ORGANIC LETTERS

2003
Vol. 5, No. 10
1701−1704

# Intramolecular Diels–Alder Reactions of 5-Vinyl-1,3-cyclohexadienes

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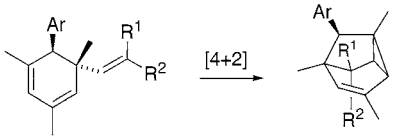
**Received February 26, 2003**

## ABSTRACT




5-vinyl-1,3-cyclohexadiene  tricyclo[3.2.1.0$^{2,7}$]oct-3-ene

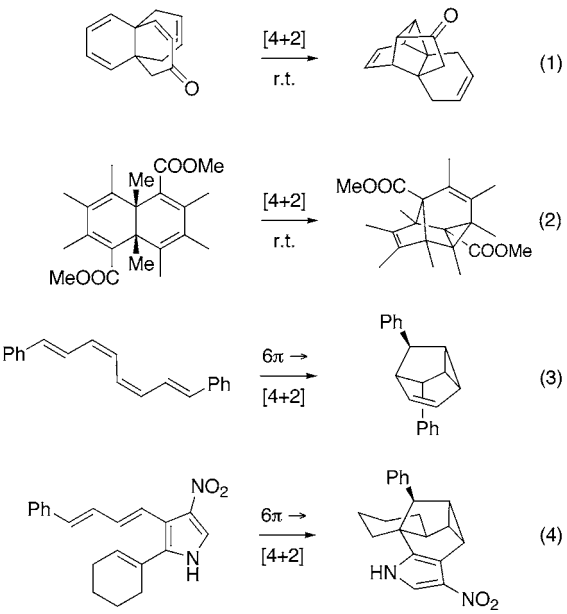
**The intramolecular Diels–Alder reaction of 5-vinyl-1,3-cyclohexadienes affording substituted tricyclo[3.2.1.0$^{2,7}$]oct-3-enes is studied.**

The intramolecular Diels−Alder reaction (IMDA) provides a powerful synthetic strategy for the construction of complex carbocyclic and heterocyclic systems.[1] As a result of its reduced entropic cost, even electronically unactivated starting materials leading to highly strained products undergo the reaction. Accordingly, it has been used as a key step in the synthesis of natural products and other complex target molecules.

5-Vinyl-1,3-cyclohexadienes represent an interesting class of substrates for IMDAs. Their products are caged tricyclo-[3.2.1.0$^{2,7}$]oct-3-enes, which consist of a fused three-, five-, and six-membered ring. Several examples of intramolecular cycloadditions involving vinylcyclohexadienes have appeared in the literature (Scheme 1).[2] In some cases, the IMDA was triggered by a 6$\pi$ electrocyclization of an octatetraene to afford the Diels−Alder substrate in situ (Scheme 1, eqs 3 and 4).[2c,d]

Most of these transformations, however, were observed as unexpected side reactions, which have never been evaluated for their synthetic potential. We now report new

**Scheme 1**




(1) (a) Roush, W. R. in *Comprehensive Organic Synthesis*; Trost, B. ed.; Vol. 5, pp 513 ff; Oxford: Pergamon Press 1991. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem.-Int. Edit.* **2002**, *41*, 1668.

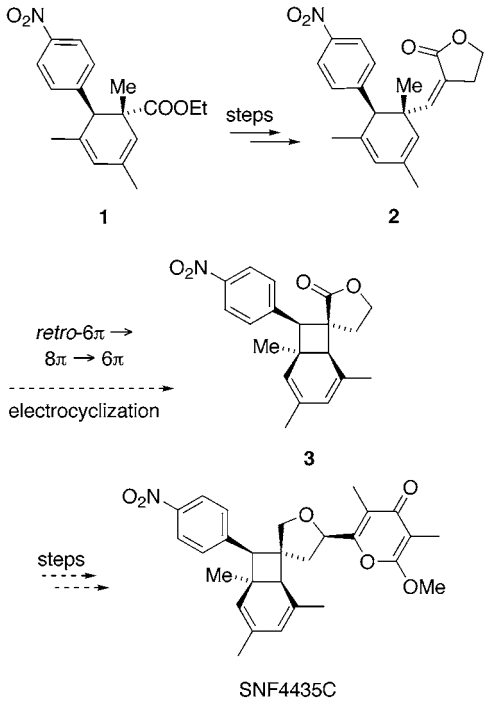
(2) (a) Jendralla, H.; Jelich, K.; Delucca, G.; Paquette, L. A. *J. Am. Chem. Soc.* **1986**, *108*, 3731. (b) Maier, G.; Wiegand, N. H.; Baum, S.; Wullner, R.; Mayer, W.; Boese, R. *Chem. Ber.* **1989**, *122*, 767. (c) Marvell, E. N.; Seubert, J.; Vogt, G.; Zimmer, G.; Moy, G.; Siegmann, J. R. *Tetrahedron* **1978**, *34*, 1323. (d) ten Have, R.; van Leusen, A. M. *Tetrahedron* **1998**, *54*, 1913. (e) Loeliger, P.; Mayer, H. *Helv. Chim. Acta* **1980**, *63*, 1604, and references therein.

