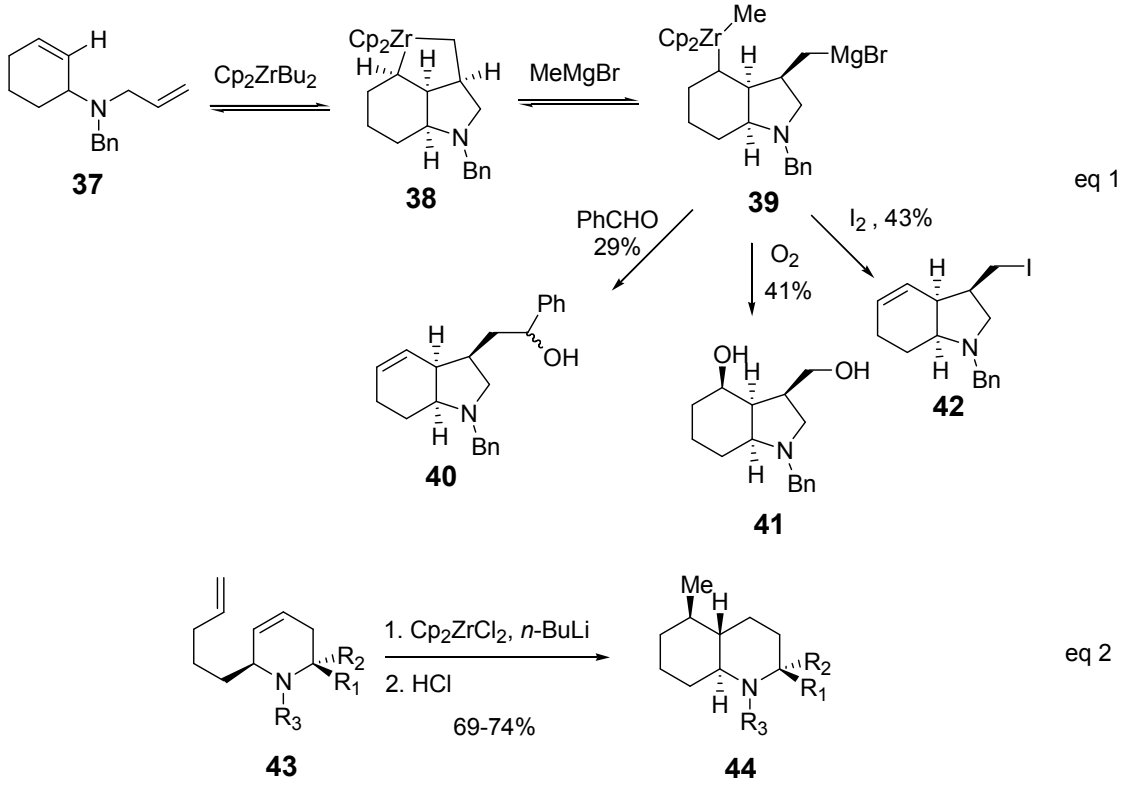
delivered hydroquinoline **36** in 40% yield (eq 3, Scheme 6).[16] The reason for selectivity still remains unclear.



Scheme 6. Transition-metal assisted cyclization to hydroindole and hydroquinoline

Along the same line, Mori demonstrated an efficient route to these bicyclic cores by using a zirconium-catalyzed cyclization (Scheme 7).[17] Diene **37** was treated with Cp_2ZrCl_2 to form zirconacycle **38** which, upon transmetallation with BuMgBr, produced **39**. The magnesium complex **39** was found to be a useful intermediate for the synthesis of numerous heterocycles. For example,

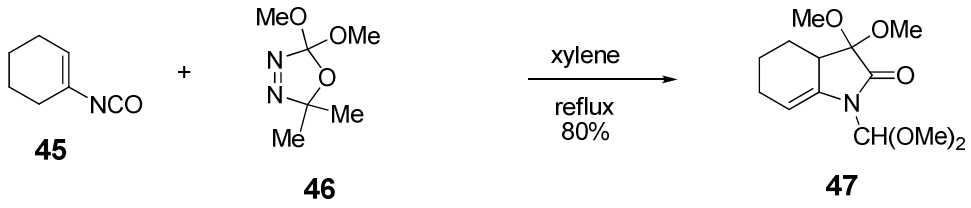
exposure of intermediate **39** to various electrophiles resulted in the formation of hydroindoles (*e.g.* **40** to **42**) *via* a one-pot cascade reaction. This method was also extended to an enyne cyclization to produce hydroindoles.[18] A similar strategy using a zirconium catalyst has also been reported for the formation of the hydroquinoline system **44** starting from piperidine ring **43**.[19]



Scheme 7. Zirconium-catalyzed cyclization reactions

The Rigby group reported an interesting approach toward the formation of hydroindoles which involves reaction of a 5-membered ring cyclic amine onto an existing carbocycle *via* an intermolecular [4+1]-cycloaddition reaction (Scheme 8).[20,21] The nucleophilic dimethoxycarbene was generated from **46** and underwent a subsequent cycloaddition reaction with cyclohexenyl

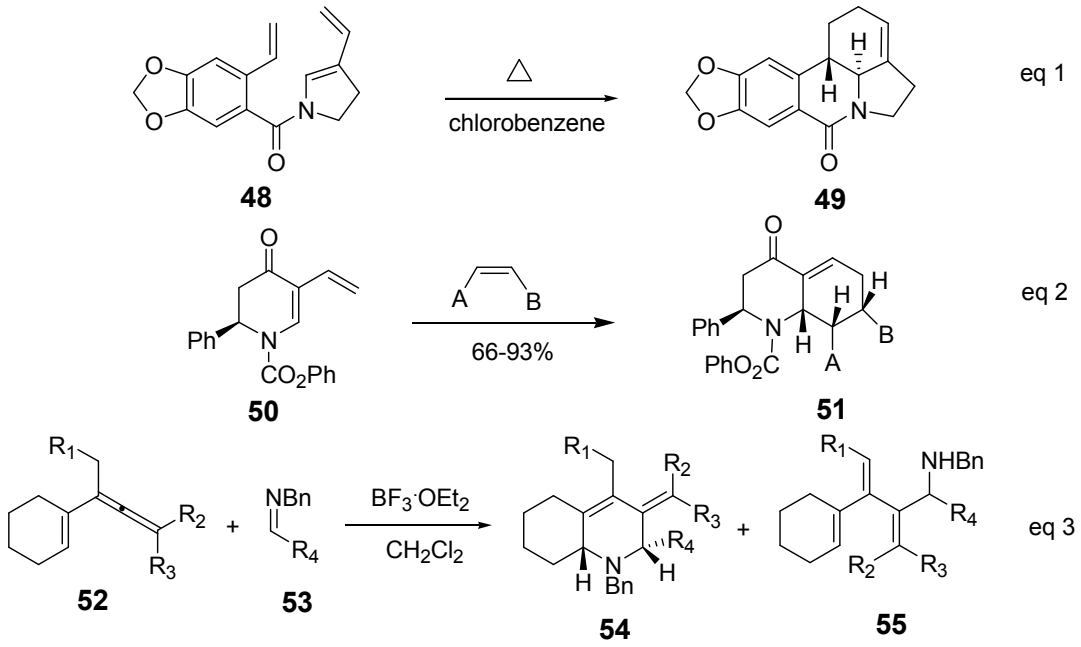
isocyanate **45**. After the initial cycloaddition reaction, a second equivalent of the carbene participated in an N–H insertion to provide hydroindole **47** in 80% yield.



Scheme 8. A [4+1]-cycloaddition reaction to hydroindole ring

Another approach to assemble both the hydroindole and hydroquinoline core involves construction of a six-membered ring unit onto an existing cyclic system. This can be easily accomplished by a Diels-Alder reaction. For example, the Stork group described the use of an intramolecular Diels-Alder reaction of amido-diene **48** to prepare the lycorane core skeleton. Heating triene **48** in chlorobenzene produced the pentacyclic structure **49** in 54% yield which was isolated as a single diastereomer. The cycloaddition proceeds by an *exo*-transition state which is preferred as a consequence of the constraints imposed by the amide tether (eq 1, Scheme 9).[22] In another example, an intermolecular Diels-Alder reaction was utilized to form octahydroquinoline **51** by using vinyl-dihydropyridone **50** with various dienophiles (eq 2, Scheme 9).[23] The hetero Diels-Alder reaction between imines and dienes corresponds to a facile and specific route to assemble the hydroquinoline system. The synthesis of octahydroquinoline derivatives can also be accomplished from the reaction of vinyl allenes **52** with various imines **53** under Lewis acid catalysis (eq 3, Scheme

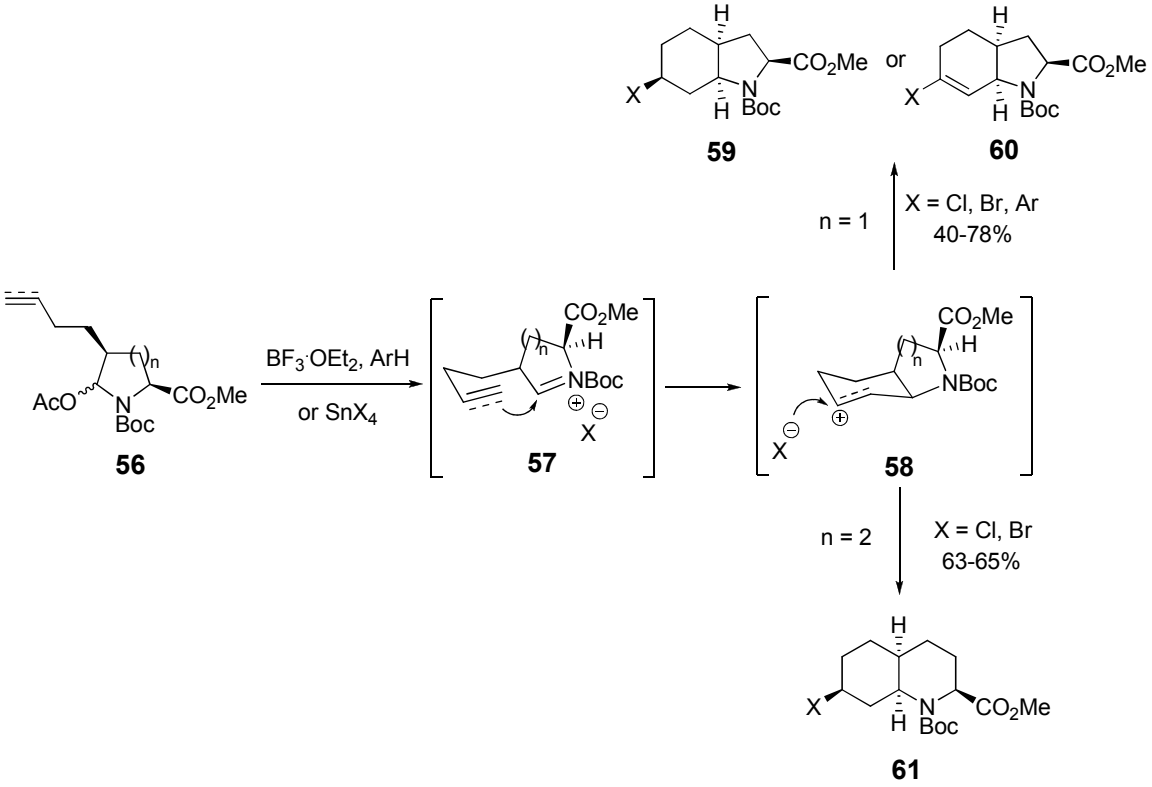
9).[24] Several by-products derived from an ene-reaction were also obtained in small quantities.



Scheme 9. Diels-Alder approach to hydroindole and hydroquinoline skeletons

Cyclization of a C-tether onto a pyrrolidine or piperidine unit represents another useful route to form bicyclic amines. Thus, Hanessian developed an interesting *N*-acyloxyiminium ion aza(azonia)-Prins-type halocarbocyclization to construct the hydroindole and hydroquinoline systems (Scheme 10). Acyliminium ions such as **57** are generated by elimination of the acetoxy group under acidic conditions and these ions underwent carbocyclization with a C-tethered 4-butenyl or 4-butynyl side chain to furnish bicyclic system **59**, **60** or **61**. The stereochemistry about the ring junction has been attributed to a favorable antiperiplanar attack of the unsaturated terminus proceeding by way of a chairlike conformation **(57)**. The ensuing secondary carbocation **58** is then captured by an

external halogen halide or an aryl group in an equatorial fashion to give either the 6-substituted hydroindole **59** and **60** or hydroquinoline **61**.[25]

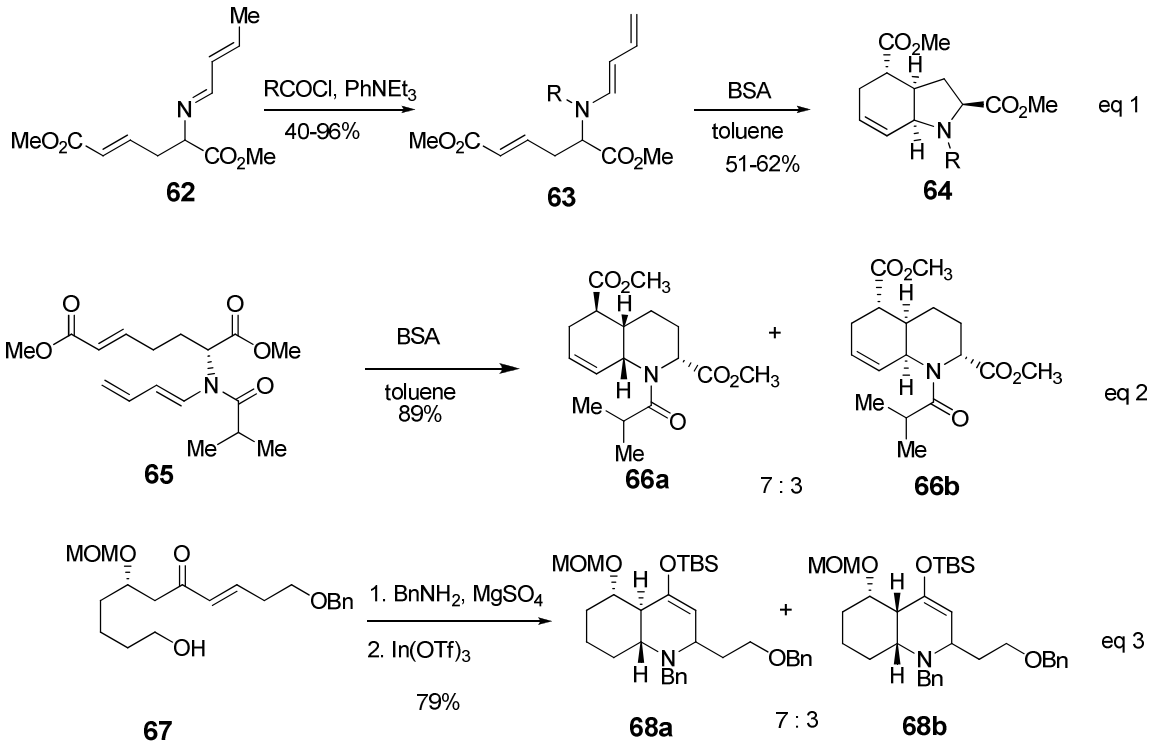


Scheme 10. Hanessian's tandem intramolecular *N*-acyloxyiminium ion carbocyclization

- **A one step transformation to hydroindoles and hydroquinolines**

A more concise method to prepare the hydroindole and hydroquinoline skeleton involves the formation of both rings in a single step. The intramolecular Diels-Alder reaction of acyclic substrates represents a straightforward example of this method. Thus, imine **62** was converted into butadienyl amine **63** by treatment with base in the presence of a variety of acid chlorides in good yield and the reaction occurred with complete *E*-stereochemistry. Heating the resulting

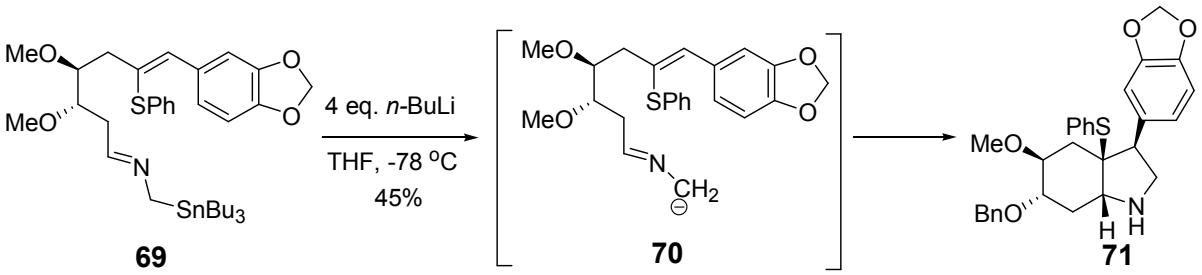
enamine **63** in the presence of *N,O*-bistrimethylsilylacetamide (BSA) promoted an intramolecular Diels-Alder reaction and gave hydroindole **64** (eq 1, Scheme 11).[26] By varying the length of the side chain, hydroquinoline **66** can also be obtained using the same strategy (eq 2, Scheme 11).[27] The hetero Diels-Alder reaction between a diene and an imine is another expedient approach for the synthesis of the hydroquinoline system and this is shown in eq 3, scheme 11.[28]



Scheme 11. Intramolecular Diels-Alder reaction to hydroindole and hydroquinoline system

Several one-step procedures have been developed for the formation of hydroindole rings. Pearson and co-workers have prepared (+)-coccinine by an intramolecular [3+2]-cycloaddition reaction (Scheme 12).[29] Stannyl imine **69** was subjected to a tin-lithium exchange at low temperatures with *n*-BuLi. The

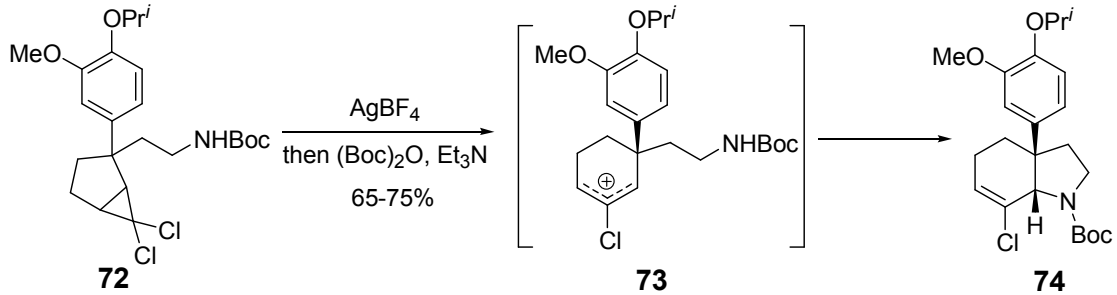
resulting azaallyl anion **70** then underwent cycloaddition across the tethered olefinic π-bond to give hydroindole **71** in 45% yield. A single isomer of the product was obtained and its formation presumably proceeded *via* a chair-like transition state.



69 **70** **71**

Scheme 12. Pearson's azaallyl anion cycloaddition

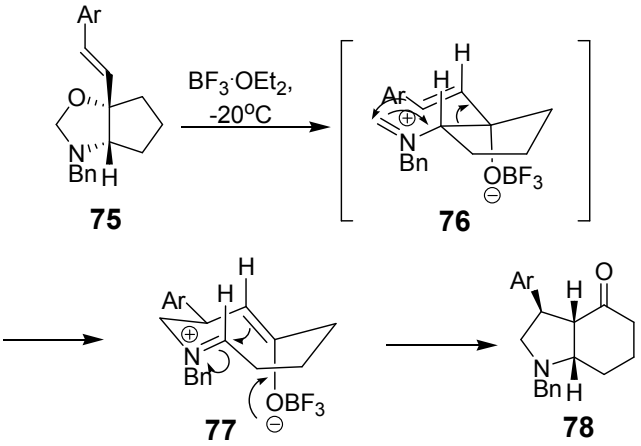
Another interesting appro ach to hexahydroindoles was reported by Banwell (Scheme 13).[30] A Ag(I) promoted electrocyclic ring-opening of gem-dibromocyclopropanes **72** was used to generate the π-allyl cation **73** and this was followed by intramolecular nucleophilic capture by the nitrogen carbamate tether to give hexahydroindole **74**.



72 **73** **74**

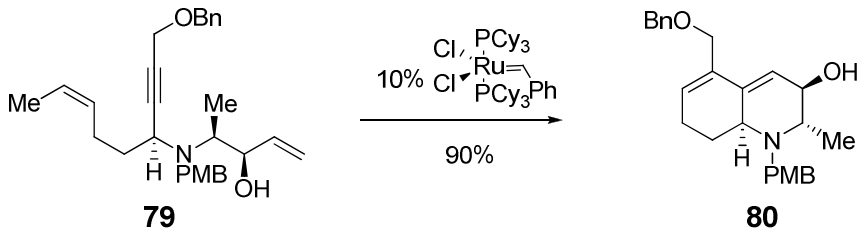
Scheme 13. Banwell's approach to hexahydroindole

The Overman group has developed an elegant tandem aza-Cope Mannich reaction which is very useful for the construction of the octahydroindole system (Scheme 14).[31] In a typical example, oxazolidine **75** was treated with $BF_3{\cdot}OEt_2$ in order to generate iminum ion **76**. This intermediate then underwent a cationic aza-Cope rearrangement followed by a subsequent Mannich reaction to afford hydroindole **78** in 97% yield. The overall process was highly stereospecific and proceeded *via* a chair transition state resulting in high *cis*-selectivity.



Scheme 14. Overman's aza-Cope Mannich Approach

One last example involves the formation of a hydroquinoline ring system by a tandem ring closing metathesis reaction from an acyclic precursor was that reported by Blechert and co-workers (Scheme 15).[32] Treatment of **79** with the Grubbs' catalyst allowed for a facile tandem ene-yne-ene cyclization to furnish the hexahydroindoline ring **80** in 90% yield.



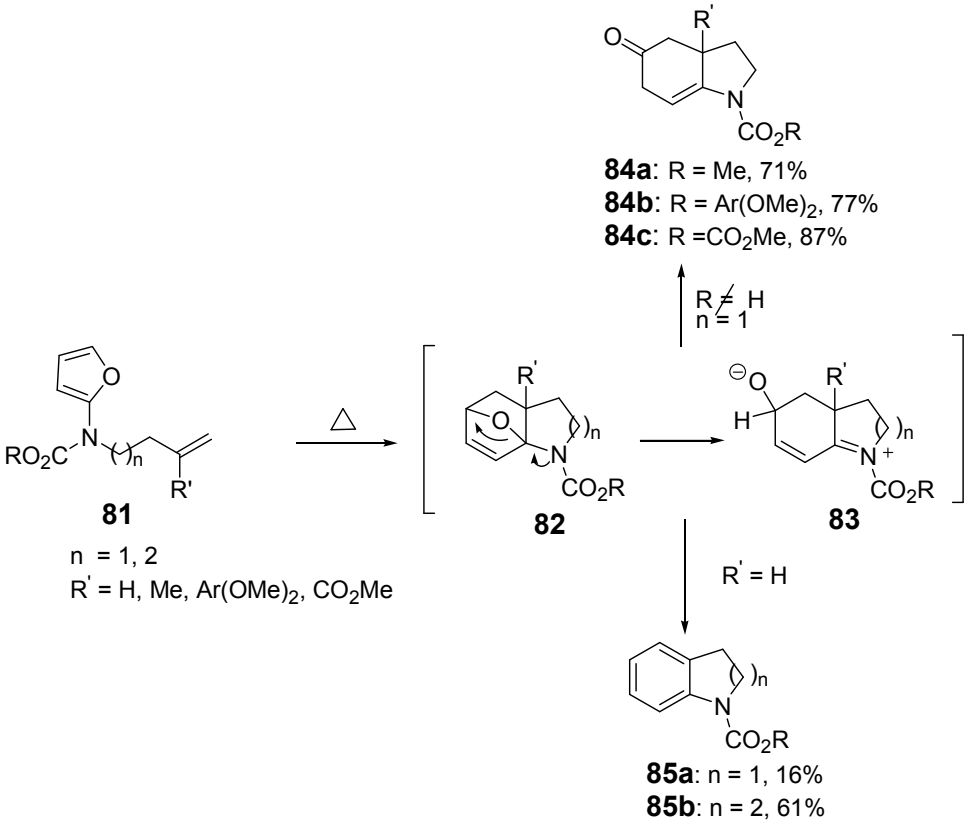
79 **80**

Scheme 15. Ene-yne-ene ring closing metathesis to hydroindoline

Padwa's IMDAF Cycloaddition/Rearrangement Cascade of 2-Amidofurans

Research in the Padwa group has involved a study of the intramolecular Diels-Alder reaction of 2-aza-substituted furans (IMDAF) and this method has been used to generate hydroindole and hydroquinoline ring systems.[33] As outlined in Scheme 16, the intramolecular Diels-Alder reaction of an alkenyl-substituted furanyl carbamate derivative proceeds by a cycloaddition/rearrangement cascade. The initially formed oxabicyclic adduct **82** derived from the Diels-Alder reaction is unstable under the reaction conditions and undergoes a nitrogen-assisted ring opening followed by proton loss to produce the aza-bicyclic system **84**. In the early investigations by the Padwa group, it was shown that when the alkenyl π-bond contains an alkyl or aryl group at the 2-position of the π-bond, the thermal reaction furnished a rearranged hexahydroindolinone system **84a**-**c**.[34] In contrast, when an unsubstituted alkenyl tether was used, dihydroindole **85b** was obtained in high yield by the thermal loss of water. When a longer tether (n = 2) was used, the cycloaddition/rearrangement/ dehydration cascade gave rise to the tetrahydroquinoline system **83b** as the major

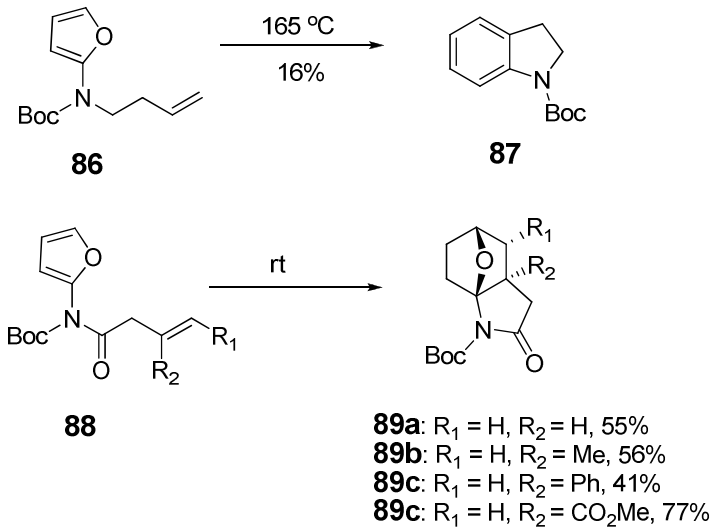
product in 61% yield. The substitution pattern on the diene and dienophile can be varied, resulting in the formation of a variety of azapolycyclic cores.



Scheme 16. The IMDAF cycloaddition/rearrangement cascade sequence of amidofurans

The presence of a sp^2 center within the tether was found to be very beneficial resulting in a significant rate enhancement of the IMDAF cycloaddition. The reaction also proceeded at a much lower temperature thereby leading to the successful isolation of the oxabicyclic cycloadduct **89** (Scheme 17).[34,35] This remarkable rate enhancement is due to the presence of the rigid amide carbonyl group which essentially places the olefinic dienophile in a much closer

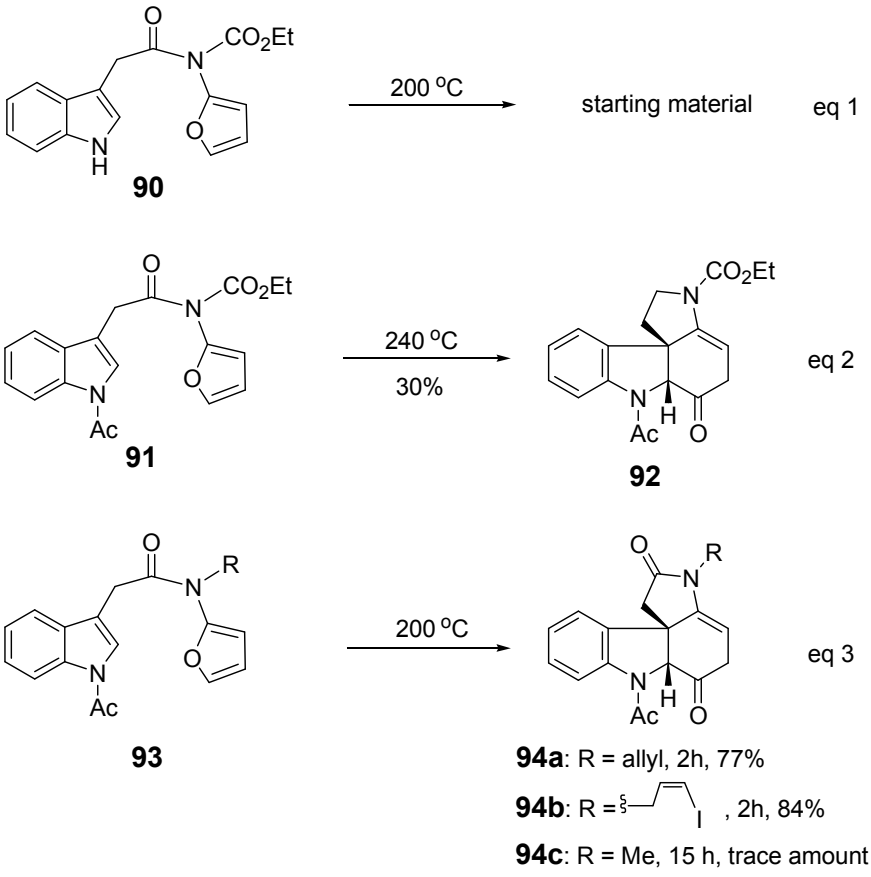
environment to the furanyl π-bonds and therefore lowers the energy gap between the ground state and reactive conformers.



Scheme 17. Rate enhancement with carbonyl present in tether

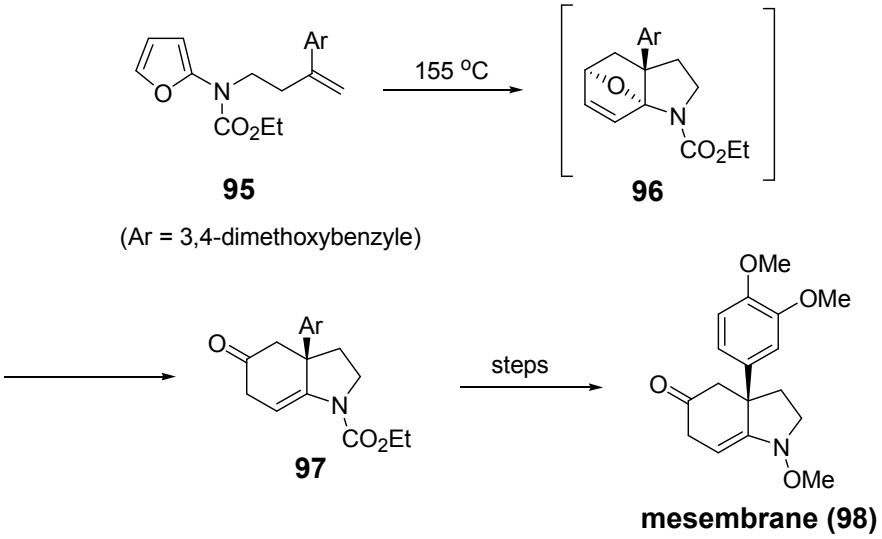
Aside from using traditional alkenyl groups as the dienophiles, a 2,3-indolyl double bond was also used. Thus, the Padwa group studied the thermolysis of various substituted indoles and determined their ability to participate in the IMDAF system.[36] There are several factors that are responsible for the success of this cycloaddition. First, the presence of an electron withdrawing group on the indole nitrogen helps to activate the 2,3-double bond towards the normal-electron demand Diels-Alder reaction (**90** *vs* **91**). Another factor is incorporation of a sp^2 amidocarbonyl group within the tether which was found to be very crucial for the reaction to proceed in the desired manner. As shown in eq 2 (Scheme 18), heating the indolyl furan **91** which is devoid of the amidocarbonyl linkage in its tether requires temperatures up to 240 °C for 18 h and only produced cycloadduct **92** in 30% yield. In contrast, when an

amidocarbonyl was incorporated into the tether, the thermolysis at 200 ^{o}C was over within 2 h and delivered cycloadducts **94** in good yield (eq 3, Scheme 18). A third factor is the bulkiness of the alkyl group anchored on the amido nitrogen which was found to significantly improve the reaction rate and yield (**94a,b** *vs* **94c**). This is due to a significant change in the ratio of *s-cis vs s-trans* isomers around the amido carbon-nitrogen bond.[37] Having a large group on nitrogen causes the reactive *s-trans* conformation to be more highly populated and this results in the furan ring being in a more proximal position to react with 2,3-indole double bond.



Scheme 18. IMDAF reaction of 2-amidofuran employing indole as dienophile

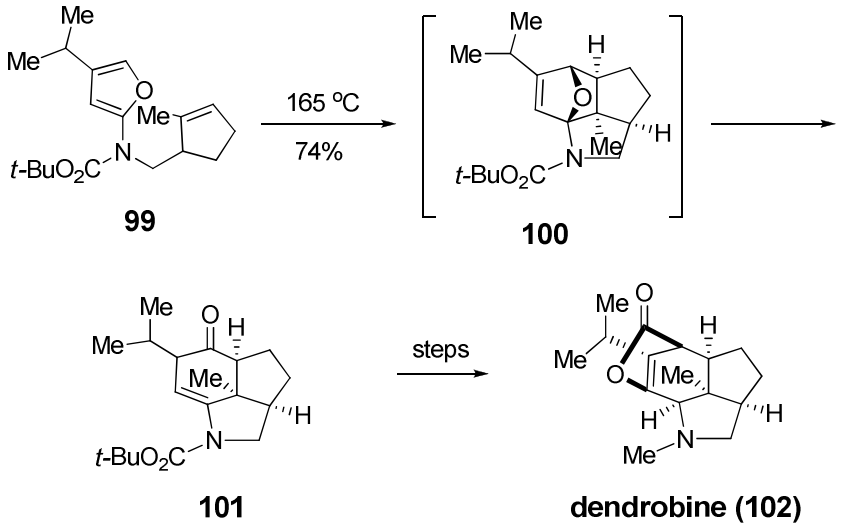
This methodology proved to be successful for preparing a number of alkaloids containing the hydroindole substructure. An early application of this methodology involved the synthesis of the *Amaryllidaceae* alkaloid mesembrane (Scheme 19). Thermolysis of amidofuran **95** at 155 ^{o}C for 20 h gave enamide **97** in 78% yield, thereby establishing the required quaternary center present in the natural product. Further functional group transformations completed the synthesis of mesembrane.



Scheme 19. Padwa's IMDAF cycloaddition/rearrangement approach to mesembrane

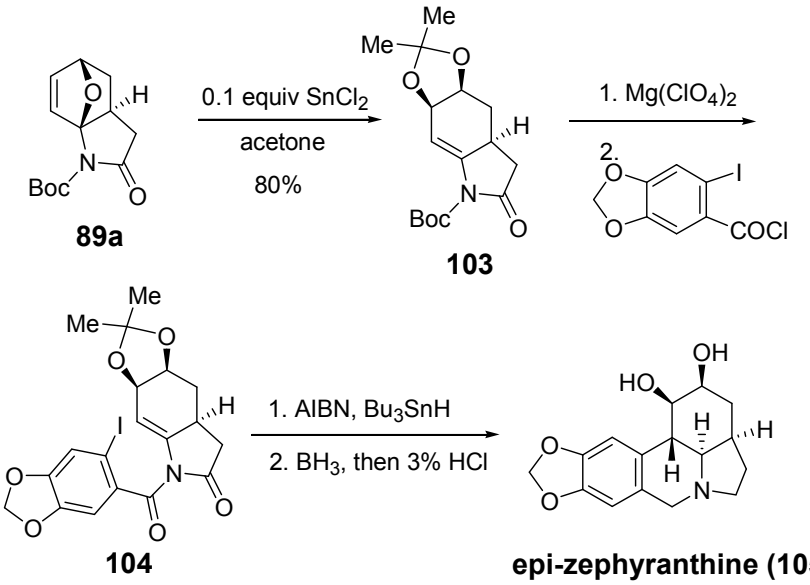
An approach towards the synthesis of the more complex target dendrobine (**102**) was also successfully completed (scheme 20).[38] The key IMDAF reaction involved a cycloaddition of the amidofuran with a tethered trisubstituted unactivated dienophile. When precursor **99** was heated at 165 ^{o}C for 15 h, the highly functionalized tricyclic enamide **101** was obtained in 74%

yield. Further functional group transformations completed the synthesis of dendrobine.



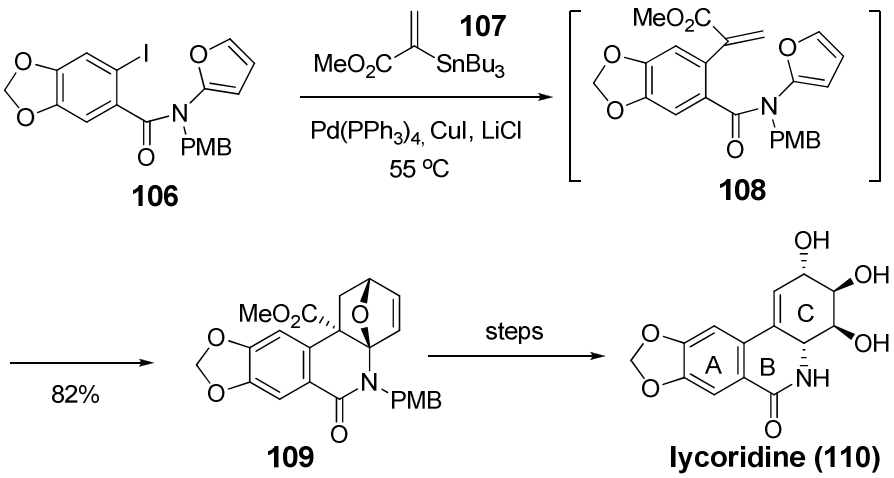
Scheme 20. Synthesis of dendrobine *via* IMDAF reaction

The synthesis of (±)-*epi*-zephyrathine took advantage of the incorporation of the carbonyl group remove, within the tether.[38] The oxabicyclic cycloadduct **89a** was easily formed at rt in high yield (see Scheme 17), and was used for further manipulation to complete synthesis of (±)-*epi*-zephyrathine. Subjecting **89a** to a Lewis acid-induced ring opening in the presence of acetone furnished acetonide **103** (Scheme 21). This was followed by reaction with a substituted benzoyl chloride after *N*-Boc-deprotection. A subsequent radical cyclization, reduction, and acidic work up afforded the target molecule **105** in 7 steps with a 15% overall yield.



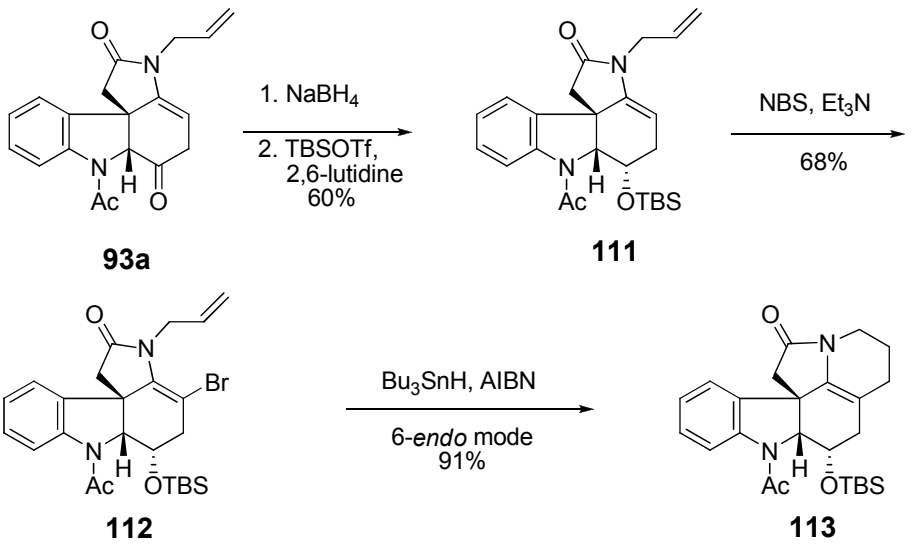
Scheme 21. Efficient synthesis of *epi*-zephyranthine *via* oxabicyclic cycloadduct from IMDAF reaction

The synthesis of alkaloids containing the hydroquinoline system by the IMDAF method also includes the synthesis of lycoricidine (**110**) (Scheme 22).[39] Generation of amidofuran **108** was accomplished by the Stille coupling between **106** and alkene **107**. This cross-coupling product was not isolated as it spontaneously underwent the intramolecular [4+2]-cycloaddition (IMDAF) at 55 ^{o}C to furnish cycloadduct **109** in 82% yield. Ring opening of the oxabridge then provided access to the hydroindoline unit as well as the hydroxyl group that was used as a handle for further manipulation to complete the total synthesis.



Scheme 22. The synthesis of lycoridine *via* one-pot Stille/IMDAF cascade on model substrate

The cycloaddition involving indole systems described in Scheme 18 has much synthetic potential as it offers a rapid and efficient entry into the tetracyclic core found in *Aspidosperma* and *Strychnos* alkaloids (Scheme 23).[40] Reduction of ketone **91** furnished a single isomer, which was protected as the TBS ether. Bromination with NBS in the presence of Et_3N resulted in the formation of **112** in 68% yield. Under radical cyclization conditions, the final ring was formed and this completed the construction of the framework **113** of the *Aspidosperma* alkaloids.



Scheme 23. Rapid construction of the pentacyclic skeleton of the *aspidosperma* alkaloid *via* IMDAF reaction

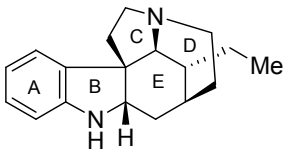
As described above, the study of the IMDAF-cycloaddition/ rearrangement cascade has proven to be extremely valuable for the synthesis of various alkaloid skeletons. An extension of the IMDAF cycloaddition/rearrangement sequence toward the synthesis of other biologically important natural products containing the hydroindole and hydroquinoline rings is of continuing interest to our group. Therefore we set out to design a synthesis of several other families of alkaloids. The first portion of this thesis involves an expansion of the previous described IMDAF reaction (Scheme 18) for a synthesis of various *Strychnos* alkaloids. The second part involves an application of the IMDAF reaction toward the *fawcettimine* alkaloids in which the formation of hydroquinoline proceeds by the key IMDAF cycloaddition.

Chapter A. 2

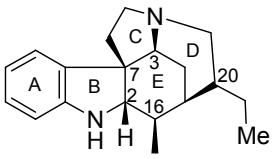
Application of the Cycloaddition/Rearrangement Cascade of 2-Amidofurans for the Synthesis of *Strychnos* Alkaloids

1. Introduction

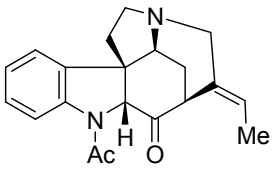
The *Strychnos* alkaloids constitute an important group of architecturally complex and widely distributed monoterpenoid indole alkaloids.[41,42] According to their biogenesis, *Strychnos* alkaloids can be classified into two classes, strychnan and aspidospermatan, with the topographical relationship shown in Figure 2. In the strychnan class, the majority of alkaloids belongs to a curan type which is characterized by the presence of a pentacyclic 3,5-ethanopyrrolo[2,3-*d*]carbazole framework (*i.e.* **115**) bearing a two-carbon appendage at C-20 and an oxidized one-carbon substituent (C-17) at the C-16 position.[43]



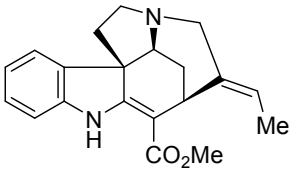
Aspidospermatan class (114)



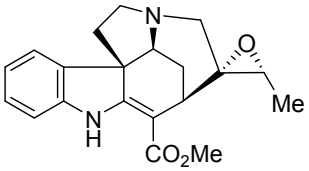
Strychnan class curan skeleton (115)



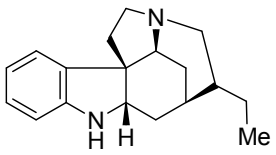
strychnopivotine (4)



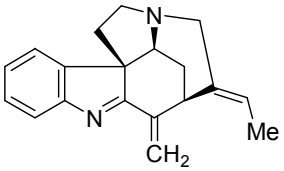
akuammicine (116)



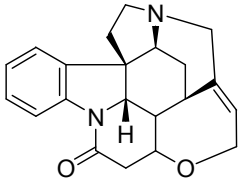
stricticine (117)



tubifolidine (118)



valparicine (119)



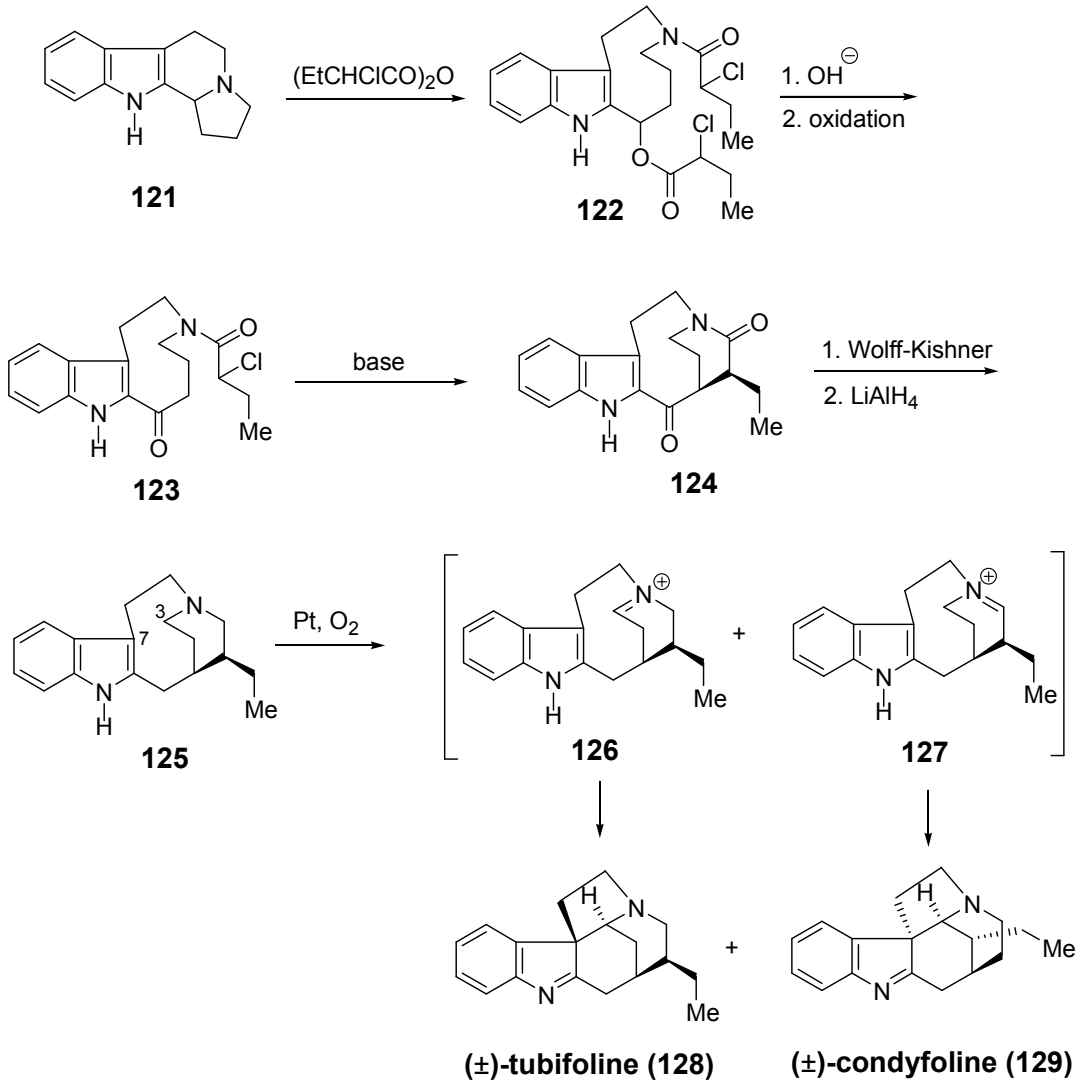
strychnine (120)

Figure 2. Some representative *Strychnos* alkaloids

During the past several decades, the *Strychnos* alkaloid family has been the subject of intense study from the synthetic community. A great deal of this continuing interest has focused on the synthesis of the heptacyclic alkaloid strychnine (**120**).[44,45] The related pentacyclic curan family, however, has received far less attention. Although there are many reports dealing with the preparation of individual members of this genus, general approaches to the core pentacyclic framework are somewhat limited. The several different known strategies can be classified into those that form the crucial quaternary center at C-7 in the last few synthetic steps and those in which the strategic bonds around C-7 are preformed at an initial stage of the synthesis.

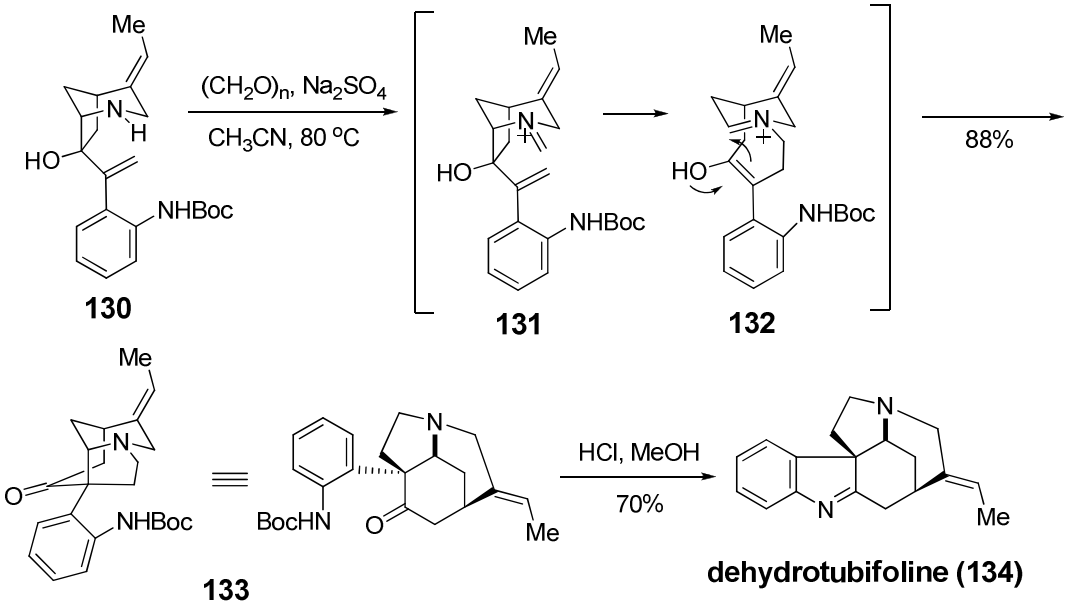
Harley-Mason carried out extensive studies on the synthesis of *Strychnos* alkaloids. His general approach to construct these alkaloids involves the construction of a tetracyclic structure having the ring skeleton of stemmadenine (*i.e.* **125**) followed by a further transannular cyclization with simultaneous formation of the C and E ring between the C-3 and C-7 position (Scheme 1).[46] For example, the synthesis of tubifoline (**128**) and condyfoline (**129**) started by cleavage of the N-C benzylic bond in the tetracyclic amine **121** induced by reaction with an acid anhydride to give the tricyclic product **122**. This compound underwent hydrolysis and oxidation to give the ketone **124**.[46a] Removal of the keto carbonyl group by Wolff-Kishner reaction followed by reduction of the carbonyl lactam gave **125**. Subjection of **125** to catalytic air oxidation over platinum promoted a transannular cyclization to provide the

pentacyclic skeleton thereby completing the synthesis of both alkaloids. Tubifoline (**128**) was formed from intermediate **126** whereas condyfolin (**129**) was obtained from intermediate **127**. The carbonyl group at C-16 can be used for other functional group transformations and the side chain at C-20 can be altered for further elaboration to other functional groups neccessary for the synthesis of *Strychnos* alkaloids.



Scheme 24. Harley-Mason's transannular approach

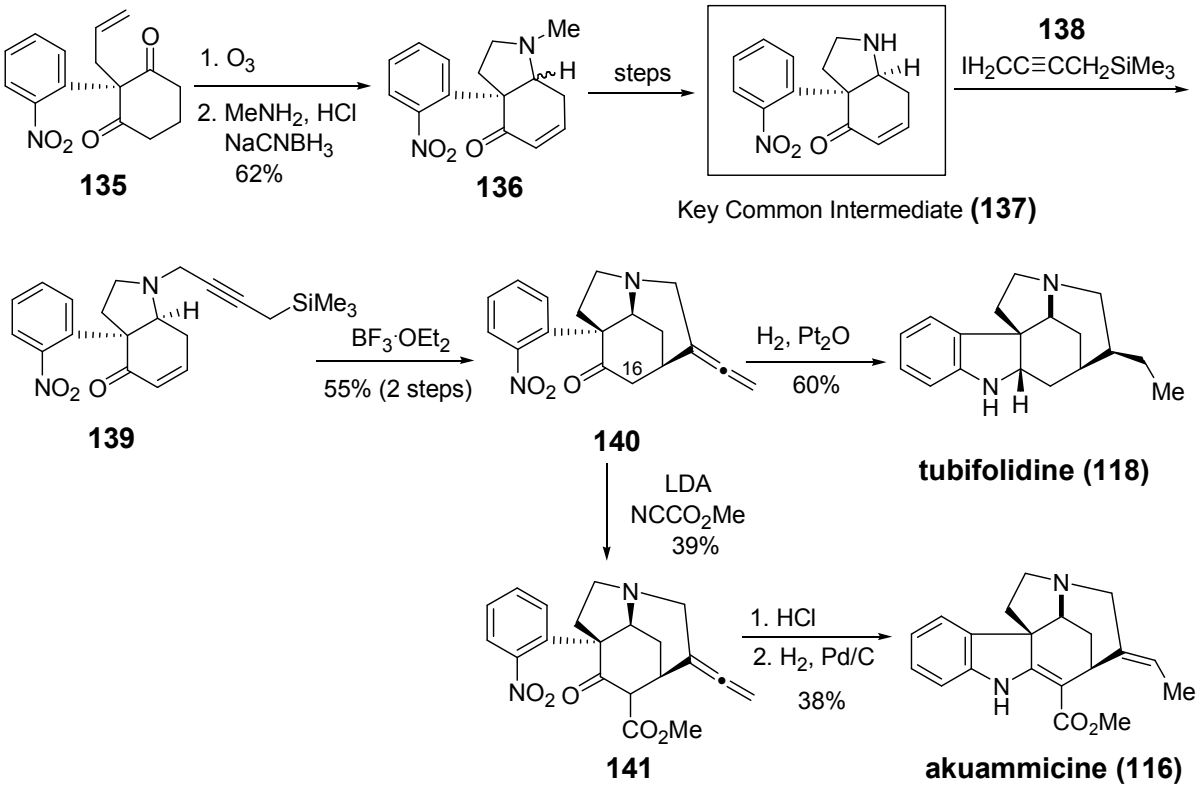
The Overman group has established a unique approach toward these alkaloids which is centered on an aza-Cope rearrangement/Mannich cyclization cascade to form the crucial C-3/C-7 bond (Scheme 2).[47] For example, in the synthesis of dehydrotubifoline, the key cascade sequence was accomplished by heating **130** with paraformaldehyde and Na_2SO_4 in CH_3CN. The initially formed iminium ion **132** underwent a [3,3]-sigmatropic rearrangement followed by an internal Mannich reaction to deliver the azatricyclic ketone **133**. The *N*-protecting amino group was released under acidic conditions to generate the B-ring thereby completing the total synthesis of dehydrotubifoline (**134**). This same approach was also successfully used for the synthesis of akuammicine and strychnine depending on the particular precursor employed for the key cascade sequence.



Scheme 25. Overman's aza-Cope/Mannich approach

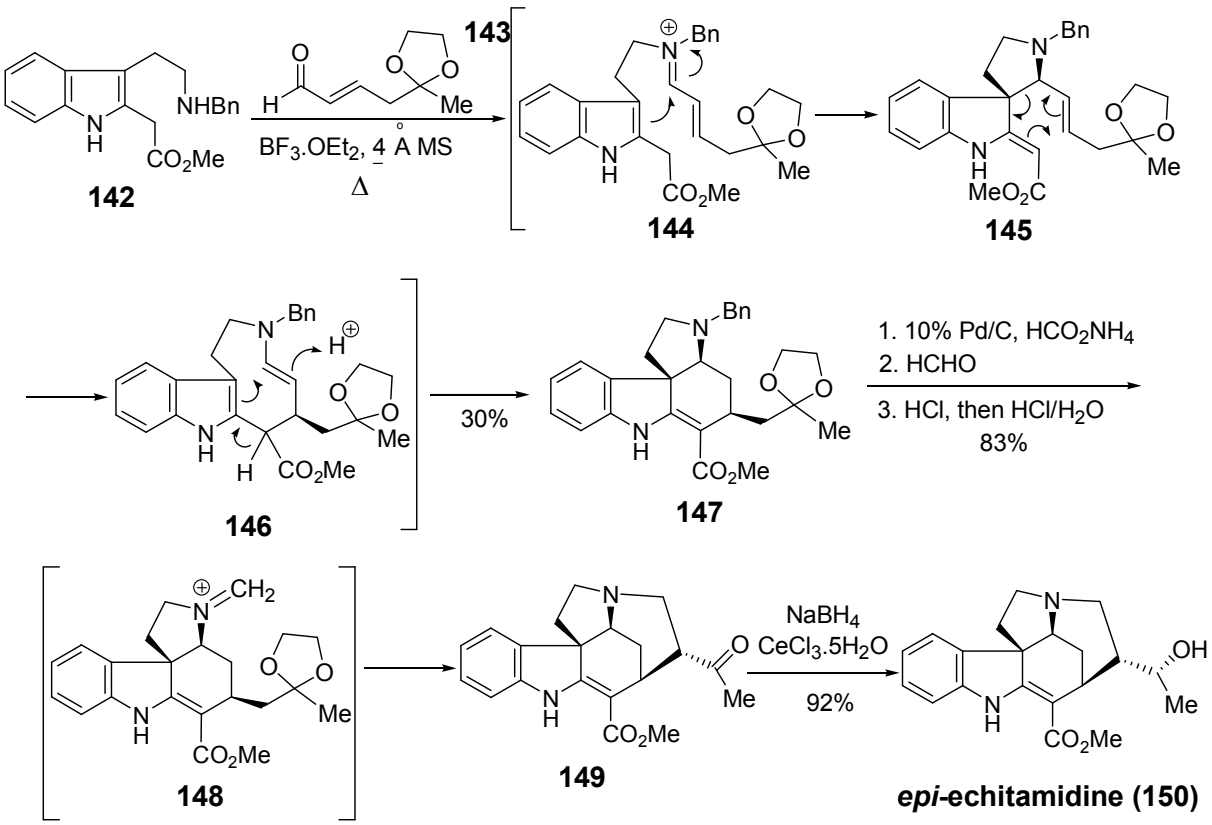
The Bonjoch group has made use of *cis*-3a-(2-nitrophenyl)octahydroindol-4-ones (**137**) as a common, pivotal building block for assembling the pentacyclic

ABCDE ring system of the *Strychnos* alkaloids (Scheme 26).[48] The approach involves a series of stepwise annulations starting from 1,3-cyclohexanedione **135** to give the key intermediate **137**. This intermediate was then used in a subsequent ring closure step to provide the pentacyclic *strychnos* framework. In the example described in Scheme 3, intramolecular cyclization of the enone-propargylic silane **139** was promoted by $BF_3.OEt_2$ to give **140**. Reductive cyclization resulted in the synthesis of tubifolidine (**118**). Introduction of a methyl ester substituent at the C-16 position of compound **140** leads to the synthesis of akuammicine (**116**).



Scheme 26. Bonjoch's approach using *cis*-3a-(2-nitrophenyl)octahydroindol-4-ones (**137**) as a key intermediate

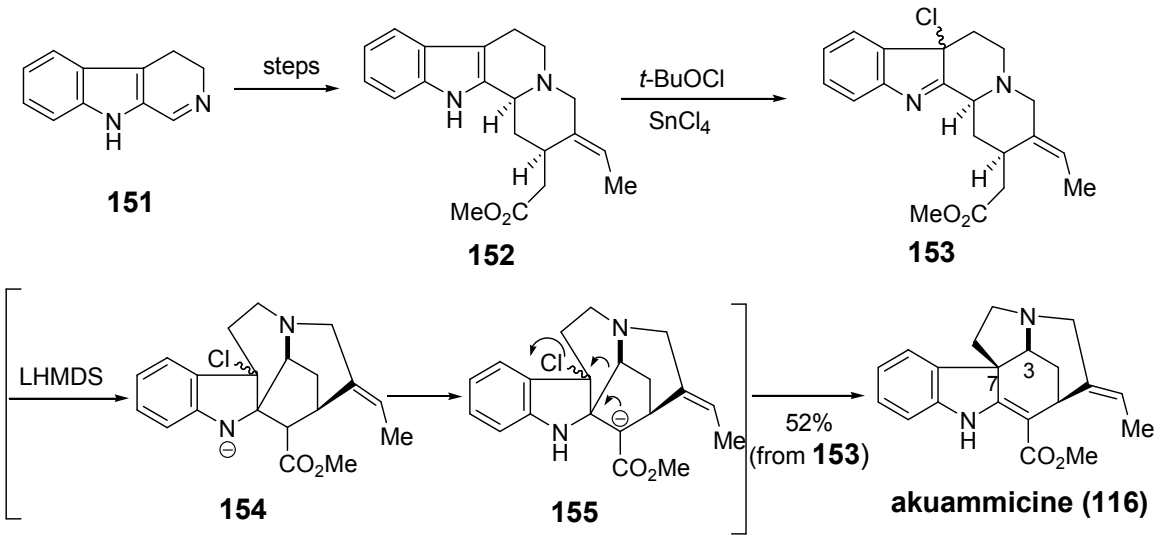
Several *Strychnos* alkaloids were prepared by Kuehne and co-workers utilizing a condensation−sigmatropic rearrangement−cyclization cascade to form the ABCE core structure starting from the tryptophan derivative **142** (Scheme 27).[49] For the synthesis of *epi*-echitamidine, heating a mixture of **142** and aldehyde **143** in the presence of $BF_3{\cdot}OEt_2$, furnished the tetracyclic pyrrolocarbazole **145** in 30% yield.[49c] The initially formed intermediate **145**, derived from a Mannich condensation between **142** and **143**, underwent a facile [3,3]-sigmatropic rearrangement to generate enamine **146**. A subsequent acid-catalyzed Mannich-like cyclization resulted in the formation of **147**. Formation of the D-ring was accomplished by debenzylation, condensation with formaldehyde, and treatment with HCl to generate the iminium-ketal **148**. This intermediate then underwent cyclization and produced ketone **149** after hydrolysis. Ketone **149** was treated with $NaBH_4$ to provide *epi*-echitamidine (**150**). A variant of the cascade cyclization strategy has also been used for the synthesis of other members of the *Strychnos* alkaloid family.



Scheme 27. Kuehne's condensation-sigmatropic rearrangement-cyclization cascade approach

Another interesting route to the *Strychnos* skeleton was reported by Martin. His synthetic plan is based on a proposed biogenetic conversion starting from the indole alkaloids.[50] Thus, a biomimetic oxidation/skeletal rearrangement sequence was employed to form the key C-3 and C-7 bond. In the synthesis of akuammicine, the tetracyclic precursor **152**, which incorporates rings A, B, D, as well as the alkene side chain, was prepared from dihydrocarboline **151** (Scheme 28). A subsequent conversion of **152** into akuammicine (**116**) was effected by oxidation with *t*-BuOCl to furnish a mixture of the two epimeric chloroindolenines **153**. The mixture was treated with LHMDS to induce the structural reorganization

shown in Scheme 28 to give akuammicine (**116**). A similar path using a slight modification of the side chain was also used for the synthesis of strychnine.



Scheme 28. Martin's biomimetic approach

Apart from the synthetic pathways mentioned above, several other clever approaches have been developed for the construction of the pentacyclic *Strychnos* framework. Most of these strategies have some limitations, specifically relating to the difficult functional group transformations at C-16. These syntheses include an approach by Mori utilizing a palladium asymmetric allylic substitution, the Amat/Bosch formation of the tetracyclic ABCE and closure of the E-ring using thionium cyclization,[51] the use of an intramolecular Diels-Alder and Heck reactions by Rawal,[52] as well as the photoisomerization of acylindoles by Ban.[53]

Despite these earlier efforts, new and efficient approaches toward the *Strychnos* pentacyclic framework are still important as they would allow not only the synthesis of other members of this family of natural products (*i.e.* strychnopivotine (**4**)) but also related non-natural analogues possessing

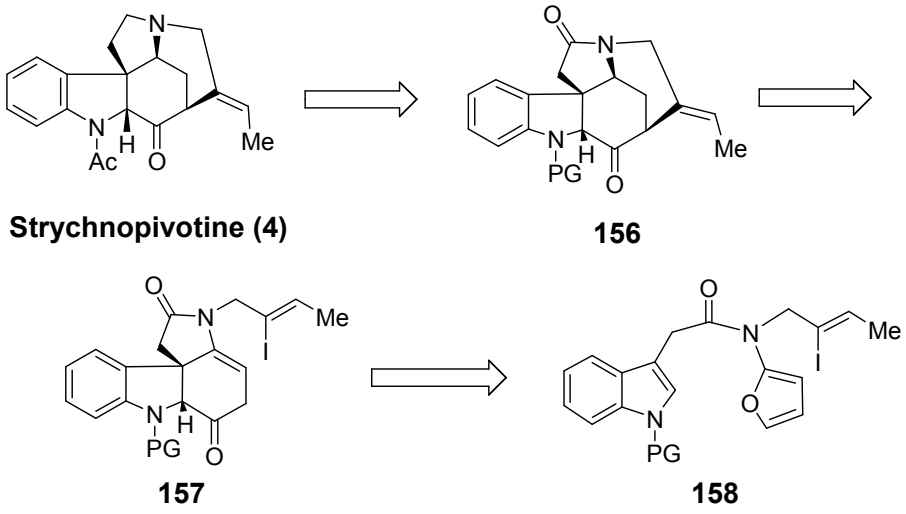
biological activity. As part of this thesis, a new approach for the construction of the pentacyclic framework present in the *Strychnos* system is described.[54]

- **Our retrosynthetic analysis**

Our synthetic approach toward the pentacyclic core found in the *Strychnos* alkaloids was guided by a long-standing interest in developing new applications of the intramolecular [4+2]-cycloaddition/rearrangement cascade of 2-amidofurans toward the synthesis of complex natural products. Specifically, our group has developed a rapid entry into the tetracyclic ABCE skeleton present in both the *Strychnos* and *Aspidosperma* alkaloid families (Scheme 29).[55] Based on this IMDAF methodology, we envisioned a general approach toward the synthesis of several *Strychnos* alkaloids which would be derived from the thermolysis of 2-amidofuran **158** (Scheme 29). A preliminary model study was carried out in order to explore the facility of construction of the ABCDE core skeleton using a combined IMDAF reaction and Pd-catalyzed enolate coupling sequence. Strychnopivotine (**4**) was identified as an appropriate model substrate, as this molecule also belongs to the *Strychnos* family, and contains a carbonyl group at C-16 position. A successful synthesis of this compound would open the door toward the synthesis of many other related alkaloids of the *Strychnos* family.

Strychnopivotine (**4**) was isolated from the root bark of *Strychnos Variabilis* and its structural elucidation was reported by Angenot and co-workers in 1980.[56] No total synthesis of this natural product has been reported, but there are two synthetic studies directed toward this alkaloid.[57] As illustrated in Scheme

29, our retrosynthetic analysis of strychnopivotine (**4**) involves closure of the D-ring in the final step of the synthesis by a Bonjoch/Solé palladium-catalyzed intramolecular coupling of the amido-tethered vinyl iodide in **157** with a keto–enolate generated anion. A critical step of our synthetic plan relies upon the efficient construction of the tetracyclic substructure found in **157** by an intramolecular [4+2]-cycloaddition/rearrangement cascade of 2-amidofuran **158**.



Strychnopivotine (4) **156**

157 **158**

Scheme 29. Retrosynthetic analysis for pentacyclic framework of *Strychnos* alkaloids

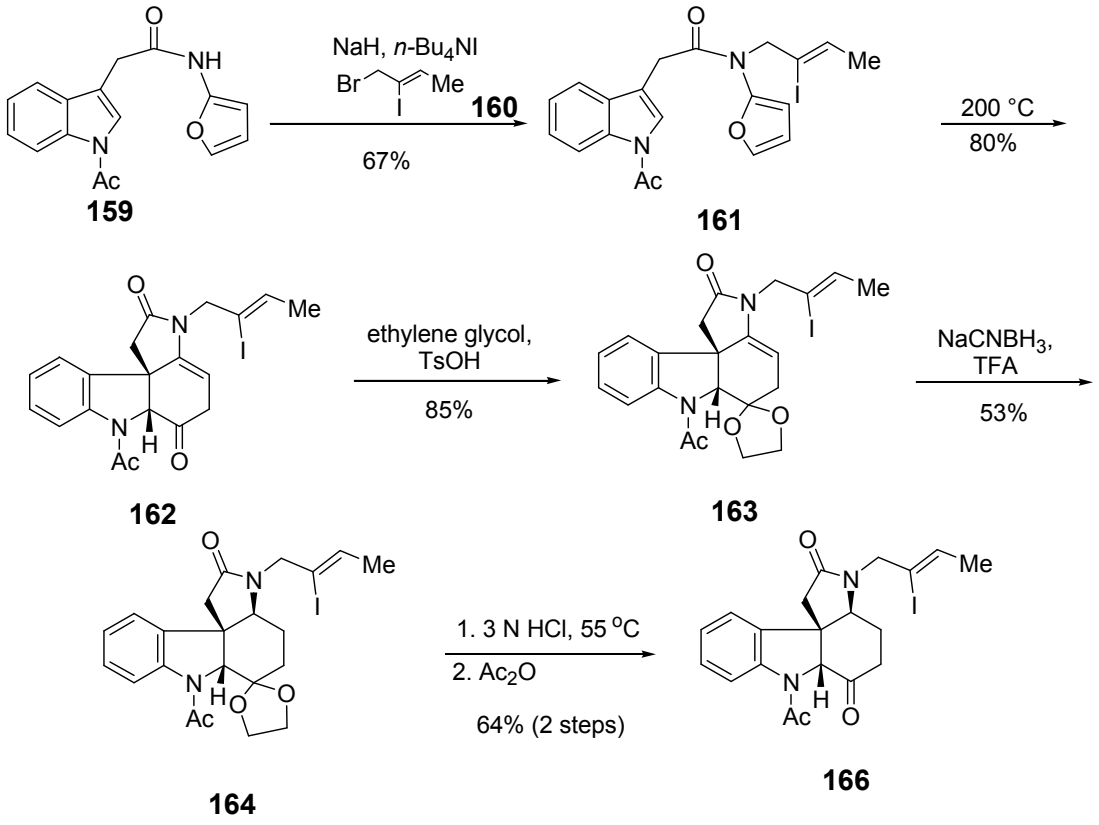
2. Results and Discussion

2.1 Total Synthesis of (±)-Strychnopivotine

First Approach toward (±)-Strychnopivotine (4).

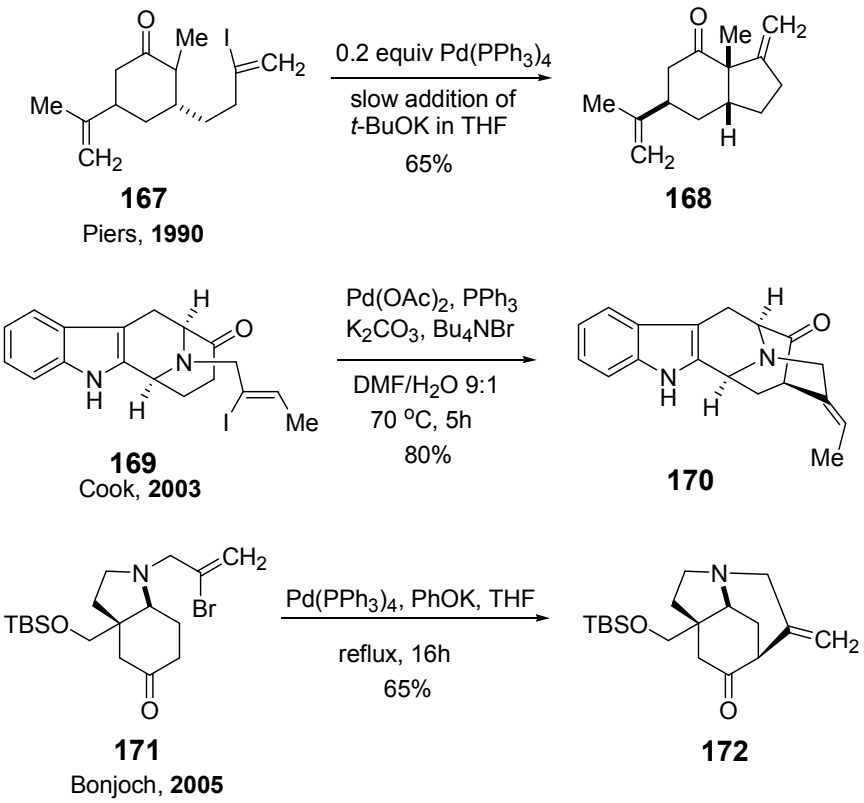
The synthesis commences with the preparation of furanylindole **159** *via* a previously reported procedure.[55] *N*-Alkylation of indole **159** with *Z*-1-bromo-2-iodobut-2-ene (**160**),[58] afforded furanyl amide **161** in 67% yield. The presence of the 2-iodo-2-butenyl side chain would serve not only in the contemplated D-ring closing reaction, but also to bias the amide into the desired *s-trans* conformation. Indeed, heating a sample of **161** in toluene at 200 ^{o}C in a sealed tube initiated the desired cycloaddition/rearrangement cascade to give **162** in 80% yield. The stereospecificity of the cascade process ensured that the *cis*-BC ring fusion was formed (Scheme 30).

Reduction of the enamido double bond present in **162** was achieved *via* a three-step sequence. Protection of the keto group was performed *via* reaction with ethylene glycol to give ketal **163**. Exposure of **163** to $NaCNBH_3$ in the presence of TFA afforded ketal **164** in 53% yield. Deprotection of the ketal was easily carried out using HCl.[59] Under the conditions, partial cleavage of the indolyl acetyl group also occurred even at low temperatures. Therefore, an additional acetylation of the crude reaction mixture was required. Reaction of the resulting intermediate **164** with Ac_2O/pyridine gave ketone **166** setting the stage for the key enolate coupling reaction.



Scheme 30. Preparation of enolate coupling precursor **166**

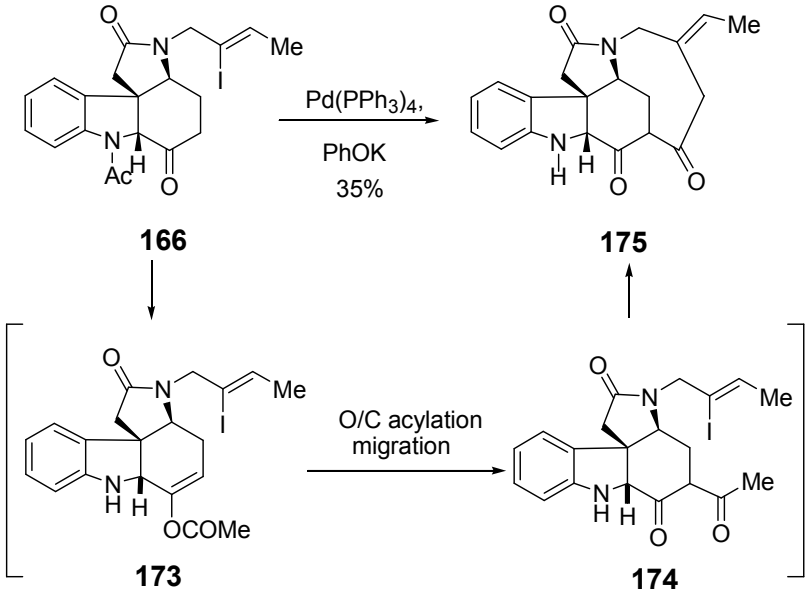
The Pd-catalyzed enolate coupling reaction of aryl halides has been extensively investigated over the past decade.[60] In contrast, the coupling of vinyl halides has received far less attention although it has great potential in the context of complex molecule synthesis (Scheme 31). Following the pioneering work of Piers in the 1990s,[61] the Cook group successfully utilized this coupling approach for a synthesis of the Sarpagine indole alkaloids, such as Vellosimine, and Panarine.[62] Bonjoch and Solé have recently carried out studies dealing with the enolate coupling of several systems including the construction of the 2-azabicyclo[3.3.1]nonane system of amino-tethered vinyl halides.[63,64]



Scheme 31. Previous examples of Pd-catalyzed enolate coupling of alkenyl halides

Our palladium catalyzed cycloalkylation studies used conditions previously reported by Bonjoch and Solé. Most surprisingly, our attempts to induce a D-ring closure by subjecting tetracycle **165** to the Bonjoch/Solé cyclization conditions ($Pd(PPh_3)_4$/PhOK) provided the unexpected β-diketone **175** in 35% yield as the only isolable product from the reaction mixture (Scheme 32). Subjecting the corresponding deacetylated compound to the same conditions, however, only resulted in the decomposition of starting material over an extended reaction time. A possible mechanism for this unusual reorganization is outlined in Scheme 32. An initial migration of the acetyl group from the indoline nitrogen onto the oxygen

atom of the enolate anion provides **173**. The transient enol-ester **173** so formed then undergoes a subsequent acyl group shift to furnish β-diketone **174**.[65] The acetyl group present in the newly formed diketone **174** is close enough in proximity to the vinyl center to undergo the enolate cross-coupling reaction. It would appear as though coupling at the more acidic position is seriously retarded as a consequence of severe nonbonding interactions in its transition state for this insertion.



Scheme 32. Initial attempt at Pd-catalyzed D-ring closure

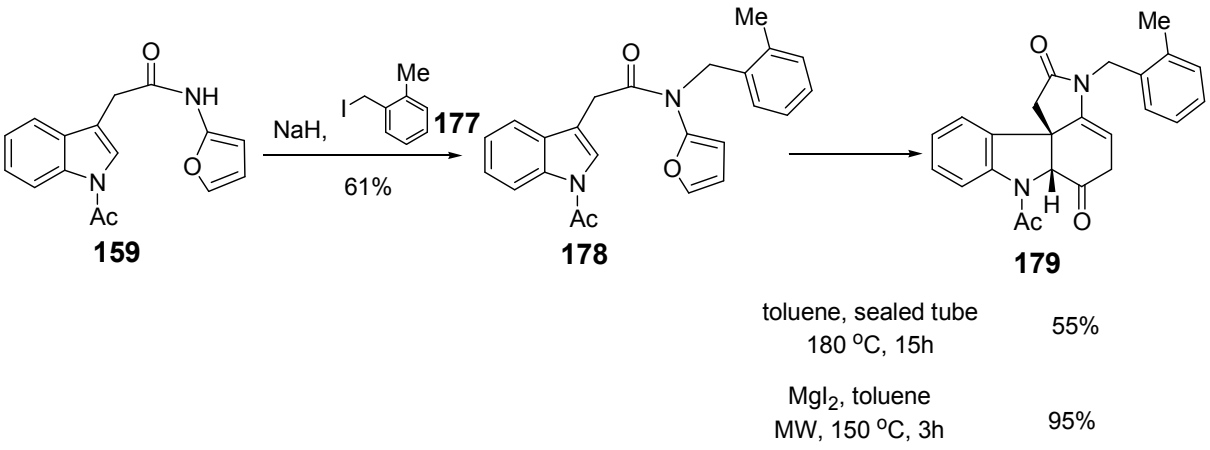
Second Generation Approach toward (±)-Strychnopivotine (3).

Considering the difficulty we encountered with the palladium-catalyzed intramolecular coupling reaction of the tetracyclic keto-lactam **166**, we decided to slightly modify our approach toward (±)-strychnopivotine (**4**). Comparison of the geometry of **166** with the various systems studied by Bonjoch and Solé (*i.e.* Scheme 31) led us to speculate that the presence of the amido carbonyl group in

the E-ring significantly increased the rigidity of the skeleton thereby creating an element of strain in the transition state for the critical coupling reaction. We reasoned that changing the hybridization of the nitrogen atom from sp^2 to sp^3 would relieve the source of strain in the transition state and the desired ring closing reaction would occur. Lactam **166** was treated with Lawesson's reagent with the anticipation of forming a thioamide which could then be reduced to give the desired tertiary amine.[66] Unfortunately, our attempts to reduce lactam **166** under various conditions were complicated with the recovery of unreacted starting material, several undesired products as well as concomitant loss of the iodine group on the side chain. Therefore the synthetic strategy had to be modified in order to accommodate lactam reduction. This issue was solved by introduction of the vinyl iodide after the reduction of the lactam ring.

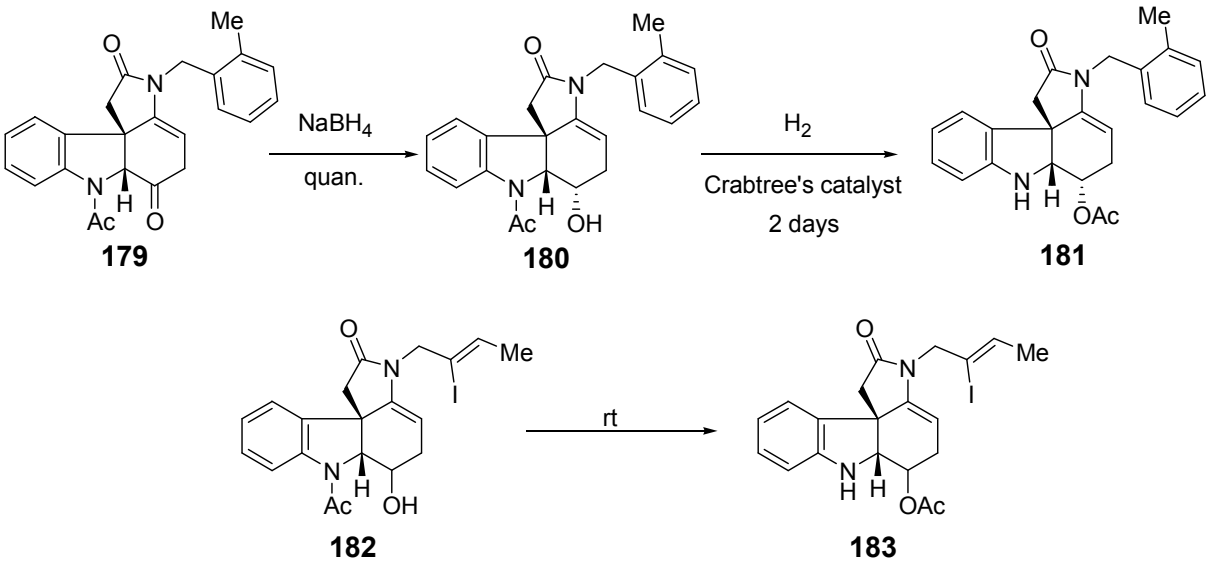
For this purpose, furanyl indole **179** was prepared from furanyl indole **43** in a manner analogous to that used for the synthesis of **161** (Scheme 33). Alkylation of furanyl indole **159** with *o*-methylbenzyl iodide proceeded in 61% yield to give the desired Diels-Alder precursor **178**. The presence of the large *o*-methylbenzyl group on the amido nitrogen atom causes the reactive *s-trans* conformer to be more highly populated thereby promoting the intramolecular cycloaddition. Heating a toluene solution of **178** in a sealed tube at 180 ºC provided cycloadduct **179** in 55% yield. It was found that the same sequence could be accomplished in a microwave reactor using catalytic quantities of MgI_2 at a lower temperature of 150 ºC and significantly faster rate (15 h *vs* 3 h). This latter procedure cleanly delivered cycloadduct **179** in 95% yield. The efficiency of

the cycloaddition/rearrangement cascade in the presence of a Lewis acid catalyst is particularly noteworthy and some further studies have been conducted, as will be discussed later.



Scheme 33. The IMDAF reaction of compound **178**

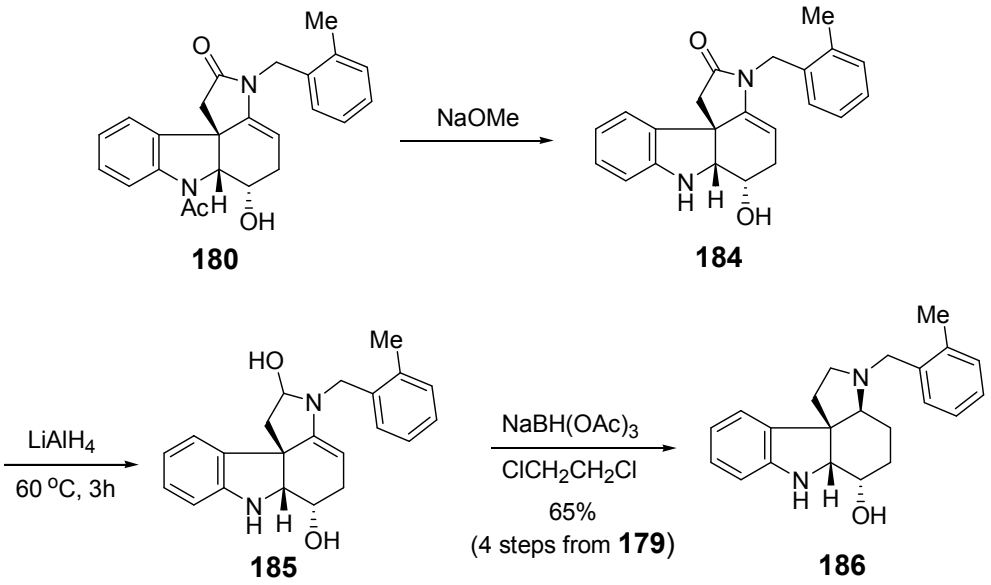
The next step in the synthesis involves removal of the carbonyl lactam present in ring-E. Initially, a hydroxy-directing hydrogenation using Crabtree's catalyst was tried in order to effect the stereoselective reduction of the enamide double bond.[67] Stereoselective reduction of the ketone functionality with $NaBH_4$ gave alcohol **180** as a single stereomer in quantitative yield. Compound **180** was then subjected to the hydrogenation conditions. However, the desired reduction did not occur and only migration of the acetyl group from the indolyl nitrogen to the hydroxy group took place to give **181**. A similar acetyl group migration was also observed with compound **182** when it was allowed to stand at room temperature for several days.



Scheme 34. Acyl group migration in compound **179** and **182**

Based on these observations, we decided to remove the acetyl group prior to attempting the other functional group adjustments. Thus, exposure of alcohol **180** to an equivalent of NaOMe in methanol induced the rapid cleavage of the acetyl group within several minutes at room temperature giving compound **184** in quantitative yield (Scheme 35). The mild conditions used for the amide bond hydrolysis presumably is related to the ability of the adjacent alkoxide ion to promote the *N*- to *O*-acyl transfer and this was followed by hydrolysis of the more labile ester. Next, the lactam group in **184** was reduced using an excess of $LiAlH_4$ in THF at reflux for 3 h. The NMR spectrum showed the quantitative formation of enaminal **185**.[68] The resulting enaminal **185** was further reduced using $NaBH(OAc)_3$ in dichloroethane. While this last step gave a mixture of stereoisomers, carrying out the reduction at -10 ºC resulted in a 4:1 mixture favoring the *cis* fused tetrahydro-1*H*-indole-2,5(3*H*,6*H*)-dione **186**. Interestingly,

when the solvent was changed to a protic solvent such as MeOH, the stereoselectivity was inverted and gave the *trans*-isomer as a major product. This observation suggests that the reduction of the enamine occurs *via* an intramolecular hydroxyl directed hydride transfer.[69] Using this four step sequence starting from **179**, alcohol **186** could be isolated in 65% yield with only a single chromatographic purification since the products obtained from the first three steps were of sufficient purity so that chromatography was not necessary (Scheme 35).



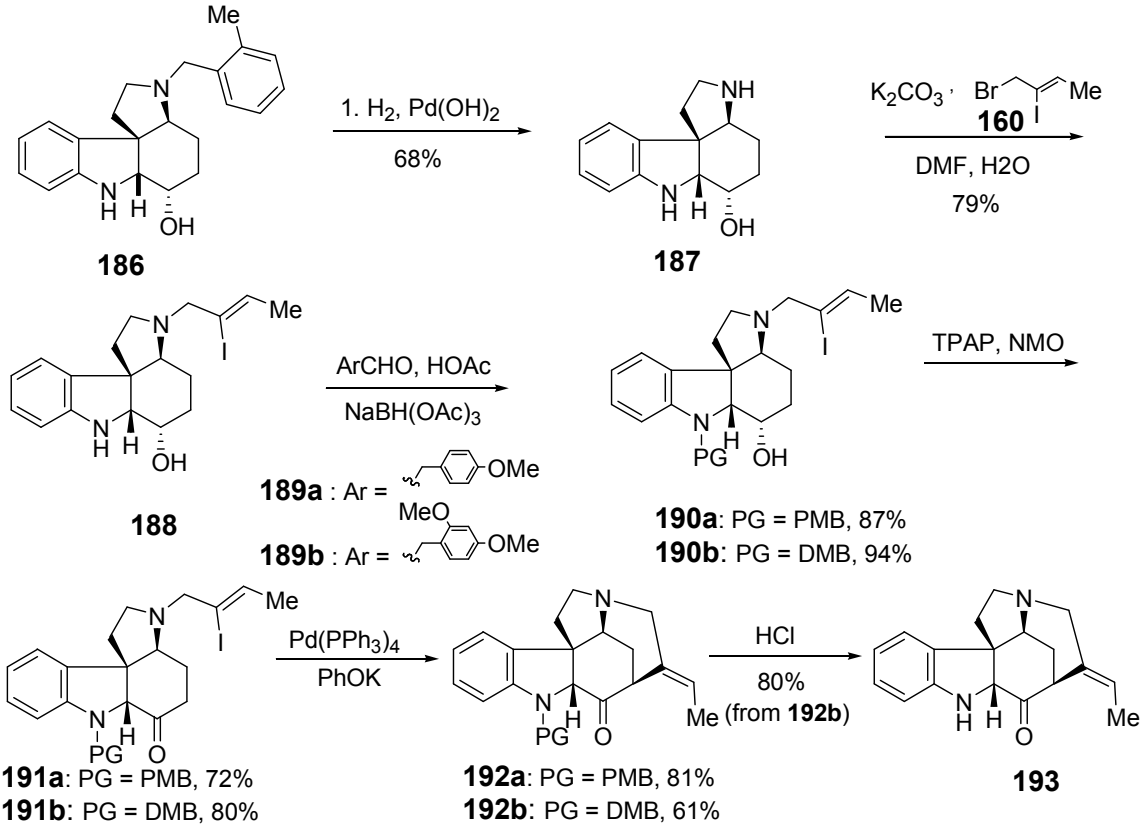
Scheme 35. Enamide reduction

Next, the *o*-methylbenzyl group was removed using H_2 and Pearlman's catalyst in 68% yield (Scheme 36). Extended reaction times were required for this transformation to be complete and it was found that the reaction worked best at room temperature. The use of elevated temperatures (>35 ºC) or using acid catalyzed conditions resulted in a complex mixture being formed. The resulting

indoline nitrogen was subsequently alkylated using *Z*-1-bromo-2-iodobut-2-ene (**160**)[58] and K_2CO_3 in DMF/water at 0 ºC. However, over-alkylation was a constant problem in this reaction but could be alleviated by the slow addition of **160** *via* a syringe pump over a 12 h period to give **188** as the major product in 79% yield.All that remained before the *D*-ring closure step was oxidation of the hydroxyl group. However, various attempts failed to effect the selective oxidation of alcohol **188** to the corresponding ketone in the presence of the unprotected indoline moiety.[70] Therefore, protection of the amine functionality was carried out by treating alcohol **186** with *para*-methoxybenzaldehyde under standard reductive amination conditions to give the protected indoline **190a** in 87% yield.[71] TPAP oxidation afforded ketone **191a** in 72% yield[72] thereby setting the stage for the key palladium enolate catalyzed coupling reaction.

The desired intramolecular coupling reaction using the Bonjoch/Solé conditions proceeded smoothly to furnish the pentacyclic ketone **192a** in 81% yield. However, removal of the PMB protecting group was found to be difficult. Numerous experiments were carried out, but all failed to give the desired product. For example, CAN oxidation led to decomposition of the substrate, while reduction with Na/NH_3 also resulted in reduction of the keto group that is present in **192a**.[73] The 2,4-methoxybenzyl (DMB) group was chosen as an alternative protecting group.[74] Following the same protocol as outlined above, the coupling precursor **191b** was generated. Subjection of **191b** to the palladium catalyzed enolate coupling conditions delivered the desired product **192b** in 61% yield. The diminished yield for this step is not so surprising, considering the presence of an

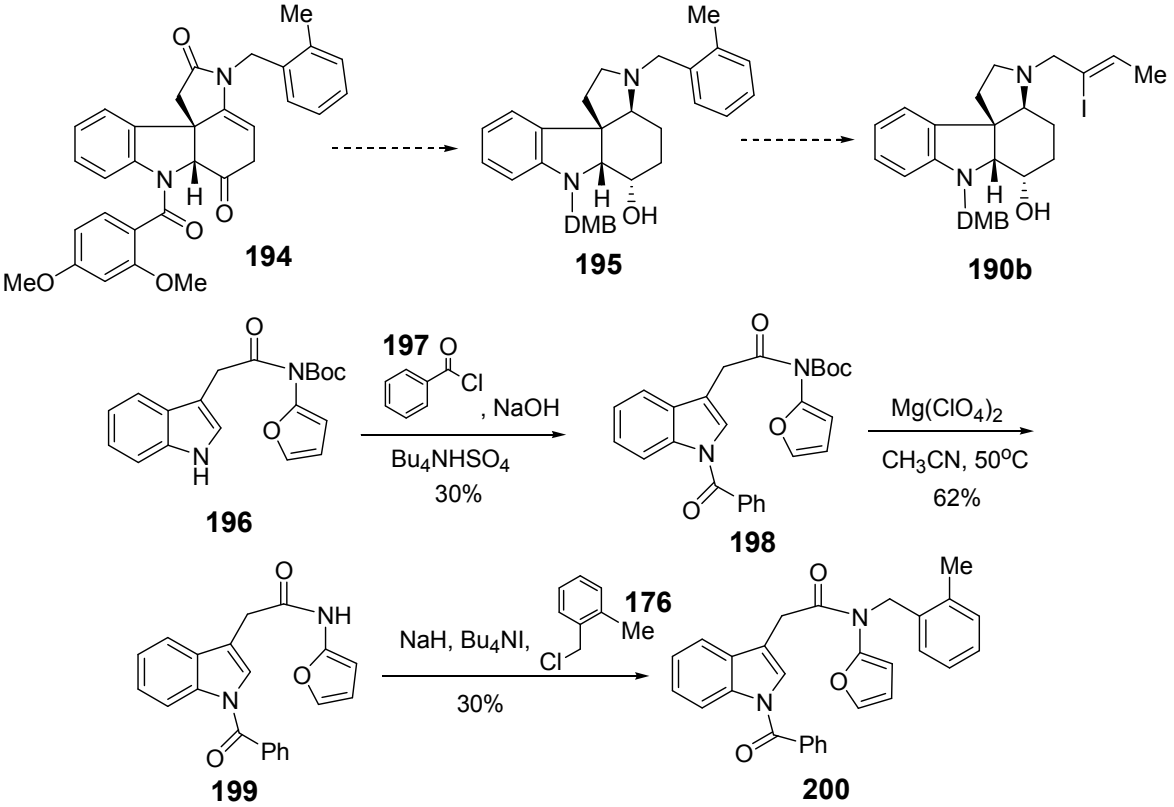
additional *ortho*-methoxy group which resides close to the reactive center of the C-16 carbonyl group. Although the desired product could not be obtained using oxidative conditions (either DDQ or CAN), treatment of **192b** with HCl in MeOH did result in the ready cleavage of the DMB group and delivered the desired product **73** in 80% yield. With the facile deprotection of **192b**, we decided to utilize this compound as a common intermediate to gain access to the *Strychnos* alkaloids (Scheme 36).



Scheme 36. Preparation of the pentacyclic common intermediate **193**

The potential of using a benzoyl derivative as an indoline protecting group was also examined with a view that this would deliver **190b** by a shorter route (Scheme 37) *via* double reduction of the lactam moieties presented in **194**

and selective *N*-deprotection at ring-E of **195**.[75] The preparation of the IMDAF precursor with a benzoyl group at the indolinyl nitrogen was evaluated. Disappointedly, furanyl indole **200** could only be obtained in a much lower yield when compared to the acetyl derivative **179**. As a consequence of this inefficiency, we decided to proceed with our original route.

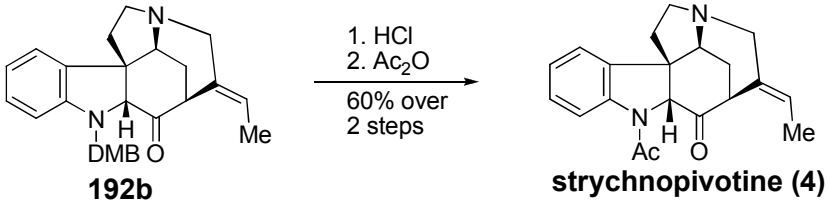


Scheme 37. Attempts to use benzoyl protecting group approach

Completion of the total synthesis of (±)-strychnopivotine (4).

With the pentacyclic intermediate **191b** in hand, completion of the synthesis of strychnopivotine was carried out in two simple steps (Scheme 38). The DMB protecting group of **191b** was removed using HCl in methanol and the crude product was treated under typical acylation conditions to form

strychnopivotine (**4**) in 60% over the two steps. The spectral data for the synthetic sample matched those reported by Tits and co-workers.[56]



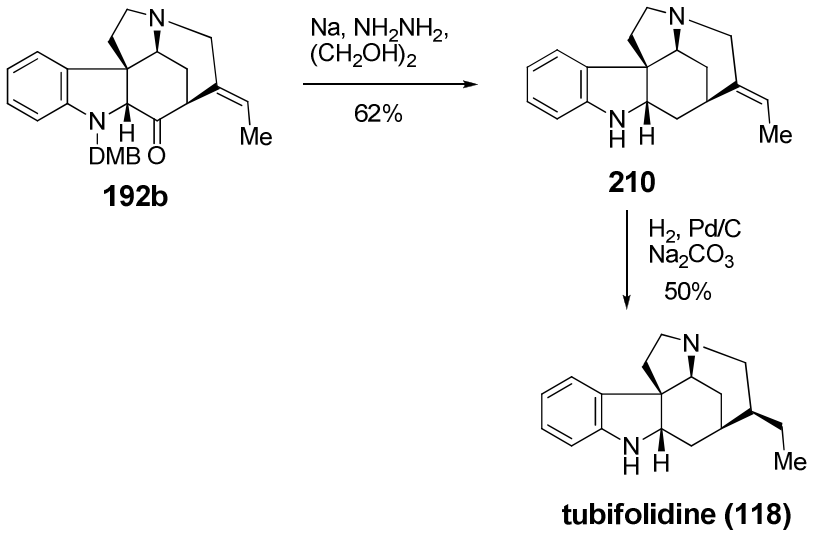
192b **strychnopivotine (4)**

Scheme 38. Completion of synthesis of (±)-strychnopivotine

2.2 Total Synthesis of (±)-tubifolidine (118).

The synthesis of the *Strychnos* alkaloid (±)-tubifolidine (**118**) was selected as the next target to further highlight the methodology (Scheme 39). Tubifolidine was isolated by Schmid and co-workers in 1964.[76] Before its isolation, this alkaloid was actually a known compound that had been obtained by a partial synthesis in the context of a chemical correlation effected for the structural elucidation of a more complex member of the *Strychnos* family.[77] Tubifolidine has been the target of several strategies toward the *Strychnos* alkaloid framework and a number of total syntheses have been reported.[78] Our synthesis of (±)-tubifolidine (**118**) could be realized by the sequential reduction of intermediate **192b**. Thus, treatment of **192b** under Wolff-Kishner type conditions (Na, hydrazine in ethylene glycol)[79] resulted in the removal of the carbonyl group as well as the dimethoxybenzyl protecting group to furnish alkene **201** in 62% yield (Scheme 39). Next, reduction of the C-20 appendage was attempted. The reaction solvent was found to be critical for successful reduction, as well as the necessity to buffer the hydrogenation reaction with Na_2CO_3. By carrying out the

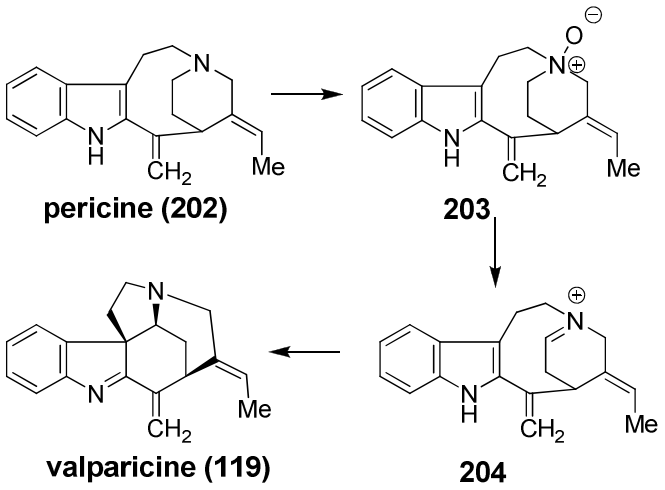
catalytic reduction of **201** with Pd/C as the catalyst in THF, the sole product obtained in 50% yield corresponded to (±)-tubifolidine (**118**).[78]



Scheme 39. Completion of synthesis of (±)-tubifolidine

2.3 Total Synthesis of (±)-valparicine (119).

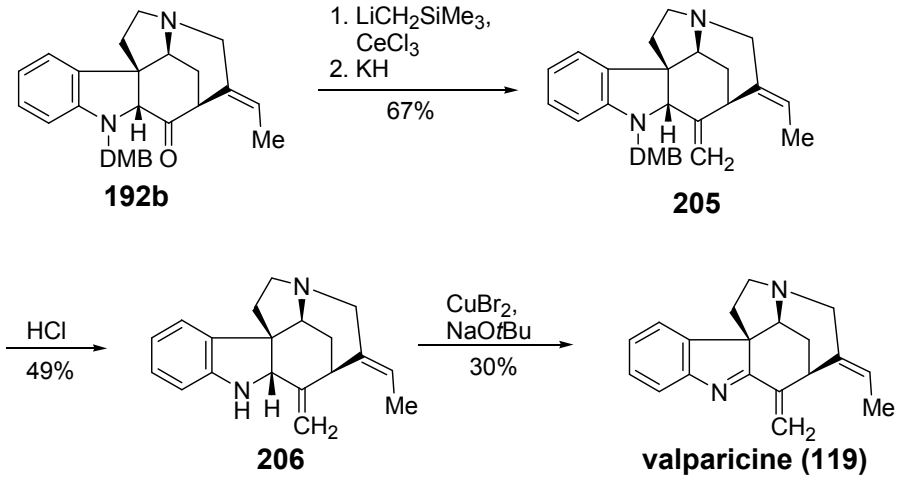
Kam and co-workers reported in 2006 on the isolation of the alkaloid valparicine (**119**) from the stem-bark extracts of *K. arborea*, a member of the *Kopsia* family.[80] Initial studies showed some pronounced cytotoxic effects against KB and Jurkat cells.[81] It has been proposed that valparicine (**119**) is biogenetically related to pericine (**202**) by means of a Polonovski reaction, wherein the E-ring of the alkaloid is formed by cyclization of the indole ring onto the resulting iminium ion as indicated in Scheme 40.



