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# Tandem Double Intramolecular [4 + 2]/[3 + 2] Cycloadditions of Nitroalkenes

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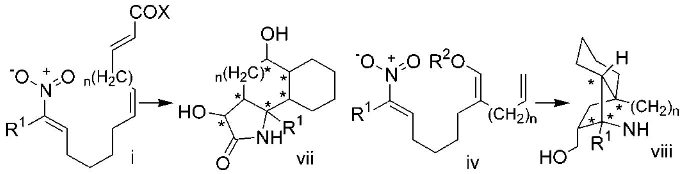
## ABSTRACT



**A new class of tandem [4 + 2]/[3 + 2] cycloadditions of nitroalkenes is described in which both pericyclic processes are intramolecular. Two subclasses of intra [4 + 2]/intra [3 + 2] cycloadditions have been explored in which the dipolarophile is tethered at either C(5) or C(6) of the nitronate. For both families of precursors, the cycloadditions occur in good yield and are found to be highly regio- and stereoselective. This method converts linear polyenes to functionalized polycyclic systems bearing up to six stereogenic centers.**

In recent years, the application of tandem reactions has emerged as a rapid and powerful strategy for the construction of highly functionalized compounds with high levels of regio-, diastereo-, and enantiocontrol.[1] In these laboratories, the tandem cycloaddition of nitroalkenes has been investigated as a general approach for the synthesis of various nitrogen-containing polycyclic compounds.[2] The structural diversity of the tandem [4 + 2]/[3 + 2] cycloaddition sequence derives from the number of permutations possible for attachment of the various components (dienophile and dipolarophile) to the nitroalkene as well as the length of the tethers. Among these different permutations, both the intra/inter[3] as well as the inter/intra[4] tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition have been extensively documented.

We have begun studies of a new variation on the tandem sequence, namely, the family of intra [4 + 2]/intra [3 + 2] cycloadditions. Because of the complementary electronic demands of the nitroalkene and intermediate nitronate, the presence of two alkenes in the molecule is not a complication. Among the different possibilities for dipolarophile attachment, we focused our initial studies on the subclass called the *fused/bridged* mode wherein the dipolarophile is tethered at the C(6) or C(5) position of the nitronate, i.e., the two ends of the dienophile (**i** and **iv**, Scheme 1). The process involves the Lewis acid promoted intramolecular [4 + 2] cycloaddition of these nitroalkenes to produce cycloadducts **ii** and **v**. These nitronates are poised to undergo thermal, intramolecular [3 + 2] cycloaddition to afford unusual tetracyclic nitroso acetals **iii** and **vi**. In this Letter, we report

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(1) (a) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992. (b) Ziegler, F. E. In *Comprhensive Organic Synthesis, Combining C−C p-Bonds*; Paquette, L. A., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.3. (c) Tietze, L. F.; Beifuss, U. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (d) Grigg, R., Ed. *Cascade Reactions*; Tetrahedron Symposium in Print; Elsevier: New York, 1996; No. 62.

(2) (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (b) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266. (c) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125. (d) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668. (e) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. (g) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1997**, *62*, 7086. (h) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046.

(3) (a) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **1998**, *63*, 3045. (b) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672. (c) Denmark, S. E.; Herbert, B. *J. Am. Chem. Soc.* **1998**, *120*, 7357. (d) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875. (e) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887.

(4) (a) Denmark, S. E.; Stolle, A.; Dixon, J. A.; Guagnano, V. *J. Am. Chem. Soc.* **1995**, *117*, 2100. (b) Denmark, S. E.; Schnute, M. E.; Marcin, L. R.; Thorarensen, A. *J. Org. Chem.* **1995**, *60*, 3205. (c) Denmark, S. E.; Guagnano, V.; Dixon, J. A.; Stolle, A. *J. Org. Chem.* **1997**, *62*, 4610. (d) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1997**, *62*, 7086. (e) Denmark, S. E.; Middleton, D. S. *J. Org. Chem.* **1998**, *63*, 1604.

