JOC*Article*

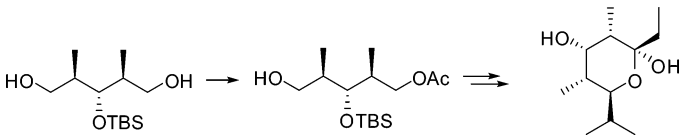
Enantioselective Synthesis of the Alcohol Moiety of Dolabriferol

Nicholas Pelchat, Dave Caron, and Robert Chênevert*

Département de chimie, CREFSIP, Faculté des sciences et de génie, Université Laval, Québec (Qc), Canada, G1K 7P4

robert.chenevert@chm.ulaval.ca

Received July 12, 2007



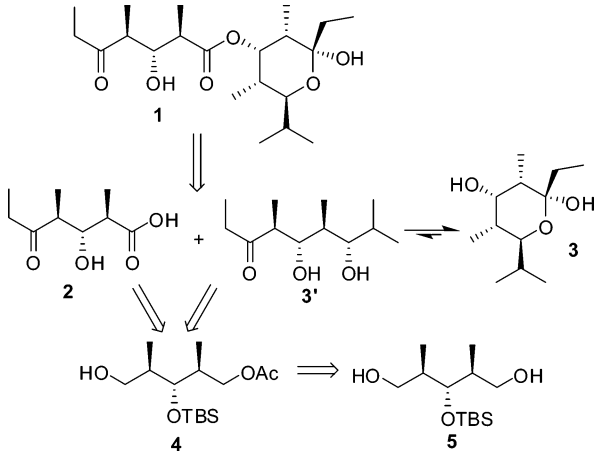
Dolabriferol is a marine polypropionate characterized by an unusual noncontiguous carbon backbone. The two polypropionate subunits are linked by an ester function. The protected alcohol moiety of dolabriferol was synthesized via the enzymatic desymmetrization of *meso*-(anti−anti)-2,4-dimethyl-1,3,5-pentanetriol.

Introduction

In 1996, Gavagnin and co-workers[1] reported the isolation of dolabriferol **1** (Scheme 1) from the anaspidean mollusk *Dolabrifera dolabrifera*. The structure was elucidated by spectral methods, and the relative configuration was unambiguously established by single-crystal X-ray analysis. The absolute stereochemistry was not assigned, and because of its limited availability, its biological activity has not been explored.

Dolabriferol is a member of a large class of secondary metabolites sharing a polyketide/polypropionate biosynthesis.[2] These natural products are known to possess a wealth of biological and pharmacological activities, including antibiotic, antifungal, anticancer, anti-inflammatory, and immunosuppressant properties.[3] The structure of dolabriferol is characterized by an unusual noncontiguous carbon backbone. The two polypropionate subunits are linked by an ester function. This structural motif is also found in a few other natural products such as baconipyrones A-D[4] and siserrone A[5]. They constitute an exception to the normal polypropionic contiguous carbon skeleton expected from polyketide biosynthesis and they have been hypothesized to arise from retro-aldol rearrangements of normal contiguous polypropionates.[5,6]

SCHEME 1. Retrosynthetic Analysis of Dolabriferol (1)



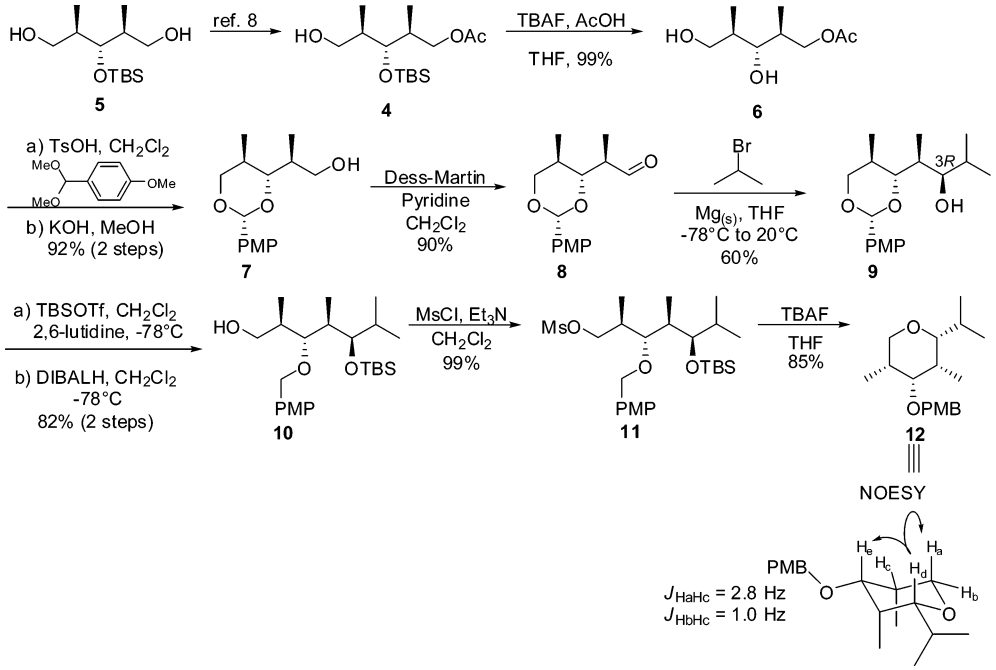
Although three approaches have been disclosed,[7−9] the total synthesis of dolabriferol has not yet been reported. Most notable among the efforts is the synthesis reported by Lister and Perkins[9] of a protected precursor to dolabriferol via the proposed retro-Claisen rearrangement.

