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Chemo-Enzymatic Synthesis of All Isomers of 2-Methylbutane-1,2,3,4-tetraol – Important Contributors to Atmospheric Aerosols

Anders Riise Moen,[a] Kjersti Ruud,[a] and Thorleif Anthonsen*[a]

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By a combination of stereospecific osmium catalyzed oxidation of dimethyl citraconate and lipase catalysed enantioselective resolution of the formed dimethyl (2*R**,3*S**)-2,3-dihydroxy-2-methylbutanedioate, followed by reduction, (2*R*,3*S*)- and (2*S*,3*R*)-2-methylbutane-1,2,3,4-tetraol were isolated. Similar reactions starting with dimethyl mesaconate gave the isomers, (2*R*,3*R*)- and (2*S*,3*S*)-2-methylbutane-1,2,3,4-tetraol.

1. Introduction

Thirty years ago 2-*C*-methyl-D-erythritol [(2*S*,3*R*)-**1**] was isolated from *Convolvulus glomeratus,* a plant growing in Pakistan.[1] The structure was deduced by NMR spectroscopy, synthesis of racemic derivatives of 2-*C*-methyl-erythritol and 2-*C*-methyl-threitol and CD.[2] Finally the enantiopure natural compound was synthesized by first generation asymmetric synthesis starting with 2,3-*O*-isopropylidene-D-glyceraldehyde.[3] Due to the presence of two stereocenters there are four possible stereoisomers as shown in Figure 1.

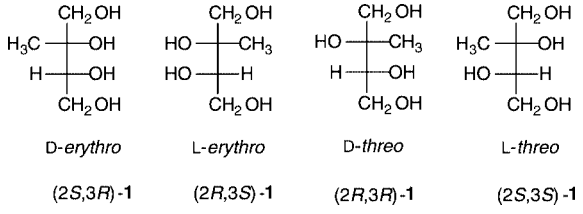


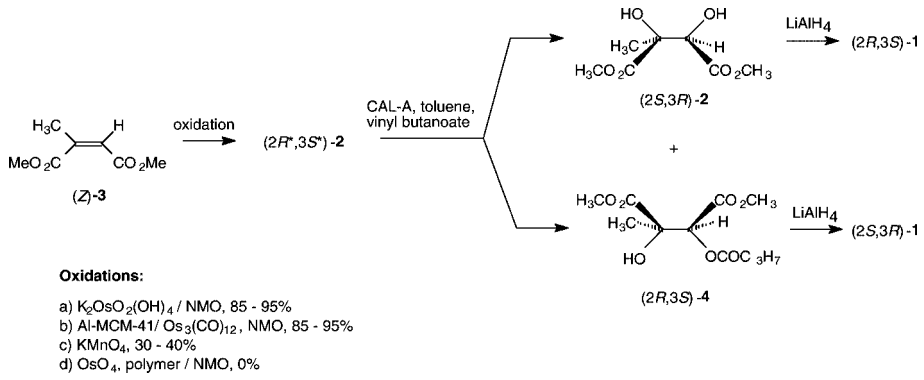
Figure 1. The four stereoisomers of 2-methylbutane-1,2,3,4-tetraol (**1**).

More recently it has been discovered that large amounts of 2-*C*-methyltetritols are present in the air above the Amazonian rain forest claimed to be due to photooxidation of isoprene and moreover, that such compounds are hitherto unknown.[4] Inspired by this statement we started to synthesize all four isomers of 2-methylbutane-1,2,3,4-tetraol. Knowledge of the absolute configurations of the Amazonian tetritols would indicate whether they were synthesized as suggested, by achiral photooxidation, or by asymmetric enzymatic catalysis in the plants, to give enantiopure tetraols such as the *Convolvulus* compound. However, the absolute configurations of the Amazonian tetritols have so far not been possible to deduce. In spite of the fact that they are claimed to be present in enormous quantities, they were only detected by mass spectroscopy. These natural products may be considered as carbohydrates and thus can be named as suggested above (see Figure 1), but also as isoprenoids. Synthesis of racemic 2-*C*-methylerythritol and 2-*C*-methylthreitol from dimethyl citraconate and dimethyl mesaconate has been described previously.[1,5] The biosynthesis of **1** from glyceraldehyde-3-phosphate and pyruvate giving a mevalonate independent origin of isoprenoids, has been discovered in bacteria and higher plants.[6] Since this discovery, there is considerable interest in the synthesis of **1**.[7–10]

