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Synthetic Approach to the AB Ring System of Ouabain

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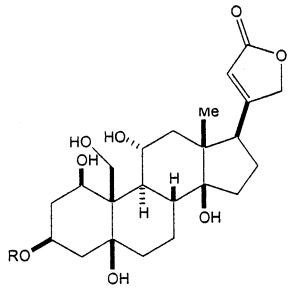
Several novel hydroxylated *cis*-decalin derivatives, potential intermediates for the synthesis of the AB ring system of the important cardiotonic steroid ouabain, have been synthesized from commercially available starting materials. The first step in the preparation of these highly functionalized intermediates is a Robinson annulation of the β-keto ester **6** and the 4-silyl-3-buten-2-one **5** to furnish the octalone **4** with good diastereoselectivity in fair yield (due to competition with a novel silicon-to-carbon phenyl migration). Reduction of the epoxy alcohol **3** (derived from **4** in two high-yielding steps) with $LiAlH_4$ gave a mixture of the desired triol **11** along with the product of an unusual reductive opening at the tertiary carbon, namely the triol **12**. A plausible mechanism for this unusual reduction is presented as are possible methods for avoiding it. In particular, reduction of the corrresponding epoxy ketone **15** with aluminum amalgam proceeded in good yield to give the hydroxy ketone **16**. Also reduction of the epoxide ester having the inverted stereochemistry at C3 afforded the desired tertiary alcohol **33** in good yield. Another approach using the β,γ-unsaturated ketal **38** permitted the formation of the tertiary alcohol **40**. Fleming oxidation of the related, very functionalized silane **39** afforded the desired 1β-alcohol **41** in fair yield. Finally a novel rearrangement was observed when the epoxy alcohol **24** was treated with DIBAL to effect loss of the angular hydroxymethyl group to produce the tetrasubstitued alkene **29** in high yield.

Introduction

The cardenolide ouabain (**1**), a species of the genus *Aconcanthera* isolated from the bark and roots of the ouabaio tree by Arnaud,[1] has been used for more than two centuries in the clinical treatment of congestive heart failure (CHF).[2] Like all cardiac glycosides, ouabain, which belongs to the family of cardiotonic steroids (digitalis glycosides), works by inhibiting Na^+,K^+-ATPase to increase the force of cardiac musculature contraction (positive inotropic effect).[3] Structurally, ouabain differs from most common steroids in that its AB and CD rings are cis rather than trans fused, it has a tertiary hydroxyl group at C-14, the 19-methyl group is hydroxylated, and the substituent at C-17 is a butenolide. The compound's novel stereochemistry and high degree of oxygenation have made it, not surprisingly, a challenging synthetic target. However, although a number of syntheses using steroidal starting materials[4] and degradation studies[5] have been reported, to date no total synthesis of ouabain has appeared in the literature.



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In our proposed total synthesis of ouabain, we envisioned that the AB ring system (**2**) could be derived from the epoxy alcohol **3** (Scheme 1), a key intermediate already possessing three oxygenated carbons and a phenyldimethylsilyl group as a masked hydroxyl with the desired all-cis stereochemistry. The decalone derivative **4**, which is produced from a Robinson annulation between the dimethyl(phenyl)silyl enone **5** and the β-keto ester **6**, seemed a suitable precursor for the epoxy alcohol **3**. We report herein our approach to the synthesis of the tetraol **2**.

Results and Discussion

A. Robinson Annulation. The Michael acceptor **5** was synthesized in five steps in high yield (Scheme 2) starting from commercially available 3-butyn-2-ol.[6] The

(1) Arnaud, M. *Compt. Rend. Acad.* **1888**, *107*, 1011.
(2) Bigelow, N. M.; Jacobs, W. A. *J. Biol. Chem.* **1932**, *96*, 647.
(3) Ruegg, U. T. *Experientia* **1992**, *48*, 1102.
(4) (a) Hanson, J. R. *Nat. Prod. Rep.* **1993**, *10*, 313. (b) Hanson, J. R. *Nat. Prod. Rep.* **1998**, *15*, 298.
(5) (a) Overman, L. E.; Rucker, P. V. *Tetrahedron Lett.* **1998**, *39*, 4643. (b) Overman, L. E.; Rucker, P. V. *Heterocycles* **2000**, *52*, 1297. (c) Hynes, J., Jr.; Overman, L. E.; Nasser, T.; Rucker, P. V. *Tetrahedron Lett.* **1998**, *39*, 4647. (d) Deng, W.; Jensen, M. S.; Overman, L. E.; Rucker, P. V.; Vionnet, J. P. *J. Org. Chem.* **1996**, *61*, 6760. (e) Laschat, S.; Narjes, F.; Overman, L. E. *Tetrahedron* **1994**, *50*, 347.

(6) Jung, M. E.; Piizzi, G. *J. Org. Chem.* **2002,** *67*, 3911.

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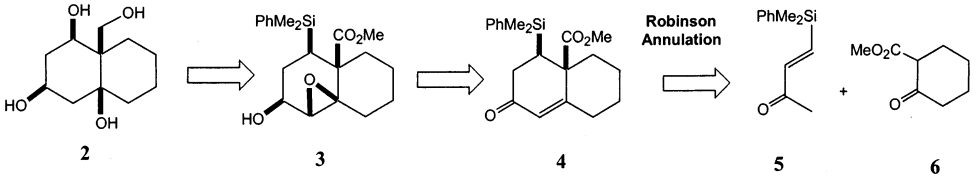
SCHEME 1



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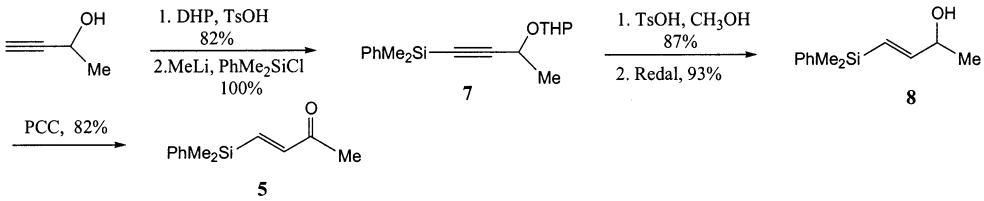
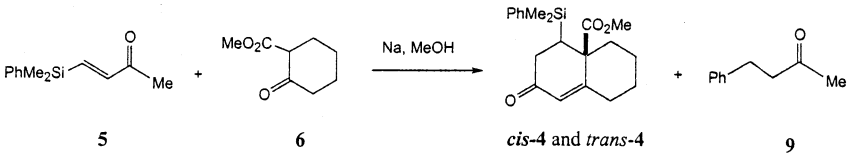
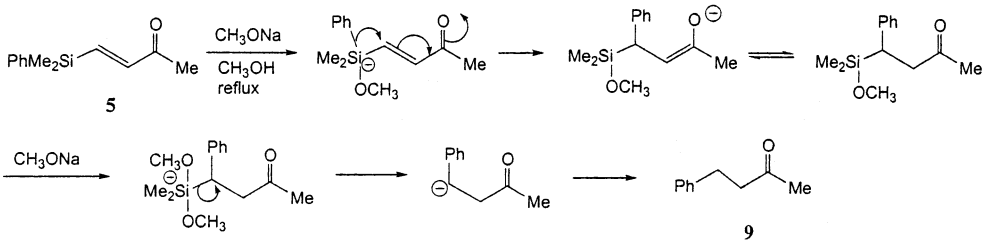


TABLE 1. Robinson Annulation



entry	[**5**] (M)	[**6**] (M)/equiv	[NaOMe] (M)/equiv	temp (°C)/time	product(s) ratio **4**:**9** (cis:trans)	yield of **4** (%)
1	0.09	0.09/1−2	0.09/0.4−1	0−80/1−2 d	0.01:1 (6:1)	<5
2	2.54	2.54/1	1.78/0.7	25−80/2.5 d	1.4:1 (6:1)	21
3	1.77	3.2/1.8	1.77/1	25−80/42 h	2.4:1 (6:1)	40
4	2.17	6.5/3	2.17/1	80/18 h	6.2:1 (1:1)	31
5	1.30	5/3.8	1.3/1	25−80/38 h	>7:1 (1.2:1)	29

SCHEME 3



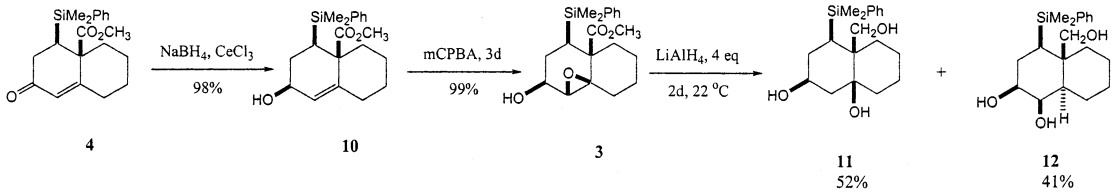
results of the Robinson annulation between the enone **5**[6] and the β-keto ester **6**[7] are summarized in Table 1. Initial attempts to build the desired decalone system were carried out under mild conditions (entry 1) to avoid the retro-Dieckmann condensation of the β-keto ester and polymerization of the Michael acceptor. However, at low concentration (<0.1 M) and temperature (<80 °C), none of the desired product was observed. When the mixture was refluxed for a prolonged period, only a trace of the Robinson annulation product **4** was detected, the starting material being consumed by unproductive pathways. A significant amount of the retro-Dieckmann fragmentation product of the β-keto ester was recovered along with 4-phenyl-2-butanone **9**. The formation of the major diastereomer (*cis*-**4**) is probably due to the greater stability of the latter in which the bulky dimethyl(phenyl)silyl group is placed in the equatorial position. A plausible mechanism for the formation of **9** is shown in Scheme 3.[6] The initial formation of a pentacovalent silicon intermediate would trigger a 1,2-phenyl migration to the adjacent electrophilic carbon.[8] A new charged silicon species could then leave behind a stabilized benzyl anion which, upon protonation, would yield the observed product **9**.

