Synthetic Studies on Thyrsiferol. Elaboration of the Bromotetrahydropyran Ring

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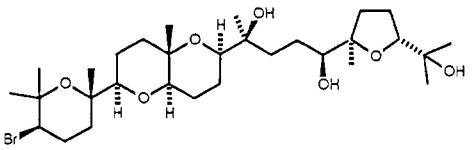
A synthesis of the tricyclic bromo ether **2**, a model for the left halves of thyrsiferol (**1**) and venustatriol, has been developed. This approach employs a series of three electrophilic cyclizations to deliver the target compound with good stereochemical control. The first of these, the mercuricyclization that stereoselectively furnishes the rightmost ring of **2**, was found to be a thermodynamically controlled process. Construction of the chair–twist-boat pyranopyran moiety characteristic of these natural products also utilizes a mercuricyclization protocol. For the elaboration of the bromotetrahydropyran ring, a novel tactic was introduced that relies on the use of a trifluoroacetyl hemithioacetal (**15**), derived via a Pummerer rearrangement, as a surrogate for a strongly hydrated and poorly reactive aldehyde. For the final bromoetherification leading to **2**, NBS was found to be the reagent of choice. A route to enantiomerically pure alcohol **24**, the precursor necessary for construction of **1** itself, is also outlined.

Thyrsiferol (**1**),[1] along with venustatriol,[2] dehydrothyrsiferol,[3] and thyrsiferol 23-acetate,[4] comprise a structurally novel family of polyethers isolated from red algae of the genus *Laurencia*. Our interest in these systems derives both from their antiviral activity[2] and pronounced cytotoxicity[4] (ED_{50} against P388 lymphocytic leukemia 0.3 ng/mL for thyrsiferol 23-acetate) as well as from the synthetic challenges associated with their construction. In a previous communication[5] we described a route to the central pyranopyran ring system of these molecules that involved a sequence of iterative mercuricyclizations and oxidative demercurations. In this report we outline that route in greater detail in the context of the synthesis of thyrsiferol left-half model **2**. Progress toward the synthesis, from D-glucose, of an optically active left-half fragment with functionality suitable for coupling with the right half of **1** is also described. Shirahama, in his recent syntheses



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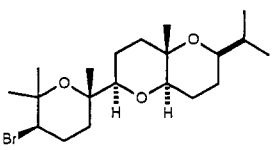


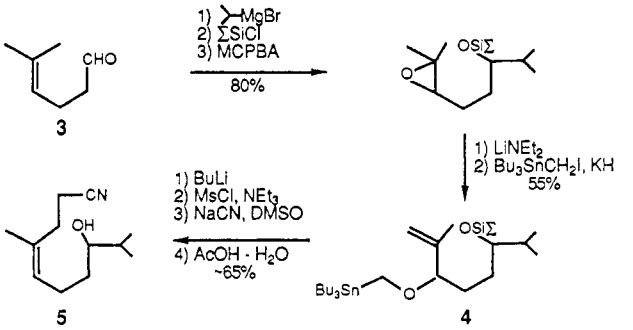
2

of thyrsiferol and venustatriol, achieved the coupling of the left and right halves of these targets by methods that can also be applied in our case.[6]

Results and Discussion

A. Chair–Twist-Boat Pyranopyran Nucleus. A problem that had to be solved if we were to succeed in synthesizing **1** was the development of a stereoselective

Scheme I



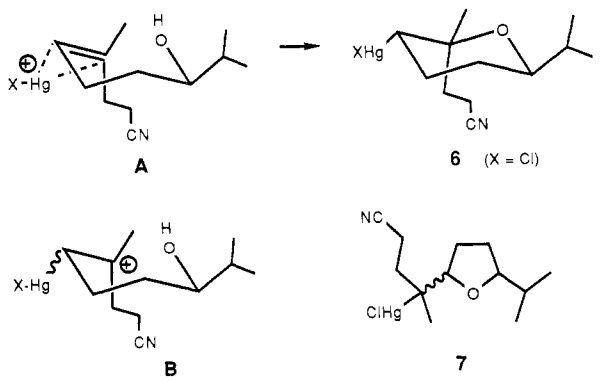
approach to the central pyranopyran unit that connects the bromotetrahydropyran moiety to the C15–C23 side chain. This fused ring system adopts a chair–twist-boat conformation in order to avoid an unfavorable diaxial interaction between the side chain and the angular methyl group. While a number of elegant approaches to fused pyranopyran systems have been developed, mainly in connection with synthetic work directed at okadaic acid[7] and the brevetoxins,[8] these methods do not, by and large, seem adaptable for preparation of **1** and **2** owing to the unusual conformation of our target ring system. The approach we developed begins with aldehyde **3**,[9] which was converted into the *Z*-homoallylic nitrile **5** by the series of reactions shown in Scheme I. The only notable step in this sequence is the highly stereoselective [2,3]-sigmatropic rearrangement, which converts **4** into **5**.[10]

The double-bond stereochemistry of nitrile **5** was crucial to the successful implementation of our strategy since it was our intention to construct the first tetrahydropyran ring of our target by means of a mercuricyclization that, we hoped, would proceed through the chair-like transition state (A). We were confident that the mercuricyclization would proceed with the desired regioselectivity, giving a tetrahydropyran system and not a tetrahydrofuran, since this tendency has been quite well documented for a variety of trisubstituted olefinic alcohols analogous to **5**.[11] We

(1) Blount, J. W.; Hartshorn, M. P.; McLennan, T. J.; Munro, M. H. G.; Robinson, W. T.; and Yorke, S. C. *Tetrahedron Lett.* **1978**, 69.
(2) Sakemi, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4287.
(3) Gonzalez, A. G.; Arteaga, J. M.; Fernandez, J. J.; Martin, J. D.; Norte, M.; Ruano, J. Z. *Tetrahedron* **1984**, *40*, 2751.
(4) Suzuki, T.; Suzuki, M.; Furusaki, A.; Matsumoto, T.; Kato, A.; Imanaka, Y.; Kurosawa, E. *Tetrahedron Lett.* **1985**, *26*, 1329.
(5) Broka, C. A.; Hu, L.; Lee, W. J.; Shen, T. *Tetrahedron Lett.* **1987**, *28*, 4993.
(6) For an alternative approach to these systems, see: (a) Hashimoto, M.; Kan, T.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1987**, *28*, 5665. (b) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1988**, *29*, 1143.
(7) Isobe, M.; Ichikawa, Y.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 962.
(8) (a) Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, T. *Tetrahedron Lett.* **1985**, *26*, 2069. (b) Nicolaou, K. C.; Duggan, M. E.; Hwang, C. K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359. (c) Duthaler, R. O.; Ganter, C. *Helv. Chim. Acta* **1976**, *59*, 415. (d) Isobe, M.; Ichikawa, Y.; Masaki, H.; Goto, T. *Tetrahedron Lett.* **1984**, *25*, 3607. (e) Ichikawa, Y.; Isobe, M.; Goto, T. *Ibid.* **1984**, *25*, 5049. (f) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693. (g) Kozikowski, Z. P.; Ghosh, A. K. *J. Org. Chem.* **1985**, *50*, 3017.
(9) Marbet, R.; Saucy, G. *Helv. Chim. Acta* **1967**, *50*, 2095.
(10) (a) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927. (b) Still, W. C.; McDonald, J. H., III; Collum, D. B.; Mitra, A. *Tetrahedron Lett.* **1979**, 593.

0022-3263/88/1953-5876$01.50/0

Scheme II

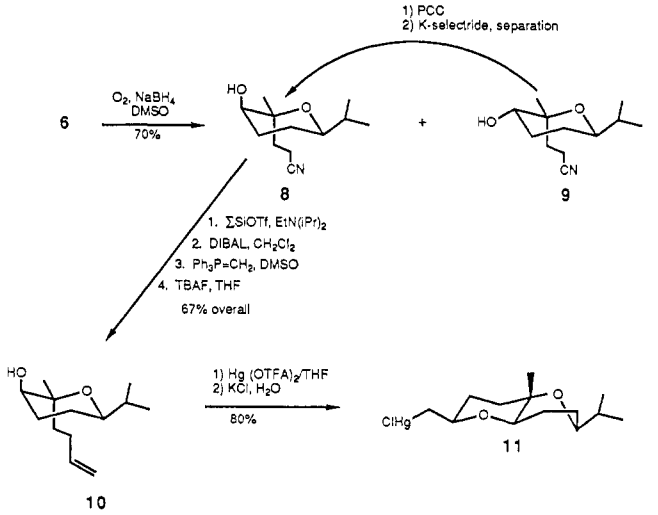


were not so certain that we could achieve an acceptable level of stereoselectivity in this reaction. To the best of our knowledge, the question of stereoselectivity in the mercuricyclization of alkenols such as **5** has not been systematically studied. Moreover, the mechanism of oxymercuration and mercuricyclization reactions has been the subject of considerable speculation,[12] with some workers rejecting the intermediacy of reversibly formed mercurinium ions (A) in favor of carbocationic intermediates (B). In any event, we were successful in generating mercurial **6** from **5** as a single crystalline stereoisomer in excellent yield using $Hg(OTFA)_2$ in DMF (Scheme II).

This success was achieved only after many failures. Using mercuric acetate in 1:1 THF/H_2O (the standard conditions employed by Mihailović[11a] and his predecessors) we obtained a ~1:1 mixture of **6** and its tetrahydrofuran isomers **7**. This was a surprising and disheartening result that seemed to contradict both literature precedent and our own early observations with systems lacking the nitrile function. We then investigated the use of $Hg(OTFA)_2$ in THF, CH_2Cl_2, CH_3NO_2, and DMF. Under these conditions **5** was transformed only into **6**. We speculated that, in the presence of a strong acid (i.e. trifluoroacetic acid) generated as the $Hg(OTFA)_2$-promoted cyclization proceeded, the oxymercuration might be rendered a reversible process. The $Hg(OAc)_2$-promoted reaction, in which only a weak acid (AcOH) was produced as a byproduct, might instead proceed in an irreversible manner. Thus the result obtained with the latter reagent might reflect a kinetically controlled process whereas **6** was the product of a thermodynamicaly controlled reaction. Indeed, this was found to be the case. When cyclizations of **5** were performed by using $Hg(OTFA)_2$ in the presence of excess HgO, which consumed the trifluoroacetic acid produced in the reaction, the same 1:1 mixture of **6** and **7** obtained with $Hg(OAc)_2$ was produced. Furthermore, when cyclizations were carried out in the presence of slightly less than the 0.5 equiv of HgO necessary to remove all the trifluoroacetic acid, one could watch as the ratio of **6**:**7** changed gradually (~1:1 at 3 h and finally >9:1 at 24 h).

