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Hao Lu Date

I. Addressing the Regioselectivity Problem in Organic Synthesis.

II. A-B-A-B-A Block Amphiphiles. Balance between Hydrophilic and Hydrophobic Segmentation.

By
Hao Lu
Doctor of Philosophy

Chemistry

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Dr. Fredric M. Menger, Advisor

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Dr. Lanny Liebeskind, Committee Member

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Dr. Simon Blakey, Committee Member

Accepted:

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Lisa A. Tedesco, Ph.D.
Dean of the Graduate School

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Date

I. Addressing the Regioselectivity Problem in Organic Synthesis

II. A-B-A-B-A Block Amphiphiles. Balance between Hydrophilic and Hydrophobic Segmentation

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B.S., Fudan University, 2001

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An Abstract of
A dissertation submitted to the Faculty of the Graduate School of
Emory University in partial fulfillment
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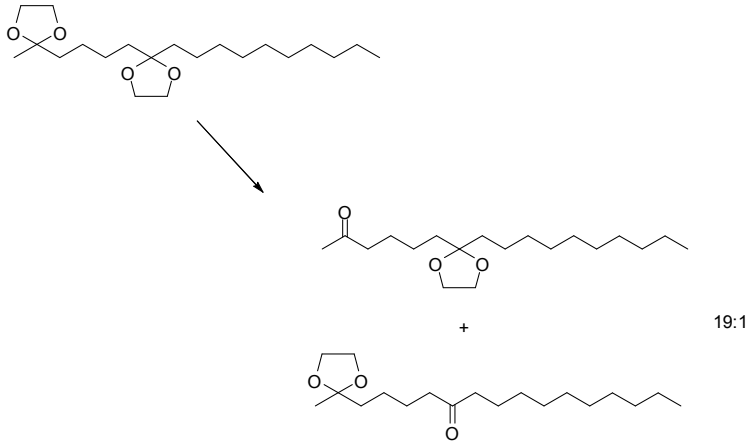
2009

Abstract

Part I. Addressing the Regioselectivity Problem in Organic Synthesis

A family of compounds with two nearly identical ketals on each has been synthesized in an effort to address the regioselectivity problem. A screening process uncovered a heterogeneous catalytic system that hydrolyzes one of two nearly identical ketals with a high selectivity.



Part II. A-B-A-B-A Block Amphiphiles. Balance between Hydrophilic and Hydrophobic Segmentation

Six penta-block amphiphiles of the general structure A-B-A-B-A or B-A-B-A-B (where A = a hydrophilic ether and B = a hydrophobic carbon chain) were synthesized and examined via water solubilities, surface activities, cloud points, and self-diffusion coefficients. It was found that segmentation can have a dramatic effect upon solute properties, including solubility, propensity to self-assemble, aggregation number, and cooperativity. These data are relevant to biological systems where segmentation is a widespread phenomenon.

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Acknowledgement

I want to start my acknowledgements with my grandparents Deyun Fang and Demei He. For years when I have been pursuing what I can not foresee, I have always seen their affectionate eyes in my mind. Wherever I have travelled, Shanghai or Atlanta, Fudan University, Emory University, or Georgia State University Law School, their eyes have inspired me as they always did when I was kid, with love, trust, and encouragement. Through the whole Ph.D. program their eyes have silently and persistently supported me, and will continue to encourage me to advance.

I want to start my acknowledgements with my advisor Dr. Menger. He impressed me with his inspirational openness when I first met him personally in the orientation for new graduate students. I always remember the story of “cat peeing on tree” he told us when I just started my life in the Chemistry Department at Emory. At that moment, I realized that I was a cat, and Dr. Menger would be the person coaching me not only how to research (“pee”), but also what to research (“tree”). Since then, I have been exposed to many great leading ideas while working in his lab. Many of these ideas have resulted in novel compounds with unusual properties. Thus, it is routine to see diversified topics in the group meetings, and not unusual to see five publications in JACS in one year covering completely different subjects. In hindsight, the diversity and unprecedentedness of his research echo his philosophy that chemists not only build on the known, but also explore beyond the known.

I want to start my acknowledgements with my wife Mao Gu. She spent a lot of time with me in the lab and was really supportive throughout all the years when I was studying here. For all these years, and across the world, we have been supporting each other, encouraging each other, and loving each other. Without her, my life is lonely and less happy.

I also want to start my acknowledgements with my parents Liangsheng Lu and Jinxian Fang. They always feel proud of me. And I promise I will keep them feel proud.

I also want to thank the faculty at Emory. They imparted not only solid scientific knowledge, but their persistence in pursuing truth. I thank Dr. McDonald, Dr. Liebeskind, Dr. Padwa, Dr. Liotta. A special thanks to my committee members, Dr. Liebeskind and Dr. Blakey, for their advice and help.

I want to thank my friends and group members here in the chemistry department, Hongjun Zhang, Xilin Harry Wang, Shuangpei Liu, Yongfeng Li, Jianwei Bian, Lei Shi, Hailing Zhang, Mary Chlebowski, Ashley Galloway, Jen Sorrells, Dr. Wu Shaoxiong, Dan Lunderberg, Yihun Chen, Jin Wang, Fuchang Ying, Weiqiang Zhan. Each of them has been part of my life during these years and we have had much fun together. Thank you.

Dedicated to My Family

In memory of my grandparents: Deyun Fang and Demei He

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Part I

Addressing the Regioselectivity Problem in Organic Synthesis

Introduction

Organic synthesis begins with differentiation.[1] By distinguishing electronic, spatial, and chemical properties, chemists have succeeded in intelligently designing the syntheses of many complex compounds.[2] Without means to differentiate, chemists would lack the most powerful and crucial weapons in their arsenal, weapons being used for the manipulation and control of chemical reactions.

Generally speaking, there are four ways to manipulate and control chemical reactions. They are chemoselectivity, regioselectivity, diastereoselectivity, and enantioselectivity.[3] Chemists may choose different reactions, reagents, and catalysts to achieve a desired selectivity, and thus diverse synthetic goals.[4]

These four types of selectivity function differently. As B. M. Trost summarized, “in defining strategies and reactions to construct complex molecules we require synthetic methods that can (i) perform a wanted structural change and none other (that is be chemoselective), (ii) orient the reacting partners in a correct fashion (be regioselective), (iii) create the correct orientations of various parts of the molecule with respect to each other (be diastereoselective), and (iv) enable the formation of a molecule of one handedness or a mirror image isomer (be enantioselective).”[5] In other words, organic chemists can differentiate not only chemical changes, but also positions and specific directions of such changes.

Traditionally, differentiation depends on either steric effect or electronic

effect, or both of them. Examples of such control abound in the literatures. For example, toluene is nitrated faster at the para position than at the *ortho* and *meta* positions. An aldehyde can be reduced in the presence of an unhindered ketone.[6] Differentiation becomes more challenging when two functionalities, with respect to local chemical environment, are identical.[7] No electronic or steric differences exist between two identical functionalities.[8] Thus, treating two identical functionalities on one single molecule with ordinary reagents or catalysts will modify both functionalities. For example, peroxyarachidonic acid has four identical, C=C double bonds (Figure 1). Due to lack of sufficient electronic or steric differences, regioselective epoxidation on a specific double bond was impossible before the invention of a new synthetic method, such as internally directed epoxidation.[9]

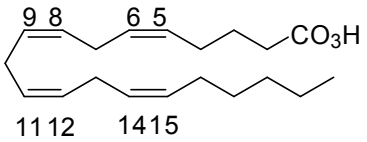
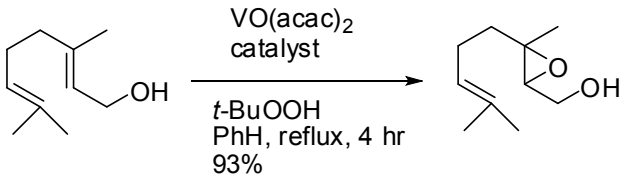


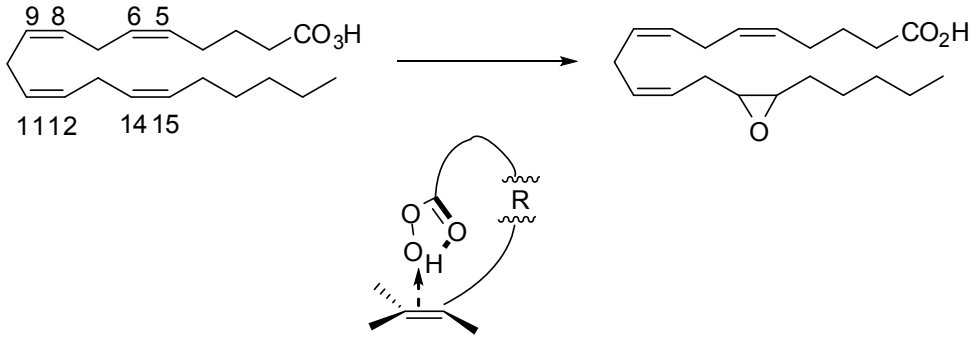
Figure 1. Peroxyarachidonic acid with similar C=C double bonds.[9]

Internally directed epoxidation was first demonstrated by K. B. Sharpless in the transitional metal catalyzed epoxidation of olefin alcohols (Scheme 1).[10] In his study, K. B. Sharpless employed the unique directing effect of alcohol to control the regioselectivity. For example, geraniol was selectively oxidized to monoepoxide by vanadium-hydroperoxide reagents with high regioselectivity on the 2,3 double bond.[11]



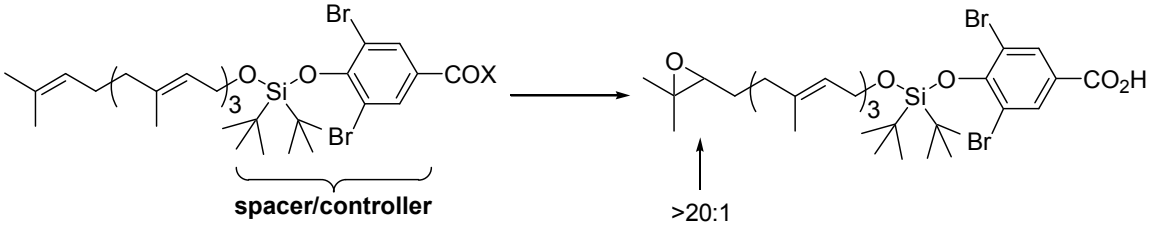
Scheme 1. Sharpless's example of internally directed epoxidation catalyzed by transitional metal.[10]

In the aforementioned selective epoxidation of peroxyarachidonic acid, E. J. Corey controlled internally directed epoxidation via the stereoelectronic effect (Scheme 2).[9] The intramolecular epoxidation of peroxyarachidonic acid generated the 14,15-epoxide with high efficiency. The selectivity is arguably controlled by the ring strain because epoxidation requires a perpendicular orientation between C=C σ plane and the internally hydrogen-bonded peroxycarbonyl ring. Epoxidation at the other three C=C double bonds has to overcome more ring strain, and thus less favored (Scheme 2).



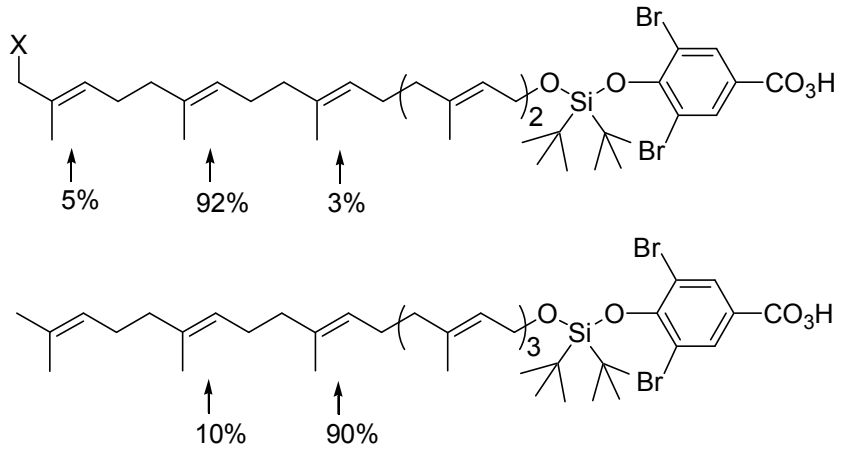
Scheme 2. Proposed mechanism for internally directed epoxidation of peroxyarachidonic acid.[9]

E. J. Corey has recently displayed more delicate control over internally directed epoxidation by using a spacer that effectively directs delivery of oxygen to a specific double bond.[12] For example, the 4-silyloxybenzoic acid spacer can effectively direct internal epoxidation to the double bond of the fourth prenyl unit from the prenyl-OH subunit (Scheme 3).[13] Thus, the internal epoxidation of tetra-unsaturated acid formed the terminal epoxide with selectivity more than 20:1.

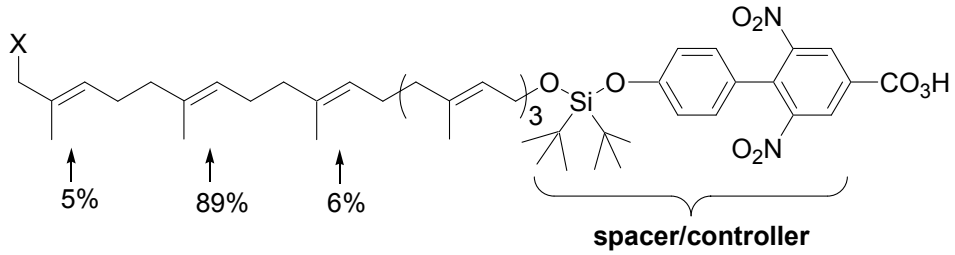


Scheme 3. Corey's spacer-controlled epoxidation of polyenes.[12]

Similar selectivities have also been observed in other polyenes with the same spacer/controller. For example, both the nona-unsaturated acid and 1-hydroxylated squalene derivative undergo internal epoxidation mainly at the double bond four units away from the spacer (Scheme 4).[12] Furthermore, Corey has also designed a new spacer/controller to tune the regioselectivity. A biphenyl spacer/controller with a longer length can direct the internal delivery of oxygen selectively to the double bond five units away from the spacer (Scheme 5).[12] Thus, the regioselective internal epoxidation of polyenes by using a specially designed space/controller has exhibited the feasibility of site-selective epoxidation of olefinic units with identical reactivities.[14] Such space/controller is



Scheme 4. Corey's example of spacer-controlled epoxidation of polyenes, with percentages of yields at different positions.[12]

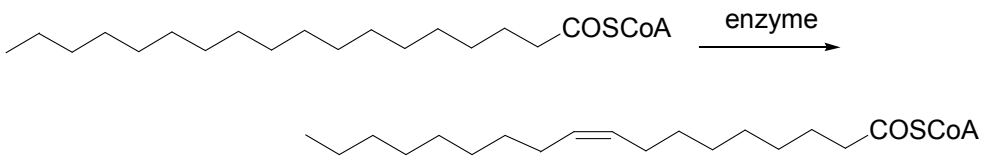


Scheme 5. Corey's example of spacer-controlled epoxidation of polyenes, with epoxidation occurring at the fifth prenyl unit from the prenyl-OH subunit.[12]

linked to the substrate molecule covalently.

While E. J. Corey has exhibited his exquisite skill in and opened a new door for differentiating two identical functionalities, natural enzymes have long demonstrated in regioselectivity their unsurpassable precision and efficiency. For instance, acyl CoA desaturase can regiospecifically dehydrogenate the stearyl CoA at the 9-position (Scheme 6).[15] It is self-evident that no electronic or steric

differences exist between 9-position and 5- or 12-position. Neither is it likely that the regioselectivity is controlled, as shown in Corey's internally directed expoxidation of polyenes, by the stereoelectronic effect. Unlike the polyenes, the carbon chain of stearyl CoA is saturated. The mechanism for this regioselective transformation remains undiscovered. Indeed, no one can duplicate this feat non-enzymatically, or propose a reasonable mechanism. Here, enzyme is a black box.



Scheme 6. Regioselective dehydrogenation of the stearul CoA by enzyme at 9-position.[15]

An example might be helpful to unveil the mystery inside the enzyme black box. In 1997, David A. MacManus and Evgeny N. Vulfson discovered that the enzymatic acylation of secondary hydroxyl groups in monosaccharide derivatives could be regioselectively controlled by the polarity of the solvent medium (Figure 2).[16] In nonpolar solvent cyclohexane, the enzyme introduced an acyl group to the monosaccharide derivative at 2-position. In contrast, the enzyme in polar solvent, such as acetone, introduced an acyl group at the 3-position. Both of these two hydroxyl groups are secondary and equatorial. Models proposed, as shown in Figure 2, show the orientations of the monosaccharide derivative inside the active site of the enzyme.[16]

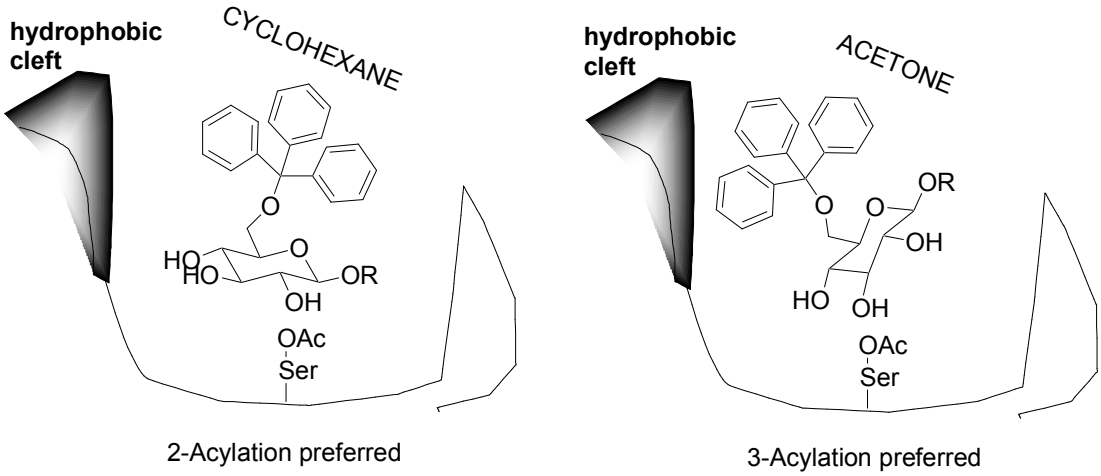


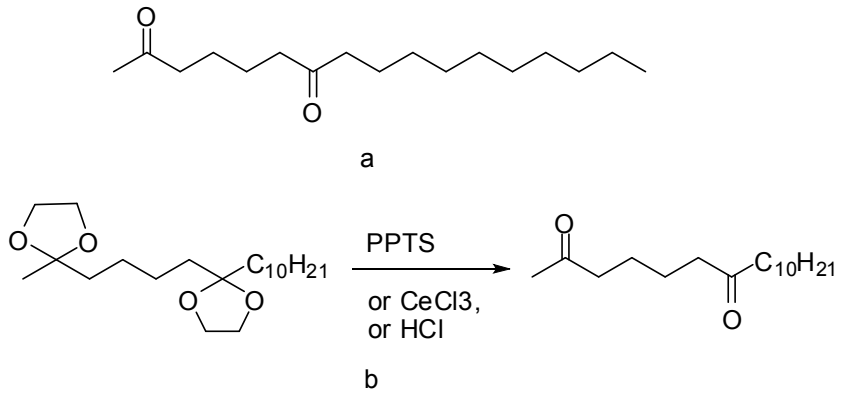
Figure 2. Regioselective acylation by enzymes in cyclohexane and acetone and proposed models.[16]

As proposed models indicate, when the medium used for acylation changes from a nonpolar solvent to a polar solvent, the hydrophobic trityl group inside the enzyme cavity adjusts its orientation. In a nonpolar solvent, the trityl group exposes itself to the solvent so that the secondary alcohol at 2-position poses in proximity to the active site that finalizes acylation. Meanwhile, the secondary alcohol at 3-position is shielded from the active site. In contrast, when a polar solvent is used, the monosaccharide derivative adjusts its orientation in the enzyme to avoid or reduce exposure of the trityl group to the polar solvent. The adjustment may also be facilitated by the hydrophobic region on the cavity wall. The secondary alcohol at 2-position now stays away from the active site and the alcohol at 3-position is acylated. The result shows that enzymes can

regioselectively acylate the monosaccharide derivatives if solvents with different polarities are carefully chosen. This experiment also teaches that enzymes can achieve regioselectivity simply by positioning a specific group among identical ones closer to the reactive site.[17]

We are to address the regioselectivity between identical functionalities based solely on their positional difference. Such spatial regioselectivity might be realized through both noncovalent bonding and cavitary restraint. Ideally, the noncovalent bonding will tether a substrate to an elaborate cavity which will further restrict the orientation of the substrate.[18] The combinative effect of both noncovalent bonding and cavitary restraint is to force the desired one of two identical functionalities into proximity of a reactive site, thus to reach both dynamic catalysis and regioselectivity.

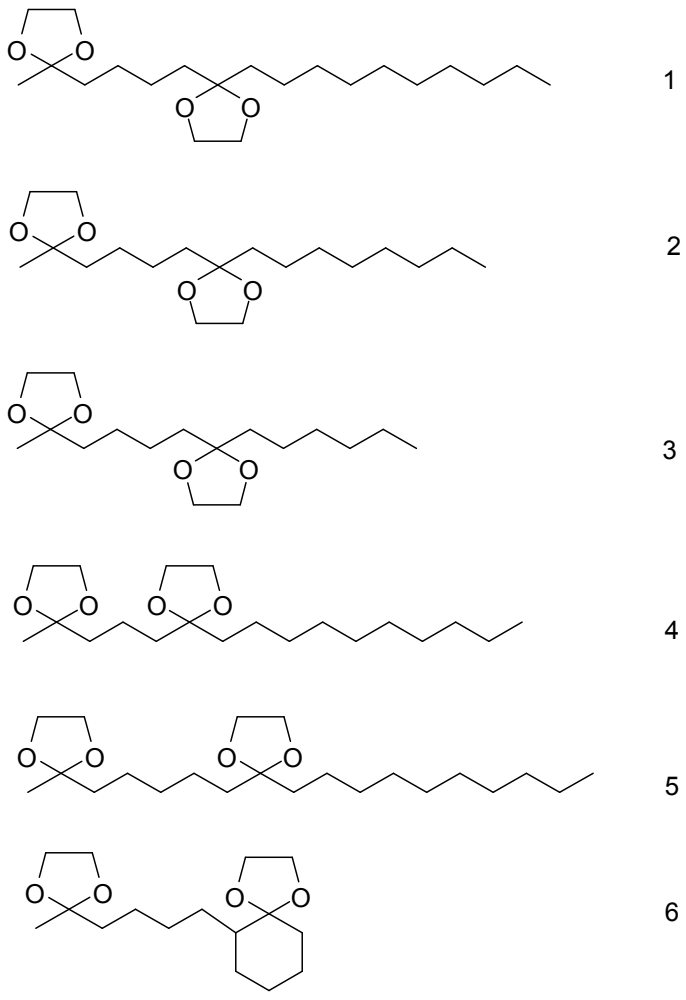
We embark on this unique venture by first carrying out a model study. The first conceived task at this preliminary stage is to differentiate two ketone functionalities on a carbon chain (Scheme 7).[19] The two protected ketone functionalities, as shown in Scheme 7a, are nearly identical both sterically and electronically, because both of them are positioned at secondary carbons on a saturated chain. An initial study shows that acids, such as pyridinium p-toluenesulfonate,[20] $CeCl_3$,[21] HCl,[22] do not distinguish two ketal functionalities on a saturated carbon chain to regioselectively deprotect one of them (Scheme 7b). However, after careful screening of potential catalysts, we have discovered one catalyst that can regioselectively deprotect one of the two identical ketal groups.



Scheme 7. a) Two nearly identical ketones on a saturated carbon chain; b) Catalysts such as pyridinium p-toluenesulfonate,[20] $CeCl_3$,[21] and HCl[22] fail to regioselectively deprotect one of two nearly identical ketals.

Syntheses

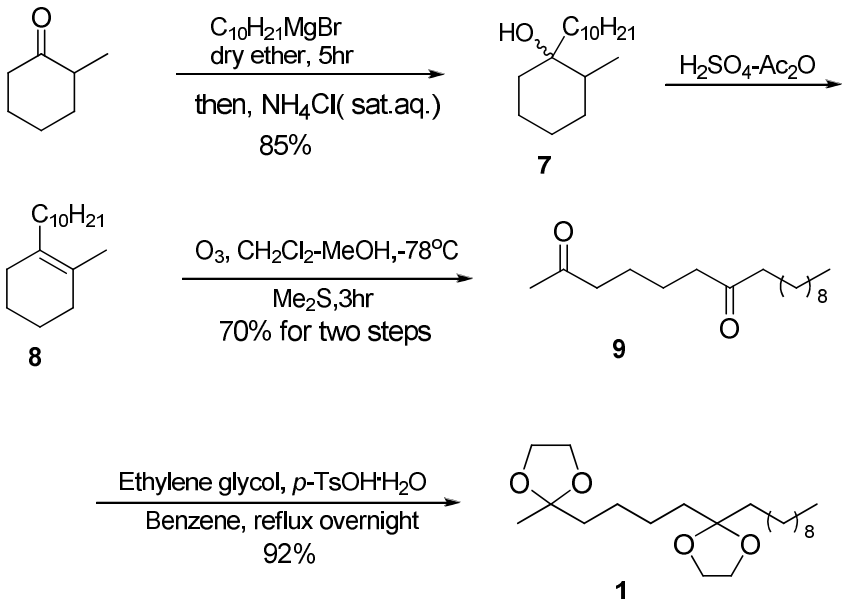
We have synthesized six diketal analogues **1** - **6** (Scheme 8). The numbers of carbons in-between two nearly identical ketal functionalities on these analogues vary. In addition, analogue **6** has a 6-member ring.



Scheme 8. List of diketal agalogues **1** – **6** with different numbers of carbons in-between two nearly identical ketals.

