Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1257–1263

TETRAHEDRON: *ASYMMETRY*

Synthesis and absolute configuration of a new chiral [2.2]paracyclophane-based diene

L. Minuti,[a,*] A. Taticchi,[a,*] C. Rosini,[b,*] D. Lanari,[a] A. Marrocchi[a] and S. Superchi[b]

[a]*Dipartimento di Chimica, Università degli Studi di Perugia, via Elce di Sotto 8, 06123 Perugia, Italy*
[b]*Dipartimento di Chimica, Università della Basilicata, via N. Sauro 85, I-85100 Potenza, Italy*

Received 7 May 2002; accepted 24 June 2002

Abstract—The synthesis of a new enantiomerically pure diene, (*S*)-(+)-**1** is reported. The absolute configuration of **1** was determined by non-empirical analysis of its CD spectrum. The synthesis and resolution of the racemic β-diketone **4** into its constituent enantiomers by the SAMP–hydrazone method is described. The enantiopure β-diketone (*S*)-(+)-**4** was then converted to diene (*S*)-(+)-**1** by a two-stage reaction sequence. Structural analysis of the products by ^{1}H and ^{13}C NMR spectroscopy is also presented.

1. Introduction

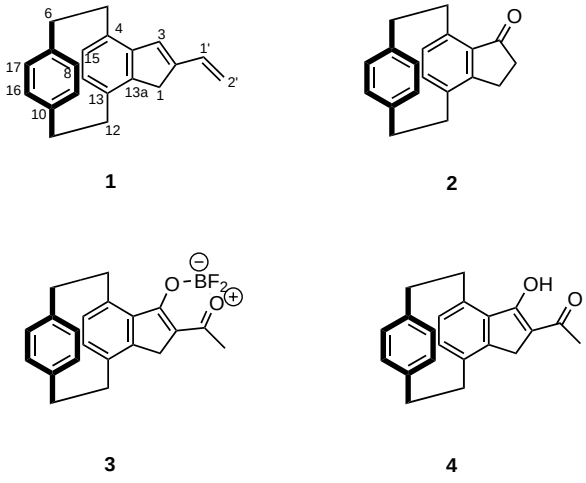
Helicenes[1] and helicenophanes[1e,2] are interesting compounds due to their extraordinary optical properties and their potential applications as new materials and chiral ligands for asymmetric catalysis. Recently, we have developed a short, flexible approach,[3] based on the Diels–Alder cycloaddition reaction of arylethenes, for synthesizing racemic and optically active helicenes[4] and helicenophanes.[5] We also described the synthesis of (*S*)-(+)- and (*R*)-(−)-4-ethenyl[2.2]paracyclophane[6] and their application in the stereoselective synthesis of enantiopure condensed[2.2]paracyclophanes.[5a]

We report herein the resolution of the β-diketone **4**, which exists predominantly in the enol form, its use for synthesizing the new optically active [2.2]paracyclophane diene **1**, a detailed structural characterization of diene **1** by NMR spectroscopy and the assignment of its absolute configuration as determined by non-empirical analysis of its CD spectrum. The application of diene **1**, which incorporates a five-membered ring element, can open the route to enantiopure non-benzenoid condensed[2.2]paracyclophanes.

2. Results and discussion

2.1. Synthesis of racemic β-diketone 4

Racemic ketone **4** was prepared as follows:[3b,4b] acetylation of ketone **2** with boron trifluoride diethyl etherate in acetic anhydride[7] gave a BF_2–diketone complex **3** (84% yield), which was then hydrolyzed by treatment with sodium acetate in acetone–water solution to afford (±)-**4** in 84% yield (Fig. 1).



1 **2** **3** **4**

Figure 1.

* Corresponding authors. E-mail: taticchi@unipg.it

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00330-0

The assignment of the structure of compounds **3** and **4** was based on the known outcome of the acetylation reaction[4b,c] and on the analysis of their NMR spectra. The full assignment of the proton and carbon spectra of β-diketone **4** followed from an examination of the ^1H–^1H and ^1H–^{13}C connectivities. Further support for the structural assignment of **4** was given by the strong NOE effect observed between the methyl group protons ($\delta = 2.22$ ppm) and 1-H ($\delta = 3.28$ ppm).

Furthermore, in the ^1H NMR spectrum of β-diketone **4**, the presence of sharp singlets of the methyl ($\delta = 2.22$ ppm) and 3-OH ($\delta = 14.1$ ppm) protons, together with a significant downfield shift of the latter, unambiguously indicated that in solution **4** exists predominantly in the enolic form, with a strong intramolecular hydrogen bond.

2.2. Resolution of β-diketone 4

To resolve ketone (±)-**4** into enantiomers, we applied the SAMP/hydrazone method which we had previously used to resolve 4-acetyl[2.2]paracyclophane.[6] We also tried to directly resolve ketone **2** by the same method but, unfortunately, all of our attempts were unsuccessful.

