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Enantiodivergent Formal Synthesis of (+)- and (−)-Cyclophellitol from D-Xylose Based on the Latent Symmetry Concept

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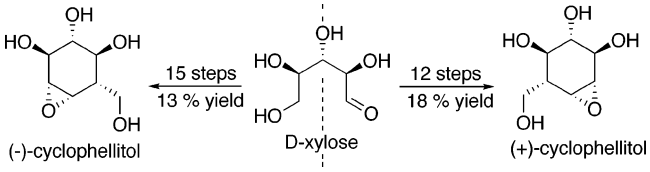
Received September 1, 2004



Formal synthesis of (+)- and (−)-cyclophellitol from D-xylose has been accomplished through utilization of the latent plane of chirality present in the starting carbohydrate. The synthetic pathway is suitable for preparation and biological evaluation of cyclophellitol analogues in both enantiomeric series.

Development of efficient chemical pathways that allow the preparation of both enantiomers of compounds of biological and medicinal significance is an important goal of synthetic organic chemistry. Enantiomers of biologically active natural products very often exhibit improved potencies or even novel activities altogether. For example, the unnatural (−)-enantiomer of the antitumor antibiotic roseophilin is 2 to 10 times more potent than the natural (+)-isomer in cytotoxicity assays.[1] (−)-Quinine is an antimalarial compound, while its quasienantiomer (+)-quinidine is an antiarrhythmic.[2] (−)-Gossypol, the enantiomer of the predominant natural (+)-isomer, has anticancer, male-contraceptive, and anti-HIV activities.[3] In addition, the switch from racemic to single enantiomer chiral pharmaceuticals is important for managing product life cycles and increasing efficacy.[4] Such processes require efficient preparation and pharmacological testing of either enantiomer of a chiral drug or drug candidate individually.

These demands can be addressed through enantioselective synthesis in which the pathway is adjusted to the production of either enantiomer of a chiral target by changing the absolute asymmetry of a chiral catalyst or auxiliary. By contrast, it has been pointed out[11s] that chemical routes emanating from "chiral pool" compounds are unsuited for this purpose, since the naturally occurring chiral molecules are usually abundant in practical quantities only in one enantiomeric form. Notwithstanding this limitation, a number of enantiodivergent approaches to complex chiral structures starting from one enantiomeric form of a "chiral pool" molecule have been reported.[5] These routes are particularly effective when the chiral source possesses a latent plane of symmetry,[5a] and simple chemical manipulation of the existing functionalities allows crossover from one enantiomeric domain to the other. Such strategies are devoid of the drawbacks associated with enzymatic or chemical asymmetric catalysis[6] and can be rather straightforward.

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10.1021/jo048459p CCC: $30.25
Published on Web 12/22/2004

