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Asymmetric cycloaddition routes to both enantiomers of *trans*-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid

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Abstract—Fumarates prepared from a series of optically active alcohols were used as dienophiles in Lewis acid catalyzed asymmetric cycloadditions to anthracene. The reactions gave high yields and d.e.'s of the diester cycloaddition products and acid hydrolysis could be performed under conditions yielding only about 10% racemization. The reactions form a valuable synthetic pathway to both enantiomers of the bicyclic dicarboxylic acid, since di-(−)-menthyl fumarate yielded the (−)-(*S*,*S*)-enantiomer and di-(+)-*iso*-menthyl fumarate the (+)-(*R*,*R*)-enantiomer of the acid. The other fumarates, obtained from (−)-borneol, (+)-fenchol and (−)-isopulegol, likewise gave the (−)-(*S*,*S*)-enantiomer of the acid. The absolute stereochemistry of the products was confirmed via a single crystal X-ray crystallographic structure determination of the brucine salt of the (−)-(*S*,*S*)-enantiomer.

1. Introduction

Asymmetric Diels–Alder reactions involving fumaric acid provide access to optically active C_2-symmetric dicarboxylic acids of interest as chiral building blocks for the synthesis of enantiopure selectors that might be useful in asymmetric catalysts or chiral stationary phases. The exploitation of Lewis acids in asymmetric cycloadditions has led to increased selectivity owing to the lower temperature that can be used during the reaction.[1] A further development was made in the late 1970's when it was found that the chiral auxiliary, previously being a part of one of the reaction components, also could be a part of the catalyst.[2]

In connection with our work on new C_2-symmetric chiral selectors for enantioselective liquid chromatography, the (−)-(*S*,*S*)-enantiomer of *trans*-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid was prepared via the reaction between fumaric acid and anthracene followed by resolution with brucine.[3] This stereoisomer has been prepared previously via Lewis acid catalyzed addition of di-(−)-menthyl fumarate to anthracene.[4] The easy access to chiral dienophiles of this type and the high selectivity (99% d.e.) achieved, prompted us to investigate the asymmetric cycloaddition of a series of chiral fumarates to anthracene.

2. Results and discussion

The cycloaddition reactions were run under the conditions outlined in Scheme 1. Due to the low reactivity of anthracene as compared to the more commonly used conjugated dienes in Diels–Alder reactions, the temperature had to be significantly higher than what usually has been the case in catalyzed, asymmetric cycloadditions.[4a] Nevertheless, as observed previously for the reaction with di-(−)-menthyl fumarate,[4] high d.e.'s[5] were obtained (Table 1).

The diesters from the asymmetric Diels–Alder reactions were hydrolysed to the corresponding dicarboxylic acid (*trans*-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid, **3**), which is resolved by enantioselective chromatography,[6] thus permitting a determination of the degree of racemization during the hydrolysis. Two different methods of hydrolysis, as described in the experimental part, were studied. On alkaline hydrolysis with the use of dilute sodium hydroxide, the product **3** showed an e.e. about 40% lower than the d.e. of the diester **2**. Acid hydrolysis with a mixture of acetic acid and hydrochloric acid, though, resulted in a degree of racemization of only about 10%. Some methods of mild hydrolysis, such as one involving a transesterification

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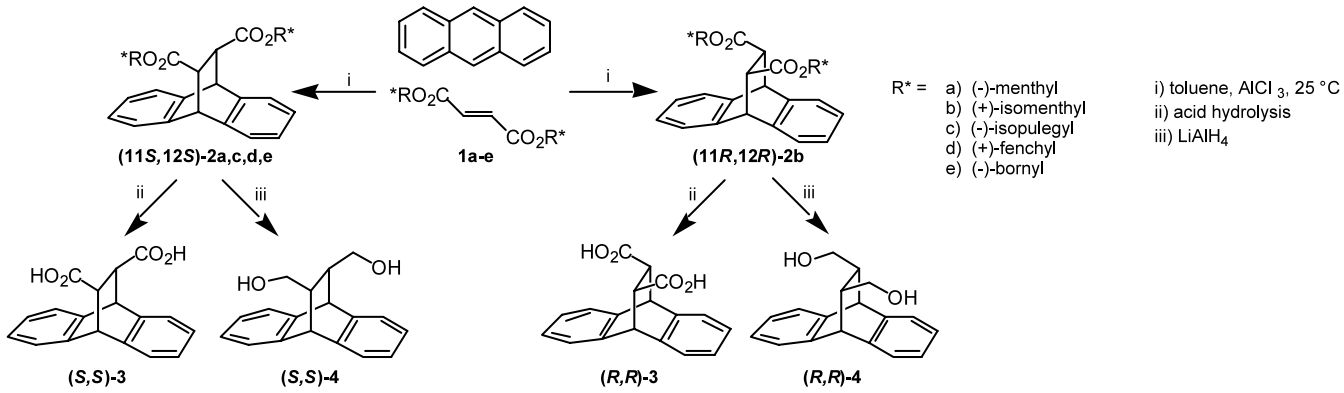

