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An improved synthesis of (*S*)-(+)- and (*R*)-(−)-4-ethenyl[2.2]paracyclophane

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Abstract

The resolution of the 4-acetyl[2.2]paracyclophane by the SAMP-hydrazone method is described. A new, short, high yield synthesis of both enantiomers (*S*)-(+)- and (*R*)-(−)-4-ethenyl[2.2]paracyclophane is reported. © 2000 Published by Elsevier Science Ltd. All rights reserved.

1. Introduction

Recently, we developed an efficient, flexible synthetic approach to racemic helicenes[1a] and helicenophanes,[1b] based on the Diels–Alder cycloaddition of arylethenes.[2] We are now interested in applying this method to the synthesis of enantiomerically pure helicenophanes, which are paracyclophane-bearing helicenes that are of interest because of their stereochemical, electronic and optical properties.[3] Since 4-ethenyl[2.2]paracyclophane **1** has been shown to be a versatile diene for synthesizing a variety of helicenophanes[1b] by using the Diels–Alder reaction to construct rapidly the basic skeleton, the availability of chiral **1** is of great importance. We report here an improved synthesis of both enantiomers of 4-ethenyl[2.2]paracyclophane **1**.

Two previously described approaches to **1** are unsatisfactory. Falk and co-workers[4] synthesized **1** in both enantiomeric forms by a seven-step procedure based on the resolution of carboxylic acid **2**, prepared from racemic 4-acetyl[2.2]paracyclophane **3**, with (−)-α-phenylethylamine in an overall low yield (less than 7%). The second route[5] was also based on the resolution of the carboxylic acid **2**, obtained by oxidation of the 4-formyl[2.2]paracyclophane **4**. Then the reduction of the optically active acid **2**, followed by oxidation of the alcohol, again gave formyl derivative **4** which was converted into 4-ethenyl[2.2]paracyclophane **1** by the Wittig reaction in 29% overall yield. Both routes are tedious and low yielding being based on the resolution of carboxylic acid **2**, and therefore, require the conversion of the precursor of **1** into acid **2** (Scheme 1).

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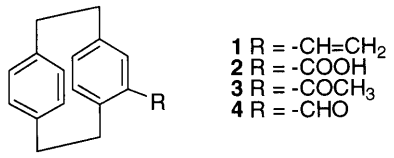
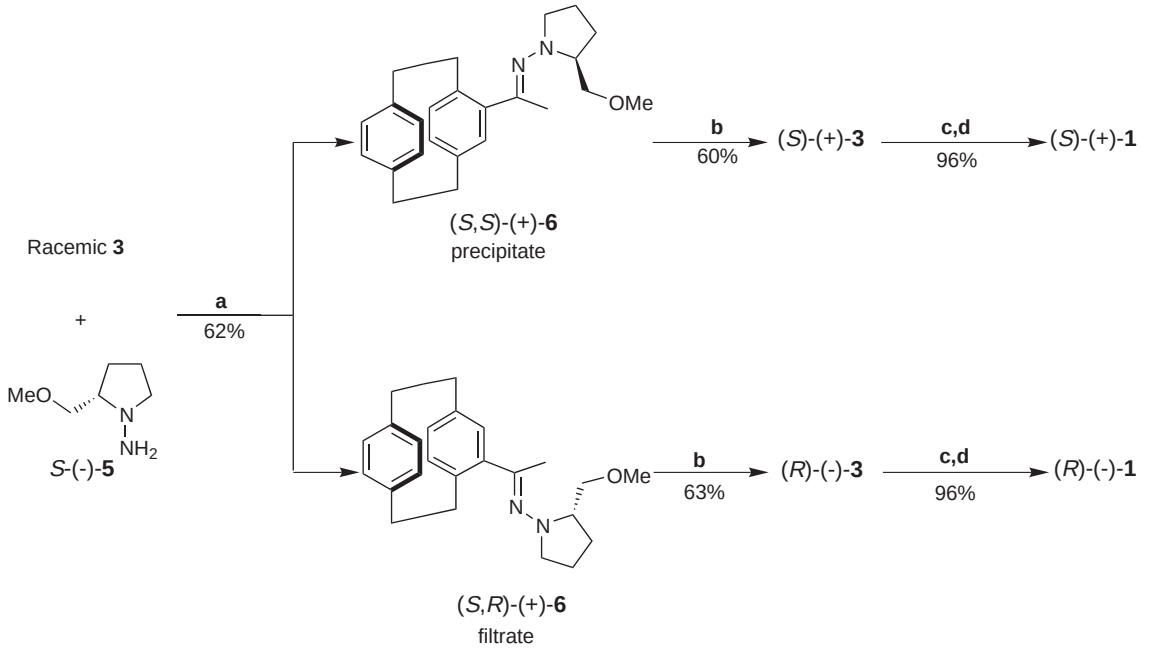


