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Synthesis of 2-Methyl-D-erythritol via Epoxy Ester−Orthoester Rearrangement

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The biomimetic epoxy ester−orthoester rearrangement has been applied to a new synthesis of 2-methyl-D-erythritol, a branched five-carbon sugar of importance to the deoxyxylulose pathway of isoprenoid biosynthesis. The intermediate orthoacetate is one of the few [2.2.1]-orthoesters to have been reported. Labeling studies with O-18 indicated that this reaction proceeds exclusively via a 5-*exo* cyclization. NMR analysis of chiral esters indicated an ee of 87% for the starting epoxide and an ee of 86% for the product. This route represents a rapid and convenient method for the synthesis of 2-methyl-D-erythritol and is expected to be useful for generating isotopically labeled intermediates for biochemical studies.

Introduction

In recent years, a new biosynthetic pathway for isoprenoid compounds has been discovered in bacteria and higher plants.[1] Starting from the linear C_5 sugar, 1-deoxy-D-xylulose-5-phosphate (**1**), the new pathway leads to

1: R = $PO_3^=$ **2**: R = $PO_3^=$
3: R = H **4**: R = H

branched isoprenoid precursors by reductive isomerization to 2-methyl-D-erythritol-4-phosphate (**2**).[2] We previously reported a simple synthesis of 1-deoxy-D-xylulose (**3**) which has allowed its efficient production in various isotopically labeled forms for investigations of the new pathway.[3,4] Although several chemical syntheses of 2-methyl-D-erythritol (**4**) have been published, these approaches provide few opportunities for the introduction of isotopic labels.[5] Herein, we describe a convenient and flexible chemical synthesis of 2-methyl-D-erythritol involving the intermediacy of an unusual [2.2.1]-bicyclic orthoester.

Our recent applications of biomimetic orthoester formation in the syntheses of the marine antiviral orthoesterol B and the natural insecticide petuniasterone D led us to consider epoxy ester−orthoester rearrangement for the synthesis of 2-methyl-D-erythritol.[6] In our biomimetic studies, the formation of [3.2.1]-bicyclic orthoesters proved to be a facile acid-catalyzed reaction that proceeds stereospecifically with inversion at the proximal carbon of the epoxide ring.[6] It was hoped that a similar reaction would be useful as an approach to **4**, although very few examples of [2.2.1]-bicyclic orthoesters could be found in the literature.[7]

Results and Discussion

Synthesis of the known epoxy alcohol **5** via Sharpless' asymmetric epoxidation[8] was readily achieved from commercially available reagents (Scheme 1).[9] Chiral analysis of **5** was accomplished by preparing the ester with (*S*)-

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(1) Reviews: (a) Eisenreich, W.; Schwarz, M.; Cartayrade, A.; Arigoni, D.; Zenk, M. H.; Bacher, A. *Chem. Biol.* **1998**, *5*, R221−R233. (b) Rohmer, M. *Nat. Prod. Rep.* **1999**, *16*, 565−574.

(2) (a) Arigoni, D.; Sagner, S.; Latzel, C.; Eisenreich, W.; Bacher, A.; Zenk, M. H. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 10600−10605. (b) Duvold, T.; Bravo, J.-M.; Pale-Grosdemange, C.; Rohmer, M. *Tetrahedron Lett.* **1997**, *38*, 4769−4772. (c) Sagner, S.; Eisenreich, W.; Fellermeier, M.; Latzel, C.; Bacher, A.; Zenk, M. H. *Tetrahedron Lett.* **1998**, *39*, 2091−2094. (d) Kuzuyama, T.; Takahashi, S.; Watanabe, H.; Seto, H. *Tetrahedron Lett.* **1998**, *39*, 4509−4512. (e) Takahashi, S.; Kuzuyama, T.; Watanabe, H.; Seto, H. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 9879−9884.

(3) Giner, J. L. *Tetrahedron Lett.* **1998**, *39*, 2479−2482.

(4) (a) Giner, J. L.; Jaun, B. *Tetrahedron Lett.* **1998**, *39*, 8021−8022. (b) Giner, J. L.; Jaun, B.; Arigoni, D. *Chem. Commun.* **1998**, 1857−1858. (c) Arigoni, D.; Giner, J.-L.; Sagner, S.; Wungsintaweekul, J.; Zenk, M. H.; Kis, K.; Bacher, A.; Eisenreich, W. *Chem. Commun.* **1999**, 1127−1128. (d) Schuricht, U.; Hennig, L.; Findeisen, M.; Welzel, P.; Arigoni, D. *Tetrahedron Lett.* **2001**, *42*, 3835−3837.

