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Total Synthesis of the Potent Microtubule-Stabilizing Agent (+)-Discodermolide

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The total synthesis of the potent microtubule-stabilizing, antimitotic agent (+)-discodermolide is described. The convergent synthetic strategy takes advantage of the diastereoselective alkylation of a ketone enolate to establish the key C15−C16 bond. The synthesis is amenable to preparation of gram-scale quantities of (+)-discodermolide and analogues.

Introduction

This paper describes the total synthesis of the potent microtubule stabilizing agent (+)-discodermolide (**1**) and its C7-epimeric analogue via a highly convergent and versatile synthetic strategy. Isolated from the Caribbean sponge *Discodermia dissoluta* in 0.002% yield,[1] **1** was identified by its apparent immunosuppressive activity in both in vitro (IC_{50} values in the 9−14 nM range)[2] and in vivo[3] studies. A subsequent series of experiments revealed discodermolide to be a microtubule-stabilizing (MT) agent that, like taxol, arrests cells at the G2/M boundary of the cell cycle.[4,5] MT-stabilizing agents comprise a growing class of promising chemotherapeutic agents that include such natural products as the epothilones, eleuthrobin, laulimalide, and discodermolide.[6] Discodermolide was found to bind to microtubules at one molecule per tubulin dimer with an approximate 100 times greater affinity than taxol.[7,8] Interestingly, synthetic samples of both antipodes of discodermolide were reported to have antiproliferative activity, in which (−)-discodermolide was found to block the cell cycle at the S phase.[9] The chemotherapeutic potential of (+)-discodermolide was recently demonstrated in its ability to inhibit growth of colon, ovarian,[10] and breast carcinoma cells.[11] Of particular interest is the recent report that discodermolide has been found to function synergistically with taxol.[12]

Results and Discussion

Discodermolide's potent biological activity and limited natural availability have spurred synthetic efforts[13,14] (Figure 1). We adopted a highly convergent strategy for the total synthesis of discodermolide, disconnecting the molecule into three subunits of similar size and complexity, to afford fragments of similar complexity (Figure 2). In the synthetic direction, the C15−C16 bond was envisioned to be formed via a chelation-controlled alkylation of the lithium enolate derived from ethyl ketone **5**

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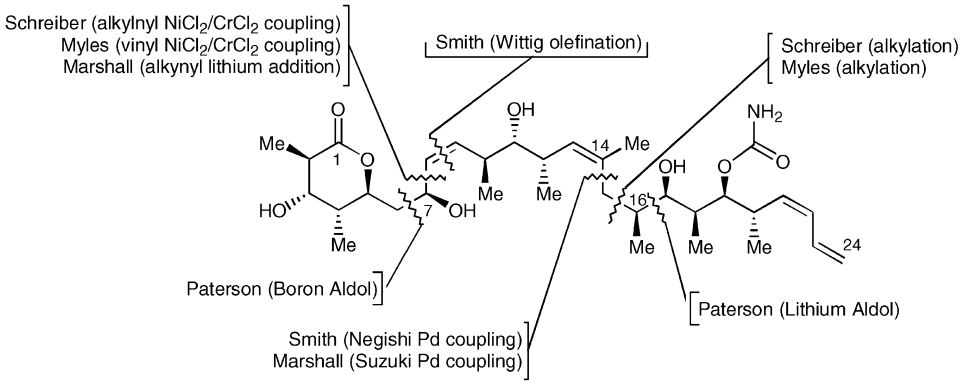

FIGURE 1. Synthese of (+)-discodermolide (**1**).

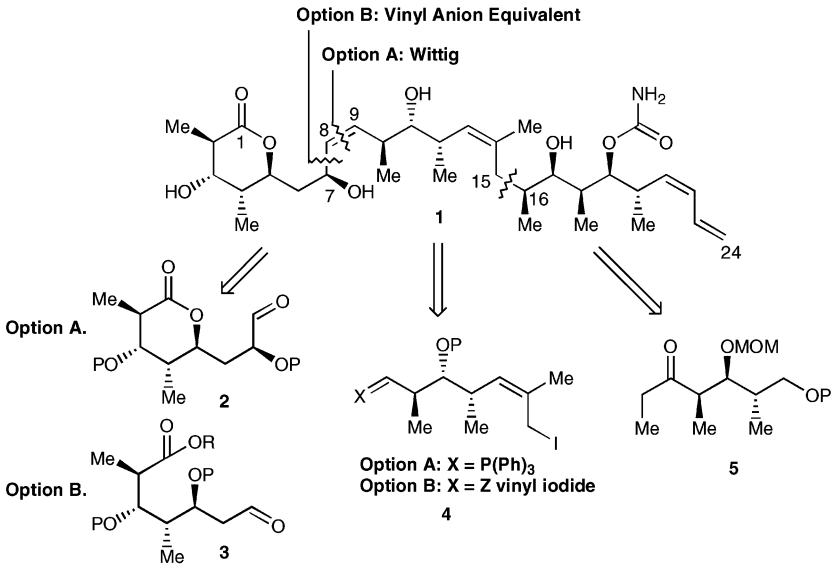

FIGURE 2. Retrosynthesis of discodermolide.

by allylic iodide **4**. We had previously demonstrated that this reaction could afford diastereoselectivities and yields suitable for the synthesis of a complex target and were confident that our methodology could be incorporated successfully in the synthesis of (+)-discodermolide.[13f,g]

We considered, and ultimately investigated (vide infra), two options for coupling in the C7 to C9 region of the discodermolide backbone. Option A called for a Wittig-type *Z*-selective olefination process to establish the C8−C9 bond. Option B called for the diastereoselective addition of a *Z*-vinyl anion equivalent at C8 to a C7 aldehyde to establish simultaneously the desired C7 stereochemistry and the C7−C8 bond. A priori, each of these approaches has visible and hidden strengths and weaknesses. It remained for experimentation to distinguish between these two options. Although portions of the work described in this paper were initially carried out in the (−)-discodermolide series, for clarity all figures depict precursors of (+)-discodermolide.

C15−C16 Alkylation. We envisioned that **4** and **5** would be joined by a stereoselective alkylative coupling in which the stereocenters of ethyl ketone **5** would provide substrate control to establish the stereocenter at C16. Our hypothesis was that a chelating alkoxy moiety at C19 would impart rotational rigidity and thereby block

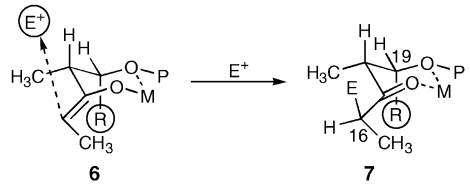

FIGURE 3. Chelation-controlled alkylation.

one face of lithium (*Z*)-enolate **6** while exposing the other face toward electrophilic attack (Figure 3). Interestingly, in the context of syntheses of discodermolide based on a similar alkylation, both Schreiber et al.[14a] and Heathcock et al.[13b] found that the use of a *p*-methoxybenzyl ether at C19 afforded alkylation products having stereochemistries opposite to that predicted by this chelation model. We had chosen methoxymethyl (MOM) as the protecting group at this position with the expectation that this blocking group would furnish high levels of chelation control in both the key alkylative coupling reaction and subsequent C17 ketone reduction (vide infra).

To investigate this alkylation reaction, we required synthons for coupling partners **4** and **5**. We prepared allylic iodide from optically active alcohol **8**[15,16] via a Lewis acid-catalyzed cyclocondensation reaction of alde-

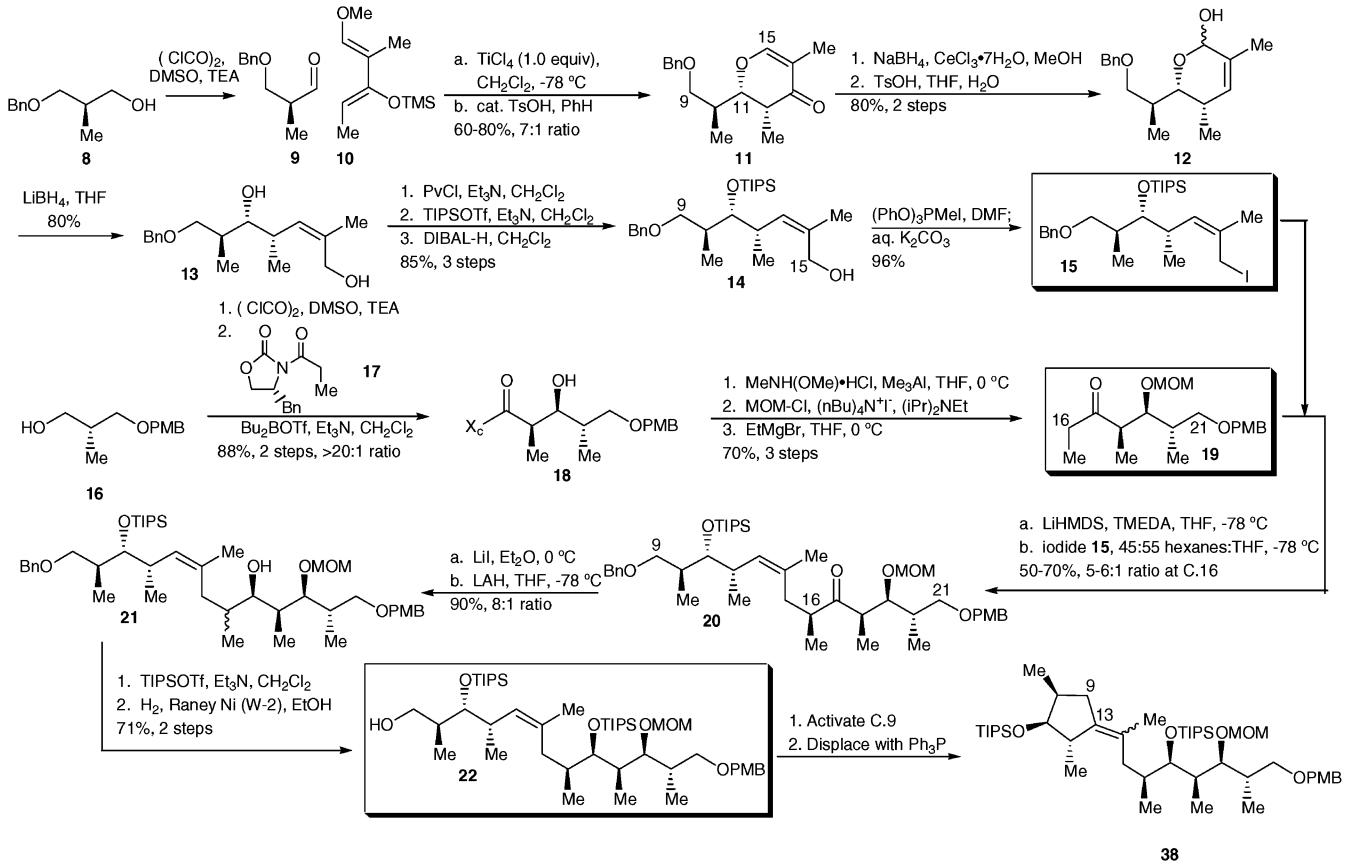

FIGURE 4. Synthesis of the C9 to C21 portion of (+)-discodermolide.

hyde **9** and diene **10**. The stereochemical considerations at C10, C11, and C12, and the presence of a *Z*-trisubstituted alkene pose barriers to the synthesis of the C9−C15 fragment. The cyclocondensation reaction elegantly addresses all of these stereochemical issues through stereochemical communication in the condensation and the creation of a cyclic framework that enforces complete control of the alkene geometry.[17] Aldehyde **9** was obtained from **8** via Swern[18] oxidation and was used immediately in the condensation with diene **10**[19] in a process promoted by precise (1.10 equiv) stoichiometric titanium(IV). The aldehyde−$TiCl_4$ complex[20] was treated with diene **10** to give a mixture of condensation products. These materials were concentrated and then taken up in benzene and treated with catalytic TsOH to provide pyrone **11** as the major component of a 7:1 diastereomeric mixture in 60−80% yield. Following Luche reduction[21,22] of pyrone **11**, a TsOH-promoted Ferrier rearrangement[23] provided lactols **12** in 80% yield over two steps. Lithium borohydride reduction opened **12** to afford diol **13**. Facile protecting group manipulations then furnished allylic alcohol **14** in 85% yield. Allylic alcohol **14** was directly converted to iodide **15** by treatment with triphenyl phosphite methiodide.[24]

With the synthesis of the allylic iodide **15** secure, we next addressed the preparation of fully functionalized analogues of ketone **5**. We have described a synthesis of this compound previously,[13f,g] but we found that a revised sequence afforded superior access to synthons for **5**.[25] PMB-protected alcohol **16** was oxidized using oxalyl chloride and DMSO and subjected to a standard Evans aldol reaction[26,27] to produce **18** in 88% yield with >20:1 diastereoselectivity. Aldol adduct **18** was converted to the analogous Weinreb amide by treatment with trimethyl aluminum and *N*,*O*-dimethylhydroxylamine.[28,29] The C19

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(25) For the large-scale synthesis of (+)-discodermolide, multigram production of ketone **19** was required. To avoid using pyrophoric trimethylaluminum in large quantities, the synthesis of fragment **19** was modified. Aldol **18** was treated sequentially with methoxymethyl chloride, lithium borohydride reduction, Swern oxidation, and ethylmagnesium bromide and resubjected to Swern oxidation to afford ketone **19** in 62% yield over five steps. Although this synthetic line requires two more steps than that outlined in Figure 4, the overall yield is only slightly lower and the large-scale handling of trimethylaluminum is circumvented.
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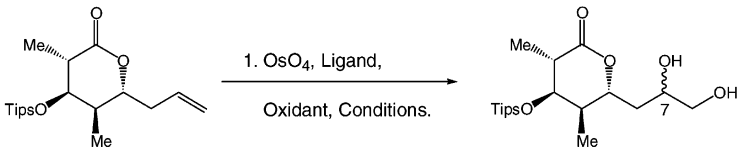
TABLE 1. Dihydroxylation of I



I

IIa: C.7 = α OH
IIb: C.7 = β OH

ligand	conditions	equiv of OsO_4	oxidant	C7 ratio	% yield
pyridine	−90 °C, CH_2Cl_2	1.0	none	1:1	80
$(DHQD)_2PHAL$	*tert*-BuOH, H_2O, 0 °C	0.01	$K_3Fe(CN)_6$	1.1:1	80
$(DHQD)_2PYR$	*tert*-BuOH, H_2O, 0 °C	0.5	$K_3Fe(CN)_6$	3.5:1	95
Corey diamine	−90 °C, CH_2Cl_2	1.0	none	>5:1	75−88

hydroxyl group was then blocked as its MOM ether. The final C−C bond of the desired ethyl ketone was then prepared by treatment of the amide with excess ethylmagnesium bromide to complete the synthesis of C16−C21 ketone **19** in 70% yield over three steps.

