Synthesis and optical resolution of axially dissymmetric pyrroles and pyrocolls: new catalysts for the enantioselective addition of diethylzinc to aromatic aldehydes

Yoshio Furusho, Akihiro Tsunoda and Takuzo Aida *

Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

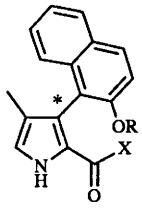
The novel axially dissymmetric pyrroles, 4-methyl-3-(2′-methoxy-1′-naphthyl)pyrrole-2-carboxylates 1 and 4-ethyl-3-(10′-methoxy-9′-phenanthryl)pyrrole-2-carboxylates 3 were synthesized from the corresponding nitroalkenes and ethyl isocyanoacetate. Optical resolution of compounds 1 was achieved *via* crystallization of a diastereoisomeric mixture of the (*R*)-1-phenylethyl esters 1d, while the antipodes of compound 3b *spontaneously* resolved upon crystallization of the racemate. The rotational barrier ($\Delta G^{\ddagger}$) at 25 °C about the pyrrole–phenanthrene bond in compound 3b (160 kJ mol^{-1}) was 30 kJ mol^{-1} higher than that about the pyrrole–naphthalene bond in compound 1b. The carboxylate 1b or 3b lost optical activity upon lactonization, while the resulting lactone 2 opened diastereoselectively by reaction with lithium (*S*)-1-phenylethylamide. The antipodes of compounds 1a and 3a were converted respectively without racemization into axially dissymmetric pyrocolls, 1,6-bis(2′-hydroxy-1′-naphthyl)-2,7-dimethylpyrocoll 5a and 2,7-diethyl-1,6-bis(10′-hydroxy-9′-phenanthryl)pyrocoll 6a, both of which effectively catalysed enantioselective addition of Et_2Zn to aromatic aldehydes.

Introduction

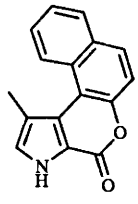
Biaryls with axial dissymmetry are compounds of particular interest and broad use as excellent chiral auxiliaries for asymmetric synthesis and recognition.[1] However, axially dissymmetric compounds bearing heterocyclic rings have been less explored to date. In the present paper, we report on novel pyrrole-based chiral biaryls and teraryls with axial dissymmetry.

We have been involved in the synthesis and applications of chiral porphyrins and metalloporphyrins derived from porphyrins with enantiotopic faces.[2,3] As an extension of this study, we have succeeded in the first predetermined synthesis of a chiral atropisomeric porphyrin starting from the antipode of an alkoxynaphthalene-substituted, pyrrole-2-carboxylic acid **1**.[4] A compound **1** is also the first axially dissymmetric pyrrole whose absolute structure was correlated with its circular dichroism (CD) profile. In the course of this study, we found that bimolecular cyclocondensation of compound **1a** takes place very efficiently in the presence of a 2-bromopyridinium salt under mild conditions, producing a diketopyrazine ring called pyrocoll (compound **5b**). Although pyrocoll **7** was discovered more than 100 years ago, it has attracted little attention because of its difficult synthesis.[5–7]

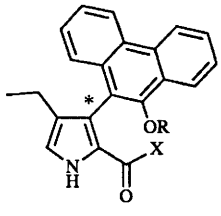
In the present paper, we report (i) the synthesis of the axially dissymmetric pyrroles **1**, **3** and pyrocolls **5**, **6** with naphthalene and phenanthrene rings, (ii) lactonization of compounds **1** and **3** and diastereoselective ring opening of the resulting lactone **2** and (iii) application of compounds **1**, **5** and **6** as chiral catalysts for asymmetric addition of diethylzinc (Et_2Zn) to aromatic aldehydes.[8]



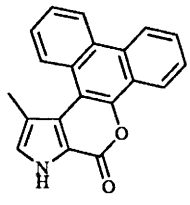
1a; X = OH, R = Me
1b; X = OEt, R = Me
1c; X = OCH_2Ph, R = Me
1d; X = (*R*)-OCH(Me)Ph, R = Me
1e; X = OEt, R = H
1f; X = (*S*)-NHCH(Me)Ph, R = H



2



3a; X = OH, R = Me
3b; X = OEt, R = Me

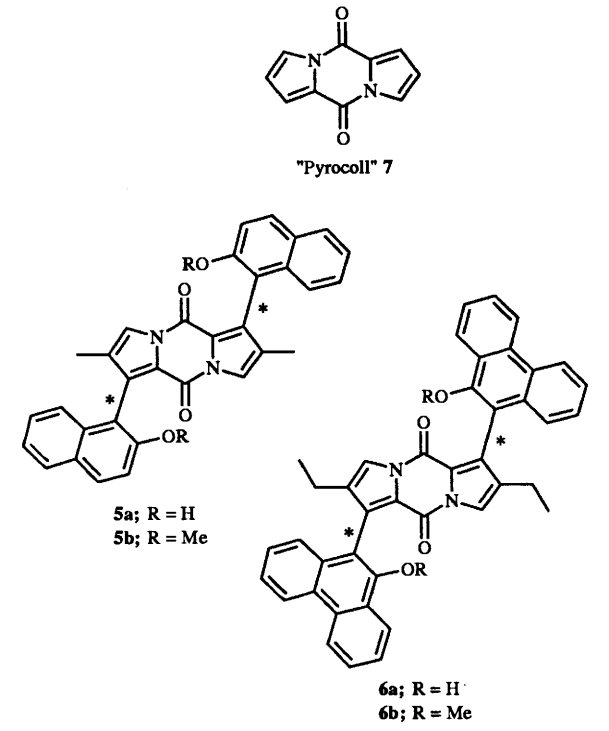


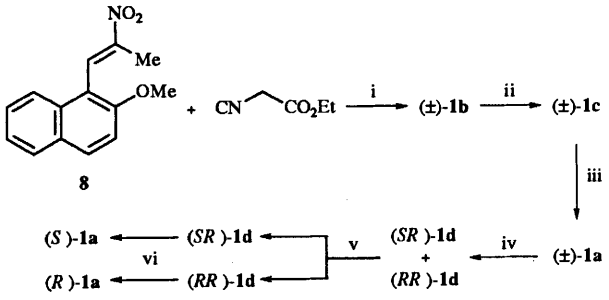
4

Results and discussion

Synthesis of axially dissymmetric pyrroles 1, 3

The axially dissymmetric pyrroles **1**, **3** were synthesized from nitroalkenes and ethyl isocyanoacetate (Scheme 1).[9] For example, nitroethane was condensed with 2-methoxy-1-naphthaldehyde to give a nitroalkene **8**, which was treated with ethyl isocyanoacetate **9** to afford racemic compound **1b**. Although the antipodes of product **1b** were directly separable by chiral high-performance liquid chromatography (HPLC) the resolution was much enhanced by crystallization of the diastereoisomeric (*R*)-1-phenylethyl ester derivative **1d**. Thus, compound (±)-**1b** was transesterified with benzyl alcohol, and the resulting ester (±)-**1c** was hydrogenolysed to yield acid (±)-**1a**, which was esterified with (*R*)-1-phenylethyl alcohol by the action of 2-bromo-1-ethylpyridinium tetrafluoroborate[10] as condensing agent. Upon crystallization of the resulting diastereoisomeric mixture [(*SR*)- + (*RR*)-**1d**] in EtOH, crystals were formed, which were identified as pure isomer (*SR*)-**1d**. Chromatography of the residue on silica gel with benzene–diethyl ether (99:1) as eluent allowed the isolation of pure isomer (*RR*)-**1d** as an oily substance. In the ^1H NMR spectra in $CDCl_3$ of the diastereoisomers of compound **1d**, isomer (*SR*)-**1d** showed a single MeO signal at δ 3.75, while diastereoisomers





Scheme 1 *Reagents and conditions* [*yields*]: i, DBU [83%]; ii, Na–$PhCH_2OH$ [89%]; iii, H_2, Pd/C [96%]; iv, (*R*)-PhCH(Me)OH, 2-Br-1-ethylpyridinium BF_4^- [91%]; v, crystallization; (*SR*)-**1d** [26% based on (±)-**1a**], then column chromatography; (*RR*)-**1d** [28% based on (±)-**1a**]; vi, H_2, Pd/C