2. Results and Discussion

Dimethyl (2*R**,3*S**)-2,3-dihydroxy-2-methylbutanedioate [(2*R**,3*S**)-**2**] was obtained from dimethylcitraconate [(*Z*)-**3**] by stereospecific dihydroxylation (Scheme 1). The *cis*-dihydroxylations were performed using various osmium catalysts in an "Upjohn" process with 4-methylmorpholine *N*-oxide for reoxidation.[11] The best results were obtained in acidic media with citric acid as additive which gave 85–95% yield.[12] Oxidation with $K_2OsO_2(OH)_4$ or osmium immobilized in mesoporous materials[13] gave similar yields. The latter can be easily separated from the product and reused. Oxidations using potassium permanganate gave poor results. The resulting racemic dimethyl esters [(2*R**,3*S**)-**2**] were resolved kinetically using lipase A from *Candida antarctica* (CAL-A, Novozym 735) and vinyl butanoate to give the dimethyl ester [(2*S*,3*R*)-**2**] and the monobutanoate (2*R*,3*S*)-**4**. The enantioselectivity, the (*E* value, was low even at 6 °C (*E* = 27) (Table 1) hence the resolution was performed twice. Firstly the reaction was stopped at 67% conversion and the remaining substrate, (2*S*,3*R*)-**2**, was isolated

[a] Department of Chemistry, Norwegian University of Science and Technology (NTNU),
7491 Trondheim, Norway
E-mail: Thorleif.Anthonsen@chem.ntnu.no



Scheme 1.

Table 1. Resolutions of dimethyl (2*R**,3*S**)-2,3-dihydroxy-2-methylbutanedioate [(2*R**,3*S**)-**2**] and [(2*R**,3*R**)-**2**] catalyzed by Novozym 735 (immobilized lipase A from *Candida antarctica*) using vinyl butanoate as acyl donor in toluene at 6 °C. Two different reactions were performed with (2*R**,3*S**)-**2**. One was stopped at 67% conversion to favour substrate enantiopurity (1st reaction) and one at 19% conversion to obtain high product enantiopurity (2nd reaction), see also Figure 2. Optical rotations were measured in CH_2Cl_2.

	E	*c*,%	ee_p,%	$[\alpha]_D^{20}$	ee_s,%	$[\alpha]_D^{20}$
(2*R**,3*S**)-**2**	27	67	–	–	98.5	–22.7
(1st reaction)					(2*S*,3*R*)-**2**	*c* = 5.3
(2*R**,3*S**)-**2**	27	19	94	–16.0	–	–
(2nd reaction)			(2*R*,3*S*)-**4**	*c* = 3.5		
(2*R**,3*R**)-**2**	272	51	94	+8.3	>99.0	–23.6
			(2*S*,3*S*)-**4**	*c* = 1.0	(2*R*,3*R*)-**2**	*c* = 1.0

with 98.5% *ee*. In a second reaction, the conversion was stopped at 19% and the produced butanoate (2*R*,3*S*)-**4** was isolated with 94% *ee*. (Figure 2) Reduction of the unreacted dimethyl ester (2*S*,3*R*)-**2** gave the natural compound (2*R*,3*S*)-**1**. The 3-butanoate, (2*R*,3*S*)-**4**, was reduced to give the enantiomer (2*S*,3*R*)-**1**.

