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Tandem Double-Intramolecular [4+2]/[3+2] Cycloadditions of Nitroalkenes. Studies toward a Total Synthesis of Daphnilactone B: Piperidine Ring Construction

Scott E. Denmark* and Ramil Y. Baiazitov

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

denmark@scs.uiuc.edu

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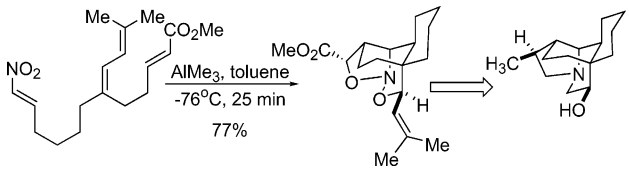
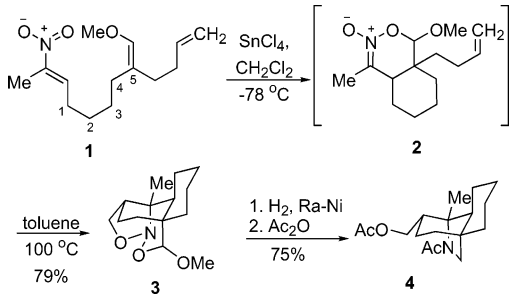


Two model studies in support of a total synthesis of the complex polycyclic alkaloid daphnilactone B have been completed. The objectives of the models studies were to demonstrate the use of a tandem double-intramolecular [4+2]/[3+2] nitroalkene cycloaddition for the stereocontrolled construction of four of the rings in the core of the natural product. The first model study established the ability to create a pyrrolidine ring corresponding to ring A of daphnilactone B through a modification of the dipolarophile and subsequent functional group manipulations. The second model study required the modification of the dienophile in the [4+2] cycloaddition to accommodate the formation of a piperidine ring (ring B of daphnilactone B). Nitroalkene **26** containing a diene as the dienophile served well in the tandem cycloaddition to afford the nitroso acetal **38a** in 77% yield. Subsequent functional group manipulations allowed for the high-yielding conversion to the core of daphnilactone B.

Introduction and Background

1. Tandem Cycloaddition. The tandem [4+2]/[3+2] cycloaddition of nitroalkenes has been extensively studied in these laboratories and has been successfully applied to the syntheses of many alkaloid natural products.[1] Recently, a novel double-intramolecular variant has been developed in which both the dienophile and dipolarophile are tethered to the nitro olefin.[2] Because the cycloadditions require electronically complimentary 2π-partners and different reaction conditions, the double-intramolecular [4+2]/[3+2] cycloaddition reaction can easily operate as a tandem sequence. The example in Scheme 1 illustrates the C(5)/*fused* mode of tethering the reaction components in nitro olefin **1**. The more electron-rich alkene in the vinyl ether first reacts with the electron-poor heterodiene forming nitronate **2**, which is an electron-rich dipole. This dipole then can react with the terminal double bond (tethered through C(5) in the nitro olefin) forming nitroso acetal **3**.[2]

SCHEME 1



The synthetic utility of the tandem nitro olefin cycloaddition is revealed by unmasking the product nitroso acetals through hydrogenolysis or other transformations to afford nitrogen-containing, highly functionalized polycyclic skeletons.[3] The reaction proceeds through cleavage of one or both N−O bonds and, when appropriate, can involve further transformations such as alkylation, reductive amination, or acylation of the nitrogen (Scheme 2).

(1) (a) Denmark, S. E.; Cottell, J. J. In *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley-Interscience: New York, 2002; pp 83−167. (b) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137−166.

(2) (a) Denmark, S. E.; Gomez, L. *J. Org. Chem.* **2003**, *68*, 8015−8024. (b) Denmark, S. E.; Gomez, L. *Org. Lett.* **2001**, *3*, 2907−2910.

(3) Denmark, S. E.; Vaugois, J.; Guagnano, V. *Can. J. Chem.* **2001**, *79*, 1606−1616.

10.1021/jo052001l CCC: $33.50
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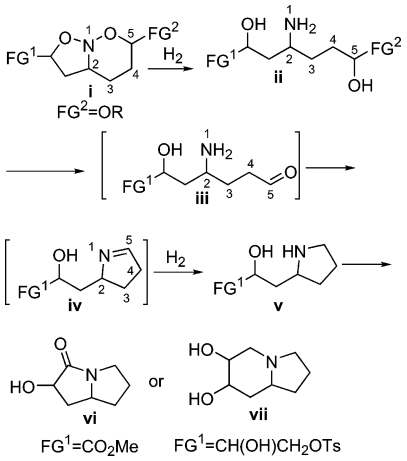
SCHEME 2

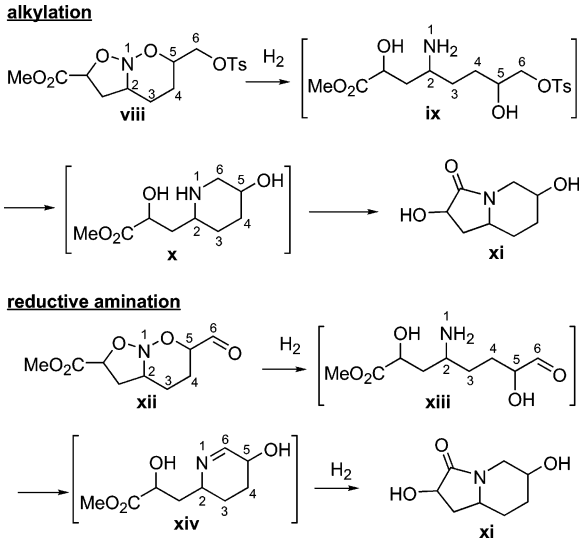


Most applications of the tandem [4+2] cycloaddition have employed an enol ether as the electron-rich dienophile. In this case, the FG^2 fragment on the nitroso acetal **i** is an alkoxy group. Hydrogenolysis of this nitroso acetal produces intermediate hemiacetal **ii**, which can act as a latent aldehyde and can undergo reductive amination to form a pyrrolidine ring. Often, FG^1 is a carboxylic ester which, upon hydrogenolysis, can participate in cyclization to produce lactam **vi**. Alternatively, FG^1 can be an activated hydroxymethyl group.[4,5] In this case, a piperidine ring in indolizidine **vii** can be formed from the isoxazolidine ring in **i**. Even though the hydrogenolysis process is a complex sequence with multiple possibilities for side reactions, it usually proceeds with high selectivity in good to excellent yields.

A consequence of the 1,5-functional disposition in the 1,2-oxazines formed from enol ethers is that hydrogenolysis of enol ether-derived nitroso acetals (such as **i**) creates pyrrolidine rings (such as **v** or **4**). Indeed, the majority of the natural[1] and unnatural[6] products prepared by this sequence contain isolated, fused, or embedded pyrrolidines. However, to construct a piperidine by this process, a nitroso acetal leading to a 1,6-functionality pattern is required. Therefore, the dienophile should contain an additional carbon appropriately functionalized to allow for six-membered ring synthesis. The sequence in Scheme 3 illustrates two proposed routes by which a piperidine ring such as in **xi** can be created from the oxazine fragment in **viii**. In both routes, the formation of the piperidine ring is initiated by the hydrogenolytic cleavage of the nitroso acetal. In the upper sequence, the piperidine is formed by alkylation of the amino group in **ix** by a tosylate. This pathway finds analogy in the formation of the piperidine ring in indolizidine **vii** from the isoxazoline portion of the nitroso acetal **i**, Scheme 2. In the lower sequence, the piperidine is formed by reductive amination of the aldehyde **xiii**. This route resembles the well-developed transformations leading from enol ether-derived nitroso acetals to pyrrolidine rings upon hydrogenolysis (**iii** to **v**, Scheme 2). The difference between these two routes is the oxidation state of the additional carbon atom needed to make the piperidine ring.

Recently, several dienophiles (at both oxidation states) designed to be precursors to piperidine rings were tested in the

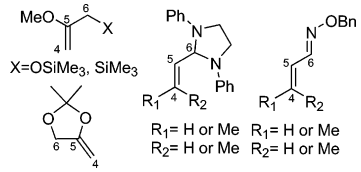
SCHEME 3



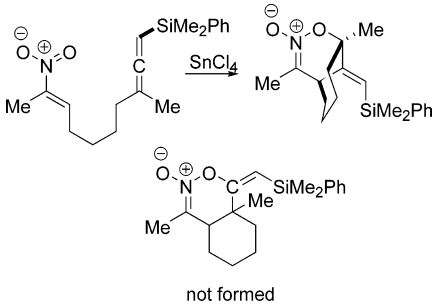
[4+2] cycloaddition with 2-methyl-2-nitrostyrene (Chart 1). These alkenes were either unreactive (under thermal conditions) or unstable upon treatment with a Lewis acid ($SnCl_4$, $TiCl_2$(O-*i*-Pr)$_2$, $AlMe_3$).[7]

Ultimately, it was found that allenylsilanes are viable dienophiles in the cycloaddition (Scheme 4).[8] The [4+2] cycloaddition step was successful; however, the regiochemical course of the reaction was reversed, and the nitroso acetals formed could not be directly used to construct piperidines.

CHART 1



SCHEME 4



2. Plan for the Synthesis of Daphnilactone B Using a Tandem Nitro Olefin Cycloaddition. The *Daphniphyllum* alkaloids are a family of structurally complex polycyclic amines that have been isolated from the fruit and bark of the Yuzuriha tree native to Japan.[9] Since antiquity, extracts of the bark and leaves of Yuzuriha have been used as a folk remedy for asthma. However, the active component remained elusive. The full stereostructures of 34 members of this family have been

(4) Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, *66*, 4276−4284.
(5) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046−3056.
(6) Denmark, S. E.; Montgomery, J. I. *Angew. Chem., Int. Ed.* **2005**, *44*, 3732−3736.
(7) Gomez, L. Postdoctoral Report, University of Illinois, Urbana, 2002.
(8) Denmark, S. E.; Gomez, L. *Heterocycles* **2002**, *58*, 129−136.
(9) Yamamura, S. *Daphniphyllum* Alkaloids. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: Orlando, 1986; pp 265−286.

established by X-ray crystal structure analysis and/or chemical correlation.[10]

One of these components, daphnilactone B (**5**) (Figure 1), was isolated by Hirata in 1972.[11] The relative stereostructure of the molecule was established by X-ray analysis.[12] This member of the class is unusual compared to other *Daphniphyllum* alkaloids because of the two embedded seven-membered rings (D and E). To date, there are no total syntheses or synthetic studies toward daphnilactone B on record nor any reports of its biological activity. The possibility of constructing the core of daphnilactone B by tandem [4+2]/[3+2] cycloaddition and the natural product therefrom made it a very interesting target.

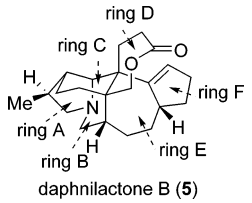
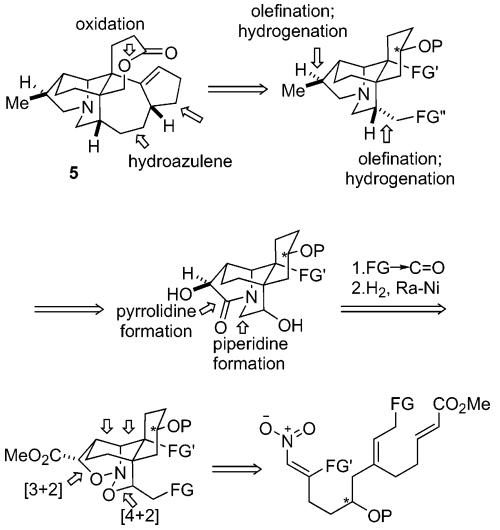


FIGURE 1. Structure of daphnilactone B.

