Synthesis of (+)-1-Epiaustraline

Scott E. Denmark* and Jeromy J. Cottell

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

denmark@scs.uiuc.edu

Received February 7, 2001

A highly efficient total synthesis of (+)-1-epiaustraline ((+)-**1**), a tetrahydroxypyrrolizidine alkaloid of the alexine/australine subclass, is described. The key step is a tandem intramolecular [4 + 2]/intermolecular [3 + 2] nitroalkene cycloaddition involving dienylsilyloxy nitroalkene **3** and chiral vinyl ether **4**, which establishes four of the five stereocenters present. The final center was installed by a diastereoselective dihydroxylation. Hydrogenolytic unmasking of the nitroso acetal tosylate **17** containing the silyl ether linkage was thwarted by a slow alkylation and an undesired Peterson-type elimination. Prior removal of the silicon moiety by Tamao−Fleming oxidation proceeded in excellent yield and provided a substrate suitable for hydrogenolysis and deprotection. The complete synthesis required only 10 steps to deliver the (+)-1-epiaustraline in 7.0% overall yield.

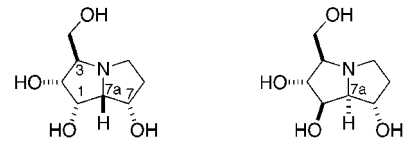
Introduction

1-Epiaustraline (1,7a-diepialexine, **1**) is one of several alkaloids produced by the plant *Castanospermum Australae* (commonly known as the Moreton Bay Chestnut). Its isolation and structural elucidation, accomplished independently in the laboratories of Fleet[1] and Harris,[2] proved **1** to be an epimer of the alkaloid alexine (**2**). Alexine-type alkaloids differ from the more common pyrrolizidines of the necine family by the position of the substituents on the pyrrolizidine ring. Whereas alexines possess a hydroxymethyl group at the C(3) position, the necines bear this substituent at the C(1) position of the pyrrolizidine and usually also contain an acidic ansa side chain (Chart 1).

As with other alexine alkaloids, 1-epiaustraline is an inhibitor of several glycosidases. The highest inhibition with **1** was observed against the α-glucosidase amyloglucosidase (50% inhibition at 2.6×10^{-5} M) and yeast α-glucosidase (50% inhibition at 2.7×10^{-4} M), while lower inhibition was obtained with mammalian digestive glycosidases.[1,2] The mode of inhibition is believed to arise from the highly oxygenated structure and the ability of the protonated pyrrolizidine to bind as a transition state analogue.[3] Sugar-mimic alkaloids have been investigated as both anti-cancer and anti-viral treatments due to their glycosidase inhibition properties.

Although there has been considerable interest in the synthesis of alexine alkaloids,[4] there are only two reported syntheses of 1-epiaustraline, accomplished by the laboratories of Fleet[5] and Ikota.[6] The synthesis by Fleet involves the elaboration of a mannose derivative in 14 steps and 7.2% overall yield. During the course of the synthesis, all of the stereocenters of mannose are utilized to provide 1-epiaustraline. In the Ikota synthesis, 1-epiaustraline is synthesized from a glutamine derivative in 15 steps and 4.7% overall yield. The resident stereocenter of gluatamine controls the installation of the remaining stereocenters in the target. For our purposes, a de novo synthesis of 1-epiaustraline provided an opportunity to further develop the tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition and its application to pyrrolizidine alkaloids.

Chart 1



Background

Recent publications from these laboratories have amply demonstrated the power of the tandem [4 + 2]/[3 + 2] nitroalkene cycloadditions for the construction of densely functionalized of nitroso acetals with high levels of stereocontrol (Scheme 1).[7] Subsequent reductive cleavage, in the presence of an ester at the C(2) position of the nitroso acetal, then results in the cyclization of the in situ generated amine to form pyrrolizidinone-type compounds. This approach has been successfully employed in the synthesis of several necine bases, including rosmarinecine,[8] playtnecine,[9] crotanecine,[10] and hastanecine.[11]

(1) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Girdhar, A.; Ramsden, L. E.; Peach, J. M.; Hegarty, M. P.; Scofield, A. M. *Phytochemistry* **1990**, *29*, 111.

(2) Harris, C. M.; Harris, T. M.; Molyneux, R. J.; Tropea, J. E.; Elbein, A. D. *Tetrahedron Lett.* **1989**, *30*, 5685.

(3) (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet. G. W. J. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1645. (b) Fellows, L. E.; Nash, R. J. *Sci. Prog.* **1990**, *74*, 245. (c) Winkler, D. A.; Holan, G. *J. Med. Chem.* **1989**, *32*, 2084. (d) Kajimoto, T.; Liu, K. K.-C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, J. A. Jr.; Wong, C. H. *J. Am. Chem. Soc.* **1991**, *113*, 6187.

(4) (a) Liddell, J. R. *Nat. Prod. Rep.* **1999**, *16*, 499. (b) Casiraghi, G.; Zanardi, F.; Rassu, G.; Pinna, L. *Org. Prep. Proced. Int.* **1996**, *28*, 641.

(5) Choi, S.; Bruce, I.; Fairbanks, A. J.; Fleet, G. W. J.; Jones, A. H.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1991**, *32*, 5517.

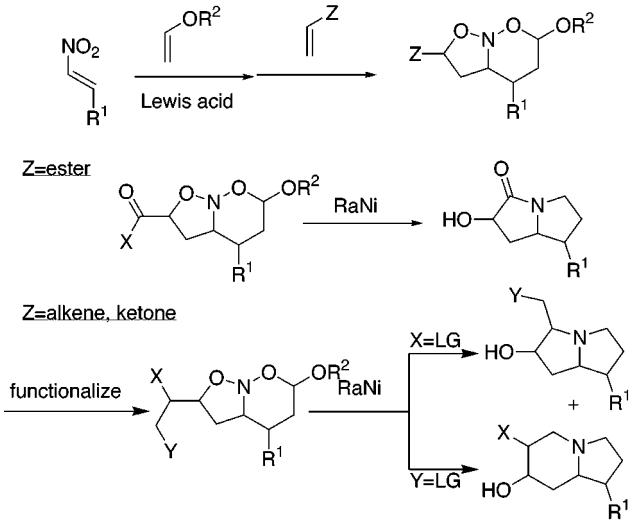
(6) Ikota, N. *Tetrahedron Lett.* **1992**, *33*, 2553.

(7) For a review on the [4 + 2]/[3 + 2] tandem cycloaddition, see: Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.

(8) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266.

