MODIFIED SYNTHESIS OF HEPTAHELICENE AND ITS RESOLUTION INTO SINGLE ENANTIOMERS

Zuzana ALEXANDROVÁ[a1], Petr SEHNAL[a2], Irena G. STARÁ[a3,*], Ivo STARÝ[a4,*], David ŠAMAN[a5], Stephen G. URQUHART[b1] and Edwige OTERO[b]

a Center for Biomolecules and Complex Molecular Systems, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic; e-mail: [1] alexa@uochb.cas.cz, [2] sehnal@uochb.cas.cz, [3] stara@uochb.cas.cz, [4] stary@uochb.cas.cz, [5] saman@uochb.cas.cz

b Department of Chemistry, University of Saskatchewan, Saskatoon SK S7N 5C9, Canada; e-mail: [1] stephen.urquhart@usask.ca

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A practical synthesis of racemic heptahelicene has been develeped being based on key [2+2+2] cycloisomerization of bis[2-(but-3-yn-1-yl)-1-naphthyl]acetylene under $CpCo(CO)_2/PPh_3$ or $CpCo(C_2H_4)_2$ catalysis. The application of the $Ni(cod)_2$ catalyst with (–)-(S_a)-(2′-methoxy-1,1′-binaphthalen-2-yl)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; Cycliosomerization; 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→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 small[1] and, to date, measurements have been elusive on small molecules such as methyloxirane[2] and amino acids[3]. We have chosen carbohelicenes as targets for the XNCD experiments. These species have a series of shape, narrow carbon 1s→p* transitions with a chiral orbital character that are ideal for measuring the XNCD effect.

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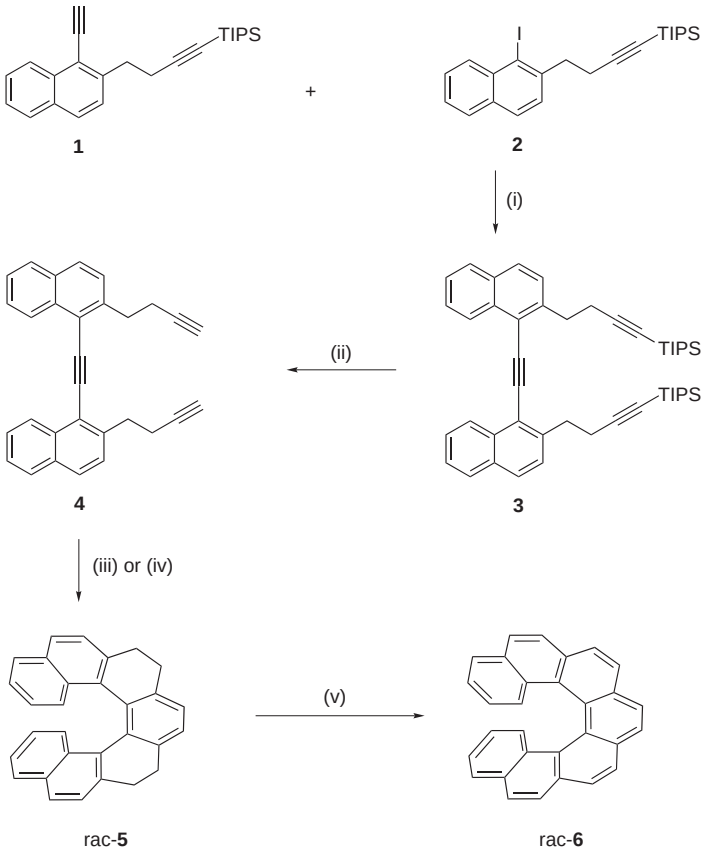
For practical reasons, we have decided to deal with heptahelicene (**6**) (Scheme 1) which is, along with its [5]helicene and [6]helicene congeners, the icon of helicene chemistry[4]. Notably, nonracemic heptahelicene exhibits a good configurational stability which manifests itself by the 41.7 kcal/mol barrier to racemization[5]. 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.), $Pd(PPh_3)_4$ (5%), CuI (10%), *i*-Pr_2NH, 80 °C, 1.5 h, 82%; (ii) Bu_4NF (2.4 equiv.), THF, r.t., 20 min, 65%; (iii) $CpCo(CO)_2$ (20%), PPh_3 (40%), decane, halogen lamp, 140 °C, 2 h, 64%; (iv) $CpCo(C_2H_4)_2$ (20%), THF, r.t., 20 min, 64%; (v) Ph_3CBF_4 (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 methodology[6], several other nonphotochemical approaches have appeared in the literature[7]. However, all of them provided heptahelicene **6** in racemic form and, therefore, its asymmetric synthesis has remained an unsolved problem[8]. Thus, the only methodologies leading to nonracemic **6** (ref.[9]) have been mechanical separation of enantiomeric crystals of a conglomerate[10] or an HPLC resolution on a chiral stationary phase[11]. 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.