The core of the molecule consists of six cycles (Figure 1): the pyrrolidine and piperidine rings (A and B) that are attached to a cyclohexane ring (C), a seven-membered lactone (D), a cycloheptane ring (E), and a cyclopentene (F). Previously, a structure resembling the core of daphnilactone B was generated using the [4+2]/[3+2] nitroalkene cycloaddition as the key step (**4**, Scheme 1). The structure **4** bears the correct fusion of the rings corresponding to B, C, and D of the natural product. This suggests that a cycloaddition reaction of a substrate 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. Building on the use of a tandem double intramolecular [4+2]/[3+2] cycloaddition as the key strategic transformation, a retrosynthetic plan for daphnilactone B was formulated and is shown in Scheme 5. This plan identifies only the key elements of the strategy and is based on our current knowledge of the tandem process. To accommodate the incorporation of the rings and needed functional groups, several questions need to be addressed: (1) how to create the piperidine and pyrrolidine rings, (2) how to stereoselectively install the vicinal stereogenic quaternary centers, (3) how to construct the hydroazulene portion, (4) how to carry the necessary functionality for creation of the lactone ring, and (5) how to provide a means for absolute stereocontrol. Discussion of how this entire plan will be reduced to practice is beyond the scope of this paper. Our goals were to establish, in two model studies, the modifications to the tandem cycloaddition and the chemical transformations needed to incorporate the pyrrolidine and piperidine rings A and B.

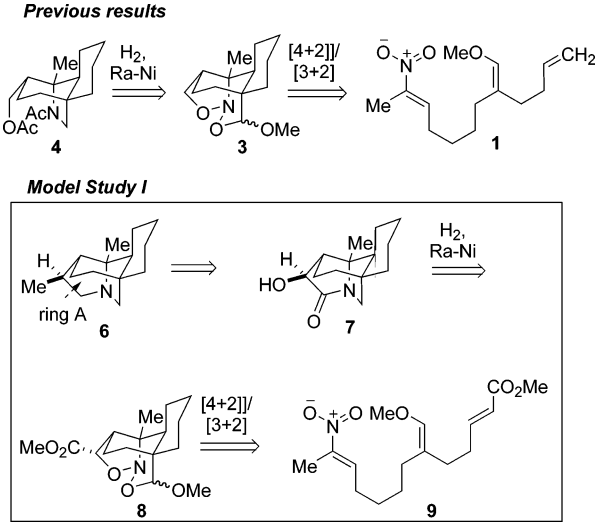
3. Objectives of the Model Studies. 3.1. Model Study I: Building Pyrrolidine Ring A. The first part of this program

SCHEME 5



addressed the task of incorporating the pyrrolidine ring A of daphnilactone B with its attendant methyl group as embodied in the target **6**. The construction of **6** from precursor **9** was envisioned by adapting the approach used in the synthesis of simpler model **4** (Scheme 6). This plan represents only a minor modification of the substrate, and both the [4+2] and [3+2] steps leading to **8** are expected to proceed uneventfully if not more readily than in **1**. The hydrogenolysis step should lead to pyrrolidinone **7** via lactamization following much precedent. However, the chemical modification of the pyrrolidinone to the methyl pyrrolidine will represent most of the new chemical challenges.

SCHEME 6



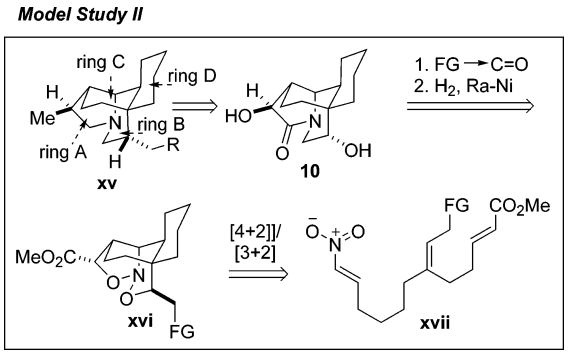
3.2. Model Study II: Building Piperidine Ring B. The goal of the second model study is to build the ABCD-ring system **xv** wherein the greatest challenge will be the construction of the piperidine ring (Scheme 7). The problems to be solved are as follows: (1) finding an appropriate functionalized dienophile to form a piperidine ring, (2) controlling the *exo/endo*-selectivity in folding the nitro olefin in the [4+2] cycloaddition step, and (3) construction of the pyrrolidine ring A along with the stereoselective installation of the methyl group in this advanced structure.

(10) (a) Toda, M.; Niwa, H.; Irikawa, H.; Hirata, Y.; Yamamura, S. *Tetrahedron* **1974**, *30*, 2683−2688. (b) Heathcock, C. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 665−681.

(11) Niwa, H.; Toda, M.; Hirata, Y.; Yamamura, S. *Tetrahedron Lett.* **1972**, *13*, 2697−2700.

(12) Sasaki, K.; Hirata, Y. *Tetrahedron Lett.* **1972**, *13*, 1891−1894.

SCHEME 7

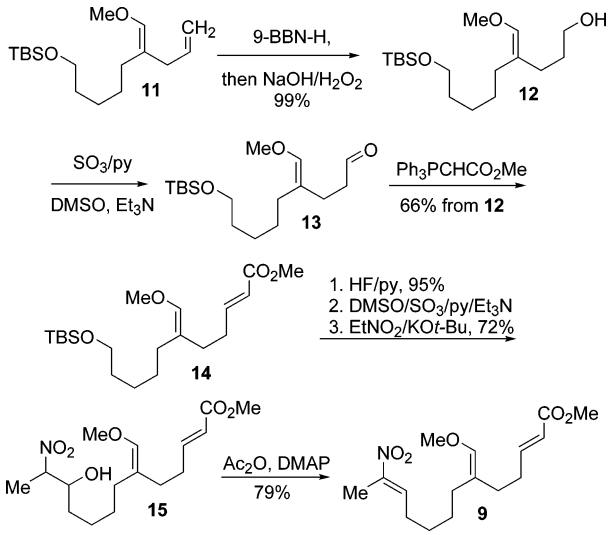


Results

1. Model Study I. Formation of the Pyrrolidine Ring A and Diastereoselective Installation of the Methyl Group. 1.1. Synthesis of Nitro Olefin 9. The preparation of the cycloaddition precursor **9** followed the synthesis route used for nitroalkene **1** (Scheme 8).[2] Diene **11**[2] was converted to alcohol **12** in excellent yield by a hydroboration/oxidation sequence with 9-BBN-H and H_2O_2. Oxidation of **12** using the von Doering protocol[13] afforded the corresponding aldehyde **13**, which was directly subjected to *E*-selective olefination to afford the unsaturated ester **14** in 66% yield for the two steps.

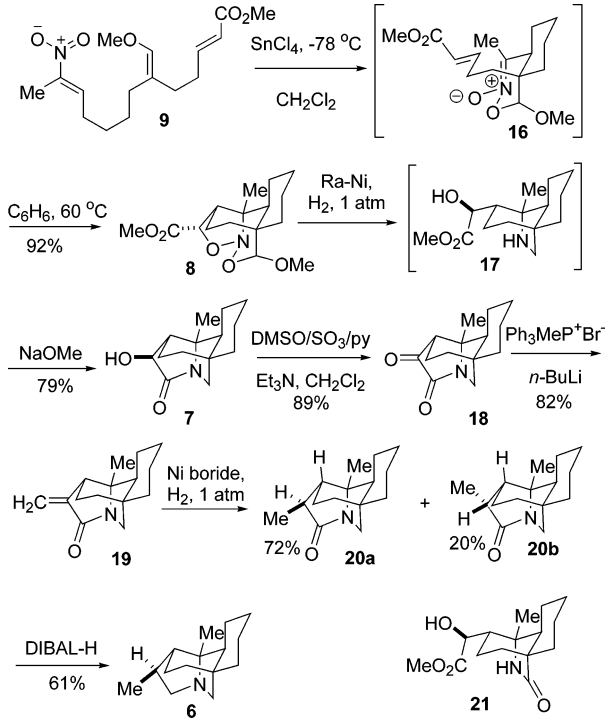
Hydrolysis of the TBS ether in **14** was accomplished by treatment with HF/pyridine in 95% yield. von Doering oxidation[13] to the corresponding aldehyde was followed immediately by Henry reaction with nitroethane to afford the nitro alcohol **15** in 72% yield. Dehydration of **15** with acetic anhydride/DMAP afforded the nitro alkene **9** in 79% yield as a single geometrical isomer. Although the elimination reaction was slow (90 h), it gave better yields than attempts to affect the elimination of the alcohol via a mesylate, tosylate, or trifluoroacetate.

SCHEME 8



1.2. Tandem Cycloaddition and Further Transformations. On the basis of prior studies,[2] we fully expected precursor **9** to undergo smooth cycloaddition in the presence of Lewis acids. Treatment of **9** with $SnCl_4$ (2.0 equiv) in toluene at −78 °C produced an insoluble dark precipitate and no detectable cycloaddition product. It is likely that the complex of tin tetrachloride and **9** is insoluble in toluene at low temperatures. The use of dichloromethane as the solvent eliminated the problem, and a mixture of the nitroso acetal **8** and the nitronate **16** was obtained in less than 30 min at −75 °C (Scheme 9). Stirring the mixture in benzene at 60 °C for several hours allowed the [3+2] cycloaddition to proceed to completion, and nitroso acetal **8** was isolated in 92% yield. Apparently, the nitronate **16** is not stable and undergoes room-temperature cyclization to nitroso acetal **8**. The stereostructure of **8** was assumed for the nitroso acetal on the basis of previous cycloaddition studies.[2] The use of 2.5 equiv of $SnCl_4$ was found to be the optimal amount of Lewis acid. ^{1}H NMR analysis of the reaction mixture revealed that only one anomer of **8** was formed. However, the configuration at this center was not determined as it is irrelevant for the synthesis of daphnilactone B, because both epimers converge to the same product **7** upon hydrogenolysis.

SCHEME 9



The hydrogenolysis of **8** was one of the crucial steps in this study because it was intended to construct the pyrrolidinone ring. If the polycycle **7** is too strained, the lactam will not close. Fortunately, hydrogenolysis of nitroso acetal **8** with Raney nickel under 1 atm of hydrogen afforded a mixture of the expected hydroxy lactam **7** (about 30% from ^{1}H NMR integration), uncyclized amino ester **17** (50%), and a side product (20%) which was identified as lactam **21**.[14] The closure of **17** could be accelerated by the action of NaOMe to produce hydroxy lactam **7** in 79% overall yield.