Scheme 40. Biogenetic synthesis of valparicine

Although strictly not a member of the *Strychnos* family, the structural similarities triggered our interest in valparicine. Having a sample of **191b** on hand, a variation of Wittig,[82] Tebbe,[83] Petasis[84] and Takai[85] reactions were examined in order to introduce the C-16 methylene unit onto the existing carbonyl but without success. Eventually, we found that by treating intermediate **192b** with trimethylsilylmethyl lithium and cerium(III) chloride[86] followed by heating the resulting alcohol with potassium hydride in THF delivered the C-16 methylene unit of **205** in 69% yield. The DMB protecting group was then removed by warming **205** with 1.0 M HCl/MeOH to produce **206** in 49% yield. To complete the synthesis, all that remained was an oxidation of the C−N single bond between the C-2 and N-1 position. A number of conditions were evaluated including IBX,[87] TPAP,[88] Swern oxidation,[89] $KMnO_4$,[90] and MnO_2[91], however all of these conditions failed to deliver the expected product.[92] Eventually, it was found that by stirring **206** with copper bromide and sodium *tert*-butoxide[93] for 40 min,

the required transformation was achieved in 30% yield (together with recovered starting material). This sequence completes the first total synthesis of this alkaloid. The ^{1}H-NMR spectral data for the obtained product was perfectly consistent with those reported by Kam and co-workers (Scheme 41).



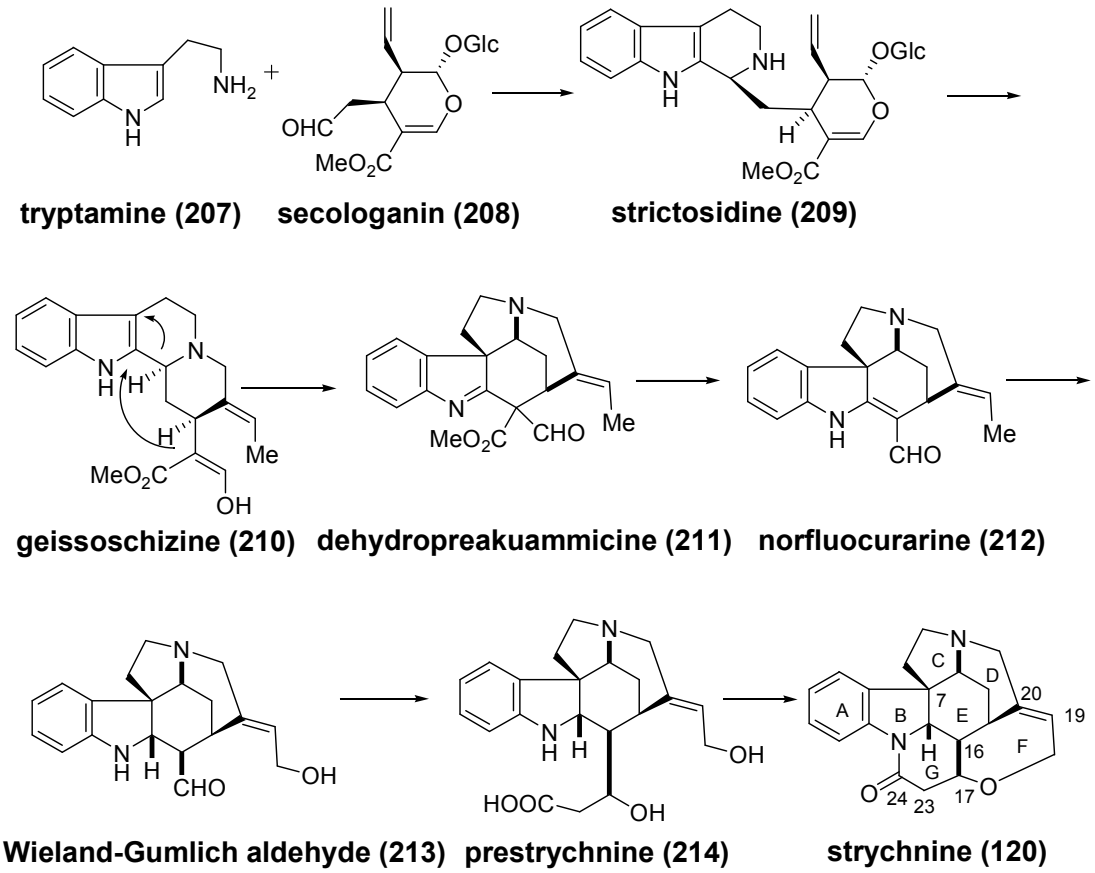
Scheme 41. Completion of synthesis of (±)-valparicine

2.4 Total Synthesis of (±)-strychnine (120).

Strychnine, a well-known poison, has a long and rich history as one of the more notorious members of the *Strychnos* alkaloid family.[94] This alkaloid was first isolated in 1818 by Pelletier and Caventou from the seed of the Indian poison nut *Strychnos nux vomica* and later found in many other species coming from Asia and other parts of the world.[95,96] The highly toxic (50~100 mg) is lethal for an adult human) properties of strychnine result from its interaction with the glycine receptor site, thereby blocking the flux of chloride ions, which results in disruption of nerve-cell signaling and leads to over excitation of the motor system and intense muscular convulsion.[97] This property has made strychnine useful as a tool in experimental pharmacology as it helps establish glycine as an inhibitory

neurotransmitter and also maps glycine receptors autoradiographically. Additionally, strychnine belongs to the analeptics group of medicine which, in small doses, increases the activity of certain functions in the central nervous system. It is also a powerful spinal cord convulsant, but the functions of the brain cortex and sub cortical centres are not influenced. [98]

Biogenetically, strychnine is derived from an enzyme-catalyzed Pictet-Spengler condensation between tryptamine (**207**) and secologanin (**208**) to form strictosidine (**209**), which is then converted into geissoschizine (**210**), the common biogenetic intermediate for all the monoterpenoid indole alkaloids (Scheme 42). Subsequent oxidative cyclization and skeletal rearrangement affords dehydropreakuammicine (**211**), which possesses the characteristic framework of the *Strychnos* alkaloids. The next few steps involve decarbomethoxylation, allylic oxidation, and reduction to produce the Wieland-Gumlich aldehyde (**213**).[99] Finally, the requisite C-23 and C-24 carbons are imported through an acetyl-CoA-assisted aldol condensation in order to deliver prestrychnine (**214**), which undergoes further cyclization to generate strychnine (**120**).[100]

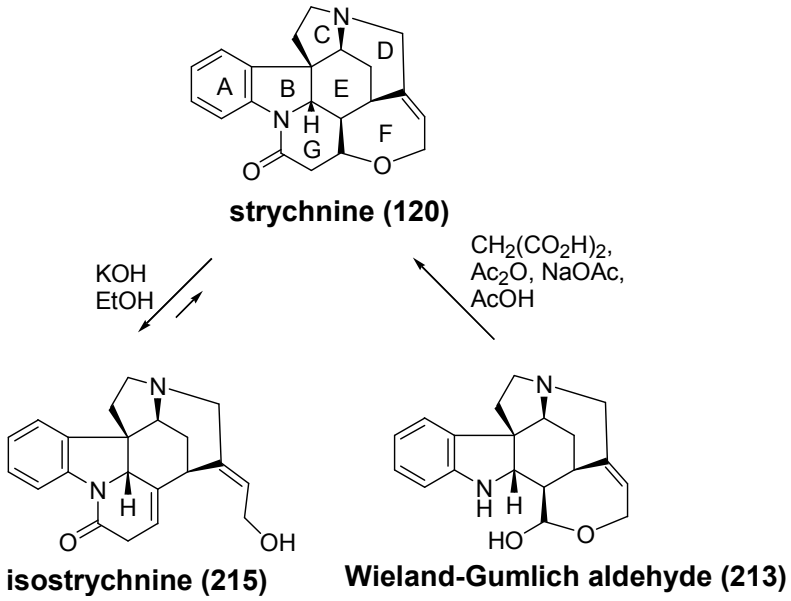


Scheme 42. Biosynthesis of strychnine

Despite being isolated in 1818, the structure of strychnine wasn't confirmed until 1946. Extensive degradative and structural studies culminated in the elucidation of strychnine's structure by Robinson.[101,102] The relative and absolute configurations were later confirmed by X-ray crystallographic analysis.[103] Over the years, strychnine has attracted considerable attention from the synthetic community mainly due to its complex heptacyclic structure, containing 24 skeletal atoms and six contiguous stereogenic centers. The first total synthesis was completed by Woodward in 1954.[104] Nearly 40 years after Woodward's pioneering achievement of strychnine, a number of other research

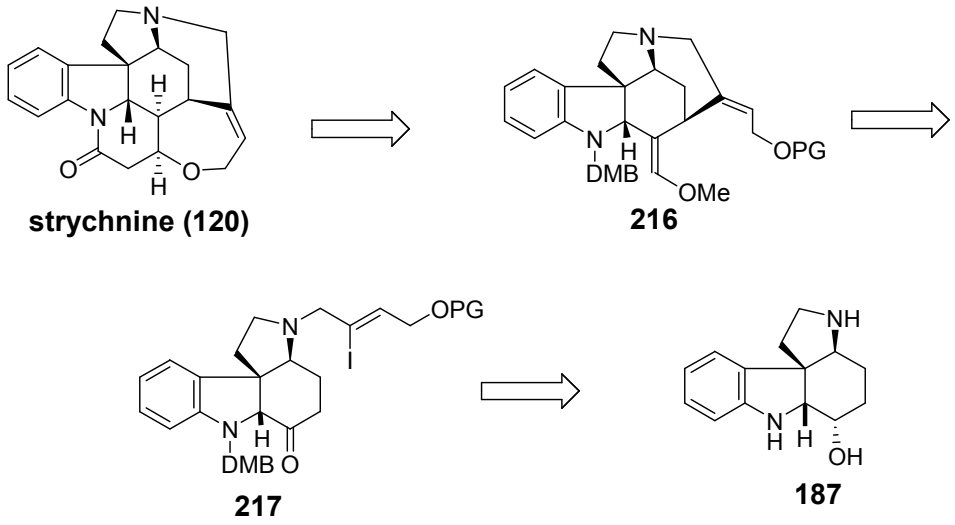
groups have reported on its synthesis.[105,106] To date thirteen syntheses of strychnine have been reported and strychnine still remains a popular target for demonstrating new reactions and novel synthetic strategies.

The reported syntheses of strychnine generally employ either isostrychnine (**215**) or the Wieland−Gumlich aldehyde (**213**) as an advanced intermediate. The Prelog−Taylor cyclization of isostrychnine (**215**) to strychnine (**120**) occurs by heating it with KOH in ethanol.[107] However this reaction suffers from an unfavorable 3:1 equilibration ratio of these two compounds and thus can only deliver strychnine in 10%-28% yield. In contrast, the alternative biomimetic route to strychnine involving the condensation of the Wieland−Gumlich aldehyde (**213**) with an acetate equivalent results in the formation of the G-ring in roughly 70% yield as it avoids the unfavorable equilibrium ratio.[108] From this perspective, the latter conversion seems to be the more attractive approach. Therefore we set out to prepare the Wieland−Gumlich aldehyde (**213**) using the IMDAF cascade/rearrangement methodology (Scheme 43).



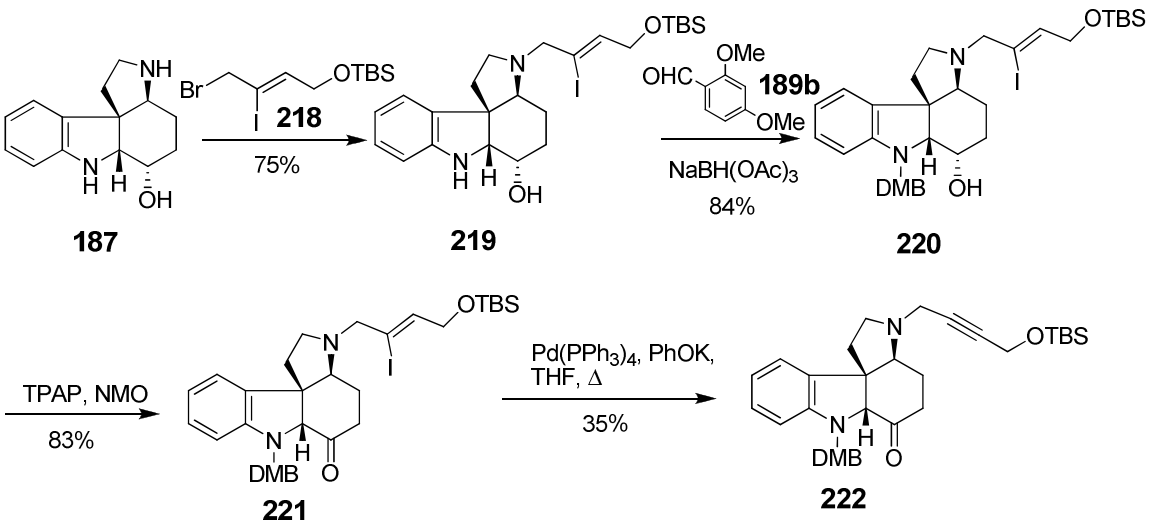
Scheme 43. Conversion of isostrychnine or Wieland-Gumlich aldehyde into strychnine

As illustrated in Scheme 44, our retrosynthetic analysis of strychnine (**120**) relies upon the efficient construction of the pentacyclic intermediate **216**, which in turn would be derived from the previously prepared tetracycle **187** used in the earlier strychnopivotine (**4**) synthesis. As before, we planned to generate the D-ring of **216** by a palladium-catalyzed intramolecular coupling of the amido-tethered vinyl iodide **217** with its keto–enolate. Intermediate **217** should be available from **187** by a simple *N*-alkylation to install the necessary side chain.



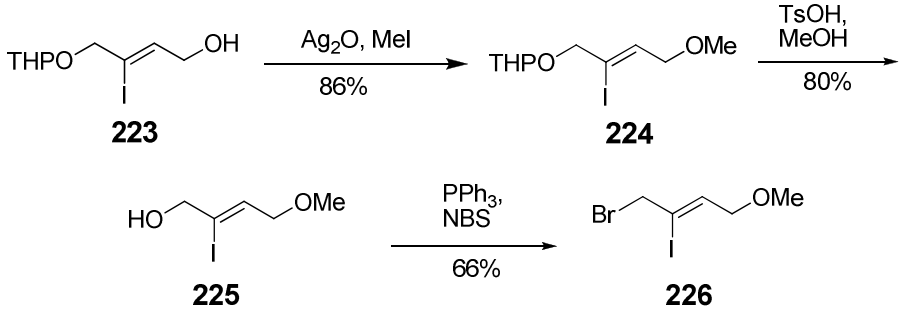
Scheme 44. Retrosynthetic analysis of strychnine

The synthesis of tetracycle **219** started from the previously prepared pyrrolidinyl substituted alcohol **187** (Scheme 22). *N*-Alkylation of **187** with the allylic bromide **218**[109] provided alcohol **219** in 75% yield. Condensation of the indoline nitrogen present in **219** with 2,4-dimethoxybenzaldehyde in the presence of $NaBH(OAc)_3$ afforded the *N*-protected DMB derivative **220** in 84% yield. Oxidation of the resulting secondary alcohol to the corresponding ketone **221** occurred smoothly in 83% yield using tetrapropylammonium perruthenate (TPAP). Unfortunately, when **221** was treated with $Pd(PPh_3)_4$ and PhOK, to bring about D-ring formation, the only isolable product was acetylene **222**. More than likely the steric properties of the TBS group inhibit the cyclization reaction. We next attempted D-ring closure using a sterically less demanding protecting group. The smaller methoxy group was chosen as a replacement for the larger TBS group.



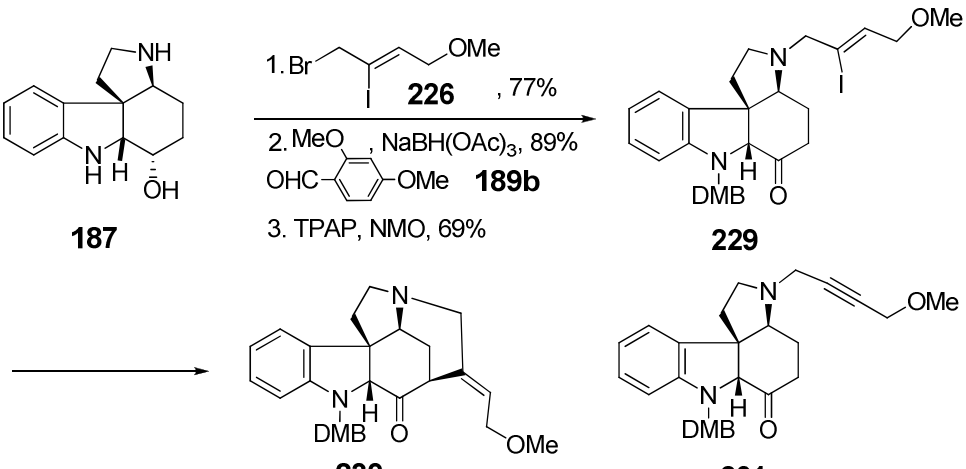
Scheme 45. Attempt for enolate coupling with TBS-protected side chain

The methyl ether derivative was prepared starting from the known alcohol **223** (Scheme 46).[110] Using NaH and MeI gave only the elimination product. However, the conversion of alcohol **223** to the corresponding methyl ether **224** occurred smoothly *via* a microwave-assisted etherification with MeI and Ag_2O. After the THP group was removed, the second hydroxyl group was converted to the corresponding bromide **226** using PPh_3 and *N*-bromosuccinimide.



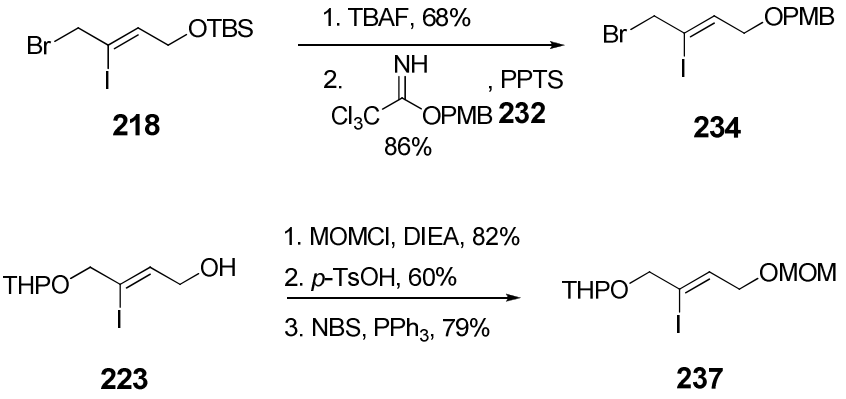
Scheme 46. Synthesis of methyl ether protected side chain

With the required allylic bromide in hand, tetracycle **187** was subjected to *N*-alkylation, reductive amination, and oxidation to deliver **229** (Scheme 47). When the critical palladium-catalyzed cyclization was carried out using the methyl ether derivative **229** with $Pd(PPh_3)_4$ and PhOK, the reaction proceeded to furnish aza-pentacycle **230** in 32% yield, together with some alkyne formation (21%). To improve the overall efficiency of the coupling reaction, we envisioned that reducing the amount of base (PhOK) might slow down the competitive elimination pathway and thereby decrease the amount of the undesirable alkyne. Indeed, reducing the amount of PhOK to 1.3 equivalents while increasing the palladium loading (0.1 equivalents to 0.2 equivalents) gave a significant improvement in the yield of pentacycle **230** (55%). Under these conditions, the elimination pathway **231** was suppressed to less than 10% yield.



Scheme 47. Optimization of Pd-enolate coupling reaction

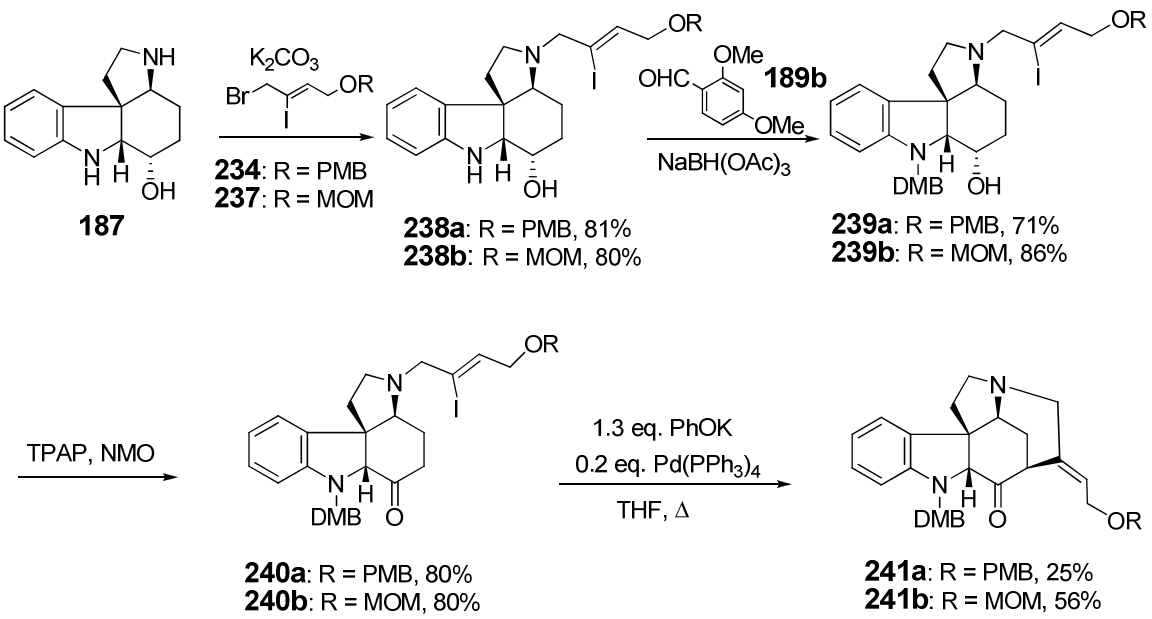
As cleavage of a methyl ether typically requires harsh condition, we decided to replace this group with another acid-labile protecting group. It was anticipated that the acid liability of the protecting group could be used in an advantageous fashion at a later stage. Therefore, the use of PMB as well as MOM protecting groups were investigated. In the synthesis of the PMB protected side chain, the etherification reaction was not successful under the mild basic conditions. Instead, trichloroacetimidate **232** was utilized to deliver the PMB protected side chain **234** under acidic conditions.[111] The synthesis of the MOM protected side chain **237** was carried out in a similar manner to that outlined in Scheme 46.



Scheme 48. Preparation of PMB and MOM protected side chains

Conversion of bromides **234** and **237** into their corresponding coupling precursors **238a** and **238b** was easily carried out as shown in Scheme 49. Exposure of the two precursors **240a** and **240b** to the modified coupling conditions (1.3 eq. PhOK and 20% Pd) afforded the desired coupling product. In the case where PMB was used as the protecting group, pentacycle **241a** was obtained in 25% yield. Fortunately, treatment of the MOM ether derivative **240b**

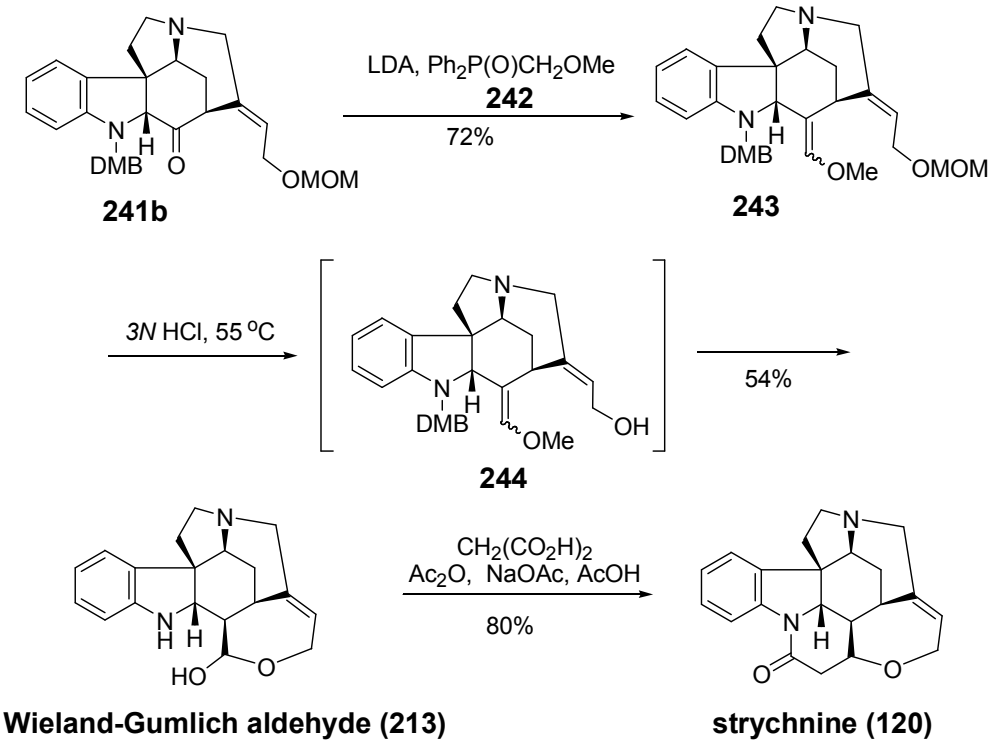
to the same reaction conditions gave pentacycle **241b** in 56% yield. We decided to continue the synthesis of strychnine using the MOM ether protected compound **241b** instead of the corresponding PMB derivative.



Scheme 49. Enolate coupling with PMB and MOM protected side chains

The next synthetic challenge was to establish a one carbon homologation of ketone **241a**. Our initial attempts to convert the keto group of **241b** into the corresponding enol ether **243** using methoxymethylene-triphenylphosphorane ($MeOCH{=}PPh_3$) were unsuccessful, probably as a consequence of steric congestion about the ketone. Consequently, we turned our attention to the phosphine oxide reagent $MeOCH_2P(O)Ph_2$ (**242**), whose anion is sterically less demanding and more nucleophilic compared to the phosphorane $MeOCH_2{=}PPh_3$.[112,113] Thus, treatment of $MeOCH_2P(O)Ph_2$ (**242**) with LDA in THF gave the lithio anion, which reacted smoothly with ketone **241b** at 0 °C to provide **240** as a single diastereomer in 72% isolated yield (Scheme 50).

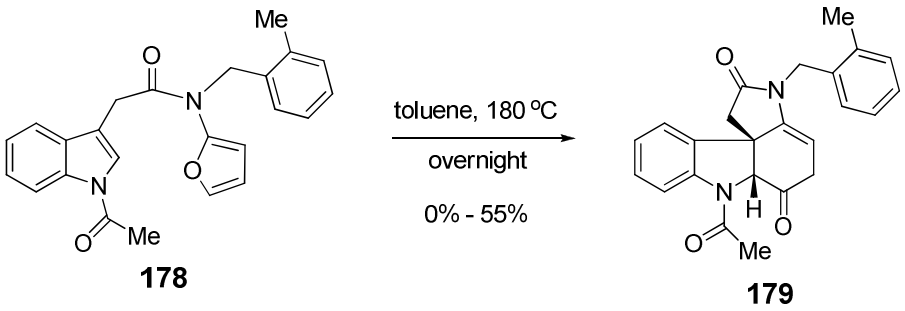
The last major hurdle involved the conversion of vinyl ether **243** into the Wieland-Gumlich aldehyde (**213**). This requires removal of the protecting groups, hydrolysis of the methoxy vinyl ether, and hemi-acetal formation. It was anticipated that under suitable acidic conditions, the desired reactions could occur sequentially. Indeed, the hydrolysis was satisfactorily accomplished by the treatment of **243** with 3N HCl in THF at 55 °C for 10 h, which gave **213** in 54% isolated yield. By using shorter reaction times and following the reaction by NMR spectroscopy, we found that the initial reaction involved sequential deprotection of the MOM group followed by hydrolysis of the DMB group to give **244** as a transient species. The resulting enol ether portion of **244** was subsequently converted into the Wieland−Gumlich aldehyde **213** (Scheme 50). Although the conversion of **213** into strychnine had been reported by Robinson in 1953,[108] we decided to reproduce the described protocol for the sake of a complete synthesis. Thus, the final biomimetic condensation of **213** with malonic acid, sodium acetate, and acetic acid provided (±)-strychnine (**120**) in 80% yield and with a 4.4% overall yield for the 13-step reaction sequence starting from furanyl indole **178**.



Scheme 50. Completion of strychnine synthesis

2.5 Lewis acid promoted IMDAF reaction

In our continuing program dealing with the application of the Diels-Alder reactions of amidofurans toward the synthesis of *Strychnos* alkaloids, we encountered a problem associated with the reactivity of different substrates. With some batches of our amidofuran precursor, only starting material was obtained, even though we used identical reaction conditions that worked well for other batches (toluene, 180 ^{o}C oil bath, sealed tube). The NMR data of the starting materials showed no difference and the use of different sources of toluene did not seem to effect the results. These inconsistent observations had also been noted several times earlier with related indole systems used in our group. We found that was necessary to prepare different batches of precursor and attempt several cyclization reactions before we had any success.



178 **179**

Scheme 51. An irreproducible IMDAF reaction

The occasion of success of these reactions can be rationalized in two ways. One possibility is that some unknown impurity is present that might retard the reaction. Another possibility is that the IMDAF reaction could actually be promoted by an impurity which exists in the system. We therefore set out to clarify this problem. The IMDAF precursor **178** was carefully purified by column chromatography and extended recrystallization from EtOAc/Hexane mixture to ensure a high level of purity. When this ultra pure precursor was heated using a standard set of conditions (toluene, 180 ^{o}C oil bath, sealed tube), no product was observed. This observation rules out the possibility of inhibition of the reaction by impurities in the system. When different solvents and temperatures were used with this pure substrate, we found that in most of the cases, no reaction had occurred. However, when **178** was heated to 250 ^{o}C using solvents such as *t*-Bu-benzene or phenylamine, the desired product could be obtained but together with a large amount of decomposition products.

We therefore decided to consider the possibility that some catalyst in the system is actually promoting the cycloaddition. Considering the synthetic route used to prepared precursor **178**, various additives (such as NaI, H_2O, silica gel,

or $Mg(ClO_4)_2$) could trigger the IMDAF reaction. Therefore, small amounts of various additives were added into a solution of the ultra pure IMDAF precursor **178** in toluene. We found that when a small amount of $Mg(ClO_4)_2$ was added to the reaction mixture and then heated in toluene at 180 ^oC overnight, some product could be detected by NMR spectroscopy. This implied that $Mg(ClO_4)_2$ might be a catalyst which promotes the reaction. We speculated that since both the free amide and the IMDAF precursor are highly polar substances that were purified by silica gel, leaching of some $Mg(ClO_4)_2$ from the chromatography column might have occurred. Possibly, in those batches which contain some $MgClO_4$ the reaction occurs, whereas in other batches that have no $Mg(ClO_4)_2$ contamination, the cycloaddition reaction does not occur under the thermal conditions used.

Several experiments associated with the temperature measurement of our IMDAF system were conducted in cooperation with Prof. Oliver Kappe's research group. The use of an internal fiber optic probe temperature monitoring device measured the temperature inside the reaction mixture compared with the oil bath temperature (Figure 3). An oil bath temperature of 190 ^oC was required to reach 150 ^oC in the internal reaction mixture. Since the reaction performed using microwave irradiation was purely thermal and not related to the microwave field, the temperature in the reactor can be much more easily controlled. Consequently, the microwave reactor was employed for the subsequent thermolysis experiments.[114,115]

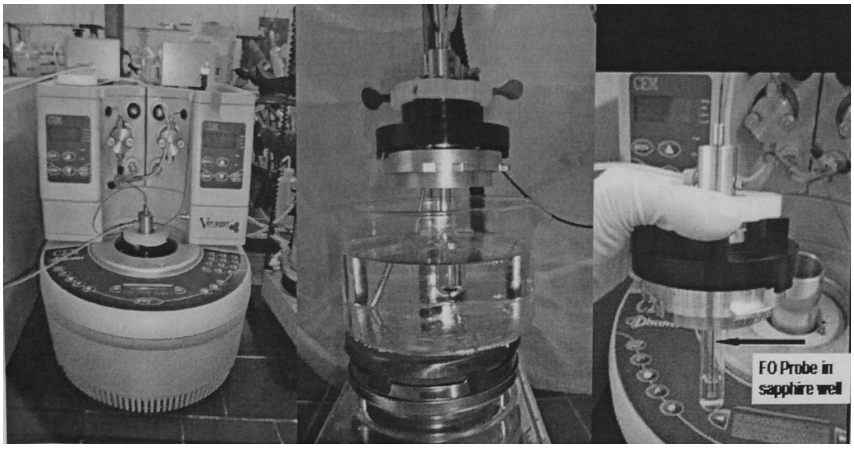
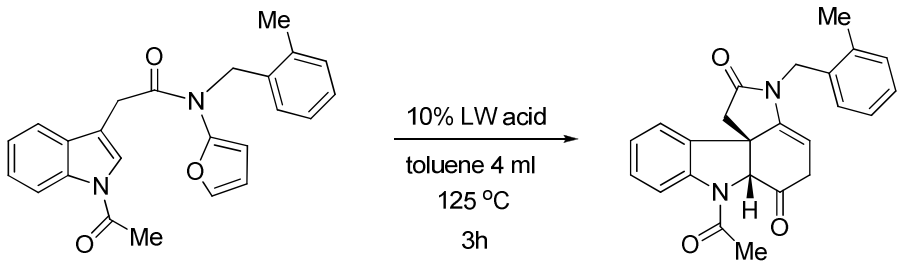


Figure 3. The temperature measurement using internal fiber optic probe

We then set out to investigate the efficiency of other Lewis acids that might also optimize the transformation. A variety of the catalysts were heated together with amido furan **178** in toluene using the microwave reactor conditions at 200W, at 125 ^{o}C for 3 h. In Table 1 the results are shown as reactant/product ratios as well as the estimated yield based on ^{1}H NMR analysis. The additive $BF_3.OEt_2$ and $AlCl_3$ gave the highest ratio and highest yield of product. However, these reaction conditions also led to the formation of significant decomposition and required extensive chromatography for purification. The use of $TiCl_4$ as a catalyst also gave a very high ratio of product (S/P = 1:1.98), but only a low yield of the product (36%) as a consequence of decomposition. We also examined the use of MgI_2 or $SnCl_2$ as the catalyst. Both of these additives provided a reasonable conversion rate (S/P ~ 1:1.45-1.48) as well as a reasonable yield without any sign of decomposition. Therefore, these two additives were selected as the catalysts of choice for future use in the IMDAF reactions. Considering the toxicity of tin, we decided to choose MgI_2 over $SnCl_2$.



178

50 mg SM

179

Microwave condition*: 200 W, 50 psi, cooling off

Run Time 2 min, hold time 60 min, 3 cycle (3 h)

Table 1. Ratio of starting material to product and yield of product in a variety of Lewis acids

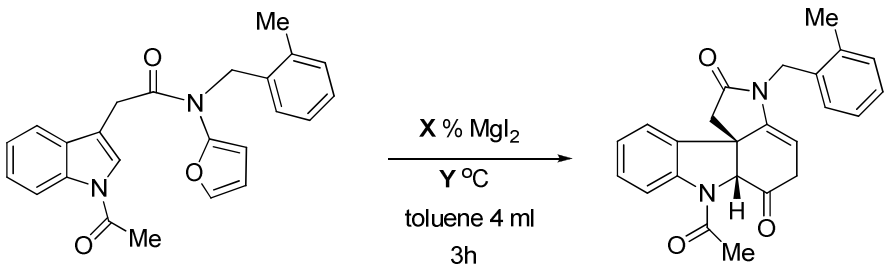
Catalyst	**Ratio SM:P**	**Yield (%) ****	**Catalyst**	**Ratio SM:P**	**Yield (%) ***
MgI_2	1 : 1.45	59	$BF_3.OEt_2$	1 : 2.38	70
$Mg(ClO_4)_2$	1 : 0.26	18	$SnCl_2$	1 : 1.48	57
$MgBr_2$	1 : 1.27	60	$SnCl_4$	1 : 0.42	32
$MgCl_2$	1 : 0.03	3	CuCl	SM only	0
$AlCl_3$	1 : 2.31	67	$CuCl_2$	1 : 0.07	7
Me_2AlCl	1 : 1.31	58	$ZnCl_2$	1 : 0.07	6
$TiCl_4$	1 : 1.98	36	ZnI_2	1 : 1.34	60

* At this conditions: the reaction does not run to completion

** Internal standard: *p*–Anisaldehyde

With MgI_2 as the additive of choice for the IMDAF reaction, another set of experiments were carried out to optimize the reaction conditions. This involved

conducting the reaction in a microwave reactor at 200W for 3 h and varying the reaction temperature and the amount of MgI_2 used. The results in Table 2 show that in the absence of MgI_2, no product was observed over a 3 h period at temperatures of 150 ^oC. Product formation was observed when the mixture was heated to 175 ^oC. In contrast to these results, when MgI_2 was added to the mixture and the reaction was carried out under the same set of conditions, we found that as little as 10% of MgI_2 can drastically promote the cycloaddition reaction and 100% conversion occurred at 150 ^oC. We were pleased to note that under these conditions, a very high purity of the product was obtained and no other by product could be detected by NMR spectroscopy. Furthermore, the Diels-Alder cycloadduct readily precipitated out of the solvent as a solid by cooling the 0.1 M solution to rt. When the amount of the additive is increased to more than 50%, the ratio of the product started to decrease. We think that this occurs since the substrate contains multiple coordination sites. A higher concentration of catalyst leads an altered coordination complex, thereby slowing down the reaction rate. From the data obtained from Table 2, we decided to make use of the optimum conditions for the IMDAF reaction; namely 10% MgI_2 in toluene with microwave conditions at 200 W, 150 ^oC for 3 h.



178

50 mg SM

179

Microwave condition 200 W, 50 psi, cooling off

Run Time 2 min, hold time 60 min, 3 cycle (3 h)

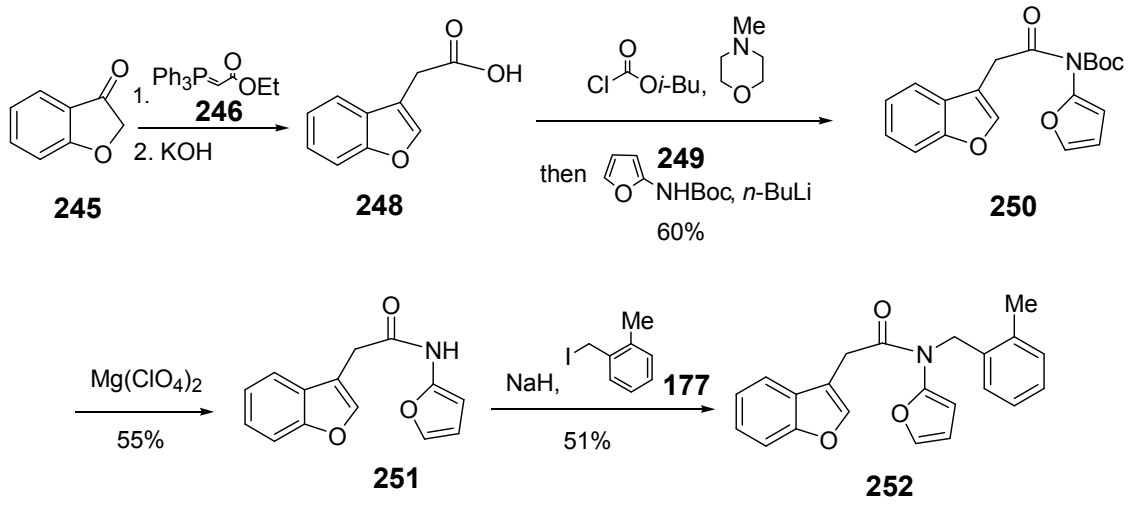
Table 2. Ratio of starting material to product in different amounts of catalysts and temperatures

Temperature	**Catalyst Loading**				
	0%	**10%**	**20%**	**50%**	**100%**
75 °C	SM only	SM only	SM only	SM only	SM only
100 °C	SM only	1 : 0.10	1 : 0.14	1 : 0.05	1 : 0.06
125 °C	SM only	1 : 1.45	1 : 1.51	1 : 1.26	1 : 1.26
140 °C	SM only	1 : 9.09	1 : 8.92	1 : 7.19	1 : 6.00
150 °C	1 : 0.04	1 : >99	1 : >99	1 : >99	1 : >99
175 °C *	1 : 10.66	1 : >99	1 : >99	1 : >99	1 : >99

* set pressure to 80 psi

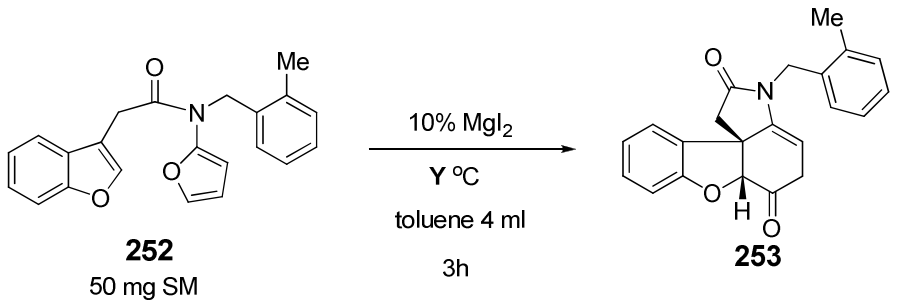
To determine whether this phenomenon is substrate dependent, we carried out several additional experiments using other substrates. Amidofuran **252** was prepared using a parallel route to that employed for the synthesis of the indole-based amidofuran **178** (Scheme 33). The known carboxylic acid **248** was

synthesized from **245**[116] and was then subjected to the standard protocol, namely coupling with furanyl carbamate **247**, Boc removal, and *N*-alkylation to give **250** (Scheme 35).



Scheme 52. Preparation of amidofuran

When amidofuran **252** was heated in toluene for 3 h, the results obtained showed that the presence of MgI_2 exerted a favorable effect with this system as well. As shown in Table 3, a higher product ratio was obtained when 10% MgI_2 was added and 100% conversion to product was achieved in 3 h at 150 ^{o}C.



252
50 mg SM

253

Microwave condition*: 200 W, 50 psi, cooling off

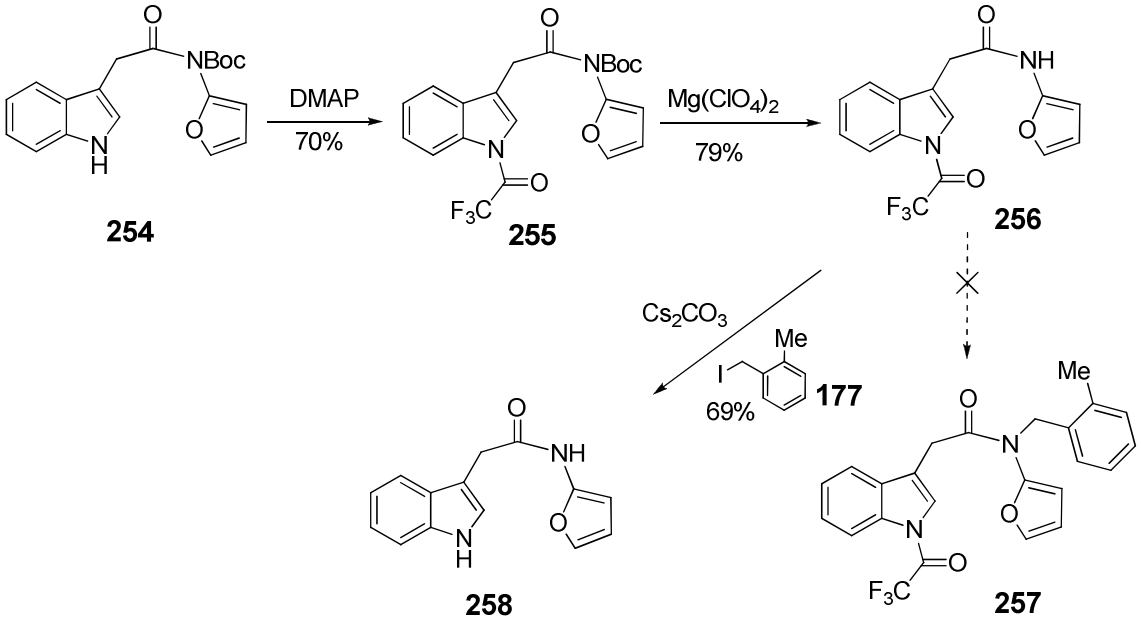
Run Time 2 min, hold time 60 min, 3 cycle (3 h)

Table 3. The ratio of starting material and product of benzofuran **247** with and without MgI_2 catalyst in different temperature

Temperature	Catalyst	Ratio S : P
100 °C	No catalyst	SM only
	10 % MgI_2	1 : 0.31
125 °C	No catalyst	SM only
	10 % MgI_2	1 : 1
150 °C	No catalyst	1:15.2
	10 % MgI_2	1: >99

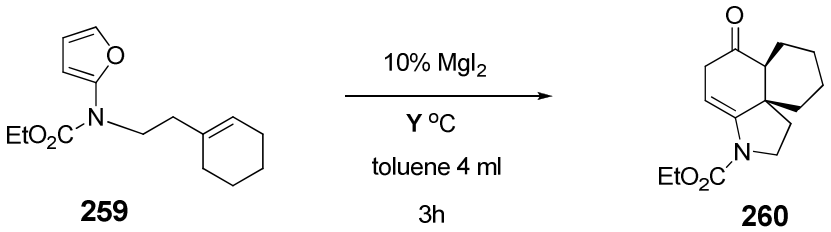
We also decided to prepare the trifluoro acetyl indole system **257** since we were interested in knowing what the effect of a different group on nitrogen would have on the reaction outcome. Protection of the indole nitrogen in **254** with a trifluoroacetyl group was carried out using trifluoroacetic anhydride with DMAP. The Boc group was removed to give **256**. Disappointedly, our attempts at alkylation on nitrogen were unsuccessful as only indole **258** was recovered.

Since the trifluoroacetyl group seems to be too labile, we discontinued studies with this system.



Scheme 53. Attempts to prepare trifluoroacetyl indole **257**

Another substrate that we employed for the catalytic Diels-Alders reaction study is amidofuran **259**[117] which was found to give **260** on heating. By heating **259** in toluene for 3 h, we found that no effect of the catalyst occurred with this substrate (Table 4). This suggests that a carbonyl group inside the tether is necessary for Lewis acid activation.



259 **260**

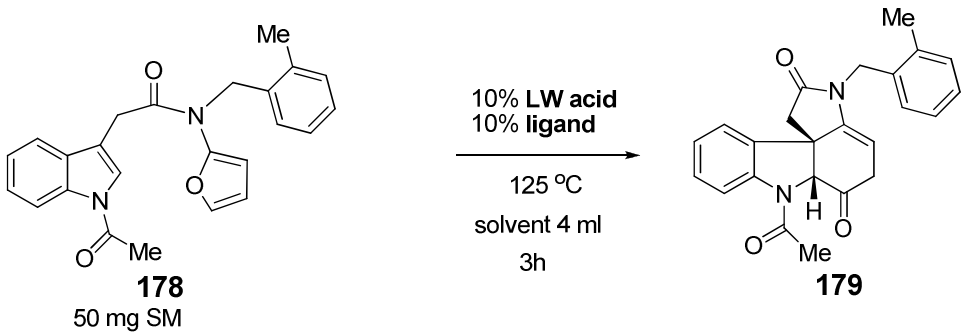
Microwave condition*: 200 W, 50 psi, cooling off

Run Time 2 min, hold time 60 min, 3 cycle (3 h)

Table 4. The ratio of starting material and product of cyclohexene **257** with and without MgI_2 catalyst in different temperature

Temperature	**Catalyst**	**Ratio S:P**
150 °C	No catalyst	SM only
	10 % MgI_2	SM only
175 °C	No catalyst	1 : 0.05
	10 % MgI_2	1 : 0.12

Since the major focus of my research dealt with the synthesis of *Strychnos* alkaloids, we decided not to pursue further studies dealing with this unusual catalyst effect. We did initiate some studies, however, concerning the possibility of carrying out an enantioselective synthesis using chiral catalysts.[118] Our results showed that only a very low level of enantioselectivity (See Table 5) could be obtained, and consequently we turned our full attention to the development of the Diels-Alder method to complete the synthesis of *Strychnos* alkaloids.



Microwave condition:* 200 W, 50 psi, cooling off

Run Time 2 min, hold time 60 min, 3 cycle (3 h)

Table 5. % *ee* obtained from initial studies of enantioselective IMDAF reaction

Metal	Ligand	Solvent	S:P	% ee
Me_2AlCl	R-BINOL	Toluene	1 : 2.95	3.7 %
Me_2AlCl	R-BINOL	Toluene/THF	1 : 0.57	13.9 %
R,R-salen-AlCl		Toluene	1 : 1.10	10.6 %
R,R-salen-AlCl		Toluene/THF	1 : 0.56	11.5 %
Mg	BOX-ligand	Toluene/THF	1 : 0.84	1.8 %
Mg	BOX-ligand	Toluene	1 : 0.12	0.1 %

HPLC condition: - chiralpack AS-RH column; flow 1.0 ml/min;

- 0 to 20 min: 20%CH_3CN/H_2O; 20 to 40 min: 50%CH_3CN/H_2O

3. Conclusion

In conclusion, we have found that using the indolyl substituted 2-amidofuran **178**, we could prepare (±)-strychnopivotine, (±)-tubifolidine, (±)-strychnine and (±)-valparicine in 14, 14, 16 and 15 distinct chemical steps, respectively. The critical strychnos scaffold was achieved by means of an intramolecular [4+2]-cycloaddition rearrangement cascade. This step was followed by D-ring installation by means of an intramolecular palladium mediated coupling reaction which allows for the rapid assembly of the core skeleton. This approach allowed for the synthesis of (±)-strychnopivotine, (±)-tubifolidine and (±)-valparicine from a common advanced intermediate. A slight modification of the sequence was used for the synthesis of (±)-strychnine which proceeded in a highly efficient manner.

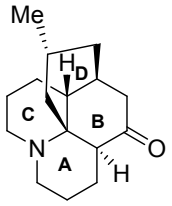
We were also able to sort out some inconsistent results encountered during our cycloaddition studies with amidofurans. We found that the presence of a small amount of Lewis catalyst was crucial for the reaction to proceed. Without the catalyst, much higher temperatures are required. The best additive was found to be MgI_2 and it needs to be present in only 10%.

Chapter A. 3

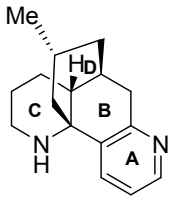
Application of the Cycloaddition/Rearrangement Cascade of 2-Amidofurans toward the Synthesis of *Fawcettimine* Alkaloids

1. Introduction

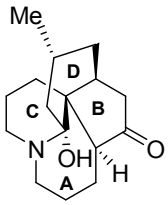
The genus *Lycopodium* consists of a large group of species that are commonly known as club mosses. These plants comprise over 500 species that are distributed around the world. To date, a subset of 53 species have been studied which have resulted in over 200 natural products isolated. This list can be divided into four topographical related classes including lycopodine (**5**), lycodine (**261**), fawcettimine (**6**), and various miscellaneous (**262**) classes as shown in Figure 1.[119] Over sixty natural products isolated from *Lycopodium* alkaloids belong to the fawcettimine class thus making this skeleton one of the major classes of this alkaloid family. Many of the *Lycopodium* species have a long history of use in Chinese folk medicine for the treatment of contusions, strains, swelling, and schizophrenia. Pharmacological studies also show that the *Lycopodium* alkaloids can be used in the treatment of diseases that affect the cardiovascular or neuromuscular system. Additionally, many of these alkaloids show potent acetylcholine esterase inhibition activity which is related to positive effects on learning and memory.[120] One of the better-known alkaloids in this family is huperzine A, which has been used as a medicine for treatment of Alzheimer's disease.[121] For the fawcettimine alkaloids, there are few reports of its biological activity and most reports in the literature usually involve only structural relationship studies.[122]



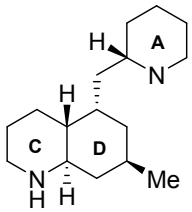
Lycopodine (5)



Lycodine (261)



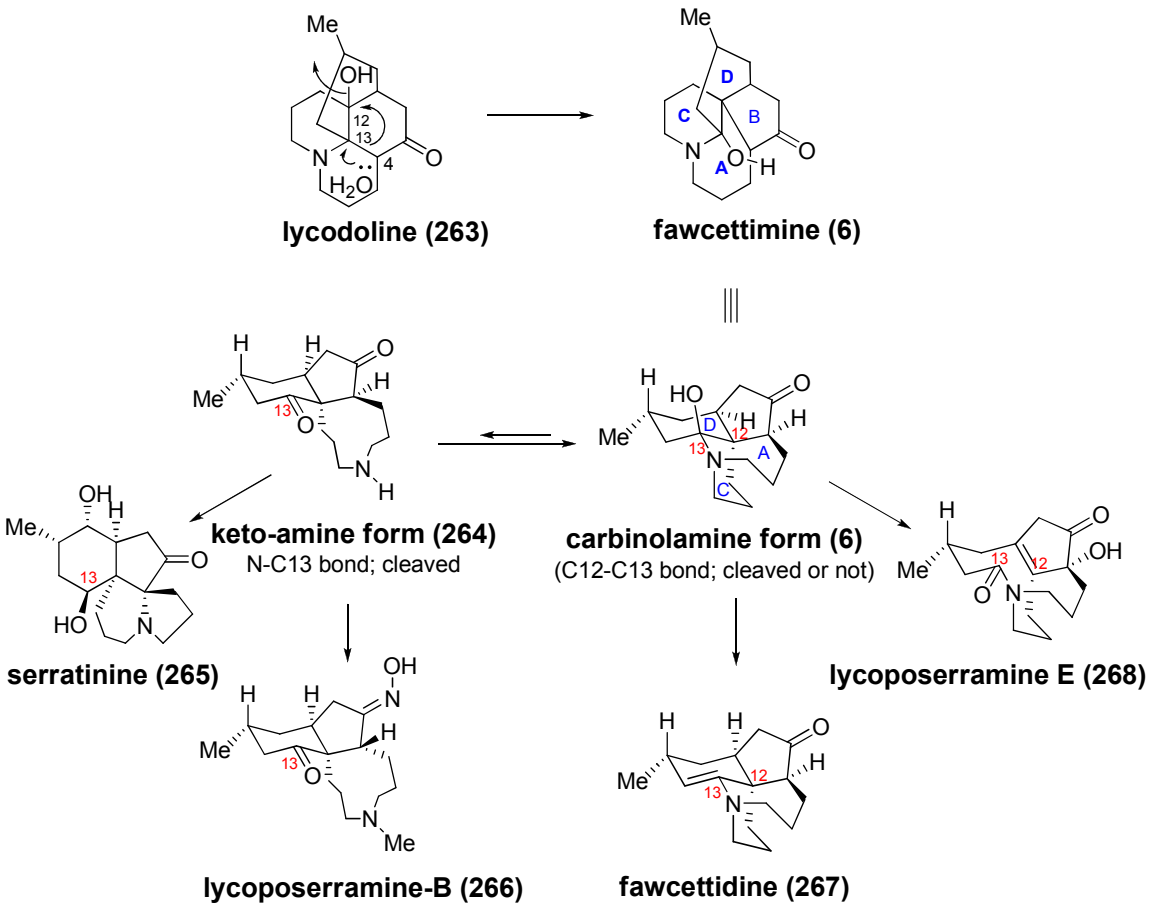
Fawcettimine (6)



miscelleneous **(262)**
i.e. **phlegmarine**

Figure 4. Four related classes of *Lycopodium* alkaloids

The first compound discovered in the fawcettimine class corresponds to (+)-fawcettimine which was isolated in 1959 by Bernell from *Lycopodium faecetti* and is found in the Blue Mountain of Jamaica.[123] Originally, this alkaloid was referred to as “Base A” and later was named as fawcettimine. From a biomimetic pathway, the fawcettimine class of alkaloids can be regarded as being formed through an oxidative rearrangement of the lycopodine core (*i.e.* from **263** to **6**, Scheme 54). This class can be divided into two categories which are based on two tautomeric forms of the original compound fawcettimine. The hydroxyl group present on the C-13 in the carbinolamine form of **6** can lead to C-N bond cleavage so as to generate a carbonyl group as indicated in the keto-amine form **264**. Other natural products are closely related to these two sub forms. For example, serratinine (**265**) and lycoposerramine-B (**266**) are derived from the keto-amine form, while fawcettimine (**6**), fawcettidine (**267**), and lycoposeramine E (**268**) come about from the carbinolamine form.



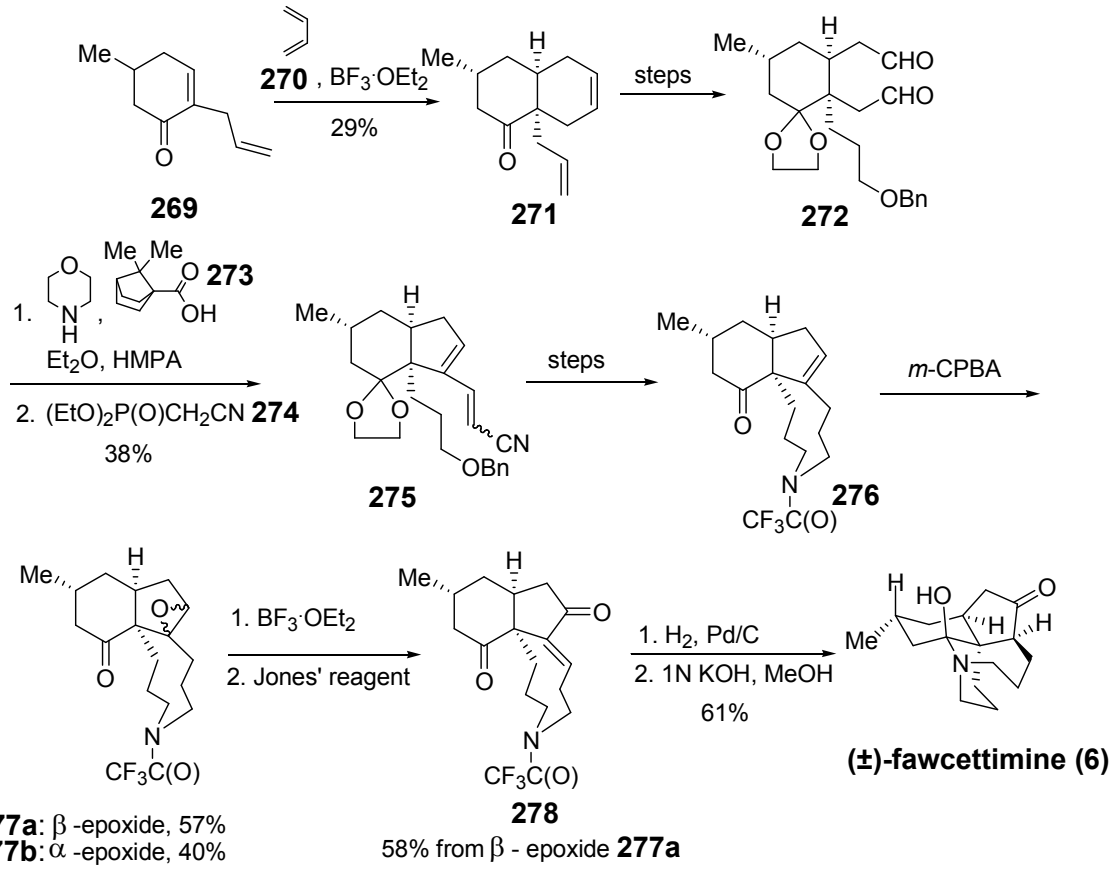
Scheme 54. Biological synthesis of fawcettimine alkaloids

Previous synthesis of the fawcettimine class of alkaloids

There are very few synthetic studies directed toward the natural products in fawcettimine class and to date only two natural products in this class have been synthesized.[124,125-128] This includes one total synthesis of serratinine (**265**) and three total syntheses of fawcettimine (**6**).

The first total synthesis of (±)-serratinine (**265**) and (±)-fawcettimine (**6**) were accomplished by Inubushi and both involved a stereoselective Diels-Alder reaction followed by a regioselective aldol condensation.[125,126] The example shown here consists of the total synthesis of (±)-fawcettimine (**6**) (Scheme 55).

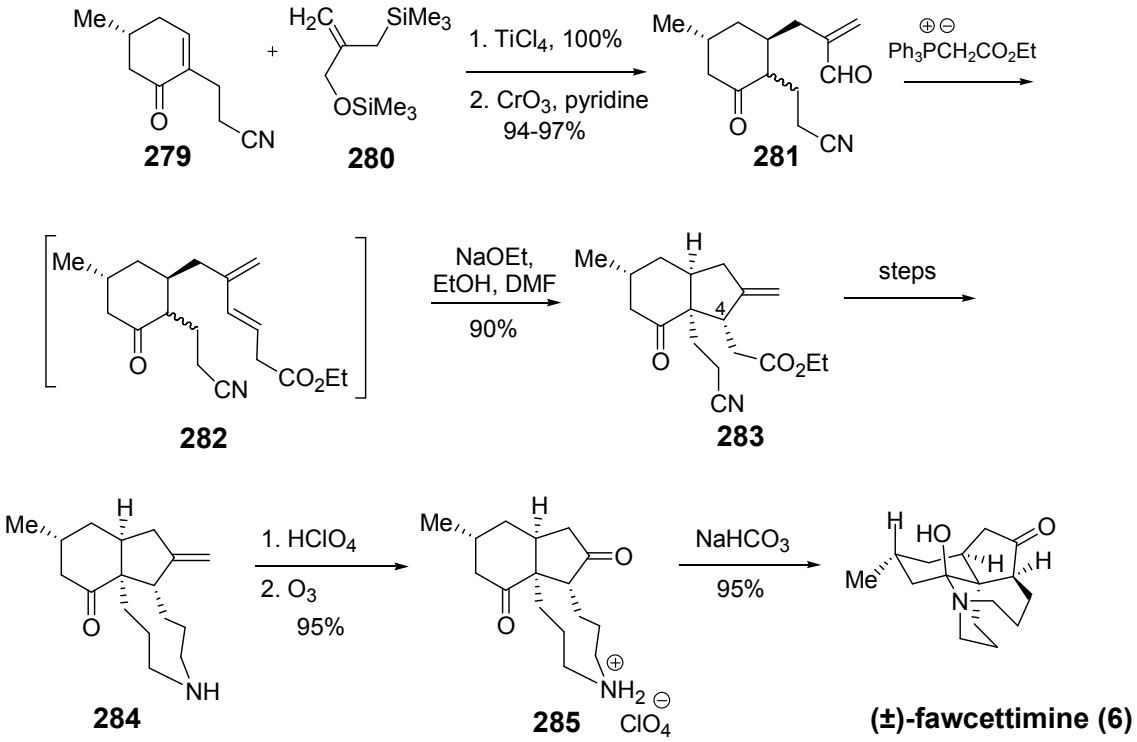
Starting from 2-allyl-3-methyl-cyclohex-2-ene-1-one (**269**), the key Diels-Alder reaction with butadiene (**270**) took place stereoselectively from the less hindered side providing bicycle **271** with three newly established stereocenters in 29% yield. This compound was then transformed into dialdehyde **272** which was then subjected to a regioselective aldol condensation. A subsequent Horner-Wadsworth-Emmons reaction gave the desired regioisomer **275** in 38% for the two-step sequence. After construction of the nine-membered ring cycloamine **276**, epoxidation of the double bond on the cyclopentene ring gave the diastereomeric epoxides **277a** and **277b**. After separation, the β-epoxide isomer **277a** was treated with $BF_3.OEt_2$ followed by Jones oxidation to give enone **278** in 58% yield. Under the same conditions, the α-epoxide **277b** gave rise to a complex mixture. Finally hydrogenation and hydrolysis of compound **278** afforded (±)-fawcettimine (**6**).



Scheme 55. Inubushi's synthesis of fawcettimine

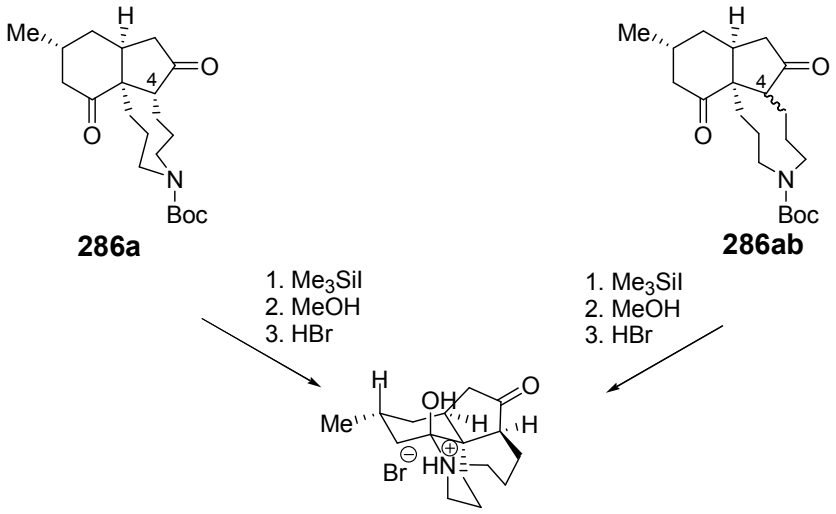
A second total synthesis of (±)-fawcettimine (**6**) was reported by Heathcock (Scheme 56).[127] Enone **279** was subjected to a Sakurai reaction with allyl silane **280** and this was followed by oxidation to provide aldehyde **281**. A Wittig reaction gave **282** and a subsequent intramolecular Michael reaction provided hydrindanone **283** in 90% yield as a single diastereomer with the C-4 stereochemistry opposite to that found in the natural product. Construction of the nine-membered ring cycloamine was carried out in 10 steps to generate amino ketone **284**. Conversion of **284** to its perchlorate salt and then ozonolysis of the

exocyclic methylene group gave **285** in 95% yield which, after neutralization with $NaHCO_3$, afforded (±)-fawcettimine (**6**).



Scheme 56. Heathcock's fawcettimine synthesis

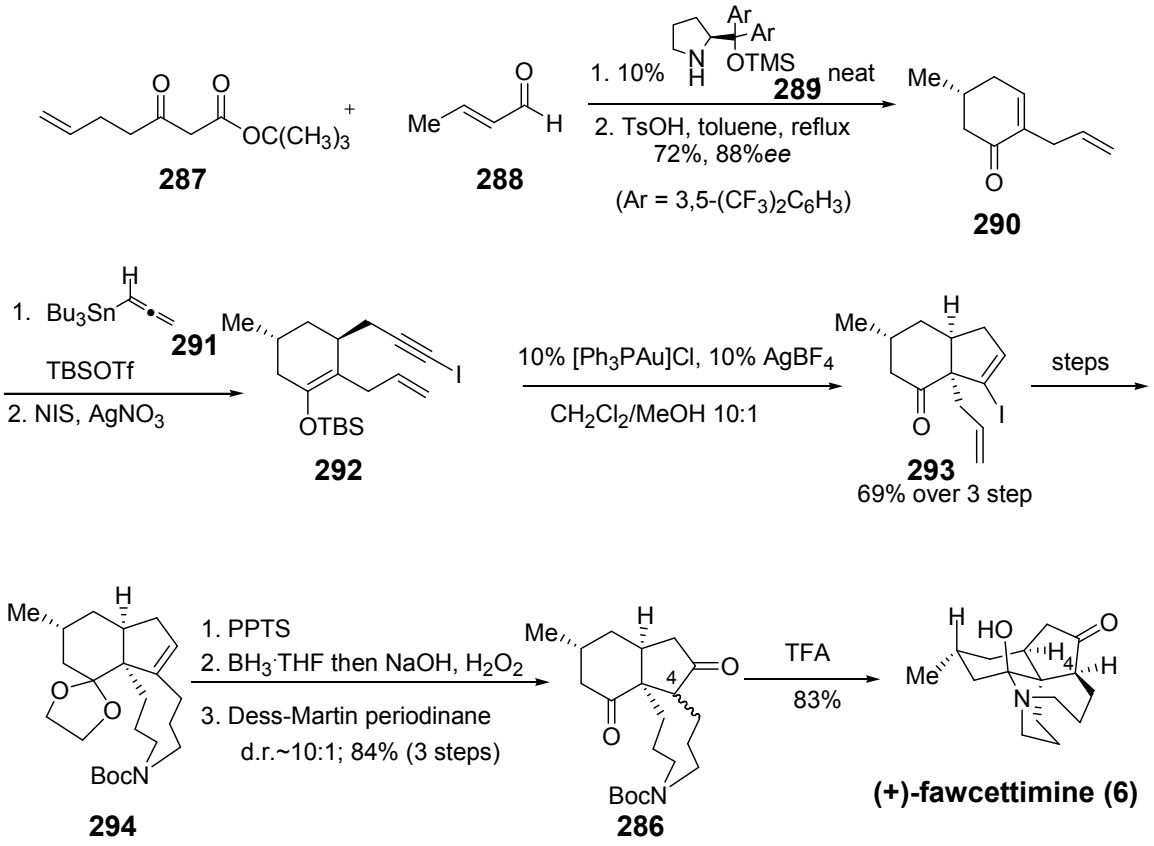
Heathcock and co-workers have further studied the relative stabilities of the C-4 diastereomers of **286** and found that the stereochemistry at C-4 does not need to be controlled since it was possible to equilibrate both isomers to eventually produce the correct stereoisomer of fawcettimine (**6**) (Scheme 57).[127b]



Scheme 57. The effect of equilibration of the keto-amine forms for the generation of fawcettimine

The first enantioselective synthesis of (+)-fawcettimine was achieved by Toste in 2007 by applying a gold-catalyzed cyclization as the key step (Scheme 58).[128] The synthesis started with an enantioselective organocatalytic Robinson annulation reaction between ester **287** and crotonaldehyde (**288**) to provide allylcyclohexanone **290** in 88% *ee* and in 72% yield. Dienone **290** was then converted to the *trans*-silyl ether **292** as a single isomer by a conjugate propargylation using allenyl tributyl stannane **291** followed by iodination of the terminal alkyne. Enyne **292** was then subjected to a Au(I)-catalyzed-5-*endo*-dig cyclization which smoothly furnished the requisite hydridanone core **293** in 69% yield over the 3-step sequence. Further functionalization resulted in construction of the nine-membered ring **294** which was subjected to carbonyl group deprotection and eventual oxidation to furnish diketone **286** as a diastereomeric

mixture. This 10:1-mixture was treated with TFA for Boc removal and this was followed by neutralization with base to yield (+)-fawcettimine (**6**) together with a small amount of its C-4 epimer that slowly isomerized to the natural product.



Scheme 58 Toste's organocatalytic/gold catalyzed cyclization approach to (+)-fawcettimine

A retrosynthetic analysis of (±)-fawcettimine using the IMDAF approach

As part of our program dealing with the application of the IMDAF cycloaddition/rearrangement cascade for natural product synthesis, we decided to expand this strategy toward the fawcettimine family. Our initial target was the carbinolamine skeleton which contains the core skeleton (**295**) as shown in Figure 2. This tetracyclic ring skeleton features a hydroquinoline at ring-C/D, a 7-

membered ring as well as a *cis*-ring fusion between ring-B and ring-D. Fawcettidine **267**, a member of this class of alkaloids was chosen as our initial target. We also envisioned that some functionality adjustment would allow us to also synthesize some related members of the fawcettimine alkaloids such as fawcettimine (**6**), lyconecidine A (**296**), and macleanine (**297**).

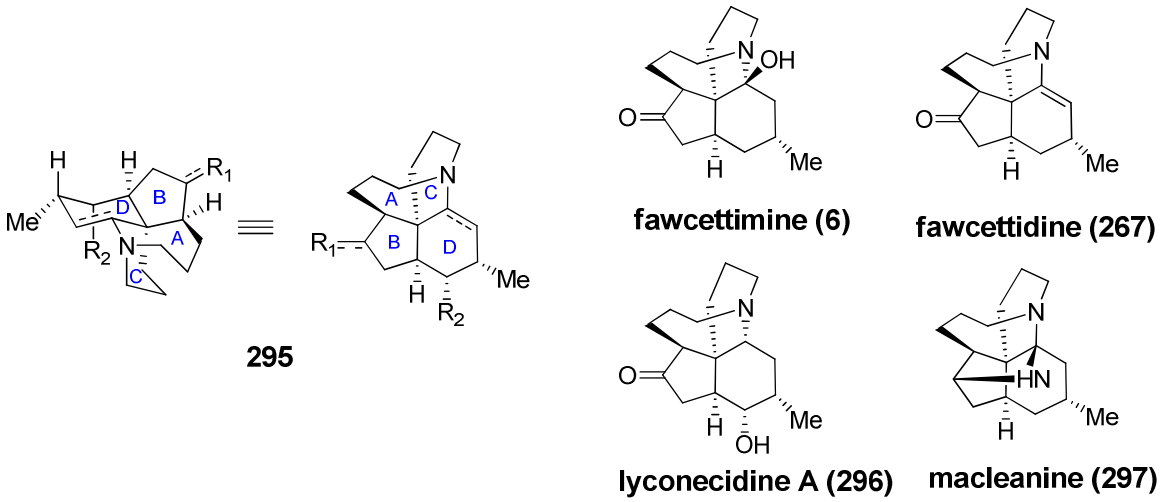
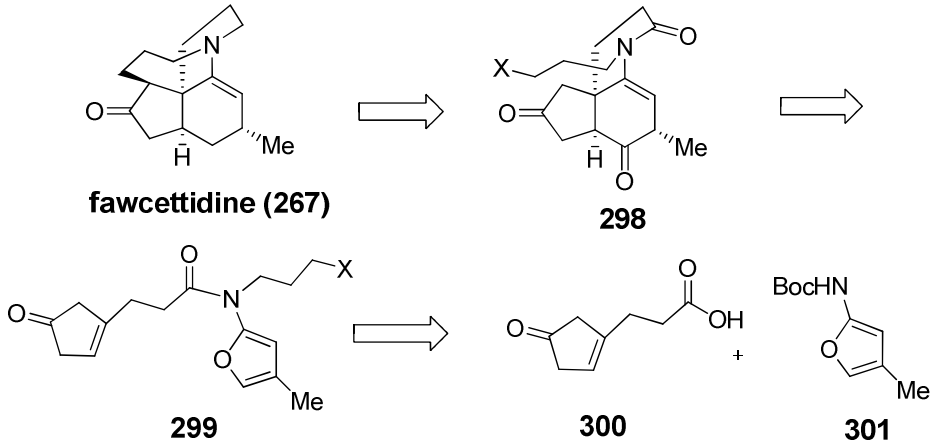


Figure 5. Various members of carbinolamine form fawcettimine alkaloids

Our retrosynthetic analysis of fawcettidine (**267**) involves formation of the tetracyclic core by ring-A closure from tricycle **298**. This tricyclic compound should be derived from an IMDAF reaction of amidofuran **299**. The preparation of the IMDAF precursor would be derived by a coupling reaction between cyclopentenyl acid **300** and methyl furan **301** (Scheme 59).

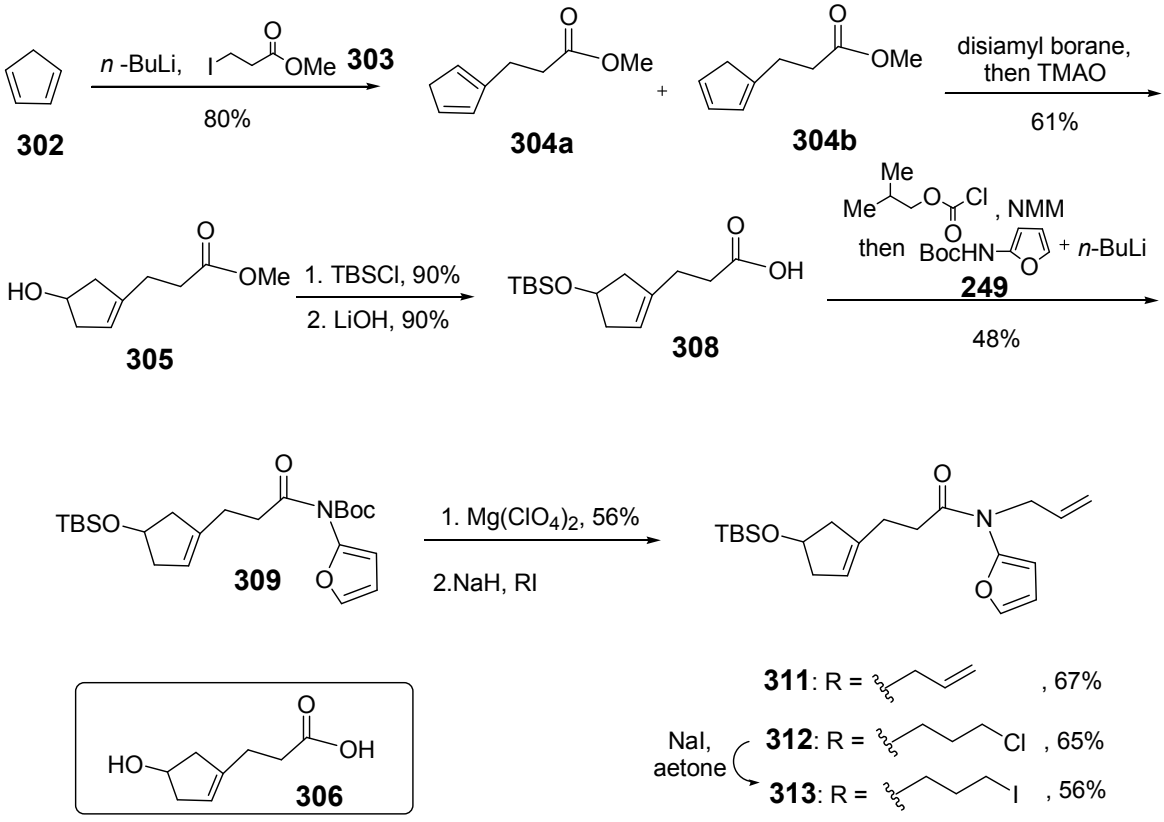


Scheme 59. Retrosynthetic analysis of fawcettidine

2. Results and Discussion

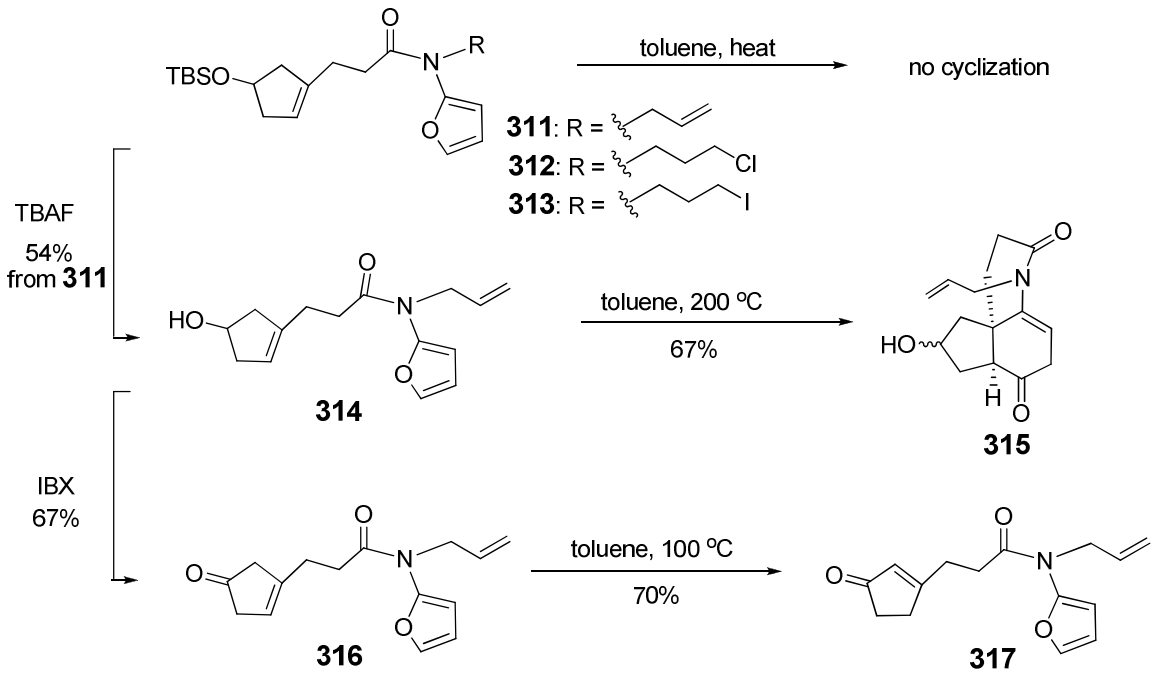
Our initial efforts dealing with IMDAF reaction focused on model substrates such as **311-313**, which contain the oxygen-substituted cyclopentene ring system (Scheme 60). Thus, reaction of the lithiate anion of cyclopentadiene (**302**) with methyl 3-iodopropanoate (**303**) gave **304** as a mixture of isomers in 80% yield.[129] Since both isomers would lead to the same product, the mixture was subjected to hydroboration using disiamylborane and a subsequent oxidation to provide alcohol **305** as a single isomer in 61% yield.[130,131] The oxidation step was very critical for the formation of this substrate and it was found that the use of TMAO in refluxing toluene represents a reliable method for this transformation.[132] Use of the standard oxidative workup with NaOH and H_2O_2 gave alcohol **305** in only 28% yield. Part of the problem is that hydrolysis of the ester occurs to give the corresponding acid **306** which was obtained in 20% yield.

The resulting alcohol **305** was then protected as the TBS ether and this was followed by hydrolysis of the methyl ester to deliver acid **308** in 81% yield over the two steps. Next, the carboxylic acid was coupled with the lithium anion of furan-2-yl-carbamic acid *tert*-butyl ester (**249**) via an intermediate acid anhydride providing furanylcyclopentene **309** in 48% yield. The Boc group was removed using $Mg(ClO_4)_2$ in CH_3CN followed by *N*-alkylation to provide the IMDAF precursor **311** in 67% yield. The alkyl-chloride **312** was obtained in a similar manner in 65% yield and conversion of **312** to the corresponding alkyl iodide **313** occurred in 56% yield. Precursors **311**, **312**, and **313** were used for a further investigation of the IMDAF reaction.



Scheme 60. The preparation of IMDAF precursor

Conditions for the key IMDAF cyclization was investigated by heating **311**, **312** or **313** in toluene under several different temperatures and solvents (Scheme 8). However, we found that the thermal cyclization of compounds **311** and **312** did not occur at all and only starting material was recovered, even at 200 ^{o}C. When heating iodide **313**, only elimination took place to give **311**. We suspected that the steric bulk of the TBS group might prevent the two IMDAF partners to be close enough in space for the cycloaddition reaction to occur. Thus, the TBS group was removed and the free alcohol **314** was subjected to the IMDAF reaction conditions. Gratifyingly, the IMDAF reaction of the free alcohol **314** did occur in toluene at 200 ^{o}C and furnished cycloadduct **315** in 67% yield as a mixture of two inseparable alcohol diastereomers. We also used ketone **316** as the IMDAF precursor, but when **316** was heated at 100 ^{o}C in toluene, the double bond isomerized into conjugation forming the α,β-unsaturated ketone **317** in 70% yield.

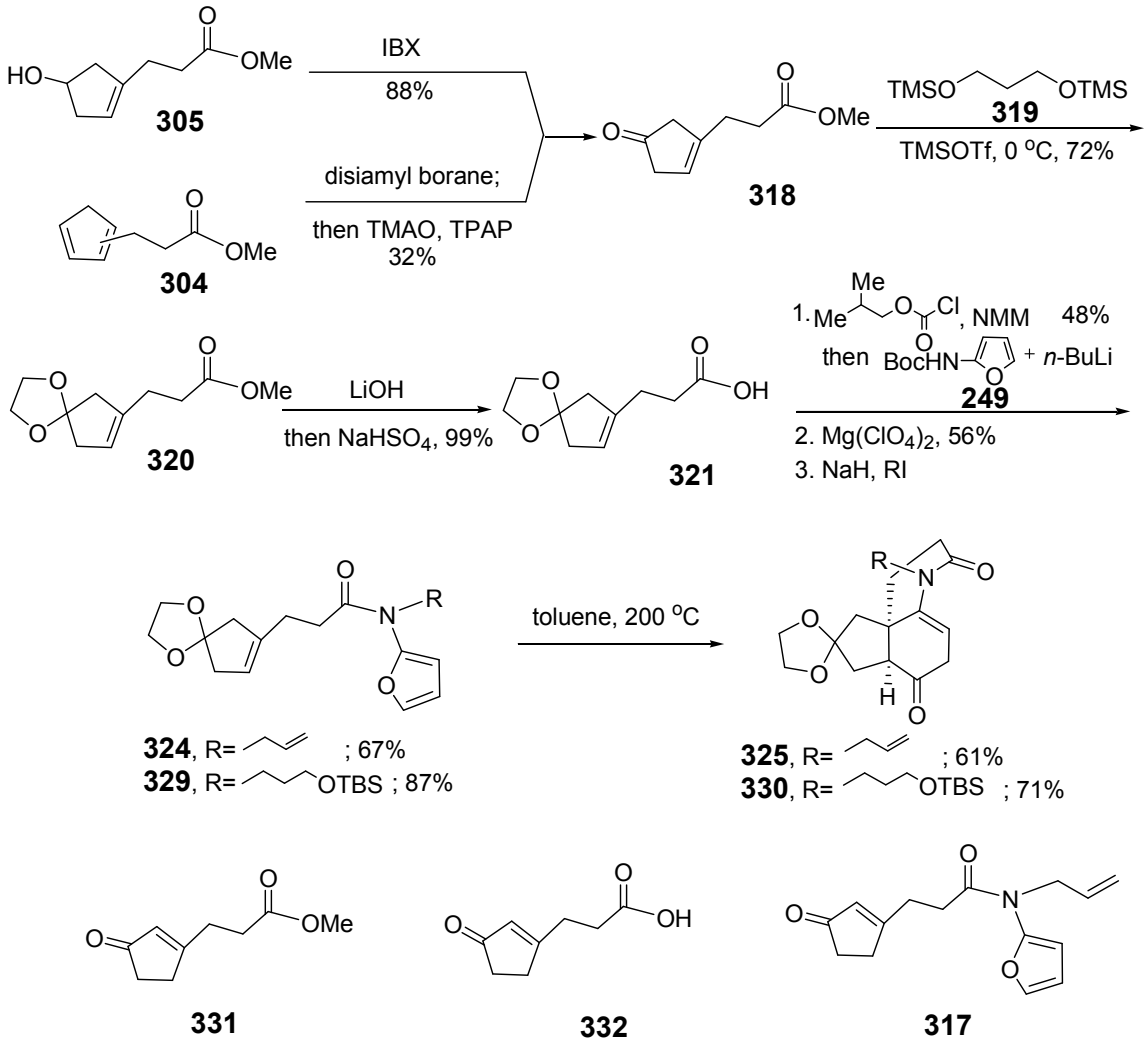


Scheme 61. The IMDAF reaction studies to BCD ring of fawcettimine core

Based on these preliminary results, we decided to utilize the acetal protected cyclopentenes **324** and **329** for further synthesis (Scheme 62). Thus, alcohol **305** was oxidized using IBX to the corresponding ketone **318** in 88% yield. Alternatively, a one step process from cyclopentene **304** can be utilized to give **318** (32%) by hydroboration and successive oxidation using TPAP/NMO.[133] Considering the tendency of compound **318** to isomerize to the α,β-unsaturated ketone (*i.e*. **316** to **317**), acetal protection of the ketone **318** was carried out under mild acidic conditions using 1,2-bis(trimethylsiloxy)ethane (**319**) in the presence of a catalytic amount of TMSOTf at 0 °C.[134] An excess amount of **319** and low temperatures is required for this step, otherwise α,β-ketone **331** is formed in a significant amount. Hydrolysis of the methyl ester **320** was performed using lithium hydroxide to afford carboxylic acid **321** in 99% yield. Quenching the

reaction with one equivalent of $NaHSO_4$ was found to work best so as to reduce the formation of α,β-unsaturated ketone **332**. With acid **321** in hand, the IMDAF precursor **324** was prepared using the standard sequence of coupling with furan **249**, deprotection of the *N*-Boc group, and *N*-alkylation of the side chain. When a solution of **324** in toluene was heated at 200 ^{o}C in a sealed tube, the IMDAF cycloadduct **325** was formed in 67% yield.

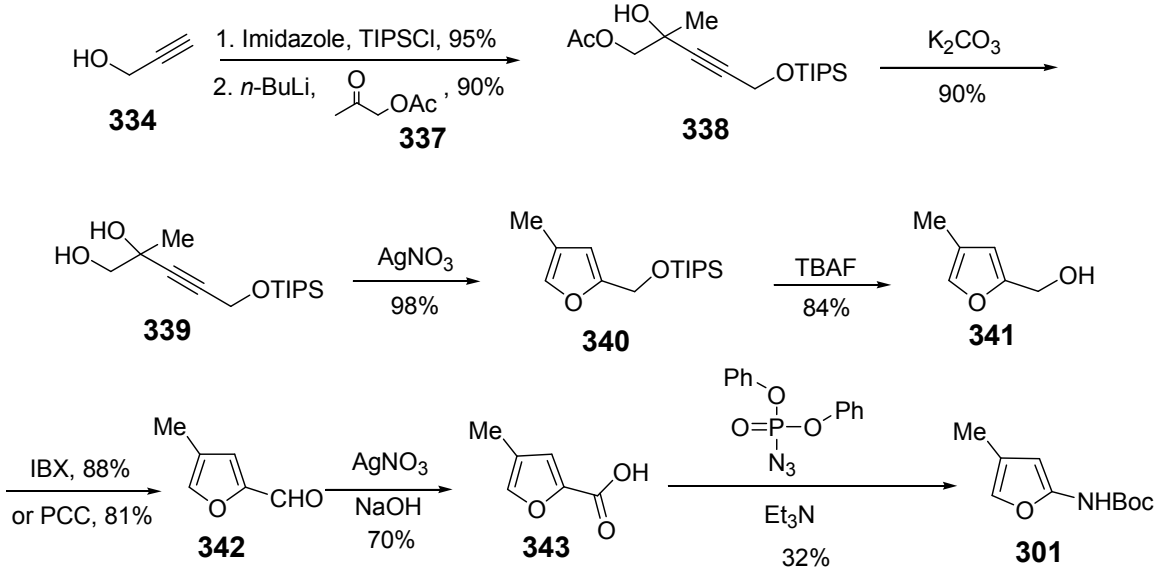
The analogous furanyl **329** bearing a TBS propanyl ether side chain was also prepared in a similar manner. This side chain was selected in order to facilitate eventual A-ring formation as well as to help the IMDAF reaction by enhancing the population of the *s-trans* conformation by the presence of the large TBS group. The IMDAF reaction using **329** proceeded at 200 ^{o}C in toluene producing a 71% yield of cycloadduct **330** based on starting material. It is noteworthy that the concentration used is critical for the success of the key IMDAF reaction. When 0.1 M solution was used, the reaction can occur in good yield without a significant decomposition. In contrast, when a more concentrate 0.25 M solution was employed, much more decomposition occurred. This is probably due to the low solubility of the IMDAF product which results in its precipitation followed by decomposition. Our attempt to catalyze the IMDAF reaction by adding 10% MgI_2 did not work well since the loss of the acetal protecting group occurred and this was followed by double bond isomerization to give **317** as the major product.



Scheme 62. Preparation of IMDAF precursor with protected acetal

Having established the success of the IMDAF cyclization using a model system, the synthesis of the methyl substituted furan **301** was undertaken, as this was required for the eventual synthesis of the natural product. Methyl substituted furan **301** was first prepared *via* a Ag(I)-catalyzed isomerization reaction of alkyne diol **339**.[135] The propargyl alcohol (**334**) was protected as the TIPS ether and was then treated with *n*-BuLi followed by reaction with 2-oxo-propyl ester **337** to provide alkyne **338**. Removal of the acetyl group by K_2CO_3

gave diol **339** which was then subjected to a Ag(I)-catalyzed isomerization to give furan **340** in 88% yield over the two steps.[136] Removal of the TIPS group, oxidation to aldehyde **342**[137] and further oxidation using Tollens reagent ($AgNO_3$ and NaOH) gave the furanyl carboxylic acid **343**.[138] Carbamate **301** was prepared by heating a sample of **343** with diphenyl phosphorylazidate in *t*-BuOH which effected a Curtius rearrangement to deliver the requisite furan **301** in 32% yield. This sequence of reactions to prepare furan **301** is very reliable and generally occurred in high yield. However, the high cost of TIPSCl hindered the scale up process. Therefore, we decided to employ an alternative route for the formation of carbamate **301**.



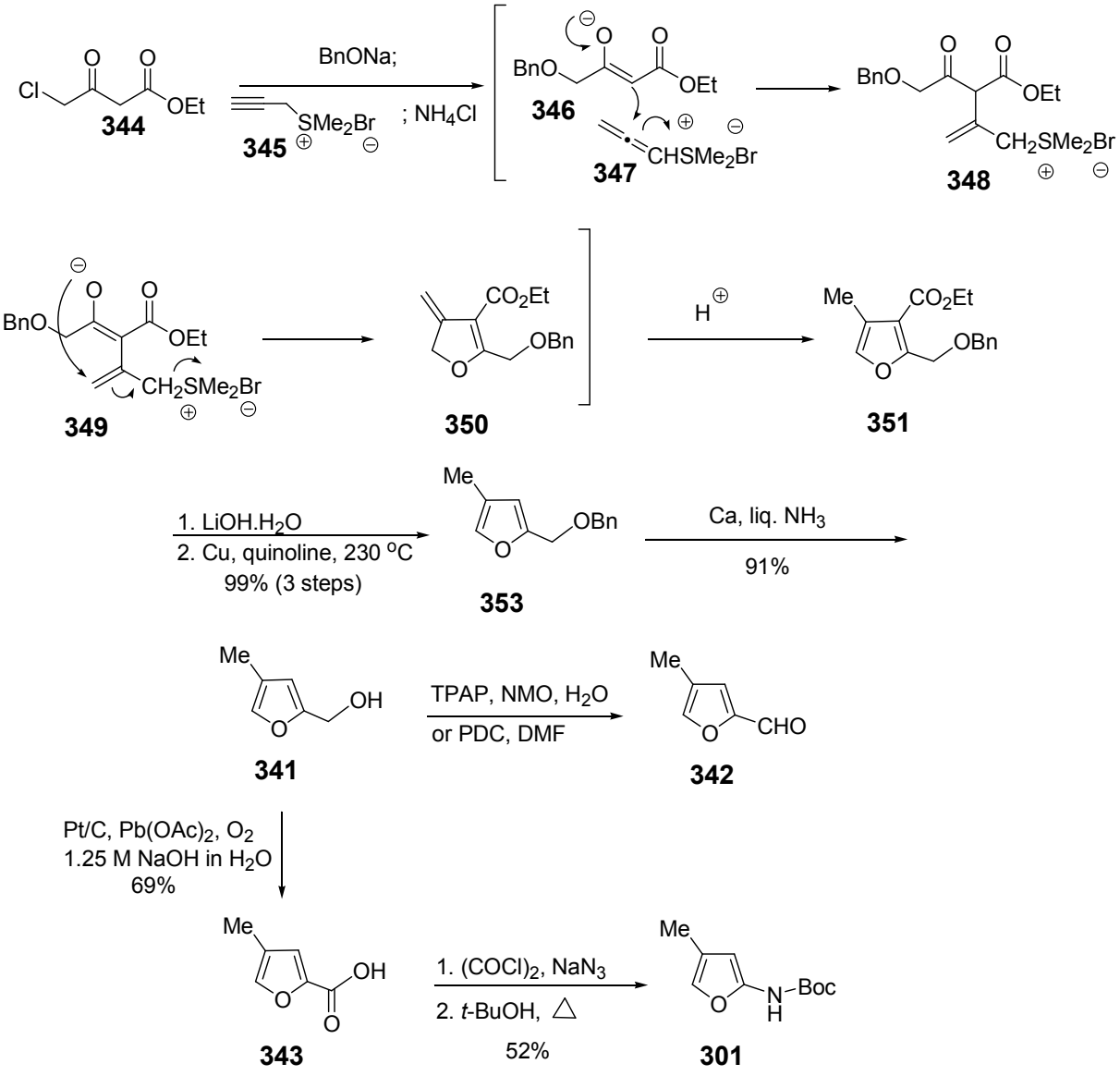
Scheme 63. The first approach for a preparation of methyl furan

A second approach toward furanyl carbamate **301** involved a modification of the method employed by Paquette.[139] Displacement of the chloro group of 4-ethyl-chloro acetoacetate (**344**) by treatment with 2 equivalent of

sodium phenylmethoxide, was followed by addition to di-methyl-2-propynylsulfomium bromide (**345**) to give furan **351**. The mechanism of this reaction is probably similar to the Feist-Banary furan synthesis where the enolate of the keto ester **346** reacts with the allenic sulfonium salt **347** followed by an intramolecular displacement the sulfonium group to give dihydrofuran **350** which is transformed into furan **351** under the acidic condition.[140] Saponification of the ethyl ester in **351** by LiOH in THF/MeOH/H_2O at 60 ^oC followed by heating at 230 ^oC in the presence of copper in quinoline afforded the furan **353** in 99% yield. A short reaction time for decarboxylation is required since the resulting furan is easily decomposed at high temperature. Chemoselective debenzylation was nicely accomplished by use of calcium metal in a mixture of THF-liquid ammonia at -78 ^oC to give **341** in 91% yield.[141] This second route provides multi-grams quantities of the product since less purification is required and all of the steps preceed in high yield using the large scale conditions (50 g-100 g).

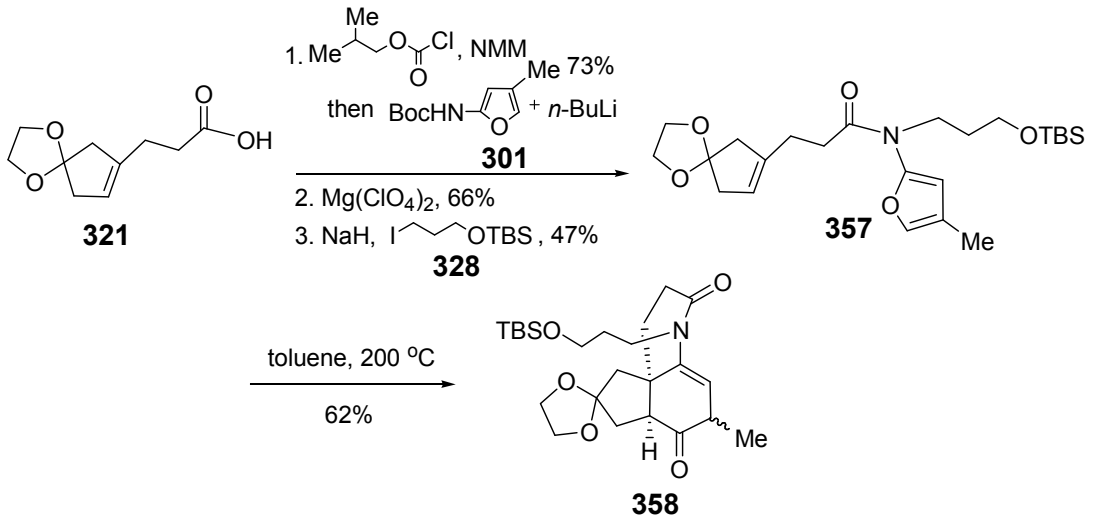
The next step of the synthesis involves the generation of the furanyl carboxylic acid **343**. While a two step reaction nicely furnished the requisite furan, we hoped to shorten the sequence by using a one step oxidation of alcohol **341** to the corresponding acid **343**.[142] Various conditions were tried. For example, TPAP and NMO in aqueous CH_2Cl_2 or PCC in DMF, only gave the aldehyde **342**.[143] On the other hand, solvent free conditions using PCC[144] or KMO_4[145] only resulted in decomposition. Eventually, a one step oxidation sequence was developed by using Pt/C and $Pb(OAc)_2$ as the oxidant in an aqueous NaOH solution with a flow of oxygen gas directly into the solution

mixture.[146] For the conversion of carboxylic acid **343** into carbamate **301,** we found that the best conditions involve the formation of the corresponding acid chloride which is then treated with NaN_3 to generate an acyl azide. Subjection of the azide to the Curtius rearrangement conditions by heating with *t*-BuOH furnished furanyl carbamate **301** in 73% yield over the three step sequence (Scheme 64).



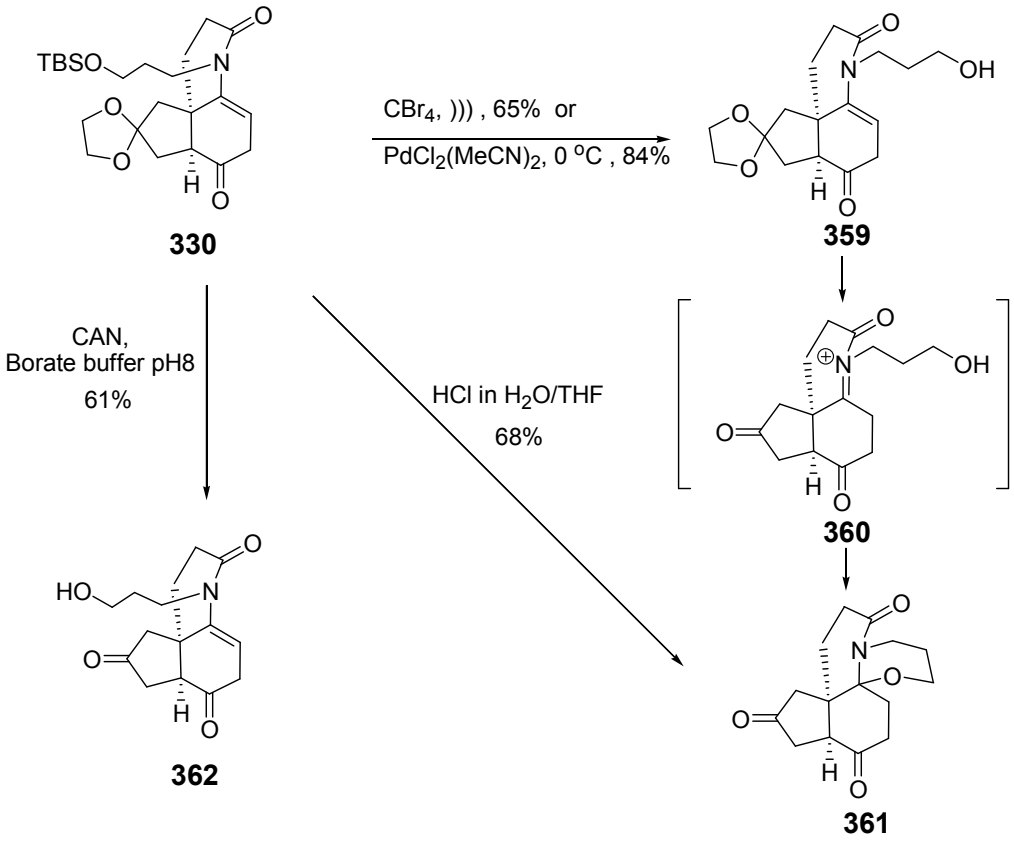
Scheme 64. The second approach for a preparation of methyl furan

With the requisite methyl substituted furanyl carbamate **301** in hand, the necessay IMDAF precursor **357** was prepared following the same protocol used with the model system starting from cyclopentene **321** (Scheme 65). The IMDAF reaction of **357** at 200 ^{o}C in toluene generated cycloadduct **358** in 62% yield as a 3:2 mixture of two diastereomers. Unfortunately, we were unable to separate both isomers by column chromatography and our attempts to epimerize them only led to a complex mixture of products. Nevertheless, we expect that the conformation about the fawcettimine skeleton would eventually result in epimerization of the methyl group to the more stable equatorial position. Unfortunately, our attempts to induce ring-A formation using the isomeric mixture were unsuccessful. So in order to reduce the complexity which results by working with a mixture of isomers, we decided to revisit the model system in order to sort out the details for ring-A formation.



