

Intramolecular Diels–Alder Cyclizations of (*E*)-1-Nitro-1,7,9-decatrienes: Synthesis of the AB Ring System of Norzoanthamine

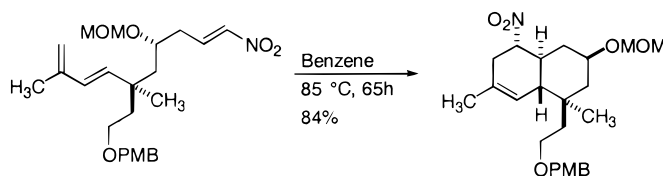
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Received December 21, 1999

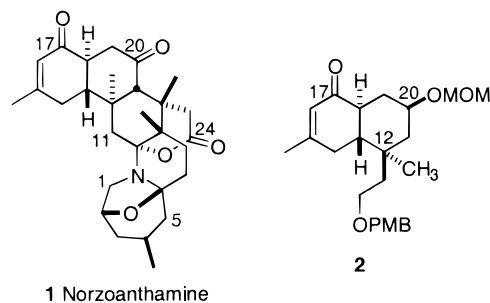
ABSTRACT



Cyclizations of substituted (*E*)-1-nitro-1,7,9-decatrienes under thermal and Lewis acid conditions have led to the formation of decalin ring systems with excellent *endo* selectivity. This strategy has been applied to the synthesis of the AB ring system of norzoanthamine.

The intramolecular Diels–Alder reaction (IMDA) has been explored extensively as a valuable tool for organic synthesis.¹ Although the thermal intermolecular Diels–Alder reactions of nitroalkenes with dienes have been widely studied,² intramolecular examples of this process are remarkably rare. Kurth has reported the thermal cyclizations of 1-nitro-1,6,8-decatrienes for the synthesis of perhydroindenes,³ and Kunesch and Tillequin have recently described the cycloaddition of a dinitroalkene and tethered furan to produce 3,7-dinitro-11-oxatricycloundec-9-ene.⁴ However, the intramolecular Diels–Alder reaction of nitroalkenes has not been

explored as a route to substituted decalin systems. In contrast, the alternative use of the nitroalkene moiety as a heterodiene component for formal [4 + 2] intermolecular cyclizations to provide nitronate intermediates has been systematically examined by Denmark and co-workers.⁵ Owing to our efforts for development of an enantioselective synthesis of the marine alkaloid norzoanthamine (**1**),^{6,7} recent studies have been focused on a stereocontrolled preparation of the substituted nonracemic decalone **2**. Herein, we describe the



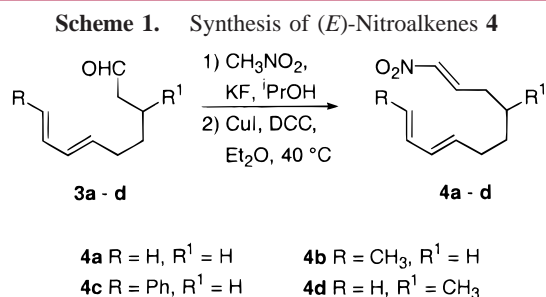
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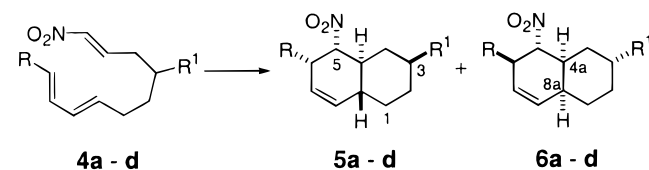
Several nitroalkenes were examined as model systems for our Diels–Alder strategy in order to evaluate issues of reactivity and stereoselectivity. As shown in Scheme 1,



nitroalkenes **4a–d** were prepared through an aldol condensation of the corresponding aldehydes **3a–d**^{8,9} with nitromethane.¹⁰ Although the dehydration of these β -hydroxy adducts is often problematic, a mild procedure using dicyclohexylcarbodiimide, as previously described by Seebach,¹¹ provided good isolated yields (~60%) of the nitroalkenes. The dehydration reaction led to nearly exclusive formation of the *E*-olefin ($\geq 97\%$), and the nitroalkenes were stable to procedures of flash silica gel chromatography.