In an attempt to minimize intramolecular quenching of the enone **5** and to favor the desired intermolecular annulation, several experimental conditions were tested (Table 1). A significant increase in the concentration of reactants resulted in a remarkable improvement in the ratio of the desired product **4** and the rearranged product **9** with a consequent increase in the yield of the former (entries 2−5). When an excess (1.8 equiv) of the β-keto ester **6** was used to compensate for its loss during the retro-Dieckmann process, the yield of the desired Robinson annulation product reached 40% (entry 3). This result is noteworthy considering that a similar Robinson

(7) Ruest, L.; Blouin, G.; Deslongchamps, P. *Synth. Commun.* **1976**, *6*, 169.

(8) Fleming, I.; Newton, T. W.; Sabin, V.; Zammattio, F. *Tetrahedron* **1992**, *48*, 7793.

SCHEME 4



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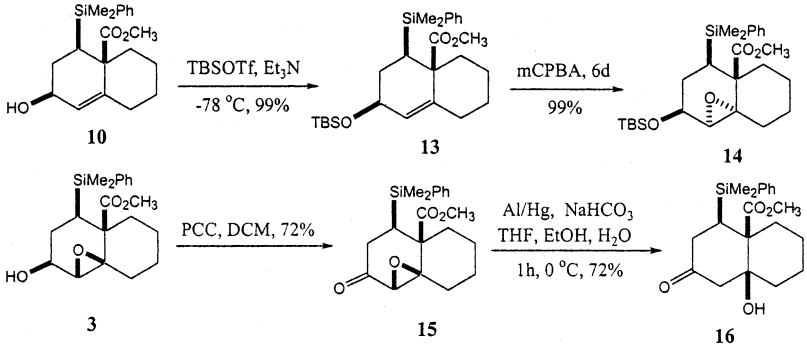

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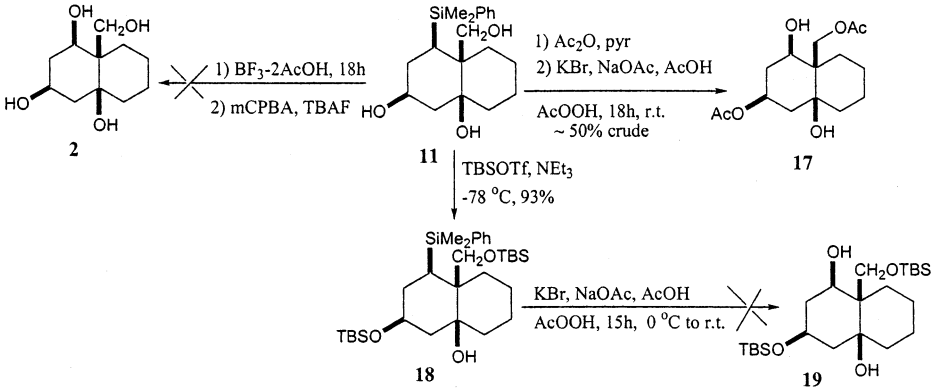


annulation using the trimethylsilyl enone, for which no such migration can occur, afforded a mixture of diastereomeric products in only 45% yield.[9] Subsequent attempts to further tune the reaction conditions failed. While the rearrangement was clearly disfavored (product ratios for entries 3−5), the yield of the desired enone **4** did not improve. Therefore we used the conditions of entry 3 to obtain consistently a 40% isolated yield of the desired enone.

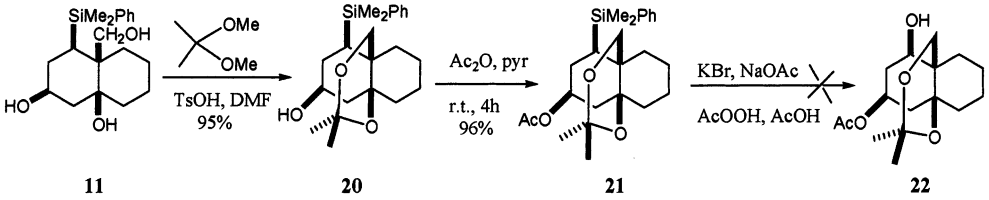
B. Toward the AB Ring System of Ouabain. For the synthesis of the target AB ring system, the Robinson annulation product *cis*-**4** was subjected to Luche reduction[10] and afforded the desired *β*-allylic alcohol **10** exclusively in nearly quantitative yield, as shown in Scheme 4. Subsequent epoxidation occurred only on the *β*-face as expected to give the desired epoxy alcohol **3**. Reduction of the ester and opening of the epoxide with $LiAlH_4$ afforded the all-cis triol **11** in 52% yield. The regioisomeric triol **12**, derived from opening of the epoxide at the tertiary center, was also isolated in 41% yield. Even though this represented a very rapid approach to the desired all-cis triol **11**, the low selectivity in the reduction prompted us to investigate other routes for the introduction of the tertiary hydroxyl group with improved selectivity.

The allylic alcohol **10** was protected as its TBS ether **13** under standard conditions in 65% yield (Scheme 5). However, attempted oxymercuration of **13** with $Hg(TFA)_2$ or $Hg(OAc)_2$ was unsuccessful. Epoxidation of **13** with mCPBA was very slow and ultimately required 6 days to go to completion to give only the undesired α-epoxide **14** in excellent yield. Nevertheless, the epoxy alcohol **3** could be oxidized in 72% yield to the corresponding ketone **15**, which upon treatment with aluminum amalgam gave exclusively the tertiary alcohol **16** in good yield.[11] Unfortunately, selective reduction of the ketone **16** with $NaBH_4$ in methanol, lithium in liquid ammonia, or Ni−Raney in ethanol only resulted in complex mixtures of products.

We then returned to the triol **11**, and attempted to oxidize the silyl group[12] of this advanced intermediate, the last step required for the synthesis of the target AB ring system (Scheme 6). Treatment of the silane **11** with mercury(II) trifluoroacetate in a mixture of acetic and trifluoroacetic acid followed by addition of peracetic acid

(9) Hwu, J. R.; Furth, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 8834.
(10) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(11) Corey, E. J.; Ensley, H. E. *J. Org. Chem.* **1973**, *38*, 3187.
(12) For an excellent review see: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.

SCHEME 7



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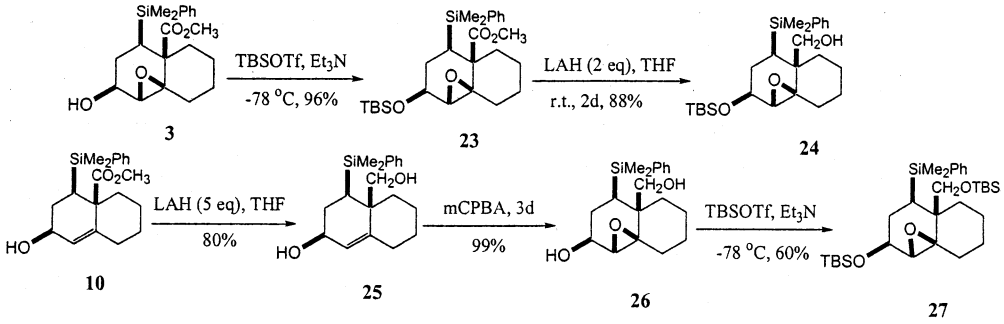


resulted in a complex mixture of products.[13] A similar result was obtained during alkoxy-mediated intramolecular displacement of the phenyl group on silicon (NaH, THF, 0−22 °C).[14]

When the oxidation of the silyl triol **11** was carried out under Fleming conditions,[15] although some peaks of the desired tetraol **2** could be detected in a crude mixture, this was difficult to purify even after peracetylation. Acetylation of the two most accessible hydroxyl groups of **11** was accomplished under standard conditions. During the oxidation of the resulting diacetate, using the mild protocol introduced by Fleming et al.,[16] the desired diacetoxy diol **17** was detected as the major product (∼50%) in the crude mixture. However, purification by conventional chromatographic techniques (flash chromatography, preparative TLC, reverse-phase HPLC) was unsuccessful. Even the bis(*tert*-butyldimethylsilyl)-protected silane **18** was found to be resistant to the same mild oxidation protocol.[16]

To circumvent the isolation problems, the triol **11** was treated with 2,2-dimethoxypropane and *p*-toluenesulfonic acid to give exclusively the acetonide **20** in high yield (Scheme 7). The C-3 hydroxyl was also protected as its acetate to afford the less hydrophilic intermediate **21**. Unfortunately, probably due to the low reactivity of the more sterically encumbered silyl group, this new silane **21** did not undergo oxidation.