10.1021/jo0101510 CCC: $20.00
Published on Web 05/12/2001

Scheme 1



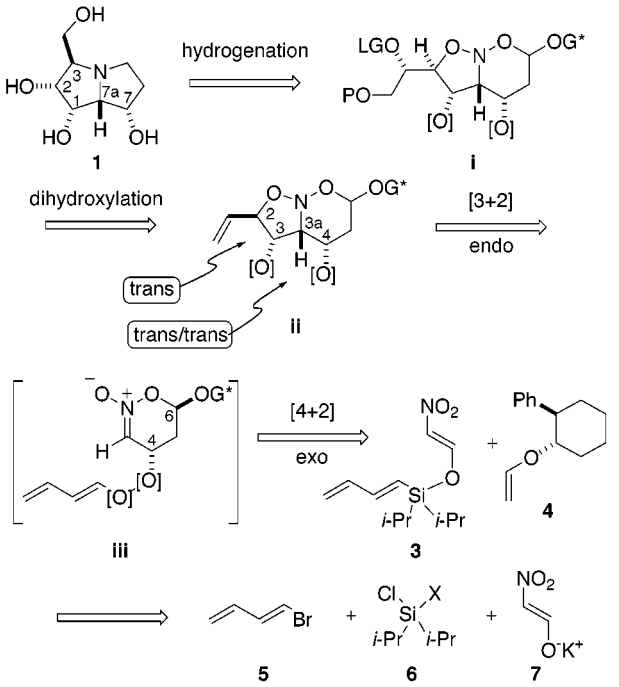
Apart from the hydrogenolytic cleavage of the nitroso acetal system, the chemistry of this functional group has not been intensively investigated.[12] As part of total synthesis endeavors in these laboratories, nitroso acetals have shown compatibility with common chemical transformations, including oxidations, reductions, and sulfonylations. These manipulations have allowed access to additional alkaloid structures by the installation of an internal alkylating agent after the tandem cycloaddition. Thus, during the reductive cleavage of the nitroso acetal, the cyclization can proceed through an alkylation event, instead of an acylation. This process was a critical part of the strategy that lead to the successful syntheses of the indolizidine castanospermine[13] and the pyrrolizidines australine[13] and casuarine.[14]

Synthetic Design

The highly oxygenated pyrrolizidine structure of 1-epiaustraline provides the main challenge to its synthesis. Specifically, this involves the stereocontrolled installation of hydroxyl groups at four of the eight carbons of the alkaloid. This necessitates the use of appropriately oxygenated components in the tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition. This approach is outlined in Scheme 2.

We envisioned the construction of the pyrrolizidine core by alkylation during the reductive cleavage of the nitroso acetal **i.** To incorporate the hydroxymethyl substituent at the C(3) position of **1**, the installation of the leaving group for the alkylation at C(3) in the appropriate configuration was required. Because this center is not created as part of the tandem cycloaddition, we needed to make use of either resident stereodirecting functions in the nitroso acetal, asymmetric reagents, or both. The chemical process chosen to introduce the center and the requisite functional group was the dihydroxylation of a

Scheme 2



terminal alkene in **ii**, followed by a selective protection and activation of the hydroxyl groups to give **i**. All of these transformations have been carried out successfully and selectively on nitroso acetals in previous syntheses.[13]

Our understanding of the tandem [4 + 2]/[3 + 2] cycloaddition provides for good predictability in the stereochemical course of the process. Examination of the nitroso acetal **ii** allows for a straightforward retrosynthetic analysis that thus identifies the requisite coupling partners. First, the trans relationship between the substituents at C(2) and C(3) of **ii** necessitates the use of a trans dipolarophile for the [3 + 2] cycloaddition. However, to create the cis/cis relationship between the hydrogens on C(3), C(3a), and C(4), the dipolarophile must approach the nitronate in an endo mode with respect to the C(3) substituent and from the same side as the C(4) substituent. Previous experience has taught us that the use of a tether between the nitronate and the dipolarophile will not only control the facial selectivity, but can also influence the mode of approach of the dipolarophile.[15] Specifically, when a two-atom linker is used, only the endo approach of the dipolarophile is observed, whereas with longer tethers, an exo approach becomes preferred. For the synthesis of 1-epiaustraline, a two-atom tether is needed to provide the proper relative configuration; however, both atoms of the tether must be converted to hydroxyl substituents in the final product. By using a silicon−oxygen tether, the two hydroxyls can be revealed at a late stage of the synthesis by the agency of a Tamao−Fleming oxidation.[16]

Under the direction of the tether, the facial approach of the dipolarophile is then dependent on the configuration of the C(4) substituent of the nitronate **iii**, which is set during the [4 + 2] cycloaddition. This requires the use of a chiral vinyl ether dienophile that will approach

(9) Denmark, S. E.; Parker, D. L.; Dixon, J. A. *J. Org. Chem.* **1997**, *62*, 435.
(10) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672.
(11) Denmark, S. E.; Throarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125.
(12) For a recent review, see: Rudchenko, V. F. *Chem. Rev.* **1993**, *93*, 725.
(13) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046.
(14) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875.
(15) Denmark, S. E.; Moon, Y.-C.; Senanayake, C. B. W. *J. Am. Chem. Soc.* **1990**, *112*, 311.
(16) For a recent review see: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.

the *Re* face of the *β*-oxygenated nitroalkene to establish the correct configuration. This can be accomplished in either exo or endo mode [4 + 2] cycloadditions with the appropriate configuration of auxiliary because the stereocenter at C(6) of the nitroso acetal is destroyed during the reductive cleavage of **i**. However, the configuration of this acetal does influence the approach of the dipolarophile during the [3 + 2] cycloaddition favoring reaction on the face opposite to that of the C(6) substituent.[17] This preference can even manifest itself when the dipolarophile is tethered to the nitronate.[13] In view of these facts, we opted to set the *R* configuration at the C(6) center of **iii** by an exo approach of the dienophile. Our previous investigations have clearly established a strong preference for the exo approach of the dienophile when MAPh (methylaluminum bis(2,6-diphenylphenoxide)) is used as the Lewis acid. The absolute configuration of the nitronate is dependent on the choice of the chiral vinyl ether **4** used as the dienophile. The vinyl ether derived from *trans*-phenylcyclohexanol is known to afford synthetically useful diastereoselectivities in combination with MAPh,[18] such that the resulting nitronate bears a 1,3-*ul* relationship.[19] Therefore, the use of (1*S*,2*R*)-phenylcyclohexanol is necessary to provide the correct absolute configuration.

