JOC Article

The Synthesis of Deoxyfusapyrone. 2. Preparation of the Bis-Trisubstituted Olefin Fragment and Its Attachment to the Pyrone Moiety

Michael G. Organ* and Junquan Wang

Department of Chemistry, York University, 4700 Keele Street, Toronto, Ontario, Canada M3J 1P3

organ@yorku.ca

Received March 21, 2003

A convergent and modular synthesis has been devised to construct the eight diastereoisomers of deoxyfusapyrone (**1**). In this paper the synthesis of the complex polyene chain is reported as is its connection to the pyrone moiety that is in the middle of the structure of the final target molecule. This route has been fully worked out for one of the isomers and will now be applied in a parallel synthesis format to make all the stereoisomers of **1**.

Introduction

Deoxyfusapyrone (**1**) is a secondary metabolite isolated from rice cultures of *Fusarium semitectum* which has demonstrated pronounced antifungal activity against plant pathogenic and/or mycotoxigenic filamentous fungi.[1] Compound **1** is a candidate for biotechnology applications and has potential as a natural and safe herbicide to suppress parasite seed germination.[2] Structurally, **1** can be divided into three components: a 4-deoxy glucose moiety, a pyrone component, and a long-chain polyene fragment. Synthetically, there are a number of challenges to consider when planning a route for the preparation of **1**, not the least of which is that three of the seven stereocenters in **1** remain undetermined. Any proposed synthetic route would have to be general enough to facilitate the preparation all possible diastereomers of **1** to confirm its relative and absolute stereochemistry. Our approach (Figure 1, X and Y = halogen, M^1 and M^2 = metal) is modular and allows for the parallel synthesis of all eight diastereomers that arise from unassigned stereocenters 8, 13, and 17 (i.e., the deoxy glucose stereochemistry has been assigned unambiguously). The disconnections outlined in Figure 1 require the synthesis of **2**, **4**, and **5** as the principal building blocks. We have already completed the synthesis of the alkyne precursor of **4**[3] and now wish to report on the preparation of **5** and its coupling with **4**.

The two chiral centers in **5** are quite challenging to build into the structure. The C13 position is bis allylic, thus there is concern over epimerization of this position while the C17 position is remote from any functional group that could be used to direct a stereoselective reaction, such as the reduction of an olefin precursor. With this in mind, we opted for a strategy that would allow us to use existing chirality and build it into the structure. While building blocks **6** and **7** appear different, in fact, we can use **8** that is commercially available in both enantiomeric forms to make both compounds, therefore maximally exploiting the synthetic methods developed to modify **8**. This modular approach offers the further advantage of only having to prepare **6** as one enantiomer. That is, groups X and Y are electronically differentiated such that one will always be the most reactive of the two (e.g., I vs Cl) in oxidative addition reactions involving metals such as Pd.[4] Thus, simply changing the order in which **4** and **7** are added to **6** will, by design, change the chirality of C13 from (*R*) to (*S*) because **6** is pseudo-C2 symmetrical. However, first as a proof of principle we opted to deal with the couplings to **4** and **7** one step at a time to ensure that they work independently and in doing so have generated one optically pure isomer of **3**.

Results and Discussion

Compound **8** was protected as the PMB ether and then the ester converted to the corresponding aldehyde (**11**, Scheme 1).[5] The Corey−Fuchs procedure[6] gave the requisite alkyne (**13**) that was regioselectively hydrozirconated[7] and quenched with iodine to give optically pure **14**.

In a related series of transformations compound **8** was protected, reduced,[9] and converted to the corresponding

(1) Evidente, A.; Conti, L.; Altomare, C. *Nat. Toxins* **1994**, *2*, 4−13.
(2) (a) Altomare, C.; Perrone, G.; Zonno, M. C. *J. Nat. Prod.* **2000**, *63*, 1131−1135. (b) Altomare, C.; Perrone, G.; Zonno, M. C. *Cereal Res. Commun.* **1997**, *25*, 349−351. (c) Zonno, M. C.; Vurro, M. *Weed Res.* **1999**, *39*, 15−20.
(3) Organ, M. G.; Wang, J. *J. Org. Chem.* **2002**, *67*, 7847−7851.
(4) (a) Organ, M. G.; Cooper, J. T.; Rogers, L. R.; Soleymanzadeh, F.; Paul, T. *J. Org. Chem.* **2000**, *65*, 7959−7970. (b) Zeng, F.; Negishi, E.-i. *Org. Lett.* **2001**, *3*, 719−722.
(5) (a) Shimizu, S.; Nakamura, S.; Nakada, M.; Shibasaki, M. *Tetrahedron* **1996**, *52*, 13363−13408. (b) Walkup, R. D.; Kahl, J. D.; Hane, R. R. *J. Org. Chem.* **1998**, *63*, 9113−9116. (c) Walkup, R. D.; Boatman, P. D.; Kane, R. R.; Cunningham, R. T. *Tetrahedron Lett.* **1991**, *32*, 3937−3940.
(6) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769−3772.
(7) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912−4913.
(8) (a) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679. For a review, see: (b) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853−12910.

10.1021/jo034371k CCC: $25.00
Published on Web 06/06/2003

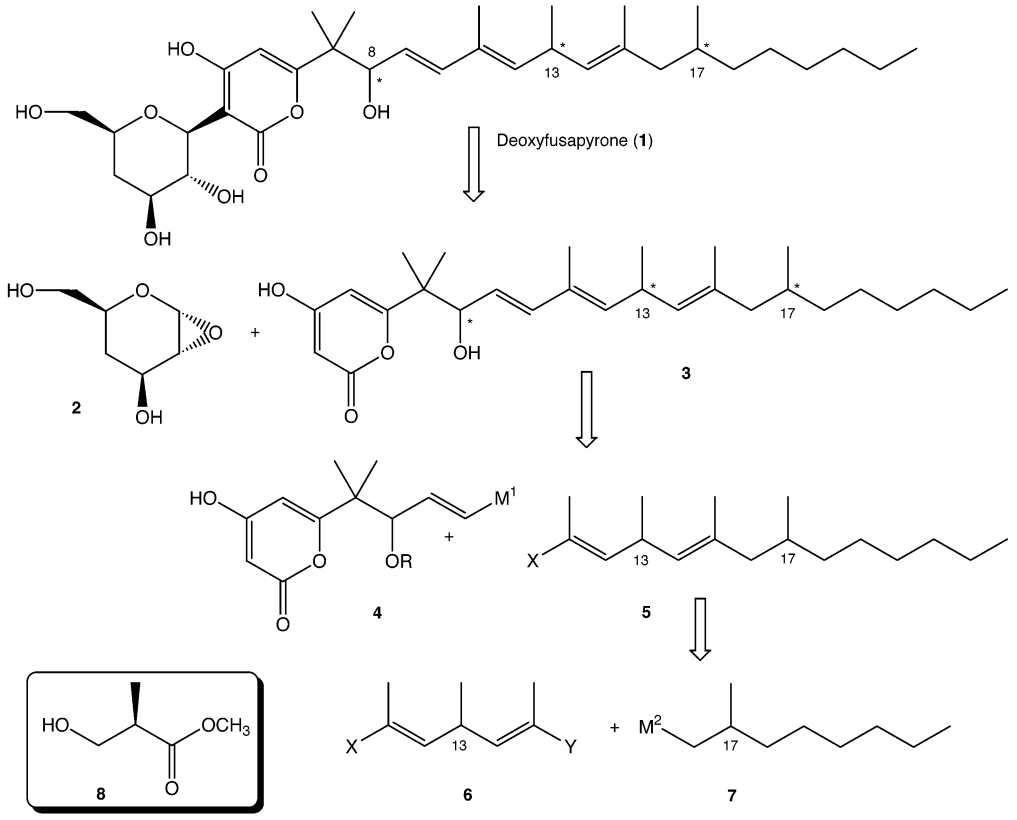
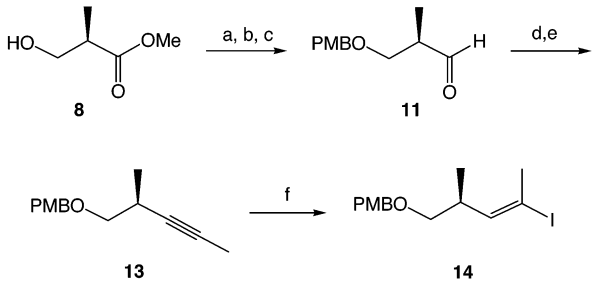


