JOC Featured Article

pubs.acs.org/joc

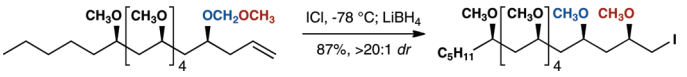
Application of Stereoselective Ether Transfer to the Synthesis of Isotactic Polyethers

Kai Liu, Joseph W. Arico, and Richard E. Taylor*

Department of Chemistry and Biochemistry and the Walther Cancer Research Center, University of Notre Dame, 251 Nieuwland Science Hall, Notre Dame, Indiana 46556-5670.

taylor.61@nd.edu

Received January 22, 2010



An efficient, convergent synthetic strategy has been developed which enables the synthesis of a series of naturally occurring isotactic polymethoxy compounds. Ether transfer followed by a hydride workup enables simultaneous, diastereoselective production of two methoxy centers in a single step. High yields and diastereoselectivity are observed even in stereochemically rich, polyoxygenated systems. Direct generation of bis-methyl ether moieties from methoxymethyl ethers minimizes the need for typical protective group strategies and the use of expensive methyl transfer reagents. Moreover, the simultaneous generation of a terminal primary iodide serves as a coupling partner for the generation of higher order congeners.

Introduction

Isotactic polymethoxy-1-alkenes constitute a family of natural products that have been found in terrestrial, tolytoxin-producing blue-green algae.[1] A combination of NMR and mass spectra analyses provide the gross structure and relative stereochemistry of these compounds shown in Figure 1. The *all-syn*, repetitive pattern attracted many synthetic attempts with a common strategy: classic methods applicable to polyketide polyols, both convergent and linear, followed by protecting group manipulation and global methyl ether formation using a methyl transfer source.[2]

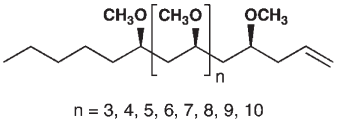
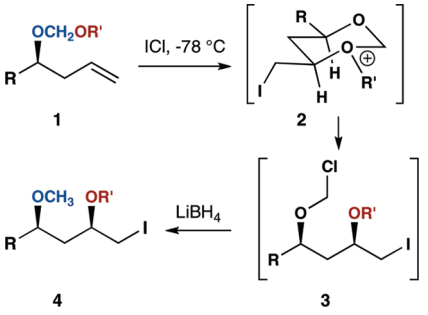


FIGURE 1. *Tolypothrix* polyethers.

Recently, we described a fundamentally new method of synthesizing 1,3-*syn*-diol, 1,3-*syn*-diol monoethers, and orthogonally protected 1,3-*syn*-diether derivatives from homoallylic alkoxymethyl ethers.[3] As shown in Scheme 1, activation with iodine monochloride initiates stereoselective ether transfer and provides an intermediate chloromethyl ether which can be reduced in situ to provide access to 1,3-*syn*-diethers. We envisioned the product, a primary iodide, as a synthetic handle for the convergent construction of more complex polyketide fragments. Herein, we report application of ether transfer for the efficient assembly of isotactic polyether structures.

SCHEME 1. Ether Transfer and in Situ Hydride Reduction



(1) (a) Desikachary, T. V. *Cyanophyta* **1959**, 503. (b) Mynderse, J. S.; Moore, R. E. *Phytochemistry* **1979**, *18*, 1181.

(2) (a) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 3205. (b) Wang, Z.; Deschenes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090. (c) Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1990**, *55*, 4431. (d) Mori, Y.; Kohchi, Y.; Noguchi, H.; Suzuki, M. *Tetrahedron* **1991**, *47*, 4889. (e) Mori, Y.; Kohchi, Y.; Suzuki, M. *J. Org. Chem.* **1991**, *56*, 631. (f) Mori, Y.; Kohchi, Y.; Ota, T.; Suzuki, M. *Tetrahedron Lett.* **1990**, *31*, 2915. (g) Nakata, T.; Suenaga, T.; Nakashima, K.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6529. (h) Menges, M.; Brückner, R. *Eur. J. Org. Chem.* **1998**, 1023. (i) Banker, R.; Teltsch, B.; Sukenik, A.; Carmeli, S. *J. Nat. Prod.* **2000**, *63*, 387.

(3) Liu, K.; Taylor, R. E.; Kartika, R. *Org. Lett.* **2006**, *8*, 5393.

