# Syntheses of Discodermolides Useful for Investigating Microtubule Binding and Stabilization

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**Abstract:** Discodermolide is a marine natural product reported to inhibit the proliferation of T cells and exhibit immunosuppresive activity. Total syntheses of the natural antipode of discodermolide and several variants are reported. These studies provide reagents to investigate discodermolide's recently discovered ability to bind and stabilize microtubules in cells. Retrosynthetically, the polypropionate is divided into three fragments of approximately equal complexity. This modular strategy provides convergency in the synthesis and facilitates the preparation of discodermolide-based reagents.

Dissecting the regulatory pathways of the cell cycle is crucial to understanding normal processes such as cell growth and division, as well as abnormal ones such as cancer. Significant progress has been made in identifying the choreographed entrance and exit of specific kinases and phosphatases acting to drive the cycle forward. Nevertheless, much of this regulation remains a mystery.[1]

The convergence of natural products chemistry with cell biology has provided new tools to probe these processes.[2] Natural products that inhibit proliferation by causing a specific block in the cell cycle provide clues to cellular targets essential to intracellular signaling pathways and provide a novel means of studying their function. An affinity-based search for these targets can aid in elucidating events in a natural product-sensitive pathway, including events downstream of the direct block.

The marine natural product discodermolide (**1a**)[3] is a promising candidate for this approach. Originally isolated from the sponge *Discodermia dissoluta*, discodermolide was shown to possess immunosuppressive activity.[4] It inhibits purified murine T cell proliferation with an $IC_{50}$ of 9 nM, inhibits the mixed leukocyte reaction, and suppresses graft-versus-host disease in transplanted mice. Since only minute amounts (9 mg) of the compound could be isolated from its natural source, a synthetic process yielding larger quantities of discodermolide, including a radiolabeled variant, was required.[5] Second, in order to use affinity-based methods to study its cellular receptor, structural variants of discodermolide are required that would allow the extension of a molecular handle without significant loss of binding affinity. Our solutions to both of these challenges are reported herein.

**Synthetic Plan.** The design of the total synthesis was based on a convergent approach to discodermolide, **1a**. Retrosynthetically, the polypropionate backbone was divided into three fragments of roughly equal complexity (Figure 1). One of the disconnections is between C7 and C8; in the synthetic direction, this manipulation corresponds to a nucleophilic addition of the appropriate synthon **3** to aldehyde **2**. The other disconnection is between C15 and C16; in the synthetic direction, this step corresponds to an alkylation of a C17-ketone, **4a** or **4b**, with an appropriate alkylating agent.

A common stereochemical triad appears in each of these three fragments (**2**, **3**, **4**) that can be retrosynthetically reduced to the homoallylic alcohols **5** and **6**. With three stereocenters set in each fragment by these homoallylic alcohols, nine of discodermolide's 13 stereocenters are quickly established by methods developed by Roush and co-workers for the addition of chiral crotylboronates to a chiral aldehyde.[6] The two homoallylic alcohols are readily prepared in high diastereomeric excess from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate.

Because the absolute stereochemistry of discodermolide was not known at the outset of this work, both antipodes of starting materials and chiral reagents were required.[7] This requirement was fulfilled by the commercial availability of both enantiomers of a 3-hydroxy-2-methylpropionate ester and access to both enantiomers of Roush's chiral boronates. All other stereocenters of discodermolide are set by substrate-controlled reactions.

**Synthesis of the Protected C1−C7 Lactone (2).** The most critical issue in the synthesis of the lactone fragment **2** was to control the configuration of the C5 stereocenter. Starting from **5**, we used the existing stereocenter and the conjugate addition method of Evans and Gauchet-Prunet[8] (Scheme 1). The homoallylic alcohol **5** was oxidatively cleaved and homologated to the *trans* enoate **7** by a Wittig olefination. Treatment of **7** with benzaldehyde and catalytic KHMDS provided, after

[⊗] Abstract published in *Advance ACS Abstracts*, November 1, 1996.

(1) (a) Murray, A. W. *Nature* **1992**, *359*, 599. (b) Hunter, T. *Cell* **1993**, *75*, 839.

(2) (a) Schreiber, S. L. *Chem. Eng. News* **1992**, *70* (43), 22. (b) Sigal, N. H.; Dumont, F. J. *Annu. Rev. Immunol.* **1992**, *10*, 519. (c) Hung, D. T.; Jamison, T. F.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 623−639.

(3) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E. *J. Org. Chem.* **1990**, *55*, 4912 (correction: *J. Org Chem.* **1991**, *56*, 1346).

(4) (a) Longley, R. E.; Caddigan, D.; Harmody, D.; Gunasekera, M.; Gunasekera, S. P. *Transplantation* **1991**, *52*, 650. *In vivo* studies were also performed: (b) Longley, R. E.; Caddigan, D.; Harmody, D.; Gunasekera, M.; Gunasekera, S. P. *Transplantation* **1991**, *52*, 656.

(5) (a) Nerenberg, J. B.; Hung. D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621. We have reported an initial communication of the total synthesis of (−)-discodermolide. Total synthesis of the (−)-enantiomer has also been reported: (b) Smith, A. B.; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011. Other synthetic efforts have been reported: (c) Golec, J. M. C.; Jones, S. D. *Tetrahedron Lett.* **1993**, *34* (50), 8259. (d) Golec, J. M. C.; Gillespie, R. J. *Tetrahedron Lett.* **1993**, *34* (50), 8167. (e) Evans, P. L.; Golec, J. M. C.; Gillespie, R. J. *Tetrahedron Lett.* **1993**, *34* (50), 8163. (f) Paterson, I.; Wren, S. P. *J. Chem. Soc., Chem. Commun.* **1993**, *24*, 1790. (g) Yang, G.; Myles, D. C. *Tetrahedron Lett.* **1994**, *35* (16), 2503.

(6) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(7) In fact, in our previously reported, initial synthesis of (−)-discodermolide,[5a] we arbitrarily chose to start with (*R*)-(−)-3-(hydroxymethyl)propionate, which resulted in the synthesis of the unnatural enantiomer. While the stereochemistry drawn in Schemes 1−9 corresponds to that of the natural enantiomer, the compounds depicted in Schemes 1, 2, and 4−9 were initially characterized as the enantiomers of those drawn.

(8) Evans, D. A.; Gauche-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.

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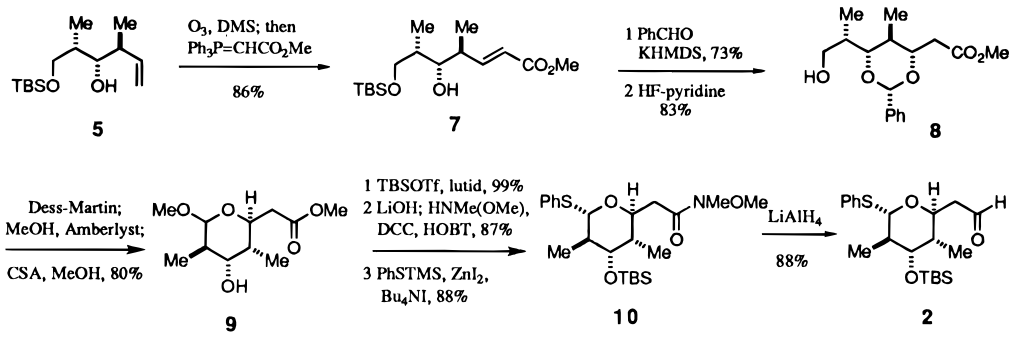
**Scheme 1**



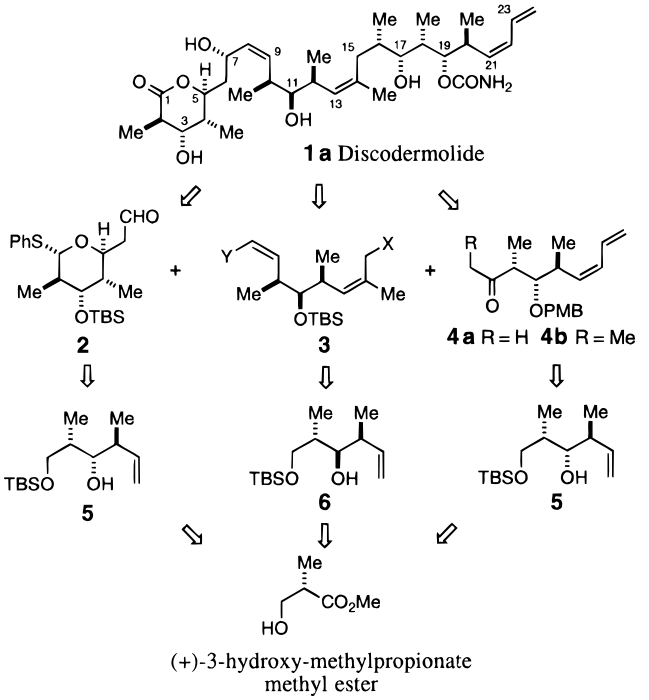



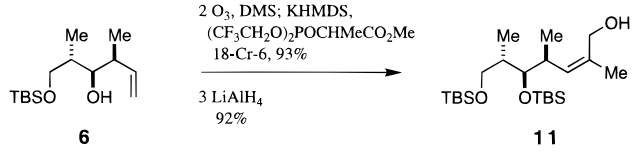

**Figure 1.** Retrosynthetic analysis of discodermolide.

deprotection, acetal **8**. The internal Michael addition of the hemiacetal intermediate proceeded with complete stereoselectivity.[9] Deprotection of the *tert*-butyldimethylsilyl (TBS) group was difficult due to the lability of the benzylidene acetal, but proceeded cleanly with anhydrous HF-pyridine to give **8**.

Dess−Martin oxidation[10] of **8** to the corresponding aldehyde, followed by immediate treatment with Amberlyst-15, an ion exchange resin, in methanol provided the dimethyl acetal of the the aldehyde. The Amberlyst-15 was removed by filtration, and camphorsulfonic acid was added to cleave the benzylidene acetal with concomitant cyclization to yield **9** as a 1.8 to 1 mixture of $\beta$ to $\alpha$ anomers. The anomers could be separated by silica gel flash chromatography or subjected as a mixture to silylation and conversion to the Weinreb amide[11] by lithium hydroxide hydrolysis of the methyl ester and dicyclohexylcarbodiimide (DCC) coupling with *N,O*-dimethylhydroxylamine.[12]

Another important issue was the choice of functionality to mask the lactone until late in the synthesis. The lactone was protected in its lower oxidation state, as the lactol, by a thiophenyl group. The thiophenyl acetal can be hydrolyzed later under mild conditions ($Hg^{+2}$), with subsequent oxidation of the lactol to the lactone. Conversion to the thiophenyl acetal was accomplished by treatment with $PhSSiMe_3$, $ZnI_2$, and $Bu_4NI$, to give **10** as a 2:1 mixture of anomers, $\beta$:$\alpha$, separable by silica gel flash chromatography.[13]

**Scheme 2**



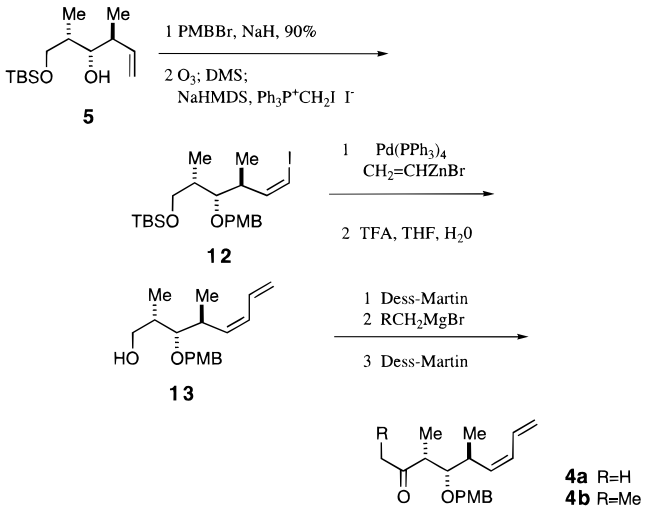

**Synthesis of the C9−C15 Fragment (3).** As the middle fragment of the three-component disconnection, the elaboration of the precise C9−C15 piece (**3**) would be determined by the order of the couplings. Our initial approach involved forming the C15−C16 bond first *via* an alkylation of an enolate derived from **4b** with a C9−C15 allylic bromide, followed by elaboration of C8 and C9 to the appropriate synthon for addition to the C1−C7 lactone fragment.

The major challenge in the synthesis of the C9−C15 fragment was the preparation of the trisubstituted olefin with stereochemical control (Scheme 2). Homoallylic alcohol **6** was silylated and oxidatively cleaved to provide an intermediate aldehyde. The efficient construction of the *cis*-trisubstituted olefin was accomplished by the method of Still and Gennari,[14] with the potassium salt of $(CF_3CH_2O)POCH(Me)CO_2Me$. Reduction of the resulting enoate by $LiAlH_4$ provided allylic alcohol **11** in good yield, without any 1,4-overreduction. Prior to coupling, this alcohol could be converted to the allylic bromide for alkylation of a C16−C24 ketone fragment.

**Synthesis of the C16−C24 Ketone (4a,b).**[15] The major considerations in the construction of the ketone fragment were the choice of protecting group for the C19 alcohol and the synthesis of the *cis*-diene. The protecting group on the C19 alcohol had to be orthogonal to the silicon-based protecting groups of the other alcohols since it would have to be removed selectively and carbamoylated late in the synthesis. In addition, we needed to protect the alcohol while preserving the chelating ability of the oxygen in the form of a protected ether since we thought that chelation would play an important role in the

(9) The relative stereochemistry was confirmed by NOE experiments.
(10) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.
(11) Levin, J. I.; Turos, E.; Weinreb S. M. *Synth. Commun.* **1982**, *12*, 989.
(12) Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016.
(13) (a) Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4696. (b) Hanessian, S.; Guindon, Y. *Carbohydr. Res.* **1980**, *86*, C3. For purposes of characterization, the anomers were separated by silica gel flash chromatography and carried on independently. However, they were equally efficacious in the remainder of the synthesis of natural discodermolide.
(14) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. Experimental modifications in: Wang, Z. Ph.D Thesis, Yale University, 1988.

**Scheme 3**




stereochemical outcome of the alkylation coupling. We chose to protect homoallylic alcohol **6** as the *p*-methoxybenzyl (PMB) ether by treating **6** with PMB bromide and sodium hydride (Scheme 3).[16] Oxidative cleavage of the PMB-protected alcohol provided an intermediate aldehyde that could be converted to the diene by a two-step procedure. Conversion to the *cis* vinyl iodide **12** was accomplished by a Wittig reaction with (iodomethylene)triphenylphosphorane.[17] The vinyl iodide was converted to the diene **13** by a palladium-catalyzed coupling with vinylzinc bromide,[18] followed by TBS deprotection with trifluoroacetic acid. Dess−Martin oxidation with subsequent Grignard addition of methyl- or ethylmagnesium bromide provided a 4:1 mixture of epimeric alcohols. A subsequent oxidation with Dess−Martin periodinane provided ketones **4a**,**b**.

**Initial Coupling Strategy.** Our initial approach to couplings involved performing the alkylation of ethyl ketone **4b** with the bromide derived from allylic alcohol **11**. There is ample precedent in the literature for facial selectivity in alkylation or aldol reactions based on enolate geometry and chelation. We anticipated that both the intermediate enolate derived from **4b** and the PMB ether oxygen would chelate a common lithium counterion[19] (Figure 2). In this model, the transient six-membered ring would allow the methyl group at C18 to confer a facial bias to the approaching bromide approach, affording the desired stereochemistry at C16.

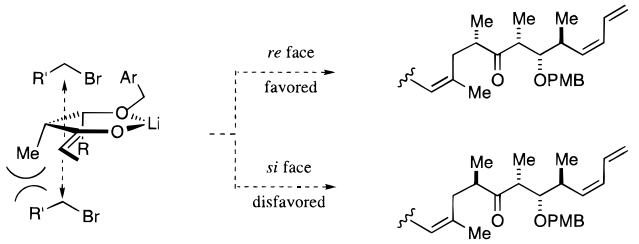



**Figure 2.** Predicted chelate model for C15−C16 alkylation reaction.

Allylic alcohol **11** was converted to the bromide by treatment with mesyl chloride, followed by lithium bromide in acetone[20] (Scheme 4). It was then treated with the (*Z*)-lithium enolate of **4b,** formed with $LiN(SiMe_2Ph)_2$ at −78 °C.[21] This provided a 10:1 ratio of diastereomers, **15**, whose configurations at C16 were not rigorously assigned at the time.[22] On the basis of the model predicted by the chelated intermediate (Figure 2), the major product was presumed to be the desired C16 epimer.

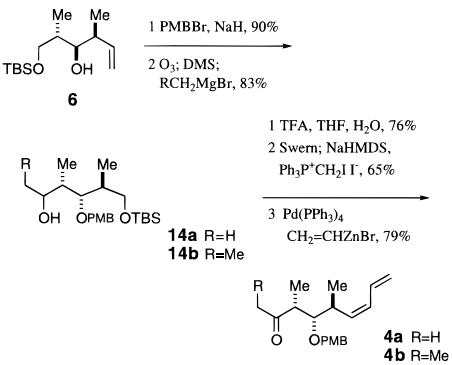
Reduction of the ketone at C17 with $LiAlH_4$ at −78 °C produced a 2:1 ratio of epimers at C17.[23] Protection of the secondary alcohol as a TBS silyl ether, followed by selective deprotection of the primary TBS group wtih TFA:$H_2O$:THF, completed the elaboration of a C9−C24 fragment. We then turned our attention to formation of the C7−C8 bond.

Model studies on nucleophilic additions to the Weinreb amide **10** had shown that lithium acetylide could be added to give the ynone in good yield. $LiAlH_4$ reduction and catalytic hydrogenation using Lindlar catalyst poisoned with quinoline demonstrated that a model *cis*-allylic alcohol could be synthesized by the nucleophilic addition of a lithium acetylide to the Weinreb amide.

On the basis of these studies, we proceeded to convert the primary alcohol derived from **15** to the requisite acetylene by Swern oxidation[24] and one carbon homologation to the desired acetylene **16** using Gilbert's reagent.[25] Deprotonation of **16** to the lithium acetylide was best accomplished by lithium diisopropylamide (LDA) as judged by deuterium quenching experiments and $^1H$ NMR. However, the lithium acetylide derived from **16** failed to add to amide **10**, even after many variations.[26] Attempted additions to aldehyde **2**, derived from the $LiAlH_4$ reduction of **10**, also were unsuccessful.[27]

A new strategy for the formation of the C7−C8 bond involved the $NiCl_2/CrCl_2$ mediated coupling of aldehydes and iodoacetylenes or iodoolefins, developed by Nozaki and Kishi.[28] These reactions are performed under mild conditions with excellent functional group compatibility. Attempted coupling with the

(15) An alternative synthesis of the ketone fragment begins with a different homoallylic diastereomer.




(16) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(17) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173.

(18) Gardette, M.; Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron* **1984**, *40*, 2741.

(19) For a discussion of protecting groups and chelation in addition reactions see: (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (b) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526. (c) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed. Academic Press: Orlando, FL, 1984; Volume 3, Chapter 2. (d) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. Use of a lithium enolate with an α-alkoxy chelating protecting group in an aldol reaction has appeared: (e) Choudhury, A.; Thornton, E. R. *Tetrahedron Lett.* **1993**, *34*, 2221.

(20) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730.

(21) Assignment of the *Z*-enolate geometry was based on correlation with literature precedents for enolate geometry resulting from formation conditions. Conditions examined included lithium hexamethyldisilazide (LiHMDS,) $LiN(SiMe_2Ph)_2$, dibutylboron triflate and Hunig's base, and lithium 2,2,6,6-tetramethylpiperidide (LiTMP).

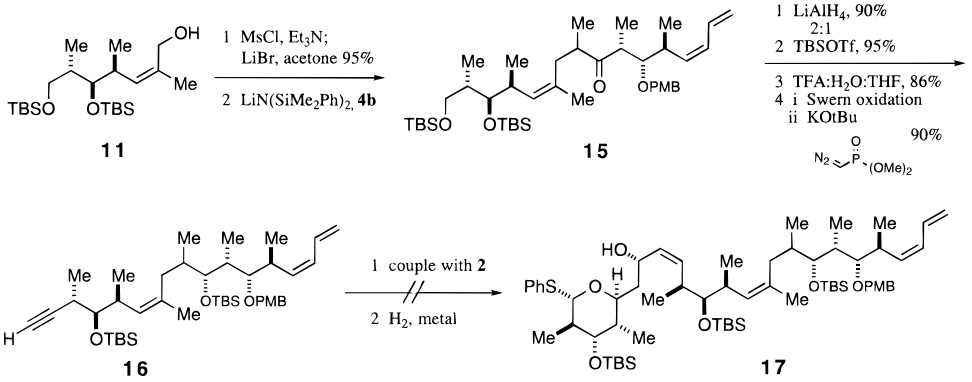
(22) Subsequent assignment of analogous substrates from this alkylation reaction now suggest that the stereochemical outcome is opposite of that predicted by the chelated transition state model.

(23) By analogy to other similar substrates that have now been rigorously assigned, the major epimer corresponds to the desired 1,3-*syn*-alcohol.

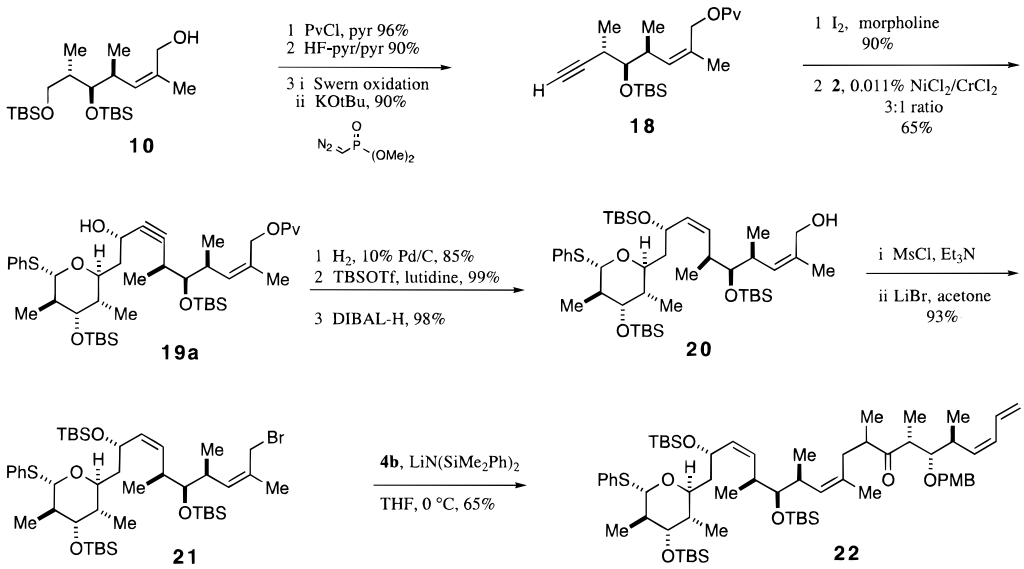
(24) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(25) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Chem. Commun.* **1973**, 151; Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.

**Scheme 4**




**Scheme 5**




*cis* vinyl iodide corresponding to **16** and aldehyde **2** resulted in recovery of the protonated olefin, suggesting that metal insertion into the C−I bond had occurred, but no addition had taken place.

Conversion of **16** to the iodoacetylene was achieved by treatment with iodine and morpholine.[29] A coupling of this iodoacetylene and aldehyde **2**, in the presence of catalytic 0.011% $NiCl_2/CrCl_2$, resulted in a 65% yield of two propargylic alcohols in a ratio of 2:1, the major epimer being the desired one.[30] The full carbon backbone of discodermolide having been assembled, only semihydrogenation of the fully coupled product remained in order to attain **17**.

Unfortunately, extensive investigation of reduction conditions failed to identify conditions that would selectively reduce the acetylene to the *cis* olefin, while leaving the terminal diene intact. Hydrogenation over Lindlar catalyst or $Pd/BaSO_4$[31] resulted in only reduction of the terminal C23−C24 olefin. Other reductions also failed to yield the desired product without scrambling of the terminal diene.[32] It became clear that the reduction of the acetylene in the presence of the competing terminal diene was problematic and that an alternative coupling strategy was required.

**Revised Coupling Strategy.** Reversing the order of the coupling reactions, namely performing the Nozaki−Kishi reaction first between aldehyde **2** and a C8−C15 acetylene fragment with subsequent reduction to the *cis* olefin, followed by alkylation of ketone **4** circumvented the difficulties encountered with the hydrogenation. This approach required a minor revision in the elaboration of the C8−C15 fragment (Scheme 5).

The allylic alcohol **10** was protected as the pivaloate and selectively deprotected with HF-pyridine buffered with excess pyridine to provide the corresponding primary alcohol. This alcohol was subjected to the same series of transformations that was performed on **15** to afford acetylene **18** in excellent yield. Conversion to the iodoacetylene and coupling of the iodoacetylene with aldehyde **2** under Nozaki−Kishi conditions yielded

(26) Changing counterions to cerium, magnesium, boron, and potassium, or adding HMPA or TMEDA to the reaction medium did not have any effect on the addition. The feasibility of a lithium vinyl anion addition to the Weinreb amide or aldehyde was also investigated. The vinyl iodide corresponding to **16** was synthesized by the addition of (iodomethylene)-triphenylphosphorane to the common aldehyde leading to **16.** Metallation using *t*BuLi, however, resulted in decomposition of the substrate.

(27) Attempted addition of the acetylide to MeI also resulted in recovery of starting material. It is now presumed that the terminal acetylene with its branched substitution pattern on the other side behaves quite sterically large, perhaps causing the difficulty in addition. Its sterically demanding behavior is confirmed by the CBS reduction of ynone **23**, in which the acetylene functionality behaves as the larger group in the directed reduction.

(28) (a) Aicher, T. D.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 3463. (b) Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5585. (c) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (d) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

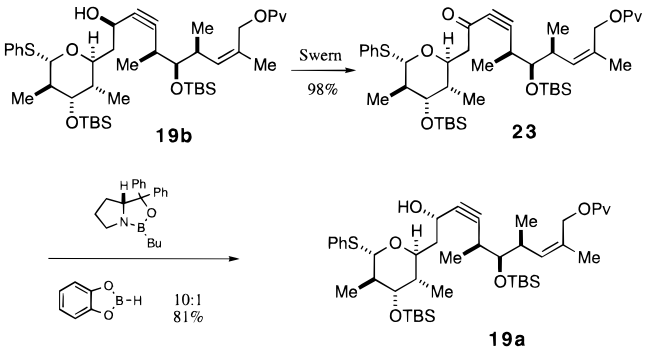
(29) Goekjian, P. G. Ph.D. Thesis, Harvard University, 1990. In our case, this conversion was accompanied by some isomerization of the terminal diene.

(30) The assignment of these alcohols is done by correlation to similar substrates that have been rigorously assigned (*vide infra*).

(31) For a review of semihydrogenation, see: Marvell, E. N.; Li, T. *Synthesis* **1973**, 457.

(32) Other reduction conditions tried were activated zinc with KCN, Cu/Ag, copper hydride, trimethylstannylcopper, or tantalum/zinc.

**Scheme 6**




**19a** as the major epimer in a 2:1 mixture.[33] The minor epimer **19b** could be efficiently recycled by Swern oxidation to ketone **23**, followed by Corey's asymmetric reduction with catecholborane and catalytic *B*-butyloxazaborolidine derived from D-proline[34] (Scheme 6). It is interesting to note that the acetylene behaves as the larger substituent relative to the methylene group in Corey's model for stereoselectivity.[35]

Semihydrogenation of **19a** with 10% palladium on carbon, TBS protection, and removal of the pivaloyl group with DIBAL-H afforded allylic alcohol **20**. Conversion to the bromide completed the synthesis of **21**, which was then ready to be coupled with ketone **4b**.

The alkylation of **4b** by **21** was peformed under the same conditions that had been used in the initial coupling strategy, forming the *Z*-enolate with $LiN(SiMe_2Ph)_2$ at −78 °C. This coupling thus afforded the full carbon backbone of discodermolide in **22**. At this time, the C16 stereochemistry was not assigned, but the major component of the 7:1 mixture was presumed to be the desired epimer based on our initial model.

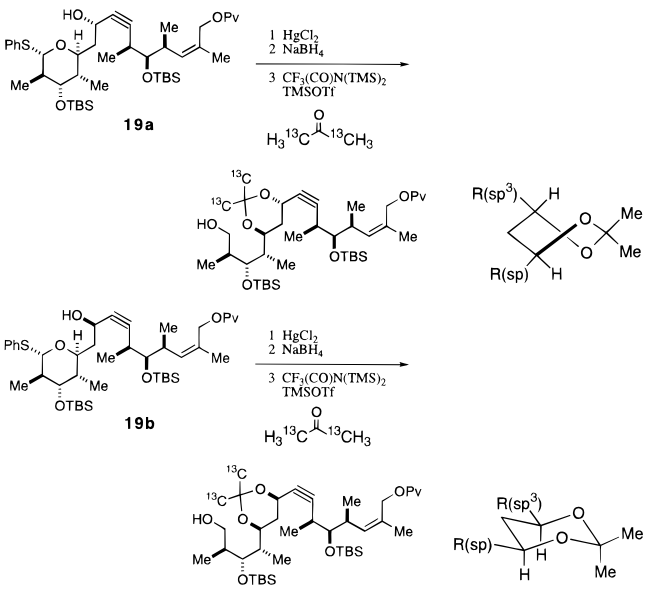
Final elaboration of **22** was achieved by the $LiAlH_4$ reduction of the ketone. The reduction at −78 °C provided a 2:1 ratio of alcohols, the major one being the desired epimer.[36] Protection of the C17 alcohol as the diethylisopropylsilyl (DEIPS) ether afforded **24**[37] (Scheme 7). Conversion of the thiophenyl acetal to the lactone was accomplished in two steps. Hydrolysis of **24** with mercuric chloride[38] afforded a mixture of lactols that was oxidized with Jones reagent[39] to provide the corresponding lactone.

Finally, DDQ deprotection of the PMB ether,[16] carbamoylation with trichloroacetyl isocyanate,[40] and hydrolysis of the trichloroacetyl group with potassium carbonate in methanol afforded **25**. Final deprotection of the silyl groups was accomplished by treatment with excess *p*-toluenesulfonic acid in THF and water to yield **1b**.

While high-resolution mass spectrometry revealed that the molecular weight of **1b** was identical to that of discodermolide, the $^1$H NMR spectrum was not identical to that obtained for the natural product. Conversion to the tetraacetate also showed discrepancies in the $^1$H NMR spectrum with that reported in the literature. It became clear that we had synthesized an isomer of discodermolide.

**Correction of the C16 Stereochemistry.** After a careful re-examination of the assignment of each of the stereocenters, and ruling out any epimerization that could have occurred during the synthesis,[41] we suspected that the most likely difference between the isomer that we had synthesized **1b** and natural discodermolide **1a** was the C16 stereocenter set by the alkylation reaction. COSY and NOESY studies on the tetraacetate of **1b** helped to confirm that we did not have a constitutional isomer of discodermolide and to suggest a more extended conformation

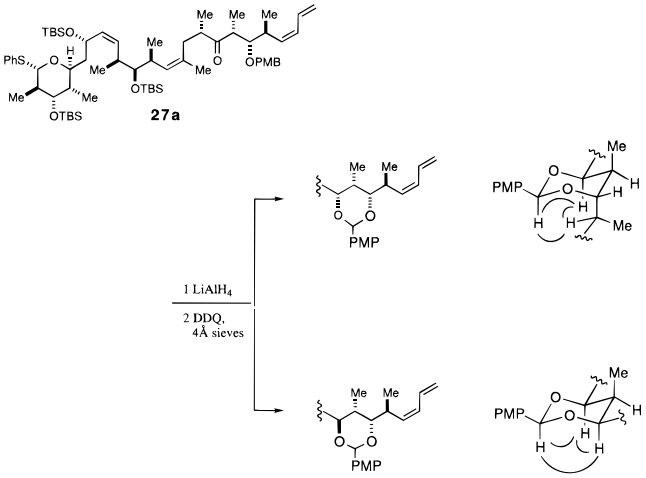
(33) The C7 stereochemistry has been assigned by two methods. Conversion to the mandelate esters by the method of Trost et al.: Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. Also, the coupling products **18a** and **18b** were converted to *anti*- and *syn*-1,3-diols, respectively, and assigned by the formation of the 13C-acetonides by stereochemical analysis. The acetonide of the major isomer had $^{13}$C resonances at 23.83 and 28.15 ppm, whereas the acetonide of the minor isomer had $^{13}$C resonances at 19.78 and 30.03 ppm. Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.




(34) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem Soc.* **1987**, *109*, 5551 and (b) Link, J. O. Ph.D. Thesis, Harvard University, 1992.

(35) Model studies on simple acetylene systems in the CBS reduction have shown no appreciable stereoselectivity. Unpublished results of K. A. Cimprich, D. T. Hung, S. L. Schreiber, and E. J. Corey. This is in contrast to other published results that are consistent with Corey's originally proposed model, with the alkynyl substituent behaving as the smaller group. Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61* (9), 3214.

(36) The C17 stereocenter in this and other related substrates was assigned by treating the alcohol with anhydrous DDQ and performing NOE studies on the resulting benzylidene acetal.




(37) DEIPSOTf was prepared from DEIPSCl in analogy to: (a) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455. DEIPSCl was prepared according to: (b) Toshima, K.; Tatsuta, K.; Kinoshita, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2369. This protecting group was chosen after the TBS ether was shown to be stable to all deprotection conditions and the TES ether was shown to be too labile to survive the subsequent Jones oxidation conditions.

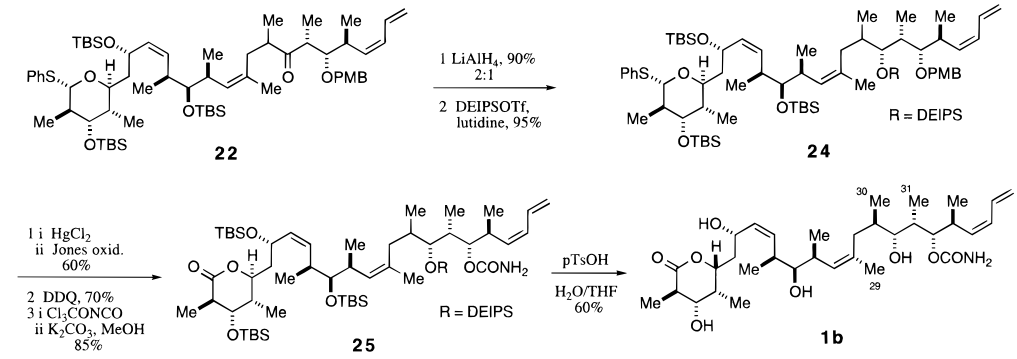
(38) Ikeda, T.; Hutchinson, C. R. *J. Org. Chem.* **1984**, *49*, 2837.

(39) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Volume 1, p 142. We found that the *ca.* 1.2 M preparation of this reagent was most effective for this oxidation.

(40) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.

(41) Epimerization during the alkylation reaction was ruled out by resubjection of the alkylated product **27a** to the reaction conditions without any change in starting material ratios.

**Scheme 7**



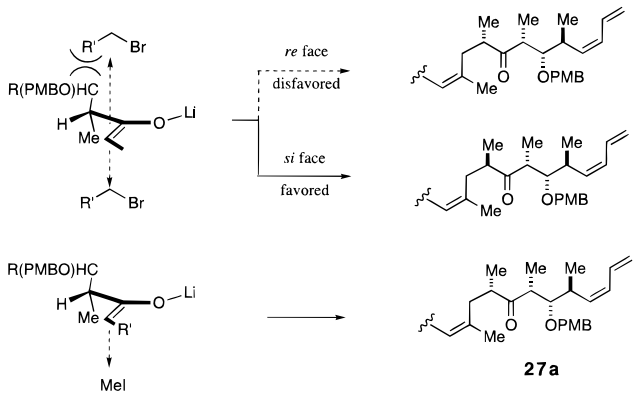




**Figure 3.** Models for C15−C16 alkylation reaction.

to the isomer, relative to discodermolide. This conformation could be consistent with a structure with the opposite stereochemistry at C16. In a model derived from the originally reported crystal structure,[3] inversion of the C16 stereochemistry would result in two *syn*-pentane interactions between C30 (the C16 methyl group) and both C29 and C31 (Scheme 7). These interactions can be minimized by twisting the structure into a more extended conformation, similar to that observed in NOESY studies.

