An Approach to the Total Synthesis of Aplysiatoxin[1]

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Abstract: An approach to the synthesis of the polyacetate tumor promoter aplysiatoxin is described. The spiroketal framework was convergently constructed in a heteroatom Diels-Alder reaction between an enol ether and a vinyl ketone. The desired spirocenter stereochemistry was obtained by acid-catalyzed isomerization to the less sterically encumbered spiroketal. Subsequent manipulation provided diastereomeric 9-hydroxy derivatives (aplysiatoxin numbering) epimeric at C-15. These spiroketal alcohols were envisaged as key intermediates for attempted introduction of the C-3 lactol, as well as for appendage of the 12-membered bis(lactone). Attempted transannular remote oxidation using the derived C-9 alkoxy radical failed, however, to introduce the lactol. The 9-hydroxy derivatives were efficiently converted into bis(acetones), utilizing the photodeprotection of a nitrobenzyl ether as a key step. Bromination and deprotection afforded both possible C-15 epimers of 3-desoxyaplysiatoxin-20-*O* methyl ether. Circular dichroism spectra of synthetic intermediates provided a means of distinguishing the diastereomer with the natural C-15 stereochemistry. Nuclear Overhauser effect difference spectra on the bis(lactones) showed signal enhancement within the rigid spiroketal framework consistent with those reported for derivatives of the natural product.

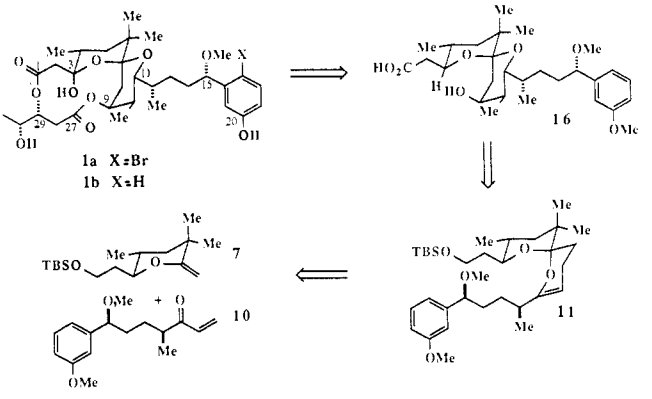
Aplysiatoxin (**1a**) and debromoaplysiatoxin (**1b**) are potent marine toxins isolated from the sea hare *Stylocheilus longicauda* as well as the blue-green algae *Lyngbya majuscula*.[3] Fully characterized only recently, these polyacetates are considered a new class of powerful tumor promoters, comparable in potency with phorbol diesters and teleocidins.[4-6] Our interest in the aplysiatoxins stems from several sources. The novel structure of the aplysiatoxins furnishes the synthetic chemist with an opportunity to explore new methodology in the pursuit of a challenging target.[7a,b] Additionally, the exciting biological activity of the toxins provides a powerful incentive for the development of efficient approaches to the molecular system. Finally, a complete stereochemical assignment of the aplysiatoxins was lacking at the inception of these studies; it was felt that a synthetic effort might elucidate key stereochemical features by furnishing fragments not easily obtained through degradation.

Any approach to the aplysiatoxins must address several fundamental problems. The reported lability of the C-3 hemiketal toward dehydration encourages the introduction of this functionality at a late stage of the synthesis.[4,8a-c] Closure of the 12-membered bis(lactone) may, according to established tenets, represent a troublesome process.[9] Additionally, the axial-equatorial spiroketal configuration represents an anomerically disfavored configuration, which may be difficult to obtain in the absence of the constraining lactone ring.[10a,b]

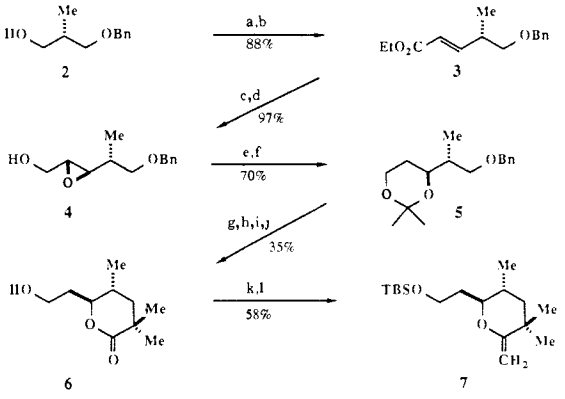
In a retrosynthetic analysis, we envisioned using the preformed spiroketal framework as the basis for introduction fo the C-3 hemiketal and the macrolactone (Scheme I). Disconnection of the bis(lactone) fragmetn and deoxygenation of the C-3 hemiketal provide alcohol **16** as a common precursor. In the forward approach, we proposed to utilize a remote oxidation across the internal cavity of alcohol **16** to functionalize the C-3 position at an advanced stage of the synthesis. The same intermediate would simultaneously contain the requisite functionality to act as a macrolactone precursor.

We proposed to derive spiroketal **16** from spiroketal enol ether **11**. In the transformation of **11** to **16**, equilibration of the spirocenter to the natural configuration would hopefully be accomplished by allowing steric interactions to override the inherent diaxial stereoelectronic bias. Spiroketal enol ether **11** offered a

Scheme I, Retrosynthetic Analysis



Scheme II, Synthesis of Enol Ether **7**[a]



[a] (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) ethyl diisopropyl phosphonoacetate, potassium *tert*-butoxide, THF; (c) Dibal, hexane/Et_2O; (d) (-)-diethyl tartrate, $Ti(O\text{-}i\text{-}Pr)_4$, *tert*-butyl hydroperoxide, CH_2Cl_2; (e) Red-Al, toluene/THF; (f) dimethoxy propane, $TsOH\cdot H_2O$, acetone; (g) Li/NH_3, THF; (h) MsCl, Et_3N, CH_2Cl_2; (i) NaI, acetone, reflux; (j) isobutyric acid dianion, THF; (k) TBSCl, imidazole, DMF; (l) $Cp_2TiCH_2(Cl)AlMe_2$, toluene/THF.

(1) No reprints of this article are available.
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(3) Moore, R. E. *Pure Appl. Chem.* **1982**, *54*, 1919-1934.
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(7) (a) A total synthesis of debromoaplysiatoxin has recently been reported: Park, P.; Broka, C. A.; Johnson, B. F.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 6205-6207. (b) For synthetic studies on the closely related oscillatoxins, see: Walkup, R. D.; Cunningham, R. T. *Tetrahedron Lett.* **1987**, *28*, 4019-4022.
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(9) See, for example: Corey, E. J.; Brunelle, D. J.; Stork, P. J. *Tetrahedron Lett.* **1976**, 3405-3408.
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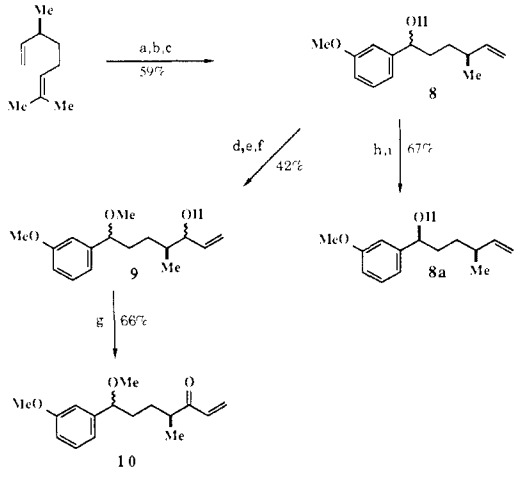
Scheme III, Synthesis of Enone **10**[a]



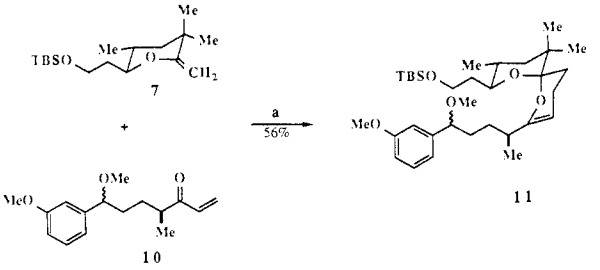
[a] (a) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (b) H_5IO_6, Et_2O; (c) *m*-bromoanisole, Mg, THF; (d) KH, MeI, THF; (c) 1, O_3, MeOH; 2, Me_2S; (f) vinylmagnesium bromide, THF; (g) $(COCl)_2$, DMSO, Et_3N, acrolein, CH_2Cl_2; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (i) (*S*)-2,2′-binaphthol, LAH, EtOH, THF.

logical entry into the spiroketal system. Not only would it provide an olefinic handle to allow necessary functionalization, but it could be convergently constructed via a heteroatom Diels–Alder cycloaddition between enol ether **7** and enone **10**.[11] The two starting materials, in turn, would derive from the "chiral pool."

The synthesis of enol ether **7** began with diol monobenzyl ether **2**, which was prepared in enantiomerically pure form from commercially available methyl (2*S*)-3-hydroxy-2-methyl propionate[12] (Scheme II). Oxidation of alcohol **2** by the method of Swern and Omura,[13] followed by treatment with ethyl triphenylphosphoranylideneacetate, led to a nearly quantitative yield of the trans unsaturated ester **3** but in only 70% enantiomeric excess (ee), judging by the optical rotation reported for the enantiomer.[14] A combination Swern–Wittig procedure reported by these laboratories gave similar results.[15] A Horner–Emmons reaction between the enantiomeric aldehyde and the potassium salt of ethyl diisopropyl phosphonoacetic acid ester has been reported to proceed without epimerization.[14] In our hands this alternative olefination proceeded in good yield but in only 80% ee. A modified Horner–Emmons procedure employing lithium chloride has been reported to minimize epimerization of chiral aldehydes;[16] however, when applied to our system, this method afforded the ester **3** in less than 50% ee. At this point, we elected to utilize the simple Horner–Emmons reaction and carry on ester **3** as a 90:10 mixture of enantiomers.

Ester **3** was reduced to the corresponding allylic alcohol with diisobutylaluminum hydride (Dibal). Sharpless asymmetric epoxidation provided epoxy alcohol **4** in high yield as a 90:10 mixture of diastereomers, implying that the epoxidation had proceeded with complete stereospecificity.[17] Reduction of this epoxy alcohol with sodium bis(2-methoxyethoxy)aluminum dihydride (Red-Al, Aldrich) afforded the 1,3-diol as the only detectable product.[18] The crude diol was directly protected with dimethoxypropane in acetone to afford acetonide **5** in good yield as a 90:10 mixture of diastereomers.

Scheme IV, Heteroatom Diels–Alder[a]



[a] (a) 4-Hydroxy TEMPO, 110 °C, 48 h.

Removal of the benzyl ether of **5** with a dissolving metal reduction provided a nearly quantitative yield of the corresponding alcohol. On a smaller scale, we had removed the benzyl ether with catalytic hydrogenation; however, on a large scale, we found that hydrogenolysis with 10% palladium on carbon led to significant equilibration of the acetonide within the 1,3,5-triol system.

The alcohol derived from **5** reacted with methanesulfonyl chloride (MsCl) to form the corresponding mesylate, which was displaced by iodide. Alkylation of isobutyric acid dianion with the crude iodide afforded hydroxy lactone **6** upon acidification.[19] Following protection of the hydroxyl group as the *tert*-butyldimethylsilyl ether (TBS), reaction of the lactone with the Tebbe reagent afforded the acid-labile enol ether **7**.[20,21a,b]

Synthesis of the enone component of the heteroatom Diels–Alder began with (*S*)-citronellene (Scheme III). Selective epoxidation of the trisubstituted olefin with *meta*-chloroperbenzoid acid (*m*-CPBA), followed by periodate cleavage of the epoxide, transformed the more substituted olefin into an aldehyde.[22] Addition of the Grignard reagent derived from *m*-bromoanisole furnished a 1:1 diastereomeric mixture of benzylic alcohols **8**. Although the mixture of epimers generated at the benzylic position of **8** was carried through the remainder of these studies, we desired to demonstrate that this alcohol could be prepared diastereomerically pure. Swern oxidation of the mixture of alcohols **8**, followed by asymmetric reduction of the resulting alkylphenone with a (*S*)-binaphthol–LAH complex, afforded a good yield of the (*S*)-benzyl alcohol, **8a**, in greater than 95% ee.[23] The enantiomeric excess was determined by comparison of the high-field proton NMR spectra of the α-methoxy-α-(trifluoromethyl)-phenylacetate (MTPA) esters formed from both **8a** and **8**.[24] The absolute stereochemistry in **8a** was assigned by precedent to other binaphthol-mediated reductions of alkylphenones.

After methylation of the mixture of alcohols **8**, the terminal olefin was cleaved with ozone. Reaction of the resultant aldehyde with vinylmagnesium bromide afforded allylic alcohols **9**. These allylic alcohols were then oxidized to a mixture of diastereomeric enones **10** by using a modified Swern procedure, in which acrolein was added as a scavenger for the liberated methyl sulfide. The moderate yield of the oxidation reflects, in part, the purification employed to ensure success in the ensuring Diels–Alder reaction.

In a key step, when a 50% excess of the diastereomeric mixture of enones **10** was heated at 110 °C in a sealed tube for 48 h with enol ether **7**, a 56% yield of the desired spiroketal enol ether **11** was formed, accompanied by substantial quantities of recovered enol ether and dimerized/oligomerized enone (Scheme IV). It was found advantageous to add a small amount of (4-hydroxy-2,2,6,6-tetramethylpipiridinyl)oxy free radical (4-hydroxy TEM-

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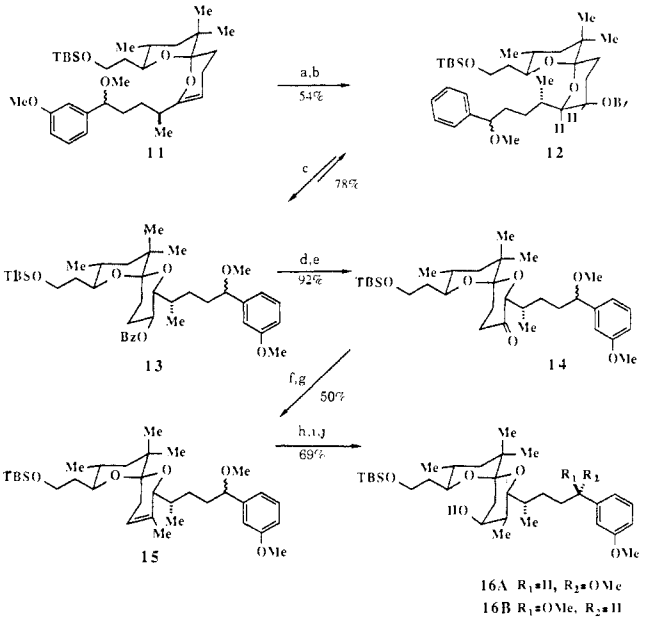
Scheme V, Synthesis of Alcohols **16A,B**[a]



[a](a) 1, BH_3·THF, THF; 2, H_2O_2, NaOH; (b) BzCl, DMAP; (d) $HCl/CHCl_3$; (d) LAH, THF; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (f) 1, $KN(TMS)_2$, THF; 2, Tf_2NPh; (g) Me_2CuLi, Et_2O; (h) 1, BH_3·THF, Et_3N, THF; 2, H_2O_2, NaOH; (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (j) K-Selectride, THF.

PO) to the reaction; in the absence of this additive, the amount of enone-derived byproducts was greatly increased. Use of only 1 equiv of enone led to a greater recovery of unreacted enol ether **7** and a lower yield of **11**.

Hydroboration of the diastereomeric spiroketal enol ethers **11** produced in the Diels–Alder cyclization afforded a mixture of axial alcohols, which were converted to benzoate esters **12**[25] (Scheme V). The exo-face hydroboration not only introduced necessary functionality but provided the steric strain required for the isomerization of **12** to **13**. The spiroketal isomerization is driven by steric strain and opposed by stereoelectronic bias. Focusing solely on steric and electronic interactions directly involved in the transformation, we can quantify individual effects by using the analysis developed by Deslongchamps.[10a] Spiroketal **12** has each spiroketal oxygen antiperiplanar to the opposite C–O linkage, electronically stabilizing this isomer by −2.8 kcal (2 × −1.4). However, the hydroboration introduced approximately 3 kcal of steric strain by forcing the isopropyl-like side chain into a diaxial relationship with the spiroketal oxygen. Additionally, each axial spiroketal oxygen forms part of two gauche *n*-propyl ether units, sterically destablizing the spiroketal by +1.6 kcal (2 × 2 × 0.4). Finally, the axial benzoate has a single gauche interaction with a methylene unit (+0.4 kcal). The Deslongchamps analysis on this isomer predicts a relative energy of approximately +2.2 kcal for this isomer.