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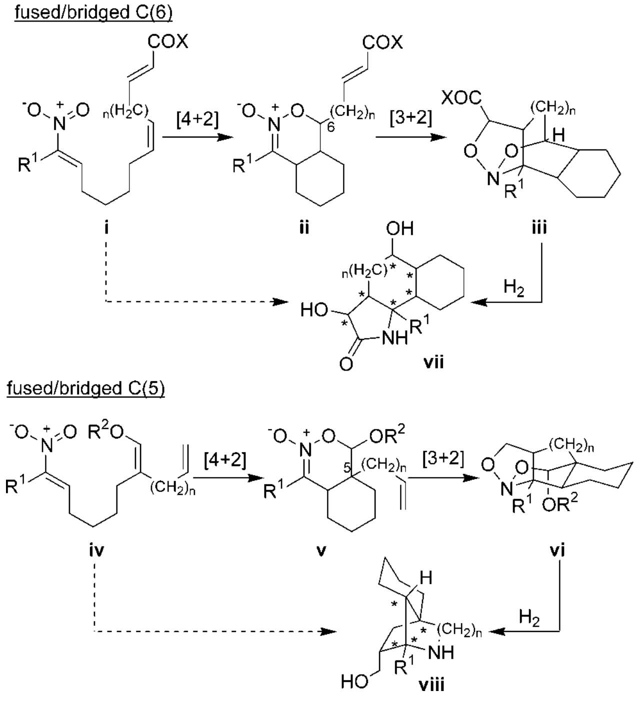
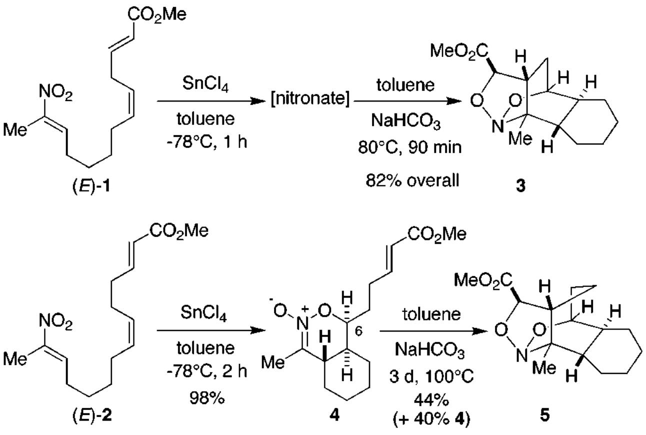
the successful realization of this construction and demonstrate the potential of this process for the synthesis of highly functionalized polycyclic compounds (**iii** → **vii** and **vi** → **viii**, Scheme 1).[5]

Scheme 1



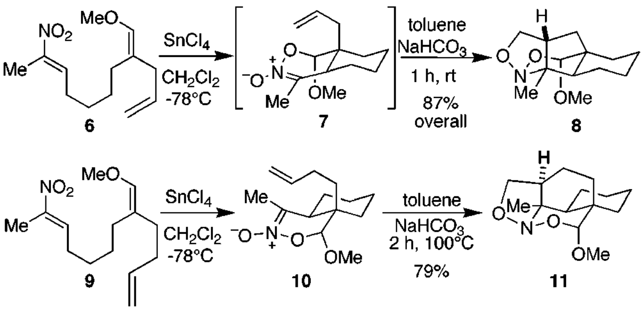
To establish the ability of the C(6)-tethered nitroalkenes to undergo an inverse electron demand intramolecular [4 + 2] cycloaddition, we first selected (*E*)-**1** and (*E*)-**2** as the test substrates,[6] which would create six- and seven-membered rings in the [3 + 2] process, respectively (Scheme 2). The intramolecular [4 + 2] cycloaddition of (*E*)-**1** proceeded readily in the presence of SnCl$_4$ (2 equiv) at −78 °C within 1 h. The nitronate could be isolated, but much to our delight it was contaminated with the nitroso acetal **3**. Thus, we chose to simply warm the crude nitronate in toluene to effect dipolar cycloaddition and obtained the nitroso acetal in 82% yield (overall) as a single diastereomer after recrystallization. The full stereostructure of **3** was confirmed by $^1$H NMR spectroscopic analysis. Thus, in just two steps a linear triene is converted stereoselectively to a tetracyclic compound.

