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Efficient Synthesis of Benzo Fused Tetrathia[7]helicenes

Deepali Waghray, Wienand Nulens, and Wim Dehaen*

Molecular Design and Synthesis, Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium

wim.dehaen@chem.kuleuven.be

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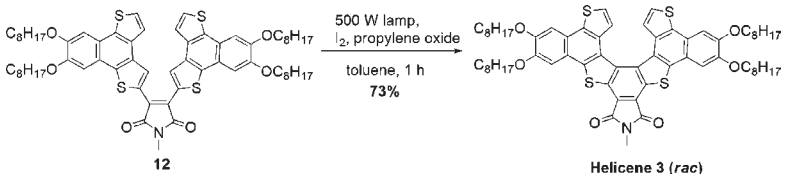
ABSTRACT



An efficient route toward the synthesis of symmetrical and unsymmetrical benzo fused tetrathia[7]helicenes substituted with electron donor (ED) and electron acceptor (EA) groups is reported. A common, readily available precursor 1,2- bis-(2-thienyl)benzene was used to synthesize different helicenes through a Wittig reaction, Stille coupling, and modified oxidative photocyclization.

Helicenes constitute a fascinating class of ortho-annulated polycyclic aromatic or heteroaromatic compounds endowed with inherent chirality due to the helical shape of their π-conjugated system.[1] These nonplanar helical molecules exhibit unique electronic[2] and chiro-optical properties.[3] Enantiopure functionalized derivatives of (hetera)helicenes can be isolated owing to their stability and rigid helical framework. They are potential candidates for chiral catalysts,[4] helical ligands,[5] and asymmetric inducers[6] and have been used as building blocks for helical conjugated polymers.[7] Since the synthesis of hexahelicene in 1956 by Newman and Lednicer[8] via Friedel–Crafts cyclization, various synthetic routes have been described for carbahelicenes. These include the widely used oxidative photocyclization, also known as the Mallory reaction,[9] and a few nonphotochemical routes[10] such as Diels–Alder reactions, cyclotrimerization of acetylenes, carbenoid coupling, radical cyclization, and olefin metathesis.

The synthesis of the first [7]helicene was reported by Martin and co-workers in 1967, who employed the oxidative photocyclization of stilbenes as the key process.[11] Since then, the Mallory reaction has remained the method

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of choice for constructing the last ring(s) in the final assembly and aromatization of the system for both carba- and heterahelicenes. This method has been optimized and is still widely applied. In 1991, Katz reported an improved method for the oxidative photocyclization using iodine as the oxidant and propylene oxide as a hydrogen iodide scavenger which reduces side reactions such as photoreduction[12] and increases the efficiency of the reaction.

In recent years, the preparation of heterohelicenes and in particular tetrathia[7]helicene derivatives has become a field of great interest in order to exploit their unique properties. These molecules show interesting self-assembling behavior in the solid state. Furthermore, they form aggregates to give helical supramolecular architectures potentially applicable to nonlinear optics and circularly polarized luminescent materials.[13] These helicenes are potential candidates for studying one- or two-dimensional molecular wires in the field of organic semiconductors.[14] The ability of tetrathia[7]helicenes to be used as chiral ligands has also been demonstrated.[15]

The potential of tetrathia[7]helicene and its derivatives suffers from major drawbacks in their synthesis. The literature procedures for the synthesis of tetrathia-[7]helicenes describe the formation of stilbene-type precursors in the trans conformation or a mixture of cis and trans isomers, where the trans isomer predominates,[16] leading to poor solubility and inadequately functionalized building blocks with low overall yield in the final photocyclization step. As a result, the homochiral forms are not readily available for investigating catalytic or material properties. The important challenge in expanding the potential of helicenes is therefore to develop synthetic strategies that provide efficient access to a variety of helical frameworks.

Our main focus was to develop efficient routes to helicenes that are amenable to scale-up and also provide flexibility for functionalization and hence tuning of the chiro-optical properties. Herein, we report progressively efficient synthetic routes toward the new heterohelicenes **1**–**3** with benzo fusion to the tetrathia[7]helicene core (Figure 1).

