Fused-Ring Systems

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Chiral Dendralenes for Rapid Access to Enantiomerically Pure Polycycles**

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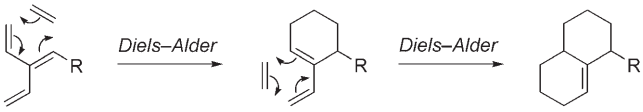
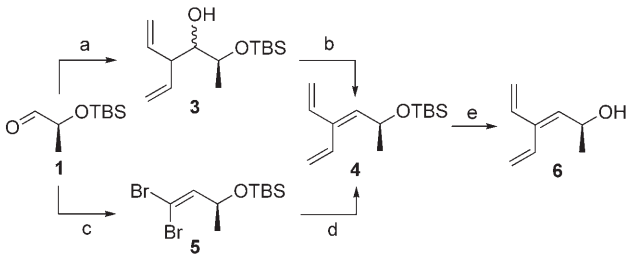
Dendralenes are acyclic cross-conjugated oligoalkenes with much synthetic potential.[1–4] They are particularly attractive precursors for cycloaddition reactions with dienophiles, since they function as multidienes, thereby allowing rapid access to cyclic frameworks. The parent [3]dendralene, for example, can be thought of as a conjoined pair of 1,3-butadienes that can undergo a stepwise sequence of two cycloaddition reactions to form a decalin ring system (Scheme 1, R = H).[5]



Scheme 1. Can a simple chiral [3]dendralene, namely, R = $CH(CH_3)OH$, undergo intermolecular cycloadditions with high stereoselectivity?

This strikingly efficient process forms four C–C bonds and as many as eight stereocentres, yet it involves only two bond-forming events. Several examples of this sequence have been reported in the literature;[6] until now, however, control over the chemo-, regio-, and stereoselectivity during intermolecular[7] "diene-transmissive" cycloaddition sequences has not been reported.[8] Furthermore, no general synthetic approach to substituted cross-conjugated systems has been reported. Herein we introduce a straightforward method for the preparation of chiral dendralenes and demonstrate their involvement in highly chemo-, regio-, and stereoselective diene-transmissive Diels–Alder sequences to form enantiomerically pure polycyclic frameworks.

To control the stereochemical outcome of the first cycloaddition event we elected to prepare chiral secondary alcohol **6**, since simple chiral dienols carrying *cis* substituents have been shown to undergo cycloaddition reactions with very high levels of π-diastereofacial selectivity.[9] Fallis and co-workers recently reported an elegant synthetic approach to substituted [3]dendralenes through an indium-mediated γ-pentadienylation of aldehydes.[6i,j,q] Application of their two-step addition–dehydration protocol to simple chiral aldehyde **1** furnished triene silyl ether **4** in 25% overall yield (Scheme 2). The modest yield for this transformation led us to develop an alternative route. Thus, Corey–Fuchs dibromomethylenation[10] of aldehyde **1** gave **5**,[11] which underwent twofold Stille or Negishi coupling[12] to furnish triene **4** in up to 51% overall yield from **1**. Cleavage of the silyl ether gave alcohol **6**. Trienes **4** and **6** are easily purified and stored, and require no special handling techniques.[13]



Scheme 2. Synthesis of a simple chiral [3]dendralene. a) In (1.1 equiv), $CH_2{=}CH{-}CH{=}CHCH_2Br$ (**2**) (1.2 equiv), DMF, 25 °C, 16 h, 54%; b) PPh_3 (2.0 equiv), DEAD (2.0 equiv), THF, reflux, 3.25 h, 46%; c) PPh_3 (4.0 equiv), CBr_4 (2.0 equiv), CH_2Cl_2, 25 °C, 4 h, 76%; d) $CH_2{=}CHSnBu_3$ (2.5 equiv), $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.10 equiv), CH_3CN, 60 °C, 26 h, 61%; or $CH_2{=}CHZnBr$ (3.3 equiv), $[Pd(PPh_3)_4]$ (0.03 equiv), THF, 25 °C, 48 h, 67%; e) TBAF (2.0 equiv), THF, 25 °C, 2.5 h, 86%. DEAD = diethylazodicarboxylate, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

The reaction of chiral [3]dendralene **6** and maleic anhydride (2 equiv) in acetonitrile at room temperature gave tetracyclic lactone acid **10** in high yield (Scheme 3). The transformation presumably proceeds[14,15] by way of the short-lived hydroxy anhydride **8**, which cyclizes rapidly to bicyclic lactone acid **9**, which in turn reacts with maleic anhydride to form **10**.