However, the route to **6** was still impractical at this stage. When the thermodynamically controlled $Hg(OTFA)_2$ cyclizations of **5** were worked up in the usual manner by dilution with saturated KCl or NaCl followed by extraction of the chloromercurial with CH_2Cl_2 substantial amounts of **5** were always recovered along with **6**. The problem was finally traced to the workup. It seems that the (trifluoroacetoxy)mercurial undergoes rapid reversion to **5** in the acidic aqueous environment provided by the saturated NaCl workup used to generate **6**, thus accounting for the apparent failure of the reactions to go to completion. This surprising difficulty was overcome by quenching the reaction with a mixture of aqueous NaCl and $NaHCO_3$, thereby neutralizing the acid present. Employing this modified workup and using DMF as the solvent, **6** could be obtained in 93% yield. The stereoselectivity of the reaction was excellent. This outcome is consistent with the intermediacy of a reversibly formed mercurinium ion cyclizing through the most stable chair-like transition state

Scheme III



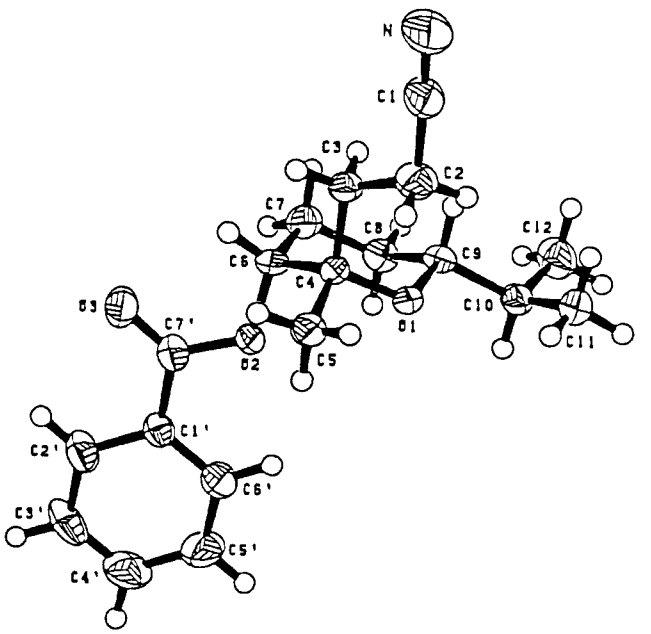
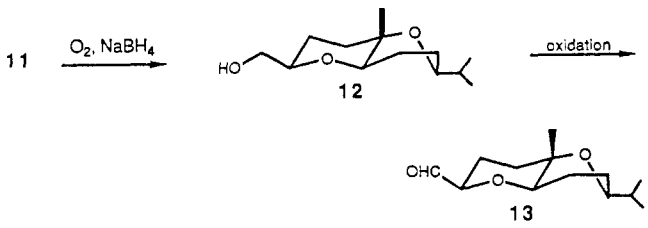


Figure 1. ORTEP drawing of 8-benzoate.

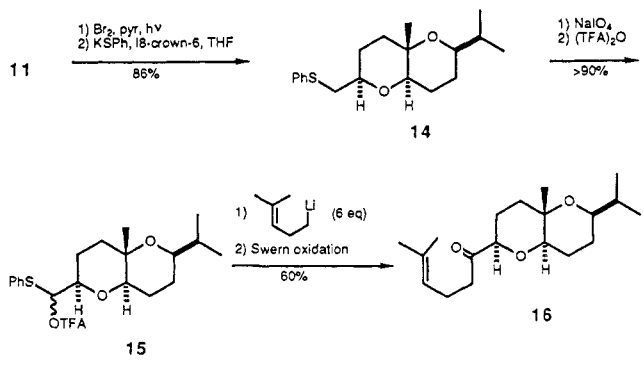
(11) (a) Mihailović, M. L.; Marinković, D.; Orbović, N.; Gojković, S.; Konstantinović, S. *Bull. Chim. Soc. Beograd* **1980**, *45*, 497. (b) Brook, A. G.; Rodgman, A.; Wright, G. F. *J. Org. Chem.* **1952**, *17*, 988. (c) Spěziale, V. Ph.D. Thesis, Paul Sabatier University, Toulouse, France, 1978. (d) Brown, H. C.; Geoghegan, P. J., Jr.; Kurek, J. T.; Lynch, G. J. *Organomet. Chem. Syn.* **1970/1971**, *1*, 7. (e) Hosokawa, T.; Yamashita, S.; Murahashi, S.-I.; Sonoda, A. *Bull. Chem. Soc. Jpn* **1976**, *43*, 3662.

(12) (a) Brown, H. C.; Liu, K.-T. *J. Am. Chem. Soc.* **1970**, *92*, 3502. Brown, H. C.; Kurk, J. T.; Rei, M.-H.; Thompson, K. L. *J. Org. Chem.* **1984**, *49*, 2551 and references cited therein (see also Brown, H. C.; Rei, M.-H.; Liu, K.-T. *J. Am. Chem. Soc.* **1970**, *92*, 1760). For a different view, see: Pasto, D. J.; Gomez, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 6902. (b) Traylor, T. G. *J. Am. Chem. Soc.* **1963**, *85*, 244. Brown, H. C.; Hammar, W. J. *J. Am. Chem. Soc.* **1967**, *89*, 1525. Tidwell, T. T.; Traylor, T. G. *J. Org. Chem.* **1968**, *33*, 2614. Crow, W. D.; Paddon-Row, M. N. *J. Am. Chem. Soc.* **1972**, *94*, 4748. (c) Bentham, S.; Chamberlain, P.; Whitham, H. G. *J. Chem. Soc. D* **1970**, 1528. We were concerned that, if such an intermediate (B) were to be involved in our cyclization, rotation around the indicated C–C bond might occur at a rate competitive with that of cyclization and that the stereochemical information contained in our double bond would be lost.

Scheme IV



Scheme V



accessible to it. The results do not, of course, exclude the possibility of a reversibly formed carbocationic intermediate that cyclizes without losing stereochemical integrity.

With **6** now in hand, it was subjected to Whitesides' oxidative demercuration protocol[13] to afford **8** along with a smaller amount of **9** (Scheme III). The unwanted epimer **9** can be converted back into a mixture of **8** and **9** (ratio 1.2:1) by PCC/NaOAc oxidation and reduction with K-Selectride (Aldrich). The two alcohols are easily separated on silica gel. The structure of **8** was verified by a single-crystal X-ray analysis of its benzoate (Figure 1). A straightforward series of operations served to convert **8** into **10**.

Most importantly, it was found that $Hg(OTFA)_2$ brought about the cyclization of **10** in excellent yield. In order for an electrophile to successfully provide access from **10** to a system such as **11**, it must fulfill several criteria. It must interact strongly enough with the target olefin to generate a concentration of reactive intermediate (bromonium ion, mercurinium ion, etc.) sufficient to capitalize on the low concentration of the twist-boat conformer of **10** present at equilibrium.[14] At the same time it must not participate in destructive side reactions that compete with the desired process. In the present case, $Hg(OTFA)_2$ met these criteria admirably. A number of other reagents, including NBS and PhSCl,[15] were examined with disappointing results.

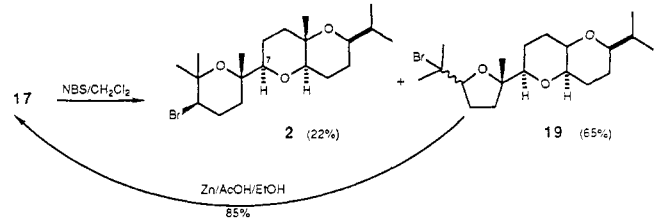
B. Elaboration of the Bromotetrahydropyran Moiety. We had initially envisioned the conversion of **11** into **2** proceeding through aldehyde **13** (Scheme IV).

This route quickly encountered difficulties. The Whitesides' oxidation leading to **12** could never be made to proceed in a satisfactory manner. The desired alcohol could be obtained, but not in yields exceeding 44%. Moreover, aldehyde **13** exhibits a strong tendency to suffer hydration and this fact complicated both its isolation and its reaction with 1-lithio-4-methyl-3-pentene.[16] Accordingly, an alternative approach (Scheme V) was developed that bypassed this aldehyde completely.

Table I

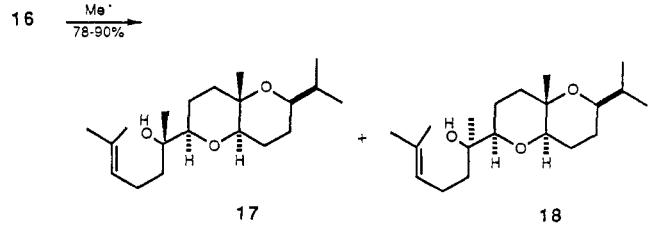
reagent/conditions	17/18
MeMgBr/THF, −78 °C	85:15
MeMgBr/Et_2O, −78 °C	85:15
MeMgBr/toluene, −78 °C	90:10
MeLi/THF, −78 °C	30:70
Me_3Al/toluene, −78 °C	80:20

Scheme VI



Treatment of mercurial **11** with Br_2 under the conditions of Hoye[17] gave the bromide, which underwent smooth displacement with thiophenoxide leading to **14**. Periodate oxidation of **14** followed by Pummerer rearrangement[18] gave **15** in excellent yield as a ~1:2 mixture of diastereomers. This trifluoroacetylated hemithioacetal functions perfectly as a masked form of the aldehyde **13**. Upon reaction of **15** with an excess of the organolithium reagent, loss of the ester unit occurs, giving the alkoxide of the corresponding hemithioacetal which further loses thiophenoxide to liberate aldehyde **13** in situ. Smooth addition of the organolithium to **13** can then take place to yield the secondary alcohols (as a ~1:1 mixture of diastereomers), which are directly oxidized to afford **16** (60%). This employment of Pummerer rearrangement derived hemithioacetal esters as surrogates for otherwise intractable aldehydes or ketones would appear to be of value in a range of circumstances under which isolation of the aldehydes or ketones themselves is contraindicated (as may be the case with β,γ-unsaturated systems prone to double-bond migration and with readily epimerizable substrates).

We next investigated the addition of a variety of organometallics to **16** in order to find the most stereoselective route to **17**. With the exception of MeLi in THF,[19] all reagents gave primarily **17** as the product of what would appear to be chelation-controlled reactions.[20] Our results are summarized in Table I.



After chromatographic purification of **17**, it only remained to perform one more electrophilic cyclization (Scheme VI) and the synthesis of **2** would be complete.

(13) Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 870 (see also Pougny, J.-R.; Nassr, M. A. M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375 and Spéziale, V.; Lattes, A. *J. Heterocycl. Chem.* **1979**, *16*, 465).

(14) The energy difference between chair and boat tetrahydropyran conformers has been estimated to be 3.9 kcal/mol, significantly smaller than the difference for the chair and boat conformers of cyclohexane. Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. In *Conformational Analysis*; Interscience: New York: 1965; p 244.

(15) Tuladhar, S. M.; Fallis, A. G. *Tetrahedron Lett.* **1987**, *28*, 523.

(16) Hudlicky, T.; Govindan, S. V.; Frazier, J. O. *J. Org. Chem.* **1985**, *50*, 4166.

(17) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1979**, *44*, 3461.

(18) For Pummerer rearrangements of other β-alkoxy sulfoxides, see: Iriuchijima, S.; Maniwa, K.; Tsuchihashi, G.-I. *J. Am. Chem. Soc.* **1974**, *96*, 4280.

(19) Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031.

(20) For a good recent review of this subject, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

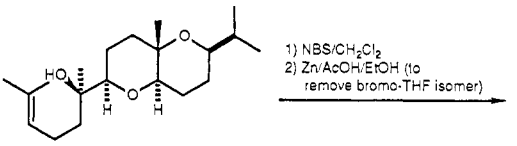
There was some reason to hope that the regioselectivity of the bromonium ion promoted cyclization of **17** could be controlled since both Kato[21] and Bartlett[22] have reported that 2,4,4,6-tetrabromocyclohexadienone (TBCO) preferentially converts alkenols such as **17** into bromotetrahydropyrans rather than their tetrahydrofuran isomers. Unfortunately, this generalization did not hold true in our case and both this reagent and NBS converted **17** into a ca. 3:1 mixture of bromotetrahydrofuran and bromotetrahydropyran products. Use of Br_2 as the electrophile led to inferior yields of both **2** and **19** whereas attempts to first cyclize **17** with $Hg(OAc)_2$ or $Hg(OTFA)_2$ and then exchange mercury for bromine produced only **19**. It is of some significance that the *p*-methoxybenzyl ether of **17** (prepared from **17** by using MPM-Cl and KH) reacted with NBS in CH_2Cl_2 to give essentially the same mixture of **2** and **19** as obtained from **17** itself. While the yield of **2** is not improved in this case, it does indicate that, in the actual synthesis of **1** (vide infra), the C-6 hydroxy group may be protected as its MPM ether while attachment of the right half to the pyranopyran nucleus is accomplished after which the final bromocyclization could be effected without the need for deprotonation of this hydroxy group.

Although the regioselectivity of this cyclization is not good, the bromotetrahydrofuran isomer can be efficiently reduced back to **17** and then recycled. It seems likely that this unfavorable outcome is a result of the fact that the cyclization leading to **2** unavoidably creates a 1,3-diaxial interaction between two methyl groups, a situation that does not obtain in the cases studied by Kato and Bartlett. In the chair-like transition state for this electrophilic cyclization, the large pyranopyran moiety adopts the equatorial orientation and thus only the desired bromine stereoisomer is produced.

