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Synthesis and resolution of a new helically chiral azahelicene

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ABSTRACT

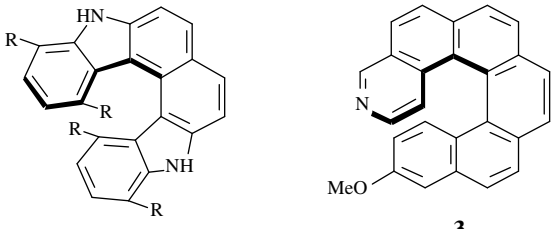
Helically chiral azahexahelicene **3** was prepared in four steps using the Mizoroki–Heck coupling followed by classical oxidative photodehydrocyclisation. Resolution of this new chiral system was achieved through separation by HPLC providing (−)- and (+)-**3** in high optical purity. The absolute configurations of (−)- and (+)-**3** were assigned as *M* and *P*, respectively, by means of circular dichroism. Each of the hexacyclic systems (*M*)-(−)- and (*P*)-(+)-**3** was reacted with boron tribromide to provide the corresponding helical pyridophenols in good yields.

Helicenes constitute a fascinating class of chiral helical molecules comprising *ortho*-fused aromatic rings. They have a powerful inherently dissymmetric chromophore which exhibits a very high specific rotation, and are further characterised by strong interactions with electron-deficient analytes. The unique structure of helicenes makes them very stable towards acids, bases and relatively high temperature.[1] These molecules are considered as potentially useful new materials such as discotic liquid crystals[2] or conjugated polymers.[3] In particular, functionalised hexahelicenes and larger [*n*]helicenes are promising candidates for chiral catalysts[4] and ligands[5] in asymmetric syntheses because they have a rigid helical framework and possess high optical stability.

In recent years, the preparation of heterohelicenes has been studied extensively in order to exploit the unique properties of these molecules.[6] However, aza[6]helicenes were not elaborated sufficiently and only a few reports have described the synthesis of such compounds despite their possible applications in various branches of chemistry. A well-known representative of this family is the racemic pyrrolo[6]helicene **1**, which has been prepared, in two steps, by Fuchs and Niszel (Fig. 1).[7] Following the same method, Pischel et al. reported the synthesis of the corresponding tetramethyl derivative **2** in low yield. Resolution was achieved only on an analytical scale by chiral HPLC.[8] Finally, Staab et al. have described the synthesis of 1,16-diaza[6]helicene, but they have not reported its resolution.[9]

We have previously reported the synthesis and characterisation of various functionalised helically chiral alcohols and phosphines,[10,11] using palladium-promoted Mizoroki–Heck coupling reactions and classical oxidative photocyclisation, while searching for new chiral ligands. Due to the small number of aza[6]helicenes we wanted to extend our approach to the synthesis of various functionalised nitrogen-containing species. Our strategy makes use of 2-bromo-10-methoxybenzo[*c*]phenanthrene **7** as the starting material for the preparation of the nitrogen-containing olefin **8**, via palladium catalysed Mizoroki–Heck reaction. The olefin is then converted into the corresponding helically chiral hexacyclic system by photolysis. The nitrogen atom in this chiral helicene could serve as a hydrogen acceptor as well as a metal chelating agent for chirality recognition.

The synthesis of the helically chiral hexacyclic framework **3** was performed as shown in Schemes 1 and 2. The Mizoroki–Heck coupling[12] of 1,4-dibromobenzene **4** with excess of commercially available 6-methoxy-2-vinylnaphthalene **5** in the presence of



1: R = H
2: R = Me

3

Figure 1. Structures of azahexahelicenes **1**, **2** and **3**.

