JOC Article

# Tandem Double Intramolecular [4+2]/[3+2] Cycloadditions of Nitroalkenes. The Fused/Bridged Mode

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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.

## Introduction

The stereoselective construction of highly functionalized, oxygen-substituted, nitrogen-containing heterocyclic compounds is a challenging task with many potential rewards in the fields of medicinal and natural product chemistry. In recent years, the hetero Diels−Alder reaction has emerged as a powerful method for the construction of this class of compounds.[1] This process allows for the rapid and predictable formation of complex ring systems with remarkably high regio-, diastereo-, and enantiocontrol. The utility of this method can be further enhanced if the resulting cycloadduct is poised to undergo a second reaction in tandem. Tandem pericyclic reactions allowing for the simultaneous construction of carbon−carbon and carbon−heteroatom bonds are extremely valuable for the expedient and efficient construction of highly functionalized polycyclic compounds.[2] In these laboratories, the tandem [4+2]/[3+2] cycloaddition of nitroalkenes has been developed as a general approach for the synthesis of a variety of nitrogen-containing heterocycles.[3] In this sequence, the Lewis acid-promoted [4+2] cycloaddition provides nitronates which undergo [3+2] cycloaddition.[4] 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. As for any tandem cycloaddition sequence, there are, in principle, four different permutations that arise from the pairwise combinations of inter- and intramolecularity for each event. Among these, three modes, the inter/inter, intra/inter,[5] and inter/intra[6] tandem [4+2]/[3+2] cycloaddition, have been extensively documented. Each mode is uniquely associated with the formation of a particular class of polycyclic nitroso acetals that can be unmasked by simple hydrogenation to reveal interesting cyclic structures.

A recent communication from these laboratories disclosed the development of a new class of the tandem sequence namely the intra [4+2]/intra [3+2] cycloadditions in which both the dienophile and the dipolarophile are attached to the nitroalkene.[7] The first subclass called the *fused/bridged* mode wherein the dipolarophile is tethered either at the C(6) or C(5) positions of the nitronate has been documented. Because of the complementary electronic demands of the nitroalkene and intermediate nitronate, the presence of two alkenes in the molecule is not a complication and we were able to transform linear trienes into α-hydroxy lactams and tricyclic amines (Scheme 1).

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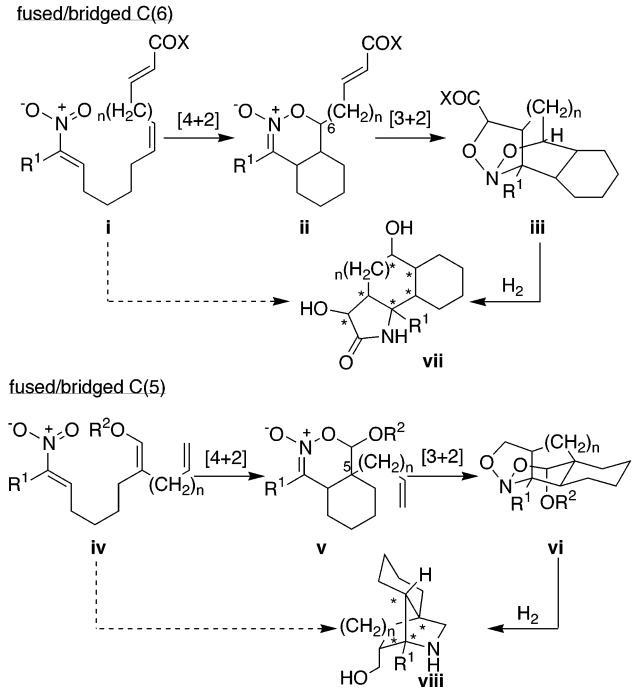
**SCHEME 1**




In this report, we provide a detailed account, in full, of our studies on the scope and limitations of this new family of tandem cycloadditions.[8] This work addresses several topics related to the *fused/bridged* mode tandem [4+2]/[3+2] cycloaddition process, including (1) the preparation of the nitroalkenes bearing tethered dienophiles and dipolarophiles, (2) the feasibility of employing such a triene in tandem cycloaddition reactions, (3) the effect of the tether length as well as the nature and the geometry of the dipolarophile, and (4) the transformation of the nitroso acetal product into α-hydroxy lactams and tricyclic amines.

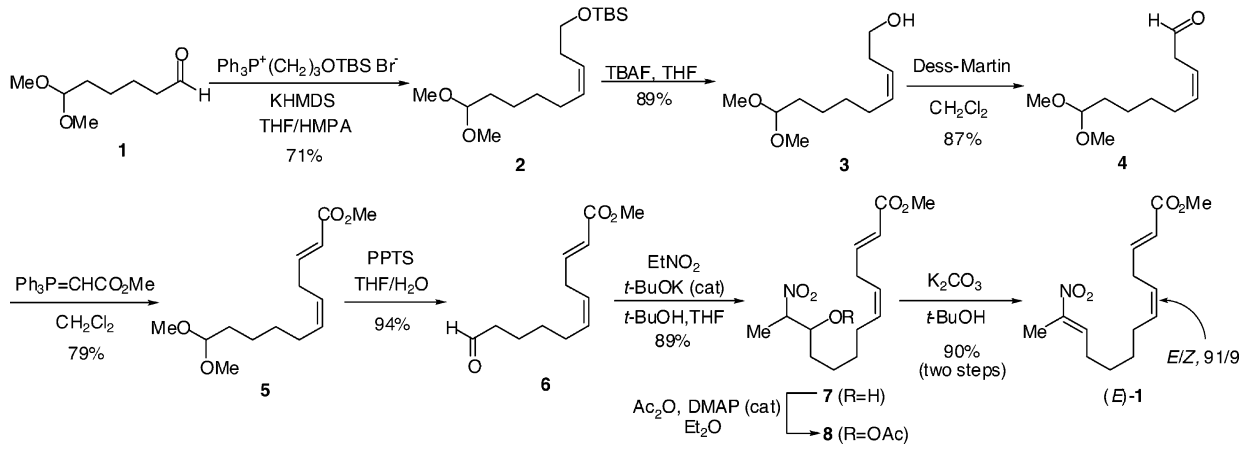
## Results

**Synthesis of Nitroalkenes.** To explore the scope and limitation of the *fused/bridged* mode tandem cycloaddition process we prepared nitroalkenes having different tether lengths between the dienophile and the dipolarophile. Among the different possibilities for dipolarophile attachment, we focused our studies on the subclass wherein the dipolarophile is tethered at the C(6) and C(5) positions. We also examined the influence of the geometry of the dipolarophile. The pronounced reactivity of nitroalkenes as Michael acceptors dictated that formation of the nitroalkene be accomplished at the latest stage of the synthesis.