Scheme 65. The formation of IMDAF reaction with methyl furan

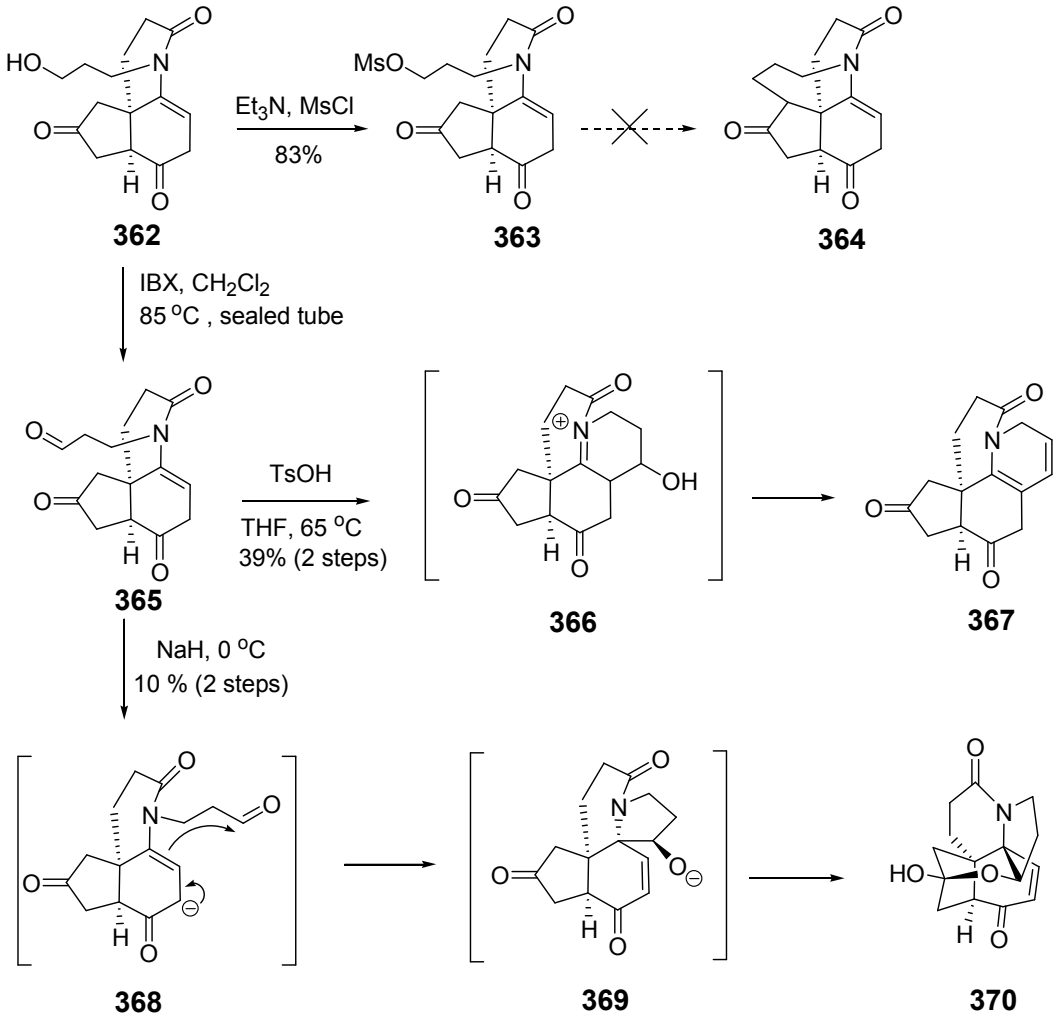
Installation of the final A-ring which is required in order to complete the synthesis of the fawcettimine core was envisioned to occur by displacement of a leaving group on the side chain using an enolate anion. In order to generate the requisite intermediate for the key cyclization, both the TBS and acetal protecting groups needed to be removed. The double deprotection of the TBS and acetal groups under a variety of known deprotection conditions were tried. Interestingly, when **330** was treated with a 5% HCl solution in THF, **361** was obtained as the exclusive product in 68% yield. This compound probably arises by the initial generation of a transient iminium ion **360** which is trapped with the free alcohol on the side chain. When CBr_4[147] or $PdCl_2(MeCN)_2$[148] was used, the product obtained corresponded to the deprotected alcohol **359** formed in 65% and 84% respectively.[149] Longer reaction times also gave tetracycle **361** as the major product. Based on the proposed mechanism of cyclization, we thought that by carrying out the reaction under basic conditions this would diminish formation of compound **361**. Indeed, when **330** was treated under mild basic conditions in the presence of a catalytic amount of CAN as the Lewis acid, the fully deprotected tricycle **362** was isolated in good yield (Scheme 66).[150]



Scheme 66. The double deprotection of tricyclic system **330**

Mesylation of alcohol **362** generated the expected mesylate **363** in 83% yield. However, our attempts to displace the mesylate with an enolate anion generated under basic conditions only resulted in recovered starting material or the corresponding alcohol (Scheme 67). Consequently, the more reactive and electrophilic aldehyde **365** was prepared. This was achieved by the oxidation of alcohol **362** using IBX in CH_2Cl_2 at 85 ^oC in a sealed tube.[151] The aldol condensation of **365** was next investigated under acidic conditions. Treating **365** with catalytic TsOH in THF at 65 ^oC led exclusively to the cyclized dihydropyridine **367** in 39% yield. The mechanism of this transformation probably involves addition of the enamide double bond onto the aldehyde carbonyl group

followed by extrusion of H_2O. The treatment of aldehyde **365** with base produced a completely different product. Various bases at different temperatures were examined and generally resulted in the formation of a mixture of products. However, when aldehyde **365** was treated with NaH in THF at 0 ^oC, the only compound that was isolated was compound **370**.



Scheme 67. Attempts for the generation of A-ring

The structure of **370** was assigned on the basis of its spectral properties. The ^{1}H-NMR spectrum of **370** showed the disappearance of the enamide double

bond proton at 5.19 as well as the aldehyde proton at 9.89 of the starting material **365**. Compound **370** showed the presence of α,β-unsaturated double bond protons at 6.02 (dd, *J* = 9.6 and 2.0 Hz) and 6.76 (d, *J* = 9.6 Hz),[152] and the alcohol proton appeared as a broad exchangeable singlet at 3.15, and the proton next to oxygen was located at 4.23. The ^{13}C-NMR showed the presence of two carbonyl peaks which correspond to the α,β-unsaturated carbonyl at 196.6 and the amide carbonyl at 169.8. In addition, the two double bond carbons of the α,β-unsaturated ketone appear at 129.4 and 152.7, and the O-C-O at 104.8. Finally, the structure of compound **370** was confirmed by a single crystal X-ray analysis (Figure 6).

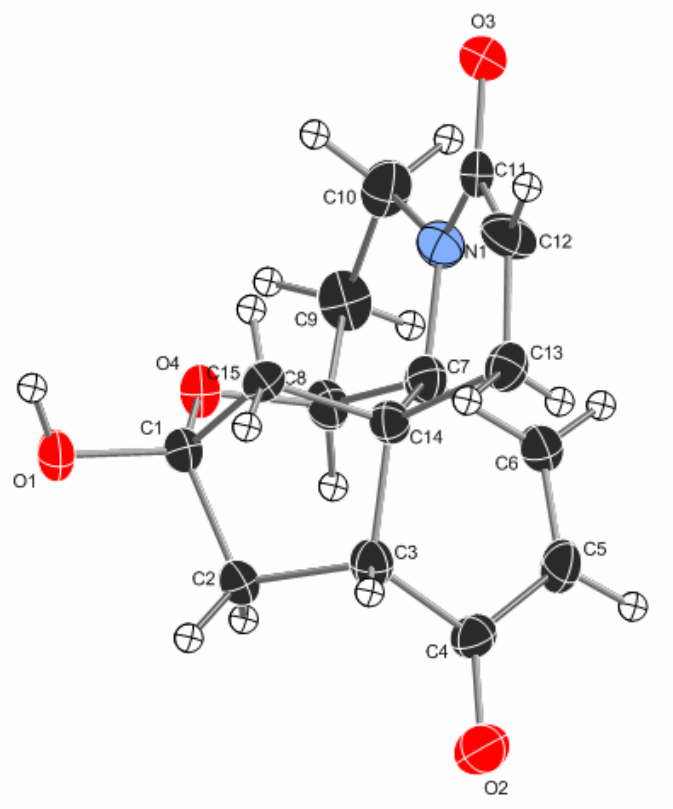
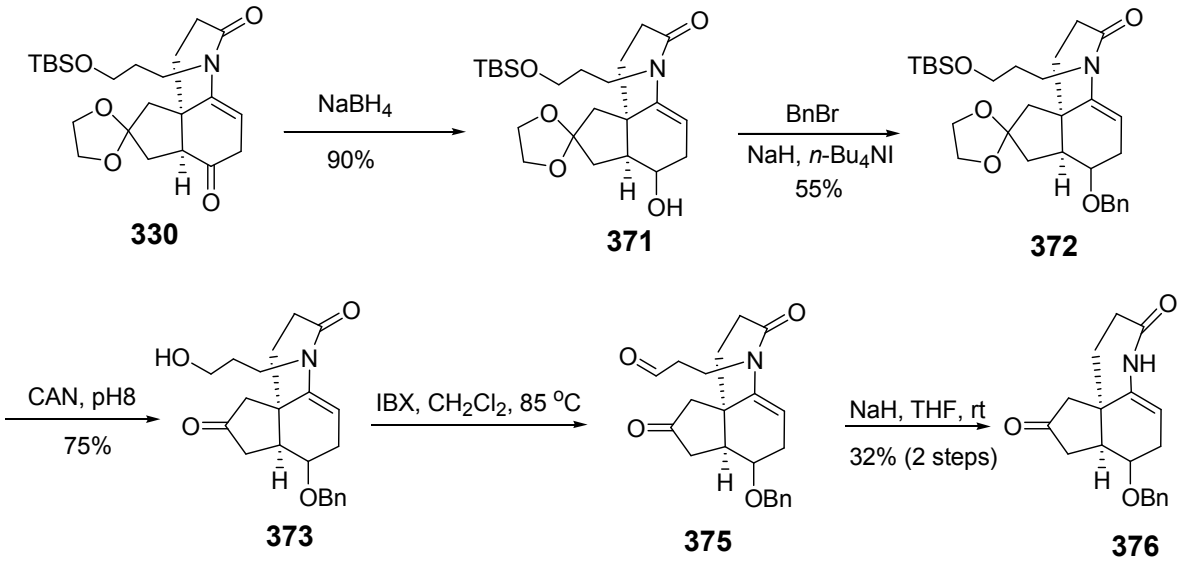


Figure 6. ORTEP of compound **370**

To suppress the formation of compound **370**, the cyclohexenone carbonyl group present in **330** was reduced to give alcohol **371** in 90% yield as a 5:1-mixture of diastereomers (Scheme 68). Prior to performing the aldol reaction, alcohol **371** was further protected as the benzyl ether **372** followed by double deprotection of TBS and acetal groups. The resulting alcohol **373** was then oxidized to give aldehyde **375**. Unfortunately, when aldehyde **375** was treated with NaH in THF at rt, the product that was obtained corresponding to the elimination of the side chain and gave amide **376** as a single product in 32% yield over the two-step sequence.



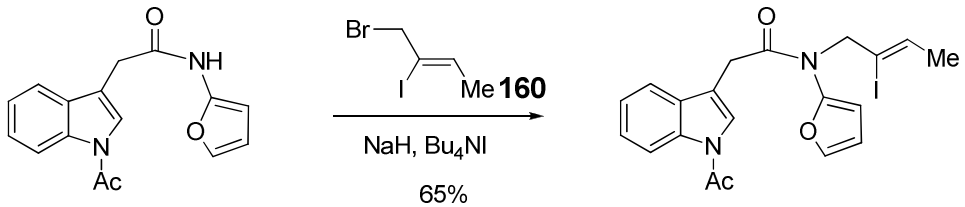
Scheme 68. Attempts toward the generation of fawcettimine core using benzyl protected alcohol

3. Conclusion

We were able to efficiently assemble the BCD core structure of the carbinolamine portion of fawcettimine by making use of the IMDAF cycloaddition/rearrangement sequence. An efficient route for the construction of the methyl furanyl carbamate necessary for the alkaloid was also developed. So far we were unable to close the ring-A by an internal displacement reaction. Further work is necessary to determine the best precursor for A-ring closure in order to finish a total synthesis of the fawcettimine class of natural products.

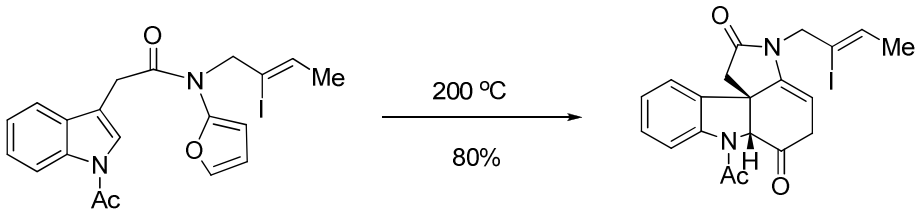
Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame dried glassware under an atmosphere of dry argon. The microwave reactor and reaction vessels were purchased fro CEM Corporation. All solids were recrystallized from ethyl acetate/hexane for analytical data.



2-(1-Acetyl-1*H*-indol-3-yl)-*N*-furan-2-yl-*N*-(2-iodo-but-2-enyl)acetamide (161). To a solution containing 0.05 g (0.11 mmol) of indole **159**[153] in 0.4 mL of DMF at 0 ^{o}C was added 0.003 g (0.13 mmol) of NaH in small portions and the mixture was stirred at 0 ^{o}C for 2 h. To this mixture was added a solution of 0.036 g (0.14 mmol) of *Z*-1-bromo-2-iodobutane **160**,[58] in 0.4 mL of DMF at 0 ^{o}C followed by the addition of a 0.008 g (0.02 mmol) of tetrabutyl ammonium iodide. The reaction mixture was stirred at 0 ^{o}C for 2 h and was slowly quenched with an aqueous $NaHCO_3$ solution and was then extracted with EtOAc. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.07 g (65%) of the titled compound **161** as a pale yellow oil; IR (thin film) 3124, 2914, 1701, 1450, and 1388 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.70 (d, 3H, *J* = 6.0 Hz), 2.58 (s, 3H), 3.62 (s, 2H), 4.59 (s, 2H),

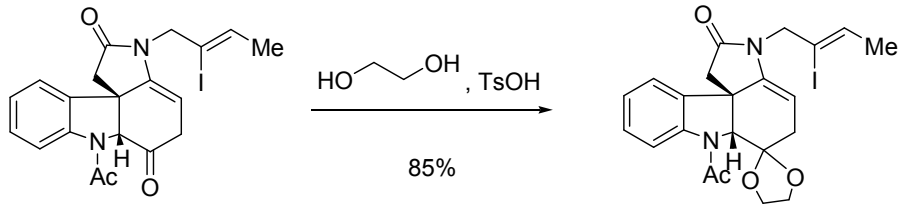
5.72 (q, 1H, *J* = 6.4 Hz), 6.18 (dd, 1H, *J* = 3.6 and 1.2 Hz), 6.39 (dd, 1H, *J* = 3.2 and 2.0 Hz), 7.20-7.42 (m, 5H), and 8.40 (d, 1H, *J* = 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.6, 23.9, 30.7, 58.5, 102.7, 106.0, 111.2, 115.4, 116.5, 118.7, 123.4, 123.7, 125.2, 130.0, 134.1, 135.5, 140.2, 147.1, 168.4, and 170.9.



161 **162**

7-Acetyl-3-(2-iodo-but-2-enyl)-3,5,6*a*,7-tetrahydropyrrolo[2,3-*d*]carbazole-2,6-dione (162). A solution containing 0.4 g (0.87 mmol) of the above furanyl indole **161** in 1.3 mL of toluene was heated in a sealed tube at 200 °C for 2 h. The reaction was cooled to rt and the mixture was concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.32 g (80%) of the titled compound **162** as a pale yellow oil; IR (thin film) 3416, 3030, 2971, 2904, 1721, 1685, 1470, and 1388 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.84 (d, 3H, *J* = 6.4 Hz), 2.37 (s, 3H), 2.72 (d, 1H, *J* = 16.8 Hz), 2.89 (dd, 1H, *J* = 20.4 and 2.8 Hz), 3.00 (d, 1H, *J* = 16.8 Hz), 4.49 (d, 1H, *J* = 15.2 Hz), 4.49 (s, 1H), 4.69 (d, 1H, *J* = 15.2 Hz), 5.13 (dd, 1H, *J* = 6.0 and 2.8 Hz), 6.03 (q, 1H, *J* = 6.4 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 7.25-7.32 (m, 2H), and 8.16 (d, 1H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.8, 23.9, 36.6, 45.7, 49.7, 51.8, 71.3, 94.6, 101.2, 117.9, 121.7, 125.2, 129.5, 134.0, 134.6,

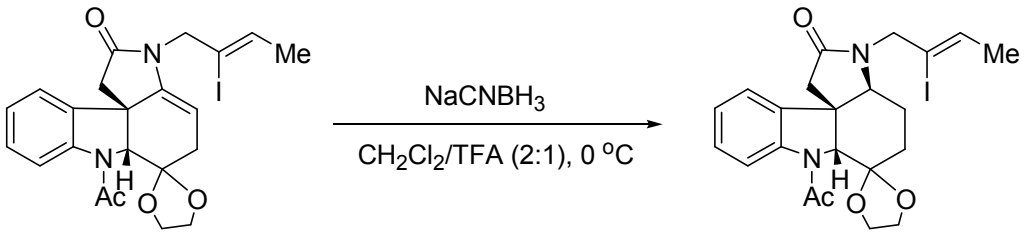
140.6, 140.9, 169.6, 171.6, and 202.7; HRMS Calcd. for $[(C_{20}H_{19}IN_2O_3)+H]^+$: 463.05132. Found: 463.05261.



162 **163**

7-Acetyl-3-(2-iodo-but-2-enyl)-6-(1,3-dioxolane)-3,5,6*a*,7-tetrahydro-pyrrolo[2,3-*d*]carbazole-2-one (163). To a solution containing 0.2 g (0.31 mmol) of the above ketone **162** in 6 mL of benzene was added 0.35 mL (6.2 mmol) of ethylene glycol followed by 0.06 g (0.3 mmol) of *p*-toluenesulfonic acid. The solution was heated under reflux for 1 h, cooled to rt, and poured into an aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.18 g (85%) of the titled compound **163** as an orange solid; mp 192-193 ^oC; IR (thin film) 1726, 1680, 1655, 1476, and 1388 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 1.70 (dd, 1H, *J* = 15.6 and 3.2 Hz), 1.80 (dt, 3H, *J* = 6.4 and 1.6 Hz), 2.25 (brs, 4H), 2.53 (d, 1H, *J* = 17.2 Hz), 3.03 (d, 1H, *J* = 17.2 Hz), 3.80-3.90 (m, 1H), 3.90-4.07 (m, 3H), 4.40 (d, 1H, *J* = 15.6 Hz), 4.45 (brs, 1H), 4.64 (dt, 1H, *J* = 15.6 and 1.6 Hz), 5.03 (dd, 1H, *J* = 7.6 and 3.2 Hz), 6.10 (qd, 1H, *J* = 6.4 and 1.2 Hz), 7.10 (td, 1H, *J* = 7.6 and 1.2 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), and 7.94 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.6, 22.6, 24.8,

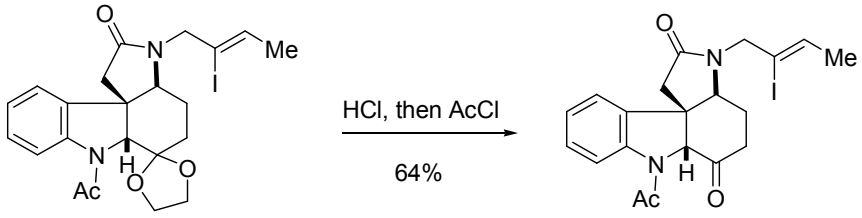
32.1, 45.9, 47.0, 50.3, 52.8, 64.5, 65.8, 66.3, 73.9, 96.8, 97.5, 103.1, 109.6, 117.7, 123.1, 125.7, 129.7, 136.2, 142.0, and 173.2; Anal. Calcd for $C_{22}H_{23}IN_2O_4$: C, 52.19; H, 4.58; N, 5.53. Found: C, 51.82; H, 4.70; N, 5.17.



163 **164**

7-Acetyl-3-(2-iodo-but-2-enyl)-6-(1,3-dioxolane)-3,5,6*a*,7-hexahydropyrrolo [2,3-*d*]carbazole-2-one (164). To a solution containing 0.2 g (0.3 mmol) of the above enamide **163** in 2 mL of CH_2Cl_2 at 0 °C was added 1 mL of TFA followed by the addition of 0.09 g (1.4 mmol) of $NaCNBH_3$ in small portions over 30 min at 0 °C. The mixture was stirred for 1 h at 0 °C, diluted with CH_2Cl_2, quenched with an aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.11 g (53%) of the titled compound **164** as a pale yellow oil; IR (thin film) 3416, 2960, 2914, 2873, 1701, 1655, and 1199 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.4-1.64 (m, 2H), 1.76-2.00 (m, 2H), 1.83 (d, 3H, *J* = 6.4 Hz), 2.35 (s, 3H), 2.42 (d, 1H, *J* = 16.8 Hz), 2.66 (d, 1H, 16.8 Hz), 3.51-3.60 (m, 1H), 3.68-3.82 (m, 3H), 3.93-4.12 (m, 2H), 4.23 (s, 1H), 4.57 (d, 1H, *J* = 14.8 Hz), 5.98 (q, 1H, *J* = 6.4 Hz), 7.04-7.17 (m, 2H), 7.21-7.28 (m, 1H), and 8.02

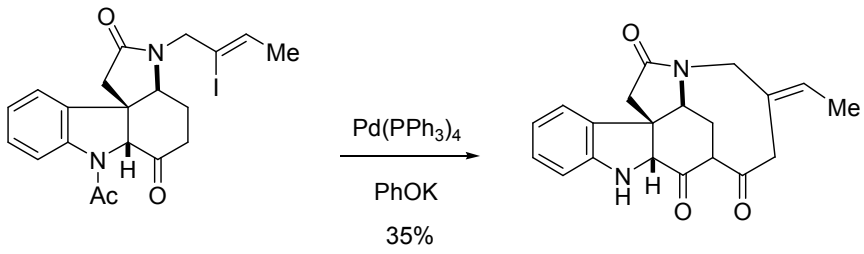
(brd, 1H, *J* = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.5, 21.8, 23.4, 27.5, 46.6, 50.3, 50.8, 55.5, 64.5, 65.9, 70.8, 103.1, 108.5, 117.1, 120.4, 124.3, 128.5, 133.3, 134.8, 143.7, 169.8, and 173.0; HRMS Calcd. for $[(C_{22}H_{23}IN_2O_4)+H]^+$: 509.09319. Found: 509.09291.



164 **166**

7-Acetyl-3-(2-iodo-but-2-enyl)-3,3*a*,4,5,6*a*,7-hexahydro-pyrrolo[2,3-*d*]carbazol-2,6-dione (166). To a solution of 0.04 g (0.08 mmol) of acetal **164** in 2.0 mL of THF was added 3.0 mL of 6N HCl and the resulting mixture was heated at 55 ^{o}C for 3 h. After cooling to rt, the reaction mixture was quenched with solid $NaHCO_3$ and was then diluted with H_2O and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the resultant residue was taken up in 1.5 mL of CH_2Cl_2 and was cooled to 0 ^{o}C. To this solution was added 50 µL of Et_3N followed by the addition of 13 µL of CH_3COCl. The reaction mixture was stirred at rt for 2 h and was then quenched with a saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers was washed with H_2O, brine, and dried over

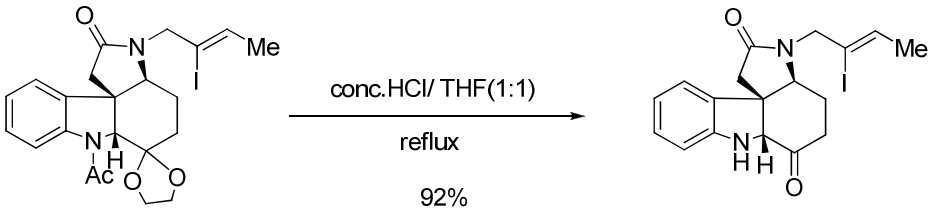
$MgSO_4$. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to give 24 mg (64%) of ketone **166** as a colorless oil; IR (neat) 1728, 1698, 1666, and 1398 cm^{-1}; ^{1}H-NMR (CD_3CN, 600 MHz) δ 1.79 (d, 3H, *J* = 6.0 Hz), 1.97-2.01 (m, 1H), 2.03 (s, 3H), 2.21-2.26 (m, 1H), 2.29-2.34 (m, 1H), 2.42 (d, 1H, *J* = 16.8 Hz), 2.66-2.72 (m, 1H), 3.04 (d, 1H, *J* = 16.8 Hz), 4.09-4.12(m, 1H), 4.11 (d, 1H, *J* = 15.0 Hz), 4.76 (d, 1H, *J* = 15.0 Hz), 4.85 (s, 1H), 6.10 (q, 1H, *J* = 6.0 Hz), 7.07 (t, 1H, *J* = 7.5 Hz), 7.26 (t, 1H, *J* = 7.5 Hz), 7.36 (d, 1H, *J* = 7.5 Hz), and 8.14 (d, 1H, *J* = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 22.1, 23.7, 24.3, 33.6, 46.9, 51.8, 53.6, 57.5, 74.1, 102.6, 118.2, 121.5, 124.8, 130.0, 131.1, 136.0, 142.6, 169.9, 172.8, and 204.1.



166 **175**

Pentacyclic Diketone 175. To a solution containing 24 mg (0.052 mmol) of vinyl iodide **166** in 2.0 mL of THF at rt was added 15 mg (0.16 mmol) of phenol, 0.13 mL of 1M *t*-BuOK in *t*-BuOH, and 6.0 mg (0.016 mmol) of $Pd(PPh_3)_4$, respectively. The reaction mixture was heated at reflux under an argon atmosphere for 4 h and was then cooled to rt. The reaction mixture was diluted with 1N NaOH and extracted with CH_2Cl_2. The combined organic extracts were washed with 1N NaOH, H_2O, brine, and dried over $MgSO_4$. After concentrating

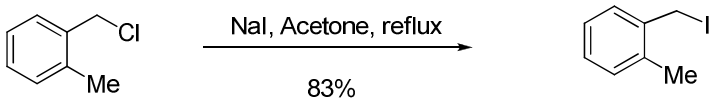
under reduced pressure, the residue was subjected to flash silica gel chromatography to give 42 mg (61%) of pentacyclic ketone **175** as pale yellow solid; IR (neat) 3488, 1690, 1484, and 1413 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.66 (dd, 3H, *J* = 7.2 and 2.0 Hz), 1.77 (dd, 1H, *J* = 15.6 and 3.6 Hz), 1.94 (ddd, *J* = 15.6, 5.6 and 2.4 Hz), 2.45 (d, 1H, *J* = 16.0 Hz), 2.65 (s, 1H), 2.68 (d, 1H, *J* = 16.0 Hz), 3.21 (s, 1H), 3.23 (d, 1H, *J* = 16.0 Hz), 3.48 (d, 1H, *J* = 16.0 Hz), 3.47-3.55 (m, 1H), 3.85 (d, 1H, *J* = 5.6 Hz), 4.44 (s, 1H), 4.55 (d, 1H, *J* = 16.0 Hz), 5.85 (q, 1H, *J* = 7.2 Hz), 7.15 (td, 1H, *J* = 7.6 and 0.8 Hz), 7.29 (d, 1H, *J* = 7.6 Hz), 7.34 (td, 1H, *J* = 7.6 and 0.8 Hz), and 7.65 (d, 1H, *J* = 7.6 Hz); HRMS Calcd for $[(C_{20}H_{21}N_2O_3)+H]^+$: 337.1547. Found: 337.1556.



164 **165**

3-(2-Iodo-but-2-enyl)-3,3*a*,4,5,6*a*,7-hexahydropyrrolo[2,3-*d*]carbazole-2,6-dione (165). To a solution containing 0.05 g (0.072 mmol) of the above amide **164** in 1 mL of THF was added 1 mL of conc. HCl . The solution was heated at reflux for 1 h, cooled to rt, and diluted with EtOAc and water. The resulting mixture was cooled to 0 ^oC and solid $NaHCO_3$ was added until the bubbling had ceased. The mixture then extracted with EtOAc, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.028 g (92%) of the titled

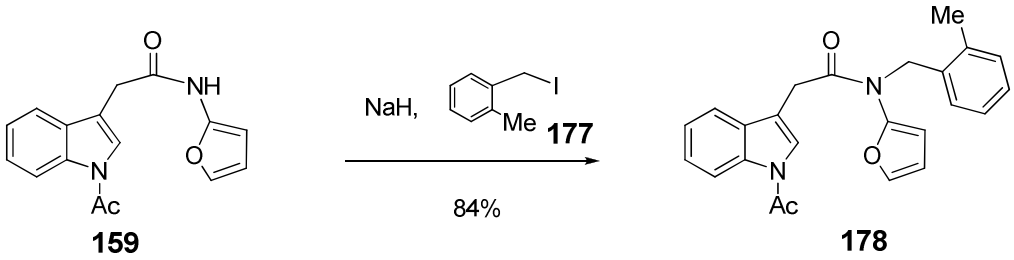
compound **165** as a pale yellow viscous oil; IR (thin film) 3342, 1691, 1601, 1405, and 751 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.88 (dd, 3H, *J* = 6.4 and 1.2 Hz), 1.94-2.04 (m, 2H), 2.18-2.38 (m, 2H), 2.44-2.55 (m, 1H), 2.67 (d, 1H, *J* = 16.8 Hz), 2.95 (d, 1H, *J* = 16.8 Hz), 3.77 (s, 1H), 3.87 (d, 1H, *J* = 15.2 Hz), 4.11 (t, 1H, *J* = 4.8 Hz), 5.00 (dt, 1H, *J* = 15.2 and 1.6 Hz), 6.02 (q, 1H, *J* = 6.4 Hz), 6.78 (d, 1H, *J* = 8.0 Hz), 6.82 (td, 1H, *J* = 8.0 and 0.8 Hz), 7.12 (td, 1H, *J* = 8.0 and 0.8 Hz), and 7.16 (d, 1H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.9, 23.9, 32.8, 45.3, 51.7, 52.3, 58.3, 72.5, 102.8, 111.2, 120.3, 122.0, 129.2, 129.4, 135.1, 150.4, 173.3, and 209.3; HRMS Calcd. for $[(C_{18}H_{19}IN_2O_2) + H]^+$: 423.05746. Found: 423.05641.



176 **177**

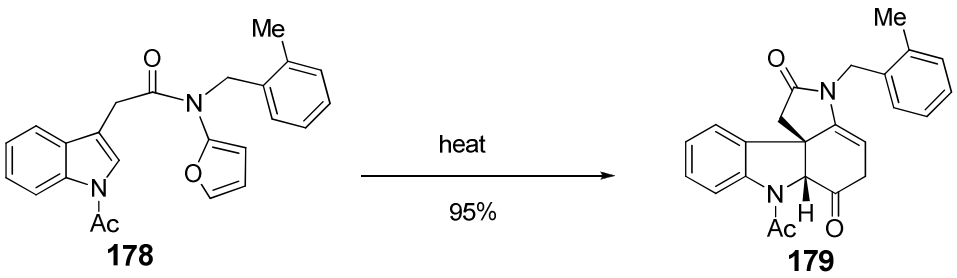
1-Iodomethyl-2-methyl-benzene (177).[4] To a 2.8 mL (19.2 mmol) sample of α-chloro-o-xylene (**176**) in 38 mL of acetone was added 3.2 g (21 mmol) of NaI in one portion. The resulting mixture was heated at reflux for 24 h, cooled to rt and concentrated under reduced pressure. The crude mixture was taken up in EtOAc, extracted with H_2O and washed with an aqueous $Na_2S_2O_3$ solution. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to provide 4.2 g (83%) of the titled compound **177** as a pale yellow oil; IR (thin film) 1593, 1482, 1458, 1148, 759, 715, and 568 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 4.45 (s, 2H), and 7.10-7.35 (m, 4H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 5.1, 18.8, 126.5, 128.4, 129.3, 130.8, 136.5, and 136.8.



2-(1-Acetyl-1H-indol-3-yl)-*N*-furan-2-yl-*N*-(2-methyl-benzyl)acetamide (178). To a solution containing 5.7 g (20 mmol) of furanyl indole **159** in 100 mL of DMF at 0 ^{o}C was added 0.8 g (20 mmol) of NaH. The mixture was stirred for 2 h at 0 ^{o}C, and then a solution of 5.6 g (24 mmol) of 1-Iodomethyl-2-methyl-benzene (**177**)in 30 mL of DMF at 0 ^{o}C was added. The reaction mixture was stirred for 3 h, quenched with water and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 4.7 g (84% based on recovered starting material) of the titled compound **178** as a yellow solid; mp 96-97 ^{o}C; IR (neat) 1695, 1674, 1601, 1442, 1368, 1258, and 739 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.58 (s, 3H), 3.65 (s, 2H), 4.90 (s, 2H), 5.63 (d, 1H, 2.4 Hz), 6.32 (dd, 1H, *J* = 3.6 and 2.4 Hz), 7.14-7.44 (m, 10H), and 8.43 (d, 1H, *J* = 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.9, 23.9, 30.6, 49.4, 105.5, 111.2, 115.5, 116.5, 118.7, 123.4, 123.6, 125.3, 125.8, 127.6, 128.9, 130.0, 130.2, 134.3, 135.5, 136.5, 140.1, 147.6, 168.4, and 170.9; Anal.

Calcd. for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.35; H, 5.81, N, 7.11.

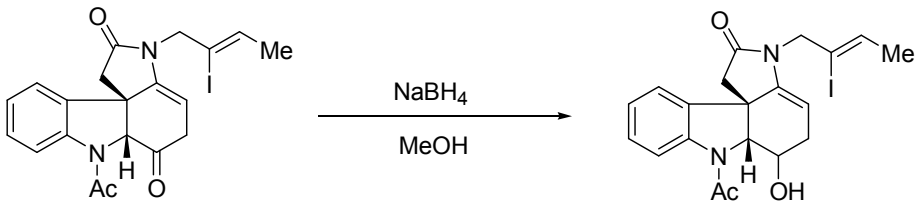


178 **179**

7-Acetyl-3-(2-methyl-benzyl)-3,5,6*a*,7-tetrahydropyrrolo[2,3-*d*]carbazole-2,6-dione (179). To a solution of 0.3 g (0.8 mmol) of indolyl furan **178** in 4 mL of toluene in a 10 mL microwave tube equipped with a magnetic stir bar was added 0.007 g (0.16 mmol) of MgI_2. The mixture was charged with N_2 and sealed with a microwave rubber cap. The sample was then placed in microwave reactor and irradiated at 200 W at 150 ^oC for 3 h. After cooling to rt, the solvent was removed under reduced pressure. The resulting residue was purified by flash silica gel column chromatography using 40% EtOAc/hexane mixture as the eluent to provide 0.29 g (95%) of the titled compound **179** as a pale yellow solid: mp 184-186 ^oC; IR (thin film) 1716, 1657, 1594, 1467, 1384, 353, and 749 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.42 (s, 3H), 2.71 (d, 1H, *J* = 16.4 Hz), 2.81 (dd, 1H, *J* = 20.4 and 2.4 Hz), 2.94 (dd, 1H, *J* = 20.4 and 5.6 Hz), 3.10 (d, 1H, *J* = 16.4 Hz), 4.57 (s, 1H), 4.79 (d, 1H, *J* = 16.0 Hz), 4.89 (d, 1H, *J* = 16.0 Hz), 4.98 (dd, 1H, *J* = 5.6 and 2.4 Hz), 6.92-7.05 (m, 2H), 7.12-7.28 (m, 5H), and 8.15 (d, 1H, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.3, 23.8, 36.6, 42.1, 45.7, 49.9, 71.2, 94.7, 117.9, 120.8, 125.1, 126.2, 126.7, 127.7, 129.5, 130.8,

132.7, 134.2, 135.5, 140.7, 140.9, 169.6, 171.9, and 202.9; HRMS Calcd. for $[(C_{24}H_{22}N_2O_3)+H]^+$: 387.17032. Found: 387.17148.

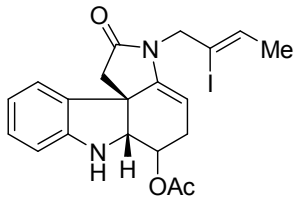
Alternatively, the reaction can be run using conventional oil bath and was conducted as following: A solution of 0.20 g (0.52 mmol) of the above indole furan **178** in 2 mL of toluene was heated in a sealed tube at 180 ^oC for 15 h. After cooling to rt, the solution was concentrated under reduced pressure The resulting residue was purified by flash silica gel column chromatography to provide 0.11 g (55%) of the titled compound **179** as a yellow solid. The spectral data is identical to that reported above.



162 **182**

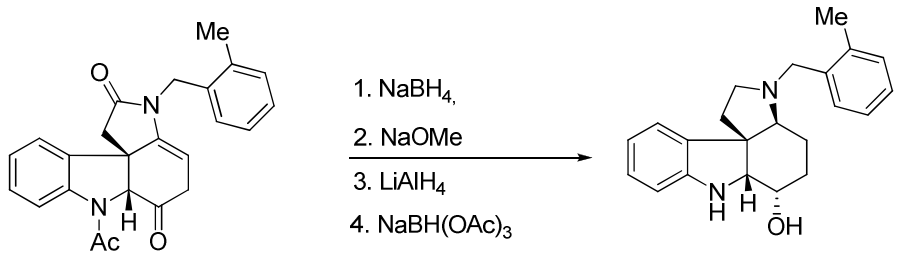
7-Acetyl-6-hydroxy-3-(2-methyl-benzyl)-5,6,6a,7-tetrahydro-3H-pyrrolo[2,3-d]carbazol-2-one (182). To a solution containing 0.81 g (0.125 mmol) of enamide **162** in 1 mL of EtOH at 0 ^oC was added 0.005 g (0.125 mmol) of $NaBH_4$ in one portion. The mixture was stirred for 30 min at 0 ^oC, then quenched with an aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give 0.06 g (74%) of a titled compound **182** as a yellow oil: IR (neat) 3401, 2909, 1721, 1675, and 1393 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.66 – 1.78 (m, 2H), 1.80 (d, 3H, *J* = 6.4 Hz), 2.14 – 2.24 (m, 1H), 2.49 (brs, 3H),

2.79 (d, 1H, *J* = 16.8 Hz), 2.92 (d, 1H, *J* = 16.8 Hz), 4.00 – 4.12 (m, 1H), 4.21 (brs), 4.41 (d, 1H, *J* = 15.2 Hz), 4.62 (d, 1H, *J* = 15.2 Hz), 4.98 (dd, 1H, *J* = 8.0 and 2.8 Hz), 5.07 (brs, 1H), 5.96 (q, 1H, *J* = 6.4 Hz), and 6.98 – 7.36 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.0, 21.8, 23.9, 26.8, 45.9, 51.8, 68.2, 71.4, 97.4, 101.3, 114.9, 123.2, 125.4, 128.3, 128.7, and 134.4.



183

Acetic acid 3-(2-methyl-benzyl)-2-oxo-2,3,5,6,6a,7-hexahydro-1H-pyrrolo[2,3-d]carbazol-6-yl Ester (186). After standing for 2 weeks the above product was transformed into a new yellow oil: IR (neat) 1742, 1680, 1496, and 1230 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.76 (d, 3H, *J* = 6.4 Hz), 2.14 (s, 3H), 2.15 – 2.23 (m, 2H), 2.28 – 2.35 (m, 2H), 2.79 (d, 1H, *J* = 16.8 Hz), 2.87 (d, 1H, *J* = 16.8 Hz), 4.19 (brs, 1H), 4.25 (dd, 1H, *J* = 4.4 and 1.2 Hz), 4.38 (t, 1H, *J* = 15.6 Hz), 4.58 (d, 1H, *J* = 15.6 Hz), 4.88 – 4.98 (m, 2H), 5.84 (q, 1H, *J* = 6.4 Hz), 6.59 – 6.70 (m, 2H), 7.05 – 7.13 (, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.3, 21.7, 23.3, 46.3, 50.6, 51.6, 62.4, 72.9, 96.8, 101.3, 108.7, 118.9, 122.3, 129.0, 133.2, 133.5, 143.4, 149.3, 170.2, and 172.9.



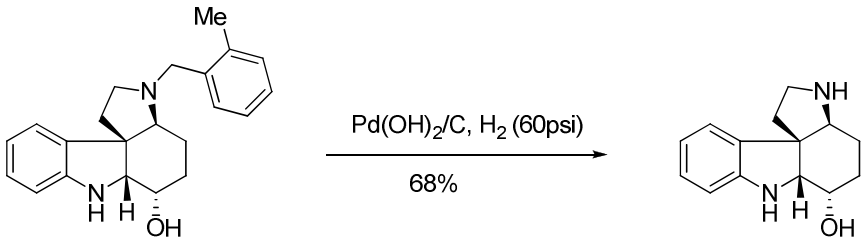
179 **186**

3-(2-Methyl-benzyl)-2,3,3a,4,5,6,6*a*,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol (186). To a solution containing 1.0 g (2.6 mmol) of enamide **179** in 24 mL of a 1:1 mixture of EtOH/THF at 0 ^{o}C was added 0.098 g (2.6 mmol) of $NaBH_4$ in one portion. The mixture was stirred for 30 min at 0 ^{o}C, then quenched with an aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was taken up in 50 mL of THF and 5.2 mL (2.6 mmol) of 0.1M NaOMe in MeOH solution was added. After stirring for 15 min, the solution was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was taken up in 52 mL of THF and 7.8 mL (7.8 mmol) of 1M $LiAlH_4$ in THF solution was added dropwise. The mixture was heated at reflux for 3 h, cooled to 0 ^{o}C, and 0.3 mL of water was added dropwise followed by 0.3 mL of a 15% aqueous NaOH solution and 0.87 mL of water. The mixture was filtered through celite and was washed with EtOAc. The filtrate was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was taken up in 52 mL of 1,2 dichloroethane, cooled to -20 ^{o}C and 2.2 g (10.4 mmol) of $NaBH(OAc)_3$ was

gradually added over a 1 h period. The reaction mixture was stirred for an additional 2 h, diluted with $CHCl_3$, quenched with an aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.56 g (65%) of the *cis* isomer of the titled compound **186** as a yellow oil and 0.20 g(24%) of trans isomer as a yellow oil; *trans*-isomer: IR (thin film) 3367, 3293, 1720, 1650, 1605, 1401, and 739 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.46-2.00 (m, 6H), 2.21 (ddd, 1H, *J* = 13.6, 9.2 and 4.4 Hz), 2.42-2.50 (m, 1H), 2.81 (td, 1H, *J* = 9.6 and 4.0 Hz), 3.42 (d, 1H, *J* = 12.8 Hz), 3.78 (d, 1H, *J* = 12.8 Hz), 3.82 (d, 1H, *J* = 4.0 Hz), 4.16-4.23 (m, 1H), 6.67 (d, 1H, *J* = 8.0 Hz), 6.78 (t, 1H, *J* = 7.6 Hz), 7.07 (td, 1H, *J* = 7.6 and 1.2 Hz), 7.12-7.18 (m, 4H), and 7.26-7.28 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.1, 19.6, 25.9, 35.9, 50.9, 54.4, 54.7, 67.8, 68.6, 69.1, 109.5, 119.0, 123.3, 125.5, 126.8, 127.6, 129.2, 130.0, 137.1, 137.6,137.7, and 149.4; HRMS Calcd. for $[(C_{22}H_{26}N_2O)+H]^+$: 335.21179. Found: 335.21138.

trans-isomer: IR (thin film) 3350, 1607, 1484, 1463, 1050 and 742 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 – 1.46 (m, 2H), 1.83 (tt, 1H, *J* =10.8 and 4.8 Hz), 1.86 – 2.25 (m, 3H), 2.34 – 2.43 (m, 1H), 2.47 (s, 3H), 2.88 (dd, 1H, *J* = 10.8 and 6.4 Hz), 3.10 (ddd, 1H, 9.2, 9.2 and 6.8 Hz), 3.17 (d, 1H, *J* = 12.8 Hz), 3.83 (d, 1H, *J* = 4.8 Hz), 4.06 (d, 1H, *J* = 12.8 Hz), 4.10 – 4.21 (m, 1H), 6.70 (d, 1H, *J* = 8.0 Hz), 6.77 (td, 1H, *J* = 7.6 and 0.8 Hz), 7.08 (td, 1H, *J* = 7.6 and 1.6 Hz), 7.16 – 7.40 (m, 1H) and 7.55 (d, 1H, *J* = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.1, 19.6,

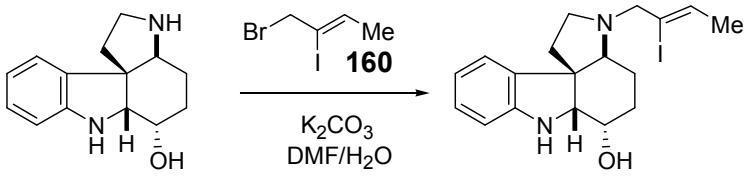
25.9, 35.9, 50.9, 54.4, 54.7, 67.8, 68.6, 69.0, 109.5, 119.0, 123.3, 125.5, 126.8, 127.6, 129.2, 130.1, 137.1, 137.1, 137.5, 137.6 and 149.4.



186 **187**

2,3,3*a*,4,5,6,6*a*,7-Octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol (187). To a sample of 0.06 g (0.09 mmol) of 20% Pd on $Pd(OH)_2/C$ (Pearlman's catalyst) in a sealed tube was added a solution of 0.1 g (0.3 mmol) of amine **186** in 1 mL of MeOH. The mixture was repeatedly flushed with H_2 and was stirred at rt under 60 psi for 2 days. At the end of this time the mixture was filtered through celite and washed with 30 mL of MeOH, 30 mL of a 1:1 mixture of $MeOH/CH_2CH_2$ and 30 mL of $Et_3N/MeOH/CH_2Cl_2$ (5:25:70). The combined organic solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography to give 0.56 g (68%) of the titled compound **187** as a pale yellow oil; IR (thin film) 3321, 3045, 1602, 1487, 1467, 1057, and 726 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ 1.38-1.51 (m, 1H), 1.65-1.74 (m, 1H), 1.79-1.90 (m, 2H), 2.14-2.32 (m, 2H), 3.04-3.12 (m, 1H), 3.36-3.46 (m, 1H), 3.55 (ddd, 1H, *J* = 12.0, 9.2 and 8.0 Hz), 3.80 (d, 1H, *J* = 4.4 Hz), 3.88 (dt, 1H, *J* = 10.8 and 4.4 Hz), 6.64 (d, 1H, *J* = 8.0 Hz), 6.66 (t, 1H, *J* = 7.2 Hz), 6.99 (td, 1H, *J* = 8.0 and 1.2 Hz), and 7.03 (d, 1H *J* = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ

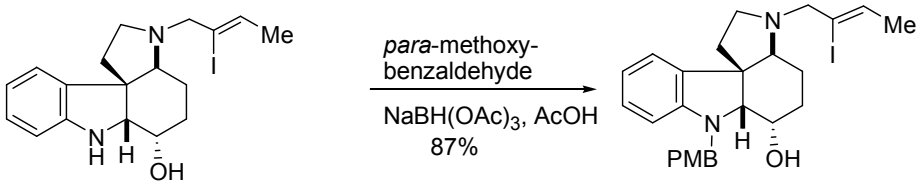
26.2, 27.1, 32.5, 44.2, 56.4, 64.6, 68.5, 69.0, 111.3, 120.1, 122.6, 129.7, 136.7, and 151.1.



187 **188**

3-(2-Iodo-but-2-enyl)-2,3,3*a*,4,5,6,6*a*,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol (16). To a solution of 25 mg (0.11 mmol) of amine **187** in 1.0 mL of DMF at rt was added 0.2 mL of H_2O and 75 mg (0.55 mmol) of K_2CO_3. The resulting mixture was cooled to 0 ^oC, and this was followed by the addition of a solution of 31 mg (0.12 mmol) of 1-bromo-2-iodo-but-2-ene in 0.6 mL of DMF. The reaction mixture was stirred at 0 ^oC for 12 h, quenched with H_2O, and extracted with Et_2O. The combined organic extracts were washed with H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to give 35 mg (79%) of **188** as a colorless oil; IR (neat) 3359, 2793,1607, 1483, 1464, and 1049 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.42-1.49 (m, 1H), 1.56-1.73 (m, 3H), 1.77 (d, 3H, *J* = 6.4 Hz), 1.93-2.00 (m, 2H), 2.19-2.26 (m, 1H), 2.47 (dd, 1H, *J* = 7.2 and 3.6 Hz), 2.66 (ddd, 1H, *J* = 9.2, 9.2 and 6.8 Hz), 2.89 (ddd, 1H, *J* = 9.2, 9.2 and 4.4 Hz), 3.14 (d, 1H, *J* = 13.8 Hz), 3.44 (d, 1H, *J* = 13.8 Hz), 3.81 (d, 1H, *J* = 3.6 Hz), 4.03 (brs, 1H), 4.21-4.29 (m, 1H), 5.84 (q, 1H, *J* = 6.4 Hz), 6.66 (d, 1H, *J* = 7.6 Hz), 6.76 (td, 1H, *J* = 7.6 and 1.0 Hz), 7.06 (td, 1H, *J* = 7.6 and 1.0 Hz), and 7.21 (dd, 1H, *J*

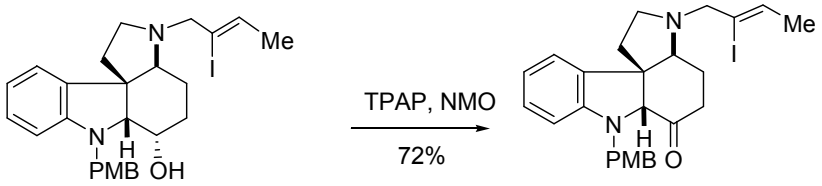
= 7.6 and 1.0 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 20.2, 21.9, 26.0, 36.2, 50.2, 54.7, 64.2, 66.7, 68.7, 69.2, 109.6, 110.4, 119.2, 123.8, 127.9, 130.9, 137.1, and 149.8; HRMS Calcd for $[(C_{18}H_{23}N_2OI)+H]^+$: 411.0928. Found: 411.0925.



188 **190a**

3-(2-Iodo-but-2-enyl)-7-(4-methoxy-benzyl)-2,3,3*a*,4,5,6,6*a*,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol (190a). To a solution of 52 mg (0.13 mmol) of benzamine **188** in 1.5 mL of $ClCH_2CH_2Cl$ at 0 ^oC was added 19 mg (0.15 mmol) of *p*-methoxybenzaldehyde and 67 mg (0.32 mmol) of $NaBH(OAc)_3$, followed by the dropwise addition of 22 µL (0.4 mmol) of CH_3COOH. The reaction mixture was stirred at 0 ^oC for 10 min, at rt for 12 h, then quenched with a saturated K_2CO_3 solution and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to give 52 mg (87%) of alcohol **190a** as a colorless oil; IR (neat) 3500, 1605, 1511, 1483, and 1245 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.28 (brd, 1H, *J* = 6.0 Hz), 1.48-1.56 (m, 1H), 1.59-1.66 (m, 1H), 1.70-1.78 (m, 2H), 1.79 (dd, 3H, *J* = 6.4 and 1.4 Hz), 1.92-2.09 (m, 3H), 2.32 (td, 1H, *J* = 8.8 and 7.0 Hz), 2.71 (t, 1H, *J* = 3.4 Hz), 2.98 (d, 1H, *J* = 13.8 Hz), 3.07 (td, 1H, *J* = 8.8 and 4.8 Hz), 3.43 (d, 1H, *J* = 3.6 Hz), 3.61 (dt, 1H, *J* = 13.8 and 1.4 Hz), 3.81 (s, 3H), 4.29 (d, 1H, *J* =

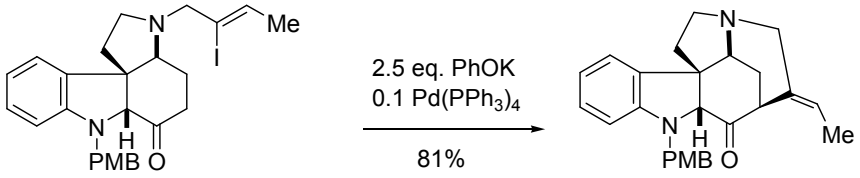
15.4 Hz), 4.35-4.42 (m, 1H), 4.59 (d, 1H, *J* = 15.4 Hz), 5.85 (q, 1H, *J* = 6.4 Hz), 6.44 (d, 1H, *J* = 7.4 Hz), 6.70 (t, 1H, *J* = 7.4 Hz), 6.88 (d, 2H, *J* = 8.4 Hz), 7.04 (d, 1H, *J* = 7.4 Hz), 7.06 (t, 1H, *J* = 7.4 Hz), and 7.29 (d, 2H, *J* = 8.4 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 18.8, 21.9, 25.0, 39.1, 51.4, 51.9, 53.5, 55.5, 65.6, 65.7, 68.2, 73.4, 106.9, 110.2, 114.2, 118.2, 122.0, 128.3, 128.6, 131.1, 131.4, 135.1, 152.8, and 158.8.



190a **191a**

3-(2-Iodo-but-2-enyl)-7-(4-methoxy-benzyl)-1,2,3,3*a*,4,5,6,6*a*,7-octahydro-pyrrolo [2,3-*d*]carbazol-6-one (191a). To a solution containing 53 mg (0.1 mmol) of alcohol **190a** and 50 mg 4Å of molecular sieves in 2.0 mL of CH_3CN at 0 ^{o}C was added 18 mg (0.15 mmol) of NMO (*N*-methyl-morpholine-*N*-oxide) and 11 mg (0.03 mmol) of TPAP (tetra-*n*-propylammonium perruthenate), respectively. After stirring at 0 ^{o}C for 20 min, the reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 38 mg (72%) of ketone **191a** as a pale yellow oil; IR (neat) 1711, 1605, 1512, 1483, and 1247 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.77 (dd, 3H, *J* = 6.4 and 1.2 Hz), 1.84-1.97 (m, 2H), 2.12-2.37 (m, 2H), 2.49-2.59 (m, 2H), 3.00 (d, 1H, *J* = 14.2 Hz), 3.14 (td, 1H, *J* = 8.0 and 2.4 Hz), 3.55 (s, 1H), 3.59 (dt, 1H, *J* = 14.2 and 1.4 Hz), 3.78 (s,

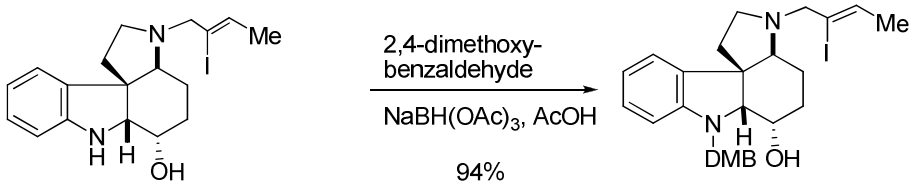
3H), 4.13 (d, 1H, *J* = 15.6 Hz), 4.28 (d, 1H, *J* = 15.6 Hz), 5.83 (q, 1H, *J* = 6.2 Hz), 6.56 (d, 1H, *J* = 7.6 Hz), 6.78 (t, 1H, *J* = 7.6 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 7.04 (d, 1H, *J* = 7.6 Hz), 7.11 (t, 1H, *J* = 7.6 Hz), and 7.18 (d, 2H, *J* = 8.4 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 20.3, 21.9, 32.5, 38.0, 51.5, 51.8, 55.4, 58.8, 64.5, 67.7, 80.7, 107.5, 108.6, 114.1, 119.0, 123.2, 128.8, 129.2, 129.8, 131.6, 133.0, 152.2, 159.0, and 210.1.



191a **192a**

Pentacyclic Ketone 192a. To a solution containing 32 mg (0.06 mmol) of vinyl iodide **191a** in 2.0 mL of THF at room temperature was added 17 mg (0.18 mmol) of phenol, 0.15 mL of 1M *t*-BuOK in *t*-BuOH, and 7 mg (0.006 mmol) of $Pd(PPh_3)_4$, respectively. The reaction mixture was heated at reflux under argon for 2 h, cooled to rt, diluted with 1N NaOH and extracted with CH_2Cl_2. The combined organic extracts were washed with 1N NaOH, H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to silica gel chromatography to give 21 mg (81%) of pentacyclic ketone **192a** as a pale yellow oil; IR (neat) 1712, 1606, 1511, 1483, and 1247 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.59 (d, 3H, *J* = 6.8 Hz), 1.99-2.03 (m, 1H), 2.09-2.17 (m, 2H), 2.28 (dt, 1H, *J* = 14.4 and 4.0 Hz), 2.77 (td, 1H, *J* = 10.0 and 6.0 Hz), 2.95 (d, 1H, *J* = 15.2 Hz), 3.28 (t, 1H, *J* = 8.4 Hz), 3.41 (s, 1H), 3.61 (s, 1H), 3.75-

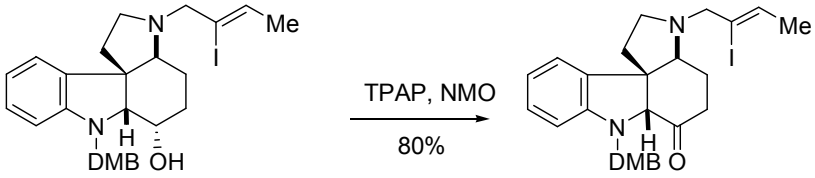
3.79 (m, 5H), 4.33 (d, 1H, *J* = 14.8 Hz), 4.59 (d, 1H, *J* = 14.8 Hz), 5.48 (q, 1H, *J* = 6.8 Hz), 6.51 (d, 1H, *J* = 7.6 Hz), 6.73 (t, 1H, *J* = 7.6 Hz), 6.83 (d, 2H, *J* = 8.6 Hz), 7.01 (d, 1H, *J* = 7.6 Hz), 7.10 (t, 1H, *J* = 7.6 Hz), and 7.20 (d, 1H, *J* = 8.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 13.6, 24.4, 39.3, 44.5, 50.3, 52.4, 52.8, 55.5, 58.2, 61.6, 74.0, 107.7, 114.1, 118.6, 122.3, 125.4, 129.0, 129.3, 130.0, 130.7, 132.2, 151.2, 159.0, and 210.7.



188 **190b**

7-(2,4-Dimethoxy-benzyl)-3-(2-iodo-but-2-enyl)-2,3,3*a*,4,5,6,6*a*,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol (190b). To a solution of 0.1 g (0.26 mmol) of benzamine **188** in 6.0 mL of $ClCH_2CH_2Cl$ at 0 ^{o}C was added 52 mg (0.3 mmol) of 2,4-methoxybenzaldehyde and 0.137 g (65 mmol) of $NaBH(OAc)_3$, followed by the dropwise addition of 44 µL (0.78 mmol) of CH_3COOH. The reaction mixture was stirred at 0 ^{o}C for 10 min, and at rt for 12 h. The mixture was quenched with a saturated K_2CO_3 solution, and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to flash chromatography to give 0.14 g (94%) of alcohol **190b** as a pale yellow oil; IR (neat) 3500, 1606, 1485, 1259, and 1036 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.52-1.65 (m, 4H), 1.72-1.78 (m, 1H), 1.79 (d, 3H, *J* = 6.3 Hz), 1.92-1.97 (m, 1H), 1.99-2.08 (m, 2H),

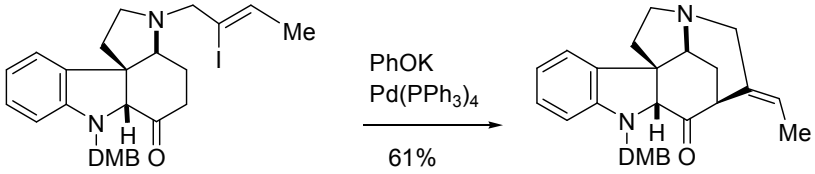
2.32-2.37 (m, 1H), 2.74 (t, 1H, *J* = 3.0 Hz), 3.01 (d, 1H, *J* = 13.5 Hz), 3.05-3.10 (m, 1H), 3.47 (d, 1H, *J* = 3.6 Hz), 3.61 (d, 1H, *J* = 13.5 Hz), 3.80 (s, 3H), 3.82 (s, 3H), 4.26-4.30 (m, 1H), 4.32 (d, 1H, *J* = 16.2 Hz), 4.50 (d, 1H, *J* = 16.2 Hz), 5.86 (q, 1H, *J* = 6.3 Hz), 6.43 (d, 1H, *J* = 8.4 Hz), 6.45 (d, 1H, *J* = 8.4 Hz), 6.49 (s, 1H), 6.68 (t, 1H, *J* = 7.2 Hz), 7.03 (d, 1H, *J* = 8.1 Hz), 7.05 (d, 1H, *J* = 7.2 Hz), and 7.25 (t, 1H, *J* = 8.1 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 18.8, 21.9, 24.8, 39.8, 48.1, 51.2, 53.7, 55.5, 55.6, 65.5, 65.6, 68.2, 73.8, 98.7, 104.2, 107.1, 110.4, 118.0, 119.8, 121.8, 128.2, 129.2, 131.0, 135.3, 152.9, 158.3, and 160.2; HRMS Calcd for $[(C_{27}H_{33}N_2OI)+H]^+$: 561.1609. Found: 561.1623.



190b **191b**

7-(2,4-Dimethoxy-benzyl)-3-(2-iodo-but-2-enyl)-1,2,3,3*a*,4,5,6,6*a*,7-octahydro-pyrrolo[2,3-*d*]carbazol-6-one (191b). To a solution containing 0.12 g (0.21 mmol) of alcohol **190b** and 0.1 g 4Å of molecular sieves in 9.0 mL of CH_3CN at 0 ^{o}C was added 38 mg (0.31 mmol) of NMO (*N*-methyl morpholine-*N*-oxide) and 22 mg (0.06 mmol) of TPAP (tetra-n-propylammonium perruthenate), respectively. After stirring at 0 ^{o}C for 20 min, the cooling bath was removed and the reaction mixture was stirred at rt for an additional 3 h. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to afford

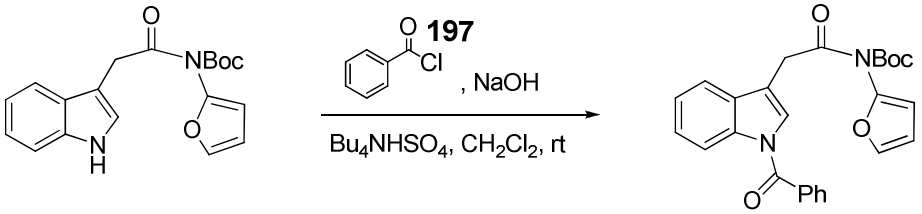
0.09 g (80%) of ketone **191b** as a pale yellow oil; IR (neat) 1711, 1606, 1484, and 1208 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.77 (dd, 3H, *J* = 6.4 and 1.2 Hz), 1.84-1.97 (m, 2H), 2.12-2.22 (m, 2H), 2.29-2.52 (m, 4H), 2.98 (d, 1H, *J* = 14.0 Hz), 3.12-3.17 (m, 1H), 3.59 (s, 1H), 3.59 (dt, 1H, *J* = 14.0 and 1.2 Hz), 3.59 (s, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.12 (d, 1H, *J* = 16.2 Hz), 4.25 (d, 1H, *J* = 16.2 Hz), 5.83 (q, 1H, *J* = 6.4 Hz), 6.38-6.43 (m, 2H), 6.55 (d, 1H, *J* = 7.6 Hz), 6.76 (td, 1H, *J* = 7.6 and 0.8 Hz), and 7.03-7.12 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 20.4, 21.9, 32.5, 37.8, 47.8, 51.6, 55.4, 55.5, 59.1, 64.6, 67.9, 81.8, 98.6, 103.8, 107.5, 108.8, 118.4, 118.7, 122.8, 128.7, 129.5, 131.5, 132.8, 152.7, 158.4, 160.3, and 210.4; HRMS Calcd for $[(C_{27}H_{31}N_2O_3I)+H]^+$: 559.1452. Found: 559.1445.



191b **192b**

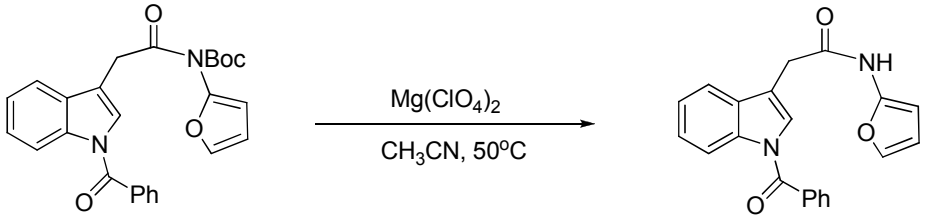
Pentacyclic Ketone 192b. To a solution of 0.09 g (0.16 mmol) of ketone **191b** in 6.0 mL of THF at room temperature was added 46 mg (0.48 mmol) of phenol, 0.4 mL of 1M *t*-BuOK in *t*-BuOH, and 19 mg (0.016 mmol) of $Pd(PPh_3)_4$, respectively. The reaction mixture was heated at reflux under an argon atmosphere for 3 h, and then cooled to room temperature. The mixture was diluted with 1N NaOH and extracted with CH_2Cl_2. The combined organic extracts were washed with 1N NaOH, H_2O, brine, and dried over $MgSO_4$. After

concentrating under reduced pressure, the residue was subjected to silica gel chromatography to give 42 mg (61%) of pentacyclic ketone **192b** as a colorless oil; IR (neat) 1713, 1606, 1485, 1462, and 1207 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.60 (d, 3H, *J* = 6.6 Hz), 2.01 (dd, 1H, *J* = 11.9 and 5.7 Hz), 2.08-2.15 (m, 2H), 2.30 (dt, 1H, *J* = 14.4 and 3.6 Hz), 2.80 (ddd, 1H, *J* = 10.8, 10.8 and 6.6 Hz), 2.97 (d, 1H, *J* = 15.0 Hz), 3.31 (t, 1H, *J* = 8.1 Hz), 3.37 (s, 1H), 3.73 (s, 1H), 3.77-3.81(m, 8H), 4.36 (d, 1H, *J* = 15.6 Hz), 4.49 (d, 1H, *J* = 15.6 Hz), 5.51 (q, 1H, *J* = 6.6 Hz), 6.39 (dd, 1H, *J* = 8.4 and 1.8 Hz), 6.44 (d, 1H, *J* = 1.8 Hz), 6.46 (d, 1H, *J* = 8.4 Hz), 6.69 (t, 1H, *J* = 7.5 Hz), 7.00 (d, 1H, *J* = 7.5 Hz), 7.08 (t, 1H, *J* = 7.5 Hz), and 7.10 (d, 1H, *J* = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 13.6, 24.5, 39.3, 44.6, 46.4, 52.3, 52.9, 55.4, 55.6, 58.6, 61.3, 75.0, 98.6, 103.8, 107.5, 118.0, 118.7, 122.0, 125.5, 129.0, 129.6, 130.2, 132.1, 151.3, 158.6, 160.3, and 210.8; HRMS Calcd for $[(C_{27}H_{30}N_2O_3)+H]^+$: 431.2329. Found: 431.2325.



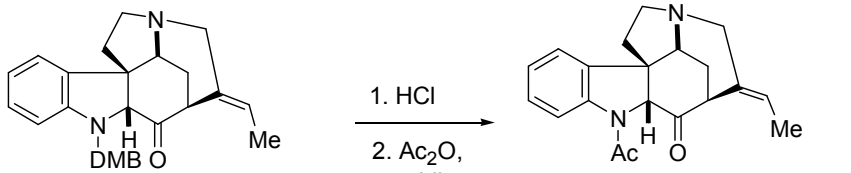
[2-(1-Benzoyl-1H-indol-3-yl)-acetyl]-furan-2-yl-carbamic Acid *tert*-Butyl Ester (198). To a vigorously stirred solution of 1.00 g (2.94 mmol) of indole **196** in 20 mL of CH_2Cl_2 at 0 ^oC was added 0.100 g (0.29 mmol) of teterabutylammonium hydrogensulfate (Bu_4NHSO_4) followed by 0.59 g (14.7 mmol) of freshly powdered NaOH. After stirring for 5 min, 0.85 mL (7.34 mmol) of

benzyl chloride was slowly added and the reaction mixture was stirred at 0 ^{o} C for 15 min and at rt for 15 min. The reaction was then quenched with H_2O and extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.67 g (51%) of the titled compound **198** as a yellow oil: IR (neat) 2983, 1724, 1744, 1671, 1605 and 1593,1364, 1250, 1087 and 743 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 4.22 ;(s, 2H), 6.11 (dd, 1H, *J* = 2.8 and 0.8 Hz), 6.40 (dd, 1H, *J* = 3.6 and 2.4.Hz) .41 (d, 1H, *J* = 8Hz), 7.31 (dd, 1H, *J* = 2.4 and 0.8 Hz), 7.32 – 7.37 (m, 2H), 7.40 (td, 1H, *J* =6.8 and 1.6 Hz), 7.48 – 7.54 (m, 2H), 7.56 – 7.62 (m, 2H), 7.70 – 7.76 (m, 2H), ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.6, 33.7, 84.1, 106.0, 111.3, 114.3, 116.4, 119.1, 123.9, 125.2, 126.5, 128.5, 129.1, 130.7, 131.8, 134.5, 136.0, 140.6, 143.5, 151.4, 168.5 and 172.0. Anal. Calcd. For $C_{26}H_{24}N_2O_5$: C, 70.26; H, 5.44, N, 6.30. Found: C, 70.05; H, 5.42; N, 6.09.



2-(1-Benzoyl-1H-indol-3-yl)-N-furan-2-yl-acetamide (199). To a solution containing 0.60 g (1.35 mmol) of indole **198** in 5.5 mL of CH_3CN was added 0.15 g (0.67 mmol) of Magnesium perchlorate ($Mg(ClO_4)_2$). The solution was heated to 45 ^{o}C for 1 h and the solvent was removed under reduced pressure. The crude

residue was preadsorbed on silica gel and purified by flash silica gel column chromatography to provide 0.38 g (82%) of the titled compound **199** as a yellow oil: IR (neat) 3285, 1667, 1601, 1516, 1352, 739 and 710 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 2H), 6.72 (d, 1H, *J* = 3.2 Hz), 6.30 (t, 1H, *J* = 2.4 Hz), 6.95 (brs, 1H), 7.31 – 7.36 (m, 1H), 7.41 (t, 1H, *J* = 7.6 Hz), 7.47 – 7.62 (m, 1H), 7.71 (d, 2H, *J* = 7.2 Hz), 7.99 (brs, 1H), 8.38 (d, 1H, *J* =8.0 Hz) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 33.1, 95.8, 111.4, 114.2, 116.7, 118.8, 124.3, 125.7, 126.7, 128.7, 129.1, 129.9, 132.1, 134.1, 135.5, 136.4, 144.7, 166.4 and 168.5; HRMS Calcd. for $[(C_{21}H_{16}IN_2O_3) + H]^+$: 345.12433. Found: 345.12337.

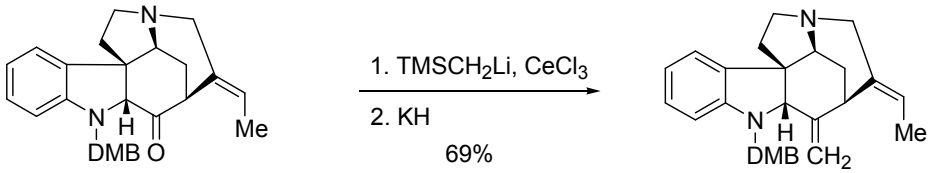


192b **Strychnopivotine (4)**

Strychnopivotine (4). To a flask containing 20 mg (0.047 mmol) of pentacyclic ketone **192b** was added 1.4 mmol of HCl (1.25 M HCl in MeOH) and the mixture was heated at 55 ^{o}C for 5 h. After cooling to room temperature, the reaction mixture was diluted with a saturated K_2CO_3 solution and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to leave behind a yellow oil which was used in the next step without purification: IR (neat) 3352, 2923, 1712, 1604, 1464, and 1109 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.57 (dt, 3H, *J* = 6.8 and 1.6 Hz), 1.73 (d, 1H, *J* = 14.8 Hz), 1.90 (ddd, 1H, *J* = 12.4, 7.6,

and 7.6 Hz), 2.18 (dd, 1H, *J* = 12.4 and 6.4 Hz), 2.48 (dt, 1H, *J* = 14.8 and 3.6 Hz), 2.91 (d, 1H, *J* = 15.2), 2.95-3.00 (m, 1H), 3.38 (dd, 1H, *J* = 10.0 and 8.0 Hz), 3.43 (brs, 1H), 3.77 (s, 1H), 3.90 (brt, 2H, *J* = 7.6 Hz), 4.94 (brs, 1H), 5.57 (q, 1H, *J* = 6.8 Hz), 6.75-6.85 (m, 2H), 6.97 (d, 1H, *J* = 6.8 Hz), and 7.08 (td, 1H, *J* = 7.6 and 1.2 Hz).

The crude residue was taken up in a mixture of 1.0 mL of pyridine and 0.5 mL CH_2Cl_2. To this solution was added 88 µL (0.94 mmol) of Ac_2O and the mixture was then stirred at room temperature for 48 h. The solution was quenched with a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extracts were washed with a saturated $NaHCO_3$ solution, H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to give 9 mg (60%) of strychnopivotine (**4**)[56] as a white solid: IR (neat) 2924, 1645, 1511, 1456, 1246, and 1038 cm^{-1}; ^{1}H-NMR (CD_3CN, 600 MHz) δ 1.54 (dt, 3H, *J* = 7.2 and 1.8 Hz), 1.60 (d, 1H, *J* = 9.0 Hz), 1.76-1.82 (m, 1H), 2.05 (s, 3H), 2.13 (dd, 1H, *J* = 13.2 and 6.0 Hz), 2.56 (dt, 1H, *J* = 9.0 and 3.6 Hz), 2.88 (d, 1H, *J* = 15.0 Hz), 3.00-3.06 (m, 1H), 3.30 (dd, 1H, *J* = 9.9 and 8.1 Hz), 3.45 (s, 1H), 3.83 (d, 1H, *J* = 15.0 Hz), 3.94 (s, 1H), 4.64 (s, 1H), 5.64 (q, 1H, *J* = 7.2 Hz), 7.06 (td, 1H, *J* = 7.2 and 1.2 Hz), 7.16 (d, 1H, *J* = 7.2 Hz), 7.22 (td, 1H, *J* = 7.2 and 1.2 Hz), and 8.13 (d, 1H, *J* = 7.2 Hz); ^{13}C-NMR (CD_3CN, 150 MHz) δ 13.7, 24.2, 26.6, 26.7, 41.5, 47.5, 52.4, 54.2, 59.8, 60.3, 71.2, 72.0, 117.4, 123.2, 123.4, 125.4, 127.2, 127.9, 128.3, 129.2, 129.7, 130.3, 131.8, 133.7, 144.4, 171.2, and 208.5; HRMS Calcd for $[(C_{20}H_{22}N_2O_2)+H]^+$: 323.1754. Found 323.1753.

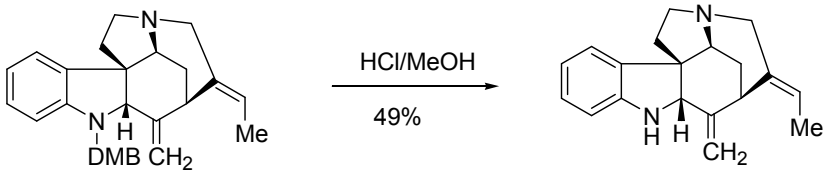


192b **205**

Pentacyclic Alkene 205. A sample of 0.81 g (2.2 mmol) of $CeCl_3$ hydrate was heated at 60 ^oC under reduced pressure for 3 h to remove the water of hydration. After cooling to rt, the crude solid was dissolve in 0.5 mL of THF and the mixture was stirred for 1 h at rt. The mixture was cooled to -78 ^oC and 0.56 mL (0.56 mmol) of 1 M trimethylsilylmethyl lithium in THF was added dropwise. After stirring at -78 ^oC for 30 min, a solution of ketone **192b** in 0.5 mL of THF was added *via* cannula. The solution was allowed to warm to rt, and was then heated at reflux for 12 h. The solution was cooled to rt, and 98 µL (0.65 mmol) of *N,N,N',N'* tetramethylethylene diamine was added in one portion. The mixture was stirred for 30 min, then poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was used in the next step without further purification.

A sample of 0.04 g (0.38 mmol) of potassium hydride (60% in mineral oil) was washed with 5 mL of hexane and was then taken up in 0.5 mL of THF. To this mixture was added the above crude residue in 0.5 mL of THF. The resulting mixture was stirred at rt for 2 h, poured into a saturated aqueous NH_4Cl solution, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The

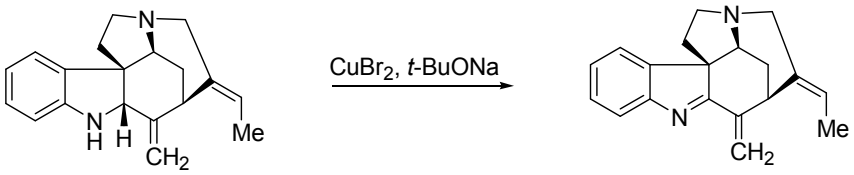
crude residue was purified by flash silica gel column chromatography to give 0.04 g (67%) of the titled compound **205** as a yellow solid: mp 138-142 ^{o}C; IR (neat) 2925, 1607, 1463, 1293, and 1207 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.69 (d, 3H, *J* = 6.4 Hz), 1.94-2.10 (m, 2H), 2.30-2.41 (m, 2H), 3.03 (dt, 2H, *J* = 11.6 and 7.4 Hz), 3.32 (d, 1H, *J* = 14.4 Hz), 3.50-3.56 (m, 1H), 3.58 (s, 1H), 3.72-3.82 (m, 2H), 3.78 (s, 3H), 3.84 (s, 1H), 4.18 (d, 1H, *J* = 16.4 Hz), 4.30 (d, 1H, *J* = 16.4 Hz), 5.14 (d, 1H, *J* = 8.8 Hz), 5.49 (q, 1H, *J* = 6.4 Hz), 6.39 (d, 1H, *J* = 7.6 Hz), 6.40 (d, 1H, *J* = 8.8 Hz), 6.46 (d, 1H, *J* = 2.4 Hz), 6.73 (t, 1H, *J* = 7.6 Hz), and 7.01-7.12 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.5, 24.1, 33.3, 36.6, 45.0, 51.8, 52.6, 54.4, 55.2, 55.3, 63.3, 73.2, 98.4, 203.7, 108.3, 117.8, 118.3, 118.6, 122.2, 125.9, 128.8, 129.4, 131.4, 145.1, 150.6, 157.9, and 160.0; HRMS Calcd for $[(C_{28}H_{32}N_2O_2)+H]^+$: 429.2523. Found: 429.2537.



205 **206**

Pentacyclic Alkene 206. To a flask containing 0.05 g (0.11 mmol) of alkene **205** was added 5 mL of HCl (1.25 M HCl in MeOH) and the mixture was heated at 55 ^{o}C for 5 h. After cooling to rt, the reaction mixture was diluted with a saturated aqueous K_2CO_3 solution and extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue was purified by flash silica gel

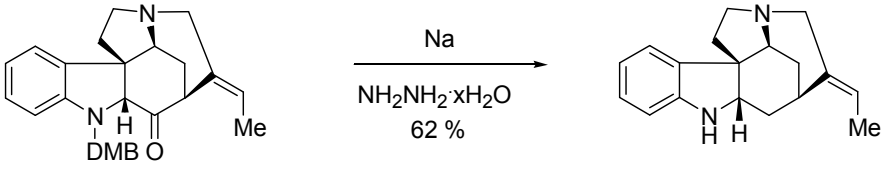
chromatography to give 0.016 g (49%) of the titled compound **206** as a yellow solid: mp 139-141 ^{o}C; IR (neat) 3367, 2925, 1607, 1484, 1464, and 741 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.65 (d, 3H, *J* = 6.8 Hz), 1.88 (dt, 1H, *J* = 13.6 and 2.4 Hz), 1.95-2.09 (m, 2H), 2.16-2.23 (m, 2H), 2.80-2.93 (m, 1H), 3.00 (d, 1H, *J* = 14.8 Hz), 3.18-3.25 (m, 1H), 3.54-3.57 (m, 3H), 4.01 (s, 1H), 4.04 (brs, 1H), 4.98 (s, 2H), 5.38 (q, 1H, *J* = 6.8 Hz), 6.64 (d, 1H, *J* = 7.2 Hz), 6.75 (td, 2H, *J* = 7.2 and 1.2 Hz), and 7.04 (qd, 2H, *J* = 7.2 and 1.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.0, 26.4, 36.3, 38.9, 53.0, 53.7, 55.8, 62.5, 67.1, 109.2, 110.9, 119.0, 120.7, 122.3, 127.9, 132.7, 137.3, 149.9, and 150.0.



206 **valparicine (119)**

Valparicine (119). To a solution containing 0.004 g (0.016 mmol) of $CuBr_2$ in 0.5 mL of THF was added a solution of 0.002 (0.016 mmol) sodium *tert*-butoxide in 0.5 mL of THF by cannula. The resulting mixture was stirred for 15 min at rt, and was then cooled to 0 ^{o}C. To this mixture was added a solution containing 0.002 g (0.007 mmol) of amine **206** in 0.5 mL of THF dropwise. After stirring at 0 ^{o}C for 40 min, the mixture was quenched with an aqueous 3.5 % NH_4OH solution and extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue was purified by flash silica gel column chromatography to give a

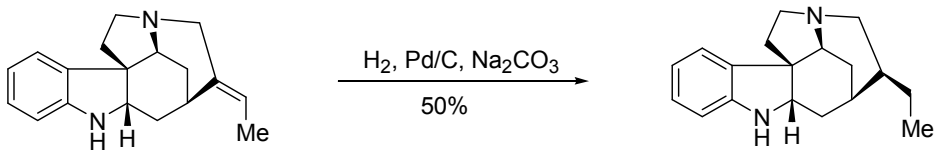
1:1-mixture of the starting material **206** and valparicine (**119**); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.15 -1.38 (2H, m), 1.77 (d, 3H, *J* = 7.2 Hz), 1.97-2.04 (m, 2H), 2.07 (dt, 1H, *J* = 13.8 and 3.0 Hz), 2.42 (ddd, 1H, *J* = 13.2, 9.0 and 6.0 Hz), 3.18 -3.24 (1H, m), 3.26 (d, 1H, *J* = 15.0 Hz), 3.31 (ddd, 1H, *J* = 11.4, 9.0 and 6.0 Hz), 3.73 (d, 1H, *J* = 15.6 Hz), 3.84 (brs, 1H), 5.34 (s, 1H), 5.49 (q, 1H, *J* = 7.2 Hz), 7.22 (t, 1H, *J* = 7.2 Hz), 7.33 (d, 1H, *J* = 7.2 Hz), 7.36 (d, 1H, *J* = 7.2 Hz), and 7.61 (d, 1H, *J* = 7.2 Hz).



192b **201**

19,20-Didehydrotubifolidine (201). To a solution containing 0.07 (0.16 mmol) of ketone **192b** in 10 mL of ethylene glycol at rt was added 1.3 mL (41 mmol) of hydrazine hydrate followed by 0.67 g (29 mmol) of sodium metal. After the sodium had dissolved, the reaction mixture was heated to 160 ^{o}C for 1 h and then at 190 ^{o}C for 1 h. The mixture was further heated at 210 ^{o}C for 3 h, cooled to rt, and extracted with H_2O and CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.03 g (62%) of the titled compound **201** as a white solid: mp 169-171 ^{o}C; IR (neat) 3360, 2925, 1607, 1583, 1465, and 740 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.22-1.33 (m, 2H), 1.55 (dt, 1H, *J* = 14.0 and 2.0 Hz), 1.64

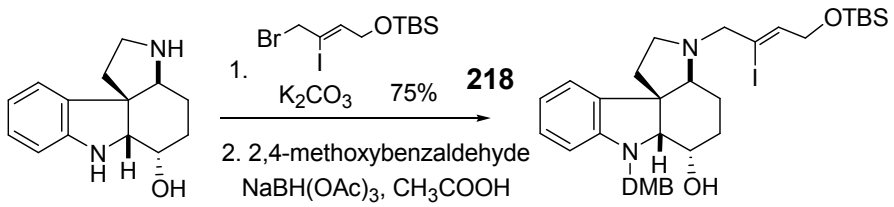
(d, 3H, *J* = 7.2 Hz), 2.03-2.21 (m, 3H), 2.70-2.84 (m, 3H), 3.24 (t, 1H, *J* = 8.8 Hz), 3.45 (dd, 1H, *J* = 10.8 and 6.4 Hz), 3.52 (brs, 1H), 3.72 (d, 1H, *J* = 14.0 Hz), 3.81 (brs, 1H), 5.37 (q, 1H, *J* = 7.2 Hz), 6.65 (d, 1H, *J* = 7.6 Hz), 6.76 (td, 1H, *J* = 7.6 and 0.4 Hz), and 7.04-7.08 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.2, 25.7, 27.8, 36.0, 38.8, 52.0, 53.0, 54.9, 59.2, 60.2, 110.0, 119.0, 121.2, 122.4, 127.8, 131.1, 136.9, and 150.4; HRMS Calcd for $[(C_{18}H_{22}N_2)+H]^+$: 267.1855. Found: 267.1256.



201 **tubifolidine (118)**

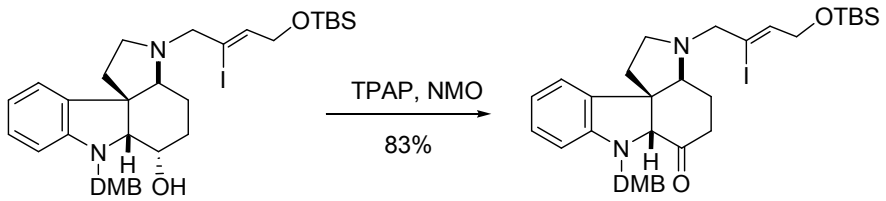
Tubifolidine (118). To a solution containing 0.002 g (0.008 mmol) of dehydrotubifoline **201** in 1 mL of THF at rt under N_2 was added 0.002 g (0.023 mmol) of Na_2CO_3, followed by 0.001 g (0.023 mmol) of 10% Pd/C. The reaction flask was flushed with H_2 and stirred under an H_2 atmosphere overnight. The mixture was filtered through celite, and the solvent was removed under reduced pressure. The crude residue was taken up in CH_2Cl_2 and was acidified with a 1N HCl solution. The aqueous layer was then basified with a 1N NaOH solution and extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give 0.001 g (50%) of tubifoline (**118**) as a white solid: mp 170-176 ^{o}C; IR (neat) 3359, 2924, 1653, 1606, and 1464 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.2 Hz), 1.26-1.40 (m, 4H), 1.74

(dt, 1H, *J* = 13.2 and 3.0 Hz), 1.78-1.80 (m, 1H), 1.86 (ddd, 1H, *J* = 13.2, 10.8 and 2.4 Hz), 1.90-1.94 (m, 1H), 1.98-2.03 (m, 1H), 2.08 (t, 1H, *J* = 12.0 Hz), 2.42 (dt, 1H, *J* = 13.2 and 8.4 Hz), 2.85 (t, 1H, *J* = 10.8 Hz), 3.02-3.11 (m, 1H), 3.13-3.12 (m, 1H), 3.37 (brs, 1H), 3.62-3.66 (m, 1H), 6.63 (d, 1H, *J* = 7.8 Hz), 6.77 (t, 1H, *J* = 7.8 Hz), and 7.03-7.06 (m, 2H); HRMS Calcd for $[(C_{18}H_{24}N_2)+H]^+$: 269.20123. Found: 269.20093.



3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-2-iodo-but-2-enyl]-7-(2,4-dimethoxy-benzyl)-2,3,3*a*,4,5,6,6*a*,7-octahydro-1*H*-pyrrolo[2,3-d]carbazol-6-ol (220). To a solution of 27 mg (0.12 mmol) of amine **187** in 2.0 mL of DMF at room temperature was added 0.5 mL of H_2O and 81 mg (0.6 mmol) of K_2CO_3. The resulting mixture was cooled to 0 ^oC and a solution of 55 mg (0.14 mmol) of (4-bromo-3-iodo-but-2-enyloxy)-tert-butyl-dimethyl-silane **218**[154] in 0.5 mL of DMF was added. The reaction mixture was stirred at 0 ^oC for 12 h and was quenched with Et_2O and H_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to give 47 mg (75%) of the mono-alkylated product as a pale yellow oil.

To a flask containing 35 mg (0.06 mmol) of the above compound was added 2.0 mL of $ClCH_2CH_2Cl$. To the resultant solution at 0 ^oC was added 13 mg (0.08 mmol) of 2,4-methoxybenzaldehyde and 34 mg (0.16 mmol) of $NaBH(OAc)_3$, followed by the addition of 11 μL (0.19 mmol) of CH_3COOH. The reaction mixture was stirred at 0 ^oC for 10 min, and then at rt for 12 h. The reaction mixture was quenched with a saturated K_2CO_3 solution, and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to give 37 mg (84%) of alcohol **220** as a colorless oil; IR (neat) 3469, 1606, 1484, 1254, 1109, and 836 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz) δ 0.09 (s, 6H), 0.91 (s, 9H), 1.51-1.66 (m, 2H), 1.71-1.80 (m, 1H), 1.92-2.08 (m, 3H), 2.37 (td, 1H, *J* = 9.6 and 0.8 Hz), 2.78 (t, 1H, *J* = 3.2 Hz), 3.02 (d, 1H, *J* = 13.8 Hz), 3.03-3.11 (m, 1H), 3.47 (d, 1H, *J* = 4.0 Hz), 3.59 (dd, 1H, *J* = 13.8 and 1.6 Hz), 3.81 (s, 3H), 3.82 (s, 3H), 4.22-4.32 (m, 1H), 4.27 (d, 1H, *J* = 4.8 Hz), 4.32 (d, 1H, *J* = 16.4 Hz), 4.50 (d, 1H, *J* = 16.4 Hz), 6.07 (t, 1H, *J* = 4.8 Hz), 6.42-6.49 (m, 3H), 6.80 (td, 1H, *J* = 7.6 and 0.8 Hz), 7.02-7.06 (m, 2H), and 7.24 (d, 1H, *J* = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ -4.9, 18.5, 18.8, 24.8, 26.1, 39.8, 48.1, 51.3, 53.6, 55.5, 55.6, 65.3, 65.4, 68.2, 68.3, 73.7, 98.7, 104.2, 106.5, 107.1, 118.0, 119.7, 121.8, 128.3, 129.2, 135.2, 136.4, 152.9, 158.2, and 160.2; HRMS Calcd for $[(C_{33}H_{47}N_2O_4ISi)+H]^+$: 691.2422. Found: 691.2413.



220 **221**

3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-2-iodo-but-2-enyl]-7-(2,4-dimethoxy-benzyl)-2,3,3*a*,4,5,6,6*a*,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-one (221). To a flask containing 48 mg (0.07 mmol) of alcohol **220** and 35 mg of 4Å of molecular sieves in 2.0 mL of CH_3CN at 0 ^oC was added 12 mg (0.10 mmol) of NMO (*N*-methyl morpholine-*N*-oxide) and 7.3 mg (0.02 mmol) of TPAP (tetra-*n*-propylammonium perruthenate), respectively. After stirring at 0 ^oC for 10 min, the cooling bath was removed and the reaction mixture was stirred at rt for an additional 2 h. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 40 mg (83%) of ketone **221** as a colorless oil; IR (neat) 1713, 1606, 1484, 1462, and 1256 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.09 (s, 6H), 0.91 (s, 9H), 1.84-1.97 (m, 2H), 2.12-2.22 (m, 2H), 2.28-2.40 (m, 2H), 2.41-2.54 (m, 2H), 2.95 (d, 1H, *J* = 13.8 Hz), 3.11-3.16 (m, 1H), 3.56 (dd, 1H, *J* = 13.8 and 1.6 Hz), 3.60 (s, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.13 (d, 1H, *J* = 16.0 Hz), 4.23-4.27 (m, 3H), 6.04 (t, 1H, *J* = 4.8 Hz), 6.40 (dd, 1H, *J* = 8.0 and 2.0 Hz), 6.43 (d, 1H, *J* = 2.0 Hz), 6.55 (d, 1H, *J* = 8.0 Hz), 6.77 (td, 1H, *J* = 7.4 and 0.8 Hz), and 7.03-7.13 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ -4.9, 18.5, 20.4, 26.1, 32.5, 37.8, 47.3, 51.6, 55.4, 55.5, 58.9, 64.3, 67.9, 68.2, 81.7, 98.6,

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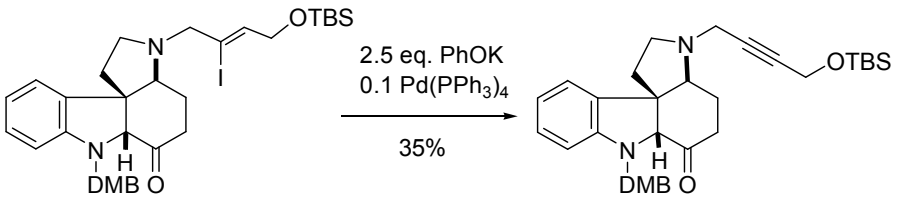
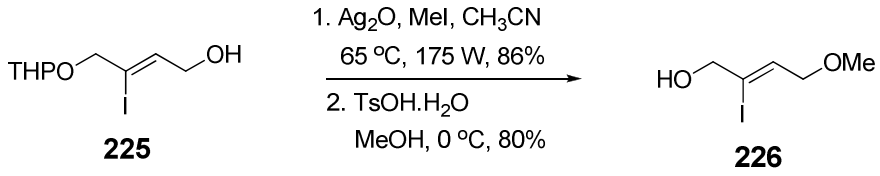


221 **222**

3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-but-2-ynyl]-7-(2,4-dimethoxybenzyl)-2,3,3*a*,4,5,6,6*a*,7-octahydro-pyrrolo[2,3-*d*]carbazol-6-one (222). To a solution of 38 mg (0.06 mmol) of vinyl iodide **221** in 2.0 mL of THF at rt was added 14 mg (0.15 mmol) of phenol, 0.14 mL of 1M *t*-BuOK in *t*-BuOH, and 6.4 mg (0.006 mmol) of $Pd(PPh_3)_4$, respectively. The reaction mixture was heated at reflux under argon for 6 h, cooled to rt, diluted with 1N NaOH and extracted with CH_2Cl_2. The combined organic extracts were washed with a 1N NaOH solution, H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to give 11 mg (35%) of alkyne **222** as a colorless oil; IR (neat) 1712, 1605, 1484, 1115, and 836 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.12 (s, 6H), 0.91(s, 9H), 1.80-1.86 (m, 1H), 1.91-1.99 (m, 1H), 2.12-2.21 (m, 3H), 2.33-2.40 (m, 1H), 2.61 (d, 1H, *J* = 3.2 Hz), 2.85 (q, 1H, *J* = 8.8 Hz), 3.01 (ddd, 1H, *J* = 14.8, 4.8 and 3.6 Hz), 3.37 (dt, 1H, *J* = 17.4 and 1.6 Hz), 3.48 (dt, 1H, *J* = 17.4 and 1.6 Hz), 3.59 (s, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.11 (d, 1H, *J* = 16.0 Hz), 4.22 (d, 1H, *J* = 16.0 Hz), 4.33 (t, 1H, *J* = 1.6 Hz), 6.40 (dd, 1H, *J* = 8.0 and 2.4 Hz), 6.43 (d, 1H, *J* = 2.4 Hz), 6.52 (d, 1H, *J*

= 8.0 Hz), 6.78 (td, 1H, *J* = 7.2 and 0.4 Hz), and 7.04-7.12 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ -4.9, 18.5, 19.7, 26.1, 32.4, 38.1, 39.1, 47.9, 50.4, 52.0, 55.4, 55.5, 58.9, 65.4, 78.8, 82.0, 84.1, 98.6, 103.8, 108.7, 118.5, 118.8, 123.0, 128.7, 129.1, 132.9, 152.7, 158.3, 160.2, and 211.1.

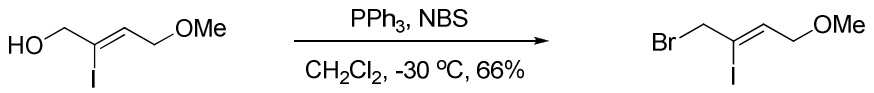


225 **226**

2-Iodo-4-methoxy-but-2-en-1-ol (225). To a solution of 0.3 g (1.0 mmol) of alkene **223** in 2.0 mL of CH_3CN in a microwave tube equipped with a magnetic stir bar was added 0.28 g (1.2 mmol) of Ag_2O and 1.3 mL (20 mmol) of MeI. The vessel was sealed with a microwave rubber cap and the sample was placed in the microwave reactor and irradiated at 175 W, 65 ^{o}C for 3 h with cooling. After cooling to rt, the mixture was filtered through celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure to give 0.26 g (86 %) of the di-protected alcohol as a pale yellow oil which was used for the next step without further purification.

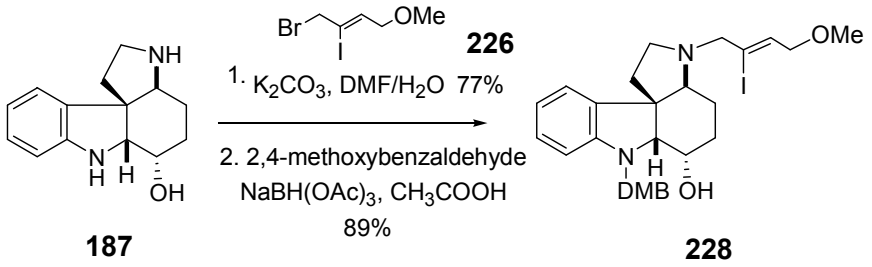
To a solution of 0.63 g (2.0 mmol) of the di-protected alcohol in 8 mL of MeOH at 0 ^{o}C was added 0.04 g (0.2 mmol) of *p*-toluenesulfoic acid. The reaction mixture was stirred at 0 ^{o}C for 1 h, and was then quenched with an aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column

chromatography to give 0.37 g (80%) of the titled compound **225** as a colorless oil; IR (thin film) 3379, 1650, 1442, 1188, 1091 and 1013 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.25 (s, 3H), 3.97 (d, 2H, *J* = 5.6 Hz), 4.13 (s, 2H), 6.09 (t, 1H, *J* = 5.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 58.1, 70.5, 75.6, 109.0 and 130.6.



225 **226**

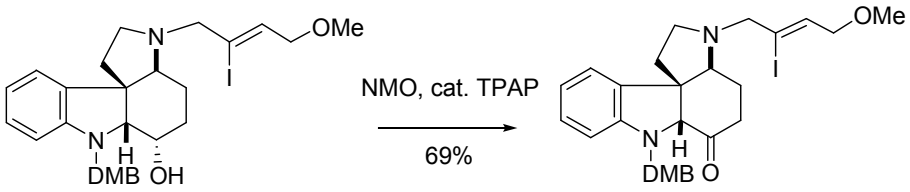
1-Bromo-2-iodo-4-methoxy-but-2-ene (226). To a solution of 0.37 g (1.6 mmol) of the above alcohol **225** in 23 mL of CH_2Cl_2 at -30 ^{o}C was added 0.5 g (1.9 mmol) of PPh_3 and 0.4 g (2.3 mmol) of *N*-bromosuccinimide. The reaction mixture was maintained at -30 ^{o}C for 1 h, diluted with Et_2O and extracted with an aqueous $NaHCO_3$ solution. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.31 g (66%) of the titled compound **226** as a colorless oil; IR (thin film) 2927, 2816, 1641, 1448, 1219 and 1112 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.97 (d, 2H, *J* = 5.6 Hz), 4.30 (d, 2H, *J* = 0.8Hz), and 6.22 (t, 1H, *J* = 5.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 42.2, 58.4, 76.1, 101.4, and 137.3.



7-(2,4-Dimethoxybenzyl)-3-(2-iodo-4-methoxy-but-2-enyl)-2,3,3*a*,4,5,6,6*a*,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol (228). To a solution of 24 mg (0.1 mmol) of amine **187** in 1.5 mL of DMF at rt was added 0.4 mL of H_2O and 72 mg (0.5 mmol) of K_2CO_3. The resulting mixture was cooled to 0 ^oC, and this was followed by the addition of a solution of 36 mg (0.13 mmol) of 1-bromo-2-iodo-4-methoxy-but-2-ene (**226**) in 0.5 mL of DMF. The reaction mixture was stirred at 0 ^oC for 12 h and quenched with Et_2O and H_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to provide 35 mg (77%) of the mono-alkylated product as a pale yellow oil.

To a flask containing 31 mg (0.07 mmol) of the above compound was added 2.0 mL of $ClCH_2CH_2Cl$. To the resultant solution at 0 ^oC was added 14 mg (0.08 mmol) of 2,4-methoxybenzaldehyde and 37 mg (0.18 mmol) of $NaBH(OAc)_3$, followed by the addition of 12 µL (0.21 mmol) of CH_3COOH. The reaction mixture was stirred at 0 ^oC for 10 min, and then at rt for 12 h. The reaction was quenched with a saturated K_2CO_3 solution, and extracted with CH_2Cl_2. The combined organics were washed with H_2O, brine, and dried over

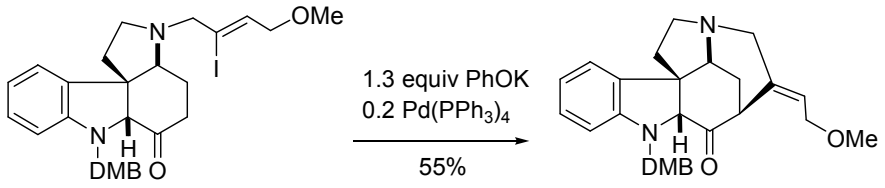
$MgSO_4$. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to give 37 mg (89%) of alcohol **228** as a colorless oil; IR (neat) 3456, 1673, 1606, and 1485 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.54-1.62 (m, 2H), 1.71-1.78 (m, 2H), 1.92-2.05 (m, 4H), 2.35-2.40 (m, 1H), 2.79 (t, 1H, *J* = 3.4 Hz), 3.05 (d, 1H, *J* = 13.8 Hz), 3.10 (td, 1H, *J* = 8.7 and 6.0 Hz), 3.36 (s, 3H), 3.46 (d, 1H, *J* = 3.0 Hz), 3.61 (d, 1H, *J* = 13.8 Hz), 3.80 (s, 3H), 3.82 (s, 3H), 4.05 (d, 1H, *J* = 5.7 Hz), 4.23-4.27 (m, 1H), 4.32 (d, 1H, *J* = 16.2 Hz), 4.49 (d, 1H, *J* = 16.2 Hz), 6.09 (t, 1H, *J* = 5.7 Hz), 6.42-6.46 (m, 2H), 6.48 (d, 1H, *J* = 1.8 Hz), 6.68 (t, 1H, *J* = 7.8 Hz), 7.02 (d, 1H, *J* = 7.8 Hz), 7.03 (t, 1H, *J* = 7.8 Hz), and 7.23 (d, 1H, *J* = 7.8 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 18.8, 24.7, 39.7, 48.0, 51.3, 53.5, 55.4, 55.5, 58.5, 65.4, 65.6, 68.0, 73.6, 76.4, 98.7, 104.1, 107.1, 110.0, 118.0, 119.6, 121.7, 128.2, 129.1, 132.9, 135.1, 152.8, 158.2, and 160.1; HRMS calcd for $[(C_{28}H_{35}N_2O_4I)+H]^+$: 591.1714. Found: 591.1704.