It remained to verify that the stereochemistry assigned to **2** was, in fact, correct. The relative configurations of three of its stereocenters had already been determined by X-ray crystallography. However, we were unsuccessful in growing suitable crystals of **2** for X-ray analysis. The equatorial orientation of the bromine substituent could be inferred from the coupling constants for the adjacent proton (J = 12.3, 4.0 Hz), as could the equatorial attachment of the bromotetrahydropyran ring to the pyranopyran nucleus (J = 11.1, 2.5 Hz for the C-7 proton). The only stereocenter remaining in doubt was that resulting from the MeMgBr addition. While there is literature precedent to suggest that chelation control should operate in this addition,[23] we obviously could not base our assignment solely on this fact. Fortunately, the ^1H and ^{13}C NMR spectra of thyrsiferol (**1**) and most of its congeners have been published and, although the resonances were not assigned, we could make use of this data in interpreting the spectra of **2**.

It was also necessary to convert the carbinol **18**, the major product obtained by reaction of **16** with MeLi, into its corresponding bromotetrahydropyran to determine how the spectra of this isomer compared with those of **2** and the natural systems.

Interestingly, the bromocyclization of **18** was found to proceed to a lesser extent than that of **17** under identical conditions. Along with **20** a small amount of what appeared to be a stereoisomer of **20**, epimeric with it at the



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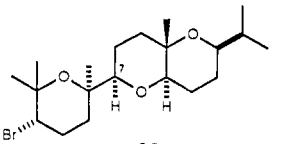

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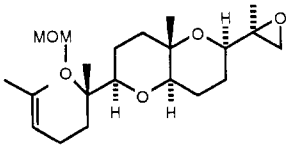
bromine-bearing carbon, could be isolated. The NMR data suggest that this compound exists with the bromotetrahydropyran ring in a boat conformation. No analogous product was formed from **17**. It also turned out that **20** was not chromatographically separable from the bromotetrahydrofuran regioisomers, which, again, constituted the majority of the cyclized material. This problem was overcome when we observed that reductive elimination of bromine from the latter isomers was far more rapid than it was in the case of **20**. Thus the mixture of **20** and the bromotetrahydrofurans could be treated with zinc in ethanolic AcOH under carefully controlled conditions to deliver unchanged **20** (30% based on recovered **18**) along with **18**, which could be removed chromatographically and recycled.

The ^1H NMR spectra of **2** and **20** could be assigned without difficulty and this provided information useful in assigning the corresponding resonances in **1** and its congeners. The ^{13}C NMR spectra of **2** and **20** were also assigned, with the help of DEPT experiments, and this allowed us to make partial assignments in the case of **1** and several of its congeners. The relevant spectral data are presented in Figure 2 along with data from two simpler systems, **21** and **22**.[24]

The most diagnostically significant resonances turn out to be those for C-7 and H-7. In the natural systems the former invariably appears between 86.5 and 86.7 ppm. In the case of **2** this signal appears at 86.5 ppm and a similar value (86.1 ppm) is obtained for **21**. The MeLi-derived systems **20** and **22** display resonances at 84.7 and 84.5 ppm, respectively, ~2 ppm upfield from the corresponding signals in the natural materials. The H-7 proton appears as a doublet of doublets at δ 3.04 in venustatriol. The chemical shift of this proton in **2** is δ 3.05. In **20** it appears at δ 3.17. This deshielding is also observed in going from **21** to **22**. Taken together, these observations provide solid evidence in favor of our stereochemical assignments. The analogues **2**, **20**, **21**, and **22** are presently being tested for cytotoxicity and antiviral activity.

C. Progress toward the Natural Systems. Epoxide **23** has already been converted to **1** by Shirahama et al.[6b]



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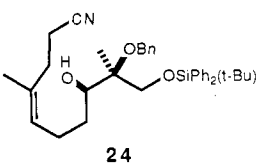

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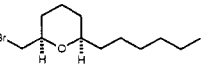
In order to utilize the previously described chemistry to provide access to these systems, an efficient route to the

(21) Kato, T.; Ichinose, I.; Hosogai, T.; Kitahara, Y. *Chem. Lett.* **1976**, 1187.

(22) Ting, P. C.; Bartlett, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 2668.

(23) For example: (a) Wolfrom, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800. (b) Nakuta, T.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2745. (c) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565. (d) Bhupathy, M.; Cohen, T. *Tetrahedron Lett.* **1985**, *26*, 2619.

(24) Prepared from **i** by the same routes utilized for **2** and **20**.



i

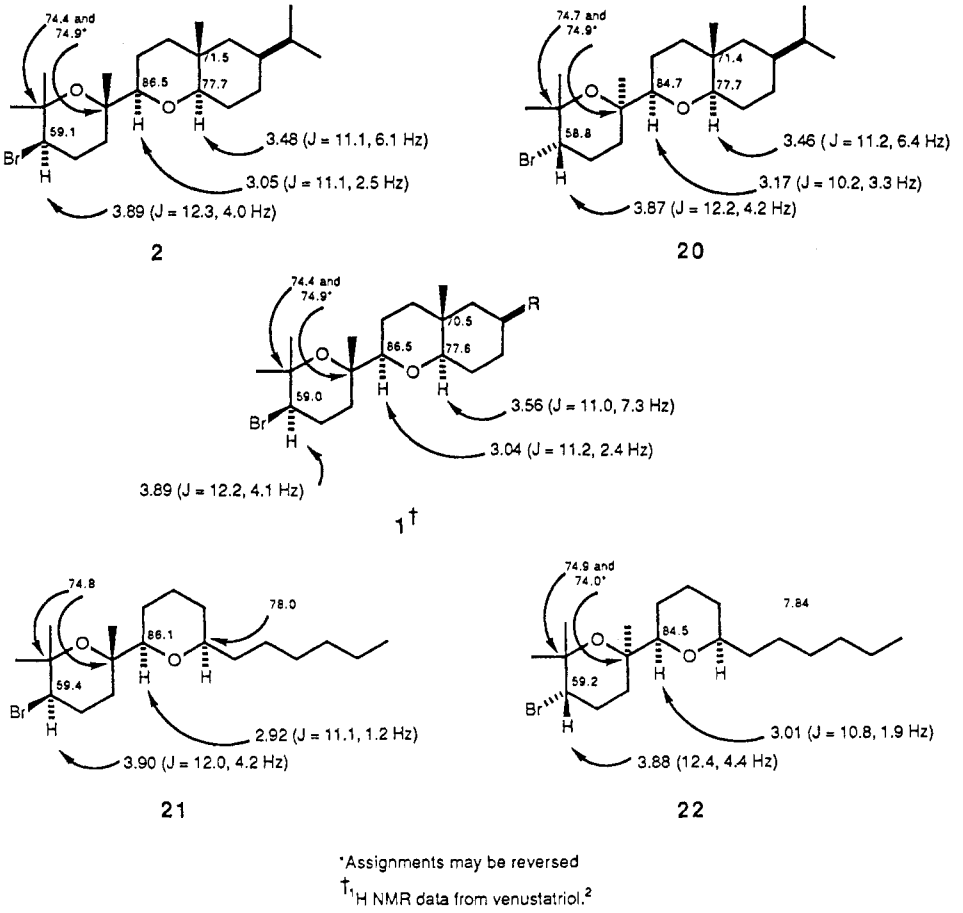
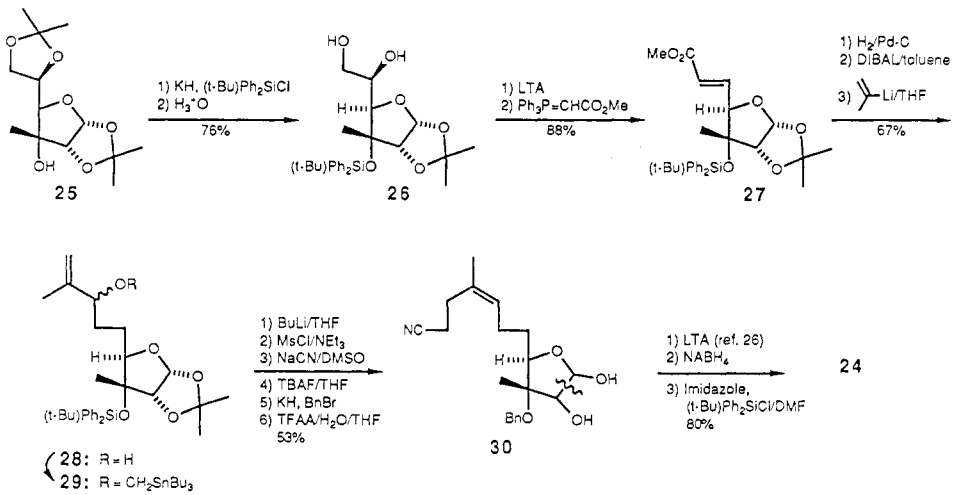


Figure 2.

Scheme VII



(enantiomerically pure) *Z*-homoallylic nitrile **24** was required. We have found that this compound can be prepared from D-gluose (Scheme VII).

Carbinol **25** is a known compound prepared[25] by addition of MeMgBr to the corresponding ketone. The latter substance is, of course, available in two steps from glucose. Protection of the free hydroxy function followed by mild acid treatment affords **26**. Cleavage of the diol unit with lead tetraacetate (LTA) and reaction of the resulting aldehyde with $Ph_3P{=}CHCO_2Me$ gives **27**. Conversion of **27** into **29** follows standard practice. As before, the [2,3]-sigmatropic rearrangement[10] proceeds with excellent stereoselectivity, yielding the expected homoallylic alcohol, which is converted into **30** with use of the same operations employed previously in the case of **5**. Acetonide hydrolysis (TFAA–H_2O–THF) and diol cleavage, again using LTA, gives the (fairly stable) aldehyde formate.[26] Borohydride reduction and selective silylation of the primary alcohol produces **24**.

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded on a General Electric QE-300 (300 MHz), a Nicolet NT-360 (360 MHz), or a GN-500 (500 MHz) NMR spectrometer in $CDCl_3$ or

(25) Brimacombe, J. S.; Rollins, A. J.; Thompson, S. W. *Carbohydr. Res.* **1973**, *31*, 108.

(26) For an analogous cleavage of a glucose-derived 1,2-diol (using periodate), see: Kinoshita, M.; Mariyama, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2081.

benzene-d_6 with tetramethylsilane or $CHCl_3$ as internal standard. Chemical shifts relative to TMS are reported as follows: chemical shift (δ) in ppm, multiplicity, number of protons, and coupling constants, when measured. Infrared spectra were obtained on an IBM Instruments IR/32 FT-IR spectrophotometer. High resolution mass spectra (HRMS) were recorded on a Finnigan-Matt 731 spectrometer using electron impact (EI) ionization and on a VG-70 SE spectrometer using chemical ionization (CI) or electron impact ionization. THF and ether were distilled from sodium and benzophenone. CH_2Cl_2 was distilled from calcium hydride, and benzene and toluene were distilled from sodium. Other reagents and solvents were purified as needed. Brine refers to a saturated solution of aqueous sodium chloride. $NaHCO_3$ (aq) refers to a saturated aqueous solution. Column chromatography was performed on Brinkman 0.05 to 0.2 mm silica gel. Preparative TLC was performed on glass plates measuring 20 cm × 20 cm with a 1.2-mm layer of Merck Kieselgel 60 PF. Merck 60 F_{254} glass-backed (0.25 mm) silica gel plates were used for analytical TLC. TLC plates were visualized with fluorescence quenching and developed with I_2 or anisaldehyde reagent. Anisaldehyde reagent was prepared from 90% aqueous EtOH (330 mL), AcOH (3.7 mL), H_2SO_4 (12.3 mL), and *p*-anisaldehyde (9.1 mL). All air- and moisture-sensitive reactions were performed in oven-dried (135 °C) glassware under argon.