**C(6) Subclass.** This new variant of tandem double intramolecular [4+2]/[3+2] was first examined with use of a simple disubstituted alkene as the dienophile and α,β-unsaturated esters as the activating group for the dipolarophile in the 1,3-dipolar cycloaddition. All the different nitroalkenes (*E*)-**1**, (*E*)-**2**, (*Z*)-**2**, and (*E*)-**3** were prepared from a common starting material, the monoprotected 1,6-dialdehyde **1**[9] (Scheme 2). The synthesis of nitroalkene (*E*)-**1** began with the formation of the alkene by treatment of aldehyde **1** with (3-*tert*-butyldimethylsilanoxypropyl)triphenylphosphonium bromide in a Wittig reaction. Generation of the ylide with potassium hexamethyldisilazide in a mixture of THF and HMPA yielded the alkene **2** as a 9/1 mixture of *Z*/*E* isomers in 71% yield. Removal of the *tert*-butyldimethylsilyl ether with tetrabutylammonium fluoride (TBAF, 1 M in THF) afforded the primary alcohol **3** in 89% yield.

Oxidation of the homoallylic alcohol was found to be a difficult task due to the sensitivity of the product. Initial attempts with Swern or PCC oxidation conditions were unsuccessful leading to a mixture of α,β- and β,γ-unsaturated aldehydes in poor yield. Ultimately, treatment of the homoallylic alcohol with Dess−Martin periodinane afforded the target aldehyde **4** in 87% yield. Conversion to the dienoate **5** was then accomplished by treatment with (methoxycarbonylmethylene)triphenylphosphorane in 79% yield. Hydrolysis of the dimethoxy acetal was effected by treatment with pyridinium *p*-toluenesulfonate (PPTS) in a THF/$H_2O$ mixture to afford the aldehyde **6** in 94% yield. The final installation of the nitroalkene moiety employed the Henry reaction[10] followed by dehydration. Thus, addition of nitroethane to aldehyde **6** in the presence of a catalytic amount of KO-*t*-Bu led to the formation of nitro alcohol **7** as a 1/1 mixture of syn/anti diastereomers in 89% yield. Dehydration of the mixture of nitro alcohols began by treatment with acetic anhydride in the presence of a catalytic amount of DMAP[11] to afford nitro acetate **8** as a 1/1 mixture of syn/anti diastereoisomers. The standard conditions for the elimination reaction (stoichiometric amount

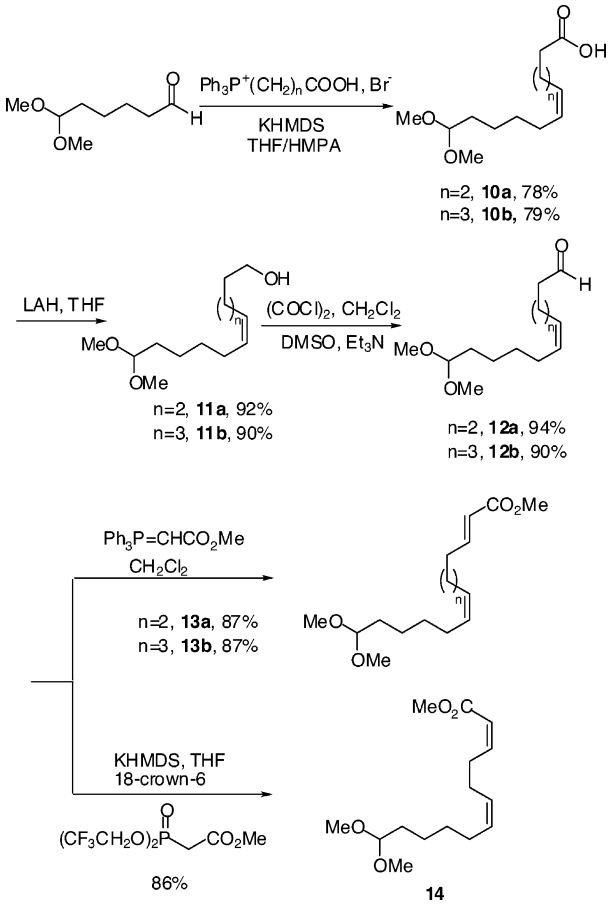
**SCHEME 2**



of DMAP or triethylamine[12]) were unsuccessful due to partial isomerization of the double bond. Simply employing milder conditions, potassium carbonate in *t*-BuOH, cleanly produced nitroalkene (*E*)-**1** in 90% overall yield (Scheme 2). Although the 2,3- and 11,12-double bonds were formed selectively, (*E*)-**1** still constituted a 91/9 mixture of *Z*/*E* isomers at the 5,6-double bond.

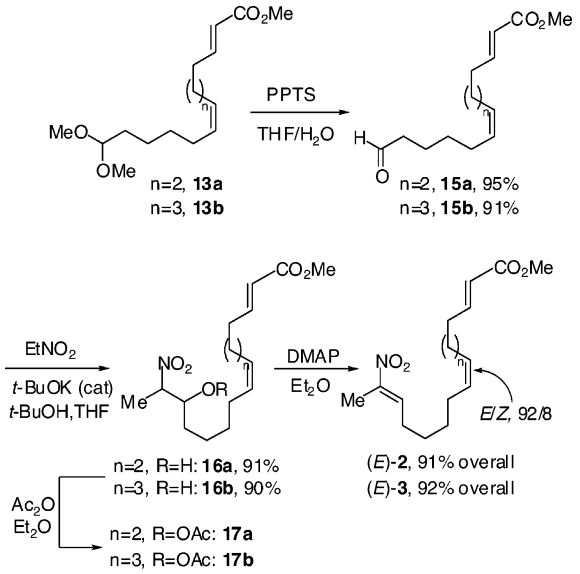
The preparation of the higher homologues (*E*)-**2**, (*Z*)-**2**, and (*E*)-**3** was accomplished in a similar manner. Treatment of the monoprotected dialdehyde **1** with the corresponding ylide (prepared from the phosphonium salt and potassium hexamethyldisilazide) in a mixture THF and HMPA afforded alkenes **10a** and **10b** in 78% and 79% yield as a 9/1 mixture of *Z*/*E* isomers (Scheme 3). The carboxylic acid moiety was then reduced with lithium aluminum hydride in THF. The resulting alcohols **11a** and **11b** were oxidized under Swern conditions to afford the stable aldehydes **12a** and **12b** in good yields. The α,β-unsaturated esters were installed with a Wittig reaction, using (carbomethoxymethylene)triphenylphosphorane to afford both **13a** and **13b** as single isomers. A *Z*-selective Horner−Emmons olefination with bis-(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl)phosphonate afforded **14** as a single isomer at the 2,3-double bond.

