ORGANIC LETTERS

2000
Vol. 2, No. 8
1023−1026

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

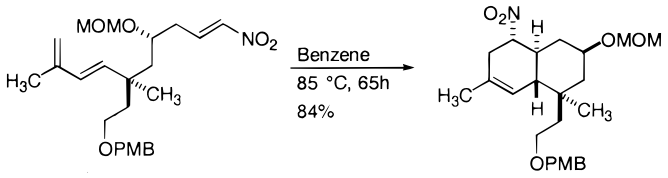
David R. Williams* and Todd A. Brugel

Department of Chemistry, Indiana University, 800 East Kirkwood Avenue, Bloomington, Indiana 47405-7102

williamd@indiana.edu

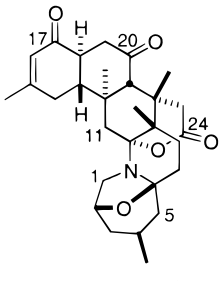
Received December 21, 1999

ABSTRACT

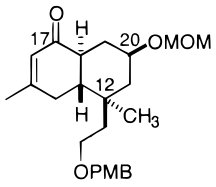


Cyclizations of substituted (*E*)-1-nitro-1,7,9-decatrienes under thermal and Lewis acid conditions have led to the formation of decalin ring systems with excellent *endo* selectivity. This strategy has been applied to the synthesis of the AB ring system of norzoanthamine.

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 intramolecular Diels−Alder protocol as a key transformation for the efficient preparation of these bicyclic enones via subsequent application of the Nef reaction.



1 Norzoanthamine



2

(1) For reviews of the intramolecular Diels−Alder reaction, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 513−550. (b) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (c) Cigarek, E. *Org. React.* **1984**, *32*, 1. (d) Brieger, G.; Bennet, J. N. *Chem. Rev.* **1980**, *80*, 63.

(2) (a) Stoodley, R. J.; Yuen, W.-H. *Chem. Commun.* **1997**, 1371. (b) Node, M.; Nishide, K.; Imazato, H.; Kurosaki, R.; Inoue, T.; Ikariya, T. *Chem. Commun.* **1996**, 2559. (c) Ayerbe, M.; Cossío, F. P. *Tetrahedron Lett.* **1995**, *36*, 4447. (d) Ono, N.; Kamimura, A.; Kaji, A. *J. Org. Chem.* **1988**, *53*, 251. (e) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574.

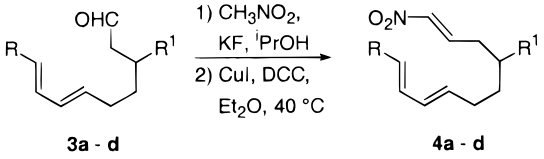
(3) Kurth, M. J.; O'Brien, M. J.; Hope, H.; Yanuck, M. *J. Org. Chem.* **1984**, *50*, 2626.

(4) Sader-Bakaouni, L.; Charton, O.; Kunesch, N.; Tillequin, F. *Tetrahedron* **1998**, *54*, 1773.

10.1021/ol9904085 CCC: $19.00
Published on Web 03/21/2000

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,

Scheme 1. Synthesis of (*E*)-Nitroalkenes **4**

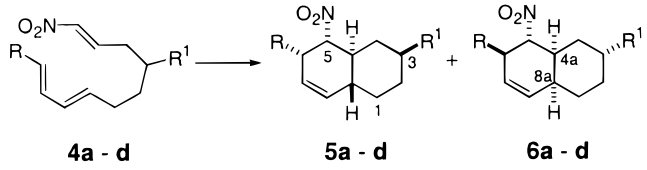


4a R = H, R^1 = H **4b** R = CH_3, R^1 = H
4c R = Ph, R^1 = H **4d** R = H, R^1 = CH_3

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 (≥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** *endo*:**6** *exo*[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, Et_2AlCl (2.0 equiv), CH_2Cl_2, −78 °C. [b] Purified yields. [c] Ratios determined from ^1H NMR (400 MHz) data of crude mixtures.

