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# Methoxymethylation of Tartrate as a Strategy for the Synthesis of Chiral Building Blocks.

Hervé Dulphy[a], Jean-Louis Gras[a*] and Tore Lejon[b]

a. Université d'AIX-MARSEILLE III, Laboratoire RéSo (Réactivité en Synthèse Organique), associé au CNRS, Faculté des Sciences St-Jérôme - D12, F - 13397 Marseille Cedex 20, France.
E-mail: *jean-louis.gras@reso.u-3mrs.fr*
b. Departement of Organic Chemistry, University of Umeå, S - 901 87 Umeå, Sweden,

***Abstract:*** Controlled methoxymethylation of tartrate affords mono- and diMOMtartrates. We took advantage of the particular reactivity of methoxymethylethers and of the conformations of the starting C4 unit, to efficiently synthezise various cyclic methyleneketals (dioxane and dioxolane) or cyclic ethers (oxolane and oxetane). Copyright © 1996 Elsevier Science Ltd

Tartaric acid is one of the few compounds available in nature as either enantiomer and reliable industrial preparations make it one of the cheapest enantiomerically pure compounds available. Therefore tartaric acid and its common esters have frequently been employed as a source of synthetically useful chiral building blocks,[1] or as chiral auxiliaries,[2] in many enantioselective chemical reactions. Derivatizations of tartaric acid that took advantage of the $C_2$ symmetry of the molecule led to the design of chiral ligands efficient at inducing chirality during catalytic synthetic processes.[3] Appropriate manipulation of diethyltartrate indirectly permitted selective protections of hydroxy groups in threitol, the corresponding tetraol.[4]

Transformations of tartaric acid have abundantly been illustrated and consist in differentiating the functions, inversion, deoxygenation, branching and chain elongation or shortening. The first step of all these transformations requires the modification of one of the two or both internal hydroxy groups. Several standard alcohol protective groups have been put in use (OAc, OBn, OMe, ...), but little work involves the formation of methoxymethyl ether(s) (MOM ethers) although methoxymethylation is a common protection for hydroxy groups. Simple procedures allow to perform this protection under various conditions, typically using $ClCH_2OMe$ under basic conditions or dimethoxymethane (DMM) under slightly acidic conditions.[5] Methoxymethylation of 1,2- or 1,3-diols by transacetalation from DMM readily leads to the corresponding cyclic methylene acetals and constitutes a convenient procedure for the protection of these diols.[6] This reaction proved highly selective when applied to polyols or sugars, and allowed the preparation of either dioxane or dioxolane rings.[7]

We report herein on several transformations of diethyl-L-tartrate (DET) **1** into useful chiral building blocks, that show the synthetic potential of the simple methoxymethylation reaction when performed under specifically designed experimental conditions.

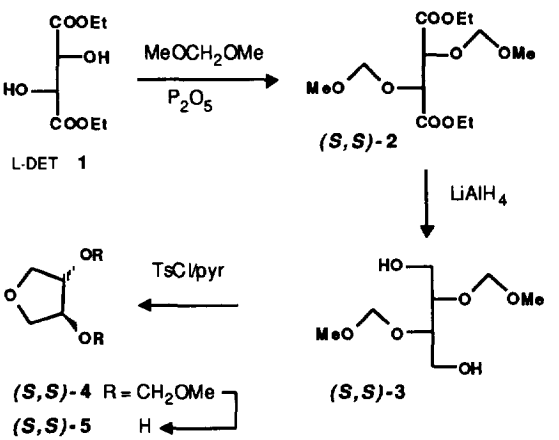
**Dimethoxymethylation**

Complete methoxymethylation of L-DET **1** using chloromethoxymethyl ether[8] or dimethoxymethane[9] leads to 2,3-*O*-bis(methoxymethyl)-L-tartrate **2**. This synthesis has been improved to afford a reproducible quantitative yield by means of the dimethoxymethane method and portionwise addition of phosphorous pentoxide (DMM, 10 eq, $P_2O_5$, 4 eq, rt, 5 h; then $P_2O_5$ 1 eq, 20 min).