C. Unexpected Epoxide Opening. The competitive opening of the epoxide **3** at the tertiary and secondary carbons might be predicted based on the similar accessibility of these two centers as shown in Figure 1 (geometry optimized by using Spartan PM3 calculation). This hypothesis prompted us to prepare alternative substrates on which to test the reductive epoxide opening (Scheme 8).

Protection of the C-3 hydroxyl of the alcohol **3** with TBSOTf gave in 96% yield the epoxide **23**, which was then treated with an excess of lithium aluminum hydride to give **24** without competitive opening of the epoxide. The bis-TBS-protected epoxide **27** was prepared from the allylic alcohol **10** in three steps under the usual conditions. We next subjected these new epoxides to several hydride-opening conditions (Table 2). When the parent epoxy-ester **3** was treated with 1 equiv of lithium aluminum hydride, no reaction took place even after refluxing at 80 °C over a long period (entry 1). Even using 3 equiv of reducing agent proved insufficient for opening the epoxide and only succeeded in reducing the ester (entry 2). Interestingly, 4 equiv of the hydride reagent was found to be the minimum amount required for the two-step process to go to completion (entry 4). However, under these conditions no selectivity was achieved and the opening occurred at the less hindered secondary carbon as well as at the tertiary center. Moreover, when the parent epoxide **3** was subjected to a large excess of lithium aluminum hydride, a similar result was obtained, namely, a 1:1 mixture of the regioisomeric triols **11** and **12** (entry 4). To exclude the possibility of a Li cation-assisted epoxide opening, the epoxide **3** was treated with sodium aluminum hydride under identical conditions as

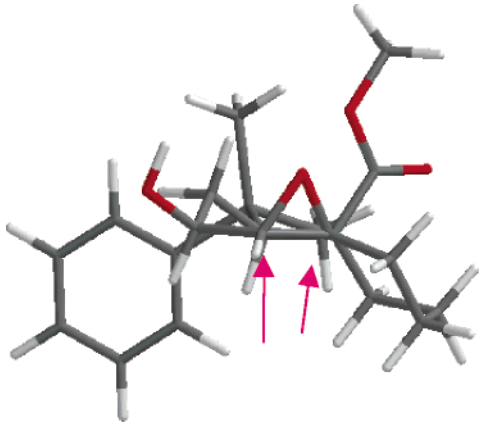
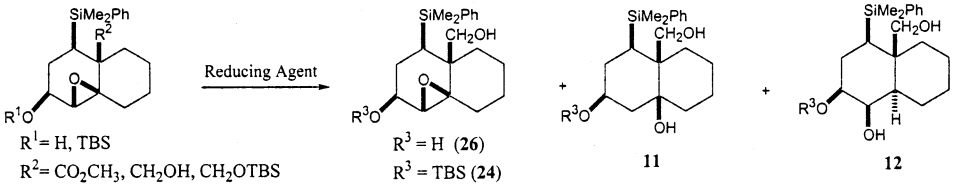


FIGURE 1. Epoxide **3**.

(13) Kolb, C. H.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2735.
(14) Harada, T.; Imanaka, S.; Ohyama, Y.; Matsuda, Y.; Oku, A. *Tetrahedron Lett.* **1992**, *33*, 5807.
(15) Fleming, I.; Newton, T. W.; Sabin, V.; Zammattio, F. *Tetrahedron* **1992**, *48*, 7793.
(16) Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, *28*, 4229.

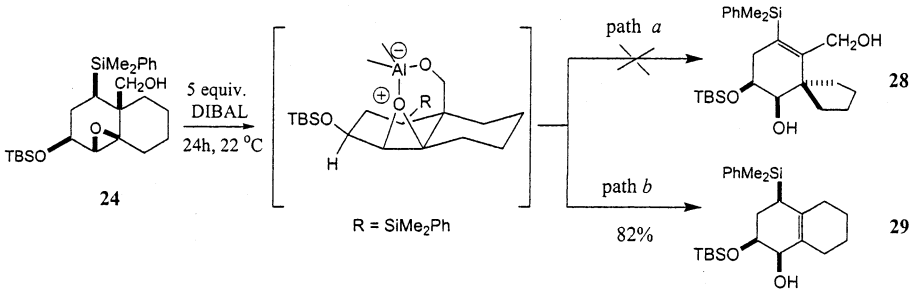
TABLE 2. Epoxide Opening[a]



entry	compd	R^1	R^2	reductant	equiv	time	product(s)[b]
1	**3**	H	CO_2CH_3	$LiAlH_4$	1	3 d[c]	SM
2	**3**	H	CO_2CH_3	$LiAlH_4$	3	2 d	**26**
3	**3**	H	CO_2CH_3	$LiAlH_4$	4	2 d	**11** (52%), **12** (41%)[d]
4	**3**	H	CO_2CH_3	$LiAlH_4$	10	7 h	**11**, **12** (~1:1)
5	**3**	H	CO_2CH_3	$NaAlH_4$	4	2 d	**11**, **12** (~1:1), SM
6	**26**	$R^3 = H$		$LiAlH_4$	2	6 d	SM
7	**23**	TBS	CO_2CH_3	$LiAlH_4$	1	2 d	**24**, SM (1:6)
8	**23**	TBS	CO_2CH_3	$LiAlH_4$	4	2 d	**24**, SM (1:1)[e]
9	**23**	TBS	CO_2CH_3	$LiAlH_4$	15	2 d	**12**
10	**23**	TBS	CO_2CH_3	DIBAL[f]	6	4 d	SM
11	**23**	TBS	CO_2CH_3	DIBAL[f]	9	4 d	SM
12	**23**	TBS	CO_2CH_3	Al, $NiCl_2$	3	2 d	SM
13	**24**	$R^3 = TBS$		$LiAlH_4$	3	2 d	SM
14	**27**	TBS	TBS	$LiAlH_4$	15	2 d	**12**

[a] All reactions were carried out in THF at 22 °C unless otherwise stated. [b] Determined from ^1H NMR analysis of the crude mixture unless otherwise stated. [c] The reaction was run at 80 °C. [d] Isolated yields. [e] Treatment of the crude mixture with an additional 6 equiv of $LiAlH_4$ and reflux in THF for 2 days yielded **24** as the only isolated product (61%). [f] The reaction was run in CH_2Cl_2.

SCHEME 9



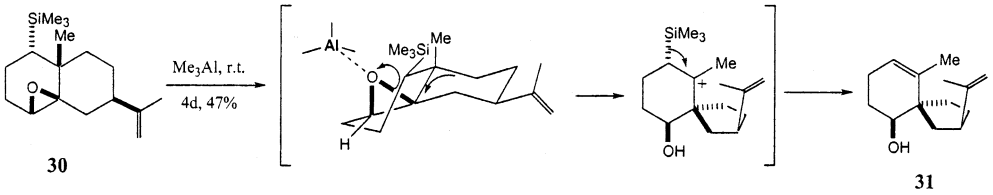
before but no selectivity was observed (entry 5). When the epoxy-diol **26** was treated with 2 equiv of $LiAlH_4$, only unreacted starting material was recovered, suggesting that the reagent is trapped by the two hydroxyl groups and is therefore unable to deliver the hydride to the epoxide (entry 6). Several attempts to reduce compound **23**, in which the C-3 hydroxyl is protected as the TBS ether, were undertaken (entries 7−12). Using a limited excess of lithium aluminum hydride gave a mixture of monoreduced product (**24**) and unreacted starting material (entries 7 and 8). Conversely, a large excess of reducing agent resulted in reduction of the ester (entry 9) and opening of the epoxide at the tertiary center, exclusively, with loss of the protecting group (entries 9 and 14). Other reducing conditions, such as an excess of diisobutylaluminum hydride (DIBAL) or a slurry of aluminum and nickel(II) chloride[17] (entries 10−12), failed to give any reaction. The same result was obtained when the epoxide **23** was refluxed with $Na[PhSeB(OEt)_3]$ and acetic acid in ethanol[18] or with PhSeNa and $Ti(OiPr)_4$,[19] thereby confirming the difficulty of opening these epoxides with nucleophilic reagents.

