Synthesis of (1*R*,2*R*,3*R*,7*R*,7a*R*)-Hexahydro-3-(Hydroxymethyl)-1*H*-pyrrolizine-1,2,7-triol: 7-Epiaustraline

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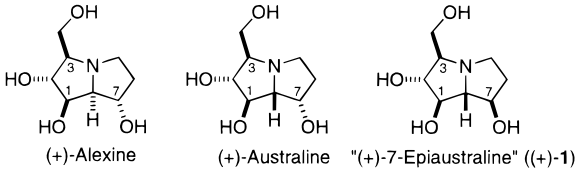
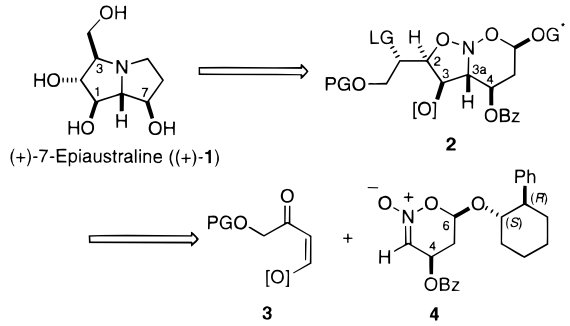
The alexines and australines are a unique subset of pyrrolizidine alkaloids.[1a,b] The presence of a hydroxymethyl group adjacent to the ring nitrogen [C(3)] distinguishes this group from the larger class of necine bases which bear carbon substituents at C(1). In addition, each member possesses (at least) five contiguous stereogenic centers, three of which bear hydroxyl groups. Several members of this alkaloid family display glucosidase inhibitory properties[1b−e,2a] as well as viral and retroviral[1f] suppression characteristics. The combination of functional group density and impressive biological activity makes the alkaloids attractive synthesis targets. We selected, as point of entry, 7-epiaustraline (**1**)[2] for an illustration of a general strategy based on the tandem [4 + 2]/[3 + 2] cycloaddition chemistry of nitroalkenes.[3] (+)-7-Epiaustraline was isolated along with another stereoisomer from extracts of *Castanospermum australe*, and its structure was assigned by spectroscopic methods as well as by analogy to crystallographically defined natural epimers.[2a] In addition, a synthesis of (+)-7-epiaustraline has been reported.[2b]

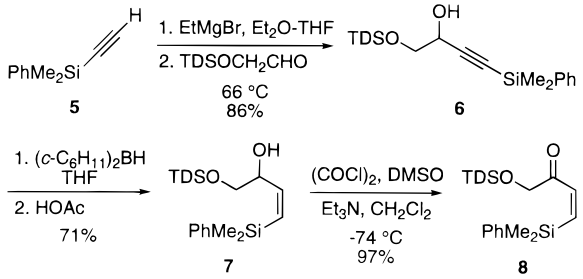


The synthesis of **1** posed several new challenges to the tandem cycloaddition technology that concern the construction and transformation of key nitroso acetal **2**, Scheme 1. First, the installation of the hydroxymethyl group at C(3) required an alkylation to close the second pyrrolidine ring and thus the installation of a suitably configured nucleofugal group LG. Second, the cis/trans/trans relationship between *H*C(2)/*H*C(3)/*H*C(3a)/*H*C(4) in **2** mandated an exo selective intermolecular [3 + 2] cycloaddition of nitronate **4** with a *Z*-configured dipolarophile (**3**) from the face of the nitronate opposite the C(4) substituent. Moreover, the dipolarophile must contain the latent hydroxyl functionality for C(1) in **1**. To accommodate these requirements, we formulated the activated dipolarophile **8** (Scheme 2) that

Scheme 1



Scheme 2



contained all of the requisite functionality and that also promised to give a rapid and regioselective [3 + 2] cycloaddition. The absolute configuration of **1** is properly established by the use of nitronate (+)-**4** (previously employed in our synthesis of (−)-hastanecine) derived from (1*S*,2*R*)-2-phenylcyclohexanol.[4]