We have already described the enantioselective synthesis of the acid moiety of dolabriferol[8] and herein we report the chemoenzymatic enantioselective synthesis of the more complex alcohol moiety of dolabriferol.

(1) Ciavatta, M. L.; Gavagnin, M.; Puliti, R.; Cimino, G.; Martinez, E.; Ortea, J.; Mattia, C. A. *Tetrahedron* **1996**, *52*, 12831−12838.
(2) (a) Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, *15*, 477−493. (b) Katz, L. *Chem. Rev.* **1997**, *97*, 2557−2575.
(3) (a) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380−416. (b) Rohr, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2847−2849.
(4) Manker, D. C.; Faulkner, D. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 5371−5374.
(5) Brecknell, D. J.; Collett, L. A.; Davies-Coleman, M. T.; Garson, M. J.; Jones, D. D. *Tetrahedron* **2000**, *56*, 2497−2502.
(6) Socorro, I. M.; Taylor, K.; Goodman, J. M. *Org. Lett.* **2005**, *7*, 3541−3544.
(7) Dias, L. C.; de Sousa, M. A. *Tetrahedron Lett.* **2003**, *44*, 5625−5628.
(8) Chênevert, R.; Courchesne, G.; Caron, D. *Tetrahedron: Asymmetry* **2003**, *14*, 2567−2571.
(9) Lister, T.; Perkins, M. V. *Org. Lett.* **2006**, *8*, 1827−1830.

10.1021/jo701524p CCC: $37.00
Published on Web 10/02/2007

SCHEME 2. Preparation of Compounds 10 and 12



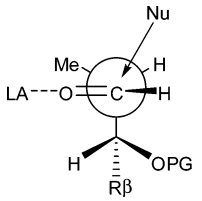
Results and Discussion

A retrosynthetic analysis of dolabriferol is outlined in Scheme 1. Bond disconnection of the ester linkage and ring opening of the cyclic hemiacetal **3** generate two closely related fragments **2** and **3′** that, in turn, can be converted retrosynthetically to the common precursors **4** and **5**. This approach exploits the structural symmetry of the polypropionate *anti*−*anti* stereotriad D.[10]

The stereoselective acylation of *meso*-3-(*tert*-butyldimethylsiloxy)-2,4-dimethyl-1,5-pentanetriol **5**[11] by vinyl acetate in the presence of *Candida rugosa* lipase in hexane provided monoester (2*R*,3*R*,4*S*)-**4** in high yield (94%) on several gram scale[8,12] (Scheme 2). Desilylation of **4** with tetrabutylammonium fluoride (TBAF) buffered with acetic acid afforded **6** in high yield. Protection of **6** as a *p*-methoxybenzylidene acetal followed by cleavage of the acetate group in KOH−MeOH gave alcohol **7**. Conversion to aldehyde **8** was achieved using the Dess-Martin periodinane reagent, which was subsequently alkylated with isopropylmagnesium bromide. Protection of the secondary hydroxyl of **9** as a TBS ether followed by a regioselective reduction of the *p*-methoxybenzylidene acetal provided **10**. The stereochemistry of the Grignard isopropenylation reaction was determined by conversion of **10** into tetrahydropyran **12** via mesylation to give **11**, desilylation, and ring closure. The illustrated NOESY interactions between Ha, Hd, and He, together with the small vicinal coupling constants between Ha−Hc (axial−equatorial, 2.8 Hz) and Hb−Hc (equatorial−equatorial, 1.0 Hz), establish the configuration of the C-3 stereocenter of **9** as (*R*)-(1,2 *syn*, 1,3 *anti*).

We initially surmised that the configuration was (*S*), arising from an addition of the nucleophile on the Si face of the chelated carbonyl function. The configuration of **9** may be rationalized in terms of the stereochemical model for merged 1,2- and 1,3-asymmetric induction proposed by Evans et al.[13] (Scheme 3). The stereochemistry at the C-3 center is epimeric to the natural product fragment and, as a consequence, an inversion of configuration is necessary. Ketone **13** was prepared in nearly quantitative yield by oxidation of alcohol **9** with the Dess-Martin periodinane (Scheme 4). Reduction with $LiAlH_4$ proceeded with the desired stereoselectivity to (3*S*)-**14** (dr = 10/1). This inversion of configuration was inspired by a similar reaction sequence reported by Lautens and Stammers.[14] Here again, the outcome of the reaction is in accordance with the model depicted in Scheme 3 where the aldehydic hydrogen is replaced by an isopropyl and the nucleophile is a hydride, thus leading to overall inversion of configuration. The transformations of **14** followed a route similar to that of its diastereomer **9**. Silylation of **14** with TBSOTf followed by DIBALH-induced acetal opening provided **15**.