**SCHEME 3**

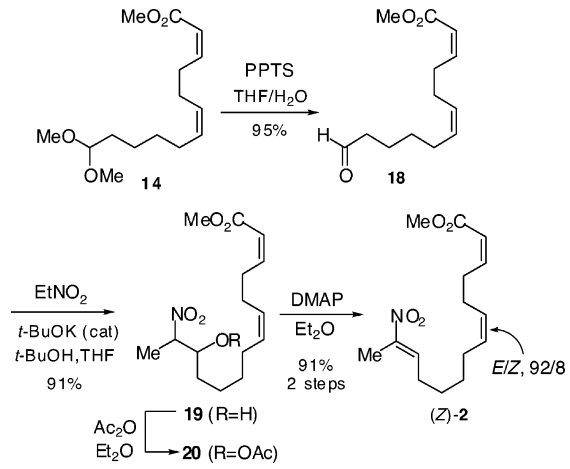



Hydrolysis of the dimethoxy acetal with PPTS generated the aldehydes **15a**, **15b**, and **18** which can be converted into the corresponding nitro alcohols by using the Henry reaction followed by acetylation to afford nitro acetates **17a**, **17b**, and **20**. For these substrates, the use of a stronger base, such as DMAP, did not lead to isomerization of the double bond. Thus, treatment of the nitro acetates with 1.2 equiv of DMAP afforded the target nitroalkenes (*E*)-**2**, (*Z*)-**2**, and (*E*)-**3** (Schemes 4 and 5). All three nitroalkenes constituted 92/8 mixtures of *Z*/*E* isomers at the isolated double bond.

**SCHEME 4**




**SCHEME 5**




**C(5) Subclass.** For the C(5) model, it was deemed prudent to employ a vinyl ether as the dienophile to allow the use of a simple terminal olefin as the dipolarophile for the [3+2] cycloaddition. Elaboration of a β-disubstituted vinyl ether bearing a remote terminal double bond was found to be challenging. The versatile Warren-olefination process appeared to be an attractive solution.

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(9) Schreiber, S. L. *Org. Synth.* **1985**, *64*, 150.

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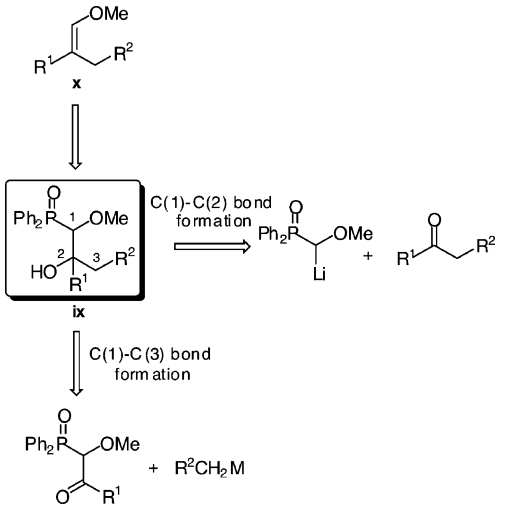
In this plan, an α-methoxy-β-hydroxy phosphine oxide (**ix**, Scheme 6) would be generated by addition of the appropriate lithiophosphine oxide to a ketone, followed by base-promoted syn-elimination to afford the β-disubstituted vinyl ether **x**.[13] The syntheses of the two C(5) nitroalkene precursors (one or two methylenes between the dienophile and the dipolarophile) were quite similar except for the sequence of steps required for the preparation of the key α-methoxy-β-hydroxy phosphine oxide **ix** (Scheme 6). The lithiophosphine oxide is a basic nucleophile such that in reaction with enolizable ketones, deprotonation competes with nucleophilic attack on the carbonyl group. This problem became severe in the case of the β,γ-unsaturated ketone ($n = 1$) wherein a mixture of the desired product along with a 1,3-diene was obtained. For that reason, the alternative approach (C(1)−C(3) bond formation) in which an organometallic agent is added to a β-keto phosphine oxide was employed.

**SCHEME 6**

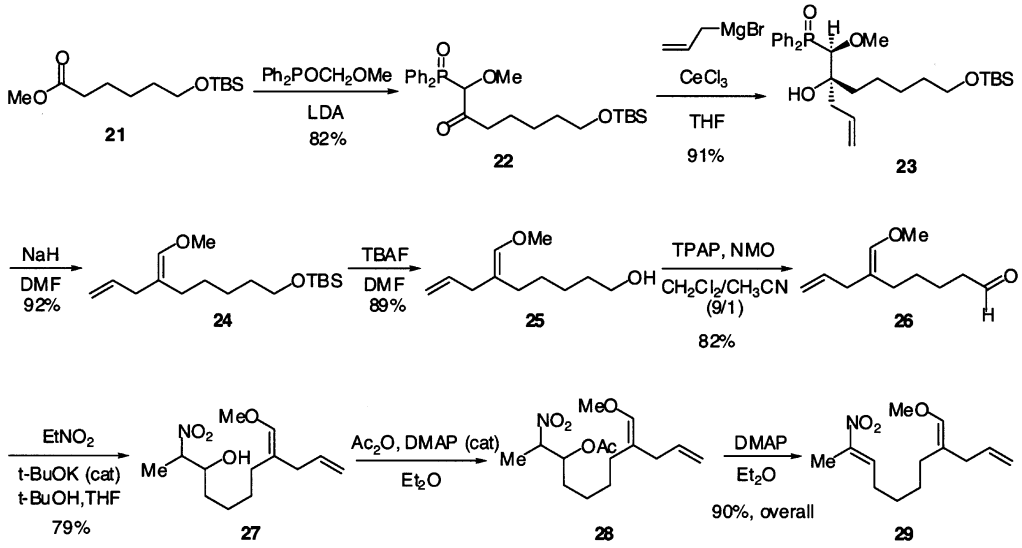



Similarly, this approach can also be thwarted by enolization if the organometallic agent is too basic.

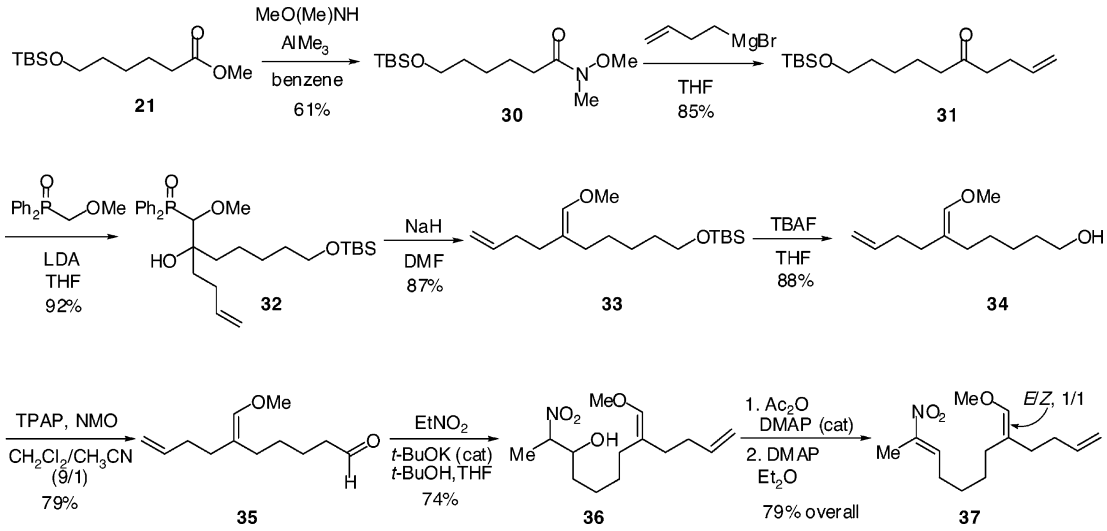
The preparation of the nitroalkene **29** starting from the protected hydroxy hexanoate ester **21** is outlined in Scheme 7. Treatment of **21** with 2.2 equiv of the lithiated diphenylmethoxymethylphosphine oxide afforded the keto phosphine oxide **22** in 82% yield. The use of 1.0 equiv of the anion led to only a 20% conversion with an 80% recovery of starting material. The following step required the introduction of the allylic moiety. Initial attempts with allylmagnesium bromide afforded the desired product in only 36% yield (as a 1/1 mixture of diastereoisomers) along with a 60% of recovery of starting material. The less basic combination of allytributyltin and titanium tetrachloride (at −78 °C) gave similar conversion with the same diastereomeric ratio. Ultimately we found that addition of organocerium(III) reagents[14] (generated by the treatment of allylmagnesium bromide with cerium(III) chloride) to the keto phosphine oxide significantly enhanced the conversion to the target alcohol (54% yield and 46% recovered starting material). A simple aqueous workup followed by two repetitions of this cycle afforded **23** in 91% yield.