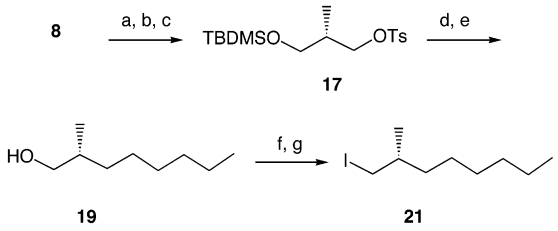
FIGURE 1. Retrosynthetic analysis of deoxyfusapyrone.

SCHEME 1[a]



[a] Reagents and conditions: (a) PMBOC(=NH)CCl_3, PPTS, CH_2Cl_2, rt (**9**, 96%); (b) LAH, ether, 0 °C (**10**, 99%); (c) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, −78 °C (used crude in the next step); (d) CBr_4, PPh_3, CH_2Cl_2 (**12**, used crude in the next step); (e) (i) *n*-BuLi (2 equiv), THF, −78 °C to rt, (ii) CH_3I (3 equiv) (75% from **10**); (f) (i) Schwartz's reagent[8] (2.5 equiv), THF, rt, 20 h, (ii) I_2, rt (63%).

SCHEME 2[a]



[a] Reagents and conditions: (a) TBDMSCl, imidazole, DMF, rt (**15**, 86%); (b) DIBAL-H (1.1 equiv), −50 °C (**16**, 79%); (c) TsCl (1.35 equiv), pyridine, rt, 5 h (used crude in the next step); (d) *n*-C_5H_9MgBr (5 equiv), Li_2CuCl_4 (5 mol %), THF, rt, 48 h (**18**, 90% from **16**); (e) TBAF (1.5 equiv), THF, rt, 3 h (92%); (f) TsCl, pyridine, rt (**20**, 80%); (g) NaI, acetone, reflux (97%).

tosylate (**17**) as depicted in Scheme 2. The alkyl chain was elongated by using dipentyl cuprate to provide **18**.[10] Deprotection and conversion to the corresponding iodide[10b] provided the organozinc precursor **21**.

The one-pot lithium/halogen exchange[11]−zinc lithium exchange−Negishi coupling[12] between **21** and **14** proceeded smoothly with Pd catalyst (Scheme 3).[13] Deprotection of **22** and elaboration with similar chemistry to that outlined in Scheme 1 provided the oxidative addition partner (**27**) to be coupled with organometallic **4**.

What was left to do now was to produce **4** and couple it to **27**. In light of the value of optically pure **4**, we decided to work out the hydrometalation/cross-coupling sequence on a model system (Scheme 4). Attempts to hydroborate **28** with pinacol borane,[14] dibromoborane,

(9) (a) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am Chem. Soc.* **1990**, *112*, 2998−3017. (b) Mulzer, J.; Mantoulidis, A.; Ohler. E. *J. Org. Chem.* **2000**, *65*, 7456−7467. (c) White, J. D.; Hanselmann, R.; Jackson, R. W.; Porter, W. J.; Ohba, Y.; Tiller, T.; Wang, S. *J. Org. Chem.* **2001**, *66*, 5217−5231. (d) Nakamura, Y.; Mori, K. *Eur. J. Org. Chem.* **2000**, 2745−2753.

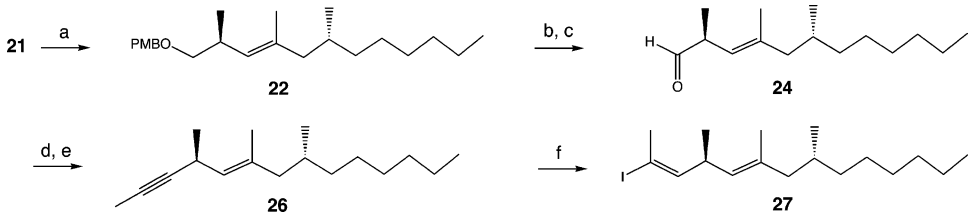
(10) (a) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed.* **1974**, *13*, 82−83. (b) Shirai, Y.; Sekei, M.; Mori, K. *Eur. J. Org. Chem.* **1999**, 3139−3145.

(11) Applequist, D. E.; O'Brien, D. F. *J. Am. Chem. Soc.* **1963**, *85*, 743−748.

(12) (a) Negishi, E.-i.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298−3299. (b) Arefolov, A.; Langille, N. F.; Panek, J. S. *Org. Lett.* **2001**, *3*, 3281−3284. For reviews, see: (c) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275−8317. (d) Erdik, E. *Tetrahedron* **1992**, *48*, 9577−9648.