SCHEME 3. Stereochemical Model for 1,2- and 1,3-Asymmetric Induction[a]



[a] LA, Lewis acid; Nu, nucleophile; PG, protecting group.

Conversion of **15** into the protected alcohol moiety of dolabriferol **18** was readily accomplished in four steps (Scheme 4). Oxidation of alcohol **15** by the Dess-Martin periodinane, followed by Grignard addition of ethylmagnesium bromide to

(10) (a) Koskinen, A. M. P.; Karisalmi, K.; *Chem. Soc. Rev.* **2005**, *34*, 677−690. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1096−1109. (c) Hoffman, R. W.; Dahmann, G.; Andersen, M. W. *Synthesis* **1994**, 629−638.

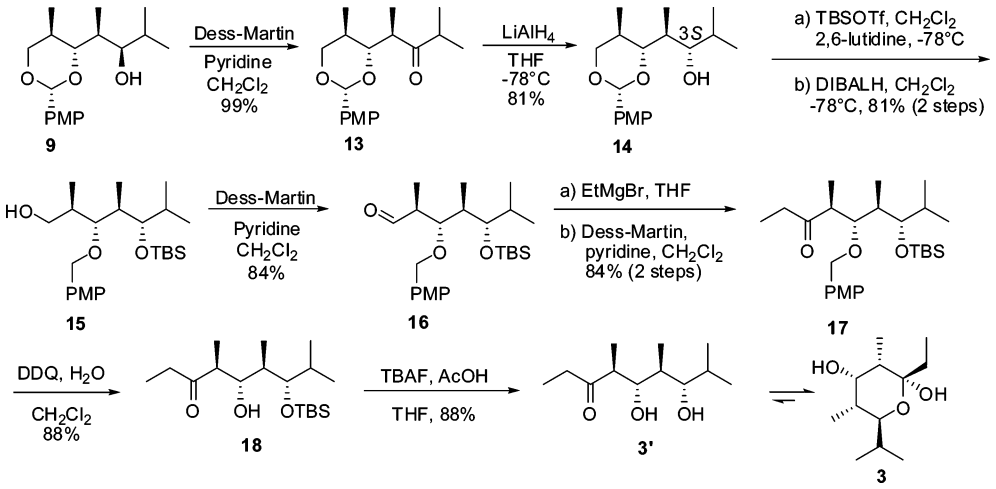
(11) Harada, T.; Inoue, A.; Wada, I.; Uchimura, J.; Tanaka, S.; Oku, A. *J. Am. Chem. Soc.* **1993**, *115*, 7665−7674.

(12) Chênevert, R.; Courchesne, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2093−2096.

(13) (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343. (b) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729−732.

(14) Lautens, M.; Stammers, T. A. *Synthesis* **2002**, *14*, 1993−2012.

SCHEME 4. Preparation of the Alcohol Moiety of Dolabriferol (3)



the resulting aldehyde **16**, furnished a diastereomeric mixture of alcohols, which were oxidized to ketone **17**. Compound **18** was obtained by oxidative cleavage of the *p*-methoxybenzyl ether with DDQ. Last, the silyl protecting group was cleaved to produce hemiacetal **3**. The spectroscopic data of **3** were in good agreement with those reported by Dias and de Sousa,[7] who have prepared the opposite enantiomer via an independent route.

Conclusion

In conclusion, the enantioselective synthesis of the alcohol moiety of dolabriferol has been achieved in 14 steps with an 18% overall yield. Both the alcohol and acid subunits of dolabriferol have been prepared from the same chiral starting material **4** obtained by enzymatic desymmetrization.[15]

