Approaches to the Total Synthesis of Aplysiatoxin

Thesis by

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In Partial Fulfillment of Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

1987

(submitted November 26, 1986)

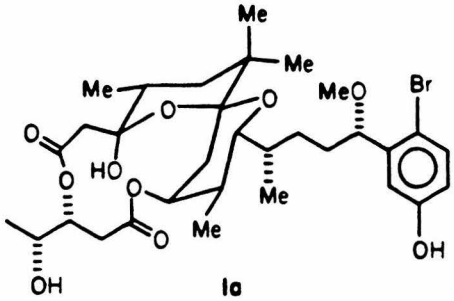
To Candace and my parents

ACKNOWLEDGEMENTS

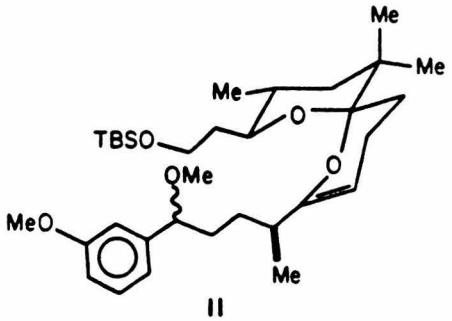
I wish to thank Professor Robert E. Ireland for his support and patience throughout this project. I would also like to thank the following people for their contributions to this project: Professor Peter Dervan, for assuming the role of my advisor during my last year of studies; members of the Ireland group, especially Bob Wardle, Mike Smith and Paul Brown, for their help and advice; Doug Meinhart and Eric Anslyn for extensive assistance with NMR studies; Professor Andrew Myers, for helpful discussions; Professor Tom Hooker of U.C. Santa Barbara for assistance with circular dichroism spectra; Sam Gellman and John Termini, for assistance with proofreading; Caltech, NIH and NSF for financial support. Most importantly, I would like to acknowledge the help and support of my wife, Candace.

ABSTRACT

Approaches to the synthesis of the polyacetate tumor promoter aplysiatoxin (**1a**) are described. The spiroketal framework was convergently constructed in a heteroatom Diels-Alder cyclization to afford spiroketal **11**. The desired spirocenter stereochemistry was achieved, in a key reaction pitting steric strain against the anomeric effect, by acid-catalyzed isomerization of spiroketal **12** to spiroketal **13**. Subsequent manipulation furnished alcohols **16A** and **16B**, which were the starting materials for investigations into macrocyclization and introduction of the C-3 lactol. **16A** and **16B** were efficiently converted to macrolactones **23A** and **23B.** The macrolactones were deprotected and brominated to furnish **27A** and **27B**, representing both possible C-15 epimers of 3-desoxyaplysiatoxin methyl ether. Attempted removal of the phenol methyl ether proved impossible. Nuclear Overhauser effect difference spectra on **27B** showed signal enhancements within the rigid spiroketal framework analogous to those observed in derivatives of the natural product. Attempted transannular remote oxidation of C-3 using a C-9 alkoxy radical derived from the nitrite ester of **16B** afforded, as the predominant product, the C-9 ketone resulting from fragmentation of the initial alkoxy radical; an alternate route involving allylic oxidation of the C-3 hydroxyethyl sidechain of **16A** or **16B** also failed to functionalize the C-3 position. Circular dichroism (CD) spectra of **16A** and **16B** imply that alcohol **16B** contains the natural (S) stereochemistry at the C-15 methyl ether.



1a



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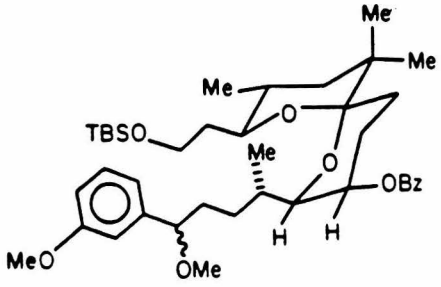

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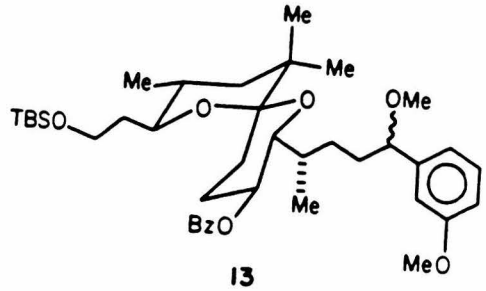

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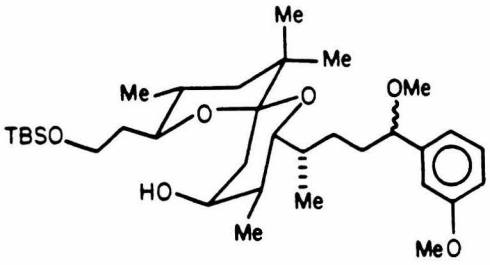
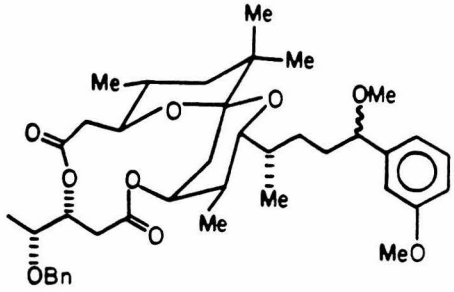
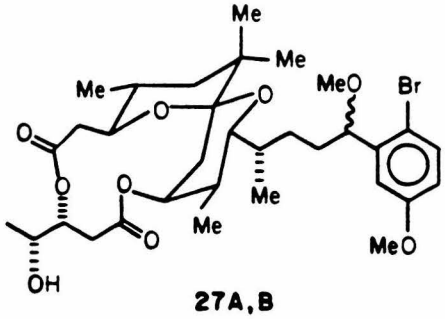


16A,B



23A,B



27A,B

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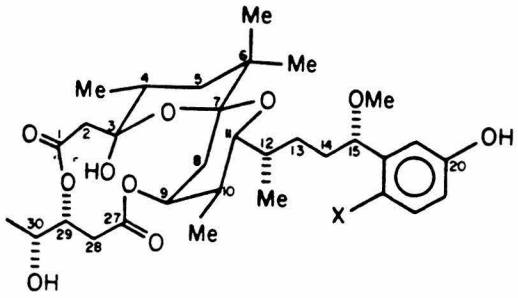
Introduction

Aplysiatoxin (**1a**) and debromoaplysiatoxin (**1b**) are potent marine toxins found in certain species of both blue-green algae (*Lyngbya majuscula*) and sea hares (*Stylocheilus longicauda*).[1] As early as the sixteenth century, the potent toxicity of some sea hares was



1a X=Br
1b X=H

noted by Grevin, a French poet: "It poisons not only those who took it in by mouth, but also those who touched or looked at it, as Pliny reports, and if a pregnant woman sees it or even comes near it, especially if this happens to be a young woman, she immediately feels pains in the belly and nausea, and then has an abortion." [2] In the early part of this century, Flury was able to identify significant toxicity in the sea hare; Winkler later traced the toxin to a midgut digestive gland.[3,4] In 1973, Watson isolated two toxic fractions from the sea hare. One of these was an ether soluble hypertensive; the other, a water soluble hypotensive.[5] In a series of papers during the 1970's, Kato and Scheuer at the Univerity of Hawaii explored the structure of Watson's ether soluble fraction by extensive degradative and spectroscopic studies.[6a-c] It was found that the ether soluble toxin was really a mixture of two components, which together had an LD_{100} of 0.3 mg/kg (i.p., mouse). Extremely unstable outside the range of pH 4-7, these components (aplysiatoxin and debromoaplysiatoxin) could be isolated in 0.025% overall yield from the sea hare, but dehydrated easily to give nontoxic anhydrotoxins. Incidental contact with either of the

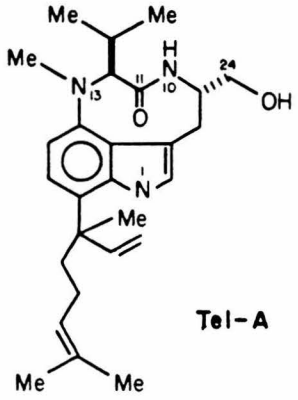
active toxins was found to produce intense dermatitis. In the course of their studies, however, Kato and Scheuer could propose only a partial stereochemical assignment of the molecule.

At this time, R.E. Moore at the University of Hawaii was performing isolation studies on Pacific blue-green algae in a search for new anticancer agents. While testing deepwater blue-green algae, he found a lipophilic extract which displayed activity against P388 leukemia cells; the active component was subsequently shown to be debromoaplysiatoxin. It was also observed at this time that *Stylocheilus longicauda* fed on seaweed coated with the blue-green algae, thereby offering a possible explanation for the presence of the poison in the mollusk.[7] Aquarium studies have shown that when raised on a diet deficient in aplysiatoxin, the sea hare contains no toxin.[8]

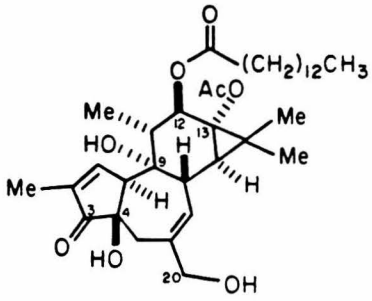
A 1980 outbreak of "swimmers itch" dermatitis among bathers in Oahu provided the opportunity to isolate, from algae-coated seaweed, substantial quantities of debromoaplysiatoxin as the active vesicatory agent. Moore confirmed the structure proposed by Kato and Scheuer; in addition, his group was able to propose the absolute stereochemistry of the toxins, based on circular dichroism studies. More recently, a crystal structure of an aplysiatoxin derivative has been published, confirming the earlier stereochemical assignments.[9]

Although they are powerful toxins, the aplysiatoxins have been of interest to the biomedical community primarily because of a high level of tumor promoting ability exhibited *in vivo*. Until recently, 12-O-tetradecanoyl-13-phorbol acetate (**TPA**) and related phorbol diesters were the only known tumor promoters which acted at nanomolar levels. Recently, however, it has been demonstrated that aplysiatoxin, as well as members of the teleocidin family, including Teleocidin A (**Tel-A**), can also induce tumorigenesis at similar concentrations.[10,11] By way of comparison, peroxides,

detergents and other weak promoters act only at micromolar levels or greater. In a typical



Tel-A



TPA

tumorigenesis experiment with mouse skin models, mice are initially pretreated with a known initiator (carcinogen) such as 7,12 dimethylbenz(a)anthracene (DMBA) in amounts which are significantly below the threshold for tumor formation from DMBA alone. After varying periods of time, typically days to weeks, small amounts of a promoter are applied to the same area of skin to which the initiator was applied; mice treated solely with the tumor promoter do not develop tumors. After repeated application of small quantities of promoter, a high percentage of the mice which had been previously exposed to an initiator will develop observable tumors.[12]

Aplysiatoxin, the teleocidins and the phorbol diesters share many common *in vitro* effects which are presumed to be related to carcinogenesis. All three classes of compounds induce increased ornithine decarboxylase (ODC) activity, as well as release of arachidonic acid from membrane phospholipids with concomitant prostaglandin E_2 (PGE_2) formation.[11,13] Interestingly, debromoaplysiatoxin and some of the weakly promoting phorbol analogues display similar levels of activity in the ODC and PGE_2 assays to the more potent promoters such as TPA. Several other observed effects shared by the strong promoters are adhesion of HL-60 cells and production of superoxide radical anion and hydrogen peroxide from monocytes exposed to the tumor promoters.[14,15] The synthesis

of a 32,000 MW protein has recently been noted in certain cell lines upon application of TPA, teleocidin or aplysiatoxin. This protein may play a central role in tumorigenesis because N-methyl N'-nitroso N-nitroso guanidine (MNNG), a "complete" carcinogen, which is capable of both initiation and promotion in animal models, also stimulates the synthesis of this protein *in vitro*.[16]

One of the more interesting effects shared by the three classes of promoters is the activation of a calcium-dependent protein kinase (PKC) through binding to the PKC receptor.[17] Binding to this receptor is thought to be responsible for the observed reduction in binding of epidermal growth factor (EGF) by the EGF receptor upon treatment with tumor promoters.[18] The activation of the protein kinase has taken on added significance with the observation that debromoaplysiatoxin, as well as some of the less active phorbol diesters, have a lower affinity for the PKC receptor and inhibit EGF receptor binding to a much lesser extent than aplysiatoxin, the teleocidins or TPA.[19]

The protein kinase is normally activated by calcium and diacylglycerols; however, a quaternary complex of the PKC receptor with phorbol diesters, Ca^{+2} and phospholipids also activates the kinase.[17] Although activation of the kinase normally requires high levels of Ca^{2+}, studies have shown that nanomolar concentrations of aplysiatoxin, teleocidin or TPA will substitute for millimolar concentrations of calcium.[20] Photoaffinity labelling has demonstrated that the phorbol diesters interact predominantly with phospholipids in the PKC receptor complex.[21] Competitive inhibition studies involving the binding of radiolabelled phorbol diesters have recently demonstrated the tight binding of the teleocidins and aplysiatoxin to this site; the level of binding to PKC receptors is now often taken as a measure of the potency of a specific tumor promoter. For example, debromoaplysiatoxin, a much weaker tumor promoter than aplysiatoxin, binds weakly to the PKC receptors in most systems when compared to aplysiatoxin.[19] The fact that these

structurally very distinct classes of promoters all bind strongly to the same cellular receptors has elicited studies aimed at deducing the spatial environment of the receptor from the similarities and contrasts in the promoters. Structure/activity studies have shown that various functional groups are required in each of the classes of compounds for full tumor-promoting activity. Aplysiatoxin requires the C3 lactol , the C30 alcohol and a free phenol.[22] Phorbol diesters must have a hydrophobic C12 ester, a C3 carbonyl oxygen, a C4 alcohol and a C20 alcohol. Molecular modeling studies have demonstrated the possibility of explaining PKC receptor binding among the different classes of molecules by superposition of certain functional groups in three-dimensional space. For instance, O27, O3, O30 and O11 of aplysiatoxin can be closely superimposed with O3, O4, O20 and O9 of TPA in 3-dimensional space. Depending upon the conformation of the lactam ring that is chosen, the teleocidins can be superimposed in three-dimensional space with aplysiatoxin or TPA by using: O_{11}, N_{13}, O_{24} and N_1; or N_{13}, O_{11}, O_{24} and N_1, respectively. The diester portion of TPA, the terpenoid portion of the teleocidins and the lipophilic face of aplysiatoxin, comprised of the methyl-substituted face of the "top" spiroketal as well as the aromatic sidechain, can all be superimposed in three-dimensional space, implying that there is a common lipophilic domain in the receptor.[23] The difference in tumor-promoting ability between aplysiatoxin and debromoaplysiatoxin points to the significance of this hydrophobic domain.[24]

The mechanism of tumorigenesis is thought to involve two broad stages, initiation and promotion.[12] In the initiation phase, a carcinogenic metabolite irreversibly interacts with cellular DNA. This defect then "waits" for a promotion event. The allowable delay between initiation "insult" and promotion appears to be quite long, as evidenced by initiator/promoter studies on mouse skin. In the promotion stage, the initiated cell is transformed into a tumor cell. Promotion appears to involve PKC receptor binding as an

early event. Upon binding to the PKC receptor, tumor promoters induce protein kinase C mediated phosphorylation of the EGF receptor on serine or threonine residues. Modification of these residues apparently inhibits EGF stimulated tyrosine-specific phosphorylation of the EGF receptor. The overall amount of EGF that is bound does not appear to be affected; however, high affinity binding to the EGF receptor is inhibited.[18] The *in vitro* level of EGF receptor inhibition generally reflects the *in vivo* tumor promotion activity of a particular promoter. Normally, the EGF receptor modulates differentiation of cells that are proliferating; the inability of EGF to bind to the altered EGF receptor inhibits the ability of cells to terminate differentiation.[12] Additionally, both strong and weak promoters induce the release of choline and arachidonic acid, producing inflammation, which is also produced by the ODC-related polyamine synthesis.[13] Inflammation is known to be a necessary phase in tumor promotion, and anti-flammatory agents are successful inhibitors of tumor promotion in the mouse-skin model system. The attenuating effect of the anti-inflammatory agents can be counteracted by the concurrent application of PGE_2 with a tumor promoter.[12] The inhibition of arachidonic acid release and PGE_2 production upon treatment with a protein synthesis inhibitor, dicyclohexyl carbodiimide, implies that the 32,000 MW protein associated with tumor promotion may be responsible for inflammation.[13] The quantity of promoter that will induce tumors at short intervals of application is less than that required at long intervals of application, suggesting that tumor promoters act reversibly to create a transient state suitable for tumorigenesis.[12]

Interestingly, tumor promotion itself is now thought to consist of at least two stages. Skin tumors can be produced in mice by application of small amounts of a strong promoter, such as TPA, followed by repeated administration of a weak promoter, such as mezerein (structurally related to the phorbol diesters), at dosages where neither regimen alone would induce tumor formation.[25] Inflammation appears to be a major event in the

second stage of promotion. Many of the weak promoters appear to be active second-stage promoters *in vivo*, implying that binding to the PKC receptor is not the sole requirement for tumor promotion. Different inhibitors appear to discriminate among first and second stage promoters. For instance, while retinoic acid, a known superoxide scavenger, is ineffective as an inhibitor in two stage studies when applied concurrently with TPA, it is a very effective inhibitor when applied at later dates along with mezerein.[26] Recently, several compounds, including a phorbol analogue, 4-methoxy TPA, have been identified as first-stage promoters, requiring subsequent application of either a complete promoter or a second-stage promotor in order to induce tumor formation.[12]

Retrosynthetic Analysis

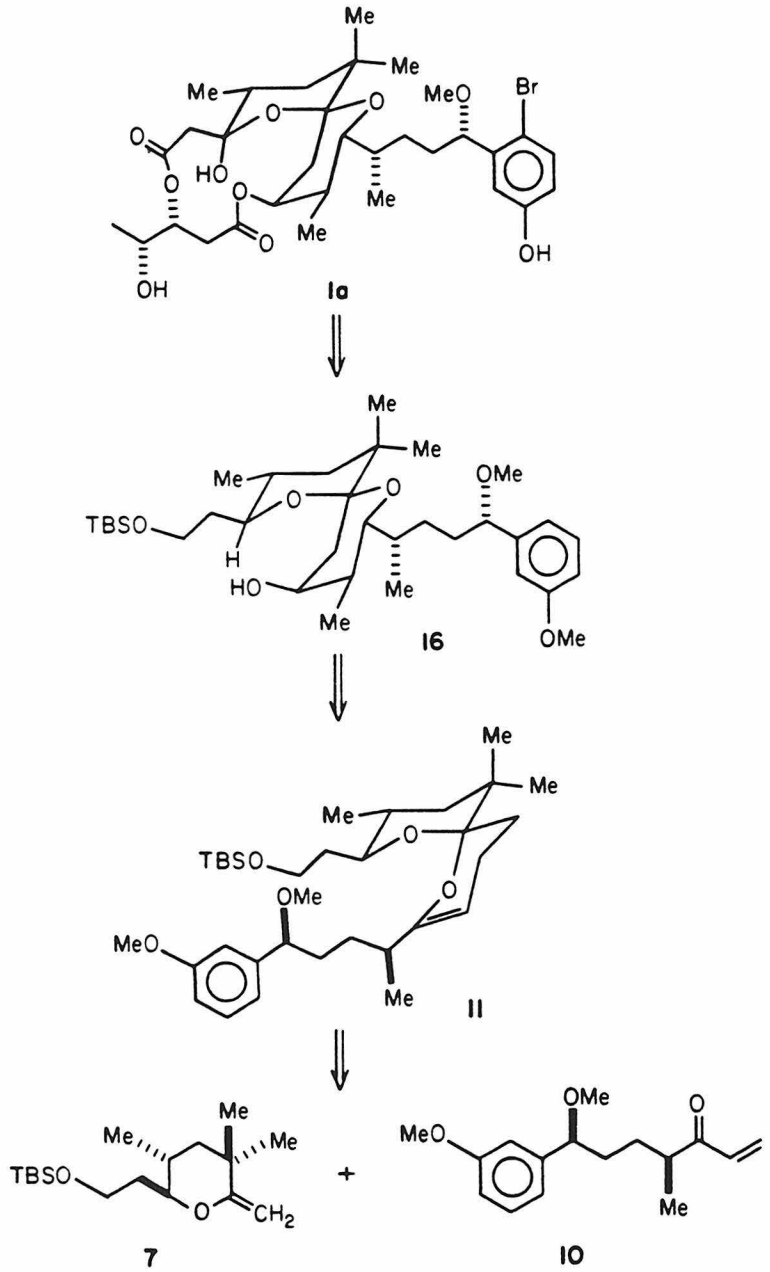
Our synthetic interest in the aplysiatoxins stemmed from several sources. First, the exciting biological activity of the toxins provided a powerful incentive for structural studies. Additionally, at the inception of this project, a complete stereochemical assignment of the molecule was lacking; a synthetic effort could provide key stereochemical information by making accessible individual fragments not easily obtained through degradation. Finally, and foremost in our minds, was the wealth of stereochemistry and novel array of diverse functionality contained in the aplysiatoxins. Because of this complexity, we reasoned that any synthetic approach to the aplysiatoxins would have the opportunity to investigate several challenging problems.

Upon inspection of the molecule, one finds an obvious synthetic challenge in the extreme lability of the C-3 lactol towards dehydration in the natural product;[1,6a-c,9] the sensitive nature of this functionality is likely to preclude early introduction. This limitation forces the synthetic chemist to use a selective and mild functionalization late in the synthesis for the incorporation of either the lactol moiety or a synthetic equivalent. Furthermore, the methodology employed subsequent to the introduction of the lactol synthon will be constrained to conditions compatible with the survival of the lactol.

A second potential area of interest is the introduction of the twelve-membered bislactone. Although the technology of macrolactonization has improved dramatically over the last decade, cyclizations of twelve-membered macrocycles generally proceed in low yield.[27] Additionally, the macrolactone linkage at C29 of aplysiatoxin places a leaving group β to the C27 ester carbonyl, creating the posssibility of facile elimination during advanced stages of the synthesis. Finally, the presence of a vicinal diol at C29 and C30 requires the selective deprotection/activation of the C29 alcohol at a late stage of the synthesis to ensure formation of the twelve, rather than the thirteen, membered lactone.

The retrosynthetic plan which we have designed (Scheme 1) involves using a single advanced intermediate as a springboard for testing the synthetic challenges described

Scheme I Retrosynthetic Analysis



above. In a retrosynthetic sense, disconnection of the bislactone moiety and deoxygenation of the C-3 lactol provide alcohol **16** as a logical common intermediate. In the forward approach, we proposed to utilize a hydroxyl-directed remote functionalization across the internal cavity of alcohol **16** to functionalize the C-3 position at a relatively late stage in the synthesis. The same precursor will also provide the basis for the bisesterification to form the macrobislactone.