We have addressed the issues of solubility of the precursors and final products by introducing long alkoxy chains and also devised an efficient method to obtain substituted precursors which are conformationally in close resemblance with the final helicene. Thus, the problems of *cis*–*trans* isomerization, [2 + 2] cycloaddition at higher

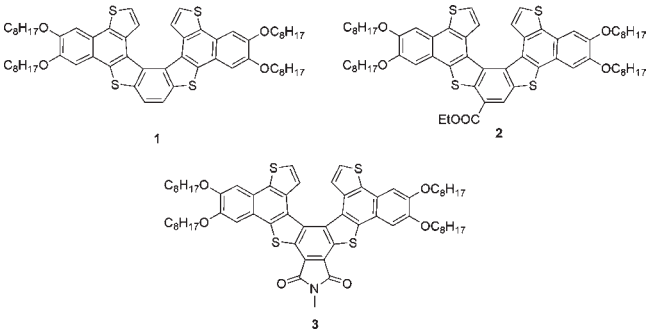

Figure 1. Benzo fused hetero[7]helicenes.

concentrations, and also low solubility are avoided, and hence photocyclization can occur efficiently. The presence of the ester functionality in helicene **2** and the maleimide functionality in helicene **3** impart electron-withdrawing character and can be used as handles for further functionalization.

Our approach makes use of 1,2-bis(octyloxy)-4,5-bis(2-thienyl)benzene **4** as a versatile building block for the synthesis of heterohelicenes **1**–**3**. This compound was easily synthesized from catechol, according to slightly modified literature procedures. Dibromination[17] of catechol using $Br_2/CHCl_3$, followed by dialkylation[18] with 1-bromooctane employing 2-butanone as the solvent, furnished dibromo-dialkoxy catechol in good yields which was in agreement with the literature procedures. A final coupling of two thiophene units to the dibromo-dialkoxy compound *via* $ZnCl_2$ and $Pd(PPh_3)_4$ promoted Negishi coupling[19] gave the compound 1,2-bis(octyloxy)-4,5-bis-(2-thienyl)benzene **4** in 87% yield (see Supporting Information). Compound **4** was subjected to oxidative photocyclization using iodine as the oxidant, excess propylene oxide as the hydrogen iodide scavenger, and toluene as the solvent. The reaction mixture was irradiated at room temperature using a UV lamp to obtain the photocyclized compound **5** in 82% yield.

Vilsmeier formylation of compound **5** using DMF, $POCl_3$, and dichloroethane as the solvent gave aldehyde **6** in 71% yield. Unfortunately, the conventional McMurry coupling of the aldehyde to obtain the alkene did not work on our substrate. The alternate route was *via* the Wittig reaction. Aldehyde **6** was reduced to alcohol **6a** in 89% yield using sodium borohydride and THF/MeOH as the solvent. The alcohol was subsequently converted to phosphonium salt **7** by reaction with triphenylphosphonium bromide in refluxing CH_3CN for 12 h with a yield of 67%.

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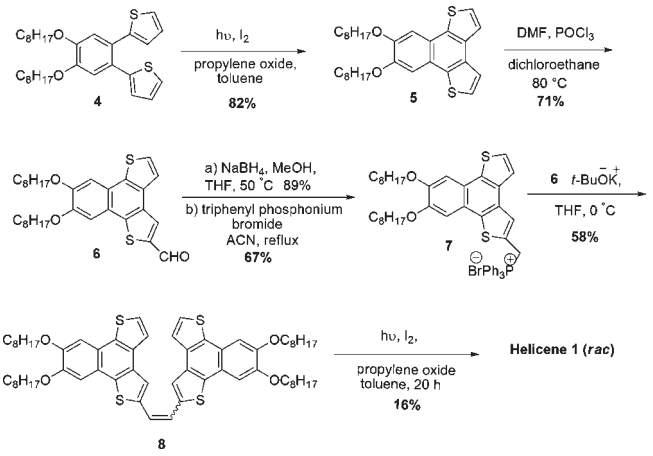
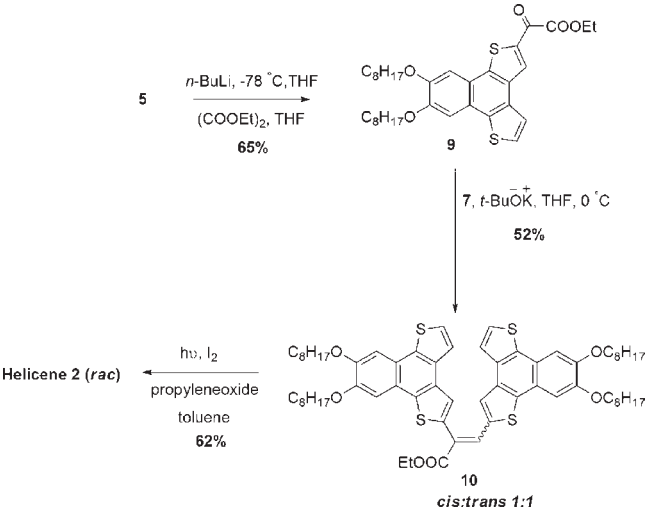
Scheme 1. Wittig Reaction and Photocyclization



