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Design, synthesis, resolution, and stereochemical assignment of a conformationally rigid chiral ligand derived from anthracene and a dienophile containing a pyridine moiety

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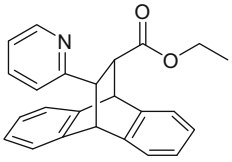
Dedicated to Professor Mariappan Periasamy on the occasion of his 57th birthday

ABSTRACT

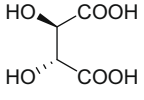
The conformationally rigid chiral ligand, *trans*-12-(pyridin-2-yl)-9,10-dihydro-9,10-ethanoanthracene-11-carboxylic acid ethyl ester, **1**, was designed and synthesized in racemic form. Both isomers were successfully obtained in enantiomerically pure form through classical resolution using L-(+)-tartaric acid in acetonitrile. The nature of the diastereomeric complex formed in this resolution was elucidated using single crystal X-ray crystallographic studies. The absolute configuration of (+)-**1** was unambiguously assigned as (11*S*,12*S*) by single crystal structural analysis of salt **5** formed from (+)-**1** and L-(+)-tartaric acid.

1. Introduction

There has been a remarkable growth in the field of designing new chiral ligands for use in metal[1] as well as organo-catalyzed asymmetric reactions.[2] Mixed donor functionality with hard and soft donor atoms is an important factor that needs to be considered while designing chiral ligands which can exert asymmetric induction in enantioselective or diastereoselective reactions.[3] Pyridine and its derivatives are used as nucleophilic catalysts in various asymmetric reactions. For example, chiral DMAP catalysts are useful motifs for the kinetic resolution of Baylis–Hillman adducts,[4] and Michael addition reactions.[5] Enantioselective allylation of aldehydes, and desymmetrization of *meso*-epoxides can be catalyzed by chiral pyridine N-oxides.[6] A pyridine moiety with an additional donor functionality such as an alcohol, amine, or phosphine[7] incorporated in a conformationally rigid skeleton would serve as a chiral ligand for various asymmetric reactions.



(±)-**1**



(+)-**2**

Based on these assumptions, molecule **1** was designed with a bicyclic skeleton possessing a pyridine moiety as one donor site and an ester group for introducing various other donor groups through simple functional group transformations.

2. Results and discussion

2.1. Synthesis of (±)-1

Analysis of the structural features of **1** reveals that the construction of the rigid bicyclic skeleton may be realized through Diels–Alder reaction between anthracene and an appropriate dienophile. As expected, compound (±)-**1** was successfully synthesized from anthracene **3** and *trans*-3-(pyridin-2-yl)-acrylic acid ethyl ester **4** in presence of anhydrous aluminum chloride. For example, when anthracene, *trans*-3-(pyridin-2-yl)-acrylic acid ethyl ester and anhydrous aluminum chloride in dichloromethane were allowed to stand at 0 °C for 48 h and then stirred at room temperature for 8 h, the reaction gave (±)-**1** in 89% yield (Eq. 1). The dienophile, *trans*-3-(pyridin-2-yl)-acrylic acid ethyl ester, was easily prepared through a Wittig reaction of carbethoxymethyltriphenylphosphorane with 2-pyridinecarboxaldehyde.[8]

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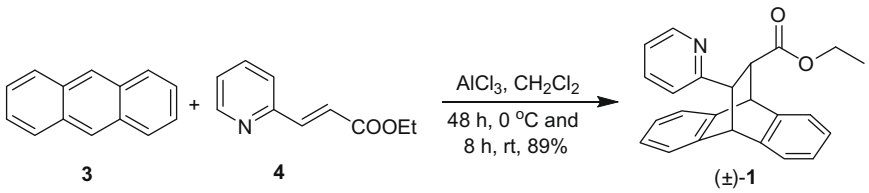


(1)