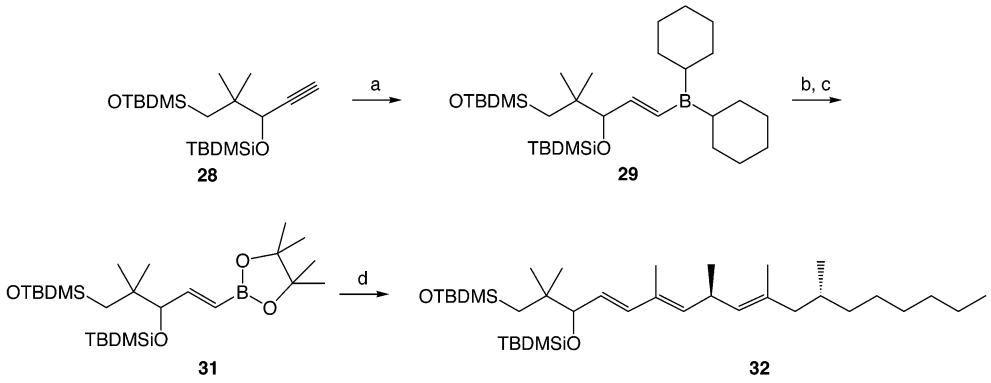
(13) The corresponding reduction product was produced in a ratio of desired product (**22**) to reduction product of 12:1.

SCHEME 3[a]



[a] Reagents and conditions: (a) (i) *t*-BuLi (2.1 equiv), ether, −78 °C, (ii) $ZnCl_2$ (1.1 equiv) in ether, −78 °C to rt, (iii) **14**, (0.67 equiv), $Pd(PPh_3)_4$ (5 mol %), THF, rt (66%); (b) DDQ (1.1 equiv), CH_2Cl_2, rt, 40 min (**23**, 90%); (c) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, −78 °C (98%); (d) CBr_4/PPh_3, CH_2Cl_2, 0 °C to rt (**25**, used crude in the next step); (e) (i) *n*-BuLi (2 equiv), THF, −78 °C to rt, (ii) MeI (2 equiv) (99%); (f) (i) Schwartz's reagent (2.1 equiv), THF, rt, 20 h, (ii) I_2, rt.

SCHEME 4[a]



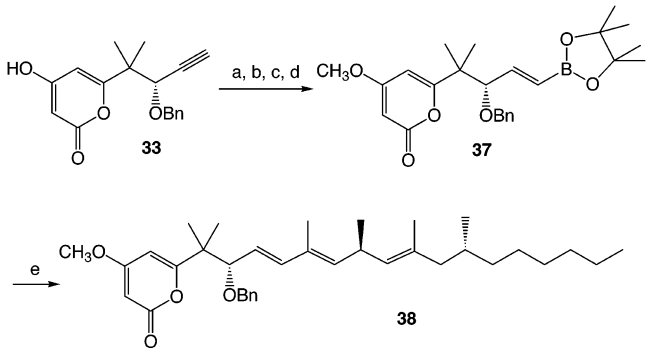
[a] Reagents and conditions: (a) dicyclohexylborane, DME, 0°C to rt; (b) trimethylamine *N*-oxide (TMANO), rt; (c) pinacol, rt; (d) **27**, KOH (aq), $Pd(PPh_3)_4$ (8 mol %), THF reflux.

catecholborane, and 9-BBN[15] all failed as did hydrozirconation with Schwartz reagent.[7] It is not clear whether the propargyllic OTBDMS substituent and/or the gem dimethyl groups made the alkyne too sterically hindered or if the allylic oxygen was exerting an unfavorable electronic effect. In any case we tried the reaction with dicyclohexylborane and this time the reaction proceeded smoothly providing **29**.[16] Oxidation (**30**) and borate esterification provided the corresponding pinacolborane (**31**), which was then smoothly coupled with **27** to give **32**.

With this last hydrometalation/coupling sequence worked out, we tried it on the chiral substrate **33** (Scheme 5).[3] After the hydroxy group was capped as a methyl ether, hydroboration, oxidation, and esterification proceeded smoothly to provide borate ester **37**. All of these steps and the subsequent cross-coupling step were conducted on unpurified material providing the desired protected compound **38** in 57% yield over these four steps. For compound **1**, deprotection of the two hydroxyl groups would take place following addition to the pyrone moiety to the epoxy glycal **2**.

In summary, we have developed a convergent, modular approach toward the synthesis of the eight possible stereoisomers of deoxyfusapyrone. Building on our reported preparation of compound **33**,[3] the middle and right-hand pieces of the final target have been completed for one of the eight stereoisomers of **38**. We are exploring currently the construction and utilization of the pseudosymmetric building block **6** for the one-pot, parallel synthesis of all the isomers and their addition to **2** to complete the work.

SCHEME 5[a]



[a] Reagents and conditions: (a) Me_2SO_4 (2.8 equiv), Na_2CO_3, acetone, reflux (**34**, 83%); (b) dicyclohexylborane (1.2 equiv), DME, 0°C to rt (**35**, used crude in the next step); (c) TMANO (2.4 equiv), rt (**36**, used crude in the next step); (d) pinacol (1.0 equiv), rt (used crude in the next step); (e) **28** (1.2 equiv), KOH (aq) (2 equiv), $Pd(PPh_3)_4$ (8 mol %), THF reflux (57% from **34**).

Experimental Section

All solvents used were dry and reactions were run under a blanket of dry nitrogen unless indicated otherwise.

(14) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482−3485.
(15) Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 6981−6990.
(16) (a) Hoffmann, R. W.; Dresely, S. *Synthesis* **1988**, 103−106. (b) Zhang, A.; Kan, Y.; Zhao, G.-L.; Jiang, B. *Tetrahedron* **2000**, *56*, 965−970.

(*R*)-Methyl 3-(4-Methoxy-benzyloxy)-2-methyl-propionate (9). To a suspension of NaH (90 mg, 3.75 mmol, 60% suspension in mineral oil) in ether (25 mL) at rt was added a solution of 4-methoxybenzyl alcohol (5.18 g, 37.5 mmol) in ether (20 mL) via cannula. The resulting suspension was stirred for 1 h and cooled to 0 °C, and trichloroacetonitrile (3.76 mL, 5.42 g, 37.5 mmol) was added. The mixture was stirred for 5 min and then for an additional 20 min at rt. Ether (50 mL) was added and the solution was washed successively with saturated $NaHCO_3$ and brine. After drying over anhydrous $MgSO_4$, the suspension was filtered and concentrated in vacuo to give the intermediate as a yellow oil. This crude intermediate was dissolved in CH_2Cl_2 (50 mL) at rt and (*R*)-methyl 3-hydroxy-2-methylpropionate (**8**, 2.77 mL, 2.95 g, 25.0 mmol) and PPTS (276 mg, 0.044 mmol) were added. The mixture was stirred for 22 h during which time a white solid formed. After washing with saturated $NaHCO_3$ and brine, the solution was dried over anhydrous $MgSO_4$ and subsequently filtered. The solvent was removed in vacuo and the resulting semisolid mixture was triturated with 1:1 hexane/CH_2Cl_2. The triturant solution was concentrated to an oil that was purified by flash chromatography on silica gel (hexane/ethyl acetate, 5:1) to provide **9** (5.7 g, 96%) as a yellow oil. $[\alpha]^{24}_D$ −9.23 (*c* 8.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 4.47 (s, 2H), 3.83 (s, 3H), 3.71 (s, 3H), 3.67−3.63 (m, 1H), 3.50−3.46 (m, 1H), 2.82−2.77 (m, 1H), 1.19 (d, J = 7.2 Hz, 3H). All spectral data compare well with the literature.[5]