The main component in the tandem inter[4 + 2]/intra-[3 + 2] cycloaddition is the nitroalkene **3**, Scheme 2. The synthesis of this nitroalkene was envisioned to follow from the addition of potassium nitroacetaldehyde to a butadienylsilyl chloride, thereby creating the tether. The silyl chloride could in turn be made from addition of a metallobutadiene to a dichlorosilane, e.g., **6**. Selection of the spectator groups on the silicon tether is important as they will influence both the reactivity of the dichlorosilane toward the metallobutadiene and the stability of the nitroalkene.

The key question raised by this strategy is the ability of the nitroso acetal to undergo clean reductive hydrogenation to a pyrrolidine that can then suffer intramolecular alkylation when constrained by the two atom tether. In two previous syntheses,[8,20] the conformational restraint imposed by the two atom tether has led to problems in the hydrogenolysis of the particular nitroso acetals (vide infra). In both of these cases, the pyrrolizidine systems were to be formed by acylation of the intermediate pyrrolidine. The proposed synthesis of 1-epiaustraline involves an alkylative cyclization for the closure that in our experience is generally slower than acylation. Thus, cognizant of a serious potential pitfall, we nonetheless embarked on the synthesis of 1-epiaustraline. As detailed below, these concerns were justified and necessitated a revision of the synthetic strategy that not only delivered the target compound but also expanded our understanding of the chemistry of nitroso acetals.

(17) Denmark, S. E.; Seierstad, M.; Herbert, B. *J. Org. Chem.* **1999**, *64*, 884.

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

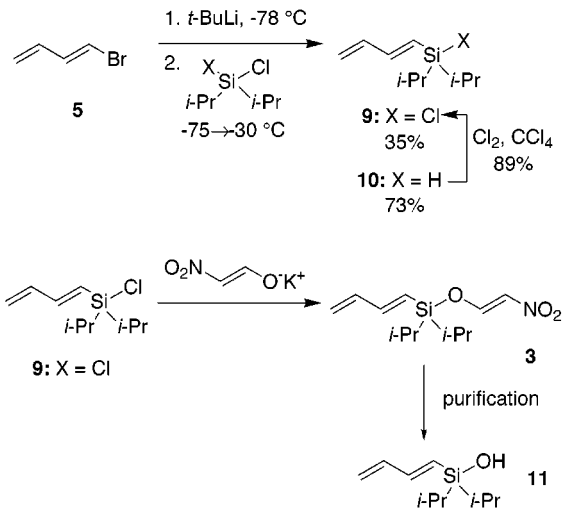
(19) This terminology refers to the relationship between the configuration of C(1) of the auxiliary and the configuration of C(6) of the resulting nitroso acetal. In this case, the auxiliary possessing an *R* configuration will typically give a product with an *S* configuration at the acetal center. Hence, this is designated an 1,3-*unlike* (*ul*) relationship.[18]

(20) Denmark, S. E.; Hurd, A. R.; Sacha. H. *J. Org. Chem.* **1997**, *62*, 1668.

Results

Preparation of Nitroalkene 3. 1-Lithiobutadiene was generated from 1-bromobutadiene (**5**) by the bromine−lithium exchange with *tert*-butyllithium in Et_2O at −75 °C. The choice of silicon electrophile was guided by the need for a sufficiently reactive group that would also be stable enough for handling and isolation. Orienting studies showed that the use of *tert*-butyl groups prevented the reaction between the dichlorosilane and 1-lithiobutadiene.[21] On the other hand, reaction of 1-lithiobutadiene with dimethyldichlorosilane provided a product very labile to hydrolysis. Ultimately, we found that isopropyl groups provided the best balance between reactivity and stability. Initial attempts at the silylation of 1-lithiobutadiene with dichlorodiisopropylsilane were plagued by low yields and oligomeric byproducts. At best, a 35% yield of the desired chlorosilane was obtained (Scheme 3). We surmised that **9** may not be stable under the reaction conditions, leading to the polymerization. Analogous silylation of vinyllithium showed consistently higher yields for monochlorosilanes over their dichloro counterparts.[22] Accordingly, the addition of 1-lithiobutadiene to chlorodiisopropylsilane proceeded in a gratifying 73% yield to provide **10** under similar conditions.

Scheme 3



The use of chlorodiisopropylsilane obviated the problem of selective C−Si bond formation, but delivered a silyldiene **10** devoid of a leaving group necessary for the construction of the nitroalkene. This was easily remedied by smooth oxidation of the silicon unit with a solution of chlorine in CCl_4 to afford the chlorosilane **9** in 89% yield. Interestingly, the chlorination takes place cleanly at the silicon center in preference to the diene. However, the use of excess chlorine or extended reaction times did lead to over-chlorination and the addition of HCl to the diene.

With the silicon center suitably activated, the formation of the Si−O linkage proceeded readily upon admixture of **9** with a slurry of the potassium salt of nitroacetadehyde (**7**) at 0 °C, over the course of 5 h. Although the nitroalkene **3** could be identified by ^1H NMR spectroscopy, the product was not amenable to purification by either chromatography or distillation (affording the

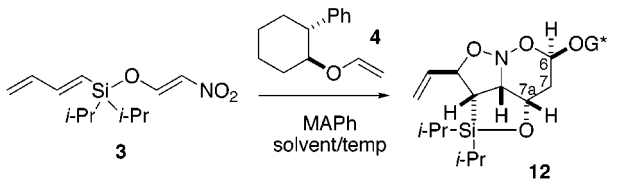
(21) Gregory Morris is thanked for early investigations into the synthesis of nitroalkene **3**.

(22) Auner, N. *Z. Anorg. Allg. Chem.* **1988**, *558*, 87.

dienylsilanol **11**) and was therefore used directly in the tandem cycloaddition.

Tandem Cycloaddition. With the desired nitroalkene **3** in hand, the tandem cycloaddition with the chiral vinyl ether **4** was investigated. In the presence of MAPh in toluene solvent, the cycloaddition proceeded over 14 h with gradual warming from −70 to 0 °C, to provide a 60% yield of a single cycloadduct (entry 1, Table 1). Optimization involved changes in solvent and temperature, as well as the stoichiometry of the Lewis acid and vinyl ether. The use of methylene chloride (an alternative solvent for MAPh-promoted cycloadditions) under the same conditions led to a decreased yield of the cycloadduct (Table 1, entry 2). To increase the rate of reaction, changes in the reaction temperature were investigated. Interestingly, by raising the temperature of the reaction, the yields again decreased. The only beneficial change in the reaction profile was to maintain the temperature at −75 °C over the course of 14 h, which provided a 66% yield of the cycloadduct (Table 1, entry 5).

