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Synthesis of 3-Hexahelicenol and Its Transformation to 3-Hexahelicenylamines, Diphenylphosphine, Methyl Carboxylate, and Dimethylthiocarbamate

Filip Teplý,[†] Irena G. Stará,*[,†] Ivo Starý,*[,†] Adrian Kollárovič,[†] David Šaman,[†] Štěpán Vyskočil,[‡] and Pavel Fiedler[†]

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám 2, 166 10 Prague 6, Czech Republic, and Department of Organic Chemistry, Charles University, Albertov 2030, 128 40 Prague 2, Czech Republic

stara@uochb.cas.cz; stary@uochb.cas.cz

Received March 20, 2003

A nonphotochemical synthetic route to 3-hexahelicenol is reported. It involves a key [2+2+2] cycloisomerization of CH_3O-substituted triyne that is readily available from 1-methoxy-3-methylbenzene and 1-bromo-2-(bromomethyl)naphthalene. Further functional group transformations led to 3-CO_2CH_3, 3-NH_2, 3-PPh_2, and 3-$SC(O)N(CH_3)_2$ substituted hexahelicenes.

Introduction

Carbohelicenes are stable nonplanar aromatic systems being inherently chiral.[1] The indispensable prerequisite to a wide exploitation of these molecules is availability of their derivatives. Although much effort has so far been devoted to the synthesis of carbohelicenes,[2] in the hexahelicene series the functional group variety is limited to OH or CO_2H and their congeners.[3,4] To the best of our knowledge, only one monodentate phosphine,[5] one bidentate phosphine,[5,6] one amine,[7] and no thiol derivative have been up to now described in the hexahelicene series.

From a synthesis point of view, two different strategies may be considered to introduce substituents: functionalizing bare helicene skeletons or assembling helicenes from functionalized building blocks. While the former approach based on aromatic electrophilic substitution is rare in the literature[8] and usually suffers from low regioselectivity, the latter approach is waiting for an effective and modular method for the helicene synthesis to be developed.[9]

Recently, we have revealed a new paradigm for the nonphotochemical synthesis of tetrahydrohelicenes/helicenes that is based on a key intramolecular [2+2+2] cycloisomerization of aromatic triynes/*cis*,*cis*-dienetriynes under Co(I) or Ni(0) catalysis.[10] Herein, we disclose this flexible methodology can easily be adapted to the syn-

[†] Academy of Sciences of the Czech Republic.
[‡] Charles University.

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(2) According to the CrossFire Beilstein database, more than 480 carbohelicenes are known within the [5]- to [14]helicene series.

(3) For alcohols and their derivatives, see: (a) Ogawa, Y.; Toyama, M.; Karikomi, M.; Seki, K.; Haga, K.; Uyehara, T. *Tetrahedron Lett.* **2003**, *44*, 2167. (b) Ogawa, Y.; Ueno, T.; Karikomi, M.; Seki, K.; Haga, K.; Uyehara, T. *Tetrahedron Lett.* **2002**, *43*, 7827. (c) Reetz, M. T.; Sostmann, S. *Tetrahedron* **2001**, *57*, 2515. (d) Paruch, K.; Vyklický, L.; Katz, T. J.; Incarvito, C. D.; Rheingold, A. L. *J. Org. Chem.* **2000**, *65*, 8774. (e) Thongpanchang, T.; Paruch, K.; Katz, T. J.; Rheingold, A. L.; Lam, K.-C.; Liable-Sands, L. *J. Org. Chem.* **2000**, *65*, 1850. (f) Dreher, S. D.; Paruch, K.; Katz, T. J. *J. Org. Chem.* **2000**, *65*, 806. (g) Meier, H.; Schwertel, M.; Schollmeyer, D. *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **2000**, *56*, 684. (h) Nuckolls, C.; Katz, T. J.; Katz, G.; Collings, P. J.; Castellanos, L. *J. Am. Chem. Soc.* **1999**, *121*, 79. (i) Meier, H.; Schwertel, M.; Schollmeyer, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2110. (j) Katz, T. J.; Liu, L.; Willmore, N. D.; Fox, J. M.; Rheingold, A. L.; Shi, S.; Nuckolls, C.; Rickman, B. H. *J. Am. Chem. Soc.* **1997**, *119*, 10054. (k) Dai, Y.; Katz, T. J. *J. Org. Chem.* **1997**, *62*, 1274. (l) Nuckolls, C.; Katz, T. J.; Castellanos, L. *J. Am. Chem. Soc.* **1996**, *118*, 3767. (m) Dai, Y.; Katz, T. J.; Nichols, D. A. *Angew. Chem.* **1996**, *108*, 2230. (n) Yang, B.; Liu, L.; Katz, T. J.; Liberko, C. A.; Miller, L. L. *J. Am. Chem. Soc.* **1991**, *113*, 8993. (o) Hassine, B. B.; Gorsane, M.; Geerts-Evrard, F.; Pecher, J.; Martin, R. H.; Castelet, D. *Bull. Soc. Chim. Belg.* **1986**, *95*, 557. (p) Brown, J. M.; Field, I. P.; Sidebottom, P. J. *Tetrahedron Lett.* **1981**, *22*, 4867.

