Asymmetric Synthesis

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Asymmetric Allenophanes: Synthesis of a Tris-*meta*-allenophane and Tetrakis-*meta*-allenophane by Sequential Cross-Coupling**

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The synthesis and design of new cyclophanes and assorted cage compounds with novel shapes and supramolecular geometries continue to be topics of current interest.[1] Our research group has an expanding interest in the design and synthesis of new carbocyclic[2] and heterocyclic[3] cyclophanes, many of which contain a twisted conformation that imparts helical chirality[4] to the assembled molecule. The extent of helical chirality is a consequence of the number, combination, and type of unsaturated linkages in these molecules.[1g,5]

Allenes are a unique family of organic molecules that participate in a diverse range of reactions. Other attributes include their axial chirality and synthetic versatility.[6] The study of allenic natural products and their total synthesis continues to expand,[7] while medical applications include the inactivation of monoamine oxidase.[8] Recently we described the asymmetric synthesis of a bis(alleno)bis(butadiynyl)*meta*-cyclophane.[9] This compound represented a new structural family of cyclophanes composed of both allene and acetylene bridges. These macrocycles possess both axial and helical chirality and thus are doubly chiral.[10] True allenophanes (containing only allene bridges; 1,2-propadiene components) are of great interest owing to their potential structural and chiroptical properties. In addition, with the appropriate substitution patterns, these molecules should be useful as chiral ligands or as hosts for metal ions and small guest molecules.[11]

A limited number of general synthetic methods are available for constructing allenophanes. Previous examples include *para*-allenophanes prepared as a mixture of diastereomers,[12] and more recently *para*-acetylenic allenophanes were prepared in which a mixture of enantiomers was resolved and purified by HPLC.[13] The generic structure **1** (Figure 1) represents the simplest member of the symmetrical *meta*-allenophane family ($n=1$), in which R represents various functional groups (hydrogen, alkyl, aryl), R^1 is a solubilizing group, and the number of allene bridges may also be varied.

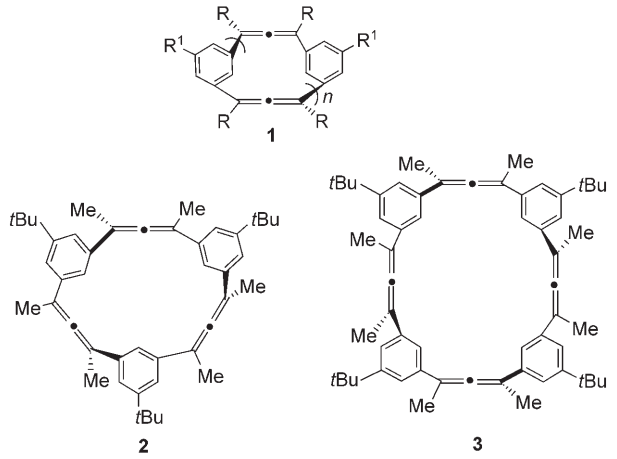
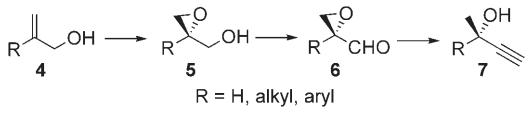


Figure 1. Allenophane macrocycles **1**, **2**, and **3** containing 12-, 18-, and 24-membered rings, respectively.

Our research group[14a,b] and others[14c] have previously observed that the termini separation of the reactive components for the cyclization of cyclophanes dictates whether the intra- or intermolecular product dominates. For alkynes, molecular modeling studies indicated that the intermolecular product is favored when the termini separation is greater than 7 Å. Our initial synthetic strategy was based on the expectation that the relatively rigid and restricted geometry provided by a substituted allene with adjacent reactive substituents (**13**, Scheme 3) should facilitate cyclization. The calculated distance between the bromobenzene and ethynyl substituents (termini) was 4.3 Å and thus supported this view.[14d] Herein we describe the synthesis of two higher homologues of **1**, namely the allenophanes **2** ($n=2$) and **3** ($n=3$).

