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SYNTHESIS OF (2*R*, 3*R*)-1,4-DIMETHOXY-1,1,4,4-TETRAPHENYL-2,3-BUTANEDIOL: A NEW C_2-SYMMETRIC VICINAL DIOL FROM DIMETHYL L-TARTRATE

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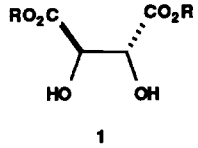
Abstract: A practical synthesis of a new C_2-symmetric vicinal diol, (2*R*, 3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol, from dimethyl L-tartrate involving five steps in overall yield of 38% is described.

Since the discovery of the inherent advantages of chiral auxiliary reagents possessing C_2-symmetry in asymmetric processes[1], a host of systems possessing this symmetry property have been prepared and become the subject of many studies in asymmetric induction. For example, encouraged by the particularly high asymmetric induction achieved in the catalytic Sharpless epoxidation process where simple natural tartrate-derived chiral auxiliaries **1** are employed,[2] this cheap and readily available chiral source has been utilized in stoichiometric carbonyl addition reactions such as allylborations,[3] crotylborations,[4] and propargylborations.[5] In addition to these efforts, L-tartrate derived 1,1,4,4-tetraphenyl-1,4-diols **2** have been employed in catalytic Diels-Alder reactions[6] and stoichiometric alkylations[7] where a Lewis acidic titanium metal center functioned as the key reaction center.



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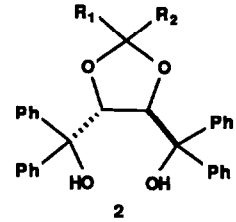
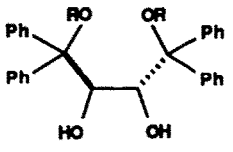


2

With the aforementioned studies as background, it seemed to us that a tartrate-derived chiral auxiliary of the general structure **3** would be worthy of synthesis and investigation for at least two reasons.[8] For one, these systems should form a five-membered chelate complex **4** with suitable metals and therefore be interesting analogues of the chiral auxiliaries employed in some of the studies mentioned above. Secondly, system **3** possesses the alkyl group R which can be varied and therefore "attenuated" in order to aid in the design of a chiral auxiliary with maximum efficiency

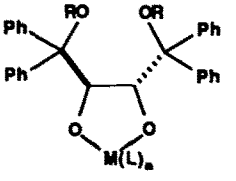
during chirality transfer. We wish to report in this paper the first synthesis of compound **5**, tl simplest structural analogue of **3**, from dimethyl L-tartrate in a preparatively useful fashion.

In our initial efforts, commercially available L-tartaric acid was converted into ketal **6** in tl usual fashion.[9] This material was then treated with excess phenyl Grignard to give the known di **7**[6,7] in 90% yield. This diol was allowed to react with methylsulfinyl carbanion (dimsyl anion) a methyl iodide to provide the corresponding dimethyl ether **8** in 80% yield. Compound **8** w readily recrystallized using ethanol and CCl_4. Our attempts at the crucial protic acid catalyz removal of the ketal moiety, however, met with repeated failure as a variety of protic acids ... several solvent systems[10] resulted in the generation of either complex product mixtures and/or the monoether **9** arising from the partial demethylation of the ether function.



3 R = alkyl

5 R = CH_3



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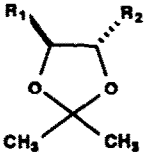


