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Asymmetric Synthesis of [7]Helicene-Like Molecules†

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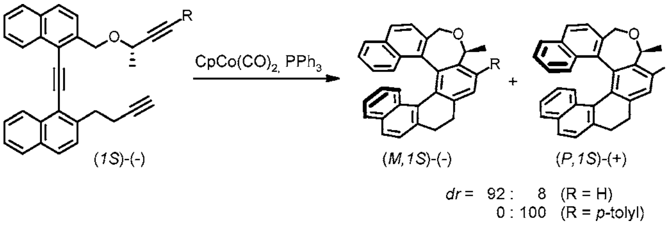
ABSTRACT



A new approach to nonracemic [7]helicene-like molecules has been developed. Stereoselective Co^I-mediated [2 + 2 + 2] cycloisomerization of aromatic triynes containing an asymmetric carbon atom produces [7]helicene-like scaffolds in diastereomeric ratios up to 100:0. This central-to-helical chirality transfer can be controlled by the absolute configuration at the asymmetric center and by the presence of carbon substituents.

Helicenes[1] possess two primary attributes: they are both unique nonplanar aromatic systems and inherently chiral molecules. While the former feature is expected to be beneficial primarily within the realm of future molecular devices,[2] the latter requires dealing with nonracemic helicenes in many areas of their recent[3] or proposed use. Focusing mostly on chirality aspects and utilization, π-conjugation over the whole molecule might not be essential provided that a not fully aromatic helicene congener mimics the helicene scaffold.

Many different routes have already been explored to produce enantiomerically enriched or pure helicenes.[4] Even classical photodehydrocyclization of stilbene-type precursors can be carried out in an amazing stereoselective fashion. This was successfully demonstrated by the pioneering works of Martin[5] and Katz[6] who used stereocenter(s) external or internal to the helix to control the stereoselectivity of helicene

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† Dedicated to Dr. J. Závada on the occasion of his 70th birthday.

(1) For selected reviews, see: (a) Urbano, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3986. (b) Hopf, H. *Classics in Hydrocarbon Chemistry: Syntheses, Concepts, Perspectives*; VCH: Weinheim, 2000; Chapter 12.2, p 323. (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*; Wiley: New York, 1992; p 156. (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.

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(3) For pioneering exploitations of helicenes in enantioselective catalysis, see: (a) Nakano, D.; Yamaguchi, M. *Tetrahedron Lett.* **2003**, *44*, 4969. (b) Sato, I.; Yamashima, R.; Kadowaki, K.; Yamamoto, J.; Shibata, T.; Soai, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1096. (c) Dreher, S. D.; Katz, T. J.; Lam, K. C.; Rheingold, A. L. *J. Org. Chem.* **2000**, *65*, 815. (d) Reetz, M. T.; Sostmann, S. *J. Organomet. Chem.* **2000**, *603*, 105. (e) Reetz, M. T.; Beuttenmuller, E. W.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 3211.

(4) For recent leading references, see: (a) Laleu, B.; Mobian, P.; Herse, C.; Laursen, B. W.; Hopfgartner, G.; Bernardinelli, G.; Lacour, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1879. (b) Carreno, M. C.; Gonzales-Lopez, M.; Urbano, A. *Chem. Commun.* **2005**, 611. (c) Miyasaka, M.; Rajca, A.; Pink, M.; Rajca, S. *Chem. Eur. J.* **2004**, *10*, 6531. (d) Rajca, A.; Miyasaka, M.; Pink, M.; Wang, H.; Rajca, S. *J. Am. Chem. Soc.* **2004**, *126*, 15211. (e) El Abed, R.; Ben Hassine, B.; Genet, J. P.; Gorsane, M.; Madec, J.; Ricard, L.; Marinetti, A. *Synthesis* **2004**, 2513. (f) Nakano, D.; Hirano, R.; Yamaguchi, M.; Kabuto, C. *Tetrahedron Lett.* **2003**, *44*, 3683. (g) Ogawa, Y.; Toyama, M.; Karikomi, M.; Seki, K.; Haga, K.; Uyehara, T. *Tetrahedron Lett.* **2003**, *44*, 2167. (h) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A. *Chem. Eur. J.* **2003**, *9*, 4118. (i) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A. *J. Am. Chem. Soc.* **2001**, *123*, 7929. (j) Reetz, M. T.; Sostmann, S. *Tetrahedron* **2001**, *57*, 2515. (k) Thongpanchang, T.; Paruch, K.; Katz, T. J.; Rheingold, A. L.; Lam, K. C.; Liablesands, L. *J. Org. Chem.* **2000**, *65*, 1850. (l) Tanaka, K.; Osuga, H.; Suzuki, H.; Shogase, Y.; Kitahara, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 935. (m) Tanaka, K.; Suzuki, H.; Osuga, H. *J. Org. Chem.* **1997**, *62*, 4465. See also refs 7a,d.

