Synthesis of optically active macrocycles consisting of helical chiral unit 1,12-dimethylbenzo[*c*]phenanthrene-5,8-dicarboxylate as a novel chiral building block

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Optically pure 1,12-dimethylbenzo[*c*]phenanthrene-5,8-dicarboxylic acid 1 is prepared in gram quantities, and a series of macrocycles consisting of the helical chiral unit are synthesized.

The helical chirality of polycyclic aromatic compounds is well known in organic chemistry.[1] However, their properties are not well understood compared to those of tetrahedral- and axis-chirality.[2,3] We describe here the preparation of the helically chiral 1,12-dimethylbenzo[*c*]phenanthrene-5,8-dicarboxylic acid (*M*)-(+)-**1**/(*P*)-(−)-**1** in optically pure form (Fig. 1). A series of macrocycles consisting of this C_2 symmetric chiral unit were also synthesized.

The synthesis of (±)-**1** started with a diketone **2** (Scheme 1).[4] ^{1}H NMR ($CDCl_3$) spectra of **2** showed two methyl absorptions at δ 1.50 and 2.13. Chiral HPLC separation (Daicel, Chiralcel OD) revealed its asymmetric structure. Since the *trans*-isomer could not be obtained by CPK modelling, **2** was assigned *cis*-stereochemistry. The diketone (±)-**2** was converted to the dinitrile by cyanation (Me_3SiCN, ZnI_2, benzene, room temp., 27 h) and dehydration ($POCl_3$–pyridine; refl., 17 h) with concomitant dehydrogenation.[5] The cyano group was hydrolysed (NaOH, ethylene glycol, 185–195 °C, 21 h) to give (±)-**1** in 58% yield from (±)-**2**. The diacid (±)-**1** was then treated with 2 equiv. of (−)-quinine, and purified by repeated recrystallization from chloroform–methanol. Compound (+)-**1** (21%) was obtained upon acidifying the salt, $[\alpha]_D^{23}$ + 313 (*c* 0.690, MeOH). The mother liquors were concentrated and recrystallized from benzene–methanol to give the antipode (−)-**1** (19%), $[\alpha]_D^{23}$ −332 (*c* 0.120, MeOH). The optical purities of the enantiomers were ≥99% ee as determined by chiral HPLC (Daicel, Chiralcel OD) of the dimethyl ester. Chromatographic resolution of (±)-**1** was also carried out *via* diastereoisomeric *d*-(−)-camphorsultam derivatives **3** and **4**[6] {**3**: $[\alpha]_D^{25}$ − 69.1 (*c* 1.05, $CHCl_3$). **4**: $[\alpha]_D^{25}$ −209 (*c* 0.906, $CHCl_3$)}. The (*P*)-configuration of the chromatographically polar isomer **3** was determined by X-ray crystallography,† (Fig. 2). The chiral auxiliary was removed from (*P*)-**3** by reduction ($LiAlH_4$, THF, room temp., 10 h; 88%) giving diol (*P*)-(−)-**5**, $[\alpha]_D^{27}$ −186 (*c* 0.190, $CHCl_3$–MeOH), to which (+)-**1** was chemically correlated (B_2H_6, THF, room temp., 15 h; 88%). These studies gave optically pure (*M*)-(−)-**1** and (*P*)-(+)-**1** in gram quantities. There have been reports of an optically active helicenedicarboxylate.[2] However, **1** may be a more attractive bifunctional chiral building block, since both enantiomers are available in large quantities.

Macrocycles were synthesized by reacting **1** with a dianiline spacer **6**.[7] (*M*)-(−)-**1** was converted to the diacid chloride ($SOCl_2$, reflux, 2 h), and then treated with an equimolar amount of **6** in CH_2Cl_2–pyridine (300 : 1) at room temperature under high dilution conditions (2 mmol dm^{-3}). This one-pot procedure gave [2+2]cycloamide (*M*,*M*)-(−)-**7**, [3+3]cycloamide (*M*,*M*,*M*)-(−)-**8**, and [4+4]cycloamide (*M*,*M*,*M*,*M*)-(−)-**9** in yields of 24, 23 and 19%, respectively (Scheme 2).[9] The oligomers were separated by preparative recycling GPC. The combined yield of the cyclized products was greater than 60%. The cyclic structure of the three compounds was inferred from NMR spectra which showed the carboxylate and the aniline moiety in a 1 : 1 ratio. The NMR chemical shifts of the three cycloamides were similar, and their compositions were determined by FAB-MS and/or vapour-phase osmometry. The order of GPC elution also supported their molecular weights. In contrast to the observations of Hunter and Vögtle,[7] catenanes were not obtained.