Surprisingly, when compound **24** was treated with an excess of DIBAL a new product was isolated in good yield (Scheme 9). Preliminary spectroscopic analysis revealed that the unexpected compound had lost the epoxide and gained a tetrasubstituted alkene. To rationalize these findings, we first postulated a DIBAL-catalyzed opening of the epoxide that could lead to the spiro compound **28** where the angular carbon is still intact (Scheme 9, path *a*). Alternatively, in the presence of DIBAL the epoxide **24** could undergo a syn-elimination with complete loss of the angular hydroxymethyl to yield the alkene **29** (Scheme 9, path *b*). The intermediate for such an elimination mechanism, shown in Scheme 9, resembles the cyclic transition state proposed by Rickborn et al. for the lithium diethylamide-induced syn-elimination of epoxides to the corresponding allylic alcohols.[20] Interestingly, extensive spectroscopic analyses (GC/MS, COSY, HMQC, and homodecoupling experiments) were consistent with compound **29**.

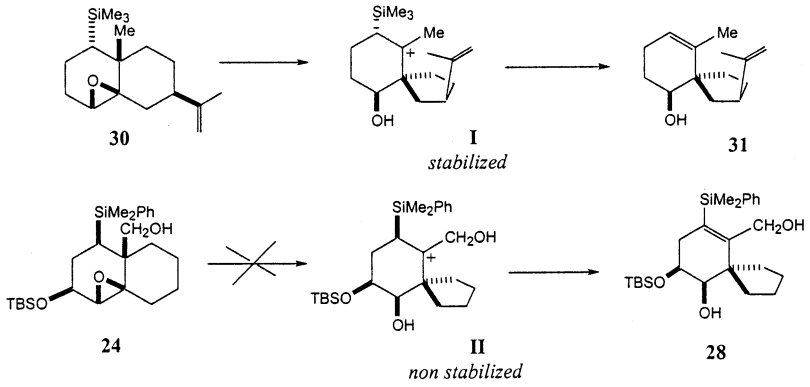
Intrigued by this finding, we found a literature precedent showing that an analogous substrate (**30**) underwent a similar rearrangement in the presence of a strong Lewis acid to give the spiro compound **31** (Scheme 10).[21]

(17) Sarmah, B. K.; Barua, N. C. *Tetrahedron* **1991**, *47*, 8587.
(18) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1989**, *111*, 3728.
(19) Blay, G.; Cardona, L.; García, B.; Pedro, J. R. *J. Org. Chem.* **1993**, *58*, 7204.
(20) Thummel, R. P.; Rickborn, B. *J. Am. Chem. Soc.* **1970**, *92*, 2064.
(21) Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1992**, *57*, 922.

SCHEME 10



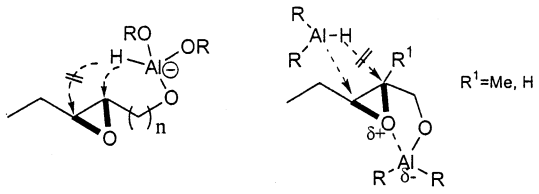
SCHEME 11



The difference in behavior of the two epoxy-decalins (**30** and **24**) can be rationalized by comparing the stability of the putative carbocations (Scheme 11). In the case of the epoxide **30**, the carbocation intermediate **I** is stabilized by the silyl group via carbon−silicon σ-bond hyperconjugation. Consequently, the optimal overlap allows for the elimination of the silyl group to give the observed alkene **31**.[21] On the other hand, inversion at the stereocenter α to the silyl group tends to disrupt this stabilization thus preventing the formation of the carbocation **II**. This is confirmed by the fact that neither the product of a proton loss (**28**) nor the product of silyl group elimination (as in **31**) was observed in the reaction of **24**. More likely, the tertiary C−O bond of the epoxide **24** breaks to give a tertiary carbocation, which is converted into the alkene **29** with loss of formaldehyde via a syn-elimination mechanism (Scheme 9).

D. Epoxide Opening: Rationale and Solution. The intriguing data shown in Table 2 regarding the unpredicted and undesired opening of a variety of epoxides prompted us to carry out further investigations. Studies on the selectivity of the opening of acyclic epoxy-alcohols can be found in the pioneering work of Kishi et al.[22] They investigated the behavior of epoxy alcohols toward the different hydride reagents, REDAL and DIBAL (Scheme 12). When REDAL is the reducing agent, an intramolecular hydride delivery takes place predominantly through a five- or six-membered-ring chelate (n = 1 or 2) to yield either a 1,3- or 1,4-diol, respectively. Conversely, the more Lewis acidic DIBAL is capable of coordinating the epoxide oxygen before delivering the hydride intermolecularly. This opening occurs predominantly at the center that allows for the formation of a five-membered-ring chelate and thus produces a 1,2-diol.

SCHEME 12

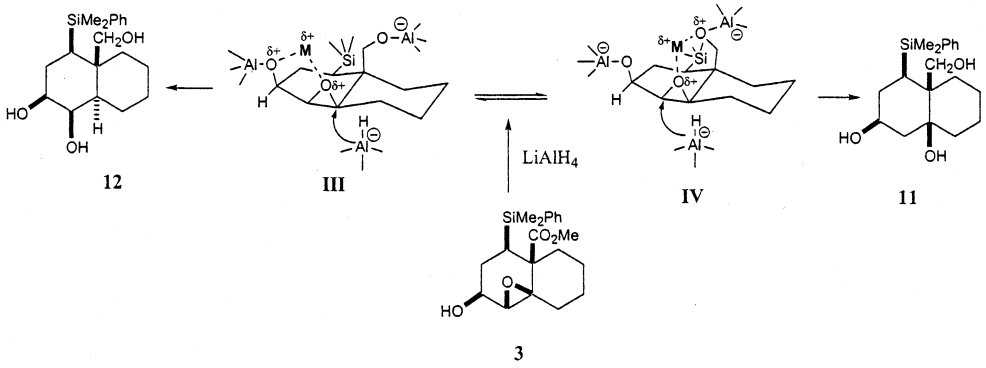


While a few examples of unusual epoxide openings on cyclic substrates can be found in the literature,[23] we were unaware of a systematic approach toward overcoming this problem. An intramolecular hydride delivery was clearly not feasible owing to conformational restrains, and it seemed unlikely that $LiAlH_4$ could act as a Lewis acid in a manner similar to DIBAL. However, this being the case, a new chelation model could be postulated (Scheme 13). After initial deprotonation of the hydroxyl groups and reduction of the ester in **3**, two equilibrating chelates **III** and **IV** can be formed. The opening of this unreactive epoxide is probably assisted by the lithium or sodium cation (M) that plays a crucial role in this process. In the chelate **III**, the C-3 hydroxyl can form a five-membered chelate with the epoxide. According to Kishi's model, intermolecular hydride delivery should then occur to give the five-membered-ring diol chelate preferentially and, as a result, the undesired triol **12** is produced. When the angular hydroxyl is involved in the chelation (**IV**), external delivery of hydride should occur at the secondary center to favor the formation of a six-membered-ring chelate and thus the desired triol **11** should be produced. The lack of selectivity observed during the openings (see Table 2) confirmed that both chelates are involved in the process. A system for testing this model and for selectively accessing the desired triol was therefore needed. The primary consideration here was to protect the hydroxyl at C-3 with a suitable protecting group (***P***), as shown in **A** (Scheme 14), a group

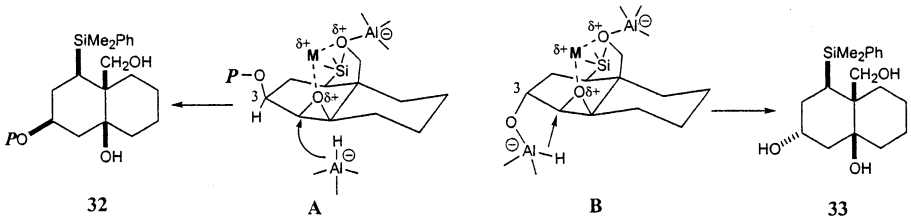
(22) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.

(23) (a) Liu, W.; Rosazza, J. P. N. *Synth. Commun.* **1996**, *26*, 2731. (b) Magar, S. S.; Desai, R. C.; Fuchs, P. L. *J. Org. Chem.* **1992**, *57*, 5360. (c) Peña, W.; López, J. T.; Cortés, M. *Synth. Commun.* **1989**, *19*, 2841.