Table 1. Optimization of Cycloaddition of 3 and 4



entry	**4** (equiv)	MAPh (equiv)	solvent	*T*, °C	yield, %[a]
1	2	2	toluene	−70 → 0	60
2	2	2	CH_2Cl_2	−70 → 0	40
3	2	2	toluene	−55	53
4	2	2	toluene	−70 → 22	55
5	2	2	toluene	−70	66
6	3	3	toluene	−70	33
7	1.25	2	toluene	−70	47
8	1.25	1.5	toluene	−70	16
9	1.5	1.5	toluene	−70	41
10	2	2	toluene	−70	49[b]

[a] Yield for two steps. [b] Preparative scale.

The initial stoichiometry (2 equiv of **4** and 2 equiv of MAPh per nitroalkene) was chosen from previous experience with related tandem cycloadditions.[20] Decreasing the relative amounts of Lewis acid and vinyl ether were investigated to increase the ease of workup for the cycloaddition. However, lowering the amount of either the Lewis acid or the chiral vinyl ether was detrimental (Table 1, entries 7−9). Lower yields were also obtained when the amount of the Lewis acid was increased (Table 1, entry 6). Unfortunately, increasing the scale of the cycloaddition also lead to lower yields due to complications associated with chromatographic purification (cf. Table 1, entries 5 and 10).

The structure of cycloadduct **12** was assured by complete spectroscopic characterization. The full stereostructure, assumed by analogy to related systems,[20] was ultimately established by single-crystal X-ray analysis of an advanced intermediate (vide infra). The presence of three vinyl signals, and the absence of dienyl internal proton signals, indicated that the [3 + 2] cycloaddition had taken place spontaneously before purification. The relative configuration of the cycloadduct was tentatively assigned to be that of **12** by comparison of the ^{1}H NMR coupling values of the acetal proton (HC(6)) and the proton at C(7a) with those at C(7). Because of the tricyclic structure of the nitroso acetal, the six-membered ring is expected to adopt a ground-state boat conformation.[23] In **12**, the signal for (HC(6)) appeared as a triplet with a coupling value of 7.3 Hz, which suggested that the auxiliary is in an pseudoaxial position, by analogy to previously studied nitroso acetals.[13,20] The signal for HC-(7a) showed very small couplings to the protons at C(7) (3.6, 2.2 Hz). Therefore, HC(7a) must be gauche to the two protons of C(7), which may be accomplished by positioning the oxygen substituent at C(7a) in a pseudoequatorial position.

Elaboration of Nitroso Acetal 12. The next stage of the synthetic plan required the functionalization of the pendant alkene to provide for the formation of the pyrrolizidine and creation of the C(3) hydroxymethyl group. Initial attempts at the diastereoselective dihydroxylation of **12** with $K_2OsO_4{\cdot}2H_2O$ and $K_3Fe(CN)_6$ proceeded slowly to give a 3/1 mixture of diols (Scheme 4). The major isomer (**13a**) was assigned the *R* configuration on the basis of related precedent in these laboratories[13] and others[24] for the dihydroxylations of terminal olefins bearing allylic heteroatoms. This assignment was later confirmed by X-ray analysis of an advanced intermediate, **17**.

Table 2. Selectivities in the Catalyzed Dihydroxylation of 12

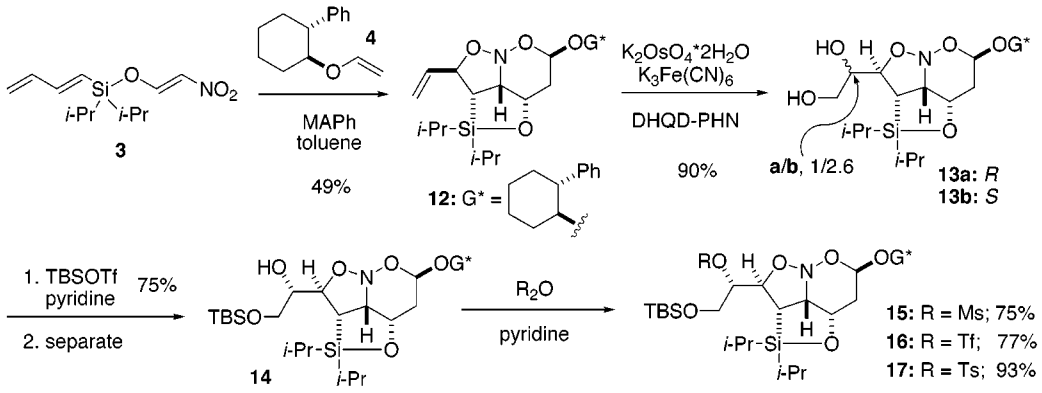
entry	ligand	selectivity **13a**/**13b**
1	none	3/1
2	$(DHQD)_2PHAL$	4.3/1
3	$(DHQD)_2AQN$	2.2/1
4	$(DHQD)_2PYR$	1.9/1
5	DHQD-MEQ	1/1
6	DHQD-IND	1/2.6
7	DHQD-PHN	1/2.8
8	DHQD-PHN	1/2.6[a]
9	DHQ-CLB	2.7/1
10	$(DHQ)_2PYR$	4.1/1
11	$(DHQ)_2PHAL$	1.8/1

[a] Preparative scale.

Clearly, a 3/1 ratio favoring the undesired isomer is not satisfactory. To reverse this selectivity and produce the desired diol in synthetically useful amounts, we made recourse to the asymmetric dihydroxylation reaction.[25] This strategy had been successfully implemented in the previous synthesis of australine and 3-epiaustraline in these laboratories.[13] On the basis of the general mnemonic developed by Sharpless for the asymmetric dihydroxylation, the dihydroquinidine (DHQD) family of ligands were predicted to provide the diol in the desired *S* configuration (**13b**). Thus, a variety of DHQD-based ligands[26] were surveyed (Table 2). Unfortunately, most of the ligands exerted at best a modest influence on the selectivity of the reaction. Some of the DHQD ligands even enhanced the production of the undesired diastereomer. In view of this fact, several dihydroquinine (DHQ) ligands were investigated as well; however, they too provided little or no selectivity. The best ligand found was a DHQD ligand with an phenanthracene modifier.[27] This additive was able to reverse the selectivity, resulting in a 2.6/1 ratio favoring **13b**. The diols **13a** and **13b** could

(23) X-ray analysis of **17** subsequently bore this out.
(24) Cha, J. K.; Christ, W.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.
(25) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(26) Table 2 only contains a partial list of ligands employed. For the complete listing, refer to the Supporting Information.

