Studies on the Total Synthesis of Disorazole C_1. An Advanced Macrocycle Intermediate

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Synthesis of protected tetradehydro-(6,6′-*S*)-(14,14′-*S*)-(16,16′-*R*)-disorazole (**3**), a potential precursor to the natural product disorazole C_1 (**1**), is described. Key features of this work include (a) an unprecedented sequential 1,5 O → O silyl rearrangement/Horner−Wadsworth−Emmons reaction used to construct **18**, (b) a highly convergent Sonogashira reaction between the dienyl iodide **7** and the alkyne **8** to assemble the dienyne monomeric fragment **5**, and (c) the selective cyclization of **5** to give either the cyclic monomer **23** or the dimer **3**.

In 1994, Jansen and co-workers reported the crude structure of disorazole C_1 (**1**), which was isolated from the fermentation broth of the gliding bacteria *Sorangium cellulosum* along with 27 other structurally related variants.[1] It may be clearly seen that **1** is a cyclic dimeric lactone of the trieneoxazole ester **4**. Comprehensive biological activity data for these compounds was not presented, but the original isolate was found to have high cytotoxic and moderate antifungal activity. In light of these data, and along with our continuing interest in the construction of oxazole-containing natural products,[2] we contemplated a synthetic route to **1**. Unfortunately, only the general structure of **1** has been reported, and the relative or absolute stereochemistry of the C6−C6′, C14−C14′, and C16′−C16 stereocenters was not described. In addition, the only known sample of disorazole C_1 has since decomposed,[3] and as such, no stereochemical information can be elucidated using degradative techniques. Nevertheless, it became compelling to examine the synthesis of this molecule in order to identify its correct structure and possibly gain insight into its biological mode of action.

Synthetic Considerations. Initial efforts in this laboratory focused on the synthesis of **1** from its monomeric triene subunit **4** via a highly convergent dilactonization reaction (Scheme 1).[4] The triene monomer **4** (P = SEM), in turn, was prepared via a Stille coupling[5] of the stereochemically designated vinyl tin moiety **6** and the chiral oxazole-containing dienyl iodide **7**. However, during the course of these investigations, it became evident that this strategy would fail due to the unstable nature of the resulting triene system, which prevented the targeted macrocycle (**1**) from being properly assembled. In light of these difficulties, a new synthetic route was devised (Scheme 1) involving the dienyne monomer **5**, wherein one of the olefinic moieties was replaced by an alkyne linkage. It was envisioned that this latter intermediate could be reached by a Sonogashira coupling of the dienyl iodide **7** and the alkyne **8**. Double-esterification of the monomer **5**, after hydrolysis of the methyl ester, could then provide the dimeric "dehydro"-disorazole C_1 (**3**), which may serve as a precursor to **1**, after silyl ether removal to give **2** and selective reduction of the alkynyl units. The latter, **2**, may also serve as a more stable derivative of the natural product **1** that could be further evaluated for biological activity. It is important to note, however, that the actual stereochemistry of disorazole C_1 was not an initial concern in this study, but rather the inherent challenges that presented themselves in constructing this highly complex molecule. As such, the primary goal was to obtain the correct gross molecular structure of **1** and then, by comparison with authentic spectral and rotation data, attempt to determine the stereochemical identity of the natural product.

Dienyl Iodide 7. Synthesis of the dienyl iodide **7** (Scheme 2) began with the readily available L-malic acid derivative **9**,[2a] which was coupled with the HCl salt of L-serine methyl ester[6] to provide **10** in 67% yield. Cyclodehydration of **10** to the intermediate oxazoline was accomplished using diethylaminosulfur triflouride (DAST)[7] in CH_2Cl_2 at −78 °C, followed by oxidation (DBU, $BrCCl_3$)[8] of the resulting oxazoline to furnish the oxazole **11** (79%). The acetonide **11** was hydrolyzed with Dowex-H^+ and furnished diol **12a**, which was converted to the methoxy hydroxy oxazole **12d** in 48% overall yield for the

(1) Jansen, R.; Irschik, H.; Reichenbach, H.; Wray, V.; Hˆfle, G. *Liebigs Ann. Chem.* **1994**, 759−773.

(2) (a) Tavares, F.; Lawson, J. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1996**, *118*, 3303−3304. (b) Dvorak, C. A.; Schmitz, W. D.; Poon, D. J.; Pryde, D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. *Angew. Chem. I. E. E.* **2000**, *39*, 1664−1666.

(3) Jansen, R. Gesellschaft für Biotechnologische Forschung mbH, personal communication, 1998. We further thank Dr. Jansen for kindly providing the spectral and mass data.

(4) Hillier, M. C.; Park, D. H.; Price, A. T.; Ng, R.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41*, 2821−2824.

(5) For a general review of the Stille reaction, see: Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 50, Chapter 1.

(6) Racemic serine methyl ester could be used in this reaction as well, which did not affect the yield of the subsequent cyclodehydration reaction.

(7) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574−578. (b) Lafargue, P.; Geunot, P.; Lellouch, J.-P. *Heterocycles* **1995**, *41*, 947−958.

(8) (a) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924−4925. (b) For an alternative method for the transformation of oxazolines to oxazoles, see: Tavares, F.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2481−2484.

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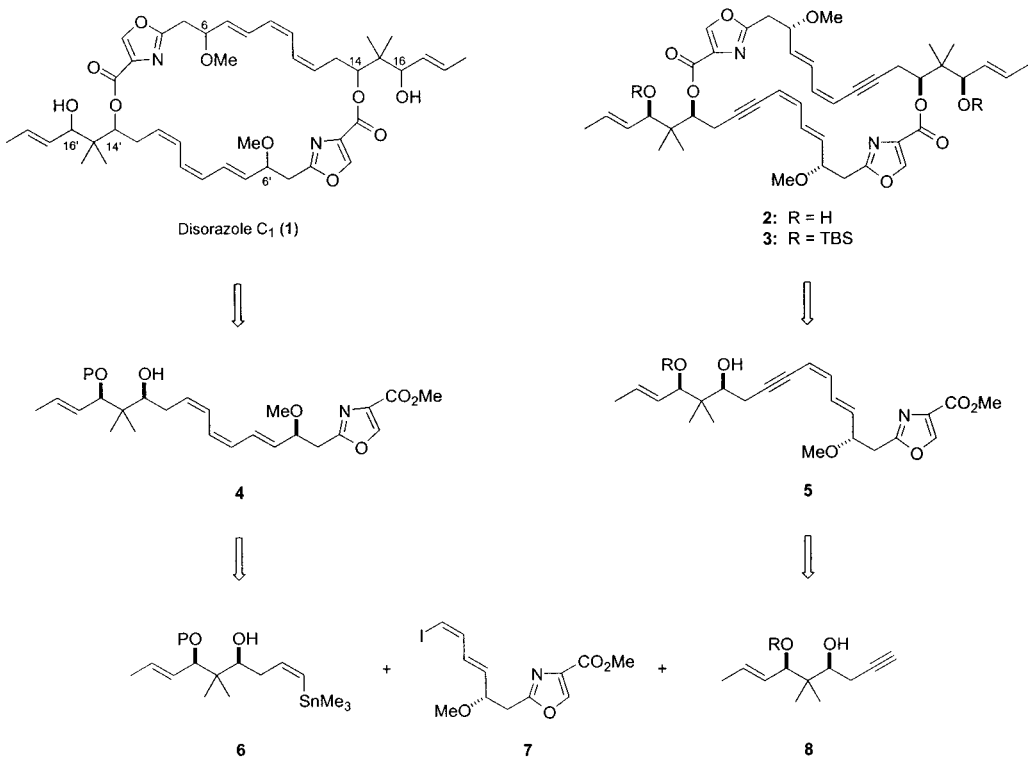
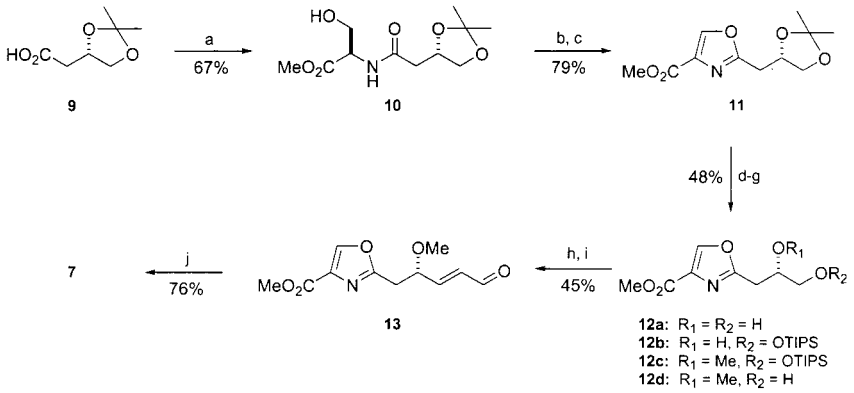
Scheme 1



Scheme 2[a]



[a] Reaction conditions: (a) HCl·L-serineOMe, 1,1′-CDI, THF; (b) DAST, CH_2Cl_2, −78 °C; (c) DBU, $BrCCl_3$, Ch_2Cl_2, 0 °C to rt; (d) Dowex-H^+, MeOH; (e) TIPSOTf, 2,6-lutidine, CH_2Cl_2 (0.05 M), −78 °C; (f) MeI, Ag_2O, CH_3CN, Δ; (g) TBAF, THF; (h) SO_3·Pyr, DMSO, Et_3N, CH_2Cl_2; (i) $Ph_3P{=}CH_2CHO$, THF; (j) $I^-Ph_3P^+CH_2I$, NaHMDS, HMPA, −78 °C.

four steps. Construction of the enal **13** was accomplished in 45% overall yield from **12a** via oxidation (SO_3·Pyr, DMSO, Et_3N)[9] and reaction of the resultant crude aldehyde with triphenylphosphoranylidine acetaldehyde[10] in THF. The enal **13**, thus obtained, was then subjected to a Stork/Zhao modified[11] Wittig reaction (I^+Ph_3PCHI,[12] NaHMDS, HMPA, −78 °C) to give the dienyl iodide **7** (76%).

Alkyne 8. The initial step toward construction of the alkyne **8** involved a modified[13] Mukaiyama aldol between (*E*)-crotonaldehyde **14** and the *tert*-butyldimethylsilyl ketene acetal **15**[14] to give **16** in 85% yield and 92% enantiomeric excess (Scheme 3).[15] Subsequently, it was discovered that treatment of the acetal **16** with base (NaH, THF, 0 °C) resulted in exclusive formation of the aldehyde **17** (71%) presumably arising from an unusual 1,5 O → O silyl migration[16] (shown in brackets) followed by elimination of ethoxide (Scheme 3). It was subsequently found that **17** could be bypassed completely by addition of NaH to a solution of **16** and triethylphosphonoacetate in THF at −78 °C and warming to room temperature, producing the α,β-unsaturated ester **18** in

(9) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(10) For a general review of this reagent see: McComsey, D. F.; Maryanoff, B. E. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 4, pp 2598−2599.

