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ZhongBo Fei

# I. Synthesis of Altromycin and Kidamycin Aglycones from a Common Intermediate

# II. Studies towards the Total Synthesis of Kidamycin

By

ZhongBo Fei
M.S., East China University of Science and Technology, 2000

Advisor: Frank E. McDonald, Ph.D.

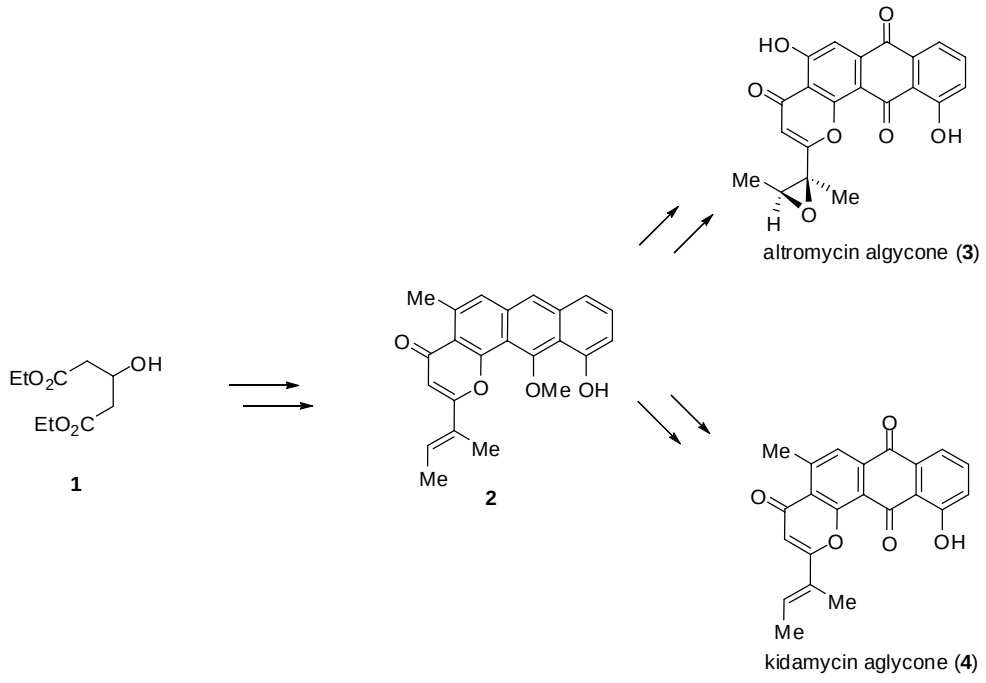
An Abstract of
A dissertation submitted to the Faculty of the Graduate
School of Emory University in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

Department of Chemistry
**2007**

# Abstracts

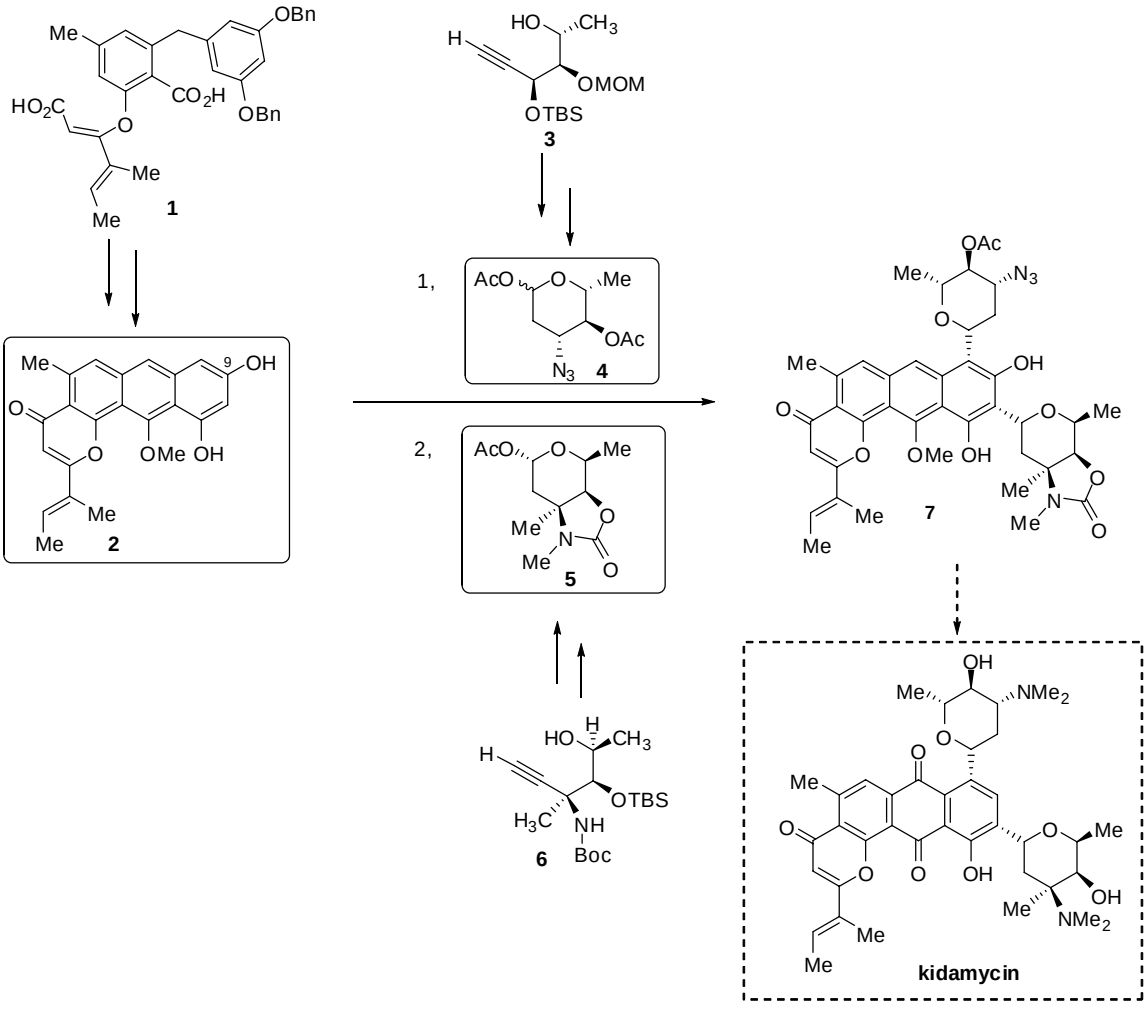
*Chapter1. Synthesis of Altromycin and Kidamycin Aglycones from a Common Intermediate*

The anthrapyran structures **3** and **4**, respectively corresponding to the aglycones of antitumor antibiotic natural products altromycin and kidamycin, have been efficiently synthesized from a common intermediate **2**. A series of Claisen condensations and aromatizations from hydroxyl glutarate **1** affords the anthracene section of **2**, and an intramolecular Friedel-Crafts reaction annulates the pyrone ring. The functional groups of **2** can be manipulated for enantioselective introduction of the epoxide side-chain of altromycin aglycone **3**, as well as synthesis of the kidamycin aglycone **2**.



*Chapter 2. Studies towards the Total Synthesis of Kidamycin*

Enantiomerically enriched angolosamine synthon **4** and vancosamine synthon **5**, corresponding to the carbohydrate moieties of kidamycin, have been identified as good glycosyl donors in kidamycin glycosylation studies, and synthesized by applying tungsten-catalyzed cycloisomerization of alkynols into glycals. Glycosylation studies with **4** and **5** have been directed at identification of a good glycosyl acceptor **2** to target the total synthesis of kidamycin. Glycosyl acceptor **2** has been efficiently synthesized via double Friedel-Crafts cyclization of **1**. Sequential glycosylations of **2** with **4** and **5** provide an advanced intermediate **7** possessing the full carbon skeleton of kidamycin.



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*Chapter1. Synthesis of Altromycin and Kidamycin Aglycones from a Common Intermediate*



*Chapter 2. Studies towards the Total Synthesis of Kidamycin*

# Abbreviations

| | |
|---|---|
| Ac | acetate |
| Anal. Calcd. | analysis calculated |
| Boc | *tert*-butoxylcarbonyl |
| Bu (n-Bu) | normal butyl |
| Calcd. | calculated |
| d | doublet |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DDQ | 2,3-dichloro-5,6-cyano-1,4-benzoquinone |
| DEAD | diethyl azodicarboxylate |
| DIBAL-H | diisobutylaluminum hydride |
| DMAP | 4-(dimethylamino)pyridine |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| er | enantiomeric ratio |
| EI | electron ionization |
| Et | ethyl |
| g | gram |
| HRMS | high resolution mass spectroscopy |
| *i*-Pr | *iso*-Propyl |

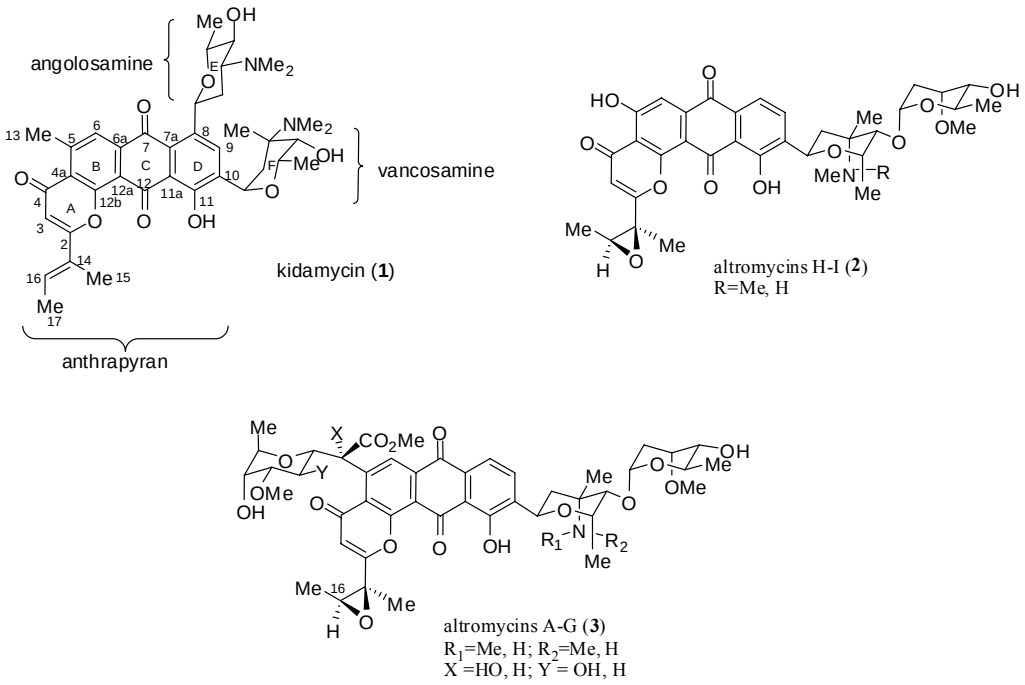
| | |
|---|---|
| IR | infrared |
| L | liter |
| M | molarity |
| m | multiplet |
| mix. | mixture |
| Me | methyl |
| mg | milligram |
| mL | milliliter |
| mmol | millimole |
| Ms | methanesulfonyl, mesyl |
| NMR | nuclear magnetic resonance |
| Nu | nucleophile |
| Ph | phenyl |
| Py. | pyridine |
| q | quartet |
| quint | quintet |
| s | singlet |
| sept | septet |
| t | triplet |
| TBAF | tetrabutylammonium fluoride |
| TBS | dimethylbutylsiyl |
| Tf | trifluoromethanesulfonyl, triflyl |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |

# Chapter 1. Synthesis of Altromycin and Kidamycin Aglycones from a Common Intermediate

## 1.1 Introduction and background

Among different classes of natural antibiotics, there is one class of antibiotic called pluramycin-type antibiotics whose members consistently contain a 4*H*-anthra [1, 2-b] pyran-4, 7, 12-trione substructure with the variation in the side chain and substitution patterns of carbohydrates on the anthrapyran.[1] This family of antibiotics is therefore also referred to as anthrapyran antiobiotics. The structural character is exemplified by kidamycin (**1**) and altromycins (**2**, **3**) as shown in figure 1.

**Figure 1.** Structure of kidamycin and altromycins

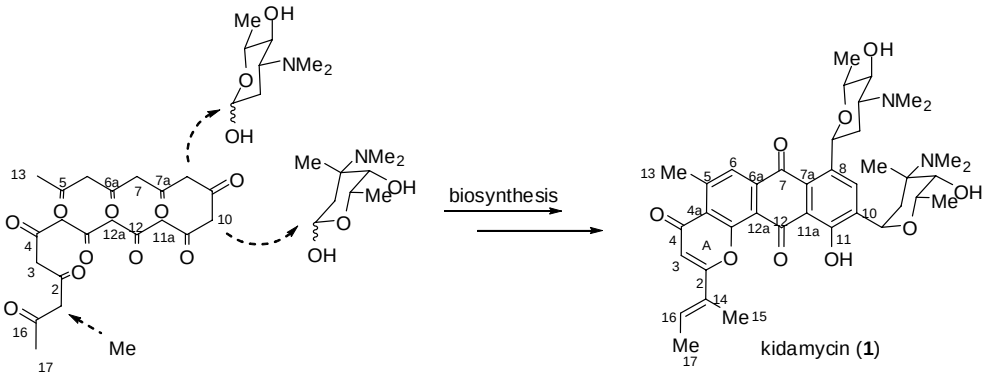



Kidamycin was isolated from *Streptomyces* soil in the early 1970s and is one of the earliest known members of anthrapyran antibiotics.[2] It demonstrates wide spectrum of antimicrobial activity against anaerobic bacteria, aerobic and facultative bacteria and yeasts.[3] It also has antitumor and cytotoxic properties. Kidamycin was shown to have

some effect against leukemia L-1210 and have a life-prolongation effect on mice bearing ascites tumors at single i.p. doses from just below the $LD_{50}$ (18 mg/kg) to 1/16 of the $LD_{50}$.[4] The interesting bioactivities of kidamycin as well as other anthrapyran antibiotics in this family drew considerable attention in the early 1970s, and the structure as well as the conformation of kidamycin was confirmed by NMR[5] and X-ray crystallographic studies[6] as shown. It seems that not much attention was paid in the following years until the 1990s, when new anthrapyran antibiotics altromycins (A-I) (**2**, **3**) were isolated[7-9] and their remarkable interactions with DNA were studied.[10-12] As new members of anthrapyran antibiotics, altromycins have selective activity against Gram-positive bacteria (Staphylococci and Streptococci) and anticancer activity, including *in vivo* activity in PS88 leukemia, as well as colon, lung, and ovarian tumors. More interestingly, Hurley has illustrated that altromycin B (**3**, $R_1 = R_2 = Me$; X = Y = OH) preferentially inhibits RNA and DNA synthesis relative to protein synthesis by covalent modification of guanine by alkylation of the epoxide at C16. Unlike kidamycin, the absolute stereochemistry of each chiral sector of altromycin has not been conclusively determined, including the stereochemistry of the epoxide on the side chain.

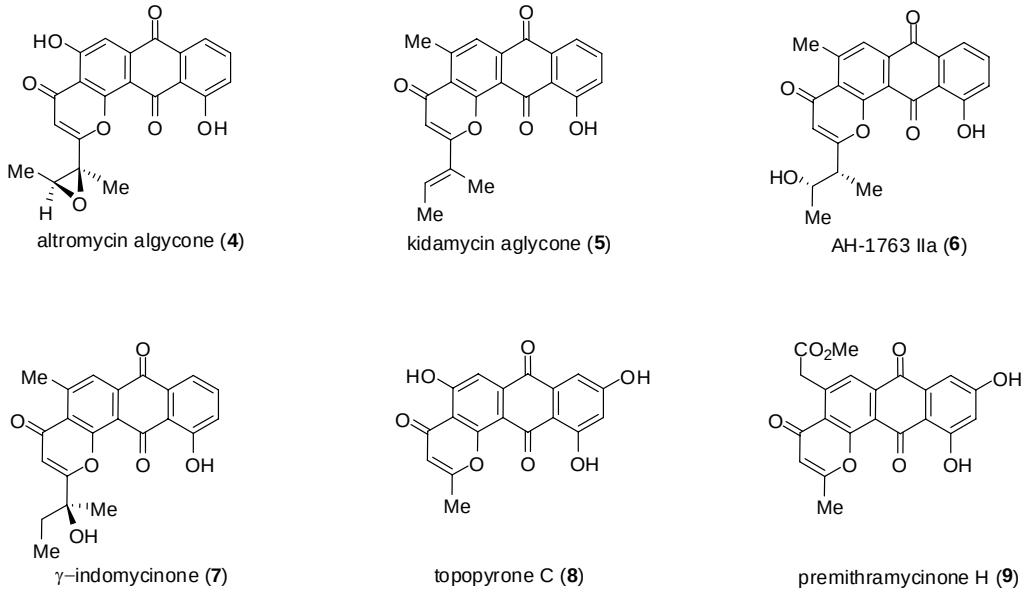
The biosynthetic pathway for kidamycin is presented in figure 2. Fricke and Furukawa proposed that the anthapyran moiety originated from a polyketide precursor and the sugar moieties might be attached to the anthrapyran skeleton at some later stage.[5] Carbon-13 labeled feeding experiments support this biogenetic hypothesis.

**Figure 2.** Prosposed biosynthesis of kidamycin



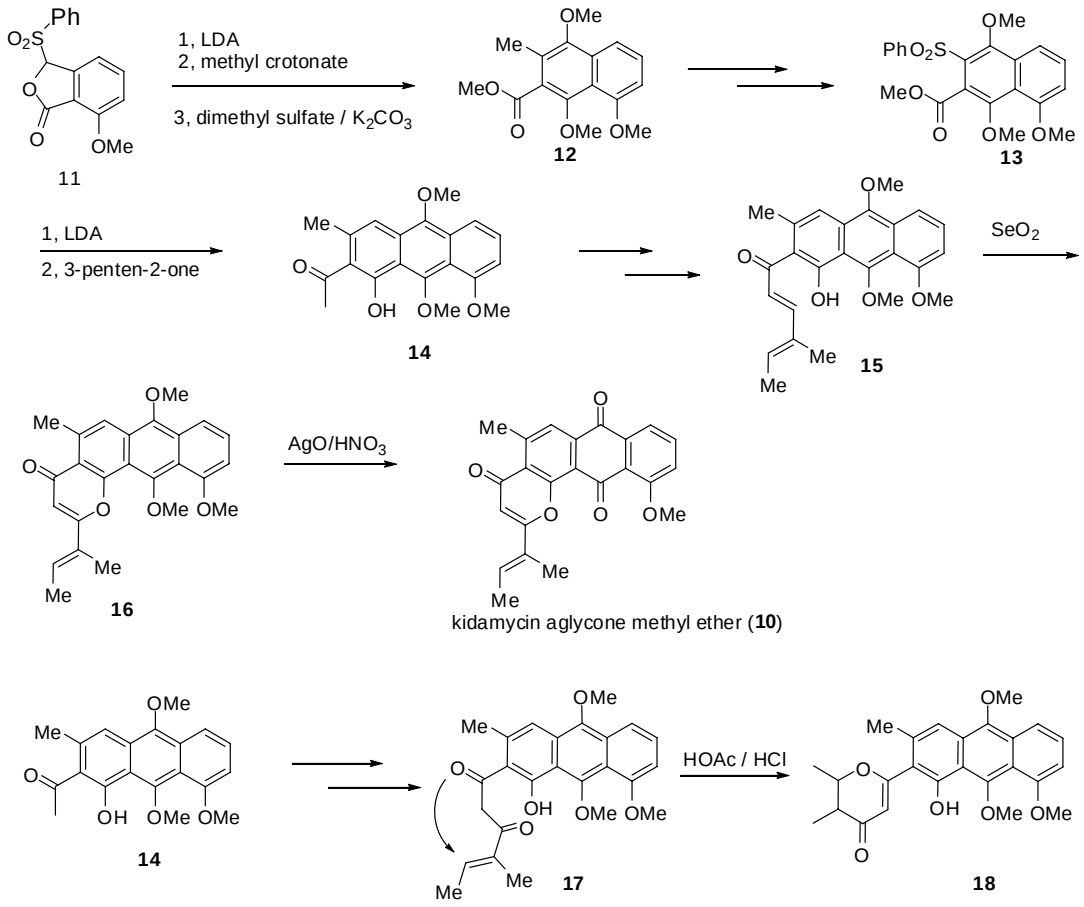

Anthrapyran substructures of altromycins and kidamycin are also referred to as altromycin aglycone (**4**) and kidamycin aglycone (**5**) to indicate their origin (figure 3). Although these aglycones are not natural products, some bioactive natural products were isolated more recently and were determined to be anthrapyran skeleta bearing no carbohydrates, including AH-1763 IIa (**6**),[13] γ-indomycinone (**7**),[14] topopyrone C (**8**)[15] and premithramycinone H (**9**).[16]

**Figure 3.** Non-natural and natural anthrapyrans



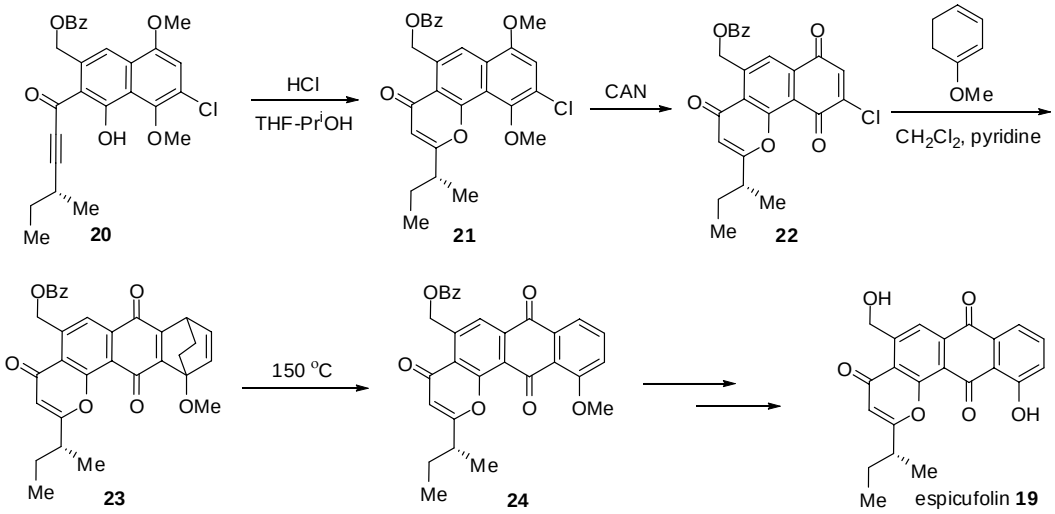
The ubiquitous anthrapyran structures of these antibiotics posed a challenge for the synthetic community. The first synthesis of this anthrapyran structure in the form of kidamycin aglycone methyl ether (**10**) was reported by Hauser's laboratory in the late 1970s[17] and early 1980s[18] (scheme 1). The synthesis utilized two applications of their signature anionic annulation reaction to construct **14**, followed by a low-yielding selenium dioxide-mediated oxidative cyclization to form the pyrone ring. Their original plan to cyclize the pyrone via 1, 3-diketone **17** under acidic conditions was derailed by the participation of the first carbonyl oxygen in a Michael addition to form **18**.

**Scheme 1.** Hauser's synthesis of kidamycin aglycone as methyl ether **10**



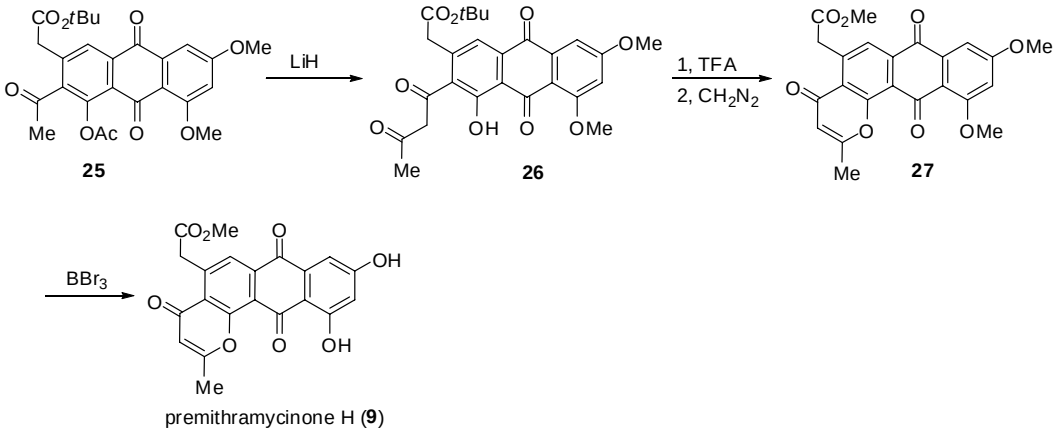
The next synthesis of an anthropyran antibiotic did not appear in the literature until Uno's report on the total synthesis of espicufolin (**19**) around the end of the century (scheme 2).[19,20] In the synthesis, *O*-alkynoylnaphthol **20** underwent an acid-promoted 6-*endo* ring closure to form the pyrone. Regioselective Diels-Alder reaction with **22**, followed by thermal retro Diels-Alder reaction to extrude ethylene furnished the anthraquinone **24**, which delivered espicufolin **19** after deprotection.

**Scheme 2.** Uno's total synthesis of espicufolin



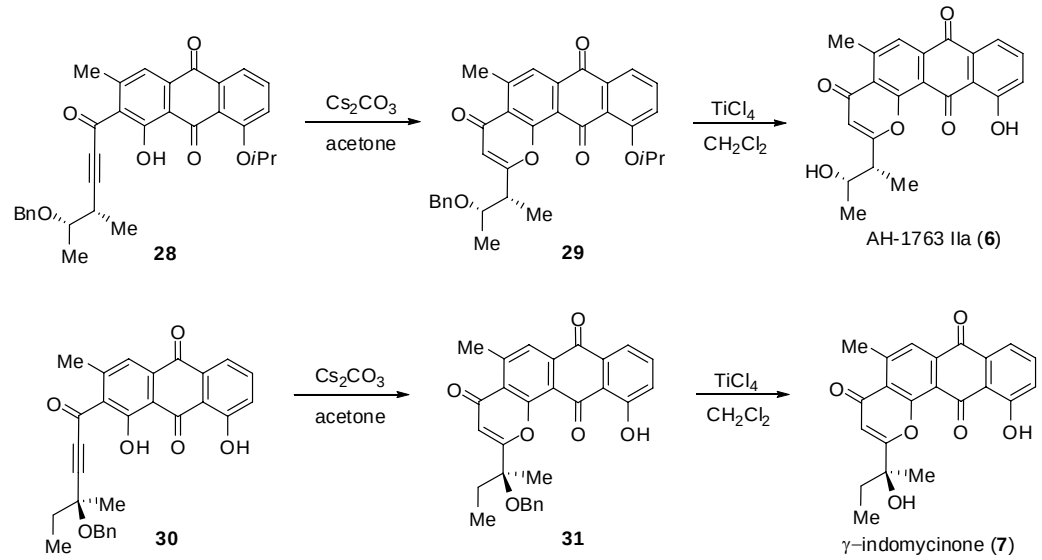

Premithramycinone H (**9**) was the next natural product that fell at the hand of synthetic chemist as its total synthesis was achieved by Krohn's laboratory in 2004 (scheme3).[21] They applied a Baker-Venkataraman chain elongation to obtain **26** from **25**. An acid promoted cyclization of the 1,3–diketone closed the pyrone ring to form **27**. Final demethylations completed the total synthesis. It is noteworthy that Hauser's approach to kidamycin from **17** (scheme 1) failed at the acid-promoted pyrone cyclization of the 1,3–diketone precursor due to the presence of an electrophilic olefin. It seems that the saturated nature of the side chain made possible the cyclization of **26**.

**Scheme 3.** Krohn's total synthesis of Premithramycinone H




Our work in this area including the synthesis of altromycin aglycone (**4**) and kidamycin aglycone (**5**) was published in 2005,[22] which will be discussed in more detail later in this chapter. In 2006, Tietze's laboratory reported the total syntheses of AH-1763 IIa (**6**)[23] and γ-indomycinone (**7**)[24] (scheme 4). They utilized the Diels-Alder reaction to construct anthraquinone precursors **28** and **30**.

**Scheme 4.** Tietze's synthesis of AH-1763 IIa and γ–indomycinone




Although acidic catalysis failed to promote the cyclization of the pyrone ring, treatment of both **28** and **30** with $Cs_2CO_3$ promoted 6-*endo*-dig cyclization, to provide

pyrone **29** and **31**, deprotections of which produced AH-1763 IIa (**6**) and γ-indomycinone (**7**), respectively.

In summary, the synthetic works towards anthrapyrans have demonstrated that Diels-Alder reactions could be applied to form the anthraquinone, and final carbon-oxygen bond formation under either acidic or basic conditions could form the pyrone ring. Baker-Venkataraman reaction or Marschalk reaction[21] are also very useful tools in the modification of anthracene skeleta. It seems that pyrone ring-closure via carbon-oxygen bond formation works well only in the case of saturated side chain as demonstrated by the synthesis of AH-1763 IIa (**6**), γ-indomycinone (**7**), espicufolin **16** and premithramycinone H (**9**). The unsaturated side chain of kidamycin aglycone methyl ether (**10**) caused problems in closing the pyrone via carbon-oxygen bond formation, and the alternative route via selenium dioxide mediated pyrone ring formation only gave modest yield.

Considering the polyketide origin of the anthrapyrans in their biosynthesis,[5] we were interested in exploring biomimetic synthesis of the anthracene sector with the flexibility for the closure of the pyrone ring via either carbon–oxygen bond or carbon-carbon bond formation, to synthesize both altromycin aglycone (**4**) and kidamycin aglycone (**5**).

## 1.2 Results and discussion

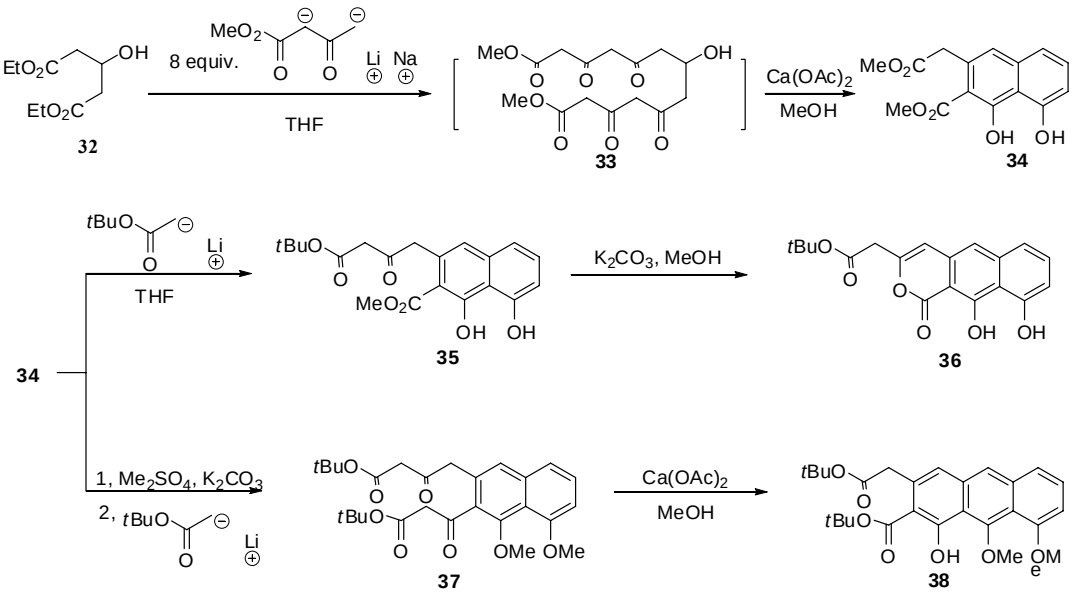
### *1.2.1 Overall description of the results*

At the beginning of the research, we planned to furnish the full carbon skeleton of anthrapyran by finalizing the pyrone closure via carbon-oxygen bond formation from a proper anthracene precursor that would be obtained via biomimetic Claisen condensation. This thinking was later modified to finalize pyrone closure via carbon-carbon bond formation. With the full carbon skeleton of anthrapyran obtained, we were able to utilize it as a common intermediate and functionalize to both altromycin aglycone (**4**) and kidamycin aglycone (**5**). The ideal evolution in preparing this common intermediate and the functionalization to target molecules will be described in more detail.

### *1.2.2 Synthesis of an anthrapyran intermediate*

The synthesis began with the preparation of naphthalene diester **34** (Scheme 5), by applying Yamaguchi's biomimetic construction of the naphthalene diester through aromatization of a crude polyketide intermediate **33** promoted by calcium acetate monohydrate.[25] We found that freshly drying the calcium acetate monohydrate is crucial for this procedure to reliably provide the naphthyl diester product. However, we were unable to obtain the reported yield of 55% for this reaction, and our typical overall yield for these two steps never exceeded 25%. Even so, we continued to utilize this method because it quickly provided naphthalene intermediate with the desired substitution pattern.

**Scheme 5.** Initial attempt to synthesize anthracene precursor

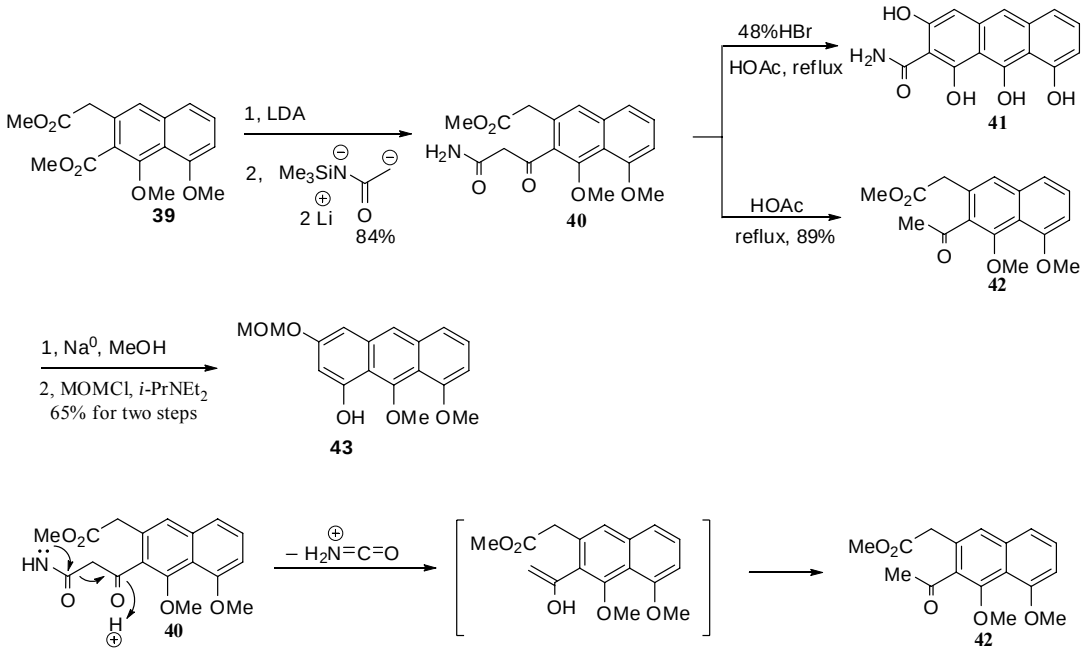



Claisen condensation of **34** with excess *tert*-butyl acetate anion obtained by treatment with LDA produced **35** via selective condensation to alkyl ester.[26] It was reportedly important to keep the phenolic hydroxyl group unprotected; otherwise a messy and unselective reaction would take place. Attempt to cyclize the third ring of the anthracene by treating substrate **35** with potassium carbonate in methanol gave **36**, presumably via *O*-acylation instead of the desired *C*-acylation. In contrast, bis-ketoester **37**, obtained via double Claisen condensation to dimethyl ether of **34**, could undergo desired carbon-carbon bond formation to complete the third ring of the anthracene upon refluxing in methanol under weak basic conditions. Unfortunately, anthracene **38** was not a useful intermediate for current project due to extra carbons on the corner of the anthracene skeleton.

Harris's laboratory has demonstrated that naphthalene with substitution pattern similar to **40** could undergo an acid-promoted cyclization and aromatization to form the anthracene skeleton.[27] By applying Harris's method, substrate **39** underwent selective

Claisen condensation with amide dianion at the aryl ester when the alkyl ester was temporarily masked as an enolate by LDA,[28] to provide **40** (scheme 6). Consistent with Harris's analogous substrate, **40** underwent cyclization and concomitant demethylation to produce **41** when refluxing in strong acid (48% HBr / HOAc = 1 / 1 by volume). Compound **41** has all desired functionalities for further transformation to targeted aglycones.

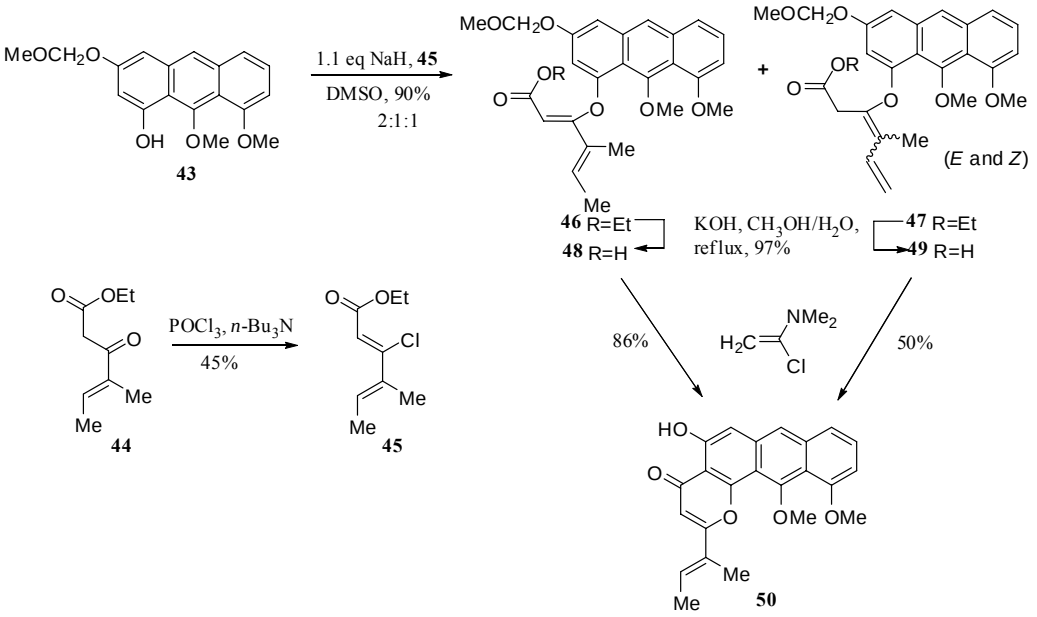
**Scheme 6.** An empirical observation led to strategy modification




It would be easier to handle further functionalization if two methyl groups on **40** were not lost in the acid-promoted cyclization step. Weak acidic conditions were tested for this purpose. Interestingly, when **40** was refluxed in *acetic acid without HB*r, the methyl ketone product **42** instead of the cyclization product was obtained in high yield. As it is unlikely that the amide could be hydrolyzed under these non-aqueous conditions, a decarboxylation process was presumably not involved, but rather an analogous acid-promoted deamidation process might be occurring, as shown at the bottom of the scheme

6. To the best of our knowledge, this is the first reported example of a decarbamidation. Substrate **42** easily underwent Dieckmann condensation to form anthracene diol that was selectively protected to provide **43**. Hydrogen bonding between the bottom hydroxyl group and the neighboring carbonyl oxygen deactivates this hydroxyl group and apparently favors the regioselective *O*-alkylation. The observation of decarbamidation and further transformation to anthracene **43** led us to modify our plan of pyrone closure from carbon-oxygen bond formation to carbon-carbon bond formation via intramolecular Friedel-Crafts reaction. This method of pyrone formation has been utilized by Bycroft in the total synthesis of flavasperone.[29] Thus, vinylic chloride **45** was prepared from known 1, 3- diketone **44**[30] for coupling with **43** by an addition-elimination reaction[31,32] (scheme 7).

**Scheme 7.** Completion of anthrapyran intermediate




Treatment of anthracene **43** with a slight excess of sodium hydride in DMSO followed by addition of vinyl chloride **45** provided the desired product **46** along with two isomers **47**-*E* and **47**-*Z* in a 2:1:1 ratio with a 90% combined yield (Scheme 7). The

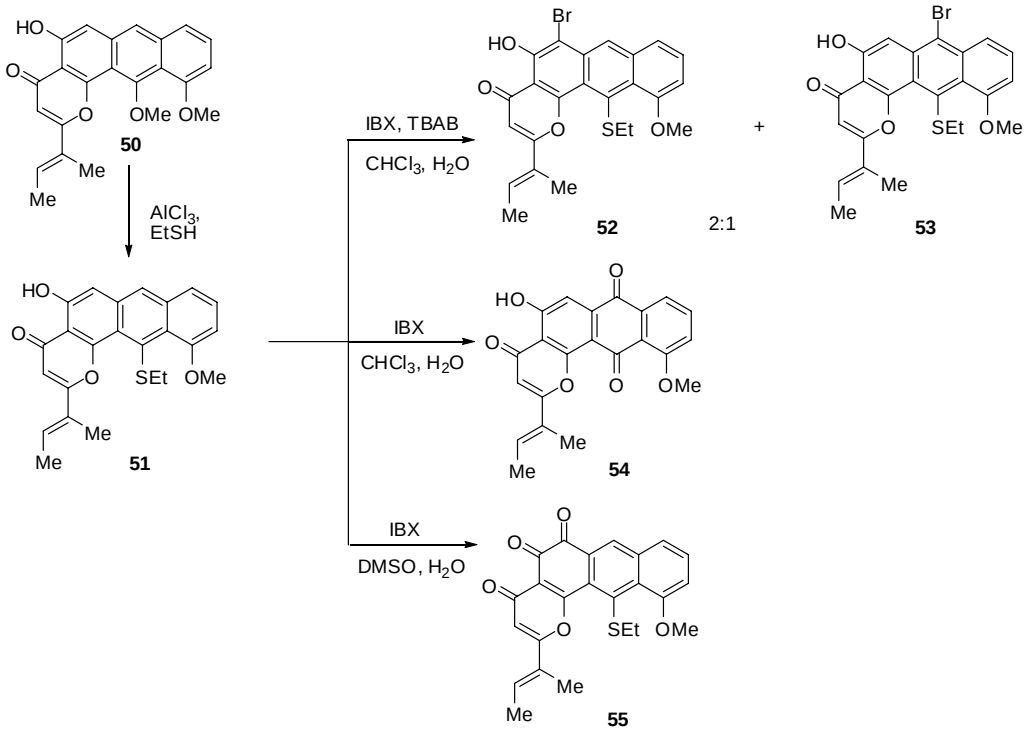
choice of DMSO as solvent was crucial. Using THF led to a sluggish and messy reaction. Neither basic nor acidic conditions could to isomerize **47**-*E* and **47**-*Z* to **46**. The mixture of these three components was subjected to saponification conditions to provide a mixture of three acids **48**, **49**-*E* and **49**-*Z*, from which acid **48** was easily separated by column chromatography. Initial attempts to close the pyrone through C4-C4a bond by generating the acid chloride from **48** with oxalyl chloride resulted in Friedel-Crafts oxalylation at C7, but activation of acid **48** with 1-chloro-*N*, *N*, 2-trimethyl-1-propenyl-amine[33] resulted in spontaneous cyclization to anthrapyran **50** in 86% yield. Interestingly, treatment of the mixture of isomers **49**-*E* and **49**-*Z* under the same conditions for two weeks also provided the desired product, although in lower yield (50%) and with much slower rate. In both cases, the methoxy-methyl (MOM) O-protective group was lost under the pyrone closure conditions.

