Synthesis of (+)-Casuarine

Scott E. Denmark* and Alexander R. Hurd

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

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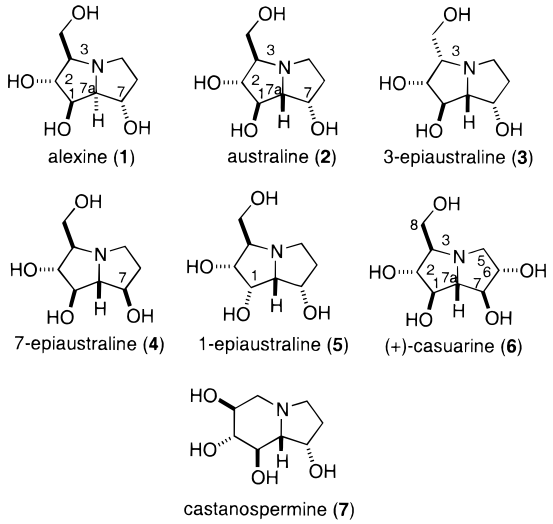
The first synthesis of (+)-casuarine ((+)-**6**), a pentahydroxy pyrrolizidine alkaloid of the alexine/australine subclass, is described. The key step is a tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition involving nitrobenzoate **13**, chiral vinyl ether **16c**, and vinyl silane **10**, which establishes five of the six stereocenters present in this potent glycosidase inhibitor. The completion of the synthesis requires only four additional steps to deliver the final product in 20% overall yield.

Introduction and Background

The alexines and australines are a growing subclass of pyrrolizidine alkaloids, many of which display potent glycosidase activity. Named after the first two identified members of this new class, alexine (**1**)[1] and australine (**2**)[2] bear a C(3) hydroxymethyl substituent, differentiating them from the more common necines which bear a C(1) hydroxymethyl group, Chart 1. Since the isolation

Chart 1



of alexine (**1**) and australine (**2**) in 1988, the identification of other members of this class quickly followed, including 3-epiaustraline (**3**),[3] 7-epiaustraline (**4**),[4] 1-epiaustraline (**5**),[4,5] and the hydroxylated derivative casuarine (**6**).[6] Unlike the necine alkaloids, which are typically isolated with an acid side chain, the alexine/australine pyrrolizidine alkaloids are isolated as the base, although glycoconjugates have also been isolated.[7] Potential anti-cancer[8] and anti-viral[9] properties of polyhydroxyl pyrrolizidine and indolizidine alkaloids stem from their resemblance to sugars and, not surprisingly, many display significant glycosidase inhibition activity.[10] In a comparative study, all australines and alexines are potent inhibitors of fungal glucan 1,4-α-glucosidase and compare in activity to the well-known glycosidase inhibitor castanospermine (**7**).[4] Additionally, both 7-epiaustraline (**4**) and 1-epiaustraline (**5**) are active in glucosidase activity mouse models[4] and have been patented.[11]

(+)-Casuarine (**6**) is the most recently isolated member of this class. It was obtained from 75% aqueous ethanolic extract of the bark of *Casuarina equisetfolia* L. (Casuarinaceae) in 0.013% yield.[6] A glycoside of casuarine, casuarine-6-α-D-glucoside, was also isolated from this plant extract in nearly equal amount.[7] The structure and the absolute configuration of casuarine were established unambiguously by single-crystal X-ray spectroscopy as (+)-**6**. Casuarine is an effective inhibitor of glucosidase I (72% inhibition at 5μg/mL) rivaling that of the indolizidine alkaloid castanosperime (84% inhibition at 5μg/mL).[12] The five hydroxyl groups make (+)-casuarine the most highly oxygenated amino-sugar analogue yet identified.[13]

Although there are no syntheses of casuarine (**6**) on record, the synthesis of four diastereomers was recently disclosed.[12] This work represents an effective method for obtaining these diastereomers, but it is inflexible in its design to access other diastereomers, as selective protection, deprotection, and activation schemes would render the approach cumbersome and lengthy. The alternative,

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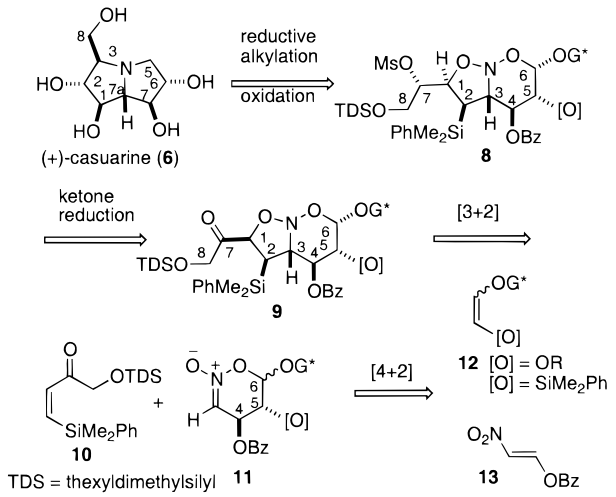
beginning with materials possessing the correct hydroxyl configurations, may be limited by the availability of carbohydrate sources.

Recent publications from these laboratories have documented the use of tandem [4 + 2]/[3 + 2] nitroalkene cycloadditions for the efficient syntheses of several polyhydroxylated pyrrolizidine and indolizidine alkaloids.[14] These studies clearly demonstrated the ability of the tandem cycloaddition strategy to assemble these skeletons with excellent control over as many as four contiguous stereogenic centers. (+)-Casuarine (**6**) with its densely oxygenated periphery represented a still greater challenge to install five of the six-contiguous stereocenters by the cycloaddition construct. Of further interest to the development of the [4 + 2]/[3 + 2] nitroalkene cycloaddition method was that the synthesis of (+)-casuarine required an intermolecular [3 + 2] cycloaddition of a suitable substituted dipolarophile and a flexible, heavily substituted nitronate. The study of intermolecular [3 + 2] dipolar cycloadditions of conformationally flexible nitronates has been limited. The successful resolution of this challenge in the synthesis of (+)-casuarine is detailed below.[15]

Synthesis Design

To accommodate the installation of so many hydroxyl groups in a stereodefined fashion, a suitably functionalized nitroalkene, dieneophile, and dipolarophile were needed. From previous endeavors we knew that oxygenated nitroalkenes[14] and dieneophiles[16] were amenable to [4 + 2] cycloaddition, but oxygenated dipolarophiles gave regioreversed cycloadducts.[17] Thus, we made recourse to the phenyldimethylsilyl substituent as a surrogate for the hydroxyl group at C(1).[18]

Scheme 1



This synthetic design is outlined in Scheme 1. It is expected that (+)-casuarine would be produced from nitroso acetal **8** by N−O bond cleavage and N-alkylation followed by Tamao−Fleming oxidation[18] of the silyl moiety. Thus, nitroso acetal **8** possesses all the required stereocenters and functionality for the synthesis of (+)-casuarine. With the exception of C(7) (nitroso acetal numbering), all the remaining stereocenters are established in the tandem cycloaddition. Ketone **9** was targeted as the key intermediate, as it would allow a substrate controlled reduction for the creation of the center at C(7) and would arise from a tandem inter [4 + 2]/inter [3 + 2] cycloaddition of components **10**, **12**, and **13**.

A predictable stereochemical outcome of the tandem event is critical for the successful synthesis of (+)-casuarine. The desired approach of the dipolarophile **10**[14g,19] in the [3 + 2] cycloaddition with nitronate **11** was difficult to predict and could hinge on the placement of the C(6) chiral auxiliary. In cases where the C(4) benzoate and the C(6) acetal center are positioned on the same side of the nitronate ring, as in the synthesis of hastanecine[14a] and 7,7a-diepiaustraline,[14g,19] the approach of the dipolarophile is exclusively on the side opposite these substituents. However, in the absence of a C(4) substituent, the C(6) acetal center alone can direct the facial attack of the dipolarophile to the opposite side.[20] Additionally, the presence of a C(5) benzoate group could exert considerable influence on the reactive conformation of the nitronate. In fact, studies on heavily substituted nitronates show a strong sensitivity of facial approach to nitronate conformation.[21] Since the configuration of the C(6) auxiliary substituent is of no consequence to the synthesis of the natural product, as it is destroyed ultimately, the placement of the C(6) alkoxy ligand could be used advantageously to direct the facial attack of the dipolarophile in the desired manner, if necessary.

One option employs a silyl substituent as a hydroxyl surrogate on the dieneophile in the [4 + 2] cycloaddition. The obvious choice to secure high facial selectivity in the [3 + 2] cycloaddition was to use the vinyl silane (*E*)-**14**[14c] in an endo (alkoxy) cycloaddition. This would produce nitronate **15** with the necessary C(4)/C(5) trans arrangement and with the C(4) and (C6) substituents on the same side of the nitronate ring, Scheme 2. Currently, the only available Lewis acid to achieve endo (alkoxy) selective cycloadditions[22] is $TiCl_2(O\textit{i}\text{-}Pr)_2$, and its compatibility with silane (*E*)-**14** is unknown. Alternatively, [4 + 2]cycloaddition of nitroalkene **13**[14a] and acyloxy vinyl ether (*Z*)-**16**[16] should provide nitronate **17**. The required C(4)/C(5) trans relationship was expected, given the high exo selectivity previously demonstrated with this chiral vinyl ether.[16] As a consequence of the *Z*-dieneophile, the α-orientation of the C(6) auxiliary would be expected. Since the C(4) benzoate and the C(6) acetal center are on opposite faces of the nitronate, the dominant controlling element for the [3 + 2] cycloaddition a priori was

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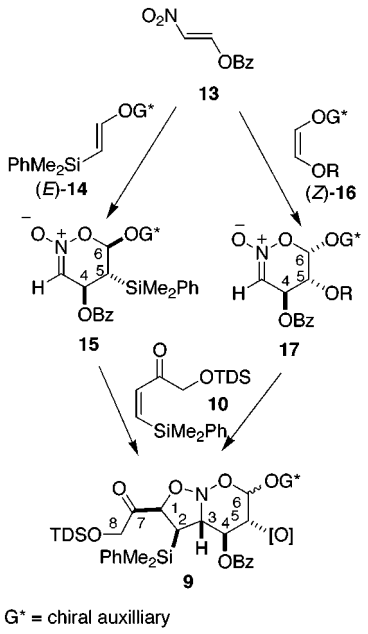
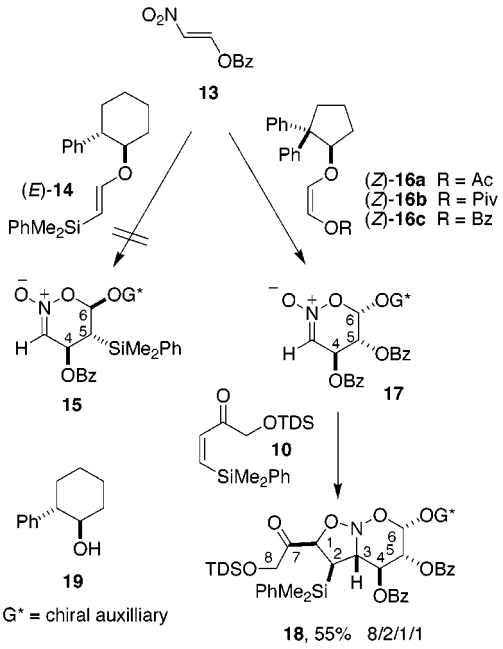
Scheme 2



Scheme 3



uncertain. Additionally, previous studies have shown that this dieneophile is poorly selective with nitroalkenes lacking a C(1) substituent, and the use of $SnCl_4$, necessary for this dieneophile, has little precedent for oxygenated nitroalkenes. Nonetheless, the acyloxy dieneophiles would be the most fitting choice, as the desired hydroxy group is liberated by simple saponification of the ester, avoiding an additional Tamao−Fleming oxidation.