Both cycloaddition steps are highly stereoselective, with **10** being formed in about 95% diastereoselectivity.[16] The intermediate monoadduct **9** can be observed by following this reaction by NMR spectroscopy, but it is not formed cleanly: the presence of **10** is detected before all the starting triene **6** is consumed. The situation is similar for protected analogues of [3]dendralene **6**, namely silyl ether **4** and MOM ether **7**, which underwent highly stereoselective domino cycloadditions to give tetracyclic bisanhydrides **14** and **15** as sole products in

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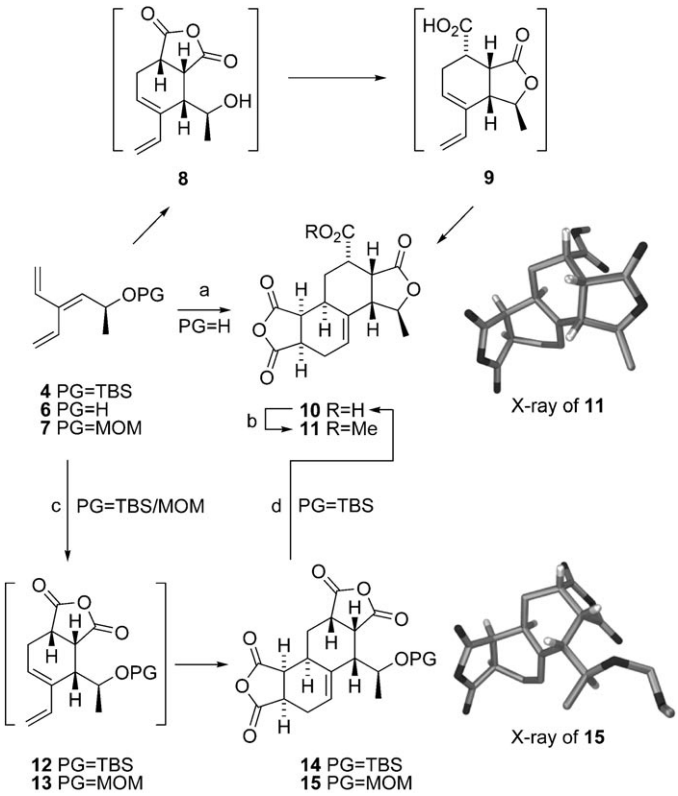
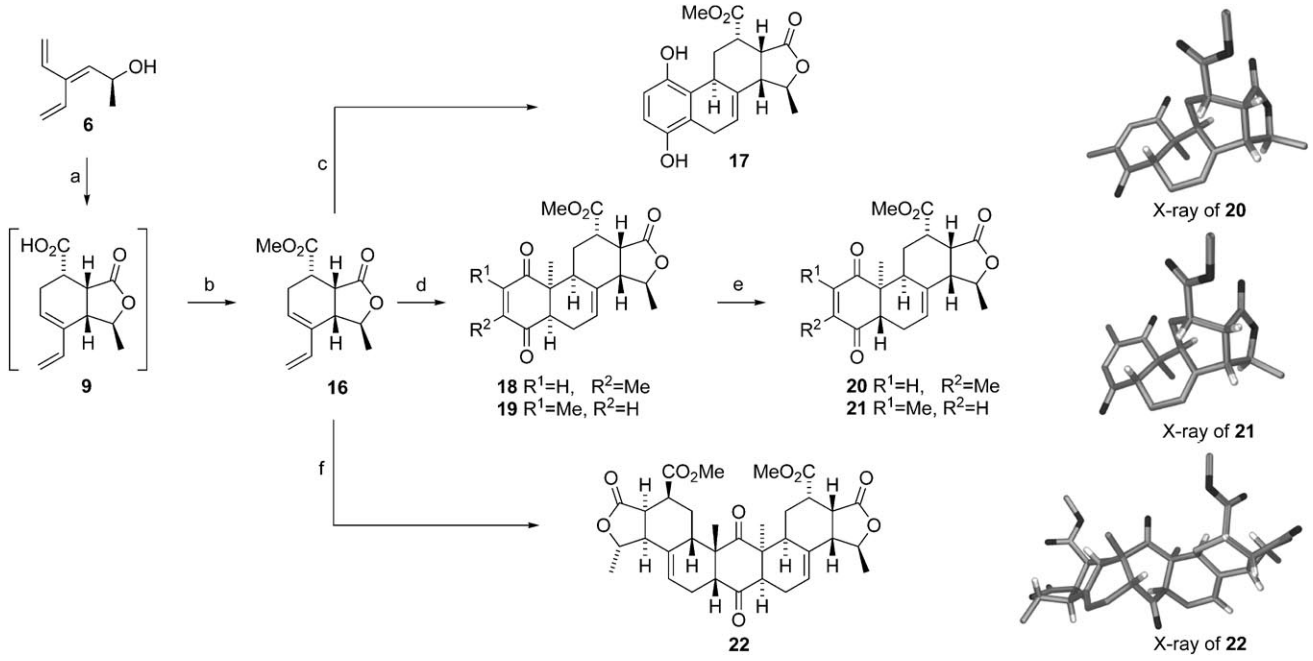


