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ASYMMETRIC SYNTHESIS OF (R)- AND (S)-CITRAMALATE IN HIGH ENANTIOMERIC PURITY

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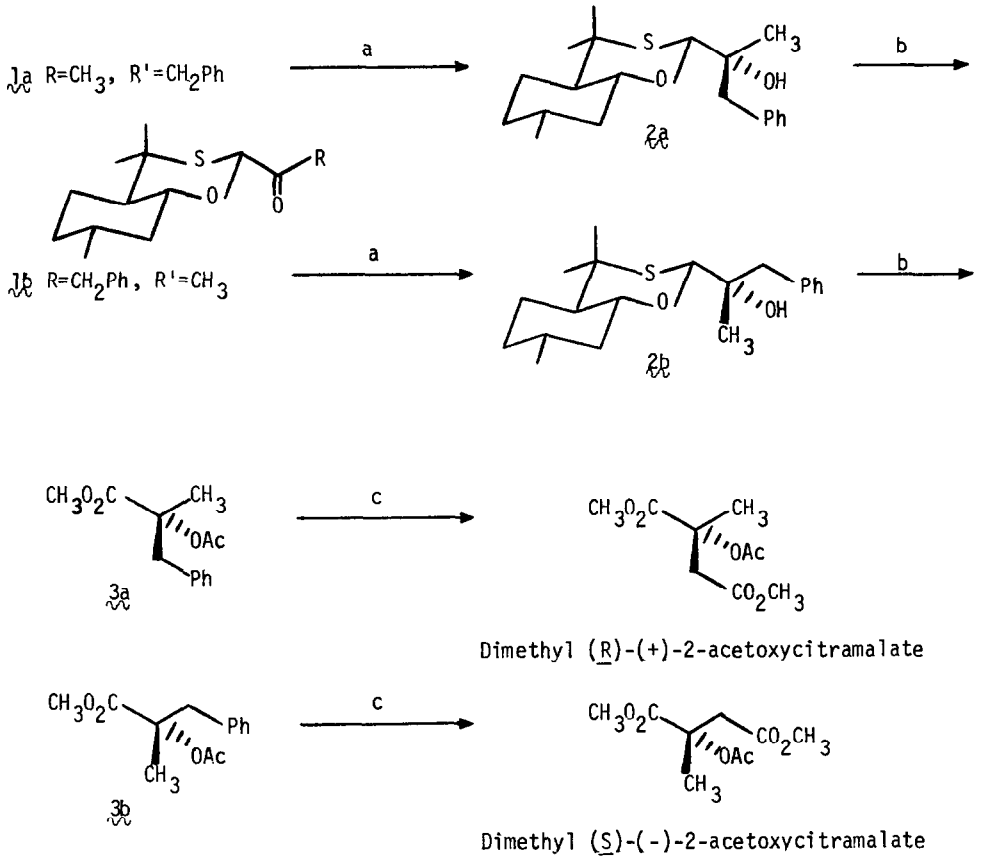
Summary. An asymmetric synthesis of both isomers of dimethyl 2-acetoxycitramalate in over 96% enantiomeric excess is described.

Citramalic acid is a member of the 2-alkylmalic acid family and has been isolated from a variety of natural sources. Its structure was determined and a method for its preparation described in the late 19th century;[1,2] however, its absolute configuration was not determined until 1965 by correlation with mevalolactone.[3] Resolution[4,5] and enzymatic synthesis[6] have until recently been the only source of optically pure citramalic acid. A number of asymmetric chemical syntheses of either (R)- or (S)-citramalic acid have appeared in the last decade,[7-11] but only one group[10] has reported material of acceptable (85%) enantiomeric purity. The use of citramalic acid as a chiral synthon in prostaglandin synthesis[12] makes its preparation of particular interest.

We describe here an asymmetric synthesis of dimethyl (R)-(+)- and (S)-(-)-2-acetoxycitramalate in over 96% enantiomeric excess using a chiral 1,3-oxathiane adjuvant developed by our group.[13-16] The synthesis is summarized in Scheme 1.