(*S*)-3-(4-Methoxy-benzyloxy)-2-methyl-propan-1-ol (10). To a solution of **9** (2.374 g, 9,98 mmol) in ether (50 mL) at 0 °C was added LAH (0.38 g, 10 mmol) in one portion. The mixture was stirred for 4 h and quenched with cold water (5 mL) in small portions. The clear solution was decanted and the residue was washed with ether. The combined ethereal solution was washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give crude **10** (2.0 g, 99%) as a yellow oil that was used in the next step without further purification. An analytical sample was obtained by chromatography on silica gel (hexane/ethyl acetate, 5:1). $[\alpha]^{24}_D$ −10.62 (*c* 4.87, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 7.0 Hz, 2H), 6.89 (d, J = 7.0 Hz, 2H), 4.46 (s, 2H), 3.82 (s, 3H), 3.63−3.59 (m, 2H), 3.53 (dd, J = 9.0, 4.7 Hz, 2H), 3.40 (t, J = 8.8 Hz, 1H), 2.70 (br s, 1H), 2.10−2.02 (m, 1H), 0.89 (d, J = 5.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ: 159.3 (+), 130.3 (+), 129.2 (−), 113.9 (−), 74.7 (+), 73.0 (+), 67.3 (+), 55.2 (−), 35.7 (−), 13.6 (−). All spectral data compare well with the literature.[5]

(*R*)-3-(4-Methoxy-benzyloxy)-2-methyl-propionaldehyde (11). To a stirred solution of oxalyl chloride (0.92 mL, 1.34 g, 10.58 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added DMSO dropwise (1.65 mL, 1.804 g, 23.1 mmol). After 0.5 h, a solution of **10** (2.02 g, 9.62 mmol) in CH_2Cl_2 (25 mL) was added via cannula. The mixture was stirred for 40 min after which triethylamine (0.87 mL, 0.63 g, 6.24 mmol) was added. The mixture was allowed to reach rt slowly and then it was quenched with water (30 mL). The separated organic layer was washed with brine (2×), dried over anhydrous $MgSO_4$, and filtered. The solvent was removed in vacuo to give crude **11** (2.00 g, quantitative) as a yellow oil that was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.26 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 8.1 Hz, 2H), 4.47 (s, 2H), 3.82 (s, 3H), 3.67−3.63 (m, 2H), 2.68−2.64 (m, 1H), 1.13 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 203.9 (−), 159.3 (+), 130.0 (+), 129.3 (−), 113.9 (−), 73.0 (+), 69.8 (+), 55.3 (−), 46.8 (−), 10.7 (−). All spectral data compare well with the literature.[5]

(*R*)-1-(4,4-Dibromo-2-methyl-but-3-enyloxymethyl)-4-methoxy-benzene (12). To a stirred brown suspension of triphenylphosphine (10.09 g, 38.48 mmol) and carbon tetrabromide (6.38 g, 19.24 mmol) in CH_2Cl_2 (55 mL) at 0 °C was added a solution of crude aldehyde **11** (2.00 g, 9.62 mmol) in CH_2Cl_2 (20 mL). After being stirred for 0.5 h, the mixture was warmed to rt and diluted with ether. The mixture was then filtered and the brown solid was washed with ether. Hexane was added to the filtrate leading to the formation of additional precipitate. After filtration and removal of the solvent in vacuo, the residue was chromatographed on silica gel (20:1 hexane/ethyl acetate) to give **12** as a light yellow oil (2.6 g, 75% from **10**). $[\alpha]^{24}_D$ +13.13 (*c* 9.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 8.3 Hz, 2H), 6.35 (d, J = 9.1 Hz, 1H), 4.49 (s, 2H), 3.84 (s, 3H), 3.42−3.37 (m, 2H), 2.85−2.78 (m, 1H), 1.09 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 159.3 (+), 141.3 (−), 130.4 (+), 129.2 (−), 113.9 (−), 88.8 (+), 72.8 (+), 55.3 (−), 38.8 (−), 38.3 (+), 15.9 (−); IR (neat) 1613 cm^{-1}; HRMS m/z calcd for $C_{13}H_{16}Br_2O_2$ (M^+) 361.9467, found 361.9517.

(*R*)-1-Methoxy-4-(2-methyl-but-3-enyloxymethyl)-benzene (13). To a stirred solution of **12** (4.94 g, 13.64 mmol) in THF (50 mL) at −78 °C was added dropwise a solution of *n*-BuLi (17.5 mL, 28.0 mmol, 2.05 equiv, 1.6 M in hexane). The mixture was allowed to reach rt over a period of 2 h and then it was cooled back to −78 °C. Methyl iodide (2.55 mL, 5.81 g, 41 mmol) was added dropwise and the mixture was allowed to reach rt slowly where it was stirred for 16 h. The reaction was quenched with saturated NH_4Cl, and then extracted with ether (2×). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed in vacuo to give crude product that was chromatographed on silica gel (hexane/ethyl acetate, 60:1) to give **13** (2.3 g, 78%) as a yellow oil. $[\alpha]^{24}_D$ −2.32 (*c* 2.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.51 (d, J = 2.1 Hz, 2H), 3.82 (s, 3H), 3.49 (dd, J = 8.9, 6.0 Hz, 1H), 3.32 (t, J = 8.7 Hz, 1H), 2.82−2.81 (m, 1H), 1.81 (d, J = 1.9 Hz, 3H), 1.19 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 159.2 (+), 130.5 (+), 129.2 (−), 113.8 (−), 81.2 (+), 77.4 (+), 74.2 (+), 72.6 (+), 55.2 (−), 26.7 (−), 18.1 (−), 3.6 (−); IR (neat) 2049, 1696, 1613 cm^{-1}; HRMS m/z calcd for $C_{14}H_{18}O_2$ (M^+) 218.1307, found 218.1297.