(11) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173−2174.

(12) Seyferth, D.; Heeren, J. K.; Singh, D.; Grim, S. O.; Hughes, W. B. *J. Organometallic Chem.* **1966**, *5*, 267−274.

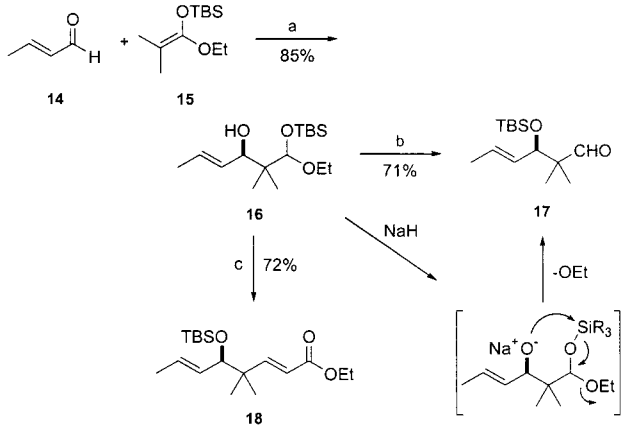
(13) Kiyooka, S,; Kaneko, Y,; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276−2278.

(14) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67−72.

(15) See the Supporting Information.

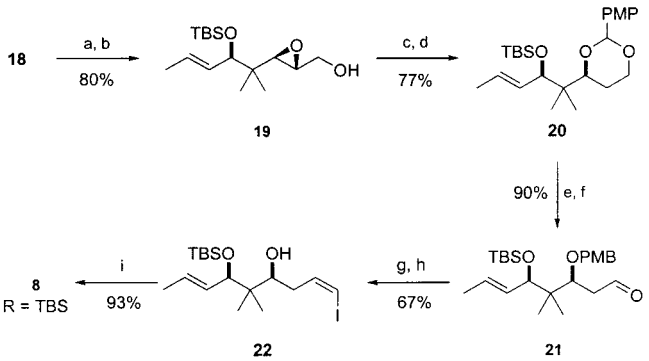
(16) For a cursory review of O → O silyl migrations, see: Rücker, C. *Chem. Rev.* **1995**, *95*, 1009−1064.

Scheme 3[a]



[a] Reaction conditions: (a) BH_3·THF, *N*-Ts-L-valine, CH_2Cl_2, −78 °C; (b) NaH (1 equiv), THF, −78 to 0 °C; (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH (2 equiv), THF, −78 °C to rt.

Scheme 4[a]

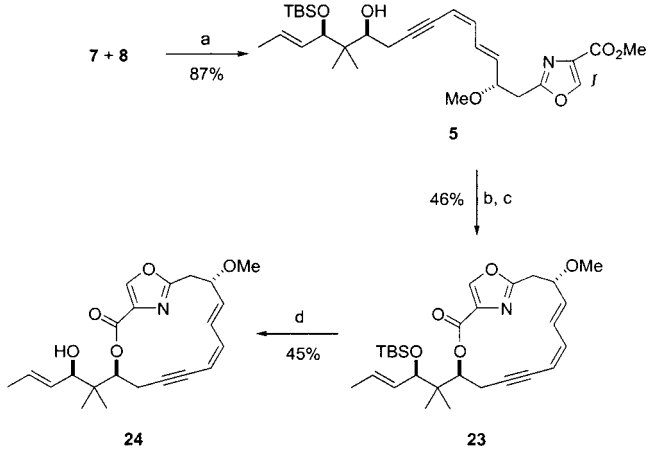


[a] Reaction conditions: (a) DIBAL, CH_2Cl_2, −78 °C; (b) D-(−)-DIPT, *t*-BuOOH, $Ti(O\text{-}i\text{-}Pr)_4$, CH_2Cl_2, −30 °C; Red-Al, THF, −20 to 0 °C; (d) *p*-methoxybenzylidene dimethyl acetal, PPTS, CH_2Cl_2; (e) DIBAL, CH_2Cl_2, −78 °C; (f) Dess−Martin periodinane, pyridine, *t*-BuOH, CH_2Cl_2; (g) $I^-Ph_3P^+CH_2I$, NaHMDS, HMPA, THF, −78 °C; (h) DDQ, CH_2Cl_2, H_2O; (i) NaHMDS (2 equiv), THF, −78 °C to rt.

72% yield. The scope of this one-pot three-step transformation is currently being examined with other substrates.[17]

The α,β-unsaturated ester **18** was next treated with Dibal in CH_2Cl_2 at −78 °C furnishing the allylic alcohol, which was oxidized, via the Sharpless procedure,[18] to provide a diastereomeric mixture (14:1) of epoxy alcohols in 80% overall yield, with **19** being the major product (Scheme 4). This mixture, containing **19**, was subjected to selective reduction with Red-Al[19] followed by protection with *p*-methoxybenzylidine dimethyl acetal and catalytic PPTS in CH_2Cl_2 to afford the *p*-methoxybenzylidine acetal **20** as a single isomer in 77% yield over the two steps. The aldehyde **21** was obtained in 81% yield in two steps via selective ring opening of the acetal **20** using Dibal,[20] followed by oxidation of the primary alcohol with the Dess−Martin periodinane.[21] Subsequently, this pivotal aldehyde was subjected to a Stork/Zhao modified[11] Wittig reaction, and the PMB protecting group was oxidatively removed to afford the vinyl iodide **22** in 67% yield for the two steps. Treatment of **22** with excess NaHMDS (2 equiv) resulted in elimination of the iodide to give the alkyne **8**[22] in high yield (93%).[23]

Scheme 5[a]



[a] Reaction conditions: (a) $PdCl_2(PPh_3)_2$, CuI, Et_3N, CH_3CN, −20 °C to rt; (b) 1 N LiOH, THF; (c) DPTC, DMAP, toluene, Δ; (d) HF·Pyr, CH_3CN.

Sonogashira Coupling and Cyclization. With the requisite subunits **7** and **8** in hand, the Sonogashira coupling[24] was performed providing the dienyne monomer **5** in 87% yield (Scheme 5). The methyl ester of **5** was hydrolyzed using 1 N LiOH in THF, and the resultant crude carboxylic acid was treated directly with dipyridyl thionocarbonate (DPTC)[25] and catalytic dimethylamino pyridine (DMAP) in refluxing toluene to afford, surprisingly, only the protected cyclic monomer **23** (46%). Furthermore, none of the expected cyclic dimer **3** was formed.[26] Changes in reactant concentration did not appear to affect the outcome of this transformation. Deprotection of the silylated alcohols in the cyclic monomer **23** with HF·pyridine gave a mixture (3:1) of products,

(17) Hillier, M. C.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 5145−5147.

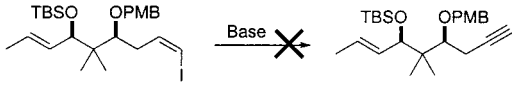
(18) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

(19) (a) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719−2722. (b) Viti, S. *Ibid.* **1982**, *23*, 4541−4544.

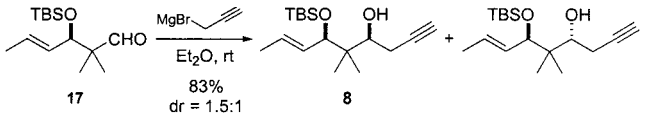
(20) Schreiber, S.; Wang, Z.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 4085−4088.

(21) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Ireland, R. E.; Liu, L. *ibid*, **1993**, *58*, 2899.

(22) This elimination did not work in the absence of the free hydroxyl:



(23) We have examined an alternative route for the synthesis of **8** from the aldehyde **17** via addition of propargylmagnesium bromide. However, while this reaction is efficient it is not selective, as an inseparable mixture (1.5:1) of diastereomeric products were formed:

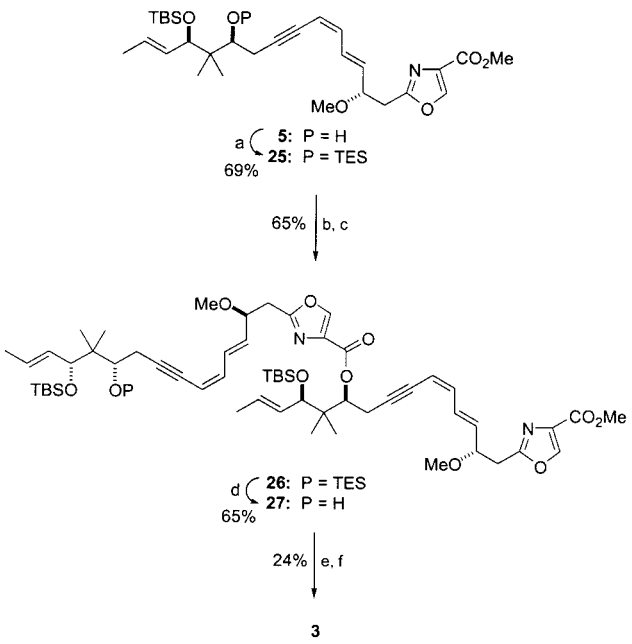


(24) (a) Campbell, I. B. In *Organocopper Reagents. A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; Chapter 10, pp 217−236. (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: Weinheim, 1997; Chapter 5, pp 203−229.

(25) Saitoh, K.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1998**, 679−680.

(26) Others have synthesized dimeric natural products via one-step dimerization of the corresponding monomeric subunits. For example: (a) Corey, E. J.; Hua, D. H.; Pan, B.-C.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 6818−6820. (b) Berger, M.; Mulzer, J. *J. Am. Chem. Soc.* **1999**, *121*, 8393−8394.