The most straightforward method to correct the C16 stereochemistry was to perform the alkylation with the *E*-enolate rather than the *Z*-enolate of **4b**. The *E*-enolate derived from **4b** was obtained with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) by the method of Collum.[42] Under these conditions, the reaction with bromide **21** resulted in a 1:1 mixture of products. This result suggests that the *E*-enolate geometry may be equilibrating during the reaction prior to addition. (The corresponding *Z*- and *E*-silyl enol ethers, formed by treatment of the enolates with TMSCl, were determined to be stereochemically pure in a ratio of greater than 10:1 by $^1$H (NOESY) and$^{13}$C NMR.) Another alternative to reversing the stereochemistry at C16 takes advantage of the stereoselectivity observed with the *Z*-enolate. Alkylation of a *Z*-enolate derived from **26a** with methyl iodide would probably proceed with the same facial bias as observed with **4b**, affording the correct desired stereochemistry in **27a** (Figure 3). Access to **26a** is provided by a prior alkylation of the methyl ketone **4a** with bromide **21** (Scheme 8).

This alkylation reaction has now been studied by several other groups with results that are consistent with those reported here.[43] We rationalize the unexpected stereochemical outcome by revising our initial chelate model. Our original model (Figure 2) assumes that approach by the allylic bromide from the *si* face of the chelate would be disfavored due to the methyl group at C18, and yet, the minor product corresponds to approach from the *re* face. An alternative model does not invoke a lithium chelate; instead, the geometry of the enolate intermediate could be determined by allylic ($A^{1,3}$) strain, and the conformation in which the double bond of the enolate eclipses the C18−H18 bond may predominate (Figure 3).

**Strategy for Final Elaboration to Discodermolide.** The final challenges in the synthesis of discodermolide were the stereoselective reduction of the C17 ketone and selective carbamoylation of the C19 alcohol. Several conditions were examined for the reduction (Table 1).

In the reduction of the C16 methyl epimer **22**, $LiAlH_4$ provided a 2:1 ratio of epimers, favoring the desired *R* configuration at C17. Under these same conditions however, reduction of **27a**, with the corrected C16 methyl stereochemistry, gave a 1:2 ratio, in favor of the undesired epimer. Other reductions, including additives to promote $\beta$-chelation[44] with the C19 PMB ether, gave the same product ratios. In contrast, reduction of the $\beta$-hydroxy ketone (resulting from deprotection of the PMB ether by DDQ) by the Prasad−Narasaka method[45] using $NaBH_4$/$Et_2BOMe$ yielded the *syn*-1,3-diol with selectivity of 15:1. These results suggest that in general, the $\beta$-alkoxy substituent in this substrate does not provide significant chelation control, either in the *syn*-reduction of the ketone or in the alkylation reaction. Instead, the $LiAlH_4$ selectivity in this substrate, for the two C16 methyl epimers, is more likely controlled by a Cram-like model of addition.

Unfortunately, the good selectivity obtained in the Prasad−Narasaka reduction could not be exploited because of the inability to carbamoylate selectively the C19 alcohol over the C17 alcohol. This problem was circumvented when it was discovered that reduction of the C17 ketone with the carbamate already installed at C19 gave excellent selectivity for the correct *R* configuration. With the bulky lithium aluminum tri-*tert*-butoxy hydride, a 30:1 preference for the desired epimer was observed. It is presumed that the neighboring carbamate may facilitate chelation-controlled reduction. This same selectivity is observed for the carbamoylated substrate with the opposite stereochemistry at C16.

The final elaboration to discodermolide proceeded by transformation of the thiophenyl acetal to the lactone, DDQ deprotection of the PMB ether, carbamoylation, and reduction of the ketone to provide fully protected discodermolide (Scheme 9).

(42) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571.

(43) (a) Yang, G.; Myles, D. C. *Tetrahedron Lett.* **1994**, *35* (9), 1313. (b) Clark D. L.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58* (22) , 5878.

(44) For examples of the importance of the $\beta$-alkoxy group in the stereochemical course of addition to aldehydes, see: (a) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847. (b) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5480.

(45) (a) Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155. (b) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233.

**Scheme 8**

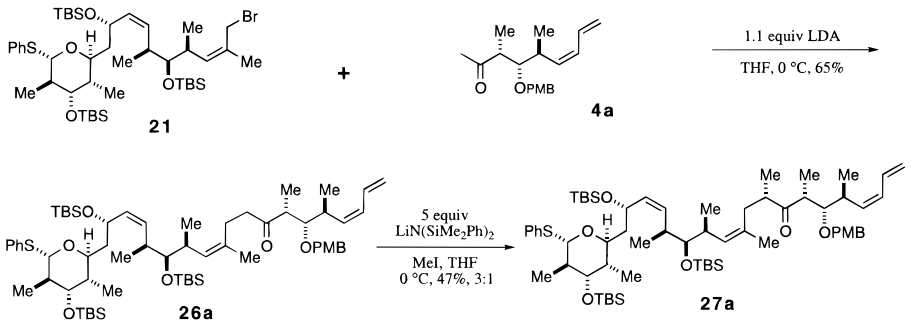
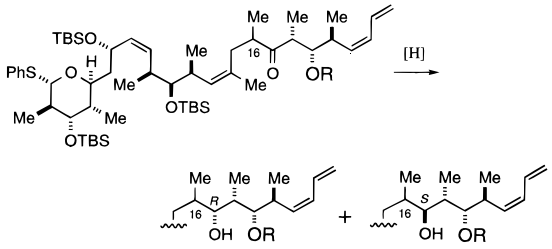



**Table 1.** Diastereoselectivities for C17-*syn* Reduction




| conditions | R | configuration at C16 | diastereoselectivity of *R*:*S* at C17 |
|---|---|---|---|
| $LiAlH_4$ | PMB | *R* | 2:1 |
| $LiAlH_4$ | PMB | *S* | 1:2 |
| $LiAlH_4$, LiI | PMB | *S* | 1:2 |
| $NaBH_4$, LiI[a] | PMB | *S* | 1:2 |
| $NaBH_4$, $MgBr_2(Et_2O)_2$[a] | PMB | *S* | 1:2 |
| DIBAL-H | H | *S* | 1:1 |
| $NaBH_4$[a] | H | *S* | 1:1 |
| $NaBH_4$, $Et_2BOMe$[b] | H | *S* | 15:1[c] |
| $NaBH_4$[a] | $CONH_2$ | *S* | 2.5:1 |
| $NaBH_4$[a] | $CONH_2$ | *R* | 2.5:1 |
| $LiAlH(OtBu)_3$[b] | $CONH_2$ | *S* | 30:1[c] |
| $LiAlH(OtBu)_3$[b] | $CONH_2$ | *R* | 30:1[c] |

[a] Reduction was performed on the lactone substrate. Treatment of the thiophenyl acetal resulted in reduction of the pyran ring. [b] Reduction was performed on both the thiophenyl acetal and the lactone substrates. Ratios were the same for both substrates. [c] Ratios were determined by HPLC. All other ratios were determined by proton NMR.

Deprotection of the silyl groups with 1% HCl in methanol provided synthetic discodermolide **1a**. This total synthesis provided natural discodermolide in 36 steps, with an overall yield of 4.3% over 24 steps (the longest linear sequence). The synthetic material was identical to natural discodermolide as judged by $^1H$ and $^{13}C$ NMR, IR, and high-resolution mass spectrometry.

The only issue that remained unresolved at the completion of the total synthesis was the assignment of absolute stereochemistry of the natural product. In contrast to the current study, the initial synthesis of discodermolide that we reported[5] began with (*R*)-(−)-3-hydroxy-2-methylpropionate and resulted in the (−)-enantiomer ($[\alpha]^{20}_D = -13.0$ ($c = 0.6$, methanol)). The signs of the optical rotations of our synthetic discodermolide and the natural product (reported:[3] ($[\alpha]^{20}_D = +7.2$ ($c = 0.72$, methanol))) were opposite; however, their small absolute values diminished the confidence with which we could claim that the two samples are enantiomeric. In addition, the assignment was complicated by the observation that the synthetic (−)-antipode was shown to be a potent inhibitor of cell proliferation.[46] The issue could only be clearly resolved by the synthesis of the other (+)-antipode ($[\alpha]^{20}_D = +14.0$ ($c = 0.6$, methanol), as described herein, and characterization of the biological activities of both enantiomers. This biological characterization allowed unequivocal assignment of the absolute stereochemistry to be as drawn in (+)-**1a**.

**Syntheses of Discodermolides Suitable for Studying Interactions with the Discodermolide Receptor.** The most direct approach to receptor isolation and purification exploits the high affinity interaction between receptor and ligand. Indeed, a tritiated variant of discodermolide (C17-[$^3$H]-(+)-discodermolide), prepared by a modification of the route described above,[46] led to the discovery that discodermolide binds directly to microtubules.[47] Binding was shown to be stoichiometric with tubulin dimer and mutually exclusive with and more potent than taxol-binding to microtubules. Discodermolide-binding to microtubules was also shown to occur in vivo. These findings are in agreement with the discovery that discodermolide stabilizes microtubules and causes mitotic cell cycle arrest.[48] Concurrent with these cellular and biochemical studies, we designed and synthesized several structural variants of (+)-discodermolide that should be useful in further characterizing the interaction of discodermolide with its receptor.

Several chemical criteria must be fulfilled in order to develop a useful binding reagent. Most importantly, in order to attach the ligand to another entity for immobilization or fluorescence-based visualization, the molecule must permit extension of a molecular "handle" off of it, without abolishing cellular activity or binding affinity. Any alteration of the molecule must neither sterically interfere with the ligand−receptor interface nor indirectly affect recognition by significantly altering the conformation of the ligand. In many cases, such derivatization may be done on the natural product itself, or some compound derived therein.[49] In other cases, the binding reagent may require extensive chemical synthesis.

**Syntheses of Structural Variants of Discodermolide.** An insufficient supply of natural (+)-discodermolide exists to provide material for derivatization of the natural product itself.[3,4] Thus, in order to develop probe reagents, synthetic variants of the natural product were prepared to determine the least intrusive modification that could be made without destroying the antiproliferative activity and, more importantly, without

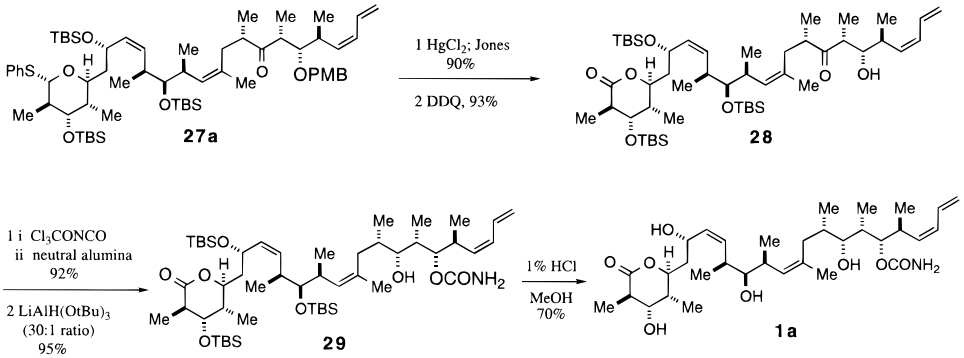
(46) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *Chem. Biol.* **1994**, *1*, 67.

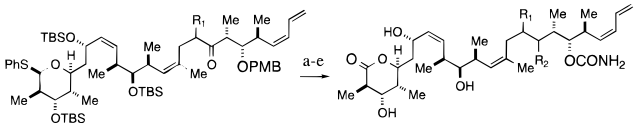
(47) Hung, D. T.; Chen, J.; Schreiber, S. L. *Chem. Biol.* **1996**, *3* (4), 287.

(48) ter Harr, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243.

(49) (a) Harding, M. W.; Galat, A.; Uehling, D. E.; Schreiber, S. L. *Nature* **1989**, *341*, 758. (b) Fretz, H.; Albers, M. W.; Galat, A.; Standaert, R. F.; Lane, W. S.; Burakoff, S. J.; Bierer, B. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 1489. (c) Nadler, S. G.; Tepper, M. A.; Schacter, B.; Mazzucio, C. E. *Science* **1992**, *258*, 484. (d) Crews,C. M.; Collins, J. L.; Lane, W. S.; Snapper, M. L.; Schreiber, S. L. *J. Bio. Chem.* **1994**, *269*, 15411. (e) Crews, C. M.; Lane, W. S.; Schreiber, S. L. *Proc. Nat. Acad. Sci. U.S.A.* **1996**, *93*, in press. (f) Taunton, J.; Hassig, C.; Schreiber, S. L. *Science* **1996**, *272*, 408.

**Scheme 9**




| Substrate | Product | $R_1$ | $R_2$ | $IC_{50}$ |
|---|---|---|---|---|
| **27b** | **1a** | *S*-Me | *R*-OH | 6 nM |
| **30** | **1b** | *R*-Me | *R*-OH | 300 nM |
| **27b** | **1c** | *S*-Me | *S*-OH | - |
| **26b** | **31** | H | *R*-OH | 10 nM |

(a) $HgCl_2$; Jones. (b) DDQ. (c) $Cl_3CONCO$; neutral alumina. (d) $LiAlH(OtBu)_3$. (e) 1% HCl, MeOH.

**Figure 4.** Synthesis of stereoisomers of discodermolide.

altering binding to the cellular receptor. Thus, any synthesis of potential probe reagents involves an active interplay between synthetic efforts and cellular assays. Each compound that was synthesized was tested for its ability to inhibit the replication of cells by using a [$^3$H]thymidine incorporation assay. Replicating cells incorporate thymidine into their DNA during the S phase of the cell cycle.

The methodology we had previously established for synthesis of the natural product[5a] influenced our choice of synthetic variants. The initial structural variants were simple stereoisomers of discodermolide, resulting from elaboration of epimeric side products to a final, fully deprotected product. Preparation of these compounds is summarized in Figure 4.

Elaboration of the minor methyl epimer from the methyl iodide alkylation (Scheme 8) resulted in 16-*epi*-discodermolide **1b**. TBS deprotection of the minor epimeric alcohol produced in the $LiAlH(OtBu)_3$ reduction that yields **29** (Scheme 9) afforded 17-*epi*-discodermolide **1c**. Additionally, a 16-desmethyl variant **31** was synthesized from the late intermediate **26b**. The cell growth-inhibitory properties of these compounds suggested that the conformation about C16 and C17 is critical to discodermolide's activity. Relative to discodermolide **1a**, which has an $IC_{50}$ of 6 nM in the [$^3$H]thymidine assay, **1b** had an $IC_{50}$ value of 300 nM and **1c** was completely inactive. In contrast, the 16-normethyl compound **31** was as active *in vivo* as discodermolide itself. This finding became important in the later development of binding reagents by obviating the second alkylation step with methyl iodide and thus eliminating material loss at that step.

The compounds that were next synthesized were truncated versions of discodermolide, **32** and **35** (Scheme 10). An examination of their activities was expected to give some indication of whether the full length of the molecule is important for receptor recognition. A C1−C15 fragment, **32**, was made by elaborating the allylic alcohol **20**. The primary alcohol **20** was protected as the TBS ether, the thiophenyl acetal was hydrolyzed with mercuric chloride, and the resulting lactols were oxidized to the lactone with Jones reagent. Silyl deprotection with 1% HCl/methanol yielded a discodermolide variant without C16−C24, **32**. Similarly, a variant containing C8−C24 of discodermolide **35**, without C1−C7, was synthesized from intermediate acetylene **18**. Hydrogenation of **18** with palladium/$BaSO_4$ poisoned with quinoline[31] provided a terminal olefin corresponding to the the *cis* C8−C9 olefin in natural discodermolide. Conversion of this olefin fragment to **35** was performed analogously to the total synthesis. The observation that neither of these two compounds was active *in vivo* implied that the full length of discodermolide is required for recognition by its receptor.

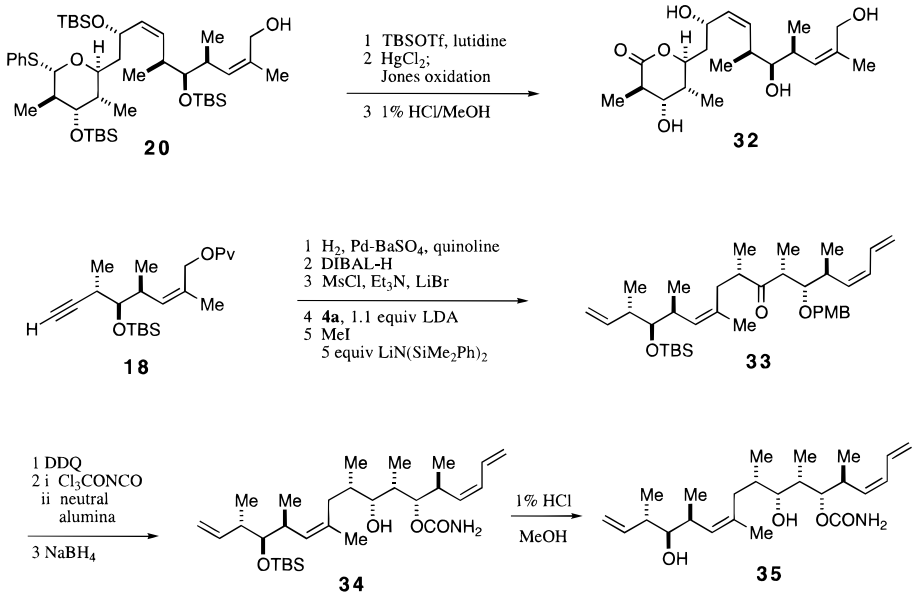
At this point, analysis of the discodermolide structure and our total synthesis allowed prioritization of potential targets that would lead to binding reagents by the addition of an extension (Figure 5). The obvious possibility is the acylation of one of the four alcohol functionalities in discodermolide. Two considerations warranted caution in this regard. Due to the substitution pattern that creates the potential for development of *syn*-pentane interactions following alteration of the natural product, minor changes to the internal hydroxyls on C7 and C11 may result in dramatic conformational changes, rendering the variant inactive. Secondly, attempts to differentiate the alcohols either by selective acylation of one hydroxyl in the presence of the others, or by selective deprotection of a tetrasilylated discodermolide, were not successful. The implication from these experiments was that any differentiation must occur at some intermediate point along the total synthesis and not at the end.

**Binding Reagent Based on Site A.** The C17-hydroxyl is easily differentiable in intermediate **29** following reduction of the ketone. This alcohol can be acylated with acetyl chloride/pyridine and then deprotected with 1% HCl/MeOH to provide the corresponding 17-acetyldiscodermolide **36** (Scheme 11). The $IC_{50}$ value of 70 nM for inhibition of proliferation was promising. Unfortunately, all attempts failed to acylate this hydroxyl with anything larger than acetyl chloride, including acylation by *N*-Aloc-aminocaproic chloride with the bases triethylamine, pyridine, and pyridine/DMAP, by *N*-Aloc-aminocaproic acid using BOP or PyBroP,[50] by *N*-Aloc-aminocaproic isocyanate,[51] and finally, even acylation by propionyl chloride/pyridine. Attempted acylations of 16-desmethyl discodermolide also did not meet with success. The C17 hydroxyl may be either too sterically hindered or too non-nucleophilic due to a hydrogen bonding interaction with the neighboring carbamate to allow addition of an extended linker that would be useful for synthesis of a probe reagent.

**Binding Reagent Based on Site B.** The C19 hydroxyl in **28** can likewise be easily differentiated and is selectively

(50) Coste, J.; Frereot, E.; Jouin, P. *J. Org. Chem.* **1994**, *59*, 2437.
(51) Satchell, D. P. N..; Satchell, R. S. *Chem. Soc. Rev.* **1975**, *4*, 231.

**Scheme 10**



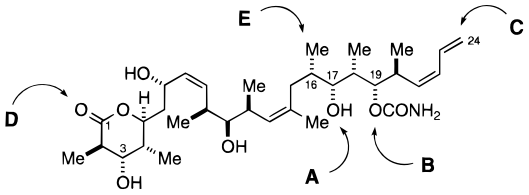




**Figure 5.** Potential sites for derivitization of discodermolide.

carbamoylated on route to the natural product. Treatment of **28** with acetyl chloride/pyridine yielded the corresponding acetate of **28** (Scheme 12). Unfortunately, sodium borohydride reduction of this compound resulted in acyl migration, giving a 1:1 ratio of C17 and C19 acetates. Any attempt to separate the acyl products failed due to migration that occurred during silica gel flash chromatography.

Carbamoylation with a substituted isocyanate was envisioned to afford a carbamate at C19 that would be less prone to migration during reduction of the C17 ketone. Unfortunately, all reactions of **28** with isocyanates or chloroformates failed, with the exception of the highly reactive trichloroacetyl isocyanate[40] used in the synthesis of the natural product. The $\beta$-hydroxy ketone was not stable to the harsher conditions needed to react the hindered secondary alcohol with an isocyanate, affording only retroaldol products. Treatment of **28** with phosgene, followed by the addition of monoprotected *N*-Aloc-1,6-hexanediamine returned only starting material.

Because of the inability to substitute selectively a linker for the C19 carbamate without migration to C17, the $\beta$-acetyl ketone, without reduction at C17, was deprotected to yield **37**, and tested for its ability to inhibit T cell proliferation. (Scheme 12). This compound was found to be completely inactive.

While thwarting efforts to produce a variant at C19 (site B), these results did suggest a potential method to derivatize C17 (site A) (Scheme 12). Acylation of the C19 hydroxyl in **28** is more facile than acylation of the C17 hydroxyl in **29**, probably due to less steric congestion $\beta$ to an $sp^2$ rather than an $sp^3$ center. Acylation of the desmethyl variant of **28** with *N*-Fmoc-aminocaproic acid using EDC, DIPEA, and catalytic DMAP afforded **38**. Reduction of **38** with $NaBH_4$ resulted in migration of the aminocaproic group to a 1:1 mixture that was trapped with $Cl_3CONCO$. The regio- and stereoisomers could be separated by HPLC and silyl deprotection of the correct isomer (carbamoylated at C19, acylated at C17, with the *R*-configuration at C17) afforded variant **39**. Deprotection of the Fmoc group with piperdine yields a reagent that may help in characterizing the binding properties of discodermolide.

**Binding Reagent Based on Site C.** Other variants that are not directly accessible from a late intermediate could be accessed fairly easily due to the convergent nature of our total synthesis. One attractive target was a discodermolide variant **45** with an extension off the terminal diene at C24. Such an addition should not interfere with the conformation of the molecule significantly. An extension was attained by a modified synthesis of the ketone fragment **42**, prior to the alkylation-based coupling (Scheme 13).

The major modification involved a palladium-catalyzed coupling for synthesis of the *cis*−*trans*-diene in **42**. Intermediate **14a** was silylated and selectively deprotected with HF-pyridine buffered with excess pyridine to give the primary alcohol **40**. Dess−Martin oxidation and Wittig olefination afforded the corresponding *cis*-vinyl iodide. Only low conversions were obtained in Stille couplings[52] of the vinyl iodide and various *E*-tributylstannanes with $Pd(PPh_3)_4$. However, Suzuki coupling[53] of the vinyl iodide and (*E*)-6-catecholboranoto-5-hexen-1-ol pivalate,[54] using Kishi's modification with thallium hydroxide,[55] afforded the *cis*−*trans*-diene **41** in better yield. The reaction was sluggish at room temperature, but proceeded quickly upon heating to reflux in THF.

Tetrabutylammonium fluoride deprotection,[56] followed by Dess−Martin periodinane oxidation, afforded ketone **42**, analogous to ketone **4a** with an additional *trans*-extension off the diene. This ketone could be coupled to allylic bromide **21**, and elaborated to afford **45** in a manner analogous to that which yielded natural discodermolide. The *in vivo* activity of **45** was encouraging, with an $IC_{50}$ value of 70 nM, making this a prime candidate for development as a binding reagent.

(52) (a) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (c) Farina, V.; Krishnana, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

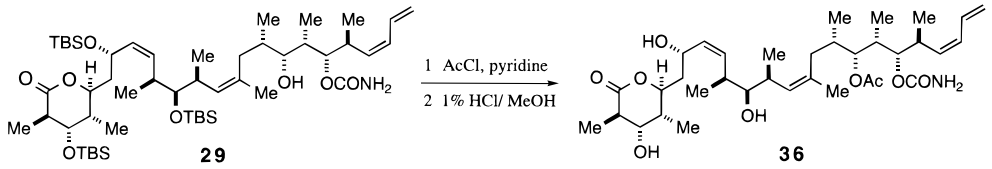
(53) (a) Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1981**, *22*, 127. (b) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.

(54) This boronate was synthesized by heating 5-hexyn-1-ol pivalate with 1.5 equiv of catecholborane overnight at 80 °C. After removal in vacuo of excess catecholborane, the product was sublimed at 160 °C, 0.5 mmHg. Miyaura, N.; Suginome, H.; Suzuki, A *Tetrahedron* **1983**, *39(20)* 3271.

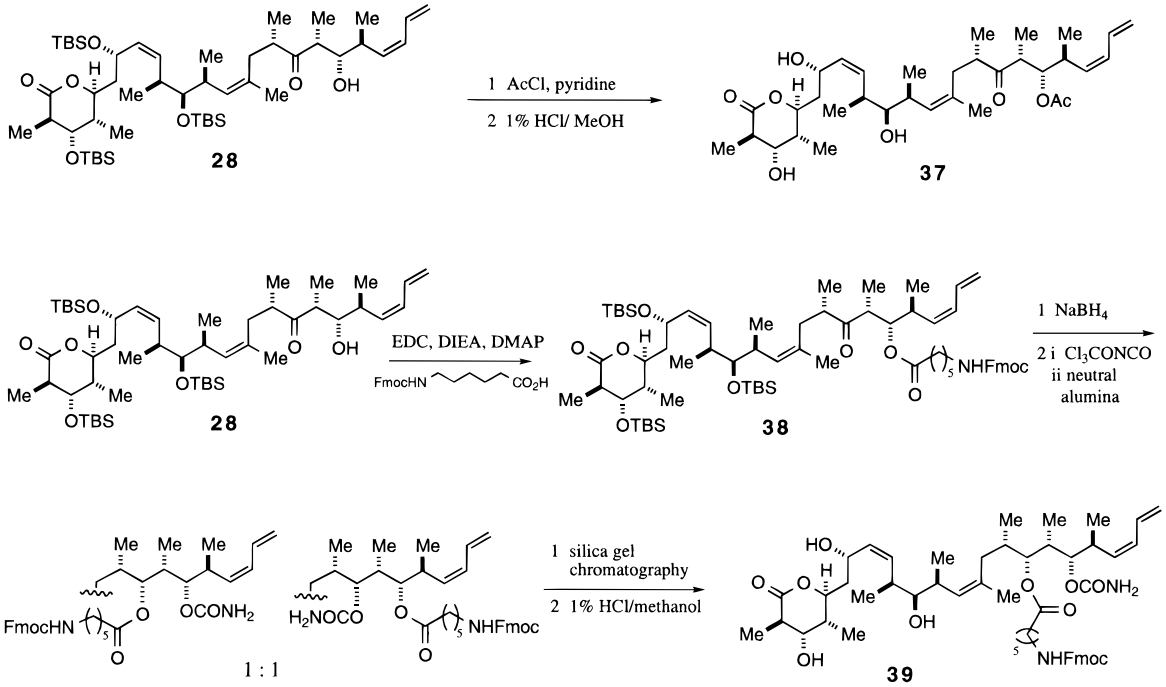
(55) Uenishi, J.; Beau, J. M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756.

(56) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.

**Scheme 11**




**Scheme 12**




In the synthesis of an actual binding probe, the ideal extension would contain a protected amine that could be easily deprotected and coupled to an activated ester. We altered the synthesis of **45** to replace the pivaloyl group with an extension to a terminal primary amine. In addition, the earlier observation that 16-desmethyl discodermolide **31** was just as active as discodermolide **1a** itself suggested that the absence of that methyl group would not be detrimental to the probe reagent. Omitting the methyl iodide alkylation step eliminated material loss obtained as the undesired epimer. Coupled product **46** was reduced with DIBAL-H at −78 °C to remove the pivaloyl group, with concomitant reduction of the C17 ketone. The stereoselectivity of the C17 reduction was inconsequential since it would be reoxidized in the Jones oxidation and selectively reduced in later steps. The diol was treated with *N,N*′-disuccinimidyl carbonate/DMAP[57] to provide selectively an intermediate mixed carbonate, which reacted with *N*-Aloc-1,6-hexanediamine to provide a carbamate.

The completion of the synthesis of this reagent mirrored that of natural discodermolide. Mercuric chloride hydrolysis of the thioacetal with subsequent Jones oxidation afforded lactone **47** in which the mixture of C17 alcohols had been reoxidized to the ketone. DDQ deprotection, carbamoylation, $LiAlH(OtBu)_3$ reduction, and deprotection afforded discodermolide variant **49** that could be coupled to a matrix or other affinity compound. When deprotected, the Aloc-carbamate would provide a terminal primary amine for coupling.

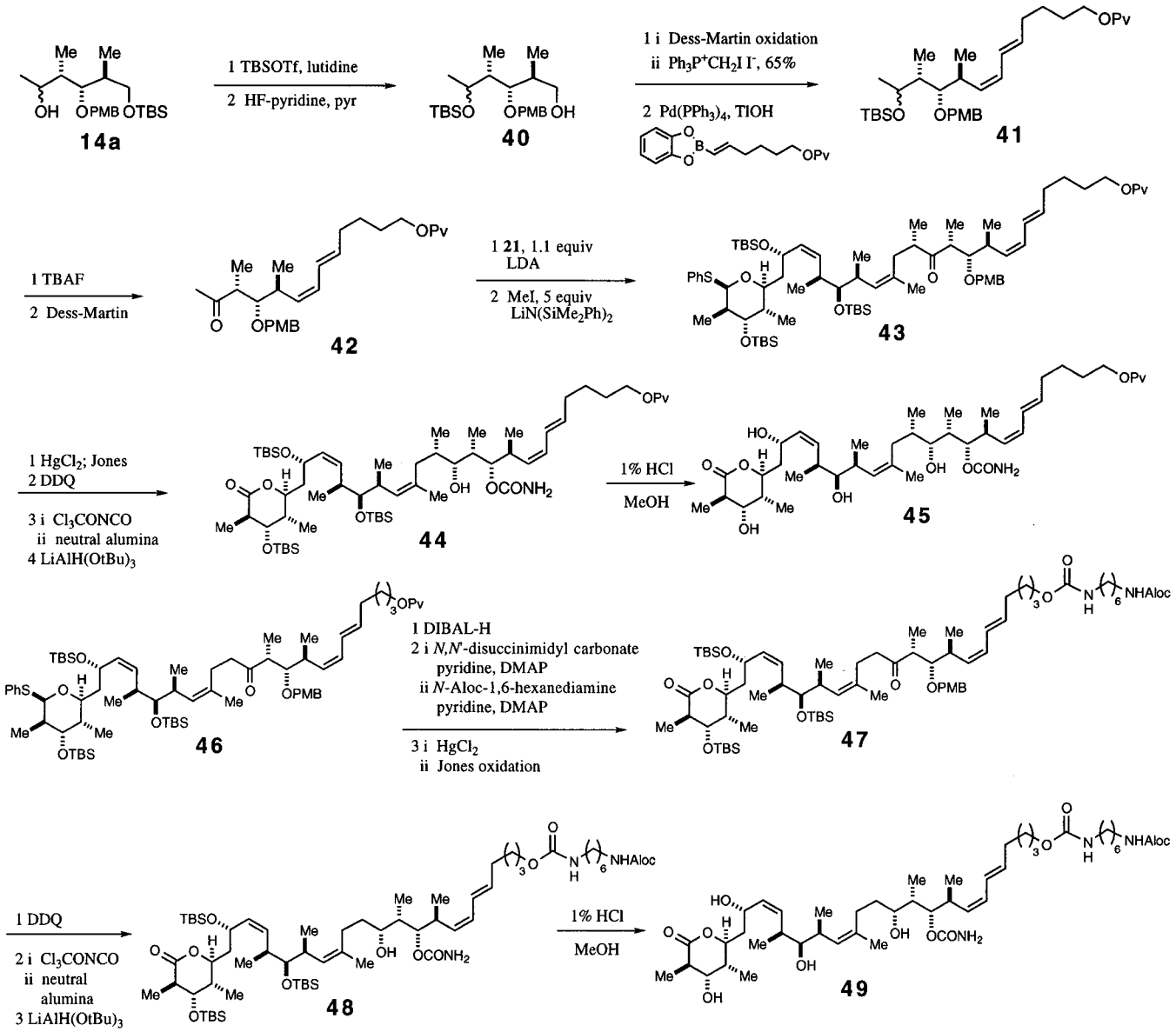
**Binding Reagent Based on Site D.** The lactone ring presented another region of the molecule that might be altered with minimal disturbance of conformation. Model studies on the feasibility of acylation or extension at the C3 hydroxyl demonstrated that a leaving group at C3 would be eliminated during the final deprotection step, affording the enone. A variant substituted at C1 in the lactol oxidation state, however, could be accessed fairly easily since the lactone is masked as a thiophenyl acetal until late in the total synthesis. Intermediate **27b** could be easily elaborated to variant **50a** in a manner analogous to the final elaboration of discodermolide, without the intervening thioacetal hydrolysis and Jones oxidation (Figure 6).

Both α and *β* thiophenyl anomers as well as the 16-desmethyl version of the *β* anomer were synthesized, affording **50a**, **50b**, and **51**, respectively, to examine differences in activity due to the stereochemistry at the anomeric center. The final deprotection of the α anomer was problematic, resulting in a 1:4 ratio of the desired product to the methyl acetal from methanolysis. In contrast, the *β* anomer resulted in a 9:1 ratio of desired to side product. The anomers however, were equally active *in vivo* in inhibiting proliferation as natural discodermolide. While these data were very encouraging, a concern is that this series of compounds may be intracellularly bioactivated, perhaps through enzyme-mediated hydrolysis of the thioacetal, and possibly even oxidation to the lactone. Nevertheless, this series of compounds was elaborated into binding reagents.

Exchange of the thiophenyl group to a different, amino-functionalized thiol to form another *S,O*-acetal was preferable to an *O,O*-acetal due to relative stability both to the deprotection and, potentially, *in vivo* conditions. On a model system corresponding to **10** (Scheme 2), protected amino-substituted thiophenols failed to react with the lactol or methyl acetal under the same conditions in which the thiophenyl group was installed (PhSTMS, $ZnI_2$, $Bu_4NI$).[13] Exchange to an alkanethiol, *N*-Aloc-

(57) Ghosh, A. K.; Duong, T. T.; McKee, S. P. *Tetahedron Lett.* **1992**, *33*, 2781.

**Scheme 13**




| Substrate | Product | $R_1$ | $R_2$ | $IC_{50}$ |
|---|---|---|---|---|
| **27b** | **50a** | β-PhS | *S*-Me | 6 nM |
| **27a** | **50b** | α-PhS | *S*-Me | 4 nM |
| **26b** | **51** | β-PhS | H | 4 nM |

(a) DDQ. (b) $Cl_3CONCO$; neutral alumina. (c) $LiAlH(OtBu)_3$. (d) 1% HCl, MeOH.

**Figure 6.** Elaboration of thiophenyl derivatives.

2-aminoethanethiol, however, could be effected with $MgBr_2 \cdot OEt_2$,[58] if the lactol had been previously converted to the acetate by acetyl chloride/pyridine. While the alkyl thioacetal was stable to deprotection conditions (1% HCl/MeOH) in the model system, it was completely hydrolyzed in the fully elaborated discodermolide intermediate.