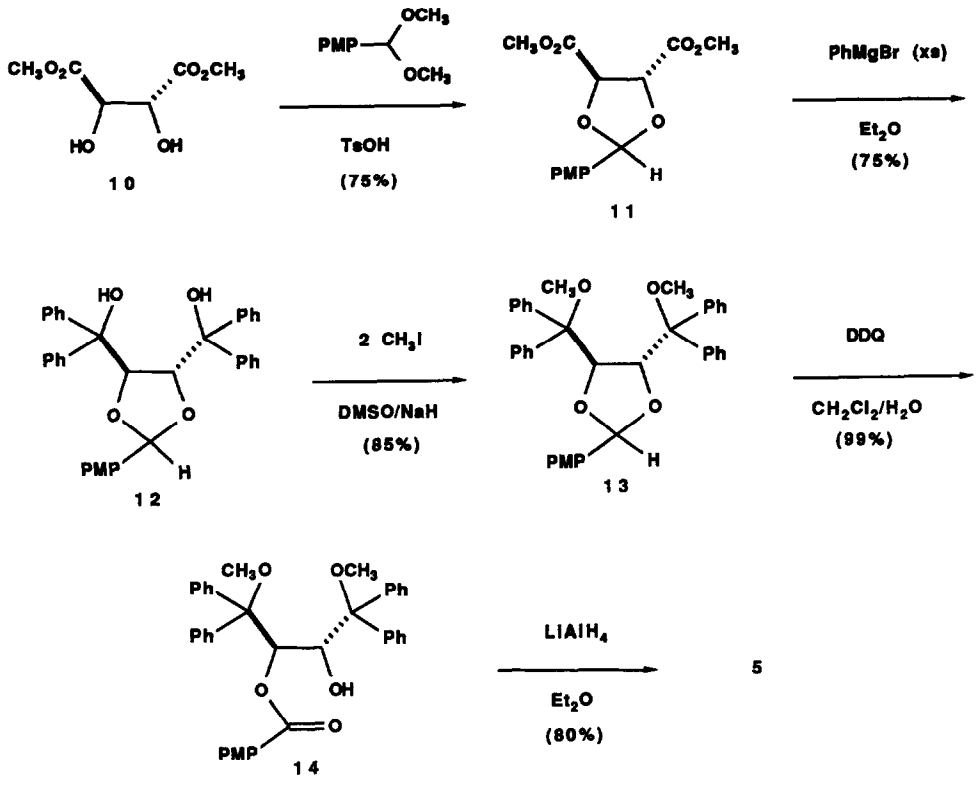
6 $R_1 = R_2 = CO_2CH_3$

7 $R_1 = R_2 = C(OH)(C_6H_5)_2$

8 $R_1 = R_2 = C(OCH_3)(C_6H_5)_2$

9 $R_1 = C(OCH_3)(C_6H_5)_2$;
$R_2 = C(OH)(C_6H_5)_2$

We, therefore, pursued an oxidative deprotection strategy by incorporating *p*-methoxybenzaldehyde as the acetal protecting group (Scheme). Protection of dimethyl L-tartrate **10** with α, α-dimethoxy-*p*-methoxybenzaldehyde according to standard procedure[11] proceeded smoothly to give *p*-methoxy phenyl (PMP) acetal **11** in 75% yield. Compound **11** was treated with excess phenyl Grignard to afford diol **12** in 75% yield. As in the case of compound **7**, diol **12** was allowed to react with dimsyl anion followed by methyl iodide to provide the corresponding dimethyl ether **13** in 85% yield. A sequential addition procedure where slightly more than one equivalent of base is added to the diol solution followed by one equivalent of the alkylating agent and the repetition of this procedure afforded the best results. The key oxidation of the acetal function of **13** with 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (DDQ)[12] proceeded smoothly to give hydroxy ester **14** in 99% yield in sufficient purity to be employed in the next step without further purification. The removal of the ester group was accomplished by treatment of **14** with lithium aluminum hydride to afford diol **5** in 80% yield.[13] The preparation of other analogues of system **3** as well as the application of these compounds in asymmetric synthesis[14] are in progress and their results will be reported in due course.