The formation of the intermediate **16** was required before either of the other problems could be addressed. The spiroketal manifold must be entered in an efficient manner which allows for easy manipulation of stereochemistry. Although the technology involved in spiroketal synthesis has gradually been refined,[28] one can easily see potential difficulties in efficiently manipulating the stereocenters of the spiroketal ring system while at the same time setting the stage for the macrolactonization and the functionalization of C-3. Furthermore, as a consequence of the anomeric effect, spiroketals are known to favor a diaxial arrangement of the spiroether oxygens on the tetrahydropyran rings.[29a,b] However, in aplysiatoxin, although O7 is axially positioned on the right hand ring, O11 is an equatorial substituent on the left hand ring, raising the possibility that the spirocenter in the natural product is not favored in the absence of the constraining bislactone linkage. We knew from earlier studies in the Ireland group, however, that a suitably substituted spiroketal framework would allow us to successfully pit steric requirements against this stereoelectronic bias.[30]

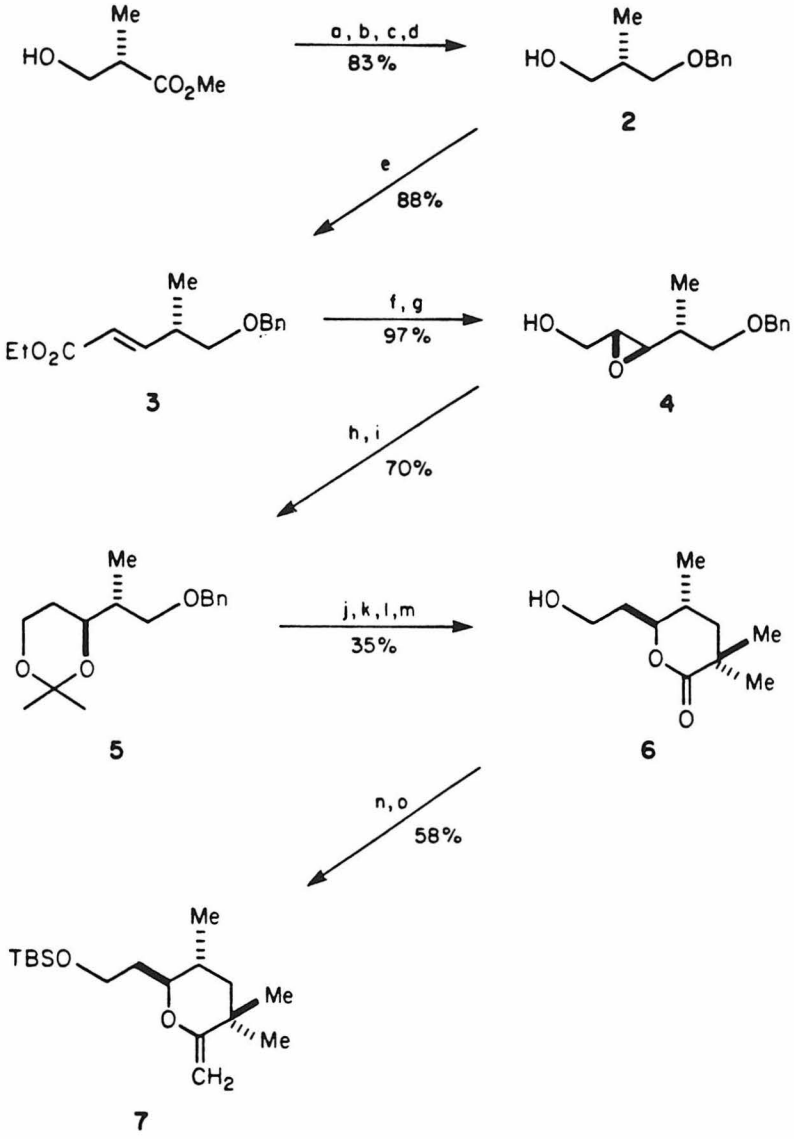
Spiroketal enol ether **11** seemed to offer a logical entry into the spiroketal system. Not only did it contain a handle to allow necessary functionalization, but it could also be efficiently constructed via a heteroatom Diels-Alder cycloaddition.[30,31] The reaction of enol ether **7** with enone **10** would afford a convergent route to the desired enol ether **11**; the two starting materials, in turn, would be netted from the "chiral pool."

Approaches to the Total Synthesis of Aplysiatoxin

The synthesis of enol ether **7** began with the commercially available Methyl (2S) 3-hydroxy-2-methyl propionate.[32] (Scheme II) Following the general scheme used by Meyers in the synthesis of maysine, the alcohol was initially protected as the 1-ethoxyethyl ether. The alcohol resulting from subsequent lithium aluminum hydride (LAH) reduction of the methyl ester was protected as a benzyl ether. Acidic deprotection of the ethoxylethyl ether provided the enantiomerically pure diol monobenzyl ether **2** in excellent overall yield.[33,34]

At this time, we had intended to perform a standard two-carbon homologation of the alcohol through Wittig olefination of the corresponding aldehyde. Oxidation of alcohol **2** by the method of Swern and Omura,[35] followed by treatment with ethyl triphenylphosphoranylidene acetate, led to nearly quantitative yields of the *trans*-unsaturated ester; however, comparison of the optical rotation with literature values indicated that the enantiomeric excess (e.e.) of the product was only 70%.[34] A combination Swern-Wittig procedure reported by these laboratories gave similar results.[36] During the synthesis of rifamycin, Nagaoka and Kishi noted that Wittig olefination of the enantiomeric aldehyde was problematic with regard to epimerization at the chiral center; Horner-Emmons olefination with the potasssium salt of ethyl diisopropyl phosphonoacetic acid reportedly led to high yields of the enantiomer of **3** in greater than 95% enantiomeric excess.[34] In our hands, however, this Horner-Emmons olefination proceeded in good yield but in only 80% enantiomeric excess. A recent modification of the Horner-Emmons procedure employing lithium chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was reported to minimize epimerization of chiral aldehydes;[37] however, when applied to our system, this method afforded the ester **3** in less than 50% e.e. At this point, we elected to utilize the Kishi protocol and carry on ester **3** as a 90:10 mixture of enantiomers.

Scheme II Synthesis of Enol Ether 7[a]



[a] (a) ethyl vinyl ether, $TsOH{\cdot}H_2O$, Et_2O. (b) LAH, THF; (c) potassium *tert*-butoxide, BnBr, THF. (d) 1:3 2*N* HCl/THF. (e) 1. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; 2. ethyl diisopropyl phosphonoacetate, potassium *tert*-butoxide, THF. (f) DIBAL, hexane/Et_2O. (g) (-) diethyl tartrate, $Ti(OiPr)_4$, *tert*-butyl hydroperoxide, CH_2Cl_2. (h) Red-Al, toluene/THF. (i) dimethoxy propane, $TsOH{\cdot}H_2O$, acetone. (j) Li/NH_3, THF. (k) MsCl, Et_3N, CH_2Cl_2. (l) NaI, acetone, reflux. (m) isobutyric acid dianion, THF. (n) TBSCl, imidazole, DMF. (o) $Cp_2TiCH_2(Cl)AlMe_2$, toluene/THF.

Ester **3** was reduced to the corresponding allylic alcohol with diisobutylaluminum hydride (DIBAL). The allylic alcohol was epoxidized using unnatural (D) diethyl tartrate in the Sharpless assymmetric epoxidation procedure to provide epoxy alcohol **4** in high yield as a 90:10 mixture of diastereomers, which were easily distinguished upon inspection of the 500 MHz proton NMR spectrum.[38] That the observed ratio of diastereomers closely corresponded to the ratio of enantiomeric esters **3** implied that the epoxidation had proceeded with complete stereospecificity. The mixture of diastereomeric epoxy alcohols was reduced with sodium bis(2-methoxyethoxy) aluminum dihydride (Red-Al) to afford the 1,3 diol as the only detectable product.[39] The crude diol was directly protected with dimethoxypropane in acetone to afford acetonide **5** in good yield as a 90:10 mixture of diastereomers. High pressure liquid chromatography (HPLC) or careful gravity chromatography separated small quantities of the pure diastereomers, but this separation was not practical on the scale required for the synthesis.

The benzyl ether of **5** was removed with a dissolving metal reduction to afford a nearly quantitative yield of the corresponding alcohol. In earlier studies, we had deprotected the benzyl ether with catalytic hydrogenation; however, on large scale, we found that hydrogenolysis with 10% palladium on carbon gave extensive amounts of a byproduct resulting from migration of the acetonide to the newly freed hydroxyl center.

The alcohol derived from **5** was subsequently reacted with methanesulfonyl chloride (MsCl), and the resulting mesylate was directly transformed into an iodide upon treatment with sodium iodide in refluxing acetone. Alkylation of the lithium dianion of isobutyric acid with the crude iodide,[40] followed by acidification, led to a moderate overall yield of the hydroxy lactone **6** from acetonide **5**. Although the dianion alkylation worked efficiently on a small scale, the elimination of HI from the iodide became problematic during large scale procedures. An alternative alkylation employing a toluenesulfonate ester

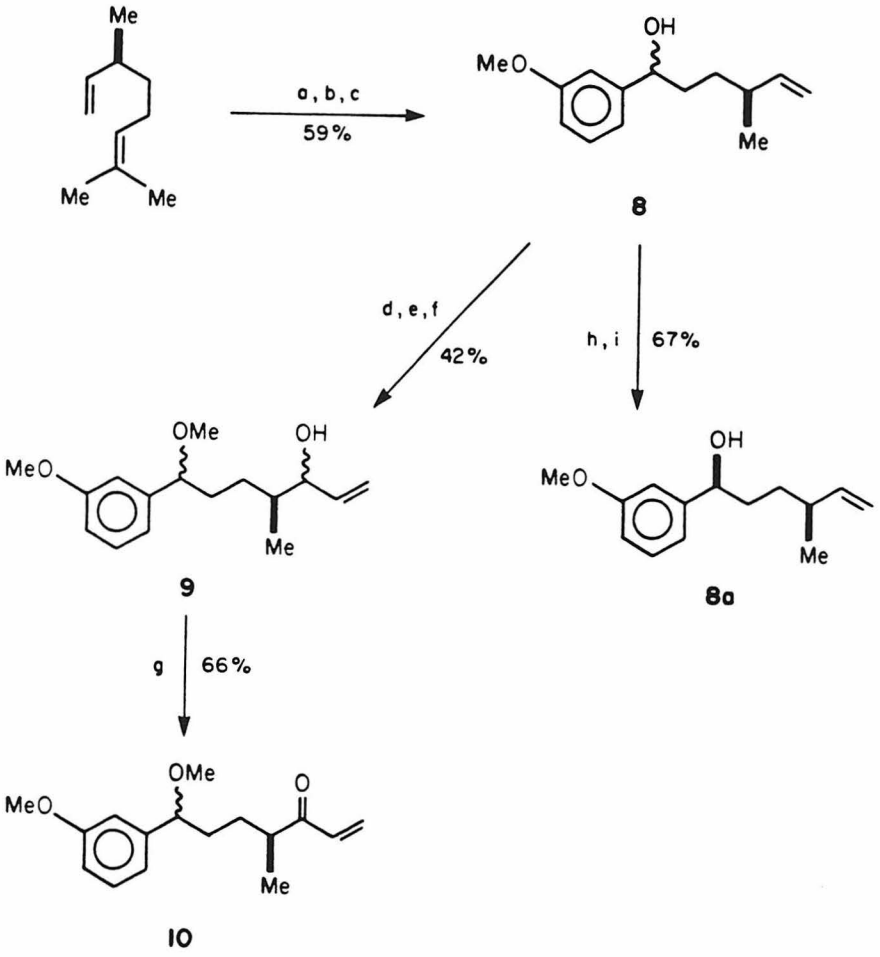
rather than the iodide gave even more olefinic byproduct.

The free alcohol of lactone **6** was protected as the *tert*-butyldimethyl silyl ether (TBS), and the resulting protected lactone was reacted with the Tebbe reagent to afford the acid-labile enol ether **7**.[41,42] Because the ensuing Diels-Alder reaction appeared to be adversely affected by contamination with extraneous metals, the crude enol ether was purified by both filtration through alumina and distillation.

The enone component of the heteroatom Diels-Alder was synthesized from (S) citronellene (Scheme III). Selective epoxidation of the trisubstituted olefin of citronellene with *meta*-chloroperbenzoic acid (*m*-CPBA), followed by periodate cleavage of the epoxide, selectively transformed the more substituted olefin into an aldehyde.[43] The Grignard reagent derived from *m*-bromo anisole was directly reacted with the crude aldehyde to furnish a diastereomeric mixture of benzylic alcohols **8**. After methylation of the mixture of alcohols, the terminal olefin was cleaved with ozone. The resultant aldehyde was directly reacted with vinyl magnesium bromide, in a poor yielding reaction, to afford a mixture of allylic alcohols **9**. The allylic alcohols were then oxidized to a mixture of diastereomeric enones **10** using a modified Swern procedure, in which acrolein was added as a scavenger for the liberated methyl sulfide.[30] The moderate yield of the oxidation reflects, in part, the purification employed to ensure success in the ensuing Diels-Alder reaction.

Although the mixture of epimers generated at the benzylic position of **8** was carried through the remainder of the synthesis, we desired to demonstrate that this alcohol could be prepared diastereomerically pure. Accordingly, the mixture of alcohols **8** was oxidized to an alkylphenone using the Swern procedure. Asymmetric reduction of the alkylphenone, using the binapthol-LAH complex reported by Noyori *et al.*, afforded a good yield of the (S) benzyl alcohol, in greater than 95% e.e.[44] The enantiomeric excess

Scheme III Synthesis of Enone 10[a]

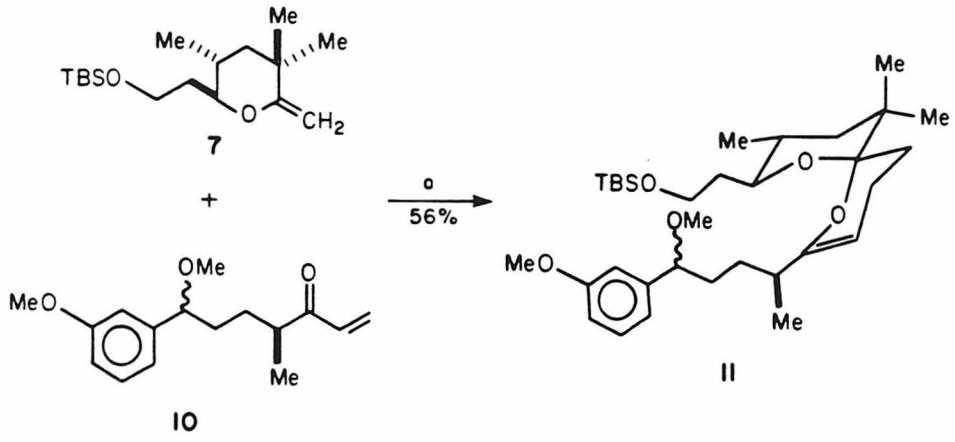


[a] (a) *m*CPBA, $NaHCO_3$, CH_2Cl_2. (b) H_5IO_6, Et_2O. (c) *m*-bromoanisole, Mg, THF; (d) KH, MeI, THF. (e) 1. O_3, MeOH; 2. Me_2S. (f) vinyl magnesium bromide, THF. (g) $(COCl)_2$, DMSO, Et_3N, acrolein, CH_2Cl_2. (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2. (i) 2, 2' binapthol, LAH, EtOH, THF.

was determined by comparison of the high-field proton NMR spectra of the α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA) esters formed from both asymmetric reduction product **8a** and the mixture of benzylic alcohols **8**.[45] The sense of the chirality in **8a** was assigned by precedent to other binapthol-mediated reductions of alkylphenones.

In a key synthetic step, a 50% excess of the diastereomeric mixture of enones **10** was heated at 110°C in a sealed tube for 48 hours with enol ether **7** to afford a 56% yield of the desired spiroketal enol ether **11**, along with extensive amounts of recovered enol ether and dimerized/oligomerized enone. (Scheme IV) It had previously been found advantageous to add a small amount of 4-hydroxy 2,2,6,6 tetramethyl pipiridinyloxy free

Scheme IV Heteroatom Diels-Alder[a]



[a] (a) 4-hydroxy TEMPO, 110°C, 48 h.

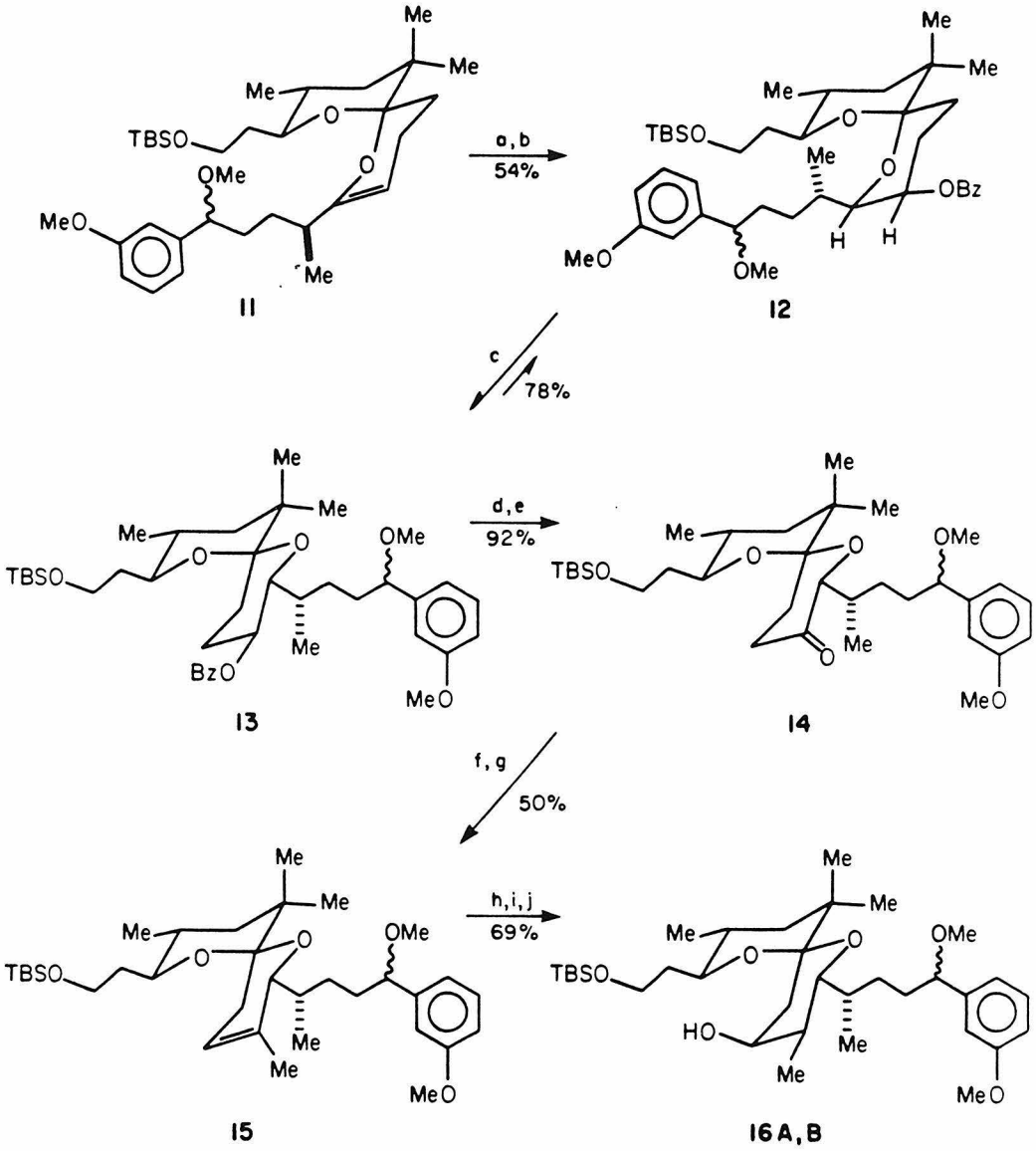
radical (4-hydroxy TEMPO) to the reaction; in the absence of this additive, the amount of enone-derived byproducts increased. Use of only one equivalent of enone also led to a lower overall yield; however, a greater quantity of unreacted enol ether was recovered.

The mixture of diastereomeric spiroketal enol ethers **11** produced in the Diels-Alder cyclization was subjected to hydroboration to afford a mixture of axial alcohols, which was converted to a diastereomeric mixture of benzoate esters **12**.[46] (Scheme V) At this point we needed to perform the isomerization that would set the desired stereochemistry at the spirocenter.

The isomerization of **12** to **13** is driven by steric strain and opposed by stereoelectronic bias. Focussing solely on steric and electronic interactions directly involved in the transformation, we can quantify individual effects using the analysis developed for spiroketals by Deslongchamps.[29a] Spiroketal **12** has both oxygens antiperiplanar to the anomeric C-O linkage, electronically stabilizing this isomer by -2.8 kcal (2 x -1.4). The latent steric strain required to counteract this stereoelectronic bias was introduced earlier by the *exo*-face hydroboration of enol ether **11**. The hydroboration forced the spiroketal sidechain into a diaxial interaction with the spiroketal oxygen, allowing us to introduce +3 kcal of $A_{1,3}$ strain into the spiroketal framework. Furthermore, each axial spiroketal oxygen creates the equivalent of two *n*-propyl ether *gauche* units, sterically destabilizing the spiroketal by +1.6 kcal (2 x 2 x 0.4). Finally, the axial benzoate has a single *gauche* interaction with a methylene unit (+0.4 kcal). The Deslongschamps analysis on this isomer predicts a relative energy of approximately +2.2 kcal.

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, 2 x 0.4), the isomerization will introduce a new source of *gauche* strain from the axial methylene (+1.6 kcal, 2 x 0.8). The newly equatorial benzoate and aromatic sidechain will have a *gauche* relationship as well (+0.4 kcal). The predicted total relative energy by this analysis for isomer **13** is +1.4 kcal; spiroketal **13** should therefore

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



[a] (a) 1. BH_3·THF, THF. 2. H_2O_2, NaOH. (b) BzCl, DMAP. (c) HCl/$ClICl_3$. (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, ClH_2Cl_2. (j) K-selectride, THF.

be theoretically favored by approximately +0.8 kcal.

Treatment of the benzoates **12** with strong acid resulted in an equilibrium favoring the isomerized spiroketals **13** by a 70:30 ratio, confirming the theoretical analysis. 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. A solution of 5 mol % HCl in chloroform was found to be an optimum system for promoting isomerization while avoiding extensive desilylation. In earlier studies, we had employed a benzyl ether in place of the silyl ether, avoiding this deprotection problem. However, we felt that use of the silyl ether gave us more flexibility later in the synthesis. Diethyl aluminum chloride was a weaker, although selective, isomerization catalyst.. Titanium tetrachloride, aluminum trichloride and toluenesulfonic acid monohydrate tended to promote an unacceptable degree of desilylation.

The diastereomeric mixture of isomerized spiroketals **13** was treated with LAH to cleave the benzoate esters; the free alcohols were then oxidized using the Swern oxidation to a diastereomeric mixture of ketones **14**. Regioselective low-temperature enolization with potassium hexamethyldisilazide, followed by trapping with N-phenyl triflimide (Tf_2NPh), afforded an excellent yield of diastereomeric enol triflates.[47] Attempted trapping of the potassium enolate of **14** with triflic imidazole gave significantly lower yields. The enol triflates derived from **14** were coupled with lithium dimethyl cuprate to produce a moderate yield of diastereomeric methyl olefins **15**.[48]

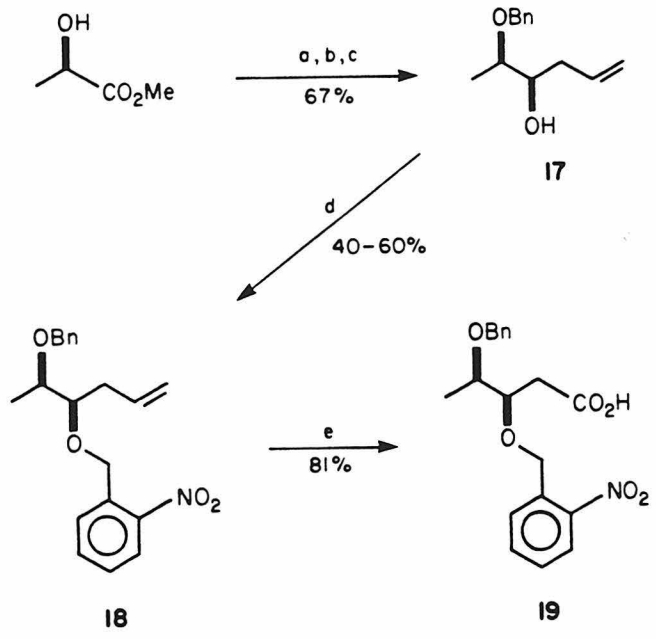
Hydroboration of **15** proved to be problematic. $BH_3 \cdot Me_2S$ or $BH_3 \cdot THF$ consumed the starting olefin but provided low yields of product under normal reaction conditions, while a more hindered borane, 9-BBN, gave no reaction even at elevated temperatures. However, the use of excess $BH_3 \cdot THF$ in the presence of one equivalent of

Et_3N gave a good yield of a mixture of diastereomeric equatorial alcohols.

To reach intermediate **16**, we needed to invert the alcohol produced in the hydroboration. Accordingly, the mixture of diastereomeric alcohols was converted to the corresponding mixture of ketones using the Swern oxidation, and the ketones were stereoselectively reduced with potassium tri-*sec*-butyl borohydride (K-Selectride) to the diastereomeric axial alcohols **16A** and **16B**, which were separable by chromatography.[49] All subsequent reactions were performed on the individual diastereomers.

At this time, we needed to synthesize the fragment that would ultimately form the bismacrolactone. (Scheme VI) As a method of deriving the vicinal *syn* -diol unit needed for this fragment, we opted for the addition of allyltrimethylsilane to a chiral

Scheme VI Synthesis of Sidechain 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) $KMnO_4$, $NaIO_4$, *t*-butanol/H_2O.