228 **229**

7-(2,4-Dimethoxy-benzyl)-3-(2-iodo-4-methoxy-but-2-enyl)-2,3,3*a*,4,5,6,6*a*,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-one (229). To a flask containing 75 mg (0.13 mmol) of alcohol **228** and 64 mg of 4Å of molecular sieves in 3.0 mL of CH_3CN at 0 ^oC was added 23 mg (0.19 mmol) of NMO (*N*-methyl-morpholine-*N*-

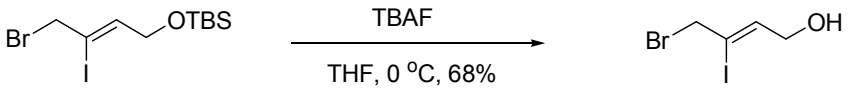
oxide) and 13 mg (0.04 mmol) of TPAP (tetra-*n*-propylammonium perruthenate), respectively. After stirring at 0 ^{o}C for 10 min, the cooling bath was removed and the solution was stirred at room temperature for an additional 1 h. The reaction mixture was filtered through celite to remove molecular sieves and the filtrate was concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 52 mg (69%) of ketone **229** as a colorless oil; IR (neat) 1711, 1606, 1484, 1208, and 736 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.84-1.96 (m, 2H), 2.14-2.21 (m, 2H), 2.31-2.49 (m, 3H), 2.53 (d, 1H, *J* = 3.6 Hz), 2.99 (d, 1H, *J* = 12.9 Hz), 3.14-3.18 (m, 1H), 3.36 (s, 3H), 3.59 (d, 1H, *J* = 12.9 Hz), 3.60 (s, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.00-4.06 (m, 1H), 4.12 (d, 1H, *J* = 15.9 Hz), 4.25 (d, 1H, *J* = 15.9 Hz), 6.06 (t, 1H, *J* = 4.8 Hz), 6.39 (dd, 1H, *J* = 8.6 and 2.0 Hz), 6.43 (d, 1H, *J* = 2.0 Hz), 6.77 (t, 1H, *J* = 7.5 Hz), and 7.04-7.11 (m, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 20.4, 32.5, 37.8, 47.7, 51.7, 55.4, 55.5, 58.5, 59.0, 64.5, 67.9, 76.4, 81.7, 98.6, 103.9, 107.0, 108.8, 118.4, 118.7, 122.8, 128.8, 129.5, 132.7, 133.7, 152.7, 158.4, 160.3, and 210.2.



229 **230**

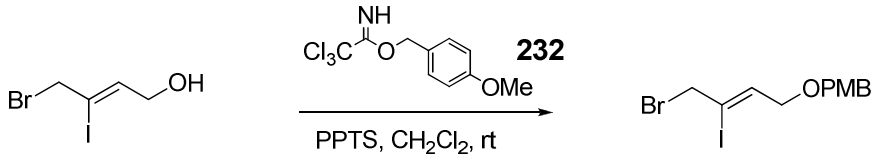
Pentacyclic Ketone 330. To a solution of 24 mg (0.04 mmol) of vinyl iodide **229** in 1.0 mL of THF at room temperature was added 9.4 mg (0.004 mmol) of $Pd(PPh_3)_4$ and a solution of PhOK in THF (prepared from the addition of 49 µL

of 1M ^{t}BuOK in ^{t}BuOH into a solution of 5.8 mg (0.06 mmol) of phenol in 1.5 mL of THF). The reaction mixture was heated at reflux under argon for 1h, cooled to rt, diluted with a 1N NaOH solution and then extracted with CH_2Cl_2. The combined organic extracts were washed with 1N NaOH, H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to silica gel chromatography to provide 10 mg (55%) of the enolate coupling product **230** as a pale yellow oil; IR (neat) 1711, 1607, 1484, and 1208 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.94 (dd, 1H, *J* = 12.8 and 5.2 Hz); 2.17-2.32 (m, 3H), 2.68-2.75 (m, 1H), 3.05 (d, 1H, *J* = 15.6 Hz), 3.24 (t, 1H, *J* = 8.4 Hz), 3.32 (s, 4H), 3.69-3.79 (m, 8H), 3.82 (d, 1H, *J* = 15.6 Hz), 3.94 (dd, 1H, *J* = 12.4 and 5.0 Hz), 4.05 (dd, 1H, *J* = 12.4 and 8.2 Hz), 4.30 (d, 1H, *J* = 16.0 Hz), 4.37 (d, 1H, *J* = 16.0 Hz), 5.58 (dd, 1H, *J* = 8.2 and 5.0 Hz), 6.40 (dd, 1H, *J* = 8.0 and 2.2 Hz), 6.44 (d, 1H, *J* = 2.2 Hz), 6.48 (d, 1H, *J* = 8.0 Hz), 6.73 (td, 1H, *J* = 7.4 and 0.6 Hz), and 7.03-7.11 (m, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 23.5, 38.7, 44.1, 46.9, 51.9, 52.5, 55.4, 55.6, 58.4, 58.5, 62.0, 68.6, 76.5, 98.6, 103.8, 108.4, 118.6, 118.8, 122.3, 126.6, 128.9, 129.4, 130.7, 136.7, 151.8, 158.5, 160.3, and 209.6; HRMS calcd for $[(C_{28}H_{32}N_2O_4)+H]^{+}$: 461.2434. Found: 461.2420.



28 **38**

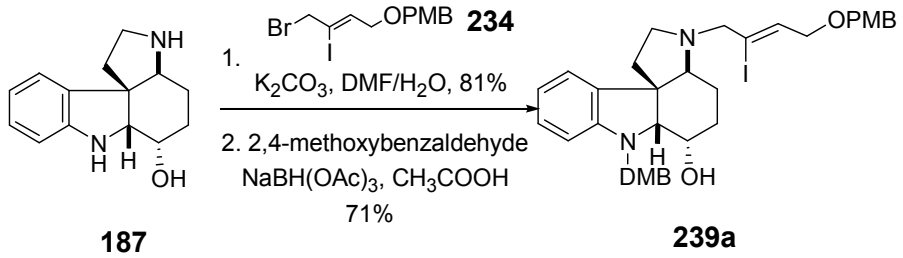
4-Bromo-3-iodo-but-2-en-1-ol (233). To a solution 0.22 g (0.56 mmol) of bromide **218**[155] in 2.2 mL of THF at 0 °C was added 0.62 mL (0.62 mmol) of tetrabutylammonium fluoride dropwise. The reaction mixture was stirred for 5 min, and was then quenched with an aqueous NH_4Cl solution and washed with Et_2O. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.35 g (68%) of the titled compound **283** as a colorless oil; IR (thin film) 3297, 1626, 1418, 1209, 1087 and 1005 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.20 (brs, 1H), 4.21 (d, 2H, *J* = 5.2 Hz) and 4.33 (s, 2H), 6.28 (t, 1H, *J* = 5.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 42.2, 67.0, 101.1 and 139.0.



233 **234**

1-(4-Bromo-3-iodo-but-2-enyloxymethyl)-4-methoxy-benzene (234). To a solution of 0.2 g (0.72 mmol) of alcohol **233** in 3 mL of CH_2Cl_2 at rt was added 0.1 g (0.36 mmol) of *p*-methoxy benzyltrichlorosuccinimidate **232** and 0.005 g (0.02 mmol) of pyridinium *p*-toluenesulfonate. The reaction mixture was stirred at rt for 2 h and then hexane was added which resulted in the precipitation of a

white solid. After being filtered through celite to remove the solid, the solvent was removed from the filtrate under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.25 g (86%) of the titled compound **234** as a colorless oil; IR (thin film) 1610, 1585, 1507, 1237 and 1025 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 1H), 4.07 (d, 2H, *J* = 5.6 Hz), 4.31 (s, 2H), 4.45 (s, 2H), 6.28 (t, 1H, *J* = 5.6 Hz), 6.88 (d, 2H, *J* = 8.0 Hz) and 7.26 (d, 2H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 42.3, 55.2, 72.4, 73.7, 101.4, 113.8, 129.5, 129.6, 137.6. and 159.3.



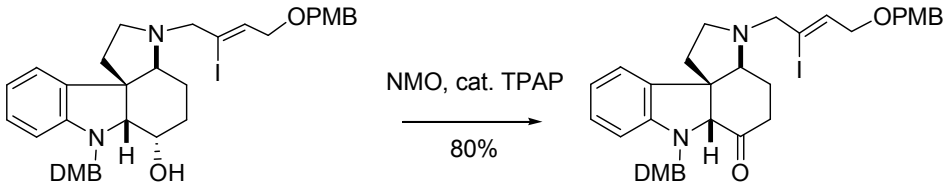
187 **239a**

7-(2,4-Dimethoxy-benzyl)-3-[2-iodo-4-(4-methoxy-benzyloyl)-but-2-enyl]-2,3,3*a*,4,5,6, 6*a*,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol (239a). To a solution of 0.98 g (0.21 mmol) of amine **187** in 2.5 mL of DMF at room temperature was added 0.6 ml of H_2O and 0.14 g (1.0 mmol) of K_2CO_3. The resulting mixture was cooled to 0 ^{o}C, and this was followed by the addition of a solution of 0.1 g (0.25 mmol) of 1-(4-bromo-3-iodo-but-2-enyloxymethyl)-4-methoxy-benzene (**234**) in 0.5 ml of DMF. The reaction mixture was stirred at 0 ^{o}C for 12h and quenched with Et_2O and H_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with H_2O, brine, and dried over $MgSO_4$. After concentration under

reduced pressure, the residue was subjected to flash silica gel chromatography to afford 92 mg (81%) of the mono-alkylated product as a yellow oil.

To a flask containing 86 mg (0.16 mmol) of the above compound was added 3.2 ml of $ClCH_2CH_2Cl$. To the resultant solution at 0 ^oC was added 29 mg (0.17 mmol) of 2,4-methoxybenzaldehyde and 83 mg (0.39 mmol) of $NaBH(OAc)_3$, followed by the addition of 27 µL (0.47 mmol) of CH_3COOH. The reaction mixture was stirred at 0 ^oC for 5 min, and then at room temperature for 12 h. The reaction mixture was quenched with a saturated K_2CO_3 solution, and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to afford 78 mg (71%) of alcohol **239a** as a colorless oil: IR (neat) 3469, 1611, 1505, 1250, and 1036 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.51-1.60 (m, 2H), 1.67 (d, 1H, *J* = 6.0 Hz), 1.71-1.80 (m, 1H), 1.91-2.07 (m, 3H), 2.37 (td, 1H, *J* = 9.2 and 6.4 Hz), 2.79 (t, 1H, *J* = 3.2 Hz), 3.05 (d, 1H, *J* = 13.6 Hz), 3.10 (td, 1H, *J* = 9.2 and 4.2 Hz), 3.47 (d, 1H, *J* = 4.0 Hz), 3.62 (dd, 1H, *J* = 13.6 and 1.6 Hz), 3.80 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 4.14 (d, 1H, *J* = 5.6 Hz), 4.22-4.29 (m, 1H), 4.33 (d, 1H, *J* = 16.4 Hz), 4.46 (s, 2H), 4.50 (d, 1H, *J* = 16.4 Hz), 6.13 (t, 1H, *J* = 5.6 Hz), 6.43-6.49 (m ,3H), 6.68 (td, 1H, *J* = 7.6 and 0.8 Hz), 6.89 (dt, 2H, *J* = 8.4 and 2.6 Hz), 7.03 (d, 2H, *J* = 8.4 Hz) 7.23-7.30 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 18.8, 24.7, 39.8, 48.1, 51.3, 53.6, 55.4, 55.5, 55.6, 65.4, 65.6, 68.1, 72.5, 73.6, 74.1, 98.7, 104.1, 107.1, 109.5, 114.0, 118.0, 119.7, 121.8, 128.3, 129.2, 129.8, 130.2,

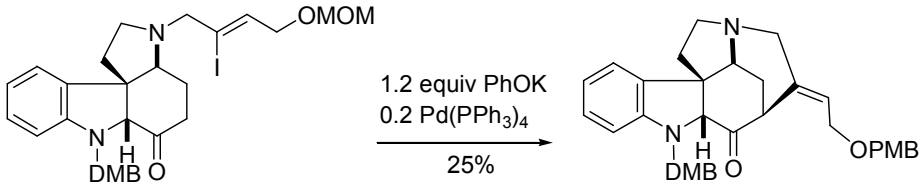
133.3, 135.2, 152.8, 158.2, 159.5, 160.2; HRMS calcd for $[(C_{35}H_{41}N_2O_5I)+H]^+$: 697.2133. Found: 697.2122.



239a **240a**

7-(2,4-Dimethoxy-benzyl)-3-[2-iodo-4-(4-methoxybenzyloxy)-but-2-enyl)-2,3,3*a*,4,5,6,6*a*,7-octahydro-pyrrolo[2,3-*d*]carbazol-6-one (240a). To a flask containing 0.17 g (0.24 mmol) of alcohol **239a** and 0.12 g of 4Å of molecular sieves in 8 ml of CH_3CN at 0 ^oC was added 44 mg (0.37 mmol) of NMO (*N*-methyl morpholine-*N*-oxide), followed by the addition of 0.26 g (0.07 mmol) of TPAP (tetra-*n*-propylammonium perruthenate) *via* several portions. After stirring at 0 ^oC for 10 min, the cooling bath was removed and the reaction mixture was stirred at rt for an additional 1 h. The reaction mixture was then filtered through celite to remove molecular sieves and the filtrate was concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to afford 0.14 g (80%) of ketone **240a** as a yellow oil; IR (neat) 1710, 1606, 1510, and 1248 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.84-1.89 (m, 1H), 1.91-1.97 (m, 1H), 2.14-2.22 (m, 2H), 2.30-2.39 (m, 2H), 2.42-2.51 (m, 1H), 2.53 (d, 1H, *J* = 3.6 Hz), 2.97 (d, 1H, *J* = 14.4 Hz), 3.12-3.16 (m, 1H), 3.57 (d, 1H, *J* = 14.4 Hz), 3.60 (s, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 4.08-4.12 (m, 2H), 4.12 (d, 1H, *J* = 16.2 Hz), 4.24 (d, 1H, *J* = 16.2 Hz), 4.46 (s, 2H), 6.11 (t, 1H, *J* = 5.1 Hz), 6.40

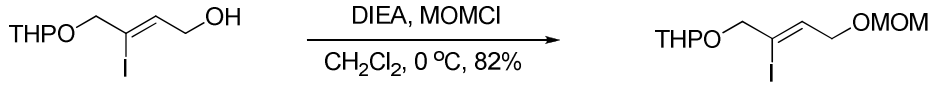
(dd, 1H, *J* = 8.1 and 2.1 Hz), 6.43 (d, 1H, *J* = 2.1 Hz), 6.55 (d, 1H, *J* = 8.1 Hz), 6.77 (t, 1H, *J* = 7.8 Hz), 6.89 (d, 2H, *J* = 9.0 Hz), 7.04 (d, 1H, *J* = 7.8 Hz), 7.06 (d, 1H, *J* = 7.8 Hz), 7.10 (t, 1H, *J* =7.8 Hz), and 7.28 (d, 2H, *J* = 9.0 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 20.4, 32.5, 37.8, 47.7, 51.7, 55.4, 55.5, 55.6, 59.0, 64.4, 67.9, 72.5, 74.0, 81.7, 98.6, 103.9, 106.9, 108.8, 114.0, 118.4, 118.7, 122.8, 128.8, 129.5, 129.8, 130.2, 132.7, 134.0, 152.7, 158.4, 159.5, 160.3, and 210.2.



240a **241a**

Pentacyclic Ketone 241a. To a solution containing 63 mg (0.09 mmol) of vinyl iodide **240a** in 2.0 ml of THF at room temperature was added 21 mg (0.02 mmol) of $Pd(PPh_3)_4$ and a solution of PhOK in THF (prepared from the addition of 0.11 ml of 1M *t*-BuOK in *t*-BuOH into a solution of 13 mg (0.14 mmol) of phenol in 3 ml of THF). The reaction mixture was heated at reflux under argon for 2 h, cooled to room temperature, diluted with a 1N NaOH solution and extracted with CH_2Cl_2. The combined organic extracts were washed with 1N NaOH, H_2O, brine, and dried over $MgSO_4$. After concentrating under reduced pressure, the residue was subjected to silica gel chromatography to afford 13 mg (25%) of the enolate coupling product **241a** as a yellow oil; IR (neat) 1713, 1610, 1510, 1462, and 1249 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.93 (dd, 1H, *J* = 12.9, and 5.1 Hz); 2.17-2.30 (m, 3H), 2.68-2.73 (m, 1H), 3.03 (d, 1H, *J* = 15.6 Hz), 3.22 (t, 1H, *J* =

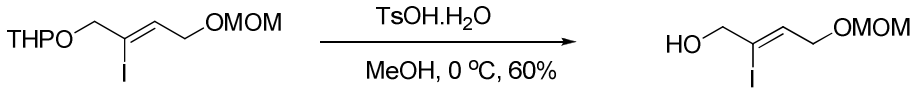
8.1 Hz), 3.30 (s, 1H), 3.67 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 3.80 (d, 1H, *J* = 15.6 Hz), 4.05 (dd, 1H, *J* = 12.6 and 4.2 Hz), 4.15 (dd, 1H, *J* = 12.6 and 8.1 Hz), 4.28 (d, 1H, *J* = 16.2 Hz), 4.36 (d, 1H, *J* = 16.2 Hz), 4.41 (d, 1H, *J* = 11.1 Hz), 4.44 (d, 1H, *J* = 11.1 Hz), 5.61 (dd, 1H, *J* = 8.1 and 4.2 Hz), 6.37 (dd, 1H, *J* = 7.5 and 2.2 Hz), 6.43 (d, 1H, *J* = 2.2 Hz), 6.47 (d, 1H, *J* = 7.5 Hz), 6.73(t, 1H, *J* = 7.5 Hz), 6.84 (d, 2H, *J* = 8.4 Hz), 7.02-7.09 (m, 3H), and 7.25 (d, 2H, *J* = 8.4 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 23.4, 38.8, 44.0, 46.9, 51.9, 52.6, 55.4, 55.5, 55.6, 58.3, 62.1, 66.2, 72.5, 76.6, 98.6, 103.8, 108.4, 114.0, 118.6, 118.7, 122.3, 126.8, 128.9, 129.4, 129.7, 130.5, 130.7, 136.5, 151.8, 158.5, 159.4, 160.3, and 209.6; HRMS Calcd for $[(C_{35}H_{38}N_2O_5)+H]^+$ 567.2853. Found 567.2849.



223 **235**

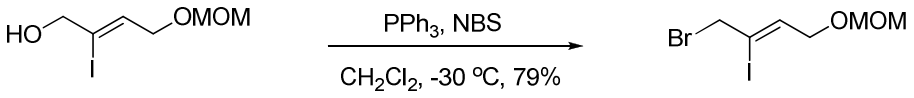
2-(2-Iodo-4-methoxymethoxy-but-2-enyloxy)-tetrahydropyran (235). To a solution of 1.0 g (3.4 mmol) of alcohol **223** in 13 mL of CH_2Cl_2 at 0 °C was added 0.13 mL (0.81 mmol) of di-isopropyl ethylamine followed with 0.06 mL (0.81 mmol) of chloromethyl methyl ether. The reaction mixture was stirred at 0 °C for 5 h, then diluted with CH_2Cl_2 and washed with an aqueous $NaHCO_3$ solution. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.95 g (82%) of the titled compound **235** as a colorless oil; IR (thin film) 1654, 1450, 1447, 1201, and 1021 cm^{-1}; ^{1}H-

NMR (400 MHz, $CDCl_3$) δ 1.45 - 1.90 (m, 5 H), 3.71 (s, 3H), 3.48 - 3.55 (m, 1H), 3.86 (ddd, 1H, *J* = 12.4, 9.2 and 3.2 Hz), 4.16 - 4.21 (m, 3H), 4.64 (s, 2H), 4.68 (t, 1H, *J* = 3.2 Hz), and 6.22 (tt, 1H, *J* = 5.6 and 1.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.7, 25.3, 30.3, 55.4, 62.0, 71.1, 74.2, 96.1, 97.1, 104.6, and 133.3.



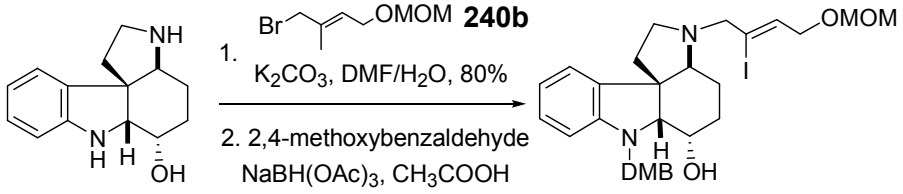
235 **236**

2-Iodo-4-methoxymethoxy-but-2-en-1-ol (236). To a solution of 1.7 g (4.9 mmol) of the alkene **235** in 49 mL of MeOH at 0 °C was added 0.09 g (0.49 mmol) of *p*-toluenesulfonic acid .The reaction mixture was stirred for 0 °C for 1 h, then was quenched with an aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.76 g (60%) of the titled compound **236** as a colorless oil; IR (thin film) 3403, 2934, 1655, 1446, and 1037 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.91 (t, 1H, *J* = 6.8 Hz), 3.38 (s, 3H), 4.17 (dt, 2H, *J* = 5.6 and 1.2 Hz), 4.23 (dd, 2H, *J* = 6.8 and 1.2 Hz), 4.62 (s, 2H), and 6.21 (tt, 1H, *J* = 5.6 and 1.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 55.4, 70.9, 71.0, 96.0, 108.9, and 131.5.



236 **237**

1-Bromo-2-iodo-4-methoxymethoxy-but-2-ene (237). To a solution of 0.48 g (1.9 mmol) of alcohol **236** in 28 mL of CH_2Cl_2 at -30 ^oC was added 0.59 g (2.2 mmol) of triphenyl phosphine followed with 0.46 g (2.6 mmol) of *N*-bromosuccinimide. The reaction mixture was maintained at -30 ^oC for 1 h, then diluted with Et_2O and extracted with an aqueous $NaHCO_3$ solution. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 0.47 g (79%) of the titled compound **237** as a colorless oil; IR (thin film) 2929, 1633, 1448, 1211, 1037 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.38 (s, 3H), 4.14 (d, 2H, *J* = 5.2 Hz), 4.33 (s, 1H), 4.64 (s, 1H), 6.28 (t, 1H, *J* = 5.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 42.1, 55.5, 71.4, 96.2, 101.6 and 137.1.



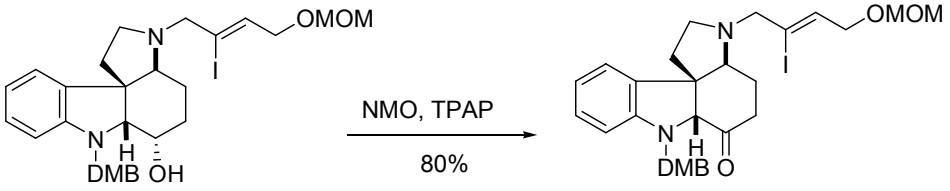
187 **239b**

7-(2,4-Dimethoxy-benzyl)-3-(2-iodo-4-methoxymethoxy-but-2-enyl)-2,3,3*a*,4,5,6,6*a*,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-6-ol (239b). To a solution of 0.12 g (0.54 mmol) of amine **187** in 5.0 mL of DMF at room temperature was

added 1.2 mL of H_2O and 0.37 g (2.7 mmol) of K_2CO_3. The resulting mixture was cooled to 0 ^oC, followed by the addition of a solution of 0.21 g (0.65 mmol) of 1-bromo-2-iodo-4-methoxymethoxy-but-2-ene in 1.0 mL of DMF. The solution was stirred at 0 ^oC for 12 h and quenched with Et_2O and H_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to flash chromatography to provide 0.2 g (80%) of the mono-alkylated product as a pale yellow oil.

To a flask containing 54 mg (0.11 mmol) of the above compound was added 3.0 mL of $ClCH_2CH_2Cl$. To the resultant solution at 0 ^oC was added 23 mg (0.14 mmol) of 2,4-methoxybenzaldehyde and 61 mg (0.29 mmol) of $NaBH(OAc)_3$, followed by the addition of 20 μL (0.34 mmol) of CH_3COOH. The reaction mixture was stirred at 0 ^oC for 10 min, and then at rt for 12 h. The reaction mixture was quenched with a saturated K_2CO_3 solution, and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected to flash silica gel chromatography to give 61 mg (86%) of alcohol **239b** as a colorless oil; IR (neat) 3456, 1673, 1606, and 1485 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.54-1.62 (m, 2H), 1.68 (d, 1H, *J* = 6.0 Hz), 1.74-1.79 (m, 1H), 1.93-2.06 (m, 3H), 2.38 (td, 1H, *J* = 9.0 and 6.6 Hz), 2.80 (t, 1H, *J* = 0.6 Hz), 3.06 (d, 1H, *J* = 13.8 Hz), 3.11 (td, 1H, *J* = 9.0 and 5.1 Hz), 3.40 (s, 3H), 3.46 (d, 1H, *J* =

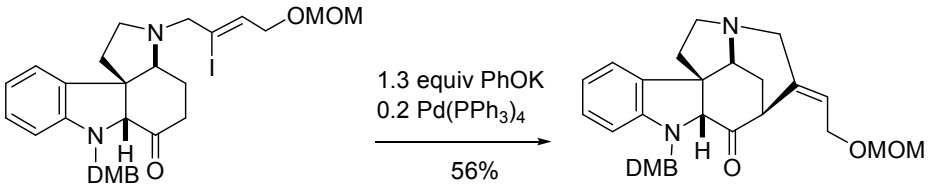
3.6 Hz), 3.62 (d, 1H, *J* = 13.8 Hz), 3.81 (s, 3H), 3.82 (s, 3H), 4.19 (d, 1H, *J* = 5.4 Hz), 4.24-4.28 (m, 1H), 4.32 (d, 1H, *J* = 16.2 Hz), 4.50 (d, 1H, *J* = 16.2 Hz), 4.66 (s, 1H), 6.14 (t, 1H, *J* = 5.4 Hz), 6.43-6.46 (m, 2H), 6.49 (d, 1H, *J* = 1.8 Hz), 6.68 (t, 1H, *J* = 7.5 Hz), 7.02-7.05 (m, 2H), and 7.24(d, 1H, *J* = 7.8 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 18.8, 24.7, 39.8, 48.0, 51.3, 53.5, 55.5, 55.6, 55.7, 65.4, 65.6, 68.1, 71.7, 73.6, 96.3, 98.7, 104.1, 107.1, 109.9, 118.0, 119.7, 121.7, 128.2, 129.1, 132.7, 135.2, 152.8, 158.2, and 160.2; HRMS Calcd for $[(C_{29}H_{37}N_2O_5I)+H]^+$: 621.1820. Found: 621.1797.



239b **240b**

7-(2,4-Dimethoxy-benzyl)-3-(2-iodo-4-methoxymethoxy-but-2-enyl)-2,3,3*a*,4,5,6,6*a*,7-octahydro-pyrrolo[2,3-*d*]carbazol-6-one (240b). To a flask containing 0.9 g (1.45 mmol) of alcohol **239b** and 0.73 g 4Å of molecular sieves in 50 mL of CH_3CN at 0 ^{o}C was added 0.26 g (2.18 mmol) of NMO (*N*-methyl morpholine-*N*-oxide), followed by the addition of 0.15 g (0.43 mmol) of TPAP (tetra-*n*-propylammonium perruthenate) *via* several portions. After stirring at 0 ^{o}C for 20 min, the cooling bath was removed and the reaction mixture was stirred at rt for an additional 2 h. The reaction mixture was filtered through celite to remove molecular sieves and the filtrate was concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.72 g (80%) of

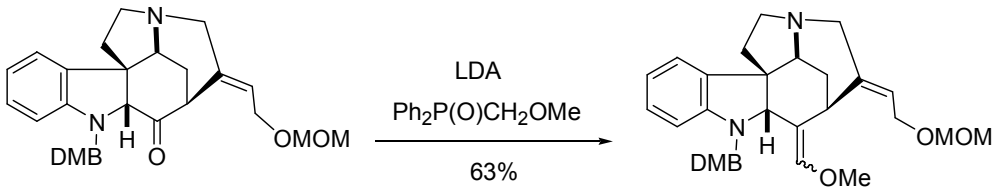
ketone **240b** as a yellow oil; IR (neat) 1707, 1601, 1479, 1209, and 1037 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.83-1.98 (m, 2H), 2.13-2.23 (m, 2H), 2.30-2.53 (m, 3H), 2.54 (d, 1H, *J* = 2.8 Hz), 2.99 (d, 1H, *J* = 14.0 Hz), 3.15-3.20 (m, 1H), 3.39 (s, 3H), 3.59 (dd, 1H, *J* = 14.0 and 1.6 Hz), 3.60 (s, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.12 (d, 1H, *J* = 16.4 Hz), 4.15-4.18 (m, 1H), 4.25 (d, 1H, *J* = 16.4 Hz), 4.65 (s, 2H), 6.10 (t, 1H, *J* = 4.2 Hz), 6.40 (dd, 1H, *J* = 8.2 and 2.4 Hz), 6.43 (d, 1H, *J* = 2.4 Hz), 6.55 (d, 1H, *J* = 8.2 Hz), 6.77 (td, 1H, *J* = 7.6 and 0.8 Hz), and 7.03-7.13 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 20.4, 32.5, 37.8, 47.8, 51.8, 55.4, 55.5, 55.7, 59.0, 64.5, 67.9, 71.6, 81.7, 96.4, 98.6, 103.9, 107.2, 108.8, 118.4, 118.7, 122.8, 128.8, 129.5, 132.7, 133.3, 152.7, 158.4, 160.3, and 210.3.



240b **241b**

Pentacyclic Ketone 241b. To a solution of 0.35 g (0.57 mmol) of vinyl iodide **240b** in 6.0 mL of THF at room temperature was added 0.13 g (0.11 mmol) of $Pd(PPh_3)_4$ and a solution of PhOK in THF (prepared from the addition of 0.74 mL of 1M *t*-BuOK in *t*-BuOH to a solution of 80 mg (0.85 mmol) of phenol in 8 mL of THF). The reaction mixture was heated at reflux under argon for 2 h, cooled to rt, diluted with a 1N NaOH solution and extracted with CH_2Cl_2. The combined organic extracts were washed with 1N NaOH, H_2O, brine, and dried over $MgSO_4$. After concentration under reduced pressure, the residue was subjected

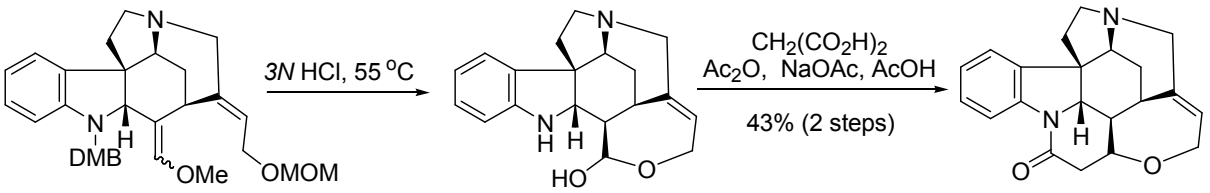
to silica gel chromatography to give 0.15 g (56%) of the enolate coupling product **241b** as a pale yellow oil; IR (neat) 1711, 1607, 1484, and 1038 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.93 (dd, 1H, *J* = 12.8, and 5.0 Hz); 2.14-2.34 (m, 3H), 2.66-2.74 (m, 1H), 3.05 (d, 1H, *J* = 16.0 Hz), 3.20 (t, 1H, *J* = 8.4 Hz), 3.33 (s, 1H), 3.35 (s, 3H), 3.65 (brs, 2H), 3.77 (s, 3H), 3.78 (s, 3H), 3.79 (d, 1H, *J* = 16.0 Hz), 4.10 (dd, 1H, *J* = 13.2 and 4.4 Hz), 4.22-4.37 (m, 3H), 4.61 (s, 2H), 5.57 (dd, 1H, *J* = 8.4 and 4.4 Hz), 6.40 (dd, 1H, *J* = 7.8 and 2.2 Hz), 6.44 (d, 1H, *J* = 2.2 Hz), 6.49 (d, 1H, *J* = 7.8 Hz), 6.74 (td, 1H, *J* = 7.4 and 0.6 Hz), and 7.03-7.11 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 23.3, 38.7, 43.8, 46.9, 51.8, 52.6, 55.4, 55.5, 55.6, 58.3, 62.3, 63.6, 76.8, 96.1, 98.6, 103.8, 108.5, 118.6, 118.7, 122.3, 125.8, 128.9, 129.3, 130.9, 137.5, 151.9, 158.4, 160.2, and 209.5; HRMS Calcd for $[(C_{29}H_{34}N_2O_5)+H]^+$: 491.2540. Found: 491.2534.



241b **243**

Pentacyclic Enol Ether 243. To a flask containing 0.45 mL (3.2 mol) of di-isopropyl amine in 4.0 mL of THF at 0 ^{o}C was added slowly 1.2 mL (2.9 mmol) of *n*-BuLi (2.5 M in hexane). The resultant LDA solution was added dropwise *via* a syringe into a suspension of $Ph_2P(O)CH_2OMe$ in 6.0 mL of THF at 0 ^{o}C. The reaction mixture was constantly stirred at this temperature for 20 min. To the resulting deep red solution was added a solution containing 0.14 g (0.29 mmol) of

pentacyclic ketone **241b** in 2.0 mL of THF. After stirring for 20 min, the cooling bath was removed and the reaction mixture was stirred at rt for 22 h. The reaction mixture was quenched with a saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to provide 90 mg (63%) of vinyl ether **243** as a yellow foam; IR (neat) 1607, 1485, 1121, and 1038 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 1.79-1.84 (m, 1H), 2.20-2.25 (m, 1H), 2.45-2.53 (m, 2H), 3.00-3.08 (m, 1H), 3.17-3.28 (m, 2H), 3.35 (s, 3H), 3.35-3.42 (m, 1H), 3.47-3.53 (m, 6H), 3.80 (s, 3H), 3.83 (s, 3H), 4.08 (dd, 1H, *J* = 12.0 and 6.0 Hz), 4.11 (d, 1H, *J* = 16.8 Hz), 4.18-4.21 (m, 2H), 4.58 (s, 1H), 4.63 (d, 1H, *J* = 6.6 Hz), 4.65 (d, 1H, *J* = 6.6 Hz), 5.38 (t, 1H, *J* = 6.0 Hz), 6.14 (s, 1H) 6.23 (d, 1H, *J* = 8.1 Hz), 6.41 (dd, 1H, *J* = 8.1 and 2.4 Hz), 6.47 (d, 1H, *J* = 2.4 Hz), 6.71 (t, 1H, *J* = 7.5 Hz), 6.99 (t, 1H, *J* = 7.5 Hz), 7.06 (d, 1H, *J* = 7.5 Hz), and 7.07 (d, 1H, *J* = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.2, 29.9, 39.2, 45.6, 52.1, 54.0, 55.1, 55.4, 55.5, 55.6, 59.9, 62.7, 66.9, 67.5, 95.7, 98.4, 103.8, 108.0, 112.4, 118.3, 120.3, 122.1, 128.0, 128.4, 128.6, 132.0, 151.4, 151.9, 157.7, and 159.6; HRMS Calcd for $[(C_{31}H_{38}N_2O_5)+H]^+$: 591.2853. Found: 591.2847.

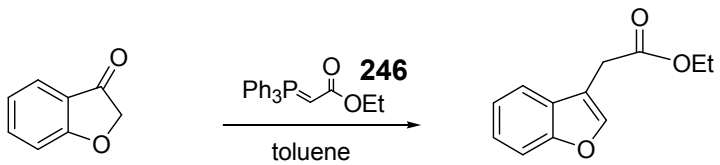


243 **Weiland-Gumlich aldehyde (213)** **strychnine (120)**

Strychnine (120). To a solution containing 8 mg (0.015 mmol) of the pentacyclic enol ether **243** in 1.5 mL of THF was added 1.5 mL of 4M HCl. The reaction mixture was heated at 55 °C for 10 h, cooled to 0 °C, neutralized with a saturated NH_4OH solution, and extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was heated at 60 °C under vacuum overnight to remove the 1,4-diol derived from the acidic hydrolysis of THF under the reaction conditions. The resulting crude residue consisted primarily of the Wieland-Gumlich aldehyde (**213**):[156] ^{1}H-NMR ($CDCl_3$, 600 MHz)δ 1.54 (d, 1H, *J* = 14.4 Hz), 1.57 – 1.62 (m, 1H), 1.82 (d, 1H, *J* = 10.8 Hz), 2.06 (dd, 1H, *J* = 12.6 and 6.6 Hz), 2.26 – 2.30 (m, 1H), 2.66 (s, 1H), 2.67 (d, 1H, *J* = 14.4 Hz), 2.80 – 2.84 (m, 1H), 3.26 (dd, 1H, *J* = 8.0 and 8.0 Hz), 3.75 (d, 1H, *J* = 14.4 Hz), 3.82 (d, 1H, *J* = 10.8 Hz), 3.92 – 3.99 (m, 2H), 4.23 (dd, 1H, *J* = 14.4 and 7.2 Hz), 5.00 (s, 1H), 5.81 (brs, 1H), 6.80 (d, 1H, *J* = 7.5 Hz), 6.88 (t, 1H, *J* = 7.5 Hz), 7.04 (d, 1H, *J* = 7.5 Hz), and 7.10 (d, 1H, *J* = 7.5 Hz).

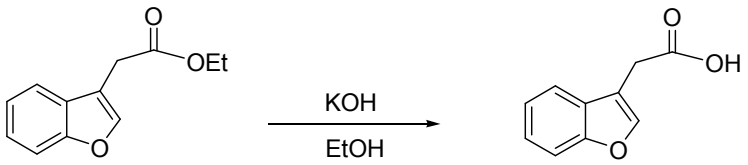
To the crude residue was added 0.5 ml of CH_3COOH, 48 mg of malonic acid, 48 mg of NaOAc, and 10 µL acetic anhydride.[157] The resulting mixture was heated at 120 °C for 2 h. The reaction mixture was cooled to rt, diluted with H_2O, basified with a 50% NaOH solution, and extracted with EtOAc.

The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to preparative TLC to give 2.3 mg (43%) of strychnine for the two step sequence as a white solid: mp 278 – 283 °C (lit mp 275 – 285 °C)[158]; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.28 (dt, 1H, *J* = 10.4 and 3.2Hz), 1.48 (d, 1H, *J* = 14.0 Hz), 1.89 – 1.93 (m, 2H), 2.37 (dt, 1H, *J* = 14.0 and 4.4 Hz), 2.67 (dd, 1H, *J* = 17.2 and 3.2 Hz), 2.76 (d, 1H, *J* = 15.2 Hz), 2.89 (dd, 1H, *J* = 18.4, and 10.0 Hz), 3.14 (dd, 1H, *J* = 17.2 and 8.4 Hz), 3.15 – 3.17 (m, 1H), 3.22 – 3.28 (m, 1H), 3.73 (dd, 1H, *J* = 15.2 and 1.2 Hz), 3.86 (d, 1H, *J* = 10.4 Hz), 3.99 (brs, 1H), 4.06 (dd, 1H, *J* = 13.6 and 5.6 Hz), 4.16 (dd, 1H, *J* = 13.6 and 7.4 Hz), 4.29 (dt, 1H, *J* = 8.4 and 3.2 Hz), 5.94 (t, 1H, *J* = 5.6 Hz), 7.10 (td, 1H, *J* = 7.6 and 1.2 Hz), 7.17 (dd, 1H, *J* = 7.6 and 1.2 Hz), 7.26 (td, 1H, *J* = 7.6 and 1.2 Hz), and 8.09 (dd, 1H, *J* = 7.6 and 1.2 Hz).



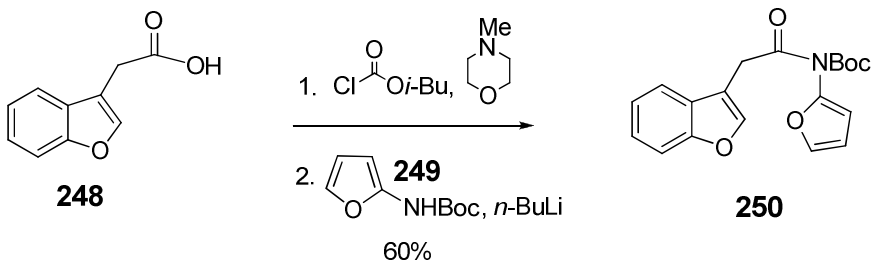
Ethyl 2-(benzofuran-3-yl)acetate (247). To a stirred solution of 3.0 g (22.4 mmol) of ketone **245** in 44 mL of toluene was added 13.6 g (39.1 mmol).of carboethoxymethylene triphenylphosphorane **246** The reaction mixture was heated at reflux for 21 h, then concentrated under reduced pressure and the residue was purified by column chromatography to provide 4.07 g (89%) of the titled compound **247** as a yellow oil: IR (thin film) 2982, 1736, 1453, 1278, 1163, 1097, 1029, and 746 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, 3H, *J* = 7.2 Hz),

3.71 (s, 2H), 4.20 (q, 2H, *J* = 14.4 and 6.8 Hz), 7.24 – 7.34 (m, 2H), 7.48 – 7.51 (m, 1H), 7.58 – 7.60 (m, 1H), and 7.65 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 14.4, 30.0, 61.3, 111.7, 113.3, 119.9, 122.8, 124.6, 127.8, 143.0, 155.4, and 170.9.



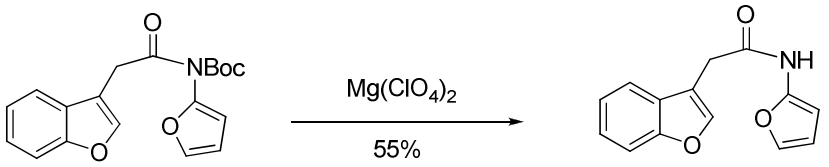
247 **248**

Benzofuran- 3-acetic Acid Ethyl Ester (248).[160] A solution containing 0.6 g (2.4 mmol) of the ester **247** in 50 mL (12 mmol) of a solution of 85% potassium hydroxide in EtOH was stirred at rt overnight. After that, the solvent was removed under reduced pressure and the residue was dissolved in water. The aqueous solution was washed with ether then acidified to pH 2 and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 0.42 g (99%) of a titled compound **248** as a yellow solid: mp 85 – 87 ^{o}C IR (thin film) 3054, 1706, 1226, 1083, and 747 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.76 (d, 2H, *J* = 1.2 Hz), 7.27 (td, 1H, *J* = 7.6 and 1.2 Hz), 7.32 (td, 1H, *J* = 7.6 and 1.2 Hz), 7.49 (brd, 1H, *J* = 7.6 Hz), 7.57 (dd, 1H, *J* = 7.6 and 1.2 Hz), and 7.64 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 29.4, 111.6, 112.3, 119.6, 122.7, 124.6, 127.4, 143.0, 155.2, and 176.8.



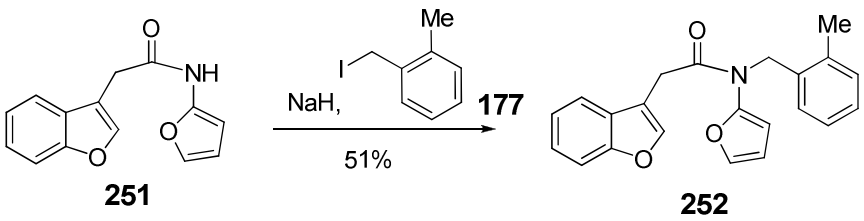
Furan-2-yl-(2-benzofuran-3-yl-acetyl)carbamic Acid *tert*-Butyl Ester (250). To a solution of 0.40 g (2.2 mmol) of furan-2-yl carbamic acid *tert*-butyl ester (**249**)[159] in 10 mL of THF at 0 ^{o}C was added dropwise 0.96 mL (2.4 mmol) of *n*-BuLi (2.5 M solution in hexane). The reaction mixture was stirred at 0 ^{o}C for 20 min. In a separate flask, 0.38 g (2.2 mmol) of benzofuran-3-acetic acid (**248**)[160] was dissolved in 15 mL of THF at 0 ^{o}C and 0.24 mL (2.2 mmol) of 4-methylmorpholine, and 0.29 mL (2.2 mmol) of isobutyl chloroformate was added dropwise. After 5 min, the white precipitate thus formed was removed *via* filtration and washed with 10 mL of THF. The filtrate was cooled to 0 ^{o}C and the preformed lithiate was added dropwise *via* cannula. After stirring at 0 ^{o}C for an additional 20 min, the reaction was quenched with H_2O and extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried over Mg_2SO_4, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel column chromatography to afford 0.45 g (60 %) of the titled compound **250** as a white solid: mp 71 – 74 ^{o}C; IR (thin film) 3125, 2980, 1787, 1747, 1257, 1152, 1094, and 744 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 4.25 (d, 2H, *J* = 0.8 Hz), 6.13 (dd, 1H, *J* = 3.2 and 0.8 Hz), 6.41 (dd, 1H, *J* = 3.2 and 2.0 Hz), 7.22 – 7.33 (m, 5H), 7.46 (d, 1H, *J* = 8.0 Hz), 7.57 (d, 1H, *J* = 8.0 Hz), and 7.66 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ

27.7, 32.6, 84.2, 106.0, 111.3, 111.4, 112.9, 119.8, 122.5, 124.3, 127.8, 140.6, 143.3, 143.5, 151.4, 155.6, and 171.9; HRMS m/z calcd. for $[C_{19}H_{20}NO_5 + H]^+$: 342.1336. Found 342.1333.

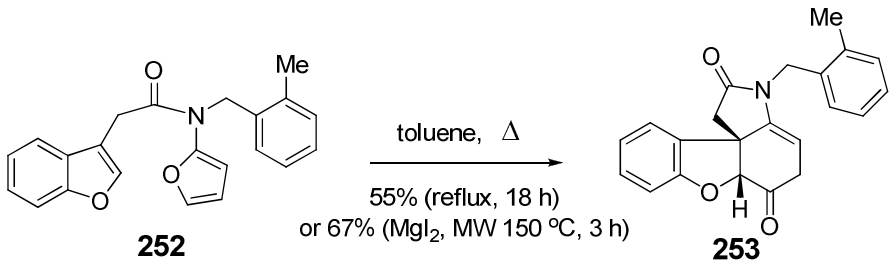


250 **251**

2-(Benzofuran-3-yl)-N-furan-2-yl Acetamide (251). To a solution of 0.10 g (0.29 mmol) of benzofuran **250** in 1.2 mL of CH_3CN was added 0.013 g (0.059 mmol) of magnesium perchlorate ($Mg(ClO_4)_2$). The solution was heated to 45 ^oC for 1 h then cooled to rt and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel chromatography to afford 0.039 g (55%) of the titled compound **251** as a white solid: mp 104 – 106 ^oC; IR (thin film) 3242, 3208, 3061, 1668, 1557, 1452, 1097, and 746 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 2H), 2.29 – 6.32 (m, 2H), 6.97 (s, 1H), 7.26 (t, 1H, *J* = 7.6 Hz), 7.33 (t, 1H, *J* = 7.6 Hz), 7.50 (d, 1H, *J* = 7.6 Hz), 7.55 (d, 1H, *J* = 7.6 Hz), 7.64 (s, 1H), 7.86 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 31.7, 95.8, 111.5, 111.8, 113.1, 119.5, 123.2, 125.1, 127.0, 135.5, 143.5, 144.7, 155.4, and 166.2. HRMS calcd for $[C_{14}H_{12}NO_3 + H]^+$: 242.0812. Found: 242.0804.



2-(Benzofuran-3-yl)-N-furan-2-yl-N-(2-methylbenzyl) Acetamide (252). To a solution containing 0.10 g (0.42 mmol) of amide **251** in 10 mL of DMF at 0 ^{o}C was added 0.017 g (0.42 mmol) of NaH (60% in mineral oil). The mixture was stirred for 2 h at 0 ^{o}C, and then a solution of 0.12 g (0.50 mmol) of the α-iodo-*o*-xylene (**177**)[161] in 5 mL of DMF at 0 ^{o}C was added by cannula. The reaction was stirred for 3 h, then quenched with H_2O and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.073 g (51%) of the titled compound **252** as a pale yellow oil: IR (thin film) 3122, 3061, 2925, 1683, 1608, 1501, 1453, 1180, 1156, 1097, and 744 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.19 (s, 3H), 3.63 (s, 2H), 4.88 (s, 2H), 5.85 (d, 1H, *J* = 3.2 Hz), 6.30 (dd, 1H, *J* = 3.2 and 1.6 Hz), 7.05 – 7.36 (m, 7H), 7.42 – 7.45 (m, 2H), and 7.52 (d, 1H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.9, 29.6, 49.4, 105.6, 111.2, 111.3, 113.6, 119.8, 122.5, 124.3, 125.8, 127.5, 127.6, 129.1, 130.2, 134.4, 136.5, 140.2, 142.7, 147.6, 155.1, and 170.8.

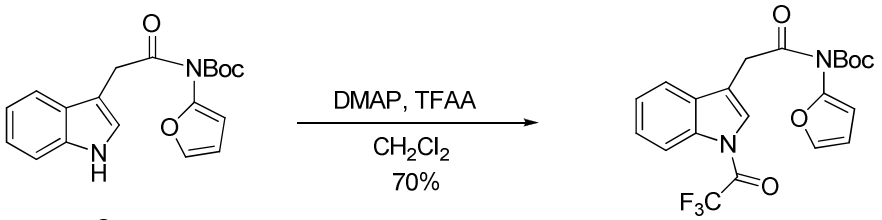


252 **253**

Cycloadduct 253. A solution of 0.073 g (0.21 mmol) of furan **252** in 5 mL of toluene was heated at reflux for 18 h. After cooling to rt, the solution was concentrated under reduced pressure. The resulting residue was purified by flash silica gel column chromatography to provide 0.040 g (55 %) of the titled compound **253** as an orange solid: mp 174 – 175 ^{o}C; IR (thin film) 3046, 2926, 1727, 1673, 1475, 1465, 1397, 1212, and 748 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 2.77 (ddd, 1H, *J* = 18.0, 7.2, and 1.6 Hz), 2.89 (d, 1H, *J* = 17.2 Hz), 2.94 (dd, 1H, *J* = 18.0 and 2.8 Hz), 3.08 (d, 1H, *J* = 17.2 Hz), 4.68 (d, 1H, *J* = 16.0 Hz), 4.71 (d, 1H, *J* = 1.6 Hz), 4.90 (d, 1H, *J* = 16.0 Hz), 4.92 (dd, 1H, *J* = 7.2 and 2.8 Hz), 6.90 (t, 1H, *J* = 8.0 Hz), 6.96 (t, 1H, *J* = 7.2 Hz), 7.09 (d, 2H, *J* = 7.2 Hz), 7.15 – 7.26 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.5, 35.2, 42.2, 45.8, 51.8, 86.3, 94.9, 110.7, 122.0, 123.0, 126.4, 126.7, 127.9, 130.3, 130.5, 130.9, 132.9, 135.7, 142.3, 158.2, 172.5, and 201.0.

Alternatively, the reaction can be run in shorter reaction time using microwave irradiation at 150 ^{o}C with catalytic amount of MgI_2. The experiment was conducted as following: To a solution containing 0.05 g (0.145 mmol) of furan **252** in 4 mL of toluene in a microwave tube equipped with a magnetic stirred bar was added a 0.004 g (0.015 mmol) sample of magnesium iodide. The vessel was sealed with a microwave rubber cap. Subsequently, the sample was

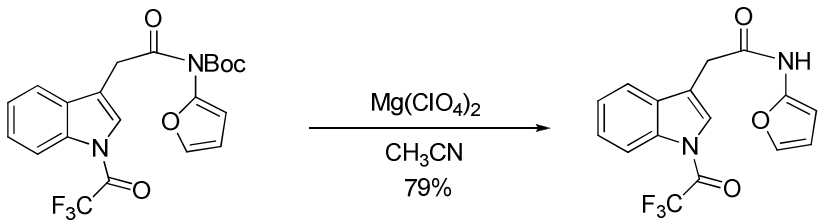
placed in microwave reactor and irradiated at 200 W at 150 ºC for 3 h. After cooling to rt, the solvent was removed under reduced pressure. The resulting residue was purified by flash silica gel column chromatography to provide 0.033 g (67%) of the titled compound **253**. The spectral data is identical to that reported above.



254 **255**

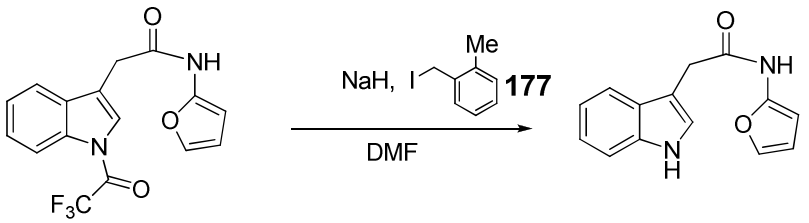
Furan-2-yl-{2-[1-(2,2,2-trifluoro-acetyl)-1H-indol-3-yl]-acetyl}-carbamic Acid *tert*-Butyl Ester (255). To a solution containing 0.10 g (0.29 mmol) of indole **254** in 1.2 mL of CH_2Cl_2 at 0 ^oC was added 0.043 g (0.35 mmol) of dimethyl-aminopyridine (DMAP), followed by 0.04 mL (0.32 mmol) of trifluoroacetic anhydride. The reaction mixture was allowed to warm to rt and stirred for 12 h. After that, the solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography to give 0.09 g (70%) of the titled compound **255** as a white solid: mp 125 – 127 ^oC; IR(thin film) 2982, 1746, 1728, 1542, 1459, and 1151 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 4.30 (s, 2H), 6.15 (d, 1H, *J* = 3.2 Hz), 6.21 (d, 1H, *J* = 3.2 and 2.0 Hz), 7.10 – 7.25 (m, 3H), 7.55 – 7.57 (m, 2H), and 8.22 (d, 1H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.6, 33.8, 84.4, 106.1, 111.3, 114.1, 116.8, 118.5, 119.7,

122.7 (q, *J* = 4.2 Hz), 125.6, 126.4, 130.5, 135.8, 140.7, 143.2, 151.4, 153.7 (q, *J* = 40 Hz), and 171.4.



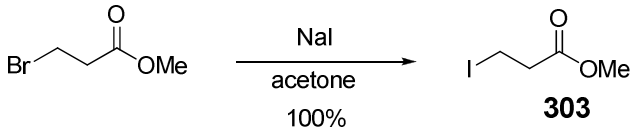
255 **256**

Furan-2-yl-(2-1H-indol-3-yl-acetyl)-carbamic Acid *tert*-Butyl Ester (256). To a solution containing 2.47 g (5.66 mmol) of indole **255** in 23 mL of CH_3CN at rt was added 0.13 g (0.57 mmol) of magnesium perchlorate $Mg(ClO_4)_2$ in one portion. The reaction was then heat to 45 ^oC and stirred for 2h. After cooling down to rt, silica gel was added to the reaction mixture and the solvent was removed under reduced pressure. The crude residue was then purified by flash silica gel column chromatography to provide 1.50 g (79%) of the titled compound **256** as a white solid: mp 152 – 153 ^oC; IR (thin film) 3265, 1726, 1674, 1460, 1207, and 1157 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 2H), 6.33 (d, 2H, *J* = 8.4 Hz), 7.00 (s, 1H), 7.41 (t, 1H, *J* = 7.6 Hz), 7.47 (t, 1H, *J* = 7.6 Hz), 7.53 (s, 1H), 7.58 (d, 1H, *J* = 7.6 Hz), 7.97 (brs, 1H), and 8.45 (d, 1H, *J* = 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 33.0, 96.1, 111.5, 116.8, 117.1, 118.5, 119.4, 122.7, 126.0, 127.0, 129.7, 135.7, 136.2, 144.5, 153.8 (q, *J* = 40 Hz), and 165.5.



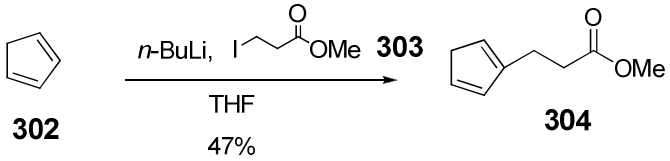
256 **258**

***N*-Furan-2-yl-2-(1H-indol-3-yl)-acetamide (258).** To a solution containing 0.150 (0.44 mmol) of trifluoro-acetyl indole **256** in 3.6 mL of DMF and 0.9 mL of THF at rt was added 0.17 g (0.54 mmol) of NaH (60% in mineral oil), followed by 0.11 g (0.49 mmol) of iodo xylene (**177**) in one portion. The reaction was stirred at 70 ^{o}C for 1.5 h. After cooling down to rt, the reaction mixture was extracted with H_2O and EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.11 g (100%) of the titled compound **258** as a yellow oil: IR (thin film) 3408, 3359, 1671, 1611, 1520, 1010, and 744 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 2H), 6.32 (d, 2H, *J* = 1.6 Hz), 6.95 (t, 1H, *J* = 1.6 Hz), 7.16 – 7.20 (m, 2H), 7.27 (td, 1H, *J* = 8.4 and 1.2 Hz), 7.43 (d, 1H, *J* = 8.4 Hz), 7.59 (d, 1H, *J* = 7.6 Hz), 7.74 (brs, 1H), and 8.41 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 33.5, 95.4, 108.0, 111.4, 111.5, 118.5, 120.4, 122.9, 124.0, 126.8, 135.3, 136.4, 145.0, and 168.0.



303

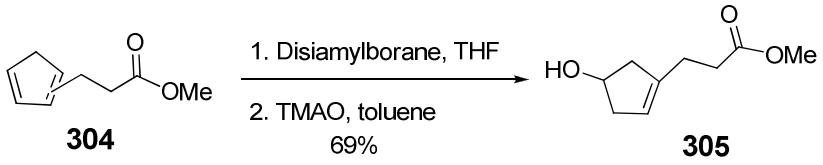
Methyl 3-iodopropanoate (303).[162] To a stirred solution containing 13.1 mL (120 mmol) of methyl 3-bromopropanoate in 300 mL of acetone was added 27.0 g (180 mmol) of sodium iodide and the resulting solution was heated at reflux for 24 h. After cooling to rt, the white precipitate that formed was removed by filtration and the solution was thoroughly washed with acetone. The filtrate was concentrated under reduced pressure and the resulting slurry was diluted with EtOAc, washed with water, a saturated aqueous Na_2SO_3 solution and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to provide 25.6 g (100%) of the titled compound **303** as a light yellow oil which was used to the next step without further purification: IR (neat) 2952, 1740, 1438, 1360, 1347, and 1219 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) 2.97 (t, 2H, *J* = 7.2 Hz), 3.31 (t, 2H, *J* = 7.2 Hz), and 3.71 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) 38.3, 52.0, and 171.6.



302 **304**

Methyl 3-(cyclopenta-1,3-dienyl)propanoate (304).[163] To a stirred solution containing 12.3 mL (149 mmol) of freshly cracked cyclopentadiene in 50 mL of THF at -78 ºC was added 60 mL (149 mmol) of *n*-BuLi (2.5 M solution in hexane)

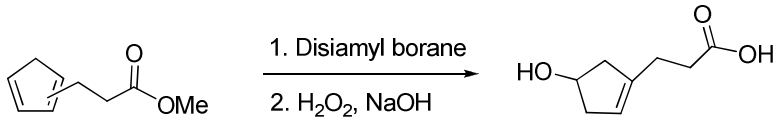
dropwise. The resulting mixture was stirred for 30 min at -78 ^{o}C and then a solution of 32.0 g (121mmol) of methyl 3-iodopropanoate (**303**) in 30 mL of THF at -78 ^{o}C was slowly added *via* cannula. The reaction mixture was allowed to warm to rt and was further stirred for 12 h. The resulting orange-red mixture was quenched with water and extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography to give 10.6 g (47%) of the titled compound **304** together with a double bond isomer and was isolated as a light yellow viscous oil: IR (neat) 2950, 1740, 1439, 1363, and 1160 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.47 – 2.54 (m, 4H), 2.60 – 2.72 (m, 4H), 2.83 (td, 2H, *J* = 1.2 and 1.2 Hz), 2.87 – 2.90 (m, 2H), 3.61 (s, 6H), 5.97 (sept, 1H, *J* = 1.6 Hz), 6.10 – 6.12 (m, 1H), 6.18 – 6.23 (m, 1H), and 6.32 – 6.38 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.9, 25.7, 33.1, 33.7, 41.1, 43.1, 51.4, 126.1, 126.7, 130.8, 132.1, 133.9, 134.0, 145.1, 147.3, 173.4, and 173.5.



304 **305**

Methyl 3-(4-hydroxycyclopent-1-enyl)propanoate (305). (i) *Preparation of disiamylborane:* To 330 mL of THF stirred at 0 ºC was added 83 mL (83 mmol) of borane·THF complex (1.0 M solution in THF) followed by the addition of 17.5 mL (165 mmol) of 2-methylbut-2-ene. The resulting solution was stirred at 0 ºC for 2 h. (ii) *Hydroboration*: A solution of 10.5 g (69 mmol) of cyclopentadiene **304** in

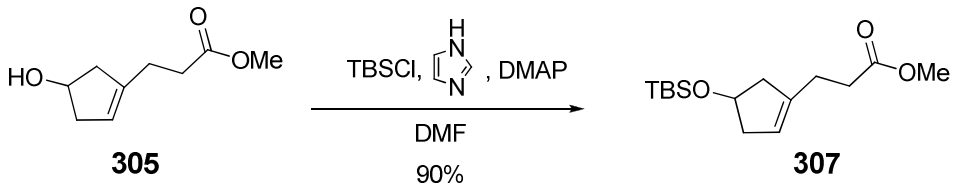
275 mL of THF was added to the above stirred solution of disiamylborane *via* cannula. The reaction mixture was stirred at 0 ^{o}C for 1 h followed by stirring for an additional 2 h at rt. The reaction mixture was then diluted with 275 mL of toluene and the more volatile THF was removed under reduced pressure. To the resulting solution was added 46.0 g (414 mmol) of trimethylamine *N*-oxide (TMAO) at rt and the mixture was vigorously stirred at reflux for 1h. After cooling to rt, Et_2O was added until a precipitate was formed. The white precipitate was removed by filtration and was washed thoroughly with Et_2O. A saturated aqueous NH_4Cl solution was added to the filtrate and the mixture was stirred for 1 h at rt. The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography to afford 8.1 g (69%) of the titled compound **305** as a light yellow viscous oil: IR (neat) 3391, 2950, 2917, 2840, 1728, 1650, 1434, and 1160 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.04 (brs, 1H), 2.16 – 2.26 (m, 2H), 2.32 – 2.38 (m, 2H), 2.44 (dd, 1H, *J* = 6.8 and 2.0 Hz), 2.46 (dd, 1H, *J* = 6.8 and 2.0 Hz), 2.53 – 2.64 (m, 2H), 3.63 (s, 3H), 4.45 (tt, 1H, *J* = 6.4 and 2.0 Hz), and 5.28 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.3, 32.3, 42.6, 45.0, 51.6, 71.9, 121.3, 140.4, and 173.8.



304 20% **306**

3-(4-Hydroxy-cyclopent-1-enyl)-propionic Acid (306). (i) *Preparation of disiamylborane:* To 15 mL of THF stirred at 0 ºC was added 4.9 mL (4.9 mmol) of

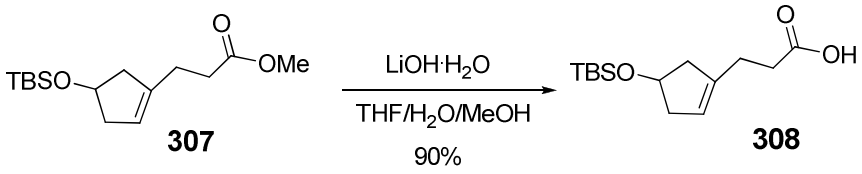
borane·THF complex (1.0 M solution in THF) followed by 0.84 mL (9.9 mmol) of 2-methylbut-2-ene. The resulting solution was stirred at 0 ºC for 2 h. (ii) *Hydroboration*: A solution of 0.5 g (3.3 mmol) of cyclopentadiene **304** in 50 mL of THF was slowly transferred to the above stirred solution of disiamylboranre *via* cannula. The reaction mixture was stirred at 0 ^{o}C for 1 h followed by an additional 2 h at rt. At the end of this time, 0.76 mL (25 mmol) of hydrogen peroxide (30% solution in water) and 2.4 mL (2.2 mmol) of an aqueous 3 M NaOH solution were added consecutively. The resulting solution was stirred at rt for 12 h, acidified with an aqueous 3 M HCl solution and extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography to afford 0.11 g (20%) of the titled compound **306** as a light yellow solid: mp 37 – 38 ^{o}C; IR (thin film) 3381, 2924, 1712, 1415, 1200, 1049, and 840 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.20 – 2.33 (m, 2H), 2.35 – 2.44 (m, 2H), 2.50 (d, 1H, *J* = 7.6 Hz), 2.52 (dd, 1H, *J* = 7.6 and 0.8 Hz), 2.55 – 2.70 (m, 2H), 4.43 – 4.52 (m, 2H), and 5.35 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.0, 32.3, 42.3, 44.7, 71.9, 121.4, 140.3, and 178.2.



305 **307**

3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopent-1-enyl]-propionic Acid Methyl Ester (307). To a stirred solution containing 0.2 g (1.18 mmol) of alcohol

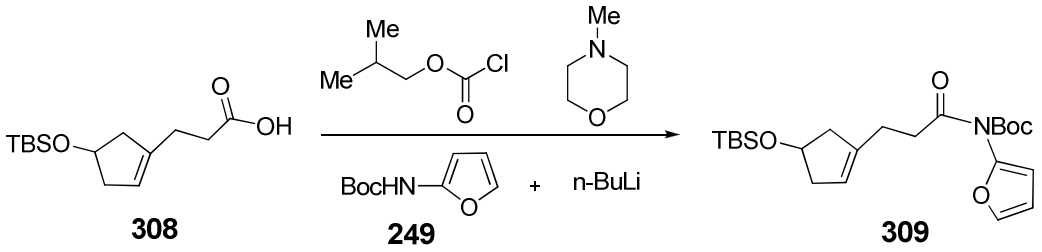
305 in 0.6 mL of DMF was added 0.2 g (2.94 mmol) of imidazole and a crystal of 4-dimethylaminopyridine (DMAP). The resulting mixture was cooled to 0 °C for 15 min and then 0.27 g (1.76 mmol) of *tert*-butyldimethylsilyl chloride (TBSCl) was added in one portion. The reaction mixture was allowed to warm to rt and was stirred for 2 h, then quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduce pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.3 g (90%) of the titled compound **307** as a clear oil: IR (neat) 2955, 2930, 2848, and 1737 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.85 (s, 9H), 2.15 – 2.60 (m, 8H), 3.62 (s, 3H), 4.47 – 4.53 (m, 1H), and 5.22 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.8, 18.2, 25.9, 26.5, 32.3, 42.6, 45.1, 51.5, 72.7, 121.4, 140.3, and 173.7.



307 **308**

3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopent-1-enyl]-propionic Acid (308). To a stirred solution of the above ester **307** in a mixture containing 2.0: 0.5: 1.5 mL of THF, water, and MeOH at rt was added 0.049 g (1.16 mmol) of $LiOH·H_2O$ in one portion. The reaction mixture was stirred at rt overnight and then quenched with an aqueous solution containing 0.16 g (1.16 mmol) of $NaHSO_4$ in 2 mL of water. The mixture was extracted with EtOAc and the combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed

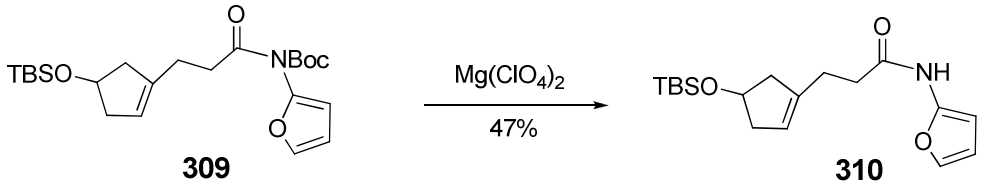
under reduced pressure to provide 0.26 g (90%) of the titled compound **308** as a pale yellow solid: IR (thin film) 2950, 2925, 2852, 1706, and 1250 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 1H), 0.88 (s, 9H), 2.16 – 2.30 (m, 2H), 2.32 – 2.40 (m, 2H), 2.45 – 2.62 (m, 4H), 4.52 (m, 1H), and 5.28 (t, 1H, *J* = 1.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.8, 18.2, 25.9, 26.2, 32.3, 42.6, 45.1, 72.7, 121.5, 140.1, and 179.4.



308 **249** **309**

{3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopent-1-enyl]-propionyl}-furan-2-yl-carbamic Acid *tert*-Butyl Ester (309). To a stirred solution containing 0.07 g (0.37 mmol) of furan-2-yl carbamic acid *tert*-butyl ester (**249**) in 1.5 mL of THF at 0 ^oC was added 0.18 mL (0.41 mmol) of *n*-BuLi (2.5 M solution in hexane). The reaction mixture was stirred at 0 ^oC for 20 min. In a separate flask, 0.1 g (0.37 mmol) of the above acid **308** was dissolved in 1.5 mL of THF at 0 ^oC and 0.04 mL (0.37 mmol) of 4-methylmorpholine and 0.048 mL (0.37 mmol) of isobutyl chloroformate were added dropwise. After stirring for 1h, the white precipitate that formed was removed by filtration and was washed with 0.5 mL of THF. The filtrate was cooled to 0 ^oC and the performed lithiate was transferred to the above solution *via* cannula. The reaction mixture was allowed to warm to rt, then quenched with water and extracted with EtOAc. The organic layer was washed

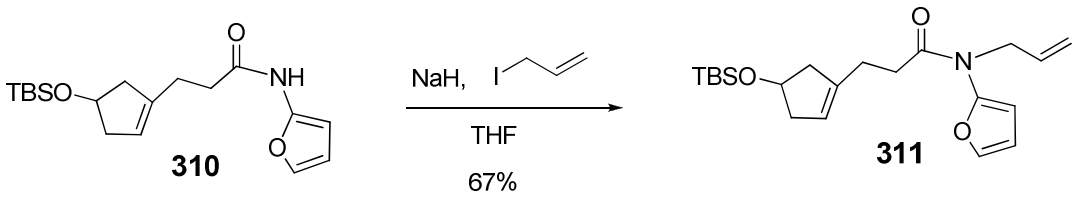
with a saturated aqueous $NaHCO_3$ solution and brine then dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by silica gel flash column chromatography to provide 0.08 g (48%) of the titled compound **309** as a pale yellow oil: IR (thin film) 2955, 2925, 2853, 1741, and 1609 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.88 (s, 9H), 1.43 (s, 9H), 2.16 – 2.28 (m, 2H), 2.34 – 2.42 (m, 2H), 2.46 – 2.61 (m, 2H), 2.86 – 2.92 (m, 2H), 4.46 – 4.55 (m, 1H), 5.27 (brs, 1H), 6.14 (d, 1H, *J* = 3.2 Hz), 6.41 (dd, 1H, *J* = 2.3 and 2.4 Hz), and 7.32 – 7.34 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.8, 18.3, 25.9, 26.2, 27.8, 35.5, 42.6, 45.2, 72.8, 83.8, 105.9, 111.2, 121.4, 140.4, 140.5, 143.9, 151.4, and 174.6.



309 **310**

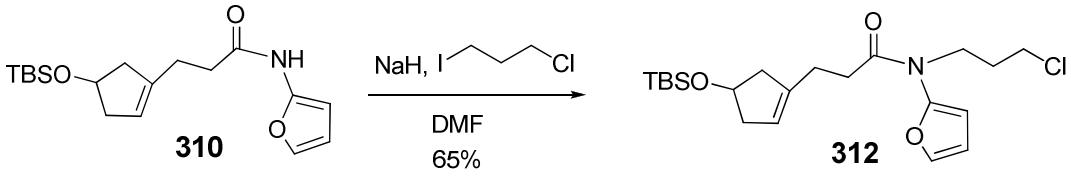
3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopent-1-enyl]-N-furan-2-yl-propionamide (310). To a stirred solution containing 0.5 g (1.15 mmol) of the above amide **309** in 5 mL of CH_3CN was added 0.51 g (0.23 mmol) of magnesium perchlorate ($Mg(ClO_4)_2$). The reaction mixture was stirred at 50 ^oC for 4 h and cooled to rt. The solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography to provide 0.18 g (47%) of the titled compound **310** as a pale yellow oil: IR (thin film) 3252, 3057, 2955, 2930, 2848, 1665, and 1557 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 2.18 – 2.62 (m, 8H), 4,.47 – 4.56 (m, 1H), 5.36 (s,

1H), 6.28 (d, 1H, *J* = 3.2 Hz), 6.35 (t, 1H, *J* = 3.2 Hz), 7.02 (s, 1H), and 7.88 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.9, 18.1, 25.8, 26.8, 34.3, 42.6, 44.9, 72.7, 95.3, 111.2, 121.8, 135.1, 140.3, 145.3, and 169.8.



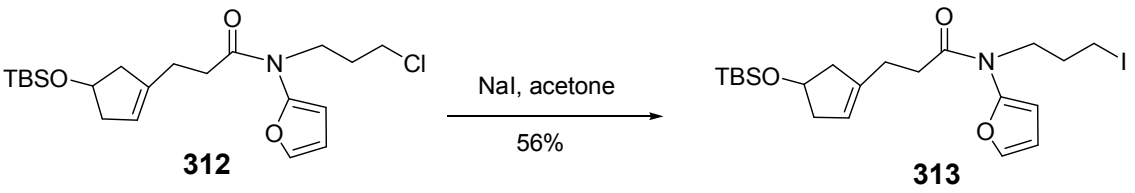
***N*-Allyl-3-[4-(*tert*-butyl-dimethyl-silanyloxy)-cyclopent-1-enyl]-*N*-furan-2-yl-propionamide (311).** To a stirred solution containing 0.08 g (0.238 mmol) of furanyl amide **310** in 1 mL of THF was added 0.011 g (0.011 mmol) of NaH (60% in mineral oil) at 0 ^{o}C. The solution was allowed to warm to rt and was stirred at this temperature for 1 h. The reaction mixture was recooled to 0 ^{o}C and 0.026 mL (0.29 mmol) of allyl iodide was added dropwise. After warming to rt the mixture was allowed to stir for 2 h. The solution was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.06 g (67%) of the titled compound **311** as a pale yellow oil: IR (thin film) 3252, 3057, 2955, 2953, 2848, 1665, and 1557 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.85 (s, 9H), 2.07 – 2.36 (m, 6H), 2.42 (dd, 1H, *J* = 16.4 and 6.8 Hz), 2.52 (dd, 1H, *J* = 16.4 and 6.8 Hz), 4.19 (d, 1H, *J* = 6.0 Hz), 4.30 – 4.51 (m, 1H), 5.09 – 5.16 (m, 3H), 5.75 – 5.86 (m, 1H), 6.70 (d, 1H, *J* = 3.2 Hz), 6.34 – 6.38 (m ,1H), and 7.25

(brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.8, 18.2, 25.9, 26.6, 32.0, 42.6, 45.0, 50.8, 72.7, 104.7, 111.1, 117.6, 121.1, 132.8, 140.1, 140.7, 148.4, and 173.4.



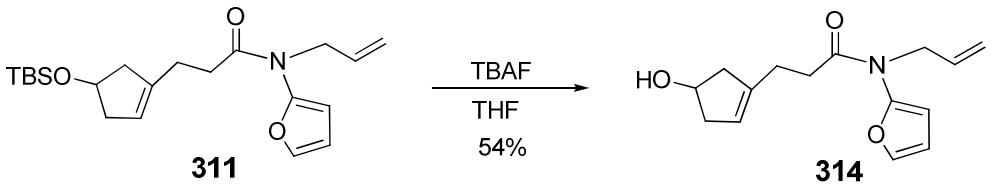
3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopent-1-enyl]-*N*-(3-chloro-propyl)-*N*-furan-2-yl-propionamide (312). To a stirred solution containing 0.53 g (1.58 mmol) of furanyl amide **310** in 6 mL of DMF was added 0.04 g (1.66 mmol) of NaH (60% in mineral oil) at 0 ^{o}C. The solution was allowed to warm to rt and was stirred for an additional 1 h. The reaction mixture was recooled to 0 ^{o}C and a solution of 0.36 g (1.74 mmol) of 1-chloro-3-iodo-propane in 2 mL of DMF was added dropwise. After being warmed to rt the mixture was stirred overnight, quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.42 g (65%) of the titled compound **312** as a pale yellow oil: IR (thin film) 2923, 1675, 1610, 1505, 1269, and 1161 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.92 (s, 9H), 2.02 (quin, 2H, *J* = 6.8 Hz), 2.06 – 2.34 (m, 8H), 2.41 (dd, 1H, *J* = 16.8 and 6.8 Hz), 2.52 (dd, 1H, *J* = 16.8 and 6.8 Hz), 3.41 (t, 2H, *J* = 6.8 Hz), 3.73 (t, 2H, *J* = 6.8 Hz), 5.15 (brd, 1H), 6.10 (d, 1H, *J* = 3.2 Hz), 6.39 (dd, 1H, *J* = 3.2 and 2.4 Hz), and 7.84 (dd, 1H, *J* = 2.4 and 1.2

Hz) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.8, 18.1, 25.8, 26.5, 31.2, 31.9, 42.1, 42.5, 45.0, 46.0, 72.6, 104.6, 111.2, 121.1, 140.2, 140.6, 148.4, and 173.7.

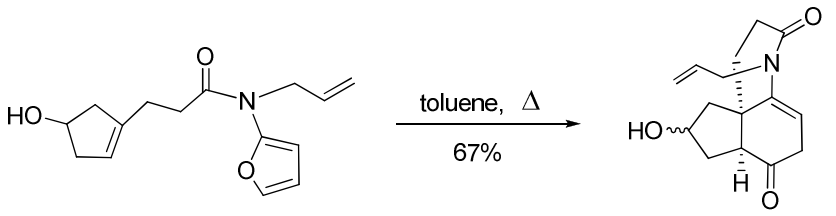


3-[4-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopent-1-enyl]-*N*-furan-2-yl-*N*-(3-iodo-propyl)-propionamide (313). To a stirred solution containing 0.25 g (0.607 mmol) of compound **312** in 2.5 mL of acetone was added 0.11 g (0.73 mmol) of sodium iodide. The resulting solution was heated at reflux for 24 h. After cooling to rt, the white precipitate that formed was removed by filtration and washed thoroughly with acetone. The filtrate was then concentrated under reduced pressure. The resulting slurry was taken up in EtOAc, washed with water followed by a saturated aqueous Na_2SO_3 solution and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide 0.17 g (56%) of the titled compound **313** as a light yellow oil which was used to the next step without further purification: IR (thin film) 2930, 2855, 1689, 1505, 1263, and 1071 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.93 (s, 9H), 2.00 – 2.35 (m, 10H), 2.41 (dd, 1H, *J* = 16.4 and 6.8 Hz), 2.53 (dd, 1H, *J* = 16.4 and 6.4 Hz), 3.14 (t, 2H, *J* = 6.8 Hz), 3.66 (t, 2H, *J* = 6.8 Hz), 4.47 (sep, 1H, *J* = 3.2 Hz), 5.14 (brs, 1H), 6.10 (d, 1H, *J* = 3.2 Hz), 6.39 (dd, 1H, *J* = 3.2 and 2.4 Hz), and 7.28 (d, 1H, *J* = 2.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -4.8, 2.1, 18.2,

25.9, 26.2, 31.9, 32.3, 42.6, 45.0, 49.0, 72.7, 104.7, 111.2, 121.1, 140.2, 140.6, 148.4, and 173.7.

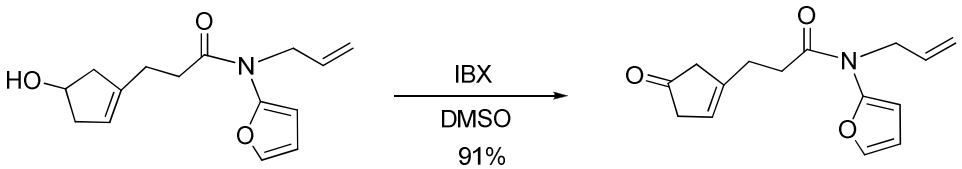


***N*-Allyl-*N*-furan-2-yl-3-(4-hydroxy-cyclopent-1-enyl)-propionamide (314).** To a stirred solution containing 0.17 g (0.45 mmol) of the protected alcohol **314** in 1.8 mL of THF was added 0.54 mL (0.54 mmol) of *tetra*-butylammonium fluoride (TBAF, 1.0 M solution in THF) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.06 g (54%) of the titled compound **314** as a pale yellow oil: IR (thin film) 3432, 2919, 2843, 1680, 1608, and 1506 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.08 – 2.38 (m, 7H), 2.45 – 2.62 (m, 2H), 4.16 (d, 2H, *J* = 6.4 Hz), 4.39 – 4.45 (m, 1H), 5.07- 5.14 (m, 2H), 5.20 (s, 1H), 5.72 – 5.84 (m, 1H), 6.05 (d, 1H, *J* = 3.2 Hz), 6.36 (dd, 1H, *J* = 3.2 and 1.6 Hz), and 7.26 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.4, 32.0, 42.6, 45.0, 50.8, 71.8, 104.7, 111.1, 117.7, 121.1, 132.7, 140.1, 140.8, 148.2, and 173.3.



314 **315**

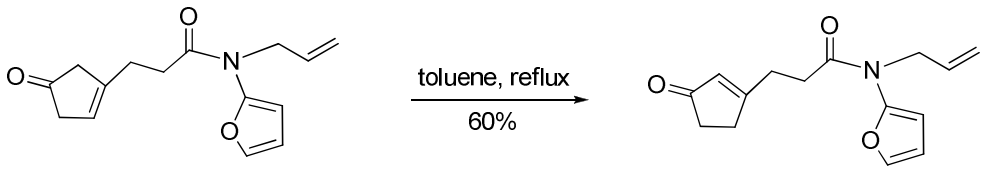
7-Allyl-2-hydroxy-1,2,3,3a,5,7,9,10-octahydro-7-aza-cyclopenta[d]naphthalene-4,8-dione (315). A solution containing 0.06 g (0.23 mmol) of pentenyl furan **314** in 1 mL of toluene was heated at 200 ^{o}C in a sealed tube for 3 d. The solution was cooled to rt and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.04 g (67%) of an inseparable mixture of diastereomers of **315** as a yellow oil: IR (thin film) 3441, 2935, 2868, 1706, 1624, and 1199 cm^{-1}; ^{13}C-NMR (100 MHz, $CDCl_3$) major isomer; δ 29.2, 31.7, 35.0, 37.1, 43.2, 46.8, 48.8, 56.7, 71.2, 100.2, 116.4, 132.7, 141.3, 168.4, and 208.1.



314 **316**

***N*-Allyl-*N*-furan-2-yl-3-(4-oxo-cyclopent-1-enyl)-propionamide (316).** To a stirred solution containing 0.08 g (0.32 mmol) of alcohol **311** in 0.7 mL of DMSO was added 0.10 g (0.35 mmol) of *o*-iodoxybenzoic acid (IBX) at rt. The reaction mixture was stirred for 3 h and was then quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by

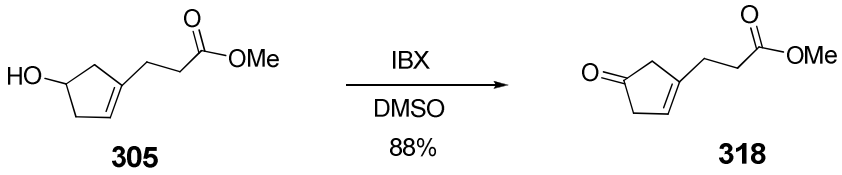
flash silica gel column chromatography to provide 0.08 g (91%) of the titled compound **316** as a pale yellow oil: IR (thin film) 2919, 1742, 1675, and 1598 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.18 (d, 1H, *J* = 6.4 Hz), 2.32 (d, 1H, *J* = 8.0 Hz), 2.45 (brt, 2H, *J* = 7.0 Hz), 2.75 (s, 2H), 2.86 (d, 2H, *J* = 2.0 Hz), 4.20 (d, 2H, *J* = 6.0 Hz), 5.09 – 5.18 (m, 2H), 5.62 (brt, 1H, *J* = 1.6 Hz), 5.75 – 5.87 (m, 1H), 6.09 (d, 1H, *J* = 3.2 Hz), 6.39 (dd, 1H, *J* = 3.2 and 2.4 Hz), and 7.29 (d, 1H, *J* = 1.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.1, 31.3, 43.6, 45.2, 50.9, 104.8, 111.2, 117.9, 121.2, 132.6, 140.2, 140.9, 148.2, 172.8, and 216.8.



316 **317**

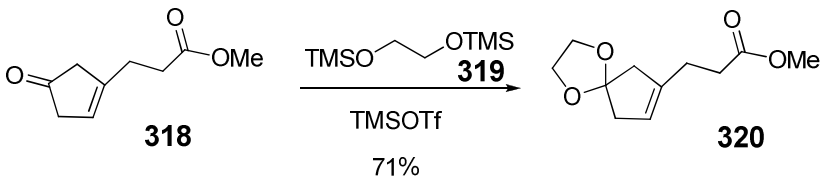
***N*-Allyl-*N*-furan-2-yl-3-(3-oxo-cyclopent-1-enyl)-propionamide (317).** A solution containing 0.05 g (0.26 mmol) of pentenoyl furan **316** in 0.8 mL of toluene was heated at reflux for 12 h. The solution was cooled to rt and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.03 g (60%) of the titled compound **317** as a yellow oil together with 0.005 g (10%) of starting material: IR (thin film) 2919, 1711, 1675, and 1614 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.35 – 2.40 (m, 2H), 2.42 (d, 1H, *J* = 6.8 Hz), 2.44 (d, 1H, *J* = 7.2 Hz), 2.53 – 2.59 (m, 2H), 2.70 (t, 2H, *J* = 7.2 Hz), 4.20 (d, 2H, *J* = 6.4 Hz), 5.08 – 5.18 (m, 2H), 5.74 – 5.86 (m, 2H), 6.11 (d, 1H, *J* = 3.2 Hz), 6.40 (dd, 1H, *J* = 3.2 and 2.0 Hz), 7.29 (d,

1H, *J* = 1.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.4, 31.1, 31.7, 35.2, 51.0, 105.0, 111.3, 118.1, 129.1, 132.5, 140.4, 147.9, 172..1, 181.3, and 209.8.

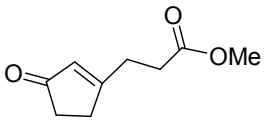


305 **318**

3-(4-Oxo-cyclopent-1-enyl)-propionic Acid Methyl Ester (318). To a stirred solution containing 1.5 g (8.81 mmol) of alcohol **305** in 35 mL of DMSO was added 2.7 g (9.7 mmol) of 2-iodoxybenzoic acid (IBX) at rt. The mixture was stirred at rt for 4 h and then quenched with water. The white precipitate that formed was removed by filtration and was washed with EtOAc. The filtrate was further extracted with EtOAc and the combined organic layer was washed several times with water followed by brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography to provide 1.3 g (88%) of the titled compound **318** as a pale yellow solid: mp 31 – 33 ^{o}C; IR (thin film) 2911, 1747, 1435, 1265, and 1167 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.40 – 2.50 (m, 4H), 2.78 (s, 2H), 2.83 (d, 2H, *J* = 1.6 HZ), 3.62 (s, 3H), and 5.65 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.9, 31.5, 43.6, 45.1, 51.6, 121.4, 140.4, 173.2, and 216.4.

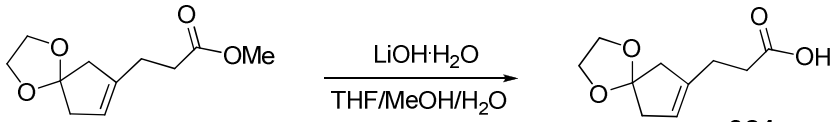


3-(1,4-Dioxa-spiro[4.4]non-7-en-7-yl)-propionic Acid Methyl Ester (320). To a stirred solution containing 11.7 g (69.6 mmol) of ketone **318** in 278 mL of CH_2Cl_2 at -78 ^oC was added 61.4 mL (250 mmol) of 1,2-bis(trimethylsiloxy)ethane (**319**). After being stirred for 15 min at -78 ^oC, a 1.26 mL (7.0 mmol) sample of trimethylsilyl trifluoromethanesulfonate (TMSOTf) was added dropwise. The resulting solution was stirred at -78 ^oC for 15 min followed by stirring for an additional 3 h at 0 ^oC. The reaction mixture was quenched using 0.56 mL (7.0 mmol) of pyridine and the mixture was allowed to warm to rt. The solution was poured into an aqueous solution of NH_4Cl and extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 10.5 g (71%) of the titled compound **320** as a yellow oil: IR (thin film) 2907, 1739, 1438, 1337, 1018, and 854 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.35 – 2.37 (m, 2H), 2.45 (d, 1H, J = 8.0 Hz), 2.49 (dd, 1H, J = 8.0 and 1.6 Hz), 2.52 (s, 2H), 2.56 (s, 2H), 3.66 (s, 3H), 3.93 (s, 4H), and 5.33 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.7, 32.0, 43.3, 45.5, 51.6, 64.2, 117.0, 120.9, 139.9, and 173.6.



331

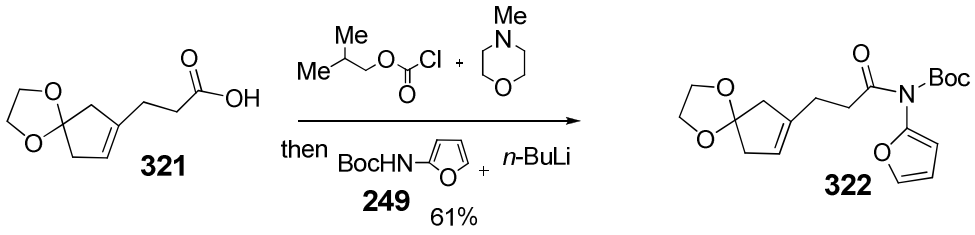
3-(3-Oxo-cyclopent-1-enyl)-propionic Acid Methyl Ester (331). The byproduct obtained from the above reaction showed the following spectral properties: IR (thin film) 2924, 1737, 1705, 1676, 1616, and 1438 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.39 – 2.42 (m, 2H), 2.58 – 2.64 (m, 4H), 2.71 (d, 1H, *J* = 7.2 Hz), 2.73 (d, 1H, *J* = 7.2 Hz), 3.68 (s, 3H), and 5.95 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.4, 31.2, 31.6, 35.2, 51.9, 129.3, 172.6, 180.4, and 209.6.



320 **321**

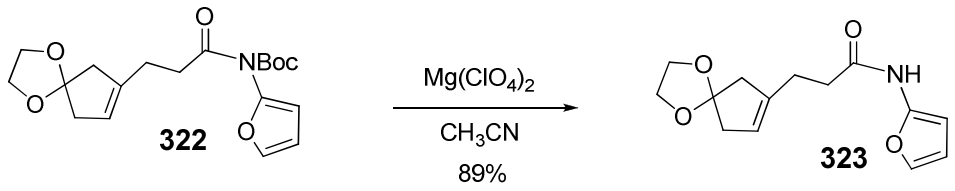
3-(1,4-Dioxa-spiro[4.4]non-7-en-7-yl)-propionic Acid (321). To a stirred solution containing 9.8 g (46 mmol) of ester **320** in 184 mL of a 4:1:3 mixture of MeOH, THF and water was added 2.3 g (55 mmol) of $LiOH{\cdot}H_2O$ at rt. The reaction mixture was stirred at rt for 12 h. A 7.7 g (55 mmol) sample of sodium hydrogen sulfate ($NaHSO_4$) was slowly added to the reaction mixture. The mixture was stirred for 30 min and the organic solvent was removed under reduced pressure. The aqueous layer was extracted with a 4:1-mixture of $CHCl_3$ and *i*-PrOH. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduce pressure. The crude residue was purified by flash silica gel column chromatography to provide 9.0 g (98%) of the titled compound **321** as a yellow oil: IR (thin film) 3492, 2906, 1707, 1651, 1424,

1342, 1016, and 851 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.34 – 2.40 (m, 2H), 2.48 – 2.53 (m, 4H), 2.57 (brs, 2H), 3.95 (s, 4H), and 5.37 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.3, 31.9, 43.3, 45.6, 64.1, 117.0, 121.1, 139.7, and 179.0.

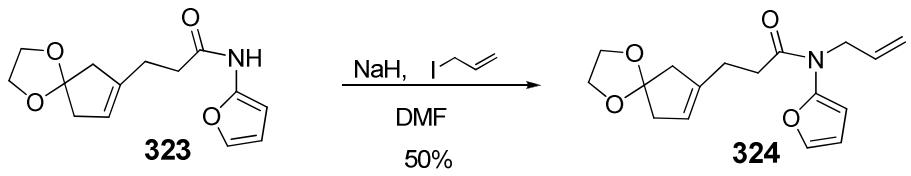


(3-1,4-Dioxa-spiro[4.4]non-7-en-7-yl-propionyl)-furan-2-yl-carbamic Acid *tert*-Butyl Ester (322). To a stirred solution containing 0.6 g (3.3 mmol) of furan-2-yl carbamic acid *tert*-butyl ester (**249**) in 13 mL of THF at -78 ^{o}C was added 1.3 mL (3.3 mmol) of *n*-BuLi (2.5 M solution in hexane). The reaction mixture was stirred at -78 ^{o}C for 1 h. In a separate flask a sample of 0.65 g (3.3 mmol) of carboxylic acid **321** was dissolved in 13 mL of THF at 0 ^{o}C and 0.36 mL (3.3 mmol) of 4-methylmorpholine and 0.42 mL (3.3 mmol) of isobutyl chloroformate were added consecutively. After stirring for 5 min, the white precipitate that formed was removed by filtration and was washed with 0.5 mL of THF. The filtrate was cooled to 0 ^{o}C and the performed lithiate was added rapidly *via* cannula to the above solution. After stirring at 0 ^{o}C for 30 min and then for an additional 2 h at rt, the mixture was quenched with water and extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to provide 0.72 g (61%) of the titled compound **322** as a pale yellow solid: mp 96 – 98 ^{o}C; IR (thin film) 2911, 1749, 1723, 1650,

1262, and 1092 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.40 (t, 2H, *J* = 7.6 Hz), 2.52 (s, 2H), 2.55 – 2.58 (m, 2H), 2.86 – 2.92 (m, 2H), 3.92 (s, 4H), 5.34 (quin, 1H, *J* = 2.0 Hz), 6.14 (dd, 1H, *J* = 2.8 and 0.8 Hz), 6.41 (dd, 1H, *J* = 2.8 and 2.0 Hz), and 7.32 (dd, 1H, *J* = 2.0 and 0.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.3, 27.7, 35.2, 43.4, 45.7, 64.1, 83.8, 105.9, 111.2, 117.1, 121.0, 140.0, 140.5, 143.8, 151.3, and 174.4.

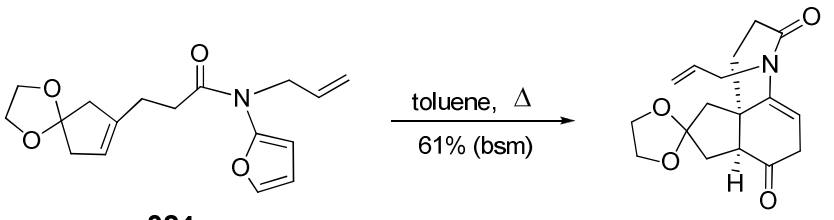


3-(1,4-Dioxa-spiro[4.4]non-7-en-7-yl)-*N*-furan-2-yl-propionamide (323). To a stirred solution containing 0.7 g (1.9 mmol) of the above amide **322** in 1.1 mL of CH_3CN was added 0.04 g (0.19 mmol) of magnesium perchlorate ($(Mg(ClO_4)_2$). The reaction mixture was stirred at 50 ^oC for 2 h and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.45 g (89%) of the titled compound **323** as an off white solid: mp 93 ^oC – 94 ^oC; IR (thin film) 3200, 3047, 2897, 1654, 1557, 1334, and 1016 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.40 – 2.60 (m, 8H), 3.92 (s, 4H), 5.34 (brt, 1H, *J* = 1.6 Hz), 6.26 (d, 1H, *J* = 2.8 Hz), 6.32 (dd, 1H, *J* = 2.8 and 2.0 Hz), 6.98 – 7.01 (m, 1H), and 8.45 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.9, 34.1, 43.2, 45.4, 64.1, 95.2, 111.3, 117.0, 121.3, 135.1, 140.0, 145.2, and 169.2.



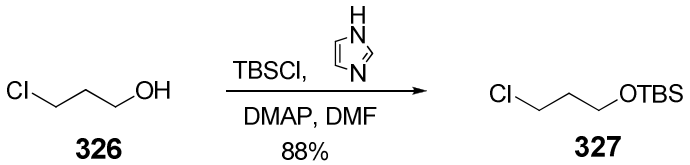
323 **324**

***N*-Allyl-3-(1,4-dioxa-spiro[4.4]non-7-en-7-yl)-*N*-furan-2-yl-propionamide (324).** To a stirred solution containing 0.42 g (1.6 mmol) of the above amide **323** in 6 mL of DMF at 0 ^{o}C was added 0.064 g (1.6 mmol) of NaH (60% in mineral oil) portionwise. The solution was warmed to rt and was stirred for an additional 1 h. The mixture was recooled to 0 ^{o}C and a 0.15 mL (1.6 mmol) sample of allyl iodide was added dropwise. After warming to rt, the mixture was stirred for 2 h, quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.24 g (50%) of the titled compound **324** as a pale yellow oil: IR (thin film) 2905, 1683, 1609, 1504, 1015, 854, and 744 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.24 – 2.27 (m,2H), 2.31 – 2.36 (m, 2H), 2.43 (s, 2H), 2.51 (s, 2H), 3.90 (s, 4H), 4.18 (d, 2H, *J* = 6.8 Hz), 5.09 (s, 1H), 5.12 (dd, 1H, *J* = 6.8 and 1.6 Hz), 5.22 (t, 1H, *J* = 1.6 Hz), 5.73 – 5.84 (m, 1H), 6.07 (dd, 1H, *J* = 3.2 and 0.8 Hz), 6.36 (dd, 1H, *J* = 3.2 and 2.0 Hz), and 7.25 – 7.28 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.8, 31.7, 43.3, 45.5, 50.8, 64.0, 104.7, 111.1, 117.0, 117.7, 120.6, 132.7, 140.1, and 140.3.



324 **325**

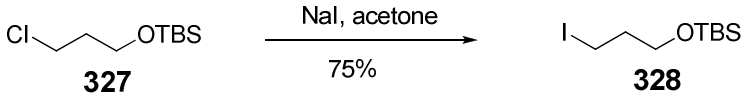
Formation of Tetracyclic (325). A mixture containing 0.06 g (0.20 mmol) of the above furanyl carbamate **324** in 1 mL of toluene was heated at 200 ^{o}C in a sealed tube for 7 d. The solution was cooled to rt and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.028 g (47%) of the titled compound **325** as a yellow oil together 0.24 g (40%) of recovered starting material: IR (thin film) 3441, 2935, 2868, 1706, 1624, and 1199 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.75 (d, 2H, *J* = 14.0 Hz), 1.83 – 1.93 (m, 2H,), 2.06 – 2.20 (m, 3H), 2.60 – 2.74 (m. 4H), 3.03 (dd, 1H, *J* = 20.8 and 4.0 Hz), 3.11 (dd, 1H, *J* = 20.8 and 4.0 Hz), 3.75 – 3.90 (m, 3H), 4.05 (dd, 1H, *J* = 16.4 and 5.2 Hz), 4.57 (dd, 1H, *J* = 16.4 and 5.2 Hz), 5.08 (t, 1H, *J* = 4.0 Hz), 5.10 (d, 1H, *J* = 10.4 Hz), 5.16 (d, 1H, *J* = 10.4 Hz), 5.70 – 5.82 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.2, 31.7, 35.0, 37.1, 43.2, 46.8, 48.8, 56.7, 71.2, 100.2, 116.4, 132.7, 141.3, 168.4, and 208.1.



326 **327**

***tert*-Butyl-(3-chloro-propoxy)-dimethyl-silane (327).** A stirred solution containing 15 g (159 mmol) of alcohol **326** in 79 mL of DMF was added 27 g (397 mmol) of imidazole and 1.9 g (16 mmol) of 4-dimethylaminopyridine (DMAP)

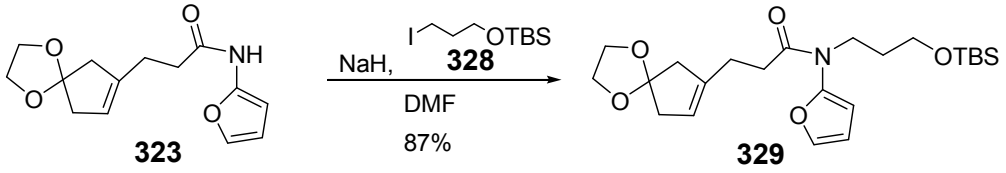
consecutively. The resulting mixture was cooled to 0 °C for 15 min and a 36 g (238 mmol) sample of *tert*-butyldimethylsilyl chloride (TBSCl) was added in one portion. The reaction mixture was allowed to warm to rt and was stirred overnight and then quenched with water, and extracted with EtOAc. The combined organic layer was washed several times with water, followed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 29.3 g (88%) of the titled compound **327** as a clear oil: IR (thin film) 2955, 1468, 1255, 1105, and 839 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.94 (quin, 2H, *J* = 6.0 Hz), 3.64 (t, 2H, *J* = 6.0 Hz), and 3.74 (t, 2H, *J* = 6.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.5, 18.3, 25.9, 35.4, 41.7, and 59.3.



327 **328**

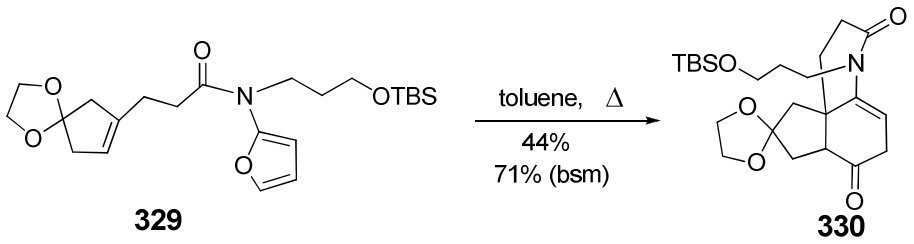
***tert*-Butyl-(3-iodo-propoxy)-dimethyl-silane (328).** To a stirred solution containing 32.3 mL (155 mmol) of the above chloride **327** in 310 mL of acetone was added 28 g (186 mmol) of sodium iodide, and the resulting mixture was heated at reflux for 24 h. After cooling to rt, the white precipitate that formed was removed by filtration through celite and washed thoroughly with acetone. The filtrate was concentrated under reduced pressure and the resulting slurry was washed with EtOAc, water, a saturated aqueous Na_2SO_3 solution, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to provide 35 g (75%) of the titled compound **328** as a light yellow oil which was

used in the next step without further purification: IR (thin film) 2953, 1468, 1253, 1101, and 836 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.64 (s, 6H), 0.89 (s, 9H), 1.94 – 2.01 (m, 2H), 3.27 (t, 2H, *J* = 6.8 Hz), and 3.66 (t, 2H, *J* = 6.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.3, 3.8, 18.3, 25.9, 36.1, and 62.3.