SCHEME

Experimental Section

General. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR model 1600 spectrophotometer as KBr pellets. ^{1}H NMR were recorded on either a Bruker AM500 spectrometer at 500 MHz or a Varian EM-360A spectrometer at 60 MHz. All NMR spectra were recorded in $CDCl_3$ and are reported in parts per million (ppm) relative to TMS (0.0 ppm). TLC analyses were carried out on Whatman (Al Sil G) aluminum-backed silica gel plates (250 μm). Optical rotations were obtained on a Cenco Kern polarimeter using a 1 dm polarimeter cell. Tetrahydrofuran (THF) and diethyl ether were distilled from $LiAlH_4$; petroleum ether (60-68 °C) was distilled from NaH; hexane was distilled prior to use; methanol was distilled from Mg turnings; CH_2Cl_2, ethyl acetate, and dimethyl sulfoxide (DMSO) were distilled from CaH_2; all other solvents used were of reagent grade. All non-aqueous reactions were carried out under a dry Ar atmosphere with flame-dried glassware.

(4*R*,5*R*)-2-(*p*-Methoxyphenyl)-4,5-bis(carbomethoxy)-1,3-dioxolane (11). From a stirred solution of dimethyl L-tartrate (10 g, 56 mmol) , α, α-dimethoxy-*p*-anisaldehyde[15] (11 g, 61 mmol) and *p*-toluene sulphonic acid (*p*-TsOH) (13 mg, 0.068 mmol) in toluene (50 mL) was azeotropically distilled toluene/methanol (63.7 °C). The solution was further heated until the temperature of the distillate had risen to 110 °C. The reaction was monitored by TLC. After all of the starting material had been consumed, the brown solution was cooled to room temperature. The solution was diluted with CH_2Cl_2 (50 mL) and neutralized by stirring for an hour over excess

K_2CO_3. The mixture was filtered and the brown solution was concentrated in vacuo to give a yellow precipitate, which was recrystallized from CH_2Cl_2: petroleum ether (60-68 °C) to afford 12.5 g (75%) of the title compound as a white solid: $[\alpha]^{24}_D$ -18.8° (*c* 21, CH_3OH); R_f 0.38 (17% ethyl acetate in hexane); mp 72-73 °C; IR 3009, 2942, 2845, 1763, 1614, 1517, 1436, 1218, 1086, 846, 686, 593 cm^{-1}; ^1H NMR (500 MHz) δ 7.47-7.45 (m, 2 H, line spacing = 8.6 Hz, aromatic CH), 6.88-6.86 (m, 2 H, line spacing = 8.6 Hz, aromatic CH), 6.05 (s, 1 H, C*H* $C_6H_4OCH_3$), 4.91 (d, 1 H, J = 4.0 Hz, C*H*CO_2CH_3), 4.80 (d, 1 H, J = 4.1 Hz, C*H*CO_2CH_3), 3.82 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3). Anal. Calcd. for $C_{14}H_{16}O$: C, 56.75; H, 5.45. Found: C, 56.73; H, 5.35.

(4*R*,5*R*)-2-(*p*-Methoxyphenyl)-α,α,α',α'-tetraphenyl-1,3-dioxolan-4,5-dimethanol (12). The phenyl Grignard reagent was prepared in the usual manner by adding phenyl bromide (17.9 mL, 170 mmol), dissolved in 80 mL of dry diethyl ether, dropwise to crushed Mg turnings (4.12 g, 170 mmol). The resulting dark brown mixture was heated to reflux for 30 minutes. The phenyl Grignard was then cooled to -15 °C using a dry ice/isopropanol-H_2O (1:1) mixture. Compound **11** (4.63 g, 15.6 mmol), dissolved in 20 mL of dry THF, was then added as quickly as possible to the Grignard solution. The resulting mixture was allowed to stir at -15°C for 15 minutes. The mixture was then warmed to 0 °C, diluted with ether (200 mL) and saturated aqueous NH_4Cl (350 mL) was added to the mixture until all solids had dissolved. The layers were separated, the aqueous phase was washed with ether (3 X 100 mL), the ether extracts were combined and washed with $NaHCO_3$ until the pH of the aqueous layer was neutral. The ether layer was dried over anhydrous Na_2SO_4 and the solution was concentrated in vacuo. The resulting yellow oil was then purified by flash chromatography using 20% ethyl acetate in hexane to afford 6.37 g (75%) of the title compound as a white hygroscopic foamy solid: $[\alpha]^{24}_D$ +28.2° (*c* 5.9, CH_3OH); R_f 0.28 (25% ethyl acetate in hexane); mp 104-109 °C, IR 3414 (br), 3058, 2932, 1614, 1517, 1447, 1304, 1251, 1086, 1033, 700 cm^{-1}; ^1H NMR (500 MHz) δ 7.53-7.07 (m, 22 H, aromatic CH), 6.78-6.76 (m, 2 H, line spacing = 8.6 Hz, aromatic CH), 5.28 (d, 1 H, J = 5.0 Hz, C*H*C(Ph)$_2$OH), 5.10 (d, 1 H, J = 5.0 Hz, C*H*C(Ph)$_2$OH), 5.09 (s, 1 H, C*H*$C_6H_4OCH_3$), 3.73 (s, 3 H, OCH_3), 3.39 (s, 1 H, OH), 2.24 (br s, 1 H, OH). Anal. Calcd for $C_{36}H_{32}O_5$: C, 79.38; H, 5.93. Found: C, 79.47; H, 6.22.