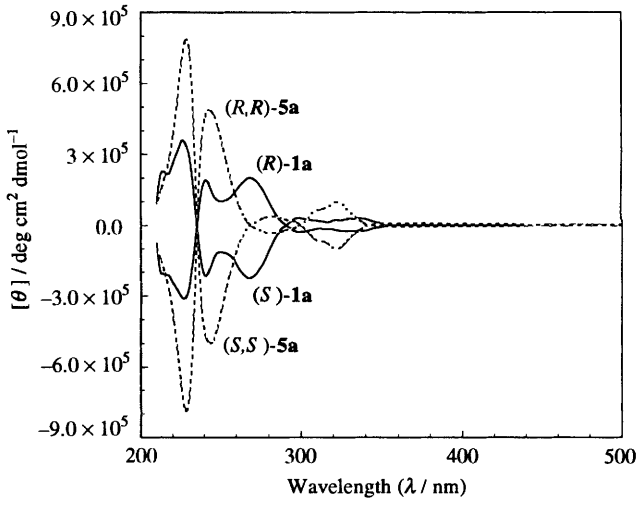
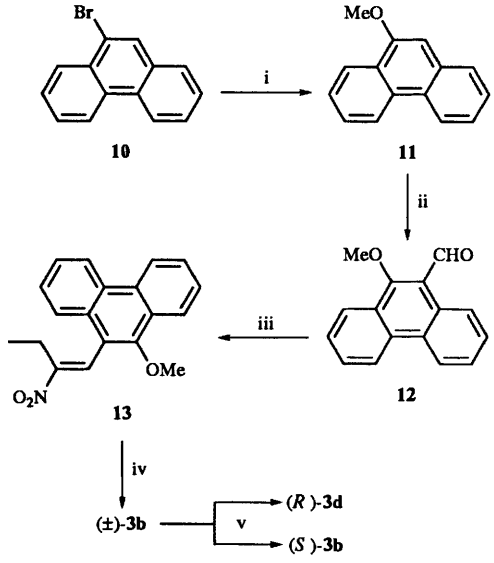


Fig. 1 Circular dichroism (CD) spectra, run in THF, of the antipodes of the naphthalene-substituted pyrrole **1a** and the pyrocoll **5a**



Scheme 2 *Reagents and conditions* [*yields*]: i, NaOMe, CuI [92%]; ii, DMF, $POCl_3$ [58%]; iii, 1-nitropropane, H^+ [72%]; iv, **9**, DBU [77%]; v, preferential crystallization

(*RR*)-**1d** exhibited the corresponding signal at δ 3.88. The (*S*)-configuration about the pyrrole–naphthalene bond in isomer (*SR*)-**1d** has been already established by X-ray crystallography,[4] where the naphthalene ring is tilted by 116° relative to the pyrrole ring. Isomers (*SR*)-**1d** and (*RR*)-**1d** were hydrogenolysed respectively at room temperature to give the antipodes of the carboxylic acid, (*S*)-**1a** and (*R*)-**1a**, whose circular dichroism (CD) spectra were perfect mirror images of each other (Fig. 1). At the maximum electronic absorption band (231 nm), the (*S*)-antipode exhibited an intense positive CD band ([θ] 300 000 units), while the (*R*)-antipode showed a negative one.

The phenanthrene-substituted pyrrole-2-carboxylate (±)-**3** was prepared similarly to the above by using 10-methoxyphenanthrene-9-carbaldehyde **12** in place of 2-methoxy-1-naphthaldehyde (Scheme 2). Of particular interest to note here is the fact that compound (±)-**3b** upon crystallization underwent *spontaneous resolution* into optically pure isomers (*R*)- and (*S*)-**3b**: crystallization of the racemate (±)-**3b** in hexane–propan-2-ol (80 : 20 v/v) formed clear crystals of sufficiently large size (~ 1 × 1 × 1 mm^3), each of which was composed of either enantiomer (*R*)- or (*S*)-**3b**, as determined by chiral HPLC (CHIRALPAK AD, Daicel). By taking advantage of this, the antipodes of compound **3b** could be resolved by preferential crystallization from a supersaturated solution of racemate (±)-**3b** upon addition of the above enantiomerically pure crystals as seeds. Since the antipodes of compound **3b** (Fig. 2) showed very similar CD spectra to those of compound **1a** (Fig. 1), the absolute configurations of the antipodes were determined from the CD profiles. The pyrrole–phenanthrene bond in compound **3b** is more reluctant to undergo thermal rotation than is the pyrrole–naphthalene bond in compound **1b**. The ethyl ester (*S*)-**3b** did not racemize at all at 100 °C for 4 h in *o*-xylene, and even at 120 °C only 1.5% of enantiomer (*S*)-**3b** was configurationally inverted. From the racemization profile of compound (*S*)-**3b**, the rotational barrier ($\Delta G^{\ddagger}$) at 25 °C about the pyrrole–phenanthrene bond was evaluated to be 160 kJ mol^{-1}, which is 30 kJ mol^{-1} higher than that of the pyrrole–naphthalene bond in compound **1b**.†[4]

Lactonization of axially dissymmetric pyrroles 2, 4

Although lactones are useful synthetic precursors, most lactone-bridged biaryls, though with a few exceptions,[11] are not resolved into stable optical isomers, since they easily *helimerize* even at room temperature.[12] Since the axially dissymmetric pyrroles **1b** and **3b** have potential hydroxy and carboxy

† $\Delta G^{\ddagger}_{298}$ of compound **1b** originally reported in ref. 4 (104 kJ mol^{-1}) was carefully re-examined, and was found to be 130 kJ mol^{-1}.

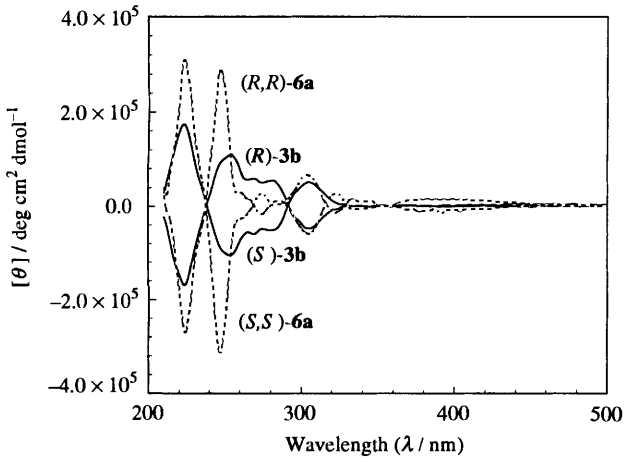
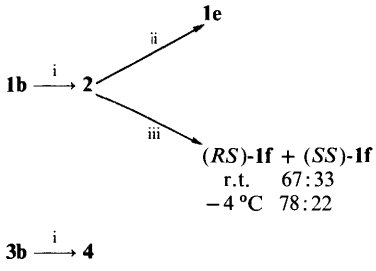


Fig. 2 Circular dichroism (CD) spectra, run in THF, of the antipodes of the phenanthrene-substituted pyrrole **3b** and the pyrocoll **6a**



Scheme 3 *Reagents* [*yields*]: i, BBr_3, then water; **2** [quant.], **4** [58%]; ii, NaOEt, EtOH [73%]; iii, (*S*)-LiNHCH(Me)Ph

functionalities, they can be converted into δ-lactones. Treatment of racemate (±)-**1b** with BBr_3 in CH_2Cl_2 at −78 °C gave the corresponding lactone **2** almost quantitatively (Scheme 3). Chiral HPLC analyses (CHIRALCEL OD or CHIRALPAK AD) of compound **2** thus obtained under various conditions showed a single, sharp elution peak without a sign of optical resolution. In conformity with this observation, compound **2** synthesized from compound (*SR*)-**1d** was optically inactive, as observed by CD, indicating the possibility of rapid helimerization at the pyrrole–naphthalene bond in compound **2**. A similar result was obtained for the lactone **4** synthesized from the optically active phenanthrene-substituted pyrrole-2-carboxylate (*R*)-**3b**.

The lactone ring of compound **2** was opened by the action of NaOEt at room temperature[12] to afford an axially dissymmetric pyrrole carrying an aromatic OH functionality (compound **1e**) (Scheme 3). On the other hand, with sodium salts of secondary alcohols such as 1-phenylethyl alcohol and menthol, the ring opening of compound **2** did not take place under similar conditions. In contrast, a lithium amide such as lithium (*S*)-1-phenylethylamide was found to cleave the lactone ring of compound **2** stereoselectively at room temperature (~20 °C), to give the corresponding pyrrole-2-carboxamide **1f** with the diastereoisomer ratio ([*RS*]:[*SS*]), as determined by ^{1}H NMR spectroscopy, of 67:33. In this case, lowering of the reaction temperature to −4 °C resulted in a higher diastereoselectivity (78:22), but at −20 °C no ring-opening reaction took place.

Fig. 3 showed the CD spectra in EtOH of the antipodes of compound **1e**, resolved by chiral HPLC.‡ Since the profiles

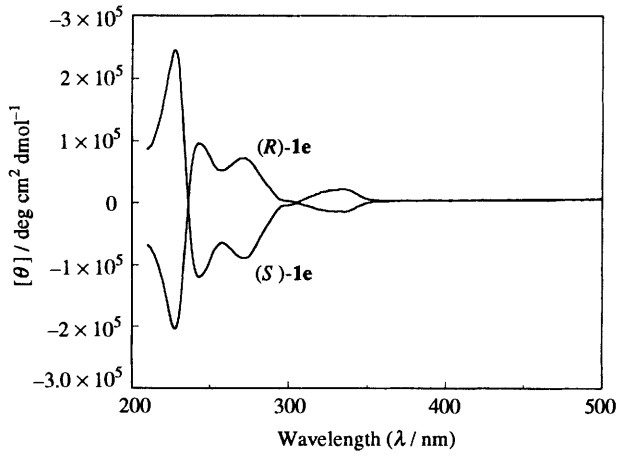
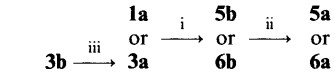


Fig. 3 Circular dichroism (CD) spectra of the antipodes of the hydroxynaphthalene-substituted pyrrole **1e** in EtOH

were almost the same as those of compound **1a** (Fig. 1), the antipode exhibiting an intense positive band at 228 nm was assigned to isomer (*S*)-**1e**, while that with a negative CD band was assigned to (*R*)-**1e**.