The syntheses of diketal **1** began with Grignard reaction of 2-methyl

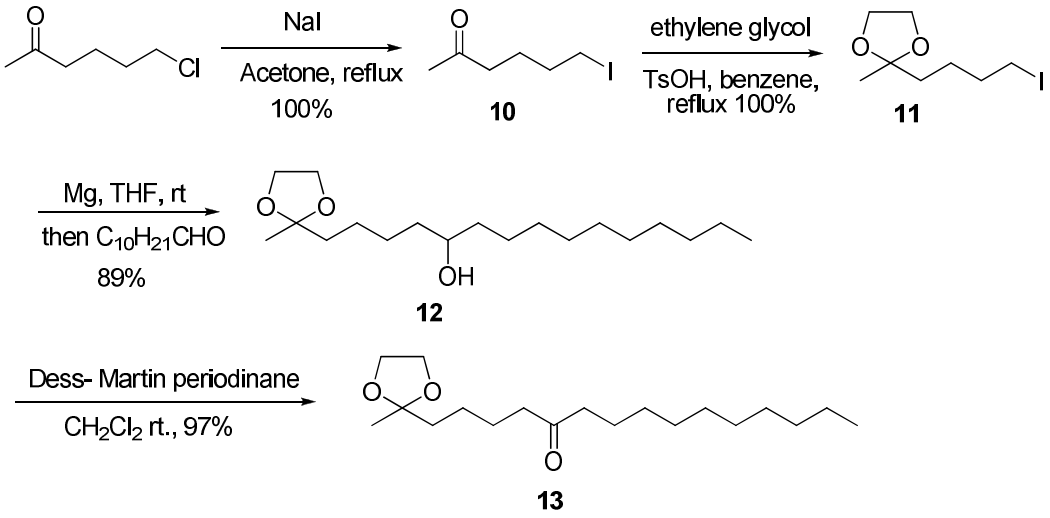
cyclohexanone (Scheme 9). Grignard reagent n-$C_{10}H_{21}MgBr$ was prepared in situ.[23] After the decyl chain was introduced on the ring to give **7**, acidic dehydration was carried out to give cyclohexene **8**. Without purification, ozonolysis of the alkene gave diketone **9** with 70% yield in two steps.[24] After refluxing overnight together with TsOH and ethylene glycol in dry benzene with Dean-Stark apparatus, the diketone was transformed to diketal **1**.[25]



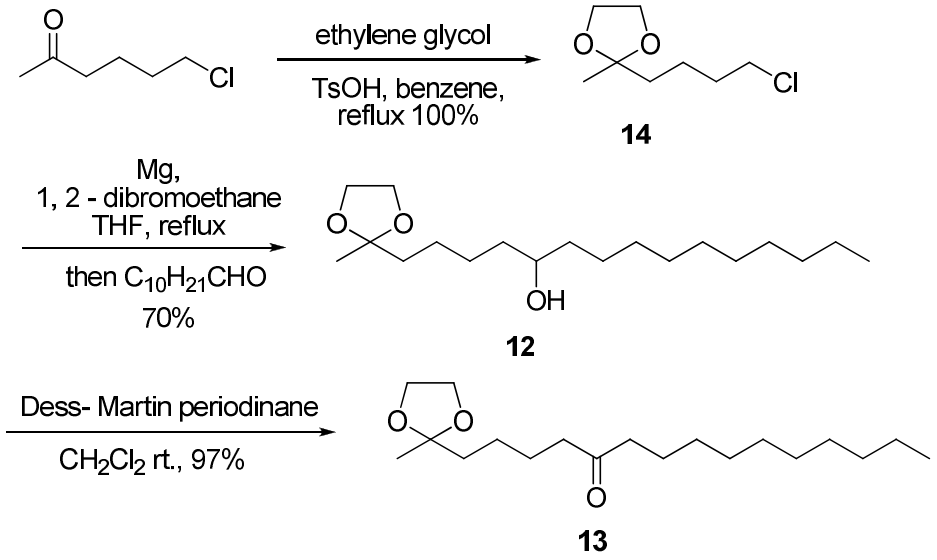
Scheme 9. Synthesis of diketal **1**.

In order to identify the two potential monoketone products from mono-deprotection of diketal **1**, 7-monoketone **13** was synthesized (Scheme 10). The synthesis of 7-monoketone **13** began with preparation of 6-iodo dioxolane **11**.[26] Two steps from commercially available 6-chloro-2-hexanone gave Grignard

substrate **11** with quantitative yield.[27] Subsequent Grignard reaction and oxidation by Dess-Martin periodinane finished the synthesis.[23, 24] When dioxalane **14** prepared from 6-chloro-2-hexanone was used to synthesize **12** via Grignard reaction, 1, 2-dibromoethane was added to overcome the weak reactivity of chloroalkane and to initiate the reaction under refluxing condition (Scheme11).[28]

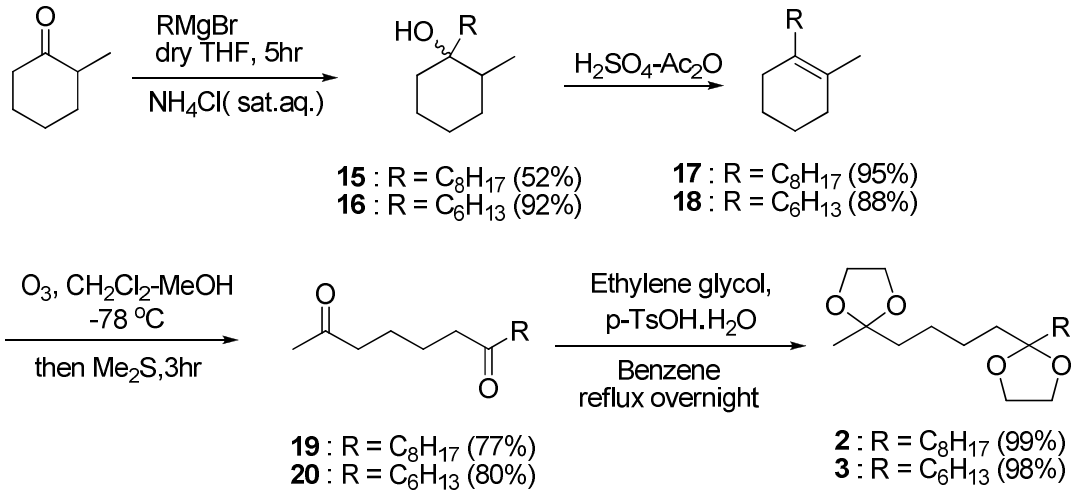


Scheme 10. Synthesis of 7-monoketone **13**.

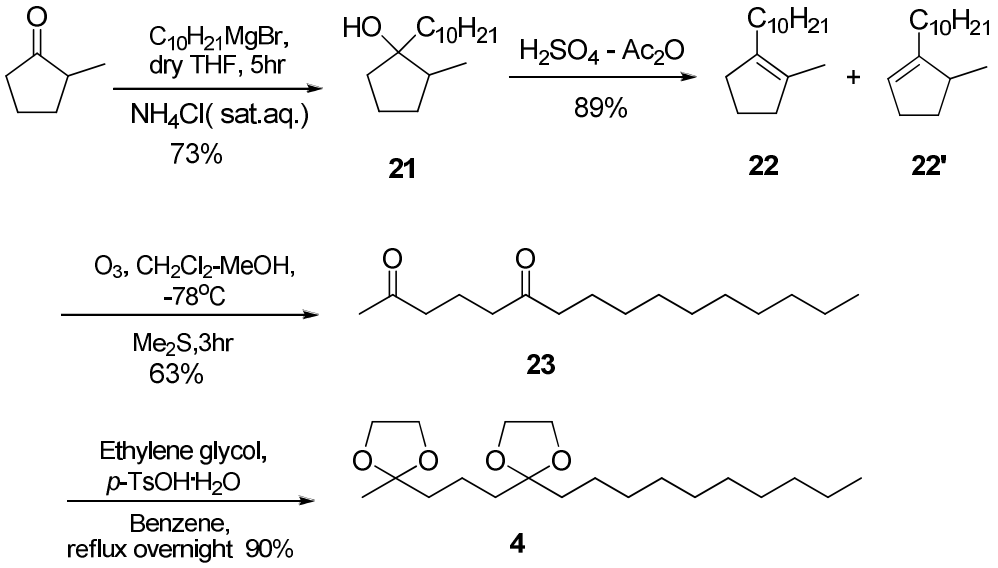


Scheme 11. Alternative synthesis of 7-monoketone **13** without transforming 6-chloro-2-hexanone to 6-iodo-2-hexanone.

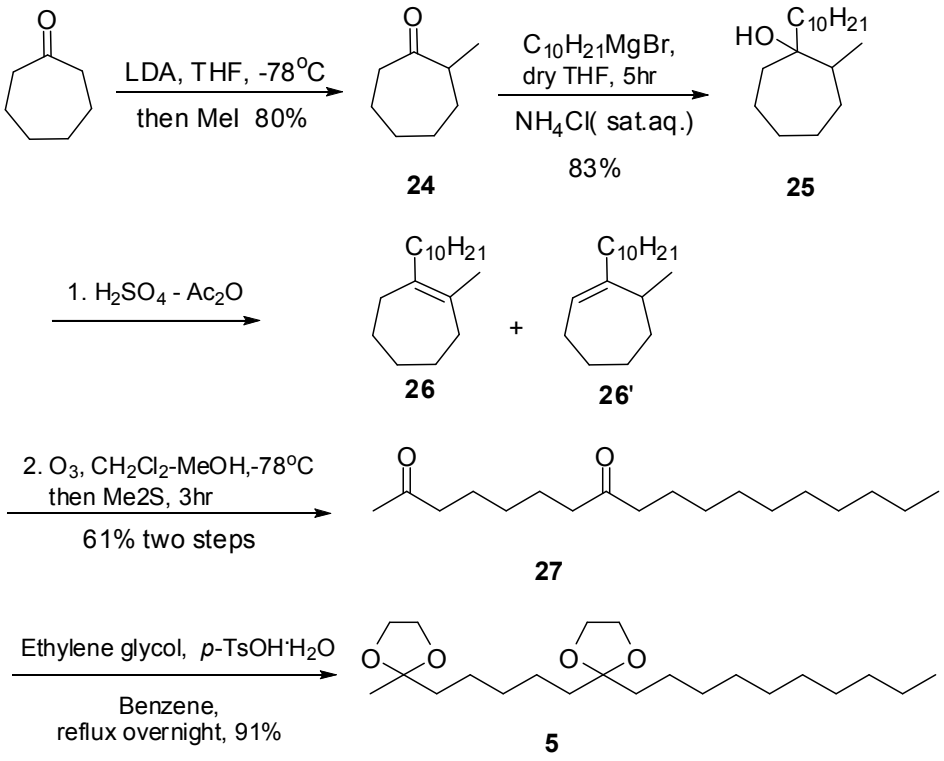
Diketal analogues **2** - **5** were synthesized similarly. Diketal **2** and **3** were respectively synthesized with an octyl and a hexyl chain (Scheme 12). Syntheses of diketal **4** started with 2-methyl cyclopentanone (Scheme 12). In addition, synthesis of diketal **5** began with lithium diisopropylamine-induced methylation to yield 2-methyl cycloheptanone **24** (Scheme 14).[29] Since dehydration in acidic condition to give cyclopentenes (**22** and **22'** in Scheme 13) and cycloheptenes (**26** and **26'** in Scheme 14) yields two isomers, the resulting isomers were ozonized without separation. Subsequent purification resulted in the desired diketones **23** and **27** respectively. Further protection of diketones gave diketals **4** and **5**.



Scheme 12. Syntheses of diketal **2** and **3**.

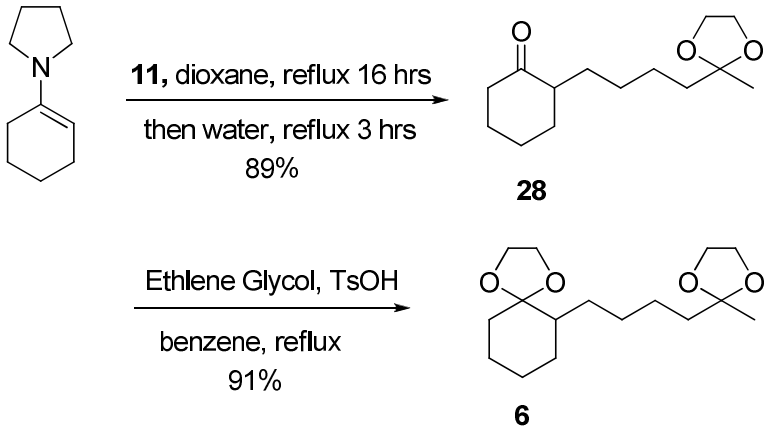


Scheme 13. Synthesis of diketal **4**.



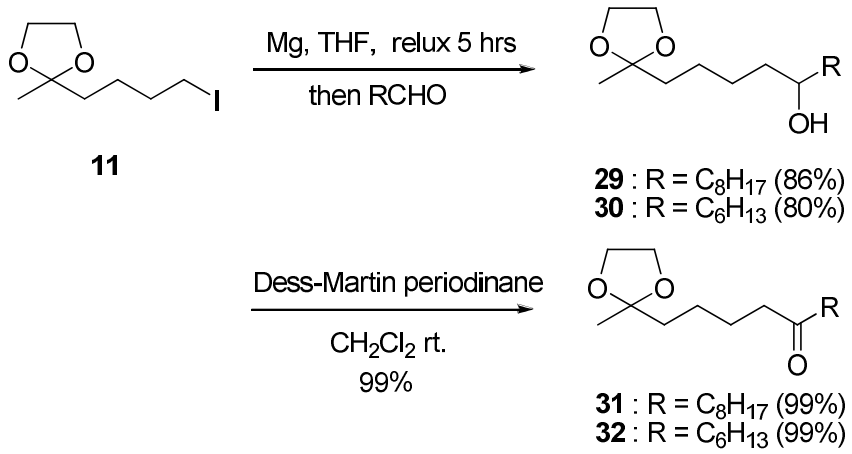
Scheme 14. Synthesis of diketal **5**.

Diketal **6** has a ring structure. Two steps from 1-pyrrolidino-1-cyclohexene gave Diketal **6** (Scheme 15).[30] Lithium diisopropylamine-induced alkylation from cyclohexanone gave product **28** with low yield.

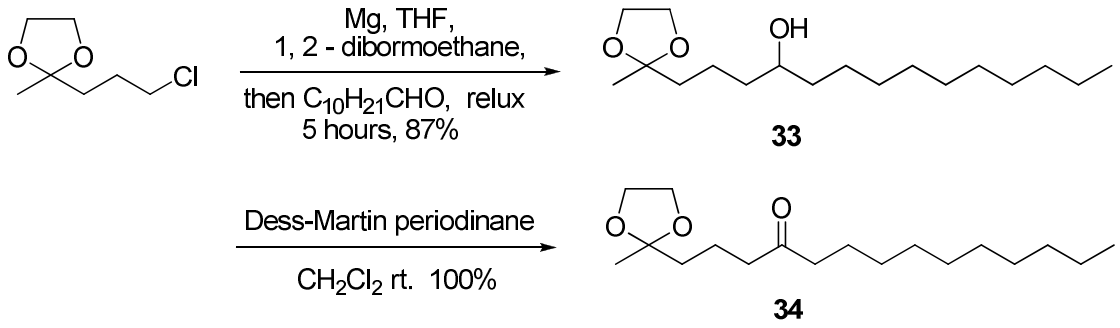


Scheme 15. Synthesis of diketal **6**.

Monoketones **31, 32** and **34** were synthesized in two steps including Grignard reaction and oxidation by Dess-Martin periodinane (Scheme 16 and 17). Synthesis of monoketone **34** began directly from commercially available 5-chloro-2-dioxolane.



Scheme 16. Syntheses of monoketone **31** and **32**.



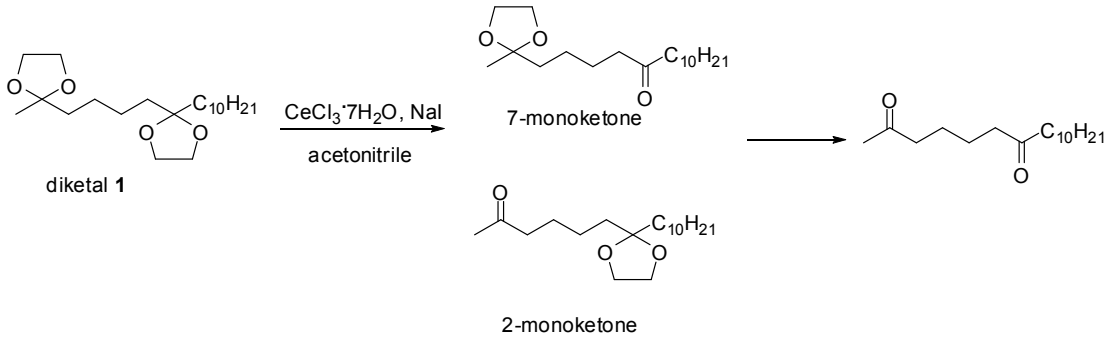
Scheme 17. Synthesis of monoketone **34**

Results and Discussion

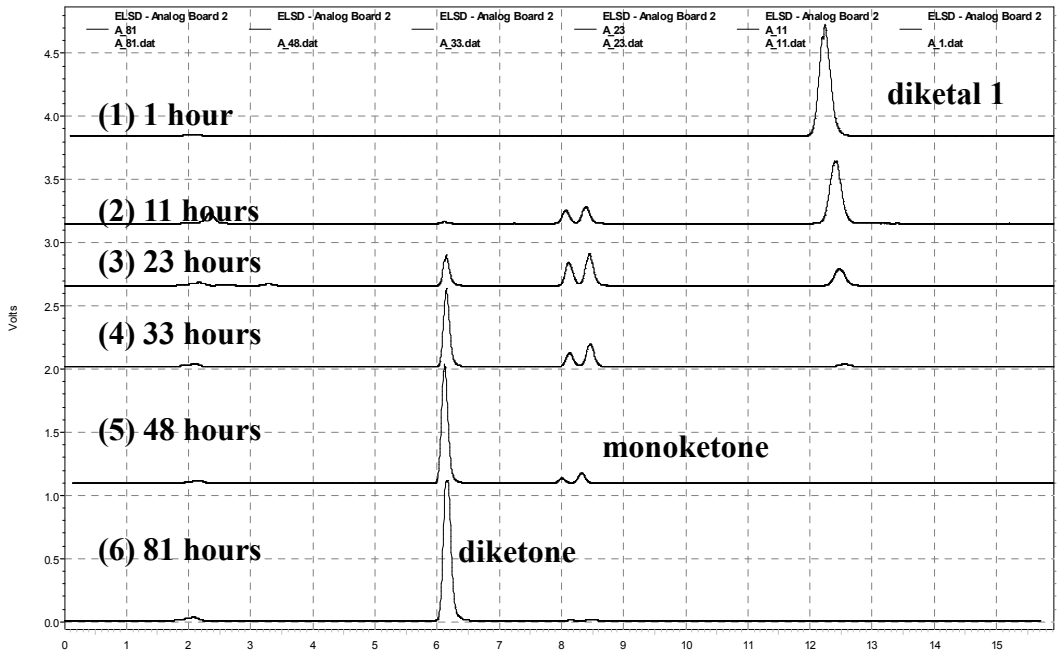
A. Monitoring method by HPLC

HPLC was used to monitor the deprotection reaction of the diketals. The deprotection reaction of diketal **1** catalyzed by $CeCl_3 \cdot 7H_2O$ and NaI in acetonitrile is given as an example to show the monitoring method by HPLC (Figure 3).[21] Deprotection reactions of other diketals and by other acids or catalysts were monitored in the same manner.

Figure 3 shows how the deprotection reaction of diketal **1** was monitored. Samples were taken at different reaction times to monitor the process of deprotection. Figure 3b shows the HPLC information of the reaction at 1, 11, 23, 33, 48, and 81 hours after the reaction started respectively. At 1 hour after the reaction started, only diketal **1** existed, which is the rightmost peak in the HPLC spectra (Figure 3b (1)). As the reaction continued, the twin peaks corresponding to the two monoketones appeared (see Figure 3b (2-5)). At 23 hours after the reaction started, there was substantial amount of diketone; at 81 hours after the reaction started, all the diketals and monoketones were deprotected to give diketone (see Figure 3b (3-6)).



(a)



(b)

Figure 3. (a) Deprotection of diketal **1** by $CeCl_3 \cdot 7H_2O$ and NaI in acetonitrile;[21] (b) HPLC spectra of reaction at (1) 1 hour; (2) 11 hours; (3) 23 hours; (4) 33 hours; (5) 48 hours; (6) 81 hours.

We further identified each peak in the HPLC spectrum for the species from the deprotection reaction of a diketal, including the diketal, the two monoketones, and the diketone. Here, the identification of the peaks corresponding to the four species in the deprotection reaction of diketal **1** is given as an example (Figure 4).

Figure 4 shows the method to identify each relevant HPLC peak. The bottom line shows peaks from a mixture of pure compounds, including diketal **1** (right), 7-monoketone **13** (middle), and diketone **9** (left); these peaks were individually identified (Figure 4a). The middle line shows the peaks from the sample taken from the deprotection reaction of diketal **1** by oxalic acid in methanol after 6 hours (Figure 4b). Thus, the combination of the two samples in Figure 4a and 4b verified that the rightmost peak in Figure 4b corresponded to diketal **1**, and that the leftmost peak signified diketone **9**.

The twin peaks left unidentified in Figure 4b were further distinguished by using 7-monoketone **13** (see Figure 4c). The sample used in Figure 4c included both the same reaction sample used in Figure 4b and some additional pure 7-monoketone **13**. The growing peak in Figure 4c confirms that 7-monoketone **13** has an HPLC retention time identical to that of the earlier-emerging peak of the two monoketone product peaks. This leaves the other one of the twin peaks as 2-monoketone.

Therefore, four species in the deprotection reaction, including diketal **1**, 2-monoketone, 7-monoketone **13**, and diketone **9** were identified. HPLC peaks from the deprotection of other diketals were identified in the same manner.

Thus, a HPLC-based method to monitor deprotection of diketal was

established and it became feasible to determine the percentages of each species during the deprotection process of the diketals.

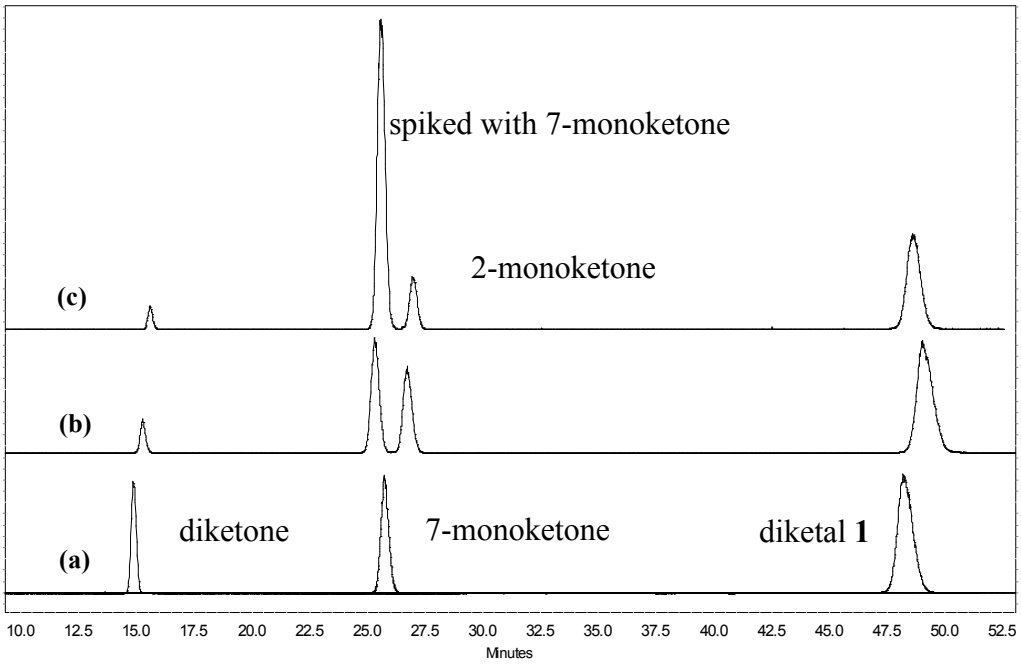


Figure 4. Identification of species in the deprotection reaction of diketal **1**: (a) mixture of pure compounds including diketal **1** (right peak), 7-monoketone (middle), and diketone (left); (b) a sample taken from reaction using oxalic acid as after 6 hours; (c) a same sample as used in (b) but spiked with 7-monoketone **13**.

B. Screening Process and Results

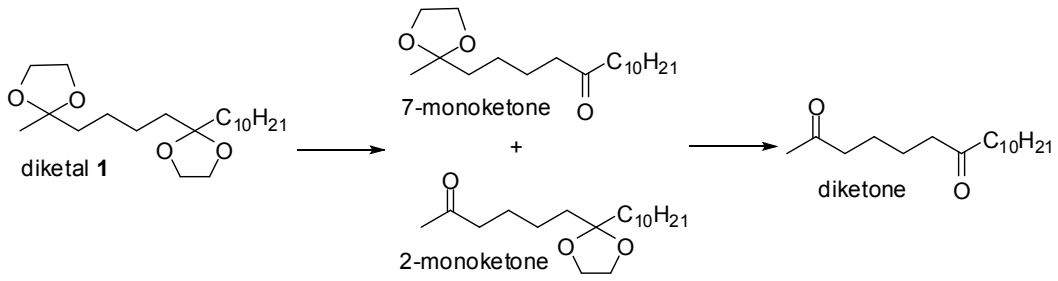
We started with diketal **1** to study the regioselective deprotection of two nearly identical ketals on a saturated carbon chain (Table 1). Both Lewis acids and Brønsted acids were used as catalysts to deprotect diketal **1**. Most acids and catalysts chosen have been reported to be used to deprotect ketals.

The acids or catalysts tested generally gave no chemically useful

selectivity, as shown in the last column of Table 1. The ratios of 7-monoketone over 2-monoketone shown in the table were the highest ratios observed during the process of deprotection of diketal **1** by each acid or catalyst, if the deprotection lasted sufficiently long. The ratios presented were based on the percentages of the two monoketones that were read directly from HPLC.[31]

When some strong Lewis acids were used, deprotection of diketal **1** was completed within minutes (see Table 1, entries 16 and 17). Both ketals on the saturated carbon chain were quickly deprotected to give diketone. In these cases, no regioselectivity could reasonably be expected, and thus no ratios were obtained. When the acids used were milder, deprotection took longer time, from hours to days (see Table 1, entries 1-15). Solvents with different polarities were also studied.

Table1. The highest ratios of 7-monotketone to 2-monoketone when diketal **1** was deprotected by various acids and catalysts.