To circumvent this hydrolysis problem, exchange to a linker could be done after the deprotection step. Studies in glycosylation chemistry have resulted in several methods for making *O,O*-acetals from thioacetals, including Nicoloau's NBS/4 Å sieves method[59] and Kahne's sulfoxide method.[60] The most reproducible method in our hands involved treating the thioacetal **51** with $HgCl_2$[38] in a 1:1 solution of alcohol, *N*-Aloc-2-aminoethanol, and THF[61] (Scheme 14). Deprotection of the Aloc group in **52** with $Pd(PPh_3)_4$ and dimedone[62] yielded a coupling reagent.

**Binding Reagent Based on Site E.** The last site for modification that seemed both accessible by our synthetic route and potentially suitable for binding was at C16. The late installation of the C16 methyl group offered the possibility of alkylating **26a** with an alkyl halide other than methyl iodide.

(58) (a) Park, J. H.; Kim, S. *Chem. Lett.* **1989**, 629. (b) Kim, S.; Park, J. H.; Lee, S. *Tetrahedron Lett.* **1989**, *30* (48), 6697.

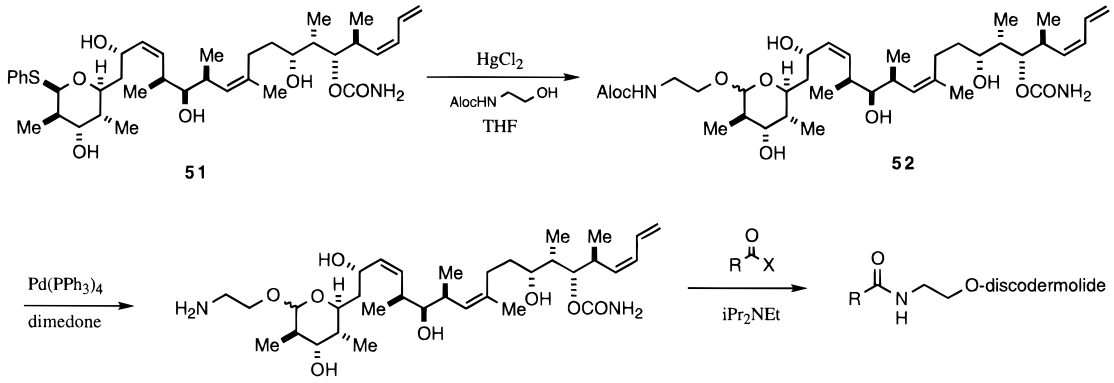
(59) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105* (8), 2430.

(60) Kahne, D.; Walker, S.; Chang, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

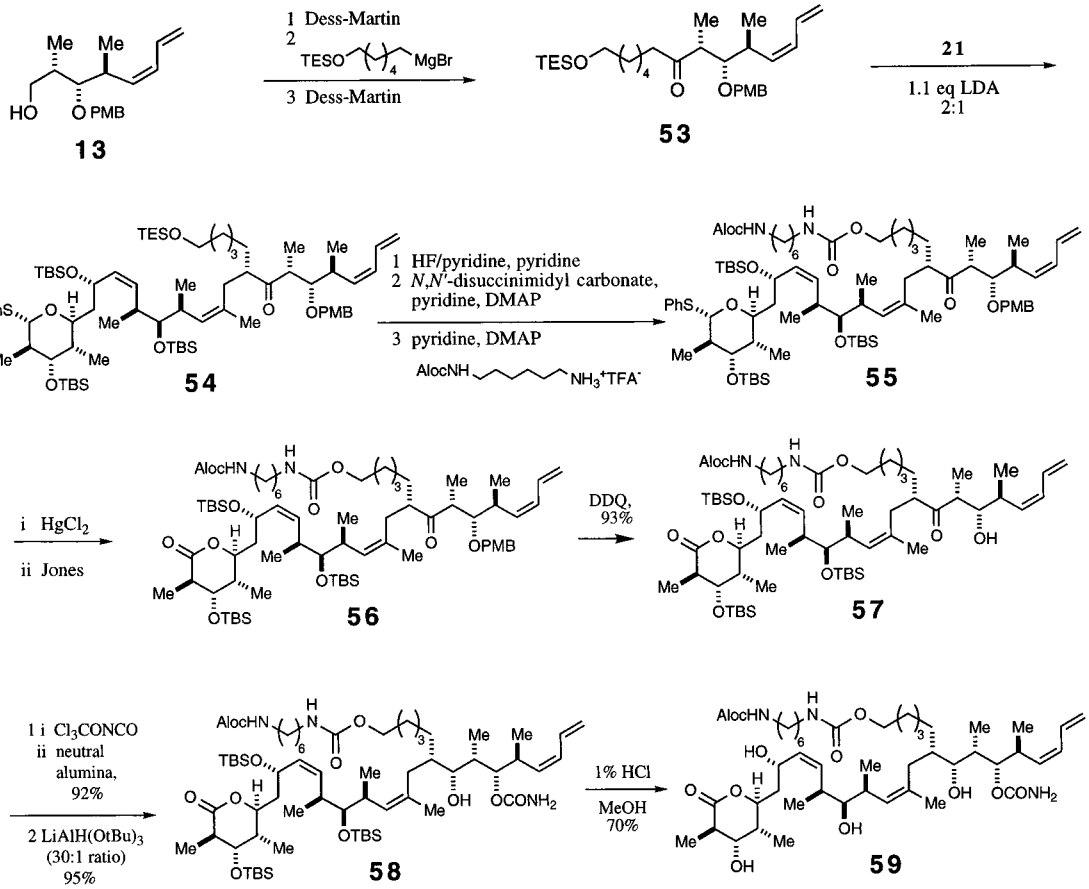
(61) The main side products recovered were lactols that were a mixture of stereoisomers at C2. This was presumably a result of some elimination to the pyran that was observed by mass spectrometry and nmr, to which water added on silica gel.

(62) Hayakawa, Y.; Kato, H.; Uchiyama, M.; Kajino, H.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 2400.

**Scheme 14**




**Scheme 15**




In addition, the result that 16-desmethyldiscodermolide **31** is no less active than natural discodermolide hinted at the possibility that no significant loss of binding is associated with the absence of this methyl group. If this is true, then the methyl group might not sit in a hydrophobic pocket, contributing to energy of binding, but instead, may be pointing out and away from the binding pocket of its receptor. We therefore undertook the synthesis of a substituted discodermolide at C16.

There were two possibilities for achieving this modification. The first, as previously mentioned, would involve the alkylation of **26a** with a substituted alkyl halide. However, even with an allylic bromide, alkylation at such a hindered site would be difficult. A recent study on the alkylation of an ethyl ketone analogous to **4b** with allyl iodide suggested an alternative method. Myles *et al.*[43] showed that using LDA as a base for formation of the enolate yielded a 2:1 ratio of desired to undesired methyl epimers. On the basis of this result, alkylation of ketone **53** with bromide **21** would probably afford **54** as the major product. The synthesis of ketone **53** required the addition of a terminally functionalized Grignard reagent to the primary aldehyde rather than methyl or ethyl magnesium bromide. A triethylsilyl (TES) protected alcohol was chosen as the functionality to be elaborated into a linker. 6-(Triethylsiloxy)hexyl magnesium bromide was the Grignard reagent of choice.

Alcohol **13** was oxidized with Dess−Martin periodinane, treated with 6-(triethylsiloxy)hexyl magnesium bromide, and reoxidized to afford ketone **53** (Scheme 15). Alkylation of this ketone with allylic bromide **21**, using LDA as the base, gave fully coupled **54**. Selective deprotection of the TES group with HF/pyridine buffered with excess pyridine, followed by treatment with *N,N′*-disuccinimidyl carbonate[56] and *N*-Aloc-1,6-hexanediamine, yielded **55**. Final elaboration in the manner analogous to discodermolide afforded compound **59**, which could be linked directly to a matrix or fluorescent reporter. Unfortunately, this compound proved to be completely inactive,

**Table 2.** $IC_{50}$ Values for Discodermolide Variants

| no. | | $IC_{50}$[a] (nM) | no. | | $IC_{50}$[a] (nM) |
|---|---|---|---|---|---|
| **1** | **1a** | 6 | **8** | **37** | |
| **2** | **31** | 10 | **9** | **45** | 70 |
| **3** | **1c** | 300 | **10** | **50a** | 6 |
| **4** | **1b** | | **11** | **50b** | 4 |
| **5** | **32** | | **12** | **51** | 4 |
| **6** | **35** | | **13** | **59** | |
| **7** | **36** | 70 | | | |

[a] $IC_{50}$ values were measured by a [$^3$H]thymidine incorporation assay using MG63 cells (Error ±5%).

suggesting that this site could not be altered without a deleterious effect on binding.

***In Vivo* Biological Activities of the Structural Variants.** The synthetic discodermolides were next examined for their potential as binding reagents. Three compounds have been synthesized that could serve to explore interactions with microtubules, namely compounds **39**, **49**, and **52**. Compounds **39** (C17 variant), **49** (C24 variant), and **52** (C1 variant) appeared promising on the basis of the *in vivo* activities of related compounds, **39** (70 nM), **45** (70 nM), and **51** (4 nM), respectively (Table 2). This potential was confirmed by testing the *in vivo* activities of the variants themselves, using a previously described binding assay,[46] and their respective $IC_{50}$ values were 80, 200, and 20 nM. Some concern exists regarding compound **52** due to the possibility that intracellular hydrolysis may account for its activity. This possibility will be examined by using the direct (*in vitro*) microtubule-binding assay using purified microtubules.[47] Compounds **39** and **49** now appear to be the best candidates for use as a binding reagent on the basis of their antiproliferative and competition activity. They provide an affinity-based approach for continued studies on the mechanism of discodermolide's action and for investigations of its ability to bind and stabilize microtubules.

## Experimental Section

**General Experimental Methods.** Optical rotations were recorded using a sodium lamp (589 nm, D line) at 20 °C; $^1$H and $^{13}$C NMR were recorded on a Bruker AM-500 (500 MHz) or AM-400 (400 MHz) spectrometer. Chemical shifts are reported using the solvent resonance internal standard (chloroform, 7.26 and 77.0 ppm). Low- and high-resonance mass spectra were obtained using fast atom bombardment (FAB) with NaI and *m*-nitrobenzyl alcohol (NBA) as a matrix. HPLC purification was accomplished on a Waters Model 510 HPLC using a Rainin Microsorb column, 10.0 × 250.0 mm.

Homoallylic alcohols **5** and **6** were the generous gifts of Hoffmann-LaRoche Co. All other chemical reagents were purchased from Aldrich Chemical Co., Fluka Chemical Corp., or Lancaster Chemical Co.

Compounds in Schemes 1, 2, and 4−9 were fully characterized as the corresponding enantiomer of the structures depicted in the schemes and are thus designated enant-# in the Experimental Section.

**(*E*)-(4*S*,5*S*,6*S*)-Methyl 7-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4,6-dimethyl-5-hydroxy-2-heptenoate (enant-7).** A solution of 432 mg (1.67 mmol) of olefin **5** in 60 mL of 3:1 methanol:dichloromethane containing 0.5 mL of pyridine was cooled to −78 °C and treated with a stream of ozone and oxygen until the colorless solution had been converted to a steel blue one. The solution was treated with 5 mL of dimethyl sulfide, the cooling bath removed, and the solution allowed to stir at ambient temperature for 3 h. The solution was concentrated to a volume of approximately 2 mL, diluted with 50 mL if hexanes, washed with 2 × 5 mL of water, and 1 × 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a colorless oil. This oil was dissolved in 10 mL of benzene, treated with 671 mg (2.01 mmol) of methyl (triphenylphosphoranylidene)acetate and allowed to stir at ambient temperature for 15 h. The pink solution was concentrated and chromatographed (10−15% EtOAc/hexane) to provide 452 mg (1.43 mmol, 86%) of enoate enant-**7**: IR (thin film/NaCl) 3800 (br), 1727 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.01 (dd, $J$ = 15.8, 8.3 Hz, 1H), 5.83 (d, $J$ = 15.8 Hz, 1H), 3.67 (s, 3H), 3.75−3.62 (m, 3H), 2.42 (m, 1H), 1.75 (m, 1H), 0.96 (d, $J$ = 6.9 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) 167.0, 152.3, 120.9, 77.2, 68.4, 51.2, 40.3, 36.4, 25.8, 18.1, 16.2, 9.5, −5.6, −5.7; HRMS (FAB, NBA/NaI) calcd for $C_{16}H_{32}O_4SiNa$ 339.1968, found 339.1967. Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.67; H, 10.19. $[\alpha]^{20}_D$ +22.8° (*c* 0.5, $CHCl_3$).

**(2*S*,4*S*,5*S*,6*R*)-4-[(Carbomethoxy)methyl]-6-[(1*S*)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-methylethyl]-5-methyl-2-phenyl-1,3-dioxane.** To a cooled (-20 °C) solution of 266 mg (0.84 mmol) of enoate enant-**7** in 8 mL of THF was added 86 μL (0.84 mmol) of freshly distilled benzaldehyde and 168 μL of KHMDS solution (0.5 M in toluene, 0.08 mmol). The yellow solution was stirred at −20 °C for 1 h when another aliquot of both reagents was added and again after another 1 h period. After a total reaction time of 3.5 h, the solution was quenched with 10 mL of saturated $NH_4Cl$ solution and extracted with 2 × 50 mL of EtOAc, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5−10% EtOAc/hexane) provided 251 mg (0.61 mmol, 73%) of benzylidene acetal: IR (thin film/NaCl) 1746 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.43−7.29 (m, 5H), 5.55 (s, 1H), 4.00 (td, $J$ = 9.6, 3.2 Hz, 1H), 3.70 (s, 3H), 3.74−3.66 (m, 3H), 3.48 (dd, $J$ = 9.5, 5.7 Hz, 1H), 2.72 (dd, $J$ = 15.4, 3.3 Hz, 1H), 2.56 (dd, $J$ = 15.4, 8.9 Hz, 1H), 1.99 (m, 1H), 1.73 (m, 1H), 0.89 (s, 9H), 0.88 (d, $J$ = 8.6 Hz, 3H), 0.81 (d, $J$ = 6.7 Hz, 3H), 0.03 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) 171.8, 138.9, 128.3, 127.9, 126.0, 100.0, 80.2, 79.1, 64.9, 51.6, 38.9, 36.6, 35.1, 25.9, 18.3, 11.7, 9.6, −5.3, −5.4; HRMS (FAB, NBA/NaI) calcd for $C_{23}H_{38}O_5SiNa$ 445.2386, found 445.2391; $[\alpha]^{20}_D$ −13.0° (*c* 0.5, $CHCl_3$).

**(2*S*,4*S*,5*S*,6*R*)-4-[(Carbomethoxy)methyl]-6-[(1*S*)-2-hydroxy-1-methylethyl]-5-methyl-2-phenyl-1,3-dioxane (enant-8).** To an ambient temperature solution of 750 mg (1.78 mmol) of silyl ether in 10 mL of THF was added 1.8 mL of HF-pyridine, and the solution was stirred for 15 min then quenched with 20 mL of saturated $NaHCO_3$ solution. This mixture was extracted with 3 × 75 mL of dichloromethane, dried over $MgSO_4$, filtered, and concentrated. Chromatography (33% EtOAc/hexane) provided 462 mg of alcohol enant-**8** (1.50 mmol, 83%) as a white solid: mp 105−107 °C; IR (thin film/NaCl) 3420 (br), 1740 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.40−7.28 (m, 5H), 5.58 (s, 1H), 3.99 (td, $J$ = 9.5, 3.3 Hz, 1H), 3.67 (s, 3H), 3.75−3.66 (m, 3H), 2.70 (dd, $J$ = 15.5, 3.3 Hz, 1H), 2.55 (dd, $J$ = 15.5, 8.8 Hz, 1H), 2.29−2.19 (br s, 1H), 1.98 (m, 1H), 0.97 (d, $J$ = 7.1 Hz, 3H), 0.80 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) 171.6, 138.4, 128.5, 128.0, 125.9, 100.1, 82.8, 79.0, 66.3, 51.6, 38.7, 35.7, 35.2, 11.5, 10.0; HRMS (FAB, NBA/NaI) calcd for $C_{17}H_{24}O_5Na$ 331.1521, found 331.1530. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 65.98; H, 7.79. $[\alpha]^{20}_D$ +10.4° (*c* 0.5, $CHCl_3$).

**Methyl [2*S*-(2α,3*β*,4*β*,5α)]-4-Hydroxytetrahydro-6-methoxy-3,5-dimethyl-2*H*-pyran-2-ethanoate (enant-9).** To an ambient temperature solution of 2.60 g (6.13 mmol) of Dess−Martin periodinane in 25 mL of dichloromethane was added a solution of 1.46 g (4.74 mmol) of alcohol **8** in 30 mL of dichloromethane (plus 2 × 5 mL rinses) *via* cannula over 5 min. After stirring 15 min, the mixture was diluted with 100 mL of ether and poured into a well-stirred mixture of 35 mL of 5% (w/w) $Na_2S_2O_3$ solution and 75 mL of saturated $NaHCO_3$ solution. This biphasic mixture was stirred 20 min until all solids had dissolved, then the layers were separated and the organic phase was washed with 2 × 20 mL of saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The resulting white solid was immediately dissolved in 40 mL of MeOH and treated with 1 g of Amberlyst 15 ion exchange resin at ambient temperature for 5 h. The reaction mixture was concentrated to a volume of approximately 10 mL, diluted with 75 mL of dichloromethane (plus 2 × 25 mL rinses), and decanted into a separatory funnel. The organic layers were washed with 2 × 25 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated to provide a colorless oil.

The above crude reaction mixture was dissolved in 30 mL of MeOH, treated with 1.65 g (7.11 mmol) of (1*S*)-(+)-10-camphorsulfonic acid, and stirred at ambient temperature for 4.5 d. The reaction was quenched by addition of 5 mL of triethylamine, concentrated, and chromatographed (15−30% EtOAc/hexane) to provide 569 mg of enant-**9a** and 311 mg of enant-**9b** (3.79 mmol, 80% from alcohol **8**). Data for enant-

**9a**: IR (thin film/NaCl) 3524 (br), 1744 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 4.49 (s, 1H), 4.07 (td, $J$ = 10.4, 2.7 Hz, 1H), 3.67 (s, 3H), 3.42 (s, 1H), 3.35 (s, 3H), 2.62 (dd, $J$ = 15.1, 2.7 Hz, 1H), 2.40 (dd, $J$ = 15.1, 10.1 Hz, 1H), 2.08 (m, 1H), 1.71 (m, 1H), 0.99 (d, $J$ = 7.4 Hz, 3H), 0.92 (d, $J$ = 6.8 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 172.1, 103.1, 73.7, 66.5, 55.1, 51.6, 38.6, 38.3, 34.0, 14.9, 13.9; HRMS (FAB, NBA/NaI) calcd for $C_{11}H_{20}O_5Na$ 255.1208, found 255.1201. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.97; H, 8.64. $[\alpha]^{20}_D$ +93.0° (*c* 1, $CHCl_3$). Data for enant-**9b**: IR (thin film/NaCl) 3501 (br), 1738 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 4.62 (d, $J$ = 2.4 Hz, 1H), 3.88 (td, $J$ = 9.9, 3.4 Hz, 1H), 3.55 (overlapping s, 4H), 3.28 (s, 3H), 2.52 (d, $J$ = 2.5 Hz, 1H), 2.46 (dd, $J$ = 15.1, 3.5 Hz, 1H), 2.34 (dd, $J$ = 15.1, 9.7 Hz, 1H), 1.87 (m, 1H), 1.62 (m, 1H), 0.81 (d, $J$ = 7.1 Hz, 3H), 0.78 (d, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 172.0, 100.8, 75.1, 72.5, 56.1, 51.3, 40.4, 38.5, 34.4, 12.6, 9.5; HRMS (FAB, NBA/NaI) calcd for $C_{11}H_{20}O_5Na$ 255.1208, found 255.1217; $[\alpha]^{20}_D$ +16.8° (*c* 0.6, $CHCl_3$).

**Methyl [2*S*-(2α,3*β*,4*β*,5α,6α)]-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]tetrahydro-6-methoxy-3,5-dimethyl-2*H*-pyran-2-ethanoate.** To a stirred solution of 311 mg (1.34 mmol) of alcohol enant-**9a** in 10 mL of dichloromethane at ambient temperature was added 624 $\mu$L (574 mg, 5.36 mmol) of 2,6-lutidine followed by 616 $\mu$L (709 mg, 2.68 mmol) of TBSOTf. After stirring for 20 min, the solution was concentrated and chromatographed to provide 460 mg (1.33 mmol, 99%) of silyl ether: IR (thin film/NaCl) 1748 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 4.32 (d, $J$ = 2.2 Hz, 1H), 4.18 (td, $J$ = 9.7, 3.4 Hz, 1H), 3.67 (s, 3H), 3.50 (t, $J$ = 4.0 Hz, 1H), 3.25 (s, 3H), 2.54 (dd, $J$ = 14.6, 3.4 Hz, 1H), 2.38 (dd, $J$ = 14.6, 10.1 Hz, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 0.95 (d, $J$ = 7.4 Hz, 3H), 0.88 (s, 9H), 0.82 (d, $J$ = 6.9 Hz, 3H), 0.02 (s, 3H), −0.02 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 172.2, 103.2, 73.3, 67.6, 54.7, 51.5, 39.0, 38.7, 35.9, 25.7, 18.1, 15.5, 13.6, −4.6, −4.8; HRMS (FAB, NBA/NaI) calcd for $C_{17}H_{34}O_5SiNa$ 369.2073, found 369.2083; $[\alpha]^{20}_D$ +60.2° (*c* 0.5, $CHCl_3$).

**Methyl [2*S*-(2α,3*β*,4*β*,5α,6*β*)]-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]tetrahydro-6-methoxy-3,5-dimethyl-2*H*-pyran-2-ethanoate.** The silyl ether of enant-**9b** was prepared in a manner identical to that of enant-**9a**, providing it as a colorless oil (90% yield): IR (thin film/NaCl) 1746 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 4.69 (d, $J$ = 2.4 Hz, 1H), 3.94 (td, $J$ = 9.9, 3.5 Hz, 1H), 3.67 (s, 3H), 3.60 (t, $J$ = 2.7 Hz, 1H), 3.40 (s, 3H), 2.55 (dd, $J$ = 15.0, 3.5 Hz, 1H), 2.43 (dd, $J$ = 15.0, 9.6 Hz, 1H), 1.88 (m, 1H), 1.69 (m, 1H), 0.90 (d, $J$ = 7.3 Hz, 3H), 0.90 (s, 9H), 0.79 (d, $J$ = 6.9 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 171.6, 100.8, 76.2, 72.6, 56.0, 51.1, 47.8, 38.4, 34.8, 25.6, 17.8, 13.3, 9.5, −4.8, −5.2; HRMS (FAB, NBA/NaI) calcd for $C_{17}H_{34}O_5SiNa$ 369.2073, found 369.2072; $[\alpha]^{20}_D$ −3.8° (*c* 0.5, $CHCl_3$).

**[2*S*-(2α,3*β*,4*β*,5α,6α)]-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-tetrahydro-*N*,6-dimethoxy-*N*,3,5-trimethyl-2*H*-pyran-2-ethanamide.** *N*,*O*-Dimethylhydroxylamine was prepared as follows: 24.3 g (250 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride was suspended in 100 mL of ethylene glycol, and 41 mL (310 mmol) of triethanolamine was added. A short-path distilling head was affixed to the flask, the resulting thick slurry heated to reflux, and 11.6 g (190 mmol, 76%) of the free amine collected (bp 47−50 °C).

To a solution of 709 mg (2.05 mmol) of ester in 20 mL of 4:1:1 THF:MeOH:$H_2O$ at ambient temperature was added 85 mg (3.54 mmol) of LiOH, and the resulting yellow solution was stirred for 5 h when the reaction was quenched with 1 N HCl until its yellow color was returned to colorless (approximately 4 mL). The solution was diluted with 100 mL of EtOAc, dried with $MgSO_4$, filtered, and concentrated. The resulting viscous oil was dissolved in 4 mL of dichloromethane, treated successively with 137 mg (2.25 mmol) of *N*,*O*-dimethylhydroxylamine, 314 mg (2.05 mmol) of 1-hydroxybenzotriazole hydrate, and 285 $\mu$L (207 mg, 2.05 mmol) of triethylamine, then cooled to 0 °C, and finally treated with 422 mg (2.05 mmol) of 1,3-dicyclohexylcarbodiimide. The resulting white slurry was warmed to ambient temperature and stirred for 10 h, then concentrated and chromatographed (25% EtOAc/hexane) to provide 669 mg (1.78 mmol, 87% from ester) of amide: IR (thin film/NaCl) 1669 $cm^{-1}$; $^1H$ NMR (125 MHz, $CDCl_3$) 4.30 (d, $J$ = 2.7 Hz, 1H), 4.24 (td, $J$ = 9.4, 3.4 Hz, 1H), 3.69 (s, 3H), 3.51 (t, $J$ = 4.4 Hz, 1H), 3.27 (s, 3H), 3.17 (s, 3H), 3.65 (br m, 1H), 2.52 (dd, $J$ = 14.5, 2.9 Hz, 1H), 1.82 (m, 1H), 1.78 (m, 1H), 0.95 (d, $J$ = 7.3 Hz, 3H), 0.87 (s, 9H), 0.84 (d, $J$ = 6.9 Hz, 3H), 0.02 (s, 3H), −0.02 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) carbonyl too broad to detect, 103.3, 73.3, 67.8, 61.2, 54.8, 38.8, 36.3, 36.0, 25.8, 18.1, 15.5, 13.5, −4.6, −4.8; HRMS (FAB, NBA/NaI) calcd for $C_{18}H_{37}O_5NSiNa$ 398.2339, found 398.2350. Anal. Calcd for $C_{18}H_{37}O_5NSi$: C, 57.56; H, 9.93; N, 3.73. Found: C, 57.55; H, 9.95; N, 3.68. $[\alpha]^{20}_D$ +23.1° (*c* 0.7, $CHCl_3$).

**[2*S*-(2α,3*β*,4*β*,5α,6*β*)]-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-tetrahydro-*N*,6-dimethoxy-*N*,3,5-trimethyl-2*H*-pyran-2-ethanamide.** Amide was prepared in a manner identical to that of its anomer, providing it as a colorless oil (85% yield): IR (thin film/NaCl)1665 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 4.58 (d, $J$ = 2.3 Hz, 1H), 3.92 (td, $J$ = 9.9, 3.2 Hz, 1H), 3.58 (s, 3H), 3.49 (t, $J$ = 2.7 Hz, 1H), 3.27 (s, 3H), 3.05 (s, 3H), 2.65 (br m, 1H), 2.35 (dd, $J$ = 14.9, 3.2 Hz, 1H), 1.75 (m, 1H), 1.59 (m, 1H), 0.77 (d, $J$ = 9.5 Hz, 3H), 0.77 (s, 9H), 0.70 (d, $J$ = 6.8 Hz, 3H), −0.08 (s, 3H), −0.10 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 172.1, 100.6, 76.4, 72.6, 60.9, 56.1, 40.7, 35.5, 35.0, 25.6, 17.8, 13.4, 9.5, −4.8, −5.1; HRMS (FAB, NBA/NaI) calcd for $C_{18}H_{37}O_5NSiNa$ 398.2339, found 398.2360; $[\alpha]^{20}_D$ −9.6° (*c* 0.5, $CHCl_3$).

**[2*S*-(2α,3*β*,4*β*,5α)]-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-tetrahydro-*N*-methoxy-6-thiophenyl-*N*,3,5-trimethyl-2*H*-pyran-2-ethanamide (enant-10a and enant-10b).** To a solution of 1.02 g (2.72 mmol) of a mixture of methyl anomers in 25 mL of dichloromethane were successively added 2.60 g (8.14 mmol) of zinc iodide, 1.20 g (3.24 mmol) of tetrabutylammonium iodide, and 2.58 mL (2.48 g, 13.60 mmol) of (phenylthio)trimethylsilane, and the solution was heated to reflux for 2 h. The reaction was cooled to ambient temperature, poured over 100 mL of hexanes plus 20 mL of saturated barium hydroxide solution. The layers were separated, and the organic layer was washed with 2 × 25 mL of saturated barium hydroxide solution. The combined aqueous layers were extracted with 50 mL of hexanes and the organic layers combined, dried over $MgSO_4$, filtered, and concentrated. Chromatography (7−10−15% EtOAc/hexane) provided 370 mg of enant-**10b** as a white solid and 712 mg of enant-**10a** (2.38 mmol combined, 88%). Data for enant-**10b**: mp 90−92 °C; IR (thin film/NaCl) 1659 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 7.36−7.11 (m, 5H), 5.38 (d, $J$ = 2.1 Hz, 1H), 4.11 (td, $J$ = 10.1, 3.0 Hz, 1H), 3.62 (s, 1H), 3.61 (s, 3H), 3.09 (s, 3H), 2.79 (br m, 1H), 2.40 (dd, $J$ = 14.4, 3.0 Hz, 1H), 2.00 (m, 1H), 1.79 (m, 1H), 1.09 (d, $J$ = 7.1 Hz, 3H), 0.86 (s, 9H), 0.84 (d, $J$ = 7.0 Hz, 3H), 0.03 (s, 3H), 0.01 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 172.0, 136.2, 128.8, 128.6, 125.8, 83.3, 76.2, 75.7, 61.1, 41.7, 35.7, 34.8, 31.8, 25.8, 18.0, 14.0, 11.7, −4.6, −4.9; HRMS (FAB, NBA/NaI) calcd for $C_{23}H_{39}O_4NSiSNa$ 476.2267, found 476.2272; $[\alpha]^{20}_D$ −25.8° (*c* 0.5, $CHCl_3$). Data for enant-**10a**: IR (thin film/NaCl) 1663 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 7.44−7.11 (m, 5H), 5.11 (s, 1H), 4.67 (td, $J$ = 9.5, 3.4 Hz, 1H), 3.60 (s, 3H), 3.58 (t, $J$ = 3.3 Hz, 1H), 3.08 (s, 3H), 2.66 (br m, 1H), 2.60 (br m, 1H), 2.14 (m, 1H), 1.90 (m, 1H), 1.12 (d, $J$ = 7.3 Hz, 3H), 0.97 (s, 9H), 0.89 (d, $J$ = 6.9 Hz, 3H), 0.11 (s, 3H), 0.05 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 172.2, 138.7, 130.9, 128.4, 126.1, 89.0, 74.1, 68.2, 61.1, 41.5, 36.1, 35.7, 31.9, 26.1, 18.2, 17.6, 14.0, −4.1, −4.9; HRMS (FAB, NBA/NaI) calcd for $C_{23}H_{39}O_4NSiSNa$ 476.2267, found 476.2281. Anal. Calcd: C, 60.89; H, 8.66; N, 3.09. Found: C, 60.79; H, 8.71; N, 3.02. $[\alpha]^{20}_D$ +145.5° (*c* 0.4, $CHCl_3$).

**[2*S*-(2α,3*β*,4*β*,5α,6α)]-4-[(*tert*-Butylsilyl)oxy]tetrahydro-*N*-methoxy-6-(thiophenyl)-*N*,3,5-trimethyl-2*H*-pyran-2-ethanal (enant-2).** To a cooled (0 °C) solution of 297 mg (0.66 mmol) of amide in 5 mL of THF was added 820 $\mu$L (0.82 mmol) of 1 M $LiAlH_4$ solution in THF, and the solution was stirred at 0 °C for 10 min when the reaction was quenched with 2 mL of 0.28 M $NaHSO_4$ solution. The mixture was warmed to room temperature, diluted with 50 mL of EtOAc, washed with 2 × 10 mL of 1 N HCl and 1 × 10 mL of brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed (5% EtOAc/hexane) to provide 227 mg (0.58 mmol, 88%) of aldehyde enant-**2** as a colorless oil which solidified on standing in a −20 °C freezer to a white powder: mp 36−38 °C; IR (thin film/NaCl) 1728, $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 9.64 (dd, $J$ = 4.0, 1.4 Hz, 1H), 7.38 (dd, $J$ = 8.5, 1.4 Hz, 2H), 7.22 (t, $J$ = 7.4 Hz, 2H), 7.15 (t, $J$ = 7.4 Hz, 1H), 5.21 (s, 1H), 4.76 (td, $J$ = 9.9, 3.3 Hz, 1H), 3.60 (t, $J$ = 2.7 Hz, 1H), 2.58 (ddd, $J$ = 15.6, 3.3, 1.4 Hz, 1H), 2.41 (ddd, $J$ = 15.6, 9.7, 4.0 Hz, 1H), 2.20 (m, 1H), 1.84 (m, 1H), 1.14 (d, $J$ = 7.3 Hz, 3H), 1.00 (s,

9H), 0.86 (d, $J$ = 6.9 Hz, 3H), 0.13 (s, 3H), 0.07 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) 202.1, 138.6, 129.7, 128.7, 126.2, 88.7, 73.8, 66.3, 46.5, 41.8, 35.3, 26.2, 18.3, 17.7, 14.0, −4.0, −4.9; HRMS (FAB, NBA/NaI) calcd for $C_{21}H_{34}O_3SiSNa$ 417.1896, found 417.1919; $[\alpha]^{20}_D$ +201.6° (*c* 0.5, $CHCl_3$).

**(3*S*,4*R*,5*S*)-4,6-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,5-dimethyl-1-hexene.** To a cooled (0 °C) solution of 1.50 g (5.81 mmol) of homoallylic alcohol enant-**6** in 20 mL of dichloromethane was added 1.60 mL (1.16 g, 11.6 mmol) of triethylamine followed by 2.00 mL (2.30 g, 8.70 mmol) of TBSOTf, and the solution was stirred for 30 min when 25 mL of brine was added. The mixture warmed to ambient temperature and extracted with 3 × 50 mL of dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and chromatographed (1% EtOAc/hexane) to provide 2.01 g (5.40 mmol, 93%) of the silyl ether as a colorless oil: IR (thin film/NaCl) 2959, 2930 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 5.80 (ddd, $J$ = 17.5, 10.3, 7.5 Hz, 1H), 4.94 (m, 2H), 3.68 (dd, $J$ = 9.8, 5.2 Hz, 1H), 3.50 (t, $J$ = 5.1 Hz, 1H), 3.36 (dd, $J$ = 9.8, 7.7 Hz, 1H), 2.35 (m, 1H), 1.80 (m, 1H), 0.96 (d, $J$ = 6.8 Hz, 3H), 0.89 (d, $J$ = 6.9 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) 143.0, 113.5, 77.6, 65.3, 41.4, 40.6, 26.2, 26.0, 18.4, 18.3, 15.3, 14.3, −3.7, −4.0, −5.2, −5.3; HRMS (FAB, NBA/NaI) calcd for $C_{20}H_{45}O_2Si_2$ 373.2958, found 373.2947. Anal. Calcd for $C_{20}H_{44}O_2Si_2$: C, 64.45; H, 11.90. Found: C, 64.40; H, 11.88. $[\alpha]^{20}_D$ +21.0° (*c* 0.5, $CHCl_3$).

***(Z)*-(4*S*,5*R*,6*S*)-Methyl 5,7-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]2,4,6-trimethyl-2-heptenoate.** A solution of 1.0 g (2.69 mmol) of olefin in 50 mL of 3:1 methanol:dichloromethane containing 1 mL of pyridine was cooled to −78 °C and treated with a stream of ozone and oxygen until the colorless solution had been converted to a steel blue one. The solution was treated with 10 mL of dimethyl sulfide, the cooling bath removed, and the solution allowed to stir at ambient temperature for 12 h. The solution was concentrated to a volume of approximately 2 mL, diluted with 100 mL of EtOAc, washed with 2 × 25 mL of water and 1 × 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a colorless oil.