Scheme 3. Double cycloadditions of chiral [3]dendralene **6**. a) Maleic anhydride (2.0 equiv), CD_3CN, 25 °C, 60 h, >90%; b) CH_2N_2, Et_2O/THF, −78 °C, 15 min, 81%; c) PG = TBS: maleic anhydride (2.0 equiv), C_6D_6, 25 °C, 48 h, 97%; PG = MOM: maleic anhydride (2.0 equiv), C_6D_6, 25 °C, 72 h, 100%; d) CF_3CO_2H, CH_2Cl_2, 25 °C, 16 h then CH_2N_2, Et_2O/THF, −78 °C to 25 °C, 0.25 h, 81%. Some hydrogen atoms are omitted from the X-ray crystal structures[21] for clarity. MOM = methoxymethyl.

high yields. In these cases, the second Diels–Alder reaction in the diene-transmissive sequence is significantly faster than the first. That the protected alcohols **4** and **7** give the same stereoisomeric double cycloadducts as alcohol **6** was confirmed by the conversion of **14** into **11** (via **10**) and the X-ray crystal structures of **11** and **15**. It is noteworthy that the same highly stereoselective outcome is obtained for the double cycloaddition process, irrespective of the nature of the oxygen substituent and the solvent. These observations bode well for the generality of the process.[17]

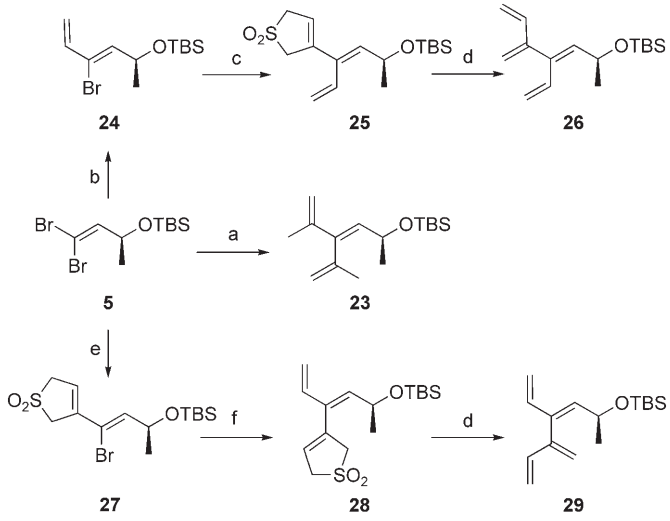
The cascade sequences depicted in Scheme 3 are very effective ways to form new fused-ring systems in a stereocontrolled manner. Nevertheless, a sequence that could be interrupted after the first cycloaddition would offer significantly greater synthetic versatility. Gratifyingly, this outcome was achieved in a very straightforward manner, by simply carrying out the reaction between alcohol **6** and maleic anhydride in benzene (Scheme 4). The highly stereoselective cycloaddition–lactonization sequence gave lactone acid **9**, which is insoluble in benzene and precipitates from solution as it forms, thereby precluding further reaction; the product is isolated in pure form simply by filtration.[18] The corresponding methyl ester **16** underwent highly selective cycloadditions with *p*-benzoquinone, 2,6-dimethyl-*p*-benzoquinone, and 2,5-dimethyl-*p*-benzoquinone. When the unsubstituted dienophile was used, attempts to purify the initial cycloadduct by column chromatography were met with aromatization to **17**. One major cycloadduct was formed in very high regio- and diastereoselectivity by reaction of diene **16** with each of the dimethyl-*p*-benzoquinones. In both cases, epimerization occurred upon exposure of the initial cyclo-