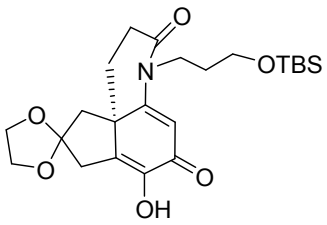
***N*-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-3-(1,4-dioxa-spiro[4.4]non-7-en-7-yl)-*N*-furan-2-yl-propionamide (329).** To a stirred solution containing 3.2 g (12 mmol) of amide **323** in 24 mL of DMF at 0 ^oC was added 0.51 g (12.8 mmol) of NaH (60% in mineral oil) portionwise. The solution was warmed to rt and was stirred for an additional 1 h. The mixture was recooled to 0 ^oC and a solution of 3.8 mL (12.8 mmol) of allyl iodide in 24 mL of DMF was added dropwise. After being warmed to rt, the mixture was stirred for 2 h, quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 4.6 g (87%) of the titled compound **329** as a pale yellow oil: IR (thin film) 3122, 2860, 1685, 1608, and 1506 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ -0.03, (s, 6H), 0.80 (s, 9H), 1.68 – 1.74 (m, 2H), 2.17 – 2.21 (m, 2H), 2.27 – 2.32 (m, 2H), 2.41 (s, 2H), 2.50 (s, 2H), 3.59 (t, 2H, *J* = 6.0 Hz), 3.63 (t, 2H, *J* = 6.8 Hz), 3.88 (s, 4H), 5.19 (s, 1H), 6.05 (d, 1H, *J* = 3.2 Hz), 6.35 (dd, 1H, *J* = 2.0 and 3.2 Hz), and 7.24 (d,

1H, *J* = 2.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.5, 18.2, 25.8, 26.9, 31.3, 31.8, 43.3, 45.5, 45.6, 60.6, 64.1, 104.5, 111.1, 117.0, 120.6, 140.0, 140.4, 148.6, and 173.3.



329 **330**

Formation of Tetracycle 330. A solution containing 4.6 g (11 mmol) of the cyclopentenyl substituted furan **329** in 110 mL of toluene was heated at 200 °C in a sealed tube for 10 d. The solution was cooled to rt and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 1.6 g (44%) of the titled compound **330** as an orange oil together with 1.57 g (34%) of recovered starting material: IR (thin film) 2928, 1743, 1720, 1652, 1602, 1378, and 1216 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 1.65 – 1.90 (m, 3H), 1.72 (d, 1H, *J* = 13.6 Hz), 2.05 – 2.15 (m, 3H), 2.56 – 2.62 (m, 2H), 2.68 (s, 1H), 2.69 (dd, 1H, *J* = 24.0 and 3.2 Hz), 3.07 (dd, 1H, *J* = 21.0 and 4.0 Hz), 3.13 (dd, 1H, *J* = 21.0 and 4.0 Hz), 3.58 – 3.96 (m, 8H), and 5.25 (t, 1H, *J* = 4.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.5, 18.1, 25.8, 29.0, 30.0, 30.7, 36.0, 37.1, 41.0, 43.9, 46.5, 55.3, 60.5, 64.2, 64.5, 99.7, 115.4, 140.5, 168.0, and 207.3.



330b

Formation of Tricycle 330b. After standing in a refrigerator for several days, the compound **330** was gradually transformed into a new compound **330b** whose structure was confirmed by a single-crystal X-ray analysis (Figure 3): mp 119 – 121 ^{o}C; IR (thin film) 3355, 2952, 2933, 2887, 2859, 1734, 1686, 1629, 1586, 1386, 1182, 1104, 838, and 778 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.05 (d, H, *J* = 4.0 Hz), 0.90 (s, 9H), 1.75 (dd, 1H, *J* = 13.2 and 1.2 Hz), 1.68 – 1.85 (m, 5H), 2.31 (d, 1H, *J* = 13.2 Hz), 2.48 – 2.56 (m, 1H), 2.78 (dd, 1H, *J* = 8.0 and 2.0 Hz), 2.76 (dd, 1H, *J* = 12.0 and 7.2 Hz), 2.84 (d, 1H, *J* = 17.6 Hz), 3.10 (d, 1H, *J* = 17.6 Hz), 3.57 – 3.67 (m, 2H), 3.80 – 3.94 (m, 6H), 4.00 – 4.06 (m, 1H), 6.00 (s, 1H), and 6.44 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) -5.5, 18.2, 25.8, 26.5, 28.8, 30.1, 37.6, 41.4, 44.3, 46.5, 60.3, 64.3, 64.8, 105.4, 114.9, 129.9, 141.8, 161.9, 168.4, and 181.1.

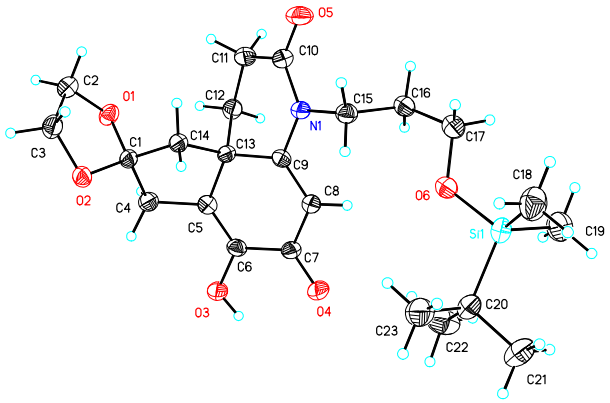
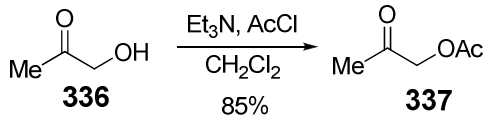
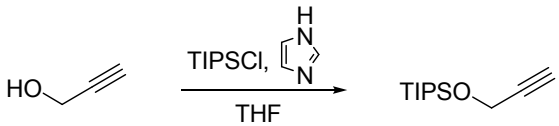


Figure 7. ORTEP of cycloadduct **330b**



336 **337**

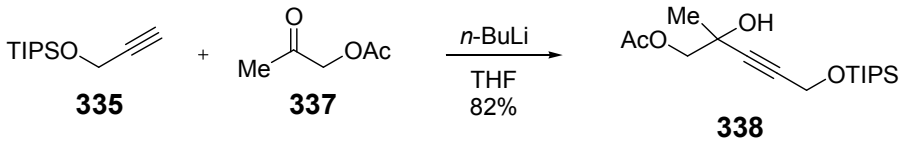
2-Oxopropyl Acetate (337). To a stirred solution containing 20.0 mL (0.29 mol) of 1-hydroxypropan-2-one (**336**) in 150 mL of CH_2Cl_2 at -10.5 ºC was added 44.7 mL (0.32 mol) of trimethylamine. To this mixture was added 22.8 mL (0.32 mol) of acetyl chloride dropwise over 30 min. The resulting suspension was allowed to warm to rt over a 4 h period and then poured into a separatory funnel containing water. The layers were separated, and the organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by distillation to afford 28.6 g (85%) of the titled compound **337** as a light yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.13 (s, 3H), and 4.62 (s, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 26.0, 68.2, 170.2, and 201.6. The spectral properties of **337** are consistent with those reported in literature.[164]



334 **335**

Triisopropyl(prop-2-ynyloxy)silane (335). To a stirred solution containing 5.19 mL (89.2 mmol) of prop-2-yn-1-ol (**334**) and 6.68 g (98.1 mmol) of imidazole in 50 mL of DMF at rt was added 18.9 mL (89.2 mmol) of triisopropylsilyl chloride (TIPSCl) at rt. The resulting mixture was stirred at rt for 4 h and then poured into a separatory funnel containing ice water and EtOAc. After separation of the layers, the organic layer was washed with water, brine and dried over $MgSO_4$.

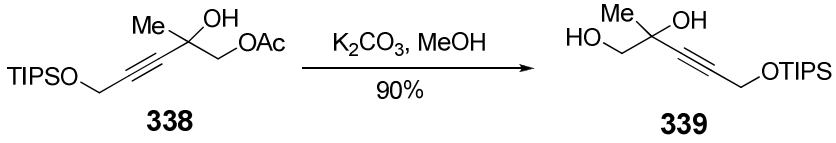
The combined organic layer was concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography to give 18.0 g (95%) of the titled compound **335** as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.01 – 1.15 (m, 21H), 2.38 (t, 1H, *J* = 2.4 Hz) and 4.37 (d, 2H, *J* = 2.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$)δ 11.9, 17.9, 51.7, 72.6, and 82.4. The spectral properties obtained are consistent with that reported in literature.[165]



2-Hydroxy-2-methyl-5-(triisopropylsilyloxy)pent-3-ynyl Acetate (338).

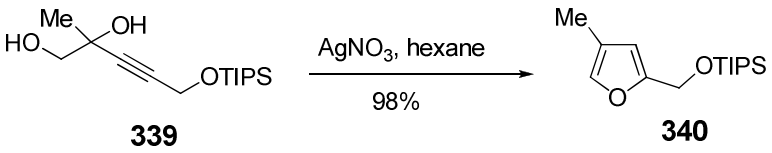
To a stirred solution containing 4.9 g (23.2 mmol) of triisopropyl(prop-2-ynyloxy)silane) (**335**) in 75 mL of THF at -78 ºC was added 9.3 mL (23.2 mmol) of *n*-BuLi (2.5 M solution in hexane). The reaction mixture was stirred for 1 h at -78 ^{o}C and then a solution of 3.2 g (27.9 mmol) of 2-oxopropyl acetate (**337**) in 10 mL of THF was added. The reaction mixture was allowed to warm to rt over 4 h, then poured into a separatory funnel containing water and EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude residue was purified by silica gel flash column chromatography to provide 6.28 g (82%) of the titled compound **338** as a colorless oil: IR (neat) 3423, 2943, 2892, 2866, 1745, 1463, 1270, and 881 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.04 – 1.11 (m, 21H), 1.46 (s, 3H), 2.09 (s, 3H), 2.56 (brs, 1H), 3.99 (d, 1H, *J* = 7.6 Hz), 4.16 (d, 1H, *J* = 7.6 Hz), and 4.37 (s,

2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.9, 17.8, 25.8, 51.8, 66.6, 70.9, 83.1, 85.1, 101.7, and 170.8.



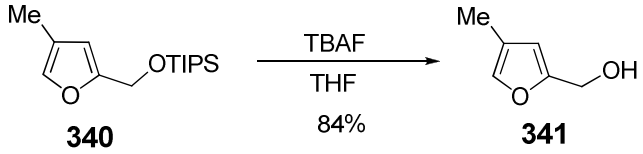
338 **339**

2-Methyl-5-(triisopropylsilyloxy)pent-3-yne-1,2-diol (339). To a stirred solution containing 5.9 g (18 mmol) of the above acetate **338** in 100 mL of MeOH at rt was added 4.9 g (36 mmol) of potassium carbonate. The resulting suspension was stirred for 4 h at rt and the solvent was removed under reduced pressure. The resultant slurry was dissolved in EtOAc and washed with water. The organic phase was washed with brine, dried over $MgSO_4$, and the solvent was removed under reduce pressure. The crude residue was purified by flash silica gel column chromatography to provide 4.6 g (90%) of the titled compound **339** as a colorless oil: IR (neat) 3375, 2942, 2864, 1458, 1099, and 878 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.04 – 1.10 (m, 21H), 1.43 (s, 3H), 2.33 (dd, 1H, *J* = 8.4 and 4.4 Hz), 2.76 (s, 1H), 3.44 (dd, 1H, *J* = 10.8 and 8.4 Hz), 3.63 (dd, 1H, *J* = 10.8 and 4.4 Hz), and 4.39 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.9, 17.8, 25.0, 51.8, 68.5, 70.6, 83.2, and 85.9.



339 **340**

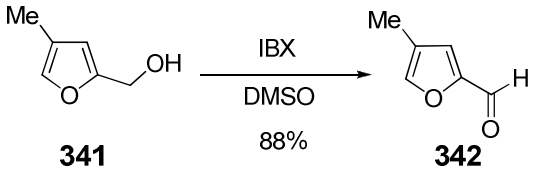
Triisopropyl((4-methylfuran-2-yl)methoxy)silane (340).[166] To a slurry containing silver nitrate adsorbed on silica gel (10% w/w, 8.0 g) in hexane (50 mL) at rt was added a solution of 4.37 g (15.25 mmol) of diol **339** in 60 mL of hexane. The resulting suspension was stirred at rt in the dark for 4 h. The reaction mixture was then filtered through a basic alumina column and washed successively with Et_2O. The filtrate was concentrated under reduced pressure and the oil obtained was purified by silica gel flash column chromatography to afford 4.0 g (98%) of the titled compound **340** as a colorless oil: IR (neat) 2938, 2856, 1454, 1242, 1062, and 874 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.04 – 1.08 (m, 21H), 1.99 (d, 3H, *J* = 0.8 Hz), 4.64 (d, 2H, *J* = 0.4 Hz), 6.09 (s, 1H), and 7.11 (t, 1H, *J* = 0.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.8, 12.0, 17.9, 58.6, 109.5, 120.4, 138.4, and 154.5.



340 **341**

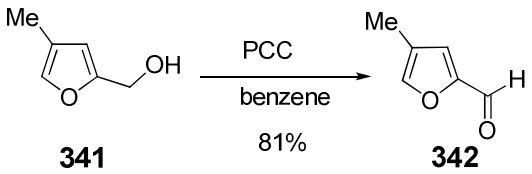
(4-Methylfuran-2-yl)methanol (341). To a stirred solution containing 1.57 g (5.85 mmol) of the above furan **340** in 70 mL of THF at 0 ºC was added a solution of 7.02 mL (7.02 mmol) of tetrabutylammonium fluoride (TBAF, 1.0 M solution in THF). The reaction mixture was allowed to warm to rt over 2 h and the resulting solution was poured into a separatory funnel containing ethyl acetate

and ice water. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the oil by silica gel flash column chromatography afforded 0.55 g (84%) of the titled compound **341** as a colorless oil: IR (neat) 3322, 2921, 2868, 1671, 1446, 1283, 1119, and 997 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.98 (d, 3H, *J* = 1.2 Hz), 2.22 (brs, 1H), 4.62 (s, 1H), 4.47 (s, 1H), 6.12 (s, 1H), and 7.13 (q, 1H, *J* = 1.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.6, 57.4, 110.4, 120.6, 139.1, and 153.9.



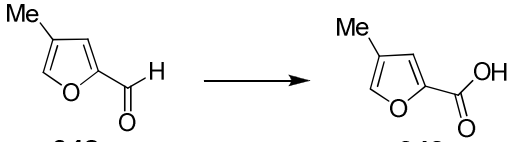
341 **342**

4-Methylfuran-2-carbaldehyde (342). To a stirred solution containing 0.77 g (6.90 mmol) of furan **341** in 30 mL of DMSO was added 2.13 g (7.59 mmol) of iodoxybenzoic acid (IBX) in one portion at rt. The mixture was stirred for 2 h at rt, water was added and the mixture was extracted with Et_2O. The combined organic layer was washed with water followed by brine. The mixture was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography to afford 0.67 g (88%) of the titled compound **342** as a light yellow oil: IR (neat) 2958, 2925, 2872, 2819, 1671, 1593, 1495, and 931 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.98 (d, 3H, *J* = 1.2 Hz), 7.01 (s, 1H), 7.36 (d, 1H, *J* = 0.8 Hz), and 9.46 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.2, 122.9, 123.1, 145.2, 152.6, and 177.7.



341 **342**

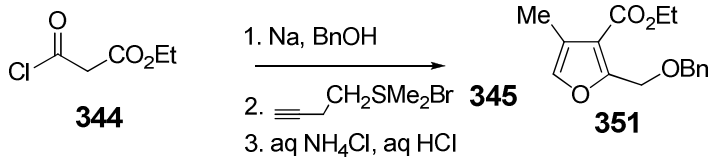
4-Methylfuran-2-carbaldehyde (342).[167] An alternate method to prepare aldehyde **341** involves the following procedure. To a stirred solution containing 0.05 g (0.45 mmol) of furan **341** in 4.5 mL of benzene was added 0.1 g (0.45 mmol) of pyridinium chlorochromate (PCC) at 0 ^{o}C. The reaction mixture was stirred for 4 h at 0 ^{o}C, water was added and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography to afford 0.04 g (81%) of the titled compound **342** as a light yellow oil.



342 **343**

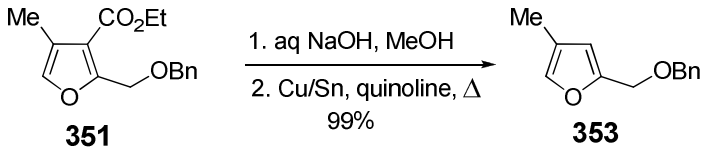
4-Methylfuran-2-carboxylic Acid (343). To a suspension of 0.1 g (0.91 mmol) of the above aldehyde **342** in 5 mL of EtOH at rt was added an aqueous solution of 0.34 g (2.2 mmol) of silver(I) nitrate ($AgNO_3$) in 3 mL of water and then an aqueous solution of 0.11 g (0.27 mmol) of sodium hydroxide in 2 mL of water. The resulting suspension was stirred vigorously for 12 h at rt and then poured into a round bottom flask containing ice water and EtOAc. The mixture was acidified to pH4 by the slow addition of a concentrated HCl solution. The solution was poured into separatory funnel and the layers were separated. The aqueous

layer was further extracted with EtOAc, and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was recrystallized from Et_2O to afford 0.08 g (70%) of the titled compound **343** as a white solid: mp 124 – 127 ^oC; IR (neat) 3387, 2917, 2860, 1671, 1601, 1307, and 935. ^1H-NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H), 7.18 (s, 1H), 7.40 (s, 1H), and 11.58 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.5, 122.3, 122.7, 145.5, 144.5, and 163.9.



2-Benzyloxymethyl-4-methyl-furan-3-carboxylic Acid Ethyl Ester (351). To a stirred suspension of 36 g (893 mmol) of NaH (60% in mineral oil) in 400 mL of THF at rt was added 92 mL (893 mmol) of benzyl alcohol dropwise over 1 h. The reaction mixture was stirred for an additional 1 h and then a solution of 57.5 mL (425 mmol) of ethyl-4-chloroacetoacetate (**344**) was added dropwise over 1.5 h. After stirring for 3 h, the mixture was transferred by cannula to a stirred suspension of 85 g (468 mmol) of dimethyl-2-propynylsulfonium bromide (**345**) [168] in 100 mL of THF at rt. The reaction mixture was stirred at rt for an additional 24 h, then quenched with 1 L of an aqueous NH_4Cl solution followed by the slow addition of 500 mL of an aqueous 10 M HCl solution. The mixture was adjusted to pH4 by the addition of an aqueous 5 M HCl solution dropwise and was then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 116 g (100%) of the

title compound **351** as a pale yellow solid: mp 155-158 ^{o}C; IR (thin film) 2984, 1715, 1612, 1556, 1272, and 1096 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, *J* = 6.8 Hz), 2.15 (d, 3H, *J* = 1.2 Hz), 4.26 (q, 2H, *J* = 6.8 Hz), 4.58 (s, 2H), 4.80 (s, 2H), 7.18 (d, 1H, *J* = 1.2 Hz), and 7.20 – 7.34 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.7, 14.0, 60.0, 63.0, 72.4, 116.2, 121.1, 127.5, 127.6, 128.1, 137.7, 139.5, 157.4, and 163.7.

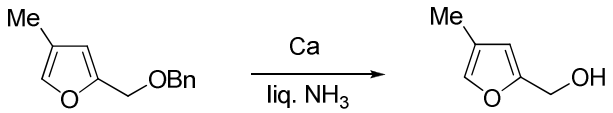


351 **353**

2-Benzyloxymethyl-4-methyl-furan (353). To a stirred solution containing 1.0 g (3.8 mmol) of the above ester **351** in 15 mL of a 2:1 mixture of MeOH and water was added 0.19 g (4.6 mmol) of $LiOH{\cdot}H_2O$ in one portion. After stirring for 48 h at 60 ^{o}C, the solvent was removed under reduced pressure and the aqueous residue was acidified to pH 3 with an aqueous 6 M HCl solution and extracted with EtOAc. The combined organic layer was concentrated under reduced pressure to provide the corresponding carboxylic acid as a pale yellow solid which was used for the next step without purification: mp 107 – 109 ^{o}C; IR (thin film) 2859, 1382, 1554, 1435, 1283, 1122, and 962 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 4.62 (s, 2H), 4.85 (s, 2H), and 7.20 – 7.45 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.8, 63.3, 72.8, 115.5, 121.8, 127.8, 128.0, 128.4, 137.5, 159.0, and 169.0.

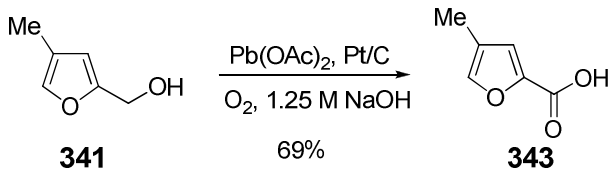
To a sample of the above furanyl acid in 2 mL (19 mmol) of quinoline was added 0.07 g (1.2 mmol) of copper at rt and the mixture was heated at 230 ^{o}C for

30 min. After cooling to rt, the mixture was treated with 0.85 g (9 mmol) of oxalic acid and stirred for 30 min at rt. The precipitate that formed was removed by filtration and was washed thoroughly with EtOAc. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash silica gel column chromatography to provide 0.94 g (99%) of the titled compound **353** as a pale yellow oil: IR (thin film) 3031, 2858, 1453, 1356, 1122, and 1071 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.02 (d, 3H, *J* = 1.2 Hz), 4.43 (s, 1H), 4.55 (s, 1H), 6.20 (s, 1H), 7.19 (t, 1H, *J* = 1.2 Hz), 7.28 – 7.38 (m, 2H), 7.34 (s, 1H), and 7.36 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.6, 63.9, 71.7, 112.0, 120.5, 127.6, 127.8, 128.3, 137.9, 139.4, and 151.6.



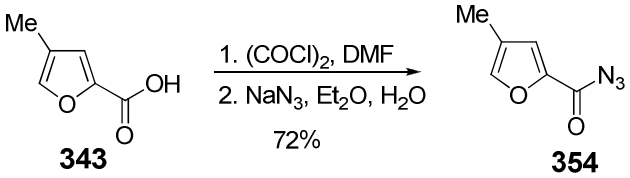
353 **341**

(4-Methyl-furan-2-yl)-methanol (341). A flask containing 1.64 g (20.5 mmol) of calcium at -78 ^{o}C was filled with approximately 200 mL of liquid NH_3. A solution of 4.15 g (20.5 mmol) of **353** in 82 mL of THF was slowly transferred into this mixture by cannula. The solution was stirred at -78 ^{o}C for 2 h and then an aqueous NH_4Cl solution was added dropwise. The reaction mixture was allowed to warm to rt and was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography to afford 2.09 g (91%) of the title compound **341** as a colorless oil.



341 **343**

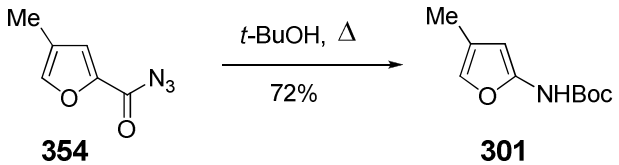
4-Methyl-furan-2-carboxylic Acid (343). To a suspension of 1.5 g (13 mmol) of alcohol **341** in 52 mL of an aqueous 1.25 M NaOH solution was added 0.05 g (0.13 mmol) of $Pb(OAc)_2{\cdot}3H_2O$ followed by 0.78 g (0.40 mmol) of Pt/C (10% w/w) at rt. The resulting mixture was stirred at rt and O_2 gas was continuously bubbled into the solution. The reaction was monitored by TLC and upon completion the mixture was filtered through celite and washed thoroughly with water. The filtrate was acidified to pH 3 by the slow addition of an aqueous 2.5 M HCl solution and was then extracted with a 4:1-mixture of $CHCl_3$ and *i*-PrOH. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduce pressure to provide 1.16 (69%) of the titled compound **343** as a light brown solid.



343 **354**

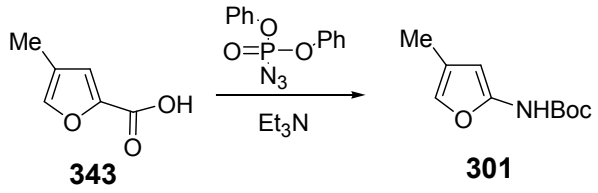
4-Methyl-furan-2-carbonyl Azide (354). To a stirred suspension of 0.93 g (7.5 mmol) of carboxylic **343** in 30 mL of CH_2Cl_2 at rt was added 0.63 mL (7.4 mmol) of oxalyl chloride $(COCl)_2$ followed by a few drops of DMF. The resulting mixture was stirred at rt for 1 h and the solvent was removed under reduce pressure. The crude residue was taken up in 30 mL of Et_2O and cooled to 0 ^oC. An aqueous solution of sodium azide (NaN_3) in 8 mL of water was added dropwise. After

being stirred at rt for 4.5 h, the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography to provide 0.81 g (72%) of the titled compound **354** as a white solid: mp 30 – 33 ^oC; IR (neat) 2927, 2143, 1703, 1505, 1198, and 1007 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 2.07 (d, *J* = 1.2 Hz), 7.11 (brs, 1H), and 7.42 (t, 1H, *J* = 1.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 8.9, 121.8, 122.7, 144.9, 145.0, and 162.0.

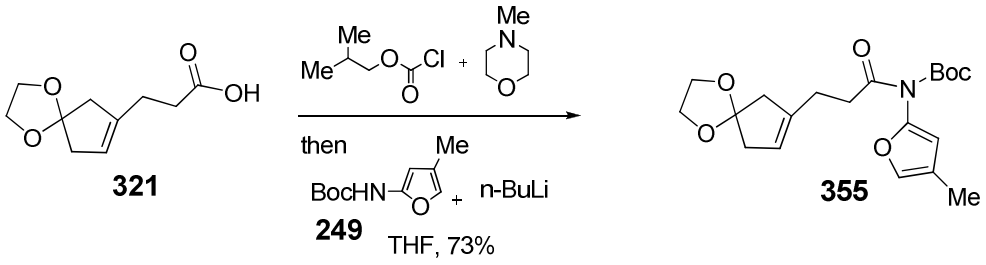


354 **301**

(**4-Methyl-furan-2-yl)-carbamic Acid *tert*-Butyl Ester (301).** A solution containing the acyl azide **354** in *t*-BuOH was heated at 80 ^oC for 5 h. The reaction was then cooled to rt and the solvent was removed under reduced pressure. The crude residue was purified by silica gel flash column chromatography to provide 0.81 g (72%) of the titled compound **301** as a yellow oil: IR (neat) 3280, 1770, 1550, and 1157 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ1.50 (s, 9H), 1.98 (d, 3H, *J* = 1.2 Hz), 5.85 (brs, 1H), 6.55 (brs, 1H), and 6.82 (t, 1H, *J* = 1.2 Hz)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 10.0, 28.0, 28.1, 97.3, 121.4, 128.7, 132.1, and 145.2.

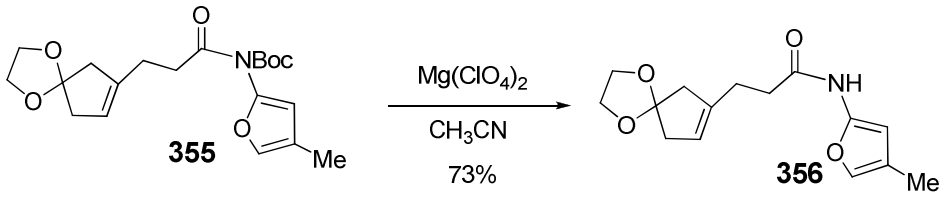


(4-Methyl-furan-2-yl)-carbamic Acid *tert*-Butyl Ester (301). An alternate method to prepare carbamate **301** involves treating a 0.2 g sample (1.59 mmol) of **343** in 6 mL of *t*-BuOH with 0.27 mL (1.90 mmol) of triethylamine and 0.4 mL (1.90 mmol) of diphenylphosphoryl azide (DPPA) at rt. The mixture was heated at 100 ^{o}C for 2 h. Water was added and the excess *t*-BuOH was removed under reduced pressure. The crude mixture was extracted with Et_2O and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.11 g (35%) of the titled compound **301** as a yellow oil.



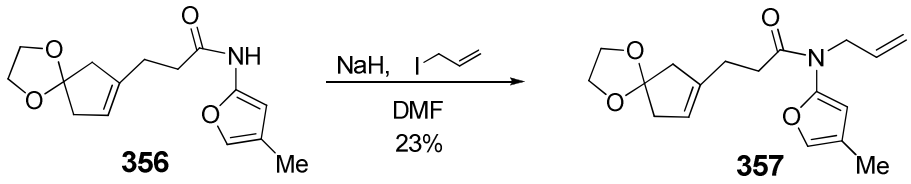
(3-1,4-Dioxa-spiro[4.4]non-7-en-7-yl-propionyl)-(4-methyl-furan-2-yl)-carbamic Acid *tert*-Butyl Ester (355). To a stirred solution containing 2.83 g (14.4 mmol) of furanyl carbamate **249** in 58 mL of THF was added 5.8 mL (14.4 mmol) of *n*-BuLi (2.5 M solution in hexane) dropwise at 0 ^{o}C and the reaction mixture was stirred at 0 ^{o}C for 20 min. In a separate flask, 2.85 g (14.4 mmol) of

the above acid was dissolved in 58 mL of THF at 0 ^{o}C and 1.58 mL (1.44 mmol) of 4-methylmorpholine and 1.87 mL (1.44 mmol) of isobutyl chloroformate were added consecutively. After stirring for 5 min, the white precipitate that formed was removed by filtration and was washed with 5.0 mL of THF. The filtrate was cooled to 0 ^{o}C and the performed lithiate was quickly transferred *via* cannula to the above solution. After stirring at 0 ^{o}C for 30 min and at rt for 2 h, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to provide 4.0 g (73%) of the titled compound **355** as a pale yellow solid: mp 96 – 98 ^{o}C; IR (thin film) 2977, 2930, 1784, 1746, 1625, 1550, and 1369 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.02 (d, 3H, *J* = 1.2 Hz), 2.39 (brt, 2H, *J* = 7.6 Hz), 2.52 (s, 2H), 2.55 – 2.59 (m, 2H), 2.84 – 2.90 (m, 2H), 2.93 (s, 4H), 5.33 (sept, 1H, *J* = 2.0 Hz), 6.00 (s, 1H), and 7.09 (t, 1H, *J* = 1.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 10.2, 26.4, 27.8, 35.2, 43.4, 45.7, 64.1, 83.8, 108.3, 117.1, 121.0, 121.5, 137.1, 140.1, 143.4, 151.5, and 174.4.



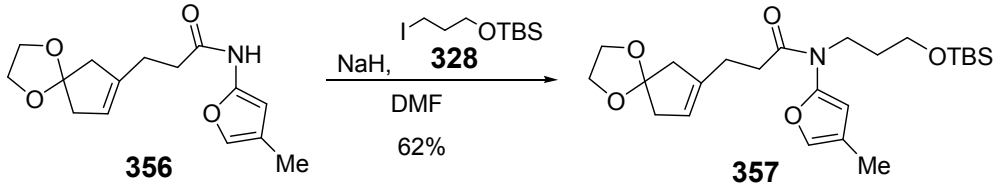
3-(1,4-Dioxa-spiro[4.4]non-7-en-7-yl)-*N*-(4-methyl-furan-2-yl)-propionamide (356). To a stirred solution containing 3.2 g (8.5 mmol) of the protected amide **355** in 34 mL of CH_3CN was added 0.19 g (0.85 mmol) of magnesium

perchlorate ($Mg(ClO_4)_2$). The reaction mixture was stirred at 45 ^oC for 2 h and the solvent was then removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 1.72 g (73%) of the titled compound **356** as a pale yellow solid: mp 100 – 102 ^oC; IR (thin film) 3244, 3222, 3055, 2898, 1728, 1657, 1557, 1332, 1081, and 851 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 1.93 (d, 3H, *J* = 0.8 Hz), 2.39 – 2.44 (m, 4H), 2.48 (brs, 2H), 2.53 (brs, 2H), 3.89 (s, 4H), 5.30 (s, 1H), 6.12 (s, 1H), 6.74 (s, 1H), and 8.43 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 10.0, 26.9, 34.1, 43.2, 45.4, 64.0, 97.8, 117.0, 121.2, 121.6, 131.5, 140.0, 145.1, and 169.0.



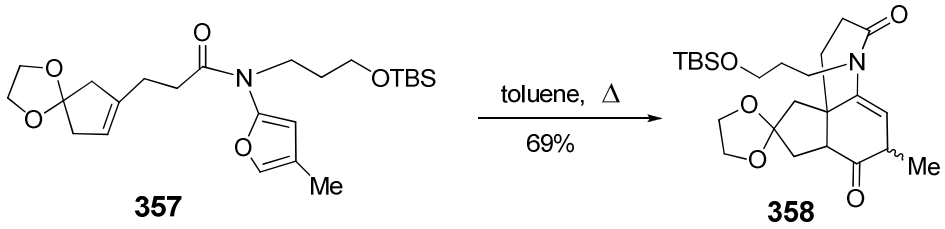
***N*-Allyl-3-(1,4-dioxa-spiro[4.4]non-7-en-7-yl)-*N*-(4-methyl-furan-2-yl)-propionamide (357).** To a stirred solution containing 0.45 g (1.61 mmol) of amide **356** in 6.4 mL of DMF at 0 ^oC was added 0.07 g (1.05 mmol) of NaH (60% in mineral oil) portionwise. The solution was warmed to rt and stirred for 1 h. The mixture was recooled to 0 ^oC and 0.16 mL (1.69 mmol) of allyl iodide was added dropwise. The resulting solution was allowed to warm to rt and was further stirred for 2 h. The mixture was then quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.12 g (23%) of the titled

compound **357** as a pale yellow oil: IR (thin film) 2908, 1684, 1624, 1553, 1453, 1114, and 1019 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.96 (d, 3H, *J* = 0.8 Hz), 2.21 – 2.30 (m, 4H), 2.40 (s, 2H), 2.48 (s, 2H), 3.87 (s, 4H), 4.11 (d, 2H, *J* = 6.0 Hz), 5.02 – 5.12 (m, 2H), 5.19 (s, 1H), 5.75 (ddt, 1H, *J* = 17.0, 10.2, and 6.0 Hz), 5.90 (s, 1H), and 6.98 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.9, 26.7, 31.5, 43.2, 45.4, 50.6, 63.9, 106.9, 116.9, 117.3, 120.6, 121.2, 132.7, 136.4, 140.2, 147.8, and 173.0.



***N*-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-3-(1,4-dioxa-spiro[4.4]non-7-en-7-yl)-*N*-(4-methyl-furan-2-yl)-propionamide (357).** To a stirred solution containing 1.45 g (5.23 mmol) of amide **356** in 10.5 mL of DMF at 0 ^oC was added 0.22 g (5.49 mmol) of NaH (60% in mineral oil) portionwise. The solution was warmed to rt and was stirred for 1 h. The reaction mixture was recooled to 0 ^oC and a solution of 1.72 g (5.49 mmol) of iodo compound **328** in 10.5 mL of DMF was added slowly *via* cannula. After warming to rt the solution was stirred for 4 h, and was then quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 1.46 g (62%) of the titled compound **357** as a pale yellow oil: IR (thin film) 2931, 2861, 1684, 1625, 1554, 1110, and

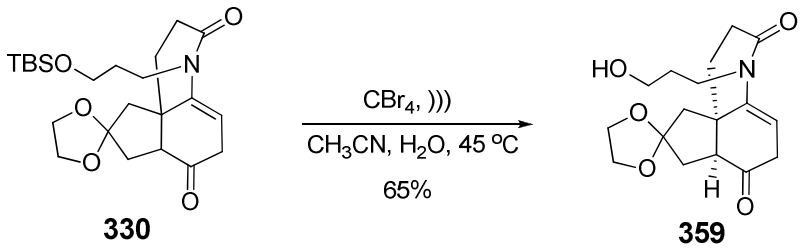
841 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ -0.01 (s, 6H), 0.83 (s, 9H), 1.71 (pent, *J* = 6.8 Hz), 1.99 (s, *J* = 3H), 2.20 – 2.24 (m, 2H), 2.20 – 2.39 (m, 2H), 2.43 (s, 2H), 2.51 (s, 2H), 3.59 (t, 2H, *J* = 6.8 Hz), 3.62 (t, 2H, *J* = 6.8 Hz), 3.89 (s, 4H), 5.21 (s, 1H), 5.92 (s, 1H), and 7.00 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.5, 10.0, 18.1, 25.8, 16.9, 31.3, 31.7, 43.3, 45.4, 45.5, 60.5, 64.0, 106.8, 117.0, 120.6, 121.3, 136.4, 140.4, 148.3, and 173.3.



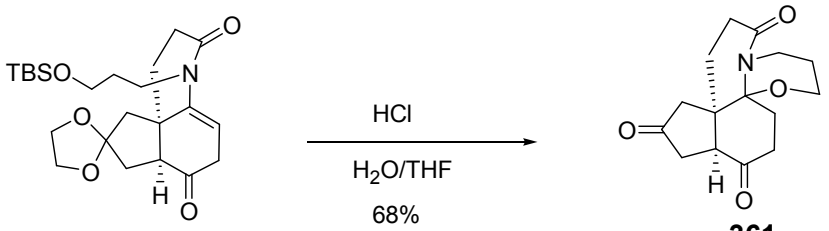
357 **358**

Formation of Tetracycle 358. A solution of 1.46 g (3.25 mmol) of the above cyclopentenyl furan **357** in 33 mL of toluene was heated at 200 ^{o}C in a sealed tube for 14 d. The solution was cooled to rt and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 1.01 g (69%) of tetracycle **358** as a yellow oil which consisted of a mixture of diastereomers: IR (thin film) 2955, 2933, 2858, 1717, 1670, 1640, 1256, 1188, 1098, and 837 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$; mixture of isomers) δ 0.04 (s, 12H), 0.88 (s, 18H), 1.19 (minor isomer, d, 3H, *J* = 6.8 Hz), 1.20 (major isomer, d, 3H, *J* = 7.2 Hz), 1.40 – 3.22 (m, 22H), 3.60 – 4.00 (m, 18H), 5.05 (minor isomer, d, 1H, *J* = 2.8 Hz), 5.08 (major isomer, d, 1H, *J* = 2.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$; mixture of isomers) δ -5.4, 16.3, 18.1, 18.2, 25.8, 25.9, 29.1, 29.2, 29.8, 29.9, 30.3, 31.3, 33.9, 37.2, 39.8, 40.6, 40.9, 41.5,

43.3, 44.1, 46.9, 48.4, 53.8, 54.7, 60.6, 64.2, 64.3, 64.4, 64.5, 106.6, 107.2, 115.5, 139.9, 140.4, 168.1, 207.5, 210.5.

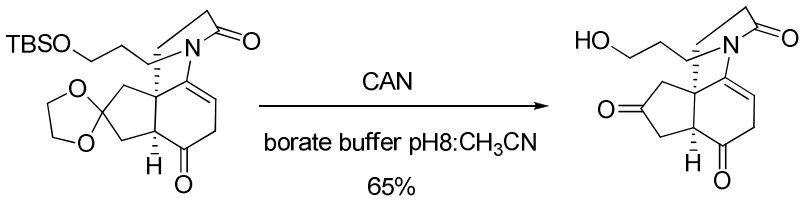


Formation of Tetracycle 359. To a solution containing 0.027 g (0.062 mmol) of the protected alcohol **330** in 0.25 mL of CH_3CN and 0.5 mL of water at rt was added 0.004 g (0.12 mmol) of carbon tetrabromide (CBr_4) in one portion. The solution was sonicated at 45 ^oC for 4 h. The reaction mixture was cooled to rt, quenched with a saturated aqueous $NaHCO_3$ solution and extracted with a 4:1-mixture of $CHCl_3$ and *i*-PrOH. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.013 g (65%) of the titled compound **359** as a clear oil: IR (thin film) 3420, 2952, 1717, 1669, and 1635 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ -1.66 (d, 1H, *J* = 14 Hz), 1.69 – 1.80 (m, 2H), 1.80 – 1.90 (m, 1H), 2.06 – 2.16 (m, 3H), 2.58 – 2.74 (m, 4H), 3.05 (dd, 1H, *J* = 21.2 and 4.4 Hz), 3.13 (dd, 1H, *J* = 21.2 and 4.4 Hz), 3.38 – 3.54 (m, 3H), 3.78 – 3.96 (m, 6H), and 5.16 (t, 1H, *J* = 4.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.9, 29.6, 30.3, 36.0, 37.2, 39.4, 44.0, 46.5, 55.3, 58.4, 64.3, 64.6, 100.4, 115.3, 140.0, 169.8, and 206.8.



330 **361**

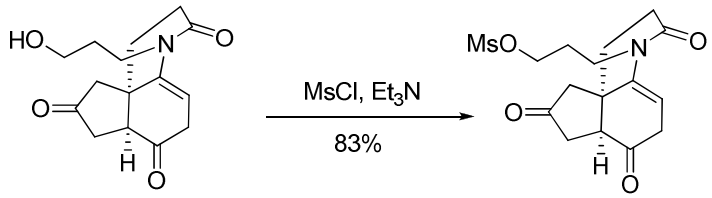
Formation of Tetracycle 361. To a solution containing tricycle **330** in 1 mL of THF at 0 °C was added 0.5 mL of a 5% solution of HCl in THF dropwise. The reaction was allowed to warm to rt and was stirred for an additional 12 h. The reaction was then quenched with a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography to give 0.013 g (68%) of the titled compound **361** as a white solid: mp 168 – 171 °C; IR (thin film) 2963, 2880, 1753, 1710, 1643, and 1404 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.65 (brd, 1H, *J* = 13.6 Hz), 1.72 (ddd, 1H, *J* = 14.0, 6.4, and 1.2 Hz), 1.83 (qt, 1H, *J* = 13.0, 5.6 Hz), 1.98 (d, 1H, *J* = 17.6 Hz), 2.04 (td, 1H, *J* = 14.0 and 4.8 Hz), 2.15 (ddd, 1H, *J* = 14.0, 12.4, and 6.4 Hz), 2.35 (brd, 1H, *J* = 15.6 Hz), 2.45 (t, 1H, *J* = 18.4 Hz), 2.46 (dt, 1H, *J* = 18.4 and 2.4 Hz), 2.50 (dd, 1H, *J* = 7.2 and 1.2 Hz), 2.63 – 2.73 (m, 2H), 2.86 (td, 1H, *J* = 11.6 and 1.2 Hz), 2.90 (td, 1H, *J* = 11.6 and 1.2 Hz), 2.90 (td, 1H, *J* = 14.0 and 3.2 Hz), 2.99 (d, 1H, *J* = 17.6 Hz), 3.01 (ddd, 1H, *J* = 14.4, 6.4, and 2.4 Hz), 3.83 (qd, 1H, *J* = 11.6 and 2.4 Hz), 3.88 (dd, 1H, *J* = 11.6 and 5.6 Hz), and 4.68 (ddt, 1H, *J* = 14.4, 3.2, and 2.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.5, 25.8, 29.4, 30.7, 33.2, 34.9, 40.6, 45.6, 48.6, 55.7, 59.9, 88.1, 167.3, 207.9 and 212.7.



330 **362**

7-(3-Hydroxy-propyl)-3,3a,5,7,9,10-hexahydro-7-aza-cyclopenta[d]naphthalene-2,4,8-trione (362). To a stirred solution containing 0.12 g (0.28 mmol) of tricycle **330** in 1.4 mL of CH_3CN and 1.4 mL of borated buffer pH8 (prepared by the addition of 41 mL of an aqueous 0.1 M HCl solution into 100 mL to an aqueous 0.025 M solution of $Na_2B_4O_7 \cdot 10H_2O$ (borax)) was added 0.015 g (0.028 mmol) of ammonium cerium nitrate (CAN) in one portion. The resulting mixture was heated at 75 ^oC. The reaction was monitored by TLC and after heating for 7 h was diluted with $CHCl_3$ and extracted with a 4:1-mixture of $CHCl_3$ and *i*-PrOH. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.07 g (65%) of the titled compound **362** as a light yellow oil: IR (thin film) 3423, 2929, 1745, 1718, 1635, 1403, and 1172 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.78 (quin, 3H, *J* = 6.0 Hz), 2.86 (dd, 1H, *J* = 14.0 and 6.8 Hz), 2.04 (d, 1H, *J* = 18.0 Hz) 2.06 – 2.18 (m, 1H), 2.35 (dd, 1H, *J* = 19.2 and 8.4 Hz), 2.50 (d, 1H, *J* =18.0 Hz), 2.60 (ddd, 1H, *J* = 19.2, 12.4, and 6.8 Hz), 2.75 (dd, 1H, *J* = 19.2 and 6.8 Hz), 3.10 (brd, 1H, *J* = 8.4 Hz), 3.11 (dd, 1H, *J* = 21.0 and 4.8 Hz), 3.23 (d, 1H, *J* = 19.2 Hz), 3.31 (dd, 1H, *J* = 21.0 and 3.2 Hz), 3.44 – 3.58 (m, 2H), 3.84 – 4.00 (m, 2H), and 5.31 (dd, 1H, *J* = 4.8 and 3.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.3,

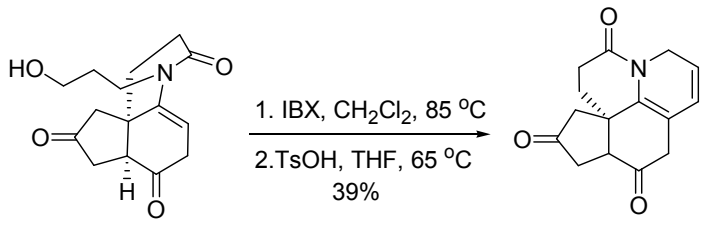
29.7, 30.3, 34.7, 37.8, 40.1, 45.5, 45.9, 53.1, 58.5, 101.5, 139.1, 168.7, 205.1, and 212.2.



362 **363**

Methanesulfonic acid 3-(2,4,8-trioxo-1,2,3,3a,4,5,9,10-octahydro-8H-7-aza-cyclopenta[d]naphthalen-7-yl) Propyl Ester (363). To a stirred solution containing 0.015 g (0.054 mmol) of alcohol **362** in 0.5 mL of CH_2Cl_2 was added 0.009 mL (0.065 mmol) of triethylamine followed by 0.005 mL (0.065 mmol) of methanesulfonyl chloride (MsCl). The resulting solution was stirred at 0 ^oC for 1 h and was then quenched with water and extracted with a 4:1 mixture of $CHCl_3$ and *i*-PrOH mixture. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.016 g (83%) of the titled compound **363** as a light yellow oil: IR (thin film) 2932, 1744, 1720, 1639, 1405, 1346, and 1172 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.85 (dd, 1H, *J* = 13.8 and 6.6 Hz), 1.97 – 2.15 (m, 3H), 2.07 (d, 1H, *J* = 18.6 Hz) 2.35 (dd, 1H, *J* = 19.2 and 9.0 Hz), 2.51 (d, 1H, *J* = 18.6 Hz), 2.56 (ddd, 1H, *J* = 19.2, 12.6, and 6.6 Hz), 2.70 (dd, 1H, *J* = 19.2 and 6.6 Hz), 3.04 (s, 3H), 3.10 (d, 1H, *J* = 9.0 Hz), 3.11 (dd, 1H, *J* = 21.0 and 4.8 Hz), 3.22 (d, 1H, *J* = 19.2 Hz), 3.30 (dd, 1H, *J* = 21.0 and 3.0 Hz), 3.82 (ddd, H, *J* = 14.0, 8.4 and 6.0 Hz), 3.94 (ddd, 1H, *J* = 14.0, 8.4 and 6.0 Hz), 4.22 – 4.30 (m, 2H), and 5.23 (dd, 1H, *J* = 4.8 and 3.0 Hz);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.1, 28.4, 30.5, 34.8, 37.4, 37.8, 40.6, 45.6, 46.0, 53.1, 68.0, 101.0, 139.3, 167.5, 205.2, and 212.3.

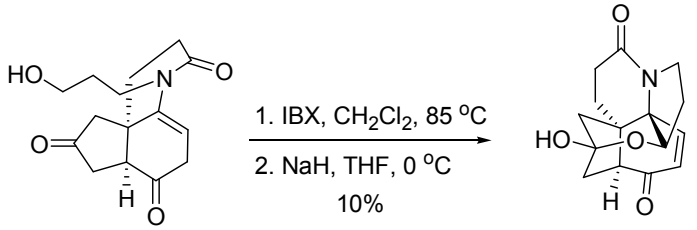


362 **367**

Formation of Tetracycle 367. To a solution containing 0.015 g (0.054 mmol) of alcohol **362** in a sealed tube was added 0.045 (0.16 mmol) of iodoxybenzoic acid (IBX) in one portion at rt. The reaction vessel was sealed and heated at 80 °C for 1 h and then cooled to 0 °C. The white precipitate that formed was removed by filtration and washed with CH_2Cl_2. The solvent was removed under reduced pressure to provide an aldehyde intermediate **365** as a pale yellow oil: IR (thin film) 2931, 2736, 1744, 1639, 1403, 1178, 915, and 732 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.85 (ddd, 1H, *J* = 13.6, 7.2, and 1.2 Hz), 2.05 (d, 1H, *J* = 17.6 Hz), 2.05 – 2.15 (m, 1H), 2.34 (ddd, 1H, *J* = 19.2, 8.4, and 1.2 Hz), 2.47 (d 1H, *J* = 17.6 Hz), 2.60 (dd, 1H, *J* = 12.8 and 7.2 Hz), 2.65 – 2.83 (m, 3H), 3.04 – 3.12 (m, 2H), 3.20 (d, 1H, *J* = 19.2 Hz), 3.28 (dd, 1H, *J* = 20.4 and 3.2 Hz), 3.97 – 4.14 (m, 2H), 5.18 (dd, 1H, *J* = 4.8 and 3.2 Hz), 9.78 (t, 1H, *J* = 1.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.6, 30.9, 35.0, 38.0, 38.1, 41.9, 45.7, 46.2, 53.3, 101.3, 139.5, 167.8, 200.1, 205.4, and 212.6.

To a stirred solution containing the above aldehyde **365** in 0.5 mL of THF was added 0.001g (0.005 mmol) of $TsOH{\cdot}H_2O$. The resulting solution was

heated at 65 °C for 2 h. The solvent was removed under reduced pressure and the crude residue was purified by silica gel chromatography to give 0.005 g (39%) of the titled compound **367** as a light yellow oil: IR (thin film) 2928, 1743, 1720, 1652, 1602, 1378, and 1216 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.85 (ddd, 1H, *J* = 13.0, 6.8, and 1.2 Hz), 2.10 (ddd, 1H, *J* = 13.0, 6.8, and 1.2 Hz), 2.16 (d, 1H, *J* = 19.0 Hz), 2.33 (ddd, 1H, *J* = 19.0, 8.8, and 1.2 Hz), 2.52 (d, 1H, *J* = 19.0 Hz), 2.60 (ddd, 1H, *J* = 19.0, 6.8, and 1.2 Hz), 2.75 (ddd, 1H, *J* = 19.0, 6.8, and 1.2 Hz), 3.03 (d, 1H, *J* = 20.0 Hz), 3.08 (d, 1H, *J* = 8.8 Hz), 3.22 (dd, 1H, *J* = 19.0 and 2.2 Hz), 3.32 (d, 1H, *J* = 20.0 Hz), 3.76 (dd, 1H, *J* = 18.0 and 2.4 Hz), 5.12 (dd, 1H, *J* = 18.0 and 5.2 Hz), 5.70 (dd, 1H, *J* = 9.6 and 2.4 Hz), and 5.7 (ddd, 1H, *J* = 9.6, 5.3, and 2.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.7, 30.2, 34.6, 40.3, 41.8, 45.4, 46.0, 53.5, 109.1, 121.9, 124.0, 132.6, 166.3, 204.8, and 121.6.

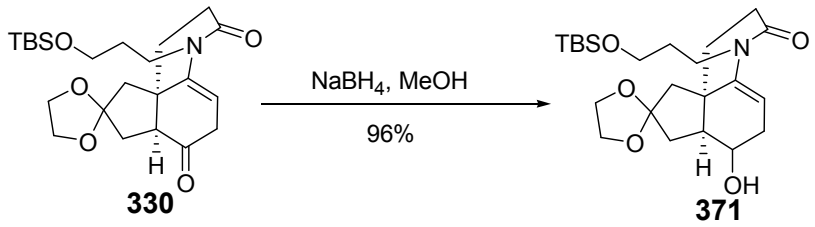


362 **370**

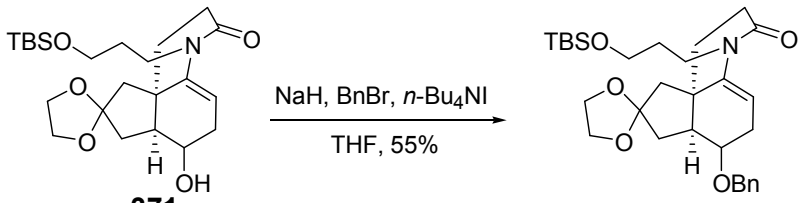
Formation of Tetracycle 370. To a solution containing 0.030 g (0.108 mmol) of alcohol **362** in a sealed tube was added 0.091 g (0.33 mmol) of iodoxybenzoic acid (IBX) in one portion at rt. The reaction vessel was sealed and heated at 80 °C for 1 h and then cooled to 0 °C. The white precipitate that formed was removed by filtration and washed with CH_2Cl_2. The solvent was removed under

reduced pressure to provide aldehyde intermediate **365** as a pale yellow oil which was used for the next step without further purification.

To a solution containing a sample of aldehyde **365** in 0.5 mL of THF was added 0.009 g (0.23 mmol) of NaH (60% in mineral oil). The resulting solution was stirred at 0 ^{o}C for 2 h after which time small pieces of ice were added. The reaction mixture was then allowed to warm to rt, and was extracted with a 4:1-mixure of $CHCl_3$ and *i*-PrOH. The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.003 g (10%) of the titled compound **370** as a white solid: IR (thin film) 3375, 2924, 1739, 1667, 1618, 1457, and 1321 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.55 – 1.65 (m, 1H), 1.75 – 1.85 (m, 1H), 2.00 – 2.05 (m, 1H), 2.10 – 2.25 (m, 2H), 2.35 – 2.43 (m,2H), 2.53 ; (t, 1H, *J* = 14.0 Hz), 2.78 (dd, 1H, *J* = 13.6 and 6.8 Hz), 3.15 (brs, 1H), 3.74 – 3.85 (m, 2H), 4.23 (t, 1H, *J* = 2.0 Hz), 6.02 (dd, 1H, *J* = 9.6 and 2.0 Hz), and 6.60 (d, 1H, *J* = 9.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.6, 27.9, 29.2, 37.0, 42.9, 45.7, 49.5, 50.8, 66.3, 85.0, 104.8, 129.4, 152.7, 169.8, and 196.6; HRMS Calcd for $[(C_{15}H_{17}NO_4)+H]^{+}$: 276.12303. Found 276.12314.

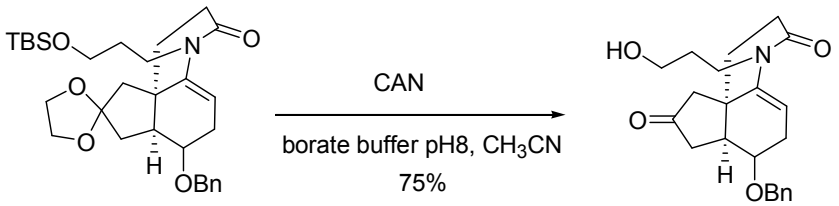


Tetracycle 371. To a stirred solution containing 0.26 g (0.59 mmol) of alcohol **330** was added 0.02 g (0.59 mmol) of $NaBH_4$ in one portion at 0 ^oC. The reaction mixture was stirred for 30 min at 0 ^oC, water was added and the MeOH was removed under reduced pressure. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.25 g (96%) of the titled compound **371** as a pale yellow oil which was used for the next step without further purification: IR (thin film) 3414, 2932, 1627, 1466, 1255, 1100, and 838 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) mixture of isomers, δ 0.03 (s, 6H), 0.09 (s, 9H), 1.60 – 2.60 (m, 10H), 3.56 – 3.95 (m, 8H), 4.00 (td, 1H, *J* = 6.8 and 4.8 Hz), 5.13 (t,, 1H, *J* = 4.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) major isomer, δ -5.5, 18.2, 25.8, 28.8, 29.7, 30.1, 32.3, 35.5, 41.4, 43.5, 45.1, 48.1, 60.8, 64.2, 64.4, 66.4, 102.0, 115.4, 141.7, and 168.5.



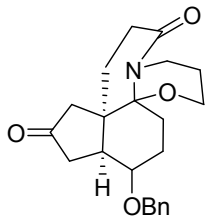
371 **372**

Tetracycle 372. To a stirred solution containing 0.02 g (0.046 mmol) of alcohol **371** in 0.5 mL of THF was added 0.002 g (0.06 mmol) of NaH (60% in mineral oil) at 0 ^{o}C. The solution was stirred at 0 ^{o}C for 10 min and for additional 30 min at rt. The mixture was recooled to 0 ^{o}C and 0.008 mL (0.07 mmol) of benzyl bromide was added followed by dropwise and 0.02 g (0.006 mmol) of tetrabutylammonium iodide (*n*-Bu_4NI). After warming to rt, the mixture was stirred for an additional 12 h. The solution was quenched with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.016 g (55%) of the titled compound **372** as a pale yellow oil: IR (thin film) 2953, 2857, 1667, 1640, 1255, 1099, and 837 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) mixture of isomers, δ 0.04 (s, 6H), 0.89 (s, 9H), 1.60 – 2.60 (m, 10H), 3.60 – 3.93 (m, 8H), 4.52 (d, 1H, *J* = 12.0 Hz), 4.57 (d, 1H, *J* = 12.0 Hz), 5.13 (dd, 1H, *J* = 6.8 and 2.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) major isomer, δ -5.4, 18.2, 25.6, 25.8, 29.9, 30.0, 32.7, 35.2, 41.2, 43.5, 45.2, 60.8, 64.1, 64.5, 70.1, 72.9, 102.1, 115.2, 127.4, 127.5, 127.6, 128.3, 138.5, 141.9, and 168.4.



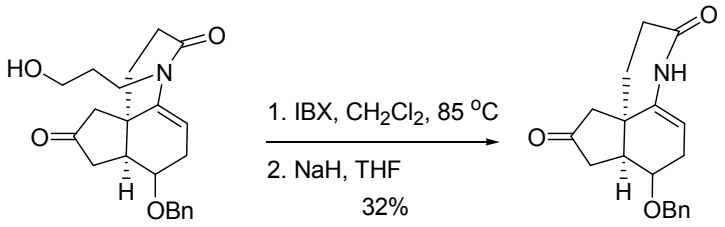
372 **373**

4-Benzyloxy-7-(3-hydroxy-propyl)-3a,4,5,7,9,10-hexahydro-3H-7-aza-cyclopenta[d]naphthalene-2,8-dione (373). To a stirred solution containing 0.06 g (0.10 mmol) of tricycle **372** in 0.7 mL of CH_3CN and 0.7 mL of borated buffer pH8 (prepared by addition of 41 mL of an aqueous 0.1 N HCl solution with 100 mL to an aqueous 0.025 M solution of $Na_2B_4O_7.10H_2O$ (borax)) was added 0.006 g (0.01 mmol) of ammonium cerium nitrate (CAN) in one portion. The resulting solution was heated at 75 ^oC. The reaction was monitored by TLC and after 1.5 was diluted with $CHCl_3$ and extracted with a mixture of a 4:1-mixture of $CHCl_3$ and *i*-PrOH. The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.03 g (75%) of the titled compound **373** as a light yellow oil: IR (thin film) 3426, 2925, 2869, 1740, 1626, 1456, 1405, and 1066 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) mixture of isomers, δ 1.68 – 1.90 (m, 5H), 2.22 – 2.34 (m, 3H), 2.46 – 2.68 (m, 5H), 3.34 – 3.55 (m, 3H), 3.72 (q, 1H, *J* = 3.2 Hz), 3.80 – 3.94 (m, 2H), 4.39 (major isomer, d, 1H, *J* = 12.0 Hz), 4.57 (major isomer, d, 1H, *J* = 12.0 Hz), 4.45 (minor isomer, d, 1H, *J* = 11.2 Hz), 4.68 (minor isomer, d, 1H, *J* = 11.2 Hz), 5.19 (dd, 1H, *J* = 5.2 and 2.8 Hz), and 7.20 – 7.40 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) major isomer, δ 26.7, 28.6, 30.2, 31.0, 40.1, 40.2, 41.0, 44.8, 45.7, 58.5, 71.2, 73.6, 102.1, 127.5, 127.7, 128.4, 137.8, 140.2, 169.3, and 215.4.



374

Tetracycle 374 was obtained as a byproduct from the above reaction and showed the following spectral properties: IR (thin film) 2956, 2875, 1740, 1639, 1404, 1276, and 1109 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.45 – 1.55 (m, 3H), 1.60 – 1.74 (m, 2H), 1.75 – 1.82 (m, 1H), 1.84 (d, 1H, *J* = 17.0 Hz), 2.12 (d, 1H, *J* = 8.4 Hz), 2.16 (d, 1H, *J* = 8.4 Hz), 2.35 – 2.41 (m, 2H), 2.54 – 2.80 (m, 4H), 2.80 (d, 1H, *J* = 17.0 Hz), 3.70 (d, 2H, *J* = 7.6 Hz), 3.80 (dt, 1H, *J* = 12.0 and 4.8 Hz), and 4.60 (dd, 1H, *J* = 13.6 and 3.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.6, 24.7, 25.1, 29.9, 34.6, 38.3, 46.5, 47.8, 59.1, 70.3, 73.5, 89.2, 127.4, 1277, 128.5, 138.2, 167.4, and 215.6.



373 **376**

Formation of Tricycle 376. To a solution containing 0.02 g (0.05 mmol) of the alcohol **373** in 1 mL of CH_2Cl_2 in a sealed tube was added 0.045 g (0.16 mmol) of iodoxybenzoic acid (IBX) in one portion at rt. The mixture was sealed and was heated at 80 °C for 1 h then cooled to 0 °C. The white precipitate that had formed was removed by filtration and was washed with CH_2Cl_2. The solvent was

removed under reduced pressure to provide an aldehyde intermediate **375** as a pale yellow oil which was used for the next step without further purification: IR (thin film) 2925, 2868, 1739, and 1637 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) mixture of isomers, δ 1.70 – 1.90 (m, 2H), 2.10 – 2.80 (m, 10H), 3.72 (q, 1H), 3.92 – 4.10 (m, 3H), 4.40 (major isomer, d, 1H, *J* = 12.0 Hz), 4.57 (major isomer, d, 1H, *J* = 12.0 Hz), 5.06 (major isomer, dd, 1H, *J* = 5.2 and 3.2 Hz), 4.45 (minor isomer, d, 1H, *J* = 11.2 Hz), 4.67 (minor isomer, d, 1H, *J* = 11.2 Hz), 5.08 (minor isomer, dd, 1H, *J* = 6.0 and 2.8 Hz), 7.18 – 7.40 (m, 5H), and 9.85 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) major isomer, δ 26.6, 28.7, 31.4, 38.1, 40.0, 41.1, 41.9, 44.8, 45.7, 71.1, 73.5, 101.9, 127.6, 127.7, 128.4, 137.8, 140.3, 168.0, 200.2, and 215.4.

To a solution containing a sample of above aldehyde **375** in 0.5 mL of THF was added 0.004 g (0.11 mmol) of NaH (60% in mineral oil). The reaction was allowed to warm to rt and stirred for an additional 1 h. The mixture was then cooled to rt, quenched with H_2O, and extracted with a 4:1-mixture of $CHCl_3$ and *i*-PrOH. The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.005 g (32%) of the tetracycle **376** as a white solid: mp 163 – 165 ^{o}C; IR (thin film) 3190, 3055, 2922, 2853, 1741, 1664, 1457, 1397, 1093, and 1024 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.72 – 1.90 (m, 2H), 2.22 – 2.30 (m, 3H), 2.35 (s, 1H), 2.48 – 2.58 (m, 4H), 2.68 (d, 1H, *J* = 18.4 Hz), 3.72 (q, 1H, *J* = 3.2 Hz), 4.35 ;(d, 1H, *J* = 12.o Hz),4.58 (d, 1H, *J* = 12.0 Hz), 4.89 (dd, 1H, *J* = 4.8 and 2.0 Hz), 7.20 – 7.36 (m, 5H), and 7.66 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.2, 28.3, 31.1, 39.5,

40.2, 44.0, 45.9, 71.4, 74.4, 100.7, 127.7, 127.8, 128.4, 137.4, 13 7.7, 169.4, and 215.9; HRMS calcd. for [($C_{19}H_{22}NO_3$)+H^+] 312.15997. Found 312.15940.

X-Ray data

Table 1. Crystal data and structure refinement for compound **330b**.

Identification code	fawdas	
Empirical formula	C23 H35 N O6 Si	
Formula weight	449.61	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.4494(3) Å	α= 114.534(3)°.
	b = 12.0453(5) Å	β= 90.775(3)°.
	c = 14.0749(8) Å	γ = 109.493(2)°.
Volume	1208.98(10) Å^3	
Z	2	
Density (calculated)	1.235 Mg/m^3	
Absorption coefficient	1.168 mm^{-1}	
F(000)	484	
Crystal size	0.43 x 0.23 x 0.06 mm^3	
Theta range for data collection	8.30 to 60.35°.	
Index ranges	-8<=h<=8, -13<=k<=13, -14<=l<=14	
Reflections collected	5231	
Independent reflections	2695 [R(int) = 0.0185]	
Completeness to theta = 60.35°	74.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9332 and 0.6337	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2695 / 0 / 286	
Goodness-of-fit on F^2	1.001	
Final R indices [I>2sigma(I)]	R1 = 0.0349, wR2 = 0.0869	
R indices (all data)	R1 = 0.0449, wR2 = 0.0931	
Largest diff. peak and hole	0.164 and -0.240 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for compound **330b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	4114(3)	-378(2)	-1873(2)	29(1)
C(2)	1882(3)	-2370(2)	-2691(2)	38(1)
C(3)	3186(3)	-2424(2)	-1974(2)	38(1)
C(4)	5470(3)	596(2)	-2152(2)	34(1)
C(5)	5570(3)	1927(2)	-1338(2)	29(1)
C(6)	6963(3)	3010(2)	-902(2)	31(1)
C(7)	7020(3)	4128(2)	98(2)	32(1)
C(8)	5539(3)	3974(2)	606(2)	31(1)
C(9)	4113(3)	2889(2)	165(2)	27(1)
C(10)	1029(3)	1955(2)	40(2)	36(1)
C(11)	824(3)	1328(2)	-1151(2)	39(1)
C(12)	2451(3)	1659(2)	-1601(2)	33(1)
C(13)	3950(3)	1764(2)	-878(2)	27(1)
C(14)	3651(3)	450(2)	-835(2)	28(1)
C(15)	2823(3)	3487(2)	1781(2)	33(1)
C(16)	2564(3)	4779(2)	2098(2)	38(1)
C(17)	3244(3)	5698(3)	3256(2)	47(1)
C(18)	5510(4)	7033(3)	5734(2)	58(1)
C(19)	6206(4)	8827(3)	4662(2)	58(1)
C(20)	8491(3)	7235(2)	4490(2)	39(1)
C(21)	9737(3)	8409(3)	5465(2)	56(1)
C(22)	9078(3)	7339(3)	3498(2)	61(1)
C(23)	8551(4)	5974(3)	4477(3)	61(1)
N(1)	2649(2)	2726(2)	632(1)	30(1)
O(1)	2678(2)	-1138(2)	-2716(1)	34(1)
O(2)	4695(2)	-1315(2)	-1790(1)	34(1)
O(3)	8416(2)	3097(2)	-1322(1)	40(1)
O(4)	8321(2)	5137(2)	491(1)	47(1)
O(5)	-203(2)	1812(2)	484(1)	53(1)

O(6)	5040(2)	6017(2)	3469(1)	45(1)
Si(1)	6284(1)	7257(1)	4571(1)	37(1)

Table 3. Bond lengths [Å] and angles [°] for compound **330b**.

C(1)-O(2)	1.417(3)	C(14)-H(14A)	0.9900
C(1)-O(1)	1.427(2)	C(14)-H(14B)	0.9900
C(1)-C(4)	1.530(3)	C(15)-N(1)	1.466(3)
C(1)-C(14)	1.532(3)	C(15)-C(16)	1.524(3)
C(2)-O(1)	1.426(3)	C(15)-H(15A)	0.9900
C(2)-C(3)	1.520(3)	C(15)-H(15B)	0.9900
C(2)-H(2A)	0.9900	C(16)-C(17)	1.505(3)
C(2)-H(2B)	0.9900	C(16)-H(16A)	0.9900
C(3)-O(2)	1.430(3)	C(16)-H(16B)	0.9900
C(3)-H(3A)	0.9900	C(17)-O(6)	1.430(3)
C(3)-H(3B)	0.9900	C(17)-H(17A)	0.9900
C(4)-C(5)	1.507(3)	C(17)-H(17B)	0.9900
C(4)-H(4A)	0.9900	C(18)-Si(1)	1.859(3)
C(4)-H(4B)	0.9900	C(18)-H(18A)	0.9800
C(5)-C(6)	1.325(3)	C(18)-H(18B)	0.9800
C(5)-C(13)	1.510(3)	C(18)-H(18C)	0.9800
C(6)-O(3)	1.361(3)	C(19)-Si(1)	1.866(3)
C(6)-C(7)	1.476(3)	C(19)-H(19A)	0.9800
C(7)-O(4)	1.235(3)	C(19)-H(19B)	0.9800
C(7)-C(8)	1.446(3)	C(19)-H(19C)	0.9800
C(8)-C(9)	1.341(3)	C(20)-C(22)	1.528(4)
C(8)-H(8)	0.9500	C(20)-C(23)	1.529(3)
C(9)-N(1)	1.403(3)	C(20)-C(21)	1.532(3)
C(9)-C(13)	1.493(3)	C(20)-Si(1)	1.878(3)
C(10)-O(5)	1.221(3)	C(21)-H(21A)	0.9800
C(10)-N(1)	1.381(3)	C(21)-H(21B)	0.9800
C(10)-C(11)	1.504(3)	C(21)-H(21C)	0.9800
C(11)-C(12)	1.523(3)	C(22)-H(22A)	0.9800
C(11)-H(11A)	0.9900	C(22)-H(22B)	0.9800
C(11)-H(11B)	0.9900	C(22)-H(22C)	0.9800
C(12)-C(13)	1.551(3)	C(23)-H(23A)	0.9800
C(12)-H(12A)	0.9900	C(23)-H(23B)	0.9800
C(12)-H(12B)	0.9900	C(23)-H(23C)	0.9800
C(13)-C(14)	1.545(3)	O(3)-H(3)	0.8400

O(6)-Si(1)	1.6514(17)	C(7)-C(8)-H(8)	119.0
O(2)-C(1)-O(1)	104.59(17)	C(8)-C(9)-N(1)	123.1(2)
O(2)-C(1)-C(4)	111.95(18)	C(8)-C(9)-C(13)	122.35(19)
O(1)-C(1)-C(4)	109.62(17)	N(1)-C(9)-C(13)	114.55(19)
O(2)-C(1)-C(14)	112.48(16)	O(5)-C(10)-N(1)	120.1(2)
O(1)-C(1)-C(14)	112.09(17)	O(5)-C(10)-C(11)	121.3(2)
C(4)-C(1)-C(14)	106.21(17)	N(1)-C(10)-C(11)	118.6(2)
O(1)-C(2)-C(3)	104.78(18)	C(10)-C(11)-C(12)	115.87(19)
O(1)-C(2)-H(2A)	110.8	C(10)-C(11)-H(11A)	108.3
C(3)-C(2)-H(2A)	110.8	C(12)-C(11)-H(11A)	108.3
O(1)-C(2)-H(2B)	110.8	C(10)-C(11)-H(11B)	108.3
C(3)-C(2)-H(2B)	110.8	C(12)-C(11)-H(11B)	108.3
H(2A)-C(2)-H(2B)	108.9	H(11A)-C(11)-H(11B)	107.4
O(2)-C(3)-C(2)	104.43(18)	C(11)-C(12)-C(13)	109.25(18)
O(2)-C(3)-H(3A)	110.9	C(11)-C(12)-H(12A)	109.8
C(2)-C(3)-H(3A)	110.9	C(13)-C(12)-H(12A)	109.8
O(2)-C(3)-H(3B)	110.9	C(11)-C(12)-H(12B)	109.8
C(2)-C(3)-H(3B)	110.9	C(13)-C(12)-H(12B)	109.8
H(3A)-C(3)-H(3B)	108.9	H(12A)-C(12)-H(12B)	108.3
C(5)-C(4)-C(1)	104.25(18)	C(9)-C(13)-C(5)	113.68(19)
C(5)-C(4)-H(4A)	110.9	C(9)-C(13)-C(14)	114.80(17)
C(1)-C(4)-H(4A)	110.9	C(5)-C(13)-C(14)	99.63(16)
C(5)-C(4)-H(4B)	110.9	C(9)-C(13)-C(12)	104.60(17)
C(1)-C(4)-H(4B)	110.9	C(5)-C(13)-C(12)	112.67(17)
H(4A)-C(4)-H(4B)	108.9	C(14)-C(13)-C(12)	111.77(17)
C(6)-C(5)-C(4)	126.2(2)	C(1)-C(14)-C(13)	103.99(16)
C(6)-C(5)-C(13)	123.2(2)	C(1)-C(14)-H(14A)	111.0
C(4)-C(5)-C(13)	108.77(19)	C(13)-C(14)-H(14A)	111.0
C(5)-C(6)-O(3)	121.3(2)	C(1)-C(14)-H(14B)	111.0
C(5)-C(6)-C(7)	120.72(19)	C(13)-C(14)-H(14B)	111.0
O(3)-C(6)-C(7)	117.9(2)	H(14A)-C(14)-H(14B)	109.0
O(4)-C(7)-C(8)	122.2(2)	N(1)-C(15)-C(16)	113.63(18)
O(4)-C(7)-C(6)	120.1(2)	N(1)-C(15)-H(15A)	108.8
C(8)-C(7)-C(6)	117.8(2)	C(16)-C(15)-H(15A)	108.8
C(9)-C(8)-C(7)	122.0(2)	N(1)-C(15)-H(15B)	108.8
C(9)-C(8)-H(8)	119.0	C(16)-C(15)-H(15B)	108.8

H(15A)-C(15)-H(15B)	107.7	C(20)-C(21)-H(21A)	109.5
C(17)-C(16)-C(15)	111.8(2)	C(20)-C(21)-H(21B)	109.5
C(17)-C(16)-H(16A)	109.3	H(21A)-C(21)-H(21B)	109.5
C(15)-C(16)-H(16A)	109.3	C(20)-C(21)-H(21C)	109.5
C(17)-C(16)-H(16B)	109.3	H(21A)-C(21)-H(21C)	109.5
C(15)-C(16)-H(16B)	109.3	H(21B)-C(21)-H(21C)	109.5
H(16A)-C(16)-H(16B)	107.9	C(20)-C(22)-H(22A)	109.5
O(6)-C(17)-C(16)	109.43(19)	C(20)-C(22)-H(22B)	109.5
O(6)-C(17)-H(17A)	109.8	H(22A)-C(22)-H(22B)	109.5
C(16)-C(17)-H(17A)	109.8	C(20)-C(22)-H(22C)	109.5
O(6)-C(17)-H(17B)	109.8	H(22A)-C(22)-H(22C)	109.5
C(16)-C(17)-H(17B)	109.8	H(22B)-C(22)-H(22C)	109.5
H(17A)-C(17)-H(17B)	108.2	C(20)-C(23)-H(23A)	109.5
Si(1)-C(18)-H(18A)	109.5	C(20)-C(23)-H(23B)	109.5
Si(1)-C(18)-H(18B)	109.5	H(23A)-C(23)-H(23B)	109.5
H(18A)-C(18)-H(18B)	109.5	C(20)-C(23)-H(23C)	109.5
Si(1)-C(18)-H(18C)	109.5	H(23A)-C(23)-H(23C)	109.5
H(18A)-C(18)-H(18C)	109.5	H(23B)-C(23)-H(23C)	109.5
H(18B)-C(18)-H(18C)	109.5	C(10)-N(1)-C(9)	122.45(18)
Si(1)-C(19)-H(19A)	109.5	C(10)-N(1)-C(15)	118.39(17)
Si(1)-C(19)-H(19B)	109.5	C(9)-N(1)-C(15)	118.96(18)
H(19A)-C(19)-H(19B)	109.5	C(2)-O(1)-C(1)	107.16(15)
Si(1)-C(19)-H(19C)	109.5	C(1)-O(2)-C(3)	105.41(16)
H(19A)-C(19)-H(19C)	109.5	C(6)-O(3)-H(3)	109.5
H(19B)-C(19)-H(19C)	109.5	C(17)-O(6)-Si(1)	122.61(14)
C(22)-C(20)-C(23)	109.3(2)	O(6)-Si(1)-C(18)	109.41(12)
C(22)-C(20)-C(21)	108.3(2)	O(6)-Si(1)-C(19)	109.40(11)
C(23)-C(20)-C(21)	108.3(2)	C(18)-Si(1)-C(19)	108.84(13)
C(22)-C(20)-Si(1)	111.13(16)	O(6)-Si(1)-C(20)	106.34(10)
C(23)-C(20)-Si(1)	110.60(18)	C(18)-Si(1)-C(20)	111.42(12)
C(21)-C(20)-Si(1)	109.22(18)	C(19)-Si(1)-C(20)	111.38(12)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for compound **330b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	27(1)	25(1)	30(1)	9(1)	0(1)	10(1)
C(2)	35(1)	31(2)	41(1)	14(1)	4(1)	8(1)
C(3)	42(2)	29(2)	41(1)	13(1)	1(1)	12(1)
C(4)	31(1)	33(2)	31(1)	11(1)	7(1)	10(1)
C(5)	30(1)	32(2)	27(1)	14(1)	6(1)	13(1)
C(6)	25(1)	34(2)	35(1)	17(1)	10(1)	11(1)
C(7)	25(1)	28(2)	41(1)	16(1)	6(1)	7(1)
C(8)	27(1)	29(2)	31(1)	10(1)	5(1)	10(1)
C(9)	25(1)	30(2)	30(1)	14(1)	4(1)	13(1)
C(10)	27(1)	30(2)	45(2)	14(1)	6(1)	8(1)
C(11)	28(1)	40(2)	41(2)	11(1)	-2(1)	12(1)
C(12)	34(1)	31(2)	33(1)	14(1)	1(1)	12(1)
C(13)	23(1)	25(1)	29(1)	11(1)	2(1)	7(1)
C(14)	27(1)	26(1)	29(1)	12(1)	4(1)	9(1)
C(15)	29(1)	36(2)	32(1)	14(1)	7(1)	10(1)
C(16)	31(1)	41(2)	37(1)	11(1)	5(1)	16(1)
C(17)	37(2)	49(2)	44(2)	8(1)	6(1)	19(1)
C(18)	70(2)	51(2)	45(2)	17(1)	15(1)	18(2)
C(19)	62(2)	48(2)	67(2)	24(2)	11(2)	26(2)
C(20)	41(1)	33(2)	37(1)	14(1)	-2(1)	9(1)
C(21)	54(2)	43(2)	58(2)	21(1)	-13(1)	4(2)
C(22)	47(2)	90(3)	54(2)	36(2)	11(1)	29(2)
C(23)	51(2)	41(2)	87(2)	26(2)	4(2)	17(2)
N(1)	24(1)	30(1)	30(1)	10(1)	6(1)	8(1)
O(1)	36(1)	29(1)	32(1)	11(1)	-5(1)	8(1)
O(2)	33(1)	31(1)	36(1)	10(1)	-1(1)	15(1)
O(3)	29(1)	35(1)	47(1)	14(1)	14(1)	8(1)
O(4)	29(1)	35(1)	56(1)	9(1)	12(1)	3(1)
O(5)	27(1)	57(1)	55(1)	14(1)	13(1)	6(1)

O(6)	32(1)	47(1)	41(1)	5(1)	3(1)	17(1)
Si(1)	43(1)	30(1)	33(1)	9(1)	5(1)	13(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **330b**.

	x	y	z	U(eq)
H(2A)	1612	-3107	-3412	45
H(2B)	815	-2415	-2399	45
H(3A)	2797	-2356	-1298	46
H(3B)	3391	-3253	-2326	46
H(4A)	6582	500	-2103	41
H(4B)	5125	462	-2879	41
H(8)	5577	4661	1272	37
H(11A)	7	1593	-1432	47
H(11B)	309	361	-1417	47
H(12A)	2701	2504	-1635	40
H(12B)	2303	965	-2329	40
H(14A)	4393	590	-213	33
H(14B)	2445	20	-798	33
H(15A)	3975	3678	2126	40
H(15B)	1980	2945	2050	40
H(16A)	3151	5208	1667	45
H(16B)	1332	4595	1946	45
H(17A)	3014	6511	3443	57
H(17B)	2665	5275	3694	57
H(18A)	4355	7043	5752	87
H(18B)	6274	7749	6388	87
H(18C)	5492	6189	5676	87
H(19A)	6547	8929	4031	87
H(19B)	6987	9568	5298	87
H(19C)	5042	8810	4704	87
H(21A)	10889	8396	5429	84
H(21B)	9387	8354	6110	84
H(21C)	9733	9228	5479	84
H(22A)	10256	7381	3497	92
H(22B)	9018	8137	3496	92

H(22C)	8336	6567	2864	92
H(23A)	7751	5210	3862	91
H(23B)	8230	5926	5130	91
H(23C)	9709	5978	4432	91
H(3)	9221	3784	-900	59

Table 6. Torsion angles [°] for compound **330b**.

O(1)-C(2)-C(3)-O(2)	-8.6(2)
O(2)-C(1)-C(4)-C(5)	-129.34(18)
O(1)-C(1)-C(4)-C(5)	115.08(18)
C(14)-C(1)-C(4)-C(5)	-6.2(2)
C(1)-C(4)-C(5)-C(6)	144.7(2)
C(1)-C(4)-C(5)-C(13)	-20.3(2)
C(4)-C(5)-C(6)-O(3)	14.5(3)
C(13)-C(5)-C(6)-O(3)	177.55(18)
C(4)-C(5)-C(6)-C(7)	-161.3(2)
C(13)-C(5)-C(6)-C(7)	1.7(3)
C(5)-C(6)-C(7)-O(4)	-179.3(2)
O(3)-C(6)-C(7)-O(4)	4.7(3)
C(5)-C(6)-C(7)-C(8)	2.9(3)
O(3)-C(6)-C(7)-C(8)	-173.05(19)
O(4)-C(7)-C(8)-C(9)	178.4(2)
C(6)-C(7)-C(8)-C(9)	-3.8(3)
C(7)-C(8)-C(9)-N(1)	-178.73(19)
C(7)-C(8)-C(9)-C(13)	0.1(3)
O(5)-C(10)-C(11)-C(12)	176.1(2)
N(1)-C(10)-C(11)-C(12)	-2.6(3)
C(10)-C(11)-C(12)-C(13)	36.6(3)
C(8)-C(9)-C(13)-C(5)	4.2(3)
N(1)-C(9)-C(13)-C(5)	-176.87(17)
C(8)-C(9)-C(13)-C(14)	118.0(2)
N(1)-C(9)-C(13)-C(14)	-63.0(2)
C(8)-C(9)-C(13)-C(12)	-119.1(2)
N(1)-C(9)-C(13)-C(12)	59.8(2)
C(6)-C(5)-C(13)-C(9)	-5.2(3)
C(4)-C(5)-C(13)-C(9)	160.40(17)
C(6)-C(5)-C(13)-C(14)	-127.8(2)
C(4)-C(5)-C(13)-C(14)	37.8(2)
C(6)-C(5)-C(13)-C(12)	113.6(2)
C(4)-C(5)-C(13)-C(12)	-80.8(2)
C(11)-C(12)-C(13)-C(9)	-63.0(2)

C(11)-C(12)-C(13)-C(5)	172.99(19)
C(11)-C(12)-C(13)-C(14)	61.8(2)
O(2)-C(1)-C(14)-C(13)	152.29(17)
O(1)-C(1)-C(14)-C(13)	-90.2(2)
C(4)-C(1)-C(14)-C(13)	29.5(2)
C(9)-C(13)-C(14)-C(1)	-162.01(17)
C(5)-C(13)-C(14)-C(1)	-40.19(19)
C(12)-C(13)-C(14)-C(1)	79.1(2)
N(1)-C(15)-C(16)-C(17)	-163.28(19)
C(15)-C(16)-C(17)-O(6)	61.7(3)
O(5)-C(10)-N(1)-C(9)	177.9(2)
C(11)-C(10)-N(1)-C(9)	-3.4(3)
O(5)-C(10)-N(1)-C(15)	-7.4(3)
C(11)-C(10)-N(1)-C(15)	171.31(19)
C(8)-C(9)-N(1)-C(10)	151.4(2)
C(13)-C(9)-N(1)-C(10)	-27.5(3)
C(8)-C(9)-N(1)-C(15)	-23.3(3)
C(13)-C(9)-N(1)-C(15)	157.80(18)
C(16)-C(15)-N(1)-C(10)	-81.8(3)
C(16)-C(15)-N(1)-C(9)	93.1(2)
C(3)-C(2)-O(1)-C(1)	-14.2(2)
O(2)-C(1)-O(1)-C(2)	32.3(2)
C(4)-C(1)-O(1)-C(2)	152.51(17)
C(14)-C(1)-O(1)-C(2)	-89.8(2)
O(1)-C(1)-O(2)-C(3)	-37.9(2)
C(4)-C(1)-O(2)-C(3)	-156.47(17)
C(14)-C(1)-O(2)-C(3)	84.0(2)
C(2)-C(3)-O(2)-C(1)	28.4(2)
C(16)-C(17)-O(6)-Si(1)	165.10(16)
C(17)-O(6)-Si(1)-C(18)	57.9(2)
C(17)-O(6)-Si(1)-C(19)	-61.2(2)
C(17)-O(6)-Si(1)-C(20)	178.36(19)
C(22)-C(20)-Si(1)-O(6)	57.6(2)
C(23)-C(20)-Si(1)-O(6)	-63.98(19)
C(21)-C(20)-Si(1)-O(6)	176.97(16)
C(22)-C(20)-Si(1)-C(18)	176.7(2)

C(23)-C(20)-Si(1)-C(18)	55.2(2)
C(21)-C(20)-Si(1)-C(18)	-63.9(2)
C(22)-C(20)-Si(1)-C(19)	-61.5(2)
C(23)-C(20)-Si(1)-C(19)	176.91(18)
C(21)-C(20)-Si(1)-C(19)	57.9(2)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for compound **330b** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3)...O(4)#1	0.84	1.97	2.725(2)	149.2
O(3)-H(3)...O(4)	0.84	2.30	2.735(2)	112.8

Symmetry transformations used to generate equivalent atoms:
#1 -x+2,-y+1,-z

Table 8. Crystal data and structure refinement for compound **370**.

Identification code	faw216_1bs	
Empirical formula	C15 H16 N O4	
Formula weight	274.29	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 15.1192(7) Å	α = 90°.
	b = 8.3556(3) Å	β = 90.894(3)°.
	c = 9.8683(3) Å	γ = 90°.
Volume	1246.51(8) $Å^3$	
Z	4	
Density (calculated)	1.462 Mg/m^3	
Absorption coefficient	0.882 mm^{-1}	
F(000)	580	
Crystal size	0.28 x 0.13 x 0.06 mm^3	
Theta range for data collection	4.48 to 65.40°.	
Index ranges	-15<=h<=15, -9<=k<=8, -9<=l<=11	
Reflections collected	2997	
Independent reflections	1346 [R(int) = 0.0212]	
Completeness to theta = 65.40°	79.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9490 and 0.7903	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1346 / 1 / 181	
Goodness-of-fit on F^2	1.057	
Final R indices [I>2sigma(I)]	R1 = 0.0378, wR2 = 0.1066	
R indices (all data)	R1 = 0.0405, wR2 = 0.1080	
Absolute structure parameter	0.2(3)	
Largest diff. peak and hole	0.301 and -0.201 $e.Å^{-3}$	

Table 9. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for compound **370**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7888(2)	6246(4)	409(3)	26(1)
C(2)	7075(2)	6380(4)	1330(3)	28(1)
C(3)	7406(2)	7429(4)	2549(3)	27(1)
C(4)	7122(3)	6812(4)	3934(3)	28(1)
C(5)	7799(2)	6101(4)	4808(3)	34(1)
C(6)	8596(3)	5742(4)	4354(3)	30(1)
C(7)	8840(2)	6014(4)	2887(3)	27(1)
C(8)	8558(2)	4486(4)	2071(3)	30(1)
C(9)	9360(3)	3413(4)	2226(4)	37(1)
C(10)	10157(3)	4517(4)	2209(3)	37(1)
C(11)	10287(3)	7398(4)	2697(3)	29(1)
C(12)	9842(3)	8989(4)	2885(4)	35(1)
C(13)	8843(2)	8973(4)	3101(3)	28(1)
C(14)	8405(2)	7566(4)	2365(3)	24(1)
C(15)	8474(2)	7650(4)	810(3)	25(1)
N(1)	9797(2)	6074(3)	2696(2)	29(1)
O(1)	7622(2)	6179(3)	-944(2)	33(1)
O(2)	6350(2)	6926(3)	4294(2)	38(1)
O(3)	11096(2)	7372(3)	2476(2)	37(1)
O(4)	8398(2)	4811(2)	668(2)	29(1)

Table 10. Bond lengths [Å] and angles [°] for compound **370**.

C(1)-O(1)	1.390(3)	O(2)-C(4)-C(5)	121.5(3)
C(1)-O(4)	1.446(4)	O(2)-C(4)-C(3)	121.0(3)
C(1)-C(15)	1.520(5)	C(5)-C(4)-C(3)	117.5(3)
C(1)-C(2)	1.544(5)	C(6)-C(5)-C(4)	121.8(3)
C(2)-C(3)	1.565(4)	C(5)-C(6)-C(7)	121.6(3)
C(3)-C(14)	1.528(5)	N(1)-C(7)-C(6)	112.6(3)
C(3)-C(4)	1.529(4)	N(1)-C(7)-C(14)	110.3(3)
C(4)-O(2)	1.228(4)	C(6)-C(7)-C(14)	109.7(3)
C(4)-C(5)	1.455(5)	N(1)-C(7)-C(8)	102.9(2)
C(5)-C(6)	1.326(5)	C(6)-C(7)-C(8)	107.5(2)
C(6)-C(7)	1.517(4)	C(14)-C(7)-C(8)	113.8(2)
C(7)-N(1)	1.463(4)	O(4)-C(8)-C(9)	109.5(3)
C(7)-C(14)	1.539(4)	O(4)-C(8)-C(7)	112.6(2)
C(7)-C(8)	1.565(4)	C(9)-C(8)-C(7)	102.7(3)
C(8)-O(4)	1.428(4)	C(8)-C(9)-C(10)	105.9(3)
C(8)-C(9)	1.513(5)	N(1)-C(10)-C(9)	103.5(3)
C(9)-C(10)	1.518(5)	O(3)-C(11)-N(1)	122.2(3)
C(10)-N(1)	1.492(4)	O(3)-C(11)-C(12)	118.7(3)
C(11)-O(3)	1.246(4)	N(1)-C(11)-C(12)	119.0(3)
C(11)-N(1)	1.332(5)	C(11)-C(12)-C(13)	117.0(3)
C(11)-C(12)	1.502(5)	C(14)-C(13)-C(12)	111.2(2)
C(12)-C(13)	1.529(5)	C(13)-C(14)-C(3)	115.0(2)
C(13)-C(14)	1.527(4)	C(13)-C(14)-C(7)	108.1(2)
C(14)-C(15)	1.542(4)	C(3)-C(14)-C(7)	108.4(2)
O(1)-C(1)-O(4)	106.3(2)	C(13)-C(14)-C(15)	113.8(3)
O(1)-C(1)-C(15)	116.1(3)	C(3)-C(14)-C(15)	101.8(3)
O(4)-C(1)-C(15)	106.7(3)	C(7)-C(14)-C(15)	109.6(2)
O(1)-C(1)-C(2)	110.4(3)	C(1)-C(15)-C(14)	100.1(3)
O(4)-C(1)-C(2)	112.6(2)	C(11)-N(1)-C(7)	125.4(3)
C(15)-C(1)-C(2)	104.9(2)	C(11)-N(1)-C(10)	121.3(3)
C(1)-C(2)-C(3)	104.1(2)	C(7)-N(1)-C(10)	112.2(3)
C(14)-C(3)-C(4)	115.1(3)	C(8)-O(4)-C(1)	114.2(2)
C(14)-C(3)-C(2)	104.9(2)		
C(4)-C(3)-C(2)	114.0(3)		

Table 11. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for compound **370**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	25(2)	31(2)	21(1)	0(1)	-2(1)	1(1)
C(2)	25(2)	35(2)	23(2)	2(1)	-4(2)	-2(1)
C(3)	30(3)	26(2)	25(2)	1(1)	-3(1)	2(1)
C(4)	26(3)	31(2)	28(2)	-4(1)	5(2)	-3(1)
C(5)	39(3)	44(2)	19(2)	4(1)	0(2)	-5(2)
C(6)	30(3)	35(2)	26(2)	2(1)	-3(2)	-3(1)
C(7)	29(2)	30(2)	23(2)	3(1)	-1(2)	1(1)
C(8)	32(3)	31(2)	26(2)	1(1)	-5(2)	-1(1)
C(9)	45(3)	26(2)	39(2)	0(1)	-6(2)	3(2)
C(10)	42(3)	35(2)	33(2)	-2(1)	0(2)	14(2)
C(11)	28(3)	41(2)	17(2)	-5(1)	-2(2)	-1(2)
C(12)	26(3)	32(2)	48(2)	-7(1)	-3(2)	-8(1)
C(13)	34(3)	24(2)	25(2)	-2(1)	3(2)	-3(1)
C(14)	23(2)	26(2)	24(2)	-3(1)	-2(1)	3(1)
C(15)	24(2)	28(2)	23(2)	2(1)	3(2)	-1(1)
N(1)	24(2)	35(2)	28(1)	-1(1)	-3(1)	4(1)
O(1)	35(2)	44(1)	19(1)	0(1)	-4(1)	-5(1)
O(2)	34(2)	46(1)	35(1)	6(1)	6(1)	2(1)
O(3)	26(2)	52(2)	32(1)	-5(1)	-1(1)	-2(1)
O(4)	36(2)	29(1)	23(1)	-1(1)	-4(1)	1(1)

Table 12. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for compound **370**.

	x	y	z	U(eq)
H(2A)	6883	5310	1643	34
H(2B)	6574	6903	845	34
H(3A)	7149	8523	2428	33
H(5A)	7667	5889	5728	41
H(6A)	9024	5303	4963	36
H(8A)	8029	3976	2484	35
H(9A)	9384	2637	1469	44
H(9B)	9340	2815	3091	44
H(10A)	10632	4121	2823	44
H(10B)	10392	4621	1283	44
H(12A)	10167	9962	2870	42
H(13A)	8724	8897	4083	33
H(13B)	8583	9987	2762	33
H(15A)	8242	8674	447	30
H(15B)	9090	7497	510	30
H(1A)	8024	6553	-1430	49

Table 13. Torsion angles [°] for compound **370**.

O(1)-C(1)-C(2)-C(3)	-146.8(2)
O(4)-C(1)-C(2)-C(3)	94.6(3)
C(15)-C(1)-C(2)-C(3)	-21.0(3)
C(1)-C(2)-C(3)-C(14)	-9.5(3)
C(1)-C(2)-C(3)-C(4)	-136.3(3)
C(14)-C(3)-C(4)-O(2)	166.4(3)
C(2)-C(3)-C(4)-O(2)	-72.3(4)
C(14)-C(3)-C(4)-C(5)	-13.0(4)
C(2)-C(3)-C(4)-C(5)	108.2(3)
O(2)-C(4)-C(5)-C(6)	169.1(3)
C(3)-C(4)-C(5)-C(6)	-11.4(5)
C(4)-C(5)-C(6)-C(7)	-1.5(5)
C(5)-C(6)-C(7)-N(1)	160.2(3)
C(5)-C(6)-C(7)-C(14)	37.0(4)
C(5)-C(6)-C(7)-C(8)	-87.1(4)
N(1)-C(7)-C(8)-O(4)	-85.9(3)
C(6)-C(7)-C(8)-O(4)	155.0(3)
C(14)-C(7)-C(8)-O(4)	33.4(4)
N(1)-C(7)-C(8)-C(9)	31.8(3)
C(6)-C(7)-C(8)-C(9)	-87.3(3)
C(14)-C(7)-C(8)-C(9)	151.1(3)
O(4)-C(8)-C(9)-C(10)	84.0(3)
C(7)-C(8)-C(9)-C(10)	-35.9(3)
C(8)-C(9)-C(10)-N(1)	25.7(3)
O(3)-C(11)-C(12)-C(13)	177.8(3)
N(1)-C(11)-C(12)-C(13)	1.5(4)
C(11)-C(12)-C(13)-C(14)	-30.9(4)
C(12)-C(13)-C(14)-C(3)	178.7(3)
C(12)-C(13)-C(14)-C(7)	57.5(3)
C(12)-C(13)-C(14)-C(15)	-64.5(4)
C(4)-C(3)-C(14)-C(13)	-74.5(3)
C(2)-C(3)-C(14)-C(13)	159.4(3)
C(4)-C(3)-C(14)-C(7)	46.5(3)
C(2)-C(3)-C(14)-C(7)	-79.6(3)

C(4)-C(3)-C(14)-C(15)	162.0(3)
C(2)-C(3)-C(14)-C(15)	35.9(3)
N(1)-C(7)-C(14)-C(13)	-56.4(3)
C(6)-C(7)-C(14)-C(13)	68.2(3)
C(8)-C(7)-C(14)-C(13)	-171.4(3)
N(1)-C(7)-C(14)-C(3)	178.4(2)
C(6)-C(7)-C(14)-C(3)	-57.0(3)
C(8)-C(7)-C(14)-C(3)	63.4(3)
N(1)-C(7)-C(14)-C(15)	68.2(3)
C(6)-C(7)-C(14)-C(15)	-167.3(3)
C(8)-C(7)-C(14)-C(15)	-46.9(4)
O(1)-C(1)-C(15)-C(14)	165.2(3)
O(4)-C(1)-C(15)-C(14)	-76.5(3)
C(2)-C(1)-C(15)-C(14)	43.1(3)
C(13)-C(14)-C(15)-C(1)	-172.9(3)
C(3)-C(14)-C(15)-C(1)	-48.6(3)
C(7)-C(14)-C(15)-C(1)	65.9(3)
O(3)-C(11)-N(1)-C(7)	-177.1(3)
C(12)-C(11)-N(1)-C(7)	-1.0(4)
O(3)-C(11)-N(1)-C(10)	-10.1(4)
C(12)-C(11)-N(1)-C(10)	166.0(3)
C(6)-C(7)-N(1)-C(11)	-93.4(3)
C(14)-C(7)-N(1)-C(11)	29.4(4)
C(8)-C(7)-N(1)-C(11)	151.1(3)
C(6)-C(7)-N(1)-C(10)	98.5(3)
C(14)-C(7)-N(1)-C(10)	-138.6(3)
C(8)-C(7)-N(1)-C(10)	-16.9(3)
C(9)-C(10)-N(1)-C(11)	-173.5(3)
C(9)-C(10)-N(1)-C(7)	-4.9(3)
C(9)-C(8)-O(4)-C(1)	-157.8(3)
C(7)-C(8)-O(4)-C(1)	-44.2(4)
O(1)-C(1)-O(4)-C(8)	-166.5(2)
C(15)-C(1)-O(4)-C(8)	69.0(3)
C(2)-C(1)-O(4)-C(8)	-45.6(3)

Symmetry transformations used to generate equivalent atoms:

Table 14. Hydrogen bonds for compound **370** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1A)...O(3)#1	0.84	1.83	2.670(3)	179.5

Symmetry transformations used to generate equivalent atoms:
#1 -x+2,y,-z

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Part B

Application of Rh(II) Catalyzed Reactions for Natural Product Synthesis Containing Oxabicyclo[3.2.1]octane Ring

Chapter B. 1

General Introduction

The oxabicyclo[3.2.1]octane ring system has became increasingly recognized as a common structural motif found in a variety of natural occurring compounds such as aspergillin PZ,[1] nardoxide,[2] and oxycolchicine.[3] Additionally, a number of natural products isolated from various plants have been reported containing this bicyclic ring system, including the *Grayanane* diterpenoids isolated from the poisonous plant *Pieris formasa* and the guaiane type sesquiterpenes curcumenol isolated from rhizomes of *Curcuma zedoaria*.[4] The recently isolated marine natural products bruguierol A-C[5] as well as bacterial metabolites such as platensimycin[6] also contain this bicyclic skeleton (Figure 1).

