Enantioselective Total Syntheses of (+)-Castanospermine, (+)-6-Epicastanospermine, (+)-Australine, and (+)-3-Epiaustraline

Scott E. Denmark* and Esther A. Martinborough

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

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Abstract: The total syntheses of the potent glycosidase inhibitors castanospermine ((+)-**1**), 6-epicastanospermine ((+)-**2**), australine ((+)-**3**), and 3-epiaustraline ((+)-**4**) are described. The syntheses of indolizidine alkaloids (+)-**1** and (+)-**2** were accomplished in eight steps and in 18% and 24% overall yields from 2,5-dihydrofuran while the pyrrolizidine alkaloids (+)-**3** and (+)-**4** were obtained in a nine-step sequence in 17% and 22% overall yields from the same starting material. These four natural products are derived from a single common intermediate, nitroso acetal (−)-**31**, which is created in the key step by the asymmetric tandem [4 + 2]/[3 + 2] cycloaddition between silaketal nitro olefin **18** and chiral vinyl ether (+)-**23**. The ability to access both 5,5- and 5,6-fused bicyclic systems was a result of a successful in situ N-alkylation strategy during the hydrogenolysis of four highly functionalized nitroso acetals. A novel silaketal tether provided exceptional levels of diastereocontrol and the ideal combination of protection and functional-group placement for the tandem nitroalkene cycloaddition process.

Introduction

The Australian legume *Castanospermum australe* is a rich source of polyhydroxylated alkaloids which are proving to be potent inhibitors of a variety of glycosidases.[1-4] Among the novel alkaloids isolated to date are the tetrahydroxindolizidines (+)-castanospermine ((+)-**1**)[5] and (+)-6-epicastanospermine ((+)-**2**),[6] along with the tetrahydroxypyrrolizidines,[7] (+)-australine ((+)-**3**),[8] (+)-3-epiaustraline ((+)-**4**),[9] and (+)-1-epiaustraline ((+)-**5**),[10] Chart 1.

Castanospermine ((+)-**1**) is the dominant alkaloidal component of the *C. australe* seed extract and is a powerful inhibitor

Chart 1

(+)-castanospermine ((+)-**1**)　　　(+)-6-epicastanospermine ((+)-**2**)

(+)-australine ((+)-**3**)　　　(+)-3-epiaustraline ((+)-**4**)

(+)-1-epiaustraline ((+)-**5**)

of both α- and β-D-glucosidases.[1] As a result, castanospermine and its derivatives elicit a wide range of biological responses which suggests their potential use in the treatment of a number of diseases. 6-Epicastanospermine ((+)-**2**) does not display the broad range of biological activity inherent to castanospermine ((+)-**1**), though it is a potent amyloglucosidase inhibitor.[2] Australine ((+)-**3**) and its epimers (**4** and **5**) fall into a unique class of pyrrolidizine alkaloids that have hydroxymethyl substituents at C(3) rather than at C(1). Like 6-epicastanospermine (**2**), the pyrrolidizines **3**−**5** are most efficient at altering amyloglucosidase activity.[3,4]

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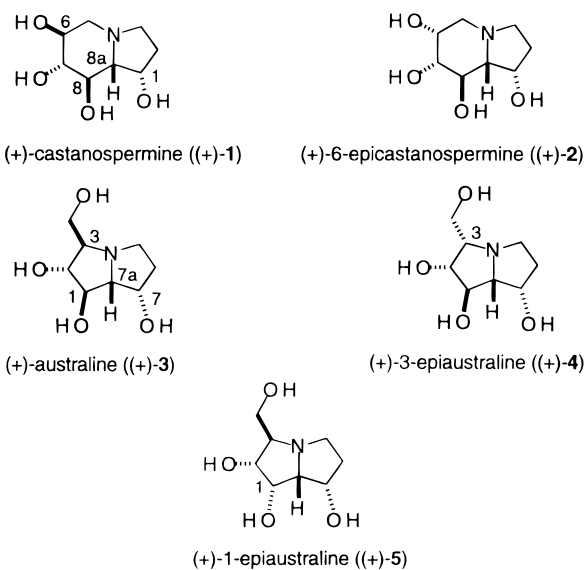
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In view of the therapeutic potential of the indolizidine alkaloids and the opportunity to gain insights into the mechanism by which glycosidases process oligosaccharides, considerable efforts have been directed toward the syntheses of **1**, its stereoisomers, and its analogues.[11] Because of their highly oxygenated architecture, most of the reported syntheses of (+)-**1** and (+)-**2** use the intrinsic chirality of carbohydrate precursors to establish four of the five contiguous stereogenic centers of targeted indolizidine alkaloids.[11a–c,e] The stereochemical configurations at C(6), C(7), C(8), and C(8a) of castanospermine and 6-epicastanospermine correspond to those of D-glucose and D-mannose, respectively. As a result, the carbohydrate-based syntheses of **1** and **2** use these hexoses or their derivatives as starting materials. In contrast to the indolizidine alkaloids, the pyrrolizidines **3**–**5** have attracted much less synthetic attention.[12] Australine, (+)-**3**, and 1-epiaustraline, (+)-**5**, have been prepared using a carbohydrate-based approach beginning with an appropriate pyranose, analogous to the transformations leading to (+)-**1** and (+)-**2**.[12a,d–f] 3-Epiaustraline ((+)-**4**) has not yet, to our knowledge, been synthesized. Although the use of sugar precursors in the construction of alkaloids **1**–**5** minimizes the need to create the requisite stereocenters and introduce oxygen functionality, the syntheses highlighting this approach are often linear, limited in their flexibility, and, in some cases, fail to demonstrate high levels of stereocontrol. Indeed, few methods

exist for the preparation of the targeted alkaloids outside of these carbohydrate-based approaches. Of the twenty-four reported syntheses of **1**, **2**, **3**, and **5**, only six syntheses involve the de novo creation of the requisite functional groups and attendant stereogenic centers.[11d,11g,12b,13]

Over the past eight years, we have extensively developed the tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes as a general method for the synthesis of pyrrolidine- and pyrrolizidine-containing compounds.[14–17] We now wish to demonstrate both the utility and the versatility of the enantioselective tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition reaction in the preparation of enantiomerically pure castanospermine ((+)-**1**), 6-epicastanospermine ((+)-**2**), australine ((+)-**3**), and 3-epiaustraline ((+)-**4**).

The syntheses of these four alkaloids would provide several new challenges for the tandem cycloaddition method. In contrast to our previously reported syntheses, a hydroxymethyl group would need to be incorporated at C(3) rather than at C(1) for the construction of pyrrolizidines **3** and **4**.[15] In addition, preparation of indolizidine alkaloids **1** and **2** requires a one-carbon homologation to access 5,6- rather than 5,5-bicyclic structures. This paper describes a novel, unified strategy which allows for the rapid and stereoselective syntheses of all four alkaloids in enantiopure form from a single common precursor.

Synthetic Strategy

In formulating the synthetic plan for these four natural products, we recognized that the absolute configurations at C(1), C(8a), C(8), and C(7) of **1** and **2** are the same as the configurations at the corresponding centers C(7), C(7a), C(1), and C(2) of **3** and **4**, namely *S, R, R,* and *R*, respectively, Scheme 1. We envisioned that these four common stereogenic centers would originate from the tandem [4 + 2]/[3 + 2] cycloaddition process, thus allowing the syntheses to diverge from a common cycloadduct. Meanwhile, the remaining stereogenic center, C(6) of **1** and **2** and C(3) of **3** and **4**, would have to be independently set in a postcycloaddition modification.