*1.2.3 Completion of altromycin aglycone synthesis*

Functionalization of **50** to altromycin aglycone began with the studies of demethylation and oxidation to quinone (scheme 8). Treatment of **50** with classical demethylation conditions developed under the principle of hard-soft Lewis acid and base[34] resulted in substitution of the middle methoxyl group by ethanethiol, used as a soft nucleophile. As the yield of this substitution reaction was high, it would be practical to advance intermediate **51** to quinone by taking advantage of the sulfide functionality via Pummerer-type reaction. The sulfide needed to be oxidized to sulfoxide to execute the Pummerer-type transformation. Interestingly, the reported oxidation conditions of IBX in $CHCl_3$ and water in the presence of tetrabutylamonium bromide (TBAB) as phase-

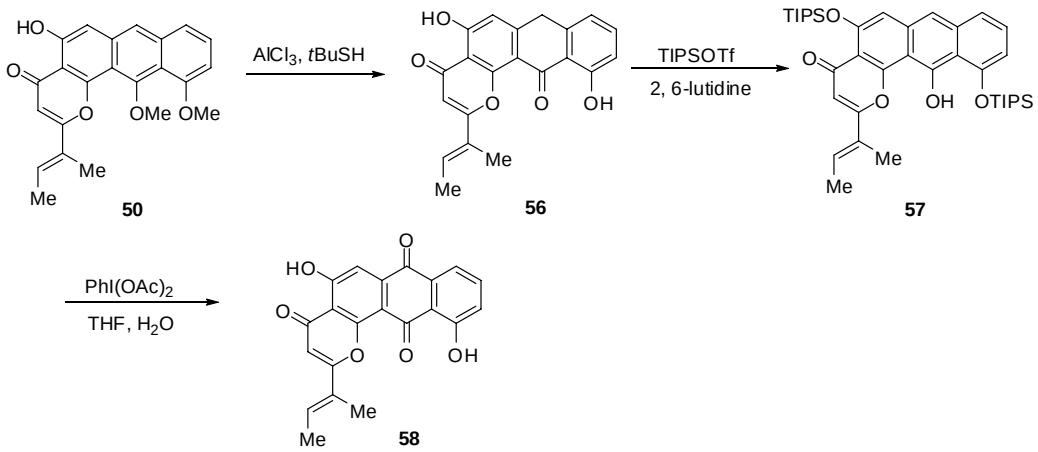
transfer catalyst[35] transformed **51** to bromination products **52** and **53** in a 2:1 ratio. Without worrying too much about the mechanism, it was speculated that water might participate in the reaction, resulting in oxidation to quinone in the absence of bromide. Indeed, treatment of **51** with IBX in $CHCl_3$ and water resulted in a slow oxidation of **51** to quinone **54**. The slow nature of the oxidation might be due to the low solubility of IBX in $CHCl_3$. The oxidation carried out using DMSO and water as solvents, however, produced *iso*-quinone **55**.

**Scheme 8.** The first oxidation study towards quinone




More efficient oxidation protocol was developed following the solution for demethylation problem. Using bulky *tert*-butanethiol as a soft nucleophile led to the double O-demethylation of **50**, followed by tautomerization to provide anthrone **56** (scheme 9). After silylation, anthracene **57** was oxidized[36,37] to quinone **58** in good yield.

**Scheme 9.** The second oxidation study towards quinone

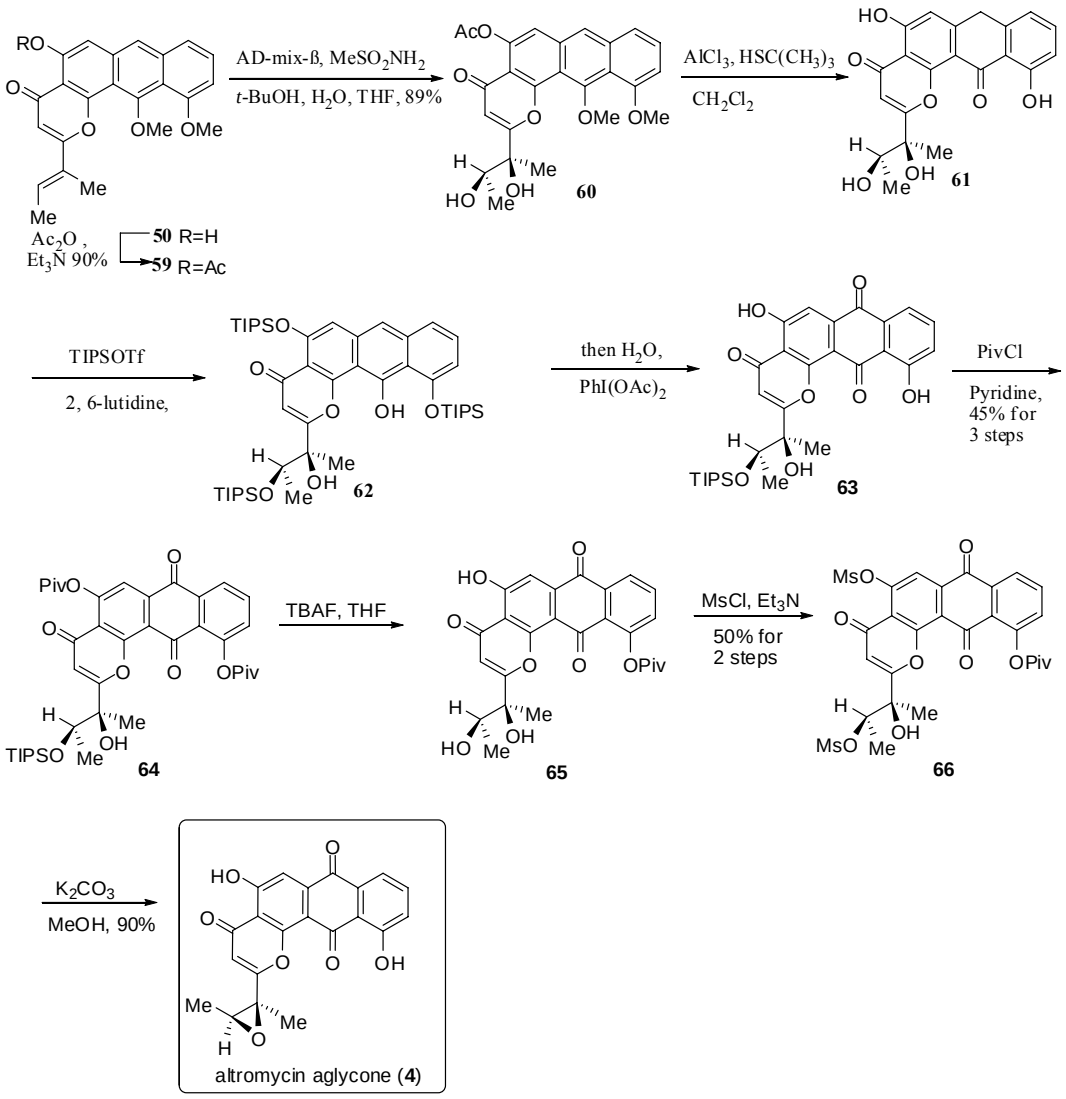



Although the extra silylation step from **56** was employed to improve the yield for oxidation, it was surprising that phenolic TIPS ether did not survive the oxidation step. Alkyl hydroxyl TIPS ether should be able to survive the oxidation conditions. As we projected to form the epoxide on the side chain of altromycin aglycone via a sequence of syn-dihydroxylation, mono-mesylation and intramolecular substitution, the oxidation protocol might provide an opportunity to differentiate the alkyl hydroxyl group from the phenolic hydroxyl group, following which the selective mesylation of alkyl hydroxyl group would be possible. This speculation was based on the premise that an undesired mesylation of phenolic hydroxyl group would introduce the difficulty in deprotection at the final stage of the synthesis.

The pictured functionalization sequence finally provided altromycin algycone (**4**) as shown in scheme 10. The acetyl protected anthracene intermediate **59** was treated with AD-mix-β[38] to provide diol **60** with an enantiomeric ratio of 12:1, as determined by Mosher ester analysis.[39] Using THF as cosolvent was important for this reaction, as the reported *t*-BuOH/$H_2O$ solvent system did not dissolve substrate **59** well and gave no reaction or a sluggish reaction rate. Due to the uncertainty of altromycin absolute

stereochemistry at the epoxide, *ent*-**60** was also produced in a 12:1 ratio by using AD-mix-α under the same conditions. Direct dihydroxylation of **50** under above discussed conditions gave a messy reaction, presumably due to fragility of the anthracene to the oxidant present in AD–mix. Global deprotection of **60** with $AlCl_3$ and bulky *tert*-butanethiol provided crude anthrone tetraol **61**, which in turn was transformed to the partially protected quinone **63** by our oxidation protocol in a one-pot fashion, by treating the anthrone tetraol **61** with excess TIPSOTf and 2, 6-lutidine in THF to provide **62,** followed by addition of water and $PhI(OAc)_2$. Being consistent with our previous observation, the second oxidation stage of this one-pot reaction cleaved the aryl TIPS ether while retaining alkyl C16 TIPS ether. This partially protected quinone compound was not purified until after the two aryl hydroxyl groups were protected as bispivaloate ester **64**, featuring two types of differently protected hydroxyl group. Although this hydroxyl group differentiation was projected to avoid undesired mesylation of the aryl hydroxyl groups in the following epoxide formation steps, it was found that removal of TIPS was always accompanied by loss of the C5 pivaloate, to afford **65**. Fortunately, the derived bismesylate compound **66** in the presence of potassium carbonate in methanol underwent epoxide formation by intramolecular $S_N2$ substitution as well as methanolysis of both mesylate and pivaloate ester of pheonlic protective group to provide crystalline altromycin aglycone **4**. The general lability of C5 O-protective groups may result from neighboring group participation of the C4 pyrone carbonyl oxygen.

**Scheme 10.** Completion of altromycin aglycone synthesis

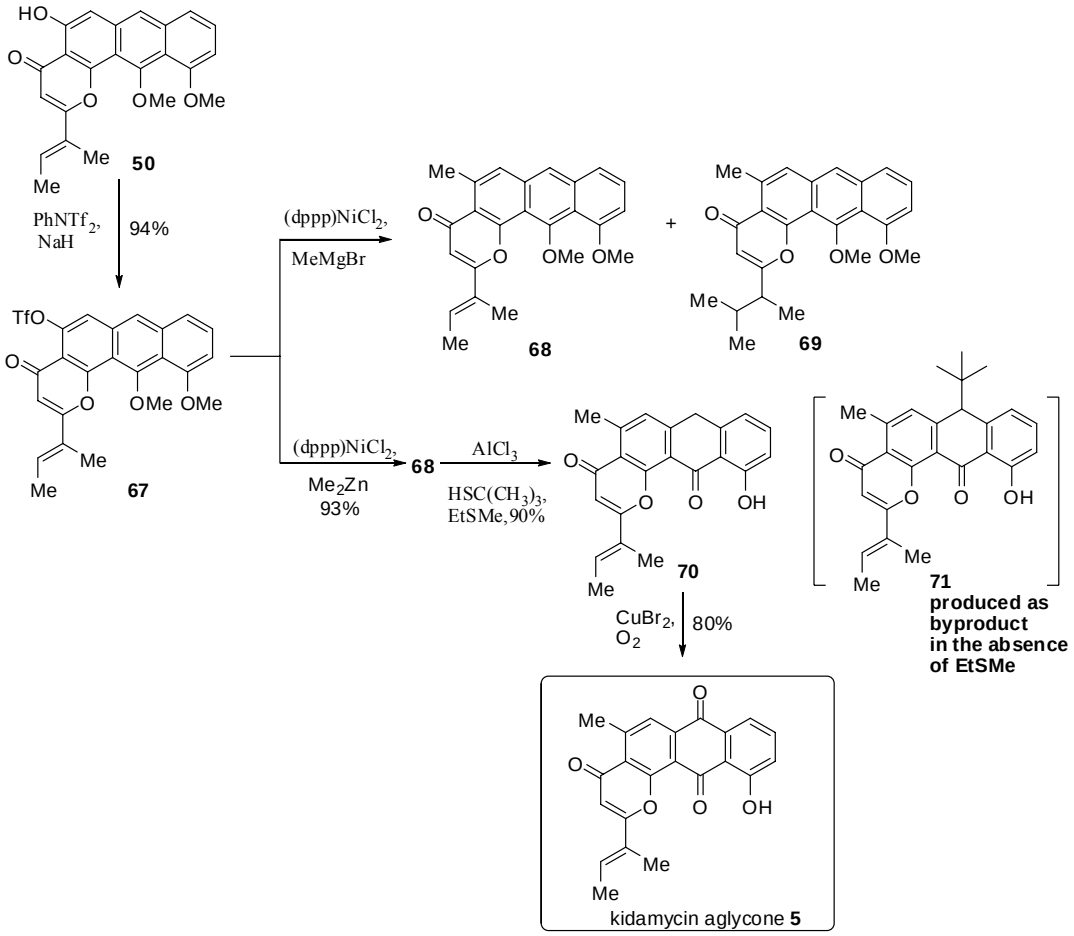



*1.2.5 Completion of kidamycin aglycone synthesis*

The anthrapyran **50** was also transformed to kidamycin aglycone **5** as shown scheme 11. Triflate **67** was initially treated with methylmagnesium bromide under Kumada coupling conditions (nickel catalysis) to introduce the methyl group. However, the product **68** reacted further with methylmagnesium bromide via 1, 6-conjugate addition to **69** if the reaction was not closely monitored and quenched within a narrow

time window. Using dimethylzinc as methylation reagent[40] under otherwise identical conditions provided **68** as the only product, and close monitoring of the reaction was not necessary in order to obtain highly reproducible production of **68**.

**Scheme 11.** Completion of kidamycin aglycone synthesis




Demethylation of **68** under previous conditions with *tert*-butanethiol gave not only **70** but also **71** as a byproduct, presumably formed via alkylation of a long-lived *tert*-butyl cation by enol form of **70**. Using small amount of methyl ethyl sulfide as an additive for this reaction effectively scavenged the cations and **70** was produced in 90% yield as the only product. Oxidation[21] of **70** provided kidamycin aglycone **5**.

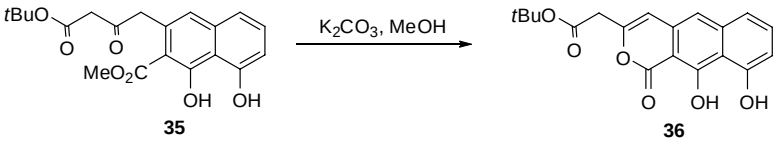
## 1.3 Conclusions

In attempting to cyclize the third ring of anthracene skeleton, we observed a decarbamidation process, which led us to modify our plan to close the pyrone via carbon–carbon bond formation. This strategy modification was quickly rewarding to provide us with anthrapyran intermediate. Functionalization of the anthrapyran achieved our goal to synthesize both altromycin aglycone and kidamycin aglycone.

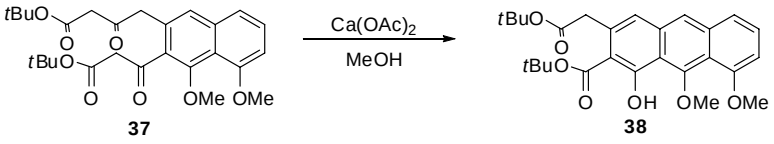
## 1.4 Experimental information

**General procedure**: $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on an Inova-400 spectrometer (400 MHz for $^{1}H$ NMR, 100 MHz for $^{13}C$ NMR), or and Inova-600 (600 MHz for $^{1}H$ NMR, 150 MHz for $^{13}C$ NMR). NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$), with residual chloroform (7.27 ppm for $^{1}H$ NMR and 77.23 ppm for $^{13}C$ NMR) taken as the internal standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were collected on a Mattson Genesis II FT-IR spectrometer as neat films. High resolution mass spectra were recorded on a VG 70-S Nier Johason Mass Spectrometer or a Thermo Finnigan LTQ FT spectrometer. Elemental analyses were performed by Atlantic Microlab Inc, P.O.Box 2288, Norcross, Georgia. UV absorptions were recorded on a Cary UV-visible spectrophotometer. Optical rotations were measured on a Perkin Elmer Model 341 Polarimeter. Analytical Thin Layer Chromatography (TLC) was performed on precoated glass backed plates purchased from Whatman (silica gel 60 F254; 0.25 mm thickness). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from EM Science.

All anhydrous solvents were dried over microwave-activated 3Å or 4Å molecular sieves. All solvents used in workup extraction procedures and chromatography were used as received from commercial suppliers without prior purification. All reagents were purchased from Aldrich. All reactions were carried out under argon except otherwise mentioned. During workup, the reaction mixture was usually diluted to three times the original volume. About equal amount of organic solvent was usually used for each extraction of certain volume of aqueous solution. Half amount of water or brine was usually used to wash certain volume of organic solution.

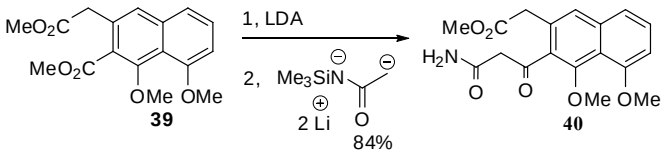



To a solution of **35**[26] (29 mg, 0.078 mmol) in THF (3 mL) and methanol (1.5 mL) was added potassium carbonate (416 mg) at room temperature. The reaction was stirred for 2 h and quenched with aq. $NaH_2PO_4$. Extraction with ethyl acetate, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexane / ethyl acetate = 2 / 1) gave product **36** (24 mg, 90%).$^1$H NMR (400 MHz, $CDCl_3$) δ 13.51 (s, 1H), 9.38 (s, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.17 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.45 (s, 1H), 3.46 (s, 2H), 1.47 (s, 9H).



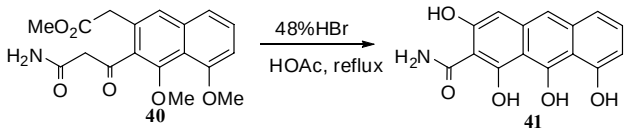

To a solution of **37** (20 mg, 0.041 mmol) in methanol (4 mL) was added calcium acetate (400 mg) at room temperature. The reaction was refluxed for 12 h and cooled to room

temperature. Dilution with water, extraction with ethyl acetate, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexane / ethyl acetate = 2 / 1) gave product **38** (12 mg, 62%).$^1$H NMR (400 MHz, $CDCl_3$) δ 11.88 (s, 1H), 7.89 (s, 1H), 7.40 (d, *J* =8.0 Hz, 1H), 7.29 (t, *J* = 8.4 Hz, 1H), 7.10 (s, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.80 (s, 2H), 1.60 (s, 9H), 1.40 (s, 9 H).



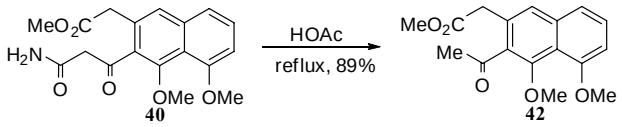

A solution of naphthalene diester **39**[25] (783 mg, 2.46 mmol) in THF (60 mL) was added dropwise to a solution of freshly prepared LDA [4.92 mmol, prepared by slow addition of *n*-BuLi (3.1 mL, 1.6 M in hexane) to diisopropylamine (0.84 mL, 6 mmol) in THF (37 mL) at -78ºC, followed by stirring at -78ºC for 30 min]. The resulting solution was stirred at -78ºC for 20 min., and subsequently cannulated into a solution of *N*-(trimethylsilyl)acetamide dianion [ 4.92 mmol; prepared by slow addition of *n*-BuLi (6.2 mL, 1.6 M in Hexanes) to the THF solution of *N*-(trimethylsilyl)acetamide (646 mg, 4.92 mmol) at 0ºC and subsequent stirring for 20min.] in THF ( 27 mL) at 0ºC. The mixture was stirred for 14 h while reaction temperature increased from 0ºC to room temperature, and then quenched by addition of 1M HCl (20 ml) followed by stirring for 20 min at room temperature. The two-layer solution was separated and the aqueous layer was extracted with ethyl acetate. Combined organic layers were washed with water, brine and dried with $Na_2SO_4$. Condensation by rotary evaporation followed by flash column chromatography on silica gel with ethyl acetate as eluent gave naphthalene amide **40** (715 mg, 84% yield). IR (neat) 3445, 3343, 1732, 1672, 1568 $cm^{-1}$; $^1$H NMR (600 MHz,

$CDCl_3$) δ 7.42 (t, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 6.96 (bs, 2H), 6.87(d, *J* = 8.4 Hz, 1H), 4.03 (s, 2H), 3.98 (s, 3H), 3.84 (s, 2H), 3.80 (s, 3H), 3.65 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 203.0, 172.0, 169.0, 156.3, 155.8, 137.7, 132.0, 129.3, 128.4, 126.7, 120.7, 118.8, 106.7, 64.1, 56.2, 52.3, 51.4, 38.2; HRMS ($FAB^+$) Calcd. for $C_{18}H_{19}O_6NLi$ [$(M + Li)^+$] 352.1372, found 352.1385.




**40** **41**

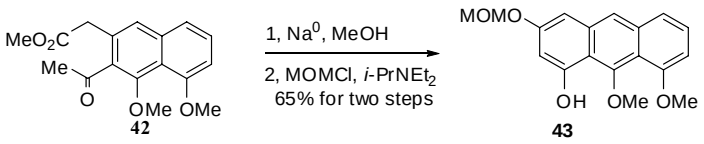
To a solution of **40** (45 mg, 0.130 mmol) in acetic acid (10 mL) was added 48% HBr (10 mL). The reaction was refluxed for 7 h and cooled to 4 ºC overnight. The next day, some yellow crystals were obtained. The compound is not soluble in common solvents, and the structure was supported by its color and by low-resolution mass (EI) Calcd. for $C_{15}H_{11}N_1O_5$ ($M^+$) 285.3, found 285.2.




**40** **42**

A solution of naphthalene amide **40** (402 mg, 1.16 mmol) in acetic acid (35 mL) was extensively refluxed under argon for 18 h, after which time the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water, brine and dried with $Na_2SO_4$. Condensation by rotary evaporation, followed by chromatography on silica gel with hexane/ether (1/2) as eluent afforded methyl ketone **42** (313 mg, 89%) as a white solid. IR (neat) 2938, 2839, 1738, 1690, 1623, 1568 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.2 Hz,

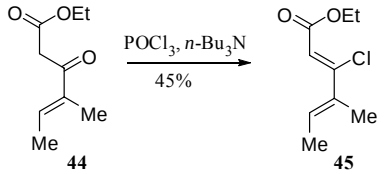
1H), 6.90 (d, $J$ = 7.2 Hz, 1H), 4.04 (s, 3H), 3.83 (s, 3H), 3.82 (s, 2H), 3.69 (s, 3H), 2.69 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 206.3, 171.9, 156.3, 155.0, 137.4, 133.5, 129.4, 127.9, 126.7, 120.9, 119.0, 106.5, 64.1, 56.3, 52.3, 38.4, 32.7; HRMS (EI) Calcd. for $C_{17}H_{18}O_5$ ($M^+$) 302.11542, found 302.11594; Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00; O, 26.46. Found: C, 67.41; H, 6.08; O, 26.49.




Sodium metal (1.196 g, 52 mmol) in pieces was slowly added to methanol (65 mL) at room temperature. After consumption of all metal solids, the solution was heated to reflux under argon, at which time a solution of methyl ketone **42** (826 mg, 2.74 mmol) in a combined solvent (THF, 10 mL; MeOH, 55 mL) was added in dropwise manner. The resulting mixture was refluxed under argon for further 30 min, subsequently cooled to 0ºC, and quenched with 1M HCl (60 mL). The mixture was extracted with $CH_2Cl_2$ three times and the combined organic layers were dried with $Na_2SO_4$. After rotary evaporation of the solvent, the residue was further dried under high vacuum, and was used for next step.

To a solution of above residue in $CH_2Cl_2$ (25 mL) was added $i$Pr$_2$NEt (619 μL, 3.56 mmol), and MOMCl (217 μL, 2.86 mmol) sequentially at 0ºC. The reaction solution was stirred at 0ºC for 2 h, and then quenched with aqueous $NaH_2PO_4$. The two-layer solution was separated and the aqueous layer was extracted three times with $CH_2Cl_2$. The combined organic layers were washed with water and dried over $Na_2SO_4$, filtered and concentrated by rotary evaporation. Column chromatography on silica gel with hexane /

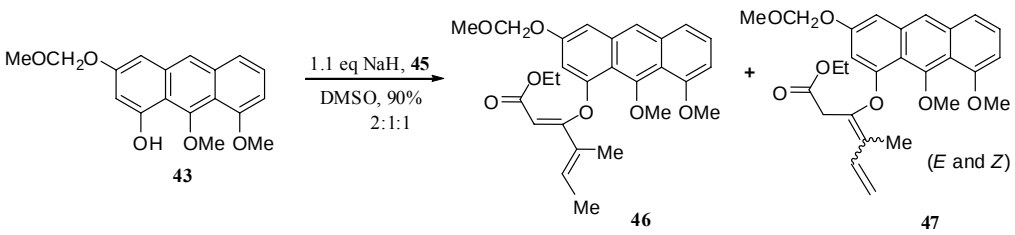
ethyl acetate (3 / 1) as eluent gave anthracene **43** (560 mg, 65% yield for two steps) as a yellow solid. IR (neat) 3288, 1641 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.00 (s, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 2 Hz, 1H), 6.73 (d, *J* = 7.2 Hz, 1H), 6.64 (d, *J* = 2 Hz, 1H), 5.31 (s, 2H), 4.08 (s, 3H), 4.04 (s, 3H), 3.54 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 156.2, 155.7, 155.6, 153.1, 135.3, 134.8, 126.0, 122.0, 121.0, 115.2, 113.5, 103.4, 102.6, 99.7, 94.4, 64.9, 56.3, 56.1; HRMS ($FAB^+$) Calcd. for $C_{18}H_{18}O_5$ ($M^+$) 314.1154, found 314.1166.




**44** **45**

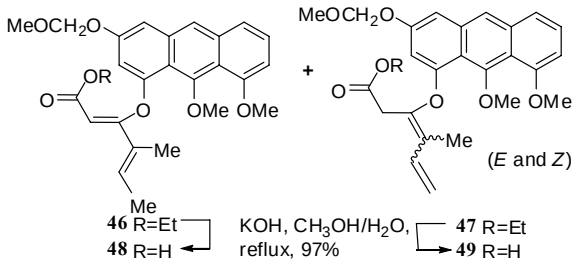
At -10ºC, *n*-$Bu_3N$ (1.81 mL, 7.6 mmol) was added dropwise to a solution of ketone **44**[30] (1.29 g, 7.6 mmol) in phosphorus oxychloride (6 mL, 65 mmol), which was then allowed to stir for 10 h while the temperature slowly rose to room temperature. The reaction was subsequently heated to 85ºC for 3 h and then phosphorus oxychloride was removed by distillation under reduced pressure of aspirator. The residue was carefully quenched with sat. $Na_2CO_3$ and extracted with ethyl acetate for three times. The combined organic layers were washed with water, brine, dried over $Na_2SO_4$ and filtered, concentrated by rotary evaporation. The residue was purified by column chromatography on silica gel with hexane / ether (12 / 1) to give vinylic chloride **45** (643 mg, 45% yield) as a colorless oil. IR (neat) 1727, 1619 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.74 (q, *J* = 6.6 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.86 (s, 3H), 1.72 (d, *J* = 6.6 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 164.5, 154.3, 132.8, 128.8, 118.6, 60.6, 14.7,

14.3, 14.0; HRMS (APCI) Calcd. for $C_9H_{14}O_2Cl$ [$(M + H)^+$] 189.06768, found 189.06746.




To a suspension of NaH (60% dispersion in mineral oil, 213 mg, 5.34 mmol) in DMSO (11 mL) was slowly added a solution of anthracene **43** (1.53 g, 4.85 mmol) in DMSO (50 mL) at room temperature, during which process an evolution of hydrogen bubbles was observed. After the resulting mixture was stirred for further 1 h and no more bubbles were observed, a solution of vinylic chloride **45** (1.37 g, 7.3 mmol) in DMSO (8 mL) was added during 10 min. The reaction solution was allowed to stir for 20 h at room temperature, then quenched with water, and neutralized with sat. aq. $NH_4Cl$ at 0ºC. The biphasic solution was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated by rotary evaporation. Column chromatography on silica gel with hexane / ether (2 / 1) as eluent gave a mixture of **46**, **47**-*E* and **47**-*Z* (2.04 g, ratio 2:1:1, 90% combined yield). Careful column chromatography with hexane/ ether (3/1 to 2/1) as gradient eluent provided some pure **46** for its characterization. $^1$H NMR (600 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.45 (d, $J$ = 7.6 Hz, 1H), 7.32 (t, $J$ = 7.6 Hz, 1H), 7.04 (d, $J$ = 2.2 Hz, 1H), 6.71 (d, $J$ = 7.6 Hz, 1H), 6.47 (q, $J$ = 6.8 Hz, 1H), 6.33 (d, $J$ = 2.2 Hz, 1H), 5.85 (s, 1H), 5.26 (s, 2H), 4.063 (s, 3H), 4.055 (s, 3H), 3.98 (bm, 2H), 3.51 (s, 3H), 1.89 (s, 3H), 1.69 (d, $J$ = 6.8Hz, 3H), 0.94 (bm, 3H); $^{13}$C NMR (150MHz, $CDCl_3$) δ 165.0,

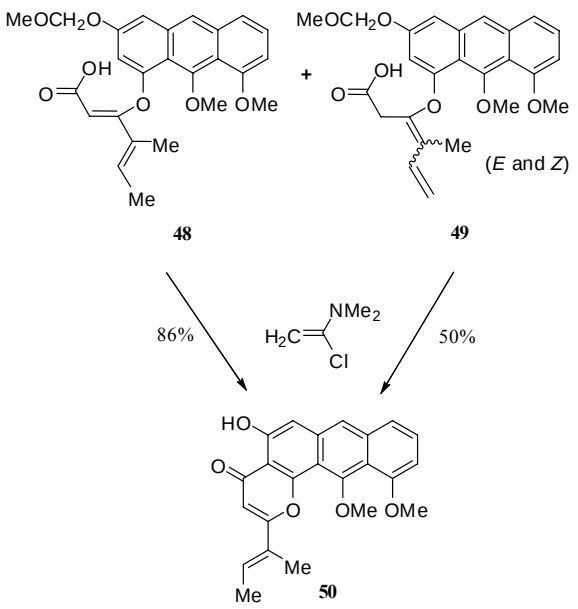
163.4, 157.2, 156.2, 155.1, 154.8, 135.6, 135.5, 132.4, 129.1, 126.1, 121.1, 120.6, 118.0, 115.8, 105.1, 103.0, 101.8, 101.7, 94.7, 64.4, 60.0, 56.5, 56.3, 14.8, 14.1, 13.3; HRMS ($FAB^+$) Calcd. for $C_{27}H_{30}O_7$ ($M^+$) 466.1992, found 466.2002.




A solution of a mixture composed of **46**, **47**-*E* and **47**-*Z* (2:1:1 ratio, 2.098 g, 4.5 mmol) in a combined solvent of methanol (180 mL) and water (30 mL) was refluxed for 2 h in the presence of potassium hydroxide (2.96 g, 45 mmol) under argon. The reaction was then cooled with ice bath and quenched with 1M HCl, followed by addition of ethyl acetate. The biphasic solution was separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic phase was washed with water, brine, dried over $Na_2SO_4$, filtered and concentrated by rotary evaporation. Separation by column chromatography on silica gel with hexane / ether (1 / 2 to 0 / 1) as eluent gave acid **48** (950 mg, 97% based on amount of **46** in starting mixture) and an inseparable mixture of **49**-*E* and **49**-*Z* (958 mg, 97% based on amount of **47**-*E* and **47**-*Z* in starting mixture). Characterization data for acid **48**: IR (neat) 2936, 1694, 1627, 1564 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.37 (q, *J* = 7.4 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 5.85 (s, 1H), 5.25 (s, 2H), 4.04 (s, 3H), 3.99 (s, 3H), 3.51 (s, 3H), 1.85 (s, 3H), 1.70 (d, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 168.5, 165.0, 156.9,

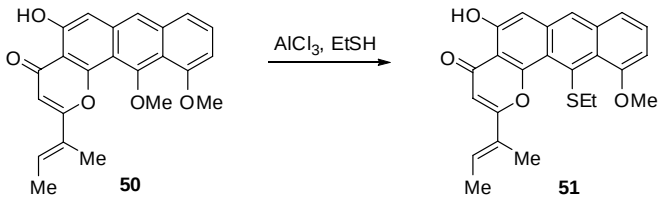
154.9, 154.5, 154.4, 135.7, 135.1, 133.2, 129.0, 126.3, 121.3, 120.6, 118.0, 115.4, 104.9, 103.4, 102.6, 94.7, 64.4, 56.5, 56.3, 14.7, 13.2; HRMS ($FAB^+$) Calcd. for $C_{25}H_{26}O_7$ ($M^+$) 438.1679, found 438.1692.

For a mixture of **49**-*E* and **49**-*Z*: IR (neat) 2935, 1716, 1626, 1564 $cm^{-1}$; **49**-*E* or **49**-*Z*: $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 2.2 Hz, 1H), 6.97 (dd, *J* = 11.0, 17.2 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.55 (d, *J* =2.2 Hz, 1H), 5.37 (d, *J* = 17.2 Hz, 1H), 5.29 (s, 2H), 5.18 (d, *J* = 11.0 Hz, 1H), 4.02 (s, 6H), 3.54 (s, 2H), 3.53 (s, 3H), 2.00 (s, 3H); **49**-*Z* or **49**-*E*: $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 2.2 Hz, 1H), 6.78 (dd, *J* = 10.8, 17.0 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 2.2 Hz, 1H), 5.43 (d, *J* = 17.0 Hz, 1H), 5.30 (d, *J* = 10.8 Hz, 1H), 5.29 (s, 2H), 4.02 (s, 6H), 3.54 (s, 2H), 3.53 (s, 3H), 1.96 (s, 3H); **49**-*E* or **49**-*Z*: HRMS ($FAB^+$) Calcd. for $C_{25}H_{26}O_7$ ($M^+$) 438.1679, found 438.1695.

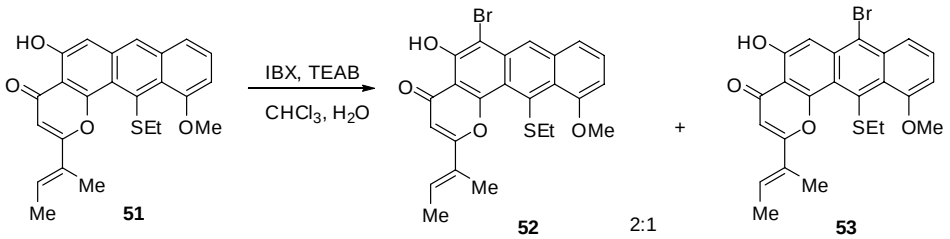



1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (282 μL, 2.07 mmol) was added dropwise to a solution of acid **48** (825 mg, 1.882 mmol) in $CH_2Cl_2$ (120 mL) at room temperature. The reaction mixture was then allowed to stir at room temperature for 1.5 h, after which time the reaction was quenched with water. The biphasic solution was separated and the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic phase was washed with water, dried over $Na_2SO_4$, filtered and concentrated by rotary evaporation. Purification with column chromatography on silica gel using hexane / ethyl acetate (4 / 1) as eluent gave tetracyclic pyrone **50** as a red solid (608 mg, 86%). Under the same conditions, the mixture of isomers **49**-*E* and **49**-*Z* was transformed to tetracyclic pyrone **50** with 50% isolated yield. IR (neat) 2927, 1670, 1618 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 12.82 (s, 1H), 7.92(s, 1H), 7.48 (d, $J$ = 7.6 Hz, 1H), 7.41 (t, $J$ = 7.6 Hz, 1H), 7.39 (dq, $J$ = 1.0, 7.0 Hz, 1H), 7.05 (s, 1H), 6.76 (d, $J$ = 7.6 Hz, 1H), 6.56 (s, 1H), 4.10 (s, 3H), 3.95 (s, 3H), 2.07 (d, $J$ = 1.0 Hz, 3H), 2.04 (d, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 183.5, 166.2, 157.1, 156.6, 156.4, 154.6, 137.6, 135.8, 133.5, 127.9, 120.7,

120.6, 117.6, 112.1, 111.8, 108.0, 104.9, 103.7, 63.7, 56.3, 15.0, 12.7; Anal. Calcd. for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36; O, 21.25. Found: C, 73.17; H, 5.28; O, 21.02.

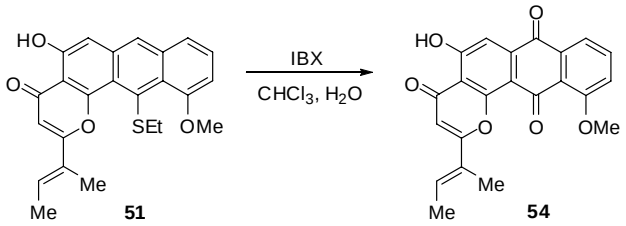



To a solution of aluminum trichloride (27mg, 0.20 mmol) in ethanethiol (0.5 mL) was added a solution of **50** (13 mg, 0.040 mmol) in dichloromethane (0.5 mL) at 0ºC. The reaction was stirred for 10 min. and quenched with aq. $NaH_2PO_4$. Extraction with ethyl acetate, drying over $Na_2SO_4$, removal of solvent by stirring the solution in a flask connected to an aspirator located in a hood with good ventilation and column chromatography (hexane / ethyl acetate = 2 / 1) gave red **51** (13 mg, 80%).$^1$H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.76 (q, *J* = 7.2 Hz, 1H), 7.45 (d, *J* =8.0 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.02 (s, 1H), 6.81 (d, *J* = 6.4 Hz, 1H), 6.50 (s, 1H), 4.09 (s, 3H), 2.57 (q, *J* = 7.6 Hz, 2H), 2.06 (s, 3H), 2.02 (d, *J* = 7.6 Hz, 3H), 0.84 (t, *J* = 7.6 Hz, 3H); HRMS ($FAB^+$) Calcd. for $C_{24}H_{23}O_4S_1[(M + H)^+]$ 407.1317, found 407.1326.

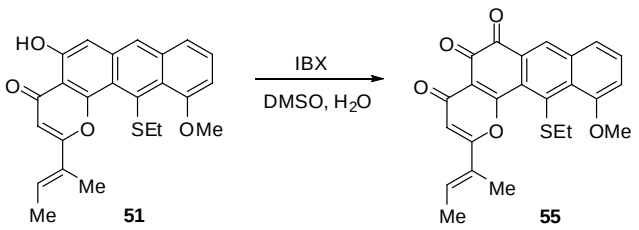



To a mixture of IBX (9.9 mg, 0.035 mmol) and TEAB ( one crystal) in chloroform (1 mL) and water (1 drop) was added a solution of **51** (13 mg, 0.032 mmol) in chloroform (0.5 mL) at room temperature. The reaction was stirred for 2.5 h and quenched with aq.

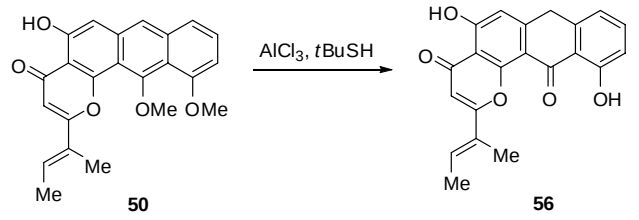
$NaH_2PO_4$. Extraction with ethyl acetate, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexane / ethyl acetate = 2 / 1) gave a mixture of **52** and **53** (2:1, together weighed 14 mg, 90%). **52**: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.76 (q, *J* = 7.2 Hz, 1H), 7.59 (d, *J* =8.4 Hz, 1H), 7.47 (t, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.53 (s, 1H), 4.10 (s, 3H), 2.58 (q, *J* = 7.6 Hz, 2H), 2.07 (s, 3H), 2.03(d, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.6 Hz, 3H); **53**: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.2 Hz, 1H), 7.76 (q, *J* = 7.2 Hz, 1H), 7.68 (s, 1H), 7.52 (dd, *J* =7.6 Hz, 8.8 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.50 (s, 1H), 4.10 (s, 3H), 2.53 (q, *J* = 7.6 Hz, 2H), 2.07 (s, 3H), 2.03(d, *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 7.6 Hz, 3H).




To a mixture of IBX (20 mg, 0.071 mmol) in chloroform (1 mL) and water (1 drop) was added a solution of **51** (8 mg, 0.020 mmol) in chloroform (0.5 mL) at room temperature. The reaction was stirred for 60 h and quenched with aq. $NaH_2PO_4$. Extraction with ethyl acetate, drying over $Na_2SO_4$ and concentration by rotary evaporation gave crude **54**. The crude material was washed with ethyl acetate to obtain pure **54** (6 mg, 80%). $^1$H NMR (600 MHz, $CDCl_3$) δ 13.86 (s, 1H), 7.91 (d, *J* =7.8 Hz, 1H), 7.71 (t, *J* = 8.4 Hz, 1H), 7.63 (q, *J* = 7.2 Hz, 1H), 7.59 (s, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 6.43 (s, 1H), 4.07 (s, 3H), 2.07(d, *J* = 7.2 Hz, 3H), 2.04 (s, 3H).

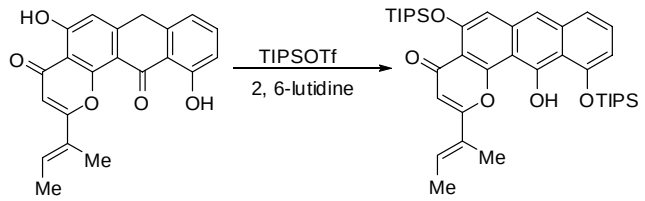



To a solution of **51** (12 mg, 0.030 mmol) in DMSO (1 mL) and water (0.5 mL) was added IBX (21 mg, 0.074 mmol) at room temperature. The reaction was stirred for 5 h and extracted with ethyl acetate. Washing with water, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 1 / 2) gave **55** (8 mg, 63%). $^1$H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.53 (t, *J* = 8.4 Hz, 1H), 7.49 (d, *J* =8.0 Hz, 1H),), 7.30 (q, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.33 (s, 1H), 4.03 (s, 3H), 2.70 (q, *J* = 7.2 Hz, 2 H), 1.90 (d, *J* = 7.2 Hz, 3H), 1.88 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); HRMS (FAB$^+$) Calcd. for $C_{24}H_{23}O_5S_1$ [(M + Li)$^+$] 423.1266, found 423.1265.



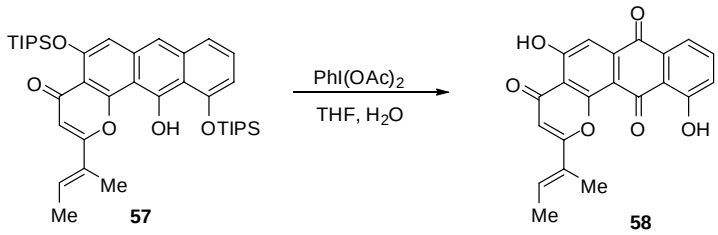

To a solution of aluminum trichloride (213 mg, 1.6 mmol) in *tert*-butanethiol (3.3 mL) was added a solution of **50** (30 mg, 0.080 mmol) in dichloromethane (1.5 mL) at 0ºC. The reaction was stirred for 4.5 h while warming to room temperature and quenched with aq. $NaH_2PO_4$. Extraction with ethyl acetate, drying over $Na_2SO_4$, removal of solvent by stirring the solution in a flask connected to an aspirator located in the hood with good ventilation and column chromatography (hexane / ethyl acetate = 2 / 1) gave colorless **56**

(23 mg, 83%).[1]H NMR (600 MHz, $CDCl_3$) δ 13.81 (s, 1H), 13.21 (s, 1H), 7.54 (q, *J* = 6.6 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 7.2 Hz, 1H), 6.72 (s, 1H), 6.37 (s, 1H), 4.35 (s, 2H), 2.03 (d, *J* = 7.2 Hz, 3H), 2.00 (s, 3H).




**56** **57**

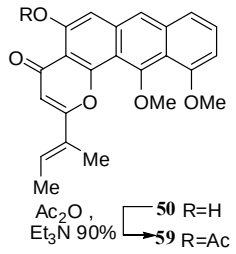
To a solution of **56** (10 mg, 0.029 mmol) in dichloromethane (1 mL) was added 2, 6-lutidine (13.4 μL, 0.12 mmol ) and TIPSOTf (15.1 μL, 0.069 mmol) at 0 ºC. The reaction was stirred for 1.5 h and quenched with methanol. Concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 4 / 1) gave **57** (11 mg, 59%). [1]H NMR (600 MHz, $CDCl_3$) δ 11.89 (s, 1H), 7.54 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.39 (q, *J* = 6.6 Hz, 1H), 7.28 (m, 1H), 6.92 (s, 1H), 6.65 (d, *J* = 7.2 Hz, 1H), 6.42 (s, 1H), 2.00 (s, 3H), 1.96 (d, *J* = 7.2 Hz, 3H), 1.55 (sept, *J* =7.2 Hz, 3H), 1.47 (sept, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 7.2 Hz, 18 H), 1.20 (d, *J* = 7.2 Hz, 18H).