α-alkoxy aldehyde.[50,51] The necessary aldehyde was formed in two steps from commercially available Methyl (R)-lactate. The lactate was benzylated under mild conditions, and the resultant benzyl ether was reduced with DIBAL to the chiral α-alkoxy aldehyde.[52,53] Addition of $SnCl_4$ and allyltrimethylsilane to this aldehyde gave a good yield of the homoallylic alcohol **17** as a 95:5 mixture of diastereomers, which were easily separable by chromatography.[50] NMR analysis of the MTPA ester derived from the major diastereomer of **17** showed little, if any, enantiomeric impurity.

We now needed a protecting group for the homoallylic alcohol which could be selectively unmasked at a later point in the synthesis. Initial studies demonstrated that a trichloroethyl carbonate was too fragile, while methoxymethyl and *tert*-butyldiphenylsilyl ethers proved overly robust.[54,55,56] We elected to investigate an *ortho*-nitrobenzyl ether, because the photochemical method of removal for this moiety was orthogonal to the remainder of our protecting scheme.[57]

Although *o*-nitrobenzyl ethers have been used in ribonucleoside synthesis, these photolabile groups have seldom been used as a protecting group for non-carbohydrate alcohols, and we were unable to alkylate **17** under reported conditions.[57,58a,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 barium oxide/barium hydroxide benzylation conditions developed by Paulsen and Lockhoff for carbohydrate protection, we were able to achieve tolerable yields of the *ortho*-nitrobenzyl ether **18**.[59]

Because of our earlier difficulties with protecting groups in this position, we decided to investigate the conditions required for photodeprotection before proceeding further. The *o*-nitrobenzyl group is normally cleaved with 250-400 nm light.[57] When we

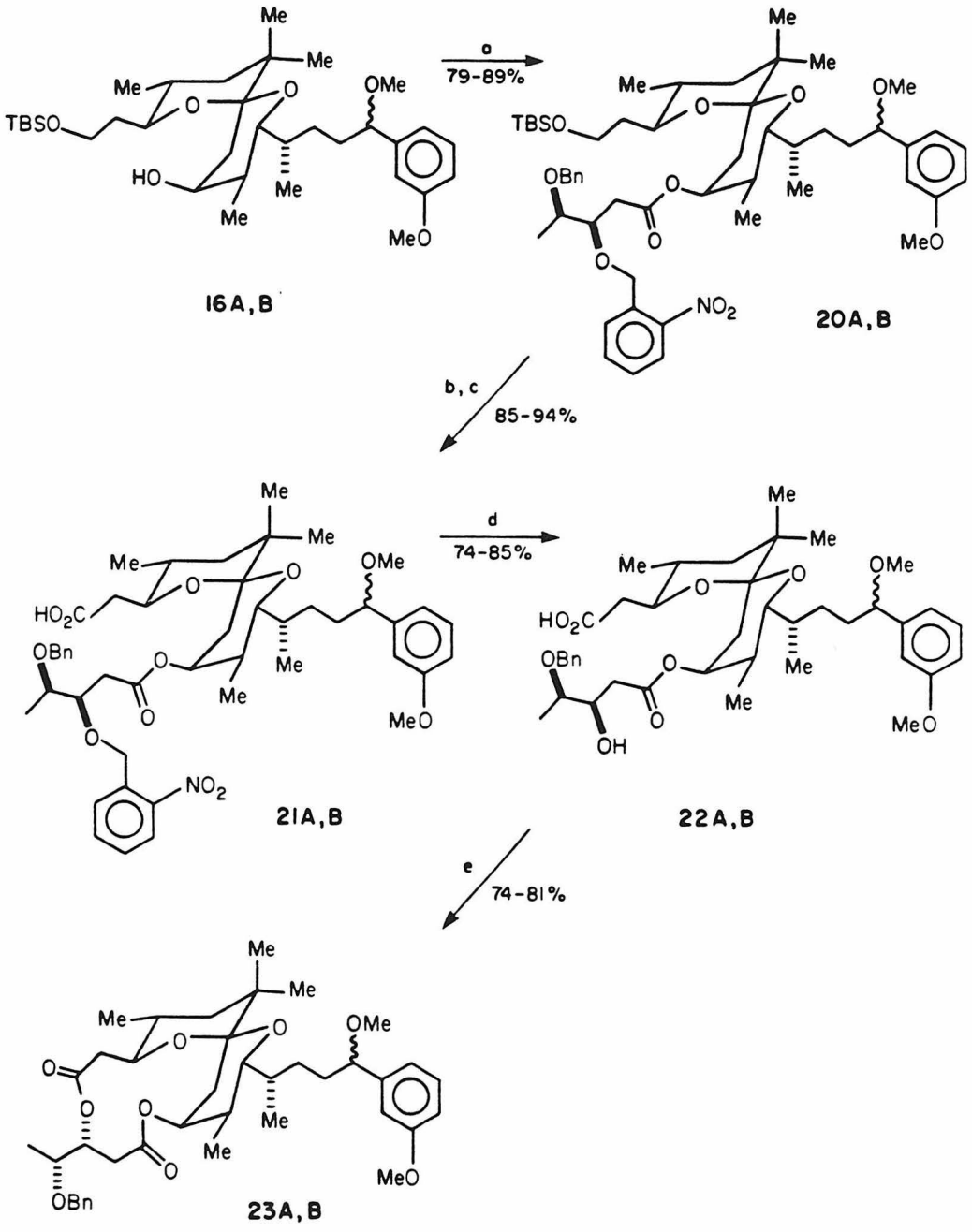
subjected samples of both nitrobenzyl ether **18** and an advanced intermediate derived from **16A** to UV-photolysis with a cutoff at 300 nm, ether **18** was cleanly photodeprotected, while the sample intermediate was destroyed. A UV spectrum of the sample intermediate showed significant absorption from the anisole functionality extending to greater than 280 nm. Accordingly, we resubmitted samples of **18** and the advanced intermediate to competitive photolysis with a 356 nm cutoff. We were gratified to observe that, while **18** was still cleanly deprotected to **17**, no photodestruction of the advanced intermediate occurred. Assured of having chosen an appropriate protecting group, we converted **18** to carboxylic acid **19** by oxidation of the vinyl group with potassium permanganate and sodium periodate.[60]

With the desired fragment in hand, we resumed our approach to the macrolactones. Attempted esterifications of alcohols **16A** or **16B** with the acid chloride or trifluoroacetic mixed anhydride of acid **19** were unsuccessful. (Scheme VII) However, esterification of acid **19** with **16A** and **16B** using DCC, DMAP and DMAP·HCl afforded esters **20A** and **20B** in excellent yield.[27,61] Whereas attempted deprotection of the silyl ether with tetra-n-butyl ammonium fluoride (TBAF) had led to extensive formation of byproducts resulting from the basicity of the reagent in earlier studies, solvolysis of **20A** and **20B** with acetic acid/THF/H_2O cleanly removed the TBS protecting group to afford the primary alcohols.[41] Chromic acid oxidation of the alcohols provided the acids **21A** and **21B** in high yield.[62]

Photolysis of acids **21A** and **21B** with UV light filtered at 356 nm resulted in clean photoremoval of the nitrobenzyl ether to afford good yields of hydroxy acids **22A** and **22B**. The main problem with the photodeprotection was the tendency to discontinue irradiation prematurely, resulting in recovered starting material.

Because the modified DCC technology had performed admirably during the

Scheme VII Formation of the Macrolactones 23A,B[a]



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

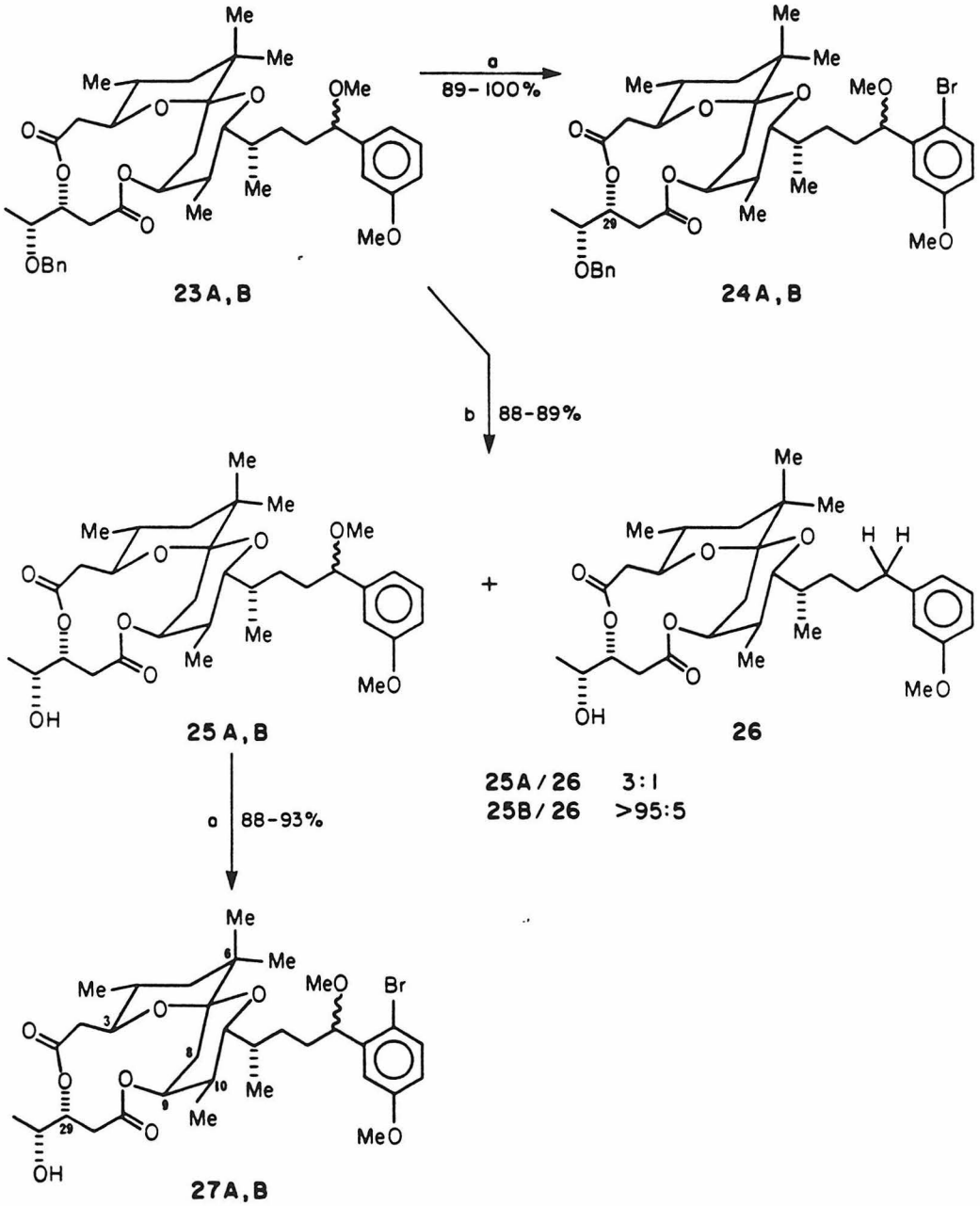
bimolecular esterification of the hindered alcohols **16A** and **16B** with acid **19**, we decided to employ the same procedure as our initial approach to the macrocyclization. After slowly adding a solution of **22A** or **22B** into a 55°C solution of DCC, DMAP and DMAP·HCl in chloroform under high dilution conditions, we were pleasantly surprised to isolate good yields (74-81%) of macrolactones **23A** and **23B**. Mass spectral analysis by fast atom bombardment (FAB) showed no sign of dimeric products. Because the cyclization to form **23A** and **23B** is considerably more efficient than the lactonization of 11-hydroxy undecanoic acid cited as an example by Boden and Keck, we concluded that the rigid atoms in the spiroketal framework contributed greatly to the facility of the cyclization.[27]

We now endeavored to explore the chemistry of these macrolactones. Bromination of **23A** and **23B** with Br_2/CCl_4 cleanly provided bromoanisoles **24A** and **24B**. (Scheme VIII) Although spectral verification of the bromination regiochemistry was difficult, the work of Nelson and Uschak on Friedel-Crafts bromination of *meta*-alkyl anisoles provided a good precedent for bromination *para* to the activating methoxy group.[63]

Hydrogenolytic removal of the benzyl ether on the C-30 alcohol with palladium/carbon in ethanol proved to be an interesting reaction. The hydrogenolysis was slow for both **23A** and **23B**. While **23B** deprotected cleanly to alcohol **25B**, **23A** furnished a 3:1 mixture of the desired alcohol **25A** along with byproduct **26**, which was the result of cleavage of the benzylic methyl ether. Ethanol appeared to be an ideal solvent for this reaction. No reaction occurred in ethyl acetate, while a 1:1 mixture of ethyl acetate and acetic acid promoted extensive formation of byproduct **26** from **23A**.

The alcohols **25A** and **25B** were cleanly brominated as before to afford bromoanisoles **27A** and **27B**, representing both possible C-15 epimers of 3-desoxyaplysiatoxin methyl ether. Nuclear Overhauser effect (NOE) difference spectra

Scheme VIII Elaboration of Macrolactones 23A,B[a]

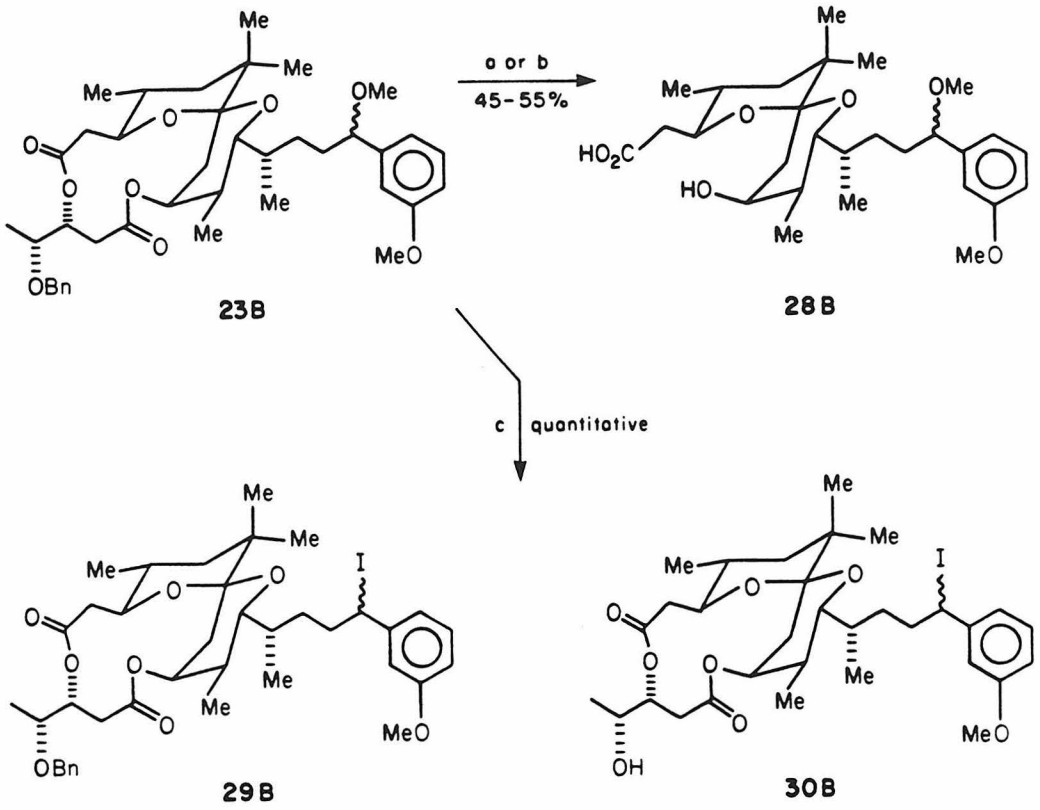


[a] (a) Br_2, $NaHCO_3$, CH_2Cl_2. (b) H_2, Pd/C, EtOH.

were obtained on compound **27B**.[64] Irradiation of the equatorial C-6 methyl led, as in the natural product, to a strong enhancement of the signal for the axial C8 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 a moderate 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 **27B** resulted in the expected enhancements of the signals for C-9 and C-11. However, the NOE observed in aplysiatoxin between the C-10 methyl and the C-29 lactone hydrogen could not be observed in **27B** because of the overlap of the signals for the C-9 and C-29 hydrogens. Because the NOE enhancement is proportional to internuclear distance r by a function of r^{-6}, the large NOE to C-9 might overshadow a smaller NOE to the more distant C-29 hydrogen. Accordingly, we acquired NOE difference spectra on bromoanisole **24B**, 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 bislactones in **24B** and aplysiatoxin are different. This was not unexpected, given the substitution of a C-3 hydrogen in **24B** for the C-3 lactol in aplysiatoxin.

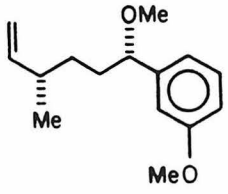
At this time, we were interested in deprotection of the aryl methyl ether to liberate the phenol. Initial attempts to deprotect **23A** or **23B** with lithium iodide, lithium iodide/sodium cyanide or sodium thiophenoxide resulted in apparent decomposition.[65,66,67] Treatment of macrolactone **23B** with either lithium iodide or sodium thiophenoxide in DMF at 140°C, followed by careful workup, led to reasonable yields of hydroxy acid **28B**, the product of bislactone cleavage. (Scheme IX) In order to ascertain the exact conditions required for deprotection while not consuming advanced intermediates, we employed **8b** as a model compound. Lithium iodide in DMF or

Scheme IX Attempted Demethylation of Macrolactone 23[a]



[a] (a) LiI, NaCN, DMF, 140°C. (b) NaSPh, DMF, 140°C. (c) BI_3, CH_2Cl_2, -78°C.

collidine, with or without added sodium cyanide, would not deprotect the phenol methyl ether of **8b** at temperatures up to 140°C. Sodium thiophenoxide in DMF cleaved the



8b

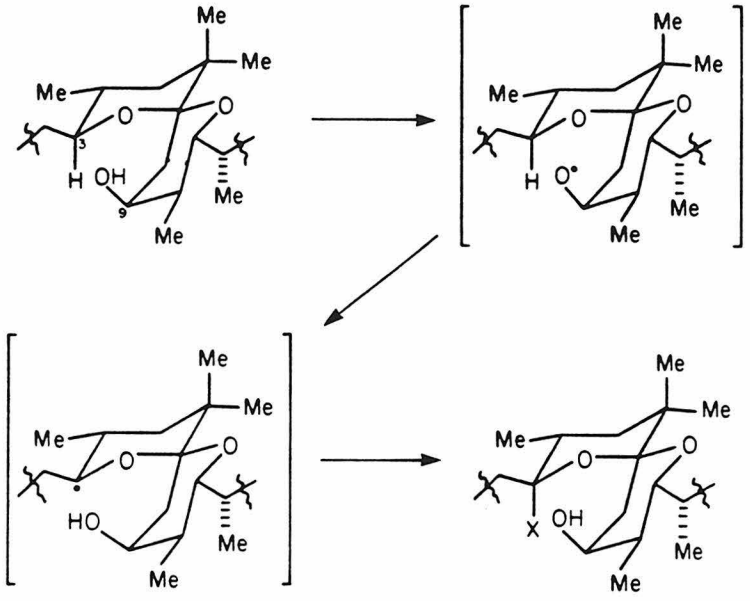
phenol methyl ether at 140°C, but the half-life of the reaction was 2-3 hours. The *para*-brominated analogue of the model compound reacted under the same conditions to yield the phenol with a half-life of 0.5-1 hour. Both sodium thiolacetate and potassium

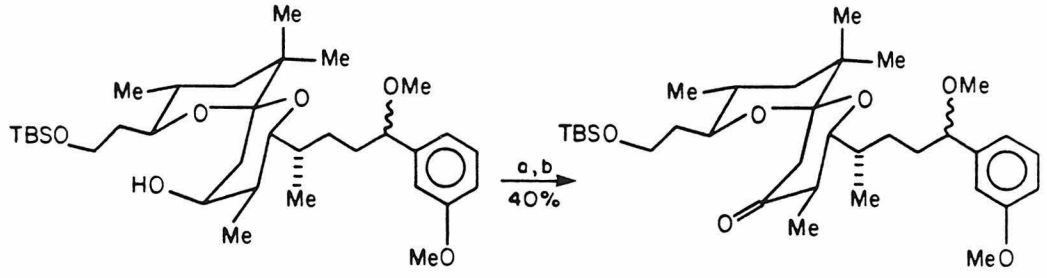
selenocyanate were investigated as potential mild demethylation reagents; both were ineffectual at 140°C in DMF. Because the conditions required for deprotection of the aryl methyl ether were more strenuous than the conditions required for destruction of the macrobislactone linkage, we abandoned this route.

We then shifted our attention to Lewis-acid mediated cleavage of aryl methyl ethers. After reduction of the vinyl linkage, the aforementioned model was used again.[68] To our surprise, treatment of the model compound at -78°C with boron tribromide, boron triiodide or dimethyl boron bromide very quickly substituted bromide or iodide for the benzylic methoxyl group.[55,69,70] Only boron triiodide also removed the phenol methyl ether, and then only after prolonged reaction periods. In order to verify these observations on the actual system in question, we submitted macrolactone **23B** to boron triiodide treatment at -78°C, only to isolate, in quantitative yield, a mixture of benzylic iodides **29B** and **30B.** (Scheme IX, reaction c) Alcohol **30B** results from cleavage of the benzyl ether protecting group in addition to displacement of the benzylic methyl ether. From these results, it is obvious that any attempted synthesis will have to either employ an alternate phenolic protecting group or exchange the phenol methyl ether for another masking group at an earlier stage in the synthesis.

The advanced spiroketal intermediates **16A** and **16B**, apart from their importance as macrolactone precursors, represented logical platforms for the remote functionalization of C-3. (Scheme X) The distance from the C-9 oxygen to C-3, as measured from Dreiding models, was 2.85-2.9A. Based on precedents in steroid chemistry, this distance was expected to be within the allowable range for intramolecular hydrogen atom transfer to an alkoxy radical.[71] 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.[72a,b]

Scheme X Attempted Remote Oxidation[a]





16 B

31 B

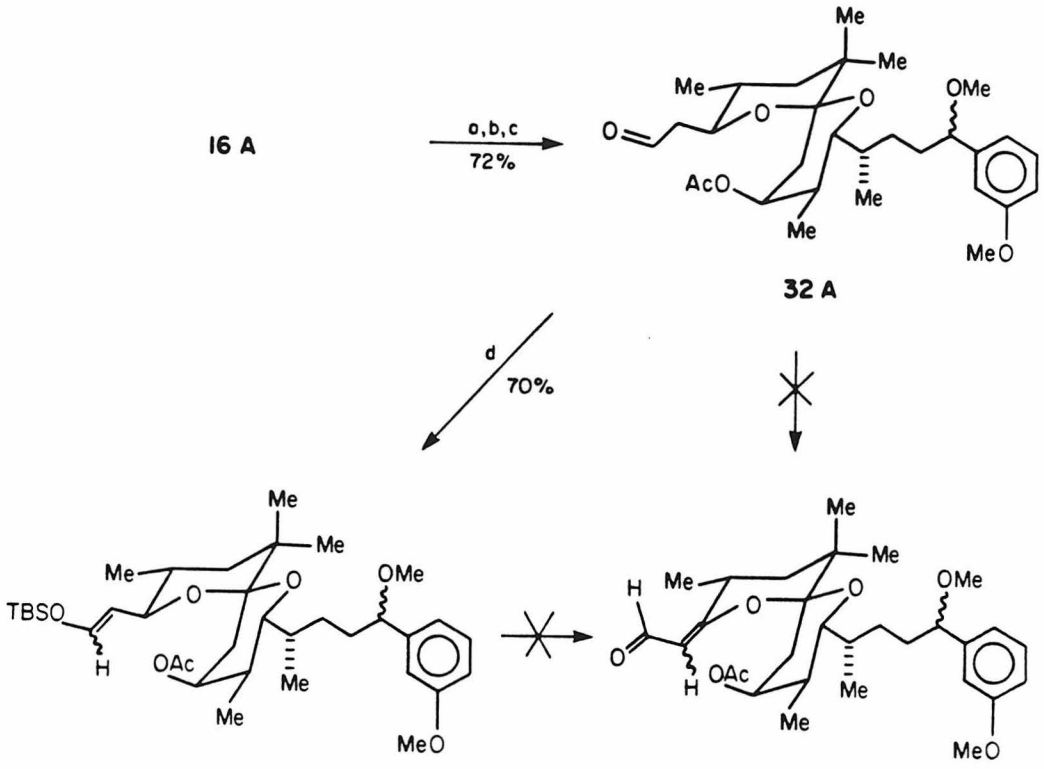
[a] (a) NOCl, pyridine. (b) hν>300 nm.

