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An Improved, Two Step Synthesis of the Chiral Templating Reagent 2,6-Dihydroxy-9,10-dihydro-11,12-dicarbomethoxyethenoanthracene.

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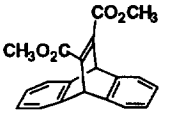
Abstract: An improved, two step synthesis, of the importrant chiral templating reagent 2,6-Dihydroxy-9,10-dihydro-11,12-dicarbomethoxyethenoanthracene **3** has been developed with an overall yield of 82% (not optimized). The reaction features a simple diastereomeric separation to afford the enantiomeric products. The reaction can be scaled up to afford multigram quantities of the ethenoanthracenes.

The molecule 9,10-dihydro-11,12-dicarbomethoxyethenoanthracene **1** is a rigid molecule with a well defined, predictable 3-dimensional structure and as such has found an important place in the field of molecular recognition as an architectural sub-unit.[1] Substitution of the aromatic rings produces chiral versions which have also found application in synthetic receptor systems.[2]



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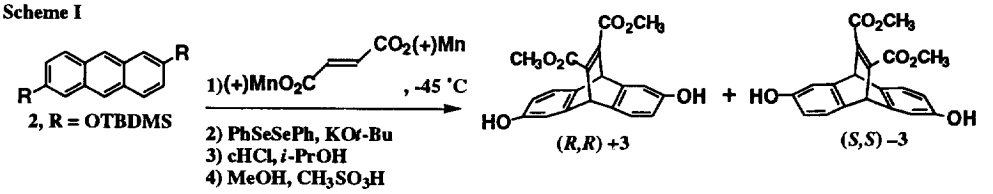
As part of a research program in molecular recognition aimed at developing a template directed synthesis of a family of chiral cyclophane receptors, we chose to explore the use of an ethenoanthracene as a chiral templating unit. The 2,6-dihydroxy-9,10-dihydro-11,12-dicarbomethoxyethenoanthracene **3**, first synthesized by Dougherty and co-workers,[2a] proved an ideal candidate. The Dougherty synthesis (Scheme I) involves a low temperature Lewis acid (Et_2AlCl) catalyzed Diels-Alder reaction using the di(+)menthyl fumarate as the dienophile to generate an ethanoanthracene (total yield of Diels-Alder adducts is 62%). Separation of the diastereomeric ethanoanthracenes is followed by an olefination using the highly toxic reagent, diphenyl diselenide (PhSeSePh). The diphenol deprotection and transesterification were then conducted in separate steps.

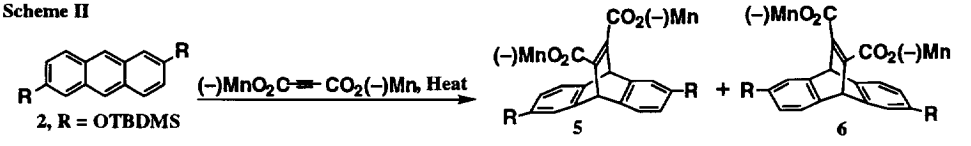
Scheme I



For safety considerations we sought to avoid the use of both Et_2AlCl and PhSeSePh. We reasoned it should be possible to generate the ethenoanthracene directly in a single step by taking advantage of the well known Diels-Alder reaction between acetylenedicarboxylate and anthracene and thus reduce the overall number

of steps. Scheme II illustrates our method. The first step involves the Diels-Alder reaction between di(–) menthyl acetylenedicarboxylate[3] **4** (DMnAD is available in high yield, in a four step synthesis starting from potassium acetylenedicarboxylate[3]) and the TBDMS protected 2,6-dihydroxyanthracene in refluxing *m*-xylene. This reaction affords an apparent 100% yield of the Diels-Alder adducts after 24 hours (Figure 1). After removal of the unreacted (DMnAD) by flash chromatography, the diastereomers are then completely separated by a simple crystallization affording, in an unoptimized recovery, a total yield of 88% of the Diels-Alder adducts. The deprotection and transesterification were then accomplished, quantitatively, in a single step by the action of methanol and catalytic sulfuric acid (Scheme III).