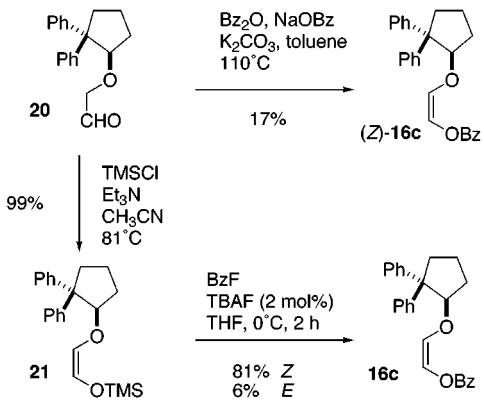
Results

Both options for the assembly of a nitronate suitable for the synthesis of casuarine were initially explored. The vinyl silane (*E*)-**14**, which was developed for the synthesis of (+)-crotanecine[14c] first was examined in combination with $Ti(Oi\text{-}Pr)_2Cl_2$, as this Lewis acid has been used for cycloadditions with oxygenated nitroalkenes.[14] The addition of $Ti(Oi\text{-}Pr)_2Cl_2$ to a cold (−78 °C) solution of **14** and nitroalkene **13** resulted in an immediate, deep red coloration. Upon workup, the only isolated material was the chiral alcohol, phenylcyclohexanol (**19**), Scheme 3. Variations in order of addition gave the same result. Since $Ti(Oi\text{-}Pr)_2Cl_2$ is the only endo selective Lewis acid for the nitroalkene cycloaddition method, the use of silane **14** was abandoned.[23]

Orienting experiments were also conducted using the acyloxy vinyl ethers (*Z*)-**16**[16] and nitroalkene **13**[14a] under previously optimized conditions for this dieneophile for the purpose of assaying the facial selectivity in the [3 + 2] cycloaddition, Scheme 3. The acetoxy vinyl ether (*Z*)-**16a**, and the pivaloyloxy vinyl ether (*Z*)-**16b** were both unsuitable for a productive cycloaddition. Instead, extensive polymerization was noticed. The benzoyloxy vinyl ether (*Z*)-**16c** produced nitronate **17** as a 4/1 mixture (^{1}H NMR analysis) of diastereomers, Scheme 3. Examination of proton NMR coupling constants indicated that both diastereomers possessed the desired C(4)/C(5) trans relationship and were thus diastereomers resulting from attack of the nitroalkene to the two diastereotopic faces of the vinyl ether. Nitronate **17** proved to be too unstable for isolation and purification, and was immediately treated with a solution of the β-silyl enone **10**[19] to afford a 8/2/1/1 mixture (^{1}H NMR analysis) of nitroso acetals **18** in 55% yield over two steps. This ratio was determined by integration of the silyl bearing methine resonance and was judged to be of the same regiochemistry. Since this mixture contained diastereomers created in the [4 + 2] cycloaddition, the [3 + 2] cycloaddition was judged to be facially selective, on the order of 8/1. After separation of the major diastereomer by preparative HPLC, the structure of this component was ultimately confirmed by conversion to the natural product. The important finding in these sets of experiments was that the C(4) benzoate was the dominant controlling element in the [3 + 2] cycloaddition with vinyl silane dipolarophile **10**. This was surprising given the placement of the C(4) benzoate and the C(6) auxiliary on opposite sides of the nitronate ring. Nonetheless, the approach for the synthesis was now deemed feasible using the acyloxy dieneophiles.

In addition to the obvious improvements needed for both yield and facial selectivity in the [4 + 2] cycloaddition, the existing synthesis[16] of the benzoate (*Z*)-**16c** was poor yielding (17%), and a new route had to be developed, Scheme 4. Low temperature and neutral conditions were

Scheme 4

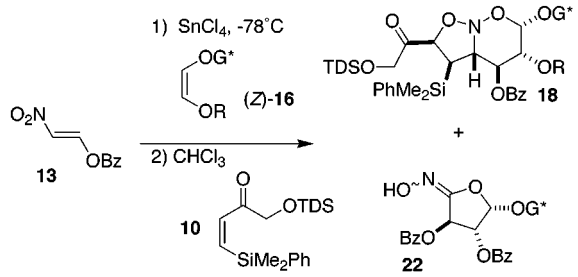


(23) The combination of the vinyl silane (*Z*)-**14** with the Lewis acid MAPh did produce a nitronate, but this decomposed before [3 + 2] cycloaddition with vinyl silane **10**.

important for the new O-acylation method in order to minimize polymerization of the base sensitive α-alkoxyaldehyde. A two step protocol was developed which ensured that the deprotonated aldehyde was not present in the reaction mixture at the same time as the free aldehyde. The chiral alkoxy aldehyde **20**[16] was converted to silyl enol ether **21** in 99% yield as a 10/1 (*Z*/*E*) mixture. O-Acylation with benzoyl fluoride and a catalytic amount of TBAF (2 mol %),[24] afforded a separable mixture of the *Z*-vinyl ether (*Z*)-**16c** in 81% yield along with 6% of the undesired *E*-vinyl ether (*E*)-**16c**.

With an improved synthesis of the dieneophile in hand, optimization of the [4 + 2] cycloaddition could be undertaken. It was discovered that changing two features of the reaction was crucial for increasing its yield, Table 1.

Table 1. Optimization of the Tandem [4 + 2]/[3 + 2] Cycloaddition



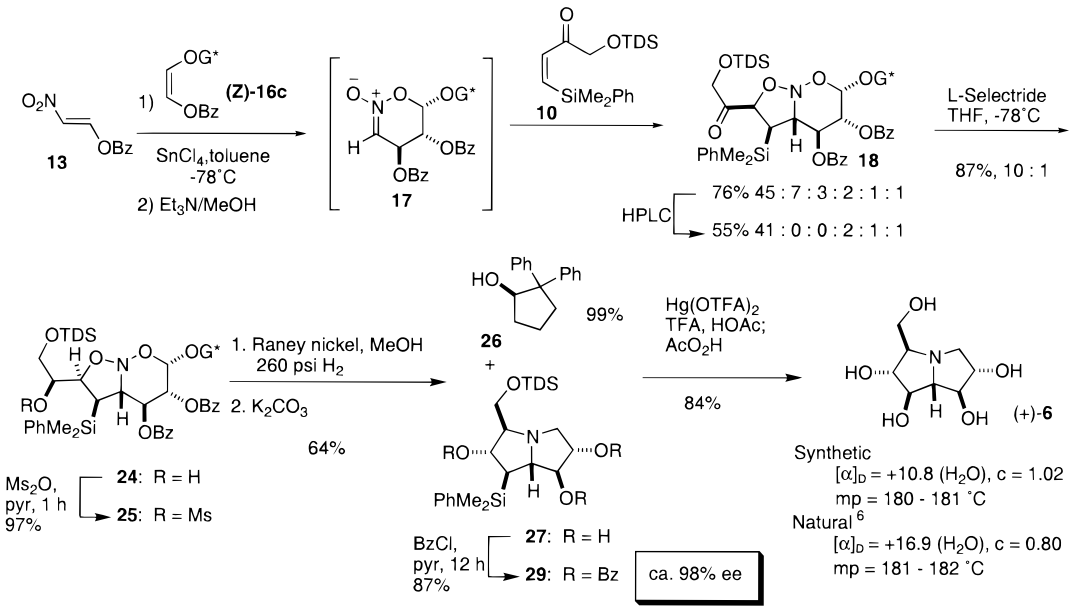
entry	R	solvent	quench	**18**, %	**22**, %
1	**16c**, Bz	CH_2Cl_2	A	55[b]	29
2	**16c**, Bz	toluene	A	63	18
3	**16c**, Bz	toluene	B	0	81
4	**16c**, Bz	toluene	C	76[c]	0
5	**16a**, Ac	CH_2Cl_2	A	0	
6	**16a**, Ac	toluene	A	23	
7	**16a**, Ac	toluene	C	55[d]	

[a] Quench method A = NaOH/MeOH (10 equiv), B = NaOH/MeOH (15 equiv), C = Et_3N/MeOH. (10 equiv) [b] dr = 8/2/1/1. [c] dr = 45/7/3/2/1/1. [d] dr = 5−6/1.

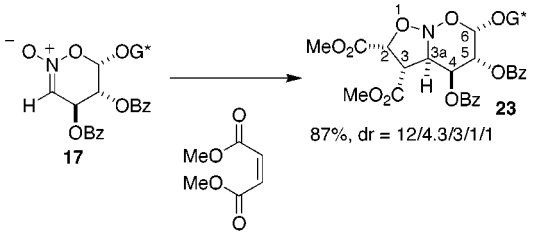
The identification of a byproduct **22** by ^1H NMR analysis of the [4 + 2] reaction prompted the examination of the quench. The standard method (entry 1) for quenching the 2.5 equiv of $SnCl_4$ (NaOH/MeOH, 10 equiv) partially converted the nitronate (up to 29%) to oxime **22**. When the reaction was conducted in toluene instead of CH_2Cl_2 and NaOH/MeOH solution was freshly prepared (entry 2), the yield was increased to 63% along with 18% of the oxime. This indicated that an accurate titration of the NaOH/MeOH solution was important for diverting the reaction away from the oxime pathway. In fact, quenching the [4 + 2] cycloaddition with a slight excess of NaOH/MeOH (15 equiv) and stirring at −78 °C for an additional 30 min led to complete conversion of the nitronate to oxime **22**, entry 3. Quenching the reaction with Et_3N/MeOH (entry 4) at low temperature led to the isolation of the nitroso acetals in 76% yield with none of the oxime detected by NMR. Although the changes in solvent and quench were significant with the benzoate vinyl ether (*Z*)-**16c**, the effect on the acetate vinyl ether (*Z*)-**16a** was even more pronounced. In CH_2Cl_2, with the standard NaOH/MeOH quench (entry 5), no nitroso acetals were isolated. By changing the solvent to toluene with NaOH/MeOH quench, the nitroso acetals were isolated in 23% yield as approximately 5−6/1 ratio of diastereomers (entry 6). In toluene with the modified Et_3N/MeOH quench, the nitroso acetals were isolated in 55% yield (entry 7). Despite the advances in the yield of acetate cycloaddition and seemingly simplified diastereoselectivity, the benzoate vinyl ether cycloaddition was more efficient overall and was selected for the synthesis of casuarine. Under optimized conditions (Scheme 5), nitroso acetal **18** was isolated as a 45/7/3/2/1/1 mixture of nitroso acetals in 76% yield.[25] The major nitroso acetal was enriched to the extent of 41/0/0/2/1/1 by preparative HPLC for an overall yield of 55%.