(5) (a) Anthonsen, T.; Hagen, S.; Sallam, M. A. E. *Phytochemistry* **1980**, *19*, 2375−2377. (b) Anthonsen, T.; Hagen, S.; Lwande, W. *Acta Chem. Scand., Ser. B* **1980**, *B34*, 41−45. (c) Duvold, T.; Cali, P.; Bravo, J.-M.; Rohmer, M. *Tetrahedron Lett.* **1997**, *38*, 6181−6184. (d) Kis, K.; Wungsintaweekul, J.; Eisenreich, W.; Zenk, M. H.; Bacher, A. *J. Org. Chem.* **2000**, *65*, 587−592. (e) Hoeffler, J.-F.; Grosdemange-Billiard, C.; Rohmer, M. *Tetrahedron Lett.* **2000**, *41*, 4885−4889. (f) Fontana, A.; Messina, R.; Spinella, A.; Cimino, G. *Tetrahedron Lett.* **2000**, *41*, 7559−7562.

(6) (a) Giner, J.-L.; Faraldos, J. A. *J. Org. Chem.* **2002**, *67*, 2717−2720. (b) Giner, J.-L.; Faraldos, J. A. *J. Org. Chem.* **2002**, *67*, xxxx.

(7) (a) Hall, H. K., Jr.; DeBlauwe, F.; Pyriadi, T. *J. Am. Chem. Soc.* **1975**, *97*, 3854. (b) Burt, R. A.; Chiang, Y.; Hall, H. K. J.; Kresge, A. J. *J. Am. Chem. Soc.* **1982**, *104* (4), 3687−3690. (c) Dube, D.; Deschenes, D.; Tweddell, J.; Gagnon, H.; Carlini, R. *Tetrahedron Lett.* **1995**, *36*, 1827−30.

(8) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−80.

(9) Garner, P.; Park, J. M.; Rotello, V. *Tetrahedron Lett.* **1985**, *26*, 3299−302.

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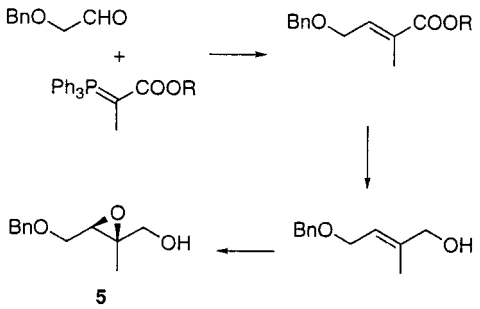
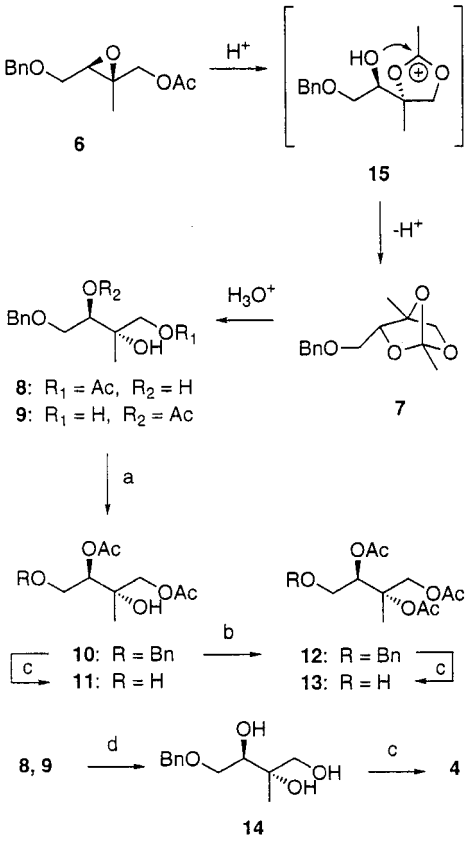
SCHEME 1



SCHEME 2[a]



[a] Key: (a) Ac_2O/pyridine; (b) Ac_2O/pyridine/DMAP; (c) H_2/10% Pd(C); (d) K_2CO_3/MeOH.