When (*M*)-(−)-**1** was treated with **6** in refluxing $ClCH_2CH_2Cl$ (1 mmol dm^{-3}) in the presence of Et_3N, [1+1]-cycloamide (*M*)-(+)-**10** (29%)‡ and (*M*,*M*)-(−)-**7** (16%) were obtained. A higher reaction temperature and a stronger base gave cycloamides with smaller rings. The *s-cis* secondary amide structure of (*M*)-(+)-**10** is supported by the lower wavenumber of N–H absorption by IR ($CHCl_3$), 3374 cm^{-1}, compared to that of (*M*,*M*,*M*)-(−)-**8**, 3414 cm^{-1}.[8] The NMR ($CDCl_3$) spectrum of (*M*)-(+)-**10** at the aniline moiety also differed from those of molecules with larger rings. Two aromatic protons and methyl protons appeared, and did not coalesce up to 80 °C. Rotation of

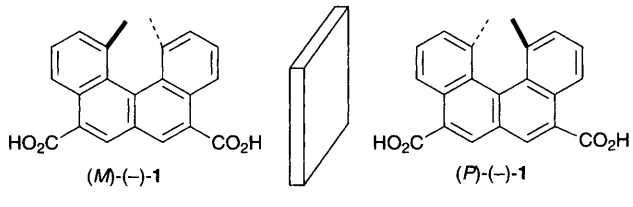
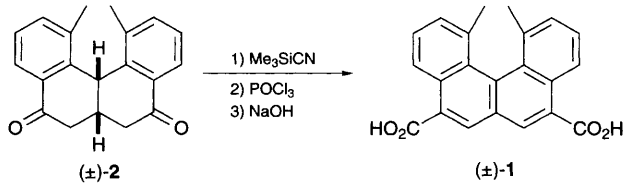


Fig. 1



Scheme 1

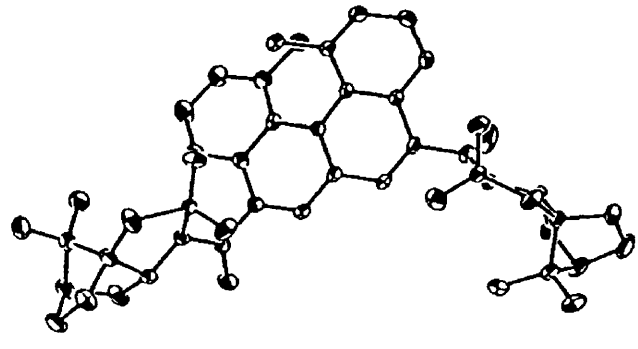


Fig. 2 ORTEP drawing of (*P*)-**3** (Protons are omitted)

the aniline ring must be restricted, and the activation energy was estimated to be more 17 kcal mol^{-1} (1 cal = 4.184 J).

Amide protons and benzo[*c*]phenanthrene 4,6-protons of (*M*,*M*,*M*)-(−)-**8** showed a down- and up-field shift, respectively, in $CDCl_3$ as the concentration increased. Hydrogen bonded N–H (3296 cm^{-1}) was observed along with the above-mentioned monomeric N–H (3414 cm^{-1}) by IR ($CHCl_3$, 1 mmol dm^{-3}). Thus, (*M*,*M*,*M*)-(−)-**8** is weakly aggregated *via* hydrogen bonding in the solvent. This concentration-dependence of the chemical shift was not observed in [$^2H_6$]Me_2SO which interferes with aggregation. While the behaviours of (*M*)-(+)-**10** and (*M*,*M*,*M*,*M*)-(−)-**9** were similar to that of (*M*,*M*,*M*)-(−)-**8**, the ^{1}H NMR ($CDCl_3$) spectrum of (*M*,*M*)-(−)-**7** was much less dependent on concentration. The absence of hydrogen bonded N–H by IR ($CHCl_3$, 10 mmol dm^{-3}) indicated a less-aggregated structure for (*M*,*M*)-(−)-**7**. These preliminary studies suggest that the secondary structures and/or the aggregated structures of the cycloamides vary considerably with ring size.

A series of optically active macrocycles consisting of 1,12-dimethylbenzo[*c*]phenanthrene-5,8-dicarboxylate were obtained. Systematic studies of such a series of oligomers can be an interesting approach in nano-chemistry.

