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One-Step Synthesis of [16]Helicene**

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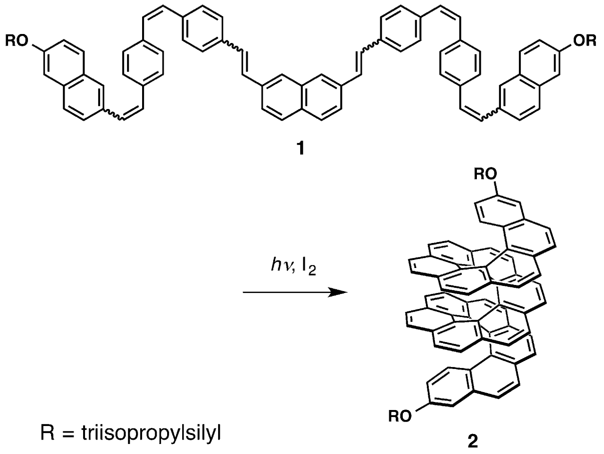
Abstract: *A single-strand arylene–vinylene precursor containing four phenylene and three naphthylene units linked together with six vinylene spacers undergoes helical folding via sextuple photocyclization to give a [16]helicene core in a single step. The phenylene and naphthylene units are arranged in the precursor such that unfavorable side reactions (anthracene or benzoperylene formation) are avoided, and this is the key to the success of the one-step synthesis of [16]helicene, which is the longest [n]helicene that has been synthesized to date.*

The [*n*]helicenes have attracted continuous interest in the past few decades, not only because of their structural curiosity and beauty but also for the unique properties caused by their helically extended chiral π systems.[1,2] With increasing *n* number, the π electrons start to form additional layers; a double layer at $n=7$ and a triple layer at $n=13$. In the triple-layered structures, the framework around the middle is tightly compressed and it is hard to release the steric distortion. This makes the synthesis of higher [*n*]helicenes with *n* numbers of 13 and over more difficult. In fact, despite numerous attempts to synthesize the higher helicenes, [14]helicene, reported by Martin and Baes in 1975,[3a] is still the longest homologue and provides one of only a few examples of a triple-layered [*n*]helicene.[3] Herein, we report the one-step synthesis of [16]helicene by the multiple photocyclization of single-strand oligo(arylene–vinylene) precursor **1** (Scheme 1). Although the oxidative photocyclization of stilbenes[4] is the most frequently employed reaction in helicene synthesis, attempts to apply this fundamental reaction to the synthesis of higher helicenes ($n \geq 13$) have failed.[5] The key to the success of the [16]helicene synthesis in this study is the rational design of precursor **1**, in which the phenylene and naphthylene units are arranged such that unfavorable side reactions are avoided.



Scheme 1. One-step synthesis of [16]helicene **2** by multiple oxidative photocyclizations of precursor **1**.

The oxidative photocyclization of (*Z*)-stilbene frameworks is still the most common and powerful method for synthesizing a variety of helicene homologues[6] because of easy access to the precursors by Wittig olefination and facile *E*/*Z*-photoisomerization that allows the use of *E*/*Z* mixtures as precursors. Martin's [14]helicene was formed by the photocyclization of a precursor olefin with a [3]+[6]+[3] or [4]+[4]+[4] triad structure, where "[*n*]" and "+" denote *ortho*-fused [*n*]helicene subunits and vinylene linkers, respectively.[3a] Our synthetic strategy utilizes only the simplest subunits [1] and [2] (namely, phenylene and naphthylene units). Larger [*n*] subunits were not included in our precursor design because of increasing synthetic difficulty, and because the [6]+[6] precursor failed to furnish [13]helicene under any conditions, despite favorable theoretical predictions.[5] We, however, avoided the simplest [1]+[1]+[1] and [2]+[2] sequences in the precursor to exclude the formation of an unfavorable [5]helicene framework that easily cyclizes into benzoperylene (Scheme 2a).[7] The [2]+[1]+[2] sequence was also avoided because it has been reported that this sequence predominantly gives planar dinaphthanthracene rather than the expected [7]helicene (Scheme 2b).[6a] Based on these considerations, we deduced the following guideline for the design of the precursor olefins: [2] units must be separated by two [1] units. Namely, only ⋯+[2]+[1]+[1]+[2]+[1]+[1]+[2]+⋯ sequences can undergo multiple oxidative photocyclizations without unfavorable benzoperylene or anthracene formation.