DiMOM ether **2** is quantitatively reduced to the 2,3-*O*-bis(methoxymethyl)-L-threitol **3**, an intermediate in the synthesis of the antibiotic aminomycin[8] and of Geissman lactone.[9]

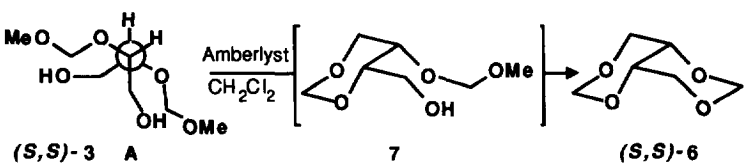
*- Deoxigenating cyclization*

Diol **3** undergoes a deoxigenating cyclization when reacted with tosyl chloride in a mixture of pyridine and $CH_2Cl_2$ directly to give dehydrothreitol derivative *(S,S)*-**4** then *(S,S)*-**5** (91% yield; lit. *ca* 25% from tartaric acid[10] and 35–50% from DET[11]). Dihydroxytetrahydrofurane **5** is an important chiral building block to prepare ligands useful for the asymmetric hydrogenation of acyclic acids[11] and for catalyzed enantioselective hydrocyanation and hydroformylation reactions.[10]




*- bicyclization*

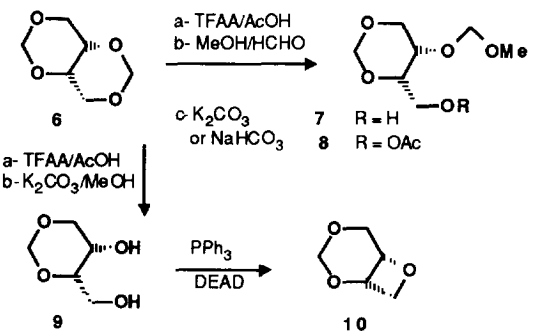
When treated with Amberlyst 15 in refluxing $CH_2Cl_2$, diol **3** smoothly affords dimethylene threitol (DMT) **6**, a building block that generated several chiral auxiliaries,[12] in a three step procedure that makes DMT even more easily available from DET rather than from threitol.[13] The selective bicyclizing process is a consequence of a preferred conformation of compound **3**, due to the *threo* configuration of the *vic* diMOM pattern, and of the kinetically favored formation of a 6- *vs* 5- membered ring by transacetalation.[14]



Conformation **A** puts the two MOM groups apart, thus favoring the cyclization that leads to dioxane **7**. It is difficult to stop the reaction at that stage as it was shown in the case of the corresponding regioisomer (secondary alcohol, primary MOM ether),[15] and **7** undergoes a second cyclization that affords **6** with 99% yield.

The bicyclization of diMOM **3** into 6-membered rings is an original application of the dimethoxymethylation of DET since **3** easily cyclizes into a furanose derivative if one of the primary alcohols is oxidized to an aldehyde.[8]

Monocyclization of **3** is indirectly achieved by partial acetolysis of DMT **6** (TFAA/AcOH) followed by methanolysis of the resulting methylenetrifluoroacetate intermediate. The procedure gives either alcohol **7** or acetate **8** according to the final treatment of the reaction mixture. Both compounds are desymmetrized DET derivatives.