Scheme 1.

with bis(tributyltin) oxide,[7] were also tried, but unfortunately gave no reaction.

Lithium aluminium hydride reduction of **2** to the corresponding diol **4** gives no racemization and provides an independent method to determine the diasteromeric excesses of all cycloaddition products **2**. The enantiomeric excess of **4** was determined by enantioselective chromatography (Fig. 1). The diol obtained, either in its (*S*,*S*)- or (*R*,*R*)-form (Table 1), should be useful in the synthesis of chiral phosphine ligands[8a] utilized in asymmetric catalysis, for example Rh- or Ru-catalyzed enantioselective hydrogenation reactions,[8b] Pd-catalyzed CO–ethylene copolymerization[8c] and Pd-catalyzed asymmetric allylic alkylations.[8d]

Table 1. Results obtained from the asymmetric Diels–Alder reactions

Entry number	D.e. (%)	Absolute configuration	CD, λ_{ext} ($\Delta\varepsilon_{ext}$)
2a	98.9	(*S*,*S*)	206 (+25.39)
2b	82.2	(*R*,*R*)	206 (−24.04)
2c	95.4	(*S*,*S*)	207 (+22.26)
2d	95.2	(*S*,*S*)	207 (+18.23)
2e	85.9	(*S*,*S*)	206 (+25.99)

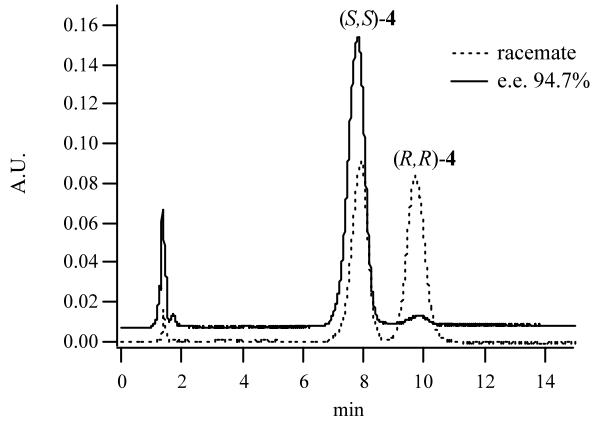

Figure 1. Chromatographic separation of the enantiomers of **4** on Kromasil CHI-DMB 250×4.6 mm I.D. column; mobile phase: 5% 2-propanol in hexane; flow rate: 1.5 mL/min; detection: UV 225 nm; $k'_1 = 4.11$, $\alpha = 1.29$.

Despite a certain degree of racemization obtained in the hydrolysis of **2**, the absolute configuration of the diastereomer obtained in excess was determined by correlation to the absolute configuration of **3** (Table 1). The enantiomers of **3** have previously been reported to be of (−)-(*S*,*S*)- or (+)-(*R*,*R*)-configuration, as determined by CD spectroscopy[9] and by stereochemical correlation.[9a] Due to the complexity involved in these determinations, however, some degree of uncertainty still remained. Therefore, in order to confirm conclusively the absolute configuration of the products, an X-ray crystallographic structural determination of the brucine salt of (−)-**3** was carried out. From the X-ray structure of the salt given in Figure 2, the (−)-(*S*,*S*)-configuration was definitely verified. Since the absolute structure parameter was 0.3(8), the absolute configuration was determined by correlation to the known configuration of brucine. The angles between the aromatic rings, C6–C7–C8 and C1–C14–C13, were 107.22(16) and 107.62(15)°, respectively.[10] This is less than in both the unbridged 9,10-dihydroanthracene at 144.7° and in the bridged but unsubstituted 9,10-ethano-9,10-dihydroanthracene at 124.7°.[11] From X-ray crystallographic studies on diethyl 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylate with an angle of 117.22(4)°, it is found that the *O*-substituent also affects the size of the angle.[11c] Figure 3 shows the interactions between the brucinium cation and the monoanion of (−)-**3** in the crystal structure.

