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Tandem double intramolecular [4+2]/[3+2] cycloadditions of nitroalkenes: construction of the pentacyclic core structure of daphnilactone B

Scott E. Denmark *, Ramil Y. Baiazitov, Son T. Nguyen

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

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ABSTRACT

An asymmetric synthesis of the ABCD ring system of daphnilactone B is described. The synthesis features a tandem, double intramolecular, [4+2]/[3+2] cycloaddition of a highly functionalized, enantiomerically enriched nitroalkene to generate a pentacyclic nitroso acetal. The cycloaddition establishes six contiguous stereogenic centers including the critical CD ring junction that bears two quaternary stereogenic centers. Hydrogenolysis of the nitroso acetal followed by amide reduction and cyclization provided the AB rings. The methyl substituent on the A ring was installed in the correct configuration via hydrogenation of an exocyclic olefin in the final step.

1. Introduction

Daphniphyllum alkaloids are a group of highly complex polycyclic alkaloids isolated from trees of the genus *Daphniphyllum* (Daphniphyllaceae).[1] To date, more than 100 of these alkaloids have been isolated, and new members of the family are discovered regularly. Hirata and co-workers first isolated and identified daphniphylline[2] and yuzurimine[3] in 1966 (Fig. 1). Additional members were later isolated, such as methyl homodaphniphyllate,[4] methyl homosecodaphniphyllate,[5] bukittinggine,[6] and daphnilactone B.[7] Daphnilactone B was isolated from the fruits of *Daphniphyllum teijsmanni* Zollinger in Japan in 1972. The structure of this alkaloid has been established by X-ray crystal structure analysis, NMR, MS, and chemical derivatization. The absolute configuration was inferred from correlation to its congeners for which the absolute configurations have been determined by X-ray analysis in the presence of a heavy atom.[8]

Biosynthetic studies of *Daphniphyllum* alkaloids have shown that some of these alkaloids, including daphnilactone B, originate from six mevalonate units via a squalene-like intermediate.[9] A proposal for the biogenesis of the core of these alkaloids has been formulated by Heathcock, and powerfully supported by the total syntheses of many members of this family such as methyl homodaphniphyllate,[10] (−)-secodaphniphylline,[11] bukittinggine,[12] methyl homosecodaphniphyllate,[13] daphnilactone A,[14] and (+)-codaphniphylline.[15]

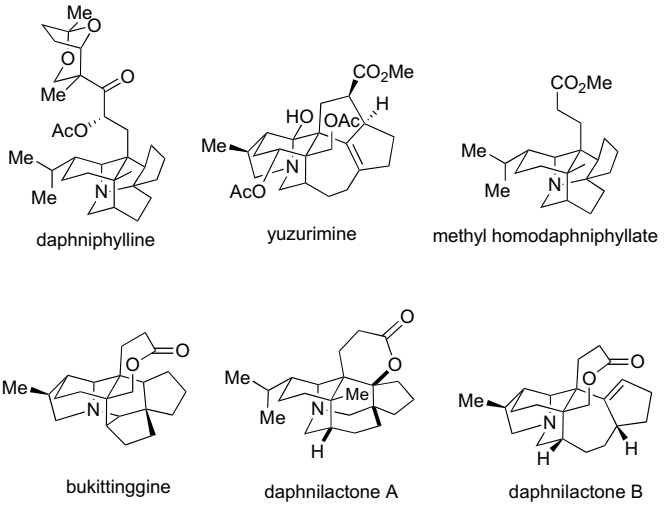

Figure 1. Structures of selected *daphniphyllum* alkaloids.

Although Heathcock's biomimetic analysis and synthesis of this class of natural products are elegant and highly efficient, we believe that it would be interesting to approach these formidable structures via an alternative disconnection.[16] In particular, we felt that a molecule of this complexity represented a suitable challenge to the nitroalkene tandem cycloadditions that has served admirably for the syntheses of simpler alkaloid families.

* Corresponding author. 245 Roger Adams Laboratory, Box 18, Department of Chemistry, University of Illinois, 600 S. Mathews Ave., Urbana, IL 61801, USA. Tel.: +1 217 333 0066; fax: +1 217 333 3984.
E-mail address: sdenmark@illinois.edu (S.E. Denmark).

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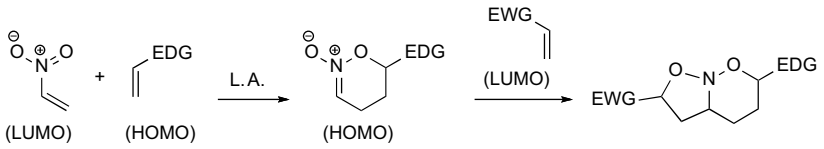


Scheme 1.

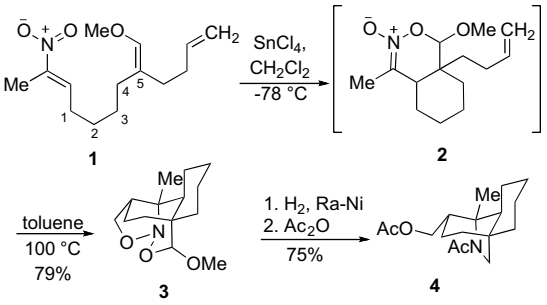
2. Background

Over the years, the synthetic utility of conjugated nitroalkenes for the construction of various azaheterocycles has been extensively investigated.[17] Classically, nitroalkenes behave as versatile 2π-components in Diels–Alder reactions, but when activated by a suitable Lewis acid, they alter their periselectivity and function as 4π-components in inverse electron demand, hetero Diels–Alder reactions. Moreover, the resulting six-membered ring nitronates are electron-rich 1,3-dipoles that can react further in [3+2] cycloadditions (Scheme 1) with an alkene.

The power of the tandem cycloaddition is amplified by different permutations of inter- and intramolecular cycloadditions that can be formulated for the three components (nitroalkene, dienophile, dipolarophile). Among the most versatile is the tandem inter [4+2]/intra [3+2] sequence because of the different points of attachment from which the dipolarophile can be tethered.[18] However, the greatest increase in molecular complexity obtains from the tandem, double intramolecular cycloaddition in which all three components are contained in a single structure.[19] This family is also associated with many permutations that are generated by the different points of attachment of the three reactive alkene moieties. Each permutation leads to structurally distinct products that provide tantalizing opportunities for complex molecule synthesis (Scheme 2).

Although all three possibilities have been explored, the intra/intra (fused/bridge C(5)) was most intriguing in view of the compact polycyclic system that is created in just three steps from a linear molecule! Preliminary proof of principle experiments demonstrated the ease of tandem cycloaddition and hydrogenolytic unmasking, Scheme 3.[19]

Comparison of the tricyclic compound **4** with daphnilactone B reveals gross similarities, e.g., compound **4** bears the correct fusion of the rings corresponding to B, C, and D of the natural product (Fig. 2). This correspondence suggests that a reaction of a substrate



Scheme 3.

similar to **1** may be used as the key step for the total synthesis of daphnilactone B. Obviously, compound **4** lacks rings A, E, and F and any precursor for daphnilactone B would need to be modified to accommodate introduction of those rings. In addition, the ring B in daphnilactone B is a piperidine ring whereas in **4** it is a pyrrolidine. Thus, a retrosynthetic plan (vide infra) for daphnilactone B was formulated to address the following strategic objectives: (1) construction of the piperidine and pyrrolidine rings, (2) stereoselective installation of the vicinal stereogenic quaternary centers, (3) annulation of the hydroazulene portion, (4) selection of appropriate

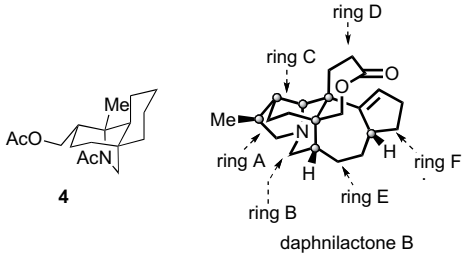
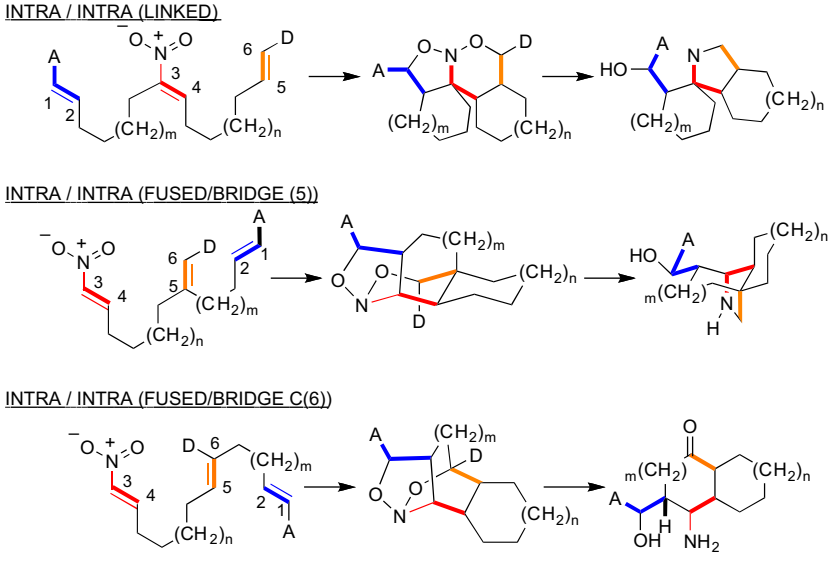


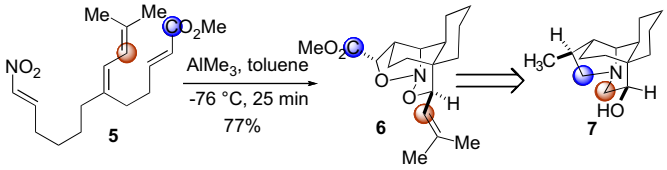
Figure 2.