Entry	Catalyst and Solvent	Time	Ratio of 7-monoketone /2 monoketone
1	PPTS in acetone [32]	5 h	1:1.4
2	PPTS in acetonitrile	5 h	1:1.3
3	PPTS in hexanes [a)]	no reaction after 3 days	
4	PPTS in methanol	5 h	1.3:1
5	$CeCl_3 \cdot 7H_2O$, NaI in acetonitrile [21]	3 d	1:2
6	$CeCl_3 \cdot 7H_2O$, NaI in methanol	5 d	1.4:1
7	TsOH in acetone [33]	6 h	1:2
8	TsOH in acetonitrile	5 h	1:1.3
9	PVTTS in methanol [a)]	4 h	3:1
10	Oxalic acid in methanol	6 h	1.7:1
11	$TiCl_4$ in ether [34]	1 h	2:1
12	HCl in acetone [35]	5 h	1:2
13	AcOH in acetone [36]	5 h	1:1.8
15	$PdCl_2$ in acetone [37]	3 h	1:1.5
16	AlI_3 in acetonitrile [38]	Completed in 5 minutes	
17	Ph_3CBF_4 in dicholoromethane [39]	Completed in 10 minutes	
18	$Er(OTf)_3$ in acetonitrile [40]	6 h	1.2:1
19	$MgSO_4$ in wet benzene [41 a), b)]	2 d	< 1:18

Table 1 (continued)

Entry	Catalyst and Solvent	Time	Ratio of 7-monoketone /2 monoketone
20	Lauric acid in methanol	no reaction after 2 days	
21	Lauric acid in pyridine	no reaction after 2 days	
22	$Mg(OTf)_3$ in methanol	no reaction after 2 days	
23	$MgCl_2 \cdot 7H_2O$ in wet benzene [a),b)]	no reaction after 2 days	
24	Magnesium phthalocyanine (dye) in methanol [a)]	no reaction after 2 days	
25	Magnesium phthalocyanine, NaI / methanol [b)]	no reaction after 2 days	

a) For those catalysts that do not dissolve in the reaction solvent, 100 mg was used.

b) Wet benzene was saturated with water and prepared by repeatedly shaking benzene with water.

During our screening, however, we did find one useful heterogeneous catalyst that significantly favored deprotection of one ketal over the other on the same saturated carbon chain: $MgSO_4$. A remarkable regioselective hydrolysis of the 2-positioned ketal (18:1) suggests that the deprotection under this specific condition favors deprotection of the terminal ketal over the middle one. HPLC data in Figure 5 and Table 2 show the process of deprotection and the ratios of reaction species at different times.

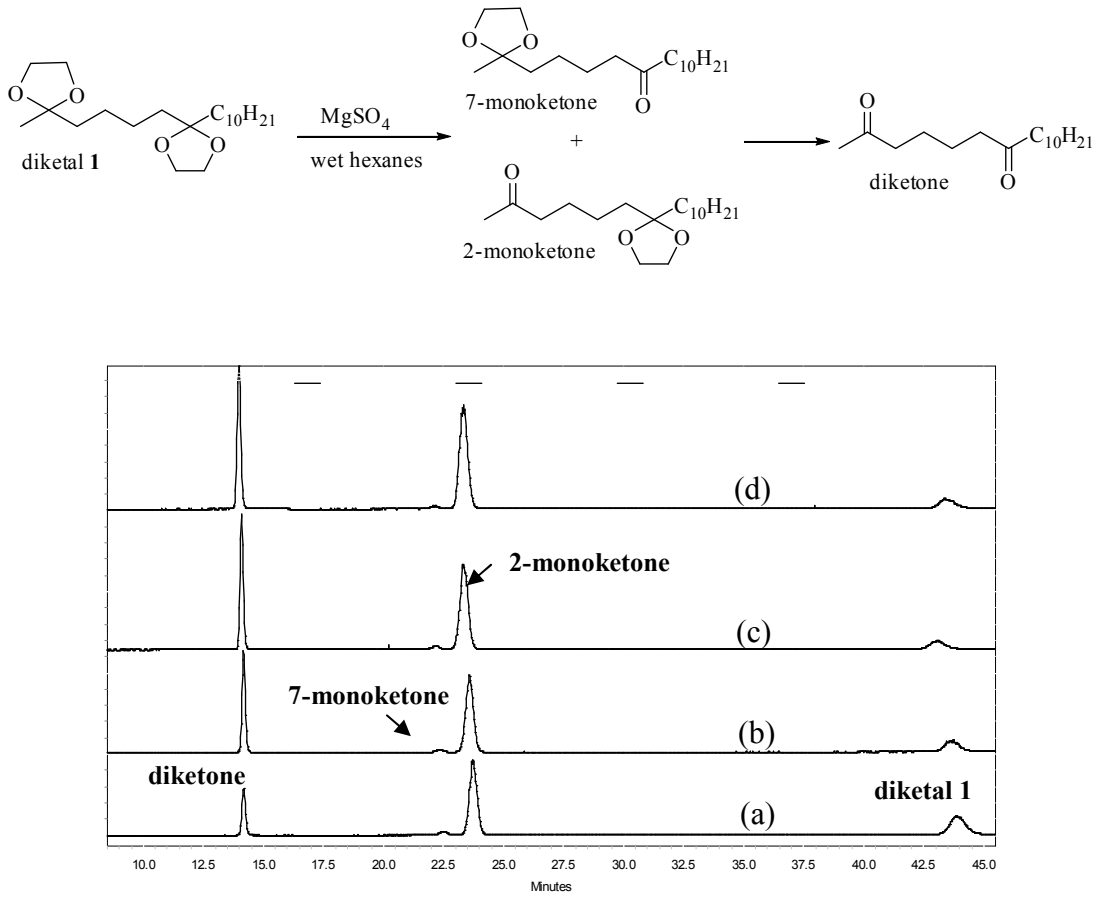
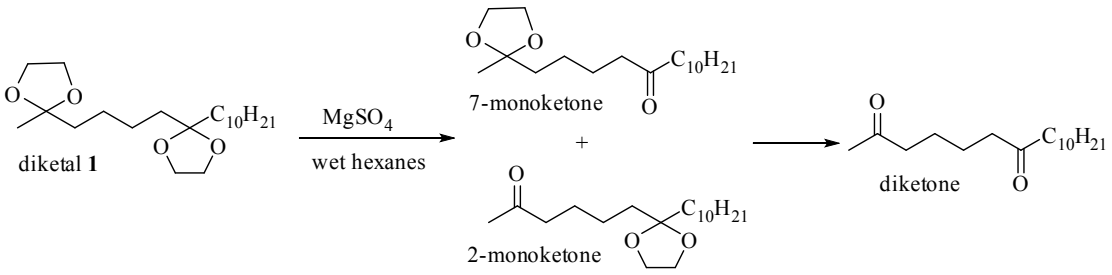


Figure 5. HPLC spectra of deprotection of diketal **1** using $MgSO_4$ in wet hexanes;[41] the peaks (in sequence of appearance from HPLC, from left to right) are diketone, 7-monoketone, 2-monoketone, and diketal **1** at (a) 8 hours, (b) 24 hours, (c) 48 hours, (d) 96 hours.

Table 2. Percentages of each specious during the deprotection of diketal **1** using $MgSO_4$ in wet hexanes.[41]



Time (hours)	diketone (%)	7-mono-ketone (%)	2-mono-ketone (%)	diketal **1** (%)	Ratio of 7-monoketone/ 2-monoketone
8	16	3	53	29	1:18
24	29	2	53	16	1:26
48	34	2	54	10	1:27
96	34	2	54	10	1:27

Several points were observed from Figure 5 and Table 2. First, the ratios of 7-monoketone over 2-monoketone were less than 1:18 (5.5%) all the time. Secondly, the product 7-monoketone accounted for less than 3% during the whole deprotecting process. Lastly, the regioselective product 2-monoketone accounts for more than 50% during the whole deprotecting process.[42]

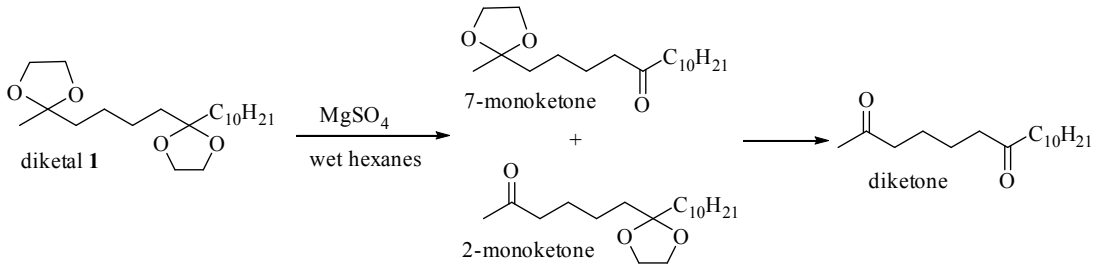
We made several preliminary conclusions based on the points observed above. Because the ratios of 7-monoketone and 2-monoketone were between 1:18 and 1:35, the hydrolysis of the ketal at 2-position is faster than that of the ketal at 7-position. Furthermore, 2-monoketone, which was from the hydrolysis of the ketal at 2-position, was the major product species of the reaction during this period of time, with percentage more than 50%. Thirdly, as expected, the

reaction shifted from diketal to diketone as diketal decreased and diketone increased. Lastly and most importantly, the reaction seemed to stop after 48 hours.

Studies were further carried out by using different doses of $MgSO_4$ as catalyst and different solvents (Table 3). Six different solvents were tested. All the solvents used were saturated with water. Three of them showed regioselectivity: benzene, toluene, and hexanes. The other three solvents, ethyl acetate, chloroform, and acetonitrile showed no reaction after 3 days. Interestingly, when 50 mg $MgSO_4$ was used, no reaction happened after 3 days in both wet benzene and wet toluene. There was little difference in regioselectivity when doubling the amount of $MgSO_4$ to 200 mg.

Deprotection of five other diketal analogues catalyzed by $MgSO_4$ were also tested (Table 4).[41] The ketal deprotection was catalyzed by $MgSO_4$ in wet hexanes. As Table 4 shows, all the diketal analogues were regioselectively deprotected. The ratios between two isomeric monoketone products varied from 1:24 to 1:55. For diketal **3** and **6**, only 2-monoketones were found in each case and no (7, or 8)-monoketones or diketones were detected. Thus complete positional selectivity was realized for diketal **3** and **6**. Continued monitoring of deprotection of diketal **3** and **6** showed that diketone began to appear after around four days, however, in neither case was (7,or 8)-monoketone found. For example, after 6 days, 7% of diketone from the deprotection of diketal **6** was detected, together with 18% of 2-monoketone and 75% of diketal **6**.

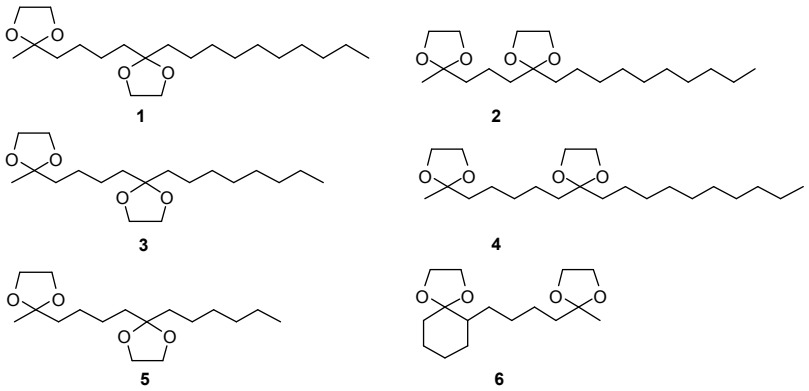
Table 3. Deprotection of diketal **1** using $MgSO_4$ as catalyst.[41]



Entry	$MgSO_4$ (mg)	Solvent	Time	Ratio of 7-monoketone/ 2-monoketone
1	200	wet benzene	20 h	1 : 16
2	100	wet benzene	60 h	1 : 16
3	50	wet benzene	72 h	x
4	200	wet toluene	20 h	1 : 10
5	100	wet toluene	40 h	1 : 10
6	50	wet toluene	72 h	x
7	200	wet ethyl acetate	72 h	x
8	200	wet chloroform	72 h	x
9	200	wet hexanes	20 h	1: 18
10	200	wet acetonitrile	72 h	x

Note: Wet solvent was saturated with water and prepared by repeatedly shaking benzene with water.

Table 4. Deprotection of diketals **1**-**6** using $MgSO_4$ in wet hexanes after 24 hours.[41]



diketal	Diketone (%)	(6,7, or 8-monoketone (%)	2-monoketone (%)	Diketal (%)	Ratio of (6,7,or 8)-monoketone/ 2-monoketone
1	21	3	58	18	1:19
2	14	1	60	25	1:55
3	0	0	18[a]	82	0
4	10	1	46	43	1:34
5	47	2	45	6	1:24
6	0	0	20[a]	80	0

[a] Little change was observed in another 24 hours.

C. Discussion

The mechanism behind the regioselective deprotection by $MgSO_4$ of one of two nearly identical ketal functionalities on a saturated carbon chain remains unclear. However, based on the information we observed from the reactions carried out in the conditions mentioned above, we have proposed a mechanism centering on bidentate binding of the diketals on the $MgSO_4$ surface (Figure 6).

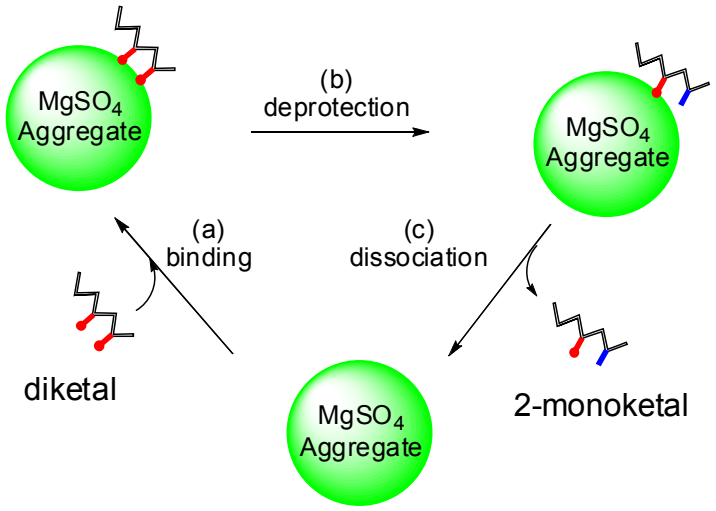


Figure 6. Proposed mechanism for regioselective deprotection of diketal catalyzed by $MgSO_4$ through bidentate binding. (a) bidentate binding of diketal to $MgSO_4$; (b) regioselective deprotection of ketal at 2-position; (c) dissociation of monoketals from $MgSO_4$.

The pertinent information used to support our proposed mechanism includes the following. First, the product 7-monoketone accounted for less than 3% during the whole deprotection process of diketal **1**. Secondly, the regioselective product 2-monoketone accounted for more than 50% during the whole deprotection process.[42] Thirdly, the deprotection reaction of diketal **1** seemed to stop after 2-3 days.

We surmise that effective binding to the $MgSO_4$ interface requires chelation to two ketals within the same molecule, after which only one is hydrolyzed (Figure 6). Thereupon, the reactant dissociates from the $MgSO_4$ surface, leading to the production of mainly mono-hydrolyzed product (Figure 6b). The mechanism of chelation to two ketals within the same molecule explains the

fact that the regioselective product 2-monoketone accounts for more than 50% during the whole deprotecting process because 2-monoketone could not effectively bind to the $MgSO_4$ interface.

This proposed mechanism was further supported by the experiment where 2-monoketone **13** was independently subject to the same deprotection condition as diketal **1** and was not deprotected to give diketone by $MgSO_4$.

Another reason that has also led us to believe that bidentate binding induced the observed regioselectivity is the stark contrast between nonpolar solvents and polar solvents used in the deprotection reactions (Table 3). Such contrast can be rationalized by the effect of the solvent's polarity on noncovalent binding of the diketals to the $MgSO_4$ surface, just like the regioselective enzymatic acylation of monosaccharide derivatives (Figure 2). When nonpolar solvents were used, the bidentate binding was facilitated and diketals were regioselectively deprotected; while polar solvents were used, the $MgSO_4$ surface became less appealing to the diketal and no protection occured.

It is suggested, therefore, that regioselectivity is predicated upon tight bidentate binding of the reactant followed by loose or non-existent monodentate binding of the product. The fact that bis-hydrolysis product was observed (Table 2) implies that it was formed prior to dissociation of the mono-product from the catalyst surface. A more detailed explanation of the observed regioselectivity demands more speculation due to lack of relevant experimental information.

It is acknowledged that 2-positioned ketal and 7-positioned ketal are not exactly identical due to the small difference between the primary methyl group

and the long carbon chain, and thus it is indisputable that the regioselective deprotection may possibly arise from such subtle difference. Further experiment is necessary to clarify this point where the primary methyl group is substituted by secondary carbon groups to determine the influence of such subtle difference. However, even if such difference plays a role in the regioselective deprotection, it alone will not suffice to produce the regioselectivity as we have observed no regioselectivity from the deprotection reactions by other catalysts. Thus, such difference's impact on regioselectivity must be magnified by or in combination with other factors, such as noncovalent bonding and cavitary restraint (here semi-cavitary restraint on the $MgSO_4$ surface).

D. Future Work

It is undoubtedly important to understand the origin of the regioselectivity as observed in the deprotection of diketals. As mentioned in the previous paragraph, we need to verify or eliminate the possibility that the observed regioselectivity resulted from the difference between the methyl group next to the 2-positioned ketal and the long chain adjacent to the middle ketal. For example, the methyl group next to the 2-positioned ketal can be substituted by ethyl group. If the regioselectivity disappears or substantially diminishes, it is then proved that the difference between the methyl group and the long chain of the diketal plays an important role in the observed regioselectivity after the bidentate binding. However, if the regioselectivity remains, some factors other than the subtle steric effect dominate the stage of regioselective deprotection of the diketals.[43]

Studies of position-selective deprotection of the diketals by specially designed catalysts have also been considered. For example, polymers such as dendrimers can create cavities with only limited access. Therefore, catalysts incorporated into polymers may have limited accessibility, and thus may regioselectively deprotect only one of the two identical ketals on a saturated carbon chain as a result of noncovalent binding and cavitary restraint. Self-assembly such as micelles gives an alternative approach. Our group has studied the rate dependence on sulfur location within the chains during the process of thioether oxidation to sulfoxide in micelles.[44] The underlying study method can also be applied to selectively deprotect our model compound diketal.

Conclusion[46]

A group of diketal analogues has been synthesized and tested for position-based regioselectivity. Diverse acids and catalysts have been examined to study regioselective deprotection of the diketals. As a result, $MgSO_4$ in nonpolar solvent has been discovered to regioselectively deprotect only one of the two identical ketal functionalities on the saturated carbon chain. The experiment results have directed to the mechanism based on bidentate biding of the diketals to the $MgSO_4$ surface. The detailed mechanism of the unusual regioselectivity remains unclear. Nonetheless, the results offer an interesting starting point in the long journey to explore the position-based regioselectivity. In addition, our data constitute a feasibility study that should encourage further research into ‘‘surface-imposed regioselectivity’’. An ability to operate on only one of two nearly identical distant functional groups constitutes a synthetically important technology. It is to be hoped that with the appropriately designed catalysts, molecular position, rather than classical stereoelectronic factors, will someday play a bigger role in dictating the outcome of synthetic reactions.

Experimental

A. HPLC monitoring

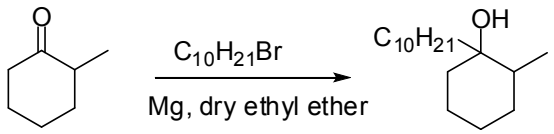
All the reactions were carried out in 4ml glass vials. 2ml 1mg/ml diketal solution was added into a vial followed by 10%mol of catalyst. 100mg catalysts, if not otherwise provided, were used for those catalysts that do not dissolve in reaction solvent. After stirring at room temperature for a certain period of time which varied with catalysts as specifically indicated, 100*u*l of solution was withdrawn, filtered with 13mm syringe filter (0.2 *u*m pore size), and injected into HPLC. In order to monitor the reaction process more efficiently, a HPLC-ELSD (Evaporating Light Scattering Detector) system was set up. ELSD was used to nebulize the column effluent to an aerosol, vaporize the solvent to produce small solute droplets, and then detect the degree of scattering.[45] Each reaction species was detected by ELSD and the data collected were processed by computer to give percentages.[42]

The HPLC/ELSD system includes a low pressure gradient pump (Shimadzu LC-10AT *vp*) and an evaporative light scattering detector (ELSD) (Sedex-55). Column used in all the tests was Alltima (C18) 5u, 250mm x 4.6mm. Methanol with 15% water was used as an isocratic mobile phase with a flow rate at 1.0 ml min^{-1}. A Rheodyne injection system (7725i) with 20µl sample loop was employed. The temperature of the evaporative light scattering detector was set at 30 º C, and Nitrogen gas flow rate at 2.2 bars.

B. Synthesis

Materials. All reagents were purchased from Aldrich or Bachem and used without additional purification. All solvents used were reagent or HPLC grade and dried over 4 Å molecular sieves.

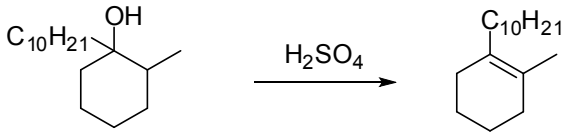
Characterization Methods. ^{1}H and ^{13}C NMR spectra were acquired on a Varian INOVA 400 MHz (100 MHz for ^{13}C) instrument at the NMR Center (Emory Univeristy). Mass spectra experiments were completed by the Emory University Mass Spectrometry Center. Elemental analyses were performed by Atlantic Microlab in Norcross, GA. Melting points were conducted on a Thomas Hoover capillary melting point apparatus and are uncorrected. All final products were dried in vacuum over P_2O_5.



7

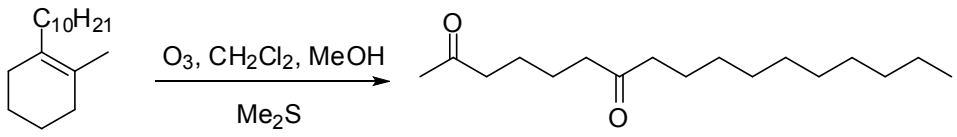
1-Decyl-2-methyl-cyclohexanol (7). To 1.02g (43mmol) Mg turnings in 40ml anhydrous ethyl ether at 0 ^{o}C was dropwise added 3.0ml n-$C_{10}H_{21}Br$ (3.13g, MW 221.19, 14 mmol) over 40 min. The solution was stirred for 1h at 0 ^{o}C and then at r.t. for 4h. The liquid layer was transferred via transfer cannula to another flask under N_2 before cooling down to 0 ^{o}C. 0.79g 2-methylcyclohexanone (MW 112.17, 7.0mmol) in 25 ml anhydrous ethyl ether was then added over 30 min. The solution was warmed up to r.t., stirred for another 4h, poured into 100ml

saturated NH_4Cl and extracted with ethyl ether (3 x 80ml). The ethyl ether solution was washed with water and brine, dried over $MgSO_4$, and concentrated to give crude product. Flash chromatography on silica gel (10:1 hexanes/EtOAc) gave 1.52g (85%) of **7** as colorless oil: ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.84-0.87 (m, 6H), 1.25-1.70 (m, 27H); ^{13}C NMR ($CDCl_3$, 300MHz) δ 14.3, 15.1, 22.0, 22.9, 23.8, 26.0, 29.6, 29.8, 29.9, 30.6, 30.7, 32.1, 36.3, 38.1, 41.2, 73.2; HRMS Calcd. for $C_{17}H_{35}O$ $[M + H]^+$: 255.2688. Found: 255.2695.



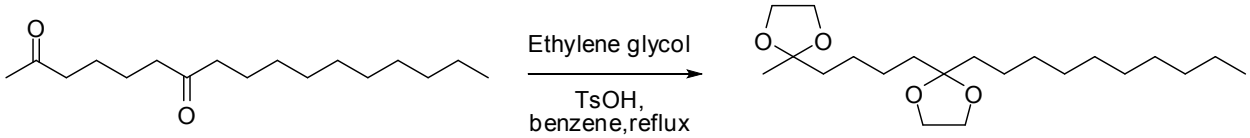
7 **8**

1-Decyl-2-methyl-cyclohexene (**8**)**.** To a solution of **7** (1.52g, MW 254.45, 6.0mmol) in 5ml of acetic acid at r.t., was added a solution of 1.0ml conc. sulfuric acid in 2ml acetic acid. The solution was stirred at r.t. for 1h. 100ml water was then added in and the solution was extracted with hexanes (3 x 80ml). The hexanes layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to give crude product. Flash chromatography on silica gel (hexanes) gave 1.30g (92%) of **8** as colorless oil: ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.89 (t, *J* = 6.6, 3H), 1.27 (br, 16H), 1.56-1.60 (m, 7H), 1.92-1.98 (m, 6H); ^{13}C NMR ($CDCl_3$, 300MHz) δ 14.4, 19.2, 22.9, 23.7, 23.8, 28.5, 29.6, 29.8, 29.9, 30.0, 32.1, 32.2, 33.7, 125.8, 130.6; Anal. Calcd. for $C_{17}H_{32}$: C, 86.35; H, 13.65. Found: C, 86.47; 13.74.



8 **9**

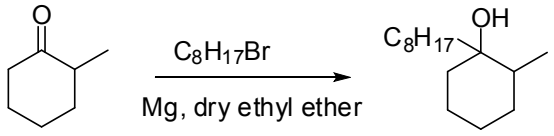
Heptadecane-2,7-dione (9). An ozone stream was passed through a solution of 510mg **8** (MW 236.44, 2.2mmol) in CH_2Cl_2 (30ml) and methanol (30ml) at -78 ^oC until the solution was saturated with ozone which is blue. Excess ozone was removed by O_2. Me_2S (1ml) was then added at -78 ^oC. The solution was stirred for 1h and then at r.t. for 2h. The solvent was evaporated to give crude product. The crude product was subjected to flash chromatography on silica gel (10:1 hexanes/ EtOAc) to give 417mg **9** (72%) as white foam: mp 68-69 ^oC; ^1H NMR ($CDCl_3$, 400MHz) δ 0.88 (t, J = 6.8, 3H), 1.26 (br, 14H), 1.55-1.58 (m, 6H), 2.14 (s, 3H), 2.37-2.45 (m, 6H); ^{13}C NMR ($CDCl_3$, 300MHz) δ 14.3, 22.9, 23.4, 23.5, 24.1, 29.5, 29.6, 29.7, 29.8, 30.1, 32.1, 42.6, 43.1, 43.7, 209.0, 211.3; HRMS Calcd. for $C_{17}H_{32}O_2Li$ $[M + Li]^+$: 275.2562. Found: 275.2553; Anal. Calcd. for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 75.99; H, 12.04.