Synthesis of axially dissymmetric pyrocolls 5, 6

According to the literature pyrocoll derivatives have been synthesized by cyclocondensation of pyrrole-2-carboxylic acid in refluxing acetic anhydride (~36% yield),[5] flash vacuum pyrolysis of the methyl ester at 650–850 °C (~90%)[6] or a base-promoted cyclization of the acid chloride (~5%),[7] all of which seem unsuitable for chiral pyrocoll synthesis from axially dissymmetric pyrroles **1,3**. However, we found that an onium salt such as 2-bromo-1-ethylpyridinium tetrafluoroborate[10] promotes this cyclocondensation very efficiently under mild conditions (Scheme 4). Thus, compound (*R*)-**1a**, obtained by



Scheme 4 *Reagents* [*yields*]: i, 2-bromo-1-ethylpyridinium BF_4^-; (*R,R*)- and (*S,S*)-**5b** [quant.], (*R,R*)- and (*S,S*)-**6b** [64% in two steps]; ii, BBr_3, then water; (*R,R*)-**5a** [80%], (*S,S*)-**5a** [quant.], (*R,R*)- and (*S,S*)-**6a** [79%]; iii,KOH, 18-crown-6, water

hydrogenolysis of ester (*RR*)-**1d**, was treated with 2-bromo-1-ethylpyridinium tetrafluoroborate in CH_2Cl_2 at 20 °C to give compound (*R,R*)-**5b** almost quantitatively in 1 h. No racemization in this process was confirmed by the single MeO signal (δ 3.93, s) in the ^{1}H NMR spectrum of the product, since compound **5b** derived from racemic acid **1a** showed two MeO singlets at δ 3.93 and 3.95 due, respectively, to the *syn* (chiral) and *anti* (achiral) isomers. Upon careful treatment with BBr_3 followed by dropwise addition of water at −78 °C, compound (*R,R*)-**5b** was demethylated without racemization to give bis-naphthol (*R,R*)-**5a**.§ Likewise, all the antipodes of pyrocolls **5** and **6** in optically pure form were obtained in satisfactory yields. It should also be noted here that the hydroxyphenanthrene-substituted pyrocoll **6a**, in contrast with the hydroxynaphthalene-substituted analogue **5a**, is labile upon exposure to room light, and should be handled with protection from light.

The (*R,R*)-antipodes of the naphthalene- (**5a** and **5b**; Fig. 1) and phenanthrene-substituted pyrocolls (**6a** and **6b**; Fig. 2)

‡ The crystals obtained from hydroxy ester (*R*)- or (*S*)-**1e** melted at 137–138 °C, while those from racemate (±)-**1e** melted at a higher temperature (150–151 °C), indicating no possibility of spontaneous resolution (non-conglomerate crystals).

§ Lack of racemization was confirmed by chiral HPLC (CHIRALPAK AD) with hexane–propan-2-ol as eluent. Addition of water at room temperature to the reaction mixture of bis-ether (*R,R*)-**5b** with BBr_3 resulted in partial racemization.

Table 1 Asymmetric ethylation of aldehydes by diethylzinc (Et_2Zn) catalysed by chiral pyrocolls (**5a**, **5b** and **6a**) and pyrroles (**1b** and **1e**)

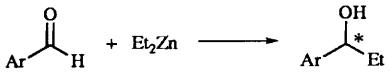
Entry	Catalyst[a]	Aldehyde	Solvent	Temp. (T/°C)	Time (t/h)	Conv. (%)[c]	ee (%)[e]
1	**5a** (*R*,*R*)	Benzaldehyde	Toluene	r.t.[b]	2	100	76 (*S*)
2	(*R*,*R*)			−4	10	98	78 (*S*)
3	(*R*,*R*)			−20	44	98	80 (*S*)
4	(*R*,*R*)			−40	120	90	73 (*S*)
5	(*S*,*S*)		CH_2Cl_2	−20	71	92	77 (*R*)
6	(*S*,*S*)			−40	168	95	69 (*R*)
7	(*S*,*S*)	3-Anisaldehyde	Toluene	−40	39	57	75 (*R*)
8	(*R*,*R*)		CH_2Cl_2	−20	51	100	82 (*S*)
9	(*R*,*R*)	2-Tolualdehyde	Toluene	−20	87	95	51 (*S*)
10	(*R*,*R*)	1-Naphthaldehyde	CH_2Cl_2	−20	86	87[d]	43 (*S*)[f]
11	(*R*,*R*)	2-Naphthaldehyde		−20	40	100[d]	73 (*S*)[f]
12	**6a** (*S*,*S*)	Benzaldehyde	Toluene	−20	9	94	67 (*R*)
13	(*S*,*S*)			−40	44	73	66 (*R*)
14	(*S*,*S*)		CH_2Cl_2	r.t.[b]	2	100	60 (*R*)
15	(*S*,*S*)			−20	22	100	82 (*R*)
16	(*S*,*S*)			−40	92	88	54 (*R*)
17	(*R*,*R*)	3-Anisaldehyde		−20	38	100	82 (*S*)
18	**5b** (*R*,*R*)	Benzaldehyde	Toluene	−20	19	0	
19	**1e** (*S*)			r.t.[b]	60	96	64 (*R*)
20				−20	158	43	56 (*R*)
21			CH_2Cl_2	r.t.[b]	45	94	46 (*R*)
22	**1b** (*S*)			−4	120	10	0

[a] $[Aldehyde]_0/[Et_2Zn]_0/[catalyst]_0$ = 1.0/2.0/0.1. [b] r.t. = room temperature. [c] By GLC. [d] By ^1H NMR analysis. [e] By GLC analysis of the corresponding (−)-methyl carbonates. [f] By chiral HPLC (CHIRALCEL OD, Diacel) analysis.

showed perfect mirror-image CD spectra to those of the (*S*,*S*)-antipodes, where the signs of the major bands remained unchanged upon conversion form pyrroles into pyrocolls.

Enantioselective alkylation of aromatic aldehydes by diethylzinc catalysed by axially dissymmetric pyrroles 1, 2 and pyrocolls 5, 6

Pyrocoll is regarded as a cyclic dimer of 'dehydroproline'. Inoue *et al.* have reported that a cyclic dipeptide from histidine and phenylalanine serves as an excellent asymmetric catalyst for hydrocyanation of aldehydes, where the rigid diketopiperazine ring plays a role.[13] For evaluating the potential of these new chiral pyrroles and pyrocolls in asymmetric recognition, we investigated their catalytic activities for ethylation of aromatic aldehydes by diethylzinc (Et_2Zn) (Scheme 5), since this reaction



Scheme 5 *Reagents:* catalytic **1a**, **1e**, **5a**, **5b** or **6a**, toluene or CH_2Cl_2

has been most extensively studied by using a variety of chiral catalysts.[8] The results are summarized in Table 1.

As a typical example, the reaction of benzaldehyde with Et_2Zn (1.0 mol equiv./2.0 mol equiv.) in CH_2Cl_2 in the presence of a catalytic amount of the pyrocoll (*S*,*S*)-**6a** (0.1 mol equiv.) at −20 °C proceeded to 100% conversion within 22 h, to give (*R*)-1-phenylpropan-1-ol in 82% enantiomeric excess (ee) (run 15). Under identical conditions, 3-anisaldehyde was enantioselectively ethylated by Et_2Zn in the presence of (*R*,*R*)-**6a** as catalyst to afford (*S*)-1-(3'-methoxyphenyl)propan-1-ol in 82% ee (run 17). The antipodes of compound **5a** also catalysed enantioselective ethylation of aromatic aldehydes under similar conditions. For example, the reaction of benzaldehyde with Et_2Zn catalysed by compound (*R*,*R*)-**5a** in toluene at −20 °C proceeded to 98% conversion in 44 h, to afford (*S*)-1-phenylpropan-1-ol in 80% ee (run 3). 2-Tolualdehyde and 1- and 2-naphthaldehyde were also enantioselectively ethylated by Et_2Zn in the presence of compound (*R*,*R*)-**5a** (runs 9–11), although the enantioselectivities of the reactions were lower than those of benzaldehyde and 3-anisaldehyde (runs 3, 7 and 8). When compound **6a** is compared with compound **5a** in terms of catalytic activity and enantioselectivity, the phenanthrene **6a** is generally more active than the naphthalene **5a** (runs 3 and 5 *vs.* runs 12 and 15, respectively). On the other hand, the enantioselectivity of the reaction with compound **5a** is less temperature-dependent (runs 1–4 and runs 5–6) than that with compound **6a** (runs 12, 13 and runs 14–16), where compound (*R*,*R*)-**5a** showed a satisfactorily high enantioselectivity even at room temperature (run 1). As for the solvent effect on the enantioselectivity of the reaction, the phenanthrene **6a** generally gave better results in CH_2Cl_2 than in toluene, while the selectivity with the naphthalene **5a** was only slightly affected by the solvent.