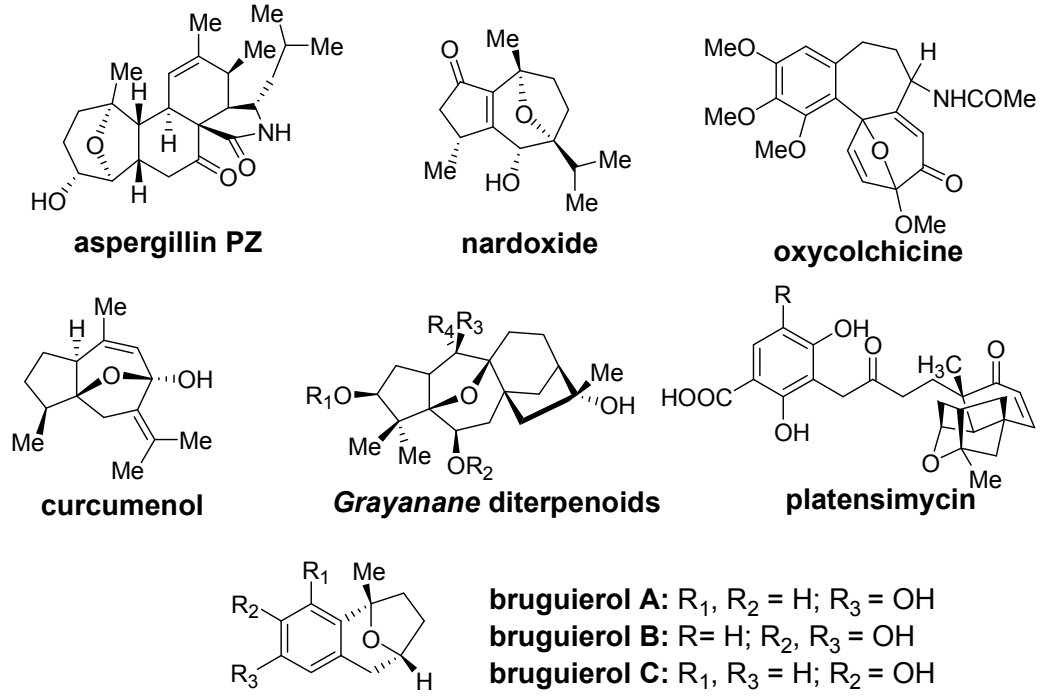
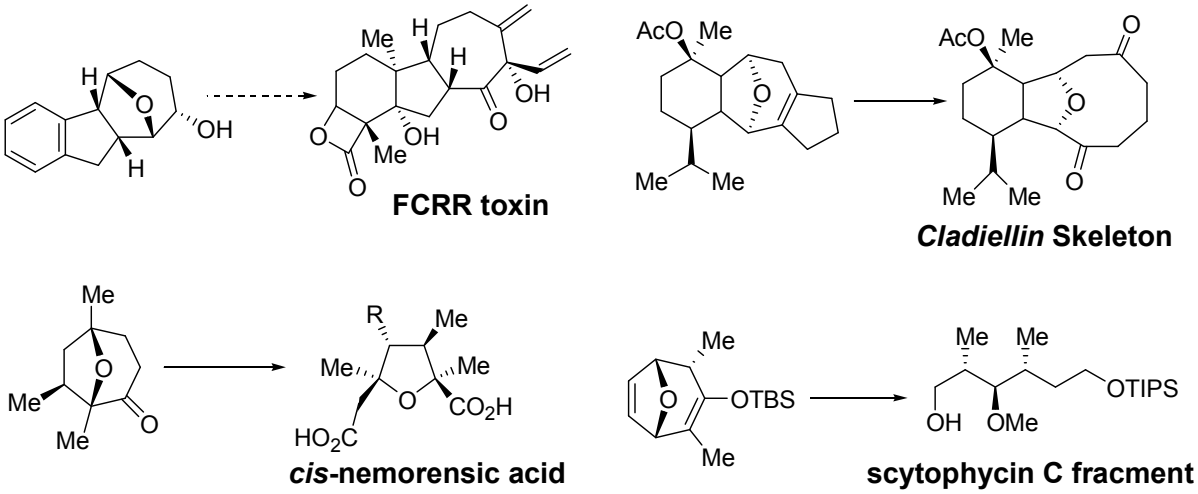


Figure 1. Example of natural products containing the oxabicyclo[3.2.1]octane system

In addition to the extensive distribution of the oxabicyclo[3.2.1]octane framework in various natural products, this medium size bicyclic ether has been

used as a key structural precursor to synthesize a wide range of oxygen containing compounds (Scheme 1). It is frequently found to play a role in the synthesis of seven-membered ring complex natural products[7] including phorbol[8] and the FCRR toxin.[9] The oxabicyclo[3.2.1]octane unit has also been used as a building block toward other core skeletons as well as acyclic targets such as *cis*-nemorensic acid,[10] the *Cladiellin* skeleton,[11] and scytophycin C fragments[12]. It is also worth noting that since the bicyclic system can provide a conformationally well-defined framework, it has also been used as an effective catalyst for asymmetric synthesis.[13]

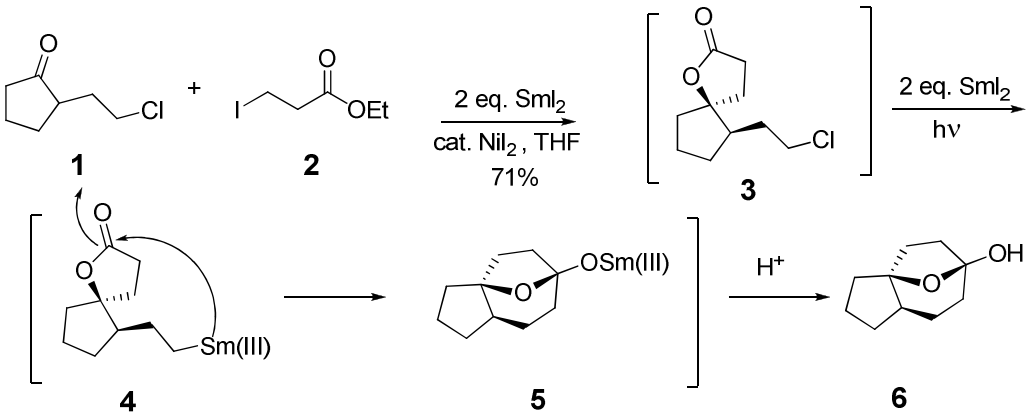


Scheme 1. Extension of the oxabicyclo[3.2.1]octane system to other natural products

Due to the increasing interest in the oxabicyclo[3.2.1]octane system as a substructure in a variety of biologically relevant natural compounds and its use as a powerful building block in total synthesis, the synthesis of such a system has attracted considerable attention.

Various routes to the oxabicyclo[3.2.1]octane system

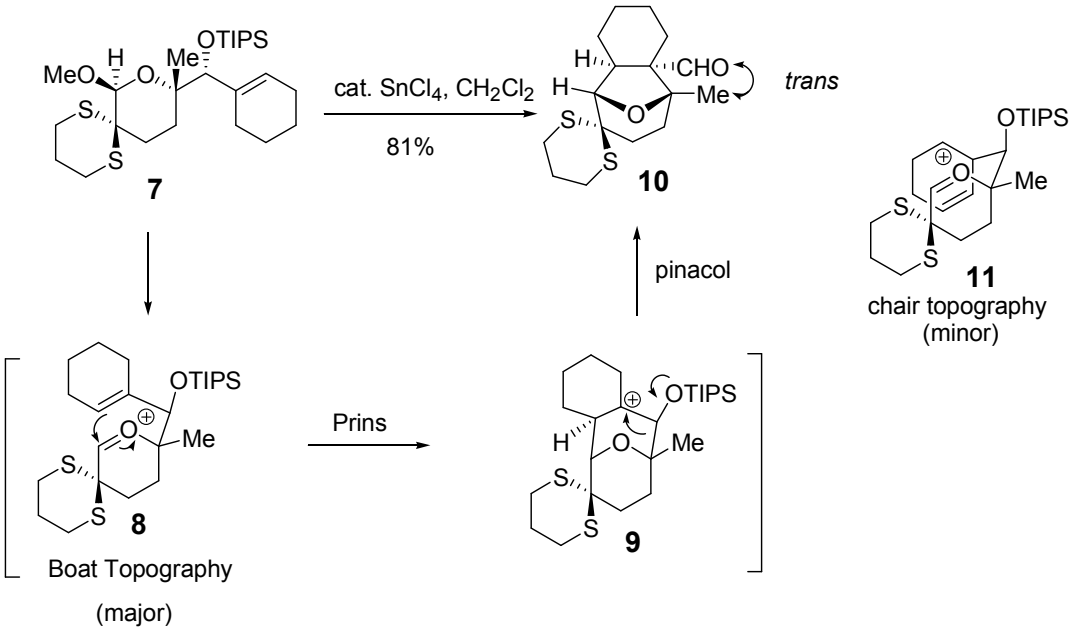
As demonstrated by Molander, SmI_2 promotes an efficient one-pot, two-step dianionic annulation sequence which has been used for the preparation of this bicyclic ring system (Scheme 2).[14] The reaction is initiated by an intermolecular carbonyl addition reaction between ketone **1** and iodo ester **2** to generate a transient lactone intermediate **3**. Subsequent irradiation with light promotes a nucleophilic addition of an organosamarium intermediate **4** derived from chloride **3** to the nearby lactone carbonyl group and delivers the oxabicyclo[3.2.1]octane ring **6** upon work up.[15]



Scheme 2. SmI_2-mediated tandem conjugate addition/nucleophilic acyl substitution

In ongoing efforts to synthesize aspergillin PZ, the Overman group reported a Prins-pinacol reaction sequence as the key step for the construction of the oxabicyclo[3.2.1]octane ring system (Scheme 3).[16] The acid promoted generation of oxocarbenium ion **8** was found to undergo a subsequent a Prins cyclization to carbocation **9**. The steric bias was made possible by the use of the

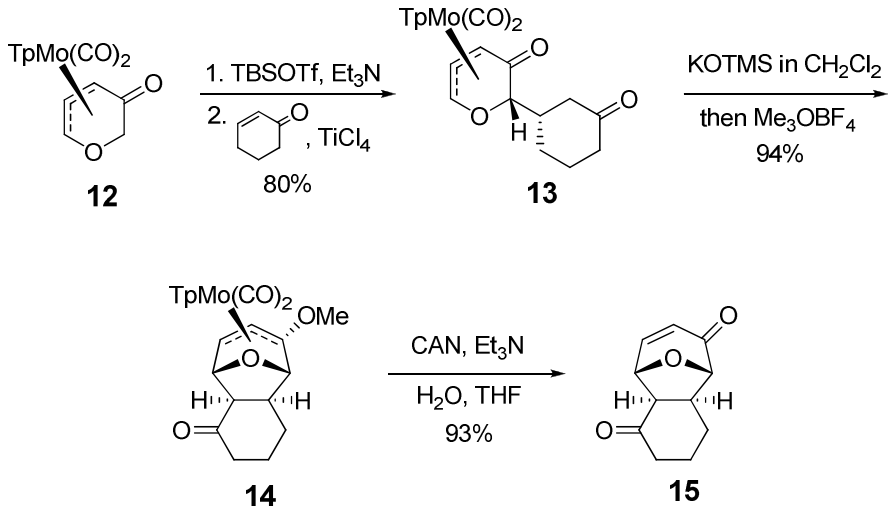
bulky dithiane which forces the reaction to proceed *via* a boat conformation and this results in formation of the *trans* oxatricyclic **9**. Finally, a Pinacol rearrangement of intermediate **9** involving carbon bond migration provides the oxabicyclo[3.2.1]octane skeleton **10** in good yield. Formation of the correct stereoisomer provides an efficient approach toward the synthesis of aspergillin PZ.



Scheme 3. Prins-Pinacol reaction for the formation of oxabibyclo[3.2.1]octane

A novel C-C bond forming strategy using a molybdenum-mediated 1,5-Michael-type reaction to generate the oxabicyclo[3.2.1]octane unit was reported by Liebeskind (Scheme 4).[17] The two-step sequence first starts with the conversion of 5-oxo-η^3-pyranylmolybdenum complex **12** into the corresponding silyl enol ether. Further reaction with $TiCl_4$ induced a Mukaiyama-Michael reaction to give adduct **13**. Subsequently, treatment of the resulting adduct **13**

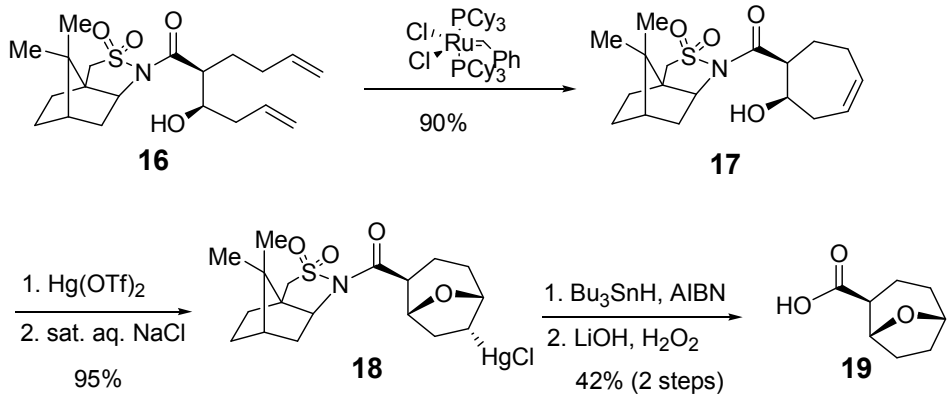
with base and quenching the initially generated 1,5-Michael intermediate with Me_3OBF_4 delivered oxatricycle **14**. Liberation of the molybdenum complex by oxidative demetallation gave enone **15** in good overall yield. The high enantiomeric selectivity and regioselectivity of this reaction is strongly influenced by the molybdenum scaffold.



Scheme 4. 1,5 Michael-type reactions of 5-oxo-η^3-allylmolybdenum complexes

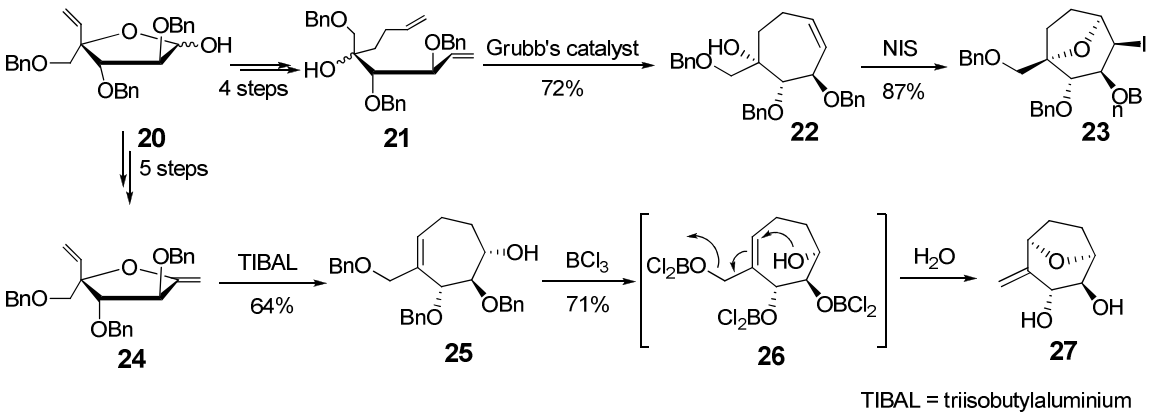
Intramolecular cyclization of an oxygen atom onto a previously formed seven membered rings has also been widely utilized to access the oxabicyclo[3.2.1]octane skeleton. For example, an intramolecular oxymercuration approach to generate the bicyclic system has been reported by Vounatsos.[18] Thus, ring closing metathesis of diene **16** provided cycloheptene **17**. Subsequent intramolecular oxymercuration of cycloheptene **17** with $Hg(II)(OTf)_2$ provided bicyclic ether **18** as a single regioisomer. An enantiomerically pure stereoisomer of the product was achieved by an asymmetric aldol reaction which was used to

prepare the starting diene **16**. In the last two steps, reductive demercuration and hydrolysis of the chiral auxiliary unit liberated the desired adduct **19** (Scheme 5).



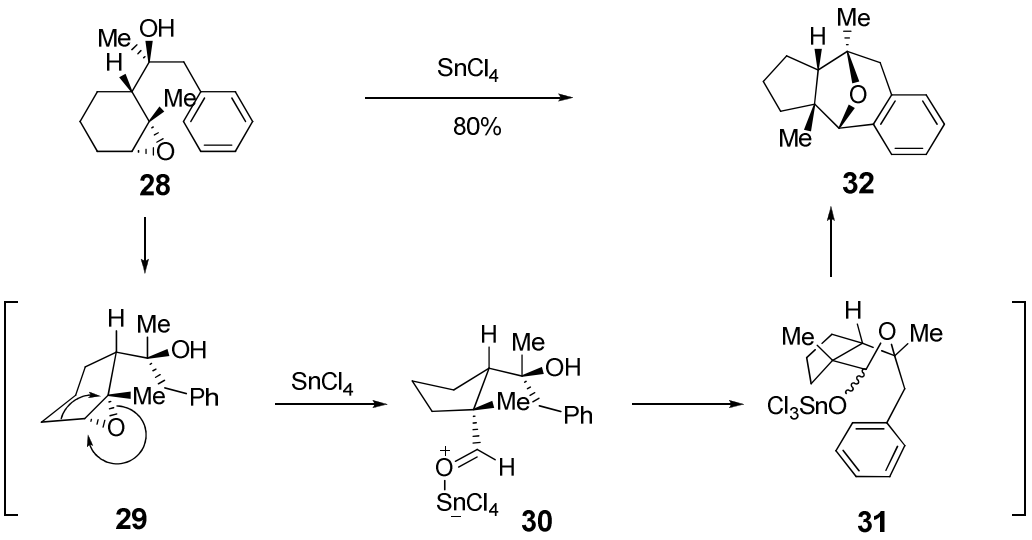
Scheme 5. Intramolecular oxymercuration to form oxabicyclo[3.2.1]octane

In a similar manner, intramolecular electrophilic addition has been reported as a method to construct highly oxygenated oxabicyclo[3.2.1]octanes from heptenes derived from d-arabinose (Scheme 6).[19] Two different sets of conditions have been utilized to deliver two different oxabicyclo[3.2.1]octane products. Ring closing metathesis of diene **21** and subsequent iodide-promoted electrophilic addition provided bicyclic ether **23**. Using another pathway, the TIBAL-promoted Claisen rearrangement of allyl vinyl ether **24** afforded heptene **25**. Treatment of **25** with BCl_3 furnished the oxabicyclic **27**.



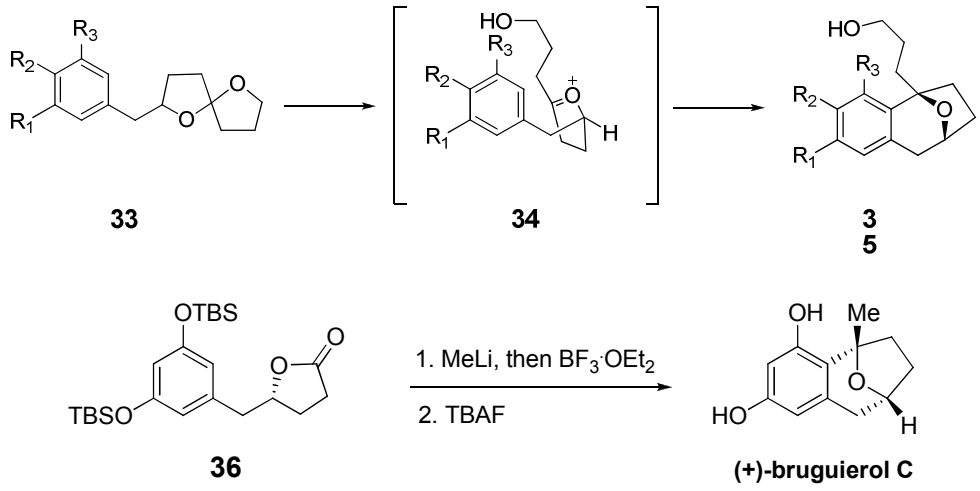
Scheme 6. Oxabicyclo[3.2.1]octane derivatives from d-arabinose

Another clever method that has been used for synthesis of the bicyclo[3.2.1]octane system was reported by Marson in 1998.[20] This novel approach was based on a $SnCl_4$-catalyzed intramolecular Friedel-Crafts reaction (Scheme 7). Cyclization involving epoxyalcohol **28** occurred through a tandem process *via* an epoxide ring opening and ring contraction. Subsequent, acetal formation and capture of an *in situ* generated oxocarbenium ion derived from **31** *via* an intramolecular Friedel-Crafts reaction delivered the bicyclic ether **32**. Under these conditions, both aryl and alkenyl π-nucleophiles were successfully utilized.



Scheme 7. Tandem cyclization to bridged ethers by Friedel-Crafts cyclization

Following Marson's work, a variation of the Friedel-Crafts cyclization to generate a benzenoid-fused oxabicyclo[3.2.1]octane has been reported (Scheme 8). The use of spiroketal **33** as an alkylating agent demonstrated the ready access to this benzo-fused ring system.[21] Still another example of this strategy was recently reported as the key step in the total synthesis of (+)-bruguierol C. [22]



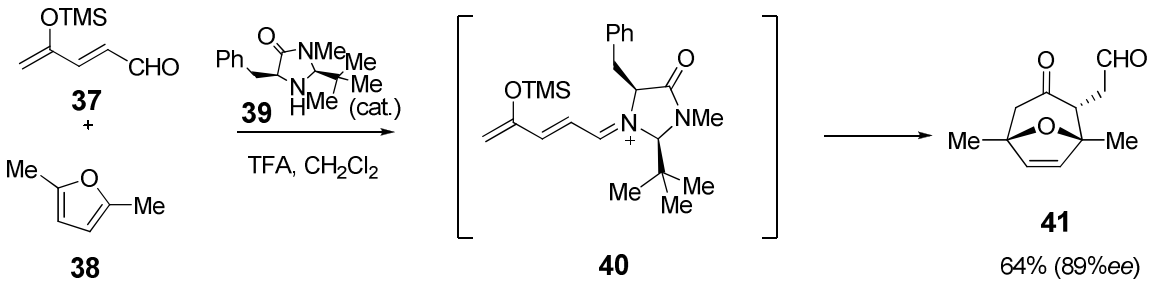
Scheme 8. Variations of intramolecular Friedel-Crafts cyclization to generate benzene-fused oxabicyclo[3.2.1]octane

Cycloaddition reactions to the oxabicyclo[3.2.1]octane system

As demonstrated with the previous examples, there are a variety of strategies reported in the literature to access the oxabicyclo[3.2.1]octane skeleton. However, one of the more useful approaches to this ring system involves some cycloaddition chemistry. Several research groups have performed studies in this area and have revealed the effectiveness of this methodology for easy and rapid generation of molecular complexity.

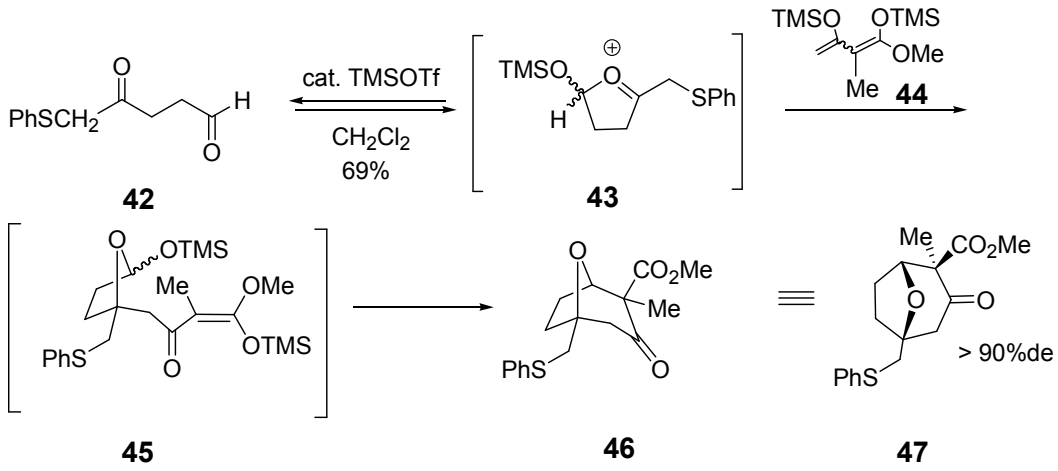
- [4+3]-Cycloaddition reactions

Among the cycloaddition approaches employed, the [4+3]-cycloaddition has been shown to be a most useful method to construct the oxabicyclo[3.2.1]octane framework. A typical example involves the cycloaddition reaction between a furan and an oxaallyl cation (Scheme 9). This strategy was first demonstrated by Hoffmann [23] and has become one of the more popular methods to access this ring system. Several variations of this method have been reported and proceed with high diastereoselectivity and enhanced efficiency.[24] A typical example shown here is represented by a method reported by Harmata.[24b] The *in situ* formation of the chiral iminium ion **40** functions as a stabilized oxaallyl cation. A subsequent [4+3]-cycloaddition reaction of **40** with furan **38** delivered the bicyclic ether **41**. The chiral amine catalyst could be regenerated by an acid-catalyzed hydrolysis.



Scheme 9. An example of [4+3]-annulation approach using furan and allyl cation

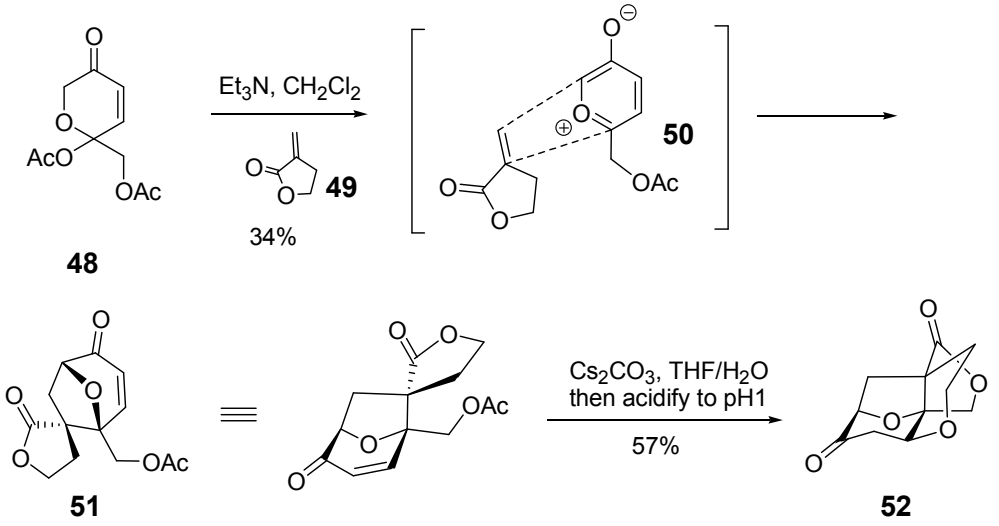
An alternative [4+3]-cycloaddition was reported by the Molander group. The method relies on the Lewis acid promoted annulation of a 1,4-dicarbonyl electrophile such as **42** with 1,3-bis(trimethylsilyl)oxy diene **44** (Scheme 10).[25] Control over the regiochemistry and stereochemistry was achieved by the involvement of a neighboring group participation mechanism which proceeds by oxocarbenium ion intermediate **43**.[25b,c]



Scheme 10. A Lewis acid-mediated [4+3]-annulation approach to the oxabicyclo[3.2.1]octane ring system

- [5+2]-Cycloaddition reactions

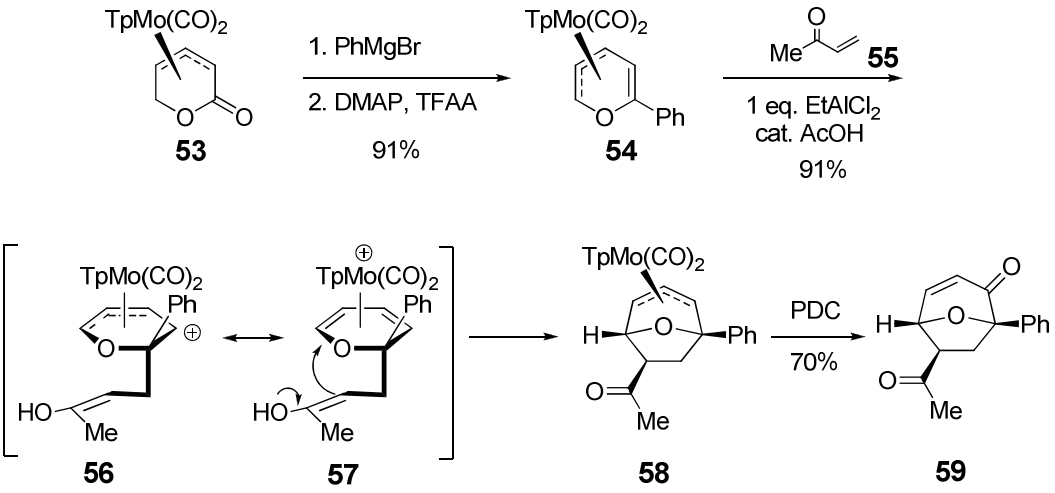
The oxidopyrylium-alkene [5+2]-cycloaddition offers another excellent approach toward the synthesis of the bicyclo[3.2.1]octane framework. Several structurally complex natural and synthetic products possessing this oxa-bridge ether have been efficiently generated by this method.[26] One interesting example was reported by Snider and Hashimoto who used a [5+2]-cycloaddition reaction for a formal synthesis of various polygalolides (Scheme 11).[27] Bisacetoxy pyranone **48** was treated with Et_3N to give 3-oxidopyrilium ylide **50** which underwent a [5+2]-cycloaddition with alkene **49** to provide the bicyclo[3.2.1]octane skeleton. Upon hydrolysis, tetracycle **52** was obtained thereby completing a formal synthesis of polygalolides.



Scheme 11. The [5+2]-cycloaddition approach to the oxabicyclo[3.2.1]octane derivative in the formal synthesis of polygalolides A and B

A related [5+2]-cycloaddition was disclosed by Liebeskind's group using molybdenum complexes as organometallic scaffolds (Scheme 12).[28] The 6-

substituted η^3-pyranylmolybdenum scaffold **54**, prepared in two steps from **53**, served as a chiral substrate for a [5+2]-cycloaddition reaction. The use of a Brønsted acid catalyst in the [5+2]-cycloaddition between the molybdenum pyranyl scaffold **54** and the electron-deficient alkene **55** provided the oxabicyclo[3.2.1]octane skeleton with total control of both regio- and stereoselectivity. Regiospecific oxidative demetallation led to a single isomer of enone **57**.

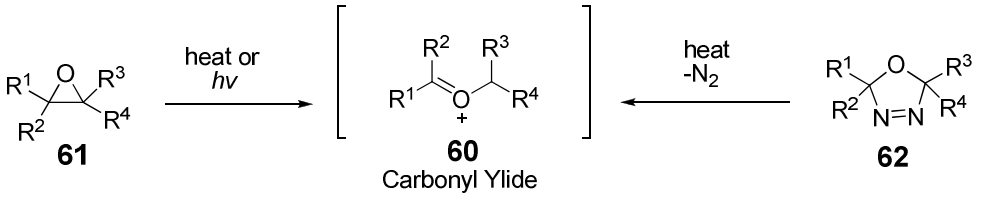


Scheme 12. Liebeskind's [5+2]-cycloaddition reaction using Mo-π-complex scaffolds

- [3+2]-Cycloaddition reactions

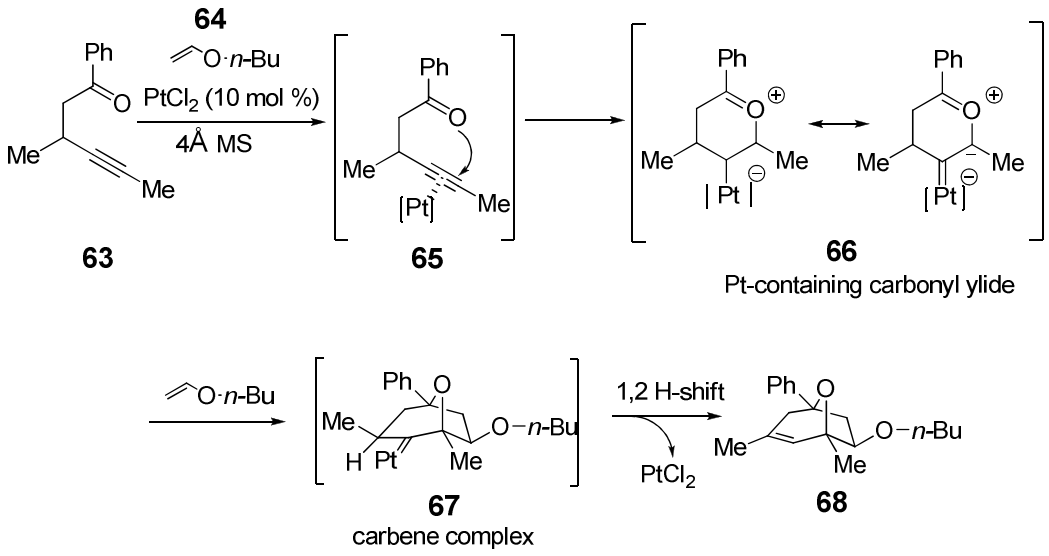
Aside from [4+3]- and [5+2]-cycloadditions, another well known approach to the oxabicyclo[3.2.1]octane skeleton involves the use of a [3+2]-cycloaddition reaction.[29] This dipolar-cycloaddition of reaction typically involves the generation of a six-membered ring carbonyl ylide as a 1,3-dipole partner which can be trapped with various π-bonds to deliver the oxabicyclic compound.

Various methods have been reported for the formation of carbonyl ylides. The photoinduced or thermal opening of oxiranes bearing an adjacent electron withdrawing group appeared as an early method for carbonyl ylide formation.[30] Another known method involves the thermal extrusion of nitrogen from 1,3,4-oxadiazolines.[31] The application of these [3+2]-cycloaddition reactions are mostly limited to the construction of five-membered rings or to the generation of the oxabicyclo[2.2.1]heptane skeleton (Scheme 13).[30,31]



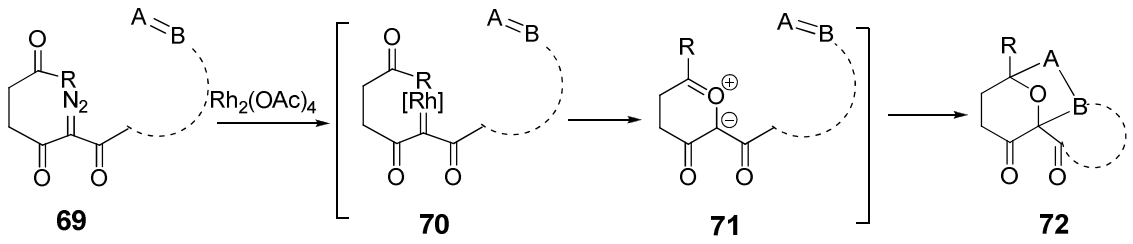
Scheme 13. Generation of carbonyl ylides from oxiranes and 1,3,4-oxadiazolines

Another innovative route for the formation of carbonyl ylides involves the use of metal mediated nucleophilic additions to alkynes. An example from the Iwasawa group showed that the oxabicyclo[3.2.1]octane ring could be efficiently obtained by exclusive *6-endo* attack of a carbonyl oxygen atom onto a metal-activated alkyne **65** thereby generating a six-membered ring Pt-containing carbonyl ylide **66**.[32] This zwitterionic intermediate **66** then underwent a [3+2]-cycloaddition reaction with an electron-rich alkene to give the oxabicyclo[3.2.1]octane derivative in good yield (Scheme 14).



Scheme 14. The construction of bicyclo[3.2.1]octane from Pt-containing carbonyl ylides

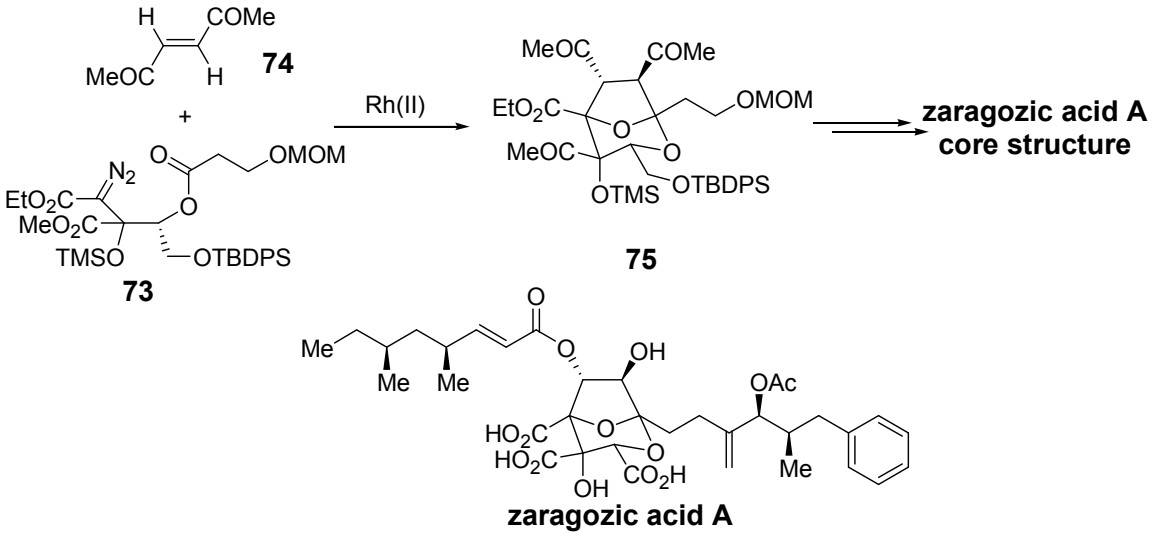
One of the simplest and more powerful techniques for the generation of carbonyl ylide dipoles involves the rhodium (II)-catalyzed decomposition of α-diazo compounds.[33] This methodology continues to be of great interest ever since the early studies by Huisgen and de March who showed that of carbonyl ylides can be generated from diazo compounds utilizing $Rh_2(OAc)_4$, $Cu(acac)_2$ or CuOTf as catalysts.[34] The [3+2]-cycloaddition reaction using this procedure was shown to proceed by the formation of a Rh-carbenoid intermediate **70** generated by the Rh(II)-catalyzed decomposition of diazo compound **69** (Scheme 15). Subsequent transannular cyclization of the electrophilic C-atom onto the adjacent keto group leads to cyclic carbonyl ylide **71**, which then undergoes a 1,3-dipolar cycloaddition with an adjacent.



Scheme 15. The Rh(II)-catalyzed tandem reactions of diazo compounds

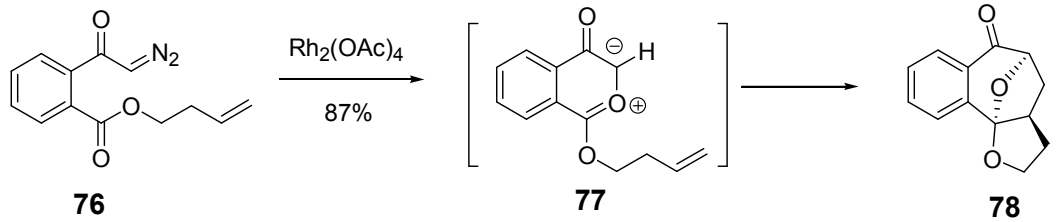
The catalytic decomposition of diazo compounds in the presence of carbonyl groups represents a very powerful method for the synthesis of a variety of oxacyclic ring systems. This reaction also includes the formation of six-membered ring carbonyl ylide intermediates which can then lead to the oxabicyclo[3.2.1]octane unit by a [3+2]-cycloaddition reaction. Most importantly, both inter- and intramolecular cycloadditions have been disclosed.

In Hashimoto's approach toward zaragozic acid, an intramolecular cyclization followed by bimolecular cycloaddition was used for the construction of the 2,8-dioxabicyclo[3.2.1]octane core **75** (Scheme 16). Thus, the carbonyl ylide dipole derived from the Rh(II)-mediated decomposition of diazo compound **73** was found to undergo a stereocontrolled intermolecular 1,3-dipolar cycloaddition with alkene **74** to give a single diastereomer of dioxabicyclo[3.2.1]octane **75**. The cyclization occurred exclusively from the β-face of the carbonyl ylide, thereby avoiding non-bonding interactions with the pseudoaxial OTMS group.



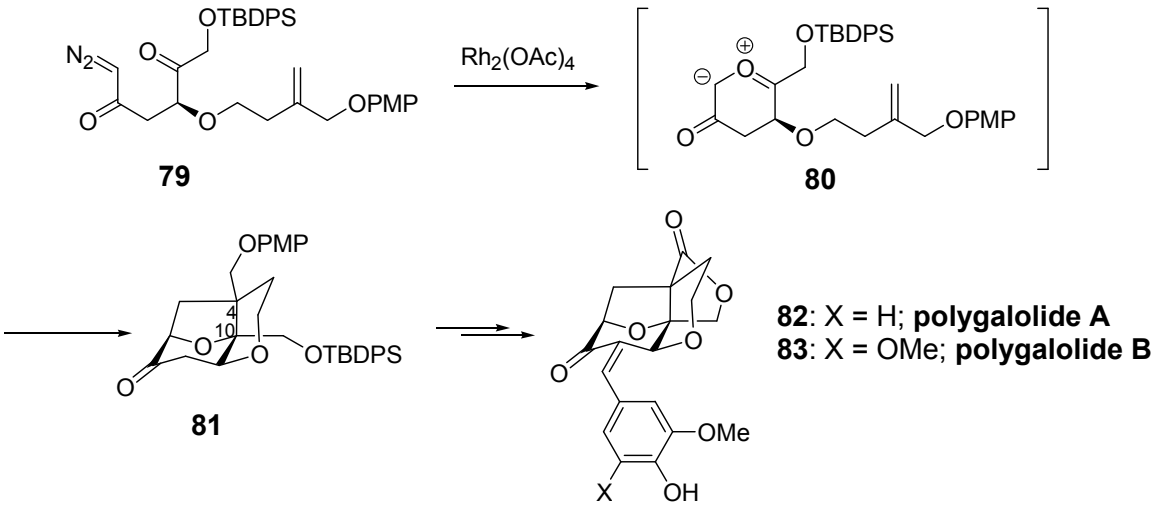
Scheme 16. The use of intramolecular Rh(II)-catalyzed [3+2]-cycloaddition toward the synthesis of zaragozic acid

[3+2]-Cycloaddition reactions that proceed in an intramolecular fashion have also provided access to more complex oxapolycyclic structures in a single step. A very early example by the Padwa group involves the smooth Rh(II) induced formation of bridge oxabicyclo[3.2.1]octanes from *o*-carboalkoxy-α-diazoacetophenone derivative **76** (Scheme 17).[35] The cyclic six-membered-ring carbonyl ylide **77** was trapped intramolecularly by the neighboring C-C double bond to give **78** in 87% overall yield.



Scheme 17. Intramolecular Rh(II)-catalyzed [3+2]-cycloaddition to oxabicyclo[3.2.1]octane

An additional example highlighting the intramolecular cascade sequence to produce oxabicyclo[3.2.1]octanes was recently reported for the synthesis of polygalolides A (**82**) and B (**83**).[36] The core oxabicyclo[3.2.1]octane structural framework was constructed by employing a Rh(II)-catalyzed 1,3-dipolar cycloaddition of diazoketone **79** containing an alkenyl tether to give **81**. The required *trans* disposition at positions C-4 and C-10 was achieved during the cycloaddition reaction. Further elaboration of **81** eventually gave polygalolides A (**82**) and B (**83**).



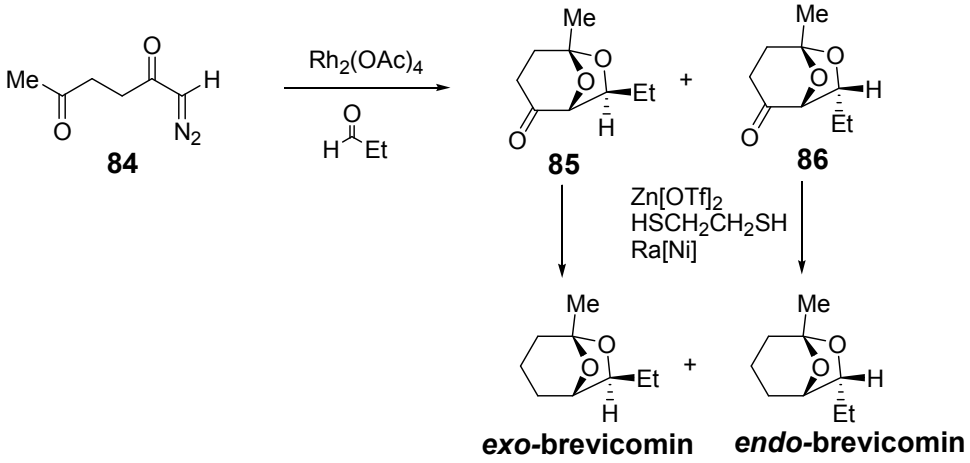
Scheme 18. Synthesis of polygalolides A and B

The Rh(II)-catalyzed cycloaddition reaction employed in the Padwa group

Research involving Rh(II)-catalyzed cyclization reactions began in the Padwa group in 1986 and has been extensively studied both mechanistically and synthetically.[37] The long standing interest in the Rh(II)-catalyzed cyclization/cycloaddition cascade in the group has been focused on developing new applications toward polycyclic core structures and their further application in natural product

synthesis. The completion of several oxapolycyclic core structures has been reported and also applied to the synthesis of natural products utilizing this methodology.

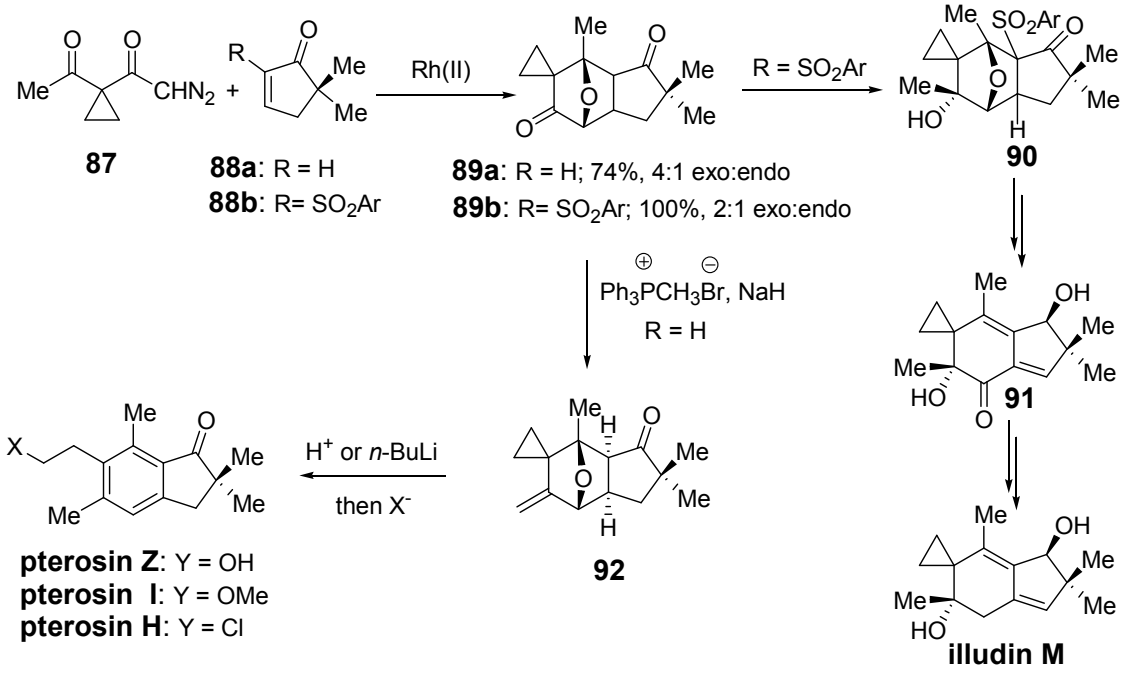
A very early application of the method toward natural product synthesis involved the preparation of *exo*- and *endo*-brevicomin (Scheme 19).[38] Reaction of 1-diazohexane-2,5-dione **84** with $Rh_2(OAc)_4$ in the presence of propanal afforded cycloadducts **85** and **86** in 60% yield as a 2:1 mixture of isomers. After separation, each isomer was converted to *exo*- and *endo*-brevicomin.



Scheme 19. Padwa's synthesis of brevicomin

The intermolecular 1,3-dipolar cycloaddition reaction was also successfully used to construct the oxa-bridge system **89** found in the illudins. This valuable intermediate could be transformed to either illudin M or to the pterosin family (Scheme 20).[39] In the synthesis of pterosin, the Rh(II)-catalyzed [3+2]-cycloaddition reaction gave cycloadduct **89a** in 74% as a 4:1-mixture of *exo:endo* isomers. A subsequent Wittig reaction gave cycloadduct **90** and this was followed by a series of transformations involving oxa-bridge ring opening

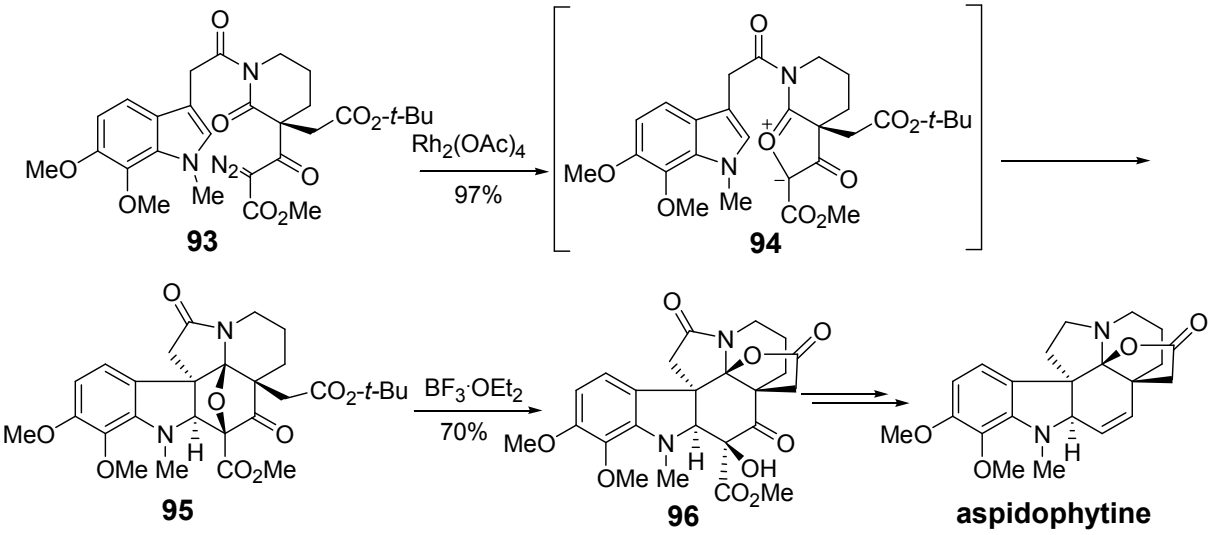
and further reaction with a variety of nucleophiles. This resulted in cyclopropyl ring opening followed by a rearomatization to give several members of the pterosin family. In the synthesis of illudin M, the more highly activated cyclopentenone **88b** was used as the dipolarophile. As expected, the Rh(II)-catalyzed reaction provided cycloadduct **89b** in much higher yield as a 2:1-mixture of *exo*:*endo* isomers. The two isomers were converted to a common intermediate **91** thereby completing the formal synthesis of illudin M.



Scheme 20. The use of Rh(II)-mediated [3+2]-cycloaddition in the synthesis of illudin M and pterosin Z, I and H

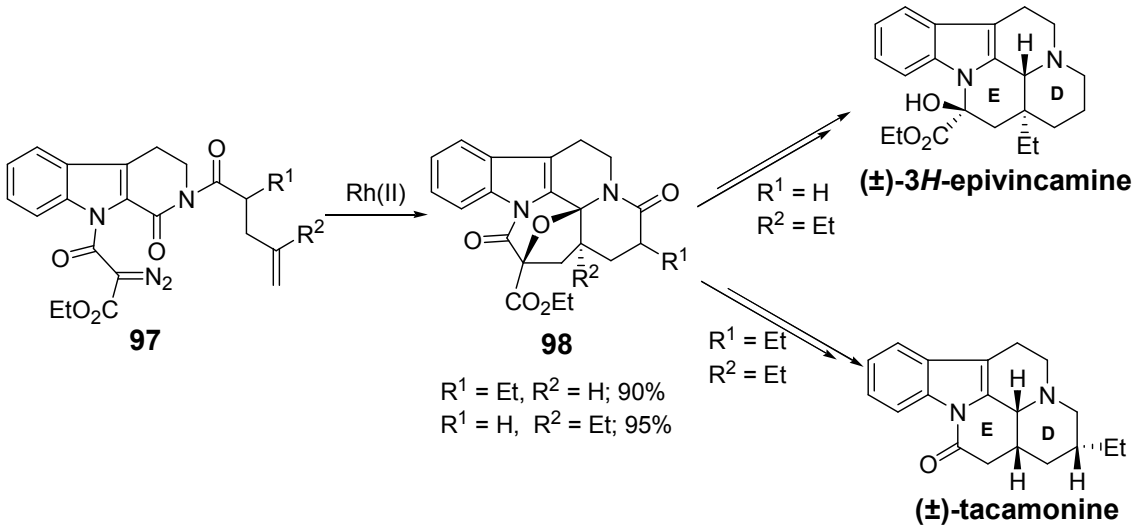
In a more recent article, the Padwa group successfully synthesized the core skeleton of several natural products of the A*spidosperma*,[40] *Kopsifoline*,[41] and *Ergot* alkaloid families.[42] The example shown below involves the synthesis of aspidosphytine (Scheme 21).[43] In the crucial Rh(II)-catalyzed reaction,

diazoimide **93** underwent a Rh(II)-catalyzed carbonyl ylide cyclization and this was followed by a subsequent [3+2]-cycloaddition onto the tethered indole double bond to give the pentacyclic indane framework **95**. The cycloaddition reaction nicely furnished a single diastereomer containing the required stereochemistry at all four of the newly formed stereocenters. Treatment of **95** with $BF_3{\cdot}OEt_2$ afforded lactone **96**, which was further transformed into aspidophytine.



Scheme 21. A [3+2]-cycloaddition reaction for the synthesis of aspidophytine

Very recently, the Padwa group also disclosed the total synthesis of several members of the *vinca* and *tacaman* classes of indole alkaloids using the Rh(II) cyclization strategy.[44] In the crucial step, an intramolecular [3+2]-cycloaddition reaction of diazo-indolamide **97** delivered the pentacyclic skeleton **98** in excellent yield. The acid labile oxabicyclic unit underwent ring opening to give a product containing the t*rans*-D/E ring fusion. Further treatment with base induced a novel keto-amide ring contraction to form the final E ring (Scheme 22).



Scheme 22. General acess to *vinca* and *tacaman* alkaloids using Rh(II)-catalyzed [3+2]-cycloaddition

As described above, the Rh(II)-catalyzed cyclization/cycloaddition strategy represents an efficient approach for the preparation of a diverse range of natural product frameworks. Oxa-bridge bicyclic formation was employed to prepare other core skeletons as well as being used directly to form various natural product skeletions.

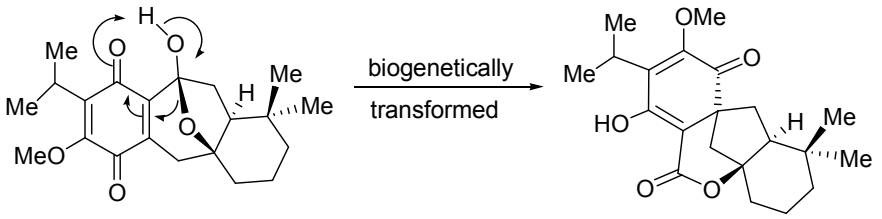
Since a large number of natural products contain the oxabicyclo[3.2.1]octane unit, we set out to further extend this methodology to several other natural products in order to further demonstrate the synthetic power of this methodology. The following sections of this thesis describe the details of our synthetic efforts dealing with both intra- and intermolecular cycloadditions toward two natural products that contain the oxabicyclo[3.2.1]octane framework, namely komaroviquinone and furanether B.

Chapter B. 2

Application of the Rh(II)-Catalyzed [3+2]-Cycloaddition towards the Synthesis of Komaroviquinone

1. Introduction

Dracocephalum komarovi known as ‘buzbosh’ is a perennial semishrub that grows around 3000 meters above sea level in the West Tien Shan mountains of Uzbekistan. The local people use the aerial parts to cure various disorders such as inflammatory diseases and hypertony.[45] During the course of a study dealing with the organic extracts of buzbosh, Honda and co-workers fractionated and isolated several icetexane diterpenes whose structures were elucidated by extensive analysis of their NMR data.[46] The major fraction isolated from the plant was assigned structure **99** and was named komaroviquinone. In addition to compound **99**, a minor diterpene **100** was also isolated from the same plant and since it possessed a novel spiro-octahydroindene skeleton, it was named komarovispirone.[47] Both compounds show *in vitro* trypanocidal activity against epimastigotes of *Trypanosoma cruzi*, the causative agent of Chagas' disease in Central and South America. However, komaroviquinone is much more potent with a minimum lethal concentration (MLC) of 0.4 μM, compared to a MLC of 23.0 μM for komarovispirone.[48] It has been proposed that komarovispirone may be derived from komaroviquinone by means of a novel ring-contraction sequence as outlined in Scheme 23.[47]



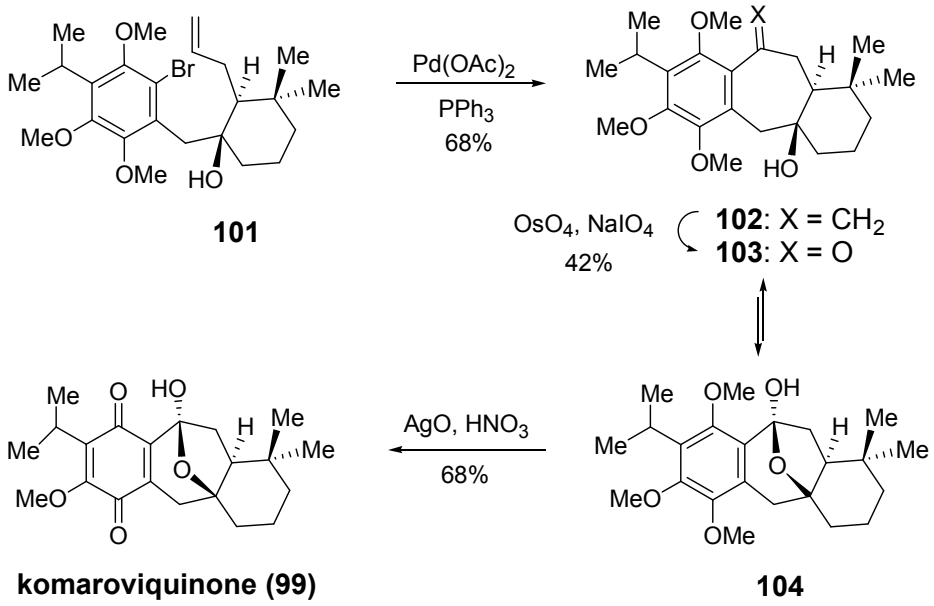
komaroviquinone (99) **komarovispirone (100)**

Scheme 23. Proposed biological transformation of komaroviquinone to komarovispirone

The total synthesis of several related diterpenes which incorporate a functionalized 6-7-6 fused tricyclic framework have recently appeared in the literature[49, 50,51]and involve generation of the core skeleton mainly through acid-catalyzed cyclialkylation reactions.[52] Most recently, the total synthesis of salviasperanol,[53] a structurally related diterpene to komaroviquinone, has been disclosed and sets the stage for potential access to komaroviquinone.

The first total synthesis of komaroviquinone was reported by Banerjee and coworkers in 2005 (Scheme 24).[54] Construction of the oxabicyclo[3.2.1]octane substructure was achieved through formation of the seven-membered ring followed by formation of the oxa-bridge. Generation of the critical structure containing the seven-membered ring core, *trans*-10-hydroxy-1,1-dimethyl-octahydrodibenzo[*a,d*]cyclohepten-7-one (**102**), was achieved by employing an intramolecular Heck reaction for the crucial carbon-carbon bond forming step.[55] This was done by treatment of the olefinic intermediate **101** with $Pd(OAc)_2$, K_2CO_3 and PPh_3 in acetonitrile under reflux which resulted in formation of the seven-membered exo-cyclic alkene **102** in good yield. Oxidative cleavage of the

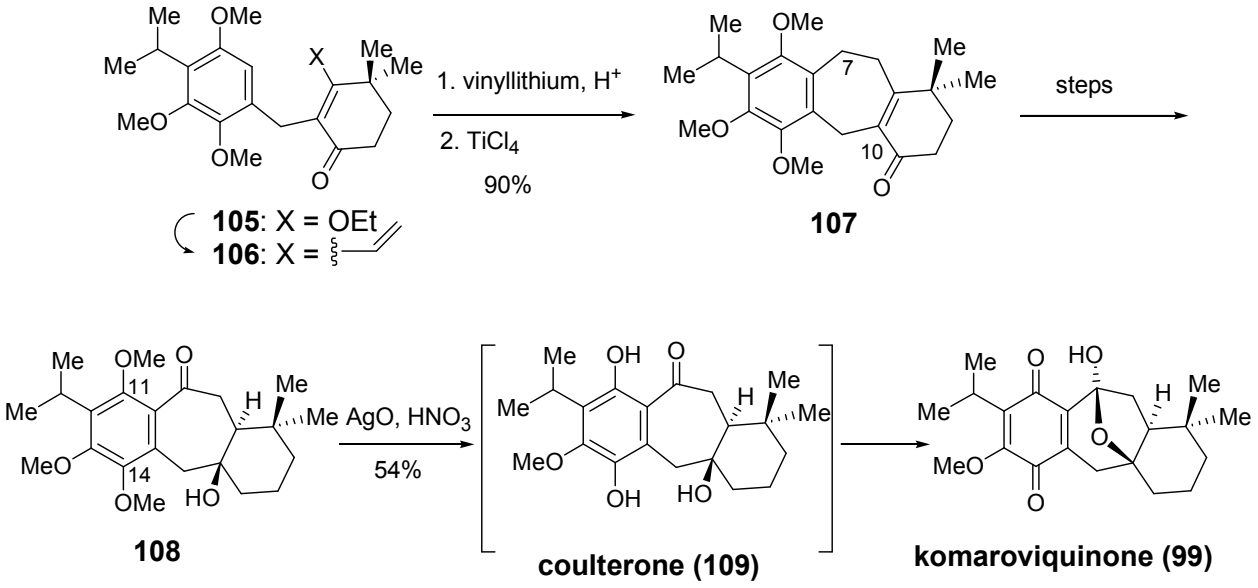
π-bond in **102** with OsO_4 and $NaIO_4$ produced hydroxy ketone **103** in 42% yield, which in solution, exists in equilibrium with the hemiketal **104** bearing the oxabicyclo[3.2.1]octane unit. Further oxidation of the equilibrating mixture with AgO in dilute HNO_3 as the oxidant afforded (±)-komaroviquinone as the major product in 68% yield for the last step.



Scheme 24. The first total synthesis of (±)-komaroviquinone by Banerjee

In 2007, Majetich disclosed the second total synthesis of (±)-komaroviquinone as well as the first enantioselective synthesis of (+)-komaroviquinone (Scheme 25).[56] 1,2-Addition of vinyllithium to enone **105** followed by mild acid hydrolysis produced enone **106**. Upon treatment with $TiCl_4$, enone **106** underwent a Friedel-Crafts cyclialkylation to give cycloheptene **107**. Further functional group elaborations involving regioselective benzylic oxidation at C-7 and introduction of the C-10 hydroxy group, provided compound **108**, which is the same intermediate as that reported by Banerjee. Finally, oxidation

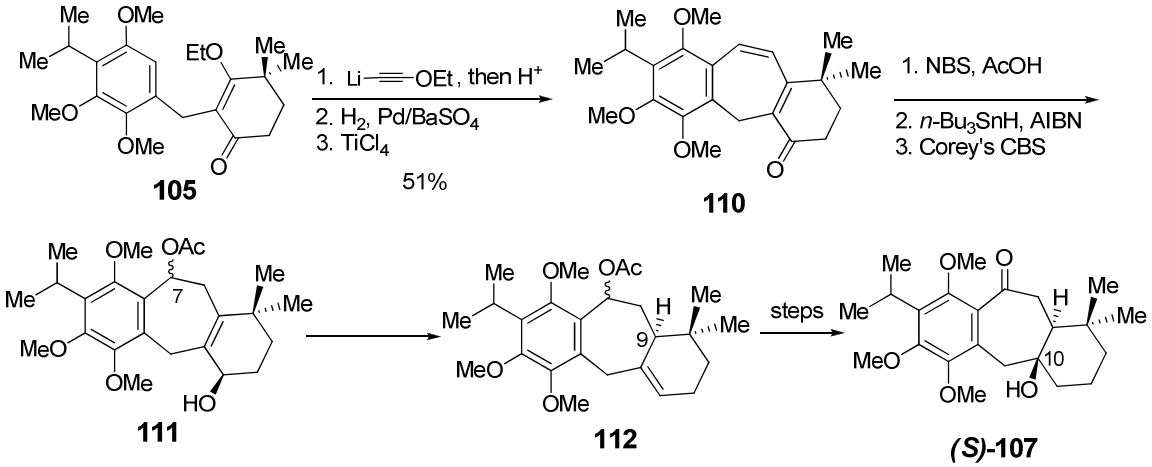
and intramolecular hemi-acetal formation furnished (±)-komaroviquinone in 54% yield. Interestingly, it was noted in this report that demethylation of the methoxy group at C-11 and C-14 first occurred to give the hydroquinone intermediate **109**, which is itself a natural product, before full oxidation to the quinone natural product.



Scheme 25. Majetich's total synthesis of (±)-komaroviquinone

Majetich's enantioselective synthesis of (+)-komaroviquinone featured a similar protocol to that described for the racemic synthesis (Scheme 26). However, an improved route was used to produce dienone **110** which allowed for a more facile addition of the carbonyl group at C-7. The oxygen atom at C-7 was introduced by regioselective bromohydrin formation and debromination. In the next step, Corey's CBS asymmetric reduction was used for 1,2-reduction of the carbonyl group to give rise to a single diastereomer of alcohol **111** which was then used to the control the stereochemistry at C-9. Stereospecific bromohydrin formation of **112** and further functional group manipulation resulted in the

formation of ***(S)*-9** as a single product. Finally, subjection of **112** to the same protocol as described above gave (+)-komaroviquinone.

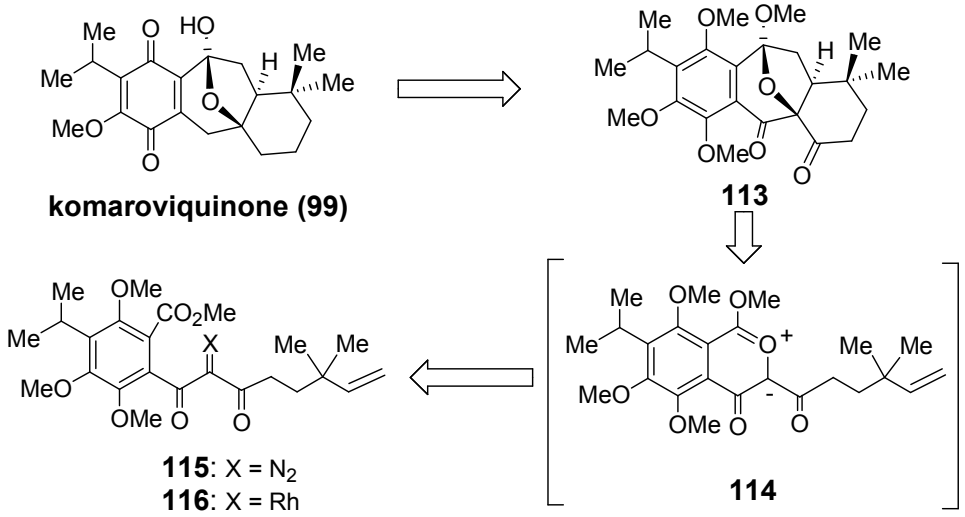


Scheme 26. Majetich's enantiospecific total synthesis of (+)-komaroviquinone

It is worth noting that Majetich later reported the conversion of komaroviquinone to komarovispirone.[57] Interestingly, the isomerization did not occur under acid or basic conditions but rather it rearranged under photo-chemical conditions. Use of a 5.5 W Hg lamp in cyclohexane gave komarovispirone in 90% yield. Exposing a solution of komaroviquinone to daylight at rt also produced komarovispirone over a 2 day period. Since komaroviquinone was isolated from the plant as the major product, Majetich suggested that komarovispirone, which was formed very rapidly under photoinduced conditions, is not a natural product but rather is an artifact of the isolation process.

- **Our retrosynthetic analysis to (±)-komaroviquinone**

As part of our continuing program to extend the Rh(II)-catalyzed [3+2]-cycloaddition reaction to natural product synthesis, we considered developing an alternative approach to the synthesis of komaroviquinone. On the basis of some earlier work in our laboratory,[58] we felt that the Rh(II)-catalyzed reaction of the diazo-dione precursor **115** might allow for a facile entry to the icetexane core of komaroviquinone (Scheme 27). The eventual formation of the oxa-tricyclo[6.3.1.$0^{0,0}$]dodecane skeleton of komaroviquinone was envisioned to come about from an intramolecular [3+2]-cycloaddition reaction of the carbonyl ylide dipole **114** with the tethered π-bond. Carbonyl ylide **114** would be formed by cyclization of the Rh-carbenoid intermediate **116** with the adjacent carbomethoxy group. The resulting cycloadduct **113** would then be converted to (±)-komaroviquinone in several steps by sequential reduction of the keto groups, oxidation to the benzoquinone core and eventual acid hydrolysis of the ketal moiety.[59]



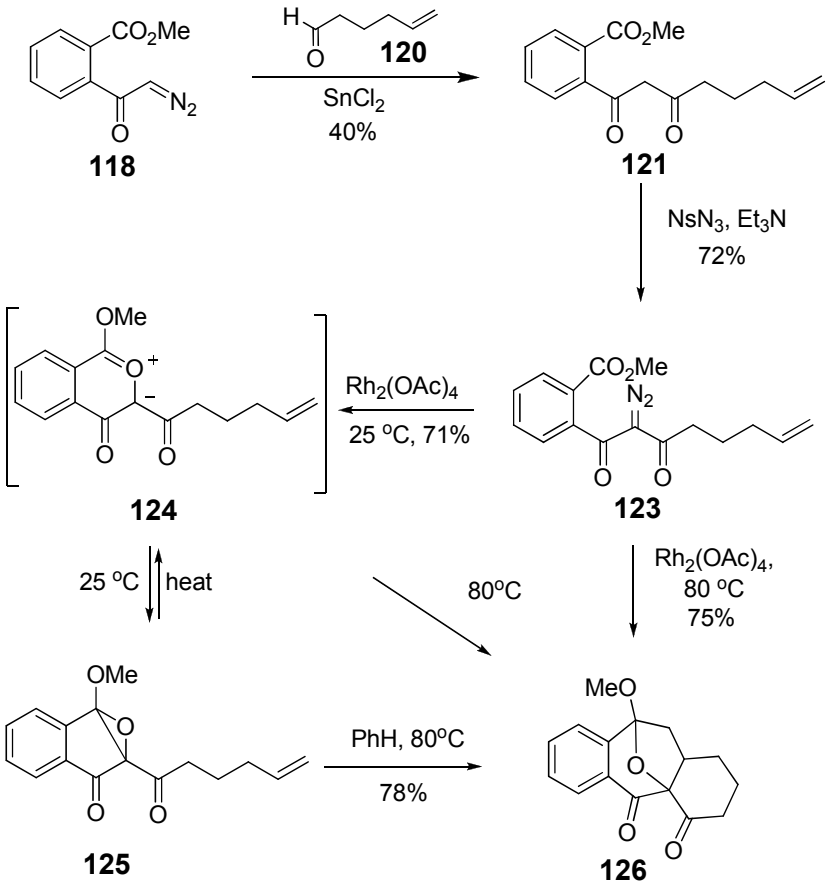
Scheme 27. Padwa's retrosynthetic analysis of (±)-komaroviquinone

2. Results and Discussion

In order to test the feasibility of the retrosynthetic strategy outlined in Scheme 27, our initial efforts were focused on some model substrates. According to our design, we hoped to employ a tandem cyclization/cycloaddition reaction of a rhodium carbenoid intermediate to rapidly generate the 9,10-benzo-12-oxa-tricyclo[6.3.1.$0^{0,0}$]dodecane-dione skeleton bearing the oxabicyclo[3.2.1]octane substructure from a relatively simple precursor (*i.e.*, **123**, scheme 28).

Our synthesis of the key diazo-dione **123** commenced within the preparation of *o*-carbomethoxy diazoketone **118**, which is readily available in high yield from phthalic acid monomethyl ester (Scheme 28). We anticipated that under suitable reaction conditions, **118** would react with hex-5-enal (**120**) to give diketone **121** following a protocol developed by Holmquist and Roskamp for β-keto esters.[60] These authors have found that aldehydes can be converted into β-keto esters by the addition of ethyl diazoacetate in the presence of tin(II) chloride. In our hands, only modest yield of **121** (ca 40%) was obtained from the reaction of **118** with hex-5-enal (**120**). However, we decided to forge ahead even with the low yield in order to test the key step without optimization at this point. Therefore, a subsequent Regitz diazo transfer reaction[61] using nosyl azide and Et_3N furnished diazo-dione **123** in 98% yield. Treating a sample of **123** with $Rh_2(OAc)_4$ in benzene at 80 ^oC generated cycloadduct **126** in 75% yield. Interestingly, when the Rh(II)-catalyzed reaction was carried out at room temperature, the major product isolated corresponded to epoxy-indanone **125** (71%) with only a small amount (<10%) of cycloadduct **126** being formed. Heating a sample of **125** at 80

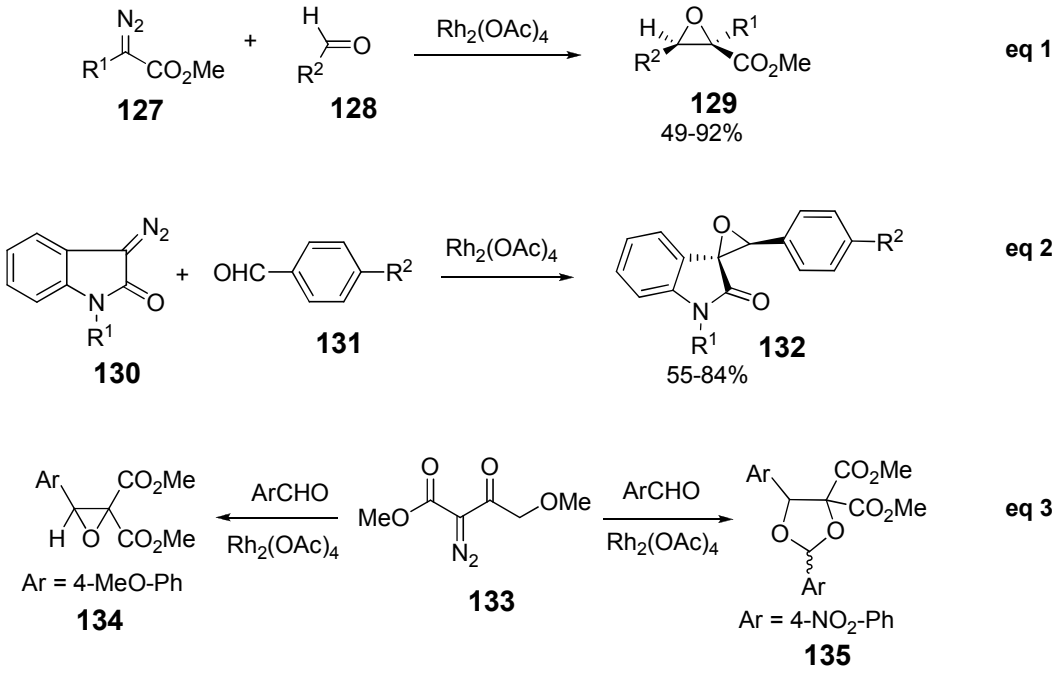
^{o}C in benzene gave **126** in 78% isolated yield. This reaction presumably occurs by thermal C-C bond cleavage of the epoxide ring to generate dipole **124** which then undergoes a subsequent intramolecular [3+2]-cycloaddition to give **126**.



Scheme 28. The formation of the oxa-tricyclo[6.3.1.0 ^{0,0}]dodecane skeleton using the Rh(II)-catalyzed reaction

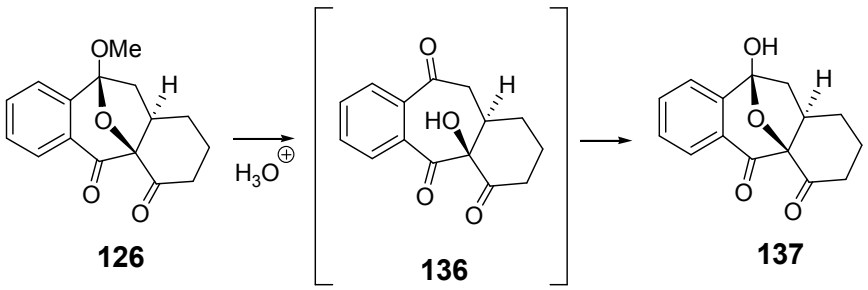
Many studies support the intermediacy of carbonyl ylides in reactions involving the reaction of a metallo carbenoid with a carbonyl oxygen.[62] The great majority of literature reports on carbonyl ylides are dominated by 1,3-dipolar cycloaddition reactions rather than cyclization of the dipole to produce the oxirane ring system.[63-67] Huisgen was the first to report the formation of an

epoxide from the reaction of dimethyl diazomalonate with benzaldehyde, but in only 7% yield when the reaction was carried out at 125 ^{o}C in the presence of 1 mol% of Cu(acac)$_2$.[63] More recently, the Doyle[64] and Davies[65] groups have reported stereospecific epoxide formation (*i.e.* **129**) from rhodium (II) acetate catalyzed reactions of aryl, heteroaryl, and vinyl diazoacetates with aldehydes or ketones (eq 1, Scheme 29). A similar epoxidation process was used to prepare spiro-indoloxiranes **132** using cyclic diazoamides by the Mathusamy group (eq 2, Scheme 29).[66] When dimethyl diazomalonate was used as the carbenoid source, a competition between dioxolane and epoxide formation was noted. Doyle was able to direct the decomposition of the diazomalonate system to produce either epoxide **134** or dioxolane **135** by influencing the stability of the intermediate carbonyl ylide dipole (eq 3, Scheme 29).[67] When the electron rich *p*-anisaldehyde was used as the trapping reagent, only epoxide formation was observed. Stabilization of the intermediate carbonyl ylide was suggested to account for its diminished reactivity toward cycloaddition with a second molecule of the added aldehyde. The fact that we were able to isolate epoxide **125** in 71% yield from the cyclization of dipole **124** is perfectly consistent with the Doyle observations. Thus, stabilization of the positive center of the dipole by interaction with the adjacent methoxy group diminishes the rate of the dipolar cycloaddition reaction and promotes cyclization of the ylide to the epoxide ring.



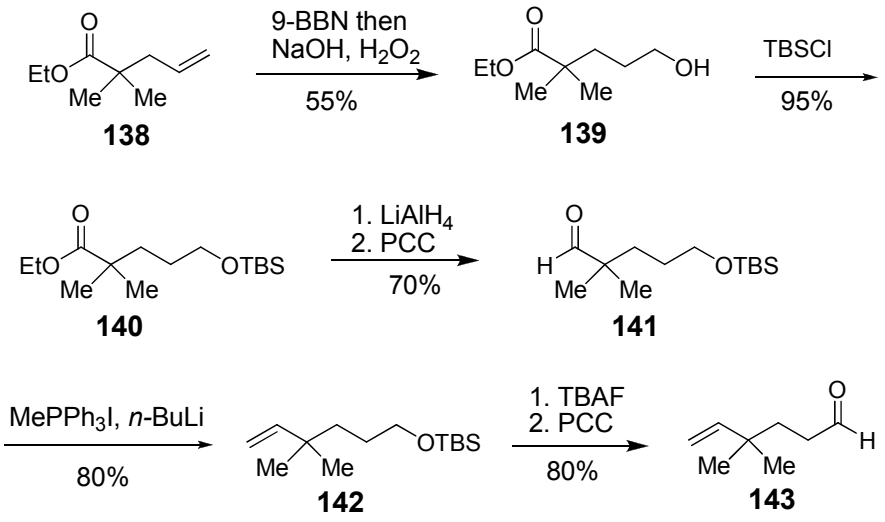
Scheme 29. Example of oxirane formations by Rh(II)-catalyzed decomposition of diazo compounds

When a sample of the methoxy substituted cycloadduct **126** was treated with aqueous acid it was smoothly converted into the corresponding hemiketal **137** (Scheme 30). We assume that the hydrolytic conversion of **126** to **137** occurs by oxabicyclic ring opening under the acidic conditions to produce hydroxy-tricarbonyl **136** as a transient species, which subsequently cyclizes to give hemiketal **137**.



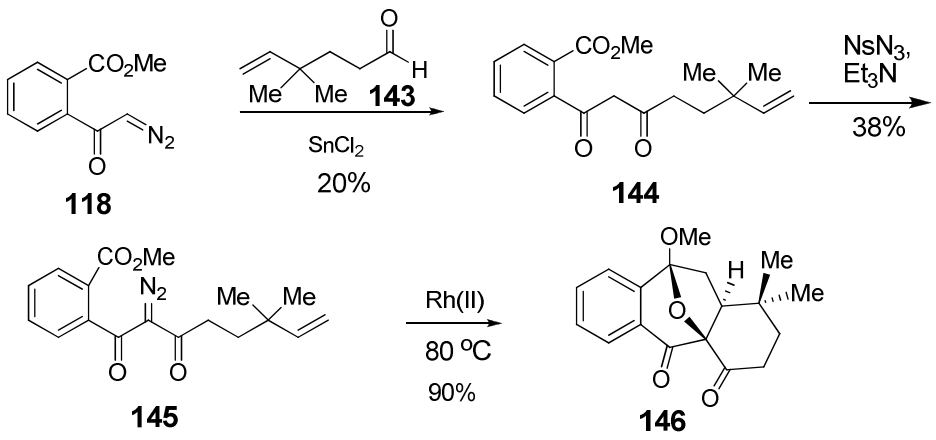
Scheme 30. The hydrolytic conversion to the corresponding hemiketal

For the appropriate substitution pattern of komaroviquinone, it was necessary to synthesize the related dimethyl substituted aldehyde **143** to test the Rh(II)-catalyzed cyclization strategy. The rate of an intramolecular reaction is often increased when alkyl groups are placed on a chain between the two reacting centers.[68] This is known as the gem-dialkyl effect and is often exploited to promote difficult cyclization reactions.[69] Therefore, we expected a higher efficiency for cycloaddition of the dimethyl substituted side chain which is eventually required for komaroviquinone. The requisite side chain for the Rh(II)-catalyzed reaction was prepared using standard chemistry starting from ethyl 2,2-dimethylpent-4-enoate (**138**) (Scheme 31). Hydroboration-oxidation followed by protection of the subsequent hydroxyl group gave ester **140**. A two step aldehyde formation followed by Wittig methylenation gave **142** in 56% yield over the three steps. The hydroxyl group was unmasked and then oxidized to give aldehyde **143** in 80% yield thereby setting the stage to test the cyclization sequence.



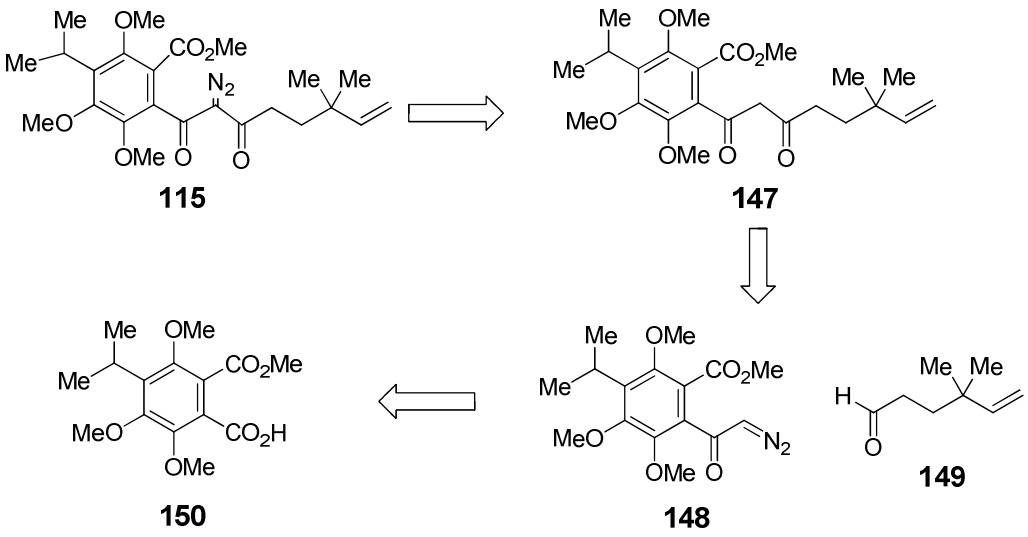
Scheme 31. The generation of 4,4-dimethyl-hex-5-enal side chain

The coupling of aldehyde **143** with diazoketone **118** gave the 1,3-dicarbonyl compound **144**, which underwent diazo transfer using NsN_3 to provide **145** as the key substrate for the Rh(II)-catalyzed investigation (Scheme 32). We were pleased to find that the reaction of diazo-dione **145** gave cycloadduct **146** in very good yield. The conversion of **145** to **146** as well as hydrolysis of **126** to **137** suggests that a similar approach could be used in our planned synthesis of komaroviquinone.



Scheme 32. The Rh(II)-catalyzed reaction of the related dimethyl substituted compound

With the promising results from our model studies in hand, we set out to prepare the hexa-substituted arene (*i.e.* **115**) which is required for our planned synthesis (Scheme 33). After the cycloaddition chemistry, oxidation of the aromatic portion of the molecule should provide the *para*-benzoquinone moiety present in the natural product. The challenge therefore, became the preparation of a hexa-substituted aromatic compound, such as **150**, which would be coupled to a suitable olefinic tether to form the desired dicarbonyl substrate **147**.



Scheme 33. The retrosynthetic analysis of the diazo key precursor

It should be noted that even though we obtained only a modest yield of the 1,3-dicarbonyl compound in the model system, we were aware that there are many procedures that have been developed for their synthesis.[70] For example, condensation of ethyl diazoacetate with aldehydes catalyzed by acids represents an alternate and efficient way that has also been reported.[71] A variety of Lewis and Brønsted acids were successfully used for this transformation.[72] So, at this point in time we were certain that we could optimize the formation of the required 1,3-dicarbonyl species for the real system.

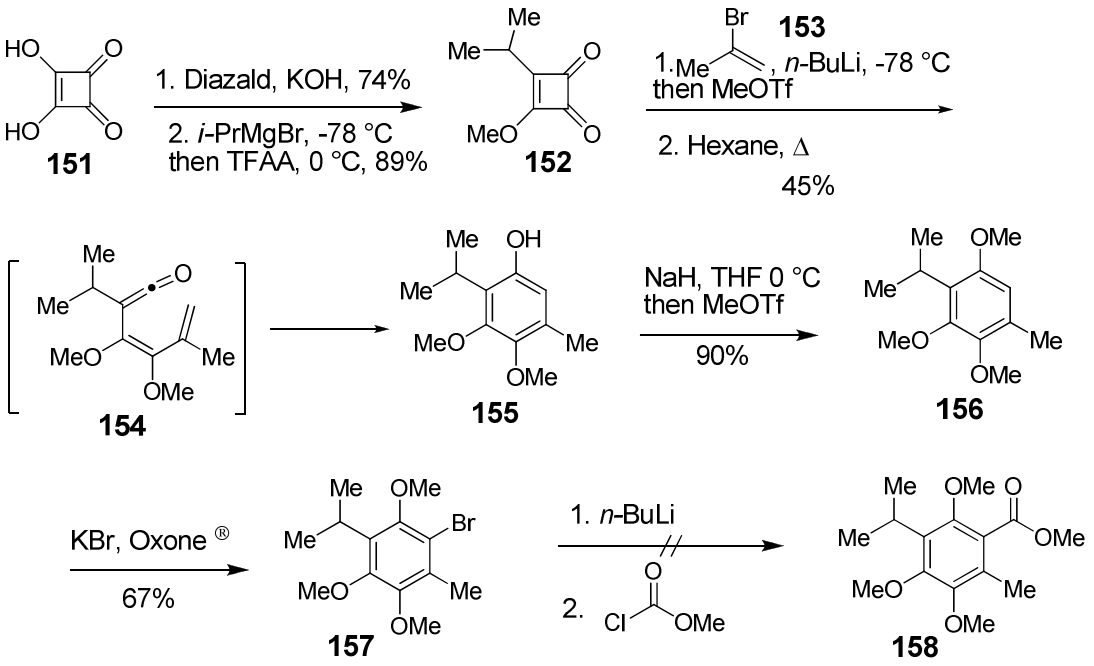
Our initial approach towards carboxylic acid **150** initially centered on the thermal rearrangement of cyclobutenones. This expedient route to highly substituted aromatic phenols involving a thermal ring expansion of cyclobutenones was studied by Danheiser.[73] Liebeskind and Moore have also employed a related strategy for the synthesis of highly substituted quinones[74]

and independently developed a regiosepecific introduction of substituents onto the cyclobutenedione core which made regiospecific synthesis of substituted quinones are possible.[75]

In our synthesis, we applied this approach toward the synthesis of compound **155**. The strategy is based on the sterospecific substitution of cyclobutenedione and a subsequent themal rearrangement (Scheme 34).[76] Starting from squaric acid (**151**), methylation with diazomethane gave dimethyl squarate.[77] Further treatment with *iso*-propyl magnesium bromide at -78 ^{o}C followed by hydrolysis produced cyclobutenedione **152** in 89% yield. The required thermal rearrangement precursor was formed by regioselective addition of 2-lithiopropene to a solution of **152** in THF at -78 ^{o}C followed by trapping with methyl triflate. Upon heating in refluxing hexane, electrocyclic ring opening of **152** gave the corresponding ketene **154** which was followed by ring closure to give phenol **154** as the only isolable product in 45% yield. The addition of the organo lithium reagent to dione **152** was completely regioselective giving rise to only one of two possible regiomeric phenols. The identification of phenol **154** was confirmed by NMR spectroscopy and was consistent with results reported elsewhere.[76] Protection of the phenolic hydroxy group was readily achieved with sodium hydride/methyl triflate in 90% yield.

Unfortunately our initial attempts to introduce functionality into the available C-2 position using lithiation chemistry were unsuccessful (Scheme 34). *ortho*-Lithiation under a range of conditions (*n*-BuLi, *n*-BuLi/TMEDA, *s*-BuLi/TMEDA) at a variety of temperatures followed by quenching with methyl

chloroformate returned only starting material. We therefore turned our attention to a mild bromination protocol developed by Kulkarni.[78] This group reported the use of KBr/oxone® as a facile method for the halogenation of a variety of aromatic compounds. In our hands, we were able to access the brominated derivative **157** in 67% yield. Both the lithium-halogen exchange reaction as well as carbonyl insertion chemistry were examined but without any success. We suspect that steric crowding around the bromine atom contributes to the difficulty in elaborating the brominated compound to the desired ester **158**.

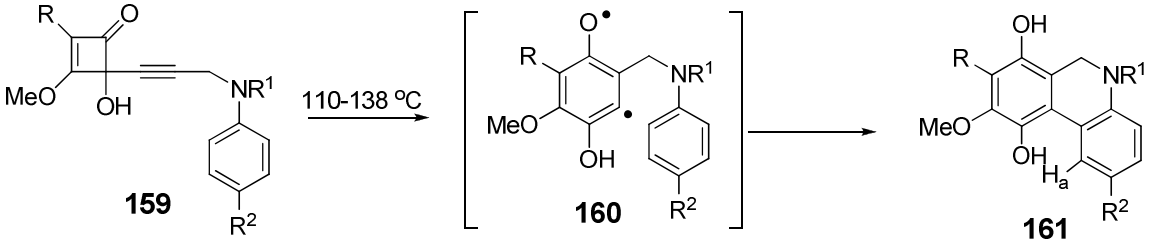


Scheme 34. Application of Moore/Liebeskind method for the synthesis of requisite phenol

Due to the congestion about the aromatic scaffold, we decided to develop an alternate approach. We reasoned that introduction of a benzylic alcohol group (*i.e*. **163**, scheme 36) into the aromatic ring might result in a better

directing group for the subsequent *ortho*-lithiation since the electron lone pair on the oxygen atom would coordinate with the lithium metal and thus increase the stability of the complex.

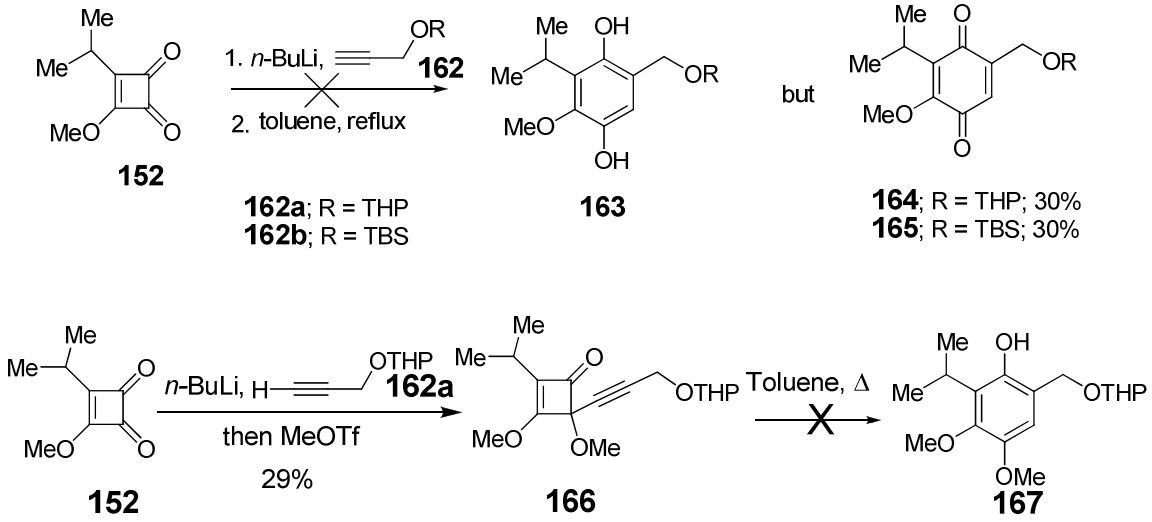
The cyclobutenone/thermolysis chemistry still seemed to be a reasonable method since the use of lithiopropyne had also been reported.[79] For example, in the synthesis of phenanthridinediones, the thermolysis of **159** resulted in the formation of the phenol derivative **161** *via* a diradical intermediate **160** (Scheme 35).



Scheme 35. Moore's synthesis of phenanthridinediols by a ring expansion procedure

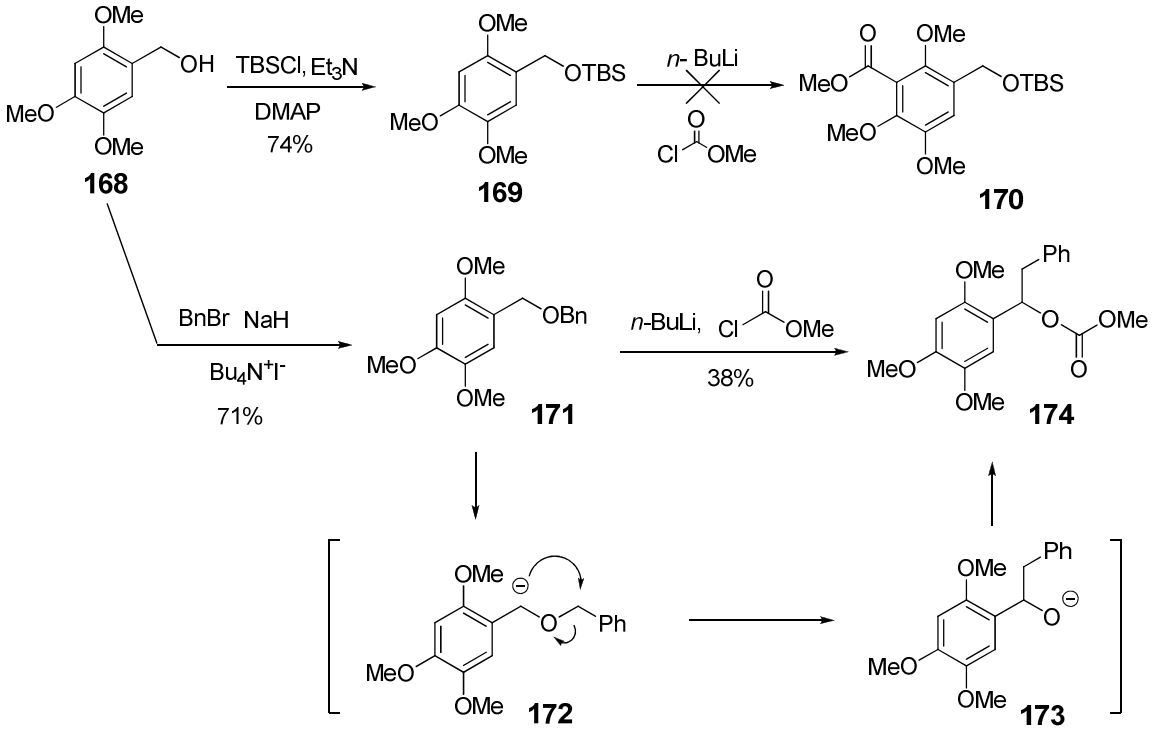
Disappointingly, the use of variously protected propargyl alcohols as lithiopropyne equivalents only resulted in the formation of quinones **164** and **165** which were obtained in low yield (30%) (Scheme 36). We thought that protection of the resulting alcohol after the lithiopropyne addition might prevent other possible diradical processes as well as the formation of the undesired quinone. Thus, the tetrahydropyranyl protected propargyl alcohol **162a** was treated sequentially with *n*-BuLi and then cyclobutenedione **152** followed by reaction with MeOTf. However, alkynylcyclobutenone **166** was obtained in very low yield.

Moreover, the expected phenol **167** was not formed from the thermolysis of **166** and so we abandoned this approach.



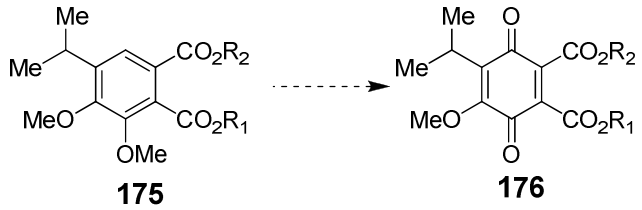
Scheme 36. The attempts to phenol using thermolysis of cyclobutenone

Another approach that we also tried toward the synthesis of **163** involved metallation of an arene (Scheme 37). However, when the TBS protected alcohol **169** was treated with *n*-BuLi and methyl chloroformate in order to introduce the ester group in the C-3 position, none of the desired product was obtained. Interestingly, when **171** was treated with *n*-BuLi and methyl chloroformate, this led to the formation of the unusual arene **174**. We suspect that deprotonation of the benzylic position occurs and this is followed by rearrangement of the benzyl group *via* a Wittig rearrangement to give intermediate **173**, which then undergoes addition with methyl chloroformate to give the observed product **174**. Benzyl alcohol **168** was also oxidized to the corresponding aldehyde, but introduction of an electrophile at the C-3 position was unsuccessful.



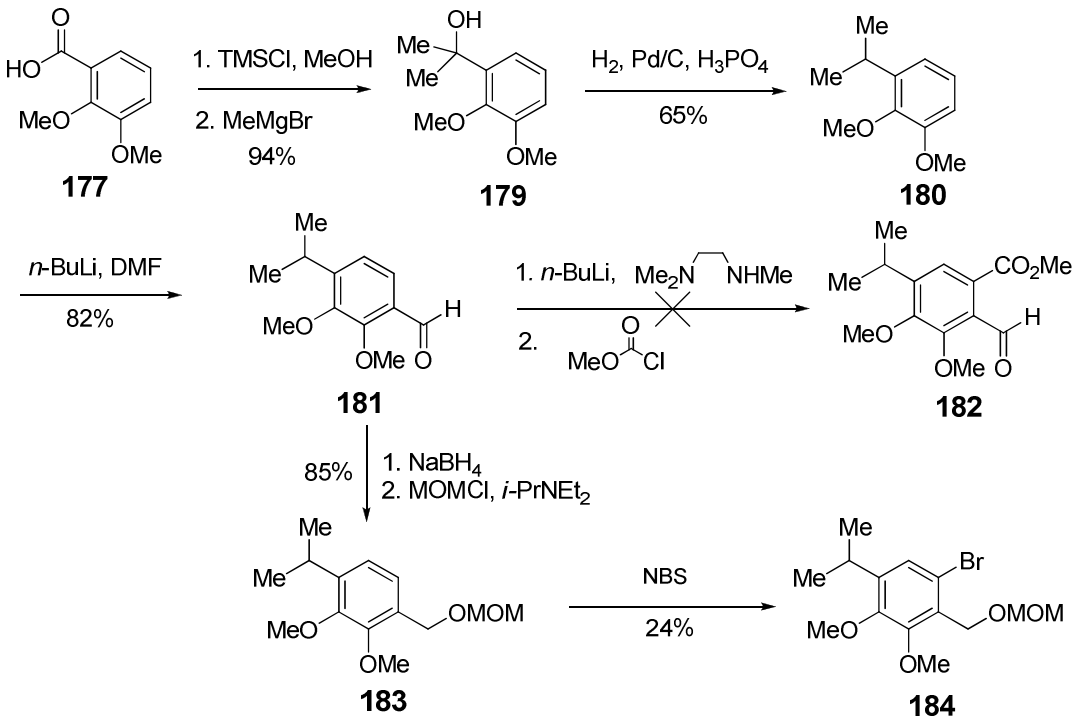
Scheme 37. Attempts to achieve the desired electrophilic aromatic substitution reactions from protected benzyl alcohol

An alternative approach that we decided to pursue in order to alleviate the steric crowding was to prepare a penta-substituted aromatic (*i.e.* **175**) and we hoped that the final substituent could be introduced by oxidation to give the desired *para*-quinone **176** (Scheme 38).[80]



Scheme 38. An alternative route to penta-substituted aromatic ring system

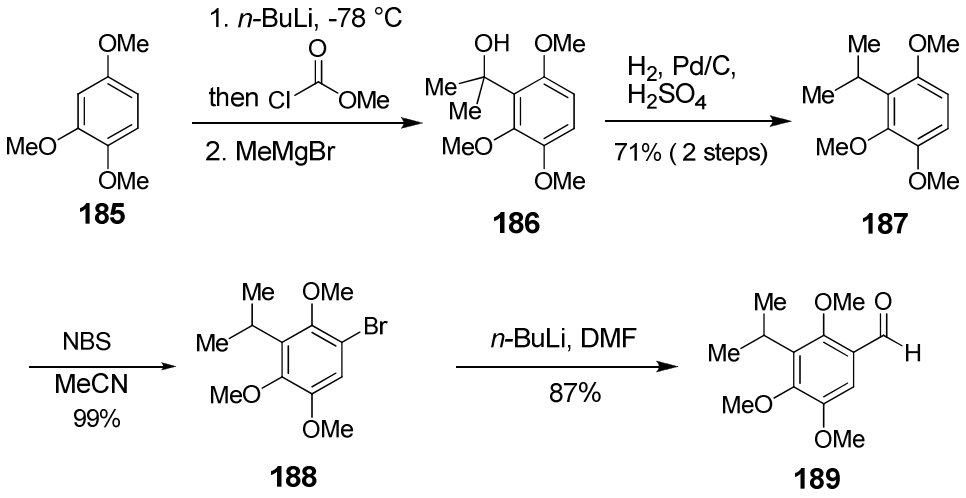
Starting from 2,3-dimethoxybenzoic acid (**177**), the initial esterification reaction was followed by Grignard addition of methyl magnesium bromide to deliver tertiary alcohol **178** in 89% for the two step sequence (Scheme 39). Dehydration-hydrogenation proceeded uneventfully using H_2 and Pd/C under acidic conditions to give isopropyl veratrole **179** in 65% yield. *ortho*-Lithiation with *n*-BuLi followed by treatment with *N,N'*-dimethyl formamide gave aldehyde **180** in 82% yield.[81,82] However, further functionalization of the aromatic framework was not possible using either Comins'[83] chemistry or by an electrophilic substitution reaction. Therefore, the carbonyl group of **180** was reduced and protected as its MOM ether derivative **182**. Lithiation of **182** returned only starting material. Instead, **182** was exposed to *N*-bromosuccinimide which successfully delivered the bromo compound **183** albeit as a mixture of regioisomers, with the desired bromide **183** being isolated in 24% yield. The two regioisomers could be distinguished by their respective NMR spectra. A minor improvement in the regiomeric ratio could be achieved by changing the reaction solvent. However, this resulted in a lower overall reaction yield. The low yield of the desired bromide eventually led us to the abandon this approach.