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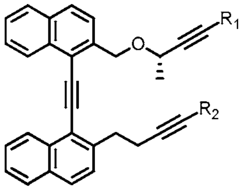
cyclizations. Despite the astonishing results achieved so far, there is a need for developing alternative methods for obtaining optically pure helicenes or helicene-like molecules. In this preliminary report, we describe a new approach to nonracemic helical scaffolds that takes advantage of the highly stereoselective Co^I-mediated [2 + 2 + 2] cycloisomerization of aromatic triynes.

A similar alkyne cyclization method has already been proven to be a reliable synthetic tool for constructing racemic helicenes and helicene-like compounds,[7] including Vollhardt heliphenes.[8] The first attempts at controlling helicity by asymmetric catalysis have been described and moderate enantioselectivities achieved,[7a,d] but this approach is still far from practical. Accordingly, we have focused on asymmetric synthesis using a chiral pool. Having been inspired by helicene-related papers by Martin and Katz and, generally, by papers by Lehn,[9a] Wulff,[9b] and Yashima,[9c] who described successful intramolecular central-to-helical chirality transfers, we proposed that the analogous stereocontrol in [2 + 2 + 2] cycloisomerization of aromatic triynes might result in nonracemic helical targets. There are many examples of intramolecular Co^I-mediated [2 + 2 + 2] enediyne cycloisomerizations or analogous intermolecular reactions of related systems described in the literature manifesting good to excellent diastereoselectivity.[7e,10] However, to the best of our knowledge, such a diastereoselective organometallic approach to nonracemic helicene-like molecules has never been systematically studied.

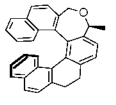
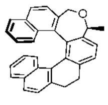
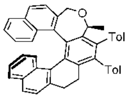
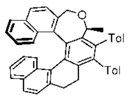
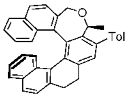
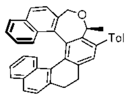
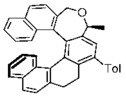
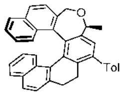
Initially, using the modular and convergent approach,[11] we prepared a complementary set of unsubstituted/*p*-tolyl-substituted triynes (1*S*)-(−)-**1**−**4** (Figure 1). To assess the feasibility of the proposed stereoselective cyclization, triyne (1*S*)-(−)-**1** was treated with a stoichiometric amount of Ni^0 complex (Table 1, entry 1). The expected product was formed in low yield but with reasonable diastereoselectivity in favor of (*M*,1*S*)-(−)-**5**. Application of a Co^I complex slightly improved the yield but led to a substantial decrease in the diastereomeric ratio (Table 1, entry 2).



(1*S*)-(-)-**1** R$_1$ = R$_2$ = H
(1*S*)-(-)-**2** R$_1$ = R$_2$ = Tol
(1*S*)-(-)-**3** R$_1$ = Tol, R$_2$ = H
(1*S*)-(-)-**4** R$_1$ = H, R$_2$ = Tol Tol = *p*-tolyl

Figure 1.