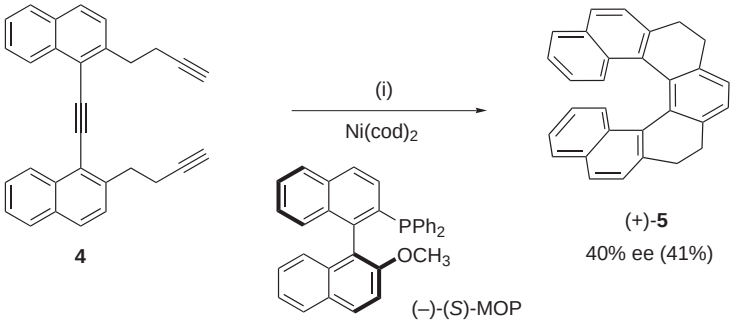
RESULTS AND DISCUSSION

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 triynes[12]. 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 Pd^0/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 PPh_3 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 $CpCo(C_2H_4)_2$ (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].

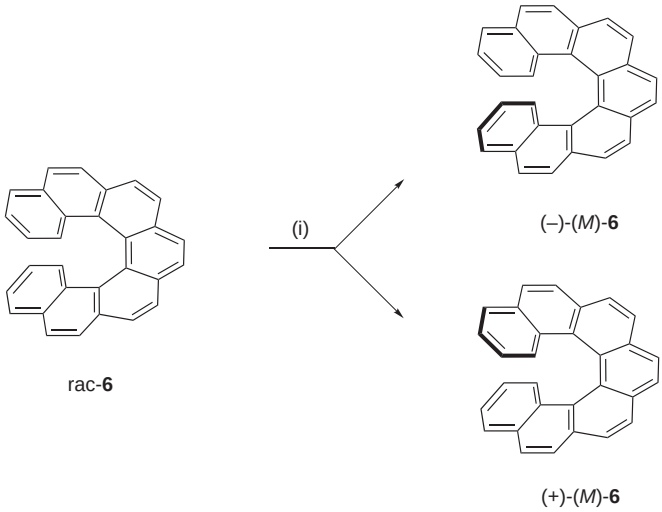
As far as nonracemic heptahelicene **6** is concerned, we have proposed first to explore enantioselective [2+2+2] cycloisomerization to control the helicity sense of precursor **5**. Stemming from successful catalytic experiments in the tetrahydrohexahelicene series, where we obtained moderate enantioselectivities[12b,12d], we used $Ni(cod)_2$ as a catalyst and Hayashi's monodentate binaphthyl-derived phosphine MOP[15] 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 μm), 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

