Halichondrin B: Synthesis of the C(1)−C(15) Subunit

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A short and efficient synthesis of the C(1)−C(15) subunit of halichondrin B in its natural configuration is described. The polycyclic caged ketal **3**, containing nine asymmetric centers, is prepared in 14 steps from α-D-glucoheptonic acid γ-lactone (**7**). Key steps in the two similar routes described include EtMgBr-promoted pinacol ring expansions of hydroxy mesylates **23** and **34**, intramolecular Michael additions of **29** and **37**, and a one-pot, HF-induced conversion of **4** to **3** involving in situ silyl ether cleavage, acetal hydrolysis, Michael addition, and caged ketal formation. Alternative protocols for carbinol inversion at C(11), one early and one late in the synthetic sequence, are also described.

Introduction

Halichondrin B (Figure 1) is the most potent in a family of cytotoxic polyether macrolides that have been isolated in low yields (1.8×10^{-8} to 4.0×10^{-5}%) from four marine sponge genera, including *Halichondria*,[1a] *Axinella*,[1b,c] *Phakellia*,[1d] and *Lissodendoryx*.[1e]

The halichondrins are mitotic inhibitors, and halichondrin B displays potent in vivo activity against a number of chemoresistant human solid tumor xenografts, including LOX melanoma, KM20L colon, FEMX melanoma, and OVCAR-3 ovarian tumor, in immune-deficient mice.[2] Researchers at the National Cancer Institute (NCI) have established that halichondrin B binds to the vinca domain of tubulin, thereby inhibiting tubulin polymerization and tubulin-dependent GTP hydrolysis.[3] Halichondrin B displays an IC_{50} value for L1210 murine leukemia cells of 0.3 nM, making it one of the most potent inhibitors in a class that includes dolastatin 10 (0.5 nM), rhizoxin (1nM), and vinblastine (20 nM).[3] Hirata and Uemura observed that increased activity among halichondrin congeners is directly related to the lipophilicity of the 2,6,9-trioxatricyclo[3.3.2.0^{3,7}]decane ring system

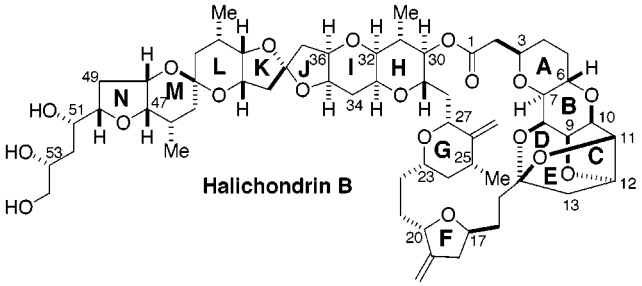

Figure 1.

(rings C, D, and E; the "cage") and the hydrophilicity of the C(50) "tail" of the halichondrins.[1a] More recently, Kishi and co-workers discovered that the C(1)−C(38) diol used in their total synthesis has an activity profile which

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(2) (a) Personal correspondence with M. R. Boyd, M.D., Ph. D., Cancer Research Center, Frederick, MD, National Cancer Institute. Dr. Boyd shared with us data and slides that resulted in the NCI Decision Network Committee's selection of halichondrin B for drug development. (b) Personal correspondence with E. Hamel, M.D., Ph.D., National Institute of Health, National Cancer Institute. Dr. Hamel informed us that halichondrin B cures in vivo human tumor xenografts transplanted in immune deficient mice.

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is very similar to that of halichondrin B against more than 60 cancer cell lines with IC_{50} values within 1 order of magnitude of those displayed by the natural product.[4a]

Stage A preclinical development has been recommended for halichondrin B by the National Cancer Institute,[2] but the scarcity of this substance has made it difficult to proceed. Recent work by Munro and co-workers has resulted in the production of halichondrin B by aquaculture, although the generation of 5 kg/year for clinical use would require the aquacultural production of *Lissodendoryx* n. sp. in estimated quantities of more than 5000 tons/year.[5] Synthetic chemists have attempted to resolve the supply issue through the development of efficient syntheses of halichondrin B and its segments. Kishi and co-workers have published the syntheses of several segments of halichondrin B,[4] including an impressive total synthesis in 1992.[4h] Synthetic approaches to the halichondrins have also been described by Salomon[6] and Yonemitsu.[7] Additionally, we have reported the synthesis of several segments of halichondrin B,[8] including a brief report on the synthesis of the C(1)−C(15) segment in 1994.[8b] This paper provides a detailed account of the synthesis of the C(1)−C(15) segment of halichondrin B, including developments subsequent to the earlier communication.

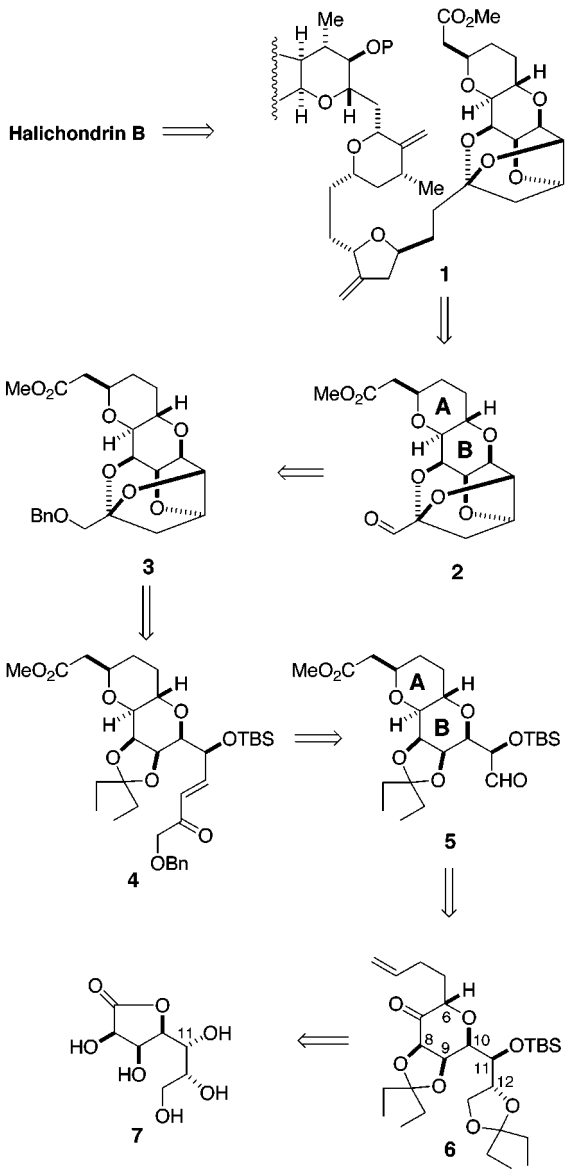
Results and Discussion

In our synthetic plan for the total synthesis of halichondrin B, the entire carbon skeleton is to be in place, with macrolactonization occurring late (Scheme 1). The macrolactonization precursor **1** is to be obtained by synthetic manipulation of an adduct of aldehyde **2**, which would, in turn, be prepared by debenzylation and oxidation of the polycyclic caged ketal **3**. Compound **3**, which has also been prepared by Salomon and co-workers,[6b] is accessible from the benzyloxymethyl enone **4** via TBS ether cleavage and selective hydrolysis of the terminal pentylidene acetal followed by intramolecular Michael addition of the C(9) hydroxyl to the enone moiety and caged ketal formation involving the C(8) and C(11) hydroxyls and the C(14) ketone. Enone **4** arises via Wittig homologation of aldehyde **5**, which is derived from pyranone **6**. The C(6) homoallyl group in compound **6** was expected to provide a facile means for A-ring installation to complete the trans-fused dioxadecalin AB-ring system present in aldehyde **5**. Pyranone **6** was envisioned to be available from the inexpensive carbohydrate derivative α-D-glucoheptonic acid γ-lactone (**7**), following a ring expansion from furanone to pyranone and installation of the C(6) homoallyl group. Four of the six stereocenters in pyranone **6** are correctly set in compound **7**, with only C(11) (halichondrin B numbering) requiring an inversion.

Our first-generation synthesis of the C(1) − C(15) subunit involved an early-stage inversion at C(11). Accordingly, the first goal was to selectively protect the hydroxyls at C(8), C(9), C(12), and C(13) to permit inversion of stereochemistry at the C(11) carbinol center. Regioselective bis(acetalization) of **7** with 3-pentanone and sulfuric acid provided **8**, in which the C(11) carbinol center was exposed for inversion (Scheme 2). Trace amounts of the bis(acetalization) regioisomer **10** in which the C(8) hydroxyl was left exposed were also isolated under these conditions. The mono(acetalization) product **9** was also isolated as a major product. Although the addition of anhydrous $MgSO_4$ or 4 Å molecular sieves to the reaction mixture failed to drive the acetalization equilibrium to completion, resubjection of **9** to the reaction conditions provided additional **8** for an overall yield of 55%. The use of acetonide protecting groups[9] or other acid catalysts resulted in the regioisomer analogous to **10** as the major product, in which C(8) was left unprotected.

With the C(11) hydroxyl now isolated, attention turned to the inversion of this stereocenter. The failure of one-

Scheme 1



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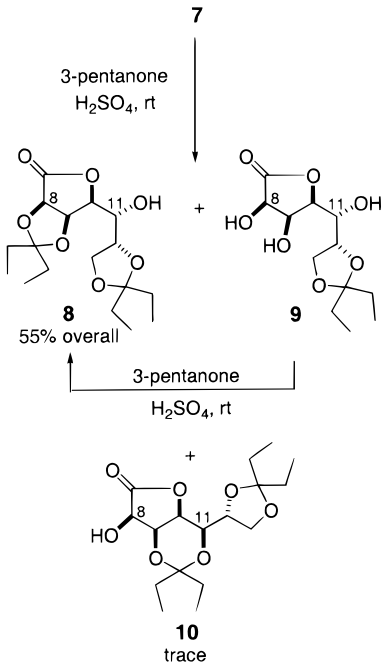
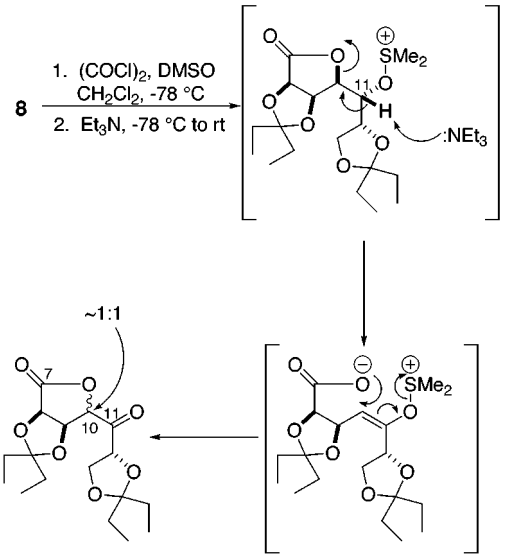
Scheme 2

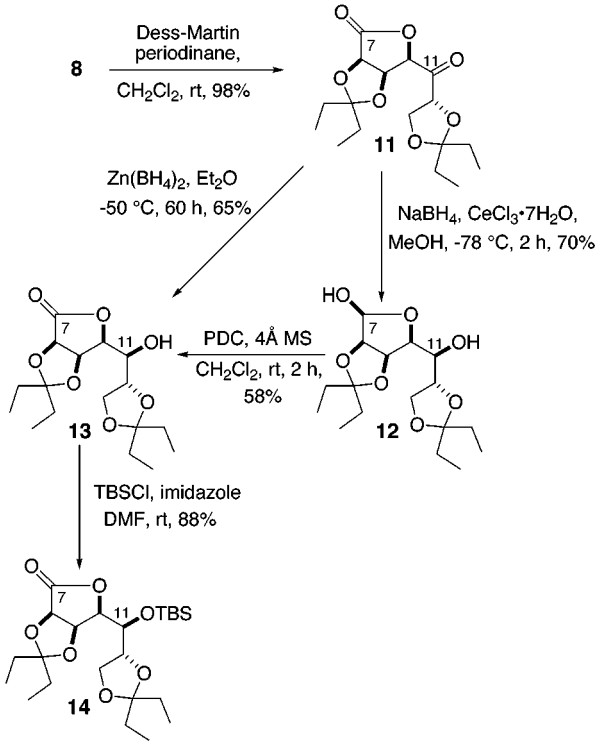


Scheme 3



step inversion protocols,[10] including several variations of the Mitsunobu reaction,[10e,f] necessitated the use of an oxidation−reduction sequence to invert the C(11) alcohol. Many oxidants were surveyed in attempts to convert **8** to the corresponding C(11) ketone. Swern conditions[11] provided the desired ketone as a 1:1 mixture of C(10) epimers, presumably resulting from β-elimination and re-addition reactions in the Swern intermediate as shown in Scheme 3. The use of tetrapropylammonium perruthenate/*N*-methylmorpholine *N*-oxide (TPAP/NMO)[12] as an oxidant resulted in extensive decomposition. Oxidation of **8** with various chromium-based oxidants[13] proceeded in poor yield and incomplete conversion. Furthermore, subsequent chromatography of the ketone product resulted in decomposition. Fortunately, use of the Dess−Martin reagent[14] gave an excellent yield of ketone **11** that was of sufficient purity to be carried forward without further purification (Scheme 4).

Scheme 4



Reduction of the ketone **11** to alcohol **13** with the desired (*S*)-configuration at C(11) could be carried out most directly with $Zn(BH_4)_2$,[15] but this reaction proved inconvenient for large-scale applications (Scheme 4). Other reducing agents such as $NaBH_4$, $LiBH_4$, and L-Selectride resulted in concomitant reduction at C(7) and/or poor diastereoselectivity at C(11).[10b] The best alternative to $Zn(BH_4)_2$ was found to be $NaBH_4/CeCl_3 \cdot 7H_2O$,[16] which gave the overreduced product **12** exclusively. Selective oxidation of the C(7) hemiacetal in **12** with pyridinium dichromate[13a] provided the alcohol **13**. Overoxidation of **12** to ketone **11** under these conditions required that the reaction be arrested prior to completion, thereby giving low and variable yields of **13**. Compound **13** was then converted to its TBDMS ether **14**. Our choice of masking the C(11) hydroxyl as a TBDMS ether was based on the need for a robust protecting group that would suffer cleavage in the presence of fluoride ion under the conditions required to effect caged ketal formation. This C(11) carbinol inversion sequence provides the inverted C(11) TBS ether **14** in four steps and 36% overall yield from compound **8**.

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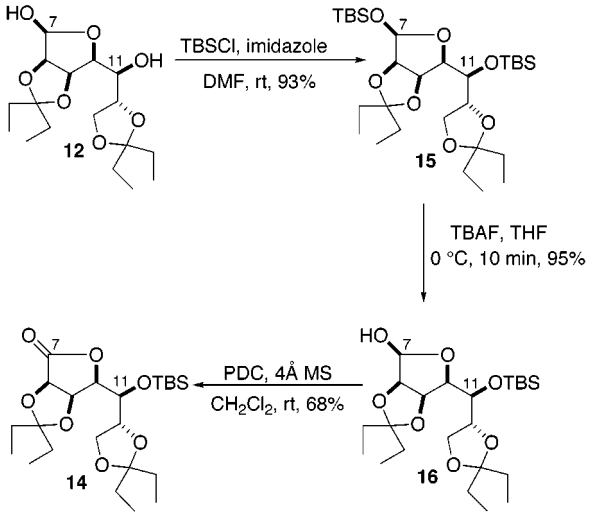
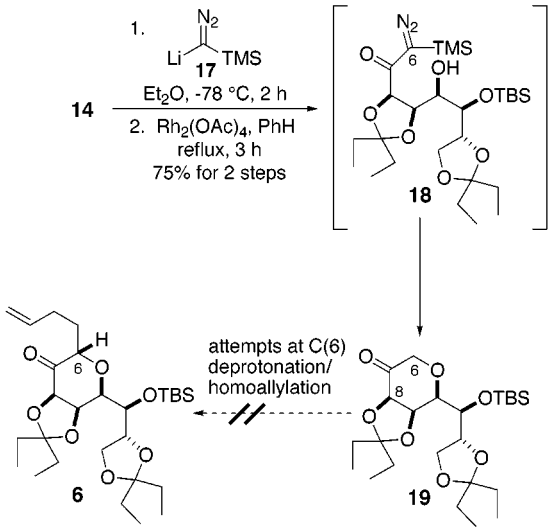
Scheme 5



Scheme 6



To circumvent the problem of overoxidation in the conversion of **12** to **13**, another strategy was devised that involved protection of the C(11) alcohol in **12** prior to hemiacetal oxidation. As depicted in Scheme 5, compound **12** is converted to the bis(*tert*-butyldimethylsilyl) ether **15** with the expectation that the hemiacetal silyl ether would be considerably more labile than the C(11) silyl ether and therefore allow for selective monodeprotection. Indeed, treatment of **15** with tetrabutylammonium fluoride for 10 min at 0 °C provided the monodeprotected compound **16** containing a free hemiacetal that was subsequently oxidized to the desired lactone **14** with pyridinium dichromate.[11a] This revised C(11) inversion protocol offers slight improvement over the previous sequence in terms of yield, delivering **14** in five steps and 42% overall yield from compound **8**. Nevertheless, a more satisfying protocol for accomplishing the C(11) carbinol inversion was still needed, and was ultimately developed (vide infra).

At hand now was the task of achieving ring expansion of lactone **14** to establish the B ring, with appropriate substitution at C(6) to provide an entry to the A ring. After unsuccessfully attempting to accomplish both goals in a single step through the use of halolithium carbenoid chemistry,[10a,b,17] the OH insertion of a metallocarbenoid was investigated. As shown in Scheme 6, treatment of lactone **14** with the diazolithium reagent **17**[18] provided the diazoketone intermediate **18**, which subsequently underwent OH insertion in the presence of rhodium(II) to give ketone **19**. Enolate formation and homoallylation at C(6) was expected to provide pyranone **6**.[19] The lower pK_a of the C(8) proton precluded such an alkylation, however, as quenching of the enolate derived from ketone **19** with deuterium oxide resulted in exclusive deuterium incorporation at C(8). This result made clear that the desired alkyl chain must be present during the ring expansion step.

In light of these results, a new strategy was devised that involved addition of an α-alkoxy carbanion to lactone **14** followed by subsequent mesylation and pinacol rearrangement to achieve the ring expansion with the requisite 3-butenyl group in place. We envisioned that transmetalation of an α-alkoxyorganostannane would generate a lithium reagent that would be suitable for this task. Accordingly, the racemic α-alkoxyorganostannane *rac*-**21** was prepared as shown in Scheme 7. Addition of tributylstannyl anion to 4-pentenal[20] provided the α-hydroxystannane *rac*-**20** as described by Still and coworkers.[21] This adduct was remarkably stable for a compound of its type and could be subjected to silica gel chromatography without significant decomposition. Protection of *rac*-**20** with α-chloroethyl ethyl ether provided the ethoxyethyl-protected α-alkoxystannane *rac*-**21** as an inseparable mixture of four stereoisomers. This compound, unlike the free alcohol, suffered severe decomposition on silica gel. Fortunately, purification was possible using silica gel that had been saturated with triethylamine.