3-(Dimethyl-*tert*-butylsiloxy)-2,7-dimethyl-6-octene. 2,7-Dimethyl-6-octen-3-ol[22] was prepared in Et_2O from **3**[9] and isopropylmagnesium bromide under standard conditions. A solution of this alcohol (6.15 g, 39 mmol) in 20 mL of THF was added slowly to KH (2.35 g, 59 mmol) in 40 mL of THF at 0 °C and the mixture was stirred for 15 min at 0 °C and 15 min at room temperature. The solution was again cooled to 0 °C and a solution of dimethyl-*tert*-butylsilyl chloride (9.2 g, 59 mmol) in 40 mL of THF was added. The mixture was stirred 30 min at 0 °C and then 1 h at room temperature. After careful destruction of the remaining KH with water, the solution was partitioned between Et_2O and water. The Et_2O layer was dried ($MgSO_4$) and the solvent was removed to leave an oil, which was distilled under reduced pressure to afford the title compound (9.8 g, 93%) as a clear oil: bp 99–105 °C/7 mm; IR (neat) 2938, 1471, 1076 cm^{-1}; ^1H NMR ($CDCl_3$) 5.11 (br t, 1 H), 3.42 (q, J = 4 Hz, 1 H), 2.10–1.85 (m, 2 H), 1.69 (m, 1 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.39 (m, 2 H), 0.89 (s, 9 H), 0.85 (d, J = 6 Hz, 3 H), 0.83 (d, J = 6 Hz, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H). Anal. Calcd for $C_{16}H_{34}OSi$: C, 71.03; H, 12.67. Found: C, 70.75; H, 12.83.

(*Z*)-7-(Dimethyl-*tert*-butylsiloxy)-3,8-dimethyl-3-nonen-1-ol. A solution of the above-prepared olefin (5.70 g, 21 mmol) in 120 mL of CH_2Cl_2 was treated with 3.7 g of Na_2CO_3 and MCPBA (6.07 g, 35.3 mmol) and stirred vigorously for 2 h. At the end of this time dimethyl sulfide (2 mL) was introduced and, after several minutes, the solvent was removed in vacuo. The residue was taken up in Et_2O and washed several times with water, aqueous $NaHCO_3$, and then with brine. The solution was dried ($MgSO_4$) and concentrated to give the epoxide (6.00 g, 95%), which was directly carried on to the next step.

A solution of $HNEt_2$ (14.2 mL, 137 mmol) in 130 mL of Et_2O was cooled to 0 °C and treated with 1.5 M *n*-BuLi in hexane (90 mL, 135 mmol). After stirring the mixture for 30 min, the epoxide (9.8 g, 34 mmol) was added in 20 mL of Et_2O. The solution was refluxed for 4 h and then partitioned between Et_2O and water. After drying the Et_2O extracts ($MgSO_4$), the solvent was removed and the residue purified by flash chromatography on silica gel (0–20% EtOAc/hexane) to obtain the allylic alcohol (9.2 g, 94%): ^1H NMR ($CDCl_3$) 4.85 (br s, 1 H), 4.72 (br s, 1 H), 3.90 (m, 1 H), 3.35 (m, 1 H), 1.66 (s, 3 H), 1.6–1.0 (m, 5 H), 0.90 (s, 9 H), 0.85 (m, 6 H), 0.02 (s, 6 H).

The allylic alcohol (1.8 g, 6.3 mmol) in 20 mL of THF was added to KH (350 mg, 8.8 mmol) in 30 mL of THF with ice-bath cooling, and the mixture was allowed to stir at room temperature for 3 h. The solution was then cooled to 0 °C and Bu_3SnCH_2I (5.0 g, 11.6 mmol) was introduced. After stirring for 4 h at room temperature, the remaining KH was decomposed with water and the product isolated by Et_2O extraction. Flash chromatography on silica gel (0–10% EtOAc/hexane) gave the stannylmethyl ether **4** (2.1 g, 57%).

A solution of **4** (4.90 g, 8.3 mmol) in 200 mL of THF was treated, at −78 °C, with 1.5 M *n*-BuLi (20 mL, 30 mmol). After 1.5 h at −78 °C, the flask was placed in an ice bath and the reaction was allowed to proceed for a further 30 min. The reaction mixture was partitioned between Et_2O and water and the product purified on silica gel (0–20% EtOAc/hexane) to obtain the title compound (1.94 g, 77%): IR (neat) 3314, 2957, 1471, 1076 cm^{-1}; ^1H NMR ($CDCl_3$) 5.28 (t, J = 6 Hz, 1 H), 3.62 (t, J = 6 Hz, 2 H), 3.41 (q, J = 5 Hz, 1 H), 2.29 (t, J = 6 Hz, 2 H), 2.02 (m, 2 H), 1.69 (s, 3 H), 1.38 (m, 2 H), 0.87 (s, 9 H), 0.83 (d, J = 6 Hz, 3 H), 0.81 (d, J = 6 Hz, 3 H) (this region observes a multiplet (1 H)), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR ($CDCl_3$) 130.9, 128.4, 76.5, 60.5, 35.0, 33.4, 32.5, 25.8, 24.0, 23.4, 18.1, 18.0, 17.6, −4.4, −4.7; HRMS calcd for $C_{17}H_{36}O_2Si$ 300.24841, found 300.24689.

Homoallylic Nitrile 5. A solution of the previously prepared alcohol (1.80 g, 6.0 mmol) and NEt_3 (1.7 mL, 12 mmol) in 15 mL of CH_2Cl_2 at 0 °C was treated with MsCl (0.65 mL, 8.4 mmol) and stirred for 30 min. After dilution with aqueous $NaHCO_3$ and extraction of the product with CH_2Cl_2, the organic phase afforded the desired mesylate (2.14 g, 94%).

The mesylate was next dissolved in 20 mL of dry DMSO and treated with NaCN (420 mg, 8.6 mmol). The mixture was stirred at 80 °C for 90 min. After Et_2O/water workup, the silylated nitrile was purified by flash chromatography on silica gel (0–10% EtOAc/hexane). The yield was 1.45 g (83%).

Removal of the silyl group was accomplished under acidic conditions. A solution of the nitrile (2.89 g, 9.3 mmol) in 30 mL of 80% AcOH and 10 mL of THF was stirred for 2 days at 20 °C and then at 60 °C for 15 h. The reaction mixture was poured onto ice and NH_4OH and then extracted with CH_2Cl_2. Purification of the product on silica gel (0–30% EtOAc/hexane) gave **5** (1.67 g, 92%): IR (neat) 3451, 2959, 2932, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) 5.27 (t, J = 6 Hz, 1 H), 3.29 (m, 1 H), 2.37 (t, J = 2 Hz, 4 H), 2.10 (m, 2 H), 1.68 (s, 3 H), 1.60–1.34 (m, 3 H), 0.86 (d, J = 6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 130.7, 128.3, 119.3, 75.2, 33.6, 33.3, 27.0, 24.0, 22.3, 18.4, 17.0, 15.4; HRMS calcd for $C_{12}H_{21}NO$ 195.16228, found 195.16188.

Mercurial 6. The alcohol **5** (1.17 g, 6.0 mmol) was dissolved in 20 mL of DMF and treated with a solution of $Hg(OTFA)_2$ (3.25 g, 7.6 mmol) in 25 mL of DMF. The mixture was stirred in the dark overnight and then poured into 200 mL of saturated KCl and 100 mL of saturated $NaHCO_3$. After extraction of the product with Et_2O it was crystallized from 25 mL of hexane to give **6** (2.38 g, 93%): mp 151–153 °C; IR ($CHCl_3$) 3022, 2249, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) 3.02 (dd, J = 9, 6 Hz, 1 H), 2.78 (m, 1 H), 2.38 (m, 2 H), 2.09 (m, 2 H), 1.74–1.50 (m, 5 H), 1.25 (s, 3 H), 0.89 (d, J = 6 Hz, 3 H), 0.84 (d, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 120.2, 75.3, 74.8, 62.0, 33.8, 32.4, 30.5, 29.9, 26.8, 18.4, 18.3, 10.9. Anal. Calcd for $C_{12}H_{20}ClHgNO$: C, 33.49; H, 4.68; N, 3.25; Hg, 46.61. Found: C, 33.51; H, 4.68; N, 3.25; Hg, 46.43.

Alcohols 8 and 9. A solution of $NaBH_4$ (137 mg, 3.6 mmol) in 10 mL of DMSO was bubbled vigorously with O_2 for 5 min. A solution of **6** (219 mg, 0.51 mmol) in 20 mL of DMSO was added over 1 h by using a syringe pump while O_2 bubbling was continued. After addition of the mercurial, the reaction was allowed to proceed 30 min longer. Water (15 mL) was added (ice-bath cooling) and the mixture was stirred for 15 min before being partitioned between Et_2O and water. The organic layer was dried ($MgSO_4$) and evaporated. The products were purified by flash chromatography on silica gel to give (in order of decreasing R_f) equatorial alcohol **9** (28 mg, 26%) [IR (neat) 3451, 2955, 2276, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) 3.47 (dd, J = 12, 4 Hz, 1 H), 2.93 (m, 1 H), 2.30 (m, 4 H), 1.87–1.24 (m, 5 H), 1.20 (s, 3 H), 10.91 (d, J = 6 Hz, 3 H), 0.86 (d, J = 6 Hz, 3 H); HRMS calcd for $C_{12}H_{21}NO_2$ 211.157194, found 211.156949] and axial alcohol **8** (45 g, 42%) [IR (neat) 3462, 2957, 2247; ^1H NMR ($CDCl_3$) 3.35 (t, J = 3 Hz, 1 H), 3.00 (m, 1 H), 2.34 (m, 4 H), 1.84–1.23 (m, 5 H), 1.13 (s, 3 H), 0.92 (d, J = 6 Hz, 3 H), 0.86 (d, J = 6 Hz, 3 H); HRMS calcd for $C_{12}H_{21}NO_2$ 211.157194, found 211.157154].

Conversion of 9 into 8. A solution of **9** (52 mg, 0.24 mmol) in 5 mL of CH_2Cl_2 was treated with 115 mg of NaOAc and 175 mg of PCC. After stirring 10 min, it was diluted with Et_2O and filtered through silica gel to obtain the corresponding ketone in quantitative yield. A solution of this ketone (182 mg, 0.87 mmol) in 16 mL of THF was cooled to −78 °C and treated with 1 M K-Selectride (in THF) (3.2 mL). After 4.5 h the reaction was quenched at 0 °C with 7 mL of 1.5 N NaOH and 8 mL of 15% H_2O_2. Once the mixture had stirred 20 min, it was partitioned

between ether and water. The ~1.2:1 mixture of **8** and **9** obtained in this manner (157 mg, 86%) was separated as described previously.

Olefinic Alcohol 10. A solution of **8** (710 mg, 3.4 mmol) in 6 mL of CH_2Cl_2 was treated with $EtN(i\text{-}Pr)_2$ (1.6 mL, 9 mmol) and TBDMS-OTf (1.15 mL, 5.0 mmol) and stirred for 90 min. The mixture was partitioned between Et_2O and water and the organic phase was dried, evaporated, and warmed in vacuo until the weight of the product was constant (1.10 g, 100%).

The silylated nitrile was dissolved in 15 mL of CH_2Cl_2 and treated, at −78 °C, with 4 mL of 1 M DIBAL in hexane. After 1 h the solution was removed from the cooling bath and treated with NaF (2 g). Water (0.7 mL) was slowly added and the mixture was stirred vigorously for 30 min, filtered through Celite, and evaporated. The aldehyde was purified by short column chromatography on silica gel.

A solution of $Ph_3P{=}CH_2$ was prepared by dissolving KH (240 mg, 6 mmol) in 3 mL of DMSO and treating the resulting solution of dimsylpotassium with methyltriphenylphosphonium bromide (2.14 g, 6 mmol) in 4 mL of DMSO. The above-prepared aldehyde was dissolved in 5 mL of DMSO and the solution of the ylide was introduced. After being stirred for 30 min, the mixture was poured into water and extracted with Et_2O. The olefin was purified by flash chromatography on silica gel (0–10% EtOAc/hexane).