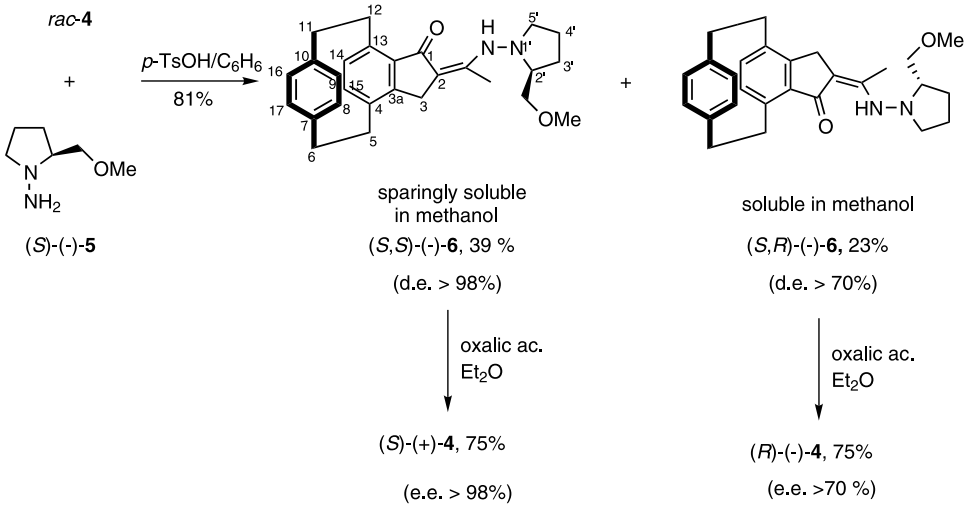
When a cyclohexane solution of (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) **5**, (±)-**4** (in equimolar ratio) and *p*-TsOH (a few crystals) was heated under reflux for 6 h, a mixture of the two diastereomeric SAMP-derivatives **6** was obtained in high yield (81%) (Scheme 1). Diastereoisomers **6** were separated by fractional crystallization from methanol, producing[8] (*S*,*S*)-**6** in good chemical yield (39%) with a d.e. greater than 98% as determined by ^1H NMR.

The filtrates obtained from the fractional crystallization of (*S*,*S*)-**6** were combined and concentrated to afford a residue, from which (*R*,*S*)-**6** was obtained with a d.e. greater than 70% after three crystallizations from methanol at −60°C (23% yield). Diastereomerically pure (*R*,*S*)-**6** could not be obtained.

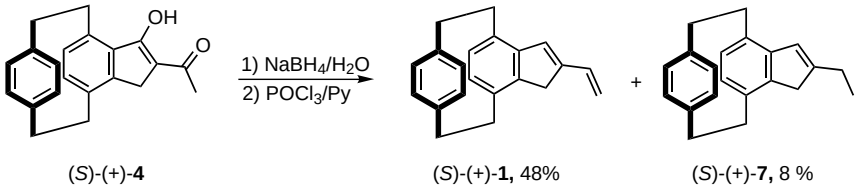
The structure and diastereomeric purities of both ketones (*S*,*S*)-**6** and (*R*,*S*)-**6** were determined by extensive NMR investigation. The (*Z*)-configuration of the aminoethylidene carbon–carbon double bond for both diastereoisomers **6** was based on the NOE effects observed on the 3-H_s and the O-CH_2-group upon selective irradiation of the methyl protons. The individual diastereoisomers (*S*,*S*)-**6** and (*R*,*S*)-**6** were hydrolyzed with oxalic acid to produce (*S*)-(+)-**4** and (*R*)-(−)-**4** in 75% yield. The enantiomeric excess of (*S*)-**4** and (*R*)-**4** (>98% and >70%, respectively) followed from the d.e. of (*S*,*S*)-**6** and (*S*,*R*)-**6** (Scheme 1).

2.3. Synthesis of enantiopure diene (*S*)-(+)-1

(*S*)-(+)-Diene **1** was prepared from the enantiomerically pure (*S*)-(+)-ketone **4** according to a previously described two-stage reaction sequence.[4b] Reduction of the ketone with sodium borohydride gave a complex mixture of diols; no component of the reaction mixture could be isolated. When the mixture of alcohols was submitted to dehydration by treating it with phosphorous oxychloride in pyridine, a 6:1 mixture of the desired diene **1** (48%) and the unexpected product **7** (8%), was obtained. These compounds were separated and purified by preparative HPLC (Scheme 2). The



Scheme 1.



Scheme 2.

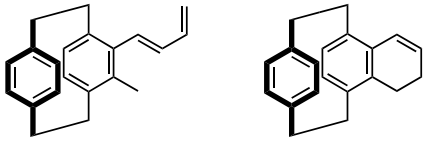
presence of product **7** in the reaction mixture may be explained considering that the reduction of the side chain carbonyl function to a methylene group partially occurred during the $NaBH_4$ reduction step. The structures of diene **1** and hydrocarbon **7** were assigned by ^1H and ^{13}C NMR spectroscopy. Proton spectra, ^{13}C multiplicities and interproton coupling constants of **1** and **7** unambiguously revealed the presence of the C(2′)=C(1′)–C(2)=C(3) diene moiety and the C(2′)–C(1′) ethyl group, respectively. Furthermore, the NOE effect observed between 1-H_s and 2′-H_s indicated a preferred *transoid* conformation of the diene moiety of **1**.

2.4. Determination of the absolute configuration of diene (*S*)-(+)-1

The absolute configuration (AC) of [2.2]paracyclophane **1** was assigned by an empirical correlation of its optical rotation and by a non-empirical analysis of its CD spectrum.