From a synthetic point of view, the partial racemization obtained during the ester hydrolysis presents no problem, since we found that for e.e. values >75%, the pure enantiomer of the dicarboxylic acid **3** can be readily obtained by recrystallization. In previous syntheses, optically active **3**, used as starting material in the synthesis of several possible chiral selectors,[3b] has been obtained by recrystallization of its brucine salts;[3a] however, due to the cost and high toxicity of brucine, this is undesirable in large scale processes.

The stereochemical outcome of the reaction is governed by the most favourable orientation of the fumarate dienophile in the transition state, which, in turn, is dependent on the configuration of the terpenyl moiety.

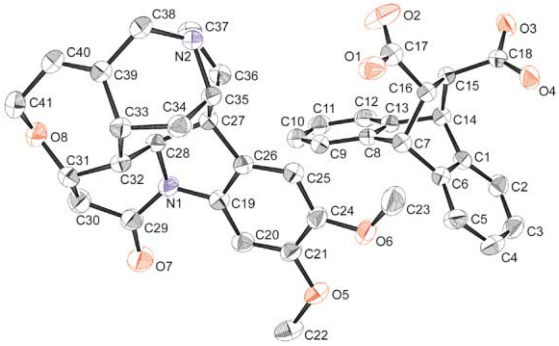

Figure 2. The structure of the brucine salt of (−)-**3** with 50% probability ellipsoids.

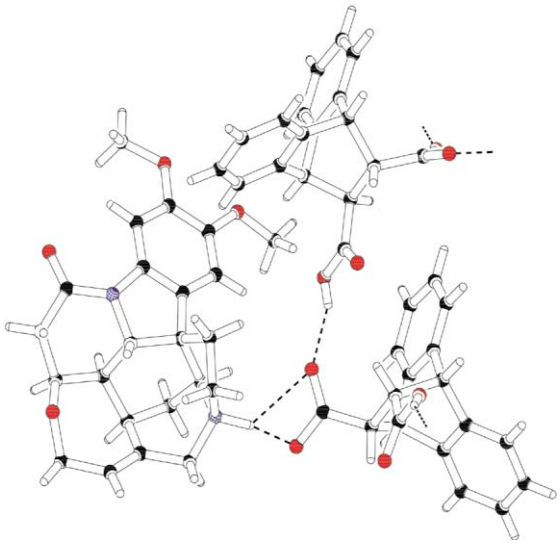

Figure 3. Interactions between brucine and (−)-**3** in the crystal structure.

Due to the small free energy differences involved, however, a rationalization of the results given in Table 1 is hard to make. The effects from small changes are evident from the reduction of d.e. from 99 to 82% by changing the configuration at C5 in the menthyl group; a part of the dienophile quite remote from the reacting π-bond. The small decrease of d.e. (from 99 to 95%) seen when changing the dienophile from **1a** to **1c** might be due to the slightly reduced steric demand of the propenyl group as compared to the isopropyl group.

Figure 4 shows the CD spectra of the two diastereomers of the dimenthyl ester **2a** and the (*S*,*S*)-enantiomer of **4**. As expected, the spectra of the two diastereomers are almost mirror images of each other. Moreover, the diastereomer obtained from the cycloaddition reaction and the diol, both of (11*S*,12*S*)-configuration, show a positive Cotton effect (CE) at 230 nm with essentially identical $\Delta\varepsilon$, resulting from a ^1L_b transition in the aromatic parts. The CE at 206 nm has a considerably larger $\Delta\varepsilon$ for **2a** as compared to **4**, showing that in **2a** this band corresponds not only to the ^1L_a transition in the aromatic parts, but is dominated by the n→π* transition in the carbonyl group[12] of the ester.