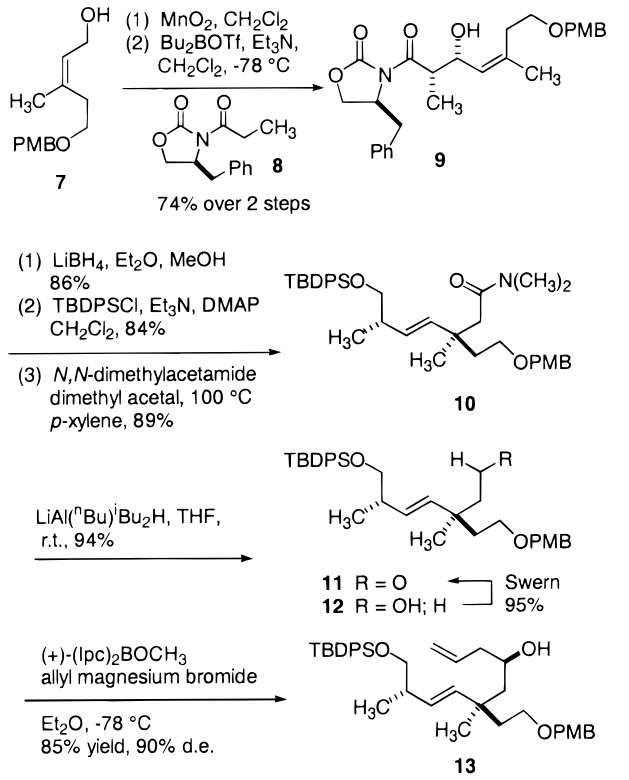
two diastereomers were detected by ^{13}C and ^1H NMR analysis. Extensive coupling constant and NOE data supported the stereochemical assignments.

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 ($AlMe_3$, $BF_3{\cdot}OEt_2$, $TiCl_4$, $TiCl_2(O^iPr)_2$) led to low yields (<10%) of decalin products. The best results were achieved using Et_2AlCl (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]

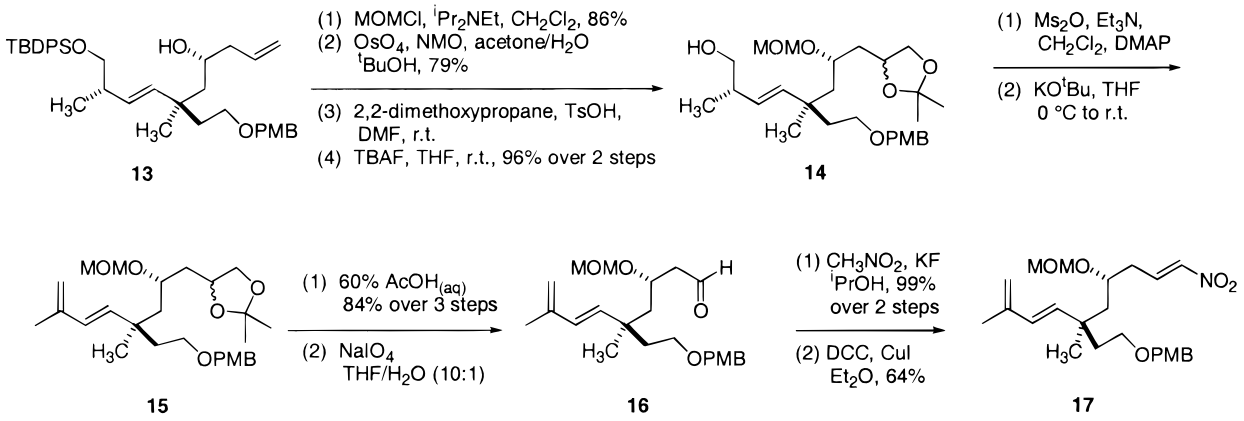
Scheme 2. Synthesis of Homoallylic Alcohol **13**



