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LETTERS

Vinylcyclopropyl TMM diyls: access to eight-membered rings

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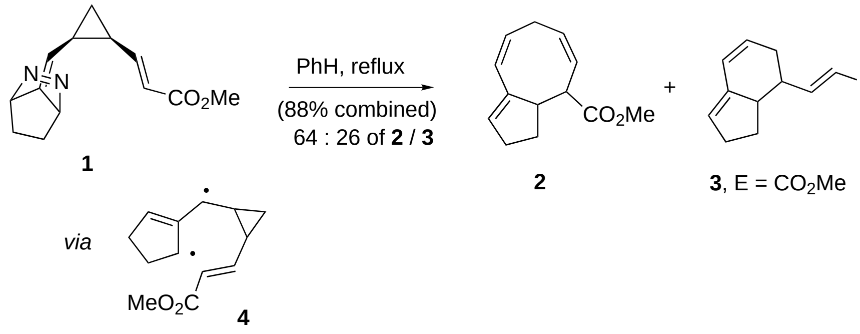
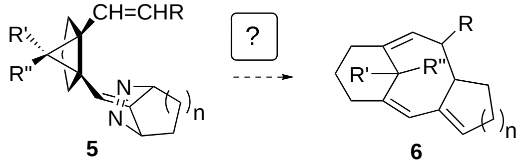
Abstract—Vinylcyclopropyl substituted diazenes (e.g. **1** and **15**) rearrange when heated. The chemistry takes place via the formation of a trimethylenemethane (TMM) diyl and provides access to eight-membered rings. When the cyclopropane is fused to a five-membered ring (e.g. **15**) rearrangement leads to a structure resembling the taxotere framework. © 2001 Elsevier Science Ltd. All rights reserved.

In 1998, we reported the first examples of the chemistry of diradicals derived from vinylcyclopropyl diazenes such as **1**.[1] Two reaction pathways were discovered, one leading to the bicyclo[6.3.0] framework **2**, the other to the [4.3.0] adduct **3**. While mechanistic detail is uncertain at this time, we are confident that the first step leads to the formation of a trimethylenemethane-like diradical, **4**. It is the pathway leading to the [6.3.0] ring system that holds particular interest for us as it could provide a versatile means of synthesizing eight-membered rings.[2] In this paper we report the results of an investigation designed to probe the effect of fusing a five-membered ring to the cyclopropane in the manner illustrated by **5**.[3] Our intent was to determine whether the transformation could be used to access ring systems **6**, which resemble the taxotere framework.[4]

Diazene **15** was synthesized in the manner portrayed in Scheme 1.[3] Treatment of dimethyl 1,3-cyclohexanedicarboxylate **7** with 2 equiv. of LDA and iodine in THF led to the formation of the [3.1.0] diester **8**.[5] Without purification, **8** was reduced using DIBAL-H in THF to





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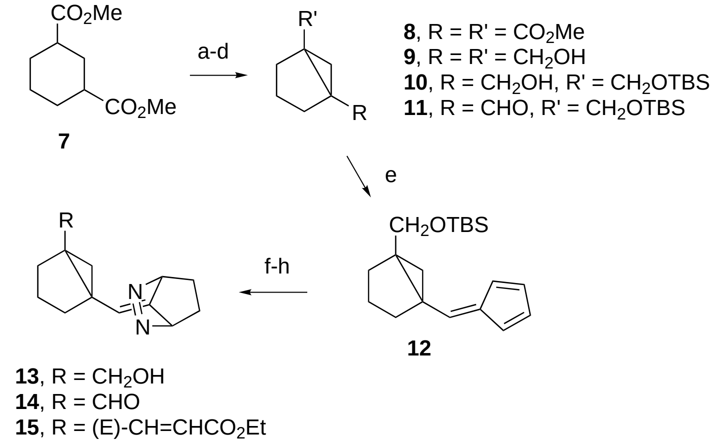
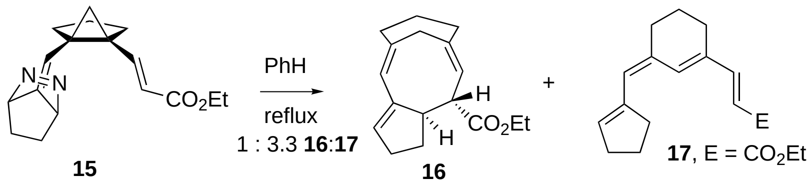


