DOI: 10.1002/chem.200800705

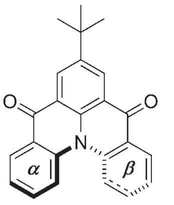
Efficient Thia-Bridged Triarylamine Heterohelicenes: Synthesis, Resolution, and Absolute Configuration Determination

Giuseppe Lamanna,[a] Cristina Faggi,[a] Francesco Gasparrini,[b] Alessia Ciogli,[b] Claudio Villani,[b] Philip J. Stephens,[c] Frank J. Devlin,[c] and Stefano Menichetti*[a]

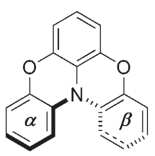
Dedicated to the memory of Professor Giuseppe (Pino) Capozzi

For many years helicenes were regarded as an academic curiosity and a nice example of chirality without stereogenic centers. The situation changed dramatically during the last decade when fascinating optical[1] and electronic[2] properties as well as attractive applications in bioorganic chemistry[3] and asymmetric synthesis[4] emerged for these helical-shaped molecules. In parallel, new synthetic methods that circumvented the problems often related with the classical photocyclization of stilbenes,[5] including Diels–Alder reactions,[6] cyclotrimerization of alkynes,[7] carbenoid couplings,[8] radical cyclizations,[9] Pd-mediated methodologies,[10] and olefin metathesis[11] were developed. Recently, bridged triarylamine heterohelicenes of the type **1**–**3** have been prepared[12,13] and studied[13,14] in the belief that the introduction of molecular helicity, sterically driven by the increasing overlap of the terminal **α** and **β** aryl rings, influences[2b] the well known photochemical and physical properties of triarylamines.[15]

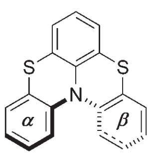
As a continuation of our efforts related to sulfur heterocycles chemistry,[16] we focused on compound **3**, which was prepared by building the triarylamine skeleton by employing a Buchwald–Hartwig type cross-coupling of an open iodo-aniline in the final step of a multistep reaction sequence.[13] We envisaged that derivatives like **3** could be accessible by a cascade of regioselective electrophilic aromatic sulfur insertions,[17] by applying the chemistry of the phthalimidesulfenyl chloride (**4**) (PhtNSCl, Pht = phthaloyl) to properly substituted triarylamines.



1



2



3

The reaction of tris(4-methylphenyl)- (**5a**) and tris(4-methoxyphenyl)amine (**5b**) with one equivalent of **4** occurred smoothly at room temperature to give mono-sulfenylation *ortho* to the amine nitrogen atom. The bis-sulfenylation can however be achieved under more forcing reaction conditions (Scheme 1), which allowed the isolation of derivatives **6a** and **6b** in 83 % yield. In line with our previous results,[18] the introduction of a *N*-thiophthalimide group strongly deactivates the aromatic system, preventing further substitutions. Moreover, using triarylamines as substrates, protonation at the amine nitrogen, due to the HCl formed during sulfenylation, represents a supplementary obstacle to the polysubstitution. Indeed, we were unable to carry out an exhaustive sulfenylation of all three aromatic rings of **5a** or **5b**.

The electrophilic character of sulfenamide sulfur in *N*-thiophthalimides can be increased by using Lewis acids.[17] Satisfyingly, reacting derivatives **6a** and **6b** with $BF_3{\cdot}Et_2O$ or $AlCl_3$ triggers an intramolecular attack of the aromatic ring on the adjacent sulfur atom, leading to the formation of hetero[4]helicenes **7a** and **7b** in 85 and 87 % yield, respectively