An additional benefit that accrued from the use of the cerium reagent was that the diastereomeric ratio improved to 93/7 erythro/threo (presumably from the chelation of the cerium reagent). These results were consistent with those from Luche reduction of similar substrates with $NaBH_4/CeCl_3$.[15] Treatment of the adduct with sodium hydride in DMF at 55°C for 3 h led to the formation of the desired vinyl ether **24** in 92% yield as a 93/7 mixture of *E*/*Z* isomers. Removal of the TBS ether with TBAF in THF afforded the primary alcohol **25** in 89% yield. The next step called for the oxidation of **25** to the aldehyde **26** that will be used later on for the construction of the nitroalkene moiety. However, the 1.4-diene function containing a vinyl ether was found to be very sensitive to acidic and basic conditions. Several oxidation conditions were investigated including Swern, PDC, TEMPO/Oxone, and 1,1-(azodicarbonyl)dipiperidine,[16] as well as catalytic oxidation methods with copper/$O_2$.[17] In all cases only decomposition products were detected. Fortunately, we found that a catalytic amount (5 mol %) of tetrapropylammonium perruthenate (TPAP)[18] and 1.5 equiv of NMO afforded the aldehyde **26** in 82% yield. Reaction of the aldehyde **26** with nitroethane in

**SCHEME 7**



**SCHEME 8**

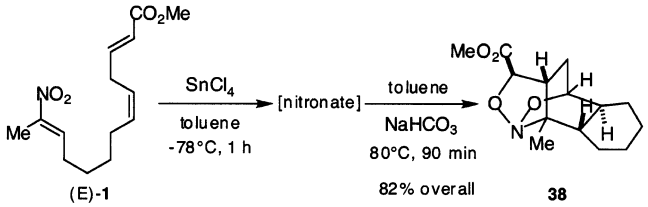



the presence of a catalytic amount of KO-*t*-Bu afforded nitro alcohol **27** as a 1/1 mixture of diastereoisomers. Acetylation with acetic anhydride followed by elimination reaction in the presence of 1.2 equiv of DMAP afforded the desired nitroalkene **29** in 90% overall yield.

Attempts to prepare the higher homologue alcohol **32** through a similar synthetic scheme were found to be unsuccessful. Treatment of the keto phosphine oxide **22** with the homoallylic organocerium(III) reagent afforded complete recovery of the starting material. Modification of the reaction conditions (reaction time, temperature, concentration, and stoichiometry) was unsuccessful. These results show clearly that the basicity of the organometallic species is incompatible with the presence of an acidic proton in the starting material. Therefore, we focused our efforts on a modified route wherein the homoallylic nucleophile is added first followed by addition of the phosphine oxide to the newly formed ketone (Scheme 8). Thus, conversion of the methyl ester **21** to the Weinreb amide[19] **30** was accomplished in 61% yield. Addition of 3-butenylmagnesium bromide to **30** proceeded in excellent yield (85%) to provide the ketone **31**. At this point we were able to add the lithiated phosphine oxide without concern for the isomerization of the double bond. This transformation was performed cleanly to afford the alcohol **32** in 92% yield as a 1/1 mixture of diastereoisomers. Treatment with sodium hydride afforded the methyl vinyl ether **33** in 87% yield as a 1/1 mixture of *E*/*Z* isomers (ultimately found to be inconsequential). Removal of the TBS group followed by oxidation of the primary alcohol with TPAP/NMO afforded the aldehyde **35** in very good yield. Conversion to the nitroalkene was then accomplished as described above to afford **37** as a 1/1 mixture of *E*/*Z* isomers at the vinyl ether double bond without any trace of nitroalkene double bond isomers.

**Tandem Double Intramolecular [4+2]/[3+2] Cycloaddition of Nitroalkenes. C(6) Subclass.** Orienting experiments (based on prior experience)[8] established the ability of an unactivated disubstituted alkene to engage in [4+2] cycloaddition with an α,*β*-substituted nitroalkene with use of tin tetrachloride as the Lewis acid. Thus, treatment of (*E*)-**1** (91% *E* at the disubstituted alkene) with $SnCl_4$ in toluene at −78 °C resulted in the rapid formation of the more polar nitronate product. Interestingly, analysis of the $^1$H NMR spectra of the crude nitronate clearly revealed the presence of approximately 10% of the nitroso acetal **38**. The intramolecular [3+2] cycloaddition was taken to completion by warming the crude mixture in toluene at 80 °C for 90 min (Scheme 9). The nitroso acetal **38** was isolated as a single diastereomer in 82% overall yield after recrystallization. The assignment of stereostructure was made by analogy to nitroso acetal **40**, which was fully analyzed by 2D NMR spectroscopy and nOe studies as described below.

**SCHEME 9**




Nitroalkenes (*E*)-**2** and (*Z*)-**2** were similarly converted to nitronates **39** and **41**, respectively, in 98% and 82% yield (Schemes 10 and 11). However, in contrast to the lower homologue, these nitronates did not undergo the

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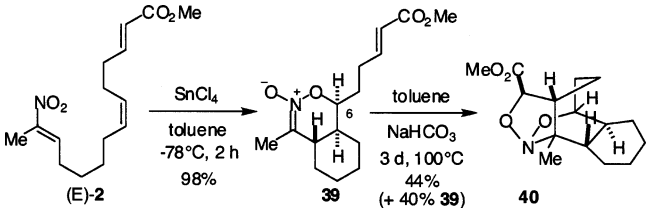
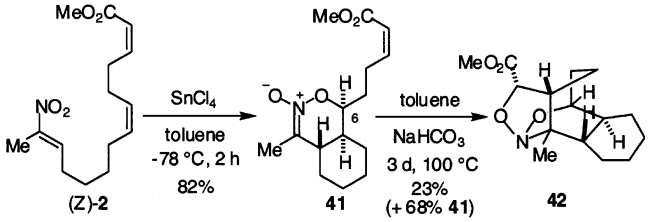
intramolecular [3+2] cycloaddition at room temperature, presumably due to the entropically disfavored formation of the seven-membered ring.

