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# Halichondrin B: synthesis of the C(37)–C(54) subunit

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**Abstract**—A synthesis of the C(37)–C(54) segment of the antimitotic polyether macrolide halichondrin B is described. β-Ketophosphonate **1**, comprising rings L, M, and N of the natural product, contains the C(44) spiroketal, about which local $C_2$ symmetry plays a key strategic role. Based upon recognition of this local $C_2$ symmetry, a Claisen self-condensation of **4** led to the dienone **3b**. Asymmetric bis(dihydroxylation) set the C(40), C(41), C(47), and C(48) stereocenters, and the resulting bicyclic spiroketal **8a** was oxidized to tetracyclic bis(lactone) **2a**. Alcohol **13** was isolated from the mono-functionalization of bis(lactone) **2a** via a carbonyl methylenation/hydroboration protocol. Chelation-controlled allylation of the derived aldehyde, followed by diastereoselective iodocarbonate formation and hydrolysis established the C(51)–C(54) sidechain in **17a**. Protection of the side-chain hydroxyl groups, and conversion of the remaining lactone to the corresponding β-ketophosphonate provided **1**, a suitable coupling subunit (with a total of 10 asymmetric centers) for the total synthesis of halichondrin B. Overall, a 22 step synthetic route from known epoxide **5** produced **1** (4% overall yield), in its natural configuration. © 2002 Elsevier Science Ltd. All rights reserved.

Halichondrin B (Fig. 1) is the most potent component of a class of polyether macrolides isolated in exceedingly low yields ($1.8\times10^{-8}$ to $4.0\times10^{-5}$%) from a variety of sponge genera.[1–5] With a tubulin-based mechanism of action as an antimitotic agent, halichondrin B displays an in vitro $IC_{50}$ value of 0.3 nM against L1210 leukemia and remarkable in vivo activities against various chemoresistant human solid tumor xenographs, including LOX melanoma, KM20L colon, FEMX melanoma, and OVCAR-3 ovarian tumors.[6–11] In spite of its extremely limited supply from natural sources, halichondrin B has been recommended by the National Cancer Institute for stage A preclinical development.[9,10] Synthetic efforts have been described by several groups,[12–34] and one total synthesis of halichondrin B by Kishi and co-workers has been reported.[19] Kishi has also recently disclosed that a synthetic C(1)–C(38) halichondrin B subunit exhibits an activity profile against >60 cancer cell lines similar to that of halichondrin B, with $IC_{50}$ values within one order of magnitude of those displayed by the natural product.[12] Munro has recently reported on the aquacultural production of *Lissodendoryx* n. sp. for the isolation of halichondrin B,[35] estimating that 5000 tons/year of harvested sponge could generate 5 kg/year of the natural product for clinical use. Our earlier synthetic work towards halichondrin B focused on the C(1)–C(15) and C(20)–C(36) segments of the natural product.[30–33] In this paper, we report the synthesis of the C(37)–C(54) subunit **1** (Scheme 1) in its natural configuration.[34]

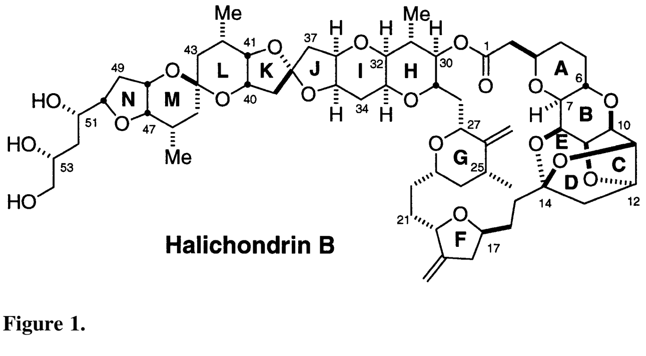

**Figure 1.**

The synthetic plan for construction of the L, M, and N rings of β-ketophosphonate **1**, including 10 asymmetric centers, was based upon the exploitation of local $C_2$ symmetry about the C(44)-spiroketal carbon, with late-stage symmetry breaking by sequential extension at C(38) and C(50). Proceeding through the tetracyclic bis(lactone) **2a** (Scheme 1), the stereocenters at C(40), C(41), C(47), and C(48) were to be established in a two-fold Sharpless asymmetric dihydroxylation (SAD)[36] of the $C_2$-symmetric dienone **3b**. Ketone **3b** was presumed to be accessible through Claisen self-condensation of ester **4**, followed by decarboalkoxylation. As a γ,δ-unsaturated ester, **4** was expected to arise from Claisen rearrangement of the appropriate allylic alcohol **7**, derivable from the chiral, enantiomerically pure epoxide **5**.

The known (*S*)-epoxide **5** was available in high enantiomeric excess (>95% ee) from (*S*)-malic acid using a slight modification of existing procedures,[37–39] or by hydrolytic kinetic resolution[40,41] of racemic **5**. In a two pot procedure,

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*Keywords*: halichondrin B; spiroketal; desymmetrization.

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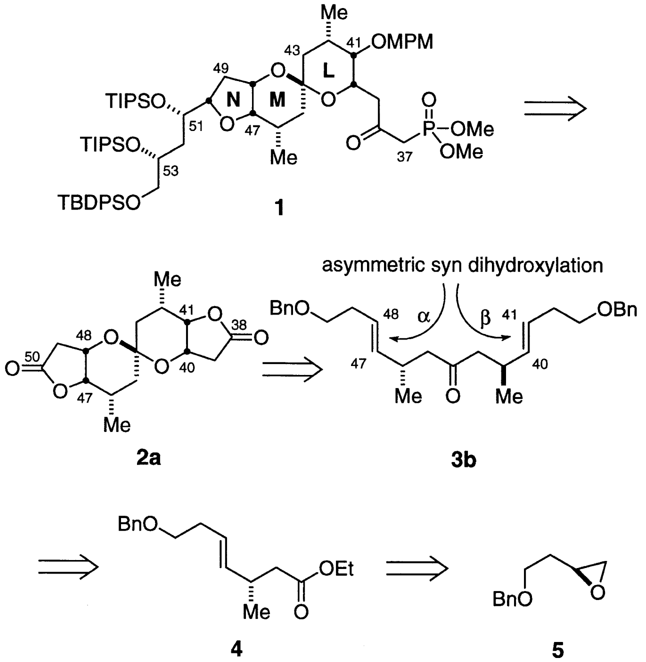
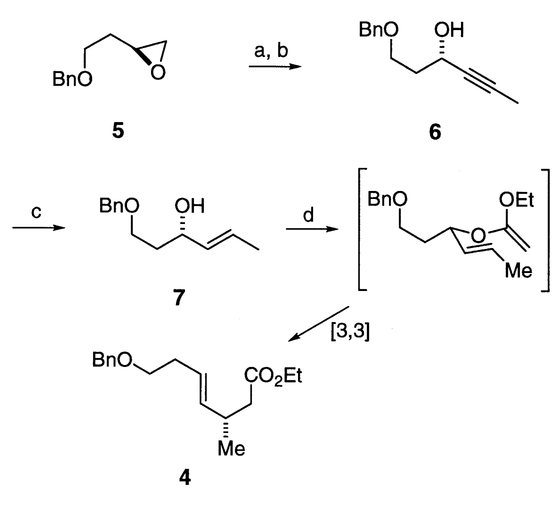
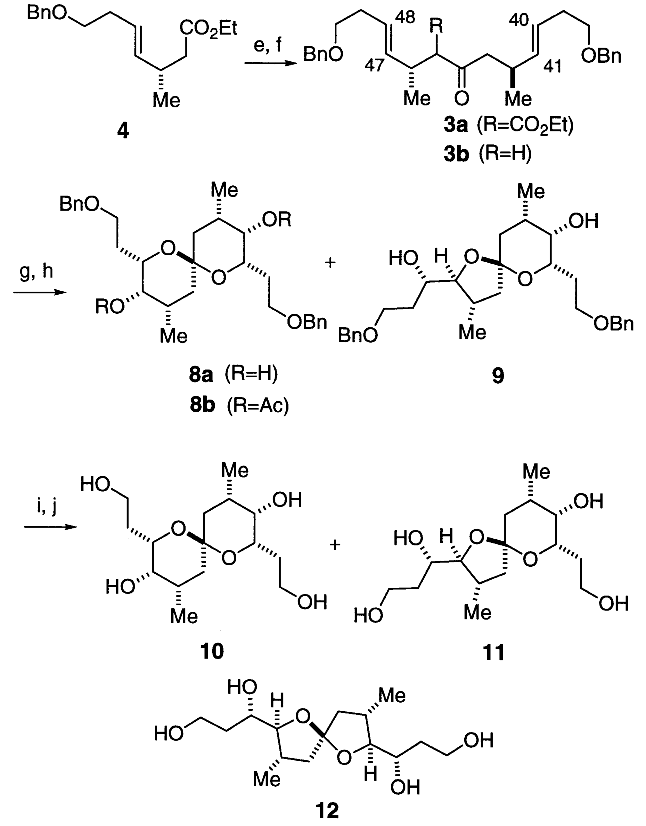


Scheme 1.

enantiopure **5** was opened with the ethylene diamine complex of lithium acetylide[42] (Scheme 2), and the resulting terminal alkyne was isomerized with KO*t*-Bu, affording the thermodynamically favored internal alkyne **6** as the sole product. Single pot conversions of epoxide **5** to propargyl alcohol **6** with these reagents, similar to reactions reported by Takano and co-workers,[42] proceeded with significantly retarded rates and poor yields (50–60%). Reduction of **6** with LAH in THF afforded the *E*-allylic alcohol **7** as a single geometrical isomer.[43] Johnson ortho ester Claisen rearrangement of allylic alcohol **7** proceeded smoothly in refluxing triethylorthoacetate to provide ester **4** via the bracketted chair transition structure shown.[44,45] Claisen self-condensation (Scheme 3) of ester **4** was effected by the slow addition of LHMDS (2.5 equiv.) and TMEDA (5.0 equiv.) to a solution of the ester in THF over 4.5 h at 0°C, affording the β-ketoester **3a** in good yield (84+8% SM). Decarboalkoxylation under Krapcho conditions[46,47] cleanly provided the $C_2$-symmetric ketone **3b** as a viscous oil (96%). SAD[36] of **3b** with 2.5 equiv. of AD-mix-α furnished the $C_2$-symmetric tetraol as virtually a single diastereomer, thus setting the C(40), C(41), C(47), and C(48) stereocenters in a single step.

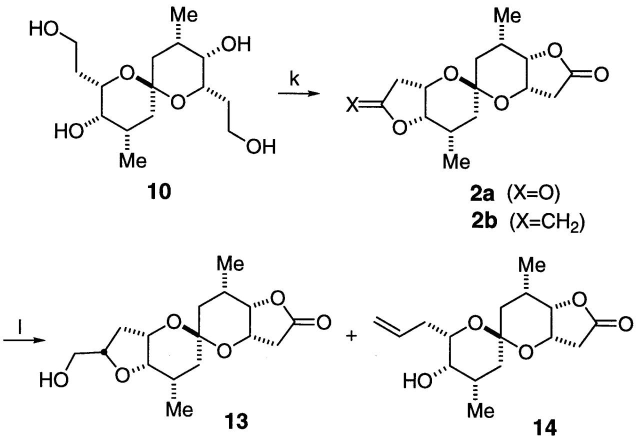


**Scheme 2.** (a) $LiCCH·H_2NCH_2CH_2NH_2$, DMSO, 15°C→rt; (b) KO*t*-Bu, DMSO, 15°C 86% two steps; (c) LAH, THF, ⇅ 96%; and (d) $CH_3C(OEt)_3$, 140°C, $CH_3CH_2CO_2H$ (4 mol%) 92–96%.



**Scheme 3.** (e) LHMDS, TMEDA, THF, 0°C 84%+8% SM; (f) LiCl, DMSO, $H_2O$, 190°C 96%; (g) AD-mix-α, 0°C, *t*-BuOH/$H_2O$ (1:1); (h) CSA, ⇅, MeOH/PhH (1:1) 85–92% two steps; (i) $Pd(OH)_2$ on Carbon, EtOH, $H_2$(g) 100%; and (j) TFA, MeOH, ⇅ 98–100%.

Partial spontaneous spiroketalization made determination of the exact diastereoselectivity of the double SAD difficult. Acid-catalyzed spiroketalization[48] of the crude tetraol in benzene/MeOH (1:1) yielded the thermodynamic ratio (1.1:1.0) of the $C_2$-symmetric 1,7-dioxaspiro[5,5]undecane **8a**, and the isomeric, unsymmetrical 1,6-dioxaspiro[4,5]-decane **9**. Ketal equilibration was slow in the absence of methanol, and a kinetic ratio of products, favoring five-membered ring formation, could be isolated from reactions run in straight benzene. All attempts to drive the formation of **8a** through selective crystallization from the equilibrating conditions failed, as the reaction products oiled out as the thermodynamic mixture. Isomers **8a** and **9** were separable by silica gel chromatography. Operationally however, the mixture of ketals was carried forward to debenzylation via hydrogenolysis and then the tetraols were equilibrated with catalytic TFA in refluxing methanol to the more favorable thermodynamic mixture of **10**, plus **11** and **12** (5:2:1). After chromatographic separation, ketals **11** and **12** were recycled to **10** (62% after one recycle) by re-exposure to the equilibrating conditions.



**Scheme 4.** (k) TPAP, NMO, 4 Å sieves, *t*-BuOH/$CH_3CN$, rt 75%; and (l) Tebbe reagent, pyr, $PhCH_3$/THF, −78°C to rt; 9-BBN; $NaBO_3{\cdot}4H_2O$, $H_2O$ 40% **13**, 5% **14**, 54% rec. **2a**.

Selective oxidation of both primary alcohols in **10** was best accomplished through the use of 5 mol% of tetrapropylammonium perruthenate(VII) (TPAP) with *N*-methylmorpholine-*N*-oxide (NMO) in *t*-BuOH and $CH_3CN$ (1:1).[49,50] The $C_2$-symmetric bis(lactone) **2a** (Scheme 4) resulted, presumably via oxidation of the intermediate five-membered hemiacetals. Confirmation of the relative and absolute stereochemistry of bis(lactone) **2a** was secured by X-ray crystal structure determination (Fig. 2), from which a structural rationale for observed reactivity was developed (vide infra).

Symmetry breaking by reaction at one of the two identical termini found in the $C_2$-symmetric bis(lactone) **2a** was required for introduction of the C(51)–C(54) side chain. Such desymmetrization by mono-functionalization is commonly a challenge, since communication between such distal reaction centers is unlikely.[51] Carbonyl methylenation with a reagent of easily controlled stoichiometry, followed by an exo face-selective hydroboration, was seen as an attractive possibility for installing a functionalized C(51) and establishing the C(50) stereocenter in its natural configuration. However, all attempts to isolate the expected vinyl ether **2b** resulting from treatment of **2a** with the Tebbe[52a–c] ($Cp_2Ti$-μ-Cl-μ-$CH_2AlMe_2$) or Petasis[52d] ($Cp_2TiMe_2$) reagents failed; facile isomerization to the endocyclic enol ether occurred readily. Ultimately, a single pot protocol was devised for the conversion of **2a** (via **2b**) to alcohol **13**, by reaction with 0.6–0.7 equiv. of the Tebbe reagent followed by in situ hydroboration/oxidation of the vinyl ether with 9-BBN/$NaBO_3$(aq). The unfavorable statistical mixture of recovered starting material, mono-functionalized, and di-functionalized products was avoided by this partial conversion protocol, in that no significant amounts of bis(functionalized) products were isolated. Alcohol **13** was isolated as a single stereoisomer, along with recovered starting material **2a** and a small amount of the alkene **14**. The fragmentation pathway leading to **14** was greatly facilitated by excess 9-BBN, and apparently involves Lewis acid activation and elimination of the tetrahydrofuran ring oxygen in the trialkylborane to intermediate. Similar decomposition pathways, facilitated by Lewis acids, have been reported during the hydroboration of vinyl ethers.[53–56] Sodium perborate oxidation of the borane intermediate afforded yields of alcohol **13** and recovered **2a** superior to those obtained with NaOH/$H_2O_2$ conditions, due to lactone saponification problems under the latter conditions.

