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Resolution of C_2-symmetric 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid and 2,3-diphenylsuccinic acid using (*S*)-proline

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Abstract

Racemic 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid is resolved to obtain the corresponding (*S*,*S*)-isomer in 96±2% ee and the (*R*,*R*)-isomer in 97±2% ee through complexation with (*S*)-proline in methanol. The racemic 2,3-diphenylsuccinic acid has been resolved to obtain the (*S*,*S*)-isomer in 93% ee using (*S*)-proline in methanol.

1. Introduction

Amino acids are an important class of chiral-pool compounds which are useful in asymmetric synthesis.[1] These compounds are obtained from natural sources or by resolution.[2a] For example, (±)-proline was resolved using optically active tartaric acid.[2b] Amino acids are also resolved using chiral resolving agents such as chiral sulphonic acids[3a] and phosphoric acids.[3b] Very recently, we and others have reported the use of (*S*)-proline for the resolution of certain racemic compounds through the corresponding diastereomeric complex formation.[4–6] These results prompted us to examine the use of (*S*)-proline as a chiral reagent for the resolution of C_2-symmetric 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid **1** and 2,3-diphenylsuccinic acid **2**, which have proven applications as starting materials for the preparation of certain useful C_2-symmetric chiral ligands.

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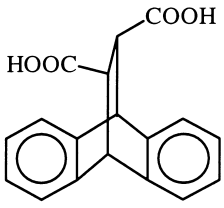
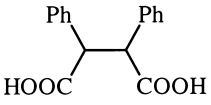


(±)-**1**



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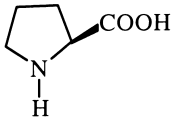

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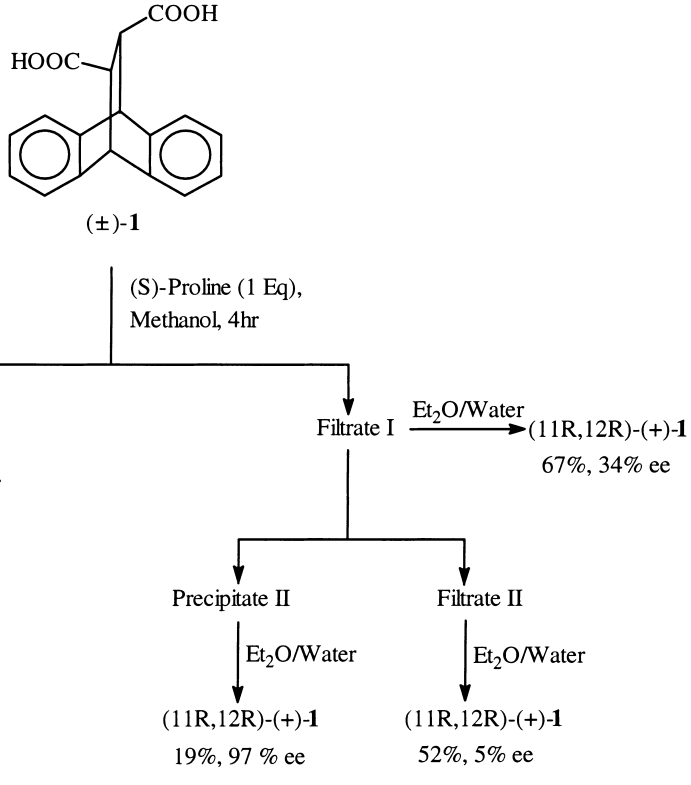
2. Results and discussion

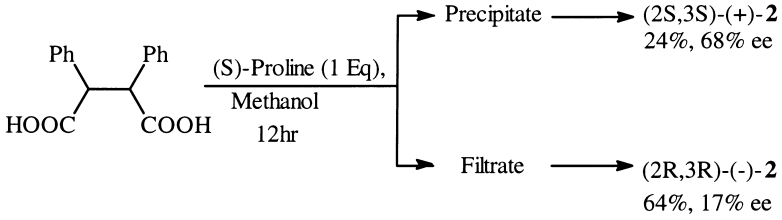
The chiral dicarboxylic acid **1** was previously obtained in enantiomerically pure form either by an asymmetric Diels–Alder reaction[7] or by resolution.[8] We have observed that it can be resolved using (*S*)-proline **3** following a convenient protocol.[5] When racemic **1** and **3** were dissolved in methanol, a precipitate was formed after 4 h (Scheme 1). After filtration and decomposition of the precipitate with an ether/water mixture, (11*S*,12*S*)-(−)-**1** was isolated (25–28% yield, 96±2% ee).