9 **1**

Heptadecane-2,7-dioxolane (1). A solution of 382mg **9** (MW 268.43, 1.4mmol), 20mg TsOH and ethylene glycol (0.8g, 12.9mmol) in 60ml dry benzene was

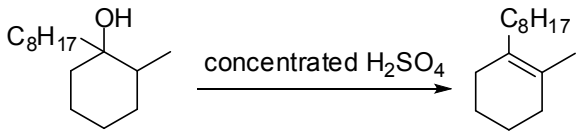
refluxed overnight with Dean-Stark apparatus. The solvent was removed to give the crude product. Flash chromatography on silica gel (10:3 hexanes/EtOAc) gave pure 480mg **1** (95%) as white solid: m.p.34 ^{o}C; ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.86 (t, *J* = 6.4, 3H), 1.24-1.37 (m, 23H), 1.54-1.62 (m, 6H), 3.90-3.93 (m, 8H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.29, 22.86, 23.88, 24.02, 24.27, 24.57, 29.50, 29.79, 30.12, 32.08, 37.21, 37.27, 39.33, 64.77, 65. 03, 110.25, 111.95; HRMS Calcd. for $C_{21}H40O_4Li$ $[M + Li]^+$: 363.3087. Found: 363.3103; Anal. Calcd. for $C_{21}H_{40}O_4$: C, 70.74; H, 11.31. Found: C, 70.95; H, 11.45.



15

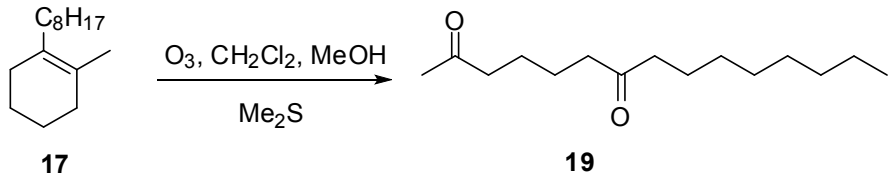
2-Methyl-1-octyl-cyclohexanol (15). Under N_2, 6ml of n-$C_8H_{17}Br$ (6.7g, MW 193.13, 35 mmol) was dropwise added into 7.2g Mg turnings (300mmol) in 50ml anhydrous ethyl ether at 0 ^{o}C over 30 min. The solution was stirred for 1h at 0 ^{o}C and then at r.t. for 4h. The liquid layer was dropwise transferred via cannula under N_2 to 2-methyl-cyclohexanone (1.95g, MW 112.17, 17.4mmol) in 20 ml anhydrous ethyl ether at 0 ^{o}C over 30 min. The solution was warmed up to r.t., stirred for 3h, poured into 100ml saturated NH_4Cl and extracted with ethyl ether (3 x 60ml). The ethyl ether solution was washed with water and brine, dried over $MgSO_4$, and concentrated to give crude product. Flash chromatography on silica gel (5:1 hexanes/EtOAc) gave 2.1g (52%) of **15** as colorless oil: ^{1}H NMR ($CDCl_3$,

400MHz) δ 0.84-0.89 (m, 6H), 1.27-1.52 (m, 24H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.30, 15.08, 22.05, 22.87, 23.85, 26.02, 29.50, 29.81, 30.57, 30.75, 32.10, 36.30, 38.08, 41.25, 73.19; Anal. Calcd. for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.28; H, 13.48.



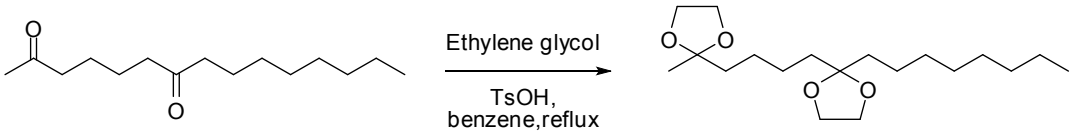
15 **17**

1-Methyl-2-octyl-cyclohexene (17). To a solution of **15** (2.1g, MW 226.23, 9.14mmol) in 8ml of acetic acid at r.t., was added 1.5ml conc. sulfuric acid in 3ml acetic acid. The solution was stirred at r.t. for 3h. 100ml water was added in and the solution was extracted with hexanes (3 x 80ml). The hexanes layers were washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to give crude product. Flash chromatography on silica gel (hexanes) gave 1.8g (95%) of **17** as colorless oil. Further purification was carried out after next step. ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.91-0.95 (t, *J* = 6.4, 3H), 1.32-1.38 (br, 13H), 1.59-1.64 (m, 6H), 1.96-2.03 (m, 6H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.30, 19.14, 22.97, 23.71, 23.80, 28.54, 29.65, 29.80, 29.92, 30.07, 32.08, 32.22, 33.72, 125.75, 130.49.



17 **19**

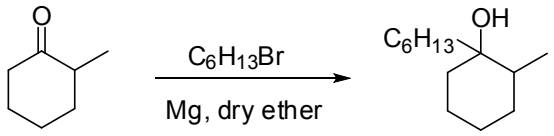
Diketone (19). An ozone stream was passed through a solution of **17** (1.8g, MW 208.22, 8.7mmol) in CH_2Cl_2 (30ml) and methanol (30ml) at -78 ^oC until the solution was saturated with ozone which is blue. Excess ozone was removed by O_2. Me_2S (6ml) was then added at -78 ^oC. The solution was stirred for 1h and then at r.t. for 2h. The solvent was evaporated to give crude product. Flash chromatography (6:1 hexanes/EtOAc) afforded 1.61g of diektone **19** (77%) as white solid: ^1H NMR ($CDCl_3$, 400MHz) δ 0.84-0.87 (t, J = 6.8, 3H), 1.24 (br, 10H), 1.52-1.55 (m, 6H), 2.11 (s, 3H), 2.34-2.42 (m, 6H); ^{13}C NMR ($CDCl_3$, 300MHz) δ 14.25, 22.80, 23.35, 23.43, 24.01, 29.29, 29.40, 29.52, 30.06, 31.97, 42.57, 43.04, 43.62, 208.90, 211.24. HRMS Calcd. for $C_{15}H_{28}O_2Li$ $[M + Li]^+$: 247.2249. Found: 247.2245.



19 **2**

Diketal (2). A solution of diketone **19** (0.34g, 328.49, 1.0mmol), 30mg $TsOH \cdot H_2O$, and ethylene glycol (1.0g, MW 62.04, 16mmol) in 70ml dry benzene was refluxed overnight with Dean-Stark apparatus. The solvent was removed to give the crude product. Flash chromatography (6:1 hexanes/EtOAc) afforded 340mg diketal **2**

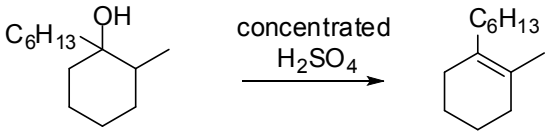
(99%) as white solid: ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.80-0.83 (t, *J* = 6.8, 3H), 1.20-1.33 (m, 19H), 1.49-1.59 (m, 6H), 3.84-3.88 (m, 8H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.18, 22.73, 23.77, 23.91, 24.16, 24.46, 29.34, 29.65, 30.02, 31.95, 37.10, 37.16, 39.24, 64.65, 64.91, 110.12, 111.81; HRMS Calcd. for $C_{19}H_{37}O_4$ $[M+H]^+$ 329.2692, found 329.2693; Anal. Calcd. for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05. Found: C, 69.63; H, 11.12.



16

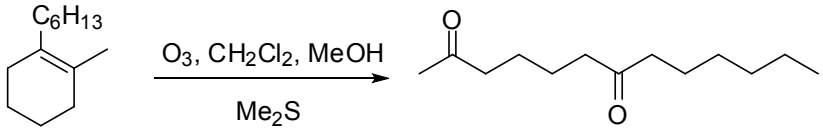
1-Hexyl-2-methyl-cyclohexanol (**16).** Under N_2, 2ml of n-$C_6H_{13}Br$ (2.35g, MW 165.08, 14.2 mmol) was dropwise added into 1.8g Mg turnings (75mmol) in 50ml anhydrous ethyl ether at 0 ^{o}C over 30 min. The solution was stirred for 1h at 0 ^{o}C and then at r.t. for 4h. The liquid layer was dropwise transferred via cannula under N_2 to 2-methylcyclohexanone (0.74g, MW 112.17, 6.6mmol) in 20 ml anhydrous ethyl ether at 0 ^{o}C over 30 min. The solution was warmed up to r.t., stirred for 3h, poured into 100ml saturated NH_4Cl and extracted with ethyl ether (3 x 60ml). The ethyl ether solution was washed with water and brine, dried over $MgSO_4$, and concentrated to give crude product. Flash chromatography on silica gel (6:1 hexanes/EtOAc) gave 1.20g of **16** (92%) as colorless oil: ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.83-0.88 (m, 6H), 1.26-1.64 (m, 20H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.24, 15.04, 22.01, 22.81, 23.79, 26.00, 30.21, 30.71, 32.03, 36.27, 38.07,

41.23, 73.13; Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.31; H, 13.25.



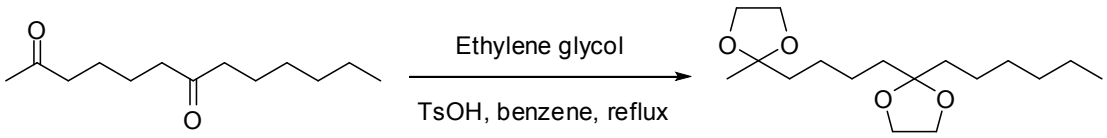
16 **18**

1-Hexyl-2-methyl-cyclohexene (**18).** To a solution of **16** (0.88g, MW 198.34, 4.4mmol) in 5ml of acetic acid at r.t., was added 1ml conc. sulfuric acid in 2ml acetic acid. After the solution was stirred at room temperature for 3h, 30ml water was added in and the solution was extracted with hexanes (3 x 30ml). The hexanes layers were combined and washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to give crude product. Flash chromatography on silica gel (hexanes) gave 0.70g (88%) of **18**. Further purification was carried out after next step. ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.91-0.94 (t, *J* = 6.8, 3H), 1.29-1.39 (br, 9H), 1.59-1.63 (m, 6H), 1.96-2.02 (m, 6H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.33, 19.16, 22.98, 23.74, 23.83, 28.53, 29.75, 29.83, 32.10, 32.20, 33.75, 125.80, 130.53.



18 **20**

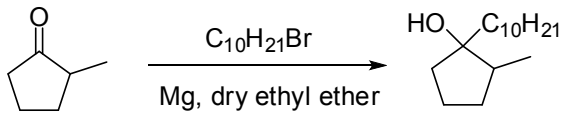
Diktone (20). An ozone stream was passed through a solution of **18** (698mg, MW 180.34, 3.9mmol) in CH_2Cl_2 (30ml) and methanol (30ml) at -78 ^oC until the solution was saturated with ozone which is blue. Excess ozone was removed by O_2. Me_2S (5ml) was then added at -78 ^oC. The solution was stirred for 1h and then at r.t. for 2h. The solvent was evaporated to give crude product. Flash chromatography on silica gel (6:1 hexanes/EtOAc) afforded 662mg of diketone **20** (80%) as white solid: ^1H NMR ($CDCl_3$, 400MHz) δ 0.83-0.87 (t, J = 6.8, 3H), 1.24-1.27 (br, 6H), 1.51-1.54 (m, 6H), 2.11 (s, 3H), 2.34-2.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.16, 22.62, 23.32, 23.40, 23.94, 29.04, 30.04, 31.73, 42.54, 43.01, 43.59, 208.90, 211.24; HRMS Calcd. for $C_{13}H_{25}O_2$ $[M+H]^+$ 213.1849, found 213.1849; Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.60; H, 11.46.



20 **3**

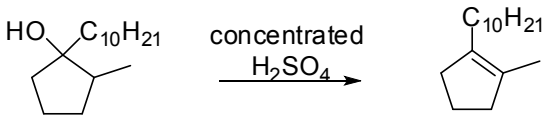
Diketal (3). A solution of diketone **20** (0.93g, 212.34, 4.4mmol), 30mg $TsOH{\cdot}H_2O$, and ethylene glycol (2.7g, MW 62.04, 44mmol) in 70ml dry benzene was refluxed overnight with Dean-Stark apparatus. The solvent was removed to give the crude product. Flash chromatography (6:1 hexanes/EtOAc) afforded 1.30mg diketal **3** (98%) as colorless oil: ^1H NMR ($CDCl_3$, 400MHz) δ 0.75-0.79 (t, J = 6.4, 3H), 1.17-1.27 (br, 15H), 1.45-1.53 (m, 6H), 3.79-3.83 (m, 8H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.06, 22.58, 23.67, 23.77, 24.06, 24.35, 29.58, 31.82, 37.01, 37.07,

39.14, 64.54, 64.80, 109.99, 111.68; HRMS Calcd. for $C_{17}H_{33}O_4$ $[M+H]^+$ 301.2379, found 301.2365; Anal. Calcd. for $C_{17}H_{32}O_4$: C, 67.96; H, 10.74. Found: C, 68.15; H, 10.80.



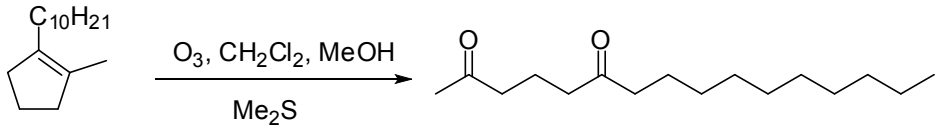
21

1-Decyl-2-methyl-cyclopentanol (21). Under N_2, 2ml of n-$C_{10}H_{21}Br$ (2.14g, MW 221.19, 9.7 mmol) was dropwise added into 3.0g Mg turnings (125mmol) in 50ml anhydrous ethyl ether at 0 ^oC over 30 min. The solution was stirred for 1h at 0 ^oC and then at r.t. for 4h. The liquid layer was dropwise transferred via cannula under N_2 to 2-methylcyclopentanone (0.46g, MW 98.15, 4.7mmol) in 10 ml anhydrous ethyl ether at 0 ^oC over 30 min. The solution was warmed up to r.t., stirred for 5h, poured into 100ml saturated NH_4Cl and extracted with ethyl ether (3 x 30ml). The ethyl ether solution was washed with water and brine, dried over $MgSO_4$, and concentrated to give crude product. Flash chromatography on silica gel (5:1 hexanes/EtOAc) gave 825mg of **21** (73%) as colorless oil: ^1H NMR ($CDCl_3$, 400MHz) δ 0.83-0.90 (m, 6H), 1.24-1.79 (br, 26H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 12.70, 14.31, 21.13, 22.89, 24.87, 29.55, 29.84, 29.87, 30.57, 32.11, 32.23, 38.38, 39.67, 43.01, 82.31; Anal. Calcd. $C_{16}H_{32}O$: C, 79.93; H, 13.42. Found: C, 79.95; H, 13.58.



21 **22**

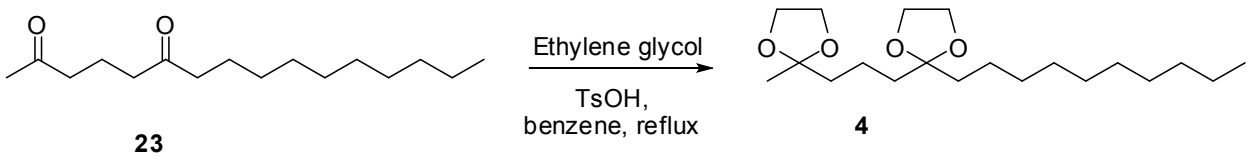
1-Decyl-2-methyl-cyclopentene (22). To a solution of **21** (0.45g, MW 240.42, 1.9mmol) in 3ml of acetic acid at r.t., was added 1ml conc. sulfuric acid in 1ml acetic acid. After the solution was stirred at r.t. for 3h, 30ml water was added in and the solution was extracted with hexanes (3 x 30ml). The hexanes layers were combined and washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to give crude product. Flash chromatography on silica gel (hexanes) gave 0.37g of **22** (89%) as colorless oil. Further purification was carried out after next step to remove isomer. ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.90-0.93 (t, *J* = 6.4, 3H), 1.30-1.38 (br, 16H), 1.63 (s, 3H), 1.76-1.80 (m, 2H), 2.04-2.08 (t, *J* = 7.2, 2H), 2.28-2.32 (t, J = 7.2, 4H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 13.96, 14.36, 21.91, 22.98, 28.41, 28.63, 29.67, 29.86, 29.90, 29.96, 32.23, 36.00, 38.74, 131.04, 135.58.



22 **23**

Diktone (23). An ozone stream was passed through a solution of **22** (374mg, MW 222.41, 1.7mmol) in CH_2Cl_2 (30ml) and methanol (30ml) at -78 ^{o}C until the solution was saturated with ozone which is blue. Excess ozone was removed by

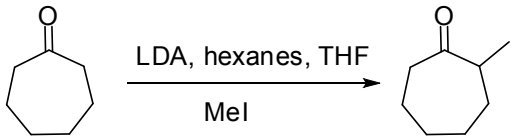
O_2. Me_2S (3ml) was then added at -78 ^oC. The solution was stirred for 1h and then at r.t. for 2h. The solvent was evaporated to give crude product. Flash chromatography on silica gel (6:1 hexanes/EtOAc) afforded 270mg of diketone **23** (63%) as white solid: ^1H NMR ($CDCl_3$, 400MHz) δ 0.85-0.89 (t, *J* = 6.4, 3H), 1.25-1.30 (br, 14H), 1.53-1.56 (m, 2H), 1.79-1.86 (m, 2H), 2.13 (s, 3H), 2.35-2.39 (t, *J* = 7.6, 2H), 2.41-2.48 (m, 4H); ^{13}C NMR ($CDCl_3$, 300MHz) δ 14.31, 17.89, 22.87, 24.05, 29.43, 29.50, 29.60, 29.66, 29.75, 30.09, 32.08, 41.62, 42.76, 43.04, 208.70, 211.08; HRMS Calcd. for $C_{16}H_{31}O_2$ $[M+H]^+$ 255.2319, found 255.2318; Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.24; H, 11.82.



23 **4**

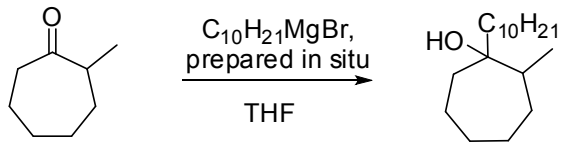
Diketal (4). A solution of diketone **23** (153mg, 254.41, 0.6mmol), 25mg $TsOH.H_2O$, and ethylene glycol (1.1g, MW 62.04, 17mmol) in 60ml dry benzene was refluxed overnight with Dean-Stark apparatus. The solvent was removed to give the crude product. Flash chromatography (6:1 hexanes/EtOAc) afforded 184mg diketal **4** (90%) as colorless oil: ^1H NMR ($CDCl_3$, 400MHz) δ 0.83-0.87 (t, *J* = 6.8, 3H), 1.23-1.30 (br, 19H), 1.43-1.46 (m, 2H), 1.54-1.62 (m, 6H), 3.89-3.92 (m, 8H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.26, 18.62, 22.83, 23.89, 23.96, 29.47, 29.76, 30.07, 32.05, 37.30, 37.36, 39.45, 64,75, 65.05, 110.15, 111.83; HRMS Calcd. for $C_{20}H_{39}O_4$ $[M+H]^+$ 343.2848, found 343.2838; Anal. Calcd. for $C_{20}H_{38}O_4$:

C, 70.13; H, 11.18. Found: C, 70.23; H, 11.27.



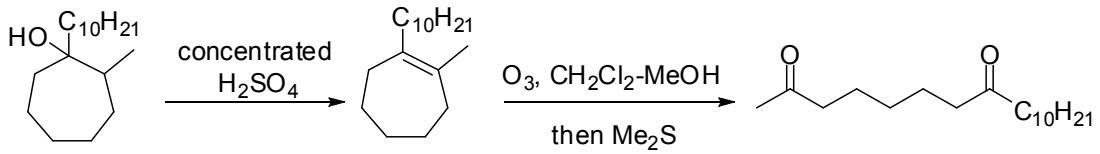
24

2-Methyl-cycloheptanone (24). Under N_2, solution of cycloheptanone (1.68g, MW 112.17, 15 mmol) in 5 ml THF was dropwise added into 30ml 1M Lithium diisopropylamine in 20ml hexanes and 10 ml THF at -78^{o}C. The solution was stirred for 30minutes, followed by rapid addition of methyl iodide (4.3g, MW 141.94, 30mmol). After 5 minutes, the reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was quentched with 20ml of water and extracted with 3 x 15 ml of ether. The combined ether solution was washed twice with water and once with saturated aqueous sodium chloride, dried over anhydrous $MgSO_4$, filtered and concentrated to give crude product. Flash chromatography on silica gel (16:1 hexanes: ethyl acetate) gave 1.52g 2-methyl-cycloheptanone **24** (80%) as colorless oil: ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.01-1.03 (d, *J* = 6.8, 3H), 1.27-1.45 (m, 3H), 1.52-1.62 (m, 1H), 1.73- 1.86 (m, 4H), 2.42-2.46 (m, 2H), 2.52-2.60(m, 1H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 17.65, 24.59, 28.74, 29.90, 33.34, 42.65, 46.65, 216.85; HRMS Calcd. for $C_8H_{15}O$ $[M+H]^+$ 127.1117, found 127.1114.

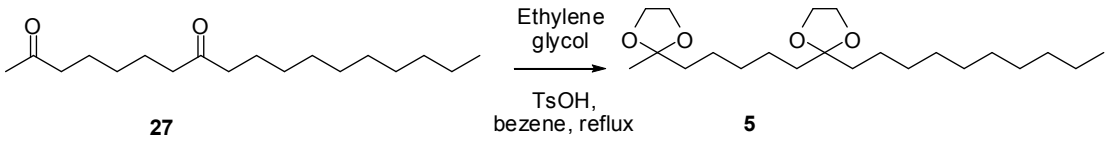


24 **25**

1-Decyl-2-methyl-cycloheptanol (25). Under N_2, 5.4ml of n-$C_{10}H_{21}Br$ (5.7g, MW 221.19, 26 mmol) was dropwise added to 0.75g Mg turnings (31mmol) in 50ml anhydrous THF over 30 min. The reaction was initiated with tiny amount of dibomomethane. The solution was stirred for 3h at around 45^{o}C till most of Mg turnings were consumed. After cooling down to room temperature, the solution was transferred to a sealed bottle via a transfer cannula for further usage. Titration of Grignard reagent with salicylic aldehyde phenylhydrazone indicated around 0.5M of concentration. 2.16 ml of 0.5M Grignard reagent (1.08mmol) was then added dropwise at 0^{o}C into **24** (118mg, MW 126.20, 0.9mmol) in 4ml anhydrous THF under N_2. The solution was stirred for 2h at room temperature, quenched with 10ml saturated NH_4Cl and extracted with ethyl ether (3 x 10ml). The ethyl ether solution was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated to give crude product. Flash chromatography on silica gel (5:1 hexanes/EtOAc) gave 200mg (83%) of **25** as colorless oil: ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.87-0.89 (t, *J* = 4.8, 3H), 0.93-0.94 (d, *J* = 4.4, 3H), 1.10-1.18 (b, 1H), 1.26-1.86 (b, 29H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.33, 17.09, 21.96, 22.90, 23.93, 27.94, 29.11, 29.55, 29.86, 29.88, 30.61, 31.08, 32.11, 39.02, 41.63, 42.04, 76.23; HRMS Calcd. for $C_{18}H_{35}$ $[M - OH]^{+}$ 251.2733, found 251.2731.

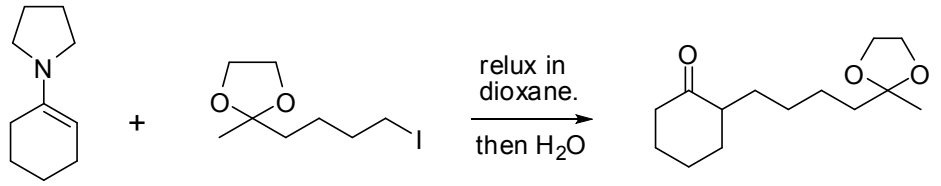


Diketone (27). To a solution of **25** (0.30g, MW 268.28, 1.1mmol) in 2ml of acetic acid at r.t., was added 0.5ml conc. sulfuric acid in 0.5ml acetic acid. After the solution was stirred at r.t. for 3h, 20ml water was added in and the solution was extracted with hexanes (3 x 20ml). The hexanes layers were combined and washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to give crude. Flash chromatography on silica gel (hexanes) gave 0.24g alkene isomers. An ozone stream was passed through a solution of 0.24g alkene isomers in CH_2Cl_2 (30ml) and methanol (30ml) at -78 ^oC until the solution was saturated with ozone which is blue. Excess ozone was removed by O_2. Me_2S (0.5ml) was then added at -78 ^oC. The solution was stirred for 1h and then at r.t. for 2h. The solvent was evaporated to give crude product. Flash chromatography on silica gel (6:1 hexanes/EtOAc) afforded 192mg of diketone **27** (61% for two steps) as white solid: ^1H NMR ($CDCl_3$, 400MHz) δ 0.86-0.88 (t, *J* = 6.6, 3H), 1.25-1.30 (b, 16H), 1.54-1.60 (m, 6H), 2.12 (s, 3H), 2.36-2.43 (m, 6H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.31, 22.87, 23.67, 24.07, 28.86, 29.45, 29.49, 29.60, 29.66, 29.75, 30.10, 32.08, 42.61, 43.08, 43.63, 209.24, 211.60; HRMS Calcd.for $C_{18}H_{35}O_2^+$ $[M+H]^+$ 283.2631, found 283.2628.



27 5

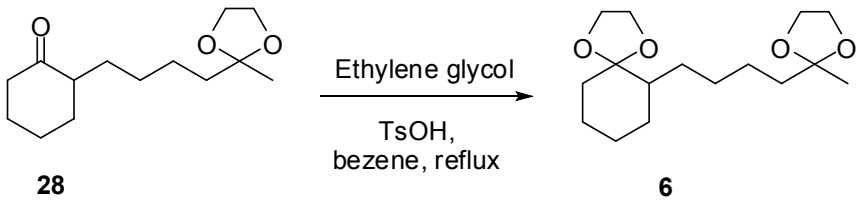
Diketal (5). A solution of diketone **27** (100mg, MW 282.26, 0.35mmol), 8mg $TsOH.H_2O$, and ethylene glycol (100mg, MW 62.04, 1.6mmol) in 60ml dry benzene was refluxed overnight with Dean-Stark apparatus. The solvent was removed to give the crude product. Flash chromatography (6:1 hexanes/EtOAc) afforded 118mg diketal **5** (91%): ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.87-0.88 (t, *J* = 6.6, 3H), 1.25-1.40 (b, 25H), 1.56-1.63 (m, 6H), 3.90-3.95 (m, 8H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.31, 22.88, 23.91, 23.98, 24.07, 24.23, 29.53, 29.82, 30.15, 30.32, 32.10, 37.22, 37.34, 39.33, 64.80, 65.07, 110.35, 112.05; HRMS Calcd. for $C_{22}H_{43}O_4$ $[M+H]^+$ 371.3156, found, 371.3163; Anal. Calcd. for $C_{22}H_{42}O_4$: C, 71.31; H, 11.42. Found: C, 71.29; H, 11.51.