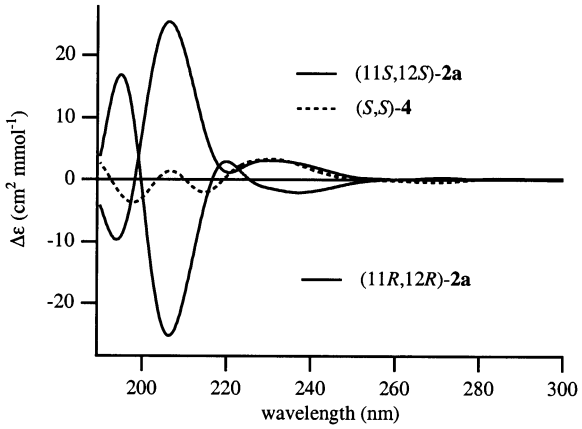

Figure 4. CD spectra of the diastereomers of **2a** and the (*S*,*S*)-enantiomer of **4**.

3. Experimental

3.1. General

Optical rotations were measured at 589 nm in a quartz microcell of 1 dm pathlength and 0.5 mL volume. Background-corrected CD spectra were recorded in acetonitrile with a spectropolarimeter using 1 mm pathlengths. Routine ^{1}H NMR spectra were recorded at 400 MHz with $CDCl_3$ or acetone-d_6 as solvent. Mass spectra were obtained with a high resolution mass spectrometer in the EI-MS and the FAB-MS mode. The mass spectrometer was calibrated with PFK or PEG 600 and 3-nitrobenzyl alcohol or glycerol was used as a matrix. Analytical liquid chromatography for determination of enantiomeric and diastereomeric excess was performed on 250×4.6 mm I.D. columns.[13]

3.2. Synthesis of fumarates 1a–e:[14] general procedure

Fumaryl chloride (16 mmol) was added to a solution of one of the optically active alcohols (32 mmol) in anhydrous toluene (30 mL) at 60°C. The solution was refluxed for 20 h under nitrogen. The cooled solution was washed with water (3×15 mL) and 10% NaOH solution (3×15 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure.

3.2.1. Di-(−)-menthyl fumarate, 1a. Yield 67%. $[\alpha]_D^{20}=-99.9$ (*c* 2.0, $CHCl_3$) (Ref. 15: $[\alpha]_D^{25}=-98.5$ (*c* 2.04, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 2H), 4.80 (m, $J=4.39$, 10.9 Hz, 2H), 2.03 (d, $J=11.9$ Hz, 2H), 1.87 (m, $J=2.76$, 6.91 Hz, 2H), 1.70 (d, $J=11.9$ Hz, 4H), 1.48, (m, $J=3.02$, 11.9 Hz, 4H), 1.05 (m, 4H), 0.91 (m, $J=6.91$ Hz, 14H), 0.76 (d, $J=6.90$ Hz, 6H) ppm.[16]

3.2.2. Di-(+)-isomenthyl fumarate, 1b. Yield 68%. $[\alpha]_D^{20}=+21.4$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (s, 2H), 5.15 (m, $J=3.40$, 6.68 Hz, 2H), 1.90 (m, 2H), 1.75 (m, $J=6.70$ Hz, 2H), 1.62 (m, 4H), 1.50 (m, 6H), 1.38 (m, $J=4.07$, 6.70 Hz, 2H), 1.24 (m, 2H), 0.95 (m, $J=4.05$ Hz, 12H), 0.86 (d, $J=6.69$ Hz, 6H) ppm.

EI-MS: m/z calculated for $C_{23}H_{37}O_4$ ($(M-15)^+$) 377.2692, found 377.270.

3.2.3. Di-(−)-isopulegyl fumarate, 1c. Yield 65%. $[\alpha]_D^{20} = -25.7$ (c 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.73 (s, 2H), 4.99 (m, $J=4.32$, 11.3 Hz, 2H), 4.72 (s, 4H), 2.16 (m, $J=3.59$, 11.3 Hz, 2H), 2.04 (d, $J=11.3$ Hz, 2H), 1.70 (m, 4H), 1.66 (s, 8H), 1.40 (m, $J=3.60$, 12.7 Hz, 2H), 1.07 (m, $J=12.6$ Hz, 2H), 0.94 (s, 8H) ppm. EI-MS: m/z calculated for $C_{24}H_{36}O_4$ (M^+) 388.2614, found 388.264.

3.2.4. Di-(+)-fenchyl fumarate, 1d. Yield 79%. $[\alpha]_D^{20} = +46.6$ (c 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 2H), 4.49 (m, $J=1.88$ Hz, 2H), 1.76 (m, $J=2.78$ Hz, 6H), 1.62 (dd, $J=1.55$, 10.3 Hz, 2H), 1.49 (m, $J=2.80$, 1.53 Hz, 4H), 1.23 (dd, $J=1.52$, 10.3 Hz, 2H), 1.14 (s, 6H), 1.07 (s, 6H), 0.80 (s, 6H) ppm. EI-MS: m/z calculated for $C_{24}H_{36}O_4$ (M^+) 388.2614, found 388.263.