Scheme 1.

Fortunately, the residue obtained after evaporation of the fraction of the complex containing (+)-isomer gave crystals upon recrystallisation from fresh methanol (Scheme 1). After decomposition of this crystalline complex with an ether/water mixture, (11*R*,12*R*)-(+)-**1** was isolated (19% yield, 97±2% ee). The same result was also obtained by concentration of the filtrate followed by crystallisation. Partial

resolution was also achieved using ethanol as solvent. For example, (11*S*,12*S*)-(−)-**1** (23% yield, 72% ee) was obtained from the precipitate and the filtrate gave (11*R*,12*R*)-(+)-**1** (56% yield, 44% ee).



Scheme 2.

It was found that stirring (*S*)-proline **3** and racemic **1** in methanol at room temperature for 4 h gave a precipitate which, on decomposition and work-up, yielded (11*S*,12*S*)-**1** in 86% ee (25%).[9] The (11*R*,12*R*)-**1** isomer was isolated from the filtrate with 38% ee (71%). This experiment indicates that the crystal growth may be an important factor for obtaining better results. When solutions of (*S*)-proline **3** and racemic **1** in methanol were mixed at 0°C and stirred for 4 h, a precipitate was obtained. After work-up, (11*S*,12*S*)-**1** was isolated only in 71% ee (40%). The filtrate fraction after work-up gave (11*R*,12*R*)-**1** with 64% ee (54%). These results indicate that both (−)-**1**:**3** and (+)-**1**:**3** complexes precipitated at 0°C, resulting in a higher chemical yield with a lower enantiomeric excess.[9]

We have also examined the resolution of the synthetically useful C_2-symmetric 2,3-diphenylsuccinic acid **2** using **3**. Previously, this acid has been obtained in enantiomerically pure form by asymmetric homocoupling,[10] resolution using brucine[11] or through synthesis of the diastereomeric monomenthyl ester.[12] We have observed that when (±)-**2** and **3** (1:1) were dissolved in methanol and allowed to stand for crystallisation at room temperature (12 h), a white precipitate was formed (Scheme 2). The precipitate was filtered and decomposed with an ether/water mixture to obtain (2*S*,3*S*)-(+)-**2** (24% yield, 68% ee). The filtrate fraction gave (2*R*,3*R*)-(−)-**2** (17% ee, 64% yield). Since only partial resolution was realised, we have undertaken efforts to enhance the enantiomeric purity further. When (2*S*,3*S*)-(+)-**2** (68% ee) was treated with **3** in methanol, (2*S*,3*S*)-(+)-**2** with 93% ee (66% yield) was obtained. A similar operation with (2*R*,3*R*)-(−)-**2** (25% ee) resulted in a precipitate from which the (2*R*,3*R*)-(−)-**2** (20% yield, 41% ee) was regenerated.

The elemental analysis of the precipitate formed in the reaction of (*S*)-proline **3** with chiral acid (+)-**1** indicated that it was a 1:1 complex. This was further confirmed by X-ray crystal structure analysis of the crystal of the compound obtained from (11*R*,12*R*)-(+)-**1** and **3** (Fig. 1). The bond lengths 1.205 Å and 1.199 Å respectively of C(23)–O(6) and C(23)–O(5), show that (*S*)-proline is in zwitterionic form. The bond lengths 1.202 Å and 1.315 Å of C(17)–O(1) and C(17)–O(2), respectively, indicate that the dicarboxylic acid **1** is in the carboxylic acid form. The hydrogen bonding between the ammonium hydrogens of the zwitterionic form of (*S*)-proline and the carbonyl oxygen of two different carboxylic acids is illustrated in the interatomic distances 2.949 Å and 2.891 Å of N(1)–O(1) and N(1)–O(4), respectively. The hydrogen bonded array in the crystal packing is shown in Fig. 2.