Experimental Section

(2*S*,3*R*,4*R*)-3,5-Dihydroxy-2,4-dimethylpentyl Acetate (6). To a solution of monoacetate **4** (101.4 mg, 0.333 mmol) in anhydrous THF (5 mL) was added glacial acetic acid (63 μL, 1.1 mmol) and the solution was stirred for 5 min at room temperature. Then, tetrabutylammonium fluoride (480 mg, 1.83 mmol) was added and the mixture was stirred at rt for 12 h. The volatiles were evaporated and the crude product was purified by flash chromatography (ethyl acetate/hexanes, 3:7) to give diol **6** (63.0 mg, 99%) as a colorless oil. $[\alpha]_D^{22}$ −26.5 (*c* 1.24, C_6H_6); $[\alpha]_D^{22}$ −21.14 (*c* 1.99, CH_2Cl_2); lit.[16] $[\alpha]_D^{22}$ 26 (*c* 4, CH_2Cl_2) for the complementary enantiomer; IR (neat) 3413, 2967, 1739, 1245, 1113, 1068, cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.78 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 1.61 (m, 1H), 1.65 (s, 3H), 1.86 (m, 1H), 3.18 (dd, J = 5.6 and 6.4 Hz, 1H), 3.30 (dd, J = 6.6 and 10.7 Hz, 1H), 3.51 (dd, J = 3.6 and 10.7 Hz, 1H), 4.17 (dd, J = 6.6 and 11.0 Hz, 2H), 4.27 (dd, J = 4.6 and 11.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 14.2, 14.9, 20.4, 35.9, 36.8, 66.1, 66.8, 78.9, 170.9; HRMS (CI, NH_3) *m*/*z* calcd for $C_9H_{19}O_4$ (MH^+) 191.1283, found 191.1280.

(*S*)-2-((2*R*,4*S*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propan-1-ol (7). To a solution of diol **6** (56 mg, 0.294 mmol) and *p*-methoxybenzaldehyde dimethyl acetal (254 μL, 1.47 mmol) in anhydrous CH_2Cl_2 (17 mL) was added *p*-toluenesulfonic acid monohydrate (5.6 mg, 0.029 mmol). The solution was stirred for 4 h at rt before the reaction was quenched by the addition of KOH (165 mg, 2.94 mmol). After 10 min at rt, methanol (17 mL) was added and the solution was stirred for 3.5 h. The volatiles were evaporated and the residue was dissolved in ether (50 mL) and washed twice with saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (gradient, 5% steps, ethyl acetate/hexanes, 15:85 to 60:40) to give **7** (72.0 mg, 92% for two steps) as a white solid. mp: 96−97 °C; $[\alpha]_D^{22}$ −22.7 (*c* 1.24, C_6H_6); IR (KBr) 3420, 3045, 2968, 1174, 1118, 1065 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.32 (d, J = 3.4 Hz, 3H), 1.16 (d, J = 7.2 Hz, 3H), 1.68 (m, 1H), 1.98 (m, 1H), 2.08 (s, 1H), 3.10 (dd, J = 11.2 and 11.0 Hz, 1H), 3.13 (dd, J = 2.2 and 10.2 Hz, 1H), 3.25 (s, 3H), 3.60 (dd, J = 4.8 and 11.2 Hz, 1H), 3.76 (dd, J = 4.0 and 11.2 Hz, 1H), 3.88 (dd, J = 4.8 and 11.2 Hz, 1H), 5.25 (s, 1H), 6.77 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 11.9, 15.3, 31.4, 35.8, 54.6, 63.5, 72.9, 87.5, 101.7, 113.7, 127.5, 131.7, 160.2; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{15}H_{22}O_4$ (M^+) 266.1518, found 266.1512.

(*R*)-2-((2*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propanal (8). To a solution of alcohol **7** (142.2 mg, 0.522 mmol) and pyridine (338 μL, 4.18 mmol) in anhydrous CH_2Cl_2 (4.5 mL) was added Dess-Martin periodinane (244 mg, 0.575 mmol). The solution was stirred for 3 h at rt before the addition of a saturated $NaHCO_3$ aqueous solution containing 25% of sodium thiosulfate and stirred for an additional 15 min. The reaction mixture was diluted with ether (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 50 mL). The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (ethyl acetate/hexanes, 1:4) to give aldehyde **8** (127.0 mg, 90%) as a colorless oil. $[\alpha]_D^{22}$ −26.74 (c 0.93, C_6H_6); IR (neat) 3068, 2964, 1724, 1372, 1171, 1087, cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.29 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 7.2 Hz, 3H), 1.87 (m, 1H), 2.26 (qdd, J = 7.2, 2.4 and 2.4 Hz, 1H), 3.04 (dd, J = 11.2 and 11.2 Hz, 1H), 3.19 (dd, J = 2.4 and 10.4 Hz, 1H), 3.27 (s, 3H), 3.80 (dd, J = 4.8 and 11.2 Hz, 1H), 5.23 (s, 1H), 6.81 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 9.65 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 11.0, 11.7, 31.5, 47.8, 54.6, 72.5, 84.3, 101.5, 113.6, 127.7, 131.5, 160.3, 202.2; HRMS (CI, NH_3) *m*/*z* calcd for $C_{15}H_{21}O_4$ (MH^+) 265.1440, found 265.1432.