The isomerization product, **13**, contains only one oxygen antiperiplanar to the anomeric C–O linkage (−1.4 kcal). While there is only one axial oxygen involved in gauche interactions (+0.8 kcal), the isomerization introduces a new source of gauche strain from the axial methylene (+1.6 kcal, 2 × 0.8). The newly equatorial benzoate and aromatic side chain will have a gauche relationship as well (+0.4 kcal). The predicted relative energy for isomer **13** is +1.4 kcal; spiroketal **13** should therefore be favored by approximately +0.8 kcal.

Treatment of the benzoates **12** with strong acid resulted in a room temperature equilibrium favoring the isomerized spiroketals **13** by a 70;30 ratio. The isomerization could be followed either by TLC or by the disappearance of the signal from the equatorial benzoate proton at 5.1 ppm and the emergence of a signal from the axial benzoate proton at 4.9 ppm in the proton NMR spectrum. Isomerizations were performed on the benzoates to circumvent the undesired formation of a 6,5-spiroketal, which occurred upon attempted equilibration in the presence of the free alcohol. Anhydrous HCl in chloroform was found to be an optimum system for promoting isomerization while avoiding extensive desilylation. Diethylaluminum chloride was a weaker, although selective, isomerization catalyst. Titanium tetrachloride, aluminum trichloride, and toluenesulfonic acid tended to promote an unacceptable degree of desilylation.

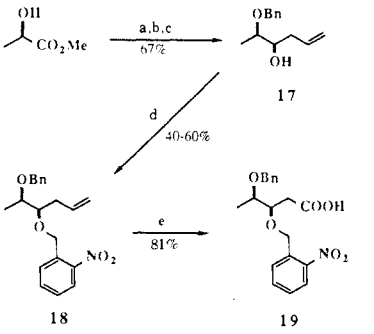
The isomerized spiroketals **13** were treated with LAH to cleave the benzoate esters. The free alcohols were then oxidized to the ketones **14**. Regioselective low-temperature enolization with potassium hexamethyldisilazide, followed by trapping with *N*-phenyl triflimide (Tf_2NPh), afforded an excellent yield of the enol trilfates.[26] The enol triflates were coupled with lithium dimethyl cuprate to produce diastereomeric methyl olefins **15**.[27]

Hydroboration of **15** proved to be problematic. BH_3·Me_2S or BH_3·THF consumed the starting olefin but provided low yields of product under normal reaction conditions, while the more hindered 9-BBN gave no reaction even at elevated temperatures. However, the use of excess BH_3·THF in the presence of Et_3N gave a good yield of the equatorial alcohols. Swern oxidation, followed by stereoselective reduction with K-Selectride (Aldrich), provided axial alcohols **16A** and **16B**, which were separable by chromatography.[28] All subsequent reactions were performed on the individual diastereomers.

In order to ascertain whether **16A** or **16B** represented the material with the natural configuration at the C-15 methyl ether, we resorted to circular dichroism spectroscopy (CD). Alcohol **16A** exhibited a positive ellipticity between 260–280 nm in the CD spectrum, while **16B** exhibited a mirror image negative ellipticity over the same spectral region. Because debromoaplysiatoxin has been shown to have a positive ellipticity in the 269–280-nm region, we believe **16A** to represent the "natural" fragment.[4]

At this time, we required the fragment that would ultimately form the bis(macrolactone) (Scheme VI). As a method of deriving the vicinal *syn*-diol unit, we opted for the addition of allyltrimethylsilane to a chiral α-alkoxy aldehyde.[29a,b] Benzylation of commercially available (*R*)-methyl lactate was followed by Dibal reduction to provide the requisite aldehyde.[30,31] $SnCl_4$-mediated addition of allyltrimethylsilane afforded the homoallylic alcohol **17** as a 95:5 mixture of diastereomers, which was easily separable by chromatography.[29a] NMR analysis of the Mosher

Scheme VI. Synthesis of Side Chain Acid **19**[a]



[a](a) BnBr, Ag_2O, Et_2O; (b) Dibal, hexane/Et_2O; (c) $SnCl_4$, allyltrimethylsilane, CH_2Cl_2; (d) *o*-nitrobenzyl bromide, BaO, $Ba(OH)_2$, DMF; (e) $KMnO_4$, $NaIO_4$, *tert*-Butyl alcohol/H_2O.

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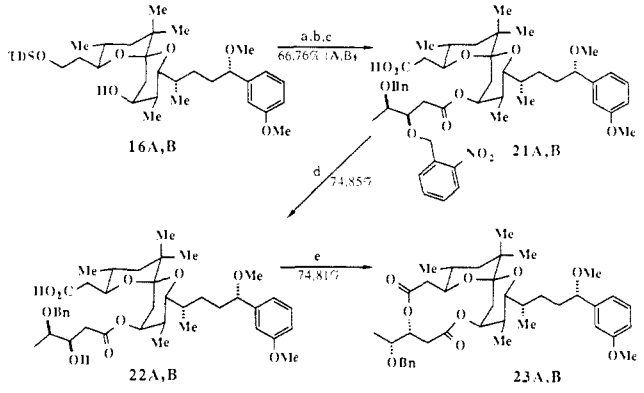
Scheme VII, Formation of the Macrolactones[a]



[a] (a) Acid **19**, DCC, DMAP, DMAP·HCl, CH_2Cl_2; (b) HOAc/THF/H_2O; (c) Jones reagent, acetone; (d) $h\nu > 350$ nm; (e) DCC, DMAP, DMAP·HCl, $CHCl_3$.

ester derived from the major diastereomer of **17** showed little, if any, enantiomeric impurity.[24]

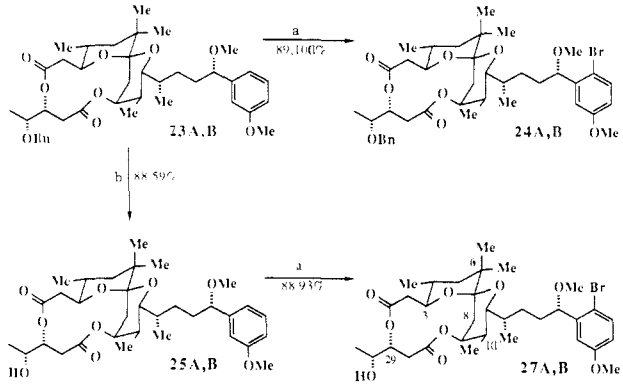
We now required a protecting group for the homoallylic alcohol that could be selectively unmasked late in the synthesis. Initial studies demonstrated that a trichloroethylcarbonate was too fragile, while methoxymethyl and *tert*-butyldiphenylsilyl ethers proved overly robust.[32-34] We elected to investigate an *ortho*-nitrobenzyl ether, since the photochemical method of removal for this moiety was orthogonal to the remainder of our protection scheme.[35]

Photolabile nitrobenzyl ethers have seldom been used as a protecting group for noncarbohydrate alcohols, and we were unable to alkylate **17** under reported conditions.[35,36a,b] Because of the acidity of the benzylic protons, all attempted alkylations involving generation of the alkoxide of **17** led to decomposition of the nitrobenzyl bromide. Silver(I)-assisted alkylations using either the nitrobenzyl bromide or iodide also proved fruitless. However, upon employing a capricious variation of the conditions developed by Paulsen and Lockhoff for carbohydrate benzylation, we were able to achieve moderate yields of the *ortho*-nitrobenzyl ether **18**.[37] Permanganate cleavage of the vinyl group then afforded carboxylic acid **19**.[38]

With the desired fragment in hand, we resumed our approach to the macrolactones (Scheme VII). Attempted esterifications of alcohols **16A** or **16B** with the acid chloride or trifluoroacetic anhydride of acid **19** were unsuccessful. However, esterification of acid **19** with **16A** or **16B** using DCC, DMAP, and DMAP·HCl afforded esters **20A** or **20B** in excellent yield.[39] (For the sake of clarity, only the natural **A** series is drawn.) Solvolysis of **20A** or **20B** with acetic acid/THF/H_2O cleanly removed the silyl protecting group and gave the primary alcohols.[20] Chromic acid oxidation of the alcohols provided the acids **21A** or **21B** in high yield.[40] Photolysis of acids **21A** or **21B** with UV light filtered at 356 nm resulted in clean photodeprotection of the nitrobenzyl ether and afforded good yields of hydroxy acids **22A** or **22B**.

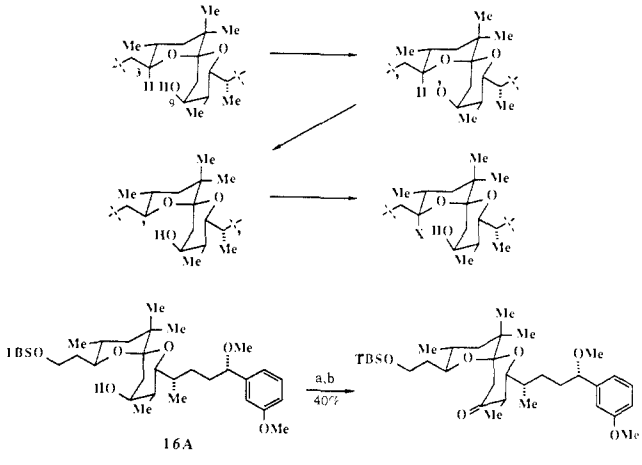
In light of the admirable performance of the modified DCC methodology during the earlier esterification, we decided to employ the same procedure as our initial approach to the macrocyclization. After slowing adding a solution of **22A** or **22B** into a heated

Scheme VIII, Elaboration of the Macrolactones[a]



[a] (a) Br_2, $NaHCO_3$, CH_2Cl_2; (b) H_2, Pd/C, EtOH.

Scheme IX, Attempted Remote Oxidation



[a] (a) NOCl, pyridine; (b) $h\nu > 300$ nm.

solution of DCC, DMAP, and DMAP·HCl in chloroform, we were pleasantly surprised to isolate good yields (74–81%) of macrolactones **23A** or **23B**. Mass spectral analysis showed no sign of dimeric products. Because the cyclizations to form **23A** or **23B** are considerably more efficient than the lactonization of 11-hydroxyundecanoic acid cited as an example by Boden and Keck, we concluded that the rigid spiroketal backbone greatly facilitated the cyclizations.[39]

We now endeavored to explore the chemistry of these macrolactones. Bromination of **23A** or **23B** cleanly provided bromoanisoles **24A** or **24B** (Scheme VIII). Although spectral verification of the bromination regiochemistry was difficult, the work of Nelson and Uschak on Friedel–Crafts bromination of *meta*-alkylanisoles provided a good precedent for bromination para to the activating methoxy group.[41] Hydrogenolytic removal of the benzyl ether protecting group was slow for both **23A** and **23B**. While **23A** deprotected cleanly to alcohol **25A, 23B** furnished a mixture of the desired alcohol **25B** along with a byproduct resulting from concomitant hydrogenolysis of the benzylic methyl ether. Ethanol appeared to be an ideal solvent for this reaction. No reaction occurred in ethyl acetate, while a mixture of ethyl acetate and acetic acid promoted extensive formation of the demethoxylated byproduct. The alcohols **25A** and **25B** were cleanly brominated as before to afford bromoanisoles **27A** and **27B**, representing the natural and unnatural C-15 epimers of 3-desoxyaplysiatoxin methyl ether.

Nuclear Overhauser effect (NOE) difference spectra were obtained on compound **27A**, presumably 3-desoxyaplysiatoxin methyl ether.[42] Irradiation of the equatorial C-6 methyl led, as

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in the natural product, to an enhancement of the signal for the axisl C-8 hydrogen, whereas irradiation of the axial C-6 methyl gave no detectable enhancement in the difference spectra. Irradiation of the equatorial C-8 hydrogen led to an enhancement of the signal for the C-3 hydrogen; this corresponds to the enhancement of the C-3 lactol hydrogen observed in aplysiatoxin. Irradiation of the equatorial C-10 methyl group in **27A** resulted in the expected enhancements of the signals for the C-9 and C-11 hydrogens. However, the NOE observed in aplysiatoxin between the C-10 methyl and the C-29 lactone hydrogen could not be observed in **27A** because of the overlap of the signals for the C-9 and C-29 hydrogens. Because the NOE enhancement is inversely proportional to internuclear distance, the large NOE to C-9 might overshadow a smaller NOE to the more distance C-29 hydrogen. Accordingly, we acquired NOE difference spectra on **24A**, which did not suffer from overlap of the signals from the C-29 and C-9 hydrogens. No significant NOE between the C-10 methyl and C-29 hydrogen could be observed, implying that the conformations of the bis(lactones) in **24A** and aplysiatoxin are different. This is not overly surprising, given the substitution of a hydrogen and a benzyl ether in **24A** for the C-3 lactol and C-30 hydroxyl, respectively, of aplysiatoxin.

At this time, we turned our attention to deprotection of the aryl methyl ether. Treatment of macrolactone **23A** with either lithium iodide or sodium thiophenoxide in DMF at 140 °C efficiently produced the hydroxy acid resulting from bis(lactone) cleavage.[43-45] Model studies quickly demonstrated that the minimal conditions for nucleophilic demethylation were incompatible with the bis(lactone) linkage. An alternate strategy involving Lewis acid deprotection also met with failure. Treatment of models with boron tribromide, boron triiodide, or dimethylboron bromide led to rapid halide displacement of the benzylic methoxyl group.[33,46,47] Boron triiodide also removed the phenol methyl ether after prolonged reaction periods. Low-temperature reaction of macrolactone **23A** with boron triiodide gave no phenolic products but rather an epimeric mixture of benzylic iodides, as well as products resulting from removal of the C-30 benzyl ether.

The advanced spiroketal intermediates **16A** and **16B**, apart from their importance as macrolactone precursors, represented the requisite platforms for the remote functionalization of C-3. (Scheme IX) The distance from the C-9 oxygen to C-3, as measured from models, was 2.8–2.9 Å. On the basis of precedents in steroid chemistry, this distance was expected to be within the allowable range for intramolecular hydrogen atom transfer to an alkoxy radical.[48] Although the hydrogen would not be abstracted through a six-membered cyclic transition state, ample precedent exists for alkoxy radical abstractions that do not fit this classic model.[49a,b] We hoped to functionalize C-3 with a hypohalite-mediated remote oxidation, because this would directly yield a labile haloalkyl ether, which could easily be converted to either the desired lactol or a protected equivalent. However, attempted oxidation of **16A** with silver carbonate/bromine, lead tetraacetate, or lead tetraacetate/iodine, gave no products attributable to a C-9 alkoxy radical; instead, these reagents either oxidized the aromatic side chain, cleaved the silyl ether, or both.[50,51]

In order to test our remote functionalization in a more easily interpretated system, we attempted a Barton oxidation.[52] We had not originally intended to employ the Barton protocol because the nitrosoalkyl adduct formed through trapping of a C-3 radical would not be easily amenable to subsequent functionalization. However, the Barton procedure represented an opportunity to preform a species that would cleanly deliver an alkoxy radical upon demand. Treatment of alcohol **16A** with nitrosyl chloride in pyridine furnished the nitrite ester, which was used immediately. Photolysis at 300 nm quickly led to complete disappearance of the nitrite ester. The only major product isolated upon workup, however, was easily identified as the ketone precursor of alcohol **16A**. The predominant formation of this ketone indicates either the disfavored nature of the desired hydrogen abstraction, the instability of the initially produced alkoxy radical, or both.[49a,53]

In conclusion, we have demonstrated an efficient spiroketal-based entry into the desoxyaplysiatoxin manifold. Further investigations are currently being directed toward modification of this sequence so as to arrange for the formation of the hemiketal at C-3 and removal of a different phenol blocking group.

Experimental Section

Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. High-resolution mass spectra were performed by the Mass Spectroscopy Laboratory, University of California at Riverside. The NSF Southern California Regional facility was the source of 500-MHz NMR spectra.

(2*S*)-3-(Benzyloxy)-2-methylpropanol (2) was prepared from methyl (*S*)-2-methyl-3-hydroxypropionate (four steps, 83% yield) by the procedure of Meyers and Hudspeth:[12] $[\alpha]_D$ −17.4° (*c* 1.4); literature values for the enantiomer $[\alpha]_D$ +17.2°, all other spectral properties were satisfactory.[14]

(2*E*,4*S*)-Ethyl 5-(benzyloxy)-4-methyl-2-pentenoate (3) was prepared from **2** according to the procedure of Nagaoka and Kishi in 88% overall yield.[14] A specific rotation of −13.1° (*c* 2.5, $CHCl_3$) was observed, in contrast to a literature value of +15° reported for the opposite enantiomer. In the ^1H NMR spectrum, the olefinic signals reported at δ 5.33 were observed at 5.76 (dd, 1 H, *J*, *J'* = 15, 1.5 Hz).