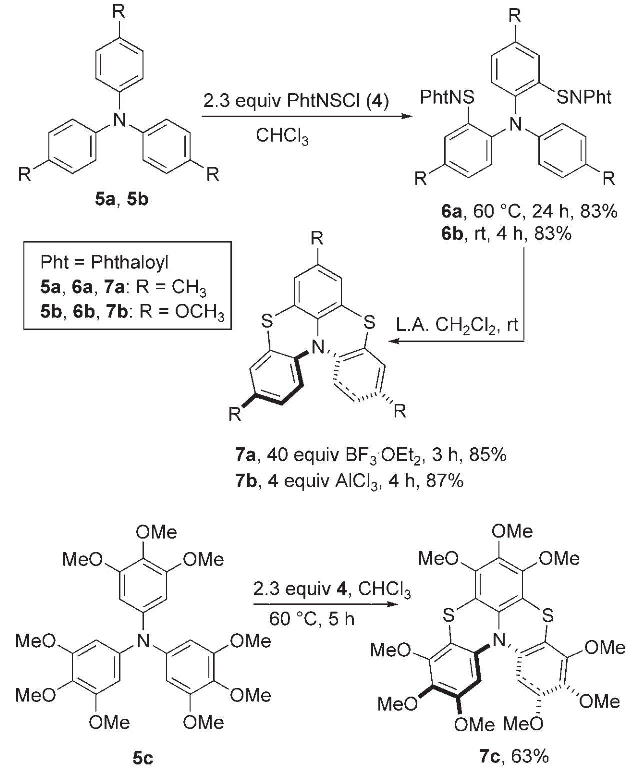
---

[a] Dr. G. Lamanna, Dr. C. Faggi, Prof. S. Menichetti
Dipartimento di Chimica Organica e Laboratorio di Progettazione
e Sintesi di Eterocicli Biologicamente Attivi (*HeteroBioLab*)
Università di Firenze
Via della Lastruccia 13, 50019 Sesto Fiorentino, Firenze (Italy)
Fax: (+39) 055-4573531
E-mail: stefano.menichetti@unifi.it

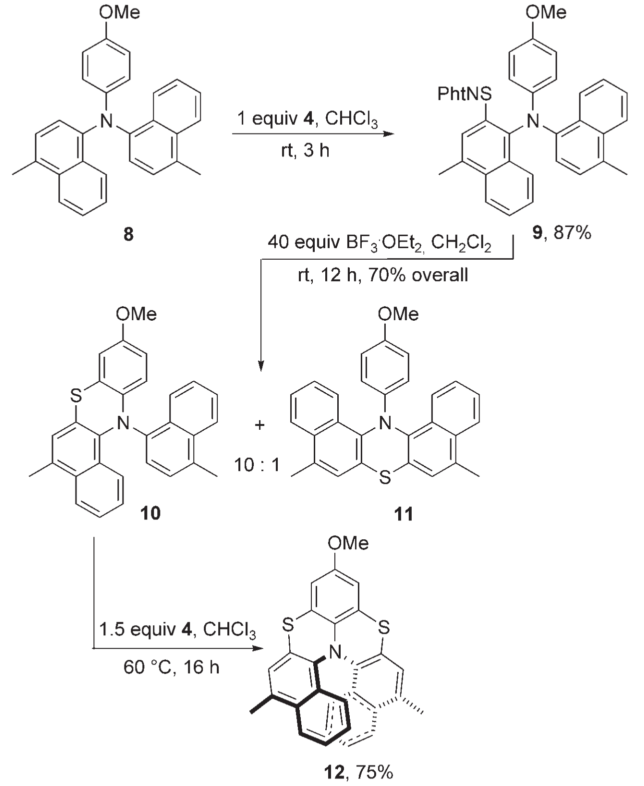
[b] Prof. F. Gasparrini, Dr. A. Ciogli, Prof. C. Villani
Dipartimento di Studi di Chimica e Tecnologia delle Sostanze
Biologicamente Attive
Università di Roma "La Sapienza", P.le A. Moro 5, 00185 Roma
(Italy)

[c] Prof. P. J. Stephens, Dr. F. J. Devlin
Department of Chemistry, University of Southern California
Los Angeles, CA 90089 (USA)

Supporting information for this article is available on the WWW under http://www.chemistry.org or from the author.



Scheme 1. Synthesis of thia-bridged hetero[4]helicenes from triarylamines by four consecutive electrophilic aromatic sulfur insertions with phthalimidesulfenyl chloride.



Scheme 2. Access to hetero[6]helicene **12**.