The difficulties encountered with literature methods for the synthesis of the allene units in our substrates have been previously described.[9] Consequently, we have devised a versatile new protocol to synthesize allenophanes using Sharpless epoxidation to give asymmetric tertiary propargyl alcohol intermediates (Scheme 1). We then applied the reliable S_N2' addition of an organocuprate to a propargyl acetate to prepare the fully substituted allenes.[15] The



Scheme 1. An enantioselective route to synthesize tertiary propargyl alcohols.

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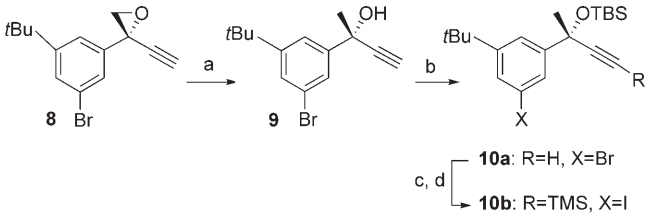
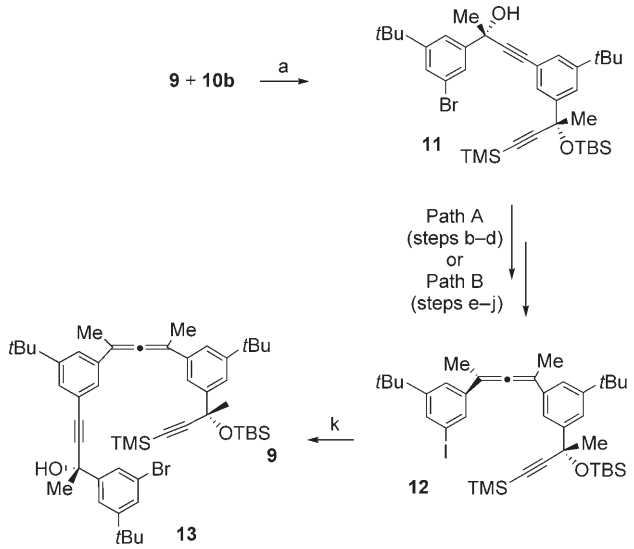
requisite bromoalkynyl epoxide **8** was prepared by this method. L-Selectride was the most selective hydride source (of the several examined) to open the epoxide and obtain propargyl alcohol **9** without racemization (Scheme 2). Protection of the reactive hydroxy groups with silyl groups and conversion of the bromine substituent into iodide afforded the requisite building blocks **9**, **10a**, and **10b** for conversion to the designed allenophanes.



Scheme 2. Synthesis of building blocks **9**, **10a**, and **10b**. Conditions and reagents: a) L-Selectride (1.2 equiv), THF, 0 °C, 20 min, 96%; b) TBSOTf (2.0 equiv), 2,6-lutidine, CH_2Cl_2, 0→22 °C, 12 h, 99%; c) LDA (1.1 equiv), THF, 0 °C, 5 min, then TMSCl (2.0 equiv), 0→22 °C, 15 min; d) *t*BuLi (2.5 equiv), THF, −78 °C, 3 min, then I_2 (1.5 equiv), 5 min, −78→22 °C, 91%. LDA = lithium diisopropylamide, L-Selectride = lithium tri-*sec*-butylborohydride, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.



