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Intramolecular [4 + 2] Cycloaddition of Nitroalkenes for Construction of Vicinal Quaternary Stereocenters

Scott E. Denmark* and Ramil Y. Baiazitov

Roger Adams Laboratory, Department of Chemistry, University of Illinois,
Urbana, Illinois 61801

denmark@scs.uiuc.edu

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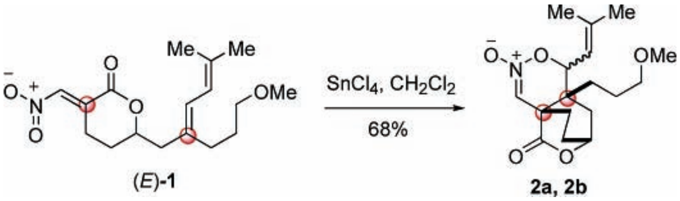
ABSTRACT



Nitroalkene (*E*)-1 has been synthesized to test the feasibility of an intramolecular [4 + 2] cycloaddition in a planned synthesis of daphnilactone B. This nitro olefin contains two unique structural features, a nitromethylene lactone and a pendant diene, that combine under the action of $SnCl_4$ in a highly selective fashion to afford nitronates 2a and 2b. These products represent the correct relationship for the vicinal quaternary stereogenic centers in the core of daphnilactone B.

The Diels−Alder reaction is a powerful method for the creation of complex polycyclic structures containing many stereogenic centers in a single step.[1] As has recently been pointed out by Overman, the stereocontrolled introduction of contiguous stereogenic quaternary carbons represents a major challenge in natural products synthesis[2] and the Diels Alder reaction has been successfully applied for this objective.[3] The tandem [4 + 2]/[3 + 2] cycloaddition of nitro olefins, which has been extensively developed in these laboratories, is also capable of constructing quaternary stereocenters in both inter- and intramolecular processes.[4] However, the creation of vicinal stereogenic quaternary centers has yet to be achieved. In this report we describe our studies on the first demonstration of a nitroalkene [4 + 2] cycloaddition to set this structural motif.

In the context of a planned total synthesis of daphnilactone B (Scheme 1), we have recently described preliminary studies that successfully demonstrated the construction of the piperidine and pyrrolidine rings in model **iii** by use of a tandem [4 + 2]/[3 + 2] cycloaddition with nitroalkene **vi** as the key step.[5] However, in this simplified system, only a single quaternary stereogenic center is created in **iii**. In the synthetic plan for daphnilactone B the most formidable challenge is the stereoselective installation of the two adjacent quaternary centers in precursor **i**. The key step in the planned synthesis is the tandem, double intramolecular [4 + 2]/[3 + 2] cycloaddition[4b] of a nitro olefin of type **ii** during which the core of the polycyclic alkaloid is created. Cycloaddition precursor **ii** contains additional functionality compared to **vi** for two important purposes: (1) the fuctional group (FG^1) *β* to the nitro group serves as the precursor to the hydroazulene unit, and (2) the functional group FG^2 is to be used later in the synthesis to form the seven-membered lactone, as well

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[1] Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41,* 1668−1698.

[2] Peterson, E. A.; Overman, L. E. *Proc. Nat. Acad. Sci.* **2004**, *101*, 11943−11948.

[3] Von Nussbaum, F.; Hanke, R.; Fahrig, T.; Benet-Buchholz, J. *E. J. Org. Chem.* **2004**, 2783−2790. (b) Nicolaou, K. C.; Vassilikogiannakis, G.; Magerlein, W.; Kranich, R. *Chem. Eur. J.* **2001**, *7*, 5359−5371. (c) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2544−2553.

[4] (a) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1994**, *59*, 4576−4595. (b) Denmark, S. E.; Gomez, L. *J. Org. Chem.* **2003**, *68,* 8015−8024. See also: (c) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675−1686.