10.1021/ol0343414 CCC: $25.00 
**Published on Web 04/15/2003**

intramolecular Diels−Alder reactions of vinylcyclohexadienes and give a preliminary account of our systematic study of the reaction.

Our initial results were also obtained serendipitously in the course of a program aimed at the SNF4435 class of immunosuppressants (Scheme 2).[3] In an attempt to salvage

**Scheme 2**




the product of an unwanted 6$\pi$ electrocyclization, compound **1**, we decided to convert it into alkylidene lactone **2**. We reasoned that **2** could be isomerized to the bicyclo[4.2.0]-octadiene core of the natural products, **3**, through a *retro* 6$\pi$ → 8$\pi$ → 6$\pi$ electrocyclization cascade. Thermodynamically, this isomerization was deemed to be feasible (calculated $\Delta\Delta H_f = -4$ kcal·mol$^{-1}$).

Reduction of **1** with diisobutylaluminum hydride (DIBAH), followed by Dess−Martin oxidation, afforded aldehyde **4** (Scheme 3). Condensation of this sterically hindered aldehyde with phosphono lactone **5**[4] was intended to afford a mixture of (*Z*)-alkylidene lactone **2** and its (*E*)-isomer **6**. To our surprise, however, we were unable to isolate **2** since it underwent rapid intramolecular Diels−Alder addition under the conditions of the Horner−Wadsworth−Emmons (HWE) reaction. The structure of the resulting spirotetracycle **7** was elucidated by extensive NMR studies and secured by X-ray analysis. The isomeric alkylidene lactone **6**, on the other hand, could be isolated. Heating this material in a sealed tube to 200 °C again failed to effect isomerization to a diastereomer of **3** but resulted in IMDA to afford **8** in good yield. Notably, **8** could not be found under the conditions of the HWE reaction.

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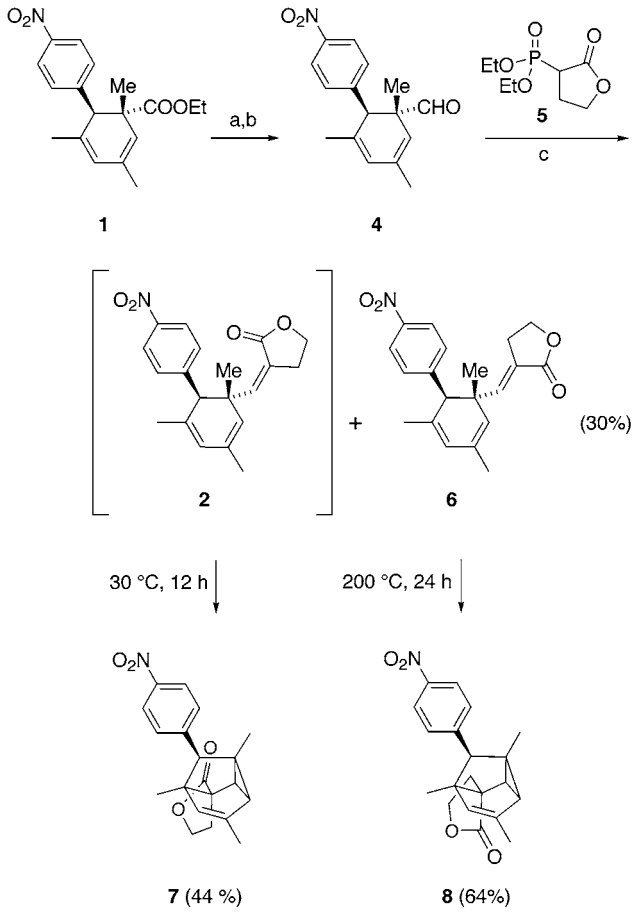
(4) Lee, K.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 5967.

**Scheme 3**[a]




[a] Reagents and conditions: (a) DIBAH, PhMe; (b) Dess−Martin periodinane, $CH_2Cl_2$ (67% from **1**); (c) **5**, KHMDS, 18-C-6, THF, 30 °C.