(2*E*,4*S*)-5-(Benzyloxy)-4-methyl-2-pentenol. To a mechanically stirred −78 °C solution of 60.0 g (244 mmol) of ester **3** in 500 mL of Et_2O were added 610 mL of nominally 1 M diisobutylaluminum hydride (Dibal)/hexane at a rate such that the internal reaction temperature did not rise above −70 °C. After 2 h, the reaction mixture was allowed to warm to ambient temperature and stirred for an additional 2 h. The reaction mixture was then recooled to 0 °C and quenched by the dropwise addition of 40 mL of reagent-grade MeOH. The resulting solution was decanted into 1 L of rapidly stirring 0.5 M aqueous sodium potassium tartrate and diluted with an additional 500 mL of the tartrate solution. The resulting emulsion was stirred until clear (3 h) and diluted with 500 mL of petroleum ether. After the phases were separated, the aqueous phase was extracted with two 500-mL portions of EtOAc, and the combined organic phases were dried ($MgSO_4$). Concentration under reduced pressure, followed by flash chromatography on 700 g of silica gel with 30% EtOAc/petroleum ether, afforded 50.3 g (quantitative) of the allylic alcohol as a colorless oil: all spectral data were consistent with the reported values with the exception of the specific optical rotation of −8.3 (*c* 1.6, $CHCl_3$); a value of +9.9° was reported for the opposite enantiomer.[14]

(2*R*,3*R*,4*R*)-5-(Benzyloxy)-2,3-epoxy-4-methylpentanol (4) was prepared from the allylic alcohol (50.8 g 247 mmol) by Sharpless asymmetric epoxidation.[17] Chromatography on 700 g of silica gel with 40% EtOAc/petroleum ether afforded 53.3 g (98%) of a 9:1 mixture of diastereomeric epoxy alcohols **4** as a colorless oil: R_f 0.25 (40% EtOAc/petroleum ether); bp 90–95 °C (0.07 mmHg); IR 3600–3100, 3120, 2980, 2850, 1730, 1440, 1370, 1080, 900, 750, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (br s, 5 H), 4.59 (s, 2 H), 3.80 (br d, 1 H, *J* = 12 Hz), 3.63 (dd, 1 H, *J*, *J'* = 5, 4 Hz), 3.45 (dd, 2 H, *J*, *J'* = 8, 5 Hz), 3.04 (dt, 0.1 H, *J*, *J'* = 5, 3 Hz), 3.0 (dt, 0.9 H, *J*, *J'* = 5, 2 Hz), 2.96 (dd, 0.9 H, *J*, *J'* = 7, 2 Hz), 2.90 (dd, 0.1 H, *J*, *J'* = 7, 2 Hz), 1.80 (apparent septet, 1 H, *J* = 6 Hz), 1.72 (m, 1 H), 1.07 (d, 3 H, *J* = 8 Hz). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.33; H, 8.06.

(4*S*)-4-[(1*R*)-2-(Benzyloxy)-1-methylethyl]-2,2-dimethyl-1,3-dioxane (5), To a stirred 0 °C solution of 52.3 g (236 mmol) of epoxy alcohols **4** in 500 mL of THF were added 92 mL of nominally 3.4 M $Na_2H_2Al(OCH_2CH_2OMe)_2$ (Red-Al)/toluene at a rate such that the internal reaction temperature did not rise above +5 °C. After 3 h, an additional 20 mL of Red-Al solution were added. The reaction mixture was stirred for 5 h and then quenched by the addition of 50 mL of reagent-grade MeOH. The reaction mixture was poured into 1 L of H_2O, and the resulting emulsion was acidified to pH 3 (methyl orange

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(53) An alternate approach to C-3 functionalization involving allylic oxidation of either the aldehyde or the silyl enol ether derived from the hydroxyethyl sidechain also failed under a variety of conditions.

endpoint) with 1 N HCl. The emulsion was diluted with 500 mL of petroleum ether, and the phases were separated. The aqueous phase was extracted with three 500-mL portions of EtOAc, and the organic phases were, in two portions, washed with 500 mL of saturated aqueous NaCl. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford 52.4 g of a yellow oil, which was used without further purification: R_f 0.19 (40% EtOAc/petroleum ether); IR 3600–3200, 2980, 2960, 2850, 1450, 1360, 1150 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.26 (br s, 5 H), 4.45 (s, 2 H), 4.05–3.65 (m, 3 H), 3.50 (d, 2 H, J = 6 Hz), 3.20 (br d, 1 H, J = 5 Hz), 2.73 (br t, 1 H, J = 4 Hze, 2.0–1.55 (m, 3 H), 0.94 (d, 3 H, J = 7 Hz).

To a 0 °C stirred solution of the above diol in 400 mL of reagent-grade acetone were added 450 mg of $TsOH·H_2O$ and 150 mL of dimethoxypropane, and the resulting solution was allowed to warm to ambient temperature. After 12 h the solution was poured into 500 mL of pentane/200 mL of saturated aqueous $NaHCO_3$, and the phases were separated. The aqueous layer was washed with 300 mL of pentane and 300 mL of EtOAc. The combined organic layers were washed with two 200-mL portions of saturated aqueous $NaHCO_3$ and dried (Na_2SO_4). Concentration under reduced pressure, followed by flash chromatography on 800 g of silica gel with 7.5% EtOAc/petroleum ether, afforded 44.0 g (70%, two steps) of the acetonide **5** as a 9:1 mixture of diastereomers. Chromatography on silica gel with 2% Ether/CH_2,cl_2 resolved small quantities of the individual diastereomers. The minor diastereomer was initially eluted: R_f 0.17 (2% ether/CH_2,cl_2); IR 2980, 2960, 2850, 1370, 1360, 1200, 1105, 960, 740, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32m (br s, 5 H), 4.487 (s, 2 H), 3.935 (dt, 1 H, J, J' = 3, 11 Hz), 3.93 (m, 1 H), 3.835 (ddd, 1 H, J, J', J'' = 12, 6, 2 Hz), 3.460 (abx, 1 H, J, J' = 9.5, 6 Hz, $\Delta\upsilon$ = 61.4), 3.338 (abx, 1 H, J, J' = 9.5, 5.5 Hz, $\Delta\upsilon$ = 61.4), 1.73 (m, 1 H), 1.683 (m, 1 H), 1.427 (s, 3 H), 1.41 (m, 1 H), 1.355 (s, 3 H), 0.960 (d, 3 H, J = 6.9 Hz). There was then eluted the major diasteromer: R_f 0.15 (2% ether/CH_2Cl_2); bp 85–90 °C (0.005 mmHg); $[\alpha]_D$ +25.9° (c 1.07, $CHCl_3$); IR, same as minor isomer; ^1H NMR (500 MHz) δ 7.32 (br s, 5 H), 4.513 (ab, 1 H, J = 12.1 Hz, $\Delta\upsilon$ = 18.5), 4.47 (ab, 1 H, J = 12.1 Hz, $\Delta\upsilon$ = 18.5), 3.94 (dt, 1 H, J = 3, 12 Hz), 3.83 (m, 2 H), 3.483 (abx, 1 H, J, J' = 9.1, 4.8 Hz, $\Delta\upsilon$ = 30.4), 3.419 (abx, 1 H, J, J' = 9.1, 6 Hz, $\Delta\upsilon$ = 30.4), 1.83 (m, 1 H), 1.60 (m, 2 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 0.945 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.70; H, 9.17.

(4*S*)-4-[(1*R*)-2-Hydroxy-1-methylethyl]-2,2-dimethyl-1,3-dioxane. To a solution of Li ribbon (454 mmol) in 600 mL of liquid NH_3 was added acetonide **5** (58.5 g, 222 mmol) in 220 mL of THF. After the solution was stirred for 40 min, the reaction was quenched by the slow addition of 12.1 g of granular NH_4Cl. A water bath was placed underneath the reaction vessel, and the NH_3 was distilled off while 600 mL of ether were gradually added to replace the lost volume. After the greater part of the NH_3 was removed, 400 mL of 5% aqueous Na_2CO_3 were added, and the phases were separated. The aqueous phase was extracted with two 500-mL portions of the EtOAc, and the combined organic layers were washed with 100 mL of saturated aqueous NaCl. Drying (Na_2SO_4) and concentration under reduced pressure furnished a colorless oil, which was filtered through 200 g of silica gel with 60% EtOAc/petroleum ether to afford 37.2 g (97.1%) of the acetonide alcohol as a colorless oil. The specific rotation was measured on a sample provided by separate debenzylation of the pure major diastereomer of **5**: R_f 0.25 (40% EtOAc/petroleum ether); bp 70–75 °C/(0.007 mmHg); $[\alpha]_D$ +13.2° (c 1.1, $CHCl_3$); IR 3400, 2980, 1370, 1190, 1090 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.1–3.8 (m, 3 H), 3.59 (br d, 2 H, J = 6 Hz), 3.0 (m, 1 H), 1.8–1.5 (m, 3 H), 1.45 (s, 3 H), 1.36 (s, 3 H), 0.90 (d, 3 H, J = 6 Hz). Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.86; H, 10.35.

(5*R*,6*S*)-6-(2-Hydroxyethyl)-3,5,5-trimethyltetrahydro-2(*H*)-pyran-2-one (6). To a stirred −25 °C ($EtOH/H_2O$) solution of 37.2 g (215 mmol) of the above hydroxy acetonide and 93.2 mL of Et_3N in 450 mL of CH_2Cl_2 was added 25.5 mL (334 mmol) of methanesulfonyl chloride (MsCl) dropwise. After the addition was complete, the reaction mixture was warmed to 0 °C and stirred for 1 h. The solution was then decanted into 300 mL of 5% aqueous Na_2CO_3 and shaken vigorously. The separted organic layer was washed with two 100-mL portions of 5% aqueous Na_2CO_3 and 100 mL of saturated aqueous $NaHCO_3$. The aqueous layer was washed with 200 mL of EtOAc, which was in turn washed with two-100 mL portions of saturated aqueous $NaHCO_3$. The combined organic layers were dried ($Na_2SO_4/NaHCO_3$) and concentrated under reduced pressure to give 57.1 g of a yellow oil. Attempts to purify an analytical sample resulted in decomposition and the crude methanesulfonate was used without further purification: R_f 0.36 (40% EtOAc/petroleum ether); IR 2980, 2960, 2930, 2870, 1730, 1460, 1350, 1170, 970, 910 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.35 (dd, 1 H, J' = 6, 2 Hz), 4.24 (t, 1 H, J = 5.5 Hz), 3.75–3.4 (m, 3 H), 3.03 (s, 3 H), 2.1 (m, 1 H), 1.83 (dd, 1 H, J, J' = 8, 5 Hz), 1.65 (m, 1 H), 1.45 (s, 3 H), 1.36 (s, 3 H), 0.80 (d, 3 H, J = 7 Hz).

To a solution of the methanesulfonate in 400 mL of reagent-grade acetone were added 66.0 g (440 mmol) of NaI, and the resulting suspension was refluxed for 6 h. The cooled reaction mixture was poured into 400 mL of petroleum ether and washed with 400 mL of 1:1 H_2O/saturated aqueous $NaHCO_3$. The separated organic phase was washed with two 200-mL portions of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 200 mL of EtOAc, and the organic wash was in turn washed with two 100-mL portions of saturated aqueous $NaHCO_3$. The combined organic layers were dried ($Na_2SO_4/NaHCO_3$) and concentrated under reduced pressure while protected from light. The crude iodide, a viscous oil that solifidied during storage at −20 °C, was filtered through silica gel with ether and was used without further purification: R_f 0.45 (33% ether/petroleum ether); IR 2960, 1680, 1460, 1370, 1250, 1170, 1110, 1060 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.83 (dd, 2 H, J, J' = 6, 4 Hz), 3.60 (s, 1 H), 3.50 (dd, 2 H, J, J' = 8, 5 Hz), 3.30 (d, 0.5 H, J = 3 Hz), 3.15 (br s, 0.5 H), 1.7–1.5 (m, 2 H), 1.8 (s, 3 H), 1.4 (s, 3 H), 0.93 (d, 3 H, J = 7 Hz).

To a stirred 0 °C solution of 44.2 mL (315 mmol) of $HN(i\text{-}Pr)_2$ in 325 mL of THF were added 133 mL of 2.22 M n-BuLi/hexane dropwise. After 50 min, 13.7 mL (147 mmol) of isobutyric acid was added slowly, raising the temperature to 25 °C. Cooling was discontinued, and the reaction was stirred at ambient temperature for 3 h. The solution was then recooled to 0 °C, and the above iodide was added by double-needle transfer in 20 mL of THF. Immediate formation of precipitate was observed. An additional 20-mL portion of THF was used to add the last of the iodide. After 30 min, the reaction was quenched by the addition of 300 mL of H_2O to yield a pH 10 solution, which was washed with two 300-mL portions of petroleum ether. The organic washes were back-extracted with two 100-mL portions of 10% aqueous NaOH. The combined aqueous layers were acidified to approximately pH 1 with 6 N HCl and extracted with three 200-mL portions of EtOAc. The combined EtOAc extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield a yellow oil, which was chromatographed on 350 g of silica gel with 50% EtOAc/petroleum ether to afford 13.51 g (35%, three steps) of hydroxy lactone **6** as a colorless oil. The optical rotation was measured on a diastereomerically pure sample, which had been carried forward separately from the major diastereomer of acetonide **5**: R_f 0.15 (40% EtOAc/petroleum ether); bp 100–110 °C (0.005 mmHg); $[\alpha]_D$ −47.4° (c 0.78, $CHCl_3$); IR 3600–3400, 1730–1700, 1450, 1380, 1280, 1140, 1040, 1010, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.32 (m, 2 H), 3.62 (dt, 1 H, J, J' = 9, 5) 2.8 (m, 1 H), 1.85 (m, 1 H), 1.78 (m, 1 H), 1.71 (s, 2 H), 1.22 (s, 3 H), 1.17 (s, 3 H), 0.98 (d, 3 H, J = 4 Hz). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.34; H, 9.57.

(5*R*,6*S*)-6-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-3,5,5-trimethyltetrahydro-2(*H*)-pyran-2-one. To a stirred solution of 23.7 g (132 mmol) of hydroxyl lactone **6** and 26.9 g (395 mmol) of imidazole in 150 mL of DMF were added 29.8 g (198 mmol) of *tert*-butyldimethylsilyl chloride (TBSCl) in small portions. The reaction mixture was stirred overnight and then decanted into 300 mL of ether. The solution was washed with 200 mL of saturated aqueous NH_4Cl/100 mL of H_2O, and the aqueous wash was back-extracted with 100 mL of ether. The combined organic layers were washed, sequentially, with 300 mL of H_2O and two 200-mL portions of saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to furnish a yellow oil, which was flash chromatographed to 500 g of silica gel with 9% EtOAc/petroleum etehr to afford 29.9 g (77%) of the silyl ether as a light yellow oil: R_f 0.17 (16% ether/petroleum ether); bp 100–105 °C (0.01 mmHg); IR 2980, 2960, 2830, 1710, 1460, 1390, 1260, 1140, 1090 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.0 (d, 1 H, J, J' = 3, 8 Hz), 3.74 (dd, 2 H, J, J' = 7, 6 Hz), 1.8–1.5 (m, 5 H), 1.20 (s, 6 H), 0.93 (obscured doublet, 3 H), 0.84 (s, 9 H), 0.03 (s, 6 H). Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.94; H, 10.73. Found: C, 63.87; H, 10.66.

***tert*-Butyl-[2-[(2*S*,3*R*)-3,5,5-trimethyl-6-methylenetetrahydro-2-(*H*)-pyran-2-yl]ethoxy]dimethylsilane (7).** Into a 250-mL flask under inert atmosphere was placed Tebbe's reagent (8.40 g, 29.8 mmol).[21a,b] The septum-sealed flask was removed from the drybox, and 60 mL of THF was added to yield a deep-red solution. The solution was cooled to −78 °C, and 6.00 g (20.0 mmol) of the above silyl ether were added dropwise by double-needle transfer in two 20-mL portions of THF. The reaction mixture was allowed to warm to −40 °C over 2 h and then brought to 0 °C for 30 min. The reaction mixture was then recooled to −10 °C and quenched by the addition of 10 mL of 15% aqueous NaOH. After the suspension had turned dark green, 40 mL of reagent-grade ether were added. The resulting emission was poured into a 1-L flask and stirred for 2 h, affording a yellow precipitate. The suspension was diluted with 100 mL of reagent-grade hexane and filtered through Celite. Concentration under reduced pressure, followed by filtration through activity III alumina with petroleum ether, gave an orange oil, which was distilled (100–105 °C /0.02 mmHg) from NH_4OH-washed, oven-dried

glassware to afford 4.56 g (76%) of enol ether **7** as a light-green oil: R_f 0.58 (alumina thin-layer plates, petroleum ether); IR 2960, 2920, 1830, 1630, 1450, 1250, 1080, 830 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.30 (s, 1 H), 4.16 (s, 1 H), 3.76 (dd, 2 H, J, J' = 8.7 Hz), 3.18 (dt, 1 H, J, J' = 3, 10 Hz), 2.1–1.3 (m, 5 H), 1.16 (s, 3 H), 1.10 (s, 3 H), 0.93 (s, 9 H), 0.83 (d, 3 H, J = 6 Hz), 0.10 (s, 3 H), 0.04 ns, 3 H). Anal. Calcd for $C_{17}H_{34}O_2Si$: C, 68.39; H, 11.48. Found: C, 68.13; H, 11.55.