Scheme 6[a]



[a] Reaction conditions: (a) TESOTf, 2.6-lutidine, CH_2Cl_2, −78 °C; (b) 1 N LiOH, THF; (c) **5**, DPTC, DMAP, toluene, Δ; (d) TFA, H_2O, THF; (e) 1 N LiOH, THF; (f) 2,4,6-trichlorobenzoyl chloride, DMAP, toluene, rt.

presumably arising from *intramolecular* transesterification. The major product **24** was isolated by recrystallization (EtOAc/hexanes) in 45% yield. A single X-ray crystal structure of **24** provided unambiguous confirmation of the structural and stereochemical assignments.[15] Interestingly, the fast atom bombardment (FAB) mass spectrum of **24** showed M + H peaks for both the monomeric material **24** (M + H = 386) *and the dimer* **3** (M + H = 771).[15] However, an electrospray mass spectrum of **24** showed only the monomeric material. The presence of the dimer **3** in the FAB spectrum of **24** invokes an intriguing aspect to this problem. Could it be that disorazole C_1 (**1**) is not the symmetrical dimer as reported?[27] Could it be a smaller, monomeric macrocycle like **23**, which upon mass spectral analysis dimerizes in the process to inadvertently suggest the presence of a dimer? To arrive at a quick, but uncertain, answer to this intriguing question, the monomer **24** was reduced at its triple bond to a triene, but the spectrum of this product did not correspond to the natural disorazole, **1**. This reduced monomer could not be completely characterized; thus, the experiment was somewhat inconclusive. These questions will have to await the completion of the synthesis and further characterization to arrive at a correct answer.

Alternate Dilactonization Strategy. In light of the tendency of the monomer **5** to undergo intramolecular cyclization, attention was then turned to a more stepwise route to avoid the lactonization to **23** (Scheme 6). In the event, the free hydroxyl of **5** was first protected with TESOTf and 2,6-lutidine in CH_2Cl_2 at −78 °C to afford the triethylsilyl (TES) ether **25** (69%). The methyl ester of **25** was saponified (1 N LiOH, THF) and the free carboxylic acid coupled to the alcohol **5** using DPTC and catalytic DMAP in refluxing toluene, thus giving only the monoester **26** in 65% yield. Acidic deprotection of **26** with TFA/H_2O (1:1) in THF led to the hydroxyl derivative **27** (65%), whose remaining methyl ester was hydrolyzed (1 N LiOH, THF) and the resultant seco acid cyclized according to the Yamaguchi protocol[28] to give the bislactone **3** in 24% yield.[29]

With the desired cyclic dimer **3** in hand, removal of the TBS protecting groups to obtain **2** was next attempted. Unfortunately, as with the cyclic monomer **23**, this transformation led to a complex mixture of transesterified products, which in this instance were not separable by column chromatography or any other means. The dimer **3** also seems to be particularly sensitive to both acidic and basic conditions necessary to remove the silyl protecting groups, giving rise to significant amounts of decomposition product. An attempt to reduce the alkynyl groups of **3** was carried out to obtain the requisite bis-triene, a protected version of the natural product **1**, but this proved to be unsuccessful.[30]

Summary. The synthesis of both monomeric and dimeric dehydro-disorazole C_1 derivatives, **24** and **3**, respectively, has been presented. During these endeavors, a novel 1,5 O → O silyl migration was discovered, which, when coupled with Horner-Wadsworth-Emmons conditions, provided for a very efficient synthesis of the α,β-unsaturated ester intermediate **18**. In addition, the dienyne monomer **5** was found to undergo only intramolecular cyclization to give **24**, necessitating a more stepwise route to the desired dimer **3**. Finally, while it was not possible to successfully desilylate the allylic alcohols in the dimer **3**, or reduce it to the natural product **1**, a stereocontrolled synthesis of the correct molecular framework of disorazole C_1 has been achieved.[31]

Experimental Section

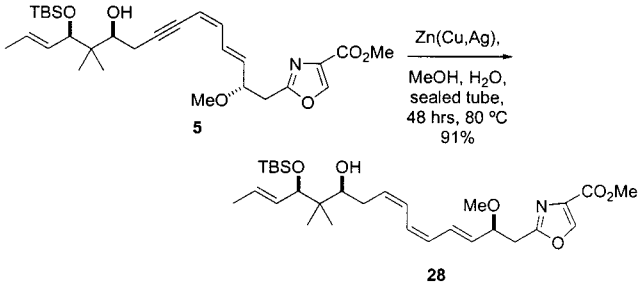
General Methods. Unless otherwise noted, all starting materials were obtained from commercial suppliers and were used without further purification. Solvents were dried according to established procedures by distillation from an appropriate drying agent under an inert atmosphere of argon in

(27) The original isolation team reported (ref 1) a chemical ionization (CI) mass spectrum for disorazole C_1 (**1**) of M + H = 775, which had an intensity of 0.3% when compared to the base peak.

(28) (a) Hikota, M.; Hitoshi, T.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613−4628. (b) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446−11459. (c) Berger, M.; Mulzer, J. *J. Am. Chem. Soc.* **1999**, *121*, 8393.

(29) A significant amount of the cyclic monomer **23** (67%) was formed in this reaction, though it was separable from the dimer **3** by column chromatography. This surprising result is due to the nonselective hydrolysis of the di-ester **27** under basic conditions. Attempts to circumvent this problematic transformation were unsuccessful.

(30) While the dimeric dienyne **3** could not be reduced to the triene found in the natural product **1**, the monomer **5** did submit to the following conditions to give **28**, though some isomerization did occur: Boland, W.; Sieler, C.; Fiegel, M. *Helv. Chim. Acta* **1987**, *70*, 1025−1040:



(31) For personal reasons, the senior author will no longer be in the position to continue this study. Hopefully, other laboratories will find reasons to pursue disorazole C_1 (**1**) to its conclusion.

glassware that had been flame-dried. Chemical shifts are reported in parts per million (ppm, δ) from an internal standard of tetramethylsilane (TMS) or deuterated chloroform ($CDCl_3$). Flash chromatography was performed using Merck silica gel 60 (230−400 mesh ASTM).

***N*-(1′-Carbomethoxy-2*R*-hydroxyethanyl)-3*S*,4-dihydroxybutanamide Acetonide, 10.** To a solution of the acid **9** (12 g, 73 mmol)[2a] in THF (70 mL) at 0 °C was added 1,1′-carbonyldiimidazole (12 g, 75 mmol), and the mixture was stirred for 30 min. The cooling bath was removed, HCl·L-serine methyl ester was added in one portion, and the reaction mixture was stirred overnight at room temperature. Solvent was removed in vacuo, and the crude residue was partitioned between EtOAc/brine (200:50 mL). The resulting biphasic mixture was separated, and the aqueous phase was extracted with EtOAc (4 × 10 mL). The organic extracts were combined, dried (Na_2SO_4), concentrated, and purified via column chromatography eluting with EtOAc/hexanes (9:1) to provide 13 g (67%) of **10** as a thick oil, which solidified to a waxy solid upon standing: $[\alpha]_D = +31.0$ (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 6.93 (d, J = 8.0 Hz, 1 H), 4.69−4.42 (m, 2 H), 4.15 (dd, J = 6.5, 8.5 Hz, 1 H), 3.96 (d, J = 4.0 Hz, 1 H), 3.78 (s, 3 H), 3.67 (dd, J = 6.5, 8.5 Hz, 1 H), 2.56 (dd, J = 3.5, 5.5 Hz, 1 H), 1.46 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR δ 171.0, 109.5, 72.6, 69.1, 62.9, 54.8, 40.5, 27.0, 25.6 cm^{-1}; IR (neat) ν 3418, 1732, 1730, 1586, 1324. Anal. Calcd for $C_{11}H_{19}NO_6$: C, 50.57; H, 7.33; N, 5.36. Found: C, 50.58; H, 7.29; N, 5.26.

4-Carbomethoxy-2-(3′*S*,4′-dihydroxy)-1,3-oxazolyl Acetonide, 11. To a solution of **10** (17 g, 63 mmol) from the preceding experiment in CH_2Cl_2 (150 mL) was added diethylaminosulfur trifluoride (DAST) (8.8 mL, 66 mmol), and the reaction was stirred for 45 min. Solid K_2CO_3 (18 g, 126 mmol) was then added, and the reaction was stirred for 1 h and then warmed to room temperature. The orange slurry was slowly added (Caution! H_2 gas evolution!) to saturated aqueous $NaHCO_3$ (50 mL), and the resultant biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organics were dried (Na_2SO_4) and concentrated in vacuo. A small portion of the oxazoline intermediate was purified for characterization purposes by passing through a small silica gel column eluting with EtOAc: $[\alpha]_D = +121.0$ (*c* 0.9, $CHCl_3$); ^{1}H NMR δ 4.76−4.70 (m, 1 H), 4.50−4.35 (m, 3 H), 4.13 (dd, J = 6.2, 8.6 Hz, 1 H), 3.78 (s, 3 H), 3.68 (dd, J = 6.2, 8.6 Hz, 1 H), 2.70 (ddd, J = 1.1, 5.9, 15.4 Hz, 1 H), 2.51 (ddd, J = 1.1, 7.5, 15.4 Hz, 1 H), 1.40 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR δ 171.7, 167.6, 109.5, 72.8, 69.6, 69.5, 68.2, 52.8, 32.9, 27.1, 25.7; IR (neat) ν 2986, 1744, 1663, 1212, 1067. The crude oxazoline was taken on without further purification, dissolved in CH_2Cl_2 (300 mL), and then cooled to 0 °C. To this solution was added DBU (19 mL, 126 mmol) followed by $BrCCl_3$ (7 mL, 70 mmol), and the black reaction mixture was stirred for 12 h without further cooling. Saturated aqueous NH_4Cl (200 mL) was then added, and the biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated, and the crude black residue was purified via column chromatography eluting with EtOAc/hexanes (2:3) to provide 12 g (79%, over two steps) of the oxazole **11** as an oil: $[\alpha]_D = -0.7$ (*c* = 1.0, $CHCl_3$); ^{1}H NMR δ 8.18 (s, 1 H), 4.61−4.52 (m, 1 H), 4.15 (dd, J = 6.0, 8.0 Hz, 1 H), 3.91 (s, 3 H), 3.77 (dd, J = 6.5, 8.5 Hz, 1 H), 3.16 (dd, J = 6.5, 15.2 Hz, 1 H), 3.02 (dd, J = 6.5, 15.2 Hz, 1 H), 1.40 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR δ 162.2, 161.6, 144.2, 133.4, 109.7, 73.1, 68.8, 52.2, 32.9, 26.9, 25.5; IR (neat) ν 2987, 1747, 1586, 1324, 1111, 1066 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.86; H, 6.29; N, 5.77.