The product derived from (−)-**1** and **3** was not suitable for crystal structure analysis. Elemental analysis of the product of (+)-**2** and **3** indicated that it was a 1:1 complex. Unfortunately, this compound also failed to give crystals suitable for X-ray analysis.[13]

The chiral dicarboxylic acid **1** has been used to prepare chiral phosphines and chiral diols for applications in palladium[14] and titanium[15] catalysed reactions. The chiral dicarboxylic acid **2** has been used to prepare C_2-chiral diamines for osmylation[16] and organometallic addition[17] reactions. Therefore, the operationally simple and convenient procedures for the resolution of **1** and **2** described here should be useful for synthetic applications involving these chiral ligands.

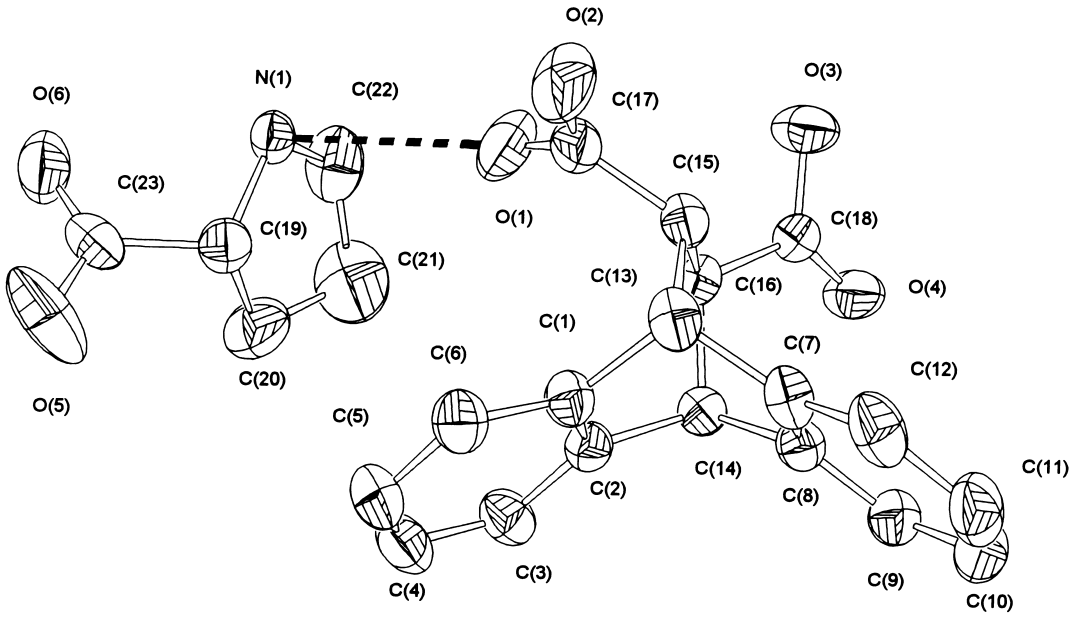


Fig. 1. ORTEP diagram for 1:1 complex of **1** and **3**

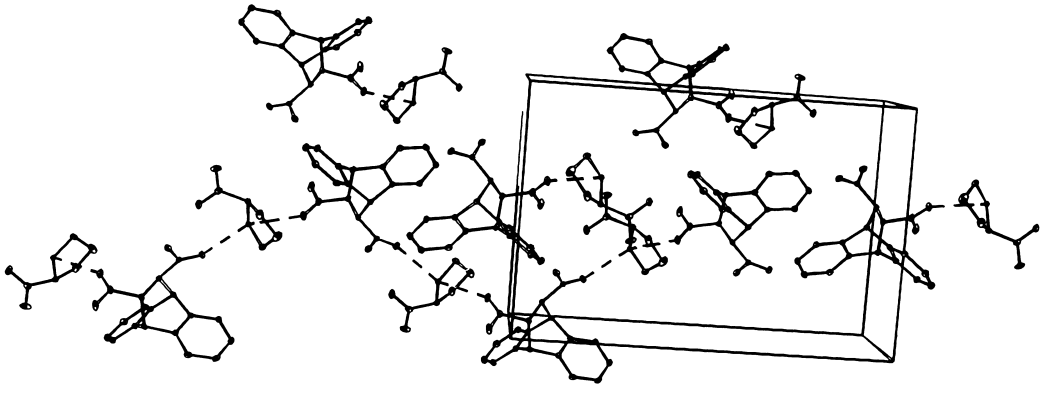


Fig. 2. Molecular packing diagram

3. Experimental section

The racemic **1**[8] and **2**[10] were prepared following reported procedures. (*S*)-Proline supplied by Aldrich (USA) was used. Enantiomeric excesses were calculated based on the previously reported $[\alpha]_D$ values. Optical rotations were measured on an Autopol-II automatic polarimeter. Elemental analyses were performed on a Perkin–Elmer elemental analyser model 240C. The methanol, ethanol and acetone solvents were distilled as recommended.[18]

*3.1. Resolution of 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid **1***

The racemic 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid **1** (28.4 g, 96.6 mmol) and (*S*)-proline (11.5 g, 100 mmol) were dissolved in methanol (300 ml) in a 500 ml round-bottomed flask by gentle heating over a water bath. The flask was closed with a glass stopper and allowed to stand at room temperature. After 4 h the crystalline material formed was filtered and washed with cold methanol (50