The lithium (*Z*)-enolate of ethyl ketone **19** (1.0 equiv) was generated at −78 °C using lithium hexamethyldisilazide (1.25 equiv) and tetramethylethylenediamine (TMEDA, 1.5 equiv). Although the precise role of the TMEDA in this reaction is not known, it likely functions by influencing the aggregation state of the enolate.[30] Allylic iodide **15** (0.5 equiv) was then added to the enolate in a 45:55 hexanes:THF solvent system. After 48−72 h at −78 °C, the reaction yielded a 50−70% mixture of diastereomers at C16 in a 5−6:1 ratio favoring what we believed, based on the chelation model and our earlier model experiments,[13g,h] to be the desired product.

After extensive experimentation, we found that many factors impact the diastereoselectivity of this alkylative process, including temperature, electrophile, counterion, additive, solvent system, and concentration. A systematic study of the percent hexanes in THF of the alkylative coupling reaction showed a remarkable solvent effect, in which the diastereoselectivity of the process changed from 1:1 in 0% hexanes in THF up to 6:1 in 45% hexanes in THF. In addition, the selectivity of this reaction was inversely related to ketone concentration, with higher selectivities found at lower ([ketone] < 0.16 M) concentrations.

The stereocenter at C17 was established using chelation control with the C18 MOM group. In this case, lithium iodide and LAH were added to ketone **20**, affording as the major product the desired diastereomer **21** in an 8:1 ratio of separable epimers at C16 in 90% yield.[31] Protection of the resulting alcohol as its TIPS ether, followed by chemoselective deprotection of the benzyl ether using H_2 and Raney Ni[32,33] (freshly prepared and then aged for 2−4 days) provided primary alcohol **22** in 71% yield over two steps. At this point, **22** is easily separated chromatographically from its C16 epimer.

With the C9 to C21 fragment of the discodermolide framework in hand, we began to consider options for formation of the C8 to C9 Z-alkene. The most inviting strategy for fabrication of this bond was the Wittig olefination. To prepare for this olefination, we studied the conversion of the C9 alcohol moiety into the phosphonium salt. Although the literature contains a plethora of examples in which a Wittig salt is prepared from a primary alcohol via the iodide,[34] we found that activated forms of the alcohol at C9 of **22** were prone to undergo an unexpected carbocyclization reaction to afford **38** as a mixture of alkene isomers. Smith et al. had observed a similar tendency for compounds that were activated at C9 to undergo cyclization; however, this side reaction was suppressed by formation of the phosphonium salt under high-pressure conditions.[14b] This propensity for cyclization can be rationalized by examining the X-ray crystal and solution structures of discodermolide, in which carbons 9 and 13 appear to be in close proximity.[35]

During the same time, we were also investigating potential strategies for the synthesis of a C1 to C8 aldehyde. Toward this end, we used unsaturated lactones I as the substrate for a study of the osmium peroxide mediated dihydroxylation reaction. Not surprisingly, the substrate-controlled dihydroxylation reaction gave no selectivity. Reagent controlled conditions would be required for successful installation of the C7 stereocenter. Initially, we focused our efforts on the asymmetric dihydroxylation chemistry of Sharpless, commercially available as the AD-mix. Although these conditions did not afford selectivity, the dihydroxylation reaction catalyzed by the $(DHQD)_2PYR$ ligand did provide a 3.5:1 ratio at C7 of an inseparable mixture of diols in 80% yield using 0.5 equiv of osmium tetroxide. Stoichiometric osmylation under the conditions of Corey and co-workers using a chiral C_2-symmetric diamine ligand [*N*,*N*′-bis(mesitylmethyl)(*R*,*R*′)-1,2-diphenyl-1,2-diaminoethane] induced a synthetically useful 5−8:1 ratio at the newly created C7 stereocenter in a good chemical yield of 75−88%.

To prepare for oxidation of C8 to the aldehyde required for the upcoming olefination, we needed to block C7 selectively, preferably as a silyl ether to maintain compatibility with our global protecting group stately. We had anticipated that this goal would be achieved via an uneventful series of protecting group manipulations. However a range of blocking group combinations failed

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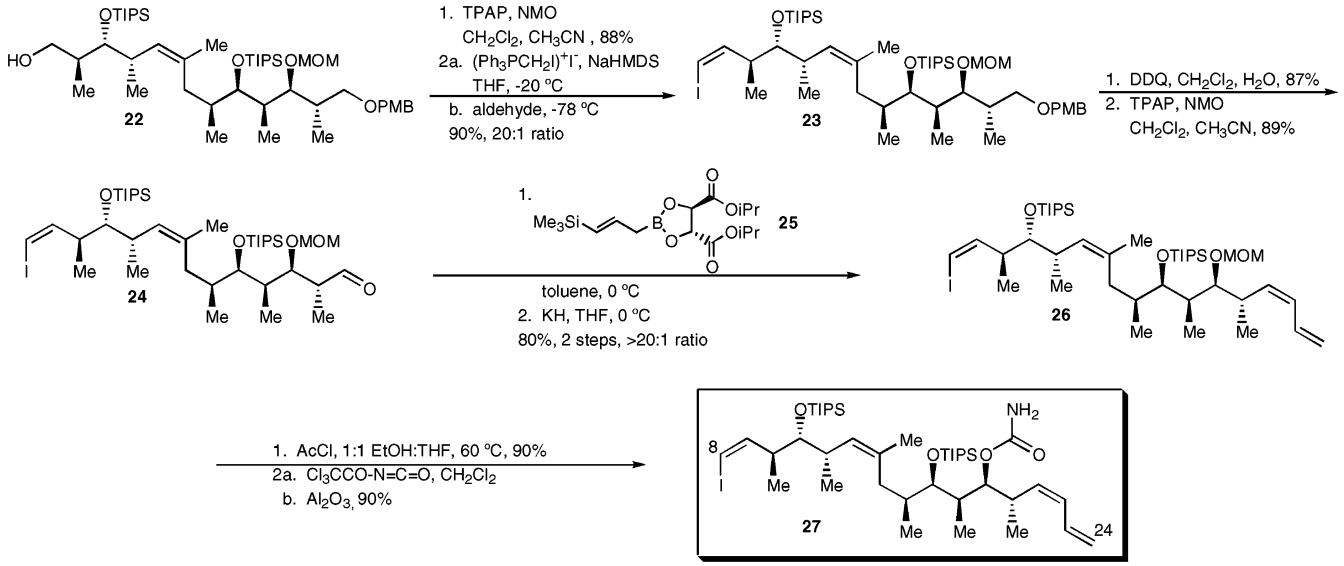

FIGURE 5. The C8 to C24 fragment.

to give the desired block group pattern, instead affording the highly unstable C1 to C7 ortho ester. The difficulties that we encountered both with activation at C9 and protecting group manipulations at C7 and C8 caused us to reconsider our strategy for assembling this region of the carbon skeleton of discodermolide.

The strategy we chose as an alternative to the Wittig coupling called for the diastereoselective addition of a *Z*-vinyl anion or equivalent at C8 to an aldehyde at C7. The method of Nozaki and Kishi for the direct coupling of vinyl halides to aldehydes under the aegis of Cr(II) and Ni(II) seemed particularly attractive because the reaction conditions were known to be chemoselective,[36] mild, and likely to be compatible with a wide range of blocking groups and other functionality. With these features in mind, we undertook to prepare suitable precursors of maximum complexity for this coupling process. Alcohol **22** was converted to a fully elaborated C8 to C24 vinyl iodide in a short but delicate series of manipulations. Homologation of **22** began with TPAP/NMO oxidation of the primary alcohol moiety to the aldehyde in 88% yield.[37] Olefination with iodomethylenetriphenylphosphorane afforded vinyl iodide **23** in 90% yield with a 20:1 ratio of *Z*:*E* isomers.[38] The PMB ether was removed under oxidative conditions using DDQ, to afford the expected primary alcohol in 87% yield.[39,40] The primary alcohol was oxidized to aldehyde **24** in 89% yield as before using TPAP and NMO. To install the terminal diene,[41] **24** was treated with (*E*)-γ-(trimethylsilyl)allylboronate reagent **25**[42] to provide the hydroxysilane adduct. This adduct was then immediately eliminated by treatment with potassium hydride to afford diene **26** in 80% yield over two steps and with >20:1 *Z*:*E* selectivity.

The removal of the methoxymethyl ether required careful optimization. Standard Lewis acid promoters for this process such as dimethylboron bromide at −78 °C,[43] *B*-chlorocatecholborane,[44] and others afforded mixtures of the desired alcohol and an undesired tetrahydrofuran formed by cyclization of an oxonium ion intermediate.[45] Extensive experimentation revealed that the C19 MOM ether could be removed with acetyl chloride in 1:1 EtOH:THF at 60 °C to afford the desired alcohol reliably in 90% yield. The required carbamate at C19 could then be installed in 90% yield by treatment of the secondary alcohol with trichloroacetyl isocyanate followed by Al_2O_3.[46,47]

The C8 to C24 fragment of **1** contains all stereochemistry and functionality required for the synthesis of the target molecule. By simply removing the silyl ethers, one could unmask this fully elaborated fragment. Thus, to achieve a synthesis of maximum convergency, we hoped to implement a synthesis of the C1 to C7 portion of **1**

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(47) An alternative sequence was developed for the conversion of alcohol **21** (Figure 4) to vinyl iodide **27** (Figure 5). Although somewhat longer, this sequence proved to be equally reliable on a large scale. Thus, alcohol **21** was silylated with triisopropyltrifluoromethanesulfonyl trifluoromethanesulfonate (TIPS−OTf) and triethylamine. After oxidative cleavage of the *p*-methoxybenzl ether, the resulting primary alcohol was silylated (TIPS−OTf). Hydrogenolysis (Pd/C, hydrogen) of the C9 benzyl ether afforded the analogous primary alcohol (99%, two steps). This alcohol was then homologated to the vinyl iodide via Swern oxidation and Zhao−Stork−Wittig reaction in 80% yield over two steps (see Figure 4). Both the C19 MOM and C21 TIPS ethers were then cleaved solvolytically (acetyl chloride, ethanol, THF) to afford the C19−C21 diol in 75% yield. Differentiation of the diol was accomplished by forming the *p*-methoxybenzylidene acetal (*p*-methoxybenzaldehyde dimethyl acetal, CSA) and reducing with DIBAL-H to give the C21 primary alcohol in 87% yield over two steps. In analogy to the sequence described in figure 5, the diene was installed. DDQ removal of the PMB ether at C19 gave the alcohol in 92% yield. This material was converted to carbamate **27** as described.

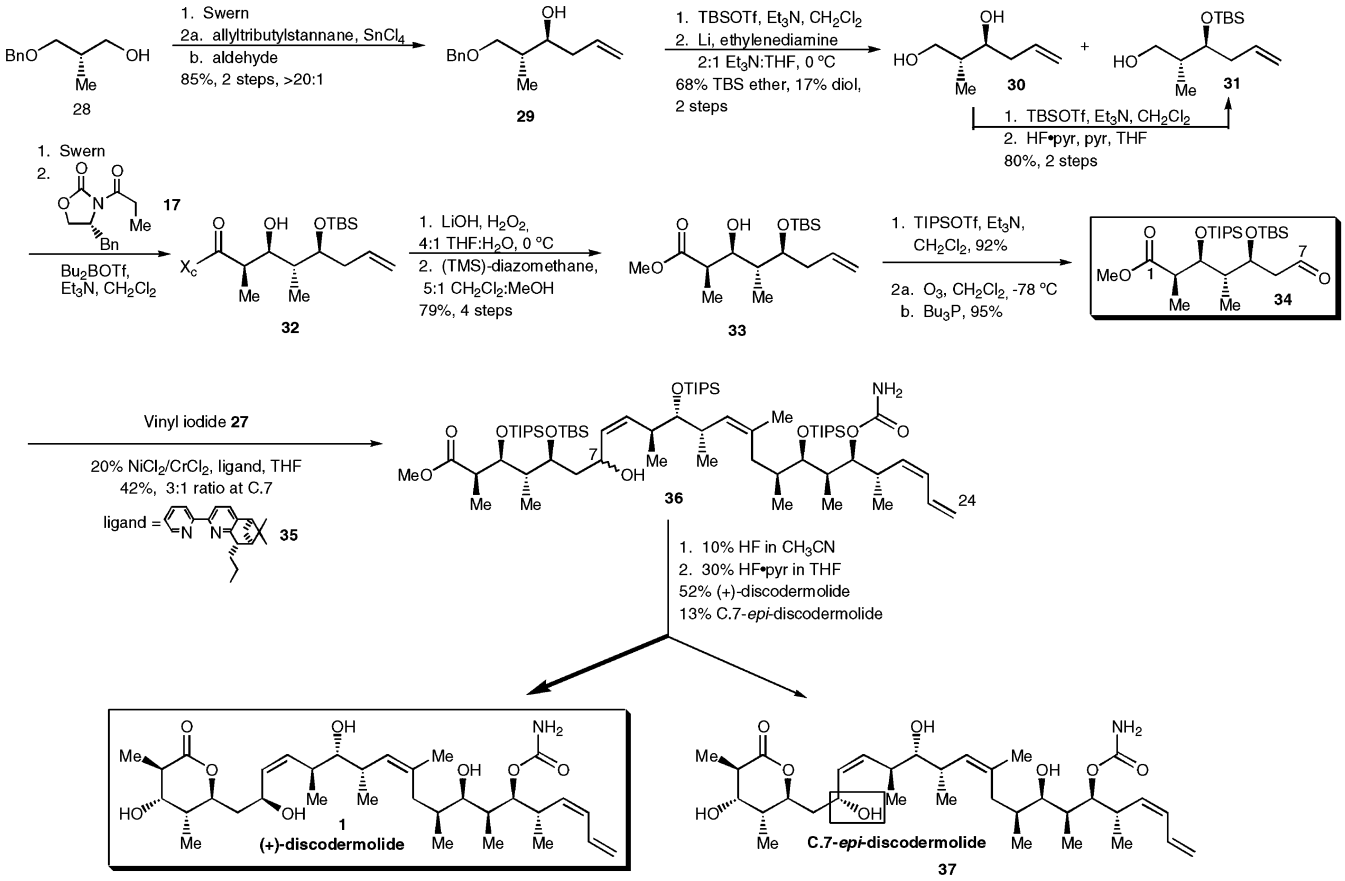

FIGURE 6. Synthesis of (+)-discodermolide.

that left the secondary alcohols of this region also blocked as silyl ethers.