Configurational assignment of the major diastereomer of nitroso acetal **18** was assisted by examining the cycloaddition of nitronate **17** with dimethyl maleate, Scheme 6. Stirring a mixture of nitronate **17**[26a] (dr = 4.8/1) and dimethyl maleate in $CHCl_3$ for 18 h afforded nitroso acetal **23** in 87% yield as a 12.0/4.8/3.0/1/1 mixture of diastereomers. The structural assignment of the major diastereomer of **23** was established by single-crystal X-ray analysis. Surprisingly, the major diastere-

Scheme 5



Scheme 6



omer in this reaction was derived from β-face approach to nitronate **17**. Figure 1 shows the X-ray crystal structure of nitroso acetal **23** with crystallographically determined indicated dihedral angles and measured ^{1}H NMR coupling constants.[26b] Figure 2 shows the ground-state calculated (MM2) conformation of nitroso acetal **18** with indicated dihedral angles and ^{1}H NMR coupling constants (the C(6) auxiliary has been replaced with a methyl group for clarity). Proton NMR coupling analysis indicated that the two nitroso acetals (**18** and **23**) existed in very different solution conformations about the oxazine ring. In the ^{1}H NMR spectrum of nitroso acetal **23**, both the C(4) and C(5) protons appeared as doublets of doublets. However, in the ^{1}H NMR spectrum of nitroso acetal **18**, both the C(4) methine and the C(5) methine resonances are singlets, indicative of a near 90° dihedral angle. Thus, four of the five sterocenters in (+)-casuarine were now set.

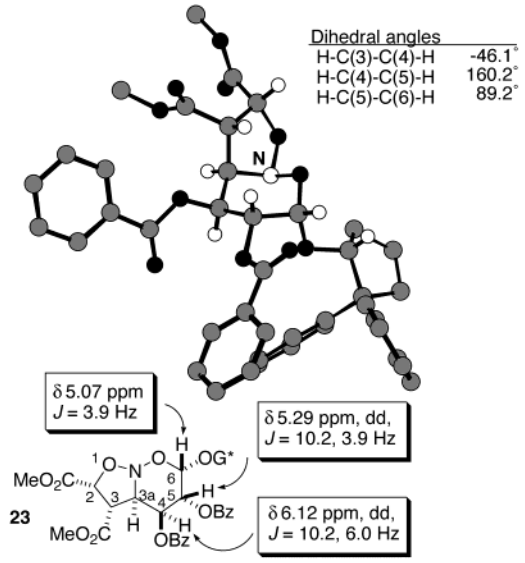


Figure 1. X-ray crystal structure of nitroso acetal **23**, with indicated dihedral angles and ^{1}H NMR coupling constants.

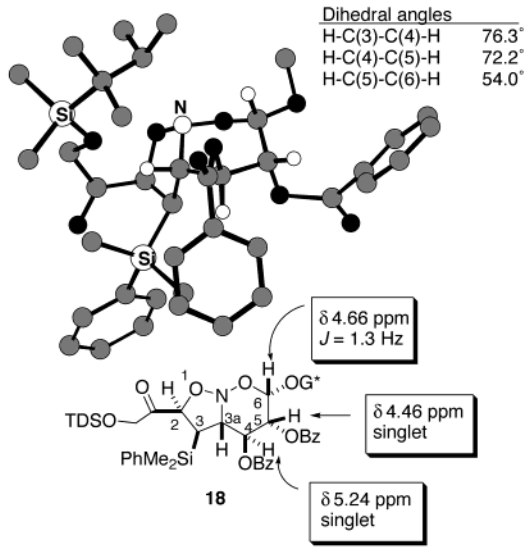
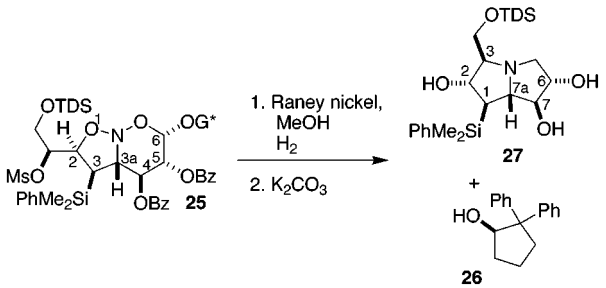


Figure 2. MM2-minimized conformation of nitroso acetal **18** with indicated dihedral angles and ^{1}H NMR coupling constants.

The final stereocenter was installed by a selective ketone reduction, Scheme 5. Treatment of keto nitroso acetal **18** with L-Selectride led to a 10/1 mixture of epimeric alcohols **24** in 87% yield.[25] Additionally, the three minor diastereomers present in the starting ketone mixture were chromatographically removed. These minor diastereomers were isolated as unreacted ketones, which was supported by spectroscopic evidence (MS, ^{13}C NMR). Furthermore, ^{1}H NMR analysis (vide supra) indicated that two of the three diastereomers were derived from the opposite [3 + 2] facial approach. The configurational assignment of the product alcohol was based on previous examples[14g] and examination of models. Ultimately, the assignment was verified by conversion to the natural product.

The resulting mixture of epimeric alcohols was activated in nearly quantitative yield with methanesulfonic anhydride in pyridine to form **25**, Scheme 5. Mesylate **25** then was reduced in the presence of Raney nickel and hydrogen. It was discovered that the C(5) benzoate suffered partial saponification under the reaction conditions. Thus, to facilitate purification, K_2CO_3 was added at the end of the reaction to affect complete removal of both benzoate groups. The hydrogenolysis of **25** showed a slight pressure and time dependence, Table 2. At 160 psi the yield of the pyrrolizidine **27** and the auxiliary **26** were the same (entry 1). When the hydrogenolysis was conducted at a higher temperature (entry 2) the yield of

Table 2. Hydrogenolysis Optimization of Nitroso Acetal 25



entry	P_{H_2}, psi	T, °C	time, h	**27**, %	**26**, %
1	160	23	40	65	64
2	160	50	48	60	90
3	260	23	44	64	99
4	260	23	64	64	99
5	500	23	45	50	93

(24) Limat, D.; Schlosser, M. *Tetrahedron* **1995**, *51*, 5799.

(25) Diastereomeric ratio was determined by chiral stationary phase supercritical fluid chromatography (SFC).

(26) (a) The synthesis of **23** is described in the Experimental Section using a chiral nonracemic dieneophile, but the X-ray crystal structure was obtained from diffraction of racemic material. (b) The crystallographic coordinates of **23** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. CCDC 136434.

the pyrrolizidine **27** was not significantly altered, but the recovery of the auxiliary **26** was increased to 90%. Similarly, at 260 psi and at room temperature the yield of the pyrrolizidine **27** was again unchanged and the recovery of the auxiliary **26** was near quantitative (entry 3). Longer reaction times at 260 psi had no effect (entry 4). At 500 psi hydrogen the recovery of the auxiliary **26** was again high, but the yield of the pyrrolizidine **27** was reduced (entry 5). Under optimized conditions, treatment of the mesylate **25** with Raney nickel in MeOH under 260 psi of H_2 for 44 h provided crystalline pyrrolizidine **27** in 64% yield along with a 99% recovery of the chiral auxiliary **26**, Scheme 5.

The completion of the synthesis required only the transformation of the C(1) silyl group to the final hydroxyl substituent and deprotection. Initial investigations were aimed at avoiding the use of mercury salts for this process due to complications in the isolation of the final product previously encountered.[14g,19] The dearylation can be conducted under acidic, basic or electrophilic conditions. Initially, a strong acid was sought to favor protodesilylation over Peterson olefination,[27] an obvious possibility given the trans relationship of the C(2)-hydroxyl and C(1) silane groups. Trifluoroacetic acid at reflux surprisingly returned starting material. Dry HCl in $CHCl_3$ slowly produced the olefin **28** (not shown), along with the insoluble HCl salt of the starting silane. Sulfonic acids were next attempted. Methanesulfonic acid at room temperature slowly produced the Peterson olefinated product, while trifluoromethanesulfonic acid cleanly and rapidly produced the olefin trifluoroacetate salt. Basic oxidation conditions as described by Woerpel[28] were ineffective, instead producing an unidentified mixture of products. Electrophilic desilylation with iodine monochloride cleanly dearylated silane **27**, but also seemed to iodinate the tertiary nitrogen and was abandoned. Since acidic, basic or electrophilic conditions were not encouraging, the use of mercury salts was reinvestigated.

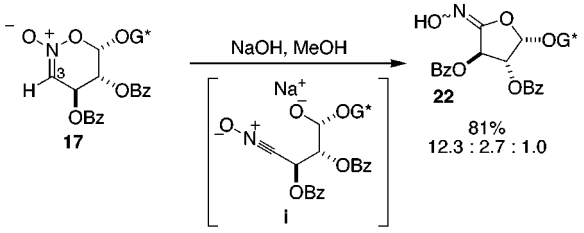
In the synthesis of 7-epiaustraline,[14g,19] mercury salts were effective for the dearylation process, but failure to remove all the mercury by ion exchange chromatography complicated the subsequent *N*-oxide reduction step. Conditions which limit the production of the *N*-oxide were sought. It was discovered that *N*-oxide production could be controlled by conducting the oxidation at room-temperature rather than the standard 50 °C protocol. This process began with dearylation of the silyl group of **27** with mercuric trifluoroacetate in trifluoroacetic acid and acetic acid for 1 h, followed by room-temperature oxidation (16 h) with peracetic acid to provide (+)-casuarine (**6**), Scheme 5.[29] If the oxidation were conducted at a higher temperature (50 °C), a significant amount of *N*-oxide was observed. Under the room-temperature oxidation conditions less than 5% *N*-oxide was detected by ^{1}H NMR analysis. After ion exchange chromatography (BioRad AG 50W-X8), casuarine was isolated by crystallization from EtOH. The *N*-oxide present in the mother liquor was reduced (H_2, MeOH, Pd/C, HOAc, 16 h) and, following ion-exchange chromatography and crystallization, provided additional amounts of casuarine to bring the combined yield to 84%.