The olefin was dissolved in 8 mL of THF and treated with 2 mL of 1 M TBAF. After being stirred overnight, the solution was partitioned between Et_2O and water and the product was purified on silica gel (0–30% EtOAc/hexane). In this way **10** (457 mg, 64% for four steps) was obtained as an oil: IR (neat) 3427, 2951, 1007 cm^{-1}; ^1H NMR ($CDCl_3$) 5.84 (m, 1 H), 5.05 (m, 2 H), 3.48 (t, J = 2 Hz, 1 H), 3.13 (m, 1 H), 2.15–1.25 (m, 9 H), 1.17 (s, 3 H), 0.94 (d, J = 6 Hz, 3 H), 0.87 (d, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 138.8, 114.1, 76.0, 74.4, 69.4, 33.4, 32.6, 26.9, 26.5, 22.5, 21.6, 18.8, 18.3; HRMS (CI) calcd for $C_{13}H_{24}O_2$ + H 213.1854, found 213.1849.

Mercurial 11. A solution of **10** (26 mg, 0.12 mmol) and $Hg(OTFA)_2$ (103 g, 0.24 mmol) in 4 mL of THF was stirred in the dark overnight and then diluted with 6 mL of saturated KCl. After being stirred vigorously for 15 min, the mixture was partitioned between CH_2Cl_2 and aqueous KCl. The organic phase afforded **11**, which can be purified on silica gel (0–15% EtOAc/hexane) (44 mg, 80%): oil; IR (neat) 2957, 2872, 1460, 1375, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) 3.82 (m, 1 H), 3.58 (m, 2 H), 2.29 (dd, J = 12.3, 4.8 Hz, 1 H), 2.07 (dd, J = 12.3, 6.3 Hz, 1 H), 1.85–1.50 (m, 9 H), 1.21 (s, 3 H), 0.88 (d, J = 6 Hz, 3 H), 0.82 (d, J = 6 Hz, 3 H); ^{13}C NMR (benzene-d_6) 77.3, 77.0, 74.8, 70.9, 39.3, 38.2, 34.4, 33.4, 23.6, 21.9, 21.6, 18.6, 18.4.

Sulfide 14. A solution of Br_2 (150 μL, 2.9 mmol) and LiBr (200 mg, 2.3 mmol) in 10 mL of pyridine was prepared. The mercurial **11** (675 mg, 1.5 mmol) was dissolved in 11 mL of pyridine and treated with 7 mL of the bromine solution. The mixture was irradiated for several minutes with a 275-W sunlamp and then stirred for 45 min. The solution was poured into aqueous $Na_2S_2O_3$ and extracted with Et_2O. In this way the bromide (413 mg, 94%) could be obtained (purity >95%) as an oil: ^1H NMR ($CDCl_3$) 3.58 (m, 3 H), 3.38 (m, 2 H), 1.81–1.55 (m, 9 H), 1.24 (s, 3 H), 0.89 (d, J = 6 Hz, 3 H), 0.83 (d, J = 6 Hz, 3 H).

The bromide prepared above was treated with a solution of KSPh prepared from PhSH (220 μL, 2.1 mmol) and KH (80 mg, 2.0 mmol) in 15 mL of THF (20 °C, 1 h). 18-Crown-6 (100 mg) was added and the reaction was allowed to proceed for 3 $^1/_2$ h. The mixture was diluted with Et_2O and washed successively with water, aqueous NaOH, and brine, dried ($MgSO_4$), and then evaporated. The residue was purified by flash chromatography on silica gel (0–5% EtOAc/hexane) to give **14** (411 mg, 92%): oil; IR (neat) 2953, 2870, 1064 cm^{-1}; ^1H NMR ($CHCl_3$) 7.33–7.15 (m, 5 H), 3.55 (m, 3 H), 3.11 (dd, J = 15, 6 Hz, 1 H), 2.91 (dd, J = 15, 6 Hz, 1 H), 1.87–1.48 (m, 9 H), 1.22 (s, 3 H), 0.88 (d, J = 6 Hz, 3 H), 0.81 (d, J = 6 Hz, 3 H); HRMS calcd for $C_{19}H_{28}O_2S$ 320.18096, found 320.18082.

Trifluoroacetyl Hemithioacetal 15. The sulfide **14** (301 mg, 0.94 mmol) was dissolved in 12 mL of acetone and treated with $NaIO_4$ (840 mg, 3.9 mmol) in 3 mL of water. After being stirred overnight, the mixture was diluted with 75 mL of acetone, filtered, and evaporated. The sulfoxide was purified on silica gel (0–4% MeOH/CH_2Cl_2) to afford a 1:1 mixture of diastereomers (312 mg, 99%), which was used directly in the next step.

To a solution of the sulfoxide (40 mg, 0.12 mmol) in THF (2 mL) was added 0.5 mL of trifluoroacetic anhydride at 0 °C. The mixture was stirred at room temperature (10 min) and then evaporated to dryness to give the two diastereomers of hemithioacetal ester **15** (51 mg, 100%). The product was homogeneous by TLC but could not be purified further owing to instability. ^1H NMR ($CDCl_3$): 7.53 (m, 2 H), 7.36 (m, 3 H), 6.23 (d, J = 4.1 Hz, 0.3 H), 6.13 (d, J = 6.6 Hz, 0.7 H), 3.89–3.44 (m, 3 H), 1.95–1.50 (m, 9 H), 1.24 (s, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.83 (d, J = 6.7 Hz, 3 H).

Ketone 16. To a solution of 5-bromo-2-methylpent-2-ene (117 mg, 0.72 mmol) in 2 mL of Et_2O was added *tert*-butyllithium in pentane (0.8 mL, 1.36 mmol) dropwise at −65 °C over a period of 20 min. The mixture was stirred at −65 °C for an additional 30 min. The thioacetal ester (51 mg, 0.12 mmol) was dissolved in 1 mL of Et_2O and then added to this solution at −65 °C. The mixture was stirred at −65 °C for 10 min and then at room temperature for 30 min. The reaction was quenched with 5 mL of saturated NaCl. The aqueous layer was extracted with Et_2O. The Et_2O extract was washed with saturated NaCl, concentrated by evaporation, and then purified by PTLC on silica gel (20% EtOAc/hexane) to give a mixture of two isomers of alcohol (24 mg, 70%) in a ratio of 1:1. More polar diastereomer: ^1H NMR ($CDCl_3$) 5.12 (br t, J = 7.0 Hz, 1 H), 3.70 (ddd, J = 3.4, 4.8, 8.6 Hz, 1 H), 3.57 (m, 2 H), 3.38 (dt, J = 8.6, 2.9 Hz, 1 H), 2.32 (br s, 1 H), 2.12 (m, 2 H), 1.95–1.35 (m, 11 H), 1.69 (s, 3 H), 1.62 (s, 3 H), 1.21 (s, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.84 (d, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 132.2, 124.0, 80.7, 77.7, 75.3, 72.5, 71.3, 38.2, 32.7, 31.9, 25.7, 24.4, 23.0, 22.8, 21.5, 20.7, 18.7, 18.0, 17.7. Less polar diastereomer: ^1H NMR ($CDCl_3$) 5.12 (br t, J = 7.0 Hz, 1 H), 3.56 (m, 2 H), 3.42 (dt, J = 6.0, 6.3 Hz, 1 H), 3.25 (m, 1 H), 2.56 (br s, 1 H), 2.13 (m, 2 H), 1.95–1.40 (m, 11 H), 1.69 (s, 3 H), 1.62 (s, 3 H), 1.21 (s, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 132.0, 124.0, 81.4, 77.5, 75.3, 73.5, 71.3, 38.4, 32.7, 26.0, 25.7, 23.9, 23.0, 21.4, 20.8, 18.7, 18.0, 17.7.

To a solution of 220 μL of DMSO in 2 mL of CH_2Cl_2 was added 120 μL of oxalyl chloride at −65 °C. The mixture was stirred at −65 °C for 15 min, and a solution of two alcohols (86 mg, 0.277 mmol) in 1 mL of CH_2Cl_2 was added; stirring was continued for an additional 15 min. Triethylamine (0.8 mL) was added and the reaction mixture was stirred at −40 °C for 30 min. Water (5 mL) was then added. The aqueous layer was extracted with CH_2Cl_2. The organic extract was washed with saturated NaCl, concentrated, and purified by PTLC on silica gel (15% EtOAc/hexane) to give the ketone **16** (73 mg, 85%): IR (neat) 2959, 2972, 1717, 1458, 1377, 1107, 1061, 1009 cm^{-1}; ^1H NMR ($CDCl_3$) 5.08 (br t, J = 7.2 Hz, 1 H), 3.87 (dd, J = 3.1, 11.1 Hz, 1 H), 3.58 (m, 2 H), 2.60 (t, J = 7.0 Hz, 2 H), 2.24 (dt, J = 7.3, 7.0 Hz, 2 H), 1.86 (m, 3 H), 1.76–1.47 (m, 6 H), 1.67 (s, 3 H), 1.62 (s, 3 H), 1.24 (s, 3 H), 0.90 (d, J = 6.4 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 210.2, 132.4, 122.9, 83.3, 77.6, 75.2, 70.7, 38.4, 38.0, 32.7, 26.5, 22.9, 21.7, 21.3, 20.8, 18.6, 18.0, 17.6; HRMS calcd for $C_{19}H_{232}O_3$ 308.235098, found 308.234829.

Alcohols 17 and 18. (1) Using Methylmagnesium Bromide. To a solution of ketone **16** (38 mg, 0.123 mmol) in 1.5 mL of toluene was added 1.5 M MeMgBr in toluene (160 μL, 0.24 mmol) at −65 °C. The mixture was stirred for 30 min and saturated NaCl (3 mL) was then added. The water layer was extracted with Et_2O. The extract was evaporated to dryness and then chromatographed on silica gel (0–10% EtOAc/hexane) to give first alcohol **18** (4 mg, 10%) and then alcohol **17** (32 mg, 80%). Alcohol **18**: IR (neat) 3578, 3476, 2961, 2872, 1458, 1377, 1325, 1109, 1088, 1010, 943 cm^{-1}; ^1H NMR ($CDCl_3$) 5.10 (br t, J = 7.0 Hz, 1 H), 3.56 (m, 2 H), 3.28 (m, 1 H), 2.45 (br s, 1 H), 2.06 (m, 2 H), 1.82 (m, 3 H), 1.71 (m, 2 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.57–1.44 (m, 6 H), 1.20 (s, 3 H), 1.10 (s, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.83 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 131.4, 124.6, 83.0, 77.6, 75.2, 73.4, 71.2, 39.0, 38.6, 32.8, 25.7, 24.0, 23.0, 22.1, 21.6, 21.4, 20.8, 18.7, 18.0, 17.6; HRMS calcd for $C_{20}H_{36}O_3$ 324.266394, found 324.266309. Alcohol **17**: IR (neat) 3472, 2959, 2870, 1458, 1375, 1325, 1105, 1065, 1009, 945; ^1H NMR ($CDCl_3$) 5.11 (br t, J = 6.9 Hz, 1 H), 3.56 (m, 2 H), 3.25 (m, 1 H), 2.38 (br s, 1 H), 2.15 (m, 1 H), 2.00 (m, 1 H), 1.80 (m, 3 H), 1.70 (m, 2 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.58 (m, 5 H), 1.36 (m, 1 H), 1.20 (s, 3 H), 1.15 (s, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.83 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$)

131.4, 124.7, 84.7, 77.8, 75.2, 73.3, 71.2, 38.6, 36.4, 32.7, 25.7, 23.7, 23.2, 22.9, 22.0, 21.4, 20.8, 18.7, 18.0, 17.6; HRMS calcd for $C_{20}H_{36}O_3$ 324.266394, found 324.266310.

