

MODIFIED SYNTHESIS OF HEPTAHELICENE AND ITS RESOLUTION INTO SINGLE ENANTIOMERS

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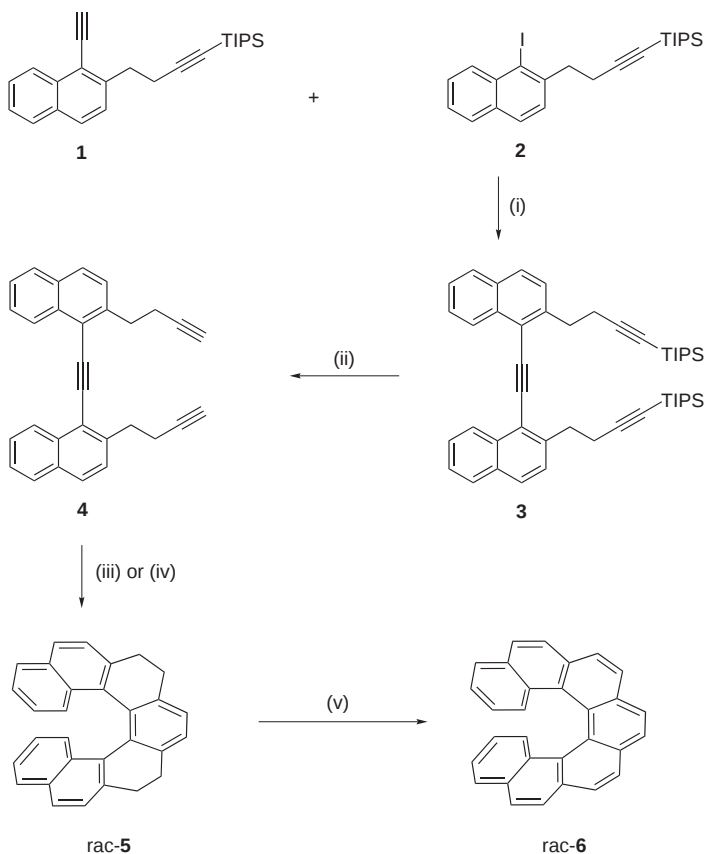
Dedicated to Professor Antonín Holý on the occasion of his 70th birthday.

A practical synthesis of racemic heptahelicene has been developed being based on key [2+2+2] cycloisomerization of bis[2-(but-3-yn-1-yl)-1-naphthyl]acetylene under $\text{CpCo(CO)}_2/\text{PPh}_3$ or $\text{CpCo(C}_2\text{H}_4)_2$ catalysis. The application of the Ni(cod)_2 catalyst with $(-)-(S_a)-(2'-\text{methoxy-1,1'-binaphthalen-2-yl})\text{diphenylphosphane}$ resulted in enantioselective triyne cyclization to provide (+)-7,8,11,12-tetrahydroheptahelicene in 40% ee. Optically pure $(-)-(M)-$ and optically highly enriched $(+)-(P)-$ heptahelicene were obtained on a milligram scale by resolution of racemate by chiral HPLC on a semipreparative Whelk-O1 column.

Keywords: Helicenes; Heptahelicene; Alkynes; Triynes; Cycloisomerization; Cobalt catalysis; Nickel catalysis; Enantioselective catalysis; Racemate resolution; Chiral HPLC.

In analogy to CD spectroscopy at UV/VIS/IR wavelengths, we propose to measure the CD spectra of chiral organic molecules at X-ray wavelengths (X-ray natural CD, or XNCD), where well defined carbon $1s \rightarrow p^*$ transitions occur. Advances in synchrotron technology, particularly the development of elliptically polarized undulators, make sensitive X-ray CD measurements possible. X-ray CD spectroscopy has been extensively studied for magnetic CD spectroscopy. Ab initio calculations predict the X-ray CD anisotropy to be small¹ and, to date, measurements have been elusive on small molecules such as methyloxirane² and amino acids³. We have chosen carbohelicenes as targets for the XNCD experiments. These species have a series of shape, narrow carbon $1s \rightarrow p^*$ transitions with a chiral orbital character that are ideal for measuring the XNCD effect.