All physical and spectral properties of synthetic (+)-casuarine (**6**) were obtained from an analytically pure sample and are in agreement with the reported measurements[6] of the natural product. However, the optical rotation of synthetic (+)-casuarine (**6**) was low (+10.8 versus +16.9 (H_2O) reported for the natural material). This discrepancy prompted us to vouchsafe the enantiomeric purity of the synthetic material by independently establishing the enantiomeric composition of a late stage synthetic intermediate. The 2,6,7-trisbenzoate **29**, obtained in 85% yield from **27** (pyridine, Bz_2O, 12 h), was determined to have an enantiomeric excess of ca. 98% by chiral stationary phase supercritical fluid chromatography (SFC). We thus conclude that the reported optical rotation for natural for (+)-casuarine is erroneously high.

Discussion

[4 + 2] Cycloaddition. In addition to providing insight into the optimization of the [4 + 2] cycloaddition, the isolation and identification of oxime **22** also provided information about the effectiveness and diastereoselectivity of the first step of the tandem process, the [4 + 2] cycloaddition. The [4 + 2] cycloaddition was judged to be high yielding (81%) and occurred with modest facial selectivity (4.8/1).[30] The rearrangement of nitronate **17** to oxime **22** is envisioned to proceed by a base-catalyzed deprotonation of HC(3) creating a nitrile oxide intermediate, which collapses to form the oxime product, Scheme 7. This fragmentation has precedent in nitronate chemistry.[31] Interestingly, by this mechanism, the hemiacetal is captured by the nitrile oxide before acetal breakdown can occur.

Scheme 7



There are two factors that influence the stereochemical outcome of the [4 + 2] cycloaddition. The first factor concerns the relative topicity of π components in the cycloaddition and this sets the relative configuration between the C(4) substituent and the C(6) substituent. The endo/exo descriptor has been traditionally employed to delineate this relative diastereoselection. An exo cycloadduct possesses a C(4)/C(6) trans, while an endo cycloadduct has a C(4)/C(6) cis relationship. As a direct consequence of the vinyl ether geometry, the relative configuration between C(4) and C(5) is also established. The second factor involves the differentiation of one of the diastereotopic π faces (*Re* or *Si)* of the vinyl ether by the chiral auxiliary and is termed internal diastereoselection. This element determines the configuration at C(6) relative to the resident stereocenter(s) of the chiral

(27) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. (b) Ager, D. J. *Synthesis* **1984**, 384. (c) Ager, D. J. *Org. React.* **1990**, *38*, 1.
(28) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044.
(29) Kolb, H. C.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2735.

(30) Diastereomeric ratio was determined by NMR. The two major diastereomers are assumed to be facial diastereomers. It is uncertain whether the third diastereomer is an oxime geometric isomer or an acetal epimer.
(31) (a) Denmark, S. E.; Moon, Y.-C.; Cramer, C. J.; Dappen, M. S.; Senanayake, C. B. W. *Tetrahedron* **1990**, *46*, 7373. (b) Colvin, E. W.; Robertson, A. D.; Seebach, D.; Beck, A. K. *J. Chem. Soc., Chem. Commun.* **1981**, 952.

auxiliary. The descriptor for this stereoinduction[22,32] combines the configuration at C(1′) of the auxiliary (*R* or *S*) with the observed face of attack (*Si* or *Re*). Attack of a nitroalkene to the *Re* face of the vinyl ether bearing an *R* configuration at C(1′) would be termed *like* (1,3-*lk)*. Similarly, attack on the *Si* face of a vinyl ether bearing an *R* configuration at C(1′) would be *unlike* (1,3-*ul*).

In nitronate **17**, the C(4) benzoate is trans to both the C(5) benzoate and the C(6) auxiliary, Figure 3. This assignment is supported by the ^{1}H NMR analysis of nitronate **17** and the X-ray crystal structure of [3 + 2] cycloadduct **23**. This relative configuration can arise only from an *exo* orientation of the vinyl ether to the nitroalkene. Additionally, the configuration at C(6) is of the *S* configuration, which arises from attack of the nitroalkene on the *Si* face of the vinyl ether. The X-ray crystal structure of **23** also confirms that the C(1′) position of the auxiliary is of the *R* configuration, making this internal stereoinduction of the (1,3-*ul*) variety. Nitronate **17** arises from an *exo*, (1,3-*ul*) cycloaddition of nitroalkene **13** and vinyl ether **16c**.

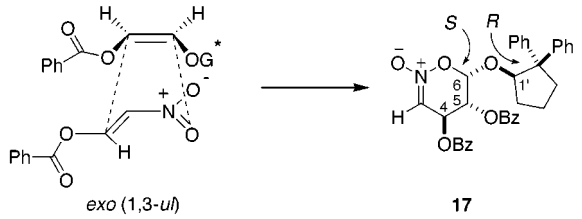


Figure 3. Exo approach of *Si* face of vinyl ether (*Z*)-**16c** to nitroalkene **13**.

An understanding of the forces responsible for the stereodifferentiation of the π faces of the vinyl ether by the chiral auxiliary may be understood by first considering the reactive conformation of vinyl ethers in general. There are two limiting reactive conformations of a vinyl ethers, s-cis and s-trans. Recent calculations and experimental work suggest that although the s-cis conformation is typically the lowest energy conformation in the ground state, the s-trans conformation is the more reactive of the two.[33] However, in tandem nitroalkene cycloadditions, reactions through both s-cis and s-trans conformations have been invoked to explain the observed facial selectivity.[22,32]

Examination of molecular models of the ground state provides some indication of facial shielding in each of the limiting reactive conformations. Both the s-trans and the s-cis ground state conformations (MM2) of vinyl ether (*Z*)-**16c** are shown in Figure 4. The s-cis conformation provides little facial discrimination for an approaching heterodiene, as one of the phenyl rings partially blocks the *Si* face and the cyclopentyl ring partially obstructs the *Re* face. To explain the observed product by reaction through this conformation, the heterodiene would have to approach the vinyl ether on the same face as the phenyl substituent, while the cyclopentyl ring is the stereocontrolling element. On the other hand, in the s-trans conformation, one of the phenyl rings provides considerable shielding to the *Re* face, leaving the *Si* face available. Approach of the *Re* face of the nitroalkene-Lewis acid complex to the *Si* face vinyl ether in the

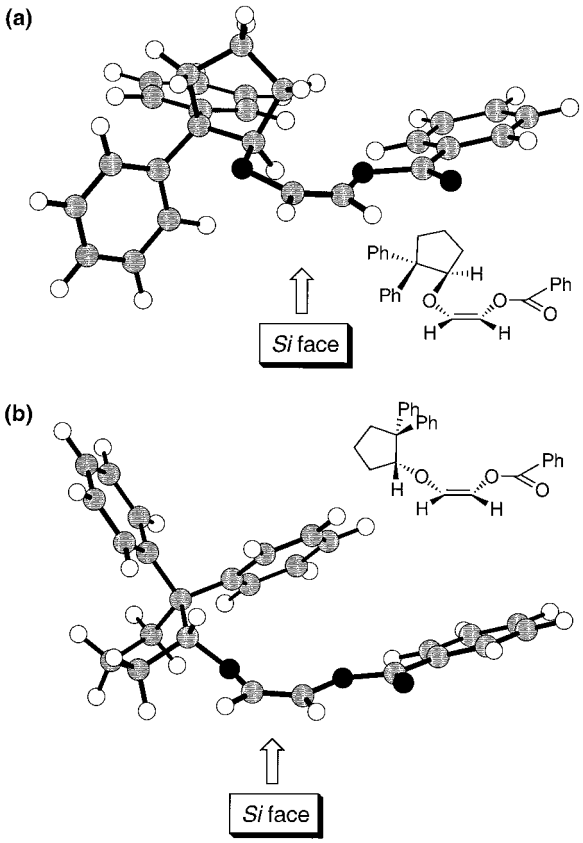


Figure 4. Representations of vinyl ether (*Z*)-**16c** (a) s-cis (b) s-trans conformation from MM2 calculations.

s-trans configuration would provide the experimentally observed nitronate product.

The current analysis stands in sharp contrast to a recent study of cycloadditions promoted by $SnCl_4$ in which it was proposed that phenylcyclohexanol modified vinyl ethers reacted in an s-cis conformation.[22,32] The switch in internal stereoinduction in these cases was rationalized by considering a nonbonded steric interaction between the auxiliary of the s-trans configured vinyl ether and $SnCl_4$ which is relieved by reaction through an s-cis vinyl ether conformation. Experimentally, reaction via the s-cis conformation seems to be a general phenomenon only with phenylcyclohexanol modified vinyl ethers, but the larger *trans*-2-cumylcyclohexyl (TCC) vinyl ether does not exhibit this trait.[34]

The disparity between the reactive conformations of phenylcyclohexanol modified vinyl ethers and vinyl ether (*Z*)-**16c** may lie in the *size* and *shape* of the auxiliary. Just as steric interactions between the Lewis acid and the auxiliary can alter a reactive conformation, the same could be stated about steric interactions of the auxiliary with the β-substituents of the vinyl ether. Clearly, the greater the size of the auxiliary, the greater the nonbonded interactions will be with both the β-substituent and the Lewis acid. The reactive conformation of the vinyl ether then depends on the interaction which incurs a greater penalty. An alternative explanation is that the shape of the diphenylcyclopentyloxy auxiliary is simply different than that of phenylcyclohexanol and no interaction with the Lewis acid occurs. To illustrate this pos-

(32) Denmark, S. E.; Dixon, J. A. *J. Org. Chem.* **1998**, *63*, 6178.
(33) Liu, J.; Niwayama, S.; You, Y.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 1064.
(34) Dixon, J. A. Ph.D. Thesis, University of Illinois, Urbana, 1998.

sibility, a model of the nitrobenzoate **13**−$SnCl_4$ complex was assembled using modified X-ray crystallographic data,[35] as in the previous analysis,[32] and was docked with the s-trans vinyl ether (*Z*)-**16c**, itself obtained from MM2 calculations, Figure 5. As before, the tin atom is presumed to be hexacoordinate (with four chlorines and the nitroalkene as the ligands) in an octahedral geometry.[36] The final coordination site is occupied by a methanol molecule for simplicity, but in the reaction this likely would be another vinyl ether, nitroalkene or the product nitronate. The nitroalkene is docked at the distances determined by transition state calculations for the Lewis acid-catalyzed cycloaddition of nitroethylene, and methyl vinyl ether.[37] This representation suggests that there are no significant nonbonded steric interactions between the chiral auxiliary and the Lewis acid. Therefore, the vinyl ether may not be forced into reaction through the s-cis conformation as is seen in $SnCl_4$ promoted reactions with phenylcyclohexanol modified vinyl ethers.

