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Synthesis of enantiopure 2-*C*-methyl-D-erythritol-4-phosphate

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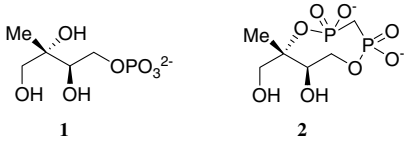
Abstract—The synthesis of enantiopure 2-*C*-methyl-D-erythritol-4-phosphate is disclosed. A 1,3-diol possessing a quaternary stereogenic centre, prepared stereoselectively from an acyclic tri-substituted alkene, has been utilized as a key intermediate.

Nature employs two biosynthetic pathways for the synthesis of one of the most diverse groups of natural products, terpenes. In addition to the mevalonate-dependent pathway,[1] the 2-*C*-methyl-D-erythritol-4-phosphate (MEP, **1**) pathway[2] has recently been found in chloroplasts, algae, cyanobacteria, eubacteria as the source of isopentenyl diphosphate (IPP). The MEP pathway while absent in animal cells, is present in many organisms, causing diseases such as tuberculosis, sexually transmitted infections, infections of the upper respiratory tract, toxoplasmosis and malaria.[3] The inhibition of the MEP pathway would provide opportunities to develop anti-parasitic and herbicidal agents.[4] Seven different enzymes are involved in the MEP pathway; the intermediates in the pathway are considered important for the mechanistic study, development of specific inhibitors and therapeutic leads. Enzymatic preparation of **1**[5] and cyclodiphosphate **2**,[6] Scheme 1, has been described.

The reported chemical methods utilize asymmetric epoxidation,[7] asymmetric dihydroxylation,[8] and chiral pool precursors.[9] We report herein a novel approach to enantiomerically pure MEP utilizing a recently disclosed methodology describing the regio and stereoselective preparation of tertiary alcohols from acyclic tri-substituted alkenes.[10] Propargyl ether **3** on reaction with methyl chloroformate followed by conjugate addition using Corey's protocol,[11] on the resulting ester **4** (74% yield), furnished ester[12] **5** (80% yield), which was reduced using alane to yield alcohol **6** (80% yield). Oxidation using Swern protocol[13] yielded aldehyde **7**, Scheme 2. The effective synthesis began with the condensation of the lithio anion of (*R*)-methyl *p*-tolyl sulfoxide **8**[14] with the unsaturated aldehyde **7** to furnish allyl alcohol **9** as an equimolar mixture of readily separable isomers (90% yield).[15] The *syn* isomer **9s** was oxidized using DMP[16] to afford the corresponding β-ketosulfoxide, which was reduced diastereoselectively using DIBAL-H[17] to furnish **9a** (80% overall yield, $[\alpha]_D^{25}$ +87 (*c* 1.5, $CHCl_3$)).



1 **2**

Scheme 1.

The reaction of **9a** with NBS proceeded cleanly to yield **10** (80%, $[\alpha]_D^{25}$ −33.3 (*c* 1.65, $CHCl_3$)).[18] Treatment of **10** with anhydrous potassium carbonate afforded a mixture of epoxides **11** and **12** in a 3:1 ratio, Scheme 3. To prepare an epoxide chemoselectively using the secondary carbinol, bromodiol **10** was transformed into 1,2-acetonide **13** (70% yield) using DDQ[19] and subsequently treated with anhydrous potassium carbonate to afford epoxy sulfoxide **14** (91% yield). Reductive elimination of **14** using Na–Hg[20] proceeded less cleanly in comparison to the corresponding sulfone **15** (89% yield) to yield *anti* 1,2-diol derivative **16** (70% yield). Protection of the hydroxyl group as its benzyl ether **17** (90% yield) followed by a one-pot oxidative cleavage of the alkene furnished aldehyde,[21] which without isolation was reduced in the same pot to yield alcohol **18** (70% yield). Conversion to the corresponding phosphate **19** (70% yield) using