We have described previously[13e] a first-generation synthesis of synthons for aldehyde **2** (Figure 2) based on the allyl- and crotylborane chemistry of Brown.[48,49] The successful application of this methodology, in our synthesis of (−)-discodermolide and many others, demonstrates its power as a tool for the preparation of complex organic structures. However, we elected to develop a second-generation synthesis of synthons **2** or **3**. Like the first-generation synthesis, our revised strategy for the synthesis of C1−C7 aldehyde **2** began with alcohol **28** (enantiomer of **8**). The single stereogenic center in this material controlled the diastereoselectivity in a chelation-controlled allyltributylstannane addition.[50] Oxidation of **28**, followed by allyltributylstannane addition at −90 °C,[51,52] produced homoallylic alcohol **29** in a >20:1 ratio of diastereomers and in 85% yield over two steps. The resulting C5 secondary alcohol was blocked as its TBS ether[53] and the benzyl ether was removed under dissolving metal conditions, affording alcohol **31** and diol **30** in 68% and 17% yields, respectively. Diol **30** was smoothly recycled to desired alcohol **31** in a two-step process by protecting both hydroxyl groups as their TBS ethers and regioselectively deprotecting the primary TBS ether.[54] The remaining two stereocenters were introduced using Evans diastereoselective aldol chemistry.[55] Following Swern oxidation of alcohol **31**, the resulting aldehyde was immediately reacted under Evans aldol conditions to give *syn*-aldol **32** in >20:1 diastereomeric ratio. The crude material was treated with lithium hydroperoxide to cleave the chiral auxiliary and provide the carboxylic acid.[56] This material was converted to its methyl ester **33** by treatment with (trimethylsilyl)diazomethane[57] in 79% yield over four steps. The decision to store C1 as its methyl ester rather than converting the material directly to the lactone present in discodermolide was driven by the observation that lactones containing the C7 aldehyde required for the upcoming coupling reaction underwent a facile epimerization at C5 (presumably via an elimination−addition mechanism). After the C3 hydroxyl group was protected as its TIPS ether in 92% yield, ozonolysis gave aldehyde **34** in 95% yield. This synthetic route to C1−C7 aldehyde is much improved from the original route, producing twice the overall yield. This sequence has been carried out at multigram scale for the synthesis of (+)-discodermolide.

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The fully elaborated C8−C24 fragment **27** was coupled to aldehyde **34** using 1% $NiCl_2/CrCl_2$ in DMSO to produce a 3:1 ratio of C7 epimers in 20−40% yield. A more reliable 42% yield was obtained when Kishi's chiral bispyridinyl ligand (**35**) was incorporated into the reaction mixture and the solvent was changed from DMSO to THF,[58] with the same 3:1 diastereomeric ratio. The chemoselectivity of this reaction allows for optimal convergency in that the carbamate, terminal diene, methyl ester, and β-silyloxy aldehyde all can be present during the coupling. Consequently, the only step remaining to complete the synthesis of (+)-discodermolide synthesis was removal of the silyl blocking groups. Alcohols **36** were subjected to 10% aqueous HF in acetonitrile, resulting in the mono-TIPS ether of discodermolide. The final TIPS ether was then removed with a second deprotection step in 30% HF·pyr in THF, to afford (+)-discodermolide in 52% yield and its separable C7 epimer in 13% yield.

This synthetically derived material was compared (^{1}H NMR, ^{13}C NMR, HRMS, IR, optical rotation, TLC) to natural (+)-discodermolide and was found to be identical in all respects. Cell-based cytotoxicity assay of the synthetic material show it to have potency similar to natural discodermolide and to arrest the cell cycle at the G2/M boundary.[58] The synthesis proceeds in a highly convergent manner, the longest linear sequence for this synthesis of discodermolide is 22 steps from aldehyde **9** in a 1.5% overall yield. The syntheses of the three key fragments, **34**, **19**, and **15**, can be easily carried out at tens of grams scale. Both fragment coupling reactions are readily amenable to large scale. The final coupling sequence has yielded hundreds of milligrams of the natural product. The convergent strategy allows for the facile preparation of analogues of discodermolide.

Experimental Section

Aldehyde 9. To a flame-dried 1 L round-bottom flask equipped with a magnetic stir bar and a rubber septum was added CH_2Cl_2 (300 mL). The flask was placed in a −78 °C bath for 10 min before adding oxalyl chloride (12.0 mL, 133.0 mmol) in one portion. Anhydrous DMSO (19.0 mL, 267 mmol) was added dropwise over 10 min, resulting in gas evolution. The resulting solution was allowed to stir for an additional 15 min before the addition of alcohol **8** (12.0 g, 66.7 mmol, 20 mL of CH_2Cl_2, 2 × 4 mL of CH_2Cl_2 rinses) via cannula. The reaction mixture was allowed to stir at −78 °C for 60 min before adding triethylamine (56 mL, 400 mmol) and then stirred for an additional 5 min at −78 °C before removing from the dry ice/acetone bath. After allowing the reaction to warm for approximately 10 min it was quenched by pouring into an aqueous solution of NH_4Cl (1 M, 500 mL) in a separatory funnel. The organic layer was washed with aqueous NH_4Cl (1 M, 5 × 300 mL) until TLC indicated that all the triethylamine was extracted away from the CH_2Cl_2. The organic layer was washed with aqueous NaCl (saturated, 1 × 500 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to a smaller volume (100 mL) before transferring to a 250 mL pear-shaped flask and then further concentrated in vacuo until almost neat. The crude aldehyde was treated with anhydrous benzene (2 × 5 mL) to azeotropically dry it and then placed under high vacuum (2 mmHg) for 30 min before addition of anhydrous CH_2Cl_2 (150 mL). This dry solution of aldehyde was immediately used in the following reaction in order to minimize racemization: R_f = 0.50, 20% EtOAc in hexanes; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.71 (d, J = 1.7 Hz, 1H), 7.34−7.24 (m, 5H), 4.51 (s, 2H), 3.65 (m, 2H), 2.63 (m, 1H), 1.11 (d, J = 7.1 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 203.8, 137.8, 128.7, 127.7, 127.5, 73.2, 70.0, 46.7, 10.7.

Homoallylic Alcohol 29. To a flame-dried 1 L round-bottom flask equipped with a magnetic stir bar and a rubber septum was added CH_2Cl_2 (400 mL). The flask was placed in a −78 °C bath for 5 min before the addition of $SnCl_4$ (neat 7.6 mL, 65.0 mmol) in one portion. To this $SnCl_4$ solution in CH_2Cl_2 was added allyltributyltin (neat 20.0 mL, 65.0 mmol) via syringe (10 mL) in a quick steady manner. The reaction was allowed to stir for 30 min at −78 °C before cooling it in a −90 °C bath (liquid N_2/MeOH), where it was allowed to stir for an additional 10 min. After this additional cooling period, a prechilled (−78 °C) solution of the above aldehyde (CH_2Cl_2) was added to the reaction via a cannula down the side of the flask. Analysis of the reaction (TLC) showed that all of the aldehyde was consumed within 2 min of its addition. The reaction was quenched after 8 min by pouring it into an aqueous solution of KF (1 M, 700 mL) in a separatory funnel (4 L) containing hexanes (600 mL). The separated organic layer was washed with aqueous KF (1 M, 700 mL), aqueous $NaCO_3$ (1 M, 700 mL), and aqueous NaCl (saturated, 700 mL) before drying with anhydrous Na_2SO_4. The dried organic layer was filtered through a short plug of silica gel and concentrated in vacuo to provide a crude product. The crude residue was purified by flash column chromatography (28 cm of silica gel on a 6 cm diameter column, 10% EtOAc in hexanes, 200−300 mL fractions) to give a clean alcohol **29** as a colorless oil (12.4 g, 56 mmol) in 85% yield from alcohol **28** (two steps) as a greater than 20:1 ratio of diastereomers (^{1}H NMR): R_f = 0.5, 10% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.30 (m, 5H), 5.94−5.86 (m, 1H), 5.14−5.09 (m, 2H), 4.52 (s, 2H), 3.61−3.57 (m, 2H), 3.50 (dd, J = 8.5, 7.0 Hz, 1H), 3.22 (br s, 1H), 2.34−2.31 (m, 1H), 2.23−2.17 (m, 1H), 1.92−1.88 (m, 1H), 0.92 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 135.3, 128.5, 127.8, 127.7, 117.2, 74.9, 74.7, 73.4, 39.4, 38.0, 13.9; IR (thin film on NaCl) 3447, 3070, 3031, 2964, 2933, 2905, 2862, 1641, 1497, 1454, 1433, 1364, 1313, 1262, 1208, 1159, 1095, 1075, 1048, 1028, 990, 960, 912, 871, 834, 737, 698 cm^{-1}; HRMS (CI) (m/z) calculated for $C_{14}H_{20}O_2$ $(M + H)^+$ = 221.1541, observed 221.1542; $[\alpha]^{20}_D$ = −8.0 (c = 2.29, CH_2Cl_2).

Primary Alcohol 31. A flame-dried 500 mL round-bottom flask containing homoallylic alcohol **29** (11.17 g, 50.77 mmol) was equipped with a magnetic stir bar and a rubber septum. The alcohol **29** was then azeotropically dried by the addition of anhydrous benzene (1 × 5 mL) followed by subjecting it to a high vacuum (2 mmHg) for 30 min. To the dry alcohol **29** was added CH_2Cl_2 (300 mL) followed by triethylamine (12.5 mL, 89.0 mmol) in one portion. The solution was allowed to stir for 5 min before adding TBSOTf (13.0 mL, 56.4 mmol) dropwise over 5 min. The solution was allowed to stir for 1 h (TLC shows complete) before pouring it into $NaHCO_3$ (1M, 400 mL) to quench the reaction. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with aqueous NaCl (saturated, 500 mL) and dried with anhydrous Na_2SO_4. The dried organic layer was filtered through a short plug of silica gel and concentrated in vacuo to provide crude TBS ether. The resulting product was used in the following procedure without any further purification: R_f = 0.95, 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5H), 5.92−5.83 (m, 1H), 5.08−5.01 (m, 2H), 4.50 (ABq, J = 12.1 Hz, $\Delta\nu$ = 22 Hz, 2H), 3.76 (ddd, J = 5.4, 5.4, 5.4 Hz, 1H), 3.53 (dd, J = 9.1, 5.5 Hz, 1H), 3.34 (dd, J = 9.1, 6.8 Hz, 1H), 2.23 (m, 2H), 2.00 (m, 1H), 0.96 (d, J = 6.9 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 135.5, 128.3, 127.5, 127.4, 116.7, 73.4, 73.0, 72.5, 38.5, 38.3, 25.9, 18.1, 13.4, −4.2, −4.7.

To a flame-dried 2 L round-bottom flask containing a magnetic stir bar and the crude TBS ether (approximately 17

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g, 50.75 mmol) from the above experimental procedure was added anhydrous benzene (15 mL). The mixture was then subjected to high vacuum (2 mmHg) for 30 min. To the dried starting material was added triethylamine (500 mL, Aldrich 99%, used as purchased) and THF (250 mL) before placing the reaction flask in a 0 °C bath. After allowing the solution to stir and cool for 10 min, Li wire (approximately 4 g) was cleaned (washed successively in hexane, MeOH, and hexane) and cut (2 mm × 3 mm chunks) before adding it portionwise to the chilled reaction flask. The reaction mixture was stirred vigorously to ensure efficient dispersion of the floating chunks of Li. Ethylenediamine (33 mL, Aldrich 99%, used as purchased) was then added in one portion. After allowing the reaction mixture to stir for 10 min, an additional portion of ethylenediamine (5 mL) was added and the reaction changed color from blue to dark brown. The reaction mixture was stirred for another 10 min before a third portion of ethylenediamine (6 mL) was added. The reaction mixture was stirred at 0 °C for a total of 2 h, at which time TLC analysis indicated that all the starting material was consumed. At this time, the excess Li was quenched by the slow addition of aqueous NH_4Cl (1 M, 500 mL) to the chilled (0 °C) reaction flask and then it was allowed to stir for 10 min (**CAUTION:** heat and H_2 evolution). The resulting mixture was poured into a separatory funnel containing $NaHCO_3$ (1 M, 1 L) producing an emulsion. The organic and aqueous layers were partitioned after the addition of CH_2Cl_2 (700 mL) and aqueous NH_4Cl (1M, 500 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 400 mL). The combined organic layers were washed with aqueous NaCl (saturated, 1 L), dried with anhydrous Na_2SO_4, and concentrated in vacuo, providing a viscous oil (12.6 g). This crude material was purified by flash column chromatography (28 cm of silica gel on a 6 cm diameter column, 10% EtOAc in hexanes, gradient to 40% EtOAc, 200−300 mL fractions), providing clean alcohol **31** as a colorless oil (8.41 g, 34.5 mmol) in 68% yield from alcohol **29** (two steps): R_f = 0.5, 20% EtOAc in hexanes. Additionally, clean diol **30** (1.16 g, 8.67 mmol) due to loss of TBS protecting group was isolated in 17% yield (two steps): R_f = 0.05, 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79−5.69 (m, 1H), 5.05−4.97 (m, 2H), 3.70 (m, 2H), 3.50 (dd, J = 10.9, 5.2 Hz, 1H), 2.83 (s, 1H), 2.32−2.26 (m, 2H), 1.74 (m, 1H), 0.94 (d, J = 7.0 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 117.2, 76.5, 65.1, 39.5, 38.1, 25.8, 17.9, 14.4, −4.3, −4.9; IR (thin film on NaCl) 3364, 2957, 2930, 2886, 2857, 1642, 1473, 1464, 1436, 1416, 1389, 1377, 1361, 1257, 1217, 1074, 1033, 1005, 940, 911, 889, 836, 809, 775, 665 cm^{-1}; HRMS (EI) (m/z) calculated for $C_{13}H_{28}O_2Si$ $(M + H)^+$ = 245.1859, observed 245.1944; $[\alpha]^{20}_D$ = 29.9 (c = 2.41, CH_2Cl_2).

Aldol 32: To a flame-dried 500 mL round-bottom flask equipped with a magnetic stir bar and a rubber septum was added CH_2Cl_2 (150 mL). The flask was placed in a −78 °C bath for 10 min before adding oxalyl chloride (4.5 mL, 50 mmol) in one portion. Anhydrous DMSO (7.0 mL, 99 mmol) was added dropwise over 10 min. The resulting solution was allowed to stir for an additional 15 min before addition of alcohol **31** (5.25 g, 21.5 mmol, 15 mL CH_2Cl_2, 2 × 4 mL CH_2Cl_2 rinses) via syringe. The reaction mixture was allowed to stir at −78 °C for 60 min before addition of triethylamine (20 mL, 142 mmol) and then stirred for an additional 5 min at −78 °C before being removed from the dry ice/acetone bath. After allowing the reaction to warm for approximately 10 min, it was quenched by pouring into an aqueous solution of NH_4Cl (1 M, 250 mL) in a separatory funnel. The layers were allowed to separate and the organic layer was washed with aqueous NH_4Cl (1 M, 5 × 200 mL) until TLC indicated that all the triethylamine was extracted away from the CH_2Cl_2 layer. The organic layer was washed with aqueous NaCl (saturated, 1 × 300 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to provide a yellow viscous oil. The product was used immediately in the following experimental: R_f = 0.75, green with vanillin stain, 20% EtOAc in hexanes.