(2) Using Methyllithium. To a solution of ketone **16** (38 mg, 0.123 mmol) in 1.5 mL of THF was added 0.6 M MeLi in Et_2O (0.4 mL, 0.24 mmol) at −65 °C. The mixture was stirred for 30 min, and saturated NaCl (5 mL) was added. The water layer was extracted with Et_2O. The combined extract was washed with saturated NaCl, evaporated to dryness, and then chromatographed on silica gel (0–10% EtOAc/hexane) to give alcohols **18** (22 mg, 55%) and **17** (9 mg, 23% yield).

Bromides 2 and 19. *N*-Bromosuccinimide (31 mg, 0.175 mmol) was added at room temperature to a solution of alcohol **17** (52 mg, 0.16 mmol) in CH_2Cl_2 (2.5 mL). The mixture was stirred for 40 min and then evaporated to dryness. The residue was extracted with hexane. The combined extract was concentrated and then chromatographed on silica gel (0–4% EtOAc/hexane) to give, first, white crystalline **2** (14 mg, 22%); mp 66–70 °C, and then an oily epimeric mixture of **19** (40 mg, 62%). For **2**: IR (neat) 2955, 2918, 2849, 1462, 1373, 1252, 1101, 1068, 1045, 1007 cm^{-1}; ^1H NMR ($CDCl_3$) 3.89 (dd, J = 3.9, 12.3 Hz, 1 H), 3.55 (m, 1 H), 3.48 (dd, J = 6.1, 11.1 Hz, 1 H, CH), 3.05 (dd, J = 2.3, 11.0 Hz, 1 H, CH), 2.24 (m, 1 H), 2.10 (m, 1 H), 1.83–1.60 (m, 6 H), 1.60–1.41 (m, 5 H), 1.39 (s, 3 H), 1.26 (s, 3 H), 1.20 (s, 3 H), 1.18 (s, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.83 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 86.6, 77.7, 75.2, 74.9, 74.4, 71.5, 59.1, 38.6, 37.1, 32.7, 31.0, 28.2, 23.6, 23.0, 22.9, 21.4, 20.8, 20.1, 18.8, 18.0; HRMS calcd for $C_{20}H_{35}O_3Br$, 402.175918, found 402.174816. For **19**: ^1H NMR ($CDCl_3$) 3.88 (m, 1 H), 3.55 (m, 2 H), 3.32 (br d, J = 11.1 Hz, 1 H), 2.07 (m, 2 H), 1.97–1.76 (m, 5 H), 1.71 (s, 6 H), 1.67–1.42 (m, 6 H), 1.20 (s, 3 H), 1.17 (s, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.83 (d, J = 6.7 Hz, 3 H).

Zinc Debromination of 19. To a solution of **19** (38 mg, 0.094 mmol) in ethanol (3 mL) were added zinc powder (260 mg, 4 mmol) and acetic acid (50 μL). The mixture was stirred at room temperature for 60 hours and filtered through a silica gel pad. The filtrate was evaporated to give alcohol **17** (26 mg, 85%).

Bromide 20. To a solution of alcohol **18** (32 mg, 0.1 mmol) in CH_2Cl_2 (2.5 mL) was added *N*-bromosuccinimide (19 mg, 0.105 mmol) at room temperature. The mixture was stirred for 30 min and then evaporated to dryness. The residue was extracted with hexane. The extract was concentrated and chromatographed on silica gel (0–4% EtOAc/hexane) to give a mixture of bromides (31 mg). The mixture was dissolved in ethanol (3 mL) and zinc powder (200 mg) and acetic acid (50 μL) were added. The mixture was stirred at room temperature for 50 h and then filtered through a silica gel pad. The filtrate was concentrated and chromatographed through a silica gel (0–10% ethyl acetate in hexane) column to give white crystalline **20** (6.5 mg, 16% from **18**) [mp 76–81 °C; IR (neat) 2963, 2872, 1472, 1381, 1371, 1262, 1125, 1103, 1059, 1040, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) 3.88 (dd, J = 4.2, 12.2 Hz, 1 H), 3.56 (m, 1 H), 3.46 (dd, J = 6.4, 11.2 Hz, 1 H), 3.16 (dd, J = 3.3, 10.8 Hz, 1 H), 2.24 (m, 1 H), 2.11 (m, 1 H), 1.88–1.64 (m, 6 H), 1.64–1.46 (m, 5 H), 1.42 (s, 3 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 1.17 (s, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.82 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 84.7, 77.8, 75.3, 75.0, 74.7, 71.4, 58.8, 38.6, 32.7, 31.3, 30.8, 28.0, 24.3, 23.7, 22.95, 22.92, 21.4, 20.7, 18.8, 18.0; HRMS calcd for $C_{20}H_{35}O_3Br$ 402.176918, found 402.175602] and recovered **18** (15 mg, 56%).

Diol 26. Furanose **25** (300 mg, 1.1 mmol) was dissolved in 3 mL of THF and KH (88 mg, 2.2 mmol) was added. The mixture was stirred at room temperature for 1 h. *tert*-Butyldiphenylchlorosilane (412 mg, 1.5 mmol) was added and the mixture heated at reflux for 8 h. Aqueous saturated NaCl was cautiously added and the mixture was extracted with Et_2O. The extract was chromatographed on silica gel (0–15% EtOAc/hexane) to give the silylated furanose (473 mg, 84%): ^1H NMR ($CDCl_3$) 7.87 (m, 4 H), 7.38 (m, 6 H), 5.37 (d, J = 3.5 Hz, 1 H), 4.12 (m, 3 H), 3.97 (m, 1 H), 3.27 (d, J = 3.5 Hz, 1 H), 1.51 (s, 3 H), 1.49 (s, 3 H), 1.45 (s, 3 H), 1.14 (s, 3 H), 1.08 (s, 3 H), 1.04 (s, 9 H); ^{13}C NMR ($CDCl_3$) 136.6, 126.3, 135.1, 134.7, 129.6, 129.3, 127.6, 127.1, 112.2, 109.2, 103.5, 83.7, 82.3, 80.1, 73.8, 67.9, 27.1, 26.8, 26.7, 25.9, 25.5, 20.3, 19.3. The 5,6-isopropylidene group was selectively removed by the treatment of this compound (2.05 g, 4 mmol) with 90% AcOH (50 mL) at 60 °C (4 h). After solvent evaporation, the product was chromatographed on silica gel to give diol **26** (1.70 g, 90%): $[\alpha]_D$ +66.3° (*c* 3.15, $CHCl_3$); IR (neat) 3476, 3048, 2930, 3857, 1428, 1374, 1211, 1015, 874, 743, 700 cm^{-1}; ^1H NMR ($CDCl_3$) 7.77 (m, 4 H), 7.39 (m, 6 H), 5.36 (d, J = 3.2 Hz, 1 H), 4.10 (d, J = 9.0 Hz, 1 H), 3.84 (m, 3 H), 3.14 (d, J = 3.2 Hz, 1 H), 3.05 (br s, 1 H), 2.53 (br s, 1 H), 1.41 (s, 3 H), 1.23 (s, 3 H), 1.06 (s, 9 H), 1.02 (s, 3 H); ^{13}C ($CDCl_3$) 136.4, 136.2, 134.1, 133.8, 129.9, 129.7, 127.4, 127.0, 112.5, 103.5, 82.6, 81.1, 78.7, 70.3, 64.6, 27.1, 26.5, 25.7, 20.2, 19.3. Anal. Calcd for $C_{26}H_{36}O_6Si$: C, 66.10; H, 7.63. Found: C, 65.66; H, 7.70.

Ester 27. Diol **26** (1.251 g, 2.65 mmol) was dissolved in benzene (50 mL) containing Celite (2 g). Lead tetraacetate (1.33 g, 3 mmol) was added at room temperature and the mixture was stirred for 30 min. The mixture was diluted with 50 mL of ether and filtered through a silica gel pad. The silica gel was flushed with Et_2O (300 mL) and the filtrate was evaporated to give 1.16 g (100%) of the corresponding aldehyde. The aldehyde was dissolved in THF (50 mL) and treated with $Ph_3P{=}CHCO_2Me$ (3 h). The mixture was then partitioned between Et_2O and water. The extract was concentrated and chromatographed through silica gel (0–20% EtOAc/hexane) to give crystalline ester **27** (1.15 g, 88%): mp 102–104 °C; $[\alpha]_D$ +17.5° (*c* 3.2, $CHCl_3$); IR ($CHCl_3$) 2932, 2897, 1725, 1474, 1373, 1258, 1134, 1098, 1109 cm^{-1}; ^1H NMR ($CDCl_3$) 7.75 (m, 4 H), 7.38 (m, 6 H), 7.03 (dd, J = 15.9, 4.6 Hz, 1 H), 6.20 (dd, J = 15.9, 1.4 Hz, 1 H), 5.46 (d, J = 3.5 Hz, 1 H), 4.78 (dd, J = 4.0, 1.6 Hz, 1 H), 3.78 (s, 3 H), 3.35 (d, J = 3.5 Hz, 1 H), 1.46 (s, 3 H), 1.10 (s, 3 H), 1.06 (s, 9 H), 0.94 (s, 3 H); ^{13}C NMR ($CDCl_3$) 166.4, 142.6, 136.3, 136.0, 134.5, 134.2, 129.6, 127.3, 127.1, 122.1, 112.4, 103.5, 82.9, 81.1, 81.0, 51.6, 27.0, 26.6, 25.8, 20.7, 19.4. Anal. Calcd for $C_{28}H_{36}O_6Si$: C, 67.74; H, 7.26. Found: C, 67.76; H, 7.17.

Alcohol 28. A solution of ester **27** (1.15 g, 2.3 mmol) in methanol (20 mL) containing 5% Pd/C (200 mg) was stirred under a hydrogen atmosphere for 3 h. The mixture was filtered, concentrated, and chromatographed through silica gel (0–20% EtOAc/hexane) to give the saturated ester (1.11 g, 96%): mp 108–110 °C; $[\alpha]_D$ +62.9° (*c* 2.83, $CHCl_3$); IR ($CHCl_3$) 3069, 2932, 2888, 2857, 1736, 1427, 1374, 1250, 1111, 1011, 876, 743 cm^{-1}; ^1H NMR ($CDCl_3$) 7.75 (m, 4 H), 7.36 (m, 6 H), 5.37 (d, J = 3.6 Hz, 1 H), 4.07 (dd, J = 9.4, 3.6 Hz, 1 H), 3.69 (s, 3 H), 3.24 (d, J = 3.6 Hz, 1 H), 2.62 (m, 1 H), 2.52 (m, 1 H), 1.98 (m, 1 H), 1.81 (m, 1 H), 1.40 (s, 3 H), 1.04 (s, 15 H); ^{13}C NMR ($CDCl_3$) 173.7, 136.3, 136.1, 134.9, 134.5, 129.5, 129.4, 127.2, 126.9, 111.9, 103.2, 83.0, 80.5, 80.1, 51.5, 31.2, 27.1, 26.4, 25.8, 23.6, 19.9, 19.3. Anal. Calcd for $C_{28}H_{38}O_6Si$: C, 67.47; H, 7.68. Found: C, 67.58; H, 7.78.