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**

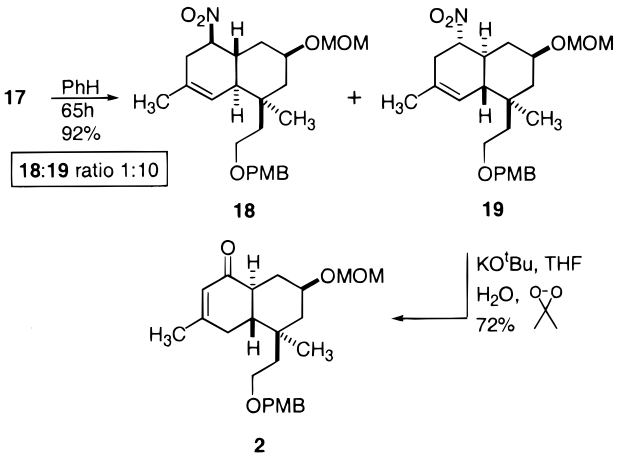


single diastereomer.[17] Direct reduction to aldehyde **11** was accomplished using a modified aluminum hydride (**11**:**12** ratio 7.7:1).[18] The small quantities of alcohol **12** formed from over-reduction were readily converted into **11**[19] for subsequent asymmetric allylboration to yield homoallylic 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 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 ^{1}H NMR coupling constants and NOE experiments (Figure 1). MM2* minimizations[21] 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.

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



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

(6) (a) Fukuzawa, S.; Hayashi, Y.; Uemura, D.; Nagatsu, A.; Yamada, K.; Ijuin, Y. *Heterocycl. Commun.* **1995**, *1*, 207. (b) Kuramoto, M.; Hayashi, K.; Fujitani, Y.; Yamaguchi, K.; Tsuji, T.; Yamada, K.; Ijuin, Y.; Uemura, D. *Tetrahedron Lett.* **1997**, *38*, 5683.

(7) Williams, D. R.; Cortez, G. S. *Tetrahedron Lett.* **1998**, *39*, 2675.

(8) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200.

(9) Ainswroth, P. J.; Craig, D.; Reader, J. C.; Slawin, A. M. Z.; White, J. P.; Williams, D. J. *Tetrahedron* **1995**, *51*, 11601.

(10) Wollenberg, R. H.; Miller, S. J. *Tetrahedron Lett.* **1978**, 3219.

(11) Knochel, P.; Seebach, D. *Synthesis* **1982**, 1017.

(12) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.

(13) For related examples of C_3-methyl stereocontrol in IMDA cycloadditions, see: (a) Williams, D. R.; Gaston, R. D.; Horton, I. B. *Tetrahedron Lett.* **1985**, *26*, 1391. (b) Williams, D. R.; Bremmer, M. L.; Brown, D. L.; D'Antuono, J. *J. Org. Chem.* **1985**, *50*, 2807.

(14) Alcohol **7** was synthesized in four steps starting from 3-butyne-1-ol using the following procedure: (1) PMBOC(NH)CCl_3, TfOH, Et_2O, rt; (2) ^{n}BuLi, EtOC(O)Cl, THF, −78 °C to rt; (3) MeCu·LiI (2 equiv), THF, −45 °C; (4) $LiAlH_4$, Et_2O, 0 °C. For an alternative preparation of alcohol **7**, see: Nagano, H.; Nakanishi, E.; Takajo, S.; Sakuma, M.; Kudo, K. *Tetrahedron* **1999**, *55*, 2591.

(15) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83.

(16) All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, HRMS, and optical rotation where appropriate. Yields are for isolated, chromatographically pure products.

(17) (a) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chem. Acta* **1964**, *47*, 2425. (b) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chem. Acta* **1969**, *52*, 1030.

(18) (a) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717. (b) Taber, D. F.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639.

(19) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(20) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.

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

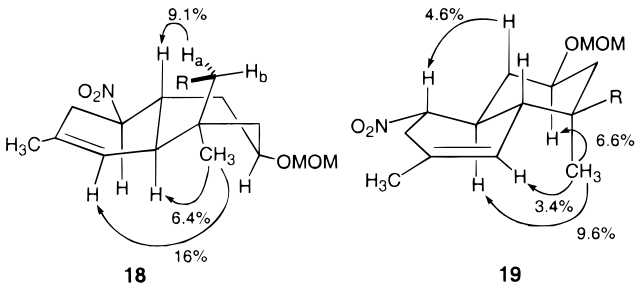


Figure 1. ^{1}H NMR studies of NOE interactions for Diels−Alder products **18** and **19**.

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 ^{1}H 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.

OL9904085

(22) Adam, W.; Makosza, M.; Saha-Möeller, C. R.; Zhao, C.-G. *Synlett* **1998**, 1335.