(3*S*,6*RS*,7*RS*)-6,7-Epoxy-3,7-dimethyloctene was prepared from (*S*)-citronellen ($[\alpha]_D$ 10.9°, neat, Fluka) by the procedure of Ireland et al. to afford, after distillation, (65 °C/15 mmHg) 17.6 g (83) of a mixture of diastereomeric monoepoxides:[22]

(1*RS*,4*S*)-1-(*m*-Methoxyphenyl)-4-methyl-5-hexen-1-ol (8), To a stirred 0 °C suspension of 31.6 g of H_5IO_6 in 400 mL of reagent ether were added 19.7 g (127 mmol) of the above mixture of epoxides in 100 mL of ether. After 3 h, and additional 2.0 g of H_5IO_6 were added. After the suspension was stirred for a total of 5 h, the reaction mixture was filtered through Celite and washed with 100 mL of saturated aqueous $NaHCO_3$ and 100 mL of 10% aqueous Na_2SO_3. The combined aqueous washes were back-extracted with 50 mL of ether, and the combined organic extracts were dried ($MgSO_4$). The solvent was removed by distillation at atmospheric pressure through a 20-cm vigreux column. A sample of the pot residue showed no acetone upon NMR analysis, and the residue was used without further purification.

To 6.50 g (264 mmol) of Mg turnings in 65 mL of THF in a 250-mL three-necked flask equipped with an addition funnel and a condenser was added 25.0 g (134 mmol) of *m*-bromoanisole in 65 mL of THF at a rate sufficient to maintain reflux. After the reaction ceased, the pot was heated to reflux for 2 h and then allowed to cool to ambient temperature. The reaction mixture was diluted with 60 mL of THF, and the solution was transferred by double-needle into a dry bottle. After the solution had been allowed to stand overnight, the supernatantr was transferred by double-needle into a 500-mL round-bottom flask and cooled to −10 °C, at which time some of the reagent crystallized from solution. The crude aldehyde was then added in 25 mL of THF at a rate that did not cause the internal temperature to exceed 0 °C. After the addition was complete, the reaction mixture was stirred at 0 °C for 1 h and then quenched by the addition of excess saturated aqueous NH_4Cl. An equal volume of hexane was added, and the phases were separated. After the aqueous layer was extracted with 100 mL of ether, the organic phases were individually washed with 100 mL of saturated aqueous NaCl. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give 29.5 g of a yellow oil. Flash chromatography on 600 g of silica gel with 11% EtOAc/petroleum ether afforded 19.7 g (71%, two steps) of a diastereomeric mixture of alcohols **8** as a colorless oil: R_f 0.35 (20% EtOAc/petroleum ether); bp 90–100 °C 0.015 mmHg); IR 3500–3300, 3000, 1580, 1475, 1250, 1140, 1040, 910 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.22 (t, 1 H, J = 8 Hz), 6.85–6.65 (m, 3 H), 5.63 (ddd, 1 H, J, J', J'' = 17, 12, 7 Hz), 4.90 (br d, 1 H, J = 17 Hz, 4.83 (br d, 1 H, J = 12 Hz), 4.56 (dd, 1 H, J, J' = 7, 6 Hz), 3.75 (s, 3 H), 2.1–1.2 (m, 5 H), 0.95 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.26; H, 9.11.

(3*S*,6*RS*)-6-Methoxy-6-(*m*-methoxyphenyl)-3-methylhexene, A suspension of KH (11.3 g, nominally 35% w/w in oil, 98.6 mmol) was placed in a 250-mL flask and washed with pentane to give an off-white powder, which was suspended in 120 mL of 0 °C THF. The mixture of diastereomeric benzylic alcohols **8** (19.7 g, 89.4 mmol) was added dropwise in two 30-mL portions of THF, and the reaction was allowed to warm to ambient temperature over a 1-h period. The reaction was then recooled to 0 °C, and 6.15 mL (98.6 mmol) of MeI were added. After 2 h, the reaction was quenched by the sequential addition of excess reagent-grade methanol and 100 mL of saturated aqueous NH_4Cl. The mixture was diluted with 100 mL of pentane, and the phases were separated. The organic phase was washed with 50 mL of 10% aqueous Na_2SO_3 and 50 mL of saturated aqueous NaCl. Drying ($MgSO_4$) and concentration under reduced pressure produced a yellow oil, which was subjected to flash chromatography on 400 g of silica gel to afford 19.9 g (95%) of the methyl ether as a light-yellow oil: R_f 0.33 (9% ether/petroleum ether); bp 70–80 °C (0.007 mmHg); IR 2970, 2830, 1600, 1580, 1480, 1260, 1100, 7690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.15 (m, 1 H), 6.76 (m, 3 H), 5.56 (ddd, 1 H, J, J', J'' = 16, 10, 7 Hz), 4.90 (d, 1 H, J = 16 Hz, 4.85 (d, 1 H, J = 10 Hz), 3.97 (dd, 1 H, 6, 5 Hz), 3.72 (s, 3 H), 3.17 (s, 3 H), 2.03 (m, 1 H), 1.8–1.1 (m, 5 H), 0.95 (d, 3 H, J = 6 Hz). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.91; H, 9.46. Found: C, 76.91; H, 9.38.

(3*RS*,4*S*,7*RS*)-7-Methoxy-7-(*m*-methoxyphenyl)-4-methylhept-1-en-3-ol (9), Into a stirred −78 °C solution of 19.9 g (84.9 mmol) of the above methyl ether and a trace of Sudan III indicator in 200 mL of reagent-grade MeOH was bubbled O_3/O_2 for 2.5 h, at which time the red color was dispelled. The reaction mixture was purged with N_2 and quenched with 20 mL of Me_2S. After the solution was stirred at −78 °C for 30 min, the reaction mixture was allowed to warm to ambient temperature over a period of 4 h. The solution was diluted with 600 mL of pentane and washed sequentially with two 200-mL portions of H_2O and 100 mL of saturated aqueous NaCl. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to afford 17.5 g of a diastereomeric mixture of aldehydes as a colorless oil, which was used without further purification.

To a −10 °C suspension of 100 mL of nominally 0.4 M vinylmagnesium bromid ein THF was added the above aldehyde by double-needle transfer in two 30-mL portions of THF at a rate that did not cause the internal reaction temperature to exceed −5 °C. After 2 h, another 20 mL of Grignard reagent was added by syringe. After 30 min, the reaction was quenched by the addition of excess saturated aqueous NH_4Cl. The resulting solution was diluted with 100 mL of reagent-grade hexane, and the phases were separated. The aqueous phase was extracted with two 100-mL portions of ether, and the organic phases were individually washed with two 100-mL portions of saturated aqueous $NaHSO_3$. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide a yellow oil. Flash chromatography on 200 g of silica gel with 20% EtOAc/petroleum ether afforded 9.8 g (44%, two steps) of a mixture of allylic alcohols **9** as a colorless oil: R_f 0.25 (20% EtOAc/petroleum ether); bp 120–130 °C (0.005 mmHg); IR 3500, 3070, 2980, 2930, 1600, 1460, 1250, 1100, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.2 (m, 1 H), 6.8 (m, 3 H), 5.8 (m, 1 H), 5.23 (m, 1 H), 5.10 (m, 1 H), 4.0 (dd, 1 H, J, J' = 8, 5 Hz), 3.76 (s, 3 H), 3.41 (q, 1 H, J = 7 Hz), 3.20 (s, 3 H), 1.66 (m, 4 H), 0.93 (m, 3 H). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.49; H, 9.18.

(4*S*,7*RS*)-7-Methoxy-7-(*m*-methoxyphenyl)-4-methylhepten-3-one (10), To a stirred −78 °C solution of 4.83 mL (55.4 mmol) of oxalyl chloride in 75 mL of CH_2Cl_2 were added 7.85 mL (110 mmol) of DMSO. After 5 min, 9.74 g (36.9 mmol) of the above mixture of allylic alcohols **9** were added, and the resulting solution was stirred for 5 min; 4.9 mL of acrolein and 20.6 mL of Et_3N were added, and the reaction mixture was allowed to warm to ambient temperature. The suspension was diluted with 50 mL of H_2O, and the phases were separated. The organic phase was washed with two 200-mL portions of water, and the combined aqueous layers were extracted with two 100-mL portions of ether. The ethereal extracts were washed with 100 mL of saturated aqueous NH_4Cl, and the combined organic layers were dried ($MgSO_4$). Concentration under reduced pressure, followed by flash chromatography on 150 g of silica gel with 15% EtOAc/petroleum ether, furnished a light-yellow oil. Distillation (140–145 °C/0.03 mmHg) furnished 6.40 g (66%) of a diastereomeric mixture of enones **10** as a colorless oil: R_f 0.48 (20% EtOAc/petroleum ether); IR 3000, 2920, 2860, 2820, 1685, 1665, 1590, 1480, 1450, 1250, 1090 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.22 (m, 1 H), 6.80 (m, 3 H), 6.30 (d, 1 H, J = 9 Hz), 6.25 (br s, 1 H), 5.69 (dd, 1 H, J, J' = 9, 3 Hze, 4.0 (dd, 1 H, J, J' = 6, 2 Hz), 3.75 (s, 3 H), 3.15 (br s, 3 H), 2.75 (m, 1 H), 1.66 (m, 4 H), 1.05 (d, 1.5 H, J = 6 Hz), 1.0 (d, 1.5 H, J = 6 Hz). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.25; H, 8.45. Found: C, 73.29; H, 8.51.

***tert*-Butyl-[2-[(2*S*,3*R*,6*S*)-8-[(1*S*,4*RS*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-3,5,5-trimethyl-1,7-dioxaspiro[5.5]undec-8-en-2-yl]ethoxy]dimethylsilane (11)**, A mixture of enol ether **7** (2.00 g, 6.71 mmol), enone **10** (2.61 g, 9.99 mmol), and (4-hydroxy-2,2,6,6-tetramethyl-1-pipiridinyl)oxy free radical (60 mg, 5 mol %) was stirred under high vacuum in an NH_4OH-washed, oven-dried Kontes resealable tube for 3 h. The tube was sealed and heated briefly to 120 °C. After being cooled to ambient temperature, the tube was evacuated again. This was repeated three times, after which the tube was sealed while evacuated and heated to 120 °C for 48 h. The reaction mixture was allowed to cool, and a ^1H NMR spectrum of the crude produt was recorded. The slightly darkened, viscous oil was then dissolved in CCl_4 and directly loaded onto 400 g of activity III alumina. Elution with a gradient ranging from 5 to 15% ether/petroleum ether initially produced 554 mg (27.7%) of recovered enol ether **7**. Further elution provided 2.105 g (56%) of spiroketal enol ether **11** as a mixture of diastereomers: R_f 0.45 (silica gel, 10% ether/petroleum ether); bp >220 °C (0.005 mmHg); IR 3050, 2980, 2960, 2900, 2860, 1670, 1590, 1580, 1480, 1450, 1250, 1100, 1050, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (dd, 1 H, J, J' = 8, 6 Hz), 6.80 (m, 3 H), 4946 (br t, 1 H, J = 7 Hz), 4.034 (t, 0.5 H, J = 7 Hz), 4.008 (t, 0.5 H, J = 7 Hz), 3.801 (s, 1.5 H), 3.800 (s, 1.5 H), 3.754 (t, 0.5 H, J = 10 Hz), 3.744 (t, 0.5 H, J = 10 Hze, 3.526 (m, 1 H), 3.30 (tt, 1 H, J, J' = 10, 2 Hz), 3.196 (s, 3 H), 2.1–1.3 (>12 H), 1.034 (d, 1.5 H, J = 7.5 Hz), 1.018 (obscured doublet, 1.5 H), 1.010 (s, 1.5 H), 1.001 (s, 1.5 H), 0.878 (br s, 9 H), 0.844 (s, 3 H), 0.788 (s, 1.5 H), 0.778 (d, 1.5 H, J = 7 Hz), 0.770 (d, 1.5 H, J = 7 Hze, 0.060 (s, 6 H). Anal. Calcd for $C_{33}H_{56}O_5Si$: C, 70.67; H, 10.06. Found: 70.51; H, 10.03.

There were then eluted 850 mg (32%) of a substance resembling a dimer of the starting enone: R_f 0.19 (11% EtOAc/petroleum ether); bp

>210 °,c (0.005 mmHg); IR 2940, 2910, 2820, 1700, 1590, 1580, 1450, 1250, 1100, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7923 (m, 2 H), 6.83 (m, 6 H), 6.43–6.35 (m, 0.5 H), 6.233 (ddd, 0.5 H, J, J', J'' = 17.4, 4.6, 1.2 Hze, 5.479 (dd, 0.5 H, J, J', J'' = 10.7, 2, 1.5 Hz), 4.47 (m, 0.5 H), 4.20 m, (0.5 H), 4.02 (m, 2 H), 3.81 (br s, 6 H), 3.33 (m, 1 H), 3.207, 3.204, 3.196, 3.190, 3.184 (s, 0.2 × 6 H), 2.1–1.5 (12 H), 1.091 (d, 1.5 H, J = 6.7 Hz), 1.062 (d, 1.5 H, J = 6.7 Hz), 0.995 (m, 3 H), 0.875 (m, 3 H). Anal. Calcd for $C_{32}H_{44}O_6$: C, 73.25; H, 8.45. Found: C, 73.15; H, 8.45.

Further elution provided intractable polymeric materials.

(2*R*,3*S*,6*S*,8*S*,9*R*)-8-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(1*S*,4*RS*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-9,11,11-trimethyl-1,7-dioxaspiro[5,5]undecan-3-ol, To a stirred −5 °C solution of 40 mL of nominally 1 M BH_3/THF was added 4.430 g (7.91 mmol) of spiroketal enol ether **11** by double-needle transfer in 5 mL of THF at a rate that did not cause the internal reaction temperature to rise above 0 °C. After 3 h, the reaction was quenched by the sequential addition of 2.1 mL of H_2O, 9 mL of 15% aqueous NaOH, and 6 mL of 30% aqueous H_2O_2. The resulting mixture was allowed to stir at ambient temperature for 30 min and was subsequently decanted into 100 mL of H_2O. The aqueous suspension was extracted with three 100-mL portions of ether, and the ether extracts were separately washed with one 50-mL portions of 10% aqueous Na_2SO_3. The combined ethereal layers were dried (Na_2SO_4) and concentrated under reduced pressure to yield a colorless oil, which was subjected to flash chromatography on 200 g of silica gel with 20% EtOAc/petroleum ether. The semipurified product was subjected to MPLC on a "Lobar" C column with 8.5% THF/0.5% *i*-PrOH/petroleum ether to afford 2.490 g (54%) of a mixture of diastereomers of the desired spiroketal alcohol as a colorless oil: R_f 0.27 (8% THF/petroleum ether); IR 3500–3300, 2960, 2920, 2840, 1600, 1580, 1460, 1260, 1190, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.233 (t, 0.5 H, J = 8.0 Hz), 7.222 (t, 0.5 H, J = 8.0 Hz), 6.82 (m, 2 H), 6.789 (dd, 1 H, J, J' = 8.5, 1.5 Hz), 4.044 (t, 0.5 H, J = 8 Hz), 4.031 (t, 0.5 H, J = 8 Hz), 3.835 (m, 1 H), 3.790 (s, 1.5 H), 3.786 (s, 1.5 H), 3.750 (br s, 0.5 H, J = 10 Hz, 3.740 (br t, 0.5 H, J = 10 Hz), 3.690 (dt, 0.5 H, J, J' = 2.5, 8.0 MHz), 3.580 (dt, 0.5 H, J, J' = 2.5, 8.0 Hz), 3.486 (m, 1 H), 3.274 (br s, 0.5 H), 3.255 (br s, 0.5 H), 3.200 (s, 1.5 H), 3.195 (s, 1.5 H), 2.182 (m, 1 H), 1.864 (apparent septet, 1 H, J = 7.5 Hze, 1.822 (m, 1 H), 1.750 (m, 2 H), 1.627 (m, 1 H), 1.62 (m, 1 H), 1.536 (m, 1 H), 1.500 (m, 2 H), 1.47 (m, 1 H), 1.340 (dt, 0.5 H, J, J' = 1, 7 Hz), 1.315 (dt, 0.5 H, J, J' = 1, 7 Hz), 0.912 (s, 3 H), 0.864 (s, 4.5 H), 0.858 (s, 4.5 H), 0.84 (obscured, 3 H), 0.802 (s, 1.5 H), 0.782 (s, 1.5 H), 0.740 (d, 1.5 H, J = 6.5 Hz), 0.728 (d, 1.5 H, J = 6.5 Hz), 0.040 (s, 3 H), 0.020 (s, 3 H). Anal. Calcd for $C_{33}H_{58}O_6Si$: C, 68.46; H, 10.09. Found: C, 68.50; H, 10.11.