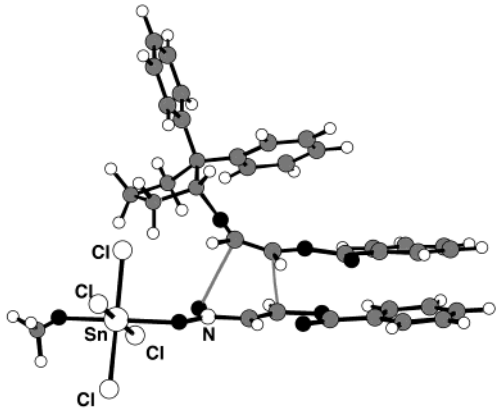


Figure 5. Approach of s-trans conformer of (*Z*)-**16c** to $SnCl_4$·**13** complex.

[3 + 2] Cycloaddition. The stereochemical analysis of the [3 + 2] cycloaddition step in this synthesis was complicated by the difficulty in establishing the identity of the minor diastereomers in the product. The [4 + 2] cycloaddition was deemed to occur in 81% yield with 4.8/1 facial selectivity, as determined by its conversion to the oximino ether **22**. The selectivity in the [3 + 2] cycloaddition step is less clear. In the worst instance, if all of the other diastereomers arose from the β−face approach to the nitronate, the [3 + 2] selectivity would be 3.2/1. However, since this diastereomeric ratio must include the [4 + 2] cycloaddition diastereomers (4.8/1), the [3 + 2] ratio is probably closer to 9/1. The sense and magnitude of this preference is astonishing because the same nitronate undergoes [3 + 2] cycloaddition with dimethyl maleate to the extent of 3/1 *favoring the opposite face.* Assuming that both dipolarophiles react with similar timing and geometry, it is surprising that the face selectivity switches by the simple substitution of the exo oriented β-substituent from a carbomethoxy to a phenyldimethylsilyl group. This suggests that the β-position of the dipolarophile is involved in a critical nonbonded steric interaction with the nitronate.

There are two likely reactive conformations of the nitronate **17** in the [3 + 2] cycloaddition: a twist-chair with an axially disposed C(6) alkoxy group (**A**) and one with an equatorially disposed C(6) alkoxy group (**B**), Figure 6. The top side of nitronate conformer **A** is expected to

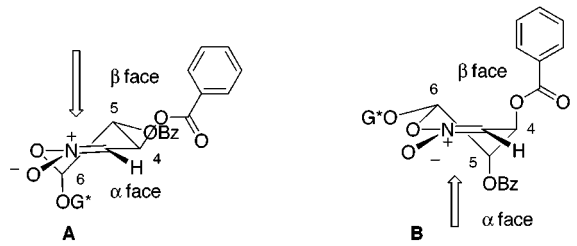


Figure 6. Preferred approach of dipolarophiles to **17**.

be the more reactive face, as it leads directly to a favorable chair conformation, and the approaching dipolarophile should encounter little steric interference from the two equatorially disposed benzoate groups at C(4) and C(5). Since the top face of nitronate conformer **B** is significantly shielded by the C(4) benzoate group, reaction is expected to take place on the bottom face of this conformer. Whereas dimethyl maleate adds preferentially to the top face of nitronate **A**, the silyl dipolarophile **10** adds to the bottom face of either conformer **A** or conformer **B**. Examination of models constructed from AM1 semiempirical calculations of conformer **A** of nitronate **17** indicate that the top face approach of silyl dipolarophile is disfavored by a severe nonbonded steric interaction between the equatorially oriented C(4) benzoate of the nitronate and the phenyldimethylsilyl moiety of **10**, Figure 7. As a consequence, reaction occurs on the bottom

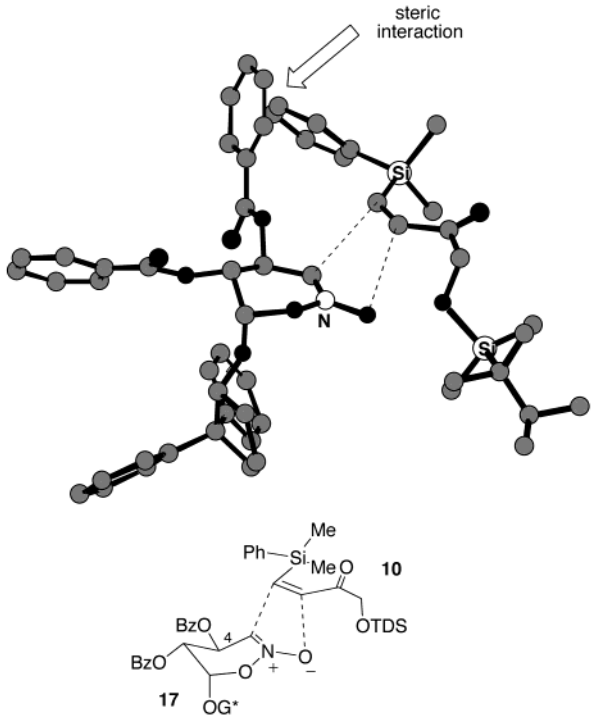


Figure 7. Disfavored [3 + 2] cycloadditions indicating nonbonded steric interactions between the C(4) benzoate of nitronate **17** and the $PhMe_2Si$ group of the dipolarophile **10**.

(35) Lewis, F. D.; Oxman, J. D.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 466.

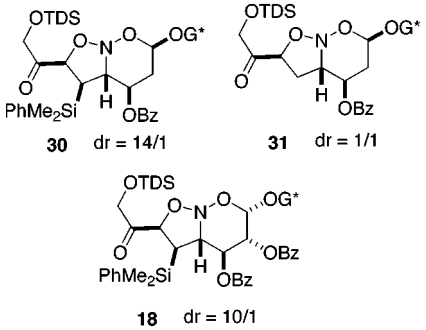
(36) (a) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1993**, *115*, 3133. (b) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256. (c) Reetz, M. T. In *Selectivities in Lewis Acid Promoted Reactions*; Schiner, D., Ed.; Kluwer: Dordrecht, 1989; pp 107−125.

(37) Domingo, L. R.; Arnó, M.; Andrés, J. *J. Org. Chem.* **1999**, *64*, 5867.

face likely through conformer **B**, as this leads directly to a chair conformation of the oxazine six-membered ring.

Ketone Reduction. The stereochemical course of hydride reduction of chiral ketones depends on the reactive conformation of the ketone, the nonbonding interactions between the approaching hydride reagent and the shielding imparted by resident stereocenters of the ketone. In the reduction of keto nitroso acetal **18**, the phenyldimethylsilyl substituent is believed to provide the steric shielding. In studies on the related nitroso acetals (**30** and **31**), the diastereomeric ratio was 14/1 when the phenyldimethylsilyl substituent was present (**30**), Chart 2.[19] In its absence (nitroso acetal **31**) the reduction was unselective (1/1).

Chart 2



Examination of reactive conformations of **18** where the phenyldimethylsilyl substituent imparts carbonyl facial shielding indicates that the Cornforth model[38] best explains the selective reduction of the keto nitroso acetal. Figure 8 depicts a ground state MM2 calculated structure in which the dihedral angle [O(24), C(18), C(6), O(4)] is 165° (the benzoate aryl rings and the chiral auxiliary have been replaced by methyl groups, and thexyldimethylsilyl methyl groups have been removed for clarity). The phenyldimethylsilyl substituent effectively shields the *Si* face of the ketone. Other models for the addition of nucleophiles to ketones do not explain the observed facial selectivity, but all are within 1 kcal/mol of the global minimum. Only in the Cornforth conformation is the *Re* face of the carbonyl exposed.

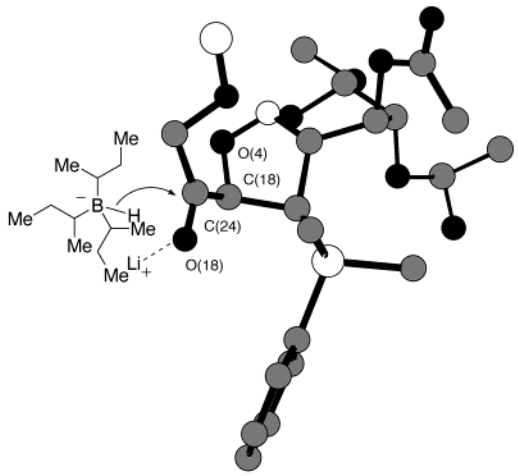


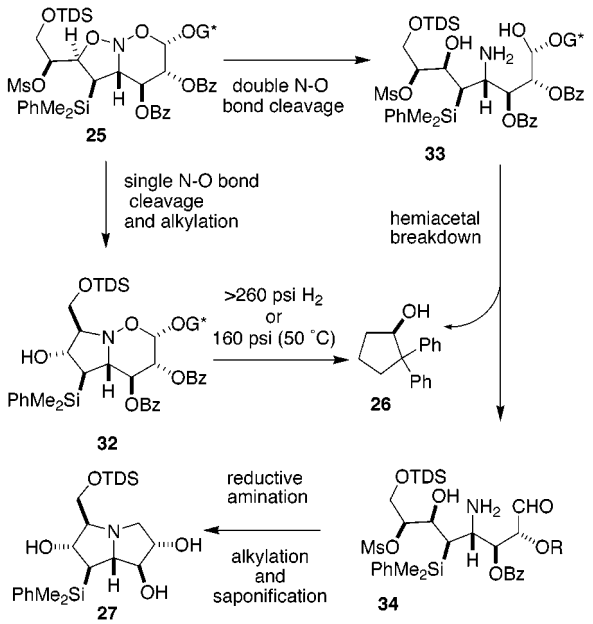
Figure 8. Reactive conformation of ketone **18** (MM2).

(38) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112.

Hydrogenolysis. The successful implementation of the tandem nitroalkene cycloaddition method requires the hydrogenolytic unmasking of nitroso acetals. Although this step is crucial for the synthesis of pyrrolizidine and indolizidine natural products, it remains a transformation about which very little is known. The hydrogenolysis of nitroso acetal **25** is no exception. Since there were no other products isolated except the pyrrolizidine silane **27** and the auxiliary **26**, very little insight into the reaction mechanism is possible. Examination of the optimization study does allow for some conjecture as to the timing of the hydrogenolysis events.