The synthesis of **8** was straightforward and high yielding as depicted in Scheme 2. Addition of the magnesio silyl acetylide prepared from **5**[5] to (dimethylthexylsilyloxy)acetaldehyde[6] provided the propargylic alcohol **6** in 86% yield.[7] While Lindlar semi-hydrogenation proved capricious, the hydroboration−protonolysis of **6** with dicyclohexylborane[8] resulted in the clean conversion to *cis*-alkene **7** (71%, >99% cis by ^{1}H NMR analysis). The preparation was completed by Swern oxidation[9] of **7** to provide **8** in 97% yield without detectable isomerization of the alkene.

The tandem sequence began with the preparation of nitronate **4** by [4 + 2] cycloaddition (67% yield, >99/1 dr) as previously described.[4] The intermolecular thermal cycloaddition between nitronate **4** and dipolarophile **8** proceeded smoothly at room temperature to provide nitroso acetal **9** in 97% yield as a 26/1 ratio of diastereoisomers, Scheme 3.[10] Comparison of the ^{1}H and ^{13}C NMR chemical shifts of C(2), C(3), and C(3a), (as assigned by 2D NMR spectroscopy), allowed the conclusion that the major nitroso acetal was formed as a head-to-head regioisomer. On the basis of our prior [3 + 2] cycloaddition studies[11] with nitronate **4**, both major and minor isomers were assigned structures

(1) Alexine isolation: (a) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett*. **1988**, *29*, 2487. Australine isolation: (b) Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198. Biological studies: (c) Harris, C. M.; Harris, T. M.; Molyneux, R. J.; Tropea, J. E.; Elbein, A. D. *Tetrahedron Lett*. **1989**, *30*, 5685. (d) Scofield, A. M.; Rossiter, J. T.; Witham, P.; Kite, G. C.; Nash, R. J.; Fellows, L. E. *Phytochemistry* **1990**, *29*, 107. (e) Tropea, J. E.; Molyneux, R. J.; Kaushal, G. P.; Pan, Y. T.; Mitchell, M.; Elbein, A. D. *Biochemistry* **1989**, *28*, 2027. (f) Fellows, L. E.; Nash, R. PCT Int. Appl. WO GB Appl. 89/7, 951; *Chem. Abstr.* **1990**, *114*, 143777f.

(2) Isolation: (a) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Girdhar, A.; Ramsden, N. G.; Peach, J. M.; Hegarty, M. P.; Scofield, A. M. *Phytochemistry* **1990**, *29*, 111. Reported synthesis: (b) Pearson, W. H.; Hines, J. V. *Tetrahedron Lett*. **1991**, *32*, 5513.

(3) (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (b) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125. (c) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668. (d) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675.

(4) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672.

(5) Fleming, I.; Takaki, K.; Thomas, A. P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2269.

(6) The aldehyde was prepared in 2 steps (86% yield) from 1,4-butenediol by diol protection and ozonolysis of the alkene.

(7) All yields reported are for analytically pure materials, and all new compounds were fully characterized (see the Supporting Information for details).

(8) Brown, H. C. *Organic Synthesis via Boranes*; Wiley: New York, 1975; pp 28, 100.

(9) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.

(10) The ratio was determined by ^{1}H NMR analysis. The minor diastereomer has been tentatively assigned as an exo head-to-tail regioisomer.

(11) Denmark, S. E.; Seierstad, M. J.; Herbert, B. Manuscript in preparation. See also ref 4.