Scheme 2.

latent functionality for creation of the lactone ring, and (5) selection of appropriate precursors for absolute stereocontrol.

In a preceding report, we disclosed the results of two model studies that introduced a modification to the tandem cycloaddition and subsequent chemical transformations needed to incorporate the pyrrolidine and piperidine rings, A and B, Scheme 4.[22a] From this model study we learned that a conjugated diene such as in **5** could be used as a dienophile for the [4+2] cycloaddition and the adduct could be further elaborated into the piperidine ring (B ring of daphnilactone B). In addition, an unsaturated ester was used as an extended dipolarophile for construction of ring A. The tetracyclic system in **7** resembles the ABCD domain of daphnilactone B, however, it still lacks one of the quaternary centers at the junction of the BD rings.



Scheme 4.

A detailed retrosynthetic analysis of daphnilactone B focused on the selection of groups that accomplish a number of the strategic objectives outlined above. Thus, to simultaneously provide the latent functionality for the hydroazulene portion and the oxygenation needed for the lactone ring, we chose generic functional groups FG_1 and OP such that a number of end-game annulations (e.g., **10**→**9**→**8**) could be accommodated (Scheme 5). The choice of FG_1 and OP was guided by the need to maintain high reactivity of the nitroalkene and also to provide ready synthetic accessibility. To meet the first criterion, the group FG_1 should be electron withdrawing, to provide additional electronic activation for the electron-poor heterodiene.[20] The oxygen-based group OP should facilitate access to the seven-membered lactone (D ring) of daphnilactone B. For these reasons, a lactone linkage was installed between the heterodiene and the dienophile in **18**. In addition, the OP group of the lactone is attached to a stereogenic center that can serve as a stereocontrol element for the [4+2] cycloaddition.

Thus, the next stage in the evolution of the synthetic strategy required the synthesis and evaluation of substrates related to **18**. The synthetic challenge was immediately obvious because very few methods are known for the synthesis of 2,2-disubstituted nitro olefins[21] and none for α-nitromethylene lactones. The reactivity challenge was equally transparent because the tandem cycloaddition must assemble a pentacyclic structure that introduces the two vicinal quaternary stereogenic centers with the correct configuration relative to one another and to the resident center bearing OP.

To probe the feasibility of the [4+2] cycloaddition step of such a highly substituted heterodiene and dienophile in a more readily accessible substrate, the unsaturated ester dipolarophile in **18** was replaced by a methyl ether (**19**). As such, the intramolecular cycloaddition process would stop at a nitronate bearing the two requisite adjacent quaternary stereogenic centers and thus facilitate establishment of relative configuration.

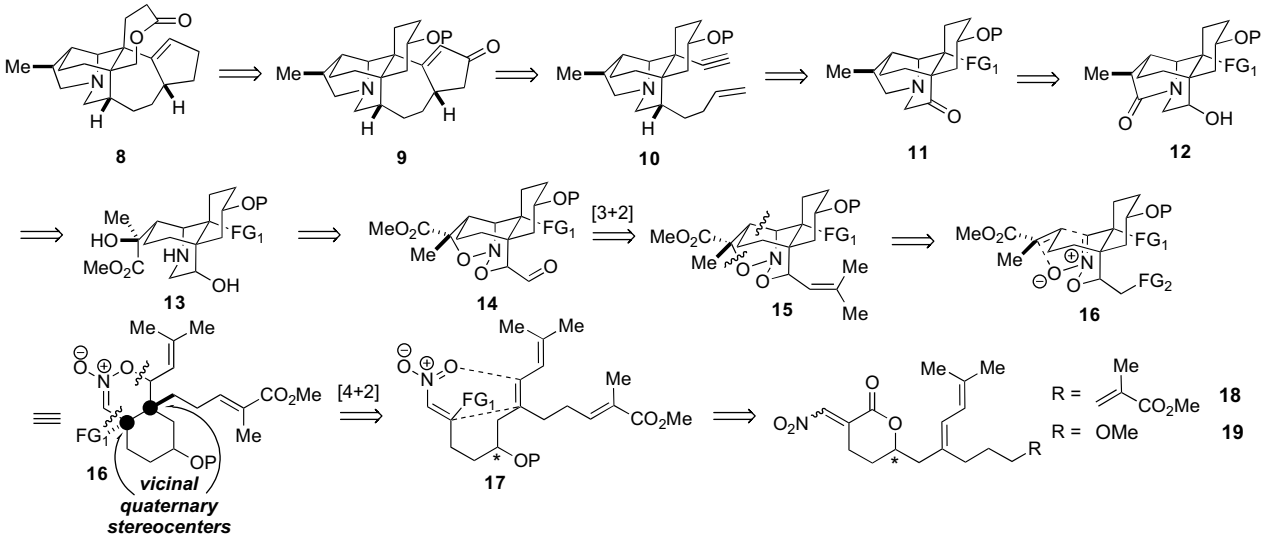
We describe herein a full account of our recent progress in applying the tandem cycloaddition strategy to the synthesis of the pentacyclic core of daphnilactone B. The studies address the challenges of the synthesis and cycloaddition of precursors **18** and **19**, and the post-cycloaddition modifications of the polycyclic products toward advanced intermediates that possess the ABCD ring system of daphnilactone B.[22]

3. Results

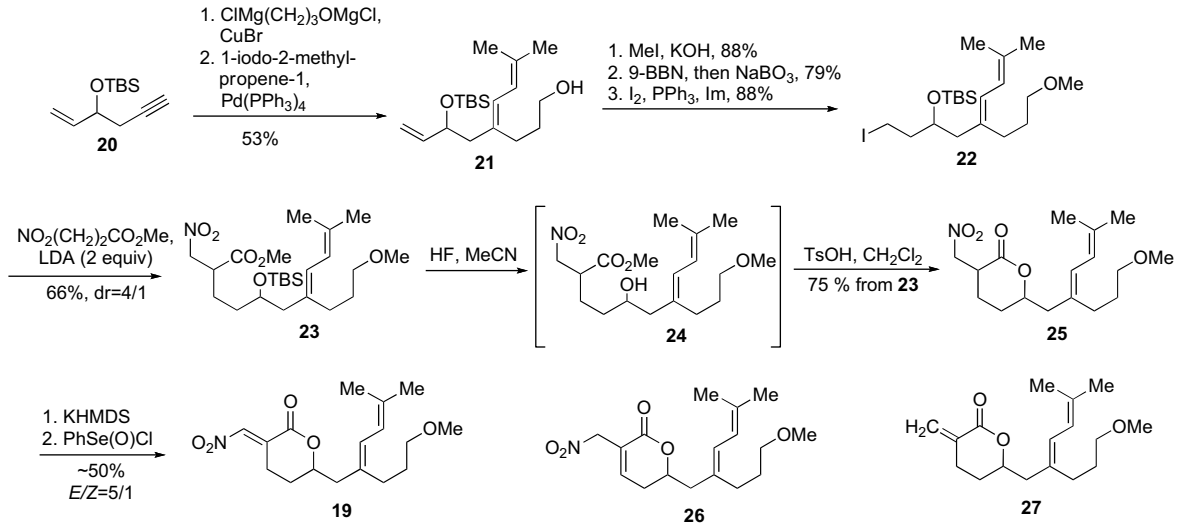
3.1. Synthesis and cycloaddition of racemic nitroalkene 19

The decision to use a nitromethylene lactone as the heterodiene in this nitroalkene tandem cycloaddition was a central feature of the strategic analysis. The major advantages of using this unusual heterodiene were the direct introduction of the requisite functionality in the pentacyclic core and the opportunity for absolute and relative stereocontrol. However, the nitromethylene lactone moiety also created significant synthetic challenges, not the least of which is that these structures are not known! We reasoned that the most sensible construction of this functional group involved the dehydrogenation of a nitromethyl lactone, a structure with some precedent, albeit for esters, not lactones.

The synthesis of nitroalkene (±)-**19** began with carbocupration of alkyne **20**[23] using the chloromagnesium salt of 3-hydroxypropylmagnesium chloride followed by Pd-catalyzed cross-coupling of the resulting alkenylcopper species with 1-iodo-2-methylpropene to provide the (±)-**21** in 53% yield (Scheme 6). The hydroxyl group was



Scheme 5.



Scheme 6.

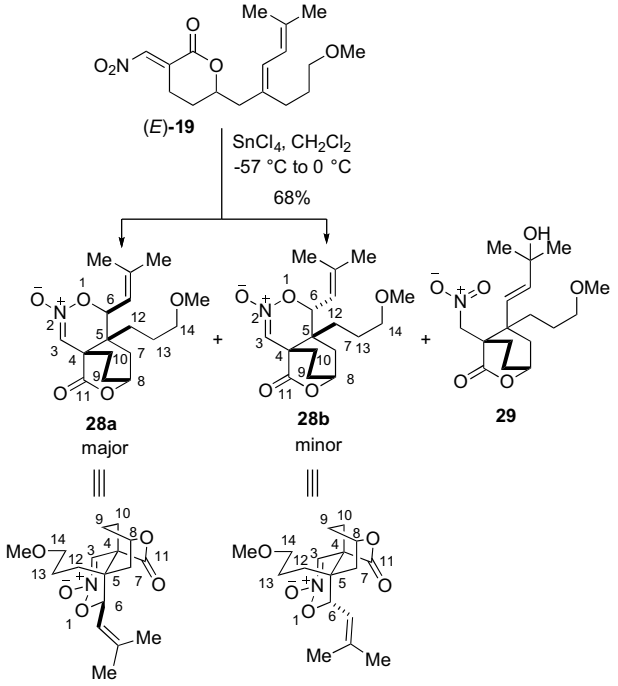
protected as its methyl ether in 88% yield. The terminal double bond in (±)-**21** serves as a masked electrophile (primary iodide), which was revealed through a chemoselective hydroboration with 9-BBN, followed by oxidation with sodium perborate, and then iodination to provide (±)-**22** in 70% overall yield.