Scheme 4

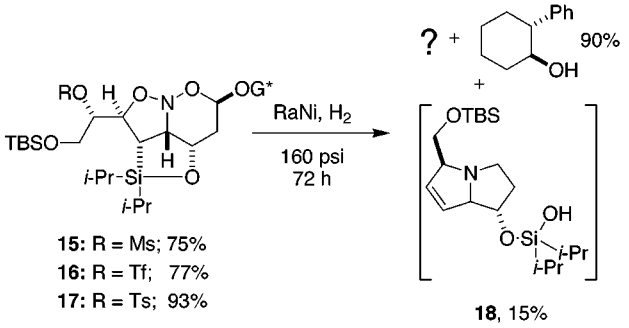


be separated via preparative MPLC; however, they were taken on as a mixture and separated at the next stage.

Selective protection of the primary hydroxyl group in **13** proceeded readily with TBSOTf in pyridine to provide the TBS ether (**14**) in 75% yield, along with a small amount of the bis TBS ether. The two diastereomers could be easily separated by silica gel column chromatography. Activation of the secondary alcohol was accomplished by the action of methanesulfonic anhydride in pyridine to provide the mesylate (**15**) in 80% yield.

Hydrogenolysis and Completion of the Synthesis. With the secondary center in **14** now suitably activated, the stage was set for the critical unmasking of the nitroso acetal to form the pyrrolizidine core structure. Initial hydrogenation of **15** was performed in the presence of activated Raney nickel (RaNi), under a hydrogen pressure of 160 psi in methanol at room temperature. Unfortunately, a complex mixture of products was obtained, from which only the chiral auxiliary could be isolated and identified, Scheme 5. This outcome was independent of the reaction time or hydrogen pressure; however, the yield of auxiliary ranged from moderate to high. This suggested that the N−O bonds were cleaved during the course of the reaction, but the cyclization was not proceeding as envisioned.

Scheme 5



The failure to obtain pyrrolizidine-derived products could be caused by several problems. First, the leaving group may not be compatible or active enough to effect the closure of the pyrrolizidine ring. Second, the ring closure may fail due to an inability to access a conformation appropriate for the displacement of the mesylate by the nitrogen, due to the presence of the two atom tether. Last, the cleavage of the N−O bonds reveals a β-hydroxy silicon unit. This provides the opportunity for a Peterson-type olefination[28] that would cleave the silyl tether, leaving an allylic mesylate.

To address the potential problems associated with the nucleofuge during the ring closure, several other leaving groups were investigated. The corresponding triflate (**16**) and tosylate (**17**) were made from their respective anhydrides in pyridine. Interestingly, the tosylate solidified after column chromatography. Recrystallization from MeOH provided X-ray-quality crystals that revealed that the absolute and relative configuration were assigned correctly.[29]

Hydrogenation of **16** in the presence of Raney nickel provided the same result as the mesylate, where no pyrrolizidine-containing products are observed, but the chiral auxiliary was recovered in good yield. However the hydrogenation of **17** behaved differently. In addition to the recovered chiral auxiliary, a second product was isolated in small amounts as well. The ^{1}H NMR spectrum of this product showed distinct olefinic peaks, and the structure was tentatively assigned as the pyrrolizidine **18**, Scheme 5. This suggested that the Peterson-type olefination process was interfering with the desired cyclization pathway.

To circumvent the problems observed during hydrogenation, it seemed prudent to cleave the silicon−oxygen linkage. Excision of this bond would help alleviate conformational restrictions that the tether may impose on the ring closure. This could then lead to a preference of the cyclization over the olefination pathway. By careful consideration of the overall strategy, an attractive alternative was identified that would introduce no additional steps. If we could perform the Tamao−Fleming oxidation on the nitroso acetal, then the strain arising from the Si−O linkage would be lost along with the possibility of Peterson olefination during hydrogenolysis. Although simple in concept, this idea presented unprecedented chemical compatibility challenges for the delicate nitroso acetal.

To avoid an elaborate protection scheme, the oxidation of the nitroso acetal would have to be performed with the leaving group already installed. Of the leaving groups previously utilized, it was believed that the tosylate had the best chance of surviving the oxidation conditions. The

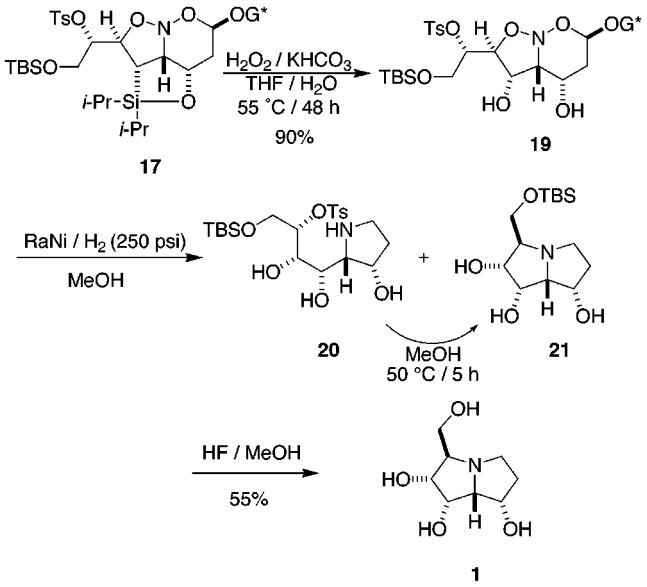
(27) The superiority of the PHN ligand for asymmetric dihydroxylation of vinyl groups bearing allylic oxygen substituents has been noted. Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 2095.

(28) Ager, D. J. *Org. React.* **1990**, *38*, 1.

(29) The crystallographic coordinates of **17** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. CCDC 157533.

tosylate **17** was therefore subjected to the normal Tamao–Fleming oxidation conditions of KF, H_2O_2, and $KHCO_3$ in a 1/1 MeOH/THF mixture. We were pleased to find that the silicon group was effectively removed while leaving the nitroso acetal intact. However, under these conditions the TBS groups was also removed, resulting in the formation of the terminal epoxide. Previous studies by Tamao have shown that the offending reagent, KF, is not, in fact, necessary to activate the silicon unit of an oxasilacyclopentane.[30] In practice, the oxidation of **17** could be successfully carried out in the absence of KF (with mild heating) and cleanly afforded the targeted diol without cleavage of the TBS group (Scheme 6). This transformation was somewhat capricious, which we ascribed to changes in concentration during the lengthy reaction times. However, attempts to maintain a constant concentration by carrying out the reaction in a sealed tube led to no improvement. Interestingly, in a normal round-bottom flask equipped with a condenser, the reaction proceeded smoothly over 48 h to provide **19** in a 90% yield. Attempts to accelerate the process at higher temperatures or with stronger bases led only to decomposition.

