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Transition Metal Catalysed Synthesis of Tetrahydro Derivatives of [5]-, [6]- and [7]Helicene

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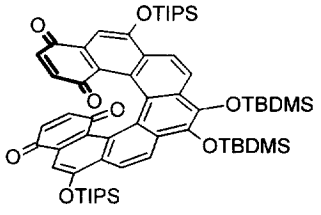
Abstract: Tetrahydro analogues of [5]-, [6]- and [7]helicene have been easily prepared by intramolecular [2+2+2] cycloisomerization of appropriate triynes under $CpCo(CO)_2/PPh_3$ or $Ni(cod)_2/PPh_3$ catalysis. This nonphotochemical methodology allows enantioselective synthesis of a helical skeleton employing the $Ni(cod)_2$/(S)-(-)-MOP catalytic system. On reaction with DDQ, tetrahydro[5]helicene was transformed to [5]helicene.

Structural features of helicenes,[1] *i. e.*, an inherently chiral, helical scaffold and a highly delocalized π-electron system, predetermine their exploitation, namely, in enantioselective catalysis[2] and material science.[3] Therefore, several new methodologies have emerged during the last decade to provide useful alternatives to the classical synthesis of helicenes based on the UV light-mediated electrocyclization of stilbene-type precursors.[4] The novel, *nonphotochemical* strategies rely on (a) the Diels-Alder cycloaddition of *p*-benzoquinone to divinyl aromatics,[5] (b) the cross-coupling reaction of thiophene or naphthalene units[6] followed by benzene ring closure,[6,7] and (c) the intramolecular Co-catalyzed [2+2+2] cycloisomerization of triynes.[8] The successful syntheses of heptacyclic representatives of carbohelicenes (**1**),[5c] heterohelicenes (**2**),[6] and helicene-like molecules (**3**)[8b] have demonstrated the efficiency of the processes noted above.



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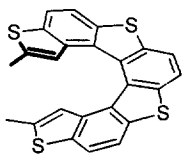

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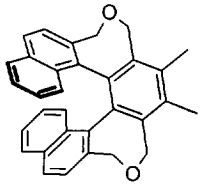

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In this paper, we describe preliminary results of a study of nonphotochemical synthesis of tetrahydro[5]helicene **6**, tetrahydro[6]helicene **13**, and tetrahydro[7]helicene **19** employing [2+2+2] cycloisomerization of triynes under Co(I) or Ni(0) catalysis (Schemes 1-3).

The synthesis of tetrahydro[5]helicene **6** started with dibromide **4** (Scheme 1), readily available from 2-iodotoluene in two steps.[9,10] Displacement of bromine with $LiCH_2C{\equiv}CTMS$ (generated *in situ* from

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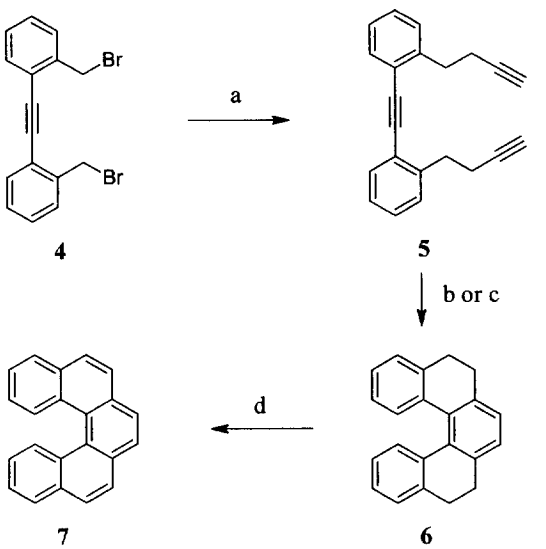
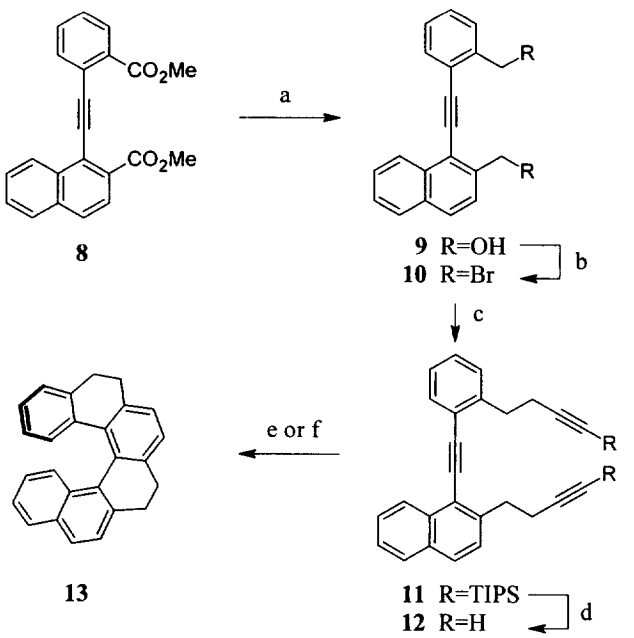