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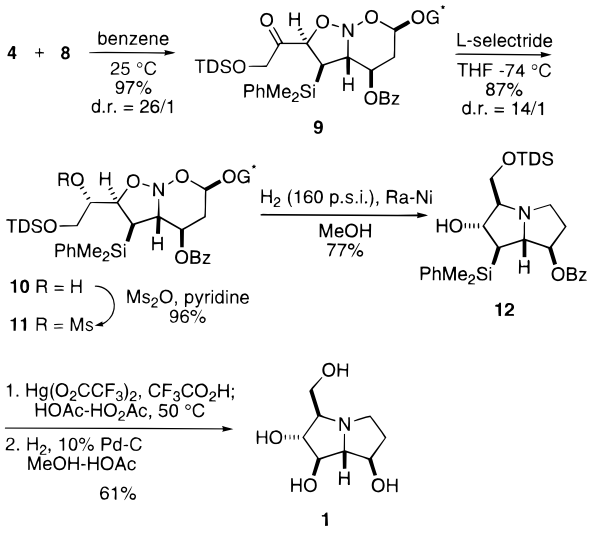
Scheme 3



consistent with the approach of the dipolarophile from the face opposite the C(4) benzoate. The high stereoselectivity was attributed to a combination of the kinetic anomeric effect[12] and the conformation of the nitronate.[4] The reduction of ketone **9** with L-Selectride at −74 °C provided the epimeric alcohols in excellent yield and diastereoselectivity (87%, 14/1). A single-crystal, X-ray structure of the major carbinol **10** confirmed that all 5 contiguous stereogenic centers required for the synthesis of 7-epiaustraline were correctly installed in both relative and absolute senses with respect to the 1*S*,2*R* auxiliary. The high selectivity was most likely due to preferential shielding of one face of the carbonyl group by the phenyldimethylsilyl moiety. The reduction then proceeded in accord with the Cornforth model.[13]

With all of the stereogenic centers required for the synthesis of 7-epiaustraline properly installed with high selectivity, we turned our attention to the activation of the secondary alcohol, the ring closing hydrogenolysis, and the completion of the synthesis. Once again, after extensive experimentation, the ideal solution proved deceptively simple. Treatment of alcohol **10** with methanesulfonic anhydride in pyridine provided mesylate **11** in 96% yield. The use of that specific reagent combination in this case was critical for clean and rapid activation. Catalytic reduction (Raney Ni, H_2/160 psi, MeOH) of the nitroso acetal-mesylate **11** proceeded according to plan to provide the pyrrolizidine **12** in 77% yield with 98% recovery of the auxiliary, (+)-2-phenylcyclohexanol. We were pleased that our standard reaction conditions provided for appropriate timing of the critical unmasking events (N−O hydrogenolysis, reductive amination and intramolecular alkylation).

The final stages of the synthesis of 7-epiaustraline involved three functional group manipulations, the removal of the silyl ether and benzoate protecting groups and the conversion of the $PhMe_2$-Si group to a hydroxyl. All three steps were efficiently accomplished under the conditions of the Tamao−Fleming oxidation.[14] Educt **12** was allowed to react with $Hg(O_2CCF_3)_2$ in trifluoroacetic acid at ambient temperature for 1 h to effect dearylation. The reaction mixture was then diluted with peroxyacetic acid and heated at 50 °C for 24 h to promote the oxidation of the silyl group. Under those conditions, the pyrrolizidine was converted to its *N*-oxide which was isolated by ion exchange chromatography (Dowex-50) and was subsequently reduced (H_2, 10% Pd−C, MeOH/HOAc) to the free base. Final purification on Dowex-50 and recrystallization from MeOH/$CHCl_3$ provided 7-epiaustraline (**1**) in 61% yield.