(Scheme 1). Applying this straightforward procedure to tris(3,4,5-trimethoxyphenyl)amine **5c**, we observed the formation of heterohelicene **7c** during the bis-sulfenylation process, without the use of any Lewis acid as catalyst. We reasoned that, after the initial introduction of the *N*-thiophthalimide groups, a possible protonation at the sulfenamide nitrogen atom[19] and the high nucleophilic character of the trimethoxy-substituted aromatic ring can contribute to activating the sulfur atom and promoting the intramolecular S_EAr processes.[20] In this way, the hetero[4]helicene **7c** was isolated in 63% yield as the result of four consecutive one-pot regioselective electrophilic sulfur insertions (Scheme 1).

A fairly simple modification of the reaction sequence allowed access to hetero[6]helicenes (Scheme 2). Monosulfenylation of amine **8** with **4** gave chemo- and regioselectively sulfenamide **9** in 87% yield. Cyclization of **9** with an excess of $BF_3{\cdot}Et_2O$ led to the two expected 1,4-thiazines **10** and **11** in a 10:1 ratio and 70% overall yield. Gratifyingly, the major isomer **10** reacts with **4** under the above-described conditions, and thereby undergoes sulfenylation followed by a spontaneous intramolecular proton-mediated cyclization, to afford hetero[6]helicene **12** in 75% yield (Scheme 2).

The assignments of the structures of the helicenes **7a**–**c** and **12** were supported by spectroscopic data and confirmed for **7a**, **7c**, and **12** by single-crystal X-ray analysis (see the Supporting Information). The length of the C_{sp^2}–S bond causes a greater overlay of the α and β aromatic rings compared with the situation in derivatives **1** and **2**[13] (Figure 1 and torsion angles in Table 1),[21] suggesting a peculiar stability against a reversal of the helicity.

Table 1. X-ray torsion angles [°][21] between the planes of terminal α and β phenyl rings in heterohelicenes **1**,[12] **2**,[13] **3**,[13] **7a**, **7c**, and **12**.

Helicene	1	2	3	7a	7c	12
angle [°]	41.9	43.0	62.3	61.4	65.3	74.5

The enantiomers of heterohelicenes **7a**–**c** and **12** were effectively separated by HPLC using a column packed with an amylose-based chiral stationary phase.[22] Positive identification of the enantiomers was obtained by dual simultaneous UV and CD detection that gave, at any wavelength between 254 and 400 nm, bisignate peaks of equal area, as expected for a racemate (see the Supporting Information).

For **7a** the analytical separation was easily scaled up to the milligram range, affording the individual enantiomers of the heterohelicenes **7a** with *ee* = 99.9% and 97.6% for the first and second eluted enantiomers, respectively. The first and second eluted enantiomers of **7a** exhibited $[\alpha]_D$ values of (+)-376 and (−)-376 ($c = 0.11$, hexane), respectively.[23] Racemization of the resolved (+)-**7a** and (−)-**7a** enantiomers was not achieved when they were heated for 8 h in decalin at 95 °C. However, thermal racemization was observed when (+)-**7a** was heated at 121, 135, and 145 °C in decalin. The decay of enantiomeric excess over time was monitored by enantioselective HPLC. Good first-order kinetics were displayed by the experimental data points, from which the rate constants of 2.2×10^{-5} (121 °C), 1.2×10^{-4} (135 °C), and $2.6\times10^{-4}\,s^{-1}$ (145 °C) were calculated for the racemization process.[24] The energy barriers of racemization $\Delta G^{\neq}=131.9$–$132.6\pm0.5\,kJ\,mol^{-1}$ in the 121–145 °C temperature range were obtained, with $\Delta H^{\neq}=137\pm0.5\,kJ\,mol^{-1}$ and $\Delta S^{\neq}=12\pm6\,J\,mol^{-1}K^{-1}$. Thus, the energy barrier for the helicity reversal in the thia-bridged hetero[4]helicene **7a** is between that of the parent [5]helicene ($\Delta G^{\neq}=101\,kJ\,mol^{-1}$ at 20 °C)[5d] and [6]helicene ($\Delta G^{\neq}=151\,kJ\,mol^{-1}$ at 27 °C),[5d] which allows an easy physical separation and chiroptical characterization of the individual *M*/*P* enantiomers at room temperature.