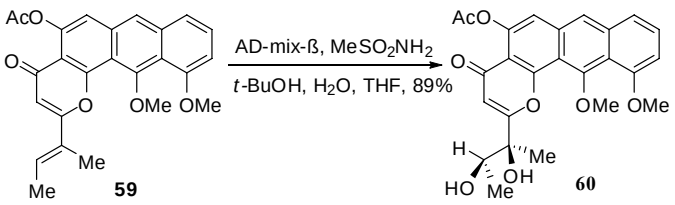

**57** **58**

To a solution of **57** (6.5 mg, 0.0098 mmol) in THF (0.4 mL) and water (0.1 mL) was added $PhI(OAc)_2$ (7.0 mg, 0.022 mmol) at room temperature. The reaction was stirred for 1.5 h. Extraction with ethyl acetate, drying over sodium sulfate, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 4 / 1) gave **58** (3 mg,

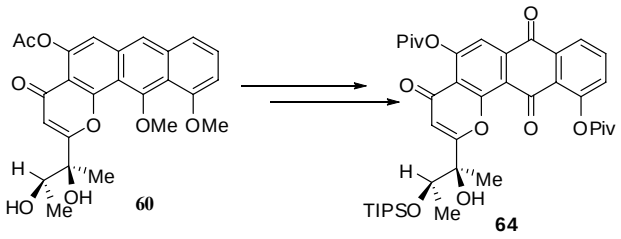
85%). $^1$H NMR (600 MHz, $CDCl_3$) δ 14.08 (s, 1H), 13.08 (s, 1H), 7.82 (d, *J* =7.2 Hz, 1H), 7.69 (s, 1H), 7.66 (t, *J* = 8.4 Hz, 1H), 7.61 (q, *J* = 7.2 Hz, 1H), 7.35 (d, *J* = 9.0 Hz, 1H), 6.46 (s, 1H), 2.08(d, *J* = 7.2 Hz, 3H), 2.05 (s, 3H).




To a solution of common intermediate pyrone **50** (30 mg, 0.08 mmol) in $CH_2Cl_2$ (5 mL) was added $Et_3N$ (22 μL, 0.16 mmol), DMAP (one crystal) and acetic anhydride (15.1 μL, 0.16 mmol) sequentially at 0ºC. The reaction mixture was stirred overnight while warming to room temperature. When TLC showed the completion of the reaction, water was added to quench the reaction. The biphasic solution was separated and the aqueous phase was washed with $CH_2Cl_2$. Combined organic phase was washed with water, dried over $Na_2SO_4$, filtered and concentrated by rotary evaporation. The residue was purified with column chromatography using hexane / ether (1 / 2) as eluent to give 5-acetoxy derivative **59** as a yellow solid (30 mg, 90%). IR (neat) 2933, 1767, 1645 $cm^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.47 (t, *J* = 8.1 Hz, 1H), 7.34 (s, 1H), 7.28 (q, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 8.1Hz, 1H), 6.42 (s, 1H), 4.11 (s, 3H), 3.94 (s, 3H), 2.49(s, 3H), 2.02 (s, 3H), 2.00 (d, *J* = 7.2 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 177.3, 170.6, 163.7, 157.0, 156.8, 156.4, 144.6, 137.0, 132.9, 131.6, 127.9, 127.7, 122.3, 120.7, 119.4, 116.6, 115.1, 114.4, 109.8, 104.8, 63.6, 56.2, 21.3, 14.7, 12.5; HRMS ($FAB^+$) Calcd. for $C_{25}H_{22}O_6Li$ [$(M + Li)^+$] 425.1576, found 425.1591.



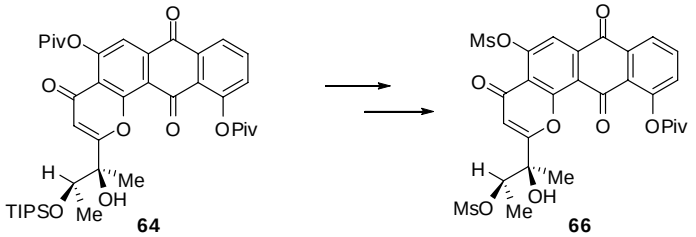

A mixture of AD-mix-β (203 mg), $MeSO_2NH_2$ (14 mg) in *t*-BuOH/$H_2O$ (1/1, 1.6 mL) was stirred at room temperature until the solution was clear. The solution was subsequently cooled to 0ºC, whereupon the inorganic salts were partially precipitated. The starting material **59** (29 mg, 0.069 mmol) in THF (1.1 mL) was added in one portion, and more water (1.1 mL) was added. The reaction mixture was allowed to stir at 0ºC for 24 h, then quenched with aq. $Na_2SO_3$ and stirred for further 20 min, which was extracted with ethyl acetate for three times. The combined organic phase was washed with water, brine, dried with $Na_2SO_4$, filtered and concentrated by rotary evaporation. Purification of the residue with column chromatography (hexane / ethyl acetate: 1 / 3) gave diol **60** as a yellow solid (28 mg, e*r*: 13:1 as determined by Mosher ester analysis, 89% yield). IR (neat) 3379, 2926, 1766, 1655 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.30 (s, 1H), 6.90 (d, *J* = 7.8 Hz, 1H). 6.68 (s, 1H), 4.42 (q, *J* = 6.6 Hz, 1H), 4.11 (s, 3H), 3.98 (s, 3H), 2.45 (s, 3H), 1.64 (s, 3H), 1.34 (d, *J* = 6.6 Hz, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 177.1, 171.1, 170.8, 157.4, 156.9, 156.8, 144.4, 137.3, 132.8, 128.4, 122.5, 120.9, 119.4, 117.3, 114.9, 114.8, 111.7, 105.3, 76.3, 71.3, 64.8, 56.4, 22.8, 21.4, 17.1; HRMS (ESI) Calcd. for $C_{25}H_{25}O_8$ $[(M + H)^+]$ 453.15439, found 453.15461; $[\alpha]^{26}_D$ = - 41 (c = 0.3, $CHCl_3$).




In a 50 mL Schlenk flask, *tert*-butanethiol (8.4 mL) was added to dissolve $AlCl_3$ (230 mg). The mixture was cooled to 0ºC, and a solution of diol **60** (39 mg) in $CH_2Cl_2$ (4.2 mL) was added in one portion. The reaction mixture was allowed to stir for 2.5 h while warming to room temperature, after which time the reaction solvent was removed by stirring in a flask connected to an aspirator located in a fume hood with good ventilation. Ethyl acetate (25 mL) and sat. aq. $NaH_2PO_4$ was added to the residue sequentially. The mixture was vigorously stirred under argon until the solids were dissolved. The biphasic solution was separated, and the aqueous phase was extracted two more times with ethyl acetate. The combined organic phase was washed with brine, dried with $Na_2SO_4$, filtered and concentrated by rotary evaporation. The residue was furthered dried under high vacuum, and used for the next one-pot oxidation step.

To a solution of the residue obtained above in THF (4.5 mL) was added 2,6-lutidine (204 μL, 1.72 mmol), TIPSOTf (234 μL, 0.862 mmol) sequentially. After the reaction mixture was stirred for about 30 min. and TLC showed completion of the reaction, water (0.9 mL) was added, followed by addition of the solid $PhI(OAc)_2$ (61 mg, 0.19 mmol) in one portion. The resulting mixture was stirred for further 30min. and then diluted with water, extracted three times with ethyl acetate. The combined organic phase was washed with sat. aq. $NaH_2PO_4$, water, brine, dried with $Na_2SO_4$, filtered and concentrated by rotary evaporation. The residue was further dried under high vacuum, and used for next protection step.

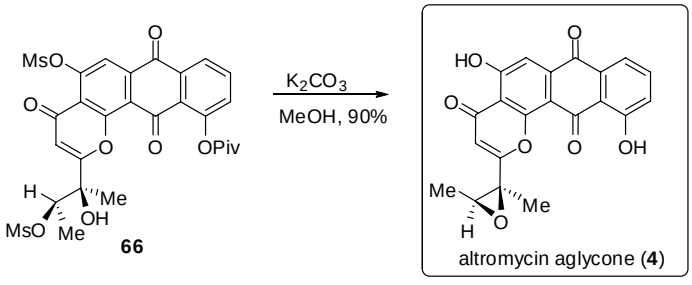
To a solution of the residue obtained above in $CH_2Cl_2$ (4.5 mL) was added sequentially DMAP (5 mg, 0.043 mmol), Pyridine (57 μL, 0.690 mmol) and PivCl (45 μL, 0.345 mmol) at room tempertature. The reaction mixture was stired until TLC showed completion of the reaction (about 40 min.), at which time the reaction was quenched with water and extracted twices with $CH_2Cl_2$. The combined organic phase was washed with water, dried with $Na_2SO_4$, filtered and concentrated by rotary evaporation. Purification of the residue with column chromatography (hexane/ethyl acetate: 6/1) gave colorless bispivaloate ester **64** (28 mg, 45% over 3 steps). IR (neat) 3520, 2941, 1760, 1680, 1662 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.8 Hz, 1H), 7.81 (s, 1H), 7.80 (t, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 6.66 (s, 1H), 4.81 (q, *J* = 6.6 Hz, 1H), 1.52 (s, 3H), 1.51 (s, 9H), 1.48 (s, 9H), 1.36 (d, *J* = 6.6 Hz, 1H), 0.91(m, 21H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 181.4, 179.1, 176.5, 176.3, 175.9, 173.7, 156.1, 154.8, 150.8, 137.0, 134.7, 134.0, 131.2, 126.6, 125.7, 121.9, 121.2, 117.2, 110.4, 76.6, 71.9, 39.5, 39.4, 27.5, 27.4, 22.4, 18.1, 18.0, 17.5, 12.8; HRMS (ESI) Calcd. for $C_{40}H_{53}O_{10}Si$ $[(M + H)^+]$ 721.34025, found 721.34106; $[\alpha]^{26}{}_D$ = - 32 (c = 0.2, $CHCl_3$).




A solution of bispivaloate ester **64** (17 mg, 0.024 mmol) in THF was treated with TBAF (1 M solution in THF, 110 μL) at room temperature for 30 min. The reaction was quenched with sat. aq. $NaH_2PO_4$ and extracted with ethyl acetate three times. The combined organic phase was washed with water, brine, dried with $Na_2SO_4$, filtered and

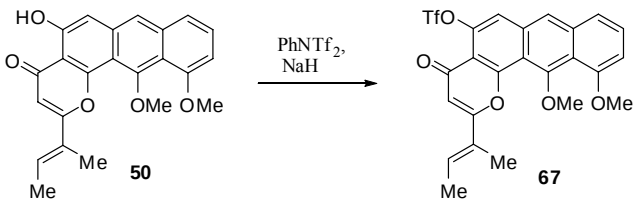
concentrated by rotary evaporation. The residue was further dried under high vacuum and used for next mesylation step.

To a solution of the residue obtained above in $CH_2Cl_2$ (1 mL) was added $Et_3N$ (9.8 mL, 0.07 mmol), MsCl (4 μL, 0.051 mmol) sequentially at -10 ºC. The reaction solution was stirred at -10 ºC for 10 min and quenched with sat. aq. $NaH_2PO_4$, extracted with $CH_2Cl_2$. The combined organic phase was washed with water, dried with $Na_2SO_4$, filtered and concentrated by rotary evaporation. The residue was purified with column chromatography (hexane / ethyl acetate: 1 / 1 to 2 / 3) to gave bismesylate **66** (8 mg, 54% over 2 steps). IR (neat) 3498, 1754, 1680, 1661 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.83 (t, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 1.2, 8.4 Hz, 1H), 6.65 (s, 1H), 5.42 (q, *J* = 6 Hz, 1H), 3.51 (s, 3H), 2.84 (s, 3H), 1.66 (s, 3H), 1.60 (d, *J* = 6 Hz, 3H), 1.52 (s, 9H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 180.5, 179.4, 176.4, 175.5, 170.3, 156.1, 150.8, 150.1, 137.3, 135.1, 133.8, 131.3, 126.5, 125.9, 122.2, 121.7, 118.4, 110.8, 81.1, 76.0, 39.7, 39.4, 38.5, 27.4, 22.8, 15.3; HRMS (ESI) Calcd. for $C_{28}H_{29}O_{13}S_2$ [(M + H)$^+$] 637.10441, found 637.10470; $[\alpha]^{26}{}_D$ = - 34 (c = 0.2, $CHCl_3$).



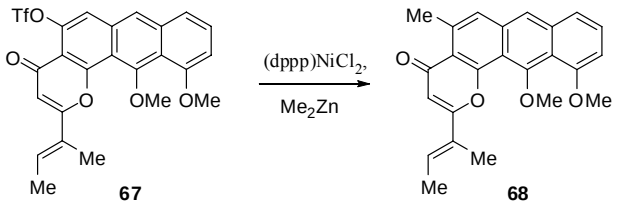

A solution of bismesylate **66** (9.0 mg, 0.014 mmol) in MeOH (4 mL) was treated with $K_2CO_3$ (40 mg, 0.28 mmol) for 5 h. The reaction was quenched with sat. aq. $NH_4Cl$ and extracted with ethyl acetate three times. The organic phase was washed with water, brine,

dried with $Na_2SO_4$, filtered and concentrated by rotary evaporation. The residue was crystallized in $CH_2Cl_2$ / ethyl ether to gave pure altromycin aglycone **4** (5 mg, 93%) as a yellow solid. IR (neat) 1639, 1572 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 13.84 (s, 1H), 13.00 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.72 (s, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 6.52 (s, 1H), 3.40 (q, *J* = 5.4 Hz, 1H), 1.94 (s, 3H), 1.33 (d, *J* = 5.4 Hz, 1H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 186.3, 182.8, 181.5, 169.7, 167.0, 162.8, 156.9, 140.1, 136.3, 132.5, 125.6, 119.8, 116.8, 113.8, 112.7, 111.2, 109.4, 63.0, 60.3, 20.0, 13.5; HRMS (FAB) Calcd. for $C_{21}H_{15}O_7$ [$(M + H)^+$] 379.0818, found 379.0818; $[\alpha]^{26}{}_D$ = - 114 (c = 0.3, $CHCl_3$); UV absorptions $\lambda^{MeOH}{}_{max}$ 226 (*A* 1.1062), 251 (0.9646), 299 (0.7365), 372 (0.3546), 495 nm (0.3750).



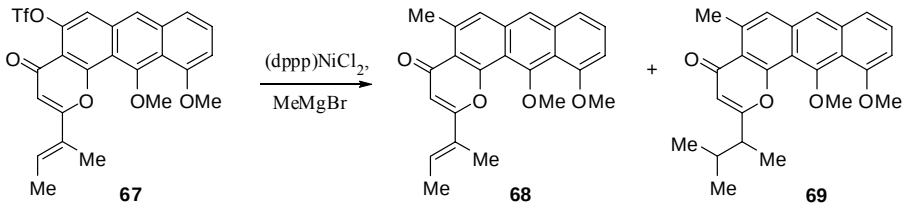

To a solution of common intermediate pyrone **50** (40 mg, 0.11 mmol) in THF (7.3 mL) was added NaH (60% dispersion in mineral oil, 4.3 mg, 0.11 mmol). The mixture was cooled to 0ºC, and a solution of $PhNTf_2$ (102.4 mg, 0.287 mmol) in THF (1.6 mL) was added in one portion. The reaction mixture was allowed to stir for 7 h, after which time the reaction was quenched with sat. aq. $NaH_2PO_4$ and was extracted with ethyl acetate for three times. The combined organic phase was washed with water, brine, dried with $Na_2SO_4$, filtered and concentrated by rotary evaporation. Purification with column chromatography (hexane / ethyl acetate: 2 / 1) gave triflate **67** (51 mg, 94%) as a yellow solid. IR (neat) 2924, 1645 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.60 (d, *J* =

8.4 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.31 (q, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 7.2Hz, 1H), 6.52 (s, 1H), 4.14 (s, 3H), 3.97 (s, 3H), 2.05 (s, 3H), 2.03 (d, *J* = 7.2 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 176.6, 164.2, 157.2, 157.1, 157.0, 143.5, 137.4, 132.3, 131.7, 128.9, 127.8, 123.6, 122.3, 120.9, 120.4, 120.2, 118.1, 117.8, 116.0, 115.5, 114.2, 110.1, 105.9, 64.1, 56.5, 15.0, 12.7; HRMS (ESI) Calcd. for $C_{24}H_{19}O_7F_3Na_1S_1$ [$(M + Na)^+$] 531.06958, found 531.06974.

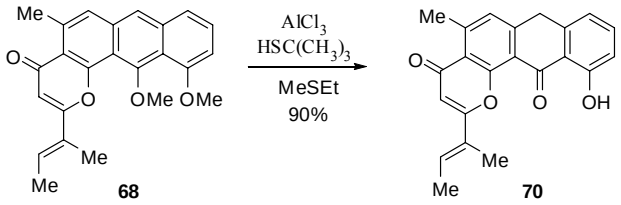



To a solution of triflate **67** (54 mg, 0.106 mmol) in THF (13 mL) was added sequentially (dppp)$NiCl_2$ (5.76 mg, 0.011 mmol), $Me_2Zn$ (2 M in toluene, 0.21 mL, 0.42 mmol) at room temperature. The solution was stirred at room temperature for 3 h and TLC showed completion of the reaction. The reaction was quenched with sat. aq. $NaH_2PO_4$ and was extracted with ethyl acetate for three times. The combined organic phase was washed with water, brine, dried with $Na_2SO_4$, filtered and concentrated by rotary evaporation. Purification with column chromatography (hexane / ethyl acetate: 2 / 1) gave methylation product **68** (33 mg, 83% yield). IR (neat) 2927, 1639 $cm^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.46 (s, 1H), 7.45 (t, *J* = 8.4 Hz, 1H), 7.31 (q, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 6.50 (s, 1H), 4.11 (s, 3H), 3.94 (s, 3H), 2.94 (s, 3H), 2.04 (s, 3H), 2.01 (d, *J* = 7.2 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 180.8, 163.5,

157.1, 156.9, 156.1, 137.1, 134.9, 134.3, 131.3, 128.0, 127.5, 126.1, 121.8, 121.0, 120.0, 119.2, 115.8, 110.2, 104.5, 63.7, 56.4, 23.8, 14.9, 12.7; HRMS (ESI) Calcd. for $C_{24}H_{23}O_4$ $[(M + H)^+]$ 375.15909, found 375.15905.

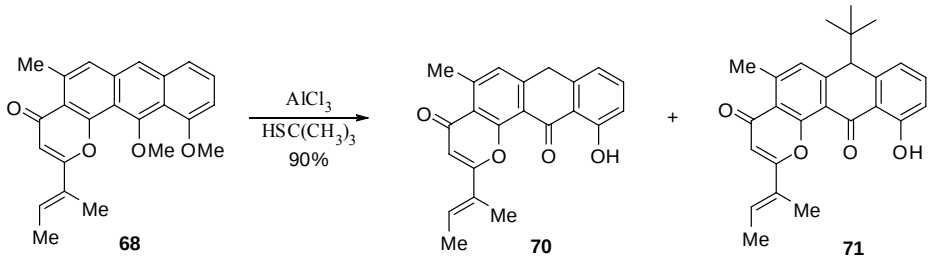



To a solution of triflate **67** (10 mg, 0.020 mmol) in THF (2.5 mL) was added sequentially (dppp)$NiCl_2$ (1.6 mg, 0.003 mmol), MeMgBr (3 M $Et_2O$, 0.033 mL, 0.098 mmol) at room temperature. The solution was stirred at room temperature for 2.5 h. The reaction was quenched with sat. aq. $NaH_2PO_4$ and was extracted with ethyl acetate three times. The combined organic phase was washed with water, brine, dried with $Na_2SO_4$, filtered and concentrated by rotary evaporation. Purification with column chromatography (hexane / ethyl acetate: 2/1) gave methylation product **68** (4 mg, 54%) and **69** (2 mg, 26%). **69**: $^1$H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.49 (s, 1H), 7.46 (t, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.43 (s, 1H), 4.11 (s, 3H), 4.01 (s, 3H), 2.94 (s, 3H), 2.70 (quint, *J* =7.2 Hz, 1H), 2.33 (sept, *J* = 6.8 Hz, 1H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H).

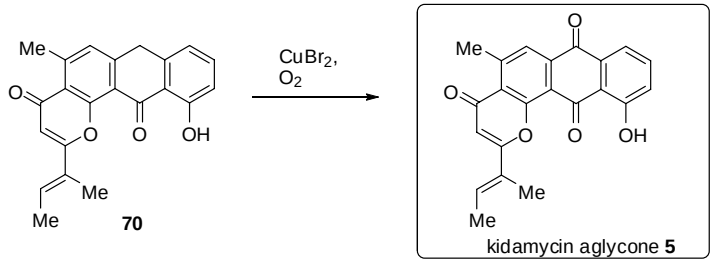



$AlCl_3$ (50 mg, 0.37) was put in a 25 mL Schlenk flask, and *tert*-butanethiol (1 mL) was added. After the solid was dissolved, the mixture was cooled to 0ºC. Ethyl methyl sulfide (0.1 mL) and a solution of **68** (7.0 mg, 0.019 mmol) in $CH_2Cl_2$ (0.4 mL) was added sequentially to the mixture. The resulting reaction mixture was stirred for 2.5 h while warming to room temperature, after which time sat. aq. $NaH_2PO_4$ and ethyl acetate was added sequentially to the reaction mixture. The biphasic solution was stirred vigorously under argon atmosphere to dissolve the solid. The organic phase was separated, and more ethyl acetate was added to the cloudy aqueous phase. This stirring-separation sequence was repeated several times until all the solids were dissolved (Note that weakly acidic workup conditions will not dissolve the solid, while strongly acidic workup conditions such as 1 M aq. HCl will decompose the product). The combined organic phase was washed with water, brine, dried with $Na_2SO_4$, filtered and concentrated by stirring in a flask connected to an aspirator located in a fume hood with good ventilation. Purification with column chromatography (hexane / ethyl acetate: 4 / 1 to 2 / 1) gave anthrone **70** (6.0 mg, 92%). IR (neat) 2925, 1636, 1587 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 13.12 (s, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.46 (q, *J* = 7.2 Hz, 1H), 7.09 (s, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 7.2Hz, 1H), 6.32 (s, 1H), 4.36 (s, 2H), 2.90 (s, 3H), 2.00 (d, *J* = 7.2 Hz, 3H), 1.97 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 188.5, 180.4, 163.6, 163.2, 157.4, 147.4, 147.3, 139.8, 135.6, 133.8, 127.6, 127.3, 121.6, 118.8, 118.2, 117.6, 115.9, 108.7, 33.6,

24.0, 15.1, 12.4; HRMS (ESI) Calcd. for $C_{22}H_{19}O_4$ [(M + H)$^+$] 347.12779, found 347.12788.




The procedure is the same as above except that methyl ethyl sulfide was not used here. The ratio of products **70** / **71** is about 2:1. **71**: $^1$H NMR (600 MHz, $CDCl_3$) δ 7.44 (q, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.13 (s, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 7.2Hz, 1H), 6.34 (s, 1H), 3.85 (s, 1H), 2.94 (s, 3H), 2.01 (d, *J* = 7.8 Hz, 3H), 1.99 (s, 3H), 0.86 (s, 9H).




To a solution of anthrone **70** (6.0 mg, 0.017 mmol) in THF (1.5 mL) was added $CuBr_2$ (2.1 mg, 0.0095 mmol) and water (0.15 mL). The reaction mixture was stirred under oxygen for 4.5 h at room temperature. The solvent was removed and the residue was dissolved in $CH_2Cl_2$. The solution was washed with water, dried with $Na_2SO_4$, filtered and concentrated by rotary evaporation. Purification with column chromatography (hexane / ethyl acetate: 4 / 1 to 2 / 1) gave kidamycin aglycone **5** (5 mg, 80% yield) as a

yellow solid. IR (neat) 2920, 1640 $cm^{-1}$; $^{1}H$ NMR (600 MHz, $CDCl_3$) δ 12.94 (s, 1H), 8.04 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.51 (q, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 6.39 (s, 1H), 3.02 (s, 3H), 2.04 (d, *J* = 7.8 Hz, 3H), 2.01 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 187.7, 182.1, 179.9, 164.3, 162.8, 156.4, 150.0, 136.6, 136.2, 134.7, 132.5, 127.5, 126.6, 125.7, 125.5, 119.8, 119.6, 117.0, 109.0, 24.4, 15.3, 12.4; HRMS (APCI) Calcd. for $C_{22}H_{17}O_5$ [$(M + H)^+$] 361.10705, found 361.10723; ); UV absorptions $\lambda^{MeOH}_{max}$ 244 (*A* 0.5772), 266 (0.4018), 327 nm (0.1870).

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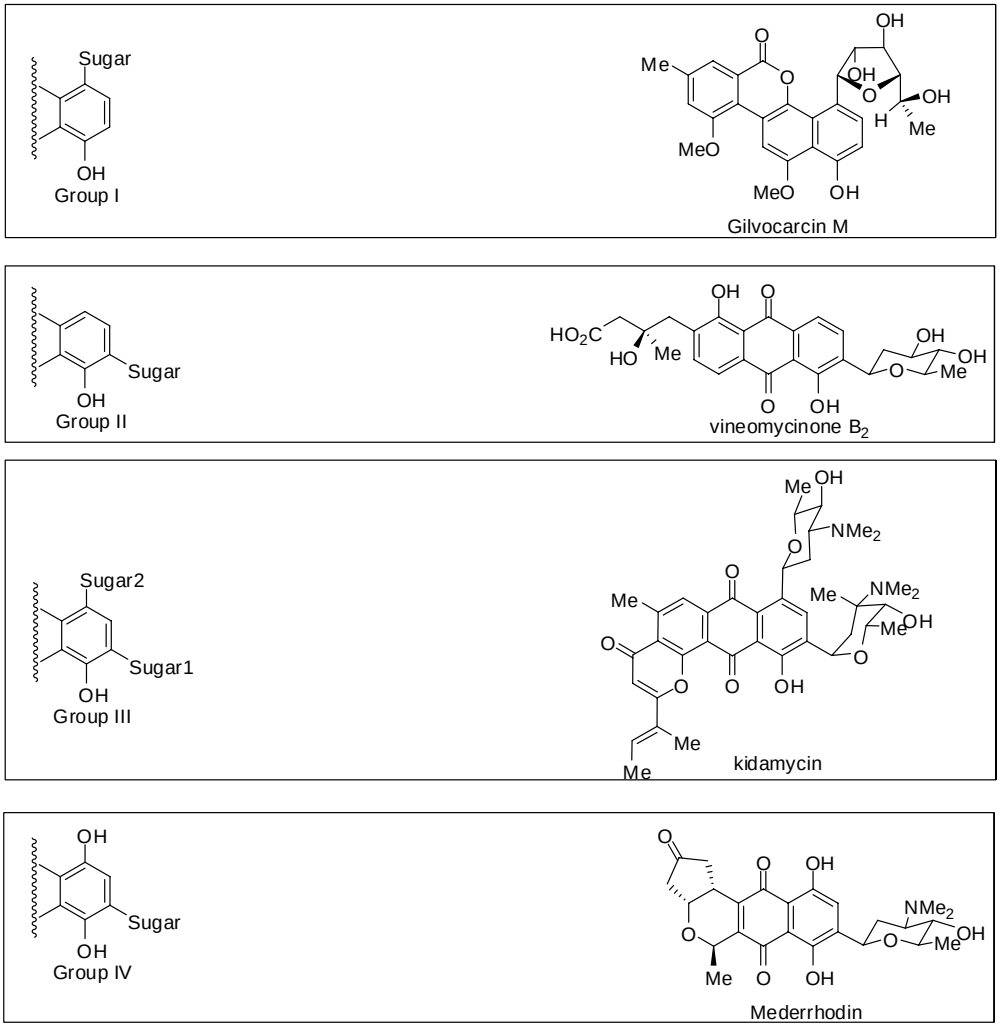
# Chapter 2. Studies towards the Total Synthesis of Kidamycin

## 2.1 Background and strategy

The defining structural character of a *C*-aryl glycoside is the carbon-carbon bond connecting C-1 of a carbohydrate moiety directly to an aromatic ring. The structures of *C*-aryl glycosides are embedded in various biologically important natural products. Based on the substitution pattern of the glycosylated aromatic ring, natural *C*-aryl glycosides have been classified into four groups to develop their synthetic approaches.[1] The group I *C*-glycoside has a sugar *para* to phenolic hydroxyl group as exemplified by gilvocarcin M (figure 1).[2] The group II *C*-glycoside has a sugar *ortho* to phenolic hydroxyl group as exemplified by vineomycinone $B_2$.[3,4] The group III *C*-glycoside has two sugars, one *para* and the other *ortho* to phenolic hydroxyl group; and kidamycin[5] is in this group. In the group IV *C*-glycoside, the sugar is *ortho* to one hydroxyl group of a hydroquinone ring and *meta* to the other as exemplified by mederrhodin B.[6]

Synthetic achievements in this area include an efficient total synthesis of gilvocarcin M,[7] several syntheses of vineomycinone $B_2$ methyl ester[8-13] and a demonstration of the biosynthesis of mederrhodin.[14] The total synthesis of kidamycin or any other group III natural glycoside has not been achieved; and only two model studies in developing methods to access to this group of natural *C*-glycoside have been reported by Parker's[15] and Martin's[16,17] laboratory.

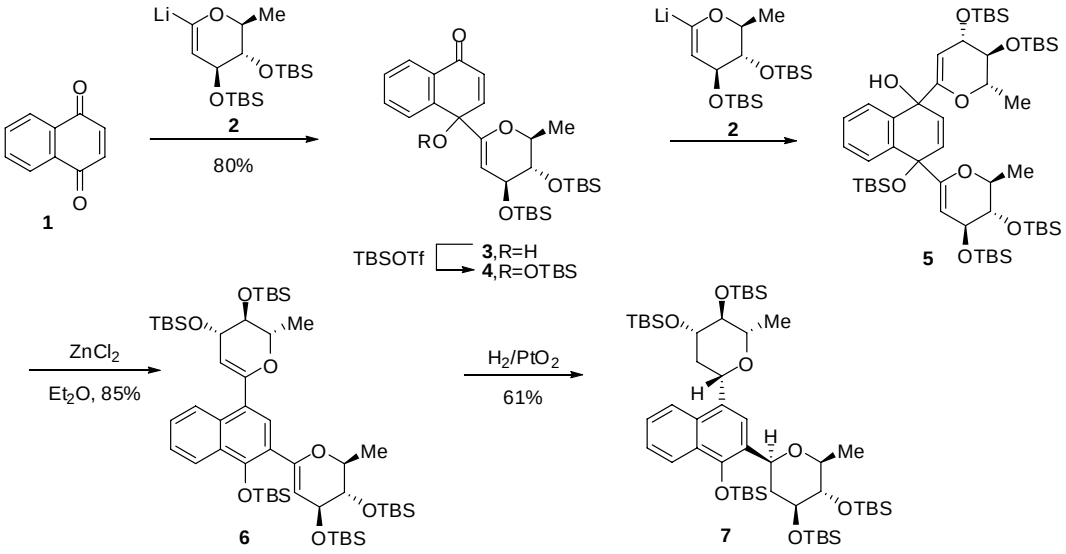
**Figure 1.** Four types of natural *C*-aryl glycoside




In combining the 'reverse polarity' approach with Lewis acid-catalyzed rearrangement, Parker's group was able to synthesize kidamycin model compound **7** as shown in scheme 1.[15] The electronic property of aromatic compound in this approach is usually reversed by oxidation to quinone so that it can accept a nucleophilic lithiated glycal. In this sense of "reverse polarity", adduct **3** was obtained from direct addition of **2** to **1** in good yield. Following a silyl protection to **4**, the second addition of lithiated glycal **2** to the other carbonyl of the quinone produced adduct **5**. Chemoselective

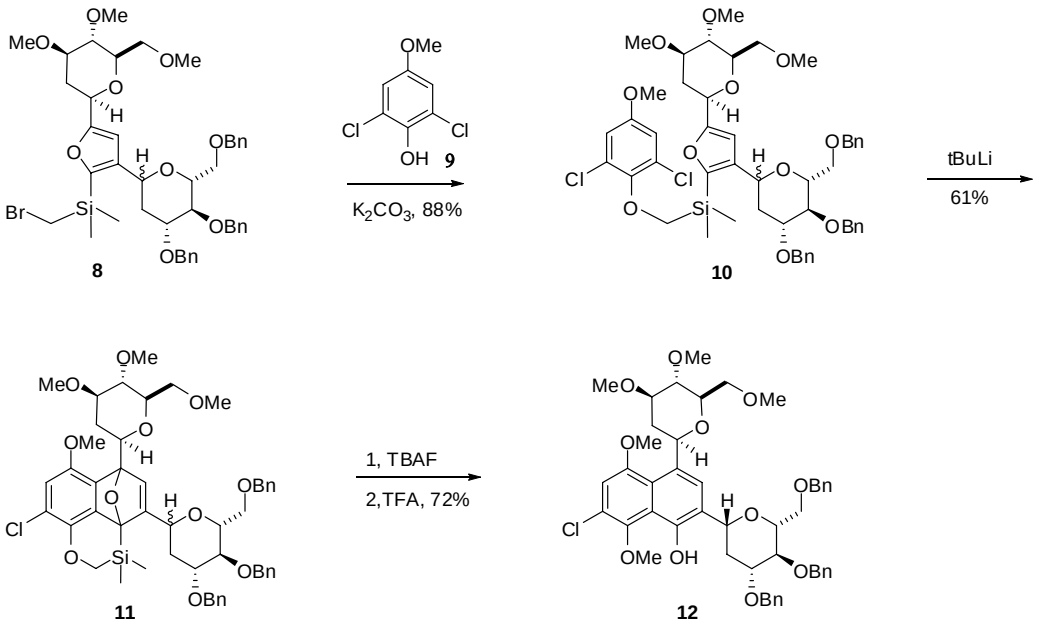
rearrangement of one glycal as a result of selective coordination of the Lewis acid to hydroxyl group instead of siloxyl group, followed by hydrogenation, led to the formation of **7** as a model compound of kidamycin. The functional compatibility due to strong basic conditions and the regioselectivity of glycal-lithiate addition to unsymmetric quinone might be difficult questions to address in applying this methodology for the total synthesis of kidamycin.

**Scheme 1.** Parker's model study for kidamycin



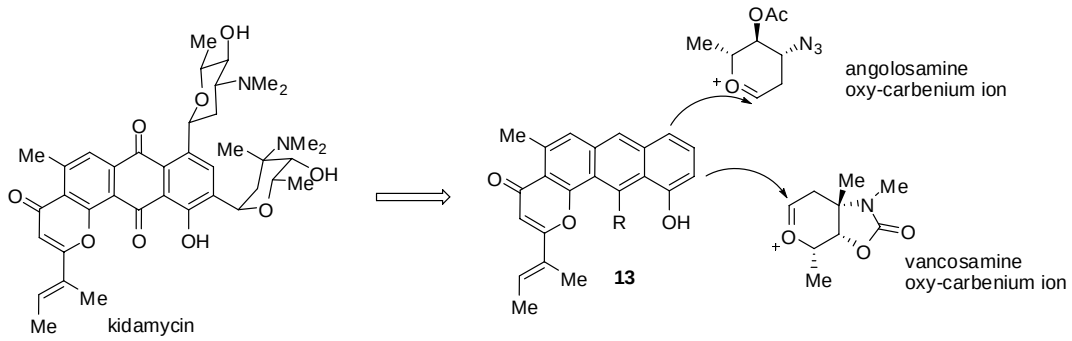

Martin's method avoided the difficult late-stage glycosylation problem by attaching the sugars at the beginning to a simple furan, which underwent a Diels-Alder cycloaddition with a benzyne to construct the aglycone portion of the glycoside.[16] In order to solve the regioselectivity problem, the furan bearing two sugars had to be tethered by silicon to an aromatic ring used as the benzyne precursor to form **10** (scheme 2)[17]. An intramolecular regiospecific Diels-Alder reaction followed by cleavage of carbon-silicon bond and acid-catalyzed ring opening delivered kidamycin model compound **12**. Though creative, this method still posed a challenge to synthesize the correct precursor for cycloaddition reaction in the scenario of kidamycin total synthesis.

**Scheme 2.** Martin's model study for kidamycin




Taking advantage of substrate electronic properties, we were generally interested in exploring direct sequential glycosylations between an aglycone intermediate as a nucleophile and two sugars as electrophiles in the form of their transient oxy-carbenium ions to access to kidamycin (Figure 2).

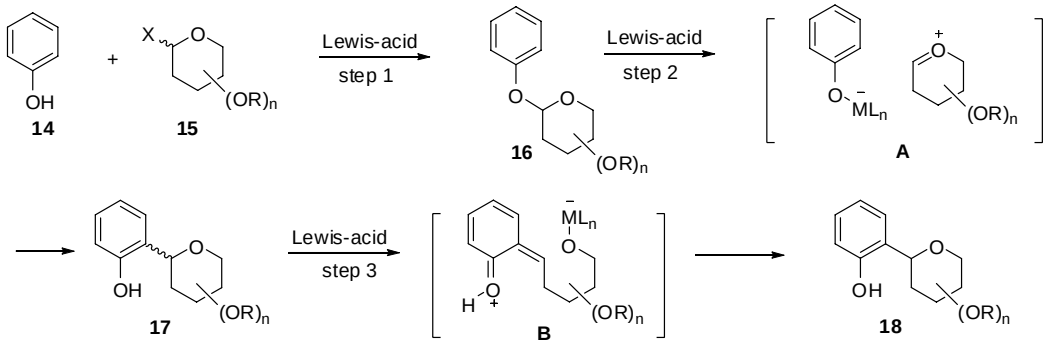
**Figure 2.** Synthetic strategy




The basis for our strategy is the availability of methods for direct glycosylation with "normal electron polarity", especially *O*→*C*-glycoside rearrangement[18] that has been applied in the total synthesis of gilvocarcins.[7] This reaction is a Lewis-acid promoted multi-step transformation, involving (1) the *O*-glycosylation to form **16**, (2) the

ortho regioselective rearrangement to form **17** via ion pair **A**, and (3) the stereochemical mutation to form **18** via quinonemethide species **B**. Various Lewis acids are employable for this reaction, such as $BF_3$-$OEt_2$,[19,20] $SnCl_4$,[21] TMSOTf,[22,23] $Sc(OTf)_3$,[18] and $Cp_2MCl_2$—AgX combinations (M=Zr, Hf).[24,25]

**Figure 3.** *O→C* - glycoside rearrangement




We speculated that the *ortho*-vancosamine could be introduced to intermediate **13** by *O→C*-glycoside rearrangement, while the *para*-angolosamine could be introduced by the same rearrangement but to the *para* position with the *ortho* position occupied, or by a direct Friedel-Crafts-type reaction.[26] The theme to a successful outcome is to find a good combination of glycosyl donors (sugar) and glycosyl acceptors (aglycone intermediate).

## 2.2 Results and discussion

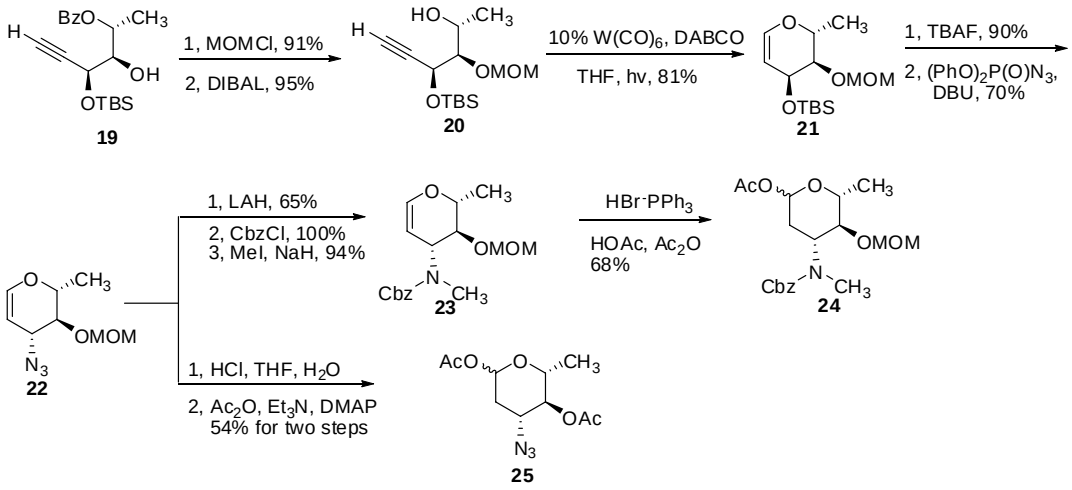
### 2.2.1 Initial glycosylation studies

#### *2.2.1.1 Angolosamine glycosyl donor*

The synthesis of angolosamine glycosyl donors began with the known compound **19**,[27] obtained by selective silylation of propargylic hydroxyl group (scheme 3). Protection of the second hydroxyl group as MOM ether followed by reductive cleavage of benzoyl protective group afforded precursor **20**, which underwent a tungsten catalyzed

cycloisomerization[27,28] to produce glycal **21**. Removal of silyl protective group allowed a direct $S_N2$ substitution[29] to introduce an azide group with inversion of stereochemistry to produce **22**. Initial advancement of **22** involved LAH reduction of azide to amine, protection as carbamate followed by methylation to provide glycal **23.** Although glycal **23** itself could be a potential glycosyl donor under promotion of protonic acid,[27] it was further treated with acetic acid under HBr-$PPh_3$ catalysis to produce **24** for broader choice of Lewis acid as promoter for glycosylations. Unfortunately, compound **24** turned out to be a problematic glycosyl donor. The nucleophilic carbonyl group of the carbamate might have competed with the aromatic compound in the glycosylation. It was also found that MOM protective group was partially deprotected under glycosylation conditions. Thus a better glycosyl donor needed to be identified.

**Scheme 3.** Synthesis of angolosamine glycosyl donor



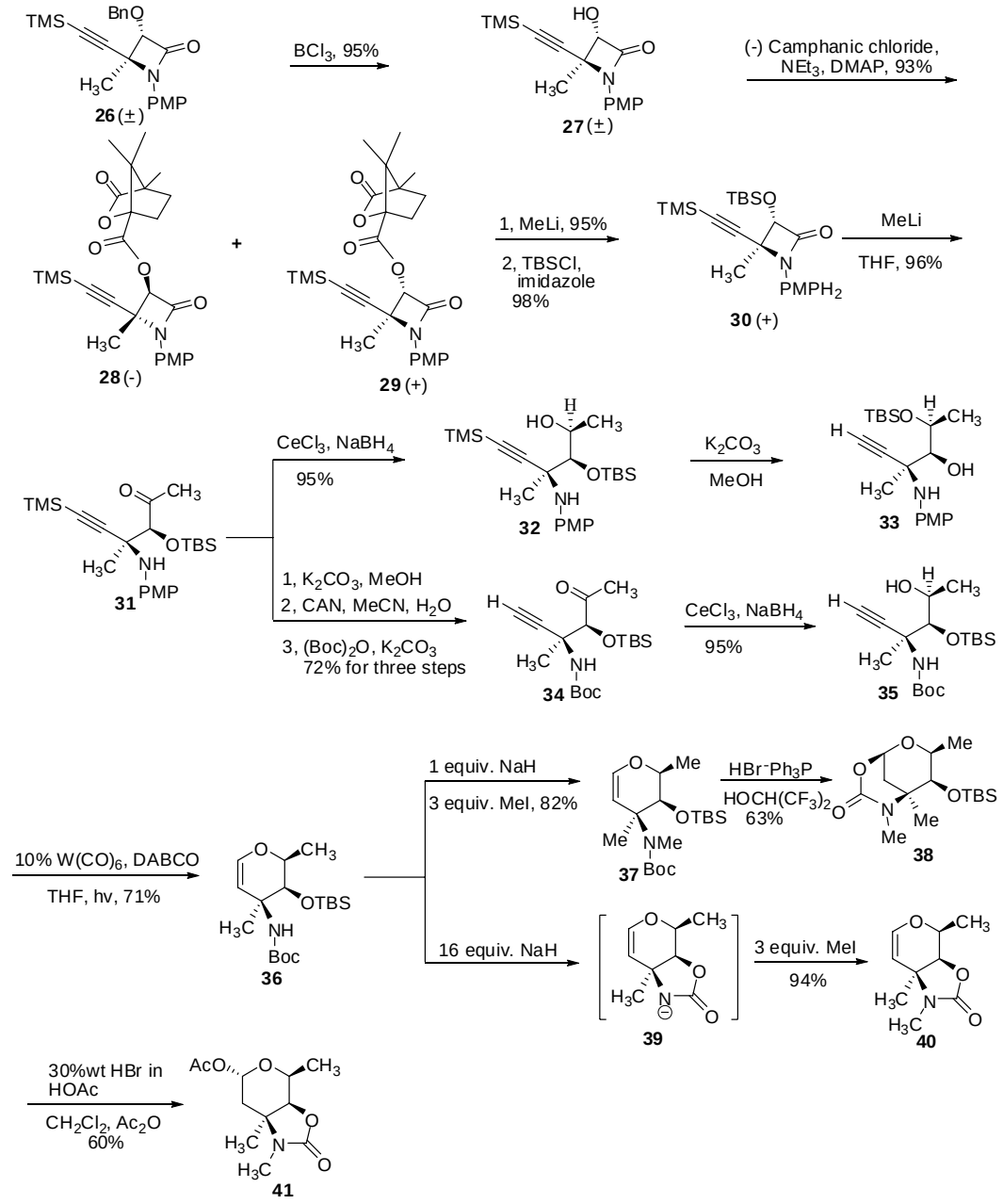

Treatment of glycal **22** with hot acidic solution[30] effectuated a one-pot hydrolysis of vinyl ether and cleavage of MOM ether to produce the diol, which were acylated to generate **25** as a better angolosamine glycosyl donor. The MOM protection was switched to acetyl in this manner to avoid the partial deprotection problem. The azide was kept

until after glycosylation because it provides a non-basic and more reactive surrogate compared to the amine alternatives.[31]

*2.2.1.2 Vancosamine glycosyl donor*

The synthesis of L-vancosamine glycosyl donor was developed on the basis of previous elegant racemic synthesis of vancosamine glycal,[32] beginning with the cleavage of benzyl ether of known racemic **26** (scheme 4). Derivatization of **27** by enantiomerically pure camphanic chloride[33] provided two chromatographically separable diastereomer **28** and **29**. The desired diastereomer **29** was treated with MeLi to cleave the auxiliary while retaining the alkynyl TMS group, followed by silyl ether protection to generate enantiomerically pure **30**. β-lactam **30** was subsequently opened by addition of MeLi to afford **31**. The presence of alkynyl TMS protection was probably important for this addition to achieve high efficiency. In following the original racemic synthesis,[32] the ketone of **31** was reduced with excellent Felkin-Anh control to provide **32** as a single diastereomer. However, the basic methanolysis reaction to remove alkynyl TMS protective group caused the undesired migration of TBS ether to the adjacent less hindered hydroxyl group to produce **33**.