To suppress the fragmentation[3] leading to **21**, the nickel catalyst was washed with 0.1 M solution of NaH_2PO_4 (pH = 4.5) before use. This modification led to an improved ratio (10/1 compared to 4/1) of the desired product **7** to the undesired lactam

(13) Doering, W. v. E.; Parikh, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(14) The structure of **21** was established by ^{1}H and ^{13}C NMR spectroscopy (two signals at 175 and 180 ppm), IR (1687 and 1738 cm^{-1}), as well as HRMS (FAB, calcd for $C_{15}H_{23}NO_4$ + H, 282.1705, found 282.1707).

21 after sodium methoxide treatment. The same improvement (**7**/**21**,12/1) was obtained when the hydrogenolysis was performed at 350 psi with non-NaH_2PO_4-washed catalyst. When the reaction was performed under 350 psi of hydrogen and the nickel catalyst was washed with 0.1 M solution of NaH_2PO_4, the ratio was improved to 17/1 producing, nevertheless, lactam **7** in the same yield (80%), suggesting that some other side reactions took place under these conditions.

To complete the objectives of the model study, the α-hydroxy lactam **7** was to be converted to a methylated pyrrolidine. This process began by von Doering oxidation[13] of **7** to the keto lactam **18**, which underwent Wittig olefination to form α-methylene lactam **19** in 73% overall yield (Scheme 9). The carbon−carbon double bond in unsaturated lactam **19** did not undergo hydrogenation in the presence of Wilkinson catalyst with either dihydrogen[15] (at 340 psi, rt, overnight) or catecholborane[16] (−20 °C, THF); only the starting material was recovered. However, nickel boride-catalyzed hydrogenation[17] at ambient pressure of hydrogen afforded a mixture of the two separable saturated amides, **20a** and **20b**, in a 3.5/1 ratio. The stereochemical assignment of the hydrogenation products was made on the basis of the coupling constants between the introduced methine proton (HC(2), Figure 2) and the adjacent methine proton HC(3), as well as through NOE determination. Semiempirical calculations (PM5)[18] showed that in the desired lactam **20a** the dihedral angle HC(2)C(3)H is 28° and $J^3_{HC(2)C(3)H}$ is expected to be 6−12 Hz (from the Karplus equation). In the undesired isomer (**20b**), the dihedral angle HC(2)C(3)H is 112°, in which case $J^3_{HC(2)C(3)H}$ should be less than 2 Hz. ^{1}H NMR analysis showed that the proton at the HC(2) methine is split into a quartet of doublets in the major product (desired isomer, **20a**, $J^3_{HC(2)C(3)H} = 5.4$ Hz, Figure 2), whereas it is a quartet in the minor product (undesired isomer, **20b**, $J^3_{HC(2)C(3)H}$ is close to zero). An NOE-experiment with the major product showed that there is an 11% enhancement between HC(2) and $H_3C(5)$ as well as a 7% enhancement between HC(2) and HC(3), also supporting structure **20a** (Figure 2).

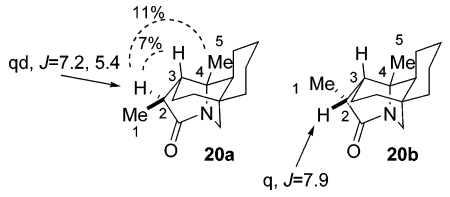
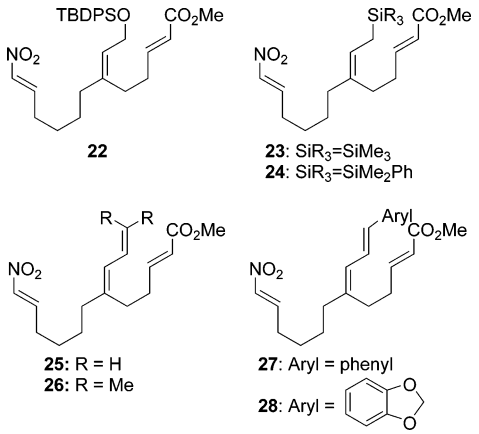


FIGURE 2. Assignment of the relative configuration of the hydrogenation products **20**.

Attempts to convert lactam **20a** into amine **6** using BH_3[19] or 9-BBN-H[20] were unsuccessful, but the reduction was ultimately accomplished by heating **20a** with 2.0 equiv of DIBAL-H[21] at 65 °C in THF/hexanes. The final product of the model study **6** was produced in 61% yield, proving that this is a viable strategy to create the pyrrolidine ring A of daphnilactone B along with the methyl bearing stereocenter.

2. Model Study II. Formation of Piperidine Ring B. The objective of the second model study is to develop a variant of the [4+2] component of the cycloaddition process that will lead to formation of a piperidine ring (Scheme 7). The principal modification of the dienophile in **xvii** (compared to the normally employed enol ether dienophiles) is inclusion of an extra carbon suitably functionalized to become incorporated into the piperidine ring upon hydrogenolysis. Modified dienophiles designed to accomplish that objective in three different ways are shown in Chart 2. Because these substrates were only marginally useful as cycloaddition substrates, their syntheses will not be presented. However, the results of attempted cyclizations were instructive in guiding the final choice of a suitable dienophile and will be described briefly below.

CHART 2



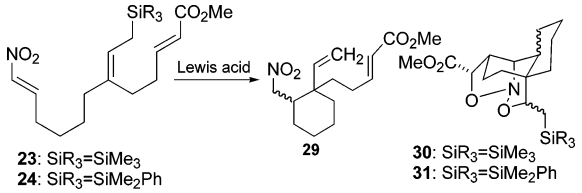
2.1. Allylic Ether and Silanes as Dienophiles. The use of an allylic ether such as **22** is the most obvious way to add a single carbon which can be activated for closure to a piperidine ring. Cycloaddition would lead to a hydroxymethyl group at C(6) of the oxazine which could be tosylated (see **viii**, Scheme 3) or mesylated prior to hydrogenolysis. Unfortunately, all attempts to effect [4+2] cycloaddition with a variety of Lewis acids led to either desilylation ($SnCl_4$, $Ti(O\text{-}i\text{-}Pr)_2Cl_2$) no reaction (MAD, MAPh)[22] or undesired side reactions (Me_3Al).[23] Also, purely thermal (199 °C, 14 h, *p*-cymene, $CaCO_3$) activation failed to afford cycloaddition products. Clearly, the modest electrophilicity of the nitroalkene mandates a more electron rich partner for successful inverse electron demand cycloaddition. The allylic oxygen substituent must inductively or hyperconjugatively deactivate the dienophile beyond the range for effective cycloaddition.

Toward that end, the allylic silanes **23** and **24** were identified and prepared. The electron-donating nature of the silyl groups should decrease the HOMO/LUMO gap for the [4+2] cycloaddition. Indeed, allyltrimethylsilane had been used successfully in intermolecular nitroalkene cycloadditions previously.[24] In the presence of 2 equiv of $TiCl_4$ in dichloromethane for 15 min at −70 °C, nitroalkene **23** did produce the corresponding nitroso acetals **30** (as a 10/1 mixture of diastereomers)[25] but only as a

(15) Jardine, F. H.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. A* **1967**, 1574−1578.
(16) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 5678−5680.
(17) Russell, T. W.; Hoy, R. C.; Cornelius, J. E. *J. Org. Chem.* **1972**, *37*, 3552−3553.
(18) Calculations were performed using a Cache Worksystem Pro Version 6.1.12.33 software from Fujitsu Limited.
(19) Brown, H. S.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912−916.
(20) Collins, C. J.; Lanz, M.; Singaram, B. *Tetrahedron Lett.* **1999**, *40*, 3673−3676.
(21) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263−5277.
(22) MAD: methyl(bis(2,6-di-*tert*-butyl-4-methylphenoxy))aluminum; MAPh: methyl(bis(2,6-diphenylphenoxy))aluminum.
(23) Pecunioso, A.; Menicagli, R. *J. Org. Chem.* **1988**, *53*, 45−49.
(24) Hurd, A. R. Ph.D. Thesis, University of Illinois at Urbana-Champaign, 2000.
(25) The relative configurations of **30a** and **30b** were not determined because this route was abandoned.

minor product (Scheme 10). The major product isolated was **29** (as a 4/1 mixture of diastereomers; (**29**/**30** = 2/1)) arising from either fragmentation of the 1,2-oxazine or Sakurai-type addition. The bulkier silane **24** was expected to be less prone to desilylation[26] and indeed led to an improved ratio of **29**/**31** = 1.5/1 under the same reaction conditions. Trimethylaluminum at 0 °C led to slow 1,4-addition of a methyl group to the nitro olefins.[23]

SCHEME 10

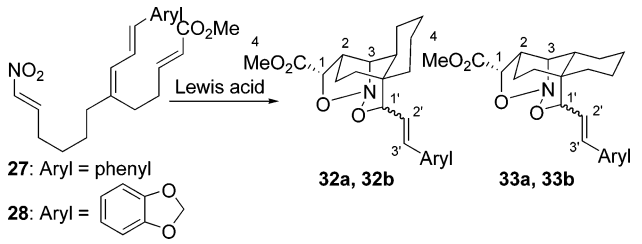


2.2. Conjugated Dienes as Dienophiles. The foregoing results and much previous experience in nitroalkene [4+2] cycloadditions support the notion of a highly asynchronous process with a significant amount of charge separation. The cationic character that accumulates on the dienophile must be stabilized for cycloaddition to be successful (see Scheme 18). A second solution for stabilizing the positive charge with additional carbon substituents involves the delocalization of that charge in a conjugated diene. Earlier studies in these laboratories have shown that cyclic conjugated dienes function well as dienophiles in intermolecular cycloadditions.[27] Four nitro olefins containing tethered dienes with different terminal groups **25**−**28** were synthesized and evaluated for competence in the in the tandem cycloaddition (Chart 2). Nitroalkene **25** bearing a diene with no terminal substituent suffered decomposition in the presence of $SnCl_4$ or $Ti(O\text{-}i\text{-}Pr)_xCl_{4-x}$, ($x = 0$, 2) at −70 °C and was unaffected by trimethylaluminum at 0 °C. Apparently, the unsubstituted diene polymerized under the strongly Lewis acidic reaction conditions.

To address the problem of polymerization and provide additional stabilization for positive charge, two other nitroalkenes, **27** and **28** bearing aromatic substituents were evaluated. Under the most favorable conditions (2.0 equiv of $SnCl_4$, CH_2Cl_2, −65 °C, 25 min) an inseparable mixture of four isomeric nitroso acetals, presumably **32a/32b** and **33a/33b**, was isolated (Scheme 11). The use of Me_3Al at −80 °C for 10 min led to no conversion and ultimately to decomposition of the substrate at room temperature. Similar results were obtained with **28** containing a more electron-rich dienophile**.** The use of conjugating aromatic substituents did allow for cycloaddition to proceed, albeit in a nonselective fashion. Thus, a different mode of stabilization of the charge was envisioned that employed the electron-donating properties of simple methyl groups as in **26**.