Transmetalation of *rac*-**21** with *n*-BuLi provided the corresponding lithium reagent, to which **14** was added at low temperature.[21] Following acidic hydrolysis of the ethoxyethyl protecting groups, diols **22a** and **22b** were isolated, and the desired diol **22a** was selectively mesylated to provide **23**. The correct C(6) epimer of pyranone **6** was expected to be formed upon stereospecific rearrangement of this diastereomer. The undesired diastereomer **22b** was recycled to **14** via oxidative cleavage with periodic acid. An alternative to recycling **22b** that was explored was the direct conversion of **22b** to **22a** via C(6)

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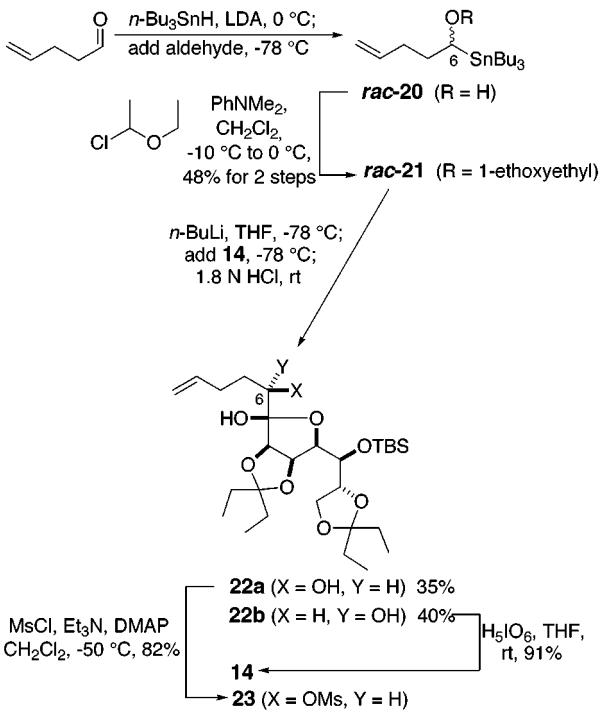
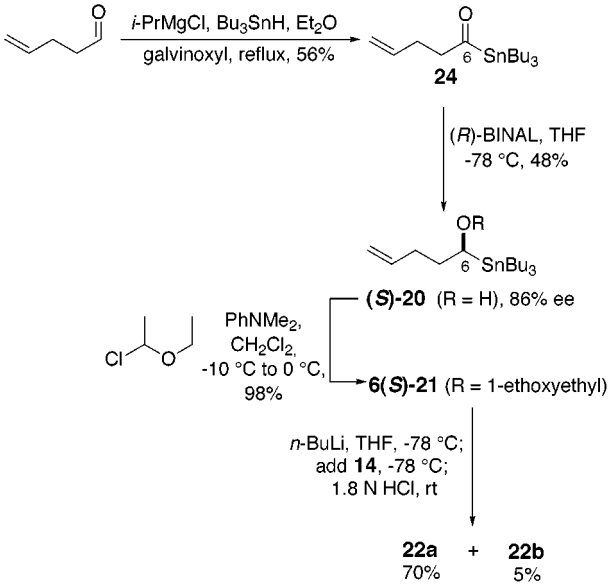
Scheme 7



Scheme 8



carbinol inversion. One-step inversion protocols failed to achieve inversion at this center, and reduction of the C(6) ketone derived from **22b** with a variety of reductants returned the unwanted diol diastereomer **22b** as the major product.

Originally, an α-alkoxystannane derived from an enantiomerically enriched α-hydroxystannane was used to avoid the formation and recycling of **22b** (Scheme 8).[8b] Reaction of tributylstannylmagnesium chloride with 2 equiv of 4-pentenal provided acyl stannane **24**[22] via a Cannizarro-type reaction. Asymmetric reduction of **24** with (*R*)-BINAL[23] provided the hydroxystannane **(*S*)-20** in 86% enantiomeric excess as determined by ^{1}H NMR analysis of the Mosher ester derived from (*R*)-(+)-methoxytrifluoromethylphenylacetic acid. Subsequent protection of (*S*)-**20** with α-chloroethyl ethyl ether provided **6(*S*)-21** and **6(*R*)-21** in 84% and 14% yields, respectively. Treatment of lactone **14** with the lithium reagent derived from **6(*S*)-21** under the same conditions employed for *rac*-**21** above delivered the desired diol **22a** in 70% yield along with 5% of the undesired **22b**. As a practical matter, acyl stannane **24** proved difficult to handle on a large scale owing to its rapid decomposition in the presence of oxygen to the corresponding tin carboxylate.[22] As a result, *rac*-**21** has remained the α-alkoxystannane reagent of choice due to the relative ease with which it can be prepared.

Ring expansion of the five-membered hemiacetal moiety of **23** was now needed to establish the B-ring. Several reagents were surveyed for their ability to promote a pinacol rearrangement of hydroxy mesylate **23**. Lewis acidic promoters such as triethylaluminum and diethylaluminum chloride, which were reported to be effective promoters of pinacol rearrangements of vicinal hydroxy mesylates,[24] were incompatible with the acid-sensitive functionality present in our system. As depicted in Scheme 9, we found that ethylmagnesium bromide[25] promoted the desired ring expansion, possibly proceeding through the seven-membered cyclic transition state shown,[24] to give the pyranone **6**. However, the furanyl ketone **25** also forms under these conditions, presumably resulting from direct displacement of the mesylate by the hemiacetal alkoxide with a resultant rearrangement of the unstable epoxide via a 1,2-hydride shift. We attempted to suppress the formation of free alkoxide that was thought to be responsible for the observed side reaction by adding anhydrous $MgBr_2$ to the reaction mixture, but no change in the product ratio was observed.

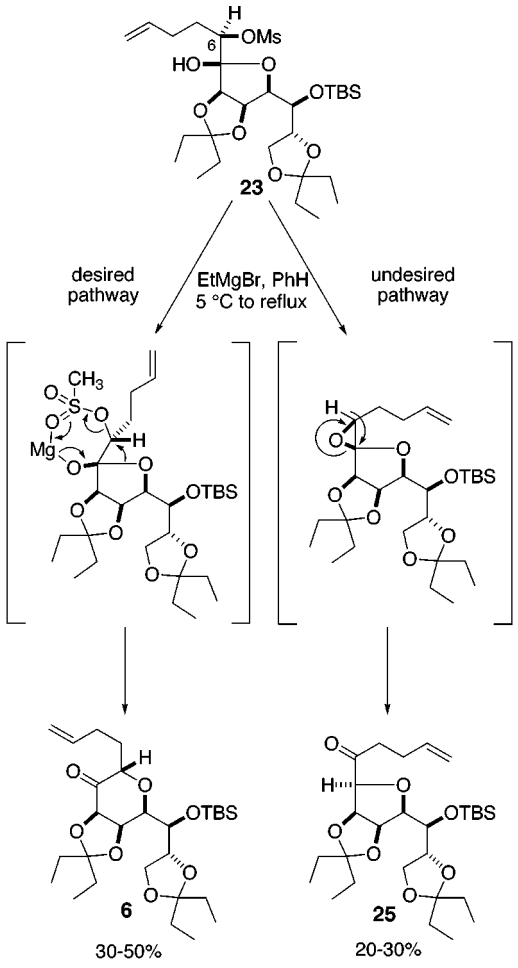
(22) (a) Chan, P. C.-M.; Chong, J. M. *J. Org. Chem.* **1988**, *53*, 5584−5586. (b) Chong, J. M.; Mar, E. K. *Tetrahedron* **1989**, *45*, 7709−7716. (c) Chong, J. M.; Mar, E. K. *Tetrahedron Lett.* **1990**, *31*, 1981−1984. (d) Chan, P. C.-M.; Chong, J. M. *Tetrahedron Lett.* **1990**, *31*, 1985−1988. (e) Kosugi, M.; Naka, H.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3462−3464.

(23) (a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709−6716. (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717−6725.

(24) For examples using aluminum reagents, see: (a) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1983**, *24*, 4997−5000. (b) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 1817−1820. (c) Suzuki, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 3715−3718. (d) Tsuchihashi, G.; Tomooka, K.; Suzuki, K. *Tetrahedron Lett.* **1984**, *25*, 4253−4256. (e) Suzuki, K.; Ohkuma, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1985**, *26*, 861−864. (f) Suzuki, K.; Tomooka, K.; Matsumoto, T.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1985**, *26*, 3711−3714. (g) Suzuki, K.; Tomooka, K.; Shimazaki, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1985**, *26*, 4781−4784. (h) Suzuki, K.; Ohkuma, T.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1986**, *27*, 373−376. (i) Schoenen, F. J.; Porco, J. A., Jr.; Schreiber, S. L.; VanDuyne, G. D.; Clardy, J.; *Tetrahedron Lett.* **1989**, *30*, 3765−3768. For examples using other acids, see: (j) Kakimoto, M.; Seri, T.; Imai, Y. *Bull. Chem. Soc. Jpn.* **1988,** *61*, 2643−2644. (k) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1992**, 81−84. (l) Kudo, K.; Saigo, K.; Hashimoto, Y.; Saito, K.; Hasegawa, M. *Chem. Lett.* **1992**, 1449−1452. (m) Paquette, L. A.; Lawhorn, D. E.; Teleha, C. A. *Heterocycles* **1990**, *30*, 765−769. (n) Paquette, L. A.; Lord, M. D.; Negri, J. T. *Tetrahedron Lett.* **1993**, *34*, 5693−5696. (o) Paquette, L. A.; Branan, B. M.; Friedrich, D.; Edmonson, S. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 506−513.

(25) (a) Gilchrist, T. L.; Stanford, J. E. *J. Chem. Soc., Perkin Trans. 1* **1987**, 225−230. (b) Sisti, A. J. *J. Org. Chem.* **1968**, *33*, 453. (c) Sisti, A. J.; Vitale, A. C. *J. Org. Chem.* **1972**, *37*, 4090−4094. (d) Corey, E. J.; Ohno, M.; Vatakencherry, P. A.; Mitra, R. B. *J. Am. Chem. Soc.* **1961**, *83*, 1251−1253. (e) Brook, P. R. *J. Chem. Soc., Chem. Commun.* **1968**, 565−567. (f) Suga, T.; Hirata, T.; Shishibori, T.; Matsuura, T. *Tetrahedron Lett.* **1968**, 5553−5555. For a review on the pinacol rearrangement, see: (g) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vol. 3, pp 721−732. For studies of migratory aptitude, see: h) Nakamura, K.; Osamura, Y. *Tetrahedron Lett.* **1990**, *31*, 251−254. (i) Collins, C. J. *J. Am. Chem. Soc.* **1955**, *77*, 5517−5523. (j) Witsuba, E.; Ruchart, C. *Tetrahedron Lett.* **1981**, *22*, 4069−4072.

Scheme 9



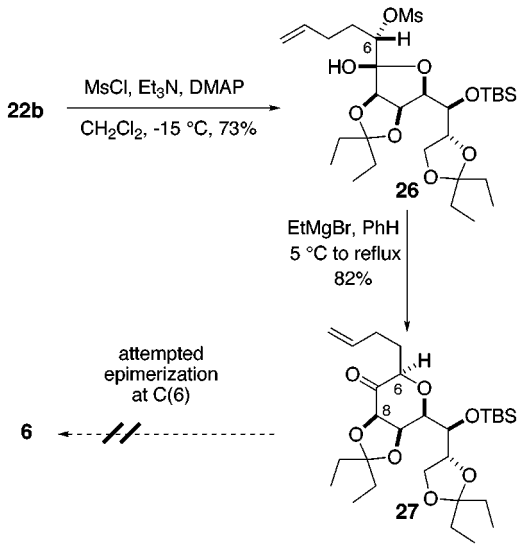
Changing the leaving group from mesylate to chloride and subjection of the chlorohydrin to the reaction conditions resulted in exclusive formation of **25**. Thermolysis of the mesylate in the presence of triethylamine in refluxing toluene also provided **25** as the sole product.

Ironically, the mesylate **26** derived from diol **22b** smoothly undergoes EtMgBr-induced pinacol rearrangement to give **27**, the C(6) epimer of pyranone **6**, in high yield (Scheme 10). Unfortunately, C(6) epimerization of this product to provide **6** could not be achieved under a variety of conditions, presumably due again to preferred enolization toward C(8).

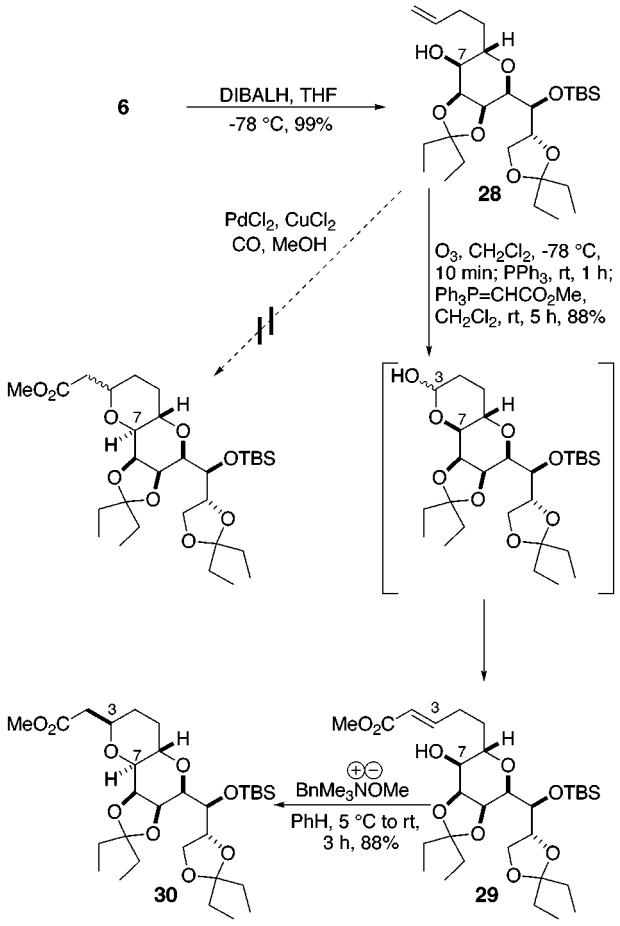
Despite the low yields of the α-alkoxyorganostannane addition and pinacol rearrangement steps, we had met our goals of effecting ring expansion to install the B-ring while establishing the correct stereochemistry at C(6). At this point, we decided to direct our efforts at completion of the A-ring. We envisioned that stereoselective reduction of ketone **6** from the α-face followed by an alkoxypalladation/carbonylation procedure[26] would complete construction of the dioxadecalin AB-ring system with appropriate substitution at C(3). Reduction at C(7) with DIBALH delivered the alcohol **28** of desired stereochemistry in nearly quantitative yield (Scheme 11). The use of Luche conditions or $Zn(BH_4)_2$ gave the same stereochemical outcome, albeit in lower yield (ca. 70%).

(26) (a) Semmelhack, M. F.; Budurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496−1498. (b) Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925−4928. (c) Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.* **1984**, *25*,. 3171−3174.

Scheme 10



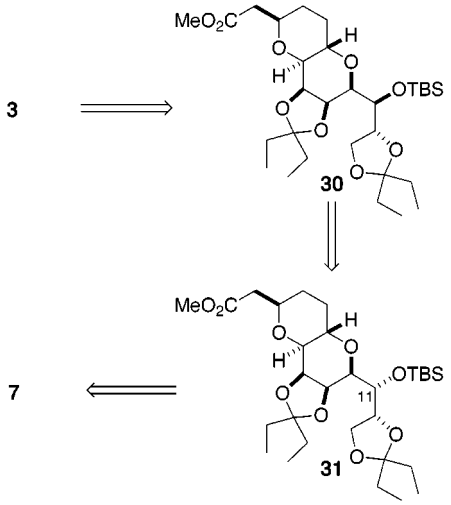
Scheme 11



Unfortunately, subjection of **28** to the alkoxypalladation/carbonylation conditions resulted in decomposition, forcing us to employ a different method for effecting A-ring closure.

We anticipated that A-ring installation might be realized by an intramolecular Michael addition of the C(7) hydroxyl with an enoate generated by Wittig homologation at C(3). Accordingly, ozonolysis of **28** and Wittig reaction with the resultant C(3) hemiacetal (in brackets) afforded enoate **29** (Scheme 11). Having established the requisite Michael acceptor and donor functionalities, we

Scheme 12

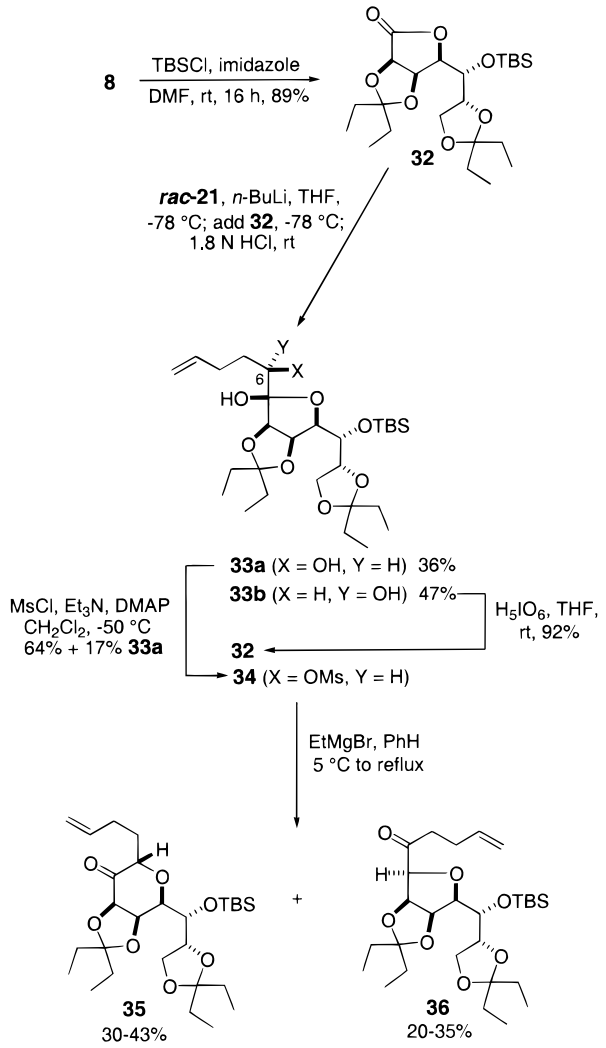


turned our attention to the conjugate addition step. Treatment of **29** with benzyltrimethylammonium methoxide in benzene at 5 °C followed by warming to 18 °C for 3 h provided the desired C(3) equatorial adduct **30** as the sole product. The starting material was consumed within 10 min at 5 °C but gave a roughly equimolar mixture of axial and equatorial C(3) epimers after this time. The prolonged reaction time and increased temperature are required to facilitate equilibration via a retro-Michael/Michael addition pathway to the more stable equatorial isomer. It is noteworthy that a 1:1 mixture of C(3) epimeric adducts was isolated upon conducting the reaction in methanol at room temperature. This result illustrates the dramatic effect that reaction media can exert upon thermodynamic equilibria. This completed the AB-ring system with all stereocenters correctly set.

The problems attending overreduction during the inversion of the C(11) carbinol center in our first-generation approach prompted us to develop an inversion plan that could be effected later in the synthesis. For this second-generation approach, we envisioned that the caged compound **3** would arise from compound **30** as before (Scheme 12). However, compound **30** would now be prepared by inversion of its C(11) epimer **31** via an oxidation−reduction sequence. With the lactone functionality absent, it was hoped that the more robust methyl ester that would now be present during the C(11) inversion sequence would survive the reduction step. It was anticipated that compound **31** could also be prepared from α-D-glucoheptonic acid γ-lactone **7** in a manner analogous to that described above, with deferral of the C(11) carbinol inversion until late in the sequence.