Deoxygenation of DET derivatives can also be done dissymmetrically from **6** *via* diol **9**, the product of partial acetolysis of **6** under standard conditions.[12a]

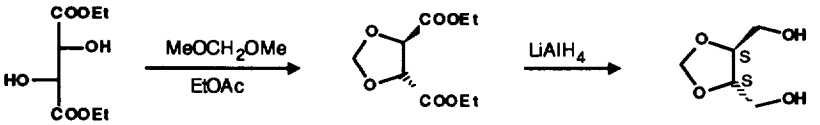
Diol **9** can be dehydrated under Mitsunobu conditions ($PPh_3$/DEAD)[16] to give unsymmetrical dehydrothreitol derivative **10**. Forming an oxetane under those conditions seems rather unusual, the Misunobu reaction being more used to produce oxiranes and oxolanes. The easy formation of oxetane **10** contrasts with the reaction of *cis*-(2-hydroxymethyl)-cyclohexanol and diethyltriphenyl phosphorane that gives acyclic ethers rather than the corresponding bicyclic oxetane.[17]

Oxetane **10** has been obtained as a side product during another study,[18] and its formation certainly is the consequence of a favorable conformation of diol **9** (OH axial, $CH_2OH$ equatorial) and of its derivatives.

## Cyclizing methoxymethylation

Methoxymethylation of L-DET with DMM, catalyzed by an acidic resin in refluxing ethyl acetate, directly leads to the chiral symmetrical dioxolane **11**. The reaction takes advantage of the capability of many MOM-alcohol and diMOM compounds to form a methyleneketal under the appropriate conditions.[6b] Careful control of the reaction conditions (the use of dry EtOAc as the solvent proved essential to get a good medium) allows the total conversion of the intermediate mono and diMOM compounds to the dioxolane **11**, thus obtained in

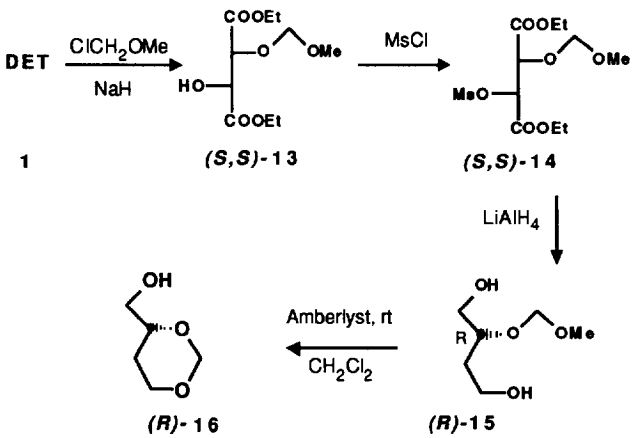
better yield than with previous syntheses. This compound can be converted to hindered diols by Grignard addition[19] or reduced to 2,3-*O* -methylene threitol **12**, providing a direct entry to this threitol derivative.[12a]