**Scheme 4.** Synthesis of vancosamine glycosyl donor




The TBS migration problem was solved by changing the functionalization sequence, by first removing alkynyl TMS protective group, followed by oxidative cleavage of PMP protection and formation of carbamate to provide **34.** Treatment of **34** with the same Luche reduction conditions produced alkynol **35** without causing silyl migration; glycal **36** was thereby obtained by applying tungsten catalyzed

cylcoisomerization reaction.[27,28] In a regular *N*-methylation reaction of substrate **36**, the formation of bicyclic byproduct **40** was found to compete with the formation of main product **37**. Although compound **37** was favored by using exactly one equivalent of the base, it was found to be a problematic glycosyl donor due to the participation of carbonyl oxygen as a nucleophile to form **38** in glycosylation model studies, and the formation of **38** could also be carried out in non-nucleophilic protonic solvent under catalysis of protonic acid. Compound **40** would not have this problem to be a glycosyl donor because of its restricted carbonyl orientation, and the bicyclic feature of **40** might favor the desired convex-side attack during glycosylation. More significantly, compound **40** is known with its optical rotation reported in the literature,[34] thus setting the basis for us to determine the absolute configuration in support of chromatographic resolution by simply tracking their optical rotations.[35] Optimization to form **40** was finally achieved by treating **36** with 16 equivalents of NaH at room temperature until complete conversion to **39 (**by TLC) followed by the addition of MeI. Later, my colleague Bonsuk Koo found that only 2.5 equivalents of NaH was needed for formation of bicyclic **40** from the Cbz anolog of **36**. Thus Cbz-**36** instead of Boc-**36** was used as the intermediate in preparing the materials. Further derivatization of glycal **40** to glycosyl acetate **41** as vancosamine glycosyl donor[36] broadened the choice of conditions for glycosylations.

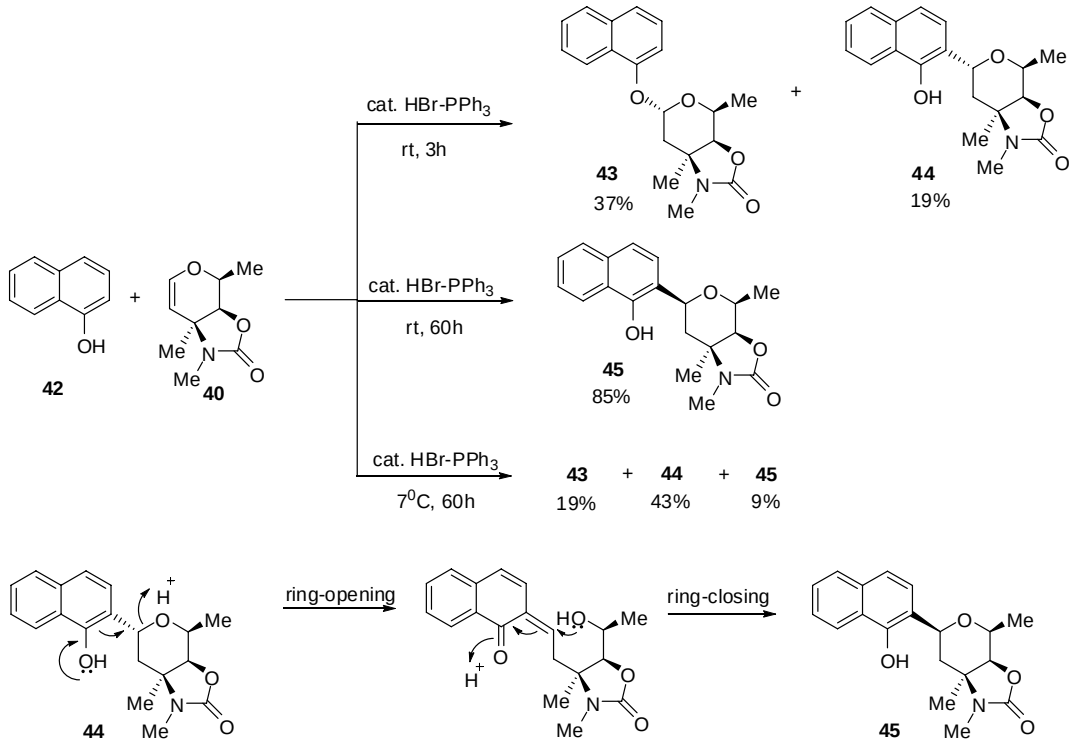
*2.2.1.3 Glycosylations with vancosamine glycosyl donor*

(1) Glycosylation of 1-naphthol

Glycosylation studies began with 1-naphthol **42** as a model compound (scheme 5). It was expected to produce *C*-glycoside compound **44** with glycal **40** through two

separate steps; namely *O*-glycosylation under catalysis of HBr-$PPh_3$[27] followed by *O*→*C*-glycoside rearrangement under Lewis acid promotion.[19]

**Scheme 5.** Glycosylation of 1-naphthol




Intriguingly, catalytic amount of HBr-$PPh_3$ not only trigged the expected *O*-glycosylation to produce **43** but also promoted further rearrangement to *C*-glycoside **44**, as **43** and **44** were isolated respectively in 37% and 19% yield after 4 hours of reaction. Extension of the reaction time to 60 hours completed the *in situ* *O*→*C*-glycoside rearrangement, while giving different *C*-glycoside anomer (**45)** as the only product, presumably due to anomerization of **44** by a pyran ring-opening and closing pathway as demonstrated in the bottom of the scheme 5. The contrast of isolating some **44** in short reaction time with only **45** in long reaction time indicates that **44** is probably the kinetically favored product, while **45** is thermodynamically favored. Temperature might therefore be an important factor in controlling the reaction outcome. Indeed, when this

reaction was done at 7ºC instead of room temperature, the desired **44** was obtained as major product (43%) along with some *O*-glycoside **43** (19%) and anomer **45** (9%). Further lowering the reaction temperature slowed down the reaction too much to be practical.

Although it is reported that kidamycin natural product anomerizes at the *C*-vancosamine moiety to produce *epi*-kidamycin upon refluxing in acidified chloroform,[37] this study indicates how easy the anomerization is with an electron-rich aromatic substructure, and provides a potential solution to solve the anomerization problem in the total synthesis.

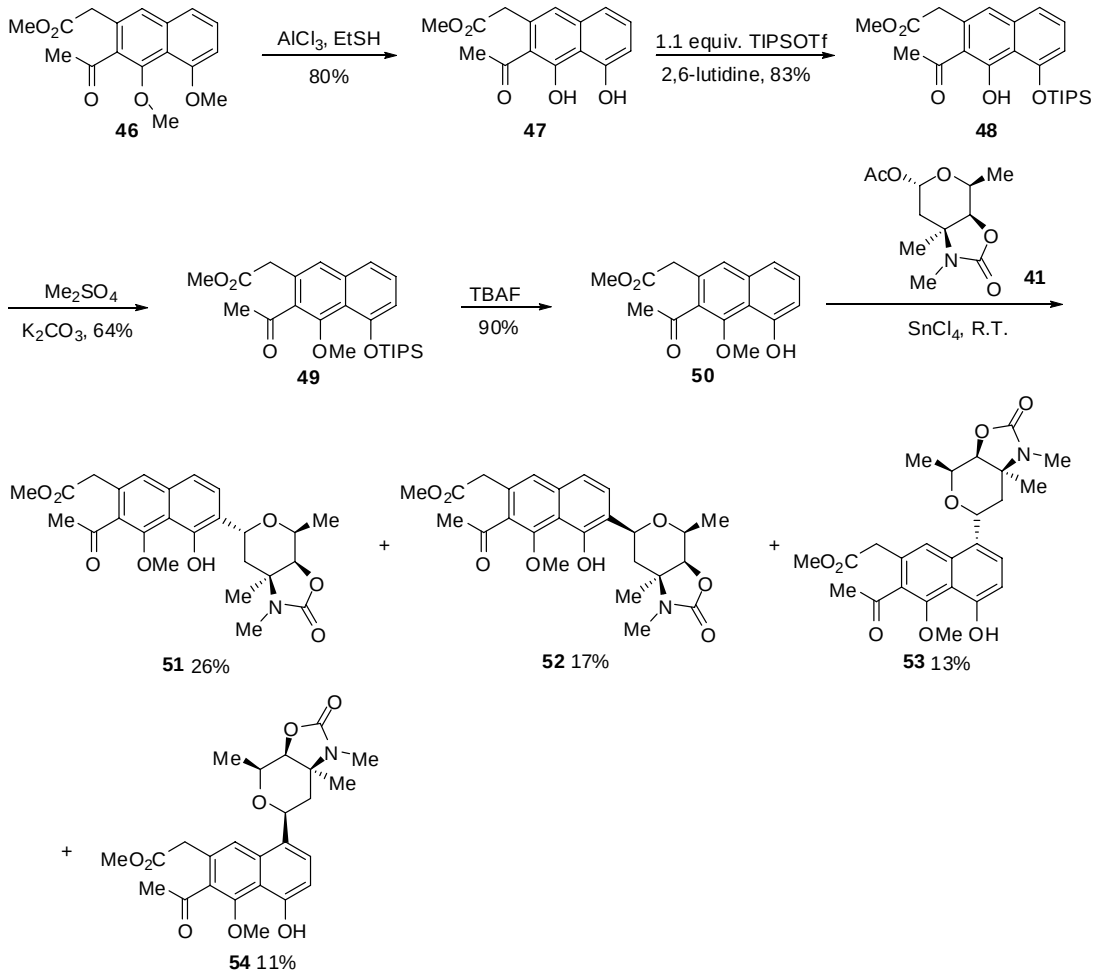
(2) Glycosylation of naphthalene-type synthetic intermediate

Identification of a good glycosyl acceptor is as important as finding good glycosyl donors for the total synthesis of kidamycin. Along the synthetic route of kidamycin agyclone as described in chapter 1, two types of intermediate were considered for glycosylations: naphthalene-type and anthracene-type. The advantage of using naphthalene-type is the easier access to large amounts of material for the relatively difficult glycosylation studies.

Modification of the known intermediate **46** to glycosyl acceptor **50** and its glycosylation with vancosamine glycosyl donor is shown in scheme 6. Following double demethylation of **46**, diol **47** was selectively silylated at the less hindered hydroxyl group to differentiate the two. Using more TIPSOTf caused enol silylation of the ketone present in **48.** Methylation of the hindered hydroxyl group was achieved in 64% yield by

$Me_2SO_4$, under which conditions **46** was also produced as a byproduct in 29% yield. Removal of silyl ether provided naphthol **50** for glycosylation.

**Scheme 6.** Modification to naphthalene-type glycosyl acceptor **50** and the glycosylation of **50**



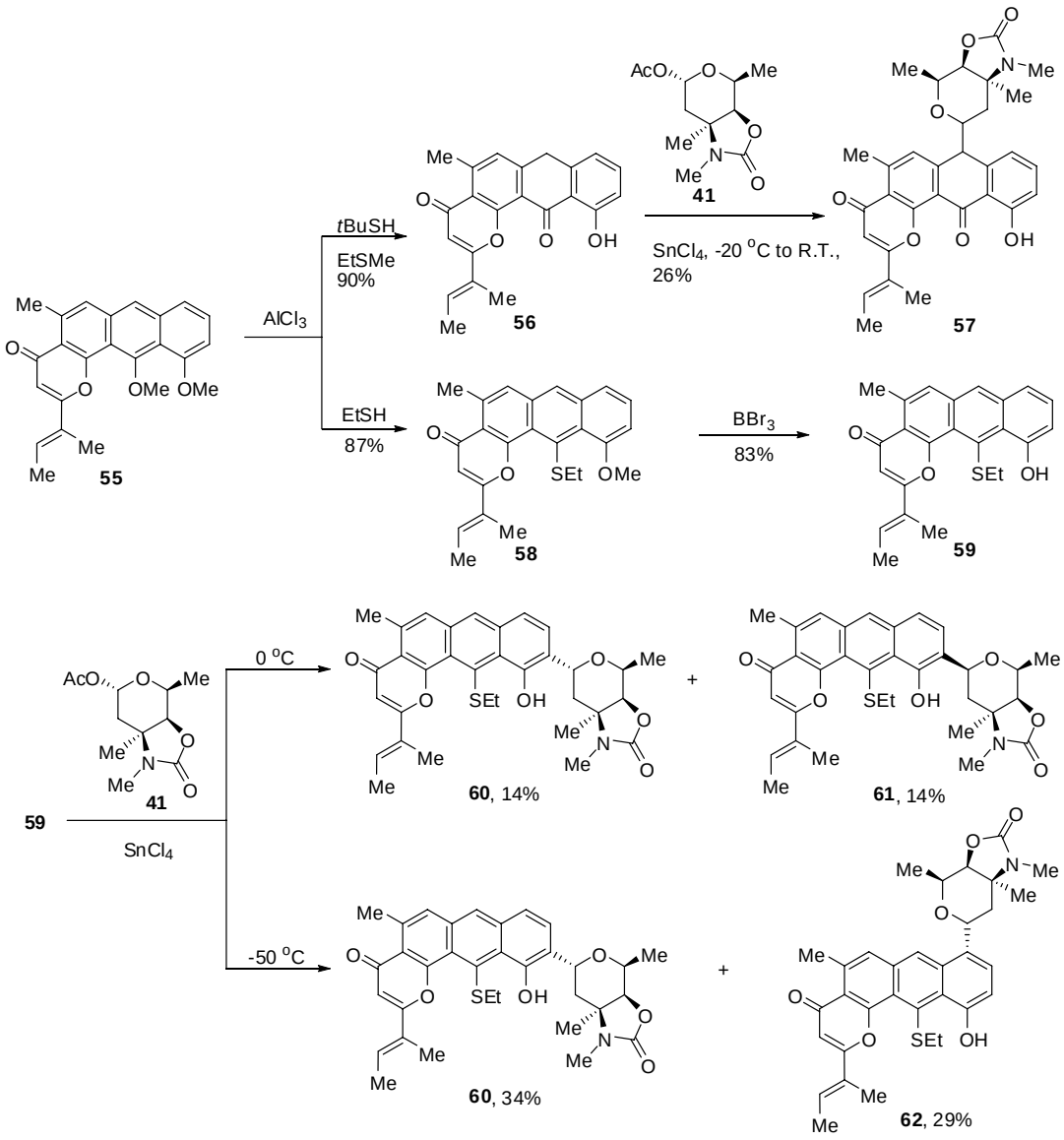

No reaction occurred when **50** was mixed with glycal **40** in the presence of HBr-$PPh_3$.[27] The lower reactivity of **50** compared to 1-naphthol **42** was probably due to hydrogen bonding of the hydroxyl group with the neighboring oxygen. However, when naphthol **50** was mixed with glycosyl donor **41** in the presence of $SnCl_4$,[31] a mixture of four products was produced, corresponding to two *ortho*-glycosylation products (**51**, **52**) and two *para*-glycosylation products (**53**, **54**). Glycoside **51** was presumably produced by

*O*→*C*-glycoside rearrangement, anomerization of which gave **52**; while glycoside **53** was produced by direct Friedel-Crafts-type glycosylation, anomerization of which generated **54** through a similar pathway.

(3) Glycosylation of anthracene-type synthetic intermediate

Glycosylation of vancosamine glycosyl donor to anthracene-type synthetic intermediates are presented in scheme 7. The known intermediate **56** from kidamycin aglycone synthesis, bearing a free hydroxyl group, was tested first for the glycosylation reaction. It was anticipated that the hydroxyl group would participate in an *O*→*C*-glycoside rearrangement to regioselectively form a glycoside *ortho* to the hydroxyl group. However, the glycosylation occurred on the middle ring, yielding two separable diastereomers of **57** whose stereochemistry were not completely assigned. This undesired regioselectivity might be due to the deactivating effect of the hydrogen bonding that slowed down the participation of hydroxyl group in the initial *O*-glycosylation step and allowed the competing direct *C*-glycosylation to occur between the enol form of anthrone **56** and the oxy-carbenium ion of glycosyl donor **41**.

**Scheme 7.** Glycosylations of anthracene-type synthetic intermediate




The observation that EtSH underwent substitution to the middle methoxyl group of **55** provided an opportunity to differentiate the two methyl ether. Thus compound **58** was produced under optimized conditions and demethylated to provide **59** as a glycosyl acceptor. Encouragingly, glycosylation of **59** with **41** in the presence of $SnCl_4$ at 0 ºC produced desired glycosylation product **60** as well as its anomer **61.** The model glycosyaltion studies with 1-naphthol **42** have demonstrated that lowering reaction temperature could be a solution to minimize the anomerization pathway. In applying this

finding, the same glycosylation was carried out at -50 ºC, which led to the formation of *ortho*-glycosylation product **60** and *para*-glycosylation product **62**. Although there appeared the problem of regioselectivity, these lower temperature conditions just gave trace, if any, of **61** or the corresponding anomer of **62**.

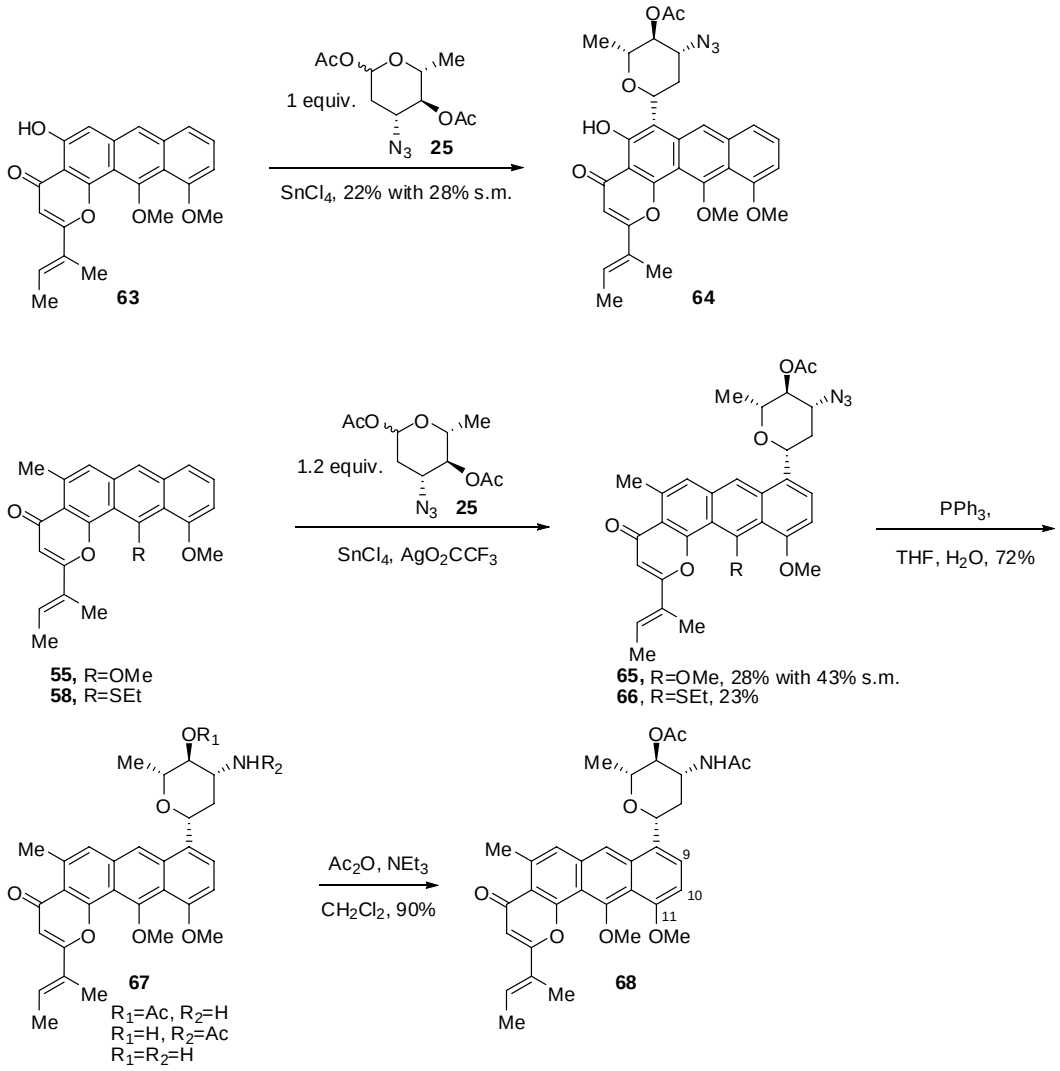
Glycosylations of vancosamine glycosyl donor to 1-naphthol, naphthalene-type synthetic intermediate and anthracene-type synthetic intermediates illustrate that vancosamine moiety is prone to anomerization under acidic conditions, a solution to which is to lower the reaction temperature. As a lesson to the total synthesis, strong acidic conditions following vancosamine glycoyslation should be avoided. Considering the planned acidic conditions for angolosamine glycosylation, it is desirable to introduce angolosamine prior to vancosamine, onto the aglycone intermediate. With angolosamine at the position *para* to the directing hydroxyl group, the regioselectivity issue would not exist for vancosamine glycosylation at low temperature.

*2.2.1.4 Glycosylations with angolosamine glycosyl donor*

Without a directing hydroxyl group, the desired angolosamine glycosylation could not be manipulated through the efficient *O*→*C*-glycoside rearrangement. A direct Friedel-Crafts-type glycosyaltion was considered in spite of limited precedents reported.[38-40] Aromatic compounds possessing high electron density would be beneficial to glycosylation. The most electron-rich intermediate **63**, known in the kidamycin aglycone synthesis, was first utilized as a glycosyl acceptor (scheme 8). However, the glycosylation occurred to the undesired position to give **64** as the only product in 22% unoptimized yield, probably produced by the participation of the hydroxyl group in

glycosylation followed by *O*→*C*-glycoside rearrangement. This observation also demonstrated the high fidelity of *ortho* selectivity in glycosylation via *O*→*C*-glycoside rearrangement, in considering the presence of multiple nucleophilic sites along the aromatic system.

**Scheme 8.** Glycosylation with angolosamine glycosyl donor **25**



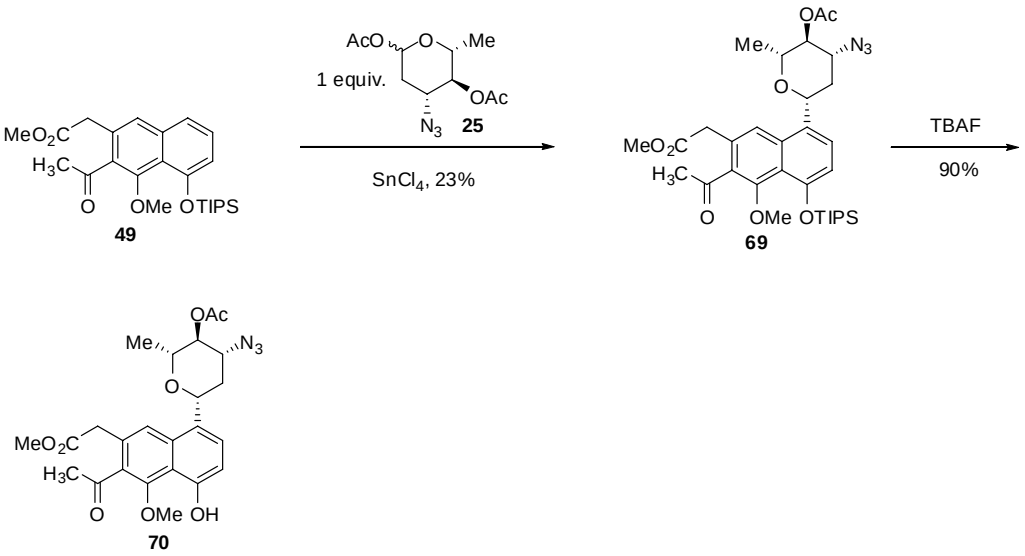

Encouragingly, glycosylation between **55** and **25** under Kuribayashi conditions[38-40] provided desired glycoside **65** in modest yield. The desired glycoside **66** was also obtained when **58** was used as a glycosyl acceptor. The next step was to remove

the phenolic methyl ether protective group to have the free phenolic hydroxyl group as the directing element for vancosamine glycosylation in a similar manner as illustrated in scheme 7. Unfortunately, all attempts to remove the *O*-methyl group were not successful, due to the fragile benzylic carbon-oxygen bond of the carbohydrate in relative to methyl carbon-oxygen bond to be cleaved. Glycoside **65** was further advanced with Staudinger reduction of azide to provide a mixture of three products corresponding to the desired amine, acetyl transfer from hydroxyl to amine group and hydrolysis of acetate. Although the three products were separated from each other for structural analysis, it was practical to acylate them as a crude mixture to give one product **68**. This intermediate advance, though useful as a model to functionalize the azide group, did not lower the difficulty for demethylation.

*2.2.1.5 Strategy modification*

The synthesis encountered a difficulty to deprotect the C11 hydroxyl group for vancosamine glycosylation. Since demethylations of glcosylated aglycone intermediate such as **65**, **66** or **68** were not successful, a tactic was to exchange methyl protective group with some other protective group before angolosamine glycosylation. When choosing protective groups, three factors were taken into consideration: (1) the new protective group should be easily removed; (2) the protective group should survive the strong Lewis acid conditions in the glycosylation step; (3) the protective group should not be highly electron-withdrawing so that the aglycone intermediate will be a good nucleophile.

**Scheme 9.** Protective group exchange for glycosylations with naphalene intermediate



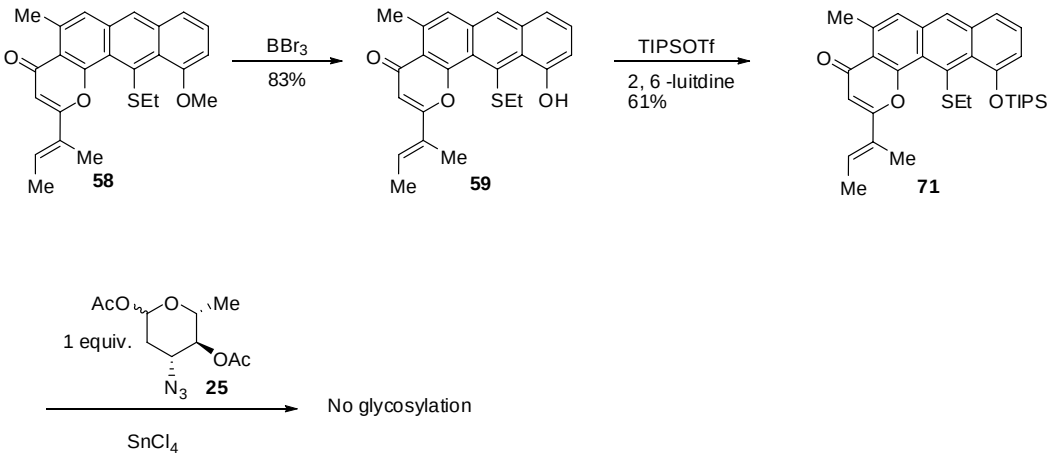

The thought of exchanging protective groups was first executed on the known naphthalene intermediate **49**. Although siloxyl is a slightly more electron- withdrawing compared to methoxyl group, **49** underwent glycosylation with **25** in a yield comparable to others reactions of this type. Some starting material was also recovered from this reaction, which was an indication that TIPS was robust enough to survive the Lewis-acid conditions. Removal of TIPS protection was easily achieved under regular TBAF conditions to provide **70**, a precursor could be used for vancosamine glycoyslation via *O*→*C*- glycoside rearrangement.

The identification of TIPS as a plausible protective group directed us to apply it on an anthracene intermediate. We wished to accomplish glycosylations at the anthracene intermediate stage to achieve a concise total synthesis of kidamycin.

The methyl protective group of **58** was exchanged by demethylation and silylation to form **71** (scheme 10). Unfortunately, **71** was not reactive enough to undergo glycosylation with **25** and about 50% of the starting material was recovered, probably due to slightly electron-withdrawing effect of siloxyl group compared to methoxyl group.

Some other protective groups were also tested. The allyl version of **71** also failed at glycosylation under the same conditions, which likely promoted Claisen rearrangement to cause migration of the allyl group to the *ortho*- position. *Iso*-propyl version of **71** did undergo glycosylation with **25**, while suffered from subsequent difficult *O*-depropylation.

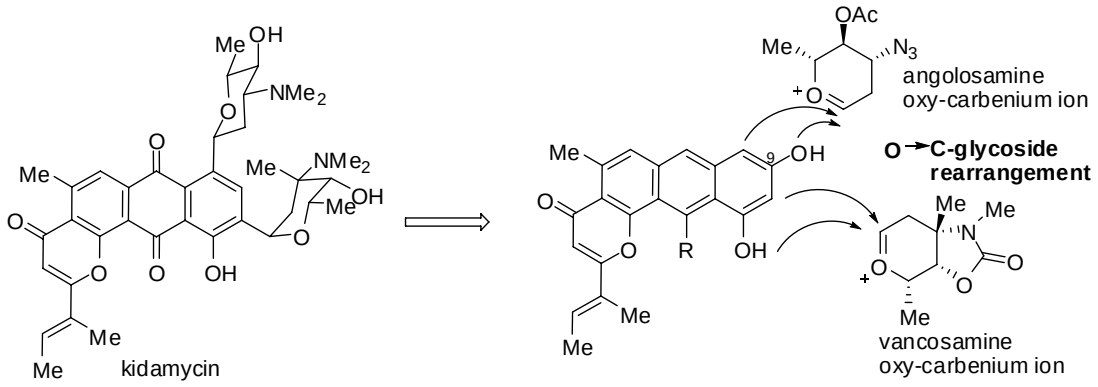
**Scheme 10.** Protective group exchange for glycosylations with anthracene intermediate




Continuing in screening for a good protective group might be one solution to produce the precursor for vancosamine glycosylation. However, this effort was quite discouraged by the modest yield of Friedel-Crafts type glycosylation, whose sensitivity to subtle electronic effect, as demonstrated by the contrast results of **58** and **71** in glycosylation with **25**, made it unlikely to achieve good optimization for this particular combination of glycosylation. Preparing a large amount of material **71** would also be a hurdle due to a hard-to-scale-up reaction involved in its preparation (the first step of dianion chemistry is very difficult to scale up due to its low yielding and dilute reaction feature). This recognition led us to think about revising aglycone intermediate to a more reactive and better glycosyl acceptor.

In view of large number of success of others[7,22,25] as well as ours in glycosylation via *O*→*C*-glycoside rearrangement, a modified aglycone intermediate with an extra hydroxyl group at C9 position was considered to be a good glycosyl acceptor for angolosamine glycosylation, as the hydroxyl group would enable the *O*→*C*-glycoside rearrangement (figure 4). It was envisioned to introduce both angolosamine and vancosamine through this uniform *O*→*C*-glycoside rearrangement to the modified aglycone intermediate, and the difficulty faced for glycosyaltions would be reduced to an easier question of removing this extra hydroxyl group. The extra hydroxyl group could be removed after glycosylation with plenty of precedents reported[41-44] and the extra steps would not affect the overall efficiency if the glycoyslation yield is improved as well as an efficient method to synthesize the modified aglycone intermediate is developed.

**Figure 4.** Modified synthetic strategy



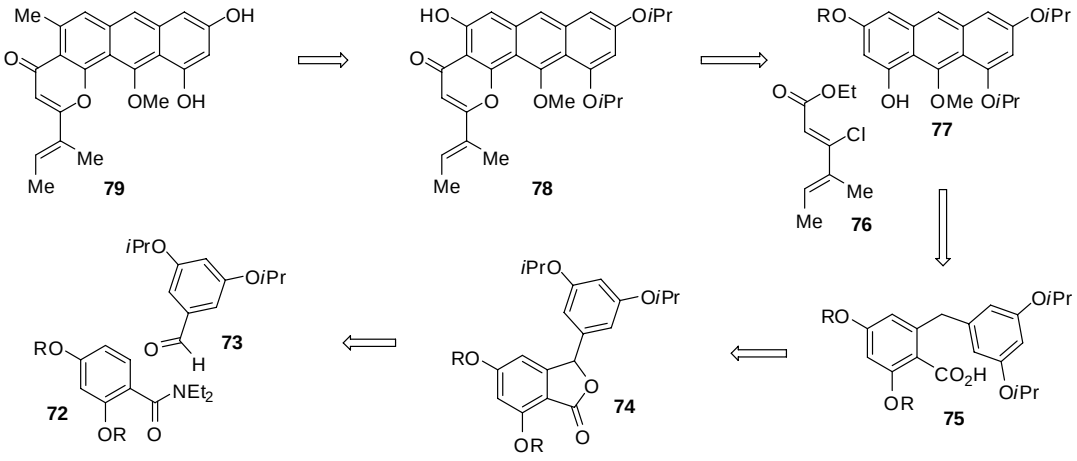
### 2.2.2 Modified strategy to the total synthesis

2.2.2.1 Synthesis of modified aglycone as good glycosyl acceptor

*(1) Initial strategy to synthesize the modified aglycone*

The initial strategy was based on the synthesis of altromycin and kidamycin aglycone as described in chapter 1, featuring coupling of vinylic chloride **76** with anthracene **77**, which is very close to a known compound in the literature[45] with the only difference in *O*-protective groups. The reported method to synthesize a compound similar to **77** is retrosynthetically delineated in figure 5, which will be applied to synthesize **77** at the starting point.

**Figure 5.** Initial strategy for the synthesis of modified aglycone

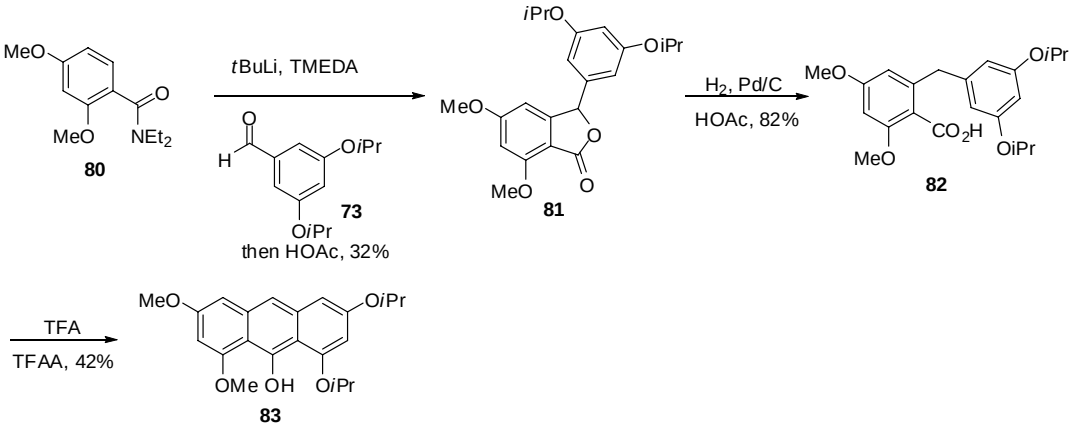



*(2) Initial attempt to synthesize the modified aglycone*

In following the literature procedure,[45] amide **80** was *ortho*-lithiated and added to aldehyde **73** (although **73** is commercially available, it is expensive and hence was prepared in the lab as described in the experimental section), followed by acidic treatment to afford lactone adduct **81** (scheme 11). Reductive opening of the lactone of **81** with palladium-catalyzed hydrogenation, followed by Friedel-Crafts cyclization, quickly

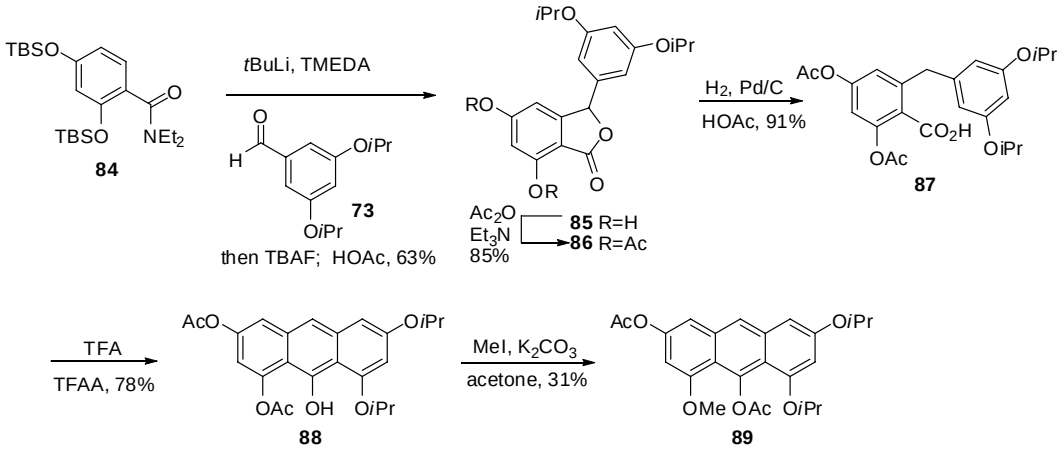
provided anthracene **83**. However, methylation of the middle hydroxyl group proved to be challenging. Compound **83** was an unstable compound, was partially lost during column chromatography on silica gel, and quickly dimerized or oxidized under basic methylation conditions, due to the high electron density of the aromatic system.

**Scheme 11.** The first synthesis of the anthracene intermediate



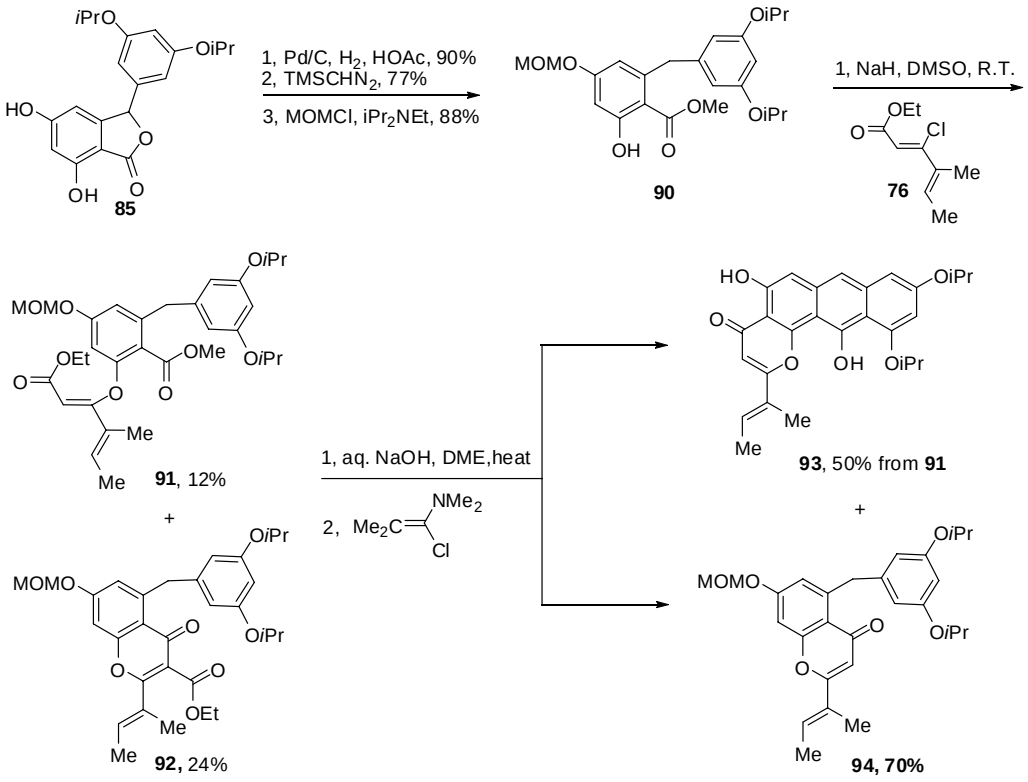

Electron-withdrawing protective groups would lower the electron density of the anthracene, therefore stabilizing the compound for further transformations. An acetyl version of **83** was synthesized in a similar fashion as shown in scheme 12. Although anthracene **88** was a stable compound, attempts at methylating the middle hydroxyl group caused acetyl migration to produce **89** as the undesired regioisomer.

**Scheme 12.** The second synthesis of the anthracene intermediate



The purpose of methylation was to generate an intermediate like **77** for coupling with vinylic chloride **76**. The difficulty encountered incubated an idea to install **76** onto an early intermediate, thereby creating a potential for double Friedel-Crafts cyclization to furnish the anthracene skeleton as well as the pyrone ring in one operation.

**Scheme 13.** Attaching vinylic chloride to an early intermediate




As shown in scheme 13, the early intermediate planned for coupling with vinylic chloride was **90**, obtained from lactone **85** through reductive opening of lactone using palladium under hydrogen gas, carboxylic acid methylation with $TMSCHN_2$, and regioselective MOM protection. Strong hydrogen bonding of the other hydroxyl group to the carbonyl oxygen allowed the MOM *O*-protection reaction to be completely regioselective. However, the coupling of **90** with **76** under previous conditions produced an inseparable mixture of **91** and **92**, with the latter as the major component**,** indicating

that the transient enolate upon initial Michael addition underwent either β-elimination of chlorine to form **91** or Dieckmann condensation to form **92**. Using mild base ($K_2CO_3$) in hot DMF (90 °C) for this coupling reaction produced exclusively **92** in about 70% yield.

The failure in obtaining pure **91** led us to use the mixture of **91** and **92** to test the projected double Friedel-Crafts reaction. Following double saponification, the crude dicarboxylic acid was treated with 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, which promoted the desired double Friedel-Crafts cyclization, accompanied by the loss of MOM protection to give anthrapyran **93**. It was also observed that the corresponding mono-carboxylic acid failed to form the pyrone ring under the same conditions, so this double cyclization is believed to be a tandem process, initiated by the first cyclization and aromatization to form an electron-rich anthrancene that triggered the second cyclization to form the pyrone ring. Compound **92** in this mixture underwent decarboxylation on its own under saponification conditions to give **94** that was not separated until after formation of **93**.