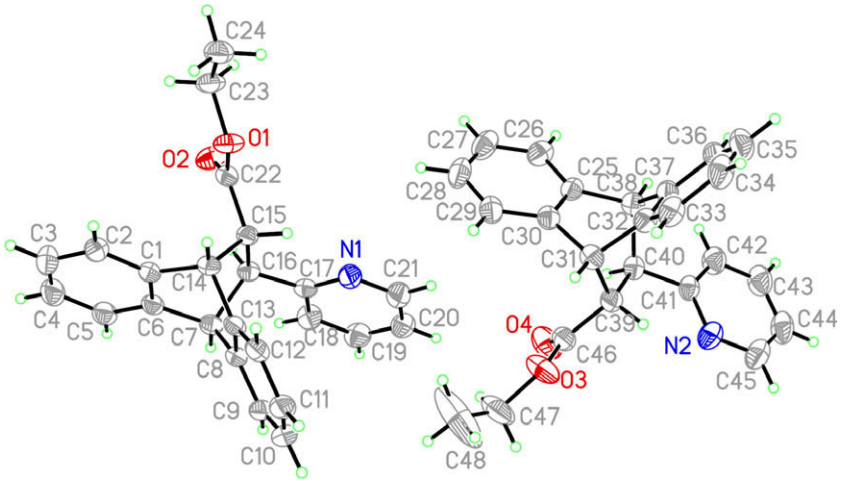


Figure 1. ORTEP representation of the X-ray crystal structure of (±)-**1** (all hydrogen atoms are unlabeled for clarity).

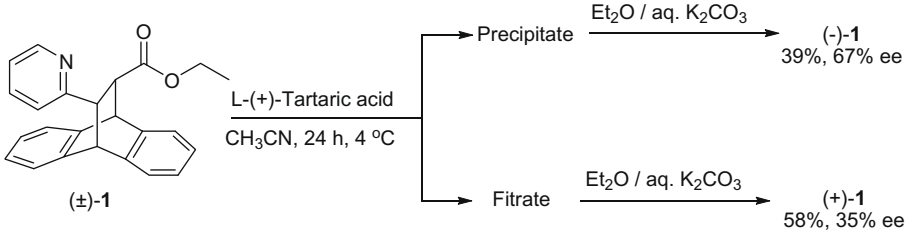
The structure of (±)-**1** was characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and HRMS and further confirmed through single crystal X-ray crystallographic analysis (Fig. 1).[9]

2.2. Resolution of (±)-1

The presence of a basic functional group, pyridine, prompted us to investigate the possibility of generating both isomers in enantiomerically pure form through a classical resolution technique via diastereomeric salt formation with a chiral acid. There are several acidic chiral resolving agents, chiral carboxylic acids and sulfonic acids, reported in the literature for the resolution of racemic bases.[10] One such versatile, commercially available and economical resolving agent is L-(+)-tartaric acid **2**. Hence, the resolution of (±)-**1** was carried out with a 1:1 mixture of (±)-**1** and L-(+)-tartaric acid in methanol at room temperature, which failed to afford a precipitate. This observation forced us to screen other solvents such as $CHCl_3$, MeOH, and CH_3CN at various temperatures to determine the appropriate solvent and optimum temperature to achieve the resolution of (±)-**1**. In this study, precipitation was observed at 4 °C from acetonitrile containing (±)-**1** and L-(+)-tartaric acid after 30 min. For example, (±)-**1** and L-(+)-tartaric acid were dissolved in acetonitrile and allowed to stand at 4 °C for 24 h. The precipitate obtained was filtered and washed with cold acetonitrile and decomposed by stirring with a 1:1 mixture of ether/aq K_2CO_3. The (−)-**1** isomer was isolated in 39% yield with 67% ee. The filtrate, on evaporation and decomposition with ether/aq K_2CO_3 mixture, afforded (+)-**1** isomer in 58% yield with 35% ee (Scheme 1).

Encouraged by this result, efforts were undertaken to determine the optimum time to obtain good yield and enantiomeric purity. Experiments were carried out with a 1:1 mixture of (±)-**1** and L-(+)-tartaric acid in acetonitrile at 4 °C by varying the precipitation time (6 h, 12 h, 18 h and 24 h) and the results are shown in Table 1.

