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Asymmetric Chemical Synthesis of (*R*)- and (*S*)-Citramalate in High Enantiomeric Purity*

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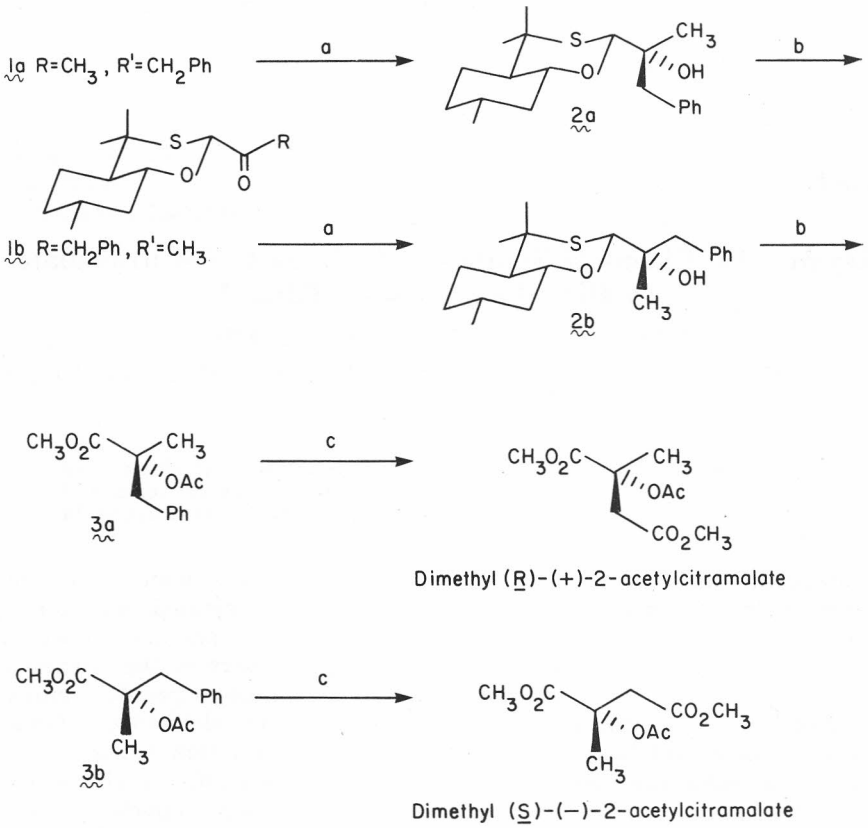
Both enantiomers of dimethyl 2-acetylcitramalate have been asymmetrically synthesized in over 96% enantiomeric excess and good overall chemical yield (50%) from 2-keto-1,3-oxathianes **1a** and **1b**.

Citramalic acid, the product of enzymatic addition of water to mesaconic and citraconic acid[1] was discovered, its structure determined, and a method for its preparation described[2,3] almost one hundred years ago. However, it was not until 1965, when research on the stereochemistry of the tricarboxylic acid cycle was under way, that the absolute configuration was determined by correlation of (+)-citramalic acid with (*S*)-(+)-mevalolactone.[1] Optically active citramalic acid has been available through resolution[4,5] and enzymatic synthesis[6] for some time and recently a number of asymmetric chemical syntheses have appeared,[7–11] of which only two[10] have been reported to lead to material of acceptable enantiomeric purity. The recent use of citramalic acid as a chiral synthon in prostaglandin synthesis,[12] and the lack of a chemical route to highly enantiomerically pure citramalic acid of either configuration provided the impetus for the present work.

We here report the details of an asymmetric synthesis which produces either isomer of dimethyl 2-acetoxycitramalate in over 96% enantiomeric excess from optically pure 2-keto-oxathianes **1a** and **1b** (Scheme 1)[13]. The 1,3-oxathiane backbone used as a chiral adjuvant is available in enantiomerically pure form from pulegone[14] and has been used in our laboratories to make a variety of enantiomerically pure compounds.[15–20] Interestingly, the use of **2a** as an intermediate in the synthesis of both isomers of mevalolactone[18] provides a further correlation of the absolute configuration of citramalic acid with that of mevalolactone.[1]

The key step in the present asymmetric synthesis is the highly diastereoselective addition of a Grignard reagent to ketones **1a** and **1b**. These additions proceed in high yield and ca. 100% diastereomeric excess to give **2a** and **2b** which were cleaved,[21] oxidized, treated with CH_2N_2, and acetylated to give enantiomers **3a** and **3b**. It was discovered that under the previously[18] developed acetylation conditions for tertiary alcohols the present compounds underwent

* Dedicated to Professor Mihailo Lj. Mihailović on the occasion of his 60th birthday.