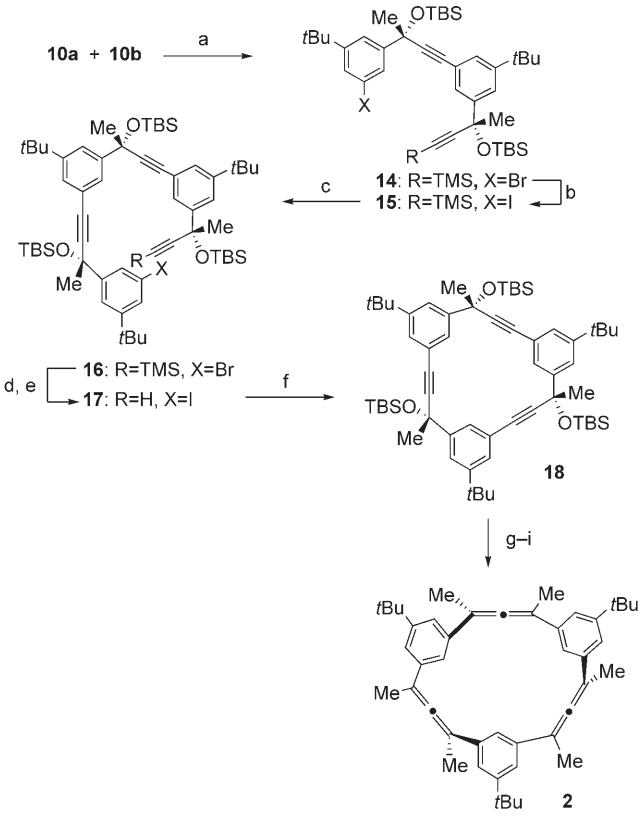
Scheme 3. Synthetic route to allenophane precursor **13.** Conditions and reagents: a) $[PdCl_2(PPh_3)_2]$ (0.05 equiv), CuI (0.1 equiv), Et_3N, THF, 66 °C, 16 h, 80%, d.r. 6:1; Path A: b) Ac_2O, DMAP (0.1 equiv), pyridine, 22 °C, 12 h, 99%; c) MeMgBr (18 equiv), CuI (18 equiv), LiBr (18 equiv), 0 °C, 2 h, 76%; d) *t*BuLi (2.5 equiv), THF, I_2 (1.5 equiv), −78→22 °C, 10 min, 92%; or Path B: e) TMSCl (2.0 equiv), Et_3N, DMAP (0.1 equiv), 22 °C, 6 h, 93%; f) *t*BuLi (2.5 equiv), −78 °C, THF, I_2 (1.5 equiv), −78→22 °C, 10 min; g) Dowex 50X-400 H^+, 22 °C, 2 h, 86% (over 2 steps); h) Ac_2O, DMAP (0.1 equiv), pyridine 22 °C, 12 h, 99%; i) MeMgBr (18 equiv), CuI (18 equiv), LiBr (18 equiv), 0 °C, 2 h, 76%; j) *t*BuLi (2.5 equiv), THF, I_2 (1.5 equiv), −78→22 °C, 10 min, 92%; k) **9** (1.2 equiv), $[PdCl_2(PPh_3)_2]$ (0.05 equiv), CuI (0.1 equiv), Et_3N, THF, reflux, 12 h, 51%. DMAP = 4-dimethylaminopyridine.

Considerable experimentation was required to efficiently effect the palladium(0)-mediated Sonogashira cross-coupling of **9** and **10b** to give **11**. The best results were obtained for the reaction with a slight excess of the silyl ether **10b** (1.2 equiv) in refluxing THF for 16 h (80% yield). Allene **12** was initially generated from the acetate derivative of alcohol **11**, which was then exposed to an organocopper reagent. Unfortunately, the basic conditions required for the bromine–iodine exchange resulted in some racemization because of deprotonation of an allenic methyl group. An alternative route (Path A, Scheme 3) involved protection of the alcohol with acetic anhydride in pyridine and subsequent cuprate addition then exposure to *t*BuLi and iodine to afford **12**. Another route (Path B, Scheme 3), employed silylation, halogen exchange, ether cleavage with acidic resin, and allene formation to also give **12**.