Construction of the nitromethyl lactone moiety began by alkylation of the dianion of methyl 3-nitropropionate[24] with (±)-**22**, which provided (±)-**23** in 66% yield (Scheme 6). Removal of the TBS ether with HF was followed by treatment with *p*-toluenesulfonic acid to provide lactone (±)-**24**. Although the lactonization of (±)-**24** was fast, the equilibrium was not favorable and the removal of methanol was required to shift the equilibrium in favor of the lactone (by heating a solution of (±)-**24** to reflux in dichloromethane using a Soxhlet apparatus charged with $CaCl_2$). Because of the base sensitivity of (±)-**25**, the dehydronitration[24] product (±)-**27** was formed in large amounts during chromatographic purification on silica gel. Addition of 1% of acetic acid to the eluent allowed for isolation of the nitro lactone (±)-**25** in 75% yield.

The dehydrogenation of (±)-**25** proved to be a formidable task. Trapping the lithium nitronate (formed with *n*-BuLi or LDA) of (±)-**25** with PhSeBr or PhSeCl[25] led to incomplete reaction (presumably, due to the proton transfer between the nitronate of (±)-**25** and the selenylation product), and a considerable amount of nitro lactone (±)-**25** was recovered. Attempted oxidation (H_2O_2, *m*-CPBA, $NaIO_4$) of the α-(phenylseleno) nitro lactone led only to decomposition, presumably because of side reactions, such as epoxidation of the electron-rich diene.[26] Fortunately, when PhSe(O)Cl[27] was used as the electrophilic reagent, the selenoxide adduct spontaneously eliminated upon workup to provide (±)-**19** (*E*/*Z* ca. 5:1). Nitroalkene (±)-**19** was highly sensitive and could not be isolated in high yield. An analytically pure sample of *E*-**19** was obtained after multiple, sacrificial crystallizations, whereas (*Z*)-**19** could not be isolated in high purity. Furthermore, storage of (±)-(*E*)-**19** at −15 °C for 3 weeks led to migration of the double bond in the product to form the endocyclic allylic nitroalkene (±)-**26**.

We were delighted to find that when nitroalkene (±)-(*E*)-**19** was treated with $SnCl_4$ (4.0 equiv) in dichloromethane at −57 °C, followed by warming to 0 °C, nitronates (±)-**28a** and (±)-**28b** (dr ~1.2:1) were isolated in 68% yield (Scheme 7). The structures of both nitronates were unambiguously established by X-ray crystal structural analyses after separation by preparative HPLC and crystallization from ethyl acetate.

The X-ray crystal structure analysis Fig. 3)[28] revealed that the quaternary stereogenic centers (C(4) and C(5)) in both nitronates have the desired relationship. The only difference is at C(6). In the major isomer, (±)-**28a**, the dienophile geometry was preserved, whereas in the minor isomer, (±)-**28b**, a formal isomerization of the dienophile has taken place at C(6).



Scheme 7.

Additional cycloaddition experiments with (±)-**19** revealed that higher dr could be achieved if reaction was run at lower temperature and to only partial conversion (Table 1, entry 7 vs entry 10). Unfortunately at lower temperatures the side product (±)-**29** was also formed in 7–10% yield.[29] Formation of (±)-**29** could be suppressed by carrying out the reaction at or above −60 °C (entries 1 and 2). A few other Lewis acids were tested but none was as good as $SnCl_4$.

This model study established that the two vicinal quaternary centers could be created from the highly substituted cycloaddition substrate. The next challenge was to introduce the dipolarophile unit and transform the nitroso acetal to the ABCD core system of daphnilactone B.

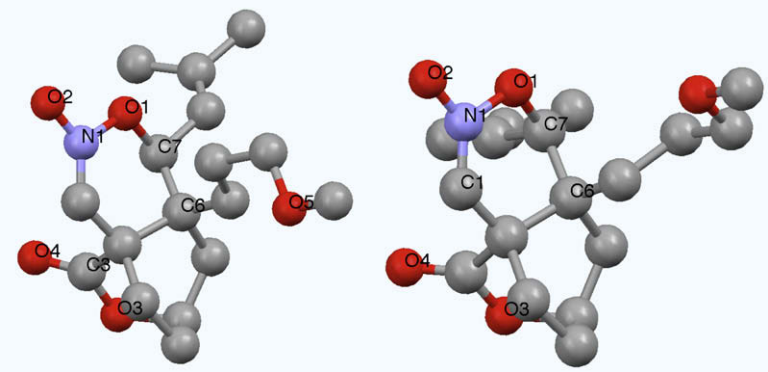


Figure 3. X-ray crystal structures of **28a** and **28b**, hydrogen atoms omitted for clarity.

Table 1
Results of cycloadditions with nitro olefin (±)-(*E*)-**19** and (±)-(*Z*)-**19**

Entry	Catalyst (equiv)	Temp (°C)	Time (h)	Product(s);[a] yield (%)
1	$SnCl_4$ (4)	−57 to 0	1.5	**28a**/**28b**=1.2:1; 68
2	$SnCl_4$ (4)	−65/−55	5.5	**28a**/**28b**=3.5:1; 80[b]
3	$AlMe_3$ (4)	−55 to 0	2.2	Decomposition
4[c]	$AlMe_3$ (4)	−55 to 0	2.2	Decomposition
5[d]	$SnCl_4$ (4)	−62 to −18	1.7	**28a**/**28b**=1:3; 24
6	$Sc(OTf)_3$ (4)	−62 to −18	1.7	No conversion
7	$SnCl_4$ (4)	−68	10 min	**28a**/**28b**=6:1; 15
8	$Ti(O^iPr)_2Cl_2$ (4)	−68 to −15	2.5	No conversion
9	$SnCl_4$ (6)	−70 to −45	2.2	**28a**/**28b**=7:1; 33[e]
10	$SnCl_4$ (4)	−75	4.7	**28a**/**28b**=2.5:1; 58[f]
11	$TiCl_4$ (4)	−75	4.7	**28a**/**28b**/**29**=1:1:2[g]

[a] Isolated yield or by integration of ^{1}H NMR spectra of the crude products.
[b] 80% conversion (from ^{1}H NMR analysis), product was not isolated, no **29** (or trace amount) was formed.
[c] Reaction conducted in toluene.
[d] Impure sample of (*Z*)-**19** was used.
[e] Impure (±)-**19** was used, the yield is for the dehydrogenation/cycloaddition process from **25**, the crude product after the cycloaddition contained ca. 10% of (*E*)-**19** and **29**.
[f] The crude product after the cycloaddition contained ca. 10% of (*E*)-**19** and 7% of **29**.
[g] The same diastereomer as was obtained with $SnCl_4$, **29**, was the major product.

3.2. Synthesis of racemic nitroalkene 18

The basic plan for the synthesis of the more advanced model **18** followed analogous to that for **19**. Two principle differences were (1) the introduction of the unsaturated ester that would serve as the dienophile and also bring the methyl group for ring A and (2) the differential protection of the two hydroxyl groups. Because the enoate would not be compatible with the 3-nitropropanoate dianion, this unit had to be installed after introduction of the nitromethyl group. In view of the base sensitivity of the nitromethyl lactone and nitromethylene lactone, the Wittig olefination step was conducted before lactone ring closure. Moreover, to install the dipolarophile, the hydroxyl groups needed to be differentially protected thus mandating the introduction of a base stable protecting group that can withstand conditions for the removal of the TBS group but that also can be removed in the presence of an acid sensitive diene. The methoxymethyl group was chosen.

The synthetic sequence began with the MOM protection and carbocupration of racemic 1-hexen-5-yn-3-ol (Scheme 8). Hydroboration/oxidation and subsequent iodination afforded the key alkylating agent **34**. To successfully carry out the alkylation of the nitropropanoate dianion with iodide **34**, the temperature had to be carefully controlled between −20 and −10 °C. Whereas the dianion is not a powerful nucleophile, the product is base sensitive, so to balance the reactivity and stability under the strongly basic conditions required optimization. Both diastereomers were produced in almost equal amounts (vs the 4:1 ratio observed with model substrate **22** (Scheme 6)). Carrying the mixture of two isomers through the subsequent steps is inconvenient and complicates characterization; however, they converge in the dehydrogenation step.