To a cooled (−78 °C) solution of 1.43 g (4.30 mmol) of ($F_3$-$CCH_2O$)$POCH(CH_3)CO_2Me$ and 1.42 g (5.37 mmol) of 18-crown-6 in 10 mL of THF was added 7.10 mL (4.30 mmol) of a 0.6 M KHMDS solution in toluene. The resulting dark red solution was stirred for 10 min and then treated with the above prepared aldehyde in 5 mL of THF (plus a 1 mL rinse) *via* cannula, and the −78 °C bath was replaced with a 0 °C bath and the reaction stirred for 5 h. The reaction was quenched by addition of 15 mL of saturated $NH_4Cl$ solution and extracted into 2 × 50 mL of hexane. The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and chromatographed (1% EtOAc/hexane) to provide 1.11 g (2.50 mmol, 93% from the olefin) of ester: IR (thin film/NaCl) 1721 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 5.85 (dd, $J$ = 10.1, 1.1 Hz, 1H), 3.72 (s, 3H), 3.62 (dd, $J$ = 9.8, 5.2 Hz, 1H), 3.57 (dd, $J$ = 5.8, 4.9 Hz, 1H), 3.38 (dd, $J$ = 9.7, 7.5 Hz, 1H), 3.32 (m, 1H), 1.88 (d, $J$ = 0.8 Hz, 3H), 1.77 (m, 1H), 0.96 (d, $J$ = 6.7 Hz, 3H), 0.90 (d, $J$ = 10.0 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 6H), 0.00 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) 168.3, 147.6, 125.0, 76.9, 65.3, 51.2, 41.1, 36.1, 26.1, 26.0, 20.8, 18.4, 18.3, 15.1, 13.5, −3.9, −4.0, −5.3, −5.4; HRMS (FAB, NBA/NaI) calcd for $C_{23}H_{48}O_4Si_2Na$ 467.2989, found 467.2975. Anal. Calcd for $C_{23}H_{48}O_4Si_2$: C, 62.11; H, 10.88. Found: C, 62.17; H, 10.84. $[\alpha]^{20}_D$ −22.0° (*c* 0.5, $CHCl_3$).

***(Z)*-(4*S*,5*R*,6*S*)-5,7-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6-trimethyl-2-hepten-1-ol (enant-11).** To a cooled (0 °C) solution of 2.15 g (4.84 mmol) of ester in 82 mL of THF is added 6.13 mL (6.13 mmol) of 1 M $LiAlH_4$ solution in THF, dropwise over 5 min. After being stirred for 30 min, the solution was diluted with 100 mL of ether, quenched with 3 mL of saturated $NH_4Cl$ solution, warmed to ambient temperature, and dried over $Na_2SO_4$. The mixture was filtered over $MgSO_4$, concentrated and chromatographed (5% EtOAc/hexane) to provide 1.86 g (4.47 mmol, 92%) of alcohol enant-**11**: IR (thin film/NaCl) 3343 (br) cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 5.12 (d, $J$ = 10.1 Hz, 1H), 4.15 (d, $J$ = 11.8 Hz, 1H), 3.96 (d, $J$ = 11.8 Hz, 1H), 3.70 (dd, $J$ = 10.0, 5.4 Hz, 1H), 3.40−3.33 (m, 2H), 2.66 (m, 1H), 1.85 (m, 1H), 1.77 (s, 3H), 0.91 (d, $J$ = 6.7 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.85 (d, $J$ = 6.9 Hz, 3H), 0.02 (s, 12H); $^{13}$C NMR (125 MHz, $CDCl_3$) 133.4, 132.9, 78.4, 65.5, 61.8, 40.5, 35.7, 26.2, 26.0, 21.6, 18.4, 18.4, 17.4, 14.6, −3.9 (2), −5.3, −5.4; HRMS (FAB, NBA/NaI) calcd for $C_{22}H_{48}O_3Si_2Na$ 439.3040, found 439.3049. Anal. Calcd: C, 63.40; H, 11.61. Found: C, 63.47; H, 11.54. $[\alpha]^{20}_D$ +14.6° (*c* 0.5, $CHCl_3$).

**(2*R*,3*S*,4*R*)-2,4-Dimethyl-1-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3-[(4-methoxyphenyl)methoxy]hex-5-ene.** To 25 g (180 mmol) of 4-methoxybenzyl alcohol was added 20 mL of 48% HBr, and the mixture was stirred at ambient temperature for 30 min. The reaction mixture was diluted with 100 mL of diethyl ether, the layers were separated, and the organic layer was washed with 3 × 30 mL of saturated $NaHCO_3$ solution. The organic layer was dried over $K_2CO_3$, filtered, concentrated *in vacuo*, and distilled under high vacuum to afford a colorless oil that was used in the following reaction,

To a cooled (0 °C) suspension of 2.3 g (58 mmol, 60% suspension in oil and washed in hexanes) of NaH in 10 mL of THF were added 10 mL of distilled DMF, a solution of 5.0 g (19 mmol) of **5** in 10 mL of THF, and 8.68 mL (48 mmol) of PMBBr. After being stirred at ambient temperature for 48 h, the reaction mixture was poured into 100 mL of 10xPBS buffer and diluted with 150 mL of diethyl ether. The organic layer was washed 3 × 100 mL of 10xPBS buffer, dried over $K_2CO_3$, filtered, concentrated *in vacuo*, and chromatographed to provide 6.4 g (18 mmol, 93%) of the PMB ether as a colorless oil: IR (thin film/NaCl) 2957, 1614 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.28 (d, $J$ = 8.7 Hz, 2H), 6.88 (d, $J$ = 8.6 Hz, 2H), 5.96 (ddd, $J$ = 7.9, 10.3, 17.4 Hz, 1H), 5.09 (ddd, $J$ = 1.1, 1.9, 17.2 Hz, 1H), 5.03 (ddd, $J$ = 0.7, 1.9, 10.3 Hz, 1H), 4.55 (d, $J$ = 10.8 Hz, 1H), 4.47 (d, $J$ = 10.7 Hz, 1H), 3.81 (s, 3H), 3.56 (dd, $J$ = 7.2, 9.8 Hz, 1H), 3.49 (dd, $J$ = 6.0, 9.8 Hz, 1H), 3.39 (dd, $J$ = 3.9, 6.9 Hz, 1H), 2.49 (ddd, $J$ = 6.8, 7.6, 13.8 Hz, 1H), 1.89 (m 1), 1.04 (d, $J$ = 6.9 Hz, 3H), 0.93 (s, 9H), 0.92 (d, $J$ = 6.9 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.0, 142.1, 141.9, 129.2, 114.0, 113.6, 82.8, 74.1, 65.7, 55.2, 41.0, 38.4, 26.1, 25.9, 18.2, 17.1, 11.3, −5.4; HRMS (CI) *m/z* calcd for $C_{22}H_{38}O_3Si$ 378.2588, found 378.2590; $[\alpha]^{20}_D$ +17.2° (*c* 0.5, $CHCl_3$).

***(Z)*-(3*S*,4*S*,5*R*)-3,5-Dimethyl-6-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-1-iodo-4-[(4-methoxyphenyl)methoxy]-hex-1-ene (12).** To a cooled (−78 °C) solution of 2.5 g (6.6 mmol) of olefin in 80 mL of 3:1 MeOH:$CH_2Cl_2$ containing 1 mL of pyridine and one drop of Sudan III solution was bubbled a stream of ozone until the pink solution became colorless. The solution was treated wtih 15 mL of dimethyl sulfide and then warmed to ambient temperature for 2 h. The solution was concentrated *in vacuo*, diluted with 50 mL of hexanes, washed with 3 × 10 mL of $H_2O$ and 1 × 10 mL of brine, dried over $MgSO_4$, concentrated *in vacuo*, and used crude in the following reaction.

To a suspension of 5.37 mg (10.1 mmol) of (iodomethyl)triphenylphosphonium iodide in 20 mL of THF was added 10.1 mL (10.1 mmol, 1 M in THF) of NaHMDS, and the slurry was stirred for 20 min at ambient temperature. After the dark red mixture was cooled to −78 °C, 3.5 mL of HMPA was added, followed by the crude aldehyde in 5 mL of THF. After the reaction mixture was warmed to ambient temperature, the reaction was stirred for 1 h before being diluted with hexanes, filtered through 100 g of silica gel, concentrated *in vacuo*, and chromatographed (3% EtOAc/hexanes) to provide 2.49 (5.0 mmol, 75%) of **12** as a colorless oil: IR (thin film/NaCl) 3744, 1612 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.29 (d, $J$ = 8.7 Hz, 2H), 6.88 (d, $J$ = 8.7 Hz, 2H), 6.27 (dd, $J$ = 7.4, 9.1 Hz, 1H), 6.17 (d, $J$ = 7.4 Hz, 1H), 4.54 (s, 2H), 3.81 (s, 3H), 3.53 (dd, $J$ = 1.7, 5.8 Hz, 2H), 3.48 (dd, $J$ = 4.6, 5.6 Hz, 1H), 2.81 (ddd, $J$ = 2.5, 4.7, 7.0 Hz, 1H), 1.79 (dd, $J$ = 5.8, 6.8 Hz, 1H), 1.06 (d, $J$ = 7.0 Hz, 3H), 1.00 (d, $J$ = 6.9 Hz, 3H), 0.93 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.0, 143.8, 131.2, 129.2, 113.6, 82.7, 81.6, 74.4, 65.3, 55.2, 42.7, 39.3, 25.9, 18.2, 17.1, 12.7, −5.2, −5.3, −5.4; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{22}H_{37}IO_3SiNa$ 527.1454, found 527.1454; $[\alpha]^{20}_D$ +52.4° (*c* 0.5, $CHCl_3$).

***(Z)*-(2*R*,3*S*,4*S*)-2,4-Dimethyl-1-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3-[(4-methoxyphenyl)methoxy]-5,7-octadiene.** To a suspension of 5.28 g (23.5 mmol) of $ZnBr_2$ in 10 mL of THF was added 23.5 mL (23.5 mmol, 1 M in THF) of vinylmagnesium bromide, and the slurry was stirred for 15 min at ambient temperature. After the reaction mixture was cooled to 0 °C, a solution of 2.96 g (5.9 mmol) of **12** in 10 mL of THF was added, followed by 678 mg (590 $\mu$mol) of Pd($PPh_3$)$_4$ in 25 mL of THF. After being stirred at room temperature for

24 h, the reaction was quenched by the addition to 30 mL of saturated $NH_4Cl$ solution and extracted into 3 × 25 mL of hexanes. The organic layers were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (2% EtOAc/hexanes) to provide 1.9 g (4.7 mmol, 80%) of diene as a colorless oil: IR (thin film/NaCl) 1614, 1514 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.4 (d, $J$ = 8.6 Hz, 2H), 6.85 (d, $J$ = 8.6 Hz, 2H), 6.65 (ddd, $J$ = 10.3, 16.1, 20.5 Hz, 1H), 6.01 (apparent t, $J$ = 10.9 Hz, 1H), 5.51 (apparent t, $J$ = 10.4 Hz, 1H), 5.18 (dd, $J$ = 1.9, 16.9 Hz, 1H), 5.08 (d, $J$ = 10.1 Hz, 1H), 4.53 (d, $J$ = 10.6 Hz, 1H), 4.44 (d, $J$ = 10.7 Hz, 1H), 3.80 (s, 3H), 3.52 (dd, $J$ = 6.8, 9.8 Hz, 1H), 3.44 (dd, $J$ = 6.1, 9.9 Hz, 1H), 3.38 (dd, $J$ = 4.4, 6.1 Hz, 1H), 2.93 (ddd, $J$ = 6.7, 10.0, 13.3 Hz, 1H), 1.83 (ddd, $J$ = 2.1, 6.5, 8.6 Hz, 1H), 1.00 (d, $J$ = 6.9 Hz, 3H), .092 (d, $J$ = 6.9 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 158.9, 135.9, 132.7, 131.5, 129.3, 128.9, 117.0, 113.6, 83.0, 74.4, 65.6, 55.2, 38.7, 35.6, 25.9, 18.4, 18.3, 11.6, −5.3, −5.4; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{24}H_{40}O_3SiNa$ 427.2642, found 427.2644; $[\alpha]^{20}_D$ +45.0° (*c* 0.5, $CHCl_3$).

**(*Z*)-(2*R*,3*S*,4*S*)-2,4-Dimethyl-3-[(4-methoxyphenyl)methoxy]-5,7-octadien-1-ol (13).** To a solution of 1.5 g (3.7 mmol) of silyl ether in 8 mL of THF was added 1 mL of $H_2O$ and then 1 mL of TFA. After being stirred at ambient temperature for 8 h, the reaction was quenched with 10 mL of saturated $NaHCO_3$ solution and extracted into 3 × 20 mL of EtOAc. The organic layers were combined, dried over $K_2CO_3$, filtered, concentrated *in vacuo*, and chromatographed (35% EtOAc/hexanes) to provide 870 mg (3.3 mmol, 88%) of **13** as a colorless oil: IR (thin film/NaCl) 3393, 1612 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.26 (d, $J$ = 8.6 Hz, 2H), 6.86 (d, $J$ = 8.7 Hz, 2H), 6.69 (ddd, $J$ = 10.8, 16.7, 18.4 Hz, 1H), 6.05 (apparent t, $J$ = 11.0 Hz, 1H), 5.55 (apparent t, $J$ = 10.4 Hz, 1H), 5.22 (dd, $J$ = 1.8, 16.8 Hz, 1H), 5.12 (d, $J$ = 10.2 Hz, 1H), 4.58 (d, $J$ = 10.7 Hz, 1H), 4.47 (d, $J$ = 10.7 Hz, 1H), 3.77 (s, 3H), 3.59 (m, 1H), 3.50 (dd, $J$ = 5.3, 10.7 Hz, 1H), 3.41 (dd, $J$ = 4.2, 6.1 Hz, 1H), 3.00 (ddd, $J$ = 6.7, 10.0, 13.3 Hz, 1H), 2.64 (br s, 1H), 1.94 (m, 1H), 1.03 (d, $J$ = 6.9 Hz, 3H), 0.97 (d, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 158.9, 135.3, 132.3, 130.7, 129.4, 129.3, 128.8, 117.2, 113.5, 113.4, 83.7, 73.8, 65.5, 55.0, 37.7, 35.0, 18.3, 11.3; HRMS (EI) *m/z* calcd for $C_{18}H_{26}O_3$ 290.1881, found 290.1882; $[\alpha]^{20}_D$ +46.6° (*c* 0.5, $CHCl_3$).

**(*Z*)-(3*R*,4*S*,5*R*)-4-[(4-Methoxyphenyl)methoxy]-3,5-dimethyl-6,8-nonadien-2-one (4a).** To a solution of 500 mg (1.73 mmol) of **13** in 5 mL of $CH_2Cl_2$ was added 950 mg (2.08 mmol) of Dess−Martin periodinane. After being stirred at ambient temperature for 10 min, the reaction was quenched by the addition of 20 mL of saturated $Na_2S_2O_3$ solution and 20 mL of saturated $NaHCO_3$ solution, and diluted with 50 mL of diethyl ether. After the mixture was stirred 30 min, the layers were separated and the organic layer was washed with 3 × 120 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (10% EtOAc/hexanes) to yield 456 mg of the aldehyde.

To a solution of 456 mg (1.58 mmol) of the aldehyde in 5 mL of THF was added 2.10 mL (6.32 mmol, 3 M in $Et_2O$) of methylmagnesium bromide. After being stirred for 30 min at ambient temperature, the reaction mixture was diluted with 30 mL of diethyl ether, washed with 1 × 20 mL of 1 N HCl and 1 × 20 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (10% EtOAc/hexanes) to provide 450 mg of a 2:1 mixture of epimers.

The mixture of alcohols was dissolved in 5 mL of $CH_2Cl_2$, and 933 mg (2.16 mmol) of Dess−Martin periodinane was added. After 30 min of stirring at ambient temperature, the reaction was quenched by the addition of 20 mL of saturated $Na_2S_2O_3$ solution and 20 mL of saturated $NaHCO_3$ solution and diluted with 50 mL of diethyl ether. After the mixture was stirred for 30 min, the layers were separated and the organic layer was washed with 3 × 120 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (5% EtOAc/hexanes) to yield 388 mg (1.28 mmol, 74% for three steps) of **4a** as a colorless oil: IR (thin film/NaCl)1711 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 7.23 (d, $J$ = 8.6 Hz, 2H), 6.84 (d, $J$ = 8.7 Hz, 2H), 6.45 (dddd, $J$ = 16.1, 11.0, 10.2, 0.8 Hz, 1H), 6.02 (apparent t, $J$ = 11.0 Hz, 1H), 5.49 (apparent t, $J$ = 10.6 Hz, 1H), 5.19 (dd, $J$ = 16.7, 1.0 Hz, 1H), 5.07 (d, $J$ = 10.2 Hz, 1H), 4.53 (d, $J$ = 10.6 Hz, 1H), 4.45 (d, $J$ = 10.6 Hz, 1H), 3.77 (s, 3H), 3.61 (dd, $J$ = 7.8, 3.8 Hz, 1H), 2.80 (m, 1H), 2.71 (m, 1H), 2.09 (s, 3H), 1.16 (d, $J$ = 7.1 Hz, 3H), 1.06 (d, $J$ = 6.9 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 212.1, 159.2, 134.1, 132.1, 130.7, 129.6, 129.3, 117.7, 113.7, 83.7, 75.0, 55.2, 50.7, 36.1, 29.6, 18.6, 13.4; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{19}H_{26}O_3Na$ 325.1780, found 325.1789; $[\alpha]^{20}_D$ +53.2° (*c* 0.5, $CHCl_3$).

**(*Z*)-(4*R*,5*S*,6*R*)-5-[(4-Methoxyphenyl)methoxy]-4,6-dimethyl-7,9-decadien-3-one (4b).** To a solution of 625 mg (2.16 mmol) of **13** in 5 mL of $CH_2Cl_2$ was added 1.18 g (2.60 mmol) of Dess−Martin periodinane. After being stirred at ambient temperature for 10 min, the reaction was quenched by the addition of 20 mL of saturated $Na_2S_2O_3$ solution and 20 mL of saturated $NaHCO_3$ solution and diluted with 50 mL of diethyl ether. After 30 min of stirring, the layers were separated and the organic layer was washed with 3 × 120 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (10% EtOAc/hexanes) to yield 560 mg of the aldehyde.

To a solution of 560 mg (1.94 mmol) of the aldehyde in 5 mL of THF was added 2.59 mL (7.76 mmol, 3 M in $Et_2O$) of methylmagnesium bromide. After being stirred for 30 min at ambient temperature, the reaction mixture was diluted with 30 mL of diethyl ether, washed with 1 × 20 mL of 1 N HCl and 1 × 20 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (10% EtOAc/hexanes) to provide 553 mg of a 2:1 mixture of epimers.

The mixture of alcohols was dissolved in 5 mL of $CH_2Cl_2$, and 1.12 g (2.16 mmol) of Dess−Martin periodinane was added. After 30 min of stirring at ambient temperature, the reaction was quenched by the addition of 20 mL of saturated $Na_2S_2O_3$ solution and 20 mL of saturated $NaHCO_3$ solution and diluted with 50 mL of diethyl ether. After 30 min of stirring, the layers were separated and the organic layer was washed with 3 × 120 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (5% EtOAc/hexanes) to yield 550 mg (1.74 mmol, 80% for three steps) of **4b** as a colorless oil: IR (thin film/NaCl)1709 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 7.25 (d, $J$ = 4.7 Hz, 2H), 6.85 (d, $J$ = 8.5 Hz, 2H), 6.42 (ddd, $J$ = 16.8, 10.7, 10.6 Hz, 1H), 6.02 (t, $J$ = 11.0 Hz, 1H), 5.52 (t, $J$ = 10.6 Hz, 1H), 5.17 (d, $J$ = 16.8 Hz, 1H), 5.07 (d, $J$ = 10.1 Hz, 1H), 4.55 (d, $J$ = 10.6 Hz, 1H), 4.48 (d, $J$ = 10.6 Hz, 1H), 3.78 (s, 3H), 3.62 (dd, $J$ = 8.2, 3.4 Hz, 1H), 2.75 (m, 2H), 2.40 (m, 2H), 1.16 (d, $J$ = 7.1 Hz, 3H), 1.07 (d, $J$ = 6.9 Hz, 3H), 0.98 (t, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 214.6, 159.2, 133.9, 132.1, 130.8, 129.5, 129.2, 117.6, 113.7, 83.9, 75.2, 55.2, 50.1, 36.2, 35.5, 18.7, 14.0, 7.5; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{20}H_{28}O_3Na$ 339.1936, found 339.1933; $[\alpha]^{20}_D$ +40.2° (*c* 0.5, $CHCl_3$).

**(*Z*)-(4*S*,5*R*,6*S*)-Methyl 5,7-Bis[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-2,4,6-trimethyl-1-[(2,2-dimethylpropanoyl)oxy]-2-heptene.** To a cooled (0 °C) solution of 393 mg (0.94 mmol) of alcohol enant-**11** in 10 mL of dichloromethane was added 229 $\mu$L (224 mg, 2.83 mmol) of pyridine followed by 233 $\mu$L (228 mg, 1.89 mmol) of pivaloyl chloride. The cooling bath was removed and the reaction stirred at ambient temperature for 4 h. The mixture was concentrated and chromatographed (3% EtOAc/hexane) to provide 455 mg (0.91 mmol, 96%) of pivaloate: IR (thin film/NaCl) 1732 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 5.28 (d, $J$ = 9.8 Hz, 1H), 4.60 (d, $J$ = 12.0 Hz, 1H), 4.50 (d, $J$ = 12.0 Hz, 1H), 3.60 (dd, $J$ = 9.8, 5.8 Hz, 1H), 3.46 (t, $J$ = 5.4 Hz, 1H), 3.35 (dd, $J$ = 9.7, 7.5 Hz, 1H), 2.61 (m, 1H), 1.79 (m, 1H), 1.70 (s, 3H), 1.18 (s, 9H), 0.90 (d, $J$ = 6.7 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.86 (d, $J$ = 4.5 Hz, 3H), 0.02 (s, 3H), 0.00 (s, 6H), 0.00 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 178.3, 135.3, 128.4, 77.4, 65.4, 63.2, 41.2, 38.8, 35.3, 27.2, 26.1, 26.0, 21.4, 18.4, 18.3, 16.6, 13.4, −4.0, −4.0, −5.3, −5.4; HRMS (FAB, NBA/NaI) calcd for $C_{27}H_{56}O_4Si_2Na$ 523.3615, found 523.3632. Anal. Calcd $C_{27}H_{56}O_4Si_2$: C, 64.74; H, 11.27. Found: C, 64.77; H, 11.23. $[\alpha]^{20}_D$ −0.8° (*c* 0.5, $CHCl_3$).

**(*Z*)-(2*S*,3*R*,4*S*)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2,4,6-trimethyl-7-[(2,2-dimethylpropanoyl)oxy]-5-hepten1-ol.** To a flask charged with 455 mg (0.91 mmol) of pivaloate was added 10 mL of HF-pyridine buffered with excess pyridine (prepared by the slow addition of 5 mL of pyridine to 1.25 mL of HF-pyridine followed by dilution with 12.5 mL of THF), and the resulting solution was stirred at ambient temperature for 9 h. The reaction was quenched by slow addition of 20 mL of saturated $NaHCO_3$ solution and extracted with 2

× 50 mL of dichloromethane. The combined organic layers were washed with 2 × 25 mL of saturated $CuSO_4$ solution, dried over $MgSO_4$, filtered, concentrated, and chromatographed (10% EtOAc/hexane) to afford 317 mg (0.82 mmol, 90%) of alcohol: IR (thin film/NaCl) 3482 (br), 1730,cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 5.19 (d, $J$ = 10.0 Hz, 1H), 4.56 (d, $J$ = 12.0 Hz, 1H), 4.50 (d, $J$ = 12.0 Hz, 1H), 3.54 (m, 1H), 3.41 (dd, $J$ = 5.9, 4.4 Hz, 1H), 2.68 (m, 1H), 2.48 (br s, 1H), 1.78 (m, 1H), 1.67 (s, 3H), 1.15 (s, 9H), 0.93 (d, $J$ = 7.3 Hz, 3H), 0.92 (d, $J$ = 6.9 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) 178.3, 134.1, 129.3, 80.5, 65.2, 63.2, 38.9, 38.8, 36.8, 27.1, 26.1, 21.3, 18.3, 17.1, 15.5, −3.8, −4.0; HRMS (FAB, NBA/NaI) calcd for $C_{21}H_{42}O_4SiNa$ 409.2750, found 409.2751. Anal. Calcd for $C_{21}H_{42}O_4Si$: C, 65.24; H, 10.95. Found: C, 65.31; H, 10.92. $[\alpha]^{20}_D$ +13.5° (*c* 0.4, $CHCl_3$).

**(*Z*)-(4*S*,5*R*,6*S*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2,4,6-trimethyl-1-[(2,2-dimethylpropanoyl)oxy]-2-octen-7-yne (enant-18).** To a solution of 290 μL (319 mg, 4.09 mmol) of DMSO in 5 mL of dichloromethane at −78 °C was added 179 μL (260 mg, 2.05 mmol) of oxalyl chloride. After 15 min, a solution of 316 mg (0.82 mmol) of alcohol in 4 mL of dichloromethane (plus 1 mL rinse) was added *via* cannula. After 45 min at −78 °C, 1.14 mL (828 mg, 8.19 mmol) of triethylamine was added, and after 5 min, the cooling bath was removed and the reaction was stirred at ambient temperature for 15 min. The resulting slurry was diluted with 50 mL of hexane and washed with 3 × 10 mL of $H_2O$, dried over $MgSO_4$, filtered, concentrated, taken up in 50 mL of ether, refiltered through $MgSO_4$, reconcentrated, and used immediately in the subsequent reaction.

To a cooled (−78 °C) solution of 101 mg (0.90 mmol) of potassium *tert*-butoxide in 1 mL of THF was added 135 mg (0.90 mmol) of dimethyl diazomethylphosphonate in 1 mL of THF *via* cannula. After stirring for 10 min, a solution of the above-prepared aldehyde (in 2 mL of THF plus 2 × 0.5 mL rinses) was added *via* cannula and the reaction removed to a constant temperature bath at −50 °C for 21 h. The reaction was removed from the cooling bath and stirred at ambient temperature for 1 h when the reaction volume was reduced to approximately 1 mL and directly chromatographed (2% EtOAc/hexane) to provide 310 mg (0.82 mmol, 99% from alcohol) of acetylene enant-**18**: IR (thin film/NaCl) 1730 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 5.20 (d, $J$ = 10.3 Hz, 1H), 4.65 (d, $J$ = 12.1 Hz, 1H), 4.53 (d, $J$ = 12.0 Hz, 1H), 3.32 (dd, $J$ = 7.0, 3.3 Hz, 1H), 2.76 (m, 1H), 2.58 (m, 1H), 1.98 (d, $J$ = 2.4 Hz, 1H), 1.68 (d, $J$ = 0.6 Hz, 3H), 1.17 (s, 9H), 1.13 (d, $J$ = 7.2 Hz, 3H), 0.94 (d, $J$ = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) 178.2, 133.9, 129.4, 86.1, 78.5, 70.0, 63.3, 38.7, 36.8, 31.5, 27.1, 25.9, 21.3, 18.3, 17.5, 17.3, −3.9, −4.0; HRMS (FAB, NBA/NaI) calcd for $C_{22}H_{40}O_3SiNa$ 403.2644, found 403.2661. Anal. Calcd for $C_{22}H_{40}O_3Si$: C, 69.42; H, 10.59. Found: C, 69.53; H, 10.60. $[\alpha]^{20}_D$ +7.4° (*c* 0.5, $CHCl_3$).

**(*Z*)-(4*S*,5*R*,6*S*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-8-iodo-2,4,6-trimethyl-1-[(2,2-dimethylpropanoyl)oxy]-2-octen-7-yne (enant-34).** To a solution of 427 mg (4.90 mmol) of morpholine in 5 mL of benzene was added 248 mg (0.98 mmol) of iodine, and the suspension was heated, shielded from light, to 45−50 °C for 1 h. The resulting red suspension was treated with 310 mg (0.82 mmol) of acetylene enant-**18** in 3 mL of benzene (plus 2 × 1 mL rinses) and stirred at 45−50 °C, shielded from light, for 22 h. The suspension was poured over 50 mL of hexanes plus 10 mL of saturated $Na_2SO_3$ solution and shaken vigourously until the organic layer was colorless. The layers were separated, and the organic layer was washed with 1 × 10 mL of $Na_2SO_3$, dried over $MgSO_4$, filtered, concentrated, and chromatographed (2% EtOAc/hexane) to afford 377 mg (0.75 mmol, 91%) of iodide: IR (thin film/NaCl) 1730 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 5.24 (d, $J$ = 10.2 Hz, 1H), 4.63 (d, $J$ = 12.0 Hz, 1H), 4.51 (d, $J$ = 12.0 Hz, 1H), 3.34 (dd, $J$ = 6.7, 3.8 Hz, 1H), 2.74 (m, 1H), 2.69 (m, 1H), 1.72 (s, 3H), 1.19 (s, 9H), 1.12 (d, $J$ = 7.1 Hz, 3H), 0.93 (d, $J$ = 6.6 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) 178.3, 133.9, 129.6, 96.8, 78.7, 63.4, 38.8, 36.7, 34.0, 27.2, 26.0, 21.6, 18.3, 17.4, 17.0, −3.8, −4.0; HRMS (FAB, NBA/NaI) calcd for $C_{22}H_{39}O_3SiINa$ 529.1613, found 529.1622; $[\alpha]^{20}_D$ −12.2° (*c* 0.5, $CHCl_3$).

**2,2-Dimethylpropanoic Acid, [2*S*-[2α(2*Z*,4*S*,5*R*,6*S*,9*S*]),3*β*,4*β*,5α,6α]]5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-10-[4-[[(1,1-dimethylethyl)dimethylsilyl]]oxy]tetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-9-hydroxy-2,4,6-trimethyl-2-decen-7-ynyl Ester (enant-19a and enant-19b).** A mixture of 227 mg (0.58 mmol) of aldehyde enant-**2** and 650 mg (1.28 mmol) of iodide was azeotropically dried with 3 × 10 mL portions of benzene, and the flask was evacuated and filled with Ar three times. The mixture was transferred to an inert atmosphere box, dissolved in 5 mL of THF, and treated with approximately 100 mg of 0.011% $NiCl_2/CrCl_2$, and the resulting slurry was stirred at room temperature for 23 h. The reaction was removed from the inert atmosphere box, filtered over a Celite pad, and rinsed with 100 mL of EtOAc. The filtrate was washed with 2 × 50 mL of saturated $NaHCO_3$, the combined aqueous layers were extracted with 2 × 50 mL of EtOAc, and the organic layers were combined, dried over $MgSO_4$, filtered, and chromatographed (2%−4%−6%−10% EtOAc/hexanes) to provide 214 mg (0.28 mmol) of propargyl alcohol enant-**19a** and 139 mg (0.18 mmol) of propargyl alcohol enant-**19b** (79% combined). Data for enant-**19a**: IR (thin film/NaCl) 3513 (br), 1728 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.50 (dd, $J$ = 8.4, 1.4 Hz, 2H), 7.26 (t, $J$ = 7.4 Hz, 2H), 7.17 (t, $J$ = 7.4 Hz, 1H), 5.24 (d, $J$ = 10.1 Hz, 1H), 5.13 (d, $J$ = 1.3 Hz, 1H), 4.69 (d, $J$ = 12.1 Hz, 1H), 4.56 (d, $J$ = 12.1 Hz, 1H), 4.56−4.51 (m, 2H), 3.58 (t, $J$ = 3.1 Hz, 1H), 3.34 (dd, $J$ = 6.6, 3.4 Hz, 1H), 2.97 (d, $J$ = 6.3 Hz, 1H), 2.75 (m, 1H), 2.58 (m, 1H), 2.17 (m, 1H), 1.95 (m, 1H), 1.80 (m, 2H), 1.72 (d, $J$ = 0.9 Hz, 3H), 1.18 (s, 9H), 1.12 (d, $J$ = 7.0 Hz, 3H), 1.11 (d, $J$ = 6.9 Hz, 3H), 0.98 (s, 9H), 0.94 (d, $J$ = 6.6 Hz, 3H), 0.89 (s, 9H), 0.86 (d, $J$ = 6.8 Hz, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.02 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) 178.6, 138.3, 134.4, 130.9, 129.1, 128.7, 126.5, 89.0, 86.5, 83.5, 78.5, 73.9, 68.1, 63.7, 59.4, 41.4, 40.6, 38.8, 36.6, 35.5, 31.9, 27.2, 26.1, 26.0, 21.4, 18.3, 18.2, 17.6, 17.5, 17.1, 13.9, −3.9, −4.0, −4.1, −4.9; HRMS (FAB, NBA/NaI) calcd for $C_{43}H_{74}O_6Si_2SNa$ 797.4642, found 797.4663; $[\alpha]^{20}_D$ +126.6° (*c* 0.5, $CHCl_3$). Data for enant-**19b.** IR (thin film/NaCl) 3517 (br), 1713 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.45 (d, $J$ = 7.5 Hz, 2H), 7.22 (t, $J$ = 8.1 Hz, 2H), 7.15 (dt, $J$ = 7.8, 1.0 Hz, 1H), 5.21 (d, $J$ = 10.2 Hz, 1H), 5.13 (s, 1H), 4.71 (d, $J$ = 12.1 Hz, 1H), 4.55 (d, $J$ = 12.1 Hz, 1H), 4.54 (m, 1H), 4.38 (td, $J$ = 10.1, 2.4 Hz, 1H), 3.57 (t, $J$ = 2.9 Hz, 1H), 3.32 (t, $J$ = 3.3 Hz, 1H), 2.78 (m, 1H), 2.51 (m, 1H), 2.15 (m, 1H), 1.92 (m, 1H), 1.87 (m, 1H), 1.81 (m, 1H), 1.73 (s, 3H), 1.18 (s, 9H), 1.12 (d, $J$ = 7.3 Hz, 3H), 1.08 (d, $J$ = 7.2 Hz, 3H), 0.98 (s, 9H), 0.93 (d, $J$ = 6.6 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H), 0.00 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) 178.9, 138.5, 134.8, 130.6, 128.8, 128.6, 126.3, 88.9, 86.8, 83.2, 78.4, 73.9, 69.7, 63.9, 61.1, 41.4, 41.0, 38.8, 36.4, 35.8, 32.1, 27.2, 26.2, 26.2, 26.0, 21.4, 18.3, 18.2, 17.6, 17.4, 16.8, 14.0, −4.0 (2), −4.1, −4.9; HRMS (FAB, NBA/NaI) calcd for $C_{43}H_{74}O_6Si_2SNa$ 797.4642, found 797.4625; $[\alpha]^{20}_D$ +119.6° (*c* 0.5, $CHCl_3$).

**2,2-Dimethylpropanoic Acid, [2*S*-[2α(2*Z*,4*S*,5*R*,6*S*,9*S*),3*β*,4*β*,5α,6α]]-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-10-[4-[[(1,1-dimethylethyl)dimethylsilyl]]oxy]tetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-2,4,6-trimethyl-9-oxo-2-decen-7-ynyl Ester (enant-23).** To a solution of 44 μL (48 mg, 0.61 mmol) of DMSO in 4 mL of dichloromethane at −78 °C was added 32 μL (47 mg, 0.37 mmol) of oxalyl chloride. After 20 min, a solution of 95 mg (0.12 mmol) of propargylic alcohol enant-**19b** in 3 mL of dichloromethane (plus 2 × 1 mL rinses) was added *via* cannula. After 2 h at −78 °C, 171 μL (125 mg, 1.23 mmol) of triethylamine was added, and after 5 min, the cooling bath removed and the reaction stirred at ambient temperature 30 min. The resulting slurry was diluted with 100 mL of hexane and washed with 3 × 25 mL of $H_2O$ and 1 × 25 mL of brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed (4% EtOAc/hexane) to provide 93 mg (0.12 mmol, 98%) of ynone enant-**23**: IR (thin film/NaCl) 1728, 1676 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) 7.40 (dd, $J$ = 7.5, 1.2 Hz, 2H), 7.21 (t, $J$ = 7.5 Hz, 2H), 7.10 (m, 1H), 5.19 (d, $J$ = 10.1 Hz, 1H), 5.11 (s, 1H), 4.81 (td, $J$ = 9.8, 3.3 Hz, 1H), 4.64 (d, $J$ = 12.2 Hz, 1H), 4.45 (d, $J$ = 12.1 Hz, 1H), 3.58 (t, $J$ = 2.6 Hz, 1H), 3.32 (dd, $J$ = 6.6, 3.8 Hz, 1H), 2.74 (dd, $J$ = 14.8, 3.5 Hz, 1H), 2.60 (m, 2H), 2.46 (m, 1H), 2.18 (m, 1H), 1.82 (m, 1H), 1.67 (d, $J$ = 1.2 Hz, 3H), 1.17 (s, 9H), 1.11 (d, $J$ = 7.3 Hz, 3H), 1.08 (d, $J$ = 7.1 Hz, 3H), 0.99 (s, 9H), 0.86 (s, 9H), 0.89−0.82 (overlapping d, 6H), 0.12 (s, 3H), 0.06 (s, 3H), −0.02 (s, 3H), −0.03 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) 185.7, 178.2, 139.4, 133.4, 129.7, 129.6, 128.5, 125.9, 96.5, 89.0, 82.7, 78.0, 74.0, 67.8, 63.2, 49.4, 42.0, 38.8, 36.7, 35.3, 32.2, 27.2, 26.2, 26.0, 21.3, 18.3, 18.2, 17.6, 17.3, 15.6, 14.1,

−3.9, −4.0, −4.1, −4.9; HRMS (FAB, NBA/NaI) calcd for $C_{43}H_{72}O_6Si_2SNa$ 795.4485, found 795.4499; $[\alpha]^{20}_D$ +63.0° (*c* 0.5, $CHCl_3$).