DOI: 10.1021/jo100094d Published on Web 05/19/2010

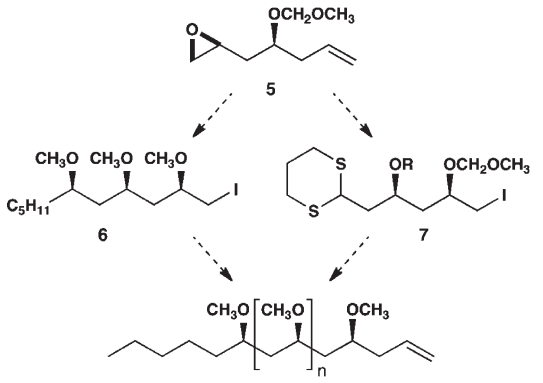


FIGURE 2. Divergent−convergent strategy for modular assembly.

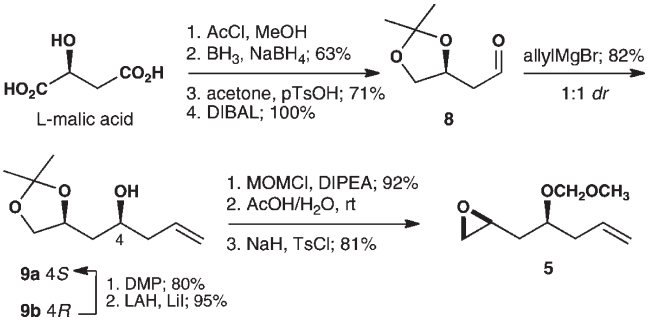
Instead of a linear approach, a divergent-convergent strategy was designed, as shown in Figure 2, using epoxide **5** as the common intermediate. The epoxide can be conveniently converted to dithiane **7** and act as the right half of the target. One the other hand, **5** is also the precursor for the MOM-protected homoallylic alcohol (not shown here), which under ICl treatment followed by reductive workup would then afford primary iodide **6** as the left portion.

Results and Discussion

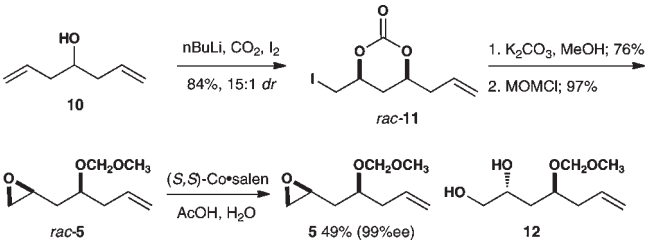
The synthesis of the common intermediate **5** started with L-malic acid. Esterification[4] followed by chelation-controlled reduction[5] produced a diol, which was then protected as the acetonide. The methyl ester was then reduced under carefully controlled conditions (1 equiv of DIBAL-H, −78 °C) to afford aldehyde **8**. Considering the lack of stability[6] of the aldehyde, it was used immediately for the subsequent allylation step. Although an enantioselective allylation could be used, a diastereorandom method proved to be more practical. Reaction with allylmagnesium bromide produced a 1:1 mixture of diastereomers which were separable by flash column chromatography. The *anti*-product **9b** was successfully converted to the *syn*-homoallylic alcohol **9a** by an oxidation/reduction[7] sequence. Protection with chloromethyl methyl ether (MOMCl) and hydrolysis of the acetonide restored the diol without harm to the MOM group. One-pot conversion[8] of the 1,2-diol to the epoxide completed the synthesis of the common intermediate **5** in eight steps (Scheme 2).

Alternatively, **5** can also be efficiently made by a simple sequence through asymmetric resolution.[9] Commercially available hepta-1,6-dien-4-ol[10] (**10**) was desymmetrized using

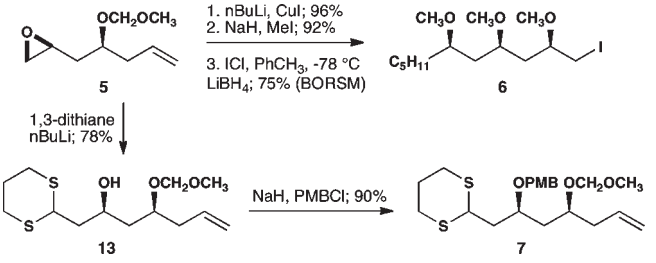
SCHEME 2. Synthesis of the Common Intermediate from L-Malic Acid