The yields of the product from both the precipitate and the filtrate did not change with time but the enantiomeric purity increased, although marginally, from 93% for 6 h to 96% for 12 h (Table 1, entries 1 and 2). A further increase in time resulted in a lower enantiomeric excess of (−)-**1** from the precipitate. Hence, the optimum time for obtaining good yield (41%) and enantiomeric purity (96%) from the precipitate is 12 h (Table 1, entry 2), whereas, the filtrate fraction afford (+)-**1** in 58% yield with 64% enantiomeric excess.



Scheme 1.

Table 1
Effect of precipitation time on enantiomeric excess

Entry[a]	Time (h)	Yield[b] (%)		ee[c] (%)	
		Precipitate	Filtrate	Precipitate	Filtrate
1	6	40	59	93	63
2	12	41	58	96	64
3	18	41	58	95	59
4	24	42	57	89	63

[a] In all experiments, (±)-**1** (355 mg, 1 mmol) and L-(+)-tartaric acid (150 mg, 1 mmol) were dissolved in acetonitrile (10 mL) and allowed to stand at 4 °C for an appropriate time as mentioned in entries 1–4 to give the precipitate.
[b] Yields are of isolated products.
[c] Enantiomeric excess of the neutralized samples were determined by chiral HPLC analysis (Chiral stationary phase: Daicel-Chiralpak AD-H, Mobile phase: hexane and isopropyl alcohol 1/1, 0.5 mL/min, t_R = 8.5 min [(−)-**1**)], t_R = 10.7 min [(+)-**1**)]).

Table 2
Effect of number of equivalents of chiral resolving agent on enantiomeric excess

Entry[a]	L-(+)-Tartaric acid (mmol)	Solvent (mL)	Yield[b] (%)		ee[c] (%)	
			Precipitate	Filtrate	Precipitate	Filtrate
1	0.50	7.5	20	77	(−)-96	(+)-17
2	1.00	10.0	41	58	(−)-96	(+)-64
3	1.25	11.2	44	55	(−)-93	(+)-76
4	1.50	12.5	47	53	(−)-92	(+)-81
5	1.75	13.7	49	48	(−)-85	(+)-86
6	2.00	15.0	60	37	(−)-44	(+)-76
7	1.00	105.0	26	23	(−)-100	(+)-99[d]
8	1.75	145.0	35	41	(−)-100	(+)-100[e]

[a] In entries 1–6, 1 mmol of (±)-**1** was used. In entries 7 and 8, 10 mmol of (±)-**1** were used.
[b] Yields are of isolated products.
[c] Enantiomeric excesses of the neutralized samples were determined by chiral HPLC analysis.
[d] The precipitate obtained upon recrystallization of the residue, from filtrate fraction, in acetonitrile.
[e] Obtained by recrystallization of (+)-**1** with 99% ee in hexane.

It is known from the literature[11] that 1.75 equiv of L-(+)-tartaric acid would furnish a better yield and enantiomeric purity of both isomers. Accordingly, experiments were carried out with various equivalents of L-(+)-tartaric acid with 1 equiv of (±)-**1** in acetonitrile at 4 °C for 12 h; the results are summarized in Table 2. Increasing the number of equivalents of chiral resolving agent with respect to (±)-**1** increases the yield of (−)-**1** isomer from the precipitate gradually while decreasing the yield of (+)-**1** isomer from the filtrate. But the enantiomeric excess of (−)-**1** isomer from the precipitate decreases while increasing the equivalent of L-(+)-tartaric acid, at the same time, the yield of (+)-**1** from the filtrate decreases with an increase in enantiomeric purity.

