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Synthesis of (+)-Casuarine

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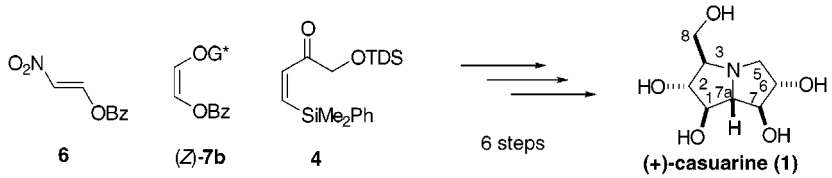
ABSTRACT



The first synthesis of (+)-casuarine, a pentahydroxy pyrrolizidine alkaloid, is described. The key bond-forming events occur in a tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition involving nitroalkene 6, chiral vinyl ether 7b, and vinyl silane 4. This process also creates five of the six stereocenters present in this potent glycosidase inhibitor. Completion of the synthesis required only four additional steps and delivered (+)-casuarine in 20% overall yield.

Polyhydroxy pyrrolizidine and indolizidine alkaloids display a variety of interesting biological activities. Potential anticancer[1] and antiviral[2] properties of these metabolites stem from their resemblance to sugars, and not surprisingly, many display significant glycosidase inhibition activity. (+)-Casuarine (**1**), isolated in 1994 from the bark of *Casuarina equisetfolia* L. (Casuarinaceae)[3] represents one of the more potent members of this class. It is an effective inhibitor of glucosidase I (72% inhibition at 5 μg/mL), rivaling that of the indolizidine alkaloid castanosperime (84% inhibition at 5 μg/mL).[4] The C(3) hydroxymethyl substituent places (+)-casuarine in the alexine/australine[5] subclass of pyrrolizidine alkaloids and differentiates it from the more common necines which bear a C(1) hydroxymethyl group. The five hydroxyl groups make (+)-casuarine the most highly oxygenated amino-sugar analogue yet identified.

Recent publications from these laboratories have documented the use of tandem [4 + 2]/[3 + 2] nitroalkene cycloadditions for the succinct syntheses of several polyhydroxylated pyrrolizidine and indolizidine alkaloids.[6] These studies had clearly demonstrated the ability of the tandem cycloaddition strategy to assemble these skeletons with excellent control over as many as four contiguous stereogenic centers. However, (+)-casuarine with its densely oxygenated periphery represented a still greater challenge to install five of the six contiguous stereocenters by the cycloaddition construct.

To accommodate the installation of so many hydroxyl groups in a stereodefined fashion, suitably functionalized nitroalkenes, dienophiles, and dipolarophiles were needed. From previous endeavors, we knew that oxygenated nitroalkenes[6] and dienophiles[7] were amenable to [4 + 2] cycloaddition but that oxygenated dipolarophiles gave regioreversed cycloadducts.[8] Thus, we made recourse to the phenyldimethylsilyl substituent as a surrogate for a hydroxyl group at C(1).[9]

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(5) Robins, D. J. *Nat. Prod. Rep.* **1990**, 377.

(6) (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (b) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672. (c) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1996**, *118*, 8266. (d) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125. (e) Denmark, S. E.; Herbert, B. *J. Am. Chem. Soc.* **1998**, *120*, 7357. (f) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3048.

(7) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1994**, *59*, 4576.

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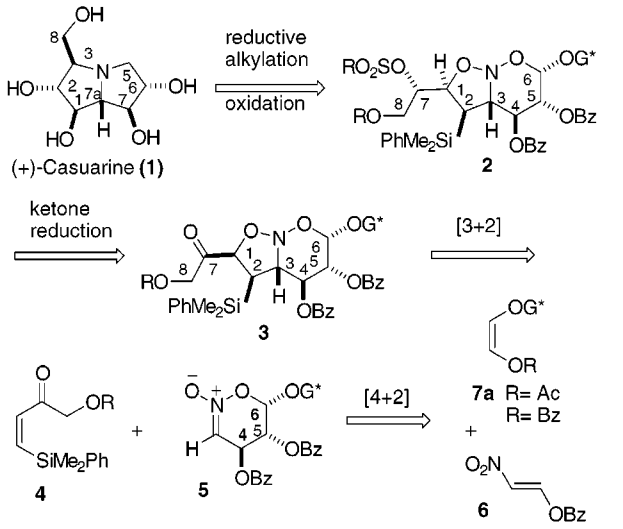
This synthetic design is outlined in Scheme 1. It is expected that casuarine would be produced from nitroso