In order to know whether the rigid diketopyrazine unit in the catalyst plays a role in the reaction or not, the ethylation of benzaldehyde with Et_2Zn was attempted by using a chiral pyrrole such as (*S*)-**1e** as catalyst (runs 19–21), where the reaction proceeded enantioselectively, but the optical purity and the yield of the product were lower than those with a chiral pyrocoll **5a** as catalyst under otherwise identical conditions (runs 1 and 3). We have also noted that the hydroxy functionality in the catalyst plays a role in the ethylation reaction: in the attempted reaction in toluene at −20 °C in the presence of compound (*R*,*R*)-**5b** bearing no hydroxy functionality, benzaldehyde was not consumed at all over a period of 19 h (run 18). It was also noted that the reaction with a chiral pyrrole such as (*S*)-**1b** carrying no hydroxy functionality but a pyrrolic NH functionality proceeded very sluggishly with no enantioselection (run 22).

In the ^1H NMR spectrum of a mixture of compound **5a** and Et_2Zn (1 : 10), in $CDCl_3$ the signal due to the hydroxy group in compound **5a** (δ 5.67) was not observed,¶ suggesting that the active structure of the catalyst may involve an EtZnOAr moiety. The higher enantioselectivities of the pyrocolls **5a**, **6a** than that for the pyrrole **1e** indicate an important stereochemical role of the rigid diketopyrazine ring in the stereospecific binding of aldehydes to the active site.

Conclusions

The novel axially dissymmetric pyrroles **1**, **3** were synthesized and optically resolved by stereoselective crystallization. The

¶ Other signals were too broad to be assigned.

thermal racemization profiles of these chiral pyrroles demonstrated that these are stable enough toward racemization for use as building blocks for constructing chiral architectures. Thanks to the high condensation activity of 2-bromopyridinium tetrafluoroborate, the antipodes of compounds **1b** and **3b** were efficiently converted without racemization into the corresponding axially dissymmetric pyrocolls **5b** and **6b**. The chiral pyrocolls with hydroxy functionality (compounds **5a**, **6a**) were found to catalyse asymmetric ethyl transfer from diethylzinc to aromatic aldehydes, indicating a potential utility of axially dissymmetric pyrocolls for chiral recognition.

Experimental

General

Mps were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra (KBr) were recorded on a JASCO FT-IR model 5300 spectrometer. ^1H (270 MHz) and ^{13}C NMR (67.5 MHz) measurements were performed in $CDCl_3$ or $(CD_3)_2SO$ on a JEOL JNM-GSX 270 spectrometer, where the chemical shifts were determined with respect to $CHCl_3$ (δ 7.26) or Me_2SO (DMSO) (δ 2.50) for ^1H and $CDCl_3$ (δ_C 77.1) or DMSO (δ_C 39.7) for ^{13}C. *J* Values are given in Hz. UV–VIS and CD spectra were measured in EtOH or tetrahydrofuran (THF) on a JASCO Ubest-50 spectrophotometer and a JASCO J-720 spectropolarimeter, respectively. Gas–liquid chromatographic analyses (GLC) were performed on a Shimadzu model GC 14A with a flame ionization detector and a capillary column CBP20-M25-025. HPLC analyses were performed on a JASCO Gulliver System using chiral columns (CHIRALCEL OD [Daicel]; 0.46 cm φ × 25 cm or 2 cm φ × 50 cm, and CHIRALPAK AD [Daicel]; 0.46 cm φ × 25 cm, Daicel). For column chromatography, Merck Kieselgel 60 (70–230 mesh) was used. TLC analyses were performed on a Merck precoated TLC plate (Kieselgel 60 F_{254}, 0.25 mm). Diethylzinc was handled under dry, oxygen free argon, with Schlenk and syringe techniques.

Materials

9-Methoxyphenanthrene 11. Although compound **11** has been synthesized in the past from fluoren-9-one and diazomethane,[14] the reaction proceeds sluggishly and the yield is not satisfactorily high. So, an alternative method *via* Ullmann coupling of 9-bromophenanthrene with NaOMe in the presence of CuI was developed. To a suspension of CuI (29.6 g, 156 mmol) and 9-bromophenanthrene **10** (20.0 g, 77.8 mmol) in dimethylformamide (DMF) (140 cm^3) was added dropwise a methanolic solution (200 cm^3) of NaOMe (16.7 g, 523 mmol), and the mixture was stirred at 90–100 °C. After 3.5 h, the reaction mixture was allowed to cool to room temperature, and diethyl ether (350 cm^3) and saturated aq. NH_4Cl (350 cm^3) were successively added. The mixture was stirred for 30 min at room temperature, and filtered to remove insoluble materials. After the aqueous and organic layers were separated, the aqueous layer was extracted twice with diethyl ether, and the extracts were combined with the organic layer, then were washed successively with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to dryness under reduced pressure at room temperature to afford the *title compound* **11** (14.9 g, 71.4 mmol) as crystalline solid in 92% yield, mp 89–91 °C (lit.,[14] 92.5–94 °C); $\delta_H(CDCl_3)$ 4.10 (3 H, s), 6.99 (1 H, s), 7.45–7.8 (5 H, m) and 8.3–8.7 (3 H, m).

10-Methoxyphenanthrene-9-carbaldehyde 12. DMF (16.8 g, 230 mmol) was added dropwise to $POCl_3$ (35.1 g, 230 mmol), and then compound **11** (14.9 g, 76.0 mmol) was added at room temperature to this reaction mixture. After being stirred for 2 h at 80 °C, the reaction mixture was allowed to cool to room temperature, and was poured into ice–water, which was then extracted with diethyl ether; the extract was washed with water, dried over $MgSO_4$, and evaporated to dryness under reduced pressure at room temperature. The residue was crystallized from hexane–EtOAc (20 : 1) to give the title aldehyde **12** (10.5 g, 44.4 mmol) as needles in 58% yield, mp 85–86 °C (lit.,[14] 84.5–86 °C); $\delta_H(CDCl_3)$ 4.17 (3 H, s), 7.6–7.9 (4 H, m), 8.30–8.36 (1 H, m), 8.6–8.8 (2 H, m), 9.31–9.36 (1 H, m) and 10.96 (1 H, s).

2-Methoxy-1-(2-nitroprop-1-enyl)naphthalene 8. A methanolic solution (84 cm^3) of a mixture of nitroethane (9.6 g, 128 mmol), 2-methoxy-1-naphthaldehyde (22.4 g, 120 mmol), KOAc (10.0 g, 100 mmol), methylamine hydrochloride (6.8 g, 100 mmol) and trimethyl orthoformate (27.6 g, 260 mmol) was refluxed for 7 h, and the reaction mixture was poured into water and extracted with diethyl ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure at room temperature to leave a powdery substance, which was crystallized from diethyl ether–MeOH (1 : 1) to give *title compound* **8** as yellow crystals (23.1 g, 79%), mp 75.0–76.6 °C (Found: C, 69.3; H, 5.5; N, 5.7. $C_{14}H_{13}NO_3$ requires C, 69.12; H, 5.38; N, 5.75%); FT-IR ν_{max}(KBr)/cm^{-1} 1514s and 1317s; $\delta_H(CDCl_3)$ 2.11 (3 H, s), 4.00 (3 H, s), 7.3–8.0 (6 H, m) and 8.34 (1 H, s); $\delta_C(CDCl_3)$ 15.0, 56.3, 112.7, 114.7, 123.9, 124.2, 127.6, 128.6, 128.7, 129.0, 131.6, 131.9, 150.2 and 154.6.

9-Methoxy-10-(2-nitrobut-1-enyl)phenanthrene 13. A MeOH solution (31 cm^3) of a mixture of 1-nitropropane (4.35 g, 48.8 mmol), aldehyde **12** (10.5 g, 44.4 mmol), KOAc (3.63 g, 37.0 mmol), methylamine hydrochloride (2.50 g, 37.0 mmol) and trimethyl orthoformate (10.2 g, 96.2 mmol) was refluxed for 3 days, and the reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and evaporated to dryness under reduced pressure at room temperature, and the residue was chromatographed on silica gel with hexane–EtOAc (90 : 10) as eluent, where the first band was collected, and evaporated to dryness, and the residue was crystallized from hexane–EtOAc (99 : 1) to give *title compound* **13** as yellow crystals (10.1 g, 72%), mp 72–75 °C (Found: C, 74.2; H, 5.55; N, 4.5. $C_{19}H_{17}NO_3$ requires C, 74.25; H, 5.58; N, 4.56%); FT-IR ν_{max}(KBr)/cm^{-1} 1512s and 1333s; $\delta_H(CDCl_3)$ 1.07 (3 H, t, *J* 7.6), 2.62 (2 H, q, *J* 7.6), 3.89 (3 H, s), 7.55–7.85 (5 H, m), 8.2–8.3 (2 H, m) and 8.65–8.75 (2 H, m); $\delta_C(CDCl_3)$ 11.4, 21.9, 62.1, 118.4, 123.1 (2 peaks), 123.5, 125.2, 126.4, 127.3, 127.5, 128.1, 128.2, 130.5, 132.2, 152.4 and 156.7.