SCHEME 13

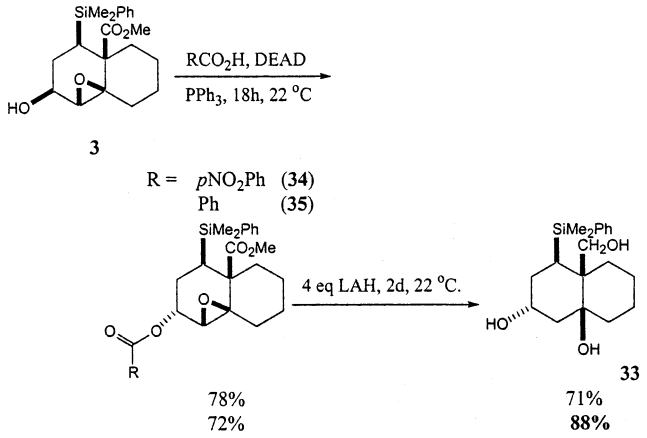


SCHEME 14



that could withstand the reaction conditions (large excess of $LiAlH_4$, 2 days at 22 °C) and reduce the possibility of chelation by the C-3 oxygen without preventing the (desirable) chelation by the angular hydroxyl group. With this optimal protecting group, the proposed model predicted that the opening would occur selectively at the secondary carbon to afford **32** as the major product. Unfortunately, finding such a protecting group proved problematic. Consequently, we changed our strategy. Chelate **B** would require inversion of the stereochemistry at C-3 but it has several advantages over **A**. The undesired chelation by the C-3 oxygen would be prevented, without the need of a protecting group. Second, the opening in **B** would take advantage not only of the assistance of the angular hydroxyl but also of an intramolecular hydride delivery by the C-3 alkoxy at the desired secondary center to give the triol **33** as the major or exclusive product. Our approach to solving the selectivity problem while giving further support to our chelation model is shown in Scheme 15.

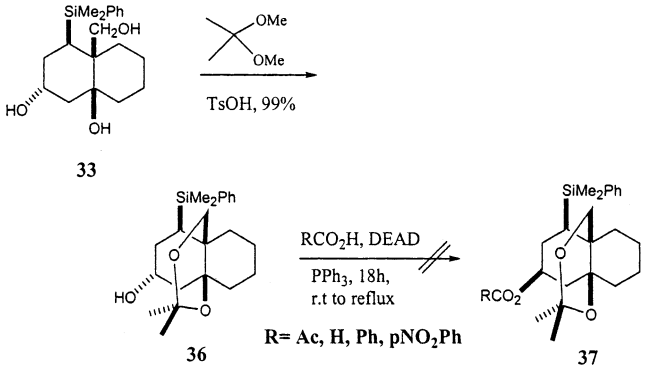
SCHEME 15



The epoxy ester **3** was subjected to standard Mitsunobu conditions with use of *p*-nitrobenzoic acid, known to be more efficient than benzoic acid for inversion of sterically hindered alcohols.[24] The benzoate **34** was treated under the usual opening conditions to give the desired epimeric triol **33** in good yield. It is noteworthy that the process accomplishes three steps: reduction of two esters and opening of the epoxide exclusively at the secondary center. However, the isolation of **33** was made difficult by the presence of a byproduct in which the nitro group had also been reduced. Therefore, we decided to use benzoic acid during the Mitsunobu reaction. The resulting inverted benzoate **35** was formed in good yield with an appreciably cleaner reduction using $LiAlH_4$.

After confirming the validity of our proposed model, we moved to the inversion of C-3 to the β-stereochemistry required for the AB ring system of ouabain (Scheme 16).

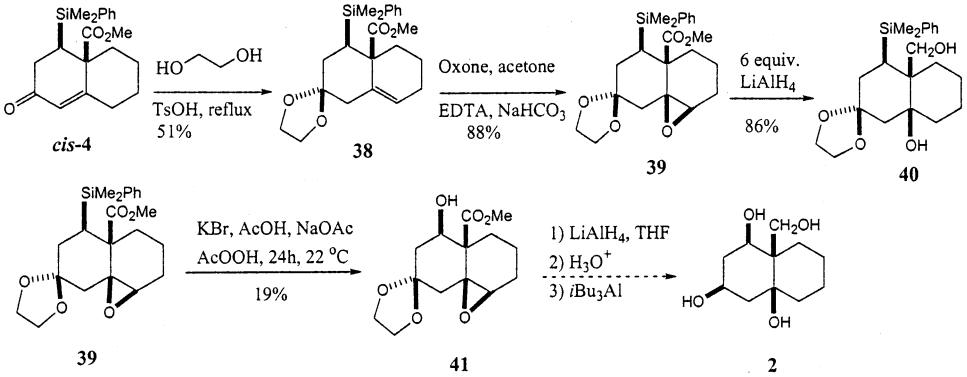
SCHEME 16



After protecting the primary and tertiary alcohols as the acetonide **36**, we attempted the Mitsunobu reaction using different conditions. However, owing to the steric congestion of the α-alcohol, the inverted ester **37** was not formed. Even activation with chloromethylsulfonyl chloride was unsuccessful. Consequently, although this strategy proved successful in the selective opening of the

(24) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *26*, 3017.

SCHEME 17



epoxide, the epimeric triol **33** was not suitable for further manipulation. We therefore undertook a new pathway to the AB ring system (Scheme 17). This approach starts with the migration of the double bond of the enone *cis*-**4** to the B ring and concomitant protection of the carbonyl at C-3 to give alkene **38** in 51% (nonoptimized) yield.[25] The stereoselective epoxidation of the double bond is carried out in high yield by using Yang's protocol.[26] In the absence of the chelating hydroxyl at C-3, the epoxide **39** opened selectively at the secondary center to afford the desired diol **40**, exclusively. Encouraged by these results, we then decided to carry out the Tamao−Fleming oxidation of the silyl group. The epoxide **39** was treated under the standard Fleming protocol[15] but a complex mixture of products resulted, which was also the case using $Hg(TFA)_2$ and AcOOH.[13] Finally, the epoxide **39** was converted to the desired alcohol **41** using the mild protocol introduced by Fleming et al.,[16] which is known to tolerate even highly substituted epoxides.[27] This advanced intermediate would then be reduced with $LiAlH_4$, as for the preparation of **40**. Then, the desired tetraol **2** would be accessed after ketal hydrolysis followed by ketone reduction using i-Bu_3Al, which has been shown to give selectively the most stable, equatorial alcohol.[28] Unfortunately, the yield of the isolated product **40** was low, confirming the difficulty of carrying out such an oxidation on a highly functionalized substrate.

Summary

While our recent results toward the synthesis of the AB ring system of ouabain were not entirely successful, they are nonetheless not without a certain intellectual interest and instructive value for future attempts at the synthesis of this compound. Despite the apparent similarities with other known decalins, this all-cis tetraol system has been shown to be unexpectedly challenging. We have nevertheless demonstrated that during the Robinson annulation, a peculiar silicon-to-carbon phenyl migration takes place and destroys the enone **5** intramolecularly. Moreover, we have increased our understanding of the unique reactivity of the epoxide **3** and have proposed a plausible mechanism and solution for its unprecedented DIBAL-promoted rearrangement and unusual $LiAlH_4$ opening. Two successful approaches to improve the selectivity of the opening have been presented; however, further manipulation of these advanced intermediates was problematic. Last, it was found that highly functionalized and sterically congested systems such as ours are not suitable candidates for the Tamao−Fleming oxidation sequence. Consequently, we are currently investigating the possibility of carrying out this process at an earlier stage in the synthesis.

Experimental Section

General. ^1H NMR spectra were obtained at 400.132 or 500.132 MHz as indicated. ^{13}C NMR spectra were recorded at 100.625 or 125.773 MHz as indicated. ^1H NMR and ^{13}C NMR data are reported in parts per million (δ) downfield from tetramethylsilane. Resonance patterns are reported with the following notations: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Second-order spectra in which coupling cannot be obtained by inspection are reported as multiplets, with the center of the signal indicated by the δ value given. Infrared spectra were recorded as neat liquid films, and only the most significant absorption bands are reported (in cm^{-1}). Thin-layer chromatography (TLC) was carried out by the use of silica gel 60 F254 0.2 mm aluminum-backed plates. Visual detection was performed with ultraviolet light or with phosphomolybdic acid or permanganate stain. Flash column chromatography was performed with silica gel 60 (230−400 mesh) and compressed air. All solvents/reagents were purified by using literature procedures. All reactions were performed under an atmosphere of argon unless otherwise noted.