Scheme 1. (a) $LiCH_2C{\equiv}CTMS$ (2.2 equiv), THF, -78 °C, 1 h, then n-Bu_4NF (8 equiv) in THF, rt, 16 h, 67 %; (b) $CpCo(CO)_2$ (20 mol %), PPh_3 (40 mol %), decane, irrad., 140 °C, 1 h, 72 %; (c) $Ni(cod)_2$ (20 mol %), PPh_3 (40 mol %), THF, rt, 0.5 h, 66 %; (d) DDQ (6 equiv), benzene, 100 °C, 40 h, 72 %.

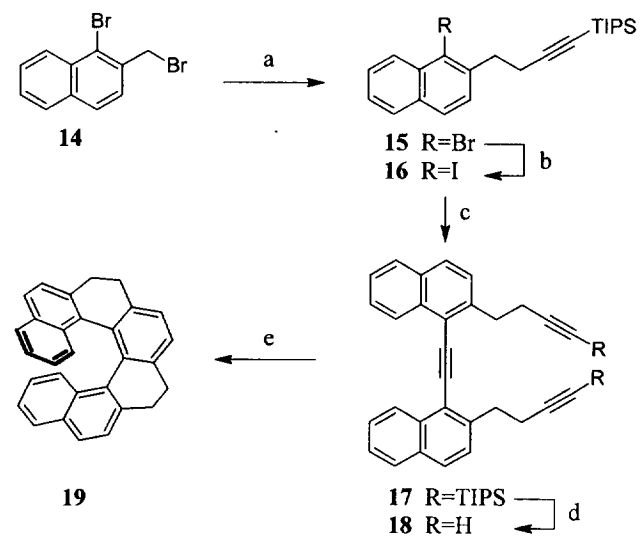
$CH_3C{\equiv}CTMS$ and *n*-butyllithium) proceeded smoothly to build up a triyne framework, however, with partially desilylated terminal alkyne units. Therefore, the reaction mixture was instantly treated with an excess of n-Bu_4NF and this one-pot procedure afforded the unprotected triyne **5** in good yield. Thus, the key intramolecular [2+2+2] cycloisomerization could be attempted. Under $CpCo(CO)_2$ catalysis, a clean reaction took place at 140 °C to provide tetrahydro[5]helicene **6**[11] in 72 % yield. In accord with our earlier observation,[8b] the presence of PPh_3 and concomitant irradiation with a halogen lamp were not essential but increased the preparative yield. Furthermore, the $Ni(cod)_2$-based catalytic system proved to be considerably more reactive allowing the cycloisomerization to be carried out at ambient temperature giving **6** as the sole product in 66 % yield. Subsequent transformation of **6** to the parent [5]helicene **7** on reaction with DDQ indicated the synthetic potential of this innovative approach.

In order to explore the applicability of the methodology to the synthesis of higher homologues, we attempted to prepare tetrahydro[6]helicene **13** and its congener tetrahydro[7]helicene **19**. Diester **8**[10a] (Scheme 2) was routinely converted into dibromide **10** that on reaction with $LiCH_2C{\equiv}CTIPS$ provided the silylated triyne **11**. The stable TIPS groups, being untouched by the lithium reagent, were easily removed by n-Bu_4NF to give the free triyne **12**. Finally, compound **12** was cyclized under the Co catalysis to **13**[12] in 64 % yield.

The synthesis of **19** relied on a slightly different strategy. Starting from the commercially available dibromide **14** (Scheme 3), a side arm with a protected alkyne unit was attached to get **15**. After halogen exchange (**15**→**16**), the naphthalene building block was coupled with gaseous acetylene under Pd(0)/Cu(I)



Scheme 2. (a) Red-Al® (1.4 equiv), toluene, 0 °C, 2 h, 99 %; (b) PBr_3 (2.3 equiv), THF, 0 °C, 2 h, 69 %; (c) $LiCH_2C{\equiv}CTIPS$ (2.2 equiv), THF, -78 °C, 1 h, 74 %; (d) n-Bu_4NF (5 equiv), THF, rt, 1 h, 97 %; (e) $CpCo(CO)_2$ (20 mol %), PPh_3 (40 mol %), decane, irrad., 140 °C, 0.5 h, 64 %; (f) $Ni(cod)_2$ (20 mol %), (S)-(-)-MOP (40 mol %), THF, -20 °C, 2 h, 53 %, 48 % ee (in favor of (+)-**13**).