Synthesis of the side-chain continued with the oxidation of primary alcohol **13** with the Dess–Martin periodinane[57–59] to yield the corresponding aldehyde (Scheme 5). The crude aldehyde was directly subjected to chelation-controlled allylation[60] with $TiCl_4$ and allyltributylstannane[61–63] to afford the homoallylic alcohol **15a** with excellent diastereocontrol (>95% by $^1H$ NMR) in good yield after 15 min at −78°C. Allyltrimethylsilane[61] failed to react with the aldehyde under identical reaction conditions.

Facial selectivity in the SAD[36] of homoallylic alcohol **15a** with $(DHQD)_2AQN$,[64] $(DHQD)_2PYR$,[65,66] or AD-mix-β proved insufficient for the next step, yielding a 1:2 ratio of **17a** (desired) to **17b**. An identical ratio (1:2) favoring the undesired C(53*S*) diastereomer was obtained when an achiral amine ligand, pyridine, was employed. It was apparent that the inherent facial selectivity of the olefin in

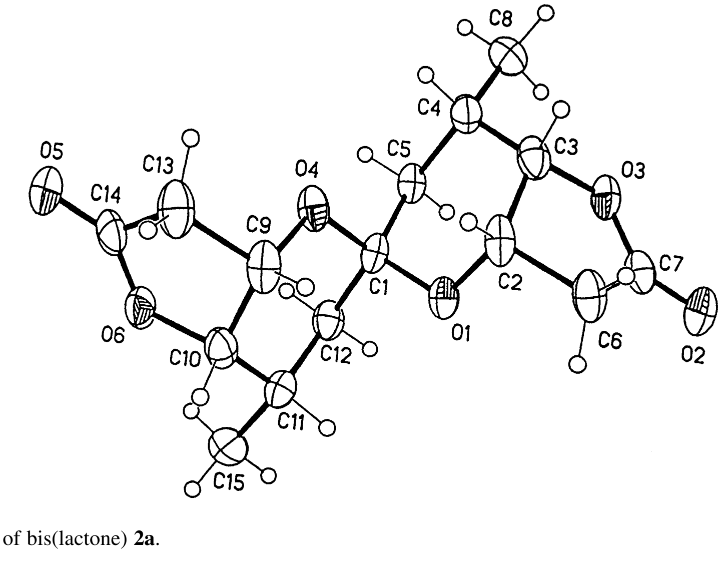
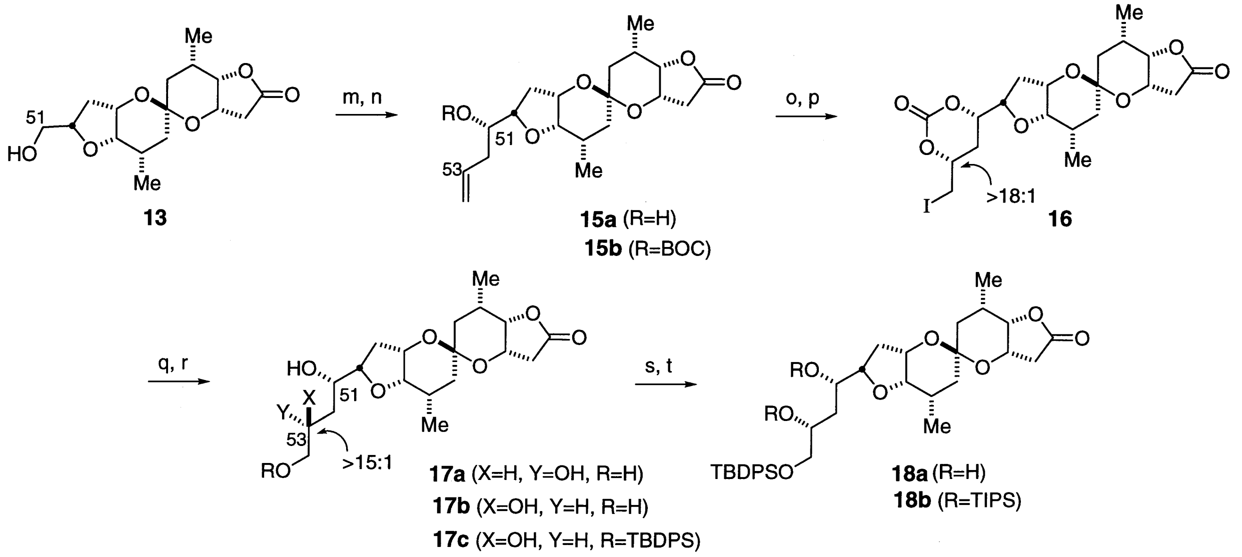


**Figure 2.** X-Ray crystal structure of bis(lactone) **2a**.



**Scheme 5.** (m) Dess–Martin, $CH_2Cl_2$, rt; (n) $TiCl_4$, (Allyl)$SnBu_3$, $CH_2Cl_2$, −78°C 77–96% (two steps); (o) $(BOC)_2O$, DMAP, pyr, $CH_2Cl_2$, rt 91–98%; (p) IBr, $PhCh_3$, −80°C 96–99%; (q) 0.5 M LiOH(aq), DME, 60–70°C; (r) CSA, PhH, Δ 80–94% (two steps); (s) TBDPSCl, DMAP, $CH_2Cl_2$, pyr, rt 90%; and (t) TIPSOTf, pyr, DMAP, rt 99%.

**15a** was overpowering the directing affect of the Cinchona alkaloid ligands in this case. Triisopropylsilyl (TIPS) protection of the C(51) homoallylic alcohol, followed by dihydroxylation with $(DHQD)_2AQN$ afforded a slightly improved 1:1 ratio of diastereomers. The stereoisomers **17a**,**b** were assigned by application of Rychnovsky's $^{13}C$-NMR analysis of the derived acetonides **19a**,**b** (Fig. 3).[67] The acetonide **19a**, derived from the syn 1,3-diol **17a**, shows distinctive axial and equatorial methyl resonances that reflect the chair conformation of the 1,3-dioxane ring. Acetonide, **19b**, in contrast, has less distinctive acetonide methyls because of a twist-boat 1,3-dioxane conformation, adopted to avoid a 1,3-diaxial methyl–methyl interaction.

Alternatively (Scheme 5), the C(53) stereocenter was successfully established (>18:1) in two steps via conversion of homoallylic alcohol **15a** to the corresponding BOC carbonate **15b** with excess $(BOC)_2O$ and DMAP, followed by treatment with iodine monobromide at −80°C to afford the iodocarbonate **16** in excellent yield (96%).[68,69] Reported procedures for converting iodocarbonates directly to the corresponding triols, such as with AMB-26-$CO_3^{2-}$,[70] failed to provide the desired triol **17a**. The conversion of iodocarbonate **16** to the triol **17a** was best accomplished with 0.5 M aqueous LiOH in DME. After 13 h at 60°C, the reaction contents were neutralized, concentrated, and the resulting solids were treated with CSA in refluxing benzene, which reclosed the γ-lactone ring and provided **17a** in

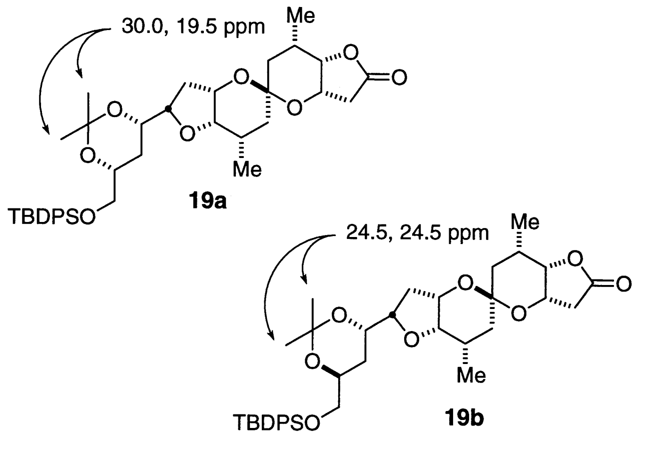
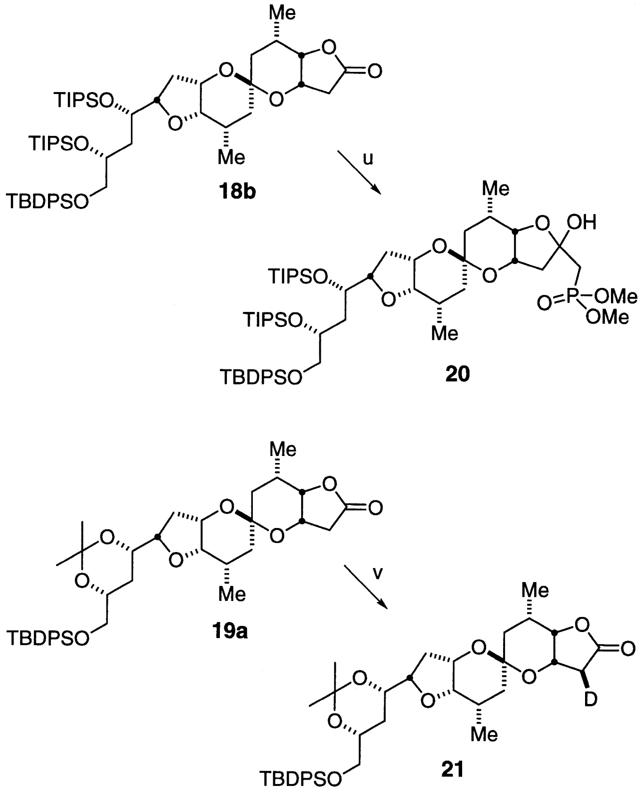
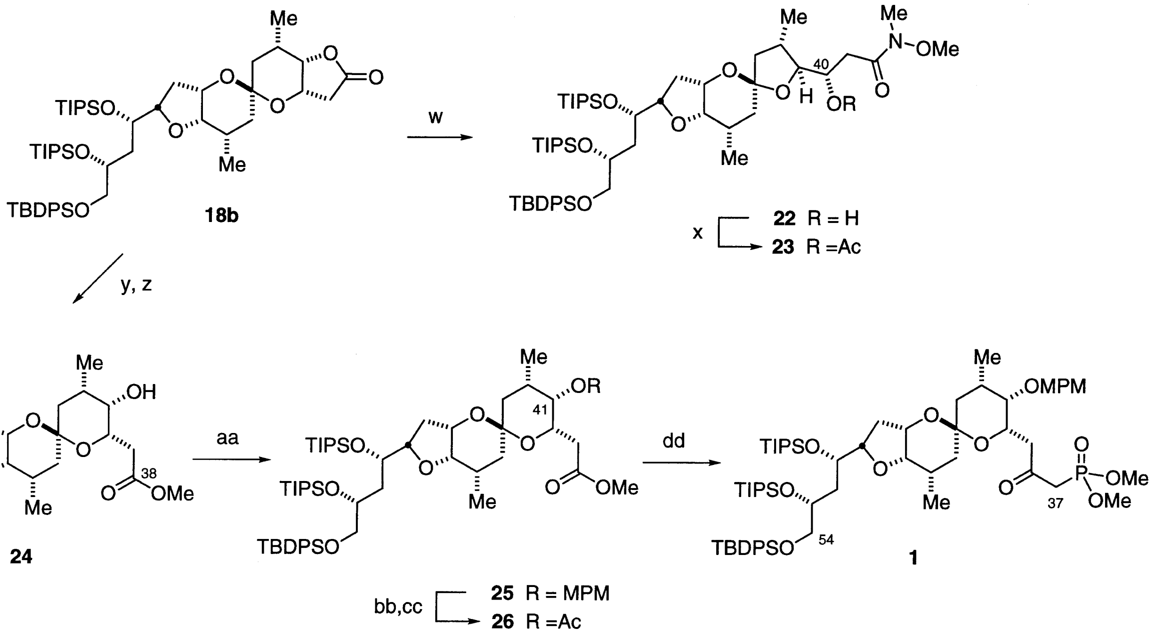


**Figure 3.**



**Scheme 6.** (u) $LiCH_2P(O)(OMe)_2$, (>100 equiv.), THF, −78°C, 20–24%+SM; and (v) $LiCH_2P(O)(OMe)_2$ (5 equiv.), THF, 5 min, −78°C, $D_2O$.



**Scheme 7.** (w) Me(Cl)Al–N(OMe)Me, PhH, 70°C, 95%; (x) $Ac_2O$, $CH_2Cl_2$, DMAP 100%; (y) 1.0 M LiOH(aq), *t*BuOH/THF, rt; (z) $TMSCHN_2$, MeOH/PhH (2:7), rt, two steps 95–100%; (aa) $MPMOC(NH)CCl_3$, $BF_3{\cdot}OEt_2$, $Et_2O$, −78°C, 88%; (bb) $H_2$(g), $Pd(OH)_2$, EtOH, 100%; (cc) $Ac_2O$, DMAP, $CH_2Cl_2$, 99%; and (dd) $LiCH_2P(O)(OMe)_2$, THF, −78°C, 54%.

excellent yield. Insufficient reaction times for the hydrolysis of iodocarbonate **16** resulted in the isolation of the intermediate C(53)–C(54) epoxide. Traces of undesired triol **17b**, arising presumably from $S_N2$ attack at the secondary position of the epoxide, were removed by silica gel chromatography. Triol **17a** isolated from the hydrolysis of **16** proved to be identical to the minor product previously isolated from the SAD of homoallylic alcohol **15a**. With the global protecting group scheme in mind for the ultimate total synthesis of halichondrin B, the primary alcohol in **17a** was selectively protected as TBDPS ether **18a**, and the two secondary alcohols were then protected with TIPSOTf, providing the desired lactone **18b** in high yield.

Attempts at nucleophilic addition to the lactone carbonyl of **18b** with (lithiomethyl)dimethyl phosphonate[71–73] resulted in disappointingly low yields of the desired β-ketophosphonate hemiacetal **20** (Scheme 6). Only in the presence of a large excess (>100 equiv.) of the nucleophile could appreciable yields of phosphonate **20** be isolated (20–24%). The reason for this was revealed by treatment of **19a** with several equivalents of the lithiated phosphonate at −78°C, followed by a $D_2O$ quench, which produced stereoselectively deuterated lactone **21** in good yield with 100% deuterium incorporation. Since deprotonated **18b** is, as the enolate, protected against nucleophilic attack, the basis for the low conversion to **20** was apparent, and all attempts to moderate the basicity of the metalated phosphonate failed to increase the yield of **20**. The conformational constraints of the *cis*-fused lactones in **18b** and **19a** evidently align the convex α-C–H bond with the carbonyl π-system, significantly increasing the acidity relative to unconstrained esters. Examination of the analogous C–H bond in the crystal structure of bis(lactone) **2a** (Fig. 2) supports this conjecture. Based upon this conclusion, β-ketophosphonate formation from an acyclic ester derived from **18b** was pursued.

At ambient temperature, lactone **18b** proved unreactive with the aluminum amide generated from trimethylaluminum and MeNH(OMe)·HCl and required elevated temperatures (refluxing benzene) to afford the corresponding Weinreb's amide.[74–76] Unfortunately, the strenuous conditions required to open the lactone and form the Weinreb's amide facilitated the clean rearrangement of the [5,5]-spiroketal to the undesired [4,5]-spiroketal **22** (Scheme 7).[48] The free hydroxyl in amide **22** was converted to the corresponding acetate **23**, resulting in a significant downfield shift of what was determined to be the C(40) hydrogen resonance. The observed splitting pattern (td) and coupling constants ($J$=5.7, 1.2 Hz) strongly supported the assignment of **22** as the undesired [4,5]-spiroketal.