Benzoic Acid, (2*R*,3*S*,6*S*,8*S*,9*R*)-8-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(1*S*,4*RS*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-9,11,11-trimethyl-1,7-dioxaspiro[5,5]undecan-3-yl Ester (12), To a stirred solution of 2.490 g (4.30 mmol) of the above mixtures of alcohols, 1.8 mL (12.9 mmol) of Et_3N, and 155 mg (1.27 mmol) of DMAP in 8 mL of CH_2Cl_2 was added 0.65 mL (5.6 mmol) of benzoyl chloride (BzCl), and the resulting solution was stirred overnight. The reaction was diluted with 100 mL of ether and washed with two 20-mL portions of saturated aqueous $NaHCO_3$. After drying (Na_2SO_4) and concentration under reduced pressure, chromatography on 150 g of silica gel with 11% ether/petroleum ether yielded 3.021 g (quantitative) of a mixture of diastereomeric benzoates **12** as a viscous, colorless oil: R_f 0.24 (10% ether/petroleum ether); IR 2960, 2920, 2850, 1700, 1450, 1280, 1260, 1100, 1080, 990, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.981 (dd, 2 H, J, J' = 7, 1.5 Hz), 7.53 (m, 1 H), 7.419 (t, 1 H, J = 7.6 Hz), 7.409 (t, 1 H, J = 7.6 Hz), 7.210 (t, 0.5 H, J = 8 Hz), 7.191 (dt, 0.5 H, J, J' = 1, 8 Hz), 6.80 (m, 3 H), 5.13 (m, 1 H), 4.000 (br t, 1 H, J = 6 Hz, collapses to multiplet when 1.51 irrad), 3.88–3.81 (m, 1 H, collapses to d, J = 8.5 Hz, when 1.51 irrad), 3.780 (s, 1.5 H), 3.777 (s, 1.5 H), 3.77–3.70 (m, 1 H), 3.66 (m, 1 H), collapses to broad singlet when 5.13 irrade, 3.54 (m, 1 H, collapses to broad singlet when 1.51 irrad), 3.166 (s, 1.5 H), 3.163 (s, 1.5 H), 2.35 (m, 1 H), 2.00–1.2 (18 H), 1.08 (m, 1 H), 1.00–0.76 (19 H), 0.876 (s, 4.5 H), 0.874 (s, 4.5 H), 0.062 (s, 3 H), 0.058 (s, 3 H). Anal. Calcd for $C_{40}H_{62}O_7Si$: C, 70.34; H, 9.15. Found: C, 70.28; H, 9.12.

Benzoic Acid, (2*R*,3*S*,6*R*,8*S*,9*R*)-8-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(1*S*,4*RS*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-9,11,11-trimethyl-1,7-dioxaspiro[5,5]undecan-3-yl Ester (13), To a stirred solution of 2.100 g (3.07 mmol) of benzoates **12** in 4 mL of $CHCl_3$ was added 0.5 mL of 0.3 M HCl/$CHCl_3$, and the septa-sealed reaction mixture was stirred overnite. The isomerization was halted by decanting the solution into 50 mL of saturated aqueous $NaHCO_3$, ether (50 mL) was added, and the phases were separated. The aqueous layer was extracted with 50 mL of ether, and the combined organic layers were washed with 50 mL of saturated aqueous $NaHCO_3$. After drying ($MgSO_4$) and concentration under reduced pressure, the crude product was subjected to flash chromatography on 100 g of silica gel with 10% ether/petroleum ether to afford a mixture of the spiroketal isomers **12** and **13**, Further elution with EtOAc furnished 152 mg (8.7%) of desilylated material. The mixture of spiroketal benzoates **12** and **13** was subjected to MPLC chromatography on a "Lobar" C column with a gradient ranging from 8 to 10% ether/petroleum ether. There were initially eluted 1.004 g (48%) of the desired product **13** as a mixture of diastereomers: R_f 0.29 (10% ether/petroleum ether); IR 2960, 2940, 2850, 1700, 1580, 1450, 1320, 1250, 1100, 1080, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (m, 2 H), 7.534 (m, 1 H), 7.412 (t, 0.5 × 2 H, J = 7.6 Hz), 7.399 (t, 0.5 × 2 H, J = 7.6 Hz), 7.200 (t, 0.5 H, J = 8.1 Hz), 7.192 (t, 0.5 H, J = 8.1 Hz), 6.81 (m, 1 H, collapses to broad singlet with 7.2–7.19 irrad), 6.804 (d, 1 H, J = 2 Hz), 6.768 (m, 1 H, collapses to broad singlet when 7.2–7.19 irrad), 4.89 (m, 1 H, begins to collapse when 4.06 irrad), 4.059 (br d, 1 H, J = 10 Hz, collapses to broad singlet when 4.89 irrad), 3.993 (m, 1 H), 3.812 (dd, 1 H, J, J' = 7.8, 5 Hz), 3.776 (s, 3 H), 3.77 (m, 1 H), 3.175 (s, 1.5 H), 3.165 (s, 1.5 H), 3.16 (m, 1 H), 2.14 (m, 1 H), 1.94 (m, 1 H), 1.89–1.17 (12 H), 0.955 (s, 1.5 H), 0.918 (s, 1.5 H), 0.840–0.820 (6 H), 0.839 (s, 4.5 H), 0.820 (s, 4.5 H), 0.795 (br d, 3 H, J = 6.5), 0.033 (s, 1.5 H), 0.007 (s, 1.5 H), 0.004 (s, 1.5 H), −0.026 (s, 1.5 H). Anal. Calcd for $C_{40}H_{62}O_7Si$: C, 70.34; H, 9.15. Found: C, 70.40; H, 9.20.

There was then eluted 205 mg (10%) of mixed fractions consisting predominantly of 13, followed by 486.7 mg (23%) of recovered **12**. Recovered **12** was resubmitted to acid equilibrated; the desilylated material recovered from the flash chromatography could be quantitatively converted to a mixture of **12** and **13** by treatment with TBSCl, Et_3N, and DMAP. The reequilibrated material was worked up as before and resubmitted to flash chromatography along with the resilylated material. The purified mixture was combined with the mixed fractions derived from the earlier MPLC purification and resubjected to MPLC. In this manner, 75–80% of the benzoate **13** could be obtained with one recycle.

(2*R*,3*S*,6*R*,8*S*,9*R*)-8-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(1*S*,4*RS*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-9,11,11-trimethyl-1,7-dioxaspiro[5,5]undecan-3-ol, To a stirred 0 °C solution of 1.122 g (1.64 mmol) of diastereomeric benzoates **13** in 4 mL of THF were added 1.65 mL of nominally 1 M LAH/THF dropwise. The reaction was quenched after 2 h by the sequential addition of 60 μL of H_2O in 0.2 mL of THF, 60 μL of 15% aqueous NaOH in 0.2 mL of THF, and 180 μL of H_2O in 0.2 mL of THF. Ether (2 mL) was added, and the mixture was stirred for 30 min. Additional ether (10 mL) and a small portion of $MgSO_4$ were then added, and the suspension was filtered through Celite. The filtrate was concentrated under reduced pressure and subjected to chromatography on 150 g of silica gel with 15% EtOAc/petroleum ether to afford 901.4 mg (95%) of a mixture of diastereomeric alcohols as a colorless oil: R_f 0.34 (15% EtOAc/petroleum ether); IR 3500, 2930, 2900, 2830, 1580, 1450, 1360 1250, 1090, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.207 (t, 1 H, J = 7.5 Hze, 6.83 (m, 1 H), 6.82 (br s, 1 H), 6.768 (br d, 1 H, J = 7.9 Hz), 4.032 (t, 0.5 H, J = 6.4 Hz), 4.012 (t, 0.5 H, J = 7.2 Hz), 3.786 (s, 3 H), 3.78–3.70 (m, 3 H), 3.614 (dd, 1 H, J, J' = 9.6, 2), 3.398 (br s, 1 H), 3.197 (s, 3 H), 3.11 (m, 1 H), 2.084 (dd, 1 H, J, J' = 13.5, 2.7 Hz), 1.84–1.39 (11 H), 1.284 (dd, 1 H, J, J' = 13.6, 4 Hz), 1.184 (t, 1 H, J = 13 Hz), 0.904 (br s, 3 H), 0.871 (s, 4.5 H), 0.852 (s, 4.5 H), 0.806 (d, 3 H, J = 6.7 Hz), 0.789 (s, 1.5 H), 0.785 (s, 1.5 H), 0.751 (d, 3 H, J = 6.5 Hz), 0.034 (s, 3 H), 0.003 (s, 1.5 H), −0.003 (s, 1.5 H). Anal. Calcd for $C_{33}H_{58}O_6Si$: C, 68.46; H, 10.09. Found: C, 68.49; H, 10.00.

(2*R*,6*R*,8*S*,9*R*)-8-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(1*S*,4*RS*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-9,11,11-trimethyl-1,7-dioxaspiro[5,5]undecan-3-one (14), To a −78 °C stirred solution of 0.29 mL (3.4 mmol) of oxalyl chloride in 3.5 mL of CH_2Cl_2 was added 0.32 mL of DMSO dropwise, and the resulting solution was stirred for 5 min. The above mixture of alcohols (1.295 g, 2.24 mmol) was added by double-needle transfer in two 2-mL portions of CH_2Cl_2. After the solution had been stirred for 5 min, 0.97 mL (7.7 mmol) of Et_3N was added, and the reaction was warmed to −40 °C. Additional Et_3N (0.3 mL) were added, and the reaction mixture was allowed to warm to 0 °C. The contents of the vessel were rinshed with ether into 50 mL of saturated aqueous $NaHCO_3$ and extracted with two 75-mL portions of ether. The organic extracts were individually washed with 50 mL of 1:1 saturated aqueous $NaHCO_3$/10% aqueous Na_2SO_3. After drying ($MgSO_4$) and concentration under reduced pressure, flash chromatography on 60 g of silica gel with a gradient ranging from 10 to 20% EtOAc/petroleum ether afforded 1.250 g (97%) of a diastereomeric mixture of ketones **11** as a colorless oil: R_f 0.51 (15% EtOAc/petroleum ether); IR 2950, 2910, 2840, 1715, 1590, 1450, 1250, 1080, 1000, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.216 (br t, 1 H, J = 7.6 Hz), 6.82 (obscured d, 1 H), 6.81 (br s, 1 H), 6.783 (br d, 1 H, J = 8.2 Hz), 4.158 (br s, 1 H), 4.020 (t, 0.5 H, J = 7.3 Hz), 4.000 (t, 0.5 H, J = 7.6 Hz),

3.788 (s, 1.5 H), 3.787 (s, 1.5 H), 3.616 (dd, 1 H, J, J' = 8, 4.3 Hz, collapses to d, J = 8 Hz when 1.51 irrad), 3.58 (m, 1 H), 3.184 (s, 3 H), 3.15 (m, 1 H, begins to collapse when 1.51 irrad), 2.45 (m, 1 H), 2.277 (m, 0.5 H), 2.23 (m, 0.5 H), 2.17–2.07 (m, 2 H), 1.78 (m, 1 H), 1.63 (m, 1 H), 1.49 (m, 1 H, begins to collapse when 3.6 irrad.), 1.382 (dd, 1 H, J, J' = 13.5, 4.5 Hz, collapses to d, J = 13 Hz when 1.63 irrad), 1.270 (t, 1 H, J = 13 Hz, collapses to d, J = 13 Hz when 1.63 irrad), 1.010 (s, 1.5 H), 0.997 (s, 1.5 H), 0.889 (s, 1.5 H), 0.883 (s, 1.5 H), 0.846 (s, 4.5 H), 0.833 (s, 4.5 H), 0.796 (d, 3 H, J = 7.6 Hz), 0.776 (d, 3 H, J = 6.4 Hz, collapses to broad singlet when 1.63 irrad), 0.19 (ns, 1.5 H), 0.014 (s, 1.5 H), 0.001 (s, 1.5 H), –0.05 (s, 1.5 H). Anal. Calcd for $C_{33}H_{56}O_6Si$: C, 68.70; H, 9.78. Found: C, 68.84; H, 9.88.

Trifluoromethanesulfonic Acid, (2*R*,6*R*,8*S*,9*R*)-8-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(1*S*,4*RS*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-9,11,11-trimethyl-1,7-dioxaspiro[5,5]undec-3-en-3-yl Ester, KH suspension (0.254 g, nominally 35% w/w in oil, 2.22 mmol) was placed in a 10-mL flask with a stir bar and washed with two 1-mL portions of pentane. The resulting white powder was suspended in 2 mL of 0 °C THF, and 0.47 mL (2.2 mmol) of $HN(TMS)_2$ was slowly added dropwise to the suspension. Following completion of the addition, the reaction was allowed to warm to ambient temperature over a period of 45 min. The supernatant was transferred by double-needle into a dry flask and cooled to –78 °C. A solution of 319 mg (0.554 mmol) of the mixture of ketones **14** was added by double-needle to the $KN(TMS)_2$ solution in two 1-mL portions of THF. After the resulting solution had been stirred for 10 min, 0.600 g (1.68 mmol) of Tf_2NPh was added by double-needle transfer in 1 mL of THF. After the solution was stirred for an additional 10 min, the reaction was warmed to –10 °C for 20 min and subsequently quenched by double-needle transfer into 50 mL of saturated aqueous $NaHCO_3$. The mixture was extracted with two 100-mL portions of pentane, and the combined organic extracts were washed with two 50-mL portions of saturated aqueous $NaHCO_3$. Drying ($MgSO_4$), followed by concentration under reduced pressure, gave a mixture of the enol triflates and recovered Tf_2NPh. Chromatography on 100 g of silica gel with 5% ether/petroleum ether afforded 343 mg (90%) of a mixture of diastereomeric enol triflates as a colorless oil: R_f 0.55 (15% ether/petroleum ether); IR 2960, 2920, 2840, 1780, 1590, 1450, 1410, 1250, 1140, 1060, 1030, 860, 830 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.22 (t, 1 H, J = 8 Hz), 6.8–6.75 (m, 3 H), 5.66 (m, 1 H, collapses to (d, J = 4.5 Hz) when 2.2 irrad), 4.1 (m, 1 H), 4.0 (m, 1 H), 3.78 (s, 3 H), 3.65 (m, 2 H), 3.20 (s, 3 H), 2.40 (br d, 1 H, J = 15 Hz), 2.1–1.1 (12 H), 1.05 (s, 1.5 H), 1.00 (s, 1.5 H), 0.95 (s, 3 H), 0.85 (s, 9 H), 0.80 (m, 6 H), 0.03 (s, 6 H). Anal. Calcd for $C_{34}H_{55}F_3O_8SSi$: C, 57.60; H, 7.82. Found: C, 57.71; H, 7.94.

