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Simple and versatile synthesis of branched polyols: (+)-2-*C*-methylerythritol and (+)-2-*C*-methylthreitol

Angelo Fontana,[a,*] Rossella Messina,[a] Aldo Spinella[b] and Guido Cimino[a]

[a]*Istituto per la Chimica di Molecole di Interesse Biologico (ICMIB), Consiglio Nazionale delle Ricerche (CNR), Via Toiano 6, 80072 Arco Felice (Na), Italy*

[b]*Dipartimento di Chimica, Facoltà di Scienze, Università degli Studi di Salerno, Baronissi (Sa), Italy*

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Abstract

The paper reports a new approach for the enantioselective synthesis of 2-*C*-methyl tetrols. The procedure has been utilized for preparing methylthreitol and methylerythritol, a putative intermediate in the mevalonate-independent biosynthesis of terpenoids in bacteria, algae and higher plants. The methodology offers straightforward access to related compounds and isotopically labeled derivatives. © 2000 Elsevier Science Ltd. All rights reserved.

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In the last few years, independent studies have accumulated evidence for the existence in Gram-negative bacteria, algae and plant chloroplasts of a mevalonate-independent pathway (MIP) for the biosynthesis of terpenoids.[1–3] Besides the general interest in a new biosynthetic route, the MIP steps are perfect targets for the development of new antimicrobial drugs.[4,5] In the MIP, the isoprene unit is derived from condensation of pyruvate and glyceraldehyde-3-phosphate via 1-deoxy-D-xylulose-5-phosphate (DXP). Methylerythritol (**1**) that is formed by DXP-reductoisomerase from DXP, has also been indicated as a putative intermediate for the formation of isopentenyl phosphate (IP). The role of **1**, as well as the remaining steps of the MIP sequence, is still to be fully clarified. Isotopic experiments have, in fact, demonstrated that the tetrol **1** is incorporated in the quinones of *Escherichia coli* with very low yield,[6] thus suggesting that other compounds (e.g. **2**) can be actually involved in the biosynthetic process.[6–8] Very recently, it has also been reported that a cytidylyltransferase that catalyzes the formation of 4-(cytidine-5′-diphospho)-2-*C*-methylerythritol (**3**) from **2**, may be involved in terpenoid synthesis by MIP.[9] It is, however, clear that more experiments with labeled compounds are necessary. Accordingly, it has become crucial to have a facile access to these products. Recently,

* Corresponding author. Fax: +39 081 8041770; e-mail: afontana@icmib.na.cnr.it

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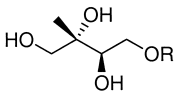
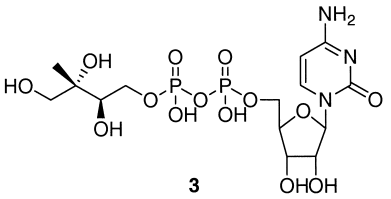
three syntheses of **1** and its 4-phosphate derivative (**2**) have been independently reported.[10–12] In this paper we wish to describe a further approach for the enantioselective synthesis of 2-*C*-methyltetrols, such as **1** and **4**, and, potentially, of other related molecules (e.g. **2**).



1 R = H
2 R = PO_3H_2



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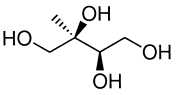

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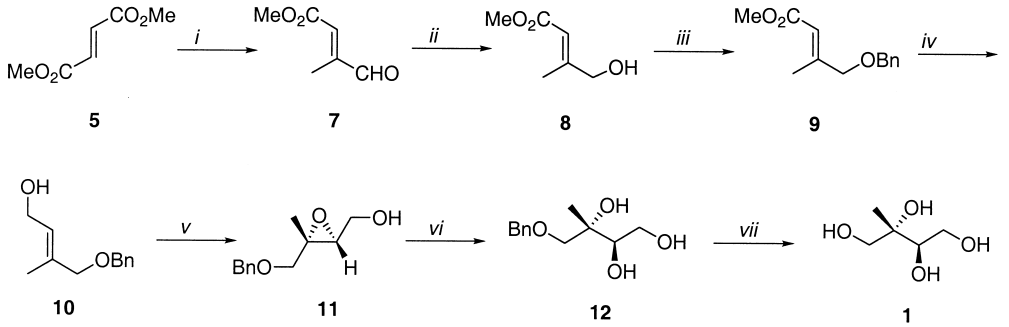
(+)-2-*C*-Methyl-D-erythritol (**1**) was obtained as reported in Scheme 1. The five-carbon scaffold of **1** was achieved by one pot reaction starting from dimethylfumarate (**5**). In fact, ozonolysis of **5** followed by Wittig reaction with the commercially available **6** gave the aldehyde **7**.[13] Direct reduction of this latter product prevented any loss of the volatile compound and yielded, after chromatographic purification, the alcohol **8** in 86% overall yield. Under the experimental conditions, addition of the triphenylphosphoranylidene **6** was highly specific and the *E* isomer was obtained with 99% selectivity.[14] Furthermore, this sequence of reactions allowed the regiodifferentiation of the carbon atoms that correspond to C-1 and C-4 of methylerythritol (**1**).† Benzylation of **8**, followed by reduction of the ester **9** with DIBALH in dry