O-acetylmandelic acid by carbodiimide coupling.[10] Analysis by ^{1}H NMR showed an enantiomeric excess of 87% (2-methyl at 1.21 ppm vs 1.11 ppm for the diastereomer), somewhat lower than the reported value of >90%.[9] Acetylation of **5** provided the epoxy ester (**6**) needed for the epoxy ester−orthoester rearrangement. Upon treatment of **6** with 0.5% TFA/$CDCl_3$ for 1 h, the disappearance of the ^{1}H NMR signal at 2.09 ppm was observed and a new singlet at 1.71 ppm appeared, consistent with the conversion of an acetate to an orthoacetate (Scheme 2). The ^{13}C NMR showed a signal at 120.5 ppm typical for an orthoester. This [2.2.1]-bicyclic orthoester (**7**) was considerably less stable than our [3.2.1]-bicyclic orthoesters and was easily hydrolyzed under acidic conditions to a 1:1 mixture of the primary and secondary acetates (**8**, **9**). However, in the presence of triethylamine it was possible to isolate the orthoester by silica gel chromatography. Acetylation of monoacetates **8** and **9** yielded the diacetate **10**, which was converted to 1,3-diacetyl-2-methyl-D-erythritol (**11**) by hydrogenolysis. Acetylation in the presence of DMAP yielded triacetate **12**, which was similarly deprotected to give 1,2,3-triacetyl-2-methyl-D-erythritol (**13**). Saponification of **8** and **9** gave 4-benzyl-2-methyl-D-erythritol (**14**),[11] which was in turn converted to 2-methyl-D-erythritol (**4**) in quantitative yield by hydrogenolysis of the benzyl ether. The NMR spectra of **4** matched the reported data,[5d,e] and the rotation $[\alpha]^{22}_D$ +11.2 (*c* 0.57, CH_3OH) was in agreement with reported values ($[\alpha]^{20}_D$ +15.7 (*c* 1.42, CH_3OH); $[\alpha]^{20}_D$ +14.6 (*c* 1.37, CH_3OH)) for the natural product.[12]

Although the reaction proceeded predominantly through the expected 5-*exo* cyclization (**6** to **15**), the presence of a competing 6-*endo* cyclization was considered possible.[13] The alternative 6-*endo* pathway would lead to the enantiomer of orthoester **7**, resulting in the loss of stereochemical purity which was difficult to judge solely on the basis of polarimetry data. An experiment was therefore carried out to directly measure the extent of 5-*exo* cyclization versus 6-*endo* cyclization by ^{18}O-labeling. The location of the label was determined by ^{13}C NMR spectrometry through the characteristic upfield shifts of the carbon signals when bonded to the heavy isotope.[14] Thus, epoxy ester **6** bearing 45% ^{18}O in the carbonyl oxygen was prepared by carbodiimide esterification of epoxy alcohol **5** with mono-^{18}O-labeled acetic acid.[15] The ^{13}C NMR spectrum of the resulting orthoester (**7**) showed 45% ^{18}O-labeling at the orthoester carbon, evident through an upfield shift of 25 ppb of the signal at 120.5 ppm, and 45% ^{18}O-labeling of the C-2, evident through an upfield shift of 34 ppb of the signal at 85.5 ppm (Figure 1). No labeling of C-3 (80.5 ppm), which would result from 6-*endo* cyclization, could be detected. Conversion of the ^{18}O-labeled orthoester to the 1,3-diacetate **10** similarly showed 45% ^{18}O-labeling at C-2 (72.9 ppm, $\delta\Delta = 24$ ppb) and no label at C-3 (72.4 ppm) within a detection limit of 3%. Further proof of the stereospecificity of the epoxy ester−orthoester rearrangement was obtained by conversion of benzyl triol **14** to its (*S*)-*O*-acetylmandelate ester. This derivative showed an 86% ee as measured by ^{1}H NMR (2-methyl at 1.13 ppm vs 1.08 ppm for the diastereomer), confirming the high stereospecificity of orthoester formation.