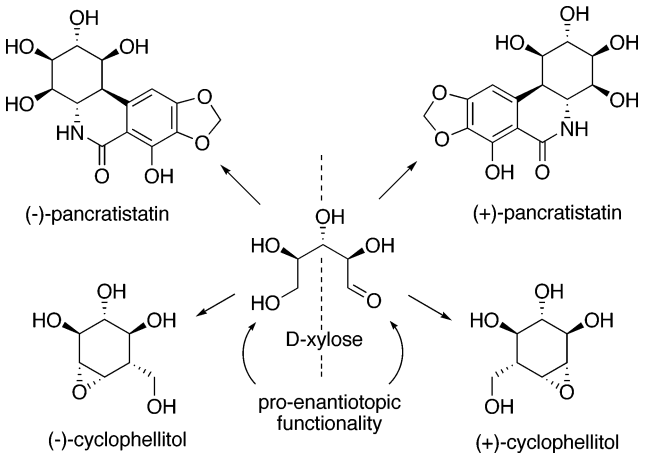


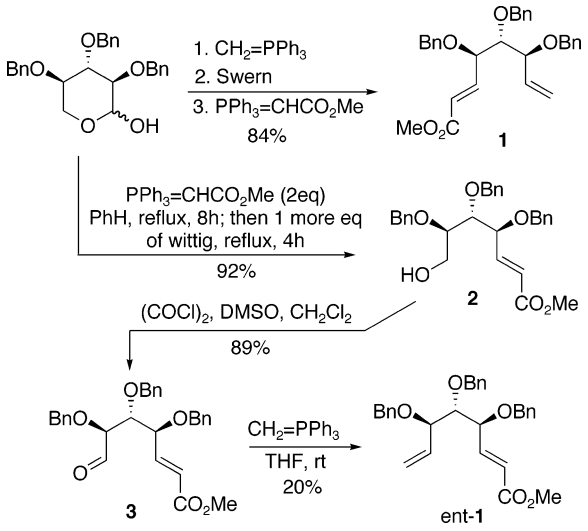
FIGURE 1. "Latent symmetry" approach for the synthesis of pancratistatin and cyclophellitol enantiomers.

While investigating novel synthetic approaches to natural cyclitols such as pancratistatin and cyclophellitol, we noticed that the starting carbohydrate, D-xylose, has a latent plane of symmetry. Therefore, both enantiomers of the cyclitol targets can be reached by exploiting the differences in chemical reactivity of the aldehyde and hydroxyl functional groups (Figure 1).[7]

The potent and diverse biological activities as well as promising medicinal applications of natural (+)-pancratistatin[8] and (+)-cyclophellitol[9] have led to a large body of synthetic effort culminating in many total syntheses of these targets and their analogues.[10,11] In addition, a synthesis of (−)-cyclophellitol has been accomplished by Trost and co-workers via the application of a dynamic kinetic asymmetric transformation process.[11s] To our knowledge, the biology of (−)-cyclophellitol or its analogues has not been investigated, despite potent glycosidase inhibitory activities found with (+)-cyclophellitol analogues in which three of the six stereocenters originally present in the natural product are inverted.[12] While (−)-pancratistatin has not been synthesized in enantiomerically pure form, the ongoing synthetic work toward this antipode has been disclosed[13] and the synthesis of (−)-7-deoxypancratistatin has been achieved by Hudlicky and co-workers.[14] Biological testing of the latter compound revealed activity similar in scope to its natural enantiomer, although of reduced magnitude.[15] These intriguing observations warrant further exploration of chemistry and biology of the above natural cyclitols and their analogues in both antipodal series. In this paper we wish to report a formal synthesis of (+)- and (−)-cyclophellitol based on the "latent symmetry" approach.

Our enantiodivergent strategy relies on the synthesis of both enantiomeric forms of enoate **1** from D-xylose. We have previously reported a straightforward preparation of **1** from tri-*O*-benzyl-D-xylose by way of Wittig methylenation, Swern oxidation, and reaction of the resulting aldehyde with $Ph_3P{=}CHCO_2Me$ (Scheme 1).[16] We explored the possibility of obtaining *ent*-**1** by directly reversing the order of the two olefination steps. Although carbohydrate derivatives free at the anomeric position react with stabilized Wittig reagents to give α,β-enoates and enones, such reactions usually suffer from the formation of cyclized *C*-glycoside products and lack of *E*-selectivity.[17] We found that performing Wittig olefination in a concentrated solution in refluxing benzene with the incremental addition of $Ph_3P{=}CHCO_2Me$ suppresses the formation of the cyclized products and gives hydroxyenoate **2** in excellent yield and *E*-selectivity (∼15:1 *E*/*Z*). Swern oxidation of **2** to give aldehyde **3** proceeds without complications. However, reaction of **3** with $CH_2{=}PPh_3$ results in complex mixtures of products under a variety of experimental conditions, possibly because of the electrophilic nature of the enoate moiety. The best experimental protocol, which provides a low (20%) yield of the desired enoate *ent*-**1**, involves a dropwise addition of an exact stoichiometric amount of the Wittig reagent to aldehyde **3** in THF. Disappointingly, the use of nonbasic titanium-based methylenation reagents[18] did not improve the outcome.