(2*S*,3*R*)-2-((2*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methylpentan-3-ol (9). To a suspension of powdered Mg (0.457 g, 18.78 mmol) in anhydrous THF (40 mL) was added dropwise 2-bromopropane (1.73 mL, 18.42 mmol) under a dry argon atmosphere. After being stirred for 1 h at rt, the mixture was cooled to −78 °C, and a solution of aldehyde **8** (0.974 g, 3.68 mmol) in anhydrous THF (33 mL) was added dropwise via cannula. The mixture was allowed to warm to rt and was stirred for 12 h. A

(15) (a) Garcia-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313−354. (b) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769−3826.

(16) Domon, L.; Vogeleisen, F.; Uguen, D. *Tetrahedron Lett.* **1996**, *37*, 2773−2776.

saturated aqueous solution of NH_4Cl (30 mL) was slowly added and the mixture was extracted with ether (300 mL). The organic phase was washed with brine, dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (gradient, 4.5% steps, ethyl acetate/hexanes, 1:9 to 3:2) to give alcohol **9** (0.693 g, 60%) as a white solid. mp: 92 °C; $[\alpha]_D^{22}$ −2.8 (*c* 0.98, C_6H_6); IR (KBr) 3513, 3076, 2973, 1518, 1463, 1167, 1068 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.30 (d, J = 6.8 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.29 (d, J = 6.4 Hz, 3H), 1.83 (m, 2H), 2.02 (m, 1H), 3.11 (dd, J = 10.8 and 10.8 Hz, 1H), 3.20 (dd, J = 2.0 and 10.4 Hz, 1H), 3.23 (s, 3H), 3.49 (br s, 1H), 3.60 (d, J = 8.8 Hz, 1H), 3.87 (dd, J = 4.6 and 10.8 Hz, 1H), 5.22 (s, 1H), 6.72 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 10.9, 11.7, 18.9, 20.3, 30.6, 31.3, 33.9, 54.5, 72.7, 75.8, 89.3, 102.2, 113.8, 127.4, 131.3, 160.3; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{18}H_{28}O_4$ (M^+) 308.1987, found 308.1991.

(2*R*,3*R*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-2,4,6-trimethylheptan-1-ol (10). To a solution of alcohol **9** (36.6 mg, 0.119 mmol) in CH_2Cl_2 (1 mL) at −78 °C were added successively 2,6-lutidine (47.4 mg, 0.442 mmol) and TBSOTf (81 mg, 0.306 mmol). After being stirred at −78 °C for 2 h, the solution was allowed to warm at rt over a 5 h period. The reaction was quenched by the addition of 2-propanol (0.25 mL) and the mixture stirred for 1 h. The mixture was diluted with ether (50 mL) and the organic phase was washed with saturated aqueous NH_4Cl (75 mL) and brine (75 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (ethyl acetate/hexanes, 7:93) to give the TBS derivative of **9** (49 mg, 97%) as a colorless oil. HRMS (CI, NH_3) *m*/*z* calcd for $C_{24}H_{43}O_4Si$ (MH^+) 423.2930, found 423.2924. The product is a mixture of diastereomeric benzylidene acetals and was used for the next step without further analysis. To a solution of the purified TBS derivative of **9** (540 mg, 1.28 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added dropwise DIBALH (1.5 M in toluene, 3.41 mL, 5.11 mmol). After the mixture was stirred at −78 °C for 2 h, the reaction was warmed to room temperature and the mixture stirred for an additional 1 h. The reaction was quenched by the addition of a saturated aqueous solution of Rochelle's salt (10 mL). The mixture was diluted with ether (100 mL), washed with a saturated aqueous solution of Rochelle's salt (100 mL) and brine (200 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (gradient, 5% steps; ethyl acetate/hexanes, 1:9 to 3:7) to give alcohol **10** (459 mg, 84%) as a colorless oil. $[\alpha]_D^{22}$ −12.60 (*c* 3.42, C_6H_6); IR (neat) 3440, 3034, 2957, 1463, 1250, 1038 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.09 (s, 3H), 0.12 (s, 3H), 0.90 (d, J = 3.2 Hz, 3H), 0.92 (d, J = 3.2 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.02 (s, 9H), 1.11 (d, J = 7.2 Hz, 3H), 1.75 (m, 1H), 1.86 (m, 1H), 2.03 (m, 1H), 2.59 (br s, 1H), 3.29 (s, 3H), 3.32 (dd, J = 3.6 and 8.0 Hz, 1H), 3.61 (dd, J = 4.8 and 10.8 Hz, 1H), 3.81 (m, 2H), 4.50 (d, J = 10.6 Hz, 1H), 4.53 (d, J = 10.6 Hz, 1H), 6.76 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ −3.4, −3.1, 12.9, 16.7, 18.3, 18.9, 19.3, 26.5, 34.6, 36.9, 39.1, 54.8, 64.9, 75.0, 76.8, 87.4, 114.3, 129.4, 130.9, 159.9; HRMS (CI, NH_3) *m*/*z* calcd for $C_{24}H_{45}O_4Si$ (MH^+) 425.3087, found 425.3080.