Protection of **8** as its TBDMS ether provided lactone **32** (Scheme 13). Addition of the organolithium species derived from the racemic ethoxyethyl-protected alkoxystannane *rac*-**21** followed by acidic hydrolysis provided a separable mixture of diols **33a** and **33b**. The unwanted diol diastereomer **33b** was recycled to **32** by oxidative cleavage with periodic acid. Mesylation of **33a** afforded **34**, which was then subjected to the ethylmagnesium bromide-promoted pinacol rearrangement to give pyranone **35** as well as the undesired furanyl ketone **36** via pathways related to those shown in Scheme 9 for the series of compounds epimeric at C(11). In converting **33a** to mesylate **34**, considerable decomposition of the product

Scheme 13

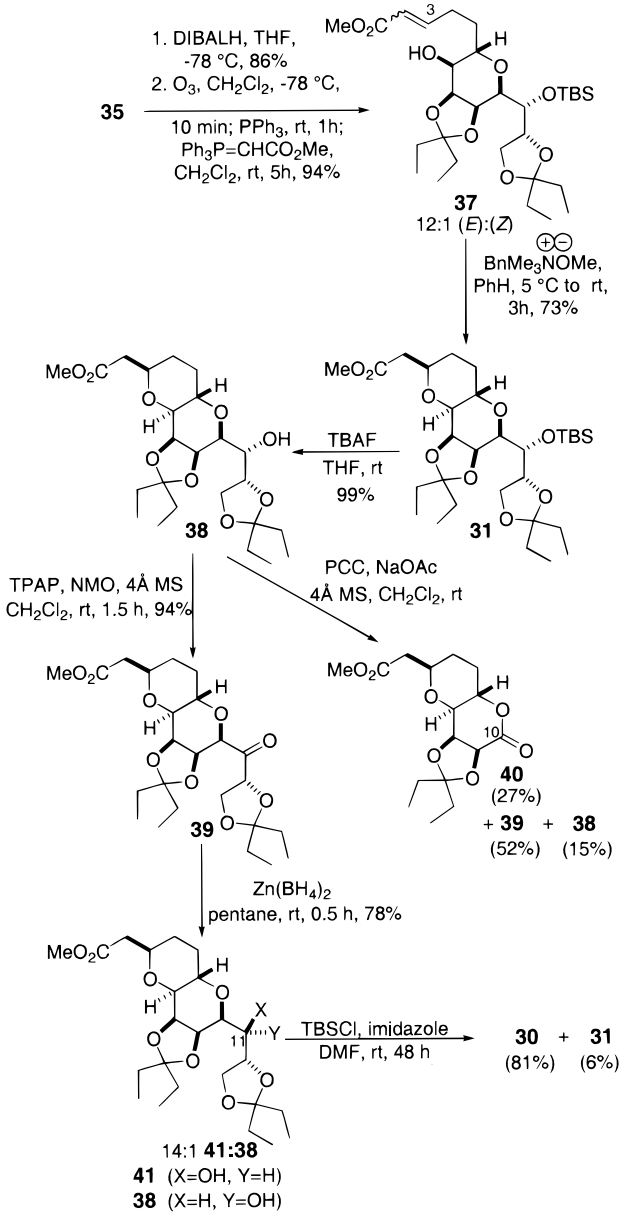


occurred at prolonged reaction times, thus the reaction was arrested early to provide 64% of **34** with 17% of **33a** being recovered. That this was not a problem in the conversion of **22a** to **23** suggests that the remote C(11) stereocenter imparts a significant effect upon the relative stabilities of mesylates **34** and **23**.

Reduction of the pyranone **35** with DIBALH was followed by ozonolysis and Wittig homologation at C(3) to afford the enoate **37** as an inseparable 12:1 mixture of (*E*) and (*Z*) isomers (Scheme 14). Base-catalyzed intramolecular Michael addition yielded a mixture of C(3) epimers which, upon equilibration for 3 h at room temperature, gave the desired thermodynamic adduct **31** as the sole product.

With the dioxadecalin AB-ring system now in place via the revised route, inversion at C(11) of **31** and correlation of the inverted TBDMS ether with compound **30** was pursued. Deprotection of **31** with TBAF afforded the alcohol **38** (Scheme 14). Several oxidants were screened for the conversion of this alcohol to ketone **39**. PCC provided the desired ketone in poor yield along with lactone **40**, a side product resulting from oxidative cleavage of the C(10)−C(11) bond. Use of the Dess−Martin periodinane resulted in only 15% conversion after several days of stirring at room temperature. Fortunately, we found that treatment of **38** with TPAP/NMO[12] in CH_2Cl_2 delivered **39** in high yield. The success of this

Scheme 14



oxidation is auspicious, given the fact that the C(11) oxidation step in our first-generation synthesis was the lowest yielding reaction in the sequence.

With ketone **39** now in hand, a chelation-controlled reduction with $Zn(BH_4)_2$ was attempted; this reagent had provided the correct C(11) epimer from the simpler ketone **11** in our first-generation synthesis. Treatment of **39** with $Zn(BH_4)_2$ in pentane at room temperature gave an inseparable 14:1 mixture (as determined by ^1H NMR spectroscopy) of C(11) epimers, favoring the desired (*S*) alcohol **41**, in good yield. The use of $Zn(BH_4)_2$, which had proven troublesome in large-scale applications in the first-generation sequence, is not a problem here due to the smaller quantities of material involved. Thus, an obvious advantage of performing this step later in the sequence is that there are fewer steps to follow, thereby lessening the need to generate the reduction product in large quantities. The product obtained from TBDMS protection of **41**, which was separable from the small amount of silyl ether **31** that was also formed during this step, was shown to be the desired compound **30**, identical in all respects to that prepared by the other sequence.

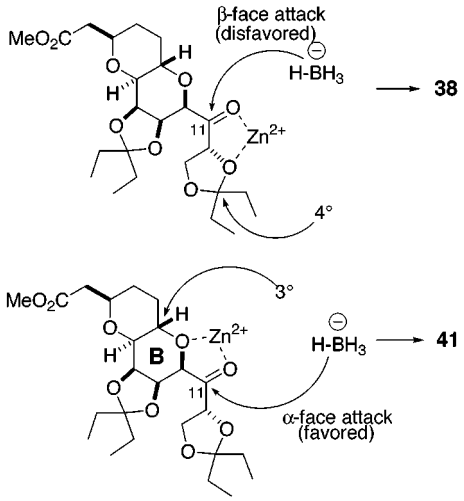


Figure 2. Rationalization of chelation-controlled reduction outcome.

The outcome of this chelation-directed reduction may be rationalized as shown in Figure 2. There are two possible five-membered zinc chelates involving the ketone carbonyl. Chelation at the more sterically encumbered pentylidene ketal oxygen would favor *β*-face attack of hydride and the undesired (*R*) stereochemistry at C(11). The desired (*S*) isomer **41** of the product alcohol, experimentally favored by a 14:1 ratio, results from α-face delivery of hydride, apparently involving the chelate with the less hindered ether oxygen of the B-ring. No products arising from reduction of the methyl ester moiety were observed under these conditions. Luche conditions ($NaBH_4$/$CeCl_3 \cdot 7H_2O$)[16] resulted in a nearly equimolar mixture of C(11) epimers. Use of $Zn(BH_4)_2$ in benzene or diethyl ether instead of pentane gave comparable yields but poorer selectivity, the worst of which (ca. 4:1 **41**:**38**) was observed with diethyl ether. Selectivity improved in benzene upon lowering the concentration, presumably due to the dilution of the diethyl ether used to transfer the hydride reagent. We believe the reason for these trends is that less polar solvents compete less effectively with the substrate for zinc binding. A Lewis-basic solvent such as diethyl ether can competitively bind zinc ions present in solution, thereby leaving a considerable fraction of substrate uncoordinated to zinc. Competing reduction of the uncomplexed substrate would proceed with no chelation-controlled stereoselectivity.

Our second-generation C(11) inversion sequence signifies a marked improvement over our first-generation protocol, as summarized in Figure 3. The late-stage inversion strategy delivers the TBS ether **30** of desired C(11) stereochemistry in three steps and 59% overall yield from the alcohol **38**. By avoiding the problem of overreduction, the number of steps in the inversion sequence is reduced by two and the overall yield is improved by 17%.

With a more satisfactory route to compound **30** now in hand, it remained to install the polycyclic CDE ring system and complete the synthesis of the C(1)−C(15) subunit **3**. Selective removal of the terminal pentylidene acetal[9,27] of **30** was followed by oxidative cleavage of the resulting diol with periodate to afford aldehyde **5** (Scheme

(27) Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 13−70.

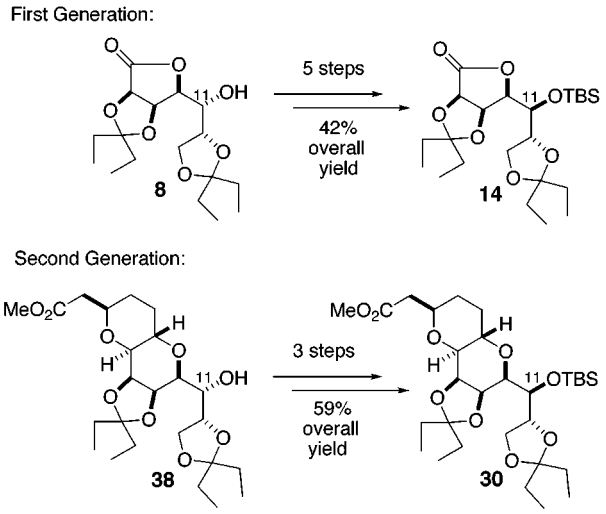
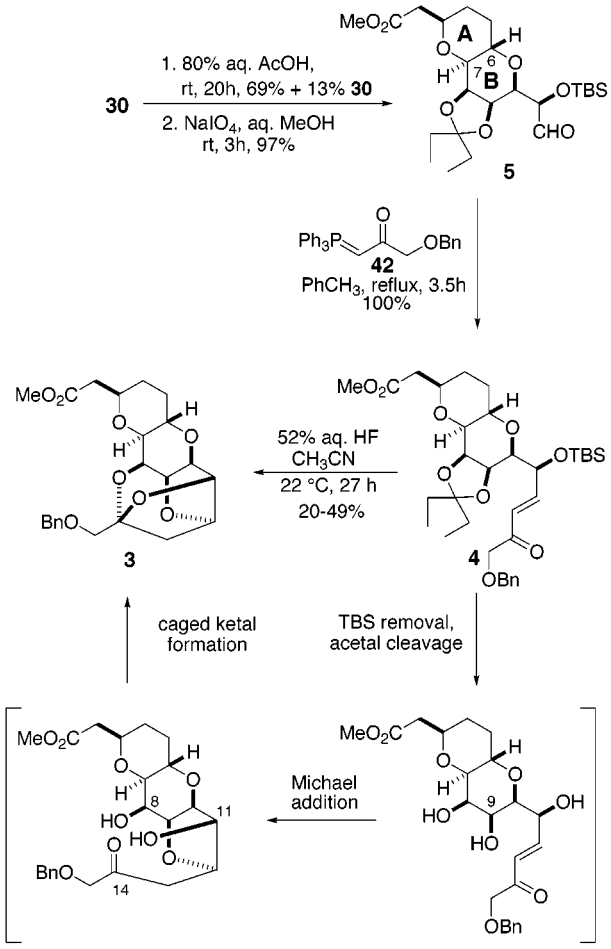


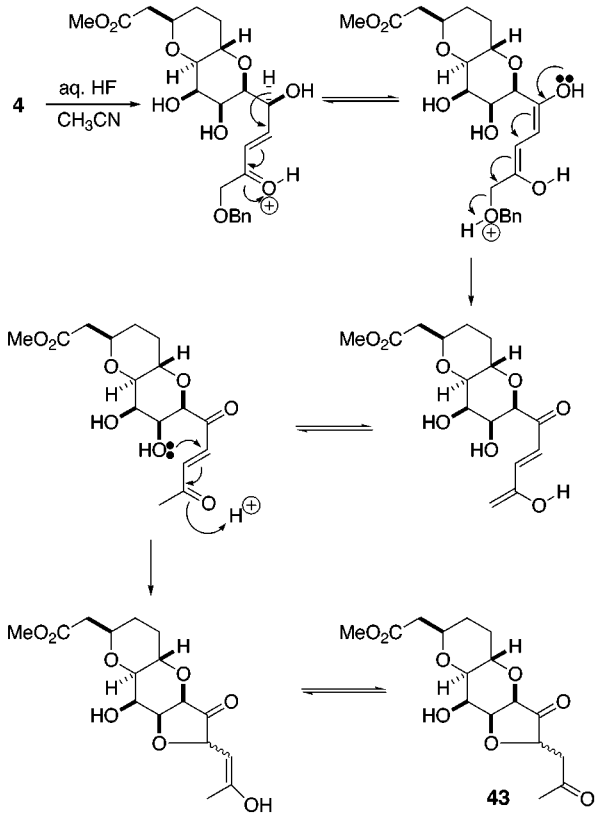
Figure 3. Comparison of C(11) carbinol inversion protocols.

Scheme 15



15). The TBS ether was prone to cleavage under the acidic conditions required to hydrolyze the terminal pentylidene ketal and so the reaction had to be arrested prior to complete conversion. With the loss of the C(13) carbon, oxidation at C(12) to give an aldehyde, and the loss of one pentylidene ketal, ^{1}H NMR analysis of compound **5** was simplified relative to many of its precursors. Therefore, we chose to verify the trans stereochemistry about the dioxadecalin AB-ring system at this stage. The three-bond coupling constant of 10.2 Hz that was observed between the H(6) and H(7) protons

Scheme 16



of **5** provided sound evidence that the desired trans AB-ring junction had been successfully installed. Homologation to the benzyloxymethyl enone **4** was accomplished by Wittig reaction of **5** with [α-(benzyloxy)acetyl]methylenetriphenylphosphorane (**42**)[28] in refluxing toluene. High temperature was required for this reaction since no conversion was observed at room temperature or in refluxing THF. The (*E*)-enone **4** was isolated in quantitative yield, containing all of the functionality necessary to effect the cage formation cascade.

It was hoped that the caged ketal moiety could be established by simply subjecting compound **4** to acidic conditions in the presence of fluoride ion. In the event, treatment of enone **4** with 52% aqueous HF in acetonitrile (1:10 v/v) at high dilution (0.01 M) assembled the polycyclic CDE ring system in **3** via a sequence of four in situ reactions illustrated in Scheme 15. Removal of the TBS and fused pentylidene acetal protecting groups precedes Michael addition of the C(9) hydroxyl to the enone, and the endo Michael adduct (shown) undergoes acetal formation at C(14) with the remaining C(8) and C(11) hydroxyls.

An intriguing, unanticipated side product that typically forms to the extent of 30−40% in this reaction is the methyl ketone **43**, in which the benzyloxy group has been lost (Scheme 16). Presumably, generation of the extended enol followed by elimination of benzyl alcohol, tautomerization of the resulting enol to the enone, and Michael addition gives **43**. The low and variable yields of **3** from **4** in this elaborate step can be attributed in large part to this side reaction.

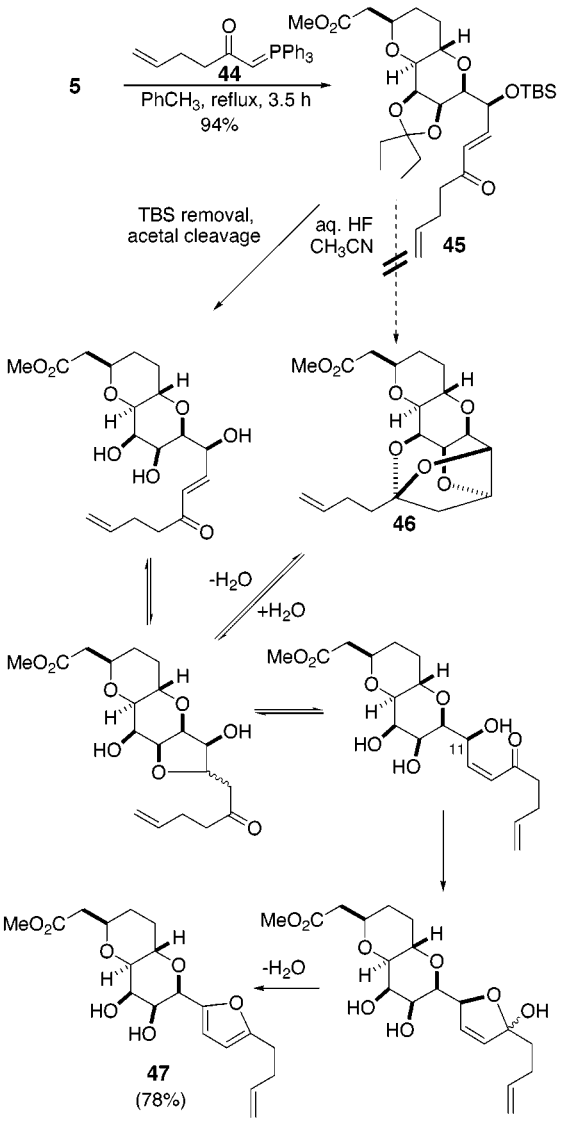
(28) (a) Bestmann, H. J.; Arnason, B. *Chem. Ber.* **1962**, *95*, 1513−1527. (b) Bestmann, H. J. *Tetrahedron Lett.* **1960**, 7−9. (c) Bestmann, H. J.; Arnason, B. *Tetrahedron Lett.* **1961**, 455−457. (d) Chopard, P. A.; Searle, R. J. G.; Devitt, F. H. *J. Org. Chem.* **1965**, *30*, 1015−1019. (e) Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41−45.