11 28

2-[4-(2-Methyl-[1,3]dioxolan-2-yl)-butyl]-cyclohexanone (28). 1-Pyrrolidino-1-cyclohexene (373mg, MW 151.25, 2.4mmol) and 2-(4-Iodo-butyl)-2-methyl-

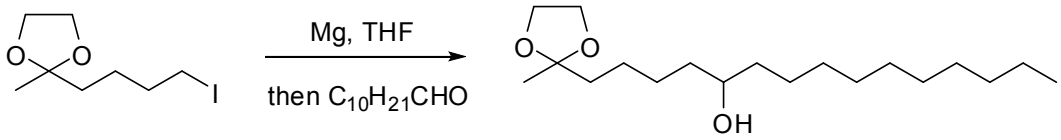
[1,3]dioxolane (**11**, 557mg, MW 270.11, 2.1mmol) were dissolved in 5ml dry dioxane. The mixture was refluxed under Nitrogen overnight. 3ml water was added and the mixture refluxed for another 2 hours. 20ml water was added into the solution and the aqueous phase was extracted with ether (3 x 20ml). The ethyl ether solution was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated to give crude product. Flash chromatography on silica gel (10:1 hexanes/EtOAc) gave 441mg (89%) of **28 :** ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.25-1.36 (b, 9H), 1.57-1.83 (m, 6H), 1.96-2.09 (m, 2H), 2.20-2.37 (m, 3H), 3.86-3.93 (m, 4H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 23.87, 24.36, 24.98, 27.52, 28.17, 29.52, 34.02, 39.21, 42.12, 50.76, 64.74, 110.23, 213.62; HRMS Calcd. for $C_{14}H_{25}O_3$ $[M+H]^+$ 241.1798, found, 241.1799; Anal. Calcd. for $C_{14}H_{24}O_3$ C, 69.96; H, 10.07; O, 19.97. Found: C, 70.05; H, 10.06; O, 20.07.



28 **6**

Diketal (6). A solution of monoketone **28** (300mg, MW 240.17, 1.25mmol), 24mg $TsOH{\cdot}H_2O$, and ethylene glycol (400mg, MW 62.04, 6.4mmol) in 60ml dry benzene was refluxed overnight with Dean-Stark apparatus. The solvent was removed to give the crude product. Flash chromatography (10:1 hexanes/EtOAc) afforded 323mg diketal **6** (91%): ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.21-1.64 (b, 20H), 3.89-3.97 (m, 8H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 23.93, 24.10, 24.65, 24.71,

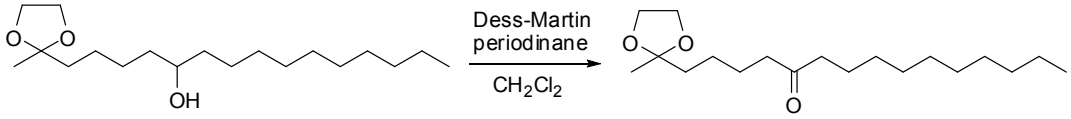
28.01, 28.18, 29.19, 34.87, 39.42, 44.75, 64.80, 64.86, 64.96, 110.39, 111.13. HRMS Calcd. for $C_{16}H_{28}O_4Li$ $[M+Li]^+$ 291.2148, found, 291.2155;



12

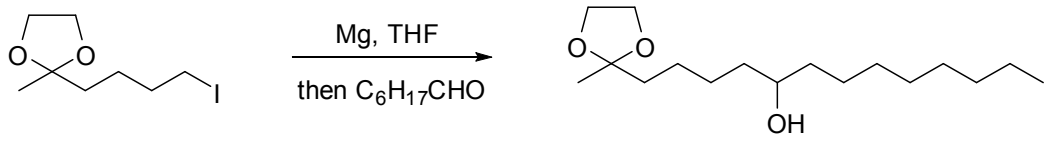
Monoalcohol (12). Under N_2, iodide-substituted compound (3.19g, MW 270.11, 11.8 mmol) was dropwise added to 0.35g Mg turnings (15mmol) in 15ml anhydrous THF over 10 min. The reaction was initiated with tiny amount of dibomomethane. The solution was slightly reluxed for 5h till most of Mg turnings were consumed. After cooling down to room temperature, the solution was transferred to a sealed bottle via a transfer cannula for further usage. Titration of Grignard reagent with salicylic aldehyde phenylhydrazone indicated around 0.8M of concentration. 4.0 ml of 0.8M Grignard reagent (3.2 mmol) was then added dropwise at 0^oC into undecylic aldehyde (540mg, MW 170.3, 3.2mmol) in 3ml anhydrous THF under N_2. The solution was stirred for 2h at room temperature, quenched with 10ml saturated NH_4Cl and extracted with ethyl ether (3 x 10ml). The ethyl ether solution was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated to give crude product. Flash chromatography on silica gel (5:1 hexanes/EtOAc) gave 900mg (89%) of **12** as colorless oil: ^1H NMR ($CDCl_3$, 400MHz) δ 0.84-0.87 (t, *J* = 6.8, 3H), 1.24-1.45 (m, 27H), 1.60-1.64 (t, *J* = 7.6, 2H), 1.69 (s, 1H), 3.53-3.56 (m, 1H), 3.87-3.94 (m, 4H); ^{13}C NMR ($CDCl_3$,

400MHz) δ 14.26, 22.83, 23.86, 24.27, 25.82, 26.00, 29.49, 29.78, 29.88, 32.06, 37.53, 37.67, 39.30, 64.74, 71.91, 110.27; HRMS Calcd. for $C_{19}H_{38}O_3Li$ $[M+Li]^+$ 321.2981, found 321.2988; Anal. Calcd. for $C_{19}H_{38}O_3$: C, 72.56; H, 12.18. Found: C, 72.37; H, 12.46.



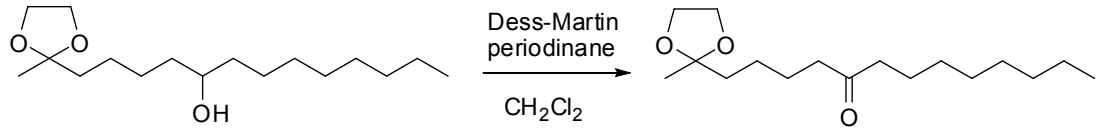
12 **13**

Monoketal (13). To a solution of monoalcohol **12** (50mg, MW 314.5, 0.16mmol) in 4 ml CH_2Cl_2 was added Dess-Martin periodinane (100mg, MW 422.39, 0.24mmol). After being stirred for 30 minutes at room temperature, the solution was quenched with 5 ml saturated aqueous $Na_2S_2O_3$ and 5ml saturated aqueous $NaHCO_3$, then extracted with 3x10ml CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography (12:1 hexanes/EtOAc) afforded monoketal **13** (48mg, 97%). ^1H NMR ($CDCl_3$, 400MHz) δ 0.86-0.89 (t, *J* = 6.4, 3H), 1.26-1.42 (m, 19H), 1.54-1.66 (m, 6H), 2.36-2.42 (q, *J* = 8, 4H), 3.89-3.97 (m, 4H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.31, 22.88, 23.93, 24.09, 24.18, 29.46, 29.51, 29.62, 29.68, 29.76, 32.09, 39.16, 42.89, 43.07, 64.82, 110.14, 211.65; HRMS Calcd. for $C_{19}H_{36}O_3Li$ $[M+Li]^+$ 319.2824, found 319.2822; Anal. Calcd. for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 73.21; H, 11.72.



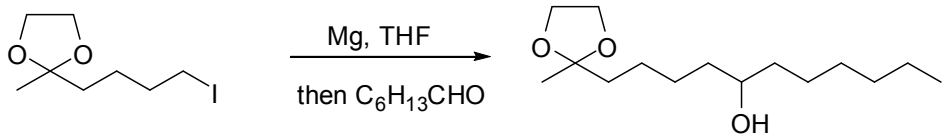
29

Monoalcohol (29). Under N_2, iodide-substituted compound (3.19g, MW 270.11, 11.8 mmol) was dropwise added to 0.35g Mg turnings (15mmol) in 15ml anhydrous THF over 10 min. The reaction was initiated with tiny amount of dibomomethane. The solution was slightly reluxed for 5h till most of Mg turnings were consumed. After cooling down to room temperature, the solution was transferred to a sealed bottle via a transfer cannula for further usage. Titration of Grignard reagent with salicylic aldehyde phenylhydrazone indicated around 0.8M of concentration. 4.0 ml of 0.8M Grignard reagent (3.2 mmol) was then added dropwise at 0^oC into nonyl aldehyde (455mg, MW 142.24, 3.2mmol) in 3ml anhydrous THF under N_2. The solution was stirred for 2h at room temperature, quenched with 10ml saturated NH_4Cl and extracted with ethyl ether (3 x 10ml). The ethyl ether solution was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated to give crude product. Flash chromatography on silica gel (5:1 hexanes/EtOAc) gave 790mg (86%) of **29**: ^1H NMR ($CDCl_3$, 400MHz) δ 0.82-0.85 (t, *J* = 6.4, 3H), 1.23-1.38 (m, 23H), 1.58-1.62 (t, *J* = 7.6, 2H), 1.86 (s, 1H), 3.52 (m, 1H), 3.84-3.92 (m, 4H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.21, 22.77, 23.80, 24.23, 25.78, 25.96, 29.40, 29.72, 29.85, 31.99, 37.48, 37.61, 39.25, 64.67, 71.81, 110.23; HRMS Calcd. for $C_{17}H_{34}O_3Li$ $[M+Li]^+$ 293.2668, found 293.2672; Anal. Calcd. for $C_{17}H_{34}O_3$: C, 71.28; H, 11.96. Found: C, 71.01; H, 12.11.



29 **31**

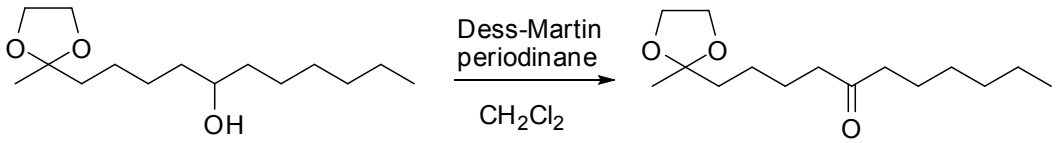
Monoketal (31). To a solution of monoalcohol **29** (104mg, MW 286.45, 0.36mmol) in 4 ml CH_2Cl_2 was added Dess-Martin periodinane (230mg, MW 422.39, 0.55mmol). After being stirred for 30 minutes at room temperature, the solution was quenched with 5 ml saturated aqueous $Na_2S_2O_3$ and 5ml saturated aqueous $NaHCO_3$, then extracted with 3x10ml CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography (12:1 hexanes/EtOAc) afforded monoketal **31** (102mg, 99%). ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.85-0.88 (t, *J* = 6.8, 3H), 1.26-1.41 (m, 15H), 1.53-1.65 (m, 6H), 2.35-2.41 (q, *J* = 8, 4H), 3.88-3.96 (m, 4H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.28, 22.83, 23.92, 24.06, 24.17, 29.32, 29.45, 29.56, 32.00, 39.14, 42.87, 43.05, 64.80, 110.12, 211.60; HRMS Calcd. for $C_{17}H_{33}O_3$ $[M+H]^+$ 285.2424, found 285.2425. Anal. Calcd. for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.73; H, 11.59.



30

Monoalcohol (30). Under N_2, iodide-substituted compound (1.51g, MW 270.11,

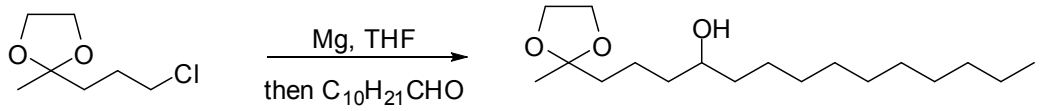
5.6 mmol) was dropwise added to 0.20g Mg turnings (8.3mmol) in 15ml anhydrous THF over 10 min. The reaction was initiated with tiny amount of dibomomethane. The solution was slightly reluxed for 5h till most of Mg turnings were consumed. After cooling down to room temperature, the solution was transferred to a sealed bottle via a transfer cannula for further usage. Titration of Grignard reagent with salicylic aldehyde phenylhydrazone indicated around 0.4M of concentration. 4.0 ml of 0.4M Grignard reagent (1.6 mmol) was then added dropwise at 0^{o}C into heptaldehyde (183mg, MW 114.19, 1.6mmol) in 4ml anhydrous THF under N_2. The solution was stirred for 2h at room temperature, quenched with 10ml saturated NH_4Cl and extracted with ethyl ether (3 x 10ml). The ethyl ether solution was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated to give crude product. Flash chromatography on silica gel (5:1 hexanes/EtOAc) gave 332mg (80%) of **30**: ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.83-0.87 (t, *J* = 6.4, 3H), 1.25-1.41 (m, 19H), 1.59-1.63 (t, *J* = 7.2, 2H), 1.76 (s, 1H), 3.54 (m, 1H), 3.86-3.94 (m, 4H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.22, 22.76, 23.83, 24.26, 25.76, 25.98, 29.52, 31.98, 37.51, 37.64, 39.28, 64.71, 71.87, 110.25; HRMS Calcd. for $C_{15}H_{30}O_3Li$ $[M+Li]^+$ 265.2355, found 265.2363; Anal. Calcd. for $C_{15}H_{30}O_3$: C, 69.72; H, 11.70. Found: C, 69.46; H, 11.90.



30 **32**

Monoketal (32). To a solution of monoalcohol **30** (97mg, MW 258.22, 0.37mmol)

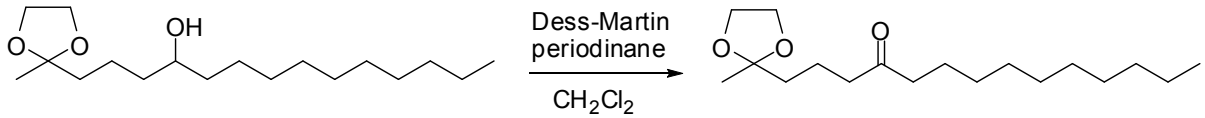
in 4 ml CH_2Cl_2 was added Dess-Martin periodinane (240mg, MW 422.39, 0.56mmol). After being stirred for 30 minutes at room temperature, the solution was quenched with 5 ml saturated aqueous $Na_2S_2O_3$ and 5ml saturated aqueous $NaHCO_3$, then extracted with 3x10ml CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography (12:1 hexanes/EtOAc) afforded monoketal **32** (95mg, 99%). IR**:** 2957, 2926, 2853, 1718, 1463, 1378, 1278 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 0.85-0.88 (t, *J* = 6.8, 3H), 1.25-1.40 (m, 11H), 1.52-1.64 (m, 6H), 2.35-2.41 (q, *J* = 7.6, 4H), 3.87-3.95 (m, 4H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.21, 22.67, 23.90, 24.01, 24.15, 29.09, 31.78, 39.13, 42.85, 43.03, 64.79, 110.10, 211.55; HRMS Calcd. calculated for $C_{15}H_{29}O_3$ $[M+H]^+$ 257.2111, found 257.2112; Anal. Calcd. for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01; O, 18.72. Found: C, 70.23; H, 11.07; O, 18.87.



33

Monoalcohol (33). Under N_2, 5-chloro-2-pentanone ethylene ketal (2.2g, MW 164.63, 13.4mmol) was dropwise added to 0.38g Mg turnings (16mmol) in 15ml anhydrous THF over 10 min. The reaction was initiated with tiny amount of dibomomethane. The solution was slightly reluxed for 5h till most of Mg turnings were consumed. After cooling down to room temperature, the solution was transferred to a sealed bottle via a transfer cannula for further usage. Titration of Grignard reagent with salicylic aldehyde phenylhydrazone indicated around

0.66M of concentration. 4.0 ml of 0.66M Grignard reagent (2.7 mmol) was then added dropwise at 0^{o}C into undecylic aldehyde (460mg, MW 170.3, 2.7mmol) in 3ml anhydrous THF under N_2. The solution was stirred for 4h at room temperature, quenched with 10ml saturated NH_4Cl and extracted with ethyl ether (3 x 10ml). The ethyl ether solution was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated to give crude product. Flash chromatography on silica gel (5:1 hexanes/EtOAc) gave 705mg (87%) of **33**. ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.86-0.89 (t, *J* = 6.8, 3H), 1.26-1.67 (m, 28H), 3.57-3.60 (m, 1H), 3.90-3.97 (m, 4H**);** ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.31, 20.36, 22.88, 23.93, 25.88, 29.53, 29.81, 29.90, 32.10, 37.69, 37.71, 39.27, 64.81, 71.98, 110.28; Anal. Calcd.for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08. Found: C, 72.06; H, 12.31.



33 **34**

Monoketal (34). To a solution of monoalcohol **33** (150mg, MW 300.27, 0.5mmol) in 4 ml CH_2Cl_2 was added Dess-Martin periodinane (317mg, MW 422.39, 0.75mmol). After being stirred for 30 minutes at room temperature, the solution was quenched with 5 ml saturated aqueous $Na_2S_2O_3$ and 5ml saturated aqueous $NaHCO_3$, then extracted with 3x10ml CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Flash chromatography (12:1 hexanes/EtOAc) afforded monoketal **34** (150mg, 100%). IR: 2957, 2926, 2856, 1718, 1463, 1378, 1278 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz) δ

0.86-0.89 (t, *J* = 6.4, 3H), 1.25-1.31 (m, 17H), 1.53-1.69 (m, 6H), 2.36-2.44 (m, 4H), 3.89-3.97 (m, 4H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 14.31, 18.58, 22.87, 23.92, 24.06, 29.46, 29.50, 29.62, 29.68, 29.76, 32.08, 38.55, 42.79, 43.01, 64.83, 110.04, 211.43; HRMS Calcd. for $C_{18}H_{34}O_3Li$ $[M+Li]^+$ 305.2668, found 305.2667; Anal. Calcd. for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48; O, 16.08. Found: C, 72.18; H, 11.48; O, 16.08.

Footnotes and References – Part I

1. Indeed, the whole university started with differentiation under the Big Bang model.
2. (a) Suh, E. M.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11205. 2; (b) *Acc. Chem. Res.* **2004**, *37*, 487 (issue devoted to asymmetric organocatalysis); (c) *Chiral Reagents for Asymmetric Synthesis*, ed. Paquette, L. A., Wiley, Chichester, **2003** (see list of review articles and monographs); (d) Ding, K.; Du, H.; Yuan, Y.; Long, J. *Chem. Eur. J.* **2004**, *10*, 2872 (see list in ref. 2b).
3. For asymmetric catalysis, see Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*, 1st Ed.; Springer: Cambridge, **1999**. Also see Ojima I. *Catalytic Asymmetric Synthesis*, 2nd Ed.; Wiley, **2000**.
4. Interestingly, the sequence of the listed four kinds of selectivity exactly represents the evolution of organic chemistry.
5. Trost, B.M. *Science* **1985**, *227*, 908.
6. Posner, G. H.; Runquist, A.W.; Chapdelaine, M. J. *J. Org. Chem.* **1977**, *42*, 1202.
7. There is no need to differentiate two exactly identical groups because transformation of each will give a same product. Thus, we only look at two functionalities within their immediate surroundings to determine similarity.
8. Sometimes the electronic or steric differences between two identical functionalities are not sufficient for differentiation.
9. Corey, E. J.; Niwa, H.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 1586.
10. Sharpless, K. B.; Michaelson, R. C. *J. Am.Chem. Soc.* **1973**, *95*, 6136.

11. In contrast, geraniol is epoxidized by peracids preferentially at the olefinic site (Δ 6-7) furthest removed from the hydroxyl group. Indirect epoxidation via bromohydrin formation would also favor the more electron-rich 6,7 double bond.

12. A Strategy for Position-Selective Epoxidation of Polyprenols, by Gnanadesikan, V.; Corey; E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8089.

13. An initial substrate concentration of 0.5 mM was employed to minimize the competing intermolecular epoxidation.

14. In his article, Corey provided stereomechanistic model for selective internal epoxidation and used the model as a reliable guide for the design of suitable spacer/controller.

15. Abeles, R. H.; Frey, P. A.; Jencks, W. P. *Biochemistry*, Jones and Bartlett: Boston, **1992**, p. 658.

16. MacManus, D. A.; Vulfson, E. N. *Enzyme Microb. Technol.* **1997**, *20*, 225.

17. The presented example shows that enzymes, according to the proposed models, employ non-covalent bonding interactions to achieve regioselectivity. Enzymes are also well known for their ability to achieve regiochemistry through multiple bindings.

18. Pauling, L. *Am. Sci.* **1948**, *36*, 51.

19. One reason to choose ketone is that the protection and deprotection of carbonyl groups play an important role in many multi-step syntheses of organic chemistry. See (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York,

1999. (b) Hanson, J. R. *Protecting Groups in Organic Synthesis*, 1st ed.; Blackwell Science, Inc: Malden, MA, **1999**. (c) Kocienski, P. J. *Protecting Groups*, 1st ed.; Georg Thieme Verlag: Stuttgart, **1994**. Additionly, we benefit from the number of methods available to protect and deprotect carbonyl groups when sifting them for a position-selective catalyst.

20. Hagiwara, H.; Uda, H. *J. Chem. Soc.*, *Chem. Commun.* **1987**, 1351; Sterozycki, R. *Synthesis*, **1979**, 724.
21. Marcantoni, E. ; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183.
22. Grieco, P. A.; Yokoyama, Y.; Withers, G. P.; Okuniewicz, F. J.; Wang, C.-L. J. *J. Org. Chem.* **1978**, *43*, 4178.
23. Lai, Y. H. *Synthesis* **1981**, 585.
24. Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442.
25. Zeng, C.-M; Manion, B. D; Benz, A.; Evers, A. S.; Zorumski, C. F.; Mennerick, S.; Covey, D. F. *J. Med. Chem.* **2005**, *48*, 3051.
26. Hughes, C. C.; Trauner, D *Ang. Chem. Int. Ed.* **2002**, *41*, 2227.
27. Zhou, J. R.; Fu, G.. *J. Am. Chem. Soc.* **2003**, 125, 14726.
28. Maynard, G. D. "1,2-Dibromoethane" in *Encyclopedia of Reagents for Organic Synthesis* (Ed: L. Paquette) **2004**, J. Wiley & Sons, New York.
29. Liu, H.; Wang, D.; Kim, J. B.; Browne, E.; Wang, Y. *Can. J. Chem.***1997**, *75*, 899.
30. Bagal, S. K.; Adlington, R. M.; Baldwin, J. E.; Marquez, R. *J. Org. Chem.*

2004, *69*, 9100.

31. Since we are looking for selectivity, the percentages of each species were not shown here.
32. Sterzycki, R. *Synthesis* **1979**, *9*, 724.
33. Bauduin, G.; Bondon, D.; Pietrasanta, Y.; Pucci, B. *Tetrahedron* **1978**, *34*, 3269.
34. Balme, G.; Gore, J. J. *Org. Chem.* **1983**, *48*, 3336.
35. Grieco, P. A.; Nishizawa M.; Oguri T.; Burke S. D.; Marinovic N. *J. Am. Chem. Soc.* **1977**, *99*, 5773.
36. Babler, J. H.; Malek, N. C.; Coghlan, M. J. *J. Org. Chem.* **1978**, *43*, 1821.
37. Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705.
38. Sarmah, P.; Barua, N. C. *Tetrahedron Lett.* **1989**, *30*, 4703.
39. Barton, D. H. R.; Magnus, P. D.; Smith, G.; Zurr, D. *J. Chem. Soc.*, *Chem. Commun.* **1971**, *15*, 861.
40. Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Nardi, M.; Procopio, A.; Tagarelli, A. *Synthesis* **2004**, *4*, 496.
41. Brown, J. J.; Lenhard, R. H.; Bernstein, S. *J. Am. Chem. Soc.* **1964**, *86*, 2183.
42. The total amount comprises the starting material and the three products.
43. Potential factors include semi-cavitary restraint on the MgSO4 surface.
44. Menger, F. M.; Shi, L *J. Am. Chem. Soc.* **2006**, *128*, 9338.
45. Mourey,T. H.; Oppenheimer, L. E. “*Principles of operation of an*

evaporative light-scattering detector for liquid chromatography.” *Anal. Chem.* **1984**, *56*, 2427.

46. Paper published: Menger, F. M.; Lu, H *Chem. Commun.* **2006**, *30*, 3235.

Part II. A-B-A-B-A Block Amphiphiles. Balance between Hydrophilic and Hydrophobic Segmentation

Introduction

Amphiphiles compounds are comprised of both hydrophilic and hydrophobic groups (Figure 1).[1] The hydrophobic group typically consists of a large hydrocarbon moiety. The hydrophilic part can be (1) anionic groups such as sulfates and phosphates; (2) cationic groups such as amines; and (3) polar groups such as alcohols.

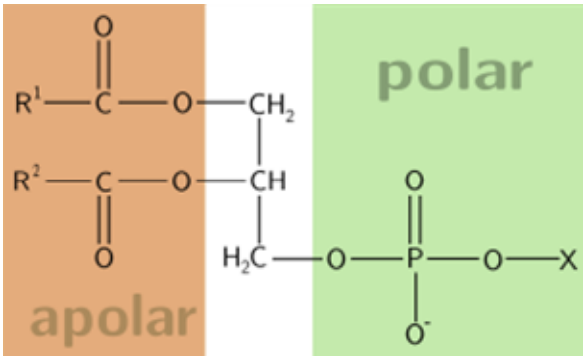


Figure 1. Phospholipids are amphiphiles.[2]

Hydrophilic-lipophilic balance (HLB) represents an important parameter of amphiphiles among many.[3] It indicates the degree to which the amphiphile is hydrophilic or hydrophobic. Several quantitative ways of correlating the chemical structure of surfactant molecules to HLB values have been devised. For example, the HLB for nonionic surfactants with polyoxyethylene solubilizing groups can be calculated by the following formula:[4]

$$HLB = \frac{\text{mol\% hydrophilic group}}{5}$$

According to the given formula, an unsubstituted polyoxyethylene glycol has an HLB value of 20; and a completely hydrophobic molecule has a HLB value of zero. Table 1 gives some HLB values for typical nonionic surfactant structures.[4] The HLB values generally increase as surfactants have more polyoxyethylene glycol.