Table 1 shows the results for the thermal and Lewis acid promoted cycloadditions of trienes **4a–d**. Thermal cyclization of **4a** (entry 1) led to a 73:27 ratio of *endo/exo* products. This represents a modest increase in *endo* selectivity compared to published results with methyl (*E,E*)-undeca-2,8,10-trienoate which gave a 51:49 *endo/exo* ratio of products (toluene, 155 °C, 45h, 92% yield).⁸ The increase in *endo* selectivity for the nitro case can be attributed to greater secondary orbital interaction with the more highly activated nitro-substituted dienophile.¹² Thermal cyclizations of several triene substrates (entries 2–4) showed consistent trends in *endo* selectivity and yield. In each experiment, only

Table 1. Diels–Alder Cyclizations of **4a–d**



entry	triene	conditions ^a	% yield ^b	5 <i>endo</i> : 6 <i>exo</i> ^c
1	4a	A, 89 h	63	73:27
2	4b	A, 28 h	70	70:30
3	4c	A, 36 h	72	61:39
4	4d	A, 42 h	80	73:27
5	4b	B, 1.5 h	39	89:11
6	4d	B, 6 h	38	92:8

^a Conditions: A, benzene, 85 °C; B, Et₂AlCl (2.0 equiv), CH₂Cl₂, –78 °C. ^b Purified yields. ^c Ratios determined from ¹H NMR (400 MHz) data of crude mixtures.

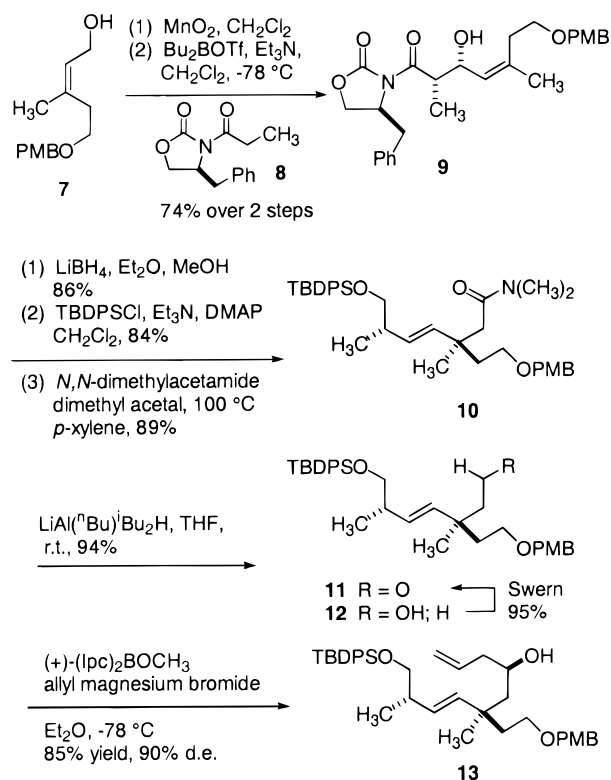
two diastereomers were detected by ¹³C and ¹H NMR analysis. Extensive coupling constant and NOE data supported the stereochemical assignments.

In the case of triene **4d** (entry 4), the preexisting stereogenic center in the tethering chain led to products **5d** and **6d** featuring a B-ring chair conformation with the C-3 methyl substituent in an equatorial orientation.¹³

Attempts to enhance the *endo* selectivity through Lewis acid activation proved difficult. Reactions using a variety of Lewis acids (AlMe₃, BF₃·OEt₂, TiCl₄, TiCl₂(OⁱPr)₂) led to low yields (<10%) of decalin products. The best results were achieved using Et₂AlCl (entries 5 and 6), which gave modest yields with significant increases in *endo* selectivity. Catalytic quantities of Lewis acid were ineffective in these studies, while stoichiometric quantities led to considerable decomposition affording highly polar materials. Decalins **5** and **6** were the only organic-soluble materials observed from these attempts.