When the reaction was carried out with 1.75 equiv of L-(+)-tartaric acid, the precipitate and filtrate respectively afforded 49% with 85% ee and 48% with 86% ee of (−)-**1** and (+)-**1** (Table 2, entry 5). Increasing the equivalents of L-(+)-tartaric acid caused a decrease in enantiomeric purity of both (−)-**1** and (+)-**1** isomers, respectively from precipitate and filtrate (Table 2, entry 6). Enantiomerically pure forms of both isomers were obtained through recrystallization of the diastereomeric salt in acetonitrile (Scheme 2, Table 2, entry 8). The recrystallization of the salt (precipitate I) containing (−)-**1** with 95% ee in acetonitrile furnished (−)-**1** isomer in enantiomerically pure isomer from precipitate II. Similarly the opposite isomer (+)-**1** was obtained in 99% enantiomeric purity via crystallization of the solid residue obtained from filtrate fraction in acetonitrile. (+)-**1** with 99% enantiomeric purity was recrystallized in hexane to afford the enantiomerically pure (+)-**1** (Scheme 2, Table 2, entry 8). An increase in solvent volume, decreases the yield of (−)-**1** isomer from precipitate while retaining the enantiomeric purity (Table 2, entries 7 and 8).

2.3. Nature of the complex—determination of the absolute configuration of (+)-1

The absolute configuration of the (+)-**1** isomer was determined via crystallographic analysis of single crystal obtained from a solution of enantiomerically pure (+)-**1** isomer and L-(+)-tartaric acid in acetonitrile (dissolved by heating at 50 °C for 10 min and then allowed to stand at room temperature).

The crystal structure (Fig. 2)[12] reveals that the L-(+)-tartaric acid was crystallized with one molecule of the (+)-**1** isomer. Furthermore, the C–O bond lengths (C44–O5 = 1.252 Å and C44–O6 = 1.247 Å) of one of the two carboxylic acid groups of L-(+)-tartaric acid were found to be nearly equal; this indicates that the substrate and L-(+)-tartaric acid form a diastereomeric pyridinium tartrate salt **5**.

The configuration of the stereogenic centers 11 and 12 of (+)-**1** was assigned relative to the known configuration of the (2*R*,3*R*)-(+)-tartaric acid. Based on this relative configuration, it was found that the configurations of stereogenic centers 11 and 12 in (+)-**1** are (*S*,*S*). Hence the absolute configurations of stereogenic centers 11 and 12 in (−)-**1** are (*R*,*R*).

3. Conclusion

In conclusion, we have developed a method for the synthesis of racemic *trans*-12-(pyridin-2-yl)-9,10-dihydro-9,10-ethanoanthracene-11-carboxylic acid ethyl ester and devised a simple and economical method for the resolution using readily available L-(+)-tartaric acid. The absolute configuration of (+)-**1** isomer was determined via single crystal X-ray crystallographic analysis. Further investigation regarding the structural modification and scope of the chiral molecule as a chiral inducer in asymmetric catalysis is currently in progress in this laboratory.