Scheme 2



The homologous nitroalkene (*E*)-**2** also reacted cleanly with SnCl$_4$ within 2 h at −78 °C. The crystalline nitronate **4** could be isolated in 98% yield as a single stereoisomer. As we had previously established, the intramolecular [4 + 2] cycloaddition reaction is stereospecific with retention of the dienophile configuration.[7] Moreover, on the basis of previous intramolecular [4 + 2] cycloadditions , we expected that the nitronate would possess a trans ring fusion from an exo mode cycloaddition;[7] all these features were subsequently confirmed by $^1$H NMR spectroscopic analysis. The isolation of **4** implied that intramolecular [3 + 2] cycloaddition was considerably slower, presumably due to thermodynamically disfavored formation of a seven-membered ring.[8] Upon surveying a variety of temperatures and solvents, the rate of the intramolecular [3 + 2] cycloaddition was indeed found to be slow. The optimal conditions for converting the nitronate **4** to the nitroso acetal **5** were found to be heating a dilute toluene solution at 100 °C for 3 days, in the presence of NaHCO$_3$ to prevent acidic degradation of the nitronate. The nitroso acetal **5** was isolated in 44% yield with 40% of recovered starting material. The regio- and stereochemical outcome of the intramolecular [3 + 2] cycloaddition is primarily determined by the constraints imposed by the tether. Nitroso acetal **5** was isolated as a single isomer and was shown to possess the fused/bridged tetracyclic structure indicated by NOE and 2D NMR spectroscopy.[9]

Scheme 3



We next examined the reactivity of the C(5)-tethered nitroalkenes in the tandem intra [4 + 2]/intra [3 + 2] cycloaddition (Scheme 3). In this case (as in the intermolecular variant of this process[4c]), we chose to distinguish the two double bonds by employing a vinyl ether as the

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(5) For an early study on the tandem double intramolecular cycloaddition in a fused/fused mode, see: Moon, Y. C. Ph.D. Thesis, University of Illinois, Urbana, 1991.

(6) These nitroalkenes were both prepared in nine steps from cyclohexene. See Supporting Information.

(7) Denmark, S. E.; Moon, Y.-C.; Cramer, C. J.; Dappen, M. S.; Senanayake, C. B. W. *Tetrahedron* **1990**, *46*, 7373.

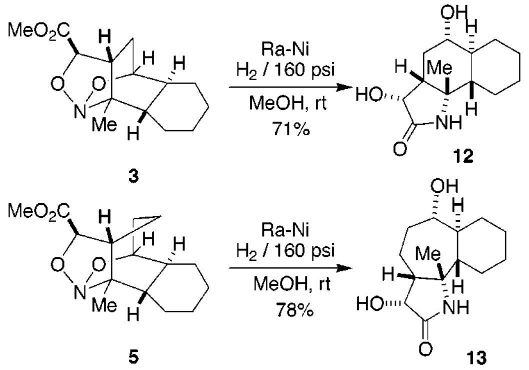
(8) (a) Padwa, A. In *1,3-DipolarCycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, Chapter 12. (b) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1.

dienophile. Thus, addition of $SnCl_4$ (1.1 equiv) to a solution of the nitroalkene **6**[10] at −78 °C resulted in the complete consumption of the starting material after 20 min and the formation of a mixture of nitronate **7** and nitroso acetal **8** in a 3/2 ratio. The intramolecular [3 + 2] cycloaddition was completed by stirring the mixture in toluene at room temperature for 1 h. The nitroso acetal could then be isolated as a single stereoisomer in 87% yield (overall). We were delighted to find that the unactivated vinyl dipolarophile was able to undergo intramolecular [3 + 2] cycloaddition very quickly at room temperature. Clearly, the rate of [3 + 2] cycloaddition is not only dependent on the reactivity of the dipolarophile but also on the ability to easily access reactive conformations in the proximity of the nitronate. The trans decalin structure of the bicyclic nitronate **7** places the allyl group in an axial orientation which is apparently favorable for a 1,3-dipolar cycloaddition.

The second C(5) nitroalkene studied was the higher homologue **9**[10] bearing a two methylene tether between the dienophile and the dipolarophile (Scheme 3). This nitroalkene was chosen to evaluate the effect of tether length and the ability to generate different ring sizes. The synthesis of this nitroalkene provided an inseparable mixture of *E* and *Z* vinyl ethers in a 1/1 ratio. The mixture of nitroalkenes was treated with $SnCl_4$ (1.1 equiv) in toluene at −78 °C to effect intramolecular [4 + 2] cycloaddition. Surprisingly, the nitronate **10** was isolated as a single stereoisomer! On the basis of previous studies,[11] this outcome can be rationalized by invoking an isomerization of either the starting vinyl ether or the product acetal in the presence of $SnCl_4$. Intermediate nitronate **10**, in contrast to **7**, did not undergo the intramolecular [3 + 2] cycloaddition spontaneously at room temperature, but the reaction could be induced by warming **10** in toluene at 100 °C for 2 h to provide nitroso acetal **11** as a single stereoisomer in 79% yield. The marked difference in the rate of intramolecular [3 + 2] cycloaddition between **7** and **10** may be rationalized by the greater entropic cost of achieving suitable alignment that attends the increased length of the dipolarophile tether from one to two methylene units.