SCHEME 1



To circumvent the enoate reactivity problem, the anomeric position of tri-*O*-benzyl-D-xylose was protected to form ethyl thioacetal **4** (Scheme 2).[11q,19] Swern oxidation of the primary hydroxyl in **4** was followed by the immediate treatment of the crude aldehyde with $Ph_3P{=}CH_2$ to give a good yield of terminal olefin **5**. Unmasking the latent aldehyde in **5** with NBS/$CdCO_3$ and subjecting the crude material to reaction with $Ph_3P{=}CHCO_2Me$ cleanly provides the desired enantiomeric enoate *ent*-**1** in excellent yield. Although this sequence involves additional protection/deprotection steps, it is high yielding and scalable.

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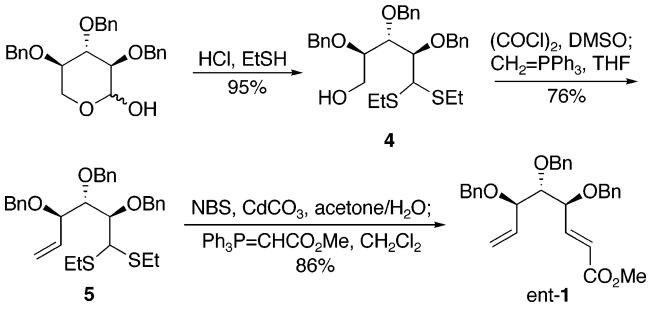
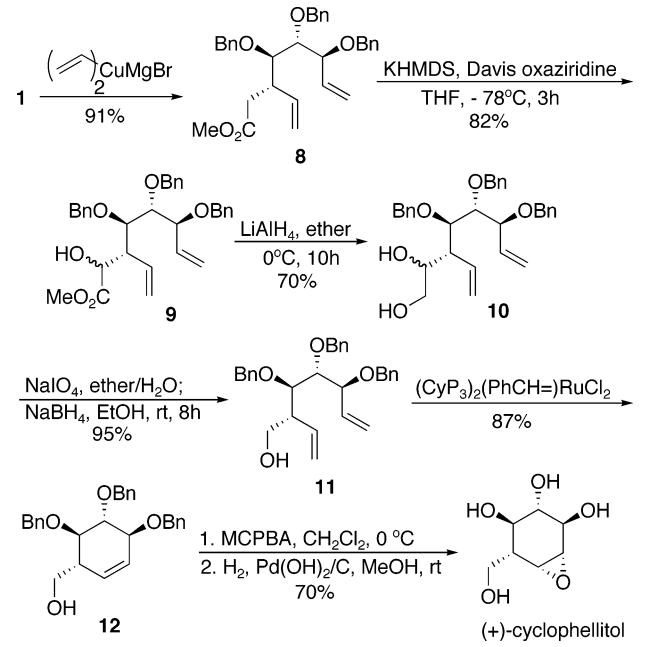
SCHEME 2