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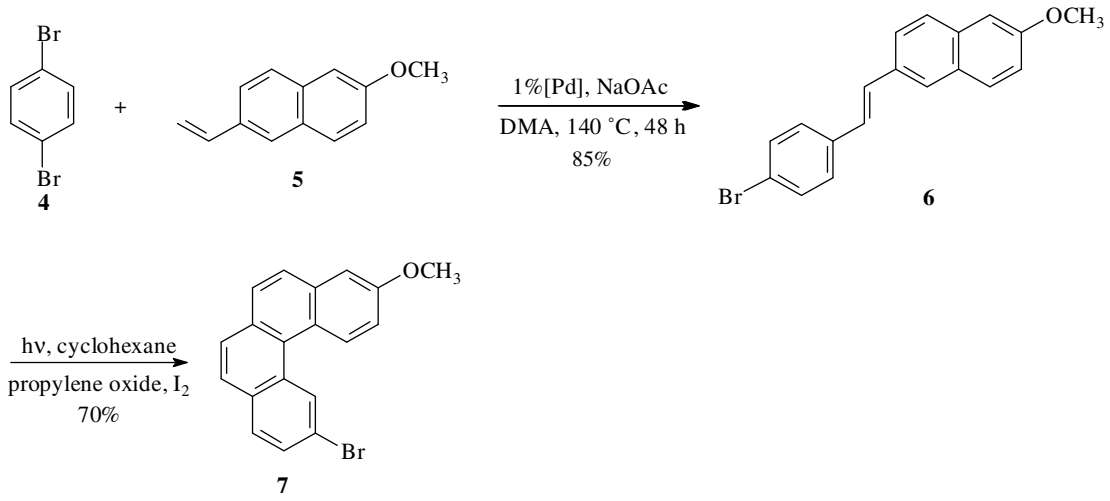
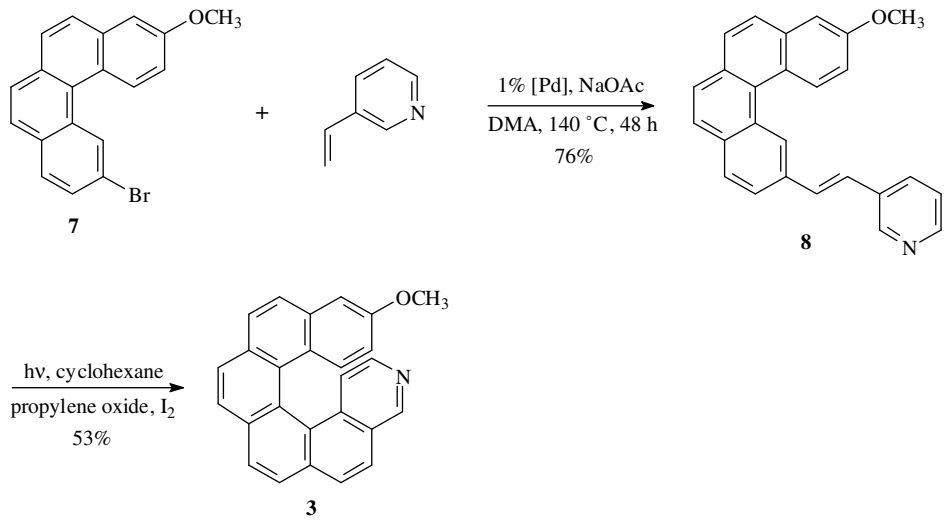


Scheme 1. Synthesis of the benzo[*c*]phenanthrene moiety **7**.



Scheme 2. Synthesis of the helically chiral hexacyclic system **3**.

sodium acetate and 1% of Hermann's palladacycle [*trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium] as the catalyst, in *N*,*N*-dimethylacetamide (DMA), afforded the diarylethene **6** in 85% yield after purification by column chromatography. Previously, we have demonstrated that the condensation reaction between 2-bromo-6-methoxynaphthalene and *p*-bromostyrene, via Heck conditions, produced only a small amount of the expected product **6**.[10a] Olefin **6** was then irradiated using a 150 W high pressure mercury immersion lamp on a 500 mg scale to give 2-bromo-10-methoxybenzo[*c*]phenanthrene **7** in 70% yield (Scheme 1).

The benzo[*c*]phenanthrene derivative **7** and 3-vinylpyridine (1.5 equiv) undergo a Mizoroki–Heck coupling using 1% of Hermann's catalyst. The desired coupled product **8**, possessing *E*-stereochemistry at the double bond, was obtained in 76% yield after heating for 48 h at 140 °C, according to Scheme 2. To complete the synthesis of [6]helicene **3**, olefin **8** was photocyclised in the presence of a stoichiometric amount of iodine as oxidising agent and an excess of propylene oxide as a hydrogen iodide scavenger.[13] Thus, photolysis of **8** in cyclohexane for about 120 min, on a 200 mg scale afforded the expected 3-aza-14-methoxy[6]helicene **3** in 53% yield, and an overall 24% yield over four steps (Scheme 2). For the photoconversion of larger amounts of the olefin **8** it was preferable to carry out the irradiation using portions of 0.55 mmol or less. The total irradiation time required for complete conversion of a large amount of **8** was not affected significantly by dividing the reactant into small batches, and the irradiated batches were combined for work-up.