***tert*-Butyl-[2-[(2*S*,3*R*,6*R*,8*R*)-8-[(1*S*,4*RS*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-3,5,5,9-tetramethyl-1,7-dioxaspiro[5,5]undec-9-en-2-yl]ethoxy]dimethylsilane (15),** To a –5 °C suspension of 2.87 g (14.0 mmol) of $CuBr\cdot Me_2S$ in 15 mL of Et_2O was added nominally 2 M MeLi/Et_2O until only a trace of yellow precipitate remained. To the resulting solution was added a solution of 990 mg (1.40 mmol) of the above enol triflates by double-needle transfer in two 2-mL portions of ether. The reaction was stirred at –5 °C for 4 h and then quenched by double-needle transfer into 50 mL of rapid stirring aqueous $CuSO_4$. The mixture was transferred to a separatory funnel and extracted with three 100-mL portions of ether. The combined ether extracts were washed with three 100-mL portions of 3 N NH_4OH, and the organic phase was dried ($MgSO_4$). Concentration under reduced pressure, followed by chromatography on 100 g of silica gel with a solvent gradient ranging from 10 to 15% ether/petroleum ether, afforded 452 mg (56%) of a mixture of diastereomeric methyl olefins **15** as a colorless oil: R_f 0.30 (10% ether/petroleum ether); IR 3020, 2970, 2950, 2880, 1600, 1450, 1260, 1100, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.225 (t, 1 H, J = 7.5 Hz), 6.840 (m, 2 H), 6.792 (d, 1 H, J = 8.0 Hz), 5.327 (br s, 1 H), 4.088 (br d, 1 H, J = 10 Hz), 4.025 (m, 1 H), 3.793 (s, 3 H), 3.666 (m, 1 H), 3.493 (m, 1 H), 3.202 (s, 1.5 H), 3.199 (s, 1.5 H), 3.009 (m, 1 H), 2.317 (br d, 1 H, J = 15 Hz), 2.025 (d, 1 H, J = 16 Hz), 1.9–1.4 (9 H), 1.501 (br s, 3 H), 1.298 (m, 1 H), 1.188 (t, 1 H, J = 7.0 Hz), 0.986 (s, 1.5 Hz), 0.963 (s, 1.5 H), 0.863 (s, 4.5 Hz), 0.842 (s, 4.5 H), 0.821 (s, 3 H), 0.742 (d, 1.5 H, J = 6.5 Hz), 0.738 (d, 1.5 H, J = 6.5 Hz), 0.697 (d, 1.5 H, J = 6.7 Hz), 0.663 (d, 1.5 H, J = 6.5 Hz), 0.003 (s, 3 H), –0.018 (s, 3 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 159.66, 144.32, 133.66, 128.99, 118.98, 117.23, 112.68, 111.70, 98.70, 84.54, 84.27, 74.98, 74.66, 74.01, 60.04, 56.33, 54.71, 44.96, 37.49, 36.84, 35.93, 34.37, 34.24, 31.32, 29.82, 25.79, 23.19, 22.02, 18.51, 18.06, 17.41, 12.93, 12.53, –5.47. Anal. Calcd for $C_{34}H_{58}O_5Si$: C, 71.03; H, 10.17. Found: C, 71.19; H, 10.23.

(2*R*,3*S*,4*R*,6*R*,8*S*,9*R*)-8-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(1*S*,4*RS*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methlbutyl]-3,9,11,11-tetramethyl-1,7-dioxaspiro[5,5]undecan-4-ol, To a stirred 0 °C mixture of 275 mg (0.475 mmol) of methyl olefins **15** and 66 μL of Et_3N were added, dropwise, 4.75 mL of nominally 1 M BH_3/THF. After the mixture was stirred overnight at 0 °C, the reaction was quenched by the sequential addition of 0.6 mL of MeOH, 3.5 mL 10% aqueous NaOH, and 1.5 mL of 30% aqueous H_2O_2. The resulting suspension was stirred at ambient temperature for 3 h and then heated to 50 °C for 30 min. After cooling to ambient temperature, the reaction was decanted into 30 mL of 10% aqueous Na_2SO_3. The separated aqueous layer was extracted with two 50-mL portions of ether. The combined organic layers were washed with two 25-mL portions of 10% Na_2SO_3. After drying (Na_2SO_4) and concentration under reduced pressure, chromatography on 20 g of silica gel with 33% ether/petroleum ether afforded 218 mg (77%) of a mixtur of diastereomeric equatorial alcohols as a colorless oil: R_f 0.31 (33% ether/petroleum ether); IR 3480, 2980, 2940, 1600, 1520, 1410, 1230, 1200 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.23 (t, 1 H, J = 8 Hz), 8.86 (m, 3 H), 4.03 (m, 1 H), 3.83 (s, 3 H), 3.75–3.33 (m, 4 H), 3.23 (s, 3 H), 3.20 (m, 1 H), 2.45 (dd, 1 H, J, J' = 12, 5 Hz), 2.0–1.2 (15 H), 0.95–0.75 (24 H), 0.08 (s, 3 H), 0.03 (s, 3 H). Anal. Calcd for $C_{34}H_{60}O_6Si$: C, 68.87; H, 10.20. Found: C, 68.73; H, 10.20.

(2*R*,3*R*,6*R*,8*S*,9*R*)-8-[2-[(*tert*-Butyldimethlsilyl)oxy]ethyl]-2-[(1*S*,4*RS*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-3,9,11,11-tetramethyl-1,7-dioxaspiro[5,5]undecan-4-one, To a stirred –78 °C solution of 47 μL (540 μmol) of oxalyl chloride in 0.5 mL of CH_2Cl_2 was added 76 μL (1.1 mmol) of DMSO dropwise. After 5 min, 159 mg (268 μmol) of the above mixture of alcohols were added by double-needle transfer in two 200-μL portions of CH_2Cl_2, and the reaction mixture was brought to –50 °C. After 10 min, 187 μL (1.33 mmol) of Et_3N were added, and the resulting suspension was warmed to –20 °C. After 10 min, the reaction was warmed to 0 °C and pipetted into 30 mL of saturated aqueous $NaHCO_3$. The resulting emulsion was extracted with two 50-mL portions of ether, and the combined ether extracts were washed with 30 mL of saturated aqueous $NaHCO_3$. Drying (Na_2SO_4), followed by concentration under reduced pressure, furnished a light-yellow oil, which was purified by flash chromatography of 25 g of silica gel with 15% ether/petroleum ether to afford 141 mg (89%) of a mixture of diastereomeric ketones as a colorless oil: R_f 0.48 (8% EtOAc/petroleum ether); IR 2950, 2920, 2840, 1705, 1600, 1450, 1250, 1080, 900, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.219 (t, 0.5 H, J = 8.4 Hz), 7.214 (t, 0.5 H, J = 8.4 Hz), 6.83–6.76 (m, 3 H), 4.023 (t, 0.5 H, J = 6.6 Hz), 3.997 (t, 0.5 H, J = 6.6 Hz), 3.787 (s, 1.5 H), 3.792 (s, 1.5 H), 3.751 (dd, 1 H, J, J' = 10, 2 Hz), 3.615 (dt, 0.5 H, J, J' = 5.4, 10 Hz), 3.543 (dt, 0.5 H, J, J' = 5.4, 10 Hz), 3.446 (dt, 0.5 H, J, J' = 5.8, 10 Hz), 3.406 (dt, 0.5 H, J, J' = 5.8, 10 Hz), 3.200 (s, 1.5 H), 3.197 (s, 1.5 H), 3.183 (m, 1 H), 3.107 (m, 0.5 H), 3.085 (m, 0.5 H), 2.886 (ab, 0.5 H, J = 12.9 Hz), 2.874 (ab, 0.5 H, J = 12.9 Hz), 2.428 (ab, 1 H, J = 13.2 Hz), 2.300 (dq, 1 H, J, J' = 10, 6.3 Hz), 1.78–1.41 (9 H), 1.302 (dd, 1 H, J, J' = 13, 4 Hz), 1.145 (d, 1 H, J = 12.9 Hz), 1.105 (m, 1 H), 0.94–0.83 (overlapping, 26 H, including singlets at 0.863, 0.832), 0.757 (d, 3 H, J = 6.3 Hz), 0.013 (s, 3 H), –0.035 (s, 1.5 H), –0.039 (s, 1.5 H). Anal. Calcd for $C_{34}H_{58}O_6Si$: C, 69.10; H, 9.89. Found: C, 69.15; H, 10.01.

(2*R*,3*S*,4*S*,6*R*,8*S*,9*R*)-8-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(1*S*,4*S*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-3,9,11,11-tetramethyl-1,7-dioxaspiro[5,5]undecan-4-ol (16A) and (2*R*,3*S*,4*S*,6*R*,8*S*,9*R*)-8-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(1*S*,4*R*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-3,9,11,11-tetramethyl-1,7-dioxaspiro[5,5]undecan-4-ol (16B), To a stirred –78 °C solution of 180 mg (298 μmol) of the above ketone in 0.3 mL of THF was added, dropwise, 2.98 mL of nominally 0.5 M K-Selectride/THF. After 30 min, the reaction was warmed, first to –40 °C, and after an additional 30 min, to 0 °C, where it was kept for 1 h. The reaction was quenched by the sequential addition of 120 μL of MeOH, 1.75 mL of 10% aqueous NaOH, and 0.39 mL 30% aqueous H_2O_2. The suspension was diluted with 50 mL of saturated aqueous $NaHCO_3$ and extracted with two 50-mL portions of ether. The combined ether extracts were washed with 20 mL of 10% aqueous Na_2SO_3 and dried (Na_2SO_4). Concentration under reduced pressure, followed by filtration through silica gel with 10% EtOAc/petroleum ether, furnished a colorless oil, which was subjected to MPLC on a "Lobar" B column. Elution with 0.5% Et_3N in 12% ether/petroleum ether afforded, initially, 87.0 mg (48%) of alcohol **16A** as a colorless oil: R_f 0.29 (15% ether/petroleum ether); $[\alpha]_D$ +1.5° (c 0.55, $CHCl_3$); $[\phi]_{275282}$ +2000, +2500 (MeOH); IR 3450, 2950, 2920, 2840, 1580, 1450, 1350, 1090, 1060, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.208 (dd, 1 H, J, J' = 8.3, 7.8 Hz, 2D experiment shows coupling to 6.82, 6.76), 6.82 (obscured doublet, 1 H, coupled to 7.21), 6.817 (br s, 1 H), 6.763 (ddd, 1 H, J, J', J'' = 8.3, 2.7, <1 Hz, coupled to 7.208), 3.99 (dd, 1 H, J, J' = 7.5, 5.5 Hz, coupled to 1.75–1.65 region), 3.785 (s, 3 H), 3.73 (m, 1 H, begins to collapse if irrad 3.19), 3.72 (dd, 1 H, J, J' = 11, 2.5 Hz; 3.73–3.72 coupled to 3.19, 2.3, 1.6–1.5 spin systems), 3.62 (t, 2 H, J = 7.1 Hz, coupled to 1.77, 1.54), 3.205 (s, 3 H), 3.176 (d, 1 H, J = 4.1 Hz, coupled to 3.73, collapses to singlet when 3.73 irrad, OH), 2.301 (dd, 1 H, J, J' = 14.2,

2.9 Hz, collapses to d, J = 14 Hz when 3.73 irrad, coupled to 1.55), 1.8–1.6 (5 H, 1.8–1.72 coupled to 3.62, 3.39, 1.55; 1.72–1.65 coupled to 1.22, 0.80; 1.6 coupled to 3.99, 3.39), 1.57 (s, H_2O, disappears when irrad 3.2), 1.539 (dd, 1 H, J, J' = 14.3, 3.7 Hz, collapses to d, J = 3 Hz when 2.3 irrad coupled to 3.72), 1.53 (m, 1 H, coupled to 3.62, 3.39, 1.82, 0.82), 1.40 (m, 1 H, coupled to 1.72), 1.285 (abx, 1 H, J, J' = 12.8, 4.9 Hz, $\Delta\nu$ = 26.4), 1.219 (ab, 1 H, J = 12.8 Hz, $\Delta\nu$ = 26.4), 0.888 (s, 3 H), 0.869 (m, 1 H), 0.846 (s, 9 H), 0.820–0.800 (obscured doublets, 6 H, coupled to 1.8–1.5), 0.803 (s, 3 H), 0.789 (d, 3 H, J = 6.4 Hz), 0.001 (s, 6 H); exact mass calcd for $C_{34}H_{59}O_5Si$ ($MH^+ - H_2O$) 575.4132; found 575.4122.

There was then eluted 96.0 mg (53%) of alcohol **16B** as a colorless oil: R_f 0.25 (15% ether/petroleum ether); $[\alpha]_D$ +15.5° (c 2.8, $CHCl_3$); $[\phi]_{275282}$ −1600, −1900 (MeOH); IR 3500, 2950, 2920, 2840, 1580, 1450, 1350, 1090, 1060, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.215 (d, 1 H, J = 8.1 Hz), 6.822 (m, 2 H), 6.775 (dd, 1 H, J, J' = 7.3, 1.9 Hz), 4.021 (t, 1 H, J = 6.5 Hz), 3.790 (s, 3 H), 3.75–3.65 (m, 4 H), 3.414 (m, 1 H), 3.257 (d, 1 H, J = 11.2 Hz), 3.200 (s, 3 H), 2.305 (dd, 1 H, J, J' = 14.4, 3.2 Hz), 1.9–1.4 (10 H), 1.279 (dd, 1 H, J, J' = 13.5, 4.7 Hz), 1.23 (m, 1 H), 0.870 (br s, 12 H), 0.829 (d, 3 H, J = 6.8 Hze, 0.794 (s, 3 H), 0.791 (d, 3 H, J = 6.4 Hz), 0.763 (d, 3 H, J = 6.8 Hz), 0.035 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.3, 144.2, 128.9, 119.0, 112.6, 111.8, 101.7, 84.3, 76.5, 70.4, 70.1, 59.8, 56.7, 55.2, 44.3, 38.2, 37.2, 36.1, 35.7, 33.4, 30.9, 30.3, 29.6, 26.3, 22.6, 18.6, 18.2, 13.7, 12.8, −4.8, −4.9; exact mass calcd for $C_{34}H_{59}O_5Si$ ($MH^+ - H_2O$) 575.4132, found 575.4111.

(2*R*)-2-(Benzyloxy)propionate was prepared in quantitative yield by a modification of the method of Mislow et al.[30] With use of freshly prepared silver oxide, only 1 equiv of benzyl bromide was required and no external heating was necessary. The crude product was used without further purification. A small sample was distilled (110–120 °C, 0.1 mmHg): $[\alpha]_D$ +151° (c 1.5, $CHCl_3$).

(2*R*)-2-(Benzyloxy)propanal was prepared from the propionate in 91% yield by a modification of the method of Massad et al.,[31] in which 3:1 hexane/Et_2O was employed as the solvent. All spectral characteristics were in agreement with literature values[54] except for the peak reported at δ 5.59 (s, 2 H, benzyl) in the ^1H NMR spectrum, which was observed at δ 4.61: $[\alpha]_D$ +64.6° (c 3.6, $CHCl_3$), literature value $[\alpha]_D$ +60° (c 1, $CHCl_3$) reported as 90% ee.[55]

(2*R*,3*R*)-2-(Benzyloxy)-5-hexen-3-ol (17) was prepared from the reaction of the (2*R*)-benzyloxypropionaldehyde with allyltrimethylsilane under conditions reported for the racemic aldehyde.[29a] Chromatography on 350 g of silica gel with 15% EtOAc/petroleum ether afforded, initially, 5.40 g (74%) of the alcohol **17** as a colorless oil: $[\alpha]_D$ −49.0° (c 1.578 $CHCl_3$); all other spectral properties were in accordance with reported values.[29a]

Further elution provided 571 mg (8%) of an approximately 1:1 mixture of the desired product and the C-3 epimer.

(4*R*,5*R*)-5-(Benzyloxy)-4-[(*o*-nitrobenzyl)oxy]-1-hexene (18). A suspension of 65.0 mg (0.316 mmol) of alcohol **17**, 200 mg (0.926 mmol) of *o*-nitrobenzyl bromide, 150 mg (0.980 mmol) of BaO, and 17.0 mg (0.099 mmol) of $Ba(OH)_2$ in 600 μL of C_6H_6 was stirred for 2 h. DMF (400 μL) was added, and the C_6H_6 was removed with a continuous stream of argon. The brown suspension was stirred at ambient temperature for 2 h and then heated to 60 °C for 2 h. MeOH (0.5 mL) was added, and the reaction mixture was allowed to cool to ambient temperature. The viscous suspension was diluted with a minimal quantity of CH_2Cl_2 and pipetted into 50 mL of H_2O. The resulting emulsion was extracted with two 50-mL portions of ether, and the combined extracts were washed with 50 mL of saturated aqueous $NaHCO_3$. Drying ($MgSO_4$), followed by concentration under reduced pressure, provided a brown solid, which was subjected to flash chromatography on 10 g of silica gel with 15% ether/petroleum ether to afford 64.4 mg (60%) of nitrobenzyl ether **18** as a yellow oil: R_f 0.63 (30% ether/petroleum ether); bp 150–155 °C (0.05 mmHg) (some decomposition); $[\alpha]_D$ +0.69° (c 0.87, $CHCl_3$); IR 3180, 3000, 2980, 2880, 1610, 1525, 1450, 1350, 1100, 1075 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.00 (dd, 1 H, J, J' = 8, 1.5 Hz), 7.85 (d, 1 H, J = 7 Hz), 7.55 (dt, 1 H, J, J' = 1.5, 7 Hz); 7.45 (m, 1 H), 7.30 (s, 5 H), 5.8 (m, 1 H), 5.09 (br d, 1 H, J = 18 Hz), 5.05 (br d, 1 H, J = 9 Hz), 5.00 (ns, 2 H), 4.63 (ab, 1 H, J = 12 Hz), 4.43 (ab, 1 H, J = 12 Hz), 3.6 (quintet, 1 H, J = 6 Hz), 3.6 (m, 1 H), 2.40 (m, 2 H), 1.2 (d, 3 H, J = 6 Hz); UV 210 nm (ϵ 12300), 260 nm (ϵ 4280); exact mass calcd for $C_{20}H_{24}O_4N$ (MH^+) 342.1705, found 342.1714.