Scheme 4. Cycloadditions with benzoquinones. a) Maleic anhydride (1.05 equiv), C_6D_6, 25 °C, 48 h, 83%; b) CH_2N_2, Et_2O/THF, −78 °C, 15 min, 70%; c) *p*-benzoquinone (1.0 equiv), C_6D_6, 80 °C, 48 h then SiO_2, CH_2Cl_2, 70% overall; d) 2,5- or 2,6-dimethyl-*p*-benzoquinone (1.2 equiv), [D_8]toluene, 110 °C, 125 h, 78% for **18**, 76% for **19**; e) SiO_2, CH_2Cl_2, 8 h, 100% for **20**; 4 h, 100% for **21**; f) 2,6-dimethyl-*p*-benzoquinone (0.5 equiv), CH_2Cl_2, 25 °C, 19 kbar, 72 h, 85%. Some hydrogen atoms are omitted from the X-ray crystal structures[21] for clarity.

adducts **18** and **19** to flash chromatography on silica gel, which led separately to **20** and **21**, the stereochemistries of which were confirmed by single-crystal X-ray analyses. Finally, semicyclic diene **16** participated in a highly selective double cycloaddition reaction with 2,6-dimethyl-*p*-benzoquinone to form chiral C_2-symmetric heptacycle **22** in high yield. This last example demonstrates the extraordinary ease by which enantiomerically pure fused-polycyclic frameworks can be prepared: **22** was assembled in only three synthetic steps from dendralene **6**, one of which involves the trivial conversion of an acid into a methyl ester.

In contrast to the seminal nucleophilic addition–dehydration approach to [3]dendralenes described by Fallis and co-workers, the route described herein is by no means limited to the synthesis of trienes substituted at the central methylene unit. The transformations depicted in Scheme 5 demonstrate



Scheme 5. A general synthetic approach to substituted dendralenes. a) $H_2C{=}C(CH_3)ZnBr$ (5.0 equiv), $[Pd(PPh_3)_4]$ (0.05 equiv), THF, RT, 18 h, 83%; b) $H_2C{=}CHSnBu_3$ (1.05 equiv), $[Pd_2(dba)_3]$ (0.025 equiv), $AsPh_3$ (0.10 equiv), THF, 50°C, 10 h, 85%; c) 3-(tributylstannyl)-3-sulfolene (1.2 equiv), $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.10 equiv), CH_3CN, 60°C, 48 h, 90%; d) PhCl, 132°C, 1.5 h, 90% for **26**, 69% for **29**; e) 3-(tributylstannyl)-3-sulfolene (1.0 equiv), tri(2-furyl)-phosphine (0.15 equiv), $[Pd_2(dba)_3]$ (0.025 equiv), PhMe, 55°C, 55%; f) $H_2C{=}CHSnBu_3$ (2.0 equiv), $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.10 equiv), CH_3CN, 60°C, 18 h, 92%. dba = *trans*,*trans*-dibenzylideneacetone.

the generality of this new approach. Thus, not only is substitution tolerated at all available positions of the triene framework, the route also lends itself to the highly stereoselective synthesis[12,19] of both geometrical isomers of unsymmetrically substituted systems, as exemplified by the first chiral [4]dendralenes **26** and **29**.[20] When the functional-group tolerance of both the Corey–Fuchs dibromomethylenation of aldehydes and metal-catalyzed cross-couplings is considered, the scope of this approach for the synthesis of cross-conjugated systems—and polycyclic systems derived therefrom—is vast.

In summary, a short and general synthetic route to substituted cross-conjugated polyenes has been developed. The cycloaddition chemistry of chiral [3]dendralenes can be controlled to allow the extremely rapid assembly of tetracyclic systems common to numerous biologically interesting terpenoid natural products such as the spongians[22] and the triptolide family.[23] The application of these efficient sequences in target synthesis is under way.

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[15] As expected, all the cycloadditions of maleic anhydride and benzoquinones reported here were found to proceed exclusively through the *endo* mode.
[16] Small amounts of products resulting from the *trans*-fused isomer of **9** are also witnessed. The *trans* isomer of **9** is formed through an intramolecular Diels–Alder reaction.[14]
[17] Computational investigations into the origins of the stereoselectivity in these reactions are under way, and the results of these investigations will be reported shortly.
[18] Precipitation of the monoadduct from solution is not necessary for the synthesis of the compounds depicted in Scheme 4; this method is preferred, however, since it leads to the clean formation of "mixed" double and quadruple cycloadducts.
[19] Clean inversion of configuration has been seen in the coupling of organozinc compounds with 2-bromo-1,3-butadienes, see: X. Zeng, Q. Hu, M. Qian, E.-i. Negishi, *J. Am. Chem. Soc.* **2003**, *125*, 13636 – 13637. The stereochemistry of geometrical isomers **25** and **28** was confirmed by NOESY experiments (see the Supporting Information).
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