For practical reasons, we have decided to deal with heptahelicene (**6**) (Scheme 1) which is, along with its [5]helicene and [6]helicene congeners, the icon of helicene chemistry⁴. Notably, nonracemic heptahelicene exhibits a good configurational stability which manifests itself by the 41.7 kcal/mol barrier to racemization⁵. This attribute is suggested to allow for thermal deposition of (+)-(*P*)- or (–)-(*M*)-**6** on a solid phase without a configurational scrambling.



- (i) **1** (1.2 equiv.), **2** (1.0 equiv.), Pd(PPh₃)₄ (5%), CuI (10%), *i*-Pr₂NH, 80 °C, 1.5 h, 82%;
 (ii) Bu₄NF (2.4 equiv.), THF, r.t., 20 min, 65%; (iii) CpCo(CO)₂ (20%), PPh₃ (40%), decane, halogen lamp, 140 °C, 2 h, 64%; (iv) CpCo(C₂H₄)₂ (20%), THF, r.t., 20 min, 64%;
 (v) Ph₃CBF₄ (3.4 equiv.), 1,2-dichloroethane, 80 °C, 20 h, 90%

SCHEME 1
Synthesis of *rac*-heptahelicene **6**

Since its first synthesis by Martin in 1967 using the photodehydrocyclization methodology⁶, several other nonphotochemical approaches have appeared in the literature⁷. However, all of them provided heptahelicene **6** in racemic form and, therefore, its asymmetric synthesis has remained an unsolved problem⁸. Thus, the only methodologies leading to nonracemic **6** (ref.⁹) have been mechanical separation of enantiomeric crystals of a conglomerate¹⁰ or an HPLC resolution on a chiral stationary phase¹¹. Herein, we report a modified synthesis of *rac*-**6**, an attempt at applying enantioselective catalysis to get a nonracemic helical backbone, and resolution of *rac*-**6** into enantiomers on a semipreparative scale using HPLC on a Whelk O1 chiral semipreparative column.

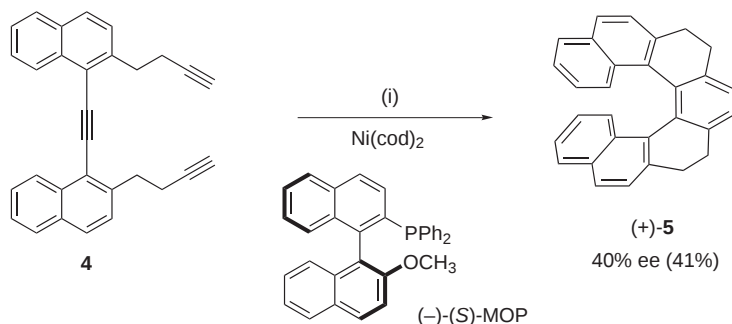
RESULTS AND DISCUSSION

We have recently proved that helically chiral molecules can be synthesized in a general and efficient way using intramolecular [2+2+2] cycloisomerization of aromatic triynes¹². Earlier, taking advantage of this methodology, we prepared *rac*-**6** by cyclizing an appropriate *cis,cis*-dienetriyne^{7a}. In this case the key [2+2+2] cycloisomerization led directly to the fully aromatic helical backbone. However, there might be an alternative which does not involve the above mentioned *cis,cis*-dienetriyne that exhibited only moderate stability. Therefore, we have turned our attention to tetrahydroheptahelicene *rac*-**5** representing a direct precursor of *rac*-**6** (Scheme 1) that we prepared earlier^{12c,12d}.

To prepare triyne **3** (refs^{12c,12d}), we have developed a different synthesis scheme circumventing the Sonogashira coupling of **2** with gaseous acetylene. Although such an approach to **3** is the most straightforward, the coupling reaction might not be clean and the preparative yield might vary. Accordingly, we have chosen a complementary process starting from known diyne **1** (ref.^{12b}) and iodide **2** (ref.¹³). Under Pd⁰/Cu^I catalysis, a clean reaction took place affording triyne **3** in high yield. The following TBAF-assisted removal of triisopropylsilyl groups provided key triyne **4** in good yield. We published earlier that [2+2+2] cycloisomerization of **4** can be catalyzed by CpCo(CO)₂ in the presence of PPh₃ under concomitant irradiation with visible light at 140 °C to afford tetrahydroheptahelicene *rac*-**5** in 64% yield^{12c}. To find a more reactive catalyst enabling us to shorten the reaction period, to decrease the reaction temperature and to increase the preparative yield, we decided to use the Jonas catalyst CpCo(C₂H₄)₂ (ref.¹⁴). Indeed, this cobalt complex showed superior reactivity when cyclizing **4** to *rac*-**5** at room temperature within 20 min but the yield was the same as