The somewhat difficult isolation of orthoester **7** prior to hydrolysis is not necessary for the synthesis of **4**, and we considered that it might be more convenient to carry out the acid-catalyzed reaction of epoxy acetate **6** in the presence of water (0.5 M H_2SO_4 in THF/H_2O 9:1). Under these hydrolytic conditions, no orthoester would be formed, and the reaction is expected to proceed via

(10) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370−2374.

(11) For the enantiomer, see: Carda, M.; Casabo, P.; Gonzalez, F.; Rodriguez, S.; Domingo, L. R.; Marco, J. A. *Tetrahedron: Asymmetry* **1997**, *8*, 559−577.

(12) (a) Dittrich, P.; Angyal, S. J. *Phytochemistry* **1988**, *27*, 935. (b) Anthonsen, T.; Hagen, S.; Lwande, W. *Acta Chem. Scand., Ser. B* **1980**, *B34*, 41−45.

(13) Baldwin, J. E. *Chem. Commun.* **1976**, 734−736.

(14) Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4389−4392.

(15) Arkowitz, R. A.; Abeles, R. H. *Biochemistry* **1989**, *28*, 4639−4644.

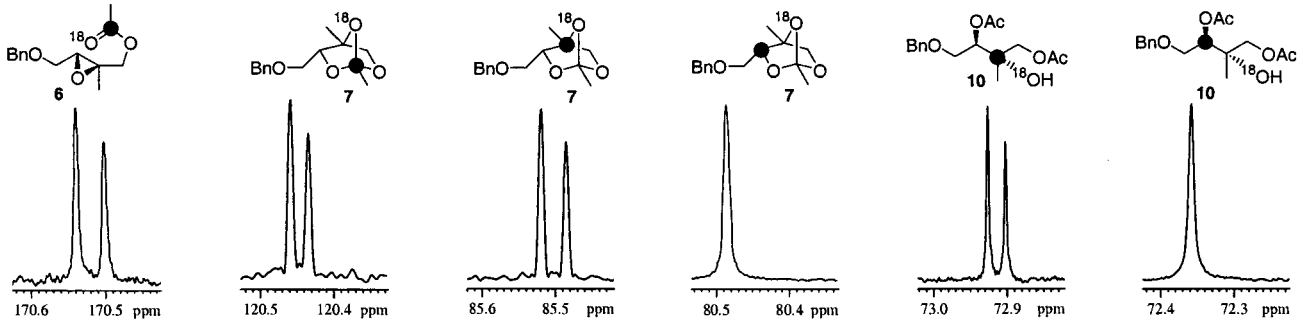


FIGURE 1. Selected ^{13}C NMR signals of ^{18}O-labeled intermediates (151 MHz). Dots indicate observed C atoms.

dioxycarbenium ion **15** by a neighboring group participation mechanism.[16] When this reaction was tested with ^{18}O-labeled **6**, only 27% ^{18}O-labeling was detected at C-2 of 1,3-diacetate **10** and no label was detected at C-3 or in the carbonyl groups. The loss of label is attributed to the exchange of the carbonyl oxygen with water. Direct hydrolysis of the epoxide would also result in a lack of ^{18}O transfer. Chiral analysis of the benzyl triol **14** prepared in this way showed 78% ee by ^{1}H NMR of its (*S*)-*O*-acetylmandelate derivative, indicating 5% ring-opening at the distal epoxide carbon, probably by direct hydrolysis. Somewhat surprisingly, when the hydrolysis was performed in the absence of neighboring group participation by employing the epoxy alcohol **5**, the same degree (*ca.* 5%) of chirality loss was observed.

Conclusions

This synthesis of 2-methyl-D-erythritol demonstrates the synthetic utility of the epoxy ester−orthoester rearrangement in the generation of triols from epoxy alcohols. This route utilizes easily accessible precursors and is shorter and more convenient than the published routes. Because a variety of isotopically labeled precursors are available for the preparation of **5** via the Wittig reaction,[9] our method will permit the convenient preparation of a variety of isotopically labeled forms of **4** for biological studies. This synthesis also provides useful precursors for the synthesis of more advanced biosynthetic intermediates in the 1-deoxyxylulose pathway. We recently have employed this route in a synthesis of 2-methyl-D-erythritol-2,4-cyclopyrophosphate[17] and are currently extending it to the synthesis of the 2-methyl-D-erythritol-4-phosphate (**2**).