The specific rotation of the mono-substituted 4-X[2.2]paracyclophanes was empirically correlated[9] to the group polarizability (P_X) of the X group. These authors also showed that in the case of 4,7-disubstituted 4-X-7-methyl[2.2]paracyclophanes, the contribution of the X and the methyl groups to the specific rotation value is roughly additive. Therefore, the specific rotation value of a generic (*S*)-4-X-7-methyl-[2.2]paracyclophane can be calculated by summing the specific rotations of (*S*)-4-X[2.2]paracyclophane and (*S*)-4-methyl[2.2]paracyclophane, respectively.[10] In our case, the [2.2]paracyclophane diene **1** can be approximated to the simpler 4-butadienyl-5-methyl[2.2]paracyclophane **8** (Fig. 2), thus tentatively allowing the same type of treatment. Therefore, the specific rotation of (*S*)-**1** should be the sum of the specific rotations of (*S*)-4-butadienyl[2.2]paracyclophane and (*R*)-4-methyl-[2.2]paracyclophane[11] ($[\alpha]_D=-75$, *c* 4.0, $CHCl_3$).[12] Moreover, since (*S*)-4-butadienyl-[2.2]paracyclophane is not reported in the literature, it can be reasonably approximated to (*S*)-4-vinyl[2.2]paracyclophane ($[\alpha]_D=+440$, *c* 0.14, $CHCl_3$),[6] assuming similar group polarizability for the vinyl and butadienyl groups. Therefore, taking into account the previous considerations and assumptions, for (*S*)-**8**, a $[\alpha]_D$ value of ca. +365 is to be expected. Our sample of **1** shows $[\alpha]_D=+223$ (*c* 0.19, $CHCl_3$), a value with the same sign and the same order of magnitude as the calculated one. A simpler and even more direct comparison could be done between (+)-**1** and the structurally similar 4,7-disubstituted[2.2]-paracyclophane **9**, whose (*S*)-enantiomer has $[\alpha]_D=+320$ ($CHCl_3$).[13] Both of these empirical comparisons may indicate an (*S*)-absolute configuration for (+)-**1**.

In order to put the previously described empirical configurational assignment of (+)-**1** on safer and more rigorous grounds, we decided to carry out a non-empirical analysis of the UV and CD spectra of (+)-**1** (Fig. 3). The optical activity of [2.2]paracyclophanes in the ^1L_b transition spectral range was interpreted by Nugent and Weigang[12] in terms of exciton coupling of two substituted benzene chromophores. We recently extended this treatment to the ^1L_a and ^1B transitions showing that the absolute configuration of a monosubstituted [2.2]paracyclophane can be assigned from non-empirical analysis of its CD spectrum.[14] The UV spectrum of (+)-**1** shows a maximum at 320 nm (ε 14000), a shoulder only at 270 nm (ε 9100), and a second maximum at 258 nm (ε 11000). At shorter wavelengths the UV increases monotonically down to 200 nm (THF cut off) presenting a shoulder at 225 nm (ε 15400). In the CD spectrum Cotton effects are clearly observed at 320 nm ($\Delta\varepsilon$ +17.5), 253 nm ($\Delta\varepsilon$ −36.2), 230 nm ($\Delta\varepsilon$ −17.7) and 215 nm ($\Delta\varepsilon$ +30.7). It is reasonable to assume that the lowest-energy absorption (at 320 nm) and the corresponding CD band are due to the 1-phenylbutadiene chromophore.[15] Groups which can give rise to conjugation (vinyl, carbonyl, amines, etc.) strongly perturb the benzene chromophore. As a result, the direction of polarization for the ^1L_a transition becomes parallel to the axis that joins the aromatic ring to the substituent, as assumed in our previous analysis[14] of the CD spectra of [2.2]paracyclophanes. The other absorptions observed in the UV spectrum are due to allowed transitions localized either on the same chromophore or on the 1,4-dimethylbenzene (i.e. the two moieties which constitute **1**). As already shown,[12,14] a coupled oscillator mechanism[16,17] is the main source of optical activity in monosubstituted [2.2]paracyclophanes. Therefore it is reasonable to assume that in the CD spectrum, the positive band at 320 nm and the negative one at 253 nm represent the two branches of a positive exciton cou-



(*S*)-**8** (*S*)-**9**

Figure 2.

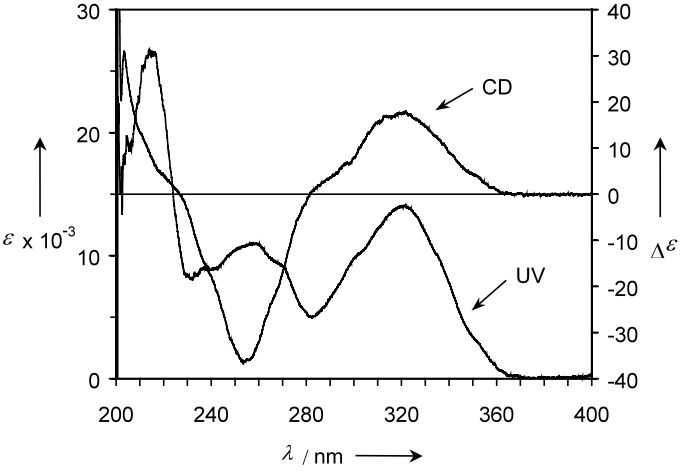


Figure 3. UV and CD spectra in THF of (*S*)-(+)-**1** in the 400–200 nm range.

plet. The origin of the above feature could then be in the coupling of the ^1L_a transition localized on the 1-phenylbutadiene moiety and polarized[14] along the C_{Ar}–C= bond and of the ^1L_a transition of the 1,4-dimethylbenzene chromophore, directed along the 1,4 axis (Fig. 4). In (*S*) configured **1**, these transition dipole moment vectors define a positive chirality (Fig. 4). A positive couplet is therefore expected, and was experimentally found. This non-empirical analysis therefore shows a (*S*) AC for (+)-**1**, that is in agreement with the proposed empirical configurational assignment based on the OR.

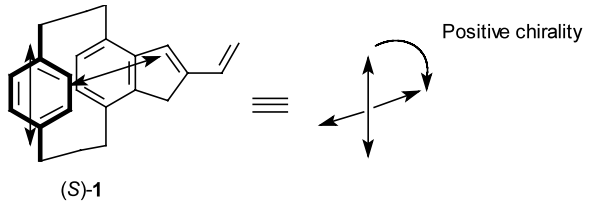


Figure 4. Exciton chirality defined by the two ^1L_a transition dipole moments in (*S*)-(+)-**1**.