The ring closure of olefin **8** is not completely regioselective since 1-aza-14-methoxyhexahelicene **9** was isolated in 8% yield as a minor product (Fig. 2).[14] Helicenes **3** and **9** were successfully separated by column chromatography on silica gel. No other

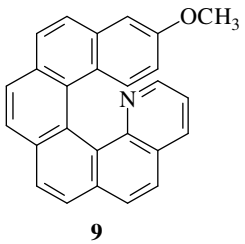
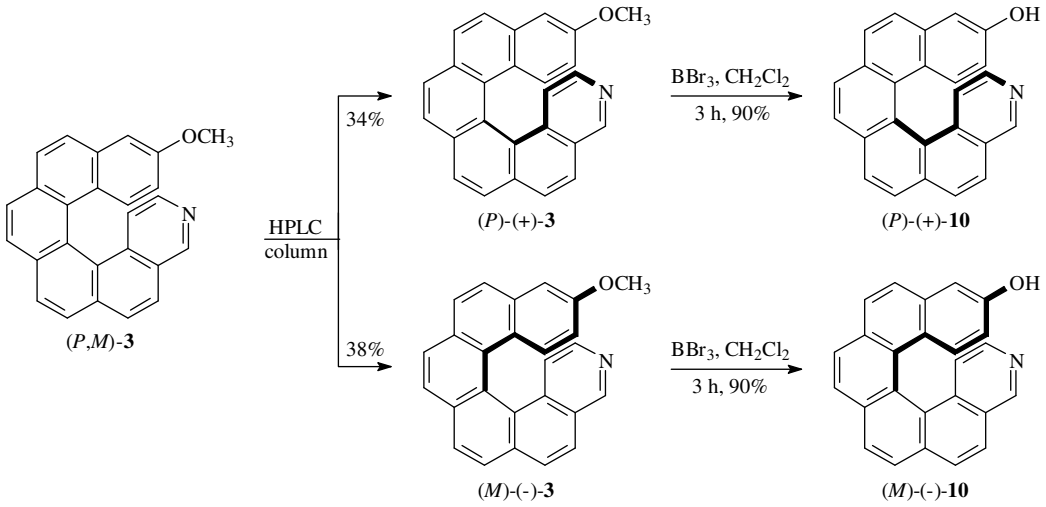


Figure 2. Structure of the helically chiral compound **9**.



Scheme 3. Resolution of azahexahelicene **3** and synthesis of helically chiral pyridophenol derivatives **10**.

isomer indicating that ring closure of **8** had occurred from the other side of the four-membered ring system, was isolated from the reaction mixture.

The separation of *rac*-**3** into its enantiomers was achieved on preparative scale by HPLC using a column packed with cellulose-tris(3,5-dimethylphenylcarbamate)[15] (250 × 20 mm) and *n*-heptane/2-propanol (95:5) mixture as the mobile phase. Thus, starting from 100 mg of *rac*-**3**, a total of 72 mg of pure product were separated, equivalent to a yield of 72%. The earlier eluting fractions, >99% ee, consisted of the enantiomer exhibiting a negative optical rotation (−) which was isolated in 38% yield. Later eluting fractions gave compound (+)-**3** in 34% yield (>99% ee) (Scheme 3).[16] The enantiomeric purity of the products (−)- and (+)-**3** was determined by chiral HPLC using the same stationary phase as above.[17]

The specific rotation values obtained for (−)-**3** and (+)-**3** were found to be $[\alpha]_D$ −1373 (*c* 0.20, CH_2Cl_2) and +1363 (*c* 0.20, CH_2Cl_2), respectively. The chiroptical properties of 3-aza-14-methoxyhexahelicene **3** in the form of the CD spectrum were also measured (Fig. 3), which indicated that complete optical resolution had occurred, which makes assignment of the absolute configurations possible. The CD spectrum of the dextrorotatory enantiomer (*P*)-(+)-**3** exhibited a distinct positive maximum at 333 nm and a negative maximum at 253 nm, as depicted in Figure 3, demonstrating no significant change relative to the CD of unsubstituted hexahelicene.[18] Thus, the absolute configuration of (−)- and (+)-helicenes **3** must be *M* (left-handed helix) and *P* (right-handed helix), respectively.