Ultimately, γ-lactone **18b** was saponified with LiOH in aqueous THF. The resulting seco acid was isolated by careful concentration at ambient temperature under reduced pressure and esterified with $TMSCHN_2$ at rt.[77] Methyl ester **24** was stable to silica gel chromatography and isolated in a near-quantitative, two-step yield. Attempts to protect the free hydroxyl in **24** as the silyl ether using tertiary amine bases with or $Ag_2O$/MPMCl re-established lactone **18b** as the exclusive product. However, treatment of hydroxy ester **24** with an excess of the MPM–trichloroacetimidate and stoichiometric $BF_3{\cdot}OEt_2$ at −78°C in $Et_2O$ provided the MPM ether **25** in good yield (88%).[78–80] While it was unlikely that the [5,5]-spiroketal had rearranged prior to MPM protection in the presence of $BF_3{\cdot}OEt_2$ at −78°C, a small portion of the MPM protected methyl ester **25** was deprotected by hydrogenolysis with $Pd(OH)_2/H_2$ and converted to the corresponding acetate **26**. The downfield methine resonance of acetate **26** appeared as a very broad singlet with coupling constants of <1 Hz. This closely matched the data collected for the diacetate **8b** (Scheme 3) of the [5,5]-spiroketal diol **8a** (bt, $J$=1.2 Hz), supporting the assignment of **25** as the desired methyl ester with the correct [5,5]-spiroketal assembly intact.

Fully protected methyl ester **25** was exposed to several equivalents of lithiomethyl dimethylphosphonate at −78°C, affording the desired β-ketophosphonate **1** (54%, unoptimized) with complete consumption of the starting material. Problems with deprotonation to the unreactive enolate, as described above for **18b**, did not occur with ester **25**.

## 1. Summary

To recapitulate, a 22 step synthesis of β-ketophosphonate **1** from the known epoxide **5** in 4% overall yield (based on recovered starting materials) has been completed. Employment and desymmetrization of $C_2$-symmetric intermediates formed the basis of the synthetic strategy. Introduction of four asymmetric centers in a single step via asymmetric dihydroxylation, followed immediately by formation of the C(44) spiroketal linkage was the central event in the synthesis. β-Ketophosphonate **1**, with 10 asymmetric centers set and rings N, M, L, and incipient ring K established, is a substantial subunit for coupling to a C(36)-terminated halichondrin B segment via an anticipated Horner–Wadsworth Emmons reaction.[81] Studies toward this end are underway.

## 2. Experimental

### 2.1. General procedures

Optical rotations were measured on a digital polarimeter at room temperature (21–22°C). Concentrations (*c*) are reported in g/100 mL. Infrared spectra (IR) are reported in wavenumbers ($\mathrm{cm}^{-1}$) with the designations (br), (s), and (w) referring to broad, strong, and weak signals, respectively. Melting points (mp) are uncorrected. Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded in deuterated solvents ($CDCl_3$, $C_6D_6$, $CD_3OD$) at 250, 300, or 500 MHz, as indicated. Chemical shifts are reported in parts per million (ppm, $\delta$) relative to tetramethylsilane (TMS, $\delta$ 0.00). Proton NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sex), septet (sep), multiplet (m), apparent (ap), and broad (br) with the coupling constants reported in hertz (Hz). Signal expansions provided on individual spectra are drawn at a scale of 20 Hz/cm. Carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded in deuterated solvents ($CDCl_3$, $C_6D_6$, $CD_3OD$) at 75.4 MHz or 125 MHz, as indicated. Chemical shifts are reported in parts per million (ppm, $\delta$) relative to tetramethylsilane (TMS, $\delta$ 0.00). Carbon resonances were assigned using distortionless enhancement by polarization transfer (DEPT) spectra obtained with a phase angle of 135°: (C) not observed; (CH) positive; ($CH_2$) negative; ($CH_3$) positive. Due to magnetically and chemically equivalent carbons, the number of carbon resonances reported may not match the actual number of carbons in the molecule. Coincidental magnetically equivalent carbons were noted when relative signal intensity allowed. Signal expansions provided on individual $^{13}$C NMR spectra are drawn at a scale of 200 Hz/cm. High resolution mass spectra (HRMS) using electron impact (EI, 70 eV) were recorded using peak matching. High and low resolution fast atom bombardment (FAB) mass spectra were obtained on a VG Analytical ZAB-2F (Ion Tech FAB gun, 8 kV, Xe carrier gas).

All moisture sensitive reactions were performed in flame-dried glassware under a stream of nitrogen unless otherwise noted. External bath temperatures were used to record all reaction temperatures. Concentrated in vacuo refers to the removal of volatile solvents via distillation using a rotary evaporator at water aspirator pressure, followed by residual solvent removal at high vacuum (approximately 5 μTorr). The acid free glassware utilized in the formation of vinyl ethers was obtained by immersing all items in a 0.5 M solution of HCl in EtOH for 1 h, rinsing with de-ionized water, immersing the items in a 0.5 M solution of KOH in EtOH for at least 1 h, rinsing again with de-ionized water, and oven drying.

Analytical thin-layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates pre-coated with silica gel 60 $F_{254}$ (250 μm layer thickness). Visualization was accomplished using UV light, iodine vapors, a *p*-anisaldehyde (PAA) charring solution (18 mL *p*-anisaldehyde, 7.5 mL glacial acetic acid, 25 mL 12.0 M $H_2SO_4$, 675 mL absolute EtOH) and/or phosphomolybdic acid solution (10% PMA in EtOH). Flash column chromatography (FCC) was performed on EM Science silica gel 60 (230–400 mesh). Solvent mixtures for TLC and FCC are reported in either $v_1/v_2$ ratios or $V_1/V_{\mathrm{total}}\times100$.

Immediately prior to use, tetrahydrofuran (THF), diethyl ether ($Et_2O$), and benzene were distilled from sodium/benzophenone ketyl; toluene ($PhCH_3$) was distilled from sodium metal/anthracene; methanol (MeOH) was distilled from magnesium methoxide; dichloromethane ($CH_2Cl_2$), hexanes (petroleum ether), diisopropylamine (*i*-$Pr_2NH$), and triethylamine ($Et_3N$) were distilled from calcium hydride. Acetonitrile ($CH_3CN$), ethylene glycol dimethylether (DME), collidine, pyridine (pyr), 1,1,1,3,3,3-hexamethyldisilazane (HMDS), and dimethylsulfoxide (DMSO) were distilled at reduced pressure from calcium hydride and stored over 4 Å molecular sieves. *t*-Butanol utilized in the TPAP oxidation was distilled from sodium metal and stored over 4 Å molecular sieves. Mesyl chloride (MsCl), titanium tetrachloride ($TiCl_4$), triethyl orthoacetate, boron trifluoride diethyl etherate ($BF_3\cdot OEt_2$), and propionic acid were distilled prior to use. 4-Dimethylaminopyridine (DMAP) was recrystallized from toluene. Lithium acetylide ethylenediamine complex was purchased from Aldrich and used without further purification. Tebbe's reagent was prepared and recrystallized from toluene/hexanes in Schlenk glassware in a slight modification of Grubb's procedure.[52c] The hydroborating agent, 9-BBN, was purchased as a 0.5 M solution in THF and was used immediately. Disiamylborane ($Sia_2BH$) was prepared immediately prior to use from 2 equiv. of 2-methyl-2-butene and one equivalent of borane THF complex in THF at −78°C followed by stirring for 1 h at 0°C. The Dess–Martin reagent was prepared in bulk via Ireland's modified procedure,[57] and recrystallized from $Ac_2O$/TsOH as necessary. The trichloroacetimidate of *p*-methoxybenzyl alcohol was prepared according to literature precedent and Kugelrohr distilled immediately prior to use.[78] All other commercially obtained reagents and solvents were used as received without further purification unless otherwise indicated.

**2.1.1. Preparation of (3*R*)-1-benzyloxy-5-hexyn-3-ol.** In a dry flask, 1.5 equiv. of lithium acetylide ethylenediamine complex (6.42 g, 69.7 mmol) were suspended in DMSO (100 mL), and the heterogeneous mixture was chilled to a semi-frozen slurry with an ice bath. A solution of epoxide **5**[37–39] (8.01 g, 44.9 mmol) was cannula transferred to the reaction flask with 40 mL of DMSO, and the reaction was allowed to warm to rt. After 12 h, the reaction was diluted with 200 mL of $Et_2O$, cooled to 0°C, quenched with 20 mL of water, and then acidified to pH 3 with 5% HCl(aq). The layers were separated, and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were dried over $Na_2SO_4$, filtered through a short plug of silica gel, and concentrated in vacuo. The crude terminal alkyne was used in the subsequent reaction without further purification. Data for (3*R*)-1-benzyloxy-5-hexyn-3-ol: $R_f$ 0.20 (50% $Et_2O$ in hexanes, PAA); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.25–7.40 (m, 5H), 4.52 (s, 2H), 3.94–4.04 (m, 1H), 3.60–3.78 (m, 2H), 3.13 (d, 1H, $J$=3.8 Hz), 2.40 (m, 2H), 2.03 (t, 1H, $J$=2.8 Hz), 1.77–1.97 (m, 2H).

**2.1.2. Preparation of (3*S*)-1-benzyloxy-4-hexyn-3-ol (6).** The crude terminal alkyne from above was dissolved in dry DMSO (150 mL) under a nitrogen atmosphere. The reaction mixture was cooled to 15°C and solid potassium *t*-butoxide (21 g, 187 mmol) added. After stirring for 40 min, the resulting dark brown solution was diluted with 200 mL of $Et_2O$ and cooled to 0°C. The reaction was carefully quenched by the dropwise addition of 3 M aqueous HCl. The layers were transferred to a separatory funnel, rinsing with $Et_2O$, and separated, and the aqueous layer was extracted with $Et_2O$. The combined organic extracts were washed with a 1:1 mixture of saturated $NaHCO_3$(aq) and brine, dried over $Na_2SO_4$, filtered through a plug of silica gel, and concentrated in vacuo. Silica gel chromatography with a 25–50% $Et_2O$/hexanes gradient elution yielded the internal alkyne **6** (7.91 g, 86% two-step yield) as a pale yellow oil. Data for **6**: $R_f$ 0.45 (1:1 $Et_2O$/hexanes, PAA); $[\alpha]_D^{22}=-20.5$ ($c$=2.0, benzene); IR (thin film) 3402 (br), 3030, 2920, 2856, 2243 (w), 1101, 1076 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.25–7.40 (m, 5H), 4.60 (tdq, 1H, $J$=6.1, 4.6, 2.2 Hz), 4.53 (s, 2H), 3.83 (ddd, 1H, $J$=9.5, 7.2, 4.4 Hz), 3.66 (ddd, 1H, $J$=9.5, 6.3, 4.8 Hz), 3.04 (d, 1H, $J$=6.1 Hz), 2.04 (ddt, 1H, $J$=14.3, 7.5, 4.6 Hz), 1.92 (dtd, 1H, $J$=14.3, 6.2, 4.4 Hz), 1.82 (d, 3H, $J$=2.2 Hz); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 137.8 (C), 128.4 (CH), 127.5 (CH), 127.5 (CH), 81.0 (C), 79.7 (C), 73.2 ($CH_2$), 67.7 ($CH_2$), 61.5 (CH), 37.0 ($CH_2$), 3.5 ($CH_3$); HRMS (EI) *m/e* (relative intensity, assignment) 204 (6, $M^+$), 203 (15, $M^+-H$), 186 (48, $M^+-H_2O$), 159 (34, $M^+-H_2O-C_2H_3$), 147 (54, $M^+-H_2O-C_3H_3$), 107 (67, $PhCH_2O^+$), 91 (100, $PhCH_2^+$); exact mass calcd for $C_{13}H_{16}O_2$ requires 204.1150, found 204.1145.

**2.1.3. Preparation of (3*S*,4*E*)-1-benzyloxy-4-hexen-3-ol (7).** Dry 95% lithium aluminum hydride (3.12 g, 82.2 mmol) was suspended in 200 mL of THF under an argon atmosphere, and the slurry was cooled to 0°C. A solution of propargyl alcohol **6** (7.90 g, 38.7 mmol) in 100 mL of THF was added dropwise via cannula. After $H_2$(g) evolution had ceased, the ice bath was removed and the reaction was heated to reflux. After 4 h at reflux, the reaction was cooled to 0°C and quenched by a slow, dropwise addition of saturated aqueous potassium sodium tartrate while maintaining an argon atmosphere. After gas and heat evolution ceased, the reaction was transferred to a larger vessel and diluted with 800 mL of $Et_2O$ and 1 L of saturated aqueous potassium sodium tartrate. This slurry was vortexed with a magnetic stir plate for 12 h, until a clean, biphasic solution was obtained. The phases were separated, and the aqueous layer was extracted with $Et_2O$. The combined organic layers were dried over $MgSO_4$, filtered through a silica gel plug with additional $Et_2O$, and concentrated in vacuo. Silica gel chromatography with 25% $Et_2O$/hexanes yielded the isomerically pure (3*S*, 4*E*)-1-benzyloxy-4-hexyn-3-ol (**7**) (7.57 g, 96%) as a colorless oil. Data for **7**: $R_f$ 0.35 (1:1 $Et_2O$/hexanes, PAA); $[\alpha]_D^{22}=1.15$ ($c$=6.0, benzene); IR (thin film) 3413, 3028, 2916, 2858, 1452, 1099 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.25–7.40 (m, 5H), 5.68 (dqd, 1H, $J$=15.3, 6.4, 1.1 Hz), 5.49 (ddq, 1H, $J$=15.3, 6.4, 1.3 Hz), 4.51 (s, 2H), 4.23–4.31 (m, 1H), 3.69 (ddd, 1H, $J$=9.4, 5.8, 5.1 Hz), 3.61 (ddd, 1H, $J$=9.4, 6.8, 5.5 Hz), 2.66 (d, 1H, $J$=3.1 Hz), 1.75–1.90 (m, 2H), 1.69 (ddd, 3H, $J$=6.4, 1.4, 0.9 Hz); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 138.0 (C), 133.6 (CH), 128.4 (CH), 127.7 (CH), 127.7 (CH), 126.4 (CH), 73.3 ($CH_2$), 71.7 (CH), 68.4 ($CH_2$), 36.7 ($CH_2$), 17.6 ($CH_3$); HRMS (EI) *m/e* (relative intensity, assignment) 206 (0.6, $M^+$), 188 (4, $M^+-H_2O$), 115 (61, $M^+-CH_2Ph$), 107 (100, $PhCH_2O^+$); exact mass calcd for $C_{13}H_{18}O_2$ requires 206.1307, found 206.1308.