Into a flame-dried 500 mL round-bottom flask were placed white, crystalline **17** (20.5 g, 88.0 mmol, 4 equiv relative to aldehyde) and a magnetic stir bar. To the dry oxazolidinone **17** were added sequentially CH_2Cl_2 (150 mL) and triethylamine (12.0 mL, 85.4 mmol). The reaction flask was then placed in a 0 °C bath. After allowing the reaction to cool for 10 min, Bu_2BOTf (1.0 M in CH_2Cl_2, 75 mL, Aldrich, yellow solution) was added in a quick, dropwise fashion via a syringe. (*Note:* Red or black solutions from Aldrich were found to give no enolization or poor diastereoselectivity. Freshly prepared reagent gave consistent and reproducible results.[40,59]) The color of the reaction remained yellow (a red color indicates moisture has entered the flask), the reaction was allowed to stir at 0 °C for 65 min before placing it in a −78 °C bath for an additional 30 min. At this time, a solution of dry aldehyde (ca. 23 mmol, 15 mL CH_2Cl_2, 3 × 3 mL rinses) from the Swern oxidation was added dropwise down the side of the reaction flask using a syringe. The reaction was allowed to stir at −78 °C for 120 min, at which time TLC analysis showed that all the aldehyde was consumed. The reaction flask was then placed in a 0 °C bath before addition of a buffer solution (1 M NaOAc in 9 MeOH: 1 H_2O, 250 mL) in one portion followed by dropwise addition of aqueous H_2O_2 (35%, 25 mL) (**CAUTION:** exothermic; add very slowly), which turned the reaction mixture cloudy. The resulting mixture was stirred for 12 h and allowed to warm to room temperature in the process before pouring into H_2O (700 mL). The layers were partioned, and the aqueous layer was extracted with CH_2Cl_2 (3 × 400 mL). The combined organic layers were concentrated in vacuo, and the resulting material was used in the following procedure: R_f = 0.35, 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.18 (m, 5H), 5.96−5.74 (m, 1H), 5.06−5.00 (m, 2H), 4.66 (m, 1H), 4.16 (m, 2H), 4.01 (m, 1H), 3.87 (qd, J = 7.0, 1.9 Hz, 1H), 3.79 (dd, J = 9.8, 1.7 Hz, 1H), 3.42 (br s, 1H), 3.26 (dd, J = 13.4, 3.2 Hz, 1H), 2.77 (dd, J = 13.4, 9.5 Hz, 1H), 2.30−2.10 (m, 2H), 1.83 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.83 (d, J = 7.0 Hz, 3H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 152.8, 135.8 135.0, 129.3, 128.8, 127.2, 116.5, 73.7, 72.9, 66.0, 55.2, 40.7, 39.7, 37.5, 37.3, 25.7, 17.9, 10.9, 8.8, −4.6, −4.8.

Hydroxy Methyl Ester 33. To the crude material from the previous experimental in a 2 L round-bottom flask containing a magnetic stir bar was added THF (500 mL) and H_2O (125 mL) before placing the reaction flask in a 0 °C bath. The solution was allowed to chill for 10 min followed by the addition of aqueous H_2O_2 (35%, 50 mL) and solid $LiOH\cdot H_2O$ (7.4 g, 176 mmol). The reaction was allowed to stir and slowly warm to room temperature over a 3 h time period, at which point TLC analysis showed that all of the starting material was consumed. The reaction was then quenched by chilling the reaction back down to 0 °C followed by addition of aqueous Na_2SO_3 (1.5 M, 200 mL). The resulting mixture was stirred for 10 min, at which time aqueous $NaHCO_3$ (1M, 200 mL) was added to the reaction flask. The remaining THF was removed by concentration in vacuo down to an approximate volume of 600 mL. The remaining aqueous phase was extracted with CH_2Cl_2 (5 × 150 mL). The combined organic extracts were washed with aqueous NaCl (saturated, 700 mL), dried with Na_2SO_4, and purified by passing through a short plug of silica gel. The resulting filtrate was concentrated in vacuo, producing a crude mixture of hydroxy acid and crystalline oxazolidinone that was directly taken on to the following procedure.

To a 1 L round-bottom flask containing the dried mixture of oxazolidinone and hydroxy acid and a magnetic stir bar was added CH_2Cl_2 (150 mL). The solution was allowed to stir and TMS-diazomethane (2.0 M, 5.0 mL) was added dropwise to the solution, causing instantaneous bubbling, along with a color change from colorless to yellow. After allowing the reaction to proceed for 5 min, TLC analysis indicated that not all of the hydroxy acid was consumed yet. So, an additional portion of TMS-diazomethane (2.0 M, 3.0 mL) was added to the reaction flask. The reaction was quenched after a total of 30 min by

addition of silica gel (approximately 300 mg), at which time gas evolved and the reaction mixture became colorless. The solvent was removed in vacuo, which resulted in the crystallization of the white oxazolidinone along with the oily methyl ester **33** as a crude mixture. Two different methods, of equal efficiency and ease, were developed to purify and separate the methyl ester **33** away from the oxazolidinone. In the first method, the oxazolidinone was recrystallized from 2:1 EtOAc: hexanes. The filtrate, containing the methyl ester **33** and residual oxazolidinone, was further purified by flash column chromatography (20% EtOAc in hexanes) providing clean, separated material. The other method of purifying the crude mixture (the one used for this experiment) involved two stages of chromatography and no recrystallization of oxazolidinone. The entire crude mixture was dissolved in CH_2Cl_2 and subjected to flash column chromatography (14 cm of silica gel on a 6 cm diameter column, CH_2Cl_2). This first flash column chromatography only provided partial separation. The fractions that contained both the compounds were collected and concentrated in vacuo (4.8 g) and resubjected to a second flash column chromatography (28 cm of silica gel on a 6 cm diameter column, 10% EtOAc in hexanes) to provide cleanly separated material. Material from both columns was combined. The methyl ester (5.33 g, 17.0 mmol) was isolated in 79% yield (four steps from primary alcohol **31** with chromatography at this step only): $R_f = 0.25$, 20% EtOAc in hexanes. Additionally, pure oxazolidinone was isolated from the columns (7.97 g, 45 mmol) in 51% yield: $R_f = 0.05$, 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85−5.75 (m, 1H), 5.04−4.98 (m, 2H), 3.96 (dt, $J = 7.5$, 4.3 Hz, 1H), 3.83 (dd, $J = 9.9$, 2.4 Hz, 1H), 3.67 (s, 3H), 3.1 (br s, 1H), 2.58 (qd, $J = 7.1$, 2.4 Hz, 1H), 2.25−2.11 (m, 2H), 1.75 (m, 1H), 1.12 (d, $J = 7.2$, 3H), 0.86 (s, 9H), 0.77 (d, $J = 7.0$, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 135.9, 116.6, 73.8, 73.2, 51.8, 41.4, 40.5, 37.5, 25.8, 18.0, 11.2, 8.8, − 4.4, − 4.6; IR (thin film on NaCl) 2955, 2930, 2888, 2857, 1721, 1644, 1472, 1437, 1381, 1314, 1254, 1202, 1181, 1073, 1059, 1005, 989, 939, 912, 885, 837, 810, 775, 685 cm^{-1}; HRMS (FAB, NBA/NaI) (*m*/*z*) calculated for $C_{17}H_{34}O_4SiNa$ $(M + Na)^+ = 353.2124$, observed 353.2127; $[\alpha]^{20}_D = 6.6$ ($c = 1.965$, CH_2Cl_2).

TIPS Ether 33a. A flame-dried 500 mL round-bottom flask containing methyl ester **33** (2.83 g, 9.04 mmol) was equipped with a magnetic stir bar and a rubber septum**.** The alcohol was azeotropically dried by addition of anhydrous benzene (2 × 3 mL) followed by subjecting it to a high vacuum (2 mmHg) for 30 min. To the dry **33** was added CH_2Cl_2 (20 mL) followed by triethylamine (2.0 mL, 14.4 mmol) in one portion. The solution was allowed to stir for 5 min before adding TipsOTf (3.0 mL, 10.8 mmol) dropwise over 5 min. The solution was allowed to stir for 24 h when TLC indicated incomplete protection of starting material. Therefore, more triethylamine (0.40 mL, 2.85 mmol) and TipsOTf (0.40 mL, 1.50 mmol) were added at this time. The reaction was allowed to stir for another 12 h before pouring it into $NaHCO_3$ (1 M, 250 mL) in order to quench the reaction. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 75 mL). The combined organic layers were washed with aqueous NaCl (saturated, 300 mL) and dried with anhydrous Na_2SO_4. The dried organic layer was filtered through a short plug of silica gel and concentrated in vacuo to provide crude product. The crude product was purified by flash column chromatography (14 cm of silica gel on a 6 cm diameter column, 3% EtOAc in hexanes) resulting in a clean, viscous oil (4.08 g, 8.34 mmol) in 92% yield: $R_f = 0.80$, 5% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87−5.79 (m, 1H), 5.09−5.04 (m, 2H), 4.59 (dd, $J = 5.0$, 2.5 Hz, 1H), 3.72 (ddd, $J = 5.3$, 5.3, 5.3 Hz, 1H), 3.64 (s, 3H), 2.80 (qd, $J = 7.1$, 2.5 Hz, 1H), 2.37 (m, 1H), 2.26 (m, 1H), 1.94 (m, 1H), 1.19 (d, $J = 7.0$ Hz, 3H), 1.05 (m, 21H), 0.90 (d, $J = 7.2$ Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 134.4, 117.0, 73.3, 71.8, 51.3, 44.1, 42.1, 38.5, 25.9, 18.3, 18.2, 18.1, 13.0, 11.7, 11.1, −4.2, −4.7; IR (thin film on NaCl) 2948, 2892, 2866, 1734, 1738, 1464, 1472, 1435, 1385, 1362, 1348, 1254, 1196, 1165, 1122, 1071, 1017, 999, 941, 912, 901, 883, 837, 810, 775, 679 cm^{-1}; HRMS (FAB, NBA/ NaI) (*m*/*z*) calculated for $C_{26}H_{54}O_4Si_2Na$ $(M + Na)^+ = 509.3458$, observed 509.3457; $[\alpha]^{20}_D = 25.6$ ($c = 2.995$, CH_2Cl_2).

Aldehyde 34. Into a flame-dried 250 mL round-bottom flask was placed a solution of alkene **33a** in CH_2Cl_2 and the solvent was then removed in vacuo. To the neat alkene was added a magnetic stir bar and anhydrous benzene (5 mL). The material was allowed to stir under high vacuum (2 mmHg) for 12 h to remove any volatile material (this process was found to remove any residual TipsOH left over from silylation). After this high vacuum treatment, argon and CH_2Cl_2 (75 mL) were added to the reaction flask. The flask was then placed in a −78 °C bath and allowed to stir and chill for 5 min. At the end of this cooling period, O_3 was bubbled into the solution through a Pasteur pipet until the persistence of a blue color (approximately 10 min). Once the blue color appeared, argon was bubbled into the solution for 2 min and then Bu_3P (1.2 mL, 4.75 mmol) was added dropwise to the chilled (−78 °C) reaction. The reaction was stirred at −78 °C for 5 min and then allowed to warm to room temperature. After stirring for 20 min at room temperature, TLC analysis showed that approximately 50% of the material was still at the ozonide oxidation state. So, a second portion of Bu_3P (0.70 mL, 2.78 mmol) was added to the reaction flask. The reduction of the ozonide was allowed to occur for a total of 90 min and then the solvent was removed in vacuo to give a colorless oil. This material was purified by flash column chromatography (18 cm of silica gel on a 3 cm diameter column, 5% EtOAc in hexanes, 10 mL fractions), providing aldehyde **34** (1.84 g): $R_f = 0.30$, 10% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (dd, $J = 2.8$, 1.8 Hz, 1H), 4.39 (dd, $J = 5.5$, 3.1 Hz, 1H), 4.31 (ddd, $J = 5.7$, 5.7, 5.7 Hz, 1H), 3.64 (s, 3H), 2.74 (dq, $J = 3.1$, 7.1 Hz; 1H), 2.63−2.51 (m, 2H), 2.01−1.95 (m, 1H), 1.18 (d, $J = 7.1$ Hz, 3H), 1.06−1.04 (m, 21H), 0.93 (d, $J = 7.2$ Hz, 3H), 0.83 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$ δ 201.8, 175.7, 73.2, 68.9, 51.5, 47.8, 45.0, 42.6, 25.7, 18.3−18.2 3 carbons, 13.2, 11.8, 11.0, −4.5, −4.6; IR (thin film on NaCl) 2949, 2894, 2887, 1732, 1464, 1386, 1253, 1086, 837, 777 cm^{-1}; HRMS (FAB, NBA/ NaI) (*m*/*z*) calculated for $C_{25}H_{52}O_5Si_2Na$ $(M + Na)^+ = 511.3251$, observed 511.3245; $[\alpha]^{20}_D = 0.96$ ($c = 3.96$, CH_2Cl_2).