(±)-(4*R*,4a*R*) Methyl 4-(Dimethylphenylsilyl)-2-oxo-2,3,4,4a,5,6,7,8-octahydronaphthalene-4a-carboxylate (*cis*-4) and (±)-(4*S*,4a*R*) Methyl 4-(Dimethylphenylsilyl)-2-oxo-2,3,4,4a,5,6,7,8-octahydronaphthalene-4a-carboxylate (*trans*-4). Sodium metal was dissolved in methanol (MeOH, 4 mL) at ambient temperature. After complete dissolution, the β-ketoester **6** (2.1 mL, 14.7 mmol) was added slowly via syringe. After 15 min, the enone **5** (1.63 g, 7.99 mmol), dissolved in MeOH (0.5 mL), was added over 7 h via syringe pump. At the end of addition, the deep-orange solution was stirred at ambient temperature for 18 h. Then the mixture was refluxed in a preheated bath at 80−85 °C for 24 h before being cooled to ambient temperature. The reaction mixture was then poured into a separatory funnel containing saturated ammonium chloride (NH_4Cl, 50 mL) and extracted with diethyl ether (Et_2O). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum to give a crude orange oil. Purification by flash column chromatography (5:1 hexanes/ethyl acetate) afforded the enones

(25) Nickisch, K.; Bittler, D.; Cleve, G.; Eckle, E.; Laurent, H. *Liebigs Ann. Chem.* **1988**, 579.
(26) Yang, D.; Jiao, G.-S. *Chem. Eur. J.* **2000**, *6*, 3517.
(27) Singleton, D. A.; Redman, A. M. *Tetrahedron Lett.* **1994**, *35*, 509.
(28) (a) Katzenellenbogen, J. A.; Bowlus, S. B. *J. Org. Chem.* **1973**, *38*, 627. (b) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355. (c) Overman, L. E.; Rucker, P. V. *Heterocycles* **2000**, *52*, 1297.

cis-**4** and *trans*-**4** as a 6:1 mixture of diastereomers (1.03 g, 40%). A second column chromatography (8:1 hexanes/ethyl acetate) yielded an analytical sample of each diastereomer.

***cis*-4**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (m, 2H), 7.34 (m, 3H), 5.89 (s, 1H), 3.49 (s, 3H), 2.61 (br d, J = 13.4 Hz, 1H), 2.50 (dd, J = 16.2, 16.2 Hz, 1H), 2.37 (m, 1H), 2.29 (dd, J = 16.2, 3.1 Hz, 1H), 2.04 (m, 1H), 1.81 (m, 1H), 1.64 (m, 2H), 1.51 (app qt, J = 13.5, 3.5 Hz, 1H), 1.40 (app qt, J = 13.0, 3.7 Hz, 1H), 1.14 (app td, J = 13.3, 3.8 Hz, 1H), 0.39 (s, 3H), 0.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 199.3, 172.5, 164.4, 136.9, 134.0, 129.2, 127.6, 125.7, 51.8, 50.9, 39.0, 35.7, 35.1, 33.6, 26.7, 23.3, −1.7, −4.0. IR (neat) 2937, 1728, 1666 cm^{-1}. HRMS (*m*/*e*) found 342.1661, calcd for $C_{20}H_{26}O_3Si$ 342.1651.

***trans*-4**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (m, 2H), 7.33 (m, 3H), 5.89 (s, 1H), 3.61 (s, 3H), 2.32 (m, 4H), 2.13 (m, 2H), 1.86 (m, 1H), 1.61 (m, 3H), 1.28 (m, 1H), 0.35 (s, 3H), 0.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 198.6, 174.2, 164.5, 137.3, 133.7, 129.1, 127.7, 125.2, 52.8, 52.2, 35.7, 35.02, 34.1, 30.7, 28.01, 22.6, −2.0, −2.6. IR (neat) 2947, 1736, 1726, 1666 cm^{-1}.

(±)-(2*S*,4*R*,4a*R*) Methyl 2-Hydroxy-4-(dimethylphenylsilyl)-2,3,4,4a,5,6,7,8-octahydronaphthalene-4a-carboxylate (10). The enone *cis*-**4** (352 mg, 1.03 mmol) was dissolved in MeOH (10 mL) and the solution was cooled to 0 °C. Then cesium(III) chloride heptahydrate (382 mg, 1.03 mmol) was added followed by sodium borohydride (78 mg, 2.04 mmol). After 5 min, the solution was warmed to ambient temperature and stirred for 4 h. Then the cloudy mixture was poured into a separatory funnel containing saturated NH_4Cl (20 mL) and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$. Solvent removal under vacuum resulted in a clear crude oil. Purification by flash column chromatography (3:1 hexanes/ethyl acetate, 1% triethylamine) yielded the alcohol **10** as a colorless oil (348 mg, 98%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (m, 2H), 7.31 (m, 3H), 5.51 (s, 1H), 4.02 (m, 1H), 3.47 (s, 3H), 2.48 (m, 1H), 2.12 (m, 1H), 1.91−1.79 (m, 2H), 1.68 (m, 1H), 1.55 (m, 2H), 1.37 (m, 1H), 1.24 (m, 1H), 1.09 (d, J = 13.4 Hz, 1H), 1.00 (m, 1H), 0.37 (s, 3H), 0.29 (s, 3H). ^{13}C NMR (CD_6CO, 125.8 MHz) δ 174.4, 140.1, 138.8, 133.8, 128.6, 128.1, 127.4, 67.4, 50.8, 49.9, 39.0, 34.4, 32.6, 30.5, 27.5, 23.7, −1.5, −5.2. IR (neat) 3515, 2932, 1728, 1699 cm^{-1}.

(±)-(1*S*,2*S*,4*R*,4a*R*,8a*R*) Methyl 2-Hydroxy-4-(dimethylphenylsilyl)decahydronaphth[1,8-*b*]oxirene-4a-carboxylate (3). The allylic alcohol **10** (290 mg, 0.843 mmol) was dissolved in dichloromethane (CH_2Cl_2, 12 mL) and treated with *m*-chloroperbenzoic acid (mCPBA, 217 mg, 1.26 mmol). After the solution was stirred for 3 d at ambient temperature, the reaction was quenched by addition of saturated sodium sulfite (8 mL). The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated sodium bicarbonate ($NaHCO_3$) and dried over $MgSO_4$. Solvent removal under vacuum resulted in a colorless oil that was purified by flash column chromatography (4:1 to 2:1 hexanes/ethyl acetate, 1% triethylamine) to afford the epoxy alcohol **3** (300 mg, 99%) as a white solid: mp 115−117 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (m, 2H), 7.31 (m, 3H), 3.74 (m, 1H), 3.63 (s, 3H), 3.07 (s, 1H), 2.36 (m, 2H), 2.10 (app td, J = 13.8, 4.8 Hz, 1H), 1.73 (m, 2H), 1.55 (m, 2H), 1.37−1.22 (m, 2H), 1.15 (br d, J = 13.7 Hz, 1H), 0.83 (dd, J = 13.3, 2.1 Hz, 1H), 0.34 (s, 3H), 0.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 174.4, 139.7, 133.7, 128.6, 127.5, 70.0, 66.0, 64.8, 51.5, 47.0, 39.1, 34.8, 33.7, 28.0, 24.1, 22.1, −1.1, −3.7. IR (neat) 3435, 2943, 1732 cm^{-1}. HRMS (*m*/*e*) found 360.1766, calcd for $C_{20}H_{28}O_4Si$ 360.1756.

(±)-(2*R*,4*R*,4a*S*,8a*S*) 4-(Dimethylphenylsilyl)-4a-hydroxymethyldecahydronaphthalene-2,8a-diol (11) and (±)-(1*R*,2*S*,4*R*,4a*R*,8a*R*) 4-(Dimethylphenylsilyl)-4a-hydroxymethyldecahydronaphthalene-1,2-diol (12). The epoxide **3** (40 mg, 0.11 mmol) was dissolved in tetrahydrofuran (4 mL) and treated with lithium aluminum hydride (0.44 mL, 0.44 mmol). After being stirred for 2 d at ambient temperature, the cloudy mixture was quenched at 0 °C by addition of saturated sodium sulfate (Na_2SO_4, 3 mL). After 5 min the mixture was stirred at ambient temperature and treated with 10% aqueous sodium hydroxide (1 mL). After 20 min, the mixture was extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4. Solvent removal afforded a crude colorless oil that was purified by preparative thin-layer chromatography (2:1 ethyl acetate/hexanes, 1% triethylamine) to yield the pure triols **11** (18.5 mg, 52%) and **12** (15 mg, 41%) as colorless oils.

11: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 (m, 2H), 7.33 (m, 3H), 4.31 (m, 1H), 3.67 (m, 2H), 3.43 (m, 1H), 3.21 (br s, 2H), 2.06 (m, 1H), 1.88 (m, 2H), 1.77 (m, 2H), 1.63 (m, 2H), 1.50 (m, 2H), 1.38 (m, 2H), 1.25 (m, 2H), 0.38 (s, 3H), 0.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 139.4, 133.5, 128.9, 127.7, 68.8, 67.6, 46.2, 42.7, 34.8, 32.6, 29.7, 27.2, 25.5, 21.2, 20.4, −0.3, −2.0. IR (neat) 3262, 2930, 2862, 1661 cm^{-1}.