To confirm our synthetic guideline for the precursor synthesis, the simplest [2]+[1]+[1]+[2] precursor **3** was prepared and its photocyclization into [9]helicene **4** was examined. Precursor **3** was easily prepared from (*Z*)-4,4′-dibromostilbene[8] by bis-formylation (*n*BuLi, DMF; 84%) and Wittig olefination with (2-naphthylmethyl)triphenylphosphonium bromide[9] (82%). A toluene solution of precursor **3** was irradiated with a high-pressure Hg lamp at 90 °C for 8 h in

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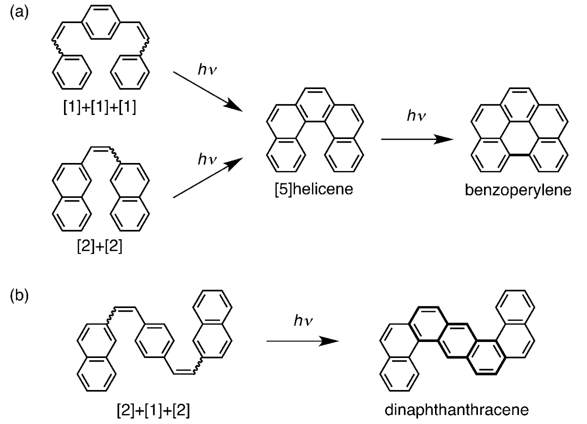


Scheme 2. Unfavorable side reactions in the photocyclization. a) Benzoperylene formation from [5]helicene. b) Predominant formation of dinaphthanthracene from the [2] + [1] + [2] precursor.

the presence of I_2 (oxidant, 3 equiv) and propylene oxide (acid scavenger, 50 equiv) to give [9]helicene (**4**) in 67 % yield (Figure 1). The yield of [9]helicene was comparable to reported yields,[3b,c,6a–c] and verifies the synthetic guideline proposed above.

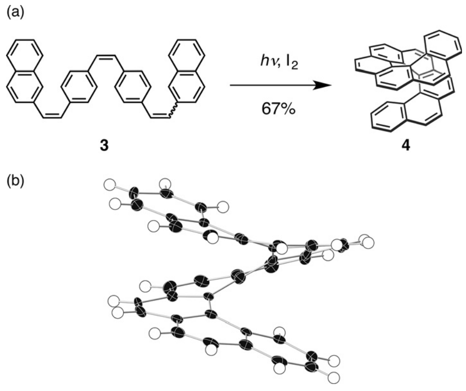
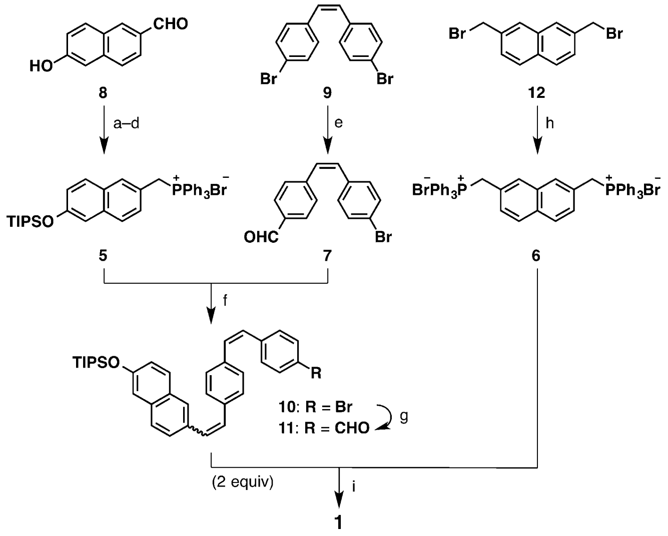