Scheme 39. Attempts to synthesize penta-substituted arene

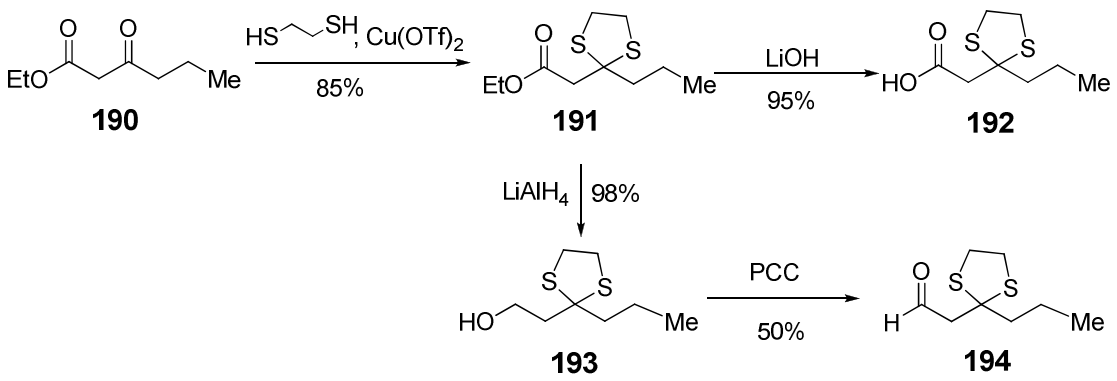
At this point we decided to embark on still another strategy which starting from 1,2,4-trimethoxybenzene (**185**) (Scheme 40). Introduction of the isopropyl group at C-3 on the arene was accomplished in three steps following the procedure described by Carreño and co-workers.[84] Treatment of **186** with *n*-BuLi at -78 ^{o}C resulted in selective lithiation at the C-3 position by virtue of coordination to the adjacent methoxy groups. Quenching with methyl chloroformate was followed by methyl Grignard addition to give alcohol **186**, which was subsequently dehydrated and hydrogenated in one pot to give **187**. The necessary bromo group was then introduced regiosectively by using NBS in MeCN [85] which gave compound **188** in nearly quantitative yield. The regioselectivity of the bromination process was found to be solvent dependent.

Bromination occurred exclusively at the C-5 position of the aryl ring with MeCN as the solvent, while a mixture of benzylic and aryl bromination occurred when CCl_4 was used as the solvent.[85] In the next step, lithium-halogen exchange occurred and this was followed by quenching with *N,N'*-dimethylformamide to provide the aldehyde functionality found in structure **189**.



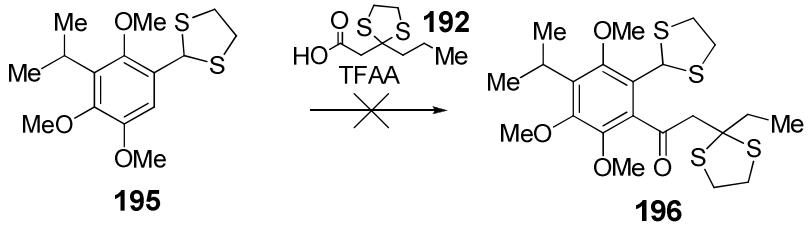
Scheme 40. The synthesis of pentasubsituted arene using Carreño's method

The model side chains found in compounds **192** and **194** were prepared for a study dealing with the aromatic substitution at the remaining arene position (Scheme 41). Formation of these compounds occurred uneventfully using the standard conditions as shown in Scheme 41. Protection of the carbonyl group as a thioketal was followed by ester hydrolysis to give acid **192**. A two step aldehyde formation sequence took place by initial reduction of the ester **191** and PCC oxidation of the resulting alcohol to produce aldehyde **194**.



Scheme 41. The synthesis of the model side chains

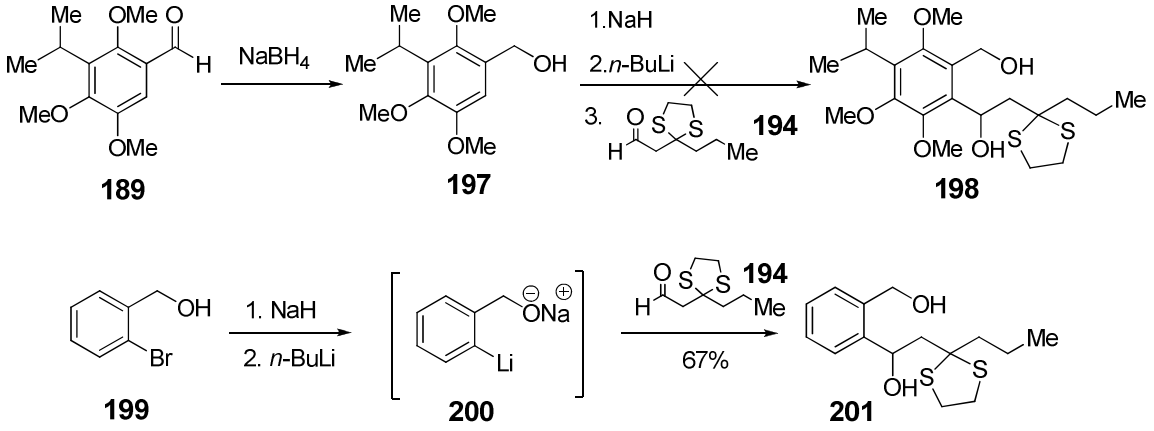
We hoped that the remaining aromatic ring position in **189** would provide a nucleophilic site which could then be treated with a suitable electrophile to produce the desired hexa-substituted arene. Taking advantage of a Friedel-Crafts acylation at the remaining position might allow us to the install the required side-chain. [86] With this in mind, aldehyde **189** was protected as the thioacetal **194** and then subjected to Friedel-Crafts acylation conditions (**192**, TFAA). Unfortunately, these conditions only led to decomposition products (Scheme 42).



Scheme 42. Introduction of diketone tether by Friedel-Crafts acylation

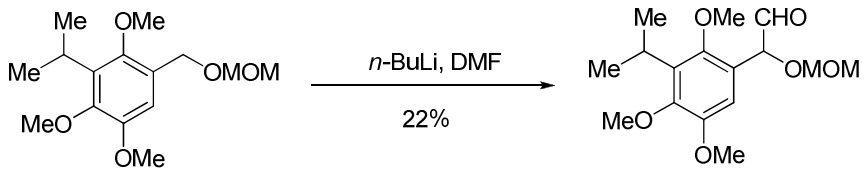
We then sought to take advantage of an *ortho*-directing metallation of the arene ring. Towards this end, aldehyde **189** was reduced with sodium

borohydride to give alcohol **197** Scheme 43). Generation of the dianion by sequential treatment of the free alcohol **197** with sodium hydride and then *n*-BuLi,[87] was followed by reaction with aldehyde **194** but this proved to be unsuccessful and only starting material was recovered. Interestingly, introduction of the same tether using the simpler alcohol **199** could be accomplished in 67% yield suggesting that the difficulty with **197** was related to steric congestion around the aromatic ring.



Scheme 43. Introduction of the tether by addition of the dianion with the aldehyde.

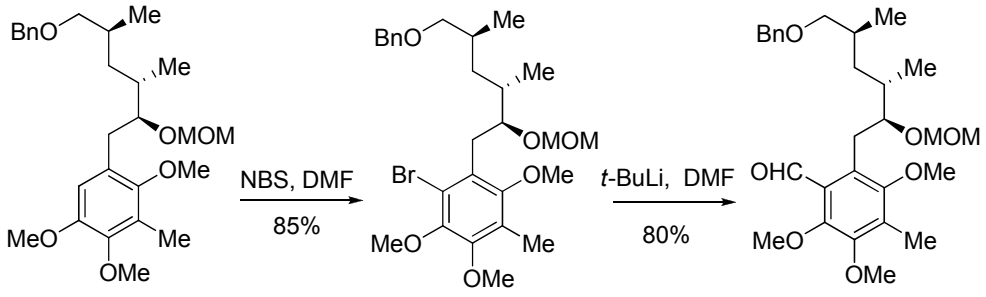
The MOM group is known to be an efficient *ortho*-directing metallating group as it coordinates well with lithium.[88] With this in mind, alcohol **197** was protected as the MOM ether **202**. Directed lithiation of the protected alcohol **202** was attempted but this only resulted in the formation of compound **203** in 22% yield, together with 60% of recovered starting material (Scheme 44).



202 **203**

Scheme 44. Attempt to direct lithiation of MOM protected benzyl alcohol **202**

A report by White provided an interesting set of conditions which we thought we could use to prepare the hexa-substituted arene **206**.[89] In his synthesis of (-)-kendomycin, the remaining unsubstituted position of arene **204** was subjected to bromination with NBS to provide the aryl substituted bromide **205**. After lithium halogen exchange with *t*-BuLi and then quenching with DMF, aldehyde **206** was obtained in 80% yield (Scheme 45).

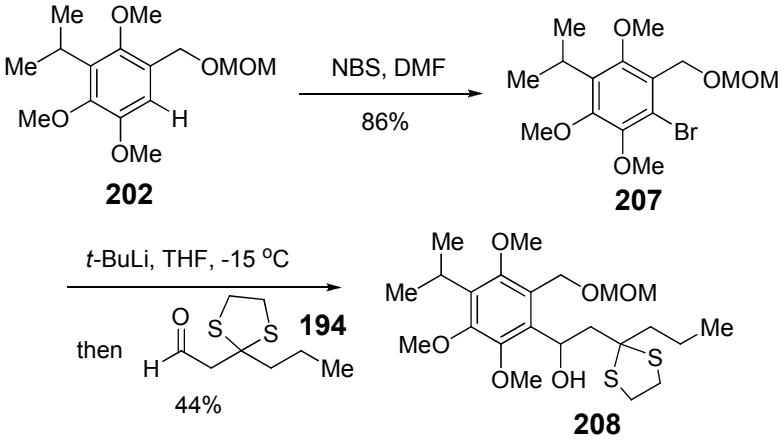


204 **205** **206**

Scheme 45. White's success of electrophilic aromatic substitution nucleophilic

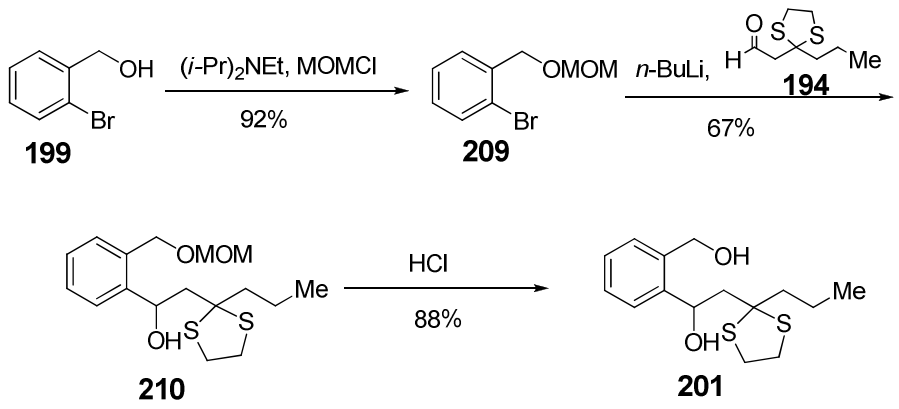
We sought to use these same conditions in our synthesis (Scheme 46). Following the above protocol, bromination of **202** was accomplished using NBS in DMF. Treatment of **207** with *t*-BuLi and aldehyde **194** gave, to our delight, alcohol **208** in 44% yield. Attempts to optimize the reaction using the acid

chloride of **192** were unsuccessful. With the availability of **208**, this set the stage for a continued synthesis of komaroviquinone.



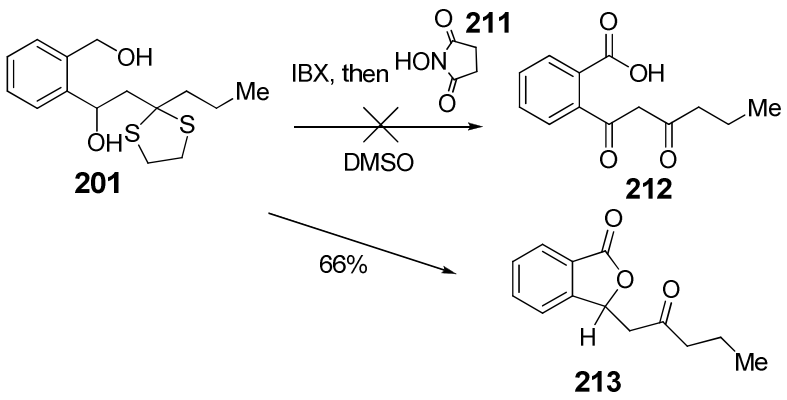
Scheme 46. The success synthesis of hexa-substituted arene

The next task in the synthesis involved the removal of the thioketal protecting group and a subsequent oxidation to the required 1,3 dicarbonyl substrate. We decided to first investigate these reactions using compound **210** as a model system. Alcohol **199** was protected as the MOM ether and allowed to react with the aldehyde tether **194** to provide **210.** The MOM group was easily removed under standard acid condition to produce the free alcohol **201** (Scheme 47).



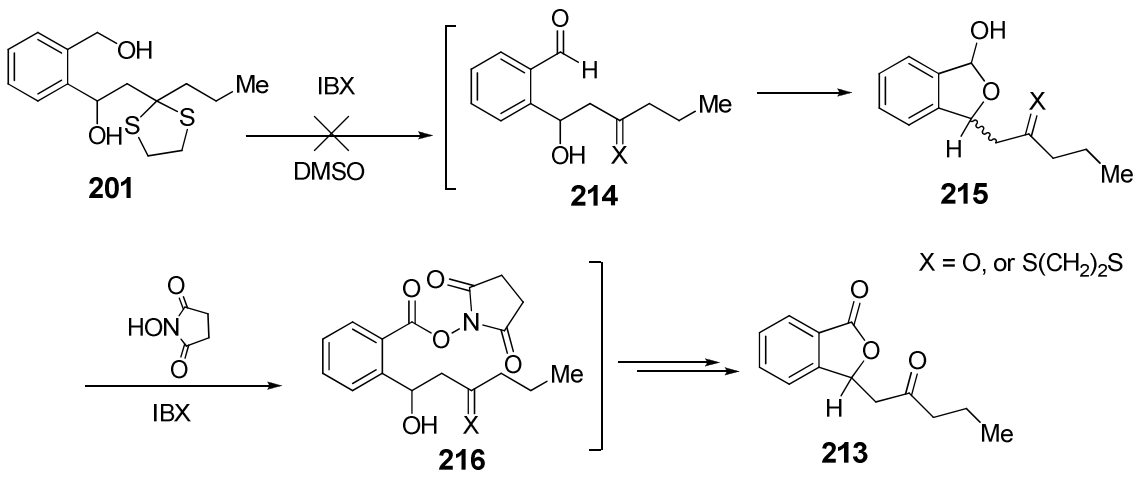
Scheme 47. The synthesis of an arene model system

There are a great number of thioketal deprotection conditions used to liberate a carbonyl group.[90] Among these methods, the use of an oxidizing agent seemed best as it would free up the carbonyl group as well as simultaneously oxidize the adjacent alcohol in one step. Recently, IBX was revealed as a mild and powerful reagent for several functional group transformations, including removal of a thioketal protecting group and oxidation of alcohols.[91] We hoped that under suitable reaction conditions, compound **201** would undergo thioketal deprotection and simultaneous alcohol oxidation when subjected to IBX. Of some importance is the report by Giannis that the oxidation of a benzylic alcohol to the corresponding carboxylic acid can be achieved using IBX and *N*-hydroxysuccinimide. [92] Unfortunately, when we subjected diol **201** to the conditions outlined by Giannis, only compound **213** was isolated in 66% yield (Scheme 48).



Scheme 48. Formation of the lactone product from IBX oxidation

Even though we were unable to obtain the desired 1,3-dicarbonyl **212** in a one-pot procedure, the deprotection as well as oxidation did indeed occur under these conditions. The formation of lactone **213** is presumably derived from a lactonization reaction between the initially generated acid and the secondary alcohol that occurred prior to the oxidation of the secondary benzylic alcohol (Scheme 49).[92] This is supported by a ^{1}H-NMR spectrum of the crude reaction mixture prior to the addition of *N*-hydroxysuccinimide, which showed only the presence of the lactol intermediate **215** without any trace of the oxidized lactone **213**.



Scheme 49. Proposed mechanism for lactone formation

There are several conditions reported in the literature for the conversion of a lactone to a dicarbonyl compound.[93] Clearly, the next step in the planned synthesis will need to address the conversion of lactone **213** to the corresponding 1,3-dicarbonyl group and then we need to apply this method to the correct side chain system of arene **202**. Further studies are currently underway to determine the feasibility of this approach.

3. Conclusion

In summary, the Rh(II)-catalyzed intramolecular dipolar-cycloaddition sequence described herein allows for a facile access to the icetexane core of komaroviquinone. Completion of the synthesis of the natural product requires the preparation of a highly substituted aromatic system. Application of some model studies to the system containing the appropriate side chain will hopefully enable the completion of the synthesis.

Chapter B. 3

The Application of Rh(II)-Catalyzed [3+2]-Cycloaddition towards the Synthesis of Furanether B

1. Introduction

Many of the sesquiterpenes isolated from a variety of mushrooms in the *Russalaceae* family possess the lactarane skeleton which consists of a complex hydrozulene framework containing a 3,4-disubstituted furan ring (Figure 2).[94] These compounds possess antifungal, antibacterial and antifeedant activities.[95] Among several of these lactarane sesquiterpenes, furanether A (**217**) exhibits the strongest antifeedant properties.[96] Furanether A (**217**) and the related furanether B (**218**) are stereoisomeric sesquiterpenes containing an oxabicyclo[3.2.1]octane as a subunit in the oxatricyclo[5.3.1.$0^{2,6}$]undecane ring system. Vita-Finzi and co-workers isolated furanether A from an ethanolic extract of the mushroom *Russula sardoniaa*[94a] and furanether B from *Lactarius scrobiculatus*[94b] in 1980. To date, synthetic work on these natural products has been very limited. So far, there is no report describing the synthesis of furanether A and only four total syntheses of furanether B have been disclosed.[97, 99-101]

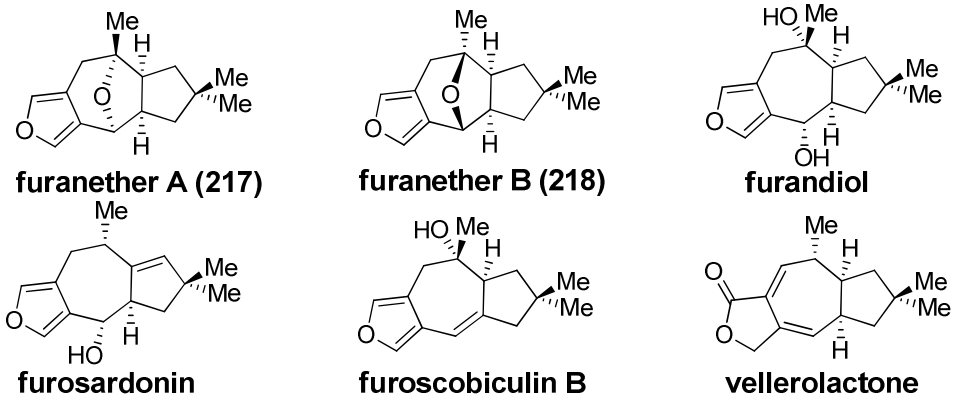
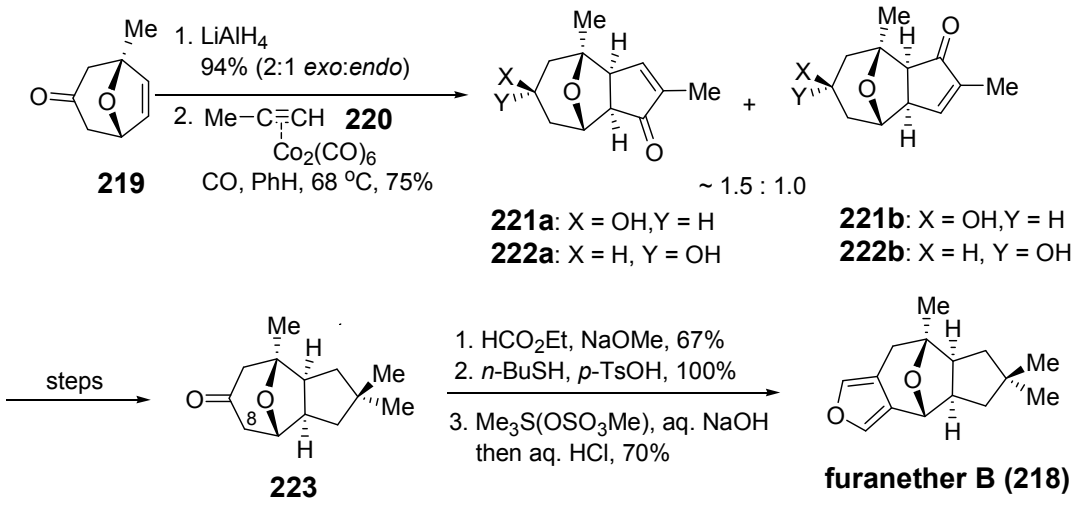


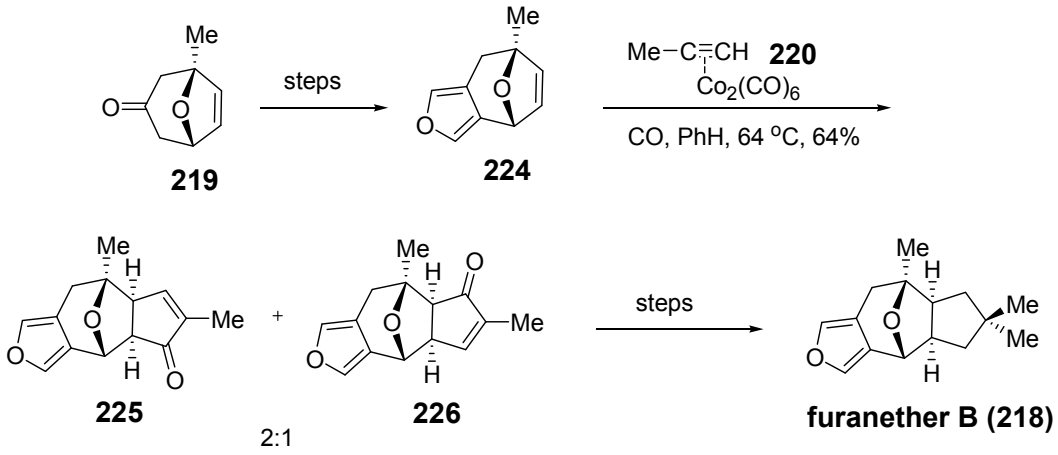
Figure 2. Some representative examples of lactarane sesquiterpenes

The first total synthesis of furanether B was reported by Schore and Price in 1989 using a Pauson-Khand cycloaddition as the key reaction (Scheme 50).[97] Reduction of the ketone present in 8-oxabicyclo[3.2.1]oct-6-ene (**219**)[98] was followed by the Pauson-Khand cycloaddition with alkyne **220** and this resulted in a 75% yield of the stereoisomeric tricyclic enones **221a,b** and **222a,b**. In all four isomers, the newly formed ring fusion contains an *exo*-configuration (*cis* relationship between the oxabridge and the newly fused carbocycle). This stereochemical outcome is necessary for the synthesis of furanether B (**218**). Several functional group manipulations were carried out which involve introduction of the methyl group, removal of the cyclopentenone carbonyl, and separation of all four isomers to provide compound **223**. Finally, a modified Garst-Spenser reaction was used to construct the furan ring. This involved formylation at the C-8 position using HCO_2Et under basic conditions, conversion of the resulting aldehyde to a thiomethylene derivative with *n*-BuSH/*p*-TsOH, and then treatment with trimethylsulfonium methylsulfate to convert the ketone to the epoxide. Finally, rearrangement and aromatization under acidic conditions gave the desired furan thereby completing the synthesis of furanether B.



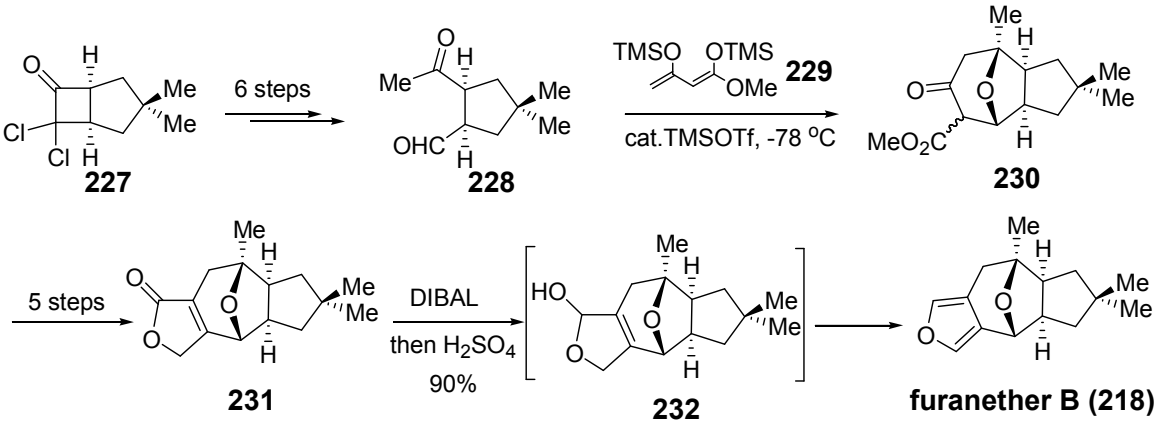
Scheme 50. Schore's first total synthesis of furanether B

A complementary synthesis of furanether B was also reported by the same authors using the Pauson-Khand cycloaddition as the key reaction.[99] The modification of the procedure involve the early construction of the furan moiety to produce 8-oxabicyclo[3.2.1]oct-6-ene (**219**)[98] by use of a modified Garst-Spenser protocol (Scheme 51). Afterwards, the Pauson-Khand cycloaddition of **224** with alkyne **220** provided the e*xo*-products **225** and **226** from the cycloaddition in 64% yield as a 2:1-mixture of regioisomers. Since both regioisomers **225** and **226** lead to the same final product, the mixture was carried through a series of functional group manipulations to complete the synthesis of furanether B (**218**).



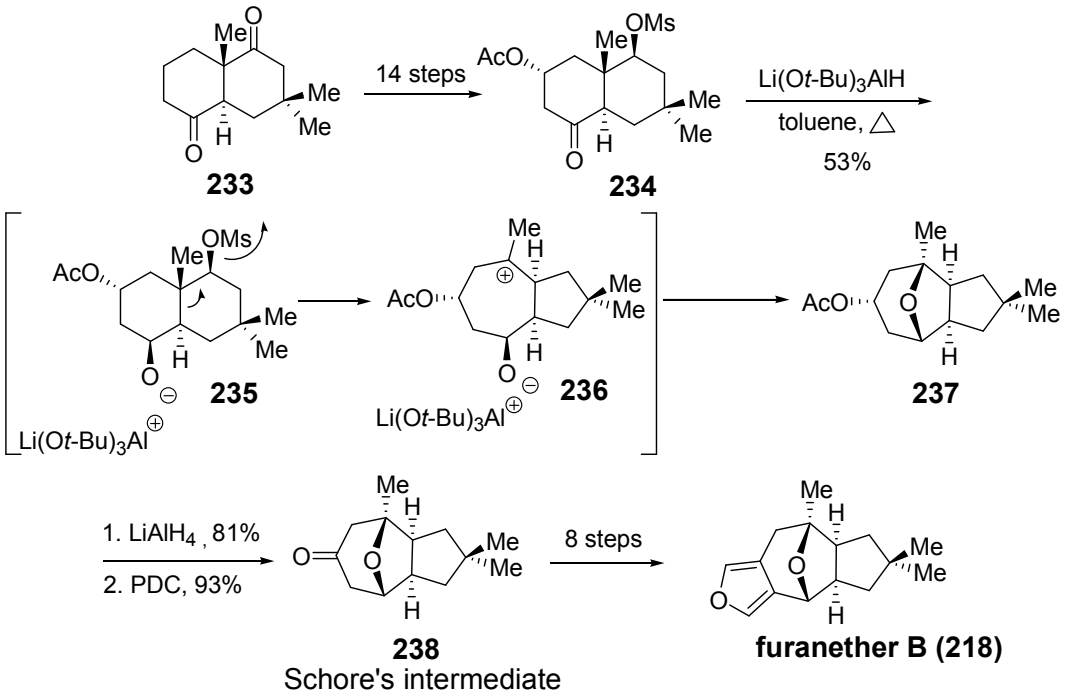
Scheme 51. Schore's second total synthesis of furanether B

Another approach to furanether B had been reported by Molander.[100] The synthesis starts from known dichloro ketone **227** (Scheme 52). Subsequent transformations involve cyclobutene formation and oxidative cleavage to provide *cis*-1,4-ketoaldehyde **228**. This compound then underwent a crucial [4+3]-annulation with bis(trimethylsilyl) enol ether **229** catalyzed by TMSOTf to afford oxabicyclo[3.2.1]heptanone **230** in 70% yield. Conversion of **230** into butenolide **231**, followed by DIBAL reduction provided lactol **232**. This lactol then underwent dehydration/aromatization upon treatment with H_2SO_4 to deliver furanether B (**218**).



Scheme 52. The total synthesis by Molander *via* [3+4]-annulation reaction

The total synthesis of furanether B reported by de Groot makes use of a base-induced rearrangement reaction as the key strategy (Scheme 53).[101] The synthesis starts with the readily available Robinson annulation compound **233**. Functional group transformations generate the required precursor **234** in 14 steps setting the stage for the key reaction. When **234** was treated with Li(O*t*-Bu)$_3$AlH at high temperature, the ketone carbonyl group was reduced providing alkoxide **235**, which undergoes an alkyl group migration with concominent mesylate expulsion to produce intermediate **236**. This zwitterionic intermediate **236** collapses to the bridged tricyclic ether **237** in 53% yield. Removal of the acetate protecting group and oxidation of the free alcohol produces ketone **238**, the intermediate in Schore's synthesis (Scheme 50), thereby completing a formal synthesis of furanether B. de Groot also developed an alternative pathway to construct the furan ring and this involved a Pummerer-induced cyclization reaction to prepare the heterocycle in 8 steps from ketone **238** thereby completing a total synthesis of furanether B.

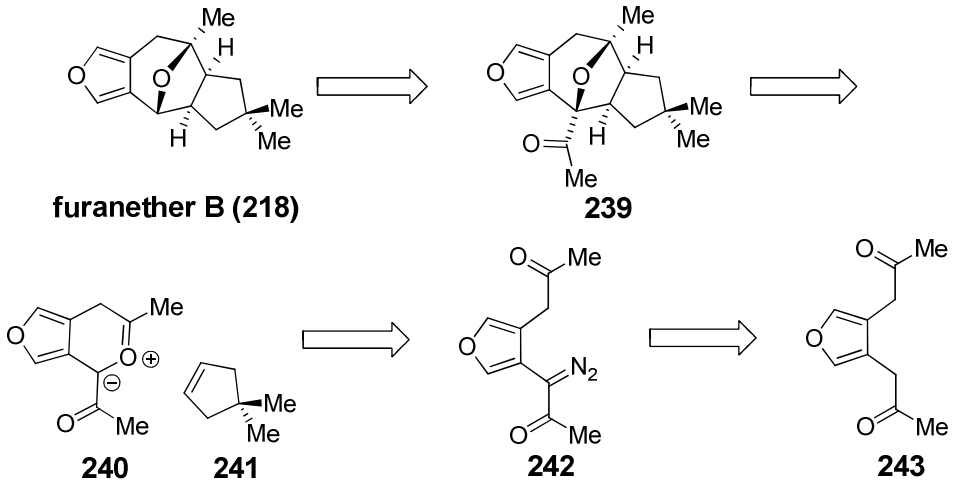


Scheme 53. The total synthesis by de Groot using a base induced rearrangement

- **Our retrosynthetic analysis to (±)-furanether B**

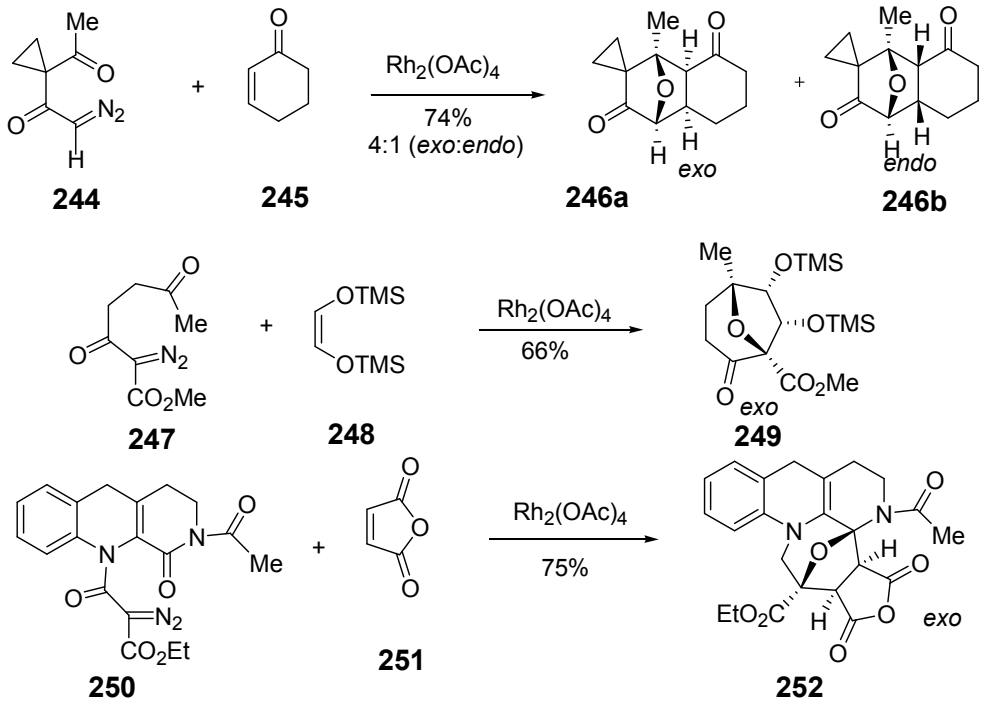
As was demonstrated in the earlier section of this thesis, the Rh(II)-catalyzed cycloaddition reaction represents an efficient method to prepare oxabicyclo systems. Consequently, we became interested in applying the Rh(II)-catalyzed cycloaddition approach to other natural products where the oxabicyclo[3.2.1]octane comprises an integral part of the core structure. Specifically, we planned to extend the methodology toward a synthesis of furanether B. As was shown in the two synthetic routes to furanether B (**218**) reported by Schore (Schemes 50 and 51), installation of the furan at an early stage eliminates problems associated with the regio- and diastereoselectivity of cycloaddition. Therefore, our retrosynthetic analysis of (±)-furanether B was envisioned to come from the substituted furan **239**. The core framework of

furanether B would be derived from a 1,3-dipolar cycloaddition of oxonium ylide **240**, which would be prepared by treatment of diazo compound **242** with a Rh(II)-catalyst with cyclopentene **241**. Structure **242** could arise from a diazo transfer from the symmetric furan **243** (Scheme 54).



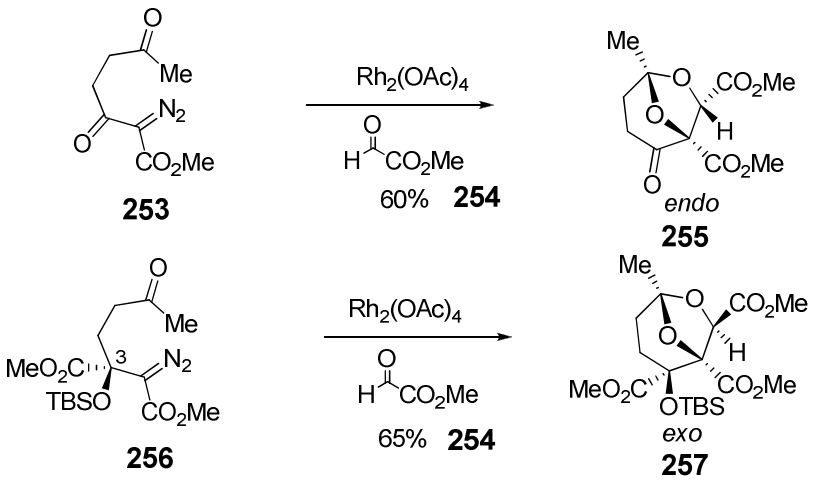
Scheme 54. Retrosynthetic analysis to (±)-furanether B

There are two potential diastereomeric products that could result from the intramolecular [3+2]-cycloaddition reaction between **240** and **241**, and these would result from either an *exo*- or *endo*-cycloaddition. Usually, related [3+2]-cycloaddition reactions proceed with high *exo*-selectivity and in many cases the cycloaddition adducts are formed exclusively from *exo*-cycloaddition, as can be seen in the example shown in Scheme 55.[102,103] We therefore anticipated that the product from the [3+2]-cycloaddition reaction of **240** with **241** would be derived from *exo*-selective process and this would provide the required *cis*-relationship between the oxabridge and the newly fused carbocycle (Scheme 54).



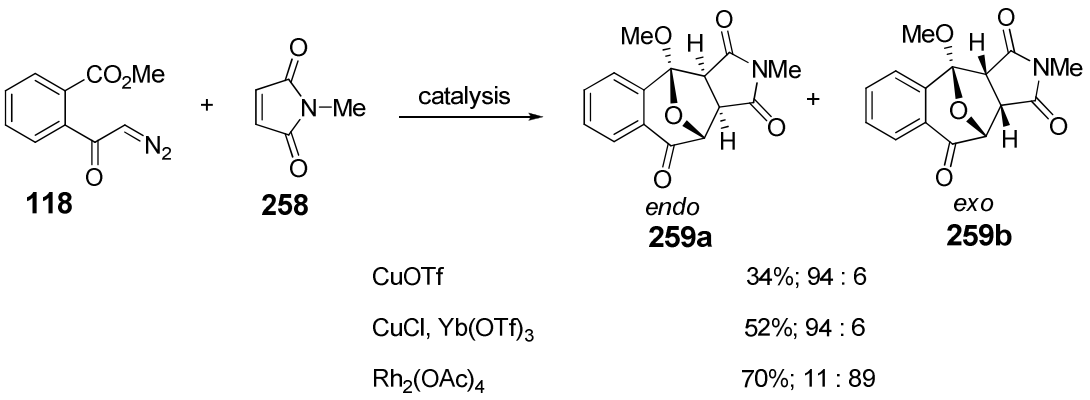
Scheme 55. Examples of [3+2]-cycloaddition reactions of various substrates leading to *exo*-diastereomers

As pointed out above, the majority of the examples in the literature involving [3+2]-cycloadditions of carbonyl ylides are dominated by *exo*-attack. However, in some cases the cycloaddition can also proceed by *endo*-attack as the dominant pathway. An increase in *exo*-selectivity might be accomplished by incorporation of a sterically bulky unit at the appropriate site of the substrate. In the synthesis of zaragozic acid that was reported by Hodgson,[104] cyclic ether **255** was obtained and this compound was derived by an *endo*-selective process. The *endo*-selectivity corresponds to the incorrect relative configuration for zaragozic acid. Impressively, the selectivity of the cycloaddition was successfully changed to give the *exo*-product **257**, when the bulky OTBS group was incorporated at the C-3 position (Scheme 56).[105]



Scheme 56. Different stereoselectivity of [3+2]-cycloadditions in different steric environment

Another interesting example was reported by Ibata and co-workers who showed that drastic changes in stereoselectivity can be caused by the metal catalyst in [3+2]-cycloaddition of carbonyl ylides derived from **118** with *N*-methylmaleimide.[106] High *endo*-selectivity occurred when catalysts such as CuOTf and CuCl-Yb$(OTf)_3$ were used which afforded a 94:6 ratio of *endo*:*exo* in both cases (Scheme 57). This stands in contrast with the high *exo*-selectivity (89:11, *exo*:*endo*) noted when $Rh_2(OAc)_4$ was employed. The reason for the high *endo*-selectivity is not totally clear, but presumably the Lewis acid helps to control the stereoselectivity by coordination with the dipolarophile.



Scheme 57. Changes in stereoselectivity of [3+2]-cycloaddition caused by different metal catalysts

Based on these examples, the general route shown in our retrosynthetic analysis (Scheme 54) should lead to the core structure of furanether B. An enhancement of product selectivity is conceivable and a structural modification to favor *endo*-selectivity would also allow for an approach to the synthesis of furanether A.

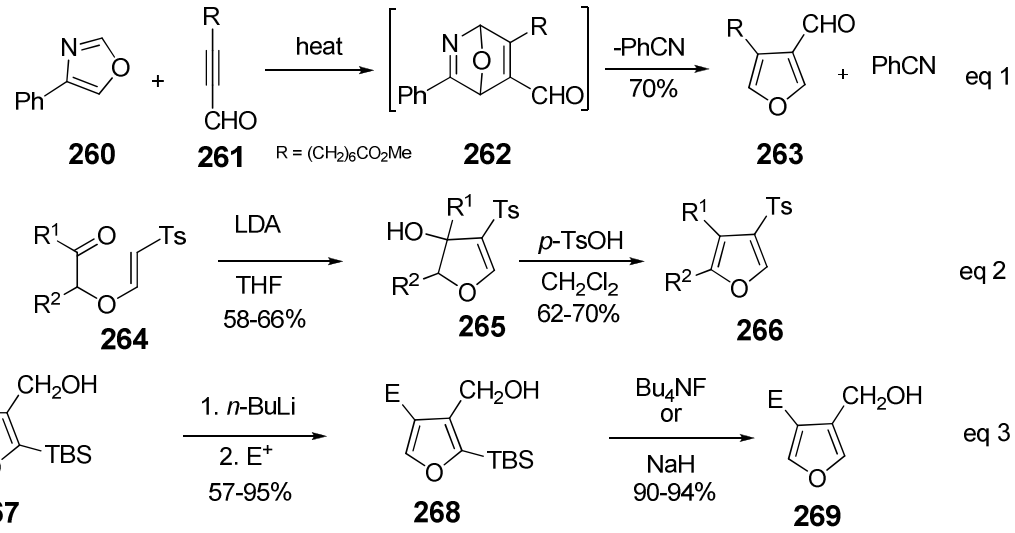
2. Results and Discussion

A crucial problem in the synthesis of these furanethers is the preparation of a 3,4-disubstituted furan such as **243**. Currently, there are very few methods available for the preparation of furans which contain substituents only at the C-3 and C-4 positions, since both electrophilic substitution and lithiation of furans generally preferred to occur at the C-2 and C-5 positions. Moreover, many acyclic furan precursors such as 1,4-dicarbonyl compounds are

more easily prepared with substituents that produce C-2 and C-5 substituted furans. [107]

Strategies for the preparation of 3,4-disubstituted furans can be classified into three general types. The first strategy is based on a tandem Diels-Alder-cycloaddition-retro-Diels-Alder reaction. For example, 4-phenyl oxazole **260** undergoes a Diels-Alder cyclization with alkyne **261** and this is followed by a subsequent retro Diels-Alder reaction with extrusion of PhCN to prepared the 3,4-disubstituted furan **263** (eq 1, Scheme 58).[108] Formation of furans having both silyl or tin substituents at the 3- and 4-positions are readily generated by this method. These products have the advantage of flexibility to introduce other functionality by electrophilic substitution at the *ipso* position.[107] A second strategy involves the formation of 3,4-disubstituted furans from acyclic precursors. Examples of this approach are the aforementioned Garst-Spencer reaction outlined in Scheme 1. The reaction of β-ethenyloxyketone **264** with a strong base can afford dihydrofuran **265**, which when subjected to dehydration under acidic conditions give the desired 3,4-disubstituted furans **266** (eq 2, Scheme 58).[109] The third procedure is based on a synthetic modification of readily available furans. Keay developed an approach to 3,4-disubstituted furans by taking advantage of the presence of a silyl protecting group at C-2.[110] Lithiation of 2,3-disubstituted furans generally takes place at C-5. However if a sterically large group such as the TBS is placed at C-2 and an *ortho*-directing group such as a hydroxy methyl is present at C-3 (eq 3, Scheme 58), lithiation will take place exclusively at the position C-4, thereby allowing introduction of additional

substitutents. Subsequent desilylation then provides the 3,4-disubstituted furan (*e.g.* **269**).

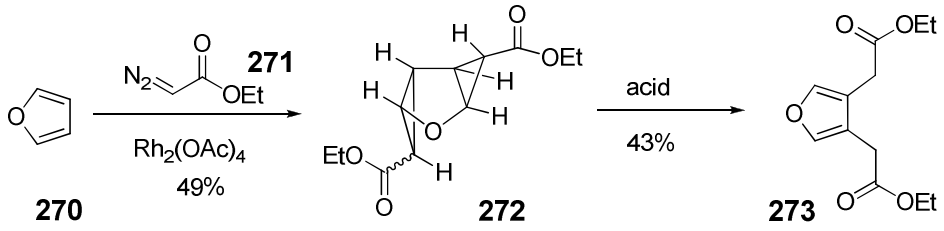


Scheme 58. Examples of 3,4-disubstituted furan formation

Although many 3,4-substituted furans are accessible by the above methods, the additional functionality that can be introduced is quite limited and mostly corresponds to simple alkyl groups. The syntheses of the required 3,4-disubsituted furan **243** for our studies contains two carbomethoxy side chains and this approach needs to be investigated further as there are no reports of this particular compound in the literature.

Only one procedure has been directed the preparation of a furan similar to furan **243** and that corresponds to a report by Wenkert, dealing with the synthesis of diethyl furan-3,4-diacetates **273**, using diazo chemistry.[111] Bis-cyclopropanation to give **272** was performed by reaction of furan and ethyl diazoacetate under $Rh_2(OAc)_4$ catalyzed conditions followed by treatment with

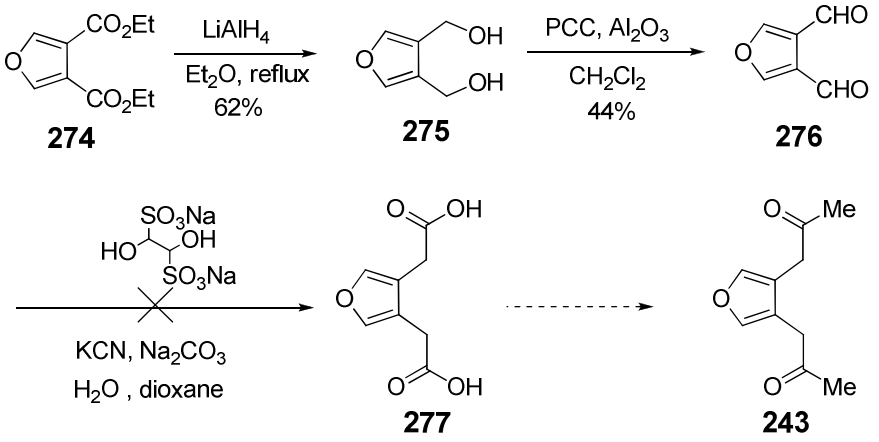
ethanolic HCl. This procedure gave 3,4-furan diacetate **273** (Scheme 59) in 21% over 2 steps. We therefore started an investigation for the synthesis of furan **243** using this method with the expectation to use furan **273** for further functionalization. Following their conditions, however, we found that in our hands the reaction only resulted in a complex mixture of products and several attempts at separation proved very difficult. After numerous attempts, we eventually abandoned this route.



Scheme 59. The synthesis of diethyl furan-3,4-diacetates by Wenkert

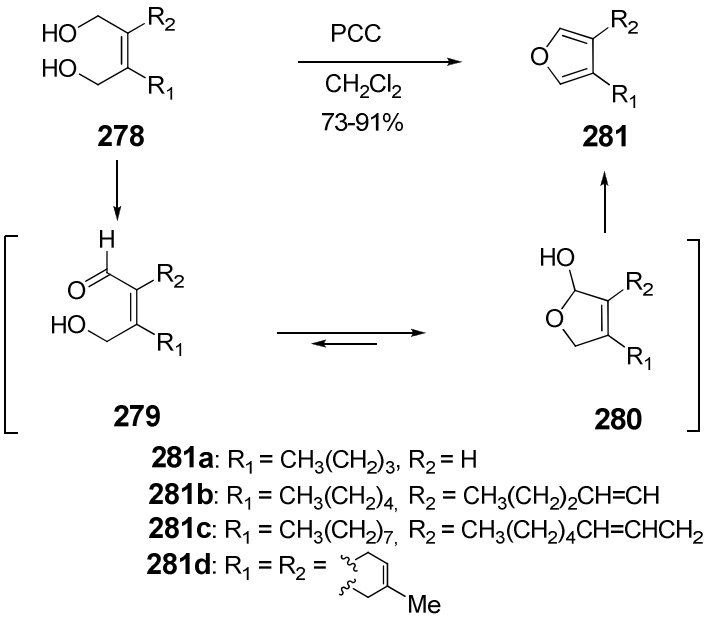
We then turned our attention to an alternative approach starting from the commercially available furan-3,4-dicarboxylic acid diethyl ester (**274**) (Scheme 60). The idea was to introduce the carbomethyl group by a one-carbon homologation process. One-carbon homologations are primarily performed *via* the Arndt-Eistert procedure which involves homologation of a carboxylic acid using diazomethane or the Kowalski procedure which proceeds by ester homologation involving an ynolate as a key intermediate.[112] However, to our knowledge there is no example reported of a one-carbon homologation involving a carbonyl side chain connected to a furan ring by either of these two procedures. A successful homologation of furans had been reported using a one pot reaction between 2-furaldehyde and potassium cyanide in the presence of sodium

carbonate and glyoxal.[113] Therefore, we targeted aldehyde **276** in order to test the homologation reaction. Furan **274** was converted to dialdehyde **276** by a two-step reduction/oxidation sequence and then we subjected **276** to the homologation conditions. Unfortunately, this sequence resulted only in a complex mixture of products.



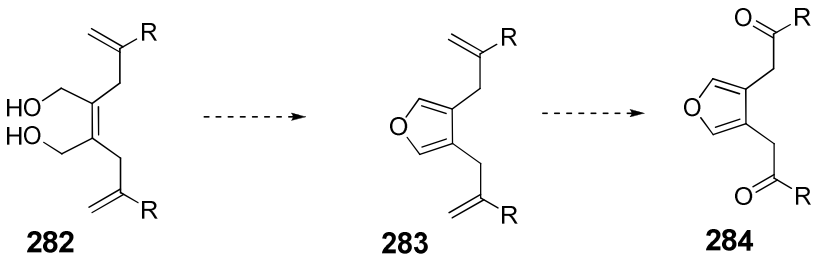
Scheme 60. Attempts to synthesize 3,4-disubstituted furan **277** using a one-carbon homologation process

While this work was being carried out, we became aware of a report by Itoh describing the efficient generation of both 3- and 3,4-disubstituted furans.[114] A one step oxidation-dehydration process was used and this involved treating *Z*-2-butene-1,4-diols (*i.e.* **278**) with pyridinium chlorochromate (PCC) which gave variously substituted 3,4-disubstituted furans in good yield (Scheme 61). Oxidation of the primary alcohol present in **278** gave intermediate **279** which is in equilibrium with hemiacetal **280**. PCC is sufficiently acidic to cause the spontaneous dehydration of the intermediate hemiacetal **280** resulting in the formation of the disubstituted furan **281**.



Scheme 61. Itoh's entry to 3- and 3,4-disubstituted furans from *Z*-2-butene-1,4-diols

We envisioned utilizing the above method to prepare furan **284** from *Z*-2-butene-1,4-diols (*i.e.* **282**). This would involve an oxidative cyclization to give furan formation and a subsequent oxidative cleavage of the two *exo*-double bonds. The procedure by Itoh to prepare *Z*-2-butene-1,4-diols using palladium(0) catalyzed cotrimerization of dimethylacetylenedicarboxylate (DMAD) and olefins has somewhat limited applicability and would not lead to the substitution pattern needed in our system.[115] Several conditions to prepare *Z*-2-butene-1,4-diols such as **282** using enolate coupling reactions[116] were tried but disappointingly resulted in complex mixtures of products (Scheme 62).



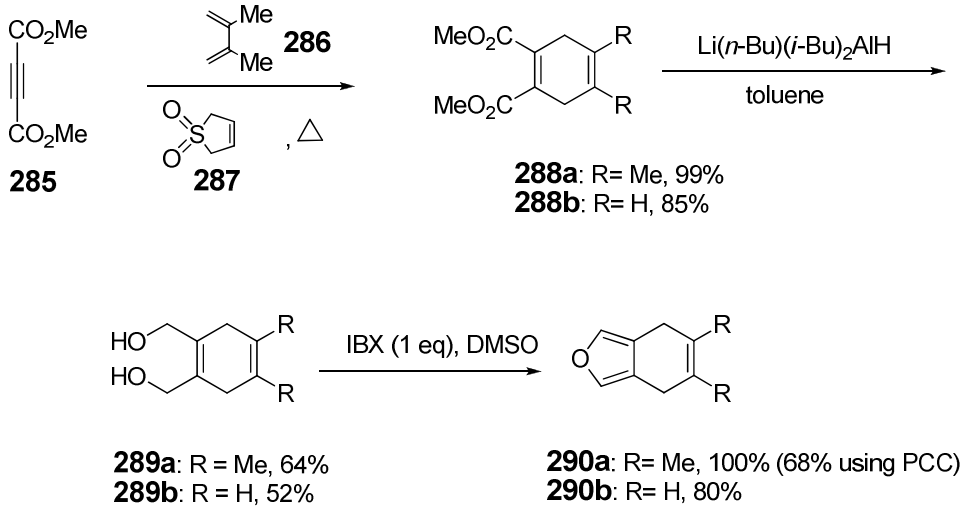
282 **283** **284**

Scheme 62. Synthetic route to furan **57** starting from *Z*-2-butene-1,4-diols

One example reported by Itoh involved the formation of bicyclic furan **281d** (Scheme 61) and its oxidative cleavage and this approach might lead to the requisite furan **243**. Applying their procedure, the formation of the key furan precursor **290a** was accomplished in three steps (Scheme 14). Cycloadduct **288a** was synthesized by a Diels-Alder reaction between butadiene **286** with DMAD. Reduction of **288b** with lithium *n*-butyldiisobutylaluminum hydride,[117] generated diol **289a** in 63% yield over two steps. Reduction of this sterically crowded hydride donor was found to be superior using DIBAL as it provided the diol **289a** in higher yield. Finally, the oxidation of diol **289a** to furan was accomplished in 68% yield by using PCC.

We found that even though PCC was an effective oxidizing agent to gain entry to the desired furan, the reactions were always accompanied by several by-products, probably resulting from the acid liability of the furan. Corey reported a highly selective oxidation of 1,4-diols to γ-lactols using IBX in DMSO without further oxidation to the lactone.[118] This selective lactol formation without being over oxidized to the lactone is probably the consequence of the relatively slow rate of oxidation of lactol to the lactone by IBX. Based on these

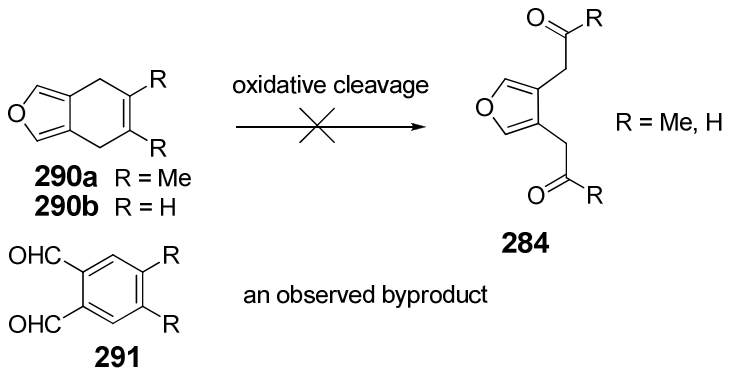
observations, we envisioned that treatment of *Z*-butene diols such **290a** with IBX and DMSO would lead to the desired furan after dehydration. Indeed using these conditions, we were pleased to note that the synthesis of furan **290a** from *Z*-butene diol **289a** proceeds in higher yield when compared with the procedure using PCC (100% vs 68%) as shown in Scheme 14. Cycloadduct **290b** was also synthesized using the same reaction sequence in 35% yield.



Scheme 63. The synthesis of dihydro-isobenzofuran **290**

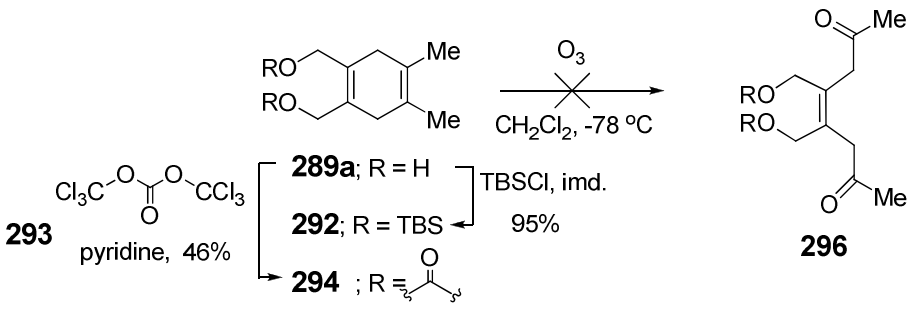
There are a number of conditions developed for the oxidative cleavage or dihydroxylation of isolated double bonds. Several of these conditions were investigated for the oxidation of **290** to **284** including the use of O_3, $KMnO_4$,[119] OsO_4/Oxone, [120] $OsO_4/NaIO_4$, [121] $RuCl_3/NaIO_4$, [122] OsO_4, [123] and RuO_4. [124] Disappointingly, in all cases only a complex mixture was obtained. The less sterically crowded double bond present in furan **290b** also gave similar results. We noticed from the ^{1}H-NMR of the crude mixture that arene **291** was one of the

by-products from this oxidation process, suggesting a competitive oxidative cleavage of the furan double bond (Scheme 64).



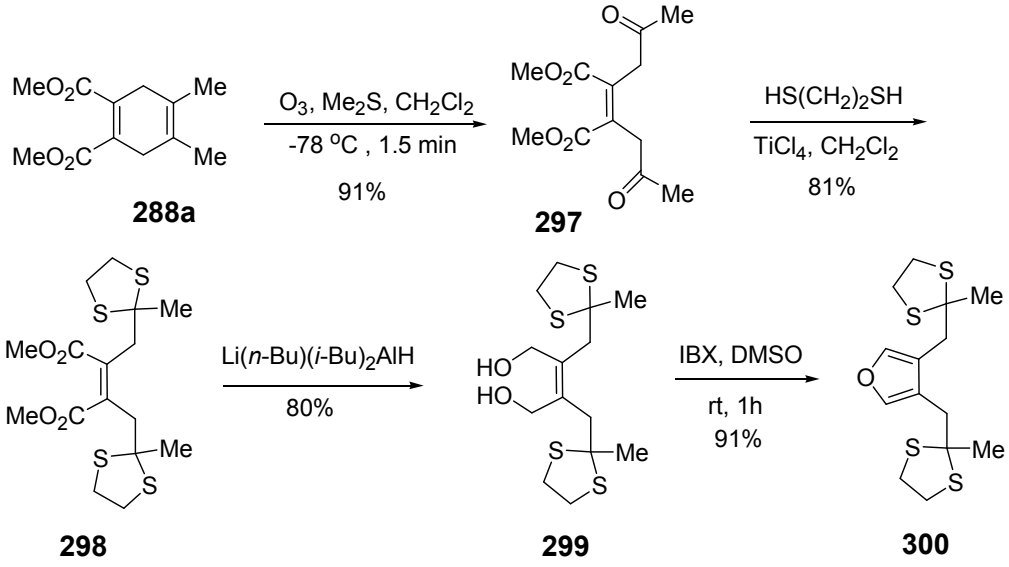
Scheme 64. Attempts for oxidative cleavage of isolated double bound of furan **290**

Since the desired oxidative cleavage using furan **290** was unsuccessful, we embarked on a modified approach whereby the oxidative cleavage was carried out prior to furan formation. In our first attempts, cyclohexadiene diols **289a**, **292**, and **294** were subjected to an ozonolysis reaction. We tried all three substrates since the rate of ozonolysis of alkenes with sterically different substituents might allow for a regioselective oxidative cleavage by careful reaction monitoring.[125] Unfortunately, the reactivity of the alkene moieties present is not sufficiently different for a successful selective ozonolysis, and several over oxidized products were obtained (Scheme 65).



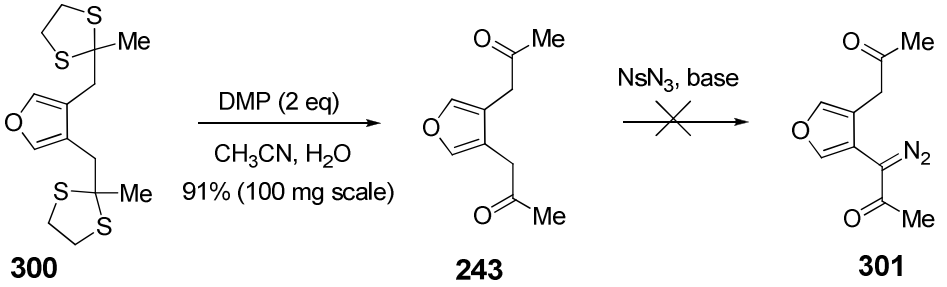
Scheme 65. Attempts for selective ozonolysis

It is known that the rate of ozonide formation using electron-rich double bonds is generally faster than with electron-deficient alkenes.[126] With this in mind, cyclohexadiene **288a** containing different electronic substituents was subjected to ozonolysis. We were please to find that when cyclohexadiene **288a** was treated with ozone at 0 °C, selective ozonolysis occurred solely at the dimethyl alkenyl portion to give **297** in 91% yield. The keto groups in **297** were protected as the thioketals and this was followed by furan formation as before using IBX to form furan **300** in 59% over the three steps (Scheme 66).



Scheme 66. The synthesis of furan **300** containing the required side chains

With thioketal **300** in hand, simple deprotection should lead to our desired furan. However, the deprotection of the thioketal group was found to be problematic. A number of conditions for hydrolysis of the thioketals were tried but all led to a complex mixture of products. Eventually, mild oxidizing conditions were found to be successful. Treatment of the Dess-Martin periodinane in CH_3CN and H_2O with **300** resulted in the formation of the deprotected dicarbonyl **243** in 91% yield (Scheme 18).[127] Unfortunately, the reaction proceeded only on a small scale. Lower yields together with the difficulty of by-product removal were encountered when the reaction was carried out on larger scale. Having a small quantity of furan **243** in hand, diazo transfer reactions were attempted using NsN_3 in the presence of Et_3N or DBU with temperatures ranging from 0 ^oC to rt. Unfortunately, all of our attempts only led to complex mixtures.



Scheme 67. Attempts to the key diazo furan **301**

Since problems associated with diazo transfer are not an uncommon occurrence in organic synthesis, several alternative diazo transfer reagents and conditions were tried. The traditional methods resulted in complex mixtures. However, other routes are possible including the Bamford-Stevens reaction,[128]

indirect deformylation or debenzoylation then diazo transfer,[129] or phase transfer protocols and these might be more successful.[130]

It is clear that we will need to find other reliable methods for the construction of furan **301** in order to have a sufficient amount of material for further investigation.

3. Conclusion

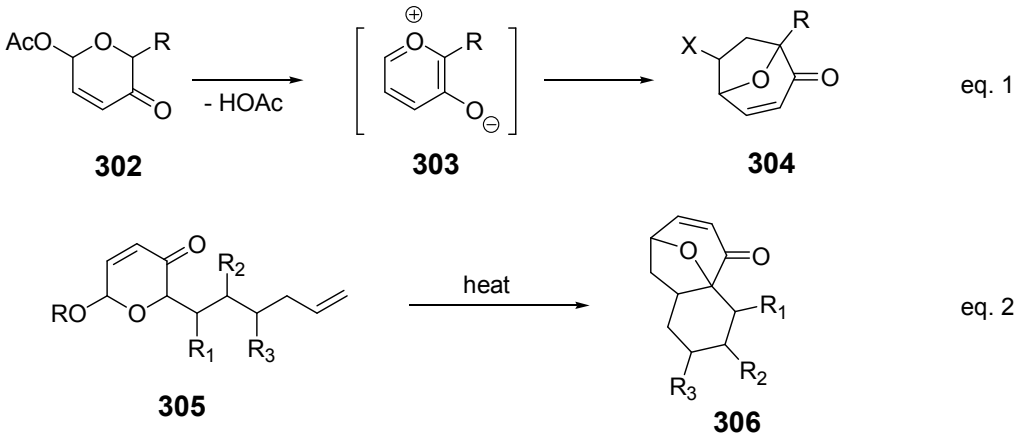
In summary, we have developed a reasonably efficient strategy to prepare the requisite 3,4-disubstituted furans necessary for the synthesis of furanether B. This approach proceeded in four steps, namely a Diels-Alder cycloaddition, ozonolysis, $LiAlH_4$ reduction, and IBX assisted furan formation. Further investigations are underway to prepare the critical diazo furanyl ketone needed for a synthesis of furanether B.

Chapter B. 4

Investigation of Novel Cycloaddition Reactions toward Ylides

1. Introduction

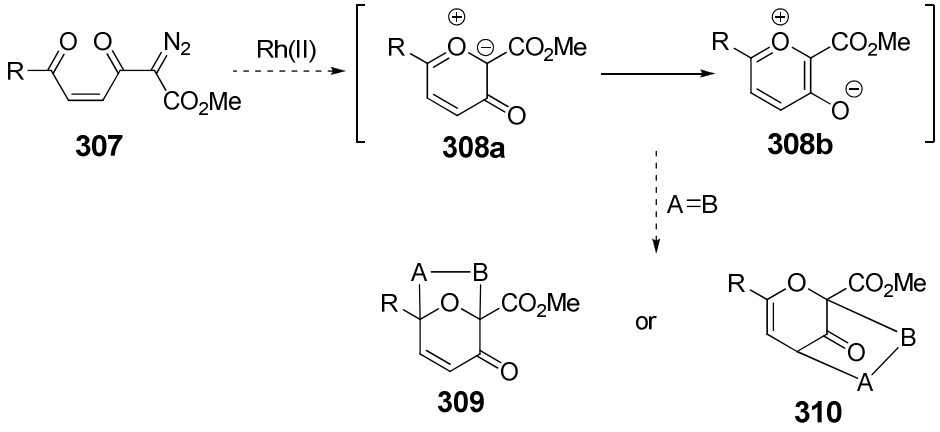
The [5+2]-cycloaddition of 3-oxidopyrylium ylides is a well-precedented reaction and has been used for the rapid access of functionalized seven-membered ring structures *via* formation of an oxabicyclo[3.2.1]octane. [131] Henderson and Farina originally discovered that [5+2]-cycloadditions can be carried out by heating acetoxypyranones such as **302** and a dipolarophile at 130 ^{o}C to afford up to 69% of cycloadduct **304** *via* the oxidopyrylium zwitterion **303** (eq.1, Scheme 68).[132] This reaction was further developed by Sammes, who found that electron rich dipolarophiles were more reactive toward dipole **305** and that the reaction can also be carried out using Et_3N to generate the oxypyrylium zwitterion at room temperature (eq. 2, Scheme 68).[133] Substituted allenes[134]and dienes[135] have also been successfully engaged as dipolarophiles in both intra and intermolecular reactions. The rapid generation of molecular complexity in a relatively easy manner has made this cycloaddition reaction extremely useful for the synthesis of seven-membered ring containing natural products. Notably, Wender and co-workers have successfully applied this strategy, in an intramolecular fashion, to the total synthesis of the natural products phorbol and resiniferatoxin. [136] Some examples of intramolecular [5 + 2]-cycloadditions of pyranones have also been discussed in the introduction section.



Scheme 68. Example of [5+2]-cycloaddition reactions to oxabicyclo[3.2.1]octane

In recent years, a widespread upsurge of activity in the application of carbonyl ylide dipoles to new synthetic transformations has occurred.[137,138] This research has also stimulated interest in the use of carbenes and carbenoids as reactive intermediates for the generation of other types of ylides.[139,140,141] In 1986, work started in the Padwa laboratory to synthesize bridged oxa-substituted bicycloalkanes from the Rh(II)-catalyzed cyclization cascade of α-diazo carbonyl compounds.[37-44] The domino reaction was shown to proceed by the formation of a rhodium carbenoid intermediate followed by a subsequent transannular cyclization of the electrophilic carbon onto an adjacent carbonyl group to generate a cyclic carbonyl ylide dipole. A subsequent 1,3-dipolar cycloaddition reaction with an added dipolarophile A = B (see Scheme 15) then occurred. Our ongoing interest in this procedurally simple methodology spurred investigations of synthetic applications of some other six-membered ring pyrylium ylide cycloadditions. The use of the oxidopyrylium ylides containing an internal double bond has not been reported and we thought that this possibility might allow prove

useful for the synthesis complex natural products. Therefore, we became interested in examining the cycloaddition behavior of the oxidopyrylium dipole **308**, where the extra double bond contained within the ring would not only allow for the formation of the [5+2]-dipolar cycloadduct **309**, but also could produce the isomeric cycloadduct **310**.

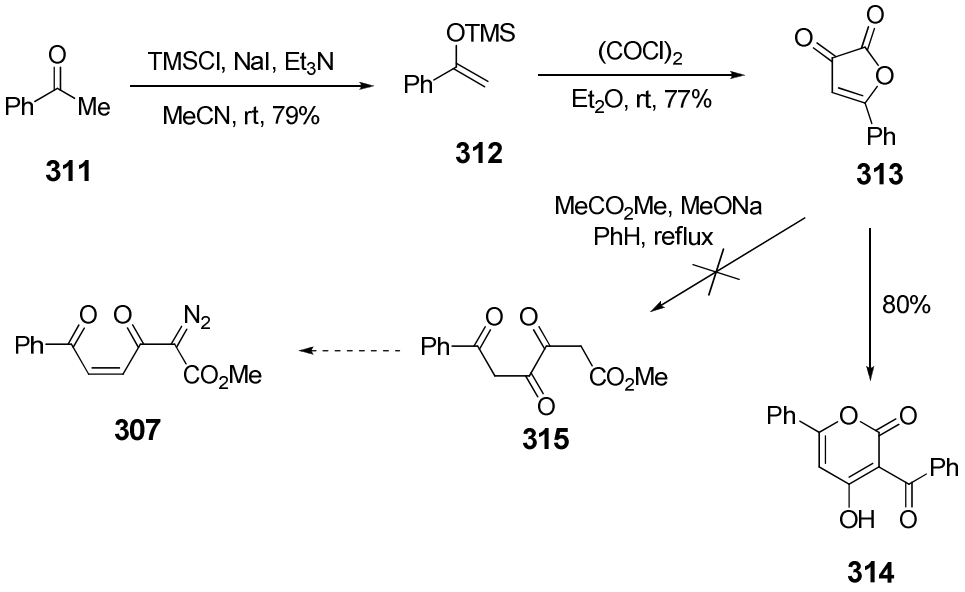


Scheme 69. The cycloaddition reaction analysis toward oxidopyrylium ylide using Rh(II)-catalyzed chemistry

2. Results and Discussion

Since we were interested in using the Rh(II)-catalyzed reaction of α-diazo ketoesters such as **307** as a way to generate various oxidopyrylium ylides (Scheme 69), we undertook a study of several methods to synthesize the required precursor α-diazo ketoesters. To this end, 5-phenylfuran-2,3-dione (**313**) was prepared in 61 % yield by formation of trimethyl (1-phenylvinyloxy)silane **312** from ketone **311** and subsequent reaction with oxalyl chloride.[142] Our intention was to heat **313** with methyl acetate in the presence of sodium methoxide with

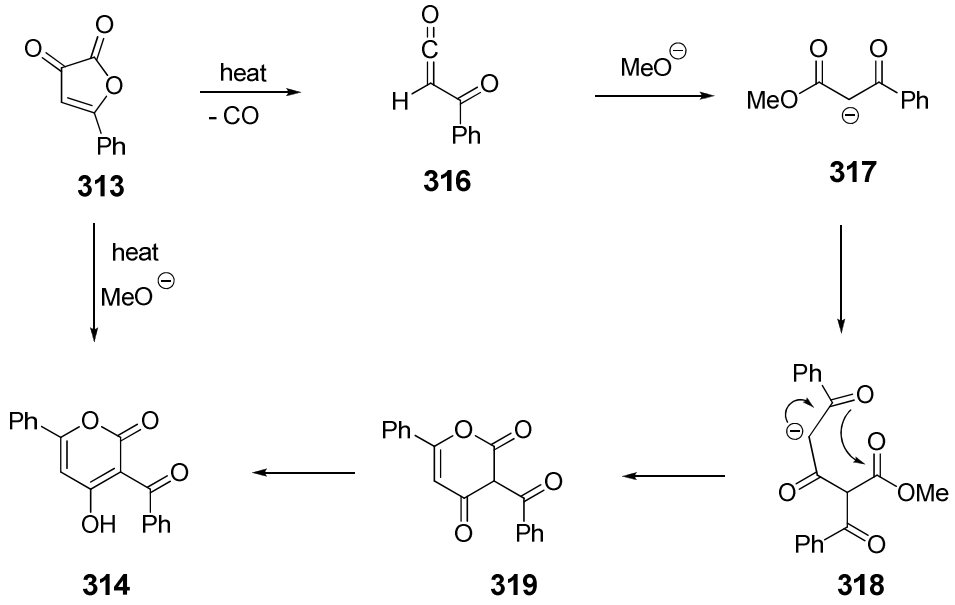
the hope that we would be able to prepare methyl 3,4,6-trioxo-6-phenylhexanoate acid (**315**), which would then be transformed into the corresponding α-diazo ketoester **307** (Scheme 70). However, during our attempts to convert furandione **313** into **315**, we encountered a rather unusual reaction. The major (80%) and unexpected product obtained from the thermal reaction of **313** under basic conditions was identified as 3-benzoyl-4-hydroxy-6-phenyl-2*H*-pyran-2-one (**314**) on the basis of its spectral data[143] and by the procurement of an X-ray crystal structure.



Scheme 70. Unusual formation of pyranone **314** from 5-phenylfuran-2,3-dione

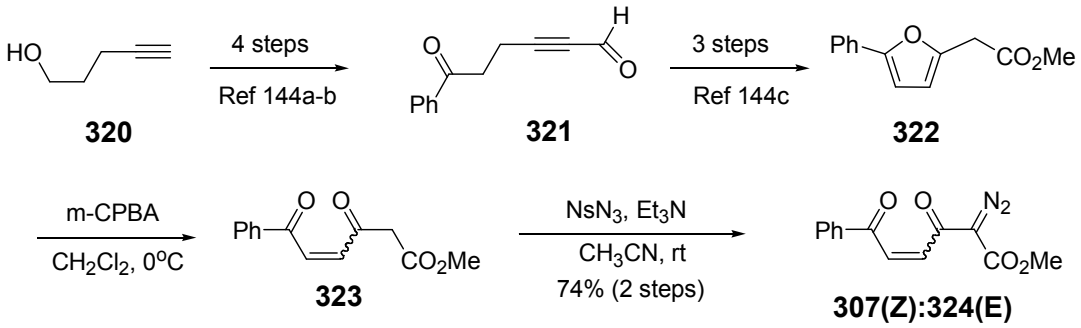
The pseudo-dimerization of **313** can be accounted for by an initial thermal extrusion of carbon monoxide from **313** to give benzoyl ketene **316** as a transient species (Scheme 71). Attack of methoxide anion at the electrophilic ketene center in **316** generates the stable anion **317**, which in turn reacts with another molecule of the ketene to furnish the 1,3-dicarbonyl anion **318**. Cyclization of **318**

to **319** followed by tautomerization to the more stable enol form nicely accounts for the formation of pyranone **314**.



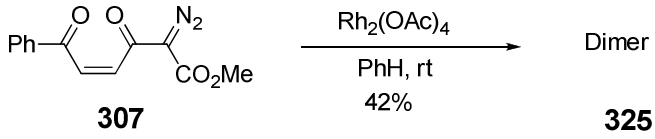
Scheme 71. The purposed mechanism of the formation of pyranone **314**

In an alternate approach that we next employed for the preparation of α-diazo ketoester **307**, we made use of an oxidation reaction of furan **322** which, in turn was prepared from alcohol **320** according to a literature procedure. [144] Methyl 2-(furan-2-yl)acetate (**322**) was treated with *m*-CPBA at 0 ^{o}C in CH_2Cl_2 [145] and this resulted in a 6:1-stereomeric mixture of the expected ring-opened butene-diones **323**, which were immediately converted to the corresponding α-diazo ketoesters (*i.e*. **307** and **324**) using *p*-nitrobenzenesulfonyl azide and Et_3N according to the standard Regitz protocol. [146] The two isomeric α-diazo compounds were separated by column chromatography and their behavior with various nucleophiles was investigated (Scheme 72).



Scheme 72. The preparation of α-diazo compounds **307** and **324**

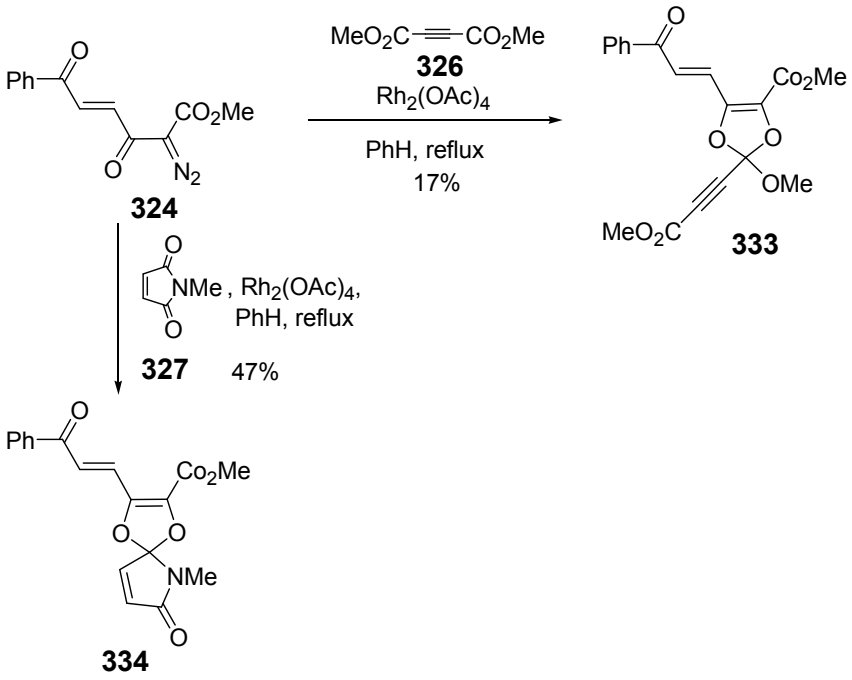
Using the minor *Z*-isomer **307**, all of our attempts to obtain a [5+2]-cycloadduct by trapping the dipole with various agents, such as DMAD and *N*-methyl maleimide, completely failed. Instead, the only compound detected in these reactions was some type of dimerization of **307** (Scheme 73). The reaction of the *Z*-isomer **307** with a Rh(II) catalyst in several solvents and at different concentrations and temperatures led to varying quantities of dimer **325** together with a tarry residue, which resisted purification. We attempted to obtain an X-ray crystal structure of dimer **325** in order to verify its structure, but unfortunately this failed due to the amorphous nature of the solid.



Scheme 73. The attempts for a [5+2]-cycloaddition of a *Z*-isomer of α-diazo compound **307**

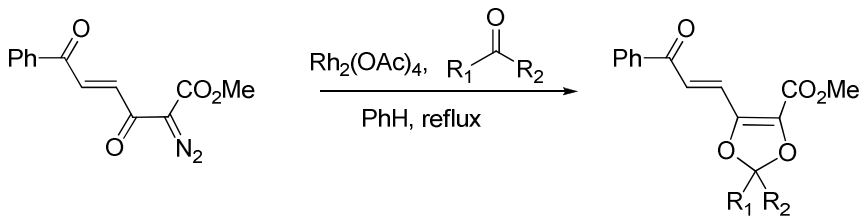
We also studied the Rh(II)-catalyzed behavior of the major *E*-diazo isomer **324**. This isomeric α-diazo ketoester clearly cannot undergo internal cyclization

to give a carbonyl ylide dipole but we were curious as to what pathway would be followed with this system. Toward this end, **324** was added to a benzene solution containing DMAD and a catalytic amount of $Rh_2(OAc)_4$ under an argon atmosphere at 80 ^oC. The reaction was monitored by TLC and column chromatographic purification of the crude reaction mixture afforded cycloadduct **333** as the only isolable product in 17% yield. A related cycloadduct (*i.e.* **324**) was isolated in 47% yield when *N*-methylmaleimide was used as the trapping dipolarophile.



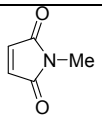
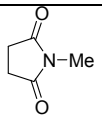
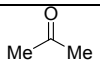
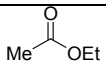
Scheme 74. The formation of 1,3-dioxoles from *E*-isomer of α-diazo compound **324**

Further investigation with other carbonyl trapping agents including *N*-methyl succinimide, benzaldehyde, cyclohexanone, acetone and ethyl acetate gave similar results. The carbonyl group of the added dipolarophile gave rise to analogous cycloadducts **333**-**339** in 17–81% yield (Table 1).



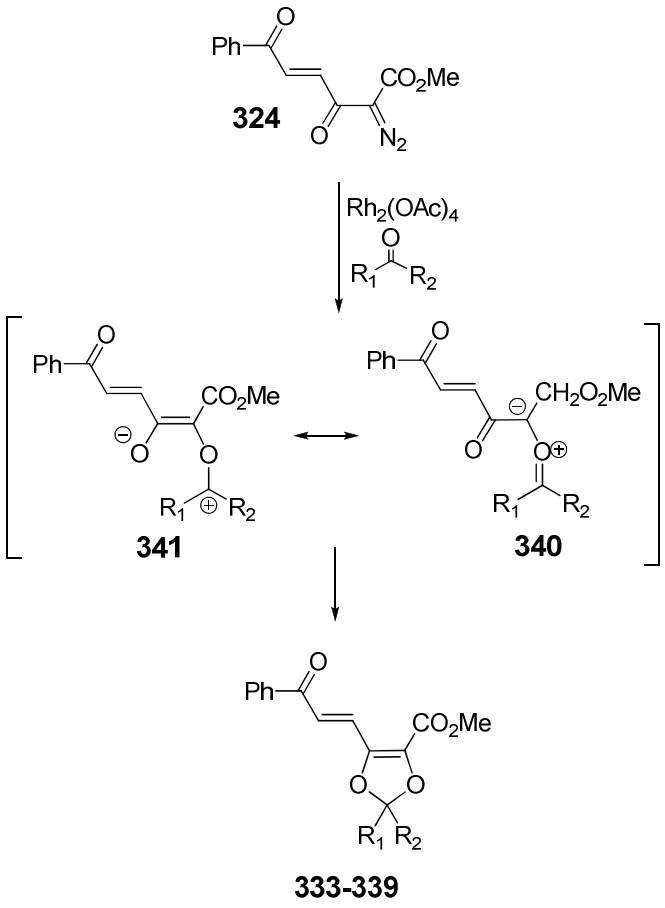
324 **333-339**

Table1. Reaction of *E*-isomer of α-diazo compound (**324**) with various carbonyl compounds

Nucleophile	equivalent	% yield
 **326**	1.1	17%
 **327**	1.1	47%
 **328**	1.1	24 %
 **329**	1.1	24%
 **330**	1.1	45%
 **331**	5	81%
 **332**	5	81%

The overall cycloaddition can be rationalized by an initial reaction of the *E*-diazo ketoester **324** with the Rh(II)-catalyst to first generate an electrophilic

metallo carbenoid (Scheme 75). This species then reacts with the nucleophilic carbonyl oxygen atom of the added dipolarophile to furnish the highly reactive carbonyl ylide intermediate **340**. The presence of the adjacent enone carbonyl group facilitates an intramolecular [1,5]-electrocyclization that eventually leads to the corresponding 1,3-dioxole derivatives **333**–**339**.[147] The importance of a resonance structure of the carbonyl ylide with the negative charge on the oxygen atom of the enone carbonyl group and a positive charge residing on the carbonyl C-atom of the added keto group undoubtedly helps the [1,5]-electrocyclization pathway.



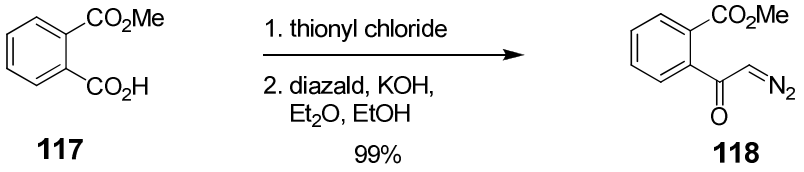
Scheme 75. The reaction profile of Rh(II)-carbenoid of *Z*-and *E*-α-diazo ketoesters

3. Conclusion

In summary, we have investigated the Rh(II)-catalyzed reaction of the *Z*-isomer of 2-diazo-3,6-dioxo-6-phenyl-hex-4-enoic acid methyl ester (**307**) and found that we were unable to trigger a [5+2]-cycloaddition. Instead a dimer was formed as the major product. We have also shown that the Rh(II)-catalyzed reaction of the related *E*-isomer (**324**), in the presence of various carbonyl compounds, undergoes cyclization to give substituted 1,3-dioxoles as the major products. An unexpected pseudo-dimerization process was encountered when the thermolysis of 5-phenyl-2,3-dione (**313**) was carried out in the presence of sodium methoxide.

Experimental Section

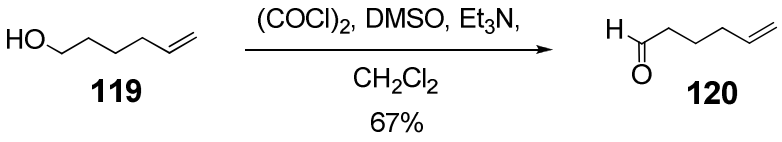
Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame dried glassware under an atmosphere of dry argon. The microwave reactor and reaction vessels were purchased fro CEM Corporation. All solids were recrystallized from ethyl acetate/hexane for analytical data.



117 **118**

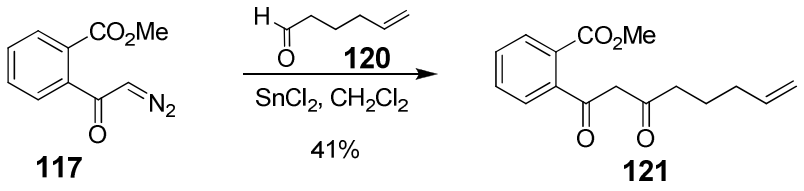
***o*-Methoxycarbonyl-α-diazoacetophenone (118).** [148] To a 5.0 g (28 mmol) sample of phthalic acid monomethyl ester (**117**) was added 24 mL (0.28 mol) of thionyl chloride ($SOCl_2$) at rt. The mixture was stirred at 25 ^oC for 3 h after which time the excess thionyl chloride was removed under reduced pressure. The crude residue was taken up in 200 mL of Et_2O and cooled to 0 °C. In a separated flask, a solution of diazomethane was prepared by the addition of 32 g (0.15 mol) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) in 60 mL of Et_2O to a mixture of a 7.7 g (0.14 mol) of potassium hydroxide in 12 mL of water and 37 mL of EtOH at 80 °C. The resulting diazomethane vapor was trapped in 60 mL of Et_2O at 0 °C. The ethereal diazomethane solution thus formed was added to the above acid chloride solution at 0 °C *via* cannula. After the addition was complete, The reaction mixture was allowed to warm to rt and excess silica gel was added. The mixture was stirred for an additional 5 min, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica

gel column chromatography using a 40% EtOAc/hexane mixture as the eluent to provide 5.1 g (99%) of the titled compound **118** as a yellow solid: mp 61 – 62 °C; IR (neat) 3094, 2100, 1726, 1619, and 1352 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 5.58 (brs, 1H), 7.39 (dd, 1H, *J* = 7.2 and 2.0 Hz), 7.44 – 7.52 (m, 2H), and 7.80 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 52.5, 56.1, 126.8, 129.8, 130.3, 130.8, 131.5, 139.6, 167.4, and 188.7.

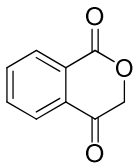


Hex-5-enal (120).[149] To a solution of 4.0 mL (56 mmol) DMSO in 100 mL of CH_2Cl_2 at -78 °C was added 2.5 mL (28 mmol) of $(COCl)_2$ dropwise. The mixture was stirred for 2 min and a solution containing 1.0 g (20 mmol) of hex-5-enol (**119**) in 100 mL of CH_2Cl_2 was transferred via cannula. After stirring for 20 min, 11.2 mL (80 mmol) of Et_3N was added. The mixture was stirred at -78 °C for 5 min and then for an additional 30 min at rt. The mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by distillation at 115 – 125 °C (760 mm) to give 1.32 g (67%) of the titled compound **120** as a clear oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.74 (quint, 2H, *J* = 7.2 Hz), 2.10 (q, 2H, *J* = 7.2 Hz), 2.46 (td, 2H, *J* = 1.5 and 7.2 Hz), 5.00 (m, 2H), 5.78 (m, 1H), 9.80 (t, 1H, *J* = 2.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.1,

32.9, 43.0, 115.4, 137.5, and 202.5. The spectral data obtained for this compound are identical to those reported in the literature. [149]

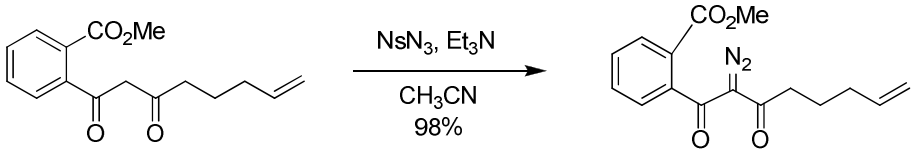


Methyl 2-(3-oxo-oct-7-enoyl)benzoate (121). To a solution containing 0.09 g (0.88 mmol) of hex-5-enal and 0.01 g (0.1 mmol) of anhydrous tin(II) chloride ($SnCl_2$) in 1 mL of CH_2Cl_2 was added a solution of 0.15 g (0.74 mmol) of diazo ketone **117** in 2 mL of CH_2Cl_2 *via* cannula . The resulting mixture was stirred at rt for 1 h, diluted with CH_2Cl_2 and washed with water. The organic phase was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 30% EtOAc/hexane mixture as the eluent to provide 0.04 g (41%) of the titled compound **121** as a yellow oil: IR (neat) 1734, 1727, 1545, 1396, 1292, and 1063 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.81 – 1.90 (m, 2H), 2.15 (q, 2H, *J* = 6.7 Hz), 2.62 (q, 2H, *J* = 7.6 Hz), 3.87 (s, 3H), 5.00 – 5.08 (m, 5H), 5.70 – 5.82 (m, 1H), 6.28 (s, 1H), 7.57 – 7.66 (m, 3H), and 7.82 – 7.86 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.8, 32.9, 37.2, 53.0, 100.2, 116.3, 129.0, 130.4, 131.4, 132.2, 132.8, 133.3, 136.9, 167.2, 186.4, and 196.8; HRMS Calcd for $[(C_{16}H_{18}O_4) + H]^+$: 275.1278. Found: 275.1274.



122

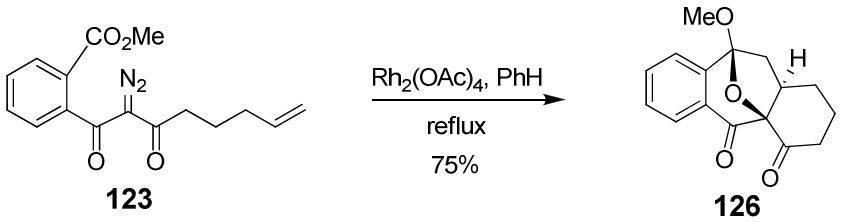
Isochroman-1,4-dione (122) was also Isolated as a by-product; mp 146 – 148 °C; IR (neat) 3083, 2924, 1726, 1701, and 1265 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 2H), 7.85 (m, 2H), 8.10 (dd, 1H, *J* = 7.2 and 1.2 Hz), 8.30 (dd, 1H, *J* = 7.2 and 1.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 73.4, 125.6, 127.9, 130.8,131.7, 134.6, 135.8, 161.3, and 189.4.



121 **123**

Methyl 2-(2-diazo-3-oxo-oct-7-enoyl)benzoate (123). To a stirred solution containing 0.09 g (0.33 mmol) of 1,3-dione **121** in 3.0 mL of CH_3CN was added 0.14 mL (0.98 mmol) of Et_3N and 0.07 g (0.39 mmol) of *p*-nitrobenzenesulfonyl azide (NsN_3)[150] consecutively at rt. The mixture was stirred at rt for 1 h. After this time, the solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 0.1 g (98%) of the titled compound **123** as a pale yellow oil: IR (neat) 2120, 1721, 1656, and 1195 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.71 – 1.77 (m, 2H), 2.09 (q, 2H, *J* = 6.7 Hz), 2.83

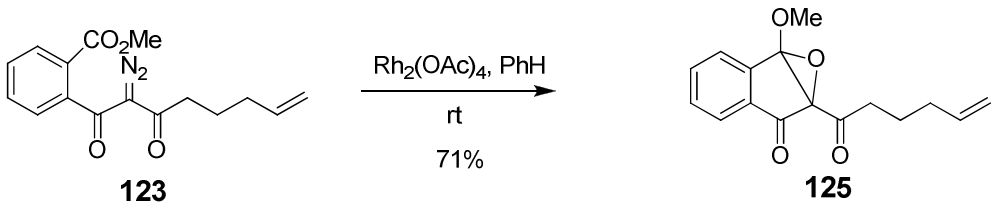
(brs, 2H), 3.87 (s, 3H), 4.95 (d, 1H, *J* = 10.5 Hz), 5.00 (d, 1H, *J* = 17.1 Hz), 5.71 – 5.81 (m, 1H), 7.34 (d, 1H, *J* = 7.6 Hz), 7.54 (td, 1H, *J* = 7.6 and 1.0 Hz), 7.62 (td, 1H, *J* = 7.6 and 1.0 Hz), and 8.03 (d, 1H, *J* = 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.1, 33.0, 40.2, 52.6, 85.8, 115.2, 126.3, 127.6, 130.1, 130.6, 132.9, 137.6, 140.5, 165.8, 186.4, and 191.8.



123 **126**

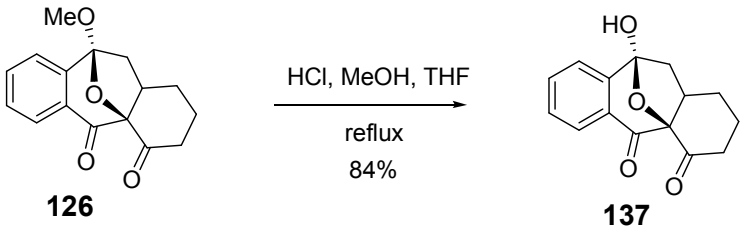
8-Methoxy-12-oxatricyclo[6.3.1.0.^{0,0}]octahydrodibenzo[*a,d*]-4,11-dione (126). To a stirred solution of 0.13 g (0.43 mmol) of diazo-dione **123** in 5 mL of benzene was added 0.01 g (0.02 mmol) of $Rh_2(OAc)_4$ at rt. The mixture was heated for 30 min at 80 °C. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 50% EtOAc/hexane mixture as the eluent to provide 0.03 g (75%) of the titled compound **126** as a pale yellow solid: mp 165 – 166 °C; IR (neat) 3025, 2910, 1726, 1693, 1600, 1305, and 1281 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.39 – 1.52 (m, 1H), 1.92 – 2.12 (m, 4H), 2.32 (dd, 1H, *J* = 12.4 and 5.6 Hz), 2.51 – 2.63 (m, 2H), 2.84 – 2.95 (m, 1H), 3.50 (s, 3H), 7.42 – 7.50 (m, 2H), 7.63 (td, 1H, *J* = 7.3 and 1.3 Hz), and 7.99 (dd, 1H, *J* = 8.3 and 1.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.7, 28.4, 37.2, 41.9, 42.0, 52.8,

90.1, 106.5, 123.5, 127.5, 128.9, 129.9, 134.5, 144.7, 193.0, and 205.8; Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.56; H, 5.93. Found: C, 70.13; H, 5.74.



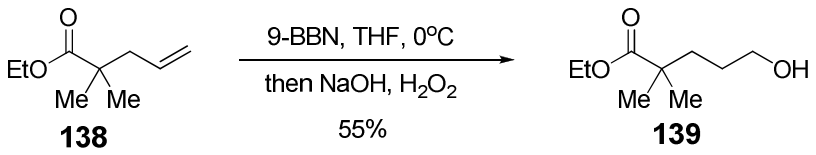
123 **125**

6*a*-Hex-5-enoyl-1*a*-methoxy-1*a*,6*a*-dihydro-1-oxa-cyclopropa[*a*]inden-6-one (125). To a stirred solution containing 0.1 g (0.33 mmol) of diazo-dione **123** in 3 mL of benzene was added 0.01 g (0.02 mmol) of $Rh_2(OAc)_4$ at rt. The mixture was stirred at rt for 30 min. and then the solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography using 50% EtOAc/hexane mixture as the eluent to provide 0.054 g (71%) of the titled compound **125** as a pale yellow solid: mp 113 – 115 °C; IR (neat) 1737, 1724, 1541, 1290, and 1061 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.67 – 1.87 (m, 2H), 2.05 – 2.20 (m, 2H), 2.80 – 2.99 (m, 2H), 3.42 (s, 3H), 4.94 – 5.08 (m, 2H), 5.76 – 5.88 (m, 1H), 7.28 (td, 1H, *J* = 7.9 and 1.3 Hz), 7.41 (ddd, 2H, *J* = 15.9, 7.9, and 1.0 Hz), and 7.58 (td, 1H, *J* = 7.9 and 1.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.0, 33.0, 40.3, 51.9, 90.3, 99.5, 115.0, 125.6, 127.2, 129.5, 130.1, 134.7, 137.4, 138.3, 187.0, and 197.8; Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.56; H, 5.93. Found: C, 69.96; H, 5.95.



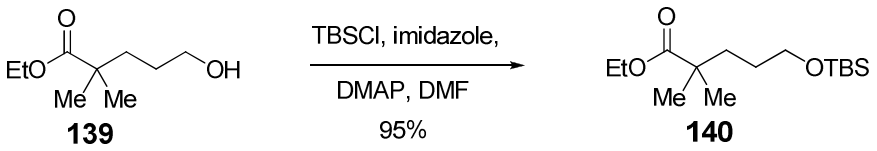
126 **137**

8-Hydroxy-12-oxa-tricyclo[6.3.1.0.^{0,0}]octahydro-dibenzo[*a,d*]-4,11-dione (137). To a solution containing 0.1 g (mmol) of cycloadduct **126** in 2 mL of a 1:2:1 mixture of THF, MeOH and H_2O was added 0.5 mL of a concentrated HCl solution. The mixture was heated at reflux for 6 h, cooled to rt and extracted with EtOAc. The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture was purified by flash silica gel column chromatography using a 50% EtOAc/hexane mixture as the eluent to provide 0.08 g (84%) of the titled compound **137** as a yellow solid: mp 156 – 158 °C; IR (KBr) 3425, 2939, 1721, 1692, and 1289 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (qd, 1H, *J* = 12.7 and 4.8 Hz), 1.86 – 2.06 (m, 3H), 1.96 (dd, 1H, *J* = 12.0 and 6.7 Hz), 2.32 (dd, 1H, *J* = 12.0 and 8.6 Hz), 2.38 – 2.47 (m, 1H), 2.53 (ddd, 1H, *J* = 16.8, 9.5, and 6.0 Hz), 2.85 (ddd, 1H, *J* = 16.8, 11.1, and 4.8 Hz), 5.79 (s, 1H), 7.28 (td, 1H, *J* = 7.6 and 1.0 Hz), and 7.43 – 7.55 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.8, 28.1, 36.7, 41.9, 43.2, 90.6, 103.6, 123.1, 127.1, 127.5, 128.4, 134.8, 146.7, 192.6, and 207.2; Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.74; H, 5.47. Found: C, 69.70; H, 5.34.



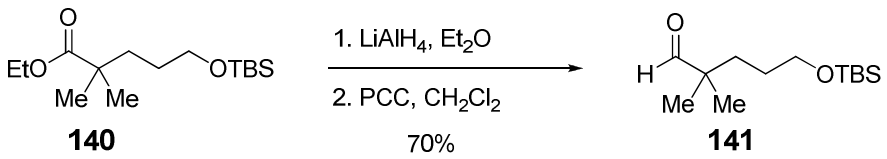
138 **139**

Ethyl 5-hydroxy-2,2-dimethylpentanoate (139). To a stirred solution of 24 mL (12.0 mmol) of 9-BBN (0.5 M solution in THF) was added a solution of 2.0 g (12.0 mmol) of 2,2-dimethyl-pent-4-enoic acid ethyl ester (**138**) [151] in 6 mL of THF at rt. After stirring for 2 h, The reaction mixture was cooled to 0 °C and was then treated with 8 mL of EtOH, followed by 2.4 mL (14.4 mmol) of an aqueous 6M NaOH solution, and 4.8 mL (39.6 mmol) of H_2O_2 (30% solution in H_2O). The mixture was heated at 50 °C for 1 h, cooled to rt and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 8% EtOAc/hexane mixture as the eluent to provide 1.2 g (55%) of the titled compound **139** as a clear oil: IR (neat) 3437, 2971, and 1634 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 6H), 1.22 (t, 3H, *J* = 7.2 Hz), 1.50 – 1.65 (m, 4H), 3.60 (brt, 2H, *J* = 6.0 Hz), and 4.15 (q, 2H, *J* = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.9, 24.8, 27.9, 36.4, 41.6, 60.1, 62.4, and 177.9.



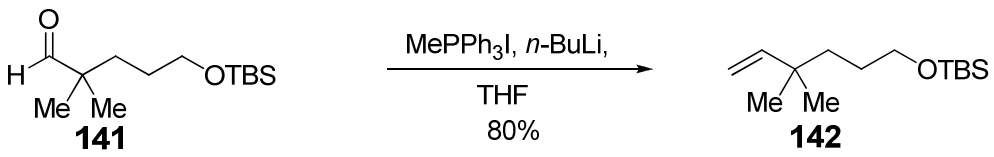
139 **140**

Ethyl 5-(*tert*-butyldimethylsilyloxy)-2,2-dimethylpentanoate (140). To a solution containing a 0.75 g (4.0 mmol) sample of alcohol **139** in 2 mL of DMF was added 0.77 g (10.7 mmol) of imidazole and a crystal of 4-dimethylaminopyridine (DMAP). The mixture was cooled at 0 °C for 15 min and a 0.77 g (5.0 mmol) sample of *tert*-butyldimethylsilyl chloride (TBSCl) was added in one portion. The reaction mixture was stirred for 2 h at 0 °C, quenched with H_2O and extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 1.0 g (95%) of the titled compound **140** as a clear oil: IR (neat) 2650, 2925, 2889, 2848, and 1726 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.84 (s, 9H), 1.12 (s, 6H), 1.20 (t, 3H, *J* = 7.4 Hz), 1.40 – 1.47 (m, 2H), 1.49 – 1.54 (m, 2H), 3.54 (t, 2H, *J* = 6.2 Hz), and 4.08 (q, 2H, *J* = 7.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.3, 14.2, 18.3, 25.1, 25.9, 28.4, 36.8, 41.8, 60.2, 63.4, and 177.9.