4-Carbomethoxy-2-(3′S,4-dihydroxy)-1,3-oxazole, 12a. The oxazole **11** (14 g, 59 mmol) was dissolved in MeOH (60 mL), treated with Dowex-H^+ resin, and stirred for 12 h at room temperature. The acidic resin was removed by filtration through a pad of Celite, and the filtrate was concentrated to provide 12 g (>95%) of **12a** as an orange oil: $[\alpha]_D = -21.3°$ (*c* 0.4, $CHCl_3$); ^{1}H NMR δ 8.13 (s, 1 H), 4.40−4.05 (m, 3 H), 3.84 (s, 3 H), 3.68 (dd, J = 4.0, 11.0 Hz, 1 H), 3.55 (dd, J = 6.0, 11.0 Hz, 1 H), 2.99−2.95 (m, 2 H); ^{13}C NMR δ 163.8, 161.7, 144.2, 132.9, 69.6, 65.7, 52.3, 32.2; IR (neat) ν 3374, 1738, 1587, 1326, 1112 cm^{-1}. Anal. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.67; H, 5.46; N, 6.89. This material proved to be of sufficient purity to proceed further.

4-Carbomethoxy-2-(3′*S*-hydroxy-4′-triisopropylsiloxy)-1,3-oxazole, 12b. To a solution of **12a** (12 g, 56 mmol) in CH_2Cl_2 (1.4 L) at −78 °C was added 2,6-lutidine (8.0 mL, 67 mmol) followed by triisopropylsilyl triflouromethanesulfonate (17 mL, 62 mmol), dropwise over 10 min. The reaction was stirred for 30 min whereupon a solution of brine (500 mL) was added and the resultant biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL), the organic layers were combined, dried ($MgSO_4$), and concentrated, and the crude product residue was purified via column chromatography eluting with EtOAc/hexanes (2:5) to provide 16 g (76%) of **12b** as an oil: $[\alpha]_D = -13.9$ (*c* = 0.9, $CHCl_3$); ^{1}H NMR δ 8.18 (s, 1 H), 4.22−4.18 (m, 1 H), 3.90 (s, 3 H), 3.76 (dd, J = 5.0, 10.0 Hz, 1 H), 3.69 (dd, J = 5.0, 10.0 Hz, 1 H), 3.05 (m, 2 H), 2.90 (brs, 1 H), 1.05−0.90 (comp, 21 H); ^{13}C NMR δ 163.6, 161.8, 144.1, 133.3, 69.7, 66.5, 52.2, 32.4, 18.0, 12.0; IR (neat) ν 3444, 2993, 1747, 1587, 1324, 1112 cm^{-1}; mass spectrum (FAB) *m*/*z* 358.2049 ($C_{17}H_{31}NO_5Si$ + H requires 358.2050).

4-Carbomethoxy-2-(2′S-methoxy-4′-triisopropylsiloxy)-1,3-oxazole, 12c. A solution of **12b** (16 g, 45 mmol) in CH_3CN (90 mL), containing Ag_2O (19 g, 81 mmol) and MeI (64 mL), was heated to 60 °C for 12 h. The resulting brown slurry was diluted with Et_2O (200 mL) and filtered through a pad of Celite. The filtrate was concentrated and the crude residue purified via column chromatography eluting with EtOAc/hexanes (1:5) to give 12 g (71%) of **12c** as an orange oil: $[\alpha]_D = -7.8$ (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 8.15 (s, 1 H), 3.89 (s, 3 H), 3.85−3.71 (m, 3 H), 3.38 (s, 3 H), 3.15 (dd, J = 3.8, 15.3 Hz, 1 H), 3.01 (dd, J = 7.5, 15.3 Hz, 1 H), 1.12−1.00 (m, 21 H); ^{13}C NMR δ 163.9, 161.9, 144.0, 133.5, 79.9, 64.6, 52.2, 31.0, 18.0, 12.5, 12.0; IR (neat) ν 2944, 1748, 1731, 1585, 1324, 1111 cm^{-1}; mass spectrum (FAB) *m*/*z* 372.2201 ($C_{18}H_{33}NO_5Si$ + H requires 372.2206).

4-Carbomethoxy-2-(2′*S*-methoxy-4′-hydroxy)-1,3-oxazole, 12d. To a solution of **12c** (12 g, 32 mmol) in THF (70 mL) at 0 °C was slowly added a solution of 1.0 M TBAF (48 mL, 48 mmol) in THF. After 12 h, solvent was removed in vacuo and the crude alcohol was purified via column chromatography eluting with EtOAc (9:1) to give 6.2 g (89%) of **12d** as an orange oil: $[\alpha]_D = +17.5°$ (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 8.14 (s, 1 H), 3.86 (s, 3 H), 3.80−3.50 (m, 3 H), 3.36 (s, 3 H), 3.12 (dd, J = 6.1, 15.2 Hz, 1 H), 3.05 (ddd, J = 1.0, 6.5, 15.2 Hz, 1 H), 2.28 (brs, 1 H); ^{13}C NMR δ 162.9, 161.5, 144.0, 133.3, 79.0, 63.0, 57.5, 52.1, 29.6; IR (neat) ν 3418, 1732, 1586, 1324, 1110 cm^{-1}; mass spectrum (FAB) *m*/*z* 216.0869 ($C_9H_{13}NO_5$ + H requires 216.0872).

4-Carbomethoxy-2-[2′*S*-methoxy-3′(*E*)-penten-5′-al]oxazole, 13. To a solution of the alcohol **12d** (2.5 g, 11 mmol) in CH_2Cl_2 (12 mL) at 0 °C were added DMSO (11 mL, 160 mmol) and Et_3N (11 mL, 80 mmol), and the mixture was stirred for 10 min. Solid SO_3·Pyr (9.1 g, 57 mmol) was then added in one portion, and the reaction was stirred for 30 min at 0 °C and for 1 h at room temperature. Solvent was removed in vacuo, and the thick residue was filtered through a plug of silica gel eluting with EtOAc (300 mL). The filtrate was concentrated, and a small portion of the crude aldehyde was purified for characterization purposes: $[\alpha]_D = -34.0°$ (*c* 2.0, $CHCl_3$); ^{1}H NMR δ 9.79 (d, J = 1.0 Hz, 1 H), 8.18 (s, 1 H), 4.15 (ddd, J = 5.3, 7.3 Hz, 1 H), 3.91 (s, 3 H), 3.50 (s, 3 H), 3.29 (dd, J = 5.3, 15.8 Hz, 1 H), 3.15 (dd, J = 7.8, 15.8 Hz, 1 H); ^{13}C NMR δ 201.2, 161.5, 144.3, 133.5, 82.6, 58.8, 52.2, 29.1; IR (neat) ν 2953, 1731, 1589, 1440, 1324 cm^{-1}. The crude aldehyde was then dissolved in THF (100 mL), treated with triphenylphosphoranylidine acetaldehyde (3.8 g, 13 mmol), and the mixture was stirred for 2 days at room temperature. Solvent was concentrated in vacuo and the crude red product residue was purified via column chromatography eluting with EtOAc/hexanes (1:1) to furnish 1.2 g (45%, over two steps) of the enal **13** as a yellow wax: $[\alpha]_D = -14.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 9.58 (d, J = 7.0 Hz, 1 H), 8.18 (s, 1 H), 6.73 (dd, J = 6.0, 15.8

Hz, 1 H), 6.27 (ddd, J = 1.3, 7.0, 15.8 Hz, 1 H), 4.50−4.38 (m, 1 H), 3.81 (s, 3 H), 3.39 (s, 3 H), 3.19 (dd, J = 7.0, 15.1 Hz, 1 H), 3.09 (dd, J = 6.0, 15.1 Hz, 1 H); ^{13}C NMR δ 193.1, 161.8, 161.6, 153.6, 144.3, 133.6, 133.5, 76.8, 57.8, 52.4, 33.9; IR (neat) ν 2954, 1738, 1694, 1586, 1324, 1110 cm^{-1}; mass spectrum (FAB) m/z 240.0874 ($C_{11}H_{13}NO_5$ + H 240.0872).

4-Carbomethoxy-2-[2′*S*-methoxy-5′-iodo-3′-(*E*,*Z*)-hexenyl]oxazole, 7. A slurry of methyltriphenylphosphonium iodide (0.57 g, 1.1 mmol) in THF (5 mL) at room temperature was treated, dropwise, with a 1.0 M solution of NaHMDS (1.1 mL, 1.1 mmol) in THF. The resultant red-orange solution was stirred for 30 min at room temperature, cooled to −78 °C, and treated with HMPA (0.94 mL, 5.4 mmol) and a solution of **13** (0.26 g, 1.1 mmol) in THF (5 mL). After 3 h at −78 °C, the mixture was quenched by saturated aqueous $NaHCO_3$ (1 mL) and diluted with Et_2O (20 mL), and the resultant slurry was filtered through a pad of Celite. The biphasic filtrate was separated, the organic phase was dried (Na_2SO_4) and concentrated, and the crude product was purified via column chromatography eluting with EtOAc/hexanes (1:19) to give 0.3 g (76%) of the dienyl iodooxazole **7** as an inseparable mixture (8:1) of *E*,*Z*-vinyl iodide isomers: ^{1}H NMR (major isomer) δ ^{1}H NMR 8.14 (s, 1 H), 6.69 (dd, J = 7.7, 9.9 Hz, 1 H), 6.37 (dd, J = 9.9, 15.4 Hz, 1 H), 6.32 (d, J = 7.7 Hz, 1 H), 5.83 (dd, J = 7.7, 15.4 Hz, 1 H), 4.20 (dt, J = 5.8, 7.7 Hz, 1 H), 3.87 (s, 3 H), 3.26 (s, 3 H), 3.06 & 3.04 (ABX, J_{AB} = 14.8 Hz, J_{AX} = 7.2 Hz, J_{BX} = 5.5 Hz, 1 H); ^{13}C NMR (major isomer) δ 162.3, 161.5, 143.9, 137.0, 136.0, 133.3, 84.1, 79.2, 56.8, 52.1, 34.5, 29.7; IR (neat) 1744, 1585, 1322, 1109 cm^{-1}; mass spectrum (FAB) m/z = 364.0047 ($C_{12}H_{14}NO_3I$ + H requires 364.0046), 307, 154 (base). This 8:1 mixture of **7** was used as such in the subsequent Sonogashira coupling step.