**1** L-DET *(R,R)*-**11** *(S,S)*-**12**

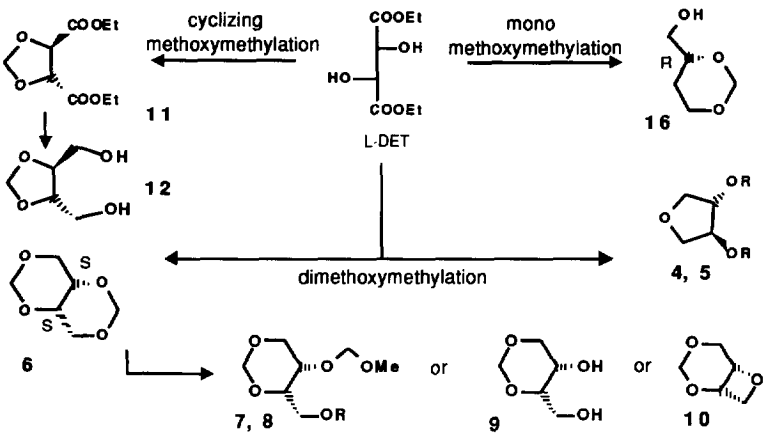
## Monomethoxymethylation

Finally, the $C_2$ axis of tartaric acid can be annulated by conversion to malic acid derivatives. Methoxymethylation of **1** with the back to the shelves chloromethoxymethyl ether and sodium hydride (1 eq each) affords monoMOM **13**, easily isolated from diMOM **2** and unreacted DET in 85% yield. Alcohol **13** is converted to mesylate **14** by a standard procedure. Concomitant reduction of the ester functionalities to primary alcohols and of the mesylate to the alkane leads to MOM compound **15**, a 1,2,4-butanetriol derivative monoprotected on the secondary position. The triol is the reduced form of malic acid and compound **15** is related to the expensive *(R)*-(+)- non natural enantiomer of the acid. Diol-MOM **15** readily affords *(2R)*-2,4-*O* -methylene butanetriol **16** with a full chemoselectivity when treated with Amberlyst 15 in dry $CH_2Cl_2$ at room temperature. Methylenebutanetriol **16** has proved to be a surprisingly efficient template for the Lewis acid promoted asymmetric Diels-Alder addition.[20]




**1** *(S,S)*-**13** *(S,S)*-**14** *(R)*-**15** *(R)*-**16**

To conclude with, methoxymethylation of tartrate is a versatile strategy for the synthesis of valuable chiral auxiliaries and chiral building blocks. Selecting the source of the methoxymethyl radical along with careful control of the experimental conditions allow the construction of variable homochiral heterocyclic systems of known configuration. Those compounds afford entries to dioxolane, dioxane, tetrahydrofurane, oxetane derivatives of tartaric and malic acids.




## Experimental

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer IR FT-1605 spectrophotometer. The $^1H$ NMR spectra and the $^{13}C$ NMR spectra were recorded on an AC 200 Brucker instrument, in $CDCl_3$ with TMS as internal reference for chemical shifts, expressed as δ values in ppm with coupling constants in Hz. Optical rotations were measured on a Perkin-Elmer 141 polarimeter with a Hg lamp, or at the sodium D line, at the designated concentration in g per ml. Chromatography was carried out on columns packed with Merck silica gel 60 (70–230 mesh).

*2,3-O-Bis(methoxymethyl)-L-tartrate* **2**.

Phosphorous pentoxide (14.2 g, 0.1 mol) was added to dry $CH_2Cl_2$ (20 ml) and dimethoxymethane (22.1 ml, 0.25 mol) before the addition of diethyl-L-tartrate (5.16 g, 25 mmol) in dry $CH_2Cl_2$ (30 ml). After 5 h of stirring at rt, fresh phosphorous pentoxide (3.6 g, 25 mmol) was added and the reaction was allowed to proceed another 15 min before it was quenched by the addition of saturated $NaHCO_3$ (50 ml). The water-phase was then extracted with three 50 ml portions of $CH_2Cl_2$. The organic layer was washed with 50 ml brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to leave 7.35 g (100% yield) of an analytically pure product that was identical to reported sample.[8]

$^1H$ NMR: 4.74 and 4.62 (4H, AB, $J$ = 7.1); 4.65 (2H, s); 4.20 (4H, q, $J$ = 7.2); 3.31 (6H, s); 1.26 (6H, t, $J$ = 7.2). $^{13}C$ NMR: 168.8, 96.4, 75.5, 61.4, 56.1, 14.0. $[\alpha]^{21}_D$ +141.1° (c $212.10^{-3}$, $CHCl_3$). Lit.[8]: $bp_{0.6}$ = 152-154 °C; $[\alpha]^{20}_D$ +142.7° (c 1.57, MeOH).

*2,3-O-Bis(methoxymethyl)-L-threitol* **3**.