Table 1. Some calculated HLB values for typical nonionic surfactant structures.[4]

Amphiphile	HLB
Sorbitan trioleate	1.8
Sorbitan tristearate	2.1
Propylene glycol monostearate	3.4
Glycerol monostearate	3.8
Sorbitan monostearate	4.3
Sorbitan monostearate	4.7
Polyoxyethylene (2) cetyl ether	5.3
Diethylene glycol monolaurate	6.1
Sorbitan monolaurate	8.6
Polyoxyethylene (10) cetyl ether	12.9
Polyoxyethylene (20) cetyl ether	15.7
Polyoxyethylene (6) tridecyl ether	11.4
Polyoxyethylene (12) tridecyl ether	14.5
Polyoxyethylene (15) tridecyl ether	15.4

These values are important because they can be used to predict the surfactant properties of the amphiphiles.[4] Typically, a value from 2 to 6 indicates that a nonionic surfactant has low water solubility and acts as solubilizer of water in oils. These amphiphiles are good Water/Oil (W/O) emulsion stabilizer. A nonionic surfactant with HLB value from 7 to 9 can be used as a wetting and spreading agent. A nonionic surfactant with HPB value from 8-12 can be an Oil/Water (O/W) emulsifier. A nonionic surfactant with HLB value from 12 to 15 is typical of detergents. A nonionic surfactant with HLB value from 15 to 20

possesses high water solubility and generally acts as good solubiliser or hydrotrope. Thus, the HLB system helps guide the surfactant chemists and formulators to select amphiphiles most suited to individual needs.

Although the formula shown above does not show the effect of individual unit constituting the amphiphile, it does reflect an **additivity principle** that takes into account each group's contribution toward HLB. For example, Table 2 shows typical group numbers for calculating HLB numbers.[4] These numbers can be applied to the following formula to obtain HLB values:

$$\text{HLB} = 7 + \Sigma \text{ (hydrophilic group numbers)} + \Sigma \text{ (hydrophobic group numbers)}$$

Consequently, HLB numbers can be calculated on the basis of group contributions.

Table 2. Typical group numbers for calculation of HLB numbers.[4]

Group	HLB Number	Group	HLB number
Hydrophilic		Hydrophobic	
$-SO_4Na$	38.7	-CH-	- 0.475
-COOK	21.1	$-CH_2-$	- 0.475
-COONa	19.1	$-CH_2-$	- 0.475
-N(tertiary amine)	9.4	=CH-	- 0.475
-Ester (sorbitan)	6.8	$-CF_2-$	- 0.87
-Ester (free)	2.4	$-CF_3$	- 0.87
-COOH	2.1	Miscellaneous	
-OH (free)	1.9	$-(CH_2CH_2O)-$	0.33
-O-	1.3	$-(CH_2CH_2\ CH_2O)-$	- 0.15
-OH (sorbitan)	0.5		

Additivity principle is also used for the quantification of noncovalent interactions. According to H.-J. Schneider and his coworkers, Coulombic, van der Waals, and hydrogen-bonding stabilization of complexes can be quantified by simple additive increments (e.g., 5 kJ/mol per salt bridge in water for up to 12 such interactions).[5] Such quantification of noncovalent interactions is of paramount importance for the development of supramolecular chemistry.[6]

Both of these two applications of additivity principle have been widely used to guide chemists in both surfactant chemistry and supramolecular chemistry. However, neither of them considers the effect of **molecular segmentation**. For example, we know little about whether a di-segmented molecule such as A-A-A-B-B differs from multi-segmented molecules such as A-A-B-A-B or A-B-A-B-A in terms of HLB and other characteristics.

Interestingly, such segmentation is a widespread attribute of living systems, a fact well illustrated by bacteriorhodopsin.[7] Bacteriorhodopsin is a purple

photosynthetic pigment from archaea. It most efficiently absorbs green light (wavelength 500-650 nm, with the absorption maximum at 568 nm).[8] This protein has a three-dimensional tertiary structure and is comprised of seven hydrophobic R-helices that embed themselves inside lipid bilayers. Interconnecting the helices are strands, rich in charged and polar amino acids, that lie in the water outside the bilayer. Figure 2 shows the interaction between bacteriorhodopsin and the cell membrane.[9] The other three interactions represent respectively: 1) interaction by an amphipathic α-helix parallel to the membrane plane (in-plane membrane helix); 3) interaction by a covalently bound membrane lipid (lipidation); 4) electrostatic or ionic interactions with membrane lipids. Thus, the activity of the protein can be ascribed in part to alternating hydrophobic and hydrophilic domains, that is, segmentation.[10]

This research examines the self-assembly of penta-segmented organic molecules of the general structure A-B-A-B-A or B-A-B-A-B, where A is a hydrophilic polyether and B is a hydrophobic carbon chain. Such understanding could serve, it would seem, as a basis for understanding biological systems (just as organic mechanisms serve as a basis for understanding enzyme action).

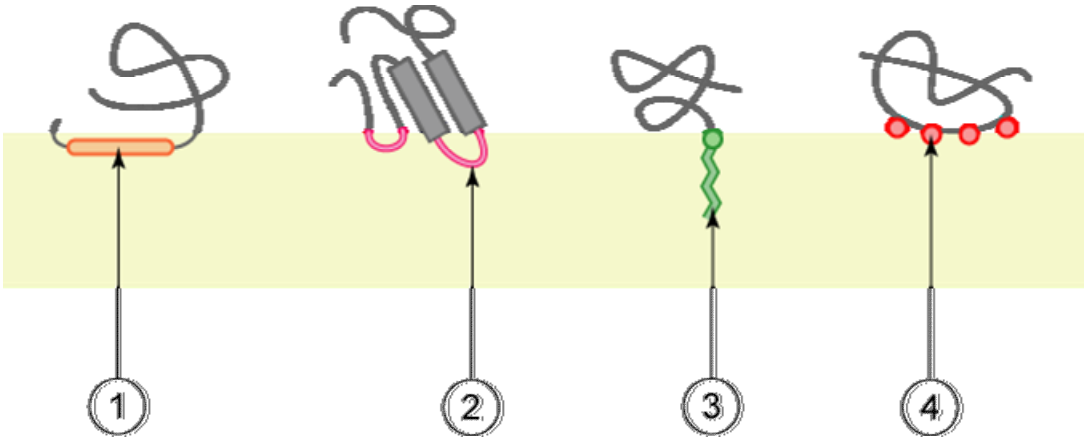


Figure 2. Schematic representation of the different types of interaction between monotopic membrane proteins and the cell membrane.[9] 1) interaction by an amphipathic α-helix parallel to the membrane plane (in-plane membrane helix); 2) interaction by a hydrophilic loop; 3) interaction by a covalently bound membrane lipid (lipidation); 4) electrostatic or ionic interactions with membrane lipids.

Syntheses

Six block amphiphiles comprising linear alkyl chains and polyethylene glycols (PEGs) were synthesized as listed in Figure 3. All compounds feature a CECEC or ECECE pattern, where C represents the linear alkyl chain and E stands for the PEG unit. The first two compounds ($C_6E_5C_6E_5C_6$ and $C_8E_5C_8E_5C_8$) are hydrophobe- terminated and have ether linkages connecting the segments; the next four compounds ($E_3C_{10}E_3C_{10}E_3$, $E_3C_8E_3C_8E_3$, $E_3C_6E_3C_6E_3$, and $E_6C_{10}E_6C_{10}E_6$) are hydrophile- terminated with ester connections.

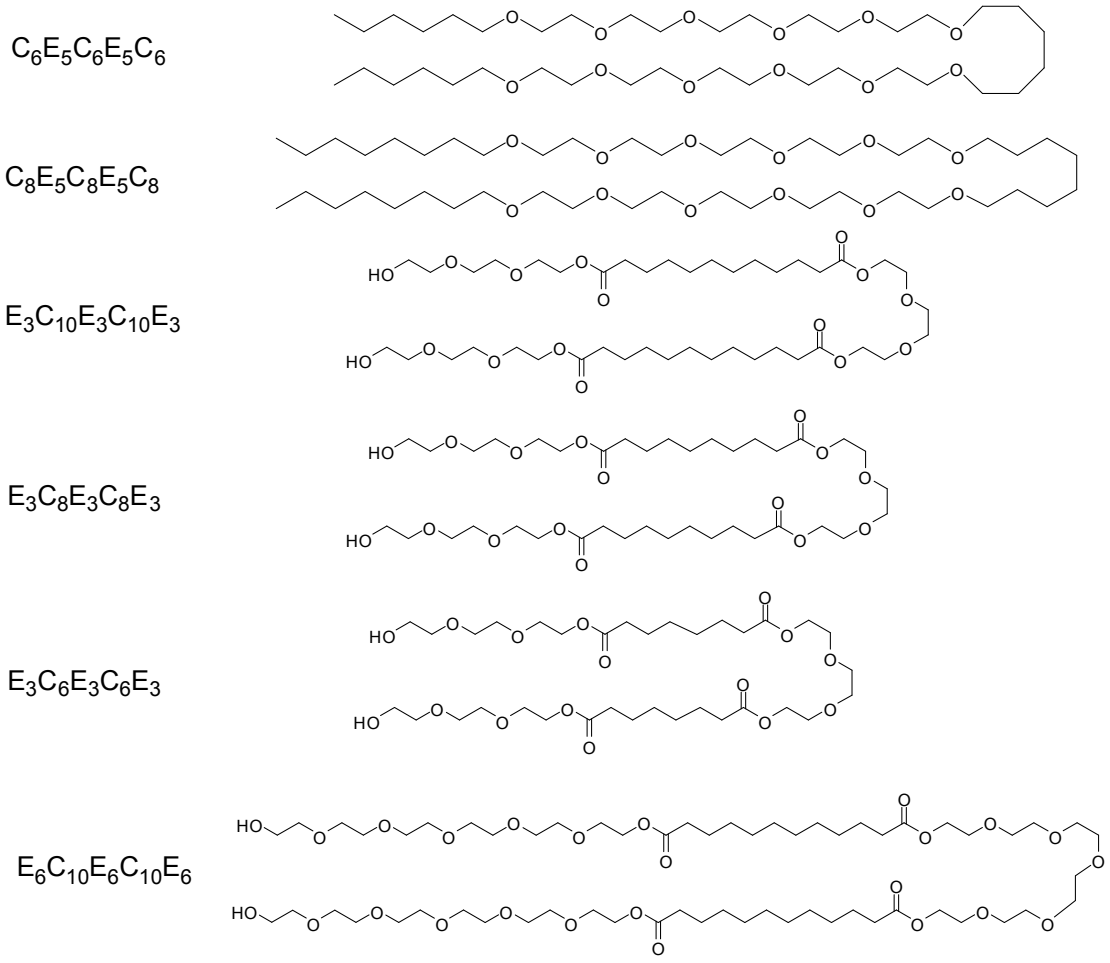
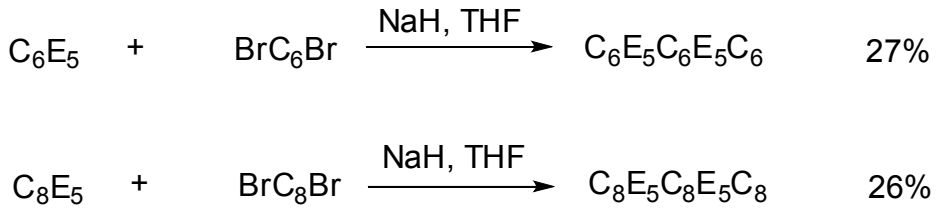


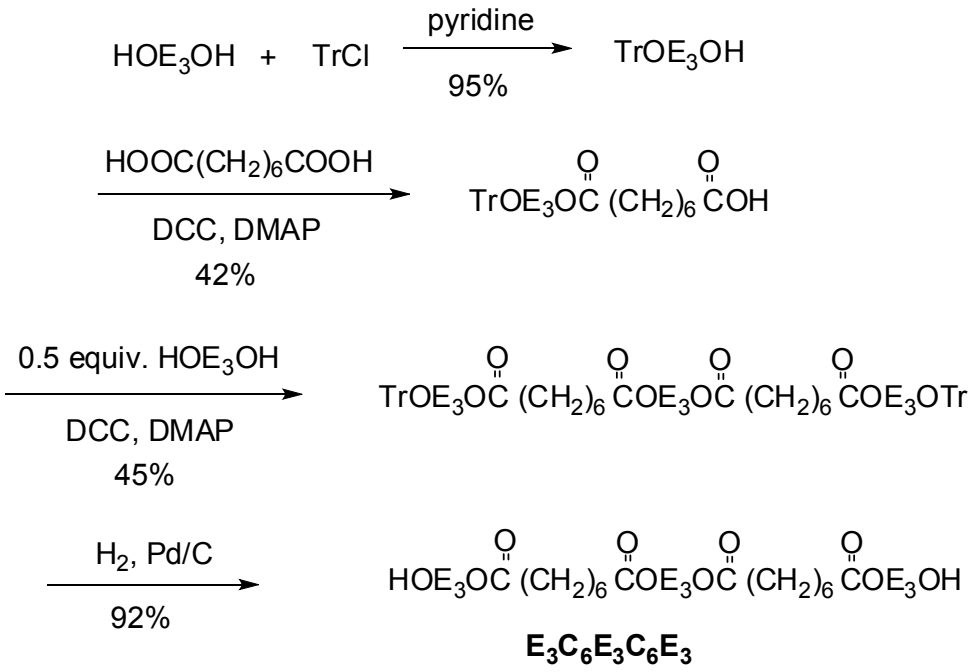
Figure 3. Penta-segmented block amphiphiles (C represents the linear alkyl chain and E stands for the PEG unit).

Amphiphiles $C_6E_5C_6E_5$ and $C_8E_5C_8E_5$ were synthesized through one single step by the substitution of di-bromoalkane with C_6E_5 and C_8E_5 (Scheme 1). The reaction was promoted by NaH in anhydrous THF as shown in Scheme 2 and gave 27% and 26% yield respectively.

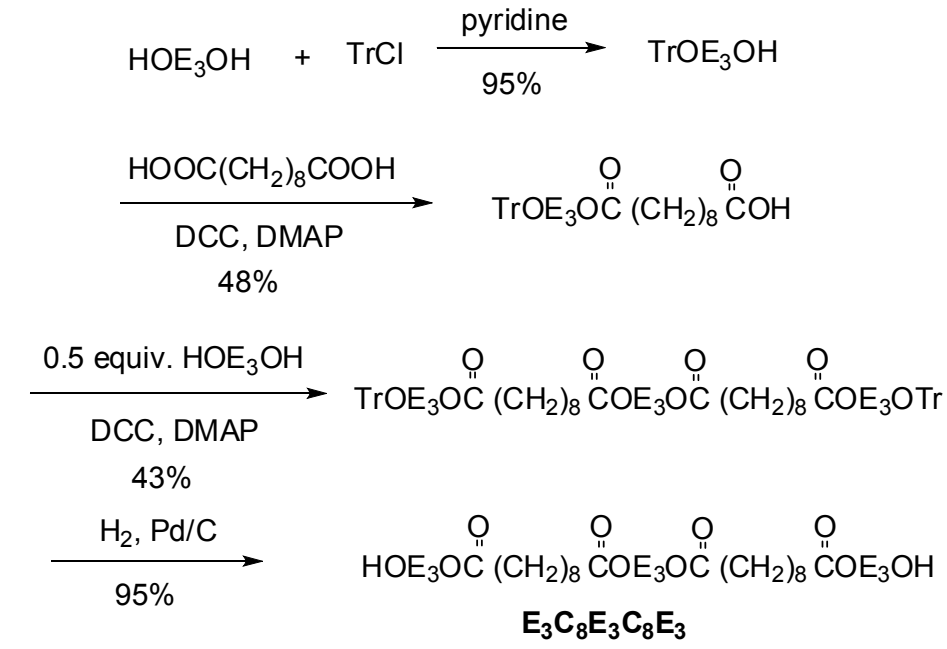


Scheme 1. Syntheses of $C_6E_5C_6E_5C_6$ and $C_8E_5C_8E_5C_8$ (C represents the linear alkyl chain and E stands for the PEG unit).

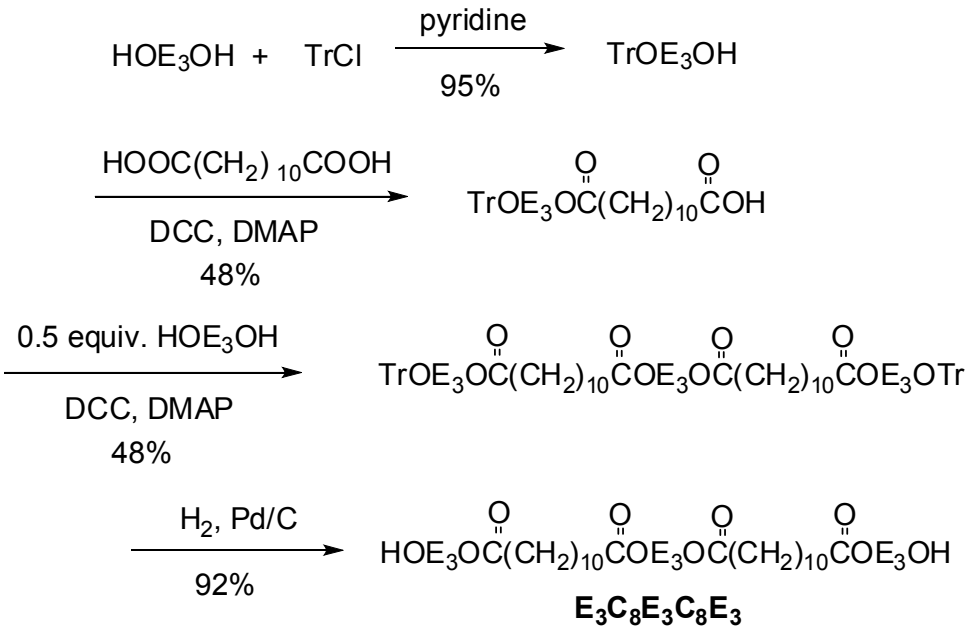
Amphiphiles $E_3C_6E_3C_6E_3$, $E_3C_8E_3C_8E_3$, $E_3C_{10}E_3C_{10}E_3$, and $E_6C_{10}E_6C_{10}E_6$ were synthesized through four steps as shown in Scheme 2 - 5. Generally, PEGs (HOE_3OH and HOE_6OH) were first mono-protected with trityl chloride. [11,12] The subsequent two coupling reactions initiated by DCC yielded the frameworks of the targeted block amphiphiles. Finally, deprotection of the trityl groups gave the final products. The syntheses seem straightforward. However, the challenge lies in the purification. As number of ethylene glycol units and size of the whole molecule increases, molecule behaves more like a polymer and purification becomes extremely difficult. The eluent used in our study had small polarity and large volume was required. Normally it took several repetitive columns to finish the purification. An extreme example was that the purification for compound $E_6C_{10}E_6C_{10}E_6$ can only be accomplished with preparative TLC.



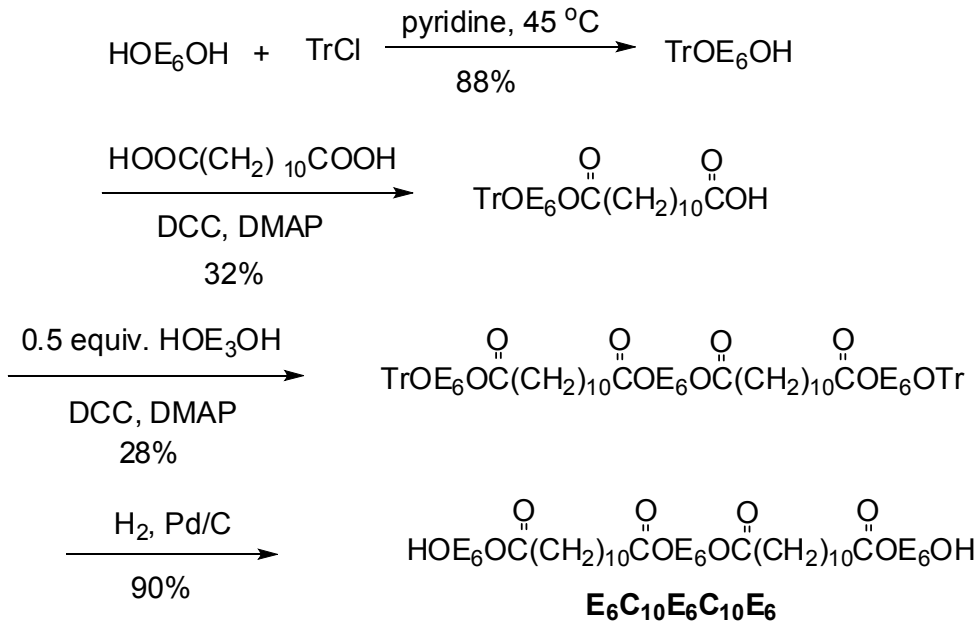
Scheme 2. Synthesis of $E_3C_6E_3C_6E_3$ (C represents the linear alkyl chain and E stands for the PEG unit).



Scheme 3. Synthesis of $E_3C_8E_3C_8E_3$ (C represents the linear alkyl chain and E stands for the PEG unit).



Scheme 4. Synthesis of $E_3C_{10}E_3C_{10}E_3$ (C represents the linear alkyl chain and E stands for the PEG unit).



Scheme 5. Synthesis of $E_6C_{10}E_6C_{10}E_6$ (C represents the linear alkyl chain and E stands for the PEG unit).

Characterization

All six amphiphiles were characterized by different techniques. The two water soluble amphiphiles were subject more detailed examination including surface activity, critical micelle concentration (CMC), interfacial area per molecule, cloud point, and aggregation number by NMR diffusion experiment.

A. Solubility

As shown in Table 3, four of six block amphiphiles ($C_6E_5C_6E_5C_6$, $C_8E_5C_8E_5C_8$, $E_3C_8E_3C_8E_3$, and $E_3C_{10}E_3C_{10}E_3$) turned out to be water insoluble at 25 °C. Various controls like temperature, sonication, and electrolytes such as LiCl, NaI, and KI, failed to make the insoluble amphiphiles dissolve in water.

Table 3. Block amphiphiles and their solubility in water at 25 °C (C represents the linear alkyl chain and E stands for the PEG unit).

	Linkage	Compounds	Solubility in water
1	ether	$C_6E_5C_6E_5C_6$	insoluble
2	ether	$C_8E_5C_8E_5C_8$	insoluble
3	ester	$E_3C_6E_3C_6E_3$	soluble
4	ester	$E_3C_8E_3C_8E_3$	insoluble
5	ester	$E_3C_{10}E_3C_{10}E_3$	insoluble
6	ester	$E_6C_{10}E_6C_{10}E_6$	soluble

The insolubility of $E_3C_8E_3C_8E_3$ and $E_3C_{10}E_3C_{10}E_3$ are more unexpected than that of $C_6E_5C_6E_5C_6$ and $C_8E_5C_8E_5C_8$ because $E_3C_8E_3C_8E_3$ and $E_3C_{10}E_3C_{10}E_3$ have two ending hydroxyl groups. The fact that $E_3C_6E_3C_6E_3$ becomes water soluble as the carbon number of the alkyl chain decreases suggests that the hydrophilicity of total 9 PEG units is not enough to overcome the hydrophobicity of the carbon chains in both $E_3C_8E_3C_8E_3$ and $E_3C_{10}E_3C_{10}E_3$.

The seemingly prosaic development has, nonetheless, useful implications. The conventional surfactant, $C_{16}E_9$, is both water soluble and surface-active (CMC = 4 x 10^{-5} M, and aggregation number = 279).[7,8] However, $E_3C_8E_3C_8E_3$, with an equivalent E/C content plus a second terminal hydroxyl, does not dissolve in water. Thus, three E_3 units lack the solubilizing capacity of a single E_9 unit, showing that Schneider's additivity principle is not applicable here. If solubility in water can be solely determined by the balance between hydrophilicity and hydrophobicity of the amphiphile, our results also suggest that segmentation does influence hydrophilicity and hydrophobicity.

The solubility of the two water soluble amphiphiles, $E_3C_6E_3C_6E_3$ and $E_6C_{10}E_6C_{10}E_6$, can reach 25 mM before it becomes cloudy.

B. Surface tension, critical micelle concentration (CMC), and interfacial area per molecule

Surface tension for water solution is caused by attraction between the molecules at the surface resulting from various intermolecular interactions.[4] Since the molecules at the surface are subjected to stronger attraction from the liquid body than from the vapor or air, an unbalance exists and gives surface tension. Surface tension tends to maintain a minimum surface area of a liquid.

Numerous methods are available for measuring surface tension of water solution.[13] The tradition Du Noüy Ring method is commonly used. The du Nouy tensiometer consists of a platinum-iridium ring attached to the beam of a torsion balance (Figure 4). When the ring is placed at the surface of a liquid, it is subject

to an attraction. This attraction is proportional to the surface tension. By pulling the ring upward and measuring the force it takes to pull, chemists are able to determine the magnitude of surface tension. For example, the surface tension of pure water is about 73 mN/m at room temperature.[4]

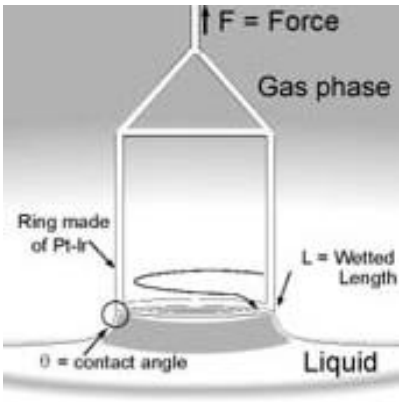


Figure 4. Schematic representation of du Noüy ring method.[14]

Amphiphiles often show surface activity which lowers the surface tension of a water solution. As the concentration of amphiphiles in the solution increases, the degree of such decrease in surface tension intensifies. Sometimes, a sudden change in the tendency in decreasing occurs. This sudden change corresponds to the phenomenon that the amphiphile molecules in the solution forms aggregations. If these aggregations are micelles, which are true for many surfactants, we call this transitional point CMC (Figure 5). Ideally, a sharp transition on surface tension vs. concentration plot appears, suggesting a cooperative effect.[15]

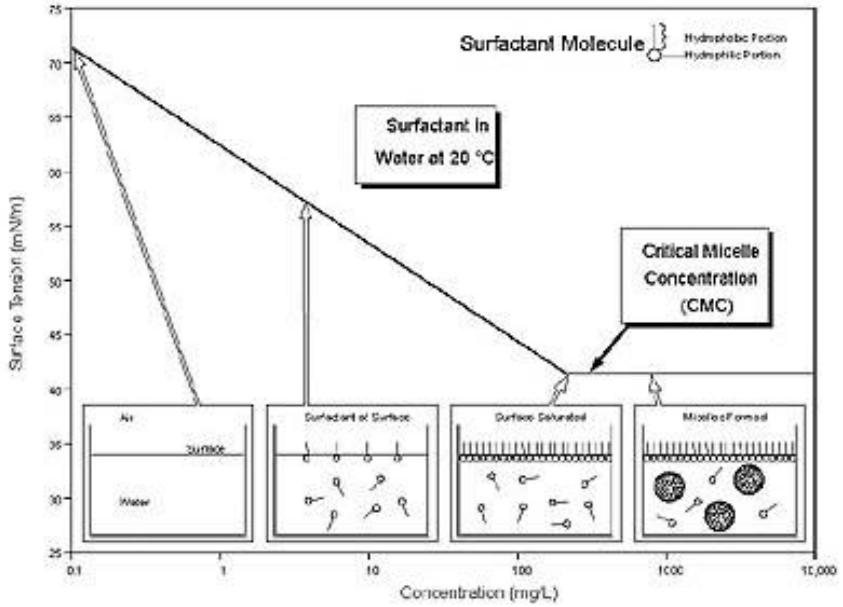


Figure 5. Schematic illustration of measurements of CMC.[14]

Figure 6 shows a typical decay of surface tension of a surfactant water solution. At low concentrations (Figure 6, region A to B), the surfactant molecule concentrate at the surface of the solution and surface tension lowers gradually. When the surface becomes saturated with surfactant molecules, the surface tension curve appears linear and the concentration of surfactant molecules in the bulk as monomer increases (Figure 6, region B to C). When the concentration of these monomers rises to a certain degree as the concentration of surfactant continues increasing, aggregation such as micellation starts and surface tension curve plateaus.