Scheme II



Scheme III

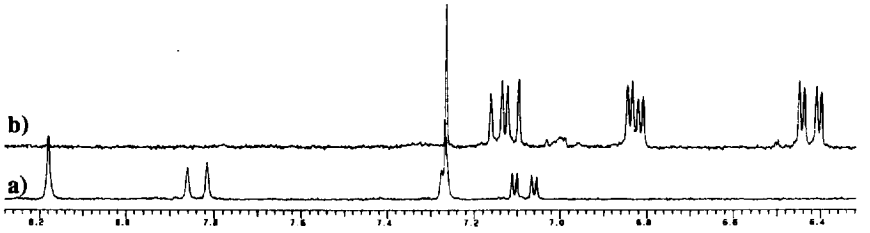
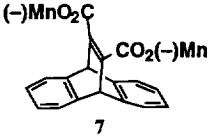


Figure 1. The aromatic region of the Diels-Alder reaction between **2** and the acetylene. **a)** Start of the reaction. **b)** After 24 hours.

We extended this method to reaction with anthracene to generate the template precurser 9,10-dihydro-11,12-dicarboxyethenoanthracene bis[(-)-menthyl ester] **7**. Previous syntheses of **7** require three steps[2b], our method affords **7** in a single step in a 94% yield. As before, we made no specific attempt at the optimization of product recovery.



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Our method affords several advantages over the previous synthesis of the chiral ethenoanthracene **3**. The reaction allows ready scale up to afford large quantities of the Diels-Alder adducts by avoiding the use of Et_2AlCl and PhSeSePh. The reaction is fast and highly efficient. Separation of the resulting diastereomers is equally efficient and simple. Finally, the excess dieneophile can be recovered nearly quantitatively and reused in subsequent reactions. Efforts are currently under way to use these products as chiral templates in the preparation of a family of cyclophane receptors.

EXPERIMENTAL

Melting points were determined on a Mel-Tem® capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs of Norcross, Georgia. Low and high resolution mass spectra were performed by the Mass Spectrometry Service of the University of Illinois. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. Proton and carbon magnetic resonance spectra were obtained on a Varian Gemini 200 MHz spectrometer. Specific rotations were measured on a AUTOPOL® II automatic polarimeter. Chemical shifts (^{1}H-NMR and ^{13}C-NMR) are expressed in parts per million (δ units) downfield from tetramethylsilane used as an internal reference. Thin layer chromatography was performed using Whatman® KGF silica gel 60 Å (0.25 mm) analytical glass plates. Davisil® grade 633 silica gel (200-425 mesh) was used for flash chromatography which was performed according to the method of Still.[4] All starting materials and solvents were purchased from Aldrich and were used as received. Reactions were run under a nitrogen atmosphere.