A successful design strategy leading to the preparation of all four alkaloids (**1**–**4**) must incorporate the ability to access both 5,5- and 5,6-fused bicyclic systems. All our previous synthetic efforts have relied on N-acylations for the formation of the C(3)–N bond, resulting in the closure of one of the rings of the pyrrolizidine subunits. We now wished to explore the potential of N-*alkylations* to accomplish a similar structural objective but with the added flexibility of readily adjusting the ring size. This strategy is illustrated in Scheme 1 for the preparation of castanospermine ((+)-**1**) and australine ((+)-**3**) via indolizidine **6** and pyrrolizidine **7**. Hydrogenolysis of nitroso

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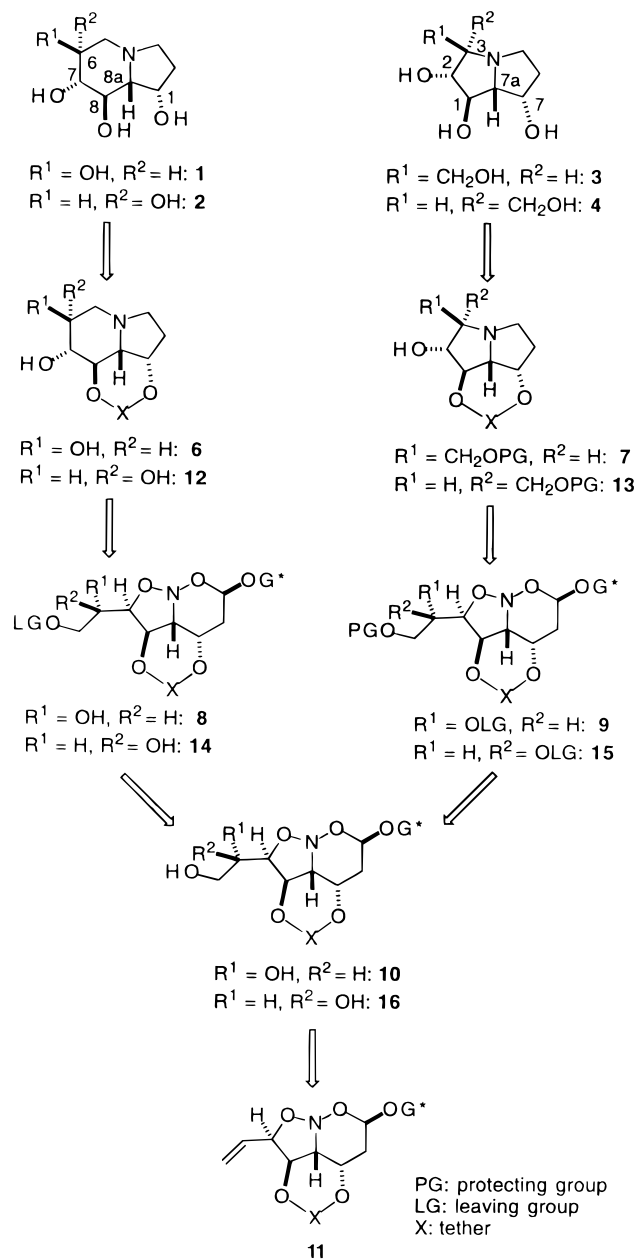
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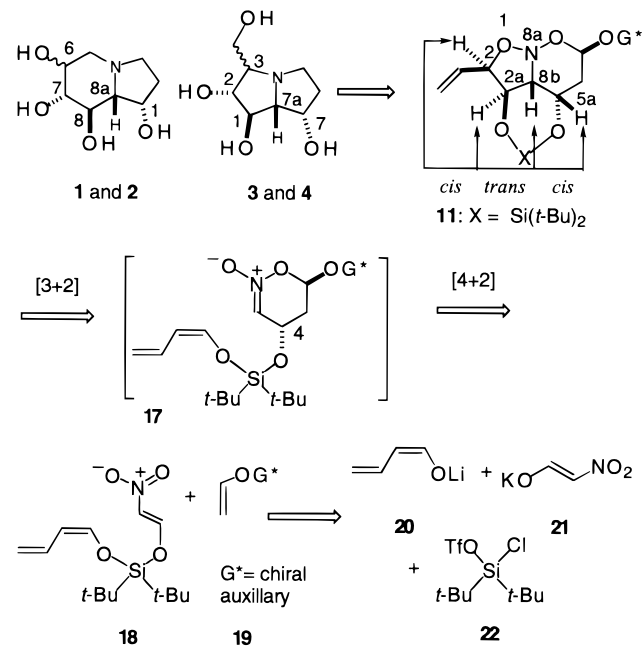(17) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668.

Scheme 1

R^1 = OH, R^2 = H: **1**
R^1 = H, R^2 = OH: **2**

R^1 = CH$_2$OH, R^2 = H: **3**
R^1 = H, R^2 = CH$_2$OH: **4**

R^1 = OH, R^2 = H: **6**
R^1 = H, R^2 = OH: **12**

R^1 = CH$_2$OPG, R^2 = H: **7**
R^1 = H, R^2 = CH$_2$OPG: **13**

R^1 = OH, R^2 = H: **8**
R^1 = H, R^2 = OH: **14**

R^1 = OLG, R^2 = H: **9**
R^1 = H, R^2 = OLG: **15**

R^1 = OH, R^2 = H: **10**
R^1 = H, R^2 = OH: **16**

PG: protecting group
LG: leaving group
X: tether

11

acetal **8** would unmask, after in situ intramolecular displacement of a leaving group, the 5,6-bicyclic framework of **1**. Similar hydrogenolytic unmasking and N-alkylation of nitroso acetal **9** would provide the 5,5-bicyclic framework of **3**. The differentially activated substrates **8** and **9** would arise from functionalization of the primary or the secondary hydroxy group of threo diol **10**, which would result from diastereoselective dihydroxylation[18] of nitroso acetal olefin **11**.

In an analogous fashion, 6-epicastanospermine ((+)-**2**) and 3-epiaustraline ((+)-**4**) would originate from the protected precursors **12** and **13** when a similar sequence of events was employed, Scheme 1. Thus, nitroso acetal **11** would be the key intermediate from which all four natural products are derived, and its diastereoselective dihydroxylation to either **10** or **16** would represent the first branching point in the synthesis. In

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Scheme 2

1 and 2

3 and 4

cis   trans   cis

11: X = Si(t-Bu)$_2$

[3+2]

17

[4+2]

18 + **19**

G* = chiral auxillary

20   **21**

22

this respect, the diastereoselective asymmetric dihydroxylation will be critical for the success of this approach.

The nitroso acetal **11** is the basic subunit that is created in the tandem [4 + 2]/[3 + 2] process, and the precursors for **11** were tailored to satisfy both its structural and stereochemical requirements. As shown in Scheme 2, nitroso acetal **11** would arise from an intramolecular [3 + 2] cycloaddition of nitronate **17**, itself constructed from a hetero Diels−Alder reaction between nitroalkene **18** and chiral vinyl ether **19**. The α-alkoxy olefin moiety in **18** constitutes the dipolarophile for the [3 + 2] cycloaddition, while the terminal olefin serves as an easily functionalized handle for postcycloaddition modifications. Nitroalkene **18** would arise from sequential substitution of lithium (Z)-1,3-butadienyloxide, **20**,[19] and potassium nitroacetaldehyde, **21**,[20] onto the differentially activated di-*tert*-butylchlorosilyl triflate, **22**.[21a] The silaketal tether introduces the required oxygenation at C(2a) and C(5a) of **11**, corresponding to C(1) and C(8) of **1** and **2** and C(1) and C(7) of **3** and **4**. Meanwhile, the di-*tert*-butylsilene would serve as a convergent protecting group for these masked alcohols at C(2a) and C(5a) of **11**.[21,22]

Nitro olefin **18** is uniquely designed to satisfy the stereochemical requirements of **11**, leading to alkaloids **1−4**. The [3 + 2] cycloaddition introduces the stereogenic centers at C(2), C(2a), and C(8b) of **11**, thus establishing the corresponding stereogenic centers at C(7), C(8), and C(8a) of **1** and **2** and C(2), C(1), and C(7a) of **3** and **4**, Scheme 2. The [4 + 2] cycloaddition process establishes the absolute configuration at C(5a) of **11** corresponding to C(1) of the indolizidines and C(7)

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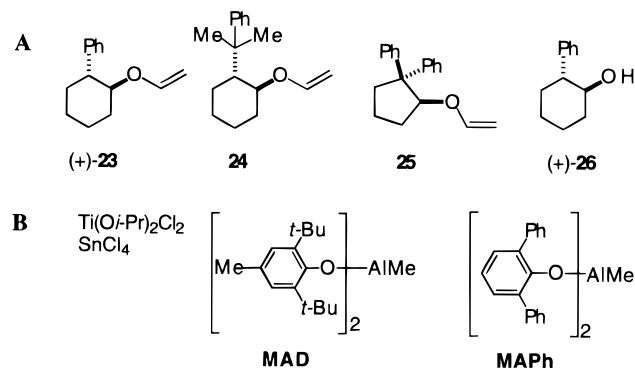
Total Syntheses of Potent Glycosidase Inhibitors

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A

(+)-**23** **24** **25** (+)-**26**

B Ti(O*i*-Pr)$_2$Cl$_2$
SnCl$_4$

MAD **MAPh**

Figure 1. (A) Chiral vinyl ethers **23**−**25** employed in the [4 + 2] cycloaddition of nitroalkenes and *trans*-2-phenylcyclohexanol, **26**, precursor of **23**. (B) Lewis acids employed in the [4 + 2] cycloaddition of nitroalkenes.

of the pyrrolizidine targets. It was anticipated that the three-atom tether O−Si(*t*-Bu)$_2$−O of nitronate **17** would assure both the desired exo and *Re*-selectivity in the [3 + 2] cycloaddition. Indeed, previous work from our laboratories has demonstrated that a three-carbon tether CH$_2$−CH$_2$−CH$_2$ enforces an exo fold of the dipolarophile[23] and a resulting trans relationship between HC(2a) and HC(8b). These syntheses provided an opportunity to determine whether the silaketal tether O−Si(*t*-Bu)$_2$−O would provide similar levels of exo selectivity.