With the synthetic pathways to **1** and *ent*-**1** available we demonstrated the feasibility of accessing each cyclophellitol enantiomer by completing the synthesis of the (+)-antipode (Scheme 3). Addition of a vinylcopper reagent to enoate **1**, which has been reported previously by Ziegler and co-workers in their synthesis of (+)-cyclophellitol based on radical methodology,[11q] provides ester **8** in excellent yield and exclusive anti selectivity. Treating the potassium enolate of ester **8** with Davis oxaziridine[20] gives a 1:1 mixture of α-hydroxylated derivatives **9**, which is reduced to diols **10** in good yield. Cleavage of the vicinal diol functionality with $NaIO_4$ followed by treatment of the crude aldehyde with $NaBH_4$ gives alcohol **11** in excellent overall yield. Finally, ring-closing metathesis of unprotected alcohol **11** with the first generation Grubbs' ruthenium catalyst results in conduritol analogue **12**, whose chromatographic purification was greatly facilitated by preliminary oxidation of the ruthenium catalyst with DMSO.[21] Since the transformation of **12** to (+)-cyclophellitol by way of directed epoxidation and hydrogenolytic deprotection was previously reported by Trost and co-workers,[11r,s] this pathway constitutes a formal synthesis of the natural product. In addition to providing access to both enantiomers of cyclophellitol, the synthesis is scalable and we have performed it on a gram quantity without compromising its efficiency. These advantages make the synthetic pathway suitable for preparation of cyclophellitol analogues in both enantiomeric series for biological evaluation.

SCHEME 3



In conclusion, the application of the latent symmetry principle to D-xylose has resulted in enantiodivergent synthesis of (+)- and (−)-cyclophellitol and studies are ongoing to utilize this strategy for the synthesis of each pancratistatin enantiomer. Being the second most abundant sugar after D-glucose,[22] D-xylose has been extensively utilized as a convenient and inexpensive "chiral pool" resource in multistep syntheses of various chiral targets. However, L-xylose is rather expensive and, therefore, it is not commonly included in synthetic planning. We hope that the chemistry described here provides a partial solution to this problem and serves as an impetus for further exploitation of the latent symmetry elements contained in the structures of "chiral pool" molecules.

Experimental Section

Methyl (2*E*,4*S*,5*R*,6*R*)-4,5,6-Tri(benzyloxy)-7-hydroxy-2-heptenoate (2). A mixture of 2,3,4-tri-*O*-benzyl-D-xylopyranose (2.10 g, 5 mmol) and methyl (triphenylphosphoranylidene)-acetate (3.34 g, 10 mmol) in benzene (50 mL) was heated under reflux for 8 h. One more equivalent of methyl (triphenylphosphoranylidene)acetate (1.67 g, 5 mmol) was added and reflux was continued for 4 h. After the mixture cooled to room temperature it was evaporated under reduced pressure. The residue was presorbed on silica gel and purified by column chromatography with gradients from 20% to 40% EtOAc/hexanes to afford enoate **2** (2.19 g, 92.0%) as a colorless oil; R_f 0.55 (5% MeOH/CH_2Cl_2); $[\alpha]^{25}_D$ −1.8 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.37−7.28 (m, 15H), 6.96 (dd, *J* = 15.9, 5.8 Hz, 1H), 6.07 (dd, *J* = 15.9, 1.4 Hz, 1H), 4.69 (s, 2H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.59 (s, 2H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.25 (m, 1H), 3.74 (s, 3H), 3.70−3.66 (m, 2H), 3.63−3.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 166.5, 145.2, 138.2, 137.9, 137.5, 128.7, 128.6, 128.6, 128.2, 128.1, 127.9, 122.8, 80.7, 79.4, 78.3, 74.9, 73.0, 71.9, 61.4, 51.8; HRMS *m/z* (EI) calcd for $C_{29}H_{32}O_6$ $(M)^+$ 476.2199, found 476.2205.