Figure 1. One-step synthesis of [9]helicene (**4**) from [2] + [1] + [1] + [2] precursor **3**. a) Reaction scheme. b) X-ray crystal structure of **4** (ORTEP, thermal ellipsoids set at 50% probability). Only one enantiomer is observed in the crystal structure because of spontaneous resolution into the $P2_1$ chiral space group. The absolute stereochemistry was not determined from the data and the *M* form is tentatively shown.

Spontaneous resolution was observed when **4** was crystallized from chloroform/hexane and the crystallographic analysis revealed only one enantiomer of **4** packed in the $P2_1$ chiral space group (Figure 1 b).

According to our guideline, we next designed extended precursor **1**, which has a [2] + [1] + [1] + [2] + [1] + [1] + [2] sequence and was expected to give [16]helicene. Both the bulky substituent (TIPSO: triisopropylsilyl ether) at both ends of the strand and the non-planar, *Z*-configured olefin parts were necessary to increase the solubility of **1**. This single-strand precursor was synthesized as shown in Scheme 3. The sequence was retrosynthetically divided into three components: terminal [2], central [2], and [1] + [1] units (**5**, **6**, and **7**, respectively). Terminal [2] unit **5** was prepared in high yield in four steps from 6-hydroxy-2-naphthaldehyde (**8**) (TIPSCl/imidazole, $NaBH_4$, CBr_4/PPh_3, and then PPh_3; see the Supporting Information). [1] + [1] unit **7** was prepared by the mono-formylation of (*Z*)-4,4′-dibromostilbene (**9**)[8] (*n*BuLi/DMF). Subsequently, **5** was coupled with **7** to give **10** in 77 % yield [(*Z*,*Z*):(*E*,*Z*) = 67:33]. Bromide **10** was again formylated to give [2] + [1] + [1] unit **11** in 79 % yield. Finally, bisphosphonium salt **6**, prepared quantitatively from 2,7-bis(bromomethyl)naphthalene (**12**),[10] was coupled with **11** by double Wittig reactions to furnish [2] + [1] + [1] + [2] + [1] + [1] + [2] precursor **1** as a yellow sticky solid in 85 % yield. The precursor was soluble in chloroform and toluene.[11]



Scheme 3. Preparation of [2] + [1] + [1] + [2] + [1] + [1] + [2] precursor **1**: a) TIPSCl, imidazole, CH_2Cl_2; b) $NaBH_4$, EtOH, 86% in 2 steps; c) CBr_4, PPh_3, CH_2Cl_2; d) PPh_3, toluene, 78% in 2 steps; e) *n*BuLi, THF then DMF, 67%; f) [18]-crown-6, KOH, CH_2Cl_2, 77%; g) *n*BuLi, THF then DMF, 79%; h) PPh_3, $CHCl_3$, quant.; i) [18]-crown-6, KOH, CH_2Cl_2, 85%.

A toluene solution of precursor **1** was irradiated with a high-pressure Hg lamp at 90 °C in the presence of I_2 (oxidant, 6 equiv) and propylene oxide (acid scavenger, 100 equiv). The photocyclization was carefully monitored by HPLC (254 nm, UV detection; Figure 2). After 24 h irradiation, precursor **1** [retention time (t_R) of the first peak = 4.68 min] completely disappeared and numerous initial products appeared, which, upon further irradiation (48 h irradiation in total), converged to some extent to a single prominent peak at $t_R = 4.58$ min. This fraction was isolated by preparative HPLC and a yellow solid was obtained in 7 % yield. To our delight, the molecular mass of the product and its isotope pattern were consistent with the calculated value for TIPSO-[16]helicene **2** ($C_{84}H_{76}O_2Si_2$, calcd for $[M]^+$: 1172.5, found: 1173.0; see the Supporting Information, Figure S10). We were thus confident that the sextuple photocyclization of **1** did proceed to give unprecedented [16]helicene **2**.