(2*R*,3*R*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-2,4,6-trimethylheptyl Methanesulfonate (11). To a solution of alcohol **10** (19.5 mg, 0.046 mmol) and triethylamine (24 μL, 0.168 mmol) in anhydrous CH_2Cl_2 (1 mL) was added methanesulfonyl chloride (9.8 μL, 0.126 mmol). The reaction mixture was stirred overnight at rt. The reaction mixture was then partitioned between ether (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (gradient, 5% steps; ethyl acetate/hexanes, 1:9 to 3:7) to give mesylate **11** (23 mg, 99%) as a colorless oil. $[\alpha]_D^{22}$ −11.8 (*c* 1.15, C_6H_6); IR (neat) 3063, 2957, 1734, 1587, 1250, 1178, 1052 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.09 (s, 3H), 0.12 (s, 3H), 0.90 (d, J = 5.6 Hz, 3H), 0.92 (d, J = 6.0 Hz, 3H), 0.98 (d, J = 7.2 Hz, 3H), 1.03 (s, 9H), 1.04 (d, J = 2.4 Hz, 3H), 1.73 (m, 1H), 1.97 (m, 1H), 2.15 (s, 3H), 2.17 (m, 1H), 3.26 (dd, J = 3.4 and 7.8 Hz, 1H), 3.30 (s, 3H), 3.77 (dd, J = 3.0 and 4.6 Hz, 1H), 4.08 (dd, J = 7.6 and 10.0 Hz, 1H), 4.35 (dd, J = 4.8 and 10.0 Hz, 1H), 4.46 (d, J = 11.0 Hz, 1H), 4.51 (d, J = 11.0 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ −3.5, −3.2, 12.6, 16.2, 18.3, 18.9, 19.4, 26.5, 34.4, 35.7, 36.5, 38.9, 54.8, 71.8, 74.6, 76.9, 84.5, 114.2, 129.3, 131.1, 159.8; HRMS (CI, NH_3) *m*/*z* calcd for $C_{25}H_{47}O_6SSi$ (MH^+) 503.2862, found 503.2851.

(2*R*,3*S*,4*R*,5*R*)-2-Isopropyl-4-(4-methoxybenzyloxy)-3,5-dimethyltetrahydro-2*H*-pyran (12). To a solution of mesylate **11** (83 mg, 0.165 mmol) in anhydrous THF (1.5 mL) was added tetrabutylammonium fluoride in THF (1 M, 1.4 mL, 1.4 mmol). The mixture was stirred at room temperature for 12 d. The solvent was evaporated and the crude product was purified by flash chromatography (ethyl acetate/hexanes, 1: 9) to give compound **12** (40 mg, 85%) as a white solid. mp: 65−66 °C; $[\alpha]_D^{22}$ −11.1 (*c* 1.75, C_6H_6); IR (KBr) 3036, 2968, 1463, 1252, 1116, 1029 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.72 (d, J = 6.4 Hz, 3H), 1.13 (d, J = 7.2 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H), 1.21 (d, J = 7.2 Hz, 3H), 1.77 (m, 1H), 1.84 (m, 1H), 2.11 (m, 1H), 2.55 (dd, J = 2.4 and 9.6 Hz, 1H), 3.25 (dd, J = 2.8 and 11.5 Hz, 1H), 3.32 (s, 3H), 3.37 (dd, J = 5.4 and 5.4 Hz, 1H), 3.73 (dd, J = 1.0 and 11.5 Hz, 1H), 4.34 (s, 2H), 6.84 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 8.7, 14.1, 18.3, 20.6, 29.7, 33.2, 34.5, 54.8, 69.0, 72.8, 79.1, 86.6, 114.1, 129.1, 131.6, 159.7; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{18}H_{28}O_3$ (M^+) 292.2038, found 292.2043.

(*R*)-2-((2*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methylpentan-3-one (13). Ketone **13** was prepared following the procedure used for **8**. Ketone **13** (0.680 g, 99%) was obtained as a colorless oil. $[\alpha]_D^{22}$ −46.20 (*c* 2.11, C_6H_6); IR (neat) 3044, 2969, 1715, 1250, 1171, 1034 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.37 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 3.2 Hz, 3H), 0.94 (d, J = 3.6 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.79 (m, 1H), 2.70 (m, 2H), 3.04 (t, J = 11.2 Hz, 1H), 3.18 (s, 3H), 3.35 (dd, J = 4.4 and 5.6 Hz, 1H), 3.75 (dd, J = 4.8 and 6.4 Hz, 1H), 5.23 (s, 1H), 6.75 (d, J = 9.2 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 12.5, 13.3, 18.6, 18.7, 32.7, 39.0, 49.2, 54.6, 72.7, 84.9, 101.4, 113.6, 127.6, 131.7, 160.2, 214.8; HRMS (CI, NH_3) *m*/*z* calcd for $C_{18}H_{27}O_4$ (MH^+) 307.1909, found 307.1914.