3.2.5. Di-(−)-bornyl fumarate, 1e. Yield 75%. $[\alpha]_D^{20} = -58.9$ (c 1.0, $CHCl_3$) (Ref. 15: $[\alpha]_D^{25} = -60.7$ (c 0.93, $CHCl_3$)). ^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (s, 2H), 5.00 (m, $J=1.82$, 2.24, 9.73 Hz, 2H), 2.41 (m, $J=1.84$, 4.08, 9.70 Hz, 2H), 1.99 (m, $J=4.07$, 11.1 Hz, 2H), 1.78 (m, 2H), 1.71 (m, $J=4.32$ Hz, 2H), 1.35 (m, $J=4.31$ Hz, 2H), 1.26 (m, $J=4.33$, 11.1 Hz, 2H), 1.03 (dd, $J=3.51$, 13.6 Hz, 2H), 0.93 (s, 6H), 0.89 (s, 6H), 0.86 (s, 6H) ppm.[17]

3.3. Asymmetric Diels–Alder reactions (2a–e): general procedure

The fumarate (**1a**–**e**, 2 mmol) dissolved in anhydrous toluene (10 mL) was added dropwise to a slurry of $AlCl_3$ (4 mmol) in the same solvent (20 mL). After 1.5 h of stirring at room temperature, anthracene (6 mmol) dissolved in toluene (170 mL) was added. The yellow solution was stirred for 48 h under nitrogen. The solution was washed with 2 M HCl (4×100 mL) and 2 M NaOH (4×100 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography on silica with hexane/dichloromethane 50:50 as eluting solvent.

3.3.1. (11*S*,12*S*)-Dimenthyloxycarbonyl-9,10-dihydro-9,10-ethanoanthracene, 2a. Yield 78%. d.e. = 98.8%. Mp 167.8–169.2°C (Ref. 18: mp 168.5–170°C). $[\alpha]_D^{20} = -29.3$ (c 2.0, $CHCl_3$) (Ref. 18: $[\alpha]_D^{20} = -30.0$ (c 5.02, $CHCl_3$)). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 230, +2.939; 206, +25.39; 194, −9.688. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, $J=7.16$ Hz, 2H), 7.19 (m, $J=7.16$ Hz, 2H), 7.08 (m, $J=1.31$, 7.19 Hz, 4H), 4.66 (s, 2H), 4.54 (m, $J=4.28$, 10.8 Hz, 2H), 3.35 (s, 2H), 1.96 (m, $J=2.72$, 6.74 Hz, 2H), 1.79 (d, $J=12.3$ Hz, 2H), 1.69, (m, 4H), 1.38 (m, $J=2.56$, 10.7 Hz, 4H), 1.01 (m, $J=2.70$, 12.3 Hz, 2H), 0.95 (d, $J=6.76$ Hz, 6H), 0.83 (d, $J=6.75$ Hz, 6H), 0.80 (m, 4H), 0.72 (d, $J=6.78$ Hz, 6H) ppm.[18] FAB-MS: m/z calculated for $C_{38}H_{50}O_4$ (MH^+) 571.3787, found 571.3884. HPLC (Dynamax Si 83-101-C, 30% dichloromethane in hexane, flow = 2.0 mL/min) $k'_1 = 16.0$, $\alpha = 1.17$.

3.3.2. (11*S*,12*S*)-Diisomenthyloxycarbonyl-9,10-dihydro-9,10-ethanoanthracene, 2b. Yield 96%. d.e. = 82.2%. Oil. $[\alpha]_D^{20} = -6.8$ (c 2.0, $CHCl_3$). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 230, −2.864; 206, −24.04; 194, +13.38. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, $J=1.47$, 6.95 Hz, 2H), 7.24 (m, 2H), 7.11 (m, $J=1.48$, 6.93 Hz, 4H), 4.95 (m, $J=3.34$, 3.67 Hz, 2H), 4.71 (s, 2H), 3.40 (s, 2H), 1.77 (m, $J=6.70$ Hz, 2H), 1.65 (m, 2H), 1.54 (m, 2H), 1.38 (m, 2H), 1.30 (m, 2H), 1.19 (m, $J=3.35$, 3.65 Hz, 2H), 0.97 (m, 2H), 0.95 (d, $J=6.70$ Hz, 6H), 0.90 (m, 4H), 0.86 (dd, $J=2.26$, 6.69 Hz, 12H) ppm. FAB-MS: m/z calculated for $C_{38}H_{50}O_4$ (MH^+) 571.3787, found 571.3837.