ml). The precipitate (mp 231–232°C) was decomposed by stirring with a mixture of diethyl ether (100 ml) and water (100 ml). The organic layer was separated and the aqueous layer was extracted with ether (3×90 ml). The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated to obtain (11*S*,12*S*)-(−)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid **1**, 7.2 g (25% yield, 96±2% ee) (mp 225–226°C, lit.[8a] mp 226–227°C); $[\alpha]_D^{27}=-7.62\pm0.15$ (c 1.574, CH_3OH), lit.[8a] $[\alpha]_D=+7.9$ (c 0.795, CH_3OH). The dimethyl ester of (11*S*,12*S*)-(−)-**1** had $[\alpha]_D^{27}=-21.33$ (c 0.1476, CH_3OH), [lit.[8a] $[\alpha]_D=+21.7$ (c 0.1476, CH_3OH), for (11*R*,12*R*)-(+)-**1**]. The filtrate was evaporated to dryness and redissolved in fresh methanol (200 ml) and allowed to crystallise. After 12 h at room temperature, the colourless crystals formed were filtered. This complex (mp 237–238°C) on decomposition followed by work-up with ether (90 ml) and water (90 ml) as mentioned above gave (11*R*,12*R*)-(+)-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid **1**, 5.3 g (19% yield, 97±2% ee) (mp 225–226°C, lit.[8a] mp 226–227°C), mp (±)-**1** 240–242°C; $[\alpha]_D^{27}=+7.73\pm0.15$ (c 1.164, CH_3OH), lit.[8a] $[\alpha]_D=+7.9$ (c 0.795, CH_3OH). Its dimethyl ester showed $[\alpha]_D^{27}=+21.19$ (c 0.378, CH_3OH), lit.[8a] $[\alpha]_D=+21.7$ (c 0.1476, CH_3OH). The filtrate obtained after removal of the (+)-**1** and **3** complex, after evaporation of methanol and usual work-up as mentioned earlier gave the (11*R*,12*R*)-(+)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid **1**, 14.77 g (52% yield, 5% ee). Anal. calcd for the 1:1 complex of (−)-**1** and **3** ($C_{23}H_{23}NO_6$): C 67.48%; H 5.62%; N 3.42%. Found: C 67.47%; H 5.73%; N 3.43% and for the complex of (+)-**1** and **3** ($C_{23}H_{23}NO_6$) found: C 67.83%; H 5.77%; N 3.69%.