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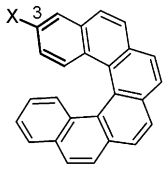
(6) For bisphosphine, see refs 3a and 5 and the following: (a) Reetz, M. T.; Sostmann, S. *J. Organomet. Chem.* **2000**, *603*, 105. (b) Reetz, M. T.; Beuttenmuller, E. W.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 3211.

(7) For amine, see: op den Brouw, P. M.; Laarhoven, W. H. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 265.

(8) For electrophilic substitution of parent hexahelicene, see ref 7.

(9) Most of the functionalized helicenes mentioned in refs 3−7 were prepared from substituted stilbene-type precursors via impractical UV light-mediated photodehydrocyclization or, in the case of hydroxy derivatives, by benzoquinone cycloaddition to (bis)vinyl aromatics. Although the latter approach published by Katz is quite general in regard to the helicene skeleton, a substitution portfolio is very limited.

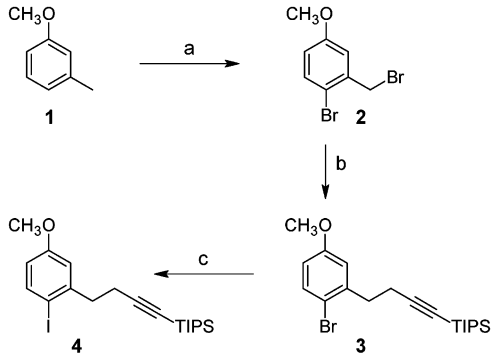
10.1021/jo034369t CCC: $25.00
Published on Web 05/24/2003



X=OR, CO_2R, NR_2, PR_2, SR

FIGURE 1. 3-Functionalized hexahelicenes.

SCHEME 1. Synthesis of the Building Block 4[a]



[a] Reagents and conditions: (a) NBS (2.1 equiv), CH_2Cl_2, IR lamp, 4 h, reflux, 99%. (b) $LiCH_2C{\equiv}CTIPS$ (1.05 equiv), THF, −78 °C, 15 min, 95%. (c) ^{n}BuLi (1.05 equiv), THF, −78 °C, 10 min, then I_2 (1.1 equiv), −78 °C, 20 min, 96%.

thesis of various substituted carbohelicenes. Starting from simple building blocks, an array of 3-functionalized hexahelicenes is now attainable (Figure 1).