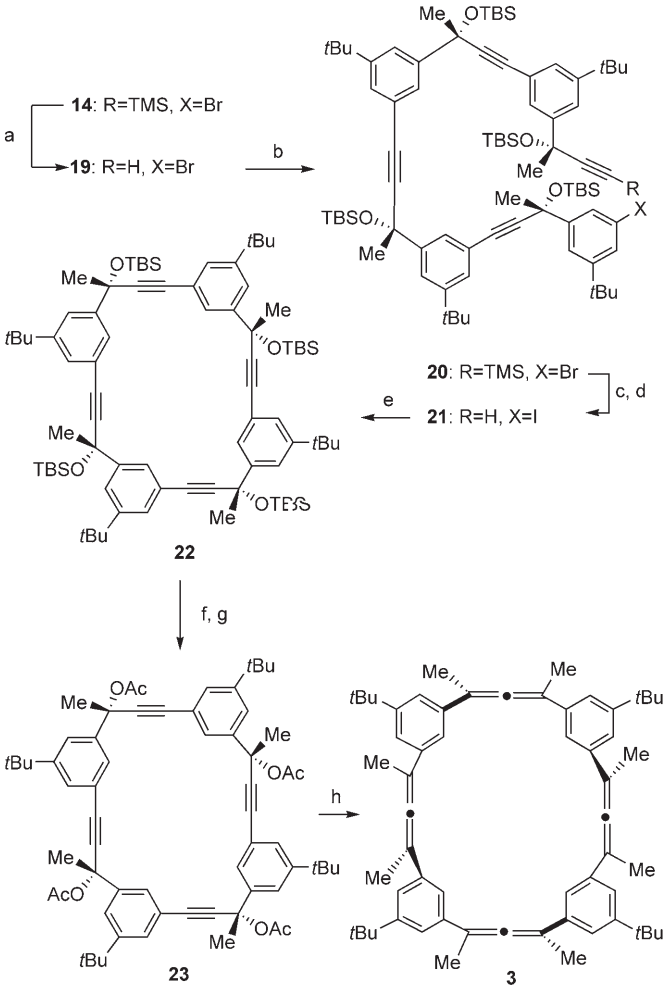
Palladium(0) coupling of **12** with the alcohol **9** generated the penultimate cyclization precursor **13** in 51% yield. However, an isomeric mixture resulted from the competitive, reversible formation of a palladium π-allyl intermediate which destroyed the integrity of the allene chirality. Thus an alternative route was selected to assemble the three chiral units before ring closure (Scheme 4). Owing to the potential flexibility of **17** (termini separation: 7.1 Å), the intramolecular product would be expected. However, this approach would require the allene-formation reactions to be conducted three times on the same molecule.

The Sonogashira cross-coupling of **10a** and **10b** proceeded to give the diyne **14** in excellent yield (91%) but required 16 h at reflux to reach completion. Base-mediated halogen exchange and additional Sonogashira cross-coupling with **10a** gave the triyne **16**. Final halogen exchange and removal of the trimethylsilyl protecting group afforded **17**. High-dilution conditions (0.003 M) were necessary for the intramolecular coupling to give the desired triyne macrocycle **18** in 45% yield. Sequential deprotection and acetylation generated a triacetate derivative, which was subjected to the cuprate allene protocol described above. This sequence proceeded smoothly in 83% yield to give the novel tris-*meta*-allenophane **2**.

Significantly, the intermediate TMS-protected acetylene **14** represents a synthetic precursor that comprises half of the tetrakis-*meta*-allenophane target **3** (Figure 1) and the bis-acetylene **15** could supply the second half of the tetra-acetylene component required to construct the marcocycle. With access to readily available precursors and the successful synthesis of **2**, we investigated the preparation of the higher homologue **3**. Cleavage of the TMS group of **14** was carried out by exposure to base to afford the free acetylene **19**, which underwent palladium(0)-mediated cross-coupling when combined with the bis-acetylene **15** to generate **20** in 73% yield (Scheme 5). The iodoacetylene **21** was generated by halogen exchange with **14** as described above. Intramolecular Sonogashira cyclization of **21** under high-dilution conditions (0.003 M) afforded the desired allene precursor **22** in 42% yield. Removal of the silyl protecting groups and subsequent introduction of four acetate groups proceeded in a direct manner to give the asymmetric macrocyclic tetraalkyne **23**. The final stage of the synthesis used the cuprate allene protocol to give tetrakis-*meta*-allenophane **3**. The direct