**CBS Reduction of Ynone 23.** A 0.2 M solution of the *B*-butyloxazaborolidine catalyst in toluene was generated as follows: To a flask fitted with a three-way stopcock containing 460 mg (1.8 mmol, azeotropically dried with toluene) of (*S*)-2-(diphenylhydroxymethyl)-pyrrolidine was added 5 mL of toluene and 360 μL (1.5 mmol) of bis(trifluoroethyl) ethylboronate with stirring. After 15 min at ambient temperature, the toluene was removed *in vacuo* and the resulting colorless oil heated at 110 °C at 1.0 Torr for 30 min. After the mixture was cooled to room temperature and returned to 1 atm, 7.2 mL of toluene was added to afford a 0.2 M catalyst solution. A solution of 423 mg (0.55 mmol) of ynone **23** in 5 mL of toluene was treated with 1.4 mL (0.28 mmol) of the above freshly prepared 0.2 M catalyst solution at room temperature. After cooling to −78 °C, freshly distilled catecholborane (430 μL, 0.85 mmol, 2 M in toluene) was added over 10 min and the reaction removed to a −20 °C freezer for 7.5 h. The reaction was quenched by addition of 5 mL of 1 N HCl and diluted with 50 mL of ether and the layers were separated. The organic layer was washed with 1 N NaOH until the aqueous layer was colorless (6 × 5 mL 1 N NaOH), the organic layer dried over $MgSO_4$, filtered, concentrated, and chromatographed (4% EtOAc/hexane) to afford 343 mg (0.44 mmol, 81%) of propargylic alcohol **19a**, identical in all respects to that prepared earlier.

**2,2-Dimethylpropanoic Acid, [2*S*-[2α(2*Z*,4*S*,5*R*,6*S*,9*S*),3*β*,4*β*,5α,6α]]-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-10-[4-[[(1,1-dimethylethyl)dimethylsilyl]]oxy]tetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-9-hydroxy-2,4,6-trimethyl-2,7-decadienyl Ester.** Through a suspension of 200 mg of 10% Pd/C in 4 mL of EtOAc was bubbled $H_2$ for 15 min (from a balloon through a needle and exiting *via* a capillary pipet inserted through the rubber septum) when 200 mg (0.26 mmol) of acetylene enant-**19a** was added by syringe in 2 mL of EtOAc (plus 2 × 1 mL rinses) and the $H_2$ bubbled through the resulting suspension for 30 min. The mixture was filtered through Celite, washed with 150 mL of EtOAc, concentrated, and chromatographed (3% EtOAc/hexanes) to provide 170 mg (0.22 mmol, 85%) of *cis*-olefin as a viscous oil: IR (thin film/NaCl) 3522 (br), 1729 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 7.44 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.15 (t, *J* = 6.5 Hz, 1H), 5.45 (apparent t, *J* = 10.7 Hz, 1H), 5.36 (dd, *J* = 11.0, 8.5 Hz, 1H), 5.25 (s, 1H), 5.20 (d, *J* = 9.1 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.52 (m, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.41 (m, 1H), 3.59 (t, *J* = 2.9 Hz, 1H), 3.30 (dd, *J* = 5.9, 4.2 Hz, 1H), 2.60 (m, 1H), 2.53 (m, 1H), 2.26 (d, *J* = 3.8 Hz, 1H), 2.16 (m, 1H), 1.85 (m, 1H), 1.75 (m, 1H), 1.69 (m, 1H), 1.67 (d, *J* = 1.2 Hz, 3H), 1.55 (m, 1H), 1.17 (s, 9H), 1.14 (d, *J* = 7.3 Hz, 3H), 0.98 (s, 9H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 178.3, 138.6, 134.7, 134.0, 131.6, 129.8, 128.7 (2), 126.2, 88.5, 80.3, 74.0, 67.5, 64.2, 63.3, 41.5, 39.8, 38.8, 37.1, 36.7, 35.4, 27.2, 26.2, 26.1, 21.4, 18.7, 18.4, 18.3, 17.7, 17.2, 14.0, −3.4, −3.9, −4.0, −4.8; HRMS (FAB, NBA/NaI) calcd for $C_{43}H_{76}O_6Si_2SNa$ 799.4799, found 799.4818; $[\alpha]^{20}_D$ +59.0° (*c* 0.5, $CHCl_3$).

**2,2-Dimethylpropanoic Acid, [2*S*-[2α(2*Z*,4*S*,5*R*,6*S*,9*S*),3*β*,4*β*,5α,6α]]-5,9-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-10-[4-[[(1,1-dimethylethyl)dimethylsilyl]]oxy]tetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-2,4,6-trimethyl-2,7-decadienyl Ester.** To a solution of 87 mg (0.11 mmol) of alcohol in 2 mL of dichloromethane at ambient temperature was added 52 μL (48 mg, 0.45 mmol) of 2,6-lutidine followed by 51 μL (59 mg, 0.22 mmol) of TBSOTf. After standing for 30 min, the solution was quenched with 0.5 mL of MeOH, concentrated, and chromatographed (1% EtOAc/hexanes) to provide 99 mg (0.11 mmol, 99%) of silyl ether: IR (thin film/NaCl) 1731 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 7.43 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 5.33 (d, *J* = 10.7 Hz, 1H), 5.32 (d, *J* = 11.0 Hz, 1H), 5.25 (d, *J* = 10.2 Hz, 1H), 5.23 (d, *J* = 1.2 Hz, 1H), 4.60 (d, *J* = 12.2 Hz, 1H), 4.51 (m, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 4.24 (t, *J* = 10.1 Hz, 1H), 3.58 (t, *J* = 3.0 Hz, 1H), 3.35 (apparent t, *J* = 4.9 Hz, 1H), 2.63 (m, 1H), 2.61 (m, 1H), 2.14 (m, 1H), 1.72 (m, 1H), 1.70 (d, *J* = 1.1 Hz, 3H), 1.69 (m, 1H), 1.46 (dd, *J* = 13.4, 10.5 Hz, 1H), 1.19 (s, 9H), 1.10 (d, *J* = 7.3 Hz, 3H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.98 (s, 9H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.79 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), −0.14 (s, 3H), −0.27 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 178.3, 140.6, 135.3, 134.6, 131.2, 128.5, 128.4, 128.1, 125.1, 87.5, 80.4, 74.2, 68.0, 66.1, 63.3, 42.9, 41.7, 38.8, 36.9, 36.0, 35.4, 27.2, 26.3, 26.2, 25.9, 21.5, 18.5, 18.3, 18.1, 18.0, 17.6, 16.0, 14.2, −3.0, −3.6, −4.0, −4.1, −4.9, -5.1; HRMS (FAB, NBA/NaI) calcd for $C_{49}H_{90}O_6Si_3SNa$ 913.5663, found 913.5674; $[\alpha]^{20}_D$ +31.8° (*c* 0.5, $CHCl_3$).

**[2*S*-[2α(2*Z*,4*S*,5*R*,6*S*,9*S*),3*β*,4*β*,5α,6α]]-5,9-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-10-[4-[[(1,1-dimethylethyl)dimethylsilyl]]oxy]-tetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-2,4,6-trimethyl-2,7-decadien-1-ol (enant-20).** To a cooled (−78 °C) solution of 764 mg (0.86 mmol) of pivaloyl ester in 10 mL of dichloromethane was added 1.7 mL of DIBAL-H (1.5 M in toluene, 2.57 mmol), and the solution was stirred for 25 min when it was quenched with 25 mL of 0.5 M NaK tartrate solution saturated with NaCl and 25 mL of brine, warmed to room temperature, and stirred until the layers separated. The layers were separated, the aqueous layer was extracted with 3 × 50 mL of dichloromethane, and the organic layers were combined, dried over $MgSO_4$, filtered, concentrated, and chromatographed (3% EtOAc/hexanes) to provide 680 mg (0.84 mmol, 98%) of primary alcohol enant-**20** as a white foam: IR (thin film/NaCl) 3452 (br) $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) 7.46 (dd, *J* = 8.5, 1.1 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 5.43−5.34 (m, 2H), 5.22 (s, 1H), 5.12 (d, *J* = 9.5 Hz, 1H), 4.49 (t, *J* = 9.2 Hz, 1H), 4.36 (t, *J* = 10.2 Hz, 1H), 4.15 (dd, *J* = 12.3, 3.8 Hz, 1H), 3.95 (dd, *J* = 12.2, 7.3 Hz, 1H), 3.58 (t, *J* = 2.9 Hz, 1H), 3.32 (dd, *J* = 6.0, 3.5 Hz, 1H), 2.63 (m, 1H), 2.50 (m, 1H), 2.15 (m, 1H), 1.99 (m, 1H), 1.78−1.69 (m, 2H), 1.67 (d, *J* = 0.8 Hz, 3H), 1.38 (m, 1H), 1.14 (d, *J* = 7.3 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 9H), 0.92 (s, 9H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.81 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), −0.10 (s, 3H), −0.23 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 140.0, 134.3, 133.6, 132.4, 130.8, 128.8, 128.4, 125.4, 87.9, 80.9, 74.2, 68.0, 65.9, 61.7, 42.7, 41.7, 36.7, 36.6, 35.4, 26.3, 26.2, 26.0, 21.2, 19.2, 18.5, 18.3, 18.0, 17.7, 17.5, 14.2, −3.2, −3.3, −3.7, −4.0, −4.7, −4.8; HRMS (FAB, NBA/NaI) calcd for $C_{44}H_{82}O_5Si_3SNa$ 829.5088, found 829.5072; $[\alpha]^{20}_D$ +51.6° (*c* 0.5, $CHCl_3$).

**[2*S*-[2α(2*Z*,4*S*,5*R*,6*S*,9*S*),3*β*,4*β*,5α,6α]]-5,9-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-bromo-10-[4-[[(1,1-dimethylethyl)dimethylsilyl]]oxy]tetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-2,4,6-trimethyl-2,7-decadiene (enant-21).** To a cooled (0 °C) solution of 113 mg (140 μmol) of alcohol enant-**20** in 2 mL of $CH_2Cl_2$ were added $Et_3N$ (78 μL, 560 μmol) in one portion and MsCl (22 μL, 280 μmol) dropwise over 10 min. After stirring for 1 h at 0 °C, during which time a white precipitate formed, a solution of LiBr (122 mg, 1.4 mmol) in 3 mL of acetone was added and the resulting suspension warmed to room temperature and stirred for an additional 15 min. Dilution with 50 mL of hexanes and filtration over $MgSO_4$ provided 113 mg (130 μmol, 93%) of bromide enant-**21** as a colorless oil used without further purification: $^1H$ NMR (500 MHz, $CDCl_3$) 7.43 (d, *J* = 6.7 Hz, 2H), 7.20 (dt, *J* = 8.6, 1.4 Hz, 2H), 7.09 (t, *J* = 7.1 Hz, 1H), 5.35−5.25 (m, 3H), 5.23 (s, 1H), 4.52 (apparent t, *J* = 8.9 Hz, 1H), 4.25 (apparent t, *J* = 10.1 Hz, 1H), 4.00 (dd, *J* = 9.6, 1.4 Hz, 1H), 3.91 (dd, *J* = 9.6, 1.4 Hz, 1H), 3.58 (apparent s, 1H), 3.42 (apparent t, *J* = 4.4 Hz, 1H), 2.64 (m, 1H), 2.56 (m, 1H), 2.14 (m, 1H), 1.78 (s, 3H), 1.81−1.65 (m, 2H), 1.40 (dd, *J* = 13.8, 10.3 Hz, 1H), 1.25 (m, 1H), 1.11 (dd, *J* = 7.3, 1.4 Hz, 3H), 1.00 (dd, *J* = 6.9, 1.3 Hz, 3H), 0.97 (s, 9H), 0.91 (s, 9H), 0.87−0.83 (2 overlapping d, 6H), 0.78 (s, 9H), 0.11 (s, 3H), 0.05 (s, 6H), 0.02 (s, 3H), −0.13 (s, 3H), −0.27 (s, 3H).

**[2*S*-[2*β*(3*Z*,5*S*,6*S*,7*R*,11*Z*,13*S*,14*S*,15*S*,16*Z*,18*S*),3*β*,4*β*,5α,6α]]-14,18-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-19-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-6-[(4-methoxyphenyl)methoxy]-5,7,11,13,15-pentamethyl-1,3,11,16-nonadecatetraen-8-one (26b).** To a cooled solution (0 °C) of 100 mg (124 μmol) of **20** in 1 mL of $CH_2Cl_2$ was added 69 μL (50 mg, 496 μmol) of $Et_3N$, followed by 19 μL (28 mg, 248 μmol) of MsCl. After stirring for 1 h, a solution of 108 mg (1.24 mmol) of LiBr in 3 mL of acetone was added. After the mixture was warmed to ambient temperature and stirred for an additional 15 min, the suspension was diluted with 20 mL of hexanes, filtered through

$MgSO_4$ and 5 g of silica gel, eluting from the silica gel with 20 mL of 10% EtOAc/hexanes, and concentrated *in vacuo* to provide crude bromide **21.**

To a cooled (−78 °C) solution of the crude bromide **21** and 115 mg (381 μmol) of ketone **4a** in 1 mL of THF was added 846 mL (423 μmol, 0.5 M solution in THF) of LDA. The mixture was stirred for 3 h at 0 °C, and then the reaction was quenched by the addition of 1.5 mL of saturated $NH_4Cl$ solution. The mixture was extracted into 30 mL of EtOAc, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (0.5%−1%−2% EtOAc/hexanes) to provide 110 mg (101 μmol, 81% for two steps) of **26b** as a colorless oil: IR (thin film/NaCl) 1710 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.49 (d, $J$ = 7.0 Hz, 2H), 7.27−7.23 (m, 5H), 6.85 (d, $J$ = 8.6 Hz, 2H), 6.45 (ddd, $J$ = 10.6, 16.9, 21.1 Hz, 1H), 6.03 (apparent t, $J$ = 10.9 Hz, 1H), 5.52 (apparent t, $J$ = 10.5 Hz, 1H), 5.31 (d, $J$ = 1.9 Hz, 1H), 5.29 (obscured dd, $J$ = 7.5, 11.1 Hz, 1H), 5.23 (d, $J$ = 10.3 Hz, 1H), 5.19 (d, $J$ = 16.2 Hz, 1H), 5.09 (overlapping d, $J$ = 9.0 Hz, 1H), 5.08 (overlapping, $J$ = d, 9.9 Hz, 1H), 4.56 (overlapping m, 1H), 4.55 (overlapping d, $J$ = 10.6 Hz, 1H), 4.49 (d, $J$ = 10.6 Hz, 1H), 3.79 (s, 3H), 3.66−3.60 (obscured m, 3H), 3.29 (apparent t, $J$ = 4.9 Hz, 1H), 2.79 (m, 1H), 2.73 (m, 1H), 2.65 (m, 1H), 2.45 (m, 3H), 2.36 (m, 1H), 2.08 (m, 1H), 2.00 (m, 1H), 1.62 (s, 3H), 1.58 (obscured m, 2H), 1.48 (dd, $J$ = 13.1, 23.8 Hz, 1H), 1.17 (s, $J$ = 7.1 Hz, 3H), 1.08 (d, $J$ = 6.9 Hz, 3H), 1.06 (d, $J$ = 7.2 Hz, 3H), 0.97 (d, $J$ = 7.0 Hz, 3H), 0.96 (d, $J$ = 7.0 Hz, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.78 (s, 9H), 0.77 (overlapping d, 3H), 0.05 (s, 3H), 0.03 (overlapping s, 6H), 0.02 (s, 3H), −0.12 (s, 3H), −0.26 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 213.5, 159.1, 135.5, 134.4, 133.9, 132.6, 132.0, 131.7, 131.6, 131.4, 130.7, 129.6, 129.3, 128.7, 127.1, 117.9, 113.7, 84.6, 83.7, 80.5, 76.5, 75.1, 74.7, 65.6, 55.2, 50.3, 42.6, 41.9, 41.0, 36.6, 36.1, 35.6, 34.1, 26.3, 25.9, 25.8, 23.2, 18.7, 18.5, 18.0, 17.9, 16.4, 14.3, 13.9, 11.4, −2.8, −4.1, −4.2, −4.6, −5.0, −5.1; LRMS (FAB, NBA/NaI) *m/z* calcd for $C_{63}H_{106}O_7Si_3SNa$ 1113, found 1113; $[\alpha]^{20}_D$ +64.8° (*c* 0.5, $CHCl_3$).

**[2*S*-[2*β*(3*Z*,5*S*,6*S*,7*R*,9*S*,11*Z*,13*S*,14*S*,15*S*,16*Z*,18*S*),3*β*,4*β*,5α,6α]]-14,18-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-19-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-6-[(4-methoxyphenyl)methoxy]-5,7,9,11,13,15-hexamethyl-1,3,11,16-nonadecatetraen-8-one (27b).** To a cooled (−78 °C) solution of 60 mg (55 μmol) of **26b** in 1 mL of THF was added 500 μL (275 μmol, 0.5 M in THF) of $LiN(SiMe_2Ph)_2$. After the reaction was stirred at −78 °C for 1 h, 342 μL (781 μg, 5.5 mmol) of methyl iodide was added. The reaction was warmed to 0 °C and stirred at ambient temperature for 3 h. After quenching the reaction with 1.5 mL of saturated $NH_4Cl$ solution, the mixture was extracted with 30 mL of EtOAc and the layers were separated. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (2% EtOAc·hexanes). The resulting colorless oil was purified by HPLC (2% EtOAc/hexanes) to provide 32 mg (26 μmol, 48%) of **27b** as a colorless oil: IR (thin film/NaCl) 1705 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.48 (d, $J$ = 8.7 Hz, 2H), 7.27−7.22 (m, 5H), 6.86 (d, $J$ = 8.7 Hz, 2H), 6.44 (ddd, $J$ = 10.3, 16.9, 20.6 Hz, 1H), 6.02 (apparent t, $J$ = 11.0 Hz, 1H), 5.60 (apparent t, $J$ = 10.3 Hz, 1H), 5.30 (d, $J$ = 2.2 Hz, 1H), 5.26 (obscured dd, $J$ = 7.6, 11.0 Hz, 1H), 5.21−5.16 (overlapping d, 3H), 5.05 (d, $J$ = 10.2 Hz, 1H), 4.56 (obscured dd, $J$ = 5.1, 9.2 Hz, 1H), 4.55 (obscured d, $J$ = 6.5 Hz, 1H), 4.54 (d, $J$ = 8.7 Hz, 1H), 3.79 (s, 3H), 3.65 (overlapping dd, $J$ = 3.0, 8.2 Hz, 1H), 3.62 (overlapping d, $J$ = 8.4 Hz, 1H), 3.59 (apparent t, $J$ = 2.5 Hz, 1H), 3.25 (dd, $J$ = 3.8, 6.3 Hz, 1H), 2.88 (m, 1H), 2.70 (overlapping m, 1H), 2.67 (overlapping m, 1H), 2.50 (m, 1H), 2.17 (dd, $J$ = 11.1, 13.5 Hz, 1H), 2.00 (dd, $J$ = 3.9, 6.5 Hz, 3H), 1.60 obscured m (2), 1.58 (d, $J$ = 0., 6 Hz, 3H), 1.53 (dd, $J$ = 6.5, 7.8 Hz, 1H), 1.20 (d, $J$ = 7.1 Hz, 3H), 1.09 (d, $J$ = 6.9 Hz, 3H), 1.05 (d, $J$ = 7.0 Hz, 3H), 0.96 (d, $J$ = 6.6 Hz, 3H), 0.95 (overlapping d, $J$ = 6.3 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.82 (d, $J$ = 7.0 Hz, 3H), 0.77 (s, 9H), 0.75 (d, $J$ = 6.8 Hz, 3H), 0.02 (overlapping s, 9H), −0.01 (s, 3H), −0.14 (s, 3H), −0.27 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 217.0, 159.1, 135.4, 134.3, 133.7, 133.6, 132.7, 132.2, 130.9, 129.7, 129.6, 129.3, 129.2, 128.7, 127.1, 117.9, 113.8, 113.7, 84.7, 83.5, 80.5, 76.5, 75.3, 74.7, 65.6, 55.3, 49.3, 43.5, 42.7, 41.9, 36.8, 36.5, 35.1, 34.1, 26.4, 25.8, 23.2, 19.2, 18.5, 18.0, 17.9, 17.7, 15.5, 15.3, 14.3, 14.2, 11.4, −2.6, −4.2, −4.3, -4.5, −4.9, −5.1; LRMS (FAB, NBA/NaI) *m/z* calcd for $C_{64}H_{108}O_7Si_3SNa$ 1127, found 1127; $[\alpha]^{20}_D$ +71.0° (*c* 0.5, $CHCl_3$).

**[2*S*-[2*β*(3*Z*,5*S*,6*S*,7*R*,9*S*,11*Z*,13*S*,14*S*,15*S*,16*Z*,18*S*),3*β*,4*β*,5α,6α]]-14,18-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-19-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-6-[(4-methoxyphenyl)methoxy]-5,7,9,11,13,15-hexamethyl-1,3,11,16-nonadecatetraen-8-one (30).** To a cooled (−78 °C) solution of 60 mg (55 μmol) of **26b** in 1 mL of THF was added 500 μL (275 μmol, 0.5 M in THF) of $LiN(SiMe_2Ph)_2$. After the reaction was stirred at −78 °C for 1 h, 342 μL (781 μg, 5.5 mmol) of methyl iodide was added. The reaction was warmed to 0 °C and stirred at ambient temperature for 3 h. After quenching the reaction with 1.5 mL of saturated $NH_4Cl$ solution, the mixture was extracted with 30 mL of EtOAc and the layers were separated. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (2% EtOAc·hexanes). The resulting colorless oil was purified by HPLC (2% EtOAc/hexanes) to provide 16 mg (13 μmol, 24%) of **30** as a colorless oil: IR (thin film/NaCl) 1710 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.49 (d, $J$ = 6.5 Hz, 2H), 7.29−7.23 (m, 5H), 6.86 (d, $J$ = 8.7 Hz, 2H), 6.43 (ddd, $J$ = 10.8, 16.6, 21.1 Hz, 1H), 6.03 (apparent t, $J$ = 11.0 Hz, 1H), 5.62 (apparent t, $J$ = 10.3 Hz, 1H), 5.30 (overlapping d, $J$ = 2.1 Hz, 1H), 5.29 (overlapping dd, $J$ = 7.6, 10.9 Hz, 1H), 5.23 (d, $J$ = 9.8 Hz, 1H), 5.18 (dd, $J$ = 1.7, 5.7 Hz, 1H), 5.15 (s, 1H), 5.12 (obscured m, 1H), 5.06 (d, $J$ = 10.1 Hz, 1H), 4.56 (obscured m, 1H), 5.54 (overlapping d, $J$ = 2.2 Hz, 2H), 3.80 (s, 3H), 3.61 (obscured t, $J$ = 10.5 Hz, 1H), 3.59 (br s, 2H), 3.27 (dd, $J$ = 3.1, 6.7 Hz, 1H), 2.84 (m, 1H), 2.75 (m, 1H), 2.68 (m, 2H), 2.52 (m, 1H), 2.32 (dd, $J$ = 5.6, 13.5 Hz, 1H), 1.99 (ddd, $J$ = 2.6, 5.3, 7.1 Hz, 1H), 1.92 (dd, $J$ = 8.6, 13.5 Hz, 1H), 1.63 (d, $J$ = 0.9 Hz, 3H), 1.59 (m, 1H), 1.53 (m, 1H), 1.16 (d, $J$ = 7.1 Hz, 3H), 1.08 (d, $J$ = 6.9 Hz, 3H), 1.05 (d, $J$ = 7.1 Hz, 3H), 0.97 (overlapping d, $J$ = 7.4 Hz, 3H), 0.96 (overlapping d, $J$ = 7.4 Hz, 3H), 0.94 (overlapping d, $J$ = 7.1 Hz, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.78 (s, 9H), 0.75 (d, $J$ = 6.8 Hz, 3H), 0.03 (overlapping s, 9H), 0.01 (s, 3H), −0.14 (s, 3H), −0.27 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 216.7, 159.1, 135.3, 134.5, 133.6, 133.4, 132.7, 132.3, 132.1, 130.8, 129.7, 129.3, 128.8, 127.2, 117.7, 113.7, 84.7, 83.7, 80.3, 77.2, 76.5, 75.4, 74.7, 65.6, 55.3, 49.6, 44.3, 42.841.9, 36.8, 36.5, 34.9, 34.1, 26.4, 25.8, 23.5, 19.3, 18.5, 18.0, 17.9, 17.7, 16.1, 15.2, 14.3, 13.9, 11.4, −2.5, −4.2, −4.5, −4.9, −5.2; LRMS (FAB, NBA/NaI) *m/z* calcd for $C_{64}H_{108}O_7Si_3SNa$ 1127, found 1127; $[\alpha]^{20}_D$ +64.3° (*c* 0.5, $CHCl_3$).

**[3*S*-[3α,4*β*,5*β*,6α (2*S*,3*Z*,5*S*,6*S*,7*S*,8*Z*,11*S*,13*R*,14*S*,15*S*,16*Z*)]]-6-[2,6-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-14-[(4-methoxyphenyl)methoxy]-5,7,9,11,13,15-hexamethyl-12-oxo-3,8,16,18-nonadecatetraenyl]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-2*H*-pyran-2-one.** To a solution of 75 mg (68 μmol) of **27b** in 1 mL of THF were added 1 mL of MeCN, 1 mL of pH 7 buffer solution concentrate, and 184 mg (679 μmol) of $HgCl_2$. The suspension was stirred for 20 min, when TLC analysis indicated no starting material remained, and then was treated with 10 mL of brine and extracted into 3 × 25 mL of $CH_2Cl_2$. The organic layers were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (1% EtOAc/hexanes) to provide 60 mg of a mixture of lactols.

The lactols were dissolved in 9 mL of acetone, cooled to 0 °C, and treated with 500 μL (500 μmol) of 1 M Jones oxidant solution. The reaction was stirred at 0 °C for 30 min, then warmed to ambient temperature for 5 min. Excess oxidant was quenched by addition of 500 μL of iPrOH and stirred for 30 min, diluted with 30 mL of diethyl ether, filtered through Celite, concentrated *in vacuo*, and chromatographed (2% EtOAc/hexanes) to provide 52 mg (52 μmol, 77% for two steps) of lactone as a colorless oil: IR (thin film/NaCl) 1738 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.27 (d, $J$ = 8.5 Hz, 2H), 6.87 (d, $J$ = 8.5 Hz, 2H), 6.44 (ddd, $J$ = 10.1, 16.2, 20.7 Hz, 1H), 6.03 (apparent t, $J$ = 11.0 Hz, 1H), 5.61 (apparent t, $J$ = 10.4 Hz, 1H), 5.31 (dd, $J$ = 7.9, 11.0 Hz, 1H), 5.18 (overlapping d, $J$ = 7.0 Hz, 1H), 5.16 (s, 1H), 5.14 (obscured dd, $J$ = 3.0, 9.9 Hz, 1H), 5.06 (d, $J$ = 10.1 Hz, 1H), 4.80 (apparent t, $J$ = 9.1 Hz, 1H), 4.57 (d, $J$ = 10.7 Hz, 1H), 4.55 (overlappign d, $J$ = 10.7 Hz, 1H), 4.52 (obscured m, 1H), 3.80 (s, 3H), 3.65 (obscured m, 1H), 3.64 (overlapping d, $J$ = 2.0 Hz, 1H), 3.24 (dd, $J$ = 4.0, 6.0 Hz, 1H), 2.58 (apparent t, $J$ = 7.4 Hz, 1H), 2.68 (overlapping m, 2H), 2.62 (m overlapping m, 2H), 2.49 (m, 1H), 2.17 (dd, $J$ = 9.1, 11.0 Hz, 1H), 1.97 (dd, $J$ = 2.8, 13.5 Hz, 1H), 1.82 (m,

1H), 1.74 (m, 1H), 1.59 (obscured m 1), 1.56 (s, 3H), 1.26 (obscured m, 3H), 1.22 (d, $J$ = 7.8 Hz, 3H), 1.20 (d, $J$ = 7.4 Hz, 3H), 1.09 (d, $J$ = 6.9 Hz, 3H), 0.96 (overlapping d, $J$ = 6.5 Hz, 3H), 0.94 (overlapping d, $J$ = 7.8 Hz, 3H), 0.90 (s, 9H), 0.87 (obscured d, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), −0.02 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 216.8, 173.3, 159.1, 133.6, 133.5, 133.4, 132.7, 132.1, 130.8, 129.7, 129.2, 117.8, 113.7, 83.5, 80.3, 75.3, 74.8, 64.6, 55.2, 49.2, 44.1, 43.5, 42.8, 37.4, 36.5, 34.9, 34.2, 34.1, 31.6, 26.3, 25.9, 25.7, 23.1, 22.6, 19.2, 18.4, 18.1, 17.9, 17.2, 16.4, 15.6, 15.3, 14.3, 14.1, 14.0, −3.0, −4.4, −4.5, −4.6, −4.9; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{58}H_{102}O_8Si_3Na$ 1033.6775, found 1033.6780; $[\alpha]^{20}_D$ −18.0° (*c* 0.5, $CHCl_3$).

**[3*S*-[3α,4*β*,5*β*,6α(2*S*,3*Z*,5*S*,6*S*,7*S*,8*Z*,11*S*,13*R*,14*S*,15*S*,16*Z*)]]-6-[2,6-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-14-hydroxy-5,7,9,11,13,15-hexamethyl-12-oxo-3,8,16,18-nonadecatetraenyl]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-2*H*-pyran-2-one (28).** To a solution of 47 mg (46 $\mu$mol) of PMB ether in 2 mL if $CH_2Cl_2$ was added 141 mg of $NaHCO_3$ and then 712 $\mu$L (70 $\mu$mol, 90 mM in $CH_2Cl_2$) of DDQ. After being stirred for 1 h at ambient temperature, the mixture was concentrated under a stream of $N_2$ and chromatographed (10% EtOAc/hexanes) to provide 30 mg (34 $\mu$mol, 91%) of **28** as a colorless oil: IR (thin film/NaCl) 3469 (br), 1711 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.59 (ddd, $J$ = 10.9, 16.7, 21.1 Hz, 1H), 6.11 (apparent t, $J$ = 11.0 Hz, 1H), 5.42 (apparent t, $J$ = 10.3 Hz, 1H), 5.31 (dd, $J$ = 11.0, 7.9 Hz, 1H), 5.33−5.12 (m, 4H), 4.79 (t, $J$ = 9.3 Hz, 1H), 4.52 (t, $J$ = 10.1 Hz, 1H), 3.70 (dd, $J$ = 8.1, 3.9 Hz, 1H), 3.64 (t, $J$ = 2.3, 3.25, dd, 6.1, 4.0 Hz, 1H), 2.82 (m, 2H), 2.75 (ddd, $J$ = 8.6, 7.0, 6.2 Hz, 1H), 2.64−2.60 (m, 2H), 2.49 (m, 1H), 2.20 (dd, $J$ = 9.4, 13.4 Hz, 1H), 2.06 (dd, $J$ = 5.2, 13.5 Hz, 1H), 1.83−1.79 (m, 1H), 1.74 (t, $J$ = 12.6 Hz, 1H), 1.61 (s, 3H), 1.25 (t, $J$ = 7.7 Hz, 1H), 1.22 (d, $J$ = 7.6 Hz, 3H), 1.17 (d, 7.1H, s), 1.01−0.87 (overlapping d, 15H), 0.89 (s, 9H), 0.86 (s, 9H), 0.07 (overlapping s, 6H), 0.05 (s, 3H), 0.04 (overlapping s, 6H), −0.01 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 218.3, 173.3, 134.3, 133.6, 133.5, 132.5, 132.1, 130.4, 129.7, 118.2, 80.2, 74.8, 74.6, 64.7, 47.0, 44.1, 43.0, 42.8, 37.3, 35.4, 35.1, 35.0, 34.6, 34.2, 31.6, 26.3, 26.2, 26.1, 25.9, 25.7, 25.3, 23.4, 22.6, 20.7, 18.4, 18.1, 17.9, 17.6, 17.4, 16.4, 16.0, 15.6, 14.1, 14.1, 9.9, −3.0, −4.4, −4.5, −4.9; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{50}H_{94}O_7Si_3Na$ 913.6200, found 913.6202; $[\alpha]^{20}_D$ −26.6° (*c* 0.5, $CHCl_3$).

**[3*S*-[3α,4*β*,5*β*,6α(2*S*,3*Z*,5*S*,6*S*,7*S*,8*Z*,11*S*,13*R*,14*S*,15*S*,16*Z*)]]-6-[2,6-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-14-(carbamoyloxy)-5,7,9,11,13,15-hexamethyl-12-oxo-3,8,16,18-nonadecatetraenyl]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-2*H*-pyran-2-one.** To a solution of 25 mg (28 $\mu$mol) of **28** in 500 $\mu$L of $CH_2Cl_2$ was added 10 $\mu$L of $Cl_3CONCO$. After 10 min of stirring at ambient temperature, 200 mg of neutral alumina (oven dried) was added. The suspension was stirred for 4 h at ambient temperature, concentrated under a stream of $N_2$, and chromatographed (10% EtOAc/hexanes) to provide 24 mg (26 $\mu$mol, 92%) of carbamate as a colorless oil: IR (thin film/NaCl) 1734, 1718 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.48 (ddd, $J$ = 10.7, 16.9, 21.3 Hz, 1H), 6.05 (apparent t, $J$ = 11.0 Hz, 1H), 5.42 (apparent t, $J$ = 10.4 Hz, 1H), 5.30 (dd, $J$ = 8.0, 11.0 Hz, 1H), 5.20 (d, $J$ = 17.1 Hz, 1H), 5.18−5.08 (overlapping d, 3H), 5.07 (d, $J$ = 5.3 Hz, 1H), 4.79 (apparent t, $J$ = 9.2 Hz, 1H), 4.63 (br s, 2H), 4.51 (t, $J$ = 10.3, 3.64, apparent s Hz, 1H), 3.24 (dd, $J$ = 4.0, 6.1 Hz, 1H), 2.95 (m, 1H), 2.88 (m, 1H), 2.75 (m, 1H), 2.62 (ovlerapping m, 2H), 2.49 (m, 1H), 2.20 (dd, $J$ = 11.3, 13.2 Hz, 1H), 1.98 (dd, $J$ = 2.0, 13.4 Hz, 1H), 1.82 (m, 1H), 1.74 (dd, $J$ = 11.2, 12.1 Hz, 1H), 1.62 (obscured m, 1H), 1.59 (s, 3H), 1.22 (d, $J$ = 7.6 Hz, 3H), 1.12 (d, $J$ = 7.0 Hz, 3H), 1.02 (d, $J$ = 6.8 Hz, 3H), 0.97−0.92 (overlapping d, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (obscured d, 3H), 0.86 (s, 9H), 0.06 (overlapping s, 6H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), −0.02 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 214.7, 173.4, 156.5, 156.5, 133.5, 133.4, 132.7, 132.5, 131.9, 130.5, 129.7, 118.4, 80.3, 74.8, 64.7, 46.7, 44.1, 42.8, 42.7, 37.4, 34.9, 34.7, 34.1, 33.9, 31.6, 26.3, 26.1, 25.9, 25.7, 23.1, 22.6, 18.4, 18.1, 18.0, 17.9, 17.3, 16.4, 15.5, 15.4, 14.1, 14.0, 14.0, 12.4, −3.0, −4.4, −4.4, −4.5, −4.9; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{51}H_{95}O_8Si_3NNa$ 956.6258, found 956.6263; $[\alpha]^{20}_D$ −22.2° (*c* 0.5, $CHCl_3$).