Scheme 6



The hydrogenation of **19** was performed in the presence of Raney nickel for 48 h under a pressure of 250 psi of hydrogen. With the silicon tether removed, the hydrogenation provided a mixture of the desired pyrrolizidine **17** and an intermediate pyrrolidine **16**. After filtration of the catalyst, the mixture was warmed to 50 °C in MeOH over 5 h to complete the conversion of **20** to **21**. Purification of **21** by silica gel chromatography provided the penultimate intermediate. Deprotection of **21** with HF/MeOH provided 1-epiaustraline in a 55% yield over the two steps. Comparison of the ^{1}H NMR data of **1** to those of an authentic sample of the natural product provided by Nash[31] were nearly superimposable, and all other spectroscopic and physical data matched those of either natural or synthetic material (see the Supporting Information). Interestingly, the optical rotation of our final product ($[\alpha]_D = 13.7$ ($c = 1.72$, H_2O) more closely matched the rotation for synthetic material ($[\alpha]_D = 13.3$ ($c = 0.1$, H_2O);[5] ($[\alpha]_D = 12.5$ ($c = 0.6$, H_2O)[6]) than the natural product (($[\alpha]_D = 8.5$ ($c = 0.41$, H_2O);[1] ($[\alpha]_D = 12.0$ ($c = 1.17$, H_2O)[2]).

Discussion

Tandem [4 + 2]/[3 + 2] Cycloaddition. Although not unexpected in view of our extensive experience with this reaction, it was nonetheless very satisfying that the tandem cycloaddition of **3** and **4** provided a single nitroso acetal (**12**) with the correct relative and absolute configuration. To produce this specific diastereomer, (1*S*,2*R*)-2-phenylcyclohexyl vinyl ether (**4**) most likely adopts a reactive *s-trans* conformation. This is in accordance with computational studies,[32] as well as previous experimental results.[18] In this conformation, the phenyl group shields the *Si* face of the vinyl ether, Figure 1. Therefore, the [4 + 2] cycloaddition will take place on the *Re* face of the vinyl ether. It is now well established that MAPh enforces an exo transition structure in these cycloadditions, which when combined with the *Re* face preference for the dienophile results in attack on the *Si* face of the nitroalkene, thus establishing the desired *S* absolute configuration at C(7).

After decomplexation of the nitronate upon the addition of MeOH, the intramolecular dipolar cycloaddition occurs spontaneously to yield the nitroso acetal **12**. The dipolarophile must approach from the same side to which it is tethered, thus controlling the facial selectivity of the [3 + 2] cycloaddition and therefrom the relative configuration of C(7) and C(1) in 1-epiaustraline. The use of a two atom tether also restricts the dipolarophile to approach in an endo mode (defined by the silicon substituent) as well as eliminates the regio-reversed cycloaddition. Therefore, the relative configuration of C(7) and C(7a) is also set by the dipolar cycloaddition.

The yield for the three steps in this sequence ((1) silyl chloride displacement, (2) [4 + 2] cycloaddition, and (3) [3 + 2] cycloaddition) was lower than expected. This can primarily be attributed to the lability of the nitroalkene **3**, which is believed to slowly decompose at a rate competitive with the cycloaddition.[33] Unfortunately, attempts to selectively increase the rate of the cycloaddition by increasing the reaction temperature did not lead to increased yields of **12**. Lower yields were also obtained when the reaction was conducted with less than 2 equiv of the Lewis acid or the chiral vinyl ether. Here, the rate of the tandem cycloaddition decreased, while the rate of decomposition of **3** remained constant, leading to yields of **12** as low as 16%. The pathway of decomposition can be envisioned as either attack by a nucleophile at the silicon unit or in a Michael-type addition on the nitro alkene portion, followed by elimination of the silanol. Water is a likely culprit in this decomposition; however, the silanol may be competent as well, and the process can be initiated by very small amounts of water. This would lead to oligomeric butadienylsilicon species that can be hydrolyzed during workup of the reaction.

(30) Tamao, K.; Ishido, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120.

(31) The sample of 1-epiaustraline provided by Nash was initially believed to be australine. Subsequent reassignment proved this material to be 1-epiaustraline.

(32) Liu, J.; Niwayama, S.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 1064.

(33) The observation of the silanol **11** in the ^{1}H NMR spectrum of the crude cycloadduct provides support for this contention.

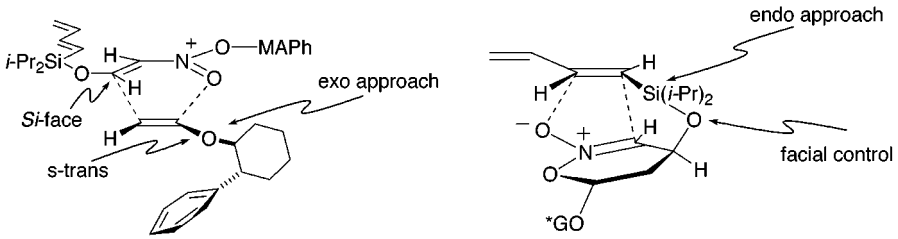


Figure 1. Proposed transition structures for the tandem cycloaddition.

Dihydroxylations. The diastereoselectivities observed in the simple dihydroxylation of **12** were disappointing, but not unexpected. In diastereoselective reactions of terminal alkenes bearing a heteroatom at an allylic position, the general preference is for the formation of the "erythro" isomer.[24] This was also observed in the dihydroxylation of a similar nitroso acetal in a previous study.[11] The diastereoselection was explained by reaction through the conformer in which the allylic proton was in the plane of the double bond, thus minimizing allylic strain. Approach of the oxidant is then directed to the face opposite to the heteroatom.

The weak influence of the tricyclic nitroso acetal on the asymmetric induction event can be rationalized by examining the calculated ground-state conformations of the cycloadduct. An MM2 conformational search provided eight conformations within 1 kcal/mol of the energy minimum and 120 conformations within 2 kcal/mol. The lowest eight conformations are overlaid in Figure 2. Though many of these conformations varied in the position of the isopropyl groups and the chiral auxiliary, there was a high degree of rotational freedom observed for the vinyl group. This suggests that many reactive conformations are available for the vinyl group during the dihydroxylation, and therefore, the core of the nitroso acetal will provide little bias.

