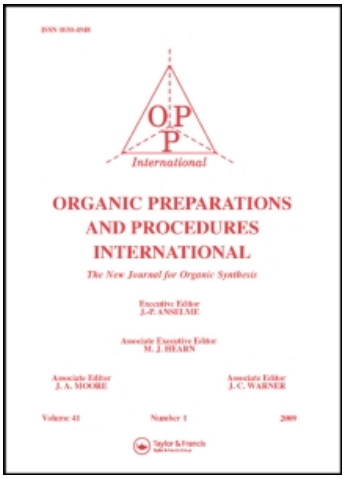

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AN IMPROVED PROCEDURE FOR THE PREPARATION AND RESOLUTION OF dl-2,3-DIMETHYLSUCCINIC ACID

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AN IMPROVED PROCEDURE FOR THE PREPARATION AND RESOLUTION OF DL-2,3-DIMETHYLSUCCINIC ACID

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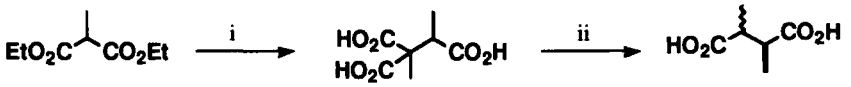
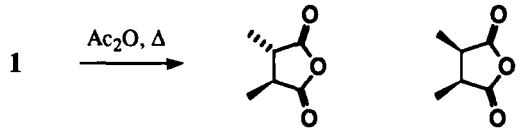
Chiral dicarboxylic acids possessing C_2-symmetry are important starting materials for chiral auxiliaries used in asymmetric synthesis.[1] Notably, several tartaric acid derivatives have served as chiral ligands in metal-induced asymmetric syntheses.[2] This led us to investigate the utility of 2,3-dimethylsuccinic acid (**1**) as a starting material for the preparation of chiral ligands. The diacid **1** may be obtained as a racemic mixture using a number of synthetic methods[3] and is also commercially available as a mixture of the DL- and *meso*-diastereomers.[4] Enantioselective synthesis of precursors to **1** have also been reported.[5] Resolution using brucine and strychnine in a tandem crystallization affords optically pure **1**[6] but the drawbacks of this option prompted us to explore the development of a simplified protocol for the resolution of DL-**1**. We report herein a convenient synthesis of **1** and a method for its optical resolution.

Our initial efforts at resolving diacid **1** used commercially available material and required prior separation of the *meso* diastereomer.[7] To avoid the expense associated with the purchase of an



2 **4** (83%) **1** (91%)

i) a. NaH, THF b. $CH_3CH(Br)CO_2Et$ (**3**) c. NaOH, Δ d. conc. HCl ii) 130°

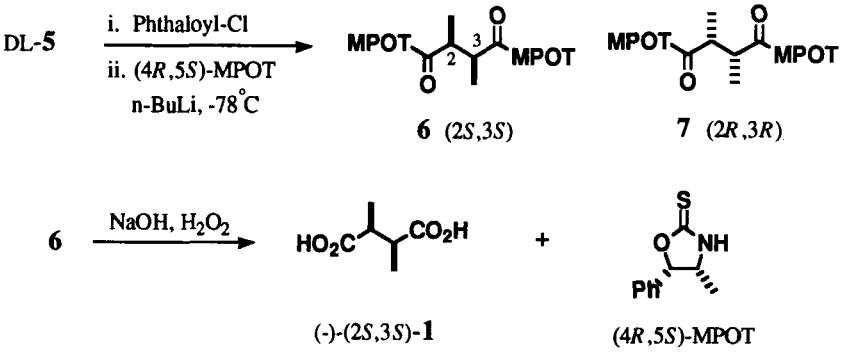


DL- **5** *meso*- **5**

undesired diastereomer, we developed a preparation of the corresponding anhydride (DL-**5**) from inexpensive starting materials. Treatment of the α-bromoester **3** with the derived enolate of malonate **2** afforded a triester which, without purification, was saponified and treated with concentrated HCl to

yield the triacid **4**. Decarboxylation by heating the crude triacid to 130° afforded the diacid **1** in 75% overall yield as a 1:1 mixture of the DL : *meso* diastereomers. Conversion of the diacid mixture to the anhydrides DL-**5** and *meso*-**5** followed by recrystallization from absolute ethanol afforded a product mixture enriched in DL-**5** (*ca.* 15:1, DL-**5** : *meso*-**5**).