A quantitative interpretation of the CD spectrum of (+)-**1** was also attempted by means of DeVoe coupled oscillator calculations.[14,18,19] In order to simplify the treatment, the CD spectrum of (*S*)-**1** was calculated in terms of two interacting dipoles. The former dipole (which describes the ^1L_a transition of the 1,4-dimethylbenzene chromophore) placed at 225 nm and carrying a polarizability of 10 D^2 was polarized along the axis joining the two methyl groups. The second dipole (which describes the ^1L_a transition of the 1-phenylbutadiene chromophore) was placed at 300 nm, polarized along the C_{Ar}-–C= direction, and carrying a polarizability of 20 D^2. The UV and CD spectra calculated for (*S*)-**1** are reported in Fig. 5 along with the experimental spectra recorded for (+)-**1**. A comparison between the calculated and experimental spectra shows that the Cotton effect at 320 nm is reproduced very well in both sign and intensity, whilst between 280 and 200 nm we succeeded in reproducing the sign of the observed optical activity but only part of the intensity. This is clearly a consequence of the simplified approach chosen, where only two transition dipoles were used to describe the 1-phenylbutadiene and the 1,4-dimethylbenzene chromophores. However, for the present purposes, the agreement between the experimental and calculated spectra in Fig. 5 (at least for the lowest-energy Cotton effect) is more than satisfactory, indicating again a (+)/(*S*) configurational assignment for **1**.

3. Conclusions

The resolution of the ketone **4** by the SAMP–hydrazone method has been successfully carried out allowing the (*S*)-(+)-enantiomer to be obtained in pure form. This was then converted to optically pure diene **1** which is of interest since it can open the route to the synthesis of optically active helicenophanes containing a cyclopentane ring.

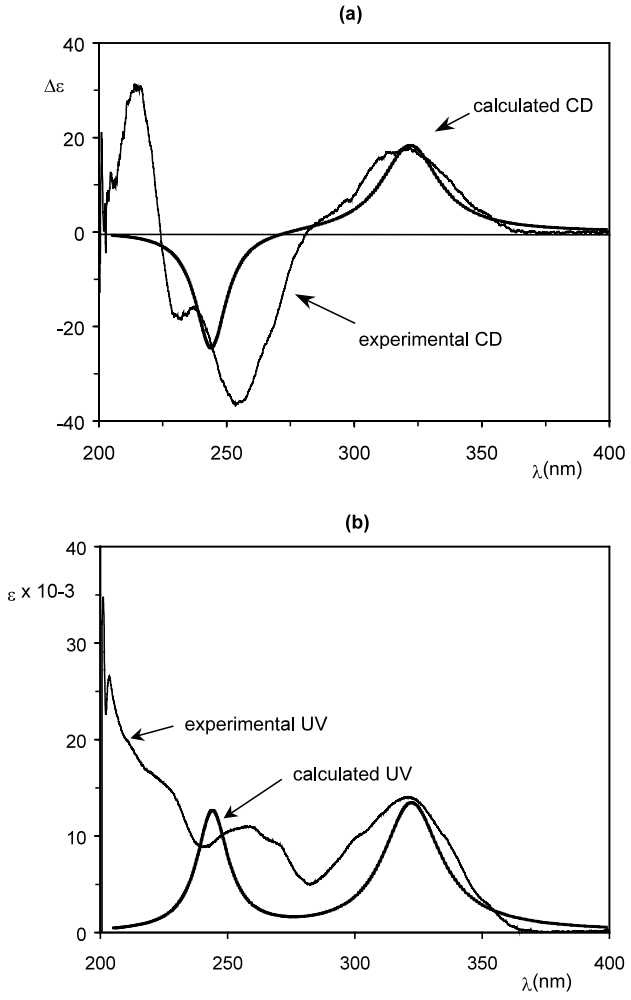


Figure 5. (a) Experimental (thin line) and calculated (bold line) CD spectra of (*S*)-(+)-**1**. (b) Experimental (thin line) and calculated (bold line) UV spectra of (*S*)-(+)-**1**.

An (*S*) absolute configuration has been assigned to (+)-**1** by means of a non-empirical analysis of its CD spectrum, carried out qualitatively on the basis of the Harada–Nakanishi chirality rules and semi-quantitatively according the DeVoe polarizability model. This study further demonstrates the efficiency and the versatility of the exciton coupling approach for the configurational assignment of organic molecules, even those of considerable complexity, such as [2.2]paracyclophanes.

4. Experimental

4.1. General

Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with Jasco DIP-360 polarimeter in a quartz cell at 23°C. Preparative HPLC was carried out on a waters Prep LC 40 mm Assembly module (column: Delta Pak C18, 100 Å, 40×100 mm) using a Waters 590 Pump and a Waters Lambda-Max 481 LC

spectrophotometer at 254 nm. Analytical HPLC was done on a Hewlett–Packard 1100 instrument (column: Supelcosil LC-PAH, 5 μm, 150×4.6 mm; mobile phase CH_3CN/H_2O 6:4; flow rate 1 mL/min; detection: UV at 254 nm). GC analyses were performed on a Hewlett–Packard 6890 chromatograph. IR spectra were recorded in $CHCl_3$ solution at room temperature on a Perkin–Elmer Paragon 500 FT IR. The NMR spectra were run using a Varian Associates VXR-400 multinuclear instrument (internal Me_4Si). Proton and carbon shift assignments were based on COSY $^1H\{^1H\}$NOE and HETCOR experiments. Absorption and CD spectra were recorded in THF on a JASCO J600 spectropolarimeter at room temperature, using 0.1 mm cell and concentrations of the order of 1×10^{-3} M. During the measurement, the instrument was thoroughly purged with nitrogen.