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

some racemization.[22] This problem was minimized by lowering the reaction temperature and using one equivalent of 4-dimethylaminopyridine (DMAP). The racemization of these alcohols may occur through formation of a resonance stabilized α-ketocarbocation.[23]

With **3a** and **3b** in hand it was necessary only to oxidize the phenyl ring to —COOH following the method of Sharpless[24] to complete the synthesis. The oxidation required somewhat milder conditions than employed in our synthesis of mevalolactone,[18] presumably because of potential cleavage of the α-acetoxy-carboxy bond at elevated temperatures in the presence of RuO_4. Treatment of the acids produced with CH_2N_2 gave dimethyl (*R*)-(+)- and (*S*)-(—)-2-acetoxycitramalate in 50% overall yield from ketones **1a** and **1b**, respectively. A chiral shift experiment using $Eu(hfc)_3$ showed the citramalates to be of 96.6 and 97.2% e. e. respectively.

EXPERIMENTAL

Proton and carbon-13 NMR spectra were recorded on a Bruker WM-250 (250 MHz or 62.89 MHz) spectrometer equipped with an Aspect 2000 computer. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane

(Me_4Si); coupling patterns are designated s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet).

IR spectra were obtained as neat liquid films between sodium chloride plates or as dilute (1—5%) solutions in 0.5 mm sodium chloride cavity cells on a Beckman 4250 spectrometer and were calibrated with the 1601 cm^{-1} band of polystyrene. Intensities are reported as a s (strong), m (medium), w (weak), and b (broad).

Optical rotations were measured on a Perkin-Elmer 141 polarimeter equipped with sodium and mercury light sources by using a 1 dm thermostated cell; reported temperatures are uncorrected.

Melting points were observed on an Electrothermal melting point apparatus and are uncorrected.

Acyloxathiane **1a**

To optically pure oxathiane[13] (1 g, 5 mmol) in absolute THF (10 mL) at —78 °C under N_2 was added, dropwise, 1.6 M *n*-BuLi (3.25 mL, 5.2 mmol) in hexane. After being stirred 3 min the solution was allowed to warm to 0 °C and was immediately recooled to —78 °C. Acetaldehyde (440 mg, 10 mmol) in THF (5 mL) was then added dropwise over 1 h. Stirring was continued at —78 °C for 2 h, then the solution was allowed to stand overnight at —25 °C. Water (1 mL) and saturated NH_4Cl (1 mL) were added, the layers separated, and the organic layers dried ($MgSO_4$) and concentrated to give a clear oil (1.21 g, 100% crude). Next, to a cold (—78 °C) solution of dry Me_2SO (450 mg, 5.75 mmol) in dry CH_2Cl_2 (5 mL) under N_2 was added, dropwise, TFAA (1.20 g, 5.70 mmol) in dry CH_2Cl_2 (7 mL) and the resulting solution stirred for 0.5 h. The crude carbinol obtained above was dissolved in dry CH_2Cl_2 (10 mL), added dropwise to the oxidant solution, the reaction stirred for 2 h; then triethylamine (1.21 g, 12 mmol) was added and the solution allowed to warm to 0 °C. It was then poured into 5% aqueous HCl (50 mL), shaken thoroughly, the organic layer washed with saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), concentrated, and flash chromatographed (8% EtOAc/hexane) to give a clear oil (970 mg, 80%) which crystallized on standing. Recrystallization from EtOH/pentane provided an analytical sample: mp 45.0—45.5 °C; $[\alpha]_D^{20}$ + 91.7° (c 3.05, 95% EtOH).

Anal. $C_{13}H_{22}O_2S$ (242.38) calc'd.: C 64.42; H 9.15; S 13.23%
found: C 64.60; H 9.34; S 13.20%

^1H NMR ($CDCl_3$): δ 5.44 (s, 1H), 3.42 (m, 1H), 2.28 (s, CH_3), and others.

^{13}C NMR ($CDCl_3$): δ 203.4, 82.8, 76.9, 50.4, 43.9, 41.6, 34.7, 31.4, 29.4, 25.6, 24.3, 22.5, 22.1.

IR (CH_2Cl_2) cm^{-1}: 2920, 2860, 1735, 1354, 1146, 1090, 1070, 1015.