[5] Denmark, S. E.; Baiazitov, R. Y. *J. Org. Chem.* in press (JO052001L).

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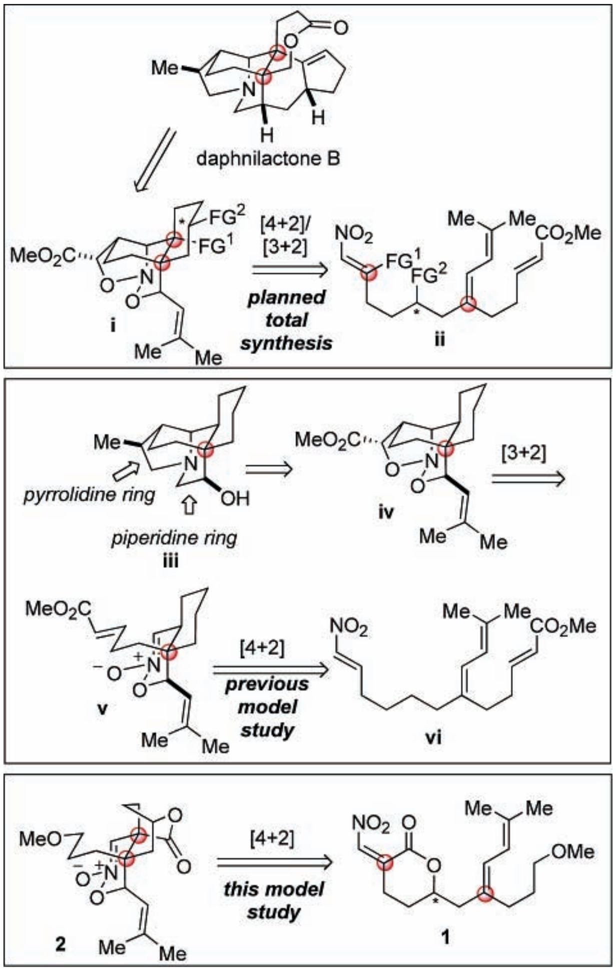
as to provide the sole element of chirality for an enantioselective total synthesis.

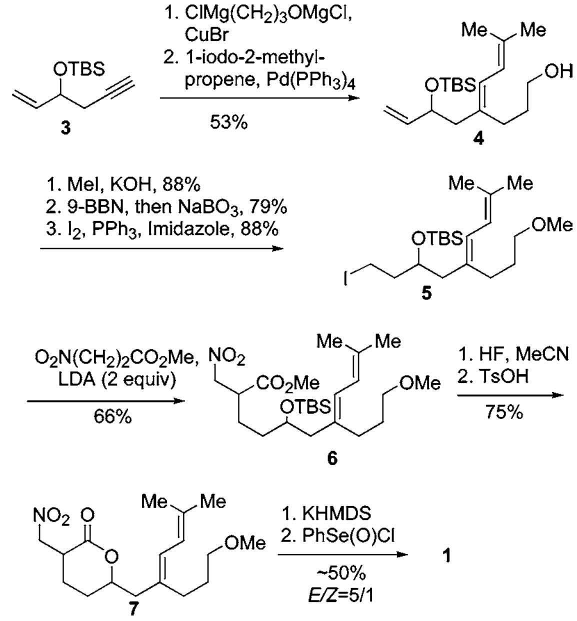
Scheme 1



The choice of FG^1 and FG^2 is guided by the need to maintain high reactivity of the nitroalkene and also ready synthetic accessibility. To meet the first criterion, the group FG^1 should be electron-withdrawing and FG^2 should be an oxygen-containing group to facilitate access to the seven-membered ring lactone. This led to the formulation of the bridging lactone unit in **1**, which should also add rigidity to the system. The less flexible substrate may allow for better stereocontrol during the cycloaddition step. The second criterion presents significant challenges as very few methods have been reported for the synthesis of 2,2-disubstituted nitro olefins[6] and none for α-nitromethylene lactones. We therefore devised an approach to this unknown moitey by adapting the methods reported from these laboratories for the synthesis of 2,2-disubstituted nitro olefins by conjugate addition to a 2-monosubstituted nitro olefin, followed by α-selenation, selenide oxidation, and elimination.[7] For simplicity, the dipolarophile was not introduced in this model study. This paper describes the synthesis of the required nitro olefin **1** and its use to form two vicinal quaternary stereocenters in **2** via an intramolecular [4 + 2] nitroalkene cycloaddition.