(*R*)-1-(4-Iodo-2-methyl-pent-3-enyloxymethyl)-4-methoxy-benzene (14). To a stirred suspension of Schwartz's reagent ($Cp_2Zr(H)Cl$, 6.82 g, 26.45 mmol) in THF (25 mL) at rt was added a solution of **13** (2.31 g, 10.58 mmol) in THF (25 mL). The mixture was stirred for 24 h and cooled to 0 °C, and a solution of iodine (5.38 g, 21.16 mmol) in THF (10 mL) was added dropwise. The reaction was warmed to rt and quenched with a dilute solution of $Na_2S_2O_3$. The mixture was extracted with ether (3×) and the combined organic layers were washed with a dilute solution of $Na_2S_2O_3$. After being washed with brine, the organic layer was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in vacuo to give a semisolid residue that was extracted with pentane (3×). Following pentane removal in vacuo, the crude product was chromatographed on silica gel (hexane/ethyl acetate, 60:1) to give **14** (2.31 g, 63%) as a yellow oil. $[\alpha]^{24}_D$ −11.77 (*c* 7.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 8.3 Hz, 2H), 6.03 (d, J = 9.4 Hz, 1H), 4.46 (s, 2H), 3.83 (s, 3H), 3.29 (dd, J = 6.7, 2.8 Hz, 2H), 2.78−2.73 (m, 1H), 2.43 (s, 3H), 1.02 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 159.2 (+), 143.9 (−), 130.5 (+), 129.1 (−), 113.8 (−), 94.5 (+), 73.9 (+), 72.7 (+), 55.3 (−), 36.2 (−), 28.0 (−), 17.1 (−); IR (neat) 1611 cm^{-1}; HRMS m/z calcd for $C_{14}H_{19}IO_2$ (M^+) 346.0430, found 346.0430.

(*S*)-Methyl 3-(*tert*-butyl-dimethyl-silanyloxy)-2-methylpropionate (15). To a solution of (*S*)-(+)-3-hydroxy-2-methylpropionate (**8**, 4.02 g, 34.03 mmol) and imidazole (6.50 g, 95.28 mmol) in DMF (80 mL) at rt was added TBDMSCl (5.4 g, 35.73 mmol) in three portions. The mixture was stirred for 5 h, poured into a dilute solution of $NaHCO_3$, and extracted with ether (3×). The combined organic extracts were washed successively with a dilute solution of $NaHCO_3$ and brine followed by drying over anhydrous $MgSO_4$. Following filtration, the solvent was removed in vacuo to give crude product that was purified by chromatography on silica gel (hexane/ethyl acetate 15:1) to give **15** (6.8 g, 86%) as a colorless oil. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 3.80 (dd, J = 9.7, 7.0 Hz, 1H), 3.70 (s, 3H), 3.67 (dd, J = 9.7, 6.2 Hz, 1H), 2.70−2.65 (m, 1H), 1.16 (d, J = 7.1 Hz, 3H), 0.90 (s, 3H), 0.06 (s, 6H). All spectral data compare well with the literature data.[9b]

(*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-propan-1-ol (16). To a stirred solution of **15** (6.84 g, 29.47 mmol) in THF (70 mL) at −50 °C was added dropwise a solution of DIBAL-H (89 mL, 88.41 mmol, 1.0 M in toluene). The mixture was stirred for 3 h and then quenched carefully at 0 °C with MeOH (5 mL). A saturated solution of sodium/potassium tartrate (Roschelle's salt, 50 mL) was added and after 10 min of stirring the mixture was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed in vacuo to give crude **16** (4.75 g, 79%) as a yellow oil that was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (dd, J = 9.9, 4.6 Hz, 1H), 3.59−3.50 (m, 3H), 2.99 (s, 1H), 1.92−1.85 (m, 1H), 0.88 (s, 9H), 0.82 (d, J = 6.9 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 68.2 (+), 67.6 (+), 37.2 (−), 25.8 (−), 18.1 (+), 13.1 (−), −5.6 (−). All spectral data compare well with the literature data.[9b]

(*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-propyl Toluene-4-sulfate (17). A mixture of **16** (4.74 g, 23.24 mmol) and tosyl chloride (5.98 g, 31.37 mmol) in dry pyridine (15 mL) at 0 °C was stirred for 5 h. Cold water (20 mL) was added and after 15 min the mixture was extracted with ether (3×). The combined organic extracts were washed successively with a dilute solution of HCl, saturated $NaHCO_3$, and brine. Following drying over anhydrous $MgSO_4$, the suspension was filtered and the solvent removed in vacuo to provide crude **16** (7.86 g, 94%) as a light yellow oil that was used in the next step without further purification. A small amount of **17** was purified by chromatography on silica gel (hexane/ethyl acetate 10:1) for analysis. $[\alpha]^{24}_D$ + 4.44 (*c* 4.73, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.03 (dd, J = 9.4, 5.9 Hz, 1H), 3.93 (dd, J = 9.0, 5.6 Hz, 1H), 3.51 (dd, J = 9.9, 4.9 Hz, 1H), 3.42 (dd, J = 9.9, 6.4 Hz, 1H), 2.45 (s, 3H), 1.98−1.94 (m 1H), 0.89 (d, J = 6.9 Hz, 3H), 0.83 (s, 9H), −0.01 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 144.6 (+), 133.2 (+), 129.8 (−), 127.9 (−), 72.1 (+), 63.7 (+), 35.7 (−), 25.8 (−), 21.6 (−), 18.1 (+), 13.2 (−), −5.6 (−); IR (neat) 1599, 1252, 1189, 1178, 1098 cm^{-1}. All spectral data compare well with the literature data.[9b]

(*R*)-*tert*-Butyl-dimethyl-(2-methyl-octyloxy)-silane (18). To a solution of crude **17** (7.74 g, 21.61 mmol) in THF (20 mL) at −78 °C was added a solution of Grignard reagent [prepared in situ from Mg (3.9 g, 162 mmol) and pentyl bromide (13.4 mL, 16.32 g, 108 mmol) in 100 mL of THF] via cannula and Li_2CuCl_4 (2.2 mL, 0.22 mmol, 0.1 M in THF). The mixture was allowed to reach rt slowly and after 36 h was quenched with saturated NH_4Cl. The solution was extracted with ether (3×) and the combined organic extracts were washed with saturated NH_4Cl and brine and then dried over anhydrous $MgSO_4$. Following filtration, the solvent was removed in vacuo to give crude product that was purified by chromatography on silica gel (hexane/ethyl acetate 50:1) to afford **18** (5.12 g, 92%) as a colorless oil. $[\alpha]^{24}_D$ +1.77 (*c* 3.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (dd, J = 9.4, 6.1 Hz, 1H), 3.39 (dd, J = 9.5, 6.8 Hz, 1H), 1.65−1.55 (m, 1H), 1.45−1.20 (m, 9H), 1.15−1.00 (m, 1H), 0.99−0.80 (m, 15H), 0.07 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 68.4 (+), 35.8 (−), 33.2 (+), 31.9 (+), 29.7 (+), 27.0 (+), 26.0 (−), 22.7 (+), 18.3 (+), 16.8 (−), 14.1 (−), −5.4 (−); IR (neat) 1251, 1100 cm^{-1}. Anal. Calcd for $C_{15}H_{34}OSi$: C, 69.69; H, 13.26. Found: C, 70.20; H, 13.72.