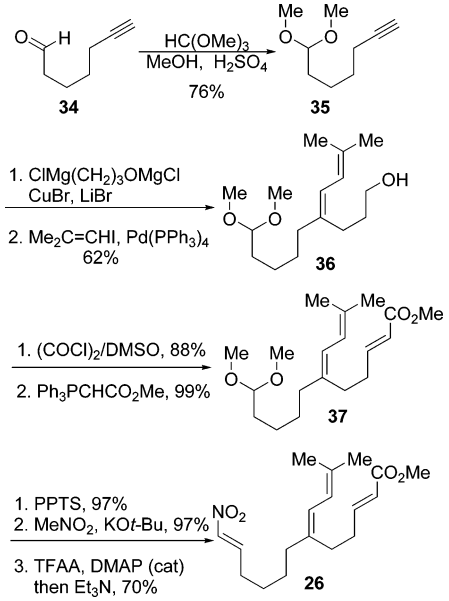
2.3. Synthesis of Nitroalkene 26. The electron-rich conjugated diene in **26** will serve a dual role. First, it will act as the electron-rich 2π-component during the [4+2] cycloaddition. Second, the isopropylidene group remaining attached to the nitroso acetal serves as a masked aldehyde which will later participate in the hydrogenolysis/reductive amination. The key

SCHEME 11



step in the planned synthesis of nitro olefin **26** is an alkyne carbocupration/cross-coupling sequence to create the 1,3-diene in **35** stereoselectively (Scheme 12).[28] Because it was not known if the diene geometry would influence the outcome of the cycloaddition, the *Z*-geometry was chosen for synthetic simplicity. Alkyne **35** was prepared from the known aldehyde **34** by acetalization in 76% yield.[29] Carbocupration of **35** with a cuprate reagent[30] formed from CuBr and $ClMg(CH_2)_3OMgCl$ followed by Pd(0)-catalyzed cross-coupling[31] with 1-iodo-2-methylpropene afforded *Z*-diene **36** as a single geometrical isomer. Optimization experiments demonstrated that it was necessary to use several equivalents of the organocopper reagent. The yield was improved from 30−40% to 62% if 3.0 equiv of the alkylcopper reagent were employed instead of 1.1 equiv. It seems that the carbocupration is relatively slow, and thermal decomposition of the alkylcuprate intermediate competes. Construction of the dipolarophile, involved a two-step sequence beginning with Swern oxidation of the alcohol **36** in 88% yield followed by treatment of the resulting aldehyde with carbomethoxymethylidenetriphenylphosphorane to provide the unsaturated ester **37** in 99% yield (*E*/*Z*, 20/1). The synthesis was completed by installation of the nitro olefin moiety.

SCHEME 12



(26) (a) Akiyama, T.; Kirina, M. *Chem. Lett.* **1995**, 723−724. (b) Danheiser, R. L.; Dixon, B. R.; Gleasont, R. W. *J. Org. Chem.* **1992**, *57*, 6094−6097.

(27) Denmark, S. E.; Kesler, B. S.; Moon, Y.-C. *J. Org. Chem.* **1992**, *57*, 4912−4924.

(28) (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, *11*, 841−871. (b) Normant, J. F. Alkyne carbocupration and polyene synthesis. In *Organocopper reagents, A practical approach*; Taylor, R. J. K., Ed.; Oxford University Press: New York, 1994. (c) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631.

(29) Hopf, H.; Kruger, A. *Chem. Eur. J.* **2001**, *7*, 4378−4385.

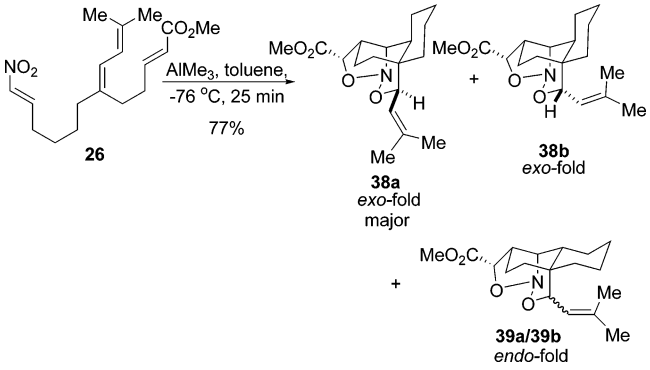
(30) Gardette, M.; Alexakis, A.; Normant, J. F. *Tetrahedron* **1985**, *41*, 5887−5899.

(31) (a) Jabri, N.; Alexakis, A.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1983**, 332−338. (b) Gardette, M.; Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron* **1984**, *40*, 2741−2750.

Removal of the dimethoxy acetal with PPTS in aqueous acetone provided the aldehyde, which was subjected to Henry reaction with nitromethane to afford the nitro alcohol. Dehydration with trifluoroacetic anhydride and triethylamine produced **26** in 66% yield for the three steps as a single *E*-isomer.

2.4. Tandem Cycloaddition of Nitroalkene 26. Initial attempts at performing the cycloaddition of **26** in the presence of $SnCl_4$ or $Ti(O\text{-}i\text{-}Pr)_xCl_{4-x}$, ($x = 0-2$) again produced an inseparable mixture of four isomeric nitroso acetals **38a/b**−**39a/b** as was seen with the aryl-substituted dienes (Scheme 13). Much to our surprise, however, Me_3Al (which had not been useful with any of the previous substrates) promoted the cycloaddition of **26** to afford two nitroso acetals. Optimization of the conditions involved decreasing the reaction temperature to −78 °C and increasing the amount of the Lewis acid to 3 equiv. Under these conditions, a 20/1 mixture of the isomeric nitroso acetals was obtained in 77% yield.[32] Fractional crystallization allowed the isolation of the major isomer (59%) whose full stereostructure was determined to be **38a** by single-crystal X-ray analysis.[33] The crystal structure revealed that **38a** arises from an *exo*-fold (tether) of the dienophile and that the configuration of the dienophile is preserved. The structures of the byproducts **38b** and **39a/b** were assumed as shown on the basis of their characteristic ^1H NMR signals, but they were not isolated and fully characterized.

SCHEME 13



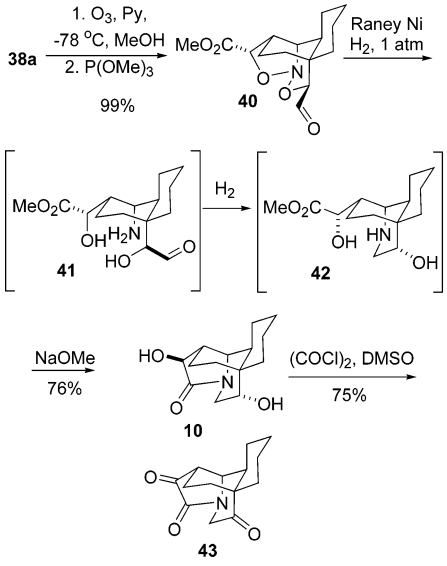
2.5. Transformation of 38a into the Tetracyclic Target of Model Study II. The selective and high-yielding construction of **38a** showed that the electron-rich 1,1,4,4-tetraalkyl diene served well in participating in the cycloaddition. The second function of that unit is to serve as a latent aldehyde which must be unmasked by oxidative cleavage. Several attempts to cleave the carbon−carbon double bond were made to install an appropriate functional group on the terminus of that fragment. Exhaustive ozonolysis followed by reduction with dimethyl sulfide[34] or sodium borohydride[35] led to recovery of uncharacterizable decomposition products in low yield. Osmylation[36] or oxidation with $KMnO_4$[37] proceeded too slowly, probably due to the hindered nature of the olefin. Ruthenium tetraoxide[38] quickly destroyed the material.

Ultimately, it was found that the cleavage could be cleanly accomplished by ozonolysis after careful optimization of the reaction conditions. The cleavage could be successfully executed in methanol containing 1 equiv of pyridine if 1 equiv of ozone was used.[39] Upon reduction with trimethyl phosphite, the aldehyde **40** could be isolated quantitatively (Scheme 14).

With the substrate required for closure by reductive amination now available, we were poised to test the piperidine ring formation. Exposure of the aldehyde to reducing conditions presented a concern that conversion to an alcohol would be competitive with the N−O bond cleavage. Gratifyingly, hydrogenolysis of **40** in presence of Raney nickel in methanol under 1 atm of hydrogen afforded lactam **10** in 76% yield. As in model study I, closure to the lactam required the assistance of sodium methoxide. *In forming the piperidine ring in **10** the major goal of the model study II has been achieved.* The remaining challenge was the transformation of lactam **10** into the final product of the study **50a** to evaluate possible intermediates in the planned synthesis of daphnilactone B (Scheme 16).

Oxidation of **10** according to the method of Swern afforded diketone **43** in 75% yield. Unlike the related α-dicarbonyl compound **18** from model study I, this intermediate was very sensitive and prone to formation of hemiacetals and hydrates. Chloroform solutions of chromatographically purified **43** displayed two ketone carbonyl resonances in the ^{13}C NMR spectrum at 201 and 207 ppm. However, in CD_3OD, the ^{13}C NMR spectrum showed signals at 212 and 102 ppm, the latter of which is characteristic of an acetal or hemiacetal. Numerous attempts to optimize this reaction and isolate the diketone in analytically pure form failed.

SCHEME 14



Intermediate **43** also behaved very differently than **18** toward olefination reagents. It was anticipated that the presence of the lactam carbonyl group and absence of the angular methyl group

(32) Nitroolefin **26** was formed as a mixture of isomers at the unsaturated ester double bond (*E*/*Z* ∼ 20/1). It is possible that the cycloaddition of **26** was completely stereoselective and the 20/1 ratio of the diastereomeric nitroso acetals reflects the presence of the two isomers in the starting material. In this case, the minor cycloadduct may be the epimer of **38a** at the ester-group-bearing stereocenter.

(33) The crystallographic coordinates of **38a** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. CCDC 275186. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk). For the Chem3D image, see the Supporting Information.

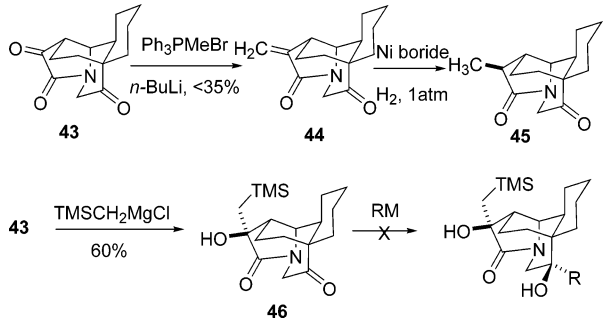
(34) Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, *7*, 4273−4278.

(35) Mukai, C.; Kataoka, O.; Hanaoka, M. *J. Org. Chem.* **1995**, *60*, 5910−5918.

would render the ketone in the five-membered ring more reactive than that in the six-membered ring. Under Wittig olefination conditions, the starting material was quickly consumed. However, only approximately 30% of the unsaturated lactam **44** could be isolated (Scheme 15). The remaining material could not be identified. Hydrogenation of **44** under the conditions used in the first model study provided the lactam **45** as a single diastereomer, whose configuration was assumed to be as shown in Scheme 15 by analogy to **20**.