At 160 psi, the yield of the silane **27** and the recovery of the auxiliary **26** are the same (64%), but at higher pressures and higher temperatures only the recovery of the auxiliary is effected (99%). One interpretation of these results is that at 160 psi and above the first N−O bond cleavage is rapid and the intermediate partitions between internal alkylation (**32**) and the second N−O bond cleavage (**33**), Scheme 8. At 160 psi, the second N−O bond of oxazine **32** is unreactive and does not release the auxiliary, such that the hemiacetal **33** is the only source of both product silane **27** and auxiliary **26**, explaining the identical recoveries of these materials. At 260 psi (23 °C) psi and at 160 psi (50 °C), the partitioning between **32** and **33** remains the same, but in these cases **32** does suffer the second N−O bond cleavage and releases the remainder of the auxiliary **26**, but no product. At 500 psi of hydrogen the partitioning between **32** and **33** was again unchanged, but the yield of the product silane was lower, probably due to competitive reduction of the intermediate aldehyde **34**. To complete the transformation, aldehyde **34** forms a Schiff's base with the tethered amine, is saturated, and is alkylated affording pyrrolizidine silane **27**. The actual timing of the reductive amination relative to the alkylation is uncertain, but is supported by the isolation of mesylate containing products in other studies.[14h]

Scheme 8



Conclusion

The first synthesis of the (+)-casuarine ((+)-**6**) has been accomplished in only eight steps from the chiral α-alkoxy

aldehyde **20** in 20% overall yield. Five of the six stereocenters were created in the tandem [4 + 2]/[3 + 2] cycloaddition, with the sixth provided by a selective, substrate controlled ketone reduction. The Lewis acid promoted [4 + 2] cycloaddition was successfully applied with two highly oxygenated components and would not have been viable without the improved synthesis of the chiral acyloxy vinyl ether. The facial selectivity in the [3 + 2] cycloaddition was found to be surprisingly dependent upon the dipolarophile, apparently due to nonbonded interactions with the β-silyl substituent.

Experimental Section

General Experimental. See the Supporting Information for details.

(*Z*)-2-[[(*R*)-(2,2-Diphenylcyclopentyl)oxy]etheneyloxy]-trimethylsilane (21). A solution of aldehyde **20**[16] (2.80 g, 10.0 mmol), Et_3N (5.6 mL, 40.2 mmol, 4.02, equiv), and TMSCl (2.60 mL, 20.5 mmol, 2.0 equiv) in CH_3CN was heated to reflux for 2 h. The suspension was allowed to cool to room temperature and the volatile components were removed in vacuo (3 h). The resulting thick, white suspension was partitioned between H_2O (25 mL) and hexane (50 mL). The phases were separated and the aqueous phase was extracted with hexane (50 mL). The combined organic extracts were washed with H_2O (25 mL), dried (Na_2SO_4), filtered, and concentrated to afford crude silyl enol ethers (7/1, *Z*/*E* (NMR)). This mixture was distilled to afford 3.492 g (99%) of **21** (10/1, *Z*/*E*) as a clear, colorless oil. Data for **21**: bp 220 °C (0.25 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10−7.34 (m, 10H), 5.43 (d, J = 3.4, 1H), 5.37 (d, J = 3.4, 1H), 4.79 (t, J = 3.8, 1H), 2.44−2.26 (m, 2H), 1.86−1.98 (m, 3H), 1.62−1.68 (m, 1H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.83, 145.00, 130.85, 128.74, 128.25, 127.66, 126.87, 125.88, 125.56, 122.65, 87.76, 59.00, 34.79, 29.34 19.93, −0.52; IR (neat) 1665 (s); MS (70 ev) 52 (M^+, 4); $[\alpha]^{26}_D = -63.2$ (CH_2Cl_2, c = 1.00); TLC R_f = 0.56 (hexane/EtOAc, 19/1). Anal. Calcd for $C_{22}H_{28}O_2Si$ (384.47): C, 74.95; H, 8.01. Found: C, 74.74; H, 7.91.

2-[(*R*)-(2,2-Diphenylcyclopentyl)oxy]-(*Z*)-ethenol Benzoate (*Z*-16c) and 2-[(*R*)-(2,2-Diphenylcyclopentyl)oxy]-(*E*)-ethenol Benzoate (*E*-16c). Tetrabutylammonium fluoride (170 μL, 1 M in THF, 0.17 mmol, 0.02 equiv) was added to a 0 °C solution of silyl enol ether **21** (3.00 g, 8.5 mmol) and benzoyl fluoride (2.00 g, 16.1 mmol, 1.9 equiv) in 8.5 mL of THF. The resulting solution was stirred for 2 h at 0 °C and then was concentrated. The resulting clear oil was then purified by silica gel chromatography (hexane/EtOAc, 19/1) and distillation to afford 210.0 mg (6.4%) of enol benzoate (*E*)-**16c** as a clear, thick oil, and 2.637 g (81%) of enol benzoate (*Z*)-**16c**, which crystallized to a white solid after distillation. Data for (*Z*)-**16c**: bp 245 °C (0.3 mmHg); mp 86−88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.2, 1.2, 2H), 7.58 (tt, J = 7.5, 1.2, 1H), 7.44 (t, J = 7.9, 2H), 7.13−7.39 (m, 10H), 6.74 (d, J = 3.6, 1H), 5.82 (d, J = 3.6, 1H), 4.90 (t, J = 4.7, 1H), 2.75 (ddd, J = 12.8, 9.0, 7.7, 1H), 2.46 (ddd, J = 12.8, 9.0, 4.0, 1H), 2.06−2.12 (m, 1H), 1.90−2.02 (m, 2H), 1.67−1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.18, 146.61, 144.55, 133.27, 132.31, 130.07, 129.32, 128.77, 128.39, 127.66, 126.86, 126.11, 125.81, 118.41, 88.06, 58.92, 35.08, 29.42, 19.81; IR (neat) 1728 (s); MS (70 eV) 384 (M^+, 1); $[\alpha]^{26}_D = -125.4$ (CH_2Cl_2, c = 1.00); TLC R_f = 0.28 (hexane/EtOAc, 9/1). Anal. Calcd for $C_{26}H_{24}O_3$ (384.47): C, 81.22; H, 6.29. Found: C, 81.15; H, 6.30. Data for (*E*)-**16c**: bp 250 °C (0.3 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, J = 8.3, 1.2, 2H), 7.59 (tt, J = 7.5, 1.2, 1H), 7.46 (t, J = 7.8, 2H), 7.13−7.33 (m, 10H), 7.30 (d, J = 10.8, 1H), 6.77 (d, J = 10.8, 1H), 4.89 (t, J = 2.4, 1H), 2.54−2.63 (m, 2H), 1.91−2.04 (m, 3H), 1.55−1.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.12, 145.86, 144.98, 138.55, 133.71, 129.81, 129.32, 128.50, 128.44, 128.28, 127.93, 126.63, 126.14, 125.81, 123.67, 86.34, 59.51, 34.42, 28.52, 20.27; IR (neat) 1725 (s); MS (70 eV) 384 (M^+, 1); $[\alpha]^{26}_D = -13.2$ (EtOH, c = 1.00); TLC R_f = 0.37 (hexane/EtOAc, 9/1). Anal. Calcd for $C_{26}H_{24}O_3$ (384.47) C, 81.22; H, 6.29. Found: C, 80.95 H, 6.29.

[(2*R*,3*R*,3a*R*,4*S*,5*R*,6*S*)-4,5-Bis(benzoyloxy)-3-(dimethylphenylsilyl)hexahydro-6-[[(1*R*)-2,2-diphenylcyclopentyl]oxy]isoxazolo[2,3-*b*][1,2]-2-oxazinyl]-2-[[dimethyl(1,1,2-trimethylpropyl)silyl]oxy]ethanone ((+)-18). Tin tetrachloride (290 μL, 2.50 mmol, 2.5 equiv) was added to a −78 °C solution of nitroalkene **13**[14a] (193.0 mg, 1.00 mmol) and dieneophile (*Z*)-**16c** (421 mg, 1.10 mmol, 1.1 equiv) in 20.0 mL of toluene. The resulting solution was stirred for 2 h at −78 °C and then quenched with 1 N Et_3N in MeOH (10 mL, 10.0 mmol, 10.0 equiv). The mixture was diluted with CH_2Cl_2 (200 mL) and washed with H_2O (3 × 50 mL). The aqueous washes were back-extracted with CH_2Cl_2 (200 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. A solution of dipolarophile **10**[14g] (377.0 mg, 1.0 mmol, 1.0 equiv) in 5 mL $CHCl_3$ was added, and the solution was then stirred at room temperature for 16 h. The mixture was concentrated and then was purified by silica gel chromatography (hexane/EtOAc, 10/1) to afford 713.9 mg (76%) of keto nitroso acetal (+)-**18** as 45/7/3/2/1/1 ratio of diastereomers (SFC). The mixture was further purified by preparative HPLC [3 injections (340 mg, 370 mg, and mixed), 50 × 2.5 silica gel column (Regis), 1.80% EtOAc in hexane, 25 mL/min] to afford 521.0 mg (55%) of ketone (+)-**18** as a 40/0/0/2/1/1 ratio of diastereomers. Data for (+)-**18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, J = 8.4, 1.7, 2H), 7.97 (dd, J = 8.3, 1.1, 2H), 7.49−7.67 (m, 8H), 6.98−7.32 (m, 12H), 6.74 (t, J = 7.4, 1H), 5.24 (s, 1H), 5.20 (d, J = 10.4, 1H), 4.86 (d, J = 4.0, 1H), 4.66 (d, J = 1.3, 1H), 4.46 (s, 1H), 3.92−4.02 (ABq J_{AB} = 19.0, ν_A = 1992.9 Hz, ν_B = 1971.9 Hz, 2H), 3.58 (d, J = 13.2, 1H), 2.93 (dd, J = 13.3, 10.4, 1H), 2.47−2.53 (m, 1H), 2.22−2.27 (m, 1H), 2.07−2.11 (m, 1H), 1.84−1.89 (m, 1H), 1.56−1.61 (m, 2H), 1.23−1.28 (m, 1H), 0.86 (d, J = 7.0, 6H), 0.81 (s, 6H), 0.44 (s, 3H), 0.27 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.78, 164.83, 164.42, 146.33, 144.10, 137.67, 136.72, 133.98, 133.70, 133.35, 130.20, 130.00, 129.46, 129.03, 128.76, 128.47, 128.39, 128.17, 127.91, 127.57, 127.16, 125.88, 97.73, 87.27, 86.96, 72.89, 68.52, 68.40, 66.74, 59.92, 34.75, 34.08, 32.14, 29.00, 25.26, 20.23, 20.13, 18.49, −2.26, −3.37, −3.50, −3.57; IR (neat) 1728 (s), 1451 (m), 1260 (s); MS (FAB) 941 (M^+ + 1, 1); $[\alpha]^{26}_D = +34.8$ ($CHCl_3$, c = 1.00); TLC R_f = 0.27 (hexane/EtOAc, 6/1); SFC t_R = 12.15 min, (WELKO-1 column, P_{CO_2} = 150 psi, 4.5 mL/min, 7.0% MeOH). Anal. Calcd for $C_{55}H_{65}NO_9Si_2$ (1020.41): C, 70.26; H, 6.97; N, 1.49. Found: C, 70.57; H, 6.98; N, 1.43.