The two other stereoisomers were isolated by a similar synthesis starting with dimethyl mesaconate [(*E*)-**3**]. Oxidation gave a mixture of the enantiomers dimethyl (2*R**,3*R**)-2,3-dihydroxy-2-methylbutanedioate [(2*R**,3*R**)-**2**] which were resolved with an *E* value of 140 at 30 °C and 272 at 6 °C. In one single reaction both the remaining (2*R*,3*R*)-**2** and the butanoate (2*S*,3*S*)-**4** were isolated with high *ee* values. (Table 1) However, at the lower temperature the reaction was much slower. To reach 50% conversion it took 6 h at 30 °C and 3 days at 6 °C. Reductions of the separated products gave (2*S*,3*S*)-**1** and (2*R*,3*R*)-**1** respectively. In both esterifications only the secondary center was esterified since tertiary centers are less reactive. Moreover, the faster reacting enantiomer is expected to have the (3*S*)-configuration. In particular when the (*E* value is high, this is taken as proof of the absolute configurations based on the knowledge of enantioselectivity of lipases.[14,15] Furthermore, based on the stereospecific reactions used to produce the dihydroxy compounds, also the configurations at C-2 was consequently proven. In addition, Sakamoto et al. has synthesized 2-*C*-methyl-L-threitol starting with D-galactose.[7] The optical rotation of 2*S*,3*S*-**1** is almost identical with this product.

In spite of the similarity of the two racemic substrates, they only differ in relative configuration, the *E* values differ a lot. Progress curves of conversion of each enantiomer

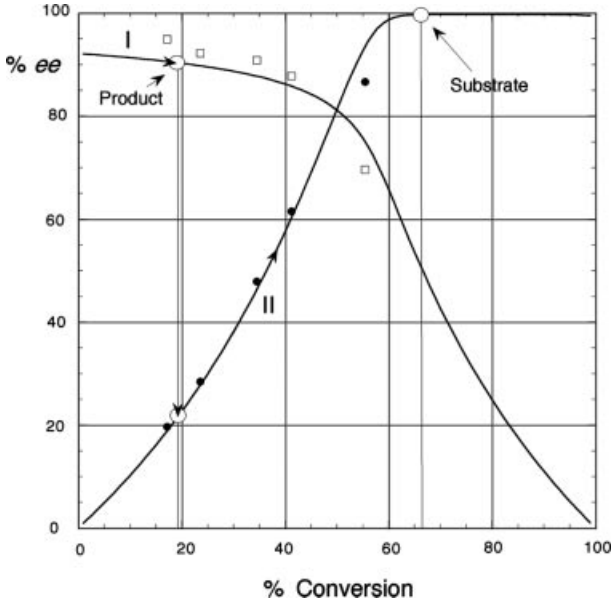


Figure 2. The enantiomeric excesses of the product fraction (I) and the substrate fraction (II) in CAL-A catalyzed resolution at 6 °C of dimethyl (2*R**,3*S**)-2,3-dihydroxy-2-methylbutanedioate [(2*R**,3*S**)-**2**] as a function of the degree of conversion. The *E* value is 27. Due to the relatively low *E* value, the product (2*R*,3*S*)-**4** was isolated after 19% conversion and the unreacted substrate after 67% conversion in two different reactions.

shown in Figure 3 may be used to elucidate this. The *E* value is the ratio of the rate constants for reactions with the two enantiomers. Consequently, when the *E* value goes down when resolution of 2*R**,3*R** is compared with the resolution of 2*R**,2*S**, the question is: Is it the faster

enantiomer that slows down or is it the slower enantiomer that speeds up? In the present case it may be seen that the faster reacting enantiomers are almost equally fast, but the slow enantiomer 2*S*,3*R* has become relatively faster than the other slow enantiomer 2*R*,3*R* in the resolution of the other diastereomer. This may be explained in detail by molecular modeling of the interaction between the substrates and CAL-A. However, the X-ray structure of this lipase has not yet been published. Previously we have experienced that CAL-A works better with more bulky substrates because it has a wider active site than CAL-B. See ref.[16] and references sited therein. For instance, CAL-B gave high *E* values in resolution of 1-[4-(benzyloxy)-3-methoxyphenyl]ethanol, but not for the corresponding more bulky 2-bromo and 2-chloro derivatives, then CAL-A was more efficient.