(9*R*,10*R*) and (9*S*,10*S*)-2,6-Bis(*tert*-butyldimethylsiloxy)-9,10-dihydro-11,12-dicarboxyethenoanthracene bis[(-)-menthyl ester] 5 and 6. A stirred solution of 0.78 g (1.8 mmol) of the 2,6-bis(*tert* -butyldimethylsiloxy)-anthracene (**2**), and 2.06 g (5.3 mmol) of the DMnAD **4** in 2.5 mL of *m*-xylene was heated at 150 °C. After 24 hours the reaction mixture was concentrated *in vacuo* and passed across a short (20mm x 40mm) SiO_2 column eluted with 4% Et_2O/hexane. The excess **4** was collected (Rf = 0.31, 1.25 g) followed by the mixed diastereomers **5** and **6** as a yellow foam (Rf = 0.17, 1.40 g). The yellow foam was then recrystallized from ~5 mL of pentane at -20 °C affording a first crop of 0.49 g of **6** as fine white needles. A second crop from ~3 mL of pentane afforded a further 0.11 g. The total yield of **6** was 0.60 g. Purification of the remaining yellow foam by flash chromatography (150mm x 40mm column of SiO_2, eluted with 4% Et_2O/hexane) afforded 0.69 g of **5** as a yellow foam. The total recovery of the diastereomeric products was 88%: **6**; mp 159-161 °C; Rf = 0.17 (SiO_2, 4% Et_2O/hexane); IR (Thin film) 2944, 2862 1718, 1610, 1580, 1467, 1251, 1134, 1103, 1041, 1021, 964, 903, 831, 780, 733 cm^{-1}; 200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.14 (d, 2H, J=8.0 Hz), 6.81 (d, 2H, J=2.0 Hz), 6.42 (dd, 2H, J=8.0, J=2.0 Hz), 5.20 (s, 2H), 4.78 (td, 2H), 2.10 (m, 2H), 1.92 (d septets, 2H), 1.71, 1.66, 1.45, 1.08 (m, 16H), 0.95 (s, 18H), 0.93 (d, 12H, J=7.0 Hz), 0.79 (d, 6H, J=7.0 Hz), 0.78 (s, 6H), 0.30 (s, 6H); 50 MHz ^{13}C-NMR ($CDCl_3$, 23 °C) δ 165.2, 153.0, 146.5, 146.0, 136.6, 124.0, 116.1, 115.3, 75.5, 52.1, 46.8, 40.8, 34.3, 31.4, 26.0, 25.6, 23.4, 22.0, 20.8, 16.3, -4.5; $[\alpha]_D^{25}$ –77.50 [*c* 3.1, CH_2Cl_2]; MS, *m/e* calcd for $C_{50}H_{76}Si_2O_6$ (M^+) 828.5180, measured 828.5182. Anal. calcd for $C_{50}H_{76}Si_2O_6$: C, 72.42; H, 9.24. Found: C, 72.65; H, 9.43. **5**; Rf = 0.18 (SiO_2, 4% Et_2O/hexane); IR (Thin film) 2954, 2861, 1707, 1610, 1417, 1251, 1102, 959, 830, 748 cm^{-1}; 200 MHz ^{1}H-NMR ($CDCl_3$) 7.12 (d, 2H, J=8.0 Hz), 6.84 (d, 2H, J=2.0 Hz), 6.42 (dd, 2H, J=8.0, J=2.0 Hz), 5.20 (s, 2H), 4.78 (td, 2H), 2.10 (m, 2H), 1.92 (d septets, 2H), 1.71, 1.66, 1.45, 1.08 (m, 16H), 0.96 (s, 18H), 0.90 (d, 12H, J=7.0 Hz), 0.80 (d, 6H, J=7.0 Hz), 0.17 (s, 6H), 0.08 (s, 3H), 0.01 (s, 3H); 125 MHz ^{13}C-NMR ($CDCl_3$) d 165.2, 153.1, 146.7, 146.2, 136.6, 124.0, 116.3, 115.3, 75.6, 52.1, 46.9, 40.8, 34.3, 31.5, 26.1, 25.7, 23.4, 22.1, 20.9, 18.1, 16.4, 1.1, -4.4; $[\alpha]_D^{25}$ –18.38 [*c* 3.7, CH_2Cl_2]; MS, *m/e* calcd for $C_{50}H_{76}Si_2O_6$ (M^+) 828.5180, measured 828.5182.