**2.1.4. Preparation of (3*S*,4*E*)-3-methyl-7-benzyloxy-4-heptenoic acid ethyl ester (4).** A solution of allylic alcohol **7** (11.1 g, 54.0 mmol) in 210 mL of triethyl orthoacetate with catalytic propionic acid (0.15 mL, 2.0 mmol) was heated at 145°C for 26 h. After cooling to rt, the contents were diluted with 400 mL of EtOAc. The solution was cooled with an ice bath, and the excess triethyl orthoacetate quenched by the addition of 50 mL of 5% HCl(aq). After 10 min, the contents were transferred to a separatory funnel and the layers were separated. The aqueous phase was extracted with EtOAc, and the combined organics were washed with 1:1 saturated $NaHCO_3$(aq)/brine. The resulting solution was dried over $MgSO_4$, filtered through a small plug of silica gel with additional EtOAc and concentrated in vacuo. Silica gel chromatography with a gradient elution of 10–25% $Et_2O$/hexanes yielded the pure ethyl ester **4** (13.7 g, 92%) as a pale yellow oil. Data for **4**: $R_f$ 0.42 (1:3 $Et_2O$/hexanes, PAA); $[\alpha]_D^{22}=11.6$ ($c$=4.3, benzene); IR (thin film) 2850, 2769, 1734, 1172, 1101 cm$^{-1}$; $^1$H NMR ($C_6D_6$, 300 MHz) $\delta$ 7.05–7.35 (m, 5H), 5.29–5.51 (m, 2H), 4.31 (s, 2H), 3.95 (q, 2H $J$=7.2 Hz), 3.30 (t, 2H, $J$=7.2 Hz), 2.70 (hept, 1H, $J$=6.7 Hz), 2.21–2.28 (m, 2H), 2.22 (dd, 1H, $J$=14.7, 7.2 Hz), 2.10 (dd, 1H, $J$=14.7, 7.4 Hz), 0.95 (t, 3H, $J$=7.2 Hz), 0.95 (d, 3H, $J$=6.8 Hz); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 172.5 (C), 138.5 (C), 136.1 (CH), 128.3 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 125.5 (CH), 72.8 ($CH_2$), 70.1 ($CH_2$), 60.1 ($CH_2$), 41.8 ($CH_2$), 33.6

(CH), 32.9 ($CH_2$), 20.2 ($CH_3$), 14.2 ($CH_3$); MS (EI) *m/e* (relative intensity, assignment) 276 (0.8, $M^+$), 258 (1, $M^+-H_2O$), 230 (44, $M^+-CH_3CH_2OH$), 189 (40, $M^+-CH_2CO_2Et$), 155 (44, $M^+-CH_2OBn$), 91 (100, $PhCH_2^+$); exact mass calcd for $C_{17}H_{24}O_3$ requires 276.1725, found 276.1729.

**2.1.5. Preparation of (5*S*,6*E*)-5-methyl-2-[(1*R*,2*E*)-1-methyl-5-(benzyloxy)-2-pentenyl]-3-oxo-9-(benzyloxy)-6-nonenoic acid ethyl ester (3a).** Ethyl ester **4** (3.82 g, 13.8 mmol) was dissolved in 10 mL of THF and cooled to 0°C. In a separate, flame-dried round bottom flask, HMDS (7.3 mL, 34.6 mmol) and TMEDA (10.4 mL, 79.2 mmol) were combined in 10 mL of dry THF and cooled to 0°C. *n*-Butyl lithium (2.68 M in hexane, 12.9 mL, 34.6 mmol) was added dropwise over 10 min, and the LHMDS solution was stirred for an additional 30 min. The freshly generated LHMDS/TMEDA solution was added dropwise to the solution of the ethyl ester over 4.5 h. (Shorter addition times led to lower yields of the β-ketoester with greater amounts of recovered starting material. Longer reaction times led to more side product formation.) The reaction was diluted with 300 mL of $Et_2O$ and quenched by the addition of 400 mL of 5% HCl(aq) immediately following the LHMDS addition. The layers were separated, and the aqueous phase was extracted with $Et_2O$. The organic layers were washed with 1:1 saturated $NaHCO_3$(aq)/brine, and combined. The combined organics were dried over $MgSO_4$, filtered through a small plug of silica gel with additional $Et_2O$, and concentrated in vacuo. Silica gel chromatography with 25% $Et_2O$/hexanes yielded the ethyl β-ketoester **3a** (2.95 g, 84%) as a mixture of diastereomers in the form of a colorless oil plus a small amount of recovered starting material (0.60 g, 8%). Data for **3a**: $R_f$ 0.42 (1:3 $Et_2O$/hexanes, PAA); $[\alpha]_D^{22}=19.9$ ($c=4.39$, benzene); IR (thin film) 3026, 2956, 1741, 1714, 1454, 1101 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.24–7.40 (m, 20H), 5.28–58 (m, 8H), 4.50 (s, 4H), 4.49 (s, 2H), 4.48 (s, 2H), 4.15 (q, 2H, $J=7.2$ Hz), 4.08 (q, 2H, $J=7.0$ Hz), 3.40–3.50 (m, 8H), 3.33 (d, 1H, $J=6.8$ Hz), 3.28 (d, 1H, $J=6.8$ Hz), 2.85–3.05 (m, 2H), 2.60–2.77 (m, 2H), 2.22–2.55 (m, 12H), 1.24 (t, 3H, $J=7.2$ Hz), 1.19 (t, 3H, $J=7.0$ Hz), 1.02 (d, 3H, $J=6.6$ Hz), 0.96 (d, 3H, $J=6.6$ Hz), 0.95 (d, 3H, $J=6.6$ Hz), 0.91 (d, 3H, $J=6.6$ Hz); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 203.3 (C), 203.2 (C), 168.4 (C), 168.3 (C), 138.5 (C), 138.4 (C), 136.4 (CH), 136.2 (CH), 133.5 (CH), 133.4 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 125.4 (CH), 125.0 (CH), 72.8 ($CH_2$), 70.0 ($CH_2$), 69.8 ($CH_2$), 66.0 (CH), 65.6 (CH), 61.1 ($CH_2$), 61.0 ($CH_2$), 49.9 ($CH_2$), 49.7 ($CH_2$), 37.0 (CH), 36.8 (CH), 32.9 ($CH_2$), 31.9 (CH), 31.5 (CH), 20.0 ($CH_3$), 19.9 ($CH_3$), 18.6 ($CH_3$), 14.1 ($CH_3$); MS (FAB) *m/e* (relative intensity, assignment) 507 (50, $M+H^+$), 461 (26, $M^+-OCH_3$), 189 (60, $BnO(CH_2)_2(CH)_3CH_3^+$); exact mass calcd for $C_{32}H_{42}O_5+H^+$ requires 507.300, found 507.3.

**2.1.6. Preparation of (3*E*,5*S*,9*S*,10*E*)-5,9-dimethyl-1,13-bis(benzyloxy)-3,10-tridecadien-7-one (3b).** β-Ketoester **3a** (12.4 g, 24.5 mmol) was dissolved in 100 mL of DMSO containing water (1.4 mL, 77.8 mmol) and lithium chloride (3.9 g, 92.0 mmol). The reaction vessel was fitted with a reflux condenser, thoroughly flushed with nitrogen, and heated to 190°C. After 40 min the reaction mixture was cooled to rt and transferred to a separatory funnel containing 50 mL of half-saturated brine with 100 mL of EtOAc. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and filtered through a silica gel plug with $Et_2O$. The $C_2$-symmetric ketone **3b** (10.2 g, 96%) was isolated after concentration in vacuo and silica gel chromatography with 3% EtOAc/benzene. Data for **3b**: $R_f$ 0.31 (1:3 $Et_2O$/hexanes, PAA); $[\alpha]_D^{22}=38.5$ ($c=1.02$, benzene); IR (thin film) 3028, 2958, 2925, 2848, 1709, 1097 $cm^{-1}$; $^1H$ NMR ($C_6D_6$, 300 MHz) $\delta$ 7.05–7.35 (m, 10H), 5.31–5.49 (m, 4H), 4.35 (s, 4H), 3.33 (t, 4H $J=6.6$ Hz), 2.75 (hept, 2H, $J=6.8$ Hz), 2.28 (ap q, 4H), 2.06 (A of ABX, 2H, $J_{AB}=16.0$ Hz, $J_{AX}=6.5$ Hz), 2.03 (B of ABX, 2H, $J_{AB}=16.0$ Hz, $J_{BX}=7.3$ Hz), 0.94 (d, 6H, $J=6.8$ Hz); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 209.3, (C), 138.5 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 125.1 (CH), 72.8 ($CH_2$), 70.0 ($CH_2$), 50.5 ($CH_2$), 33.0 ($CH_2$), 32.4 (CH), 20.3 ($CH_3$); MS (FAB) *m/e* (relative intensity, assignment) 435 (48, $M+H^+$), 343 (31, $M^+-C_7H_7$), 221 (56, $M+H^+-2\times(C_7H_7O)$), 147 (100, $BnOC_3H_4^+$); exact mass calcd for $C_{29}H_{38}O_3+H^+$ requires 435.290, found 435.2.

**2.1.7. Preparation of (3*S*,4*S*,5*S*,9*S*,10*S*,11*S*)-1,13-bis-(benzyloxy)-5,9-dimethyl-3,4,10,11-tetrahydroxytridecane-7-one.** AD-mix-α (74 g, 2.3 equiv.) was dissolved in 400 mL of water and 360 mL of *t*-butyl alcohol at rt. The homogeneous solution was cooled to 0°C with an ice bath, initiating the precipitation of iron salts and the development of distinct organic and aqueous phases. The $C_2$-symmetric ketone **3b** (10.1 g, 23.2 mmol) in 40 mL of *t*-butyl alcohol was added dropwise over 10 min. The reaction was vortexed with a magnetic stir bar at 0°C for 24 h. (Reaction rates were appreciably slower at higher concentrations.) The reaction was diluted with 50 mL of water and excess oxidizing agent was then quenched by the addition of solid $Na_2S_2O_3$ (80 g, 500 mmol). After 10 min, the reaction was warmed to rt and stirred for an additional 30 min. The reaction contents were transferred to a separatory funnel with 300 mL of EtOAc and 100 mL of water. The phases were separated and the aqueous portion was further extracted with EtOAc. The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude keto tetraol, prone to spontaneous spiroketalization, was used in the subsequent reaction without further purification. Data for tetraol: $R_f$ 0.20 (1:19 $MeOH/CH_2Cl_2$, PAA).

**2.1.8. Preparation of (2*S*,3*S*,4*S*,8*S*,9*S*,10*S*)-2,8-di(2-benzyloxyethyl)-3,9-dihydroxy-4,10-dimethyl-1,7-dioxa-spiro[5,5]undecane (8a).** The crude tetraol from above was dissolved in 300 mL of benzene/methanol (2:1) in a round bottom flask equipped with a Dean/Stark trap. Catalytic CSA (158 mg, 0.68 mmol) was added to the reaction vessel, and the reaction was heated to reflux. The reaction volume was then reduced by two-thirds via the Dean/Stark trap. After cooling to rt, the resulting solution was transferred to a separatory funnel with EtOAc and washed with saturated $NaHCO_3$(aq)/brine (1:1). The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Silica gel chromatography with gradient elution (10–30% $EtOAc/CH_2Cl_2$) yielded a 1.1:1 mixture (9.84 g, 88%) of the desired spiroketal **8a** and the unsymmetrical spiroketal **9**. Trace amounts of the 1,5-dioxaspiro[4,4]nonane were also observed. Data for symmetrical spiroketal **8a**: $R_f$ 0.65 (1:1 EtOAc/$CH_2Cl_2$, PAA); $[\alpha]_D^{22}=-59.7$ ($c$=1.52, benzene); mp 108–109°C; IR (thin film) 3427 (br), 3032, 2954, 1454, 1205, 1103, 987, 743, 698 cm$^{-1}$; $^1$H NMR ($C_6D_6$, 300 MHz) $\delta$ 7.05–7.30 (m, 10H), 4.25 (s, 4H), 3.81 (ddd, 2H, $J$=8.8, 4.9, 0.9 Hz), 3.49 (ap dd, 4H, $J$=6.4, 5.5 Hz), 3.17 (br d, 2H, $J$=5.6 Hz), 1.96–2.15 (m, 4H), 1.79–1.92 (m, 2H), 1.75 (br d, 2H $J$=6.5 Hz), 1.28–1.42 (ap d, 4H), 0.99 (D, 6H, $J$=5.0 Hz); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 138.1 (C), 128.2 (CH), 127.6 (CH), 127.5 (CH), 96.5 (C), 72.9 ($CH_2$), 70.3 (CH), 69.4 (CH), 66.7 ($CH_2$), 36.9 ($CH_2$), 31.6 ($CH_2$), 30.0 (CH), 17.4 ($CH_3$); MS (FAB) *m*/*e* (relative intensity, assignment) 485 (100, M+H$^+$); exact mass calcd for $C_{29}H_{40}O_6+H^+$ requires 485.286, found 485.3. Data for spiroketal **9**: $R_f$ 0.68 (1:1 EtOAc/$CH_2Cl_2$, PAA); IR (thin film) 3450 (br), 3030, 2954, 2925, 1454, 1097, 981 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.20–7.35 (m, 10H), 4.47 ($AB_q$, 2H, $J_{AB}$=11.9 Hz, $\Delta\nu_{AB}$=19.8 Hz), 4.04 (br t, 1H, $J$=6.2 Hz), 3.58–3.68 (m, 2H), 3.45–3.55 (m, 4H), 3.33 (br d, 1H, $J$=5.3 Hz), 2.61 (d, 1H, $J$=8.3 Hz), 2.49–2.62 (m, 1H), 2.17 (dd, 1H, $J$=12.5, 7.0 Hz), 1.98–2.11 (m, 1H), 1.40–1.95 (m, 8H), 1.02 (d, 3H, $J$=6.6 Hz), 0.97 (d, 3H, $J$=6.8 Hz); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 138.5 (C), 138.1 (C), 128.3 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 105.7 (C), 90.7 (CH), 73.2 ($CH_2$), 72.7 ($CH_2$), 70.3 (CH), 69.9 (CH), 68.7 (CH), 67.3 ($CH_2$), 65.9 ($CH_2$), 47.2 ($CH_2$), 36.2 ($CH_2$), 35.0 ($CH_2$), 32.5 (CH), 31.8 ($CH_2$), 31.5 (CH), 17.7 ($CH_3$), 17.3 ($CH_3$); MS (FAB) *m*/*e* (relative intensity, assignment) 485 (100, M+H$^+$); exact mass calcd for $C_{29}H_{40}O_6+H^+$ requires 485.286, found 485.2. Data for the 1,5-dioxaspiro[4,4]nonane: $R_f$ 0.68 (1:1 EtOAc/$CH_2Cl_2$, PAA); IR (thin film) 3450 (br), 3030, 2954, 2925, 1454, 1097, 981 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.20–7.35 (m, 10H), 4.48 ($AB_q$, 4H, $J_{AB}$=12.0 Hz, $\Delta\nu_{AB}$=22.7 Hz), 3.57–3.75 (m, 6H), 3.45 (dd, 2H, $J$=8.4, 2.8 Hz), 3.32 (br s, 1.5 H), 2.46–2.63 (m, 2H), 2.12 (dd, 2H, $J$=12.3, 6.8 Hz), 1.67–1.92 (m, 4H), 1.66 (dd, 2H, $J$=12.3, 12.1 Hz), 1.03 (d, 6H, $J$=6.6 Hz); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 138.4 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 113.7 (C), 89.4 (CH), 73.1 ($CH_2$), 68.8 (CH), 68.0 ($CH_2$), 44.0 ($CH_2$), 35.0 ($CH_2$), 33.5 (CH), 17.5 ($CH_3$).