SCHEME 3. Alternative Route to the Common Intermediate via Kinetic Resolution



SCHEME 4. Coupling Partners Prepared from a Common Intermediate

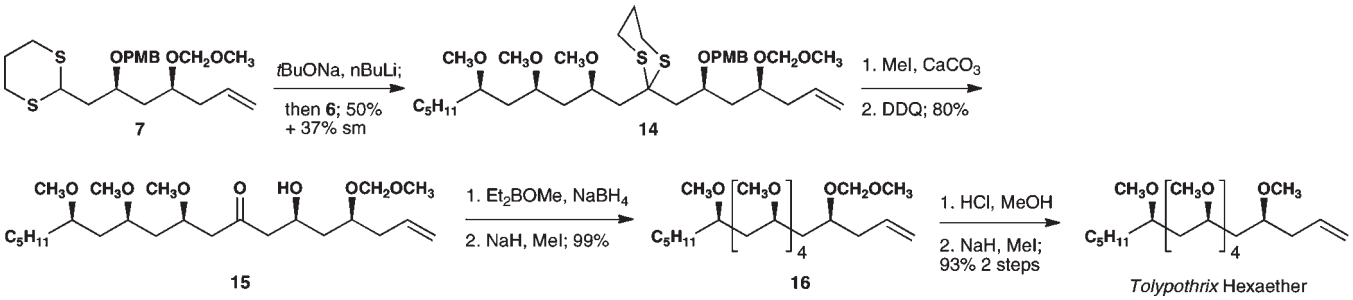


iodine-induced carbonate cyclization[9,11] to produce iodocarbonate ***rac*-11** with excellent diastereoselectivity (dr 15:1 by ^{1}H NMR). Solvolysis of the carbonate led to the corresponding epoxide. The efficiency of this particular route was further enhanced by performing both operations in a single pot process. The secondary alcohol was then protected as a MOM ether (*rac*-**5**). Hydrolytic kinetic resolution[12] using Jacobsen's cobalt−salen complex finished the alternative synthesis of common intermediate **5** with >99% ee in just four steps (Scheme 3).

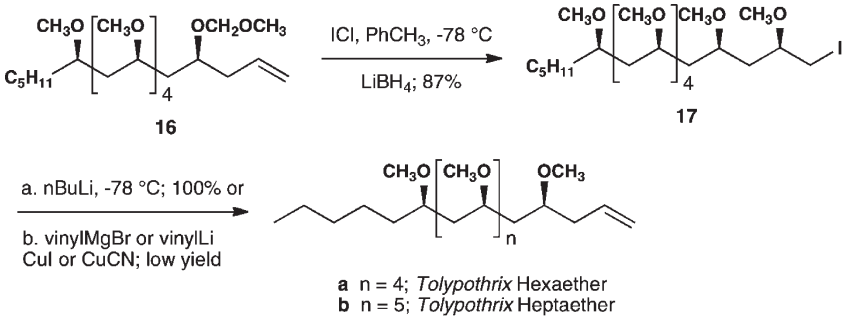
For the construction of the left-hand portion, epoxide **5** was reacted with lithium dibutyl cuprate[13] and the resulting secondary alcohol was subsequently converted to its methyl ether. ICl-induced methyl ether transfer with reductive workup demonstrated satisfactory efficiency, producing iodide **6** as a single diastereomer (Scheme 4). In a complementary fashion, epoxide **5** was opened by 2-lithio-1,3-dithiane to afford alcohol **13**, which was converted to **7** (Scheme 4).

(4) Gaunt, M. J.; Jessiman, A. S.; Orsini, P.; Tanner, H. R.; Hook, D. F.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4819.
(5) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.
(6) Kocienski, P. J.; Yeates, C.; Street, S. D. A.; Campbell, S. F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2183.
(7) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419.
(8) (a) Murthy, V. S.; Gaitonde, A. S.; Rao, S. P. *Synth. Commun.* **1993**, *23*, 285. (b) Rao, A. V. R.; Murthy, V. S.; Sharma, G. V. M. *Tetrahedron Lett.* **1995**, *36*, 139.
(9) Kim, Y.-J.; Tae, J. *Synlett* **2006**, 61.
(10) Parks, B. W.; Gilbertson, R. D.; Domaille, D. W.; Hutchison, J. E. *J. Org. Chem.* **2006**, *71*, 9622.
(11) (a) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013–4018. (b) Butler, D. E.; Deering, C. F.; Millar, A.; Nanninga, T. N.; Roth, B. D. (Warner-Lambert Co.) US Patent 5,245,047. (c) Rádl, S.; Stach, J.; Hajicek, J. *Tetrahedron Lett.* **2002**, *43*, 2087.
(12) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
(13) Mori, Y.; Kohchi, Y.; Suzuki, M. *J. Org. Chem.* **1991**, *56*, 631.

SCHEME 5. Dithiane-Based Fragment Assembly and Completion of the Hexaether



SCHEME 6. Efficient Late-Stage Ether Transfer and Terminal Functionalization



Deprotonation[14] of dithiane **7** was not effective with traditional bases. However, the Schlosser-type base developed by Lipshutz[15] induced full deprotonation (evidenced by quantitative methylation with MeI), and the coupling reaction with iodide **6** gave adduct **14** in 50% yield as shown in Scheme 5. Sequential deprotection of the dithiane and the PMB ether followed by diastereoselective reduction[16] of β-hydroxyketone **15** and methylation provided pentamethyl ether **16**. This compound was readily converted to *Tolypothrix* hexaether by acidic removal of the MOM group and subsequent methylation.