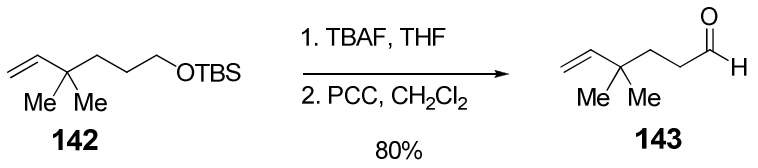


140 **141**

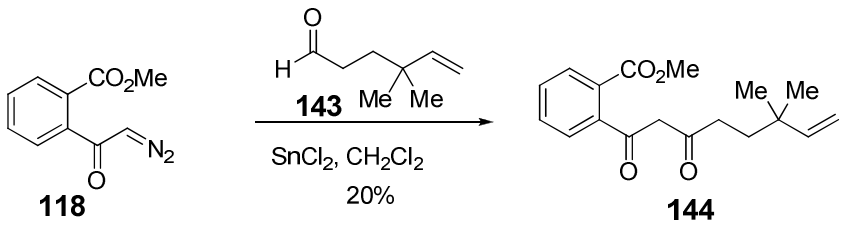
5-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylpentanal (141). To a suspension of a 0.13 g (3.0 mmol) sample of $LiAlH_4$ in 25 mL of Et_2O at 0 °C was slowly added a solution of 0.99 g (3.0 mmol) of ester **140** in 10 mL of Et_2O. After stirring for 30 min at 0 °C, The reaction mixture was quenched by the slow addition of 30 mL of H_2O and then extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude alcohol was dissolved in 15 mL of CH_2Cl_2 and was transferred to a mixture of 1.1 g (4.5 mmol) of pyridinium chlorochromate (PCC) in 10 mL of CH_2Cl_2 at rt. The resulting mixture was stirred at rt overnight, filtered through celite, and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 0.59 g (70%) of the titled compound **141** as a clear oil: IR (neat) 2960, 2925, 1726, 1701, 1470, and 1255 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.85 (s, 9H), 1.15 (s, 6H), 1.35 – 1.50 (m, 4H), 3.60 (t, 2H, J = 6.0 Hz), and 9.40 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.4, 18.3, 21.2, 25.9, 27.6, 33.3, 45.4, 63.1, and 206.2.



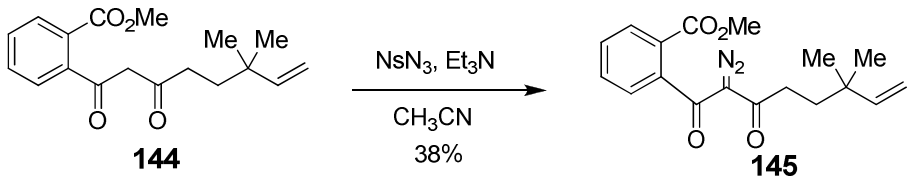
***tert*-Butyl-4,4-dimethylhex-5-enyloxyldimethylsilane (142).** To a stirred solution of 0.48 g (1.2 mmol) of methyltriphenylphosphonium iodide ($MePPh_3I$) in 5 mL of THF at 0 °C was slowly added 0.6 mL (1.2 mmol) of *n*-BuLi (2.1 M solution in THF). The reaction mixture was stirred for 30 min at 0 °C followed by an additional 1 h at rt. After this time, the mixture was cooled to 0 °C and a solution of 0.29 g (1.1 mmol) of aldehyde **141** in 2 ml of THF was slowly added *via* cannula. The resulting mixture was then allowed to warm to rt and was stirred overnight. The reaction mixture was then quenched with H_2O and extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 6% EtOAc/hexane mixture as the eluent to provide 0.23 g (80%) of the titled compound **142** as a clear oil: IR (neat) 3083, 2960, 2930, 2852, 1634, and 1096 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.08 (s, 9H), 0.99 (s, 6H), 1.23 – 1.29 (m, 2H), 1.40 – 1.48 (m, 2H), 3.47 (t, 2H, *J* = 6.8 Hz), 4.90 (dd, 1H, *J* = 17.6 and 1.2 Hz); 4.91 (dd, 1H, *J* = 10.4 and 1.2 Hz), and 5.76 (dd, 1H, *J* = 17.6 and 10.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.3, 18.3, 26.0, 26.7, 28.1, 36.1, 38.6, 63.9, 110.3, and 148.4.



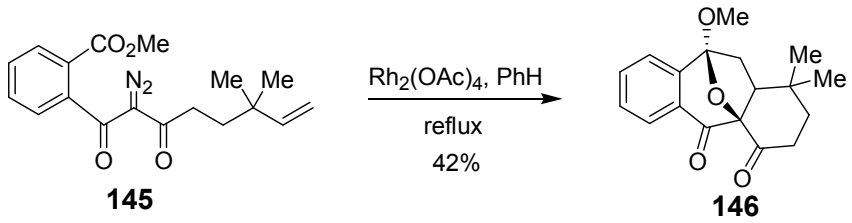
4,4-Dimethylhex-5-enal (143).[152] To a stirred solution containing 0.45 g (1.9 mmol) of alkene **142** in 8 mL of THF was added 2.3 mL (2.3 mmol) of tetra-butylammonium fluoride (TBAF, 1.0 M solution in THF) at 0 °C. The reaction mixture was stirred for 2 h after which time a 1:1-mixture of H_2O and Et_2O was added to the solution. The aqueous layer was extracted with Et_2O and the combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude residue was dissolved in 3 mL of CH_2Cl_2 and was transferred to a stirred solution of 0.6 g (2.7 mmol) of pyridinium chlorochromate (PCC) in 2 mL of CH_2Cl_2 at rt. The solution was stirred overnight and filtered through celite. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 6% EtOAc/hexane mixture as the eluent to provide 0.19 g (80%) of the titled compound **143** as a clear oil: IR (neat) 3084, 2955, 2852, 2807, 2709, 1726, and 1639 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 6H), 1.60 (t, 2H, *J* = 8.0 Hz), 2.34 (td, 2H, *J* = 8.0 and 1.6 Hz), 4.91 (dd, 1H, *J* = 17.2 and 1.2 Hz), 4.95 (dd, 1H, *J* = 10.8 and 1.2 Hz); 5.68 (dd, 1H, *J* = 17.2 and 10.8 Hz), and 9.74 (t, 1H, *J* = 1.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.5, 33.9, 36.0; 39.8; 111.6, 147.0, and 202.8.



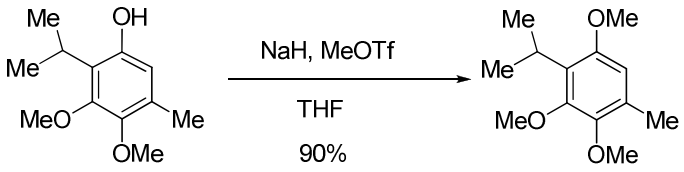
Methyl 2-(6,6-Dimethyl-3-oxo-oct-7-enyl)benzoate (144). To a stirred solution containing 0.34 g (1.6 mmol) of diazo ketone **118** and 0.03 g (0.16 mmol) of anhydrous tin(II) chloride ($SnCl_2$) in 4 mL of CH_2Cl_2 was added a solution of 0.25 g (1.9 mmol) of aldehyde **143** in 4 mL of CH_2Cl_2 and the mixture was stirred at rt for 18 h. The reaction mixture was then quenched with H_2O and extracted with Et_2O**.** The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 20% EtOAc/hexane mixture as the eluent to provide 0.1 g (20%) of the titled compound **144** as a clear oil: IR (neat) 3500, 1721, 1701, 1588, and 1265 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 6H), 1.62 – 1.70 (m, 2H), 2.28 – 2.35 (m, 2H), 3.83 (s, 3H), 4.90 – 5.00 (m, 2H), 5.75 (dd, 1H, *J* = 17.6 and 10.8 Hz), 5.84 (s, 1H) 7.47 – 7.53 (m, 3H), and 7.72 – 7.77(m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.5, 34.0, 36.4, 38.0, 52.5, 99.0, 111.5, 127.9, 129.5, 130.5, 131.0, 131.1, 137.5, 147.1, 168.4, 188.4, and 194.4; HRMS Calcd for $[(C_{18}H_{22}O_4) + H]^+$: 303.1591. Found: 303.1591.



Methyl 2-(2-diazo-6,6-dimethyl-3-oxooct-7-enyl)benzoate (145). To a stirred solution containing 1.0 g (0.32 mmol) of diketo-ester **144** and 0.11 g (0.44 mmol) of *p*-nitrobenzenesulfonyl azide (NsN_3) [3] in 3 mL of CH_3CN at 0 °C was added 0.09 g (0.65 mmol) of Et_3N dropwise. The reaction mixture was stirred for 3 h at 0 °C and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 50% EtOAc/hexane mixture as the eluent to provide 0.4 g (38%) of the titled compound **145** as a clear oil: IR (neat) 3078 , 2955, 2120, 1716, 1650, and 1280 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 6H), 1.55 – 1.65 (m, 2H), 2.65 (brs, 2H), 3.85 (s, 3H), 4.87 (dd, 2H, *J* = 17.2 and 1.2 Hz), 5.69 (dd, 1H, *J* = 17.2 and 10.8 Hz), 7.33 (dd, 1H, *J* = 7.6 and 0.8 Hz), 7.53 (td, 1H, *J* = 8.0 and 1.2 Hz), 7.62 (td, 1H, *J* = 8.0 and 1.2 Hz), and 8.03 (dd, 1H, *J* = 7.6 and 0.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 26.5, 36.0, 36.2, 36.9, 52.6, 86.1, 111.3, 126.4, 127.7, 130.1, 130.6, 133.0, 140.7, 147.2, 165.8, 186.5, and 192.2.

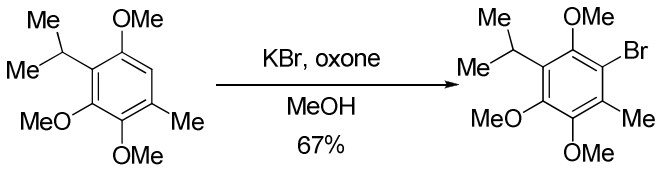


1,1-Dimethyl-8-methoxy-12-oxa-tricyclo[6.3.1.0.^{0,0}]octahydrodibenzo[*a,d*]-4,11-dione (146). To a stirred solution containing 0.04 g (0.12 mmol) of diazo-dione **145** in 1 mL of benzene was added 0.004 g (0.01 mmol) of $Rh_2(OAc)_4$. The mixture was heated at 80 °C for 18 h. After this time, the reaction mixture was cooled to rt and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 6% EtOAc/hexane mixture as the eluent to provide 0.012 g (42%) of the titled compound **146** as a clear oil: IR (neat) 2955, 1721, 1690, and 1270 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 0.95 (s, 3H), 1.81 (ddd, 1H, *J* = 14.0, 9.2, and 1.6 Hz), 1.93 (dt, 1H, *J* = 14.0 and 9.6 Hz), 2.03- 2.22 (m, 2H), 2.40 (t, 1H, *J* = 8.8 Hz), 2.65 (dt, 1H, *J* = 19.2 and 9.6 Hz), 2.81 (ddd, 1H, *J* = 19.2, 9.6, and 1.6 Hz) , 3.49 (s, 3H), 7.48 (d, 2H, *J* = 7.6 Hz), 7.63 (td, 1H, *J* = 7.6 and 1.2 Hz), and 7.98 (dd, 1H, *J* = 8.4 and 1.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.3, 29.8, 32.9, 35.7, 36.1, 36.5, 51.5, 52.7, 88.7, 106.5, 123.6, 127.5, 128.9, 129.6, 134.4, 144.6, 193.1, and 206.7; HRMS (FAB) Calcd for $[(C_{18}H_{20}O_4)+Li]^+$: 300.1361. Found 300.1373.



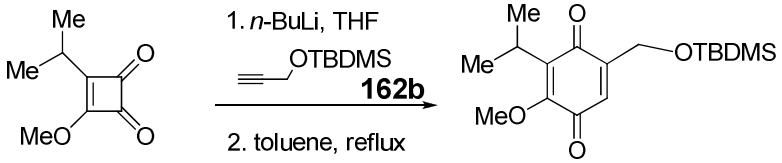
155 **156**

2-Isopropyl-1,3,4-trimethoxy-5-methylbenzene (156). To a stirred solution containing a 1.2 g (5.7 mmol) sample of the penta-substituted arene **155**[x] in 30 mL of THF at -78 °C was added 1.52 g (22.8 mmol) of NaH (60% in mineral oil) in one portion. The mixture was warmed to 0 °C and was stirred at this temperature for 30 min. After that, the resulting solution was cooled to -78 °C and a 0.97 ml (8.6 mmol) sample of MeOTf was added dropwise. The solution was allowed to warm to rt and was stirred for an additional 2 h. The mixture was then quenched with H_2O and extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 1.15 g (90%) of the titled compound **156** as a pale yellow solid: mp 26 – 27 °C; IR (neat) 1582, 1455, 1403, 1231, 1135, 1073, and 840 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.29 (d, 6H, *J* = 7.2 Hz), 2.24 (s, 3H), 3.47 (sept, 1H, *J* = 7.2 Hz), 3.76 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), and 6.20 (s, 1H); ^{13}C-NMR (100 MHz,$CDCl_3$) δ 15.9, 21.3, 25.0, 55.6, 60.1, 60.9, 108.5, 127.9, 128.9, 145.5, 151.6, and 154.2.



156 **157**

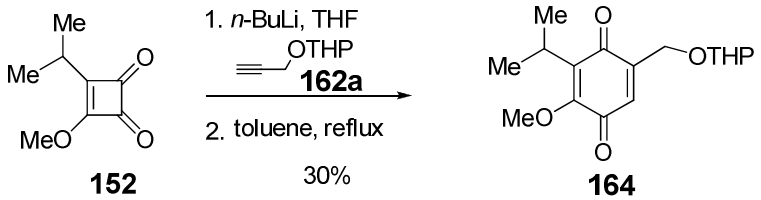
1-Bromo-3-isopropyl-2,4,5-trimethoxy-6-methylbenzene (157). To a stirred solution containing 0.09 g (0.4 mmol) of the penta-substituted arene **156** in 4 mL of THF at rt was added 0.05 g (0.44 mmol) of potassium bromide followed by 0.27 g (0.44 mmol) of potassium peroxymonosulfate (oxone®). The resulting mixture was stirred at rt for 1 h. The mixture was then filtered through funnel and the filtrate was evaporated under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 0.08 g (67%) of the titled compound **157** as a yellow oil: IR (neat) 2935, 1454, 1398, 1231, 1120, and 1030cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (d, 6H, *J* = 7.2 Hz), 2.30 (s, 3H), 3.43 (sept, 1H, *J* = 7.2 Hz), 3.72 (s, 3H), 3.73 (s, 3H), and 3.80 (s, 3H); ^{13}C-NMR (100 MHz,$CDCl_3$) δ 16.3, 22.1, 26.7, 60.1, 60.5, 61.4, 114.7, 130.5, 133.6, 148.5, 151.0, and 151.9.



152 **165**

5-(*tert*-Butyldimethylsilanyloxymethyl)-3-isopropyl-2-methoxy[1,4]benzoquinone (165). To a stirred solution containing 0.3 mL (1.8 mmol) of tert-butyl-dimethylprop-2-ynyloxysilane (**162b**)[153] in 3 mL of THF at -78

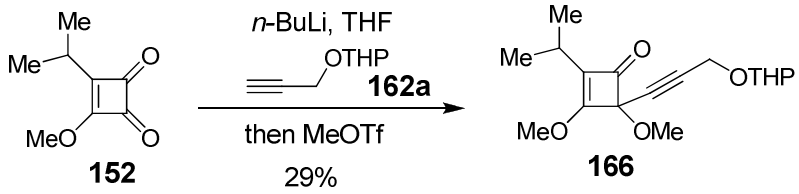
°C was added 0.84 mL (2.1 mmol) of *n*-BuLi (2.5 M solution in hexane). The solution was stirred for 1 h at – 78 °C and transferred *via* cannula to a -78 °C solution of 0.25 g (1.6 mmol) of dione **152** in 3 mL of THF. The resulting solution was warmed to 0 °C and stirred for an additional 30 min. The solution was then cooled to -78 °C and quenched with a saturated aqueous NH_4Cl solution. The mixture was allowed to warm to rt and was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting crude intermediate was dissolved in 5 mL of toluene and the solution was heated at reflux for 1 h. The solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography using a 2.5% EtOAc/hexane mixture as the eluent to provide 0.15 g (30%) of the titled compound **165** as an orange oil: IR (neat) 2957, 2559, 1655, 1600, 1466, 1141, 841, and 780 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.93 (s, 9H), 1.20 (d, 6H, *J* = 6.8 Hz), 3.22 (sept, 1H, *J* = 6.8 Hz), 3.99 (s, 3H), 4.53 (d, 2H, *J* = 2.0 Hz), and 6.29 (t, 1H, *J* = 2.0 Hz); ^{13}C-NMR (100 MHz,$CDCl_3$) δ-5.5, 18.3, 20.4, 24.4, 25.8, 59.4, 61.1, 128.7, 137.4, 148.6, 156.0, 184.2, and 184.5.



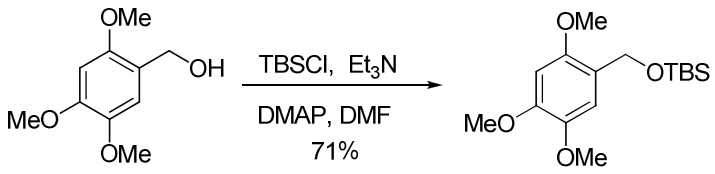
152 **164**

3-Isopropyl-2-methoxy-5-(tetrahydropyran-2-yloxymethyl)-[1,4]benzoquinone (165). To a stirred solution of 2.0 mL (14.3 mmol) of 2-prop-

2-ynyloxy-tetrahydro-pyran (**162a**)[154] in 25 mL of THF at -78 °C was added 6.7 mL (17 mmol) of *n*-BuLi (2.5 M solution in hexane). The solution was stirred for 1 h at -78 °C and transferred *via* cannula to a -78 °C solution of 2.0 g (13 mmol) of dione **152** in 25 mL of THF. The resulting mixture was warmed to 0 °C and was stirred for 30 min, then cooled to -78 °C and quenched with a saturated aqueous NH_4Cl solution. The mixture was allowed to warm to rt and was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 30% EtOAc/hexane mixture as the eluent to provide 2.91 g of the crude intermediate as a yellow oil. The above intermediate was dissolved in 5 mL of toluene and the solution was stirred at reflux for 1 h. After this time, the solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 0.87 g (30%) of the titled compound **165** as an orange oil: IR (neat) 2924, 1730, 1651, 1602, 1454, 1136, and 1037 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.19 (d, 6H, *J* = 7.2 Hz), 1.50 – 1.90 (m, 6H), 3.22 (sept, 1H, *J* = 7.2 Hz), 3.49 – 3.56 (m, 1H), 3.80 (ddd, 1H, *J* = 3.2 Hz), 3.99 (s, 3H), 3.43 (dd, 1H, *J* = 17.6 and 2.0 Hz), 4.60 (dd, 1H, *J* = 17.6 and 2.0 Hz), 4.70 (t, 1H, *J* = 3.2 Hz), and 6.66 (t, 1H, *J* = 2.0 Hz); ^{13}C-NMR (100 MHz,$CDCl_3$) δ 19.1, 20.4, 24.4, 25.2, 30.3, 61.0, 62.1, 62.6, 98.5, 129.2, 137.6, 146.1, 155.9, 184.0, and 187.4.

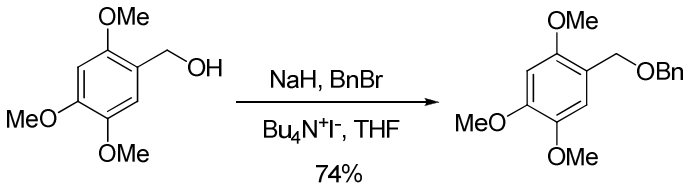


2-Isopropyl-3,4-dimethoxy-4-[3-(tetrahydro-pyran-2-yloxy)prop-1-ynyl] cyclobut-2-enone (166). To a stirred solution of 0.25 mL (1.8 mmol) of 2-prop-2-ynyloxytetrahydropyran (**162a**)[154] in 3 mL of THF was added 0.84 mL (2.1 mmol) of *n*-BuLi (2.5 M solution in hexane) dropwise at -78 °C. The solution was stirred for 1 h at -78 °C and transferred *via* cannula to a -78 °C solution containing 0.25 g (1.6 mmol) of dione **152** in 3 mL of THF. A 0.24 mL (2.1 mmol) sample of MeOTf was added to the reaction mixture and the resulting solution was allowed to warm to 0 °C and stirred for an additional 30 min. The solution was quenched by the slow addition of a saturated aqueous NH_4Cl solution, and then extracted with Et_2O. The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent to provide 0.14 g (29%) of the titled compound **166** as an orange oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.07 (d, 6H, *J* = 7.2 Hz), 1.40 – 1.80 (m, 6H), 2.43 (sept, 1H, *J* = 7.2 Hz), 3.50 (s, 3H), 3.45 – 3.50 (m, 1H), 3.72 – 3.79 (m, 1H), 4.05 (s, 3H), 4.30 (dd, 2H, *J* = 3.0 and 1.2 Hz), and 4.72 (t, 1H, *J* = 2.0 Hz); ^{13}C-NMR (100 MHz,$CDCl_3$) δ 18.8, 19.9, 23.9, 25.2, 30.0, 54.1, 54.2, 59.4, 61.8, 78.3, 87.6, 96.8, 135.6, 177.4, and 184.3.



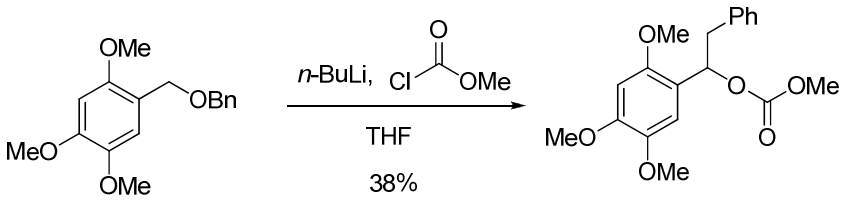
168 **169**

***tert*-Butyldimethyl(2,4,5-trimethoxy-benzyloxy)silane (169).** To a solution of 0.50 g (0.52 mmol) of (2,4,5-trimethoxyphenyl)methanol (**168**) in 0.25 mL of DMF at 0 ^{o}C was added 0.42 mL (3.0 mmol) of Et_3N followed by 0.002 g (0.005 mmol) of 4-dimethylaminopyridine (DMAP) and 0.42 mL (2.8 mmol) of *tert*-butyldimethylsilyl chloride (TBSCl). Stirring for 5 min, the cooling bath was removed and the mixture was allowed to stir at rt overnight. The reaction was then quenched with H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude residue was purified on flash silica gel column chromatography using 10% EtOAc/Hexane as the eluent to provide 0.89 g (71%) of the titled compound **169** as a colorless oil: IR (neat) 2965, 1610, 1516, 1464, 1215, 1128 842, and 778 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.95 (s, 9H), 3.79 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 4.71 (d, 1H, *J* = 0.8 Hz), 6.49 (s, 1H), and 7.05 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.3, 18.4, 25.9, 56.1, 56.2, 56.3, 59.7, 97.0, 111.2, and 121.3.



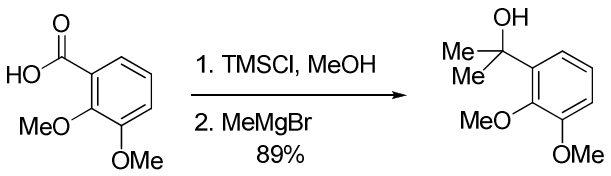
168 **171**

1-Benzyloxymethyl-2,4,5-trimethoxybenzene (171). To a stirred solution containing 0.5 g (2.5 mmol) of (2,4,5-trimethoxyphenyl)methanol (**168)** in 5 ml THF at 0 °C was slowly added 0.1 g (2.6 mmol) of NaH (60% in mineral oil). After stirring for 30 min, 0.3 mL (2.6 mmol) of BnBr and 0.09 g (0.3 mmol) of tetra-methylammonium iodide (*t*-Bu_4NI) was added to the reaction mixture, consecutively. The resulting mixture was allowed to warm to rt and was stirred for an additional 2 h. After that time, the reaction was then quenched by the slow addition of a saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using 25% EtOAc/hexane as the eluent to provide 0.73 g (74%) of the titled compound **171** as a pale yellow solid: mp 32 – 33 °C; IR (neat) 2935, 1612, 1515, 1455, 1205, 866, 739, and 699 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 4.55 (s, 2H), 4.58 (s, 2H), 6.53 (s, 1H), 6.98 (s, 1H), and 7.25 – 7.41 (m, 5H); ^{13}C-NMR (100 MHz,$CDCl_3$) 56.1, 56.5, 66.5, 72.1, 97.4, 113.3, 118.0, 127.5, 127.8, 128.3, 138.5, 142.9, 149.0, and 151.7.



171 **174**

Benzyloxy-(2,4,5-trimethoxyphenyl)-acetic acid methyl ester (174). To a solution containing 0.2 g (0.69 mmol) of arene **171** in 1 mL of THF at -78 °C was added 0.31 mL (0.76 mmol) of *n*-BuLi (2.5 M solution in hexane). The solution was stirred for 1 h at -78 °C and 0.06 mL (0.83 mmol) of methyl chloroformate was added dropwise. After stirring for an additional 1 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using 40% EtOAc/hexane as the eluent to provide 0.09 g (38%) of the titled compound **174** as a yellow solid: mp 56 – 59 °C; IR (neat) 2955, 1748, 1514, 1269, 1038, and 701 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.10 (d, 1H, *J* = 6.4 Hz), 3.12 (d, 1H, *J* = 6.4 Hz), 3.70 (s, 3H), 3.71 (s, 3H), 3.78 (s, 3H), 3.88 (s, 3H), 5.77 (t, 1H, J = Hz), 6.48 (s, 1H), 6.49 (s, 1H), and 7.25 – 7.36 (m, 5H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 37.0, 54.6, 56.0, 56.2, 56.4, 79.7, 97.0, 115.1, 116.2, 126.4, 128.0, 128.3, 140.0, 142.3, 148.3, 151.8, and 155.1.

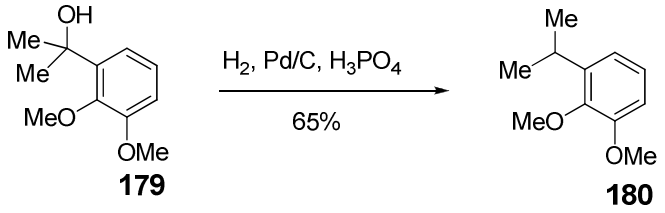


177 **179**

2-(2,3-Dimethoxyphenyl)propan-2-ol (179).[81] To a stirred solution containing 9.1 g (50.0 mmol) of 2,3-dimethoxybenzoic acid (**177**) in 100 mL of methanol was slowly added 6.3 mL (50.0 mmol) of TMSCl at 0 ºC. The resulting mixture was stirred for 12 h at rt and was then concentrated under reduced pressure to afford 9.31 g (95%) of the ester intermediate as a white solid; mp 47 – 48 ºC (Et_2O) [lit. 47 ºC][155]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 3.91 (s, 6H), 7.05 – 7.11 (m, 2H), and 7.31 – 7.33 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 52.4, 56.3, 61.7, 116.0, 122.4, 124.0, 126.3, 149.3, 153.4, and 167.0.

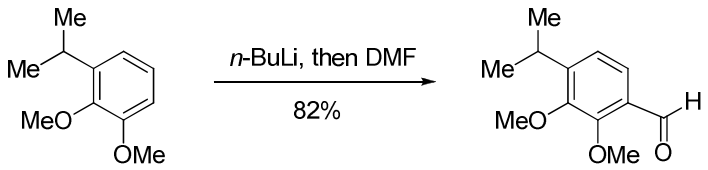
To a solution containing of 9.3 g (47.5 mmol) of the above intermediate in 100 mL of THF at 0 ºC was slowly added 50 mL of methyl magnesium bromide (3.0 M solution in THF). The solution was then heated at reflux for 6 h. After cooling to 0 ºC, the reaction mixture was quenched by the cautious addition of 50 mL of an aqueous 1M HCl solution and the mixture was extracted with Et_2O. The organic phase was washed successively with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography using a 20% EtOAc/hexane mixture as the eluent to provide 8.7 g (94%) of the titled compound **179** as a clear oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 6H), 3.88 (s, 3H), 4.00 (s, 3H), 6.86 (dd, 1H, *J* = 8.0 and 2.0 Hz), 6.94 (dd, 1H, *J* = 8.0 and 2.0 Hz), and 7.02 (t,

1H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 31.0, 56.0, 61.2, 73.0, 111.8, 118.2, 123.9, 141.4, 147.0, and 152.9.



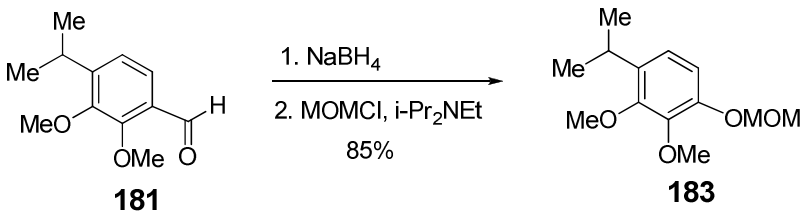
179 **180**

1-Isopropyl-2,3-dimethoxybenzene (180).[81] To a solution containing 1.62 g (8.7 mmol) of alcohol **179** in 7 mL of EtOH at rt was added 0.5 mL of phosphoric acid (H_3PO_4) followed by 0.12 g (0.13 mmol) of Pd/C (10% w/w). The reaction mixture was stirred at 50 ºC for 5 h, filtered through celite and washed thoroughly with EtOH. The solvent was evaporated under reduce pressure to provide 0.96 g (60%) of the titled compound **180** as a clear oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.22 (d, 6H, *J* = 7.0 Hz), 3.38 (sept, 1H, *J* = 7.0 Hz), 3 .83 (s, 3H), 3.87(s, 3H), 6.76 (dd, 1H, *J* = 8.0 and 1.2 Hz), 6.86 (dd, 1H, *J* = 8.0 and 1.2 Hz), and 7.05 (td, 2H, *J* = 8.0 and 1.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.8, 26.9, 55.9, 61.1, 109.8, 118.5, 124.2, 142.8, 146.5, and 152.8.



180 **181**

4-Isopropyl-2,3-dimethoxybenzaldehyde (181).[82] To a solution containing 2.1 g (10.5 mmol) of arene **180** in 20 mL Et_2O at 0 ºC was added 2.37 g (15.7 mmol) of tetramethylethylene diamine (TMEDA) followed by the slow addition of 6.5 mL (15.7 mmol) of *n*-BuLi (2.5 M solution in hexane). The solution was allowed to warm to rt and was stirred for 90 min. After this time, the mixture was cooled to -78 ºC and was treated with 1.6 mL (21 mmol) of DMF. The resulting solution was allowed to warm to rt and was stirred for 20 h. The reaction mixture was quenched by the addition of a saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed successively with water followed by brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 20% EtOAc/hexane mixture as the eluent to provide 2.0 g (82%) of the titled compound **181** as a pale yellow; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22 (d, 6H, *J* = 7.0 Hz), 3.48 (sept, 1H, *J* = 7.0 Hz), 3.85 (s, 3H), 4.00 (s, 3H), 7.03 (d, 2H, *J* = 8.2 Hz), 7.55 (d, 2H, *J* = 8.2 Hz), 10.35 (s, 1H). The spectroscopic properties of **181** are identical to that reported in literature.[82]

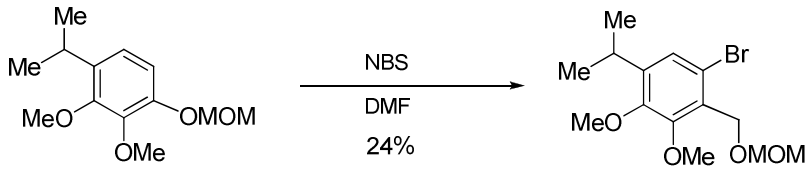


181 **183**

1-Isopropyl-2,3-dimethoxy-4-((methoxymethoxy)methyl)benzene (183). To a solution of 0.33 g (1.6 mmol) of aldehyde **181** in 5 mL of EtOH at 0 ºC was added 0.03 mg (0.8 mmol) of $NaBH_4$. The solution was stirred for 1 h at 0 ºC and was quenched by the slow addition of an aqueous 1M HCl solution, and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 0.27 g (81%) of the expected alcohol intermediate[81] as a clear oil which was used for the next step without further purification: ^{1}H-NMR ($CDCl_3$,300 MHz) δ 1.22 (d, 6H, *J* = 7.1 Hz), 3.32 (sept, 1H, *J* = 7.1 Hz), 3.83 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.06 (s, 1H), 4.65 (s, 2H), 6.96 (d, 1H, *J* = 8.1 Hz), and 7.04 (d, 1H, *J* = 8.0 Hz).

To a solution of 0.27 g (1.29 mmol) of the above alcohol in 5 mL of CH_2Cl_2 was added 0.66 mL (3.86 mmol) of diisopropylethylamine. To this mixture was slowly added 0.2 mL (2.57 mmol) of chloromethyl methyl ether (MOMCl) at 0 ºC and The reaction mixture was allowed to warm to rt and was stirred for an additional 15 h. The mixture was then quenched by the addition of a saturated NH_4Cl solution and was extracted with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to leave behind a pale yellow residue. Purification by flash silica gel column chromatography using a 10% EtOAc/hexane mixture as the eluent afforded

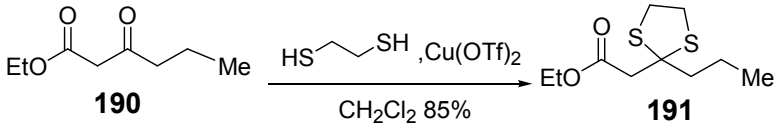
0.23 g (71%) of the titled compound **183** as a clear liquid: IR(thin film) 2961, 1457, 1414, 1276, 1150, 1042, 918, and 818 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.22 (d, 6H, *J* = 7.0 Hz), 3.33 (sept, 1H, *J* = 7.0 Hz), 3.44 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 4.60 (s, 2H), 4.74 (s, 2H), 6.98 (d, 1H, *J* = 8.0 Hz), and 7.09 (d, 1H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.7, 27.0, 55.5, 60.9, 61.0, 64.5, 96.0, 121.5, 125.0, 129.4, 143.2, 150.5, and 151.5.



183 **184**

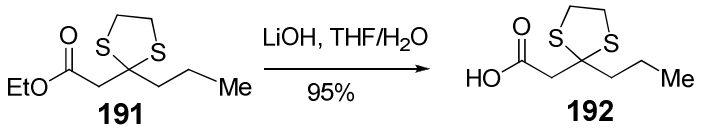
Bromo-5-isopropyl-3,4-dimethoxy-2-((methoxymethoxy)methyl)benzene (184). To a stirred solution of 0.50 g (1.98 mmol) of arene **183** in 5 mL of DMF was added 0.35 g (1.98 mmol) *N*-bromosuccinimide (NBS) at rt. After 12 h, the reaction mixture was quenched by the addition of a saturated aqueous $NaHCO_3$ solution and was then extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography using a 66% CH_2Cl_2/hexane mixture as the eluent to afford 0.16 g (24%) of the titled compound **184** as a clear oil: IR (thin film) 2962, 2882, 1591, 1467, 1400, 1333, 1150, 1102, 1039, and 943 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.29 (d, 6H, *J* = 6.7 Hz), 3.28 (sept, 1H, *J* = 6.7 Hz), 3.47 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 4.70 (s, 2H), 4.77 (s, 2H), and 7.21 (s, 1H); ^{13}C-NMR

(100 MHz, $CDCl_3$) δ 23.4, 27.1, 55.7, 60.8, 61.5, 64.3, 96.6, 120.0, 126.0, 129.1, 145.0, 150.2, and 153.4.



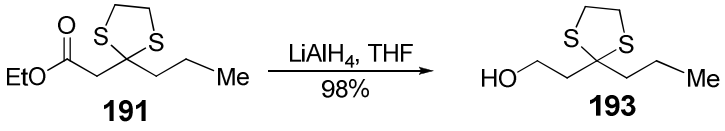
190 **191**

(2-Propyl-[1,3]dithiolan-2-yl)-acetic acid ethyl ester (191). To a solution containing 5.0 g (31.6 mmol) of 3-oxo-hexanoic acid ethyl ester (**190**) in 125 mL of CH_2Cl_2 at rt was added 3.2 mL (37.9 mmol) of 1,2 ethane-dithiol followed by 1.1 g (3.2 mmol) of copper(II) triflate ($Cu(OTf)_2$). The reaction mixture was stirred at rt for 12 h, then diluted with CH_2Cl_2 and washed with an aqueous 1M NaOH solution. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography using a 25% EtOAc/hexane mixture as the eluent to give 7.41 g (72%) of the titled compound **191** as a yellow oil: IR (neat) 2961, 1731, 1460, and 1184 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, *J* = 7.3 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.46 – 1.52 (m, 2H), 2.02 – 2.10 (m, 2H), 3.03 (s, 2H), 3.29 (s, 4H), and 4.15 (q, 2H, *J* = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.7, 13.9, 20.1, 39.2, 44.5, 47.7, 60.1, 66.6, and 169.6.



191 **192**

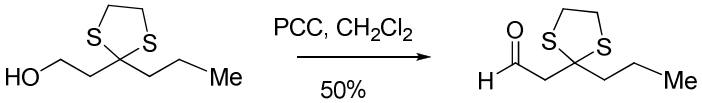
(2-Propyl-[1,3]dithiolan-2-yl)-acetic acid ethyl ester (192). To a solution containing 1.04 g (4.47 mmol) of ester **191** in 33 mL of a 2:1 mixture of THF and H_2O was added 11 mL (11 mmol) of an aqueous 1M LiOH solution at 0 ºC dropwise. The mixture was allowed to warm to rt and was stirred overnight. After this time, the mixture was acidified by the slow addition of an aqueous 1M HCl solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 0.87 g (94%) of the titled compound **192** as a white solid: mp 80 – 81 ºC; IR (neat) 3038, 2959, 1704, 1633, 1408, and 1275, cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.3 Hz), 1.48 – 1.59 (m, 2H), 2.07 – 2.12 (m, 2H), 3.10 (s, 2H), and 3.35 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.0, 20.4, 39.6, 44.8, 47.8, 66.6, and 175.6.



191 **193**

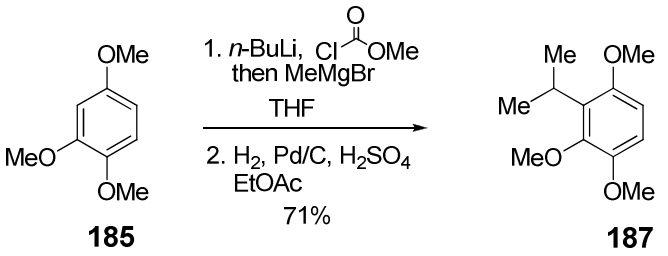
2-(2-Propyl-[1,3]dithiolan-2-yl)ethanol (193). To a stirred solution containing 2.0 g (8.3 mmol) of ester **191** in 34 mL of THF at 0 ºC was added 0.49 g (13.0 mmol) of $LiAlH_4$. The reaction mixture was warmed to rt and stirred for 1 h after which time H_2O was added to the mixture dropwise until there was no more gas evolution. The crude mixture was filtered and washed with EtOAc. The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure to furnish 1.61

g (98%) of the titled compound **193** as a yellow oil: IR (neat) 3365, 1731, 1465, 1271, and 1040 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, *J* = 7.2 Hz), 1.45 – 1.60 (m, 2H), 1.85 – 1.95 (m, 2H), 2.18 (t, 2H, *J* = 5.7 Hz), 2.49 (t, 1H, *J* = 6.2 Hz), 3.30 (s, 4H), and 3.90 (q, 2H, *J* = 6.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.0, 15.9, 39.7, 44.3, 47.3, 60.6, and 69.7.



193 **194**

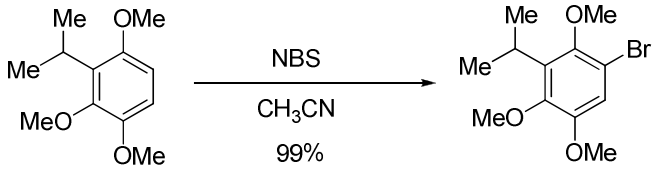
(2-Propyl-[1,3]dithiolan-2-yl)acetaldehyde (194). To a solution of 2.5 g (13.0 mmol) of alcohol **193** in 52 mL of CH_2Cl_2 was added 3.4 g (15.6 mmol) of pyridinium chlorochromate (PCC) at rt. The reaction mixture was stirred for 2 h at rt after which time the solvent was evaporated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to give 1.23 g (50%) of the titled compound **194** as a clear oil: IR (neat) 2960, 2734, 1724, 1465, and 1278 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, *J* = 7.1 Hz), 1.45 – 1.60 (m, 2H), 1.95 – 2.06 (m, 2H), 2.92 (d, 2H, *J* = 2.4 Hz), 3.34 (d, 4H, *J* = 0.9 Hz), and 9.80 (t, 1H, *J* = 2.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.8, 19.8, 40.0, 47.3, 54.1, 65.6, and 200.8.



185 **187**

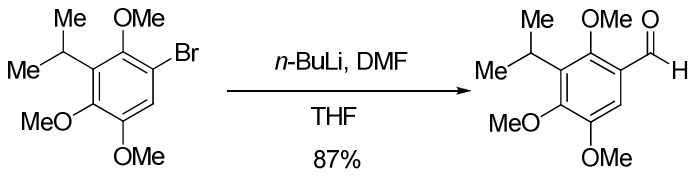
2-(2,3,62-Isopropyl-1,3,4-trimethoxybenzene (187).[84] To a solution of 5.0 g (29.7 mmol) of arene **185** in 30 mL of THF at -78 ºC was added 13.1 mL (32.7 mmol) of *n*-BuLi (2.5 M solution in hexane) dropwise. The reaction mixture was stirred for 1h after which time 2.7 mL (35.7 mmol) of methyl chloroformate was added. The solution was stirred at -78 ºC for an additional 1 h then 59.5 mL (178 mmol) of MeMgBr (3.0 M solution in Et_2O) was added. After stirring for 1 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude mixture was then taken up in 100 mL of EtOAc and 2.35 g (2.21 mmol) of Pd/C (10% w/w) was added. To this mixture was added 2-3 drops of H_2SO_4. The resulting dark brown solution was purged with H_2 gas and the mixture was stirred under H_2 balloon overnight. The mixture was filtered through celite, evaporated under reduced pressure, and purified by flash silica gel column chromatography using 25% EtOAc/hexane as the eluent to give 4.44 g (71%) of the titled compound **187** as a white solid: mp 46 – 47 ºC; IR (neat) 2954, 2832, 1484, 1254, 1118, 1056, 791, and 721 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.31 (d, 6H, *J* = 7.0 Hz), 3.54 (sept, 1H, *J* = 7.0 Hz), 3.76 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 6.56 (d, 1H, *J*

= 9.0 Hz), and 6.69 (d, 1H, *J* = 9.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.2, 25.2, 55.9, 56.1, 61.0, 106.3, 109.4, 130.9, 147.3, 147.8, and 152.9.



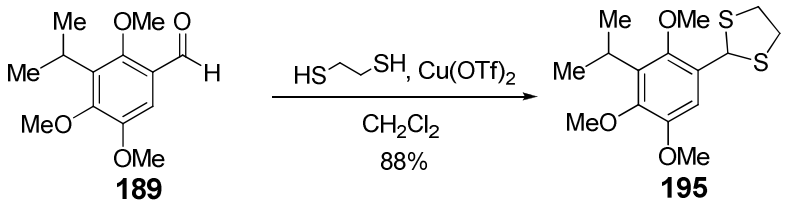
187 **188**

1-Bromo-3-isopropyl-2,4,5-trimethoxybenzene (188).[156] To a stirred solution containing 3.79 g (17.6 mmol) of arene **187** in 70 mL of CH_3CN was added 6.26 g (35.0 mmol) of *N*-bromosuccinimide (NBS) at rt. The reaction mixture was stirred for 1.5 h after which time the solvent was evaporated under reduced pressure. The residue was then taken up in 10 mL of CCl_4 and the mixture was stirred at rt for 5 min. The white precipitate that formed was removed by filtration through celite and the filtrate was concentrated under reduced pressure to give 5.05 g (99%) of the titled compound **188** as a yellow oil: IR (neat) 2956, 2938, 1473, 1422, 1225, 1040, and 768 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.32 (d, 6H, *J* = 7.0 Hz), 3.44 (Sept, 1H, *J* = 7.0 Hz), 3.75 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), and 6.92 (s, 1H)); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.8, 26.7, 56.0, 60.7, 61.5, 110.8, 114.0, 114.0, 136.6, 148.0, 148.9, and 150.1.



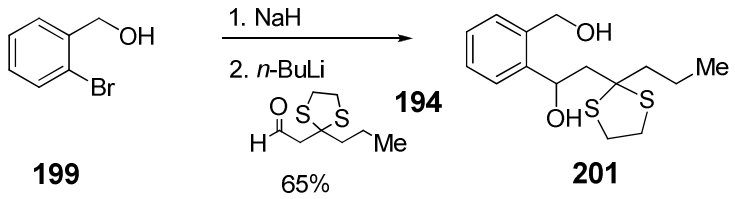
188 **189**

3-Isopropyl-2,4,5-trimethoxybenzaldehyde (189). To a solution of 4.0 g (13.8 mmol) of the arene **188**[85,156] in 55 mL of THF at -78 ºC was added 6.1 mL (15.2 mmol) of *n*-BuLi (2.5 M solution in hexane) dropwise. The solution was stirred for 1 h at -78 ºC and then 1.34 mL (17.3 mmol) of DMF was added dropwise to the reaction flask. After stirring at -78 ºC for 2 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution. The mixture was allowed to warm to rt and was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 20% EtOAc/hexane mixture as the eluent to provide 2.9 g (87%) of the titled compound **189** as a white solid: mp 45 – 47 ºC; IR (neat) 2955, 2842, 1685, 1583, and 1083 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.33 (9d, 6H, J = 7.1 Hz), 3.43 (sept, 1H, J = 7.1 Hz), 3.81 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 7.22 (s, 1H), and 10.24 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.6, 25.4, 55.8, 60.8, 65.4, 107.7, 124.4, 135.4, 150.0, 154.8, 156.8, and 189.1.

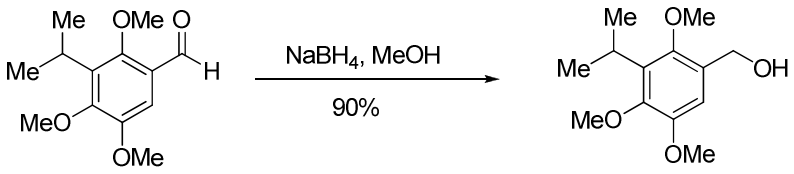


189 **195**

2-(3-Isopropyl-2,4,5-trimethoxy-phenyl)-[1,3]dithiolane (195). To a solution containing 0.3 g (0.63 mmol) of aldehyde **189** in 5 mL of CH_2Cl_2 was added 0.13 mL (1.2 mmol) of 1,2-ethanedithiol followed by 0.05 g (0.1 mmol) of copper(II) triflate ($Cu(OTf)_2$) at rt. The mixture was stirred overnight at rt, diluted with CH_2Cl_2 and washed with an aqueous 1M NaOH solution. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by flash silica gel column chromatography using 20% EtOAc/hexane as the eluent to provide 0.35 g (88%) of the titled compound **195** as a pale yellow oil: IR (thin film) 1954, 2933, 1477, 1425, 1330, 1235, 1107, and 1039 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ1.33 (d, 6H, *J* = 7.2 Hz), 3.36 (m, 3H), 3.52 (m, 2H), 3.74 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 6.40 (s, 1H), and 7.85 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.8, 26.0, 40.0, 49.7, 55.8, 60.6, 63.0, 110.0, 126.9, 134.5, 148.7, 149.5, and 149.9.

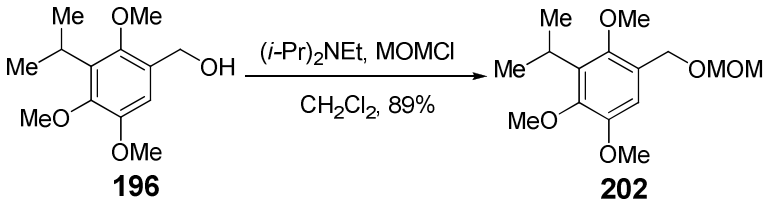


1-(2-Hydroxymethylphenyl)-2-(2-propyl-[1,3]dithiolan-2-yl)-ethanol (201). To a solution containing 0.12 g (0.63 mmol) of alcohol **199** in 2 mL of THF was added 0.03 g (0.74 mmol) of NaH (60% in mineral oil) at 0 ºC. After stirring for 1 h, the reaction mixture was cooled down to -78 ºC and 0.26 mL (0.66 mmol) of *n*-BuLi (2.5 M solution in hexane) was added dropwise. The reaction mixture was stirred for an additional 1 h and a solution of 0.12 g (0.63 mmol) of aldehyde **193** in 0.5 mL of THF was transferred to The reaction mixture flask *via* cannula. The resulting mixture was stirred at -78 ºC for 1 h and allowed to warm to rt and then quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduce pressure. The crude residue was purified by flash silica gel column chromatography using 20% EtOAc/hexane as the eluent to provide 0.1 g (66%) of the titled compound **201** as a white solid: mp 47 – 49 ºC; IR (thin film) 3397, 3289, 2955, 1454, 1418, 1111, 1043, and 764 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* = 7.2 Hz), 1.48 – 1.60 (m, 2H), 1.93 – 2.05 (m, 2H), 2.21 (dd, 1H, *J* = 15.2 and 1.2 Hz), 2.45 (dd, 1H, *J* = 15.2 and 1.2 Hz), 3.33 – 3.50 (m, 4H), 4.68 (d, 1H, *J* = 12.4 Hz), 4.82 (d, 1H, *J* = 12.4 Hz), 5.46 (d, 1H, *J* = 8.0 Hz), 7.25 – 7.34 (m, 3H), and 7.46 (d, 1H, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.1, 19.9, 40.1, 40.4, 48.7, 49.1, 63.8, 70.6, 70.8, 126.9, 127.8, 128.4, 129.9, 137.7, and 142.2.



189 **197**

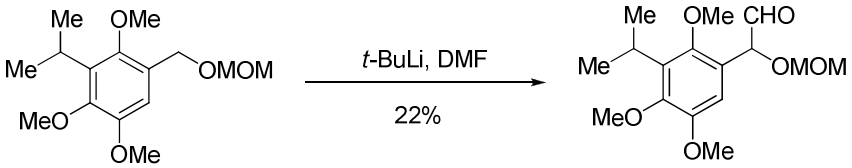
(3-Isopropyl-2,4,5-trimethoxyphenyl)methanol (197). To a stirred solution containing 2.6 g (10.9 mmol) of aldehyde **189** in 44 mL of MeOH at 0 ºC was added 0.5 g (13 mmol) of $NaBH_4$ portionwise. The mixture was stirred at 0 ºC for 1 h. After this time, H_2O was added to the reaction mixture and the solvent was removed under reduced pressure. The aqueous residue was extracted with EtOAc and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography using a 25% EtOAc/hexane mixture as the eluent to provide 2.4 g (90%) of the titled compound **196** as a yellow oil: IR (neat) 3416, 2955, 1598, 1480, 1224, 1107, and 1040 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.35 (d, 6H, *J* = 7.1 Hz), 2.13 (t, 1H, *J* = 5.7 Hz), 3.40 (sept, 1H, *J* = 7.1 Hz), 3.71 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.68 (d, 2H, *J* = 5.7 Hz), and 6.79 (s, 1H); ^{13}C-NMR (100 MHz,$CDCl_3$) δ 21.8, 25.8, 55.7, 60.6, 61.0, 62.3, 110.0, 128.7, 135.0, 148.2, 149.3, and 149.6.



196 **202**

3-Isopropyl-1,2,4-trimethoxy-5-methoxymethoxymethylbenzene (202). To a stirred solution of 1.57 g (6.5 mmol) of arene **197** in 26 mL of CH_2Cl_2 was added

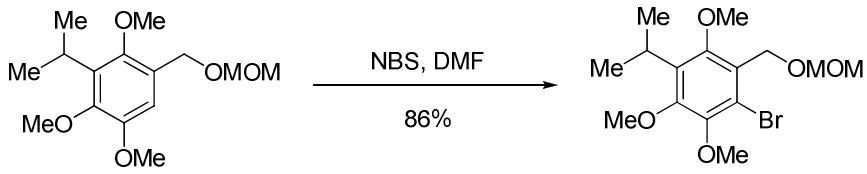
1.37 mL (7.84 mmol) of diisopropylethyl amine (Hünigs base) followed by the slow addition of 0.6 mL (7.84 mmol) of chloromethyl methyl ether (MOMCl) at 0ºC. The reaction mixture was allowed to warm to rt and was stirred for 15 h. The solution was quenched by the addition of a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash silica gel column chromatography using 20% EtOAc/hexane mixture as the eluent afforded 1.65 g (89%) of the titled compound **202** as a yellow oil: IR (neat) 2991, 2995, 2873, 1593, and 1486 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.35 (d, 6H, *J* = 7.0 Hz), 3.40 (sept, 1H, *J* = 7.0 Hz), 3.80 (s, 3H), 3.82 (d, 6H), 4.62 (s, 2H), and 6.80 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.8, 26.0, 41.8, 55.8, 60.7, 62.9, 111.5, 125.4, 135.3, 149.5, 149.8, and 150.1.



202 **203**

(3-Isopropyl-2,4,5-trimethoxy-phenyl)-methoxymethoxyacetaldehyde (203). To a stirred solution containing 0.06 g (0.21 mmol) of arene **202** in 1 mL of THF at -78 ºC was added 0.26 mL (0.44 mmol) of *t*-BuLi (1.7 M solution in THF) dropwise. The reaction mixture was stirred for 1 h and then treated with 0.02 mL (0.25 mmol) of DMF followed by additional stirring for 1 h at -78 ºC. The solution was quenched with a saturated aqueous solution of NH_4Cl. The resulting mixture

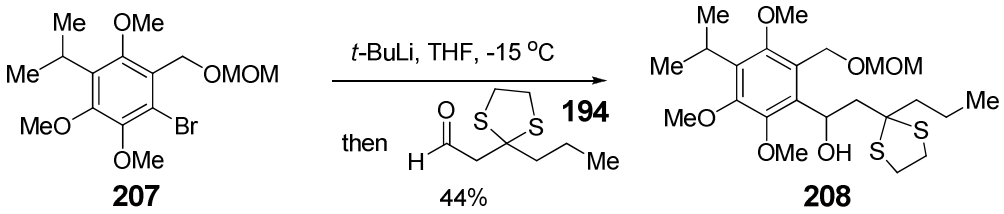
was allowed to warm to rt and was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography using a 20% EtOAc/hexane mixture as the eluent to afford 0.015 g (22%) of the titled compound **203** as a yellow oil together with 0.036 g (60%) of recovered starting material **202**; IR (neat) 2950, 1731, 1685, 1593, 1481, and 1040 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (d, 3H, *J* = 7.0 Hz), 1.33 (d, 3H, *J* = 7.0 Hz), 3.35 (sept, 1H, *J* = 7.0 Hz), 3.40 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 4.78 (s, 2H), 5.30 (s, 1H), 5.30 (s, 1H), 6.72 (s, 1H), and 9.62 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ21.7, 21.8, 26.1, 55.9, 56.0, 60.6, 63.0, 78.5, 94.9, 110.3, 122.1, 135.6, 150.0, 150.2, 150.3, and 197.5.



202 **207**

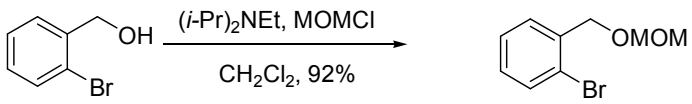
1-Bromo-4-isopropyl-2,3,5-trimethoxy-6-methoxymethoxymethylbenzene (207). To a stirred solution of 1.5 g (5.28 mmol) of arene **202** in 20 mL of DMF was added 1.88 g (10.6 mmol) of *N*-bromosuccinimide (NBS) at rt. After stirring for 2 h, The reaction mixture was quenched by the addition of a saturated aqueous $NaHCO_3$ solution and extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography using a 25% EtOAc/hexane mixture as the eluent to furnish 1.65

g (86%) of the titled compound **207** as a yellow oil: IR (neat) 2934, 1562, 1450, 1398, 1122, and 1035 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.32 (d, 6H, *J* = 7.0 Hz), 3.44 (sept, 1H, *J* = 7.0 Hz), 3.48 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 3.90 (s, 3H), 4.72 (s, 2H), and 4.80 (s, 2H) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.7, 26.0, 55.8, 60.1, 60.6, 63.5, 65.0, 98.9, 119.3, 126.3, 135.0, 147.7, 154.1, and 154.2.



1-(4-Isopropyl-2,3,5-trimethoxy-6-methoxymethoxymethyl-phenyl)-2-(2-propyl-[1,3]dithiolan-2-yl)ethanol (208). To a stirred solution containing 0.08 g (0.22 mmol) of arene **207** in 0.5 mL of THF at -15 ºC was added 0.27 mL (0.46 mmol) of *t*-BuLi (1.7 M solution in THF) dropwise. After the mixture was stirred for 1 h, a solution of 0.046 g (0.24 mmol) of aldehyde **194** in 0.5 mL of THF at -15 °C was transferred *via* cannula to the above reaction mixture. The resulting solution was stirred for an additional 1 h at -15 ºC and then quenched with a saturated aqueous NH_4Cl solution. The mixture was allowed to warm to rt and was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography using a 25% EtOAc/hexane mixture as the eluent to yield 0.046 g (44%) of the titled compound **208** as a yellow oil: IR (neat) 2991, 2995, 2873, 1593, and 1486 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H, *J* = 7.2 Hz), 1.30 (d, 3H, *J* = 6.8 Hz), 1.31 (d, 1H, *J* = 6.8

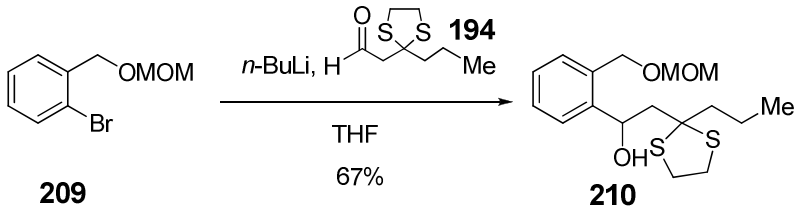
Hz), 1.50 – 1.70 (m, 2H), 2.00 – 2.15 (m, 2H), 2.29 (dd, 1H, *J* = 15.2 and 2.8 Hz), 2.70 (dd, 1H, *J* = 15.2 and 9.6 Hz), 3.26 – 3.34 (m, 4H), 3.38 (sept, 1H, *J* = 6.8 Hz), 3.44 (s, 3H), 3.70 (s, 3H), 3.82 (s, 3H), 3.90 (s, 3H), 4.63 (d, 1H, *J* = 10.4 Hz), 4.74 (dd, 2H, *J* = 10.8 and 6.4 Hz), 4.77 (d, 1H, *J* = 10.4 Hz), 5.30 (brd, 1H, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz,$CDCl_3$) δ 14.2, 20.3, 21.9, 22.0, 26.0, 39.0, 39.6, 46.1, 49.8, 55.8, 59.9, 60.3, 61.5, 63.2, 69.3, 70.9, 96.6, 123.3, 134.6, 136.1, 148.6, 153.2, and 153.3.



199 **209**

1-Bromo-2-methoxymethoxymethyl-benzene (209).[157] To a stirred solution of 3.0 g (16.0 mmol) of arene **199** in 64 mL of CH_2Cl_2 was added 3.4 mL (19.2 mmol) of diisopropylethyl amine (Hünigs base) followed by the slow addition of 1.46 mL (19.2 mmol) of chloromethyl methyl ether (MOMCl) at 0 ºC. The reaction mixture was allowed to warm to rt and was stirred for 15 h. The mixture was quenched by the addition of a saturated aqueous NH_4Cl solution and was extracted with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash silica gel column chromatography using 20% EtOAc/hexane mixture as the eluent afforded 3.4 g (92%) of the titled compound **209** as a yellow oil: IR (thin film) 2940, 2887, 1444, 1157, 1649, and 751 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.42 (s, 3H), 4.62 (s, 2H), 4.78 (s, 2H), 7.15 (td, 1H, *J* = 7.6 and 1.6 Hz), 7.31 (td, 1H, *J* = 7.6 and

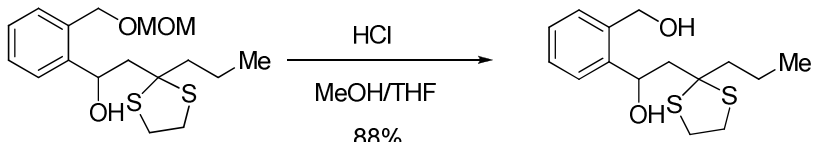
0.8 Hz), 7.48 (brd, 1H, *J* = 7.6 Hz), and 7.54 (dd, 1H, *J* = 7.6 and 1.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 55.5, 68.8, 96.1, 122.9, 127.4, 129.0, 129.3, 132.6, and 137.3.



209 **210**

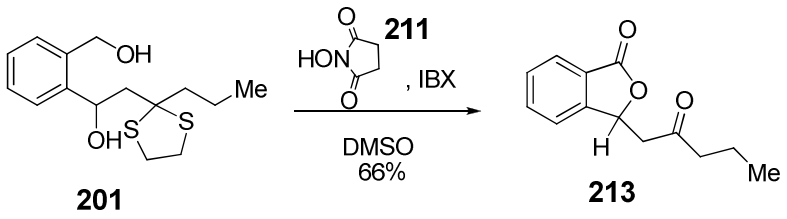
1-(2-Methoxymethoxymethyl-phenyl)-2-(2-propyl-[1,3]dithiolan-2-yl)-ethanol (210). To a stirred solution containing 0.1 g (0.43 mmol) of arene **209** in 1.7 mL of THF at -78 ºC was added 0.18 mL (0.45 mmol) of *n*-BuLi (2.5 M solution in THF) dropwise. The reaction mixture was stirred for 1 h. and then a solution of 0.1 g (0.52 mmol) of aldehyde **194** in 0.5 mL of THF at -78 ºC was transferred via cannula to the above reaction mixture. The resulting solution was stirred for an additional 1 h at -78 ºC and then quenched with a saturated aqueous NH_4Cl solution. The mixture was allowed to warm to rt and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography using a 20% EtOAc/hexane mixture as the eluent to yield 0.10 g (67%) of the titled compound **209** as a white solid: mp 46 – 48 ºC; IR (thin film) 3442, 2960, 1721, 1312, 1125, and 600 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.6 Hz), 1.45 – 1.60 (m, 2H), 1.92 – 1.99 (m, 2H), 2.18 (dd, 1H, *J* = 15.2 and 1.6 Hz), 2.31 (dd, 1H, *J* = 15.2 and 9.2 Hz), 3.30

– 3.42 (m, 4H), 3.40 (s, 3H), 4.02 (brs, 1H), 4.62 (d, 1H, *J* = 11.6 Hz), 4.70 (q, 2H, *J* = 6.8 Hz), 4.74 (d, 1H, *J* = 11.6 Hz), 5.45 (d, 1H, *J* = 9.2 Hz), 1.21 – 7.22 (m, 1H), 7.30 – 7.36 (m, 2H), and 7.56 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.1, 19.8, 39.8, 40.0, 48.4, 49.8, 55.4, 66.8, 68.6, 70.6, 95.7, 126.3, 127.2, 128.4, 129.5, 133.5, and 143.3.

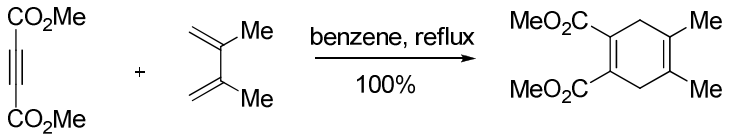


210 **201**

1-(2-Hydroxymethyl-phenyl)-2-(2-propyl-[1,3]dithiolan-2-yl)-ethanol (201). To a solution containing 0.10 g (0.29 mmol) of arene **210** in a 1:1 mixture of MeOH and THF at 0 ºC was added 0 7 mL of an aqueous 4 M HCl solution dropwise. The solution was stirred at 0 ºC for 3 h and then diluted with H_2O. The organic solvent was then removed under reduced pressure. The aqueous residue was extracted with EtOAc and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash silica gel column chromatography using 20% EtOAc/hexane mixture as the eluent gave 0.77 g (88%) of the titled compound **201** as a pale yellow oil.

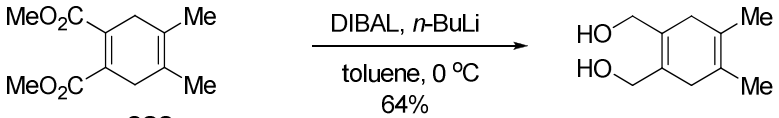


3-(2-Oxo-pentyl)-3H-isobenzofuran-1-one (213). To a stirred solution containing 0.29 g (1.02 mmol) of *o*-iodoxybenzoic acid (IBX) in 1 mL of DMSO at rt was added 0.08 g (0.27 mmol) of arene **201**. After stirring for 10 min, a 0.15 g (1.34 mmol) sample of *N*-hydroxysuccinimide was slowly added. The mixture was stirred at rt overnight and then quenched with an 50% aqueous $NaHCO_3$ solution. The reaction mixture was stirred for an additional 5 min and extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash silica gel column chromatography using 20% EtOAc/hexane mixture as the eluent afforded 0.038 g (66%) of the titled compound **213** as a pale yellow oil: IR (thin film) 2930, 1919, 1757, 1706, 1475, 1286, and 1066 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* = 7.6 Hz), 1.64 (hex, 2H, *J* = 7.6 Hz), 2.40 – 2.56 (m, 2H), 2.85 (dd, 1H, *J* = 17.2 and 6.8 Hz), 3.10 (dd, 1H, *J* = 17.2 and 6.8 Hz), 5.95 (t, 1H, *J* = 6.8 Hz), 7.45 (d, 1H, *J* = 7.6 Hz), 7.53 (t, 1H, *J* = 7.6 Hz), 7.66 (td, 1H, *J* = 7.6 and 0.8 Hz), 7.89 (d, 1H, *J* = 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6, 17.0, 29.7, 45.5, 47.2, 122.3, 125.8, 128.0, 129.4, 134.3, 149.5, 170.1, and 206.9.



286 **285** **288a**

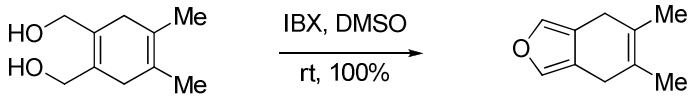
4,5-Dimethylcyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester (288a). [158] To a solution containing 2.6 mL (21 mmol) of dimethyl acetylenedicarboxylate (DMAD) (**285**) in 12 mL of benzene in a sealed tube was added 2.6 mL (23 mmol) of 2,3-dimethylbutadiene (**286**) in one portion. The tube was stirred at 80 ^{o}C for 2 days. After this time, the solvent was removed under reduced pressure to provide 4.7 g (100%) of the titled compound **288a** as an off-white solid: mp 70 – 72 ^{o}C; IR (thin film) 2950, 2863, 1716, 1660, 1434, and 1265 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 6H), 2.90 (s, 4H), and 3.75 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.9, 34.1, 52.2, 121.5, 132.7, and 168.4.



288a **289a**

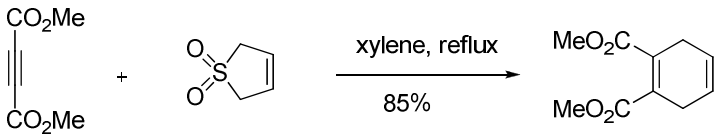
(2-Hydroxymethyl-4,5-dimethylcyclohexa-1,4-dienyl) methanol (289a). To a vigorously stirred solution of 59 mL (59 mmol) of DIBAL (1.0 M solution in hexane) at 0 ^{o}C was added 23 mL (59 mmol) of *n*-BuLi (2.5 M solution in hexane) using a syringe pump over the course of 30 min. The solution was then stirred for 30 min at 0 ^{o}C and a 3.3 g (14.6 mmol) solution of ester **288a** in toluene (59 mL) was slowly added *via* cannula. The reaction mixture was allowed to stir at 0 ^{o}C for 2 h and was slowly quenched with a saturated aqueous $NaHSO_4$ solution and

extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 1.58 g (64%) of the titled compound **289a**[159] as a white solid: mp 124 – 125 ^{o}C; IR (neat) 3268, 2909, 2868, 2797, 1465, and 1414 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 6H), 2.75 (s, 4H), and 4.75 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.0, 36.7, 62.1, 122.9, and 132.5.



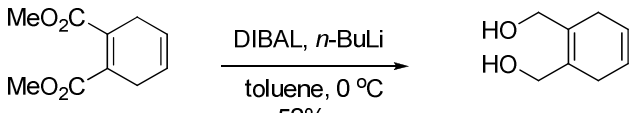
289a **290a**

5,6-Dimethyl-4,7-dihydro-isobenzofuran (290a). To a solution containing 0.08 g (0.59 mmol) of alcohol **289a** in 2.3 mL of DMSO was added 0.18 g (0.65 mmol) of 2-iodoxybenzoic acid (IBX) at rt. The reaction mixture was stirred for 90 min. and then quenched with H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to provide 0.09 g (100%) of the titled compound **290a** as an off-white solid; mp 50 – 52 ^{o}C; IR (thin film) 2919, 2832, 1439, 1260, and 1034 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.76 (s, 6H), 3.08 (s, 4H), and 7.20 (s, H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.4, 26.8, 120.0, 112.9, and 136.4.



285 **287** **288b**

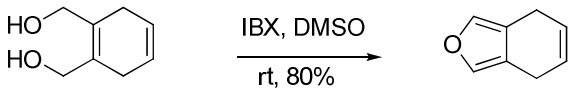
Cyclohexa-1,4-diene-1,2-dicarboxylic acid dimethyl ester (288b). To a 2.2 mL (18 mmol) sample of dimethyl acetylenedicarboxylate (DMAD) in 4 mL of xylene was added 2.1 g (18 mmol) of butadiene sulfone (**287**). The solution was heated at reflux for 8 h using a double cooling system equipped with a regular condenser using ice cooled water and a dewar condenser containing dry ice/acetone on top of the regular condenser. After this time, the solvent was removed under reduced pressure to provide 4.7 g (85%) of the titled compound **288b**[160] as a clear oil: IR (neat) 2953, 1721, 1434, 1255, and 1065 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.00 (s, 4H), 3.68 (s, 6H), and 5.70 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.3, 52.1, 122.4, 132.4, and 168.4.



288b **289b**

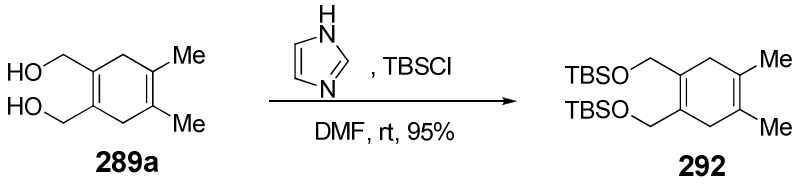
(2-Hydroxymethylcyclohexa-1,4-dienyl) methanol (289b). To a vigorously stirred solution of 25 mL (24 mmol) of DIBAL (1.0 M solution in hexane) at 0 °C was slowly added 9.5 mL (24 mmol) of *n*-BuLi (2.5 M solution in hexane) using a syringe pump over the course of 30 min. The solution was then stirred for 30 min at 0 °C followed by the slow addition of a sample of 1.2 g (6.0 mmol) of ester **288b** in 24 mL of toluene *via* cannula. The reaction mixture was allowed to stir at

0 ^{o}C for 2 h and was slowly quenched with a saturated aqueous $NaHSO_4$ solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.4 g (52%) of the titled compound **289b** as a white solid: mp 44 – 45 ^{o}C; IR (thin film) 3365, 3021, 2812, 1644, 1429, and 984 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.81 (s, 4H), 3.23 (s, 2H), 4.11 (s, 4H), and 5.70 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.5, 61.9, 124.0, and 131.9.

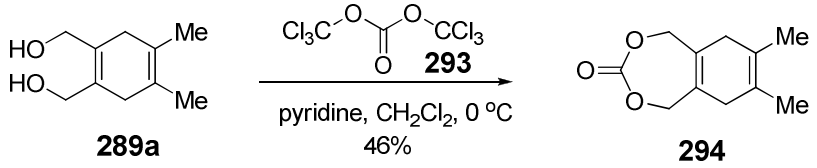


289b **290b**

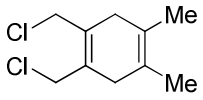
4,7-Dihydro-isobenzofuran (290b). To a solution containing 0.21 g (1.5 mmol) of diol **289b** in 3 mL of DMSO was added 0.42 g (1.5 mmol) of 2-iodoxybenzoic acid (IBX) at rt. The reaction mixture was stirred at rt for 90 min and was then quenched with H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to provide 0.18 g (80%) of the titled compound **290b**[161] as an off-white solid; IR (thin film) 3032, 2889, 2832, 1644, 1429, and 1373 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.10 (s, 4H), 5.85 (s, 2H), and 7.22 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.3, 118.7, 123.9, and 137.2.



1,2-Bis-(*tert*-butyldimethylsilanyloxymethyl)-4,5-dimethylcyclohexa-1,4-diene (292). To a solution containing 0.23 g (1.33 mmol) of diol **289a** in 3 mL of DMF was added 0.46 g (6.7 mmol) of imidazole and a crystal of 4-dimethylaminopyridine (DMAP). The resulting mixture was cooled to 0 °C for 15 min and 0.48 g (3.2 mmol) of *tert*-butyldimethylsilyl chloride (TBSCl) was added in one portion. The reaction mixture was allowed to warm to rt and was stirred overnight. After this time, the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.53 g (95%) of the titled compound **292** as a white crystal: mp 33 – 36 ^{o}C; IR (thin film) 2955, 2524, 2853, 1470, and 1255 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 12H), 0.90 (s, 18H), 1.64 (s, 6H), 2.69 (s, 4H), and 4.19 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -5.3, 18.1, 18.4, 26.0, 35.6, 61.9, 122.8, and 130.1.

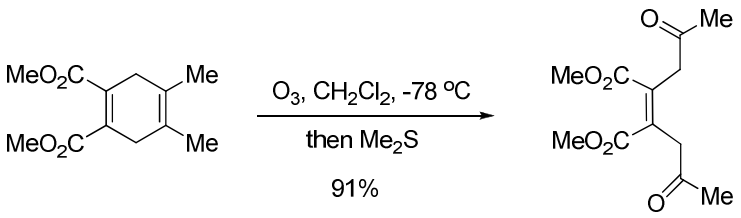


2,3-Dimethyl-5,9-dihydro-6,8-dioxa-benzocyclohepten-7-one (294). To a solution containing 0.15 g (0.89 mmol) of diol **289** in 3.6 mL of CH_2Cl_2 at -78 ^oC was added 0.13 g (0.45 mmol) of bis(trichloromethyl) carbonate (triphosgene) followed by 0.43 mL (5.4 mmol) of pyridine. The reaction mixture was then stirred at -78 ^oC for 5 h, quenched with a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.08 g (46%) of the titled compound **294** as a white solid; mp 67 – 68 ^oC IR (thin film) 3001, 2914, 2863, 2812, 1767, and 1455 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 6H), 2.50 (s, 4H), and 4.57 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.0, 34.9, 70.2, 122.2, 126.5, and 155.0.



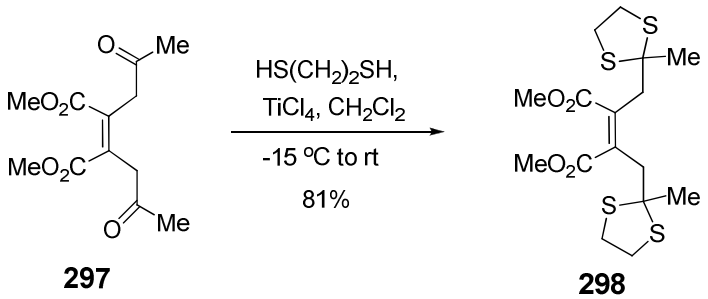
295

1,2-Bis(chloromethyl)-4,5-dimethyl-cyclohexa-1,4-diene (295) was also isolated as a white solid from the above reaction in 10% yield; mp 69 – 71 ^oC; IR (thin film) 2981, 2914, 2863, 2811, 1414, and 1255 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 6H), 2.78 (s, 4H), and 4.12 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 17.9, 36.2, 42.8, 122.3, and 131.2.



288a **297**

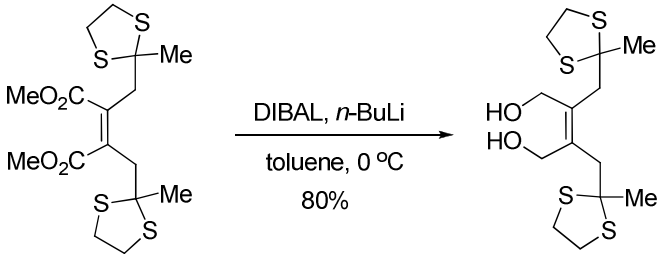
2,3-Bis(2-oxopropyl)but-2-enedioic acid dimethyl ester (297). To a stirred solution containing 0.5 g (2.2 mmol) of alkene **288a** in 45 mL of CH_2Cl_2 was bubbled in ozone gas at -78 ^oC. The reaction was monitored by TLC and following completion; the reaction was quenched with dimethylsufide at -78 ^oC and allowed to warm up to rt. The mixture was then diluted with EtOAc and extracted with H_2O. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure to provide 0.52 g (91%) of the titled compound **15** as a pale yellow solid: mp 52 – 60 ^oC; IR (thin film) 2945, 2919, 1721, 1629, 1429, and 1265 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 6H), 3.23 (s, 4H), and 3.75 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.7, 44.7, 52.6, 134.0, 167.7, and 203.1.



297 **298**

2,3-Bis(2-methyl-[1,3]dithiolan-2-ylmethyl)but-2-enedioic acid dimethyl ester (298). To a solution containing 0.2 g (0.78 mmol) of ketone **297** and 0.16

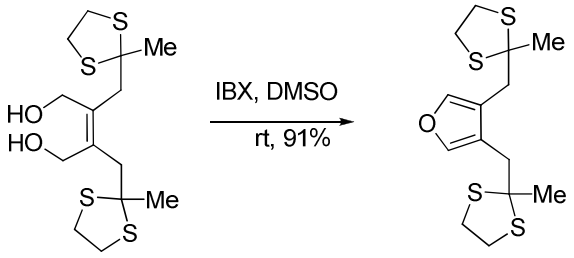
mL (1.95 mmol) of ethane dithiol in 0.4 mL of CH_2Cl_2 at -15 ^oC was added 0.01 mL (0.08 mmol) of $TiCl_4$. The reaction mixture was allowed to warm up to rt and was stirred for 2 h. The resulting solution was poured into H_2O and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.26 g (81%) of the titled compound **298** as a yellow oil: IR (thin film) 2950, 2914, 1726, 1624, 1537, and 1429 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.70 (s, 6H), 3.12 (s, 4H), 3.22 (s, 8H), and 3.61 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 32.0, 40.2, 45.0, 52.0, 65.4, 137.2, and 169.5.



298 **299**

2,3-Bis(2-methyl-[1,3]dithiolan-2-ylmethyl)but-2-ene-1,4-diol (299). To a vigorously stirred solution containing 57 mL (58 mmol) of DIBAL (1.0 M solution in hexane) at 0 ^oC was slowly added 23 mL (58 mmol) of *n*-BuLi (2.5 M solution in hexane) using a syringe pump over the course of 30 min. The solution was then stirred for 30 min at 0 ^oC, followed by the slow addition of a solution of 5.2 g (13 mmol) of ester **298** in 51 mL of toluene *via* cannula. The reaction mixture was allowed to stir at 0 ^oC for 2 h and was slowly quenched with a saturated

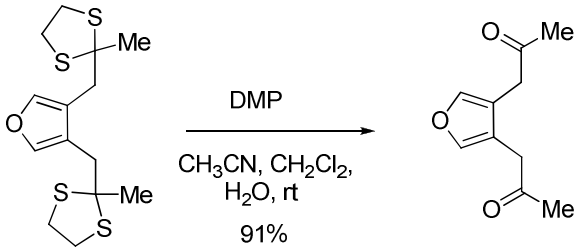
aqueous $NaHSO_4$ solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduce pressure. The crude residue was purified by flash silica gel column chromatography using 50% EtOAc/hexane mixture as the eluent to provide 3.6 g (80%) of the titled compound **299** as a yellow solid: mp 63 – 68 ^oC; IR (thin film) 3380, 2970, 2914, 1629, and 1450 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.73 (s, 6H), 2.98 (s, 4H), 3.25-3.36 (m, 8H), 3.50 (brs, 2H), and 4.30 (s, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 33.0, 39.6, 46.5, 63.1, 66.6, and 140.4.



299 **300**

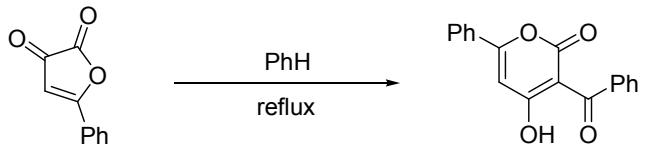
3,4-Bis(2-methyl-[1,3]dithiolan-2-ylmethyl)furan (300). To a solution containing 0.29 g (0.80 mmol) of alcohol **299** in 1.6 mL of DMSO was added 0.25 g (0.90 mmol) of 2-iodoxybenzoic acid (IBX) in one portion. The reaction mixture was stirred at rt for 90 min. and was quenched with H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.25 g (91%) of the titled compound **19** as a pale yellow solid: mp 74 – 46 ^oC; IR (thin film) 3129, 2950, 2914, 1531, and 1440 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 6H),

3.10 (s, 4H), 3.20-3.37 (m, 8H), and 7.45 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 31.8, 39.8, 40.1, 66.9, 121.8, and 140.8.



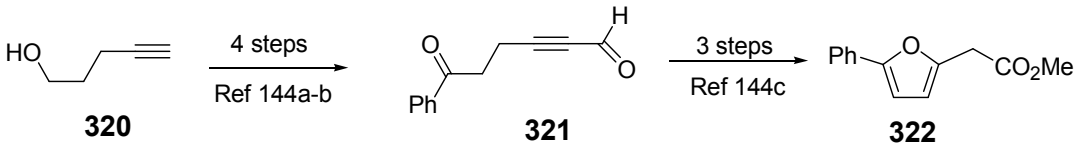
300 **243**

1-[4-(2-Oxo-propyl)-furan-3-yl]propan-2-one (243). To a solution containing 0.04 g (0.11 mmol) of furan **300** in a mixture of 0.9 mL of CH_3CN and 0.1 mL of H_2O was added a solution of 0.74 mL (0.22 mmol) of Dess-Martin periodinane (0.3 M solution in CH_2Cl_2) in one portion via syringe. The reaction mixture was allowed to stir at rt for 1 h. After this time, the reaction mixture was quenched with an aqueous 50% $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography to provide 0.01 g (91%) of the titled compound **243** as a white solid; IR (thin film) 2914, 1706, 1420, and 1358 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 6H), 3.45 (s, 4H), and 7.35 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.3, 38.8, 117.8, 141.4, and 205.7.



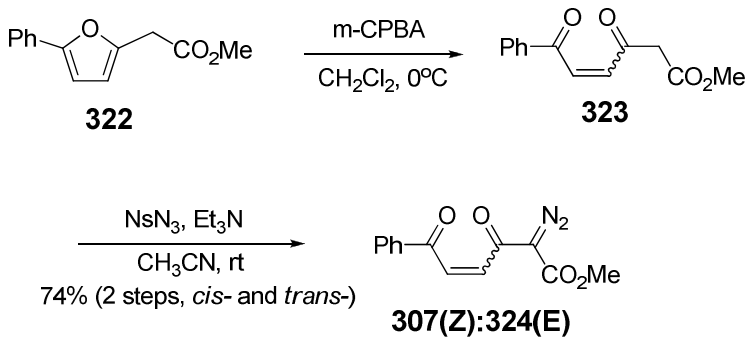
311 **314**

3-Benzoyl-2-hydroxy-6-phenyl-pyran-4-one (314). A solution of 0.1 g (0.57 mmol) of 5-phenyl-furan-2,3-dione (**311**)[162] in 2.0 mL of benzene was stirred in sealed tube at 100 ^{o}C. The reaction mixture was monitored by TLC and upon completion of the reaction the solution was cooled to rt and the solvent was removed under reduced pressure The crude residue was purified by flash silica gel column chromatography to provide 0.08 g (80%) of the titled compound **314**[163] as a yellow solid: IR (thin film) 3099, 1739, 1626, 1545, and 1060 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.66 (s, 1H), 7.42 – 5.59 (m, 6H), 7.66 – 7.22 (m, 2H), and 7.88 – 7.94 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 99.2, 99.7, 126.8, 128.0, 128.4, 129.3, 130.3, 132.5, 132.9, 138.2, 160.3, 166.2, 181.1, and 200.5.



320 **321** **322**

(5-Phenyl-furan-2-yl)-acetic acid methyl ester (322) was prepared by a known literature procedure.[144] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 3.86 (s, 2H), 6.32 (d, 1H, *J* = 2.4 Hz), 6.60 (d, 1H, *J* = 2.4 Hz), 7.24 (t, 1H, *J* = 4.8 Hz), 7.37 (t, 2H, *J* = 4.8 Hz), 6.64 (d, 2H, *J* = 4.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 34.1, 52.3, 102.0, 105.9, 110.2, 123.6, 127.2, 128.6, 130.7, 147.2, 153.5, 169.8.



322 **323** **307(Z):324(E)**

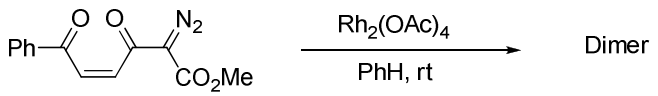
2-Diazo-3,6-dioxo-6-phenyl-hex-4-enoic acid methyl ester (307(Z)/324(E)). To a solution containing 2.4 g (11 mmol) of the furan **322**[3] in 44 mL of CH_2Cl_2 was added a 2.7 g (15 mmol) of *m*-chloroperbenzoic acid (*m*-CPBA) at 0 ^oC. The reaction mixture was stirred for 3 h at 0 ^oC and was then quenched with a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to give the unsaturated dione **323** which used in the next step without purification.

A sample of the unsaturated dione **323** was dissolved in 44 mL of CH_3CN and was cooled to 0 ^oC. To this solution was added 3.0 g (13 mmol) of *p*-nitrobenzenesulfonyl azide (NsN_3) followed by 1.6 mL (11 mmol) of Et_3N. The reaction mixture was stirred at 0 ^oC for 3 h and then the solvent was removed under reduced pressure and the crude residue was purified by flash silica gel column chromatography to provide 0.31 g (11%) of the *cis* - diazo isomer as a yellow solid and 1.80 g (63%) of the *trans*-isomer as a yellow solid.

cis-isomer **307**: mp 101 – 102 ^oC; IR(neat) 3032, 2950, 2141, 1726, and 1393 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.85 (d,1H, *J* = 11.6 Hz), 7.37

(d, 1H, *J* = 11.6 Hz), 7.43 – 7.48 (m, 2H), 7.56 (tt, 2H, *J* = 7.2 and 1.2 Hz), and 7.90 – 7.96 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 52.3, 128.4, 128.6, 130.1, 133.4, 135.5, 139.0, 161.1, 181.4, and 194.4.

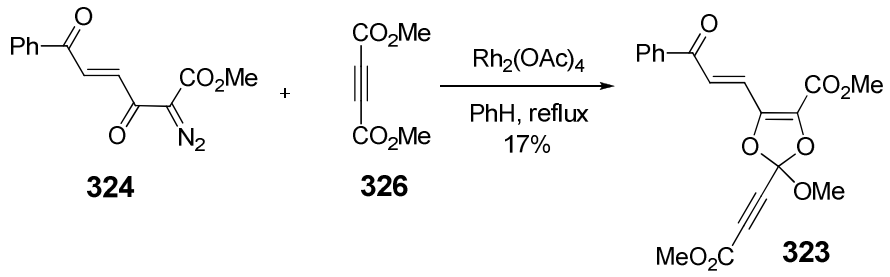
trans-isomer **324**: mp 82 – 84 ^{o}C; IR (neat) 2960, 2146, 1706, 1629, and 1347 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.46-7.53 (m, 2H), 7.61 (t, 1H, *J* = 7.2 Hz), 7.88 (d, 1H, *J* = 15.6 Hz), and 8.08 (d, 1H, *J* = 15.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 52.6, 128.2, 128.9, 133.7, 134.2, 134.8, 136.8, 161.0, 181.1, and 190.0.



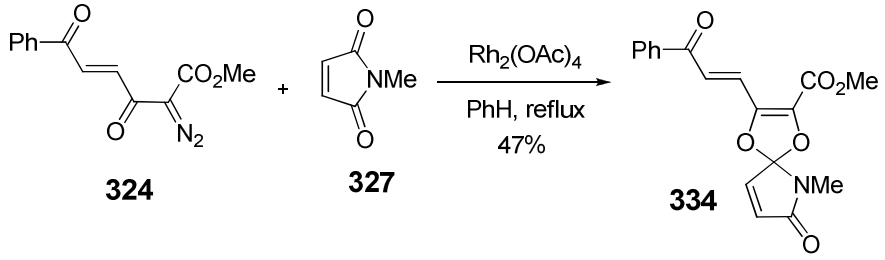
307 **325**

Formation of Dimer 325 To a solution containing 0.1 g (0.38 mmol) of the *cis*-unsaturated diazo-dione **307** in 1.6 mL of benzene was added 0.01 g (0.02 mmol) of $Rh_2(OAc)_4$. The reaction mixture was stirred for 1 h and the solvent was removed under reduced pressure. The crude product was purified by flash silica gel column chromatography to provide 0.02 g (42 %) of dimer **325** as a thick oil: IR (neat) 2955, 2930, 2843, 1767, 1731, and 1296 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.82 (dd, 1H, *J* = 16.0 and 0.8 Hz), 2.95 (dd, 1H, *J* = 16.0 and 4.4 Hz), 3.35 (d, 1H, *J* = 7.2 Hz), 3.67 (s, 3H), 3.80 (s, 3H), 5.65 (d, 1H, *J* = 7.2 Hz), 5.66 (dd, 1H, *J* = 4.4 and 0.8 Hz), 7.34 – 7.41 (m,6H), 7.56 – 7.60 (m, 2H), and 7.63 – 7.66 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 38.8, 45.1, 53.0, 53.1, 73.5, 86.3,

87.6, 89.2, 93.4, 99.1, 125.1, 126.8, 128.3, 128.5, 129.1, 129.2, 133.2, 133.3, 153.0, 165.2, 167.3, and 203.0.

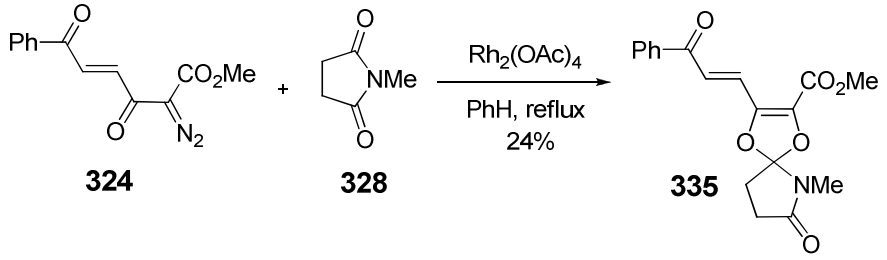


2-Methoxy-2-methoxycarbonylethynyl-5-(3-oxo-3-phenyl-propenyl)[1,3]dioxole-4-carboxylic acid methyl ester (333). To a solution containing 0.05 g (0.19 mmol) of *trans*-diazo-dione **324** in 0.08 mL of benzene was added 0.03 g (0.21 mmol) of dimethyl acetylenedicaboxylate (DMAD). The reaction mixture was heated to reflux and 0.004 g (0.01 mmol) of $Rh_2(OAc)_4$ was rapidly added in one portion. The mixture was stirred for 30 min and the solvent was removed under reduced pressure. The crude product was purified by flash silica gel column chromatography to provide 0.012 g (17%) of the titled compound **333** as a thick yellow oil: IR (neat) 2955, 2920, 2853, 1721, 1629, 1265, and 1081 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.54, (s, 3H), 3.82 (s, 3H), 3.92 (s, 3H), 7.45 (d, 1H, *J* = 15.6 Hz), 7.51 (m, 2H), 7.60 (tt, 1H, *J* = 7.2 and 2.0 Hz), 7.82 (d, 1H, *J* = 15.6 Hz), and 7.99 – 8.03 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.7, 51.3, 52.7, 53.4, 75.3, 76.4, 125.5, 126.0, 128.6, 128.8, 131.3, 133.4, 137.2, 143.3, 152.4, 158.3, and 188.8.



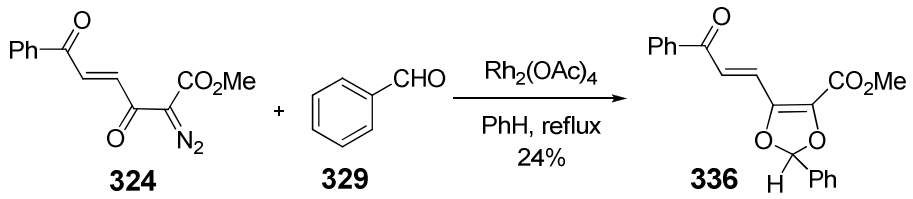
324 **327** **334**

6-Methyl-7-oxo-3-(3-oxo-3-phenyl-propenyl)-1,4-dioxa-6-aza-spiro[4.4]nona-2,8-diene-2-carboxylic acid methyl ester (334). To a solution containing 0.05 g (0.194 mmol) of the *trans*-diazo-dione **324** in 0.8 mL of benzene was added 0.024 g (0.213 mmol) of *N*-methylmaleimide. The reaction mixture was heated to reflux and 0.004 g (0.009 mmol) of $Rh_2(OAc)_4$ was rapidly added in one portion. The mixture was then stirred for 30 min and solvent was removed under reduced pressure. The crude product was purified by flash silica gel column chromatography to provide 0.07 g (47 %) of the titled compound **334** as a yellow solid: IR (thin film) 3098, 2955, 1731, 1624, and 1260 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.85 (s, 3H), 3.92 (s, 3H), 6.32 (d, 1H, *J* = 6.0 Hz), 6.92 (d, 1H, *J* = 6.0 Hz), 7.42 (d, 1H, *J* = 15.6 Hz), 7.50 (t, 2H, *J* = 7.2 Hz), 7.60 (t, 1H, *J* = 7.2 Hz), 7.86 (d, 1H, *J* = 15.6 Hz), and 8.00 (d, 1H, *J* = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.7, 52.6, 120.1, 125.5, 125.6, 128.5, 128.7, 129.6, 132.3, 133.3, 137.1, 139.5, 144.2, 158.5, 167.2, and 188.6.



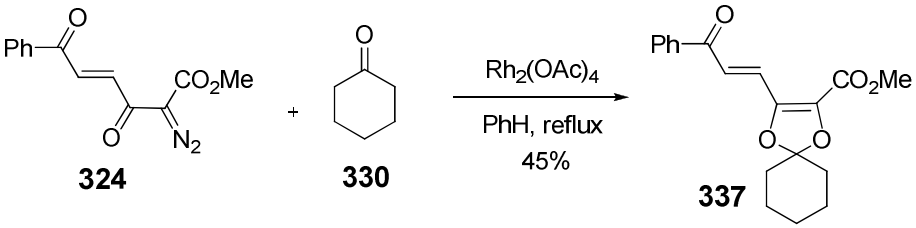
324 **328** **335**

6-Methyl-7-oxo-3-(3-oxo-3-phenyl-propenyl)-1,4-dioxa-6-aza-spiro[4.4]non-2-ene-2-carboxylic acid methyl ester (335). To a solution containing 0.05 g (0.19 mmol) of the *trans*-diazo-dione **324** in 0.8 mL of benzene was added 0.024 g (0.21 mmol) of *N*-methylsuccinimide. The reaction mixture was heated to reflux and 0.004 g (0.01 mmol) of $Rh_2(OAc)_4$ was rapidly added in one portion. The mixture was then stirred for 30 min and solvent was removed under reduced pressure. The crude product was purified by flash silica gel column chromatography to provide 0.015 g (24 %) of the titled compound **335** as a yellow solid: IR (thin film) 3068, 2496, 2853, 1731, 1705, 1629, and 1280 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.55 – 2.70 (m, 4H), 2.78 (s, 3H), 3.90 (s, 3H), 7.32 (d, 1H, *J* = 15.6 Hz), 7.50 (t, 2H, *J* = 7.6 Hz), 7.59 (t, 1H, 7.6 Hz), 7.84 (d, 1H, *J* = 15.6 Hz), and 8.00 (d, 1H, *J* = 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 23.6, 28.6, 31.6, 52.7, 124.2, 125.2, 126.0, 128.5, 128.7, 133.4, 137.3, 143.3, 158.8, 172.2, and 188.8.



324 **329** **336**

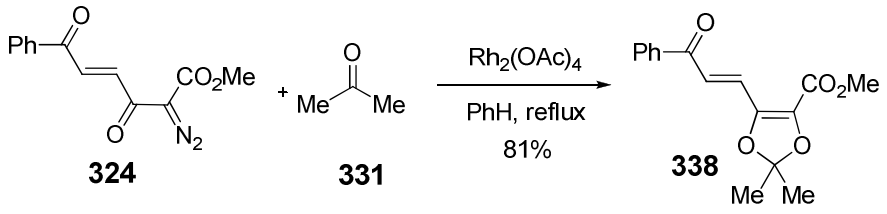
5-(3-Oxo-3-phenyl-propenyl)-2-phenyl-[1,3]dioxole-4-carboxylic acid methyl ester (336). To a solution containing 0.05 g (0.194 mmol) of *trans*-diazo-dione **324** in 0.8 mL of benzene was added 0.023 g (0.213 mmol) of benzaldehyde. The reaction mixture was heated to reflux and 0.004 g (0.004 mmol) of $Rh_2(OAc)_4$ was rapidly added in one portion. The mixture was stirred for 30 min and the solvent was removed under reduced pressure. The crude product was purified by flash silica gel column chromatography to provide 0.017 g (24%) of the titled compound **336** as a pale yellow oil: IR (thin film) 3062, 2955, 2919, 2843, 1721, 1665, and 1614 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 6.92 (s, 1H), and 7.35 – 7.70 (m, 9H), 7.94 (d, 1H, 15.2), and 7.97 – 8.20 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 52.5, 109.2, 125.0, 126.5, 126.9, 128.6, 128.7, 128.8, 129.2, 130.7, 133.2, 135.1, 137.5, 145.0, 159.6, and 189.3.



324 **330** **337**

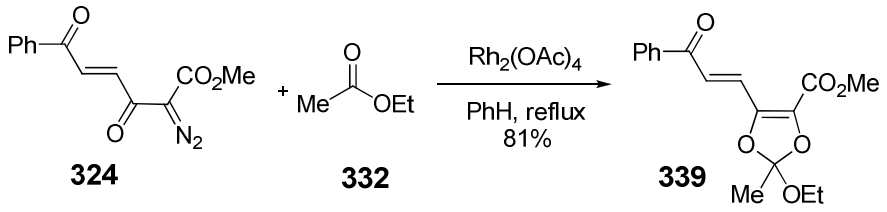
3-(3-Oxo-3-phenyl-propenyl)-1,4-dioxa-spiro[4.5]dec-2-ene-2-carboxylic acid methyl ester (337). To a solution containing 0.05 g (0.194 mmol) of *trans*-diazo-dione **324** in 0.8 mL of benzene was added 0.035 mL (0.341 mmol) of

cyclohexanone. The reaction mixture was heated to reflux and 0.004 g (0.009 mmol) of $Rh_2(OAc)_4$ was rapidly added in one portion. The mixture was stirred for 30 min and solvent was removed under reduced pressure. The crude product was purified by flash silica gel column chromatography to provide 0.046 g (45%) of the titled compound **337** as a clear oil: IR (thin film) 3058, 2940, 2858, 1726, 1614, 1337, and 1260 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.20 - 2.00 (m, 10H), 3.84 (s, 3H), 7.28 (d, 1H, *J* = 15.0 Hz), 7.48 (t, 2H, *J* = 7.2 Hz), 7.57 (t, 1H, *J* = 7.2 Hz), 7.88 (d, 1H, 15.0 Hz), and 7.98 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.8, 24.3, 34.8, 52.3, 117.9, 124.0, 128.0, 128.5, 128.6, 132.7, 133.0, 137.7, 144.0, 160.1, and 189.6.



2,2-Dimethyl-5-(3-oxo-3-phenyl-propenyl)-[1,3]dioxole-4-carboxylic acid methyl ester (338). To a solution containing 0.05 g (0.194 mmol) of *trans*-diazo-dione **324** in 0.8 mL of benzene was added 0.71 mL (0.97 mmol) of acetone. The reaction mixture was heated to reflux and 0.004 g (0.009 mmol) of $Rh_2(OAc)_4$ was rapidly added in one portion. The mixture was then stirred for 30 min and solvent was removed under reduced pressure. The crude product was purified by flash silica gel column chromatography using a 20 % EtOAc/hexane mixture as the eluent to provide 0.045 g (81%) of the titled compound **338** as a yellow solid: mp 93 – 94 ^{o}C;

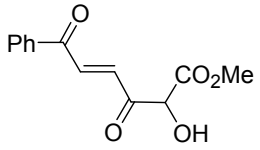
IR (neat) 2991, 2495, 1726, 1660, and 1619 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.70 (s, 6H), 3.90 (s, 3H), 7.30 (d, 1H, *J* = 15.6 Hz), 7.46 – 7.55 (m, 2H), 7.58 (tt, 1H, *J* = 7.6 and 1.2 Hz), 7.89 (d, 1H, *J* = 15.6 Hz), and 7.80 – 8.25 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 25.7, 52.4, 117.1, 124.2, 127.7, 128.5, 128.6, 132.4, 133.0, 137.6, 144.0, 160.0, and 189.4.



324 **332** **339**

2-Ethoxy-2-methyl-5-(3-oxo-3-phenyl-propenyl)-[1,3]dioxole-4-carboxylic acid methyl ester (339). To a solution containing 0.05 g (0.194 mmol) of *trans*-diazo-dione **7b** in 0.8 mL of benzene was added 0.08 mL (0.968 mmol) of EtOAc. The reaction mixture was heated to reflux and 0.004 g (0.004 mmol) of $Rh_2(OAc)_4$ was rapidly added in one portion. The mixture was stirred for 30 min and the solvent was removed under reduced pressure. The crude product was purified by flash silica gel column chromatography to provide 0.050 g (81%) of the titled compound **339** as a yellow solid: IR (neat) 2991, 2439, 1705, 1624, and 1327 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.23 (t, 3H, *J* = 7.6 Hz), 1.81 (s, 3H); 3.53 – 3.68 (m, 2H), 3.90 (s, 3H), 7.39 (d, 1H, *J* = 15.6 Hz), 7.49 (t, 2H, *J* = 7.6 Hz), 7.56 – 7.61 (tt, 1H, *J* = 7.6 and 1.2 Hz), 7.85 (d, 1H, *J* = 15.6 Hz), and 7.98 – 8.30 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$)

δ 14.7, 24.5, 52.4, 58.2, 124.6, 126.1, 126.6, 128.5, 128.7, 132.0, 133.2, 137.5, 143.5, 159.2, and 189.1.



340

2-Hydroxy-3,6-dioxo-6-phenyl-hex-4-enoic acid methyl ester (340). After standing at rt for 5 d, compound **339** was transformed into a new white solid: IR (thin film) 3431, 1752, 1710, 1659, and 1285cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.98 (brs, 2H), 7.30 (d, 1H, *J* = 15.6 Hz), 7.50 – 7.56 (m, 2H), 7.65 (tt, 1H, *J* = 7.2 and 1.6 Hz), 7.98 – 8.20 (m, 2H), and 8.08 (d, 1H, *J* = 15.6 Hz) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 54.2, 92.3, 128.9, 129.0, 131.1, 134.3, 136.3, 137.7, 169.0, 188.9, and 191.6.

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