The optical resolution of diacid **1** proceeds from anhydride DL-**5**. The diastereomeric 1,3-oxazolidine-2-thiones **6** and **7** were prepared by reaction of the dicarboxylic dichloride, derived[8] from the anhydride DL-**5**, with (4R,5S)-4-methyl-5-phenyl-1,3-oxazolinidine-2-thione (MPOT).[9] Separation of **6** and **7** was effected by recrystallization from toluene-hexane to give the highly crystalline 1,3-oxazolidine-2-thiones with ≥ 98% purity. The assignment of stereochemistry shown for **6** is based on a single crystal X-ray analysis.[10] Hydrolysis of **6** under basic peroxide conditions[11] gave the optically pure diacid (-)-**1** in quantitative yield. Similarly, **7** was converted into diacid (+)-**1** in 91% yield.



In summary, this work describes the convenient synthesis and optical resolution of DL-2,3-dimethylsuccinic acid, a precursor to potentially useful C_2-symmetric ligands. Our work using diacid **1** in the syntheses of chiral ligands is ongoing and will be described in due course.

EXPERIMENTAL SECTION

Infrared spectra were recorded on a IBM FTIR-32 with an IBM 9000 data system. NMR spectra were determined with a General Electric QE-300 spectrometer (^{1}H at 300MHz and ^{13}C at 75MHz). Melting points were obtained on an Electrothermal digital melting-point apparatus model IA8100-A and are uncorrected. Optical rotations were taken using a Jasco DIP-370 digital polarimeter. For anhydrous reactions, THF was distilled from NaK-benzophenone immediately prior to use. All reagents were used as received.

2,3-Dimethyl 2-carboxybutanedioic Acid (4).- Diethyl methylmalonate (50.0 mL, 291 mmol) was added slowly to a slurry of sodium hydride (10.5 g, 437 mmol) in THF (1L) at 0°. After complete addition, the reaction was warmed to room temperature and stirred until the evolution of hydrogen had ceased (*ca.* 15 min.). Ethyl 2-bromopropionate (42.0 mL, 320 mmol) was then added dropwise. After 20 hrs at 25°, the reaction mixture was cooled to 0° and quenched with saturated aqueous

NH_4Cl (100 mL) and water (500 mL). Ethyl acetate (500 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The organic extract was washed with brine, dried ($MgSO_4$), and the solvents were removed under reduced pressure to give 74.6 g (93%) of the crude triester as a yellow oil having the following spectral properties: ^1H NMR ($CDCl_3$): δ 1.21-1.28 (m, 12 H), 1.54 (s, 3 H), 3.30 (q, J = 7.3 Hz, 1 H), 4.09-4.23 (m, 6 H); ^{13}C ($CDCl_3$): δ 12.8, 13.6, 16.7, 43.4, 56.0, 60.2, 61.1, 170.5, 173.1; IR (neat): 1736, 1458, 1381, 1257, 1118 cm^{-1}.

The crude triester (46.0 g, 168 mmol) was dissolved in methanol (400 mL) and treated with a solution of sodium hydroxide (61 g, 1.5 mol) in water (270 mL). The resulting mixture was heated at 60° for 24 hrs. The methanol was removed under reduced pressure and the concentrated mixture was acidified at 0° with conc. HCl (120 mL). Brine (100 mL) was added and the triacid was extracted with a 4:1 mixture of ethyl acetate-THF (200 mL, then 4 x 100 mL). The organic extract was dried ($MgSO_4$) and the solvents were removed under reduced pressure to yield 28.4 g (89%) of triacid **4** as a tan solid, mp. 130° (decarboxylation), ^1H NMR (DMSO-d_6): δ 1.10 (d, J = 7.3 Hz, 3 H), 1.38 (s, 3 H), 3.14 (q, J = 7.3 Hz, 1 H), 12.6 (OH, br, 3 H); ^{13}C (DMSO-d_6): δ 13.6, 16.7, 43.2, 55.8, 172.7, 175.5; IR (KBr): 3700-2300 (br), 1728, 1462, 1416, 1242, 938 cm^{-1}.