We had hoped to functionalize C-3 with a hypohalite-mediated remote oxidation, because this would directly yield a labile halolkyl ether, which could easily be converted to either the desired lactol or a protected equivalent. However, attempted oxidation of **16B** with silver carbonate/bromine, lead tetraacetate or lead tetraacetate/iodine, gave no observable reaction via the alkoxy radical; instead, these reagents either oxidized the aromatic side chain, cleaved the silyl ether, or both.[73,74]

In order to test our remote functionalization in a more easily interpretated system, we attempted a Barton oxidation.[75] This remote functionalization is similar to the hypohalite oxidation except that the transferred species is a nitrosyl radical; consequently, the initial adduct is an alkyl nitroso compound. We had not originally intended to employ the Barton reaction in the synthesis because the nitrosoalkyl compound formed would not be 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 **16B** with nitrosyl chloride in pyridine furnished the nitrite ester, which was used immediately. Irradiation at 300 nm for 30 minutes led to complete disappearance of the nitrite ester by TLC. After chromatography, 40% of ketone **31B**, identical to the ketone precursor of alcohols **16A** and **16B**, was isolated, along with several minor products. The predominant formation of this ketone in moderate yield indicates either the disfavored nature of the desired hydrogen abstraction, the instability of the initially produced alkoxy radical, or both.[72a]

After the failure of the remote oxidation route, we eyed another approach to the functionalization of the C-3 position. The C-3 hydroxyethyl side chain would be used to set the stage for an allylic oxidation that would introduce unsaturation at C-3, thereby entering the anhydroaplysiatoxin manifold. (Scheme XI) The alcohol of **16A** was acetylated, and the silyl ether was removed by protonolysis. The resultant primary alcohol

Scheme XI Alternative Oxidation Routes[a]



[a] (a) Ac_2O, pyridine, DMAP. (b) HOAc/THF/H_2O or TBAF, THF. (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2. (d) TBSOTf, Et_3N, CH_2Cl_2.

was oxidized to provide aldehyde **32A**. Attempts to directly dehydrogenate **32A** with DDQ failed.[76] The aldehyde was reacted with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and triethylamine to afford the TBS enol ether as a 60:40 mixture of *trans* and *cis* geometric isomers.[77] The triethylsilyl (TES) enol ether could also be obtained in this manner; the trimethylsilyl enol ether did not appear stable and was not used.

Various reagents were applied in an effort to oxidize the enol ethers. Attempted allylic oxidation of either the TES or TBS enol ethers with stoichiometric palladium acetate or DDQ slowly consumed the starting materials but failed to provide identifiable

products.[76,78a,b] An ene reaction with singlet oxygen was attempted, but no functionalization of C-3 was observed.[79] Diastereomeric α-phenylselenoaldehydes were formed by treatment of the enol ethers with phenylselenyl bromide; however, the selenoxides produced upon oxidation of the selenides failed to afford any unsaturation upon heating.[80,81]

Because of our inability to oxidize the C-3 position, we could not directly compare our diastereomeric advanced intermediates with the natural product. Accordingly, in order to ascertain whether the intermediates derived from **16A** or those from **16B** represented the material with the natural configuration at the C-15 methyl ether, we resorted to circular dichroism spectroscopy (CD). Alcohol **16B** exhibited a positive ellipticity between 260-280 nm in the CD spectrum, while **16A** 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 **16B** to represent the "natural" fragment of 3-desoxyaplysiatoxin.[9]

EXPERIMENTAL

Reactions were run under an atmosphere of argon except where indicated. Reported reaction temperatures were measured externally except where indicated. Reaction vessels were flame-dried *in vacuo* whenever possible. All other glassware was dried at least 12 h in a 120-140°C oven and cooled in a dessicator over "Drierite" prior to use. Solvents for reactions were distilled from an appropriate drying agent unless otherwise indicated. THF and Et_2O were distilled from sodium/benzophenone ketyl under argon. Benzene, methylene chloride, and hexane were distilled from powdered CaH_2 under argon. DMF and DMSO were distilled from powdered CaH_2 at reduced pressure and stored over 4Å molecular sieves, which had been activated by baking at 400°C for 24 h. Ethyl acetate was stored over activated 4Å sieves. NH_3 was distilled from the cylinder and passed through a KOH drying tower prior to use. $CHCl_3$ was passed through a column of activity I alumina; *tert* -butanol was distilled. Pyridine was distilled from powdered CaH_2 and stored over activated 4Å sieves.

Reagents were used as commercially supplied unless otherwise indicated. Et_3N, $EtN(iPr)_2$, $HN(iPr)_2$, $HN(TMS)_2$, benzoyl chloride and oxalyl chloride were distilled from powdered CaH_2. Benzyl bromide and methyl iodide were passed through a column of activity I alumina. Isobutyric acid was stirred with P_2O_5 and distilled. Acrolein was distilled immediately prior to use. DMAP·HCl was prepared by bubbling dry HCl gas through a solution of DMAP in THF. Jones reagent was prepared by a literature procedure.[62] Ag_2O was prepared by a literature procedure immediately prior to use.[82] $SnCl_4$ was distilled from mossy tin. Lithium ribbon was cleaned by sequential immersion into petroleum ether, MeOH and ether. NaI was dried overnight at 70°C/0.05 mm Hg. 2,2' binapthol phosphoric acid was synthesized and resolved by the method of Jacques and Fouquey.[83a,b] The subsequent transformation to 2,2' binapthol was carried out by

the procedure of Kyba *et al.*[84] Nitrosyl chloride was prepared by a literature procedure.[85] Anhydrous *tert*-butyl hydroperoxide/dichloroethane was prepared and titrated by a literature procedure.[86] Butyllithium/hexane was titrated with 1,10 phenanthroline and 2-butanol/xylene. Allyltrimethylsilane was distilled. EtOH was distilled from Na/diethyl phthalate.

Chromatography solvents were reagent or HPLC grade except for THF and Et_3N, which were distilled before use. "Ether" refers to anhydrous diethyl ether supplied by J.T. Baker. "Petroleum ether" refers to the "analyzed reagent" grade (b.p. 35-60°C) supplied by Baker. "Chromatography" refers to gravity chromatography utilizing E. Merck silica gel 60 (70-230 mesh ASTM); "Flash chromatography" was performed on E. Merck silica gel 60 (230-400 mesh ASTM) according to a published procedure.[87] "MPLC" refers to medium pressure liquid chromatography at 10-40 psi on E. Merck "Lobar" silica gel columns. "Alumina" refers to the activity I neutral grade manufactured by M. Woelm; Activity III alumina was obtained by the addition of 6% (w/w) water to activity I alumina. "Acidic silica gel" refers to Silicar CC-4 Special "for column chromatography" supplied by Mallinckrodt Chemical.

Boiling points are uncorrected. Optical rotations were measured in a 1 dm cell of 1 mL capacity using a JASCO DIP-181 polarimeter. $CHCl_3$ used as a solvent for optical rotations was filtered through neutral alumina prior to use. $[\alpha]_D$ refers to the specific rotation at the sodium D line (589 nm) at a temperature of 22°-23°C. Concentration is reported in units of grams/100 mL. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrometer. $CHCl_3$ was used as a solvent for IR spectroscopy unless otherwise indicated. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on either a Varian EM-390, a Jeol GX-400 or a Bruker WM-500 (Southern California NSF regional facility) spectrometer and were recorded in $CDCl_3$, unless otherwise indicated. ^1H NMR

spectral data are reported as follows: chemical shift (multiplicity, integrated intensity, coupling constants in Hz, decoupling information when relevant). Chemical shifts are reported as δ values in parts-per-million relative to tetramethylsilane (δ=0.0) as an internal standard. Analytical thin-layer chromatography (TLC) was conducted on precoated TLC plates (silica gel 60 F-254, layer thickness 0.25mm, E.Merck & Co., Darmstadt, West Germany). TLC plates were visualized by one or more of the following methods: 254nm UV lamp, I_2 vapor, 0.2% $Ce(SO_4)_2$/5% $NH_4Mo_7O_{24}$ in 10% sulfuric acid, 5% phosphomolybdic acid in 95% EtOH or a solution of 1 g vanillin/50 mL H_2SO_4 in 450 mL of 5/4 MeOH/H_2O. Organic acids were also visualized with 0.05% bromocresol green in EtOH.

Elemental combustion 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.

Monobenzyl ether 2 was prepared from either (S)-2-methyl-3-hydroxy propionic acid[32] or the corresponding methyl ester (4 steps, 83% yield) by the procedure of Meyers, *et al.*: $[\alpha]_D$= -17.4 (c = 1.4); literature value for the enantiomer: $[\alpha]_D$= +17.2 ; all other spectral properties were satisfactory.[33,34]

Ester 3 was prepared from **2** according to the procedure of Nagaoka and Kishi in 88% overall yield.[34] After chromatography, 3% of the *cis* olefin was isolated in contrast to the 1.4% reported. 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 signals at δ 6.86 (dd, 1H, J, J' = 15, 6) and 5.76 (dd, 1H, J, J' = 15, 1.5) were reported to have chemical shifts of 6.53 and 5.9, respectively.

Reduction to the allylic alcohol

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 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 was allowed to warm to ambient temperature and stirred for an additional 2 h. The reaction 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 +10 was reported for the opposite enantiomer.[34]

Epoxy alcohol 4

To a stirred -40°C solution of 69.7 mL (234 mmol) of $Ti(OiPr)_4$ in 1.2 L CH_2Cl_2 were added 42.2 mL (246 mmol) of (-) diethyl tartrate at a rate such that the internal reaction temperature did not rise above -30°C. After 10 min, 50.8 g (247 mmol) of the allylic alcohol were added by double-needle transfer in three 65-mL portions of CH_2Cl_2 at a rate such that the internal reaction temperature did not rise above -35°C. 117 mL of 4.2 *M* *tert*-butyl hydroperoxide in dichloroethane were added and the resulting solution was stirred for 5 min at -40°C before being placed in a -20°C freezer. After 48 h, the solution was decanted into a mechanically stirred -5°C solution of 125 g $FeSO_4$ and 80 g *dl* -tartaric acid in 700 ml H_2O. After 30 min, the cooling bath was removed and the green-brown emulsion was allowed to stir for 1 h. Stirring was discontinued and the emulsion was

allowed to stand for 1 h, whereupon the phases separated. The aqueous layer was extracted with two 200-mL portions of CH_2Cl_2, and the combined organic phases were washed with 200 ml of 10% aqueous Na_2CO_3. The organic layer was then concentrated under reduced pressure until a constant mass of 150 g was achieved. To a mechanically stirred 0°C solution of the crude product in 700 mL of reagent-grade ether were added 700 mL of a +3°C solution of 1*N* NaOH in saturated aqueous NaCl. The mixture was stirred for 1 hour and the phases were separated. The aqueous layer was washed with two 100-mL portions of ether and one 200-mL portion of EtOAc. The combined organic layers were washed with 200 mL of saturated aqueous NH_4Cl and 200 mL of saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Concentration under reduced pressure followed by flash chromatography on 700 g silica gel with 40% EtOAc/petroleum ether afforded 53.3 g (98%) of a greater than 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 mm Hg; IR 3600-3100, 3120, 2980, 2850, 1730, 1440, 1370, 1080, 900, 750, 695 cm^{-1}; ^1H NMR (500 MHz) δ 7.34 (bs, 5H), 4.59 (s, 2H), 3.80 (bd, 1H, J = 12), 3.63 (dd, 1H, J, J' = 5, 4), 3.45 (dd, 2H, J, J' = 8, 5), 3.04 (dt, 0.1H, J, J' = 5, 3), 3.0 (dt, 0.9H, J, J' = 5, 2), 2.96 (dd, 0.9H, J, J' = 7, 2), 2.90 (dd, 0.1H, J, J' = 7, 2), 1.80 (apparent septet, 1H, J = 6), 1.72 (m, 1H), 1.07 (d, 3H, J = 8); Anal. calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; Found: C, 70.33; H, 8.06.

Formation of acetonide 5

To a stirred 0°C solution of 52.3 g (236 mmol) of epoxy alcohols **4** in 500 mL 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 was stirred for 5 h and then quenched by the addition of 50 mL reagent-grade MeOH. The reaction was poured into 1L of H_2O,

and the resulting emulsion was acidified to pH 3 (Methyl orange endpoint) with 1N 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) δ 7.26 (bs, 5H), 4.45 (s, 2H), 4.05 - 3.65 (m, 3H), 3.50 (d, 2H, J = 6), 3.20 (bd, 1H, J = 5), 2.73 (bt, 1H, J = 4), 2.0 - 1.55 (m, 3H), 0.94 (d, 3H, J = 7).

To a 0°C stirred solution of the above diol in 400 mL of reagent-grade acetone were added 450 mg $TsOH \cdot H_2O$ and 150 mL 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 pentane and 300 mL 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_2Cl_2 resolved small quantities of the individual diastereomers. The minor diastereomer was initially eluted: R_f = 0.17 (2% Ether/CH_2Cl_2); IR 2980, 2960, 2850, 1370, 1360, 1200, 1105, 960, 740, 690 cm^{-1}; ^1H NMR (500 MHz) δ 7.327 (bs, 5H), 4.487 (s, 2H), 3.935 (dt, 1H, J, J' = 3, 11), 3.93 (m, 1H), 3.835 (ddd, 1H, J, J', J'' = 12, 6, 2), 3.460 (abx, 1H, J, J' = 9.5, 6, Δv = 61.4), 3.338 (abx, 1H, J, J' = 9.5, 5.5, Δv = 61.4), 1.73 (m, 1H), 1.683 (m, 1H), 1.427 (s, 3H), 1.41 (m, 1H), 1.355 (s, 3H), 0.960 (d, 3H, J = 6.9). There was then eluted the

major diastereomer: R_f = 0.15 (2% Ether/CH_2Cl_2); bp 85-90°C/0.005 mm Hg; $[\alpha]_D$= +25.9 (c = 1.07, $CHCl_3$); IR-same as minor isomer; ^1H NMR (500 MHz) δ 7.32 (bs, 5H), 4.513 (ab, 1H, J = 12.1, Δv = 18.5), 4.47 (ab, 1H, J = 12.1, Δv = 18.5), 3.94 (dt, 1H, J = 3, 12), 3.83 (m, 2H), 3.483 (abx, 1H, J, J' = 9.1, 4.8, Δv = 30.4), 3.419 (abx, 1H, J, J' = 9.1, 6, Δv = 30.4), 1.83 (m, 1H), 1.60 (m, 2H), 1.42 (s, 3H), 1.35 (s, 3H), 0.945 (d, 3H, J = 7); Anal. calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15; Found: C, 72.70; H, 9.17.

Debenzylation

To 600 mL of liquid NH_3 were added 67.3 cm of Li ribbon (46.8 mg/cm, 454 mmol); 58.5g (222 mmol) of acetonide **5** were added by double-needle transfer in 220 mL of THF to the resulting deep blue solution. After the solution was stirred for 40 min, the reaction was quenched by the slow addition of 12.1 g 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 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 mm Hg; $[\alpha]_D$ = +13.2 (c = 1.1, $CHCl_3$); IR 3400, 2980, 1370, 1190, 1090 cm^{-1}; ^1H NMR (90 MHz) δ 4.1-3.8 (m, 3H), 3.59 (bd, 2H, J = 6), 3.0 (m, 1H), 1.8-1.5 (m, 3H), 1.45 (s, 3H), 1.36 (s, 3H), 0.90 (d, 3H, J = 6); Anal. calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41; Found: C, 61.86; H, 10.35.

Hydroxy lactone 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 Et_3N in 450 mL CH_2Cl_2 were added 25.5 mL (334 mmol) of methanesulfonyl chloride (MsCl) dropwise. After the addition was complete, the reaction 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 separated 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 material 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) δ 4.35 (dd, 1H, J, J' = 6, 2), 4.24 (t, 1H, J = 5.5), 3.75 - 3.4 (m, 3H), 3.03 (s, 3H), 2.1 (m, 1H), 1.83 (dd, 1H, J, J' = 8, 5), 1.65 (m, 1H), 1.45 (s, 3H), 1.36 (s, 3H), 0.80 (d, 3H, J= 7).

To a solution of the above 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 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 solidified 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) δ 3.83 (dd, 2H, J, J' = 6, 4), 3.60 (s, 1H), 3.50 (dd, 2H, J, J' = 8, 5), 3.30 (d, 0.5H, J = 3), 3.15 (bs, 0.5H), 1.7-1.5 (m, 2H), 1.8 (s, 3H), 1.4 (s, 3H), 0.93 (d, 3H, J = 7).

To a stirred 0°C solution of 44.2 mL (315 mmol) of HN(*i*-Pr)$_2$ in 325 mL 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 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 6N 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 silica gel with 50% EtOAc/petroleum ether to afford 13.51 g (35%, 3 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 mm Hg; $[\alpha]_D$= -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) δ 4.32 (m, 2H), 3.62 (dt, 1H, J, J' = 9, 5), 2.8 (m, 1H), 1.85 (m, 1H), 1.78 (m, 1H), 1.71 (s, 2H), 1.22 (s, 3H), 1.17 (s, 3H), 0.98 (d, 3H, J =

4); Anal. calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74; Found: C, 64.34; H, 9.57.

Silylation

To a stirred solution of 23.7 g (132 mmol) of hydroxylactone **6** and 26.9 g (395 mmol) imidazole in 150 mL DMF were added 29.8 g (198 mmol) of *tert*-butyldimethylsilyl chloride (TBSCl) in small portions. The reaction was stirred overnight and then decanted into 300 mL ether. The solution was washed with 200 mL of saturated aqueous NH_4Cl/100 mL H_2O, and the aqueous wash was back-extracted with 100 mL ether. The combined organic layers were washed, sequentially, with 300 mL 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 on 500 g silica gel with 9% EtOAc/petroleum ether 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 mm Hg; IR 2980, 2960, 2830, 1710, 1460, 1390, 1260, 1140, 1090 cm^{-1}; ^1H NMR (90 MHz) δ 4.0 (dt, 1H, J, J' = 3, 8), 3.74 (dd, 2H, J, J' = 7, 6), 1.8-1.5 (m, 5H), 1.20 (s, 6H), 0.93 (obscured doublet, 3H), 0.84 (s, 9H), 0.03 (s, 6H); Anal. calcd. for $C_{16}H_{32}O_3Si$: C, 63.94; H, 10.73; Found: C, 63.87; H, 10.66.

Enol ether 7

8.40 g (29.8 mmol) Tebbe reagent was transferred into a 250 mL round-bottom flask under inert atmosphere in a dry box.[42a,b] The septum-sealed flask was removed from the drybox and 60 mL of THF were 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 was allowed to warm to -40°C over 2 h and then brought to 0°C for 30 min. The reaction 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 emulsion was poured into a 1 L flask and stirred for 2 h, affording a yellow precipitate. The suspension was diluted with 100 mL 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 mm Hg) 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) δ 4.30 (s, 1H), 4.16 (s, 1H), 3.76 (dd, 2H, J, J' = 8.7), 3.18 (dt, 1H, J, J' = 3, 10), 2.1-1.3 (m, 5H), 1.16 (s, 3H), 1.10 (s, 3H), 0.93 (s, 9H), 0.83 (d, 3H, J = 6), 0.10 (s, 3H), 0.04 (s, 3H); Anal. calcd. for $C_{17}H_{34}O_2Si$: C, 68.39; H, 11.48; Found: C, 68.13; H, 11.55.

Citronellene monoepoxide

By the procedure of Ireland *et al.*, 18.93 g of (S) (+) citronellene ($[\alpha]_D$ = 10.9, neat, Fluka) was epoxidized to afford, after distillation (65°C/15 mm Hg), 17.6 g (83%) of a mixture of diastereomeric monoepoxides:[43] R_f = 0.43 (9% ether/petroleum ether); IR 3070, 2990, 2980, 2950, 2900, 1640, 1460, 1380,1240, 1120, 910 cm^{-1}; ^1H NMR (90 MHz) δ 5.66 (m, 1H), 4.92 (bd, 1H, J = 16), 4.90 (bd, 1H, J = 12), 2.66 (t, 1H, J = 5), 2.15 (m, 1H), 1.6 - 1.35 (m, 4H), 1.30 (s, 3H), 1.25 (s, 3H), 1.0 (d, 3H, J = 6).

Benzylic alcohols 8

To a stirred 0°C suspension of 31.6 g 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, an additional 2.0 g of H_5IO_6 were added. After the suspension was stirred for a total of 5 h, the reaction was filtered through celite and washed with 100 mL 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 THF in a 250 mL 3N flask equipped with an addition funnel and a condenser were added 25.0 g (134 mmol) of *m*-bromoanisole in 65 mL 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 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 supernatant 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 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 mm Hg); IR 3500-3300, 3000, 1580, 1475, 1250, 1140, 1040, 910 cm^{-1}; ^1H NMR (90 MHz) δ 7.22 (t, 1H, J = 8), 6.85 - 6.65 (m, 3H), 5.63 (ddd, 1H, J, J', J'' = 17, 12, 7), 4.90 (bd, 1H, J = 17), 4.83 (bd, 1H, J = 12), 4.56 (dd, 1H, J, J' = 7, 6), 3.75 (s, 3H), 2.1 - 1.2 (m, 5H), 0.95 (d, 3H, J = 7); Analysis calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; Found: C, 76.26; H, 9.11.

Methylation

11.3 g of KH suspension (nominally 35% w/w KH, 98.6 mmol) were 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. 19.7 g (89.4 mmol) of the mixture of diastereomeric benzylic alcohols **8** were 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 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 mm Hg; IR 2970, 2830, 1600, 1580, 1480, 1260, 1100, 790 cm^{-1}; ^1H NMR (90 MHz) δ 7.15 (m, 1H), 6.76 (m, 3H), 5.56 (ddd, 1H, J, J', J'' = 16, 10, 7), 4.90 (d, 1H, J = 16), 4.85 (d, 1H, J = 10), 3.97 (dd, 1H, J = 6, 5), 3.72 (s, 3H), 3.17 (s, 3H), 2.03 (m, 1H), 1.8 - 1.1(m, 5H), 0.95 (d, 3H, J = 6); Anal. calcd. for $C_{15}H_{22}O_2$: C, 76.91; H, 9.46; Found: C, 76.91; H, 9.38.

Allylic alcohols 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 reagent-grade MeOH was bubbled O_3/O_2 for 2.5 hours, at which time the red color was dispelled. The reaction 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 was allowed to warm to ambient temperature over a period of 4 h. The solution was diluted with 300 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 nominally 0.4*M* vinyl magnesium bromide in 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 were 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 mm Hg; IR 3500, 3070, 2980, 2930, 1600, 1460, 1250, 1100, 690 cm^{-1}; ^1H NMR (90 MHz) δ 7.2 (m, 1H), 6.8 (m, 3H), 5.8 (m, 1H), 5.23 (m, 1H), 5.10 (m, 1H), 4.0 (dd, 1H, J, J' = 8, 5), 3.76 (s, 3H), 3.41(q, 1H, J = 7), 3.20 (s, 3H), 1.66 (m, 4H), 0.93 (m, 3H); Anal. calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15; Found: C, 72.49; H, 9.18.

Enones 10

To a stirred -78°C solution of 4.83 mL (55.4 mmol) oxalyl chloride in 75 mL CH_2Cl_2 were added 7.85 mL (110 mmol) 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 resulting suspension was allowed to warm to ambient temperature. The suspension was diluted with 50 ml 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 silica gel with 15% EtOAc/petroleum ether, furnished a light-yellow oil. Distillation (140-145°C/0.03 mm Hg) 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) δ 7.22 (m, 1H), 6.80 (m, 3H), 6.30 (d, 1H, J = 9), 6.25 (bs, 1H), 5.69 (dd, 1H, J, J' = 9, 3), 4.0 (dd, 1H, J, J' = 6, 2), 3.75 (s, 3H), 3.15 (bs, 3H), 2.75 (m, 1H), 1.66 (m, 4H), 1.05 (d, 1.5H, J = 6), 1.0 (d, 1.5H, J = 6); Anal. calcd. for $C_{16}H_{20}O_3$: C, 73.25; H, 8.45; Found: C, 73.29; H, 8.51.