Table 1. Diastereoselective [2 + 2 + 2] Cycloisomerization[12]

entry	educt	cond.^{a} (°C, h)	products^b	yield (%)^c
1	(1*S*)-**1**	A rt, 0.1	 (*M*,1*S*)-(-)-**5**  (*P*,1*S*)-**5** 84:16	16
2	(1*S*)-**1**	B 95°, 60	(*M*,1*S*)-(-)-**5** (*P*,1*S*)-**5** 60:40	25
3	(1*S*)-**1**	C^d 95°, 60	(*M*,1*S*)-(-)-**5** (*P*,1*S*)-**5** 92:8 ($[\alpha]_D$ -674 for *dr*=100:0)	60
4	(1*S*)-**2**	C 95°, 63	 (*M*,1*S*)-**6**  (*P*,1*S*)-(+)-**6** 0:100 ($[\alpha]_D$ +43)	63
5	(1*S*)-**3**	C 120°, 70	 (*M*,1*S*)-**7**  (*P*,1*S*)-(+)-**7** 0:100 ($[\alpha]_D$ +199)	66
6	(1*S*)-**4**	C 120°, 40	 (*M*,1*S*)-(-)-**8**  (*P*,1*S*)-**8** 86:14 ($[\alpha]_D$ -241)	95

[a] A: Ni(cod)$_2$ (1.0 equiv), PPh$_3$ (2.0 equiv), THF. B: CpCo(CO)$_2$ (1.0 equiv), dioxane. C: CpCo(CO)$_2$ (1.0 equiv), PPh$_3$ (2.0 equiv), dioxane. [b] Sense of optical rotation is indicated only if it was measured for a diastereomerically pure or highly enriched compound; the values of optical rotation measured for the diastereomer ratios are indicated. [c] Isolated. [d] Irradiated with a halogen lamp.

Interestingly, we observed high diastereoselectivity and good chemical yield of the cyclization of triyne (1*S*)-(−)-**1** when employing the Co^I complex together with triphenylphosphine (Table 1, entry 3). Both diastereomers, major (*M*,1*S*)-(−)-**5** and minor (*P*,1*S*)-**5**, could be separated by a careful flash chromatography on silica gel. However, such a procedure would be impractical on a preparative scale, as only the partial resolution of corresponding peaks can be achieved by a single chromatography procedure. Therefore, we aimed at further increasing the diastereoselectivity of the cyclization.

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(7) For recent examples of [2 + 2 + 2] cycloisomerization of triynes used in the synthesis of helicenes or helicene-like molecules, see: (a) Teplý, F.; Stará, I. G.; Starý, I.; Kollárovič, A.; Šaman, D.; Vyskočil, Š.; Fiedler, P. *J. Org. Chem.* **2003**, *68*, 5193. (b) Stará, I. G.; Starý, I.; Kollárovič, A.; Teplý, F.; Šaman, D.; Fiedler, P. *Collect. Czech. Chem. Commun.* **2003**, *68*, 917. (c) Teplý, F.; Stará, I. G.; Starý, I.; Kollárovič, A.; Šaman, D.; Rulíšek, L.; Fiedler, P. *J. Am. Chem. Soc.* **2002**, *124*, 9175. (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.

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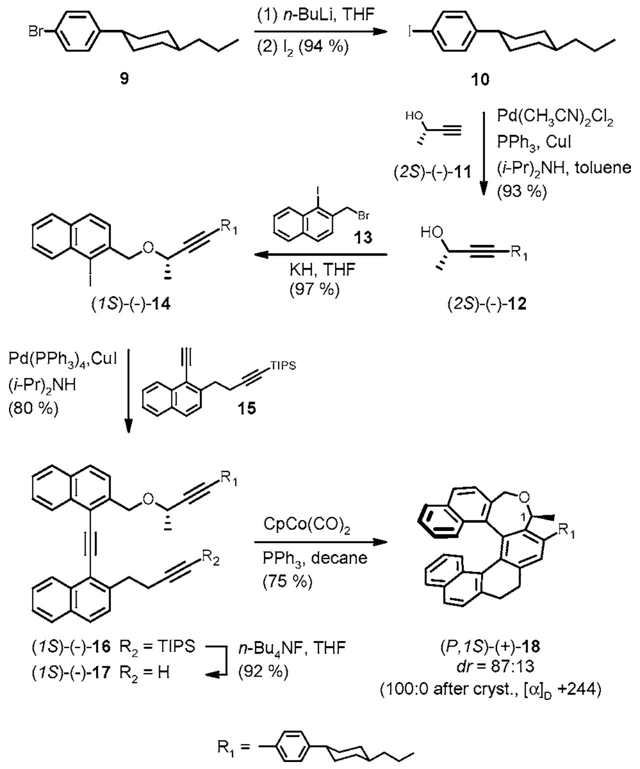
We assumed that attaching more bulky substituents to pendant acetylene units of (1*S*)-(−)-**1** might lead to a more congested transition state being decisive for the stereochemical outcome. Actually, the cyclization of triyne (1*S*)-(−)-**2** bearing two *p*-tolyl groups exclusively furnished diastereomer (*P*,1*S*)-(+)-**6** in good yield. To our surprise, its helicity was opposite, although we maintained absolute stereochemistry at the governing asymmetric center (Table 1, cf. entries 3 and 4).