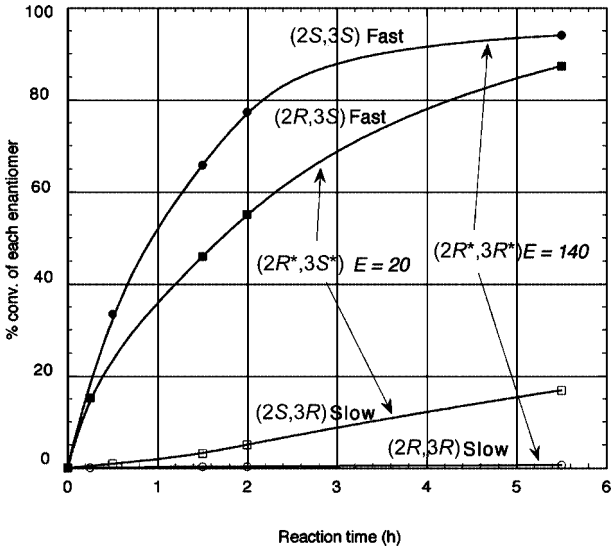


Figure 3. Progress curves of conversion of each enantiomer at 30 °C of (2*R**,3*S**)-**2** and (2*R**,3*R**)-**2**. The *E* values were 20 and 140 as depicted in the graphs. When the reactions were performed at 6 °C the *E* values increased to 27 and 272, respectively.

3. Conclusion

Combined stereospecific osmium-catalyzed oxidation of dimethyl citraconate and lipase-catalysed enantioselective resolution of the formed dimethyl (2*R**,3*S**)-2,3-dihydroxy-2-methylbutanedioate, followed by reduction, yields (2*R*,3*S*)- and (2*S*,3*R*)-2-methylbutane-1,2,3,4-tetraol. The enantioselectivity of the resolution is low (*E* = 27 at 6 °C). Similar reactions starting with dimethyl mesaconate give the isomers (2*R*,3*R*)- and (2*S*,3*S*)-2-methylbutane-1,2,3,4-tetraol. In this case the *E* value is 272.

4. Experimental Section

4.1. General: Osmium tetraoxide on poly(4-vinylpyridine), potassium osmate dihydrate and tri-osmium dodecacarbonyl were purchased from Sigma–Aldrich, Merck, and Fluka, respectively. Lipase A from *Candida antarctica* (CAL-A, Novozym 735 on Accurel) was from Novozymes, Denmark. The transesterification reactions were performed at 30 °C in an Infors MINITRON Shaker Incubator. The product and the remaining substrate were separated by chromatography with Versaflash system from Supelco with versaPak silica cartridge 40×150 mm or 40×75 mm. Optical rotations were determined using a Perkin–Elmer 243B Polarimeter, concentrations are given in g/100 mL.

4.1.1. Analyses: Chiral analyses of the transesterification reactions were performed on Varian 3400 gas chromatograph equipped with a chiral CP Chirasil Dex CB column (25 m, 0.25 mm id and 0.32 μm film thickness), column pressure 8 psi, split flow 60 mL/min.

Temperature program for analysis of products resulting from (*E*)-**3**: 110–140 °C 4 °C/min, 140–180 °C 10 °C/min. Retention times of the enantiomers of the alcohol were 6.4 min for (2*R*,3*R*)-**2** and 7.5 min for (2*S*,3*S*)-**2**, and 9.3 min for the butanoate (2*R*,3*R*)-**4**, 9.4 min for (2*S*,3*S*)-**4**.

Temperature program for analysis of products resulting from (*Z*)-**3**: 90 °C (10 min hold), 90–138 °C 2 °C/min, 138–180 °C 10 °C/min. Retention times of the enantiomers of the alcohol were 15.6 min for (2*S*,3*R*)-**2** and 16.0 min for (2*R*,3*S*)-**2**, 23.1 min for the butanoate (2*R*,3*S*)-**4** and 23.4 min for (2*S*,3*R*)-**4**.

NMR spectra were recorded in $CDCl_3$ solutions using Bruker DPX 300 and 400 instruments. Chemical shifts are given in ppm relative to TMS and coupling constants in Hz. MS was performed by direct infusion with a infusion pump for continues injection to a Agilent LC-MSD Trap SL with positive APCI ionization. Enantiomeric ratios (*E*) were calculated using the computer program *E and K calculator version 2.03*.