**3,7,11-Tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-discodermolide (29).** To a solution of 21 mg (22.5 mol) of carbamate in 2 mL of THF was added 67 $\mu$L (67 $\mu$mol, 1 M in THF) of $LiAl(OtBu)_3H$. After 2 h of stirring at ambient temperature, the reaction was quenched with 200 $\mu$L of saturated $NH_4Cl$ solution, stirred for 2 h, dried over $Na_2SO_4$, filtered, concentrated *in vacuo*, and chromatographed (25% EtOAc/hexanes) to provide 19 mg (20.3 $\mu$mol, 90%) of **29** as a colorless oil: IR (thin film/NaCl) 3510 (br), 3364 (br), 1723, cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.62 (ddd, $J$ = 10.3, 16.9, 21.4 Hz, 1H), 6.04 (apparent t, $J$ = 10.1 Hz, 1H), 5.37 (apparent t, $J$ = 10.5 Hz, 1H), 5.31−5.21 (overlapping d, 3H), 5.14 (d, $J$ = 10.1 Hz, 1H), 5.10 (d, $J$ = 9.9 Hz, 1H), 4.80 (t, $J$ = 8.5 Hz, 1H), 4.75 (dd, $J$ = 6.5, 5, 0 Hz, 1H), 4.51 (m, 3H), 3.64 (t. 2.3, 1H), 3.27 (m, 2H), 3.03 (ddd, $J$ = 6.7, 10.2, 6.7 Hz, 1H), 2.65−2.60 (m, 2H), 2.47 (m, 1H), 1 (94−1.70, $J$ = m Hz, 6H), 1.60 (overlapping s and t, 4H), 1.22 (overalpping d and m, 4H), 1.01 (d, $J$ = 6.8 Hz, 3H), 0.99 (d, $J$ = 6.9 Hz, 3H), 0.97−0.95 (overlapping d, $J$ = 6.9 Hz, 6H), 0.91 (s, 9H), 0.88−0.81 (overlapping s and d, 12H), 0.86 (s, 9H), 0.79 (d, $J$ = 6.3 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.5, 157.0, 133.4, 133.1, 132.5, 132.1, 130.9, 129.9, 118.1, 80.6, 79.1, 76.6, 74.8, 64.6, 44.1, 42.7, 37.7, 37.2, 35.6, 64.7, 34.2, 26.3, 25.9, 25.7, 23.1, 18.5, 18.1, 18.0, 17.7, 17.5, 16.5, 15.8, 14.2, 14.1, 13.9, 8.6, −3.2, −4.2, −4.3, −4.5, −4.9; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{51}H_{97}O_8NSi_3Na$ 958.6414, found 958.6411; $[\alpha]^{20}_D$ −26.6° (*c* 0.5, $CHCl_3$).

**(+)-Discodermolide (1a).** To 12 mg (13.1 $\mu$mol) of **29** was added 2 mL of 1% HCl in MeOH. (The HCl solution was made by the addition of 500 $\mu$L of concentrated HCl to 50 mL of MeOH.) After being stirred for 48 h at ambient temperature, the reaction was quenched by the addition of 50 mg of $NaHCO_3$, concentrated under a stream of $N_2$, and chromatographed (5% MeOH/$CHCl_3$) to provide 9 mg (10.1 $\mu$mol, 77%) of **1a** as a white solid: IR (thin film/NaCl) 3409 (br), 1705 cm$^{-1}$; $^1$H NMR (500 MHz, 10% v/v $D_3COD/CDCl_3$) 6.53 (ddd, $J$ = 16.9, 10.8, 10.4 Hz, 1H), 5.94 (apparent t, $J$ = 11.0 Hz, 1H), 5.39-5.32 (m, 2H), 5.27 (apparent t, $J$ = 10.5 Hz, 1H), 5.12 (d, $J$ = 16.9 Hz, 1H), 5.03 (m, 2H), 4.64 (t, $J$ = 5.9 Hz, 1H), 4.58 (td, $J$ = 7.5, 2.2 Hz, 1H), 4.48 (t, $J$ = 9.8 Hz, 1H), 3.56 (t, $J$ = 3.8 Hz, 1H), 3.15 (t, $J$ = 4.9 Hz, 1H), 3.08 (t, $J$ = 5.7 Hz, 1H), 2.94 (m, 1H), 2.62 (m, 1H), 2.58 (m, 1H), 2.43 (m, 1H), 1.81−1.70 (m, 6H), 1.53 (m, 1H), 1.53 (s, 3H), 1.20 (d, $J$ = 7.4 Hz, 3H), 0.96 (d, $J$ = 6.9 Hz, 3H), 0.93 (d, $J$ = 8.3 Hz, 3H), 0.91 (d, $J$ = 7.2 Hz, 3H), 0.86 (d, $J$ = 6.9 Hz, 3H), 0.84 (d, $J$ = 6.7 Hz, 3H), 0.72 (d, $J$ = 5.7 Hz, 3H); $^{13}$C NMR (125 MHz, 10% v/v $D_3COD/CDCl_3$) 175.2, 157.8, 133.9, 133.3, 132.7, 132.4, 132.0, 130.0, 129.8, 117.8, 78.9, 77.5, 75.7, 72.5, 63.5, 43.0, 41.0, 37.2, 36.0, 35.7, 35.5, 35.1, 34.4, 33.1, 23.0, 18.0, 17.3, 15.5, 15.4, 13.8, 12.4, 8.6; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{33}H_{55}O_8NNa$ 616.3826, found 616.3818; $[\alpha]^{20}_D$ +14.0° (*c* 0.6, MeOH).

**16-Epidiscodermolide (1b):** IR (thin film/NaCl) 3854 (br), 3422 (br), 1701 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.53 (ddd, $J$ = 10.8, 16.8, 21.2 Hz, 1H), 5.95 (apparent t, $J$ = 11.0 Hz, 1H), 5.41 (apparent t, $J$ = 10.8 Hz, 1H), 5.29 (overlapping m, 2H), 5.19 (d, $J$ = 9.6 Hz, 1H), 5.12 (d, $J$ = 16.8 Hz, 1H), 5.04 (4.69, $J$ = apparent t, 6.3 Hz, 1H), 4.61 (t, $J$ = 9.1 Hz, 1H), 4.49 (t, $J$ = 10.2 Hz, 1H), 3.56 (br s, 1H), 3.45−3.37 (obscured, 4H), 3.28 (t, $J$ = 1.3 Hz, 1H), 3.16 (dd, $J$ = 5.4, 7.4 Hz, 1H), 3.07 (dd, $J$ = 2.2, 5.2 Hz, 1H), 2.47 (m 1), 2.65−2.57 (overlapping m, 2H), 2.48 (m, 1H), 2.24 (d, $J$ = 12.3 Hz, 1H), 1.82−1.70 (overlapping m, 4H), 1.62 (obscured m, 1H), 1.59 (s, 3H), 1.22 (d, $J$ = 7.4 Hz, 3H), 0.97 (d, $J$ = 6.8 Hz, 3H), 0.93 (d, $J$ = 6.7 Hz, 3H), 0.89 (d, $J$ = 6.7 Hz, 3H), 0.84 (d, $J$ = 6.8 Hz, 3H), 0.80 (d, $J$ = 6.8 Hz, 3H), 0.59 (d, $J$ = 6.4 Hz, 3H), 0.; $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.9, 157.4, 134.3, 134.0, 133.36, 133.1, 132.1, 130.3, 130.0, 118.0, 80.4, 78.6, 77.8, 77.2, 73.3, 64.5, 43.2, 41.0, 37.0, 36.4, 35.7, 35.6, 34.8, 34.6, 34.4, 24.1, 18.1, 17.7, 15.9, 15.6, 14.2, 12.6, 7.6; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{33}H_{55}O_8NNa$ 616.3822, found 616.3825; $[\alpha]^{20}_D$ +18.0° (*c* 0.4, $CHCl_3$).

**17-Epidiscodermolide (1c):** IR (thin film/NaCl) 3400 (br), 1707 cm$^{-1}$; $^1$H NMR (500 MHz, 10% $CD_3OD$-$CDCl_3$) $\delta$ 6.65 (ddd, $J$ = 11.0, 16.9, 21.2 Hz, 1H), 6.04 (overlapping dd, $J$ = 11.1 Hz, 1H), 5.52 (dd, $J$ = 8.1, 11.3 Hz, 1H), 5.42 (overlapping dd, $J$ = 10.8 Hz, 1H), 5.29 (overlapping dd, $J$ = 10.4 Hz, 1H), 5.24 (obscured dd, 1H), 5.21 (obscured dd, 1H), 5.12 (d, $J$ = 10.0 Hz, 1H), 4.84 (dd, $J$ = 1.6, 7.6 Hz, 1H), 4.75 (m, 1H), 4.62 (ddd, $J$ = 2.4, 9.9, 12.2 Hz, 1H), 4.56 (br s, 2H), 3.74 (br s, 1H), 3.68 (d, $J$ = 4.6 Hz, 1H), 3.20 (dd, $J$ = 4.5, 6.9 Hz, 1H), 3.15 (m, 1H), 2.98 (ddd, $J$ = 2.7, 9.4, 16.2 Hz, 1H), 2.77

(ddd, $J$ = 6.8, 9.7, 13.6 Hz, 1H), 2.68 (m, 1H), 2.63 (m, 1H), 2.21 (dd, $J$ = 11.4, 12.9 Hz, 1H), 2.04 (br s, 1H), 2.00−1.80 (overlapping m, 4H), 1.73 (m, 1H), 1.68 (d, $J$ = 0.8 Hz, 3H), 1.32 (d, $J$ = 7.3 Hz, 3H), 1.07 (d, $J$ = 7.0 Hz, 3H), 1.02 (d, $J$ = 6.8 Hz, 3H), 0.98 (d, $J$ = 6.8 Hz, 3H), 0.96 (d, $J$ = 6.7 Hz, 3H), 0.91 (d, $J$ = 6.7 Hz, 3H), 0.89 (d, $J$ = 7.0 Hz, 3H); HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{33}H_{55}O_8$-NNa 616.3822, found 616.3825.

**16-Desmethyldiscodermolide (31):** IR (thin film/NaCl) 3854 (br), 3744 (br), 1701 cm$^{-1}$; $^1$H NMR (500 MHz, 10% $CD_3OD$-$CDCl_3$) $\delta$ 6.54 (ddd, $J$ = 10.9, 17.4, 21.9 Hz, 1H), 5.97 (overlapping dd, $J$ = 11.0 Hz, 1H), 5.42 (dd, $J$ = 7.8, 11.1 Hz, 1H), 5.36 (apparent t, $J$ = 9.4 Hz, 1H), 5.29 (apparent t, $J$ = 10.6 Hz, 1H), 5.16 (dd, $J$ = 1.7, 16.7 Hz, 1H), 5.06 (d, $J$ = 10.1 Hz, 1H), 5.03 (d, $J$ = 9.9 Hz, 1H), 4.67 (t, $J$ = 5.6 Hz, 1H), 4.62 (overlapping ddd, $J$ = 2.8, 10.3 Hz, 1H), 4.52 (ddd, $J$ = 2.0, 10.4, 12.1 Hz, 1H), 3.59 (t, $J$ = 3.6 Hz, 1H), 3.48 (m, 1H), 3.32 (t, $J$ = 1.6 Hz, 2H), 3.12 (t, $J$ = 5.0 Hz, 1H), 2.95 (ddd, $J$ = 6.6, 10.2, 13.2 Hz, 1H), 2.66 (ddd, $J$ = 6.6, 9.3, 13.3 Hz, 1H), 2.60 (ddd, $J$ = 3.3, 7.4, 10.7 Hz, 1H), 2.46 (ddd, $J$ = 6.7, 9.6, 12.2 Hz, 1H), 2.07 (m, 1H), 1.89 (m, 1H), 1.82 (ddd, $J$ = 3.4, 6.8, 10.1 Hz, 1H), 1.75 (ddd, $J$ = 2.2, 10.0, 12.2 Hz, 1H), 1.68 (ddd, $J$ = 3.8, 5.2, 7.0 Hz, 1H), 1.60 (d, $J$ = 1.1 Hz, 1H), 1.58 (obscured m, 1H), 1.43 (m, 1H), 1.23 (d, $J$ = 7.4 Hz, 3H), 0.99 (d, $J$ = 6.9 Hz, 3H), 0.96 (d, $J$ = 6.6 Hz, 3H), 0.94 (d, $J$ = 6.8 Hz, 3H), 0.88 (d, $J$ = 0.7 Hz, 3H), 0.86 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 174.0, 157.4, 134.4, 134.2, 133.5, 133.0, 132.1, 130.0, 129.1, 118.0, 79.7, 79.0, 73.2, 73.1, 64.2, 43.2, 41.1, 40.0, 36.4, 35.7, 35.4, 34.9, 33.1, 28.7, 23.4, 18.4, 17.6, 15.6, 15.5, 12.6, 8.0; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{32}H_{53}O_8NH$ 580.3846, found 580.3849; $[\alpha]^{20}_D$ +23.2° (*c* 0.5, $CHCl_3$).

**[3*R*[3*β*,4*β*,5*β*,6α(2*R*,3*Z*,5*R*,6*R*,7*R*,8*Z*)]]-4-Hydroxy-6-[2,6,10-trihydroxy-5,7,9-trimethyl-3,8-decadienyl]tetrahydro-3,5-dimethyl-2*H*-pyran-2-one (32).** To 5 mg (6 mol) of silyl ether was added 100 $\mu$L of 0.5% HCl in MeOH. (The HCl solution was made by the addition of 500 $\mu$L of concentrated HCl to 100 mL of MeOH.) After 3 days of stirring at ambient temperature, the reaction was quenched by the addition of 50 mg of $NaHCO_3$, concentrated under a stream of $N_2$, and chromatographed (5% MeOH/$CHCl_3$) to provide 1.2 mg (3 $\mu$mol, 54%) of **32** as a colorless oil: IR (thin film/NaCl) 3366, 1711 cm$^{-1}$; $^1$H NMR (500 MHz, 10% $CD_3OD$-$CDCl_3$) $\delta$ 5.54 (dd, $J$ = 8, 11.1 Hz, 1H), 5.49 (dd, $J$ = 13.7, 24.7 Hz, 1H), 5.22 (d, $J$ = 9.9 Hz, 1H), 4.71 (td, $J$ = 3.5, 8.7 Hz, 1H), 4.59 (td, $J$ = 1.9, 10.3 Hz, 1H), 4.18 (d, $J$ = 11.8 Hz, 1H), 3.96 (d, $J$ = 11.9 Hz, 1H), 3.73 (br s, 1H), 3.23 (t, $J$ = 5.6 Hz, 1H), 2.80 (ddd, $J$ = 6.6, 9.8, 13.3 Hz, 1H), 2.69 (m, 1H), 2.64 (m, 1H), 1.92 (m, 1H), 1.86 (m, 1H), 1.82 (s, 3H), 1.70 (m, 3H), 1.33 (d, $J$ = 7.4 Hz, 3H), 1.07 (d, $J$ = 7.0 Hz, 3H), 1.05 (d, $J$ = 6.8 Hz, 3H), 1.02 (d, $J$ = 6.9 Hz, 3H); HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{20}H_{34}O_6Na$ 393.2251, found 393.2253.

**2,2-Dimethylpropanoic Acid, (2*Z*,4*S*,5*S*,6*S*)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2,4,6-trimethyl-2,7-octadienyl Ester.** Through a suspension of 75 mg of 10% Pd·$BaSO_4$ and 50 $\mu$L of quinoline in 4 mL of MeOH was bubbled a stream of $H_2$ for 30 min. To this suspension was added 150 mg (395 $\mu$mol) of **10** in 2 mL of MeOH and stirred for 10 min under a constant stream of $H_2$. The mixture was filtered through Celite, concentrated *in vacuo*, and chromatographed (1% EtOAc/hexanes) to provide 133 mg (348 $\mu$mol, 88%) of olefin as a colorless oil: IR (thin film/NaCl) 1732, cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.80 (ddd, $J$ = 8.2, 10.3, 17.5 Hz, 1H), 5.17 (d, $J$ = 10.1 Hz, 1H), 4.92 (dd, $J$ = 1.9, 33.7 Hz, 1H), 4.92 (dt, $J$ = 1.0, 1.6, 6.4 Hz, 1H), 4.58 (d, $J$ = 12.0 Hz, 1H), 4.47 (d, $J$ = 12.1 Hz, 1H), 3.31 (dd, $J$ = 3.3, 7.0 Hz, 1H), 2.56 (ddd, $J$ = 6.8, 11.1, 14.7 Hz, 1H), 2.31 (m, 1H), 1.70 (s, 3H), 1.26 (m, 1H), 1.19 (s, 9H), 0.99 (d, $J$ = 7.1 Hz, 3H), 0.92 (d, $J$ = 6.7 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 178.4, 141.0, 134.5, 128.6, 114.3, 80.3, 63.4, 42.9, 38.8, 36.7, 27.2, 26.1, 21.3, 18.4, 17.8, 17.7, −3.6, −3.7; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{22}H_{42}O_3Si$ 383.2979, found 383.2981; $[\alpha]^{20}_D$ +4.8° (*c* 0.5, $CHCl_3$).

**(3*S*,4*S*,5*S*,6*Z*,11*R*,12*S*,13*S*,14*Z*)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,5,7,9,11,13-hexamethyl-12-[(4-methoxyphenyl)methoxy]-1,6,14,16-heptadecatetraen-10-one (33).** To a cooled (−78 °C) solution of 85 mg (146 $\mu$mol) of ketone in 1 mL of THF was added 1.46 mL (730 $\mu$mol, 0.5 M in THF) of $LiN(SiMe_2Ph)_2$. After the reaction was stirred at −78 °C for 1 h, 934 $\mu$L (15 mmol) of methyl iodide was added. The reaction was warmed to 0 °C and stirred at ambient temperature for 3 h. After quenching the reaction with 1.5 mL of saturated $NH_4Cl$ solution, the mixture was extracted with 30 mL of EtOAc and the layers were separated. The organic layer was dried over MgSO4, filtered, concentrated *in vacuo*, and chromatographed (2% EtOAc.hexanes). The resulting colorless oil was purified by HPLC (2% EtOAc/hexanes) to provide 38 mg (64 $\mu$mol, 44%) of **33** as a colorless oil: IR (thin film/NaCl) 1705 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.28 (d, $J$ = 8.6 Hz, 2H), 6.87 (d, $J$ = 8.5 Hz, 2H), 6.45 (ddd, $J$ = 10.5, 16.8, 20.8 Hz, 1H), 6.04 (apparent t, $J$ = 11.0 Hz, 1H), 5.83 (ddd, $J$ = 8.0, 10.5, 17.8 Hz, 1H), 5.61 (apparent t, $J$ = 10.4 Hz, 1H), 5.18 (dd, $J$ = 1.0, 16.7 Hz, 1H), 5.06 (apparent t, $J$ = 10.0 Hz, 2H), 4.96 (dd, $J$ = 1.9, 10.4 Hz, 1H), 4.92 (dd, $J$ = 0.7, 18.0 Hz, 1H), 4.57 (d, $J$ = 10.7 Hz, 1H), 4.54 (d, $J$ = 10.7 Hz, 1H), 3.80 (s, 3H), 3.66 (dd, $J$ = 3.0, 8.0 Hz, 1H), 3.28 (dd, $J$ = 3.7, 6.5 Hz, 1H), 2.90 (m, 1H), 2.71 (m, 2H), 2.47 (m, 1H), 2.32 (m, 1H), 2.22 (dd, $J$ = 11.3, 13.5 Hz, 1H), 1.96 (dd, $J$ = 2.9, 13.6 Hz, 1H), 1.57 (s, 3H), 1.21 (d, $J$ = 7.1 Hz, 3H), 1.10 (d, $J$ = 6.9 Hz, 3H), 0.99 (d, $J$ = 7.0 Hz, 3H), 0.96 (d, $J$ = 6.9 Hz, 3H), 0.92 (s, 9H), 0.89 (d, $J$ = 6.8 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 217.0, 159.2, 141.4, 133.6, 132.8, 132.1, 130.8, 130.2, 129.7, 129.3, 117.8, 114.0, 113.7, 83.5, 80.7, 75.3, 55.3, 49.2, 43.4, 42.8, 36.5, 36.3, 34.4, 26.2, 23.1, 19.2, 18.4, 17.6, 17.4, 15.3, 14.3, −3.6, −3.7; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{37}H_{60}O_4SiNa$ 619.4155, found 619.4158; $[\alpha]^{20}_D$ +24.6° (*c* 0.5, $CHCl_3$).

**(3*S*,4*S*,5*S*,6*Z*,11*R*,12*S*,13*S*,14*Z*)-12-(Carbamoyloxy)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,5,7,9,11,13-hexamethyl-1,6,14,16-heptadecatetraen-10-ol (34).** To a solution of 7 mg (13 $\mu$mol) of carbamate in 500 $\mu$L of THF was added 15 mg (390 $\mu$mol) of $NaBH_4$ in 500 $\mu$L of EtOH. After the reaction was stirred at ambient temperature for 1.5 h, it was quenched with 1 mL of MeOH, stirred for 1 h, concentrated under a stream of $N_2$, and chromatographed (25% EtOAc/hexanes) to provide 4 mg (7 $\mu$mol, 57%) of **34** as a colorless oil: IR (thin film/NaCl) 3358 (br), 3354 (br), 1713 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.62 (ddd, $J$ = 10.1, 16.0, 20.4 Hz, 1H), 6.05 (apparent t, $J$ = 11.0 Hz, 1H), 6.85 (ddd, $J$ = 8.1, 10.4, 17.4 Hz, 1H), 5.36 (t, $J$ = 10.5 Hz, 1H), 5.24 (d, $J$ = 16.8 Hz, 1H), 5.13 (d, $J$ = 10.1 Hz, 1H), 4.97 (d, 10.1H, a), 4.94 (dd, $J$ = 2.1, 10.1 Hz, 1H), 4.89 (dd, $J$ = 3.1, 17.3 Hz, 1H), 4.76 (dd, $J$ = 5.2, 6.4 Hz, 1H), 4.52 (br s, 2H), 3.28 (m 2), 3.02 (ddd, $J$ = 6.7, 10.3, 13.2 Hz, 1H), 2.43 (ddd, $J$ = 6.8, 10.0, 13.7 Hz, 1H), 2.33 (ddd, $J$ = 3.3, 7.7, 10.3 Hz, 1H), 1.98−1.91 (m 2), 1.87 (m, 1H), 1.73 (d, $J$ = 5.6 Hz, 1H), 1.60 (d, $J$ = 1.0 Hz, 3H), 1.02 (d, $J$ = 6.8 Hz, 3H), 0.98 (d, $J$ = 7.0 Hz, 3H), 0.96 (d, $J$ = 7.0 Hz, 3H), 0.92 (s, 9H), 0.89 (d, $J$ = 6.7 Hz, 3H), 0.81 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 157.0, 141.5, 133.3, 132.0, 131.6, 131.4, 130.0, 118.1, 113.9, 80.9, 79.5, 77.2, 42.7, 37.0, 36.5, 35.8, 34.7, 33.2, 26.2, 22.9, 18.5, 18.0, 17.5, 14.3, 8.3, -3.5, −3.6; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{30}H_{55}NO_4SiNa$ 544.3795, found 544.3798; $[\alpha]^{20}_D$ +26.0° (*c* 0.5, $CHCl_3$).

**(3*S*,4*S*,5*S*,6*Z*,11*R*,12*S*,13*S*,14*Z*)-12-(Carbamoyloxy)-3,5,7,9,11,13-hexamethyl-1,6,14,16-heptadecatetraen-4,10-diol (35).** To 1.6 mg (3 mol) of **34** was added 250 $\mu$L of 1% HCl in MeOH. (The HCl solution was made by the addition of 500 $\mu$L of concentrated HCl to 50 mL of MeOH.) After 6.5 h of stirring at ambient temperature, the reaction was quenched by the addition of 50 mg of $NaHCO_3$, concentrated under a stream of $N_2$, and chromatographed (30% EtOAc/hexanes) to provide 1.0 mg (2.5 $\mu$mol, 83%) of **35** as a colorless oil: IR (thin film/NaCl) 3452 (br), 3358 (br), 1716 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.63 (ddd, $J$ = 6.5, 11.2, 17.2 Hz, 1H), 6.04 (apparent t, $J$ = 9.0 Hz, 1H), 5.80 (ddd, $J$ = 8.0, 10.4, 17.4 Hz, 1H), 5.37 (apparent t, $J$ = 10.5 Hz, 1H), 5.22 (dd, $J$ = 1.5, 16.8 Hz, 1H), 5.12 (br s, 1H), 5.14−5.10 (obscured dd, 2H), 5.06 (dd, $J$ = 0.9, 17.4 Hz, 1H), 4.75 (dd, $J$ = 4.6, 6.9 Hz, 1H), 4.50 (br s, 2H), 3.29 (br s, 1H), 3.17 (br s, 1H), 3.02 (ddd, $J$ = 6.8, 11.2, 14.6 Hz, 1H), 2.51 (ddd, $J$ = 6.7, 10.0, 13.3 Hz, 1H), 2.37 (dd, $J$ = 6.9, 12.3 Hz, 1H), 1.96−1.86 (m, 5H), 1.65 (d, $J$ = 1.1 Hz, 3H), 1.06 (d, $J$ = 6.9 Hz, 3H), 1.02 (d, $J$ = 6.7 Hz, 3H), 0.99 (d, $J$ = 6.9 Hz, 3H), 0.97 (d, $J$ = 6.9 Hz, 3H), 0.84 (d, $J$ = 6.0 Hz, 3H); HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{24}H_{41}O_4NNa$ 430.2931, found 490.2934.

**17-Acetoxydiscodermolide (36).** To 1.8 mg (1.8 $\mu$mol) of acetate was added 200 $\mu$L of 1% HCl in MeOH. (The HCl solution was made by the addition of 500 $\mu$L of concentrated HCl to 50 mL of MeOH.)

After 48 h of stirring at ambient temperature, the reaction was quenched by the addition of 50 mg of $NaHCO_3$, concentrated under a stream of $N_2$, and chromatographed (5% MeOH/$CHCl_3$) to provide 0.5 mg (0.8 $\mu$mol, 42%) of **36** as a colorless oil: IR (thin film/NaCl) 3377 (br), 1716 $cm^{-1}$; $^1H$ NMR (500 MHz, 10% $CD_3OD$-$CDCl_3$) $\delta$ 6.71 (ddd, $J$ = 11.0, 16.8, 21.2 Hz, 1H), 6.05 (overlapping dd, $J$ = 11.0 Hz, 1H), 5.53−5.43 (obscured dd, 2H), 5.34 (apparent t, $J$ = 10.5 Hz, 1H), 5.23 (dd, $J$ = 2.0, 16.8 Hz, 1H), 5.16 (d, $J$ = 10.1 Hz, 1H), 5.12 (d, $J$ = 9.8 Hz, 1H), 4.81 (t, $J$ = 5.9 Hz, 1H), 4.71 (br t, $J$ = 7.2 Hz, 1H), 4.64−4.59 (partially obscured d, 2H), 4.58 (br s, 2H), 3.76 (dd, $J$ = 4.1, 8.2 Hz, 1H), 3.15 (br t, $J$ = 5.6 Hz, 1H), 3.12 (partially obscured ddd, $J$ = 6.1, 10.8, 17.2 Hz, 1H), 2.74 (ddd, $J$ = 6.6, 9.3, 13.1 Hz, 1H), 2.68 (m, 1H), 2.43 (m, 1H), 2.10 (s, 3H), 2.06 (partially obscured m, 1H), 1.97 (m, 1H), 1.82 (ddd, $J$ = 2.3, 7.6, 14.3 Hz, 1H), 1.71 (dd, $J$ = 2.9, 10.3 Hz, 1H), 1.68 (t, $J$ = 2.7 Hz, 1H), 1.65 (d, $J$ = 0.9 Hz, 3H), 1.32 (d, $J$ = 7.3 Hz, 3H), 1.08 (d, $J$ = 7.0 Hz, 3H), 1.01 (d, $J$ = 6.8 Hz, 3H), 0.98 (d, $J$ = 6.8 Hz, 3H), 0.94 (d, $J$ = 6.7 Hz, 3H), 0.93 (d, $J$ = 6.7 Hz, 3H), 0.73 (d, $J$ = 6.7 Hz, 3H); HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{35}H_{57}O_9NNa$ 658.3928, found 658.3931.

**[3*S*-[3*β*,4α,5α,6α(2*R*,3*Z*,5*R*,6*R*,7*R*,8*Z*,11*S*,13*R*,14*S*,15*S*,16*Z*)]]-6-[14-Acetoxy-2,6-dihydroxy-5,7,9,11,13,15-hexamethyl-12-oxo-3,8,16,18-nonadecatetraenyl]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-2*H*-pyran-2-one (37).** To 9 mg (9 $\mu$mol) of silyl ether was added 1 mL of 1% HCl in MeOH. (The HCl solution was made by the addition of 500 $\mu$L of concentrated HCl to 50 mL of MeOH.) After for 48 h of stirring at ambient temperature, the reaction was quenched by the addition of 50 mg of $NaHCO_3$, concentrated under a stream of $N_2$, and chromatographed (5% MeOH/$CHCl_3$) to provide 3 mg (5 $\mu$mol, 56%) of **37** as a colorless oil: IR (thin film/NaCl) 3441 (br), 1713 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.48 (dddd, $J$ = 10.3, 16.0, 16.9, 20.5 Hz, 1H), 6.04 (apparent t, $J$ = 10.9 Hz, 1H), 5.56 (dd, $J$ = 8.0, 11.0 Hz, 1H), 5.40−5.35 (obscured, 2H), 5.27 (d, $J$ = 9.7 Hz, 1H), 5.22 (m, 1H), 5.18 (dd, $J$ = 5.8, 6.8 Hz, 1H), 5.11 (d, $J$ = 10.1 Hz, 1H), 4.75 (t, $J$ = 7.9 Hz, 1H), 4.62 (ddd, $J$ = 2.3, 10.1, 12.2 Hz, 1H), 3.75 (d, $J$ = 3.6 Hz, 1H), 3.14 (dd, $J$ = 3.2, 7.6 Hz, 1H), 2.90−2.84 (overlapping m, 3H), 2.75 (ddd, $J$ = 7.1, 9.5, 14.4 Hz, 1H), 2.69 (m, 1H), 2.54 (ddd, $J$ = 3.6, 6.7, 10.1 Hz, 1H), 2.30 (dd, $J$ = 6.3, 13.5 Hz, 1H), 2.17 (br s, 1H), 2.01 (s, 3H), 1.97−1.92 (overlapping m, 2H), 1.88 (ddd, $J$ = 2.4, 6.6, 11.4 Hz, 1H), 1.73 (dd, $J$ = 3.0, 10.2 Hz, 1H), 1.69 (d, $J$ = 1.2 Hz, 3H), 1.32 (d, $J$ = 7.4 Hz, 3H), 1.07 (overlapping d, $J$ = 7.2 Hz, 3H), 1.06 (overlapping d, $J$ = 7.2 Hz, 3H), 0.99 (overlapping d, $J$ = 7.0 Hz, 3H), 0.95 (d, $J$ = 6.8 Hz, 3H), 0.91 (d, $J$ = 6.7 Hz, 3H); HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{34}H_{54}O_8Na$ 613.3713, found 613.3716.

**[3*S*-[3*β*,4α,5α,6α(2*R*,3*Z*,5*R*,6*R*,7*R*,8*Z*,11*S*,13*R*,14*S*,15*S*,16*Z*)]]-6-[2,6-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-14-[[[5-[[(9′-fluorenylmethoxy)carbonyl]amino]pentyl]carbonyl]oxy]-5,7,9,11,13,15-hexamethyl-12-oxo-3,8,16,18-nonadecatetraenyl]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-2*H*-pyran-2-one (38).** To as solution of 26 mg (29 $\mu$mol) of hydroxy ketone and 50 mg (143 $\mu$mol) of Fmoc-*N*-aminocaproic acid in 500 $\mu$L of $CH_2Cl_2$ was added 27.4 mg (143 $\mu$mol) of EDC, 48 $\mu$L (286 $\mu$mol) of DIEA, and 2 mg of DMAP. After stirring at ambient temperature for 5 h, the reaction mixture was concentrated under a stream of $N_2$ and chromatographed (5% EtOAc/hexanes) to provide 24 mg (19.8 $\mu$mol, 68%) of **38** as a colorless oil: IR (thin film/NaCl) 1734, 1718 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.76 (d, $J$ = 7.6 Hz, 2H), 7.59 (d, $J$ = 7.6 Hz, 2H), 7.40 (t, $J$ = 7.3 Hz, 2H), 7.31 (t, $J$ = 1.0, 7.5 Hz, 2H), 6.48 (ddd, $J$ = 10.7, 16.4, 21.1 Hz, 1H), 6.04 (apparent t, $J$ = 10.8 Hz, 1H), 5.28−5.33 (overlapping m, 2H), 5.19−5.26 (overlapping m, 3H), 5.11 (d, $J$ = 10.1 Hz, 1H), 5.04 (d, $J$ = 9.2 Hz, 1H), 4.87 (br s, 1H), 4.78 (br t, $J$ = 9.2 Hz, 1H), 4.52 (t, $J$ = 10.1 Hz, 1H), 4.39 (d, $J$ = 6.8 Hz, 2H), 4.21 (t, $J$ = 6.5 Hz, 1H), 3.64 (t, $J$ = 2.5 Hz, 1H), 3.26 (t, $J$ = 5.1 Hz, 1H), 3.19 (dd, $J$ = 6.6, 15.6 Hz, 1H), 2.90 (m, 1H), 2.79 (m, 1H), 2.62 (overlapping dd, $J$ = 2.7, 7.6 Hz, 1H), 2.60 (obscured m, 1H), 2.50 (dd, $J$ = 5.4, 11.0 Hz, 1H), 2.45 (obscured m, 1H), 2.35 (m, 1H), 2.28 (t, $J$ = 7.3 Hz, 2H), 2.02 (dd, $J$ = 4.8, 10.2 Hz, 1H), 1.83 (m, 1H), 1.73 (m, 1H), 1.60 (d, $J$ = 1.0 Hz, 3H), 1.50 (obscured m, 3H), 1.33 (overlapping m, 6H), 1.22 (d, $J$ = 7.6 Hz, 3H), 1.07 (d, $J$ = 7.0 Hz, 3H), 0.98 (d, $J$ = 6.7 Hz, 3H), 0.97 (d, $J$ = 6.7 Hz, 3H), 0.95 (d, $J$ = 7.0 Hz, 3H), 0.87 (obscured d, 3H), 090 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.07 (overlapping s, 6H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), −0.01 (s, 3H); LRMS (FAB, NBA/NaI) *m/z* calcd for $C_{70}H_{113}NO_{10}Si_3Na$ 1234, found 1234.