This ester (90 mg, 0.18 mmol) in 3 mL of toluene was treated with DIBAL (180 μL, 0.18 mmol) at −78 °C. The mixture was stirred at −78 °C for 30 min. Additional DIBAL (70 μL, 0.07 mmol) was introduced and stirring was continued for 30 min. The reaction was quenched with saturated NaCl, neutralized with 0.5 N HCl, and extracted with Et_2O. The extract was concentrated and purified by PTLC on silica gel (30% EtOAc/hexane) to give the aldehyde (67 mg, 79%): ^1H NMR ($CDCl_3$) 9.85 (s, 1 H), 7.76 (m, 4 H), 7.36 (m, 6 H), 5.37 (d, J = 3.4 Hz, 1 H), 4.05 (dd, J = 9.7, 3.7 Hz, 1 H), 3.26 (d, J = 3.4 Hz, 1 H), 2.71 (m, 2 H), 1.97 (m, 1 H), 1.79 (m, 1 H), 1.41 (s, 3 H), 1.04 (s, 15 H); ^{13}C NMR ($CDCl_3$) 201.8, 136.4, 136.1, 134.9, 134.5, 129.6, 129.5, 127.2, 127.0, 111.9, 103.2, 83.0, 80.7, 80.1, 41.2, 27.1, 26.5, 25.8, 20.6, 19.9, 19.4.

tert-Butyllithium in pentane (2.1 mL, 3.5 mmol) was added at −65 °C over a period of 20 min to a solution of 2-bromopropene (218 mg, 1.8 mmol) in 5 mL of Et_2O. The mixture was stirred for an additional 30 min and then a solution of the previously prepared aldehyde (638 mg, 1.35 mmol) in 5 mL of Et_2O was introduced. The mixture was stirred (30 min) and then quenched with saturated NaCl. The water layer was extracted with Et_2O. The extract was concentrated and chromatographed on silica gel (0–25% ethyl acetate in hexane) to give the diastereomeric alcohols **28** (616 mg, 88%): ^1H NMR ($CDCl_3$) 7.76 (m, 4 H), 7.38 (m, 6 H), 5.39 (d, J = 3.4 Hz, 1 H), 5.00 (m, 1 H), 4.86 (m, 1 H), 4.12 (m, 2 H), 3.27 (d, J = 3.4 Hz, 0.4 H), 3.26 (d, J = 3.4 Hz, 0.6 H), 2.07 (br s, 1 H), 1.81 (m, 2 H), 1.76 (br s, 3 H), 1.69 (m, 1 H), 1.50 (m, 1 H), 1.42 (s, 3 H), 1.06 (s, 3 H), 1.03 (s, 9 H), 1.00 (s, 3 H); ^{13}C NMR ($CDCl_3$) 147.5, 147.4, 136.4, 136.2, 135.1, 124.7, 129.5, 129.4, 127.2, 127.0, 112.0, 111.9, 110.9, 110.8, 103.2, 83.0, 81.6, 81.5, 80.2, 75.9, 75.4, 32.6, 32.2, 27.1, 26.5, 25.9, 24.7, 24.1, 20.0, 19.4, 17.9, 17.8.

Stannyl Ether 29. To a solution of **28** (3.036 g, 5.95 mmol) in 25 mL of THF was added KH (400 mg, 10 mmol). The mixture

was stirred at room temperature for 4 h and then (iodomethyl)tributyltin (4.09 g, 9.5 mmol) was introduced. The mixture was stirred at room temperature for 8 h. The reaction was quenched with saturated NaCl and the mixture was extracted with Et_2O. The extract was concentrated and chromatographed on silica gel (0–10% EtOAc/hexane) to give the stannyl ether **29** (3.97 g, 83%): ^1H NMR ($CDCl_3$) 7.75 (m, 4 H), 7.37 (m, 6 H), 5.37 (d, J = 3.5 Hz, 0.4 H), 5.36 (d, J = 3.9 Hz, 0.6 H), 4.93 (m, 2 H), 4.04 (m, 1 H), 3.71 (dd, J = 10.2, 3.6 Hz, 1 H), 3.44 (m, 2 H), 3.25 (d, J = 3.5 Hz, 0.4 H), 3.22 (d, J = 3.9 Hz, 0.6 H), 1.78 (m, 2 H), 1.65 (s, 3 H), 1.61–1.42 (m, 8 H), 1.40 (s, 3 H), 1.38–1.21 (m, 6 H), 1.04 (s, 15 H), 0.99–0.84 (m, 15 H).

Nitrile 30. To a solution of stannyl ether **29** (432 mg, 0.53 mmol) in THF (5 mL) was added *n*-butyllithium (1.4 mL, 1.9 mmol) at −65 °C over a period of 5 min. The mixture was stirred at −65 °C (3 h) and then quenched with saturated NaCl. The mixture was extracted with Et_2O. The extract was concentrated and chromatographed through silica gel (0–30% EtOAc/hexane) to give the homoallylic alcohol **36** (228 mg, 82%): $[\alpha]_D$ +42.6° (*c* 5.05, $CHCl_3$); IR (neat) 3453, 3071, 2932, 2857, 1427, 1373, 1213, 1109, 876, 741 cm^{-1}; ^1H NMR ($CDCl_3$) 7.75 (m, 4 H), 7.36 (m, 6 H), 5.39 (m, 2 H), 4.08 (dd, J = 9.5, 3.2 Hz, 1 H), 3.70 (t, J = 6.6 Hz, 2 H), 3.26 (d, J = 3.4 Hz, 1 H), 2.37 (t, J = 6.6 Hz, 2 H), 2.28 (m, 2 H), 1.78 (br s, 3 H), 1.74–1.49 (m, 3 H), 1.40 (s, 3 H), 1.04 (s, 12 H), 1.00 (s, 3 H); ^{13}C NMR ($CDCl_3$) 136.4, 136.1, 135.1, 134.7, 132.1, 129.5, 129.4, 127.6, 127.2, 127.0, 111.8, 103.3, 83.0, 80.7, 80.0, 60.7, 35.2, 28.2, 27.1, 26.4, 25.8, 25.0, 23.5, 20.0, 19.4. Anal. Calcd for $C_{231}H_{44}O_5Si$: C, 70.99; H, 8.40. Found: C, 70.87; H, 8.44.

A solution of the homoallylic alcohol (255 mg, 0.49 mmol) in 2 mL of CH_2Cl_2 was treated with triethylamine (74 mg, 0.73 mmol) and methanesulfonyl chloride (81 mg, 0.7 mmol). The mixture was stirred at room temperature (40 min) and then partitioned between ether and water. The aqueous layer was extracted with Et_2O. The extract was evaporated to give 294 mg (100%) of the mesylate: ^1H NMR ($CDCl_3$) 7.74 (m, 4 H), 7.38 (m, 6 H), 5.38 (m, 2 H), 4.26 (t, J = 7.5 Hz, 2 H), 4.40 (dd, J = 9.5, 3.2 Hz, 1 H), 3.26 (d, J = 3.9 Hz, 1 H), 2.99 (s, 3 H), 2.54 (br t, J = 7.5 Hz, 2 H), 2.23 (m, 2 H), 1.80 (br s, 3 H), 1.65 (m, 1 H), 1.52 (m, 1 H), 1.40 (s, 3 H), 1.04 (s, 12 H), 1.00 (s, 3 H).

The mesylate (294 mg, 0.49 mmol) and potassium cyanide (96 mg, 1.47 mmol) were dissolved in 2 mL of DMSO. The mixture was stirred at 70 °C (3 h) and then partitioned between Et_2O and water. The extract was concentrated and purified by PTLC on silica gel (25% EtOAc/hexane) to give the silylated nitrile (233 mg, 90%): $[\alpha]_D$ +41.7° (*c* 2.35, $CHCl_3$); IR (neat) 3046, 2932, 2855, 2245, 1428, 1374, 1211, 1094, 1015, 876, 741 cm^{-1}; ^1H NMR ($CDCl_3$) 7.75 (m, 4 H), 7.38 (m, 6 H), 5.38 (m, 2 H), 4.04 (dd, J = 9.5, 3.1 Hz, 1 H), 3.26 (d, J = 3.9 Hz, 1 H), 2.42 (br s, 4 H), 2.23 (m, 2 H), 1.78 (br s, 3 H), 1.70–1.48 (m, 2 H), 1.40 (s, 3 H), 1.04 (s, 12 H), 1.00 (s, 3 H); ^{13}C NMR ($CDCl_3$) 136.3, 136.1, 135.0, 134.6, 131.9, 129.5, 129.3, 128.0, 127.1, 126.9, 119.5, 111.7, 103.2, 82.9, 80.6, 79.9, 27.9, 27.5, 27.1, 26.4, 25.8, 25.0, 22.8, 19.9, 19.3, 15.9. Anal. Calcd for $C_{32}H_{43}NO_4Si$: C, 72.00; H, 8.11. Found: C, 71.61; H, 8.19.

This nitrile (815 mg, 1.53 mmol) was dissolved in 6 mL of THF and a solution of tetrabutylammonium fluoride in THF (4.6 mL, 4.6 mmol) was added. The mixture was stirred for 18 h and then partitioned between Et_2O and water. The aqueous layer was extracted with Et_2O. The extract was concentrated and chromatographed through silica gel (0–25% ethyl acetate in hexane) to give the alcohol (420 mg, 93%): ^1H NMR ($CDCl_3$) 5.73 (d, J = 3.9 Hz, 1 H), 5.29 (br t, J = 71.2 Hz, 1 H), 4.11 (d, J = 3.9 Hz, 1 H), 3.65 (dd, J = 9.2, 3.9 Hz, 1 H), 2.54 (s, 1 H), 2.40 (br s, 4 H), 2.19 (m, 2 H), 1.74 (br s, 3 H), 1.55 (s, 3 H), 1.52 (m, 2 H), 1.34 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR ($CDCl_3$) 131.8, 127.6, 119.5, 111.9, 103.0, 83.9, 80.4, 76.9, 27.6, 27.3, 26.4, 26.3, 24.7, 22.7, 18.0, 15.8.

This alcohol (365 mg, 1.24 mmol) was dissolved in 8 mL of THF and KH (70 mg, 1.74 mmol) was added. After 1 h BnBr (240 mg, 1.4 mmol) was added and stirring was continued for 5 h. The reaction was quenched with saturated NaCl and partitioned between Et_2O and water. The extract was concentrated and chromatographed through silica gel (0–20% ethyl acetate in hexane) to give the benzyl ether **30** (450 mg, 94%): $[\alpha]_D$ +21.0° (*c* 3.95, $CHCl_3$); IR (neat) 3032, 2982, 2940, 2245, 1454, 1373, 1250, 1132, 1090, 1017, 874, 741 cm^{-1}; ^1H NMR ($CDCl_3$) 7.33 (m, 5 H), 5.72 (d, J = 3.8 Hz, 1 H), 4.27 (br t, J = 7.2 Hz, 1 H), 4.61 (d, J = 10.9 Hz, 1 H), 4.56 (d, J = 10.9 Hz, 1 H), 4.34 (d, J = 3.8 Hz, 1 H), 4.00 (dd, J = 9.2, 3.9 Hz, 1 H), 2.34 (br s, 4 H), 2.17 (m, 2 H), 1.71 (br s, 3 H), 1.58 (s, 3 H), 1.52 (m, 2 H), 1.35 (s, 3 H), 1.18 (s, 3 H); ^{13}C NMR ($CDCl_3$) 138.7, 131.7, 128.2, 127.9, 127.6, 127.4, 119.6, 112.4, 103.8, 82.8, 82.4, 80.0, 66.5, 28.2, 27.4, 26.7, 26.5, 24.8, 22.8, 16.1, 15.9. Anal. Calcd for $C_{23}H_{31}O_4N$: C, 71.69; H, 8.05; N, 3.64. Found: C, 71.70; H, 8.04; N, 3.54.

Alcohol 24. Benzyl ether (448 mg, 1.16 mmol) was dissolved in $H_2O/THF/CF_3COOH$ (2:1:3). The mixture was stirred at room temperature (5 h) and then neutralized with saturated $NaHCO_3$. The Et_2O extract was evaporated to give 402 mg (100%) of a mixture of the two diol anomers **30** in a ratio of 1:9 [^1H NMR ($CDCl_3$) of major isomer: 7.34 (m, 5 H), 5.30 (br t, J = 6.9 Hz, 1 H), 5.22 (dd, J = 11.0, 4.2 Hz, 1 H), 4.55 (d, J = 10.7 Hz, 1 H), 4.49 (d, J = 10.7 Hz, 1 H), 4.17 (d, J = 11.0 Hz, 1 H, OH), 4.08 (dd, J = 10.1, 3.2 Hz, 1 H), 3.82 (dd, J = 6.7, 4.2 Hz, 1 H), 2.95 (d, J = 6.7 Hz, 1 H, OH), 2.38 (m, 4 H), 2.28 (m, 1 H), 2.18 (m, 1 H), 1.73 (br s, 3 H), 1.60–1.40 (m, 2 H), 1.37 (s, 3 H)].