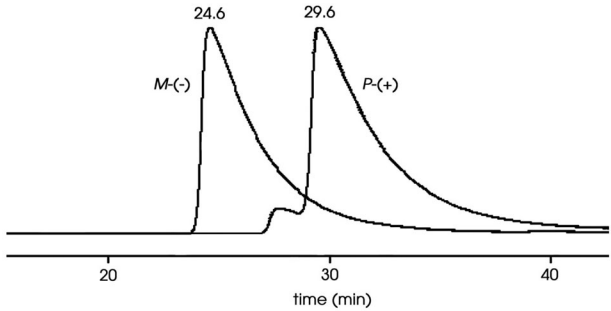


FIG. 1
Chromatographic analyses (–)-(*M*)-**6** and (+)-(*P*)-**6** after resolution. Resolution of *rac*-**6** into (–)-(*M*)-**6** and (+)-(*P*)-**6** enantiomers by chiral HPLC on an (*R*,*R*)-Whelk-O1 column (250 × 4.6 mm, 5 μm, *n*-heptane, 1.0 ml/min, 25 °C, UV detector)

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 nonracemic heptahelicene are currently in progress.

EXPERIMENTAL

General

^{1}H 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 $Ni(cod)_2$ (Sigma–Aldrich) and Jonas catalyst, $CpCo(C_2H_4)_2$ (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 $Ce(SO_4)_2 \cdot 4H_2O$ (1%) and $H_3P(Mo_3O_{10})_4$ (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.), $Pd(PPh_3)_4$ (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. ^{1}H NMR (200 MHz, $CDCl_3$) spectrum was in accord with the literature data[13].

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

Following the literature procedure[13], 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%). ^{1}H NMR (200 MHz, $CDCl_3$) spectrum was in accord with the literature data[13].

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 $CpCo(C_2H_4)_2$ (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. ^{1}H NMR (200 MHz, $CDCl_3$) 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 $KHCO_3$. The solution was dried over anhydrous Na_2SO_4 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. ^{1}H NMR (200 MHz, deuterochloroform) 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**: $[\alpha]_D^{25}$ –2276 (*c* 0.063, $CHCl_3$)[16]. (+)-(*P*)-**6**: $[\alpha]_D^{25}$ +2231 (*c* 0.084, $CHCl_3$).