The synthesis of nitro olefin **1** (Scheme 2) followed a strategy similar to that used for the construction of **vi**.[5] Sequential carbocupration of alkyne **3**[8] (with the chloromagnesium salt of 3-hydroxypropylmagnesium chloride) followed by Pd-catalyzed cross-coupling of the resulting alkenylcopper with 1-iodo-2-methylpropene provided alcohol **4** in 53% yield. The hydroxyl group was protected as a methyl ether, and the terminal double bond was converted to a primary alcohol (hydroboration (9-BBN), oxidation ($NaBO_3$)), which was transformed into primary iodide **5**. The nitromethyl lactone was introduced by alkylation of the dianion of methyl-3-nitropropionate[9] with **5** to provide **6** in 66% yield. Removal of the TBS group and treatment with *p*-toluenesulfonic acid led to the clean formation of lactone **7**. Interestingly, although the lactonization was fast, the equilibrium was not favorable and the removal of methanol was required (Soxhlet apparatus charged with $CaCl_2$) to drive the reaction to completion, suggesting that the lactone **7** is not thermodynamically very stable. Because of the obvious base-sensitivity of **7**, large amounts of the dehydronitration[9] product were formed during chromatographic purification on silica gel. Addition of 1% of acetic acid to the eluent allowed for isolation of the nitro lactone in 75% yield.

Scheme 2



The dehydrogenation of **7** proved to be a formidable task. Trapping the lithium enolate (*n*-BuLi or LDA) of **7** with PhSeBr or PhSeCl[7,10] led to incomplete reaction (probably

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(6) (a) Tamura, R.; Sato, M.; Oda, D. *J. Org. Chem.* **1986**, *51*, 4368−4375. (b) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1995**, *60*, 1013−1019.

(7) (a) Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5431−5438. (b) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3850−3856.

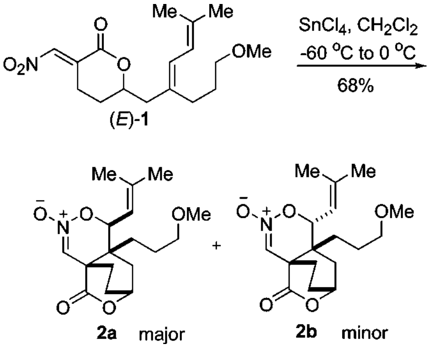
(8) Roulland, E.; Monneret, C.; Florent, J.-C. *J. Org. Chem.* **2002**, *67*, 4399−4406.

(9) Seebach, D.; Henning, R.; Mukhopadhyay, T. *Chem. Ber.* **1982**, *115*, 1705−1720.