12: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61 (m, 2H), 7.40 (m, 3H), 4.08 (d, J = 12.4 Hz, 1H), 3.66 (m, 1H), 3.48 (d, J = 12.1 Hz, 1H), 3.45 (m, 1H), 1.91 (ddd, J = 13.0, 13.0, 13.0 Hz, 1H), 1.78 (m, 2H), 1.67 (m, 2H), 1.30 (m, 6H), 0.91 (m, 1H), 0.83 (br d, J = 12.3 Hz, 1H), 0.41 (s, 3H), 0.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 139.7, 133.7, 128.8, 127.8, 73.7, 72.7, 64.3, 50.4, 40.5, 39.5, 36.8, 29.5, 26.6, 26.3, 22.1, −0.6, −2.1. IR (neat) 3323, 2922, 2856, 1728, 1714 cm^{-1}. HRMS (*m*/*e*) found for (M + H)$^+$ 335.2049, calcd for $C_{19}H_{31}O_3Si$ 335.2042.

(±)-(1*R*,4*R*,4a*R*,8a*R*) Methyl 2-Oxo-4-(dimethylphenylsilyl)decahydronaphth[1,8a-*b*]oxirene-4a-carboxylate (15). The epoxide **3** (25 mg, 0.069 mmol) was dissolved in CH_2Cl_2 (3 mL) and treated with pyridinium chlorochromate (PCC, 18 mg, 0.076 mmol). After being stirred for 6 h at ambient temperature, the mixture was filtered through a pad of Celite and silica gel, washing with CH_2Cl_2 and ethyl acetate. After solvent removal under vacuum, the dark crude oil was purified by flash column chromatography (4:1 hexanes/ethyl acetate) to give the epoxy ketone **15** (18 mg, 72%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47 (m, 2H), 7.31 (m, 3H), 3.61 (s, 3H), 2.94 (s, 1H), 2.77 (dd, J = 16.4, 7.9 Hz, 1H), 2.41 (m, 1H), 2.23 (m, 2H), 1.83 (m, 1H), 1.65 (m, 1H), 1.58 (app td, J = 12.7, 3.6 Hz, 1H), 1.53 (dd, J = 7.8, 5.9 Hz, 1H), 1.38 (m, 2H), 1.17 (m, 1H), 0.33 (s, 3H), 0.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 206.1, 173.6, 138.4, 133.9, 129.0, 127.6, 69.4, 61.1, 51.6, 49.4, 37.3, 35.3, 32.7, 32.1, 24.8, 22.3, −1.9, −3.2. IR (neat) 2943, 1732, 1703 cm^{-1}.

(±)-(4*R*,4a*R*,8a*S*) Methyl 2-Oxo-4-(dimethylphenylsilyl)-8-hydroxydecahydronaphthalene-4a-carboxylate (16). The epoxide **15** (54 mg, 0.15 mmol) was dissolved in THF (6 mL), H_2O (3 mL), ethanol (EtOH, 3 mL), and saturated $NaHCO_3$ (0.6 mL) and the mixture was cooled to 0 °C. Then aluminum foil (600 mg) was cut in small pieces and immersed in 2% aqueous mercury(II) chloride (10 mL) for 20 s. The aluminum pieces were then washed with EtOH (50 mL) and Et_2O (60 mL) and added to the reaction flask. After 1 h at 0 °C, the aluminum pieces were removed by filtration through filter paper washing with ethyl acetate. The aqueous layer was washed with ethyl acetate and dried over $MgSO_4$. After solvent removal, the crude oil was purified by flash column chromatography (2:1 hexanes/ethyl acetate, 1% triethylamine) to give the ketol **16** (39 mg, 72%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (m, 2H), 7.35 (m, 3H), 3.65 (s, 3H), 3.31 (br s, 1H), 3.05 (br d, J = 13.7 Hz, 1H), 2.53 (dd, J = 14.1, 14.1 Hz, 1H), 2.34 (m, 2H), 2.06 (m, 1H), 1.86 (m, 2H), 1.54 (m, 4H), 1.36 (m, 2H), 0.38 (s, 3H), 0.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 208.9, 176.4, 138.2, 133.6, 129.1, 127.8, 75.5, 53.5, 52.5, 51.7, 40.1, 34.6, 29.1, 26.5, 20.9, 20.3, −1.9, −3.0. IR (neat) 3433, 2924, 2864, 1720, 1713, 1693 cm^{-1}.

(±)-(1*S*,2*S*,4*R*,4a*R*,8a*R*) Methyl 2-((1,1-Dimethyl)ethyldimethylsilyloxy)-4-(dimethylphenylsilyl)decahydronaphth[1,8a-*b*]oxirene-4a-carboxylate (23). The alcohol **3** (92 mg, 0.26 mmol) was dissolved in CH_2Cl_2 and treated with triethylamine (0.1 mL, 0.76 mmol). The resulting mixture was cooled to −78 °C and TBSOTf (95 μL, 0.4 mmol) was added. After being stirred for 2 h, the mixture was poured into a separatory funnel containing water and extracted with Et_2O.

The combined organic layers were dried over $MgSO_4$ and solvent removal yielded a crude white solid. Purification by flash column chromatography (3:1 hexanes/ethyl acetate, 1% triethylamine) afforded the silyl ether **23** (116 mg, 96%) as a white solid: mp 97−99 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (m, 2H), 7.31 (m, 3H), 3.77 (ddd, J = 10.2, 4.9, 0.8 Hz, 1H), 3.65 (s, 3H), 2.92 (s, 1H), 2.36 (br d, J = 14 Hz, 1H), 2.10 (dd, J = 9.0, 9.0 Hz, 1H), 1.81 (m, 2H), 1.53 (m, 2H), 1.32 (m, 3H), 1.16 (m, 1H), 0.84 (s, 9H), 0.78 (dd, J = 13.5, 2.1 Hz, 1H), 0.346 (s, 3H), 0.342 (s, 3H), −0.007 (s, 3H), −0.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 174.6, 140.0, 133.6, 128.5, 127.5, 71.4, 65.0, 64.7, 51.4, 47.3, 39.5, 35.1, 33.8, 27.8, 25.7, 24.3, 22.2, 18.0, −1.2, −3.99, −4.5, −4.8. IR (neat) 2951, 1732 cm^{-1}. HRMS (*m*/*e*) found 474.2615, calcd for $C_{26}H_{42}O_4Si$ 474.2621.

(±)-(1*S*,2*S*,4*R*,4a*S*,8a*R*) 2-((1,1-Dimethyl)ethyldimethylsilyloxy)-4-(dimethylphenylsilyl)decahydronaphth[1,8a-*b*]oxirene-4a-methanol (24). The ester **23** (35 mg, 0.07 mmol) was dissolved in THF (2 mL) and treated with $LiAlH_4$ (0.15 mL, 0.14 mmol) at ambient temperature. After being stirred for 44 h, the mixture was poured into a separatory funnel containing water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and solvent removal under vacuum afforded a crude colorless oil. Purification by flash column chromatography (5:1 hexanes/ethyl acetate, 1% triethylamine) yielded the alcohol **24** (28 mg, 88%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50 (m, 2H), 7.32 (m, 3H), 4.05 (dd, J = 11.4, 1.8 Hz, 1H), 3.77 (dd, J = 10.3, 5.0 Hz, 1H), 3.63 (dd, J = 11.3, 8.5 Hz, 1H), 2.57 (dd, J = 8.6, 3.0 Hz, 1H), 2.12 (ddd, J = 13.6, 13.6, 4.9 Hz, 1H), 1.76 (m, 3H), 1.4−1.12 (m, 7H), 0.88 (m, 1H), 0.82 (s, 9H), 0.74 (br d, J = 12.7 Hz, 1H), 0.41 (s, 3H), 0.38 (s, 3H), −0.02 (s, 6H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 140.0, 133.6, 128.6, 127.6, 71.6, 67.7, 67.4, 65.1, 39.3, 37.8, 35.2, 33.1, 28.6, 25.7, 24.4, 21.5, 18.1, −0.9, −3.3, −4.6, −4.9. IR (neat) 3437, 2930 cm^{-1}. HRMALDI (*m*/*e*) found for $(M + Na)^+$ 469.2564, calcd for $C_{25}H_{42}O_3Si_2Na$ 469.2586.

(±)-(1*R*,2*S*,4*R*) 2-((1,1-Dimethyl)ethyldimethylsilyloxy)-4-(dimethylphenylsilyl)-1,2,3,4,5,6,7,8-octahydronaphthalen-1-ol (29). The alcohol **24** (8 mg, 0.02 mmol) was dissolved in CH_2Cl_2 (1 mL) and treated with diisobutylaluminum hydride (DIBAL, 0.1 mL, 0.1 mmol) at ambient temperature. After being stirred for 24 h, the reaction was quenched by addition of saturated sodium, potassium tartrate (2 mL). After being stirred for 30 min, the mixture was extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4. Solvent removal under vacuum gave a crude colorless oil. Purification by preparative thin-layer chromatography (1:1 hexanes/ethyl acetate) afforded the alcohol **29** (6.2 mg, 82%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (m, 2H), 7.32 (m, 3H), 3.71 (ddd, J = 11.4, 4.0, 4.0 Hz, 1H), 3.68 (m, 1H), 2.47 (m, 1H), 2.38 (m, 1H), 1.84 (m, 2H), 1.76 (t, J = 12 Hz, 1H), 1.68 (m, 1H), 1.58 (m, 4H), 1.41 (m, 1H), 1.34 (m, 1H), 0.87 (s, 9H), 0.34 (s, 3H), 0.28 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 139.4, 133.9, 133.4, 128.6, 127.5, 127.2, 72.1, 70.4, 31.3, 30.0, 29.3, 27.4, 25.7, 22.9, 22.5, 18.0, −2.8, −3.7, −4.5, −4.8. IR (neat) 3540, 2928 cm^{-1}. For HMBC, HMQC, COSY, and homodecoupling experiments see the Supporting Information.