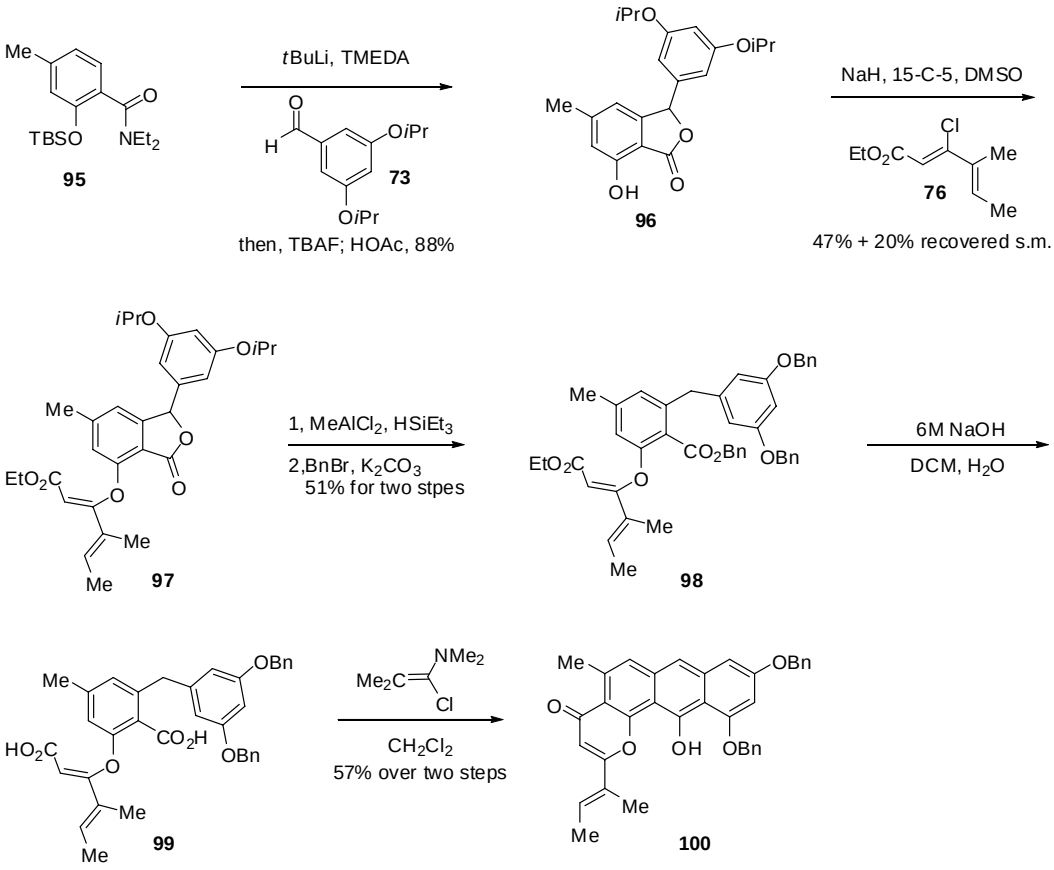
The success in double Friedel-Crafts cyclization encouraged us to solve the Dieckmann condensation problem occurred while coupling **90** with **76**. If two hydroxyl groups of **85** could be differentiated, the produced intermediate might not undergo Dieckmann condensation when coupling with **76**, because the carbonyl function would be kept away from the reacting site by the lactone structure. It was not surprising to find the same conditions used to form **90** (MOMCl, *i*PrNEt$_2$) were not effective in differentiating two hydroxyl groups of **85**, as no hydrogen bonding exists in **85** with the carbonyl oxygen bent away, a feature we will rely on to solve vinylic chloride installation problem. The hydroxyl differentiation difficulty would be easily avoided if the methyl group of

kidamycin were already in the early intermediates such as **85.** This speculation led us to start the synthesis with a compound already bearing the C13 methyl group of kidamycin.

*(3) Final success in synthesis of the modified aglycone*

Compound **95** with methyl group in place was lithiated and added to aldehyde **73**, the adduct of which was treated sequentially with TBAF and acetic acid to afford hydroxyl lactone **96** in one-pot (scheme 14). TBAF cleavage of silyl protective group was important for the acid-promoted lactonization, probably because the presence of TBS disfavors the lactonization by its steric size. Hydroxyl lactone **96** underwent an addition-elimination reaction with vinylic chloride **76** without producing any Dieckmann condensation byproduct; in consistency with the hypothesis that lactone structure would protect the carbonyl from participating in the reaction. However, being forced on the same plane as aromatic ring, the carbonyl group significantly deactivates the hydroxyl group to be a good nucleophile due to electron withdrawing property through a better conjugation compared to substrate **90**. The addition-elimination reaction with **96** was carried out under more forcing conditions (58 ºC, 15-C-5, 36 to 60 h) in comparison to previous milder conditions for substrate **90** (room temperature, no crown ether, 14 h). Although the yield is still modest due to lower reactivity, 12 grams of product **97** were prepared in one batch.

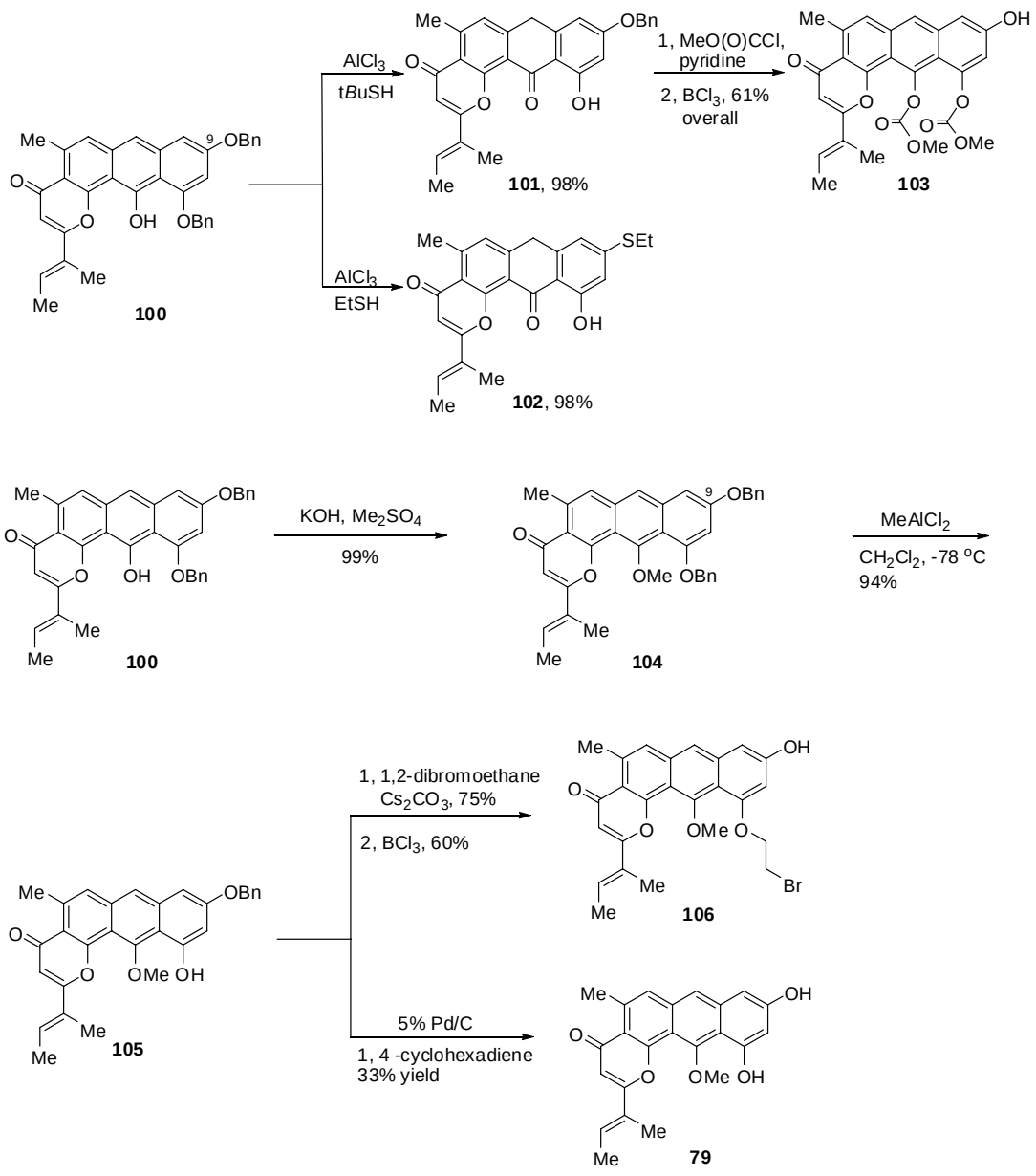
**Scheme 14.** Synthesis of a key intermediate towards modified aglycone glycosyl acceptor




Reductive opening of lactone **97** under promotion of Lewis acid[46] also led to O-de-isopropylation; and the crude product was used for global benzylation to provide **98**, which was easily purified. Double saponification of **98** produced crude dicarboxylic acid **99** that underwent smooth double Friedel-Crafts cyclization to provide the key anthrapyran **100**. The formation of **100** needed longer time in comparison with the formation of **93**, as a result of lower electron-donating ability of methyl group compared to hydroxyl group.

Protective group manipulation of **100** towards the glycosyl acceptor began with O-debenzylations (scheme 15). It was surprising to find debenzylation of the benzyl protection on the C9 hydroxyl group was difficult, as **101** was obtained under strong debenzylation conditions using bulky *tert*-butyl thiol as a soft nucleophile, whereas using ethanethiol as a soft nucleophile for this debenzylation led to substitution at C9 to produce **102**. Although **102** might be an interesting intermediate towards glycosylation studies, we were still more interested in advancing **101** by carbonate formation and removal of the corner benzyl protection to provide **103** bearing the free hydroxyl group for angolosamine glycosylation via *O*→*C*-glycoside rearrangement. Alternatively, **100** underwent methylation to provide **104**, selective mono-debenzylation of which was easily achieved to generate **105**. Attempts to obtain double debenzylation by utilizing more $MeAlCl_2$ and higher reaction temperature led to partial migration of the C9 *O*-benzyl group to aromatic ring, the product of which was not separable from the double debenzylation product. Using methyl ethyl sulfide as a cation scavenger was not effective in obtaining a clean reaction. Fortunately, mild hydrogenation could selectively remove benzyl protection on **105** without reducing the olefin on the side chain to provide pure **79** as a glycosyl acceptor. **105** was also derivatized to glycosyl acceptor **106** by bromo-ethyl ether formation and $BCl_3$ cleavage of benzyl ether. Therefore, modified aglycone intermediates **103**, **106** and **79** were the candidates for designed glycosylations.

**Scheme 15.** Synthesis of modified aglycone glycosyl acceptors

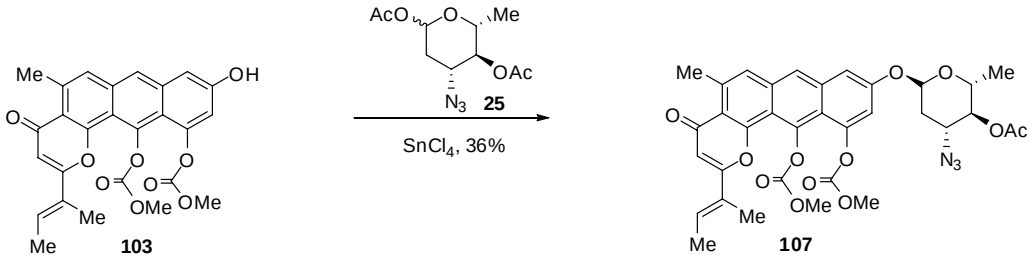



2.2.2.2 Glycosylations with modified aglycone intermediates

The treatment of **103** with angolosamine glycosyl donor **25** in the presence of $SnCl_4$ at room temperature for 16 hours only gave the *O*-glycoside **107** without *O*→*C*-glycoside rearrangement (scheme 16). Indeed, the two electron withdrawing carbonates

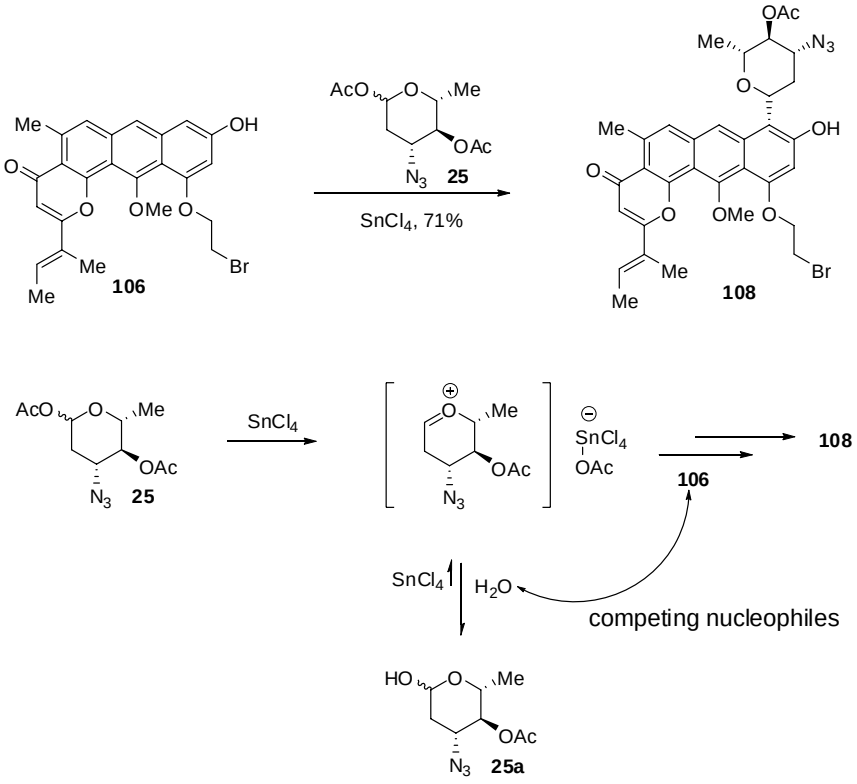
deactivated the aromatic ring to be a good nucleophile and the second rearrangement step did not occur.

**Scheme 16.** Glycosylaton of **103**




A good glycosylation was obtained when treating **106** with **25** in the presence of $SnCl_4$, as the desired glycosylation product **108** was isolated in 71% yield (scheme 17). In the literature, two equivalents of aromatic compounds[19] are usually used in order to achieve good conversion of glycosyl donor due to relatively low reactivity of aromatic compounds, in contrast to high reactivity of oxy-carbenium ion generated from glycosyl donor. However, substrate **106** was able to go complete conversion when 1.1 equivants of **25** were used, which therefore merits some comment and appreciation. When monitoring glycosylations with **25** by TLC, it was always observed that glycosyl donor **25** quickly turned into another species, which in a separate experiment was identified as hydrolysis product **25a** by $^1$H-NMR. Although it could not be excluded that the observed hydrolysis took place on the TLC plate, it might also take place in the reaction solution due to unavoidable trace of water present, no matter if molecular sieves was used. The unavoidable water-consumption of glycosyl donor might be the reason for the observed partial conversion of low-reactive glycosyl acceptor even though excess of glycosyl donor was used.

**Scheme 17.** Glycosylation of **106**

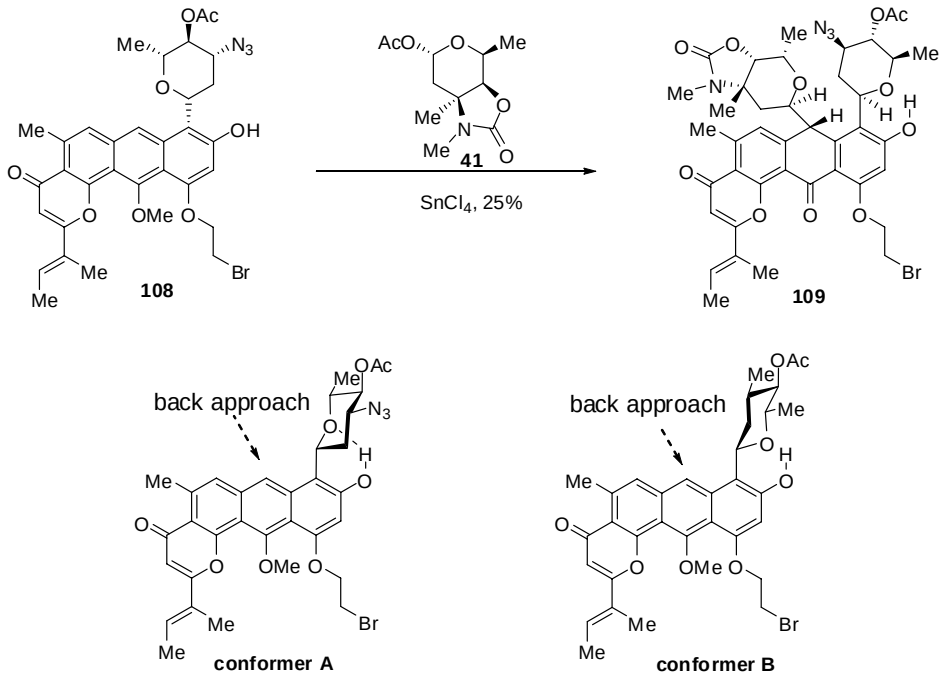



Following the analysis, there are two possibilities accounting for the complete conversion of **106**. Firstly, glycosyl acceptor **106** was just reactive enough to undergo complete conversion before too much **25** was hydrolyzed. Alternatively, although **25** had already been completely hydrolyzed to **25a** with the trace of water prior to the complete consumption of **106**, substrate **106** was reactive enough to nucleophilically compete against water for the limit oxy-carbenium ion generated from **25a**, as shown at the bottom of scheme 17. Either way supports that **106** is a very reactive glycosyl acceptor and is a perfect match with glycosyl donor **25**.

After directing the first angolosamine glycosylation, the hydroxyl group in **108** was anticipated to direct the second vancosamine glycosylation. However, treatment of **108** with **41** in the presence of $SnCl_4$ gave **109** with undesired regioselectivity (scheme 18). In avoiding *peri*-interaction on the same plane of two carbohydrates, the robust *O*-

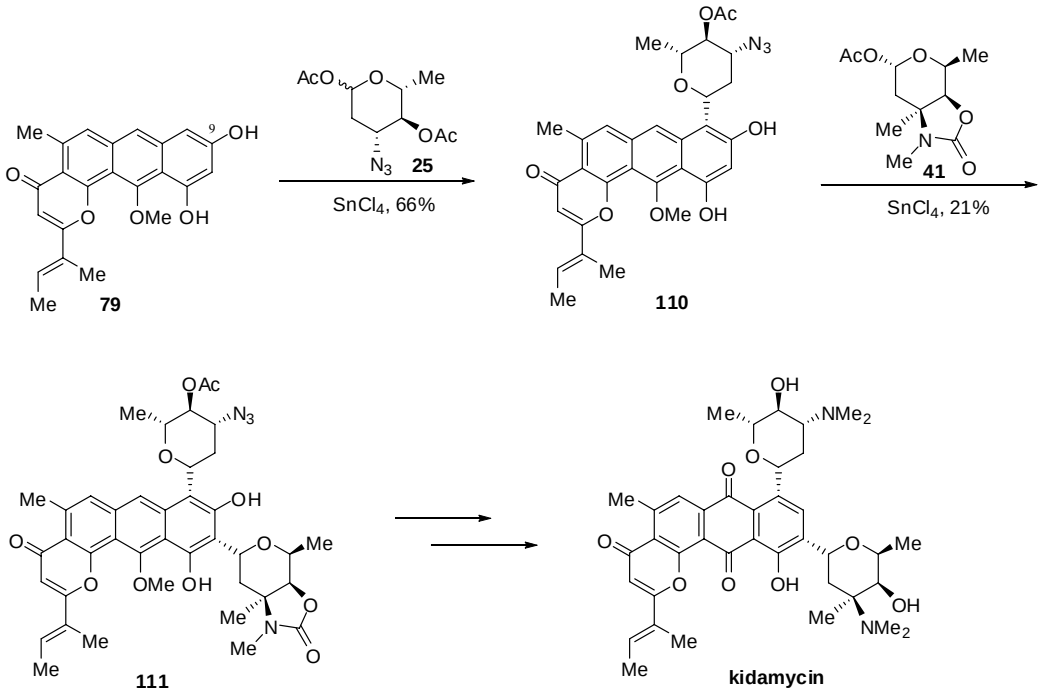
methyl ether protective group was lost in the reaction. The stereochemical outcome was predicted on the basis of two possible substrate conformations **A** or **B**, in both of which a hydrogen bonding between the hydroxyl group and the angolosamine-oxygen locked the carbohydrate chair to be in the front of aromatic plane, directing vancosamine glycosyl donor to approach from the back. Conformers **A** and **B** differ as a result of the alternative participartion of two diastereotopic electron-pairs of the angolosamine-oxygen in the hydrogen bonding. The presence of hydrogen bonding was evident by $^{1}$H-NMR, as the hydroxyl hydrogen was shifted to the low magnetic field (8.90ppm), which might also be the reason for the lower reactivity of the hydroxyl group due to the stabilizing effect to hydroxyl proton, thus favoring undesired direct carbon-carbon bond formation to generate **109**. The problematic second glycosylation led us to explore glycosylations with **79** as a glycosyl acceptor.

**Scheme 18.** The second glycosylation of **108**



Substrate **79** turned out to be another very reactive glycosyl acceptor, as it underwent complete glycosylation with slight excess of glycosyl donor **25** (1.1 equivlant) under the promotion of $SnCl_4$ to provide **110** in 66% yield (scheme 19). The selective participation of the more reactive non-hydrogen bonded C9 hydroxyl group in the *O*→*C*-glycoside rearrangement accounted for the observed regioselective glycosylation. Molecular sieves were not applied for this reaction either, which are believed not to be able to give absolutely anhydrous conditions. The key for this efficient glycoyslation is that the nucleophilicity of substrate **79** is comparable to that of any trace of water present in the reaction system.

**Scheme 19.** The sequential glycosylations of **79**




A second glycosylation with vancosamine glycosyl donor **41** at -30 ºC provided **111** possessing the full carbon skeleton of kidamycin, in 21% unoptimized yield with recovery of 68% starting material. The low reaction temperature presumably prevented anomerization of **111** at vanocosamine moiety from occurring. The continuing effort will

focus on completing the total synthesis from either the double glycosylated intermediate **111** or, less aggressively, intermediate **108** by removing the extra hydroxyl group prior to the second glycosylation.

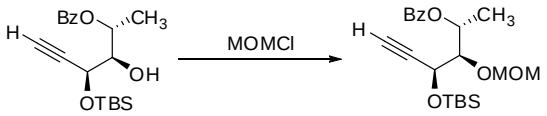
## 2.3 Conclusions

In solving the key glycosylations for the total synthesis of kidamycin, a group III natural glycoside, glycosyl donors of appropriate reactivity corresponding to angolosamine and vancosamine have been identified and prepared by applying tungsten-catalyzed cycloisomerizations of alkynols to the corresponging glycals. The glycosylation of vancosamine glycosyl donor with the first-generation aglycone intermediates disclosed the potential anomerization problem of vancosamine moiety and provided a low-temperature technique to address this issue, which also led to revise our original glycosylation sequence of these two sugars. Modest yield of anogolaosmine glycosylation with the first-generation aglycone intermediates as well as the difficulty in obtaining the precursor for the second glycosylation inspired us to modify the first generation-aglycone intermediates by strategically installing a C9 hydroxyl group. This hydroxyl group not only introduced a symmetric element, leading to the discovery of double Friedel-Crafts cyclization reaction, but also increased the reactivity of the substrate as a glycosyl acceptor. The sequential glycosylation of this modified aglycone intermediate with glycosyl donors of anglosamine and vancosamine provided an advanced intermediate possessing the full carbon skeleton of kidamycin. Either the advanced material accessed or the knowledge gained in accessing this advanced material will be a direct benefit to complete the total synthesis of kidamycin.

## 2.4 Experimental information

**General procedure**: $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on an Inova-400 spectrometer (400 MHz for $^{1}H$ NMR, 100 MHz for $^{13}C$ NMR), or and Inova-600 (600 MHz for $^{1}H$ NMR, 150 MHz for $^{13}C$ NMR). NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$), with residual chloroform (7.27 ppm for $^{1}H$ NMR and 77.23 ppm for $^{13}C$ NMR) taken as the internal standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sept, septet; m, multiplet. IR spectra were collected on a Mattson Genesis II FT-IR spectrometer as neat films. High resolution mass spectra were recorded on a VG 70-S Nier Johason Mass Spectrometer or a Thermo Finnigan LTQ FT spectrometer. Optical rotations were measured on a Perkin Elmer Model 341 Polarimeter. Analytical Thin Layer Chromatography (TLC) was performed on precoated glass backed plates purchased from Whatman (silica gel 60 F254; 0.25 mm thickness). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from EM Science.

All anhydrous solvents were dried over microwave-activated 3Å or 4Å molecular sieves. All solvents used in workup extraction procedures and chromatography were used as received from commercial suppliers without prior purification. All reagents were purchased from Aldrich. All reactions were carried out under argon except otherwise mentioned. During workup, the reaction mixture was usually diluted to three times the original volume. About equal amount of organic solvent was usually used for each abstraction of certain volume of aqueous solution. Half amount of water or brine was usually used to wash certain volume of organic solution.



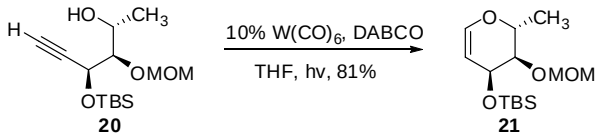

**19** **19a**

To a solution of **19** (7.40 g, 21.0 mmol) in $CH_2Cl_2$ was slowly added *i*$Pr_2$NEt (11.0 mL, 63.7 mmol) and MOMCl (3.06 mL, 40.3 mmol) at room temperature. After stirring for 36 hours, another portion of i$Pr_2$NEt (4.00 mL) and MOMCl (2.00 mL) was added and was stirred for additional 24 hours when TLC showed only trace amount of starting material present. The reaction was quenched with aq. $NaH_2PO_4$ solution and purified by column chromatography (hexanes/ethyl acetate=8/1) to give the product **19a** (7.60 g, 91%). $^1$H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.60 (t, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 5.45 (dq, *J* = 4.2 Hz, 6.6 Hz, 1H), 4.97 (d, *J* = 7.2 Hz, 1H), 4.82 (d, *J* = 7.2 Hz, 1H), 4.52 (d, *J* = 5.4 Hz, 1H), 3.97 (t, *J* = 5.4 Hz, 1H), 3.45 (s, 3H), 2.47 (s, 1H), 1.44(d, *J* = 6.6 Hz, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H).

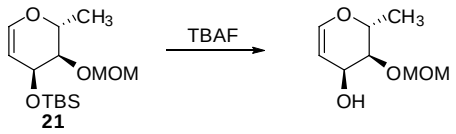

**19a** **20**

To a solution of starting material **19a** (7.60 g, 19.4 mmol) in $CH_2Cl_2$ was slowly added DIBAL-H (48.9 mmol, 48.9 mL of 1 M in $CH_2Cl_2$) at -78 ºC. The reaction was stirred for 1 hour at this temperature and then quenched with ethyl acetate, followed by addition of aq. Rochelle's salt. Extraction with ethyl acetate followed by column chromatography (hexane / ethyl acetate = 4/1) gave **20** (5.30 g, 95%). $^1$H NMR (300 MHz, $CDCl_3$) δ 4.82

(d, *J* = 6.9 Hz, 1H), 4.72 (d, *J* = 6.6 Hz, 1H), 4.41 (dd, *J* = 2.1 Hz, 6.3 Hz, 1H), 3.96 (dq, *J* = 4.80, 6.6 Hz, 1H), 3.57 (dd, *J* = 4.5 Hz, 6.3 Hz, 1H), 3.41 (s, 3H), 2.94 (bs, 1H), 2.43 (d, *J* = 2.1 Hz, 1H), 1.19 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H).

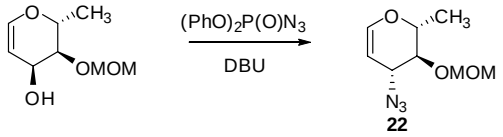



A solution of **20** (150 mg, 0.520 mmol), $W(CO)_6$ (36.6 mg, 0.104 mmol) and DABCO (117 mg, 1.04 mmol) in THF (3 mL) was irradiated to reflux in a UV photo chamber under argon atmosphere for 6 hours. The solvent was evaporated and the residue was purified by column chromatography (hexanes / ethyl acetate = 8/1) to get **21** (119 mg, 81%). $^1$H NMR (600 MHz, $CDCl_3$) δ 6.32 (d, *J* = 5.4 Hz, 1H), 4.82 (d, *J* = 6.6 Hz, 1H), 4.78 (t, *J* = 5.4 Hz, 1H), 4.63 (d, *J* = 6.6 Hz, 1H), 4.26 (dd, *J* = 3.6 Hz, 5.4 Hz, 1H), 4.18 (dq, *J* = 9 Hz, 6 Hz, 1H), 3.53 (dd, *J* = 3 Hz, 9 Hz, 1H), 3.42 (s, 3H), 1.36 (d, *J* = 6 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).



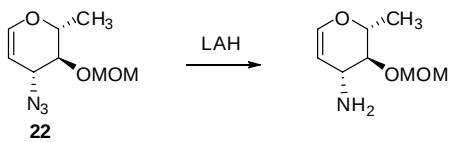

To a solution of **21** (119 mg, 0.412 mmol) in THF (2 mL) was added TBAF (1.40 mmol, 1.4 mL of 1M solution in THF) at room temperature. The reaction was stirred for 2 hours and quenched with water. Extraction with $Et_2O$ and flash column chromatography

(hexanes / ethyl acetate = 2/1) purification afforded product (64.6 mg, 90%). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, *J* = 6.0 Hz, 1H), 4.92 (t, *J* = 5.6 Hz, 1H), 4.82 (d, *J* = 6.4 Hz, 1H), 4.75 (d, *J* = 6.8 Hz, 1H), 4.23 (dd, *J* = 3.6 Hz, 5.6 Hz, 1H), 4.09 (dq, *J* = 6.4 Hz, 9.6 Hz, 1H), 3.54 (dd, *J* = 4.0 Hz, 9.6 Hz, 1H). 3.45 (s, 3H), 2.50 (d, *J* = 3.6 Hz, 1H), 1.36 (d, *J* = 6.4 Hz, 3H).



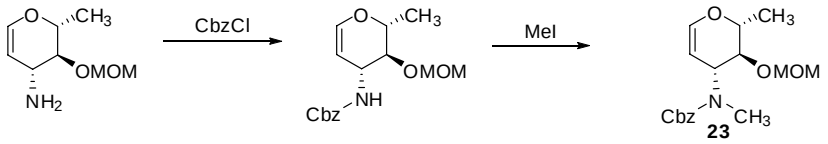
**22**

To a solution of starting material (174 mg, 1.00 mmol) and DBU (388 μL, 2.60 mmol) in toluene (2 mL) was added $(PhO)_2P(O)N_3$ (388 μL, 1.8o mmol) at room temperature. The reaction was stirred for about 3 hours at room temperature and quenched with aq. $NaH_2PO_4$ solution. Extraction with $Et_2O$ and concentration to a residue that was dissolved in a small amount of $CH_2Cl_2$ to load on a column filled with silica gel. Chromatography (pentane / ether = 1/0 → 15/1 →10/1) gave product **22** (150mg, 77%). IR (neat) 2938, 2101, 1647 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, *J* = 6.0 Hz, 1H), 4.91(d, *J* = 7.2 Hz, 1H), 4.76 (d, *J* = 7.2 Hz, 1H), 4.73 (d, *J* = 5.6 Hz, 1H), 3.96 (d, *J* = 7.2 Hz, 1 H), 3.92 (dq, *J* = 6.4 Hz, 8.8 Hz, 1H), 3.49 (d, *J* = 7.2 Hz, 1H), 3.47 (s, 3H), 1.40 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 146.4, 98.1, 97.3, 76.9, 74.2, 60.1, 56.4, 17.5; $[\alpha]^{26}_D$ = - 128 (c = 1.4, $CHCl_3$).



**22**

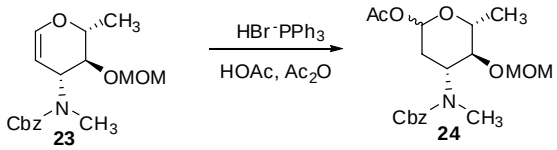
To a solution of **22** (37 mg, 0.19 mmol) was added LAH (0.27 mL of 1 M solution in $Et_2O$) at 0 ºC. The reaction was stirred for 35 minutes and then quenched by aq. Rochelle's salt solution. The cloudy two-phase mixture was stirred for couple of hours until being clear. Purification by column (ether / methanol = 5/2) afforded amine product (21 mg, 65%). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 2.0 Hz, 5.6 Hz, 1H), 4.84 (d, *J* = 6.8 Hz, 1H), 4.75 (d, *J* = 6.8 Hz, 1H), 4.64 (dd, *J* = 2.0 Hz, 6.0 Hz, 1H), 3.81 (dq, *J* = 6.4 Hz, 9.6 Hz, 1H), 3.45 (s, 3H), 3.41 (m, 1H), 3.08 (dd, *J* = 7.6 Hz, 9.6 Hz, 1H), 1.34 (d, *J* = 6.4 Hz, 1H).




To a solution of amine starting material (67.0 mg, 0.387 mmol) in acetone (2 mL) and water (2 mL) was added $K_2CO_3$ (80.0 mg, 0.580 mmol) and CbzCl (82.0 μL, 0.580 mmol) at room temperature. The reaction was stirred overnight and extracted with ethyl acetate. Concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 4 /1) gave Cbz protected product (119mg, 100%). %). $^1$H NMR (600 MHz, $CDCl_3$) δ 7.34 (m, 5H), 6.29 (d, *J* = 6.0 Hz, 1H), 5.31 (d, *J* = 6.0 Hz, 1H), 5.10 (m, 2H), 4.69 (d, *J* = 6.0 Hz, 2H), 4.30 (m, 1H), 3.94 (dq, $J_1$= $J_2$ = 7.8 Hz, 1H), 3.30 (t, *J* = 8.4 Hz, 1H), 3.29 (s, 3H), 1.33 (d, *J* = 6.6 Hz, 3H).

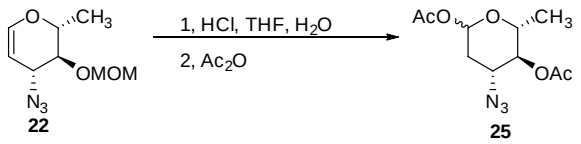
To a solution of protected amine starting material (119 mg, 0.387 mmol) in DMF (3 mL) was added NaH (31 mg of 60% on mineral oil, 0.774 mmol). After stirring for 15

minuties at room temperature, MeI (145 μL, 2.32 mmol) was added and stirring was continued for 2 hours when TLC showed completion of the reaction. The reaction was quenched with aq. $NH_4Cl$. Extraction with ethyl acetate and column chromatography afforded product **23** (117 mg, 94%) detected by H-NMR as two rotamers with *ca* 1:2 ratio. When some peaks of the two rotamers are overlapped are hard to identify, it will be indicated and "m (multiple)" will be used to describe the shape of peak. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, overlapping, 5H), 6.43 (m, overlapping, 1H), 5.17 (m, overlapping, 2H), 5.06 (dt, *J* = 2.4 Hz, 8.8 Hz, 1H), 4.59 (m, overlapping, 2H), 4.46 (m, overlapping, 1H), 3.95 (q, overlapping, 1H), 3.49 (dd, *J* = 10 Hz, 19.2 Hz, 1H), 3.22 (s, 3H), 2.81 (s, 3H), 1.38 (d, overlapping *J* = 6.4 Hz, 3H).

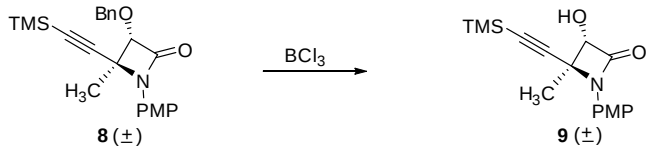



To a solution of **23** (26 mg, 0.081 mmol) in $CH_2Cl_2$ (1.2 mL) and $Ac_2O$ (0.2 mL) was added HOAc (2 drops using 1 mL syringe) and HBr-$PPh_3$ (5.5 mg, 0.016mmol) at room temperature. The reaction was stirred for 16 hours and quenched with aq. $NaHCO_3$. Extraction with ethyl acetate and column chromatography (hexanes / ethyl acetate = 3 / 1) to afford product **24** (21 mg, 68% with some starting material **23** recovered) as a mixture of two anomers with 1:2 ratio. The H-NMR data of the major anomer is shown in the following. Some overlapping of peaks from different anomer may cause difficulty in identifying peak shapes and coupling constants, under which circumstance "m (multiple)" will be used and overlapping will be indicated. $^1$H NMR (600 MHz, $CDCl_3$) δ

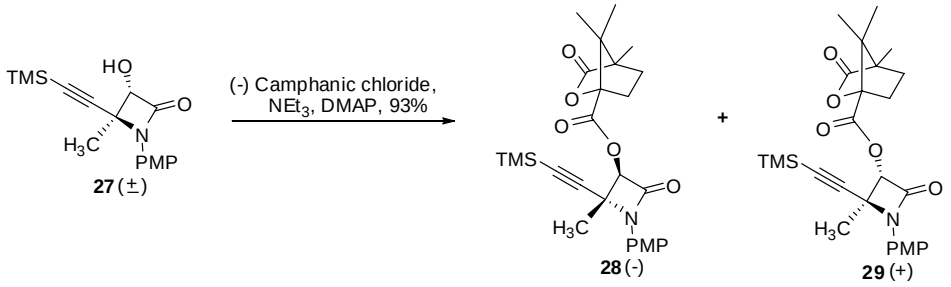
7.37 (m, overlapping, 5H), 6.16 (d, *J* = 3 Hz, 1H), 5.20 (d, *J* = 12.6 Hz, 1H), 5.11 (d, *J* = 12.6 Hz, 1H), 4.60 (d, *J* = 7.2 Hz, 1H), 4.56 (m, overlapping, 2H), 3.89 (q, *J* = 6.6 Hz, 1H), 3.37 (bs, 1H), 3.20 (s, 3H), 2.87 (s, 3H), 2.11 (s, 3H), 2.10 (m, 1H), 1.88 (dd, J = 4.8 Hz, 13.2 Hz, 1H).




To a solution of **22** (300 mg, 1.51 mmol) in THF (7 mL) and water (7 mL) was added aq. HCl (6 M, 7mL). The reaction was warmed at 50 ºC to 55 ºC for 4 hours and then cooled to room temperature. After dilution with water, exhaustive extraction with ethyl acetate and flash column chromatography (hexanes / ethyl acetate = 1/1) afforded the diol (203 mg, not very pure). To this diol solution in $CH_2Cl_2$ (30 mL) was added $Et_3N$ (814 μL, 5.85 mmol), $Ac_2O$ (552 μL, 5.85 mmol) and DMAP (0.12 mmol, 14.3 mg) at room temperature. The reaction was done in about two hours and quenched by 1M HCl. Extraction with ethyl acetate and column chromatography (hexanes / ethyl acetate = 4 / 1) afforded product as mixture of two anomers (210 mg, α : β = 4:1). $^1$H NMR (600 MHz, $CDCl_3$) δ α-anomer: 6.18 (d, *J* = 2.4 Hz, 1H), 4.75 (t, *J* = 10.0 Hz, 1H), 3.88 (dq, *J* = 6.4 Hz, 12.4 Hz, 1H), 2.19 (ddd, *J* = 1.2 Hz, 4.8 Hz, 13.6 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 3H), 1.87 (ddd, *J* = 3.6 Hz, 12.4 Hz, 13.6 Hz, 1H), 1.19 (d, *J* = 6.4 Hz, 1H); β-anomer: 5.75 (dd, *J* = 2.0 Hz, 10.0 Hz, 1H), 4.70 (t, *J* = 9.6 Hz, 1H), 3.59 (m, 1H), 2.27 (ddd, *J* = 2.4 Hz, 3.6 Hz, 12.4 Hz, 1H), 2.14 (s, 3H), 2.13 (s, 3H), 1.78 (q, *J* = 10 Hz, 1H).




To a solution of **8** (12.6 g, 32.0 mmol) in $CH_2Cl_2$ (200 mL) was added $BCl_3$ (96 mmol, 1M solution) in a dropwise manner at -10 ºC. The reaction was stirred for 1 hour while temperature went up to 0 ºC. The reaction was quenched and extracted with $CH_2Cl_2$.. Purification by flash column chromatography afforded **9** (9.5 g, 98%). IR (neat) 3367, 1727cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 5. 05 (d, *J* = 6.6 Hz, 1H), 4.04 (broad d, *J* = 5.4 Hz, 1H), 3.80 (s, 3H), 1.73 (s, 3H), 0.18 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 116.6, 156.9, 129.4, 119.9, 114.4, 104.1, 92.5, 83.3, 59.0, 55.6, 20.0, -0.1; HRMS (ESI) Calcd. for $C_{16}H_{22}O_3NSi$ [$(M + H)^+$] 304.13635, found 304.13623.

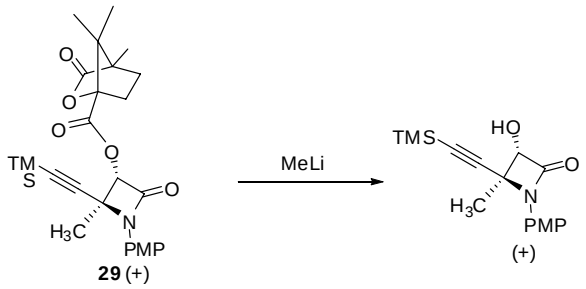



To a solution of racemic **27** (9.9 g, 0.033 mol) in $CH_2Cl_2$ (200 mL) was added $Et_3N$ (14 mL, 0.099 mol), DMAP (0.4 g, 3.3 mmol) and (-) camphonic chloride (9.2 g, 0.042 mol) at room temperature. The reaction was completed in 2 hours, at which time the reaction was quenched with aq. $NaH_2PO_4$. After extraction with $CH_2Cl_2$ and concentration, the crude mixture was divided into two portions and loaded on two 2000-mL columns filled with silica gel. A slow chromatography using pentane / ether = 3 / 1 → 2 / 1 as eluant

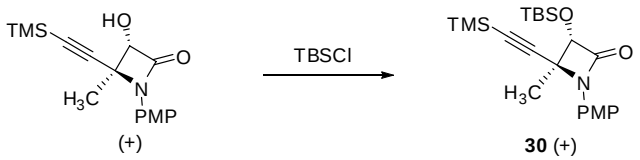
gave the first fraction as pured (-) **28**, then the second fraction as overlapping of (-) **28** and (+) **29**, and finally the third fraction as (+) **29**. The overlapping fraction from above two columns was combined, concentrated and chromatographed in the same manner. These overall three separations gave pure (-) **28** (7.00 g, 44%), mixture of (-) **28** and (+) **29** (0.41 g, 2.6%) and (+) **29** (7.37 g, 46%).

(-) **28**-top: IR (neat) 2966, 1765 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 9.2 Hz, 2H), 6.88 (d, *J* = 9.2 Hz, 2H), 6.00 (s, 1H), 3.80 (s, 3H), 2.52 (ddd, *J* = 4.0 Hz, 10.8 Hz, 14.8 Hz, 1H). 2.09 (ddd, *J* = 4.4 Hz, 9.2 Hz, 13.6 Hz, 1H), 1.97 (ddd, *J* = 4.8 Hz, 10.8 Hz, 15.6 Hz, 1H), 1.72 (ddd, *J* = 5.6 Hz, 10.0 Hz, 15.2 Hz, 1H), 1.69 (s, 3H), 1.13 (s, 3H), 1.1 (s, 3H), 1.0 (s, 3H), 0.2 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 177.9, 166.4, 159.7, 157.1, 129.2, 119.8, 114.5, 102.2, 93.6, 90.9, 82.0, 57.4, 55.6, 55.0, 54.8, 31.0, 28.9, 20.5, 17.0, 16.8, 9.9, -0.2; HRMS (ESI) Calcd. for $C_{26}H_{34}O_6NSi$ $[(M + H)^+]$ 484.21499, found 484.21462; $[\alpha]^{26}{}_D$ = - 47.2 (c = 1.2, $CHCl_3$).

(+) **29**-bottom: IR (neat) 2965, 1766 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 9.2Hz, 2H), 6.90 (d, *J* = 9.2 Hz, 2H), 5.99 (s, 1H), 3.81 (s, 3H), 2.47 (ddd, *J* = 4.4 Hz, 10.8 Hz, 15.2 Hz, 1H), 2.14 (ddd, *J* = 4.4 Hz, 9.6 HZ, 13.6 Hz, 1H), 1.97 (ddd, *J* = 4.8 Hz, 10.8 Hz, 13.6 Hz, 1H), 1.74 (ddd, *J* = 4.0 Hz, 9.2 Hz, 13.2 Hz, 1H), 1.66 (s, 3H), 1.143 (s, 3H), 1.135 (s, 3H), 1.04 (s, 3H), 0.2 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 177.8, 166.2, 159.8, 157.2, 129.2, 119.9, 114.6, 102.1, 93.7, 90.8, 81.8, 57.5, 55.7, 55.0, 54.8, 31.1, 29.1, 20.3, 17.1, 16.9, 9.9, -0.2; $[\alpha]^{26}{}_D$ = + 44.2 (c = 1.5, $CHCl_3$).

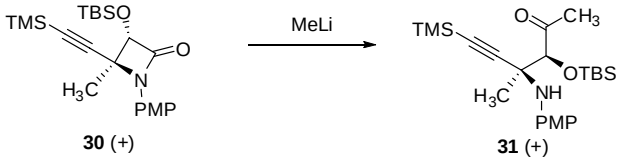



To a solution of **29** (7.37 g, 0.0152 mol) in THF (300 mL) was added MeLi (0.038 mmol, 24 mL solution of 1.6 M MeLi in $Et_2O$) at – 78 ºC. The reaction was stirred at this temperature for about half an hour, at which time TLC showed completion of the reaction. The reaction was quenched with aq. $NaH_2PO_4$. Extraction with ethyl acetate and clumn chromatography (hexanes / ethyl acetate = 4/1) gave product as shown above (4.45 g, 97%).The IR, $^1$H NMR and $^{13}$C NMR data is the same as racemic compound **27**. $[\alpha]^{26}_D$ = + 129.3 (c = 1.1 $CHCl_3$).