Table 1. Selected ^{1}H NMR Data for Caged Ketal Segments of Halichondrin B[a]

position	Burke (R = CH_2OBn)	Salomon[6b] (R = CH_2OBn)	Kishi[4b] (R = $(CH_2)_4CH_3$)	halichondrin B[1a]
2	2.41 (dd, *J* = 15.8, 5.0)	2.41 (dd, *J* = 15.8, 5.1)	2.45 (dd, *J* = 15.8, 5.1)	2.44 (dd, *J* = 16.5, 3.0)
	2.49 (dd, *J* = 15.8, 8.1)	2.49 (dd, *J* = 15.8, 7.8)	2.52 (dd, *J* = 15.8, 7.6)	2.57 (dd, *J* = 16.5, 9.3)
3	3.81 (m)	3.8 (m)	3.81 (m)	3.88 (m)
4 and 5	1.33, 1.73, 1.41, 2.04 (m)	1.3−1.4, 1.74, 1.3−1.4, 2.04 (m)	1.40, 1.80, 1.40, 2.05 (m)	1.35, 1.75, 1.41, 2.04 (m)
6	4.25 (ddd, *J* = 10.0, 9.6, 4.4)	4.25 (ddd, *J* = 10, 9.6, 4.6)	4.29 (ddd, *J* = 10.0, 9.6, 4.3)	4.33 (ddd, *J* = 9.3, 9.3, 4.0)
7	2.97 (dd, *J* = 9.6, 1.8)	2.97 (dd, *J* = 9.6, 4.6)	2.96 (dd, *J* = 9.6, 1.9)	2.98 (dd, *J* = 9.3, 2.4)
8	4.39 (dd, *J* = 3.9, 1.8)	4.39 (dd, *J* = 3.9, 1.8)	4.33 (dd, *J* = 4.1, 1.9)	4.31 (dd, *J* = 3.6, 2.4)
9	4.14 (dd, *J* = 6.5, 3.9)	4.14 (dd, *J* = 6.5, 3.9)	4.11 (dd, *J* = 6.6, 4.1)	4.13 (dd, *J* = 6.0, 3.6)
10	4.20 (dd, *J* = 6.5, 4.5)	4.21 (dd, *J* = 6.5, 4.6)	4.17 (dd, *J* = 6.6, 4.6)	4.18 (dd, *J* = 6.0, 4.5)
11	4.65 (dd, *J* = 4.5, 4.4)	4.65 (dd, *J* = 4.5, 4.5)	4.58 (dd, *J* = 4.6, 4.4)	4.60 (dd, *J* = 4.5, 4.5)
12	4.71 (dd, *J* = 5.0, 4.4)	4.72 (dd, *J* = 4.6, 4.6)	4.67 (dd, *J* = 4.7, 4.4)	4.71 (dd, *J* = 4.5, 4.5)
13	1.98 (d, *J* = 13.4)	1.98 (d, *J* = 13.4)	1.98 (dd, *J* = 13.3, 4.7)	1.98 (dd, *J* = 12.6, 4.5)
	2.24 (dd, *J* = 13.4, 5.0)	2.24 (dd, *J* = 13.4, 5.1)	2.03 (d, *J* = 13.3)	2.09 (d, *J* = 12.6)

[a] Chemical shifts are reported in ppm relative to the TMS signal. Coupling constants (in parentheses) are reported in Hz.

Scheme 17



Accordingly, we attempted to modify the Michael acceptor to avoid side reactions of this type. The homoallyl enone **45** was obtained by reaction of Wittig reagent **44** with aldehyde **5** (Scheme 17). Although this Michael acceptor avoids the problem of elimination described above for **4**, an alternative side reaction occurs in this case. Subjection of **45** to various conditions, including aqueous HF in acetonitrile, failed to provide the desired

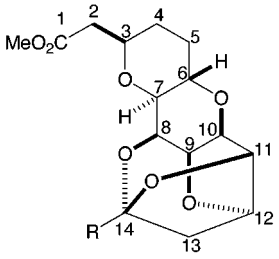


Figure 4. Caged ketal substructure.

caged product **46** and instead gave the furan **47** in good yields (47−85%). Apparently, the initial Michael adduct can either undergo acetalization to form the caged ketal or can equilibrate via a retro-Michael addition to the (*E*)- and (*Z*)-enones, of which the latter can undergo cyclization with the C(11) hydroxyl, giving rise to a cyclic hemiacetal which eliminates water to give furan **47**. The absence of the inductively withdrawing ketone α-alkoxy substituent likely disfavors both Michael addition and ketalization relative to **4**, thereby promoting the retro-Michael process that leads ultimately to **47**. The competing equilibria possible for **4** and **45** leading to **3**, **43** and **47** illustrate how subtle structural changes can greatly influence complex reaction pathways. Although the elaborate transformation of **4** to the caged ketal **3** was accomplished, more options must be explored in order to suppress the unwanted side reactions and increase the yield of caged product comprising the ABCDE ring system of halichondrin B.

We were able to compare the ^{1}H and ^{13}C NMR data we obtained for **3** with reported data for other relevant caged ketal-containing compounds, including halichondrin B (Figure 1),[1a] Kishi's model system **48**,[4b] and Salomon's model system[6b] with the same reported structure as **3**. The caged ketal substructure common to all of these compounds is shown in Figure 4. All of the data, shown in Tables 1 and 2, correlate well with the exception of the chemical shifts and multiplicities of the C(13) protons. The neighboring aromatic group, present in our segment (and Salomon's), is the likely cause of the deviation from the observed resonances in halichondrin B and **48**. Our data (and Salomon's) show a doublet for the signal at δ 1.98 and a doublet of doublets for the signal at δ 2.24. The data for Kishi's model system **48**

Table 2. Selected ^{13}C NMR Data for Caged Ketal Segments of Halichondrin B[a]

position	Burke (R = CH_2OBn)	halichondrin B[1a]
1	173.3	172.8
2	41.1	41.2
3	75.1	74.9
4		
5		
6	69.6	69.6
7	79.3	79.1
8	76.0	75.8
9	76.6	73.3
10	78.0	78.0
11	83.9	83.8
12	82.1	82.5
13	44.9	49.4
14	110.9	111.3

[a] Chemical shifts are reported in ppm relative to the center line of the $CDCl_3$ signal.

and halichondrin B show the opposite, with the upfield signal appearing as a doublet of doublets and the downfield signal appearing as a doublet. This reflects either a chemical shift anisotropy effect on both C(13) protons[6b] or (less probably) a conformational change stemming from the nature of the group appended to C(14).

Conclusion

A short (14−16 step), efficient synthesis of the C(1)−C(15) ABCDE ring system of halichondrin B has been developed from the inexpensive carbohydrate α-D-glucoheptonic acid γ-lactone (**7**), possessing the desired C(8), C(9), and C(10) structural features. To enable the employment of this starting material, two protocols have been developed for carbinol inversion at C(11), one early and one late in the synthetic sequence, with the latter having substantial practical advantages. Key ring forming reactions include a Mg^{2+}-catalyzed pinacol ring expansion, an intramolecular Michael addition, and a one-pot multistep cage-forming reaction cascade. Further studies of subunit synthesis and coupling leading to the total synthesis of halichondrin B are currently in progress.

Experimental Section

General Methods. Melting points (mp) are uncorrected. Optical rotations were measured on a digital polarimeter; concentrations (*c*) are reported in g/100 mL. Infrared (IR) spectra are reported in wavenumbers (cm^{-1}) with broad signals denoted by (br). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 300 MHz in deuterated solvents. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 75 MHz. ^{13}C NMR spectral assignments were aided by distortionless enhancement by polarization transfer (DEPT) experiments with a phase angle of 135°: (C) not observed; (CH) positive; (CH_2) negative; (CH_3) positive. Mass spectra (MS) were obtained using electron impact (EI) at 70 eV with peak matching. Fast atom bombardment MS (FAB) were obtained on a VG Analytical ZAB-2F mass spectrometer (Ion Tech FAB gun, 8 kV, Xe carrier gas) or a Kratos MS 50 (primary beam was 1 mA of 7kV Xe carrier gas, 8 kV ion acceptation voltage).

All moisture-sensitive reactions were performed in flame-dried glassware under a stream of nitrogen, unless indicated otherwise. Bath temperatures were used to record the reaction temperature in all cases. All reactions were stirred magnetically unless otherwise indicated. When prolonged cooling was necessary, an immersion cooler was employed. Analytical thin-layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates precoated with silica gel 60 F_{254} (250 μm layer thickness). Preparative TLC was carried out using 0.5 and 2.0 mm × 10 cm × 10 cm E. Merck precoated silica gel 60 (60 F_{254}) plates. TLC visualization was accomplished using either a UV lamp, iodine adsorbed on silica gel, or charring solution [*p*-anisaldehyde (PAA), phosphomolybdic acid (PMA)]. Flash column chromatography (FCC) was done according to the procedure by Still[29] on EM Science silica gel 60 (230−400 mesh) or Florisil (100−200 mesh) purchased from Aldrich.

Tetrahydrofuran (THF), diethyl ether (Et_2O), and benzene were distilled from sodium/benzophenone ketyl. Toluene ($PhCH_3$) was distilled from sodium metal. Triethylamine (Et_3N), pyridine, dichloromethane (CH_2Cl_2), and acetonitrile (CH_3CN) were distilled from calcium hydride. Dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) were distilled under reduced pressure from calcium hydride and stored over 4 Å molecular sieves. Deuteriochloroform (chloroform-*d*; $CDCl_3$), deuterioacetone (acetone-d_6), and deuteriobenzene (benzene-d_6; C_6D_6) were stored over 4 Å molecular sieves before use. Deuteriomethanol (methanol-d_4) was used as received from Aldrich in glass ampules. Methanesulfonyl chloride (MsCl) was distilled under reduced pressure prior to use. Methanol (MeOH) was distilled from magnesium methoxide. Hexanes were distilled at atmospheric pressure. All other commercially obtained reagents and solvents were used as received without further purification unless indicated otherwise.

Preparation of Alcohol 8. To a cloudy suspension of α-D-glucoheptonic acid γ-lactone (**7**) (30 g; 0.14 mol) in 3-pentanone (1.6 L; 0.088 M) was added concentrated sulfuric acid in dropwise fashion (30 mL; 0.56 mol; 4 equiv). The mixture was stirred at room temperature for 3 d after which time it was poured into cold distilled water (200 mL). The aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Filtration and evaporation of solvents in vacuo gave a brown oil. Flash column chromatography (2:1 to 1:1 hexanes−Et_2O, then Et_2O) gave the desired alcohol **8** as colorless plates (19.7 g; 0.0573 mol; 39%) and the monoprotected acetal **9** as a sticky colorless oil (15.9 g; 0.0576 mol; 39%). Triol **9** was resubjected to the reaction conditions to provide an additional 7.7 g of **8** for a total of 27.4 g (0.0797 mol; 55%). Data for **8**: R_f 0.59 (Et_2O); mp 74−77 °C; $[\alpha]^{24}_D$ −46.9° (*c* 1.17, $CHCl_3$); IR (thin film) 3520 (br), 1785 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86−0.96 (m, 12 H), 1.58−1.78 (m, 8 H), 3.26 (br s, O*H*), 3.87−3.99 (m, 2 H), 4.07−4.13 (m, 2 H), 4.58 (t, *J* = 3.5 Hz, 1 H), 4.86 (d, *J* = 5.4 Hz, 1 H), 4.92 (dd, *J* = 5.4, 3.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.50 (CH_3), 7.93 (CH_3), 8.09 (CH_3), 28.69 (CH_2), 29.23 (CH_2), 29.29 (CH_2), 67.60 (CH_2), 71.41 (CH), 74.81 (CH), 76.47 (CH), 77.09 (CH), 78.23 (CH), 113.44 (C), 118.63 (C), 173.15 (C); HRMS calcd for $C_{15}H_{23}O_7$ ($M^+ - C_2H_5$) 315.1444, found 315.1436.

Preparation of Ketone 11. To a slurry of freshly prepared Dess−Martin periodinane (147 mg; 0.347 mmol; 1.1 equiv) in CH_2Cl_2 (2.5 mL; 0.14 M) was added alcohol **8** (105 mg; 0.305 mmol) in CH_2Cl_2 (2.5 mL; 0.061 M in **8**). The solution became completely homogeneous after stirring for 10 min at room temperature and was quenched with saturated $NaHCO_3$ (10 mL). The layers were partitioned, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 0.5 N NaOH to remove periodinane byproducts, dried over $MgSO_4$, filtered, and concentrated in vacuo to give ketone **11** as a colorless oil (102 mg; 0.298 mmol; 98%). Data for **11**: R_f 0.33 (1:2 hexanes−Et_2O); $[\alpha]^{24}_D$ +44.3° (*c* 1.11, $CHCl_3$); IR (thin film) 1775, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.77−0.98 (m, 12 H), 1.56−1.81 (m, 8 H), 3.96 (t, *J* = 7.9 Hz, 1 H), 4.28 (t, *J* = 7.9 Hz, 1 H), 4.66 (t, *J* = 7.9 Hz, 1 H), 4.88 (d, *J* = 5.9 Hz, 1 H), 5.25 (dd, *J* = 5.9, 4.6 Hz, 1 H), 5.40 (d, *J* = 4.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.18 (CH_3), 7.59 (CH_3), 7.65 (CH_3), 8.12 (CH_3), 27.55 (CH_2), 28.68 (CH_2), 29.14 (CH_2), 29.21 (CH_2), 65.78 (CH_2), 75.69 (CH), 76.25

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(CH), 79.12 (CH), 81.57 (CH), 114.96 (C), 118.72 (C), 172.77 (C), 199.13 (C); HRMS calcd for $C_{15}H_{21}O_7$ ($M^+ - C_2H_5$) 313.1287, found 313.1290.

Preparation of Alcohol 13 from 11. Freshly prepared Zn(BH$_4$)$_2$ (0.16 M in Et$_2$O, 5.0 mL, 0.80 mmol) was added dropwise at −78 °C under nitrogen to a solution of ketone **11** (840 mg, 2.46 mmol) in dry Et$_2$O (10 mL) over 6 min. The clear solution was stirred at −78 °C for 1 h, and stirring was continued at −50 °C for 2.5 d. The reaction was quenched slowly with 0.6 N HCl (10 mL) and then warmed to room temperature. The biphasic solution was poured into 0.6 N HCl (10 mL) and extracted with Et$_2$O. The extract was neutralized with saturated NaHCO$_3$, dried over MgSO$_4$, and filtered. After concentration in vacuo, FCC provided alcohol **13** (550 mg, 1.60 mmol, 65%). Data for **13**: R_f 0.31 (1:2 hexanes−Et$_2$O); $[\alpha]^{24}_D$ −46.1° (*c* 1.10, CHCl$_3$); IR (thin film) 3500 (br), 1785 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.83−0.93 (m, 12 H), 1.57−1.72 (m, 8 H), 2.64 (d, J = 7.7 Hz, O*H*), 3.86−3.93 (m, 2 H), 4.08 (m, 1 H), 4.31 (td, J = 7.1, 2.8 Hz, 1 H), 4.40 (dd, J = 9.1, 3.6 Hz, 1 H), 4.82 (d, J = 5.4 Hz, 1 H), 4.95 (dd, J = 5.4, 3.6 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 7.44 (CH$_3$), 7.90 (CH$_3$), 8.01 (CH$_3$), 8.06 (CH$_3$), 28.53 (CH$_2$), 29.16 (CH$_2$), 29.38 (CH$_2$), 29.77 (CH$_2$), 65.72 (CH$_2$), 67.94 (CH), 75.30 (CH), 75.99 (CH), 76.35 (CH), 77.91 (CH), 113.19 (C), 118.12 (C), 173.27 (C); HRMS calcd for $C_{15}H_{23}O_7$ ($M^+ - C_2H_5$) 315.1444, found 315.1465.

Preparation of Hemiacetal 12. Crushed cerium(III) chloride heptahydrate (8.06 g; 21.7 mmol; 1.5 equiv) was added in portions to ketolactone **11** (4.96 g; 14.5 mmol) in MeOH (150 mL; 0.0967 M) at room temperature. The temperature was lowered to −78 °C, causing the reaction mixture to become quite viscous. Finely crushed sodium borohydride (1.10 g; 29.0 mmol; 2 equiv) was added in one portion, and stirring was continued for 2 h at −78 °C, 15 min at 0 °C and a few minutes at room temperature. The solution was reduced to a minimal volume by removal of solvent in vacuo, and it was further diluted with Et$_2$O (30 mL), which precipitated cerium salts. The salts were dissolved in 0.6 N HCl (20 mL), and upon partitioning, the aqueous layer was exhaustively extracted with Et$_2$O. The combined ethereal extracts were washed with saturated NaHCO$_3$, dried over MgSO$_4$, filtered, and concentrated in vacuo. FCC (9:1 to 4:1 PhH−Et$_2$O) gave an inseparable mixture of the desired hemiacetal **12** and the overreduced triol (5 g total; ∼3.5 g hemiacetal; 10.1 mmol, ∼70%). This mixture was taken directly into the following oxidation.

Preparation of Alcohol 13 from 12. To the hemiacetal/triol mixture above (3.5 g/1.5 g; 10 mmol/4 mmol) in CH$_2$Cl$_2$ (100 mL; 0.17 M) at room temperature was added crushed 4 Å molecular sieves (30 g) that had been allowed to cool after being placed in a 350 °C oven for at least a week. Pyridinium dichromate (9.6 g; 25 mmol; 1.5 equiv) was added in portions, and the mixture was stirred vigorously for 2 h, at which point the overoxidized ketone **11** was observed on TLC. Celite was added until stirring became difficult, and dry Et$_2$O (300 mL) was added slowly, creating a fine brown powder that could be easily filtered from the reaction mixture through silica gel. Concentration of the filtrate in vacuo followed by FCC of the crude residue (9:1 PhH-Et$_2$O) gave the desired alcohol **13** (3.4 g; 9.8 mmol; 58%). See data for **13** above.

Preparation of Silyl Ether 14. To a solution of alcohol **13** (2.00 g; 5.81 mmol) in *N*,*N*-dimethylformamide (5.8 mL; 1.0 M) were added imidazole (3.95 g; 58.1 mmol; 10 equiv) and *tert*-butyldimethylsilyl chloride (4.38 g; 29.1 mmol; 5.0 equiv). The resulting solution was stirred at ambient temperature for 16 h. Dilution with water (10 mL) was followed by extraction with Et$_2$O. The combined organic layers were washed with water and brine, dried over MgSO$_4$, filtered, and concentrated in vacuo. Recrystallization of the crude solid from hexanes gave 2.3 g (5.1 mmol; 88%) of **14** as colorless crystals. Data for **14**: R_f 0.62 (1:2 hexanes−Et$_2$O); mp 91−92 °C; $[\alpha]^{24}_D$ −20.3° (*c* 1.16, CHCl$_3$); IR (thin film) 1794 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.13 (s, 3 H), 0.16 (s, 3 H), 0.83−0.93 (m, 21 H), 1.58−1.73 (m, 8 H), 3.59−3.67 (m, 1 H), 3.99−4.14 (m, 3 H), 4.26 (dd, J = 9.1, 3.3 Hz, 1 H), 4.78 (d, J = 5.3 Hz, 1 H), 4.87 (dd, J = 5.3, 3.3 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −5.15 (CH$_3$), −4.15 (CH$_3$), 7.69 (CH$_3$), 8.07 (CH$_3$), 8.47 (CH$_3$), 18.43 (C), 26.00 (CH$_3$), 29.36 (CH$_2$), 29.69 (CH$_2$), 29.84 (CH$_2$), 66.56 (CH$_2$), 70.83 (CH), 75.89 (CH), 75.96 (CH), 78.65 (CH), 78.80 (CH), 112.32 (C), 118.20 (C), 173.30 (C); HRMS calcd for $C_{23}H_{41}O_7Si$ (M^+ − H) 457.2621, found 457.2597.

Preparation of Bis(Silyl Ether) 15. To a solution of hemiacetal **12** (2.78 g; 8.03 mmol) in *N*,*N*-dimethylformamide (8.0 mL; 1.0 M) were added imidazole (1.91 g; 28.6 mmol; 3.5 equiv) and *tert*-butyldimethylsilyl chloride (3.02 g; 20.0 mmol; 2.5 equiv). The resulting solution was stirred at ambient temperature for 16 h. Dilution with water (8 mL) was followed by extraction with Et$_2$O. The combined organic layers were washed with water and brine, dried over MgSO$_4$, filtered, and concentrated in vacuo. FCC (3:1 hexanes−Et$_2$O) provided the bis(silyl ether) **15** (4.29 g; 7.47 mmol; 93%). Data for **15**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.07 (s, 3 H), 0.09 (s, 3 H), 0.14 (s, 3 H), 0.16 (s, 3 H), 0.80−0.95 (m, 30 H), 1.50−1.75 (m, 8 H), 3.53−3.64 (m, 1 H), 3.83−3.91 (m, 1 H), 3.94−4.07 (m, 2 H), 4.47 (d, J = 7.8 Hz, 1 H), 4.77 (dd, J = 7.8, 4.0 Hz, 1 H), 5.20 (s, 1 H).