Alkylphenone

To a stirred -60°C solution of 2.97 mL (33.9 mmol) oxalyl chloride in 40 mL CH_2Cl_2 were added 4.8 mL (68 mmol) DMSO. After the reaction was stirred for 5 min, 5.00 g (22.7 mmol) of the diastereomeric mixture of benzylic alcohols **8** were added in 20 mL of CH_2Cl_2 over a 5 min period. After 10 additional minutes, 12.7 mL (90.6 mmol) Et_3N and 20 mL CH_2Cl_2 were added, and the reaction was allowed to warm to ambient temperature. The suspension was diluted with 100 ml H_2O and extracted with 150 mL ether. The aqueous phase was re-extracted with 50 mL ether, and the combined organic phases were washed with 50 mL of H_2O and 50 mL of saturated aqueous $NaHCO_3$. The solution was dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography on 100 g of silica gel with 10% EtOAc/petroleum ether afforded 4.69 g (95%) of the alkylphenone as a yellow oil: R_f = 0.40 (15% ether/petroleum ether); bp 90-100°C/0.01 mm Hg; IR 3080, 2960, 1675, 1595, 1585, 1460, 1425, 1260, 1030,

980, 915 cm^{-1}; ^1H NMR (90 MHz) 7.4 (m, 2H), 7.25 (t, 1H, J = 8), 7.05 (m, 1H), 5.60 (ddd, 1H, J, J', J'' = 17, 10, 7), 4.9 (bd, 1H, J = 17), 4.85 (bd, 1H, J = 11), 3.75 (s, 3H), 2.85 (t, 2H, J = 7), 2.2 (m, 1H), 1.7 (m, 2H), 1.05 (d, 3H, J = 6); Anal. calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; Found: C, 77.07; H, 8.28.

Asymmetric reduction

To a stirred 0°C suspension of 39.87 mL 1.60*M* LAH/THF were added 32.55 mL of 2*M* EtOH/THF and 18.64 g (S) 2,2' binapthol in 97 mL THF. The resulting suspension was cooled to an internal temperature of -100°C (LN_2/Ether/MeOH), and 4.69 g (21.5 mmol) of the above alkylphenone was added in 21 mL THF at a rate such that the internal reaction temperature did not rise above -95°C. The reaction was stirred at -100°C for 4 h and then allowed to warm to -78°C, where it was kept for 16 h. The reaction was subsequently decanted into 230 mL of rapidly stirring aqueous 1:1 2*N* HCl/THF. The resulting mixture was diluted with 200 mL ether and 100 mL saturated aqueous NH_4Cl, and the phases were separated. The aqueous phase was extracted with 200 mL ether, and the combined organic layers were dried (Na_2SO_4). Concentration under reduced pressure furnished a crystalline mass, which was dissolved in a minimum amount of acetone and diluted with 30 mL of C_6H_6. The resulting solution was concentrated until the onset of crystallization was observed. Petroleum ether was added to precipitate the greater part of the binapthol, which was removed by vacuum filtration. The filtered precipitate was recrystallized using the same procedure to afford a nearly quantitative recovery of pure binapthol. The combined filtrates were concentrated under reduced pressure and subjected to flash chromatography on 200 g of silica gel. Elution with 15% EtOAc/petroleum ether initially afforded 758 mg (16%) of recovered alkylphenone. Further elution provided 3.365 g (71%) of benzylic alcohol **8a**: R_f = 0.33 (20% EtOAc/petroleum ether); bp 120 - 125°C/0.01 mm Hg; $[\alpha]_D$= -24.5 (c = 1.2, $CHCl_3$); IR 3600, 3500-3300, 3180, 3000,

2970, 2940, 2870, 1600, 1590, 1480, 1450, 1250, 1160, 1050, 920 cm^{-1}; ^1H NMR (400 MHz, d-6 DMSO) δ 7.181 (t, 1H, J = 7.8), collapses to (d, J = 7) when 6.743 irrad.), 6.844 (s, 1H), 6.83 (obscured d, 1H, collapses to broad singlet when 7.18 irrad.), 6.743 (dd, 1H, J, J' = 8, 2.5, collapses to (d, J = 2) when 7.18 irrad.), 5.628 (ddd, 1H, J, J', J'' = 17.3, 10.2, 7.3), 4.894 (d, 1H, J = 18), 4.858 (d, 1H, J = 10.5), 4.301 (m, 1H), 3.706 (s, 3H), 2.038 (apparent p, 1H, J = 7), 1.53 (m, 2H), 1.33 (m, 1H), 1.18 (m, 1H), 0.891 (d, 3H, J = 6.8); Anal. calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; Found: C, 76.37; H, 9.14.

Further elution provided a small amount of 1,1 binapthol.

Mosher ester of 8a

To a stirred solution of 100 mg (0.454 mmol) of asymmetric reduction product **8a** and 138 mg (0.589 mmol) (-) α–methoxy-α(trifluoromethyl)phenylacetic acid (MTPA) in 2 mL CH_2Cl_2 were added 121 mg (0.589 mmol) DCC in 1 mL CH_2Cl_2. The immediately cloudy reaction was stirred for 6 h and then diluted with 80 mL of petroleum ether. After filtration through celite, the solution was washed, sequentially, with 50 mL of 10% aqueous Na_2CO_3 and 30 mL of saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography on 20 g silica gel with 7.5% EtOAc/petroleum ether afforded 190 mg (94%) of a 97:3 mixture of diastereomeric esters, as assessed by the ratio of singlets at δ 3.787/3.715 in the ^1H NMR spectrum: R_f = 0.38 (7.5% EtOAc/petroleum ether); bp 140 - 150°C/ 0.005 mm Hg; IR 2950, 2860, 1745, 1600, 1590, 1490, 1260, 1170, 1120, 1015, 995, 920 cm^{-1}; ^1H NMR (400 MHz) δ 7.440 (bd, 2H, J = 7.3), 7.40 - 7.31 (m, 3H), 7.265 (t, 1H, J = 9), 6.931 (d, 1H, J = 7.6), 6.883 (d, 1H, J = 2.1), 6.858 (dd, 1H, J, J' = 8.2, 2.4), 5.910 (dd, 1H, J, J' = 7.9, 5.8), 5.557 (ddd, 1H, J, J', J'' = 17, 10.5, 7.8), 4.904 (bd, 1H, J = 17.1), 4.895 (bd, 1H, J = 10.4), 3.787 (s, 3 x 0.97H, major isomer), 3.715 (s, 3 x

0.03H, minor isomer), 3.465 (bs, 3H), 2.03 (m, 1H), 1.95-1.71 (m, 2H), 1.27-1.11 (m, 3H), 0.902 (d, 3H, J = 6.7); Anal. calcd. for $C_{24}H_{27}F_3O_4$: C, 66.04; H, 6.22; Found: C, 66.20; H, 6.24.

To ensure that no diastereoselection had taken place during chromatography, NMR analysis was run on a small sample of crude material. The ratio of diastereomers was identical to that found for the chromatographed sample; however, approximately 20% of MTPA anhydride was also present in the crude NMR.

Mosher esters of 8

By the same procedure used for the formation of the above ester, 55 mg of the diastereomeric mixture of alcohols **8** were esterified to yield 161.5 mg (quantitative)of a 60:40 mix of MTPA esters. The mixture was identical to the above ester by TLC and IR: ^{1}H NMR (400 MHz) δ 7.437 (bd, 1H, J = 7.0), 7.367 (m, 2H), 7.335 (m, 2H), 7.263 (m, 0.6H, J = 7.8), 7.206 (t, 0.4H, J = 7.9), 6.929 (bd, 0.6H, J = 7.6), 6.875 (m, 1H), 6.845 (m, 0.6H), 6.801 (m, 0.8H), 6.720 (d, 0.6H, J = 1.5), 5.906 (dd, 0.6H, J, J' = 7.9, 5.8), 5.848 (dd, 0.4H, J, J' = 7.9, 5.8), 5.60 (m, 0.4H), 5.56 (m, 0.6H), 3.786 (s, 3 x 0.6H), 3.714 (s, 3 x 0.4H), 3.547 (bd, 3 x 0.4H, J = 1.2), 3.461 (bd, 3 x 0.6H, J = 1.2), 2.1 - 1.75 (m, 3H), 1.37 - 1.1 (m, 2H), 0.957 (d, 3 x 0.4H, J = 6.7), 0.899 (d, 3 x 0.6H, J = 6.7).

Spiroketal enol ether 11

2.00 g (6.71 mmol) of enol ether **7**, 2.61 g (9.99 mmol) enone **10** and 60 mg (5 mol %) of 4-hydroxy 2,2,6,6 tetramethyl-1-pipiridinyloxy free radical were 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 cooling 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 was allowed to cool, and a ^{1}H NMR

spectrum of the crude product 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 5-15% 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 mm Hg; IR 3050, 2980, 2960, 2900, 2860, 1670, 1590, 1580, 1480, 1450, 1250, 1100, 1050, 830 cm^{-1}; ^1H NMR (500 MHz) δ 7.23 (dd, 1H, J, J' = 8, 6), 6.80 (m, 3H), 4.46 (bt, 1H, J = 7), 4.034 (t, 0.5H, J = 7), 4.008 (t, 0.5H, J = 7), 3.801 (s, 1.5H), 3.800 (s, 1.5H), 3.754 (t, 0.5H, J = 10), 3.744 (t, 0.5H, J = 10), 3.526 (m, 1H), 3.30 (tt, 1H, J, J' = 10, 2), 3.196(s, 3H), 2.1 - 1.3 (>12H), 1.034 (d, 1.5H, J = 7.5), 1.018 (obscured doublet, 1.5H), 1.010 (s, 1.5H), 1.001 (s, 1.5H), 0.878 (bs, 9H), 0.844 (s, 3H), 0.788 (s, 1.5H), 0.778 (d, 1.5H, J = 7), 0.770 (d, 1.5H, J = 7), 0.060 (s, 6H); Anal. calcd. for $C_{33}H_{56}O_5Si$: C, 70.67; H, 10.06; Found: C, 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 mm Hg; IR 2940, 2910, 2820, 1700, 1590, 1580, 1450, 1250, 1100, 830 cm^{-1}; ^1H NMR (400 MHz) δ 7.23 (m, 2H), 6.83 (m, 6H), 6.43 - 6.35 (m, 0.5H), 6.233 (ddd, 0.5H, J, J', J'' = 17.4, 4.6, 1.2), 5.749 (ddd, 0.5H, J, J', J'' = 10.7, 2, 1.5), 4.47 (m, 0.5H), 4.20 (m, 0.5H), 4.02 (m, 2H), 3.81 (bs, 6H), 3.33 (m, 1H), 3.207, 3.204, 3.196, 3.190, 3.184 (s, 0.2 x 6H), 2.1 - 1.5 (12H), 1.091 (d, 1.5H, J = 6.7), 1.062 (d, 1.5H, J = 6.7), 0.995 (m, 3H), 0.875 (m, 3H); 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.

Hydroboration

To a stirred -5°C solution of 40 mL 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 H_2O, 9 mL 15% aqueous NaOH and 6 mL 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 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 portion 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 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) δ 7.233 (t, 0.5H, J = 8.0), 7.222 (t, 0.5H, J = 8.0), 6.82 (m, 2H), 6.789 (dd, 1H, J, J' = 8.5, 1.5), 4.044 (t, 0.5H, J = 8), 4.031 (t, 0.5H, J = 8), 3.835 (m, 1H), 3.790 (s, 1.5H), 3.786 (s, 1.5H), 3.750 (bt, 0.5H, J = 10), 3.740 (bt, 0.5H, J = 10), 3.690 (dt, 0.5H, J, J' = 2.5, 8.0), 3.580 (dt, 0.5H, J, J' = 2.5, 8.0), 3.486 (m, 1H), 3.274 (bs, 0.5H), 3.255 (bs, 0.5H), 3.200 (s, 1.5H), 3.195 (s, 1.5H), 2.182 (m, 1H), 1.864 (apparent septet, 1H, J = 7.5), 1.822 (m, 1H), 1.750 (m, 2H), 1.627 (m, 1H), 1.62 (m, 1H), 1.536 (m, 1H), 1.500 (m, 2H), 1.47 (m, 1H), 1.340 (dt, 0.5H, J, J' = 1, 7), 1.315 (dt, 0.5H, J, J' = 1, 7), 0.912 (s, 3H), 0.864 (s, 4.5H), 0.858 (s, 4.5H), 0.84 (obscured, 3H), 0.802 (s, 1.5H), 0.782 (s, 1.5H), 0.740 (d, 1.5H, J = 6.5), 0.728 (d, 1.5H, J = 6.5), 0.040 (s, 3H), 0.020 (s, 3H); Anal. calcd. for $C_{33}H_{58}O_6Si$: C, 68.46; H, 10.09; Found: C, 68.50; H, 10.11.

Benzoate esters 12

To a stirred solution of 2.490 g (4.30 mmol) of the above mixture of alcohols, 1.8 mL (12.9 mmol) Et_3N and 155 mg (1.27 mmol) DMAP in 8 mL CH_2Cl_2 was added 0.65 mL (5.6 mmol) benzoyl chloride (BzCl), and the resulting solution was stirred overnight. The reaction was diluted with 100 mL 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 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) δ 7.981 (dd, 2H, J, J' = 7, 1.5), 7.53 (m, 1H), 7.419 (t, 1H, J = 7.6), 7.409 (t, 1H, J = 7.6), 7.210 (t, 0.5H, J = 8), 7.191 (dt, 0.5H, J, J' = 1, 8), 6.80 (m, 3H), 5.13 (m, 1H), 4.000 (bt, 1H, J = 6, collapses to multiplet when 1.51 irrad.), 3.88 - 3.81 (m, 1H, collapses to (d, J = 8.5) when 1.51 irrad.), 3.780 (s, 1.5H), 3.777 (s, 1.5H), 3.77 - 3.70 (m, 1H), 3.66 (m, 1H, collapses to broad singlet when 5.13 irrad), 3.54 (m, 1H, collapses to broad singlet when 1.51 irrad.), 3.166 (s, 1.5H), 3.163 (s, 1.5H), 2.35 (m, 1H), 2.00 - 1.2 (18H), 1.08 (m, 1H), 1.00 - 0.76 (19H), 0.876 (s, 4.5H), 0.874 (s, 4.5H) 0.062 (s, 3H), 0.058 (s, 3H); Anal. calcd. for $C_{40}H_{62}O_7Si$: C, 70.34; H, 9.15; Found: C, 70.28; H, 9.12.

Isomerization to equatorial benzoates 13

To a stirred solution of 2.100 g (3.07 mmol) of benzoates **12** in 4 mL $CHCl_3$ was added 0.5 mL of 0.3*M* HCl/$CHCl_3$, and the septa-sealed reaction was stirred overnite. After 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 ether and the combined organic layers were washed with 50 mL 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 chromatographty on a "Lobar" C column with a gradient ranging from 8-10% 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) δ 7.98 (m, 2H), 7.534 (m, 1H), 7.412 (t, 0.5 x 2H,, J = 7.6), 7.399 (t, 0.5 x 2H, J = 7.6), 7.200 (t, 0.5H, J = 8.1), 7.192 (t, 0.5H, J = 8.1), 6.81 (m, 1H, collapses to broad singlet when 7.2-7.19 irrad.), 6.804 (d, 1H, J = 2), 6.768 (m, 1H, collapses to broad singlet when 7.2-7.19 irrad.), 4.89 (m, 1H, begins to collapse when 4.06 irrad), 4.059 (bd, 1H, J = 10, collapses to broad singlet when 4.89 irrad.), 3.993 (m, 1H), 3.812 (dd, 1H, J, J' = 7.8, 5), 3.776 (s, 3H), 3.77 (m, 1H), 3.175 (s, 1.5H), 3.165 (s, 1.5H), 3.16 (m, 1H), 2.14 (m, 1H), 1.94 (m, 1H), 1.89 - 1.17 (12H), 0.955 (s, 1.5H), 0.918 (s, 1.5H), 0.840 - 0.820 (6H), 0.839 (s, 4.5H), 0.820 (s, 4.5H), 0..795 (bd, 3H, J = 6.5), 0.033 (s, 1.5H), 0.007 (s, 1.5H), 0.004 (s, 1.5H), -0.026 (s, 1.5H); Anal. calcd. for $C_{40}H_{62}O_7Si$: C, 70.34; H, 9.15; Found: C, 70.40; H, 9.20.

There were 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 equilibration; 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 re-equilibrated 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.

Cleavage of the benzoate ester

To a stirred 0°C solution of 1.122 g (1.64 mmol) of diastereomeric benzoates **13** in 4 mL THF were added 1.65 mL nominally 1*M* LAH/THF dropwise. The reaction was quenched after 2 h by the sequential addition of 60 μL H_2O in 0.2 mL THF, 60 μL 15% aqueous NaOH in 0.2 mL THF and 180 μL H_2O in 0.2 mL THF. 2 mL of ether were added, and the mixture was stirred for 30 min. 10 mL ether and a small portion of $MgSO_4$ were then added, and the suspension was filtered through celite with ether. The filtrate was concentrated under reduced pressure and subjected to chromatography on 150 g 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) δ 7.207 (t, 1H, J = 7.5), 6.83 (m, 1H), 6.82 (bs, 1H), 6.768 (bd, 1H, J = 7.9), 4.032 (t, 0.5H, J = 6.4), 4.012 (t, 0.5H, J = 7.2), 3.786 (s, 3H), 3.78 - 3.70 (m, 3H), 3.614 (dd, 1H, J, J' = 9.6, 2), 3.398 (bs, 1H), 3.197 (s, 3H), 3.11 (m, 1H), 2.084 (dd, 1H, J, J' = 13.5, 2.7), 1.84 - 1.39 (11H), 1.284 (dd, 1H, J, J' = 13.6, 4), 1.184 (t, 1H, J = 13), 0.904 (bs, 3H), 0.871 (s, 4.5H), 0.852 (s, 4.5H), 0.806 (d, 3H, J = 6.7), 0.789 (s, 1.5H), 0.785 (s, 1.5H), 0.751 (d, 3H, J = 6.5), 0.034 (s, 3H), 0.003 (s, 1.5H), -0.003 (s, 1.5H); Anal. calcd. for $C_{33}H_{58}O_6Si$: C, 68.46; H, 10.09; Found: C, 68.49; H, 10.00.

Ketones 14

To a -78°C stirred solution of 0.29 mL (3.4 mmol) oxalyl chloride in 3.5 mL CH_2Cl_2 was added 0.32 mL DMSO dropwise and the resulting solution was stirred for 5 min. 1.295 g (2.24 mmol) of the above mixture of alcohols 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) Et_3N was added, and the reaction was warmed to -40°C. 0.3 mL additional Et_3N was added, and the white suspension was allowed to warm to 0°C. The reaction was rinsed 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 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 10-20% EtOAc/petroleum ether afforded 1.250 g (97%) of a diastereomeric mixture of ketones **14** 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) δ7.216 (bt, 1H, J = 7.6), 6.82 (obscured d, 1H), 6.81 (bs, 1H), 6.783 (bd, 1H, J = 8.2), 4.158 (bs, 1H), 4.020 (t, 0.5H, J = 7.3), 4.000 (t, 0.5H, J = 7.6), 3.788 (s, 1.5H), 3.787 (s, 1.5H), 3.616 (dd, 1H, J, J' = 8, 4.3, collapses to (d, J = 8) when 1.51 irrad.), 3.58 (m, 1H), 3.184 (s, 3H), 3.15 (m, 1H, begins to collapse when 1.51 irrad.), 2.45 (m, 1H), 2.277 (m, 0.5H), 2.23 (m, 0.5H), 2.17 - 2.07 (m, 2H), 1.78 (m, 1H), 1.63 (m, 1H), 1.49 (m, 1H, begins to collapse when 3.6 irrad.), 1.382 (dd, 1H, J, J' = 13.5, 4.5, collapses to (d, J = 13) when 1.63 irrad.), 1.270 (t, 1H, J = 13, collapses to (d, J = 13) when 1.63 irrad.), 1.010 (s, 1.5H), 0.997 (s, 1.5H) 0.889 (s, 1.5H), 0.883 (s, 1.5H), 0.846 (s, 4.5H), 0.833 (s, 4.5H), 0.796 (d, 3H, J = 7.6), 0.776 (d, 3H, J = 6.4, collapses to broad singlet when 1.63 irrad.), 0.19 (s, 1.5H), 0.014 (s, 1.5H), 0.001 (s, 1.5H), -0.05 (s, 1.5H); Anal. calcd. for $C_{33}H_{56}O_6Si$: C, 68.70; H, 9.78; Found: C, 68.84; H, 9.88.

Formation of the enol triflates

0.254 g of KH suspension (nominally 35% w/w KH, 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 dropwise to the suspension. Following completion of the addition, the reaction was allowed to warm to ambient temperature over a period of 45 minutes. 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 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}; ^1H NMR (90 MHz) δ 7.22 (t, 1H, J = 8), 6.8 - 6.75 (m, 3H), 5.66 (m, 1H, collapses to (d, J = 4.5) when 2.2 irrad.), 4.1 (m, 1H), 4.0 (m, 1H), 3.78 (s, 3H), 3.65 (m, 2H), 3.20 (s, 3H), 2.40 (bd, 1H, J = 15), 2.1 - 1.1 (12H), 1.05 (s, 1.5H), 1.00 (s, 1.5H), 0.95 (s, 3H), 0.85 (s, 9H), 0.80 (m, 6H), 0.03 (s, 6H); Anal. calcd. for $C_{34}H_{55}F_3O_8SSi$: C, 57.60; H, 7.82; Found: C, 57.71; H, 7.94.

Methyl olefins 15

To a -5°C suspension of 2.87 g (14.0 mmol) $CuBr{\cdot}Me_2S$ in 15 mL 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 hrs and then quenched by double-needle transfer into 50 mL of rapidly 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 10-15% 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}; ^1H NMR (400 MHz) δ 7.225 (t, 1H, J = 7.5), 6.840 (m, 2H), 6.792 (d, 1H, J = 8.0), 5.327 (bs, 1H), 4.088 (bd, 1H, J = 10), 4.025 (m, 1H), 3.793 (s, 3H), 3.666 (m, 1H), 3.493 (m, 1H), 3.202 (s, 1.5H), 3.199 (s, 1.5H), 3.009 (m, 1H), 2.317 (bd, 1H, J = 15), 2.025 (d, 1H, J = 16), 1.9-1.4 (9H), 1.501 (bs, 3H), 1.298 (m, 1H), 1.188 (t, 1H, J = 7.0), 0.986 (s, 1.5H), 0.963 (s, 1.5H), 0.863 (s, 4.5H), 0.842 (s, 4.5H), 0.821 (s, 3H), 0.742 (d, 1.5H, J = 6.5), 0.738 (d, 1.5H, J = 6.5), 0.697 (d, 1.5H, J = 6.7), 0.663 (d, 1.5H, J = 6.5), 0.003 (s, 3H), -0.018 (s, 3H); ^{13}C NMR (22.5 MHz, $CDCl_3$) 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.

Hydroboration

To a stirred 0°C mixture of 275 mg (0.475 mmol) methyl olefins **15** and 66 uL Et_3N were added, dropwise, 4.75 mL 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 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 hours and then heated to 50°C for 30

min. After cooling to ambient temperature, the reaction was decanted into 30 mL 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 presure, chromatography on 20 g of silica gel with 33% ether/petroleum ether afforded 218 mg (77%) of a mixture 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}; ^1H NMR (90 MHz) δ 7.23 (t, 1H, J = 8), 6.86 (m, 3H), 4.03 (m, 1H), 3.83 (s, 3H), 3.75 - 3.33 (m, 4H), 3.23 (s, 3H), 3.20 (m, 1H), 2.45 (dd, 1H, J, J' = 12, 5), 2.0 - 1.2 (15H), 0.95 - 0.75 (24H), 0.08 (s, 3H), 0.03 (s, 3H); Anal. calcd. for $C_{34}H_{60}O_6Si$: C, 68.87; H, 10.20; Found: C, 68.73; H, 10.20.