(4*R*,5*R*)-4,5-Bis(methoxymethyl)-2-(*p*-methoxyphenyl)-α,α,α',α'-tetraphenyl-1,3-dioxolane (13). A solution of dimsyl anion was prepared from NaH (2.13 g, 92.5 mmol) and 50 mL dry DMSO according to the procedure of Corey and Chaykovsky.[16] To a stirred solution of **12** (3.03 g, 5.58 mmol) in 50 mL dry DMSO kept at ambient temperature by a room temperature water bath was added freshly prepared dimsyl anion until a dark brown solution persisted. To the solution was then added methyl iodide (0.4 mL, 6.1 mmol) and the mixture was stirred at ambient temperature for 30 minutes, after which the color of the solution had changed to pale brown. The above procedure (addition of base followed by alkylating agent) was repeated. The reaction progress was followed by TLC and, if necessary, a third addition of dimsyl anion and methyl iodide was performed. Workup of the reaction was accomplished by addition of 100 mL H_2O followed by 100 mL ether. The phases were separated, the aqueous layer was washed with ether (3 X 100 mL), the ether extracts combined and concentrated in vacuo. The resulting oil, which contained DMSO, was filtered through a short pad of silica gel (25% ethyl acetate in hexane). The filtrate was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting pale yellow foam was purified by flash chromatography (5% ethyl acetate in hexane) to afford 2.71 g (85%) of the title compound as a white foamy solid: $[\alpha]^{24}_D$ -17.8° (*c* 7.3, CH_3OH); R_f 0.71 (20% ethyl acetate in hexane); mp 88-93 °C; IR 3056, 2936, 2834, 1616, 1517, 1446, 1250, 1172, 1076, 1034, 701 cm^{-1}; ^1H NMR (500 MHz) δ 7.44-7.22 (m, 20 H, aromatic CH), 6.85-6.83 (m, 2 H, line spacing = 8.6 Hz, aromatic CH), 6.67-6.66 (m, 2 H, line spacing = 8.6 Hz, aromatic CH), 5.33 (d, 1 H, J = 5.2 Hz, C*H*C(Ph)$_2$OCH$_3$), 5.10 (d, 1 H, J = 5.2 Hz, C*H*C(Ph)$_2$OCH$_3$), 4.86 (s, 1 H, C*H*$C_6H_4OCH_3$), 3.70 (s, 3 H, OCH_3), 3.03 (s, 3 H, OCH_3), 2.98, (s, 3 H, OCH_3). Anal. Calcd. for $C_{38}H_{36}O_5$: C, 79.68; H, 6.35. Found: C, 79.87; H, 6.33.