The reactivity of the complementary triynes (1*S*)-(−)-**3** and (1*S*)-(−)-**4** told us which of the *p*-tolyl groups was responsible for the stereoselectivity improvement and/or the dramatic change of the helicity sense. While (1*S*)-(−)-**3** behaved almost identically to (1*S*)-(−)-**2**, producing only (*P*,1*S*)-(+)-**7** (Table 1, cf. entries 4 and 5), (1*S*)-(−)-**4** followed the reactivity of (1*S*)-(−)-**1** (Table 1, cf. entries 3 and 6), giving major (*M*,1*S*)-(−)-**8** along with minor (*P*,1*S*)-**8**.

The helicity assignment of compounds **5**−**8** requires an explanation. The absolute stereochemistry at the chiral center was known, as the syntheses of **1**−**4** and, consequently, **5**−**8** started from optically pure commercially available (2*S*)-(−)-**11** (Scheme 1), leaving the chiral center untouched. The task was to determine the diastereomeric relationship between the asymmetric center and the helical backbone in **5**−**8**. The ROESY ^{1}H NMR experiments enabled unequivocal handedness assignment of helices further supported by CD spectra, vide infra.

Scheme 1



First, we compared the ROESY spectra of diastereomerically pure (*M*,1*S*)-(−)-**5** and enriched (*P*,1*S*)-**5**. In the case of (*M*,1*S*)-(−)-**5**, a through-space interaction between 1-CH$_3$ and 19-H was observed, but no interaction between 1-H and 19-H was observed (Figure 2). In contrast, (*P*,1*S*)-**5** exhibited an interaction between 1-H and 19-H but no interaction between 19-H and 1-CH$_3$. This is in full agreement with corresponding models and relevant proton distances. The helicity of (*M*,1*S*)-(−)-**8** was assigned in the same way.

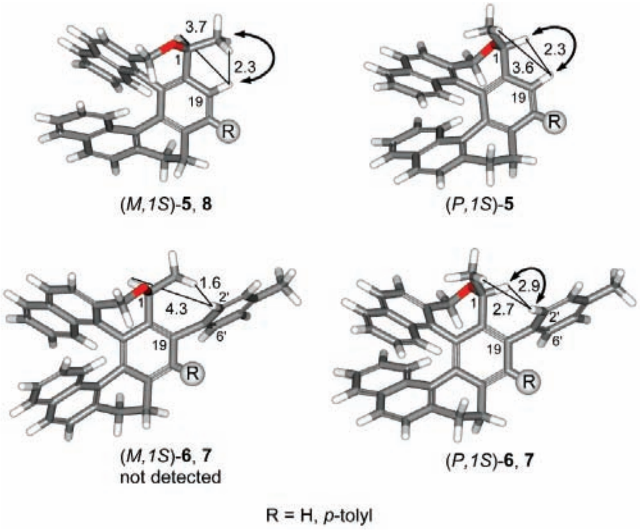


Figure 2. Approximate distances (in Å) between protons relevant for helicity assignment and observed ^{1}H−^{1}H correlations in ROESY ^{1}H NMR spectra (indicated by arrows).[13]

Similarly, in the case of 19-tolyl derivatives (*P*,1*S*)-(+)-**6** and (*P*,1*S*)-(+)-**7**, helicity assignment relied on the presence of a through-space interaction between 1-H and 2′,6′-H of the tolyl group and the absence of one between 1-CH$_3$ and the tolyl group. Moreover, the chemical shift of the 1-CH$_3$ signal was significant for (*M*)- and (*P*)-helicity. While doublets of corresponding "*exo*" 1-CH$_3$ groups appeared within a 1.58−1.67 ppm interval for (*M*)-helices, shielding the "*endo*" 1-CH$_3$ with a proximal naphthalene unit (adjacent to the dihydrooxepine ring) at the (*P*)-helices resulted in an