NMR spectroscopy provided further structural information for TIPSO-[16]helicene **2** (Figure 3). In the 1D ^1H NMR spectrum, the terminal aromatic protons (H_p and H_q) are

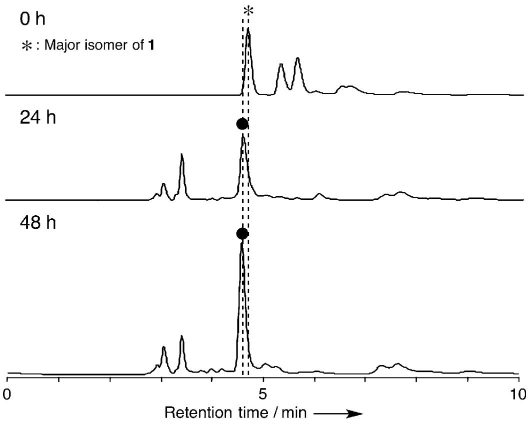


Figure 2. HPLC chromatograms for the time course (0–48 h) of the sextuple photocyclization of **1** to **2**. The prominent peak, denoted by the black circle, was isolated by preparative HPLC after 48 h irradiation.

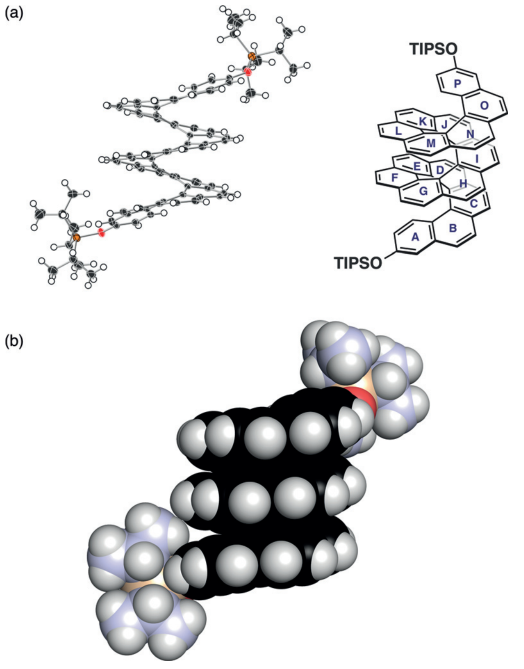


Figure 4. a) Left: ORTEP representation (thermal ellipsoids set at 50% probability) of the X-ray crystal structure of TIPSO-[16]helicene **2**. Right: labeling scheme of the aromatic rings. b) Space-filling representation of X-ray crystal structure of **2**. Red O, yellow Si, blue/black C.

considerably upfield shifted ($\delta = 5.51$ and 5.78 ppm, respectively), indicating that these aromatic protons are located above the other aromatic rings. The signal of H_p is a doublet of doublets, and this is characteristic of the inner *ortho*-protons of the terminal benzenes. The two methyl groups of each isopropyl group in the TIPS terminals are diastereotopic owing to the chiral environment provided by the aromatic helix.

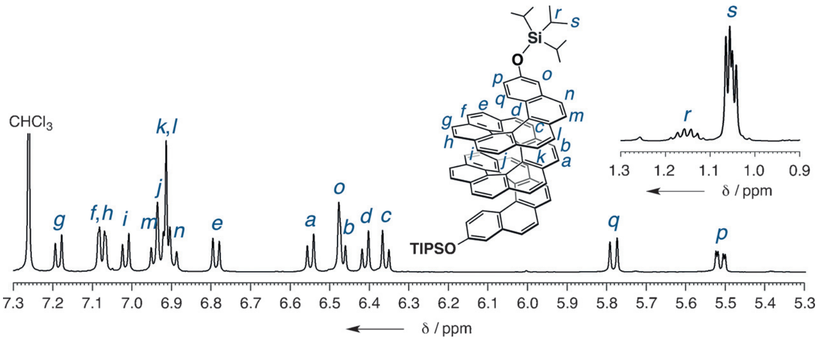


Figure 3. Aromatic region of the ^1H NMR spectrum of TIPSO-[16]helicene **2** (500 MHz, $CDCl_3$, 300 K). Inset: the aliphatic region.