(9*R*,10*R*) and (9*S*,10*S*)-2,6-Dihydroxy-9,10-dihydro-11,12-dicarbomethoxyethenoanthracene (+)-3 and (–)-3 To a stirred solution of either **5** or **6** (190 mg, 0.229 mmol) in methanol (15 mL) was added 0.5 mL of conc. H_2SO_4, which was then brought to a reflux. After 24 hours the reaction mixture

was poured into 50 mL of ethyl acetate and washed with 3x25 mL portions of water. The organic layer was dried ($MgSO_4$) and concentrated *in-vacuo* to afford a brown glass or foam. The diphenols (–)-**3** or (+)-**3** were purified by flash chromatography (150mm x 20mm column of SiO_2, eluted with 15% Et_2O/petether) affording 77.0 mg (96%) as a white foam. Rf = 0.33 (SiO_2, 15% Et_2O/petether); IR (Thin film) 3395(bs), 2944, 1713, 1615, 1451, 1333, 1262, 1220, 1133, 1103, 1062, 948, 872, 831 cm^{-1}; 200 MHz ^{1}H-NMR (CD_3CN) δ 7.16 (d, 2H, J=8.0 Hz), 6.87 (d, 2H, J=2.0 Hz), 6.84 (s, 2H), 6.42 (dd, 2H, J=2.0, 8.0 Hz), 5.33 (s, 2H), 3.71 (s, 6H); 50 MHz ^{13}C-NMR (CD_3CN) δ 166.2, 154.9, 147.7, 146.8, 135.5, 124.6, 117.6, 112.1, 111.0, 52.3, 51.5; (+)-**3** $[\alpha]_D^{25}$ +57.82 [*c* 0.47, CH_3CN], (–)-**3** $[\alpha]_D^{25}$ –57.98 [*c* 0.78, CH_3CN]; MS, *m/e* calcd for $C_{20}H_{16}O_4$ (M^+) 352.0947, measured 352.0942.

9,10-Dihydro-11,12-dicarboxyethenoanthracene Bis[(-)-menthyl ester 7. A stirred solution of 0.78 g (1.8 mmol) of anthracene, and 2.06 g (5.3 mmol) of **4** in 2.5 mL of *m*-xylene was refluxed at 150 °C. After 24 hours the reaction mixture was concentrated *in vacuo* and passed across a short (20mm x 40mm) SiO_2 column eluted with 4% Et_2O/hexane. The excess acetylenedicarboxylate was collected (0.59 g) followed by the adduct **7** as a yellow foam (Rf 0.06, 1.40 g). The yellow glass foam was then recrystallized from ~10-15 mL of pentane at -20 °C affording a first crop of 0.65 g of **7** as fine white needles. A second crop from ~3-5 mL of pentane afforded a further 0.31 g. The total yield of **7** was 0.96 g (94%); mp 167-168 °C; Rf = 0.31 (SiO_2, 10% Et_2O/hexane); IR (Thin film) 2954, 2872, 1703, 1636, 1456, 1323, 1287, 1256, 1210, 1154, 1108, 1046, 954, 739 cm^{-1}; 200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.36 (m, 4H), 7.02 (m, 4H), 5.40 (s, 2H), 4.79 (td, 2H), 2.10 (m, 2H), 1.95 (d septets, 2H), 1.71 (s, 4H), 1.66 (s, 2H), 1.54 (s, 4H), 1.45 (m, 4H) 1.02 (m, 2H), 0.91 (d, 6H, J=7.0 Hz), 0.90 (d, 6H, J=6.0 Hz), 0.81 (d, 6H, J=7 Hz); 50 MHz ^{13}C-NMR ($CDCl_3$) δ 165.1, 146.2, 144.1, 144.0, 125.3, 123.8, 123.7, 75.7, 52.8, 46.9, 40.8, 34.3, 31.5, 26.1, 23.4, 22.1, 20.9, 16.4; $[\alpha]_D^{25}$ –63.46 [*c* 0.91, CH_2Cl_2]; MS, *m/e* calcd for $C_{38}H_{48}O_4$ (M^+) 568.3539, measured 568.3544. Anal. calcd for $C_{38}H_{48}O_4$: C, 80.26; H, 8.54. Found: C, 80.26; H, 8.56.

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