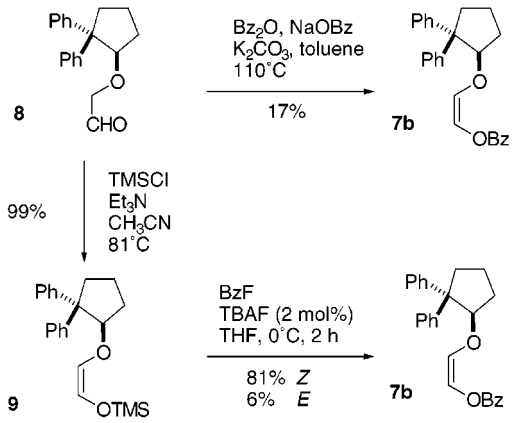
Scheme 1



acetal **2** by N−O bond cleavage and N-alkylation followed by Tamao−Fleming oxidation[9] of the silyl moiety. Thus, nitroso acetal **2** 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 **3** 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 simple components **6**, **7**, and **4**. Most importantly, a predictable stereochemical outcome of these events is critical for the successful synthesis of (+)-casuarine. [4 + 2] cycloaddition of nitroalkene **6**[6b] and *Z*-acyloxy vinyl ether **7**[7]should provide nitronate **5**. The required C(4)/C(5) trans relationship was expected, given the high exo selectivity which has been demonstrated previously with this chiral vinyl ether.[7] The desired approach of the dipolarophile in the [3 + 2] cycloaddition for the assembly of the nitroso acetal framework was more difficult to predict. In cases where the C(4) benzoate and the C(6) acetal center are positioned on the same side of the nitronate ring, the approach of the dipolarophile is exclusively on the side opposite these substituents.[6b,e,8] This outcome has been attributed to a cooperative effect between these two 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 to a significant degree.[10] Since the C(4) benzoate and the C(6) acetal center are on opposite faces of the nitronate, the dominant controlling element a priori was uncertain. 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.[11]

Orienting experiments indicated that the acetoxy vinyl ether **7a**, the preferred bisalkoxy dienophile in previous studies,[7] was unsuitable for a productive cycloaddition with nitroalkene **6**.[12] Instead, the more reactive benzoyloxy vinyl ether **7b**[7] effectively produced the desired nitronate. Unfortunately, the existing synthesis of the benzoate **7b** gave a very poor yield (17%),[7] so a new route had to be developed (Scheme 2). The chiral alkoxy aldehyde **8**[7] was converted

Scheme 2



to silyl enol ether **9** in 99% yield as a 10/1 (*Z*/*E*) mixture. O-Acylation with benzoyl fluoride and a catalytic amount of TBAF (2 mol %)[13] afforded the *Z*-vinyl ether in 81% yield along with 6% of the undesired *E*-vinyl ether which was easily separated by silica gel chromatography.

With an improved synthesis of the dienophile in hand, the optimization of the [4 + 2] cycloaddition could be undertaken. Combining the chiral vinyl ether (*Z*)-**7b** and the nitroalkene in the presence of 2.5 equiv of $SnCl_4$ provided the nitronate **5** as a 4.8:1 mixture of diastereomers (vide infra) (Scheme 3). We have discovered that quenching the reaction with Et_3N/MeOH at low temperature proved to be critical to obtain the cycloadduct in a high yield. The standard method for quenching the Lewis acid (NaOH/MeOH) partially converted the nitronate (up to 29%) to oxime **10**. In fact, quenching with a slight excess of NaOH/MeOH led to complete conversion of the nitronate to oxime **10** (Scheme 4).[14] The [4 + 2] cycloaddition was judged to be high yielding (81%) and occurred with modest facial selectivity

(9) (a) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694. (b) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, C37. (c) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29. (d) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 317.

(10) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **1998**, *63*, 3045.