Compared to the homoallylic methoxymethyl ether that led to **6**, compound **16** contains four additional methoxy groups. Successful ether transfer within **16** would be the key to our synthetic strategy toward more complex congeners. We were delighted to find that the reaction occurred with high yields, and iodide **17** was isolated as a single diastereomer in 87% yield (Scheme 6). This example provided further evidence[17] that the ether transfer method can be efficient even when performed in a polyoxygenated environment.

We fully expected a simple vinylation of **17** would complete the synthesis of the heptaether ($n = 5$). Disappointingly, a variety of conditions failed to affect the desired coupling. Classic Cu(I)-promoted Grignard[18] or a higher order cuprate[19] provided only trace amounts of the natural product, while Negishi coupling under the conditions of Fu[20] or Knochel[21] resulted in dehalogenation or no reaction, respectively. A two-step ethynylation−Lindlar reduction approach to the natural product was also unsuccessful: the use of sodium acetylide, CuI-promoted (trimethylsilyl)acetylene coupling[22] or lithium trimethylsilylacetylide (either with[23] or without Pd catalysis) to displace the terminal iodide resulted only in decomposition. Despite the failure in homologating **17** to the terminal alkene in reasonable yield, the primary iodide is expected to exhibit excellent electrophilicity toward dithiane-based nucleophiles for further elongation (i.e., **17**+**7**, Scheme 5). However, it was also found that iodide **17** underwent quantitative elimination[24] with *n*-BuLi to afford an alternative route to the *Tolypothrix* hexaether.

Conclusions

In summary, we have successfully utilized our ICl-induced methyl ether transfer for the construction of isotactic polymethoxy structural units. In situ reduction of an intermediate chloromethyl ether provided stereospecific formation of bis-methyl ether with a 1,3-*syn* relationship. The resulting primary iodide proved to be a good coupling partner for dithiane-based nucleophiles providing a strategy for the generation of higher order congeners of the *Tolypothrix* polyethers. Additional applications of the ether transfer

(14) Deprotonation of 2-substituted-1,3-dithianes are often substrate-specific. For summaries and related studies, see: (a) Smith, A. B., III; Adams, D. M. *Acc. Chem. Res.* **2004**, *37*, 365. (b) Ide, M.; Yasuda, M.; Nakata, M. *Synlett* **1998**, 936. (c) Ide, M.; Nakata, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2491.

(15) Lipshutz, B. H.; Garcia, E. *Tetrahedron Lett.* **1990**, *31*, 7261.

(16) Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J. *Chem. Lett.* **1987**, *16*, 1923.

(17) For previous examples that used an ether-transfer method toward syntheses of complex molecules, see: (a) Kartika, R.; Taylor, R. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 6874. (b) Kartika, R.; Gruffi, T. R.; Taylor, R. E. *Org. Lett.* **2008**, *10*, 5047.

(18) Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1976**, *36*, 3225.

(19) (a) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672. (b) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305.

(20) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527.

(21) Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79.

(22) Inack-Ngi, S.; Rahmani, R.; Commeiras, L.; Chouraqui, G.; Thibonnet, J.; Duchêne, A.; Abarbri, M.; Parrain, J.-L. *Adv. Synth. Catal.* **2009**, *351*, 779.

(23) Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* **2004**, *6* (9), 1461.

(24) Maeda, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1996**, *61*, 6770.

reaction are currently under exploration in our laboratory and will be reported in due course.

Experimental Section

General Experimental Methods. ^{1}H NMR spectra were collected at 300 or 500 MHz, and ^{13}C NMR spectra were collected at 75 or 126 MHz. Chemical shifts for ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) relative to residual chloroform (7.27, 77.23 ppm) in $CDCl_3$, and coupling constants are reported in hertz (Hz). Mass spectra were obtained employing the fast atom bombardment (FAB) ionization method. Optical rotation was measured on a polarimeter in a 1 dm cell. Reagents were purchased commercially and used without further purification. Reactions were performed under nitrogen atmosphere. Solvents were purified by standard procedures. Column chromatography was performed using silica gel (230−400 mesh). Thin-layer chromatography was performed on aluminum-backed silica gel plates (250 μm thickness), and spots were visualized with UV light (254 nm), *p*-anisaldehyde, or potassium permanganate stain.