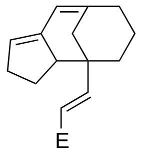
Scheme 1. Synthesis of diyl precursor, diazene **15**. (a) 2 equiv. LDA; I_2, THF, −78 to −4°C; (b) DIBAL-H, $PhCH_3$/THF, −78°C to rt; (c) NaH, THF, TBSCl, rt (83%); (d) PCC, NaOAc, CH_2Cl_2, rt (66%); (e) CpH, pyrrolidine, *i*-PrOH; AcOH, rt (>99%); (f) DEAD, CH_2Cl_2, −20°C; TBAF, THF, rt; diimide; KOH, EtOH, reflux, then Pd/O_2, 4°C (28% over four steps); (g) Swern oxidation (74%); (h) $(MeO)_2POCH_2CO_2Et$, NaH, THF, 4°C (>95%).

afford diol **9** in a 71% combined yield over three steps (esterification to produce **7**, cyclization, reduction). Mono protection as the TBS–ether was achieved in 83% yield by treating **9** with NaH in THF followed by the addition of TBSCl. PCC oxidation to afford the protected aldehyde **11** (66%), its conversion to fulvene **12** (>99%), a Diels–Alder reaction using DEAD followed, in turn, by desilylation, an in situ hydrogenation of the endocyclic π-bond of the resulting [2.2.1] adduct and conversion of the biscarbamate linkage to that of a diazene, produced **13** in a 28% yield over four steps. A Swern oxidation and a Horner–Emmons–Wadsworth reaction using ethyl dimethylphosphonoacetate completed the sequence leading to diazene **15**.

When diazene **15**, dissolved in benzene, was added dropwise to a refluxing solution of the same solvent, rearrangement occurred to afford a 1/3 ratio of two products, **16** and tetraene **17**.[†] Unfortunately, mass balances in the range of 32–41% were observed. We speculate, but have not unambiguously proven, that this is due to the thermal lability of the products. A low mass balance is an uncommon outcome for fragmentation–recombination reactions of this variety; in all of the other cases we have investigated, mass balances are consistently in excess of 80%.[1,6]



It is interesting, though certainly not unanticipated, that the tricyclic adduct **18** that could have resulted from cyclization to form a six- rather than an eight-membered ring, was not observed. We presume that the strain expressed along the reaction coordinate leading to it is sufficient to allow the pathway leading to tetraene **17** to be competitive. The appearance of tetraene **17** was unanticipated. It presumably arises via an intramolecular hydrogen atom transfer in the manner portrayed by **19**.



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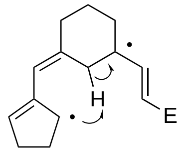

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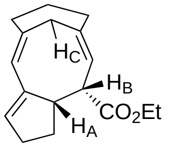
[†] **Tricyclo(8.3.1.0^{3,7})tetradeca-1,3,9-triene-8-carboxylic acid methyl ester (16, methyl ester).** ^1H NMR (400 MHz, $CDCl_3$) δ 5.62 (s, brd, 1H), 5.52 (broad s, 1H), 4.95 (d, $J=7.2$, 1H), 3.69–3.73 (m, 4H), 3.41 (d, $J=10.4$, 1H), 2.02–2.54 (m, 9H), 1.99 (d, $J=10.0$, 1H), 1.51–1.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 152.0, 152.0, 143.7, 132.8, 116.6, 114.4, 52.2, 51.6, 46.1, 38.8, 36.2, 36.2, 36.1, 30.5, 29.6; IR (KBr, neat) 2934, 2849, 1739, 1594, 1465, 1320, 1249, 1161, 1031, 1008, 718, 756, 687 cm^{-1}; exact mass (M)–244.145466, calculated for $C_{16}H_{20}O_2$ 244.146330; mass spectrum (EI) *m*/*z* 244, 186, 155, 141, 131, 117, 97, 83, 71, 57.