4.1.2. Chemical Vapor Deposition of $Os_3(CO)_{12}$ on Al-MCM-41: Al-MCM-41 was prepared as reported.[12] A glass ampoule containing Al-MCM-41 (0.4 g) and $Os_3(CO)_{12}$ (50 mg, 0.055 mmol) was evacuated ($P = 4 \cdot 10^{-2}$ mbar), sealed and heated at 150 °C for 40 h before the ampoule was cooled to room temp. The ampoule was broken, the powder was washed with water and methanol and centrifuged. The dried powder (25 mg) was mixed in water (50 mL) and stirred for 24 h. ICP-MS analysis of the filtrate showed that leaching of Os from the matrix was less than 5 ppm.

4.2. (2*R,3*R**)-Dimethyl 2,3-Dihydroxy-2-methylbutanedioate [(2*R**,3*R**)-2]:** Dimethyl mesaconate [(*E*)-**3**] (0.5 g, 3.16 mmol) and citric acid (0.46 g, 2.4 mmol) were dissolved in 5 mL of a 1:1 mixture of *tert*-butyl alcohol/water. Potassium osmate, $K_2OsO_2(OH)_4$, (0.003 g, 0.26 mol-%) was added followed by 4-methylmorpholine *N*-oxide (0.4 g, 3.4 mmol). The reaction was stirred at room temp for 15 h before Na_2SO_3 (0.3 g) was added. The reaction mixture was further stirred for 1 h and *tert*-butyl alcohol was evaporated before the aqueous residue was extracted with Et_2O (4 × 10 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated to give (2*R**,3*R**)-**2** (0.58 g, 3.0 mmol, 94.9%) as an oil. ^{1}H NMR: δ = 4.35 (s, 1 H), 3.83 and 3.82 (both s, 3 H, 2×OCH_3), 1.49 (s, 3 H, CH_3). ^{13}C NMR: δ = 174.8, 171.6, 76.9, 75.2, 53.3, 52.8, 21.8. MS: 193.1 (M + 1), 133.2 (100%), 87.

4.3. (2*R,3*S**)-Dimethyl 2,3-Dihydroxy-2-methylbutanedioate [(2*R**,3*S**)-2]:** Dimethyl citraconate [(*Z*)-**3**] (0.5 g, 3.16 mmol) and citric acid (0.46 g, 2.4 mmol) were dissolved in 5 mL of a 1:1 mixture of *tert*-butyl alcohol/water. Potassium osmate, $K_2OsO_2(OH)_4$, (0.003 g, 0.26 mol-%) was added followed by 4-methylmorpholine *N*-oxide (0.4 g, 3.4 mmol). The reaction was stirred at room temp. for 15 h before Na_2SO_3 (0.3 g) was added. The reaction mixture was further stirred for 1 h. *tert*-Butyl alcohol was evaporated before the aqueous residue was extracted with Et_2O (4 × 10 mL). The

combined organic extracts were dried with $MgSO_4$ and concentrated to give (2*R**,3*S**)-**2** as a solid (0.51 g, 2.66 mmol, 84.2%), m.p. 93–94 °C. ^{1}H NMR: δ = 4.37 (s, 1 H), 3.83 and 3.78 (both s, 3 H, 2× OCH_3), 3.47 (s, 1 H, OH), 3.09 (s, 1 H, OH), 1.52 (s, 3 H, CH_3). ^{13}C NMR: δ = 175.0, 172.0, 77.3, 75.7, 53.4, 53.1, 22.8 (ref.[1]).

In alternative procedures the potassium osmate was exchanged with immobilized Os, [$Os_3(CO)_{12}$-Al MCM-41] or osmium tetraoxide on poly(4-vinylpyridine). The workup was started by filtering off the osmium catalyst. Na_2SO_3 was not added when immobilized osmium was used, The catalyst was reused.

4.4. Transesterification Reactions: Small scale reactions were carried out in order to find the best conditions for high *E* values. A typical reaction contained 20 mg of the substrate in hexane or toluene (3 mL), immobilized lipase (20 mg) and vinyl butanoate (3 equiv.). The reactions were monitored by chiral GLC-analyses.