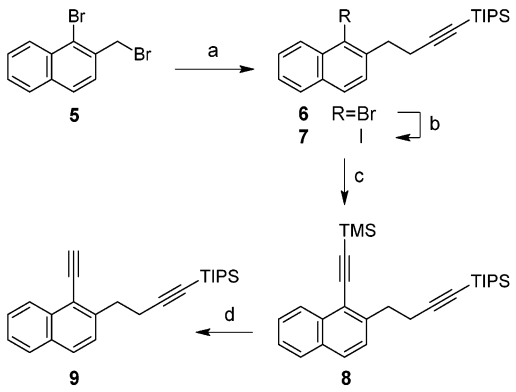
Results and Discussion

Synthesis of Building Blocks. 3-Methyl anisole **1**, whose methoxy group appears as a useful functionality in a desired position at the hexahelicene scaffold, vide infra, was brominated with *N*-bromosuccinimide according to the literature procedure[11] to obtain dibromide **2** (Scheme 1). On treatment with $LiCH_2C{\equiv}CTIPS$ (generated in situ from $CH_3C{\equiv}CTIPS$ and *n*-butyllithium), bromide **3** was produced bearing a protected alkyne unit in the sidearm. To avoid the tethered alkyne unit participating in the planned Sonogashira coupling, bromide **3** was converted to iodide **4** by lithiation/iodination.

The synthesis of the unsubstituted naphthalene building block **9** starts from dibromide **5** (Scheme 2). After the attachment of the sidearm with the alkyne unit, bromide **6** was transformed to the known iodide **7**[12] to ensure a clean Sonogashira coupling with HC≡CTMS providing diyne **8**. The selective removal of the TMS group completed the synthesis of **9**. The easy preparation of **4** and **9** was carried out on a multigram scale and high yields were throughout both the synthesis schemes.

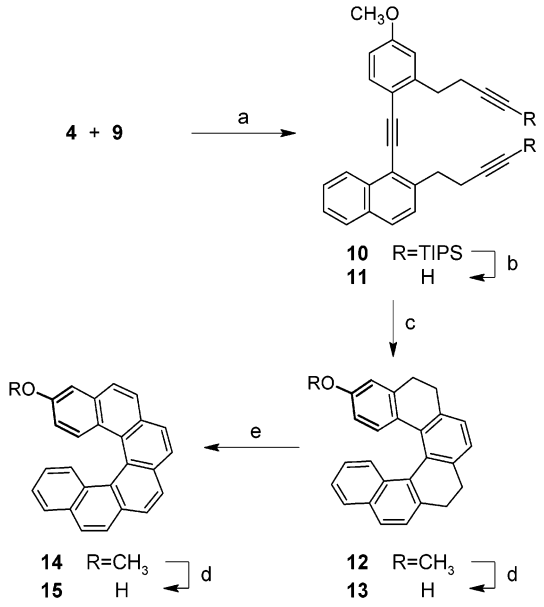
Construction of 3-Hexahelicenol 15. Having prepared the suitable building blocks, we could approach assembling the hexahelicene scaffold. Smooth and clean

SCHEME 2. Synthesis of the Building Block 9[a]



[a] Reagents and conditions: (a) $LiCH_2C{\equiv}CTIPS$ (1.04 equiv), THF, −78 °C, 1 h, 92%. (b) ^{n}BuLi (1.04 equiv), THF, −78 °C, 15 min, then I_2 (1.1 equiv), −78 °C, 20 min, 98%. (c) $TMS{-}C{\equiv}CH$ (1.2 equiv), $Pd(PPh_3)_4$ (1%), CuI (2%), $^i Pr_2NH$, autoclave, 80 °C, 1.5 h, 99%. (d) CH_3ONa (1.7 equiv), methanol, rt, 16 h, 99%.

SCHEME 3. Construction of 3-Hexahelicenol 15 and Its Tetrahydroanalogue 13[a]



[a] Reagents and conditions: (a) **4** (1.0 equiv), **9** (1.0 equiv), $Pd(PPh_3)_4$ (2%), CuI (4%), $^i Pr_2NH$, 80 °C, 15 min, 90%. (b) $^n Bu_4NF$ (2.4 equiv), THF, rt, 15 min, 74%. (c) $CpCo(CO)_2$ (20%), PPh_3 (40%), decane, halogen lamp, 140 °C, 2.5 h, 68%. (d) BBr_3 (4.6 equiv), CH_2Cl_2, rt, 20−40 min, 89% (**13**) or 83% (**15**). (e) Ph_3CBF_4 (3.4 equiv), 1,2-dichloroethane, 80 °C, 2 h, 99%.