Preparation of Hemiacetal 16. A solution of tetra-*n*-butylammonium fluoride (1.0 M in THF; 7.55 mL; 7.55 mmol; 1.1 equiv) was added dropwise to a solution of the bis(silyl ether) **15** (3.94 g; 6.87 mmol) in THF (34 mL; 0.20 M) at 0 °C. After 10 min of stirring at this temperature, the reaction mixture was filtered through a plug of silica gel, rinsed with ether, and concentrated in vacuo. FCC (3:1 hexanes−Et$_2$O) of the crude residue provided hemiacetal **16** (3.00 g; 6.53 mmol; 95%). Data for **16**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.14 (s, 3 H), 0.16 (s, 3 H), 0.83−0.97 (m, 21 H), 1.52−1.74 (m, 8 H), 3.53−3.62 (m, 1 H), 3.96−4.09 (m, 3 H + O*H*), 4.54 (d, J = 7.8 Hz, 1 H), 4.77 (dd, J = 7.8, 3.6 Hz, 1 H), 5.30 (s, 1 H).

Preparation of Lactone 14 from 16. To a solution of hemiacetal **16** (4.40 g; 9.57 mmol) in CH$_2$Cl$_2$ (80 mL; 0.12 M) were added crushed 4 Å molecular sieves (17.5 g) and pyridinium dichromate (5.39 g; 14.3 mmol; 1.5 equiv) in portions. After the mixture was stirred at room temperature for 2 h, Celite was added followed by filtration of the reaction mixture through silica gel. Purification by FCC (3:1 hexanes−Et$_2$O) provided 2.98 g of lactone **14** (6.51 mmol; 68%). See data for **14** above.

Preparation of Pyranone 19. A solution of *n*-butyllithium (0.81 mL of a 2.33 M solution in hexanes; 1.9 mmol) was added dropwise to a solution of (trimethylsilyl)diazomethane (0.98 mL of a 2.0 M solution in hexane; 2.0 mmol) in dry Et$_2$O (5 mL) at −5 °C. This solution was stirred at −5 to 0 °C for 20 min before being added to a solution of lactone **14** (570 mg; 1.25 mmol) in Et$_2$O (10 mL; 0.12 M) at −78 °C. The resulting yellow solution was stirred at −78 °C for 3 h followed by quenching with 0.6 N HCl (10 mL). After being warmed to 0 °C, the mixture was poured into 0.6 N HCl (10 mL) and extracted with Et$_2$O. The combined ether layers were washed with saturated NaHCO$_3$, dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was dissolved in dry benzene (5 mL) and 4 Å MS (ca. 15 beads) were added. After being stirred at room temperature for 1 h, the solution was added to rhodium(II) acetate dimer (11 mg; 0.025 mmol) in refluxing benzene (80 mL). The mixture was heated at reflux for 40 min, cooled to room temperature, and concentrated in vacuo. Purification of the crude residue by FCC (2:1 hexanes−Et$_2$O) provided 443 mg of pyranone **19** (0.939 mmol; 75%). Data for **19**: ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.13 (s, 3 H), 0.16 (s, 3 H), 0.79−0.97 (m, 21 H), 1.51−1.81 (m, 8 H), 3.39 (d, J = 12.2 Hz, 1 H), 3.60 (at, J = 13.0 Hz, 1 H), 3.84−4.09 (m, 4 H), 4.27−4.44 (m, 2 H), 4.75 (dd, J = 9.8, 2.2 Hz, 1 H).

Preparation of Diols 22a and 22b from *rac*-21. α-Alkoxystannane *rac*-**21** (13.5 g; 30.0 mmol; 1.7 equiv) was dissolved in THF (60 mL; 0.50 M) and cooled to −78 °C for the dropwise addition of a 1.14 M solution of *n*-BuLi in hexanes (26 mL; 30 mmol; 1.7 equiv) over 30 min. Stirring was continued for 10 min, and a solution of **14** (8.0 g; 17 mmol) in THF (116 mL; 0.15 M) was added dropwise to the organolithium species over 30 min. Stirring was continued for approximately 1 h, and the reaction mixture was quenched with 1.8 N HCl (350 mL) followed by slow warming to room temperature. The turbid mixture was extracted thoroughly

with Et_2O, and the ethereal layers were concentrated and redissolved in THF (60 mL) and 1.8 N HCl (60 mL) and stirred at room temperature for 2 h. (This second hydrolysis was necessary to completely remove the ethoxyethyl protecting group.) Extraction with Et_2O was followed by washes of the combined extracts with water, saturated $NaHCO_3$, and brine. The organic extracts were then dried over $MgSO_4$, filtered, concentrated in vacuo, and subjected to FCC (3:1 to 1:1 hexanes−Et_2O) to afford 3.3 g of the desired diastereomer **22a** (6.1 mmol; 35%) and 3.8 g of the undesired diastereomer **22b** (7.0 mmol; 40%). Data for **22a**: R_f 0.21 (1:1 hexanes−Et_2O); $[\alpha]^{24}_D$ +6.5° (*c* 1.04, $CHCl_3$); IR (thin film) 3450 (br), 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.14 (s, 3 H), 0.80−0.98 (m, 21 H), 1.52−1.79 (m, 10 H and O*H*), 2.15 (m, 1 H), 2.27−2.43 (m, 2 H), 2.72 (m, O*H*), 3.46−3.56 (m, 1 H), 3.80−4.04 (m, 4 H), 4.52 (d, J = 5.9 Hz, 1 H), 4.82 (dd, J = 5.9, 3.0 Hz, 1 H), 4.96−5.09 (m, 2 H), 5.74−5.89 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.28 (CH_3), −4.09 (CH_3), 7.86 (CH_3), 7.99 (CH_3), 8.13 (CH_3), 8.44 (CH_3), 18.43 (C), 26.07 (CH_3), 28.78 (CH_2), 28.90 (CH_2), 29.62 (CH_2), 29.75 (CH_2), 29.97 (CH_2), 67.24 (CH_2), 70.89 (CH), 71.50 (CH), 79.77 (CH), 80.03 (CH), 80.89 (CH), 85.05 (CH), 106.30 (C), 111.87 (C), 115.02 (CH_2), 116.80 (C), 138.13 (CH); HRMS calcd for $C_{26}H_{47}O_8Si$ ($M^+ - C_2H_5$) 515.3040, found 515.3053. Data for **22b**: R_f 0.47 (1:1 hexanes−Et_2O); $[\alpha]^{24}_D$ −9.7° (*c* 1.16, $CHCl_3$); IR (thin film) 3200−3600 (br), 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.75−0.97 (m, 21 H), 1.49−1.81 (m, 10 H), 2.16 (m, 1 H), 2.22−2.41 (m, 1 H and O*H*), 3.61 (t, J = 8.3 Hz, 1 H), 3.83 (m, 1 H), 3.90 (s, O*H*), 3.92−4.00 (m, 3 H), 4.10 (m, 1 H), 4.44 (d, J = 5.9 Hz, 1 H), 4.81 (dd, J = 5.9, 3.0 Hz, 1 H), 4.94−5.10 (m, 2 H), 5.76−5.90 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.13 (CH_3), −4.24 (CH_3), 7.92 (CH_3), 8.09 (CH_3), 8.18 (CH_3), 8.44 (CH_3), 18.47 (C), 26.05 (CH_3), 28.69 (CH_2), 28.82 (CH_2), 29.56 (CH_2), 29.59 (CH_2), 29.62 (CH_2), 29.70 (CH_2), 66.65 (CH_2), 71.22 (CH), 72.41 (CH), 79.37 (CH), 79.57 (CH), 80.69 (CH), 84.09 (CH), 106.15 (C), 112.25 (C), 114.60 (CH_2), 116.35 (C), 138.38 (CH); HRMS calcd for $C_{26}H_{47}O_8Si$ ($M^+ - C_2H_5$) 515.3040, found 515.3015.

Recycling of 22b. Solid periodic acid (478 mg; 2.10 mmol; 1.2 equiv) was added at room temperature to a solution of **22b** (956 mg; 1.75 mmol) in THF (35 mL; 0.050 M). After 30 min, dry Et_2O (9 mL) and Na_2SO_4 (525 mg) were added, and stirring was continued at room temperature for another 20 min. Slow filtration of the reaction mixture through a frit funnel half full of Et_2O-saturated silica gel ensured complete separation of the solid byproduct from the desired product. The crude product was recrystallized from hexanes to give 730 mg of lactone **14** (1.59 mmol; 91%). See data for **14** above.

Preparation of Diol 22a from 6(*S*)-21. α-Alkoxystannane 6(*S*)-**21** (180 mg; 0.402 mmol; 2.0 equiv) was dissolved in THF (0.5 mL; 0.8 M) and cooled to −78 °C for the dropwise addition of a 2.5 M solution of *n*-BuLi in hexanes (0.16 mL; 0.40 mmol; 2.0 equiv) over 30 min. Stirring was continued for 10 min, and a solution of **14** (90 mg; 0.20 mmol; 1.0 equiv) in THF (1.0 mL; 1.0 M) was added dropwise to the organolithium species over 30 min. Stirring was continued for approximately 2.5 h, and the reaction mixture was quenched with 1.8 N HCl (4 mL) followed by slow warming to room temperature with continued stirring for 15 min. The turbid mixture was extracted thoroughly with Et_2O, and the ether layers were concentrated and redissolved in THF (5 mL) and 1.8 N HCl (5 mL) and stirred at room temperature for 2 h. (This second hydrolysis was necessary to completely remove the ethoxyethyl protecting group.) Extraction with Et_2O was followed by washes of the combined extracts with water, saturated $NaHCO_3$ and brine. The organic extracts were then dried over $MgSO_4$, filtered, concentrated in vacuo, and subjected to FCC (3:1 to 1:1 hexanes−Et_2O) to give 75 mg of **22a** (0.14 mmol; 70%) and 5 mg of **22b** (0.009 mmol; 5%) as colorless oils. See data for **22a** and **22b** above.

Preparation of Hydroxy Mesylate 23. Diol **22a** (136 mg; 0.250 mmol) and a catalytic amount of DMAP (2.0 mg; 0.013 mmol; 0.05 equiv) were dissolved in CH_2Cl_2 (2.5 mL; 0.10 M) at room temperature. Triethylamine (42 μL; 0.30 mmol; 1.2 equiv) was added, and the solution was cooled to −50 °C for the addition of MsCl (21 μL; 0.28 mmol; 1.1 equiv). Stirring was continued for 45 min, keeping the temperature between −40 and −50 °C, at which point the reaction mixture was quenched with water (5 mL) and allowed to warm to room temperature. The layers were partitioned, and the aqueous layer was extracted with CH_2Cl_2 followed by washes of the combined organic layers with 0.6 N HCl, water, and saturated $NaHCO_3$. The organic layers were then dried over $MgSO_4$, filtered, concentrated in vacuo and subjected to FCC (3:1 to 1:1 to 1:2 hexanes−Et_2O) to give 127 mg of mesylate **23** (0.204 mmol; 82%) as a colorless oil. Data for **23**: R_f 0.36 (1:2 hexanes−Et_2O); $[\alpha]^{24}_D$ −3.3° (*c* 2.40, $CHCl_3$); IR (thin film) 3200−3600 (br), 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.14 (s, 3 H), 0.83−0.97 (m, 21 H), 1.53−1.90 (m, 10 H), 2.15−2.40 (m, 2 H), 2.85 (s, O*H*), 3.14 (s, 3 H), 3.48−3.53 (m, 1 H), 3.95−4.07 (m, 4 H), 4.48 (d, J = 5.9 Hz, 1 H), 4.86 (dd, J = 6.0, 2.2 Hz, 1 H), 4.95 (at, J = 6.4, 1 H), 4.99−5.12 (m, 2 H), 5.74−5.89 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.22 (CH_3), −4.14 (CH_3), 7.86 (CH_3), 8.00 (CH_3), 8.09 (CH_3), 8.47 (CH_3), 18.45 (C), 26.06 (CH_3), 28.61 (CH_2), 28.77 (CH_2), 28.82 (CH_2), 29.14 (CH_2), 29.57 (CH_2), 29.96 (CH_2), 38.73 (CH_3), 66.99 (CH_2), 71.13 (CH), 79.56 (CH), 80.09 (CH), 80.71 (CH), 81.24 (CH), 84.27 (CH), 104.86 (C), 112.06 (C), 115.52 (CH_2), 117.29 (C), 137.16 (CH); HRMS calcd for $C_{26}H_{45}O_7Si$ ($M^+ - C_2H_5 - CH_3SO_3H$) 497.2934, found 497.2890.

Preparation of Pyranone 6. A solution of hydroxy mesylate **23** (150 mg; 0.241 mmol) in benzene (24 mL; 0.01 M) was cooled to 5 °C for the dropwise addition of a 3.0 M solution of EtMgBr in Et_2O (0.080 mL; 0.24 mmol; 1.0 equiv). The solution was stirred at 5 °C for 1 h and was warmed to room temperature where it was stirred for 10 min before being heated to a vigorous reflux for 25 min. The reaction mixture was then cooled to room temperature and poured into 10 mL of 0.6 N HCl. The aqueous phase was extracted with Et_2O, and the combined organic layers were washed with water followed by saturated $NaHCO_3$ and dried over Na_2SO_4. Filtration and concentration in vacuo gave a crude oil that was purified by FCC (20:1 benzene−Et_2O followed by 1:1 to 1:2 hexanes−Et_2O) to yield 63 mg of pyranone **6** (0.12 mmol; 50%) and 38 mg of ketone **25** (0.072 mmol; 30%). Data for **6**: R_f 0.45 (3:1 hexanes−Et_2O); $[\alpha]^{24}_D$ −24.1° (*c* 1.15, $CHCl_3$); IR (thin film) 1738, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 3 H), 0.15 (s, 3 H), 0.87−0.96 (m, 21 H), 1.56−1.95 (m, 10 H), 2.07−2.32 (m, 2 H), 3.53 (m, 1 H), 3.69 (t, J = 8.4 Hz, 1 H), 3.93 (dd, J = 8.4, 6.4 Hz, 1 H), 4.00 (dd, J = 8.4, 6.4 Hz, 1 H), 4.13 (dt, J = 8.4, 6.4 Hz, 1 H), 4.34 (d, J = 7.4 Hz, 1 H), 4.36 (dd, J = 9.4, 4.0 Hz, 1 H), 4.70 (dd, J = 7.4, 1.3 Hz, 1 H), 4.99−5.07 (m, 2 H), 5.73−5.81 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.71 (CH_3), −3.98 (CH_3), 8.00 (CH_3), 8.27 (CH_3), 8.35 (CH_3), 8.51 (CH_3), 18.55 (C), 26.20 (CH_2), 27.85 (CH_2), 28.92 (CH_2), 28.97 (CH_2), 29.07 (CH_2), 29.61 (CH_2), 29.65 (CH_2), 66.78 (CH_2), 71.93 (CH), 73.22 (CH), 76.06 (CH), 76.50 (CH), 77.94 (CH), 79.23 (CH), 112.03 (C), 115.81 (CH_2), 116.38 (C), 136.91 (CH), 207.42 (C); HRMS calcd for $C_{26}H_{45}O_7Si$ ($M^+ - C_2H_5$) 497.2934, found 497.2930. Data for **25**: R_f 0.43 (3:1 hexanes:Et_2O); IR (neat) 1718, 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 3 H), 0.14 (s, 3 H), 0.85−0.95 (m, 21 H), 1.50−1.75 (m, 8 H), 2.31 (m, 2 H), 2.64 (m, 2 H), 3.49 (dd, J = 8.0, 3.4 Hz, 1 H), 3.68 (t, J = 8.2 Hz, 1 H), 3.95−4.16 (m, 3 H), 4.33 (br s, 1 H), 4.68 (dd, J = 6.4, 3.4 Hz, 1 H), 4.95−5.12 (m, 3 H), 5.70−5.85 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.08 (CH_3), −4.22 (CH_3), 7.67 (CH_3), 8.10 (CH_3), 8.20 (CH_3), 8.30 (CH_3), 18.47 (C), 26.08 (CH_2), 27.16 (CH_2), 29.16 (CH_2), 29.47 (CH_2), 29.55 (CH_2), 29.95 (CH_2), 38.07 (CH_2), 66.84 (CH_2), 71.19 (CH), 79.38 (CH), 80.64 (CH), 81.80 (CH), 83.39 (CH), 88.89 (CH), 112.01 (C), 115.60 (CH_2), 117.00 (C), 136.68 (CH), 209.05 (C); MS (FAB) *m/e* (relative intensity, assignment) 549.2 (83, $M + Na^+$), 497.2 (25, $M^+ - C_2H_5$).

Preparation of Hydroxy Mesylate 26. Diol **22b** (75 mg; 0.14 mmol) and a catalytic amount of DMAP (0.5 mg; 0.004 mmol; 0.03 equiv) were dissolved in CH_2Cl_2 (1.5 mL; 0.09 M) at room temperature. The solution was cooled to −15 °C for the successive addition of triethylamine (81 μL; 0.58 mmol; 4.1 equiv) and methanesulfonyl chloride (20 μL; 0.26 mmol; 1.9 equiv). Stirring was continued for 10 min, keeping the

temperature between −15 and −10 °C, at which point the reaction mixture was quenched with water (1 mL) and allowed to warm to room temperature. The layers were partitioned, and the aqueous layer was extracted with Et_2O followed by washes of the combined organic layers with 0.6 N HCl, water, and saturated $NaHCO_3$. The combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo, and subjected to FCC (1:1 hexanes−Et_2O) to provide 64 mg of hydroxy mesylate **26** (0.10 mmol; 73%) as a colorless oil. Data for **26**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.13 (as, 6 H), 0.75−1.00 (m, 21 H), 1.48−1.77 (m, 6 H), 1.87−2.04 (m, 2 H), 2.11−2.40 (m, 2 H), 2.63 (s, O*H*), 3.09 (s, 3 H), 3.63−3.78 (m, 1 H), 3.96−4.16 (m, 4 H), 4.47 (d, J = 8.1 Hz, 1 H), 4.84 (dd, J = 8.1, 3.9 Hz, 1 H), 4.91 (dd, J = 11.7, 5.6 Hz, 1 H), 4.98−5.21 (m, 2 H), 5.71−5.94 (m, 1 H).

Preparation of Pyranone 27. A solution of hydroxy mesylate **26** (62 mg; 0.10 mmol) in benzene (5.0 mL; 0.020 M) was cooled to 5 °C for the dropwise addition of a 0.3 M solution of EtMgBr in PhH−Et_2O (0.33 mL; 0.10 mmol; 1.0 equiv). The solution was stirred at 5 °C for 10 min and was warmed to room temperature where it was stirred for 10 min before being heated to a vigorous reflux for 25 min. The reaction mixture was then cooled to room temperature and poured into 10 mL of 0.6 N HCl. The aqueous phase was extracted with Et_2O, and the combined organic layers were washed with water followed by saturated $NaHCO_3$ and dried over $MgSO_4$. Filtration and concentration in vacuo gave a crude oil that was purified by FCC (3:1 hexanes−Et_2O) to yield 43 mg of pyranone **27** (0.082 mmol; 82%). Data for **27**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.14 (s, 3 H), 0.19 (s, 3 H), 0.73−1.04 (m, 21 H), 1.51−1.96 (m, 10 H), 2.02−2.35 (m, 2 H), 3.40 (d, J = 11.9 Hz, 1 H), 3.66 (at, J = 11.4 Hz, 1 H), 3.83 (dd, J = 11.1, 7.2 Hz, 1 H), 3.89−4.15 (m, 3 H), 4.33 (d, J = 10.0 Hz, 1 H), 4.74 (dd, J = 10.0, 2.5 Hz, 1 H), 4.94−5.13 (m, 2 H), 5.67−5.91 (m, 1 H).