Swern oxidation

To a stirred -78°C solution of 47 uL (540 μmol) oxalyl chloride in 0.5 mL CH_2Cl_2 was added 76 μL (1.1 mmol) 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 was brought to -50°C. After 10 minutes, 187 μL (1.33 mmol) Et_3N were added, and the resulting suspension was warmed to -20°C. After 10 minutes, 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 on 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}; ^1H NMR (400 MHz) δ 7.219 (t, 0.5H, J = 8.4),

7.214 (t, 0.5H, J = 8.4), 6.83-6.76 (m, 3H), 4.023 (t, 0.5H, J = 6.6), 3.997 (t, 0.5H, J = 6.6), 3.787 (s, 1.5H), 3.792 (s, 1.5H), 3.751 (dd, 1H, J, J' = 10, 2), 3.615 (dt, 0.5H, J, J' = 5.4, 10), 3.543 (dt, 0.5H, J, J' = 5.4, 10), 3.446 (dt, 0.5H, J, J' = 5.8, 10), 3.406 (dt, 0.5H, J, J' = 5.8, 10), 3.200 (s, 1.5H), 3.197 (s, 1.5H), 3.183 (m, 1H), 3.107 (m, 0.5H), 3.085 (m, 0.5H), 2.886 (ab, 0.5H, J = 12.9), 2.874 (ab, 0.5H, J = 12.9), 2.428 (ab, 1H, J = 13.2), 2.300 (dq, 1H, J, J' = 10, 6.3), 1.78 - 1.41 (9H), 1.302 (dd, 1H, J, J' = 13, 4), 1.145 (d, 1H, J = 12.9), 1.105 (m, 1H), 0.94-0.83 (overlapping, 26H, including singlets at 0.863, 0.832), 0.757 (d, 3H, J = 6.3), 0.013 (s, 3H), -0.035 (s, 1.5H), -0.039 (s, 1.5H); Anal. calcd. for $C_{34}H_{58}O_6Si$: C, 69.10; H, 9.89; Found: C, 69.15; H, 10.01.

Spiroketal alcohols 16A, B

To a stirred -78°C solution of 180 mg (298 μmol) of the above ketone in 0.3 mL THF were added, dropwise, 2.98 mL 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 MeOH, 1.75 mL 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 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 **16B** as a colorless oil: R_f = 0.29 (15% ether/petroleum ether); $[\alpha]_D$= +1.5 (c = 0.55, $CHCl_3$); IR 3450, 2950, 2920, 2840, 1580, 1450, 1350, 1090, 1060, 830 cm^{-1}; ^1H NMR (400 MHz) δ 7.208 (dd, 1H, J, J' = 8.3, 7.8, 2D experiment shows coupling to 6.82, 6.76), 6.82 (obscured

doublet, 1H, coupled to 7.21), 6.817 (bs, 1H), 6.763 (ddd, 1H, J, J', J'' = 8.3, 2.7, <1, coupled to 7.208), 3.99 (dd, 1H, J, J' = 7.5, 5.5, coupled to 1.75 - 1.65 region), 3.785 (s, 3H), 3.73 (m, 1H, begins to collapse if irrad. 3.19), 3.72 (dd, 1H, J, J' = 11, 2.5; 3.73-3.72 coupled to 3.19, 2.3, 1.6 - 1.5 spin systems), 3.62 (t, 2H, J = 7.1, coupled to 1.77, 1.54), 3.205 (s, 3H), 3.176 (d, 1H, J = 4.1, coupled to 3.73, collapses to singlet when 3.73 irrad, -OH), 2.301 (dd, 1H, J, J' = 14.2, 2.9, collapses to (d, J = 14) when 3.73 irrad, coupled to 1.55), 1.8 - 1.6 (5H: 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, 1H, J, J' = 14.3, 3.7, collapses to (d, J = 3) when 2.3 irrad., coupled to 3.72), 1.53 (m, 1H, coupled to 3.62, 3.39, 1.82, 0.82), 1.40 (m, 1H, coupled to 1.72), 1.285 (abx, 1H, J, J' = 12.8, 4.9, Δv = 26.4), 1.219 (ab, 1H, J = 12.8, Δv = 26.4), 0.888 (s, 3H), 0.869 (m, 1H), 0.846 (s, 9H), 0.820 - 0.800 (obscured doublets, 6H, coupled to 1.8 - 1.5), 0.803 (s, 3H), 0.789 (d, 3H, J = 6.4), 0.001 (s, 6H); Exact mass calcd. for $C_{34}H_{59}O_5Si$ (MH^+-H_2O): 575.4132; Found: 575.4122

There were then eluted 96.0 mg (53%) of alcohol **16A** as a colorless oil: R_f = 0.25 (15% ether/petroleum ether); $[\alpha]_D$ = +15.5 (c = 2.8, $CHCl_3$); IR 3500, 2950, 2920, 2840, 1580, 1450, 1350, 1090, 1060, 830 cm^{-1}; ^1H NMR (400 MHz) δ 7.215 (d, 1H, J = 8.1), 6.822 (m, 2H), 6.775 (dd, 1H, J, J' = 7.3, 1.9), 4.021 (t, 1H, J = 6.5), 3.790 (s, 3H), 3.75 - 3.65 (m, 4H), 3.414 (m, 1H), 3.257 (d, 1H, J = 11.2), 3.200 (s, 3H), 2.305 (dd, 1H, J, J' = 14.4, 3.2), 1.9 - 1.4 (10H), 1.279 (dd, 1H, J, J' = 13.5, 4.7), 1.23 (m, 1H), 0.870 (bs, 12H), 0.829 (d, 3H, J = 6.8), 0.794 (s, 3H), 0.791 (d, 3H, J = 6.4), 0.763 (d, 3H, J = 6.8), 0.035 (s, 6H); ^{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.

Benzylation of methyl lactate

To a stirred water-cooled solution of 4.00g (38.4 mmol) (R) (+) methyl lactate and 4.79 mL (40.2 mmol) of benzyl bromide in 80 mL Et_2O were added, over a 15 minute period, 9.0 g (40 mmol) of Ag_2O. After 2 h, the reaction mixture was filtered through celite with reagent-grade ether. The solvent was removed under reduced pressure to furnish 7.8 g of a clear oil, which was used without further purification. A small sample was distilled (110-120°C/0.1 mm Hg) for analysis: R_f = 0.35 (8% EtOAc /petroleum ether); $[\alpha]_D$ = $+151^o$ (c=1.5, $CHCl_3$); IR 3080, 3000, 2980, 2900, 1740, 1460, 1380, 1280, 1200, 1140, 1050, 1020 cm^{-1}; ^1H NMR (90MHz) δ 7.34 (s, 5H), 4.69 (ab, 1H, J = 12), 4.40 (ab, 1H, J = 12), 4.04 (q, 1H, J = 7), 4.04 (q, 1H, J = 7), 3.72 (s, 3H), 1.38 (d, 3H, J = 7); Anal. calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.12; H, 7.29.

DIBAL reduction

To a stirred -78°C solution of the above ester in 80 mL 3:1 hexane/Et_2O were added 47 mL of nominally 0.9*M* DIBAL/hexane at a rate that did not cause the internal reaction temperature to exceed -75°C. After the addition was complete, the reaction was stirred at -78°C for 5 min and quenched by the addition of 5 mL of reagent-grade methanol. The mixture was allowed to warm to 0°C over a 30 min period, and 25 mL 0.5 *N* aqueous sodium potassium tartrate were added. The resulting emulsion was rapidly stirred for 3 h and then extracted with two 50-mL portions of ether. The combined organic extracts were washed with 50 mL of saturated aqueous NaCl and dried (Na_2SO_4). Concentration under reduced pressure followed by bulb-to-bulb distillation (90-110°C/0.1 mm Hg) yielded 5.75g (91%, two steps) of the aldehyde as a colorless oil: R_f = 0.25 (8% EtOAc/petroleum ether); $[\alpha]_D$=+64.6 (c = 3.6, $CHCl_3$); IR 3010, 3000, 2950, 2880, 2820, 2720, 1745, 1460, 1380, 1130, 1100, 1040, 1030, 700 cm^{-1}; ^1H NMR (90MHz) δ 9.66 (d, 1H, J = 2), 7.30 (s, 5H), 4.61 (s, 2H), 3.87 (dq, 1H, J, J' = 2, 7), 1.32,(d,

3H, J = 7).

Homoallylic alcohol 17

To a stirred -78°C solution of 4.1 mL (35.0 mmol) of $SnCl_4$ in 140 mL CH_2Cl_2 were added 5.74 g (35.0 mmol) of the above aldehyde in 35 mL CH_2Cl_2 at a rate that did not cause the internal reaction temperature to exceed -70°C. The ensuing white suspension was stirred for 3 min at -78°C and allyltrimethylsilane (5.12 mL) was added. After 15 min, the reaction was quenched by the addition of 5 mL H_2O. The resulting suspension was allowed to warm to 0°C and was decanted into 200 mL of saturated aqueous $NaHCO_3$. The aqueous emulsion was extracted with 200 mL of CH_2Cl_2, and, after dilution with 200 mL of H_2O, was re-extracted with 200 mL of EtOAc. The combined organic extracts were washed with 100 mL of saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Concentration under reduced pressure gave a colorless oil, which was subjected to chromatography on 350 g of silica gel with 15% EtOAc/petroleum ether to afford, initially, 5.40 g (74%) of the alcohol **17** as a colorless oil: R_f = 0.34 (15% EtOAc/petroleum ether); bp 100–105°C/0.05 mm Hg; $[\alpha]_D$ = -49.0 (c = 1.57, $CHCl_3$); IR 3580, 3010, 2890, 1460, 1070 cm^{-1}; ^1H NMR (90 MHz) δ 7.36 (s, 5H), 5.85 (m, 1H), 5.15 (dd, 1H, J, J' = 8, 2), 4.95 (d, 1H, J = 2), 4.63 (ab, 1H, J = 11), 4.40 (ab, 1H, J = 11), 3.4 (m, 2H), 2.5 (bs, 1H), 2.3 (m, 2H), 1.2 (d, 3H, J = 6); Anal. calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79; Found: C, 75.76; H, 8.69.

Further elution provided 571 mg (8%) of an approximately 1:1 mix of the desired product and the C3 epimer.

Mosher ester of alcohol 17

To a stirred solution of 14.4 mg (69.9 umol) of alcohol **17** and 24 mg (100 umol) of (-) MTPA acid in 100 uL $CHCl_3$ were added 2 mg DMAP and 3 mg DMAP·HCl. The reaction was heated to 50°C for 12 h and then allowed to cool to ambient temperature. The

resulting suspension was diluted with 0.5 mL CH_2Cl_2 and poured into 2 ml of ether. After the precipitated dicyclohexyl urea was removed by filtration through celite, the filtrate was concentrated under reduced pressure. The precipitation was repeated, and the crude oil was filtered through 5 g silica gel with 15% ether/petroleum ether to afford 25.1 mg (85%) of a light yellow oil consisting of greater than 90% of a single stereoisomer, as evidenced by the ratio of methyl doublets at 1.060 and 1.288 in the ^1H NMR spectrum: R_f = 0.56 (30% ether/petroleum ether); IR 3170, 2980, 2940, 1750, 1450, 1280, 1170, 1120, 1020, 1000, 930 cm^{-1}; ^1H NMR (400 MHz) δ 7.540 (bd, 1H, J = 7.3), 7.376-7.25 (9H), 5.758 (dddd, 1H, J, J', J'', J''' = 17, 9, 8, 6), 5.246 (dt, 1H, J, J' = 8.5, 4.5), 5.110 (dd, 1H, J, J' = 18.9, 1.3), 5.098 (bd, 1H, J = 9), 4.550 (ab, 1H, J = 11.9, Δv = 46.3), 4.431 (ab, 1H, J = 11.9, Δv = 46.3), 3.659 (dq, 1H, J, J' = 5.2, 6.4), 3.516 (d, 3H, J = 0.9), 2.571 (dddd, 1H, J, J', J'', J''' = 15, 8, 4, 1.5), 2.385 (dt, 1H, J, J' = 15, 8), 1.288 (d, <0.3H, J = 6.4), 1.060 (d, 3H, J = 6.4); Exact mass calcd. for $C_{23}H_{26}F_3O_4$ (MH^+): 423.1784; Found: 423.1794.

Nitrobenzyl ether 18

A suspension of 65.0 mg (0.316 mmol) alcohol **17**, 200 mg (0.926 mmol) *o*-nitrobenzyl bromide, 150 mg (0.980 mmol) BaO and 17.0 mg (0.099 mmol) $Ba(OH)_2$ in 600 μL C_6H_6 was stirred for 2 h. 400 μL DMF were 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. 0.5 mL MeOH was added, and the reaction 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 mm Hg (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) δ 8.00 (dd, 1H, J, J' = 8, 1.5), 7.85 (d, 1H, J = 7), 7.55 (dt, 1H, J, J' = 1.5, 7); 7.45 (m, 1H), 7.30 (s, 5H), 5.8 (m, 1H), 5.09 (bd, 1H J = 18), 5.05 (bd, 1H, J = 9), 5.00 (s, 2H), 4.63 (ab, 1H, J = 12), 4.43 (ab, 1H, J = 12), 3.6 (quintet, 1H, J = 6), 3.6 (m, 1H), 2.40 (m, 2H), 1.2 (d, 3H, J = 6); UV 210nm (ε = 12,300), 260 nm (ε = 4280); Exact mass calcd. for $C_{20}H_{24}O_4N$ (MH^+): 342.1705; Found: 342.1714.

Acid 19

To a solution of 78.2 mg (0.213 mmol) nitrobenzyl ether **18** in 2 mL *tert*-butanol was added a solution of 7 mg $KMnO_4$, 225 mg $NaIO_4$ and 29 mg K_2CO_3 in 29 mL of 7:3 *tert*-butanol/H_2O. After 2.5 h, the reaction mixture was poured into 50 mL ether/30 mL 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 10-50% 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) δ 8.05 (dd, 1H, J, J' = 7, 1), 7.75 (d, 1H, J = 7), 7.6 (t, 1H, J = 6), 7.5(m, 1H), 7.33(s, 5H), 5.0 (s, 2H), 4.63 (ab, 1H, J = 11), 4.5 (ab, 1H, J = 11), 4.12 (m, 1H), 3.77 (m, 1H, collapses to (d, J = 5) when 1.2 irrad.), 2.70 (m, 2H, collapses to bs when 4.12 irrad.), 1.2 (d, 3H, J = 6); Exact mass calcd. for $C_{19}H_{22}O_6N$ (MH^+): 360.1447; Found: 360.1457.

Ester 20A

To a stirred solution of 23.6 mg (39.9μmol) of alcohol **16A** and 0.5 mL of a 0.160*M* solution of acid **19** in CH_2Cl_2 were added 17 mg (82.5 μmol) of DCC and 80 μL of a 0.1*M* solution of DMAP/DMAP·HCl in CH_2Cl_2. After 24 h, the resulting white suspension was diluted with ether and filtered through celite. Concentration under reduced pressure provided a colorless oil, which was directly subjected to chromatography on 10 g of silica gel. Elution with a gradient ranging from 10-30% ether/petroleum ether initially returned 3.1 mg of **16A**. Further elution provided 32.9 mg (89%) of ester **20A** as a colorless oil: R_f = 0.33 (30% ether/petroleum ether); $[\alpha]_D$ = +37.1 (c = 2.5, $CHCl_3$); IR 2960, 2930, 2870, 1725, 1600, 1450, 1380, 1340, 1100, 1075, 840 cm^{-1}; ^1H NMR (400MHz) δ 7.961 (d, 1H, J = 8.2), 7.694 (d, 1H, J = 7.6), 7.501 (t, 1H, J = 7.1), 7.325 (t, 1H, J = 7.5), 7.25-7.14 (m, 9H), 6.78 (m, 1H), 6.772 (d, 1H, J = 1.5), 6.717 (dd, 1H, J, J' = 7, 2), 4.958 (m, 1H, begins to collapse when 2.09 irrad.), 4.973 (ab, 1H, J = 14.6, Δν = 40.2), 4.872(ab, 1H, J = 14.6, Δν = 40.2), 4.543 (ab, 1H, J = 11.9, Δν = 33.2), 4.460 (ab, 1H, J = 11.6, Δν = 33.2), 4.14 (m, 1H, collapses to (d, J = 5) when 2.61-2.5 irrad.), 3.960 (t, 1H, J = 6.4), 3.780 (bd, 1H, J = 8.5), 3.78 - 3.65 (m, 2H), 3.729 (s, 3H), 3.59 (m,1H), 3.141 (s, 3H), 2.94 (m, 1H), 2.614 (abx, 1H, J, J' = 15.8, 3, Δν = 42.2), 2.508 (abx, 1H, J, J' = 15.9, 9.3, Δν = 42.2), 2.088 (dd, 1H, J, J' = 14.6, 4.5, collapses to (d, J = 15) when 4.96 irrad.), 1.85-1.30 (m, 11H), 1.59 (dd, 1H, J, J' = 15.2, 4, collapses to (d, J = 15) when 4.96 irrad., collapses to broad singlet when 2.09 irrad.), 1.18 (m, 1H), 1.140 (d, 3H, J = 6.1), 1.03 (m, 1H), 0.817 (s, 9H), 0.711 (s, 3H), 0.69 - 0.65 (m, 6H), 0.670 (s, 3H), 0.592 (d, 3H, J = 6.7), -0.18 (s, 6H); Exact mass calcd. for $C_{53}H_{79}NO_{11}Si$ (M^-): 933.5424; Found: 933.5445.

Ester 20B

To a stirred mixture of 350 μL of a 0.3M solution of acid **19** in CH_2Cl_2 and 31.0 mg (52 μmol) of alcohol **16B** 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 dicyclohexyl urea and filtered through celite. Concentration under reduced pressure provided a colorless oil, which was directly applied to 10 g of silica gel. Elution with a gradient ranging from 10-30% ether/petroleum ether initially returned 3.1 mg of recovered **16B**. Further elution afforded 38.0 mg (79%) of ester **20B** 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) δ 8.046 (dd, 1H, J, J' = 7.6, 1.2), 7.76 (d, 1H, J = 7.6), 7.569 (t, 1H, J = 7.6), 7.397 (t, 1H, J = 7.2), 7.309 (bs, 5H), 7.236 (t, 1H, J = 7.9), 6.85 (m, 2H), 6.790 (dd, 1H, J, J' = 7.3, 1.8), 5.039 (ab, 1H, J = 14.7, Δv = 40.8), 5.024 (m, 1H), 4.934 (ab, 1H, J = 14.7, Δv = 40.8), 4.613 (ab, 1H, J = 11.9, Δv = 33.3), 4.525 (ab, 1H, J = 11.9, Δv = 33.3), 4.191 (m, 1H), 4.025 (t, 1H, J = 6.5), 3.808 (s, 3H), 3.8 (m, 3H), 3.686 (m, 1H), 3.217 (s, 3H), 3.010 (m, 1H), 2.679 (abx, 1H, J, J' = 15.9, 3.4, Δv = 47), 2.562 (abx, 1H, J, J' = 16.2, 9.15, Δv = 47), 2.118 (dd, 1H, J, J' = 14.8, 5.0), 1.8 - 1.64 (m, 7H), 1.495 (m, 1H), 1.39 (m, 2H), 1.239 (d, 1H, J = 11.3), 1.199 (d, 3H, J = 6.4), 1.100 (dd, 1H, J, J' = 13.6, 12.5), 1.082 (m, 1H), 0.896 (s, 3H), 0.885 (bs, 9H), 0.795 (m, 3H), 0.791 (s, 3H), 0.737 (d, 3H, J = 6.7), 0.655 (d, 3H, J = 6.7), 0.0420 (s, 3H), 0.0359 (s, 3H); Exact mass calcd. for $C_{53}H_{79}O_{11}NSi$ (M^-): 933.5422; Found: 933.5427.

Desilylation of 20A

1 mL of 1:1:1 THF/HOAc/H_2O was added to 24.0 mg of ester **20A**. After being stirred for 12 h, the mixture was pipetted into 20 mL of H_2O and extracted with two 30-mL

portions of ether. Drying (Na_2SO_4), and concentration under reduced pressure provided a yellow oil, which was subjected to flash chromatography on 10 g of silica gel with 50% ether/petroleum ether to afford 20.6 mg (98%) of the alcohol as a colorless oil: R_f = 0.23 (50% ether/petroleum ether); $[\alpha]_D$ = +29.0 (c = 1.07); IR 3500, 2970, 2910, 2850, 1725, 1600, 1540, 1380, 1340, 1100, 1060 cm^{-1}; ^1H NMR (400 MHz) δ 8.038 (dd, 1H, J, J' = 8.2, 1), 7.784 (d, 1H, J = 7.9), 7.585 (t, 1H, 7.6), 7.400 (t, 1H, J = 7.6), 7.33 - 7.26 (m, 5H), 7.232 (t, 1H, J = 8.0), 6.87 (obscured d, 1H, collapses to (s, 1H) when 7.23 irrad.), 6.86 (bs, 1H), 6.791 (dd, 1H, J, J' = 7.3, 1.8, collapses to (d, J = 2) when 7.23 irrad.), 5.124 (m, 1H, collapses to (t, J = 3) when 2.25 irrad.), 5.044 (ab, 1H, J = 14.8, Δv = 32.6), 4.963 (ab, 1H, J = 14.8, Δv = 32.6), 4.618 (ab, 1H, J = 11.6, Δv = 34), 4.533 (ab, 1H, J = 11.6, Δv = 34), 4.22 (m, 1H, collapses to (d, J = 5) when 2.76 - 2.71 irrad.), 4.053 (t, 1H, J = 6.5); 3.84 (m, 1H, collapses to (d, J = 5) when 1.23 irrad.), 3.83 - 3.65 (m, 2H), 3.815 (s, 3H), 3.785 (dd, 1H, J, J' = 10.5, 2), 3.220 (s, 3H), 2.759 (abx, 1H, J, J' = 16, 4, collapses to (ab, 1H, J = 16, Δv = 18.3) when 4.22 irrad.), 2.713 (abx, 1H, J = 15, 3, collapses to (ab, 1H, J = 16, Δv = 18.3) when 4.22 irrad.), 2.334 (dd, 1H, J, J' = 15, 3), 1.93 - 1.8 (m, 2H), 1.75 (m, 1H, begins to collapse when 0.732 irrad.), 1.73-1.56 (m, 10H), 1.52 (m, 1H, begins to collapse when 0.732 irrad.), 1.43 (m, 1H), 1.285 (dd, 1H, J, J' = 13.5, 4.5), 1.27 (m, 1H), 1.227 (d, 3H, J = 6.4), 1.14 (m, 1H), 0.888 (s, 3H), 0.799 (s, 3H), 0.732 (d, 6H, J = 7), 0.654 (d, 3H, J = 7); Exact mass calcd. for $C_{47}H_{65}NO_{11}$ (M^-): 819.4558; Found: 819.4589.