Sonogashira coupling of the building blocks **4** and **9** led to the silylated triyne **10** (Scheme 3). Deprotection of the terminal alkyne units afforded the key triyne **11** in reasonable yield.

To achieve the desired [2+2+2] cycloisomerization and, accordingly, to build up the helix, triyne **11** was exposed to various transition metal catalysts. Initial attempts with Grubbs catalyst recently used in this context[13] were unsuccessful (Table 1, entry 1). In the case of $Co_2(CO)_8$ (ref 13), the desired cyclization took place and substituted tetrahydrohexahelicene **12** was formed in moderate yield (Table 1, entry 2). By changing the catalyst to $CpCo(CO)_2$

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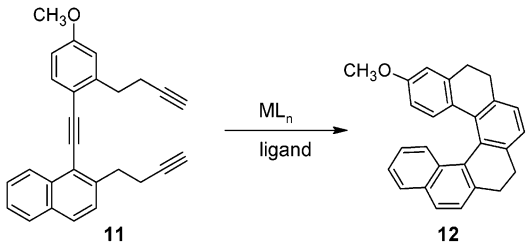
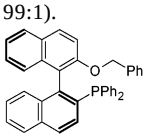
TABLE 1. [2+2+2] Cycloisomerization of 11



11 12

entry	ML_n (mol %)	ligand (mol %)	temp, °C (time, h)	yield of **12**, %[a]
1	$(Cy_3P)_2Cl_2$-Ru=CHPh (40)		rt (24)[b]	no rxn
2	$Co_2(CO)_8$ (40)		100 (1)[c]	54
3	$CpCo(CO)_2$ (20)	PPh_3 (40)	140 (2.5)[d]	68
4	$Ni(cod)_2$ (20)	(*S*)-(−)-BOP (40)	−20 (0.1)[e]	74 42% ee[f]

[a] Isolated. [b] In CH_2Cl_2. [c] In dioxane. [d] In decane, irradiated with a halogen lamp. [e] In THF. [f] (+)-Enantiomer prevails; determined by HPLC on a Chiracel OD-H column (*n*-heptane:2-propanol 99:1).

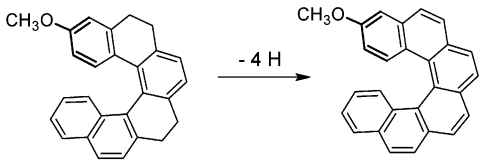


(S)-(-)-BOP

(ref 14), a better yield was achieved (Table 1, entry 3). Halogen lamp irradiation and triphenylphosphine addition were not essential but the former promoted the reaction via the catalyst activation and the latter kept the active catalyst alive for a longer period although slightly decreasing the cyclization rate. Most notably, nickel(0) catalysts[10] have proven to be very active and by employing chiral ligands absolute stereochemistry could be controlled at the helix formation. By using $Ni(cod)_2$ with the Hayashi's monophosphine ligand,[15] triyne **11** was cyclized to **12** in reasonable yield and with moderate enantioselectivity (Table 1, entry 4).[16]

To transform tetrahydrohexahelicene **12** to hexahelicene **14**, several attempts at aromatization[17] were undertaken. Both dehydrogenation of **12** by treatment with palladium on charcoal under severe conditions[18] and oxidation of **12** with manganese dioxide[19] were totally ineffective, leaving the starting material unreacted (Table 2, entries 1 and 2). Even reaction with DDQ commonly used as a dehydrogenating agent[20] afforded **14** in very low yield (Table 2, entry 3) and the bulk of the educt was recovered. Fortunately, the trityl cation as a hydride-abstracting species has been found to aromatize **12** efficiently. Being generated in situ from triphenylmethanol in trifluoroacetic acid,[21] fully aromatic **14** was produced in reasonable yield (Table 2, entry 4). Further optimization and the use of the trityl cation as a substance[22] resulted in a quantitative yield of **14** (Table 2, entry 5).[23]

