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The Cyclotrimerisation of (+)-Camphor

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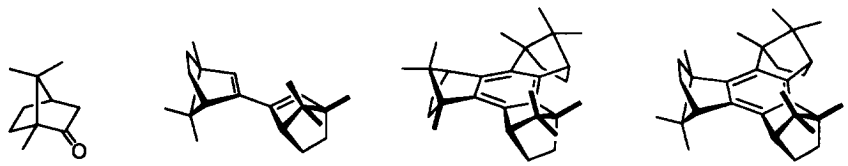
Abstract: Naturally occurring (+)-camphor was converted into 2-bromobornene and metallated at the 3-position by lithium and trimethyltin. The latter tin derivative, treated with $Cu(NO_3)_2 \cdot 3H_2O$ in THF affords the *syn* and *anti* cyclotrimers plus a number of byproducts. The rather unexpected formation of the *anti* stereoisomer plus the structure of several byproducts confirm a mechanistic proposal based on a Sn-Sn coupling process.

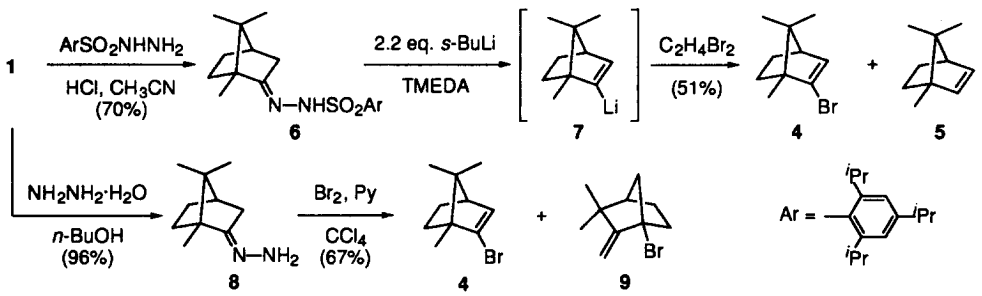
Keywords: Asymmetry, terpenes, tin compounds, copper compounds, cyclotrimerisation

For some time we have been trying to combine simple monoterpenes into more complex molecular structures embedded with a secondary chirality given by the overall geometry of the molecule.[1] The aim of the research is to provide effective chiral scaffolds from inexpensive compounds present in large quantities in the natural chiral pool. Within this project we have already reported on the oxidative dimerisation of carvone, dihydrocarvone, pinocarvone and related structures[2] as well as the coupling of menthone and menthene and the chemistry of the dimers.[3] Here we present a study on (+)-camphor **1** that has led to a number of dimers (diterpenes) and trimers (triterpenes) the most notable of which are dimer **2** and the cyclotrimers *syn*- and *anti*-**3**. The trimers **3** belong to the class of the hexasubstituted polycyclic benzenes that are compounds of current importance, either to explain the Mills-Nixon effect,[4] or to study molecular recognition[5] or to build fullerene substructures.[6]



(+)-Camphor **1** was transformed into 2-bromobornene **4** *via* the known variant of the Shapiro reaction[7] shown in Scheme 1. Since product **4** is always contaminated with bornene **5** (in our hands this was unavoidable probably because of protonation of anion **7** by unreacted tosylhydrazone **6**) we turned to the alternative synthesis shown below.[8]

Scheme 1



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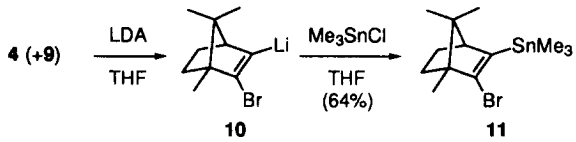
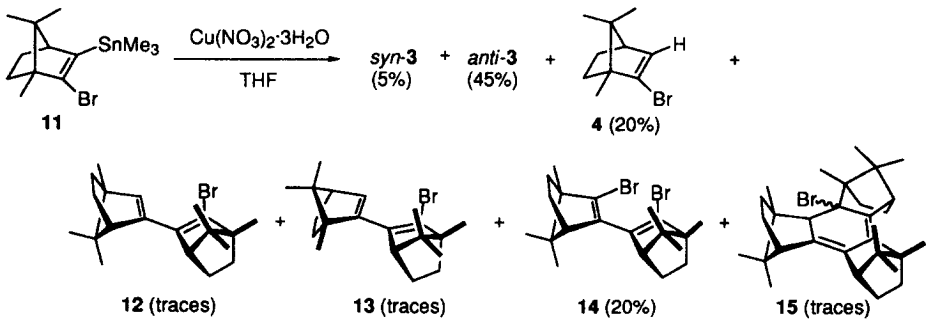
Beside engaging less expensive reagents and being more practical, this route affords as a by-product bromocamphene **9** that does not interfere in the subsequent step of cyclotrimerisation and thus does not require separation from **4**.