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(9) (a) Zarges, W.; Hall, J.; Lehn, J. M.; Bolm C. *Helv. Chim. Acta* **1991**, *74*, 1843. (b) Vorogushin, A. V.; Wulff, W. D.; Hansen, H.-J. *J. Am. Chem. Soc.* **2002**, *124*, 6512. This paper refers to central-to-axial chirality transfer. However, products described therein can be regarded also as small helices. (c) Maeda, K.; Morino, K.; Okamoto, Y.; Sato, T.; Yashima, E. *J. Am. Chem. Soc.* **2004**, *126*, 4329 and refs 8 and 9 cited therein.

(10) (a) Slowinski, F.; Aubert, C.; Malacria, M. *J. Org. Chem.* **2003**, *68*, 378. (b) Slowinski, F.; Aubert, C.; Malacria, M. *Eur. J. Org. Chem.* **2001**, 3491. (c) Pérez, D.; Siesel, B. A.; Malaska, M. J.; David, E.; Vollhardt, K. P. C. *Synlett* **2000**, 306. (d) Slowinski, F.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1999**, *40*, 5849. (e) Pelissier, H.; Rodriguez, J.; Vollhardt, K. P. C. *Chem. Eur. J.* **1999**, *5*, 3549. (f) Germanas, J.; Aubert, C.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 4006. (g) Johnson, E. P.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 381. (h) Boese, R.; Rodriguez, J.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 993. (i) Clinet, J.-C.; Duñach, E.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6710.

(11) Syntheses of triynes **1**−**4** have been published recently; see: Alexandrová, Z.; Stará, I. G.; Sehnal, P.; Teplý, F.; Starý, I.; Šaman, D.; Fiedler, P. *Collect. Czech. Chem. Commun.* **2004**, *69*, 2193. The preparation of (*P*,1*S*)-(+)-**18** (Scheme 1) illustrates in details the general synthesis strategy.

upfield shift of 1-CH_3 signals appearing within a 0.54−0.62 ppm range. The opposite helicity of (*M*,1*S*)-(−)-**5** versus (*P*,1*S*)-(+)-**6** is further shown by their CD spectra displaying an obvious pseudoenantiomeric relationship (Figure 3).

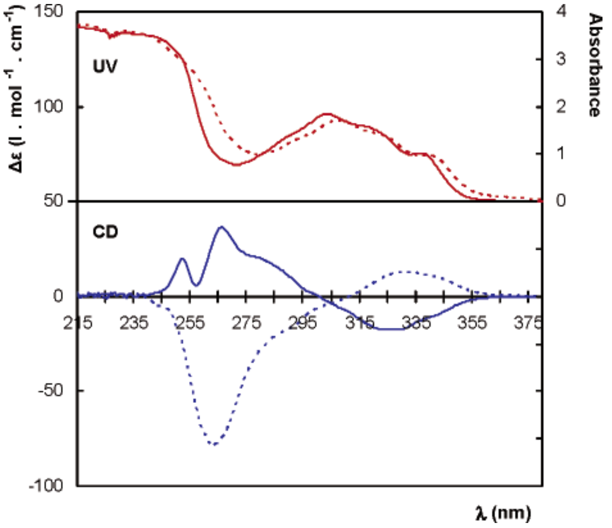

Figure 3. UV absorption spectrum (top, ordinate on the right, red) and CD spectrum (bottom, ordinate on the left, blue) of a 1.0 × 10^{-3} M solution of pseudoenantiomers (*M*,1*S*)-(−)-**5** (solid line) and (*P*,1*S*)-(+)-**6** (dashed line) in CH_3CN.

Encouraged by the high stereocontrol in the [2 + 2 + 2] cycloisomerization step, we decided to synthesize the [7]helicene-like compound (*P*,1*S*)-(+)-**18**, representing a new structural type of possible liquid-crystalline materials (Scheme 1).