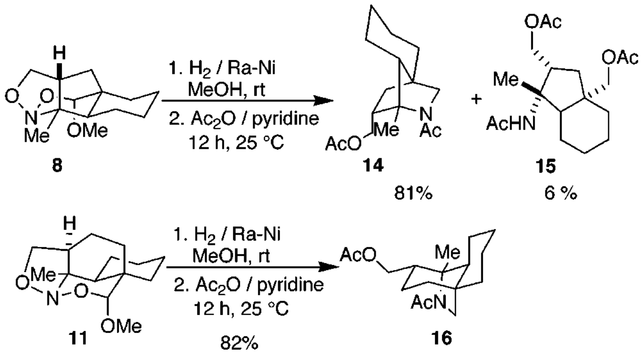
The synthetic utility of the tandem process is revealed by the facile transformation of the nitroso acetal by hydrogenolytic N−O bond cleavage. The conversion of the nitroso acetals **3** and **5** to the respective α-hydroxy lactams was accomplished by using a catalytic amount of Raney nickel in methanol under 160 psi of hydrogen for 12 h to afford **12** and **13** as single isomers in 71 and 78% yields, respectively (Scheme 4). Thus, in just three steps, linear trienes (*E*)-**1** and (*E*)-**2** are converted to functionalized tricyclic compounds bearing six contiguous stereogenic centers.

**Scheme 4**



Similarly, the nitroso acetal **8** was subjected to hydrogenolysis (Raney nickel/MeOH/1 atm/rt) to give a highly polar amino alcohol (Scheme 5). Isolation of the product was facilitated by acetylation after removal of catalyst and methanol to afford the tricyclic amine **14** in 81% yield along with a minor byproduct **15** (6% yield). The byproduct is generated by over-reduction of the aldehyde derived from **8**. On the other hand, nitroso acetal **11** reacted cleanly in methanol at 1 atm of $H_2$ for 12 h at rt to afford, after acetylation, the amido acetate **16** in 82% yield (Scheme 5).

**Scheme 5**



In summary, we have documented the feasibility of a novel class of tandem intra [4 + 2]/intra [3 + 2] cycloaddition called the *fused/bridged* mode. We have shown that both families of nitroalkenes bearing dipolarophiles tethered at C(6) and C(5) are competent. In addition, simple alkenes and vinyl ethers (both *E* and *Z*) can serve as dienophiles whereas vinyl groups and unsaturated esters (attached with different chain lengths) both function well as dipolarophiles. Hydrogenolysis of the nitroso acetal provides functionalized, nitrogen-containing, polycyclic compounds in high yields. Extension of the method to incorporate a stereocontrolling element as well as applications to alkaloid synthesis are in progress.

**Acknowledgment.** We are grateful to the National Institutes of Health (GM30938) for generous financial

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(9) The *Z* isomer of **2** was also investigated (see Supporting Information). Cycloaddition of (*Z*)-**2** proceeded smoothly in the presence of $SnCl_4$ to provide the nitronate in 82% yield. However, reaction of the nitronate bearing a cis dipolarophile in the [3 + 2] cycloaddition was found to be still slower than that of **4**. Heating the nitronate in toluene at 100 °C for 3 days provided the nitroso acetal in 23% yield and 68% of recovered starting material. The effects of dipolarophile geometry on the rate of the intramolecular [3 + 2] cycloaddition of cyclic nitronates has been previously observed. (a) Denmark, S. E.; Senanayake, C. B. W. *Tetrahedron* **1996**, *52*, 11579. (b) Denmark, S. E.; Seierstad, M. J.; Herbert, B. *J. Org. Chem.* **1999**, *64*, 884.

(10) Nitroalkenes **6** and **9** were prepared in 10 and 11 steps, respectively, starting from caprolactone. See Supporting Information.

(11) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1998**, *63*, 6178.

support. L.G. also thanks the Association pour la Recherche sur le Cancer (ARC) for a postdoctoral fellowship.

**Supporting Information Available:** Schemes detailing the preparation of (*E*)-**1**, (*E*)-**2**, (*Z*)-**2**, **6**, and **9**, general and experimental procedures, complete spectroscopic and analytical data for all characterized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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