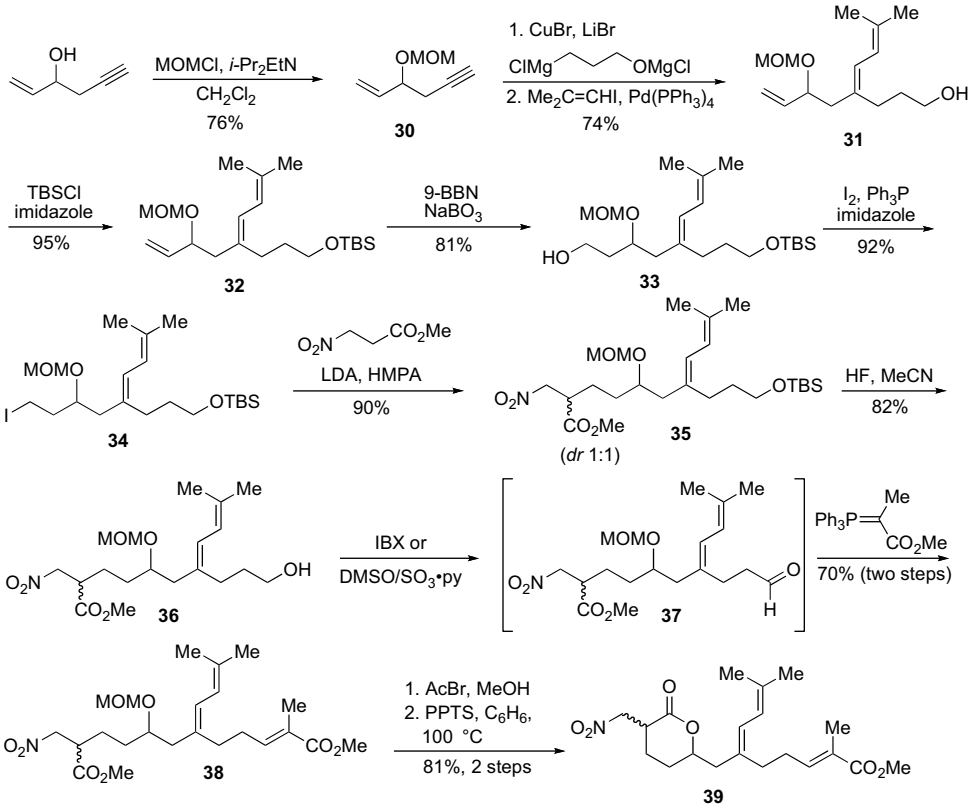
To install the dipolarophile, olefination of aldehyde **37** with the stabilized phosphorane was needed. This step raised concerns because of the base sensitivity of the β-nitro ester. Dehydronitration or Henry reaction under basic conditions could form unwanted side products. Not surprisingly, aldehyde **37** was rather unstable and could not be isolated in high yield. Nevertheless, when **36** was oxidized either with IBX or with DMSO/SO_3·pyridine and then used directly without isolation for the olefination, the unsaturated ester **38** was obtained in 70% yield for the two steps.[30]

The methoxymethyl group had served its function admirably, but now had to be removed to close the nitromethyl lactone. Surprisingly, the MOM group was resistant to mild Brønsted or Lewis acids. Equally surprising (and also gratifying) was the discovery that anhydrous HBr in methanol smoothly removed the MOM group without affecting the conjugated diene. To complete the lactonization, the crude product was treated with PPTS and methanol was trapped in refluxing benzene.

As was the case in the foregoing model study, dehydrogenation of the nitromethyl lactone **39** was problematic. Previously, this simple transformation was accomplished by deprotonation of the nitromethyl lactone with KHMDS followed by trapping the enolate with PhSe(O)Cl and spontaneous elimination to give a modest yield of the nitroalkene. However, despite numerous experiments using these conditions with **39**, the yield of the nitro olefin **18** was unsatisfactory.

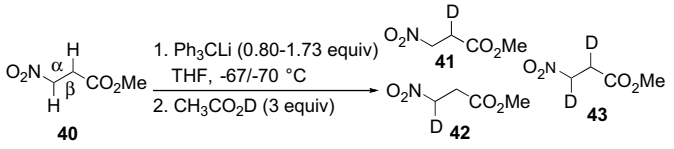
For the dehydrogenation of **39**, selective deprotonation to give the nitronate is necessary. To systematically study this process a simpler substrate, methyl 3-nitropropionate (**40**), was used in a series of deprotonation/deuteration experiments, the results of which are summarized in Table 2. These data indicate that acidity of the C(α)H and C(β)H is close. Even when less than 1 equiv of base was used, considerable amounts of the β-deuterated product(s) were observed. On the other hand, addition of more than 1 equiv of Ph_3CLi did not lead to complete deuterium incorporation at the α-position, entry 3.[31] Similar results were obtained when lactone **44** (Scheme 10) was used as the model substrate.

Because selective monodeprotonation of nitro lactone **44** could not be achieved, the preparation and oxidation of a silyl nitronate was investigated. Interestingly, addition of 2 equiv of Ph_3CLi or LDA to a mixture of **44** and TBSCl (2.2 equiv) at −70 °C, followed by warming to room temperature and concentration, led to quantitative formation of bis-silylated product **45**.[32] When the diene **45** was treated with 1.0 equiv of NBS at −70 °C, followed by addition of aqueous HF, nitroalkene **47** formed cleanly (Scheme 9).[33]



Scheme 8.

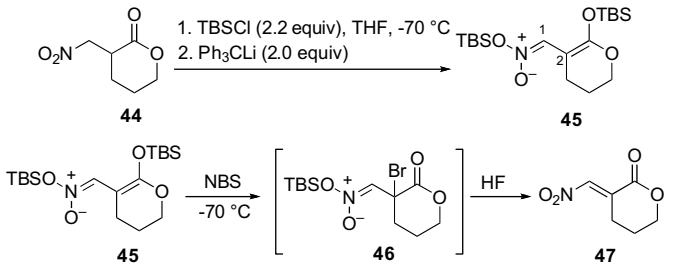
Table 2
Deprotonation/deuteration experiments with **40**[a]



Entry	Ph_3CLi (equiv)	α-Deuteration	β-Deuteration	Total deuteration
1	0.80	0.39	0.27	0.66
2	1.07	0.73	0.26	0.99
3	1.73	0.81	0.65	1.46

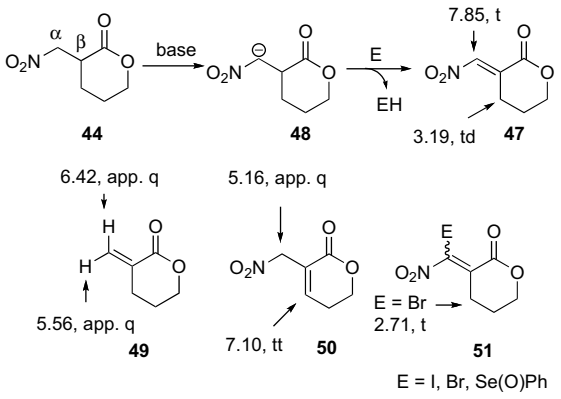
[a] Determined based on ^1H NMR integration values.

Unfortunately, when applying the bis-silylation conditions (and many variations thereof) to the advanced substrate **39**, no identifiable products could be isolated. This failure likely arises from the incompatibility of the unsaturated ester in **39** to strong bases.



Scheme 9.

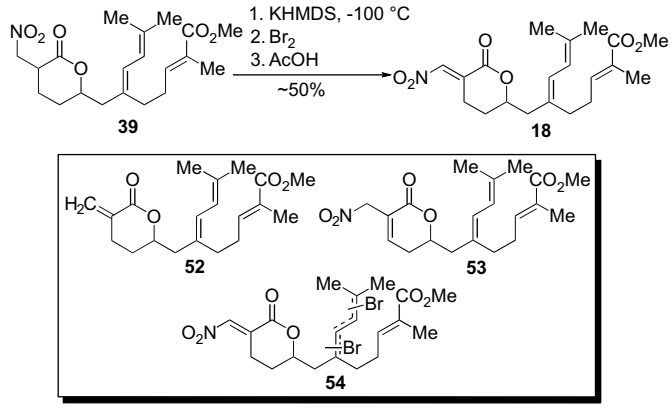
An empirical survey of reaction conditions was carried out using different reagents. The bases included Et_3N, DBU, NaOMe, KO^{t}Bu, potassium 2-methyl-2-butoxide, NaH, KH, LDA, LHMDS, KHMDS; and the electrophiles included PhSe(O)Cl, I_2, IBr, Br_2. Analysis of the reaction mixtures by ^1H NMR spectroscopy showed some desired nitro olefin **47** and unreacted starting material along with the products of dehydronitration (**49**), over oxidation (**51**), and isomerization of the double bond into the more thermodynamically stable endocyclic position (**50**) in variable proportions (Scheme 10). The best conditions identified were to treat **44** with KHMDS (1.1 equiv) in THF at −78 °C, followed by rapid addition of bromine (1.1 equiv). Dehydrobromination of the bromide occurred upon warming to room temperature and concentration. The desired product, (*E*)-**47**, was isolated in 68% yield.



Scheme 10.

When these conditions were applied to **39**, the temperature was lowered to approximately −100 °C to minimize the addition of Br_2 to the diene unit (Scheme 11). During the optimization, it was found that the side product **53** was formed in varying amounts. To suppress the base-catalyzed isomerization leading to **53**, acetic acid (3.0 equiv) was added before the reaction mixture was allowed to warm to room temperature. With these modifications, the desired

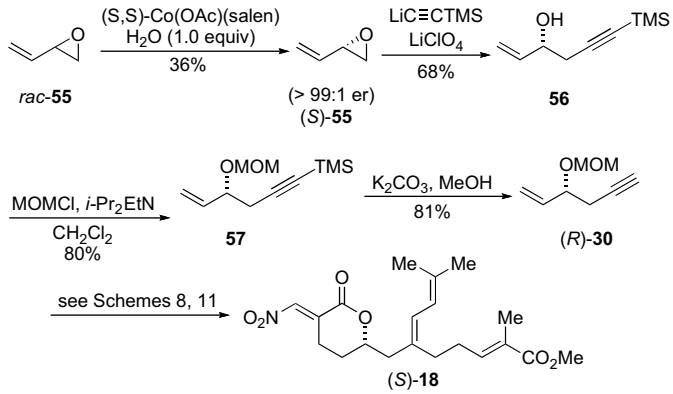
nitro olefin **18** was isolated in moderate yield. To avoid isomerization of **18** on silica gel and upon storage, the crude nitro olefin was used immediately in the next step.