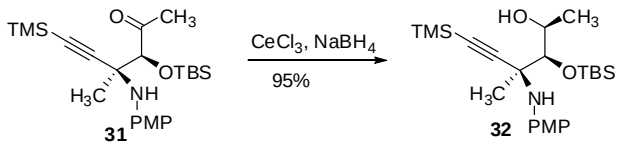

To a solution of starting material (4.45 g, 0.015 mol) in $CH_2Cl_2$ (100 mL) was added imidazole (2.00 g, 0.0294 mol), DMAP (90 mg, 0.74 mmol) and TBSCl (2.66 g, 0.0176 mmol) at room temperature. The reaction was completed in about 1 hour, and quenched with 1M HCl. Concentration and flash chromotagraphy (hexanes / ethyl acetate = 6 / 1) gave product **30** (6.00 g, 98%). IR (neat) 2955, 1758 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 9.2 Hz, 2H), 6.88 (d, *J* = 9.2 Hz, 2H), 4.92 (s, 1H), 3.79 (s, 3H), 1.63 (s, 3H), 0.97 (s, 9H), 0.22 (s, 3H), 0.21 (s, 3H), 0.17 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.7, 156.5, 130.2, 119.4, 114.4, 104.5, 92.2, 84.2, 58.2, 56.6, 25.9, 20.3, 18.5, -0.1, -

4.66, -4.75; HRMS (ESI) Calcd. for $C_{22}H_{36}O_3NSi_2$ [(M + H)$^+$] 418.22283, found 418.22261; $[\alpha]^{26}_D$ = + 94.4 (c = 1.1, $CHCl_3$).




**30** (+) **31** (+)

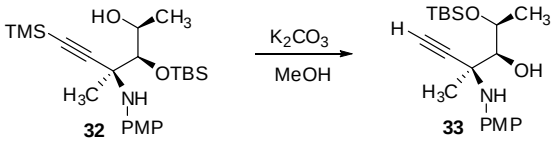
To a solution of **30** (318 mg, 0.760 mmol) in THF (7 mL) was added MeLi (1.22 mmol, 0.763 mL solution of 1.6 M MeLi in $Et_2O$ ) dropwisely at – 78 ºC. The reaction was stirred at this temperature for about 2 hours, by which time the reaction was completed and quenched by aq $NaH_2PO_4$. Concentration and column chromatography (hexanes / ethyl acetate = 6 / 1) gave **31** (319 mg, 96%). (IR (neat) 2955, 1714, 1510 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 4.06 (s, 1H), 3.82 (s, 1H), 3.77 (s, 3H), 2.34 (s, 3H), 1.40 (s, 3H), 1.00 (s, 9H), 0.15 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 209.3, 154.9, 138.5, 122.8, 114.1, 106.9, 91.4, 84.1, 56.5, 55.7, 28.0, 25.9, 24.1, 18.3, -0.1, -4.6, -5.0; HRMS (ESI) Calcd. for $C_{23}H_{40}O_3NSi_2$ [(M + H)$^+$] 434.25413, found 434.25385; $[\alpha]^{26}_D$ = + 23.3 (c = 1.0, $CHCl_3$).



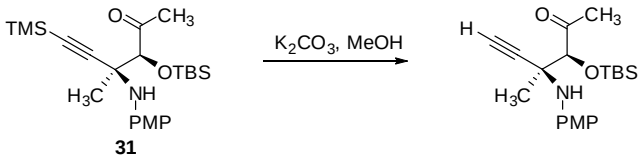

**31** **32**

To a solution of **31** (373 mg, 0.860 mmol) in $CH_2Cl_2$ (5.6 mL) and methanol (1.1 mL) was added $CeCl_3$-$7H_2O$ (802 mg, 2.15 mmol) at room temperature. After stirring at room temperature for 20 minutes, the mixture was cooled to -78 ºC, and $NaBH_4$ (81.4 mg, 2.15 mmol) was added in one portion. After stirring at -78 ºC for 2 hours, another portion of

$NaBH_4$ (81.4 mg, 2.15 mmol) was added to the reaction mixture. Stirring continued for 16 hours at -78 ºC. The reaction was quenched with aq. $NaH_2PO_4$, and extracted with ethyl acetate. Concentration and column chromatography gave product **32** (282 mg, 75%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 4.66 (dq, *J* = 1.6 Hz, 6.8 Hz, 1H), 3.78 (s, 3H), 3.57 (d, *J* = 1.2 Hz, 1H), 1.41 (s, 3H), 1.24 (d, *J* = 6.4 Hz, 3H), 1.01 (s, 9H), 0.21 (s, 3H), 0.18 (s, 9H), 0.17 (s, 3H).

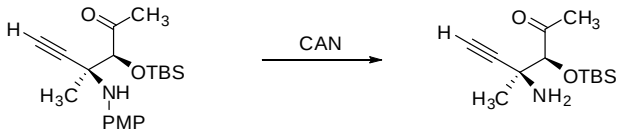



To a solution of **32** (282 mg, 0.647 mmol) in methanol (7 mL) was added $K_2CO_3$ (179 mg, 1.30 mmol) at room temperature. The reaction was stirred for 2 hours and quenched with aq. $NaH_2PO_4$. Extraction, concentration and column chromatography (hexanes / ethyl acetate = 10 /1) gave product **33** (182 mg, 77%) as the major product, and the minor product is the one with TBS on the other hydroxyl group (not the silyl migration). IR (neat) 2953, 1713, 1511 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 4.58 (dq, *J* = 2.0 Hz, 6.4 Hz, 1H), 3.78 (s, 3H), 3.33 (d, *J* = 4.8 Hz, 1H), 2.45 (s, 1H), 1.47 (s, 3H), 1.34 (d, *J* = 6.0 Hz, 3H), 0.93 (s, 9H), 0.16 (s, 6H).

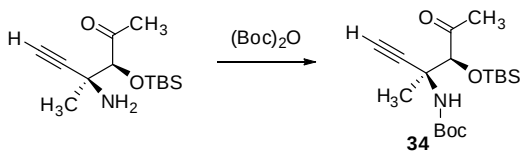



To a solution of **31** (218 mg, 0.503 mmol) in methanol (6 mL) was added $K_2CO_3$ (139 mg, 1.01 mmol) at room temperature. The reaction was stirred for 1.5 hours and

quenched with aq. $NaH_2PO_4$. Extraction, concentration and flash column chromatography (hexanes / ethyl acetate = 6 /1) gave product as shown above (165 mg, 91%). IR (neat) 2953, 1713, 1511 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 4.07 (s, 1H), 3.87 (s, 1H), 3.77 (s, 3H), 2.49 (s, 1H), 2.34 (s, 3H), 1.45 (s, 3H), 1.00 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 209.3, 154.8, 138.4, 122.2, 114.3, 84.8, 84.0, 75.1, 55.9, 55.7, 26.0, 25.9, 24.3, 18.3, -4.6, -5.0; HRMS (ESI) Calcd. for $C_{20}H_{32}O_3NSi$ [$(M + H)^+$] 362.21460, found 362.21442; $[\alpha]^{26}{}_D$ = - 5.4 (c = 1.0, $CHCl_3$).

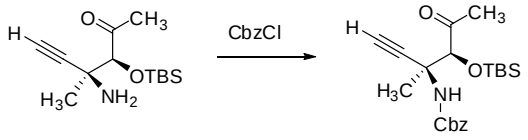



To a solution of starting material (504 mg, 1.39 mmol) in MeCN (10 mL) was added a solution of CAN (1.68 g, 3.07 mmol) in water (3 mL) slowly at room temperature. The reaction was completed in about 20 minutes, and diluted with water. Extraction with ethyl acetate, concentration and column chromatography (hexanes / ethyl acetate = 4 /1, per 200 mL eluant was treated with 1 mL $Et_3N$) gave product as shown above (295 mg, 83%). IR (neat) 3308, 2954, 1713 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 3.79 (d, *J* = 1.2 Hz, 1H), 2.34 (d, *J* = 0.8 Hz, 1H), 2.26 (s, 3H), 1.65 (bs, 2H), 1.33 (s, 3H), 0.92 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 210.0, 87.2, 85.1, 72.0, 51.2, 27.7, 27.1, 25.8, 18.2, -4.8, -5.0; $[\alpha]^{26}{}_D$ = - 14.1 (c = 1.75, $CHCl_3$).

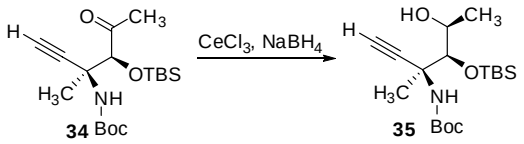



**34**

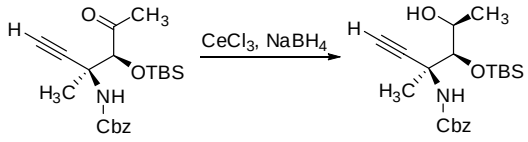
To a solution of amine starting material (295 mg, 1.16 mmol) in acetone (7 mL) and water (7 mL) was added $K_2CO_3$ (192 mg, 1.39 mmol) and $(Boc)_2O$ (1.26 g, 5.80 mmol) at room temperature. The reaction was stirred overnight and was extracted with ethyl acetate. Concentration and column chromatograhy (hexanes / ethyl acetate = 4/1) gave product **34** (391 mg, 95%). $^1$H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.29 (s, 1H), 2.41 (s, 1H), 2.27 (s, 3H), 1.58 (s, 3H), 1.45 (s, 9H), 0.93 (s, 9H), 0.12 (s, 3H), 0.03 (s, 3H).



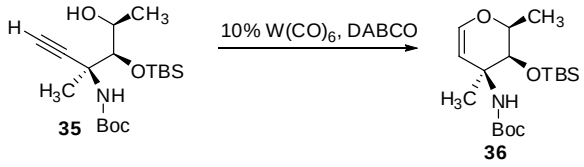

To a solution of amine starting material (638 mg, 2.50 mmol) in acetone (25 mL) and water (25 mL) was added $K_2CO_3$ (449 mg, 3.25 mmol) and CbzCl (512 mg, 3.00 mmol) at room temperature. The reaction was stirred and completed in 2 hours. Extraction with ethyl acetate, concentration and column chromatography gave product (954 mg, 98%). IR (neat) 3308, 2953, 1718 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 4H), 7.30 (m, 1H), 5.40 (bs, 1H), 5.11(d, *J* = 12.0 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 4.35(s, 1H), 2.45 (s, 1H), 2.27 (s, 3H), 1.63 (s, 3H), 0.95 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 209.1, 154.9, 136.4, 128.6, 128.2, 83.5, 81.0, 73.2, 66.9, 53.3, 28.2, 25.8, 22.9, 18.2, -4.7, -4.9; HRMS (ESI) Calcd. for $C_{21}H_{32}O_4NSi$ [$(M + H)^+$] 390.20951, found 390.20939; $[\alpha]^{26}{}_D$ = - 5.3 (c = 0.5, $CHCl_3$).



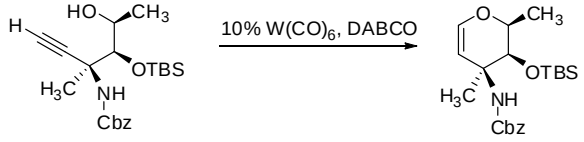

To a solution of **34** (385 mg, 1.08 mmol) in $CH_2Cl_2$ (20 mL) and methanol (4mL) was added $CeCl_3$-$7H_2O$ (1.01 g, 2.70 mmol) at room temperature. After stirring at room temperature for 20 minutes, the mixture was cooled to -78 ºC, and $NaBH_4$ (53.1 mg, 1.40 mmol) was added in one portion. After stirring at -78 ºC for 2 hours, another portion of $NaBH_4$ (49.0 mg, 1.30 mmol) was added to the reaction mixture. Stirring continued overnight while the temperature was warmed to room temperature. The reaction was quenched with aq. $NaH_2PO_4$, and extracted with ethyl acetate. Concentration and column chromatography gave product **35** (368 mg, 95%). $^1$H NMR (600 MHz, $CDCl_3$) δ 5.58 (bs, 1H), 4.23 (dq, *J* = 6.0 Hz, 7.2 Hz, 1H), 3.83 (s, 1H), 2.41 (d, *J* = 9.0 Hz, 1H), 2.37 (s, 1H), 1.61 (s, 3H), 1.42 (s, 9H), 1.21 (d, *J* = 7.2 Hz, 3H), 0.98 (s, 9H), 0.22 (s, 3H), 0.90 (s, 3H).




The procedure is the same as the transformation from **34** to **35**. The yield for this reaction is also comparable. IR (neat) 3308, 2953, 1721, 1515 $cm^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 4H), 7.31 (m, 1H), 6.16 (bs, 1H), 5.10 (s, 2H), 4.30 (q, *J* = 6.6 Hz, 1H), 3.77 (s, 1H), 2.42 (s, 1H), 1.68 (s, 3H), 1.23 (d, *J* = 7.2 Hz, 3H),, 0.79 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 155.0, 136.6, 128.5, 128.1, 85.3, 78.8, 72.2, 66.8, 66.5, 55.3, 26.4, 24.7, 23.0, 18.7, -3.49, -3.53; HRMS (ESI) Calcd. for $C_{21}H_{34}O_4NSi$ [$(M + H)^+$] 392.22516, found 392.22501; $[\alpha]^{26}{}_D$ = + 3.9 (c = 1.0, $CHCl_3$).

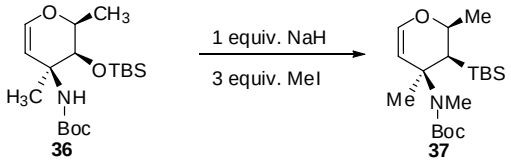



To a solution of **35** (368 mg, 1.03 mmol) in THF (35 mL) was added DABCO (288 mg, 2.57 mmol) and $W(CO)_6$ (54 mg, 0.154 mmol), the solution was irradiated to reflux in a UV photochamber at 350 nm for 5 hours. The reaction mixture was concentrated and loaded on a column filled with silica gel for purification (hexanes / ethyl acetate = 10 / 1) to give product **36** (262 mg, 71%). $^1$H NMR (600 MHz, $CDCl_3$) δ 6.18 (d, *J* = 6.0 Hz, 1H), 5.17 (m, 2H), 4.01 (q, *J* = 6.4 Hz, 1H), 3.61 (s, 1H), 1.31 (s, 12H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H).

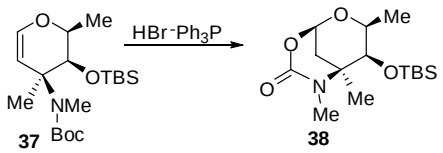



To a solution of starting material (844 mg, 2.16 mmol) in THF (90 mL) was added DABCO (485 mg, 4.32 mmol) and $W(CO)_6$ (152 mg, 0.43 mmol), the solution was irradiated to reflux in a UV photochamber at 350 nm for 5 hours. The reaction mixture was concentrated and loaded on a column filled with silica gel for purification (hexanes / ethyl acetate = 10 / 1) to give product as shown above (671 mg, 79%). IR (neat) 3434, 2953, 1730, 1648cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) δ 7.36 (m, 4H), 7.32 (m, 1H), 6.18 (d, *J* = 6.6 Hz, 1H), 5.53 (s, 1H), 5.25 (bs, 1H), 5.09 (AB pattern, *J* = 12.0 Hz, 2H), 4.15 (dq, *J* = 4.8 Hz, 7.2 Hz, 1H), 3.82 (d, *J* = 4.2 Hz, 1H), 1.46 (s, 3H), 1.33 (d, *J* = 7.2 Hz, 3H), 0.97 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 154.9, 140.7, 137.1, 128.6, 128.0, 127.9, 104.2, 73.9, 72.1, 66.1, 50.8, 30.5, 26.8, 26.0, 18.3, -4.1, -4.5;

HRMS (ESI) Calcd. for $C_{21}H_{34}O_4NSi$ [$(M + H)^+$] 392.22516, found 392.22511; $[\alpha]^{26}{}_D$ = + 17.6 (c = 1.0, $CHCl_3$).

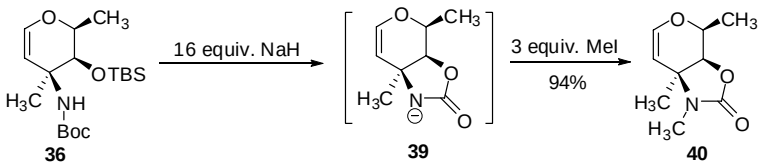



To a solution of **36** (42 mg, 0.12 mmol) in DMF (2 mL) was added NaH (4.7 mg of 60% NaH on mineral oil, 0.12 mmol) and MeI (29 μL, 0.468 mmol) at room temperature. The reaction was stirred overnight and quenched with water. Extraction with ethyl acetate and column chromatography (hexanes / ethyl acetate = 4 / 1) gave **37** (37 mg, 82%).[1]H NMR (400 MHz, $CDCl_3$) δ 6.25 (d, *J* = 6.4 Hz, 1H), 4.78 (dd, *J* = 2.0 Hz, 6.4 Hz, 1H), 4.18 (s, 1H), 4.07 (q, *J* = 6.4 Hz, 1H), 2.92 (s, 3H), 1.63 (s, 3H), 1.48 (s, 9H), 1.25 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.02 (s, 3H).

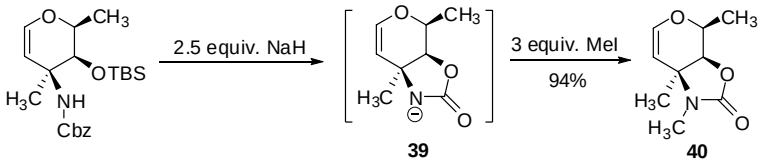



To a solution of **37** (15 mg, 0.040 mmol) in $HOCH(CF_3)_2$ (1.0mL) was added $PPh_3$-HBr (0.7 mg, 0.002 mmol) at room temperature. The reaction was stirred for 3 hours and then quenched with water. Extraction with ethyl acetate, concentration and column chromatography gave **38** (8 mg, 63%). [1]H NMR (600 MHz, $CDCl_3$) δ 5.50 (s, 1H), 4.29 (dq, *J* = 6.6 Hz, 6.6 Hz, 1H), 3.82 (d, *J* = 7.2 Hz, 1H), 3.12 (s, 3H), 2.05 (dd, *J* = 2.4 Hz, 13.8 Hz, 1H), 1.90 (dd, *J* = 2.4 Hz, 13.8 Hz, 1H), 1.43 (s, 3H), 1.30 (d, *J* = 7.2 Hz, 3H),

0.95 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); HRMS (ESI) Calcd. for $C_{15}H_{30}O_4NSi$ [$(M + H)^+$] 316.19386, found 316.19403.

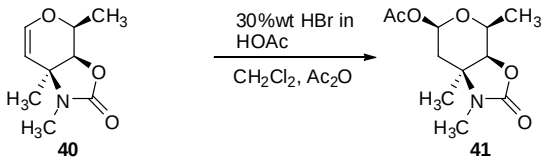



To a solution of **36** (42 mg, 0.12 mmol) in DMF (2 mL) was added NaH (76.8 mg of 60% NaH on mineral oil, 1.92 mmol) at room temperature. The reaction was stirred about 2 hours when TLC showed complete formation of **39** (very large palarity difference between **36** and **39**). MeI (29 μL, 0.468 mmol) was added to the reaction and stirring continued overnight. The reaction was quenched with water. Extraction with ethyl acetate and column chromatography (hexanes / ethyl acetate = 4 / 1) gave **40** (21 mg, 96%). The $^1$H NMR and $^{13}$C NMR sptetra is identical to the reported data.

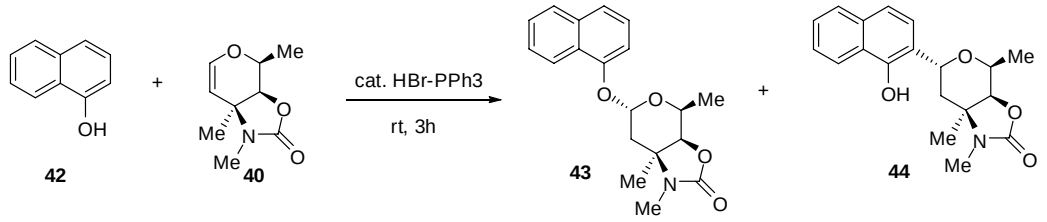



To a solution of starting material (671 mg, 1.71 mmol) in DMF (2 mL) was added NaH (171 mg of 60% NaH on mineral oil, 4.28 mmol) at room temperature. The reaction was stirred about 2 hours when TLC showed complete formation of **39** (very large palarity difference between starting material and **39**). MeI (231 μL, 3.71 mmol) was added to the reaction and stirring continued overnight. The reaction was with water. Extraction with ethyl acetate and column chromatography (hexanes / ethyl acetate = 4 / 1) gave **40** (265 mg, 85%). The $^1$H NMR and $^{13}$C NMR sptetra is identical to the reported data.

Especially, $[\alpha]^{26}_{D}$ = + 95.4 (c = 0.9, $CHCl_3$) in comparison with $[\alpha]^{26}_{D}$ = + 100 (c = 0.9, $CHCl_3$) in the literature.

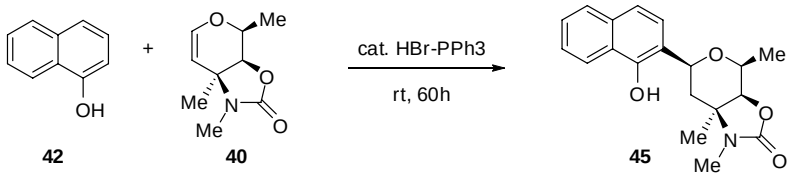



To a solution of **40** (20 mg, 0.11 mmol) in $CH_2Cl_2$ (1.2 mL) and acetic anhydride (0.4 mL) was added a solution of 30% weight HBr in HOAc (5.5 μL, 0.07 mmol HBr contained) at 0 ºC. The reaction was stirred overnight while warming to room temperature. The reation was quenched with water, extracted with $CH_2Cl_2$. Column chromatography (hexanes / ethyl acetate = 1 / 2) gave **41** (16 mg, 60%) with recovered **40** (6 mg, 30%).$^1$H NMR (400 MHz, $CDCl_3$) δ 6.00 (dd, *J* = 5.6 Hz, 8.0 Hz, 1H), 4.11 (dq, *J* = 2.0 Hz, 6.4 Hz, 1H), 4.02 (d, *J* = 2.4 Hz, 1H), 2.79 (s, 3H), 2.25 (dd, *J* = 5.6 Hz, 15.2 Hz, 1H), 2.07 (s, 3H), 1.77 (dd, *J* = 8.0 Hz, 15.2 Hz, 1H), 1.39 (s, 3H), 1.33 (d, *J* = 6.0 Hz, 3H).



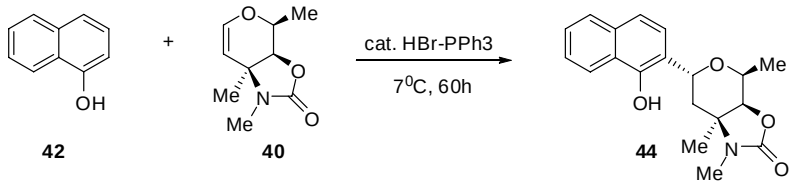

To a solution of **42** (15 mg, 0.082 mmol) and **40** (14 mg, 0.098 mmol) in $CH_2Cl_2$ was added $PPh_3$-HBr (2.8 mg, 0.0082 mmol) at room temperature. The reaction was stirred for 4 hours and quenched with water. Extraction with ethyl acetate, concentration and column chromatography (hexanes / ethyl acetate = 1 /1) gave **43** (10mg, 37%) and **44**

(5mg, 19%). **43**: IR (neat) 2924, 1754 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.50 (m, 3H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 5.67 (t, *J* = 6.0 Hz, 1H), 4.26 (q, *J* = 6.0 Hz, 1H), 4.06 (d, *J* = 0.6 Hz, 1H), 2.84 (s, 3H), 2.37 (dd, *J* = 5.4 Hz, 15.0 Hz, 1H), 2.21 (dd, *J* = 6.0 Hz, 14.4 Hz, 1H), 1.56 (s, 3H), 1.34 (d, *J* = 6.6 HZ, 3H). **44**: IR (neat) 3283, 2920, 1739 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.27 (m, 1H), 7.76 (m, 1H), 7.49 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 5.28 (dd, *J* = 3.6 Hz, 12.0 Hz, 1H), 4.19 (dq, *J* = 1.8 Hz, 6.6 Hz, 1H), 4.15 (d, *J* = 0.6 Hz, 1H), 2.91 (s, 3H), 2.30 (dd, *J* = 3.6 Hz, 15.0 Hz, 1H), 2.13 (dd, *J* = 12.0 Hz, 15.0 Hz, 1H), 1.47 (s, 3H), 1.45 (d, *J* = 6.0 Hz, 1H).



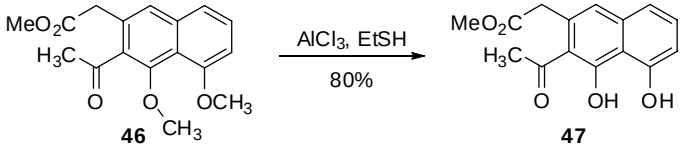

42 40 45

To a solution of **42** (22 mg, 0.15 mmol) and **40** (23 mg, 0.13 mmol) in $CH_2Cl_2$ was added $PPh_3$-HBr (6.8 mg, 0.020 mmol) at room temperature. The reaction was stirred for 60 hours and quenched with water. Extraction with ethyl acetate, concentration and column chromatography (hexane / ethyl acetate = 1 / 1) gave **45** (35mg, 85%). $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.26 (m, 1H), 7.75 (m, 1H), 7.48 (m, 2H), 7.34 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 4.65 (dd, *J* = 3.2 Hz, 10.8 Hz, 1H), 3.99 (dq, *J* = 2.0 Hz, 6.8 Hz, 1H), 3.81 (d, *J* = 2.0 Hz, 1H), 2.72 (s, 3H), 2.02 (m, 2H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.50 (s, 3H).



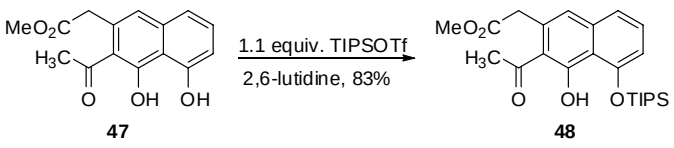

**42** **40** **44**

To a solution of **42** (25 mg, 0.17 mmol) and **40** (26 mg, 0.14 mmol) in $CH_2Cl_2$ was added $PPh_3$-HBr (5.0 mg, 0.014 mmol) at 7 ºC. The reaction was stirred for 60 hours at 7 ºC and quenched with water. Extraction with ethyl acetate, concentration and column chromatography (hexane / ethyl acetate = 1 / 1) gave **44** (20 mg, 43%) and **43** (9 mg, 19%), **45** (4mg, 9%).




**46** **47**

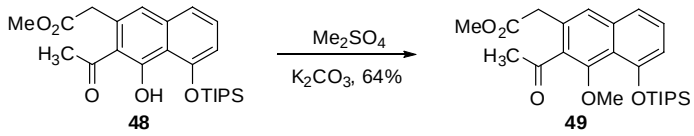
To a solution of $AlCl_3$ (67 mg, 0.50 mmol) in EtSH (1 mL) was added a solution of **46** (30 mg, 0.10 mmol) in $CH_2Cl_2$ (0.5 mL) at 0 ºC. The reaction was stirred at 0 ºC for 10 minutes, and then quenched with aq. $NaH_2PO_4$. Abstraction with ethyl acetate, and concentration in a fume hood with good ventilation, column chromatography (hexanes / ether = 1 / 2) gave product **47** (23 mg, 84%). $^1$H NMR (300 MHz, $CDCl_3$) δ 16.75 (s, 1H), 10.12 (s, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.03 (s, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.00 (s, 2H), 3.74 (s, 3H). 2.71 (s, 3H).




**47** **48**

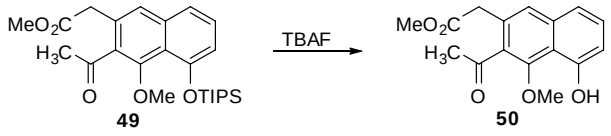
To a solution of **47** (30 mg, 0.11 mmol) in $CH_2Cl_2$ (2 mL) was added 2, 6–lutidine (28 μL, 0.24 mmol), TIPSOTf (26 μL, 0.12 mmol) at 0 ºC. The reaction was stirred at this

temperature for 1.5 hours, and quenched with aq $NaH_2PO_4$. Extraction with ethyl ether, concentration and column chromatography (hexanes / ethyl acetate = 4/1) gave product **48** (39 mg, 83%).[1]H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H), 7.47 (m, 3H), 6.93 (dd, *J* = 1.2 Hz, 7.2 Hz, 1H), 4.04 (s, 2H), 3.87 (s, 3H). 2.87 (s, 3H), 1.64 (sept, *J* = 7.6 Hz, 3H), 1.36 (d, *J* = 8.0 Hz, 18H).




**48** **49**

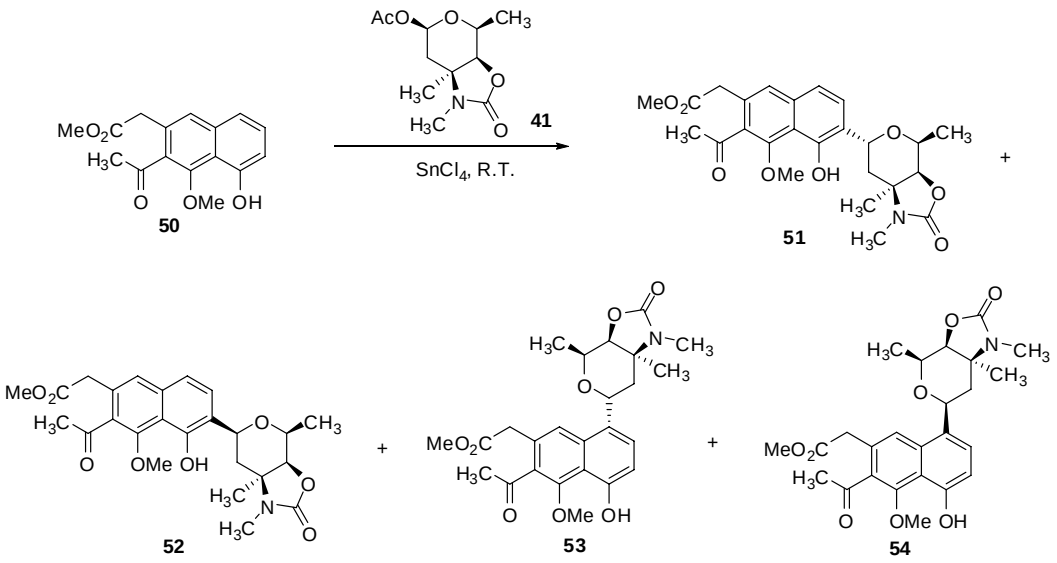
To a solution of **48** (39 mg, 0,091 mmol) in acetone (10 mL) was added $K_2CO_3$ (50 mg, 0.36 mmol) and $Me_2SO_4$ (22 μL, 0.226 mmol). The reaction was refluxed for 16 hours and then cooled to room temperature. Filtration of the solid, removal of the solvent and column chromatography (hexanes / ethyl acetate = 6 /1) gave **49** (28 mg, 64%) and **46** (8 mg, 29%). [1]H NMR (400 MHz, $CDCl_3$) δ 7.41(s, 1H), 7.34 (m, 2H), 6.89 (dd, *J* = 1.6 Hz, 6.8 Hz, 1H), 3.83 (s, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 2.67 (s, 3H), 1.41 (sept, *J* = 7.6 Hz, 3H), 1.14 (d, *J* = 7.6 Hz, 18H).




**49** **50**

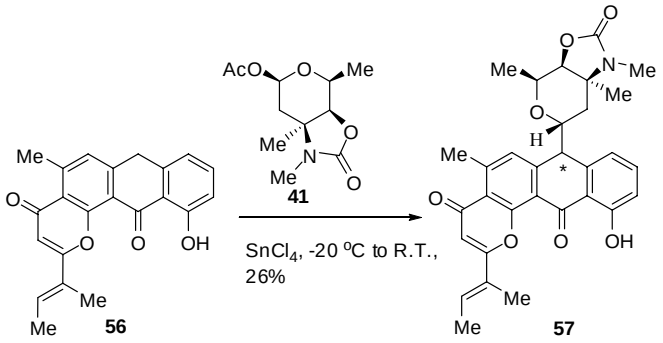
To a solution of **49** (28 mg, 0.063 mmol) in acetone (THF 4mL) was added TBAF (0.2 mmol, 0.2 mL of 1 M TBAF in THF) at room temperature. The reaction was stirred until TLC showed completion. The reaction was quenched with water, extraction with ethyl acetate and concentration. A column chromatography (hexanes / ethyl acetate = 4 /1) gave **50** (17 mg, 94%). [1]H NMR (600 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.47 (s, 1H), 7.44 (t, *J*

= 8.4 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H),3.95 (s, 3H), 3.88 (s, 2H), 3.70 (s, 3H). 2.72 (s, 3H).



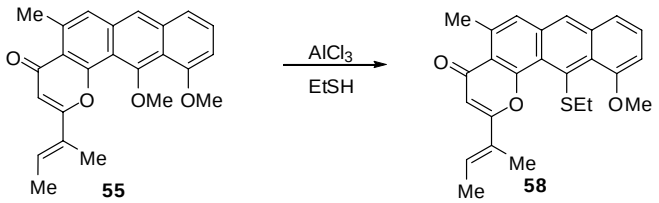

To a solution of **50** (11 mg, 0.038 mmol) and **41** (10 mg, 0.042 mmol) in 1, 2-dichloroethane (1.5 mL) was added microwave- activated 4 Å molecular sieves powder (90 mg) and $SnCl_4$ (0.076 mmol, 0.076 mL solution of 1 M $SnCl_4$ in dichloromethane) at room temperature. The reaction was stirred overnight and then quenched with aq. $NaHCO_3$. The mixture was filtered through a layer of well packed celite bed, extracted with dichloromethane, dried over $Na_2SO_4$ and concentrated under reduced pressure. Column chromatography (hexanes / ethyl acetate = 1 / 1) eluted out sequentially **52** (3 mg, 17%), **54** (2 mg, 11%), finally mixed **51** and **53** (2: 1 ratio, 7 mg and 39% combined yield). **52**: $^1$H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.44 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 4.92 (dd, *J* = 2.0 Hz, 11.2 Hz, 1H), 4.00 ( dq, *J* = 2.0 Hz, 6.4 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 1H), 3.83 (s, 2H), 3.69 (s, 3H), 2.71 (s, 6H), 2.14 (d, *J* = 2.0 Hz, 13.6 Hz, 1H), 1.63 (d, *J* = 13.2 Hz, 1H), 1.54 (s, 3H), 1.52 (d, *J* = 6.8 Hz, 3H);

**54**: $^1$H NMR (600 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.53 (s, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 4.85 (dd, *J* = 1.8 Hz, 11.4 Hz, 1H), 4.05 ( dq, *J* = 1.8 Hz, 6.6 Hz, 1H), 3.92 (s, 3H), 3.89 (d, *J* = 3.6 Hz, 1H), 3.87 (d, *J* = 1.8 Hz, 1H), 3.71 (s, 3H), 2.73 (s, 3H), 2.71 (s, 3H), 2.11 (d, *J* = 1.8 Hz, 13.2 Hz, 1H), 1.88 (t, *J* = 12.0 Hz, 1H), 1.57 (s, 3H), 1.52 (d, *J* = 6.6 Hz, 3H); **51**: $^1$H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.44 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 5.29 (dd, *J* = 4.0 Hz, 12.4 Hz, 1H), 4.27 ( dq, *J* = 1.2 Hz, 4.8 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 2H), 3.82 (s, 1H), 3.69 (s, 3H), 2.95 (s, 3H), 2.71 (s, 3H), 2.41 (dd, *J* = 4.0 Hz, 15.2Hz, 1H), 1.73 (dd, *J* = 12.4 Hz, 15.6 Hz, 1H), 1.44(d, *J* = 4.8 Hz, 3H), 1.40 (s, 3H).

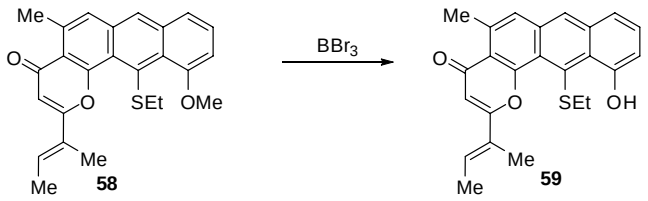



To a solution of **56** (10 mg, 0.029 mmol) and **41** (7 mg, 0.029 mmol) in $CH_2Cl_2$ (1.5 mL) was added microwave- activated 5 Å molecular sieves powder (75 mg) and $SnCl_4$ (0.047 mmol, 0.047 mL solution of 1 M $SnCl_4$ in dichloromethane) at -20 ºC. The reaction was stirred overnight while warming to room temperature. The reaction was quenched with water and filtered through a layer of well packed celite. Extraction with dichloromethane, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 1 / 1) gave two separable diastereomers of **57** (2 mg each, 26% together). One diastereomer: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, *J* =

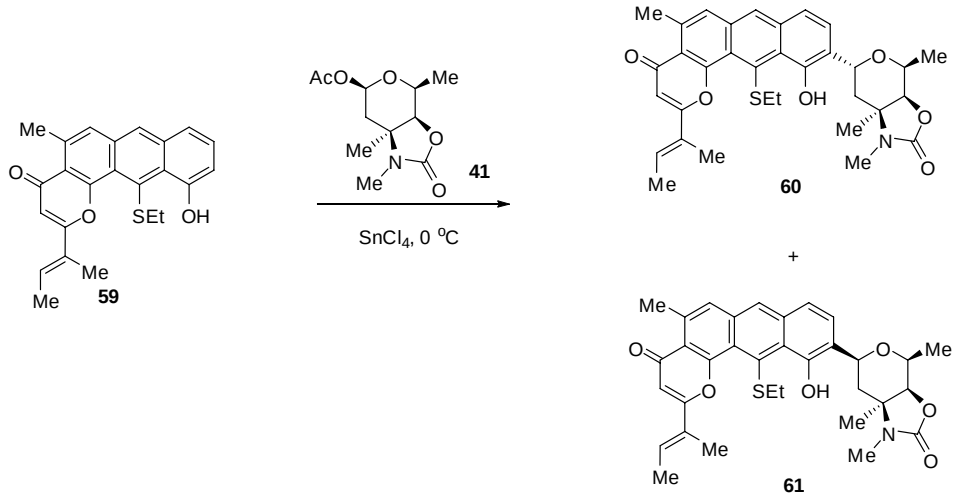
8.0 Hz, 1H), 7.49 (q, *J* = 5.2 Hz, 1H), 7.15 (s, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.37 (s, 1H), 4.50 (d, *J* = 4.4 Hz, 1H), 4.14 (dt, *J* = 4.4 Hz, 12.8 Hz, 1H), 3.79 (d, *J* = 1.2 Hz, 1H), 3.17 (dq, *J* = 1.6 Hz, 6.4 Hz, 1H), 2.95 (s, 3H), 2.46 (s, 3H), 2.01 (m, 7H), 1.24 (m, 1H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.14 (s, 3H). HRMS (APCI) Calcd. for $C_{31}H_{32}O_7N_1[(M + H)^+]$ 530.21733, found 530.21727.




To a solution of $AlCl_3$ (133 mg, 1.00 mmol) in EtSH (6.1 mL) was added a solution of **55** (152 mg, 0.406 mmol) in $CH_2Cl_2$ (6.1 mL) at 0 ºC. The reaction was stirred and completed in 5 minutes and quenched with aq. $NaH_2PO_4$. More equivalents of $AlCl_3$ and longer reaction time will cause side reaction to occur. The reaction was extracted by ethyl acetate, dried over $Na_2SO_4$ and concentrated by stirring in a flask connetcted to an aspirator located in a fume hood with good ventilation. Flash column chromatography afforded red **58** (143 mg, 87%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.68 (q, *J* = 6.8 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.44 (m, 2H), 6.89 (d, *J* = 6.8 Hz, 1H), 6.48 (s, 1H), 4.11 (s, 3H), 2.92 (s, 3H), 2.57 (q, *J* = 7.2 Hz, 2H), 2.04 (s, 3H), 2.00 (d, *J* = 6.8 Hz, 3H), 0.83 (t, *J* = 7.2 Hz, 3H).

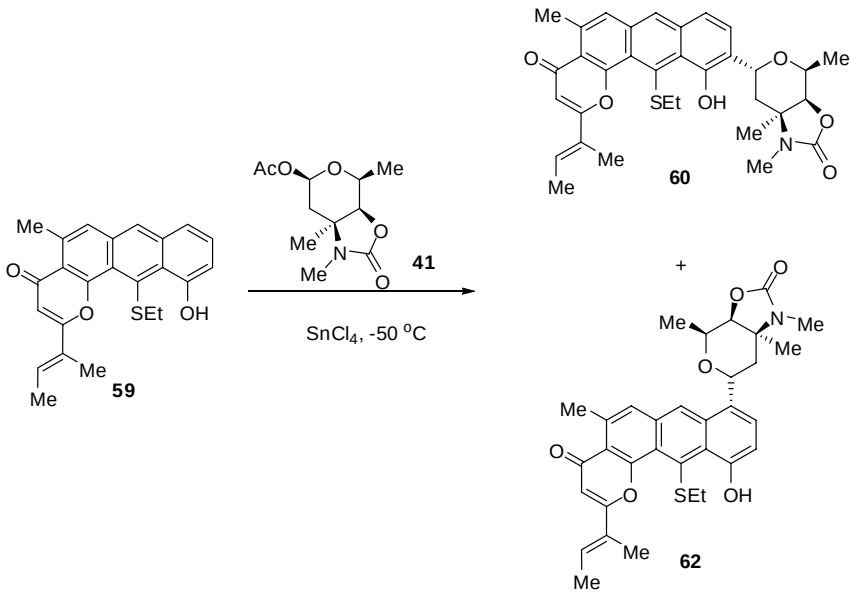



To a solution of **58** (24 mg, 0.059 mmol) in $CH_2Cl_2$ (7.2 mL) was added $BBr_3$ (0.235 mmol, 235 μL solution of 1 M $BBr_3$ in $CH_2Cl_2$) at 0 ºC. The reaction was stirred overnight while warming to room temperature. The reaction was quenched by aq. $NaHCO_3$, extracted by ethyl acetate, dried with $Na_2SO_4$ and concentrated by rotary evaporation. Flash column chromatography (hexanes / ethyl acetate = 2/1 to pure ether) afforded red **59** (19 mg, 83%). $^1$H NMR (600 MHz, $CDCl_3$) δ 11.09 (s, 1H), 8.26 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 8.4 Hz, 1H), 7.49 (s, 1H), 7.23 (q, *J* = 6.6 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.49 (s, 1H), 2.95 (s, 3H), 2.65 (bs, 2H), 2.06 (s, 3H), 1.99 (d, *J* = 6.6 Hz, 3H), 0.74 (t, *J* = 7.2 Hz, 3H); HRMS (APCI) Calcd. for $C_{24}H_{23}O_3S_1[(M + H)^+]$ 391.13624, found 391.13641.