Carbinol **2a**

To magnesium turnings (100 mg, 4 mmol) in absolute ether (2 mL) at 0 °C under N_2 was added, dropwise, benzyl bromide (340 mg, 2 mmol) in ether (3 mL). This mixture was sonicated for 0.5 h and then added via a double-ended needle to a cold (—78 °C) solution of acyloxathiane 1 (100 mg, 0.4 mmol) in absolute THF (10 mL) under N_2. The resulting solution was stirred overnight and allowed to warm to room temperature at which time H_2O (5 mL) and saturated NH_4Cl (5 mL) were added and the mixture stirred until two clear layers formed. The organic layer was washed with brine (15 mL), the combined aqueous layers were extracted with ether (20 mL), and the combined organic solution dried ($MgSO_4$) and concentrated, giving **2a** as an oil, 130 mg (97%). Distillation (Kugelrohr, bp ca. 200 °C/0.1 mm) gave a sample for elemental analysis.

Anal. $C_{20}H_{30}O_2S$ (334.52) calc'd.: 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.

Comparison with the spectra (^{13}C and ^1H NMR) of the epimeric carbinol **2b** indicated no diastereomeric impurities in this compound.

Carbinol **2b**

This compound was prepared in similar fashion to **2a** starting from 2-lithiooxathiane and phenylacetaldehyde. Swern oxidation of the resulting carbinols and addition of methylmagnesium bromide to the ketone gave **2b** as a clear, viscous oil. This epimer is more polar than **2a** (the two diastereomers are easily separable on TLC) and displays somewhat different spectra.

^{1}H 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, $J = 6$Hz, 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.

Comparison with the spectra (^{13}C and ^{1}H NMR) of the epimeric carbinol **2a** again indicated no diastereomeric impurities in this compound.

(R)-(+)-*Methyl-2-acetoxy-2-methyl-3-phenylpropanoate* **3a**

Carbinol **2a** (450 mg, 1.35 mmol) in ether (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). A grey-white precipitate (AgCl) formed immediately. The mixture was stirred for 5 min and quenched by successive 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 (3×10 mL) and the combined organics 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, 1.6 M) was added dropwise over a few minutes. The solution turned light yellow intially, but the color quickly faded. The reaction was stirred overnight, then 3 M NaOH was added until the pH reached 10 and the material was concentrated to a wet solid via rotary evaporation. The solid was dissolved in H_2O (20 mL), the H_2O washed with hexane/ether (50%, 20 mL, extracts contain the oxathiane backbone as a sultine[16]), acidified and extracted with ether (3×25 mL). The combined ether extracts were dried ($MgSO_4$), filtered, cooled to 0 °C and diazomethane in ether added (15 mL, ca. 0.3 M). 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, 0.88 mmol) and stirred overnight in a flask with a drying tube attached. The solution was poured into ice cold H_2O (20 mL) and $NaHCO_3$ (10 g, 0.12 mol) was added over 30 min. The resulting mixture was extracted with ether (3×30 mL), the ether extracts dried ($MgSO_4$), concentrated and flash chromatographed (15% EtOAc/hexane) to give 205 mg (65% of **3a** as a clear oil, $[\alpha]_D^{20}$ + 28.4° (c 1.179, $CHCl_3$).

Anal. $C_{13}H_{16}O_4$ (236.27) calc'd.: C 66.09; H 6.83%
found: C 66.24; H 6.99%

^{1}H 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.

IR (neat) cm^{-1}: 3100—2900 (s), 1750 (s), 1600 (w).

(S)-(—)-*Methyl-2-acetoxy-2-methyl-3-phenylpropanoate* **3b**

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, $CHCl_3$).

Dimethyl (R)-(+)-*2-acetylcitramalate*

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. 0.3 M). 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, $CHCl_3$). A chiral shift experiment [Eu(hfc)$_3$] revealed 1.7% of the *S* isomer in this material (96.6% e. e.). The signal of the methoxy group adjacent to the chiral center is clearly doubled in the ^1H NMR of the racemic material.

Anal. $C_9H_{14}O_6$ (218.21) calc'd.: C 49.54; H 6.47%
found.: C 49.19; H 6.25%

^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.

Dimethyl (S)-(—)-*2-acetylcitramalate*

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

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SAŽETAK

Asimetrična kemijska sinteza (*R*)- i (*S*)-citramalata sa visokom enantiomernom čistoćom

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Oba enantiomera dimetil 2-acetoksicitramalata su asimetrično sintetizirana iz 2-keto-1,3-oksatiana **1a** i **1b**, s više od 96%-tnim enantiomernim i s dobrim kemijskim iskorištenjem (50%).