Scheme 11.

3.3. Synthesis and cycloaddition of enantiomerically enriched nitroalkene (*S*)-18[34]

For the synthesis of (*S*)-**18** in enantiomerically enriched form, butadiene monoxide was used as the starting material. The desired *S* enantiomer was obtained in >99:1 er using Jacobsen's hydrolytic kinetic resolution (Scheme 12).[35] In the presence of $LiClO_4$, reaction of (*S*)-**55** with lithium trimethylsilylacetylide gave the desired product **56** in good yield with excellent site selectivity. The alcohol was then protected as a methoxymethyl ether, **57**. The TMS group was removed under basic conditions to deliver the desired, enantiomerically enriched alkyne (+)-**30**. The remainder of the synthetic sequence followed the conditions developed in the racemic route.



Scheme 12.

The conditions for the cycloaddition from the model study (Table 2, entry 1) were applied first to (±)-**18** (used directly from a dehydrogenation reaction) to afford the nitroso acetal **58** in 48% yield over the two steps. However, the product was a mixture of two inseparable diastereomers (dr ~1:1). Because of the different reactivity of the diastereomers in later steps (vide infra), a more selective cycloaddition was desirable. Thus, various Lewis acids were surveyed in search of improved selectivity, but as seen from the results in Table 3 (using (*S*)-**18**), **58** was not formed with these agents.

Variable temperature ^{1}H NMR investigation of the combination of (*S*)-**18** and $SnCl_4$ revealed that the nitroalkene began to react at about −60 °C. Hence, reactions were carried out at this temperature in different solvents. In dichloromethane/toluene (9:1, v/v) the reaction provided a mixture of diastereomers in a ~2.5:1 ratio (Scheme 13). Fortunately, recrystallization of this mixture from methanol-d_4 delivered X-ray quality crystals. X-ray diffraction analysis revealed the presence of two isomers in the crystal enriched in **58b**, the diastereomer that has the isopropylidene group in the axial position at C(6) (**58b**/**58a** ~5:1 in the crystal) (Fig. 4).[36] Comparing ^{1}H NMR spectra of the dissolved crystals and the original mixture of reaction products showed that the major component in the crystal was the minor component of the reaction mixture. Thus, the diastereomeric ratio of 2.5:1 in the product mixture represents **58a**/**58b**. The fact that **58a** is the major product is important because, as was subsequently discovered, only **58a** could be converted to the desired ABCD ring system.

3.4. Elaboration of nitroso acetals 58a/58b

To prepare the advanced nitroso acetals **58a**/**58b** for conversion into the critical pyrrolo-piperidine core, the isopropylidene group had to be cleaved to an aldehyde in preparation for the reductive unmasking. Although this sequence was carried out successfully in the foregoing model series, many attempts to prepare aldehydes **64a**/**64b** from **58a**/**58b** and subsequently lactam **65** were unsuccessful. Two obstacles became apparent: (1) the ozonolysis was very low yielding and (2) the hydrogenolysis of the nitroso acetal in the subsequent step resulted in premature reduction of the aldehyde group in many conditions (solvent, catalyst, pressure) (Scheme 14).

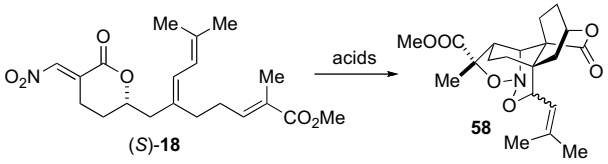
To address these problems, the oxidative cleavage was carried out in basic methanol, which converted the isopropylidenes directly to the corresponding esters **67a**/**67b** (Scheme 15).[37] The two diastereomers were separated by silica gel chromatography and purified by crystallization. The full stereostructure of **67b** was confirmed by single crystal X-ray analysis (Fig. 5).[38]

Because of the differences in the steric environment around the nitroso acetal unit, hydrogenolyses of **67a** and **67b** required separate optimizations (Scheme 15). In this reaction, the nitroso acetal is first reduced to the corresponding amino diol whereupon the amino group reacts further with the proximal methyl ester to form a five-membered lactam (ring A). Meanwhile, the secondary alcohol participates in a translactonization reaction with the boat-like six-membered lactone to form a thermodynamically more favorable five-membered lactone. When **67a** was hydrogenolyzed, the five-membered lactam **68a** was the major isolated product (in 70–80% yield); however, six-membered lactam **69** was also formed, and isolated in 10–20% yield (as the TBS ether). The assignment of the characteristic NMR signals was accomplished from ^{1}H, ^{13}C, and 2D NMR spectra.[39] Because the products of the hydrogenolysis were very polar and difficult to purify, the crude products were converted to the *tert*-butyldimethylsilyl ethers **68a**/**68b**.

To introduce the requisite methyl group in the pyrrolidine ring, dehydration of the tertiary alcohol in **68a**/**68b** was investigated. Attempted activation of the hydroxyl group as a mesylate, triflate, thiocarbamate, or xanthate failed (decomposition or recovered starting material). Moreover, treatment of **68b** with Burgess dehydrating reagent led to decomposition of the starting material. Gratifyingly, reaction of **68b** with Martin's sulfurane cleanly provided the endocyclic olefin **70** (Scheme 16).[40] Although inspections of molecular models and preliminary computational modeling suggested that hydrogenation of **70** could be facially selective, the tetrasubstituted nature of the double bond and the possibility for epimerization of the critical nitrogen-bearing center redirected the plan to closing the A and B rings first. With these rings constructed, the elimination would be forced to create a more readily reducible *exo* methylidene group to avoid the formation of a bridgehead olefin.

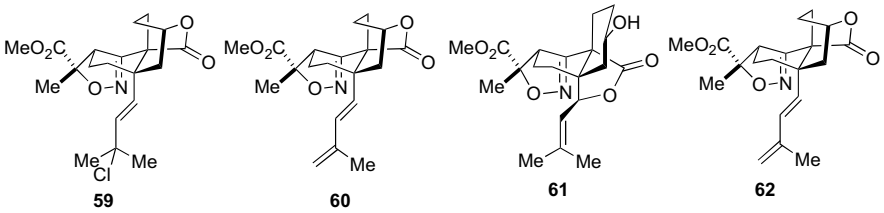
Accordingly, the lactam function in **68a** and **68b** was reduced using BH_3·THF to provide the amine-borane complexes **71a** and **71b** (Scheme 17). Treatment of **71a** with Pd/C in methanol removed the

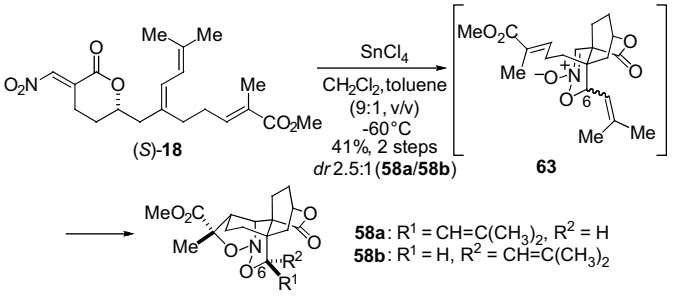
Table 3
Attempted cycloaddition of nitroalkene (*S*)-**18** under different reaction conditions



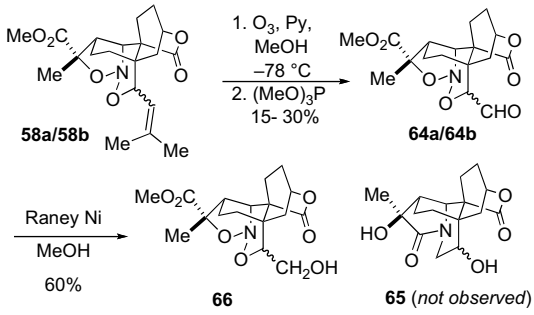
Acids	Solvents	Temperature (°C)	Yield, product(s)
$SnCl_4$[a]	CH_2Cl_2	−35	**48**%, **58**, dr 1:1
$TiCl_3(O^iPr)$	CH_2Cl_2	−78 to −20	Decomposed
$MeSnCl_3$	CH_2Cl_2	−78 to 0	No reaction
$MeAlCl_2$	CH_2Cl_2	−78 to −20	Decomposed
$SbCl_5$	CH_2Cl_2	−78 to −20	Decomposed
BCl_3	CH_2Cl_2	−78 to −30	**60**%, **59** and **60**
$La(OTf)_3$	CH_3CN	rt	No reaction
$Yb(OTf)_3$	CH_3CN	rt	No reaction
$Nd(OTf)_3$	CH_3CN	rt	No reaction
$Zn(OTf)_3$	CH_3CN, CH_2Cl_2	rt	No reaction
$Sc(OTf)_3$	CH_3CN	rt	**44**%, **61** and **62**
TfOH	CH_3CN	rt	Alkene rearrangement
Bu_2BOTf	CH_2Cl_2	−78 to −30	No reaction

[a] Compound (±)-**18** was used.





Scheme 13.



Scheme 14.