Wittig olefination of **6** and **7** in the presence of *t*-BuOK as base in dry THF at 0 °C gave the alkene **8** in 58% yield. The alkene obtained could not be characterized by NMR spectroscopy due to its poor solubility in various organic solvents. This can be attributed to the fact that the trans isomer predominates. Since in principle *E*−*Z* isomerization occurs during the irradiation process, no specific configuration of the alkene precursor was required. Thus, we subjected the alkene obtained to oxidative photocyclization using the same conditions as those for the synthesis of compound **5**. This afforded helicene **1** in 16% yield, which was fully characterized by NMR spectroscopy and HRMS and shows good solubility in a variety of medium-polarity solvents such as CH_2Cl_2, ethyl acetate, and THF. The ^{1}H NMR spectrum of the helicene **1** is straightforward and shows sharp signals for each proton. Singlets at δ = 7.99, 7.56, and 7.52 ppm corresponded to aromatic protons, and doublets at 6.94 and 6.74 ppm corresponded to the terminal thiophene protons; these signals are indicative of aromatization of the system. A major drawback encountered in the process is the poor solubility of the trans alkene **8** which requires isomerization to the less stable *cis* form and then cyclization, hence increasing the reaction time. Furthermore, to avoid the [2π+2π] dimerization the reaction has to be run under high dilution conditions (0.3 mM). The presence of alkoxy chains did not significantly effect the solubility of the intermediates in this case.

To solve this problem, we proceeded with the approach to obtain precursors which are in a *cis* conformation.[20] We devised a route which could lead us to a precursor with better solubility and reduces the problems with *cis*−*trans* isomerization. To prove this we prepared the monoester alkene **10** which has indeed better solubility in various organic solvents and photocyclized efficiently in comparison to the earlier alkene **8**. The monoester alkene could be easily obtained starting from building block **5**. Monolithiation of compound **5** at −78 °C using *n*-BuLi (2.5 M in hexane) in dry THF, followed by treatment with diethyl oxalate, furnished oxoester **9** in 65% yield while 12% of compound **5** was recovered. Wittig olefination of oxoester **9** with Wittig reagent **7** gave alkene **10** as a 1:1 mixture of *cis*−*trans* isomers in 52% yield. Unlike alkene **8**, compound **10** was fully characterized by ^{1}H and ^{13}C NMR spectroscopy owing to its better solubility. The ratio of the isomers was determined by ^{1}H NMR. Sharp singlets at δ = 7.87 and 6.81 ppm corresponded to the vinylic protons of the *cis* and *trans* isomers respectively. Compound **10** was subjected to oxidative photocyclization under the optimized conditions mentioned in Scheme 1. The reaction was run at high dilution conditions (0.45 mM) (Scheme 2).

Scheme 2. Wittig Reaction with Oxoester and Photocyclization



As envisaged, the photocyclization proceeded efficiently and with a significant increase in the yield of helicene **2** to 62% as compared to 16% of helicene **1**. Interestingly, it was the *cis* isomer that converted completely and a significant amount of the unreacted *trans* isomer was recovered from the reaction mixture. Monoester helicene **2** was completely characterized by NMR spectroscopy and HRMS. ^{1}H NMR showed sharp singlets at δ = 8.76, 7.73, 7.55, and 7.54 ppm, and a multiplet at 6.8 ppm corresponding with the terminal thiophene protons. These signals give a clear indication of ring closure and final aromatization of the system. The substitution on the alkene with the ester group did prove to give better results, and we could observe that the *cis* conformation of the precursor indeed leads to better solubility and efficient photocyclization.