2,3-Dimethylsuccinic Acid (1).- Triacid **4** (35.5 g, 187 mmol) was heated (130°) at which time slow evolution of carbon dioxide was observed. Heating was continued for 0.5 hr followed by cooling to 25°. The resulting tan solid was cooled to 0° and dissolved in 1N NaOH (450 mL). The aqueous phase was washed with ether until the rinses were colorless, cooled to 0°, acidified to pH 1 with conc. HCl, and extracted with a 4:1 mixture of ethyl acetate-THF (3 x 100 mL). The organic extract was dried ($MgSO_4$) and the solvents were removed under reduced pressure to give 24.8 g (91%) of crude diacid **1**: ^1H NMR (D_2O/KOD), 1:1 mixture of DL : *meso*; DL: δ 0.98 (d, J = 5.9 Hz, 3H), 2.58-2.65 (m, 2 H); meso: δ 1.05 (d, J = 5.2 Hz, 3 H), 2.24-2.34 (m, 2 H).

DL-2,3-Dimethylsuccinic Anhydride (DL-5).- A 125 mL Erlenmeyer flask was charged with crude diacid **1** (24.2 g, 166 mmol) and acetic anhydride (19.0 ml, 199 mmol). Several boiling stones were added and the mixture was refluxed until the volume was reduced by two thirds. The amber solution was then cooled to 0° and the resultant crystals were collected. The filtrate was heated until the volume was reduced by one half. Cooling the solution to -10° for 3 hrs yielded a second crop of crystals. The volume of the filtrate was reduced by one half again and then cooled to -10° for 12 hrs to yield a third crop of crystals. The crude anhydride was recrystallized from absolute ethanol to yield 7.7 g (73%) of **DL-5**, as a white solid, mp. 88-89°, lit.[6c] 100-103°. ^1H NMR ($CDCl_3$): 15:1 diastereomeric mixture: δ 2.68-2.87 (m, 2H), 1.40 (d, J = 6.9 Hz, 3H); ^{13}C ($CDCl_3$): δ 13.6, 42.8, 173.2; IR (CCl_4) 1861 (w), 1794 (s), 1220, 1116, 958 cm^{-1}.

(4R,5S)-3,3'-[(2RS,3RS)-2,3-Dimethylsuccinyl]-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (6 + 7).- A 50 mL two-neck round bottom flask was equipped with a spin bar and a vacuum jacketed fractionating column (l = 30 cm, i.d. = 1.5 cm) packed with Wilson rings (ht. = 15 cm). The top of the column was fitted with a vacuum jacketed distillation head and a 50 mL receiving flask. **DL-5** (8.46

g, 66.0 mmol) and anhydrous zinc chloride (450 mg, 3.30 mmol) were added to the reaction flask. The apparatus was evacuated and flushed with dry argon several times. Phthaloyl chloride (12.4 mL, 85.8 mmol) was added and the mixture was heated to 60°. After 0.5 hr, the reaction was cooled to 40° and the receiving flask was cooled (-30°). Vacuum distillation afforded 11.4 g (94%) of a colorless oil, bp. 31-32° (0.08 Torr). [**Note**: The oil bath must be kept below 120° to avoid decomposition]. DL-2,3-dimethylsuccinyl dichloride: ^{1}H NMR ($CDCl_3$) 6:1 diastereomeric mixture: δ 1.35 (d, J = 6.8 Hz, 3 H), 3.38 (dq, J = 5.0, 2.0 Hz, 2 H); ^{13}C ($CDCl_3$): δ 13.2, 53.0, 175.7; IR (neat): 1790 (s), 1456, 954, 920, 745, 712 cm^{-1}.