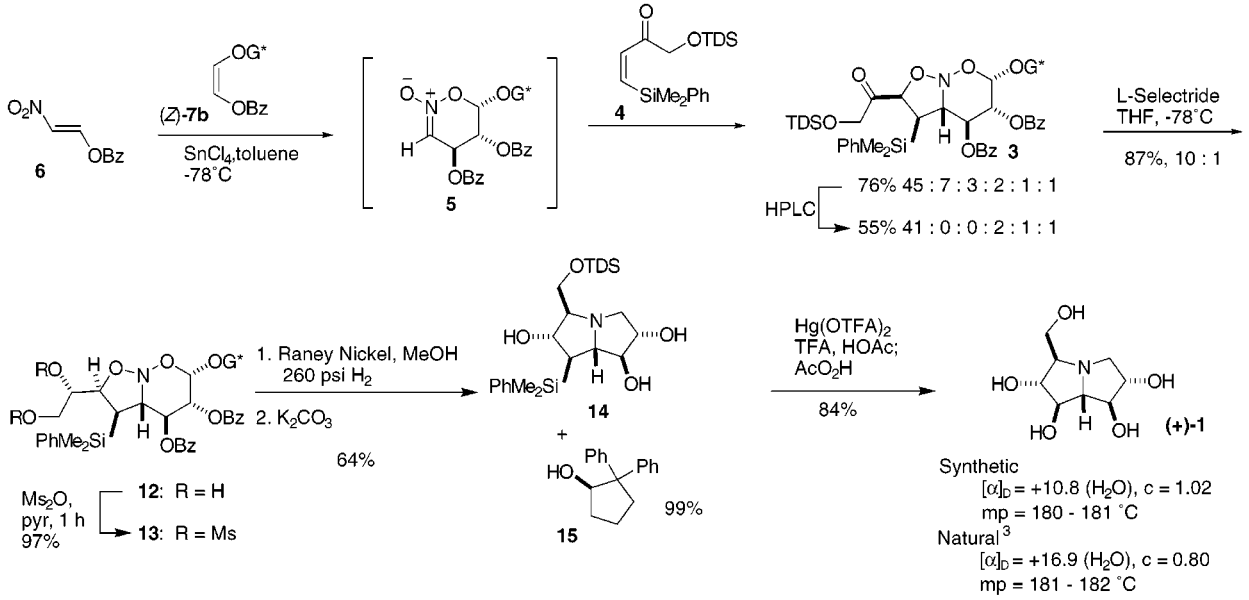
(11) Schnute, M. E. Ph.D. Thesis, University of Illinois, 1995.

(12) In CH_2Cl_2, extensive polymerization occurred and no nitronate was detected. With toluene as the solvent, the nitronate was produced; however, the yield of [4 + 2]/[3 + 2] was unsatisfactory (54%).

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

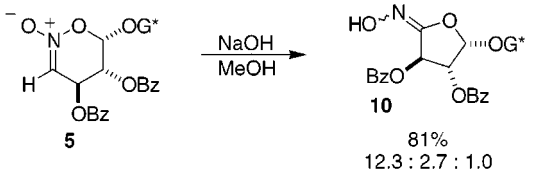
(14) (a) Denmark, S. E.; Moon, Y.-C.; Cramer, C. J.; Dappen, M. S.; Senanayake, C. B. *Tetrahedron* **1990**, *46*, 7373. (b) Colvin, E. W.; Robertson, A. D.; Seebach, D.; Beck, A. K. *J. Chem. Soc., Chem. Commun.* **1981**, 952.

Scheme 3



(4.8:1) in view of the conversion of **5** to **10**.[15] Nitronate **5** proved to be too unstable for isolation and purification and was immediately treated with the β-silyl enone **4**[8] to afford a 45:7:3:2:1:1 mixture of nitroso acetals in 76% yield.[16] 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%. Thus four of the five stereocenters in (+)-casuarine were now set.

Scheme 4



The final stereocenter was installed by a selective ketone reduction. Treatment of keto nitroso acetal **3** with L-Selectride led to 10:1 mixture of epimeric alcohols **12** in 87% yield.[17] Additionally, the minor diastereomers present in the starting ketone mixture were chromatographically removed. The selectivity demonstrated in this reduction can be rationalized by assuming a reactive conformation invoked in the Cornforth model[18] wherein the phenyldimethylsilyl group provides the facial shielding to hydride attack. The resulting alcohols were activated in near quantitative yield with methanesulfonic anhydride in pyridine. Treatment of the mesylate with Raney nickel in MeOH under 260 psi of H_2 provided crystalline pyrrolizidine **14** in 64% yield along with a 99% recovery of the chiral auxiliary **15**. The C(6) benzoate suffered partial saponification under the reaction conditions. Thus, to facilitate purification, K_2CO_3 was added at the end of the reaction to effect complete removal of both benzoate groups.