The absolute configuration at C(4) of **17** must be set as *S* to correspond to the *S* configuration at C(1) of alkaloids **1** and **2** and at C(7) of targets **3** and **4**. Since the stereocenters at C(8b), C(2a), and C(2) of **11** are all created relative to C(5a), it is essential to correctly establish the corresponding absolute configuration of C(4) of nitronate **17** in the [4 + 2] cycloaddition. This can be accomplished by *Si*-face attack of the vinyl ether **19** on the nitroalkene **18**, Scheme 2. Our experience shows that, without exception, the (1*S*,2*R*) isomer of 2-phenylcyclo-hexyl vinyl ether ((+)-**23**) is *Si*-face selective with 2-oxygenated nitroalkenes in the presence of methylaluminum bis(2,6-diphenylphenoxide) (MAPh), Figure 1.[24,25] Alternatively, *Si*-face selectivity can be achieved with the (1*R*,2*S*) derivative (−)-**23** in the presence of Ti(O*i*-Pr)$_2$Cl$_2$.[24] Vinyl ether **23** was chosen because of ready availability of both enantiomers of *trans*-2-phenylcyclohexanol, **26**, Figure 1.[26]

We anticipated several challenges associated with the use of a silaketal tether and a dienyl fragment in the tandem cycload-dition of **18**. First, the potential lability of the untested O−SiR$_2$−O tether was a source of concern, especially in view of the Lewis acidic conditions required for the [4 + 2] cyclization. Second, nitroalkene **18** has the potential to undergo undesired intramolecular Lewis acid promoted [4 + 2] cycload-dition with the vinyl ether portion of its alkoxydienyl fragment. However, previous studies on this mode of intramolecular reaction suggest that it would be disfavored.[27] Thus, with these

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(25) (a) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573. (b) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316. (c) Maruoka, K.; Itoh, T. Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310.
(26) Schwartz, A.; Madan, P.; Whitesell, J. K.; Laurence, R. M. *Org. Synth.* **1990**, *69*, 1.
(27) Denmark, S. E.; Moon, Y.-C.; Cramer, C. J.; Dappen, M. S.; Senanayake, C. W. B. *Tetrahedron* **1990**, *46*, 7373.

design considerations in mind, we embarked on the preparation of the nitro olefin **18** and its subsequent tandem cycloaddition.

Results

Preparation of Cycloaddition Precursor 18. The construction of the nitro olefin **18** began with the generation of 1,3-butadienyllithium alkoxide, **20**, by stereoselective cycloelimi-nation of 2,5-dihydrofuran,[19] Scheme 3. In the presence of *n*-BuLi at −23 °C, ring opening is rapid and affords exclusively the *Z* isomer. Silylation of the lithium alkoxide with di-*tert*-butylchlorosilyl triflate, **22**,[21a] provided the chromatographically stable chlorosilane **27** in a 73% yield.
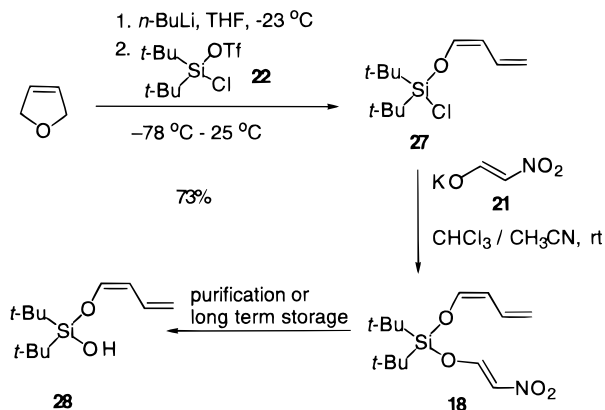
Scheme 3

Table 1. Reaction Between **21** and **27**: Solvent Optimization

entry	solvents	solvent ratios	yield **18**[a], %	yield **28**[a], %
1	THF/CH$_3$CN	4/1	40	25
2	Et$_2$O/CH$_3$CN	4/1	42	8
3	CHCl$_3$/CH$_3$CN	4/1	65	5
4	CHCl$_3$/CH$_3$CN	3/1	52	5
5	CHCl$_3$/CH$_3$CN	2/1	85	15
6	CHCl$_3$/CH$_3$CN	1/1	67	13

[a] Approximate yields based on 500 MHz ^{1}H NMR analysis. Conversions ranged between 50 and 100%.

The next step, involving displacement of the chloride of **27** with potassium nitroacetaldehyde, **21**,[20] to afford **18**, required extensive experimentation, Table 1. Polar solvents, such as THF, CH$_3$CN, acetone, and CH$_3$NO$_2$ were essential for solubilizing **21**; however, clean additions were not observed in these solvents alone. The reactivity of the potassium salt could be modulated by the addition of less polar solvents such as CHCl$_3$ and Et$_2$O. Our most successful protocol involved stirring chlorosilane, **27**, and potassium nitroacetaldehyde, **21**, in a 2/1 mixture of CHCl$_3$ and CH$_3$CN at room temperature for 8 h (entry 5, Table 1).

The resulting nitroalkene **18** was found to be intrinsically unstable and, in addition, labile under all conventional methods of purification. Storage under N$_2$ for more than a day at room temperature resulted in loss of the nitroalkene fragment and production of silanol **28**. In addition, distillation (5 × 10^{-5} mmHg), chromatography (silica gel, Et$_3$N treated silica gel, basic and neutral alumina plugs) and cold chromatography (basic and neutral alumina plug, −60 °C) only promoted the production of **28** in varying degrees. As a result, **18** was filtered through Celite, stored in Et$_2$O at −20 °C under N$_2$, and then used directly in the cycloaddition sequence.

Tandem [4 + 2]/[3 + 2] Cycloaddition of 18. Extensive efforts were directed toward the development of a mild protocol that would ensure the integrity of the labile silaketal **18** while providing good exo/endo and facial selectivity. Various Lewis

acids were surveyed for their ability to promote the diastereo-selective reaction between nitroalkene **18** and (±)-**23**, Scheme 4. Both MAPh and Ti(O*i*-Pr)$_2$Cl$_2$ promoted highly selective Diels−Alder processes. The major MAPh-derived cycloadduct (13/1) was determined to be the trans nitronate (±)-**29** arising from an exo mode of cycloaddition; whereas the Ti(O*i*-Pr)$_2$Cl$_2$ promoted reaction provided exclusively the cis nitronate (±)-**30**, the result of an endo mode of cycloaddition.[24b] The isomeric nitronates could be purified chromatographically, but the isolated yields were low (20−30%). The low yields were due partly to the chromatographic sensitivity of (±)-**29** and (±)-**30** and partly to decomposition of the nitro olefin.

Having pure samples of (±)-**29** and (±)-**30** allowed us to examine their viability in the [3 + 2] cycloaddition. Since either cis or trans nitronates could, in principle, be used to access alkaloids **1**−**4**, both (±)-**29** and (±)-**30** were heated to reflux in benzene to effect the thermal [3 + 2] cycloaddition, Scheme 4. The trans nitronate (±)-**29** underwent clean cycloaddition to afford the racemic nitroso acetal (±)-**31** virtually quantitatively. The cis nitronate (±)-**30**, however, did not undergo cycloaddition to (±)-**32** and decomposed upon prolonged heating. Thus, we established that the trans nitronate **29**, arising from an exo selective [4 + 2] cycloaddition, is the most viable intermediate in the tandem process and undertook the optimization of the reaction conditions to improve the yield and diastereoselectivity of its production with MAPh.