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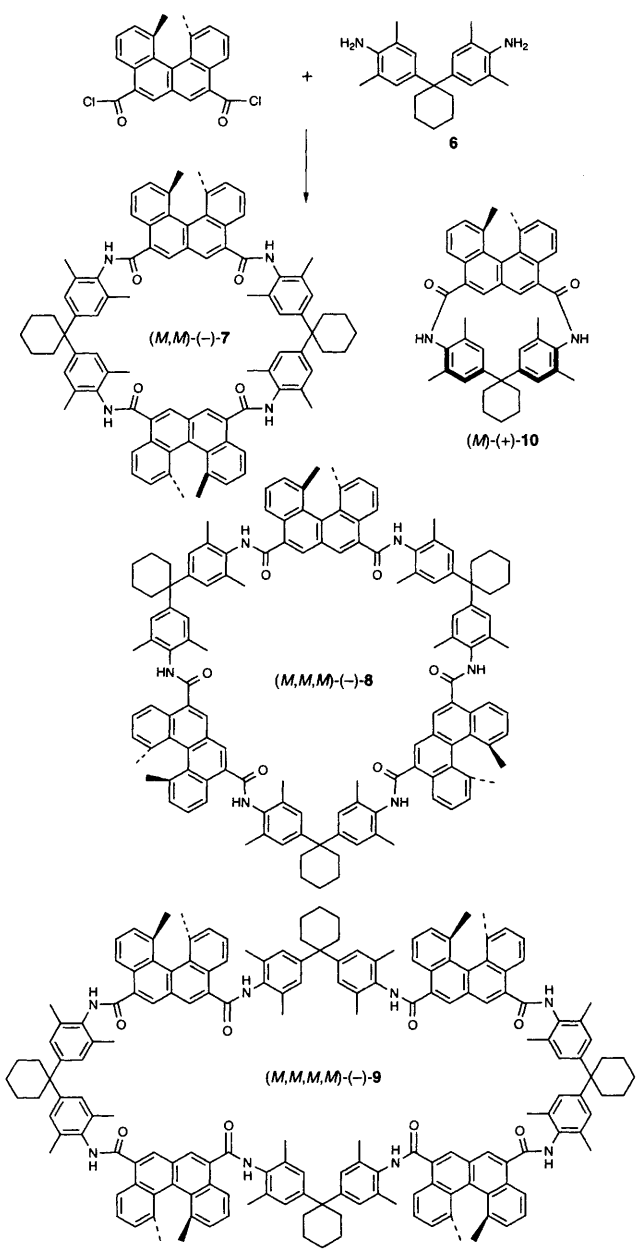

Scheme 2

Footnotes

† *Crystal data* for **3**. $C_{42}H_{46}O_6N_2S_2$, M_r = 738.96; *a* = 10.900(2), *b* = 14.974(2), *c* = 12.060(2) Å, β = 112.04(1)°, *V* = 1824.5(4) Å^3; space group $P2_1$; *Z* = 2, D_c = 1.345 g cm^{-3}; μ(Mo-Kα) = 16.997 cm^{-1}; Rigaku AFC5PR diffractometer; graphite monochromated Mo-Kα radiation; 3042 ($2\theta_{max}$ = 63°) measured reflections; 2995 observed reflections with $F_o > 3\sigma(F_o)$. Final *R* factor = 0.040 (*R*w = 0.047). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/138.

‡ *Spectroscopic data* for (*M*,*M*)-(−)-**7**: $[\alpha]_D^{26}$ −179 (*c* 0.332, $CHCl_3$). MS (FAB, NBA) *m*/*z* 1261 (M^+ + 1). For (*M*,*M*,*M*)-(−)-**8**: $[\alpha]_D^{27}$ −147 (*c* 0.230, $CHCl_3$). MS (FAB, NBA) *m*/*z* 1892 (M^+ + 2). VPO ($CHCl_3$, 35 °C, 5.3 mmol dm^{-3}) 1840 ± 100 gmol^{-1} (benzil as a standard). For (*M*,*M*,*M*,*M*)-(−)-**9**: $[\alpha]_D^{26}$ −178 (*c* 0.220, $CHCl_3$). MS (FAB, NBA) *m*/*z* 2523 (M^+ +3). VPO ($CHCl_3$, 35 °C, 4 mmol dm^{-3}) 2440 ± 120 gmol^{-1} (benzil as a standard). For (*M*)-(+)-**10**: $[\alpha]_D^{27}$ +35.3 (*c* 0.774, $CHCl_3$). HRMS (EI, 70 eV) Calcd. for $C_{22}H_{20}O_2$: 630.3247. Found: 630.3246. ^{1}H NMR (600 MHz, $CDCl_3$, 32 mmol dm^{-3}) δ 1.80 (6 H, s), 1.91 (6 H, s), 2.06 (6 H, s), 6.37 (2 H, s), 6.78 (2 H, s), 6.98 (2 H, s), 7.41 (2 H, d, *J* 7.0 Hz), 7.64 (2 H, dd, *J* 7.0, 8.2 Hz), 7.73 (2 H, s), 8.51 (2 H, d, *J* 8.2 Hz).

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