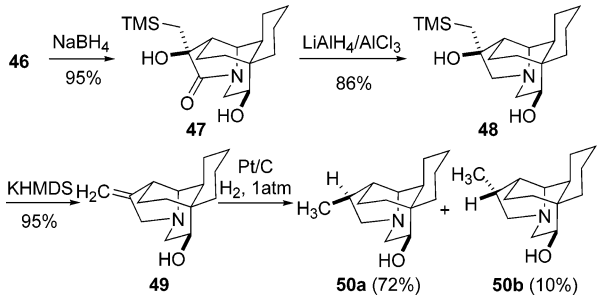
In an attempt to induce Peterson olefination, **43** was combined with Me_3SiCH_2MgCl to provide adduct **46** as a single diastereomer in 60% yield. The relative configuration was assumed as shown in Scheme 15 but is inconsequential because that stereocenter will be destroyed later. Unfortunately, elimination of trimethylsilanol could not be accomplished. When the β-hydroxysilane **46** was treated with KHMDS, a complex mixture of unidentified products was formed. Also different acidic reagents did not effect conversion of the silane (AcOH, HCl, TFA, BF_3/Et_2O, $SnCl_4$).[40] Because it was believed that presence of the lactam carbonyl makes the olefin **44** unstable, it was decided that the hydroxysilane should be subjected to the elimination after the lactam is reduced to the amine.

SCHEME 15



Attempts to add a nucleophile to the cyclohexanone moiety in **46** failed. Addition of *n*-BuLi or *n*-BuMgCl led to enolization (proved by deuterium incorporation upon quench with D_2O). A less basic reagent prepared by transmetalation of *n*-BuLi with $CeCl_3$[41] did not act on the starting material (and no D-incorporation was noted either). Ultimately, this carbonyl group was reduced stereoselectively with sodium borohydride to form the secondary alcohol **47** (Scheme 16). Only one isomer was observed which was assigned to be the equatorial alcohol from the following considerations. First, the borohydride ion is assumed to approach from the less hindered face, and second, the ^{1}H NMR coupling constants are consistent with this configuration. Minimized energy conformations of **47** and ***epi*-47** (Figure 3) were calculated at the PM3 level.[18] Accordingly, the calculated dihedral angles for **47** are as follows: $H_aC(1)C(2)H = 82°$ (expected $^3J_{HaC(1)C(2)H}$ is less than 1 Hz from the Karplus equation), $H_bC(1)C(2)H = 34°$ (expected $^3J_{HbC(1)C(2)H}$ is 7−13 Hz). The calculated dihedral angles for ***epi*-47** are: $H_aC(1)C(2)H = 51°$ (expected $^3J_{HaC(1)C(2)H}$ is 3−7 Hz), $H_b(C1)C(2)H = 169°$ (expected $^3J_{HbC(1)C(2)H}$ is 8−14 Hz). In the ^{1}H NMR spectrum of the reduction product, *H*HC(1) is a doublet (3.86 ppm, $J^2_{HaC(1)Hb} = 14.9$, $^3J_{HaC(1)C(2)H}$ is close to 0 Hz), H*H*C(1) is a doublet of doublets (3.24 ppm, $^2J_{HbC(1)Ha} = 14.9$, $^3J_{HbC(1)C(2)H} = 6.1$), HC(2) is a triplet (3.62 ppm, $^3J_{HC(2)C(1)Hb} = 5.6$) due to a coupling to the hydroxyl proton. The observation of one medium and one very small coupling between HC(2) and the HC(1) protons is consistent with structure **47**, and not ***epi*-47**.

SCHEME 16



The amide function in **47** was reduced with dihydrochloroalane[21] to produce the amine **48** in 86% yield (Scheme 16). Fortunately, elimination of trimethylsilanol under the strongly Lewis acidic conditions of this reaction was not observed. However, treatment of the amine **48** with KHMDS cleanly provided the olefin **49** in 95% yield.

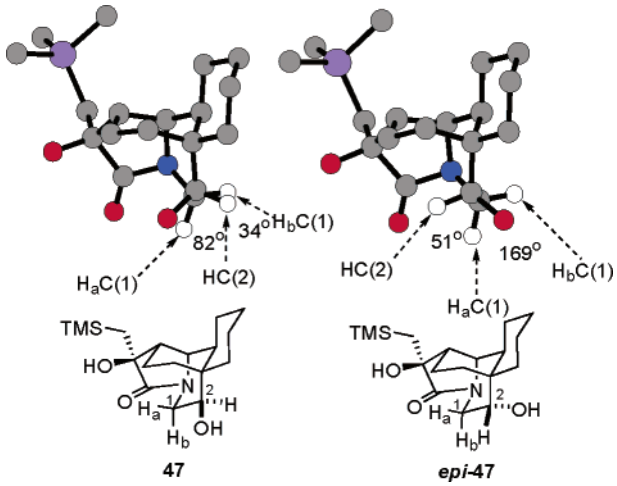


FIGURE 3. Configurational assignment of reduction product **47**.

The last step of the sequence was the introduction of the methyl group by hydrogenation of the *exo*-methylidene group. Although homogeneous hydrogenation[42] ($RhCl(PPh_3)_3$,1 atm) was not effective, hydrogenation over Pt/C[43] was successful but afforded two diastereomers. The major isomer was separated by column chromatography, and its structure was assigned to be **50a** by NOE spectroscopy (Figure 4). The fact that there is

(36) Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463−8464.
(37) (a) Lee, D. G.; Chang, V. S. *J. Org. Chem.* **1978**, *43*, 1532−1536. (b) Herriott, A. W.; Picker, D. *Tetrahedron Lett.* **1974**, *15*, 1511−1514.
(38) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.
(39) (a) Liang, J.; Hoard, D. W.; Khau, V. V.; Martinelli, M. J.; Moher, E. D.; Moore, R. E.; Tius, M. A. *J. Org. Chem.* **1999**, *64*, 1459−1463. (b) Slomp, G.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915−921.
(40) (a) AcOH: Boeckman, R. K.; Silver, S. M. *Tetrahedron Lett.* **1973**, *14*, 3497−3500. (b) TFA: Marchand, A. P.; Kaya, R. *J. Org. Chem.* **1983**, *48*, 5392−5395. (c) BF_3/Et_2O: Hudrlik, P. F.; Hudrlik, A. M.; Misra, R. N.; Peterson, D.; Withers, G. P.; Kulkarni, A. K. *J. Org. Chem.* **1980**, *45*, 4444−4448.
(41) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.
(42) Hussey, A. S.; Takeuchi, Y. *J. Am. Chem. Soc.* **1969**, *91*, 672−675.
(43) Marx, J. N.; McGaughey, S. M. *Tetrahedron* **1972**, *28*, 3583−3586.

3.8% NOE between HC(2) and HC(4) proves that they lie on the same face of the pyrrolidine ring, which is consistent only with structure **50a**. The final product was converted into its borane adduct **51** for full characterization.

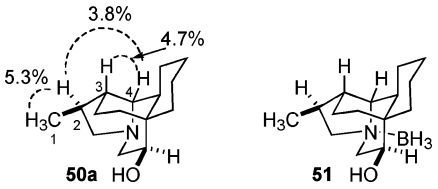


FIGURE 4. Proof of the structure of **50a** by NOE and borane adduct **51**.

Discussion

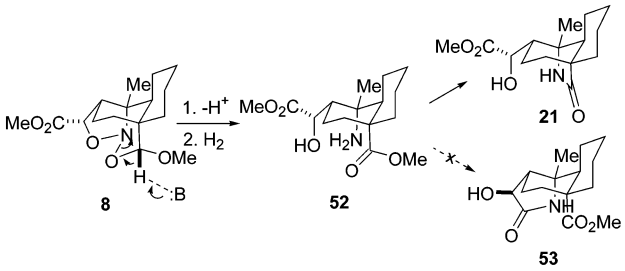
1. Model Study I. The primary objective of model study I was to demonstrate that the pyrrolidine ring in **6** corresponding to ring A of daphnilactone B can be introduced using the tandem double-intramolecular [4+2]/[3+2] cycloaddition from nitro olefin **9**. This outcome was fairly assured as the only difference between **9** and proven precursor **1** was the carbomethoxy group attached to the dipolarophile. Because the [3+2] step prefers an electron-poor dipolarophile, this change should have only made the dipolar cycloaddition easier.

As was established in previous studies,[2] the cycloaddition of **9** proceeded readily to afford the nitroso acetal **8** in very good yield as a single isomer. It was assumed that the [4+2] step proceeded through the *exo*-transition state by analogy to the formation of **3**. The reason for this preference is the presence of the β-methyl group on the nitroalkene, which typically disfavors the *endo*-transition structure through nonbonding interactions.[2,44,45] The formation of **8** during workup at room temperature showed that the intermediate nitronate **16** did manifest the dipolarophile activation as expected. Obviously, the directing effect of the tether to the dipolarophile was strong enough to lead to a single cycloadduct in this step as well.

The carbomethoxy group in **9** also served to provide the additional carbon needed to produce the pyrrolidinone ring in **7** upon hydrogenolysis of nitroso acetal **8**. Even though it was not unprecedented,[2] there was some concern whether the lactam **7** was not too strained to form spontaneously as had been seen in previous pyrrolizidine ring assemblies.[46] Indeed, the clean conversion to **7** required activation by NaOMe.

The formation of byproduct **21** during hydrogenolysis of nitroso acetal **8** is intriguing. This lactam most likely arises by (acid- or base-catalyzed) fragmentation of the nitroso acetal with concomitant N−O bond cleavage to afford the amino diester **52** (Scheme 17). The primary amino group in **52** can attack either ester moiety to form **21** or **53**. The reason for the preferred formation of **21** may be the fixed, diaxial position of both the amine and the carbonyl groups. The formation of **21** could be suppressed by washing the Raney nickel to remove basic contaminants or by executing the hydrogenation at 350 psi. These observations suggest that **21** and **7** are formed via two competing pathways and the formation of **7** is favored by increased hydrogen pressure (leading to faster N−O bond cleavage) and that formation of **21** is a base-catalyzed fragmentation.

SCHEME 17



The second goal of model study I was the stereoselective installation of the methyl group on the pyrrolidine ring. Although hydrogenation of lactam **19** provided a 3.5/1 mixture of two diastereomers favoring the desired epimer **20a**, this outcome was viewed as satisfactory. The angular methyl group in **19** is an artifact of the model system and is absent in the structure of daphnilactone B. We expected that approach of hydrogen from the convex face would be more facile and the overall selectivity greater in a true precursor devoid of this methyl group. This expectation was realized in model study II.

2. Model Study II. 2.1. [4+2] Cycloaddition. The primary objective of model study II was the development of a new variant of the tandem cycloaddition that would lead to the formation of the piperidine ring in **10** that corresponds to the ring B of daphnilactone B. Subsequent introduction of the pyrrolidine ring (ring A) and stereoselective introduction of the ring A methyl group was also planned.