Scheme 4
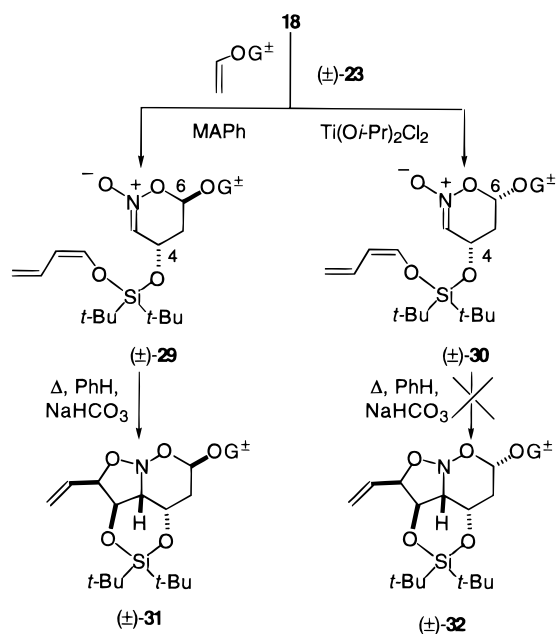
In this second stage of optimization, we evaluated the success of the [4 + 2] cycloaddition, not by the yields of isolated (±)-**29**, since its purification was problematic, but by the yields of the isolated tandem cycloadduct (±)-**31**. The yields of isolated **31** should directly correspond to the yields of the [4 + 2] reaction since NMR analysis indicated that the thermal [3 + 2] process was virtually quantitative. The effects of temperature, reaction times, stoichiometry, and order of addition of reagents are summarized in Table 2 for the MAPh promoted [4 + 2] cycloaddition between **18** and (±)-**23**. We found that the optimal conditions for this tandem cycloaddition process involved dropwise addition of silaketal **18** over 15 min to a CH$_2$Cl$_2$ solution of 3 equiv of MAPh and 4 equiv of vinyl ether (±)-**23** at −50 °C, with a total reaction time of 2 h (entry 5, Table 2).

**Table 2.** Optimization of MAPh-Promoted Cycloadditions between **18** and (±)-**23**

entry	stoichiometry MAPh/(±)-**23**	time, h temp, °C	(±)-**29**/(±)-**30**[a]	yield, % (±)-**31**[b]
1	1.2/1.5[c]	5.0/−50	13/1	37
2	2.0/2.0[c]	6.0/−50	13/1	27
3	3.0/4.0[c]	3.0/−50	22/1	39
4	5.0/6.0[c]	3.0/−50	19/1	35
5	3.0/4.0[d]	2.0/−50	>50/1	44
6	3.0/4.0[d]	4.0/−50	>50/1	35

[a] Diastereomeric ratios were determined by 500 MHz ^{1}H NMR analysis. [b] Conversions ranged between 60 and 93%. Yields of chromatographically homogeneous (±)-**31** over 3 steps from **27**. [c] MAPh is added last to a solution of **18** and (±)-**23**. [d] **18** is added last to a solution of MAPh and (±)-**23**.

The increased amount of vinyl ether and the short reaction times maximized the rate of [4 + 2] cycloaddition over the rate of Lewis acid induced decomposition of silaketal **18**. In addition, the increased amounts of vinyl ether and the inverse order of addition enhanced the diastereoselectivity to >50/1. Finally, the inverse order of addition may also suppress any intra- or intermolecular reaction between the nitroalkene and the dienyl fragment of **18**. The resulting crude trans nitronate (±)-**29** was filtered through Celite to remove aluminum byproducts and, without further purification, was heated in benzene to induce the thermal [3 + 2] cycloaddition. Since nitronate (±)-**29** is acid-labile, NaHCO$_3$ was added to ensure the stability of the nitronate during heating.[28] Nitroso acetal (±)-**31** could be purified by silica-gel chromatography and was isolated as a white crystalline solid in a 44% overall yield from **27** and as a single diastereoisomer.

We next addressed the preparation of **31** with enantiopure vinyl ether. Since the optimal route proceeded via the trans nitronate **29** and, as a result, required MAPh for the exo selective cycloaddition, we employed the (1*S*,2*R*)-2-phenylcyclohexyl vinyl ether (+)-**23** to establish the correct absolute configurations for all four alkaloids. Starting from chlorosilyldiene, **27**, substitution with potassium nitroacetaldehyde, **21**, MAPh promoted [4 + 2] cycloaddition between **18** and (+)-**23**, and intramolecular [3 + 2] cycloaddition provided the desired nitroso acetal (−)-**31** in a 45% yield over three steps and as a 44/1 mixture of diastereomers, Scheme 5. Nitroso acetal (−)-**31** could then be recrystallized to diastereomeric purity in a 40% overall yield from **27**.

Scheme 5
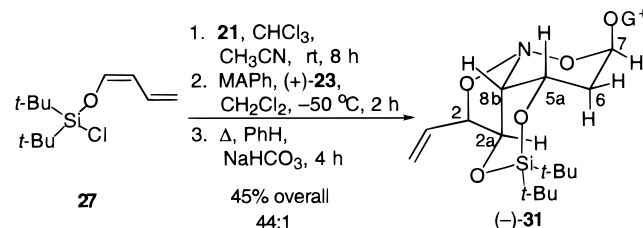
Cycloadduct (−)-**31** arises solely from an exo mode [4 + 2] cycloaddition with excellent diastereofacial selectivity (*Si/Re* = 44/1). In addition, the [3 + 2] cycloaddition proceeded with exclusive exo selectivity and complete facial selectivity. The structure of (−)-**31** was assigned by ^{1}H NMR analysis and by analogy to established precedent.[24] Although the ^{1}H NMR coupling constant pattern established by 2D NMR (^{1}H/^{1}H COSY and ^{1}H/^{13}C HETCOR) experiments ($J_{2a,8b}$ = 8.1 Hz, $J_{8b,5a}$ =

(28) (a) Denmark, S. E.; Stolle, A.; Dixon, J. A.; Guagnano, V.; *J. Am. Chem. Soc.* **1995**, *117*, 2100. (b) Denmark, S. E.; Dixon, J. D. *J. Org. Chem.* **1997**, *62*, 7086.

6.5 Hz, $J_{6,7} = 3.9$ Hz ($J_{2,2a}$ could not be resolved)) does not unambiguously prove the stereochemical assignments, it is compatible with the proposed structure.

Asymmetric Dihydroxylation. The asymmetric dihydroxylation (AD) of the C(1′)−C(2′) double bond of (−)-**31** was now required to introduce the final hydroxylated stereogenic center and provide a functional handle to subsequent closure of the second ring.

We first investigated the inherent facial bias in the diastereoselective dihydroxylation of (−)-**31**, Table 3. The intrinsic diastereoselectivity in the catalytic dihydroxylation of nitroso acetal (−)-**31** is small, and in the absence of chiral additives the (1′R,2S) diol (−)-**33** is favored over the (1′S,2S) diol (−)-**34** by a ratio of only 2/1 (entry 1, Table 3). The chromatographically separable diols were unambiguously assigned at a latter stage of the syntheses (vide infra). Straightforward analysis of the configuration consequences of our plan reveals that the (1′S,2S) epimer (−)-**34** would give rise to castanospermine ((+)-**1**) and australine ((+)-**3**), while the (1′R,2S) epimer (−)-**33** would lead to 6-epicastanospermine ((+)-**2**) and 3-epiaustraline ((+)-**4**). In view of the usefulness of both epimeric diols, the olefin (−)-**31** was subjected to the conditions of the Sharpless asymmetric dihydroxylation using both dihydroquinine (DHQ) and dihydroquinidine (DHQD) derived ligands.[18]

Table 3. Asymmetric Dihydroxylation of (−)-**31**
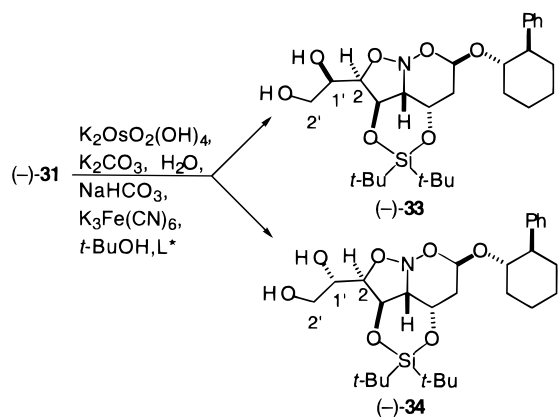
entry	ligand	(−)-**33**/(−)-**34**[a]
1	none	2/1
2	(DHQ)₂-PHAL	1/1
3	(DHQ)₂-CLB	6/1
4	(DHQ)₂-PYR	24/1
5	DHQ-PHN	208/1
6	DHQD-IND	1/1.2
7	(DHQD)₂-PHAL	1/1.8
8	(DHQD)₂-AQN	1/12.0

[a] Conversions ranged between 98 and 100%. Diastereomeric ratios were determined by 500 MHz ¹H NMR analysis.