Preparation of Alcohol 28. A solution of pyranone **6** (450 mg; 0.856 mmol) in THF (28 mL; 0.03 M) was cooled to −78 °C for the dropwise addition of a 1.0 M solution of DIBALH in $PhCH_3$ (5.1 mL; 5.1 mmol; 6 equiv). The reaction mixture was stirred for 3 h and was transferred into a freshly prepared saturated solution of potassium sodium tartrate (50 mL). The cloudy solution was allowed to warm to room temperature and stir for 30 min during which time it became clear indicating that all the aluminum salts had dissolved. Extraction with Et_2O was followed by a brine wash of the combined ether layers, which were then dried over $MgSO_4$, filtered, and concentrated in vacuo. FCC (8:1 to 2:1 hexanes−Et_2O) resulted in a 99% yield of the desired alcohol **28** (447 mg; 0.847 mmol). Data for **28**: R_f 0.52 (1:1 hexanes−Et_2O); $[\alpha]^{24}_D$ −25.4° (*c* 0.820, $CHCl_3$); IR (thin film) 3200−3600 (br) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.87−0.96 (m, 21 H), 1.53−1.79 (m, 10 H), 1.96 (d, J = 10.7 Hz, O*H*), 2.05−2.35 (m, 2 H), 3.35 (dd, J = 8.7, 0.7 Hz, 1 H), 3.52 (td, J = 10.1, 2.7 Hz, 1 H), 3.58−3.71 (m, 2 H), 3.78 (m, 1 H), 3.95−4.05 (m, 2 H), 4.47−4.52 (m, 2 H), 4.94−5.05 (m, 2 H), 5.77−5.84 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.76 (CH_3), −4.05 (CH_3), 8.01 (CH_3), 8.17 (CH_3), 8.27 (CH_3), 8.60 (CH_3), 18.52 (C), 26.21 (CH_3), 28.20 (CH_2), 28.71 (CH_2), 29.30 (CH_2), 29.72 (CH_2), 29.81 (CH_2), 31.94 (CH_2), 67.18 (CH_2), 68.89 (CH), 71.50 (CH), 72.36 (CH), 72.87 (CH), 73.23 (CH), 73.83 (CH), 79.07 (CH), 111.53 (C), 113.87 (CH_2), 114.71 (C), 138.12 (CH); HRMS calcd for $C_{26}H_{47}O_7Si$ ($M^+ - C_2H_5$) 499.3091, found 499.3067.

Preparation of Enoate 29. The alcohol **28** (154 mg; 0.292 mmol) was added to a two-neck flask equipped with a gas inlet tube and a drying tube with the aid of CH_2Cl_2 (10 mL; 0.029 M). Nitrogen was bubbled through the solution for 10 min, and the solution was then cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted for 5 min. The reaction mixture was then purged with nitrogen until the blue color dissipated, and Ph_3P (153 mg; 0.584 mmol; 2 equiv) was added to quench. Stirring was continued at −78 °C for 5 min, and the solution was then allowed to warm to room temperature where it stirred for 1 h. Methyl(triphenylphosphoranylidene)acetate (968 mg; 2.90 mmol; 10 equiv) was added, and stirring was continued for 5 h at room temperature. The solvent was removed in vacuo, and the crude residue was triturated with hexanes to remove excess ylide and $Ph_3P(O)$. The hexanes solution was concentrated in vacuo, and the remaining residue was purified by FCC (8:1 to 1:1 hexanes−Et_2O) to give 150 mg (0.256 mmol; 88%) of enoate **29**. Data for **29**: R_f 0.26 (1:1 hexanes−Et_2O); $[\alpha]^{24}_D$ −34.9° (*c* 2.03, $CHCl_3$); IR (thin film) 3450 (br), 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 3 H), 0.12 (s, 3 H), 0.86−0.95 (m, 21 H), 1.56−1.90 (m, 10 H), 2.06 (d, J = 10.4 Hz, O*H*), 2.20−2.47 (m, 2 H), 3.37 (dd, J = 8.7, 1.0 Hz, 1 H), 3.51 (td, J = 10.1, 2.7 Hz, 1 H), 3.62−3.72 (m, 2 H), 3.72 (s, 3 H), 3.77 (dd, J = 8.4, 6.4 Hz, 1 H), 3.94 (dd, J = 8.4, 6.4 Hz, 1 H), 4.03 (dt, J = 9.1, 6.4 Hz, 1 H), 4.45−4.51 (m, 2 H), 5.82−5.85 (m, 1 H), 6.97 (dt, J = 15.8, 6.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.73 (CH_3), −4.07 (CH_3), 8.01 (CH_3), 8.19 (CH_3), 8.28 (CH_3), 8.62 (CH_3), 18.51 (C), 26.19 (CH_3), 28.08 (CH_2), 28.26 (CH_2), 28.66 (CH_2), 29.25 (CH_2), 29.75 (CH_2), 31.07 (CH_2), 51.39 (CH_3), 66.97 (CH_2), 68.84 (CH), 71.44 (CH), 72.11 (CH), 72.60 (CH), 73.08 (CH), 73.60 (CH), 78.81 (CH), 111.64 (C), 113.94 (C), 121.12 (CH), 148.78 (CH), 166.95 (C); HRMS calcd for $C_{28}H_{49}O_9Si$ ($M^+ - C_2H_5$) 557.3146, found 557.3159.

Preparation of Ester 30. A 40% solution of benzyltrimethylammonium methoxide in MeOH (0.75 mL; 1.5 mmol; 3 equiv) was added dropwise to a solution of **29** (294 mg; 0.502 mmol) in benzene (50 mL; 0.010 M) that had been cooled to 5 °C. The reaction mixture was stirred at 5 °C for 10 min and was then warmed to 18 °C where it was stirred for 3 h. Although **29** is consumed within 10 min at 18 °C, the additional stirring time is necessary to ensure complete equilibration of the initially formed C(3) axial isomer to the desired C(3) equatorial isomer. Quenching with 0.6 N HCl (20 mL) was followed by extraction of the aqueous layer with Et_2O. The combined organic layers were washed again with 0.6 N HCl and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. FCC (3:1 hexanes−Et_2O) of the crude residue provided 260 mg (0.444 mmol; 88%) of ester **30** as a colorless oil. Data for **30**: R_f 0.39 (1:1 hexanes−Et_2O); $[\alpha]^{24}_D$ −2.7° (*c* 2.64, $CHCl_3$); IR (thin film) 1743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 3 H), 0.13 (s, 3 H), 0.86−1.00 (m, 21 H), 1.40−1.85 (m, 11 H), 1.96 (m, 1 H), 2.42 (*A*B*X*, J_{AB} = 16.2 Hz, J_{AX} = 5.9 Hz, 1 H), 2.71 (A*B*X, J_{AB} = 16.2 Hz, J_{BX} = 6.9 Hz, 1 H), 3.44−3.61 (m, 3 H), 3.66 (s, 3 H), 3.74−3.99 (m, 5 H), 4.51 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.01 (CH_3), −4.09 (CH_3), 7.64 (CH_3), 7.99 (CH_3), 8.06 (CH_3), 8.56 (CH_3), 18.37 (C), 26.10 (CH_3), 28.10 (CH_2), 28.52 (CH_2), 29.60 (CH_2), 29.94 (CH_2), 30.08 (CH_2), 30.26 (CH_2), 40.09 (CH_2), 51.46 (CH_3), 66.44 (CH), 67.52 (CH_2), 71.75 (CH), 71.92 (CH), 72.83 (CH), 73.85 (CH), 75.50 (CH), 76.62 (CH), 80.02 (CH), 111.11 (C), 113.89 (C), 171.29 (C); HRMS calcd for $C_{28}H_{49}O_9Si$ ($M^+ - C_2H_5$) 557.3146, found 557.3147.

Preparation of Silyl Ether 32. To a solution of alcohol **8** (7.17 g; 20.9 mmol) in *N*,*N*-dimethylformamide (21 mL; 1.0 M) were added imidazole (2.14 g; 31.4 mmol; 1.5 equiv) and *tert*-butyldimethylsilyl chloride (4.41 g; 29.3 mmol; 1.4 equiv). The resulting solution was stirred at room temperature for 16 h. Dilution with water (30 mL) was followed by extraction with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. FCC (3:1 hexanes−Et_2O) of the crude product afforded 8.52 g (18.6 mmol; 89%) of the silyl ether **32** as a clear colorless oil which solidified upon drying under vacuum. Data for **32**: R_f 0.34 (1:1 hexanes−Et_2O); mp 72−73.5 °C;$[\alpha]^{23}_D$ −24.0° (*c* 1.14, $CHCl_3$); IR (thin film) 1776 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3 H), 0.16 (s, 3 H), 0.86−0.95 (m, 21 H), 1.58−1.75 (m, 8 H), 3.80−3.92 (m, 1 H), 4.04−4.24 (m, 3 H), 4.28 (dd, J = 9.0, 2.9 Hz, 1 H), 4.80 (d, J = 5.2 Hz, 1 H), 4.86 (dd, J = 5.2, 2.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.67 (CH_3), −4.21 (CH_3), 7.53 (CH_3), 8.04 (CH_3), 8.10 (CH_3), 18.16 (C), 25.80 (CH_3), 28.75 (CH_2), 29.47 (CH_2), 29.52 (CH_2), 29.75 (CH_2), 67.90 (CH_2), 71.32 (CH), 76.53 (CH), 76.62 (CH), 77.19 (CH), 81.01 (CH), 113.69 (C), 117.63 (C), 173.23 (C); HRMS calcd for $C_{23}H_{42}O_7Si$ ($M + Na^+$) 481.2598, found 481.2610.

Preparation of Diols 33a and 33b. α-Alkoxystannane *rac*-**20** (1.89 g; 4.23 mmol; 1.2 equiv) was dissolved in THF (5.0 mL; 0.85 M) and cooled to −78 °C for the dropwise addition of

a 2.35 M solution of *n*-BuLi in hexanes (1.80 mL; 4.23 mmol; 1.2 equiv) over 30 min. Stirring was continued for 10 min, and a solution of **32** (1.61 g; 3.53 mmol) in THF (9.7 mL; 0.37 M) was added dropwise to the organolithium species over 30 min. Stirring was continued for approximately 1 h, and the reaction mixture was quenched with 1.8 N HCl (70 mL) followed by slow warming to room temperature. The turbid mixture was extracted thoroughly with Et_2O, and the ethereal layers were concentrated and redissolved in THF (12 mL) and 1.8 N HCl (12 mL) and stirred at room temperature for 2 h. (This second hydrolysis was necessary to completely remove the ethoxyethyl protecting group.) Extraction with Et_2O was followed by washes of the combined extracts with water, saturated $NaHCO_3$, and brine. The extracts were then dried over $MgSO_4$, filtered, concentrated in vacuo and subjected to FCC (5:1 to 3:1 to 1:1 hexanes−Et_2O) to give 697 mg of the desired diastereomer **33a** (1.28 mmol; 36%) and 911 mg of the undesired diastereomer **33b** (1.67 mmol; 47%). Data for **33a**: R_f 0.10 (1:1 hexanes−Et_2O); $[\alpha]^{23}_D$ +3.9° (*c* 2.28, $CHCl_3$); IR (thin film) 3449 (br), 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (as, 6 H), 0.81−0.97 (m, 21 H), 1.49−1.85 (m, 10 H), 2.11−2.45 (m, 2 H + 2 O*H*), 3.83−3.94 (m, 3 H), 3.97 (dd, J = 7.3, 6.1 Hz, 1 H), 4.14 (ddd, J = 8.8, 6.0, 4.0 Hz, 1 H), 4.27 (dd, J = 9.1, 4.1 Hz, 1 H), 4.57 (d, J = 6.0 Hz, 1 H), 4.71 (dd, J = 6.0, 3.3 Hz, 1 H), 4.96−5.11 (m, 2 H), 5.76−5.91 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.29 (CH_3), −4.10 (CH_3), 7.92 (CH_3), 8.18 (CH_3), 8.41 (CH_3), 8.53 (CH_3), 18.30 (C), 25.91 (CH_3), 28.58 (CH_2), 28.61 (CH_2), 28.72 (CH_2), 28.78 (CH_2), 29.70 (CH_2), 30.02 (CH_2), 66.01 (CH_2), 70.40 (CH), 71.56 (CH), 76.93 (CH), 80.29 (CH), 81.97 (CH), 85.85 (CH), 105.90 (C), 112.93 (CH_2), 115.07 (C), 116.64 (C), 138.17 (CH); HRMS calcd for $C_{28}H_{52}O_8Si$ (M + Na^+) 567.3329, found 567.3330. Data for **33b**: R_f 0.44 (1:1 hexanes−Et_2O); $[\alpha]^{23}_D$ -7.4° (*c* 1.82 $CHCl_3$); IR (thin film) 3600, 3446 (br), 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (as, 6 H), 0.79−0.95 (m, 21 H), 1.47−1.88 (m, 10 H + O*H*), 2.09−2.40 (m, 2 H), 3.10 (s, O*H*), 3.82 (dd, J = 9.2, 3.5 Hz, 1 H), 3.87 (dd, J = 8.7, 7.6 Hz, 1 H), 3.92−3.97 (m, 1 H), 3.96 (dd, J = 7.5, 6.3 Hz, 1 H), 4.16 (ddd, J = 8.8, 5.9, 3.9 Hz, 1 H), 4.28 (dd, J = 9.3, 4.1 Hz, 1 H), 4.48 (d, J = 5.9 Hz, 1 H), 4.70 (dd, J = 5.9, 3.6 Hz, 1 H), 4.95−5.13 (m, 2 H), 5.79−5.94 (m, 1 H); ^{13}C NMR δ −4.19 (CH_3), −4.03 (CH_3), 7.87 (CH_3), 8.17 (CH_3), 8.41 (CH_3), 8.50 (CH_3), 18.34 (C), 25.83 (CH_3), 28.60 (CH_2), 28.68 (CH_2), 28.74 (CH_2), 28.84 (CH_2), 29.45 (CH_2), 29.71 (CH_2), 65.86 (CH_2), 70.55 (CH), 72.74 (CH), 76.84 (CH), 80.78 (CH), 81.02 (CH), 84.54 (CH), 105.50 (C), 112.87 (CH_2), 114.67 (C), 116.27 (C), 138.34 (CH); HRMS calcd for $C_{28}H_{52}O_8Si$ (M + Na^+) 567.3329, found 567.3331.

Recycling of 33b. Solid periodic acid (150 mg; 0.656 mmol; 1.2 equiv) was added at room temperature to a solution of **33b** (286 mg; 0.525 mmol) in THF (11 mL; 0.048 M). After 30 min, dry Et_2O (3.2 mL) and Na_2SO_4 (163 mg) were added, and stirring was continued at room temperature for another 20 min. Slow filtration of the reaction mixture through a frit funnel half full of Et_2O-saturated silica gel ensured complete separation of the solid byproduct from the desired product. Flash column chromatography (3:1 hexanes−Et_2O) provided 220 mg of lactone **32** (0.481 mmol; 92%) as a colorless oil that solidified upon drying under vacuum. See data for **32** above.

Preparation of Hydroxy Mesylate 34. Diol **33a** (211 mg; 0.387 mmol) and DMAP (2.5 mg; 0.20 mmol; 0.5 equiv) were dissolved in CH_2Cl_2 (3.9 mL; 0.10 M) at room temperature. Triethylamine (0.17 mL; 1.2 mmol; 3.2 equiv) was added, and the solution was cooled to −50 °C for the addition of MsCl (93 μL; 1.2 mmol; 3.0 equiv). Stirring was continued for 45 min, keeping the temperature between −40 and −50 °C, at which point the reaction mixture was quenched with water (5 mL) and allowed to warm to room temperature. The layers were partitioned, and the aqueous layer was extracted with CH_2Cl_2 followed by washes of the combined organic layers with 0.6 N HCl, water, and saturated $NaHCO_3$. The organic layers were then dried over $MgSO_4$, filtered, concentrated in vacuo, and subjected to FCC (3:1 benzene-Et_2O) to give 156 mg of hydroxy mesylate **34** (0.251 mmol; 64%) and 36 mg of recovered **33a** (0.066 mmol, 17%) as colorless oils. Data for **34**: R_f 0.27 (1:2 hexanes−Et_2O); $[\alpha]^{23}_D$ +1.3° (*c* 4.23, $CHCl_3$); IR (thin film) 3475 (br), 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.81−1.01 (m, 21 H), 1.49−1.80 (m, 8 H), 1.80−2.08 (m, 2 H), 2.17−2.49 (m, 2 H), 2.44 (s, O*H*), 3.17 (s, 3 H), 3.86 (dd, J = 8.3, 7.7 Hz, 1 H), 3.91 (dd, J = 9.2, 3.5 Hz, 1 H), 3.97 (dd, J = 7.6, 6.1 Hz, 1 H), 4.14 (ddd, J = 8.7, 6.0, 4.1 Hz, 1 H), 4.28 (dd, J = 9.1, 4.1 Hz, 1 H), 4.52 (d, J = 6.0 Hz, 1 H), 4.76 (dd, J = 5.9, 3.5 Hz, 1 H), 4.96−5.15 (m, 3 H), 5.75−5.91 (m, 1 H); ^{13}C NMR (75 MHz, $CHCl_3$) δ −4.19 (CH_3), −4.10 (CH_3), 7.89 (CH_3), 8.19 (CH_3), 8.41 (CH_3), 8.55 (CH_3), 18.21 (C), 25.87 (CH_3), 28.65 (CH_2), 29.31 (CH_2), 29.64 (CH_2), 38.82 (CH_3), 66.00 (CH_2), 70.21 (CH), 76.90 (CH), 80.37 (CH), 81.61 (CH), 82.08 (CH), 84.97 (CH), 104.34 (C), 113.02 (CH_2), 115.49 (C), 117.17 (C), 137.18 (CH); HRMS calcd for $C_{29}H_{54}O_{10}SiS$ (M^+ + Na) 645.3105, found 645.3090.