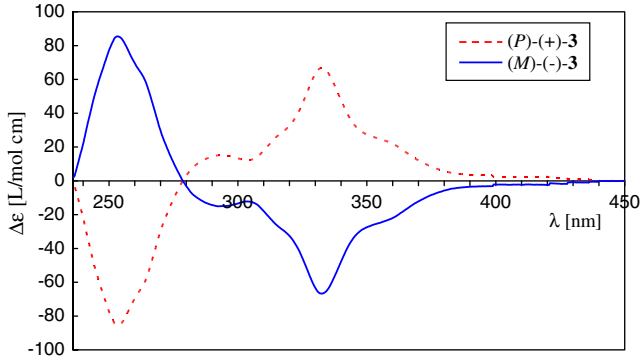


Figure 3. CD spectra of (*P*)-(+)-**3** and (*M*)-(−)-**3** in CH_2Cl_2.

Having established a short and effective route to the azahelicene **3**, we next investigated its demethylation in order to obtain new helically chiral pyridophenols. Thus, treatment of (*M*)-(−)-**3** and (*P*)-(+)-**3** with BBr_3 solutions in CH_2Cl_2 at room temperature provided the corresponding optically pure derivatives (*M*)-(−)-**10** and (*P*)-(+)-**10**, respectively, in 90% yields[19] according to Scheme 3 (>99% ee as shown by chiral HPLC analysis).[20] The optical rotation obtained for the *M*-configured pyridophenol was −1559 (*c* 0.30, MeOH).

In summary, we have prepared chiral azahexahelicene **3** in four steps, with an overall yield of 24%. Resolution of the latter was successfully achieved affording the corresponding enantiomers in high optical purity. This hexacyclic system was found to be a useful precursor for the preparation of helically chiral pyridophenols, which could serve as *N*–O bidentate ligands in asymmetric synthesis or as building blocks for supramolecular architectures. Work in this field is currently in progress.