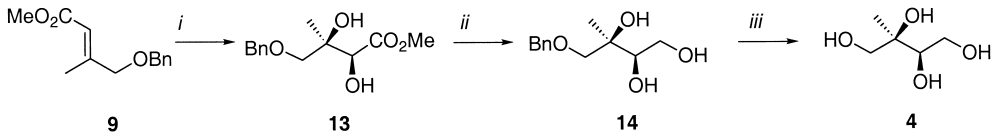


Scheme 1. i. O_3, $Ph_3P{=}C(CH_3)CHO$ (**6**); ii. $NaBH_4$ (86% from **6**); iii. BnBr, NaH, THF (56%); iv. DIBALH −78°C, THF (87%); v. Ti(*i*-PrO)$_4$, (+)-DET, *t*-BuOOH, −23°C in CH_2Cl_2 (93:7, 78%); vi. *t*-BuOH, 0.5 N NaOH, H_2O, 75°C (93%); vii. 10 Pd/C, H_2 (100%)

† Preparation of **9**. In a typical procedure, 11 g of dimethyl fumarate (73.6 mmol) in dry CH_2Cl_2 (600 mL) were reacted with ozone at −78°C. When the starting material was totally consumed, 10 g (31.1 mmol of 2-triphenylphosphoranylidene)-3-propionaldehyde and 20 mL of Et_3N were added slowly, and stirring was continued for 30 min. The reaction mixture was left to warm up to room temperature and stirred for a further 4 h. The clear mixture was then concentrated at reduced pressure. The slurry residue was dissolved in MeOH (400 mL) and an excess of $NaBH_4$ was added over a period of 30 min. The reaction was stirred at room temperature overnight. After evaporation of the solvent and addition of 1N HCl, the mixture was extracted with Et_2O three times. The organic layers were evaporated and the colorless oil was fractionated on SiO_2 column (petroleum ether/Et_2O 80:20) to give 3.45 g (26.6 mmol) of **8**, that, after benzylation with benzylbromide and NaH, afforded **9** (48% from **6**).

THF led to the desired substrate (**10**) for the Sharpless epoxidation. A Payne rearrangement was used to open the epoxide **11** with very high stereoselectivity and 93% yield.[14] Hydrogenolysis of the triol **12** yielded (+)-methylerythritol (**1**) in 84% enantiomeric excess and 31% overall yield after 6 steps.‡

In a similar manner, the benzyl derivative **9** was converted to optically active threitol (**4**) (Scheme 2). In this case, enantioselective dihydroxylation with AD-mix β was used to prepare the diol **13** in 82% enantiomeric excess. Reduction of **13** with DIBALH led to the 1-benzyl derivative of 2-*C*-methylthreitol (**14**) in almost quantitative yield. Deprotection of **14** afforded (+)-**4** in 78% enantiomeric excess and 38% overall yield.§



Scheme 2. i. AD-mix β, *t*-BuOH–H_2O, −4°C (89%); ii. DIBALH −78°C, THF (91%); iii. 10% Pd/C, H_2 (97%)