Experimental Section

General methods. NMR spectra were acquired using 300 and 600 MHz instruments and referenced to the $CDCl_3$ solvent peaks (^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm). NMR assignments were made on the basis of DEPT, HMBC, and HSQC experiments. TLC was performed on aluminum backed plates coated with a 0.25 mm layer of Si gel 60 F254.

(*R*,*R*)-4-Benzyloxy-2,3-epoxy-2-methylbutanol (5). Prepared by the literature procedure (81% yield).[9] $[\alpha]^{23}_D$ +8.19 (*c* 1.19, $CHCl_3$). Lit.: $[\alpha]^{22}_D$ +22 (*c* 0.87, $CHCl_3$).[9]

(*R*,*R*)-4-Benzyloxy-2,3-epoxy-2-methylbutyl Acetate (6). Treatment of 4.23 g of **5** with 20 mL of 1:1 acetic anhydride/pyridine gave, after silica gel chromatography, 4.35 g (87%). TLC R_f 0.44 (hexane/ethyl acetate 1:1). $[\alpha]^{23}_D$ +9.35 (*c* 1.04, CH_2Cl_2). ^{1}H NMR (600 MHz): 7.37−7.33 (4H), 7.33−7.28 (1H, m), 4.64 (1H, d, J = 11.9 Hz), 4.54 (1H, d, J = 11.9 Hz), 4.19 (1H, d, J = 11.9 Hz), 3.95 (1H, d, J = 11.9 Hz), 3.71 (1H, dd, J = 11.3, 4.7 Hz), 3.60 (1H, dd, J = 11.3, 5.9 Hz), 3.18 (1H, dd, J = 5.9, 4.7 Hz), 2.09 (3H, s), 1.31 (3H, s). ^{13}C NMR (150 MHz): 170.5, 137.7, 128.5, 127.9, 127.8, 73.3, 68.1, 67.6, 59.1, 57.7, 20.7, 14.5. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.17; H, 7.35.

(*R*,*R*)-4-Benzyloxy-2,3-epoxy-2-methylbutyl (*R*)-*O*-Acetylmandelate. Prepared in quantitative yield by esterification of **5** with (*R*)-*O*-acetylmandelic acid in DCM using EDC with DMAP catalysis.[10] TLC R_f 0.55 (hexane/ethyl acetate 2:1). ^{1}H NMR (600 MHz): 7.50−7.45 (2H), 7.41−7.27 (8H), 5.94 (1H, s), 4.58 (1H, d, J = 11.8 Hz), 4.48 (1H, d, J = 11.8 Hz), 4.26 (1H, d, J = 11.8 Hz), 3.99 (1H, d, J = 11.8 Hz), 3.61 (1H, dd, J = 11.4, 4.7 Hz), 3.50 (1H, dd, J = 11.4, 6.0 Hz), 3.04 (1H, dd, J = 6.0, 4.7 Hz), 2.20 (3H, s), 1.11 (3H, s).

(*R*,*R*)-4-Benzyloxy-2,3-epoxy-2-methylbutyl (*S*)-*O*-Acetylmandelate. Prepared as above using (*S*)-*O*-acetylmandelic acid. TLC R_f 0.55 (hexane/ethyl acetate 2:1). ^{1}H NMR (600 MHz): 7.49−7.46 (2H), 7.41−7.28 (8H), 5.94 (1H, s), 4.59 (1H, d, J = 11.8 Hz), 4.49 (1H, d, J = 11.8 Hz), 4.23 (1H, d, J = 11.8 Hz), 3.99 (1H, d, J = 11.8 Hz), 3.64 (1H, dd, J = 11.3, 4.8 Hz), 3.53 (1H, dd, J = 11.3, 5.9 Hz), 3.04 (1H, dd, J = 5.9, 4.8 Hz), 2.19 (3H, s), 1.21 (3H, s).