The absolute configuration of **7a** was determined by comparison of the vibrational circular dichroism (VCD) spectra of the two enantiomers, *P*-**7a** and *M*-**7a**, calculated by using density functional theory (DFT), to the experimental VCD spectrum of (+)-**7a**, a methodology used previously in determining the absolute configurations of chiral-chromatography-resolved enantiopure molecules[25] (see the Supporting Information). Conformational analysis of **7a**, using the MMFF94 force field, showed **7a** to be a conformationally rigid molecule. Reoptimization of the MMFF94 geometry, using DFT at the B3PW91/TZ2P level, and calculation of the B3PW91/TZ2P harmonic vibrational frequencies and rotational strengths, led to the VCD spectrum of *P*-**7a** and to the predicted structure of *P*-**7a**, which is shown in Figure 1 together with the X-ray structure of *rac*-**7a** (*P* enantiomer was arbitrarily chosen among the two molecules included in the asymmetric unit, see Supporting Information). The predicted VCD spectrum of *P*-**7a** is in excellent qualitative agreement with the experimental VCD spectrum of (+)-**7a**, leading to the conclusion that the absolute configuration of **7a** is unambiguously *P*-(+). Further support for the reliability of the DFT calculations for **7a** is provided by the excellent agreement of the predicted B3PW91/TZ2P equilibrium geometry and the X-ray structure. The X-ray structure torsion angle between the terminal **α** and **β** phenyl ring planes of **7a** is 61.4° (Table 1); the B3PW91/TZ2P torsion angle is 66.3° (Figure 1).

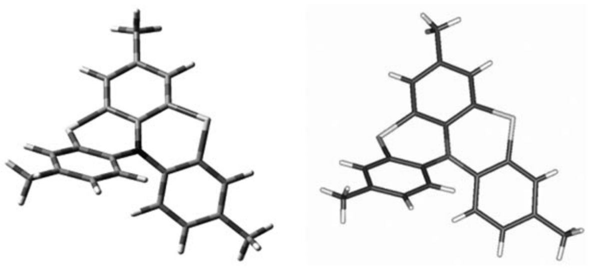


Figure 1. B3PW91/TZ2Pstructure of *P*-**7a** (left), and X-ray structure of *rac*-**7a** (right, *P* enantiomer chosen arbitrarily).

In summary we have shown a very practical access to thia-bridged triarylamine hetero[4]- and -[6]helicenes by four consecutive (one-pot) electrophilic regioselective aromatic sulfur insertions. Owing to their remarkably high racemization barrier, these derivatives can be resolved by HPLC, and the absolute configuration for **7a** has been determined as *P*-(+) by ab initio calculations and by experimental measurement of VCD spectra. The synthesis of similar helicenes with potential application in asymmetric synthesis or biorganic chemistry is ongoing.

Experimental Section

A detailed experimental procedure including synthesis, X-ray structure determination, HPLC separation, and determination of absolute configuration is available in the Supporting Information. The following procedure for the synthesis of helicene **7a** from amine **5a** is reported as demonstrative.

Bis-*N*-thiophthalimide (6a): To a solution of tris(*p*-tolyl)amine (**5a**) (1.0 mmol) in dry $CHCl_3$ (15 mL) was added phthalimidesulfenyl chloride (**4**) (2.3 mmol) under a nitrogen atmosphere. After stirring at 60 °C for 24 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL), and washed with a saturated $NaHCO_3$ solution (2×30 mL) and water (2×30 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and the crude material purified by flash chromatography (CH_2Cl_2/petroleum ether 4:1) to provide the thiophthalimide **6a** as a yellow solid (83 % yield). M.p. 259–261 °C; ^1H NMR ($CDCl_3$, 400 MHz): $\delta=2.22$ (s, 6H), 2.26 (s, 3H), 6.68–6.71 (m, 2H), 6.86 (d, $J=1.2$ Hz, 2H), 7.03–7.07 (m, 4H), 7.49 (d, $J=8.0$ Hz, 2H), 7.76–7.81 (m, 4H), 7.91–7.96 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta=20.92$, 21.37, 118.42, 124.13, 127.10, 128.92, 129.83, 130.36, 130.56, 132.26, 133.75, 134.71, 136.35, 141.61, 146.31, 167.96 pm; IR (KBr): $\tilde{\nu}=1787+1742+1709$ (C=O stretching PhtN), 1278 cm^{-1}; MS (70 eV): *m*/*z* (%): 641 (3) [$M^{\cdot+}$], 147 (43), 76 (100), 50 (88); elemental analysis calcd (%) for $C_{37}H_{27}N_3O_4S_2$: C 69.25, H 4.24, N 6.55; found: C 69.38, H 4.10, N 6.12.