Preparation of Pyranone 35. A solution of hydroxy mesylate **34** (252 mg; 0.404 mmol) in benzene (25 mL; 0.016 M) was cooled to 5 °C for the dropwise addition of a 3.0 M solution of EtMgBr in Et_2O (0.14 mL; 0.40 mmol; 1.0 equiv). The solution was stirred at 5 °C for 1 h and was warmed to room temperature where it was stirred for 10 min before being heated to a vigorous reflux for 25 min. The reaction mixture was then cooled back down to room temperature and poured into 20 mL of 0.6 N HCl. The aqueous phase was extracted with Et_2O, and the combined organic layers were washed with water followed by saturated $NaHCO_3$ and dried over Na_2SO_4. Filtration and concentration in vacuo gave a crude oil that was purified by flash column chromatography (5:1 hexanes−Et_2O) to yield 94 mg of pyranone **35** (0.18 mmol; 43%) and 74 mg of ketone **36** (0.14 mmol; 35%). Data for **35**: R_f 0.31 (3:1 hexanes−Et_2O); $[\alpha]^{23}_D$ −9.89° (*c* 1.81, $CHCl_3$); IR (thin film) 1735, 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3 H), 0.13 (s, 3 H), 0.85−0.96 (m, 21 H), 1.50−1.84 (m, 10 H), 2.06−2.36 (m, 2 H), 3.63 (d, J = 7.2 Hz, 1 H), 3.92 (at, J = 7.9 Hz, 1 H), 4.03 (dd, J = 7.9, 6.6 Hz, 1 H), 4.17 (dd, J = 7.4, 4.1 Hz, 1 H), 4.26 (ddd, J = 7.4, 6.2, 3.9 Hz, 1 H), 4.32 (m, 2 H), 4.65 (dd, J = 6.8, 1.3 Hz, 1 H), 4.98−5.10 (m, 2 H), 5.72−5.87 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.59 (CH_3), −3.86 (CH_3), 7.81 (CH_3), 8.34 (CH_3), 18.12 (C), 25.98 (CH_3), 27.95 (CH_2), 28.00 (CH_2), 29.13 (CH_2), 29.22 (CH_2), 29.36 (CH_2), 29.40 (CH_2), 66.16 (CH_2), 71.92 (CH), 72.37 (CH), 75.59 (CH), 75.87 (CH), 76.91 (CH), 79.82 (CH), 112.72 (C), 115.59 (CH_2), 115.68 (C), 136.95 (CH), 207.31 (C); HRMS calcd for $C_{28}H_{50}O_7Si$ (M^+ + Na) 549.3224, found 549.3197. Data for **36**: R_f 0.15 (3:1 hexanes:Et_2O); $[\alpha]^{23}_D$ −33.7 (*c* 1.72, $CHCl_3$); IR (thin film) 1721, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 3 H), 0.18 (s, 3 H), 0.78−0.96 (m, 21 H), 1.46−1.74 (m, 8 H), 2.30−2.40 (m, 2 H), 2.72−2.80 (m, 2 H), 3.27 (dd, J = 8.8, 3.3 Hz, 1 H), 3.89 (at, J = 8.3 Hz, 1 H), 3.90 (d, J = 4.0 Hz, 1 H), 4.01 (dd, J = 7.6, 6.4 Hz, 1 H), 4.16 (ddd, J = 8.4, 6.1, 5.1 Hz, 1 H), 4.34 (dd, J = 8.8, 4.8 Hz, 1 H), 4.65 (dd, J = 6.2, 3.3 Hz, 1 H), 4.93 (dd, J = 6.1, 4.3 Hz, 1 H), 4.94−5.09 (m, 2 H), 5.77−5.92 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.44 (CH_3), −4.04 (CH_3), 8.01 (CH_3), 8.21 (CH_3), 8.37 (CH_3), 8.43 (CH_3), 18.35 (C), 25.94 (CH_3), 26.44 (CH_2), 28.10 (CH_2), 28.68 (CH_2), 28.71 (CH_2), 29.64 (CH_2), 39.61 (CH_2), 66.57 (CH_2), 70.86 (CH), 80.11 (CH), 82.50 (CH), 84.50 (CH), 86.24 (CH), 113.14 (C), 114.84 (CH_2), 116.48 (C), 137.19 (CH), 206.44 (C); HRMS calcd for $C_{28}H_{50}O_7Si$ (M + Na^+) 549.3224, found 549.3211.

Preparation of Enoate 37. A solution of pyranone **35** (36 mg; 0.068 mmol) in THF (2.3 mL; 0.030 M) was cooled to −78 °C for the dropwise addition of a 1.0 M solution of DIBALH in $PhCH_3$ (0.41 mL; 0.41 mmol; 6.0 equiv). The reaction mixture was stirred for 3 h and was transferred into a freshly prepared saturated solution of potassium sodium tartrate (5 mL). The cloudy solution was allowed to warm to room temperature and stir for 30 min, during which time it became clear, indicating that all the aluminum salts had dissolved. Extraction with Et_2O was followed by a brine wash of the ether layers, which were then dried over $MgSO_4$, filtered and concentrated in vacuo. FCC (2:1 hexanes−Et_2O) resulted in an 86% yield of the desired alcohol (31 mg; 0.059 mmol). Data for the alcohol: R_f 0.25 (1:1 hexanes−Et_2O); $[\alpha]^{23}_D$ −2.25 (*c* 1.42, $CHCl_3$); IR (thin film) 3449 (br), 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ

0.08 (s, 3 H), 0.12 (s, 3 H), 0.84−1.00 (m, 21 H), 1.55−1.86 (m, 10 H), 2.08 (d, J = 10.4 Hz, O*H*), 3.43 (d, J = 7.1 Hz, 1 H), 3.55 (atd, J = 10.2, 2.3 Hz, 1 H), 3.74 (ddd, J = 10.3, 7.3, 3.4 Hz, 1 H), 3.91 (at, J = 7.7 Hz, 1 H), 3.96 (dd, J = 7.8, 6.5 Hz, 1 H), 4.10 (dd, J = 7.2, 2.3 Hz, 1 H), 4.29 (ddd, J = 7.7, 6.5, 2.8 Hz, 1 H), 4.43 (m, 2 H), 4.93−5.09 (m, 2 H), 5.75−5.91 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.50 (CH_3), −4.09 (CH_3), 7.97 (CH_3), 8.39 (CH_3), 8.46 (CH_3), 8.61 (CH_3), 18.11 (C), 25.96 (CH_3), 27.56 (CH_2), 27.75 (CH_2), 28.52 (CH_2), 29.03 (CH_2), 29.34 (CH_2), 31.65 (CH_2), 65.35 (CH_2), 68.65 (CH), 71.65 (CH), 72.03 (CH), 72.23 (CH), 72.71 (CH), 73.16 (CH), 76.39 (CH), 112.10 (C), 113.73 (CH_2), 114.53 (C), 138.60 (CH); HRMS calcd for $C_{28}H_{52}O_7Si$ (M + Na^+) 551.3380, found 551.3404.

The alcohol from above (220 mg; 0.416 mmol) was added to a two-neck flask equipped with a gas inlet tube and a drying tube with the aid of CH_2Cl_2 (14 mL; 0.030 M). Nitrogen was bubbled through the solution for 10 min, and it was cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted for 5 min. The reaction mixture was then purged with nitrogen until the blue color dissipated, and Ph_3P (218 mg; 0.832 mmol; 2 equiv) was added to quench. Stirring was continued at −78 °C for 5 min, and the solution was then allowed to warm to room temperature where it stirred for 1 h. Methyl(triphenylphosphoranylidene)acetate (1.39 g; 4.16 mmol; 10 equiv) was added, and stirring was continued overnight at room temperature. The solvent was removed in vacuo, and the crude residue was triturated with hexanes to remove excess ylide and Ph_3P(O). The hexanes solution was concentrated in vacuo, and the remaining residue was purified by FCC (8:1 to 1:2 hexanes−Et_2O) to give 228 mg (0.389 mmol; 94%) of enoate **37** as a 12:1 mixture of (E):(Z) isomers. Data for **37**: R_f 0.17 (1:1 hexanes−Et_2O); $[\alpha]^{23}_D$ −18.0° (*c* 1.65, $CHCl_3$); IR (thin film) 3450 (br), 1725, 1657 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.12 (s, 3 H), 0.84−0.99 (m, 21 H), 1.55−1.80 (m, 9 H), 1.81−1.94 (m, 1 H), 2.08 (d, J = 10.7 Hz, O*H*), 2.25−2.51 (m, 2 H), 3.44 (d, J = 7.1 Hz, 1 H), 3.49−3.58 (m, 1 H), 3.68−3.78 (m, 1 H), 3.72 (s, 3 H), 3.91 (at, J = 7.8 Hz, 1 H), 3.96 (dd, J = 8.0, 6.6 Hz, 1 H), 4.08 (dd, J = 6.9, 2.9 Hz, 1 H), 4.28 (ddd, J = 7.7, 6.7, 3.0 Hz, 1 H), 4.40−4.47 (m, 2 H), 5.85 (dt, J = 15.6, 1.5 Hz, 1 H), 6.99 (dt, J = 15.6, 6.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.51 (CH_3), −4.07 (CH_3), 7.96 (CH_3), 8.40 (CH_3), 8.45 (CH_3), 8.60 (CH_3), 18.10 (C), 25.93 (CH_3), 27.54 (CH_2), 27.61 (CH_2), 27.67 (CH_2), 28.53 (CH_2), 29.34 (CH_2), 30.84 (CH_2), 51.36 (CH_3), 65.42 (CH_2), 68.64 (CH), 71.66 (CH), 71.68 (CH), 72.26 (CH), 72.63 (CH), 72.98 (CH), 76.38 (CH), 112.17 (C), 113.82 (C), 121.06 (CH), 149.21 (CH), 167.07 (C); HRMS calcd for $C_{30}H_{54}O_9Si$ (M^+ + Na) 609.3435, found 609.3428.

Preparation of Ester 31. A 40% solution of benzyltrimethylammonium methoxide in MeOH (0.57 mL; 1.2 mmol; 3.0 equiv) was added dropwise to a solution of **37** (228 mg; 0.388 mmol) in benzene (39 mL; 0.010 M) that had been cooled to 5 °C. The reaction mixture was stirred at 5 °C for 10 min and was then warmed to room temperature where it was stirred for 3 h. Although **37** is consumed within 10 min at room temperature, the additional stirring time is necessary to ensure complete equilibration of the initially formed C(3) axial isomer to the desired C(3) equatorial isomer. Quenching with 0.6 N HCl (15 mL) was followed by extraction of the aqueous layer with Et_2O. The combined organic layers were washed again with 0.6 N HCl and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. FCC (3:1 hexanes−Et_2O) of the crude residue provided 167 mg (0.285 mmol; 73%) of ester **31** as a colorless oil. Data for **31**: R_f 0.33 (1:1 hexanes−Et_2O); $[\alpha]^{23}_D$ +3.8° (*c* 3.28, $CHCl_3$); IR (thin film) 1742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3 H), 0.10 (s, 3 H), 0.83−0.95 (m, 18 H), 1.00 (at, J = 7.3 Hz, 3 H), 1.33−1.86 (m, 11 H), 2.03−2.14 (m, 1 H), 2.42 (*A*BX, J_{AB} = 16.2 Hz, J_{AX} = 6.2 Hz, 1 H), 2.72 (A*B*X, J_{AB} = 16.2 Hz, J_{BX} = 7.0 Hz, 1 H), 3.49 (dd, J = 10.3, 2.5 Hz, 1 H), 3.51 (dd, J = 7.3, 0.8 Hz, 1 H), 3.67 (s, 3 H), 3.78−3.99 (m, 4 H), 4.07 (dd, J = 7.5, 3.8 Hz, 1 H), 4.22 (ddd, J = 8.0, 6.3, 3.9 Hz, 1 H), 4.43 (*ABXY*, J_{AB} = 8.7 Hz, J_{AX} = 0.3 Hz, 1 H), 4.46 (A*B*XY, J_{AB} = 8.7 Hz, J_{BY} = 2.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.57 (CH_3), −3.95 (CH_3), 7.43 (CH_3), 8.25 (CH_3), 8.31 (CH_3), 8.62 (CH_3), 18.22 (C), 25.93 (CH_3), 27.95 (CH_2), 28.01 (CH_2), 28.23 (CH_2), 29.40 (CH_2), 30.02 (CH_2), 30.65 (CH_2), 40.19 (CH_2), 51.49 (CH_3), 65.95 (CH_2), 65.97 (CH), 71.35 (CH), 72.25 (CH), 72.54 (CH), 73.66 (CH), 75.16 (CH), 76.56 (CH), 112.39 (C), 113.42 (C), 171.42 (C); HRMS calcd for $C_{30}H_{54}O_9Si$ (M + Na^+) 609.3435, found 609.3455.

Preparation of Alcohol 38. A 1.0 M solution of tetra-*n*-butylammonium fluoride (0.15 mL; 0.15 mmol; 1.2 equiv) was added dropwise to a solution of **31** (73 mg; 0.12 mmol) in THF (1.2 mL; 0.10 M) at room temperature. The reaction mixture was stirred for 24 h and was then directly applied to a silica gel column and eluted with Et_2O. Evaporation of the solvent in vacuo afforded 58 mg of alcohol **38** (0.12 mmol, 99%) as a clear oil. Data for **38**: R_f 0.31 (1:2 hexanes−Et_2O); $[\alpha]^{23}_D$ −22.4° (*c* 1.86, $CHCl_3$); IR (thin film) 3529 (br), 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85−0.94 (m, 9 H), 1.00 (at, J = 7.3 Hz, 3 H), 1.38−1.53 (m, 1 H), 1.56−1.70 (m, 7 H), 1.75−1.92 (m, 3 H), 2.08−2.19 (m, 1 H), 1.56−1.70 (m, 7 H), 1.75−1.92 (m, 3 H), 2.08−2.19 (m, 1 H), 2.44 (*ABX*, J_{AB} = 16.3 Hz, J_{AX} = 6.2 Hz, 1 H), 2.73 (A*B*X, J_{AB} = 16.2 Hz, J_{BX} = 7.1 Hz, 1 H), 3.43 (as, 1 H), 3.60 (dd, J = 10.2, 2.8 Hz, 1 H), 3.68 (s, 3 H), 3.75 (d, J = 6.7 Hz, 1 H), 3.84−3.96 (m, 3 H), 3.98 (ddd, J = 10.5, 4.6 Hz, 1 H), 4.09−4.21 (m, 2 H), 4.50 (*ABXY*, J_{AB} = 8.5 Hz, J_{AX} = 1.3 Hz, 1 H), 4.56 (A*B*XY, J_{AB} = 8.5 Hz, J_{BY} = 2.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.73 (CH_3), 7.99 (CH_3), 8.18 (CH_3), 8.64 (CH_3), 27.78 (CH_2), 28.30 (CH_2), 29.27 (CH_2), 29.62 (CH_2), 30.10 (CH_2), 30.44 (CH_2), 40.19 (CH_2), 51.62 (CH_3), 66.78 (CH), 67.85 (CH), 67.92 (CH_2), 72.02 (CH), 74.10 (CH), 74.80 (CH), 75.50 (CH), 76.48 (CH), 77.97 (CH), 112.96 (C), 114.60 (C), 171.43 (C); HRMS calcd for $C_{24}H_{40}O_9$ (M + Na^+) 495.2570, found 495.2554.

Preparation of Ketone 39. To a solution of alcohol **38** (27 mg; 0.057 mmol) in CH_2Cl_2 (0.57 mL; 0.10 M) were added tetra-*n*-propylammonium perruthenate (2 mg; 0.006 mmol; 0.1 equiv), *N*-methylmorpholine *N*-oxide (8.2 mg; 0.070 mmol; 1.2 equiv), and crushed 4 Å molecular sieves (7.3 mg). The reaction mixture turned black within 5 min. After being stirred at room temperature for 1.5 h, the mixture was filtered through a plug of silica gel and rinsed with Et_2O. Removal of the solvent in vacuo was followed by column chromatography (1:2 hexanes−Et_2O) to afford 26 mg (0.055 mmol, 94%) of ketone **39** as a clear oil that solidified upon drying under vacuum. Data for **39**: R_f 0.21 (1:2 hexanes−Et_2O); $[\alpha]^{23}_D$ +19.7° (*c* 1.43, $CHCl_3$); IR (thin film) 1735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82−1.01 (m, 12 H), 1.41−1.88 (m, 11 H), 2.09−2.20 (m, 1 H), 2.44 (*ABX*, J_{AB} = 16.2 Hz, J_{AX} = 6.1 Hz, 1 H), 2.73 (A*B*X, J_{AB} = 16.2 Hz, J_{BX} = 7.0 Hz, 1 H), 3.44 (dd, J = 10.3, 3.1 Hz, 1 H), 3.68 (s, 3 H), 3.80−3.90 (m, 1 H), 3.98 (ddd, J = 10.8, 10.6, 4.8 Hz, 1 H), 4.08 (dd, J = 8.2, 8.0 Hz, 1 H), 4.32 (at, J = 8.1 Hz, 1 H), 4.33 (d, J = 2.2 Hz, 1 H), 4.54 (dd, J = 8.5, 3.0 Hz, 1 H), 4.78 (dd, J = 8.3, 1.8 Hz, 1 H), 4.96 (at, J = 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.89 (CH_3), 8.10 (CH_3), 8.58 (CH_3), 27.30 (CH_2), 28.26 (CH_2), 28.71 (CH_2), 29.08 (CH_2), 29.87 (CH_2), 30.55 (CH_2), 40.09 (CH_2), 51.65 (CH_3), 65.79 (CH_2), 66.34 (CH), 71.10 (CH), 75.27 (CH), 75.34 (CH), 75.44 (CH), 78.91 (CH), 114.29 (C), 114.44 (C), 171.36 (C), 205.20 (C); HRMS calcd for $C_{24}H_{38}O_9$ (M + Na^+) 493.2414, found 493.2422.

Preparation of Ketone 39 and Lactone 40. To a solution of alcohol **38** (117 mg; 0.248 mmol) in CH_2Cl_2 (1.7 mL; 0.15 M) were added pyridinium chlorochromate (160 mg, 0.742 mmol, 3.0 equiv), sodium acetate (160 mg), and 4 Å molecular sieves (198 mg) at room temperature. The reaction mixture was stirred at room temperature for 48 h, and then Celite (124 mg) was added and stirring was continued for another 40 min. The mixture was then filtered through a plug of Celite, and the dark brown filtrate was concentrated in vacuo. FCC (1:2 hexanes−Et_2O) of this crude residue gave 60 mg of ketone **39** (52%; 0.13 mmol), 17 mg of recovered alcohol **38** (15%; 0.036 mmol), and 22 mg of lactone **40** (27%; 0.067 mmol), all as colorless oils. Data for **38** and **39** shown above. Data for **40**: R_f 0.18 (1:2 hexanes:Et_2O); IR (thin film) 1744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (at, J = 7.4 Hz, 3 H), 0.95 (at, J = 7.3 Hz, 3 H), 1.42−1.94 (m, 7 H), 2.30−2.39 (m, 1 H), 2.48 (*ABX*, J_{AB} = 16.1 Hz, J_{AX} = 5.7 Hz, 1 H), 2.74 (A*B*X, J_{AB} = 16.1 Hz, J_{BX} = 7.1 Hz, 1 H), 3.55 (dd, J = 9.6, 2.2 Hz, 1 H), 3.70 (s, 3 H), 3.94 (dddd, J = 11.2, 7.7, 5.8, 2.1 Hz, 1 H), 4.55

(ddd, J = 10.9, 9.4, 4.9 Hz, 1 H), 4.60−4.67 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.74 (CH_3), 8.42 (CH_3), 28.87 (CH_2), 29.02 (CH_2), 29.29 (CH_2), 39.93 (CH_2), 51.78 (CH_3), 70.44 (CH), 73.31 (CH), 74.26 (CH), 75.17 (CH), 75.80 (CH), 116.36 (C), 167.60 (C), 171.08 (C); MS *m/e* (relative intensity, assignment) 299.1 (100, $M^+ - C_2H_5$).