Aldol 18: To a flame-dried 500 mL round-bottom flask was placed white, crystalline **17** (12.08 g, 51.78 mmol) and a magnetic stir bar. The oxazolidinone **17** was azeotropically dried by the addition of anhydrous benzene (15 mL) followed by subjecting it to high vacuum (2 mmHg) for 30 min. To the dried oxazolidinone **17** was sequentially added CH_2Cl_2 (100 mL) and triethylamine (9.5 mL, 67.6 mmol) before placing the reaction flask in a 0 °C bath. After allowing the reaction to cool for 10 min, Bu_2BOTf (1.0 M in CH_2Cl_2, 60 mL, Aldrich, yellow solution) was added in a quick dropwise fashion via an addition funnel. (*Note:* red or black solutions from Aldrich were found to give no enolization or poor diastereoselectivity. Freshly prepared reagent gave consistent and reproducible results.[40,59]) The color of the reaction stayed yellow to slightly brown (a red color indicates moisture has entered the flask). The reaction was allowed to stir at 0 °C for 60 min before placing it in a −78 °C bath for an additional 30 min. At this time, dry aldehyde (approximately 70 mmol, 75 mL of CH_2Cl_2, 3 × 3 mL rinses) from a Swern oxidation was added dropwise down the side of the reaction flask using a syringe. The reaction was allowed to stir at −78 °C and slowly warm to room temperature overnight (12 h). At this time, the reaction flask was then placed in a 0 °C bath before the addition of a buffer solution (1 M NaOAc in 9:1 MeOH:H_2O, 150 mL) in one portion followed by dropwise addition of aqueous H_2O_2 (30%, 25 mL) (**CAUTION:** exothermic; add very slowly), which turned the reaction mixture cloudy. The resulting mixture was stirred for 90 min and allowed to warm to room temperature in the process before pouring the mixture into H_2O (200 mL). The layers were partioned, and the aqueous

layer was extracted with CH_2Cl_2 (4 × 150 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (1 M, 400 mL) and aqueous NaCl (saturated, 400 mL). The organic layers were then dried with Na_2SO_4, filtered, and concentrated in vacuo to give a crude mixture (31.6 g). This crude mixture was purified by flash column chromatography (28 cm of silica gel on a 6 cm diameter column, 20% EtOAc in hexanes, 200 mL fractions) to give aldol **18** (20.09 g, 45.56 mmol) in 88% yield as a pale, viscous oil: R_f = 0.20, 25% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.19 (m, 7H), 6.85 (d, J = 8.7 Hz, 2H), 4.65 (m, 1H), 4.43 (s, 2H), 4.15 (m, 2H), 3.92 (m, 1H), 3.86 (m, 1H), 3.78 (s, 3H), 3.77 (m, 1H), 3.58−3.50 (m, 2H), 3.30 (dd, J = 13.4, 3.2 Hz, 1H), 2.76 (dd, J = 13.3, 9.6 Hz, 1H), 1.95 (m, 1H), 1.25 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 159.3, 153.2, 135.4, 129.9, 129.5, 129.4, 129.0, 127.3, 113.8, 75.5, 74.7, 73.2, 66.2, 55.6, 55.3, 40.7, 37.7, 36.0, 13.6, 9.7.

Ethyl Ketone 19. To a cooled (0 °C) suspension of *N*,*O*-dimethylhydoxlamine hydrochloride (1.28 g, 13.12 mmol) in THF (20 mL) in a vented reaction flask was added dropwise Me_3Al (2.3 M in benzene, 5.0 mL) (**CAUTION:** Me_3Al is pyrophoric and reactive to moisture). The resulting homogeneous solution was stirred for 10 min and then removed from the 0 °C ice bath. The clear solution was stirred at room temperature for 30 min and then cooled to 0 °C. The substrate **18** (2.32 g, 5.25 mmol) in THF (10 mL, 3 × 2 mL rinses) was added dropwise over 10 min, causing more gas to evolve. The reaction was allowed to stir for 3.5 h and then quenched by the addition of CH_2Cl_2 (50 mL) and aqueous tartaric acid (1 M, 25 mL) to the cooled (0 °C) reaction. The quenched mixture was allowed to stir at 0 °C for 1 h and then diluted with H_2O (50 mL). The layers were allowed to separate, and the aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with aqueous NaCl (saturated, 250 mL) and dried with Na_2SO_4. The dried organic layer material was filtered and concentrated in vacuo to give a crude mixture (2.66 g). The crude material was purified by flash column chromatography (18 cm of silica gel on a 3 cm diameter column, 40% EtOAc in hexanes) to give the Weinreb amide (1.47 g, 4.51 mmol) in 86% yield: R_f = 0.45, 50% EtOAc in hexanes. Additionally, oxazolidinone (0.73 g. 4.13 mmol) was recovered from the column in 78% yield: R_f = 0.40, 50% EtOAc in hexanes. Alternatively, the crude mixture was subjected to a recrystalization step (2:1 EtOAc:hexane) to remove 60−75% of the side product oxazolidinone. The partially purified mother liquor containing the Weinreb amide was routinely taken on to the next experiment without any further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 4.44 (ABq, J = 11.6 Hz, $\Delta\nu$ = 10.3 Hz, 2H), 3.95 (d, J = 2.8 Hz, 1H), 3.73 (s, 3H), 3.65 (m, 1H), 3.60 (s, 3H), 3.56 (m, 1H), 3.48 (dd, J = 8.7, 5.9 Hz, 1H), 3.11 (s, 3H), 2.99 (brs, 1H), 1.83−1.79 (m, 1H), 1.12 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.6, 129.2, 113.7, 113.6, 73.9, 72.9, 72,7, 61.4, 55.2, 36.5, 36.0, 14.3, 10.5; IR (thin film on NaCl) 3449, 2963, 2936, 1640, 1612, 1585, 1514, 1462, 1421, 1387, 1248, 1175, 1090, 1034, 820 cm^{-1}.

To the crude Weinreb amide (approximately 42 mmol) (containing residual oxazolidinone from the previous experiment) in a 500 mL round-bottom flask was added diisopropylethylamine (75 mL). The flask was placed in a 0 °C bath and allowed to stir for 5 min. After this cooling period, MOM-Cl (20.0 mL, 214 mmol) (**CAUTION:** carcinogen) was added dropwise. The reaction was allowed to stir for 15 min and then (^{n}Bu)$_4$N$^+$I$^-$ (1.5 g, 4.2 mmol) was added to the reaction in one portion. The reaction mixture was then stirred for another 2.5 h, during which time a white precipitated formed and TLC analysis indicated that the reaction was complete. At this time, MeOH (20 mL) was added to the reaction, causing the solid to dissolve and heat to evolve. To the quenched reaction was added aqueous $NaHCO_3$ (1 M, 200 mL) and the mixture was allowed to stir for 45 min. The layers were separated, and the aqueous layer was extracted with Et_2O (4 × 125 mL) and EtOAc (1 × 200 mL). The combined organic layers were washed with aqueous NH_4Cl (1 M, 400 mL) and aqueous NaCl (saturated, 400 mL). The organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo to give a viscous, thick oil. This material was purified by flash column chromatography (14 cm of silica gel on a 6 cm diameter column, 30% EtOAc in hexanes, 100−200 mL fractions) to give methoxymethyl ether (13.0 g, 35.1 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 4.55 (ABq, J = 6.6 Hz, $\Delta\nu$ = 15.4 Hz, 2H), 4.33 (s, 2H), 3.72−3.68 (m, 4H), 3.52−3.48 (m, 4H), 3.27 (s, 3H), 3.22 (dd, J = 9.1, 7.0 Hz, 1H), 3.10−3.06 (m, 4H), 1.86 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 159.0, 130.7, 129.2, 113.6, 98.3, 82.2, 72.7, 71.8, 61.1, 56.1, 55.1, 38.4, 37.2, 32.2,15.3, 12.9.

A flame-dried 500 mL round-bottom flask containing methoxymethyl ether (13.0 g, 35.1 mmol) was equipped with a magnetic stir bar and a rubber septum. The methoxymethyl ether was azeotropically dried by the addition of anhydrous benzene (5 mL) followed by subjecting it to high vacuum (2 mmHg) for 30 min. The dried methoxymethyl ether was dissolved in THF (350 mL) and placed in a 0 °C ice bath. After 5 min, a solution of EtMgBr (3.0 M in Et_2O, 30 mL) was added to the reaction flask. The reaction was allowed to stir at 0 °C for 7 h and then the excess reagent was quenched by the slow addition of MeOH (15 mL), causing a gas to evolve. The quenched reaction solution was concentrated in vacuo to a gelatinous mixture (250 mL) that was dissolved in aqueous HCl (5%, 400 mL). The aqueous phase was extracted with EtOAc (2 × 300 mL) and Et_2O (2 × 300 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (1 M, 500 mL) and aqueous NaCl (saturated, 500 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo to give a crude product. The crude material was purified by flash column chromatography (14 cm on a 6 cm diameter column, 15% EtOAc in hexane, 150 mL fractions) providing clean ethyl ketone **19** (10.8 g, 32.0 mmol) in 70% yield over three steps from aldol **18** as a thick, viscous oil: R_f = 0.50, 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 4.55 (ABq, J = 6.7 Hz, $\Delta\nu$ = 29.9 Hz, 2H), 4.34 (s, 2H), 3.81 (dd, J = 6.6, 4.8 Hz, 1H), 3.72 (s, 3H), 3.48 (dd, J = 9.1, 5.1 Hz, 1H), 3.33 (dd, J = 9.1, 5.5 Hz, 1H), 3.21 (s, 3H), 2.72 (m, 1H), 2.60−2.38 (m, 2H), 1.91 (m, 1H), 1.03 (d, J = 7.0 Hz, 3H), 0.96−0.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 159.1, 130.5, 129.2, 113.6, 97.9, 81.3, 72.7, 71.6, 55.9, 55.1, 48.4, 37.1, 34.3, 14.9, 11.0, 7.7; IR (thin film on NaCl) 2971, 2938, 2901, 1713, 1613, 1514, 1460, 1302, 1248, 1173, 1148, 1098, 1084, 1036, 976, 920, 820 cm^{-1}; HRMS (FAB, NBA/NaI) (m/z) calculated for $C_{19}H_{30}O_5Na$ (M + Na)$^+$ = 361.1991, observed 361.1994; $[\alpha]^{20}_D$ = 32.7 (c = 2.94, CH_2Cl_2).

Dihydropyrone 11. To a flame-dried 500 mL round-bottom flask containing freshly prepared aldehyde **9** (30 mmol) was added CH_2Cl_2 (80 mL). The flask was placed in a −78 °C bath. To a separate 100 mL pear-shaped flask was added freshly distilled $TiCl_4$ (4.0 mL, 37 mmol) and CH_2Cl_2 before cooling the solution to −78 °C. The cooled solution of $TiCl_4$ in CH_2Cl_2 was added to the cold aldehyde over 2 min via cannula causing the solution of aldehyde to turn from pale yellow to an orange/red color. A similarly prechilled (−78 °C) solution of diene **10** (10.0 g, 49.9 mmol) in CH_2Cl_2 (85 mL) was added via cannula over 3 min, causing the solution of the aldehyde−$TiCl_4$ complex to turn from orange/red to black. The reaction was allowed to stir at −78 °C for 1 h before MeOH (50 mL) was added to quench the reaction. After warming to room temperature, aqueous $NaHCO_3$ (1 M, 200 mL) was added to the quenched reaction, causing the aqueous layer to turn milky white and the organic layer to become orange/red. The aqueous layer was extracted with CH_2Cl_2 (1 × 150 mL) and Et_2O (3 × 150 mL). The combined organic layers were washed with aqueous NaCl (saturated, 700 mL) and dried with Na_2SO_4. The dried organic solution was filtered and concentrated in vacuo to an oil. To

the oil was added benzene (250 mL) and PPTs (87 mg) and the solution was allowed to stir for 12 h before pouring into aqueous $NaHCO_3$ (1 M, 300 mL). The layers were allowed to separate and the aqueous layer was extracted with Et_2O (3 × 200 mL). The organic layers were dried with $MgSO_4$ and then concentrated in vacuo to a crude residue. The crude residue was purified by flash column chromatography to give the major diastereomer **11** (4.72 g, 17.2 mmol) in 56% yield: $R_f = 0.60$, 25% EtOAc in hexanes. Additionally, the minor diastereomer (0.60 g, 2.18 mmol) was isolated in 7% yield: $R_f = 0.65$, 25% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.33 (m, 5H), 7.18 (br s, 1H), 4.52 (ABq, $J = 12.1$ Hz, $\Delta\nu = 14.8$ Hz, 2H), 4.17 (dd, $J = 10.5$, 2.7 Hz, 1H), 3.61 (m, 2H), 2.44 (qd, $J = 7.4$, 2.8 Hz, 1H), 2.16 (m, 1H), 1.67 (d, $J = 1.1$ Hz, 3H), 1.05 (d, $J = 7.4$ Hz, 3H), 1.00 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 159.0, 138.5, 128.2, 127.4, 127.4, 112.0, 82.0, 73.1, 71.0, 41.1, 34.3, 12.9, 10.5, 9.3.

Alcohol 11a. To a 250 mL round-bottom flask were added $CeCl_3 \cdot 7H_2O$ (3.10 g, 8.31 mmol) and MeOH (15 mL). The solution was allowed to stir for 1.5 h at room temperature and then cooled to 0 °C. A solution of **11** (1.95 g, 7.11 mmol) in MeOH (15 mL, 3 × 3 mL rinses) was added to the reaction flask. After 5 min, solid $NaBH_4$ (310 mg, 8.20 mmol) was added in one portion, causing a gas to evolve. The reaction was allowed to stir for 15 min and then quenched by the dropwise addition of aqueous HCl (5%, 10 mL). After 10 min, Et_2O (30 mL) and H_2O (30 mL) were added. The layers were allowed to separate, and the aqueous layer was extracted with Et_2O (4 × 40 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (1 M, 200 mL) and aqueous NaCl (saturated, 200 mL) before being dried with $MgSO_4$. The dried organic layer was filtered and subjected to a short plug of silica gel and then concentrated in vacuo to provide clean alcohol (1.93 g, 6.98 mmol) in 98% yield as a white solid: $R_f = 0.40$, 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 6.08 (s, 1H), 4.51 (ABq, $J = 12.1$ Hz, $\Delta\nu = 12.2$ Hz, 2H), 4.43 (m, 1H), 3.70 (dd, $J = 10.2$, 1.3 Hz, 1H), 3.61 (dd, $J = 8.9$, 3.1 Hz, 1H), 3.47, (dd, $J = 8.9$, 6.2 Hz, 1H), 2.19−2.13 (m, 1H), 2.04−1.97 (m, 1H), 1.58 (br s, 3H), 1.34 (dd, $J = 7.8$, 2.6 Hz, 1H), 1.04 (d, $J = 6.9$ Hz, 3H), 0.89 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 138.8, 128.3, 127.5, 127.5, 109.5, 79.0, 73.2, 72.2, 69.4, 35.1, 33.0, 13.6, 13.4, 4.8.

Diol 13. To a 500 mL round-bottom flask containing alcohol **11a** (1.89 g, 6.8 mmol) was added a magnetic stir bar and THF (150 mL). H_2O (15 mL) and TsOH (100 mg) were added to the reaction mixture. The round-bottom flask was fitted with a reflux condenser and the reaction was allowed to reflux for 7 h. At this time, the reaction was allowed to cool and then poured into aqueous $NaHCO_3$ (1 M, 100 mL). The quenched reaction was extracted with Et_2O (4 × 100 mL), washed with aqueous NaCl (saturated, 400 mL), dried with $MgSO_4$, and concentrated in vacuo to provide crude lactol **12** (1.93 g) as an off-yellow solid: $R_f = 0.50$, 25% EtOAc in hexanes. This material was taken directly on to the next reaction without any further purification.