due to the proton transfer between the enolate of **7** and the selenylation product), and considerable amounts of the nitrolactone could be recovered. Attempted oxidation (H_2O_2, m-CPBA, $NaIO_4$) of the formed α-phenylseleno nitro lactone led only to decomposition, possibly due to side reactions such as epoxidation of the electron-rich diene.[11] However, the use of a Se(IV) electrophilic reagent PhSe(O)Cl[12] allowed for the direct formation of the selenoxide, which spontaneously eliminated phenylselenenic acid upon workup. The proton-transfer did not complicate the reaction, because no starting material could be observed by ^{1}H NMR or HPLC analysis of the crude reaction mixture when KHMDS was used for the deprotonation. In this process, the *E/Z* ratio for the nitro olefins **1** was approximately 5/1. Unfortunately, the nitro olefins were highly sensitive materials and could not be isolated in high yield. An analytically pure sample of the *E*-nitro olefin was obtained after multiple sacrificial crystallizations, but the *Z*-nitro olefin could not be isolated with high purity. Furthermore, storage of the nitro olefin (*E*)-**1** in the freezer at −15 °C for 3 weeks led to 50% migration of the double bond to form the endocyclic allylic nitro olefin. The highest yield of the *E*- and *Z*-nitro olefins was below 50%. Although this is clearly not ideal for the total synthesis endeavor, for the purposes of this model study we were satisfied that a method was developed and we were able to probe the key cycloaddition reaction.

To our delight exposure of nitro lactone (*E*)-**1** to $SnCl_4$ resulted in the formation of a mixture of epimeric nitronates **2a** and **2b** (Scheme 3) in up to 68% yield but with varying diasteromeric ratios (1/1 to 6/1). The relative configuration of each nitronate was unambiguously established by single-crystal X-ray structural analysis of both isomers after separation through preparative HPLC and crystallization from ethyl acetate.[13] In the major isomer, **2a**, the dienophile geometry was preserved, whereas in the minor isomer, **2b**, a formal isomerization of the dienophile has taken place (Figure 1). The ORTEP image clearly reveals the rigidity of the oxabicyclo[2.2.2]octane skeleton and the difficulty of achieving overlap of the dieneophile with the nitroalkene unit (vide infra).

Scheme 3



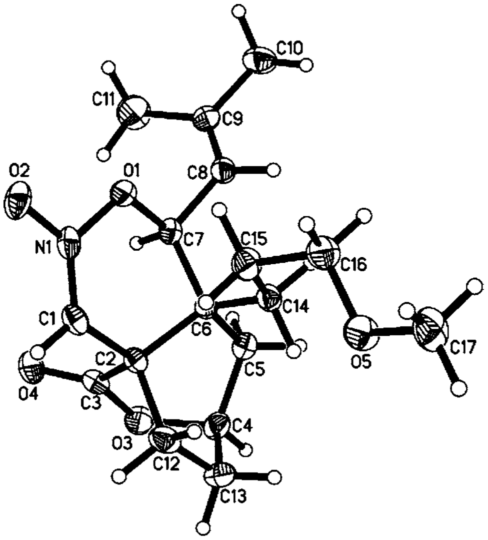


Figure 1. ORTEP image of X-ray crystal structure of **2a**.

Surprisingly, at lower temperatures (< −70 °C) the reaction was not as clean and 10% of a byproduct was isolated, which was identified as **8** (Scheme 4). Interestingly, only one diastereomer of **8** was observed. The production of **8** could be suppressed by carrying out the reaction at −60 °C or higher. The formation of **8** can be explained by the stepwise mechanism presented in Scheme 4. Thus, from (*E*)-**1** the C−C bond is formed first to provide the intermediate zwitterion **vii**, which can either collapse to form the nitronate **2a** or be intercepted by chloride from $SnCl_4$ to form the tertiary allylic chloride **viii**. Upon aqueous workup, **viii** is converted to alcohol **8**. Formation of only one diastereomer of **8** correlates well with formation of only one set of the adjacent quaternary stereocenters in **2a**/**2b**, suggesting involvement of the same intermediate **vii** before the course of the reaction diverges toward the nitronates or the allylic chloride. The formation of epimer **2b** can also be accommodated by this mechanism in that the cationic species **vii** could rotate around the C−C bond before collapse. Alternatively, **2b** could be derived from isomerization of the allylic ether in the presence of a strong Lewis acid after formation of nitronate **2a**. In a control experiment a 3.6/1 mixture of **2a**/**2b** was exposed to $SnCl_4$ under standard reaction conditions. After workup, the nitronates were isolated in a 2/1 ratio. When the nitro olefin (*E*)-**1** was allowed to react for a shorter time (10 min at −70 °C, 15% isolated yield of **2a** and **2b**), the **2a**/**2b** ratio was 6/1. This suggests that **2a** is the initially formed product, but it can undergo further epimerization upon prolonged exposure to the Lewis acid.