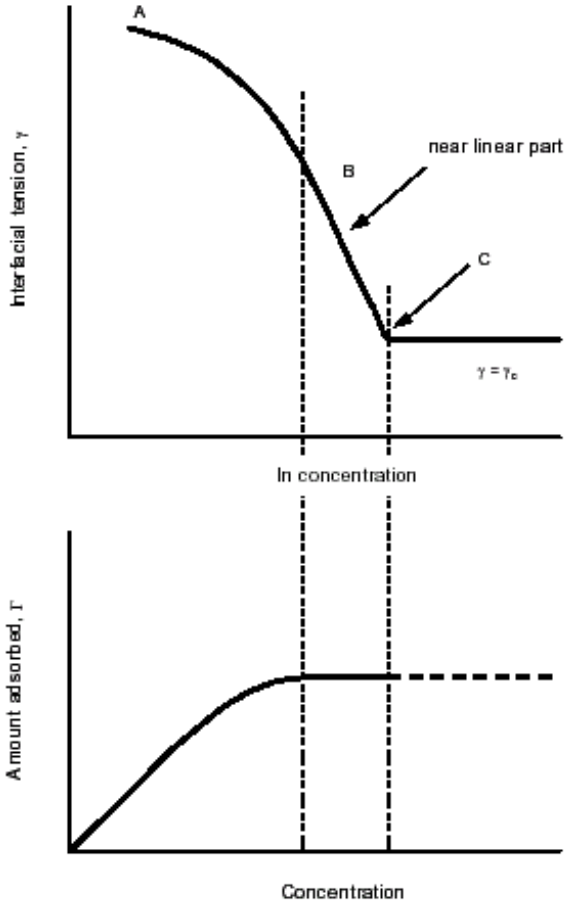


Figure 6. Surface tension measurement and the interfacial adsorption isotherm.[15]

The region with linearity before CMC can be applied to Gibbs equation to calculate the concentration of surfactant at the surface.[4] Gibbs equation (shown below) is derived from the constant concentration that is often referred as surface excess. Detailed deduction of Gibbs equation is not given here. However, from the equation we can see that when the change of surface tension (γ) is proportional to the change of ln C (natural logarithm of concentration), the surface excess (Γ) keeps constant.

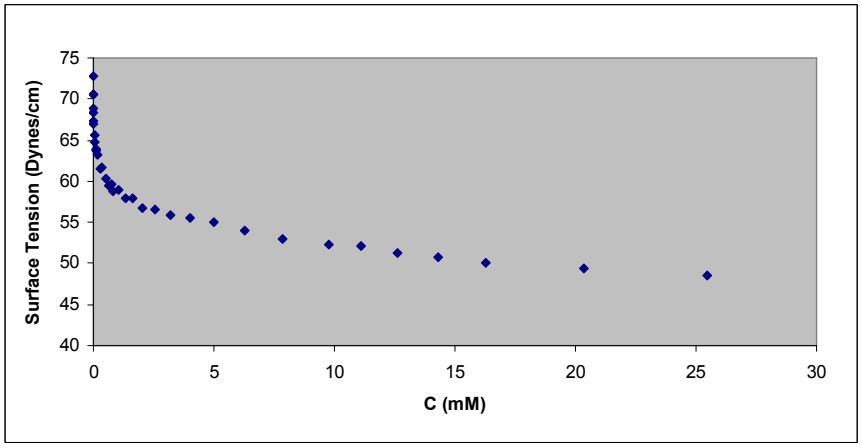
Gibbs equation: $$\Gamma = -\frac{1}{RT}\left(\frac{\partial \gamma}{\partial \ln C}\right)$$

Further application of the constant surface excess is to calculate the interfacial area per molecule at and after CMC point. When the change of surface tension (γ) becomes proportional to the change of ln C, the surface is saturated with surfactant molecules. Thus, we can use this constant surface excess to determine the interfacial area per molecule after surface saturation.

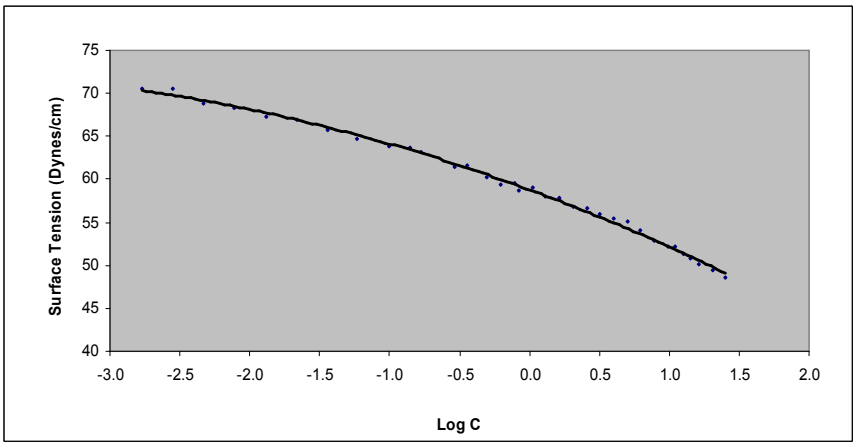
Surface tension was measured for both $E_3C_6E_3C_6E_3$ and $E_6C_{10}E_6C_{10}E_6$ as displayed in Figure 7 and 8.

The surface tension versus concentration plot of $E_3C_6E_3C_6E_3$ shows a modest surface activity (48.5 mN/m) up to its solubility limit 25mM. By comparison, $C_{16}E_9$ can reach 36 mN/m.[16] Moreover, the plot indicates that no CMC exists. This perhaps can be explained by the segmented and relatively short alkyl chain.

Although surface tension plot of $E_6C_{10}E_6C_{10}E_6$ shows no better surface activity than $E_3C_6E_3C_6E_3$, it does show a break at 0.19mM suggesting the onset of aggregation. The relatively large CMC of $E_6C_{10}E_6C_{10}E_6$ compared with that of $C_{16}E_{21}$ (3.9 M) indicates that $E_6C_{10}E_6C_{10}E_6$ has a much smaller propensity to micellize.[17]

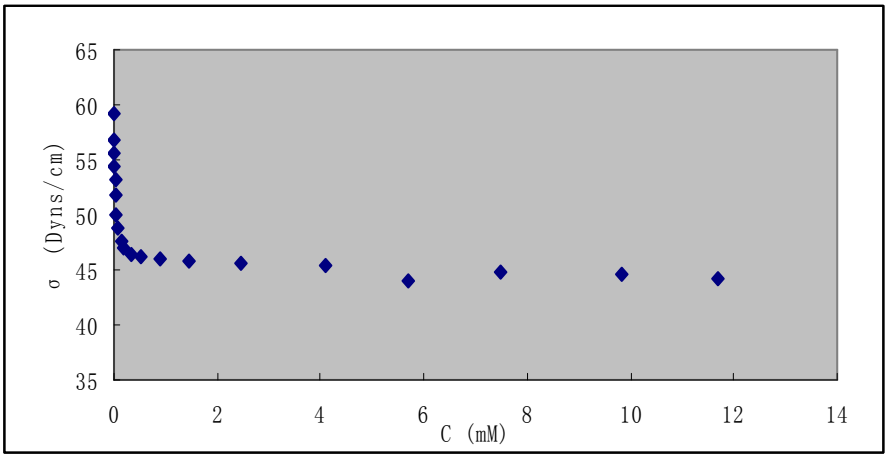


(a)

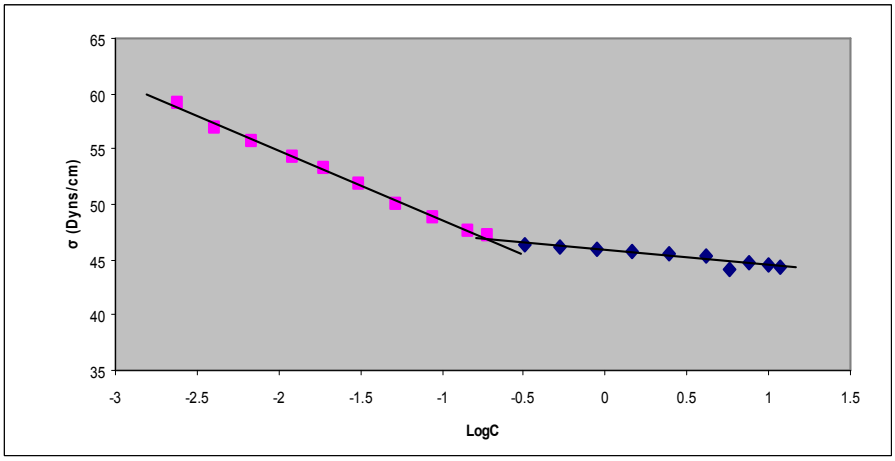


(b)

Figure 7. Surface tension measurement of $E_3C_6E_3C_6E_3$ (C represents the linear alkyl chain and E stands for the PEG unit). (a) surface tension versus concentration; (b) surface tension versus log(concentration).



(a)



(b)

Figure 8. Surface tension measurement of $E_6C_{10}E_6C_{10}E_6$ (C represents the linear alkyl chain and E stands for the PEG unit). (a) surface tension versus concentration; (b) surface tension versus log(concentration).

Interfacial area of $E_6C_{10}E_6C_{10}E_6$ can be obtained from the Gibbs equation:

$$\Gamma = -\frac{1}{RT}\left(\frac{\partial \gamma}{\partial \ln C}\right)$$

By plotting surface tension (mN/m) versus ln C (M), the slope obtained represents the $d\gamma/d\ln C$ term in the Gibbs equation. Since the slope equals - 2.71 mN/m, the surface excess concentration Γ equals 1.11 *u*mole/m^2. The definition of surface excess concentration is defined as the number of molecules at per interfacial area. Thus, the interfacial area per molecule $s = 1/\Gamma N_A = 150$ $Å^2$ /molecule.

The cross-sectional area of molecule $E_6C_{10}E_6C_{10}E_6$ is around 450 $Å^2$. Therefore, for molecule $E_6C_{10}E_6C_{10}E_6$ the interfacial area only accounts for one third of the cross-sectional area. Consequently we surmise that the reasonable conformation at the air/water interface has the PEG segments partially immersed in water, while the two carbon chains between then are looped in the air. Figure 9 shows the proposed conformation. The red segments represent PEG and the blue segments represent carbon chains. The proposed packing peculiarities resemble the interaction by a hydrophilic loop of membrane proteins as shown in Figure 2.

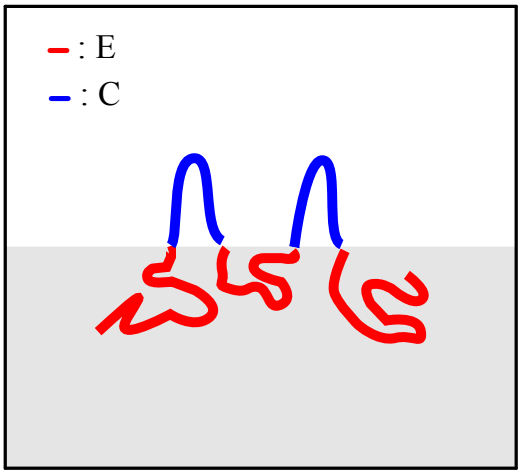


Figure 9. Proposed conformation of $E_6C_{10}E_6C_{10}E_6$ at the air/water interface (representing that $E_6C_{10}E_6C_{10}E_6$'s interfacial area only accounts for one third of the cross-sectional area of the molecule; C represents the linear alkyl chain and E stands for the PEG unit)).

C. Cloud point

Nonionic surfactants often exhibit an inverse temperature-solubility relationship. The characteristic is attributed to a disruption of specific interactions between water and the hydrophilic units in the amphiphile molecule. When such disruption reaches a certain degree, the amphiphilic molecules precipitate from solution and the solution becomes cloudy. Cloud point is the temperature at which the precipitation begins.[4]

$E_6C_{10}E_6C_{10}E_6$'s cloud point above CMC ranges from from 37 - 45 ^oC (Table 4). Since there is no data available for $C_{20}E_{18}$, with an equivalent E/C content, for comparison, we will not directly recognize the difference caused by segmentation. However, we can make several other comparisons.

Table 4. Cloud points of $E_6C_{10}E_6C_{10}E_6$ at different concentrations (C represents the linear alkyl chain and E stands for the PEG unit).

Concentration (mM)	Clouding point (^oC)
76	37.2
40	37.1
30	37.4
20	38.2
12	38.8
6	39.1
2	40
1	40.9
0.5	42
0.25	45

If we look at the influence brought by the change in hydrophilic groups, the cloud point of a given family of surfactants will generally increase with the hydrophilic groups. For example, the cloud point of $C_{16}E_6$ is 35.5 ^oC; the cloud point of $C_{16}E_9$ is 75 ^oC; and the cloud point of $C_{16}E_{12}$ is 92 ^oC.[18] These three amphiphiles share a hydrophobic carbon chain and differ in the number of PEGs. As the number of PEGs increases, the cloud point rises. Accordingly, we could speculate that according to this generalization the cloud point of $C_{16}E_{18}$, if it exists, is above 100 ^oC. Similarly, we can look at the trend of cloud point with the change in hydrophobic groups. For example, the cloud point of C_8E_8 is 96 ^oC; the cloud point of $C_{10}E_8$ is 84.5 ^oC; and cloud point of $C_{12}E_8$ is 77.9 ^oC; the cloud point of $C_{14}E_8$, 70.5 ^oC; and the cloud point of $C_{16}E_8$ is 65.0 ^oC. Obviously, the increase in the size of hydrophobic groups will lower the corresponding cloud point. Thus, if we extend such tendency and apply it on $C_{20}E_8$, the cloud point of $C_{20}E_8$, if there is one, is supposed to be around or below 60.0 ^oC.

Combination of the influence from both the hydrophilic group and the hydrophobic group, we can guess that the cloud point of $C_{20}E_{18}$ will be between 60.0 ^{o}C and 100 ^{o}C if such a cloud point exists.

Therefore, the fact that $E_6C_{10}E_6C_{10}E_6$ has a cloud point of 37 ^{o}C sufficiently explains how the segmentation changes the properties of the amphiphile. The low cloud point of $E_6C_{10}E_6C_{10}E_6$ indicates the ease with which the segmented amphiphile $E_6C_{10}E_6C_{10}E_6$ can desolvate its ether groups and phase separate from solution.

D. Aggregation by NMR diffusion

The previous study on surface tension shows that there is no significant aggregation in water for amphiphile $E_3C_6E_3C_6E_3$, and $E_6C_{10}E_6C_{10}E_6$ has some degree of aggregation in water as indicated by its CMC point. Detailed information on the nature of the amphiphile aggregates was further investigated by PGSE-NMR, a technique that provides a direct measurement of translational motions.[19] Since the translational mobility of a solute depends upon its effective size, namely its self-assembly, PGSE-NMR can be used to determine the size and self-aasembly of an amphiphile.

Self-diffusion is the net result of thermally induced and random motion experienced by molecules or particles in solution. NMR spectroscopy is one of the most important methods for studying self-diffusion. The NMR parameters including the spin-lattice relaxation time (T_1), the spin-spin relaxation time (T_2), line width, spectral pattern, and cross-peaks in multidimensional NMR are

sensitive to molecular motions and can be used to clarify reorientational and translational motions. Pulsed gradient spin-echo (PGSE) NMR developed from the old generation of technology field gradient (FG) NMR and becomes a powerful tool to study translational motions. [19]

All PGSE-NMR experiments were performed on a Varian INOVA 600 spectrometer equipped with a pulsed field gradient generator using a Hahn-echo sequence with intervening pulsed field gradients, that is, a complete pulse sequence of 90°-PG-180°-PG. In each experiment, the strength of the pulsed gradient was incremented in 16 steps, and the values of *D* were calculated from the attenuation of the relevant echo peaks via the Stejskal-Tanner equation. In all experiments, the observed echo decays were single-exponential and gave very good fits to the equation.

Plots of *D* versus concentration for the two block amphiphiles are given in Figure 10. If one assumes that excluded volume effects are negligible and that disperse molecules as well as the aggregates can be approximated as spheres, the *D* values provide effective sizes of the diffusing entities using the Stokes-Einstein equation. At the lowest investigated concentration (0.5 mM), $E_3C_6E_3C_6E_3$ particles have a hydrodynamic radius of about 0.7 nm and a volume of 1.4 nm^3. This is roughly the volume of one solute molecule from which one can conclude that the amphiphile is predominantly monomeric. At 25 mM, *D* corresponds to a volume that is about 50% larger than the volume at 0.5 mM. Hence, the average aggregation number increases gradually with concentration, but only to a value of 1.5. Despite its 12 methylenes, $E_3C_6E_3C_6E_3$ exists only as monomers and

dimers up to its solubility limit. Segmentation, plus possibly an “edge effect” of the proximate hydrophilic segments, severely impedes self-assembly.

The concentration dependence of *D* for $E_6C_{10}E_6C_{10}E_6$, which is much more pronounced than for $E_3C_6E_3C_6E_3$, resembles that of a conventional surfactant. The *D*’s of a typical micelle-forming amphiphile are, to a good approximation, represented by the population-weighted sum of the *D*’s for the monomers and micelles. If observed *D*’s are plotted versus the reciprocal of the concentration, one gets two straight lines intersecting sharply at the CMC. In Figure 11, such a plot is given for $E_6C_{10}E_6C_{10}E_6$ (circles) along with a hypothetical plot (dotted line) for a conventional surfactant with a CMC of 0.19 mM. The dashed line shows a prediction of the expected *D* for a conventional micelle-forming amphiphile with a CMC of 0.19mM, a $D_{monomer}$ of 2.2×10^{-10} m^2/s, and a $D_{micelle}$ of 6.1×10^{-11} m^2/s (i.e. the observed D at 25mM). The obvious deviation for $E_6C_{10}E_6C_{10}E_6$ at higher concentrations is most simply explained by a lower degree of cooperativity during self-assembly. In other words, the block amphiphile assemblies grow continuously as opposed to the molecules precipitously forming micelles of a discrete aggregation number.

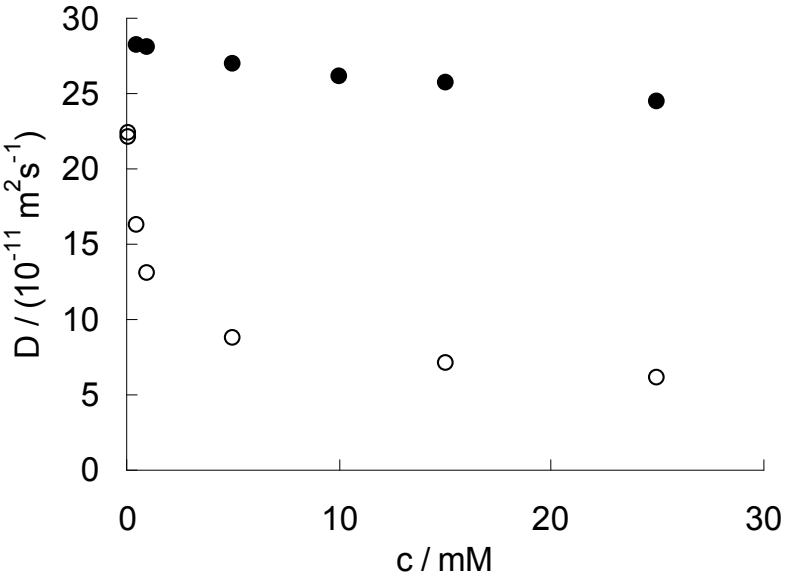


Figure 10. The observed self-diffusion coefficients of $E_3C_6E_3C_6E_3$ (●) and $E_6C_{10}E_6C_{10}E_6$ (○) at different concentrations (25 ^oC) (C represents the linear alkyl chain and E stands for the PEG unit).

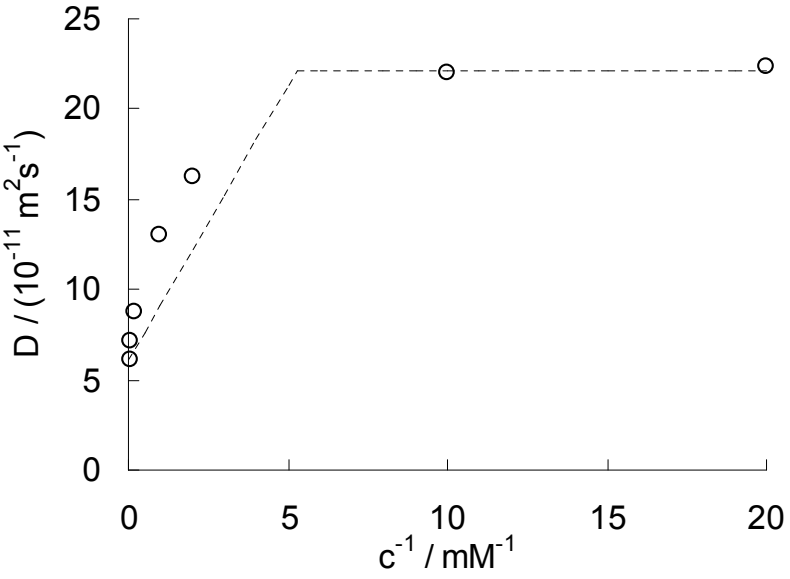


Figure 11. The self-diffusion coefficients of $E_6C_{10}E_6C_{10}E_6$ (○) presented versus reciprocal concentration (C represents the linear alkyl chain and E stands for the PEG unit).

By again invoking the Stokes-Einstein equation, we estimated the hydrodynamic radii of the $E_6C_{10}E_6C_{10}E_6$ aggregates to be 2.2 and 3.2 nm at 5 and 25 mM, respectively. These correspond to maximum average aggregation numbers of approximately 20 and 60. The aggregation numbers are maximum values because each ethylene oxide group can be expected to bind several water molecules that contribute to the overall aggregate volume. The orientation of the surfactant molecules in the self-assemblies is not as well defined as it is at the air/water interface.

Conclusion[20]

Six block amphiphiles with segemented PEGs and carbon chains have been synthesized to investigate the effect of segmentation on hydrophilic-lipophilic balance. Such effect was addressed with respect to solubility, surface activity, cloud point, and aggregation. Four out of six synthesized amphiphiles were found water insoluble. One of the two water soluble amphiphile, $E_3C_6E_3C_6E_3$, shows limited surface activity. Studies by surface tension and PGSE-NMR diffusion also indicate that $E_3C_6E_3C_6E_3$ has no large aggregation in water. The other water soluble amphiphile, $E_6C_{10}E_6C_{10}E_6$, has a much lower cloud point compared with the theoretical cloud point of unsegmented amphiphile $C_{20}E_{18}$. The CMC generated from surface tension study is relatively high compared to unsegmented nonionic amphiphiles. Studies by both surface tension and PGSE-NMR diffusion demonstrate the existence of aggregation. We conclude that segmentation has a dramatic effect upon all the addressed solute properties, including solubility, propensity to self-assemble, aggregation number, and cooperativity.

Experimental

Materials. All reagents were purchased from Aldrich or Bachem and used without additional purification. All solvents used were reagent or HPLC grade and dried over 4 Å molecular sieves.

Characterization Methods. ^{1}H and ^{13}C NMR spectra were acquired on a Varian INOVA 400 MHz (100 MHz for ^{13}C) instrument. Mass spectra experiments were completed by the Emory University Mass Spectrometry Center. Surface tension measurements were conducted on a Fisher Surface Tensiomat following the du Noüy ring procedure. Elemental analyses were performed by Atlantic Microlab in Norcross, GA. Melting points were conducted on a Thomas Hoover capillary melting point apparatus and are uncorrected. All final products were dried in vacuum over P_2O_5.