**2.1.9. Preparation of (2*S*,3*S*,4*S*,8*S*,9*S*,10*S*)-2,8-di(2-benzyloxyethyl)-3,9-diacetoxy-4,10-dimethyl-1,7-dioxaspiro[5,5]undecane (8b).** The spiroketal **8a** (10.1 mg, 0.021 mmol) was combined with $Ac_2O$ (0.2 mL) in 2.0 mL of pyridine at rt. After 14 h, the products were diluted with 30 mL of $Et_2O$ and washed first with a saturated $CuSO_4$(aq) and then brine. The organic layer was dried over $MgSO_4$, filtered through a short silica gel plug with additional $Et_2O$ and concentrated in vacuo. Silica gel chromatography using a 25–50% $Et_2O$/hexanes gradient elution provided the diacetate as a white solid (9.1 mg, 77%). Data for **8b**: $R_f$ 0.9 (1:9 MeOH/$CH_2Cl_2$, PAA); mp 96–97°C; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.21–7.36 (m, 10H), 4.83 (br t, 2H, $J$=1.3 Hz), 4.35 (s, 4H), 3.78 (ddd, 2H, $J$=9.2, 4.2, 0.9 Hz), 3.48 (t, 4H, $J$=6.9 Hz), 2.12–2.28 (m, 2H), 2.10 (s, 6H), 1.60–1.78 (m, 4H), 1.52 (A of ABX, 2H, $J_{AB}$=13.4 Hz, $J_{AX}$=4.3 Hz), 1.43 (B of ABX, 2H, $J_{AB}$=13.4 Hz, $J_{BX}$=10.5 Hz), 1.61 (d, 6H, $J$=7.0 Hz); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 171.0 (C), 138.3 (C), 128.3 (CH), 127.9 (CH), 127.6 (CH), 96.6 (C), 73.1 ($CH_2$), 71.9 (CH), 68.0 (CH), 66.7 ($CH_2$), 37.5 ($CH_2$), 31.7 ($CH_2$), 28.7 (CH), 20.8 ($CH_3$), 17.0 ($CH_3$).

**2.1.10. Preparation of (2*S*,3*S*,4*S*,8*S*,9*S*,10*S*)-3,9-dihydroxy-2,8-di(2-hydroxyethyl)-4,10-dimethyl-1,7-dioxaspiro[5,5]undecane (10).** The thermodynamic mixture of spiroketals **8a** and **9** (8.5 g, 17.5 mmol) was dissolved in 200 mL of absolute ethanol. Catalytic palladium(II) hydroxide (20 w/w% on carbon, 369 mg, 0.529 mmol) was suspended in the ethanol solution, and the system was placed under 1 atm of hydrogen. The reaction was vortexed with rapid stirring at rt for 12 h, with periodic regeneration of the hydrogen atmosphere. The resulting mixture was diluted with 400 mL of $CH_2Cl_2$ and filtered through a plug of silica gel. The plug was flushed with 10% MeOH/$CH_2Cl_2$, and the solution was concentrated in vacuo. Residual hydroxylic solvents were removed azeotropically with benzene, and the residue was placed under vacuum overnight to afford a 5:2:1 mixture of tetraol spiroketals **10–12** (5.33 g, 100%). Silica gel chromatography with 3% MeOH/EtOAc cleanly separated 1,7-dioxaspiro[5,5]undecane ketal **10** from the undesired spiroketals **11** and **12**. Data for 1,7-dioxyspiro[5,5]undecane **10**: $R_f$ 0.23 (1:9 MeOH/EtOAc, PAA); $[\alpha]_D^{22}=-110$ ($c$=0.200, MeOH); mp 123–124°C; IR (thin film) 3363 (br), 2922, 2872 cm$^{-1}$; $^1$H NMR ($CD_3OD$, 300 MHz) $\delta$ 3.72 (dd, 2H, $J$=10.1, 2.9 Hz), 3.65–3.70 (m, 4H), 3.20 (br d, 2H, $J$=1.5 Hz), 1.96–2.04 (m, 2H), 1.80 (ddt, 2H, $J$=14.5, 10.1, 5.0 Hz), 1.55 (dddd, 2H, $J$=14.5, 7.8, 6.6, 3.3 Hz), 1.35 (AB of ABX, 4H), 0.85 (d, 6H, $J$=6.8 Hz); $^{13}$C NMR ($CD_3OD$, 75.4 MHz) $\delta$ 97.9 (C), 71.7 (CH), 70.2 (CH), 59.8 ($CH_2$), 38.0 ($CH_2$), 35.9 ($CH_2$), 31.6 (CH), 18.1 ($CH_3$); MS (FAB) *m*/*e* (relative intensity, assignment) 305 (100, M+H$^+$), 289 (65, M+H$^+$−$H_2O$); exact mass calcd for $C_{15}H_{28}O_6+H^+$ requires 305.1523, found 305.1. Data for spiroketal **11**: $R_f$ 0.19 (1:9 MeOH/EtOAc, PAA); $^1$H NMR ($CD_3OD$, 300 MHz) $\delta$ 3.98 (ddd, 1H, $J$=9.8, 3.6, 0.2 Hz), 3.44–65 (m, 6H), 3.35 (dd, 1H, $J$=8.6, 4.6 Hz), 3.15–3.22 (m, 2H), 2.29–2.46 (m, 1H), 1.90–2.12 (m, 2H), 1.44–1.78 (m, 6H), 1.13–1.42 (m, 3H), 0.94 (d, 3H, $J$=6.6 Hz), 0.85 (d, 3H, $J$=6.6 Hz); $^{13}$C NMR ($CD_3OD$, 75.4 MHz) $\delta$ 106.7 (C), 94.6 (CH), 71.4 (CH), 70.4 (CH), 70.1 (CH), 60.0 ($CH_2$), 59.1 ($CH_2$), 48.4 ($CH_2$), 37.6 ($CH_2$), 37.2 ($CH_2$), 35.6 ($CH_2$), 33.9 (CH), 32.9 (CH), 18.2 ($CH_3$), 17.6 ($CH_3$). Data for spiroketal **12**: $R_f$ 0.16 (1:9 MeOH/EtOAc, PAA); $^1$H NMR ($CD_3OD$, 300 MHz) $\delta$ 4.57 (br s, 4H), 3.52–3.63 (m, 6H), 3.30 (dd, 2H, $J$=8.4, 2.7 Hz), 2.32–2.51 (m, 2H), 2.02 (dd, 2H, $J$=12.3, 6.7 Hz), 1.50–1.73 (m, 6H), 0.96 (d, 6H, $J$=6.6 Hz); $^{13}$C NMR ($CD_3OD$, 75.4 MHz) $\delta$ 114.8 (C), 90.6 (CH), 68.7 (CH), 60.1 ($CH_2$), 45.1 ($CH_2$), 38.6 ($CH_2$), 34.8 (CH), 17.6 ($CH_3$).

**2.1.11. Equilibration to (2*S*,3*S*,4*S*,8*S*,9*S*,10*S*)-3,9-dihydroxy-2,8-di(2-hydroxyethyl)-4,10-dimethyl-1,7-dioxaspiro[5,5]undecane (10).** The undesired spiroketal **11** (2.1 g, 6.9 mmol) was dissolved with 50 mL of MeOH in a round bottom flask equipped with a reflux condenser. Catalytic triflic acid (0.06 mL, 0.78 mmol) was added, and the system was heated to reflux for 50 min. After cooling, the contents were diluted with 100 mL of benzene and concentrated in vacuo. The resulting mixture of ketals

(2.06 g, 98%) was further azeotroped with two 100 mL portions of benzene, and then subjected to silica gel FCC with 3% MeOH/EtOAc. Any mixed fractions favoring the desired 1,7-dioxaspiro-[5,5]-undecane ketal **10** were recrystallized from EtOAc. All spectroscopic data for the recrystallized product **10** were consistent with those above.

**2.1.12. Preparation of (2*S*,3*S*,4*S*,8*S*,9*S*,10*S*)-2,8-bis(2-ethanoic acid-γ-lactone)-3,9-dihydroxy-4,10-dimethyl-1,7-dioxaspiro[5,5]undecane (2a).** The $C_2$-symmetric 1,7-dioxaspiro[5,5]undecane **10** (1.85 g, 6.08 mmol) was combined with powdered 4 Å molecular sieves and NMO (4.5 g, 38.4 mmol) in 100 mL of *t*-butyl alcohol/acetonitrile (1:1). After the heterogeneous solution was stirred at rt for 20 min, TPAP (107 mg, 5 mol%) was added, and the reaction was stirred for 60 min. An additional 5 mol% of TPAP was added, and the reaction stirred for 12 h, after which the starting tetraol was no longer present. The solution was diluted with 30 mL of $CH_2Cl_2$, and 1 mol% portions of TPAP were added every 20 min until partially oxidized intermediates were no longer observed by TLC. The reaction was diluted again with $CH_2Cl_2$ (500 mL) and filtered through a plug of silica gel, removing the 4 Å molecular sieves, TPAP, and excess NMO. The silica gel plug was rinsed with 25% $Et_2O/CH_2Cl_2$, and the pale yellow solution was concentrated in vacuo. Complete removal of the oxidizing agents prior to concentration was necessary for optimum yields. The resulting bis(lactone) was immediately purified by silica gel chromatography (1:9 $Et_2O/CH_2Cl_2$). Any mixed fractions were further purified by dissolving the impure bis(lactone) **2a** in a minimal amount of hot benzene, adding an equivalent volume of hot hexanes, and allowing overnight crystal growth at room temperature. Careful and rapid purification resulted in reproducibly high yields of the $C_2$-symmetric bis(lactone) **2a** (1.35 g, 75%) as a white crystalline solid. Data for **2a**: $R_f$ 0.55 (1:3 $Et_2O/CH_2Cl_2$, PAA); $R_f$ 0.1 (2% $MeOH/Et_2O$, PAA); $[\alpha]_D^{22}=-188$ ($c=0.365$, $CH_2Cl_2$); mp (dec.) 231°C; IR (thin film) 2933, 1776, 1186, 1159, 1014 $cm^{-1}$; $^1H$ NMR ($C_6D_6$, 300 MHz) $\delta$ 3.32 (t, 2H, $J=2.6$ Hz), 3.21 (dd, 2H, $J=4.4$, 2.2 Hz), 2.16 (A of ABX, 2H, $J_{AB}=16.9$ Hz, $J_{AX}=0.1$ Hz), 1.90 (B of ABX, 2H, $J_{AB}=16.9$ Hz, $J_{BX}=4.3$ Hz), 1.71–1.85 (m, 2H), 1.03 (A of ABX, 2H, $J_{AB}=13.6$ Hz, $J_{AX}=14.7$ Hz), 0.94 (B of ABX, 2H, $J_{AB}=13.6$ Hz, $J_{BX}=6.1$ Hz), 0.88 (d, 6H, $J=7.0$ Hz); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 175.6 (C), 96.5 (C), 80.3 (CH), 69.2 (CH), 38.4 ($CH_2$), 35.7 ($CH_2$), 25.4 (CH), 17.1 ($CH_3$); HRMS (EI) *m*/*e* (relative intensity, assignment) 297 (0.9, $M+H^+$), 296 (3.6, $M^+$), 208 (23, $M^+-2\times CO_2$), 169 (22, $C_{10}H_{17}O_2^+$), 168 (100, $C_{10}H_{16}O_2^+$); exact mass calcd for $C_{15}H_{20}O_6$ requires 296.1260, found 296.1256.

**2.1.13. Preparation of primary alcohol (13).** $C_2$-Symmetric bis(lactone) **2a** (67.8 mg, 0.229 mmol) was dissolved in 2.0 mL of THF and 2.0 mL of toluene with a catalytic amount of pyridine (1.1 mg, 0.015 mmol) under an argon atmosphere, and the solution was cooled to −78°C. A 0.7 M solution of the Tebbe reagent[52c] in toluene (0.24 ml, 0.168 mmol) was added dropwise, and after 5 min at −78°C, the dry ice bath was removed and the reaction was warmed to rt. After 40 min, a 0.5 M solution of 9-borabicyclononane (9-BBN) in THF was added via syringe (0.46 mL, 0.23 mmol), and the reaction was stirred at rt for 30 min. The reaction was quenched with 2 mL of water, diluted with 10 mL of THF, and oxidized by adding excess sodium perborate tetrahydrate (75 mg, 0.69 mmol) and stirring for 2 h. The reaction contents were poured onto 10 mL of saturated $NaHSO_3$(aq), and after 15 min, 30 mL of saturated Rochelle's salt(aq) was added. After 10 additional min, the biphasic system was transferred to a separatory funnel containing 10 mL of 1.25 M NaOH(aq). The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting mixture of recovered starting material **2a**, mono-functionalized alcohol **13**, and side products was loaded onto a silica gel column with $CH_2Cl_2$/hexanes (1:1). One column volume of hexanes followed by 10 column volumes of $Et_2O$ were used to elute higher $R_f$ side products. Recovered starting material **2a** and the desired primary alcohol **13** were then co-eluted with 1:1 $Et_2O/CH_2Cl_2$. The starting material **2a** (37 mg, 54%) and primary alcohol **13** (29 mg, 40%) were then separated by FCC using a 10–25% $Et_2O/CH_2Cl_2$ gradient. Data for primary alcohol **13**: $R_f$ 0.2 (2% $MeOH/Et_2O$, PAA); IR (thin film) 3462 (br), 2928, 2828, 1780, 1117 $cm^{-1}$; $^1H$ NMR ($C_6D_6$, 300 MHz) $\delta$ 3.87–3.95 (m, 1H), 3.76 (ddd, 1H, $J=11.2$, 3.7, 3.3 Hz), 3.48 (dt, 1H, $J=11.2$, 4.6 Hz), 3.40–3.42 (m, 1H), 3.38 (dd, 1H, $J=4.1$, 2.4 Hz), 3.34 (dd, 1H, $J=3.2$, 2.4 Hz), 3.16 (br t, 1H, $J=2.4$ Hz), 2.24 (br t, 1H, $J=4.0$ Hz), 2.22 (A of ABX, 1H, $J_{AB}=16.9$ Hz, $J_{AX}=0.1$ Hz), 1.91–2.10 (m, 2H), 1.92 (B of ABX, 1H, $J_{AB}=16.9$ Hz, $J_{BX}=4.3$ Hz), 1.600–1.74 (m, 2H), 1.31 (A of ABX, 1H, $J_{AB}=13.3$ Hz, $J_{AX}=12.7$ Hz), 1.17 (ap d, 1H), 1.09 (B of ABX, 1H, $J_{AB}=16.9$ Hz, $J_{BX}=4.4$ Hz), 1.02 (d, 3H, $J=7.2$ Hz), 0.86 (d, 3H, $J=7.2$ Hz); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 175.8 (C), 96.9 (C), 80.4 (CH), 79.6 (CH), 72.4 (CH), 68.9 (CH), 65.0 (CH), 38.4 ($CH_2$), 36.4 ($CH_2$), 36.2 ($CH_2$), 34.6 ($CH_2$), 29.6 ($CH_2$), 25.5 (CH), 25.5 (CH), 17.7 ($CH_3$), 17.2 ($CH_3$); HRMS (EI) *m*/*e* (relative intensity, assignment) 313 (0.3, $M+H^+$), 281 (17, $M^+-CH_2OH$), 144 (58, $C_7H_{12}O_3^+$); exact mass calcd for $C_{16}H_{24}O_6+H^+$ requires 313.1651, found 313.1645. Data for terminal alkene **14**: $R_f$ 0.7 (2% $MeOH/Et_2O$, PAA); IR (thin film) 3394 (br), 2917, 2848, 1780, 1191, 1016 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 5.84 (dddd, 1H, $J=17.1$, 10.2, 7.7, 6.8 Hz), 5.15 (ddt, 1H, $J=17.1$, 2.0, 1.4 Hz), 5.07 (ddt, 1H, $J=10.2$, 2.0, 0.9 Hz), 4.24 (t, 1H, $J=2.6$ Hz), 4.21 (dd, 1H, $J=4.0$, 2.2 Hz), 3.63 (ddd, 1H, $J=8.5$, 5.5, 0.9 Hz), 3.42 (dd, 1H, $J=7.8$, 0.9 Hz), 2.68 (A of ABX, 1H, $J_{AB}=17.1$, $J_{AX}=4.1$ Hz), 2.51 (B of ABX, 1H, $J_{AB}=17.1$, $J_{BX}=0.1$ Hz), 2.23–2.48 (m, 3H), 1.98–2.15 (m, 1H), 1.35–1.60 (m, 5H), 1.11 (d, 3H, $J=7.2$ Hz), 0.97 (d, 3H, $J=6.8$ Hz); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 176.1 (C), 134.7 (CH), 117.5 ($CH_2$), 96.6 (C), 80.6 (CH), 72.9 (CH), 69.8 (CH), 68.3 (CH), 38.4 ($CH_2$), 36.4 ($CH_2$), 36.1 ($CH_2$), 36.0 ($CH_2$), 30.0 (CH), 25.8 (CH), 17.4 ($CH_3$), 17.2 ($CH_3$); MS (FAB) *m*/*e* (relative intensity, assignment) 297 (10, $M+H^+$); exact mass calcd for $C_{16}H_{24}O_5+H^+$ requires 297.1702, found 297.2.