The mixture of **4** and **9** was lithiated by lithium diisopropylamide in THF at room temperature and the resulting vinyllithium **10** was reacted with trimethyltin chloride to afford **11** in 64% yield. The allylbromide **9** was not affected by lithiation and was readily removed from the reaction mixture by evaporation *in vacuo*.



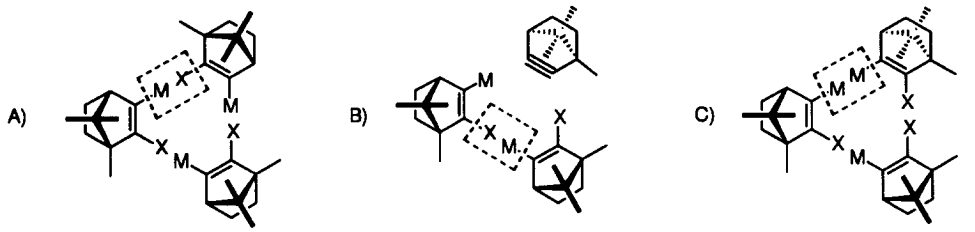
Treatment of the bromo-tin reagent **11** with copper(II)nitrate trihydrate[9] in THF (1*M* to 0.1*M* solutions) afforded a complex mixture of products that, after removal of **4** by evaporation, was separated into three main fractions by flash chromatography eluting with *n*-hexane and analysed by GC-MS and NMR spectroscopy.[10] The first fraction was composed of pure *anti*-isomer **3**, the second was a mixture of **12** and **13**, and the third was a mixture of **14**, **15** and *syn*-**3**. The separation and purification of *syn*-**3** from the latter mixture was achieved by treatment of the entire third fraction with *n*-BuLi in THF followed by quenching with water. This operation produced hydrocarbons **2** and *anti*-**3** and left unchanged *syn*-**3**. Since the three components are now well differentiated by silica gel, a second flash chromatography, cleanly and effectively separated *anti*-**3** from **2** and *syn*-**3**. While diene **2** results from debromination of **14**, *anti*-**3** is the product of HBr elimination from **15** and corroborates the proposed structure. Products **4**, **12** and **13** arise from protodestannylation of either **11** or its dimers. The formation of relatively large quantities of protodestannylated products and of dimers suggests that, at variance with other substrates,[9] the cyclotrimerisation of camphor occurs with more difficulty, probably because of steric hindrance given by the methyl groups.



The assignment of the structure to *syn* and *anti*-**3** rests on GC-MS analysis, NMR and microanalysis. The MS spectrum shows the parent peak at 402 m/z; the ^{1}H HMR and ^{13}C NMR spectra show the expected one third number of signals for the *syn*-compound with respect to the *anti* isomer. Of particular interest are the strong Overhauser effects in NOESY experiments between the bridgehead methyl and the juxtaposed bridgehead hydrogen in the case of *syn*-**3** and for the remaining non-C_3-symmetric compound between two bridgehead methyls, two bridgehead hydrogens and the remaining bridgehead methyl and hydrogen atom.

The formation of the *anti* isomer **3** was unexpected because the reaction was thought to proceed *via* a "chain" mechanism as illustrated in mechanism A below. Because the substrate is enantiopure, this mechanism should have provided *syn*-**3** only. The observed formation of *anti*-**3** may be accounted for by two mechanistic

proposals. The first suggests that the reaction proceeds *via* formation of a bornine intermediate (mechanism B below) and that for steric reasons the latter cyclises preferentially to the *anti* product. Alternatively, confirming recently reported data, one may propose a mechanism that suggests a Sn-Sn coupling as represented in mechanism C.[11] Both the B and C hypothesis find precedents in the literature. The bornine hypothesis is actually the mechanism put forward by H. Hart in the cyclotrimerisation reaction of 2-chloro[2.2.2]bicyclo-[3,4:5,6]dibenzooct-2-ene with *n*-BuLi and it is largely accepted in subsequent reports by other authors.[12] The Sn-Sn coupling is known to occur for vinyl stannanes[13] and such coupling products have always been observed in our cyclotrimerisation reactions.[9]



Chain hypothesis gives *syn*-**3** only

Bornine hypothesis gives *syn*- plus *anti*-**3** (*anti* represented)