with CpCo(CO)_2 . Finally, the synthesis of *rac*-heptahelicene **6** was completed by smooth aromatization of *rac*-**5** with trityl cation which has been found earlier to be a reagent of choice to aromatize tetrahydrohelicenes^{12b}.

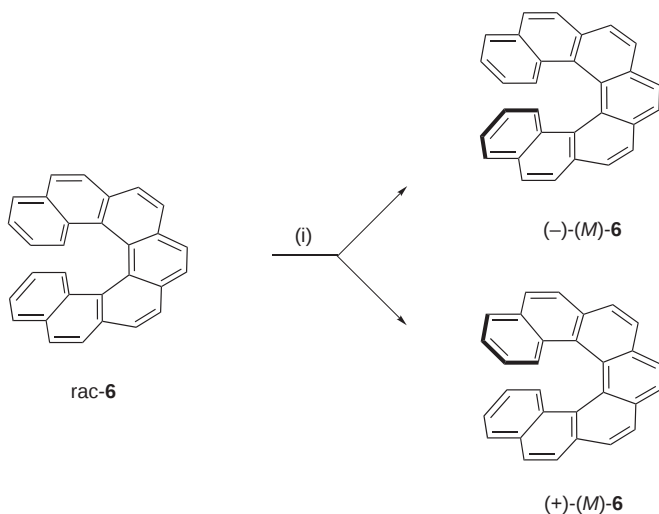
As far as nonracemic heptahelicene **6** is concerned, we have proposed first to explore enantioselective [2+2+2] cycloisomerization to control the helicity sense of precursor **5**. Stemming from successful catalytic experiments in the tetrahydrohexahelicene series, where we obtained moderate enantioselectivities^{12b,12d}, we used Ni(cod)_2 as a catalyst and Hayashi's monodentate binaphthyl-derived phosphine MOP¹⁵ as a chirality inducer in enantioselective cyclization of **4** (Scheme 2). Although we monitored promising 40% ee in favor of (+)-**5**, such an enantioselectivity level



(i) Ni(cod)_2 (20%), (-)-(S)-MOP (40%), THF, r.t., 1.5 h

SCHEME 2
Asymmetric synthesis of (+)-7,8,11,12-tetrahydroheptahelicene

achieved was not sufficient to use this method for producing optically pure heptahelicene **6**. Thus, we paid attention to the heptahelicene racemate resolution into enantiomers by liquid chromatography on a chiral stationary phase (Scheme 3). For this purpose we used commercially available semi-preparative (*R,R*)-Whelk-O1 column in combination with an automated preparative HPLC system. As the resolution of single enantiomers of *rac*-**6** did not proceed entirely down to the base line and, therefore, a higher column loading was not possible, multiple injections of *rac*-**6** were necessary to get optically pure or optically highly enriched (-)-(*M*)-**6** (>99% op) and (+)-(*P*)-**6** (92% op), respectively (Fig. 1).



(i) HPCL separation on semipreparative (*R,R*)-Whelk-O1 column (250 x 10mm, 5 μ m), heptane, automated repeated 0.5–0.7 mg injections of *rac*-6, 43% of *(-)-(M)*-6 (>99% op), 40% of *(+)-(M)*-6 (92% op)