3,4-Bis(benzoyloxy)-5-[[(1*R*)-2,2-diphenylcyclopentyl]-oxy]tetrahydrofuran-2-one Oxime ((+)-22). Tin tetrachloride (290 μL, 2.50 mmol, 2.5 equiv) was added to a −78 °C solution of nitroalkene **13**[14a] (193.0 mg, 1.00 mmol) and dieneophile (*Z*)-**16c** (421 mg, 1.10 mmol, 1.1 equiv) in 20.0 mL of toluene. The resulting solution was stirred for 2 h at −78 °C and then quenched with 1 N NaOH in MeOH (15 mL, 15 mmol, 15 equiv) and stirred at −78 °C for 30 min. The mixture was partitioned between CH_2Cl_2 (200 mL) and pH =7.0 phosphate buffer (50 mL) and the organic layer then was washed with H_2O (200 mL). The aqueous washes were back-extracted with CH_2Cl_2 (200 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The mixture then was purified by silica gel chromatography (hexane/EtOAc, 2/1) to afford 469.3 mg (81%) of oxime **22** as 12.3/2.7/1.0 ratio of diastereomers (NMR). An analytical sample (147.3 mg, 25%) of the major diastereomer as an Et_2O inclusion complex was obtained by crystallization from Et_2O. Data for **22**: mp 120−121 °C (Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.5, 2H), 7.90 (d, J = 8.5, 2H), 6.80−7.60 (m, 16H), 6.33 (br s, 1H), 6.33 (d, J = 7.60, 1H), 5.79 (d, J = 4.4, 1H), 5.39 (dd, J = 7.8, 4.4, 1H), 4.85 (t, J = 4.4, 1H), 3.85 (q, J = 7.1, 1.6H), 2.53−2.60 (m, 1H), 2.20−2.31 (m, 2H), 1.88−1.97 (m, 2H), 1.54−1.63 (m, 1H), 1.21 (t, J = 7.1, 2.4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.35, 165.21, 151.60, 146.48, 143.90, 133.70, 133.62, 130.20, 130.12, 128.69, 128.34, 128.25, 128.19, 127.61, 126.58, 125.91, 125.76, 101.41, 86.88, 74.17, 70.43, 65.91, 58.96, 34.86, 31.02, 19.59, 15.23; IR (KBr) 3462 (br s), 2970 (s), 1749 (s), 1284 (s); MS (FAB) 578 (M^+ + 1, 16); $[\alpha]^{26}_D = +43.2$ ($CHCl_3$, c = 1.00); TLC R_f = 0.21 (hexane/

EtOAc, 2/1). Anal. Calcd for $C_{35}H_{31}NO_7 \cdot 0.4Et_2O$ (577.64): C, 72.39; H, 5.81; N, 2.39. Found: C, 72.35; H, 5.97; N, 2.51.

(2*R*,3a*R*,3*S*,4*R*,5*R*,6*S*)-3-Carbomethoxy-4,5-bis(benzoyloxy)-6-[((1*R*)-2,2-diphenylcyclopentyl)oxy]hexahydroisoxazole-[1,7-*b*][1,2]oxazine-2-carboxylic Acid Methyl Ester ((+)-**23**)**.** Tin tetrachloride (290 μL, 2.50 mmol, 2.5 equiv) was added to a −78 °C solution of nitroalkene **13**[14a] (193.0 mg, 1.00 mmol) and dieneophile (*Z*)-**16c** (421 mg, 1.10 mmol, 1.1 equiv) in 20.0 mL of toluene. The resulting solution was stirred for 2 h at −78 °C and then quenched with 1 N Et_3N in MeOH (10 mL, 10.0 mmol, 10.0 equiv). The mixture was diluted with CH_2Cl_2 (200 mL) and then was washed with H_2O (3 × 50 mL). The aqueous washes were back-extracted with CH_2Cl_2 (200 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. A solution of dimethyl maleate (125.0 μL, 1.0 mmol, 1.0 equiv) in 5 mL of $CHCl_3$ was added, and the solution then was stirred at room temperature for 18 h. The mixture was concentrated and then was purified by silica gel chromatography (hexane/EtOAc; 3/1) to afford 628 mg (87%) of nitroso acetal **23** as 12.4/4.3/3.0/1.4/1.0 ratio of diastereomers (SFC). An analytical sample of the major ketone diastereomer was obtained by prep HPLC [50 × 2.5 cm silica gel column (Regis), 15% EtOAc/hexane, 25 mL/min] to afford 57.0 mg (8%) of nitroso acetal **23** as a 45/0/1.0/2.9/0 ratio of diasteromers. Data for **23**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4, 2H), 7.84 (d, J = 7.1, 2H), 6.78−7.56 (m, 16H), 6.12 (dd, J = 10.2, 6.0, 1H), 5.37 (d, J = 10.4, 1H), 5.29 (dd, J = 10.3, 3.9, 1H), 4.84 (t, J = 5.3, 1H), 4.59 (dd, J = 10.6, 6.0, 1H), 4.10 (t, J = 10.5, 1H), 3.72 (s, 3H), 3.26 (s, 3H), 2.61−2.63 (m, 1H), 2.24−2.31 (m, 3H), 1.90−1.92 (m, 1H), 1.48−1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.68, 167.65, 165.67, 164.71, 146.99, 144.27, 133.59, 133.43, 130.09, 129.73, 128.88, 128.58, 128.44, 128.38, 128.33, 128.09, 127.54, 126.69, 125.71, 125.63, 97.77, 84.67, 73.81, 67.70, 65.80, 59.12, 52.82, 52.53, 47.75, 35.01, 30.60, 19.83; IR (KBr) 1737 (s); HRMS for $C_{41}H_{40}NO_{11}$ (721.79) (FAB) calcd 722.2601123, found 722.260000; $[\alpha]^{26}_D$ = +37.5 ($CHCl_3$, c = 0.89); TLC R_f = 0.18 (hexane/EtOAc, 2/1).

(α*S*,2*R*,3*R*,3a*R*,4*S*,5*R*,6*S*)-4,5-Bis(benzoyloxy)-3-(dimethylphenylsilyl)-α-[[[dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]hexahydro-6-[[(1*R*)-2,2-diphenylcyclopentyl]oxy]-isoxazolo[2,3-*b*][1,2]oxazine-2-methanol ((+)-**24**)**.** L-Selectride (4.00 mL, 0.76 M in THF, 3.04 mmol, 2.1 equiv) was added to a −78 °C solution of ketone **18** (1.350 g, 1.44 mmol) in 30.0 mL of THF. The resulting solution was stirred for 2 h at −78 °C and then was quenched slowly by careful addition of glycerol/pH = 7 buffer (15 mL). The mixture was extracted with Et_2O (200 mL) and washed with H_2O (75 mL) and brine (75 mL). The aqueous washes were back-extracted with Et_2O (200 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated on to silica gel (2 g). The mixture then was purified by silica gel chromatography (hexane/EtOAc, 6/1) to afford 1.169 g (86%) of alcohol **24** as 10/1 ratio of alcohol epimers (SFC) and 89.5 mg of unreacted ketones. Residual ketone **18** present in the isolated unreacted ketones was further reduced with L-Selectride (250 μL, 0.76 M in THF, 0.190 mmol) in 5 mL THF at −78 °C for 2 h. Following quench, workup and silica gel purification afforded 70.9 mg of unreacted ketones (5.2%) as a 2/1/1 ratio of diastereomers. Data for **24**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.3, 1.2, 2H), 8.02 (dd, J = 8.3, 1.2, 2H), 7.46−7.70 (m, 8H), 7.14−7.28 (m, 10H), 7.06 (t, J = 7.8, 2H), 6.79 (t, J = 7.3, 1H), 5.46 (d, J = 1.0, 1H), 4.93 (d, J = 3.9, 1H), 4.80 (d, J = 10.3, 1H), 4.72 (d, J = 1.2, 1H), 4.51 (br s, 1H), 3.72 (d, J = 13.4, 1H), 3.40−3.56 (m, 3H), 2.93 (dd, J = 13.4, 10.0, 1H), 2.53−2.57 (m, 1H), 2.23−2.31 (m, 1H), 2.11−2.15 (m, 1H), 1.94 (d, J = 5.4, 1H), 1.91−1.93 (m, 1H), 1.55−1.63 (m, 2H), 1.28−1.32 (m, 1H), 0.87 (d, J = 6.8, 6H), 0.81 (s, 6H), 0.55 (s, 3H), 0.31 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.99, 164.60, 146.45, 144.20, 137.67, 133.59, 133.23, 130.23, 129.21, 128.80, 128.31, 128.15, 127.98, 127.58, 127.21, 125.96, 125.87, 97.60 86.76, 86.07, 72.67, 71.82, 68.52, 67.07, 64.44, 59.96, 34.76, 34.14, 32.23, 27.49, 25.05, 20.31, 20.11, 18.51, 18.48, −1.05, −3.54, −3.56, −3.78; IR (KBr) 3567 (br, w), 3458 (br, w), 1729 (s); MS (FAB) 943 (M^+ + 1, 11); $[\alpha]^{26}_D$ = +31.0 ($CHCl_3$, c = 1.00); TLC R_f = 0.23 (hexane/EtOAc, 6/1); SFC t_R = 1.862 min, (SiO_2 column, P_{CO_2} = 150 psi, 4.5 mL/min, 3.0% MeOH). Anal. Calcd for $C_{55}H_{67}NO_9Si_2$ (1020.41): C, 70.11; H, 7.17; N, 1.49. Found: C, 70.19; H, 7.23; N, 1.51.