**2.1.14. Preparation of the C(51) aldehyde.** Primary alcohol **13** (125 mg, 0.40 mmol) was combined with the Dess–Martin periodinane reagent[57] (281 mg, 0.67 mmol) in 10 mL of $CH_2Cl_2$. The reaction was stirred for 2.5 h at rt, at which time only traces of starting material remained.

The resulting heterogeneous mixture was diluted with 10 mL of EtOAc and quenched with 20 mL of a saturated aqueous solution of sodium bicarbonate doped with sodium thiosulfate (25 g/100 mL). After 10 min, the contents were transferred to a separatory funnel with an additional 30 mL of EtOAc, separated, and the organic layer was washed with brine. The aqueous layers were extracted one additional time with EtOAc, and the combined organics were dried over $Na_2SO_4$, filtered, and concentrated at 25°C in vacuo. The crude aldehyde was used without further purification. Data for the aldehyde: $R_f$ 0.32 (1:3 $Et_2O/CH_2Cl_2$, PAA); $^1H$ NMR ($C_6D_6$, 300 MHz) $\delta$ 9.57 (br d, 1H, $J$=0.7 Hz), 3.95 (br d, 1H, $J$=9.9 Hz), 3.31–3.33 (m, 2H), 3.26–3.28 (m, 2H), 2.20 (A of ABX, 1H, $J_{AB}$=16.7 Hz, $J_{AX}$=0.1 Hz), 1.90 (m, 2H), 1.93 (B of ABX, 1H, $J_{AB}$=16.7 Hz, $J_{BX}$=0.1 Hz), 1.76–1.88 (m, 1H), 1.58–1.70 (m, 1H), 1.06–1.27 (m, 4H), 1.02 (d, 3H, $J$=7.2 Hz), 0.85 (d, 3H, $J$=7.0 Hz).

### 2.1.15. Preparation of C(51)-(*S*)-homoallylic alcohol (15a).

The crude C(51) aldehyde from above (0.40 mmol) was dissolved in 10 mL of dry $CH_2Cl_2$ under an argon atmosphere and cooled to −78°C. Freshly distilled $TiCl_4$ (60 μL, 0.547 mmol) was added dropwise, and the reaction mixture was aged for 10 min. Allyltri(*n*-butyl)stannane (0.19 mL, 0.612 mmol) was added dropwise via syringe, and the reaction was stirred for 20 min. One milliliter of water was added to quench the reaction, and the dry ice/acetone bath was removed. After the slurry had reached rt, it was acidified with 3% HCl(aq) and transferred to a separatory funnel with 30 mL of EtOAc. The layers were separated, and the organic phase was washed once with a 1:1 mixture of saturated $NaHCO_3$(aq) and brine. The aqueous layers were extracted with EtOAc, and the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Silica gel chromatography with EtOAc/$CH_2Cl_2$/hexanes (1:1:1) yielded the desired homoallylic alcohol **15a** (109 mg, 77%) as a pale yellow oil. Stannane impurities often contaminated the homoallylic alcohol and necessitated repeated chromatography for high levels of purity. Data for **15a**: $R_f$ 0.26 (1:3 $Et_2O/CH_2Cl_2$, PAA), $R_f$ 0.20 (1:1:1 EtOAc/$CH_2Cl_2$/hexanes, PAA); $[\alpha]_D^{22}=-109$ ($c$=0.210, $CH_2Cl_2$); IR (thin film) 3465, 2927, 1786, 1200, 1016 $cm^{-1}$; $^1H$ NMR ($C_6D_6$, 300 MHz) $\delta$ 5.82 (ddt, 1H, $J$=17.1, 10.2, 7.0 Hz), 5.08 (dq, 1H, $J$=17.1, 1.5 Hz), 5.04 (dm, 1H, $J$=10.2 Hz), 4.28 (dd, 1H, $J$=3.9, 2.3 Hz), 4.22 (dd, 1H, $J$=3.2, 2.3 Hz), 4.01–4.06 (m, 2H), 3.85–3.92 (m, 1H), 3.65–3.80 (m, 1H), 3.52 (dd, 1H, $J$=3.0, 1.8 Hz), 2.84 (d, 1H $J$=2.4 Hz), 2.67 (A of ABX, 1H, $J_{AB}$=17.1 Hz, $J_{AX}$=4.3 Hz), 2.50 (B of ABX, 1H, $J_{AB}$=17.1 Hz, $J_{BX}$=0.1 Hz), 1.97–2.41 (m, 5H), 1.37–1.52 (m, 4H), 1.06 (d, 3H, $J$=7.0 Hz), 1.01 (d, 3H, $J$=7.2 Hz); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 175.8 (C), 134.6 (CH), 117.2 ($CH_2$), 97.0 (C), 80.4 (CH), 80.0 (CH), 79.1 (CH), 72.2 (CH), 71.6 (CH), 68.9 (CH), 38.6 ($CH_2$), 38.4 ($CH_2$), 36.5 ($CH_2$), 36.1 ($CH_2$), 32.1 ($CH_2$), 25.4 (CH×2), 17.7 ($CH_3$), 17.2 ($CH_3$).

### 2.1.16. Preparation of C(51,53,54) triols 17a and b by asymmetric dihydroxylation of alkene 15a.

Potassium ferricyanide (12.1 mg, 0.037 mmol), potassium carbonate (9.0 mg, 0.065 mmol), $(DHQD)_2AQN$ (<1 mg, <0.001 mmol), and $OsO_4$ (0.12 mg, 0.00048 mmol) were combined in 1 mL of *t*-butanol with 2 mL of water and stirred at rt until a homogeneous solution was achieved. The mixture was then cooled to 0°C, and distinct organic and aqueous phases developed. A solution of homoallylic alcohol **15a** (4.0 mg, 0.011 mmol) in 1 mL of *t*-butanol was added. After 2 h at 0°C, the reaction was quenched by the addition of $NaHSO_3$ and warmed to rt. The system was diluted with 10 mL of water and 30 mL of EtOAc, and the layers were separated. The aqueous phase was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered through a short plug of silica gel with 10% MeOH in $CH_2Cl_2$, and concentrated in vacuo. Azeotropic removal of trace MeOH with benzene was followed by silica gel chromatography (3% MeOH/$CH_2Cl_2$) cleanly provided a 1:2 mixture of diastereomeric triols **17a** and **b** (4.2 mg, 96%) as a viscous oil. The diastereomers could be separated via silica gel FCC (3% MeOH/EtOAc). Data for (53*R*)-triol **17a**: $R_f$ 0.29 (1:9 MeOH/EtOAc, PAA); $[\alpha]_D^{22}=-86.4$ ($c$=0.550, EtOAc); IR (thin film) 3431 (br), 2929, 2875, 1784, 1198, 1016, 976 $cm^{-1}$; $^1H$ NMR ($C_6D_6$, 300 MHz) $\delta$ 4.05 (dt, 1H, $J$=10.2, 3.0 Hz), 3.77–3.86 (m, 1H), 3.66 (dt, 1H, $J$=9.6, 3.5 Hz), 3.47 (dd, 1H, $J$=10.8, 3.9 Hz), 3.28–3.40 (m, 4H), 3.07 (t, 1H, $J$=2.1 Hz), 2.22 (A of ABX, 1H, $J_{AB}$=16.7 Hz, $J_{AX}$=0.1 Hz), 1.82–2.08 (m, 3H), 1.92 (B of ABX, 1H, $J_{AB}$=16.7 Hz, $J_{BX}$=4.3 Hz), 1.61 (ddd, 1H, $J$=14.3, 9.7, 5.0 Hz), 1.05–1.53 (m, 6H), 1.01 (d, 3H, $J$=7.0 Hz), 0.83 (d, 3H, $J$=7.0 Hz), 0.45 (br s, 3H); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 175.8 (C), 97.1 (C), 80.6 (CH), 80.3 (CH), 79.2 (CH), 72.5 (CH), 72.2 (CH), 71.8 (CH), 69.1 (CH), 66.2 ($CH_2$), 38.4 ($CH_2$), 36.5 ($CH_2$), 36.3 ($CH_2$), 36.1 ($CH_2$), 32.4 ($CH_2$), 25.5 (CH×2), 17.7 ($CH_3$), 17.2 ($CH_3$); HRMS (FAB+NaI) $m/e$ (relative intensity, assignment) 409 (100, $M+Na^+$); exact mass calcd for $C_{19}H_{30}O_8+Na^+$ requires 409.1838, found 409.1836. Data for (53*S*)-triol 17b: $R_f$ 0.23 (1:9 MeOH/EtOAc, PAA); IR (thin film) 3430 (br), 2929, 2876, 1784, 1198, 1016 $cm^{-1}$; $^1H$ NMR ($C_6D_6$, 300 MHz) $\delta$ 4.13 (dt, 1H $J$=9.0, 3.4 Hz), 3.87–3.94 (m, 1H), 3.78 (dt, 1H, $J$=9.5, 3.6 Hz), 3.27–3.46 (m, 5H), 3.11 (t, 1H, $J$=2.4 Hz), 2.23 (A of ABX, 1H, $J_{AB}$=16.9 Hz, $J_{AX}$=0.1 Hz), 1.85–2.08 (m, 3H), 1.91 (B of ABX, 1H, $J_{AB}$=16.9 Hz, $J_{BX}$=3.6 Hz), 1.50–1.73 (m, 2H), 1.05–1.47 (m, 8H), 1.01 (d, 3H, $J$=7.2 Hz), 0.87 (d, 3H, $J$=7.2 Hz); $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 4.30 (dd, 1H, $J$=4.0, 3.4 Hz), 4.25 (dd, 1H, $J$=3.3, 2.2 Hz), 3.93–4.12 (m, 4H), 3.66 (dd, 1H, $J$=11.1, 3.6 Hz), 3.54–3.61 (m, 2H), 3.16 (br s, 1H), 3.04 (br s, 1H), 2.70 (A of ABX, 1H, $J_{AB}$=17.1 Hz, $J_{AX}$=4.2 Hz), 2.53 (B of ABX, 1H, $J_{AB}$=17.1 Hz, $J_{BX}$=0.1 Hz), 2.16 (ddd, 1H, $J$=14.1, 9.4, 4.8 Hz), 2.02 (dd, 1H, $J$=14.1, 3.6 Hz), 1.68 (br s, 1H), 1.42–1.65 (m, 5H), 1.11 (d, 3H, $J$=7.0 Hz), 1.04 (d, 3H, $J$=7.1 Hz); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 175.8 (C), 97.1 (C), 80.7 (CH), 80.4 (CH), 79.2 (CH), 72.3 (CH), 69.9 (CH), 66.8 ($CH_2$), 38.5 ($CH_2$), 36.6 ($CH_2$), 36.5 ($CH_2$), 36.2 ($CH_2$), 32.6 ($CH_2$), 25.4 (CH×2), 17.7 ($CH_3$), 17.2 ($CH_3$).

### 2.1.17. Preparation of (51*S*)-BOC carbonate 15b.

To homoallylic alcohol **15a** (20.1 mg, 0.057 mmol) and DMAP (25 mg, 0.22 mmol) in pyridine (0.7 mL, 8.6 mmol), was added $(BOC)_2O$ (185 mg, 0.85 mmol) at rt. After 24 h, the reaction was diluted with 2 mL of $CH_2Cl_2$ and monitored by TLC for starting material. Additional $(BOC)_2O$ (61 mg, 0.28 mmol) was added, and the reaction stirred for 3 h. The reaction was quenched with

5% aqueous HCl and extracted with EtOAc. The organic phase was washed with saturated $NaHCO_3$(aq)/brine (1:1). The aqueous layers were extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and filtered through a short plug of silica gel with additional EtOAc. After concentration in vacuo, silica gel chromatography with 50% $Et_2O$ in hexanes yielded the BOC carbonate **15b** (23.3 mg, 91%) as an amorphous white solid. Data for BOC carbonate **15b**: $R_f$ 0.25 (3:1 $Et_2O$/hexanes, PAA); $[\alpha]_D^{22}=-107$ ($c$=0.510, $CH_2Cl_2$); IR (thin film) 2962, 2929, 1785, 1741, 1277, 1250, 1163, 1016 cm$^{-1}$; $^1$H NMR ($C_6D_6$, 300 MHz) $\delta$ 5.82 (dddd, 1H, $J$=17.3, 10.3, 7.7, 6.6 Hz), 5.12 (dq, 1H, $J$=17.3, 1.3 Hz), 5.05 (ddt, 1H, $J$=10.3, 1.9, 1.0 Hz), 4.76 (td, 1H, $J$=7.7, 4.0 Hz), 4.28 (dd, 1H, $J$=4.0, 2.3 Hz), 4.22 (dd, $J$=2.8, 2.6 Hz), 3.95–4.02 (m, 2H), 3.59 (dd, 1H $J$=2.9, 2.4 Hz), 2.68 (A of ABX, 1H, $J_{AB}$=17.1 Hz, $J_{AX}$=0.4 Hz), 2.52–2.62 (m, 1H), 2.50 (B of ABX, 1H, $J_{AB}$=17.1 Hz, $J_{BX}$=4.1 Hz), 2.20–2.47 (m, 3H), 2.18 (ddd, 1H, $J$=14.1, 9.2, 5.0 Hz), 1.88 (dd, 1H $J$=14.1, 3.8 Hz), 1.37–1.60 (m, 4H), 1.48 (s, 9H), 1.11 (d, 3H, $J$=7.0 Hz), 1.02 (d, 3H, $J$=7.0 Hz); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 176.1 (C), 153.0 (C), 133.8 (CH), 117.5 ($CH_2$), 96.6 (C), 81.8 (C), 80.8 (CH), 79.9 (CH), 77.7 (CH), 77.6 (CH), 72.1 (CH), 68.8 (CH), 38.5 ($CH_2$), 36.6 ($CH_2$), 36.4 ($CH_2$), 35.7 ($CH_2$), 35.5 ($CH_2$), 27.8 ($CH_3\times3$), 25.5 (CH), 17.7 ($CH_3$), 17.2 ($CH_3$); MS (FAB+NaI) *m/e* (relative intensity, assignment) 475 (92, $M+Na^+$), 375 (100, $M+Na^+-BOC$); exact mass calcd for $C_{24}H_{36}O_8+Na^+$ requires 475.2310, found 475.2.