4.2. Synthesis of racemic 1-(3-hydroxy-5,6,11,12-tetrahydro-1*H*-4,13:7,10-diethenocyclopenta[12]annulen-2-yl) ethanone, 4

BF_3–Et_2O (0.9 mL, 1.56 mmol) was added under nitrogen to a stirred mixture of ketone **2**[7] (1.2 g, 4.59 mmol) and dry acetic anhydride (1.8 mL). The reaction mixture was heated at 65°C for 1.5 h and then at reflux temperature for 2 h according to a previous procedure.[4b,c] Usual work up gave a yellow crystalline BF_2–diketone complex **3** (1.35 g, 84%): mp 178–179°C (diethyl ether); ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H, Me), 2.85–3.84 (m, 9H, Hs-1, H-5, H_s-6, H_s-11, H_s-12), 4.16 (m, 1H, H-5), 6.22 (d, 1H, $J=7.2$ Hz, H-8), 6.32 (d, 1H, $J=6.9$ Hz, H-16), 6.45 (d, 1H, $J=7.2$ Hz, H-9), 6.61 (d, 1H, $J=6.9$ Hz, H-17), 6.77 (d, 1H, $J=7.9$ Hz, H-14), 6.80 (d, 1H, $J=7.9$ Hz, H-15). Anal. calcd for $C_{21}H_{19}BF_2O_2$: C, 71.62; H, 5.44. Found: C, 71.7; H, 5.0%.

The complex **3** (1.3 g, 3.69 mmol) was then refluxed for 24 h in 1:1 acetone-saturated aqueous sodium acetate solution (10 mL). After usual work up,[4b] the product was purified by column chromatography on silica gel: elution with CH_2Cl_2 afforded pure ketone **4** (0.95 g, 84%); mp 127–128°C (CH_2Cl_2); IR 1656, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22 (s, 3H, Me), 2.85 (m, 1H, H-5), 2.95 (m, 1H, H-12), 3.00–3.16 (m, 5H, H-1, H_s-6, H_s-11), 3.23 (m, 1H, H-12), 3.28 (m, 1H, H-1), 4.19 (m, 1H, H-5), 6.25 (dd, 1H, $J=7.8$, 1.9 Hz, H-8), 6.40 (dd, 1H, $J=7.8$, 2.0 Hz, H-9), 6.46 (dd, 1H, $J=7.8$, 2.0 Hz, H-16), 6.57 (dd, 1H, $J=7.8$, 1.9 Hz, H-17), 6.61 (d, 1H, $J=7.7$ Hz, H-15), 6.67 (dd, 1H, $J=7.7$ Hz, H-14), 14.10 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 21.2 (Me), 29.5 (C-1), 31.5 (C-5), 31.7 (C-12), 33.9, 34.2 (C-6, C-11), 110.1 (C-2), 126.4 (C-9), 130.0 (C-8), 133.0 (C-3a), 133.2$_7$,133.3$_3$ (C-16, C-17), 134.1 (C-14), 136.3 (C-13), 137.5 (C-15), 138.7, 139.2, 139.9, 140.0 (C-4, C-7, C-10, C-13a), 177.5 (C-3), 192.6 (C=O); MS m/z (rel. int.) 51 (23), 77 (54), 104 (100), 128 (42), 157 (38), 304 (M^+, 51). Anal. calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.9; H, 6.6%.

4.3. Resolution of ketone (±)-4

SAMP **5** (0.41 mL, 3.1 mmol) and *p*-TsOH (40 mg) were added to a solution of (±)-**4** (0.95 g, 3.1 mmol) in cyclohexane (5 mL) and the resulting mixture was stirred under reflux for 6 h. Usual work up[6] gave a mixture of diasteroisomeric aminoethylidenes (*S*,*S*)-**6** and (*S*,*R*)-**6** (1.08 g, 81%) in equimolar ratio (according to HPLC analysis). The mixture was crystallized from 4.5 mL of methanol at 4°C and the resulting orange precipitate (0.4 g) was then recrystallized from methanol (2 mL) at 4°C to yield partially enriched (*S*,*S*)-**6** (0.3 g). Diastereomerically pure (*S*,*S*)-**6** (0.25 g, 39%) was obtained as yellow crystals by final recrystallization from 2 mL of methanol: mp 137–138°C (methanol); $[\alpha]_D=-95$ (*c* 0.61, $CHCl_3$); IR 1623, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72–2.05 (m, 4H, H_s-3′, H_s-4′), 2.26 (s, 3H, CH_3), 2.81 (m, 1H, H-12), 2.84 (m, 1H, H-5′), 2.92 (m, 1H, H-5), 2.93 (dddd, 1H, $J=8.4$, 8.1, 5.4, 4.0 Hz, H-2′), 3.03-3.21 (m, 6H, H_s-3, H_s-6, H_s-11), 3.30 (s, 3H, -OCH_3), 3.33-3.34 (m, 3H, H-5, -OCH_2-, H-5′), 3.38 (dd, 1H, $J=9.7$, 4.0 Hz, -OCH_2-), 4.36 (m, 1H, H-12), 6.26 (dd, 1H, $J=7.8$, 1.8 Hz, H-9), 6.43 (dd, 1H, $J=7.8$, 1.9, H-8), 6.46 (dd, 1H, $J=7.9$, 1.8 Hz, H-16) 6.53 (bs, 2H, H-14, H-15), 6.57 (dd, 1H, $J=7.9$, 1.9 Hz, H-17), 11.05 (s, 1H,–NH); ^{13}C NMR ($CDCl_3$) δ 15.6 (-CH_3), 21.1 (C-4′), 25.8 (C-3′), 30.5 (C-3), 31.2 (C-12), 31.6 (C-5), 34.1, 34.3 (C-6, C-11), 57.4 (C-5′), 59.0 (-OCH_3), 66.4 (C-2′), 73.3 (-OCH_2-), 102.5 (C-2), 126.5, 130.0 (C-8, C-9), 133.0, 133.1 (C-16, C-17), 133.6, 135.5 (C-14, C-15), 135.6 (C-4), 138.7, 140.2 (C-7, C-10), 138.8 (C-13a), 142.5 (C-13), 147.6 (C-3a), 160.4 (=CNH), 191.7 (C-1). Anal. calcd for $C_{27}H_{32}N_2O_2$: C, 77.85; H, 7.74; N, 6.73. Found: C, 77.8; H, 7.8; N, 6.7%.