Expanding on this, we expected that a precursor which is locked in a *cis* conformation would have no options for *cis*−*trans* isomerization and hence would be able to be photocyclized even more efficiently. This would reduce both reaction time and the need for high dilution conditions, allowing for a more efficient scale-up. Thus,

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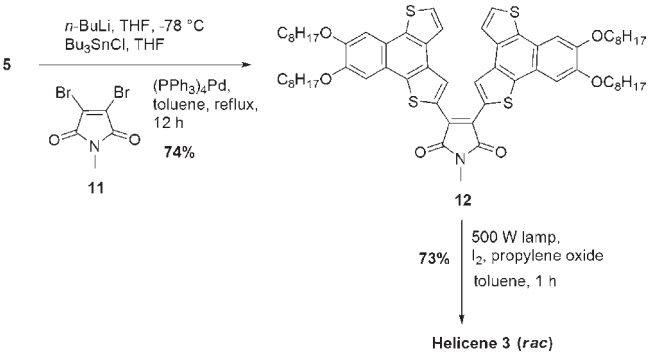
palladium-mediated coupling between dibromomaleimide **11** and the *in situ* prepared monostannyl derivative of compound **5** was employed to give the highly conjugated compound **12** in one step (Scheme 3). Compound **5** was

Scheme 3. Stille Coupling and Photocyclization



monolithiated using *n*-BuLi and then treated with tributyl stannyl chloride to obtain the monostannyl derivative in quantitative yield. Since protodestannylation was observed to occur during chromatographic purification on silica gel, the stannyl derivative was used without further purification. The intensely violet compound **12**, the key precursor, was obtained in 74% yield by Stille coupling between the monostannyl derivative and dibromo maleimide **11**.[21] This precursor **12** closely resembles the helicene and has good solubility in various organic solvents. Compound **12** was characterized by NMR and HRMS. The ^{1}HNMR spectrum was straightforward, and a sharp singlet at δ = 8.52 ppm corresponded to the thiophene protons attached to the maleimide group. Compound **12** was subjected to irradiation using a 500 W high intensity lamp (visible light) in the presence of iodine and propylene oxide with toluene as the solvent (1.0 mM). In contrast to the earlier compounds, which required more than 12 h to finish the photocyclization, this reaction was completed in 1 h and helicene **3** was obtained in 73% yield. The reaction time was reduced drastically, the reaction concentration could be increased, and as a result the efficiency of the reaction increased. Helicene **3** was obtained in a substantial amount in three steps starting from building block **4**. It was characterized completely by spectroscopy. Disappearance of the ^{1}H NMR signal at δ = 8.52 ppm for helicene **3** clearly indicated the occurrence of photocyclization and final aromatization of the system.

The absorption spectra for helicenes **1**, **2**, and **3** in dilute $CHCl_3$ solutions are shown in Figure 2. We observed that the absorption of helicenes **2** and **3** were red-shifted in

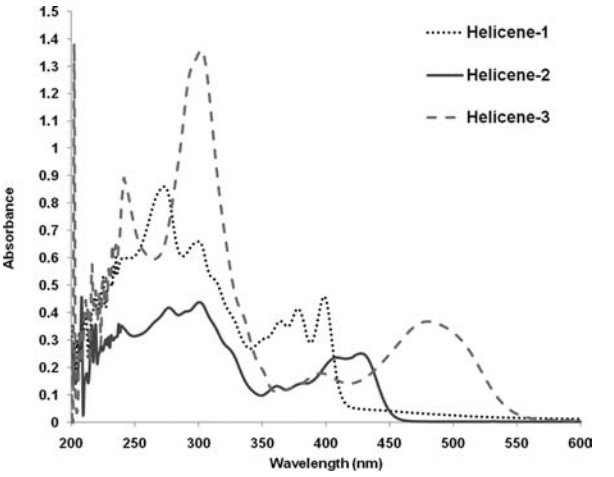


Figure 2. UV−visible spectra of helicenes **1**, **2**, and **3** in dilute $CHCl_3$ solution.

comparison to helicene **1** which was due to the presence of ester and maleimide functionalities.

In summary, we demonstrated an efficient route to new hetero[7]helicenes which allows the synthesis of precursors in a conformation closely resembling the final helicene. Obtaining the precursors in a *cis*-helicene-like conformation by substituting the double bond assists in increasing the solubility of the substrates, allows for easier characterization, and increases the efficiency of final photocyclization to the corresponding helicenes to a considerable extent. The methodology used here can be amenable to scale-up, especially for the maleimide derivatives and also to a variety of modifications.

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Supporting Information Available. Detailed experimental procedures, additional spectroscopic data, and NMR spectra of all the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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