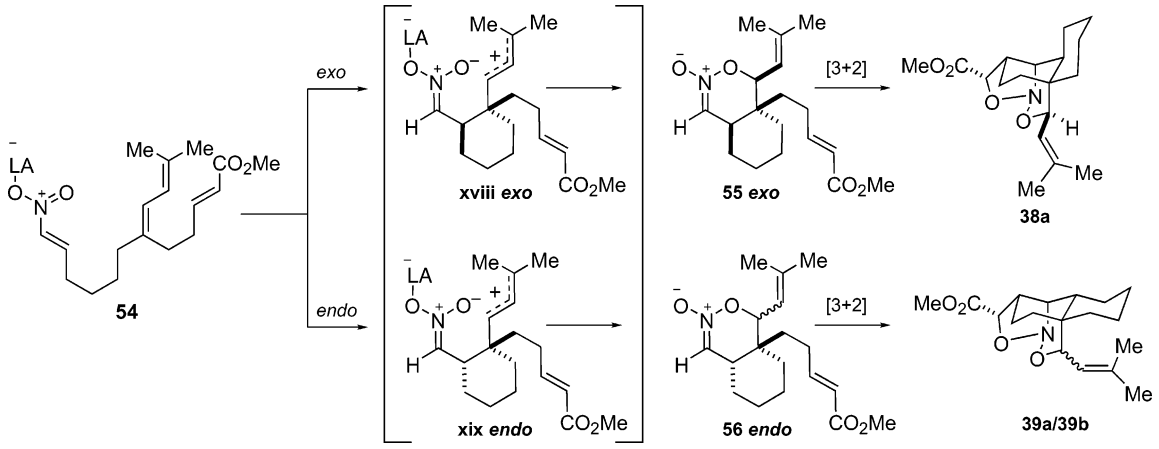
The electronic demands of the [4+2] component of the cycloaddition required that a newly invented dienophile must be (1) capable of introducing an additional carbon for the piperidine ring, (2) highly electron rich, and (3) convertible to an electrophilic function for subsequent ring closure. The successful cycloadditions of **26**, **27**, and **28** showed that dienes could serve as the requisite dienophiles, albeit with poor stereoselectivity. Remarkably, reaction of **26** in the presence of $AlMe_3$ was not only high yielding but also very stereoselective.

From extensive prior experience with both simple alkenes and enol ethers as dienophiles, we now view the [4+2] process as concerted but highly asynchronous.[1] In most cases, the geometry of the dienophile is preserved, but occasionally secondary products arising from ionic pathways are isolated, which suggests the intermediacy of a zwitterionic species similar to **xviii/xix** (Scheme 18). The preservation of the dienophile geometry in **38a** implies that the [4+2] step is concerted and not a stepwise process when promoted by $AlMe_3$ (Scheme 18). The nonpolar solvent toluene also disfavors ionic processes. The formation of the four isomers **38a/38b** and **39a/39b** in the presence of the stronger Lewis acids in dichloromethane as the solvent can be explained by a combination of unselective side chain folding in the [4+2] transition state (*exo* vs *endo*) and the isomerization of the dienophile during the ionic [4+2] cycloaddition.

The high stereoselectivity of the [4+2] cycloaddition of **26** was remarkable. The striking preference for reaction via an *exo* (tether) transition structure demands explanation. Factors that

(44) Denmark, S. E.; Moon, Y.-C.; Cramer, C. J.; Dappen, M. S.; Senanayake, C. B. W. *Tetrahedron* **1990**, *46*, 7373−7392.
(45) Moon, Y.-C. Ph.D. Thesis, University of Illinois, Urbana, 1991.
(46) For a summary of recent strained and troublesome lactamizations, see ref 4.

SCHEME 18



must be considered are (1) the structures of the nitroalkene and dienophiles, (2) the connecting tether, and (3) the nature of the Lewis acid. In previous studies of intramolecular [4+2] cycloadditions of nitroalkenes tethered by four methylene groups to simple alkene dienophiles, the preference for *exo*-selectivity (with $SnCl_4$ as the Lewis acid) was strongly dependent on the substitution of the nitroalkene. In cases with no α-substituent, the *exo*-transition structure was favored, but not strongly.[44] The role of Me_3Al is difficult to evaluate because it has only been employed for intermolecular cycloadditions with enol ethers as the dienophiles. In these cases, it was found that the cycloadditions proceed via the *endo* (enol ether oxygen) transition structure ascribable to secondary orbital interactions between the heterodiene and the approaching dienophile and small size and monodentate character of this Lewis acid.[47] The cycloaddition of **26** proceeded in the same sense, placing the vinylic substituent on the dienophile *endo* in the transition structure (Figure 5). The previously observed "*endo*-rule" for intermolecular [4+2] cycloadditions between nitro olefins and dienes promoted by Lewis acids can also support the involvement of the secondary orbital interactions in these systems.[27] However, in this case, in the absence of favorable interactions between the dienophile oxygen and the complexed Lewis acid, the preference for the *exo* (side chain)-transition structure is more difficult to understand.

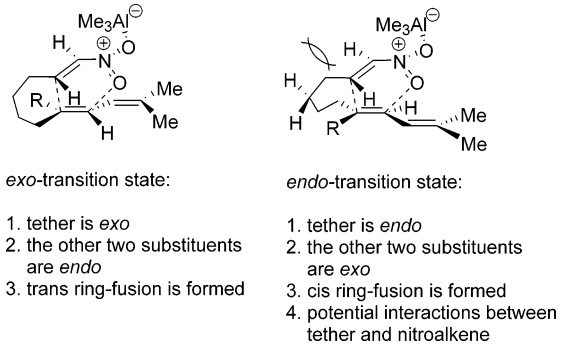


FIGURE 5. Steric interactions during the [4+2] step in nitro olefin **26**.

To gain insight into origins of the high *exo* (side chain)-selectivity of the [4+2] step, transition structures leading from **26** to **xviii-*exo*** and **xix-*endo*** were calculated at the PM5 level,[18,48] and the results are presented in Figure 6. The calculations suggest that in each case the [4+2] cycloaddition is highly asynchronous, perhaps stepwise with ~20 kcal/mol activation energy barrier for the formation of the C−C bond and very low (~1 kcal/mol) barrier for the O−C bond-forming step. The low activation energy for the latter step, leading from **xviii/xix** to nitronates **55/56**, means that the transient intermediate has a very short lifetime and quickly collapses to form the cycloadduct. Nevertheless, this short lifetime may be long enough to form minor amounts of the epimers via the C−C bond rotation. The *exo*-transition structure is 2.5 kcal/mol lower in energy than the *endo*-transition structure in accordance with the observed stereoselectivity. In the *exo*-transition structure, the C−C bond length is 1.98 Å and the N−O bond length is 2.86 Å. In the *endo*-structure, the C−C bond is 1.96 Å and the N−O bond is 2.80 Å. Inspection of the two transition structures reveals the following:

1. The formation of **xix-*endo*** proceeds through a slightly later *endo*-transition structure (the C−C bond is 0.02 Å shorter), suggesting that additional steric interactions must be overcome to reach transition state compared to the *exo*-transition structure.

2. The decisive steric difference in the two transition structures can be seen by examining the interactions around the incipient cyclohexane ring. In the *exo*-transition structure, the forming cyclohexane and nitronate rings are *trans*-fused. Thus, only the dipolarophile tether has 1,3-diaxial-type interactions with neighboring hydrogens. However, in the *endo*-transition

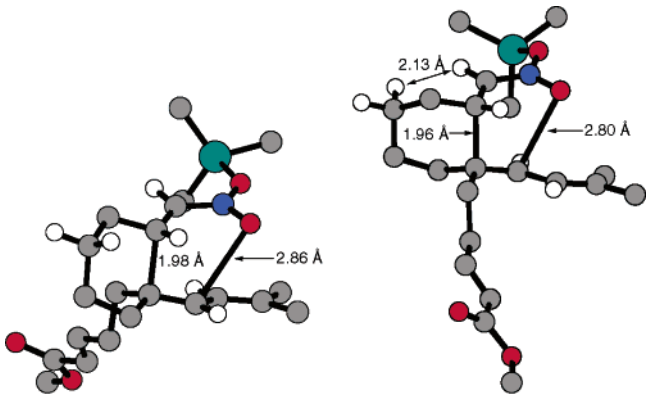


FIGURE 6. Calculated *exo*- and *endo*-transition structures for the C−C bond-forming step leading from **26** to **xviii-*exo*** and **xix-*endo***.

(47) Denmark, S. E.; Seierstad, M. *J. Org. Chem.* **1999**, *64*, 1610−1619.

structure, the cyclohexane and nitronate rings are *cis*-fused. Thus, both the dipolarophile tether and the nitronate carbon are axial in the cyclohexane ring. This arrangement creates an additional nonbonding interaction in the *endo*-TS between the α-hydrogen of the nitro group and a hydrogen on the tether to the dienophile at the *δ*-position (the distance between them is 2.13 Å).[49] In the *exo*-TS, these interactions are absent because these two hydrogen atoms lie on the opposite faces of the forming ring.

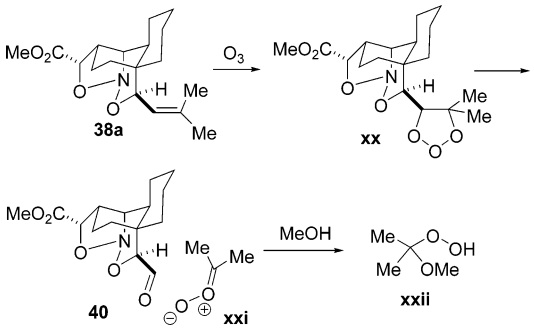
To summarize, the *exo*-selectivity of the reaction may be explained by the stabilizing secondary orbital interactions between the 2*π*- and 4*π*-components in the *exo*-TS, as well as destabilizing steric interactions present in the *endo*-transition state.

2.2. [3+2] Cycloaddition. An interesting difference between the cycloadditions in model studies I and II is the ease with which the [3+2] step took place in the latter case. The cycloaddition of **9** produced a mixture of the nitroso acetal **8** and the intermediate nitronate **16** (Scheme 9), which relatively slowly collapsed into the acetal. The nitronates **55/56** (Scheme 18) were not observed and must have suffered the [3+2] step at room temperature. This observation most likely arises from the additional steric interactions provided by the methyl group in **16**.

2.3. Elaboration of Rings A and B. The oxidative cleavage of the isopropylidene group in nitroso acetal **38a** to an aldehyde took extensive experimentation. Exactly 1 equiv of ozone had to be used which was also buffered by 1 equiv of pyridine. Presumably, the pyridine forms a less electrophilic complex with ozone, which makes the oxidant milder and more selective.[39] The nitroso acetal **38a** has limited solubility in methanol at low temperatures. However, when dichloromethane was used as the reaction solvent, or even as a 1/1 cosolvent with methanol, the aldehyde yield dropped. Cleavage of the primary ozonide **xx** probably proceeds in the direction shown in Scheme 19.[50] In this case, aldehyde **40** and the carbonyl oxide **xxi** (which is stabilized by the two alkyl groups and is trapped by methanol forming **xxii)** are formed directly upon the fragmentation when the reaction is done in methanol. It is not clear why more than a stoichiometric amount of ozone was detrimental. Perhaps oxidation of the nitroso acetal becomes competitive.

The hydrogenolysis step for the formation of the key piperidine ring was of greatest concern because many potential complications could be envisioned. Most serious among these concerns was the premature reduction of the aldehyde to the corresponding alcohol before the amine **41** could be revealed for reductive amination (Scheme 14). Second, even if the nitroso acetal were cleaved first, we anticipated complications from the revealed α-hydroxy aldehyde such as epimerization or tautomerization to an α-hydroxy ketone. Finally, we also anticipated that the primary amino group in **41** could first react with the ester instead of the aldehyde to form a pyrrolidinone which would not undergo reductive amination. Remarkably, the hydrogenolysis of the aldehyde **40** provided diol **10** in very good yield for such a complex series of transformations.