Hetero[4]helicene 7a: To a solution of bis-*N*-thiophthalimide **6a** (1.0 mmol) in dry CH_2Cl_2 (50 mL) was added $BF_3{\cdot}Et_2O$ (40.0 mmol) under a nitrogen atmosphere. After the mixture had been stirred for 3 h at room temperature, the mixture was diluted with CH_2Cl_2 (15 mL) and washed with a saturated Na_2CO_3 solution (2×60 mL) and a saturated NaF solution (2×60 mL). The organic layer was dried over Na_2SO_4. Evaporation of the solvent gave a crude product that was purified by flash chromatography (petroleum ether/CH_2Cl_2 2:1) to afford the heterohelicene **7a** as a white solid (85 % yield) further purified by recrystallization from $CHCl_3$. M.p. 162–164 °C; ^1H NMR (C_6D_6, 400 MHz): $\delta=1.80$ (s, 3H), 1.96 (s, 6H), 6.55–6.59 (m, 4H), 6.87 (d, $J=1.2$ Hz, 2H), 6.95 ppm (d, $J=8.4$ Hz, 2H); ^{13}C NMR (C_6D_6, 50 MHz): $\delta=20.25$, 20.56, 120.56, 125.98, 126.38, 127.31, 128.35, 134.07, 134.54, 137.78, 137.95, 140.90 ppm; MS (70 eV): *m*/*z* (%): 347 (100) [$M^{\cdot+}$], 315 (47), 158 (50); elemental analysis calcd (%) for $C_{21}H_{17}NS_2$: C 72.58, H 4.93, N 4.03; found: C 72.10, H, 4.98, N 3.99.

Acknowledgements

Financial support from MiUR (Research project “Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni” contract 2005035330), the U.S. National Science Foundation, CHE-0209957 and CHE-0614577 are acknowledged. We thank Brunella Innocenti and Maurizo Passaponti for MS spectra and elemental analysis.

Keywords: aromatic substitution · chiral resolution · heterohelicenes · sulfur heterocycles · vibrational circular dichroism

---

[1] a) T. J. Wigglesworth, D. Sud, T. B. Norsten, V. S. Lekhi, N. R. Branda, *J. Am. Chem. Soc.* **2005**, *127*, 7272–7273; b) E. Botek, B. Champagne, M. Turki, J.-M. André, *J. Chem. Phys.* **2004**, *120*, 2042–2048; c) T. J. Katz, *Angew. Chem.* **2000**, *112*, 1997–1999; *Angew. Chem. Int. Ed.* **2000**, *39*, 1921–1923.

[2] a) F. Furche, R. Ahlrichs, C. Wachsmann, E. Weber, A. Sobanski, F. Vögtle, S. Grimme, *J. Am. Chem. Soc.* **2000**, *122*, 1717–1724; b) G. Treboux, P. Lapstun, Z. Wu, K. Silverbrook, *Chem. Phys. Lett.* **1999**, *301*, 493–497; c) S. Grimme, L. Harren, A. Sobanski, F. Vögtle, *Eur. J. Org. Chem.* **1998**, 1491–1509.

[3] a) Y. Xu, X. Y. Zhang, H. Sugiyama, T. Umano, H. Osuga, K. Tanaka, *J. Am. Chem. Soc.* **2004**, *126*, 6566–6567; b) S. Honzawa, H. Okubo, S. Anzai, M. Yamaguchi, K. Tsumoto, I. Kumagai, *Bioorg. Med. Chem.* **2002**, *10*, 3213–3218.