**SCHEME 10**



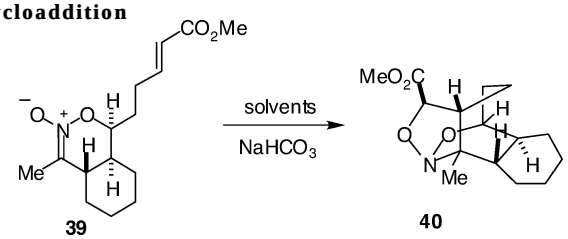

**SCHEME 11**




Results from optimization of the thermal cycloaddition of **39** are collected in Table 1. The influence of temperature on the rate of the [3+2] cycloaddition in apolar solvents was first examined. Heating a toluene solution of nitronate **39** at 80 °C for 5 days led to a 40% conversion to **40**. Raising the temperature to 100 °C was found to improve the conversion (50% after 3 days). However, further increase in the temperature to 120−160 °C afforded no detectable amount of nitroso acetal and only decomposition of the starting material. Variation in the polarity of the solvent brought no significant effect on the rate of the cycloaddition. For example, **39** was recovered unchanged after being heated for 5 days in refluxing THF. Both acetonitrile and propionitrile provided the cycloadduct in 30% conversion after 3 days. Nitromethane and DME were ineffective, whereas chlorobenzene appeared to be slightly better. These investigations demonstrated that the rate of the [3+2] cycloaddition was indeed slow but the reaction was found to be clean because unreacted starting material could be recovered in almost all cases. Finally, all attempts to activate the dipolarophile with Lewis acids such as Sc(OTf)$_3$, TMSOTf, AlMe$_3$, or Cl$_2$Pd(NCMe)$_2$ were unsuccessful and led to decomposition of the nitronate. Under the optimal conditions (heating a dilute toluene solution at 100 °C for 3 days) the pure nitroso acetal **40** could be isolated as a single isomer in 44% yield along with 40% of recovered starting material (Scheme 10).

The stereostructure of **39** was established first by assignment of all proton and carbon resonances by 2D NMR experiments (Table 2). With those assignments in hand, the preservation of the cis relationship in the dienophile was assured by inspection of the HC(6)/HC(7) $^3J_{HH}$, which was found to be 1.0 Hz. Further, the trans ring fusion was established by analysis of the HC(7)/HC(12) $^3J_{HH}$, which was 15.5 Hz. Nitroso acetal **40** was shown to possess the *fused/bridged* tetracyclic structure again by full assignment of all resonances with the aid of 2D NMR spectroscopy. The configurations of the two new stereocenters were established by a combination of

**TABLE 1. Optimization of the Intramolecular [3+2] Cycloaddition**

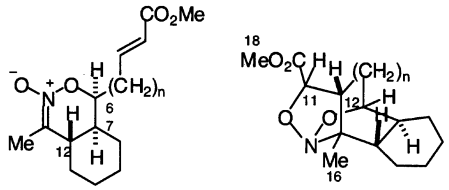



| entry | solvents | *T*, °C | time | **40**, %[b] |
|---|---|---|---|---|
| 1 | toluene | 80 | 5 d | 40 |
| 2 | toluene | 100 | 3 d | 50 |
| 3 | mesitylene | 120−160 | 2 h | decomp |
| 4 | THF | 66 | 5 d | <10[c] |
| 5 | $CH_3CN$ | 80 | 3 d | 30 |
| 6 | $C_2H_5CN$ | 100 | 3 d | 30 |
| 7 | $CH_5NO_2$ | 100 | 3 d | 16 |
| 8 | $C_6H_5Cl$ | 100 | 3 d | 40 |
| 9 | DME | 100 | 2 d | 20 |

[a] All reactions were performed in degassed solvents, using sodium bicarbonate to prevent acidic degradation of the nitronate. [b] The percentage of product was determined by crude $^1$H NMR in comparison of integration with recovered starting material. [c] Small amounts of byproducts were also detected.

$^3J_{HH}$ analysis and nOe experiments. First, the preservation of the trans relationship in the dipolarophile was apparent from inspection of the HC(11)/HC(12) $^3J_{HH}$, which was 5.0 Hz. Moreover, the configuration of the C(12) center on the newly created ring was confirmed by irradiation of HC(12) (2.56 ppm), which led to an enhancement at H3C(16) of 2.15% and at H3C(18) of 2.08%. The stereostructures of other nitronates and nitroso acetals in the C(6) tether series were assigned by comparison of the relevant $^3J_{HH}$, which are collected in Table 2.

**TABLE 2. Coupling Constants (Hz) for Nitronates and Nitroso Acetals**



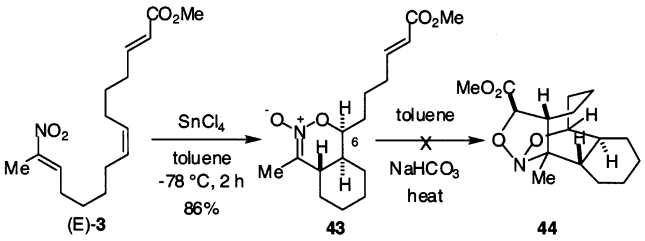

| no. | compd type | *n* | HC(6)/HC(7) | HC(7)/HC(12) | HC(11)/HC(12) |
|---|---|---|---|---|---|
| **39** | nitronate | 1 | 1.0 | 15.5 | |
| **41** | nitronate | 2 | 1.5 | 16.9 | |
| **38** | nitroso acetal | 1 | | | 0.0 (trans) |
| **40** | nitroso acetal | 2 | | | 5.0 (trans) |
| **42** | nitroso acetal | 2 | | | 9.5 (cis) |

Nitronate (*Z*)-**2** bearing a cis dipolarophile was found to react even more slowly. Heating the nitronate in toluene at 100 °C for 3 days provided the nitroso acetal in 23% yield along with 68% of recovered starting material (Scheme 11). The effects of dipolarophile geometry on the rate of the intramolecular [3+2] cycloaddition of cyclic nitronates have been previously noted and will be discussed below.

(19) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.

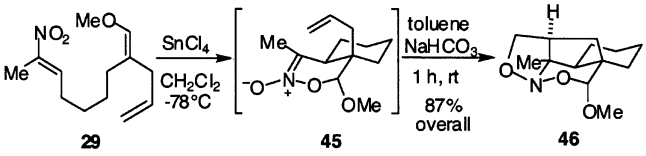
The intramolecular [4+2] cycloaddition of nitroalkene (*E*)-**3** proceeded successfully, as was observed with (*E*)-**2** and (*Z*)-**2**, to afforded nitronate **43** in 86% yield. However, all attempts to induce the intramolecular [3+2] cycloaddition with **43** leading to the formation of an eight-membered ring failed under an assortment of reaction conditions (Scheme 12).