Scheme 1.

2. Results and discussion

We have found a more convenient procedure based on the resolution of the acetyl derivative **3** by applying the SAMP-hydrazone method.[6] The mixture of the two diastereoisomeric SAMP-hydrazones **6** (Scheme 2), easily prepared by treating ketone **3** with commercial (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) (62% yield) was crystallized from 95% ethanol. The precipitate was again crystallized to afford diastereomerically pure (*S*,*S*)-**6** (78%). The (*R*,*S*)-diastereoisomer **6**, which remained in the mother liquor of the first crystallization was obtained in diastereomerically pure form by two subsequent crystallizations from 95% ethanol (69%). Enantiomerically pure (*S*)-(+)- and (*R*)-(−)-4-acetyl-[2.2]paracyclophane **3** were obtained in 60 and 63% yield, respectively, upon hydrolysis of the corresponding SAMP-hydrazones **6** with oxalic acid. It should be noted that the SAMP was recovered in 80% yield.[6c]



Scheme 2. *Reagents and conditions*: (a) *p*-TsOH, C_6H_6, Δ, 19 h; (b) oxalic acid; (c) $NaBH_4$, $EtOH/H_2O$; (d) PBr_3, Li_2CO_3, LiBr

The (*S*)-(+)- and (*R*)-(−)-4-ethenyl[2.2]paracyclophane **1** were prepared from (*S*)-(+)-**3** and (*R*)-(−)-**3**, respectively, in a two-stage reaction sequence: reduction of the carbonyl group with $NaBH_4$ and subsequent dehydration of the carbinol by treating it with PBr_3 in CH_2Cl_2 and then with LiBr and Li_2CO_3 (96% overall yield).

In conclusion, a facile resolution of acetyl derivative **3** together with a short and efficient synthesis of 4-ethenyl[2.2]paracyclophane **1** in both enantiomeric forms has been reported. This method greatly increases the power and the synthetic utility of compounds **1** and **3**. The synthesis of enantiomerically pure helicenophanes, using homochiral (*S*)-(+)-**1** and (*R*)-(−)-**1** in Diels–Alder reactions, is under investigation.

3. Experimental

3.1. General

Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a 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: DeltaPak 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: Restek Ultra IBD C18, 5 μm, 250×4.6 mm; mobile phase: CH_3CN/H_2O 70:30; flow rate: 1 ml/min; detection: UV at 254 nm). GC analyses were performed on a Hewlett Packard 6890 chromatograph. 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. 4-Acetyl[2.2]paracyclophane **3** was prepared according to a procedure reported in the literature.[7]