Preparation of Alcohol 41. To a slurry of ketone **39** (28 mg; 0.060 mmol) in pentane (1.2 mL) was added freshly prepared zinc borohydride (0.16 M in Et_2O; 0.38 mL; 0.061 mmol; 1 equiv) at room temperature. The cloudy white mixture stirred for 25 min at room temperature and was then quenched with 0.6 N HCl (2 mL). The aqueous phase was extracted with Et_2O, the combined organic phases were washed with water and sat. $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. FCC (1:2 hexanes−Et_2O) of the crude product afforded 22 mg (0.047 mmol, 78%) of an inseparable 14:1 mixture of the C(11) epimeric alcohols **41** and **38** as a clear oil: R_f 0.34 (1:2 hexanes−Et_2O); IR (thin film) 3479 (br), 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85−0.95 (m, 9 H), 0.99 (at, J = 7.4 Hz, 3 H), 1.40−1.72 (m, 8 H), 1.74−1.87 (m, 3 H), 1.97−2.07 (m, 1 H), 2.43 (*A*BX, J_{AB} = 16.1 Hz, J_{AX} = 6.2 Hz, 1 H), 2.48 (d, J = 6.2 Hz, O*H*), 2.73 (A*B*X, J_{AB} = 16.2 Hz, J_{BX} = 6.8 Hz, 1 H), 3.51 (dd, J = 10.4, 2.8 Hz, 1 H), 3.58 (dd, J = 8.5, 1.4 Hz, 1 H), 3.68 (s, 3 H), 3.69 (ddd, J = 8.3, 6.0, 4.4 Hz, 1 H), 3.81 (at, J = 8.0 Hz, 1 H), 3.81−3.95 (m, 2 H), 4.03 (dd, J = 8.2, 6.7 Hz, 1 H), 4.22 (ddd, J = 7.8, 6.4, 4.4 Hz, 1 H), 4.53 (dd, J = 8.7, 2.6 Hz, 1 H), 4.63 (dd, J = 8.6, 1.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.53 (CH_3), 8.04 (CH_3), 8.68 (CH_3), 28.32 (CH_2), 28.49 (CH_2), 29.05 (CH_2), 29.63 (CH_2), 30.11 (CH_2), 30.45 (CH_2), 40.17 (CH_2), 51.59 (CH_3), 66.41 (CH), 66.80 (CH_2), 70.17 (CH), 71.02 (CH), 71.49 (CH), 74.28 (CH), 75.44 (CH), 76.71 (CH), 112.47 (C), 113.84 (C), 171.46 (C); HRMS calcd for $C_{24}H_{40}O_9$ ($M + Na^+$) 495.2570, found 495.2592.

Preparation of Silyl Ether 30. To a solution of the 14:1 mixture of **41**:**38** (40 mg; 0.085 mmol) in *N*,*N*-dimethylformamide (0.12 mL; 0.71 M) were added imidazole (57 mg; 0.84 mmol; 10 equiv) and *tert*-butyldimethylsilyl chloride (64 mg; 0.42 mmol; 5 equiv). The resulting solution was stirred at room temperature for 48 h. Dilution with water (2 mL) was followed by extraction with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. FCC (3:1 hexanes−Et_2O) of the crude product afforded 32 mg (0.055 mmol; 81%) of silyl ether **30** and 3 mg (0.005 mmol; 6%) of silyl ether **31** as clear colorless oils. Data for **30** and **31** are shown above.

Preparation of Aldehyde 5. Acetal **30** (183 mg; 0.312 mmol) was dissolved in an 80% solution of AcOH in water (31 mL; 0.010 M) and was stirred at room temperature for 20 h. The reaction mixture was then transferred to a large round-bottom flask with the aid of CH_2Cl_2 and water (∼5 mL of each), and the acetic acid was carefully neutralized with solid K_2CO_3. This mixture was exhaustively extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by FCC (2:1 to 1:2 hexanes−Et_2O, then 100% Et_2O) to afford 112 mg of the terminal 1,2-diol (0.215 mmol; 69%) and 24 mg recovered **30** (0.041 mmol; 13%). Data for diol: R_f 0.34 (Et_2O); $[\alpha]^{24}_D$ −13.0° (*c* 3.15, $CHCl_3$); IR (thin film) 3442 (br), 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 6 H), 0.87 (s, 9 H), 0.91 (t, J = 7.3 Hz, 3 H), 0.99 (t, J = 7.3 Hz, 3 H), 1.35−1.85 (m, 7 H), 2.00 (m, 1 H), 2.43 (*A*BX, J_{AB} = 16.2 Hz, J_{AX} = 5.9 Hz, 1 H + O*H*), 2.72 (A*B*X, J_{AB} = 16.2 Hz, J_{BX} = 6.9 Hz, 1 H), 3.30 (br s, O*H*), 3.50 (dd, J = 10.2, 2.6 Hz, 1 H), 3.64 (s, 3 H), 3.64−3.98 (m, 7 H), 4.05 (dd, J = 8.9, 3.0 Hz, 1 H), 4.40 (dd, J = 8.9, 1.3 Hz, 1 H), 4.53 (dd, J = 8.6, 2.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.05 (CH_3), −4.77 (CH_3), 7.67 (CH_3), 8.59 (CH_3), 17.92 (C), 25.74 (CH_3), 27.94 (CH_2), 28.45 (CH_2), 29.99 (CH_2), 30.51 (CH_2), 40.01 (CH_2), 51.54 (CH_3), 63.11 (CH_2), 66.80 (CH), 69.40 (CH), 71.45 (CH), 72.25 (CH), 73.71 (CH), 74.03 (CH), 75.42 (CH), 76.23 (CH), 114.02 (C), 171.23 (C); HRMS calcd for $C_{23}H_{41}O_9Si$ ($M^+ - C_2H_5$) 489.2520, found 489.2530.

Sodium periodate (26 mg; 0.12 mmol; 2 equiv) was added to a solution of the diol from above (34 mg; 0.066 mmol) in 50% aqueous MeOH (3 mL; 0.02 M). The cloudy reaction mixture was stirred for 3 h and was subsequently poured into water (5 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo, and subjected to FCC (2:1 to 1:1 hexanes−Et_2O). Aldehyde **5** was isolated in 97% yield (29 mg; 0.060 mmol) as a stable white crystalline solid: R_f 0.28 (1:1 hexanes−Et_2O); $[\alpha]^{24}_D$ −52.5° (*c* 2.10, $CHCl_3$); IR (thin film) 1741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3 H), 0.08 (s, 3 H), 0.88−0.93 (m, 12 H), 1.00 (t, J = 7.5 Hz, 3 H), 1.39−1.90 (m, 7 H), 2.02 (m, 1 H), 2.42 (*A*BX, J_{AB} = 16.4 Hz, J_{AX} = 5.9 Hz, 1 H), 2.72 (A*B*X, J_{AB} = 16.4 Hz, J_{BX} = 6.9 Hz, 1 H), 3.48 (dd, J = 10.2, 2.6 Hz, 1 H), 3.67 (s, 3 H), 3.78 (dd, J = 9.1, 1.5 Hz, 1 H), 3.79−3.97 (m, 2 H), 4.22 (dd, J = 9.1, 2.2 Hz, 1 H), 4.47 (dd, J = 8.4, 1.5 Hz, 1 H), 4.56 (dd, J = 8.4, 2.6 Hz, 1 H), 9.70 (d, J = 2.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.47 (CH_3), −4.62 (CH_3), 7.80 (CH_3), 8.60 (CH_3), 18.13 (C), 25.60 (CH_3), 27.83 (CH_2), 28.54 (CH_2), 30.01 (CH_2), 30.46 (CH_2), 40.10 (CH_2), 51.56 (CH_3), 66.52 (CH), 71.26 (CH), 71.55 (CH), 73.54 (CH), 75.42 (CH), 75.52 (CH), 76.45 (CH), 114.12 (C), 171.34 (C), 201.53 (CH); HRMS calcd for $C_{24}H_{43}O_8Si$ ($M^+ + H$) 487.2727, found 487.2703.

Preparation of Enone 4. Aldehyde **5** (95 mg; 0.20 mmol) and ylide **42** (250 mg; 0.590 mmol; 3 equiv) were combined with $PhCH_3$ (4 mL; 0.05 M) at room temperature and subsequently heated to a vigorous reflux for 3.5 h. The reaction mixture was then cooled to room temperature, the solvent was removed in vacuo, and the crude residue was dissolved in minimal CH_2Cl_2 and applied directly to a column for FCC (2:1 to 1:1 hexanes−Et_2O) to give 130 mg of enone **4** (0.206 mmol; 100%): R_f 0.24 (1:1 hexanes−Et_2O); $[\alpha]^{24}_D$ −26.3° (*c* 2.50, $CHCl_3$); IR (thin film) 1741, 1715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3 H), 0.08 (s, 3 H), 0.85−0.93 (m, 12 H), 0.99 (t, J = 7.4 Hz, 3 H), 1.36−1.94 (m, 8 H), 2.41 (*A*BX, J_{AB} = 16.2 Hz, J_{AX} = 5.9 Hz, 1 H), 2.70 (A*B*X, J_{AB} = 16.2 Hz, J_{BX} = 7.0 Hz, 1 H), 3.39−3.44 (m, 2 H), 3.66 (s, 3 H), 3.78−3.89 (m, 2 H), 4.24 (s, 2 H), 4.39 (ddd, J = 8.5, 5.0, 1.3 Hz, 1 H), 4.50 (m, 2 H), 4.60 (s, 2 H), 6.48 (dd, J = 16.2, 1.3 Hz, 1 H), 7.08 (dd, J = 16.2, 5.0 Hz, 1 H), 7.29−7.37 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.29 (CH_3), −4.28 (CH_3), 7.76 (CH_3), 8.59 (CH_3), 17.95 (C), 25.69 (CH_3), 27.79 (CH_2), 28.54 (CH_2), 29.97 (CH_2), 30.39 (CH_2), 40.08 (CH_2), 51.48 (CH_3), 66.44 (CH), 70.42 (CH), 71.68 (CH), 73.13 (CH_2), 73.61 (CH), 73.89 (CH_2), 74.18 (CH), 75.35 (CH), 76.48 (CH), 113.89 (C), 125.22 (CH), 127.80 (CH), 127.83 (CH), 128.32 (CH), 137.16 (C), 148.89 (CH), 171.30 (C), 196.85 (C); HRMS calcd for $C_{34}H_{52}O_9Si$ (M^+) 632.3380, found 632.3392.

Preparation of Caged Ketal 3 and Methyl Ketone 43. Enone **4** (9 mg, 0.01 mmol) was dissolved at room temperature in a mixture of CH_3CN (1.2 mL) and 52% aqueous HF (0.12 mL) in a small plastic bottle. After being stirred at 22 °C for 27 h, the solution was poured into water (5 mL) and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. FCC gave caged ketal **3** (3 mg; 0.007 mmol; 49%) and methyl ketone **43** (1−2 mg; 0.004−0.006 mmol; 30−40%). Data for **3**: R_f 0.37 (Et_2O); $[\alpha]^{24}_D$ −34.0° (*c* 0.685, $CHCl_3$); IR (thin film) 1739 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 1.23−1.47 (m, 2 H), 1.73 (m, 1 H), 1.98 (d, J = 13.4 Hz, 1 H), 2.04 (m, 1 H), 2.24 (dd, J = 13.4, 5.0 Hz, 1 H), 2.41 (*A*BX, J_{AB} = 16.2 Hz, J_{AX} = 4.2 Hz, 1 H), 2.48 (A*B*X, J_{AB} = 16.2 Hz, J_{BX} = 8.4 Hz, 1 H), 2.97 (dd, J = 9.6, 1.8 Hz, 1 H), 3.61−3.66 (m, 5 H), 3.81 (m, 1 H), 4.14 (dd, J = 6.5, 3.9 Hz, 1 H), 4.20 (dd, J = 6.5, 4.5 Hz, 1 H), 4.25 (ddd, J = 10.0, 9.6, 4.4 Hz, 1 H), 4.39 (dd, J = 3.9, 1.8 Hz, 1 H), 4.59 (*A*B, J_{AB} = 12.2 Hz, $\Delta\nu_{AB}$ = 27.6 Hz, 1 H), 4.65 (dd, J = 4.5, 4.4 Hz, 1 H), 4.69 (A*B*, J_{AB} = 12.2 Hz, $\Delta\nu_{AB}$ = 27.6 Hz, 1 H), 4.71 (dd, J = 5.0, 4.4 Hz, 1 H), 7.26−7.36 (m, 5 H); ^{13}C NMR (75 MHz, CD_3OD) δ 31.13 (CH_2), 31.43 (CH_2), 41.11 (CH_2), 44.89 (CH_2), 52.14 (CH_3), 69.60 (CH), 73.07 (CH_2), 74.61 (CH_2), 75.09 (CH), 76.01 (CH), 76.60 (CH), 77.98 (CH), 79.33 (CH), 82.06 (CH), 83.88 (CH), 110.88 (C), 128.60 (CH), 128.75 (CH), 129.12 (CH), 129.32 (CH), 129.45 (CH), 139.64, (C) 173.25 (C); HRMS calcd for $C_{23}H_{28}O_8$ (M^+) 432.1784, found 432.1783. Data for methyl ketone **43**: R_f 0.16 (Et_2O); IR (KBr pellet) 3409 (br), 1774, 1729, 1728 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30−1.60 (m, 2 H +

O*H*), 1.68 (m, 1 H), 2.02 (m, 1 H), 2.04 (s, 3 H), 2.39 (*A*BX, J_{AB} = 12.0 Hz, J_{AX} = 3.8 Hz, 1 H), 2.43 (A*B*X, J_{AB} = 12.0 Hz, J_{BX} = 6.3 Hz, 1 H), 2.69 (dd, *J* = 14.0, 6.0 Hz, 1 H), 2.83 (dd, *J* = 14.0, 3.8 Hz, 1 H), 2.97 (dd, *J* = 7.8, 1.8 Hz, 1 H), 3.54 (td, *J* = 7.8, 4.0 Hz, 1 H), 3.56 (s, 3 H), 3.75 (m, 1 H), 4.21 (dd, *J* = 3.6, 1.8 Hz, 1 H), 4.32 (dd, *J* = 6.6, 3.6 Hz, 1 H), 4.52 (dd, *J* = 6.0, 3.8 Hz, 1 H), 4.71 (d, *J* = 6.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 28.61 (CH_2), 30.06 (CH_2), 30.14 (CH_3), 40.33 (CH_2), 45.70 (CH_2), 51.71 (CH_3), 64.83 (CH), 69.50 (CH), 72.05 (CH), 73.71 (CH), 74.36 (CH), 75.85 (CH), 76.97 (CH), 171.15 (C), 204.54 (C), 212.58 (C); MS (FAB) *m*/*e* (relative intensity, assignment) 365 (100, M + Na^+).

Preparation of Enone 45. The aldehyde **5** (132 mg; 0.272 mmol) was dissolved in $PhCH_3$ (10 mL; 0.027 M), and a solution of ylide **44** (200 mg; 0.559 mmol; 2 equiv) in $PhCH_3$ (5 mL) was added to it. The resulting reaction mixture was heated to a vigorous reflux for 3 h. The solvent was removed in vacuo, and the crude residue was purified by FCC (3:1 to 1:1 hexanes−Et_2O) to provide 147 mg (0.260 mmol; 94%) of enone **45**. Data for **45**: R_f 0.38 (1:1 hexanes−Et_2O); IR (thin film) 1740, 1699, 1676, 1638 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) *δ* 0.06 (s, 3 H), 0.17 (s, 3 H), 0.80 (t, *J* = 8.2 Hz, 3 H), 1.02 (s, 9 H), 1.06 (t, *J* = 7.9 Hz, 3 H), 1.13−1.26 (m, 2 H), 1.44−1.54 (m, 2 H), 1.75−1.85 (m, 3 H), 2.01 (dd, *J* = 15.6, 5.7 Hz, 1 H), 2.30−2.50 (m, 6 H), 3.00 (dd, *J* = 10.2, 3.3 Hz, 1 H), 3.26 (d, *J* = 9.0 Hz, 1 H), 3.31 (s, 3 H), 3.74 (m, 1 H), 3.99 (td, *J* = 10.2, 5.7 Hz, 1 H), 4.19 (dd, *J* = 9.3, 3.3 Hz, 1 H), 4.34 (d, *J* = 9.3 Hz, 1 H), 4.54 (ddd, *J* = 9.0, 4.5, 1.8 Hz, 1 H), 4.90−5.03 (m, 2 H), 5.67−5.82 (m, 1 H), 6.47 (dd, *J* = 15.6, 1.8 Hz, 1 H), 7.09 (dd, *J* = 15.6, 4.5 Hz, 1 H); MS (FAB) *m*/*e* (relative intensity, assignment) 567 (100, M^+ + H), 537 (83, $M^+ - C_2H_5$), 509 (67, $M^+ - C_4H_9$).

Preparation of Furan 47. To a small plastic bottle was added enone **45** (13 mg; 0.023 mmol) and CH_3CN (2 mL; 0.01 M). A 52% aqueous solution of hydrofluoric acid (0.2 mL) was added slowly to the enone solution, and the resulting reaction mixture was stirred at room temperature for 24 h. It was then poured into water (2 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. FCC of the crude residue (1:2 hexanes−Et_2O) gave the furan **47** in 78% yield as a colorless oil (7 mg; 0.02 mmol). Data for **47**: R_f 0.38 (100% Et_2O); IR (thin film) 3463 (br), 1738, 1640, 1562 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) *δ* 0.89−1.02 (m, 1 H), 1.19−1.37 (m, 2 H), 1.84−1.90 (m, 2 H), 2.05 (dd, *J* = 15.3, 5.7 Hz, 1 H), 2.23 (ap dq, *J* = 8.7, 1.0 Hz, 2 H), 2.35 (br s, O*H*), 2.37 (dd, *J* = 15.3, 8.7 Hz, 1 H), 2.50 (ap t, *J* = 2.7 Hz, 1 H), 2.85 (dd, *J* = 9.3, 2.7, 1 H), 3.35 (s, 3 H), 3.54 (ddd, *J* = 10.8, 9.3, 5.7 Hz, 1 H), 3.67 (m, 1 H), 3.95 (dd, *J* = 9.3, 2.7 Hz, 1 H), 4.09 (t, *J* = 2.7 Hz, 1 H), 4.66 (d, *J* = 9.3 Hz, 1 H), 4.87−4.98 (m, 2 H), 5.62−5.74 (m, 1 H), 5.85 (d, *J* = 3.3 Hz, 1 H), 6.31 (d, *J* = 3.3 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) *δ* 27.58 (CH_2), 28.78 (CH_2); 30.44 (CH_2), 31.83 (CH_2), 40.56 (CH_2), 51.76 (CH_3), 69.04 (CH), 69.49 (CH), 70.06 (CH), 72.02 (CH), 74.45 (CH), 78.67 (CH), 105.86 (CH), 110.44 (CH), 115.22 (CH_2), 137.52 (CH), 149.73 (C), 156.33 (C), 171.38 (C); MS (FAB) *m*/*e* (relative intensity, assignment) 367 (20, M^+ + H).

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Supporting Information Available: Experimental procedures for preparation of *rac*-**20**, *rac*-**21**, **24**, (*S*)-**20**, 6(*S*)-**21**, **42** and **44**; ^{1}H and/or ^{13}C NMR spectra for compounds **3**−**6**, **8**, **11**, **13**, **14**, *rac*-**20**, *rac*-**21**, **22a**, **22b**, **23**, **25**, **27**−**41**, **43**, **45**, **47**, and unnumbered intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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