Sn-Sn Coupling hypothesis gives *anti*-**3** only

The latter C hypothesis implies that, under the reaction conditions used, Sn-Sn coupling generates the dibromodimer **14** and is followed by a formal Br-Sn exchange that generates a new activated tin species that allows for further coupling towards the trimer. Because the starting material is enantiopure, the dimer **14** possesses a C_2 symmetry and, whatever the approach to this dimer, the outcome will always be an *anti* structure. As the very last step, the formation of the central aromatic ring may occur *via* a Cope rearrangement as it is known to happen with remarkable ease in these systems.[4] On the basis of recent mechanistic work on the subject,[11] we actually think that the reaction occurs exclusively *via* the latter mechanism C and that the presence of the observed small quantity of *syn*-**3** is due to some Br-Sn exchange on the starting monomer **11**. In other words, we suggest that the reaction proceeds *via* a copper activated tin intermediate able to perform Sn-Sn coupling, Br-Sn exchange and protodestannylation. Proof of such a proposal is the formation of the species detected in the reaction mixture.

In conclusion, with this work we have provided the synthesis of the enantiopure diene of C_2 symmetry **2** and of its dibromoderivative **14**. In analogy to previous reports,[3] both **2** and **14** can be transformed into useful molecules and ligands for catalysts. Above all, in our minds, is of interest the first synthesis of *syn*-**3** that represents a hitherto unknown rigid enantiopure C_3 chiral benzene ring. In view of the inexpensive method of preparation and the uniqueness of its structure, *syn*-**3** can be used as substrate for the type of complexes that electron rich aromatic hydrocarbon are known to provide.[4]

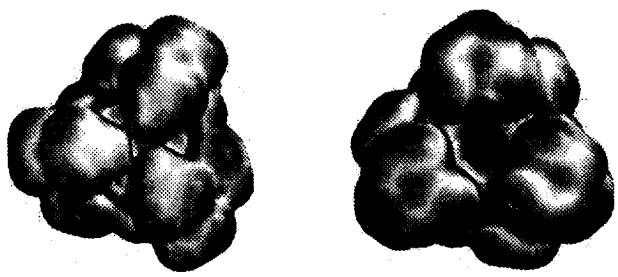


Figure 1. Top and bottom views of semiempirically calculated (AM1)[15] electrostatic surfaces of *syn*-**3**. The values [kcal·mol^{-1}] of most negative electrostatic potentials on the electron density surfaces are –7.8 (top center) and –28.0 (bottom center).

In this perspective, the calculated structure and electron density shown in Figure 1 compare well with data presented in the literature[16] and suggest that *syn*-**3** is a highly promising molecule for future practical applications.

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(10) *Cylcotrimerisation reaction:* In a Pyrex test tube **11** (560 mg, 2.0 mmol) and $Cu(NO_3)_2 \cdot 3H_2O$ (520 mg, 2.2 mmol) was vigorously stirred under argon atmosphere. Anhydrous THF (320 μL, 4.0 mmol) was introduced *via* syringe and the mixture was stirred for 18 hrs. The mixture was diluted in pentane (100 mL), washed with 5% ammonium hydroxide (3×20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash-chromatography over silica-gel (eluant hexanes). *Anti*-**3** (oil), 120 mg (45% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.98 (1 H, d, J = 4.0 Hz), 2.65 (1 H, d, J = 3.9 Hz), 2.61 (1 H, d, J = 3.8 Hz), 2.01-1.90 (3 H, m), 1.78-1.68 (3 H, m), 1.84 (6 H, s), 1.30 (3 H, s), 1.29-1.20 (2 H, m), 1.13-0.94 (4 H, m), 0.90 (3 H, s), 0.87 (3 H, s), 0.86 (3 H, s), 0.53 (3 H, s), 0.46 (3 H, s), 0.42 (3 H, s).
Purification of syn-**3**: The mixed fraction of **14** and *syn*-**3** in dry THF was treated with excess of *n*-BuLi at –78 °C under nitrogen for 15 min. The temperature was raised to 0 °C and a small amount of water was introduced. The mixture was diluted in pentane, dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was purified by flash-chromatography over silica-gel (eluant hexanes). *First eluate:* **2** (waxy solid), 80 mg (15% yield), mp 42-44 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.42 (2 H, s), 2.36 (2 H, d, J = 3.1 Hz), 1.84-1.60 (4 H, m), 1.36-1.26 (2 H, m), 1.19-1.04 (2 H, m), 0.98 (6 H, s), 0.83 (6 H, s), 0.79 (6 H, s). *Second Eluate: syn*-**3** (waxy solid), 15 mg (5% yield), mp 56-58 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.98 (3 H, d, J = 4.0 Hz), 1.99-1.91 (3 H, m), 1.76-1.68 (3 H, m), 1.29 (9 H, s), 1.16-1.00 (6 H, m), 0.89 (9 H, s), 0.55 (9 H, s).

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