On the basis of the well-precedented mnemonic,[18] the DHQ containing ligands are expected to enhance the formation of (1′R,2S) diol (−)-**33**, and the observed selectivities obtained from a survey of a battery of DHQ derived catalysts are highlighted in Table 3 (see Supporting Information for chiral-ligand structures and other ligands investigated). Using the standard dihydroxylation conditions, stirring a solution of (−)-**31** at room temperature for 48 h with 5 mol % of potassium osmate and 2 mol % of the phenanthracene ligand (DHQ-PHN)[29a] provided almost exclusively the (1′R,2S) diol (−)-**33** (entry 5, Table 3). The (1′R,2S) diol (−)-**33** could then be

recrystallized to diastereomeric purity in 93% yield. The enantiomeric purity of (1′R,2S) diol (−)-**33** was determined by CSP SFC analysis to be 99.8% ee.

To access the (1′S,2S) diol (−)-**34**, DHQD-derived chiral ligands were surveyed for their ability to reverse the intrinsic selectivity of the dihydroxylation reaction, and these results are also shown in Table 3. Surprisingly, few ligands were capable of overcoming the weak inherent diastereofacial preference of olefin (−)-**31**.[30] Although the phthalazine (PHAL)[29b] and indoline (IND)[29c] derived ligands favored the formation of (−)-**34**, the low selectivities were not of synthetic utility (entries 6 and 7, Table 3). We were pleased to observe that the recently developed anthraquinone ligand ((DHQD)₂-AQN),[29d] which has been reported to provide exceptional facial selectivity for terminal olefins with heteroatoms in the allylic positions,[29d] proved to be the necessary complement in the asymmetric dihydroxylation leading to (−)-**34** (entry 8, Table 3). Utilizing 4 mol % of potassium osmate and 5 mol % of (DHQD)₂-AQN provides a 12/1 mixture of (1′S,2S) and (1′R,2S) diols which could be chromatographically separated to exclusively afford the desired (1′S,2S) diol, (−)-**34**, in 86% yield. The enantiomeric purity of (1′S,2S) diol (−)-**34** was determined by CSP SFC analysis to be 99.9% ee.

Synthesis of (+)-Castanospermine ((+)-1). The first test of the hydrogenation−alkylation strategy involved activation of the primary alcohol of diol (−)-**34** and hydrogenolytic unmasking of the resulting nitroso acetal to afford indolizidine **35**. Accordingly, the ability to prepare a primary tosylate and induce N-alkylation under various hydrogenation conditions was evaluated. Selective tosylation of the primary position of diol (−)-**34** could be achieved using p-toluenesulfonyl chloride (TsCl) and pyridine as the solvent, Scheme 6. The chromatographically stable tosylate **36** could be stored at room temperature for up to 48 h, but in general, it was used directly in the following reduction. The success of the hydrogenolysis was strongly dependent on both H₂ pressure (160, 260, and 450 psi) and reaction times (36 and 48 h). The conditions found to be most suitable for the formation of (−)-**35** involved the Raney-nickel-catalyzed unmasking of the tosylate **36** at 160 psi of H₂ pressure for 36 h in MeOH. Purification of (−)-**35** by silica-gel chromatography led to the formation of hygroscopic silicates. The free base could be readily obtained as a white foam by filtration through a plug of basic alumina followed by neutral alumina (activity III), and indolizidine (−)-**35** could be isolated in a 73% overall yield from diol (−)-**34**. The chiral auxiliary, (+)-trans 2-phenylcyclohexanol, (+)-**26**, was also recovered in a 98% yield.

The di-*tert*-butylsilylene proved to be a robust protecting group, and since an aqueous workup would be unsuitable for these polyhydroxylated alkaloids, we sought conditions that would provide facile isolation of (+)-**1**. For example, heating with CsF in DMF, treatment with TBAF or DAST, or stirring with concentrated HCl resulted either in incomplete deprotection of (−)-**35** or difficult isolation of (+)-**1**. In contrast, deprotection with HF in MeOH provided clean conversion of (−)-**35** to the fluoride salt of (+)-**1**, and the free base was obtained by cation-exchange chromatography on AG 50W-X8. Recrystallization of (+)-**1** from MeOH and Et₂O[31] afforded the analytically pure
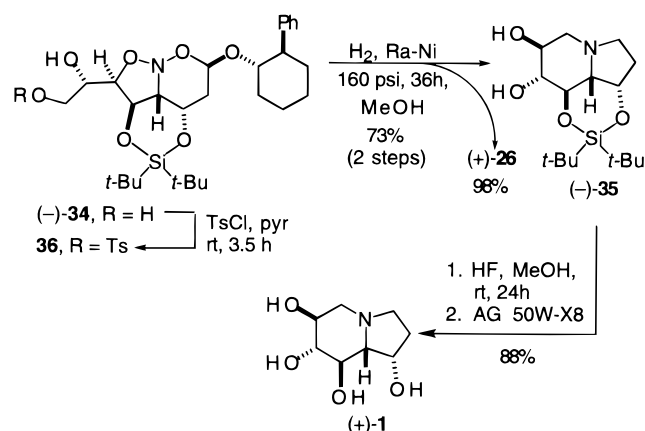
(29) (a) Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 2095. (b) Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940. (c) Wang, L.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 7568. (d) Becker, H.; Sharpless, B. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448.

(30) Other ligands tested in the DHQD series are found in Supporting Information.

(31) Gerspacher, M.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 3700.

(+)-castanospermine ((+)-**1**) in an 88% yield from (−)-**35** as white needles.

Scheme 6

Scheme 7

preparation of the known hydrochloride salt (−)-**39** in a 19% overall yield.

Comparison, by ^{1}H and ^{13}C NMR analysis, of our synthetic material with a sample of naturally occurring castanospermine showed them to be identical (see Supporting Information). In addition, the physical properties of synthetic (+)-**1** matched those reported in the literature ($[\alpha]^{20}_D$ +79.7 (c = 1.06, H$_2$O, pH = 8.71), lit.[5] $[\alpha]_D$ +79.9 (c = 0.93, H$_2$O); mp 212 °C dec, lit. mp[5] 212−215 °C dec). Thus, the total synthesis of natural castanospermine ((+)-**1**) was accomplished in eight steps from 2,5-dihydrofuran and in an 18% overall yield.

Preparation of (+)-6-Epicastanospermine ((+)-2). The final stages of the synthesis of (+)-6-epicastanospermine could be formulated by an analogous set of transformations from diol (−)-**33**, Scheme 7. Tosylate **37** was readily obtained using TsCl and pyridine, and its hydrogenolytic behavior was surveyed as a function of H$_2$ pressures. As in the case of tosylate **36**, a marked pressure effect was observed for **37**, which, in addition, reached a maximum at 260 psi of H$_2$ and afforded high yields of indolizidine (−)-**38**.

The overall sequence was then carried out with 1 mmol of diol (−)-**33**. Silica-gel purification of the indolizidine followed by filtration through a plug of basic and neutral alumina (activity III) provided (−)-**38** in an 81% yield over two steps, Scheme 7. The chiral auxiliary (+)-**26** was recovered in quantitative yield. Desilylation of (−)-**38** with HF followed by cation-exchange chromatography afforded (+)-6-epicastanospermine ((+)-**2**) in a 96% yield as a brown oil.