(α*S*,2*R*,3*R*,3a*R*,4*S*,5*R*,6*S*)-4,5-Bis(benzoyloxy)-3-(dimethylphenylsilyl)-α-[[[dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]hexaneahydro-6-[[(1*R*)-2,2-diphenylcyclopentyl]oxy]isoxazolo[2,3-*b*][1,2]oxazine-2-methanol Methanesulfonate Ester ((+)-**25**)**.** Solid methanesulfonic anhydride (1.05 g, 0.9 mmol, 6.0 equiv) was added to a solution of alcohol **24** (942.0 mg, 1.00 mmol) in 8.0 mL of pyridine at room temperature. The resulting brown suspension was stirred for 1 h and then was placed on a silica gel chromatography column. The mixture was purified by silica gel chromatography (hexane/EtOAc, 2/1) to afford 992.8 mg (97%) of mesylate **25** as a white foam. Data for **25**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.5, 1.2, 2H), 8.07 (dd, J = 8.5, 1.5, 2H), 7.48−7.70 (m, 8H), 7.18−7.32 (m, 10H), 7.08 (t, J = 8.0, 2H), 6.85 (t, J = 7.3, 1H), 5.46 (s, 1H), 5.03 (d, J = 10.7, 1H), 4.93 (d, J = 3.7, 1H), 4.74 (d, J = 0.7, 1H), 4.59 (s, 1H), 4.48 (t, J = 6.6, 1H), 3.92 (dd, J = 10.6, 6.0, 1H), 3.71 (dd, J = 10.5, 7.1, 1H), 3.69 (d, J = 13.4, 1H), 3.01 (dd, J = 10.7, 9.8, 1H), 2.97 (s, 3H), 2.53−2.59 (m, 1H), 2.26−2.32 (m, 1H), 2.13−2.17 (m, 1H), 1.91−1.97 (m, 1H), 1.55−1.67 (m, 2H), 1.29−1.45 (m, 1H), 0.87 (d, J = 6.8, 6H), 0.80 (s, 6H), 0.64 (s, 3H), 0.31 (s, 3H), 0.05 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.11, 164.82, 146.40, 144.21, 136.53, 133.73, 133.69, 133.31, 130.19, 130.07, 129.71, 129.02, 128.80, 128.44, 128.41, 128.25, 128.20, 128.14 127.61, 127.19, 126.00, 125.88, 97.65, 86.88, 84.13, 81.85, 72.05 68.76, 67.15, 61.54, 59.92, 39.67 34.79, 33.95, 32.14, 27.56, 25.13, 20.22, 20.19, 20.11, 18.49, −0.52, −3.56, −3.60, −3.95; IR (KBr) 1735 (s), 1737 (s); HRMS (FAB) calcd 1020.420816, found 1020.420400; $[\alpha]^{26}_D$ = +42.8 ($CHCl_3$, c = 1.00); TLC R_f = 0.43 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{56}H_{69}NO_{11}Si_2S$ (1020.41): C, 65.92; H, 6.82; N, 1.37; S, 3.14. Found: C, 65.35; H, 6.73; N, 1.12.

(1*S*,2*S*,5*R*,6*R*,7*R*,7a*R*)-7-(Dimethylphenylsilyl)-5-[[[dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]hexahydro-1*H*-pyrrolizine-1,2,6-triol ((−)-**27**). To a solution of mesylate **25** (918.0 mg, 0.9 mmol) in 120 mL of MeOH in a glassed lined steel autoclave was added A5000 Raney nickel[39] (washed 3 × 100 mL MeOH). The autoclave was sealed, pressurized to 260 psi with H_2, and stirred at room temperature for 42 h. H_2 was carefully released from steel autoclave and the reaction mixture then was filtered through a 4 cm pad of Celite. The filter cake was washed with MeOH (500 mL), and the filtrate was concentrated to approximately 25 mL. Solid K_2CO_3 (5 g) was added, and the resulting slurry was stirred at room temperature for 4 h. The slurry was then dry loaded onto activity III basic alumina (2 g) the mixture was purified by activity III basic alumina chromatography (hexane/EtOAc, 8/1,2/1; CH_2Cl_2/MeOH; 0/1,50/1, 25/1, 10/1). to afford alcohol (+)-**26** and pyrrolizidine (−)-**27**. The alcohol **26** was distilled to provide 212 mg (99%) of alcohol **26**, and the pyrrolizidine **27** was recrystallized from hexane (2 crops) to afford 269.7 mg (64%) of pyrrolizine **27** as a white crystalline solid. Data for **27**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60−7.63 (m, 2H), 7.30−7.48 (m, 3H), 4.17 (dt, J = 6.3, 5.6, 1H), 4.01 (ddd, J = 11.0, 7.8, 1.7, 1H), 3.81 (dd, J = 9.5, 5.1, 1H), 3.56 (t, J = 5.1, 1H), 3.52 (t, J = 9.2, 1H), 3.26 (dd, J = 10.6, 5.6, 1H), 3.15 (dd, J = 11.0, 4.9, 1H), 2.83 (ddd, J = 9.2, 7.8, 5.1, 1H), 2.76 (d, J = 1.7, 1H), 2.74 (dd, J = 10.6, 6.6, 1H), 2.01 (br s, 1H), 2.66 (sept, J = 6.8, 1H), 1.64 (t, J = 11.0, 1H), 0.921 (s, 3H), 0.918 (s, 3H), 0.889 (s, 3H), 0.886 (s, 3H), 0.480 (s, 3H), 0.473 (s, 3H), 0.155 (s, 3H), 0.147 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.78, 133.67, 129.53, 128.18, 83.27, 80.44, 79.92, 73.97, 70.33, 67.14, 58.44, 38.94, 33.94, 25.01, 20.22, 20.08, 18.38, 18.30, −3.26, −3.69, −3.76, −6.23; IR (KBr) 3546 (br s), 3444 (br s); MS (FAB) 466 (M^+ + 1, 100); $[\alpha]^{26}_D$ = −38.2 ($CHCl_3$, c = 1.00). Anal. Calcd for $C_{24}H_{43}NO_4Si_2$ (465.786): C, 61.89; H, 9.31; N, 3.01. Found: C, 61.80; H, 9.34; N, 2.70.

(39) A5000 Raney Nickel was purchased from Activated Metals and Chemicals, Inc.

(1*S*,2*S*,5*R*,6*R*,7*R*,7a*R*)-7-(dimethylphenylsilyl)-5-[[[dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]hexahydro-1*H*-pyrrolizine-1,2,6-triol Tribenzoate (28). Benzoyl chloride (90 μL, 0.74 mmol, 20 equiv) was added to a solution of amino triol (−)-**27** (1.7 mg, 0.0365 mmol) in pyridine (0.5 mL). The solution was stirred at room temperature for 20 h and then was concentrated. The residue was purified by silica gel chromatography (toluene/Et_2O, 49/1) to afford 2.5 mg of trisbenzoate **28**. Data for **28**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.3, 1.2, 2H), 7.98 (dd, J = 8.3, 1.2, 2H), 7.88 (dd, J = 8.3, 1.2, 2H), 7.60−7.64 (m, 4H), 7.43−7.59 (m, 6H), 7.39 (t, J = 7.8, 2H), 7.05−7.09 (m, 2H), 5.49 (t, J = 1.7, 1H), 5.46 (dd, J = 9.3, 7.1, 1H), 5.34 (s 1H, H(7)), 3.71 (dd, J = 10.0, 2.2, 1H), 3.65 (dd, J = 10.3, 4.4, 1H), 3.55 (dd, J = 10.3, 7.3, 1H), 3.50 (m, 2H), 3.38 (dt, J = 7.1, 4.4, 1H), 2.21 (t, J = 9.6, 1H), 1.48 (sept, J = 6.8, 1H), 0.74 (d, J = 6.8, 3H), 0.73 (d, J = 6.8, 3H), 0.71 (s, 3H), 0.70 (s, 3H), 0.40 (s, 3H), 0.39 (s, 3H), 0.01 (s, 3H, −0.06 (s, 3H); MS (FAB) 779 (M^++1, 63); SFC t_R = 4.301 min, t_R = 4.908 min; (Chiralcel OD column P_{CO_2} = 150 psi, 5.5 mL/min, 5.0% MeOH).

(1*R*,2*R*,3*R*,6S,7*R*,7a*R*)-Hexahydro-3-(hydroxymethyl)-1*H*-pyrrolizine-1,2,6,7-tetraol (Casuarine) ((+)-**6**). Mercuric trifluoroacetate (462.7 mg, 1.08 mmol, 1.5 equiv) was added to a solution of (−)-**27** (337 mg, 0.723 mmol, 1 equiv) in CF_3CO_2H (4 mL), $CHCl_3$ (4 mL), and HOAc (2 mL) and was stirred at room temperature for 60 min. The reaction mixture was then cooled to 0 °C and peroxyacetic acid (37% in HOAc, 12 mL) was added dropwise, after which the cooling bath was removed and the solution was stirred at room temperature for 18 h. The reaction mixture was cooled to 0 °C and slowly quenched with Me_2S, maintaining the internal temperature ≤ 15 °C, until a negative starch/I_2 test was achieved. The contents of the reaction were transferred to a column of BioRad AG 50W-X8 resin (10 g) and then was washed with H_2O (40 mL) to remove nonamine containing products and then with 2 M NH_4OH (80 mL) to elute casuarine. Evaporation of the NH_4OH eluant afforded a pale-yellow powder that was recrystallized from EtOH to provide 84.4 mg of casuarine (57%). The mother liquor was concentrated and redissolved in MeOH (5 mL). 10% Palladium on carbon and 10 drops of HOAc were added and the mixture was stirred under 1 atm of H_2 for 16 h. The catalyst was removed by filtration through Celite, then was rinsed with MeOH (100 mL) and concentrated. The resulting, pale-yellow oil was transferred to a column of BioRad AG 50W-X8 resin (10 g), then was washed with H_2O (40 mL) to remove acetic acid, and then with 2 M NH_4OH (80 mL) to elute casuarine. Evaporation of the NH_4OH eluant afforded a pale-yellow powder which was recrystallized (2 crops) from EtOH to provide 40.3 mg of casuarine (27%). The combined crops were treated with pentane and concentrated to azeotropically remove the remaining EtOH for a combined yield of 124.7 mg (84%) of casuarine as a white powder. Data for (+)-**6**: mp 180−181 °C (EtOH); ^{1}H NMR (500 MHz, D_2O) δ 4.21−4.24 (m, 2H), 4.19 (t, J = 8.1, 1H), 3.81 (t, J = 8.8, 1H), 3.78 (dd, J = 11.7, 3.7, 1H), 3.63 (dd, J = 11.7, 6.6, 1H), 3.29 (dd, J = 12.1, 4.3, 1H), 3.10 (dd, J = 8.3, 2.9, 1H), 3.07 (ddd, J = 8.8, 6.6, 3.7, 1H), 2.94 (dd, J = 12.1, 3.6, 1H); ^{13}C NMR (125 MHz, D_2O) δ 79.55, 78.53, 78.29, 77.37, 73.13, 70.87, 62.99, 58.90; IR (KBr), 3362 (br, s); MS (FAB) 206 (M^++1, 80); $[\alpha]^{27}_D$ = +10.8 (H_2O, c = 1.020). Anal. Calcd for $C_8H_{15}NO_5$ (205.212): C, 46.82; H, 7.37; N, 6.83. Found: C, 46.59; H, 7.28; N, 6.49.

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Supporting Information Available: Full ^{1}H NMR and ^{13}C NMR with assignments, complete listing of IR peaks, and MS fragments of compounds **6**, (*E*)-**16c**, (*Z*)-**16c**, **18**, **21**−**25**, and **27** along with comparison ^{1}H NMR spectra of synthetic (+)-casuarine and ^{1}H NMR of natural (+)-casuarine. This material is available free of charge via the Internet at http://pubs.acs.org.

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