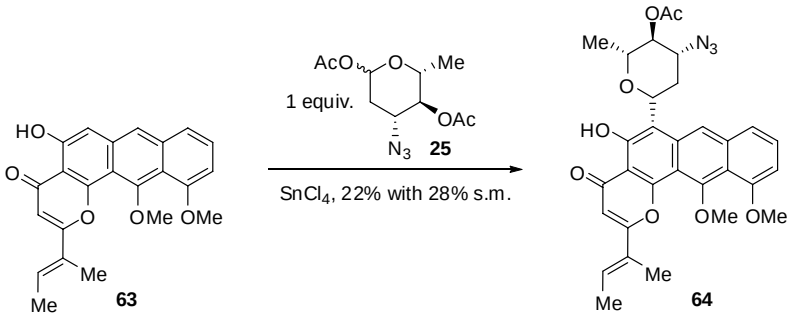



To a solution of **59** (5.0 mg, 0.013 mmol) and **41** (4.0 mg, 0.029 mmol) in 1, 2-dichloroethane (1.3 mL) was added microwave- activated 4 Å molecular sieves powder

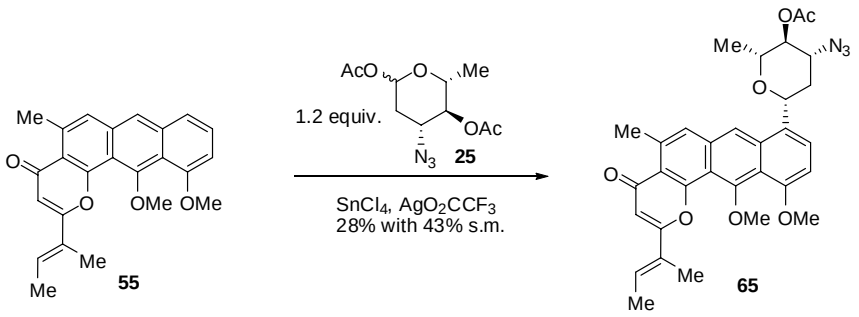
(60 mg) and $SnCl_4$ (0.026 mmol, 0.026 mL solution of 1 M $SnCl_4$ in dichloromethane) at 0 ºC. The reaction was stirred overnight at 0 ºC, quenched with aq. $NaHCO_3$ and filtered through a layer of well packed celite. Extraction with dichloromethane, drying over $Na_2SO_4$, concentration by rotary evaporation and preparative TLC (hexanes / ethyl acetate = 1 / 1) gave red **60** (1 mg, 14%) and red **61** (1 mg, 14%).**60**: $^1$H NMR (600 MHz, $CDCl_3$) δ 11.22 (bs, 1H), 8.24 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.50 (s, 1H), 7.23 (q, *J* = 6.6 Hz, 1H), 6.59 (s, 1H), 5.48 (d, *J* = 10.2 Hz, 1H), 4.34 (q, *J* = 6.0 Hz, 1H), 4.18 (s, 1H), 3.01 (s, 3H), 2.94 (s, 3H), 2.61 (m, 3H), 2.07 (s, 3H), 2.00 (d, *J* = 7.2 Hz, 3H), 1.77 (m, 1H), 1.49 (d, *J* = 6.6 Hz, 3H), 1.41 (s, 3H), 0.66 (bs, 3H); **61**: $^1$H NMR (600 MHz, $CDCl_3$) δ 11.31 (bs, 1H), 8.29 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.59 (s, 1H), 7.38 (q, *J* = 6.6 Hz, 1H), 7.14 (s, 1H), 5.09 (d, *J* = 11.4 Hz, 1H), 4.06 (q, *J* = 6.6 Hz, 1H), 3.87 (s, 1H), 2.94 (s, 3H), 2.71(s, 3H), 2.64 (bs, 2H), 2.19 (m, 1H), 2.12 (s, 3H), 2.02 (d, *J* = 7.2 Hz, 3H), 1.77 (m, 1H), 1.58 (s, 3H), 1.56 (d, *J* = 6.6 Hz, 3H), 0.69 (bs, 3H).



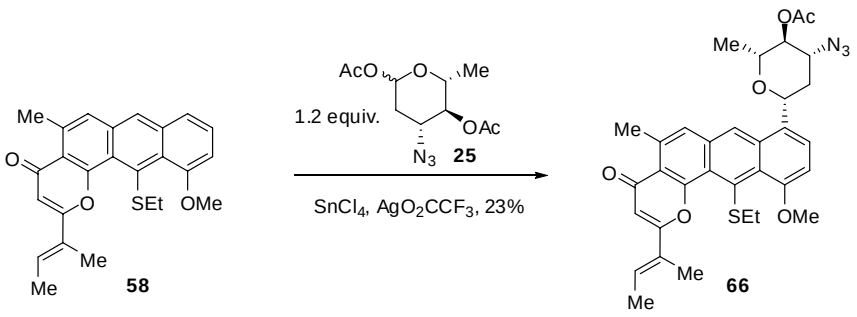

To a solution of **59** (12.0 mg, 0.031 mmol) in $CH_2Cl_2$ (1 mL) was added sequentially microwave- activated 4 Å molecular sieves powder (90 mg), $SnCl_4$ (0.093 mmol, 0.093 mL solution of 1 M $SnCl_4$ in dichloromethane) and a solution of **41** (9.0 mg, 0.037 mmol) in $CH_2Cl_2$ (1 mL) at -78 ºC. The reaction was stirred at -50 ºC for 36 hours, quenched with aq. $NaHCO_3$ and filtered through a layer of well packed celite bed. Extraction with dichloromethane, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 1 / 1) gave recovered **59** (4 mg, 30%), **60** (6 mg, 34%) and red **62** (5 mg, 29%). **62**: $^1$H NMR (600 MHz, $CDCl_3$) δ 11.18 (s, 1H), 8.36 (s, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.53 (s, 1H), 7.23 (q, *J* = 6.6 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.59 (s, 1H), 5.58 (d, *J* = 11.4 Hz, 1H), 4.25 (q, *J* = 6.6 Hz, 1H), 4.22 (s, 1H), 3.02 (s, 3H), 2.96 (s, 3H), 2.61 (bs, 2H), 2.27 (dd, *J* = 3.0 Hz, 15.0 Hz, 1H), 2.07 (s, 3H), 2.00 (d, *J* = 7.2Hz, 3H), 1.77 (dd, *J* = 7.8 Hz, 15.0 Hz, 1H), 1.48 (s, 3H), 1.44 (d, *J* = 6.6 Hz, 3H), 0.70 (t, *J* = 7.2 Hz, 3H).



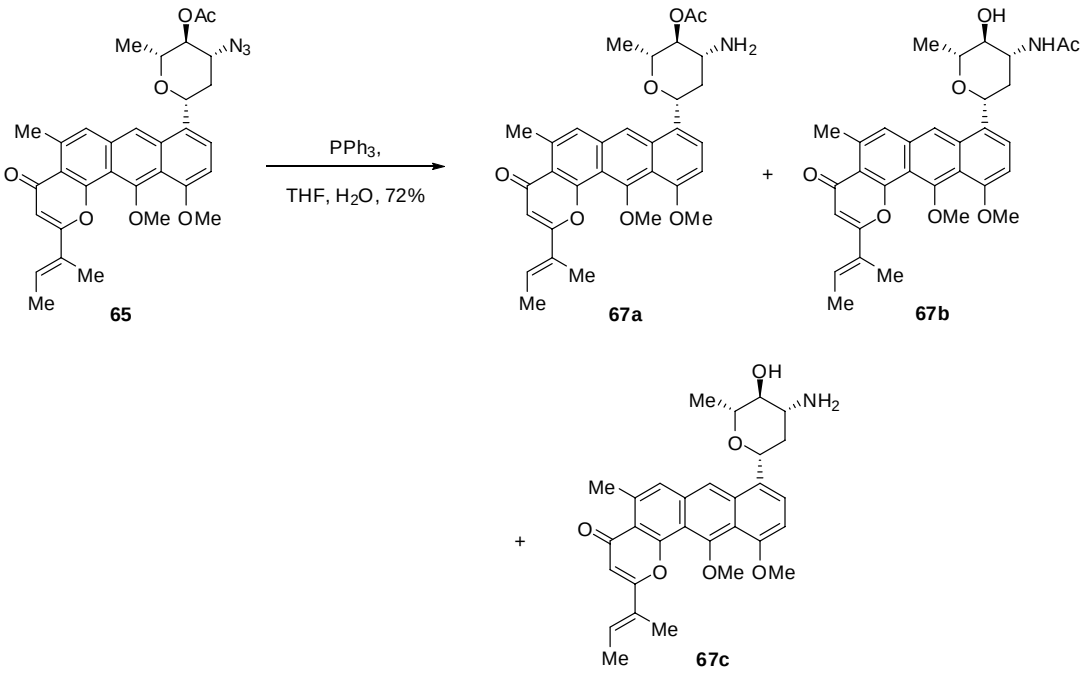

To a solution of **63** (17 mg, 0.045 mmol) and **25** (10 mg, 0.039 mmol) in $CH_2Cl_2$ (1.5 mL) was added sequentially microwave- activated 4 Å molecular sieves powder (70 mg), $SnCl_4$ (0.094 mmol, 0.094 mL solution of 1 M $SnCl_4$ in dichloromethane) at room temperature. The reaction was stirred for 2 hours, quenched with aq. $NaHCO_3$ and filtered through a layer of well packed celite bed. Extraction with dichloromethane, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 4 / 1) gave recovered **63** (5 mg, 29%) and red **64** (5 mg, 22%). $^1$H NMR (600 MHz, $CDCl_3$) δ 13.68 (s, 1H), 8.83 (s, 1H), 7.57 (d, $J$ = 8.4 Hz, 1H), 7.47 (t, $J$ = 7.8 Hz, 1H), 7.40 (q, $J$ = 5.4 Hz, 1H), 6.80 (d, $J$ = 7.8 Hz, 1H), 6.56 (s, 1H), 5.69 (dd, $J$ = 3.0 Hz, 12.6 Hz, 1H), 5.01 (t, $J$ = 9.6 Hz, 1H), 4.11 (s, 3H), 3.92 (m, 1H), 3.91 (s, 3H), 3.76 (dd, $J$ = 6.0 Hz, 9.6 Hz, 1H), 2.59 (q, $J$ = 12.0 Hz, 1H), 2.24 (m, 1H), 2.23 (s, 3H), 2.07 (s, 3H), 2.04 (d, $J$ = 7.2 Hz, 3H), 1.35 (d, $J$ = 6.0 Hz, 3H); HRMS (ESI) Calcd. for $C_{31}H_{32}O_8N_3[(M + H)^+]$ 574.21839, found 574.21707.




To a solution of **55** (9.4 mg, 0.025 mmol) and **25** (6.4 mg, 0.025 mmol) in $CH_2Cl_2$ (1.5 mL) was added sequentially microwave- activated 5 Å molecular sieves powder (90 mg), $AgO_2CCF_3$ (8.3 mg, 0.038 mmol) and $SnCl_4$ (0.050 mmol, 0.050 mL solution of 1 M $SnCl_4$ in dichloromethane) at room temperature. The reaction was stirred for 14 hours, then quenched with aq. $NaHCO_3$ and filtered through a layer of well packed celite. Extraction with dichloromethane, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 4 / 1) gave recovered **55** (4 mg, 43%) and red **65** (4 mg, 28%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.29 (q, *J* = 6.8 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.48 (s, 1H), 5.20 (d, *J* = 10.8 Hz, 1H), 4.90 (t, *J* = 9.6 Hz, 1H), 4.11 (s, 3H), 3.92 (s, 3H), 3.88 (m, 2H), 2.96 (s, 3H), 2.53 (dd, *J* = 3.2 Hz, 12.0 Hz, 1H), 2.22 (s, 3H), 2.09 (m, 1H), 2.04 (s, 3H), 2.01 (d, *J* = 6.8 Hz, 3H), 1.35 (d, *J* = 6.0 Hz, 3H); HRMS (APCI) Calcd. for $C_{32}H_{34}O_7N_3[(M + H)^+]$ 572.23913, found 572.23851.

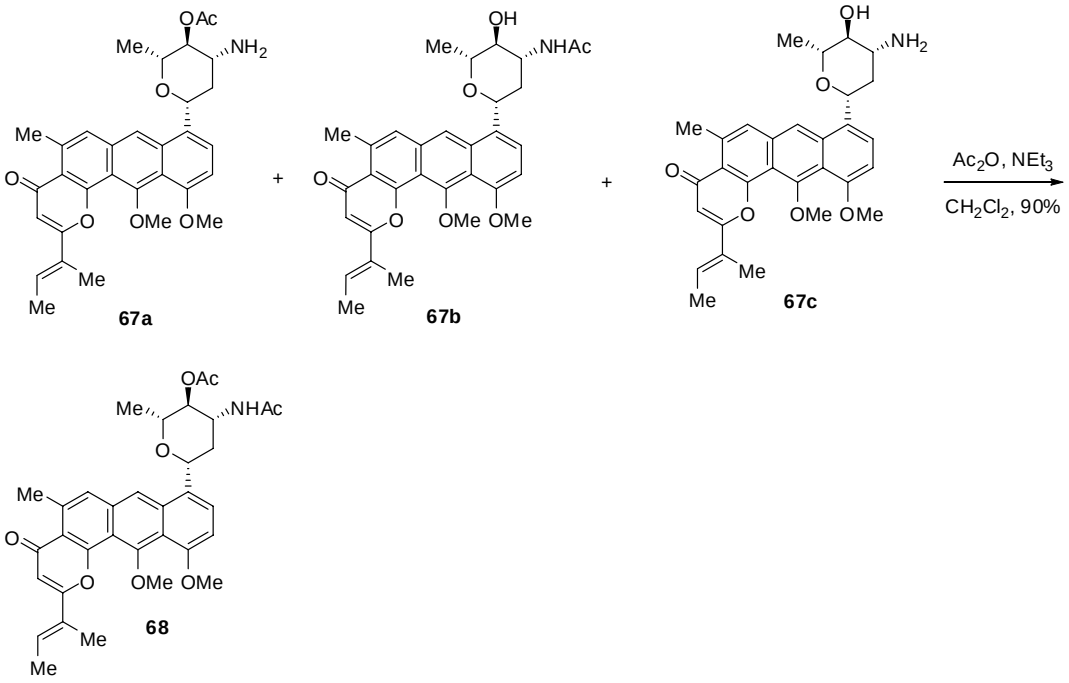



To a solution of **58** (9.0 mg, 0.022 mmol) and **25** (6.4 mg, 0.025 mmol) in $CH_2Cl_2$ (1.5 mL) was added sequentially microwave- activated 5 Å molecular sieves powder (90 mg), $AgO_2CCF_3$ (14.6 mg, 0.066 mmol) and $SnCl_4$ (0.044 mmol, 0.044 mL solution of 1 M $SnCl_4$ in dichloromethane) at room temperature. The reaction was stirred for 14 hours, then quenched with aq. $NaHCO_3$ and filtered through a layer of well packed celite. Extraction with dichloromethane, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 4 / 1) gave red **66** (3 mg, 23%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.71 (q, $J$ = 6.0 Hz, 1H), 7.61 (d, $J$ = 8.0 Hz, 1H), 7.50 (s, 1H), 6.89 (d, $J$ = 8.4 Hz, 1H), 6.73 (s, 1H), 5.19 (d, $J$ = 10.0 Hz, 1H), 4.90 (t, $J$ = 9.2 Hz, 1H), 4.10 (s, 3H), 3.86 (m, 2H), 2.94 (s, 3H), 2.53 (m, 3H), 2.22 (s, 3H), 2.08 (m, 1H), 2.06 (s, 3H), 2.01 (d, $J$ = 7.2 Hz, 3H), 1.35 (d, $J$ = 6.4 Hz, 3H), 0.83 (t, $J$ = 7.2 Hz, 3H); HRMS (APCI) Calcd. for $C_{33}H_{36}O_6N_3S_1[(M + H)^+]$ 602.23193, found 602.23160.



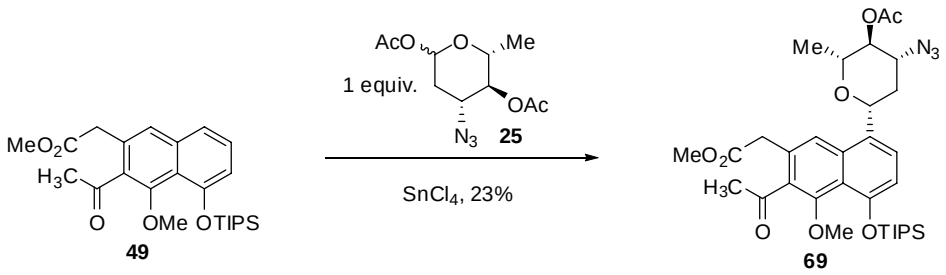

To a solution of **65** (9.0 mg, 0.016 mmol) in THF (3 mL) and water (0.3 mL) was added $PPh_3$ (12 mg, 0.047 mmol) at room temperature. The reaction was warmed to 60 ºC for 12 hours and cooled to room temperature. Dilution with ethyl acetate, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (ethyl acetate→ ethyl acetate / methanol = 10 / 1 → methanol) gave **67a** (3.5 mg, 41%), **67b** (1.6 mg, 19%) and **67c** (1.0 mg, 12%). **67a**: $^1$H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.51 (s, 1H), 7.29 (q, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.48 (s, 1H), 5.20 (d, *J* = 10.2 Hz, 1H), 4.65 (t, *J* = 9.6 Hz, 1H), 4.10 (s, 3H), 3.91 (s, 3H), 3.82 (dq, *J* = 6.0 Hz, 9.6 Hz, 2H), 3.26 (m, 1H), 2.96 (s, 3H), 2.49 (dd, J = 2.4 Hz, 13.2 Hz, 1H), 2.22 (s, 3H), 2.04 (s, 3H), 2.01 (d, *J* = 7.2 Hz, 3H),1.91 (m, 1H), 1.33 (d, *J* = 6.0 Hz, 3H); **67b**: $^1$H NMR (600 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.52 (s, 1H), 7.28 (q, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.47 (s, 1H), 5.64 (d, 1H), 5.22 (d, *J* = 10.2 Hz, 1H), 4.26 (m, 1H), 4.20 (bs, 1H), 4.10 (s, 3H), 3.91 (s, 3H), 3.74 (dq, *J* = 6.0 Hz, 9.6 Hz, 2H), 3.28 (t, *J* = 9.6 Hz, 1H), 2.96 (s, 3H), 2.44 (dd, *J* = 2.4 Hz, 13.2 Hz,

1H), 2.09 (s, 3H), 2.04 (s, 3H), 2.01 (d, *J* = 7.2 Hz, 3H),1.89 (q, J = 12.0 Hz, 1H), 1.48 (d, *J* = 6.0 Hz, 3H); **67c**: $^1$H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.50 (s, 1H), 7.30 (q, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.48 (s, 1H), 5.20 (d, *J* = 10.2 Hz, 1H), 4.10 (s, 3H), 3.92 (s, 3H), 3.74 (dq, *J* = 6.0 Hz, 9.6 Hz, 1H), 3.13 (t, *J* = 9.6 Hz, 1H), 3.07 (m, 1H), 2.96 (s, 3H), 2.38 (d, *J* = 13.2 Hz, 1H), 2.05 (s, 3H), 2.01 (d, *J* = 7.2 Hz, 3H),1.88 (q, *J* = 12.0 Hz, 1H), 1.47 (d, *J* = 6.0 Hz, 3H).

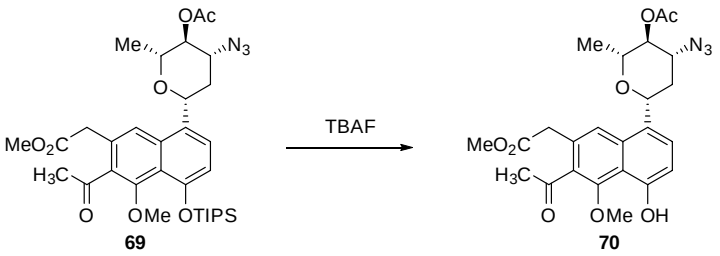



A solution of mixed **67a**, **67b**, **67c** (7 mg) was treated with $Ac_2O$ (3 drops) and pyridine (5 drops) in $CH_2Cl_2$ (3 mL) at room temperature overnight. The reaction was quenched with water and extracted with $CH_2Cl_2$. Column chromatography (hexanes / ethyl acetate = 1 / 1) gave one product **68** (6 mg, ~90%). $^1$H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.54 (s, 1H), 7.29 (q, *J* = 6.0 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.48 (s, 1H), 5.80 (d, *J* = 7.8 Hz, 1H), 5.24 (d, *J* = 10.2 Hz, 1H), 4.69 (t, *J* =

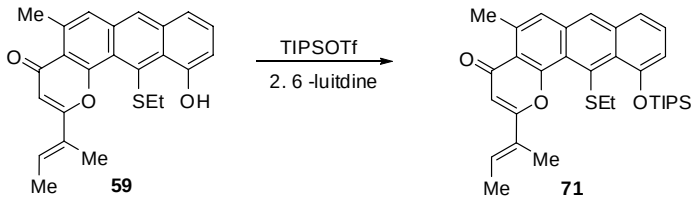
10.2 Hz, 1H), 4.48 (m, 1H), 4.09 (s, 3H), 3.96 (dq, *J* = 6.0 Hz, 9.6 Hz, 1H), 3.91 (s, 3H), 2.96 (s, 3H), 2.65 (dd, *J* = 4.2 Hz, 13.2 Hz, 1H), 2.17 (s, 3H), 2.04 (s, 3H), 2.01 (d, *J* = 7.2 Hz, 3H), 1.96 (s, 3H), 1.91 (q, *J* = 13.2 Hz, 1H), 1.36 (d, *J* = 6.0 Hz, 3H).




To a solution of **49** (9.0 mg, 0.020 mmol) and **25** (6.2 mg, 0.024 mmol) in 1, 2-dichloroethane (1.3 mL) was added microwave- activated 4 Å molecular sieves powder (90 mg) and $SnCl_4$ (0.061 mmol, 0.061 mL solution of 1 M $SnCl_4$ in dichloromethane) at room temperature. The reaction was stirred overnight for 27 hours, quenched with aq. $NaHCO_3$ and filtered through a layer of well packed celite. Extraction with dichloromethane, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 4 / 1) gave **69** (3 mg, 23%) and some starting material **49** recovered. $^1$H NMR (600 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.83 (*t*, J = 9.6 Hz, 1H), 3.87 (m, 1H), 3.86 (d, *J* = 9.6 Hz, 2H), 3.82 (m, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 2.66 (s, 3H), 2.42 (dd, *J* = 3.0 Hz, 12.0 Hz, 1H), 2.19 (s, 3H), 1.96 (q, *J* = 9.6 Hz, 1H), 1.40 (sept, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 6.0 Hz, 3H), 1.40 (d, *J* = 7.2 Hz, 18 H).

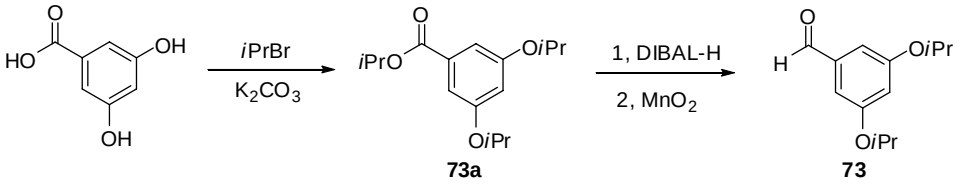



To a solution of **69** (3.0 mg, 0.0046 mmol) was added TBAF (two drops of 1 M TBAF in THF) at room temperature. The reaction was stirred for 30 minutes and quenched with water. Extraction with ethyl acetate, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 4/1) afforded product **70** (2 mg, 90%). $^1$H NMR (600 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.61 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.84 (t, *J* = 9.6 Hz, 1H), 3.93 (s, 3H), 3.89 (d, *J* = 9.6 HZ, 2H), 3.81 (m, 1H), 3.74 (dq, *J* = 6.0 Hz, 9.6 Hz, 1H), 3.71 (s, 3H), 2.72 (s, 3H), 2.38 (dd, *J* = 3.0 Hz, 12.0 Hz, 1H), 2.19 (s, 3H), 2.01 (q, *J* = 9.6 Hz, 1H), 1.31 (d, *J* = 6.0 Hz, 3H).




To a solution of **59** (13 mg, 0.033 mmol) in $CH_2Cl_2$ (2 mL) was added 2, 6–lutidine (12 μL, 0.099 mmol) and TIPSOTf (11 μL, 0.05 mmol) at 0 ºC. The reaction was stirred for 1 hour and quenched with aq. $NH_4Cl$. Extraction with $CH_2Cl_2$, drying over $Na_2SO_4$, condensation under reduced pressure and flash column chromatography (hexanes / ethyl acetate = 8 / 1) gave **71** (11 mg, 61%). $^1$H NMR (600 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.74 (q, *J* = 6.6 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.43 ( s, 1H), 7.36 (t, *J* = 8.4 Hz, 1H), 6.92

(d, *J* = 8.0 Hz, 1H), 6.56 (s, 1H), 2.92 (s, 3H), 2.61 (bd, 2H), 2.03 (s, 3H), 1.96 (d, *J* = 6.6 Hz, 3H), 1.52 (sept, *J* = 7.2 Hz, 3H), 1.18 (bs, 18H), 0.79 (t, *J* = 7.2 Hz, 3H).



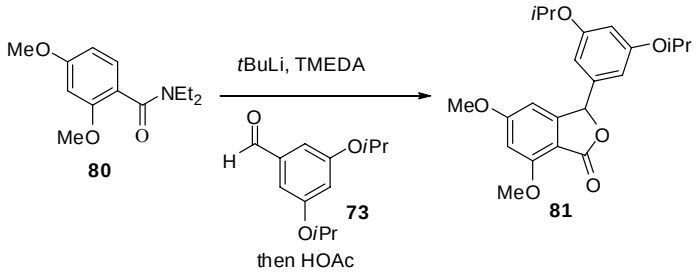

**73a** **73**

Although aldehyde **73** is commercially available from Aldrich, it is very expensive and sold at 50$ for one gram. We prepared **73** from cheap 3, 5 – dihydroxyl benzoic acid which is 0.25$ for one gram, through three steps as shown above.

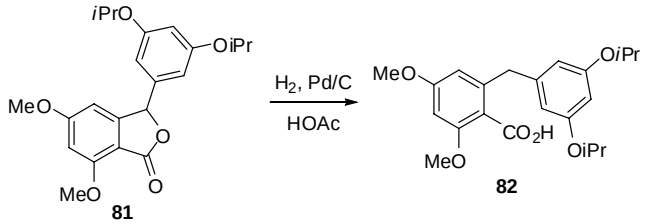
To a solution of 3, 5 – dihydroxyl beznoic acid (10 g, 65 mmol) and iso propyl bromide (34 mL, 357 mmol) in DMF (50 mL) was added potassium carbonate (36 g, 259 mmol). The reaction was warmed at 80 °C for 60 hours and cooled to room temperature. Filtration of the solid, dilution with ethyl acetate, washed with water, drying over $Na_2SO_4$, concentration under reduced pressure and column chromatography (hexanes / ethyl acetate = 4 / 1) gave the ester product **73a** (11 g, 60%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 2.4 Hz, 2H), 6.60 (t, *J* = 2.4 Hz,1H), 5.23 (sept. *J* = 6.4 Hz, 1H), 4.58 (sept. *J* = 6.4 Hz, 2H), 1.353 (d, *J* = 6. 0 Hz, 6 H), 1.347 (d, *J* = 6.0 Hz, 12H).

To a solution of **73a** (10.6 g, 37.8 mmol) in $CH_2Cl_2$ (200 mL) was added DIBAL-H (83 mmol, 83 mL solution of 1 M DIBAL-H in $CH_2Cl_2$) at -78 ° C in a dropwise manner. After addition, the reaction was stirred at -78 ° C for further 30 minutes. TLC showed that **73a** was completely consumed and converted partially to aldehyde **73,** and partially to the alcohol. At this point, the reaction was quenched with Rochelle's salt. Extraction with $CH_2Cl_2$, drying over $Na_2SO_4$ and concentration by rotary evaporation gave a crude

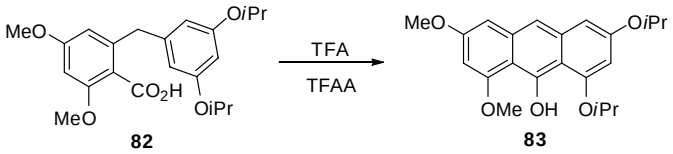
mixture of aldehyde **73** and the overreduced alcohol. This mixture was dissolved in $CH_2Cl_2$ (150 mL), and treated with freshly dried $MnO_2$ (10 g) for three days. Filtration of the solid, concentration by rotary evaporation and flash column chromatography (hexanes / ethyl acetate = 6 / 1) gave product **73** (7 g, 49% overall yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 6.97 (d, *J* = 2.0 Hz, 2H), 6.68 (t, *J* = 2.4 Hz, 1H), 4.60 (sept. *J* = 6.0 Hz, 2H), 1.35 (d, *J* = 6. 0 Hz, 12H).



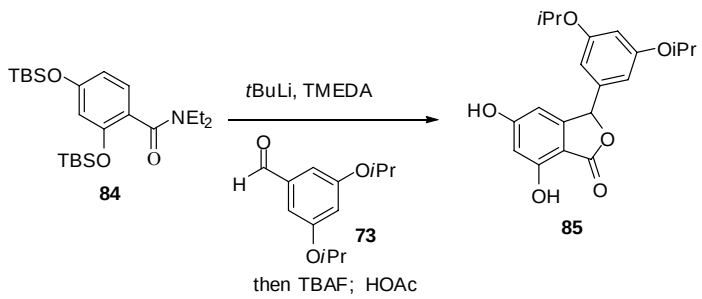

To a solution of **80** (161 mg, 0.68 mmol) and TMEDA (130 µL, 0.86 mmol) in THF (5 mL) was added *t*BuLi (0.95 mmol, 0.56 mL solution of 1.7 M *t*BuLi in pentane) at -78 °C in a dropwise manner. The reaction was stirred at -78 ° C for 25 minutes after addition, and a solution of **73** (151 mg, 0.68 mmol) in THF (1.5 mL) was added at -78 °C, in a dropwise manner. The reaction was stirred for additional 2 hours while the temperature warmed to room temperature. The reaction was quenched with 3 M HCl (5 mL) and acetic acid (2mL). The mixture was then stirred overnight to form the lactone. The next day, the mixture was taken up into ethyl acetate, dried over $Na_2SO_4$, concentrated rotary evaporation and column chromatography to give **81** (85 mg, 32%, not optimized). $^1$H NMR (600 MHz, $CDCl_3$) δ 6.43 (s, 1H), 6.40 (s, 1H), 6.38 (s, 2H), 6.32 (s, 1H), 6.10 (s, 1H), 4.48 (sept. *J* = 6.6 Hz, 2H), 3.97 (s, 3H), 3.82 (s, 3H), 1.31 (d, *J* = 6.0 Hz, 6H), 1.29 (d, *J* = 6.0 Hz, 6 H).



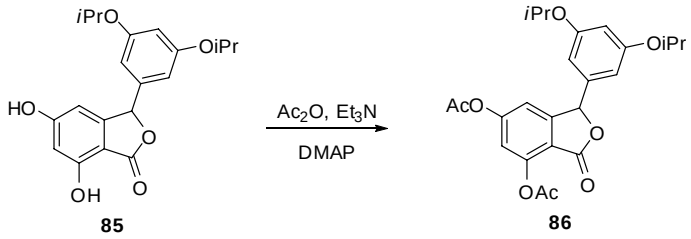

A solution of **81** (85 mg, 0.22 mmol) in acetic acid (6 mL) was heated to 70 °C in the presence of 5% Pd / C (22 mg) under hydrogen atmosphere for 3 hours. Filtration through a well packed celite bed, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 1 / 1) gave **82** (70 mg, 82%) with recovering some **81**. $^1$H NMR (600 MHz, $CDCl_3$) δ 6.42 (m, 1H), 6.37 (m, 1H), 6.32 (m, 2H), 6.27 (m, 1H), 4.47 (sept. *J* = 6.0 Hz, 2H), 4.06 (s, 2H), 3.87 (s, 3H), 3.75 (s, 3H), 1.29 (d, *J* = 6.0 Hz, 12H).



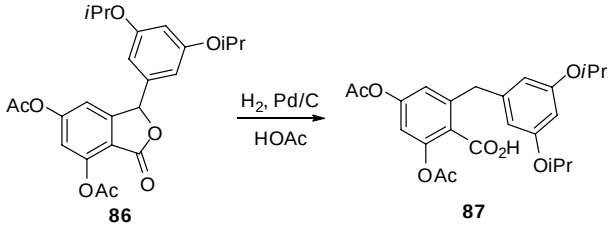

To a solution of **82** (10 mg, 0.026 mmol) in TFA (1 mL) was added TFAA (0.5mL) at -15 ° C slowly. The reaction was stirred at -15 ° C for 1 hour. The solvent was removed under reduced pressure and diltuted with ethyl acetate. Washing with water, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography gave **83** (4 mg, 42%, not optimized). $^1$H NMR (600 MHz, $CDCl_3$) δ 11.04 (s, 1H), 7.41 (s, 1H), 6.60 (d, *J* = 10.2 Hz, 2H), 6.30 (d, *J* = 5.4 Hz, 2H), 4.86 (sept. *J* = 6.0 Hz, 1H), 4.70 (sept. *J* = 6.0 Hz, 1H), 4.02 (s, 3H), 3.92 (s, 3H), 1.54 (d, *J* = 6.6 Hz, 6H), 1.42 (d, *J* = 6.6 Hz, 6H).



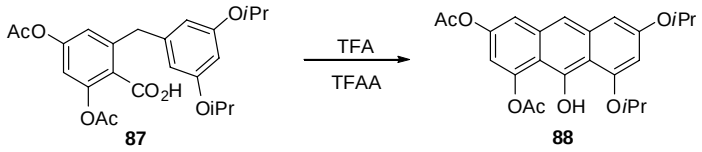

To a solution of TMEDA (837 μL, 5.58 mmol) and *t*BuLi (6.2 mmol, 3.65 mL solution of 1.7 M *t*BuLi in pentane) in THF (7 mL) was added a solution of **84** (1.94 g, 4.43 mmol) in THF (3 mL) at -78 °C in a dropwise manner. The reaction was stirred at -78 °C for 45 minutes after addition, and a solution of **73** (1.18 g, 5.31 mmol) in THF (3 mL) was added at -78 ° C in a dropwise manner. The reaction was stirred for additional 2 hours while the temperature warming to 0 °C. The reaction was quenched with 3 M HCl (15 mL) and acetic acid (2 mL). Solid TBAF was added to remove silyl protective groups. The mixture was then stirred overnight to form the lactone. The next day, the mixture was taken up into ethyl acetate, dried over $Na_2SO_4$, concentrated by rotary evaporation and column chromatography to give **81** (1.00 g, 63%, not optimized). $^1$H NMR (600 MHz, $CDCl_3$) δ 6.43 (t, *J* = 1.8 Hz, 1H), 6.39 (d, *J* = 1.8 Hz, 1H), 6.38 (d, *J* = 1.8 Hz, 2H), 6.31 (s, 1H), 6.20 (s, 1H), 4.51 (sept. *J* = 6.0 Hz, 2H), 1.33 (d, *J* = 6.0 Hz, 6H), 1.31 (d, *J* = 6.0 Hz, 6H).



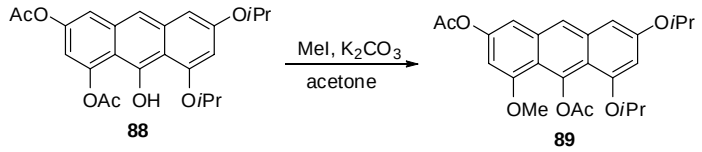

To a solution of **85** (400 mg, 1.12 mmol) in $CH_2Cl_2$ (25 mL) was added $Ac_2O$ (242 µL, 2.57 mmol), $Et_3N$ (623 µL, 4.48 mmol), DMAP (12mg, 0.1 mmol) at room temperature. The reaction was stirred for 2 hours and quenched with aq. $NH_4Cl$. Extraction with ethyl acetate, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography to give **86** (420 mg, 85%).$^1$H NMR (600 MHz, $CDCl_3$) δ 7.10 (m, 2H), 6.42 (s, 1H), 6.35 (s, 2H), 6.23 (s, 1H), 4.50 (sept. *J* = 6.0 Hz, 2H), 2.45 (s, 3H), 2.30 (s, 3H), 1.31 (d, *J* = 6.0 Hz, 6H), 1.30 (d, *J* = 6.0 Hz, 6 H).



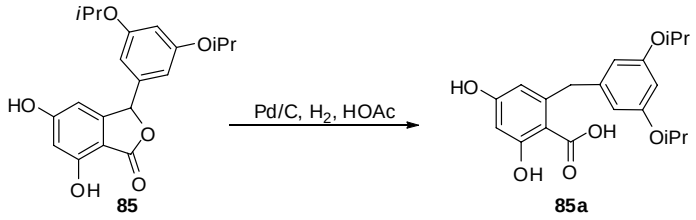

A solution of **86** (476 mg, 1.08 mmol) in acetic acid (30 mL) was heated to 60 °C in the presence of 5% Pd / C (120 mg) under hydrogen atmosphere for 2.5 hours. Filtration through a well packed celite bed, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 1 / 1) gave **87** (433 mg, 91%).$^1$H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.78 (s, 1H), 6.29 (s, 3H), 4.46 (sept. *J* = 6.0 Hz, 2H), 4.07 (s, 2H), 2.25 (s, 6H), 1.28 (d, *J* = 6.0 Hz, 12H).




To a solution of **87** (400 mg, 0.900 mmol) in TFA (6 mL) was added TFAA (3 mL) at -5 ° C slowly. The reaction was stirred at -5 ° C for 1 hour. The solvent was removed by rotary evaporation and diltuted with ethyl acetate. Washing with water, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography gave **88** (600 mg, 78%). $^1$H NMR (600 MHz, $CDCl_3$) δ 10.87 (s, 1H), 7.57 (s, 1H), 7.41 (s, 1H), 6.72 (s, 1H), 6.66 (s, 1H), 6.35 (s, 1H), 4.85 (sept. *J* = 6.6 Hz, 1H), 4.70 (sept. *J* = 6.6 Hz, 1H), 2.41 (s, 3H), 2.34 (s, 3H), 1.55 (d, *J* = 6.6 Hz, 6H), 1.41 (d, *J* = 6.6 Hz, 6H).

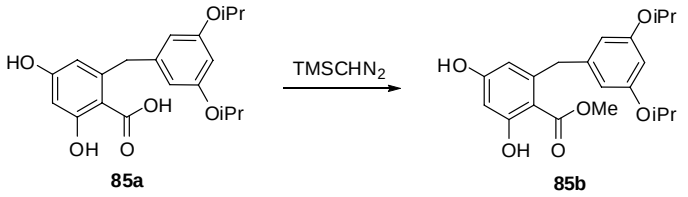



A solution of **88** (38 mg, 0.089 mmol), MeI (56 µL, 0.896 mmol) in acetone (3 mL) was refluxed in the presence of $K_2CO_3$ (37 mg, 0.268 mmol) for 6 hours. Filtration of the solid, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 4 / 1) gave product **89** (12 mg, 31%).$^1$H NMR (600 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 6.69 (d, *J* = 2.4 Hz, 1H), 6.42 (d, *J* = 1.8 Hz, 1H), 6.41 (d, *J* = 1.8 Hz, 1H), 4.71 (sept. *J* = 6.6 Hz, 2H), 3.95 (s. 3H), 2.45 (s, 3H), 2.36 (s, 3H), 1.42 (m, 12H).



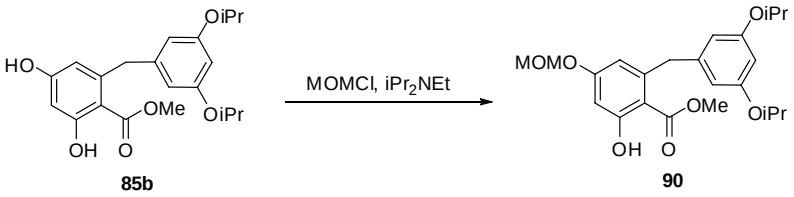

**85** **85a**

A solution of **85** (730 mg, 2.04 mmol) in acetic acid (40 mL) was heated to 60 °C in the presence of 5% Pd / C (285 mg) under hydrogen atmosphere for 3 hours. Filtration through a well packed celite bed and concentration by rotary evaporation gave **85a** (686 mg, 93%) as crude that was used for the next step without purification.



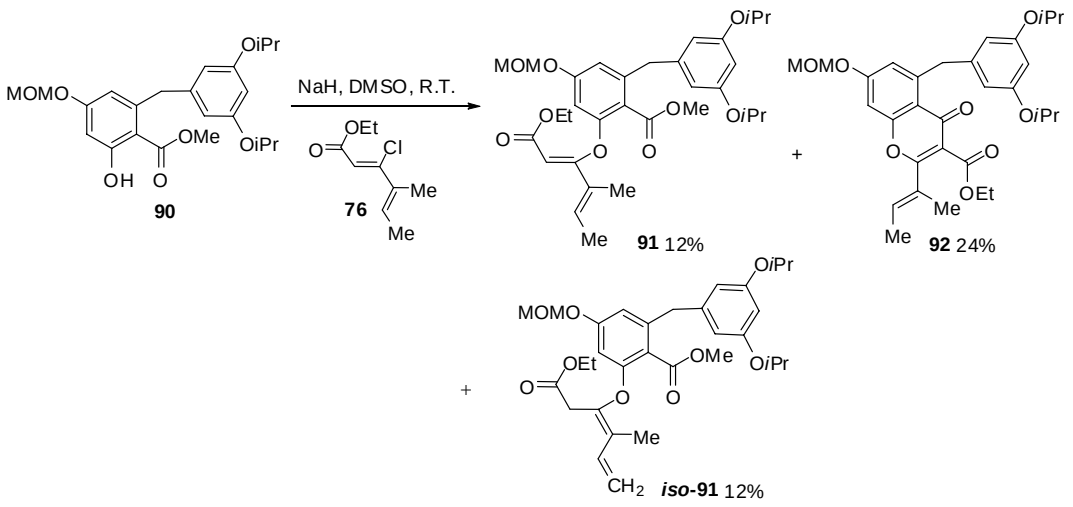

**85a** **85b**

To a solution of **85a** (94 mg, 0.26 mmol) in methanol (3 mL) was added $TMSCHN_2$ (2.4 mmol, 1.2 mL solution of 2 M $TMSCHN_2$ in $Et_2O$) at room temperature slowly. The reaction was stirred overnight and quenched with water. Extraction with ethyl acetate, washing with water, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 4 / 1) gave **85b** (75 mg, 77%). $^1$H NMR (400 MHz, $CDCl_3$) δ 11.76 (s, 1H), 6.31 (d, *J* = 2.4 Hz, 1H), 6.29 (t, *J* = 2.4 Hz, 1H), 6.21 (d, *J* = 2.0 Hz, 1H), 6.18 (d, *J* = 2.4 Hz, 1H), 4.47 (sept. *J* = 6.0 Hz, 2H), 4.14 (s, 2H), 3.79 (s, 3H), 1.30 (d, *J* = 6.4 Hz, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 171.9, 165.5, 161.0, 159.0, 145.5, 143.3, 112.4, 109.0, 105.4, 102.1, 101.5, 70.2, 52.0, 22.2.



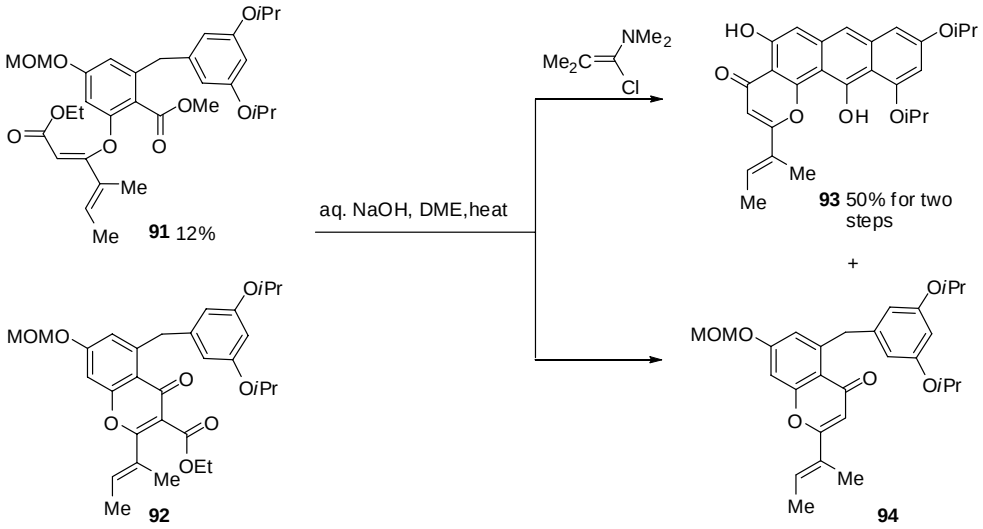

**85b** **90**

To a solution of **85b** (75 mg, 0.20 mmol) and *i*PrNEt$_2$ (45 μL, 0.26 mmol) in $CH_2Cl_2$ (4 mL) was added MOMCl (16 μL, 0.21 mmol) at 0 °C slowly. The reaction was stirred for 2 hours and quenched with aq $NH_4Cl$. Extraction with ethyl acetate, washing with water, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate =6 / 1) gave **90** (74 mg, 88%).$^1$H NMR (400 MHz, $CDCl_3$) δ 11.60 (s, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 6.28 (t, *J* = 1.8 Hz, 1H), 6.19 (d, *J* = 2.4 Hz, 2H), 5.17 (s, 2H), 4.46 (sept. *J* = 6.0 Hz, 2H), 4.18 (s, 2H), 3.78 (s, 3H), 3.47 (s, 3H), 1.30 (d, *J* = 6.0 Hz, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.7, 165.5, 161.7, 159.1, 144.8, 143.3, 113.1, 108.6, 106.2, 102.2, 101.3, 94.1, 69.9, 56.5, 51.9, 42.5, 22.2.