**17-[[[5-[[(9′-Fluorenylmethoxy)carbonyl]amino]pentyl]carbonyl]oxy]discodermolide (39).** To 5 mg (5 $\mu$mol) of silyl ether was added 500 $\mu$L of 1% HCl in MeOH. (The HCl solution was made by the addition of 500 $\mu$L of concentrated HCl to 50 mL of MeOH.) After 72 h of stirring at ambient temperature, the reaction was quenched by with 50 mg of $NaHCO_3$, concentrated, and chromatographed (5% MeOH/$CHCl_3$) to provide 1.6 mg (5 $\mu$mol, 56%) of **39** as a colorless oil: IR (thin film/NaCl) 3354 (br), 1711 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.70 (d, $J$ = 7.5 Hz, 2H), 7.53 (d, $J$ = 7.4 Hz, 2H), 7.34 (t, $J$ = 7.4 Hz, 2H), 7.25 (t, $J$ = 7.4 Hz, 2H), 6.67 (ddd, $J$ = 10.6, 16.8, 21.3 Hz, 1H), 6.05 (apparent t, $J$ = 10.9 Hz, 1H), 5.43 (apparent t, $J$ = 10.2 Hz, 1H), 5.34 (ap t, $J$ = 10.6 Hz, 1H), 5.24 (s, 1H), 5.20 (obscured d, 1H), 5.14 (d, $J$ = 10.1 Hz, 1H), 5.06 (d, $J$ = 9.4 Hz, 1H), 4.92 (dd, $J$ = 4.1, 7.9. Hz, 2H), 4.71 (t, $J$ = 7.3 Hz, 1H), 4.66 (apparent t, $J$ = 5.9 Hz, 1H), 4.61 (apparent t, $J$ = 8.9 Hz, 1H), 4.53 (br s, 2H), 4.40 (d, $J$ = 7.0 Hz, 2H), 4.21 (d, $J$ = 6.5 Hz, 1H), 3.73 (br s, 1H), 3.19 (m, 4H), 3.15 (m, 1H), 3.09 (m, 1H), 2.74 (m, 1H), 2.67 (m, 1H), 2.40 (m, 2H), 2.35 (m, 2H), 2.08 (br s, 1H), 1.99-1.67 (overlapping m, 10H), 1.66 (apparent s, 3H), 1.64−1.38 (overlapping m, 3H), 1.31 (d, $J$ = 7.3 Hz, 3H), 1.06 (d, $J$ = 7.0 Hz, 3H), 1.00 (d, $J$ = 6.8 Hz, 3H), 0.97 (d, $J$ = 6.7 Hz, 3H), 0.95 (d, $J$ = 6.7 Hz, 3H), 0.93 (d, $J$ = 6.9 Hz), 3H); HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{53}H_{76}N_2O_{11}Na$ 939.5343 found 939.5345.

**(2*R*,3*S*,4*R*)-2,4-Dimethyl-5-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-3-[(4-methoxyphenyl)methoxy]hexan-1-ol (40).** To 2.41 g (4.9 mmol) of silyl ether was added 37.5 mL of a HF-pyridine buffered with excess pyridine solution (prepared by adding 2.5 mL of HF-pyridine and then 25 mL of THF to 10 mL of pyridine). After 6 h of stirring at ambient temperature, the reaction was quenched by the slow addition of a saturated $NaHCO_3$ solution and extracted 3 × 50 mL of $CH_2Cl_2$. The combined organic layers were washed with 2 × 50 mL of saturated $CuSO_4$, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (2% EtOAc/hexanes) to provide 1.6 g (4.0 mmol, 83%) of **40** as a colorless oil: IR (thin film/NaCl) 3450 (br), 1614 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ (assigned resonances of major epimer (5:1)), 7.26 (d, $J$ = 8.6 Hz, 2H), 6.87 (d, $J$ = 8.6 Hz, 2H), 4.60 (d, $J$ = 10.5 Hz, 1H), 4.50 (d, $J$ = 10.5 Hz, 1H), 3.82 (dd, $J$ = 6.3, 7.2 Hz, 1H), 3.79 (s, 3H), 3.70 (dd, $J$ = 2.8, 7.5 Hz, 1H), 3.65 (dd, $J$ = 2.0, 4.1 Hz, 1H), 1.85 (ddd, $J$ = 4.3, 6.7, 11.2 Hz, 1H), 1.69 (apparent ddd, $J$ = 2.7, 7.1, 9.9 Hz, 1H), 1.18 (d, $J$ = 6.2 Hz, 3H), 0.97 (d, $J$ = 7.0 Hz, 3H), 0.96 (d, $J$ = 7.0 Hz, 3H), 0.94 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ (mixture of epimers), 159.3, 130.8, 129.2, 129.1, 113.9, 113.8, 84.2, 74.5, 71.0, 66.6, 55.2, 44.6, 38.8, 26.0, 26.0, 21.4, 18.1, 15.0, 10.5, −3.6, −4.4; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{22}H_{40}O_4SiNa$ 419.2591, found 419.2594.

**(*Z*)-(3*R*,4*S*,5*R*)-3,5-Dimethyl-6-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-1-iodo-4-[(4-methoxyphenyl)methoxy]hex-1-ene.** To a solution of 159 mg (400 $\mu$mol) of **40** in 3 mL of $CH_2Cl_2$ was added 215 mg (480 $\mu$mol) of Dess−Martin periodinane. After being stirred at ambient temperature for 10 min, the reaction was quenched by the addition of 10 mL of saturated $Na_2S_2O_3$ solution and 10 mL of saturated $NaHCO_3$ solution and diluted with 30 mL of diethyl ether. After 30 min of stirring, the layers were separated and the organic layer was washed with 3 × 120 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and used crude in the next reaction.

To a suspension of 473 mg (890 $\mu$mol) of (iodomethyl)triphenylphosphonium iodide in 2 mL of THF was added 890 $\mu$L (890 $\mu$mol, 1 M in THF) of NaHMDS, and the slurry was stirred for 20 min at ambient temperature. After the dark red mixture was cooled to −78 °C, 550 $\mu$L of HMPA was added, followed by the crude aldehyde in 2 mL of THF. After being warmed to ambient temperature, the reaction mixture was stirred for 1 h before being diluted with hexanes, filtered through 50 g of silica gel, concentrated *in vacuo*, and chromatographed (3% EtOAc/hexanes) to provide 182 mg (352 mol, 88%) of vinyl iodide as a colorless oil: IR (thin film/NaCl) 1612 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.30 (d, $J$ = 8.8 Hz, 2H), 6.88 (d, $J$ = 8.7 Hz, 2H), 6.30 (dd, $J$ = 7.3, 9.1 Hz, 1H), 6.18 (d, $J$ = 7.4 Hz, 1H), 4.55 (obscured d, $J$ = 7.8 Hz, 1H), 4.55 (obscured d, $J$ = 8.5 Hz, 1H), 3.98 (ddd, $J$ = 3.1, 6.2, 9.3 Hz, 1H), 3.81 (s, 3H), 3.39 (dd, $J$ = 2.7, 8.1 Hz, 1H), 2.89 (apparent ddd, $J$ = 2.6, 6.8, 9.4 Hz, 1H), 1.48 (apparent ddd, $J$ = 3.0,

6.8, 10.0 Hz, 1H), 1.13 (d, $J = 6.2$ Hz, 3H), 1.12 (d, $J = 7.0$ Hz, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 0.95 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 158.9, 131.1, 129.1, 113.7, 83.8, 81.8, 74.9, 68.2, 55.2, 44.3, 42.5, 25.9, 17.1, 9.4, −3.8, −4.6; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{23}H_{39}IO_3SiNa$ 541.1611, found 541.1611.

**2,2-Dimethylpropanoic Acid, (5*E*,7*Z*,9*S*,10*S*,11*R*)-9,11-Dimethyl-12-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-10-[(4-methoxyphenyl)-methoxy]-5,7-tridecadienyl Ester (41).** To a solution of 1.64 g (3.2 mmol) of vinyl iodide and 1.43 g (4.7 mmol) of (*E*)-6-catecholboranoto-5-hexen-1-ol pivalate in 100 mL of degassed THF was added 9.5 mL (10% in $H_2O$) of thallium hydroxide. To this solution was added a solution of 915 mg (790 $\mu$mol) of $Pd(PPh_3)_4$ in 40 mL of degassed THF. After heating to reflux for 30 min under an argon atmosphere, the reaction was diluted with 250 mL of diethyl ether and the layers were separated. The organic layer was dried over $MgSO_4$, filtered through 100 g of silica gel, concentrated *in vacuo*, and chromatographed to provide 680 mg (1.2 mmol, 38%) of **41** as a colorless oil: IR (thin film/NaCl) 1730 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.28 (d, $J =$ 8.6 Hz, 2H), 6.86 (d, $J = 8.2$ Hz, 2H), 6.29 (dd, $J = 10.7$, 15.1 Hz, 1H), 5.97 (ddd, $J = 2.6$, 11.0, 13.6 Hz, 1H), 5.64 (overlapping ddd, $J$ = 7.0, 14.5, 22.0 Hz, 1H), 5.42 (dd, $J = 10.6$, 21.2 Hz, 1H), 4.55 (d, $J = 10.7$ Hz, 1H), 4.47 (d, $J = 10.8$ Hz, 1H), 4.06 (t, $J = 6.6$ Hz, 2H), 3.83 (dd, $J = 4.3$, 6.1 Hz, 1H), 3.79 (s, 3H), 3.33 (m, 1H), 2.97 (m, 1H), 2.14 (dd, $J = 7.3$, 14.6 Hz, 2H), 1.64 (m, 2H), 1.58 (ddd, $J =$ 4.3, 6.8, 11.0 Hz, 1H), 1.47 (m, 2H), 1.21 (s, 9H), 1.08 (apparent t, $J$ = 7.3 Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.93 (partially obscured d, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 178.4, 158.9, 158.9, 134.1, 134.0, 132.5, 131.5, 131.4, 129.0, 128.9, 128.3, 128.2, 126.2, 113.5, 83.9, 83.7, 74.4, 74.3, 69.6, 69.0, 64.1, 55.1, 43.9, 43.7, 38.6, 36.1, 35.4, 32.4, 32.3, 28.1, 27.1, 26.0, 25.9, 25.8, 25.7, 21.6, 19.8, 18.6, 18.5, 18.0, 18.0, 10.1, 9.7, −4.0, −4.1, −4.7, −4.8; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{34}H_{58}O_5$-SiNa 597.3948, found 597.3951.

**2,2-Dimethylpropanoic Acid, (5*E*,7*Z*,9*S*,10*S*,11*R*)-9,11-Dimethyl-10-[(4-methoxyphenyl)methoxy]-12-oxo-5,7-tridecadienyl Ester (42).** To a solution of 323 mg (650 $\mu$mol) of alcohol in 5 mL of $CH_2Cl_2$ was added 413 mg (970 $\mu$mol) of Dess−Martin periodinane. After stirring at ambient temperature for 10 min, the reaction was quenched by the addition of 10 mL of saturated $Na_2S_2O_3$ solution, 10 mL of saturated $NaHCO_3$ solution, and diluted with 30 mL of diethyl ether. After 30 min of stirring, the layers were separated and the organic layer was washed with 3 × 120 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed to provide 277 mg (560 $\mu$mol, 86%) of **42** as a colorless oil: IR (thin film/NaCl) 1726, 1711cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.24 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 6.15 (ddd, $J = 0.9$, 11.0, 15.0 Hz, 1H), 5.98 (overlapping dd, $J = 11.0$ Hz, 1H), 5.64 (overlapping ddd, $J =$ 7.0, 14.4, 21.9 Hz, 1H), 5.35 (apparent t, $J = 10.6$ Hz, 1H), 4.54 (d, $J$ = 10.6 Hz, 1H), 4.46 (d, $J = 10.7$ Hz, 1H), 4.04 (apparent t, $J = 6.5$ Hz, 2H), 3.78 (s, 3H), 3.62 (dd, $J = 3.9$, 7.7 Hz, 1H), 2.78 (m, 1H), 2.74 (m, 1H), 2.09 (s, 3H), 1.62 (m, 2H), 1.43 (m, 2H), 1.18 (s, 9H), 1.17 (d, $J = 6.7$ Hz, 3H), 1.06 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 212.2, 178.5, 159.1, 134.7, 131.4, 130.7, 129.2, 129.0, 125.9, 113.6, 83.7, 74.9, 64.1, 55.1, 50.6, 38.6, 36.0, 32.3, 29.6, 28.1, 27.1, 25.7, 18.6, 13.3; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{28}H_{42}O_5$-Na 481.2928, found 481.2930; $[\alpha]^{20}_D$ +53.4° (*c* 0.5, $CHCl_3$).

**2,2-Dimethylpropanoic Acid, [2*S*-[2α(5*E*, 7*Z*,9*S*,10*S*,11*R*,13*R*, 15*Z*,17*R*,18*R*,19*R*,20*Z*,22*R*),3*β*,4*β*,5α,6*β*]]-18,22-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-23-[4-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]tetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-9,11, 13,15,17,19-hexamethyl-10-[(4-methoxyphenyl)methoxy]-12-oxo-5,7,15,20-trieicosatetraenyl ester (43).** To a cooled (−78 °C) solution of 141 mg (11 $\mu$mol) of ketone in 1 mL of THF was added 1.13 mL (565 $\mu$mol, 0.5 M in THF) of $LiN(SiMe_2Ph)_2$. After the reaction was stirred at −78 °C for 1 h, 704 $\mu$L (1.6 g, 11 mmol) of methyl iodide was added. The reaction was warmed to 0 °C and stirred at ambient temperature for 3 h. After the reaction was quenched with 1.5 mL of saturated $NH_4Cl$ solution, the mixture was extracted with 30 mL of EtOAc and the layers were separated. The organic layer was dried over MgSO4, filtered, concentrated *in vacuo*, and chromatographed (2% EtOAc.hexanes). The resulting colorless oil was purified by HPLC (4% EtOAc/hexanes) to provide 51 mg (41 $\mu$mol, 36%) of **43** as a colorless oil: IR (thin film/NaCl) 1730 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.49 (dd, $J = 1.4$, 8.3 Hz, 2H), 7.28−7.21 (overlapping m, 5H), 6.86 (dd, $J = 2.8$, 9.5 Hz, 2H), 6.15 (dd, $J = 11.0$, 14.2 Hz, 1H), 5.98 (apparent t, $J = 11.0$ Hz, 1H), 5.63 (overlapping ddd, $J = 7.1$, 14.4 Hz, 1H), 5.44 (apparent t, $J = 10.2$ Hz, 1H), 5.31 (d, $J = 1.8$ Hz, 1H), 5.29 (partially obscured dd, $J = 7.5$, 11.0 Hz, 1H), 5.20 (br d, $J$ = 9.8 Hz, 1H), 5.15 (t, $J = 10.2$ Hz, 1H), 4.56 (partially obscured t, $J = 11.0$ Hz, 1H), 4.54 (partially obscured d, 1H), 4.52 (d, $J = 10.7$ Hz, 1H), 4.04 (obscured m, 1H), 3.80 (s, 3H), 3.64−3.59 (overlapping m, 3H), 3.27 (dd, $J = 3.7$, 6.2 Hz, 1H), 2.90 (apparent t, $J = 7.2$ Hz, 1H), 2.72−2.64 (overlapping m, 3H), 2.51 (m, 1H), 2.18 (dd, $J = 11.1$, 13.4 Hz, 1H), 2.12−1.98 (overlapping m, 4H), 1.64−1.59 (obscured m, 4H), 1.59 (s, 3H), 1.50 (m, 1H), 1.46−1.39 (overlapping m, 2H), 1.19 (s, 9H), 1.07 (d, $J = 7.7$ Hz, 3H), 1.06 (d, $J = 7.3$ Hz, 3H), 0.98 (d, $J = 7.0$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.91 (s, 9H), 0.90 (obscured d, 3H), 0.88 (s, 9H), 0.80 (obscured d, 3H), 0.78 (s, 9H), 0.75 (d, $J = 6.8$ Hz, 3H), 0.03 (overlapping s, 9H), 0.01 (s, 3H), −0.13 (s, 3H), −0.26 (s, 3H); LRMS (FAB, NBA/NaI) *m/z* calcd for $C_{73}H_{124}O_9Si_3SNa$ 1283, found 1283.

**[3*R*-[3α,4*β*,5*β*,6α(2*R*,3*Z*,5*R*,6*R*,7*R*,8*Z*,11*S*,12*R*,13*R*,14*S*,15*S*, 16*Z*,17*E*)]]-6-[2,6-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-14-(carbamoyloxy)-23-[(2,2-dimethylpropanoyl)oxy]-5,7,9,11,13,15-hexamethyl-12-hydroxy-3,8,16,18-trieicosatetraenyl]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-2*H*-pyran-2-one (44).** To a solution of 4 mg (3.5 $\mu$mol) of ketone in 500 $\mu$L of THF was added 14 $\mu$L (14 $\mu$mol, 1 M in THF) of $LiAl(OtBu)_3H$. After being stirred for 2 h at ambient temperature, the reaction was quenched with 200 $\mu$L of saturated $NH_4Cl$ solution, stirred for 1 h, dried over $Na_2SO_4$, filtered, concentrated *in vacuo*, and chromatographed (25% EtOAc/hexanes) to provide 2 mg (1.8 $\mu$mol, 51%) of **44** as a colorless oil: IR (thin film/NaCl) 1726 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.29 (dd, $J = 9.2$, 14.4 Hz, 1H), 5.98 (apparent t, $J = 11.0$ Hz, 1H), 5.68 (overlapping ddd, $J = 6.9$, 14.3 Hz, 1H), 5.29 (dd, $J = 7.8$, 11.2 Hz, 1H), 5.26−5.20 (overlapping dd, 2H), 5.19 (d, $J = 9.8$ Hz, 1H), 4.80 (t, $J = 8.8$ Hz, 1H), 4.75 (dd, $J = 5.0$, 6.5 Hz, 1H), 4.53 (obscured t, $J = 10.2$ Hz, 1H), 4.51 (br s, 2H), 4.06 (t, $J = 6.6$ Hz, 2H), 3.64 (t, $J = 2.4$ Hz, 1H), 3.28 (ddd, $J = 3.7$, 5.8, 8.1 Hz, 2H), 3.00 (ddd, $J =$ 6.6, 9.8, 13.3 Hz, 1H), 2.63 (obscured m, 1H), 2.63 (dd, $J = 2.7$, 7.5 Hz, 1H), 2.46 (m, 1H), 2.15 (m, 2H), 1.96−1.87 (overlapping m, 3H), 1.82 (m, 3H), 1.72 (m, 1H), 1.64 (m, 2H), 1.60 (s, 3H), 1.47 (t, $J =$ 7.5 Hz, 2H), 1.23 (d, $J = 7.7$ Hz, 3H), 1.20 (s, 9H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.96 (d, $J = 7.0$ Hz, 3H), 0.91 (s, 9H), 0.88 (s, 9H), 0.88 (obscured d, 3H), 0.87 (s, 9H), 0.80 (d, $J = 6.2$ Hz, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H); LRMS (FAB, NBA/NaI) *m/z* calcd for $C_{60}H_{113}O_{10}Si_3NNa$ 1114, found 1114.

**2,2-Dimethylpropanoic Acid, 24-(Hydroxybutyl)discodermolide Ester (45).** To 2 mg (1.8 $\mu$mol) of **44** was added 200 $\mu$L of 1% HCl in MeOH. (The HCl solution was made by the addition of 500 $\mu$L of concentrated HCl to 50 mL of MeOH.) After stirring for 48 h at ambient temperature, the reaction was quenched by the addition of 50 mg of $NaHCO_3$, concentrated under a stream of $N_2$, and chromatographed (5% MeOH/$CHCl_3$) to provide 0.8 mg (1.1 $\mu$mol, 61%) of **45** as a colorless oil: IR (thin film/NaCl) 3427 (br), 1713 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.27 (dd, $J = 9.8$, 13.8 Hz, 1H), 5.98 (apparent t, $J =$ 11.2 Hz, 1H), 5.67 (m, 1H), 5.53 (dd, $J = 7.9$, 11.2 Hz, 1H), 5.44 (apparent t, $J = 10.5$ Hz, 1H), 5.23 (t, $J = 10.7$ Hz, 1H), 5.16 (d, $J =$ 9.9 Hz, 1H), 4.71 (overlapping m, 2H), 4.63 (overlapping m, 2H), 4.06 (t, $J = 6.6$ Hz, 2H), 3.73 (m, 1H), 3.29 (m, 1H), 3.20 (m, 1H), 2.97 (m, 1H), 2.80 (m, 1H), 2.69 (m, 1H), 2.59 (m, 1H), 2.14 (overlapping m, 2H), 2.09 (br s, 1H), 1.97−1.88 (overlapping m, 4H), 1.67 (m, 1H), 1.66 (s, 3H), 1.49 (overlapping m, 4H), 1.32 (d, $J = 7.3$ Hz, 3H), 1.20 (s, 9H), 1.08 (d, $J = 7.0$ Hz, 3H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.99 (d, $J = 6.6$ Hz, 3H), 0.98 (d, $J = 6.7$ Hz, 3H), 0.95 (d, $J = 6.7$ Hz, 3H), 0.83 (d, $J = 5.6$ Hz, 3H); HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{42}H_{71}O_{10}N$ 772.4972, found 772.4976.

**[3*R*-[3a,4b,5b,6a(2*R*,3*Z*,5*R*,6*R*,7*R*,8*Z*,11*S*,13*R*,14*S*,15*S*,16*Z*,17*E*)]]-6-[2,6-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,7,9,11,13,15-hexamethyl-14-[(4-methoxyphenyl)methoxy]-12-oxo-20-[[[[[[(2-propenyl-oxy)carbonyl]amino]hexyl]amino]carbonyl]oxy]3,8,16,18-trieicosatetraenyl]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-tetrahydro-3,5-dimethyl-2*H*-pyran-2-one (47).** To a cooled (−78 °C)

solution of 68 mg (54 $\mu$mol) of **46** in 200 $\mu$L of $CH_2Cl_2$ was added 800 $\mu$L (800 $\mu$mol, 1 M in $CH_2Cl_2$) of DIBAL-H. After being stirred at −78 °C for 2 h, the reaction was quenched by the addition of 10 mL of 0.5 M NaK tartrate saturated with NaCl and diluted with 25 mL of $CH_2Cl_2$. After 12 h of stirring at ambient temperature, the layers were separated and the aqueous layer was extracted with 3 × 20 mL of $CH_2Cl_2$. The organic layers were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed to provide 60 mg (50 $\mu$mol, 93%) of a mixture of epimeric diols that was used directly in the following reaction.

To a solution of 60 mg (50 $\mu$mol) of diols in 1 mL of MeCN was added 42 $\mu$L (40 mg, 510 $\mu$mol) of pyridine, 132 mg (510 $\mu$mol) of *N*,*N*′-disuccinimidyl carbonate, and 5 mg of DMAP. After being stirred at ambient temperature for 30 min, the reaction mixture was concentrated under a stream of $N_2$ and chromatographed (25% EtOAc/hexanes) to provide 45 mg of the mixed carbonate that was used directly in the following reaction.

To a solution of the mixed carbonate in 2 mL of $CH_2Cl_2$ was added 76 mg (750 $\mu$mol) of *N*-Aloc-1,6-hexanediamine and 42 mg (340 $\mu$mol) of DMAP. After 10 min of stirring at ambient temperature, the reaction mixture was concentrated under a stream of $N_2$ and chromatographed (20% EtOAc/hexanes) to provide 56 mg (40 $\mu$mol, 80% for two steps) of carbamate that was used directly in the following reaction.

To a solution of 56 mg (40 $\mu$mol) of carbamate in 500 $\mu$L of THF were added 500 $\mu$L of MeCN, 500 $\mu$L of pH 7 buffer solution concentrate, and 108 mg (400 $\mu$mol) of $HgCl_2$. The suspension was stirred for 20 min, when TLC analysis indicated no starting material remained, and then was treated with 10 mL of brine and extracted into 3 × 25 mL of $CH_2Cl_2$. The organic layers were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (25% EtOAc/hexanes) to provide 44 mg of a mixture of lactols.

The lactols were dissolved in 6 mL of acetone, cooled to 0 °C, and treated with 500 $\mu$L (500 $\mu$mol) of 1 M Jones oxidant solution. The reaction was stirred at 0 °C for 30 min, then warmed to ambient temperature for 5 min. Excess oxidant was quenched by addition of 500 $\mu$L of iPrOH and stirred for 30 min, diluted with 30 mL diethyl ether, filtered through Celite, concentrated *in vacuo*, and chromatographed (20% EtOAc/hexanes) to provide 28 mg (22 $\mu$mol, 55% for two steps) of **47** as a colorless oil: IR (thin film/NaCl) 1709 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.23 (d, $J$ = 8.6 Hz, 2H), 6.84 (d, $J$ = 8.6, 6.12, m Hz, 1H), 5.96 (apparent t, $J$ = 11.0 Hz, 1H), 5.90 (m, 1H), 5.63 (m, 1H), 5.35 (t, $J$ = 10.5 Hz, 1H), 5.31 (obscured m, 2H), 5.30 (obscured d, $J$ = 1.6 Hz, 1H), 5.27 (obscured d, $J$ = 1.3 Hz, 1H), 5.19 (dd, $J$ = 6.3, 10.4 Hz, 1H), 5.02 (d, $J$ = 9.2 Hz, 1H), 4.75 (overlapping m, 3H), 4.53 (dd, $J$ = 6.8, 9.7 Hz, 2H), 4.47 (apparent t, $J$ = 10.6 Hz, 1H), 4.02 (br s, 2H), 3.78 (s, 3H), 3.63 (overlapping m, 2H), 3.34 (m, 1H), 3.25 (m, 1H), 3.15 (br t, $J$ = 6.4 Hz, 4H), 2.72 (overlapping m, 2H), 2.60 (overlapping m, 2H), 2.43 (overlapping m, 2H), 2.35 (m, 1H), 2.07 (m, 2H), 2.01 (m, 2H), 1.73 (m, 1H), 1.70 (m, 1H), 1.67 (s, 3H), 1.58 (m, 3H), 1.49 (m, 4H), 1.42 (m, 2H), 1.32 (m, 5H), 1.25 (m, 1H), 1.25 (m, 1H), 1.21 (d, $J$ = 7.6 Hz, 3H), 1.16 (d, $J$ = 7.0 Hz, 3H), 1.04 (d, $J$ = 6.7 Hz, 3H), 0.96 (d, $J$ = 6.2 Hz, 3H), 0.95 (d, $J$ = 8.1 Hz, 3H), 0.90 (obscured d, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.865 (s, 9H), 0.06 (overlapping s 6), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), −0 (02, $J$ = s Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 213.3, 173.3, 159.1, 156.7, 156.3, 134.9, 134.2, 133.6, 133.0, 132.3, 131.6, 131.4, 131.3, 130.9, 130.8, 129.3, 129.1, 125.9, 117.5, 113.7, 96.2, 83.6, 80.4, 79.8, 76.8, 74.9, 74.8, 65.4, 64.7, 64.6, 64.4, 55.2, 50.1, 44.1, 42.7, 40.8, 40.7, 37.3, 36.1, 35.3, 34.2, 32.4, 2/9.9, 29.8, 28.7, 28.6, 28.0, 26.3, 26.2, 26.1, 26.0, 25.9, 25.9, 25.8, 25.7, 23.1, 23.0, 19.0, 18.7, 18.4, 18.3, 1831, 18.0, 17.9, 17.4, 17.3, 16.4, 16.3, 14.0, 13.5, −3.1, −4.3, −4.5, −4.9; LRMS (FAB, NBA/NaI) *m/z* calcd for $C_{72}H_{126}N_2O_{12}Si_3Na$ 1317 found 1317; $[\alpha]^{20}_D$ +32.0° (*c* 0.5, $CHCl_3$).

**[3*R*-[3a,4b,5b,6a (2*R*,3*Z*,5*R*,6*R*,7*R*,8*Z*,11*S*,12*R*,13*R*,14*S*,15*S*,16*Z*,17*E*)]]-6-[2,6-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-14-(carbamoyloxy)-5,7,9,11,13,15-hexamethyl-12-hydroxy-20-[[[[[[(2-propenyloxy)carbonyl]amino]hexyl]amino]carbonyl]oxy]-3,8,16,18-trieicosatetraenyl]-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-2*H*-pyran-2-one (48).** To a solution of 12 mg (9.7 mol) of ketone in 2 mL of THF was added 50 $\mu$L (50 $\mu$mol, 1 M in THF) of $LiAl(OtBu)_3H$. After 2 h of stirring at ambient temperature, the reaction was quenched with 200 $\mu$L of saturated $NH_4Cl$ solution, stirred for 1 h, dried over $Na_2SO_4$, filtered, concentrated *in vacuo*, and chromatographed (30% EtOAc/hexanes) to provide 8 mg (6.5 $\mu$mol, 67%) of **48** as a colorless oil: IR (thin film/NaCl) 1717, 1701 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.29 (overlapping dd, $J$ = 11.5 Hz, 1H), 5.97 (apparent t, $J$ = 10.9 Hz, 1H), 5.90 (m, 1H), 5.67 (m, 1H), 5.29 (obscured d, $J$ = 17.9 Hz, 1H), 5.29 (obscured m, 1H), 5.23 (obscured d, $J$ = 10.7 Hz, 1H), 5.20 (obscured m, 2H), 5.05 (d, $J$ = 9.5 Hz, 1H), 4.80 (overlapping m, 4H), 4.75 (br s, 1H), 4.59 (br s, 1H), 4.55 (d, $J$ = 5.2 Hz, 2H), 4.50 (obscured t, $J$ = 10.2 Hz, 1H), 4.06 (br t, $J$ = 10.3 Hz, 2H), 3.64 (t, $J$ = 2.3 Hz, 1H), 3.58 (m, 1H), 3.28 (dd, $J$ = 4.4, 9.8 Hz, 1H), 3.16 (overlapping m, 3H), 2.96 (ddd, $J$ = 7.0, 9.8, 13.6 Hz, 1H), 2.61 (m, 2H), 2.49 (m, 1H), 2.29 (m, 1H), 2.14 (m, 5H), 1.91 (m, 1H), 1.78 (m, 3H), 1.71 (m, 3H), 1.64 (2, 3H), 1.62 (obscured m, 2H), 1.49 (m, 5H), 1.33 (m, 4H), 1.22 (d, $J$ = 7.0 Hz, 3H), 0.99 (d, $J$ = 6.8 Hz, 3H), 0.96 (overlapping d, $J$ = 6.7 Hz, 3H), 0.95 (overlapping d, $J$ = 6.4 Hz, 3H), 0.94 (d, $J$ = 7.1 Hz, 3H), 0.90 (obscured d, $J$ = 7.1 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.80 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.6, 157.2, 156.8, 135.0, 133.3, 132.7, 131.0, 130.9, 129.4, 125.9, 80.6, 79.8, 74.8, 73.3, 65.4, 64.7, 44.1, 42.8, 40.8, 39.8, 37.5, 35.5, 34.8, 34.2, 33.2, 32.3, 29.9, 28.8, 26.3, 26.2, 25.9, 25.7, 25.5, 23.4, 18.5, 18.1, 17.9, 17.7, 16.4, 15.9, 14.1, 8.1, −3.1, −4.1, −4.3, −4.5, −4.9; LRMS (FAB, NBA/NaI) *m/z* calcd for $C_{65}H_{121}N_3O_{12}Si_3Na$ 1242, found 1242; $[\alpha]^{20}_D$ +38.0° (*c* 0.2, $CHCl_3$).

**[[[[(2-Propenyloxy)carbonyl]amino]hexyl]amino]carbonyl]oxy]-24-(hydroxybutyl)discodermolide carbamate (49).** To 3.3 mg (1.8 $\mu$mol) of **48** was added 200 $\mu$L of 1% HCl in MeOH. (The HCl solution was made by the addition of 500 $\mu$L of concentrated HCl to 50 mL of MeOH.) After stirring for 48 h at ambient temperature, the reaction was quenched by the addition of 50 mg of $NaHCO_3$, concentrated under a stream of $N_2$, and chromatographed (5% MeOH/$CHCl_3$) to provide 1.0 mg (0.8 $\mu$mol, 42%) of **49** as a colorless oil: IR (thin film/NaCl) 3746 (br), 3345 (br), 1701 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.27 (dd, $J$ = 11.3, 14.4 Hz, 1H), 5.97 (apparent t, $J$ = 11.0 Hz, 1H), 5.90 (m, 1H), 5.66 (m, 1H), 5.53 (dd, $J$ = 8.1, 11.2 Hz, 1H), 5.43 (t, $J$ = 10.6 Hz, 1H), 5.30 (dd, $J$ = 1.4, 17.2 Hz, 1H), 5.20 (dd, $J$ = 7.6, 9.4 Hz, 2H), 5.12 (d, $J$ = 9.5 Hz, 1H), 4.76-4.61 (overlapping m, 6H), 4.55 (d, $J$ = 5.0 Hz, 2H), 4.03 (br t, $J$ = 6.0 Hz, 2H), 3.72 (m, 2H), 3.71−3.46 (overlapping m, 5H), 3.18 (obscured m, 1H), 3.16 (m, $J$ = obscured m Hz, 2H), 2.96 (ddd, $J$ = 6.8, 9.9, 13.6 Hz, 1H), 2.77 (ddd, $J$ = 6.8, 9.7, 13.5 Hz, 1H), 2.68 (m, 1H), 2.56 (m m, 1H), 2.34 (m, 1H), 2.13 (overlapping m, 4H), 2.05 (m, 3H), 1.94 (m, 2H), 1.86 (dd, $J$ = 2.3, 9.6 Hz, 1H), 1.83 (dd, $J$ = 2.3, 7.6 Hz, 1H), 1.70 (m, 4H), 1.67 (d, $J$ = 1.0 Hz, 3H), 1.60 (m, 4H), 1.49 (m, 4H), 1.34 (m, 2H), 1.32 (obscured d 3), 1.07 (d, $J$ = 7.0 Hz, 3H), 1.01 (d, $J$ = 6.7 Hz, 3H), 0.99 (d, $J$ = 6.8 Hz, 3H), 0.95 (d, $J$ = 6.8 Hz, 3H), 0.93 (d, $J$ = 7.0 Hz, 3H); HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{47}H_{79}N_3O_{12}$-Na 900.5557, found 900.5554.

**[2*S*-[2α(3*Z*,5*S*,6*R*,7*R*,8*R*,9*S*,11*Z*,13*S*,14*S*,15*S*,16*Z*,18*S*),3*β*,4*β*,5α,6*β*]]-6-(Carbamoyloxy)-19-[4-hydroxytetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-5,7,9,11,13,15-hexamethyl-1,3,11,16-nonadecatetraen-8,14,18-triol (50b).** To 2 mg (2 $\mu$mol) of silyl ether was added 200 $\mu$L of 1% HCl in MeOH. (The HCl solution was made by the addition of 500 $\mu$L of concentrated HCl to 50 mL of MeOH.) After stirring for 3 days at ambient temperature, the reaction was quenched by the addition of 50 mg of $NaHCO_3$, concentrated under a stream of $N_2$, and chromatographed (5% MeOH/$CHCl_3$) to provide 1.0 mg (1.5 $\mu$mol, 78%) of **50b** as a colorless oil: IR (thin film/NaCl) 3752 (br), 3443 (br), 1711 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.49 (dd, $J$ = 1.4, 8.5 Hz, 2H), 7.32−7.25 (m, 3H), 6.62 (ddd, $J$ = 10.9, 16.8, 21.2 Hz, 1H), 6.04 (apparent t, $J$ = 11.1 Hz, 1H), 5.47 (dd, $J$ = 8.3, 11.1 Hz, 1H), 5.38−5.31 (overlapping m, 3H), 5.20 (dd, $J$ = 1.7, 6.8 Hz, 1H), 5.15 (dd, $J$ = 11.6 Hz, 1H), 4.74 (dd, $J$ = 4.4, 7.1 Hz, 1H), 4.45 (dd, $J$ = 8.1 Hz, 1H), 4.35 (ddd, $J$ = 2.4, 10.5, 18.9 Hz, 1H), 3.65 (t, $J$ = 3.5 Hz, 1H), 3.27 (br s, 1H), 3.17 (dd, $J$ = 4.8, 6.5 Hz, 1H), 3.01 (ddd, $J$ = 6.9, 10.2, 14.0 Hz, 1H), 2.61−2.51 (overlapping m, 2H), 2.27 (m, 2H), 2.23 (d, $J$ = 7.0 Hz, 1H), 1.97−1.83 (overlapping m, 4H), 1.72 (m, 1H), 1.62 (d, $J$ = 1.2 Hz, 3H), 1.20 (d, $J$ = 7.2 Hz, 3H), 1.00 (d, $J$ = 6.7 Hz, 3H), 0.99 (obscured d, 3H), 0.99 (d, $J$ = 7.0 Hz, 3H), 0.98 (d, $J$ = 7.2 Hz, 3H), 0.93 (d, $J$ = 6.9 Hz, 3H), 0.84 (d, $J$ = 6.2 Hz, 3H); HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{39}H_{61}O_7$-NSNa 710.4063, found 710.4066.