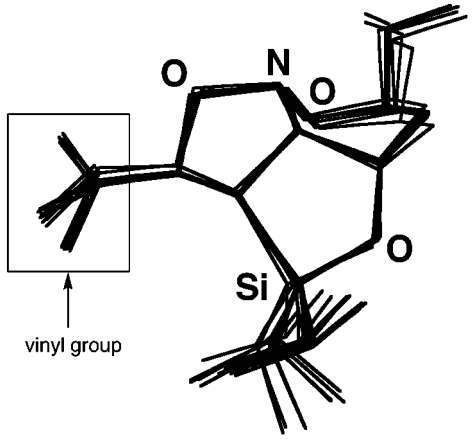
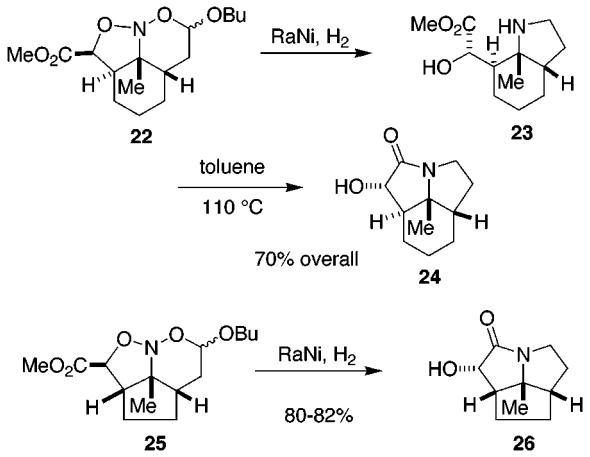


Figure 2. Overlay of the eight lowest minimum energy conformations calculated for 12.

The low selectivity observed in the presence of chiral ligands was again disappointing in light of our previous success,[13] but overall, not surprising. Terminal alkenes commonly afford the lowest selectivities in the asymmetric dihydroxylation reaction[25] and occasionally provide selectivities contrary to the sense predicted by the empirical model.[34] There is an interesting trend, however, in the selectivities with nitroso acetal **12**. In this case, the monomeric ligands consistently gave higher proportions of the desired diol **13b**. This suggests that the nitroso acetal may be unable to fit properly into the reactive pocket created by the OsO_4-complexed dimeric ligands.

Hydrogenations. The hydrogenolytic cleavage of nitroso acetals is a very powerful, albeit inadequately understood, transformation. This process allows for the conversion of the nitroso acetal to several azacyclic structures applicable to the synthesis of alkaloids. From the products, and in some cases the byproducts, it is assumed that this transformation proceeds through the amino alcohol generated upon N−O bond cleavage. Reductive amination of the hemiacetal and either acylation or alkylation then provide the observed bicyclic products. However, the timing of the each N−O bond cleavage and the subsequent cyclizations is not known. It is the believed that the dependence on hydrogen pressure observed in some cases is due to the availability of several different pathways. Not suprisingly, the hydrogenation of nitroso acetals has been found to be highly substrate dependent.

Scheme 7



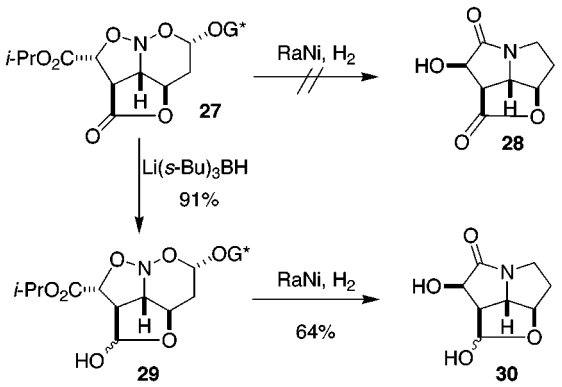
Although the hydrogenation of nitroso acetals generally proceeds smoothly to the desired product, this is not always the case, especially when the nitroso acetal is fused to another ring. This problem was first noticed in early studies of the hydrogenation of **22** in which the nitroso acetal is trans fused to six-membered carbocycle (Scheme 7).[15] Hydrogenation of the analogous nitroso acetal **25** (with a cis fusion to a five-membered ring) proceeded uneventfully at atmospheric pressure to the tricyclic lactam **26**. However, similar treatment of **22** left the oxazine ring intact. Elevated hydrogen pressures (160 psi) were necessary to cleave both N−O bonds to afford the intermediate **23**, where the acylation had not taken

(34) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. *J. Am. Chem. Soc.* **1997**, *119*, 311.

place. Conversion to the lactam required heating in refluxing toluene for 42 h. The difference in reactivity was attributed to the formation of a trans ring fusion in the case of the three-atom tether.

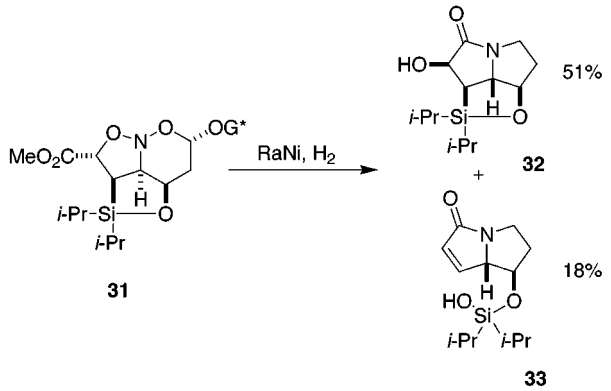
Other instances of problems during the hydrogenation step were encountered on route to the synthesis of rosmarinecine[11] and detoxinine.[20] In the case of rosmarinecine, hydrogenation of the cycloadduct **27** containing a fused lactone ring led to a complex mixture of products devoid of the desired tricyclic lactam **28** (Scheme 8). It was surmised that the conformational restriction imposed by the sp^2-hybridized carbon and short C−O bond lengths prevented the acylation process. This was alleviated by prior reduction of the carbonyl group to a hemiacetal. Hydrogenation of the less strained nitroso acetal **29** proceeded in 64% yield.

Scheme 8



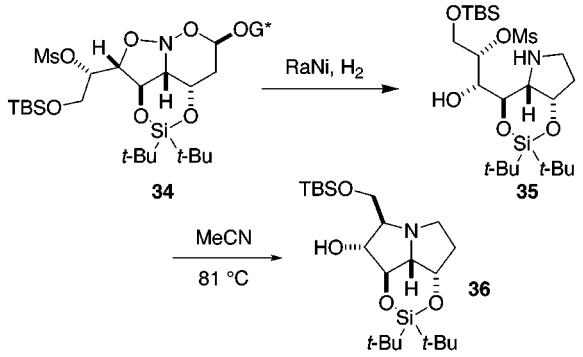
In the synthesis of detoxinine, hydrogenation of the intermediate **31** proceeded to give the desired lactam **32**, along with unsaturated side product **33** (Scheme 9). The ratio of **32** to **33** was found to be independent of changes in several reaction conditions. The byproduct **33** is believed to be a result of a Peterson-type olefination.[35] However by resubjecting the tricyclic lactam to the hydrogenation conditions, it was found that the olefination does not occur after lactam formation. Thus, the elimination must be a competing process during the hydrogenation. Here again, the fused ring (this time a siloxane) hampers the acylation event and provides an undesirable pathway of destruction.