The filtrates from the above crystallization were combined and concentrated, the residue (0.7 g) was dissolved in methanol (4 mL) and cooled to −60°C. Separation of the precipitate by decanting the supernatant solution from the solid afforded partially enriched (*S*,*R*)-**6** (0.3 g) which was then recrystallized twice from methanol at −60°C to afford (*S*,*R*)-**6** (0.15 g, 23%) with d.e. of greater than 70%: $[\alpha]_D=-110$ (*c* 0.42, $CHCl_3$); IR 1624, 1581 cm^{-1}; ^1H NMR[10] ($CDCl_3$) δ 1.76–2.07 (m, 4H, H_s-3′, H_s-4′), 2.28 (s, 3H, -CH_3), 2.80–3.29 (m, 11H, H-2′, H_s-3, H_s-5, H-5′, H_s-6, H_s-11, H-12), 3.35 (m, 1H, H-5′), 3.42 (s, 3H, -OCH_3), 3.46 (dd, 1H, $J=9.6$, 5.3 Hz, -OCH_2), 3.54 (dd, 1H, $J=9.6$, 4.4 Hz, O-CH_2-), 4.37 (m, 1H, H-12), 6.29 (m, 1H, H-9), 6.46 (m, 2H, H-8, H-16), 6.55 (bs, 2H, H-14, H-15), 6.58 (dd, 1H, $J=8.1$, 2.0 Hz, H-17), 11.07 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$) δ 15.6 (-CH_3), 21.1 (C-4′), 25.8 (C-3′), 30.5 (C-3), 31.3 (C-12), 31.7 (C-5), 34.0 (C-11), 34.3 (C-6), 57.7 (C-5′), 59.1 (-OCH_3), 66.0 (C-2′), 73.9 (-OCH_2-), 102.7 (C-2), 126.4, 129.9 (C-8, C-9), 133.1, 133.2 (C-16, C-17), 133.6, 135.6 (C-14, C-15), 135.5 (C-4), 138.7, 140.2 (C-7, C-10), 138.8 (C-13a), 142.5 (C-13), 147.7 (C-3a), 160.5 (=CNH), 191.8 (C-1).

The diastereomeric purity of (*S*,*S*)-**6** and (*S*,*R*)-**6** was monitored by HPLC and quantitatively determined by ^1H NMR.

A saturated aqueous solution of oxalic acid (1.2 mL) was added to an ethereal solution (8 mL) of (*S*,*S*)-**6** (0.2 g, 0.48 mmol). The resulting mixture was vigorously stirred at 25°C for 20 h. Usual work up[6] gave a residue which was purified by flash column chromatography on silica gel. Elution with a 97:3 hexane/EtOAc solution gave an enantiomerically pure (e.e. >98%): (*S*)-(+)-**4** (0.11 g, 75%) mp 149–150°C (hexane); $[\alpha]_D^{25}=+155$ (*c* 0.48, $CHCl_3$).

The procedure described above was applied to (*R*,*S*)-**6** (0.01 g, 0.024 mmol) to yield 5.5 mg (75%) of a partially enriched sample of (*R*)-(−)-**4** (e.e. >70%): mp 146–148°C, $[\alpha]_D^{25}=-108$ (*c* 0.55, $CHCl_3$).

4.4. (*S*)-(+)-2-Vinyl-5,6,11,12-tetrahydro-1*H*-4,13:7,10-diethenocyclopenta[12]annulene, 1

A solution of $NaBH_4$ (0.1 g, 2.7 mmol) in H_2O (1.6 mL) was added to a refluxing solution of ketone (*S*)-(+)-**4** (0.12 g, 0.39 mmol) in ethanol (50 mL) and refluxing was continued for 3 h. Usual work up[4b,c] gave 0.11 g (0.36 mmol) of a mixture of diols which was used directly in the next step, without purification.

Anhydrous pyridine (0.45 mL) and $POCl_3$ (0.05 mL, 0.58 mmol) were added to a stirred solution of the above mixture of diols (0.11 g, 0.36 mmol) in anhydrous toluene (4 mL). The reaction mixture was heated under reflux for 2 h under nitrogen, allowed to cool to room temperature, and poured into ice-water. After thorough extraction with toluene, the combined extracts were washed with brine and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was purified by preparative HPLC (mobile phase: CH_3CN/H_2O 3:2; flow rate 82 mL/min) to give pure (*S*)-(+)-**1** (53 mg, 48%) and (*S*)-(+)-**7** (9 mg, 8%).