The triple-layered structure of **2** was unambiguously determined by X-ray crystallographic analysis (Figure 4).[12] A single crystal suitable for analysis was obtained by vapor diffusion of methanol into a chloroform solution of **2** at 4 °C over 1 day. Unlike [9]helicene, spontaneous resolution was not observed. A racemic mixture of **2** crystallized in the $P2_1/c$ space group and the crystal structure contains molecules of both (*P*)-**2** and (*M*)-**2** that are closely engaged with each other. The crystal structure of **2** shows that, as expected, the i, $i+6$, and $i+12$ benzene rings ($i = 1, 2, 3$, or 4) are forced to form the triple-layered structure. Benzene ring **H**, embedded in the middle of the molecule, is compressed by rings **B** and **N** with interplanar angles[13] of 6.2° and 4.1°, respectively. Tail-end ring **A** is, in contrast, slightly warped with a relatively large interplanar angle (14.2°) with respect to ring **G**, presumably a result of the release of steric distortion and electronic repulsion. The shortest pitch of 3.23 Å is found between rings **A** and **G** at their inner edges, whereas the largest pitch (4.13 Å) is at the peripheral edges of rings **J** and **P**.[14] The average C–C bond lengths at the inner and outer edges are, respectively, 1.44 Å and 1.36 Å, slightly elongated and shortened compared with the C–C bond length in benzene (1.40 Å)[15] (Supporting Information, Figure S3).

The racemic mixture of **2** was easily resolved by chiral HPLC. The circular dichroism (CD) spectra of (*P*)-**2** and (*M*)-**2** were complete mirror images (Supporting Information, Figure S13), and the absolute configurations were assigned based on the empirical rule that (*P*)-helicenes exhibit strong positive Cotton effects for the major absorption at a long-wave region.[16]

Finally, TIPSO-[16]helicene **2** was converted into unsubstituted [16]helicene **13** in three steps: 1) desilylation with TBAF; 2) trifluoromethanesulfonation with Tf_2O/pyridine; then 3) reduction with $Pd(OAc)_2/PPh_3/Et_3N/HCO_2H$ (Figure 5a). [16]helicene **13** was obtained as a yellow solid in approximately 10% yield. Although **13** is almost insoluble in all common solvents, data acquisition (8000 times) with a CryoProbe-equipped 500 MHz NMR spectrometer afforded a clear ^1H NMR spectrum of **13** that shows two triplet-like signals at $\delta = 5.86$ and 6.66 ppm. These signals are characteristic of H_b and H_c, respectively, and are thus