The completion of the synthesis required only the transformation of the C(1) silyl group to the final hydroxyl substituent and deprotection. This process began with dearylation of the silyl group 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.[19] If the oxidation were conducted at higher temperature (50 °C), a significant portion of *N*-oxide was observed. Although this could be converted back to casuarine by hydrogenation, failure to remove all the mercury by ion exchange chromatography was known to complicate this step.[6e] Under the current oxidation conditions less than 5% *N*-oxide was detected by ^{1}H NMR analysis. After ion exchange chromatography, 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 were obtained from an analytically pure sample and are in agreement with the reported measurements of the natural product. However, the optical rotation of synthetic (+)-casuarine was low (+10.8° versus +16.9° (H_2O, pH 8.4) reported for the natural material). This discrepancy prompted us to vouchsafe the enantiomeric purity of the synthetic

(15) Diastereomeric ratio was determined by NMR. The two major diastereomers are assumed to be facial diastereomers. It is uncertain whether the minor diastereomer is an oxime geometric isomer or an acetal epimer.

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

(17) Diastereomeric ratio was determined by SFC.

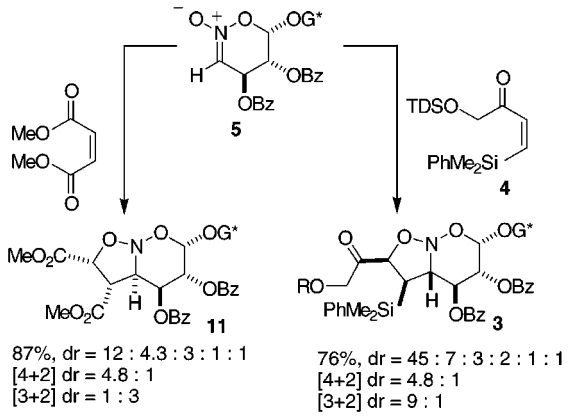
(18) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, *112*.

(19) Kolb, H. C.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2735.

material by independently establishing the enantiomeric composition of a late-stage synthetic intermediate. The 2,6,7-trisbenzoate of pyrrolizidine **14** was determined to have an enantiomeric excess of ca. 98% by chiral stationary phase supercritical fluid chromatography (SFC).[20] We thus conclude that the reported optical rotation for natural (+)-casuarine is erroneously high.

The stereochemical analysis of the key 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 **10**. The selectivity in the [3 + 2] cycloaddition step is less clear. In the worst instance, if all 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 selfsame nitronate undergoes [3 + 2] cycloaddition with dimethyl maleate to the extent of 3/1 *favoring the opposite face*, Scheme 5.[21] 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. Examination of molecular models indicates that the β face approach is disfavored by a nonbonded steric interaction between the axially oriented C(4) benzoate of the nitronate and the phenyldimethylsilyl moiety of **4**.

Scheme 5



In summary, we have accomplished the first synthesis of the (+)-casuarine in only eight steps from the chiral α-alkoxy aldehyde **8** in 20% overall yield. Five of the six stereocenters were created in the tandem 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 suprisingly dependent upon the dipolarophile, apparently due to nonbonded interactions with the β-silyl substituent. Further studies with highly functionalized cycloaddition components are in progress.

Acknowledgment. We gratefully acknowledge the gift of natural (+)-casuarine from R. J. Nash (Aberystwyth). Financial support was provided by the National Institutes of Health (GM 30938). A.R.H. gratefully acknowledges the University of Illinois for a Graduate Fellowship, Eastman Chemical Company for an Eastman Summer Fellowship, and Zeneca Pharmaceuticals for the Zeneca Graduate Fellowship in Synthetic Organic Chemistry.

Supporting Information Available: Preparation and full characterization of (+)-casuarine and ^{1}H NMR spectra of both natural and synthetic (+)-casuarine. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Chiralcel OD column, 150 psi, 5.5 mL/min, 5% MeOH.

(21) The structural assignment of the vinyl silane cycloadduct (**3**) was determined by conversion to the natural product. The structural assignment of the dimethyl maleate cycloadduct (**11**) was determined by single-crystal X-ray analysis.