3.2. Resolution of 4-acetyl[2.2]paracyclophane *3*

A few crystals of *p*-TsOH were added to a solution of *rac*-**3**[7] (1.5 g, 6 mmol) and SAMP **5** (0.8 ml, 6 mmol) in cyclohexane (10 ml) and then heated under reflux temperature for 19 h;[6b] the progress of the reaction was monitored by HPLC. After cooling at room temperature, the reaction mixture was diluted with Et_2O, washed with saturated aq. $NaHCO_3$ and dried (Na_2SO_4). Evaporation of the solvent under vacuum afforded a crude residue which was purified by preparative HPLC (mobile phase: CH_3CN/H_2O 3:2; flow rate: 81 ml/min) to give a 1:1 mixture of two diastereoisomeric hydrazones **6** (1.34 g, 62% yield), which was then crystallized from 95% EtOH (41 ml). The diastereoisomer (*S*,*S*)-**6** precipitated first as greenish needles (0.63 g, 94%), which was then recrystallized yielding 0.52 g (83%) of the diastereomerically pure (*S*,*S*)-**6**. $[\alpha]_D = +486$ (*c* 0.35, $CHCl_3$); mp 133–134°C (95% EtOH); ^1H NMR ($CDCl_3$) δ 1.75 (m, 1H, H-3′), 1.92–2.01 (m, 2H, Hs-4′), 2.13 (m, 1H, H-3′), 2.19 (s, 3H, –CH_3), 2.7 (ddd, 1H, J=9.6, 8.0, 8.0 Hz, H-5′), 2.86 (ddd, 1H, J=12.7, 10, 6 Hz, H-2), 2.91–3.16 (m, 6H, Hs-1, Hs-10, Hs-9), 3.39 (s, 3H, –OCH_3), 3.40 (m, 1H, H-5′), 3.42 (dd, 1H, J=9.1, 7.0 Hz, –OCH_2–), 3.59 (m, 1H, H-2′), 3.61 (dd, 1H, J=9.1, 4.0 Hz, –OCH_2–), 3.73 (ddd, 1H, J=12.7, 3, 9.8 Hz, H-2), 6.37 (dd, 1H, J=7.9, 1.5 Hz, H-12), 6.44 (d, 1H, J=7.6 Hz, H-8), 6.46 (dd, 1H, J=7.6, 1.7 Hz, H-7), 6.54 (dd, 2H, J=1.5, 1.5 Hz, H-15, H-16), 6.58 (dd, 1H, J=1.7, 1.2 Hz, H-5), 6.74 (dd, 1H, J=7.9, 1.5 Hz, H-13); ^{13}C NMR ($CDCl_3$) δ 19.64 (–CH_3), 22.77 (C-4′), 26.97 (C-3′), 34.98 (C-2), 35.20 (C-1), 35.36 (C-10), 35.71 (C-9), 54.27 (C-5′), 59.31 (–OCH_3), 66.99 (C-2′), 75.81 (–OCH_2–), 130.90 (C-13), 132.19 (C-5), 132.51, 132.61, 132.72 (C-7, C-12, C-15, C-16), 135.87 (C-8), 138.22 (C-3), 139.19, 139.22 (C-11, C-14), 139.93, 140.03 (C-4, C-6), 160.42 (–C=N–).

The EtOH filtrate, containing the diastereoisomer (*S*,*R*)-**6**, was evaporated and then recrystallized twice from 95% EtOH to afford 0.46 g (69%) of diastereomerically pure (*S*,*R*)-**6** as white needles. $[\alpha]_D = +521$ (*c* 0.29, $CHCl_3$); mp 108–110°C (95% EtOH); ^{1}H NMR ($CDCl_3$) δ 1.77 (m, 1H, H-3′), 1.92–2.01 (m, 2H, Hs-4′), 2.13 (m, 1H, H-3′), 2.28 (s, 3H, –CH_3), 2.55 (ddd, 1H, $J = 9.6$, 7.3, 8.6 Hz, H-5′), 2.85 (ddd, 1H, $J = 12.6$, 9.8, 6.5 Hz, H-2), 2.91–3.17 (m, 6H, Hs-1, Hs-9, Hs-10), 3.40 (m, 1H, H-5′), 3.41 (dd, 1H, $J = 9.2$, 7.0 Hz, –OCH_2–), 3.42 (s, 3H, –OCH_3), 3.59 (m, 1H, H-2′), 3.63 (dd, 1H, $J = 9.2$, 4.2 Hz, –OCH_2–), 3.89 (ddd, 1H, $J = 12.6$, 9.6, 3.5 Hz, H-2), 6.44 (ddd, 1H, $J = 7.9$, 1.5, 1.5 Hz, H-12), 6.45 (dd, 1H, $J = 7.8$, 1.7 Hz, H-7), 6.48 (d, 1H, $J = 7.8$ Hz, H-8), 6.55 (dd, 2H, $J = 1.5$, 1.5 Hz, H-15, H-16), 6.58 (d, 1H, $J = 1.7$ Hz, H-5). ^{13}C NMR ($CDCl_3$) δ 18.99 (–CH_3), 22.87 (C-4′), 27.00 (C-3′), 35.27 (C-2), 35.30 (C-1), 35.44 (C-10), 35.77 (C-9), 54.49 (C-5′), 59.43 (–OCH_3), 66.95 (C-2′), 76.31 (–OCH_2–), 131.13 (C-13 or C-12), 131.81 (C-7, C-15 or C-16), 132.00 (C-12 or C-13), 132.40 (C-5), 132.67, 132.86 (C-7, C-15 or C-16), 136.24 (C-8), 137.88 (C-3), 139.11, 139.21 (C-11, C-14), 139.96, 140.01 (C-4, C-6), 159.49 (–C=N–).