TABLE 2. Aromatization of 12

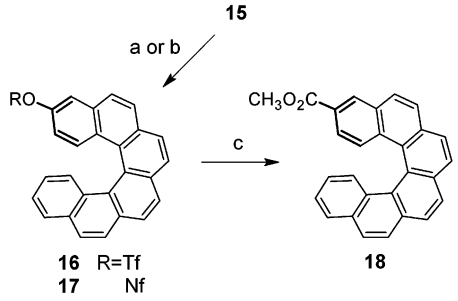


12 14

entry	reagent (equiv)	solvent	temp, °C (time, h)	yield of **14**, %[a]
1	Pd/C[b]	1-methylnaphthalene	360 (5)	no rxn
2	MnO_2 (10)	C_6H_6	80 (20)	no rxn
3	DDQ (10)	C_6H_6	100[c] (7)	6
4	Ph_3COH (3.3)	TFA	72 (2)	51
5	Ph_3CBF_4 (3.4)	1,2-dichloroethane	80 (2)	99

[a] Isolated. [b] 10% Pd/C, 100 mg/mmol of **12**. [c] In a sealed tube.

SCHEME 4. Methoxycarbonylation of Perfluoroalkylsulfonates 16 and 17[a]



16 R=Tf
17 Nf
18

[a] Reagents and conditions: (a) ^{n}BuLi (1.04 equiv), THF, −78 °C, 10 min, then Tf_2O (1.4 equiv), −78 °C, 20 min, 50%. (b) NaH (2.2 equiv), DMF, rt, 20 min, then NfF (2.0 equiv), 0 °C to room temperature, 30 min, 85%. (c) CO (atm. pressure), $Pd(OAc)_2$ (10%), dppp (10%), Et_3N (3.0 equiv), DMSO−methanol (3:2), 70 °C, 1.5−2 h, 59% (from **16**) or 89% (from **17**).

The synthesis of 3-hexahelicenol **15** was accomplished by demethylation of **14** with boron tribromide.[24] Under the same conditions, the methoxy derivative **12** also could be converted to alcohol **13** in comparable yield.

Conversion of 3-Hexahelicenol to the Corresponding C-, N-, P-, and S-Analogues. To displace the 3-hydroxy group in **15** with other functionalities, reactive triflate **16** or nonaflate **17** had to be prepared first (Scheme 4). Reaction of alcohol **15** with triflic anhydride in pyridine[15] failed but treatment of lithium alkoxide generated from **15** with triflic anhydride furnished tri-

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(16) To the best of our knowledge, this is the first example of enantioselective transition metal catalysis applied to the synthesis of substituted helicenes. Enantioselectivity achieved is not sufficient for the practical synthesis of nonracemic **12** and further search for a more effective chiral ligand is under way.

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(20) (a) Tashiro, M.; Yamato, T.; Kobayashi, K.; Arimura, T. *J. Org. Chem.* **1987**, *52*, 3196. (b) Hayakawa, K.; Takewaki, M.; Fujimoto, I.; Kanematsu, K. *J. Org. Chem.* **1986**, *51*, 5100.

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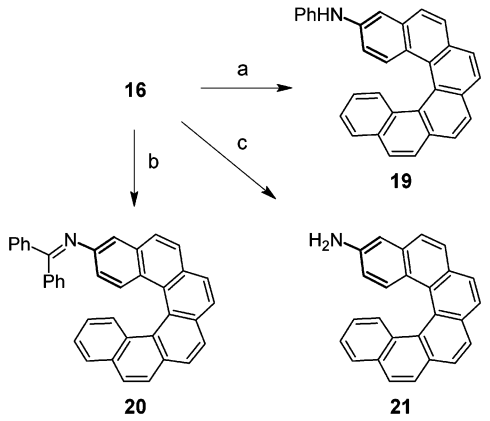
(22) Lindow, D. F.; Harvey, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 3786.

(23) 3-Methoxyhexahelicene **14** can be resolved into enantiomers on an inexpensive triacetylcellulose column. Unfortunately, its solubility in ethanol is too poor for the preparative HPLC separation.