**SCHEME 12**

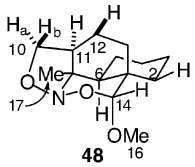



**C(5) Subclass.** The reactivity of the C(5) tethered nitroalkenes in the tandem double intramolecular cycloaddition was next examined. Nitroalkene **29** was expressly designed to differentiate the pendant alkenes for their disparate roles in the two cycloaddition processes. In the event, the [4+2] cycloaddition of **29** (93% *E* at the vinyl ether position) was rapidly promoted by $SnCl_4$ (20 min at −78 °C) to afford a mixture of the expected nitronate **45** along with the nitroso acetal **46** in a 3/2 ratio. The intramolecular [3+2] cycloaddition was taken to completion by stirring the mixture in toluene at room temperature for 1 h. The nitroso acetal **46** could then be isolated as a single isomer in 87% yield overall (Scheme 13). The assignment of the relative configuration of the tetracyclic nitroso acetal **46** was determined by assignment of all proton and carbon NMR resonances and comparison of relevant coupling constants to the higher homologue **48**, which was fully assigned as described below.

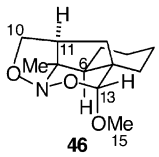
**SCHEME 13**

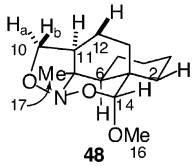



The triene **37** bearing a two-methylene tether at C(5) between the dienophile and the dipolarophile was next evaluated. This substrate, which comprised a 1/1 mixture of *E*/*Z* isomers of the vinyl ether, was treated with $SnCl_4$ in toluene at −78 °C to effect the intramolecular [4+2] cycloaddition. Surprisingly, the nitronate **47** was isolated as a single stereoisomer. On the basis of previous studies in the C(5) bridged mode cycloaddition, this observation has been rationalized by an isomerization of either the vinyl ether or the nitronate and will be discussed in detail below.[3f] Obviously, **47** in contrast to **45** did not undergo the intramolecular [3+2] cycloaddition spontaneously at room temperature but the reaction could be induced by warming a toluene solution of **47** at 100 °C for 2 h to provide nitroso acetal **48** as a single stereoisomer in 79% yield (Scheme 14).




| irradiation at, ppm | enhancement at, % |
|---|---|
| HC(14), 4.25 | HC(16), 6.37; HC(2), 4.04 |
| HC(16), 3.44 | HC(14), 3.02, HC(6), 0.76 |
| $H_aC$(10), 4.33 | $H_bC$(10), 21.78, HC(11), 6.16 HC(17), 2.66 |
| $H_bC$(10), 4.08 | $H_aC$(10), 24.56, HC(12) 5.96 |

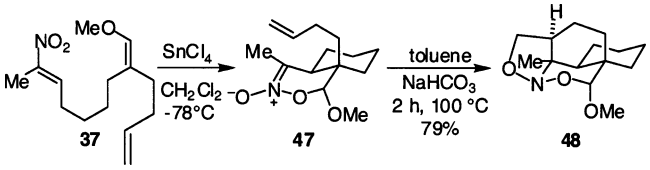



| 46 | 48 |
|---|---|
| 4.40 (dd, *J*=15.5, 5.5, HC(10)) | 4.33 (dd, *J*=11.5, 7.5, $H_aC$(10)) |
| 4.35 (dd, *J*=7.5, 2.5 HC(10)) | 4.25 (s, HC(14)) |
| 4.28 (s, HC(13)) | 4.08 (dd, *J*=7.5, 2.0 $H_bC$(10)) |
| 3.47 (s, HC(15)) | 3.44 (s, HC(16)) |
| 2.53 (tdd, *J*=3.0, 8.0, 11.0 HC(11)) | 2.22 (dd, *J*=12.0, 4.0 HC(6)) |
| 2.44 (dd, *J*=12.5, 5.0 HC(6)) | 2.12 (qd, *J*=1.5, 9.0 HC(11)) |

**FIGURE 1.** Stereochemical assignments for C(5) tether nitroso acetals.

**SCHEME 14**

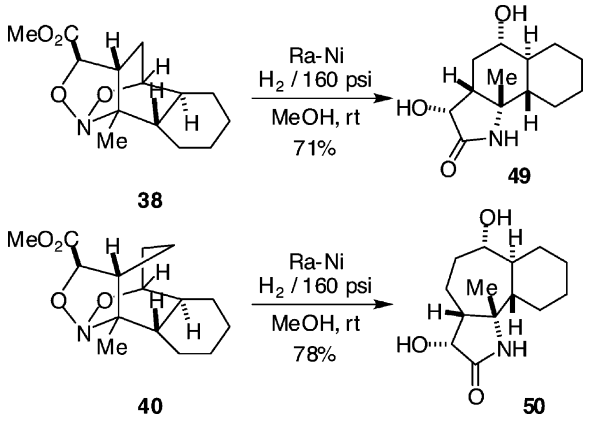



The determination of the stereostructure of the C(5) nitroso acetals began by assigning all the carbon and proton resonances of 2D NMR experiments as summarized in Figure 1. The relative configurations of the key centers at C(6), C(11), and C(14) were established by nOe experiments. Most significant was the observation of an nOe enhancement among HC(10), HC(11), and HC(17), which established the endo fold of the tether. Also, the positive nOe between HC(6) and HC(16) established the cis fusion in the newly created ring. Assignment of the stereostructure of **46** was made on the basis of similar chemical shifts and coupling constants for HC(6), HC(10), the acetal proton HC(13/14), and the methoxy group H3C(15/16).

**Hydrogenolytic Cleavage of Nitroso Acetals: Preparation of α-Hydroxy Lactams.** 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 nitroso acetals **38** and **40** to their respective α-hydroxy lactams was accomplished with a catalytic amount of Raney nickel in

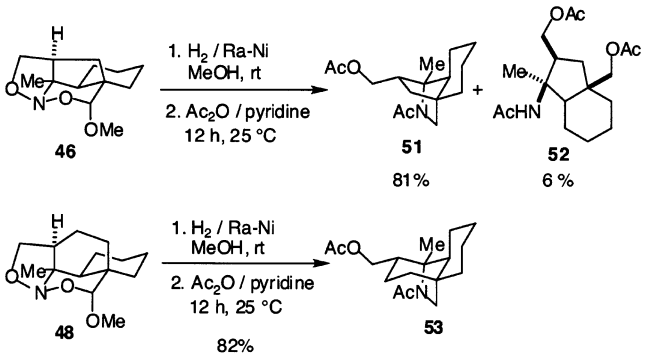
methanol under 160 psi of hydrogen for 12 h to afford **49**and **50** as single isomers in 71% and 78% yields,respectively (Scheme 15).