(*R*)-2-Methyl-octan-1-ol (19). To a solution of **18** (3.56 g, 13.8 mmol) in THF (20 mL) at rt was added a solution of TBAF (20.7 mL, 20.7 mmol, 1.0 M in THF). The mixture was stirred for 20 h and water (20 mL) was added. The mixture was extracted with ether (3×) and the combined organic extracts were washed successively with a saturated solution of NH_4Cl and brine. After drying over anhydrous $MgSO_4$, the suspension was filtered and the solvent removed in vacuo. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate 10:1) to afford **19** (1.632 g, 92%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (dd, J = 10.5, 5.5 Hz, 1H), 3.40 (dd, J = 10.5, 6.0 Hz, 1H), 1.81−1.09 (m, 12H), 1.06−0.78 (m, 6H). All spectral data compare well with the literature data.[10b]

(*R*)-2-Methyl-octyl Toluene-4-sulfonate (20). A mixture of **19** (1.63 g, 11.33 mmol) and tosyl chloride (2.81 g, 14.73 mmol) in pyridine (8 mL) was stirred for 0.5 h at 0 °C, then additionally for 5 h at rt. Cold water (20 mL) was added, and the solution was stirred for 15 min and then extracted with ether (3×). The combined organic extracts were washed successively with a dilute solution of HCl, saturated $NaHCO_3$, and brine. After drying over anhydrous $MgSO_4$, the suspension was filtered and the solvent was removed in vacuo. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate 20:1) to afford **20** (2.67 g, 80%) as a colorless oil. $[\alpha]^{24}_D$ − 2.22 (*c* 6.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 3.85 (dd, J = 9.3, 5.9 Hz, 1H), 3.78 (dd, J = 9.3, 6.2 Hz, 1H), 2.41 (s, 3H), 1.76−1.71 (m, 1H), 1.32−1.05 (m, 10H), 0.86−0.82 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 144.6 (+), 133.2 (+), 129.8 (−), 127.8 (−), 75.1 (+), 32.8 (−), 32.6 (+), 31.7 (+), 29.3 (+), 26.5 (+), 22.5 (+), 21.5 (−), 16.4 (−), 14.0 (−); IR (neat) 1599, 1466, 1362, 1177, 1097 cm^{-1}. All spectral data compare well with the literature data.[10b]

(*R*)-1-Iodo-2-methyl-octane (21). A mixture of **20** (2.669 g, 8.96 mmol) and sodium iodide (2.02 g, 13.43 mmol) in dry acetone (20 mL) was refluxed for 20 h and then cooled to rt. Water (40 mL) was added and the mixture was extracted with ether (3×). The combined organic extracts were washed successively with dilute $Na_2S_2O_3$ and brine, and then dried over anhydrous $MgSO_4$. The suspension was filtered and the solvent was removed in vacuo to give crude product that was purified by chromatography on silica gel (pentane) to give iodide **21** (2.20 g, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (dd, J = 9.6, 4.4 Hz, 1H), 3.13 (dd, J = 9.7, 5.2 Hz, 1H), 1.62−1.11 (m, 11H), 1.06−0.79 (m, 6H). All spectral data compare well with the literature data.[10b]

(*R*)-1-Methoxy-4-[(2*R*),(6*R*)-2,4,6-trimethyl-dodec-3-enyloxymethyl]-benzene (22). To a stirred solution of iodide **21** (2.13 g, 8.39 mmol) in ether (30 mL) at −78 °C was added dropwise a solution of *t*-BuLi (10.4 mL, 17.61 mmol, 1.7 M in pentane) via syringe. The resulting light yellow suspension was stirred for 30 min. after which a solution of $ZnCl_2$ (9.2 mL, 1.0 M in ether) was added dropwise. The mixture was slowly brought to rt where it was stirred for an additional 30 min. A solution of **14** (2.34 g, 6.76 mmol) and $(PPh_3)_4Pd$ (0.39 g, 0.338 mmol, 5 mol %) in THF (35 mL) was added via cannula. The resulting brown suspension was stirred for 19 h during which time it turned black. The mixture was quenched carefully with a solution of saturated NH_4Cl and then extracted with ether (3×). The combined organic extracts were washed successively with saturated NH_4Cl and brine. After drying over anhydrous $MgSO_4$, the suspension was filtered and the solvent removed in vacuo to give the crude product that was purified by chromatography on silica gel (hexane/ethyl acetate 50:1) to give **70** (1.54 g, 66%) as a light yellow oil. $[\alpha]^{24}_D$ +13.72 (*c* 5.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.94 (d, J = 9.0 Hz, 1H), 4.50 (d, J = 11.2 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 3.83 (s, 3H), 3.33 (dd, J = 8.9, 6.2 Hz, 1H), 3.25 (t, J = 8.1 Hz, 1H), 2.78−2.71 (m, 1H), 2.01 (dd, J = 13.1, 6.1 Hz, 1H), 1.76 (dd, J = 12.9, 8.3 Hz, 1H), 1.64 (s, 3H), 1.64−1.58 (m, 1H), 1.31 (br s, 9H), 1.11−1.07 (m, 1H), 1.02 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 6.2 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 159.1 (+), 134.6 (+), 131.0 (+), 129.1 (−), 128.9 (−), 113.7 (−), 75.3 (+), 72.6 (+), 55.2 (−), 47.9 (+), 36.9 (+), 33.1 (−), 32.0 (+), 30.6 (−), 29.7 (+), 27.0 (+), 22.7 (+), 19.5 (−), 18.0 (−), 16.2 (−), 14.1 (−); IR (neat) 1613, 1248 cm^{-1}; HRMS *m*/*z* calcd for $C_{23}H_{38}O_2$ (M^+) 346.2872, found 346.2836.

(2*R*),(6*R*)-2,4,6-Trimethyl-dodec-3-en-1-ol (23). To a stirred solution of **22** (1.17 g, 3.37 mmol) in CH_2Cl_2 (20 mL) at rt was added water (1 mL) and DDQ (0.84 g, 3.71 mmol). The resulting suspension was stirred for 30 min during which time it turned green, yellow-green, and ultimately, yellow. The mixture was diluted with ether and washed successively with saturated $NaHCO_3$ (2×) and brine. After removal of the solvent in vacuo, the residue was dissolved in pentane and washed successively with saturated $NaHSO_3$ (2×, to remove the byproduct, *p*-anisaldehyde) and brine. The pooled organic layers were dried over anhydrous $MgSO_4$ and filtered and the solvent was removed in vacuo. The crude product was purified by chromatography on silica gel (pentane/ethyl ether, 10:1) to give **23** (0.68 g, 90%) as a light yellow oil. $[\alpha]^{24}_D$ −22.43 (*c* 4.73, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (d, J = 9.3 Hz, 1H), 3.46 (dd, J = 10.1, 6.1 Hz, 1H), 3.34 (t, J = 10.3 Hz, 1H), 2.66−2.59 (m, 1H), 2.02 (dd, J = 13.1, 6.2 Hz, 1H), 1.77 (dd, J = 13.0, 8.2 Hz, 1H), 1.65 (br s, 1H), 1.63 (s, 3H), 1.60−1.55 (m, 1H), 1.27 (br s, 9H), 1.10−1.05 (m, 1H), 0.94 (d, J = 6.7 Hz, 3H), 0.89 (t, J = 6.3 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 136.8 (+), 128.4 (−), 67.9 (+), 48.0 (+), 36.8 (+), 35.5 (−), 31.9 (+), 30.5 (−), 29.6 (+), 27.0 (+), 22.7 (+), 19.5 (−), 17.0 (−), 16.3 (−), 14.1 (−); IR (neat) 3344 (br) cm^{-1}; HRMS *m*/*z* calcd for $C_{15}H_{30}O$ (M^+) 226.2297, found 226.2281