A solution of 2,3-*O*-bis(methoxymethyl)-L-tartrate **2** (1.47 g, 5 mmol) in dry THF (15 ml) was added to a suspension of $LiAlH_4$ (570 mg, 15 mmol) in THF (30 ml) at 0 °C. After addition the mixture was stirred for an additional 3.5 h at rt, when all starting material was consumed. The reaction was quenched by adding 15 g of Celite and 15 g of sodium sulphate decahydrate followed by 1.5 ml of 10% aq NaOH. Filtration followed by solvent removal under reduced pressure left a colorless oil that crystallized upon standing (1.02 g, 97% yield).

mp = 64 °C. IR ($CDCl_3$), $cm^{-1}$: 3620, 3460, 1430, 1255, 1035. $^1H$ NMR: 4.74 and 4.67 (4H, AB, $J$ = 6.8), 3.73 (6H, br s), 3.41 (6H, s), 2.62 (2H, br s). $^{13}C$ NMR: 97.4, 80.3, 61.9, 56.0. $[\alpha]^{21}_D$ -7.9° (c $209.10^{-3}$,

MeOH). Lit.[8]: $[\alpha]^{24}_D$ -2.9°(c 2.66, MeOH).

*(3S,4S)-3,4-O-Bis(methoxymethoxy)tetrahydrofurane* **4**.

Pyridine (2 ml) and tosyl chloride (374 mg, 1.8 mmol) were added to a solution of diol **3** (130 mg, 0.6 mmol) in dry $CH_2Cl_2$ (2 ml). The mixture was kept at reflux for 4 h then the solvents were removed under reduced pressure. Heptane (10 ml) was added to azeotropically distil traces of pyridine and the reaction mixture was chromatographed using methanol (gradient 1–3%) in $CH_2Cl_2$ as eluent to afford **4** (110 mg, 96% yield) as a colorless oil.

IR ($CDCl_3$), $cm^{-1}$: 1450, 1390, 1360, 1150-1030, 920. $^1H$ NMR: 4.86 and 4.56 (4H, AB, $J$ = 10.1), 4.20–4.27 (2H, m), 4.02 and 3.81 (4H, dAB, $J$ = 9.9, 4.2, 2.3), 3.40 (6H, s). $^{13}C$ NMR: 95.7, 80.9, 71.9, 55.6. $[\alpha]^{21}_{546}$ -23.0°(c 224.$10^{-3}$, $CHCl_3$). Anal. Calcd: C, 49.99; H, 8.39. Found: C, 49.94; H, 8.43.

*(3S, 4S)-3,4-dihydroxytetrahydrofurane* **5**.

DiMOM **4** (70 mg) is refluxed in methanol (2 ml) along with Amberlyst 15 ion-exchange resin (10 mg) for 1 h. The mixture is diluted with 6 ml $CH_2Cl_2$ then filtrated, concentrated and chromatographed to afford diol **5** (38 mg, 98% yield).

$^1H$ NMR: 4.94 (2H, s), 4.14 (2H, dd, $J$ = 3.4, 0.5), 4.01 and 3.70 (4H, dAB, $J$ = 9.5, 3.4, 0.5).

$^{13}C$ NMR: 78.1, 74.4. $[\alpha]^{21}_D$ -4.0° (c 153.$10^{-3}$, MeOH). Anal. Calcd: C, 46.15; H, 7.75. Found: C, 46.08; H, 7.82. Lit.[10]: $bp_{0.001}$ = 110 °C; $[\alpha]_D$ -4.5°(c 0.9, $H_2O$).

*Dimethylenethreitol* **6**.

2,3-*O*-Bis(methoxymethyl)-L-threitol **3** (111 mg) was refluxed for 24 h in dry $CH_2Cl_2$ (2 ml) together with 30 mg of Amberlyst 15 ion-exchange resin. Filtration and solvent removal under reduced pressure left 75 mg (99%) of analytically pure white crystals, identical to earlier published data.[13]

mp = 180–181 °C. IR ($CDCl_3$), $cm^{-1}$: 1175, 1085, 1035, 1010, 910. $^1H$ NMR: 5.18 and 4.80 (4H, AB, $J$ = 6.2), 4.16 and 3.83 (4H, AB, $J$ = 12.7), 3.63 (2H, s). $^{13}C$ NMR: 93.3, 69.5, 70.1 . $[\alpha]^{21}_D$ +10.7° (c 110.$10^{-3}$, $CHCl_3$)

*(2S,3S)-2-O-methoxymethyl-1,3-O-methylenethreitol* **7** and *acetate* **8**.