3.3.3. (11*S*,12*S*)-Diisopulegyloxycarbonyl-9,10-dihydro-9,10-ethanoanthracene, 2c. Yield 34%. d.e. = 95.4%. Mp 185.2–186.9°C. $[\alpha]_D^{20} = +3.3$ (c 2.1, $CHCl_3$). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 299, +2.978; 207, +22.26; 194, −25.94. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (m, 2H), 7.17 (m, 2H), 7.06 (m, 4H), 4.87 (s, 2H), 4.65 (m, $J=4.51$ Hz, 2H), 4.58 (m, $J=8.17$ Hz, 4H), 3.28 (s, 2H), 1.86 (dd, $J=2.99$, 11.7 Hz, 2H), 1.70 (m, 2H), 1.67 (m, 6H), 1.47 (m, 2H), 1.42 (m, 4H), 1.33 (m, $J=2.98$ Hz, 2H), 1.04 (m, $J=11.7$ Hz, 2H), 0.93 (m, $J=6.55$ Hz, 4H), 0.87 (m, $J=6.55$ Hz, 4H) ppm. FAB-MS: m/z calculated for $C_{38}H_{46}O_4$ (MH^+) 567.3474, found 567.3503. HPLC (Dynamax Si 83-101-C, 35% dichloromethane in hexane, flow = 2.0 mL/min) $k'_1 = 19.5$, $\alpha = 1.43$.

3.3.4. (11*S*,12*S*)-Difenchyloxycarbonyl-9,10-dihydro-9,10-ethanoanthracene, 2d. Yield 69%. d.e. = 95.2%. Mp 173.7–173.9°C. $[\alpha]_D^{20} = +35.3$ (c 2.0, $CHCl_3$). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 230, +3.483; 207, +18.23; 194, −13.13. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (m, $J=1.39$, 6.94 Hz, 2H), 7.28 (m, $J=1.38$ Hz, 2H), 7.10 (m, $J=1.37$, 6.94 Hz, 4H), 4.72 (s, 2H), 4.24 (s, 2H), 3.43 (s, 2H), 1.67 (m, 2H), 1.53 (m, 8H), 1.44 (m, $J=1.27$ Hz, 2H), 1.13 (m, $J=1.28$, 9.78 Hz, 2H), 1.05 (d, $J=9.77$ Hz, 6H), 0.98 (m, 2H), 0.78 (d, $J=6.58$ Hz, 6H), 0.76 (m, 4H) ppm. FAB-MS: m/z calculated for $C_{38}H_{46}O_4$ (MH^+) 567.3474, found 567.3424. HPLC (Dynamax Si 83-101-C, 25% dichloromethane in hexane, flow = 2.0 mL/min) $k'_1 = 27.7$, $\alpha = 1.10$.

3.3.5. (11*S*,12*S*)-Dibornyloxycarbonyl-9,10-dihydro-9,10-ethanoanthracene, 2e. Yield 78%. d.e. = 85.9%. Mp 128.5–129.2°C. $[\alpha]_D^{20} = -8.7$ (c 2.0, $CHCl_3$). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 230, +2.915; 206, +25.99; 194, −12.70. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (m, $J=1.12$, 7.08 Hz, 2H), 7.26 (m, 2H), 7.12 (m, $J=1.15$, 7.10 Hz, 4H), 4.75 (m, $J=2.66$, 9.49 Hz, 2H), 4.71 (s, 2H), 3.44 (s, 2H), 2.24 (m, $J=3.90$, 9.48 Hz, 2H), 1.88 (m, $J=3.92$, 10.7 Hz, 2H), 1.72 (m, $J=3.90$ Hz, 2H), 1.56 (s, 2H), 1.33 (m, 2H), 1.14 (m, $J=4.30$, 10.7 Hz, 2H), 0.86 (m, 2H), 0.80 (m, $J=3.38$ Hz, 16H), 0.76 (m, $J=3.39$ Hz, 2H) ppm. FAB-MS: m/z calculated for $C_{38}H_{46}O_4$ (MH^+) 567.3474, found 567.3411. HPLC (Dynamax Si 83-101-C, 35% dichloromethane in hexane, flow = 2.0 mL/min) $k'_1 = 23.2$, $\alpha = 1.20$.