TBS Acetal, 16. To a flame-dried, two-neck flask, fitted with a low-temperature thermometer, were added *N*-tosyl-L-valine (8.3 g, 31 mmol) and CH_2Cl_2 (76 mL), and the resulting solution was cooled to 0 °C. A solution of 1.0 M BH_3·THF (28 mL, 28 mmol) was slowly added (Caution! H_2 gas evolution), and the mixture was stirred at 0 °C for 30 min and at room temperature for 30 min and then cooled to −78 °C. A solution of crotonaldehyde **14** (2.3 mL, 28 mmol) in CH_2Cl_2 (21 mL) was added followed by a solution of *tert*-butyldimethylsilyl ketene acetal **15**[14] (8.3 g, 36 mmol), and the mixture was stirred for 3 h at − 78 °C before being quenched with pH 7 buffer (100 mL). The resultant biphasic mixture was stirred at room temperature, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL), the combined organic layers were dried (Na_2SO_4) and concentrated, and the crude product was purified via flash chromatography eluting with EtOAc/hexanes (2:98) to afford 7.1 g (85%) of **16** as an oil: $[\alpha]_D$ = +15.6 (*c* 1.5, CH_2Cl_2); ^{1}H NMR δ 5.70 (ddq, J = 9.9, 15.6 Hz, 1 H), 5.45 (ddq, J = 3.5, 7.6, 15.6 Hz, 1 H), 4.49 (s, 1 H), 4.17−4.10 (m, 1 H), 3.72 (q, J = 7.2 Hz, 2 H), 3.69 (d, J = 3.3 Hz, 1 H), 1.70 (d, J = 7.2 Hz, 3 H), 1.21 (t J = 7.2 Hz, 3 H), 0.91 (s, 9 H), 0.98 (s, 3 H), 0.85 (s, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR δ 130.0, 127.7, 104.8, 76.3, 65.1, 42.9, 25.6, 21.4, 18.8, 18.2, 17.8, 15.2, −3.5, −4.1; IR (neat) ν 3510, 2980 cm^{-1}.

α,β-Unsaturated Ester, 18. A solution of **16** (14 g, 41 mmol) and triethylphosphonoacetate (8 mL, 41 mmol) in THF (200 mL) at −78 °C was treated with oil-free NaH (2.0 g, 81 mmol), and the cooling bath was removed. After 2 h at room temperature, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (50 mL) and the biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layers were dried (Na_2SO_4), concentrated, and the crude residue was purified via column chromatography eluting with EtOAc/hexanes (1:20) to provide 11 g (72%) of **18** as an oil: $[\alpha]_D$ = −4.6 (*c* 13.9, CH_2Cl_2); ^{1}H NMR δ 7.00 (d, J = 16.0 Hz, 1 H), 5.67 (d, J = 16.0 Hz, 1 H), 5.47 (dq, J = 6.3, 15.3 Hz, 1 H), 5.27 (ddq, J = 1.4, 7.9, 15.3 Hz, 1 H), 4.13 (q, J = 7.3 Hz, 2 H), 3.68 (d, J = 7.9 Hz, 1 H), 1.62 (dd, J = 1.4, 6.3 Hz, 3 H), 1.24 (t, J = 7.3 Hz, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H), 0.83 (s, 3 H), −0.04 (s, 3 H), −0.09 (s, 3 H); ^{13}C NMR δ 167.1, 156.6, 131.1, 128.1, 118.8, 80.8, 60.3, 42.3, 26.1, 23.6, 22.4, 18.4, 17.9, 14.5, −3.6, −4.7; IR (neat) ν 2958, 1722, 1651, 1472 cm^{-1}, mass spectrum (FAB) m/z 326.2228 ($C_{18}H_{34}O_3Si$ requires 326.2277), 282 (base).

Epoxy Alcohol, 19. (a) Allylic Alcohol. A solution of **18** (11 g, 29 mmol) in CH_2Cl_2 (100 mL) at −78 °C was treated with neat Dibal (10 mL, 59 mmol), and the cooling bath was removed. After 15 min, the reaction was quenched by addition of MeOH (5 mL), saturated aqueous Rochelle's salt (50 mL) was added, and the biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), the combined organic layers were dried (Na_2SO_4) and concentrated, and the crude product was purified via column chromatography eluting with EtOAc/hexanes (5:95) to afford 8.2 g (85%) of the intermediate allylic alcohol as a slightly yellow oil: $[\alpha]_D$ = +1.9 (*c* 3.8, CH_2Cl_2); ^{1}H NMR δ 5.71 (dt, J = 1.1, 15.8 Hz, 1 H), 5.48 (dt, J = 6.0, 15.8 Hz, 1 H), 5.42 (dq, J = 6.1, 15.2 Hz, 1 H), 5.27 (ddq, J = 1.2, 7.6, 15.2 Hz, 1 H), 4,04 (brs, 2 H), 3.60 (d, J = 7.6 Hz, 1 H), 1.65 (brs, 1 H), 1.61 (dd, J = 1.2, 6.1 Hz, 3 H), 0.90 (s, 3 H), 0.89 (s, 3 H), 0.82 (s, 9 H), −0.05 (s, 3 H), −0.1 (s, 3 H); ^{13}C NMR δ 140.3, 131.5, 127.1, 125.9, 81.1, 64.2, 40.8, 25.9, 24.0, 23.1, 18.2, 17.7, −3.8, −4.9; IR (neat) ν 3317, 2958, 2929, 2857, 1472, 1382, 1360, 1254 cm^{-1}; mass spectrum (FAB) m/z 285.2089 ($C_{16}H_{32}O_2Si$ + H requires 285.2093) 185 (base).

(b) A flame-dried 100 mL three-neck flask, fitted with a low-temperature thermometer, was charged with crushed 3 Å molecular sieves and a solution of (−)-diethyl tartrate (DET, 0.24 g. 1.0 mmol) in CH_2Cl_2 (15 mL) and then cooled to −20 °C. Ti(O-*i*-Pr)$_4$ (0.25 mL, 0.84 mmol) and 5.5 M *tert*-butyl hydroperoxide (TBHP, 4.0 mL, 22 mmol) were then added, and the resultant mixture was aged for 30 min before being treated with a solution of the allylic alcohol from above (2.4 g, 8.4 mmol) from the preceding experiment in CH_2Cl_2 (10 mL). The solution was stirred overnight, a solution of $FeSO_4$·$7H_2O$ (5.6 g, 20 mmol) and citric acid (2.1 g, 9 mmol) in H_2O (33 mL) was added, and the biphasic mixture was stirred for 45 min before being filtered through a plug of Celite. The filtrate was cooled to 0 °C, treated with 1 N NaOH (5 mL), and stirred at this temperature for 1 h. The biphasic mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the crude product residue was purified via flash chromatography eluting with EtOAc/hexanes (1:5) to provide 2.4 g (94%) of **19** an inseparable mixture (14:1) of epoxy alcohol diastereomers; ^{1}H NMR (major diastereomer) δ 5.54−5.34 (comp, 2 H), 3.84 (ddd, J = 2.5, 6.1, 12.5 Hz, 1 H), 3.71 (d, J = 7.5 Hz, 0.93 H), 3.47 (ddd, J = 5.0, 6.6, 12.5 Hz, 1 H) 2.96 (dt, J = 2.5, 5.0 Hz, 1 H), 2,88 (d, J = 2.5 Hz, 1 H), 2.14 (dd, J = 6.1, 6.6 Hz, 1 H), 1.64 (d, J = 5.1 Hz, 3 H), 0.83 (s, 9 H), 0.81 (s, 6.0 H), 0.73 (s, 6 H), −0.03 (s, 6 H), −0.07 (s, 6 H); ^{13}C NMR (diastereomeric mixture) δ 131.2, 127.6, 80.3, 62.3, 60.3, 55.0, 38.7, 25.9, 20.8, 19.0, 18.2, 17.7, −3.7, −5.0; IR (neat) ν 3429, 2957, 2857, 1472, 1386, 1361, 1255 cm^{-1}; mass spectrum (FAB) m/z 301.2197 ($C_{16}H_{32}O_3Si$ + H requires 301.2199), 154 (base).

PMB Acetal, 20. (a) Diol. The epoxy alcohol **19** (3.4 g, 11 mmol) was dissolved in THF (20 mL), cooled to −20 °C, and treated with a 70% solution of Red-Al in toluene (8.2 g, 29 mmol). This mixture was stirred for 12 h at −20 °C and then at 0 °C for 2 days before being quenched by addition of saturated aqueous Rochelle's salt (10 mL). The biphasic mixture was separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried ($MgSO_4$), concentrated, and purified via flash chromatography eluting with EtOAc/hexanes (1:1) to provide 1.7 g (77%) of the diol as as a single diastereomer: $[\alpha]_D$ = −8.8 (*c* 8.9, CH_2Cl_2); ^{1}H NMR δ 5.48 (dq, J = 5.9, 15.3 Hz, 1 H), 5.36 (ddq, J = 1.2, 8.1, 15.3 Hz, 1 H), 3.95 (brs, 1 H), 3.87 (d, J = 8.1 Hz, 1 H), 3.78−3.68 (comp, 3 H), 3.34 (t, J = 4.9 Hz, 1 H), 1.64 (dd, J = 1.2, 5.9 Hz, 3 H), 1.63−1.56 (m, 2 H), 0.83 (s, 3 H), 0.82 (s, 9 H), 0.64 (s, 3 H), 0.00 (s, 3 H), −0.05 (s, 3 H); ^{13}C NMR δ 131.0, 128.6, 83.2, 79.5, 79.4, 62.5, 41.4, 32.8, 25.9, 21.2, 18.1, 17.7, 15.9, −3.2, −4.7; IR (neat) ν 3377, 2957, 2930, 2883, 2857, 1472, 1254 cm^{-1}; mass spectrum (FAB) m/z 303.2354 ($C_{16}H_{34}O_3$-Si + H requires 303.2355), 185 (base).

(b) To a solution of the diol (1.2 g, 3.9 mmol) from the preceding experiment in CH_2Cl_2 (30 mL) was added *p*-methoxybenzylidine dimethyl acetal (1.2 g, 6.3 mmol) followed by a catalytic amount of pyridinium *p*-toluensulfonate (PPTS, 0.1 g, 0.4 mmol), and the mixture was stirred for 12 h. The reaction was neutralized by addition of saturated aqueous $NaHCO_3$ (15 mL), the resulting biphasic mixture was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried ($MgSO_4$), concentrated, and purified via column chromatography eluting with EtOAc/hexanes (1:9) to give 1.6 g (>95%) of **20** as a clear oil: $[\alpha]_D = +35.6$ (*c* 4.7, CH_2Cl_2); ^{1}H NMR δ 7.41−7.23 (m, 2 H), 6.89−6.83 (m, 2 H), 5.55−5.38 (m, 2 H), 5.36 (s, 1 H), 4.24 (ddd, J = 1.3, 4.7, 11.0 Hz, 1 H), 3.95 (d, J = 7.5 Hz, 1 H), 3.88 (dt, J = 2.6, 11.8 Hz, 1 H), 3.78 (s, 3 H), 3.71 (dd, J = 2.2, 11.8 Hz, 1 H), 1.86 (ddd, J = 2.6, 4.7, 12.6 Hz, 1 H), 1.68 (d, J = 5 Hz, 3 H), 1.39 (ddd, J = 1.3, 2.2, 12.6 Hz, 1 H), 0.98 (s, 3 H), 0.87 (s, 9 H), 0.77 (s, 3 H), −0.01 (s, 3 H), −0.04 (s, 3 H); ^{13}C NMR δ 159.5, 131.8, 131.4, 127.4, 127.1, 113.4, 100.8, 81.1, 78.3, 67.3, 55.2, 41.9, 26.0, 25.6, 19.1, 18.2, 18.1, 17.8, −3.4, −4.9; IR (neat) ν 2958, 2931, 2856, 1616, 1518, 1464, 1391, 1302, 1250, 1170, 1116, 1053, 835, 775 cm^{-1}; mass spectrum (FAB) *m*/*z* 421.2757 ($C_{24}H_{40}O_4Si$ + H requires 421.2774), 185 (base).