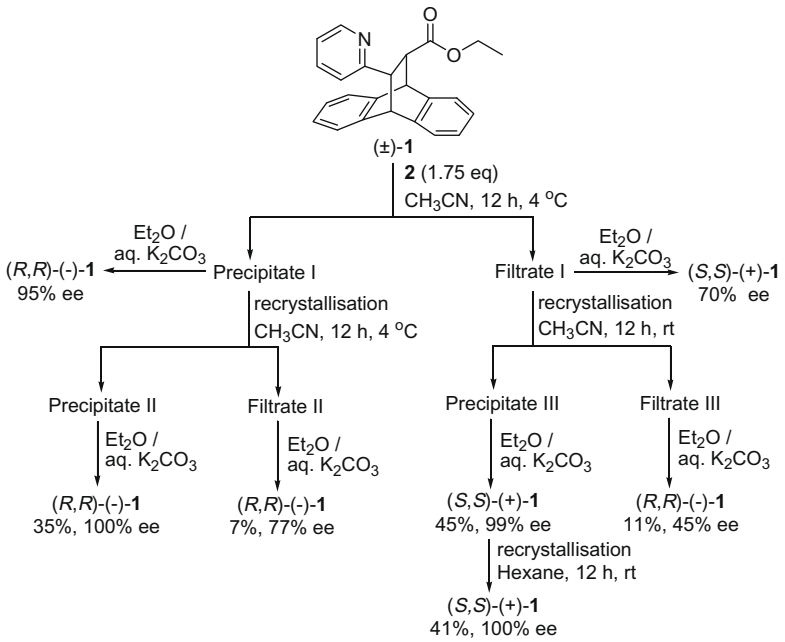
4. Experimental

4.1. General

Melting points reported in this paper are uncorrected and were determined using EZ Melt, Stanford research systems, USA. Infrared spectra were recorded on ABB BOMEM MB 104 FT-IR Spectrophotometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were recorded on Q-Tof Micro mass spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on Brucker Avance-400 spectrometer. NMR spectra for all the samples were measured in deuterated chloroform using TMS as an internal standard. The chemical shifts are expressed in δ ppm down field from the signal of internal TMS. Enantiomeric excess were determined by HPLC analysis using chiral stationary phase Daicel Chiralpak AD-H (4.6 × 250 mm 5 μm) column. Optical rotations were measured at 35 °C, with Autopol IV—Rudolph Research Analytical Polarimeter.

4.1.1. Synthesis of *trans*-(±)-12-(pyridin-2-yl)-9,10-dihydro-9,10-ethanoanthracene-11-carboxylic acid ethyl ester, (±)-1

To a stirred mixture of anthracene (5.35 g, 30 mmol) and 3-(pyridin-2-yl)-acrylic acid ethyl ester (4.43 g, 25 mmol) in dichloromethane (75 mL) at 0 °C was added anhydrous aluminum chloride (5.83 g, 43.75 mmol) and the stirring continued at 0 °C. After 48 h, the reaction mixture was brought to room temperature and stirring was continued for 8 h. The dark black colored solution was poured into water. The organic layer was separated and the



Scheme 2.

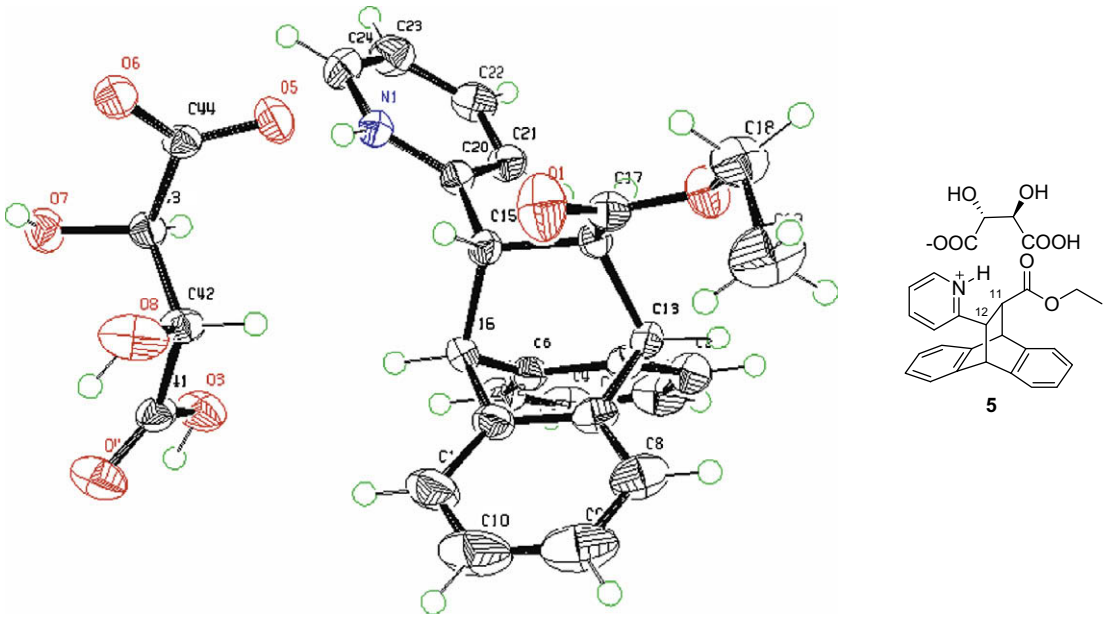


Figure 2. ORTEP representation of the X-ray crystal structure of (+)-**1**:L-(+)-tartaric acid.

aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure to afford viscous liquid. The crude material was purified through silica gel column chromatography (hexane/ethyl acetate = 90:10) to afford (±)-**1** as a colorless solid (7.88 g, 89%); Mp: 91–92 °C, IR (KBr, cm^{-1}): 2980, 1720, 1588, 1566, 1467, 1430, 1195, 770, 750. ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.37 (ddd, J = 4.8, 2.0, 1.2 Hz, 1H), 7.46 (td, J = 7.6, 2.0 Hz, 1H), 7.41 (d, J = 7.2 Hz, 1H), 7.38–7.35 (m, 1H), 7.31–7.29 (m, 1H), 7.17–7.09 (m, 3H), 7.02 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 6.98 (td, J = 7.6, 1.2 Hz, 1H), 6.89 (d, J = 6.8 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 4.82 (d, J = 2.4 Hz, 1H), 4.49 (d, J = 2.4 Hz, 1H), 4.12–3.99 (m, 2H), 3.91 (dd, J = 5.6, 2.8 Hz, 1H), 3.53 (dd, J = 5.6, 2.8 Hz, 1H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.0, 161.4, 148.7, 143.5, 142.6, 140.5, 140.4, 135.9, 126.3, 126.0, 125.9, 125.8, 125.5, 124.7, 123.5, 123.4, 121.9, 121.3, 60.7, 50.8, 50.0, 49.7, 47.4, 14.2; HRMS m/z $[M+H]^+$ found 356.1651, calcd 356.1651 for $C_{24}H_{21}NO_2$.

4.1.2. Resolution of *trans*-(±)-12-(pyridin-2-yl)-9,10-dihydro-9,10-ethanoanthracene-11-carboxylic acid ethyl ester, (±)-1

L-(+)-Tartaric acid (2.625 g, 17.5 mmol) was dissolved by heating at 60 °C in acetonitrile (105 mL). To this solution was added (±)-**1** (3.55 g, 10 mmol) and stirred for 15 min. The reaction mixture was brought to room temperature and then allowed to stand at 4 °C for 12 h to afford precipitate I, which was filtered and washed with cold acetonitrile (175 mL). The precipitate I was

redissolved in acetonitrile (63 mL) and allowed to stand at 4 °C for 12 h to afford precipitate II. The precipitate II was filtered and decomposed by stirring with a mixture of ether (50 mL)/aq K_2CO_3 (10%, 50 mL). The organic layer was separated and aqueous layer was extracted with ether (3 × 100 mL). The combined organic extract was washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure to afford a colorless solid, which was purified by silica gel column chromatography (hexane/ethyl acetate = 90:10) to furnish (−)-**1** (35%, 100% ee), [$[\alpha]_D^{35} = -89.4$, (*c* 1, $CHCl_3$); Mp: 106–107 °C]. Evaporation of acetonitrile from filtrate I under reduced pressure gave a residue, which was dissolved in acetonitrile (74.5 mL) and allowed to stand at room temperature for 12 h. The crystalline material (precipitate III) was filtered and decomposed with ether (50 mL)/aq K_2CO_3 (10%, 50 mL) as mentioned above. The (+)-**1** isomer was isolated with 99% ee (45%), which on recrystallization in hexane gave enantiomerically pure (+)-**1** isomer (41%, 100% ee), {$[\alpha]_D^{35} = +89.4$ (*c* 1, $CHCl_3$); Mp: 106–107 °C}. Enantiomeric excesses of non-racemic samples were determined by HPLC analysis of the neutralized sample using chiral column Daicel-Chiralpak AD-H; mobile phase: hexane and isopropyl alcohol 1/1, 0.5 mL/min, t_R = 8.5 min [(−)-**1**)], t_R = 10.7 min [(+)-**1**)].

Acknowledgments

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