To a solution of **90** (74 mg, 0.18 mmol) in DMSO (2.5 mL) was added NaH (7.8 mg, 0.20 mmol) in one portion at room temperature. The reaction was stirred for 1 hour and a solution of **76** (50 mg, 0.27 mmol) in DMSO (1 mL) was added. The reaction was stirred at room temperature for 13 hours and quenched with aq $NH_4Cl$. Extraction with ethyl acetate, washing with water, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (pentane / ethyl ether = 2 / 1) gave ***iso*-91** (12 mg, 12%), mixed **91** (12 mg, 12%) and **92** (25 mg, 26%). ***iso*-91:** $^1$H NMR (600 MHz, $CDCl_3$) δ 6.60 (dd, 1H), 6.50 (m, 1H), 6.39 (d, 1H), 6.31 (m, 2H), 6.28 (m, 1H), 5.34 (d, 1H), 5.19 (d, 1H), 5.06(s, 2H), 4.48 (sept. 2H), 4.10 (q, 2H), 3.88 (s, 2H), 3.78 (s, 3H), 3.40 (s, 3H), 3.36 (s, 2H), 1.80 (s, 3H), 1.30 (d, 12H), 1.21 (t, 3H); **91**: $^1$H NMR (600 MHz, $CDCl_3$) δ δ 6.45 (d, $J$ = 1.8 Hz, 1H), 6.37 (q, $J$ = 7.2 Hz, 1H), 6.35 (m, 1H), 6.31 (d, $J$ = 1.8 Hz, 1H), 6.23 (d, $J$ = 2.4 Hz, 1H), 5.74 (s, 1H), 5.03 (s, 2H), 4.49 (sept. $J$ = 6.0 Hz, 2H), 4.04 (q, $J$ = 7.2 Hz, 2H), 3.90 (s, 2H), 3.82 (s, 3H), 3.39 (s, 3H), 1.83 (s, 3H), 1.75 (s, $J$ = 7.2 Hz, 3H), 1.30 (d, $J$ = 6.0 Hz, 12H), 1.06 (t, $J$ = 7.2 Hz, 3H); HRMS (ESI) Calcd. for $C_{32}H_{43}O_9$ [$(M + H)^+$] 571.29071, found 571.28955; **92**: $^1$H NMR (600 MHz, $CDCl_3$) δ 6.92 (d, $J$ = 2.4 Hz, 1H), 6.67 (d, $J$ = 1.8 Hz, 1H), 6.36 (d, $J$ = 1.8 Hz, 1H),

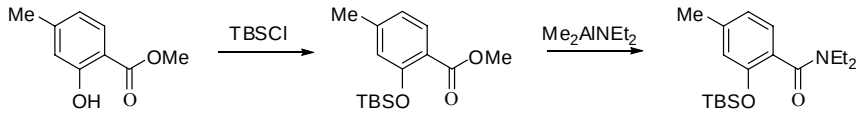
6.29 (t, *J* = 1.8 Hz, 1H), 6.24 (q, *J* = 7.2 Hz, 1H), 5.19 (s, 2H), 4.62 (s, 2H), 4.49 (sept. *J* = 6.0 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.47 (s, 3H), 1.99 (s, 3H), 1.81 (d, *J* = 7.2 Hz, 3H), 1.32 (t, 3H), 1.31 (d, *J* = 6.6 Hz, 12H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 176.7, 165.9, 164.2, 160.7, 159.2, 158.8, 145.7, 142.6, 133.0, 129.4, 118.3, 117.8, 115.9, 109.5, 101.7, 101.4, 94.4, 69.9, 61.7, 56.7, 40.0, 22.3, 14.4, 13.7; HRMS (ESI) Calcd. for $C_{31}H_{39}O_8$ $[(M + H)^+]$ 539.26395, found 539.26257.




The mixed **91** (12 mg, 0.021 mmol) and **92** (25 mg, 0.046 mmol) in DME (3 mL) and 15 M NaOH solution (3 mL) was refluxed for 14 hours. The reaction was cooled to 0 °C and acidified with 2 M HCl. The solution was extracted with ethyl acetate and washed with water, dried over $Na_2SO_4$ and concentrated by rotary evaporation. The residue was further dried under high vacumm pump prior to the following step.

The mixture obtained above was dissolved in $CH_2Cl_2$ and treated with 1-chloro-*N*, *N*, 2-trimethyl-1-propenylamine (7 drops by 1 mL syringe). Instant color change was observed upon addition of this chlorination reagent. The reaction was stirred for 2 hours and quenched with water. Extraction with $CH_2Cl_2$, drying over $Na_2SO_4$, concentration by

rotary evaporation and column chromatography (petane / ether = 2 / 1) gave **93** (5 mg, 50% for two steps) and **94** (15 mg, 70%). **93**: $^1$H NMR (400 MHz, $CDCl_3$) δ 11.50 (s, 1H), 7.38 (m, 2H), 6.84 (s, 1H), 6.66 (d, *J* = 2.0 Hz, 1H), 6.51 (s, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 4.92 (sept, *J* = 6.0 Hz,, 1H), 4.73 (sept, *J* = 6.0 Hz, 1H), 2.05 (s, 3H), 2.00 (d, *J* = 7.2 Hz, 3H), 1.60 (d, *J* = 6.0 Hz, 6H), 1.44 (d, *J* = 6.0 Hz, 6H); **94**: $^1$H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 2.4 Hz, 1H), 6.75 (q, *J* = 7.2 Hz, 1H),6.68 (d, *J* = 2.4 Hz, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 6.28 (t, *J* = 2.0 Hz, 1H), 6.19 (s, 1H), 5.21 (s, 2H), 4.64 (s, 2H), 4.49 (sept. *J* = 6.0 Hz, 2H), 3.48 (s, 3H), 1.91 (s, 3H), 1.91 (d, *J* = 6.8 Hz, 3H), 1.30 (d, *J* = 6.0 Hz, 12H); HRMS (ESI) Calcd. for $C_{28}H_{35}O_6$ [$(M + H)^+$] 467.24282, found 467.24133.

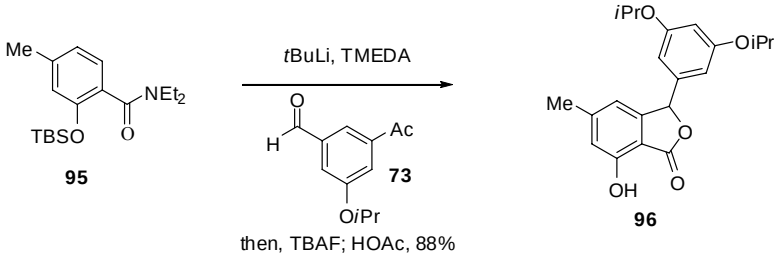



**95a** **95b** **95**

To a solution of **95a** (8 g, 44 mmol) and imidazole (9 g, 132 mmol) in DMF (20 mL) was added TBSCl (7.3 g, 48 mmol) in one portion at room temperature. The reaction was stirred for 2 hour and quenched with water. Dilution with ethyl acetate, washing with water, drying over $Na_2SO_4$ and concentration by rotary evaporation gave crude **95b** for the next step.

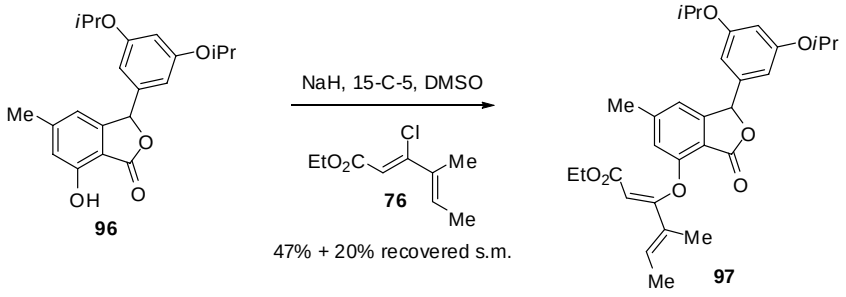
To a solution of $HNEt_2$ (14 mL, 132 mmol) in toluene (25 mL) was added 2 M $AlMe_3$ (66 mL, 132 mmol) at -10 ºC in a dropwise manner. The solution was warmed to room temperature and stirred for one hour, after which, a solution of crude **95b** obtained as above in toluene (25 mL) was added in and the resulting solution was heated to 90 ºC for 16 hours. The reaction was cooled to 0 ºC and very slowly quenched with ice. Dilution with ethyl acetate, washing with aq. Rochelle's salt, drying over $Na_2SO_4$, concentration

by rotary evaporation and column chromatography (hexanes / ethyl acetate = 4 / 1) gave product **95** (12 g, 85% for two steps). IR (neat) 2957, 2859, 1638 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.07 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.2 Hz, 1H), 6.61 (s, 1H), 3.61 (m, 1H), 3.45 (m, 1H), 3.24 (m, 1H), 3.11 (m, 1H), 2.30(s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 6.6 Hz, 3H), 0.96 (s, 9 H), 0.23 (s, 3H), 0.20 (s, 3H); HRMS (ESI) Calcd. for $C_{18}H_{32}N_1O_2Si_1$ [$(M + H)^+$] 322.21968, found 322.21957.



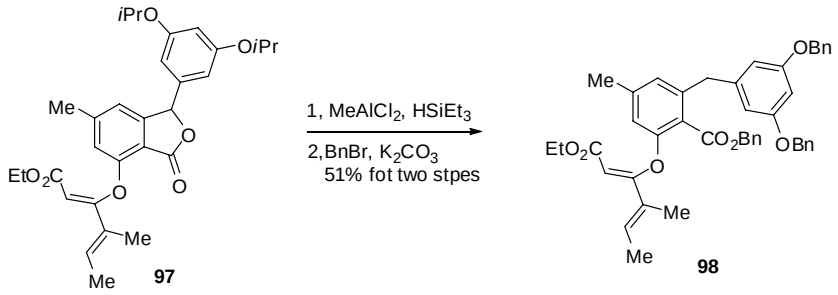

To a solution of TMEDA (2.64 mL, 17.6 mmol) and *t*BuLi (18.4 mmol, 10.8 mL solution of 1.7 M *t*BuLi in pentane) in THF (25 mL) was added a solution of **95** (4.92 g, 15.3 mmol) in THF (10 mL) at -78 °C in a dropwise manner. The reaction was stirred at -78 °C for 1 hour after addition, and a solution of **73** (3.74 g, 16.8 mmol) in THF (10 mL) was added at -78 ° C in a dropwise manner. The reaction was stirred for additional 1 hour at -78 ° C and warmed to 0 ° C for another 1 hour. Finally, the reaction was warmed to room temperature and a solution of TBAF (1.2 equiv. solid) in THF (10 mL) was added to remove the silyl protective group. After stirring at room temperature for 30 minutes, 2 M HCl (10 mL) and HOAc (25 mL) was added and the resulting solution was stirred overnight to form the lactone. The next day, the mixture was taken up in ethyl acetate, dried over $Na_2SO_4$, concentrated by rotary evaporation and purified by column chromatography to give **96** (4.81 g, 88%). IR (neat) 3442, 2977, 1738, 1607 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.75 (s, 1H), 6.66 (s, 1H), 6.42 (t, *J* = 2.4 Hz,

1H), 6.38 (d, *J* = 2.4 Hz, 2H), 6.23 (s, 1H), 4.50 (sept, *J* = 6.0 Hz, 2H), 2.37 (s, 3H), 1.32 (d, *J* = 6.0 Hz, 6H), 1.31 (d, *J* = 6.6 Hz, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$) δ 172.0, 159.6, 156.1, 150.1, 149.3, 138.4, 116.4, 115.2, 108.5, 106.6, 104.1, 83.7, 70.2, 22.5, 22.1; HRMS (ESI) Calcd. for $C_{21}H_{25}O_5$ [$(M + H)^+$] 357.16965, found 357.16940.




To a solution of **96** (330 mg, 0.93 mmol) in DMSO (5 mL) was added NaH (37 mg of 60% solid on mineral oil, 0.93 mmol) in one portion at room temperature. The reaction was stirred for 1 hour, and 15-C-5 (184 μL, 0.93 mol) was added followed by addition of a solution of **76** (226 mg, 1.2 mmol) in DMSO (2 mL). The reaction was warmed to 58 ºC (temperature of the sand bath) for 36 hours, then cooled to room temperature and quenched with aq $NH_4Cl$. Extraction with ethyl acetate, washing with water, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (pentane / ethyl ether = 2 / 1) gave **97** (220 mg, 47%) and some side chain isomer as well as starting material **96**. IR (neat) 2977, 1722, 1464 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.47 (s, 1H), 6.43 (d, *J* = 2.0 Hz, 2H), 6.40 (t, *J* = 2.0 Hz, 1H), 6.37 (q, *J* = 7.2 Hz, 1H), 6.17 (s, 1H), 5.82 (s, 1H), 4.51 (sept, *J* = 6.0 Hz, 2H), 4.01 (q, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 1.88 (s, 3H), 1.75 (d, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 6.0 Hz, 12 H), 1.07 (t, *J* = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.1, 164.4, 161.6, 159.5, 156.3, 152.3, 147.9, 139.2, 132.4, 128.9, 116.4, 114.2, 110.6, 106.4, 105.9, 103.8, 81.4, 70.1, 60.2, 22.4, 22.1,

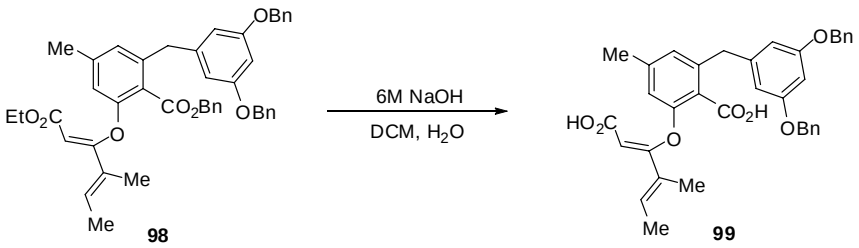
14.7, 14.2, 13.0; HRMS (ESI) Calcd. for $C_{30}H_{37}O_7[(M + H)^+]$ 509.25338, found 509.25308.



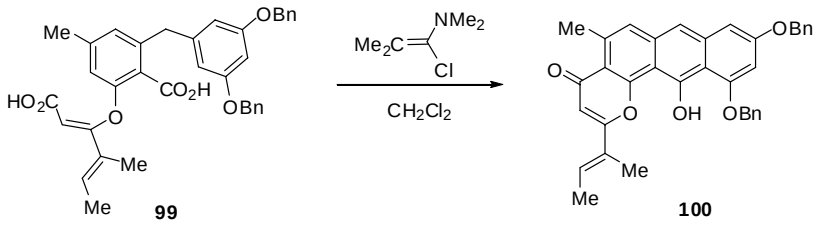

To a solution of **97** (1.14 g, 2.24 mmol) in $CH_2Cl_2$ (20 mL) was added $HSiEt_3$ (1.44mL, 9.00 mmol) and 1 M solution of $MeAlCl_2$ in hexanes (18.0 mL, 18.0 mmol) at 0 º slowly. The reaction was stirred for 34 hours while warming to room temperature, and quenched with water, aq. Rochelle's salt. Extraction with ethyl acetate, drying over $Na_2SO_4$ and concentration by rotary evaporation gave crude product used diretctly for the next global benzylation step. HRMS (ESI) Calcd. for $C_{24}H_{27}O_7[(M + H)^+]$ 427.17513, found 427.17490.

The solution of the material obtained above and BnBr (1.6 mL, 13.44 mmol) in acetone (80 mL) was refluxed in the presence of $K_2CO_3$ for 15 hours. After cooling to room temperature, the solid was filtered. Removal of solvent and column chromatography (hexane / ethyl acetate = 6 / 1) gave **98** (792 mg, 51% for two steps). IR (neat) 2925, 1725, 1606 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 7.30 (m, 15H), 6.57 (s, 1H), 6.47 (d, J = 1.8 Hz, 1H), 6.45 (d, *J* = 1.2 Hz, 2H), 6.34 (s, 1H), 6.33 (q, *J* = 7.2 Hz, 1H), 5.76 (s, 1H), 5.27 (s, 2H), 4.95 (s, 4H), 3.97 ( q, *J* = 7.2 Hz, 2H), 3.92 (s, 2H), 2.20 (s, 3H), 1.88 (s, 3H), 1.64 (d, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 167.9, 165.1, 161.6, 160.0, 155.3, 142.7, 140.9, 139.5, 137.1, 135.9, 132.2, 129.2, 128.7,

128.51, 128.47, 128.1, 127.8, 124.1, 120.5, 111.6, 108.7, 108.5, 106.0, 100.0, 70.1, 67.2, 60.3, 39.3, 21.8, 14.7, 14.0, 13.0; HRMS (ESI) Calcd. for $C_{45}H_{48}O_7N_1$ [$(M + NH_4)^+$] 714.34253, found 714.34186.

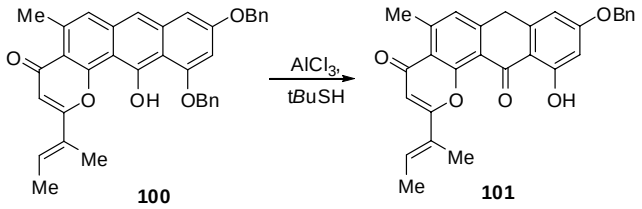



A solution of **98** (680 mg, 0.976 mmol) in DME (20 mL) and 6 M NaOH (20 mL) was refluxed overnight. The next day, the reaction was cooled to room temperature and acidified with 2 M HCl. Extraction with ethyl acetate, drying over $Na_2SO_4$ and concentration by rotary evaporation gave crude **99** that was furthered dried under high vacumme pump and used for the next cyclization step. $^1$H NMR (600 MHz, $CDCl_3$) δ 7.3, (m, 10H), 6.58, (s, 1H), 6.44 (d, $J$ = 2.4 Hz, 2H), 6.42 (q, $J$ = 7.2 Hz, 1H), 6.39 (t, $J$ = 1.8 Hz, 1H), 6.18 (s, 1H), 5.71 (s, 1H), 4.91 (s, 4H), 4.01 (s, 2H), 2.12 (s, 3H), 1.82 (s, 3H), 1.75 (d, $J$ = 7.2 Hz, 3H); HRMS (ESI) Calcd. for $C_{45}H_{48}O_7N_1$ [$(M + NH_4)^+$] 596.26428, found 596.26369.

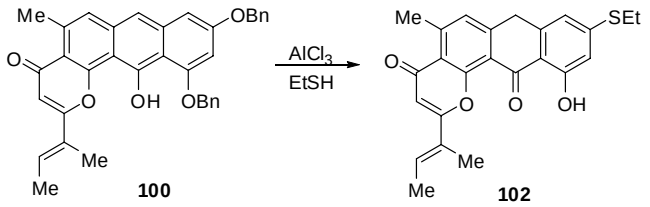



To a solution of crude **99** obtained as above in $CH_2Cl_2$ (150 mL) was added 1-chloro-*N*, *N*, 2-trimethyl-1-propenylamine (388 μL, 2.93 mmol) slowly. The reaction was stirred at

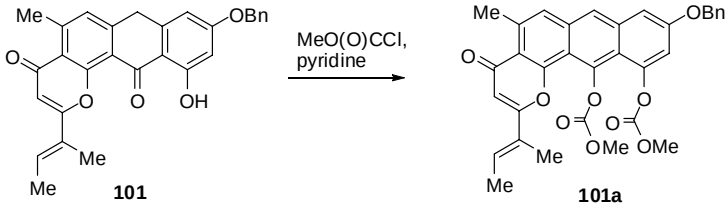
room temperature for 20 hours and quenched with water. Extraction with dichloromethane, drying over $Na_2SO_4$ and concentration by rotary evaporation gave crude yellow **100**. The crude **100** was poorly soluble in most solvents and could not be purified by column chromtagrophy will cause losing the material on the column. It was purified by crystalization in $CH_2Cl_2$ and ethyl ether (300 mg, 57% for two steps). $^1$H NMR (600 MHz, $CDCl_3$) δ 11.11 (s, 1H), 7.40~7.60 (m, 11H), 7.25 (s, 1H), 7.15 (q, *J* = 7.2 Hz, 1H), 6.87 (s, 1H), 6.64 (s, 1H), 6.43 (s, 1H), 5.32 (s, 2H), 5.20 (s, 2H), 2.89 (s, 3H), 1.96 (s, 3H), 1.81 (d, *J* = 7.2 Hz, 3H); HRMS (ESI) Calcd. for $C_{36}H_{31}O_5$ [$(M + H)^+$] 543.21660, found 543.21594.



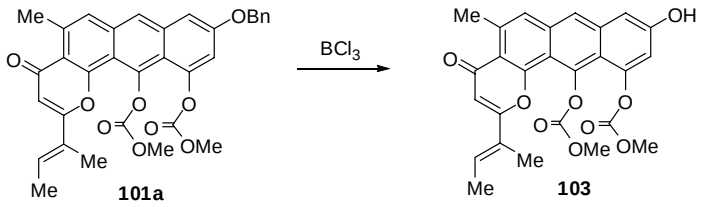

To a solution of $AlCl_3$ (12 mg, 0.09 mmol) in *t*BuSH (1 mL) was added a solution of yellow **100** (5 mg, 0.009 mmol) in $CH_2Cl_2$ (3 mL) at 0 ºC. The reaction was stirred for 1 hour and quenched with aq. $NaH_2PO_4$. The reaction was extracted by ethyl acetate, dried with $Na_2SO_4$ and concentrated by stirring in a flask connected to an aspirator located in a fume hood with good ventilation. Flash column chromatography afforded colorless **101** (4 mg, 98%).$^1$H NMR (600 MHz, $CDCl_3$) δ 7.50 (q, *J* = 7.2 Hz, 1H),7.44 (m, 4H),7.38 (m, 1H), 7.10 (s, 1H), 6.53 (s, 1H), 6.52 (s, 1H), 6.34 (s, 1H), 5.14 (s, 2H), 4.33 (s, 2H), 2.92 (s, 3H), 2.01 (d, *J* = 7.2 Hz, 3H), 1.99 (s, 3H).




To a solution of $AlCl_3$ (48 mg, 0.36 mmol) in EtSH (1 mL) was added a solution of **100** (5 mg, 0.009 mmol) in $CH_2Cl_2$ (2 mL) at 0 ºC. The reaction was stirred for 1 hour and quenched with aq. $NaH_2PO_4$. The reaction was extracted by ethyl acetate, dried with $Na_2SO_4$ and concentrated by stirring in a flask connected to an aspirator located in a fume hood with good ventilation. Flash column chromatography afforded colorless **102** (4 mg, 98%).[1]H NMR (600 MHz, $CDCl_3$) δ 7.49 (dq, *J* = 1.2 Hz, 7.2 Hz, 1H), 7.09 (s, 1H), 6.76 (d, *J* = 1.8 Hz, 1H), 6.73 (s, 1H), 6.33 (s, 1H), 4.31 (s, 2H), 3.05 (q, *J* = 7.2 Hz, 2H), 2.92 (s, 3H), 2.01 (d, *J* = 7.8 Hz, 3H), 1.99 (s, 3H), 1.42 (t, *J* = 7.8 Hz, 3H).



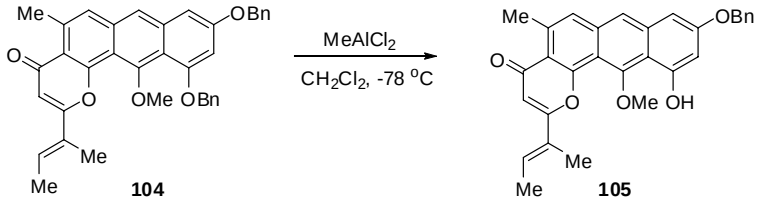

To a solution of **101** (11 mg, 0.024 mmol) in $CH_2Cl_2$ (2 mL) was added MeO(O)CCl (7.5 μL, 0.10 mmol), pyridine ( 12 μL, 0.15 mmol) and DMAP (one crystal) at room temperature. The reaction was stirred for 30 min and quenched with water. Extraction with $CH_2Cl_2$, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 4 / 1 → 2 / 1) gave yellow **101a** (9 mg, 67%, not optimized). [1]H NMR (600 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.50~7.34 (m, 6H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.04 (q, *J* = 7.2 Hz, 1H), 6.40 (s, 1H), 5.21 (s, 2H), 4.02 (s, 3H), 3.86 (s, 3H), 2.92 (s, 3H), 2.20 (s, 3H), 1.96 (d, *J* = 7.2 Hz, 3H).



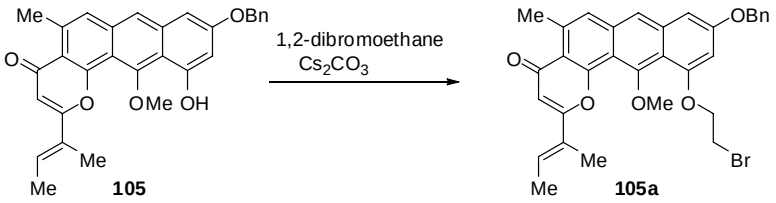

To a solution of **101a** (9.0 mg, 0.016 mmol) in $CH_2Cl_2$ (3 mL) was added 1M solution of $BCl_3$ in $CH_2Cl_2$ (0.031 mL, 0.031 mmol) at 0 ºC. The reaction was stirred for 20 minutes and quenched with water. Extraction with ethyl acetate, drying over $Na_2SO_4$, concentration under reduced pressure and column chromatography (hexanes / ethyl acetate = 1 / 1) gave yellow **103** (7 mg, 91%). $^1$H NMR (600 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.38 (s, 1H), 7.08 (q, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.50 (s, 1H), 4.05 (s, 3H), 3.89 (s, 3H), 2.91 (s, 3H), 2.04 (s, 3H), 1.96 (d, *J* = 7.2 Hz, 3H).


To a cloudy solution of **100** (1.15 g, 2.11 mmol) in THF (190 mL) was added a solution of sodium dithionite (1.74 g, 85 %, 8.47 mmol) in water (6 mL). Five minutes later, a solution of potassium hydroxide (1.67g, 85%, 25 mmol) in water (5 mL) was added. The reaction was stirred at room temperature for 10 minutes and cooled to 0 ºC, to which $Me_2SO_4$ (2.4 mL, 25 mmol) was added. The reaction was stirred for 3 hours and completed. Dilution with water, extraction with ethyl acetate, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 3 / 1) gave yellow **104** (1.16 g, 99%). IR (neat) 2925, 1622, 1563 cm$^{-1}$; $^1$H NMR (600

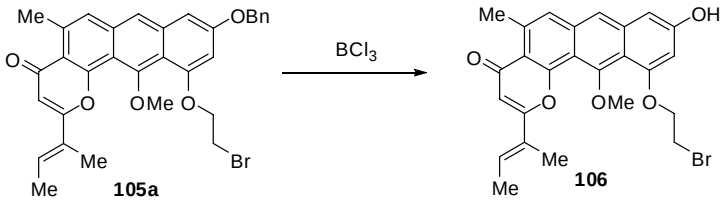
MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.45 (dt, *J* = 1.6 Hz, 7.2 Hz, 4H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.29 (s, 3H), 7.23 (q, *J* = 7.2 Hz, 1H), 6.91 (d, *J* =2.4 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.39 (s, 1H), 5.18 (s, 2H), 3.68 (s, 3H), 2.91 (s, 3H), 1.98 (s, 3H), 1.94 (d, *J* = 7.2 Hz, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) δ 180.6, 162.8, 158.0, 157.3, 156.7, 156.5, 137.8, 136.9, 136.6, 134.9, 134.8, 130.7, 128.8, 128.5, 128.4, 128.0, 127.9, 127.8, 127.4, 125.5, 119.8, 119.1, 116.0, 114.4, 109.9, 100.7, 98.6, 71.1, 70.2, 63.6, 23.7, 14.7, 12.3; HRMS (ESI) Calcd. for $C_{37}H_{33}O_5[(M + H)^+]$ 557.23225, found 557.23178.




To a solution of **104** (140 mg, 0.252 mmol) in $CH_2Cl_2$ (9mL) was added a solution of 1M $MeAlCl_2$ in hexanes (0.553 mmol, 0.553 mL) at -78 ºC. The reaction was stirred at -78 ºC for 15 minutes and quenched with water. Extraction with ethyl acetate, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 3 / 1) gave red **105** (110 mg, 94%). $^1H$ NMR (600 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.86 (s, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.38 (m, 2H), 7.15 (q, *J* = 7.2 Hz, 1H), 6.85 (d, *J* =2.4 Hz, 1H), 6.72 (d, *J* = 1.2 Hz, 1H), 6.45 (s, 1H), 5.21 (s, 2H), 3.99 (s, 3H), 2.92 (s, 3H), 2.03 (s, 3H), 2.01 (d, *J* = 7.2 Hz, 3H); HRMS (ESI) Calcd. for $C_{30}H_{27}O_5[(M + H)^+]$ 467.18530, found 467.18518.

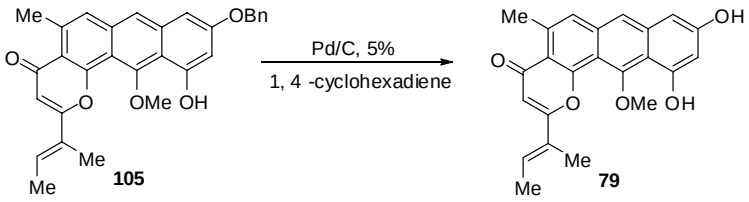



A solution of **105** (37 mg, 0.079 mmol) and 1, 2-dibromoethane (205 μL, 2.4 mmol) in acetone (12 mL) was refluxed for 5 hours in the presence of $Cs_2CO_3$ (64 mg, 0.20 mmol). The reaction was cooled to room temperature and the solid was filtered off. Concentration under reduced pressure and column chromatography (hexanes / ethyl acetate = 2 / 1) gave red **105a** (34 mg, 75%). $^1$H NMR (600 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.39 (m, 2H), 7.32 (q, *J* = 7.2 Hz, 1H), 6.93 (d, *J* =2.4 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.44 (s, 1H), 5.20 (s, 2H), 4.50 (t, 2H), 3.95 (s, 3H), 3.89 (t, 2H), 2.92 (s, 3H), 2.05 (s, 3H), 2.00 (d, *J* = 7.2 Hz, 3H); HRMS (ESI) Calcd. for $C_{32}H_{30}O_5Br_1$ $[(M + H)^+]$ 573.12711, found 573.12665.

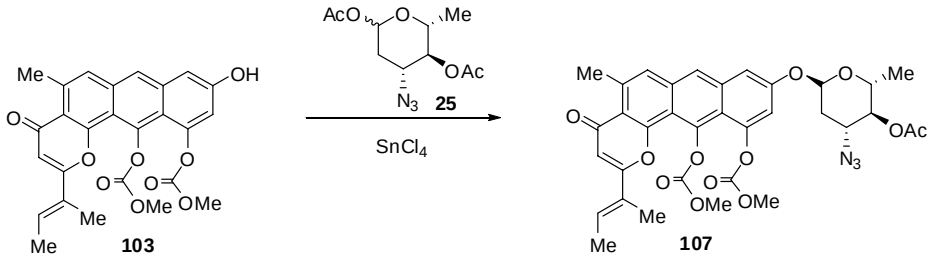



To a solution of **105a** (10 mg, 0.017 mmol) in $CH_2Cl_2$ (9mL) was added a solution of 1M $BCl_3$ in heptane (0.034 mmol, 0.034 mL) at 0 ºC. The reaction was stirred at 0 ºC for 15 minutes and quenched with water. Extraction with ethyl acetate, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 3 / 1) gave red **106** (5mg, 60%). $^1$H NMR (600 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.36 (s, 1H), 7.32 (q, *J* = 7.2 Hz, 1H), 6.85 (s, 1H), 6.55 (s, 1H), 6.47 (s, 1H), 4.51 (t, 2H), 3.94

(s, 3H), 3.90 (t, 2H), 2.92 (s, 3H), 2.05 (s, 3H), 1.98 (d, *J* = 7.2 Hz, 3H); HRMS (ESI) Calcd. for $C_{25}H_{24}Br_1O_5$ $[(M + NH_4)^+]$ 483.08016, found 483.08005.

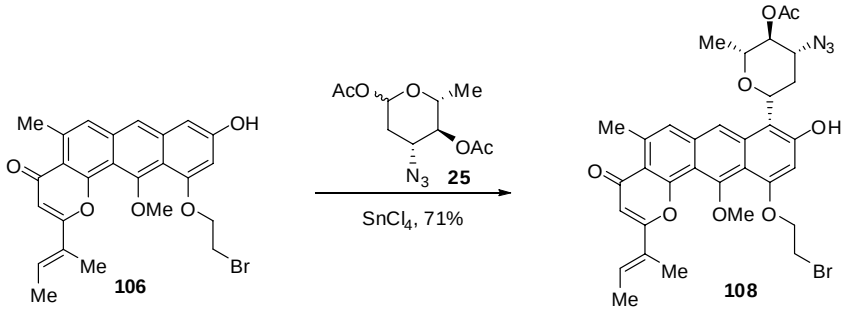



To a solution of **105** (34 mg, 0.075 mmol) in EtOH (4.5mL) and ethyl acetate (0.75 mL) was added 5% Pd / C (48 mg) and 1, 4-cyclohexadiene (130 μL) at room temperature. The reaction was stirred for 8 hours and filtered through a well packed celite bed. Removal of solvent and column chromatography (hexanes / ethyl acetate = 2 / 1) gave red **79** (9 mg, 33%) with some **106** recovered. $^1$H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.82 (s, 1H), 7.38 (s, 1H), 7.16 (q, *J* = 7.2 Hz, 1H), 6.82 (d, *J* =2.4 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.46 (s, 1H), 4.00 (s, 3H), 2.92 (s, 3H), 2.04 (s, 3H), 2.01 (d, *J* = 7.2 Hz, 3H).



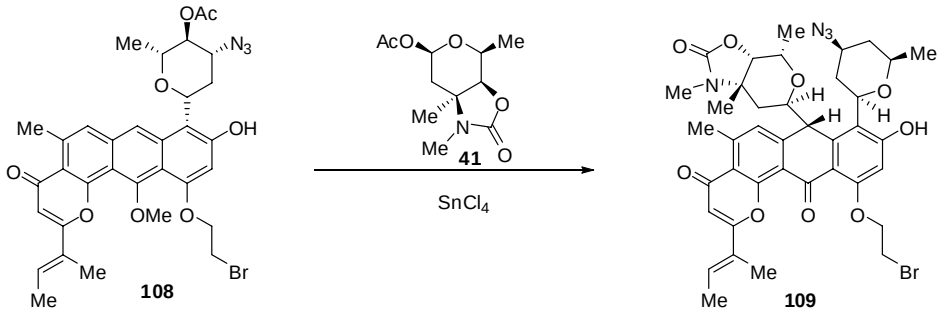

To a solution of **103** (12.0 mg, 0.025 mmol) and **25** (7.0 mg, 0.028 mmol) in $CH_2Cl_2$ (2.0 mL) was added sequentially microwave-activated 3 Å molecular sieves powder (80 mg) and $SnCl_4$ (0.050 mmol, 0.050 mL solution of 1 M $SnCl_4$ in dichloromethane) at -78 ºC. The reaction was stirred for 14 hours while warming to room temperature, and then

quenched with water. Extraction with ethyl acetate, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 2 / 1) gave yellow **107** (6 mg, 36%) and recovered **103** (3 mg). IR (neat) 2102, 1769, 1634 $cm^{-1}$; $^1H$ NMR (600 MHz, $CDCl_3$) δ 8.16 (d, *J* = 3.0 Hz, 1H), 7.52 (t, *J* = 2.4 Hz, 1H), 7.48 (s, 1H), 7.07 (d, *J* = 1.8 Hz, 1H), 7.05 (q, *J* = 6.6 Hz, 1H), 6.42 (s, 1H), 5.80 (t, *J* = 4.2 Hz, 1H), 4.83 (t, *J* = 9.0 Hz, 1H), 4.11 (m, 1H), 4.04 (d, *J* = 3.0 Hz, 3 H), 3.91 (m, 1H), 3.87 (d, *J* = 2.4 Hz, 3H), 2.93 (s, 3H), 2.45 (m, 1H), 2.16 (s, 3H), 2.02 (s, 3H), 1.98 (m, 1H), 1.96 (d, *J* = 7.2 Hz, 3H), 1.18 (dd, *J* = 2.4 Hz, 6.0 Hz, 3H).

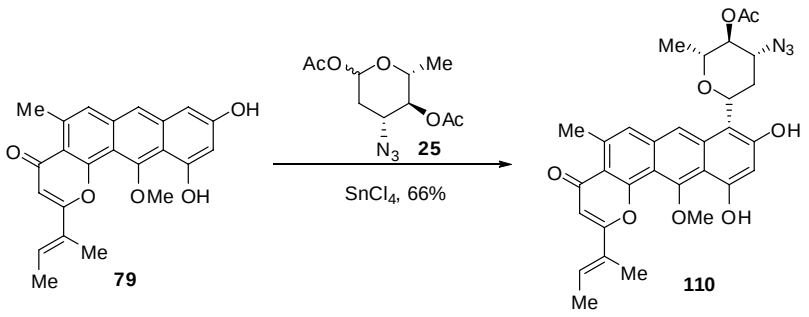



To a solution of **106** (25.0 mg, 0.052 mmol) and **25** (15.0mg, 0.057 mmol) in $CH_2Cl_2$ (20.0 mL) was added $SnCl_4$ (0.078 mmol, 0.078 mL solution of 1 M $SnCl_4$ in dichloromethane) at -78 ºC. The reaction was stirred for 14 hours while warming to room temperature, and then quenched with water. Extraction with $CH_2Cl_2$, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 2 / 1→1 / 1)) gave yellow **108** (25 mg, 71%). IR (neat) 3333, 2923, 2098, 1746, 1615 $cm^{-1}$; 1H NMR (600 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.62 (s, 1H), 7.42 (s, 1H), 7.31 (q, *J* = 7.2 Hz, 1H), 6.49 (s, 1H), 6.45 (s, 1H), 5.52 (d, *J* = 10.2 Hz, 1H), 4.94 (t, *J* = 9.6 Hz, 1H), 4.51 (t, *J* = 5.4 Hz, 2H), 3.94 (m, 1H), 3.93 (s, 3 H), 3.89 (t, *J* = 5.4 Hz, 2H), 3.83 (m, 1H), 2.95 (s, 3H), 2.49 (d, *J* = 12.6 Hz, 1H), 2.22 (s, 3H), 2.07 (q, *J* = 13.2 Hz, 1H), 2.03

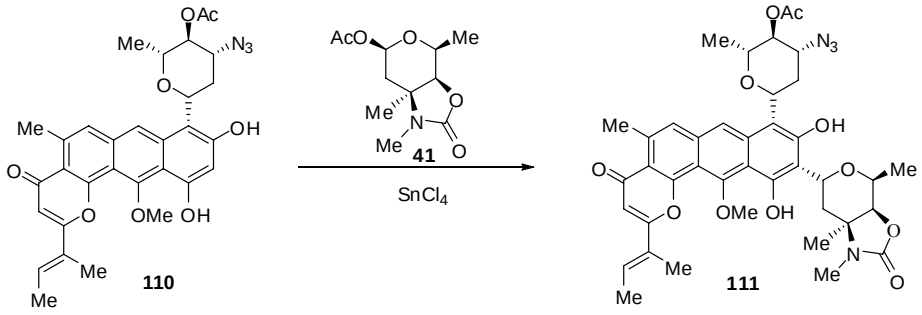
(s, 3H), 1.99 (d, *J* = 7.2 Hz, 3H), 1.40 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 180.7, 170.3, 163.2, 157.4, 157.1, 156.6, 155.4, 135.9, 135.0, 134.3, 131.3, 127.9, 125.7, 119.4, 115.6, 113.8, 113.5, 110.0, 105.9, 101.5, 77.4, 76.5, 75.2, 69.3, 64.1, 61.0, 36.1, 29.3, 23.8, 21.1, 18.2, 14.8, 12.5; HRMS (ESI) Calcd. for $C_{33}H_{35}O_8N_3Br_1[(M + H)^+]$ 680.16020, found 680.15981.




To a solution of **108** (10.0 mg, 0.015 mmol) and **41** (5.4 mg, 0.022 mmol) in $CH_2Cl_2$ (3.0 mL) was added $SnCl_4$ (0.030 mmol, 0.030 mL solution of 1 M $SnCl_4$ in dichloromethane) at -78 ºC. The reaction was stirred for 36 hours after warming to 4 ºC, and then quenched with water. Extraction with $CH_2Cl_2$, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 2 / 1) gave white **109** (4 mg, 25%). $^1$H NMR (600 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.35 (s, 1H), 7.32 (q, *J* = 7.8 Hz, 1H), 6.53 (s, 1H), 6.33 (s, 1H), 5.04 (dd, *J* = 2.4 Hz, 12.0 Hz, 1H), 4.86 (t, *J* = 10.2 Hz, 1), 4.51 (m, 1H), 4.35 (d, *J* = 4.8 Hz, 1H), 4.24 (m, 1H), 4.10 (dt, *J* = 4.2 Hz, 12.0 Hz, 1H), 3.88 (m, 1H), 3.84 (m, 1H), 3.79 (d, *J* = 1.2 Hz, 1H), 3.77 (m, 1H), 3.74 (m, 1H), 3.20 (q , *J* = 6.6 Hz, 1H), 2.95 (s, 3H), 2.47 (s, 3H), 2.41 (d, *J* = 9.6 Hz, 1H), 2.21 (s, 3H), 2.17 (m, 1H), 2.09 (q, *J* = 11.4 Hz, 1H), 2.02 (m, 1H), 1.99 (d, *J* = 6.6 Hz, 3H), 1.98 (s, 3H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.23 (d, *J* = 7.2 Hz, 3H), 1.12 (s, 3H); HRMS (ESI) Calcd. for $C_{41}H_{46}O_{11}N_4Br_1[(M + H)^+]$ 849.23410, found 849.23326.




To a solution of **79** (9.0 mg, 0.024 mmol) and **25** (6.8 mg, 0.026 mmol) in $CH_2Cl_2$ (9.0 mL) was added $SnCl_4$ (0.048 mmol, 0.048 mL solution of 1 M $SnCl_4$ in dichloromethane) at -78 ºC. The reaction was stirred for 14 hours while warming to room temperature, and then quenched with water. Extraction with $CH_2Cl_2$, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 2 / 1) gave yellow **110** (8 mg, 66%). $^1$H NMR (600 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.87 (s, 1H), 7.68 (d, *J* = 10.2 Hz, 1H), 7.44 (s, 1H), 7.13 (bs, 1H), 6.63 (s, 1H), 6.45 (s, 1H), 5.50 (d, *J* = 9.6 Hz, 1H), 4.93 (t, *J* = 9.6 Hz, 1H), 3.98 (s, 3 H), 3.90 (m, 1H), 3.83 (dq, *J* = 6.0, 9.6 Hz, 1H), 2.94 (s, 3H), 2.44 (m, 1H), 2.22 (s, 3H), 2.09 (m, 1H), 2.03 (s, 3H), 2.01 (d, *J* = 7.2 Hz, 3H), 1.40 (d, *J* = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 180.3, 170.2, 162.8, 156.9, 156.1, 155.1, 135.6, 134.6, 133.6, 130.7, 128.2, 126.0, 119.5, 114.7, 114.6, 113.3, 111.3, 110.3, 104.6, 104.2, 77.4, 76.4, 75.2, 64.9, 61.0, 36.1, 23.7, 21.1, 18.2, 14.9, 12.6.




To a solution of **110** (25 mg, 0.044 mmol) and **41** (13.8 mg, 0.057 mmol) in $CH_2Cl_2$ (9.0 mL) was added powdered 4 Å molecular sieves (70 mg). The solution was cooled to -78 ºC, and $SnCl_4$ (0.048 mmol, 0.048 mL solution of 1 M $SnCl_4$ in dichloromethane) was added. The reaction was standing in the freezer at -30 ºC for 48 hours and quenched with water. Extraction with $CH_2Cl_2$, drying over $Na_2SO_4$, concentration by rotary evaporation and column chromatography (hexanes / ethyl acetate = 2 / 1) gave yellow **111** (7 mg, 21%) with recovering **110** (17 mg, 68%). $^1$H NMR (600 MHz, $CDCl_3$) δ 10.85 (s, 1H), 9.53 (s, 1H), 8.17 (s, 1H), 7.46 (s, 1H), 7.11 (bm, 1H), 6.46 (s, 1H), 5.73 (d, *J* = 11.4 Hz, 1H), 5.55 (d, *J* = 10.8 Hz, 1H), 4.98 (t, *J* = 10.2 Hz, 1H), 4.49 (bm, 1H), 4.20 (s, 1H), 3.96 (bs, 3H), 3.88 (m, 1H), 3.77 (m, 1H), 2.96 (s, 3H), 2.94 (s, 3H), 2.30 (m, 2H), 2.23 (s, 3H), 2.09 (m, 2H), 2.04 (s, 3H), 2.02 (d, *J* = 7.2 Hz, 3H), 1.45 (s, 6H), 1.39 (d, *J* = 6.0 Hz, 3H); HRMS (ESI) Calcd. for $C_{40}H_{45}O_{11}N_4$ [$(M + H)^+$] 757.30794, found 757.30716.

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