3.4. Synthesis of racemic 2a–e: general procedure

Dioxane (100 mL) was added to a mixture of fumaric acid (1.69 g, 14.5 mmol) and anthracene (12.5 g, 67 mmol).[19] After refluxing for 70 h the solvent was evaporated under reduced pressure. A 5% potassium bicarbonate solution (100 mL) was added and the mixture was stirred for 3 h. The mixture was filtered and conc. HCl was added to the filtrate until pH 1. The product was isolated from the remaining fumaric acid by means of filtration of the hot solution, yielding 82% (±)-**3**. Mp 253.1–253.7°C (Ref. 3a: mp 252.5°C).

Thionyl chloride (12 mmol) was added to a slurry of (±)-**3** (3 mmol) in anhydrous toluene (13 mL) and one drop of DMF. After refluxing for 4 h under a nitrogen atmosphere, the solvent with the excess of thionyl chloride was evaporated under reduced pressure. Anhydrous toluene (2×10 mL) was added and evaporated under reduced pressure. The acid chloride was dissolved in anhydrous toluene (10 mL) and added to a solution of the respective terpene alcohol (6 mmol) in the same solvent (8 mL) at 45°C. After refluxing for 15 h under nitrogen, the solution was washed with water (4×10 mL) and 10% NaOH solution (4×10 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography on silica with hexane/dichloromethane 50:50 as eluting solvent.

3.5. Hydrolysis of 2a–e to 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid, 3: general procedures

3.5.1. Method A (alkaline hydrolysis). To a solution of the diester (**2a**–**e**, 0.3 mmol) in toluene (20 mL), a 3 M NaOH solution (20 mL) was added. After reflux for 2 h the phases were separated. The aqueous phase was extracted with diethyl ether (3×10 mL) and conc. HCl was added until pH 2. The acidic aqueous phase was extracted with diethyl ether (3×30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure.

3.5.2. Method B (acid hydrolysis). The diester (**2a**–**e**, 0.03 mmol) was dissolved in acetic acid (1 mL) and conc. HCl (1 mL). After refluxing for 16 h, a 3 M NaOH solution was added until pH 14. The solution was extracted with diethyl ether (3×3 mL) and conc. HCl was added to the aqueous phase until pH 2, followed by extraction with diethyl ether (4×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. (*S*,*S*)-**3** (e.e. >99%): Mp 219.8–220.2°C (Ref. 3a: mp 220.5°C). $[\alpha]_{546}^{20} = -15.5$ (*c* 2.03, dioxane) (Ref. 3a: $[\alpha]_{578}^{20} = -15.3$ (*c* 2, dioxane)). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 218, −4.740; 206, +3.392; 197, −8.604. ^1H NMR (400 MHz, acetone-d_6): δ 7.42 (m, $J = 1.69$, 6.35 Hz, 2H), 7.32 (m, $J = 1.70$, 6.33 Hz, 2H), 7.11 (m, $J = 1.67$, 6.32 Hz, 4H), 4.83 (s, 2H), 3.38 (s, 2H) ppm. HPLC (Kromasil CHI-TBB, 2% 2-propanol and 0.2% acetic acid in hexane, flow = 2.0 mL/min): $k'_1 = 7.48$, $\alpha = 1.28$.