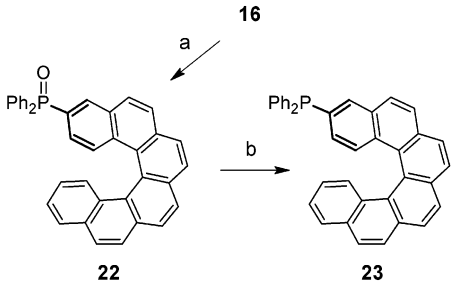
(24) 3-Hexahelicenol **15** was converted to the corresponding nonracemic camphor sulfonate, menthyl carbonate, and camphanate. No separation of diastereomers was observed in TLC (silica gel) or HPLC (Whelk O1) analyses.

SCHEME 5. Hartwig−Buchwald Amination of Triflate 16[a]



[a] Reagents and conditions: (a) $PhNH_2$ (3.1 equiv), $Pd(dba)_2$ (6%), (*R*)-(+)-BINAP (7%), Cs_2CO_3 (2.4 equiv), toluene, 90 °C, 14 h, 69%. (b) PhC(NH)Ph (1.5 equiv), $Pd(OAc)_2$ (6%), (*R*)-(+)-BINAP (6%), Cs_2CO_3 (1.4 equiv), THF, 65 °C, 40 h, 85%. (c) PhC(NH)Ph (1.2 equiv), $Pd(OAc)_2$ (4%), (*R*)-(+)-BINAP (6%), Cs_2CO_3 (1.4 equiv), THF, 65 °C, 40 h, then HCl (aq, 2 M), rt, 10 min, 57%.

SCHEME 6. Transformation of Triflate 16 to Phosphine 23[a]

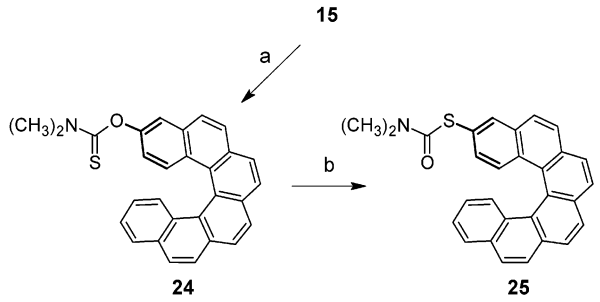


[a] Reagents and conditions: (a) $Ph_2P(O)H$ (2.0 equiv), $Pd(OAc)_2$ (6%), dppb (6%), $^iPr_2NEt$ (5.5 equiv), DMSO, 100 °C, 1 h, 74%. (b) $HSiCl_3$ (12.0 equiv), Et_3N (9.0 equiv), xylene, 120 °C, 3 h, 73%.

flate **16** in acceptable yield. Analogously, sodium salt derived from **15** reacted smoothly with perfluoro-1-butanesulfonyl fluoride to provide nonaflate **17** in high yield. Both triflate **16** and nonaflate **17** were subjected to methoxycarbonylation reaction under palladium catalysis[25] to afford the methyl ester of 3-hexahelicenecarboxylic acid **18** in reasonable or excellent yield, respectively.

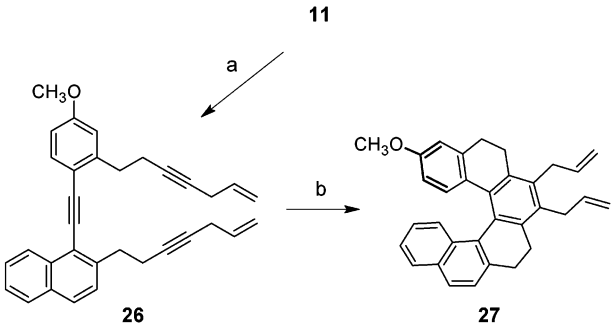
Moreover, we have demonstrated that triflate **16** could serve also as a common starting point for introducing other substituents. Being inspired by the breakthrough discovery of Pd-catalyzed aryl halide amination by Hartwig and Buchwald,[26] we applied their chemistries to the helicene series. Accordingly, on treatment of **16** with aniline or benzophenone imine under the standard reaction conditions,[27] derivatives **19** and **20** along with the parent 3-hexahelicenylamine **21** were prepared in good

SCHEME 7. Transformation of Alcohol 15 to Thiocarbamate 25[a]



[a] Reagents and conditions: (a) NaH (2.2 equiv), DMF, rt, 20 min, then $(CH_3)_2NC(S)Cl$ (1.3 equiv), 85 °C, 20 min, 83%. (b) 280 °C, 30 min, 86%.