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REFERENCES AND NOTES

1. Plashkevych O., Carravetta V., Vahtras O., Agren H.: *Chem. Phys.* **1998**, *232*, 49.
2. Turchini S., Zema N., Zennaro S., Alagna L., Stewart B., Peacock R. D., Prosperi T.: *J. Am. Chem. Soc.* **2004**, *126*, 4532.
3. Prümper G., Viefhaus J., Cvejanović S., Rolles D., Gessner O., Lischke T., Hentges R., Wienberg C., Mahler W., Becker U., Langer B., Prosperi T., Zema N., Turchini S., Zada B., Senf F.: *Phys. Rev. A: At., Mol., Opt. Phys.* **2004**, *69*, 062717.
4. For selected reviews on helicenes, see: a) Urbano A.: *Angew. Chem., Int. Ed.* **2003**, *42*, 3986; b) Hopf H.: *Classics in Hydrocarbon Chemistry: Syntheses, Concepts, Perspectives*, p. 323. VCH, Weinheim 2000; c) Katz T. J.: *Angew. Chem., Int. Ed.* **2000**, *39*, 1921; d) Oremek G., Seiffert U., Janecka A.: *Chem.-Ztg.* **1987**, *111*, 69; e) Vögtle F.: *Fascinating Molecules in Organic Chemistry*, p. 156. Wiley, New York 1992; f) Meurer K. P., Vögtle F.: *Top. Curr. Chem.* **1985**, *127*, 1; g) Laarhoven W. H., Prinsen W. J. C.: *Top. Curr. Chem.* **1984**, *125*, 63.
5. Martin R. H., Marchant M. J.: *Tetrahedron* **1974**, *30*, 349.
6. a) El Abed R., Ben Hassine B., Genet J.-P., Gorsane M., Marinetti A.: *Eur. J. Org. Chem.* **2004**, 1517; b) Sudhakar A., Katz T. J.: *Tetrahedron Lett.* **1986**, *27*, 2231; c) Flammang-Barbieux M., Nasielski J., Martin R. H.: *Tetrahedron Lett.* **1967**, *8*, 743.
7. a) Collins S. K., Grandbois A., Vachon M. P., Cote J.: *Angew. Chem., Int. Ed.* **2006**, *45*, 2923; b) Teplý F., Stará I. G., Starý I., Kollárovič A., Šaman D., Rulíšek L., Fiedler P.: *J. Am. Chem. Soc.* **2002**, *124*, 9175; c) Gingras M., Dubois F.: *Tetrahedron Lett.* **1999**, *40*, 1309.
8. a) Nakano K., Hidehira Y., Takahashi K., Hiyama T., Nozaki K.: *Angew. Chem., Int. Ed.* **2005**, *44*, 7136; b) Carreno M. C., Gonzalez-Lopez M., Urbano A.: *Chem. Commun.* **2005**, 611; c) Miyasaka M., Rajca A., Pink M., Rajca S.: *Chem. Eur. J.* **2004**, *10*, 6531; d) Bernstein W. J., Calvin M., Buchardt O.: *J. Am. Chem. Soc.* **1972**, *94*, 494.
9. For chemical resolution of heptahelicene-like molecules, see: a) Thongpanchang T., Paruch K., Katz T. J., Rheingold A. L., Lam K.-C., Liable-Sands L.: *J. Org. Chem.* **2000**, *65*, 1850; b) Paruch K., Katz T. J., Incarvito C., Lam K.-C., Rhatigan B., Rheingold A. L.: *J. Org. Chem.* **2000**, *65*, 7602.
10. Martin R. H., Marchant M. J.: *Tetrahedron* **1974**, *30*, 343.
11. a) Bürgi T., Urakawa A. Behzadi B., Ernst K.-H., Baiker A.: *New J. Chem.* **2004**, *28*, 332; b) Kim Y. H., Tishbee A., Gil-Av E.: *J. Am. Chem. Soc.* **1980**, *102*, 5915; c) Mikeš F., Boshart G.: *J. Chromatogr.* **1978**, *149*, 455; d) Lochmueller C. H., Ryall R. R.: *J. Chromatogr.* **1978**, *150*, 511.
12. a) Stará I. G., Alexandrová Z., Teplý F., Sehnal P., Starý I., Šaman D., Buděšínský M., Cvačka J.: *Org. Lett.* **2005**, *7*, 2547; b) Teplý F., Stará I. G., Starý I., Kollárovič A., Šaman D., Fiedler P., Vyskočil Š.: *J. Org. Chem.* **2003**, *68*, 5193; c) Stará I. G., Starý I., Kollárovič A., Teplý F., Šaman D., Fiedler P.: *Collect. Czech. Chem. Commun.* **2003**, *68*, 917; d) Stará I. G., Starý I., Kollárovič A., Teplý F., Vyskočil Š., Šaman D.: *Tetrahedron*

Lett. **1999**, *40*, 1993; e) Stará I. G., Starý I., Kollárovič A., Teplý F., Šaman D., Tichý M.: *J. Org. Chem.* **1998**, *63*, 4046.

13. Stará I. G., Kollárovič A., Teplý F., Starý I., Šaman D., Fiedler P.: *Collect. Czech. Chem. Commun.* **2000**, *65*, 577.
14. a) Cammack J. K., Jalisatgi S., Matzger A. J., Negrón A., Vollhardt K. P. C.: *J. Org. Chem.* **1996**, *61*, 4798; b) Jonas K., Deffense E., Habermann D.: *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 716; c) Jonas K., Deffense E., Habermann D.: *Angew. Chem. Suppl.* **1983**, 1005.
15. Uozumi Y., Tanahashi A., Lee S.-Y., Hayashi T.: *J. Org. Chem.* **1993**, *58*, 1945.
16. Optical rotation of (–)-(*M*)-**6** published by Martin (ref.[10], $[\alpha]_{579}^{25}$ –5900 ± 200, *c* 0.06, $CHCl_3$) 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 ^{13}C NMR and enantiopurity by HPLC on a chiral column. The CD spectrum was in full agreement with the literature data.