An aqueous saturated solution of oxalic acid (3.12 ml) was added to an ethereal solution (21 ml) of (*S*,*S*)-**6** (0.52 g, 1.44 mmol).[6c] The resulting mixture was vigorously stirred at room temperature for 3 days. Usual work up gave a residue which was purified by flash column chromatography on silica gel. Elution with a 9:1 hexane/EtOAc solution gave 0.22 g (0.86 mmol) of pure (*S*)-**3** (60%); $[\alpha]_D = +65$ (*c* = 0.26, $CHCl_3$); mp: 129–130°C (heptane) [lit.[4,8] $[\alpha]_D = +65$ (*c* 0.5, $CHCl_3$); mp 120–124°C].

Hydrolysis of (*S*,*R*)-**6** (0.46 g) followed by column chromatography (SiO_2, 9:1 hexane/EtOAc) of the crude residue afforded 0.46 g (1.27 mmol, 63%) of (R)-**3**; $[\alpha]_D = -65$ (*c* 0.35, $CHCl_3$); mp 127–128°C (heptane) [lit.[4,8] $[\alpha]_D = -65$ (*c* 1, $CHCl_3$); mp 127–128°C].

3.3. (+)-(S)-4-Ethenyl[2.2]paracyclophane **1**

A solution of 0.11 g of $NaBH_4$ in 2 ml of H_2O was added to a refluxing solution of (*S*)-**3** (0.22 g, 0.86 mmol) in EtOH (11 ml) and the reflux was continued for 2 h. The reaction mixture was then poured into water and extracted three times with $CHCl_3$. The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated under vacuum to obtain 0.21 g of a mixture of alcohols[9] (99%) which was used without further purification for the next step.

A solution of PBr_3 (0.06 ml) in dry CH_2Cl_2 (3 ml) was added dropwise and under nitrogen to a stirred solution of the above mixture of alcohols (0.21 g, 0.85 mmol) in DMF (5 ml) at −10°C.[10] The mixture was then warmed to 0°C and stirred at this temperature for 3 h. After that, 0.43 g of LiBr and 0.57 g of Li_2CO_3 were added and the resulting mixture was stirred at 100°C for 3 h. After that, the reaction mixture was cooled, poured into 2N aq. HCl solution and extracted three times with Et_2O. The combined extracts were washed with brine and dried (Na_2SO_4). The solvent was evaporated at reduced pressure and the residue was chromatographed on silica gel. Elution with hexane afforded 0.19 g (0.82 mmol, 96%) of pure (*S*)-**1**; $[\alpha]_D = +440$ (*c* 0.14, $CHCl_3$); mp 78–79°C (hexane) [lit.[4,5] $[\alpha]_D = +443$ ($CHCl_3$); mp 78°C (petroleum ether)].

3.4. (−)-(R)-4-Ethenyl[2.2]paracyclophane **1**

(*R*)-**1** was obtained in 96% yield using the procedure described above, from 0.2 g (0.8 mmol) of (*R*)-**3**; $[\alpha]_D = -440$ (*c* 0.14, $CHCl_3$); mp 81–82°C [lit.[4] $[\alpha]_D = -330$ ($CHCl_3$); mp 95–98°C].

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