Both the physical properties and the ^{1}H and ^{13}C spectral data of our synthetic material matched those reported in the literature ($[\alpha]_D$ +1.6 (c = 1.00, MeOH), lit.[31] $[\alpha]_D$ +2.2 (c = 0.7, MeOH), lit[6] $[\alpha]_D$ +8.0 (c = 1.09, MeOH)).[32] However, an unknown contaminant, arising from the ion-exchange resin and not detectable by spectral methods, prohibited our obtaining analytically pure material. Therefore, the free base was converted to the HCl salt (−)-**39**[2b] with concentrated HCl in methanol, Scheme 7. Recrystallization of (−)-6-epicastanospermine hydrochloride from MeOH and Et$_2$O[31] provided analytically pure (−)-**39** in an 80% yield. The spectral and physical properties of the HCl salt matched those reported in the literature (see Supporting Information): $[\alpha]^{24}_D$ −1.19 (c = 1.01, H$_2$O), lit.[2b] $[\alpha]_D$ ~0 (c = 1.5, H$_2$O); mp 258−259 °C dec, lit. mp[31] >250 °C dec. This first noncarbohydrate-based total synthesis of 6-epicastanospermine ((+)-**2**) was thus accomplished in 24% yield over eight steps and was further confirmed by the
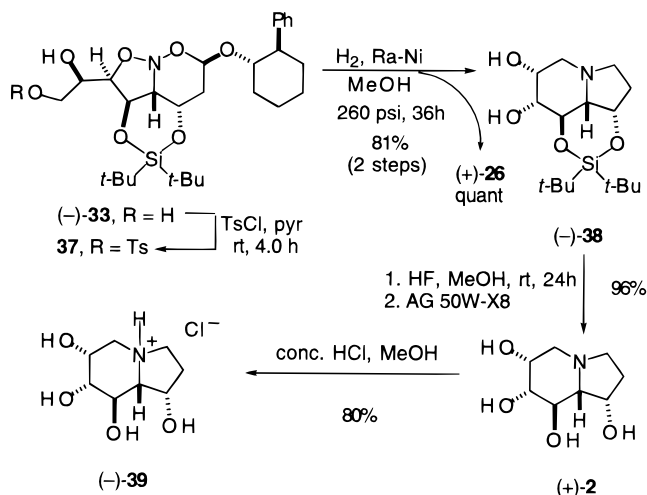
Preparation of (+)-3-Epiaustraline ((+)-4). The second application of the hydrogenation−alkylation sequence involves nucleophilic substitution at a more hindered, secondary center of the activated nitroso acetal to eventually furnish pyrrolizidine alkaloids (+)-**3** and (+)-**4**. Intermediate diol (−)-**33** presented several viable options, Figure 2. Epoxide **40** offers the potential for in situ, 5-exo-tet opening during hydrogenolysis.[12a,e] This epoxide is an attractive intermediate, especially since it could be readily obtained from tosylate **37**. A cyclic sulfate could lead to the desired pyrrolizidine structures from a 9-endo opening of **41**. Finally, simple activation at the secondary alcohol,[12d,15] such as in protected mesylate **42**, would directly complement our initial approach.
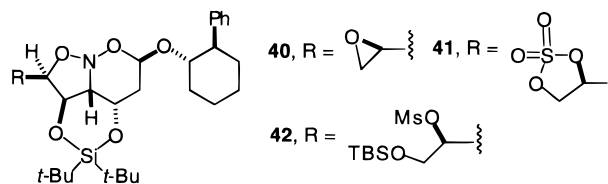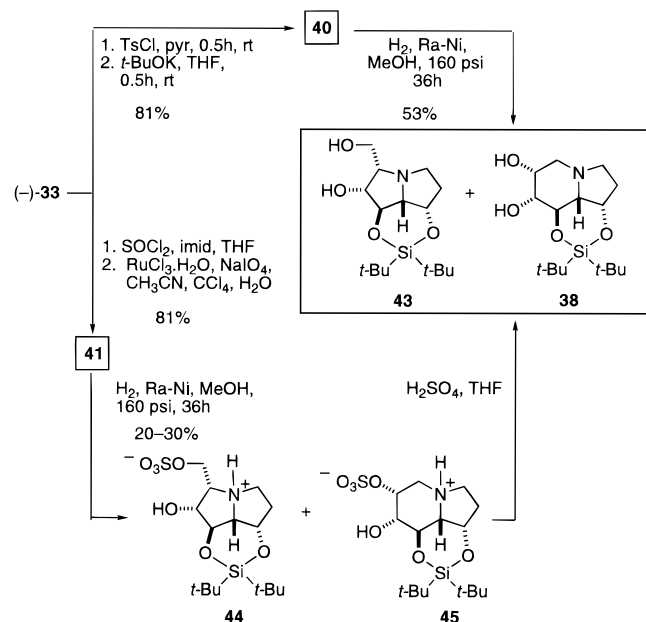
Figure 2. Three possible hydrogenation intermediates leading to (+)-3-epiaustraline ((+)-**4**): epoxide **40**, cyclic sulfate **41**, and secondary mesylate **42**.

Treatment of tosylate **37** with *t*-BuOK in THF afforded the epoxide **40** which was subjected to hydrogenation at 160 psi in the presence of Raney-nickel, Scheme 8. The two products isolated after the hydrogenolytic unmasking of **40** were the desired pyrrolizidine **43** and, in this case, the undesired indolizidine **38** in ratios of approximately 2:1. As an alternative, the cyclic sulfate **41**, prepared by a two-step procedure,[33] was investigated for its ability to undergo hydrogenolysis, Scheme 8. The zwitterionic salts **44** and **45** were obtained in low yield (20−30%) and with modest selectivity (**44:45** ≈ 4:1). Sulfuric acid hydrolysis afforded a mixture of **43** and **38**, along with desilylated materials. Although the desired 5-exo-tet opening of the epoxide **40** and 9-endo opening of cyclic sulfate **41** are slightly favored, the modest selectivities and the difficulty of separating these two isomeric structures made these routes unattractive. We then turned our attention on the selective activation of the secondary hydroxyl group of diol (−)-**33**.

(32) The $[\alpha]_D$ of (+)-**2** is very sensitive to pH; see ref. 31.

(33) Ramaswamy, S.; Prasad, K.; Repic, O. *J. Org. Chem.* **1992**, *57*, 6344.

Total Syntheses of Potent Glycosidase Inhibitors

J. Am. Chem. Soc., Vol. 121, No. 13, 1999 3053

Scheme 8

Scheme 9
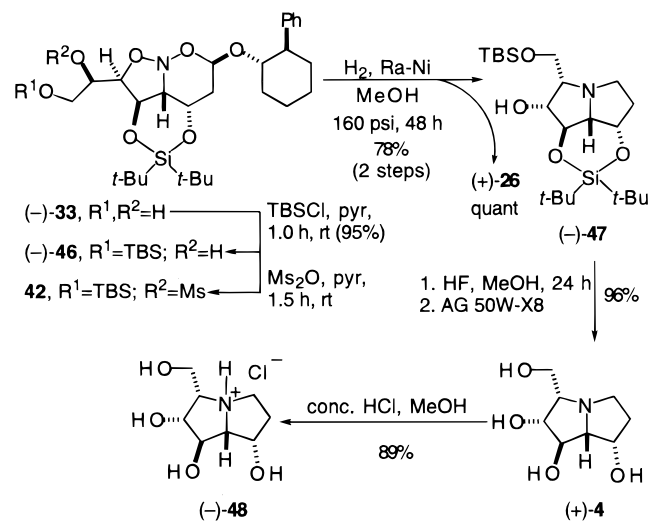
Table 4. Hydrogenation of Mesylate **42**

entry	pressure, psi	time, h	yield (−)-**47**, %
1	80	36	30
2	160	36	60
3	160	48	70−75
4	260	3	0
5	260	36	68
6	260	48	59
7	350	36	43

To gain access to mesylate **42**, the diol (−)-**33** was selectively protected as the primary TBS ether (−)-**46** which was then subjected to various conditions to effect sulfonylation, Scheme 9. A survey of mesylating agents demonstrated that the combination of methanesulfonic anhydride and pyridine provided the required balance between mildness and efficiency of the sulfonating reagent. The resulting mesylate **42** was hydrogenated under a variety of conditions to ascertain the pressures and times most suitable for the production of (−)-**47**, Table 4.