Trifluoroacetic anhydride (1.4 ml, 10 mmol) and freshly distilled acetic acid (0.6 ml, 10 mmol) were added to an ice cooled solution of dimethylenethreitol **6** (730 mg, 5 mmol) in dry $CH_2Cl_2$ (7.5 ml) under argon. The ice bath was removed and, after 10 min, oven dried paraformaldehyde (150 mg, 5 mmol) was added. The mixture was magnetically stirred for 1.5 h at rt. Then paraformaldehyde (300 mg, 10 mmol), dry DMM (3.75 ml) and dry methanol (11.25 ml) were added. The mixture was stirred for 5h at rt then cooled to 0 °C before careful addition of $K_2CO_3$ (4.14 g, 30 mmol). After 5 h more stirring, the solution was filtered through silica gel, concentrated and chromatographed to afford MOM-alcool **7** (673 mg, 76% yield) along with diol **9** (120 mg). IR ($CDCl_3$), $cm^{-1}$: 3700, 3630, 3495, 1240-1210, 1185, 1160, 1040. $^1H$ NMR: 5.14 and 4.74 (2H, AB, $J$ = 6.2), 4.77 and 4.69 (2H, AB, $J$ = 7.0), 4.18 and 3.74 (2H, AB, $J$ = 12.4), 3.89-3.78 (3H, m), 3.59 (1H, s), 3.42 (3H, s), 2.07 (1H, s). $^{13}C$ NMR: 95.4, 93.3, 78.5, 69.4, 68.7, 61.6, 55.6. $[\alpha]^{21}_{546}$ +103.9°(c 137.$10^{-3}$, $CHCl_3$). Anal. Calcd: C, 47.45; H, 7.4. Found: C, 47.40; H, 7.42.

If $Na_2CO_3$ was used in place of $K_2CO_3$ the reaction led to the corresponding acetate **8** (803 mg, 73%). IR ($CDCl_3$), $cm^{-1}$: 1740, 1210, 1155, 1130, 1105, 1080, 1035. $^1H$ NMR: 5.10 and 4.73 (2H, AB, $J$ = 6.2), 4.77 and 4.64 (2H, AB, $J$ = 7.2), 4.21 (2H, m), 4.20 and 3.71 (2H, AB, $J$ = 12.6), 3.93 (1H, m), 3.54 (1H, br s), 3.38 (3H, s), 2.04 (3H, s).$^{13}C$ NMR: 170.7, 95.5, 93.5, 76.1, 69.1, 68.5, 63.8, 55.8, 20.7.

$[\alpha]^{21}_{546}$ +53.3°(c 152.$10^{-3}$, $CHCl_3$). Anal. Calcd: C, 49.31; H, 6.9. Found: C, 49.25; H, 6.88.

*(2S,3S)-1,3-O-Methylenethreitol* **9**

Diol **9** is prepared according to ref. 12a.

IR ($CDCl_3$), $cm^{-1}$: 34580, 3450, 1095, 1064, 1025, 900. $^1H$ NMR: 4.90 and 4.60 (2H, AB, $J$ = 6.0), 4.72 (2H, s), 4.03 and 3.84 (2H, AB, $J$ = 12.0), 3.78-3.67 (3H, m), 3.60 (1H, s). $^{13}C$ NMR: 93.8, 79.0, 72.1, 65.1, 62.4. $[\alpha]^{21}_{546}$ +2.3°(c $88.10^{-3}$, $CHCl_3$).

*(5S, 8S)-2,4,7-Trioxabicyclo-[4,2,0]-octane* **10**

A solution of diethyl azodicarboxylate (348 mg, 2 mmol) in THF (2 ml) was added dropwise to a solution of diol **9** (268 mg, 2 mmol) and triphenylphosphine (524 mg, 2 mmol) in THF (3 ml) at rt. The solution was stirred for 24 h then filtered, concentrated and the residue chromatographed to afford oxetane **10** (165 mg, 71% yield).