Scheme 3. (a) $LiCH_2C{\equiv}CTIPS$ (1.2 equiv), THF, -78 °C, 3 h, 71 %; (b) n-BuLi (1.1 equiv), THF, -78 °C, 0.5 h, then I_2 (1.1 equiv) in THF, -78 °C to rt, 0.5 h, 92 %; (c) gaseous $HC{\equiv}CH$, $Pd(PPh_3)_4$ (5 mol %), CuI (10 mol %), piperidine, 80 °C, 2 h, 77 %; (d) n-Bu_4NF (4 equiv), THF, rt, 1 h, 70 %; (e) $CpCo(CO)_2$ (20 mol %), PPh_3 (40 mol %), decane, irrad., 140 °C, 2 h, 64 %.

catalysis to give **17**. Desilylation of **17** with n-Bu_4NF, followed by Co-catalyzed cycloisomerization of **18**, furnished **19**[13] in 64 % yield.

The feasibility of the key helicity-forming [2+2+2] cycloisomerization of triynes under Ni catalysis calls for an enantiocontrolled procedure employing chiral phosphine ligands. Thus, cyclization of **12** in the presence of (S)-(-)-MOP[14] yielded (+)-**13** with 48 % ee[15] (Scheme 2). To our best knowledge, this is the first example of enantioselective catalysis being applied to the construction of a helicene or helicene-like skeleton.

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11. **6**, ^{1}H NMR (500 MHz, $CDCl_3$/TMS): 2.62-3.00 (m, 8 H), 6.91 (dt, 2 H, J = 7.7, 7.7, 1.5 Hz), 7.10 (s, 2 H), 7.10 (dt, 2 H, J = 7.5, 7.5, 1.3 Hz), 7.22 (dd, 2 H, J = 7.9, 1.5 Hz), 7.25 (dd, 2 H, J = 7.5, 1.3 Hz).
12. **13**, ^{1}H NMR (500 MHz, $CDCl_3$/TMS): 2.66 (ddt, 1 H, J = 15.0, 4.3, 1.4, 1.4 Hz), 2.69 (ddt, 1 H, J = 15.2, 4.4, 1.4, 1.4 Hz), 2.75 (ddt, 1 H, J = 15.2, 4.4, 1.4, 1.4 Hz), 2.86 (ddd, 1 H, J = 14.8, 4.3, 2.2 Hz), 2.88 (ddt, 1 H, J = 14.1, 4.1, 2.0, 2.0 Hz), 2.91 (ddd, 1 H, J = 15.2, 4.5, 2.1 Hz), 3.01 (brddd, 1 H, J = 14.7, 10.1, 4.2 Hz), 3.04 (brddd, 1 H, J = 14.2, 10.0, 4.4 Hz), 6.34 (ddt, 1 H, J = 7.8, 6.8, 1.2, 1.2 Hz), 6.36 (dd, 1 H, J = 7.8, 1.9 Hz), 6.81 (ddd, 1 H, J = 7.4, 6.8, 1.9 Hz), 6.84 (ddd, 1 H, J = 8.3, 6.8, 1.3 Hz), 7.10 (ddd, J = 8.0, 6.8, 1.2 Hz), 7.15 (dq, 1 H, J = 7.3, 0.8, 0.8, 0.8 Hz), 7.20 (dd, 1 H, J = 7.4, 1.0 Hz), 7.25 (dd, 1 H, J = 7.4, 1.0 Hz), 7.47 (d, 1 H, J = 8.0 Hz), 7.47 (dq, 1 H, J = 8.5, 1.0, 1.0, 1.0 Hz), 7.64 (brd, 1 H, J = 8.1 Hz), 7.70 (brd, 1 H, J = 8.2 Hz).
13. **19**, ^{1}H NMR (500 MHz, $CDCl_3$/TMS): 2.76 (dddd, 2 H, J = 15.8, 14.9, 4.1, 1.3 Hz), 2.96 (ddd, 2 H, J = 14.8, 4.1, 2.0 Hz), 2.99 (ddd, 2 H, J = 15.8, 4.2, 2.0 Hz), 3.10 (ddd, 2 H, J = 14.9, 14.8, 4.2 Hz), 6.53 (ddd, 2 H, J = 8.6, 6.8, 1.3 Hz), 6.82 (ddd, 2 H, J = 8.1, 6.8, 1.2 Hz), 6.96 (dddd, 2 H, J = 8.6, 1.3, 1.2, 0.7 Hz), 7.20 (ddd, 2 H, J = 8.1, 1.3, 0.7 Hz), 7.33 (dd, 2 H, J = 8.2, 1.0 Hz), 7.34 (s, 2 H), 7.34 (d, 2 H, J = 8.2 Hz).
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15. Enantiomers of **13** were separated by HPLC on a chiral column ((R,R)-Whelk-O1, Merck).