**SCHEME 15**




**Preparation of Tricyclic Amines.** The nitroso acetal **46** was also subjected to hydrogenolysis, under milder conditions (Raney nickel/MeOH/1 atm $H_2$), to produce a highly polar amino alcohol. To facilitate purification, the amino alcohol was acetylated to provide the tricyclic acetamide **51** in 81% yield along with a minor byproduct **52** (6% yield) (Scheme 16). This byproduct arose from overreduction of the intermediate aldehyde before it collapsed to form the imine (vide infra). Attempts to inhibit the side reaction by using less catalyst failed. On the other hand, the nitroso acetal **48** reacted cleanly in methanol at 1 atm of $H_2$ for 12 h to afford after acetylation the amino acetate **53** in 82% yield.

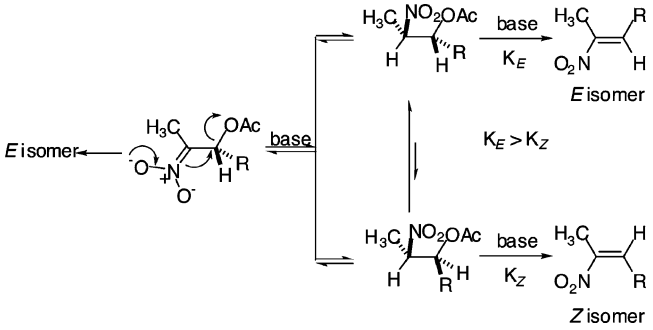
**SCHEME 16**




## Discussion

**Preparation of Nitroalkenes**. Under the conditions of the Henry reaction,[10] an approximately 1/1 mixture of syn and anti nitro alcohols was produced. Acetylation by acetic anhydride and a catalytic amount of 4-*N*,*N*-dimethylamiopyridine (DMAP, 5−10 mol %) followed by dehydroacetylation with DMAP or triethylamine (1.2 equiv) produced *E*-nitroalkenes exclusively (>98%) and in high yield (>90%). If the elimination occurs stereospecifically by an anti-process, since it is an intermolecular reaction, a 1/1 mixture of nitroalkenes will result. The fact that the DMAP−$Ac_2O$ method produced the *E*-nitroalkene exclusively implies that epimerization of intermediates of products must occur at some stage of the reaction. Although a thorough analysis of the mechanism of the elimination is beyond the scope of the present investigation, we have shown that epimerization does not take place during acetylation as the nitro acetates are also formed as a 1/1 mixture. Moreover, previous studies in these laboratories have established that DMAP and other nucleophiles can isomerize nitroalkenes, however, at a rate significantly lower than the rate of elimination.[20] Thus, it would appear most likely that the elimination takes place via either an E1cb mechanism or by an E2 mechanism in which the isomeric nitro acetates can interconvert (Scheme 17).

**SCHEME 17**




**Tandem Intra [4+2]/Intra [3+2] Cycloaddition of Nitroalkenes. Mechanism of [4+2] Cycloaddition.** One of the central mechanistic questions in the Lewis acid-induced [4+2] cycloaddition of nitroalkenes is the timing of the bond formation, i.e., concerted or stepwise? The results described in this report do not allow an unambiguous conclusion. However, in the intramolecular [4+2] cycloaddition of nitroalkenes tethered at the C(6) position, we have shown that the *cis*-alkene (dienophile) reacted with the nitroalkene to afford nitronates with a complete preservation of the dienophile configuration and thus a cis relationship between HC(6) and HC(5). These results are consistent with previous studies from these laboratories and support the conclusion that these reactions are stereochemically coupled but not necessarily concerted.[21] Furthermore, we have also shown that a 1/1 *E*/*Z* mixture of vinyl ethers in the C(5) tethered nitroalkene mode was cleanly converted into its corresponding nitronate as a single isomer. This result is clearly inconsistent with a concerted pathway unless the isomerization were occurring after the cycloaddition. We have previously noted the facile isomerization of C(6) alkoxy nitronates in the presence of tin tetrachloride in intermolecular [4+2] cycloadditions and we presume that the same process is operative in these substrates.[22]

**Stereochemical Course of the Tandem Intra-[4+2]/Intra [3+2] Cycloaddition of Nitroalkenes.** A key stereochemical issue in the intramolecular [4+2] cycloaddition is the configuration at the ring fusion that arises from the relative orientation of the dienophile and the nitroalkene. This feature is, in turn, controlled by the folding of the side chain. The main factors that influence the preference for side chain folding are (1) the

(20) (a) Cramer, C. J. Ph.D. Thesis, University of Illinois, Urbana, IL, 1989. (b) Moon, Y. C. Ph.D. Thesis, University of Illinois, Urbana, IL, 1991

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

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

substitution on and configuration of the nitroalkene and (2) any mechanistically dictated interactions between the termini of the reacting double bonds (Figure 2). Independent of double bond geometry, a trans ring fusion arises from an exo fold (side chain away from diene) whereas a cis ring fusion arises from an endo fold (side chain under diene). Examination of models of the exo transition structure clearly shows steric interactions between the methyl group and the $R^2$ substituent in the dienophile as between the tin complex and the $R^3$ substituent in the dienophile. In the endo mode, the steric interactions that the methyl group experiences are more severe, now including the allylic methylene group on the dienophile and another methylene in the tether. The tin complex in this mode now experiences steric interactions with the $R^1$ substituent on the dienophile.

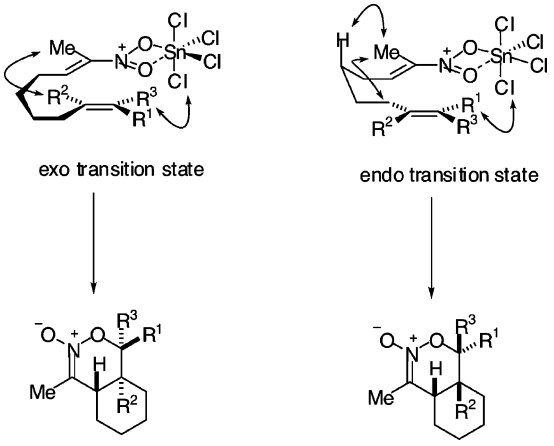
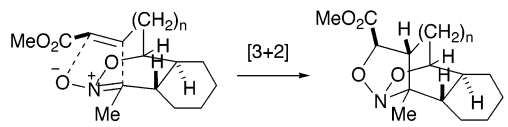



**FIGURE 2.** Steric interactions responsible for the stereoselectivity of the intramolecular [4+2] cycloaddition.

In the C(6)-tethered systems, $R^2$ and $R^3$ are hydrogen, so the exo transition structure is clearly more favorable and this was the exclusive outcome of this mode. The trans relationship was assured by the magnitude of the vicinal coupling constant in the $^1$H NMR spectra of nitronates **39**, **41**, and **43**. This trans selectivity from an exo fold is well-precedented in other intramolecular [4+2] cycloadditions of nitroalkenes with simpler dienophiles.[21] In the C(5)-tethered systems, wherein $R^2$ is a methylene group, the exo mode is also expected to be favored. The formation of a single cycloadduct, assigned as the trans nitronate (or nitroso acetal), was confirmed by nOe studies as the new quaternary center precluded analysis of vicinal coupling constants.