3.6. Reduction of 2a–e to 11,12-bis-(hydroxymethyl)-9,10-dihydro-9,10-ethanoanthracene, 4: general procedure

A solution of the diester (**2a**–**e**, 0.03 mmol) in anhydrous diethyl ether (0.5 mL) was added dropwise to a slurry of $LiAlH_4$ (0.18 mmol) in the same solvent (0.5 mL). After refluxing for 3 h under nitrogen, diethyl ether saturated with water (1 mL) was added and the slurry was refluxed for 10 min. Water (1 mL) and 10% H_2SO_4 were added until a clear solution was obtained. The phases were separated and the organic layer was washed with water (1 mL), dried over $MgSO_4$, filtered and the solvent was removed by evaporation under reduced pressure. Mp ((±)-**4**) 199.4–200.5°C (Ref. 20: mp ((±)-**4**) 198.5–199.5°C). Mp ((*S*,*S*)-**4**) 132.7–134.2°C (Ref. 8a: mp ((*R*,*R*)-**4**) 131–132°C). (*S*,*S*)-**4** $[\alpha]_D^{20} = -15.0$ (*c* 1.0, dioxane), $[\alpha]_D^{20} = +11.1$ (*c* 0.9, methanol) (Ref. 8a: $[\alpha]_{546}^{20} = -15.2$ (*c* 1, dioxane), $[\alpha]_D^{20} = +11.1$ (*c* 1.0, methanol)). CD (acetonitrile): λ_{ext} (nm), $\Delta\varepsilon_{ext}$ (cm^2 $mmol^{-1}$) 270, −0.406; 230, +3.291; 215, −2.015; 207, +1.346; 198, −3.641. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, $J = 2.30$ Hz, 2H), 7.24 (m, $J = 2.32$ Hz, 2H), 7.11 (m, $J = 2.30$, 4.85 Hz, 4H), 4.23 (d, $J = 1.58$ Hz, 2H), 3.48 (m, $J = 6.34$ Hz, 2H), 3.09 (m, $J = 1.60$ Hz, 2H), 1.73 (m, $J = 6.35$ Hz, 2H) ppm. HPLC (Kromasil CHI-DMB, 5% 2-propanol in hexane, flow = 1.5 mL/min): $k'_1 = 4.11$, $\alpha = 1.29$.

3.7. X-Ray crystallography

Crystal, experimental and refinement data are summarised in Table 2. Diffracted intensities were measured with a Rigaku R-AXIS IIc image plate system using graphite-monochromated Mo Kα radiation from a RU200 rotating anode operated at 50 kV and 90 mA. Using the CrystalClear software package, 90 oscillation photos with a rotation angle of 2° were collected and processed. An empirical absorption correction was applied using the REQAB program in CrystalClear. The structure was solved by direct methods (SHELXS) and refined with full-matrix least-squares calculations on F^2 using SHELXL-97.[21] operating in the WinGX program package.[22] Anisotropic thermal displacement parameters were refined for all non-hydrogen atoms while hydrogen atoms (except H17 on O1, H18 on N2 and H40) were included in calculated positions and refined using a riding model. H17, H18 and H40 were identified from a difference map and the positional parameters were refined. Figure 2 shows the structure of the monobrucinium salt of (−)-**3** drawn with ORTEP-3 under WinGX. The illustration of the spatial organization of brucine and (−)-**3** in Figure 3 has been drawn with PLUTON under WinGX. Crystallographic data for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-188176. Copies of the data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CD21EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Table 2. X-Ray crystallographic data for the brucine salt of (−)-**3**

Empirical formula	$C_{41}H_{40}N_2O_8$
Formula weight (g/mol)	688.75
Temperature (K)	293
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$ (#19)
a (Å)	10.3854(14)
b (Å)	13.8236(19)
c (Å)	22.973(3)
α (°)	90
β (°)	90
γ (°)	90
V (Å^3)	3298.1(8)
Z	4
D_{calcd} (mg/m^3)	1.387
Reflections collected	26980
Independent reflections	7466 ($R_{int}=0.0688$)
Absorption coefficient (mm^{-1})	0.096
$F(000)$	1456
θ Range for data collection (°)	2.61–27.50
Completeness to $\theta=27.50°$ (%)	98.6
Index ranges	$-12\le h\le 13$, $-17\le k\le 17$, $-29\le l\le 29$
Crystal size (mm)	$0.2\times0.2\times0.2$
Data/restraints/parameters	7466/0/452
Goodness-to-fit on F^2	1.004
Final R indices [$I>2\sigma(I)$]	$R_1=0.0494$, $wR_2=0.1088$
R indices (all data)	$R_1=0.0616$, $wR_2=0.1141$
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e/Å^3)	0.301, −0.240

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5. The diastereomeric excesses were determined by liquid chromatography on silica using 30% of dichloromethane in hexane.
6. Resolution is achieved by a Kromasil CHI-TBB 250×4.6 mm I.D. column; mobile phase: 2% 2-propanol and 0.2% acetic acid in hexane; flow rate: 2 mL/min; detection: UV 225 nm; amount injected: 20 μL of 5 mg/mL; $k'_1=7.28$, $\alpha=1.28$.
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