The synthesis was started from commercially available phenylbromide **9** that was converted into the corresponding iodide **10** using the routine lithiation/iodination protocol. The following Sonogashira coupling with propargylic alcohol (2*S*)-(−)-**11** (being commercially available in both enantiomeric forms) under Pd^{II}/Cu^{I} catalysis created alcohol (2*S*)-(−)-**12**. Its potassium salt was treated with benzylic bromide **13**[14] to afford functionalized naphthyliodide (1*S*)-(−)-**14**. Note, the use of potassium salt in THF was key to our success, as analogous lithium or sodium salts exhibited poor reactivity under various conditions. The Sonogashira coupling of (1*S*)-(−)-**14** with **15**[7a] under Pd^{0}/Cu^{I} catalysis allowed us to assemble triyne (1*S*)-(−)-**16** that subsequently, on reaction with TBAF, produced unprotected triyne (1*S*)-(−)-**17**. In the final step of the synthesis sequence, this key intermediate was cycloisomerized in the presence of $CpCo(CO)_2/PPh_3$ to get the target [7]helicene-like compound (*P*,1*S*)-(+)-**18**. The reaction proceeded with good diastereoselectivity and could be mediated by a stoichiometric or catalytic amount of Co^{I} complex.[15] Diastereomerically pure (*P*,1*S*)-(+)-**18** was obtained after crystallization.

The helicity assignment was done in the same way as for (*P*,1*S*)-(+)-**6** and **7**, vide supra. In ROESY ^{1}H NMR spectrum, a through-space interaction between 1-H and 2′,6′-H of the 1,4-phenylene group and the absence of one between 1-CH_3 and the 1,4-phenylene group was obvious. Furthermore, the chemical shift of 1-CH_3 at 0.57 ppm lying within the 0.54−0.62 ppm interval indicated an “*endo*” position of 1-CH_3 and, accordingly, (*P*)-helicity of the backbone.

In summary, we have developed highly stereoselective [2 + 2 + 2] cycloisomerization of aromatic triynes producing a [7]helicene-like scaffold in diastereomeric ratios up to 100:0. This efficient central-to-helical chirality transfer can be controlled by an absolute configuration at the asymmetric center and by the position of carbon substituents. Synthetic studies on the transformation to parent helicenes and on the preparation of nonracemic, functionalized derivatives are in progress.

Acknowledgment. The financial support from the Grant Agency of the Czech Republic (Reg. No. 203/02/0248) is gratefully acknowledged. We thank the group of Dr. K. Ubik for the mass spectra, Dr. H. Dlouhá and Dr. P. Maloň for the CD spectra, and Dr. P. Fiedler for the IR spectra (all from the IOCB). We also thank Dr. E. Poetsch (Merck, Darmstadt) for initializing the synthesis of (*P*,1*S*)-(+)-**18** and providing the starting material **9**.

Supporting Information Available: Experimental procedures for cyclization of **1**−**4** and **17**, experimental details for the synthesis of **18** from **9**, characterization data and ^{1}H NMR spectra for cyclic products **5**−**8** and **18** and compounds **9**, **10**, **12**, **14**, **16**, and **17**, and UV and CD spectra for cyclic products **5**−**8** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Diastereomeric ratios were inferred from ^{1}H NMR spectra by integrating the signals of the methyl groups attached to the dihydrooxepine ring of both diastereomers. The prolonged reaction periods did not affect the diastereomeric ratios of the products.

(13) Optimized structures were obtained using *Quantum CAChe for Windows 3.0* (Oxford Molecular Group/Fujitsu) at the semiempirical AM1 level. The nature of the R group (H or *p*-tolyl) did not substantially affect the distances between the protons discussed. In the case of the 1-CH_3 and 19-tolyl groups we were aware of their rotation (only the closest distances taken from the optimized “frozen” structures are displayed).

(14) Stará, I. G.; Kollárovič, A.; Teplý, F.; Starý, I.; Šaman, D.; Fiedler, P. *Collect. Czech. Chem. Commun.* **2000**, *65*, 577.

(15) Use of substoichiometric amounts of $CpCo(CO)_2$ (40 mol %) and PPh_3 (40 mol %) led to a substantially prolonged reaction period (25 h) and lower yield (64%).