[4] a) H. Sugiura, Y. Takahira, M. Yamaguchi, *J. Org. Chem.* **2005**, *70*, 5698–5708; b) I. Sato, R. Yamashima, K. Kadowaki, J. Yamamoto, T. Shibata, K. Soai, *Angew. Chem.* **2001**, *113*, 1130–1132; *Angew. Chem. Int. Ed.* **2001**, *40*, 1096–1098; c) S. D. Dreher, T. J. Katz, K.-C. Lam, A. L. Rheingold, *J. Org. Chem.* **2000**, *65*, 815–822; d) M. T. Reetz, S. Sostmann, *J. Organomet. Chem.* **2000**, *603*, 105–109; e) E. Murguly, R. McDonald, N. R. Branda, *Org. Lett.* **2000**, *2*, 3169–3172; f) K. Deshayes, R. D. Broene, I. Chao, C. B. Knobler, F. Diederich, *J. Org. Chem.* **1991**, *56*, 6787–6795.

[5] a) R. El Abed, B. B. Hassine, J.-P. Genêt, M. Gorsane, A. Marinetti, *Eur. J. Org. Chem.* **2004**, 1517–1522; b) A. Urbano, *Angew. Chem.* **2003**, *115*, 4116–4119; *Angew. Chem. Int. Ed.* **2003**, *42*, 3986–3989; c) L. Liu, B. Yang, T. J. Katz, M. K. Poindexter, *J. Org. Chem.* **1991**, *56*, 3769–3775; d) R. H. Janke, G. Haufe, E.-U. Würthwein, J. H. Borkent, *J. Am. Chem. Soc.* **1996**, *118*, 6031–6035; e) M. Flammang-Barbieux, J. Nasielski, R. H. Martin, *Tetrahedron Lett.* **1967**, *8*, 743–744.

[6] a) M. Carmen Carreno, A. Enriquez, S. Garcia-Cerrada, M. J. Sanz-Cuesta, A. Urbano, F. Maseras, A. Nonell-Canals, *Chem. Eur. J.* **2008**, *14*, 603–620; b) M. C. Carreno, M. Gonzalez-Lopez, A. Urbano, *Chem. Commun.* **2005**, 611–613; c) M. C. Carreno, S. Garcia-Cerrada, A. Urbano, *Chem. Eur. J.* **2003**, *9*, 4118–4131; d) M. C. Carreno, S. Garcia-Cerrada, A. Urbano, *J. Am. Chem. Soc.* **2001**, *123*, 7929–7930.

[7] a) K. Tanaka, A. Kamisawa, T. Suda, K. Noguchi, M. Hirano, *J. Am. Chem. Soc.* **2007**, *129*, 12078–12079; b) I. G. Stará, Z. Alexandrová, F. Teply, P. Sehnal, I. Stary, D. Saman, M. Budesínsky, J. Cvacka, *Org. Lett.* **2005**, *7*, 2547–2550; c) F. Teply, I. G. Stará, I. Stary, A. Kollárovic, D. Saman, L. Rulísek, P. Fiedler, *J. Am. Chem. Soc.* **2002**, *124*, 9175–9180.

[8] a) M. Gingras, F. Dubois, *Tetrahedron Lett.* **1999**, *40*, 1309–1312; b) F. Dubois, M. Gingras, *Tetrahedron Lett.* **1998**, *39*, 5039–5040.

[9] a) D. C. Harrowven, I. L. Guy, L. Nanson, *Angew. Chem.* **2006**, *118*, 2300–2303; *Angew. Chem. Int. Ed.* **2006**, *45*, 2242–2245; b) D. C. Harrowven, M. I. T. Nunn, D. R. Fenwick, *Tetrahedron Lett.* **2002**, *43*, 7345–7347; c) D. C. Harrowven, M. I. T. Nunn, D. R. Fenwick, *Tetrahedron Lett.* **2002**, *43*, 3189–3191.

[10] K. Nakano, Y. Hidehira, K. Takahashi, T. Hiyama, K. Nozaki, *Angew. Chem.* **2005**, *117*, 7298–7300; *Angew. Chem. Int. Ed.* **2005**, *44*, 7136–7138.

[11] S. K. Collins, A. Grandbois, M. P. Vachon, J. Côté, *Angew. Chem.* **2006**, *118*, 2989–2992; *Angew. Chem. Int. Ed.* **2006**, *45*, 2923–2926.

[12] J. E. Field, T. J. Hill, D. Venkataraman *J. Org. Chem.* **2003**, *68*, 6071–6078.