Synthesis of axially dissymmetric pyrroles

Ethyl (±)-3-(2′-methoxy-1′-naphthyl)-4-methylpyrrole-2-carboxylate (±)-1b. To an ice-cooled THF solution (300 cm^3) of a mixture of compound **8** (38.9 g, 160 mmol) and ethyl isocyanoacetate **9** (23.1 g, 205 mmol) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 31.3 g, 205 mmol), and the mixture was stirred at 20 °C for 5 days. The reaction mixture was poured into water, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure at room temperature, to leave a pale orange oil, which was crystallized from EtOH to give *title racemate* (±)-**1b** as crystals (40.7 g, 83%), mp 149.0–150.0 °C (Found: C, 73.7; H, 6.2; N, 4.7. $C_{19}H_{19}NO_3$ requires C, 73.75; H, 6.20; N, 4.53%); FT-IR ν_{max}(KBr)/cm^{-1} 3304s and 1663s; $\delta_H(CDCl_3)$ 0.70 (3 H, t, *J* 7), 1.83 (3 H, s), 3.88 (3 H, s), 3.92 (2 H, q, *J* 7), 6.95 (1 H, d, *J* 3), 7.3–7.5 (4 H, m), 7.8–7.9 (2 H, m) and 9.11 (1 H, s); $\delta_C(CDCl_3)$ 10.5, 13.6, 56.7, 59.6, 113.6, 118.6, 120.6, 120.7, 122.0, 123.2, 124.6, 125.3, 126.0, 127.7, 128.8, 128.9, 134.1, 154.5 and 161.5. For chiral HPLC analysis, a 0.46 φ × 25 cm column (CHIRALCEL OD) was used with hexane–EtOH (98 : 2) as eluent at a flow rate of 1.0 cm^3 min^{-1}, detection; 280 nm, t_R: 13 and 17 min for (*R*)- and (*S*)-**1b**, respectively.

Benzyl (±)-3-(2′-methoxy-1′-naphthyl)-4-methylpyrrole-2-carboxylate (±)-1c. To a reaction mixture of sodium (355 mg, 15.4 mg-atom) and benzyl alcohol (200 cm^3) was added ethyl ester (±)-**1b** (30.0 g, 97.0 mmol) at 50 °C under argon, and the mixture was refluxed for 4 h at 105 °C under slightly reduced

pressure, and then was evaporated to dryness under reduced pressure with heating. The residue was dissolved in CH_2Cl_2, and the solution was washed successively with aq. NH_4Cl and brine, dried over $MgSO_4$, and evaporated to dryness, and the residue was crystallized from $CHCl_3$–hexane (1:1) to give *racemic benzyl ester* (±)-**1c** as a crystalline solid (32.1 g, 89%), mp 142.0–143.0 °C (Found: C, 77.5; H, 5.6; N, 3.9. $C_{24}H_{21}NO_3$ requires C, 77.61; H, 5.69; N, 3.77%); FT-IR ν_{max}(KBr)/cm^{-1} 3323s and 1682s; δ_H($CDCl_3$) 1.81 (3 H, s), 3.37 (3 H, s), 4.98 (2 H, s), 6.62 (2 H, d, *J* 1), 6.95–7.50 (8 H, m), 7.80–7.90 (2 H, m) and 9.18 (1 H, s); δ_C($CDCl_3$) 10.4, 56.6, 65.4, 113.8, 118.4, 120.3, 121.2, 122.2, 123.4, 124.9, 125.2, 126.2, 127.1, 127.4, 127.8, 128.1, 128.9, 129.1, 134.0, 135.8, 154.6 and 161.4.

(±)-3-(2′-Methoxy-1′-naphthyl)-4-methylpyrrole-2-carboxylic acid (±)-1a. To a THF solution (220 cm^3) of benzyl ester (±)-**1c** (15.0 g, 40.4 mmol) were successively added 10% Pd on C (2.08 g) and triethylamine (10 drops); the mixture was stirred at room temperature for 24 h under hydrogen, and was then filtered. The filtrate was evaporated under reduced pressure at room temperature to give the racemic acid (±)-**1a** as a crystalline solid (10.9 g, 96%), mp 213.0–214.0 °C; FT-IR ν_{max}(KBr)/cm^{-1} 3451w, 3326s and 1672s; δ_H[$(CD_3)_2SO$] 1.60 (3 H, s), 3.78 (3 H, s), 6.92 (1 H, d, *J* 2), 7.3 (3 H, m), 7.46 (1 H, d, *J* 9), 7.84 (1 H, m), 7.90 (1 H, d, *J* 9) and 11.5 (1 H, s); δ_C[$(CD_3)_2SO$] 10.5, 56.4, 114.4, 119.1, 120.1, 120.5, 121.3, 123.2, 123.7, 125.1, 126.1, 128.0, 128.6, 128.7, 133.8, 154.5 and 162.1. The acid (±)-**1a** was used for the next step without further purification. For elemental analysis, acid (±)-**1a** was sublimed at 190 °C/0.1 mmHg to afford a solid (Found: C, 72.3; H, 5.4; N, 5.0. $C_{17}H_{15}NO_3$ requires C, 72.58; H, 5.37; N, 4.98%).

(*R*)-1-Phenylethyl (±)-3-(2′-methoxy-1′-naphthyl)-4-methylpyrrole-2-carboxylate (*SR*)- and (*RR*)-1d. To a refluxing CH_2Cl_2 solution (10 cm^3) of a mixture of 2-bromo-1-ethylpyridinium tetrafluoroborate (1.17 g, 4.27 mmol) and (*R*)-1-phenylethanol (430 mg, 3.6 mmol) was dropwise added a CH_2Cl_2 solution (10 cm^3) of a mixture of acid (±)-**1a** (1.00 g, 3.56 mmol) and Et_3N (0.86 g, 8.5 mmol) over a period of 15 min under argon, and the solution was refluxed for 1 h and poured into aq. NH_4Cl. The organic layer which has separated was washed with brine, dried over $MgSO_4$, and evaporated to dryness, and the residue was chromatographed on silica gel with $CHCl_3$ as eluent, where the pyrocoll **5b**, a by-product of this reaction, first eluted, and the second fraction was collected and evaporated to leave a crude mixture of phenylethyl ester (*SR*)- and (*RR*)-**1d** (1.25 g, 91.0%), which was crystallized from EtOH to give pure isomer (*SR*)-**1d** (100% de) as crystals [350 mg, 26% yield based on acid (±)-**1a**]. The residual solution was evaporated, and the residue was chromatographed on silica gel with benzene–diethyl ether (99:1) as eluent, where the second band was collected and evaporated under reduced pressure at room temperature to give pure isomer (*RR*)-**1d** (100% de) as oily substance [390 mg, 28% yield based on (±)-**1a**]. Isomer (*SR*)-**1d**: mp 163–164 °C (Found: C, 77.9; H, 6; N, 3.90. $C_{25}H_{23}NO_3$ requires C, 77.90; H, 6.01; N, 3.63%); λ_{max}(THF, 12 μmol dm^{-3})/nm (ε) 394 (2200), 325 (7700) and 230 (110 000). CD λ_{ext}(THF, 12 μmol dm^{-3}/nm ([θ]) 273 (−132 000), 244 (−144 000) and 230 (253 000); FT-IR ν_{max}(KBr)/cm^{-1} 3358s and 1690s; δ_H($CDCl_3$) 0.81 (3 H, d, *J* 6.5), 1.84 (3 H, s), 3.75 (3 H, s), 5.72 (1 H, q, *J* 6.5), 6.63 (2 H, m), 6.97 (1 H, m), 7.1–7.2 (3 H, m), 7.3–7.4 (3 H, m), 7.5–7.55 (1 H, m), 7.81–7.96 (2 H, m) and 9.14 (1 H, s); δ_C($CDCl_3$) 10.5, 22.3, 56.6, 71.7, 113.8, 118.9, 120.8, 121.0, 122.3, 123.4, 124.6, 125.5, 125.7, 126.1, 127.3, 127.8, 128.1, 128.8, 129.1, 134.5, 141.9, 154.5 and 160.9.

For isomer (*RR*)-**1d**: FAB-HRMS for $C_{25}H_{23}NO_3$ (Found: M$^+$, 385.1652. M requires *m/z*, 385.1678); λ_{max}(THF, 12 μmol dm^{-3})/nm (ε) 398 (2200), 326 (8000) and 230 (75 000); CD λ_{ext}(THF, 12 μmol dm^{-3})/nm ([θ]) 270 (54 000), 242 (100 000) and 230 (−10 800); FT-IR ν_{max}(KBr)/cm^{-1} 3418s and 1688s; δ_H($CDCl_3$) 1.10 (3 H, d, *J* 6.5), 1.84 (3 H, s), 3.88 (3 H, s), 5.76 (1 H, q, *J* 6.5), 6.34–6.42 (2 H, m), 6.9–7.1 (4 H, m), 7.25–7.45 (4 H, m), 7.85–7.96 (2 H, m) and 9.10 (1 H, s); δ_C($CDCl_3$) 10.5, 22.9, 56.8, 71.5, 113.8, 119.0, 120.7, 121.0, 122.0, 123.4, 124.7, 125.3, 125.4, 126.3, 127.1, 127.8, 128.0, 128.9, 129.1, 134.3, 141.8, 154.8 and 160.9.

Isomer (*RR*)-**1d** was crystallized from hexane, mp 104–107 °C (Found: C, 77.8; H, 6.0; N, 3.8. $C_{25}H_{23}NO_3$ requires C, 77.90; H, 6.01; N, 3.63%).