(2*R*,4*R*,6*R*)-1-Iodo-2,4,6-trimethoxyundecane (6). To a stirred diethyl ether suspension (50 mL) containing CuI (2.59 g, 13.6 mmol) was added *n*-BuLi (2.5 M in hexanes, 10.9 mL, 27.2 mmol) at −20 °C. The solution turned black immediately. A solution of **5** (1.56 g, 9.06 mmol) in 10 mL of diethyl ether was then added dropwise. After 10 min, TLC indicated complete reaction, and cold water was added. Minimum amount of saturated ammonium hydroxide was used to achieve clear separation of the two phases, and the aqueous phase was extracted with diethyl ether for a second time. The combined organic layers were then washed with $NaHCO_3$ and dried with $MgSO_4$. After removal of the solvents at reduced pressure and flash column chromatography, (4*S*,6*R*)-4-(methoxymethoxy)undec-1-en-6-ol (2.00 g, 8.70 mmol, 96%) was isolated as a colorless oil. This alcohol was then dissolved in THF (40 mL) in a 100 mL round-bottomed flask equipped with a condenser. Under nitrogen gas environment and with magnetic stirring, NaH (418 mg, 17.4 mmol) was added in several batches over 1 min. After 20 min, MeI (1 mL) was added, and the solution was gently heated to maintain a mild reflux. TLC analysis indicated complete methylation after 4 h. The flask was allowed to cool to room temperature, and cold water was added very carefully along the side of the flask into the stirred solution until all of the hydride was destroyed. More water (20 mL) was added to dissolve the inorganic byproduct and to achieve clear phase separation. The organic layer was separated, and the aqueous layer was extracted with diethyl ether for a second time. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. After flash column chromatography, (4*S*,6*R*)-4-(methoxymethoxy)-6-methoxyundec-1-ene (1.83 g, 8.00 mmol, 92%) was obtained as a colorless oil. This alkene was dissolved in toluene (100 mL), and the stirred solution was cooled to −78 °C. ICl (1 M in dichloromethane, 8.8 mL, 8.8 mmol) was added dropwise. After an additional 15 min of stirring, $LiBH_4$ (2 M solution in THF, 8.8 mL, 17.6 mmol) was added dropwise, and gentle foaming was observed while the red-brown color of the solution quickly disappeared. Aqueous NH_4Cl (about 10 mL) was added, and the mixture was stirred at room temperature. The whole content in the flask was then poured into a 250 mL separatory funnel. When gas evolution stopped, the organic layer was collected, and the aqueous layer was extracted with diethyl ether for a second time. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. After flash column chromatography on silica gel (5% EtOAc/hexane), iodide **6** (1.54 g, 4.06 mmol, 51%, 75% based on recovered starting material) was isolated as a colorless oil: $[\alpha]^{20}_D = -14.61$ (*c* 2.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.89 (3H, t, J = 6.82 Hz), 1.25−1.35 (8H), 1.40−1.59 (2H, m), 1.80−1.90 (2H, m), 3.10−3.22 (1H, m), 3.25−3.50 (4H) 3.38 (3H, s), 3.39 (3H, s), 3.40 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 10.9, 14.3, 22.9, 24.8, 32.3, 33.5, 37.8, 38.5, 56.5, 56.7, 56.8, 75.3, 76.4, 78.0; HRMS calcd for $C_{14}H_{29}IO_3$ $[M + H]^+$ 373.1248, found 373.1234.

(2*S*,4*S*)-1-(1,3-Dithian-2-yl)-4-(methoxymethoxy)hept-6-en-2-ol (13). To a stirred solution of 1,3-dithiane (635 mg, 5.28 mmol) in THF (10 mL) at 0 °C under N_2 atmosphere was added *n*-BuLi (2.1 M in hexanes, 2.3 mL, 4.88 mmol) dropwise. After 20 min, epoxide **5** (700 mg, 4.06 mmol) in THF (5 mL) was added dropwise. TLC analysis indicated complete reaction after 2 h, and satd NH_4Cl (20 mL) was added to quench the reaction. Diethyl ether was used to extract twice (2 × 50 mL), and the combined organic layers were washed with $NaHCO_3$ and brine, dried with $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and flash column chromatography (20→30% EtOAc in hexanes) yielded **13** as a colorless liquid (926 mg, 3.17 mmol, 78%): $[\alpha]^{20}_D = +31.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.52−1.70 (2H, m), 1.72−1.90 (3H), 2.02−2.12 (1H, m), 2.27−2.33 (2H, m), 2.72−2.93 (4H), 3.25 (1H, dd, J = 2.73, 0.57 Hz), 3.35 (3H, s), 3.77−3.87 (1H, m), 3.99−4.09 (1H, m), 4.24 (1H, dd, J = 9.47, 4.95 Hz), 4.61 (2H, d, J = 6.85 Hz), 4.69 (2H, d, J = 6.85 Hz), 5.01−5.08 (2H, m), 5.66−5.80 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 26.0, 30.0, 30.5, 39.0, 41.4, 43.1, 43.8, 56.0, 67.2, 76.6, 95.4, 117.9, 133.8; HRMS calcd for $C_{13}H_{24}NaO_3S_2$ $[M + Na]^+$ 315.1059, found 315.1058