4-Benzyl-2-*C*-methyl-D-erythritol 1,2,3-Orthoacetate (7). Rearrangement of **6** (27.0 mg) was accomplished by treatment with 0.7 mL of 0.5% TFA/$CDCl_3$ (rt, 1 h). The reaction was stopped by the addition of 50 mg of TEA, and the product was purified by preparative TLC (5% TEA in hexane/ethyl acetate 4:1) to yield 11.0 mg of **7** (41%), 4.6 mg of **8** (16%), 3.2 mg of **9** (11%), and 7.6 mg of **14** (31%). TLC R_f 0.66 (hexane/ethyl acetate 2:1). $[\alpha]^{23}_D$ +9.29 (*c* 1.11, CH_2Cl_2). ^{1}H NMR (600 MHz, 0.5% d_5-pyridine/$CDCl_3$): 7.38−7.27 (5H, Ph), 4.61 (1H, d, J = 11.9 Hz, PhCH_2), 4.51 (1H, d, J = 11.9 Hz, PhCH_2), 3.97−3.94 (1H, m, C-3), 3.95 (1H, d, J = 7.2 Hz, C-1), 3.80 (1H, dd, J = 10.0, 6.2 Hz, C-4), 3.59 (1H, dd, J = 10.0, 7.2 Hz, C-4), 3.44 (1H, dd, J = 7.3, 2.3 Hz, C-1), 1.71 (3H, s, orthoAc), 1.56 (3H, s, 2-Me). ^{13}C NMR (150 MHz): 137.6 (Ph), 128.4 (Ph), 127.8 (Ph), 127.6 (Ph), 120.5 (orthoAc), 85.5 (C-2), 80.5 (C-3), 73.6 (PhCH_2), 69.5 (C-1), 69.0 (C-4), 16.4 (orthoAc Me), 14.5 (2-Me).

4-Benzyl-2-*C*-methyl-D-erythritol 1-Acetate (8). TLC R_f 0.58 (hexane/ethyl acetate 1:2). $[\alpha]^{22}_D$ +9.65 (*c* 0.99, CH_2Cl_2). ^{1}H NMR (600 MHz): 7.38−7.28 (5H), 4.55 (2H, s), 4.20 (1H, d, J = 11.4 Hz), 3.98 (1H, d, J = 11.4 Hz), 3.73−3.68 (2H, m), 3.62 (1H, dd, J = 10.5, 7.2 Hz), 2.09 (3H, s), 1.20 (3H, s). ^{13}C NMR (150 MHz): 171.3 (s), 137.3 (s), 128.5 (d), 128.0 (d), 127.8 (d), 73.8 (t), 73.2 (s), 72.5 (d), 70.7 (t), 68.7 (t), 20.8 (q), 20.3 (q). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.81; H, 7.28.

4-Benzyl-2-*C*-methyl-D-erythritol 3-Acetate (9). TLC R_f 0.46 (hexane/ethyl acetate 1:2). ^{1}H NMR (600 MHz) 7.38−7.33 (2H), 7.33−7.27 (3H), 5.02 (1H, dd, J = 6.4, 4.2 Hz), 4.56 (1H,

(16) Roush, W. R.; Brown, R. J.; DiMare, M. *J. Org. Chem.* **1983**, *48*, 5083−5093.
(17) Giner, J.-L.; Ferris, W. V., Jr. *Org. Lett.* **2002**, *4*, 1225−1226.

d, J = 11.9 Hz), 4.54 (1H, d, J = 11.9 Hz), 3.86 (1H, dd, J = 10.5, 4.2 Hz), 3.74 (1H, dd, J = 10.5, 6.4 Hz), 3.46 (1H, d, J = 12.0 Hz), 3.31 (1H, d, J = 11.9 Hz), 3.11 (1H, br s), 2.83 (1H, br s), 2.12 (3H, s), 1.09 (3H, s). ^{13}C NMR (75 MHz): 171.5 (s), 137.3 (s), 128.5 (d), 127.9 (d), 127.7 (d), 73.9 (d), 73.5 (t), 73.1 (s), 68.5 (t), 67.1 (t), 21.0 (q), 19.3 (q).