(*R*)- and (*S*)-3-(2′-Methoxy-1′-naphthyl)-4-methylpyrrole-2-carboxylic acid (*R*)- and (*S*)-1a. In a manner similar to that for racemate (±)-**1a**, enantiomers (*S*)- and (*R*)-**1a** were synthesized by hydrogenolysis of phenylethyl esters (*SR*)-**1d** and (*RR*)-**1d**, respectively, and identified by ^{1}H and ^{13}C NMR spectroscopy. Isomer (*S*)-**1a**: mp 215–216 °C; FAB-HRMS for $C_{17}H_{15}NO_3$ (Found: M$^+$, 281.1081. M requires *m/z*, 281.1052); FT-IR ν_{max}(KBr)/cm^{-1} 3457m, 3302m and 1665s; CD λ_{ext}(THF, 5.5 μmol dm^{-3})/nm ([θ]) 270 (−222 000), 240 (−210 000) and 230 (300 000).

For isomer (*R*)-**1a**: mp 215–216 °C; FAB-HRMS for $C_{17}H_{15}NO_3$ (Found: M$^+$, 281.1078); FT-IR ν_{max}(KBr)/cm^{-1} 3455m, 3308m and 1665s; CD λ_{ext}(THF, 11 μmol dm^{-3})/nm ([θ]) 270 (200 000), 240 (190 000) and 230 (−310 000).

Ethyl (±)-3-(2′-hydroxy-1′-naphthyl)-4-methylpyrrole-2-carboxylate (±)-1e. Lactone **2** (15 mg, 0.060 mmol; see the following section) was dissolved in a 0.1 mol dm^{-3} ethanolic solution (1 cm^3) of NaOEt, and the mixture was stirred at room temperature for 12 h. Then, the reaction mixture was shaken with aq. NH_4Cl, and the organic layer was separated, and evaporated at room temperature under reduced pressure, to leave a solid, which was recrystallized from hexane–EtOH (1:1) to give title ester (±)-**1e** (13 mg, 0.044 mmol) as needles, mp 150–151 °C (Found: C, 73.2; H, 5.8; N, 5.0. $C_{18}H_{17}NO_3$ requires C, 73.20; H, 5.80; N, 4.74%); FT-IR ν_{max}(KBr)/cm^{-1} 3466m, 3308m and 1669s; δ_H($CDCl_3$) 0.77 (3 H, t, *J* 13.5), 1.84 (3 H, s), 3.98 (2 H, m), 5.27 (1 H, s), 7.02–7.06 (1 H, m), 7.25–7.38 (4 H, m), 7.78–8.84 (2 H, m) and 9.3 (1 H, s); δ_C($CDCl_3$) 10.3, 13.5, 60.2, 114.2, 117.1, 121.3 (2 peaks), 121.9, 122.8, 123.0, 124.8, 126.2, 128.0, 128.9, 129.3, 133.8, 151.1 and 161.2.

Optical resolution of compound (±)-1e. Optical resolution of compound (±)-**1e** (500 mg) was carried out with a chiral HPLC column (CHIRALCEL OD); 2 cm φ × 50 cm, eluent: hexane–propan-2-ol (90:10), flow rate: 10 cm^3 min^{-1}, t_R: 30 and 58 min for (*R*)- and (*S*)-**1e**, respectively, where the antipodes were obtained almost quantitatively.

Isomer (*R*)-**1e**: mp 138 °C (Found: C, 73.1; H, 5.8; N, 4.8%); λ_{max}(EtOH, 14 μmol dm^{-3})/nm (ε) 334 (6000), 278 (18 000) and 228 (60 000); CD λ_{ext}(EtOH, 14 μmol dm^{-3})/nm ([θ]) 330 (−15 000), 272 (72 000), 243 (96 000) and 228 (−200 000); FT-IR ν_{max}(KBr)/cm^{-1} 3453s, 3370m and 1667s.

Isomer (*S*)-**1e**: mp 137 °C (Found: C, 73.1; H, 6.0; N, 4.7%). The CD spectrum was a perfect mirror image of that for isomer (*R*)-**1e**.

Ethyl (±)-4-ethyl-3-(10′-methoxy-9′-phenanthryl)pyrrole-2-carboxylate (±)-3b. Compound (±)-**3b** was prepared in a similar way to its analogue (±)-**1b** in 77% yield, mp 154–170 °C (Found: C, 77.4; H, 6.35; N, 3.8. $C_{24}H_{23}NO_3$ requires C, 77.19; H, 6.21; N, 3.75%); FT-IR ν_{max}(KBr)/cm^{-1} 3270s and 1665s; δ_H($CDCl_3$) 0.56 (3 H, t, *J* 7.1), 1.00 (3 H, t, *J* 7.6), 2.13–2.38 (2 H, m), 3.66 (3 H, s), 3.81–3.94 (2 H, m), 6.99 (1 H, d, *J* 2.9), 7.39–7.74 (5 H, m), 8.24–8.33 (1 H, m), 8.63–8.78 (2 H, m) and 9.45 (1 H, s); δ_C($CDCl_3$) 13.6, 14.4, 18.8, 59.8, 60.7, 119.7, 120.8, 121.6, 122.4, 122.9, 123.2, 124.0, 125.1, 126.3, 126.5, 126.6, 126.7, 127.9, 128.1, 129.3, 131.6, 133.3, 151.7 and 161.4. The antipodes of compound (±)-**3b** resolved spontaneously upon recrystallization from hexane–propan-2-ol (80:20), where each crystal was optically pure, as observed by chiral HPLC (column: CHIRALPAK AD); 0.46 φ × 25 cm, eluent: hexane–propan-2-ol (80:20), flow rate: 1.0 cm^3 min^{-1}, t_R: 4.3 and 7.7 min for (*R*)- and (*S*)-**3b**, respectively.

Optical resolution of racemate (±)-3b. Compound (±)-**3b** (910 mg, 2.4 mmol) was dissolved in hexane–propan-2-ol (80:20; 80 cm^3) upon reflux to give a saturated solution, which was then allowed to cool to room temperature (23 °C). To this supersaturated solution, gently stirred (~60 rpm) at 0 °C, were added fine crystals of antipode (*R*)-**3b** (1 mg, 0.003 mmol). After being stirred for 1 h, the crystals formed were isolated by filtration and dried over silica gel under reduced pressure at room temperature, to afford more isomer (*R*)-**3b** (55 mg, 0.15 mmol) in 90–100% ee, which was recrystallized from the same solvent to give optically pure compound (*R*)-**3b**: mp 168–169 °C (Found: C, 77.3; H, 6.3; N, 3.8. $C_{24}H_{23}NO_3$ requires C, 77.19; H, 6.21; N, 3.75%); CD λ_{ext}(EtOH, 18 μmol dm^{-3})/nm ([θ]) 304 (51 000), 280 (−52 000), 254 (−110 000) and 224 (+170 000). Likewise, addition of fine crystals of antipode (*S*)-**3b** to the above gently stirred filtrate at 0 °C gave crude antipode (*S*)-**3b** crystals (90–100% ee), which were recrystallized from hexane–propan-2-ol (80:20) to give optically pure isomer (*S*)-**3b**: mp 168–169 °C (Found: C, 77.2; H, 6.2; N, 3.8%); CD λ_{ext}(EtOH, 13 μmol dm^{-3})/nm ([θ]) 304 (−48 000), 280 (55 000), 254 (110 000) and 224 (−170 000). Repetition of this procedure gave sufficient amounts of stereoisomers (*R*)- and (*S*)-**3b**.

Synthesis of pyrrolecarbolactone

4-Methyl-3-(1′-naphthyl)pyrrole-2,2′-carbolactone 2. To a CH_2Cl_2 solution (90 cm^3) of compound (±)-**1b** (2.9 g, 9.3 mmol) was added BBr_3 (23 g, 93 mmol) at −78 °C under argon, and the mixture was stirred for 30 min, and stored overnight at room temperature. Then, the reaction mixture was washed twice with water, and extracted with EtOAc. The extract was evaporated under reduced pressure at room temperature, and the residue was crystallized from $CHCl_3$–THF–hexane (1:1:2) to give title lactone **2** as a crystalline solid (2.7 g, quantitative yield), mp 240.0–242.5 °C (Found: C, 77.0; H, 4.6; N, 5.6. $C_{16}H_{11}NO_2$ requires C, 77.09; H, 4.44; N, 5.61%); FT-IR ν_{max}(KBr)/cm^{-1} 3233s and 1697s; δ_H[$(CD_3)_2SO$] 2.55 (3 H, s), 7.5–7.7 (4 H, m), 7.95–8.05 (2 H, m), 8.55 (1 H, d, *J* 8.1) and 12.7 (1 H, s); δ_C[$(CD_3)_2SO$] 16.3, 114.1, 115.0, 117.8, 118.4, 125.5, 126.1, 127.1, 128.5, 128.6 (2 peaks), 130.9, 131.2, 149.0 and 154.6.