As observed in the hydrogenolysis of the primary tosylates, the N-alkylation of secondary mesylates also demonstrated a significant pressure dependence. What is unique to this substrate is the increase in yield with prolonged reaction times at 160 psi (entries 2−3, Table 4). As a result, the TBS ether (−)-**46**, when transformed to the secondary mesylate (**42**), was hydrogenated for 48 h at 160 psi of H_2 pressure to afford pyrrolizidine (−)-**47**, Scheme 9. In analogy to the indolizidines, the formation of silicates accompanied silica-gel purification of (−)-**47**, and a plug of basic and neutral alumina (activity III) was relied upon to ensure formation of the free base. In this manner, pyrrolizidine (−)-**47** was isolated in a 78% overall yield from (−)-**46** as a white solid. The chiral auxiliary trans 2-phenylcyclohexanol, (+)-**26**, was also recovered in a 100% yield. The now standard deprotection protocol (HF, MeOH) was employed to access the third alkaloidal product, (+)-3-epiaustraline ((+)-**4**), as a brown oil in a 96% yield, Scheme 9.
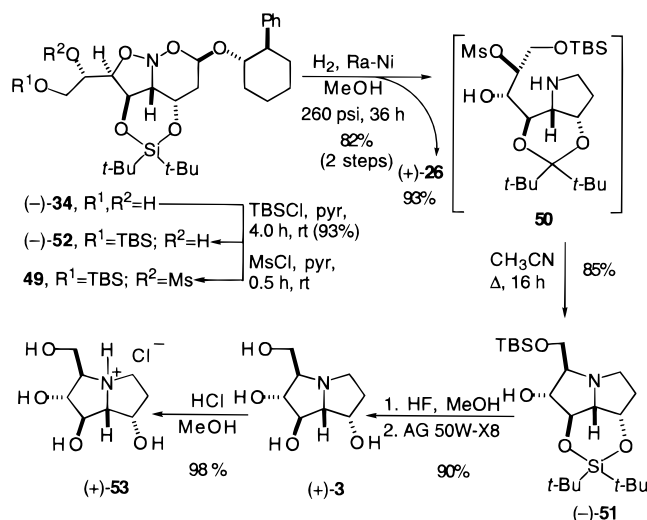
Comparison of our synthetic material to a naturally occurring sample of 3-epiaustraline by ^{1}H and ^{13}C NMR analysis found them to be identical (see Supporting Information): $[\alpha]_D = +6.2$ ($c = 1.00$ in MeOH). The hydrochloride salt of 3-epiaustraline, (−)-**48**, was prepared to obtain crystalline material and to make further comparisons with the reported physical data,[9] Scheme 9. Recrystallization of (−)-3-epiaustraline hydrochloride from MeOH/Et$_2$O provided analytically pure (−)-**48** in an 89% yield, the physical properties of which were in agreement with those reported in the literature: $[\alpha]^{24}_D$ −6.1 ($c = 1.01$, H$_2$O), lit.[9] $[\alpha]_D$ −3.5 ($c = 1.35$, H$_2$O; mp 159−160 °C dec (recrystallization from MeOH/Et$_2$O), lit. mp[9] 148−152 °C dec (recrystallization from methanolic HCl). On the basis of these comparisons, we report the first total synthesis of (+)-3-epiaustraline ((+)-**3**) in a 22% yield over eight steps from 2,5-dihydrofuran.

Preparation of (+)-Australine ((+)-3). In view of the successful execution of the mesylation and hydrogenation sequence with 3-epiaustraline ((+)-**4**), the same strategy was employed in the final modification leading to australine (+)-**3**. Mesylate **49** was obtained by treatment of diol (−)-**34** with TBSCl followed by methanesulfonic anhydride, Table 5. We were surprised to discover that the hydrogenolytic behavior of **49** was not analogous to that of its epimer, **42**. At pressures of 160 and 260 psi the uncyclized mesylate intermediate, **50**, could be isolated (entries 2−3, Table 5). Closure to pyrrolizidine (−)-**51** occurred only during hydrogenolysis at 80 psi and in low yield (entry 1, Table 5). In an attempt to alter the electronic and steric environment at the secondary position, triflates were prepared, $R^2 = CF_3$, and the TBS protecting group was modified to an acetyl group, $R^1 = Ac$. However, both these strategies led to a complex mixture of unidentifiable hydrogenation products. Since the intermediate pyrrolidine mesylate, **50**, could be isolated in good yield, efforts were then made to effect cyclization after the hydrogenolysis.

Table 5. Hydrogenolysis of Sulfonates **49**

| entry	R^1	R^2	pressure, psi	time, h	isolated yield, % **50**/(−)-**51**
1	TBS	CH$_3$	80	48	0/40
2	TBS	CH$_3$	160	48	50/<10
3	TBS	CH$_3$	260	36	73/<5

Scheme 10

Figure 3. (A) Proposed approach of vinyl ether (+)-**23** to nitroalkene **18** in the [4 + 2] cycloaddition. (B) Proposed exo approach of the dipolarophile to the same face of the nitronate dipole to which the tether is attached in the [3 + 2] cycloaddition of **29**.

The mesylate **50** did not spontaneously cyclize with prolonged stirring in MeOH at room temperature; however, upon heating in CH$_3$CN for 16 h, the desired closure did take place. Thus, pyrrolizidine (−)-**51** was obtained from TBS ether (−)-**52** by mesylation followed by hydrogenation at 260 psi for 36 h to afford **50** in 82% yield, which then suffered cyclization in refluxing acetonitrile in 85% yield, Scheme 10. After treatment with basic and neutral alumina (activity III), pyrrolizidine (−)-**51** was isolated in 70% overall yield from (−)-**52**. The chiral auxiliary (+)-**26** was recovered in 93% yield. Australine ((+)-**3**) was then obtained as a yellow oil by desilylation of (−)-**51** using the standard protocol; however, this material required further silica-gel chromatography (CHCl$_3$/MeOH/NH$_4$OH, 5/5/1) to obtain pure material, Scheme 10.

Comparison of the data for our synthetic material with the revised ^{1}H and ^{13}C NMR data reported for naturally occurring australine[7] revealed that they were identical. Our spectral data also matched the data given by Pearson et al.[12a] and White et al.[12b] for synthetic australine (see Supporting Information). The physical properties of our synthetic material were also in good agreement with those reported for the natural material: [α]$^{20}_D$ +18.6 (c = 2.51, MeOH), lit.[8] [α]$^{26}_D$ +19.3 (c = 2.09, MeOH). Australine turned brown upon standing at room temperature and was highly susceptible to salt formation; therefore, australine was stored as the hydrochloride salt (+)-**53** (98% yield). Both the physical and spectral properties of australine hydrochloride ((+)-**53**) matched those reported in the literature: [α]$^{20}_D$ +22.2 (c = 0.50, H$_2$O), lit.[11g] [α]$_D$ +23.1 (c = 1.00, H$_2$O). Thus, the fourth alkaloidal product, (+)-australine ((+)-**3**), has been prepared in a 17% yield over eight steps from 2,5-dihydrofuran.

Discussion

Tandem Cycloaddition. The tandem [4 + 2]/[3 + 2] cycloaddition of **18** is the singular stereodetermining event which establishes four of the five stereocenters of the targeted alkaloids. The stereochemical outcome of the tandem process is determined by the exo/endo selectivities and the diastereo-facial selectivities of both the [4 + 2] and subsequent [3 + 2] cycloadditions. Viewed within this context, the stereochemical issues that govern this [4 + 2] process are the following: the *Re-* or *Si*-facial approach of the vinyl ether (+)-**23**, its reactive conformation, i.e., s-cis or s-trans, and its exo vs endo approach to the nitroalkene **18**. All these factors are influenced by the Lewis acid MAPh.[14,24] Nitronate **29** results from an exclusively
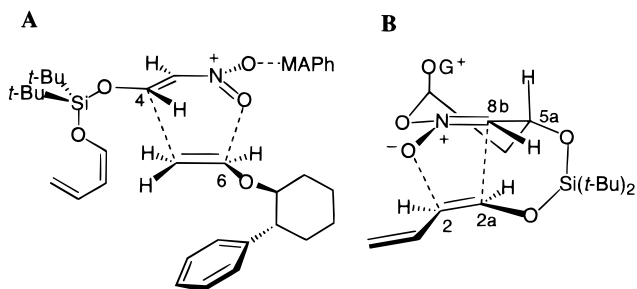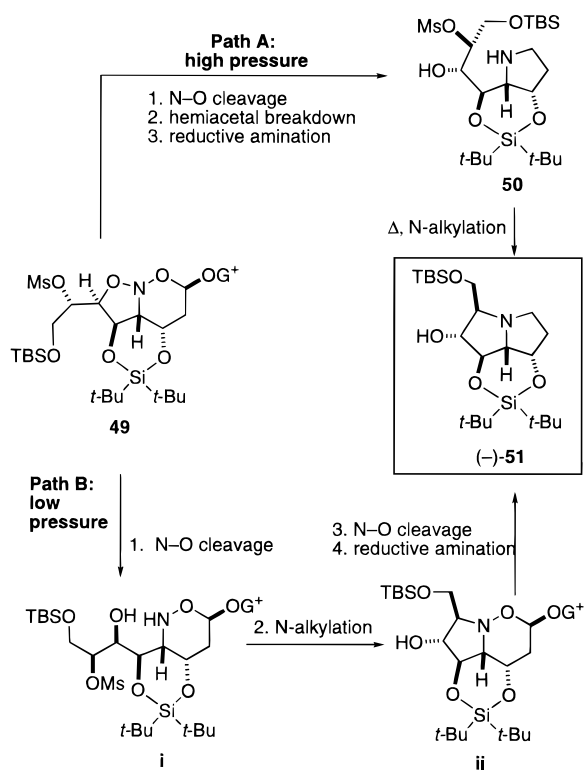
exo approach of an s-trans-configured vinyl ether to the *Si* face of **18**, Figure 3A. These events, which control the absolute configuration at C(4) and establish the trans relationship between HC(4) and HC(6), are in agreement with the established precedent for MAPh-promoted cycloaddition using this vinyl ether.