4-Benzyl-2-*C*-methyl-D-erythritol 1,3-Diacetate (10). Treatment of **8** (28.4 mg) with 22 mg of acetic anhydride in 0.8 mL of pyridine gave, after silica gel chromatography, 29.2 mg (89%). TLC R_f 0.21 (hexane/ethyl acetate 2:1). $[\alpha]^{22}_D$ −5.81 (*c* 0.91, CH_2Cl_2). ^{1}H NMR (600 MHz): 7.38−7.32 (2H, Ph), 7.32−7.27 (3H, Ph), 5.10 (1H, t, J = 4.9 Hz, C-3), 4.55 (1H, d, J = 11.9 Hz, PhCH_2), 4.53 (1H, d, J = 11.9 Hz, PhCH_2), 4.13 (1H, d, J = 11.6 Hz, C-1), 3.93 (1H, d, J = 11.6 Hz, C-1), 3.74 (2H, d, J = 4.9 Hz, C-4), 3.28 (1H, br s, OH), 2.08 (3H, s, Ac), 2.07 (3H, s, Ac), 1.20 (3H, s, Me). ^{13}C NMR (150 MHz): 170.9 (Ac), 170.1 (Ac), 137.1 (Ph), 128.5 (Ph), 128.0 (Ph), 127.7 (Ph), 73.6 (PhCH_2), 72.9 (C-2), 72.4 (C-3), 68.6 (C-4), 68.3 (C-1), 20.9 (Ac Me), 20.8 (Ac Me), 20.7 (2-Me). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.14. Found: C, 61.99; H, 7.15.

2-*C*-Methyl-D-erythritol 1,3-Diacetate (11). Hydrogenation of **10** (2.51 g) in 100 mL of ethyl acetate with 0.63 g of 10% Pd/C for 1.5 h, followed by filtration and evaporation of the solvent, gave 1.74 g (98%). TLC R_f 0.21 (hexane/ethyl acetate 1:1). $[\alpha]^{23}_D$ −2.26 (*c* 0.88, CH_2Cl_2). ^{1}H NMR (300 MHz): 4.92 (1H, dd, J = 5.7, 4.6 Hz), 4.15 (1H, d, J = 11.6 Hz), 3.96 (1H, d, J = 11.6 Hz), 3.95 (1H, dd, J = 11.8, 4.5 Hz), 3.81 (1H, dd, J = 12.0, 5.5 Hz), 3.16 (1H, br s), 2.69 (1H, br s), 2.11 (3H, s), 2.10 (3H, s), 1.23 (3H, s). ^{13}C NMR (75 MHz): 171.0 (s), 170.8 (s), 75.0 (d), 73.2 (s), 68.5 (t), 61.8 (t), 20.9 (q), 20.7 (q), 20.2 (q). Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 48.94; H, 7.28.

4-Benzyl-2-*C*-methyl-D-erythritol 1,2,3-Triacetate (12). Acetylation of **10** (190 mg) with 2 mL of acetic anhydride/pyridine 1:1 and 40 mg of DMAP (overnight at rt) gave **12** (quantitative). TLC R_f 0.36 (hexane/ethyl acetate 4:1). ^{1}H NMR (600 MHz): 7.37−7.27 (5H), 5.58 (1H, dd, J = 7.1, 3.1 Hz), 4.59 (1H, d, J = 12.1 Hz), 4.51 (1H, d, J = 12.1 Hz), 4.48 (1H, d, J = 12.1 Hz), 4.35 (1H, d, J = 12.1 Hz), 3.73 (1H, dd, J = 11.0, 3.0 Hz), 3.64 (1H, dd, J = 11.0, 7.1 Hz), 2.09 (3H, s), 2.05 (3H, s), 1.98 (3H, s), 1.52 (3H, s). ^{13}C NMR (75 MHz): 170.5, 169.8, 169.7, 137.9, 128.4, 127.7, 127.6, 81.6, 73.0, 71.3, 68.3, 64.1, 22.0, 21.0, 20.7, 17.7. Anal. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 61.51; H, 6.79.

2-*C*-Methyl-D-erythritol 1,2,3-Triacetate (13). Hydrogenation of **12** (48 mg) in 20 mL of ethyl acetate with 16 mg of 10% Pd/C for 30 min, followed by filtration and evaporation of the solvent, gave **13** (quantitative). NMR showed this material to be only 85% pure. The contaminant appears to be formed by transesterification and could not be removed by chromatography. TLC R_f 0.31 (hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz): 5.30 (1H, dd, J = 7.1, 2.8 Hz), 4.54 (1H, d, J = 12.1 Hz), 4.35 (1H, d, J = 12.1 Hz), 3.95 (1H, br m), 3.74 (1H, br m), 2.12 (3H, s), 2.06 (3H, s), 2.02 (3H, s), 1.52 (3H, s). ^{13}C NMR (150 MHz): 170.9, 170.4, 169.7, 81.5, 74.6, 63.8, 61.9, 22.0, 20.9, 20.7, 17.4.