(2*S*),(6*R*)-2,4,6-Trimethyl-dodec-3-enal (24). To a stirred solution of oxalyl chloride (0.29 mL, 0.42 g, 3.32 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added dropwise DMSO (0.54 mL, 0.59 g, 7.55 mmol). The mixture was stirred for 30 min after which a solution of **23** (0.683 g, 3.02 mmol) in CH_2Cl_2 (10 mL) was added via cannula. After the solution was stirred for 30 min, triethylamine (1.27 mL, 0.924 g, 9.06 mmol) was added and the mixture was allowed to reach rt slowly. At that time, the reaction was quenched with water (30 mL) and the phases separated. The organic layer was washed successively with saturated $NaHCO_3$ (2×) and brine (2×). After drying over anhydrous $MgSO_4$, the suspension was filtered and the solvent was removed in vacuo. The crude product (**24**) (0.663 g, 98%), a yellow oil, was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (d, J = 1.7 Hz, 1H), 4.96 (d, J = 4.6 Hz, 1H), 3.30−3.28 (m, 1H), 2.08 (dd, J = 13.2, 6.1 Hz, 1H), 1.82 (dd, J = 13.1, 8.3 Hz, 1H), 1.68 (s, 3H), 1.29 (br s, 10H), 1.17 (d, J = 6.8 Hz, 3H), 1.18−1.05 (m, 1H), 0.91 (t, J = 6.3 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H).

(2*S*),(6*R*)-1,1-Dibromo-3,5,7-trimethyl-trideca-1,4-diene (25). To a stirred brown suspension of triphenylphosphine (3.15 g, 12.0 mmol) and carbon tetrabromide (2.00 g, 6.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added a solution of crude aldehyde **24** (0.663 g, 3.0 mmol) in CH_2Cl_2 (12 mL) via cannula. The mixture was stirred for 1 h, diluted with pentane, and filtered. The brown solid was washed with pentane and combined with the filtrate. The solvent was removed in vacuo and hexane was added to the residue resulting in additional precipitation. After filtration and evaporation, the crude product was chromatographed on silica gel (pentane) to give dibromide **25** (0.952 g, 83% from **23**) as a colorless oil. $[\alpha]^{24}_D$ −20.89 (*c* 6.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (d, J = 9.3 Hz, 1H), 4.97 (d, J = 8.8 Hz, 1H), 3.39−3.33 (m, 1H), 1.99 (dd, J = 13.2, 6.3 Hz, 1H), 1.75 (dd, J = 13.2, 8.2 Hz, 1H), 1.65 (s, 3H), 1.60−1.55 (m, 1H), 1.29 (br s, 10H), 1.08 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 6.4 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 142.9 (−), 135.7 (+), 127.2 (−), 86.8 (+), 47.7 (+), 37.6 (−), 36.8 (+), 32.0 (+), 30.6 (−), 29.6 (+), 27.0 (+), 22.7 (+), 20.1 (−), 19.5 (−), 16.6 (−), 14.1 (−); IR (neat) 1618, 1454, 1194, 1114 cm^{-1}; HRMS *m*/*z* calcd for $C_{16}H_{28}Br_2$ (M^+) 378.0558, found 378.0536.

(4*S*),(8*R*)-3,5,7-Trimethyl-dodec-3-en-1-ol (26). To a stirred solution of dibromide **25** (0.952 g, 2.505 mmol) in THF (15 mL) at −78 °C was added a solution of *n*-BuLi (3.2 mL 5.14 mmol, 1.6 M in hexane). The mixture was allowed to reach rt slowly, where it was stirred for 10 min and then re-cooled to −78 °C. Methyl iodide (2 equiv, 5.01 mmol, 706 mg) was then added. The resulting mixture was warmed to rt slowly and quenched subsequently with saturated NH_4Cl. The solution was extracted with ether (3×) and the combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The suspension was filtered and the solvent removed in vacuo to give crude product that was chromatographed on silica gel (pentane) to give enyne **26** (0.585 g, 99%) as a colorless oil. $[\alpha]^{24}_D$ +56.88 (*c* 3.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (d, J = 8.8 Hz, 1H), 3.29−3.25 (m, 1H), 1.96 (dd, J = 13.3, 6.8 Hz, 1H), 1.80 (d, J = 1.9 Hz, 3H), 1.83−1.74 (m, 1H), 1.61 (s, 3H), 1.28 (br s, 10H), 1.19 (d, J = 7.0 Hz, 3H), 1.11−1.02 (m, 1H), 0.90 (t, J = 6.3 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 133.9 (+), 128.5 (−), 83.1 (+), 74.7 (+), 47.5 (+), 36.6 (+), 31.9 (+), 30.7 (−), 29.6 (+), 26.9 (+), 24.6 (−), 22.7 (+), 22.3 (−), 19.6 (−), 15.9 (−), 14.1 (−), 3.5 (−); IR (neat) 2051, 1689, 1121 cm^{-1}; HRMS *m*/*z* calcd for $C_{17}H_{30}$ (M^+) 234.2348, found 234.2332.

(4*S*),(8*R*)-2-Iodo-4,6,8-trimethyl-tetradeca-2,5-diene (27). To a stirred suspension of Schwartz's reagent ($Cp_2Zr(H)Cl$, 1.36 g, 5.26 mmol) in THF (15 mL) at rt was added a solution of **26** (0.585 g, 2.50 mmol) in THF (15 mL). After being stirred for 24 h, the mixture was cooled to 0 °C and a solution of iodine (1.27 g, 5.0 mmol) in THF (8 mL) was added dropwise. The resulting mixture was stirred at rt for 30 min, and then quenched with a dilute solution of $Na_2S_2O_3$. The mixture was extracted with ether (3×) and the combined organic extracts were washed successively with a dilute solution of $Na_2S_2O_3$ and brine. After drying over anhydrous $MgSO_4$, the suspension was filtered and the solvent was removed in vacuo to give a semisolid residue that was extracted with pentane (3×). After removal of the pentane in vacuo, the crude product was chromatographed on silica gel (pentane) to give **27** (0.732 g, 81%) as a yellow oil. Some minor impurities could not be removed so **27** was used for Suzuki coupling without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (d, J = 8.7 Hz, 1H), 4.96 (d, J = 8.8 Hz, 1H), 3.31−3.27 (m, 1H), 2.42 (d, J = 1.2 Hz, 3H), 2.00−1.95 (m. 1H), 1.76−1.71 (m, 1H), 1.60 (s, 3H), 1.29 (br s, 10H), 1.15−1.00 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H), 0.92 (t, J = 9.5 Hz, 3H), 0.81 (dd, J = 6.6, 3.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 145.9 (−), 133.6 (+), 129.1 (−), 92.0 (+), 47.7 (+), 36.7 (+), 34.8 (−), 31.9 (+), 30.7 (−), 29.6 (+), 27.7 (−), 27.0 (+), 22.7 (+), 21.2 (−), 19.5 (−), 16.1 (−), 14.1 (−); IR (neat) 1631, 1456, 1114 cm^{-1}; HRMS *m*/*z* calcd for $C_{17}H_{31}I$ (M^+) 362.1471, found 362.1468.