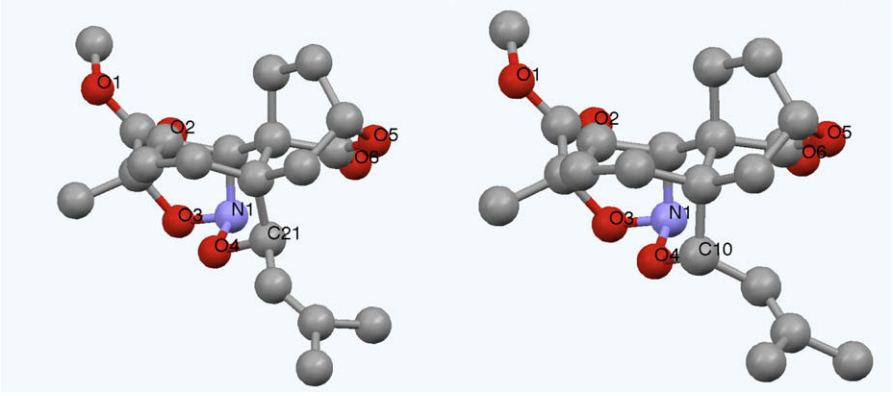
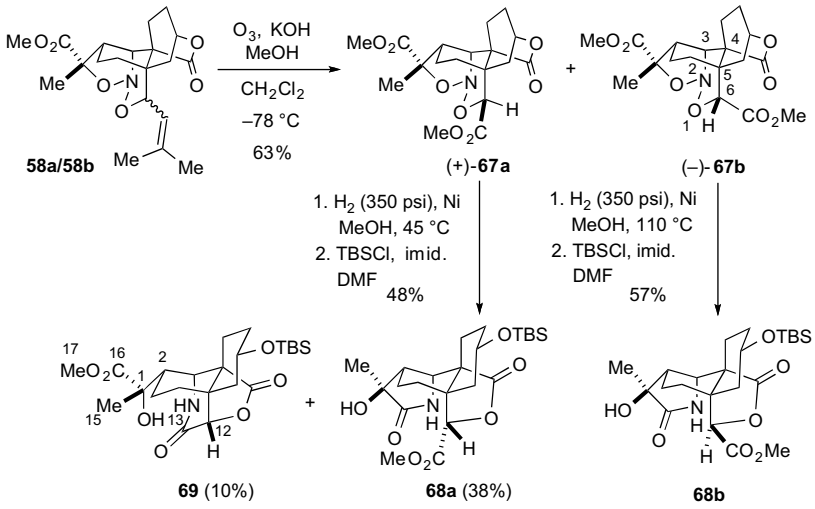


Figure 4. X-ray crystal structures of **58a** and **58b** (hydrogen atoms omitted for clarity).



Scheme 15.

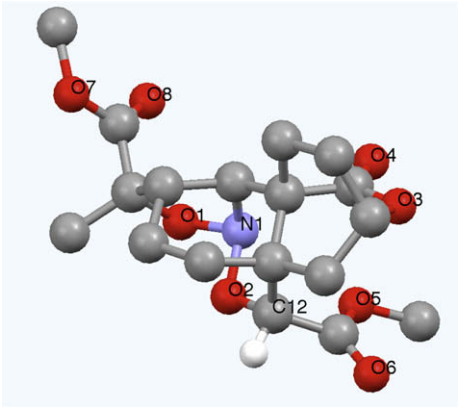
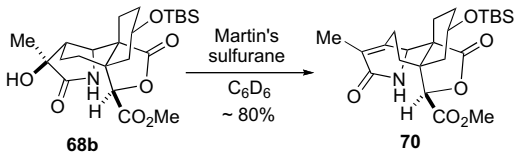


Figure 5. X-ray crystal structure of **67b** (hydrogen atoms omitted for clarity).



Scheme 16.

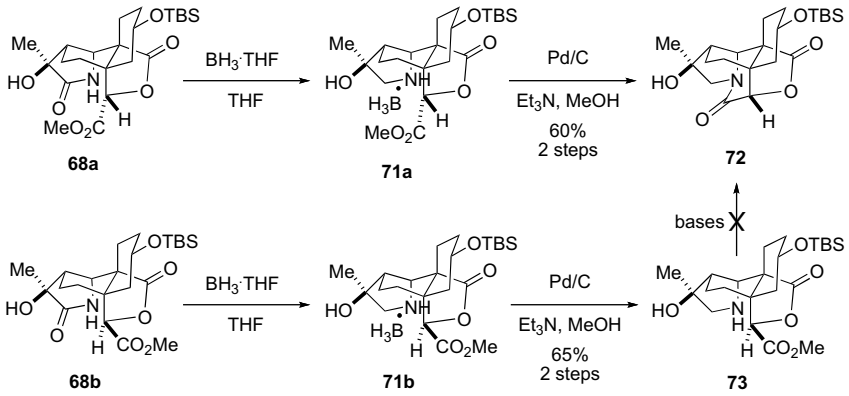
borane to reveal the free amine that underwent subsequent lactamization to provide the desired lactam **72**.[41] Under the same conditions, **68b** was converted to **73**, but this amine could not be converted to **72**, despite many attempts at epimerization/cyclization under basic conditions (e.g., triethylamine, DBU, K_2CO_3, KHMDS).

With the AB ring system in place, dehydration of the alcohol **72** occurred as expected upon treatment with Martin's sulfurane to provide exocyclic olefin **74** in 80% yield (Scheme 18). Hydrogenation of **74** at 1 atm H_2 with Pt/C (5%) provided a quantitative yield of **75** and its epimer **76** in a 9:1 ratio. For the same transformation, Wilkinson's catalyst provided a 4:1 diastereomeric mixture also favoring **75**. The configuration of the methyl bearing stereogenic center in **75** was determined by NOE correlations.

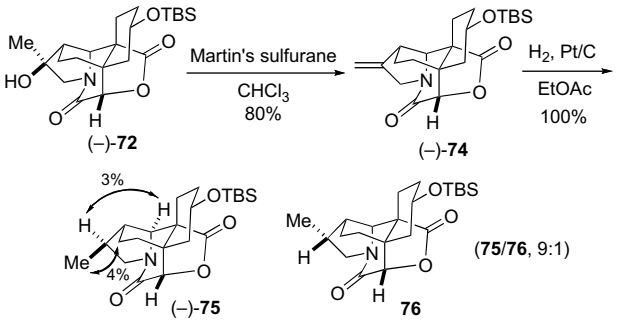
4. Discussion

4.1. Synthesis of the cycloaddition precursors

The syntheses of cycloaddition precursors (±)-**18** and (±)-**19** were accomplished in good overall yields using scalable reactions. Moreover, the route to the enantiomerically enriched precursor (*S*)-**18** could be readily adapted to the existing scheme with minor modification early on. Perhaps not surprisingly, the greatest synthetic challenge was the introduction of the key nitromethylene lactone moiety. Because of the presence of the sensitive diene subunit, the number of different reactions that could be envisioned to create a β-nitro enoate was limited (e.g., electrophilic nitration methods were excluded). Fortunately, the Seebach precedent[24] for the



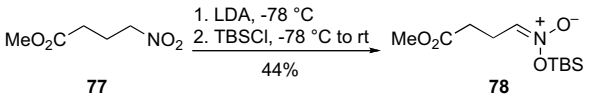
Scheme 17.



Scheme 18.

generation and reaction of 3-nitropropanoate dianions served well to introduce the critical functional groups, but the seemingly simple operation of removing two hydrogen atoms from that unit proved to be the greatest difficulty in the synthesis. The basis of that difficulty resides in the surprising inability to cleanly generate a monoanion.

The results in Table 2 indicate that deprotonation of the methylene group next to the ester in **40** competes with deprotonation of the methylene group next to the nitroalkane. This problem is not seen when the groups are separated by more than two methylenes. Thus, silyl nitronate **78** could be prepared in moderate yield through the monosilylation of 4-nitrobutyrate **77** (Scheme 19). Perhaps when nitro and ester groups are separated by a two-methylene linker such as in **40**, **44**, **25**, and **39** a hybrid functional group is created with unique acidic properties.



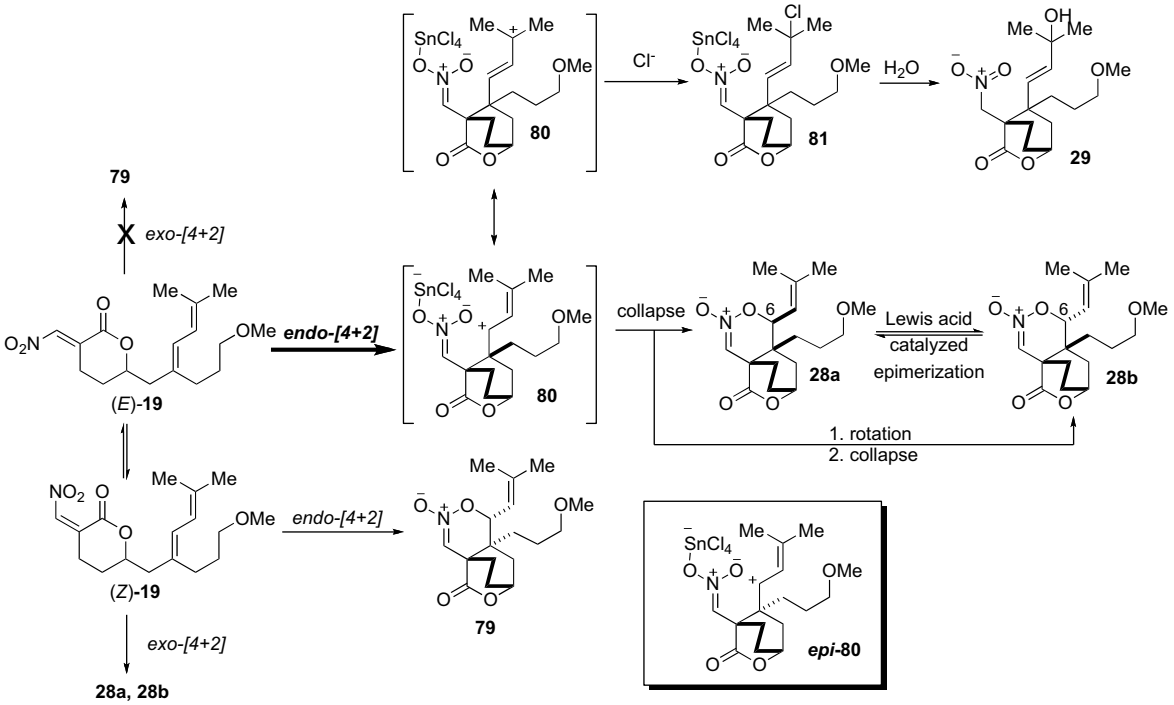
Scheme 19.