(*S*)-(+)-1: mp 132–133°C (*n*-hexane); $[\alpha]_D^{25}=+225$ (*c* 0.19, $CHCl_3$) ^{1}H NMR ($CDCl_3$) δ 2.86 (m, 1H, H-5), 2.88 (m, 1H, H-12), 2.98-3.11 (m, 5H, H-1, H_s-6, H_s-11), 3.17 (m, 1H, H-5), 3.27 (m, 1H, H-1), 3.28 (m, 1H, H-12), 5.17 (dd, 1H, $J=0.6$, 1.3 Hz, H-2′), 5.44 (dd, 1H, $J=17.4$, 0.5 Hz, H-2′), 6.30 (m, 2H, H-8, H-9), 6.37 (d, 1H, $J=7.7$ Hz, H-15), 6.46 (d, 1H, $J=7.7$ Hz, H-14), 6.52 (m, 2H, H-16, H-17), 6.60 (bs, 1H, H-3), 6.80 (dd, 1H, $J=17.4$, 10.6 Hz, H-1′); ^{13}C NMR ($CDCl_3$) δ 32.3, 32.4 (C-5, C-12), 34.1, 34.6 (C-6, C-11), 36.7 (C-1), 113.8 (C-2′), 125.6 (C-3), 128.4, 130.9 (C-8, C-9), 131.0, 132.5 (C-14, C-15), 132.8, 133.0 (C-16, C-17), 132.9, 134.9 (C-2, C-3a), 133.5 (C-1′), 138.7, 138.9 (C-7, C-10), 143.1, 145.4, 146.7 (C-4, C-13, C-13a); MS, *m*/*z* (rel. int.) 142 (10), 153 (46), 168 (100), 272 (M^+,49). Anal. calcd for $C_{21}H_{20}$: C, 92.60; H, 7.40. Found: C, 92.5; H, 7.5%.

(*S*)-(+)-7: mp 151–152°C (*n*-hexane); $[\alpha]_D^{25}=+235$ (*c* 0.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, $J=7.5$ Hz, H_s-2′), 2.55 (q, 2H, $J=7.5$ Hz, H-1′), 2.76 (d, 1H, $J=22.4$ Hz, H-1), 2.83–2.91 (m, 3H, H-1, H-5, H-12), 2.99-3.06 (m, 4H, H_s-6, H_s-11), 3.13 (m, 1H, H-5), 3.29 (m, 1H, H-12), 6.26 (d, 1H, $J=7.9$ Hz, H-15), 6.35 (m, 2H, H-8, H-4), 6.38 (m, 1H, H-3), 6.45 (d, 1H, $J=7.9$ Hz, H-14), 6.52 (m, 2H, H-14, H-17), ^{13}C NMR ($CDCl_3$) δ 13.8 (C-2′), 24.5 (C-1′), 32.3 (C-5, C-12), 34.1, 34.5 (C-6, C-14), 40.6 (C-1), 125.1, 125.4 (C-3, C-15), 127.6, 124.3 (C-8, C-9), 131.6 (C-2), 132.1, 132.7, 133.0 (C-14, C-16, C-17), 134.6 (C-3a), 138.5, 138.9 (C-7, C-10), 143.3, 147.3 151.3 (C-4, C-13, C-13a); MS, *m*/*z* (rel. int.) 115 (15), 128 (11), 142 (20), 155 (62), 170 (100), 274 (M^+,73). Anal. calcd for $C_{21}H_{22}$: C, 91.92; H, 8.08. Found: C, 91.9; H, 8.0%.

Acknowledgements

D.L., A.M., L.M. and A.T. thank the M.I.U.R., C.N.R. and Università degli Studi di Perugia for financial support of the work in Perugia. C.R. and S.S. thank Università della Basilicata and MIUR (COFIN 2001: *Nuovi metodi teorici e sperimentali per l'assegnamento della configurazione assoluta molecolare in soluzione*) for financial support.

References

1. Inter alia: (a) Mallory, F. B.; Mallory, C. W. *Organic Reactions*; Wiley-Sons: New York, 1984; Vol. 30, pp. 1–456; (b) Wynberg, H. *Acc. Chem. Res.* **1971**, *4*, 65–73; (c) Martin, R. H. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 649–660; (d) Vogtle, F. *Fascinating Molecules in Organic Chemistry*; Wiley-Sons: New York, 1992; p. 156; (e) Meurer, K. P.; Vogtle, F. *Top. Curr. Chem.* **1985**, *127*, 1–76; (f) Willmore, N. D.; Hoic, D. A.; Katz, T. J. *J. Org. Chem.* **1994**, *59*, 1889–1891; (g) Nuckolls, C.; Katz, T. J.; Castellanos, L. *J. Am. Chem. Soc.* **1996**, *118*, 3767–3768; (h) Verbiest, T.; Van Elshocht, S.; Kauranen, M.; Hellemans, L.; Snauwaert, J.; Nuckolls, C.; Katz, T. J.; Persoons, A. *Science* **1998**, *282*, 913–915.
2. Inter alia: (a) Tribout, J.; Martin, R. H.; Doyle, M.; Wynberg, H. *Tetrahedron Lett.* **1972**, 2839–2842; (b) Nakazaki, M.; Yamamoto, K.; Maeda, M. *Chem. Lett.* **1980**, 1553–1554; (c) Hopf, H.; Mlynek, C.; El-Tamany, S.; Ernst, L. *J. Am. Chem. Soc.* **1985**, *107*, 6620–6627; (d) Hopf, H.; El-Tamany, S. *Chem. Ber.* **1983**, *116*, 1682–1685; (e) Hopf, H.; El-Tamany, S.; Raulfs, F. W. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 633.
3. (a) Minuti, L; Taticchi, A.; Gacs-Baitz, E. *Tetrahedron* **1994**, *50*, 10359–10366; (b) Minuti, L; Taticchi, A.; Gacs-Baitz, E.; Marrocchi, A. *Tetrahedron* **1995**, *51*, 8953–8958; (c) Gacs-Baitz, E.; Minuti, L.; Taticchi, A. *Polycyclic Aromatic Compounds* **1996**, *8*, 213–227; (d) Minuti, L.; Taticchi, A.; Marrocchi, A.; Morozzi, G.; Pampanella, L.; Gacs-Baitz, E. *Polycyclic Aromatic Compounds* **1999**, *13*, 9–24; (e) Minuti, L.; Taticchi, A.; Marrocchi, A.; Gacs-Baitz, E. *Tetrahedron* **1998**, *54*, 10891–10898.
4. (a) Minuti, L.; Taticchi, A.; Marrocchi, A.; Gacs-Baitz, E. *Tetrahedron* **1997**, *53*, 6873–6878; (b) Minuti, L.; Taticchi, A.; Marrocchi, A.; Gacs-Baitz, E. *Synth. Commun.* **1998**, *28*, 2181–2190; (c) Minuti, L.; Taticchi, A.; Marrocchi, A.; Gacs-Baitz, E.; Galeazzi, R. *Eur. J. Org. Chem.* **1999**, 3155–3163.