SCHEME 8. Synthesis of Alkylated Derivative 27[a]



[a] Reagents and conditions: (a) EtMgBr (2.4 equiv), THF, 50 °C, 1 h, then CuCl (2.0 equiv), CH_2=$CHCH_2Br$ (4.0 equiv), 70 °C, 45 min, 67%. (b) $CpCo(CO)_2$ (20%), PPh_3 (40%), decane, halogen lamp, 140 °C, 3 h, 74%.

or high yield (Scheme 5). Despite the use of chiral (*R*)-(+)-BINAP as a ligand for palladium in the reaction of racemic triflate **16**, no significant kinetic resolution was observed.

Helicene-based phosphines are envisaged to serve as unique ligands for transition metals in enantioselective catalysis.[6] Due to the still limited family of effective chiral monodentate phosphines and the lasting quest for them, we decided to explore the synthetic route to the novel 3-hexahelicenyl diphenylphosphine **23** (Scheme 6). Exploiting the methodology used by Hayashi in the binaphthyl series,[15] triflate **16** was converted to diphenylphosphine oxide **22** on reaction with diphenylphosphine oxide under Pd catalysis. The following reduction with trichlorosilane led to the desired monophosphine **23**. Both steps provided good yields.

Aiming to anchor helicene-based components to the gold surface, we needed to develop the synthetic access to unprecedented helicene thiol derivatives. Therefore, the sodium salt of 3-hexahelicenol **15** was reacted with dimethylthiocarbamoyl chloride to give the corresponding *O*-hexahelicenyl thiocarbamate **24** (Scheme 7). The subsequent Newman−Kwart rearrangement[28] proceeded smoothly to provide isomeric *S*-hexahelicenyl thiocar-

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bamate **25**. Throughout the sequence high yields were achieved.[29]

Introducing Alkyl Substituents. The methodology described also allows introduction of alkyl substituents into desired positions. Starting from triyne **11**, in situ generated bisacetylide was alkylated with allyl bromide to furnish **26** in reasonable yield (Scheme 8). Then, under $CpCo(CO)_2/PPh_3$ catalysis, triyne **26** was cyclized to bisallylated tetrahydrohexahelicene **27** in good yield.

Conclusion

In summary, a synthetic sequence relying on the Co(I)- and Ni(0)-catalyzed intramolecular [2+2+2] cycloisomerization of aromatic triynes provided a reliable route to novel substituted hexahelicenes. By using simple building blocks, 3-hexahelicenol **15** was synthesized in a convergent way allowing most of the synthetic steps to be carried out on a multigram scale. Standing on the crossroads, 3-hexahelicenol **15** could be easily transformed to a series of C-, N-, P-, and S-substituted analogues in a divergent way. Thus, the carbohelicene-based primary amine, monodentate phosphine, and thiol derivative were prepared. The key helicity-forming cyclization was shown to proceed enantioselectively when making use of nickel(0) catalysis in the presence of chiral ligands. Further studies on the practical nonracemic synthesis of subtituted carbohelicenes are in progress.

Acknowledgment. The financial support by the Grant Agency of the Czech Republic (Reg. No. 203/99/1448 and 203/02/0248) and the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic (Research Project Z4 055 905) is gratefully acknowledged. We are very indebted to Dr. J. Závada of this Institute for valuable and stimulating discussions.

Supporting Information Available: Experimental details and characterization data for all synthesized compounds and ^1H NMR spectra for **3**, **4**, **6**, and **8**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034369T

(29) On treatment of **25** with lithium aluminium hydride in tetrahydrofuran, free corresponding thiol was produced in nearly quantitative yield after flash chromatography. Its structure was confirmed only by HR EI MS (calculated for $C_{26}H_{16}S$ 360.097272, found 360.095867) as ^1H NMR and IR provided complex spectra due to the partial formation of diastereomeric disulfides.