To the crude lactol **12** in a 500 mL round-bottom flask was added benzene (5 mL), which was removed in vacuo. The flask was then charged with THF (200 mL) and argon and chilled in a 0 °C bath. After cooling for 10 min, $LiBH_4$ (310 mg, 14 mmol, 2 equiv) was added to the reaction in one portion. The reaction was allowed to stir at 0 °C for 4 h and then quenched with wet Et_2O (10 mL), followed by H_2O (150 mL). The quenched reaction was allowed to stir for 1 h and then extracted with EtOAc (4 × 150 mL). The combined organics were washed with aqueous NaCl (saturated, 400 mL), dried with $MgSO_4$, and concentrated in vacuo to give a crude oil. This material was purified by flash column chromatography (15% gradient to 30% EtOAc in hexanes) to provide clean diol **13** (1.58 g, 5.68 mmol) in 84% yield for two steps: $R_f = 0.20$, 25% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 5.20 (d, $J = 9.95$ Hz, 1H), 4.48 (ABq, $J = 12.1$ Hz, $\Delta\nu = 14.8$ Hz, 2H), 4.07 (d, $J = 11.8$ Hz, 1H), 3.91 (d, $J = 11.8$, 1H), 3.54 (dd, $J = 4.2$, 9.2 Hz, 1H), 3.45 (dd, $J = 6.4$, 9.2 Hz, 1H), 3.28 (dd, $J = 5.5$, 10.6 Hz, 1H), 2.63 (m, 1H), 1.96 (m, 1H), 1.77 (s, 3H), 0.99−0.96 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 134.3, 131.4, 128.5, 127.9, 127.9, 80.3, 74.3, 73.6, 61.6, 36.2, 35.5, 21.8, 16.5, 15.3.

Allylic Alcohol 14. To a chilled (0 °C) 500 mL round-bottom flask containing diol **13** (2.73 g, 9.8 mmol) were added CH_2Cl_2 (100 mL), triethylamine (1.65 mL, 11.76 mmol), and pivaloyl chloride (1.2 mL, 9.81 mmol). A catalytic amount of DMAP was added to the reaction before it was allowed to warm to room temperature and stir for 24 h. After this time, the reaction was poured into aqueous NH_4Cl (1 M, 100 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organics were washed with aqueous NaCl (saturated, 300 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to provide crude pivalate (3.5 g). This crude oil was purified by flash column chromatography (18 cm of silica gel on a 3 cm diameter column) to provide pure pivaloate ester (3.14 g) in 88% yield: $R_f = 0.50$, 20% EtOAc in hexanes.

This pivaloate ester (3.14 g, 8.67 mmol) was subjected to high vacuum (2 mmHg) for 45 min and then dissolved in CH_2Cl_2 (50 mL). To the solution was added a magnetic stir bar and triethylamine (1.83 mL, 13.00 mmol) in one portion. TipsOTf (3.0 mL, 11.3 mmol) was added dropwise via a syringe. The reaction was allowed to stir for 24 h and then poured into aqueous NH_4Cl (1 M, 100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with aqueous NaCl (saturated, 200 mL) and dried with Na_2SO_4. The dried solution was filtered and subjected to a short plug of silica gel and then concentrated in vacuo to a crude mixture (4.77 g) that was taken directly to the following experiment.

The crude mixture from above was dissolved in CH_2Cl_2 (100 mL) and then placed on a −78 °C bath. To the magnetically stirred solution was added dropwise a solution of DIBAL-H (1.5 M, 10 mL) in toluene. The reaction was allowed to stir for 20 min before MeOH (10 mL) was added dropwise at −78 °C to quench any excess hydride. After warming to room temperature, aqueous sodium potassium tartrate (1 M, 150 mL) was added to the reaction flask and the mixture was allowed to stir for 1 h and then poured into Et_2O (150 mL) in separatory funnel. The layers were separated, and the aqueous was extracted with Et_2O (2 × 150 mL) and EtOAc (150 mL). The organic layers were washed with aqueous NaCl (saturated, 500 mL) and dried with $MgSO_4$. The solvent was concentrated in vacuo to provide a crude oil (4.0 g) that was purified by flash column chromatography (18 cm of silica gel on a 3 cm diameter column) to give pale yellow oil (3.76 g) that was a mixture of product **14** and a silyl impurity (TipsOH or $(Tips)_2O$). This mixture was subjected to high vacuum (2 mmHg) with magnetic stirring for 4 days to remove the silyl impurity (^{1}H NMR: δ 1.06 singlet) and give pure, clean primary alcohol **14** (3.61 g, 8.32 mmol) in 95% yield over two steps: $R_f = 0.55$, 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H), 5.12 (d, $J = 10.2$ Hz, 1H), 4.48 (s, 2H), 4.14 (dd, $J = 11.8$, 5.0 Hz, 1H), 3.88 (dd, $J = 11.8$, 7.5 Hz, 1H), 3.68 (dd, $J = 6.6$, 3.2 Hz, 1H), 3.59 (dd, $J = 9.3$, 6.6 Hz, 1H), 3.24 (dd, $J = 9.3$, 6.5 Hz, 1H), 2.73 (m, 1H), 2.12 (m, 1H), 1.93 (dd, $J = 7.5$, 5.0 Hz, 1H), 1.75 (s, 3H), 1.08 (br s, 21H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 133.3, 132.7, 128.3, 127.8, 127.6, 79.0, 73.2, 72.8, 61.6, 38.8, 36.2, 21.7, 18.4, 18.4, 18.1, 14.8, 13.5; IR (thin film on NaCl) 3389, 2963, 2943, 2892, 2866, 1464, 1454, 1383, 1365, 1251, 1090, 1067, 1012, 884, 830, 785, 735, 698, 679 cm^{-1}; HRMS (FAB, NBA/NaI) (m/z) calculated for $C_{26}H_{46}O_3SiNa$ $(M + Na)^+ = 457.3114$, observed 457.3113; $[\alpha]^{20}_D = 4.80$ ($c = 8.0$, CH_2Cl_2).

Allylic Iodide 15. To a 250 mL round-bottom flask equipped with a magnetic stir bar and rubber septum were added triphenyl phosphite methiodide (3.8 g, 8.4 mmol, 3.5 equiv, Aldrich) and DMF (5 mL). The flask was wrapped in aluminum

foil and kept in the dark. After stirring for 5 min, the allylic alcohol **14** (1.0 g, 2.42 mmol) was added as a solution in DMF (6 mL). The reaction was allowed to stir for 30 min and then poured into a separatory funnel containing aqueous K_2CO_3 (1 M, 50 mL) and hexanes (50 mL). The layers were separated, and the organic layer was washed with aqueous K_2CO_3 (1 M, 4 × 50 mL) and aqueous NaCl (saturated, 50 mL). The organic layer was dried with Na_2SO_4, filtered, and then concentrated in vacuo to approximately 5 mL of hexanes/DMF. This solution was quickly purified by flash column chromatography on a short plug (4 cm of silica gel on a 3 cm diameter column, 1% EtOAc in hexanes) to provide clean allylic iodide **15** (1270 mg, 2.33 mmol) in 96% yield as a viscous oil: $R_f = 0.80$, 10% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5H), 5.29 (d, J = 10.1 Hz, 1H), 4.51 (ABq, J = 12.0 Hz, $\Delta\nu$ = 27.7 Hz, 2H), 3.98 (d, J = 9.0 Hz, 1H), 3.85 (t, J = 5.7 Hz, 1H), 3.81 (d, J = 9.0 Hz, 1H), 3.50 (dd, J = 6.6, 9.1 Hz, 1H), 3.32 (dd, J = 7.2, 9.1 Hz, 1H), 2.64 (m, 1H), 2.13 (m, 1H), 1.78 (s, 3H), 1.11 (br s, 21H), 1.08−1.03 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 134.7, 130.3, 128.4, 128.3, 127.5, 127.4, 76.7, 73.0, 39.8, 36.2, 22.4, 18.4, 18.3, 15.7, 13.5, 13.5, 7.0.

Ketone 20. To a flame-dried 250 mL round-bottom flask equipped with a magnetic stir bar and rubber septum was placed lithium hexamethyldisilazide (820 mg, 4.68 mmol, solid, 97%, Aldrich) inside a N_2 atmosphere drybox. The round-bottom flask was sealed and removed from the drybox before adding THF (5 mL) and hexane (5 mL). The reaction flask was placed in a −78 °C bath before adding dry (2 × 3 mL of benzene azeotrope) ethyl ketone **19** (1267 mg, 3.75 mmol) in THF (4 mL, 2 × 1 mL rinses) dropwise over 15 min. The reaction mixture was stirred at −78 °C for 45 min before the addition of tetramethylethylenediamine (0.850 mL, 5.63 mmol) in THF (3 mL) dropwise over 5 min. The resulting reaction mixture was allowed to stir for 30 min at −78 °C before adding dry (30 mL benzene azeotrope) allyl iodide **15** (1020 mg, 1.875 mmol) in hexane (5 mL, followed by 2 × l mL of hexane rinses and 1 × 1 mL of THF rinse) dropwise. The reaction mixture was stirred in the dark at −78 °C for 49 h and then quenched by addition of aqueous $NaHCO_3$ (1 M, 50 mL). The resulting mixture was extracted with Et_2O (4 × 50 mL). The combined organic layers were washed with aqueous NaCl (saturated, 250 mL) and dried with $MgSO_4$. The dried organic layers were filtered through a short plug of silica gel and concentrated in vacuo, providing a colorless, viscous oil. The crude material was purified by flash column chromatography (20 cm of silica gel on a 3 cm diameter column, 7% EtOAc in hexanes), providing clean ketone **20** (980 mg, 1.30 mmol) in 70% yield as an approximately 6:1 ratio of inseparable epimers at C16 (^{1}H NMR integration and mass of separated diastereomers at a latter stage of synthesis): $R_f = 0.5$, 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 7.25 (d, J = 9 Hz, 2H), 6.87 (d J = 9 Hz, 2H), 5.13 (d, J = 10 Hz, 1H), 4.60−4.40 (m, 6H), 3.80 (s, 3H), 3.75 (m, 2H), 3.51−3.30 (m, 7H), 3.00−2.85 (m, 2H), 2.53 (m, 1H), 2.40−1.50 (m, 7H), 1.12−0.87 (m, 36H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.2, 159.1, 138.8, 133.0, 130.6, 130.5, 129.1, 128.2, 127.4, 127.3, 113.6, 97.9, 80.9, 78.0, 73.2, 72.9, 72.7, 71.6, 56.0, 55.2, 47.4, 42.1, 39.8, 37.3, 37.3, 35.2, 22.9, 18.3, 18.3, 17.4, 15.4, 14.8, 13.6, 13.4, 11.0.

Alcohol 21. To a stirred solution of **20** (300 mg, 0.398 mmol) in dry Et_2O (5 mL) at 0 °C was added LiI (532 mg, 3.98 mmol) in diethyl ether (5 mL). The solution was stirred until the LiI was completely dissolved (10 min). The mixture was then cooled to −78 °C for 10 min. A fresh solution of LAH in THF (1.0 M, 4 mL, centrifuged) was added in one portion (dropwise addition gave poor diastereoselectivity). The stirring was continued at −78 °C for 30 min, and then sodium potassium tartrate solution (1 N, 30 mL) was added. The mixture was stirred at room temperature for 30 min, and the phases were allowed to separate. The aqueous layer was extracted with EtOAc (4 × 30 mL). The combined organic extracts were then washed with aqueous NaCl (saturated, 100 mL), dried (Na_2SO_4), filtered, and concentrated. The material was purified by flash column chromatography (20 cm of silica gel on 3 cm diameter column, 80% EtOAc in hexanes). Concentration in vacuo of the appropriate fractions provided chelation-controlled alcohol **21** (240 mg) in 80% yield as pale yellow oil: $R_f = 0.25$, 20% EtOAc in hexanes. Additionally, the nonchelation isomer at C17 (β-OH) was isolated (30 mg) in 10% yield: $R_f = 0.35$, 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 7.25 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 5.16 (d, J = 9.9 Hz, 0.1H), 5.06 (d, J = 10.1 Hz, 0.9H), 4.66 (ABq, J = 6.2 Hz, $\Delta\nu$ = 19.1 Hz, 2H), 4.46 (m, 4H), 3.80 (s, 3H), 3.70 (m, 1H), 3.56−3.37 (m, 5H), 3.37 (s, 3H), 3.26 (m, 1H), 2.88 (brs, 0.7 H), 2.56 (m, 1H), 2.10−1.70 (m, 6H), 1.62 (s, 0.9H), 1.59 (s, 3H), 1.13−0.81 (m, 36H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 138.8, 131.6, 131.6, 130.5, 129.3, 128.3, 127.5, 127.4, 113.8, 98.7, 85.1, 79.2, 78.3, 73.3, 72.8, 72.0, 56.1, 55.3, 39.8, 37.2, 36.5, 35.8, 35.5, 33.7, 23.2, 18.4, 18.4, 17.3, 14.9, 14.3, 13.6, 13.4, 7.7; IR (thin film on NaCl) 3513, 2963, 2942, 2867, 1514, 1455, 1248, 1090, 1036 cm^{-1}.

Primary Alcohol 22. To a stirred solution of alcohol **21** (2050 mg, 2.71 mmol) in CH_2Cl_2 (17 mL) were added excess triethylamine (0.84 mL, 6.0 mmol), TipsOTf (1.0 mL, 4.0 mmol), and catalytic DMAP (20 mg). The stirring was continued at room temperature for 48 h, at which time $NaHCO_3$ (1 M, 20 mL) was added to the reaction flask. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were then washed with aqueous NaCl (saturated, 200 mL) and dried with Na_2SO_4. The dried solution was filtered through a plug of silica gel and concentrated in vacuo to provide a crude residue (2.95 g). This crude material was used in the following reaction without any further purification: $R_f = 0.8$, 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.97 (d, J = 10.3 Hz, 1H), 4.59 (ABq, J = 6.6 Hz, $\Delta\nu$ = 24.3 Hz, 2H), 4.45 (m, 4H), 3.80 (s, 3H), 3.73 (dd, J = 7.3, 3.4 Hz, 1H), 3.39 (dd, J = 8.9, 3.5 Hz, 1H), 3.44 (m, 2H), 3.38 (m, 3H), 3.35 (s, 3H), 3.28 (m, 1H), 2.51 (m, 1H), 2.41 (m, 1H), 2.17−1.93 (m, 3H), 1.88−1.71 (m, 2H), 1.55 (s, 3H), 1.20−0.85 (m, 54H), 0.70 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 138.9, 131.7, 131.0, 130.7, 129.1, 128.2, 127.5, 127.3, 113.7, 98.7, 83.0, 79.1, 78.0, 73.4, 73.0, 72.8, 72.7, 56.1, 55.2, 40.5, 38.7, 37.1, 36.8, 35.9, 33.7, 22.7, 18.5, 18.4, 18.4, 18.2, 17.7, 15.4, 14.2, 13.4, 12.6, 11.7, 11.0.