(2*S*,3*S*)-2-((2*R*,4*R*,5*R*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-4-methylpentan-3-ol (14). To a solution of ketone **13** (0.680 g, 2.22 mmol) in anhydrous THF (73 mL) at −78 °C was added LAH (0.163 g, 4.29 mmol). After the mixture was stirred for 5 h at −78 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The solvent was evaporated and the residue was dissolved in ether (200 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (ethyl acetate/hexanes, 1:4) to give alcohol **14** (0.536 g, 81%) as a colorless oil. $[\alpha]_D^{22}$ −11.84 (*c* 1.47, C_6H_6); IR (neat) 3530, 3044, 2961, 1248, 1171, 1112, 1035 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.46 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 2.4 Hz, 3H), 0.87 (d, J = 2.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 1.64 (m, 1H), 1.86 (m, 1H), 2.13 (br s, 1H), 2.32 (m, 1H), 3.09 (t, J = 11.2 Hz, 1H), 3.18 (s, 3H), 3.26 (dd, J = 2.0 and 8.0 Hz, 1H), 3.48 (br d, J = 9.2 Hz, 1H), 3.87 (dd, J = 4.8 and 6.4 Hz, 1H), 5.29 (s, 1H), 6.73 (d, J = 9.2 Hz, 2H), 7.52 (d, J = 9.6 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 12.4, 14.6, 16.7, 20.6, 30.5, 32.8, 37.7, 54.6, 73.5, 77.3, 88.4, 101.7, 113.7, 127.6, 131.9, 160.2; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{18}H_{28}O_4$ (M^+) 308.1987, found 308.1990.

(2*R*,3*R*,4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-2,4,6-trimethylheptan-1-ol (15). Compound **15** was prepared following the procedure used for **10**. Flash chromatography (ethyl acetate/hexanes, 7:93) provided **15** (0.591 g, 81% for two steps) as a colorless oil. $[\alpha]_D^{22}$ −9.56 (*c* 2.29, C_6H_6); IR (neat) 3432, 3036, 2956, 1249, 1173, 1040 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.87 (d, J = 4.8 Hz, 3H), 0.89 (d, J = 4.4 Hz, 3H), 0.95 (s, 9H), 0.97 (d, J = 6.8 Hz, 3H), 1.04

(d, J = 7.2 Hz, 3H), 1.75 (m, 1H), 1.87 (m, 1H), 2.11 (m, 1H), 2.29 (br s, 1H), 3.21 (s, 3H), 3.24 (dd, J = 3.6 and 4.0 Hz, 1H), 3.54 (dd, J = 4.8 and 6.4 Hz, 1H), 3.74 (m, 2H), 4.37 (dd, J = 8.4 and 10.8 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, C_6D_6) δ −4.4, −3.7, 12.5, 16.1, 18.4, 18.5, 22.4, 26.2, 30.5, 37.1, 42.8, 54.6, 64.7, 74.6, 77.3, 86.1, 114.1, 129.2, 130.8, 159.7; HRMS (CI, NH_3) m/z calcd for $C_{24}H_{45}O_4Si$ (MH^+) 425.3087, found 425.3084.

(2*S*,3*S*,4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-2,4,6-trimethylheptanal (16). Aldehyde **16** was prepared following the procedure used for **8**. Flash chromatography (ethyl acetate/hexanes, 6:94) provided **16** (0.440 g, 84%) as a colorless oil. $[\alpha]_D^{22}$ 2.78 (c 1.71, C_6H_6); IR (neat) 3029, 2956, 1720, 1249, 1172, 1046 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ −0.02 (s, 3H), −0.01 (s, 3H), 0.77 (d, J = 7.2 Hz, 3H), 0.83 (d, J = 7.2 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.92 (s, 9H), 1.01 (d, J = 7.2 Hz, 3H), 1.74 (m, 1H), 2.05 (m, 1H), 2.43 (qd, J = 1.6 and 2.0 Hz, 1H), 3.22 (s, 3H), 3.57 (dd, J = 2.8 and 5.6 Hz, 1H), 3.67 (dd, J = 4.0 and 4.4 Hz, 1H), 4.19 (d, J = 11.2 Hz, 1H), 4.21 (d, J = 11.2 Hz, 1H), 6.73 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 9.65 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ −4.3, −3.8, 10.5, 12.2, 18.4, 18.5, 21.7, 26.2, 30.6, 41.6, 48.4, 54.6, 72.2, 77.4, 81.9, 113.9, 129.2, 130.6, 159.7, 202.5; HRMS (CI, NH_3) m/z calcd for $C_{24}H_{43}O_4Si$ (MH^+) 423.2930, found 423.2920.