PMB Aldehyde, 21. (a) PMB Alcohol. The acetal **20** (1.6 g, 3.8 mmol) was dissolved in CH_2Cl_2 (38 mL) and cooled to −78 °C, whereupon a solution of 1.5 M Dibal in CH_2Cl_2 (13 mL, 19 mmol) was added, and the solution was stirred for 20 min at −78 °C and for 1 h at 0 °C. The reaction was quenched by addition of saturated aqueous Rochelle's salt (15 mL), and the biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layers were dried ($MgSO_4$) and concentrated, and the crude product residue was purified via column chromatography eluting with EtOAc/hexanes (1:3) to afford 1.5 g (90%) of the PMB alcohol as a clear oil: $[\alpha]_D = -2.6$ (*c* 6.1, CH_2Cl_2); ^{1}H NMR δ 7.31−7.23 (m, 2 H), 6.90−6.83 (m, 2 H), 5.54−5.37 (m, 2 H), 4.50 (s, 2 H), 3.86 (d, J = 7.3 Hz, 1 H), 3.80 (s, 3 H), 3.84−3.65 (m, 1 H), 3.61 (dd, J = 3.1, 9.5 Hz, 1 H), 2.01 (brs, 1 H), 1.91−1.71 (comp, 2 H), 1.68 (d, J = 5 Hz, 3 H), 0.99 (s, 3 H), 0.89 (s, 9 H), 0.76 (s, 3 H), 0.01 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR δ 158.9, 131.4, 130.9, 129.0, 127.9, 113.7, 82.1, 79.0, 74.2, 61.4, 55.2, 43.8, 33.2, 26.0, 19.7, 19.1, 18.2, 17.8, −3.3, −4.9; IR (neat) ν 3398, 2956, 2931, 2882, 2856, 1614, 1514, 1471, 1249 cm^{-1}; mass spectrum (FAB) *m*/*z* 423.2764 ($C_{24}H_{42}O_4Si$ + H requires 423.2774).

(b) A solution of the PMB alcohol (1.5 g, 3.4 mmol) from the preceding experiment in CH_2Cl_2 (13 mL) was treated with pyridine (0.6 mL, 6.86 mmol) and Dess−Martin periodinane[21] (2.9 g, 6.9 mmol) followed by *tert*-butyl alcohol (2 drops), and the resultant slurry was stirred for 1 h at room temperature. Saturated aqueous $NaHCO_3$ (1 mL) was then added, and the biphasic mixture was filtered through a plug of Celite washing with CH_2Cl_2 (2 × 5 mL). The filtrate was dried ($MgSO_4$) and concentrated, and the crude residue was purified via flash chromatography eluting with EtOAc/hexanes (1:9) to give 1.3 g (90%) of **21** as a clear oil: $[\alpha]_D = +14.3$ (*c* 1.7, CH_2Cl_2); ^{1}H NMR δ 9.88 (dd, J = 1.5, 2.8 Hz, 1 H), 7.31−7.25 (m, 2 H), 6.93−6.88 (m, 2 H), 5.58−5.41 (m, 2 H), 4.53 and 4.44 (AB, J_{AB} = 11.0 Hz, 1 H), 4.01 (d, J = 3.6, 7.3 Hz, 1 H), 3.94 (d, J = 7.3 Hz, 1 H), 3.84 (s, 3 H), 2.84 (ddd, J = 1.5, 3.6, 16.7 Hz, 1 H), 2.66 (ddd, J = 2.8, 7.3, 16.7 Hz, 1 H), 1.74 (d, J = 5.1 Hz, 3 H), 1.02 (s, 3 H), 0.94 (s, 9 H), 0.83 (s, 3 H), 0.06 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR δ 202.1, 158.9, 131.1, 130.7, 128.9, 128.1, 113.6, 79.2, 78.1, 72.8, 55.3, 46.0, 43.5, 26.0, 20.0, 19.2, 18.2, 17.8, −3.4, −4.8; IR (neat) ν 2956, 2856, 1726, 1613, 1514, 1471, 1249 cm^{-1}; mass spectrum (FAB) 421.2615 ($C_{24}H_{39}O_4Si$ + H requires 421.2618).

Vinyl Iodide, 22. (a) PMB Vinyl Iodide. A slurry of methyltriphenylphosphonium iodide (1.9 g, 3.5 mmol) in THF (20 mL) at room temperature was treated, dropwise, with a 1.0 M solution of NaHMDS (3.5 mL, 3.5 mmol) in THF. The resultant red-orange solution was stirred for 30 min, cooled to −78 °C, and then treated with HMPA (2.7 mL, 15.3 mmol) and a solution of **21** (1.3 g, 3.1 mmol) in THF (5 mL). After 3 h at −78 °C, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL), diluted with Et_2O (50 mL), and then filtered through a pad of Celite. The biphasic filtrate was separated, the organic phase was dried ($MgSO_4$) and concentrated, and the crude product was purified via column chromatography eluting with EtOAc/hexanes (1:19) to give 1.4 g (78%) of the protected vinyl iodide as an orange oil: ^{1}H NMR δ 7.29−7.21 (m, 2 H), 6.90−6.83 (m, 2 H), 6.36 (ddd, J = 6.3, 7.0, 7.2 Hz, 1 H), 6.21 (ddd, J = 1.4, 1.7, 7.2, 1 H), 5.55−5.37 (comp, 2 H), 4.51 (d, J = 11.0 Hz, 1 H), 4.36 (d, J = 11.0 Hz, 1 H), 3.95 (d, J = 7.3 Hz, 1 H), 3.80 (s, 3 H), 3.50 (dd, J = 4.3, 6.9 Hz, 1 H), 2.49 (dddd, J = 1.7, 4.3, 6.3, 15.6 Hz, 1 H), 2.37 (dddd, J = 1.4, 6.9, 7.0, 15.6 Hz, 1 H), 1.67 (d, J = 4.9 Hz, 3 H), 0.95 (s, 3 H), 0.88 (s, 9 H), 0.79 (s, 3 H), 0.03 (s, 3 H), −0.02 (s, 3 H); ^{13}H NMR δ 158.8, 139.8, 131.5, 131.1, 128.8, 127.7, 113.6, 82.6, 81.7, 79.1, 72.8, 55.3, 43.8, 36.2, 26.0, 19.8, 19.3, 18.2, 17.8, −3.3, −4.7; IR (neat) ν 2935, 2929, 2855, 1612, 1514, 1470, 1302 cm^{-1}; mass spectrum (FAB) *m*/*z* 545.1800 ($C_{25}H_{40}O_3SiI$ + H requires 545.1792), 185, 121 (base).

(b) To a solution of the protected vinyl iodide (1.2 g, 2.2 mmol) from the preceding experiment in CH_2Cl_2/H_2O (22:1.2 mL) was added DDQ (0.53 g, 2.4 mmol), and the dark reaction mixture was stirred at room temperature for 3.5 h. Solvent was removed in vacuo and the crude product residue was purified via column chromatography eluting with EtOAc/hexanes (1:19) to provide 0.81 g (86%) of **22** as a clear oil: $[\alpha]_D = -46.4$ (*c* 2.3, CH_2Cl_2); ^{1}H NMR δ 6.36 (ddd, J = 6.4, 6.6, 7.3 Hz, 1 H), 6.23 (ddd, J = 1.4, 1.4, 7.3 Hz, 1 H), 5.52 (dq, J = 6.1,15.6 Hz, 1 H), 5.40 (ddq, J = 1.5, 8.0, 15.6 Hz, 1 H), 3.91 (d, J = 8.0 Hz, 1 H), 3.61 (dt, J = 3.2, 10.2 Hz, 1 H), 3.20 (dd, J = 1.3, 3.2 Hz, 1 H), 2.33 (ddddd, J = 1.4, 1.4, 6.4, 10.2, 14.8 Hz), 2.17 (dddd, J = 1.4, 6.6, 10.2, 14.8 Hz, 1 H), 1.67 (dd, J = 1.5, 6.1 Hz, 1 H), 0.89 (s, 3 H), 0.85 (s, 9 H), 0.75 (s, 3 H), 0.03 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR δ 139.6, 131.1, 128.6, 83.4, 82.9, 77.2, 41.7, 37.6, 26.0, 21.3, 18.1, 17.8, 16.3, −3.3, −4.7; IR (neat) ν 3478, 2957, 2930, 2857, 1471, 1255 cm^{-1}; mass spectrum (FAB) *m*/*z* 425.1374 ($C_{17}H_{33}O_2SiI$ + H requires 425.1373), 185 (base).

Alkyne 8. A solution of **22** (0.37 g, 0.87 mmol) in THF (9 mL) at −78 °C was treated with 1.0 M NaHMDS (1.7 mL, 1.7 mmol) in THF, and the cooling bath was removed. After being stirred at room temperature for 2 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and diluted with Et_2O (30 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 5 mL), the combined organic layers were dried ($MgSO_4$) and concentrated, and the crude alkyne was purified via column chromatography eluting with EtOAc/hecanes (1:9) to give 0.24 g (93%) of **8** as a clear oil: $[\alpha]_D = -10.3$ (*c* 2.0, CH_2Cl_2); ^{1}H NMR δ 5.56 (dq, J = 5.9, 15.4 Hz, 1 H), 5.40 (ddq, J = 1.5, 7.8, 15.4 Hz, 1 H), 3.93 (d, J = 8.0 Hz, 1 H), 3.69 (dd, J = 3.0, 9.6 Hz, 1 H), 2.94 (brs, 1 H), 2.45 (ddd, J = 3.0, 3.0, 16.9 Hz, 1 H), 2.28 (ddd, J = 2.5, 9.6, 16.9 Hz, 1 H), 2.03 (dd, J = 2.5, 3.0 Hz, 1 H), 1.70 (dd, J = 1.5, 5.9 Hz, 1 H), 0.90 (s, 3 H), 0.88 (s, 9 H), 0.75 (s, 3 H), 0.05 (s, 3 H), −0.01 (s, 3 H); ^{13}C NMR δ 131.2, 128.6, 82.9, 81.5, 75.7, 70.1, 42.1, 26.2, 22.9, 20.3, 18.4, 17.5, 0.3, −3.1, −4.5; IR (neat) ν 3487, 3312, 2957, 2930, 2857, 1472, 1255 cm^{-1}; mass spectrum (FAB) *m*/*z* 297.2238 ($C_{17}H_{32}O_2Si$ + H requires 297.2250), 185 (base).