Table 1. Comparative ^{1}H NMR Data for 7-epiaustraline (**1**)

proton	isolated[a]	Pearson's synthetic[b]	(−)-**1**[c]
*H*C(1)	4.02 (dd)	4.06 (t, J = 7.7)	3.55 (t, J = 7.9)
*H*C(2)	3.70 (dd)	3.73 (t, J = 8.8)	3.61 (t, J = 8.4)
*H*C(3)	2.50 (m)	2.58 (m)	2.51 (ddd, J = 9.3, 6.4, 3.8)
*H*C(5)	2.97 (m)	3.00 (m)	2.92 (m)
	2.50 (m)	2.58 (m)	2.72 (m)
*H*C(6)	1.85 (m)	1.85 (m)	1.92 (m)
	1.73 (m)	1.79 (m)	1.62 (m)
*H*C(7)	4.19 (m)	4.21 (m)	4.19 (m)
*H*C(7a)	2.98 (dd)	3.05 (dd, J = 7.6, 4.4)	2.85 (dd, J = 7.9, 2.0)
*H*C(8)	3.59 (dd)	3.63 (dd, J = 11.8, 3.4)	3.62 (dd, J = 11.7, 3.8)
	3.42 (dd)	3.45 (dd, J = 11.9, 6.6)	3.48 (dd, J = 11.7, 6.4)

[a] Spectra taken in D_2O and assigned by COSY. [b] Spectra taken in D_2O and assigned by comparison with data for isolated material (J values are given in hertz). [c] Spectra taken in D_2O and assigned by COSY (J values are given in hertz).

Upon completion of the synthesis it was immediately apparent that the physical and spectroscopic data for our final product did not match either those reported for the natural product or those reported for the synthetic material prepared by Pearson.[2b] For example, the synthetic product is a highly crystalline (mp 193−194 °C) levorotatory material ($[\alpha]_D^{23}$ −13.0° (c = 0.55, H_2O)) while "natural" 7-epiaustraline is described as a dextrorotatory oil ($[\alpha]_D^{23}$ +11.6° (c = 0.37, H_2O)).[2a] The most striking difference in the ^{1}H spectra was the chemical shift position of *H*C(1), Table 1. In the synthetic material, that proton was found at 3.55 ppm, 0.5 ppm upfield from the natural material. The chemical shifts of the adjacent protons, *H*C(2) and *H*C(7a) in our sample were also displaced (by 0.10−0.15 ppm upfield) relative to the reported data. These disturbing discrepancies prompted us to unambiguously confirm the structure of the our product. Single-crystal, X-ray analysis (see the Supporting Information) clearly established the identity of the synthetic material as (1*R*,2*R*,3*R*,7*R*,7a*R*)-hexahydro-3-(hydroxymethyl)-1*H*-pyrrolizine-1,2,7-triol.[15,16]

In conclusion, a highly efficient and selective synthesis of the title compound has been completed in nine steps from silane **5**. A single-crystal, X-ray structure analysis of synthetic (−)-**1** confirmed that the targeted structure was successfully synthesized. However, the spectroscopic and physical characteristics of the synthetic material did not match the published data for the natural material. Subsequent reinvestigation has revealed that 7-epiaustraline is not a known natural product.

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Supporting Information Available: Preparation and full spectroscopic and analytical data (^{1}H NMR, ^{13}C NMR, IR, MS, TLC, $[\alpha]_D$) for all new compounds along with ^{1}H and ^{13}C NMR spectra, crystallographic parameters, atomic coordinates, and bond lengths and angles for **1** (40 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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

(14) Review: Fleming, I. *Chemtracts: Organic Chem.* **1996**, *9*, 1.

(15) As a direct consequence of our work, the assignment of the substance reported as 7-epiaustraline[2a] is incorrect and this has led to a complete reevaluation of all the published data on naturally occurring australines (Wormald, Nash, Hrnciar, White, Molyneux, and Fleet, submitted; M. R. Wormald, personal communication). Thus, 7-epiaustraline had not yet been reported as a natural product.

(16) Pearson has learned that his synthetic material[2b] originally assigned as 7-epiaustraline on the basis of NMR comparisons is in fact australine and that some of the literature NMR data are incorrect. A full account of Pearson's work will be forthcoming (W. Pearson, personal communication).