4-Ethyl-3-(9′-phenanthryl)pyrrole-2,10′-carbolactone 4. Compound **4** was prepared in a similar way to that for its analogue **2** in 58% yield, mp 216–217 °C; FAB-HRMS for $C_{21}H_{15}NO_2$ (Found: M^+, 313.1092. M requires *m/z*, 313.1103); λ_{max}(THF, 20 μmol dm^{-3})/nm (ε) 363 (2 600), 327 (13 000) and 258 (57 000); FT-IR ν_{max}(KBr)/cm^{-1} 3230m and 1720s; δ_H[$(CD_3)_2$-SO] 1.08 (3 H, t, *J* 7.3), 2.95 (2 H, q, *J* 7.3), 7.62 (1 H, s), 7.7–7.9 (4 H, m), 8.35–8.5 (2 H, m), 8.8–9.1 (2 H, m) and 12.9 (1 H, s); δ_C[$(CD_3)_2SO$] 15.24, 22.51, 111.6, 118.5, 122.1, 122.3, 123.3, 123.5, 123.9, 125.6, 126.3, 126.4, 127.4, 127.5, 127.7, 127.9, 129.8, 130.1, 144.7, 154.3 and 156.1.

Synthesis of axially dissymmetric pyrocolls

(*R*,*R*)- and (*S*,*S*)-1,6-Bis(2′-methoxy-1′-naphthyl)-2,7-dimethylpyrocoll (*R*,*R*)- and (*S*,*S*)-5b. To a CH_2Cl_2 solution (10 cm^3) of a mixture of 2-bromo-1-ethylpyridinium tetrafluoroborate (1.23 g, 4.26 mmol) and acid (*R*)-**1a** (500 mg, 1.78 mmol) was added Et_3N (857 mg, 8.48 mmol) at room temperature under nitrogen, and the mixture was stirred for 1 h and then was poured into aq. NH_4Cl. The organic layer that separated was washed with brine, dried over $MgSO_4$, and evaporated to dryness, and the residue was chromatographed on silica gel with $CHCl_3$–MeOH (100:1) as eluent, to afford crude compound (*R*,*R*)-**5b** which was crystallized from $CHCl_3$–diethyl ether (1:1) to give pure compound (*R*,*R*)-**5b** (469 mg, quantitative yield) as yellow crystals, mp > 300 °C (Found: C, 77.3; H, 5.1; N, 5.3. $C_{34}H_{26}N_2O_4$ requires C, 77.55; H, 4.98; N, 5.32%); λ_{max}(THF, 13 μmol dm^3)/nm (ε) 384 (8000), 324 (19 000), 296 (29 000) and 233 (140 000); CD λ_{ext}(THF, 13 μmol dm^{-3})/nm ([θ]) 352 (−6500), 322 (99 000), 284 (−37 000), 244 (560 000) and 230 (−730 000); FT-IR ν_{max}(KBr)/cm^{-1} 1699s; δ_H($CDCl_3$) 1.79 (6 H, d, *J* 0.7), 3.93 (6 H, s), 7.3–7.55 (10 H, m) and 7.8–8.0 (4 H, m); δ_C($CDCl_3$) 10.4, 56.7, 113.3, 115.1, 120.7, 120.9, 123.7, 124.4, 126.8, 126.9, 128.4, 129.0, 130.4, 132.9, 134.7, 150.3 and 154.7. The MeO signal of isomer (*R*,*S*)-**5b** (δ 3.95, s) was not detected. Likewise, stereoisomer (*S*,*S*)-**5b** was prepared from acid (*S*)-**1a** in quantitative yield, mp > 300 °C (Found: C, 77.3; H, 5.1; N, 5.3%). The CD spectrum was a perfect mirror image of that of enantiomer (*R*,*R*)-**5b**.

(*R*,*R*)- and (*S*,*S*)-1,6-Bis(2′-hydroxy-1′-naphthyl)-2,7-dimethylpyrocoll (*R*,*R*)- and (*S*,*S*)-5a. To a magnetically stirred CH_2Cl_2 solution (70 cm^3) of bis-ether (*R*,*R*)-**5b** (545 mg, 1.04 mmol) was dropwise added BBr_3 (1.89 cm^3, 20 mmol) at −78 °C. After 2 h, water was added to the reaction mixture, which was then extracted with EtOAc, and the extract was washed successively with water and brine, dried over $MgSO_4$, and evaporated to dryness under reduced pressure at room temperature. The residue was chromatographed on silica gel with $CHCl_3$–MeOH (9:1) as eluent to afford crude diol (*R*,*R*)-**5a**, which was crystallized from $CHCl_3$–diethyl ether (1:1) and dried over silica gel *in vacuo* at 60 °C to give pure *diol* (R,R)-**5a** (435 mg, 80%) as yellow needles, mp > 300 °C; FAB-HRMS for $C_{32}H_{22}N_2O_4$ (Found: M^+, 498.1591. M requires *m/z* 498.1580); λ_{max}(THF, 10 μmol dm^{-3})/nm (ε) 323 (19 000), 292 (27 000) and 231 (140 000); CD λ_{ext}(THF, 10 μmol dm^{-3})/nm ([θ]) 322 (99 000), 282 (−33 000), 244 (480 000) and 228 (−780 000); FT-IR ν_{max}(KBr)/cm^{-1} 1701s; δ_H($CDCl_3$) 1.81 (6 H, d, *J* 0.7), 5.67 (2 H, s), 7.15 (2 H, d, *J* 9.0), 7.3–7.45 (6 H, m), 7.59 (2 H, d, *J* 1.0) and 7.8–7.9 (4 H, m); δ_C($CDCl_3$) 10.5, 111.6, 118.3, 121.0, 121.9, 123.7, 124.2, 127.0, 127.9, 128.6, 129.1, 130.8, 132.6, 134.0, 150.6 and 151.5.

Likewise, diol (*S*,*S*)-**5a** was prepared from compound (*S*)-**5b**, mp > 300 °C; FAB-HRMS for $C_{32}H_{22}N_2O_4$ (Found: M^+, 498.1630). The CD spectrum was a perfect mirror image of that of diol (*R*,*R*)-**5a**.

(*R*,*R*)- and (*S*,*S*)-2,7-Diethyl-1,6-bis(10′-methoxy-9′-phenanthryl)pyrocoll (*R*,*R*)- and (*S*,*S*)-6b. Ester (*R*)-**3b** (310 mg, 0.831 mmol) and 18-crown-6 (219 mg, 0.831 mmol) were dissolved in EtOH (5 cm^3), and 20% aq. KOH (5 cm^3) was added to this mixture. The mixture was heated at 60 °C for 14 h, and then cooled in an ice-bath, acidified with 2 mol dm^{-3} HCl, and extracted with $CHCl_3$ (250 cm^3). The extract was washed twice with brine, dried over $MgSO_4$, and evaporated under reduced pressure at room temperature, to leave the corresponding acid (*R*)-**3a** (287 mg) as solid, FT-IR ν_{max}(KBr)/cm^{-1} 3416m, 3295m and 1657s; δ_H($CDCl_3$) 0.98 (3 H, t, *J* 7.6), 2.1–2.3 (2 H, m), 3.68 (3 H, s), 6.99 (1 H, d, *J* 3.2), 7.4–7.8 (5 H, m), 8.25–8.35 (1 H, m), 8.65–8.85 (2 H, m) and 9.2 (1 H, s); δ_C($CDCl_3$) 14.2, 18.7, 61.0, 119.7, 120.8, 121.0, 122.5, 122.9, 123.3, 125.1, 125.4, 126.2, 126.7, 126.8, 127.0, 128.0, 128.1, 129.7, 131.8, 132.8, 151.8 and 164.0.

Compound (*R*,*R*)-**6b** was prepared from acid (*R*)-**3a** in a similar way to that used for compound (*R*,*R*)-**5b**, in 64% yield as yellow needles, mp > 300 °C; FAB-HRMS for $C_{44}H_{34}N_2O_4$ (Found: M^+, 654.2503. M requires *m/z*, 654.2519); λ_{max}(THF, 10 μmol dm^{-3})/nm (ε) 370 (7200), 325 (17 000), 302 (43 000), 291 (44 000), 281 (38 000), 271 (41 000), 256 (100 000), 250 (96 000) and 223 (37 000); CD λ_{ext}(THF, 13 μmol dm^{-3})/nm ([θ]) 368 (−12 000), 312 (−16 000), 302 (74 000), 272 (−24 000), 264 (14 000), 258 (−11 000), 244 (330 000) and 224 (−340 000); FT-IR ν_{max}(KBr)/cm^{-1} 1699s; δ_H($CDCl_3$) 1.01 (6 H, t, *J* 7.6), 2.1–2.4 (4 H, m), 3.80 (6 H, s), 7.5–7.8 (12 H, m), 8.25–8.35 (4 H, m) and 8.7–8.85 (2 H, m). The MeO signal of compound (*R*,*S*)-**6b** (δ 3.82, s) was not detected; δ_C($CDCl_3$) 13.4, 18.5, 61.7, 118.8, 120.2, 121.0, 123.1, 123.2, 123.4, 125.4, 125.9, 127.0, 127.2, 127.5, 127.7, 128.4, 131.5, 132.3, 133.7, 134.5, 150.5 and 153.4.

Likewise compound (*S*,*S*)-**6b** was prepared from compound (*S*)-**3b**, mp > 300 °C; FAB-HRMS for $C_{44}H_{34}N_2O_4$ (Found:

M^+, 654.2515) The CD spectrum was a perfect mirror image of that of enantiomer (*R*,*R*)-**6b**.