2-((2*S*,4*S*)-2-(4-Methoxybenzyloxy)-4-(methoxymethoxy)hept-6-enyl)-1,3-dithiane (7). To a stirred solution of **13** (330 mg, 1.13 mmol) in THF (5 mL) was added NaH (54 mg, 2.3 mmol) at 0 °C. After 30 min, PMBCl (0.28 mL, 2.03 mmol) was added dropwise, and a few crystals of tetrabutylammonium iodide were added. The solution was heated to reflux for 16 h before TLC analysis indicated complete reaction. Saturated $NaHCO_3$ solution was added to quench the reaction, and diethyl ether was used to extract the product twice. The combined organic layers were washed with brine, dried with $MgSO_4$, and filtered. Removal of solvent under reduced pressure followed by flash column chromatography gave **7** as a colorless, viscous oil (420 mg, 1.02 mmol, 90%): $[\alpha]^{20}_D = +19.76$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.59−1.67 (1H, m), 1.78−1.98 (4H), 2.04−2.14 (1H, m), 2.25−2.34 (2H, m), 2.75−2.89 (4H), 3.38 (3H, s), 3.65−3.73 (1H, m), 3.79 (3H, s), 3.80−3.88 (1H, m), 4.17 (1H, dd, J = 6.20, 8.27 Hz), 4.43 (2H, d, J = 10.99), 4.49 (2H, d, J = 10.99), 4.64 (2H, d, J = 6.91), 4.67 (2H, d, J = 6.91), 5.04−5.12 (2H, m), 5.72−5.87 (1H, m); ^{13}C NMR (125 MHz, CDCl3) δ_C 26.1, 30.1, 30.4, 38.9, 39.2, 40.4, 44.0, 55.3, 55.9, 70.8, 72.5, 74.0, 95.7, 113.8, 117.6, 129.6, 130.8, 134.3, 159.2; HRMS calcd for $C_{21}H_{32}O_4S_2$ $[M + Na]^+$ 435.1615, found 435.1634.

2-((2*S*,4*S*)-2-(4-Methoxybenzyloxy)-4-(methoxymethoxy)hept-6-enyl)-2-((2*R*,4*R*,6*R*)-2,4,6-trimethoxyundecyl)-1,3-dithiane (14). An oven-dried flask containing finely powdered *t*-BuONa (197 mg, 2.05 mmol) under Ar atmosphere was charged with hexanes (4 mL) and *n*-BuLi (2.0 M in hexanes, 0.96 mL, 1.92 mmol) at 0 °C. After 30 min, the flask was cooled to −78 °C, and **7** (690 mg, 1.67 mmol) in THF (4 mL) was added via syringe. The solution turned orange immediately. After 2 min, **6** (478 mg, 1.28 mmol) in THF (4 mL) was added by syringe and the mixture allowed to stir for another 10 min. Saturated NH_4Cl (20 mL) was added to quench the reaction, and ether (2 × 30 mL) was used to extract. The combined organic layers were washed with satd $NaHCO_3$ and brine, dried with $MgSO_4$, and filtered. Removal of solvent under reduced pressure followed by column chromatography (5%→25% EtOAc in hexanes) yielded **14** as a colorless oil (410 mg, 50%). Unreacted **7** (174 mg) and **6** (180 mg, 37%) were also recovered: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.90 (3H, t, J = 6.80 Hz), 1.28−1.36 (6H, m), 1.47−1.54 (3H, m), 1.57−1.64 (1H, m), 1.75−1.95 (6H, m), 2.11−2.24 (3H, m), 2.27−2.43 (3H, m),

2.77−2.82 (2H, m), 2.78−2.90 (2H, m), 3.21−3.27 (1H, m), 3.30 (3H, s), 3.31 (3H, s), 3.32 (3H, s), 3.35−2.39 (1H, m), 3.40 (3H, s), 3.66−3.71 (1H, m), 3.73−3.78 (1H, m), 3.79 (3H, s), 3.83−3.90 (1H, m), 4.42 (2H, d, J = 10.40 Hz), 4.50 (2H, d, J = 10.40 Hz), 4.69 (2H, d, J = 6.85 Hz), 4.73 (2H, d, J = 6.85 Hz), 5.06−5.13 (2H, m), 5.78−5.88 (1H, m), 6.83−6.87 (2H, m), 7.27−7.32 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 14.3, 22.86, 24.9, 25.2, 26.5, 26.9, 32.2, 33.7, 38.0, 38.9, 39.8, 40.1, 44.9, 45.4, 52.5, 55.5, 55.9, 56.1, 56.4, 56.5, 70.4, 74.3, 75.5, 76.0, 78.1, 96.2, 113.8, 117.6, 129.8, 131.1, 134.8, 159.2; HRMS calcd for $C_{35}H_{60}O_7S_2Na$ $[M + Na]^+$ 679.3673, found 679.3682.