**[2*S*-[2α(3*Z*,5*S*,6*R*,7*R*,8*R*,9*S*,11*Z*,13*S*,14*S*,15*S*,16*Z*,18*S*),3*β*,4*β*,5α,6α]]-6-(Carbamoyloxy)-19-[4-hydroxytetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-5,7,9,11,13,15-hexamethyl-1,3,11,16-nonadecatetraen-8,14,18-triol (50a).** To 20 mg (19 $\mu$mol) of silyl ether was added 2 mL of 1% HCl in MeOH. (The HCl solution was made by the addition of 500 $\mu$L of concentrated HCl to 50 mL of MeOH.) After stirring for 48 h at ambient temperature, the reaction was quenched by the addition of 50 mg of $NaHCO_3$, concentrated under a stream of $N_2$, and chromatographed (2% MeOH/$CHCl_3$). The residue was purified by HPLC (2.5% MeOH/$CH_2Cl_2$) to provide 1.8 mg (2.6 $\mu$mol, 14%) of **50a** as a colorless oil: IR (thin film/NaCl) 1734, 1717 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.50 (ddd, $J$ = 1.4, 3.5, 7.4 Hz, 2H), 7.31−7.22 (overlapping m, 3H), 6.61 (ddd, $J$ = 0.7, 10.9, 16.7 Hz, 1H), 6.03 (apparent t, $J$ = 11.0 Hz, 1H), 5.42 (dd, $J$ = 6.0, 9.2 Hz, 1H), 5.38−5.30 (overlapping m, 3H), 5.23 (dd, $J$ = 0.7, 5.7 Hz, 1H), 5.16 (d, $J$ = 9.9 Hz, 1H), 5.11 (d, $J$ = 10.0 Hz, 1H), 4.73 (dd, $J$ = 4.5, 7.1 Hz, 1H), 4.62 (t, $J$ = 7.8 Hz, 1H), 4.57 (br s, 2H), 3.83 (ddd, $J$ = 2.9, 8.8, 11.1 Hz, 1H), 3.71 (d, $J$ = 2.1 Hz, 1H), 3.28 (overlapping dd, $J$ = 5.0 Hz, 1H), 3.16 (dd, $J$ = 4.5, 6.9 Hz, 1H), 3.00 (ddd, $J$ = 6.8, 10.2, 13.7 Hz, 1H), 2.80 (br s, 1H), 2.67 (ddd, $J$ = 6.8, 9.6, 13.6 Hz, 1H), 2.57 (m, 1H), 2.17 (ddd, $J$ = 2.5, 5.0, 7.1 Hz, 1H), 2.04−1.85 (overlapping m, 5H), 1.78 (ddd, $J$ = 3.1, 9.0, 12.2 Hz, 1H), 1.74 (br d, $J$ = 2.5 Hz, 2H), 1.66 (ddd, $J$ = 2.6, 8.7, 11.3 Hz, 1H), 1.63 (d, $J$ = 1.1 Hz, 3H), 1.60 (br s, 1H), 1.15 (d, $J$ = 7.2 Hz, 3H), 1.00 (d, $J$ = 6.8 Hz, 3H), 0.99 (d, $J$ = 6.5 Hz, 3H), 0.98 (d, $J$ = 6.7 Hz, 3H), 0.92 (d, $J$ = 6.8 Hz, 3H), 0.90 (d, $J$ = 7.0 Hz, 3H), 0.83 (d, $J$ = 6.0 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 157.0, 134.5, 133.6, 133.5, 133.3, 133.2, 132.1, 131.1, 130.0, 129.7, 128.7, 127.1, 117.9, 84.8, 78.9, 77.2, 75.8, 75.7, 75.4, 65.0, 41.4, 39.4, 37.2, 36.0, 35.8, 34.9, 34.7, 33.8, 33.0, 26.6, 18.1, 17.4, 15.4, 13.9, 13.2, 11.7, 8.8; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{39}H_{61}O_7NSNa$ 710.4063, found 710.4066; $[\alpha]^{20}_D$ +87.6° (*c* 0.5, $CHCl_3$).

**[2*S*-[2α(3*Z*,5*S*,6*R*,7*R*,11*Z*,13*S*,14*S*,15*S*,16*Z*,18*S*),3*β*,4*β*,5α,6α]]-6-(Carbamoyloxy)-19-[4-hydroxytetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-5,7,11,13,15-pentamethyl-1,3,11,16-nonadecatetraene (51).** To 20 mg (15 $\mu$mol) of silyl ether was added 200 $\mu$L of 1% HCl in MeOH. (The HCl solution was made by the addition of 500 $\mu$L of concentrated HCl to 50 mL of MeOH.) After 48 h of stirring at ambient temperature, the reaction was quenched by the addition of 50 mg of $NaHCO_3$, concentrated under a stream of $N_2$, and chromatographed (5% MeOH/$CHCl_3$) to provide 9 mg (12 $\mu$mol, 82%) of **51** as a colorless oil: IR (thin film/NaCl) 3428 (br), 1713 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.49 (dd, $J$ = 1.3, 8.5 Hz, 2H), 7.31−7.22 (m 3), 6.60 (ddd, $J$ = 10.6, 17.1, 21.0 Hz, 1H), 6.04 (apparent t, $J$ = 11.0 Hz, 1H), 5.38 (dd, $J$ = 8.1, 11.1 Hz, 1H), 5.35 (d, $J$ = 2.2 Hz, 1H), 5.32 (obscured m, 1H), 5.22 (dd, $J$ = 1.3, 16.8, 5.14, overlapping d, 6.3 Hz, 1H), 5.12 (overlapping d, $J$ = 8.1 Hz, 1H), 4.74 (dd, $J$ = 4.5, 6.7 Hz, 1H), 4.61 (br s, 2H), 3.81 (m 1), 3.70 (br s, 1H), 3.58 (m, 1H), 3.15 (dd, $J$ = 4.4, 6.9 Hz, 1H), 2.98 (ddd, $J$ = 6.7, 10.0, 13.5 Hz, 1H), 2.87 (br s, 1H), 2.65 (ddd, $J$ = 6.8, 9.6, 13.8 Hz, 1H), 2.55 (m 1), 2.32 (br s, 1H), 2.19−2.15 (m 1), 2.14−2.09 (m 1), 1.98 (m 1), 1.89−1.79 (overlapping m, 2H), 1.78−1.73 (overlapping m, 2H), 1.67 (d, $J$ = 0.8 Hz, 3H), 1.55−1.47 (m 2), 1.14 (d, $J$ = 7.2 Hz, 3H), 0.99 (d, $J$ = 6.9 Hz, 3H), 0.98 (d, $J$ = 6.8 Hz, 3H), 0.93 (d, $J$ = 6.9 Hz, 3H), 0.92 (d, $J$ = 6.8 Hz, 3H), 0.89 (d, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 157.3, 135.1, 134.5, 133.5, 133.4, 133.3, 132.1, 131.1, 130.0, 129.0, 128.9, 127.1, 118.0, 89.8, 79.7, 78.8, 77.2, 75.8, 75.4, 73.3, 65.1, 41.3, 39.9, 39.5, 36.0, 34.9, 34.6, 33.8, 33.1, 28.8, 23.5, 18.0, 17.6, 14.9, 13.2, 11.7, 7.9; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{39}H_{59}NO_7SNa$ 708.2987, found 708.2984; $[\alpha]^{20}_D$ +82.4° (*c* 0.5, $CHCl_3$).

**[(3*Z*,5*S*,6*R*,7*R*,11*Z*,13*S*,14*S*,15*S*,16*Z*,18*S*),3*β*,4*β*,5α,6α]-6-(Carbamoyloxy)-19-[4-hydroxytetrahydro-3,5-dimethyl-6-[2-[[(2′-Propenyl-oxy)carbonyl]amino]ethoxy]-2*H*-pyran-2-yl]-5,7,11,13,15-pentamethyl-1,3,11,16-nonadecatetraene (52).** To a solution of 7.5 mg (10.7 $\mu$mol) of **51** and 50 $\mu$L of *N*-Aloc-ethanolamine in 50 $\mu$L of THF was added 10 mg (110 $\mu$mol) of $NaHCO_3$ and then 15 mg (55 $\mu$mol) of $HgCl_2$. After stirring for 10 min at ambient temperature, the reaction was directly chromatographed (2%−4%−10% MeOH/$CHCl_3$) to provide 2.5 mg (3.5 $\mu$mol, 33%) of **52** as a colorless oil: IR (thin film/NaCl) 1701 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.60 (ddd, $J$ = 10.9, 16.8, 21.2 Hz, 1H), 6.04 (apparent t, $J$ = 11.0 Hz, 1H), 5.92 (m, 1H), 5.56 (dd, $J$ = 8.1, 10.7 Hz, 1H), 5.42−5.12 (overlapping d, 8H), 4.74 (dd, $J$ = 4.5, 6.8 Hz, 1H), 4.69 (obscured m, 1H), 4.64 (s, 1H), 4.57 (obscured m, 5H), 3.96 (br t, $J$ = 10.4 Hz, 1H), 3.88 (m, 1H), 3.58 (m, 2H), 3.51 (m, 2H), 3.47 (br d, $J$ = 1.9 Hz, 2H), 3.41 (s, 1H), 3.38 (m, 1H), 3.33 (m, 1H), 3.20 (dd, $J$ = 4.8, 6.9 Hz, 2H), 2.98 (ddd, $J$ = 6.7, 9.9, 13.5, 12.75, m Hz, 1H), 2.59 (m, 1H), 2.25 (m, 1H), 2.12 (dd, $J$ = 1.7, 6.9 Hz, 2H), 2.03 (m, 1H), 2.00 (m, 1H), 1.77 (m, 3H), 1.68 (d, $J$ = 1.1 Hz, 3H), 1.54 (m, 3H), 1.04 (overlapping d, $J$ = 7.4 Hz, 3H), 1.03 (overlapping d, $J$ = 7.4 Hz, 3H), 1.00 (d, $J$ = 6.8 Hz, 3H), 0.95 (overlapping d, $J$ = 6.7 Hz, 3H), 0.94 (overlapping d, $J$ = 6.7 Hz, 3H), 0.94 (overlapping d, $J$ = 7.0 Hz, 3H); HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{38}H_{64}O_{10}N_2Na$ 731.4455, found 731.4459.

**(8*R*,9*S*,10*S*,11*Z*)-8,10-Dimethyl-9-[(4-methoxyphenyl)methoxy]-1-[(triethylsilyl)oxy]-11,13-tetradecadien-7-one (53).** To a solution of 400 mg (1.38 mmol) of **13** in 5 mL of $CH_2Cl_2$ was added 760 mg (1.66 mmol) of Dess−Martin periodinane. After being stirred at ambient temperature for 10 min, the reaction was quenched by the addition of 20 mL of saturated $Na_2S_2O_3$ solution and 20 mL of saturated $NaHCO_3$ solution and diluted with 50 mL of diethyl ether. After 30 min of stirring, the layers were separated and the organic layer was washed with 3 × 120 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (10% EtOAc/hexanes) to yield 312 mg of the aldehyde.

To make a 1 M solution of the Grignard reagent, 1.18 g (4 mmol) of 1-bromo-6-[(triethylsilyl)oxy]hexane in 4 mL of THF was heated with 117 mg (4.8 mmol) of magnesium turnings. To a solution of 312 mg (1.08 mmol) of the aldehyde in 2 mL of THF was added 3.25 mL (3.25 mmol, 1 M in THF) of the Grignard reagent. After 30 min of stirring at ambient temperature, the reaction mixture was diluted with 30 mL of diethyl ether, washed with 1 × 20 mL of 1 N HCl and 1 × 20 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (10% EtOAc/hexanes) to provide 458 mg of a 2:1 mixture of epimers.

The mixture of alcohols was dissolved in 5 mL of $CH_2Cl_2$, and 492 mg (1.16 mmol) of Dess−Martin periodinane was added. After being stirred 30 min at ambient temperature, the reaction was quenched by the addition of 20 mL of saturated $Na_2S_2O_3$ solution and 20 mL of saturated $NaHCO_3$ solution and diluted with 50 mL of diethyl ether. After 30 min of stirring, the layers were separated and the organic layer was washed with 3 × 120 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (5% EtOAc/hexanes) to yield 368 mg (733 $\mu$mol, 53% for three steps) of **53** as a colorless oil: IR (thin film/NaCl) 1709 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.27 (d, $J$ = 8.5 Hz, 2H), 6.87 (d, $J$ = 8.6 Hz, 2H), 6.46 (ddd, $J$ = 10.8, 16.8, 21.2 Hz, 1H), 6.04 (apparent t, $J$ = 11.0 Hz, 1H), 5.55 (apparent t, $J$ = 10.6 Hz, 1H), 5.19 (d, $J$ = 16.8 Hz, 1H), 5.08 (d, $J$ = 10.1 Hz, 1H), 4.57 (d, $J$ = 10.6 Hz, 1H), 4.50 (d, $J$ = 10.6 Hz, 1H), 3.79 (s, 3H), 3.64 (dd, $J$ = 3.3, 8.2 Hz, 1H), 3.59 (t, $J$ = 6.6 Hz, 2H), 2.77 (obscured m, 1H), 2.74 (obscured m, 1H), 2.44 (m, 1H), 2.37 (m, 1H), 1.52 (overlapping m, 4H), 1.28 (overlapping m, 4H), 1.17 (d, $J$ = 7.1 Hz, 3H), 1.09 (d, $J$ = 6.8 Hz, 3H), 0.97 (t, $J$ = 7.9 Hz, 9H), 0.60 (1, $J$ = 7.9 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 272.4, 159.1, 133.9, 132.1, 130.7, 129.5, 129.2, 117.6, 113.6, 83.7, 75.2, 62.7, 55.1, 50.2, 42.4, 36.1, 32.7, 28.9, 25.6, 23.2, 18.7, 13.9, 6.7, 4.3; HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{30}H_{50}O_4SiNa$ 525.3373, found 525.3376; $[\alpha]^{20}_D$ +31.0° (*c* 0.5, $CHCl_3$).

**[2*S*-[2*β*(3*Z*,5*S*,6*S*,7*R*,9*S*,11*Z*,13*S*,14*S*,15*S*,16*Z*,18*S*),3*β*,4*β*,5α,6α]]-14,18-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-19-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-6-[(4-methoxyphenyl)methoxy]-5,7,11,13,15-pentamethyl-9-[5-[(triethylsilyl)oxy]pentyl]-1,3,11,16-nonadecatetraen-8-one (54).** To a cooled solution (0 °C) of 120 mg (144 $\mu$mol) of **20** in 1 mL of $CH_2Cl_2$ was added 83 $\mu$L (60 mg, 596 $\mu$mol) of $Et_3N$, followed by 23 $\mu$L (44 mg, 298 $\mu$mol) of MsCl. After 1 h of stirring, a solution of 130 mg (1.49 mmol) LiBr in 3 mL of acetone was added. After the mixture was warmed to ambient temperature and stirred for an additional 15 min, the suspension was diluted with 20 mL of hexanes, filtered through $MgSO_4$ and 5 g of silica gel, eluting from the silica gel with 20 mL of 10% EtOAc/hexanes, and concentrated *in vacuo* to provide crude bromide **21**.

To a cooled (−78 °C) solution of the crude bromide **21** and 300 mg (596 $\mu$mol) of ketone **53** in 1 mL of THF was added 1.20 mL (596 $\mu$mol, 0.5 M solution in THF) of LDA. The reaction was stirred for

3 h at 0 °C and then quenched by the addition of 1.5 mL of saturated $NH_4Cl$ solution. The mixture was extracted into 30 mL of EtOAc, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (0.5%−1%−2% EtOAc/hexanes). The residue was purified by HPLC (2% EtOAc/hexanes) to provide 51 mg (39 $\mu$mol, 27% for two steps) of **54** as a colorless oil: IR (thin film/NaCl) 1707 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.44 (d, $J$ = 7.4 Hz, 2H), 7.24 (m, 4H), 7.12 (m, 1H), 6.85 (d, $J$ = 8.6 Hz, 2H), 6.47 (ddd, $J$ = 10.8, 16.9, 21.8 Hz, 1H), 6.03 (apparent t, $J$ = 11.1 Hz, 1H), 5.62 (apparent t, $J$ = 10.2 Hz, 1H), 5.33 (dd, $J$ = 7.8, 11.0 Hz, 1H), 5.23 (d, $J$ = 19.0 Hz, 1H), 5.22 (obscured m, 1H), 5.16 (obscured m, 1H), 5.07 (d, $J$ = 10.2 Hz, 1H), 4.56 (apparent t, $J$ = 8.9 Hz, 1H), 4.52 (s, 2H), 4.24 (apparent t, $J$ = 10.1 Hz, 1H), 3.79 (apparent s, 3H), 3.64 (dd, $J$ = 3.2, 7.3 Hz, 1H), 3.57 (overlapping m, 3H), 3.30 (dd, $J$ = 3.2, 6.6 Hz, 1H), 2.73 (obscured m, 2H), 2.70 (obscured m, 2H), 2.60 (m, 1H), 2.44 (dd, $J$ = 7.8, 15.8 Hz, 1H), 2.14 (m, 1H), 1.89 (dd, $J$ = 6.0, 13.6 Hz, 1H), 1.89 (dd, $J$ = 10.3, 13.7 Hz, 1H), 1.67 (obscured m, 1H), 1.63 (d, $J$ = 0.7 Hz, 3H), 1.59 (obscured m, 1H), 1.50 (overlapping m, 4H), 1.26 (overlapping m, 5H), 1.14 (d, $J$ = 7.1 Hz, 3H), 1.10 (d, $J$ = 7.2 Hz, 3H), 1.09 (d, $J$ = 6.9 Hz, 3H), 1.01 (d, $J$ = 6.8 Hz, 3H), 0.99 (s, 9H), 0.96 (t, $J$ = 8.0 Hz, 9H), 0.91 (s, 9H), 0.89 (obscured d, $J$ = 7.2 Hz, 3H), 0.84 (d, $J$ = 6.8 Hz, 3H), 0.08 (s, 9H), 0.59 (q, $J$ = 7.8 Hz, 6H), 0.12 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), −0.12 (s, 3H), −0.26 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 215.6, 159.1, 140.7, 134.6, 133.7, 133.2, 132.3, 132.1, 130.9, 130.1, 129.7, 129.1, 128.5, 127.8, 125.0, 117.7, 113.6, 87.2, 82.6, 80.4, 76.6, 74.9, 74.1, 67.9, 66.1, 62.8, 55.2, 50.1, 49.2, 42.8, 41.7, 36.8, 36.7, 35.2, 34.8, 33.3, 32.8, 31.2, 31.1, 27.7, 26.4, 26.2, 23.0, 25.9, 25.8, 23.4, 19.2, 18.5, 18.2, 17.9, 17.8, 17.5, 14.9, 14.3, 12.9, 6.8, 4.4, −2.7, −3.7, −4.0, −4.3, −5.0, −5.3; LRMS (FAB, NBA/NaI) *m/z* calcd for $C_{75}H_{132}O_8SSi_4Na$ 1313, found 1313; $[\alpha]^{20}_D$ −8.0° (*c* 0.5, $CHCl_3$).

**[2*S*-[2*β*(3*Z*,5*S*,6*S*,7*R*,9*S*,11*Z*,13*S*,14*S*,15*S*,16*Z*,18*S*),3*β*,4*β*,5α,6α]]-14,18-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-19-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-6-(phenylthio)-2*H*-pyran-2-yl]-5,7,11,13,15-pentamethyl-6-[(4-methoxyphenyl)methoxy]-9-[[[[5-[(2-propenyloxy)carbonyl]pentyl]amino]carbonyl]oxy]-1,3,11,16-nonadecatetraen-8-one (55).** To a solution of 48 mg (41 $\mu$mol) of alcohol in 1 mL of MeCN was added 35 $\mu$L (34 mg, 430 $\mu$mol) of pyridine, 112 mg (430 $\mu$mol) of *N*,*N*′-disuccinimidyl carbonate, and 5 mg of DMAP. After being stirred at ambient temperature for 30 min, the reaction mixture was concentrated under a stream of $N_2$ and chromatographed (25% EtOAc/hexanes) to provide 51 mg of the mixed carbonate that was used directly in the following reaction.

To a solution of the mixed carbonate in 2 mL of $CH_2Cl_2$ was added 34 mg (170 $\mu$mol) of *N*-Aloc-1,6-hexanediamine and 21 mg (170 $\mu$mol) of DMAP. After being stirred for 10 min at ambient temperature, the reaction mixture was concentrated under a stream of $N_2$ and chromatographed (20% EtOAc/hexanes) to provide 43 mg (30 $\mu$mol, 73%) of **55** as a colorless oil: IR (thin film/NaCl) 1707 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.44 (d, $J$ = 7.4 Hz, 2H), 7.26 (m, 4H), 7.11 (m, 1H), 6.85 (d, $J$ = 8.6 Hz, 2H), 6.46 (ddd, $J$ = 10.5, 17.4, 21.7 Hz, 1H), 6.02 (apparent t, $J$ = 11.1 Hz, 1H), 5.91 (m, 1H), 5.62 (apparent t, $J$ = 10.2 Hz, 1H), 5.34 (obscured dd, $J$ = 7.8, 11.0 Hz, 1H), 5.31 (dd, $J$ = 2.3, 3.7 Hz, 1H), 5.27 (d, $J$ = 1.5 Hz, 1H), 5.22 (d, $J$ = 19.7 Hz, 1H), 5.21 (obscured m, 1H), 5.16 (obscured m, 1H), 5.07 (d, $J$ = 10.3 Hz, 1H), 4.66 (br s, 1H), 4.57 (br s, 1H), 4.55 (d, $J$ = 4.8 Hz, 2H), 4.51 (apparent s, 2H), 4.23 (apparent t, $J$ = 10.1 Hz, 1H), 4.00 (apparent t, $J$ = 6.3 Hz, 2H), 3.79 (s, 3H), 3.64 (dd, $J$ = 3.1, 7.4 Hz, 1H), 3.58 (obscured m, 1H), 3.29 (dd, $J$ = 3.1, 6.5 Hz, 1H), 3.16 (m, 4H), 2.73 (obscured m, 2H), 2.68 (obscured m, 2H), 2.58 (m, 1H), 2.45 (dd, $J$ = 7.8, 13.4 Hz, 1H), 2.14 (m, 1H), 1.86 (dd, $J$ = 5.8, 13.5 Hz, 1H), 1.70 (dd, $J$ = 11.0, 14.2 Hz, 1H), 1.63 (br s, 3H), 1.54 (obscured dd, 3H), 1.49 (overlapping m, 6H), 1.33 (overlapping m, 5H), 1.31 (overlapping m, 6H), 1.13 (d, $J$ = 7.1 Hz, 3H), 1.11 (d, $J$ = 7.3 Hz, 3H), 1.09 (d, $J$ = 6.9 Hz, 3H), 1.01 (d, $J$ = 6.8 Hz, 3H), 0.99 (s, 9H), 0.91 (s, 9H), 0.88 (ovlerapping d, 3H), 0.84 (overlapping d, 3H), 0.79 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H), −0.13 (s, 3H), −0.27 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 215.5, 159.1, 156.7, 156.3, 140.7, 134.6, 133.7, 133.3, 133.0, 132.9, 132.3, 132.1, 130.8, 130.0, 129.7, 129.3, 129.2, 129.1, 128.7, 127.8, 125.0, 117.7, 117.5, 113.7, 87.2, 82.6, 80.4, 77.2, 76.5, 74.9, 74.1, 67.9, 66.1, 65.4, 64.7, 55.2, 50.1, 49.2, 42.8, 41.7, 40.8, 6.8, 36.7, 35.2, 34.9, 33.4, 31.0, 29.9, 28.8, 27.4, 26.4, 26.2, 26.1, 26.0, 25.9, 25.8, 23.5, 19.7, 18.5, 18.2, 17.9, 17.8, 17.5, 14.9, 14.3, 12.9, −2.7, −3.7, −4.0, −4.3, −4.5, −4.9, −5.0, −5.3; LRMS (FAB, NBA/NaI) *m/z* calcd for $C_{79}H_{134}N_2O_{11}SSi_3Na$ 1425, found 1425; $[\alpha]^{20}_D$ −2.8° (*c* 0.5, $CHCl_3$).

**[3*S*-[3α,4*β*,5*β*,6α(2*S*,3*Z*,5*S*,6*S*,7*S*,8*Z*,11*S*,13*R*,14*S*,15*S*,16*Z*)]]-6-[2,6-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-14-[(4-methoxyphenyl)methoxy]-9-[[[[5-[(2-propenyloxy)carbonyl]pentyl]amino]carbonyl]oxy]-5,7,11,13,15-pentamethyl-12-oxo-3,8,16,18-nonadecatetraenyl]-4-[[(1,1-dimethylethyl) dimethylsilyl]oxy]tetrahydro-3,5-dimethyl-2*H*-pyran-2-one (56).** To a solution of 43 mg (30 $\mu$mol) of **55** in 500 $\mu$L of THF were added 500 $\mu$L of MeCN, 500 $\mu$L of pH 7 buffer solution concentrate, and 164 mg (600 $\mu$mol) of $HgCl_2$. The suspension was stirred for 20 min, when TLC analysis indicated no starting material remained, and then was treated with 10 mL of brine and extracted into 3 × 25 mL of $CH_2Cl_2$. The organic layers were combined, dried over $MgSO_4$, filtered, concentrated *in vacuo*, and chromatographed (4% EtOAc/hexanes) to provide 33 mg of a mixture of lactols.

The lactols were dissolved in 4 mL of acetone, cooled to 0 °C, and treated with 300 $\mu$L (300 $\mu$mol) of 1 M Jones oxidant solution. The reaction was stirred at 0 °C for 30 min, then warmed to ambient temperature for 5 min. Excess oxidant was quenched by addition of 300 $\mu$L of iPrOH and stirred for 30 min, diluted with 30 mL of diethyl ether, filtered through Celite, concentrated *in vacuo*, and chromatographed (20% EtOAc/hexanes) to provide 24 mg (18 $\mu$mol, 60% for two steps) of **56** as a colorless oil: IR (thin film/NaCl) 1716, 1707 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.25 (d, $J$ = 8.6 Hz, 2H), 6.85 (d, $J$ = 8.6 Hz, 2H), 6.46 (ddd, $J$ = 10.5, 17.2, 21.0 Hz, 1H), 6.01 (apparent t, $J$ = 11.2 Hz, 1H), 5.88 (m, 1H), 5.62 (apparent t, $J$ = 10.2 Hz, 1H), 5.31 (obscured m, 1H), 5.29 (obscured m, 1H), 5.21 (m, 2H), 5.19 (s, 1H), 5.15 (d, $J$ = 9.9 Hz, 2H), 5.11 (d, $J$ = 10.0 Hz, 1H), 5.06 (d, $J$ = 10.4 Hz, 1H), 4.80 (obscured t, $J$ = 8.9 Hz, 1H), 4.75 (br s, 1H), 4.68 (br s, 1H), 4.54 (apparent d, $J$ = 5.1 Hz, 2H), 4.52 (apparent d, $J$ = 3.7 Hz, 2H), 3.99 (apparent t, $J$ = 6.1 Hz, 2H), 3.74 (s, 3H), 3.62 (m, 2H), 3.24 (dd, $J$ = 2.9, 6.6 Hz, 1H), 3.15 (m, 4H), 2.71 (m, 2H), 2.63 (m, 2H), 2.58 (m, 1H), 2.40 (m, 1H), 1.82 (obscured dd, 2H), 1.70 (obscured m, 3H), 1.61 (br s, 3H), 1.59−1.25 (overlapping m 24), 1.20 (d, $J$ = 7.6 Hz, 3H), 1.11 (d, $J$ = 7.4 Hz, 3H), 1.09 (d, $J$ = 7.2 Hz, 3H), 0.97 (d, $J$ = 6.7 Hz, 3H), 0.95 (d, $J$ = 6.7 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.85 (d, $J$ = 7.2 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (overlapping s, 6H), 0.02 (s, 3H), −0.03 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 215.3, 173.3, 159.1, 156.7, 156.3, 133.7, 133.5, 133.4, 133.0, 132.8, 132.3, 131.9, 130.8, 129.9, 129.3, 129.1, 117.7, 117.5, 113.7, 82.8, 82.7, 80.4, 77.2, 76.4, 75.0, 74.8, 65.4, 64.7, 55.2, 50.1, 49.3, 44.1, 42.7, 40.8, 67.4, 36.6, 34.8, 34.1, 33.2, 31.0, 29.9, 28.8, 27.4, 26.3, 26.2, 26.0, 25.9, 25.7, 23.5, 19.2, 18.9, 18.5, 18.1, 17.9, 17.5, 16.4, 15.0, 14.1, 13.0, 12.9, −2.8, −4.4, −4.5, −4.9; LRMS (FAB, NBA/NaI) *m/z* calcd for $C_{72}H_{128}N_2O_{12}SSi_3Na$ 1331, found 1331; $[\alpha]^{20}_D$ +23.0° (*c* 0.5, $CHCl_3$).

**3,7,11-Tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-9-[[[[5-[(2-propenyloxy)carbonyl]pentyl]amino]carbonyl]oxy]discodermolide (58).** To a solution of 14 mg (11 $\mu$mol) of ketone in 2 mL of THF was added 55 $\mu$L (55 $\mu$mol, 1 M in THF) of $LiAl(OtBu)_3H$. After being stirred for 2 h at ambient temperature, the reaction was quenched with 200 $\mu$L of saturated $NH_4Cl$ solution, stirred for 1 h, dried over $Na_2SO_4$, filtered, concentrated *in vacuo*, and chromatographed (40% EtOAc/hexanes) to provide 12 mg (9.4 $\mu$mol, 86%) of **58** as a colorless oil: IR (thin film/NaCl) 3339 (br), 1711 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.61 (ddd, $J$ = 10.5, 16.8, 21.2 Hz, 1H), 6.01 (apaprent t, $J$ = 10.9 Hz, 1H), 5.91 (m, 1H), 5.37 (t, $J$ = 10.4 Hz, 1H), 5.31 (s, 1H), 5.29 (dd, $J$ = 5.2, 13.5 Hz, 1H), 5.21 (obscured d, $J$ = 11.4 Hz, 1H), 5.20 (obscured d, 1H), 5.19 (br s, 1H), 5.12 (d, $J$ = 10.4 Hz, 1H), 4.86 (br s, 1H), 4.81 (br t, $J$ = 9.4 Hz, 1H), 4.76 (overlapping br s, 1H), 4.75 (dd, $J$ = 4.5, 7.0 Hz, 1H), 4.61 (br s, 2H), 4.54 (d, $J$ = 5.4 Hz, 1H), 4.51 (obscured t, $J$ = 10.2 Hz, 1H), 4.01 (overlapping m, 2H), 3.64 (t, $J$ = 2.4 Hz, 1H), 3.46 (dd, $J$ = 5.4, 10.8 Hz, 1H), 3.32 (dd, $J$ = 3.1, 5.8 Hz, 1H), 3.15 (overlapping m, 3H), 3.02 (ddd, $J$ = 6.8, 10.0, 13.7 Hz, 1H), 2.60 (overlapping m, 2H), 2.56 (m, 1H), 2.06 (d, $J$ = 5.1 Hz, 1H), 2.02 (ovlerapping m, 2H), 1.92 (m, 1H), 1.88 (m, 1H), 1.80 (m, 1H), 1.74 (dd, $J$ = 12.3, 25.2 Hz, 1H), 1.69 (s, 3H), 1.57 (m, 2H), 1.48 (m, 4H), 1.32−1.24 (m, 17H), 1.01 (d, $J$ = 6.7 Hz, 3H), 0.98 (d, $J$ = 6.7 Hz, 3H), 0.96 (d, $J$ = 6.8 Hz, 3H), 0.94 (d, $J$ = 6.7 Hz, 3H),

0.90 (s, 9H), 0.88 (obscured d, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.5, 156.9, 156.8, 133.9, 133.3, 133.0, 132.7, 132.6, 132.4, 132.2, 129.8, 117.8, 117.6, 80.4, 78.3, 78.3, 77.3, 77.1, 74.7, 74.2, 65.4, 64.9, 64.7, 44.1, 42.8, 40.8, 37.9, 37.5, 37.0, 35.4, 34.5, 34.2, 31.9, 30.4, 29.9, 28.9, 26.4, 26.3, 26.2, 26.0, 25.9, 25.7, 23.7, 18.5, 18.1, 17.9, 17.5, 16.4, 15.2, 14.0, 9.4, -3.0, −4.1, −4.3, −4.5, −4.9; LRMS (FAB, NBA/NaI) *m/z* calcd for $C_{66}H_{123}N_3O_{12}Si_3$-Na 1256, found 1256; $[\alpha]^{20}_D$ +17.6° (*c* 0.5, $CHCl_3$).

**9-[[[[5-[(2-Propenyloxy)carbonyl]pentyl]amino]carbonyl]oxy]-discodermolide (59).** To 12 mg (9.4 $\mu$mol) of **58** was added 1.2 mL of 1% HCl in MeOH. (The HCl solution was made by the addition of 500 $\mu$L of concentrated HCl to 50 mL of MeOH.) After being stirred for 48 h at ambient temperature, the reaction was quenched by the addition of 50 mg of $NaHCO_3$, concentrated under a stream of $N_2$, and chromatographed (5% MeOH/$CHCl_3$) to provide 5.0 mg (5.6 $\mu$mol, 60%) of **59** as a colorless oil: IR (thin film/NaCl) 3343 (br), 1699, $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.61 (dd, $J$ = 10.5, 17.1, 20.9 Hz, 1H), 6.02 (apparent t, $J$ = 11.0 Hz, 1H), 5.92 (m, 1H), 5.54 (dd, $J$ = 8.1, 11.0 Hz, 1H), 5.39 (d, $J$ = 11.1 Hz, 1H), 5.34 (d, $J$ = 10.8 Hz, 1H), 5.31 (d, $J$ = 1.4 Hz, 1H), 5.27 (apparent t, $J$ = 1.6 Hz, 1H), 5.25 (m, 1H), 5.19 (s, 1H), 5.11 (d, $J$ = 10.1 Hz, 1H), 4.95 (br s, 1H), 4.82 (br s, 1H), 4.76 (br t, $J$ = 7.6 Hz, 1H), 4.73 (dd, $J$ = 3.9, 7.5 Hz, 1H), 4.63 (br t, $J$ = 8.2 Hz, 1H), 4.58 (br s, 2H), 4.54 (m, 2H), 4.00 (overlapping m, 2H), 3.72 (m, 1H), 3.48 (m, 1H), 3.15 (overlapping m, 5H), 3.01 (m, 1H), 2.75 (m, 1H), 2.68 (m, 1H), 2.61 (m, 1H), 2.54 (m, 1H), 2.46 (m, 1H), 2.20 (br s, 1H), 2.13 (dd, $J$ = 9.0, 19.0 Hz, 1H), 2.01 (dd, $J$ = 3.9, 13.7 Hz, 1H), 1.94 (overlapping m, 4H), 1.88 (overlapping m, 4H), 1.72 (d, $J$ = 0.8 Hz, 3H), 1.69 (obscured m, 1H), 1.53 (obscured m, 4H), 1.32 (obscured m, 6H), 1.30 (obscured d, $J$ = 7.4 Hz, 3H), 1.19 (overlapping m, 3H), 1.07 (d, $J$ = 6.9 Hz, 3H), 1.02 (d, $J$ = 6.8 Hz, 3H), 1.00 (d, $J$ = 6.6 Hz, 3H), 0.99 (d, $J$ = 6.6 Hz, 3H), 0.94 (d, $J$ = 6.7 Hz, 3H); HRMS (FAB, NBA/NaI) *m/z* calcd for $C_{48}H_{81}N_3O_{12}Na$ 914.5713, found 914.5716.

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**Supporting Information Available:** Complete physical and spectral data and experimental details for all compounds (16 pages). See any current masthead page for ordering and Internet access information.

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