Acknowledgement

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14. *Selected spectral data for 1-aza-14-methoxyhexahelicene* **9**: yellow solid; mp = 227–229 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 3.86 (s, 3H, OCH_3), 6.27 (dd, J_1 = 2.7 Hz, J_2 = 9.3 Hz, 1H, H-15), 7.15 (dd, J_1 = 4.2 Hz, J_2 = 8.1 Hz, 1H, H-3), 7.21 (d, J = 2.7 Hz, 1H, H-13), 7.46 (d, J = 9.3 Hz, 1H, H-16), 7.82–7.92 (m, 4H), 7.96–8.02 (m, 4H), 8.09 (d, J = 8.1 Hz, 1H), 8.12 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 55.23 (OCH_3), 106.83 (C-13), 115.27 (C-15), 120.77 (C-3), 123.96 (C), 125.23 (C–H), 126.18 (C–H), 126.39 (C–H), 126.53 (C), 126.62 (C–H), 126.72 (C–H), 127.36 (C–H), 127.44 (C–H), 127.94 (C–H), 128.31 (C–H), 128.57 (C), 128.77 (C–H), 129.85 (C), 130.12 (C), 132.69 (C), 133.14 (C), 133.47 (C), 135.47 (C), 145.59 (C), 146.75 (C–H), 156.61 (C–O); ESI-MS: m/z = 360.1 ([M+H]$^+$); HRMS (MALDI-TOF) calcd for $C_{26}H_{18}NO$ [M+H]$^+$: 360.1388. Found: 360.1380.
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16. *Selected spectral data for (P)-(+)-3-aza-14-methoxyhexahelicene* **3** (>99% ee): pale yellow solid; mp = 243–245 °C; $[\alpha]_D$ +1363 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm): 3.87 (s, 3H, OCH_3), 6.41 (dd, J_1 = 3 Hz, J_2 = 9.5 Hz, 1H, H-15), 7.23 (d, J = 2.5 Hz, 1H, H-13), 7.36 (d, J = 6.3 Hz, 1H, H-2), 7.46 (d, J = 9 Hz, 1H, H-16), 7.85 (d, J = 6.3 Hz, 1H, H-1), 7.92 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 8.00–8.04 (m, 4H), 8.09 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H), 9.23 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 55.20 (OCH_3), 107.34 (C-13), 116.17 (C-15), 120.10 (C-2), 123.88 (C), 124.72 (C), 125.91 (CH), 125.98 (C and CH), 126.34 (C), 126.68 (CH), 127.06 (CH), 127.61 (C), 127.82 (CH), 127.88 (CH), 127.95 (CH), 128.91 (C-16), 128.96 (CH), 130.57 (C), 133.07 (C), 133.30 (C), 133.42 (C), 133.77 (C), 142.78 (C-1), 151.33 (C-4), 157.54 (C-14); ESI-MS: m/z = 360.1 [M+H]$^+$; HRMS (MALDI-TOF) calcd for $C_{26}H_{18}NO$ [M+H]$^+$: 360.1388. Found: 360.1382.
(M)-(−)-3-Aza-14-methoxyhexahelicene **3** (>99% ee): pale yellow solid; mp = 242–244 °C; $[\alpha]_D$ −1373 (*c* 0.20, CH_2Cl_2); ESI-MS: m/z = 360.1 [M+H]$^+$.
17. Determination of % ee was accomplished using the following analytical conditions. Column: Chiralcel OD (250 × 4.6 mm); mobile phase: *n*-C_6H_{14}/2-propanol = 80/20 v/v; flow rate 1.0 mL min^{-1}; temperature 303; detection: UV, λ = 270 nm; retention times of the two enantiomers were: 10.054 and 11.999 (the enantiomer exhibiting negative optical rotation (−) was the first to be eluted).
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19. *Selected spectral data for (P)-(+)-3-aza-14-hydroxyhexahelicene* **10** (>99% ee): pale yellow solid; mp >300 °C; $[\alpha]_D$ +1551 (*c* 0.30, MeOH); ^{1}H NMR (selected data, 300 MHz, CD_3OD): δ (ppm): 6.16 (dd, J_1 = 9 Hz, J_2 = 2.4 Hz, 1H, H-15), 7.08 (d, J = 2.4 Hz, 1H, H-13), 7.13 (d, J = 9 Hz, 1H, H-16), 7.32 (d, J = 5.7 Hz, 1H, H-2), 7.59 (br s, 1H, H-1), 7.74 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H); 8.05 (d, J = 8.4 Hz, 1H); 8.10 (d, J = 8.1 Hz, 1H); 8.13 (d, J = 8.4 Hz, 1H), 9.18 (s, 1H, H-4); ^{13}C NMR (selected data, 75 MHz, CD_3OD): δ (ppm): 111.88 (C-13), 117.60 (C-15), 123.01 (CH), 124.95 (C), 125.35 (C), 127.22 (C), 127.29 (CH), 127.38 (CH), 128.12 (CH), 128.49 (CH), 128.89 (C), 129.34 (2CH), 129.99 (CH), 130.14 (CH), 131.15 (CH), 131.88 (CH), 132.41 (CH), 135.30 (C), 135.75 (C), 135.89 (C), 136.73 (C), 139.77 (C), 150.68 (C), 157.25 (C-14); ESI-MS: m/z = 346.1 [M+H]$^+$.
(M)-(−)-3-Aza-14-hydroxyhexahelicene **10** (>99% ee): pale yellow solid; mp >300 °C; $[\alpha]_D$ −1559 (*c* 0.30, MeOH); ESI-MS: m/z = 346.1 [M+H]$^+$.
20. *Analytical conditions are as follows*. Column: Chiralcel OD (250 × 4.6 mm); mobile phase: *n*-C_6H_{14}/2-propanol = 90/10 v/v; flow rate 1.0 mL min^{-1}; temperature 303; detection: UV, λ = 270 nm; retention times of the two enantiomers were: 14.903 and 18.374 (the enantiomer exhibiting negative optical rotation (−) was the first to be eluted).