Scheme 9

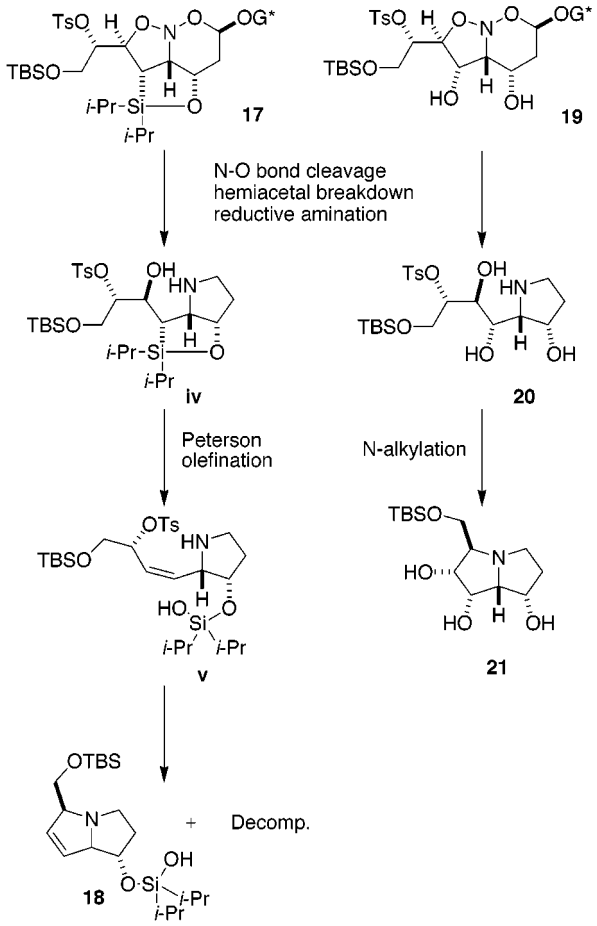


(35) A similar Peterson-type olefination has been observed upon hydrogenolysis of other silicon-bridged nitroso acetals. Righi, P.; Marotta, E.; Rosini, G. *Chem. Eur. J.* **1998**, *4*, 2501.

Scheme 10



Scheme 11



In all the cases discussed above, the final cyclization event is the formation of a lactam, whereas in the case at hand, the second ring closure requires an intramolecular alkylation. Typically, alkylations (especially with secondary centers) proceed more slowly than the corresponding acylations, as was observed in the synthesis of australine (Scheme 10).[13] Hydrogenation of the nitroso acetal **34**, in which a six-membered silyl acetal is embedded, provided the intermediate **35**. This intermediate did not access a secondary reaction pathway, and closure of the pyrrolizidine ring was effected upon heating in refluxing acetonitrile for 16 h.

The problems encountered during the synthesis of 1-epiaustraline described herein embody various aspects of the problems described in the foregoing examples (Scheme 11). In the hydrogenation of **17** (**15** or **16**), recovery of the chiral auxiliary indicated that the N−O

bonds of the nitroso acetal were being cleaved. The resulting amino aldehyde likely underwent intramolecular reductive amination to provide the intermediate **iv**; however, the alkylation did not proceed. Presumably, the amine cannot access a conformation favorable for the displacement of the leaving group due to the presence of the silicon−oxygen linkage. However, **iv** can access a secondary pathway where the alcohol formed from hydrogenolysis can engage in a Peterson olefination. The result is an allylic sulfonate that presumably proceeded on to unidentifiable products. By installing a better leaving group (triflate **15**), it was hoped that N-alkylation could occur in preference to elimination, but this was not the case. The use of a less active leaving group (tosylate **17**) allowed the intermediate allylic tosylate to survive long enough to proceed to the unsaturated pyrrolizidine **18**.

According to this analysis the silyl ether tether plays a dual role in thwarting the success of the hydrogenolysis. First, it conformationally restricts the tosylate from achieving a proper alignment for displacement and second, it provides an facile and deleterious shunt to undesired products. Thus, removal of the silicon was the ideal solution as it eliminated the germ of destruction and added no steps to the synthesis. The remarkably high-yielding Tamao−Fleming oxidation revealed the oxidative and hydrolytic stability of the nitroso acetal function and allowed for the synthesis to be completed.[36] Indeed, hydrogenolysis of **19** did provide the desired product **21** along with amino triol **20** thereby verifying that the intramolecular alkylation was slow even in the absence of the silicon tether. The sluggishness of the alkylation can be understood on the basis of the well-known rate retarding effects of electronegative β-substituents on S_N2 reactions.[37] It is also conceivable that intramolecular hydrogen bonding restricts access to conformations with a suitable alignment of the groups.

Conclusion

1-Epiaustraline was synthesized in 10 steps from 1-bromobutadiene in a 7.0% overall yield. This synthesis further demonstrates the applicability of the tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition to the synthesis of alkaloids. All but one of the stereocenters present in 1-epiaustraline are created in the tandem cycloaddition step, with very high stereocontrol. The remaining stereocenter is introduced via a diastereoselective dihydroxylation. The demonstration that the Tamao−Fleming oxidation can be done prior to the hydrogenation step further expands repertoire of transformations tolerated by nitroso acetals and allows for more flexible synthetic planning.

Acknowledgment. We are grateful to the National Institutes of Health (GM 30938) for generous financial support. J.J.C. thanks the Procter and Gamble Co. for a graduate fellowship. We are also grateful to Professor Robert Nash (Aberswyth) for providing a sample of natural 1-epiaustraline and to Dr. Esther Martinborough for the purification and characterization of this sample.

Supporting Information Available: Complete experimental details with full spectroscopic and analytical data for all new compounds along with comparison ^{1}H NMR spectra of synthetic and natural (+)-1-epiaustraline. A full listing of ligand structures and dihydroxylation selectivities is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0101510

(36) For a previous example of Tamao-Fleming type oxidation in the presence of a nitroso acetal see ref 35.

(37) (a) Bunton, C. A. *Nucleophilic Substitution at a Saturated Carbon Atom*, Elsevier: Amsterdam, 1963. (b) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1958**, *58*, 737.