On the basis of thermodynamic acidities, the methylene group that is activated by the nitro group should be more acidic than the methylene group that is activated by the carbonyl group (pK_a of nitromethane in DMSO is 17.2,[42] whereas pK_a of ethyl acetate in DMSO is 30.5[43]). However, equilibrium acidities of organic acids do not necessarily correlate with their kinetic acidities. Deprotonations of functional groups that are accommodated by a large change in hybridization and geometry proceed more slowly than deprotonations that involve little rehybridization, according to the '*principle of least nuclear motion*'.[44] Because deprotonation of a nitroalkane involves considerable reorganization of the substrate, nitroalkanes are deprotonated more slowly than their equilibrium acidities would predict. The rates of proton transfer from nitroalkanes have been estimated to be 1000 times slower than those from ketones.[45,46]

Unfortunately, 3-nitropropionates are not stable enough to be deprotonated under the conditions of thermodynamic control such as with weaker bases for longer time or at higher temperature. Obviously, these compounds would suffer dehydronitration under these conditions. In fact, small amounts (5–10%) of the dehydronitration products (such as **27** and **52**) were detected in the product mixtures, even when deprotonation was conducted at temperature as low as −100 °C.

4.2. The [4+2] cycloaddition of 19

From initial analysis of models of the cycloaddition transition structures, it was not certain which configuration of nitro olefin **19** would provide the desired configuration of the cycloadduct **28**. Although the nitro olefin was formed in exclusively the *E* geometry, we could not rule out rapid isomerization in the presence of a Lewis acid to a more reactive *Z* nitroalkene.[47] Cycloaddition of either (*E*)-**19** or (*Z*)-**19** can provide the nitronates **28** (desired) or **79** (undesired) through complimentary orientations of the tether in the transition structures (Scheme 20). From (*Z*)-**19**, an *exo*-(tether)-transition structure would lead to the formation of cycloadduct **28a**, whereas an *endo*-(tether)-transition structure would produce the diastereomer, **79**, which cannot be used for the total synthesis of daphnilactone B. Alternatively, for nitroalkene (*E*)-**19**, cycloaddition through the *endo*-(tether)-transition structure leads to desired nitronate **28a**, whereas *exo*-selective cycloaddition leads to the undesired nitronate **79**. This analysis does not require the



Scheme 20.

cycloadditions to be concerted. The *exo*/*endo* folding of the tether is roughly the same in stepwise reactions, though the proximity of the nitro oxygen and the dienophile methine is not fixed.

Fortunately, both diastereomeric products generated from the cycloaddition, **28a** and **28b**, were formed with the correct relative configuration for the two quaternary stereogenic centers. X-ray crystallographic analysis showed that the two products are epimeric at C(6) of the 1,2-oxazine. The crystallographically determined structure of images of **28a** and **28b** (Fig. 3) clearly shows that the very strained 'all-boat' bicyclic lactone units were formed during the [4+2] cycloaddition. It is remarkable that such strained structures could be formed in high yield through the [4+2] cycloaddition of the highly substituted nitro olefin (*E*)-**19**.

Inspection of the crystal structures also revealed that the bonds between the vicinal quaternary centers (C(4)–C(5), 1.561 Å for **28a**; 1.554 Å for **28b**) are longer than a typical sp^3–sp^3 C–C bond (for example, C(12)–C(13), 1.521 Å for **28a**; 1.528 Å for **28b**; also C(5)–C(12), 1.547 Å for **28a**; 1.548 Å for **28b**). This elongation of the C(4)–C(5) bond is most likely a manifestation of the strain in the ring system.

Isolation of side product **29** suggests that a stepwise mechanism is operative (Scheme 20). From (*E*)-**19** the C–C bond is probably formed first to provide the intermediate zwitterion **80**, which can either collapse to form the nitronate **28a** or be intercepted by chloride from $SnCl_4$ to form the tertiary allylic chloride **81**. Upon aqueous workup, **81** is converted to alcohol **29**. The formation of only one diastereomer of **29** correlates well with the formation of only one set of the adjacent quaternary stereocenters in **28a**/**28b**, suggesting the common intermediacy of **80**. The formation of epimer **28b** can also be accommodated by this mechanism through a rotation around the C–C bond in cationic species **80** before collapse.

Alternatively, **28b** could be derived from isomerization of the allylic nitronate in the presence of a Lewis acid ($SnCl_4$) after the formation of nitronate **28a**. In a control experiment, a 3.6:1 mixture of **28a**/**28b** was exposed to $SnCl_4$ under standard reaction conditions (4.0 equiv of $SnCl_4$, dichloromethane, −40 °C to −8 °C). After workup, the nitronates were isolated in a 2:1 ratio thus supporting the hypothesis that product isomerization causes the formation of **28b**. Additional support for the formation of the two diastereomers through post facto epimerization of the cycloadduct was available from the results of the following experiments: (1) at extended reaction times (entry 10, 4.7 h at −75 °C) the isomers were produced in a 2.5:1 ratio; however, (2) when the nitro olefin (*E*)-**19** was allowed to react for a shorter time (entry 7, 10 min, −70 °C), the **28a**/**28b** ratio was 6:1. The epimerization is more extensive not only with longer reaction time, but also when it is conducted at higher temperature. Thus, when the reaction mixture was allowed to warm (entry 1, −57 °C to 0 °C over 1.5 h), the stereoselectivity of the cycloaddition was lower, dr=1.2:1, than when the temperature was kept low (entry 2, −55 °C and −65 °C for 5.5 h), dr=3.5:1. Thus, we propose that **28a** is the initially formed product, and **28b** is formed upon prolonged exposure to the Lewis acid.

An alternative mechanism may involve the in situ isomerization of (*E*)-**19** into (*Z*)-**19**.[47] The latter could provide **28a** through an *exo*-transition structure. To test this hypothesis, an (impure) sample of nitroalkene (*Z*)-**19** was subjected to the same reaction conditions used for (*E*)-**19**. These experiments provided the same nitronates **28a** and **28b**; however, **28b** was favored (**28b**/**28a**, 3:1). Furthermore, (*Z*)-**19** reacts considerably more slowly than the (*E*)-**19**. Because a different product, **28b**, is formed preferentially when (*Z*)-**19** is used in the cycloaddition, its intermediacy in the cycloaddition of (*E*)-**19** can be ruled out.

The cycloaddition of advanced model substrate (*S*)-**18** is assumed to proceed by an analogous pathway. In this case, however, the nitronate could not be isolated as the [3+2] cycloaddition took place spontaneously on **63**. Nevertheless, X-ray crystallographic analysis of the two cycloadducts **58a**/**58b** unambiguously demonstrated that, here again, the vicinal quaternary stereogenic centers were formed with the desired relative configuration (i.e., via an *endo*-(tether)-transition structure with (*E*)-(*S*)-**18**) and that the products were epimeric at C(6) from a process not unlike that described above.

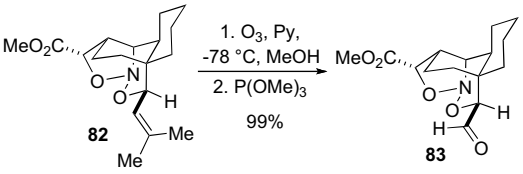
4.3. The [3+2] cycloaddition

An important lesson from the first model study was that late stage introduction of the methyl group in A ring via Wittig or Peterson olefination required too many steps.[22a] Therefore, in the current route, the methyl group was installed in the dipolarophile. This modification made the route significantly shorter. However, increasing the steric encumbrance of the dipolarophile was expected to make the [3+2] cycloaddition more difficult. Indeed, the [3+2] cycloaddition of nitronate **63** was relatively slow (Scheme 13). By ^1H NMR analysis of a cycloaddition reaction mixture after aqueous workup (but before chromatography) a singlet at 6.27 ppm was observed (ca. 0.2H). This signal disappeared upon standing at room temperature for 2 h without producing extraneous signals and was tentatively assigned as the methine hydrogen of **63**. Moreover, an HPLC analysis of the same reaction mixture demonstrated the presence of a UV-active component, which disappears over 2 h at room temperature. This UV-active component may also be the intermediate nitronate **63**.

Overall, the [4+2]/[3+2] sequence is remarkable in terms of generating molecular complexity. *In a single event, four bonds were created to generate four rings and seven stereogenic centers including two quaternary carbons and one pyramidal nitrogen, all with the correct relative configuration with respect to C(5).* Notably, the tandem sequence also created a bond between two atoms that were 12 atoms away in the starting material.