3-(3-Cyclopent-1-enylmethylene-cyclohex-1-enyl)-acrylic acid methyl ester (17, methyl ester). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, $J=15.6$, 1H), 7.08 (s, 1H), 6.10 (s, 1H), 5.87 (d, $J=16.0$, 1H), 5.81 (broad s, 1H), 3.76 (s, 3H), 2.64 (broad t, $J=6.8$, 2H), 2.38–2.40 (m, 2H), 2.35 (t, $J=6.0$, 2H), 2.27 (t, $J=6.0$, 2H), 1.97 (app. q, $J=7.6$, 2H), 1.80 (app. q, $J=6.0$, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 147.8, 141.8, 136.1, 134.7, 134.5, 133.9, 127.0, 115.6, 51.5, 35.2, 32.5, 32.2, 24.8, 24.3, 22.4; IR (KBr, neat) 29.46, 28.40, 1716, 1619, 1578, 1434, 1306, 1165, 979, 834 cm^{-1}; exact mass (M)–244.146057, calculated for $C_{16}H_{20}O_2$ 244.146330 mass spectrum (EI) *m*/*z* 244, 229, 185, 57, 141, 129, 115, 91, 83.



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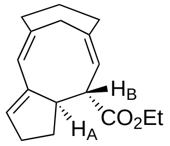
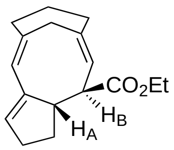


B



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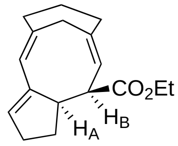
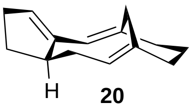


D

diastereomer	dihedral angle (H_A/H_B)	d(H_A-H_C)	d(H_B-H_C)
A	42°	1.91	2.65
B	177°	3.75	1.99
C	162°	1.93	3.88
D	60°	3.68	3.76

The tricyclic cyclooctanoid **16** was isolated as a single diastereomer whose stereochemistry was determined using NOE experiments in combination with semi-empirical AM1 geometry optimizations (PC Spartan Pro v. 6.0.4). The calculations were used to determine the dihedral angle between the bridgehead proton, H_A, and the methine hydrogen H_B positioned α to the ester since this quantity can be correlated with the magnitude of the ^1H NMR coupling constant. The rather large observed value, $J_{AB} = 10.8$ Hz, is consistent with structures **B** and **C** where the calculated angles are 162 and 177°, but not with the other two diastereomers. To differentiate between **B** and **C** we took advantage of the fact that the methylene proton, H_C, positioned *syn* to the eight-membered ring is close to H_B (1.93 Å, calculated) in diastereomer **B**, while it is near H_A (1.99 Å, calculated) in **C**. The chemical shift for H_C (3.38 ppm) is well separated from other signals thereby making it a good candidate for an NOE experiment. That it appears so far downfield is undoubtedly due to its proximity to the anisotropic influence of the two π-bonds. Irradiation of H_C afforded a 13.2% enhancement of H_B with a negligible effect upon H_A. This result clearly establishes the structure of the product as that of diastereomer **B** (**B**=**16**).

An intriguing point that is not apparent from the drawings is that the 1,3-diene subunit is forced to assume two very different geometries, **20** and **21**, depending upon whether the bridgehead hydrogen is on the α- or the β-face. In the former, that is with diastereomers **B** and **D**, the π-units are substantially twisted so that they are out of conjugation, whereas near planarity can be achieved when it is on the β-face. It is interesting, therefore, that the isolated product **16** corresponds to one wherein conjugation is significantly reduced. While we have not demonstrated experimentally the effect of this arrangement, it is reasonable to assume that each of the C–C π-bonds may behave independently in attempts to use them to introduce functionality.



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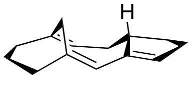

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The chemistry described demonstrates that the rearrangement of vinylcyclopropyl-substituted trimethylenemethane diradicals, typified by the conversion of **1** to **2** and **15** to **16**, can be used to construct the taxotere framework. While the conversion of **15** to **16** is not nearly as efficient as we would have liked, the problems seem correctable simply by replacing the abstractable hydrogens with a non-transferable group (e.g. *gem*-methyl). Efforts to do so are underway.

Acknowledgements

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