4.4.1. Lipase catalyzed esterification of (2*R,3*R**)-2:** (2*R**,3*R**)-Dimethyl 2,3-dihydroxy-2-methylbutanedioate [(2*R**,3*R**)-**2**] (1.0 g, 5.2 mmol), vinyl butanoate (3.05 g, 26.7 mmol) were dissolved in toluene (50 mL) and Novozym 735 (0.1 g) was added. The reaction was monitored by GLC and stopped at 51% conversion. The enzyme was filtered off and washed with Et_2O (10 mL) and the combined organic phases were concentrated under reduced pressure. Ester and alcohol were separated by flash chromatography (EtOAc/hexane, 1:1). Alcohol (2*R*,3*R*)-**2** (0.335 g, 1.74 mmol, 33.5%), *ee* > 99%, butanoate: (2*S*,3*S*)-**4** (0.649 g, 2.48 mmol, 47.7%), *ee* 94%.

Alcohol (2*R*,3*R*)-**2**: ^{1}H NMR: δ = 4.35 (s, 1 H), 3.83 and 3.82 (both s, 3 H, 2× OCH_3), 1.49 (s, 3 H, CH_3). ^{13}C NMR: δ = 174.8, 171.6, 76.9, 75.2, 53.3, 52.8, 21.8. MS: 193.1 (M + 1), 133.2 (100%), 87. $[\alpha]_D^{20}$ = –23.6 (*c* = 1.0, CH_2Cl_2).

Butanoate (2*S*,3*S*)-**4**: ^{1}H NMR: δ = 5.12 (s, 1 H), 4.72 (s, 6 H, OCH_3), 1.50 (s, 3 H, CH_3), $ABMNX_3$ system: 2.30 (AB), 1.60 (MN), 0.90 (X_3) (J_{AB}, J_{MNX} = 7.5). ^{13}C NMR: δ = 174.1, 172.7, 167.4, 76.4, 75.6, 53.7, 53.0, 36.0, 22.4, 18.7, 13.9. MS: 263.1 (M + 1), 245 (–18, 100%), 231, 203, 185, 131, 115. $[\alpha]_D^{20}$ = +8.3 (*c* = 1.0, CH_2Cl_2).

4.4.2. Lipase-Catalyzed Esterification of (2*R,3*S**)-2:** Two parallel reactions were prepared where (1.0 g, 5.2 mmol), vinyl butanoate (3.02 g, 26.5 mmol) were dissolved in toluene (50 mL) before Novozym 735 (0.1 g) was added. The reactions were monitored on a chiral GLC-column and stopped at 19% conversion (ee_p = 94%) in one reaction and at 67% conversion (ee_s = 98.5%) in the parallel reaction. The enzyme was filtered off and washed with Et_2O (10 mL) before the combined organic solvents were removed under reduced pressure. Ester and alcohol were separated by flash chromatography (EtOAc/hexane; 1:1). The butanoate was isolated from the first reaction and in the second reaction the alcohol was isolated.

Alcohol (2*S*,3*R*)-**2**: ^{1}H NMR: δ = 4.37 (s, 1 H), 3.83 and 3.78 (both s, 3 H, 2× OCH_3), 3.47 (s, 1 H, OH), 3.09 (s, 1 H, OH), 1.52 (s, 3 H, CH_3). ^{13}C NMR: δ = 175.0, 172.0, 77.3, 75.7, 53.4, 53.1, 22.8. $[\alpha]_D^{20}$ = –22.7 (*c* = 5.3, CH_2Cl_2).

Butanoate (2*R*,3*S*)-**4**: ^{1}H NMR: δ = 5.43 (s, 1 H), 3.80 and 3.65 (both s, 3 H, 2× OCH_3), 1.40 (s, 3 H, CH_3), $ABMNX_3$ system: 2.45 (AB), 1.65 (MN), 0.90 (X_3) (J_{AB}, J_{MNX} = 7.3). ^{13}C NMR: δ = 177.0, 173.3, 167.8, 75.1, 74.5, 53.6, 52.6, 35.6, 22.9, 18.6, 13.8. $[\alpha]_D^{20}$ = –16.0 (*c* = 3.5, CH_2Cl_2).