**2.1.18. Preparation of C(54)-iodo-(51*S*,53*R*) cyclic carbonate (16).** Homoallylic carbonate **15b** (23.1 mg, 0.051 mmol) was dissolved in dry toluene under an argon atmosphere and cooled with a dry ice/$Et_2O$ bath to −80°C. A 1.0 M solution of IBr in $CH_2Cl_2$ (0.12 mL, 0.12 mmol) was added dropwise over 2 min, and the reaction was held at −80°C for 3 h. After warming to 0°C and stirring for 15 min, the reaction was quenched with 10 mL saturated aqueous solution of sodium bicarbonate doped with sodium thiosulfate (25 g/100 mL), diluted with 10 mL of EtOAc, and stirred until colorless. The layers were transferred to a separatory funnel, and the aqueous layer extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered through a short silica gel plug with additional EtOAc, and concentrated in vacuo. Silica gel chromatography with a 0–50% EtOAc/$Et_2O$ solvent gradient provided the iodocarbonate **16** in excellent yield (26.6 mg, 99%) as a single diastereomer within the detection limits of $^1$H NMR. Data for **16**: $R_f$ 0.58 (100% EtOAc, PAA); $[\alpha]_D^{22}=-47.8$ ($c$=1.16, $CH_2Cl_2$); IR (thin film) 2926, 1754, 1187, 1116, 1018 cm$^{-1}$; $^1$H NMR ($C_6D_6$, 300 MHz) $\delta$ 3.83 (ddd, 1H, $J$=10.9, 7.0, 2.8 Hz), 3.54 (ddd, 1H, $J$=11.0, 9.0, 2.8 Hz), 3.41–3.45 (m, 2H), 3.29–3.38 (m, 1H), 3.37 (dd, 1H, $J$=4.6, 1.8 Hz), 3.10 (dd, 1H, $J$=2.6, 2.3 Hz), 2.53 (A of ABX, 1H, $J_{AB}$=10.7 Hz, $J_{AX}$=5.6 Hz), 2.44 (B of ABX, 1H, $J_{AB}$=10.7 Hz, $J_{BX}$=6.9 Hz), 2.26 (A of ABX, 1H, $J_{AB}$=16.7 Hz, $J_{AX}$=0.1 Hz), 2.01 (B of ABX, 1H, $J_{AB}$=16.7 Hz, $J_{BX}$=4.1 Hz), 1.90–2.08 (m, 3H), 1.84 (dd, 1H, $J$=14.1, 3.4 Hz), 1.72 (ddd, 1H, $J$=14.0, 9.8, 4.8 Hz), 1.09–1.36 (m, 5H), 1.01 (d, 3H, $J$=7.1 Hz), 0.95 (d, 3H, $J$=6.9 Hz); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 174.6 (C), 147.1 (C), 96.6 (C), 80.0 (CH), 79.6 (CH), 79.5 (CH), 78.3 (CH), 76.5 (CH), 72.0 (CH), 69.1 (CH), 38.4 ($CH_2$), 36.8 ($CH_2$), 36.7 ($CH_2$), 35.5 ($CH_2$), 30.6 ($CH_2$), 25.8 (CH), 25.7 (CH), 17.9 ($CH_3$), 17.5 ($CH_3$), 5.9 ($CH_2$).

**2.1.19. Preparation of C(51*S*,53*R*,54)-triol lactone 17a from iodocarbonate 16.** Iodocarbonate **16** (31.4 mg, 0.601 mmol) was combined with 1.0 M LiOH(aq) (0.9 mL, 0.9 mmol) in 3.5 mL of DME and 0.9 mL of water. The reaction was heated at 60°C for 13 h, then cooled to 0°C and neutralized to pH 7.0 with HCl(aq). The reaction mixture was concentrated in vacuo, azeotroped with benzene (2×20 mL), and the resulting solids placed under vacuum for several hours. The flask was then fitted with a reflux condenser and charged with 10 mL of benzene and one equivalent of CSA (140 mg, 0.602 mmol). The reaction was heated at reflux for 1 h, cooled to rt, and transferred to a separatory funnel with EtOAc. The solution was washed once each with saturated aqueous $NaHCO_3$ and brine. The aqueous phases were extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Silica gel chromatography (3% MeOH/$CH_2Cl_2$) cleanly provided the triol **17a** (21.0 mg, 90%). Generally, the aqueous layers were saved until the mass recovery of the lactone triol **17a** was confirmed. In cases of low mass recovery, the saved aqueous phases were combined, brought to neutral pH with HCl(aq), and the extraction process repeated to recover additional **17a**. See data for **17a** above.

**2.1.20. Preparation of C(54)-*t*-butyldiphenylsilyloxy-(51*S*,53*R*)-diol 18a.** Triol **17a** (10.9 mg, 0.028 mmol), DMAP (3 mg, 0.027 mmol), and excess pyridine (0.5 mL, 6.2 mmol) were combined in 1 mL of $CH_2Cl_2$. A slight excess of TBDPSCl (10 μL, 0.034 mmol) was added, and the reaction was stirred for 16 h at rt. The excess TBDPSCl was consumed by the addition of 0.2 mL of MeOH. After 15 min, the reaction contents were transferred to a separatory funnel with 30 mL of EtOAc and washed with 5% aqueous HCl and then saturated $NaHCO_3$(aq). The aqueous layers were extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$. After concentration in vacuo, the selectively protected diol **18a** was purified by silica gel chromatography with a 50–100% $Et_2O$/hexanes gradient elution (15.9 mg, 90%). Data for **18a**: $R_f$ 0.70 (100% EtOAc, PAA); $[\alpha]_D^{22}=-62.7$ ($c$=0.415, benzene); IR (thin film) 3417 (br), 2954, 2929, 2856, 1786, 1427, 1113, 1016 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.59–7.70 (m, 4H), 7.30–7.45 (m, 6H), 4.30 (dd, 1H, $J$=3.9, 2.3 Hz), 4.24 (br t, 1H, $J$=2.7 Hz), 4.03 (dd, 1H, $J$=4.4, 1.8 Hz), 3.90–4.00 (m, 3H), 3.62 (A of ABX, 1H, $J_{AB}$=10.1 Hz, $J_{AX}$=6.0 Hz), 3.60 (A of ABX, 1H, $J_{AB}$=10.1 Hz, $J_{BX}$=4.8 Hz), 3.55 (dd, 1H, $J$=2.9, 2.0 Hz), 3.42 (br s, 1H), 3.36 (br s, 1H), 2.69 (A of ABX, 1H, $J_{AB}$=17.1 Hz, $J_{AX}$=4.1 Hz), 2.52 (B of ABX, 1H, $J_{AB}$=17.1 Hz, $J_{BX}$=0.1 Hz), 2.20–2.45 (m, 2H), 2.14 (ddd, 1H, $J$=14.1, 9.2, 5.0 Hz), 2.03 (dd, 1H, $J$=14.1, 3.4 Hz), 1.74 (dt, 1H, $J$=15.0, 2.1 Hz), 1.22–1.52 (m, 5H), 1.09 (d, 3H, $J$=7.0 Hz), 1.06 (s, 9H), 1.02 (d, 3H, $J$=7.0 Hz); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 175.8 (C), 135.6 ($CH\times4$), 133.3 ($C\times2$), 129.8 ($CH\times2$), 127.8 ($CH\times4$), 97.0 (C), 80.6 (CH), 80.5 (CH), 79.3 (CH), 72.8 (CH), 72.3 (CH), 72.1 (CH), 69.0 (CH), 67.7 ($CH_2$), 38.5 ($CH_2$), 36.5 ($CH_2\times2$), 36.3 ($CH_2$), 33.0 ($CH_2$), 26.5 ($CH_3\times3$), 25.5 ($CH\times2$), 19.3 (C), 17.7 ($CH_3$), 17.2 ($CH_3$); MS (FAB+NaI) *m/e* (relative intensity, assignment) 647.4 (100, $M+Na^+$); exact mass calcd for $C_{35}H_{48}O_8Si+Na^+$ requires 647.3016, found 647.4.

**2.1.21. Preparation of C(54)-*t*-butyldiphenylsilyloxy-(51*S*,53*S*)-diol 17c.** Triol **17b** (11.0 mg, 0.028 mmol), DMAP (13 mg, 0.077 mmol), and excess pyridine (0.5 mL, 6.2 mmol) were combined in 1 mL of $CH_2Cl_2$. A slight excess of TBDPSCl (10 μL, 0.034 mmol) was added, and the reaction was stirred for 16 h at rt. The excess TBDPSCl was consumed by the addition of 0.2 mL of MeOH. After 15 min, the reaction contents were transferred to a separatory funnel with 30 mL of EtOAc and washed with 5% aqueous HCl and then saturated $NaHCO_3$(aq). The aqueous layers were extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$. After concentration in vacuo, the selectively protected diol **17c** was purified by silica gel chromatography with a 50–100% $Et_2O$/hexanes gradient elution (16.6 mg, 93%). Data for **17c**: $R_f$ 0.70 (100% EtOAc, PAA); IR (thin film) 3458 (br), 3070, 2929, 2856, 1786, 1427, 1112, 1016 $cm^{-1}$; $^1H$ NMR ($C_6D_6$, 300 MHz) $\delta$ 7.60–7.70 (m, 4H), 7.35–7.49 (m, 6H), 4.29 (dd, 1H, $J$=4.2, 2.8 Hz), 4.23 (dd, 1H, $J$=3.1, 2.4), 4.00–4.10 (m, 4H), 3.68 (dd, 1H, $J$=10.1, 4.2 Hz), 3.53–3.68 (m, 2H), 3.03 (br d, 1H, $J$=2.7 Hz), 2.86 (br d, 1H, $J$=3.9 Hz), 2.68 (A of ABX, 1H, $J_{AB}$=17.0 Hz, $J_{AX}$=4.2 Hz), 2.52 (B of ABX, 1H, $J_{AB}$=17.0 Hz, $J_{BX}$=0.1 Hz), 2.32–2.42 (m, 1H), 2.22–2.31 (m, 1H), 2.12 (ddd, 1H, $J$=14.0, 9.4, 5.0 Hz), 1.99 (dd, 1H, $J$=14.0, 3.7 Hz), 1.55 (ddd, 1H, $J$=14.9, 7.0, 4.0 Hz), 1.39–1.48 (m, 5H), 1.07 (d, 3H, $J$=7.2 Hz), 1.06 (s, 9H), 1.02 (d, 3H, $J$=7.2 Hz); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 175.9 (C), 135.5 (CH×4), 133.2 (C×2), 129.8 (CH×2), 127.8 (CH×4), 97.0 (C), 80.6 (CH), 80.5 (CH), 79.2 (CH), 72.3 (CH), 69.7 (CH), 69.3 (CH), 69.0 (CH), 68.0 ($CH_2$), 38.5 ($CH_2$), 36.5 ($CH_2$), 36.2 ($CH_2$), 36.1 ($CH_2$), 32.7 ($CH_2$), 26.8 ($CH_3$×3), 25.5 (CH×2), 19.3 (C), 17.7 ($CH_3$), 17.2 ($CH_3$); MS (FAB+NaI) *m*/*e* (relative intensity, assignment) 647.4 (100, $M+Na^+$); exact mass calcd for $C_{35}H_{48}O_8Si+Na^+$ requires 647.3016, found 647.4.

**2.1.22. Preparation of C(54)-*t*-butyldiphenylsilyloxy-(51*S*,53*R*) acetonide 19a.** To diol **18a** (8.3 mg, 0.013 mmol) in excess 2,2-dimethoxypropane (1 mL), was added catalytic CSA (0.5 mg, 0.0022 mmol) at rt. After 20 min, the reaction contents were rinsed into a separatory funnel with 30 mL $Et_2O$ and washed with saturated $NaHCO_3$(aq). The aqueous layer was extracted with $Et_2O$, and the combined organic layers were dried over $MgSO_4$. Filtration through a short plug of silica gel with additional $Et_2O$ and concentration in vacuo was followed by silica gel FCC with 50% $Et_2O$ in hexanes. The acetonide **19a** (7.1 mg, 80%) was isolated as a colorless oil. Data for **19a**: $R_f$ 0.55 (1:1 $Et_2O$/hexanes, PAA); $[\alpha]_D^{22}=-37.9$ ($c$=0.34, $CH_2Cl_2$); IR (thin film) 2924, 2854, 1789, 1111 $cm^{-1}$; $^1H$ NMR ($C_6D_6$, 300 MHz) $\delta$ 7.75–7.90 (m, 4H), 7.18–7.28 (m, 6H), 3.92–4.05 (m, 1H), 3.80–3.90 (m, 3H), 3.70 (dd, 1H, $J$=10.4, 4.6 Hz), 3.45–3.52 (m, 2H), 3.42 (br t, 1H, $J$=2.9), 3.28 (br t, 1H, $J$=2.4 Hz), 2.68 (A of ABX, 1H, $J_{AB}$=17.1, $J_{AX}$=0.1 Hz), 2.53 (B of ABX, 1H, $J_{AB}$=17.1, $J_{BX}$=4.1 Hz), 1.70–2.15 (m, 4H), 1.52 (s, 3H), 1.13–1.45 (m, 6H), 1.30 (s, 3H), 1.20 (s, 9H), 1.05 (d, 3H, $J$=6.8 Hz), 0.95 (d, 3H, $J$=6.8 Hz); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 176.0 (C), 135.7 (4×CH), 133.9 (C), 133.8 (C), 129.6 (2×CH), 127.6 (4×CH), 98.4 (C), 96.4 (C), 80.6 (CH), 80.2 (CH), 79.7 (CH), 72.5 (CH), 71.5 (CH), 70.1 (CH), 68.9 (CH), 67.5 ($CH_2$), 38.5 ($CH_2$), 37.0 ($CH_2$), 36.6 ($CH_2$), 35.2 ($CH_2$), 31.1 ($CH_2$), 30.0 ($CH_2$), 29.7 ($CH_2$), 26.8 (3×$CH_3$), 25.7 (CH), 25.6 (CH), 19.5 ($CH_3$), 19.3 (C), 17.7 ($CH_3$), 17.3 ($CH_3$); HRMS (FAB+$Na^+$) *m*/*e* (relative intensity, assignment) 687.3 (100, $M+Na^+$); exact mass calcd for $C_{38}H_{52}O_8Si+Na^+$ requires 687.3329, found 687.3328.

**2.1.23. Preparation of C(54)-*t*-butyldiphenylsilyloxy-(51*S*,53*S*) acetonide 19b.** To diol **17c** (15.5 mg, 0.025 mmol) in excess 2,2-dimethoxypropane (1 mL), was added catalytic CSA (1.0 mg, 0.0043 mmol) at rt. After 20 min, the reaction contents were rinsed into a separatory funnel with 30 mL of $Et_2O$ and washed with saturated $NaHCO_3$(aq). The aqueous layer was extracted twice with $Et_2O$, and the combined organic layers were dried over $MgSO_4$. Filtration through a short plug of silica gel with additional $Et_2O$ and concentration in vacuo was followed by silica gel FCC with 50% $Et_2O$ in hexanes. The acetonide **19b** (14.2 mg, 89%) was isolated as a colorless oil. Data for **19b**: $R_f$ 0.55 (1:1 $Et_2O$/hexanes, PAA); IR (thin film) 3070, 2929, 2856, 1788, 1379, 1113, 1016 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.66 (m, 4H), 7.32–7.46 (m, 6H), 4.28 (dd, 1H, $J$=3.9, 2.4 Hz), 4.22 (br t, 1H, $J$=2.7 Hz), 4.00 (dd, 1H, $J$=4.3, 2.0 Hz), 3.86–3.98 (m, 2H), 3.60–3.82 (m, 4H), 2.67 (A of ABX, 1H, $J_{AB}$=17.1 Hz, $J_{AX}$=4.2 Hz), 2.50 (B of ABX, 1H, $J_{AB}$=17.1 Hz, $J_{BX}$=0.1 Hz), 2.29–2.43 (m, 1H), 2.18–2.27 (m, 1H), 2.13 (ddd, 1H, $J$=13.6, 8.8, 4.6 Hz), 1.97 (dd, 1H, $J$=4.6, 2.7 Hz), 1.65–1.87 (m, 2H), 1.23–1.45 (m, 4H), 1.35 (s, 3H), 1.31 (s, 3H), 1.07 (d, 3H, $J$=7.0 Hz), 1.06 (s, 9H), 1.00 (d, 3H, $J$=7.0 Hz); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 176.1 (C), 135.7 (4×CH), 133.8 (C), 129.6 (2×CH), 127.6 (4×CH), 100.2 (C), 96.5 (C), 80.7 (CH), 80.1 (CH), 79.8 (CH), 72.5 (CH), 69.1 (CH), 68.9 (CH), 67.7 (CH), 66.7 ($CH_2$), 38.5 ($CH_2$), 36.7 ($CH_2$), 36.6 ($CH_2$), 35.7 ($CH_2$), 31.7 ($CH_2$), 26.9 (3×$CH_3$), 25.6 (2×CH), 24.8 (2×$CH_3$), 19.3 (C), 17.8 ($CH_3$), 17.3 ($CH_3$); MS (FAB+NaI) *m*/*e* (relative intensity, assignment); exact mass calcd for $C_{38}H_{52}O_8Si+Na^+$ requires 687.3329, found 687.4.