The previously described[17] oxathianyl ketone **1a** (500 mg, 2.0 mmol) in THF (50 mL) was treated with ethereal benzylmagnesium bromide (25 mL, 5 eq.) at -78°C, the resulting solution stirred overnight under N_2 and quenched cold with saturated NH_4Cl (25 mL). The layers were separated, the aqueous layer extracted with Et_2O (25 mL), the combined organic material dried ($MgSO_4$) and concentrated to give **2a** (650 mg, 97%) as a clear oil after distillation (Kugelrohr, bp ca. 200°C/0.1 mm). Compound **2b** was prepared in analogous fashion by addition of methylmagnesium bromide to **1b**. Each diastereomer was formed in ca. 100% d.e. as evidenced by their ^1H and ^{13}C NMR spectra which exhibited significant differences and were free from cross contamination.[18]

Carbinol **2a** (450 mg, 1.35 mmol) in Et_2O (5 mL) was added to 80% CH_3CN/H_2O (20 mL) which contained $AgNO_3$ (460 mg, 2.7 mmol) and N-chlorosuccinimide (360 mg, 2.7 mmol).[19] A grey-white precipitate (AgCl) formed immediately; the mixture was stirred for 5 min and quenched by



a) R'MgBr b) i. NCS, $AgNO_3$ ii. $NaClO_2$ iii. CH_2N_2 iv. Ac_2O, DMAP c) i. RuO_4 ii. CH_2N_2

Scheme 1

addition of Na_2SO_3, Na_2CO_3, and NaCl (1.8 mL each, all saturated aqueous solutions) at ca. 2 min intervals. The material was then filtered, the filter cake washed with ether (20 mL), the layers separated, the aqueous layer extracted with ether (3X10 mL) and the combined organic layers concentrated to an oil. (Some Ag salts were present but did not interfere with subsequent reactions.) The oil was dissolved in t-butyl alcohol (10 mL) containing 2-methyl-2-butene (2 mL) and a solution of $NaClO_2$ (200 mg, 2.2 mmol) in NaH_2PO_4 buffer (3 mL, 1.6M) was added dropwise over a few minutes. The initially developed yellow color faded quickly. The mixture was allowed to stir overnight, then 3N NaOH was added until the pH reached 10 and the material was concentrated to a wet solid by rotary evaporation. The solid was dissolved in H_2O (20 mL), the H_2O washed with hexane/ether (50%, 20 mL), acidified and extracted with ether (3X25 mL). The combined ether extracts were dried ($MgSO_4$), filtered, cooled to 0°C and

diazomethane in ether added (15 mL, ca. 0.3M). The excess diazomethane was allowed to evaporate as the solution warmed to room temperature. The material was then concentrated, dissolved in Ac_2O (6 mL) containing 4-dimethylaminopyridine (DMAP, 110 mg, 0.88mmol) and allowed to stir 10 h in a flask with a drying tube attached. This solution was poured into ice cold H_2O (20 mL) and $NaHCO_3$ (10 g, 0.12 mol) added over 30 min. The resulting mixture was extracted with ether (3X30 mL), the ether extracts dried ($MgSO_4$), concentrated and flash chromatographed (15% EtOAc/hexanes) to give 205 mg (65%) of **3a** as a clear oil, $[\alpha]_D^{20}$ +28.4° (c 1.179, $CHCl_3$). This compound gave satisfactory spectral and elemental analysis.[20]

Compound **3b** was prepared in analogous fashion from carbinol **2b**. All physical properties were identical to **3a** except for the rotation, $[\alpha]_D^{20}$ -27.2° (c 1.518, $CHCl_3$).