Dienyne Oxazole Monomer 5. To a solution of the alkyne **8** (230 mg, 0.68 mmol) and dienyl iodide **7** (250 g, 0.68 mmol) in CH_3CN (5 mL) at −20 °C were added $PdCl_2(PPh_3)_2$ (24 mg, 0.03 mmol), CuI (21 mg, 0.10 mmol), and Et_3N (0.47 mL, 3.38 mmol). The reaction was stirred for 20 min at −20 °C and for 2 h at room temperature before being partitioned between EtOAc (20 mL) and pH 7 buffer (10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified via column chromatography eluting with EtOAc/hexanes (1:2) to give 340 mg (87%) of **5** as a thick syrup: $[\alpha]_D = -21.0$ (*c* 0.5, CH_2Cl_2); ^{1}H NMR δ 8.16 (s, 1 H), 6.74 (dd, J = 11.0, 15.4 Hz, 1 H), 6.30 (dd, J = 10.4, 11.0 Hz, 1 H), 5.69 (dd, J = 8.8, 15.4 Hz, 1 H), 5.62−5.38 (comp, 3 H), 4.20 (dt, J = 5.1, 7.8 Hz, 1 H), 3.95 (d, J = 8.0 Hz, 1 H), 3.90 (s, 3 H), 3.73 (dt, J = 3.2, 9.4 Hz, 1 H), 3.26 (s, 3 H), 3.12 &

3.01 (ABX, J_{AB} = 14.7 Hz, J_{AX} = 7.8 Hz, J_{BX} = 5.1 Hz, 2 H), 2.96 (d, J = 3.0 Hz, 1 H), 2.67 (ddd, J = 2.1, 3.2, 16.9 Hz, 1 H), 2.49 (ddd, J = 2.2, 9.4, 16.9 Hz, 1 H), 1.70 (dd, J = 1.3, 6.5 Hz, 3 H), 0.93 (s, 3 H), 0.89 (s, 9 H), 0.79 (s, 3 H), 0.06 (s, 3 H), −0.01 (s, 3 H); ^{13}C NMR δ 162,8, 161.0, 149.9, 144.1, 137.9, 134.0, 133.4, 131.2, 128.6, 111.5, 95.6, 81.5, 79.6, 79.0, 75.9, 56.9, 52.4, 42.2, 35.1, 26.2, 24.2, 20.4, 18.4 18.0, 17.5, 0.3, −3.1, −4.5; IR (neat) ν 3484, 2955, 2931, 2856, 1748, 1585 cm^{-1}; mass spectrum (FAB) m/z 532.3081 ($C_{29}H_{45}NO_6Si$ + H requires 532.3094), 185 (base).

TBS Dienyne Lactone Monomer 23. A solution of the monomer **5** (88 mg, 0.17 mmol) in THF (1.4 mL) was treated with 1 N LiOH (0.20 mL, 0.20 mmol) and stirred for 7 h, and solvent was removed in vacuo. The crude product was diluted with water (2 mL), acidified with 1 N HCl (0.25 mL, 0.25 mmol), and extracted with EtOAc (4 × 1 mL), and the combined organic layers were dried (Na_2SO_4) and then concentrated. The crude acid was then dissolved in toluene (17 mL) and treated with DPTC (46 mg, 0.20 mmol) and DMAP (2.0 mg, 0.02 mmol), and the mixture was heated to reflux for 12 h. Solvent was concentrated in vacuo and the crude product residue purified via column chromatography eluting with EtOAc/hexanes (1:4) to give 38 mg (46% over two steps) of the lactone monomer **23** as an oil: $[\alpha]_D$ = +7.9 (c 0.7, CH_2Cl_2); ^{1}H NMR δ 8.10 (s, 1 H), 6.70 (dd, J = 11.0, 16.3 Hz, 1 H), 6.14 (dd, J = 10.7, 11.0 Hz, 1 H), 5.59 (dq, J = 6.1, 15.3 Hz, 1 H), 5.51−5.37 (comp, 3 H), 5.24 (dt, J = 2.2, 10.2 Hz, 1 H), 4.47 (ddd, J = 5.2, 8.0, 10.8 Hz, 1 H), 3.84 (d, J = 7.2 Hz, 1 H), 3.39 (s, 3 H), 3.36 (dd, J = 5.2, 14.5 Hz, 1 H), 2.92 (ddd, J = 2.2, 10.2, 16.4 Hz, 1 H), 2.76 (dt, J = 3.6, 16.4 Hz, 2.85 (dd, J = 10.8, 14.5 Hz, 1 H), 1.72 (d, J = 5.9 Hz, 3 H), 1.02 (s, 3 H), 0.99 (s, 3 H), 0.92 (s, 9 H), 0.06 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR δ 182.3, 170.3, 161.7, 161.5, 144.8, 144.1, 138.2, 134.4, 133.5, 132.8, 130.5, 128.9, 111.3, 93.8, 80.9, 79.6, 57.2, 42.6, 34.4, 26.2, 21.9, 21,2, 19.6, 18.4, 18.0, 0.3, −3.2, −4.7; IR (neat) ν 2955, 2930, 2857, 1721, 1581, 1314 cm^{-1}; mass spectrum (FAB) m/z 500.2823 ($C_{28}H_{41}NO_5Si$ + H requires 500.2832), 185 (base).

Hydroxyl Dienyne Lactone Monomer 24. To a solution of **23** (13 mg, 0.027 mmol) and THF (0.6 mL) in a Teflon vial was added HF·pyridine (50 μL), and the mixture was stirred for 12 h at room temperature. The solution was partitioned between saturated aqueous $NaHCO_3$ (1.0 mL) and EtOAc (1 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (2 × 0.2 mL), the organic layers were combined, dried (Na_2SO_4), concentrated, and the crude material was dissolved in EtOAc and filtered through a plug of alumina. The filtrate was concentrated to give 7 mg (66%) of product that was recrystallized from EtOAc/hexanes to provide 5 mg (45%) of pure **24** as a white solid: mp = 171−172 °C; $[\alpha]_D$ = +23.0 (c 0.2, CH_2Cl_2); ^{1}H NMR (MeOD-d_3) δ 8.35 (s, 1 H), 6.56 (dd, J = 11.0, 16.1 Hz, 1 H), 6.17 (dd, J = 10.2, 11.0 Hz, 1 H), 5.69 (dq, J = 6.8, 15.5 Hz, 1 H), 5.57 (ddd, J = 1.5, 7.3, 15.5 Hz, 1 H), 5.47 (dd, J = 9.0, 16.0 Hz, 1 H), 5.38 (dd, J = 4.4, 10.3 Hz, 1 H), 5.24 (ddd, J = 1.3, 2.9, 7.4 Hz, 1 H), 4.39 (ddd, J = 5.1, 8.0, 10.9 Hz, 1 H), 3.87 (d, J = 7.3 Hz, 1 H), 3.37 (dd, J = 5.1, 14.8 Hz, 1 H), 3.37 (s, 3 H), 2.95 (ddd, J = 2.8, 10.7, 16.8 Hz, 1 H), 2.85 (dd, J = 11.9, 14.8 Hz, 1 H), 2.76 (ddd, J = 2.6, 4.6, 16.9 Hz, 1 H), 1.72 (d, J = 5.7 Hz, 3 H), 0.99 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR (100 MHz) δ 163.7, 162.9, 146.2, 139.3, 135.4, 134.5, 134.1, 129.7, 112.1, 101.6, 101.4, 94.6, 82.3, 80.2, 78.6, 78.0, 57.4, 42.8, 34.9, 22.1, 20.1, 19.8, 18.2; IR (neat) ν 3440, 2972, 2935, 1718, 1580, 1315, 1167 cm^{-1}; mass spectrum (FAB) m/z 386.1959 ($C_{22}H_{27}NO_5$ + H requires 386.1967), 154 (base). This sample was subjected to an X-ray crystallographic procedure.[15]

Bis-Protected Dienyne Monomer, 25. To a solution of the monomer **5** (380 mg, 0.71 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added 2,6-lutidine (120 μL, 1.10 mmol) followed by triethylsilyl trifluoromethanesulfonate (160 μL, 0.71 mmol), and the reaction was stirred to room temperature over 4.5 h. Saturated aqueous $NaHCO_3$ (3 mL) was then added,and the resulting biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 1 mL), the combined organic layers were dried (Na_2SO_4) and concentrated, and the crude product was residue purified via column chromatography eluting with EtOAc/hexanes (1:4) to give 320 mg (69%) of **25** as an oil: $[\alpha]_D$ = −33.6 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 8.16 (s, 1 H), 6.75 (dd, J = 11.0, 15.3 Hz, 1 H), 6.28 (dd, J = 11.0, 11.2 Hz, 1 H), 5.67 (dd, J = 8.3, 15.3 Hz, 1 H), 5.54 (dq, J = 5.9, 15.4 Hz, 1 H), 5.51−5.47 (m, 1 H), 5.40 (ddq, J = 1.6, 8.2, 15.4 Hz), 4.18 (dt, J = 5.7, 7.9 Hz, 1 H), 3.91 (s, 3 H), 3.87 (dd, J = 3.0, 8.1 Hz), 3.26 (s, 3 H), 3.16 & 3.02 (ABX, J_{AB} = 15.0 Hz, J_{AX} = 7.6 Hz, J_{BX} = 5.6 Hz, 2 H), 2.72 (ddd, J = 2.7, 3.0, 16.7 Hz, 1 H), 2.41 (ddd, J = 2.0, 7.1, 16.7 Hz, 1 H), 1.70 (d, J = 6.0 Hz, 1 H), 0.97 (t, J = 8.1 Hz, 9 H), 0.90 (s, 3 H), 0.89 (s, 9 H), 0.75 (s, 3 H), 0.68 (q, J = 8.1 Hz, 6 H), 0.04 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (100 MHz) δ 162.7, 161.8, 144.1, 137.2, 133.6, 133.4, 131.6, 131.3, 127.8, 111.9, 97.6, 79.7, 78.8, 76.1, 56.8, 52.4, 43.8, 35.2, 26.3, 24.6, 19.9, 18.7, 18.5, 18.0, 7.5, 5.9, −3.1, −4.5; IR (neat) ν 2955, 2877, 1751, 1584, 1323 cm^{-1}; mass spectrum (FAB) m/z 646.3942 ($C_{35}H_{59}NO_6Si_2$ + H requires 646.3959), 185 (base).