(3*R*,4*R*)-4-(Benzyloxy)-3-[(*o*-nitrobenzyl)oxy]pentanoic Acid (19). To a solution of 78.2 mg (0.213 mmol) of nitrobenzyl ether **18** in 2 mL of *tert*-butyl alcohol was added a solution of 7 mg of $KMnO_4$, 225 mg of $NaIO_4$, and 29 mg of K_2CO_3 in 29 mL of 7:3 *tert*-butyl alcohol/H_2O. After 2.5 h, the reaction mixture was poured into 50 mL of ether/30 mL of H_2O and was acidified to pH 2 with 1 N HCl. The aqueous phase was drawn off and extracted with 50 mL of ether. The combined organic layers were washed with 60 mL of 0.1 N HCl. Drying (Na_2SO_4), followed by concentration under reduced pressure, furnished a brown oil, which was subjected to chromatography on acidic silica with an elution gradient ranging from 10 to 50% ether/petroleum ether to afford 62.1 mg (81%) of acid **19** as a colorless oil: R_f 0.31 (ether); $[\alpha]_D$ +25.7° (c 1.6, $CHCl_3$); IR 3600–2500, 3000, 2920, 1715, 1525, 1340, 1100, 1070 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 8.05 (dd, 1 H, J, J' = 7, 1 Hz), 7.75 (d, 1 H, J = 7 Hz), 7.6 (t, 1 H, J = 6 Hz), 7.5 (m, 1 H), 7.33 (s, 5 H), 5.0 (s, 2 H), 4.63 (ab, 1 H, J = 11 Hz), 4.5 (ab, 1 H, J = 11 Hz), 4.12 (m, 1 H), 3.77 (m, 1 H, collapses to d, J = 5 Hz when 1.2 irrad), 2.70 (m, 2 H, collapses to br s when 4.12 irrad), 1.2 (d, 3 H, J = 6 Hz); exact mass calcd for $C_{19}H_{22}O_6N$ (MH^+) 360.1447, found 360.1457.

(3*R*,4*R*)-4-(Benzyloxy)-3-[(*o*-nitrobenzyl)oxy]pentanoic Acid, (2*R*,3*R*,4*S*,6*R*,8*S*,9*R*)-8-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(1*S*,4*S*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-3,9,11,11-tetramethyl-1,7-dioxaspiro[5.5]undecan-4-yl Ester (20A). To a stirred mixture of 350 μL of a 0.3 M solution of acid **19** in CH_2Cl_2 and 31.0 mg (52 μmol) of alcohol **16A** were added, sequentially, 22 mg (104 μmol) DCC and 52 μL of 0.2M DMAP/DMAP·HCl in CH_2Cl_2. After 15 h, 50 μL additional DMAP/DMAP·HCl solution were added. After 24 h, the reaction was diluted with ether to precipitate dicyclohexylurea and filtered through Celite. Concentration under reduced pressure provided a colorless oil, which was directly applied to a 10 g of silica gel. Elution with a gradient ranging from 10 to 30% ether/petroleum ether initially returned 3.1 mg of recovered alcohol. Further elution afforded 38.0 mg (79%) of ester **20A** as a viscous, colorless oil: R_f 0.46 (30% ether/petroleum ether); $[\alpha]_D$ +10.4° (c 1.2, $CHCl_3$); IR 2980, 2960, 1730, 1540, 1460, 1350, 1100, 1080, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.046 (dd, 1 H, J, J' = 7.6, 1.2 Hz), 7.76 (d, 1 H, J = 7.6 Hz), 7.569 (t, 1 H, J = 7.6 Hz), 7.397 (t, 1 H, J = 7.2), 7.309 (br s, 5 H), 7.236 (t, 1 H, J = 7.9 Hz), 6.85 (m, 2 H), 6.790 (dd, 1 H, J, J' = 7.3, 1.8 Hz), 5.039 (ab, 1 H, J = 14.7 Hz, $\Delta\nu$ = 40.8), 5.024 (m, 1 H), 4.934 (ab, 1 H, J = 14.7 Hz, $\Delta\nu$ = 40.8), 4.613 (ab, 1 H, J = 11.9 Hz, $\Delta\nu$ = 33.3)8 4.525 (ab, 1 H, J = 11.9 Hz, $\Delta\nu$ = 33.3), 4.191 (m, 1 H), 4.025 (t, 1 H, J = 6.5 Hz), 3.808 (s, 3 H), 3.8 (m, 3 H), 3.686 (m, 1 H), 3.217 (s, 3 H), 3.010 (m, 1 H), 2.679 (abx, 1 H, J, J' = 15.9, 3.4 Hz, $\Delta\nu$ = 47), 2.562 (abx, 1 H, J, J' = 16.2, 9.15 Hz, $\Delta\nu$ = 47), 2.118 (dd, 1 H, J, J' = 14.8, 5.0 Hz), 1.8–1.64 (m, 7 H), 1.495 (m, 1 H), 1.39 (m, 2 H), 1.239 (d, 1 H, J = 11.3 Hze, 1.199 (d, 3 H, J = 6.4 Hz), 1.100 (dd, 1 H, J, J' = 13.6, 12.5 Hz), 1.082 (m, 1 H), 0.896 (s, 3 H), 0.885 (br s, 9 H), 0.795 (m, 3 H), 0.791 (s, 3 H), 0.737 (d, 3 H, J = 6.7 Hz), 0.655 (d, 3 H, J = 6.7 Hz), 0.0420 (s, 3 H), 0.0359 (s, 3 H); exact mass calcd for $C_{53}H_{79}O_{11}NSi$ (M^-) 933.5422, found 933.5427.

(3*R*,4*R*)-4-(Benzyloxy)-3-[(*o*-nitrobenzyl)oxy]pentanoic Acid, (2*R*,3*R*,4*S*,6*R*,8*S*,9*R*)-8-(2-Hydroxyethyl)-2-[(1*S*,4*S*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-3,9,11,11-tetramethyl-1,7-dioxaspiro[5.5]undecan-4-yl Ester, Ester 20A (38.0 mg, 40.7 μmol) was dissolved in 2 mL of 2:2:1 THF/HOAc/H_2O, and the resulting solution was stirred for 10 h. The reaction was poured into 40 mL of ether and washed sequentially with 20 mL of H_2O and 20 mL of saturated aqueous $NaHCO_3$. The aqueous washes were back-extracted with 20 mL of ether, and the combined ethereal layers were dried (Na_2SO_4). Concentration under reduced pressure, followed by chromatography on 10 g of silica gel with 20% EtOAc/petroleum ether, afforded 33.1 mg (99%) of the alcohol as a colorless oil: R_f 0.23 (20% EtOAc/petroleum ether); $[\alpha]_D$ +13.6 (c 0.85, $CHCl_3$); IR 3550, 2980, 2940, 1735, 1610, 1540, 1460, 1380, 1260, 1100, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.034 (d, 1 H, J = 7.6 Hz), 7.770 (d, 1 H, J = 7.3 Hz), 7.566 (t, 1 H, J = 7.3 Hz), 7.391 (t, 1 H, J = 7.6 Hz), 7.31 (m, 5 H), 7.24 (m, 1 H), 6.894 (m, 2 H), 6.796 (d, 1 H, J = 9.4 Hz), 5.127 (m, 1 H), 5.035 (ab, 1 H, J = 14.9 Hz, $\Delta\nu$ = 32.1), 4.954 (ab, 1 H, J = 14.6 Hz, $\Delta\nu$ = 32.1), 4.605 (ab, 1 H, J = 11.8 Hz, $\Delta\nu$ = 34.0), 4.520 (ab, 1 H, J = 11.8 Hz, $\Delta\nu$ = 34.0), 4.20 (m, 1 H), 4.121 (q, 1 H, J = 7.0 Hz), 4.028 (t, 1 H, J = 6.3 Hz), 3.818 (s, 3 H), 3.759 (d, 1 H, J = 11 Hz), 3.646 (m, 1 H), 3.480 (q, 3 H, J = 7.1 Hz), 3.227 (s, 3 H), 3.2 (m, 1 H), 2.956 (br s, 1 H), 2.707 (m, 2 H), 2.245 (dd, 1 H, J, J' = 15.0, 5.0), 1.95–1.20 (25 H), 1.206 (d, 3 H, J = 6.4 Hz), 0.954 (s, 3 H), 0.880 (m, 4 H), 0.823 (s, 3 H), 0.793 (d, 3 H, J = 6.1 Hz), 0.734 (d, 3 H, J = 6.4 Hz), 0.634 (d, 3 H, J = 6.4 Hz), 0.071 (br s, 6 H); exact mass calcd for $C_{47}H_{65}O_{11}N$ (M^-) 819.4558, found 819.4541.

(3*R*,4*R*)-4-(Benzyloxy)-3-[(*o*-nitrobenzyl)oxy]pentanoic Acid, (2*S*,3*R*,6*R*,8*R*,9*R*,10*S*)-2-(Carboxymethyl)-8-[(1*S*,4*S*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-3,5,5,9-tetramethyl-1,7-dioxaspiro-[5.5]undecan-10-yl Ester (21A). To a stirred solution of 33.0 mg (40.3 μmol) of the above alcohol in 0.5 mL of reagent-grade acetone was added

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45 μL of 1.75 M Jones reagent in acetone. After 25 min, the reaction was quenched by the addition of 0.5 mL of reagent-grade isopropyl alcohol, along with a small amount of Celite. The resulting suspension was stirred for 5 min, and the blue-green precipitate was removed by filtration through Celite with acetone. After concentration under reduced pressure, chromatography on 10 g of acidic silica with a solvent gradient ranging from 7.5 to 30% EtOAc/petroleum ether afforded 32.3 mg (95%) of acid **21A** as a viscous, colorless oil: R_f 0.18 (20% EtOAc/petroleum ether); $[\alpha]_D$ +26.0 (*c* 0.85, $CHCl_3$); IR 3500–2800, 2970, 2930, 2860, 1730, 1600, 1530, 1460, 1380, 1350, 1100, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.037 (dd, 1 H, *J*, *J'* = 7.3, 0.9 Hz), 7.760 (d, 1 H, *J* = 7.3 Hz), 7.576 (dt, 1 H, *J*, *J'* = 0.9, 7.3 Hz), 7.400 (t, 1 H, *J* = 7.6 Hz), 7.31 (m, 6 H), 6.922 (t, 1 H, *J* = 2.4 Hz), 6.90 (obscured d, 1 H), 6.811 (dd, 1 H, *J*, *J'* = 8.1, 1.7 Hz), 5.101 (m, 1 H), 5.025 (ab, 1 H, *J* = 14.7 Hz, Δν = 26.8), 4.958 (ab, 1 H, *J* = 14.7 Hz, Δν = 26.8), 4.609 (ab, 1 H, *J* = 11.4 Hz, Δν = 38.2), 4.513 (ab, 1 H, *J* = 11.4 Hz, Δν = 38.2), 4.200 (ddd, 1 H, *J*, *J'*, *J''* = 7.4, 4.8, 4.6 Hz), 4.053 (t, 1 H, *J* = 6.9 Hz), 3.84 (m, 1 H), 3.834 (s, 3 H), 3.812 (m, 1 H), 3.481 (q, 1 H, *J* = 7.0 Hz), 3.315 (m, 1 H, begins to collapse when 2.43 irrad), 3.235 (s, 3 H), 2.653 (s, 1 H), 2.639 (d, 1 H, *J* = 2.7 Hz), 2.602 (abx, 1 H, *J*, *J'* = 15.0, 4.6 Hz, Δν = 70), 2.422 (abx, 1 H, *J*, *J'* = 15.0, 2.7 Hz, Δν = 70), 2.04 (m, 1 H), 1.90 (m, 1 H), 1.76 (m, 2 H), 1.70–1.58 (m, 2 H), 1.650 (dd, 1 H, *J'*, *J''* = 15.2, 4.0 Hz), 1.537 (br q, 1 H, *J* = 6.7 Hz), 1.40 (m, 1 H), 1.324 (dd, 1 H, *J*, *J'* = 13.8, 4.5 Hze, 1.253 (br s, 3 H), 1.219 (d, 3 H, *J* = 7.0 Hz), 1.21 (m, 1 H), 0.909 (s, 3 H), 0.808 (s, 3 H), 0.782 (d, 6 H, *J* = 6.7 Hz), 0.666 (d, 3 H, *J* = 7.0 Hz); exact mass calcd for $C_{47}H_{63}O_{12}N$ (M^-) 833.4350, found 833.4331.

(3*R*,4*R*)-4-(Benzyloxy)-3-hydroxypentanoic Acid, (2*S*,3*R*,6*R*,8*R*,9*R*,10*S*)-2-(Carboxymethyl)-8-[(1*S*,4*S*)-4-methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-3,5,5,9-tetramethyl-1,7-dioxaspiro-[5,5]undecan-10-yl Ester (22A), A stirred solution of 32.2 mg (38.7 μmol) of acid **21A** in 40 mL of degassed reagent-grade MeOH in a 100-mL Pyrex round-bottom flask was irradiated for 1 h with a 1000-W Hg–Xe lamp. The lamp output was filtered through water-cooled filters (356 nm (1% cutoff, Schott GG-375); 297 nm (1% cutoff, IR > 800 nm cutoff, Schott KG-5)) prior to contact with the sample, which was immersed in a water bath. Following photolysis, the MeOH was removed under reduced pressure, and the yellow residue was directly applied to acidic silica. Elution with a solvent gradient ranging from 15 to 40% EtOAc/petroleum ether initially afforded 4.2 mg (13%) of recovered starting material. Further elution provided 19.8 mg (74%) of hydroxy acid **22A** as a viscous light-yellow oil: R_f 0.44 (40% EtOAc/petroleum ether); $[\alpha]_D$ +14.5° (*c* 1.3, $CHCl_3$); IR 3500–2700, 2980, 2940, 1760–1730, 1460, 1400, 1370, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (br s, 5 H), 6.84 (br s, 1 H), 6.82 (m, 1 H), 6.74 (dd, *J*, *J'* = 7.8, 2Hz), 5.073 (m, 1 H), 4.596 (ab, 1 H, *J* = 11.6 Hz, Δν = 73), 4.411 (ab, 1 H, *J* = 11.6 Hz, Δν = 73), 3.99 (t, 1 H, *J* = 6.5 Hz), 3.91 (m, 1 H, collapses to dd, *J*, *J'*, *J''* = 9, 4, 1 Hze, when 3.581 irrad), 3.815 (dd, 1 H, *J* = 11, 2 Hz), 3.759 (s, 3 H), 3.581 (dd, 1 H, *J*, *J'*, *J''* = 11.5, 6.5, 6 Hz, collapses to q, *J* = 6 Hz when 3.91 irrad), 3.30 (ddd, 1 H, begins to collapse when 2.327 irrad), 3.165 (s, 3 H), 2.59 (abx, 1 H, *J*, *J'* = 14.6, 4.3 Hz, Δν = 79.5, collapses to ab, *J* = 15 Hz when 3.30 irrad), 2.578 (abx, 1 H, *J*, *J'* = 15.7, 8.5 Hz, Δν = 17.3, collapses to ab, *J* = 16 Hz when 3.91 irrad), 2.535 (abx, 1 H, *J*, *J'* = 15.7, 4.1 Hz, Δν = 17.3, collapses to (ab, *J* = 16 Hz when 3.91 irrad), 2.327 (abx, 1 H, *J*, *J'* = 14.6, 5.5 Hz, Δν = 79.5), 2.235 (dd, 1 H, *J*, *J'* = 15.4, 3.2, collapses to d, *J* = 15 Hz when 5.07 irrad), 1.91 (m, 1 H), 1.788 (apparent q, 2 H, *J* = 7.3 Hz), 1.734 (dd, 1 H, *J*, *J'* = 15.3, 4, collapses to d, *J* = 15 Hz when 5.07 irrad), 1.73–1.67 (m, 1 H), 1.576 (br q, 1 H, *J* = 6.5 Hz), 1.44–1.31 (m, 2 H), 1.360 (dd, 1 H, *J*, *J'* = 13.7, 4.3 Hz), 1.17 (m, 1 H), 1.155 (m, 1 H), 1.151 (d, 3 H, *J* = 6.4 Hz, collapses to broad singlet when 3.581 irrad), 0.850 (s, 3 H), 0.768 (s, 3 H), 0.741 (d, 3 H, *J* = 6.4 Hz), 0.725 (d, 3 H, *J* = 6.3 Hz), 0.681 (d, 3 H, *J* = 7 Hz); exact mass calcd for $C_{40}H_{57}O_{10}$ (M − 1) 697.3952, found 697.3981.