SCHEME 3

Resolution of *rac*-heptahelicene to single enantiomers via chiral HPLC

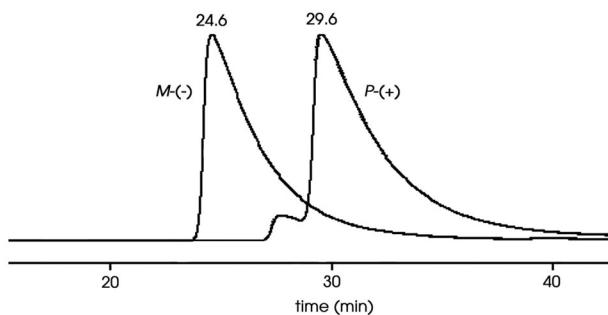


FIG. 1

Chromatographic analyses *(-)-(M)*-6 and *(+)-(P)*-6 after resolution. Resolution of *rac*-6 into *(-)-(M)*-6 and *(+)-(P)*-6 enantiomers by chiral HPLC on an (*R,R*)-Whelk-O1 column (250 $\times$ 4.6 mm, 5 μ m, *n*-heptane, 1.0 ml/min, 25 $^{\circ}$ C, UV detector)

Summarizing, we have developed a practical synthesis of racemic heptahelicene which is based on key [2+2+2] cycloisomerization of aromatic triyne under Co^{I} catalysis. The application of the Ni^0 catalyst bearing chiral monophosphine ligands resulted in enantioselective triyne cyclization to provide tetrahydroheptahelicene (+)-**5** in moderate enantiomeric excess. Optically pure heptahelicene (–)-(*M*)-**6** and optically highly enriched (+)-(*P*)-**6** were obtained on a milligram scale by resolution of *rac*-**6** by semipreparative HPLC on a chiral column. The XNCD experiments with non-racemic heptahelicene are currently in progress.

EXPERIMENTAL

General

^1H NMR spectra were measured at 200.0, 499.8 or 500.13 MHz, ^{13}C NMR spectra at 125.7 MHz, in CDCl_3 with TMS as an internal standard. Chemical shifts are given in ppm (δ -scale), coupling constants (*J*) in Hz. Compounds **1** (ref.^{12b}), **2** (ref.¹³), and (–)-(*S*)-MOP (ref.¹⁵) were prepared according to the literature procedures. Commercially available reagent grade materials were used as received. Solid $\text{Ni}(\text{cod})_2$ (Sigma–Aldrich) and Jonas catalyst, $\text{CpCo}(\text{C}_2\text{H}_4)_2$ (ref.¹⁴), were handled in a glovebox. Decane and diisopropylamine were degassed by three freeze-pump-thaw cycles before use; 1,2-dichloroethane was distilled from calcium hydride under argon; THF was freshly distilled from sodium/benzophenone under nitrogen. TLC was performed on Silica gel 60 F_{254} -coated aluminium sheets (Merck) and spots were detected with a solution of $\text{Ce}(\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$ (1%) and $\text{H}_3\text{P}(\text{Mo}_3\text{O}_{10})_4$ (2%) in sulfuric acid (10%). Flash chromatography was performed on Silica gel 60 (0.040–0.063 mm or <0.063 mm, Merck) or on Biotage KP-Sil® Silica cartridges (0.040–0.063 mm) used in Horizon® or Sp1® HPFC system (Biotage, Inc.). HPLC separations on a chiral semipreparative (*R,R*)-Whelk-O1 column (250 × 10 mm, 5 μm , Merck) were performed with the Agilent 1100 system equipped with a UV detector, autosampler and fraction collector. Enantiomeric excess of (+)-**5** was determined by chiral HPLC on a (*R,R*)-Whelk-O1 column (250 × 4.6 mm, 5 μm , *n*-heptane, 1.0 ml/min, 25 °C) while optical purity of (–)-(*M*)-**6** and (+)-(*P*)-**6** was determined on a Chiralcel OD-H column (250 × 4.6 mm, *n*-heptane, 0.8 ml/min, 25 °C) using UV and polarimetric detectors.

Bis[2-[4-(triisopropylsilyl)but-3-yn-1-yl]-1-naphthyl]acetylene (**3**)

A Schlenk flask was charged with naphthyl diyne **1** (1.12 g, 3.11 mmol), naphthyl iodide **2** (1.58 g, 3.42 mmol, 1.1 equiv.), $\text{Pd}(\text{PPh}_3)_4$ (180 mg, 0.156 mmol, 5 mole %), CuI (59 mg, 0.310 mmol, 10 mole %), and flushed with argon. Diisopropylamine (50 ml) was added and the reaction mixture was stirred at 80 °C for 2 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel (petroleum ether–ether, 100:0 to 98:2) to obtain **3** (1.78 g, 82%) as an oil. ^1H NMR (200 MHz, CDCl_3) spectrum was in accord with the literature data¹³.