IR ($CDCl_3$), $cm^{-1}$: 1265, 1190, 100, 1020. $^1H$ NMR: 5.08 and 4.75 (2H, AB, $J$ = 6.4), 4.80 -4.71 (2H, m), 4.56 and 4.39 (2H, AB, $J$ = 6.1), 4.07 and 3.76 (2H, AB, $J$ = 13.8). $^{13}C$ NMR: 89.6, 76.2, 76.1, 70.0, 68.6. $[\alpha]^{21}_{546}$ +10.5°(c $80.10^{-3}$, $CHCl_3$) . Anal. Calcd: C, 46.15; H, 7.75. Found: C, 46.1; H, 7.77.

*2,3-O-Methylene diethyl-L-tartrate* **11**.

Diethyl-L-tartrate **1** (3.09 g, 15 mmol) was dissolved in dimethoxymethane (15 ml) and ethyl acetate (75 ml) then an Amberlyst 15 ion-exchange resin (600 mg) was added. The flask was fitted with a Dean-Stark apparatus charged with activated 3Å molecular sieves for the removal of methanol formed during the reaction. The solution was kept at reflux for 24 h with GC monitoring of dioxolane formation. Filtration and concentration afforded dioxolane **11** (3.27 g, 100% yield). A small amount of the material was distilled and was in all respects identical with reported data.[19]

$bp_{0.5}$ = 78 °C. $^1H$ NMR: 5.24 (2H, s), 4.71 (2H, s), 4.27 (4H, q, $J$ = 7.2), 1.31 (6H, t, $J$ = 7.2).

$^{13}C$ NMR: 169.2, 97.5, 76.8, 56.0, 14.1. $[\alpha]^{24}_D$ -77.9°(c $330.10^{-3}$, $CHCl_3$). Anal. Calcd: C, 49.54; H, 6.47. Found: C, 49.58; H, 6.42. Lit.[19]: $bp_{15}$ = 150 °C; $[\alpha]^{rt}_D$ -70.1°(c 1.11, EtOH).

*Synthesis of 2,3-O-methylene-L-threitol* **12**.

A solution of crude 2,3-*O*-methylene-diethyl-L-tartrate **11** (1.09 mg, 5mmol) in dry THF (15 ml) was added to $LiAlH_4$ (570 mg, 15 mmol) in dry THF (30 ml) cooled to 0 °C. The reaction was allowed to proceed for 6 h at rt then it was quenched with a mixture of Celite (15 g) and sodium sulphate decahydrate (15 g), followed by the addition of 10% aq NaOH (1.5 ml). The mixture was diluted with $Et_2O$, filtered and the solvent was removed under reduced pressure. Chromatography with 10% methanol in $CH_2Cl_2$ as eluent gave diol **12** (652 mg, 97%).[12a] IR ($CDCl_3$), $cm^{-1}$: 3380, 1110, 1090, 1030. $^1H$ NMR: 4.30 (2H, s), 3.10 (6H, m), 2.60 (2H, s). $^{13}C$ NMR: 95.9, 79.6, 62.7. $[\alpha]^{21}_{546}$ -30.0°(c $100.10^{-3}$, MeOH)

*Synthesis of 2-O-methoxymethyl-diethyl-L-tartrate* **13**.

Sodium hydride (106 mg, 4.4 mmol) was dissolved in dry DMF (10 ml) and diethyl-L-tartrate **1** (907 mg) was added at -40 °C. After stirring for 30 min methoxymethyl chloride (370 µl, 4.85 mmol) was added and the reaction mixture was stirred for another 6h at -40 °C. The mixture was hydrolysed with brine and extracted with $CH_2Cl_2$. The solvents were distilled off under vacuum and the residue was flash chromatographed to afford monoMOM **13** (936 mg, 85%), along with little diMOM **2**.