The application of this methodology for norzoanthamine synthesis required an enantiocontrolled route to enone **2** with installation of a quaternary carbon at C-12 adjacent to the *trans* ring fusion. Oxidation of allylic alcohol **7**¹⁴ (Scheme 2) was followed by Evans aldolization with the Z(O) boron enolate of **8** to yield *syn*-alcohol **9**.^{15,16}

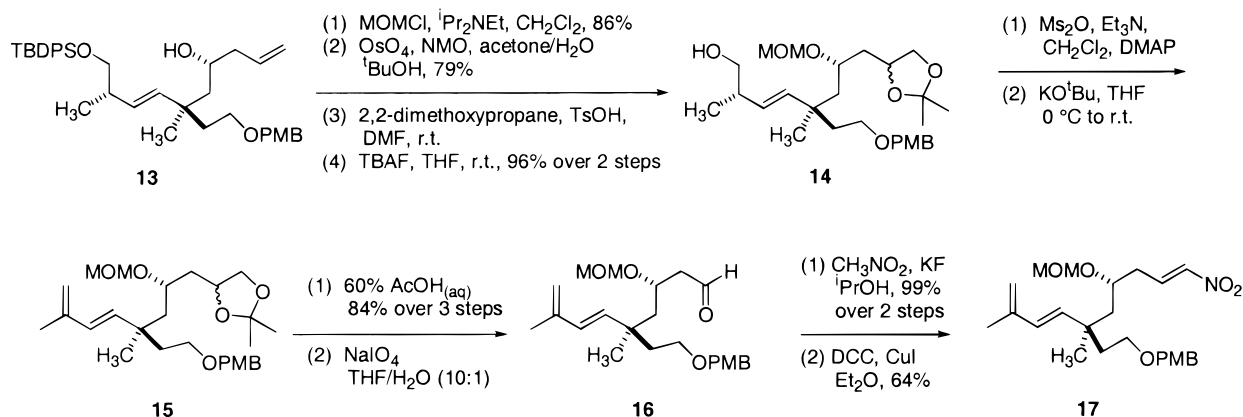
Scheme 2. Synthesis of Homoallylic Alcohol **13**



Oxazolidinone cleavage, protection, and subsequent Eschenmoser–Claisen rearrangement gave amide **10** as a

(5) (a) For a recent publication in this area, see: Denmark, S. E.; Seierstad, M. *J. Org. Chem.* **1999**, *64*, 1610. (b) For a review of tandem [4 + 2]/[3 + 2] cycloaddition reactions of nitroalkenes, see: Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.

Scheme 3. Synthesis of (*E,E*)-Nitrotriene 17



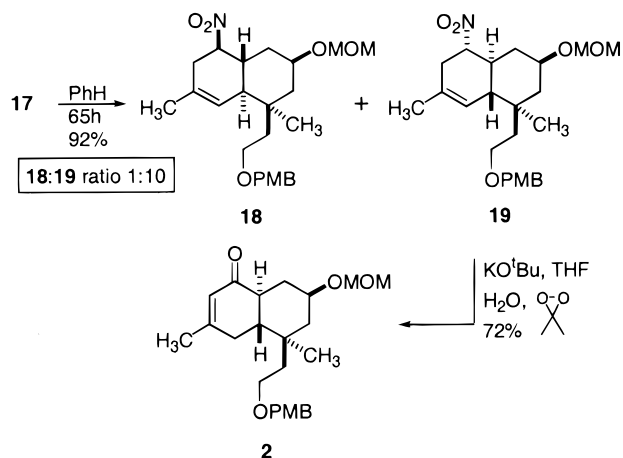
single diastereomer.¹⁷ Direct reduction to aldehyde **11** was accomplished using a modified aluminum hydride (**11:12** ratio 7.7:1).¹⁸ The small quantities of alcohol **12** formed from over-reduction were readily converted into **11**¹⁹ for subsequent asymmetric allylboration to yield homoallylic alcohol **13**.²⁰