SCHEME 19



As expected, differentiation between the two keto groups in **43** was not problematic. The α-keto amide function was more reactive than the simple ketone flanked by a quaternary carbon center. The ease of hemiacetal and hydrate formation from **43** is a manifestation of its higher electrophilicity compared to **18**. This unusually high electrophilicity of the α-methylidene lactam is manifested in its rapid decomposition in the presence of nucleophilic species. This character required that the lactam carbonyl be removed prior to introduction of the methylidene function. The Petersen olefination served admirably in this capacity because the hydroxy silane intermediate allowed manipulation of the molecule elsewhere. For example deoxygenation of the lactam **47** could be achieved by the action of chloroalane. This reagent is known to favor amine formation in reduction of lactams as opposed to the formation of amino alcohols by C−N bond cleavage.[21] Elimination of trimethylsilanol under the acidic conditions of this reaction was not observed. However, under basic conditions, the elimination was fast and clean.

Finally, hydrogenation of **49** afforded the target structure **50a**. The diastereoselectivity of this reaction was higher than in the similar reaction of **19**; however, it was lower than in hydrogenation of **44**. The attenuated diastereoselectivity in the reduction of **49** compared to **44** may be the directing effect of the hydroxy group in **49**.[51] In the synthesis of daphnilactone B, this alcohol can be functionalized to eliminate its directing effect and to create more bulk on the concave face of the pyrrolidine ring, which may further improve the diastereoselectivity.

Conclusions

An extension of the tandem double intramolecular [4+2]/[3+2] nitroolefin cycloaddition has been developed that allows the generation of piperidines by the use of an electron-rich 1,3-diene as a 2*π*-component in the cycloaddition. The crucial tandem cycloaddition could be affected by trimethylaluminum to afford nitroso acetal **38a** in high yield and stereoselectively via an *exo*-transition structure. Unmasking the isopropylidene group in **38a** to an aldehyde was possible by careful ozonolysis. Upon hydrogenolysis of nitroso acetal aldehyde, a cascade of steps generated the piperidine and pyrrolidinone rings in **10** by intramolecular reductive alkylation/lactamization. This intermediate was transformed into **50a**, with formation of the fully functionalized pyrrolidine ring (corresponding to ring A of daphnilactone B).

(48) In each case, to locate the saddle point, an energy surface map was calculated in the gas phase starting with the corresponding nitronate (bound to a molecule of trimethylaluminum) and systematically varying the C−C and N−O bond length. Frequency calculations were used to confirm the nature of the saddle points. All transition structures had only one imaginary frequency corresponding to the formation of the expected bonds. Reaction coordinate calculations were performed to determine the connections of the cycloaddition transition structures with the reactants and the products.

(49) van der Waals radius of hydrogen is 1.20 Å (Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441−451.

(50) Bunnelle, W. H. *Chem. Rev.* **1991**, *91*, 335−362.

(51) Thompson, H. W.; McPherson, E.; Lences, B. L. *J. Org. Chem.* **1976**, *41*, 2903−2906.

Future challenges include further development of the tandem intra/intramolecular [4+2]/[3+2] cycloaddition for a general route to piperidine-containing natural products. In the context of the total synthesis of daphnilactone B, the major challenges are to build a more complex cycloaddition substrate that can incorporate the functionality needed to introduce the two adjacent quaternary stereocenters and provide the potential for stereocontrol and the locus for elaboration of the hydroazulene rings. These studies will be reported in due course.

Experimental Section

General Experimental Procedures. See the Supporting Information.

***rel*-(1*S*,2*S*,4*R*,6a*R*,10a*S*,10b*R*)-Methyl Octahydro-6-methoxy-10b-methyl-6*H*-1,6a-ethanoisoxazolo[2,3-*c*][2,3]benzoxazine-2-carboxylate (8).** A 250-mL, three-neck, round-bottom flask equipped with a nitrogen inlet, a thermocouple, a rubber septum, and a stir bar was charged with **9** (2.58 g, 8.30 mmol, 1.0 equiv) and 80.0 mL of CH_2Cl_2 and cooled in CO_2/acetone bath (internal temperature < −75 °C). $SnCl_4$ was added dropwise via syringe (2.43 mL, 5.40 g, 20.7 mmol, 2.5 equiv), and the reaction mixture was stirred at this temperature for 30 min. The reaction was then quenched by the addition of ethyl acetate (30 mL), followed by a solution of Et_3N in methanol (1 M, 30 mL) and a satd aq solution of $NaHCO_3$ (120 mL). The contents were extracted with ethyl acetate (3 × 100 mL), and the combined organic layers were washed with a satd aq solution of NH_4Cl (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The colorless oily residue (2.71 g) was placed into a one-neck, round-bottom flask equipped with a nitrogen inlet and a stir bar, and then 60 mL of benzene and 0.9 g of $NaHCO_3$ were added. The mixture was stirred for 6 h in an oil bath (60 °C, external temperature). The reaction mixture was then filtered and concentrated in vacuo to provide 2.63 g of greenish-yellow solid material, which was purified by chromatography (silica gel, hexanes/EtOAc, gradient 3/1−1/1) to afford **8** as a colorless oil (2.37 g, 7.61 mmol, 92%). Crystallization from heptane yielded **8** as a white crystalline compound (2.13 g, 6.85 mmol, 82%). Data for **8**: mp 89−90 °C (heptane); ^{1}H NMR (500 MHz, $CDCl_3$) 4.85 (t, J = 3.9, 1 H, HC(2)), 4.24 (s, 1 H, HC(6)), 3.77 (s, 3 H, H_3C(15)), 3.48 (s, 3 H, H_3C(16)), 2.44−2.48 (m, 1 H, HC(1)), 2.17−2.27 (m, 2 H, HC(10a) and *H*HC(11)), 1.87−1.97 (m, 2 H, H*H*C(11) and *H*HC(12)), 1.76−1.82 (m, 1 H, *H*HC(9)), 1.69−1.75 (m, 1 H, *H*HC(10)), 1.53−1.60 (m, 2 H, *H*HC(8) and *H*HC(7)), 1.15−1.45 (m, 4 H, H*H*C(12), H*H*C(7), H*H*C(9), and H*H*C(10)), 1.12 (s, 3 H, H_3C(13)), 1.08−1.12 (m, 1 H, H*H*C(8)); ^{13}C NMR (126 MHz, $CDCl_3$) 171.1 (C(14)), 108.5 (C(6)), 90.1 (C(2)), 74.2 (C(10b)), 55.1 (C(16)), 52.4 (C(15)), 43.1 (C(1)), 36.2 (C(10a)), 34.1 (C(6a)), 31.2 (C(7)), 26.7 (C(11)), 25.6 (C(12) or C(10)), 25.6 (C(12) or C(10)), 23.5 (C(13)), 23.4 (C(9)), 20.6 (C(8)); IR (neat) 3494 (w), 3005 (w), 2954 (s), 2935 (s), 2861 (s), 2833 (m), 1772 (s), 1452 (s), 1439 (s), 1369 (m), 1344 (m), 1288 (m), 1273 (m), 1211 (s), 1138 (s), 1099 (s), 1007 (s), 972 (s), 901 (m), 825 (m), 800 (m); MS (FAB) 312 (99), 281 (13), 280 (55), 252 (23), 249 (10), 195 (10), 189 (21), 161 (26), 159 (10), 155 (24), 153 (17), 152 (22), 149 (12), 147 (14), 137 (12), 135.0 (44), 133 (28), 121 (19), 120 (10), 119.0 (100), 117 (16), 107 (12); TLC R_f = 0.16 (hexanes/EtOAc, 4/1) [silica gel, I_2, CAM]. Anal. Calcd for $C_{16}H_{25}NO_5$ (311.17): C, 61.72; H, 8.09; N, 4.50. Found: C, 61.74; H, 8.12; N, 4.63.

***rel*-(1*S*,2*S*,4*S*,6*R*,6a*R*,10a*S*,10b*R*)-Methyl Octahydro-6-(2-methylpropenyl)-6*H*-1,6a-ethanoisoxazolo[2,3-*c*][2,3]benzoxazine-2-carboxylate (38a).** A 50-mL, one-neck, round-bottom flask equipped with a nitrogen inlet and a stir bar was charged with **26** (422 mg, 1.31 mmol, 1.0 equiv) and toluene (10 mL) and cooled to −76 °C (external temperature). Trimethylaluminum (2.0 M solution in toluene, 1.97 mL, 3.94 mmol, 3.0 equiv) was added at once via syringe. A deep red solution was instantly formed, which became yellow in 5 min. After 25 min at −75/−76 °C, the reaction mixture was quenched with methanol (1.0 mL) and diluted with MTBE (20 mL). Brine (5 mL) was added, and the mixture was warmed to rt and was washed with sodium hydroxide (10% aq solution, 5 mL). The organic layer was washed with satd aq solution of ammonium chloride, dried (Na_2SO_4), filtered, and concentrated in vacuo. The almost colorless oily material was purified by chromatography (silica gel; hexanes/EtOAc, gradient, 7/1−3/1) to afford **38a** (327 mg, 1.02 mmol, 77%) as a white solid. Additional purification by repeated crystallization (hexanes, three times) provided **38a** (248 mg, 0.77 mmol, 59%) as a white crystalline material. Data for **38a**: mp 99−100 °C (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) 5.12 (doublet of apparent pentets, J = 9.3, 1.5, 1 H, HC(13)), 4.71 (d, J = 1.5, 1 H, HC(2)), 4.26 (dd, J = 9.0, 1.5, 1 H, HC(6)), 3.74 (s, 3 H, H_3C(18)), 3.38 (dd, J = 5.9, 2.4, 1 H, HC(10b)), 2.55−2.63 (m, 1 H, HC(1)), 2.09−2.17 (m, 2 H, H_2C(11)), 2.03−2.09 (m, 1 H, HC(10a)), 1.88−1.99 (m, *H*HC(12)), 1.76−1.83 (m, 1 H, *H*HC(9)), 1.74 (s, 3 H, H_3C(15) or H_3C(16)), 1.70 (s, 3 H, H_3C(15) or H_3C(16)), 1.38−1.56 (m, 5 H, H_2C(8), H_2C(10) and H*H*C(12)), 1.24−1.34 (m, 1 H, H*H*C(9)), 1.16−1.24 (m, 1 H, *H*HC(7)), 0.85 (td, J = 13.0, 4.8, 1 H, H*H*C(7)); ^{13}C NMR (101 MHz, $CDCl_3$) 171.2 (C(17)), 139.9 (C(14)), 118.3 (C(13)), 90.3 (C(2)), 84.9 (C(6)), 71.5 (C(10b), 52.3 (C(18)), 38.9 (C(10a)), 38.2 (C(1)), 32.9 (C(6a)), 32.0 (C(7)), 28.3 (C(11)), 26.1 (C(15) or C(16)), 25.8 (C(9)), 25.1 (C(10)), 22.1 (C(12)), 20.7 (C(8)), 18.9 (C(15) or C(16)); IR (neat from CH_2Cl_2 solution, salt plates) 2925 (s), 2869 (m), 1755 (s), 1748 (s), 1674 (w), 1440 (m), 1377 (w), 1274 (w), 1226 (m), 1199 (m), 1180 (m), 1141 (w), 1058 (w), 1038 (w), 995 (w), 971 (m), 907 (w); MS (EI, 70 eV) 321 (3), 291 (8), 262 (16), 237 (21), 205 (16), 203 (57), 178 (18), 175 (22), 161 (10), 150 (13), 149 (13), 148 (25), 147 (59), 145 (16), 135 (27), 134 (16), 133 (66), 131 (16), 121 (36), 119 (17), 109 (19), 107 (24), 105 (21), 100 (10), 95 (31); HRMS (ESI) calcd for $C_{18}H_{27}NO_4Na$ 344.1838, found 344.1850; TLC R_f 0.21 (hexanes/EtOAc 3/1) [silica gel, I_2, CAM]. Anal. Calcd for $C_{17}H_{25}NO_5$ (323.38): C, 67.26; H, 8.47; N, 4.36. Found: C, 67.54; H, 8.55; N, 4.42.