Acid 21A

To a stirred solution of 20.5 mg (25 μmol) of the above alcohol in 0.5 mL reagent-grade acetone were added 24 μL of 1.75*M* Jones reagent in acetone. After 30 min, the reaction was quenched by the addition of 5 drops of reagent-grade isopropanol, along with a small amount of celite. The resulting suspension was stirred for 10 min, and the blue-green

precipitate was removed by filtration through celite with acetone. After concentration under reduced pressure, chromatography on 5 g of acidic silica with a solvent gradient ranging from 7.5-40% EtOAc/petroleum ether afforded 17.5 mg (87%) of acid **21A** as a viscous, colorless oil: R_f = 0.45 (40% EtOAc/petroleum ether); $[\alpha]_D$ = +60.3 (c = 1.75, $CHCl_3$); IR 3500-2900, 2980, 2940, 2870, 1760-1720, 1600, 1530, 1460, 1350, 1100, 1080 cm^{-1}; ^1H NMR (400 MHz) δ 8.043 (dd, 1H, J, J' = 7.3, 1), 7.776 (d, 1H J = 8), 7.584 (t, 1H, J = 7.2), 7.405 (t, 1H, J = 7.5), 7.35-7.28 (m, 4.5H), 7.258 (t, 1H, J = 7.8), 6.87 (m, 1H), 6.856 (d, 1H, J = 1), 6.826 (bd, 1H, J = 8), 5.106 (m, 1H, collapses to broad triplet when 2.23 irrad.), 5.040 (ab, 1H, J = 14.7, Δv = 26.4), 4.974 (ab, 1H, J = 14.7, Δv = 26.4), 4.606 (ab, 1H, J = 11.8, Δv = 25.5), 4.543 (ab, 1H, J = 11.8, Δv = 25.5), 4.220 (m, 1H, collapses to (d, J = 4.5) when 2.68 irrad.), 4.048 (dd, 1H, J, J' = 7.7, 5.6), 3.983 (dd, 1H, J, J'= 10.7, 1), 3.84 (m, 1H, collapses to (d, J = 5) when 1.23 irrad.), 3.822 (s, 3H), 3.31 (m, 1H, collapses to (dd, J, J' = 11, 5) when 2.43 irrad.), 3.243 (s, 3H), 2.675 (d, 2H, J = 7, collapses to singlet when 4.22 irrad.), 2.633 (abx, 1H, J, J' = 13.8, 5, Δv = 81, collapses to (d, J = 14) when 3.31 irrad.), 2.431 (abx, 1H, J, J' = 13.8, 3.5, Δv = 81, collapses to (d, J = 14) when 3.31 irrad.), 2.241 (dd, 1H, J, J' = 15.2, 2.9, collapses to (d, J = 15) when 5.11 irrad.), 2.08 (m, 2H, collapses to (apparent ddd, J, J', J" = 22, 11, 4) when 0.783 irrad.), 1.66 (m, 1H), 1.659 (dd, 1H, J = 15, 3.7, colllapses to (d, J = 15) when 5.11 irrad.), 1.58-1.36 (m, 3H), 1.335 (dd, 1H, J, J' = 14, 4.6), 1.236 (d, 3H, J = 6.4), 1.150 (t, 1H, J = 13), 0.973 (s, 3H), 0.828 (s, 3H), 0.783 (d, 3H, J = 6.4), 0.736 (d, 3H, J = 6.4), 0.667 (d, 3H, J = 6.7); Exact mass calcd. for $C_{47}H_{62}O_{12}N$ (M-1): 832.4272; Found: 832.4296

Desilylation of 20B

2 mL of 2:2:1 THF/HOAc/H_2O were added to 38.0 mg (40.7 μmol) of ester **20B**, and the resulting solution was stirred for 10 h. The reaction was poured into 40 mL of ether and

washed sequentially with 20 mL H_2O and 20 mL 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 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) δ 8.034 (d, 1H, J = 7.6), 7.770 (d, 1H, J = 7.3), 7.566 (t, 1H, J = 7.3), 7.391 (t, 1H, J = 7.6), 7.31 (m, 5H), 7.24 (m, 1H), 6.894 (m, 2H), 6.796 (d, 1H, J = 9.4), 5.127 (m, 1H), 5.035 (ab, 1H, J = 14.9, Δv = 32.1), 4.954 (ab, 1H, J = 14.6, Δv = 32.1), 4.605 (ab, 1H, J = 11.8, Δv = 34.0), 4.520 (ab, 1H, J = 11.8, Δv = 34.0), 4.20 (m, 1H), 4.121 (q, 1H, J = 7.0), 4.028 (t, 1H, J = 6.3), 3.818 (s, 3H), 3.759 (d, 1H, J = 11), 3.646 (m, 1H), 3.480 (q, 3H, J = 7.1), 3.227 (s, 3H), 3.2 (m, 1H), 2.956 (bs, 1H), 2.707 (m, 2H), 2.245 (dd, 1H, J, J' = 15.0, 5.0), 1.95-1.20 (25H), 1.206 (d, 3H, J = 6.4), 0.954 (s, 3H), 0.880 (m, 4H), 0.823 (s, 3H), 0.793 (d, 3H, J = 6.1), 0.734 (d, 3H, J = 6.4), 0.634 (d, 3H, J = 6.4), 0.071 (bs, 6H); Exact mass calcd. for $C_{47}H_{65}O_{11}N$ (M^-): 819.4558; Found: 819.4541.

Acid 21B

By the same procedure employed in the oxidation of the diastereomeric alcohol, 33.0 mg (40.3 μmol) of the alcohol derived from ester **20B** were oxidized with Jones reagent to afford 32.3 mg (95%) of acid **21B** as a 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) δ 8.037 (dd, 1H, J, J' = 7.3, 0.9), 7.760 (d, 1H, J = 7.3), 7.576 (dt, 1H, J, J' = 0.9, 7.3), 7.400 (t, 1H, J = 7.6), 7.31 (m, 6H), 6.922 (t, 1H, J = 2.4), 6.90 (obscured d, 1H), 6.811 (dd, 1H, J, J' = 8.1, 1.7), 5.101 (m, 1H), 5.025 (ab, 1H, J = 14.7, Δv = 26.8), 4.958 (ab, 1H, J =

14.7, Δv = 26.8), 4.609 (ab, 1H, J = 11.4, Δv = 38.2), 4.513 (ab, 1H, J = 11.4, Δv = 38.2), 4.200 (ddd, 1H, J, J', J'' = 7.4, 4.8, 4.6), 4.053 (t, 1H, J = 6.9), 3.84 (m, 1H), 3.834 (s, 3H), 3.812 (m, 1H), 3.481 (q, 1H, J = 7.0), 3.315 (m, 1H, begins to collapse when 2.43 irrad.), 3.235 (s, 3H), 2.653 (s, 1H), 2.639 (d, 1H, J = 2.7), 2.602 (abx, 1H, J, J' = 15.0, 4.6, Δv = 70), 2.422 (abx, 1H, J, J' = 15.0, 2.7, Δv = 70), 2.04 (m, 1H), 1.90 (m, 1H), 1.76 (m, 2H), 1.70-1.58 (m, 2H), 1.650 (dd, 1H, J', J'' = 15.2, 4.0), 1.537 (bq, 1H, J = 6.7), 1.40 (m, 1H), 1.324 (dd, 1H, J, J' = 13.8, 4.5), 1.253 (bs, 3H), 1.219 (d, 3H, J = 7.0), 1.21 (m, 1H), 0.909 (s, 3H), 0.808 (s, 3H), 0.782 (d, 6H, J = 6.7), 0.666 (d, 3H, J = 7.0); Exact mass calcd. for $C_{47}H_{63}O_{12}N$ (M-): 833.4350; Found: 833.4331.

Hydroxy acid 22A

A stirred solution of 17.5 mg (21 μmol) of acid **21A** in 21 mL degassed reagent-grade MeOH in a 50-mL Pyrex roundbottom flask was irradiated for 40 min 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 7.5-40% EtOAc/petroleum ether afforded 12.4 mg (85%) of hydroxy acid **22A** as a viscous light-yellow oil: R_f = 0.33 (40% EtOAc/petroleum ether); $[\alpha]_D$ = +50.0 (c = 1.25, $CHCl_3$); IR 3500-2900, 2970, 2930, 2880, 1760-1700, 1600, 1460, 1260, 1100, 1080 cm^{-1}; ^1H NMR (400 MHz) δ 7.36 - 7.29 (m, 5H), 7.256 (t, 1H, J = 7.8), 6.87 (m, 1H), 6.86 (bs, 1H), 6.822 (m, 1H), 5.147 (m, 1H, collapses to singlet when 2.32 irrad.), 4.675 (ab, 1H, J = 11.6, Δv = 75), 4.487 (ab, 1H, J = 11.6, Δv = 75), 4.060 (dd, 1H, J, J' = 7, 5.5), 4.05 - 3.97 (m, 2H), 3.820 (s, 3H), 3.598 (dq, 1H, J, J' = 4.9, 6.4, collapses to (d, J = 5) when

1.24 irrad.), 3.359 (apparent dt, 1H, J, J' = 5.5, 4.6), 3.243 (s, 3H), 2.635 (abx, 1H, J = 13.8, 5, Δv = 89, collapses to (d, 1H, J = 14) when 3.36 irrad.), 2.583 (m, 2H), 2.413 (abx, 1H, J, J' = 13.8, 4, Δv = 89, collapses to (d, J = 14) when 3.36 irrad.), 2.325 (dd, 1H, J, J' = 15.3, 3), 2.17-2.0 (m, 2H), 1.733 (dd, 1H, J, J' = 15, 4, collapses to (d, J = 14) when 2.41 irrad.), 1.71 (m, 2H, collapses to (dd, J, J' = 11, 3.5) when 0.754 irrad.), 1.51 - 1.40 (m, 4H), 1.365 (dd, 1H, J, J' = 14, 4.5), 1.243 (d, 3H, J = 6.4, collapses to (s, 3H) when 3.598 irrad.), 1.19 (m, 1H), 0.985 (s, 3H), 0.856 (s, 3H), 0.811 (d, 3H, J = 6.4), 0.758 (d, 3H, J = 7), 0.745 (d, 3H, J = 6.7); Exact mass calcd. for $C_{40}H_{57}O_{1O}$ (M-1): 697.3952; Found: 697.3974.

Hydroxy acid 22B

A solution of 32.3 mg of acid **21B** in 40 mL of MeOH in a 100-mL flask was photodeprotected in the same manner as acid **21A**, to afford, after workup and chromatography, 4.2 mg (13%) of recovered starting material and 19.8 mg (74%) of hydroxy acid **22B** as a colorless, viscous 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) δ 7.20 (bs, 5H), 6.84 (bs, 1H), 6.82 (m, 1H), 6.74 (dd, J, J' = 7.8, 2), 5.073 (m, 1H), 4.596 (ab, 1H, J = 11.6, Δv = 73), 4.411 (ab, 1H, J = 11.6, Δv = 73), 3.99 (t, 1H, J = 6.5), 3.91 (m, 1H, collapses to (ddd, J, J', J'' = 9,4,1) when 3.581 irrad.), 3.815 (dd, 1H, J = 11, 2), 3.759 (s, 3H), 3.581 (ddd, 1H, J, J', J'' = 11.5, 6.5, 6, collapses to (q, J = 6) when 3.91 irrad.), 3.30 (ddd, 1H, begins to collapse when 2.327 irrad.), 3.165 (s, 3H), 2.59 (abx, 1H, J, J' = 14.6, 4.3, Δv = 79.5, collapses to (ab, J = 15) when 3.30 irrad.), 2.578 (abx, 1H, J, J' = 15.7, 8.5, Δv = 17.3, collapses to (ab, J = 16) when 3.91 irrad.), 2.535 (abx, 1H, J, J' = 15.7, 4.1, Δv = 17.3, collapses to (ab, J = 16) when 3.91 irrad.), 2.327 (abx, 1H, J, J' = 14.6, 5.5, Δv = 79.5), 2.235 (dd, 1H, J, J' = 15.4, 3.2, collapses to (d, J = 15) when 5.07 irrad.), 1.91

(m, 1H), 1.788 (apparent q, 2H, J = 7.3), 1.734 (dd, 1H, J, J' = 15.3, 4, collapses to (d, J = 15) when 5.07 irrad.), 1.73 - 1.67 (m, 1H), 1.576 (bq, 1H, J = 6.5), 1.44-1.31 (m, 2H), 1.360 (dd, 1H, J, J' = 13.7, 4.3), 1.17 (m, 1H), 1.155 (m, 1H), 1.151 (d, 3H, J = 6.4, collapses to broad singlet when 3.581 irrad.), 0.850 (s, 3H), 0.768 (s, 3H), 0.741 (d, 3H, J = 6.4), 0.725 (d, 3H, J = 6.3), 0.681 (d, 3H, J = 7); Exact mass calcd. for $C_{40}H_{57}O_{10}$ (M-1): 697.3952; Found: 697.3981.

Macrolactone 23A

400 μL of 0.1*M* DCC/$CHCl_3$ and 400 μL of 0.1*M* DMAP/DMAP·HCl in $CHCl_3$ were placed in a 1-mL tube and heated to 55°C while being stirred, and 14.0 mg (20 μmol) of hydroxy acid **22A** were drawn into a 1-mL "Gas-Tight" syringe in a total of 0.5 mL $CHCl_3$. The syringe was clamped over the reaction vessel, and the hydroxy acid solution was then added at a rate of approximately 1 drop/15 min for 12 h. Addition was then stopped, and the reaction was stirred for 12 h. Addition was resumed at the former rate 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 chromatography on 5 g of silica gel. Elution with a solvent gradient ranging from 7.5% EtOAc/petroleum ether to neat EtOAc afforded 11.0 mg (81%) of macrolactone **23A** as a viscous, colorless oil: R_f = 0.54 (20% EtOAc/petroleum ether); $[\alpha]_D$ = +37.6 (c = 0.55, $CHCl_3$); IR 3000, 2970, 2930, 2880, 1750-1720, 1600, 1460, 1300, 1280, 1260, 1100, 1080, 730 cm^{-1}; ^1H NMR (400 MHz) δ 7.352 (s, 1-2H), 7.341 (s, 1-2H), 7.33-7.26 (m, 1-2H), 7.226(t, 1H, J = 7.8), 6.930 (d, 1H, J = 7.9, collapses to singlet when 7.23 irrad.), 6.915 (d, 1H, J = 2.5), 6.775 (dd, 1H, J, J' = 8, 2.7, collapses to (d, J = 2.5) when 7.23 irrad.), 5.248 (dt, 1H, J, J' = 12.2, 3.5, collapses to (dd, 1H, J, J' =

11, 4) when 2.715 irrad.), 5.04 (m, 1H), 4.662 (ab, 1H, J = 11.9, Δv = 45), 4.550 (ab, 1H, J = 11.9, Δv = 45), 4.177 (t, 1H, J = 6), 3.95 - 3.85 (m, 2H, begins to collapse when 1.158 irrad), 3.804 (s, 3H), 3.356 (dt, 1H, J, J' = 2.5, 10.5, collapses to (dd, 1H, J, J' = 10, 2.5) when 2.22 irrad.), 3.285 (s, 3H), 2.836 (abx, 1H, J, J' = 17.2, 11.7, Δv = 46.6, collapses to (d, J = 17) when 5.25 irrad.); 2.719 (abx, 1H, J, J' = 17.1, 3, Δv = 46.6, collapses to (d, J = 17) when 5.25 irrad.), 2.653 (dd, 1H, J, J' = 12.2, 2.5, collapses to (d, J = 12) when 3.285 irrad.), 2.376 (dd, 1H, J , J'= 15.3, 2, collapses to (d, J = 15) when 5.04 irrad.), 2.220 (t, 1H, J = 11.5, collapses to (d, J = 11) when 3.285 irrad.), 1.99 (m, 2H), 1.72-1.43 (7H + H_2O), 1.24 (m, 2H), 1.2 - 1.13 (m, 2H), 1.158 (d, 3H, J = 6.4), 0.785 (obscured d, 3H), 0.777 (bs, 6H), 0.741 (d, 3H, J = 6.7), 0.710 (d, 3H, J = 7); Exact mass calcd. for $C_{39}H_{53}O_8$ (MH^+ - MeOH): 649.3740; Found: 649.3765.

Macrolactone 23B

19.5 mg (28.0 μmol) of hydroxy acid **22B** were lactonized in an identical fashion to hydroxy acid **22A** to afford 14.0 mg (74%) of macrolactone **23B** as a 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) δ 7.33 - 7.30 (bs, 4H), 7.23 (t, 1H, J = 8.0), 6.95 (m, 2H), 6.78 (dd, 1H, J, J' = 8.0, 1.3), 5.228 (ddd, 1H, J, J', J'' = 12, 4, 3), 5.034 (m, 1H), 4.636 (ab, 1H, J = 11.9, Δv = 46.1), 4.521 (ab, 1H, J = 11.9, Δv = 46.1), 4.080 (dd, 1H, J, J' = 7.0, 5.8), 3.90 (dd, 1H, J, J' = 10.5, 2.1), 3.860 (dq, 1H, J, J' = 4.0, 6.4, collapses to (q, J = 6.4) when 5.228 irrad.), 3.804 (s, 3H), 3.343 (dt, 1H, J, J' = 2.5, 10.5), 3.256 (s, 3H), 2.819 (abx, 1H, J, J' = 17.3, 11.9, Δv = 46.3, collapses to (ab, 1H, J = 17.3) when 5.228 irrad.), 2.702 (abx, 1H, J, J' = 17.3, 3.0, Δv = 46.3, collapses to (ab, 1H, J = 17.3) when 5.2 irrad.), 2.613 (abx, 1H, J, J' = 12.2, 2.7, Δv = 190), 2.379 (dd, 1H, J, J' =

15.3, 2.1), 2.135 (abx, 1H, J, J' = 11.9, 10.9, Δv = 190), 1.89 (m, 1H), 1.87 (m, 1H), 1.65 (m, 1H), 1.647 (dd, 1H, J = 15, 4), 1.51 (m, 1H), 1.40 (m, 2H), 1.20 (m, 2H), 1.140 (d, 3H, J = 6.4), 0.864 (s, 3H), 0.793 (s, 3H), 0.789 (d, 6H, J = 6.6), 0.692 (d, 3H, J = 6.7); Exact mass calcd. for $C_{39}H_{53}O_8$ (MH^+- MeOH): 649.3740; Found: 649.3753.

Bromoanisole 24A

To a stirred mixture of 2.0 mg (2.9 μmol) of macrolactone **23A** and 1.2 mg $NaHCO_3$ in 50 μL CH_2Cl_2 were added 12 μL of 0.5*M* Br_2/CH_2Cl_2. After 30 min, 200 μL CCl_4 were added, and a continuous stream of argon was blown over the reaction 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 2.6 mg (quantitative) of bromoanisole **24A** as a colorless oil, which formed a glass upon standing: R_f = 0.29 (15% EtOAc/petroleum ether); $[\alpha]_D$ = +26.8 (c = 0.2, $CHCl_3$); IR 2960, 2920, 2860, 1740-1710, 1600, 1450, 1380, 1280, 1090, 1070, 910 cm^{-1}; ^1H NMR (400 MHz) δ 7.360 (d, 1H, J = 8.8), 7.35 - 7.33 (m, 5H), 7.034 (d, 1H, J = 3.0), 6.667 (dd, 1H, J, J' = 8.8, 3.0), 5.254 (ddd, 1H, J, J', J'' = 12, 3.1, 2.9), 5.045 (m, 1H), 4.649 (ab, 1H, J = 11.9, Δv = 40.7), 4.615 (dd, 1H, J, J' = 6.5, 4.8), 4.547 (ab, 1H, J = 11.9, Δv = 40.7), 3.918 (dd, 1H, J, J' = 10, 1.5), 3.85 (m, 1H, begins to collapse when 1.144 irrad.), 3.798 (s, 3H), 3.362 (dt, 1H, J, J' = 2, 10), 3.276 (s, 3H), 2.832 (abx, 1H, J, J' = 17.1, 11.7, Δv = 48.6), 2.711 (abx, 1H, J, J' = 17.1, 3.1, Δv = 48.6), 2.633 (abx, 1H, J, J' = 12.2, 2.7, Δv = 147), 2.385 (dd, 1H, J, J' = 15.3, 2.2, collapses to (d, J = 15) when 5.045 irrad.), 2.260 (t, 1H, J = 11.6, abx, Δv = 147), 1.9 (m, 1H), 1.75 - 1.4 (m), 1.35 - 1.08 (m), 1.144 (d, 3H, J = 6.4), 0.834 (s, 3H), 0.790 - 0.775 (m, 9H), 0.719 (d, 3H, J = 7); Exact mass calcd. for $C_{39}H_{52}BrO_8$ (MH^+-MeOH): 727.2846; Found: 727.2836.

Bromoanisole 24B

By the same procedure employed for the bromination of macrolactone **23A**, 2.3 mg (3.4 μmol) of epimeric macrolactone **23B** were brominated to afford 2.3 mg (89%) of bromoanisole **24B** as a light-yellow 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) δ 7.359 (d, 1H, J = 8.8), 7.32 - 7.25 (m, 5H), 7.098 (d, 1H, J = 3.1), 6.655 (dd, 1H, J = 8.7, 3.2), 5.188 (dt, 1H, J, J' = 12, 4), 5.02 (m, 1H), 4.617 (ab, 1H, J = 11.9, Δv = 44.3), 4.524 (dd, 1H, J, J' = 7.6, 4.6), 4.506 (ab, 1H, J = 11.6, Δv = 44.3), 3.890 (dd, 1H, J, J' = 10.7, 1.8), 3.825 (m, 1H), 3.766 (s, 3H), 3.321 (dt, 1H, J, J' = 2.5, 10.5), 3.242 (s, 3H), 2.786 (abx, 1H, J, J' = 17.2, 11.8, Δv = 42.3), 2.681 (abx, 1H, J = 17.2, 3.4, Δv = 42.3), 2.570 (dd, 1H, J, J' = 12.2, 2.7), 2.362 (dd, 1H, J, J' = 15.5, 2), 2.165 (t, 1H, J = 11.5), 1.90 (m, 1H), 1.65-1.40 (m, >7H), 1.30-1.07 (m, 4H), 1.106 (d, 3H, J = 6.7), 0.876 (s, 3H), 0.840 (m, 1H), 0.785 (s, 3H), 0.778 (obscured doublet, 3H), 0.759 (d, 3H, J = 6.7), 0.693 (d, 3H, J = 6.7); Exact mass calcd. for $C_{39}H_{52}BrO_8$ (MH^+): 759.3107; Found: 759.3131.

Hydroxy lactone 25A

To a solution of 4.2 mg (6.2 μmol) of macrolactone **23A** in 100 μL absolute EtOH was added approximately 1 mg of 10% Pd/C. The reaction was placed under a balloon of hydrogen and followed by TLC. After 8 h, the catalyst was removed by filtration through celite, and the solvent was removed under reduced pressure. The crude product was directly subjected to flash chromatography on 1 g of silica gel with 20% EtOAc/petroleum ether to initially afford 0.9 mg of the demethoxylated byproduct **26**: R_f = 0.57 (40% EtOAc/petroleum ether); IR 2960, 2920, 2870, 1750-1720, 1460, 1260, 1070, 1010 cm^{-1}; ^1H NMR (400 MHz) δ 7.159 (t, 1H, J = 7.7), 6.835 (d, 1H, J = 7.6), 6.813 (bs, 1H), 6.688 (bd, 1H, J = 7.9), 5.051 (ddd, 1H, J, J', J'' = 10.2, 5.3, 4.7),

5.010 (m, 1H), 3.947 (dd, 1H, J, J' = 11, 2), 3.908 (m, 1H), 3.774 (s, 3H), 3.365 (dt, 1H, J, J' = 2.4, 10.5), 2.728 (m, 2H), 2.681 (abx, 1H, J = 12.2, 2.7, Δv = 170), 2.584 (t, 1H, J = 7.5), 2.435 (dd, 1H, J, J' = 15.3, 2.1), 2.331 (bd, <1H, J = 5, hydroxyl), 2.257 (abx, 1H, J, J' = 12.2, 11, Δv = 170), 1.85-1.5 (m), 1.30-1.21 (m), 1.175 (d, 3H, J = 6.4), 0.900 (s, 3H), 0.807 (s, 3H), 0.786 (d, 3H, J = 6.4), 0.776 (d, 3H, J= 7.3), 0.737 (d, 3H, J = 7); Exact mass calcd. for $C_{32}H_{49}O_8$ (MH^+): 561.3427; Found: 561.3417.

There were then eluted 2.5 mg (59%) of hydroxy lactone **25A** as a colorless oil: R_f = 0.41 (40% EtOAc/petroleum ether); $[\alpha]_D$ = +41 (c = 0.30, $CHCl_3$); IR 2960, 2920, 1740-1720, 1450, 1270, 1100, 1070, 1020 cm^{-1}; ^1H NMR (400 MHz) δ 7.212 (t, 1H, J = 7.9), 6.910 (d, 1H, J = 7.6), 6.90 (s, 1H), 6.761 (dd, 1H, J, J' = 7.5, 1.5), 5.036 (dt, 1H, J, J' = 9.8, 5.5), 4.984 (m, 1H), 4.135 (t, 1H, J = 6), 3.92 (m, 1H, coupling changes when 1.179 irrad.), 3.892 (dd, 1H, J, J' = 11, 2), 3.790 (s, 3H), 3.344 (dt, 1H, J, J' = 2.4, 10.5, collapses to broad triplet when 2.674 irrad.), 3.251 (s, 3H), 2.734 (d, 1H, J = 5.2, collapses to singlet when 5.04 irrad.), 2.716 (s, 1H), 2.674 (abx, 1H, J, J' = 12.7, 2.7, Δv = 173), 2.415 (dd, 1H, 15.5, 2.3), 2.364 (d, 1H, J = 5.8), 2.240 (abx, 1H, J, J' = 12.2, 11, Δv = 173, collapses when 2.67 irrad.), 1.95 (m, 1H), 1.8-1.4 (m), 1.179 (d, 3H, J = 6.7), 0.776 (d, 3H, J = 6.4), 0.774 (s, 3H), 0.765 (s, 3H), 0.730 (d, 3H, J = 6.7), 0.719 (d, 3H, J = 7); Exact mass calcd. for $C_{33}H_{51}O_9$ (MH^+): 590.3456; Found: 590.3435; Calcd. for $C_{32}H_{47}O_8$ (MH^+- MeOH): 559.3271; Found: 559.3261.