(±)-(1*S*,2*R*,4*R*,4a*R*,8a*R*) Methyl 2-[4-Nitrobenzoyloxy]-4-(dimethylphenylsilyl)decahydronaphth[1,8a-*b*]oxirene-4-carboxylate (34). The alcohol **3** (30 mg, 0.08 mmol) was dissolved in benzene (2 mL) and treated with triphenylphosphine (110 mg, 0.42 mmol) and *p*-nitrobenzoic acid (70 mg, 0.42 mmol) at ambient temperature. After being stirred for 5 min, the white suspension was treated with diethyl azodicarboxylate (65 μL, 0.42 mmol). The solution turned orange immediately and clear within 3 min. After the mixture was stirred for 18 h, the solvent was removed in vacuo and the residue was purified by flash column chromatography (5:1 hexanes/ethyl acetate) to afford the ester **34** (31 mg, 78%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.25 (d, J = 8.6 Hz, 2H), 7.98 (d, J = 8.6 Hz, 2H), 7.47 (m, 2H), 7.25 (m, 3H), 5.38 (m, 1H), 3.69 (s, 3H), 3.09 (s, 1H), 2.41 (m, 1H), 2.27 (ddd, J = 13.7, 13.7, 4.8 Hz, 1H), 2.09 (m, 1H), 1.81 (m, 1H), 1.68 (m, 1H), 1.57 (m, 3H), 1.39 (m, 1H), 1.31 (m, 1H), 1.18 (m, 1H), 0.37 (s, 3H), 0.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 174.4, 163.6, 150.4, 140.0, 135.2, 133.5, 130.5, 128.4, 127.5, 123.4, 70.2, 62.6, 59.5, 51.6, 48.1, 38.6, 33.1, 28.3, 24.5, 24.2, 22.0, −0.9, −3.7. IR (neat) 2949, 1732, 1728, 1608 cm^{-1}.

(±)-(1*S*,2*R*,4*R*,4a*R*,8a*R*) Methyl 2-Benzoyloxy-4-(dimethylphenylsilyl)decahydronaphth[1,8a-*b*]oxirene-4a-carboxylate (35). The alcohol **3** (140 mg, 0.39 mmol) was dissolved in THF (6 mL) and treated with triphenylphosphine (204 mg, 0.77 mmol) and benzoic acid (95 mg, 0.77 mmol) at ambient temperature. After 5 min, the white suspension was treated with diethyl azodicarboxylate (130 μL, 0.77 mmol). The solution turned orange immediately and clear within 3 min. Then the mixture was refluxed for 18 h and stirred at ambient temperature for an additional 18 h. The solvent was then removed in vacuo and the residue was purified by preparative thin-layer chromatography (6:1 hexanes/EtOAc, 2 runs) to give the ester **35** (130 mg, 72%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.9 (m, 2H), 7.58 (m, 1H), 7.46 (m, 4H), 7.24 (m, 3H), 5.38 (m, 1H), 3.65 (s, 3H), 3.11 (d, J = 2.2 Hz, 1H), 2.39 (m, 1H), 2.24 (ddd, J = 13.7, 13.7, 4.9 Hz, 1H), 2.09 (m, 1H), 1.80 (m, 1H), 1.68 (m, 1H), 1.57 (m, 3H), 1.42 (m, 2H), 1.17 (m, 1H), 0.36 (s, 3H), 0.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 174.5, 165.5, 139.8, 133.6, 132.9, 129.9, 129.4, 128.5, 128.2, 127.5, 68.9, 62.4, 59.7, 51.5, 48.0, 38.6, 33.2, 27.9, 24.6, 24.3, 22.1, −0.9, −3.4. IR (neat) 2949, 1724 cm^{-1}. HRMS (*m*/*e*) found 464.2016, calcd for $C_{27}H_{32}O_5Si$ 464.2019; $(M + H)^+$ found 465.2093, calcd 465 2097.

(±)-(2*S*,4*R*,4a*S*,8a*S*) 4-(Dimethylphenylsilyl)-4a-hydroxymethyldecahydronaphthalene-2,8a-diol (33). The epoxide **35** (23 mg, 0.05 mmol) was dissolved in THF (3 mL) and treated with $LiAlH_4$ (0.25 mL, 0.24 mmol) at ambient temperature. The resulting mixture was stirred for 2 d and then was quenched by addition of aqueous 10% NaOH (1 mL) at 0 °C. After being stirred for 15 min at 0 °C and 20 min at ambient temperature, the mixture was diluted with ethyl acetate and poured into a separatory funnel and the layers were separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over $NaSO_4$. After solvent removal under vacuum, the crude residue was purified by preparative thin-layer chromatography (1:2 hexanes/ethyl acetate, 1% triethylamine) to give the triol **33** (14 mg, 88%) as a white solid. ^{1}H NMR (CD_3OD, 500 MHz) δ 7.54 (m, 2H), 7.29 (m, 3H), 4.03 (m, 2H), 3.46 (m, 1H), 2.0−1.9 (m, 3H), 1.77 (ddd, J = 13.8, 13.8, 3.5 Hz, 1H), 1.6 (m, 3H), 1.5−1.2^{13}13 (m, 6H), 0.35 (s, 6H). ^{13}C NMR (CD_3OD, 125.8 MHz) δ 140.2, 133.4, 128.1, 127.2, 74.8, 66.5, 65.8, 43.2, 42.9, 36.0, 30.0, 28.2, 21.3, 20.5, −1.4, −2.3 (one high-field carbon unresolved). IR (neat) 3306, 2912 cm^{-1}.

(±)-(4′*R*,4′a*R*,8′*R*,8′a*S*) Methyl 4′-Hydroxyl-1′,3′,4′,5′,6′,7′-8′-decahydrospiro[1,3]dioxolane-2,2′-naphth[8′,8′a-*b*]-oxirene-4′a-carboxylate (41). The epoxide **39** (25 mg, 0.06 mmol) was dissolved in glacial acetic acid (3 mL) and was treated with potassium bromide (15 mg, 0.93 mmol) and sodium acetate (76 mg, 0.93 mmol). After 5 min the reaction was cooled to 0 °C and peracetic acid (32 wt % in AcOH, 0.2 mL, 0.9 mmol) was added. After 15 min, another aliquot of peracetic acid (0.2 mL, 0.9 mmol) was added. After being stirred for 10 min at 0 °C, the reaction was warmed to ambient temperature and stirred for 28 h. Then the reaction was quenched by addition of saturated $Na_2S_2O_3$. After being stirred for 20 min, the mixture was poured into a separatory funnel containing saturated $NaHCO_3$ and CH_2Cl_2 was added. Solid $NaHCO_3$ was added slowly until bubbling stopped. Then the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. Solvent removal under vacuum gave a yellowish residue that was purified by flash column chromatography (1:3 hexanes/ethyl acetate) to afford the alcohol **41** (3.2 mg, 19%) as a clear oil. ^{1}H NMR ($CDCl_3$,

500 MHz) δ 3.96 (m, 5H), 3.91 (s, 3H), 3.68 (d, J = 11.2 Hz, 1H), 2.93 (d, J = 4.6 Hz, 1H), 2.35 (d, J = 13.3 Hz, 1H), 2.16 (ddd, J = 13.0, 4.0, 2.9 Hz, 1H), 2.03 (m, 2H), 1.88 (dd, J = 12.6, 12.6 Hz, 2H), 1.72 (ddd, J = 13.2, 13.2, 3.7 Hz, 1H), 1.52 (m, 2H), 1.45 (m, 1H), 1.27 (dd, J = 13.4, 2.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 176.4, 106.5, 67.9, 64.5, 64.2, 58.5, 58.1, 52.2, 51.6, 41.9, 41.1, 24.9, 22.4, 14.6. IR (neat) 3474, 2924, 1714 cm^{-1}. HRMS (*m*/*e*) found for M^+ 284.1259, calcd for $C_{14}H_{20}O_6$ 284.1259; found for $(M + H)^+$ 285.1342, calcd for $C_{14}H_{21}O_6$ 285.1338.

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Supporting Information Available: Experimental details for compounds **3**, **4**, **10**, **11**, **12**, **15**, **16**, **23**, **24**, **29**, **33**, **34**, **35**, and **41**; proton and carbon NMR spectra for all new compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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