*3.2. Resolution of 2,3-diphenylsuccinic acid **2***

The racemic 2,3-diphenylsuccinic acid **2** (2.7 g, 10 mmol) and (*S*)-proline (1.15 g, 10 mmol) were dissolved in 30 ml of methanol. The flask was closed and allowed to stand at room temperature for 12 h. The precipitated material was filtered. The filtrate was concentrated to dryness and decomposed with a mixture of ether (40 ml) and water (40 ml). The organic layer was separated and the aqueous layer was extracted with ether (3×25 ml). The combined organic extracts were washed with brine solution, dried over anhydrous $MgSO_4$, filtered and then evaporated to obtain (2*R*,3*R*)-(−)-2,3-diphenylsuccinic acid **2**, 1.72 g (64% yield, 17% ee); $[\alpha]_D^{27}=-62$ (c 0.322, ethanol), lit.[11] $[\alpha]_D^{13}=-368.9$ (c 2.33, ethanol). The precipitate fraction on decomposition with an ether/water mixture, extraction and evaporation gave the (2*S*,3*S*)-(+)-2,3-diphenylsuccinic acid **2**, 0.58 g (24% yield, 68% ee); $[\alpha]_D^{27}=+254$ (c 0.26, ethanol), lit.[11] $[\alpha]_D^{15}=+369.5$ (c 1.49, ethanol).

*3.3. Enrichment of partially resolved (+)-2,3-diphenylsuccinic acid **2***

The (2*S*,3*S*)-(+)-**2** (68% ee, 0.42 g, 1.6 mmol) and (*S*)-proline (0.2 g, 1.7 mmol) were dissolved in 6 ml of methanol and kept for crystallisation for 5 h. The precipitated material was filtered. The filtrate on evaporation followed by decomposition with a mixture of ether (20 ml) and water (20 ml) and usual work-up gave the (2*S*,3*S*)-(+)-2,3-diphenylsuccinic acid **2**, 0.138 g (32% yield, 43% ee); $[\alpha]_D^{27}=+159$ (c 0.088, ethanol). The precipitate after treatment with a mixture of ether (20 ml) and water (20 ml) for 1–2 h, work-up and evaporation gave (2*S*,3*S*)-(+)-2,3-diphenylsuccinic acid **2**, 0.28 g (66% yield, 93% ee) (mp 183–185°C, lit.[11] mp 183°C) [mp (±)-**2** 183°C, solidifies and remelts at 220–221°C]; $[\alpha]_D^{27}=+343$ (c 0.108, ethanol), lit.[11] $[\alpha]_D^{27}=+369.5$ (c 1.49, ethanol). The corresponding dimethyl ester showed $[\alpha]_D^{27}=+333.3$ (c 0.105, acetone), lit.[11] $[\alpha]_D^{27}=+341.9$ (c 1.082, acetone). Anal. calcd for the 1:1 complex of (+)-**2** and **3** ($C_{21}H_{23}NO_6$): C 65.45%; H 5.97%; N 3.64%. Found: C 64.03%; H 5.50%; N 2.86%.

Acknowledgements

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13. The colourless orthorhombic crystal of the complex of (+)-**1** and **3** (0.3×0.3×0.4 mm) contained four molecules of 1:1 in the unit cell; empirical formula, $C_{23}H_{23}NO_6$ (f_w 409.42); space group $P2_12_12_1$; a=8.436(8) Å, b=18.9881(12) Å, c=12.6937(11) Å; V=2033(2) Å^3, D_{calc}=1.337 Mg/m^3; α=β=γ=90°; Mo-Kα radiation (0.71073 Å) at 293 K; 3998 reflections were collected, with 2043 independent reflections; refinement method full-matrix least squares of F^2; GOF on F^2=1.040. Final R indices [I>2σ(I)], R1=0.0507, wR2=0.1237; R indices (all data)=0.0606, wR2=0.1330; absolute structure parameter=−1(3). Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
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