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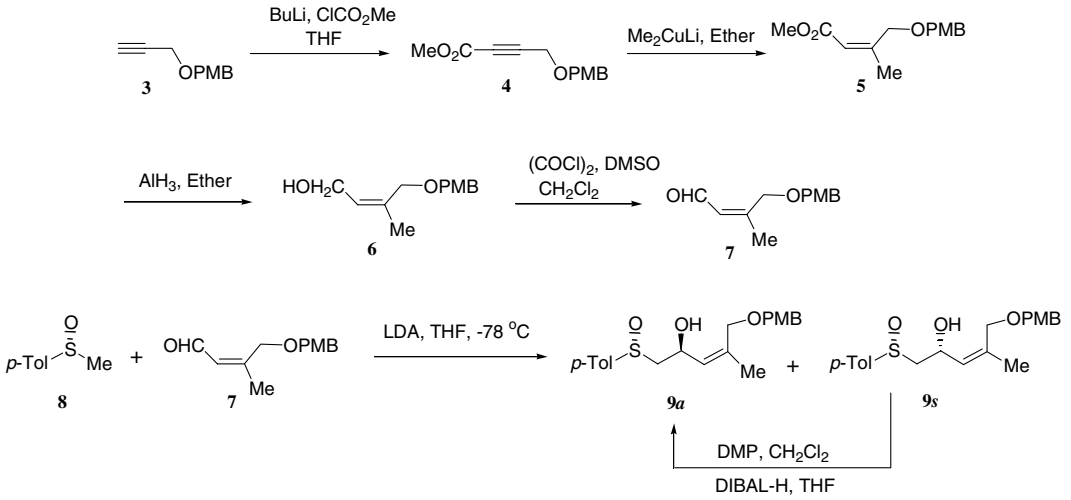
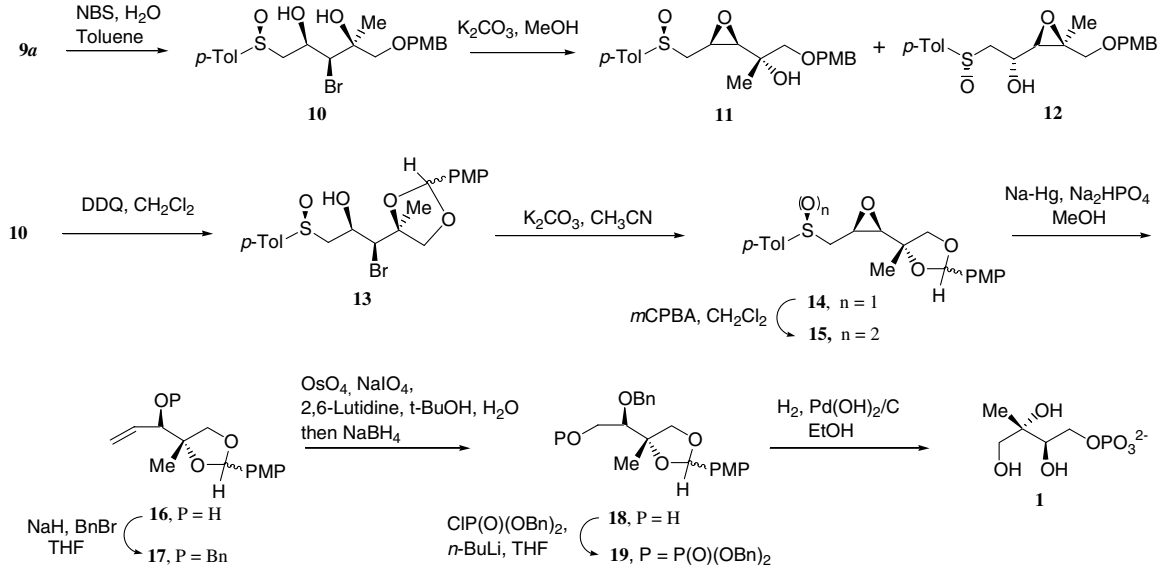


Scheme 2.



Scheme 3.

dibenzylphosphorochloridate[22] and subsequent hydrogenolysis by treatment with Pd/C under an atmosphere of hydrogen yielded **1** (81% yield). The NMR spectra as well as the optical rotation of synthetic **1** ($[\alpha]_D^{25}$ +7.2 (*c* 0.2, H_2O) were consistent with those reported for an enzymatically prepared sample.[5a]

In summary, we report a straightforward approach to enantiopure MEP. Also using appropriate reducing agents, C4 labelled derivatives can be prepared.