A. Syntheses of $E_mC_nE_mC_nE_m$ (C represents the linear alkyl chain and E stands for the PEG unit)

$$H(OCH_2CH_2)_3OH + TrCl \xrightarrow[45\ ^oC]{Pyridine} H(OCH_2CH_2)_3OTr$$

$TrOE_3OH$: Under N_2, 10.109g TrCl (MW 278.78, 36.3mmol) was added into a 100ml 3-neck round bottom flask charged with 62.6ml $H(OCH_2CH_2)_3OH$ (70.429g, 363mmol) and 4.302g pyridine (54.4mmol) and the reaction was stirred at 45 ^oC overnight. The reaction mixture was poured into a separatory funnel and 70ml distilled water was added. The mixture was shaken vigorously and allowed to

settle for 3 h. The bottom layer was separated from the aqueous solution, and the aqueous solution was extracted with toluene. The bottom layer was dissolved in toluene and combined with the toluene extract. The toluene solution was washed with distilled water and dried over $MgSO_4$ for 1 h with stirring, filtered, and concentrated to give gel-like crude. The crude was purified by flash chromatography (hexanes/ EtOAc 2:1) and gave 13.578g (95%) colorless gel-like product: ^{1}H NMR ($CDCl_3$, 400MHz) δ 2.29 (b, 1H), 3.26 (t, *J* = 5.2, 2H), 3.63-3.74 (m, 10H), 7.22-7.32 (m, 9H), 7.47-7.48 (d, *J* = 7.6, 6H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 62.03, 63.47, 70.76, 70.90, 71.02, 72.68, 86.77, 127.14, 127.96, 128.89, 144.26.[1]

$$TrOE_3OH + HOOC(CH_2)_{10}COOH \xrightarrow{DCC,\ DMAP} TrOE_3OOC(CH_2)_{10}COOH$$

$TrOE_3OOC(CH_2)_{10}COOH$: Under N_2, one 250ml round bottom flask was charged with 2.00g $TrOE_3OH$ (MW 392.49, 5.1mmol), 1.15g 1,10-decanedicarboxlic acid (MW 230.30, 5.0mmol), 60mg DMAP (MW 122.17, 0.5mmol), 120ml dry CH_2Cl_2, and a stirrer bar. Via a pressure-equalized addition funnel was added dropwise 1.03g DCC (MW 206.33, 5.0mmol) in 70ml dry CH_2Cl_2 over 1 hr. The reaction was stirred for another 5 hours at r.t. The reaction was filtered and concentrated to give crude. The crude was dissolved in 30ml acetone, filtered again, and concentrated to give oil crude. The oil crude was subjected to flash chromatography (EtOAC/ CH_2Cl_2 8:1) to give colorless gel-like product (1.39g, 48%): ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.27 (b, 12H), 1.64-1.63 (m, 4H), 2.84-2.37

(m, 4H), 3.28 (t, *J* = 5.2, 2H), 3.69-3.75 (m, 8H), 4.24 (t, *J* = 4.8, 2H), 7.22-7.32 (m, 9H), 7.47-7.49 (d, *J* = 7.6, 6H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 24.85, 25.03, 29.21, 29.25, 29.37, 29.51, 34.20, 34.35, 63.49, 63.60, 69.47, 70.84, 70.90, 70.96, 86.73, 127.11, 127.95, 128.89, 144.27, 174.12, 179.80.

$$TrOE_3OOC(CH_2)_{10}COOH + HOE_3OH \xrightarrow{DCC,\ DMAP} TrOE_3OOC(CH_2)_{10}COOE_3OOC(CH_2)_{10}COOE_3OTr$$

$TrOE_3OOC(CH_2)_{10}COOE_3OOC(CH_2)_{10}COOE_3OTr$: Under N_2, a 50ml round bottom flask was charged with 966mg monoester (MW 604.34, 1.6mmol), 155mg tri(ethylene glycol) (MW 194.23, 0.8mmol), 330mg DCC (MW 206.33, 1.6mmol), 20mg DMAP (MW 122.17, 0.16mmol), and stirring bar in 30ml CH_2Cl_2. The reaction was carried overnight at r.t., and filtered, concentrated to give crude. The crude was dissolved in 20ml acetone, and filtered again, concentrated to give gel-like crude. Flash chromatography on silica (CH_2Cl_2/EtOAc 8:1 → 2:1) gave colorless gel-like product (510mg, 48%): ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.24 (b, 24H), 1.58-1.60 (m, 8H), 2.25-2.33 (m, 8H), 3.23 (t, *J* = 5.2, 4H), 3.64-3.72 (m, 24H), 4.20-4.22 (m, 8H), 7.19-7.30 (m, 18H), 7.43-7.46 (m, 12H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 25.09, 29.32, 29.45, 29.59, 34.38, 34.36, 63.51, 63.60, 69.45, 69.49, 70.74, 70.89, 70.91, 70.99, 86.72, 127.12, 127.96, 128.90, 144.29, 174.02.

$$TrOE_3OOC(CH_2)_{10}COOE_3OOC(CH_2)_{10}COOE_3OTr \xrightarrow{H_2,\ Pd/C} HOE_3OOC(CH_2)_{10}COOE_3OOC(CH_2)_{10}COOE_3OH$$

$E_3C_{10}E_3C_{10}E_3$: One 25ml round bottom flask was charged with 240mg ditrityl-protected ester (MW 1322.75, 0.18mmol), 5mg 5% Pd/C, 15ml CH_2Cl_2, and a stirrer bar. Hydrogenolysis was carried out at room temperature under 1~2 atm of H_2 for 24 hours using a balloon. Upon completion of the reaction, the catalyst was filtered and washed with CH_2Cl_2. The filtrate was concentrated and subjected to flash chromatography on silica (Hexanes/EtOAc 1:1 → Hexanes/EtOAc /MeOH 1:1:0.2). The product was collected as white solid (141mg, 92%): ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.28 (b, 24H), 1.58-1.63 (m, 8H), 2.14 (b, 2H), 2.31-2.35 (m, 8H), 3.61-3.75 (m, 28H), 4.22-4.25 (m, 8H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 25.09, 29.32, 29.45, 29.59, 34.39, 61.97, 63.41, 63.51, 69.42, 69.45, 70.55, 70.75, 72.681, 174.08; HRMS Calcd. for $C_{42}H_{78}NaO_{16}$ $[M+Na]^+$ 861.5188, found 861.5166. Anal. Calcd.(%) for $C_{42}H_{78}O_{16}$ + 1/2 H_2O: C, 59.48; H, 9.39; O, 31.13. Found: C, 59.71; H, 9.35; O, 31.01.

$$TrOE_3OH + HOOC(CH_2)_8COOH \xrightarrow{DCC,\ DMAP} TrOE_3OOC(CH_2)_8COOH$$

$TrOE_3OOC(CH_2)_8COOH$: Under N_2, one 250ml round bottom flask was charged with 2.62g $TrOE_3OH$ (MW 392.49, 6.7 mmol), 1.35g sebacic acid (MW 202.25, 6.68mmol), 82mg DMAP (MW 122.17, 0.67mmol), 130ml dry CH_2Cl_2, and a

stirrer bar. Via a pressure-equalized addition funnel was added dropwise 1.38g DCC (MW 206.33, 6.7mmol) in 70ml dry CH_2Cl_2 over 1 hr. The reaction was stirred for another 5 hours at r.t. The reaction was filtered and concentrated to give crude. The crude was dissolved in 30ml acetone, filtered again, and concentrated to give oil crude. The oil crude was subjected to flash chromatography (EtOAc/ CH_2Cl_2 3:1) to give colorless gel-like product (1.83g, 48%): ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.27 (b, 8H), 1.57-1.62 (m, 4H), 2.27-2.34 (m, 4H), 3.24 (t, *J* = 5.6, 2H), 3.67-3.73 (m, 8H), 4.22 (t, *J* = 5.2, 2H), 7.19-7.30 (m, 9H), 7.45-7.47 (d, *J* = 8.0, 6H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 24.70, 24.88, 29.02, 29.09, 34.11, 34.20, 63.38, 63.52, 69.33, 70.71, 70.80, 70.84, 86.63, 127.01, 127.84, 128.78, 144.17, 174.02, 179.99.

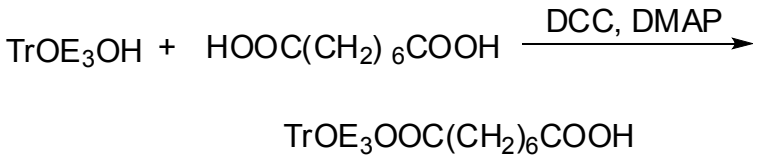
$$TrOE_3OOC(CH_2)_8COOH + HOE_3OH \xrightarrow{DCC,\ DMAP} TrOE_3OOC(CH_2)_8COOE_3OOC(CH_2)_8COOE_3OTr$$

$TrOE_3OOC(CH_2)_8COOE_3OOC(CH_2)_8COOE_3OTr$: Under N_2, a 100ml round bottom flask was charged with 3.23g monoester (MW 576.72, 5.6mmol), 0.54g tri(ethylene glycol) (MW 194.23, 2.8mmol), 1.16g DCC (MW 206.33, 5.6mmol), 35mg DMAP (MW 122.17, 0.28mmol), 380mg HOBt (MW 135.13, 2.8mmol), and stirring bar in 50ml CH_2Cl_2. The reaction was kept at 0 ^{o}C for two hours and overnight at r.t., and filtered, concentrated to give crude. The crude was dissolved in 20ml acetone, and filtered again, concentrated to give gel-like crude. Flash chromatography on silica (CH_2Cl_2/EtOAc 5:1) gave colorless gel-like product (1.54g, 43%): ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.26 (b, 16H), 1.58-1.60 (m,

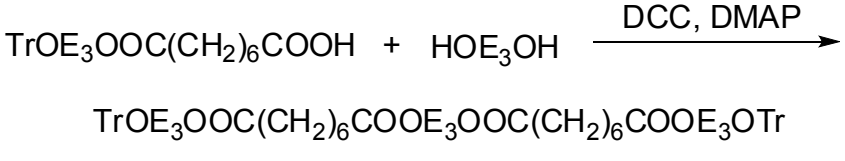
8H), 2.25-2.33 (m, 8H), 3.23 (t, *J* = 5.2, 4H), 3.64-3.72 (m, 24H), 4.20 (t, *J* = 4.8, 8H), 7.19-7.30 (m, 18H), 7.44-7.47 (m, 12H); ^{13}C NMR ($CDCl_3$, 400MHz) δ □24.95, 24.97, 29.20, 34.24, 34.27, 63.44, 63.54, 69.37, 69.41, 70.66, 70.80, 70.84, 70.92, 86.65, 127.05, 127.89, 128.83, 144.23, 173.92.

$$TrOE_3OOC(CH_2)_8COC(CH_2)_8COOE_3OTr \xrightarrow{H_2,\ Pd/C} HOE_3OOC(CH_2)_8COOE_3OOC(CH_2)_8COOE_3OH$$

$E_3C_8E_3C_8E_3$: One 50ml round bottom flask was charged with 1.47g ditrityl-protected ester (MW 1267.58, 1.16mmol), 28mg 5% Pd/C, 30ml CH_2Cl_2, and a stirrer bar. Hydrogenolysis was carried out at room temperature under 1~2 atm of H_2 for 36 hours using a balloon. Upon completion of the reaction, the catalyst was filtered and washed with CH_2Cl_2. The filtrate was concentrated and subjected to flash chromatography on silica (Hexanes/EtOAc 1:1 → Hexanes/EtOAc /MeOH 1:1:0.2). The product was collected as colorless oil (860mg, 95%): ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.23 (b, 16H), 1.528-1.56 (m, 8H), 2.23-2.28 (m, 8H), 2.70 (b, 2H), 3.53-3.66 (m, 28H), 4.14-4.17 (m, 8H); ^{13}C NMR ($CDCl_3$, 400MHz) δ □24.84, 29.04, 29.07, 34.13, 61.69, 63.25, 63.34, 69.18, 69.23, 70.34, 70.55, 72.54, 173.80; HRMS Calcd. for $C_{38}H_{70}NaO_{16}$ $[M+Na]^+$ 805.4562, found 805.4542. Anal. Calcd.(%) for $C_{38}H_{70}O_{16}$: C, 58.29; H, 9.01; O, 32.70. Found: C, 58.13; H, 9.08; O, 32.42.



$TrOE_3OOC(CH_2)_6COOH$: Under N_2, one 250ml round bottom flask was charged with 7.67g $TrOE_3OH$ (MW 392.49, 19.6 mmol), 3.41g suberic acid (MW 174.2, 19.6mmol), 240mg DMAP (MW 122.17, 1.96mmol), 120ml dry CH_2Cl_2, and a stirrer bar. Via a pressure-equalized addition funnel was added dropwise 4.04g DCC (MW 206.33, 19.6mmol) in 60ml dry CH_2Cl_2 over 1 hr. The reaction was stirred for another 6 hours at r.t. The reaction was filtered and concentrated to give crude. The crude was dissolved in 30ml acetone, filtered again, and concentrated to give oil crude. The oil crude was subjected to flash chromatography (EtOAC/ CH_2Cl_2 3:1) to give colorless gel-like product (1.83g, 42%): ^{1}H NMR ($CDCl_3$, 400MHz) δ □1.32-1.33 (m, 4H), 1.60-1.64 (m, 4H), 2.29-2.34 (m, 4H), 3.26 (t, *J* = 3.2, 2H), 3.69-3.75 (m, 8H), 4.24 (t, *J* = 3.2, 2H), 7.22-7.31 (m, 9H), 7.47-7.49 (d, *J* = 5.2, 6H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 24.62, 24.78, 28.80, 34.02, 34.18, 63.47, 63.64, 69.46, 70.83, 70.89, 70.96, 86.72, 127.11, 127.94, 128.89, 144.28, 173.93, 179.53.



$TrOE_3OOC(CH_2)_6COOE_3OOC(CH_2)_6COOE_3OTr$: Under N_2, a 100ml round bottom flask was charged with 3.50g monoester (MW 548.67, 6.37mmol), 0.62g

tri(ethylene glycol) (MW 194.23, 3.2mmol), 1.31g DCC (MW 206.33, 6.37mmol), 40mg DMAP (MW 122.17, 0.32mmol), 220mg HOBt (MW 135.13, 1.6mmol), and stirring bar in 50ml CH_2Cl_2. The reaction was kept at 0 ^oC for two hours and overnight at r.t., and filtered, concentrated to give crude. The crude was dissolved in 20ml acetone, and filtered again, concentrated to give gel-like crude. Flash chromatography on silica (CH_2Cl_2/EtOAc 4:1) gave colorless gel-like product (1.74g, 45%): ^1H NMR ($CDCl_3$, 400MHz) δ 1.25 (b, 8H), 1.57-1.60 (m, 8H), 2.26-2.31 (m, 8H), 3.23 (t, *J* = 2.8, 4H), 3.63-3.71 (m, 24H), 4.21 (t, *J* = 2.8, 8H), 7.19-7.28 (m, 18H), 7.45-7.46 (m, 12H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 24.79, 28.84, 34.18, 63.45, 63.56, 69.35, 69.39, 70.66, 70.81, 70.83, 70.92, 86.65, 127.05, 127.89, 128.83, 144.23, 173.77.

$$TrOE_3OOC(CH_2)_6COOE_3OOC(CH_2)_6COOE_3OTr \xrightarrow{H_2,\ Pd/C} HOE_3OOC(CH_2)_6COOE_3OOC(CH_2)_6COOE_3OH$$

$E_3C_6E_3C_6E_3$: One 50ml round bottom flask was charged with 1.62g dityrityl-protected ester (MW 1211.46, 1.34mmol), 32mg 5% Pd/C, 30ml CH_2Cl_2, and a stirrer bar. Hydrogenolysis was carried out at room temperature under 1~2 atm of H_2 for 36 hours using a balloon. Upon completion of the reaction, the catalyst was filtered and washed with CH_2Cl_2. The filtrate was concentrated and subjected to flash chromatography on silica (Hexanes/EtOAc 1:1 → Hexanes/EtOAc /MeOH 1:1:0.2). The product was collected as colorless oil (885mg, 91%): ^1H NMR ($CDCl_3$, 400MHz) δ 1.31-1.34 (m, 8H), 1.60-1.63 (m, 8H), 2.30-2.34 (m, 8H), 3.59-3.73 (m, 28H), 4.20-4.24 (m, 8H); ^{13}C NMR ($CDCl_3$,

400MHz) δ 24.83, 28.90, 34.21, 61.91, 63.41, 63.52, 69.35, 69.39, 70.49, 70.71, 72.68, 173.89; HRMS Calcd. for $C_{34}H_{62}NaO_{16}$ $[M+Na]^+$ 749.3936, found 749.3933. Anal. Calcd.(%) for $C_{34}H_{62}O_{16}$ + 1/2 H_2O: C, 55.50; H, 8.63; O, 35.88. Found: C, 55.54; H, 8.76; O, 35.69.

$$H(OCH_2CH_2)_6OH + TrCl \xrightarrow[45\ ^oC]{Pyridine} H(OCH_2CH_2)_6OTr$$

$TrOE_6OH$: Under N_2, 8.2 TrCl (MW 278.78, 29.4mmol) was added into a 100ml 3-neck round bottom flask charged with 25g $H(OCH_2CH_2)_3OH$ (MW 282.34, 88mmol) and 10ml pyridine and the reaction was stirred at 45 ^{o}C overnight. After the reaction is completed, 200ml DI water was added and 3 x 100ml toluene was used to extract the product. The combined organic solution was dried over Na_2SO_4 and the solvent was removed to give crude. Flash chromatography (5% MeOH in EtOAc) resulted 13.6g colorless product (88%): ^{1}H NMR ($CDCl_3$, 400MHz) δ 3.24 (t, *J* = 4.4, 2H), 3.59-3.73 (m, 22H), 7.21-7.31 (m, 9H), 7.46-7.48 (d, *J* = 7.6, 6H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 61.94, 63.53, 70.53, 70.77, 70.82, 70.89, 70.99, 71.50, 72.74, 86.73, 127.13, 127.98, 128.93, 144.34.

$$TrOE_6OH + HOOC(CH_2)_{10}COOH \xrightarrow{EDCI,\ DMAP} TrOE_6OOC(CH_2)_{10}COOH$$

$TrOE_6OOC(CH_2)_{10}COOH$: Under N_2, one 250ml round bottom flask was charged

with 5.72g $TrOE_6OH$ (MW 524.65, 10.9mmol), 5.02g 1,10-decanedicarboxlic acid (MW 230.30, 21.8mmol), 266mg DMAP (MW 122.17, 2.18mmol), 150ml dry THF, and a stirrer bar. After all the 1,10-decanedicarboxlic acid dissolved, 4.179g EDCI (MW 191.71, 21.8mmol) was added. The reaction was stirred for two days and the solution was filtered. The filtrate then was concentrated to give crude. Flash chromatography (7:1 DCM/ EtOAc) resulted 2.57g colorless product (32%): ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.26 (b, 12H), 1.59-1.60 (m, 4H), 2.29-2.33 (m, 4H), 3.22 (t, *J* = 4.8, 2H), 3.62-3.68 (m, 20H), 4. 20 (t, *J* = 4.8, 2H), 7.19-7.29 (m, 9H), 7.44-7.46 (d, *J* = 7.2, 6H); ^{13}C NMR ($CDCl_3$, 400MHz) δ □24.70, 24.86, 29.03, 29.06, 29.19, 29.33, 34.01, 34.16, 63.29, 63.36, 69.14, 70.49, 70.53, 70.55, 70.65, 70.74, 86.51, 126.92, 127.75, 128.69, 144.10, 173.87, 178.86.

$$TrOE_6OOC(CH_2)_{10}COOH + HOE_6OH \xrightarrow{EDCI,\ DMAP} TrOE_6OOC(CH_2)_{10}COOE_6OOC(CH_2)_{10}COOE_6OTr$$

$TrOE_6OOC(CH_2)_{10}COOE_6OOC(CH_2)_{10}COOE_6OTr$: Under N_2, a 50ml round bottom flask was charged with 715mg monoester (MW 736.95, 0.97mmol), 136mg hexta(ethylene glycol) (MW 282.34, 0.48mmol), 372mg EDCI (MW 191.71, 1.94mmol), 24mg DMAP (MW 122.17, 0.19mmol), and stirring bar in 30ml dry THF. The reaction was carried overnight at r.t., and filtered, concentrated to give crude. Preparative TLC (EMD, 20cm x 20cm x 2mm, 3:1 CH_2Cl_2 : EtOAc) was used to separate crude mixture and resulted 231mg colorless gel-like product (28%): ^{1}H NMR ($CDCl_3$, 400MHz) δ □1.25 (b, 24H),

1.57-1.60 (m, 8H), 2.28-2.31 (m, 8H), 3.20 (t, *J* = 5.6, 4H), 3.61-3.68 (m, 64H), 4.18-4.21 (m, 8H), 7.18-7.28 (m, 18H), 7.43-7.46 (m, 12H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 25.03, 29.27, 29.40, 29.55, 34.33, 63.45, 63.50, 69.33, 70.72, 70.81, 70.93, 86.65, 127.06, 127.90, 128.85, 144.26, 173.98; HRMS Calcd. for $C_{98}H_{143}O_{25}$ $[M+H]^+$ 1719.9935, found 1719.9935.

$$TrOE_6OOC(CH_2)_{10}COOE_6OOC(CH_2)_{10}COOE_6OTr \xrightarrow{H_2,\ Pd/C} HOE_6OOC(CH_2)_{10}COOE_6OOC(CH_2)_{10}COOE_6OH$$

$E_6C_{10}E_6C_{10}E_6$: One 25ml round bottom flask was charged with 350mg ditrityl-protected ester (MW 1720.16, 0.2mmol), 5mg 5% Pd/C, 15ml CH_2Cl_2, and a stirrer bar. Hydrogenolysis was carried out at room temperature under 1~2 atm of H_2 for 48 hours using a balloon. Upon completion of the reaction, the catalyst was filtered and washed with CH_2Cl_2. The filtrate was concentrated and subjected to flash chromatography on silica (Hexanes/EtOAc 1:1 → Hexanes/EtOAc /MeOH 1:1:0.2). The product was collected as colorless oil (226 mg, 90%): ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.81 (b, 24H), 1.50-1.53 (m, 8H), 2.21-2.25 (m, 8H), 3.52-3.66 (m, 64H), 4.11-4.17 (m, 8H); ^{13}C NMR ($CDCl_3$, 400MHz) δ 24.89, 29.09, 29.24, 29.38, 34.16, 34.19, 61.12, 63.25, 63.35, 69.17, 69.34, 69.84, 70.11, 70.16, 70.23, 70.31, 70.55, 70.58, 72.28, 173.82; HRMS Calcd. for $C_{60}H_{114}NaO_{25}$ $[M+Na]^+$ 1257.7547, found 1257.7504. Anal. Calcd.(%) for $C_{60}H_{114}O_{25}$: C, 58.33; H, 9.30; O, 32.37. Found: C, 55.45; H, 8.92; O, 32.48.

Note: EA was taken on material recovered after all the experiments on it were completed.

B. NMR Diffusion Experiments

All NMR experiments were performed at 25°C on a Varian INOVA 600 spectrometer equipped with a pulsed field gradient (PFG) generator and a PFG amplifier. The samples were inserted into the probe at least 20 minutes prior to the experiments to allow for thermal equilibrium to be attained.

The experiments were run using a Hahn-echo sequence with intervening pulsed field gradients.[2] The delay between the gradient pulses (Δ) and the width of the pulsed gradient pulses (δ) were kept constant at 140 ms and 7 ms, respectively, while the strength of the pulsed gradient (*G*) was linearly incremented from 0.01 up to 0.2 T/m (maximum varied among experiments and samples) in 16 steps. The gradient strength was calibrated by making a measurement on H_2O in D_2O (D=1.902*10^{-9} m^2/s), and linearity of the gradient amplifier in the used gradient strength interval was verified by measurements on poly(ethylene glycols) with known *D*.[21]

The self-diffusion coefficients (*D*) of solutes were calculated from the attenuation of the relevant echo peaks by a linear least-squares fit to the Stejskal-Tanner equation [22]:

$$\ln(I/I_0) = -(\gamma G\delta)^2 D(\Delta - \delta/3)$$

where *I* is the measured signal intensity, I_0 the signal intensity in the absence of gradient pulses, γ the magnetogyric ratio of protons, and the rest of the

parameters as defined above. In all experiments, the observed echo-decays gave very good fits to the Stejskal-Tanner equation.

Footnotes and References – Part II

1. Holmberg, K.; Jönsson, B.; Kronberg, B.; Lindman, B. *Surfactants and Polymers in Aqueous Solution*. 2nd Ed.; John Wiley & Sons: Chichester, UK, **2003**.
2. Figure comes from http://en.wikipedia.org/wiki/Amphiphile.
3. (a) Griffin, W.C. Classification of Surface-Active Agents by "HLB". *J. Soc. Cosmetic Chem.* **1949**, *1*, 311. (b) The HLB System, ICI United States, Inc. (now ICI Americas, Inc.) Wilmington, **1976**.
4. Myers, D. In *Surfactant Science and Technology*; John Wiley & Sons: New Jersey, **2005**.
5. Schneider, H-J.; Schiestel, T.; Zimmermann, P. *J. Am. Chem. Soc.* **1992**, *114*, 7698.
6. (a) VBgtle, F. *Supramolecular Chemistry*; Wiley: Chichester, England, **1991**. (b) Roberts, S. M., Ed. *Molecular Recognition; Chemical and Biochemical Problems*; Royal Society of Chemistry: Cambridge, **1989**. (c) Schneider, H.-.J., Diirr, H. Eds. *Frontiers in Supramolecular Organic Chemistry and Photo-chemistry;* VCH: Weinheim, Germany **1991**.
7. Ovchinnikov, Y. A.; Abdulaev, N. G..; Feigina, M. Y.; Kisele; A. V.; Lobanov, N. A. *FEBS lett*. **1979**, *100*, 219.
8. Wilson, J.; Hunt, T. in *Molecular Biology of the Cell, Fourth Edition: A Problems Approach*. 4th Ed.; Garland Science: New York, NY, **2002**.
9. Interaction between monotopic membrane proteins and the cell membrane: http://en.wikipedia.org/wiki/Peripheral_membrane_protein.

10. For other studies of small-molecule segmentation see Chen, Y.; Baker, G. L. *J. Org. Chem.* **1999**, *64*, 6870. Menger, F. M.; Galloway, A. L. *J. Am. Chem. Soc.* **2004**, *126*, 15883.

11. Chen, Y.; Baker, G.L. *J. Org. Chem*. **1999**. *64*, 6870.

12. Miller, M.L. *J. Med. Chem.* **2004**. *47*, 4802.

13. Widely used methods measuring surface tension include: Du Noüy Ring method, Wilhelmy plate method, Spinning drop method, Pendant drop method, Bubble pressure method, Drop volume method, Capillary rise method, Stalagmometric method, and Sessile drop method.

14. Pictures from http://www.kruss.info/index.php?content=http%3A// www.kruss. info/ techniques/surface_tension_e.html.

15. Rosen, M. J. Surfactants and Interfacial Phenomenon. John Wiley & Sons: New York, NY. **1978**.

16. Elworthy, P. H.; McDonald, C.; *Kolloid-Z*. **1964**, *195*, 6.

17. Jönsson, B; Lindman, B; Holmber, K; Kronberg, B. *Surfactants and Polymers in Aqueous Solution* Wiley: Chichester, **1998**; p.38.

18. (a) Becker, P. *In Nonionic Surfactants*; Schick, M. J., Ed.; Marcel Dekker: New York, **1966**. (b) Huibers, P. D. T.; Shah, D. O.; Katritzky, A. R. *J. Colloid Interface Sci.* **1997**, *193*, 132.

19. Price, W. S. Concepts Magn. Reson. **1997**, *9*, 299 and **1998**, *10*, 197.

20. Paper published: Menger, F.; Lu, H.; Lundber, D. *J. Am. Chem. Soc.* **2007**, *129*, 272.

21. Håkanson B.; Nydén M.; Söderman O. *Colloid Polym. Sci.* **2000***, 278*, 399.

22. Stejskal E. O.; Tanner J. E. *J. Chem. Phys.* **1965***, 42*, 288.