Methyl (2*E*,4*S*,5*R*,6*S*)-4,5,6-Tri(benzyloxy)-7-oxo-2-heptenoate (3). To oxalyl chloride (2.3 mL of 2 M in CH_2Cl_2, 4.6 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C was added DMSO (0.69 mL, 9.7 mmol) in CH_2Cl_2 (5 mL) over 10 min and the mixture was stirred for 30 min. Hydroxyenoate **2** (1.0 g, 2.1 mmol) in CH_2Cl_2 (10 mL) was added over 10 min and the mixture was stirred for an additional 1 h. Triethylamine (1.74 mL, 11.6 mmol) in CH_2Cl_2 (10 mL) was added over 10 min and the white slurry was stirred for 30 min at −78 °C. The resulting mixture was allowed to warm to −20 °C. Water (50 mL) was added to the reaction mixture, the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was presorbed on silica gel and purified by column chromatography with gradients from 5%−20% EtOAc/hexanes to afford oxoenoate **3** (0.96 g, 96%) as a colorless oil; R_f 0.49 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 9.65 (s, 1H), 7.36−7.20 (m, 15H), 6.88 (dd, *J* = 16.0, 6.1 Hz, 1H), 6.02 (dd, *J* = 16.0, 1.4 Hz, 1H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.49 (m, 2H), 4.38 (d, *J* = 11.6 Hz, 1H), 4.27 (m, 1H), 3.88

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(m, 1H), 3.82 (ψt, J = 4.4 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 201.3, 166.3, 144.7, 137.2, 137.1, 137.0, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 123.2, 81.9, 80.8, 74.4, 73.4, 72.1, 51.7; HRMS *m/z* (EI) calcd for $C_{29}H_{30}O_6$ $(M)^+$ 474.2042, found 474.2051.

Methyl (2*E*,4*S*,5*S*,6*R*)-4,5,6-Tri(benzyloxy)-2,7-octadienoate (*ent*-1). Method 1: To a stirred suspension of methyltriphenylphosphonium bromide (0.36 g, 1 mmol) in THF (15 mL) was added BuLi (0.4 mL of 2.5 M solution in pentane, 1 mmol) dropwise at 0 °C. The mixture was stirred for 1 h at room temperature. The resulting red solution was transferred dropwise to the solution of oxoenoate **3** (0.47 g, 1 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with 1 M NH_4-Cl (10 mL) and extracted with ether (3 × 20 mL). The organic extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was presorbed on silica gel and purified by column chromatography with gradients from 10%−20% EtOAc/hexanes to afford enoate *ent*-**1** (0.096 g, 20%) as a colorless oil; R_f 0.56 (25% EtOAc/hexanes); $[\alpha]^{25}_D$ −4.16 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.18 (m, 15H), 6.86 (dd, J = 9.6, 6.3 Hz, 1H), 6.00 (dd, J = 16.0, 1.4 Hz, 1H), 5.81 (m, 1H), 5.21 (m, 2H), 4.71 (s, 2H), 4.57 (d, J = 11.5 Hz, 1H), 4.55 (d, J = 11.5 Hz, 1H), 4.34 (d, J = 11.5 Hz, 1H), 4.32 (d, J = 11.5 Hz, 1H), 4.21 (ψt, J = 5.2 Hz, 1H), 3.97 (dd, J = 5.2 Hz, 2.5 Hz, 1H), 3.72 (s, 3H), 3.46 (t, J = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 166.6, 145.5, 138.3, 138.2, 137.7, 135.3, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 122.8, 118.9, 83.5, 80.8, 79.1, 75.3, 71.8, 70.7, 51.6; HRMS *m/z* (EI) calcd for $C_{30}H_{32}O_5$ $(M)^+$ 472.2256, found 472.2265.

Method 2: A solution of **5**[19] (1 g, 1.92 mmol) in acetone (10 mL) and water (1 mL) was treated with cadmium carbonate (2.6 g, 15.1 mmol) and *N*-bromosuccinimide (0.739 g, 4.1 mmol). The suspension was stirred for 40 min at 40 °C, filtered, and evaporated. The crude product was taken up in ether and washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated, giving a yellowish oil. To a solution of the crude aldehyde (0.76 g, 1.92 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added methyl (triphenylphosphoranylidene)acetate (1.28 g, 3.8 mmol) in one portion, and the resulting mixture was stirred for 10 h while it was allowed to warm to room temperature. Water (100 mL) was added to the reaction mixture, the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was presorbed on silica gel and purified by chromatography with gradients from 5%, 15% EtOAc/hexanes to afford enoate *ent*-**1** (0.77 g, 86%) as a colorless oil.