(4*S*,5*S*,6*R*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-4,6,8-trimethylnonan-3-one (17). To a solution of aldehyde **16** (0.440 g, 1.04 mmol) in anhydrous THF (15 mL) at −78 °C was added ethylmagnesium bromide (1 M in THF, 3.13 mL, 3.13 mmol). After being stirred for 4 h at −78 °C, the solution was allowed to warm to room temperature and the reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL). Ether was added (150 mL) and the organic phase washed with saturated aqueous NH_4Cl (150 mL), saturated aqueous $NaHCO_3$ (2 × 75 mL), and brine (2 × 75 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (ethyl acetate/hexanes, 1:19) to give an inseparable mixture of alcohol diastereoisomers (0.408 g, 87%) as a colorless oil. HRMS (CI, NH_3) m/z calcd for $C_{26}H_{49}O_4Si$ (MH^+) 453.3400, found 453.3393. The mixture was oxidized by the Dess-Martin periodinane following the procedure used for **8**. Flash chromatography (ethyl acetate/hexanes, 1:19) provided **17** (0.391 g, 96%) as a colorless oil. $[\alpha]_D^{22}$ 17.18 (c 1.56, C_6H_6); IR (neat) 3064, 2956, 1715, 1249, 1173, 1043 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.04 (s, 3H), 0.10 (s, 3H), 0.90 (d, J = 2.0 Hz, 3H), 0.92 (d, J = 2.4 Hz, 3H), 0.94−1.06 (m, 9H), 0.96 (s, 9H), 1.93 (m, 1H), 2.02 (m, 1H), 2.14 (m, 1H), 2.25 (m, 1H), 2.65 (m, 1H), 3.21 (s, 3H), 3.73 (m, 2H), 4.31 (dd, J = 8.4 and 10.4 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ −4.3, −3.6, 7.7, 11.9, 12.9, 17.9, 18.5, 22.1, 26.2, 30.8, 35.9, 42.4, 48.4, 54.6, 73.2, 76.8, 83.2, 113.9, 129.3, 131.0, 159.6, 211.5; HRMS (CI, NH_3) m/z calcd for $C_{26}H_{47}O_4Si$ (MH^+) 451.3243, found 451.3229.

(4*S*,5*S*,6*R*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-4,6,8-trimethylnonan-3-one (18). To a solution of compound **17** (85.1 mg, 0.189 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added water (0.5 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (51.5 mg, 0.227 mmol). After being stirred for 1 h at room temperature, the mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL). Ethyl acetate (70 mL) was added and the organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography (ethyl acetate/hexanes, 1:19) to give compound **18** (55 mg, 88%) as a colorless oil. $[\alpha]_D^{22}$ −16.55 (c 1.10, C_6H_6); IR (neat) 3497, 2958, 1252, 1114, 1048 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ −0.02 (s, 3H), −0.01 (s, 3H), 0.80 (d, J = 7.2 Hz, 3H), 0.85−0.93 (m, 9H), 0.90 (s, 9H), 1.04 (d, J = 7.2 Hz, 3H), 1.81 (m, 2H), 2.00 (m, 1H), 2.16 (m, 1H), 2.47 (m, 1H), 3.36 (m, 1H), 3.60 (d, J = 7.6 Hz, 1H), 3.79 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ −4.8, −4.2, 7.4, 13.8, 15.1, 18.3, 18.7, 21.2, 26.0, 31.1, 35.8, 43.3, 47.3, 77.3, 78.7, 216.1; HRMS (CI, NH_3) m/z calcd for $C_{18}H_{39}O_3Si$ (MH^+) 331.2668, found 331.2665.

(2*R*,3*S*,4*S*,5*R*,6*S*)-2-Ethyl-6-isopropyl-3,5-dimethyltetrahydro-2*H*-pyran-2,4-diol (3). Hemiacetal **3** was prepared following the procedure used for **6**. Hemiacetal **3** (36.5 mg, 88%) was obtained as a white solid. mp: 86 °C; $[\alpha]_D^{22}$ −66.2 (c 1.82, $CHCl_3$), lit.[7] $[\alpha]_D^{22}$ 52.8 (c 1.04, $CHCl_3$) for the complementary enantiomer; IR (KBr) 3254, 2946, 2932, 1485, 1158, 1132, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 7.6 Hz, 3H), 0.92 (d, J = 7.2 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 7.2 Hz, 3H), 1.54−1.71 (m, 4H), 1.78−1.86 (m, 1H), 3.04 (d, J = 7.6 Hz, 1H, OH), 3.52 (br s, 1H, OH), 3.59 (dd, J = 2.0 and 12.8 Hz, 1H), 3.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.5, 13.4, 13.9, 14.4, 20.7, 28.3, 32.5, 37.9, 39.5, 72.3, 76.3, 100.5.

Acknowledgment. The authors would like to acknowledge the support of this work by the Natural Sciences and Engineering Research Council of Canada (NSERC).

Supporting Information Available: General experimental procedures and ^{1}H and ^{13}C NMR spectra for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701524P