To the solution containing the residue from the preceding reaction in absolute EtOH (20 mL), was added aged (48 h) W-2 Raney Ni (400 mg) (1−2 h old material was too active to provide selective debenzylation; material over a week old was inactive). The reaction mixture was stirred at room temperature under 1 atm of H_2 for 24 h, at which time TLC analysis indicated that all of the starting material had been consumed. At this time, the Raney Ni was removed by filtration through Celite (4 cm) on top of a plug of silica gel (10 cm). The filtrate was then concentrated in vacuo, providing a crude residue. Flash column chromatography (10% EtOAc in hexanes) of the residue resulted in complete separation of the C16 epimers and gave **22** as a clear oil (1.59 g, 1.93 mmol). in 71% yield from **21** (two steps): $R_f = 0.40$, 20% EtOAc in hexanes. Additionally, the C16 minor epimer (0.213 g, 0.26 mmol) was isolated in 9% yield: $R_f = 0.45$, 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.07 (d, J = 10.1 Hz, 1H), 4.58 (ABq, J = 6.6 Hz, $\Delta\nu$ = 25.4 Hz, 2H), 4.42 (brs, 2H), 3.81 (m, 1H), 3.80 (s, 3H), 3.70 (dd, J = 7.1, 3.5 Hz, 1H), 3.57 (d, J = 5.8 Hz, 2H), 3.48 (dd, J = 8.9, 3.5 Hz, 1H), 3.44 (dd, J = 7.3, 3.6 Hz, 1H) 3.36 (m, 1H), 3.35 (s, 3H), 2.60 (m, 1H), 2.40 (m, 1H), 2.10 (m, 1H), 2.03−1.94 (m, 3H), 1.83 (m, 2H), 1.63 (s, 3H), 1.14−1.09 (m, 42H), 1.01−0.88 (m, 12H) 0.71 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 133.0, 130.7, 130.4, 129.1, 113.7, 98.7, 83.0, 80.3, 78.0, 72.8, 72.0, 65.8, 56.0, 55.3, 40.6, 38.6, 37.1, 36.7, 36.6, 33.9, 31.6, 22.9, 22.7, 18.5, 18.5, 18.4, 18.3, 15.4, 14.1, 13.5, 11.9, 11.0; IR (thin film on NaCl) 3463,

2944, 2867, 1514, 1464, 1377, 1248, 1090, 1036 cm^{-1}; $[\alpha]^{20}_D$ = − 3.9 (c = 1.25, $CHCl_3$).

Iodoalkene 23. To alcohol **22** (540 mg, 0.657 mmol) in a 50 mL round-bottom flask equipped with a magnetic stir bar was added dry benzene (3 mL). The solution was concentrated in vacuo in order to azeotropically remove any water. To the dried alcohol were added CH_2Cl_2 (4.5 mL), acetonitrile (0.70 mL) and 4 Å molecular sieves (powdered, 330 mg, Aldrich, used as received). After allowing the solution to stir for 5 min, anhydrous NMO (115 mg, 0.985 mmol) was added in one portion followed by TPAP (12 mg, 30 mmol), causing an instant color change from colorless to green. The oxidation reaction was allowed to stir for 2 h, during which time the color changed from green to black, and the reaction was judged to be complete by TLC analysis. The crude mixture was then concentrated in vacuo in order to remove the acetonitrile, a polar solvent that causes the Ru to pass through the silica gel during flash chromatography. The crude residue was purified by flash column chromatography (4 cm of silica gel on a 3 cm diameter column elute CH_2Cl_2) to give clean aldehyde (475 mg, 0.577 mmol) in 88% yield. The aldehyde was then dried azeotropicaIly with benzene (3 mL) in vacuo and then dissolved in THF (10 mL). This solution was immediately used in the following procedure: R_f = 0.65, 20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, J = 0.5 Hz, 1H), 7.23 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.73 (d, J = 10.8 Hz, 1H), 4.56 (ABq, J = 6.6 Hz, $\Delta\nu$ = 23.7 Hz, 2H), 4.42 (s, 2H), 4.10 (dd, J = 8.8, 3.1 Hz, 1H), 3.80 (s, 3H), 3.78 (m, 1H), 3.48−3.35 (m, 3H), 3.33 (s, 3H), 2.56−2.37 (m, 3H), 2.15−1.72 (m, 4H), 1.56 (s, 3H), 1.18−1.05 (m, 45H), 1.02 (d, J = 6.5 Hz, 3H), 0.99 (m, 6H), 0.68 (d, J = 6.8 Hz, 3H).

To a flame-dried, single-neck 500 mL round-bottom flask equipped with a magnetic stir bar and rubber septum were added solid, white iodomethylenetriphenylphosphonium iodide (930 mg, 1.75 mmol) and THF (20 mL) to give a white suspension. The suspension was placed in a −20 °C bath for 10 min before a NaHMDS (solid, 334 mg, 1.85 mmol) solution in THF (10 mL) was added dropwise, transforming the white suspension to a bright yellow solution. Upon completion of the addition of NaHMDS, the reaction mixture was allowed to stir at −20 °C for an additional 5 min. The reaction mixture was then placed in a −78 °C bath for 3 min before adding the freshly prepared THF (10 mL) solution of aldehyde from the previous experimental via a cannula. Care was taken to cool the THF solution of aldehyde by passing it down the side of the reaction flask during the addition. The reaction mixture was allowed to stir for 10 min and then quenched by pouring it into aqueous NH_4Cl (1 M, 50 mL). The resulting mixture was extracted with EtOAc (3 × 50 mL) and CH_2Cl_2 (1 × 20 mL). The combined organic layers were washed with aqueous NaCl (saturated, 1 × 200 mL) and dried with anhydrous Na_2SO_4. The dried organic layers were filtered through a short plug of silica gel and concentrated in vacuo to provide the crude product (1.75 g). This crude residue was purified by flash column chromatography (20 cm of silica gel on a 3 cm diameter column, 5% EtOAc in hexane), providing clean iodoalkene **23** as a colorless foamy oil (493 mg, 0.521 mmol) in 90% yield: R_f = 0.4, 10% EtOAc in hexanes; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.39 (dd, J = 8.4, 7.3 Hz, 1H), 6.17 (d, J = 7.3 Hz, 1H), 5.01 (d, J = 10.3 Hz, 1H), 4.68 (d, J = 6.6 Hz, 1 H), 4.63 (d, J = 6.6 Hz, 1H), 4.50 (br s, 2H), 3.86−3.83 (m, 4H), 3.65 (dd, J = 8.3, 2.1 Hz, 1H), 3.55−3.48 (m, 2H), 3.45−3.41 (m, 4H), 2.79−2.76 (m, 1H), 2.46−2.35 (m, 2H), 2.17−2.09 (m, 1H), 2.05−2.00 (m, 1H), 1.90−1.86 (m, 2H), 1.70 (s, 3H), 1.23−1.10 (m, 38H), 1.08−1.02 (m, 12H), 0.76 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 142.8, 133.0, 130.6, 129.9, 129.0, 113.6, 98.5, 82.7, 81.7, 80.5 79.0, 72.6, 71.9, 55.9, 55.0, 44.3, 38.6, 37.9, 37.0, 31.5, 22.8, 22.5, 18.7, 18.4, 18.4, 16.5, 15.2, 14.0, 14.0, 13.6, 13.3, 11.6, 10.8; IR (thin film on NaCl) 2963, 2944, 2867, 1613, 1514, 1464, 1248, 1086, 884, 677 cm^{-1}; HRMS (FAB, NBA/NaI) (m/z) calculated for $C_{48}H_{89}0_6Si_2INa$ $(M + Na)^+$ = 967.5141, observed 967.5140; $[\alpha]^{20}_D$ = −56.7 (c = 1.06, CH_2Cl_2).

Aldehyde 24. To a 50 mL round-bottom flask containing PMB ether **23** (540 mg, 0.571 mmol) and a magnetic stir bar were added CH_2Cl_2 (10 mL) and H_2O (0.5 mL). The solution was allowed to stir for 5 min before adding DDQ (190 mg, 0.831 mmol) in one portion, causing an instant color change from colorless to green. The reaction mixture was allowed to stir at room temperature for 45 min and then quenched by pouring the reaction into aqueous $NaHCO_3$ (1 M, 100 mL). Upon quenching the reaction, the aqueous layer became burgundy in color. The layers were partitioned and the aqueous layer was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were washed with aqueous NaCl (saturated, 1 × 200 mL) and dried with anhydrous Na_2SO_4. The organic layer was filtered and concentrated in vacuo to provide crude product (495 mg) as a colorless oil. This material was purified by flash column chromatography (20 cm of silica gel on a 3 cm diameter column, 5% EtOAc in hexanes, gradient to 10% EtOAc in hexanes), providing clean primary alcohol (412 mg, 0.500 mmol) in 87% yield: R_f = 0.2, 10% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (dd, J = 8.5, 7.4 Hz, 1H), 6.10 (d, J = 7.3 Hz, 1H), 4.94 (d, J = 10.3 Hz, 1H), 4.67 (d, J = 6.5 Hz, 1H), 4.61 (d, J = 6.5 Hz, 1H), 3.79 (dd, J = 11.5, 3.3 Hz, 1H), 3.73 (dd, J = 7.5, 1.7 Hz, 1H), 3.57 (dd, J = 8.2, 2.0 Hz, 1H), 3.53 (dd, J = 11.2, 4.2 Hz, 1H), 3.46 (dd, J = 7.7, 3.2 Hz, 1H), 3.41 (s, 3H), 2.72−2.66 (m, 2H), 2.36−2.26 (m, 2H), 2.06−1.98 (m, 1H), 1.90−1.81 (m, 2H), 1.64 (s, 3H), 1.16−1.07 (m, 42H), 1.02−0.95 (m, 12H), 0.54 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 132.7, 130.3, 98.9, 84.3, 81.8, 78.8, 65.0, 56.3, 44.4, 39.4, 38.1, 38.0, 31.6, 25.3, 23.0, 18.8, 18.6, 18.5, 18.5, 18.5, 16.6, 15.1, 14.1, 14.0, 13.7, 12.1, 10.9; IR (thin film on NaCl) 3438, 2944, 2889, 1464, 1385, 1260, 1035, 884 cm^{-1}; HRMS (FAB/NaI) (m/z) calculated for $C_{40}H_{81}IO_5Si_2Na$ $(M + H)^+$ = 847.4565, observed 847.4561; $[\alpha]^{20}_D$ = −46.8 (c = 2.40, CH_2Cl_2).

To the alcohol from above (190 mg, 0.230 mmol) in a 50 mL, round-bottom flask equipped with a magnetic stir bar were added CH_2Cl_2 (4 mL), acetonitrile (0.4 mL), and 4 Å molecular sieves (powdered, 120 mg). After allowing the solution to stir for 5 min, NMO (40 mg, 0.345 mmol) was added in one portion, followed by TPAP (5 mg, 1.42 μmol), which caused an instant color change from colorless to green. The oxidation reaction was allowed to stir for 40 min and then judged to be complete by TLC analysis. The color of the reaction solution turned from green to black over the 40 min of reaction time. After 1 h, the reaction mixture was concentrated in vacuo. The crude residue was purified by flash column chromatography (5 cm of silica gel on a 2 cm diameter column, 5% EtOAc in CH_2Cl_2). The eluate was concentrated in vacuo to give pure aldehyde **24** (170 mg, 0.206 mmol) in 89% yield. This compound was immediately used in the following procedure.

(*Z*)-Terminal Diene 26. To aldehyde **24** in a 100 mL round-bottom flask were added toluene (3 mL), a stir bar, and 4 Å molecular sieves (powdered, 100 mg). The reaction mixture was placed in a 0 °C bath and allowed to stir for 5 min before adding (*E*)-γ-(trimethylsilyl)allylboronate (2 mL of a crude 1 M solution in toluene) **25** dropwise over 2 min. The reaction mixture was allowed to stir for 1 h and then judged to be complete by TLC. At this time, the reaction mixture was purified by flash column chromatography (20 cm of silica gel on a 3 cm diameter column, 5% EtOAc in hexane) by loading the reaction mixture directly on to a column. The eluate was concentrated in vacuo to give hydroxytrimethylsilane (176 mg), which was immediately used in the following procedure.

To the hydroxy trimethylsilane in a 100 mL round-bottom flask equipped with a magnetic stir bar was added THF (10 mL). The reaction mixture was placed in a 0 °C bath and stirred for 10 min before adding KH (approximately 100 mg, from 20 to 25 wt. % dispersion in mineral oil, rinsed and decanted 3 × 50 mL of hexanes) (**CAUTION:** cleaned KH is

pyrophoric). After 10 min, the reaction was quenched by the addition of aqueous $NaHCO_3$ (1 M, 20 mL). The resulting mixture was extracted with Et_2O (4 × 20 mL). The combined organic layers were wash with aqueous NaCl (saturated, 50 mL) and then dried with anhydrous Na_2SO_4. The dried organic layers were filtered and concentrated in vacuo, furnishing the crude product (172 mg) as a colorless, viscous oil. The crude product was purified by flash column chromatography (20 cm of silica gel on a 3 cm diameter column, 3% EtOAc in hexanes). The eluate was concentrated in vacuo, providing clean terminal diene **26** (141 mg, 0.166 mmol) in 80% yield from aldehyde **24**. The *Z:E* ratio is >20:1 as judged by ^{1}H NMR: R_f = 0.8, 5% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (ddd, J = 16.8, 11.1, 11.1 Hz, 1H), 6.32 (dd, J = 8.6, 7.3 Hz, 1H), 6.10 (d, J = 7.3 Hz, 1H), 6.00 (dd, J = 11.2, 11.2 Hz, 1H), 5.43 (dd, J = 10.2, 10.2 Hz, 1H), 5.19 (dd, J = 16.8, 1.9 Hz, 1H), 5.10 (d, J = 10.l Hz, 1H), 4.93 (d, J = 10.4 Hz, 1H), 4.66 (d, J = 6.8 Hz, 1H), 4.56 (d, J = 6.8 Hz, 1H), 3.75 (dd, J = 6.2, 2.8 Hz, 1H), 3.58 (dd, J = 8.2, 2.2 Hz, 1H), 3.39−3.30 (m, 4H), 2.98−2.92 (m, 1H), 2.78−2.66 (m, 1H), 2.40−2.32 (m, 1H), 2.22 (t, J = 12.5 Hz, 1H), 2.04−1.96 (m, 1H), 1.83−1.76 (m, 2H), 1.63 (s, 3H), 1.18−1.09 (m, 42H), 1.03 (d, J = 7.4 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.69 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 135.0, 133.0, 132.5, 130.1, 129.4, 117.6, 98.5, 84.7, 81.8, 80.6 78.7, 56.1, 44.5, 39.3, 38.0, 36.5, 35.7, 34.1, 31.6, 22.9, 22.7, 18.7, 18.6, 18.5, 18.3, 16.5, 14.1, 13.7, 12.8, 11.0; IR (thin film on NaCl) 2963, 2946, 2892, 2868, 1464, 1377, 1260, 1152, 1121, 1088, 1036, 970, 905, 883, 714, 677, 646 cm^{-1}; HRMS (FAB, NBA/NaI) (m/z) calculated for $C_{43}H_{83}O_4Si_2INa$ $(M + Na)^+$ = 869.4773, observed 869.4787; $[\alpha]^{20}_D$ = − 64.7 (c = 1.7, CH_2Cl_2).