The facial selectivity of the intramolecular [3+2] cycloaddition is controlled by predisposition of the tethered dipolarophile to fold to one side of the nitronate. In the C(6) mode with a one-methylene-unit tether ($n = 1$), the trans ring fusion places the dipolarophile in an axial orientation, which favors the 1,3-dipolar cycloaddition (Scheme 18). In addition, the facial selectivity with respect to the dipolarophile is controlled by the limited degrees of freedom and the constraints imposed by effective overlap with the cyclic nitronate.

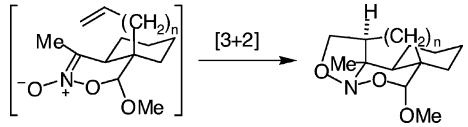
**SCHEME 18**




The nitronate containing a short tether ($n = 1$) was heated at 80 °C for 90 min to afford the corresponding nitroso acetal **38** in 82% yield. However, the nitronate **39** bearing a longer chain ($n = 2$) suffers from a greater entropic cost in reaching the cycloaddition transition state. Additionally, this substrate must overcome the disfavored enthalpy contribution in forming a seven-member ring.[23] Indeed, the intramolecular [3+2] cycloaddition was found to be very slow; the nitroso acetal **40** was isolated in 44% yield after 3 days at 100 °C in toluene. These factors became prohibitively severe in the intramolecular [3+2] cycloaddition in the nitronate **43** bearing a longer tether ($n = 3$). All our attempts to form the eight-membered ring failed. We also noticed a significant effect of dipolarophile geometry on the rate of the intramolecular [3+2] cycloaddition. The nitronate **41** containing a *Z* dipolarophile reacted more slowly than **39**; only a 23% yield of the nitroso acetal **43** was obtained after 3 days at 100 °C. This trend has been observed previously and can be understood in view of the increased steric interactions between the nitronate ring and the methyl ester that must be oriented directly above.[24]

The trans ring fusion that results from the exo [4+2] transition structure in the C(5) systems played a significant role in facilitating the intramolecular [3+2] cycloaddition. An important consequence of the trans fusion is the placement of the dipolarophile in an axial orientation in close proximity to the nitronate dipole (Scheme 19). Much to our delight, the unactivated vinyl group underwent the intramolecular [3+2] cycloaddition readily at room temperature.[24a] Clearly, the rate of intramolecular [3+2] cycloaddition is dependent not only on the reactivity of the dipolarophile but also on the ability to easily access reactive conformation in the proximity of the nitronate. The marked difference in the rates of the intramolecular [3+2] cycloadditions between **45** and **47** may be rationalized again by the greater entropic cost of achieving suitable alignment that attends the increased length of the dipolarophile tether from one to two methylene units.

**SCHEME 19**




**Hydrogenolytic Cleavage of Nitroso Acetals. Preparation of α-Hydroxy Lactams and Tricyclic Amines.** The conversion of nitroso acetals **38** and **40** to their respective α-hydroxy lactams was accomplished by using a suspension of Raney nickel in methanol at 160 psi of hydrogen. After 12 h, their corresponding lactams **49** and **50** were isolated in good yield as single isomers. The deconvolution of these nitroso acetals is relatively straightforward as the products arise directly from the

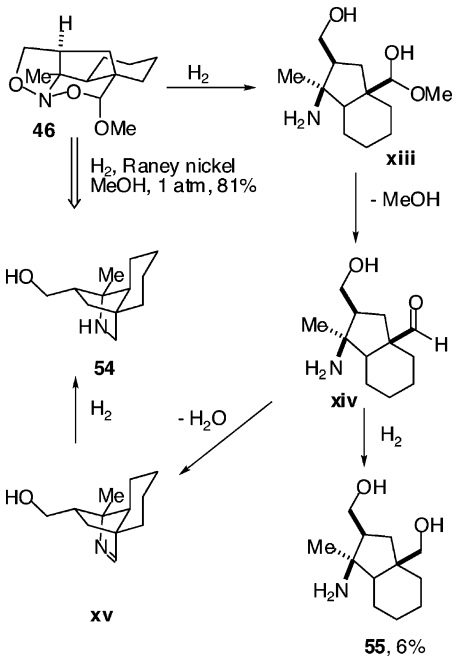
(23) (a) Padwa, A. In *1,3-DipolarCycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, Chapter 12. (b) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1.

(24) (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.

insertion of two molecules of hydrogen followed by the spontaneous lactamization of the generated amino ester. It is noteworthy that the creation of these tricyclic lactams as single stereoisomers bearing six contiguous stereogenic centers in three steps from linear trienes constitutes a remarkable increase in molecular complexity and control.

In a similar manner, nitroso acetals **46** and **48** were treated with a catalytic amount of Raney nickel under only 1 atm of hydrogen to afford the tricyclic amines in good yield. The formation of these amines is believed to proceed through a number of discrete intermediates as postulated in Scheme 20. Hydrogenolytic N−O bond cleavage of **46** should form hemiacetal **xiii**, which upon loss of methanol should afford amino aldehyde **xiv**. This compound can undergo intramolecular imine formation (to **xv**) that, under the reducing atmosphere, would lead to amine **54**. However, the imine formation requires the construction of an azabicyclic [2.2.1] system and may be slow compared to the direct reduction of the aldehyde to produce amino diol **55**. Support for this hypothesis is found in the absence of the related reduction product from hydrogenolysis of **48**. In this case the intramolecular imine formation creates a less strained azabicyclic [3.2.1] system that leads readily to the observed tricyclic amine **53** (after acetylation).

**SCHEME 20**




## Conclusion

The novel class of tandem double intramolecular [4+2]/[3+2] cycloadditions called the *fused/bridged* mode has been documented. Families of nitroalkenes bearing dipolarophiles tethered both at C(6) and at C(5) can participate in this process. In addition, simple alkenes as well as vinyl ethers can serve as dienophiles. The stereochemical course of the intramolecular [4+2] cycloaddition is determined by the folding of the side chain, which minimizes interactions with the nitroalkene moiety. Unsaturated esters and simple vinyl groups function well as dipolarophiles depending upon the location of the tether. The disposition and the geometry of the tethered dipolarophile have significant effects on the rates of the intramolecular [3+2] cycloadditions. Hydrogenolysis of the nitroso acetals provides polycyclic lactams and tricyclic amines in high yields and remarkable stereoselectivities.

Extension of this new class of reactions to other families wherein the attachment of the dipolarophiles extends from other positions along with applications of these reactions in target oriented synthetic endeavors are underway.

**Acknowledgment.** We are grateful to the National Institutes of Health (GM30938) for generous financial support. L.G. also thanks the Association pour la Recherche sur le Cancer (ARC) for a postdoctoral fellowship.

**Supporting Information Available:** Full experimental details for the preparation of all intermediates and products, as well as complete spectroscopic and analytical data for all characterized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034853W