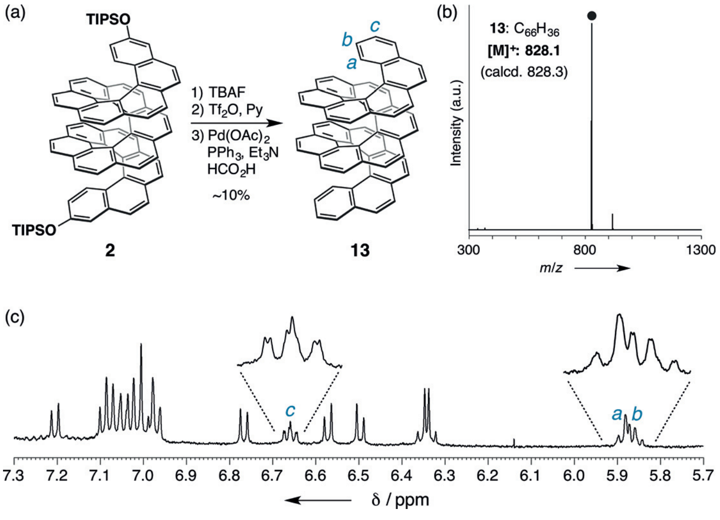


Figure 5. a) Synthesis of unsubstituted [16]helicene **13**. b) MALDI-TOF mass spectrum of **13** (corresponding peak marked with black circle, matrix: 9-nitroanthracene). c) ^{1}H NMR spectrum (500 MHz, CD$_2$Cl$_2$, 300 K) of the aromatic region of **13**.

evidence of the desiloxylation of **2** (Figure 5 c). The molecular mass of **13** was clearly revealed by MALDI-TOF mass spectrometry (Figure 5 b).

In summary, we synthesized [16]helicene through sextuple photocyclization of a single-strand oligo(arylene–vinylene) precursor. The scientific significance of this work is attributed not simply to updating the world record for the longest [*n*]helicene, but to the development of a new guideline for the facile and efficient synthesis of higher helicenes. We propose that even simple arylene–vinylene oligomers containing only [1] and [2] units can be good precursors for the synthesis of higher helicenes, provided that the [1] and [2] units are appropriately arranged in the precursor sequence. We presume that the pre-designed precursors have an intrinsic propensity to exhibit spontaneous helical folding under photoirradiation, which may help the formation of helicene skeletons.

Experimental Section

One-step synthesis of TIPSO-[16]helicene **2** by sextuple photocyclization of precursor olefin **1**: A toluene solution of precursor olefin **1** (59.2 mg, 50 μmol in 250 mL of toluene, 0.20 mM) was bubbled with argon gas for 15 min. Aliquots (20 mL) of the precursor solution were transferred to a screw tube with argon gas flow, then a toluene solution (0.40 mL) containing iodine (24 μmol, 6 equiv) and propylene oxide (0.40 mmol, 100 equiv) was added. After sealing, up to 11 sample tubes were set around the UV light source (high-pressure Hg lamp), and the samples were heated at 90 °C in an oil bath (Supporting Information, Figure S7). After UV light irradiation at 90 °C for 48 h, the sample solutions were cooled to room temperature, combined, and quenched with an aqueous Na$_2$S$_2$O$_3$ solution. The organic layer was concentrated in vacuo to afford a brown oily residue, which was roughly purified by silica gel column chromatography (CS$_2$ to CS$_2$/CH$_2$Cl$_2$ = 19/1). The CS$_2$ eluent was effective in separating the product from other byproducts on silica gel. The brown solid obtained was further purified by preparative HPLC (hexane/CHCl$_3$ = 97/3) to give pure product **2** in 7 % yield (a total of 7.8 mg of **2** was obtained from 109 mg of precursor **1** using 23 sample tubes).

Crystal data of TIPSO-[16]helicene **2**: Monoclinic space group $P2_1/c$, $T = 90(2)$ K, $a = 20.518(5)$, $b = 20.834(5)$, $c = 14.490(4)$ Å, $\beta = 94.050(4)°$, $V = 6179(3)$ Å^3, $Z = 4$, $\rho_{\text{calcd}} = 1.262$ Mg m^{-3}, $F(000) = 2496$, reflections collected/unique 65 733/12 525 ($R_{\text{int}} = 0.1579$). The structure was solved by direct methods (SHELXS-97) and refined by full-matrix least-squares methods (SHELXL-2014/7) on F^2 with 805 parameters. $R_1 = 0.0711$ ($I > 2\sigma(I)$), $wR_2 = 0.1892$, GOF 1.010. CCDC 1051159 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

For full experimental details, characterization, and crystallographic analysis, see the Supporting Information.

Keywords: helical structures · photocyclization · π–π interactions · polycyclic aromatic compounds · regioselectivity

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