Installation of the conjugated diene was completed through a mesylation/elimination sequence to give acetonide **15** (Scheme 3). All reactions in this pathway were generally straightforward. However, the key intermediate aldehyde **16** was very unstable and particularly prone to β -elimination of the MOM ether. The mild oxidative cleavage of the diol resulting from hydrolysis of **15** provided a ready source of **16**, which could be used without further purification. Treatment with nitromethane in the presence of KF afforded a quantitative aldol condensation. Dehydration gave the

desired Diels–Alder precursor **17** in 64% yield following silica gel chromatography.

Thermal cyclization of **17** in benzene (reflux, 65 h) led to a 1:10 ratio of a separable mixture of **18/19** (Scheme 4) in

Scheme 4. Diels–Alder Cyclization of (*E,E*)-Nitrotriene 17 and Completion of the Synthesis of Enone 2



excellent yield (92%). Both cycloadducts arise from the diastereomeric *endo* transition states. Cyclization of **17** in acetonitrile produced a more rapid reaction (7 h at 70 °C) with a more favorable diastereomeric ratio (95:5) but a reduced overall yield (66%). Assignment of stereochemistry for the two diastereomers was based on ¹H NMR coupling constants and NOE experiments (Figure 1). MM2* minimizations²¹ of **18** support the notion that the B-ring twist-boat (as shown) may provide a significant conformational contribution in order to avoid the 1,3-diaxial interaction of the corresponding chair.

The desired *trans*-decalin **19** has been efficiently converted to the desired α,β -unsaturated enone **2** in good yield (72%)

(21) Molecular mechanics calculations were performed using the MacroModel program version 7.0 (MM2* force-field).

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(14) Alcohol **7** was synthesized in four steps starting from 3-butyne-1-ol using the following procedure: (1) PBOC(NH)CCl₃, TfOH, Et₂O, rt; (2) ⁿBuLi, EtOC(O)Cl, THF, -78 °C to rt; (3) MeCu·LiI (2 equiv), THF, -45 °C; (4) LiAlH₄, Et₂O, 0 °C. For an alternative preparation of alcohol **7**, see: Nagano, H.; Nakanishi, E.; Takajo, S.; Sakuma, M.; Kudo, K. *Tetrahedron* **1999**, *55*, 2591.

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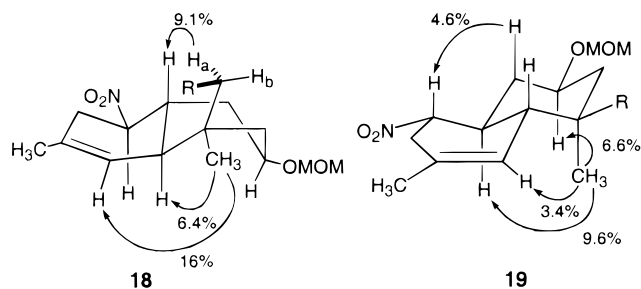


Figure 1. ¹H NMR studies of NOE interactions for Diels–Alder products **18** and **19**.

by way of an oxidative Nef reaction.²² In the process, the C-14/C-15 alkene migrated into conjugation with the C-17 ketone to provide a successful synthesis of the functionalized

AB-ring system of the zoanthamine alkaloids. Further efforts are underway to apply this approach to the synthesis of norzoanthamine.

Acknowledgment. The authors gratefully acknowledge the National Institutes of Health (GM-41560) for generous support of our work. We also thank the Indiana University College of Arts and Science for a summer fellowship for T.A.B.

Supporting Information Available: Experimental procedures and spectral data for compounds **18**, **19**, and **2** and ¹H NMR data for compounds **5a**, **5c**, **5d**, **6c**, and **6d**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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