Methyl (2*R*+*S*,3*R*,4*R*,5*R*,6*S*)-4,5,6-Tri(benzyloxy)-2-hydroxy-3-vinyl-7-octenoate (9). To a solution of **8**[11q] (2.05 g, 4.1 mmol) in THF (80 mL) was added KHMDS (0.5 M in toluene, 11.36 mL, 5.65 mmol) at −78 °C. The resulting mixture was stirred for 30 min and a solution of the Davis oxaziridine reagent[20] (2.89 g, 11.1 mmol) in THF (20 mL) was added. The reaction was continued for 3 h at −78 °C and quenched with saturated NH_4Cl (100 mL). The mixture was extracted with EtOAc (3 × 100 mL) and the combined organic extracts were washed with saturated NH_4Cl and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was presorbed on silica gel and purified by column chromatography (5, 12% EtOAc/hexanes) to give **9** as an oil (1.74 g, 82%); R_f 0.36 (25% EtOAc/hexanes). Selected ^{1}H NMR ($CDCl_3$) δ 7.60−7.28 (m, 15H), 5.90 (m, 1H), 5.72 (m, 1H), 5.45−5.09 (m, 4H), 5.0−4.56 (m, 5H), 4.44 (d, J = 11.8 Hz, 1H), 4.26 (t, J = 7.1 Hz, 1H), 3.93 (m, 1H), 3.79 (m, 1H), 3.72 (s, 3H), 3.67 (m, 1H), 3.55 (s, 1H), 3.11 (m 1H); selected ^{13}C NMR ($CDCl_3$) δ 173.1, 138.5, 138.3, 137.8, 136.2 135.2, 128.4, 128.3, 128.0, 127.8, 127.7, 119.2, 118.3, 82.8, 82.5, 80.8, 74.9, 74.7, 71.7, 70.8, 65.2, 49.1, 46.3; HRMS *m/z* (MALDI) calcd for $C_{32}H_{36}O_6$ $(M + Na)^+$ 539.2409, found 539.2402.

(2*R*+*S*,3*R*,4*R*,5*R*,6*S*)-4,5,6-Tri(benzyloxy)-3-vinyl-7-octene-1,2-diol (10). To a solution of epimeric hydroxyesters **9** (1.7 g, 3.3 mmol) in ether (20 mL) was added 95% $LiAlH_4$ (0.32 g, 8.5 mmol) in one portion at 0 °C. After 10 h at 0 °C the reaction mixture was quenched with 1 M HCl (80 mL) and extracted with ether (3 × 150 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was presorbed on silica gel and purified by column chromatography (30, 50% EtOAc/hexanes) to afford a mixture of epimeric diols **10** (1.12 g, 70%) as a colorless oil; R_f 0.6 (50% EtOAc/hexanes); selected ^{1}H NMR ($CDCl_3$) δ 7.60−7.25 (m, 15 H), 5.93 (m, 2H), 5.34 (m, 2H), 5.14−5.05 (m, 2H), 4.82−4.54 (m, 5H), 4.37 (d, J = 11.8 Hz, 1H), 4.02 (ψt, J = 4.6 Hz, 1H), 3.94−3.84 (m, 1H), 3.6−3.2 (m, 3H), 2.39 (m, 1H), 2.30 (m, 1H), 1.94 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 138.5, 138.3, 137.8, 135.4, 135.0, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 119.2, 118.4, 83.4, 82.7, 80.1, 75.4, 75.0, 71.0, 70.7, 65.5, 46.3; HRMS *m/z* (EI) calcd for $C_{31}H_{36}O_5$ $(M)^+$ 488.2563, found 488.2570.