Hydroxy lactone 25B

To a stirred solution of 4.9 mg (7.2 μmol) of macrolactone **23B** in 50 μL absolute EtOH were added 1.5 mg (10 mol%) 10% Pd/C. The reaction was placed under a balloon of hydrogen and stirred for 24 h. The reaction 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 20-40% EtOAc/petroleum ether initially afforded 0.4 mg (8%) of recovered starting material. Further elution provided 3.7 mg (88%) of macrolactone alcohol **25B** 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) δ 7.257 (t, 1H, J = 8.1), 6.952 (s, 1H), 6.944 (d, 1H, J = 8.5), 6.785 (dd, 1H, J, J' = 8, 2.4), 5.040 (dt, 1H, J, J' = 9.8, 5.2, collapses to (dd, 1H, J, J' = 10, 5) when 3.92 irrrad., collapses to a broad doublet of doublets when 2.7 irrad.), 5.00 (m, 1H), 4.065 (t, 1H, J = 6.4), 3.92 (m, 1H, coupling changes when 1.18 irrad.), 3.905 (dd, 1H, J, J' = 10.4, 1.8), 3.811 (s, 3H), 3.352 (dt, 1H, J, J' = 2.7, 10.7), 3.251 (s, 3H), 2.735 (d, 1H, J = 9.8), 2.726 (d, 1H, J = 5.2), 2.659 (abx, 1H, J, J' = 12.2, 2.8, Δv = 187), 2.430 (dd, 1H, J, J' = 15.6, 2.4), 2.394 (bd, 1H, J = 5.8, collapses to broad singlet when 3.92 irrad.), 2.183 (abx, 1H, J, J' = 12.2, 11, Δv = 187), 1.89 (m, 1H), 1.76-1.62 (m, 4H), 1.53 (m, 2H, collapses to (m, 1H) and (q, 1H, J = 7) when 3.92 irrad.), 1.40 (m, 2H), 1.29-1.18 (m, 3H), 1.179 (d, 3H, J = 6.4), 0.847 (s, 3H), 0.802 (s, 3H), 0.798 (d, 3H, J = 6.4), 0.787 (d, 3H, J = 6.7), 0.718 (d, 3H, J = 7.0); Exact mass calcd. for $C_{32}H_{47}O_8$ (MH^+- MeOH): 559.3271; Found: 559.3278.

Bromoanisole 27A

To a stirred mixture of 1.3 mg (2.2 μmol) of hydroxy lactone **25A** and 1 mg of $NaHCO_3$ in 50 μL CH_2Cl_2 were added 6.6 μL of 0.5*M* Br_2/CH_2Cl_2. After 20 min, 200 μL of CCl_4 were added, and the remaining bromine was removed with a continuous stream of argon. The crude product was directly subjected to flash chromatography on 1 g of silica gel with a solvent gradient ranging from 20-40% EtOAc/petroleum ether to afford 1.4 mg (93%) of bromoanisole **27A** as a light yellow oil: R_f = 0.19 (20% EtOAc/petroleum ether); $[\alpha]_D$ = +36.9 (c = 0.1, $CHCl_3$); IR 3600-3400, 2970, 2920, 1740-1720, 1450,

1290, 1100, 1080, 910 cm^{-1}; ^1H NMR (400 MHz) δ 7.360 (d, 1H, J = 8.5), 7.019 (d, 1H, J = 3.0), 6.657 (dd, 1H, J, J' = 8.5, 3.3), 5.049 (ddd, J, J' J'' = 10, 5.5, 4.5), 4.987 (m, 1H), 4.581 (dd, 1H, J, J' = 6.7, 4.9), 3.893 (m, 2H), 3.781 (s, 3H), 3.35 (m, 1H), 3.243 (s, 3H), 2.724 (d, 1H, J = 5.5), 2.705 (bs, 1H), 2.650 (abx, 1H, J, J' = 12.2, 2.8, Δv = 150), 2.421 (dd, 1H, J, J' = 15.4, 2.2), 2.353 (d, 1H, J = 5.8), 2.275 (abx, 1H, J, J' = 12.2, 11), 1.86 (m, 1H), 1.65 - 1.5 (m), 1.4 - 1.17 (m), 1.174 (d, 3H, J = 6.4), 0.92 - 0.85 (m, 2H), 0.826 (s, 3H), 0.777 (s, 3H), 0.776 (d, 3H, J = 6.4), 0.77 (obscured doublet, 3H), 0.722 (d, 3H, J = 7.0); Exact mass calcd. for $C_{32}H_{46}BrO_8$: 637.2376; Found: 637.2368.

Bromoanisole 27B

By the same procedure employed for the bromination of **25A**, 2.4 mg of epimeric hydroxy lactone **25B** were brominated to afford 2.4 mg (88%) of bromoanisole **27B** 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) δ 7.381 (d, 1H, J = 8.5), 7.113 (d, 1H, J = 3.1), 6.671 (dd, 1H, J, J' = 8.5, 3.1), 5.015 (dt, 1H, J, J' = 9.2, 5.7), 5.00 (m, 1H), 4.528 (dd, 1H, J, J' = 7.6, 4.9), 3.914 (dd, 1H, J, J' = 10.7, 2.1), 3.90 (m, 1H), 3.798 (s, 3H), 3.348 (dt, 1H, J, J' = 2.7, 10.7), 3.256 (s, 3H), 2.738 (abx, 1H, J, J' = 11.3, 4, Δv = 15.3), 2.699 (ab, 1H, J = 11.3, Δv = 15.3), 2.631 (abx, 1H, J, J' = 12.5, 2.8, Δv = 150), 2.439 (dd, 1H, J, J' = 15.4, 2.3); 2.42 (bs, 1H), 2.248 (dd, 1H, J, J'= 12.2, 11), 1.90 (m, 1H), 1.70-1.20 (20H, H_20), 1.169 (d, 3H, J = 6.4), 0.895 (s, 3H), 0.811 (s, 3H), 0.809 (d, 3H, J = 6.4), 0.794 (d, 3H, J = 6.1), 0.746 (d, 3H, J = 6.7); Exact mass calcd. for $C_{33}H_{50}BrO_9$ (MH^+): 669.2638; Found: 669.2648.

Hydroxy acid 28B

To a stirred solution of 0.8 mg (1 μmol) of lactone **23B** in 25 μL 2,4,6 collidine were

added 1 mg (7.5 μmol) LiI and a trace of NaCN. After 1 h, the reaction was heated to 70°C; after 3 h, the temperature was increased to 120°C. After 2 h at 120°C, the reaction was allowed to cool to ambient temperature. The crude mixture was rinsed with ether and H_2O into a separatory funnel and extracted with two 20-mL portions of ether from 20 mL 0.1*N* HCl. The combined ether extracts were washed with 20 mL 0.1*N* HCl and concentrated under reduced pressure. Chromatography on 1 g of acidic silica with a solvent gradient ranging from 40% EtOAc/petroleum ether to neat EtOAc afforded 0.3 mg (45-55%) of hydroxy acid **28B** as a colorless, viscous oil: R_f = 0.20 (2.5% MeOH/EtOAc); IR 3600-3100, 2980, 2960, 2870, 1760-1720, 1600, 1460, 1390, 1370, 1260, 1120, 1080, 1050, 830 cm^{-1}; ^1H NMR (400 MHz) δ 7.228 (t, 1H, J = 7.6), 6.877 (bs, 1H), 6.86 (obscured doublet, 1H), 6.78 (dd, 1H, J, J' = 8.4, 1.8), 4.044 (t, 1H, J = 7), 3.810 (s, 3H), 3.78 (m, 2H), 3.675 (ddd, 1H, J, J', J'' = 11, 7, 4), 3.206 (s, 3H), 2.641 (dd, 1H, J, J' = 15.1, 4.1), 2.410 (dd, 1H, J, J' = 15.1, 6.9), 2.329 (dd, 1H, J, J' = 14.3, 3.0), 1.778 (q, 1H, J = 7.6), 1.75-1.45 (m, 2 - 3H), 1.65 (bs, 1H), 1.578 (dd, 1H, J, J' = 14.4, 3.7), 1.35-1.22 (m, 4H), 1.188 (t, 1H, J = 7), 0.836 (s, 3H), 0.819 (d, 6H, J = 6.7), 0.783 (s, 3H), 0.758 (d, 3H, J = 6.7); Exact mass calcd. for $C_{28}H_{43}O_7$ (M-H): 491.3009; Found: 491.3000.

Iodides 29B and 30B

To a stirred -78°C solution of 2.2 mg (3.2 μmol) of macrolactone **23B** in 50 μL CH_2Cl_2 were added 20 μl (5.0 μmol) of 0.25*M* BI_3/CH_2Cl_2. After five minutes, the reaction was diluted with CH_2Cl_2 and syringed into 20 mL H_2O. Extraction with two 20 mL portions of ether, drying (Na_2SO_4) and concentration under reduced pressure furnished a yellow oil, which was subjected to chromatography on 1 g of acidic silica gel. Elution with a solvent gradient ranging from 7.5% EtOAc/petroleum ether to neat EtOAc afforded, initially, 1.7 mg (68%) of a mixture of epimeric iodides **29B** as a light yellow oil: R_f =

0.48 (20% EtOAc/petroleum ether); IR 2960, 2860, 2930, 1740-1720, 1600, 1460, 1260, 1080, 1060, 990 cm^{-1}; ^1H NMR (400 MHz) δ 7.33-7.25 (m, 5H), 7.173 (t, 0.4H, J = 7.9), 7.164 (t, 0.6H, J = 7.9), 7.09-7.05 (m, 2H), 6.74-6.71 (m, 1H), 5.247 (dt, 0.5H, J, J' = 13, 4), 5.239 (dt, 0.5H, J, J' = 13, 3), 5.08 (m, 0.5H), 5.03 (m, 0.5H), 4.648 (ab, 0.6H, J = 11.9, Δv = 48), 4.634 (ab, 0.4H, J = 11.6, Δv = 51.8), 4.527 (ab, 0.6H, J = 11.9, Δv = 48), 4.504 (ab, 0.4H, J = 11.6, Δv = 51.8), 3.95 (m, 0.4H), 3.933 (dd, 0.6H, J, J' = 10.7, 2.4), 3.83 (m, 0.6H), 3.774 (s, 3H), 3.36 (dt, 0.4H, J, J' = 10.5, 2.5), 3.31 (dt, 0.6H, J, J' = 10.5, 2.5), 2.848 (abx, 0.4H, J, J' = 17.5, 11.9, Δv = 58.5), 2.820 (abx, 0.6H, J, J' = 17.4, 11.9, Δv = 50), 2.687 (abx, 1H, J, J' = 17.5, 3.0, Δv > 50), 2.651 (dd, 0.4H, J, J' = 11.9, 2.7), 2.567 (dd, 0.6H, J, J' = 12.2, 2.7), 2.36 (m, 2H), 2.23 (m, 1H), 2.060 (dd, 1H, J, J' = 12.0, 11.9), 1.95 (m, 1H), 1.67-1.20 (>20H, H_2O), 1.141 (d, 3 x 0.4H, J = 6.1), 1.125 (d, 3 x 0.6H, J = 6.4), 0.836 (s, 3H), 0.809 (s, 3 x 0.4H), 0.795 (d, 3H, J = 6.7), 0.780 (s, 3 x 0.6H), 0.763 (d, 3 x 0.4H, J = 6.1), 0.748 (d, 3 x 0.6H, J = 6.4), 0.709 (d, 3 x 0.6H, J = 7.0), 0.691 (d, 3 x 0.4H, J = 7.0); Exact mass calcd. for $C_{39}H_{54}O_8I$ (MH^+): 777.2865; Found: 777.2876

There was then eluted 0.9 mg (30-40%) of a mixture of epimeric hydroxy iodides **30B** as a yellow oil: R_f = 0.47 (40% EtOAc/petroleum ether); IR 2960, 2920, 1740-1720, 1600, 1560, 1460, 1380, 1280, 1080, 1060, 1020, 990 cm^{-1}; ^1H NMR (400 MHz) δ 7.165 (t, 1H, J = 8.2), 7.05 (m, 2H), 6.73 (m, 1H), 5.075-4.975 (m, 3H), 4.00-3.86 (m, 2H), 3.784 (s, 3 x 0.5H), 3.781 (s, 3 x 0.5H), 3.35 (m, 0.5H), 3.31 (m, 0.5H), 2.73 (m, 2.5H), 2.604 (dd, 0.5H, J, J' = 12.2, 2.7), 2.44 (dd, 0.5H, J, J'= 15.5, 2.5), 2.415 (dd, 0.5H, J, J' = 15.5, 2.5), 2.320 (dd, 1H, J, J' = 11.9, 11), 2.28 (m, 1H), 1.85 - 1.40 (30H, H_2O), 1.35 - 1.22 (10H), 1.188 (t, 1H, J = 7), 1.174 (d, 3H, J = 6.4), 0.850 - 0.725 (>15H); Exact mass calcd. for $C_{32}H_{48}IO_8$ (MH^+): 687.2394; Found: 687.2418

Attempted Barton oxidation of 16B

Into a stirred 0°C solution of 18 mg (30 μmol) of alcohol **16B** in 300 μL pyridine was bubbled argon, which had been passed through a -78°C trap containing nitrosyl chloride. After 30 min, the solution was decanted into 25 mL of saturated aqueous NH_4Cl and extracted with two 30-mL portions of ether. The combined ether layers were washed with two 30-mL portions of saturated aqueous $NaHCO_3$ and diluted with 10 mL petroleum ether. The solution was dried (Na_2SO_4) and concentrated under reduced pressure to provide a brown solid. The crude material was subjected to flash chromatography on 3 g of silica gel with 15% ether/petroleum ether to afford 21 mg (quantitative) of white crystals which yellowed quickly: $R_f = 0.70$ (30% ether/petroleum ether).

The nitrite ester was then immediately dissolved in 35 mL of degassed C_6H_6 and irradiated in a water-cooled 250-ml pyrex flask with a 500W Hg lamp. After 30 min, no starting material was visible by TLC, and irradiation was discontinued. The reaction was diluted with 30 mL of ether and washed with two 20-mL portions of 10% aqueous $Na_2S_2O_3$. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide a yellow oil, which was subjected to flash chromatography on 5 g of silica gel. Elution with a gradient ranging from 15% ether/petroleum ether to neat ether afforded 7.0 mg (40%) of ketone **31B**, as well as lesser amounts of several unidentified products. Ketone **31B** was identical to the ketone precursor of alcohols **16A** and **16B**, except that it was a single diastereomer: ^1H NMR (400 MHz) δ 7.216 (t, 1H, J = 8.2), 6.82 (m, 1H), 6.815 (d, 1H, J = 1.5), 6.772 (dd, 1H, J, J' = 8.2, 2.4), 4.000 (t, 1H, J = 6.4), 3.785 (s, 3H), 3.751 (dd, 1H, J, J' = 10.1, 2.1), 3.546 (m, 1H), 3.411 (m, 1H), 3.200 (s, 3H), 3.087 (bt, 1H, J = 6.3), 2.878 (ab, 1H, J = 13.1), 2.432 (ab, 1H, J = 13.1), 2.305 (dq, 1H, J, J' = 10.1, 6.4), 1.8-1.37 (12H including H_2O), 1.683 (t, 1H, J = 7.1), 1.307 (dd, 1H, J, J' = 13.9, 4.5), 1.136 (t, 1H, J = 13.1), 0.942 (s, 3H), 0.906 (d, 3H, J = 6.7), 0.866 (s, 3H), 0.845 (m, 3H), 0.835 (s, 9H), 0.759 (d, 3H, J = 6.4), -0.032 (s, 3H), -0.035 (s,

3H).

Acetate ester

To a stirred solution of 18.5 mg (31.3 μmol) alcohol **16A** and a crystal of DMAP in 150 μL pyridine were added 9 μl (90 μmol) Ac_2O. The slightly yellow solution was stirred for 7.5 h and then rinsed with ether into 20 mL saturated aqueous NaCl. The aqueous layer was extracted with two 25-mL portions of ether, and the combined ether extracts were washed with 20 mL of saturated aqueous NaCl. After drying (Na_2SO_4) and concentration under reduced pressure, flash chromatography on 5 g silica gel with 15% ether/petroleum ether afforded 18.5 mg (93%) of an acetate ester as a colorless oil: R_f = 0.32 in 15% ether/petroleum ether; $[\alpha]_D$ = +45.1 (c = 1.80, $CHCl_3$); IR 2960, 2920, 2850, 1720, 1600, 1450, 1380, 1250, 1100, 1070, 840 cm^{-1}; ^1H NMR (400 MHz) δ 7.217 (t, 1H, J = 7.8), 6.837 (d, 1H, J = 7.1), 6.825 (bs, 1H), 6.776 (ddd, 1H, J, J', J'' = 8.5, 2.3, 0.7), 5.017 (bd, 1H, J = 4), 4.019 (t, 1H, J = 6.4), 3.878 (dd, 1H, J, J' = 10.3, 2), 3.84 (m, 1H), 3.790 (s, 3H), 3.66 (m, 1H), 3.199 (s, 3H), 3.01 (m, 1H), 2.261 (dd, 1H, J, J' = 15.1, 3.7), 2.065 (s, 3H), 1.95-1.1 (26H, including H_2O), 0.877 (s, 9H), 0.868 (s, 3H), 0.785 (s, 3H), 0.750 (d, 3H, J = 6.6), 0.745 (d, 3H, J = 6.6), 0.719 (d, 3H, J = 6.8), 0.039 (s, 3H), 0.036 (s, 3H); Exact mass calcd. for $C_{34}H_{59}O_5Si$ (MH^+ - HOAc): 575.4131; Found: 575.4122

Desilylation

17.7 mg of the above silyl ether was dissolved in 1 mL of 2:2:1 HOAc/THF/H_2O, and the resulting solution was stirred for 9 h. The reaction was rinsed with ether into 20 mL saturated aqueous NaCl and extracted with two 40-mL portions of ether. The combined ether extracts were washed with 20 mL saturated aqueous NaCl and dried (Na_2SO_4). Concentration under reduced pressure, followed by chromatography on 5 g flash gel with 70% ether/petroleum ether, afforded 12.0 mg (83%) of the alcohol as a colorless oil: R_f =

70% ether/petroleum ether, afforded 12.0 mg (83%) of the alcohol as a colorless oil: R_f = 0.28 in 70% ether/petroleum ether; $[\alpha]_D$ = +49.4 (c = 1.20, $CHCl_3$); IR 3520, 3000, 2970, 2940, 2870, 1725, 1600, 1450, 1380, 1250-1200, 1080, 1050, 1020, 990 cm^{-1}; ^1H NMR (400 MHz) δ 7.215 (t, 1H, J = 8.0), 6.86 (obscured doublet, 1H), 6.846 (bs, 1H), 5.08 (m, 1H), 4.039 (dt, 1H, J = 6.4), 3.92 (m, 1H), 3.798 (s, 3H), 3.78 (m, 1H), 3.718 (m, 1H), 3.23 (m, 1H), 3.200 (s, 3H), 3.19 (obscured doublet, 1H), 2.329 (dd, 1H, J, J' = 14.2, 2.0), 2.123 (s, 3H), 1.88 (m, 1H), 1.678 (dd, 1H, J, J' = 13.7, 4.5), 1.65 (m, 1H), 1.6-1.35 (2H) 1.18 (m, 1H), 0.880 (s, 3H), 0.842 (m, 2H), 0.800 (s, 3H), 0.750 (d, 3H, J = 6.6), 0.739 (d, 3H, J = 6.6), 0.731 (obscured doublet, 3H); Exact mass calcd. for $C_{30}H_{48}O_7$ (MH^+): 521.3479; Found: 521.3469.

Aldehyde 32A

To a -78°C stirred solution of 10 μL oxalyl chloride in 100 μL CH_2Cl_2 were added 16 μL DMSO. After 5 min, 20.0 mg (38.5 μmol) of the above alcohol were added by double-needle transfer in two 100-μl portions of CH_2Cl_2. The resulting cloudy reaction was stirred for 5 min, and 54 μL Et_3N were added. The resulting white suspension was allowed to warm to ambient temperature and decanted into 50 mL of saturated aqueous $NaHCO_3$. The mixture was extracted with two 30-mL portions of ether, and the combined organic extracts were washed with 30 mL saturated aqueous $NaHCO_3$. The ethereal solution was dried (Na_2SO_4) and concentrated under reduced pressure to furnish a yellow oil. Flash chromatography on 3 g of silica gel with 50% ether/petroleum ether afforded 18.4 mg (93%) of aldehyde **32A** as a colorless oil: R_f = 0.19 in 30% ether/petroleum ether; $[\alpha]_D$ = +52.7 (c = 1.11, $CHCl_3$); IR 2940, 2900, 2830, 1705, 1590, 1450, 1240, 1060, 1010, 830 cm^{-1}; ^1H NMR (400 MHz) δ 9.725 (t, 1H, J = 2.7), 7.228 (t, 1H, J = 8.1), 6.83 (m, 2H), 6.771 (ddd, J, J', J'' = 8.1, 2.6, 1.1), 5.064 (apparent quartet, J = 3.3), 3.988 (dd, 1H, J, J' = 7.7, 5.5), 3.861 (dd, 1H, J, J' = 10.7, 2.6), 3.786 (s, 3H),

2.462 (dt, 1H, J = 14.6, 3.4), 2.322 (dd, 1H, J, J' = 15.4, 2.6), 2.303 (dd, 1H, J, J' = 15.4, 3.3), 1.982 (s, 3H), 1.8-1.4 (6H), 1.680 (dd, 1H, J, J' = 15.4, 4.0), 1.297 (dd, 1H, J, J' = 13.7, 4.6), 1.221 (d, 1H, J = 5.5), 1.165 (d, 1H, J = 13.9) 0.911 (s, 3H), 0.818 (s, 3H), 0.801 (d, 3H, J = 6.6), 0.746 (d, 3H, J = 6.6), 0.693 (d, 3H, J = 7.0).

Formation of silyl enol ether 33A

To a stirred 0°C solution of 18.4 mg (35.5 μmol) of aldehyde **32A** and 24 uL (180 μmol) Et_3N in 200 μL THF were added 70 μL of 1*M* *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)/CH_2Cl_2. After 20 min, cooling was discontinued, and the solution was allowed to warm to room temperature. After an additional 15 min, 24 μL Et_3N and 70 μL of the TBSOTf solution were added. After 3 h, the reaction was rinsed with ether into 50 mL saturated aqueous $NaHCO_3$ and extracted with two 50-mL portions of ether. The combined ether extracts were washed with 30 mL saturated aqueous $NaHCO_3$ and dried (Na_2SO_4). Concentration under reduced pressure, followed by chromatography on 5 g of activity III alumina with 30% ether/petroleum ether, afforded 15.7 mg (70%) of TBS enol ether **33A** as a 60:40 mix of *trans /cis* isomers: R_f = 0.55 (30% ether/petroleum ether); IR 2980, 2940, 2860, 1730, 1670, 1610, 1460, 1380, 1260, 1100, 1080, 1050, 850, 730 cm^{-1}; ^1H NMR (400 MHz) δ 7.211 (m, 1H), 6.85 (m, 1H), 6.84 (bs, 1H), 6.776 (bd, 1H, J = 7), 6.384 (d, 0.6H, J = 11.3), 6.176 (d, 0.4H, J = 6.7), 4.990 (dd, 0.6H, J, J' = 11.9, 6.7), 4.98 (m, 0.4H), 4.944 (m, 0.6H), 4.426 (dd, 0.4H, J, J' = 7.9, 6.4), 4.036 (t, 1H, J = 6.4), 3.965 (bd, 1H, J = 10), 3.794 (s, 3H), 3.270 (dd, 1H, J, J' = 10, 7), 3.219 (s, 3H), 2.312 (dd, 1H, J, J' = 15.3, 3.0), 2.027 (s, 3 x 0.6H), 2.012 (s, 3 x 0.4H), 2.0-0.65 (45H), 0.126 (s, 3H), 0.103 (s, 1.5H), 0.094 (s, 1.5H); Exact mass calcd. for $C_{36}H_{61}O_7Si$ (MH^+): 633.4189; Found: 633.4202.

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