Conversion of **3a** to dimethyl (R)-2-acetoxycitramalate was accomplished with RuO_4 employing the modification due to Sharpless.[21] Acetate **3a** (165 mg, 0.7 mmol) was dissolved in CH_3CN, CCl_4 (3.3 mL each) and H_2O (6.7 mL), and $NaIO_4$ (2.8 g, 18 eq) and a catalytic amount of $RuCl_3$ (ca. 10 mg) were added. The resulting triphasic (liquid/liquid/solid) mixture was stirred at room temperature for three days and then filtered through a silica pad, the pad washed with ether and $CHCl_3$ (25 mL each), the filtrate concentrated, cooled to 0°C, and diazomethane in ether added (10 mL, ca. 0.3M). The excess diazomethane was allowed to evaporate, the solution dried ($MgSO_4$), concentrated and purified by preparative scale TLC (30% EtOAc/hexanes) to give 125 mg (81%) of a clear oil, $[\alpha]_D^{20}$ +36.4° (c 1.191, $CHCl_3$).[22] A chiral shift experiment [Eu(hfc)$_3$] revealed 1.7% of the S enantiomer in this material (96.6% e.e.). (The signal of the methoxy group on the carbonyl adjacent to the chiral center is clearly doubled in the ^1H NMR of the racemic material.) It was discovered that a small amount of racemization occurred during the acetylation step. Prolonged exposure to the reaction conditions leads to further racemization, which must occur through formation of a resonance stabalized α-ketocarbocation.[23]

The S isomer was prepared in analogous fashion to its enantiomer and a chiral shift experiment showed 1.4% of the R isomer (97.2% e.e.).

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18. Compound **2a**: Anal. Calcd for $C_{20}H_{30}O_2S$: C, 71.81; H, 9.04. Found: C, 71.63; H, 9.09. ^1H NMR ($CDCl_3$): δ 7.23 (m, 5H), 4.61 (s, 1H), 3.28 (dt, J = 4, 11 Hz, 1H), 2.90 (d, J = 13 Hz, 1H), 2.81 (d, J = 13 Hz, 1H), 2.66 (s, 1H), 1.29 (s, CH_3), 1.26 (s, CH_3), 1.23 (s, CH_3), 0.91 (d, J = 6 Hz, 3H), and others. ^{13}C NMR ($CDCl_3$): δ 136.9, 130.6, 127.6, 126.2, 83.9, 77.3, 74.1, 50.8, 44.3, 43.0, 41.6, 34.6, 31.3, 29.7, 24.2, 23.5, 22.6, 22.0. Compound **2b**: ^1H NMR ($CDCl_3$): δ 7.26 (m, 5H), 4.75 (s, 1H), 3.37 (dt, J = 4, 11 Hz, 1H), 2.97 (d, J = 13 Hz, 1H), 2.82 (d, J = 13 Hz, 1H), 2.26 (s, 1H), 1.37 (s, CH_3), 1.30 (s, CH_3), 1.17 (s, CH_3), 0.93 (d, J = 6Hz, 3H), and others. ^{13}C NMR ($CDCl_3$): δ 137.3, 130.7, 127.9, 126.3, 85.5, 77.6, 74.3, 50.9, 43.9, 43.2, 41.7, 34.7, 31.5, 29.9, 24.4, 23.4, 22.8, 22.1.
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20. Compound **3a**: Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.24; H, 6.99. ^1H NMR ($CDCl_3$): δ 7.28 (m, 3H), 7.16 (m, 2H), 3.70 (s, 3H), 3.29 (d, J = 13 Hz, 1H), 3.05 (d, J = 13 Hz, 1H), 2.07 (s, 3H), 1.51 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.5, 169.9, 135.1, 130.5, 128.2, 127.1, 80.7, 52.3, 43.6, 21.3; (CD_3COCD_3): δ 172.3, 169.9, 135.8, 131.1, 128.6, 127.5, 80.9, 52.0, 43.7, 21.2, 20.8. I.R. (neat) cm^{-1}: 3100-2900 (s), 1750 (s), 1600 (w).
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22. Dimethyl 2-acetoxycitramalate: ^1H NMR ($CDCl_3$): δ 3.77 (s, 3H), 3.71 (s, 3H), 3.15 (d, J = 16 Hz, 1H), 2.90 (d, J = 16 Hz, 1H), 2.09 (s, 3H), 1.68 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 171.5, 169.8, 169.4, 77.8, 52.6, 51.8, 40.8, 22.5, 20.9.
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