(1*R*,3*R*,4*R*,5*S*,9*R*,13*S*,14*R*)-3-[(1*S*,4*S*)-4-Methoxy-4-(*m*-methoxyphenyl)-1-methylbutyl]-9-[(1*R*)-1-(benzyloxy)ethyl]-4,14,16,16-tetramethyl-2,6,10,17-tetraoxatricyclo[11,3,1,1^{1,5}]octadecane-7,11-dione (23A), A solution consisting of 560 μL of 0.1 M DCC/$CHCl_3$ and 560 μL of 0.1 M DMAP/DMAP·HCl/$CHCl_3$ was placed in a 5-mL round-bottom flask and heated to 55 °C. A solution of hydroxy acid **22A** (19.5 mg, 28 μmol) in 0.5 mL of $CHCl_3$ was drawn into a 1-mL "Gas-Tight" syringe, and the syringe was clamped over the reaction vessel. The hydroxy acid solution was then added at a rate of approximately 1 drop/15 min for 12 h. After the addition was complete, the reaction was stirred overnight at 55 °C and then allowed to cool to ambient temperature. The suspension was diluted with methylene chloride and ether to precipitate dicyclohexyl urea and then filtered through Celite with ether. Following concentration under reduced pressure, the colorless oil was directly subjected to flash chromatography on 5 g of silica gel. Elution with 15% EtOAc/petroleum ether afforded 14.0 mg (74%) of macrolactone **23A** as a viscous, colorless oil: R_f 0.55 (20% EtOAc/petroleum ether); $[\alpha]_D$ +15° (*c* 0.7, $CHCl_3$); IR 2980, 2940, 2860, 1750-1720, 1600, 1460, 1280, 1260, 1100, 1080, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.30 (br s, 4 H), 7.23 (t, 1 H, *J* = 8.0), 6.95 (m, 2 H), 6.78 (dd, 1 H, *J*, *J'* = 8.0, 1.3), 5.228 (ddd, 1 H, *J*, *J'*, *J''* = 12, 4, 3 Hz), 5.034 (m, 1 H), 4.636 (ab, 1 H, *J* = 11.9 Hz, Δν = 46.1), 4.521 (ab, 1 H, *J* = 11.9 Hz, Δν = 46.1), 4.080 (dd, 1 H, *J*, *J'* = 7.0, 5.8 Hz), 3.90 (dd, 1 H, *J*, *J'* = 10.5, 2.1 Hz), 3.860 (dq, 1 H, *J*, *J'* = 4.0, 6.4 Hz, collapses to q, *J* = 6.4 Hz when 5.228 irrad), 3.804 (s, 3 H), 3.343 (dt, 1 H, *J*, *J'* = 2.5, 10.5 Hz), 3.256 (s, 3 H), 2.819 (abx, 1 H, *J*, *J'* = 17.3, 11.9 Hz, Δν = 46.3, collapses to (ab, 1 H, *J* = 17.3 Hz) when 5.228 irrad), 2.702 (abx, 1 H, *J*, *J'* = 17.3, 3.0 Hz, Δν = 46.3, collapses to ab, 1 H, *J* = 17.3 Hz when 5.2 irrad), 2.613 (abx, 1 H, *J*, *J'* = 12.2, 2.7 Hz, Δν = 190), 2.379 (dd, 1 H, *J*, *J'* = 15.3, 2.1 Hz), 2.135 (abx, 1 H, *J*, *J'* = 11.9, 10.9 Hz, Δν = 190), 1.89 (m, 1 H), 1.87 (m, 1 H), 1.65 (m, 1 H), 1.647 (dd, 1 H, *J* = 15, 4 Hz), 1.51 (m, 1 H), 1.40 (m, 2 H), 1.20 (m, 2 H), 1.140 (d, 3 H, *J* = 6.4 Hz), 0.864 (s, 3 H), 0.793 (s, 3 H), 0.789 (d, 6 H, *J* = 6.6 Hz), 0.692 (d, 3 H, *J* = 6.7 Hz); exact mass calcd for $C_{39}H_{53}O_8$ (MH^+ − MeOH) 649.3740, found 649.3753.

(1*R*,3*R*,4*R*,5*S*,9*R*,13*S*,14*R*)-3-[(1*S*,4*S*)-4-(2-Bromo-5-methoxyphenyl)-4-methoxy-1-methylbutyl]-9-[(1*R*)-1-(benzyloxy)ethyl]-4,14,16,16-tetramethyl-2,6,10,17-tetraoxatricyclo[11,3,1,1^{1,5}]octadecane-7,11-dione (24A), To a stirred mixture of 2.3 mg (3.4 μmol) of macrolactone **23A** and 1.5 mg of $NaHCO_3$ in 25 μL of CH_2Cl_2 were added 30 μL of 0.5 M Br_2/CH_2Cl_2. After 30 min, 200 μL of CCl_4 were added, and a continuous stream of argon was blown over the reaction mixture to remove the remaining bromine. After this purge was repeated, the crude residue was directly subjected to flash chromatography on 1 g of silica gel with 15% EtOAc/petroleum ether to afford 2.3 mg (89%) of bromoanisole **24A** as a colorless oil: R_f 0.21 (15% EtOAc/petroleum ether); $[\alpha]_D$ +5.0° (*c* 0.2, $CHCl_3$); IR 2960, 2920, 2860, 1740, 1720, 1460, 1380, 1280, 1110, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.359 (d, 1 H, *J* = 8.8 Hz), 7.32–7.25 (m, 5 H), 7.098 (d, 1 H, *J* = 3.1 Hz), 6.655 (dd, 1 H, *J* = 8.7, 3.2 Hz), 5.188 (dt, 1 H, *J*, *J'* = 12, 4 Hz), 5.02 (m, 1 H), 4.617 (ab, 1 H, *J* = 11.9 Hz, Δν = 44.3)8, 4.524 (dd, 1 H, *J*, *J'* = 7.6, 4.6 Hz), 4.506 (ab, 1 H, *J* = 11.6 Hz, Δν = 44.3), 3.890 (dd, 1 H, *J*, *J'* = 10.7, 1.8), 3.825 (m, 1 H), 3.766 (s, 3 H), 3.321 (dt, 1 H, *J*, *J'* = 2.5, 10.5 Hz), 3.242 (s, 3 H), 2.786 (abx, 1 H, *J*, *J'* = 17.2, 11.8 Hz, Δν = 42.3), 2.681 (abx, 1 H, *J* = 17.2, 3.4 Hz, Δν = 42.3), 2.570 (dd, 1 H, *J*, *J'* = 12.2, 2.7 Hz), 2.362 (dd, 1 H, *J*, *J'* = 15.5, 2 Hz), 2.165 (t, 1 H, *J* = 11.5 Hz), 1.90 (m, 1 H), 1.65–1.40 (m, >7 H), 1.30–1.07 (m, 4 H), 1.106 (d, 3 H, *J* = 6.7 Hz), 0.876 (s, 3 H), 0.840 (m, 1 H), 0.785 (s, 3 H), 0.778 (obscured doublet, 3 H), 0.759 (d, 3 H, *J* = 6.7 Hz), 0.693 (d, 3 H, *J* = 6.7 Hz); exact mass calcd for $C_{39}H_{52}BrO_8$ (MH^+) 759.3107, found 759.3131.

17-Debromo-3-deoxy-20-*O*-methylaplysiatoxin (25A), To a stirred solution of 4.9 mg (7.2 μmol) of macrolactone **23A** in 50 μL of absolute EtOH were added 1.5 mg (10 mol %) of 10% Pd/C. The reaction mixture was placed under a balloon of hydrogen and stirred for 24 h. The reaction mixture was then filtered through Celite with ether and concentrated under reduced pressure. Flash chromatography on 1 g of silica gel with an elution gradient ranging from 20 to 40% EtOAc/petroleum ether initially afforded 0.4 mg (8%) of recovered starting material. Further elution provided 3.7 mg (88%) of macrolactone alcohol **25A** as a colorless oil: R_f 0.38 (40% EtOAc/petroleum ether); $[\alpha]_D$ +29.4° (*c* 0.35, $CHCl_3$); IR 3600–3400, 2960, 2920, 1720, 1600, 1460, 1280, 1070, 1010, 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.257 (t, 1 H, *J* = 8.1 Hz), 6.952 (s, 1 H), 6.944 (d, 1 H, *J* = 8.5 Hz), 6.785 (dd, 1 H, *J*, *J'* = 8, 2.4 Hz), 5.040 (dt, 1 H, *J*, *J'* = 9.8, 5.2 Hz, collapses to dd, 1 H, *J*, *J'* = 10, 5 Hz) when 3.92 irrad, collapses to a broad doublet of doublets when 2.7 irrad), 5.00 (m, 1 H), 4.065 (t, 1 H, *J* = 6.4 Hz), 3.92 (m, 1 H, coupling changes when 1.18 irrad), 3.905 (dd, 1 H, *J*, *J'* = 10.4, 1.8 Hz), 3.811 (s, 3 H), 3.352 (dt, 1 H, *J*, *J'* = 2.7, 10.7 Hz), 3.251 (s, 3 H), 2.735 (d, 1 H, *J* = 9.8 Hz), 2.726 (d, 1 H, *J* = 5.2 Hz), 2.659 (abx, 1 H, *J*, *J'* = 12.2, 2.8 Hz, Δν = 187), 2.430 (dd, 1 H, *J*, *J'* = 15.6, 2.4 Hz), 2.394 (br d, 1 H, *J* = 5.8 Hz, collapses to broad singlet when 3.92 irrad), 2.183 (abx, 1 H, *J*, *J'* = 12.2, 11 Hz, Δν = 187), 1.89 (m, 1 H), 1.76–1.62 (m, 4 H), 1.53 (m, 2 H, collapses to m, 1 H and q, 1 H, *J* = 7 Hz when 3.92 irrad), 1.40 (m, 2 H), 1.29–1.18 (m, 3 H), 1.179 (d, 3 H, *J* = 6.4 Hz), 0.847 (s, 3 H), 0.802 (s, 3 H), 0.798 (d, 3 H, *J* = 6.4 Hz), 0.787 (d, 3 H, *J* = 6.7 Hze, 0.718 (d, 3 H, *J* = 7.0 Hz); exact mass calcd for $C_{32}H_{47}O_8$ (MH^+ − MeOH) 559.3271, found 559.3278.

3-Deoxy-20-*O*-methylaplysiatoxin (27A), To a stirred mixture of 2.4 mg (4.0 μmol) of hydroxy lactone **25A** and 1.5 mg of $NaHCO_3$ in 25 μL of CH_2Cl_2 were added 16 μL of 0.5 M Br_2/CH_2Cl_2. After 5 min, 300 μL of CCl_4 were added, and the remaining bromine was removed with a continuous stream of argon. The evaporative removal of Br_2 was repeated, and the crude product was directly subjected to flash chromatography on 1 g of silica gel with a solvent gradient ranging from 20 to 40% EtOAc/petroleum ether to afford 2.4 mg (88%) of bromoanisole

27A as a colorless oil: R_f 0.53 (40% EtOAc/petroleum ether); $[\alpha]_D$ +10.0° (*c* 0.23, $CHCl_3$); IR 3600-3300, 2980, 2940, 1750-1730, 1460, 1290, 1080, 1015, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.381 (d, 1 H, J = 8.5 Hz), 7.113 (d, 1 H, J = 3.1 Hz), 6.671 (dd, 1 H, J, J' = 8.5, 3.1 Hz), 5.015 (dt, 1 H, J, J' = 9.2, 5.7 Hz), 5.00 (m, 1 H), 4.528 (dd, 1 H, J, J' = 7.6, 4.9 Hz), 3.914 (dd, 1 H, J, J' = 10.7, 2.1 Hz), 3.90 (m, 1 H), 3.798 (s, 3 H), 3.348 (dt, 1 H, J, J' = 2.7, 10.7 Hz), 3.256 (s, 3 H), 2.738 (abx, 1 H, J, J' = 11.3, 4 Hz, $\Delta\nu$ = 15.3), 2.699 (ab, 1 H, J = 11.3 Hz, $\Delta\nu$ = 15.3), 2.631 (abx, 1 H, J, J' = 12.5, 2.8 Hz, $\Delta\nu$ = 150), 2.439 (dd, 1 H, J, J' = 15.4, 2.3 Hz), 2.42 (br s, 1 H), 2.248 (dd, 1 H, J, J' = 12.2, 11 Hz), 1.90 (m, 1 H), 1.70-1.20 (20 H, H_2O), 1.169 (d, 3 H, J = 6.4 Hz), 0.895 (s, 3 H), 0.811 (s, 3 H), 0.809 (d, 3 H, J = 6.4 Hz), 0.794 (d, 3 H, J = 6.1 Hz), 0.746 (d, 3 H, J = 6.7 Hz); exact mass calcd for $C_{33}H_{50}BrO_9$ (MH^+) 669.2638, found 669.2648.

Acknowledgment. We would like to thank Prof. Tom Hooker of UC Santa Barbara for assistance with CD spectroscopy. Both REI and PHD wish to thank Prof. Peter B. Dervan for his role as advisor during the final year of studies. This work was made possible by grants from the National Institutes of Health and the National Science Foundation to whom grateful acknowledgement is made.

Supplementary Material Available: General experimental conditions; experimental details for **8a**, **20b-27B**, attempted deprotection of **23A**, Barton oxidation and Mosher esters of **8**, **8a**, and **17** (18 pages). Ordering information is given on any current masthead page.

Synthesis of Chirally Deuteriated Phthalimidopropanols and Evaluation of Their Absolute Stereochemistry

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Abstract: (1*R*)-[1-^{2}H]- and (1*S*)-[1-^{2}H]-3-phthalimido-1-propanols were synthesized by two independent routes and were initially analyzed for absolute stereochemistry by ^1H NMR spectroscopy of the derived (-)-camphanate esters, **8a** and **8b**, in the presence of Eu(fod)$_3$. As subsequently determined by conversion of one of the sample alcohols to 1(*S*)-[1-^{2}H]heptanol and analysis of its (-)-camphanate by Eu(dpm)$_3$/^1H NMR, the europium-induced shift of the phthalimidopropanol camphanate resonances resulted in the *pro*-1*R* resonance appearing *downfield* from the *pro*-1*S* resonance. This result was contrary to the empirical rule that the *pro*-1*S* hydrogen resonance of primary alcohol camphanates appears downfield of the *pro*-1*R* hydrogen resonance in the presence of europium.

In order to probe the stereochemistry involved in the biosynthesis of acivicin[2] and blasticidin[3] and in the reaction catalyzed by the enzyme spermidine synthase (EC 2.51.16),[4] ornithine, **1**, arginine, **2**, and decarboxylated *S*-adenosyl-L-methionine (dcSAM), **3**, each chirally deuteriated at C-3, were needed. An activated form of chirally deuteriated phthalimidopropanol **4** was envisioned as the key intermediate, which could be converted to the above chirally deuteriated precursors as illustrated in Scheme I. Two independent routes for the synthesis of **4** were developed. In each case the chirality at the labeled center was analyzed by ^1H NMR of the (-)-camphanate derivative in the presence of europium. The results reported here unequivocally establish the absolute stereochemistry of each sample and reveal that the presence of the phthalimido group altered the camphanate-europium interaction from the well-accepted empirical formulation[5] and would, if undetected, have led to erroneous conclusions.

Results

One synthesis of **4** applied a purely chemical route whereby chirality was introduced by stereospecific reduction of the deuteriated aldehyde **6a** (Figure 1). Commercially available ethyl 3-chloropropionate, **5**, was reduced with $LiAlD_4$ and the resulting 3-chloro-1,1-dideuteriopropanol was converted into 1,1-dideuteriophthalimidopropanol in 50-55% overall yield. This product was oxidized to deuterio aldehyde **6a**, by using Swern's procedure,[6] in 95% yield. Portions of the deuterio aldehyde were reduced to a chirally deuteriated phthalimidopropanol, **7a** or **7b**, with either *S*-Alpine-Borane or *R*-Alpine-Borane (Aldrich), respectively.[7]

The stereochemistry of the Midland reduction could be assumed from the large number of literature precedents:[7,8] reduction of a deuteriated aldehyde with *R*-Alpine-Borane yields the *S* alcohol and with *S*-Alpine-Borane yields the *R* alcohol. Rather than rely

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