Nitro olefin (*E*)-**1** cannot form nitronate **2a** directly through a pericyclic mechanism because of the geometrical restrains imposed by the tether. Rather, **2c** should be formed in a concerted process, but this cycloadduct was not observed.

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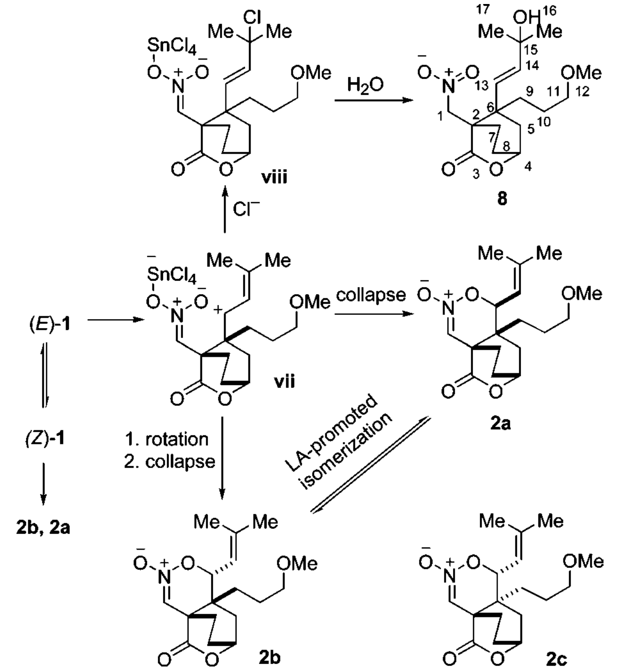
(13) The crystallographic coordinates of **2a** and **2b** have been deposited with the Cambridge Crystallographic Data Centre, deposition nos. CCDC 282324 and 282325, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax (+44) 1223-336-033; email deposit@ccdc.cam.ac.uk).

If the cycloaddition is not stepwise as depicted in Scheme 4, another mechanism may be in situ isomerization of (*E*)-**1** into (*Z*)-**1**.[4a,c] The latter could provide **2a** through a concerted process. To test this hypothesis, an (impure) sample of nitroalkene (*Z*)-**1** was subjected to the same reaction conditions used for (*E*)-**1**. These experiments provided the same nitronates **2a** and **2b** but in variable diastereomeric ratios in which **2b** was usually favored (**2b**/**2a** = 1.1/1 to 3/1). Furthermore, (*Z*)-**1** reacted considerably more slowly than the (*E*)-**1**.

Scheme 4



No matter what the reaction mechanism may be, the two adjacent quaternary centers in these cycloadducts were formed with excellent stereoselectivity. We attribute this stereoselectivity to the directing effect of the rigid lactone tether. The formation of epimers at C(7) (Figure 1) is of no consequence to the synthesis plan. As was demonstrated in the previous model study (**iv** → **iii** Scheme 1),[5] this center becomes a secondary hydroxyl group in the piperidine ring, which will be oxidized to a ketone for annulation of the seven membered ring.

In summary we have demonstrated that the [4 + 2] cycloaddition of nitro olefin (*E*)-**1** can be used to selectively create the vicinal quaternary stereocenters in **2a**/**2b** that correspond to the two vicinal quaternary stereocenters in daphnilactone B. We are currently investigating the preparation and tandem [4 + 2]/[3 + 2] cycloaddition of a more advanced precursor that contains the dipolarophilic enoate in the tether. These results will be reported in due course.

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Supporting Information Available: Full characterization of all products, detailed experimental procedures, and crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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