5. (a) Minuti, L.; Taticchi, A.; Marrocchi, A.; Costantini, L.; Gacs-Baitz, E. *Tetrahedron: Asymmetry* **2001**, *12*, 1179–1183; (b) Marrocchi, A.; Minuti, L.; Taticchi, A.; Dix, I.; Hopf, H.; Gacs-Baitz, E.; Jones, P. T. *Eur. J. Org. Chem.* **2001**, 4259–4268.
6. Minuti, L.; Taticchi, A.; Marrocchi, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4221–4225.
7. (a) Dannheim, J.; Ph.D. Dissertation 1987, Technische Universität Braunschweig, Braunschweig, Germany; (b) Hopf, H.; Raulfs, F.-W. *Israel J. Chem.* **1985**, *25*, 210–216.
8. Absolute configuration of (*S*,*S*)-**6** was assigned by means of chemical correlation with (*S*)-(+)-**1**, whose absolute configuration was, in turn, determined by CD analysis (see Section 2.4).
9. Cipiciani, A.; Fringuelli, F.; Mancini, V.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. *J. Org. Chem.* **1997**, *62*, 3744–3747.
10. The 4-Hs and 7-Hs protons of [2.2]paracyclophane are equivalent, therefore mono substitution in 4 or 7 position gives rise to compounds having the same configuration.
11. It should be noted that a substituent in either the 4 or 5 position in [2.2]paracyclophane gives rise to compounds having opposite configurations.
12. Nugent, M. J.; Weigang, O. E. *J. Am. Chem. Soc.* **1969**, *91*, 4556–4558.
13. Falk, H.; Schlögl, K. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 383–384.
14. Rosini, C.; Ruzziconi, R.; Superchi, S.; Fringuelli, F.; Piermatti, O. *Tetrahedron: Asymmetry* **1998**, *9*, 55–62.
15. 1-Phenylbutadiene shows the low-energy allowed π–π* transition at 280 nm (ε 20000) [see: (a) Jaffé, H. H.; Orchin, M. *Theory and applications of Ultraviolet Spectroscopy*; Wiley: New York, 1962; p. 232]. The large red shift (ca. 40 nm) observed could be due to the boat-type deformation of the aromatic rings in the paracyclophanes, see: (b) Issberner, J.; Bohme, M.; Grimme, S.; Nieger, M.; Paulus, W.; Vogtle, F. *Tetrahedron: Asymmetry* **1996**, *7*, 2223–2232.
16. Treatments of exciton coupling and its application in organic stereochemistry: (a) Mason, S. F. *Quart. Rev.* **1963**, *17*, 20–66; (b) Mason, S. F. In *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Snatzke, G., Ed. Theory II; Heyden and Son: London, UK, 1967; Chapter 4, p. 71; (c) Gottarelli, G.; Mason, S. F.; Torre, G. *J. Chem. Soc. (B)* **1970**, 1349–1353; (d) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257; (e) Mason, S. F. *Molecular Optical Activity and the Chiral Discriminations*; Cambridge University Press: Cambridge: 1982; (f) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy: Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983; (g) Berova, N.; Nakanishi, K. In *Circular Dichroism: Principles and Applications*, 2nd ed.; Berova, N.; Nakanishi, K.; Woody, R. W., Eds.; Wiley-VCH: New York, 2000.
17. The success of the exciton model for interpreting the CD spectrum of [2.2]paracyclophanes has been pointed out clearly in Ref. 15b.
18. (a) DeVoe, H. *J. Chem. Phys.* **1964**, *41*, 393–400; (b) DeVoe, H. *J. Chem. Phys.* **1965**, *43*, 3199–3208.
19. Rosini, C.; Salvadori, P.; Zandomeneghi, M. *Tetrahedron: Asymmetry* **1993**, *4*, 545–554. More recent applications of this treatment to the solution of structural problems can be found in: (a) Rosini, C.; Superchi, S.; Peerlings, H. W. I.; Meijer, E. W. *Eur. J. Org. Chem.* **2000**, 61–71; (b) Iuliano, A.; Voir, I.; Salvadori, P. *J. Org. Chem.* **1999**, *64*, 5754–5756; (c) Iuliano, A.; Voir, I.; Salvadori, P. *Eur. J. Org. Chem.* **2000**, 1767–1772; (d) Di Bari, L.; Pescitelli, G.; Reginato, G.; Salvadori, P. *Chirality* **2001**, *13*, 548–555; (e) Clericuzio, M.; Toma, L.; Vidari, G. *Eur. J. Org. Chem.* **1999**, 2059–2065.