(4*S*,6*S*,10*R*,12*R*,14*R*)-6-Hydroxy-10,12,14-trimethoxy-4-(methoxymethoxy)nonadec-1-en-8-one (15). To a stirred solution of **14** (174 mg, 0.27 mmol) in CH_3CN (8 mL) at room temperature were added H_2O (2 mL), MeI (3 mL) and $CaCO_3$ (358 mg). The suspension was allowed to stir for 12 h and filtered through a pad of Celite. The solvent was removed under reduced pressure to afford a colorless liquid. The liquid was then dissolved in CH_2Cl_2 (20 mL). To this solution were added DDQ (67.3 mg, 0.30 mol) and H_2O (1 mL) at 0 °C. After 1 h, saturated $Na_2S_2O_3$ (5 mL) was added, and diethyl ether (2 × 20 mL) was used to extract. The combined organic layers were washed with $NaHCO_3$, dried with $MgSO_4$, and filtered. Removal of solvent under reduced pressure followed by flash column chromatography (40% EtOAc in hexanes) afforded ketone **15** as a colorless oil (95 mg, 0.21 mmol, 80% two steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.90 (3H, t, J = 6.86 Hz), 1.28−1.38 (6H), 1.46−1.55 (2H, m), 1.59−1.68 (3H), 1.72−1.85 (3H), 2.32−2.40 (2H), 2.57−2.75 (4H), 3.22−3.28 (1H, m), 3.30 (3H, s), 3.31 (3H, s), 3.31 (3H, s), 3.37−3.41 (1H, m), 3.39 (3H, s), 3.49 (2H, br. d, J = 2.31 Hz), 3.81−3.85 (1H, s), 3.85−3.91 (1H, s), 4.20−4.27 (1H, s), 4.66 (1H, d, J = 6.89 Hz), 4.72 (1H, d, J = 6.89 Hz), 5.07−5.12 (2H, m), 5.75−5.85 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 14.3, 22.9, 24.8, 32.2, 33.6, 37.7, 37.7, 37.8, 38.9, 40.8, 48.3, 50.8, 56.0, 56.3, 56.4, 57.0, 66.4, 74.8, 75.3, 75.8, 78.0, 95.5, 117.9, 134.2, 210.1; HRMS calcd for $C_{24}H_{46}NaO_7$ $[M + Na]^+$ 469.3136, found 469.3131.

(4*S*,6*R*,8*R*,10*R*,12*R*,14*R*)-6,8,10,12,14-Pentamethoxy-4-(methoxymethoxy)nonadec-1-ene (16). A stirred solution of **15** (90.0 mg, 0.20 mmol) in THF (5 mL) and MeOH (1 mL) was cooled to −78 °C before Et_2BOMe (1.0 M in THF, 0.81 mL, 0.81 mmol) was added dropwise. After 15 min, sodium borohydride (15.2 mg, 0.40 mmol) was added in one batch. TLC analysis after 10 min indicated complete reaction. The solution was allowed to warm to room temperature, and 1 mL of AcOH was added to quench the reaction, followed by addition of H_2O. Ethyl acetate was used to extract the product (2 × 15 mL). The combined organic layers were washed with $NaHCO_3$ and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product (89 mg) was a colorless oil and contained only one diastereomer by NMR analysis. To a stirred solution of the crude diol (38 mg, 0.085 mmol) in THF (3 mL) were added NaH (100 mg, excess) and MeI (3 mL). The solution was then heated to reflux for 48 h. Water was added very carefully to destroy extra NaH, and diethyl ether was used to extract the product. The organic layer was then dried with $MgSO_4$ and filtered. Removal of the solvent under reduced pressure followed by flash column chromatography (2% MeOH in CH_2Cl_2) afforded **16** as a colorless liquid (94.9 mg, 0.20 mmol, 99% two steps): $[\alpha]^{20}_D$ = +1.6 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.89 (3H, t, J = 6.82 Hz), 1.25−1.35 (6H), 1.46−1.66 (6H), 1.75−1.85 (6H), 2.27−2.43 (2H, m), 3.25−3.45 (5H, m), 3.29 (3H, s), 3.30 (9H), 3.31 (3H, s), 3.38 (3H, s), 3.73−3.78 (1H, s), 4.65 (1H, d, J = 6.89 Hz), 4.67 (1H, d, J = 6.89 Hz), 5.07−5.14 (2H, m), 5.79−5.88 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 14.3, 22.9, 24.8, 32.3, 33.6, 38.1, 38.2, 38.3, 38.4, 38.6, 39.2, 55.8, 56.3, 56.42, 56.44, 56.47, 56.48, 74.5, 75.36, 75.38, 75.5, 75.6, 78.1, 95.8, 117.6, 134.7; HRMS calcd for $C_{26}H_{52}O_7Na$ $[M + Na]^+$ 499.3598, found 499.3605.