‡ Conversion of **9** to (+)-2-*C*-methylerythritol (**1**). In dry THF, the benzyl derivative **9** (358 mg, 1.63 mmol) was reduced with 1M DIBALH in hexane (10.9 mL) at −78°C. The reaction was quenched by addition of MeOH/H_2O 1:1. The slurry suspension was diluted with Et_2O and filtered through silica to give an oily residue from which **10** (270 mg, 1.42 mmol) was purified by SiO_2 column (*n*-hexane/EtOAc 85:15). To a stirred solution of titanium(IV)isopropoxide (284 μL, 0.9 mmol) and (+)-diethyl tartrate (61.8 mg, 1.18 mmol) in dry CH_2Cl_2 was added **10** (152 mg, 0.79 mmol) at −23°C. The mixture was stirred at −23°C for 15 min and then TBHP in nonane (1.61 mmol) was added through the septum. After 18 h at −23°C, the reaction was quenched with Na_2SO_4 and Et_2O. The epoxide **11** (128 mg, 0.62 mmol) was obtained as colorless oil after extraction of the reaction mixture and purification on SiO_2 column (*n*-hexane/EtOAc 80:20). Compound **11** (120 mg, 0.58 mmol) was dissolved in 10 mL *t*-BuOH. To this solution were added 5 mL 0.5M NaOH and 15 mL of distilled water. The clear mixture was stirred at 75°C for 8 h and then extracted by EtOAc. The organic layer was evaporated at reduced pressure to give 122 mg (0.54 mmol) of **12**. After purification on silica gel, hydrogenation of **12** by 10% Pd/C gave quantitatively (+)-2-*C*-D-methylerythritol (**1**). $[\alpha]_D = +7.2$ (*c* 0.4, MeOH) (lit. Ref. 6 and bibliography cited therein $[\alpha]_D = +7.6$ (*c* 1.6, MeOH), {$[\alpha]_D = +14.6$ (*c* 0.3, H_2O),) (lit. Ref. 10 and bibliography cited therein $[\alpha]_D = +9.0$ (*c* 1.0, H_2O)}; ^{1}H NMR (400 MHz, D_2O) δ 1.03 (3H, s, H_3-5), 3.37 (1H, d, $J = 11.7$ Hz, H-1a), 3.48 (1H, d, $J = 11.7$ Hz, H-1b), 3.51 (1H, d, $J = 11.4$ Hz, H-4a), 3.57 (1H, bd, $J = 8.8$ Hz, H-3), 3.73 (1H, d, $J = 11.4$ Hz, H-4b); ^{13}C NMR (100 MHz, D_2O) δ 20.4 (C-5), 63.2 (C-4), 63.9 (C-1), 73.2 (C-2), 76.9 (C-3). CIMS *m*/*z* 137 (35, M+H^+), 119 (45), 101 (100). The enantiomeric excess (e.e.) was determined by esterification with camphanic chloride of racemic and optically active **12**. Integration of the signals at δ 5.42 and 5.46 (dd, $J = 8.7$ and 2.1 Hz, H-3) in the ^{1}H NMR spectrum was used to calculate the reported e.e.

§ Conversion of **9** to (+)-2-*C*-methylthreitol (**1**). The alcohol **9** (367 mg, 1.66 mmol) was added at 0°C to 2.27 g AD-mix β and 166 mg methanesulfonamide in 18 mL *t*-BuOH/H_2O (1:1). The mixture was stirred at −4°C for 72 h. The reaction was quenched by adding of Na_2SO_3 (2.47 g), and stirring was continued for 1 h at room temperature. The yellow suspension was extracted with CH_2Cl_2 and the organic layer was washed with 2N NaOH and concentrated. Column fractionation of the slurry gave 375 mg (1.47 mmol) of colorless oil **13**. This latter compound was reduced to **14** (305 mg, 1.34 mmol) with DIBALH under the experimental conditions described above. Final removal of the benzyl group afforded (+)-2-*C*-methylthreitol (**4**) in almost quantitative yield (178 mg, 1.31 mmol). Compound **4** was obtained as colorless oil, $[\alpha]_D = +7.3$ (*c* 0.8, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 1.11 (3H, s, H_3-5), 3.48 (1H, d, $J = 12.0$ Hz, H-1a), 3.53 (1H, d, $J = 12.0$ Hz, H-1b), 3.60 (1H, bd, $J = 11.5$ Hz, H-4a), 3.68 (1H, bm, H-3), 3.76 (1H, d, $J = 11.5$ Hz, H-4b); ^{13}C NMR (100 MHz, D_2O) δ 21.5 (C-5), 64.2 (C-4), 68.5 (C-1), 76.4 (C-2), 77.5 (C-3). CIMS *m*/*z* 137 (35, M+H^+), 119 (75), 101 (100), 89 (20). HRCIMS (isobutane) *m*/*z* 137.1551 (required 137.1543 for $C_5H_{12}O_4$+H^+). The enantiomeric excess (e.e.) was determined by NMR analysis of the camphanyl derivatives of racemic and optically active **13** and **14**.

One of the most interesting aspects of the methodology described here is its versatility. Simple and quantitative reduction with $LiAlD_4$ or similar reagents gives access easily to deuterium containing products. Otherwise, the use of the commercially available [U-^{13}C]-fumarate may lead to [3,4-$^{13}C_2$]-2-*C*-methyl-D-erythritol in an easy and convenient manner. As demonstrated by the short synthesis of (+)-**4**, the methodology has a very general application and can reliably afford related products (e.g. **2**). With respect to other syntheses, one of which leads to enantiopure **2**, the approach we have reported in this paper offers the possibility to introduce labeling isotopes (^{2}H or ^{13}C) in every position of the erythritol molecule starting from commercially available precursors. Syntheses of these compounds are now under way and they will be the subject of a further communication.

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