4-Benzyl-2-*C*-methyl-D-erythritol (14). A mixture of **8** and **9** (6.3 mg) in 1 mL of MeOH was treated with 10 mg of K_2CO_3 at rt for 16 h. Evaporation, followed by extraction with ether, filtration, and evaporation of the solvent, gave 5.3 mg of **14** (quantitative). TLC R_f 0.25 (hexane/ethyl acetate 1:2). $[\alpha]^{21}_D$ +8.04 (*c* 0.98, $CHCl_3$). Lit. (enantiomer): $[\alpha]_D$ −8.2 (*c* 1.5, $CHCl_3$).[11] NMR data matched those reported for the enantiomer.[11]

2-*C*-Methyl-D-erythritol (4). Hydrogenation of **14** (18.5 mg) in 1 mL of methanol with 3 mg of 10% Pd/C for 3 h, followed by filtration and evaporation of the solvent, gave 11.1 mg (quantitative) of a clear, colorless oil. $[\alpha]^{22}_D$ +11.2 (*c* 0.57, CH_3OH). ^{1}H NMR (600 MHz, D_2O): 3.78 (1H, dd, J = 11.5, 2.7 Hz), 3.62 (1H, dd, J = 8.5, 2.7 Hz), 3.55 (1H, dd, J = 11.5, 8.5 Hz), 3.54 (1H, d, J = 11.8 Hz), 3.43 (1H, d, J = 11.8 Hz), 1.08 (3H, s). ^{13}C NMR (151 MHz, D_2O): 75.4, 74.5, 66.7, 62.4, 18.8.

4-Benzyl-2-*C*-methyl-D-erythritol 1-(*R*)-*O*-Acetylmandelate. This was produced in quantitative yield by esterification of **14** with 1 equiv of (*R*)-*O*-acetylmandelic acid in DCM using EDC with DMAP catalysis (67% yield).[10] TLC R_f 0.66 (hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz): 7.48−7.44 (2H), 7.41−7.33 (5H), 7.33−7.28 (3H), 5.92 (1H, s), 4.50 (2H, s), 4.23 (1H, d, J = 11.3 Hz), 4.08 (1H, d, J = 11.3 Hz,), 3.63−3.53 (3H, m), 2.81 (1H, br s), 2.61 (1H, br d, J = 5.1 Hz), 2.20 (3H, s), 1.08 (3H, s). ^{13}C NMR (150 MHz): 170.4, 168.8, 137.4, 133.5, 129.4, 128.9, 128.5, 128.0, 127.8, 127.6, 74.6, 73.7, 73.1, 72.8, 70.6, 69.4, 20.7, 20.3.

4-Benzyl-2-*C*-methyl-D-erythritol 1-(*S*)-*O*-Acetylmandelate. This was made as above using (*S*)-*O*-acetylmandelic acid. TLC R_f 0.66 (hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz): 7.48−7.43 (2H), 7.42−7.33 (5H), 7.33−7.27 (3H), 5.92 (1H, s), 4.48 (2H, s), 4.24 (1H, d, J = 11.2 Hz), 4.03 (1H, d, J = 11.2 Hz), 3.59−3.44 (3H, m), 2.86 (1H, br s), 2.75 (1H, br d, J = 5.4 Hz), 2.20 (3H, s), 1.13 (3H, s). ^{13}C NMR (150 MHz): 170.5, 168.9, 137.3, 133.5, 129.4, 128.9, 128.5, 128.0, 127.8, 127.6, 74.6, 73.7, 73.2, 72.3, 70.7, 69.5, 20.7, 20.4.

Hydrolysis of 6: Treatment of **6** (51.0 mg) with 0.5 M H_2SO_4 in 5 mL of 9:1 THF/H_2O (rt, 4 h) gave, after silica gel chromatography, 28.0 mg of **8** (51%), 5.3 mg of **9** (10%), and 9.3 mg of **14** (20%).

Hydrolysis of 5: Treatment of **5** (50 mg) with 0.5 M H_2SO_4 in 2.5 mL of 9:1 THF/H_2O (rt, overnight) gave, after silica gel chromatography, 39.4 mg of **14** (73%).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **4** and **7**, and 2D NMR spectra for **4** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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