(2*R*,4*R*,6*R*,8*R*,10*R*,12*R*,14*R*)-1-Iodo-2,4,6,8,10,12,14-heptamethoxynonadecane (17). To a stirred solution of **16** (19 mg, 0.04 mol) in toluene at −78 °C was added ICl (1 M in dichloromethane, 0.06 mL, 0.06 mmol) dropwise. After 20 min, $LiBH_4$ (2 M solution in THF, 0.04 mL, 0.08 mmol) was added, and the solution turned colorless upon completion. The dry ice bath was removed, and the reaction was allowed to warm to room temperature over 15 min. HCl (1 M, 10 mL) was used to quench the extra hydride, and diethyl ether (2 × 20 mL) was used to extract the product twice. The combined organic layers were washed with $NaHCO_3$ and brine, dried with $MgSO_4$, and filtered. Removal of the solvent under reduced pressure followed by flash column chromatography (2% MeOH in dichloromethane) afforded **17** as colorless liquid (21 mg, 0.0347 mmol, 87%): $[\alpha]^{20}_D$ = −5.33 (c 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.89 (3H, t, J = 6.82 Hz), 1.25−1.35 (8H), 1.46−1.66 (6H), 1.75−1.86 (6H), 3.25−3.45 (7H), 3.31 (3 H, s), 3.32 (12H, s), 3.33 (3H, s), 3.36 (3H, s), 3.36−3.45 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 10.7, 14.3, 22.9, 24.8, 32.3, 33.6, 38.08, 38.09, 38.10, 38.30, 38.35, 38.5, 56.46, 56.47, 56.49, 56.52, 56.53, 56.6, 56.9, 75.2, 75.40, 75.41, 75.5, 75.6, 76.4, 78.1; HRMS calcd for $C_{26}H_{53}IO_7$ $[M + H]^+$ 605.2914, found 605.2910.

(4*S*,6*S*,8*S*,10*R*,12*R*,14*R*)-4,6,8,10,12,14-Hexamethoxynonadec-1-ene. To a stirred solution of **17** (7.1 mg, 0.01 mmol) in hexanes at −30 °C was added 0.1 mL of *n*-BuLi (2.2 M in hexanes). TLC analysis indicated immediate reaction, and H_2O was added to quench. The organic layer was washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford *Tolypothrix* hexaether (5.2 mg, 0.01 mmol, 99%) as a colorless oil without further purification.

Alternatively, the hexaether was produced by the following two-step sequence. To a stirred solution of **16** (8.0 mg, 0.02 mmol) in MeOH (2 mL) were added two drops of concd HCl. The reaction was stirred at 50 °C for 15 min, and TLC analysis indicated complete reaction. All volatile components were removed under reduced pressure. The crude product was subjected to methylation conditions similar to those used in the preparation of **16**. The reaction was finished in 12 h of reflux for this substrate. Column chromatography (2% MeOH in CH_2Cl_2) produced *Tolypothrix* hexaether as a colorless oil (7.0 mg, 0.02 mmol, 93% two steps): $[\alpha]^{20}_D$ = +3.33 (c 0.39, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 0.89 (3H, t, J = 6.82 Hz), 1.25−1.35 (6H), 1.46−1.66 (6H), 1.75−1.85 (6H), 2.27−2.43 (2H, m), 3.25−3.45 (6H), 3.31 (12H, s), 3.32 (3H, s), 3.35 (3H, s), 5.07−5.14 (2H, m), 5.79−5.87 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 32.3, 33.6, 37.8, 37.9, 38.1, 38.3, 38.38, 38.40, 56.42, 56.44, 56.47, 56.48, 56.52, 56.6, 75.49, 75.51, 75.52, 75.7, 77.5, 78.1, 117.5, 134.6; HRMS calcd for $C_{25}H_{50}O_6$ $[M+H]^+$ 447.3686, found 447.3695.

Acknowledgment. The Department of Chemistry & Biochemistry at University of Notre Dame is acknowledged for support of this work through a Reilly Fellowship (K.L.). Partial support provided by funds from the National Institutes of Health, National Institute of General Medical Sciences (GM084922). J.W.A. thanks the Walther Cancer Research Center (Notre Dame) for fellowship support.

Supporting Information Available: Full experimental and characterization data for compounds **10**, **11**, and *rac*-**5**, (*S*)-**5**, as well as proton and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.