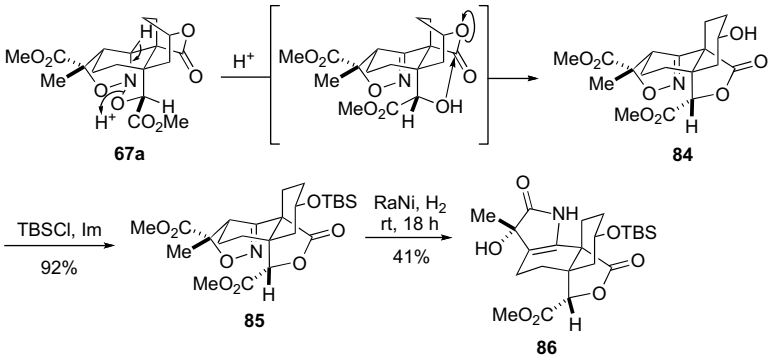
4.4. Oxidative unmasking

The inability to oxidatively degrade **58a**/**58b** to aldehydes **64a**/**64b** in good yield was unexpected and disappointing. In a model study, ozonolysis of a simpler substrate, **82**, provided aldehyde **83** in excellent yield (Scheme 21). Thus, it appeared that the proximity of the strained lactone ring introduced pathways for decomposition of intermediates in the ozonolysis.



Scheme 21.

Sensitive α-alkoxy aldehydes are often produced in poor yield via ozonolysis of allylic ethers with reductive workup. On the other hand, ozonolysis to form the corresponding α-alkoxy esters with oxidative workup under basic conditions is often more reliable.[37] Presumably, in this process the intermediate aldehyde (formed from breakdown of the primary ozonide)[48] reacts in situ with methanol to form the corresponding hemiacetals. These intermediates are further oxidized with excess of ozone via a hydride abstraction, to form the stable methyl ester.[49] Indeed, under these conditions the desired esters **67a**/**67b** were obtained in satisfactory yield. Excess ozone did not decompose the nitroso acetals thus making it a reliable process.

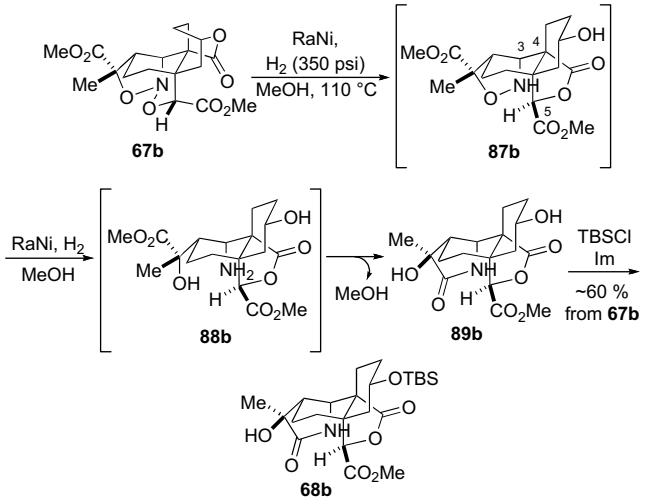


Scheme 22.

4.5. Hydrogenolytic unmasking

Nitroso acetals **67a**/**67b** are sensitive compounds that undergo fragmentation under acidic conditions with the formation of 4,5-dihydroisoxazoles (Scheme 22).[50] Occasionally, trace amounts of acid present in $CDCl_3$ could effect this fragmentation. The Raney-nickel catalyst[51] used for hydrogenolysis of **67a**/**67b** was slightly acidic even after washing sequentially with water and methanol (pH ca. 6), and the acid sensitivity of the nitroso acetal resulted in diminished yield, presumably through formation of **84**. In control experiments, Raney nickel catalyzed hydrogenation of **85** does not lead to saturation of the C=N bond, but rather to the hydrogenolysis of the N–O bond and tautomerization to form **86**.[52] Addition of a small amount of triethylamine to the reaction mixture before hydrogenolysis is important to maintain a mildly basic medium for improved yield and consistent results.

Hydrogenolysis of each epimer **67a**/**67b** using Raney nickel in methanol was slower than hydrogenolysis of nitroso acetals in previous model studies. Upon hydrogenation of nitroso acetal **67b** in methanol with Raney nickel under 1 atm of hydrogen at room temperature, the N–O bond in the oxazine ring was cleaved, and the hydroxyl group engaged in a translactonization to generate isoxazolidine **87b** (Scheme 23), which could be isolated and identified by ^{1}H, ^{13}C, and 2D NMR analysis.[53] Attempts to cleave the N–O bond in **87b** at hydrogen pressure of up to 4000 psi were unsuccessful. However, at higher reaction temperature the hydrogenolysis could be accomplished. Therefore, the hydrogenolysis of **67b** was conducted at 110 °C (oil bath temperature) under 350–400 psi of hydrogen. Under these conditions intermediate **87b** underwent further reduction, and lactam **89b** was isolated in ca. 70% yield. The reaction must proceed through the intermediate amino diester **88b**. Because one of the ester groups in this intermediate is locked in a position away from the amine, the formation of only the five-membered lactam is possible. As a consequence, the pyrrolidine ring (ring A) was constructed in **68b** through hydrogenolysis of **67b**.



Scheme 23.

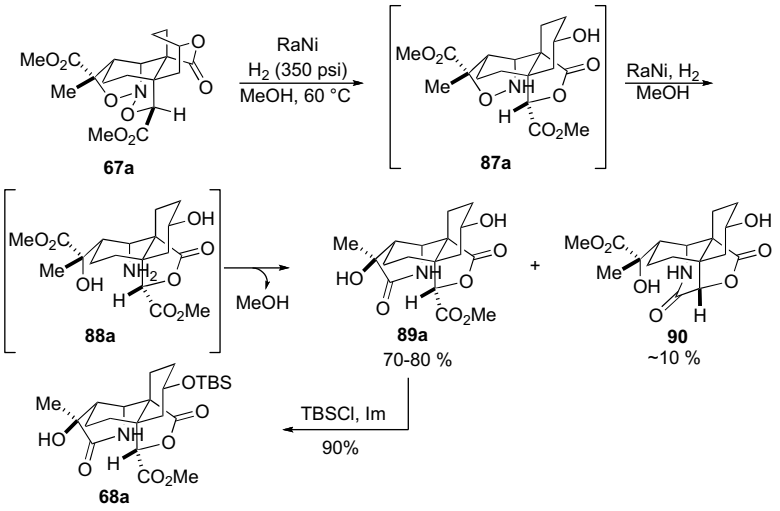
The epimeric nitroso acetal, **67a**, displayed a similar behavior upon hydrogenolysis but two differences compared to **67b** should be noted (Scheme 24). First, hydrogenolysis of **67a** requires less forcing conditions such that on heating to 60 °C (oil bath temperature) under 350 psi of hydrogen, lactam **89a** could be formed in 70–80% yield. Second, amino diester **88a** can form either a γ-lactam (**89a**) or a δ-lactam (**90**) by attack of the amine at the corresponding ester. A lower temperature was required to cleave the N–O in isoxazolidine of **67a**/**87a** (60 °C) compared to **67b**/**87b** (100 °C). In each structure the N–O bonds are quite sterically hindered because of the tetrasubstituted carbons in the vicinity of the bond. In **87a** the carbomethoxy group is pointed toward the N–O bond whereas in **87b** it is pointed away. Although carboalkoxy groups have only weak haptophilicity, it may be sufficient to explain the difference in rates of hydrogenolysis of these two substrates.[54]

4.6. Hydrogenation of (−)-74

The final step in the introduction of the ring A methyl group involved the hydrogenation of an *exo* methylidene group with 9:1 facial selectivity. The high selectivity seen in this reduction was anticipated on the basis of catalytic hydrogenation of previously reported model systems.[22a] The selectivity of the hydrogenation can be rationalized by the preferred approach of the convex face of the ring system to the platinum surface to avoid the steric bulk of the BC rings. The epimers could not be separated by chromatography or crystallization, the assignment of the major diastereomer was secured by 1D NOE analysis.

5. Conclusion

In summary, pentacyclic compound (−)-**75** bearing the ABCD ring fusion of the daphnilactone B has been synthesized in 22 steps, 0.36% overall yield starting from (*S*)-butadiene monoxide. The synthesis features an efficient tandem double intramolecular [4+2]/[3+2] cycloaddition based on the Lewis acid activated nitroalkene platform. The relative stereoinduction was created and relayed throughout the entire molecule from a single stereogenic center of (*S*)-butadiene monoxide. Studies on various endgame strategies for introducing the hydroazulene portion of



Scheme 24.

daphnilactone B and completion of the total synthesis are in progress.

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Supplementary data

Complete experimental details for all compounds reported along with full characterization and ^{1}H NMR spectra for **69** and (−)-**75**/**76** are (62 pages) provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.060.

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29. The structure of **29** was established from ^{1}H NMR, ^{13}C NMR, COSY, HMBC, HMQC, and mass spectrometric analysis, see the Supplementary data for details.
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$H_3C(15)$, C(16) and OH, and between C(16) and $H_3C(17)$ (3.68, s, 3H). MS analysis of **69** (EI, 70 eV) shows signals 452.3 (6.6%, M^+-Me) and 410.2 (100%, M^+-Bu), which is similar to the MS analysis of **67a** (452.2, 2.9%; 410.2, 100%).
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