(2*R*,3*R*)-1,4-Dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol (5). To a stirred solution of **13** (1.05 g, 1.83 mmol) in 36 mL CH_2Cl_2: H_2O (17:1) at room temperature was added DDQ (0.62 g, 2.74 mmol). Immediately upon addition, the solution turned deep red. TLC indicated consumption of all starting material after 1.5 hours. During this time, the color of the reaction mixture changed from deep red to orange and a solid (DDQH) precipitated out of solution. Saturated $NaHCO_3$ (40 mL) followed by CH_2Cl_2 (100 mL) were then added to the resulting dark green solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 X 50 mL). The CH_2Cl_2 extracts

were combined, washed with saturated $NaHCO_3$ (3 X 60 mL), brine (2 X 50 mL), and then dried over Na_2SO_4. The yellow solution was concentrated in vacuo to give a dark brown liquid which was filtered through a short pad of silica gel (25% ethyl acetate in hexane). Concentration of the filtrate in vacuo afforded 1.10 g (>99%) of crude **14** as a white foam. This material was of sufficient purity to be employed in the subsequent reduction without further purification. Rf 0.43 (17% ethyl acetate in hexane); IR 3487 (br), 3058, 2938, 2835, 1724, 1606, 1257, 1167, 1095, 701 cm^{-1}; ^1H NMR (500 MHz) δ 7.74-7.72 (m, 2 H, line spacing = 8.7 Hz, aromatic CH), 7.46-6.78 (m, 22 H, aromatic CH), 6.27 (s, 1 H, C*H*C(Ph)$_2$OCH$_3$), 5.04 (d, 1 H, J = 5.2 Hz, C*H*C(Ph)$_2$OCH$_3$), 3.80 (s, 3 H, OCH_3), 2.97 (s, 3 H, OCH_3), 2.94 (s, 3 H, OCH_3), 2.64 (d, 1 H, J = 5.2 Hz, OH).

To a stirred suspension of $LiAlH_4$ (226 mg, 5.95 mmol) in 20 mL dry ether under Ar at room temperature was slowly added a solution of the hydroxy ester **14** (702 mg, 1.19 mmol) in 10 mL dry ether. After two hours, the reaction was quenched by sequential addition of H_2O (0.25 mL), NaOH (15 %, 0.25 mL), and then another portion of H_2O (0.75 mL). The resulting white solid was filtered and the filter cake was washed repeatedly with ether. The ether layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oil was purified by flash chromatography (5% ethyl acetate in hexane) to provide 434 mg (80%) of the title compound as a white hygroscopic foam: $[\alpha]^{24}_D$ +17.6° (*c* 19.6, CH_3OH); Rf 0.47 (17% ethyl acetate in hexane); mp 76-78°C; IR 3377 (br), 3052, 2941, 2832, 1449, 1446, 1071, 766, 700 cm^{-1}; ^1H NMR (60 MHz) δ 7.41-7.19 (m, 20 H, aromatic CH), 4.68 (d, 2 H, J = 4 Hz, C*H*C(Ph)$_2$OCH$_3$), 3.13 (s, 6 H, OCH_3), 2.72 (br d, 2 H, J = 4 Hz, OH). Anal. Calcd for $C_{30}H_{30}O_4$: C, 79.26; H, 6.66. Found: C, 79.30; H, 6.49.

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10. Deprotection of the ketal was attempted using: 10% H_2SO_4 in THF, 20% H_2SO_4 in THF, 30% H_2SO_4 in THF, 10% HCl in methanol, and *p*-toluene sulphonic acid in methanol. Each of these attempts were carried out both at 24 °C and reflux.
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13. We attributed the presence of minor peaks in the 500 MHz NMR spectra of compounds **11-13** to the presence of conformers of these compounds. The possibility that these peaks were due to epimers of **11-13** was ruled out by the repeated crystallization of compound **11** prior to analysis. The NMR spectra of compounds **14** and **5** did not show any additional peaks.

14. Preliminary studies carried out in our laboratories in which **5** was employed as a chiral auxiliary in the allylboration of benzaldehyde with allylborane at -78 °C resulted in (*R*)-1-phenyl-1-propen-1-ol in 40% ee. This result stands in sharp contrast to that of Roush and coworkers in which the use of (*R*,*R*)-diisopropyl tartrate afforded the same allyl alcohol with *S* configuration in 60% ee (see ref 3).
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