Presumably, the quaternary center of the substrates plays a role in these remarkable reactions by preventing competing hydrogen shifts and exerting a Thorpe−Ingold effect. The resulting caged tricyclo[3.2.1.0$^{2,7}$]oct-3-enes **7** and **8** feature three quaternary stereocenters, two of them adjacent. Their X-ray crystal structures are shown in Figure 1.[12]

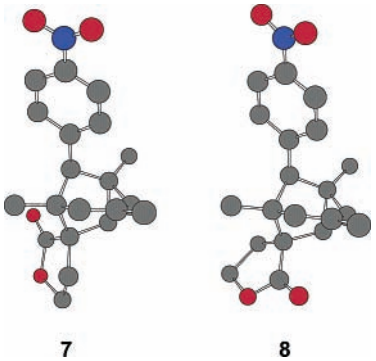
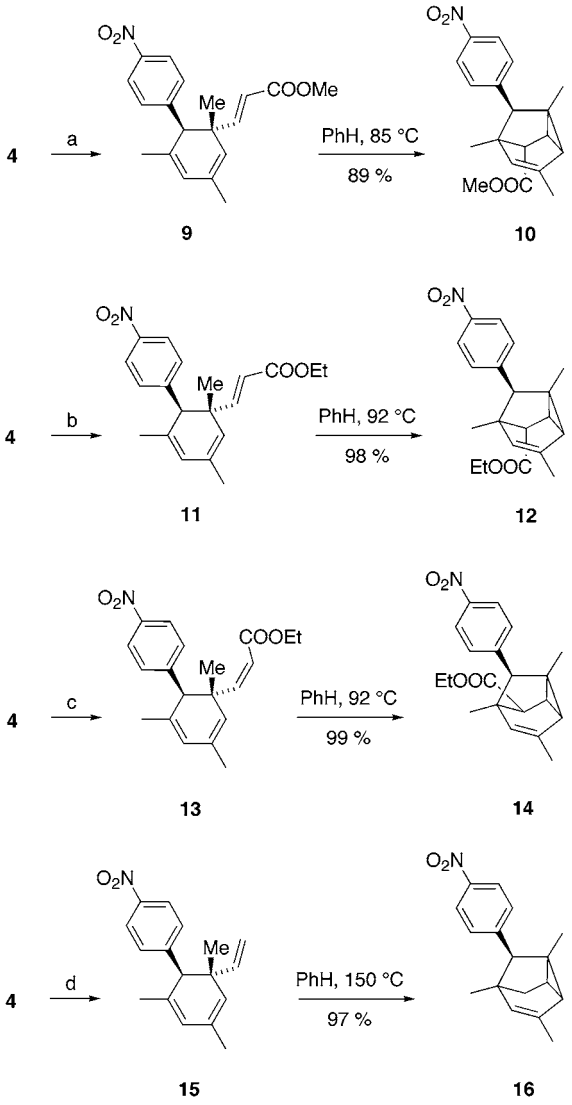



**Figure 1.** X-ray structure of compounds **7** and **8**. Hydrogens are omitted for clarity.

**Scheme 4**[a]




[a] Reagents and conditions: (a) $Ph_3P{=}CHCOOMe$, $CH_2Cl_2$, rt (41%); (b) $Ph_3P{=}CHCOOEt$, $CH_2Cl_2$, rt (52%); (c) $(TFEO)_2P(O)$-$CH_2COOEt$, KHMDS, THF, 18-C-6, −78 → 0 °C (61%); (d) $Ph_3P{=}CH_2$, THF, rt (78%).

The enormous difference in IMDA reactivity between geometrical isomers **2** and **6** under the conditions of the HWE reaction is remarkable. Its source is not obvious from simple steric and stereoelectronic considerations using molecular models. The potassium phosphate formed in the course of the olefination presumably acts as a Lewis acid, facilitating the cyclization of the inherently more reactive (*Z*)-isomer **2** at relatively low temperature.[5] Unfortunately, since compound **2** is not isolable, the rate of its cyclization in the absence of a Lewis acid could not be determined.

To gain more insight into the scope and limitations of the reactions we decided to systematically vary the nature of the dienophile moiety (Scheme 4). Accordingly, α,β-unsaturated esters **9**, **11**, **13** and **15** were prepared from aldehyde **4** using various olefination methods.[6] All substrates smoothly underwent the intramolecular cycloaddition at elevated temperatures to afford caged compounds **10**, **12**, and **14**, respectively. Even the electronically less activated vinylcyclohexadiene **15** cleanly afforded tricyclo[3.2.1.$0^{2,7}$]oct-3-ene **16** upon heating. No cycloreversions and electrocyclizations were observed in any of these cases.