The outcome of the subsequent [3 + 2] cycloaddition process is controlled by the three-atom silaketal tether. By analogy to the three-carbon tether,[23] the silaketal tether enforces an exclusively exo approach of the dipolarophile to the 1,3-dipole from the face to which the tether is attached, Figure 3B. These events establish the cis relationship between HC(5a) and HC(8b) and the trans relationship between HC(8b) and HC(2a) in the forming nitroso acetal (−)-**31**. The cis relationship between HC(2) and HC(2a) arises from the *Z* configuration of the dipolarophile, Figure 3B. Thus, the silaketal tether is responsible for the complete diastereocontrol observed in the intramolecular [3 + 2] cycloaddition.

Osmylation. The inherent facial bias demonstrated in the osmylation of nitroso acetal (−)-**31** resulting in the preferential formation of the (1′R,2S) diol (−)-**33** over the (1′S,2S) diol (−)-**34** is in accordance with Kishi's model[34a] and Danishefsky's observations[34b] concerning the facial approach of osmium tetraoxide to α-alkoxy olefins. Application of their model to nitroso acetal (−)-**31** predicts that the diol displaying an erythro relationship between HC(1′) and HC(2) would be preferentially formed, and indeed, erythro diol **33** is favored by a factor of 2/1. However, this intrinsic preference is weak, and it is unclear what other factors contribute to the observed selectivity. This bias, however, does manifest itself in the dihydroxylation employing chiral ligands. The participation of DHQ ligands represents matched pairing, whereas the involvement of the DHQD derived ligands represents a mismatched pairing in this example of double diastereoselection. Within the DHQ series, excellent levels of diastereofacial control were achieved using the phenanthryl ether spacer (208/1). The widely utilized phthalazine (PHAL) and pyrimidine (PYR) spacers were not as effective as DHQ-PHN in enhancing the observed intrinsic selectivities. Our case represents one of the few exceptions where DHQ-PHN gives better selectivities than either the PHAL or PYR spacers. Within the DHQD series the inherent bias could hardly be overcome, and only (DHQD)$_2$-AQN provided good selectivities (12:1). The anthraquinone-derived ligand is the only AD chiral additive with a linear tricyclic-fused aromatic spacer, and perhaps the larger binding pocket provided by this more extended spacer is required to achieve good levels of diastereofacial control with the sterically demanding olefin (−)-**31**.

(34) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (b) Danishefsky, S. J.; Larson, E.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274.

Total Syntheses of Potent Glycosidase Inhibitors

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Scheme 11

Figure 4. (A) S_N2 displacement of the pyrrolidine nitrogen of mesylate **iii**. (B) Steric interactions between the pyrrolidine ring and CH_2OTBS group which impede S_N2 displacement of mesylate **50**.

There is also a marked difference between the hydrogenolytic behavior of the two epimeric nitroso acetals **42** and **49**. Since hydrogenolysis of nitroso acetal **42** occurs at high pressures, the intermediate pyrrolidine mesylate **iii** is presumably the penultimate intermediate leading to (−)-**47**, Figure 4A. Mesylate **iii** undergoes facile and efficient S_N2 displacement of the mesylate group to afford pyrrolizidine (−)-**47**, Figure 4A. In sharp contrast, hydrogenolysis of the epimeric nitroso acetal **49** provides the pyrrolidine mesylate **50**, which does not undergo facile S_N2 displacement to (−)-**51**, Figure 4B. Steric interactions between the pyrrolidine ring and the CH_2OTBS group of **50** presumably account for its inability to cyclize to (−)-**51** at room temperature. Our mechanistic hypothesis has always implicated the intermediacy of pyrrolidine mesylate **50** in the hydrogenolytic pathway. The unique steric interactions that allowed the isolation of **50** provided the rare opportunity to verify one of the proposed species and demonstrate the efficiency of this transformation.

Synthetic Summary

The total syntheses of castanospermine ((+)-**1**), 6-epicastanospermine ((+)-**2**), australine ((+)-**3**), and 3-epiaustraline ((+)-**4**) have been accomplished. Construction of the indolizidine alkaloids requires eight steps starting from chlorosilyl triflate **22** to afford (+)-castanospermine ((+)-**1**) and (+)-6-epicastanospermine ((+)-**2**) in 18 and 24% overall yields, respectively. The pyrrolizidine alkaloids (+)-australine ((+)-**3**) and (+)-3-epiaustraline ((+)-**4**) were obtained in a nine-step sequence in 17 and 22% overall yields, respectively, from **22**. The ability to access both 5,5- and 5,6-fused bicyclic systems was a result of successful in situ N-alkylation during the hydrogenolysis of four highly functionalized nitroso acetals. These four substrates were derived from a single intermediate, which was created by the enantioselective tandem [4 + 2]/[3 + 2] cycloaddition of nitro olefins. Despite its initial lability, the silaketal functionality served to provide exceptional levels of diastereocontrol and the ideal combination of protection and functional-group placement. Application of this strategy toward the synthesis of other highly oxygenated alkaloids is in progress.

Experimental Section

See Supporting Information.

Hydrogenolysis of Nitroso Acetal Tosylates. The hydrogenolysis of these nitroso acetals is a remarkable process in which a series of discrete transformations determines the formation of the highly functionalized bicyclic structures. A plausible mechanism for the hydrogenolysis has been discussed in detail previously.[14] The sequence herein described differs only in the closure of the second pyrrolidine ring by an alkylation rather than an acylation reaction. For the primary tosylates **36** and **37**, this transformation proceeded smoothly and the 5,6-bicyclic structures of (+)-**1** and (+)-**2** were obtained in exceptional yields (73−81%) considering the complexity of this transformation.

The hydrogenolysis of the secondary mesylates provided a unique insight into the mechanism of the hydrogenation and the effect of H_2 pressure. There is an interesting dichotomy in the fate of nitroso acetal **49** at high vs low H_2 pressures, Scheme 11. At 260 psi the pyrrolidine mesylate **50** was obtained almost exclusively, while at 80 psi only the pyrrolizidine (−)-**51** was obtained, albeit in low yields. These results suggest that there exists more than one pathway for the hydrogenolysis of nitroso acetal **49** and that these pathways show different pressure dependencies. This hypothesis is supported by the fact that **50** is not converted to (−)-**51** upon prolonged stirring in MeOH at 23 °C, although cyclization does occur at higher temperatures. We believe that at high H_2 pressures (160−260 psi) rapid cleavage of *both* N−O bonds occurs (path A, Scheme 11). Hemiacetal breakdown and reductive amination provides **50** which is unable to spontaneously cyclize to (−)-**51**. At lower pressures, it is reasonable to posit asynchronous N−O bond cleavage (path B, Scheme 11). Rapid cleavage of the isoxazoline N−O bond would provide amino alcohol **i** that could undergo N-alkylation to afford the pyrrolidine **ii**. Cleavage of the 1,2-oxazine ring, hemiacetal breakdown, and subsequent reductive amination could then afford (−)-**51** without the intermediacy of **50**. It is therefore possible that the difference between high- and low-pressure hydrogenations could be the relative rate of N−O bond cleavage and the timing of N-alkylations.
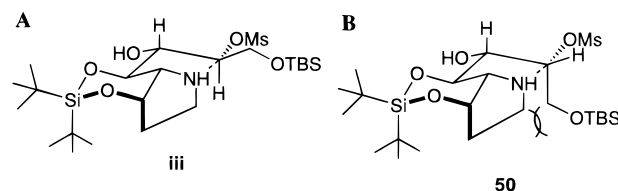
Supporting Information Available: The general experimental methods and full experimental, spectroscopic, and analytical details for all new compounds described. Comparative 750 MHz ^{1}H NMR data for natural and synthetic (+)-castanospermine ((+)-**1**) and (+)-3-epiaustraline ((+)-**4**) along with ^{1}H NMR, ^{13}C NMR, COSY, and HETCOR spectra for (+)-castanospermine ((+)-**1**), 6-epicastanospermine ((+)-**2**) and its hydrochloride salt (−)-**39**, 3-epiaustraline ((+)-**4**) and its hydrochloride salt (−)-**48**, and australine ((+)-**3**) and its hydrochloride salt (+)-**53** are provided. The structures of the DHQD-derived chiral ligands are also given. This material is available free of charge via the Internet at http://pubs.acs.org.

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