Bis[2-(but-3-yn-1-yl)-1-naphthyl]acetylene (**4**)

Following the literature procedure¹³, triyne **3** (690 mg, 1.80 mmol) in THF (15 ml) was desilylated with tetrabutylammonium fluoride (1.0 M solution in THF, 2.40 ml, 2.40 mmol, 2.4 equiv.) at room temperature within 20 min. Flash chromatography on silica gel (petroleum ether–ether, 100:0 to 98:2) gave triyne **4** (247 mg, 65%). ¹H NMR (200 MHz, CDCl₃) spectrum was in accord with the literature data¹³.

7,8,11,12-Tetrahydroheptahelicene (**5**)

A flask with triyne **4** (162 mg) was flushed with argon. The material was dissolved in THF (5 ml) and CpCo(C₂H₄)₂ (15 mg, 0.085 mmol, 20 mole %) in THF (2 ml) was added. The reaction mixture was stirred at room temperature for 40 min and evaporated to dryness in vacuo. Flash chromatography on silica gel (petroleum ether–ether, 100:0 to 98:2) provided tetrahydroheptahelicene **5** (104 mg, 64%) as an amorphous solid. ¹H NMR (200 MHz, CDCl₃) spectrum was in accord with the literature data^{12c}.

(+)–7,8,11,12-Tetrahydroheptahelicene (**5**)

A Schlenk flask was charged with (–)-(S)-MOP (9.3 mg, 0.020 mmol, 40 mole %), flushed with argon and the ligand was dissolved in THF (2 ml) at room temperature. Then a solution of Ni(cod)₂ (160 μl, 0.061 M in THF, 20 mole %) was added and the mixture was stirred for 5 min. Triyne **4** (19 mg, 0.050 mmol) in THF (1 ml) was added and the mixture was stirred at room temperature for 1.5 h. Volatiles were removed in vacuo and the residue was chromatographed on silica gel (petroleum ether–ether, 100:0 to 96:4) to obtain (+)-**5** (7.7 mg, 41%, 40% ee) as an amorphous solid.

Heptahelicene (**6**)

A Schlenk flask was charged with tetrahydroheptahelicene **5** (100 mg, 0.261 mmol) and trityl tetrafluoroborate (290 mg, 0.878 mmol, 3.4 equiv.) and flushed with argon. The materials were dissolved in 1,2-dichloroethane (13 ml) and the reaction mixture was stirred at 80 °C for 20 h. The mixture was diluted with 1,2-dichloroethane and washed with aqueous KHCO₃. The solution was dried over anhydrous Na₂SO₄ and evaporated to dryness. Flash chromatography on silica gel (petroleum ether–ether, 100:0 to 98:2) afforded heptahelicene **6** (89 mg, 90%) as an amorphous solid. ¹H NMR (200 MHz, deuteriochloroform) spectrum was in accord with the literature data^{7a}.

Resolution of *rac*-Heptahelicene into Enantiomers

Using a semipreparative (*R,R*)-Whelk-O1 column, multiple injections (0.5–0.7 mg portions in heptane) of racemic heptahelicene *rac*-**6** (35 mg) and reinjections of the not fully resolved fractions led to optically pure (–)-(M)-**6** (>99% op, 15 mg) and optically highly enriched (+)-(P)-**6** (92% op, 14 mg). (–)-(M)-**6**: [α]_D²⁵ –2276 (c 0.063, CHCl₃)¹⁶. (+)-(P)-**6**: [α]_D²⁵ +2231 (c 0.084, CHCl₃).

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16. Optical rotation of (–)-(M)-**6** published by Martin (ref.¹⁰, $[\alpha]_{579}^{25} -5900 \pm 200$, *c* 0.06, CHCl₃) is substantially higher than the value measured by us, despite the fact that we repeatedly checked the purity of (–)-(M)-**6** (purified by HPLC or recrystallized from heptane) by ¹H NMR and ¹³C NMR and enantiopurity by HPLC on a chiral column. The CD spectrum was in full agreement with the literature data.