Scheme 4. Final steps for the synthesis of (−)-allenophane **2.** Conditions and reagents: a) $[PdCl_2(PPh_3)_2]$ (0.05 equiv), CuI (0.1 equiv), Et_3N, THF, 66 °C, 16 h, 91 %, d.r. 6:1; b) *t*BuLi (2.5 equiv), THF, −78 °C, I_2 (1.5 equiv), −78→22 °C 10 min, 85 %; c) **10a** (1.2 equiv), $[PdCl_2(PPh_3)_2]$ (0.05 equiv), CuI (0.1 equiv), Et_3N, THF, 66 °C, 16 h, 70 %; d) *t*BuLi (2.5 equiv), THF, −78 °C, I_2 (1.5 equiv), −78→22 °C, 10 min, 91 %; e) KOH (2.0 equiv), MeOH/*i*PrOH/Et_2O (2:2:1), 22 °C, 2 h, 71 %; f) $[PdCl_2(PPh_3)_2]$ (0.05 equiv), CuI (0.1 equiv), Et_3N, THF, 0.003 M with respect to 17, 66 °C, 24 h, 45 %; g) TBAF, THF, 22 °C, 2 h, 83 %; h) Ac_2O, pyridine, DMAP (0.1 equiv), 12 h, 85 %; i) MeMgBr (18 equiv), LiBr (18 equiv), CuI (18 equiv), THF, 0→22 °C, 1.5 h, 83 %. TBAF = tetrabutylammonium fluoride.



Scheme 5. Final steps for the assembly of (+)-allenophane **3**. Conditions and reagents: a) KOH (2.0 equiv), MeOH/*i*PrOH/Et_2O (2:2:1), 22 °C, 2 h, 86 %; b) **15** (1.0 equiv), **19** (1.2 equiv), $[PdCl_2(PPh_3)_2]$ (0.05 equiv), CuI (0.1 equiv), Et_3N, THF, 66 °C, 16 h, 73 %; c) *t*BuLi (2.5 equiv), THF, −78 °C; I_2, −78→22 °C, 10 min; d) KOH (2.0 equiv), MeOH/*i*PrOH/Et_2O (1:1:2), temp, 2 h, 80 % (over 2 steps); e) $[PdCl_2(PPh_3)_2]$ (0.05 equiv), CuI (0.1 equiv), Et_3N, THF, 0.003 M with respect to 21, 66 °C, 16 h, 42 %; f) TBAF, THF, 22 °C, 1 h; g) Ac_2O, pyridine, DMAP (0.1 equiv), 22 °C, 12 h, 65 %; h) MeMgBr (30 equiv), LiBr (30 equiv), CuI (30 equiv), THF, 0 °C, 3.5 h, 22 °C, 15 min, 85 %.

manner in which these components are assembled demonstrates the utility and versatility of the building blocks for the construction of acetylenic macrocycles by our sequential cross-coupling strategy.

Both macrocycles (**2** and **3**) are very sensitive to mild acid (e.g. silica gel or $CDCl_3$) and were therefore purified by chromatography on basic alumina. Upon storage (neat) they continued to deteriorate, and this degradation was also observed during ^{1}H NMR spectroscopic analysis in $[D_6]$benzene. Exposure to air and moisture is also deleterious. Fortunately, these macrocycles were stable when handled in hydrocarbons or ethers and stored in a freezer (−20 °C).

Modeling studies[16] indicated very little twisting across the ring, and the resulting structure diagrams were very similar to the structural formulae drawn for macrocycles **2** and **3**. Instead it appears that the allene bridges are considerably strained and are likely distorted from their preferred geometry. However, the modeling calculations may not be at a high enough level of theory to confirm this observation (X-ray analysis was not possible for these compounds). In our previous studies with cyclic butadiynes the strain was not evenly distributed throughout the ring but instead was concentrated in a single bent triple bond (153.5°).[17] Macrocycles **2** and **3** are likely to be similar examples, and this accounts for their acid sensitivity. Consequently one or more of the allene components behaves like a strained olefin with increased reactivity and it is therefore prone to decomposition.