A mixture of the diols **30** (402 mg, 1.17 mmol) was dissolved in 10 mL of benzene containing 500 mg of Celite. Lead tetraacetate (620 mg, 1.4 mmol) was added and stirring continued 20 min. The mixture was diluted with 20 mL of Et_2O and filtered through a silica gel pad. The silica gel was flushed with an additional 200 mL of ether. The filtrate was evaporated to give the formate aldehyde (390 mg, 97%): $[\alpha]_D$ +34.6° (*c* 5.7, $CHCl_3$); IR (neat) 3034, 2928, 2245, 1725, 1454, 1383, 1161, 1047, 739 cm^{-1}; ^1H NMR ($CDCl_3$) 9.62 (s, 1 H), 8.12 (s, 1 H), 7.34 (m, 5 H), 5.35 (dd, J = 8.2, 4.6 Hz, 1 H), 5.25 (br t, J = 6.9 Hz, 1 H), 4.57 (d, J = 11.2 Hz, 1 H), 4.44 (d, J = 11.2 Hz, 1 H), 2.36 (m, 4 H), 2.05 (m, 2 H), 1.75 (m, 2 H), 1.71 (br s, 3 H), 1.37 (s, 3 H); ^{13}C NMR ($CDCl_3$) 202.2, 160.0, 137.4, 132.0, 128.0, 127.4, 127.0, 126.5, 119.1, 82.9, 73.4, 65.9, 28.7, 23.7, 22.2, 15.3, 13.7; HRMS calcd for $C_{19}H_{24}O_3N$ (M − CHO) 314.175576, found 314.174931.

To a solution of the formate aldehyde (390 mg, 1.13 mmol) in 5 mL of EtOH was added $NaBH_4$ (87 mg, 2.3 mmol). The mixture was stirred at room temperature for 30 min. The solution was neutralized with 0.5 N HCl and then extracted with Et_2O. The extract was concentrated and purified by PTLC silica gel (4% $MeOH/CH_2Cl_2$) to give the diol (340 mg, 94%): $[\alpha]_D$ +23.0° (*c* 2.0, $CHCl_3$); IR (neat) 3430, 3032, 2932, 2245, 1453, 1383, 1053, 739 cm^{-1}; ^1H NMR ($CDCl_3$) 7.34 (m, 5 H), 5.32 (br t, J = 7.1 Hz, 1 H), 4.53 (s, 2 H), 3.72 (m, 3 H), 3.02 (br s, 1 H, OH), 2.89 (br s, 1 H, OH), 2.39 (br s, 4 H), 2.31 (m, 1 H), 2.17 (m, 1 H), 1.72 (br s, 3 H), 1.58 (m, 2 H), 1.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) 138.7, 131.5, 128.3, 127.4, 127.3, 119.6, 78.9, 74.8, 64.7, 63.9, 31.1, 27.3, 24.9, 22.6, 16.3, 15.8; HRMS calcd for $C_{19}H_{27}O_3N$ 317.199048, found 317.200052.

The diol (73 mg, 0.23 mmol), imidazole (32 mg, 0.46 mmol), and *tert*-butylchlorodiphenylsilane (110 mg, 0.4 mmol) were dissolved in 2 mL of DMF. After being stirred at 70 °C (30 h), the mixture was partitioned between Et_2O and water. The extract was concentrated and chromatographed on silica gel (0–25% EtOAc/hexane) to give **24** (113 mg, 88%): $[\alpha]_D$ +1.4° (*c* 3.5, $CHCl_3$); IR (neat) 3511, 3071, 2932, 2857, 2245, 1472, 1428, 1111, 824, 741 cm^{-1}; ^1H NMR ($CDCl_3$) 7.66 (m, 4 H), 7.35 (m, 11 H), 5.31 (br t, J = 7.5 Hz, 1 H), 4.55 (d, J = 11.2 Hz, 1 H), 4.48 (d, J = 11.2 Hz, 1 H), 3.76 (m, 3 H), 2.67 (d, J = 5.4 Hz, 1 H), 2.39 (br s, 4 H), 2.31 (m, 1 H), 2.17 (m, 1 H), 1.73 (br s, 3 H), 1.69–1.47 (m, 2 H), 1.22 (s, 3 H), 1.07 (s, 9 H); ^{13}C NMR ($CDCl_3$) 139.3, 135.6, 132.8, 132.7, 131.4, 129.8, 129.7, 128.5, 128.1, 127.7, 127.6, 127.3, 127.2, 127.1, 119.6, 79.1, 74.2, 67.2, 64.4, 31.1, 27.4, 26.8, 24.8, 22.8, 19.1, 16.4, 15.8. Anal. Calcd for $C_{35}H_{45}NO_3Si$: C, 75.63; H, 8.16; N, 2.52. Found: C, 75.47; H, 8.12; N, 2.40.

Single-Crystal X-ray Structure Determination of 8-Benzoate. Crystal data for 8-benzoate $C_{19}H_{25}NO_3$: colorless prismatic crystal, 0.2 × 0.2 × 0.6 mm, monoclinic, space group $P2_1/n$, a = 13.558 (2) Å, b = 5.652 (2) Å, c = 23.441 (3) Å, β = 90.77 (1)°, V = 1796 (1) Å,^{3} and ρ_{calcd} = 1.166 g/cm^3 for Z = 4. Diffraction data: Enraf-Nonius CAD4 automated κ-axis diffractometer, graphite-monochromated Mo radiation ($\lambda(K\bar{\alpha})$ = 0.71073 Å), range $2.0 < 2\theta < 51.0°$ ($\pm h, \pm k, +l$), 3861 reflections (3338 unique, R_i = 0.022, 1371 observed, $I > 2.58\sigma(I)$); corrected for anomalous dispersion, Lorentz and polarization effects, but not for absorption or extinction. Solution: direct methods (SHELXS-86) and difference Fourier syntheses, hydrogen atoms included as fixed contributors in "idealized" positions owing to

the paucity of data. Refinement: anisotropic thermal coefficients for non-hydrogen atoms, isotropic group thermal parameter for hydrogen atoms (SHELX-76). Final: no significant features in the difference Fourier map (range $-0.20 < e/Å^3 < 0.18$); agreement factors, $R = 0.049$ and $R_w = 0.052$.

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Registry No. 1, 66873-39-0; 2, 116726-51-3; 3, 764-32-9; 4, 116808-55-0; 4 (alcohol), 116726-35-3; (±)-5, 116726-37-5; (±)-5 (*t*-BuSiMe$_2$ ether), 116747-43-4; (±)-6, 116784-19-1; (±)-8, 116726-39-7; (±)-8 (ketone), 116726-40-0; (±)-8 (benzoate), 116726-70-6; (±)-8 (*t*-BuSiMe$_2$ ether), 116726-41-1; (±)-8 (aldehyde, *t*-BuSiMe$_2$ ether), 116733-73-4; (±)-9, 116726-38-6; (±)-10, 116726-43-3; (±)-10 (*t*-BuSiMe$_2$ ether), 116726-42-2; (±)-11, 116839-32-8; (±)-11 (bromide), 116726-44-4; (±)-14, 116726-45-5; (±)-14 (sulfoxide, isomer 1), 116726-46-6; (±)-14 (sulfoxide, isomer 2), 116836-81-8; (±)-15 (isomer 1), 116726-47-7; (±)-15 (isomer 2), 116836-82-9; (±)-16, 116726-49-9; (±)-16 (alcohol, isomer 1), 116726-48-8; (±)-16 (alcohol, isomer 2), 116836-83-0; (±)-17, 116836-84-1; (±)-18, 116726-50-2; (±)-19 (isomer 1), 116726-52-4; (±)-19 (isomer 2), 116836-85-2; (±)-20, 116836-86-3; (±)-24, 116726-69-3; 24 (formate aldehyde), 116726-67-1; 24 (diol), 116726-68-2; 25, 35784-67-9; 25 (*t*-BuSiPh$_2$ ether), 116726-53-5; 26, 116726-54-6; 27, 116726-56-8; 27 (dihydro deriv), 116726-57-9; 27 (dihydro aldehyde), 116726-58-0; 28 (isomer 1), 116726-59-1; 28 (isomer 2), 116726-60-4; 29 (isomer 1), 116784-20-4; 29 (isomer 2), 116784-21-5; α-30, 116726-66-0; β-30, 116836-87-4; α-30 (acetonide, *t*-BuSiPh$_2$ ether), 116726-63-7; α-30 (acetonide), 116726-65-9; 31, 116726-64-8; 36, 116726-61-5; 36 (mesylate), 116726-62-6; (±)-$(CH_3)_2C{=}CH(CH_2)_2CH(OH)CH(CH_3)_2$, 116726-32-0; (±)-$(CH_3)_2C{=}CH(CH_2)_2CH(OSiMe_2Bu\text{-}t)CH(CH_3)_2$, 116726-33-1; (±)-(*Z*)-$HO(CH_2)_2C(CH_3){=}CH(CH_2)_2CH(OSiMe_2Bu\text{-}t)CH(CH_3)_2$, 116726-36-4; (±)-(*Z*)-$MSO(CH_2)_2C(CH_3){=}CH(CH_2)_2CH(OSiMe_2Bu\text{-}t)CH(CH_3)_2$, 116747-01-4; $Ph_3P{=}CH_2$, 3487-44-3; $(CH_3)_2C{=}CH(CH_2)_2Br$, 2270-59-9; $Ph_3P{=}CHCO_2Me$, 2605-67-6; $CH_2{=}CBrCH_3$, 557-93-7; 3-(dimethyl-*tert*-butylsiloxy)-2,7-dimethyl-6,7-epoxyoctane, 116726-34-2; 3-*O*-(*tert*-butyldiphenylsilyl)-1,2-isopropylidene-3-*C*-methyl-α-D-ribofuranodialdose, 116726-55-7.

Synthesis of (±)-4-De(3′-hydroxypropionyl)betaenone B, an Advanced Model for the Betaenones and Stemphyloxin I

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A stereocontrolled synthesis of (±)-3, a model for the stereochemically complex naturally occurring phytotoxins 1, 2, and 6, is reported. The synthesis relies upon the steric bias of a cis decalone skeleton for the establishment of appendage stereochemistry. The tricyclic bromo enone 9 prepared in five steps from methoxybenzoquinone was converted in nine steps to the dione 37. Ten additional steps were required to transform 37 to cis decalone 48. As predicted by molecular mechanics calculations, the cis decalone 48 was equilibrated essentially quantitatively to trans decalone 49 on exposure to base. Deprotection of 49 afforded (±)-3, the structure of which was proven by single-crystal X-ray analysis.

In 1983, Ichihara and co-workers reported the isolation and characterization by single-crystal X-ray analysis of the phytotoxin betaenone A (6).[2] Obtained from the same fungal source was the closely related compound betaenone B (1), whose spectroscopic properties were consistent with formulation as shown.[2] In the same year, Clardy and co-workers reported the structure of a closely related phytotoxin of fungal origin, stemphyloxin I (2), whose structure was proven by single-crystal X-ray analysis.[3] The stereochemical density and complexity of these substances renders them challenging targets for total synthesis. A synthesis of a structurally related mycotoxin, diplodiatoxin, has recently been reported by Ichihara et al.[4] We describe herein a conceptually distinct synthetic approach to the phytotoxins 1, 2, and 6.[5] These studies have culminated in the synthesis of (±)-4-de(3′-hydroxypropionyl)betaenone B (3) by an approach that resolves the stereochemical issues surrounding the synthesis of this family.[6]

It has previously been shown that oxidation of betaenone B (1) with PCC followed by exposure to base affords betaenone A (6).[2] As such, we focused our attention at the outset on betaenone B (1) as a synthetic target. The trans decalone skeleton of 1 appeared not particularly attractive as a synthetic cornerstone, since its essentially planar structure lacked the steric bias that would be useful for the stereocontrolled delivery of appendages. In contrast, the corresponding cis decalone (1, H-10α) was of interest, because this skeleton possesses a relatively less sterically encumbered α-face, the face upon which alkyl substituents are required at carbons 2–4, 6, and 8. The synthetic plan, therefore, was to utilize a cis decalone nucleus as a key structural feature, in anticipation of epimerization of C-10

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