Bis-Protected Ester, 26. To a solution of **25** (76 mg, 0.12 mmol) in THF (0.5 mL) was added 1 N LiOH (150 μL), the reaction was stirred for 2 h at room temperature, and solvent was concentrated in vacuo. The crude acid was dissolved in H_2O (0.5 mL), acidified by the addition of 1 N HCl (200 μL), and then extracted with EtOAc (4 × 0.2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the crude product residue was dissolved toluene (1 mL) under an atmosphere of argon. A solution of the monomer **5** (40 mg, 0.08 mmol) in toluene (1 mL) was then added followed by DPTC (31 mg, 0.13 mmol) and catalytic DMAP (1.5 mg, 0.012 mmol). This mixture was heated to reflux for 2 days whereupon solvent was removed in vacuo and the crude product was purified via column chromatography eluting with EtOAc/hexanes (1:3) to provide 56 mg (65%) of **26** as an oil: $[\alpha]_D$ = −37.9 (c 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 8.17 (s, 1 H), 8.13 (s, 1 H), 6.78 (dd, J = 11.0, 15.4 Hz, 1 H), 6.70 (dd, J = 11.0, 15.5 Hz, 1 H), 6.29 (dd, J = 10.2, 11.0 Hz, 1 H), 6.22 (dd, J = 11.0, 11.0 Hz, 1 H), 5.70 (dd, J = 7.8, 15.0 Hz, 1 H), 5.64 (dd, J = 8.9, 15.7 Hz, 1 H), 5.56−5.35 (comp, 7 H), 4.22−4.15 (comp, 2 H), 3.92−3.84 (comp, 3 H), 3.90 (s, 3 H), 3.25 (s, 6 H), 3.11 & 3.01 (ABX, J_{AB} = 14.7 Hz, J_{AX} = 7.8 Hz, J_{BX} = 6.8 Hz, 2 H), 3.10 & 3.00 (ABX, J_{AB} = 14.9 Hz, J_{AX} = 8.0 Hz, J_{BX} = 6.0 Hz, 2 H), 2.91 (ddd, J = 2.3, 3.0, 16.9 Hz, 1 H), 2.76−2.30 (comp, 2 H), 2.40 (ddd, J = 2.3, 7.8, 17.1 Hz, 1 H), 1.68 (d, J = 5.4 Hz, 6 H), 0.96 (t, J = 7.9 Hz, 9 H), 0.93 (s, 3 H), 0.91 (s, 6 H), 0.88 (s, 18 H), 0.74 (s, 3 H), 0.65 (q, J = 7.9 Hz, 6 H), 0.04 (s, 3 H), 0.03 (s, 3 H), −0.02, (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR (100 MHz) δ 163.0, 162.8, 161.9, 160.6, 144.2, 143.8, 137.7, 137.3, 133.9, 133.8, 133.7, 133.5, 131.7, 131.4, 131.2, 130.6, 129.0, 127.9, 111.9, 111.4, 97.6, 94.1, 79.5, 79.4, 79.3, 79.0, 78.9. 78.8, 77.4, 76.2, 56.8, 56.7, 52.3, 43.8, 42.9, 35.1, 35.0, 26.2, 26.1, 24.5, 21.9, 20.6, 19.8, 19.4, 18.7, 18.4, 18.3, 18.0, 17.9, 7.4, 5.8, −3.3, −3.4, −4.7, −4.8; IR (neat) ν 2955, 2933, 2878, 2856, 1748, 1584 cm^{-1}; mass spectrum (FAB) m/z 1145.6692 ($C_{63}H_{100}N_2O_{11}Si_3$ + H requires 1145.6713), 185 (base).

Hydroxyl Ester 27. To a solution of **26** (40 mg, 0.04 mmol) in THF (0.4 mL) were added H_2O (70 μL) and TFA (70 μL), and the reaction was stirred for 1 h at room temperature. The reaction was partitioned between saturated aqueous $NaHCO_3$ (0.2 mL) and EtOAc (1.5 mL), and the layers were separated. The organic phase was dried (Na_2SO_4) and concentrated, and the crude product residue was purified via column chromatography eluting with EtOAc/hexanes (1:2) to afford 34 mg (65%) of **27** as a slightly orange film: $[\alpha]_D$ = −37.3 (c 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 8.18 (s, 1 H), 8.14 (s, 1 H), 6.78 (dd, J = 10.9, 14.9 Hz, 1 H), 6.69 (dd, J = 11.0, 14.5 Hz, 1 H), 6.31 (dd, J = 11.0, 11.0 Hz, 1 H), 6.23 (dd, J = 10.8, 11.0 Hz, 1 H), 5.72 (dd, J = 8.7, 15.5 Hz, 1 H), 5.65 (dd, J = 7.5, 14.7 Hz, 1 H), 5.62−5.36 (comp, 7 H), 4.25−4.18 (comp, 2 H), 3.97 (d, J = 8.8 Hz, 1 H), 3.91 (s, 3 H), 3.85 (d, J = 7.9 Hz, 1 H), 3.73 (dd, J = 3.1, 9.5 Hz, 1 H), 3.27 (s, 3 H), 3.26 (s, 3 H), 3.11 & 3.03 (ABX, J_{AB} = 14.8, J_{AX} = 7.8 Hz, J_{BX} = 5.6 Hz, 2 H), 3.10 & 3.01 (ABX, J_{AB} = 15.5 Hz, J_{AX} = 8.1 Hz, J_{BX} = 5.5 Hz, 2 H), 2.93 (ddd, J = 2.3, 3.0, 17.1 Hz, 1 H), 2.73 (ddd, J = 7.1, 8.4, 17.1 Hz, 1 H), 2.67 (ddd, J = 2.3, 3.3, 16.9 Hz, 1 H), 2.51 (ddd, J = 2.2, 9.1, 16.9 Hz, 1 H), 1.71 (d, J = 7.7 Hz, 3 H), 1.69 (d, J = 6.3 Hz, 3 H), 0.97 (s, 3 H), 0.94 (s, 6 H), 0.90 (s, 18

H), 0.80 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.01 (s, 3 H), −0.01 (s, 3 H); ^{13}C NMR (100 MHz) δ 163.0, 162.8, 162.0, 160.6, 144.2, 143.8, 137.8, 137.7, 134.2, 133.9, 133.8, 133.5, 131.3, 131.0, 130.6, 129.0, 128.7, 111.5, 105.0, 101.7, 95.7, 94.0, 81.5, 81.4, 79.5, 79.3, 79.1, 77.4, 76.2, 75.9, 56.9, 56.8, 52.3, 42.9, 42.2, 35.1, 35.0, 26.2, 26.1, 24.2, 21.9, 20.6, 20.3, 19.4, 19.3, 18.3, 18.0, 17.9, 17.4, −3.2, −3.4, −4.6, −4.8; IR (neat) ν 2955, 2929, 2856, 1744, 1725, 1584 cm^{-1}; mass spectrum (FAB) *m*/*z* 1031.5864 ($C_{57}H_{86}N_2O_{11}Si_2$ + H requires 1031.5848), 185 (base).

Protected Tetradehydrodisorazole, 3. To a solution of **27** (36 mg, 0.035 mmol) in THF (0.5 mL) was added 1 N LiOH (40 μL), and the reaction was stirred for 2 days at room temperature. Solvent was removed in vacuo, and the crude hydrolyzed material was dissolved in H_2O (0.5 mL) and then acidified by addition of 1 N HCl (50 μL). This mixture was extracted with EtOAc (4 × 0.2 mL), and the combined organics were dried (Na_2SO_4) and concentrated. The crude carboxylic acid was then dissolved in toluene (35 mL) under an atmosphere of argon and treated with Et_3N (30 μL, 0.22 mmol), 2,4,6-trichlorobenzoyl chloride (33 μL, 0.21 mmol), and DMAP (6.0 mg, 0.05 mmol). The resultant cloudy solution was stirred for 2 days at room temperature, CH_2Cl_2 (30 mL) was added, and the solution was washed with 0.1 N $NaHSO_4$ (5 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified via column chromatography eluting with EtOAc/hexanes (1:5) to provide 9 mg (24%) of **3** as an oil: $[\alpha]_D$ = +106.0 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 8.21 (s, 1 H), 6.58 (dd, *J* = 10.9, 15.4 Hz, 1 H), 6.20 (dd, *J* = 10.9, 11.1 Hz, 1 H), 5.60 (dd, *J* = 8.2, 15.3 Hz, 1 H), 5.54 (dq, *J* = 5.4, 15.4 Hz, 1 H), 5.45−5.37 (comp, 2 H), 4.06 (dt, *J* = 4.8, 8.8 Hz, 1 H), 3.82 (d, *J* = 8.1 Hz, 1 H), 3.17 (s, 3 H), 3.12 (dd, *J* = 5.8, 10.8 Hz, 1 H), 2.98−2.90 (comp, 2 H), 2.74 (ddd, *J* = 2.2, 9.4, 17.1 Hz, 1 H), 1.68 (d, *J* = 5.1 Hz, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H), 0.90 (s, 9 H), 0.03 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (100 MHz) δ 162.9, 160.5, 143.7, 137.8, 134.1, 133.8, 131.4, 130.5, 129.1, 111.5, 94.1, 79.6, 79.0, 78.9, 77.4, 76.1, 56.4, 42.9, 35.0, 26.1, 22.0, 21.2, 19.4, 18.4, 18.0, −3.4, −4.8; IR (neat) ν 2956, 2929, 2856, 1748, 1576, 1252 cm^{-1}; mass spectrum (FAB) *m*/*z* 999.5589 ($C_{56}H_{82}N_2O_{10}Si_2$+H requires 999.5586), 185 (base); and 12 mg (67%) of **23**.

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Supporting Information Available: Experimentallp;&4q;1data for the preparation of **17**, determination of the enantiomeric purity of **16** via preparation of a suitable derivative, X-ray crystal structure data and ORTEP diagram of **24**, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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