(*R*)-6-(2-Benzyloxy-1,1-dimethyl-but-3-ynyl)-4-methoxy-pyran-2-one (34). A mixture of **33** (0.35 g, 1.19 mmol), Na_2CO_3 (0.10 g, 0.95 mmol), and Me_2SO_4 (0.30 mL, 0.40 g, 3.17 mmol) in dry acetone (4 mL) was refluxed for 20 h and then cooled to rt. After removal of the solvent in vacuo, the residue was purified by chromatography on silica gel (hexane/ethyl acetate, 3:1) to furnish **34** (0.313 g, 85%) as a yellow powder. Mp 99−101 °C (ether/hexane); $[\alpha]^{24}_D$ +171.5 (*c* 0.867, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 5.94 (d, J = 1.5 Hz, 1H), 5.42 (d, J = 1.4 Hz, 1H), 4.79 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 4.41 (d, J = 1.3 Hz, 1H), 3.79 (s, 3H), 2.51 (d, J = 1.4 Hz, 1H), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 171.3 (+), 168.4 (+), 164.4 (+), 137.5 (+), 128.4 (−), 127.8 (−), 127.7 (−), 99.7 (−), 87.8 (−), 79.9 (+), 76.0 (+), 73.5 (−), 71.2 (+), 55.9 (−), 44.0 (+), 22.6 (−), 20.3 (−); IR (neat) 1720, 1643, 1093 cm^{-1}. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.40; H, 6.83.

6-[2-Benzyloxy-1,1-dimethyl-4-(4,4,5,5-tertamethyl[1,3,2]-dioxaborolan-2-yl)-but-3-enyl]-4-methoxy-pyran-2-one (37). To a solution of borane−dimethyl sulfide complex (0.06 mL, 10.0 M, 0.6 mmol) in DME (1.5 mL) at 0 °C was added cyclohexene (0.121 mL, 99 mg, 1.2 mmol). After 15 min, the mixture was allowed to reach rt and the resulting white suspension was stirred for 1 h and then cooled to 0 °C. Solid **34** (0.156 g, 0.5 mmol) was added in one portion. The mixture was stirred at rt for 3 h during which time the white solid gradually dissolved. The reaction was then cooled to 10 °C and trimethylamino *N*-oxide (TMANO, 90 mg, 1.2 mmol) was

added in one portion resulting in an exothermic reaction. After 10 min, the cold-water bath was removed and the mixture was stirred for 2 h at rt. At this time, pinacol (60 mg, 0.5 mmol) was added and the mixture was stirred for 16 h after which the solvent was removed in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate, 5:1) to afford borate **37** (0.207 g) as a yellow oil that was contaminated with some impurities, but was suitable to be used directly in the next reaction (i.e., Suzuki coupling) without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.16 (m, 5H), 6.47 (dd, J = 18.2, 6.5 Hz, 1H), 5.88 (s, 1H), 5.73 (d, J = 18.0 Hz, 1H), 5.39 (s, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.24 (d, J = 11.9 Hz, 1H), 4.15 (d, J = 6.8 Hz, 1H), 3.79 (s, 3H).

6-[(2*R*),(7*S*),(11*R*)-2-Benzyloxy-1,1,5,7,9,11-hexamethyl-heptadeca-3,5,8-trienyl]-4-methoxy-pyran-2-one (38). To a solution of crude pinacol borate **37** (0.199 g, 0.452 mmol) in THF (0.5 mL) at rt was added KOH (0.91 mL, 1.0 M solution). After 5 min, a solution of **28** (0.197 g, 0.543 mmol) and Pd-$(PPh_3)_4$ (42 mg, 0.036 mmol, 8 mol %) in THF (2 mL) was added via cannula. The mixture was heated to 65 °C for 70 min, cooled to rt, and diluted with ether (30 mL). The mixture was washed with brine (2×), dried over anhydrous $MgSO_4$, and filtered. The solvent was removed in vacuo and the crude residue was chromatographed on silica gel (hexane/ethyl acetate, 5:1) to give **38** (0.156 g, 57% from **34**) as a brown oil. $[\alpha]^{24}_D$ +21.7 (*c* 2.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.18 (m, 5H), 6.23 (d, J = 15.7 Hz, 1H), 5.90 (d, J = 1.8 Hz, 1H), 5.45−5.37 (m, 3H), 5.02 (d, J = 8.8 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.28 (d, J = 12.1 Hz, 1H), 4.10 (d, J = 8.5 Hz, 1H), 3.79 (s, 3H), 3.43−3.37 (m, 1H), 1.98 (dd, J = 13.2, 6.4 Hz, 1H), 1.78 (s, 3H), 1.77−1.73 (m, 1H), 1.63 (s, 3H), 1.60−1.52 (m, 1H), 1.32−1.20 (m, 13H), 1.17 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.91 (t, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) APT δ 171.4 (+), 170.5 (+), 164.7 (+), 140.6 (−), 139.1 (−), 138.7 (+), 132.7 (+), 130.6 (+), 130.4 (−), 128.2(−), 127.4 (−), 127.3 (−), 122.1 (−), 99.2 (−), 87.4 (−), 84.2 (−), 70.4 (+), 55.7 (−), 47.8 (+), 44.2 (+), 36.7 (+), 32.1 (−), 31.9 (+), 30.7 (−), 29.6 (+), 26.9 (+), 22.8 (−), 22.7 (+), 21.7 (−), 20.3 (−), 19.5 (−), 16.2 (−), 14.1 (−), 12.7 (−); IR (neat) 2970, 2924, 2857, 1727, 1644, 1570, 1453, 1403 cm^{-1}; HRMS *m*/*z* calcd for $C_{36}H_{52}O_4$ (M^+) 548.3859, found 548.3866.

Acknowledgment. This work was supported by funding from NSERC Canada and the Ontario Research and Development and Challenge Fund.

Supporting Information Available: Proton and/or carbon NMR spectra are included for compounds **14**, **22**, **23**, **24**, **25**, **26**, **27**, and **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034371K