To a solution of (4R,5S)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione [(4R,5S)-MPOT][9] (27.8 g, 144 mmol) in dry THF (300 mL) at -78° was added n-BuLi (58.0 ml of a 2.52M solution in hexanes, 147 mmol) over 15 min. A solution of DL-2,3-dimethylsuccinyl dichloride (13.8 g, 75.4 mmol) in dry THF (25 mL) was added dropwise over 10 min. The reaction was warmed to 25° and was quenched by the addition of water (200 mL). Ethyl acetate (200 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The organic extract was washed with brine and dried ($MgSO_4$). Removal of the solvents under reduced pressure gave 39.5 g of a yellow solid which was dissolved in hot toluene (150 mL). Hexane (450 mL) was added and the solution was allowed to cool to 25°. The precipitated white solid was collected and dissolved in hot toluene (3 mL/g). Hexane (0.5 mL/g) was added and, after cooling to 25°, **(2S,3S)-6** (10.8 g, 67%), precipitated as white needles, mp. 239-241°. Concentration of the filtrate under reduced pressure followed by recrystallization from toluene (3 mL/g)-hexane (1 mL/g) yielded **7** as colorless prisms with trace amounts of **6** as white needles. The prisms were collected and recrystallized from toluene-hexane to yield 11.0 g (69%), of diastereomerically pure **(2R,3R)-7**, mp. 143-144°.

(2S,3S)-6: $[\alpha]_D^{28}$ = 74.9° (c 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.84 (d, J = 6.6 Hz, 6H), 1.34 (d, J = 6.7 Hz, 6H), 4.94 (overlapping q, J = 6.7 Hz, 2H), 5.07-5.13 (m, 2H), 5.73 (d, J = 7.2 Hz), 7.31-7.42 Hz (m, 10H); ^{13}C NMR ($CDCl_3$): δ 184.4, 177.5, 132.5, 128.8, 128.7, 125.9, 82.8, 59.0, 41.1, 14.7, 13.9; IR ($CHCl_3$): 1695, 1456, 1374, 1341, 1312, 1286, 1185 cm^{-1}.

Anal. Calcd for $C_{26}H_{28}N_2O_4S_2$: C, 62.88; H, 5.68; N, 5.64; S, 12.91
Found: C, 62.44; H, 5.71; N, 5.57; S, 12.61

(2R,3R)-7: $[\alpha]_D^{26}$ = 6.0° (c 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.89 (d, J = 6.6 Hz, 6H), 1.38 (d, J = 6.1 Hz, 6H), 4.78-4.85 (m, 2H), 5.00 (overlapping q, J = 6.9 Hz, 2H), 5.80 (d, J = 7.4 Hz, 2H), 7.32-7.48 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 184.3, 177.6, 132.6, 128.9, 128.7, 125.8, 83.0, 58.7, 41.6, 15.3, 14.2; IR 1694, 1456, 1374, 1342, 1317, 1287 cm^{-1}.

Anal. Calcd for $C_{26}H_{28}N_2O_4S_2$: C, 62.88; H, 5.68; N, 5.64; S, 12.91
Found: C, 62.96; H, 5.64; N, 5.55; S, 12.92

(-)-(2S,3S)-2,3-Dimethylsuccinic Acid [(-)-1].- A 0.05 M solution of **6** (8.45 g, 17.0 mmole) in 10:1 THF-H_2O was treated at 0° with 30% hydrogen peroxide (23.0 mL, 204 mmole) followed by 5 N NaOH (13.6 mL, 68.0 mmol). After 15 min., the excess peroxide was quenched at 0° with Na_2SO_3

(28.3 g, 224 mmol). After stirring for 0.5 hr, the pH was adjusted to 8-9 with saturated aqueous Na_2CO_3 and the THF was removed under reduced pressure. The (4R,5S)-MPOT was recovered by CH_2Cl_2 extraction and was recrystallized from toluene-hexane (3:1). The aqueous layer was carefully acidified with 6 N HCl at 0° to pH 1-2 and extracted with 4:1 ethyl acetate-THF (3 x 20 mL). The organic extract was washed with brine, dried ($MgSO_4$), and concentrated to yield 2.48 g (100%) of a white solid. A small portion was purified by washing with cold CH_2Cl_2, mp. 134-136°, lit.[6b] 135-136°; $[\alpha]_D^{25} = -8.01°$ (c 4.0, H_2O), lit.[6b] $[\alpha]_D^{25} = -8.06°$ (c 4.0, H_2O).

(+)-(2R,3R)-2,3-Dimethylsuccinic Acid [(+)-1].- 7 was treated in a similar manner as **6**; mp. 134-136°, lit.[6b] 135-136°; $[\alpha]_D^{28} = 8.06°$ (c 4.0, H_2O), lit.[6b] $[\alpha]_D^{25} = 8.02°$ (c 4.0, H_2O).

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