(2*R*,3*R*,4*R*,5*S*)-3,4,5-Tri(benzyloxy)-2-vinyl-6-heptene-1-ol (11). To a solution of diols **10** (1.0 g, 2.0 mmol) in ether (20 mL) at 0 °C was added $NaIO_4$ (534 mg, 2.5 mmol). To the resulting suspension was added water (13 mL). The resulting mixture was stirred for 28 h. The organic layer was separated, and the aqueous fraction was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was dissolved in abs. EtOH (15 mL). To this solution at 0 °C was added $NaBH_4$ (1.5 g, 39.6 mmol) in one portion and glacial acetic acid (3 mL). Stirring was continued for 12 h, and then the reaction mixture was quenched with a mixture of concentrated NH_4OH−sat. NH_4Cl (1:8, 90 mL). The aqueous phase was extracted with EtOAc (5 × 100 mL). The combined organic layers were washed with sat. NH_4Cl (2 × 100 mL) and brine, dried ($MgSO_4$), and concentrated under reduce pressure. The residue was presorbed on silica gel and purified by column chromatography (8%, 12%, and 50% EtOAc/hexanes) to give **11** as a colorless oil (0.95 g) in quantitative yield; R_f 0.53 (25% EtOAc/hexanes); $[\alpha]^{25}_D$ 32.81 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.60−7.28 (m, 15H), 5.90 (m, 1H), 5.76 (m, 1H), 5.36−5.07 (m, 4H), 4.85−4.56 (m, 5H), 4.36 (d, J = 11.8 Hz, 1H), 4.06 (ψt, J = 5.8 Hz, 1H), 3.81 (t, J = 5.8 Hz, 1H), 3.76−3.63 (m, 3H), 2.65−2.57 (m, 1H), 2.31−2.27 (br t, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 138.7, 138.5, 138.1, 137.4, 135.3, 128.4, 128.3, 128.16, 128.10, 127.8, 127.7, 127.68, 127.6, 119.1, 117.8, 82.7, 81.5, 80.9, 75.0, 74.3, 70.6, 63.3, 47.2; HRMS *m/z* (EI) calcd for $C_{30}H_{34}O_4$ $(M)^+$ 458.2457, found 458.2463.

(3*R*,4*R*,5*R*,6*S*)-4,5,6-Tri(benzyloxy)-3-hydroxymethylcyclohexene (12).[11s] To a solution of diene **11** (0.95 g, 2.0 mmol) in dry CH_2Cl_2 (100 mL) was added $(Cy_3P)_2(PhCH{=})RuCl_2$ (0.082 g, 0.1 mmol). The reaction mixture soon turned dark. After overnight stirring DMSO (0.72 mL, 10.0 mmol) was added and the reaction mixture was stirred for an additional 6 h. The mixture was concentrated under reduced pressure and the residue was presorbed on silica gel and purified by column chromatography (30 and 50% EtOAc/hexanes) to afford pure **12** (0.77 g, 87%) as a colorless oil; R_f 0.25 (25% EtOAc/hexanes); $[\alpha]^{25}_D$ 96.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.6−7.3 (m, 15 H), 5.76 (dd, J = 10.2, 2.7 Hz, 1H), 5.56 (dd, J = 10.2, 1.9 Hz, 1H), 5.0 (d, J = 11.3 Hz, 1H), 4.95 (s, 2H), 4.75 (s, 2H), 4.70 (d, J = 11.3 Hz, 1H), 4.25 (m, 1H), 3.86 (dd, J = 10.2, 7.7 Hz, 1H), 3.67 (m, 3H), 2.50 (m, 1H), 1.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 138.8, 138.5, 138.4, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 85.2, 80.9, 78.6, 75.4, 75.2, 72.2, 63.3, 45.8.

Acknowledgment. We thank Professors Marc d'Alarcao, Patrick S. Mariano, and Willem A. L. van Otterlo for insightful discussions. This work is supported by the National Institutes of Health (1-R15-CA099957-01).

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds *ent*-**1**, **2**, **3**, **8**, **1**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048459P