[13] a) M. Kuratsu, M. Kozaki, K. Okada, *Angew. Chem.* **2005**, *117*, 4124–4126; *Angew. Chem. Int. Ed.* **2005**, *44*, 4056–4058; b) M. Kuratsu, M. Kozaki, K. Okada, *Chem. Lett.* **2004**, *33*, 1174–1175; c) C. Herse, D. Bas, F. C. Krebs, T. Bürgi, J. Weber, T. Wesolowski, B. W. Laursen, J. Lacour, *Angew. Chem.* **2003**, *115*, 3270–3274; *Angew. Chem. Int. Ed.* **2003**, *42*, 3162–3166.

[14] a) M. Spassova, I. Asselberghs, T. Vierbiest, K. Clays, E. Botek, B. Champagne, *Chem. Phys. Lett.* **2007**, *439*, 213–218; b) R. Hassey, E. J. Swain, N. I. Hammer, D. Venkataraman, M. D. Barnes, *Science* **2006**, *314*, 1437–1439; c) J. E. Field, G. Muller, J. P. Riehl, D. Venkataraman, *J. Am. Chem. Soc.* **2003**, *125*, 11808–11809.

[15] a) T. D. Selby, K.-Y. Kim, S. C. Blackstock, *Chem. Mater.* **2002**, *14*, 1685–1690; b) Y. Shirota, *J. Mater. Chem.* **2000**, *10*, 1–25; c) E. Bellmann, S. E. Shaheen, S. Thayumanavan, S. Barlow, R. H Grubbs, S. R. Marder, B. Kippelen, N. Peyghambarian, *Chem. Mater.* **1998**, *10*, 1668–1676.

[16] a) R. Amorati, A. Cavalli, M. G. Fumo, M. Masetti, S. Menichetti, C. Pagliuca, G. F. Pedulli, C. Viglianisi, *Chem. Eur. J.* **2007**, *13*, 8223–8230; b) A. Contini, S. Leone, S. Menichetti, C. Viglianisi, P. Trimarco, *J. Org. Chem.* **2006**, *71*, 5507–5514; c) S. Menichetti, M. C. Aversa, F. Cimino, A. Contini, A. Tomaino, C. Viglianisi, *Org. Biomol. Chem.* **2005**, *3*, 3066–3072; d) S. Menichetti, C. Nativi, *Targets in Heterocyclic Systems—Chemistry and Properties* **2003**, *7*, 108–139.

[17] a) G. Lamanna, S. Menichetti, *Adv. Synth. Catal.* **2007**, *349*, 2188–2194; b) G. Capozzi, F. de Sio, S. Menichetti, C. Nativi, P. L. Pacini, *Synthesis* **1994**, 521–525.

[18] G. Delogu, D. Fabbri, S. Menichetti, C. Nativi, *Tetrahedron* **2003**, *59*, 2131–2136.

[19] A. Bagno, S. J. Eustace, L. Johansson, G. Scorrano, *J. Org. Chem.* **1994**, *59*, 232–233.

[20] In fact, reacting amine **5a** with three equivalents of **4** at 80 °C for 48 h allowed the isolation of helicene **7a** in 13 % yield.

[21] Torsional angles were calculated by using the corresponding cif files in the Mercury 1.4.2 program to generate the planes, where **α** and **β** phenyl rings lay. For [6]helicene **12**, the angle was calculated by using the external ring of the naphthalene moiety.

[22] T. Zhang, C. Kientzy, P. Franco, A. Ohnishi, Y. Kagamihara, H. Kurosawa, *J. Chromatogr. A* **2005**, *1075*, 65–75.

[23] Analytical separation was similarly achieved for [6]helicene **12**. The first and second eluted enantiomers of **12** exhibited $[\alpha]_D$ values of (−)-405 and (+)-405 ($c = 0.06$, hexane), respectively.

[24] The racemization rate is twice the $M \rightleftharpoons P$ enantiomerization rate.

[25] a) P. J. Stephens, F. J. Devlin, F. Gasparrini, A. Ciogli, D. Spinelli, B. Cosimelli, *J. Org. Chem.* **2007**, *72*, 4707–4715; b) V. Cerè, F. Peri, S. Pollicino, A. Ricci, F. J. Devlin, P. J. Stephens, F. Gasparrini, R. Rompietti, C. Villani, *J. Org. Chem.* **2005**, *70*, 664–669.

Received: April 14, 2008