**2.1.24. Preparation of C(54)-*t*-butyldiphenylsilyloxy-(51*S*,53*R*)-bis(triisopropylsilyloxy) lactone 18b.** Diol **18a** (125 mg, 0.200 mmol) was combined with DMAP (44 mg, 0.39 mmol) under a nitrogen atmosphere and then dissolved in 0.6 mL of dry pyridine. TIPSOTf (0.4 mL, 1.49 mmol) was added via syringe, and the reaction was stirred for 15 h. Excess TIPSOTf was consumed by the addition of 1.5 mL of dry MeOH. After 15 min, the reaction was transferred to a separatory funnel with $Et_2O$ and washed first with 5% HCl and then with a 1:1 mixture of saturated $NaHCO_3$(aq) and brine. The aqueous layers were extracted with $Et_2O$, and the combined organic layers were dried over $MgSO_4$. Filtration through a short silica gel plug with additional $Et_2O$ and concentration in vacuo provided the crude product, which was purified by silica gel chromatography (25% $Et_2O$ in hexanes) to afford 187 mg (99%) of the lactone **18b** as a pale yellow oil. Data for **18b**: $R_f$ 0.35 (1:1 $Et_2O$/hexanes, PAA); $[\alpha]_D^{22}=+61.0$ ($c$=0.115, benzene); IR (thin film) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.63–7.70 (m, 4H), 7.32–7.44 (m, 6H), 4.28 (dd, 1H, $J$=3.9, 2.4 Hz), 4.21 (br t, 1H, $J$=2.5 Hz), 4.07–4.15 (m, 2H), 3.98 (dd, 1H, $J$=6.0, 2.2 Hz), 3.83 (ddd, 1H, $J$=9.5, 6.6, 3.4 Hz), 3.66 (A of ABX, 1H, $J_{AB}$=10.3 Hz, $J_{AX}$=4.7 Hz), 3.61 (B of ABX, 1H, $J_{AB}$=10.3 Hz, $J_{BX}$=5.5 Hz), 3.34 (br t, 1H, 2.6 Hz), 2.67 (A of ABX, 1H, $J_{AB}$=17.3 Hz, $J_{AX}$=4.5 Hz), 2.51 (B of ABX, 1H, $J_{AB}$=17.3 Hz, $J_{BX}$=0.1 Hz), 2.30–2.40 (m, 1H), 2.19–2.30 (m, 1H), 1.95–2.06 (m, 2H), 1.85–1.91 (m, 2H), 1.32–151 (m, 4H), 0.97–1.08 (m, 57H); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 174.6 (C), 136.1 (CH), 136.0 (CH), 134.1 (C), 133.7 (C), 130.0 (CH), 128.0 (CH), 96.8 (C), 81.2 (CH), 80.0 (CH), 79.8 (CH), 72.4 (CH), 71.8 (CH), 71.2 (CH), 69.0 (CH), 68.4 ($CH_2$), 38.7 ($CH_2$), 38.4 ($CH_2$), 37.0 ($CH_2$), 36.5 ($CH_2$), 34.9 (4×$CH_3$), 27.2 ($CH_2$), 25.8 (CH), 19.4 (C), 18.6 (2×$CH_3$), 18.0 (CH), 17.5 (CH), 13.5 ($CH_3$), 13.1 ($CH_3$); MS (FAB+NaI) *m/e* (relative intensity, assignment) 959.6 (100, $M+Na^+$); exact mass calcd for $C_{53}H_{88}O_8Si_3+Na^+$ requires 959.5687, found 959.6.

**2.1.25. Preparation of the C(38)-methyl ester 24.** Fully protected lactone **18b** (34.8 mg, 0.037 mmol) in 2.5 mL of THF and 2.0 mL of *t*-butanol was combined with excess 1.0 M LiOH(aq) (2.0 mL, 2.0 mmol) at rt. The heterogeneous system was stirred rapidly for 2 h and then diluted with 20 mL of $Et_2O$ and acidified to pH 3 with 5% HCl(aq). The layers were separated, and the aqueous phase was extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo at 22°C. The crude hydroxy acid (0.037 mmol) was dissolved in 1.3 mL of benzene/MeOH (7:2) at rt. Several drops of a 2.0 M solution of trimethylsilyldiazomethane in hexanes was added, and the reaction stirred until the seco acid was no longer visible by TLC (15 min). The resulting solution was concentrated in vacuo at 22°C and the crude methyl ester was purified by silica gel FCC (1:3 $Et_2O$/hexanes). In vacuo concentration of the fractions at 22°C cleanly provided the methyl ester **24** (34.2 mg, 95% two steps) as a pale yellow oil. Data for **24**: $R_f$ 0.19 (1:1 $Et_2O$/hexanes, PAA); IR (thin film) 3483 (br), 2942, 2864, 1742, 1462, 1111, 1003 cm$^{-1}$; $^1$H NMR ($C_6D_6$, 300 MHz) $\delta$ 7.80–7.89 (m, 4H), 7.20–7.32 (m, 6H), 4.39–4.49 (m, 2H), 4.27 (br q, 1H, $J$=5.3 Hz), 4.16 (ddd, 1H, $J$=10.1, 3.8, 1.1 Hz), 3.88–3.98 (m, 3H), 3.36 (s, 3H), 3.32 (br t, 1H, $J$=2.7 Hz), 3.04 (br d, 1H, $J$=8.1 Hz), 2.80 (A of ABX, 1H, $J_{AB}$=15.8 Hz, $J_{AX}$=9.7 Hz), 2.26 (B of ABX, 1H, $J_{AB}$=15.8 Hz, $J_{BX}$=3.8 Hz), 1.95–2.43 (m, 6H), 1.08–1.65 (m, 43H), 1.12 (d, 3H, $J$=7.2 Hz), 0.96 (d, 3H, $J$=7.0 Hz); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 171.9 (C), 136.2 (CH), 136.1 (CH), 134.2 (C), 133.9 (C), 129.9 (CH), 128.0 (CH), 97.1 (C), 81.3 (CH), 80.1 (CH), 72.3 (CH), 72.1 (CH), 71.5 (CH), 70.3 (CH), 69.7 (CH), 68.4 ($CH_2$), 51.0 ($CH_3$), 38.3 ($CH_2$), 37.6 ($CH_2$), 37.3 ($CH_2$), 37.0 ($CH_2$), 35.3 ($CH_2$), 30.2 CH), 27.2 (3×$CH_3$), 26.4 (2×CH), 19.5 (C), 18.6 (*n*×$CH_3$), 18.5 (*n*×CH), 18.3 ($CH_3$), 17.7 (CH), 13.5 ($CH_3$), 13.2 ($CH_3$).

**2.1.26. Preparation of the C(41)-(methoxybenzyloxy) methyl ester 25.** Alcohol **24** (3.0 mg, 0.0031 mmol) and 5 equiv. of the MPM–trichloroacetimidate[78–80] in 1 mL of $Et_2O$ were cooled to −78°C. An aliquot from a 0.10 M solution of $BF_3{\cdot}Et_2O$ in $Et_2O$ (68 μL, 0.0068 mmol) was added to the reaction. After 30 min, only traces of starting material remained, and the reaction was quenched by the addition of 5% HCl(aq) and warmed to rt. The mixture was diluted with $Et_2O$, and the phases were separated. The organic phase was washed with a saturated solution of $NaHCO_3$(aq)/brine (1:1), dried over $MgSO_4$, and filtered. Concentration in vacuo was followed by silica gel FCC with 2% $Et_2O$ in benzene to yield the MPM protected methyl ester **25** (3.1 mg, 91%) as a thin film. Data for **25**: $R_f$ 0.60 (1:9 $Et_2O$/benzene, PAA); $[\alpha]_D^{22}$=−75.9 ($c$=0.145, $CH_2Cl_2$); IR (thin film) 2943, 2865, 1740, 1248, 1111, 1081, 1055, 1038, 998 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.64–7.71 (m, 4H), 7.32–7.42 (m, 6H), 7.23–7.29 (m, 2H), 6.84–6.90 (m, 2H), 4.50 ($AB_q$, 2H, $J_{AB}$=11.1 Hz, $\Delta\nu/2$=26.1 Hz), 4.12–4.17 (m, 1H), 4.08 (ddd, 1H, $J$=8.9, 5.0, 1.1 Hz), 4.03–4.07 (m, 2H), 3.80 (s, 3H), 3.78 (ddd, 1H, $J$=9.1, 6.2, 5.0 Hz), 3.64 (s, 3H), 3.61–3.64 (m, 1H), 3.30 (br t, 1H, $J$=2.8 Hz), 3.25 (br s, 1H), 2.64 (A of ABX, 1H, $J_{AB}$=15.4 Hz, $J_{AX}$=9.1 Hz), 2.32 (B of ABX, 1H, $J_{AB}$=15.4 Hz, $J_{BX}$=4.9 Hz), 2.12–2.23 (m, 2H), 1.93–2.05 (m, 2H), 1.80–1.91 (m, 2H), 1.31–1.52 (m, 4H), 0.99–1.05 (m, 51H), 0.95 (d, 3H, $J$=7.1 Hz), 0.94 (d, 3H, F $J$=7.0 Hz); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 172.5 (C), 158.8 (C), 135.8 (CH), 135.7 (CH), 133.9 (C), 133.7 (C), 130.7 (C), 129.9 (CH), 129.5 (CH), 127.5 (CH), 113.6 (CH), 97.0 (C), 80.8 (CH), 79.8 (CH), 77.2 (CH), (74.8 ($CH_2$), 71.6 (CH), 70.7 (CH), 69.6 (CH), 67.9 ($CH_2$), 55.3 ($CH_3$), 51.5 ($CH_3$), 37.8 ($CH_2$), 36.9 ($CH_2$), 34.8 ($CH_2$), 30.2 (CH), 26.9 (3×$CH_3$), 25.8 (CH), 19.2 (C), 18.2 (*n*×$CH_3$), 18.1 ($CH_3$), 17.8 (CH), 13.1 ($CH_3$), 12.7 ($CH_3$); HRMS (FAB+NaI) *m/e* (relative intensity, assignment) 1111.6574 (100, $M+Na^+$); exact mass calcd for $C_{62}H_{100}O_{10}Si_3+Na^+$ requires 1111.6522, found 1111.6574.

**2.1.27. Preparation of the β-ketophosphonate 1.** In a flame-dried flask, dimethyl methylphosphonate (50 μL, 0.46 mmol) was combined with 4 mL of THF and cooled to −78°C under an argon atmosphere. One equivalent of *n*-butyllithium (0.46 mmol) was added via syringe, and the mixture was allowed to stir for 15 min. In a separate flask the methyl ester **25** (5.5 mg, 0.0051 mmol) was dissolved in 1 mL of THF and cooled to −78°C. Approximately 0.2 mL of the lithiated dimethyl methylphosphonate solution was cannula transferred to the reaction flask. After 15 min, the reaction was quenched with 5% HCl(aq) and allowed to warm to rt. The resulting mixture was diluted with $Et_2O$. The organic phase was separated, washed with saturated $NaHCO_3$(aq)/brine (1:1), and dried over $MgSO_4$. Concentration in vacuo was followed by silica gel FCC using a 0–2% MeOH/$Et_2O$ gradient elution to provide the β-ketophosphonate **1** (3.2 mg, 54%) as a thin film. Data for **1**: $R_f$ 0.09 (100% $Et_2O$, PAA); $[\alpha]_D^{22}$=−21.6 ($c$=0.25, $CH_2Cl_2$); IR (thin film) 2922, 2851, 1717, 1514, 1462, 1250, 1057, 1036, 997, 883, 819 cm$^{-1}$; $^1$H NMR ($C_6D_6$, 300 MHz) $\delta$ 7.65–7.72 (m, 4H), 7.33–7.45 (m, 6H), 7.25–7.31 (m, 2H), 6.87–6.91 (m, 2H), 4.49 ($AB_q$, 2H, $J_{AB}$=11.3 Hz, $\Delta\nu/2$=36.4 Hz), 4.12 (m, 1H), 4.10 (ddd, 1H, $J$=7.5, 4.4, 0.3 Hz), 4.01–4.07 (m, 1H), 4.00 (dd, 1H, $J$=5.8, 2.4 Hz), 3.83 (s, 3H), 3.75–3.81 (m, 1H), 3.77 (d, 3H, $J_{P-H}$=11.8 Hz), 3.76 (d, 3H, $J_{P-H}$=11.9 Hz), 3.60–3.69 (m, 2H), 3.31 (bt, 1H, $J$=2.8 Hz), 3.23 (bs, 1H), 3.11 (A of ABX, 1H, $J_{AB}$=14.1 Hz, $J_{AX}$=$J_{H-P}$=22.7 Hz), 3.03 (B of ABX, 1H, $J_{AB}$=14.1 Hz, $J_{BX}$=$J_{H-P}$=22.1 Hz), 2.97 (dd, 1H, $J$=16.1, 8.5 Hz), 2.45 (dd, 1H, $J$=16.1, 4.3 Hz), 2.09–2.23 (m, 2H), 1.93–2.05 (m, 2H), 1.80–1.91 (m, 2H), 1.15–1.60 (m, 4H), 0.98–1.06 (m, 45H), 0.95 (d, 3H,

$J$=6.8 Hz), 0.94 (d, 3H, $J$=6.9 Hz), 0.80–0.90 (m, 6H); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 201.2, 199.9, 159.3, 135.8, 135.7, 133.9, 133.6, 130.8, 129.8, 129.5, 127.5, 113.8, 96.9, 80.8, 79.6, 77.2, 74.8, 71.8, 71.6, 70.7, 69.4, 67.9, 55.3, 52.9, 46.0, 37.8, 37.0, 34.8, 31.9, 30.1, 29.7, 26.9, 25.8, 23.2, 22.7, 19.1, 18.2, 17.8, 14.1, 13.1, 12.7; $^{31}$P NMR ($CDCl_3$, 75.4 MHz) $\delta$ 23.4 (s); MS (FAB) *m/e* (relative intensity, assignment); exact mass calcd for $C_{64}H_{105}O_{12}PSi_3+Na^+$ requires 1203.6549, found 1203.6592.

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10. (a) Personal correspondence with Ernest Hamel, MD, PhD, Senior Investigator, Laboratory of Molecular Pharmacology, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, NIH. Dr Hamel informed us that halichondrin B cures in vivo human tumors transplanted into immunodeficient nude mice. (b) Personal correspondence with Michael R. Boyd, MD, PhD, Chief, Laboratory of Drug Discovery Research and Development, NCI Cancer Research Center, Frederick, MD. Dr Boyd shared with us his data and slides that resulted in the NCI Decision Network Committee's selection of halichondrin B for drug development.
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