The IMDA reactions involving geometrical isomers **11** and **13** were studied in detail by NMR spectroscopy. As expected, first-order kinetics was observed (Figure 2). The first-order

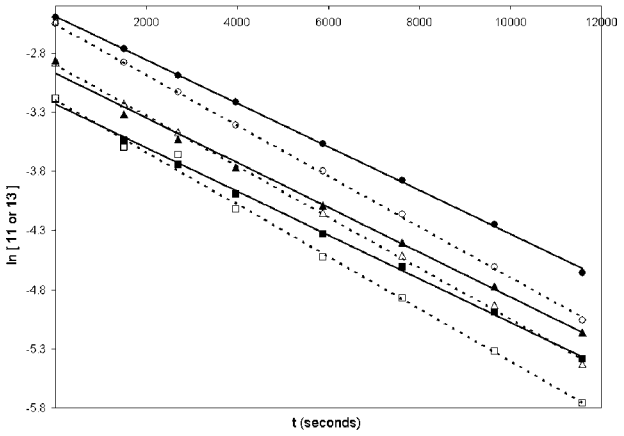



**Figure 2.** IMDA of (*E*)-isomer **11** (closed symbols) and (*Z*)-isomer **13** (open symbols) at three different concentrations. The reactions were run in sealed NMR tubes at 92 °C in benzene-$d_6$.

rate constants for consumption of **11** and **13** were determined to be $1.87 \times 10^{-4}$ and $2.26 \times 10^{-4}$ $s^{-1}$, respectively, at 92 °C in benzene-$d_6$ (see Supporting Information). The faster formation of cycloaddition product **14** ($k_{rel} = 1.21$) can be explained by its somewhat sterically less congested nature, which is presumably reflected in the transition state.

The tricyclo[3.2.1.$0^{2,7}$]oct-3-ene nucleus occurs in several natural products, for instance, in alkaloids of the staphirine class[7] and in the unusual diterpene dehydrotrachylobanoic acid (Scheme 5).[8] A brief retrosynthetic analysis of the latter is shown in Scheme 5.

It is interesting to speculate whether the biosynthesis of this natural product involves the intramolecular Diels−Alder reaction of a pimarane-type precursor.[9,10] The facile conversion of unactivated substrate **15** into **16** suggests that such a reaction should be possible in the laboratory. Synthetic

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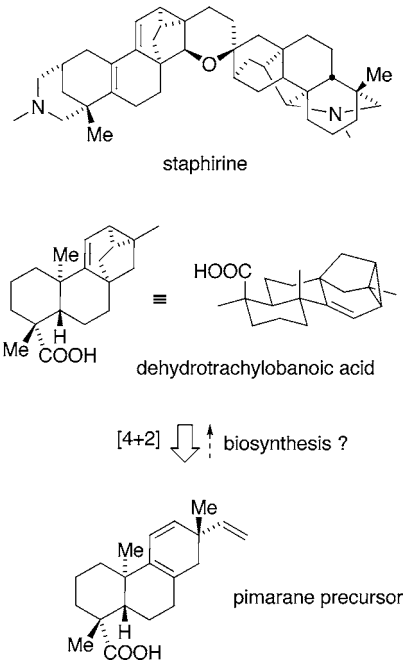
(9) For an account on pimarane diterpenes, see: Hanson, J. R. *Nat. Prod. Rep.* **2002**, *19*, 125, and previous reviews in this series.
(10) For Diels−Alder reactions in Nature, see: Ose, T.; Watanabe, K.; Mie, T.; Honma, M. Watanabe, H.; Yao, H.; Oikawa, H.; Tanaka, I. *Nature* **2003**, *422*, 185, and references therein.

**Scheme 5**




studies directed at dehydrotrachylobanoic acid and its saturated congener trachylobanoic acid[11] are well underway in our laboratories and will be reported in due course. In addition to this, the reason for the large rate difference in the IMDA of isomers **2** and **6** will be further investigated with computational methods.

**Acknowledgment.** We thank Dr. Frederick J. Hollander and Dr. Allen G. Oliver for the crystal structure determination of compounds **7** and **8**. Financial support by Merck & Co. is gratefully acknowledged.

**Supporting Information Available:** Experimental procedures and spectroscopic data for compounds **1**, **4**, **6**, **7**, **8**, **9**-**16**. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data (excluding structure factors) for compounds **7** and **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 207911 and CCDC 207912. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; E-mail: deposit@ccdc.cam.ac.uk).

OL0343414

(11) Biosynthetically, trachylobanoic acid could also arise from a beyerane or kaurane type precursor through carbocationic intermediates.