***rel*-(1*S*,2*S*,4*R*,6*S*,6a*R*,10a*S*,10b*R*)-1,6a-Ethano-2,6-dihydroxydecahydropyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (10).** A pea-sized amount of Raney nickel was washed with water (3 × 20 mL) and methanol (3 × 20 mL). The suspension of the washed catalyst in methanol (50 mL) was transferred via pipet into a 100-mL, one-neck, round-bottom flask equipped with a stir bar and charged with **40** (390 mg, 1.32 mmol). The flask was attached to a glass hydrogen line, cooled in an ice bath (0 °C, external temperature), evacuated, and flushed with hydrogen five times, and the mixture was stirred vigorously under 1 atm of hydrogen for 15 h with warming to rt. Sodium methoxide (230 mg, 4.25 mmol, 3.2 equiv) was added, and the mixture was stirred under nitrogen for 50 min. After acidification with acetic acid (0.3 mL, 5.0 mmol, 3.8 equiv), the reaction mixture was diluted with MTBE (50 mL), filtered through Celite, concentrated in vacuo, and dried by azeotropic distillation with benzene in vacuo at rt to provide a white solid. This residue was purified by chromatography (silica gel; EtOAc/methanol, gradient, 20/1−10/1) to afford **10** (310 mg, 1.24 mmol, 93%) as a light yellow solid. Additional purification by crystallization from toluene/hexanes provided **10** (251 mg, 1.00 mmol, 76%) as a white crystalline material (fine needles). Data for **10**: mp 183−184 °C (toluene/hexanes); ^{1}H NMR (400 MHz, CD_3OD) 4.87 (s, 2 H, OH), 4.46 (dd, J = 4.2, 0.7, 1 H, HC(2)), 4.13 (dd, J = 13.4, 7.3, 1 H, *H*HC(5)), 3.60 (dd, J = 9.3, 7.6, 1 H, HC(6)), 3.52 (t, J = 3.8, 1 H, HC(10b)), 2.77 (ddd, J = 13.8, 9.3, 0.8, 1 H, H*H*C(5)), 2.43−2.50 (m, 1 H, HC(1)), 1.95−2.02 (m, 1 H, HC(10a)), 1.90 (ddd, J = 14.4, 10.3, 6.1, 1 H, H*H*C(12)), 1.77−1.85 (m, 1 H, H*H*C(8)), 1.56−1.70 (m, 3 H, *H*HC(7), *H*HC(9), and *H*HC(11)), 1.36−1.56 (m, 4 H, H_2C(10), H*H*C(9) and H*H*C(11)), *H*HC(7)), 1.22−1.34 (m, 2 H, H*H*C(7) and H*H*C(8)), 1.02 (dt, J = 14.4, 5.9, 1 H, H*H*C(12)); ^{13}C NMR (101 MHz, $CDCl_3$) 173.9 (C(3)), 75.4 (C(2)), 73.1 (C(6)), 56.9 (C(10b)), 43.4 (C(5)), 40.7 (C(1)), 36.1 (C(6a)), 34.1 (C(10a)), 33.0 (C(7)), 29.7 (C(12)), 26.6 (C(8)), 24.9 (C(10)), 22.4

(C(9)), 17.4 (C(11)); IR (neat from methanol/CH_2Cl_2 solution, salt plates) 3363 (s, br), 2933 (s), 2864 (s), 1685 (s), 1458 (m), 1328 (w), 1288 (w), 1237 (w), 1215 (w), 1194 (w), 1114 (w), 1063 (w), 1025 (w); MS (EI, 70 eV) 252 (10), 251 (25), 224 (15), 223 (100), 222 (33), 209 (10), 208 (12), 206 (23), 205 (56), 204 (42), 194 (12), 192 (17), 190 (12), 176 (12), 175 (18), 163 (10), 149 (12), 148 (13), 147 (19), 145 (13), 136 (20), 135 (97), 134 (20), 133 (28), 131 (12); HRMS (ESI) calcd for $C_{14}H_{22}NO_3$ 252.1600, found 252.1598; TLC R_f 0.28 (EtOAc/methanol 9/1) [silica gel, I_2, CAM]. Anal. Calcd for $C_{14}H_{21}NO_3$ (251.32): C, 66.91; H, 8.42; N, 5.57. Found: C, 66.84; H, 8.54; N, 5.65.

***rel*-(1*S*,6*S*,6a*R*,10a*S*,10b*R*)-1,6a-Ethano-2-methyldodecahydropyrrolo[2,1-*a*]isoquinolin-6-ol (50a) and *rel*-(1*S*,6*S*,6a*R*,10a*S*,10b*R*)-1,6a-Ethano-2-methyldodecahydropyrrolo[2,1-*a*]isoquinolin-6-ol Borane Adduct (51).** In a 100-mL, one-neck, round-bottom flask equipped with a stir bar were placed **49** (74 mg, 0.32 mmol), methanol (3.0 mL), and platinum on carbon (5% w/w, 20 mg). The flask was attached to a glass hydrogen line and then was evacuated and flushed with hydrogen five times. The mixture was stirred vigorously under 1 atm of hydrogen for 13.5 h, diluted with MTBE (20 mL), filtered through Celite, and concentrated in vacuo. The residue was purified by chromatography (silica gel; dichloromethane/methanol/ammonium hydroxide, gradient, 10/1.5/0.2−10/2/0.4) to afford **50a** as a colorless glassy solid (53 mg, 0.23 mmol, 72%). To purify the material further, 47 mg (0.20 mmol, 1.0 equiv) of **50a** was placed into a 10-mL, one-neck, round-bottom flask equipped with a nitrogen inlet and a stir bar. THF (1.0 mL) was added, the solution was cooled −62 °C (external temperature), and BH_3 (1.0 M solution in THF, 0.60 mL, 0.6 mmol, 3.0 equiv) was added via syringe. After 20 min at −62 °C, the reaction mixture was quenched with 2 mL of satd aq solution of $NaHCO_3$, warmed to rt, extracted with dichloromethane (3 × 5 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography (silica gel; hexanes/EtOAc, gradient, 4/1−2/1) to afford **51** as a colorless oily material (29 mg, 0.12 mmol, 60%). Crystallization from heptane and then hexanes provided **51** (26 mg, 0.10 mmol, 50%) as a white crystalline solid. Data for **50a**: ^{1}H NMR (400 MHz, $CDCl_3$) 5. 43 (s br, 1 H, OH), 3.40−3.48 (m, 2 H, HC(6) and *H*HC(5)), 3.37 (dd, J = 11.1, 9.4, 1 H, *H*HC(3)), 2.68 (t, J = 2.9, 1 H, HC(10b)), 2.58 (t, J = 13.7, 1 H, *H*HC(5)), 2.14−2.28 (m, 2 H, HC(2) and H*H*C(3)), 1.90−1.99 (m, 1 H, HC(1)), 1.68−1.81 (m, 3 H, *H*HC(7), HHC(8) and *H*HC(12)), 1.45−1.58 (m, 4 H, *H*HC(9), HC(10a), *H*HC(11) and H*H*C(12)), 1.32−1.45 (m, 4 H, H*H*C(9), H_2C(10) and H*H*C(11)), 1.12−1.26 (m, 1 H, H*H*C(8)), 0.99 (d, J = 6.8, 3 H, H_3C(13)), 0.93 (td, J = 13.1, 4.8, 1 H, H*H*C(7)); ^{13}C NMR (101 MHz, $CDCl_3$) 77.2 (C(6)), 64.9 (C(10b)), 62.8 (C(3)), 62.5 (C(5)), 38.5 (C(10a)), 38.3 (C(2)), 36.2 (C(1)), 35.4 (C(7)), 34.8 (C(6a)), 26.2 (C(8)), 25.5 (C(10)), 21.5 (C(9)), 21.2 (C(11)), 20.6 (C(12)), 14.5 (C(13)); MS (EI, 70 eV) 235 (15), 207 (21), 206 (16), 192 (10), 111 (12), 110 (100), 96 (34); HRMS (ESI) calcd for $C_{15}H_{26}NO$: 236.2014, found 236.2007; TLC R_f 0.14 (CH_2Cl_2/methanol/ammonium hydroxide = 10/2/0.5) [silica gel, I_2, CAM]. Data for **51**: mp 91−92 °C (hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) 3.81 (ddd, J = 10.5, 7.2, 0.9, 1 H, HC(6)), 3.65 (dd, J = 12.9, 10.7, 1 H, *H*HC(3)), 3.49 (dd, J = 12.7, 7.1, 1 H, *H*HC(5)), 2.98 (dd, J = 4.5, 3.2, 1 H, HC(10b)), 2.81 (t, J = 11.8, 1 H, H*H*C(5)), 2.71 (dd, J = 12.9, 7.7, 1 H, H*H*C(3)), 2.45−2.55 (m, 1 H, HC(2)), 2.17−2.25 (m, 1 H, HC(1)), 2.10 (dt, J = 11.9, 3.5, 1 H, HC(10a)), 1.55−1.90 (m, 10 H), 1.25−1.5 (m, 5 H), 1.06 (td, J = 13.0, 4.5, 1 H), 1.02 (d, J = 6.9, 3 H, H_3C(13)); ^{13}C NMR (126 MHz, $CDCl_3$) 75.3 (C(6)), 73.6 (C(3)), 72.0 (C(10b), 65.8 (C(5)), 35.6 (C(1)), 35.0 (C(7)), 34.9 (C(2)), 34.8 (C(10a)), 34.7 (C(6a)), 25.9, 25.1, 21.3, 20.4, 20.0, 4.2 (C(13)); IR (neat from dichloromethane) 3438 (w, br), 2925 (s), 2858 (m), 2370 (s), 2318 (s), 2270 (m), 1494 (w), 1463 (w), 1458 (w), 1447 (w), 1380 (w), 1231 (w), 1164 (s), 1084 (w), 1046 (w), 1025 (s), 956 (m), 939 (w), 867 (w), 831 (w); MS (EI, 70 eV) 249 (17), 248 (92), 247 (32), 246 (44), 245 (12), 235 (33), 234 (100), 232 (11), 217 (13), 207 (15), 110 (23), 108 (12), 107 (11), 105 (11), 96 (11), 95 (13); HRMS (ESI) calcd for $C_{15}H_{27}NOB$ 248.2186, found 248.2189; TLC R_f 0.18 (hexanes/EtOAc, 3/1) [silica gel, I_2, CAM]. Anal. Calcd for $C_{15}H_{28}BNO$ (249.20): C, 72.30; H, 11.33; N, 5.62. Found: C, 72.49; H, 11.41; N, 5.77.

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

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