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References and notes

1. Bochar, D. A.; Friesen, J. A.; Stauffacher, C. V.; Rodwell, V. W. In *Comprehensive Natural Products Chemistry*; Cane, D. E., Ed.; Isoprenoids Including Carotenoids and Steroids; Elsevier: Amsterdam, 1999; Vol. 2, pp 15–44.
2. (a) Rohmer, M. In *Comprehensive Natural Products Chemistry*; Cane, D. E., Ed.; Isoprenoids Including Carotenoids and Steroids; Elsevier: Amsterdam, 1999; Vol. 2, pp 45–67; (b) Rohmer, M. *Nat. Prod. Rep.* **1999**, *16*, 565.
3. Jomaa, H.; Wisner, J.; Sanderbrand, S.; Altineicek, B.; Weidemeyer, M.; Hintz, M.; Tubachova, I.; Eberl, M.; Zeidler, J.; Lichtenthaler, H. K.; Soldati, D.; Beck, E. *Science* **1999**, *285*, 1573.

4. Takahashi, S.; Kuzuyama, T.; Watanabe, H.; Seto, H. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 9879.
5. (a) Kuzuyama, T.; Takahashi, S.; Watanabe, H.; Seto, H. *Tetrahedron Lett.* **1998**, *39*, 4509; (b) Hecht, S.; Wungsintaweekul, J.; Rohdich, F.; Kis, K.; Radykewicz, T.; Schuhr, C. A.; Eisenreich, W.; Richter, G.; Bacher, A. *J. Org. Chem.* **2001**, *66*, 7770.
6. (a) Ostrovskii, D.; Kharatyan, E.; Malarova, I.; Shipanova, I.; Sibeldina, L.; Shashkov, A.; Tantsirev, G. *BioFactors* **1992**, *3*, 261; (b) Takagi, M.; Kuzuyama, T.; Kaneda, K.; Watanabe, H.; Dairi, T.; Seto, H. *Tetrahedron Lett.* **2000**, *41*, 3395; (c) Schuhr, C. A.; Hecht, S.; Kis, K.; Eisenreich, W.; Wungsintaweekul, J.; Bacher, A.; Rohdich, F. *Eur. J. Org. Chem.* **2001**, 3221.
7. (a) Fontana, A. *J. Org. Chem.* **2001**, *66*, 2506; (b) Giner, J.-L.; Ferris, W. V., Jr. *Org. Lett.* **2002**, *4*, 1225.
8. (a) Koppisch, A. T.; Blagg, B. S. J.; Poulter, C. D. *Org. Lett.* **2000**, *2*, 215; (b) Koppisch, A. T.; Poulter, C. D. *J. Org. Chem.* **2002**, *67*, 5416.
9. (a) Kis, K.; Wungsintaweekul, J.; Eisenreich, W.; Zenk, M. H.; Bacher, A. *J. Org. Chem.* **2000**, *65*, 587; (b) Hoeffler, J.-F.; Pale-Grosdemange, C.; Rohmer, M. *Tetrahedron* **2000**, *56*, 1485.
10. Manuscript under review for publication.
11. Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
12. A similar strategy has been used to prepare a silyl ether, see: Ref. 8a.
13. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
14. Drago, C.; Caggiano, L.; Jackson, R. F. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 7221.
15. Attempted reaction of the anion derived from **8** with ester **5** afforded a mixture of isomeric β-ketosulfoxides differing due to olefin geometry. Diastereomeric allyl alcohols **9*a*** and **9*s*** were separated by column chromatography on silica gel using 40% EtOAc/petroleum ether (v/v) as eluent.
16. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
17. (a) Solladie, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, *26*, 435; (b) Solladie, G.; Frechou, C.; Demailly, G.; Greck, C. *J. Org. Chem.* **1986**, *51*, 1912; (c) Carreno, M. C.; Garcia Ruano, J. L.; Martin, A.; Pedregal, C.; Rodrigues, J. H.; Rubio, A.; Sanchez, J.; Solladie, G. *J. Org. Chem.* **1990**, *55*, 2120.
18. The stereochemistry of two new stereogenic centres of bromohydrin **10** was assigned by ^{1}H NMR and NOE study on the acetonide derived by its reaction with benzaldehyde dimethyl acetal, see Ref. 10.
19. Hanessian, S.; Cooke, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276.
20. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
21. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.
22. Hall, R. H.; Khorana, H. G. *J. Am. Chem. Soc.* **1954**, *76*, 5056.