Carbamate 27. To a flame-dried 50 mL round-bottom flask was added a benzene solution of methoxymethyl ether **26** (32.5 mg, 0.0384 mmol) and then the solution was placed under high vacuum (2 mmHg) for 30 min to azeotropically dry the starting material. After this drying procedure, EtOH (absolute, 3 mL) and THF (3 mL) were added to the reaction flask, and the flask was equipped with a reflux condenser. The flask was then placed in a 60 °C oil bath and warmed over 5 min. At this time, AcCl (0.6 mL) was added to the reaction flask in one portion. As soon as the AcCl was added to the reaction, a brief gas evolution occurred. After 30 s, analysis of the reaction by TLC showed that approximately 50% of the starting material was cleanly deprotected. The reaction was allowed to stir a total of 8 min after the addition of the AcCl and then poured into aqueous $NaHCO_3$ (1 M, 100 mL). The layers were partioned, and the aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried with Na_2SO_4, filtered through a short plug of silica gel, and concentrated in vacuo to provide a crude residue (37 mg). The crude residue was purified by flash column chromatography (18 cm of silica gel on a 2 cm diameter column, 5% EtOAc in hexanes) resulting in pure secondary alcohol (28 mg, 0.0350 mmol) in 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (dt, J = 16.8, 10.4 Hz, 1H), 6.33 (dd, J = 8.6, 7.4 Hz, 1H), 6.15 (dd, J = 10.9, 10.9 Hz, 1H), 6.11 (d, J = 7.3 Hz, 1H), 5.31 (dd, J = 10.5, 10.5 Hz, 1H), 5.24 (dd, J = 16.8, 1.5 Hz, 1H), 5.15 (d, J = 10.1 Hz, 1H), 4.94 (d, J = 10.1 Hz, 1H), 3.83 (dd, J = 6.4, 2.3 Hz, 1H), 3.59 (dd, J = 8.0, 2.3 Hz, 1H), 3.36 (dd, J = 8.4, 2.0 Hz, 1H), 2.87−2.75 (m, 1H), 2.75−2.66 (m, 1H), 2.44−2.33 (m, 1H), 2.28 (dd, J = 12.4, 12.4 Hz, 1H), 2.07−1.93 (m, 1H), 1.91−1.79 (m, 2H), 1.63 (s, 3H), 1.54 (br s, 1H), 1.20−1.09 (m, 42H), 1.03−0.93 (m, 12H), 0.74 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 134.9, 133.0, 132.2, 131.3, 130.1, 118.5, 81.8, 80.6, 80.0, 75.9, 44.4, 38.2, 38.0, 36.6, 36.4, 34.2, 31.6, 23.l, 22.7, 18.6, 18.5, 17.1, 16.6, 14.1, 14.0, 13.7, 13.0, 9.5; IR (thin film on NaCl) 3582, 2963, 2943, 2866, 1462, 1379, 1259, 1087, 884, 877 cm^{-1}; HRMS (FAB, NBA/NaI) (m/z) calculated for $C_{41}H_{79}O_3ISi_2Na$ $(M + Na)^+$ = 825.4510, observed 825.4520; $[\alpha]^{20}_D$ = − 83.0 (c = 1.40, CH_2Cl_2).

In a flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar and rubber septum was placed the secondary alcohol from above (78 mg, 0.0947 mmol), which was then azeotropically dried with benzene (2 × 1 mL). To the dried alcohol was added CH_2Cl_2 (4 mL), followed by dropwise addition of trichloroacetyl isocyanate (100 μL, 0.937 mmol) over 1 min. The reaction was allowed to stir at room temperature for 30 min and then directly placed on a short pad of Al_2O_3 (neutral, activity II) that was prewetted with a 1:1 benzene to CH_2Cl_2 solution. The reaction mixture was allowed to soak on the column of Al_2O_3 for 30 min before eluting it with 1:1 benzene:CH_2Cl_2 solution (60 mL). Concentration of the eluate provided a crude residue (88 mg) which was purified by flash column chromatography (18 cm of silica gel on 2 cm diameter column, 8% EtOAc in hexanes). Concentration of the eluate in vacuo provided carbamate **27** (62 mg, 0.073 mmol) as a white foamy solid in 75% yield: R_f = 0.2, 10% EtOAc in hexanes.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (ddd, J = 16.7, 11.2, 11.2 Hz, 1H), 6.34 (dd, J = 6.1, 6.1 Hz, 1H), 6.16 (d, J = 7.0 Hz, 1H), 6.02 (dd, J = 10.9, 10.9 Hz, 1H), 5.36 (dd, J = 10.3, 10.3 Hz, 1H), 5.21 (d, J = 9.1 Hz, 1H), 5.11 (d, J = 10.3 Hz, 1H), 4.92 (d, J = 10.3 Hz, 1H), 4.72 (dd, J = 7.6, 4.3 Hz, 1H), 4.45 (brs, 2H), 3.67 (dd, J = 6.3, 2.2 Hz, 1H), 3.58 (dd, J = 8.2, 2.2 Hz, 1H), 3.05−2.95 (m, 1H), 2.76−2.63 (m, 1H), 2.42−2.31 (m, 1H), 2.38 (dd, J = 9.6, 9.6 Hz, 1H), 2.09−1.90 (m, 2H), 1.82−1.75 (m, 1H), 1.63 (s, 3H), 1.17−1.05 (m, 42H), 1.03−0.95 (m, 12H), 0.72 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 143.2, 134.1, 133.0, 132.3, 130.0, 129.8, 128.3, 117.7, 81.7, 80.4 78.4, 78.2, 44.5, 37.9, 37.8, 36.4, 34.8, 34.5, 29.8, 22.9, 18.7, 18.5, 18.5, 17.4, 16.3, 14.0, 13.7, 12.8, 10.3; IR (thin film on NaCl) 3507, 3360, 2965, 2946, 2869, 1727, 1601, 1464, 1385, 1325, 1259, 1038, 884 cm^{-1}; HRMS (FAB, NBA/NaI) (m/z) calculated for $C_{42}H_{80}O_4INSi_2Na$ $(M + Na)^+$ = 868.4568, observed 868.4578; $[\alpha]^{20}_D$ = − 51.3 (c = 0.71, CH_2Cl_2).

Allylic Alcohol 36. To a flame-dried 50 mL pear-shaped flask equipped with a magnetic stirring bar and Teflon stopcock were added aldehyde **34** (139 mg, 0.285 mmol) and vinyl iodide **27** (241 mg, 0.285 mmol). To a separate flame-dried 25 mL pear-shaped flasked equipped with a magnetic stirring bar and Teflon stopcock was added (−)-bispyridinyl ligand **35** (419 mg, 1.42 mmol). The azeotroped starting materials (3 × 1 mL of benzene) were placed under vacuum and transported into a nitrogen atmosphere drybox. To the (−)-bispyridinyl ligand **35** were added anhydrous and deoxygenated THF (10 mL) and 20% $NiCl_2/CrCl_2$ (175 mg, 1.42 mmol). The homogeneous brown solution was allowed to stir for 1 h, at which time it was transferred to the flask containing aldehyde **34** and vinyl iodide **27** in THF (5 mL, followed by 2 × 5 mL rinses). After stirring for 5 days, the reaction mixture was removed from the drybox. To the mixture were added ethyl acetate (10 mL) and 1 M sodium serinate (10 mL). The resulting purple mixture was allowed to stir for 1 h, at which time it was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with water (2 × 60 mL) and brine (60 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (5% EtOAc in hexanes, gradient to 14% EtOAc in hexanes) to provide a white solid (144 mg, 42%) as a 3:1 mixture of inseparable diastereomers: R_f = 0.32, 10% EtOAc in hexanes; IR (thin film on NaCl) 2946, 2867, 1732, 1464, 1385, 1325, 1256, 1044, 884 cm^{-1}. LRMS (FAB, NBA/NaI) (m/z) calculated for $C_{67}H_{133}NO_9Si_4Na$ $(M + Na)^+$ = 1231, observed 1231.

(+)-Discodermolide 1. To a 1.5 mL polypropylene vial equipped with a magnetic stirring bar was added Nozaki−Kishi adduct **36** (16 mg, 0.013 mmol) in a solution of anhydrous dichloromethane. After evaporating the dichloromethane over a stream of air then under high vacuum, 10% HF in acetonitrile (0.5 mL) was added. The reaction mixture was allowed to stir for 24 h, at which time the mixture was poured into a separatory funnel containing 1 M $NaHCO_3$ (10 mL). After

adding additional solid $NaHCO_3$ to the separatory funnel until the solution reached saturation, the mixture was extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was used in the next step without further purification: $R_f = 0.45$, 5% methanol in dichloromethane.

To a 1.5 mL polypropylene vial equipped with a magnetic stirring bar was added mono-TIPS ether (ca. 0.013 mmol) in a solution of anhydrous dichloromethane. To a separate 1.5 mL polypropylene vial was added anhydrous THF (0.5 mL) and 70% HF·pyr (0.2 mL). The azeotroped mono-TIPS ether (2 × 5 drops benzene) was treated with the HF·pyr in THF solution (0.7 mL). After stirring for 40 h, additional HF·pyr in THF solution (0.1 mL) was added. The reaction mixture was allowed to stir for 63 h before additional HF·pyr in THF solution (0.1 mL) was added. After allowing the mixture to stir for a total of 82 h, the mixture was poured into a separatory funnel containing 1 M $NaHCO_3$ (10 mL). Additional solid $NaHCO_3$ was added to the separatory funnel until the solution reached saturation. The mixture was extracted with ethyl acetate (10 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (5% methanol in dichloromethane) to provide a white solid (4 mg, 52% over two steps). A second white solid, the C7 epimer of discodermolide, was also isolated (1 mg, 13% over two steps). **(+)-Discodermolide 1**: $R_f = 0.38$, 10% methanol in dichloromethane; ^{1}H NMR (360 MHz, 10% CD_3OD in $CDCl_3$) δ 6.54 (ddd, $J = 16.7$, 10.6, 10.6 Hz, 1H), 5.95 (dd, $J = 10.9$, 10.9 Hz, 1H), 5.37 (m, 2H), 5.29 (dd, $J = 11.2$, 11.2 Hz, 1H), 5.14 (d, $J = 16.9$ Hz, 1H), 5.04 (m, 2H), 4.65 (t, $J = 5.8$ Hz, 1H), 4.59 (m, 1H), 4.50 (t, $J = 10.0$ Hz, 1H), 3.57 (t, $J = 3.7$ Hz, 1H), 3.16 (m, 1H), 3.10 (t, $J = 5.7$ Hz, 1H), 2.96 (m, 1H), 2.61 (m, 2H), 2.43 (m, 1H), 1.81 (m, 6H), 1.54 (m, 1H), 1.54 (s, 3H), 1.22 (d, $J = 7.4$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 6.5$ Hz, 3H), 0.88 (d, $J = 7.1$ Hz, 3H), 0.86 (d, $J = 7.2$ Hz, 3H), 0.74 (d, $J = 5.4$ Hz, 3H); ^{13}C NMR (90 MHz, 10% CD_3OD in $CDCl_3$) δ 175.3, 157.8, 133.5, 133.1, 132.5, 132.3, 131.8, 129.9, 129.7, 117.8, 78.8, 77.3, 76.6, 75.6, 72.4, 63.2, 42.9, 40.9, 37.1, 35.8, 35.5, 35.3, 35.1, 34.2, 33.0, 22.9, 17.9, 17.3, 15.7, 15.4, 13.9, 12.4, 8.5; IR (thin film on NaCl) 3366, 2967, 2932, 1713, 1601, 1387, 1325, 1101, 1028, 974 cm^{-1}; HRMS (FAB, NBA/NaI) (*m*/*z*) calculated for $C_{33}H_{55}NO_8Na$ $(M + Na)^+ = 616.3826$, observed 616.3827. $[\alpha]^{20}_D = +14.9$ ($c = 0.18$, CH_3OH) **C7-epi-Discodermolide 37**: $R_f = 0.49$, 10% methanol in dichloromethane; ^{1}H NMR (360 MHz, 10% CD_3OD in $CDCl_3$) δ 6.52 (ddd, $J = 16.8$, 10.6, 10.6 Hz, 1H), 5.92 (dd, $J = 10.8$, 10.8 Hz, 1H), 5.30 (m, 3H), 5.13 (m, 2H), 5.02 (d, $J = 10.4$ Hz, 1H), 4.61 (m, 2H), 4.26 (dt, $J = 9.8$, 2.4 Hz, 1H), 3.57 (t, $J = 3.3$ Hz, 1H), 3.16 (m, 1H), 3.04 (dd, $J = 5.9$, 3.3 Hz, 1H), 2.93 (m, 1H), 2.53 (m, 2H), 2.37 (m, 1H), 1.81 (m, 6H), 1.56 (m, 1H), 1.56 (s, 3H), 1.20 (d, $J = 7.4$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.90 (d, $J = 7.0$ Hz, 3H), 0.89 (d, $J = 6.7$ Hz, 3H), 0.85 (d, $J = 6.9$ Hz, 3H), 0.84 (d, $J = 6.4$ Hz, 3H), 0.73 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (90 MHz, 10% CD_3OD in $CDCl_3$) δ 174.8, 157.8, 136.4, 133.4, 133.1, 131.9, 131.6, 129.9, 129.6, 117.6, 80.4, 78.8, 78.5, 75.6, 72.2, 64.0, 43.0, 40.2, 37.0, 35.8, 35.5, 35.4, 34.9, 34.3, 32.9, 23.0, 17.7, 17.2, 15.6, 15.5, 13.2, 12.6, 8.7; IR (thin film on NaCl) 3366, 2969, 2934, 1712, 1603, 1387, 1327, 1097, 1040, 974, 737 cm^{-1}; HRMS (FAB, NBA/NaI) (*m*/*z*) calculated for $C_{33}H_{55}NO_8Na$ $(M + Na)^+ = 616.3826$, observed 616.3840. $[\alpha]^{20}_D = +29.8$ ($c = 3.06$, CH_3OH).

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Supporting Information Available: General experimental methods and selected ^{1}H and ^{13}C NMR and IR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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