Allenic compounds usually display a unique antisymmetrical C=C=C IR stretching band in the region of 1950–2150 cm^{-1}.[18] This characteristic signal is observed as a sharp band at 2150 cm^{-1} for allene **13**. We were initially surprised to observe no distinct corresponding band for macrocycle **3**. However, previous IR studies have shown the intensity of these signals to be very sensitive to their environment. Key

criteria, including strain, symmetry, and alkyl and aryl substitution, collectively reduce the intensity of this ν_1 band. This is illustrated by the IR spectra of a triphenylallene ($PhHC{=}C{=}CPh_2$), in which the band is very weak, and the tetraphenyl homologue ($Ph_2C{=}C{=}CPh_2$), in which the ν_1 band is absent.[18] Macrocycles **2** and **3** also display IR bands of reduced intensity. Given this situation, it is not surprising to observe an extremely weak band at 1956 cm^{-1} for **2**; owing to its higher symmetry, **3** should exhibit no absorption, and this is indeed the case. In principle the Raman spectrum should display a band corresponding to the allene vibration. The three allene bridges in compound **2** give rise to a strong signal at 1941 cm^{-1}, while for **3** the four allene bridges exhibit a weaker, but still visible, band at 1930 cm^{-1}. The circular dichroism (CD) spectra of macrocycles **2** and **3** (Figure 2) were recorded in hexanes. These are the first such reported spectra of asymmetric *meta*-allenophanes.

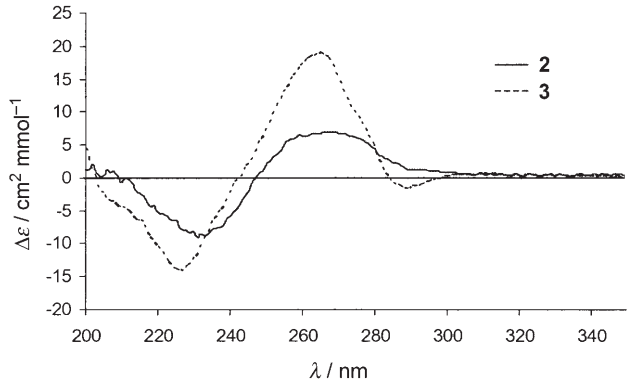


Figure 2. CD spectra of allenophanes (−)-**2** and (−)-**3**.

In summary, we have developed a general synthetic strategy for the rapid assembly of both acetylenic and allenic macrocycles from asymmetric tertiary propargyl alcohols. The sequential application of Sonogashira cross-coupling reactions[2,19] generated the core structures in a direct manner. This protocol facilitated the synthesis of two new allenophanes, the tris-*meta*-allenophane **2** and the higher homologue, tetrakis-*meta*-allenophane **3**. These transformations were accomplished in nine and seven steps, respectively, from propargyl ethers.

Experimental Section

2: Anhydrous LiBr (95 mg, 1.1 mmol, 18 equiv) and CuI (210 mg, 1.1 mmol, 18 equiv) were suspended in THF (5 mL). The stirred suspension was cooled to 0 °C, and MeMgBr (3 M in diethyl ether, 0.37 mL, 1.1 mmol, 18 equiv) was added. The resulting yellow mixture was stirred for 10 min at 0 °C before triacetate **18** (45 mg, 62 μmol) in THF (2 mL) was added. The reaction mixture was then stirred for a further 1.5 h at 0 °C. Pentane (30 mL) was added, and the insoluble material was removed by filtration through a pad of Celite. The solvents were removed in vacuo, and the crude product was purified by flash chromatography (pentane) on basic alumina to give allenophane **2** (30 mg, 83 %) as a pale yellow, waxy solid. ^{1}H NMR (500 MHz, C_6D_6): $\delta = 7.70$ (t, $J = 1.5$ Hz, 3H), 7.45 (d, $J = 1.5$ Hz, 6H), 2.13 (s, 18H), 1.33 ppm (s, 27H); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 205.9(\times)$, 145.4(×), 123.0(+), 121.3(+), 102.7(×), 34.5(x), 31.1(+), 17.5(+) ppm; HRMS (EI) calcd for $C_{45}H_{54}$: 594.4225, found: 594.4214; IR: $\tilde{\nu} = 2593$, 2924, 2854, 1759, 1688, 1684, 1593, 1456, 1365, 1242, 879, 700 cm^{-1}; $[\alpha]_D^{20} = -211$ deg cm^3 g^{-1} dm^{-1} ($c = 0.15$ g cm^{-3}, hexanes). [(+) and (×) denote the signal phase in the DEPT NMR spectrum.]

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