IR ($CDCl_3$), $cm^{-1}$: 3690, 3620, 3560, 1740, 1200, 1155, 1130, 1105, 1045. $^1H$ NMR: 4.79 and 4.58 (2H, AB, $J$ = 7.0), 4.52-4.69 (2H, m), 4.11 (2H, q, $J$ = 7.0), 4.25 (2H, q, $J$ = 7.1), 3.26 (3H, s, $J$ = 1.3), 1.20-1.30 (6H, m). $^{13}C$ NMR: 171.1, 169.0, 98.2, 75.8, 72.1, 61.9, 61.4, 56.0, 14.0. $[\alpha]^{21}_{546}$ +76.5°(c $293.10^{-3}$, $CHCl_3$). Anal. Calcd: C, 48.0; H, 7.25. Found: C, 47.91; H, 7.32.

*Synthesis of 2-O-methoxymethyl-3-methylsulfonyloxy-diethyl-L-tartrate* **14**.

2-*O*-Methoxymethyl-diethyl-L-tartrate **8** (250 mg, 1 mmol) was dissolved in dry $CH_2Cl_2$ (5 ml) and triethylamine (420 µl, 3 mmol) then mesyl chloride (250 µl, 3 mmol) were added. The reaction proceeded 1 h at rt before addition of dry $Et_2O$ (10 ml) and filtration of the white precipitate that formed. The solvent was removed under reduced pressure to afford a quantitative yield (331 mg) of crude unstable mesylate.

*Synthesis of (2R)-2-O-methoxymethyl-1,2,4-butanetriol* **15**.

Crude mesylate **14** (158 mg, 0.48 mmol) in dry $Et_2O$ (4 ml) was added to $LiAlH_4$ (102 mg, 2.68 mmol) in dry $Et_2O$ (8 ml) cooled to 0 °C. After 72 h at rt the reaction was quenched by adding 2.68 g of celite, 2.68 g of sodium sulphate decahydrate and 300 µl of water. The solution was filtered, concentrated and the residue (102 mg) treated in the next step as such. A sample of diol **15** was chromatographed for analysis.

IR ($CDCl_3$), $cm^{-1}$: 3630, 3450, 1155, 1105, 1040. $^1H$ NMR: 4.71 (2H, AB, $J$ = 6.9), 3.53-3.79 (5H, m), 3.40 (3H, s), 2.84 (2H, br s), 1.74 (2H, dt, $J$ = 6.0, 5.7). $^{13}C$ NMR: 96.9, 79.4, 65.5, 59.3, 55.8, 34.4. $[\alpha]^{21}_{546}$ -13.9°(c $28.10^{-3}$, $CHCl_3$). Anal. Calcd: C, 47.99; H, 9.4. Found: C, 47.89; H, 9.39.

*Synthesis of (2R)-2,4-O-methylene-1,2,4-butanetriol* **16**.

Crude diol **15** (102 mg) in $CH_2Cl_2$ (2 ml) was stirred in the presence of Amberlyst 15 ion-exchange resin (20 mg) for 2 h. The solution was concentrated, filtered over silica gel to give alcohol **16** (26 mg, 48% yield from **13**). $^1H$ NMR: 5.06 and 4.70 (2H, AB, $J$ = 6.3), 4.10 and 3.50-3.80 (2H, ABX, $JAB$ = 11.5), 3.80-3.50 (3H, m), 2.40 (1H, s br), 1.94-1.73 (1H, m), 1.40-1.29 (1H, m). $^{13}C$ NMR: 93.5, 76.9, 66.1, 65.2, 27.4. $[\alpha]^{25}_{546}$ -24.8°(c $12.10^{-3}$, $CHCl_3$). Anal. Calcd: C, 50.84; H, 8.53. Found: C, 50.78; H, 8.59.

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