(*R*,*R*)- and (*S*,*S*)-2,7-Diethyl-1,6-bis(10′-hydroxy-9′-phenanthryl)pyrocoll (*R*,*R*)- and (*S*,*S*)-6a. Compound (*R*,*R*)-**6a** was prepared from compound (*R*,*R*)-**6b** in the same way as compound (*R*,*R*)-**5a** in 79% yield, mp 225 °C (decomp.) FAB-HRMS for $C_{42}H_{30}N_2O_4$ (Found: M^+, 626.2238. M requires *m*/*z*, 626.2206); λ_{max}(THF, 4.6 μmol dm^{-3})/nm (ε) 401 (7400), 359 (7800), 298 (48 000), 277 (52 000), 249 (120 000) and 212 (84 000); CD λ_{ext}(THF, 4.6 μmol dm^{-3})/nm ([θ]) 392 (−14 000), 332 (15 000), 322 (−15 000), 304 (66 000), 274 (−17 000), 248 (290 000) and 224 (−270 000); FT-IR ν_{max}-(KBr)/ cm^{-1} 1703s; $\delta_H(CDCl_3)$ 0.99 (6 H, t, *J* 7.6), 2.1–2.3 (4 H, m), 5.63 (2 H, s), 7.4–7.85 (12 H, m), 8.41 (2 H, d, *J* 7.8) and 8.73 (4 H, t, *J* 8.3); $\delta_C(CDCl_3)$ 13.6, 18.6, 108.1, 121.3, 121.6, 122.7, 123.1, 123.4, 124.6, 124.7, 125.3, 126.8, 126.9, 127.2, 127.9, 131.2, 131.8, 132.5, 134.7, 147.1 and 150.3. Likewise, compound (*S*,*S*)-**6a** was prepared from compound (*S*)-**6b**, mp 225 °C (decomp.); FAB-HRMS for $C_{42}H_{30}N_2O_4$ (Found: M^+, 626.2224. $C_{40}H_{30}N_2O_4$ requires *m*/*z*, 626.2206). The CD spectrum was a perfect mirror image of that of enantiomer (*R*,*R*)-**6a**. Since diols (*R*,*R*)- and (*S*,*S*)-**6a** were unstable under light, they were stored and handled with protection from room light as much as possible.

Procedures

Diastereoselective ring opening of pyrrolecarbolactone 2 by lithium (*S*)-1-phenylethylamide. Typically, to a THF solution (4 cm^3) of (*S*)-1-phenylethylamine (27 mg, 0.22 mmol) was added BuLi (0.22 mmol, 140 mm^3 of 1.66 mol dm^{-3} hexane solution) at 0 °C, the mixture was stirred for 30 min, and the lactone **2** (50 mg, 0.20 mmol) was then added. The reaction mixture was stirred at −4 °C for 19 h, poured into aq. NH_4Cl, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and evaporated to dryness under reduced pressure at room temperature to give a mixture of amides (*SS*)- and (*RS*)-**1f** as a pale yellow oil. The diastereoisomer ratio was determined by ^1H NMR signals due to *Me*CH [δ 0.98 (d, *J* 6.9) and 0.77 (d, *J* 6.9) for (*SS*)- and (*RS*)-**1f**, respectively] to be 22:78. The diastereoisomers (*SS*)- and (*RS*)-**1f** were separated by preparative TLC with hexane–EtOAc (1:1) as eluent, R_f = 0.3 and 0.4 for (*SS*)- and (*RS*)-**1f**, respectively. Isomer (*SS*)-**1f**: $\delta_H(CDCl_3)$ 0.98 (3 H, d, *J* 6.8), 1.83 (3 H, d, *J* 0.7), 4.86 (1 H, dt, *J* 7.0 and 7.0), 5.42 (1 H, s), 5.53 (1 H, d, *J* 7.0), 6.4–6.45 (2 H, m), 6.9–7.1 (4 H, m), 7.3–7.4 (4 H, m), 7.8–8.0 (2 H, m) and 9.65 (1 H, s); $\delta_C(CDCl_3)$ 10.2, 22.8, 48.5, 112.5, 115.5, 117.4, 120.7, 121.6, 123.9, 124.1, 124.5, 125.2, 126.7, 127.4, 128.3, 128.5, 129.2, 130.7, 133.5, 143.3, 152.2 and 160.0. For isomer (*RS*)-**1f**: $\delta_H(CDCl_3)$ 0.77 (3 H, d, *J* 7.0), 1.83 (3 H, d, *J* 0.7), 4.82 (1 H, dt, *J* 7.0 and 7.0), 5.42 (1 H, s), 5.66 (1 H, d, *J* 7.0), 6.65–6.75 (2 H, m), 7.1–7.5 (7 H, m), 7.8–7.9 (2 H, m) and 9.95 (1 H, s); $\delta_C(CDCl_3)$ 10.2, 22.5, 48.8, 112.3, 115.1, 117.4, 120.5, 121.6, 124.0, 124.3, 124.5, 125.4, 127.0, 127.4, 128.3, 128.5, 129.2, 130.6, 133.3, 143.3, 152.1 and 159.9. Isomers (*SS*)- and (*RS*)-**1f** showed intense positive and negative CD bands respectively, at 230 nm (EtOH).

Catalysed enantioselective ethylation of aldehydes. Typically, to a 10 cm^3 Schlenk flask, wrapped in aluminium foil, containing a toluene (1.0 cm^3) solution of the pyrocoll diol (*R*)-**5a** (0.025 mmol) as catalyst, was added at 0 °C a toluene solution (1.0 mol dm^{-3}; 10 cm^3) of Et_2Zn (1.0 mmol) under an argon atmosphere, and the mixture was stirred magnetically at room temperature for 30 min, and then benzaldehyde (25 mm^3, 0.25 mmol) was added at −20 °C. An aliquot of the reaction mixture was periodically taken out from the flask, and subjected to GLC analysis, where the conversion of benzaldehyde was determined from the peak-area ratio of 1-phenylpropan-1-ol to benzaldehyde. The reaction mixture was poured into 2 mol dm^{-3} HCl, which was then extracted with diethyl ether. The extract was washed successively with aq. $NaHCO_3$ and brine, and the organic layer was separated, dried over $MgSO_4$, and evaporated to dryness. The residue was treated with (−)-menthyl chloroformate in the presence of pyridine at room temperature, and the resulting (−)-menthyl carbonate was subjected to GLC analysis to determine the optical purity of 1-phenylpropan-1-ol.[15] In the case of 1- or 2-naphthaldehyde as the substrate, the conversion and optical purity of the product were determined by ^1H NMR and chiral HPLC analyses of the reaction mixture, respectively.

Acknowledgements

We thank Dr N. Morisaki of the Institute of Molecular and Cellular Bioscience, and Mrs K. Saeki and Miss T. Seki of the Department of Chemistry, Graduate School of Science, the University of Tokyo, for FAB-MS measurements and elemental analyses, respectively.

References

1 C. Rosini, L. Franzini, A. Raffaelli and P. Salvadori, *Synthesis*, 1992, 503; K. Narasaka, *Synthesis*, 1991, 1; K. Tomioka, *Synthesis*, 1990, 541.
2 K. Konishi, K. Oda, K. Nishida, T. Aida and S. Inoue, *J. Am. Chem. Soc.*, 1992, **114**, 1313.
3 H. Kubo, T. Aida, S. Inoue and Y. Okamoto, *J. Chem. Soc., Chem. Commun.*, 1988, 1015.
4 Y. Furusho, T. Aida and S. Inoue, *J. Chem. Soc., Chem. Commun.*, 1994, 653.
5 G. L. Ciamician and P. Silber, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 103.
6 G. Gross and C. Wentrup, *J. Chem. Soc., Chem. Commun.*, 1982, 360.
7 R. J. Boatman and H. W. Whitlock, *J. Org. Chem.*, 1976, **41**, 3050.
8 For a recent review, see: K. Soai and S. Niwa, *Chem. Rev.*, 1992, **92**, 833.
9 D. H. R. Barton and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1985, 1098; N. Ono, H. Kawamura, M. Bougauchi and K. Maruyama, *Tetrahedron*, 1990, **46**, 7483.
10 K. Saigo, M. Usui, K. Kikuchi, E. Shimada and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 1863.
11 G. Bringmann, T. Hartung, O. Kröcher, K.-P. Gulden, J. Lange and H. Burzlaff, *Tetrahedron*, 1994, **50**, 2831; G. Bringmann, B. Schöner, O. Schupp, K. Peters, E.-M. Peters and H.-G. Schnering, *Liebigs Ann. Chem.*, 1994, 91.
12 G. Bringmann, R. Walter and R. Weinrich, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 977.
13 J. Oku and S. Inoue, *J. Chem. Soc., Chem. Commun.*, 1981, 229; K. Tanaka, A. Mori and S. Inoue, *J. Org. Chem.*, 1990, **55**, 181.
14 L. C. Washburn and D. E. Pearson, *J. Med. Chem.*, 1974, **17**, 676.
15 A. Mori, D. Yu and S. Inoue, *Synlett.*, 1992, 427.

Paper 5/04096E
Received 26*th June* 1995
Accepted 24*th July* 1995