4.5. 2-*C*-Methyl-D-threitol [(2*R*,3*R*)-1]: A solution of (2*S*,3*S*)-**4** (0.592 g, 2.26 mmol) in dry THF (5 mL) was added to a suspension of $LiAlH_4$ (0.707 g, 18.6 mmol) in THF (20 mL). The mixture was stirred at room temp. for 6 h before it was poured into water (25 mL). Solid material was removed by centrifugation. The solution was evaporated almost to dryness, mixed with methanol/water, 1:1 (40 mL) and solid carbon dioxide. The residue was filtered off and the filtrate evaporated to dryness before methanol was added and centrifuged. The liquid phase was again evaporated almost to dryness. Acetone/methanol, 19:1 (20 mL) was added before the mixture was filtered and the solvents evaporated to dryness to yield an oil: 0.18 g (1.32 mmol, 58.4%) of (2*R*,3*R*)-**1**. ^{1}H NMR (D_2O): δ = 3.67 (dd, *J* = 2.8 and 12 Hz, H-4b), 3.55 (dd, *J* = 2.8 and 12 Hz, H-3), 3.40–3.46 (3 H, H-1a, H-1b, H-4a), 1.0 (s, 3 H). ^{13}C NMR (D_2O): δ = 75.4 (C-3), 74.4 (C-2), 66.4 (C-1), 62.2 (C-4), 19.4 (C-5). $[\alpha]_D^{20}$ = +13 (*c* = 0.5, MeOH).

4.6. 2-*C*-Methyl-L-threitol [(2*S*,3*S*)-1]: Reduction of (2*R*,3*R*)-**2** (0.280 g, 1.46 mmol) and workup of (2*S*,3*S*)-**1** (0.04 g, 0.29 mmol, 19.9%) were performed by the same procedure as above. ^{1}H NMR (D_2O): δ = 3.67 (dd, *J* = 2.8 and 12 Hz, H-4b), 3.55 (dd, *J* = 2.8 and 12 Hz, H-3), 3.40–3.46 (3 H, H-1a, H-1b, H-4a), 1.0 (s, 3 H). ^{13}C NMR (D_2O): δ = 75.4 (C-3), 74.4 (C-2), 66.4 (C-1), 62.2 (C-4), 19.4 (C-5). $[\alpha]_D^{20}$ = –12.5 (*c* = 0.5, MeOH), ref.[7] –11.7 (*c* = 0.5, MeOH). Elemental analysis data also given.

4.7. 2-*C*-Methyl-D-erythritol [(2*S*,3*R*)-1]: Reduction of (2*R*,3*S*)-**4** (0.35 g, 1.3 mmol) and workup of solid (2*S*,3*R*)-**1** (0.12 g, 0.88 mmol, 67.7%) were performed by the same procedure as above. ^{1}H NMR (D_2O): δ = 3.75 (dd, *J* = 2.3 Hz, 11.4 Hz, H-4b), 3.58 (dd, *J* = 2.3 and 8.5 Hz, H-3), 3.52 (dd, *J* = 8.5 and 11.4 Hz, H-4a), 3.50 (d, *J* = 11.7 Hz, H-1b), 3.4 (d, *J* = 11.7 Hz, H-1b), 1.1 (s, 3 H). ^{13}C NMR (D_2O): δ = 76.6, 75.8, 67.9, 63.6, 20.6. $[\alpha]_D^{20}$ = +16.5 (*c* = 0.5, MeOH), ref.[3] +15.7 (*c* = 1.42, MeOH).

4.8. 2-*C*-Methyl-L-erythritol [(2*R*,3*S*)-1]: Reduction of (2*S*,3*R*)-**2** (0.22 g, 1.15 mmol) and workup of (2*R*,3*S*)-**1** (0.109 g, 0.8 mmol, 69.6%) were performed by the same procedure above. ^{1}H NMR (D_2O): δ = 3.75 (dd, *J* = 2.3 and 11.4 Hz, H-4b), 3.58 (dd, *J* = 2.3 and 8.5 Hz, H-3), 3.52 (dd, *J* = 8.5 and 11.4 Hz, H-4a), 3.50 (d, *J* = 11.7 Hz, H-1b), 3.4 (d, *J* = 11.7 Hz, H-1b), 1.1 (s, 3 H). ^{13}C NMR (D_2O): 76.6, 75.8, 67.9, 63.6, 20.0. $[\alpha]_D^{20}$ = –12 (*c* = 0.5, MeOH).

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