Chemo-Enzymatic Total Synthesis of 3-Epiaustraline, Australine, and 7-Epialexine

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Sequential enzymatic aldol reaction and bis-reductive amination leads to the total syntheses of tetrahydroxylated pyrrolizidine alkaloids, 3-epiaustaline (**14**), australine (**1**), and 7-epialexine (**11**). This approach allows for their rapid construction without the need for protecting group manipulation of the hydroxyl functionality. In addition, an improved procedure for the asymmetric epoxidation of divinyl carbinol (**3**) was described, and the product was used in a concise synthesis of the required triol **7** and *ent*-**7**.

Naturally occurring tetrahydroxlated pyrrolizidines such as australine (**1**) and alexine (**2**) (Figure 1), and their stereoisomers, have been isolated from the genera *Castanospermum* and *Alexa*.[1] Interest in their total synthesis has arisen due to their ability to inhibit glucosidases,[2] as well as for their antiviral and retroviral activities.[3] Although there are several methodologies for constructing simple pyrrolizidines, no direct de novo synthetic methods have been developed until recently for constructing complex molecules such as **1** and **2**.[4] Many of the earlier synthetic methods that have been reported entailed routes employing carbohydrates as starting materials,[5] all of which, including the most recent approaches, require protecting group strategies.

Synthetic efforts toward iminocyclitols by us[6a,b] and others[6c,d] have demonstrated the utility of a sequential enzymatic aldol and reductive amination reaction sequence for the stereoselective construction of hydroxlated piperidines and pyrrolidines. In our continuing efforts to expand the scope of enzymes in organic synthesis, we now illustrate the first chemo-enzymatic approach to the synthesis of bicyclic iminocyclitols, 3-epiaustraline, australine, and 7-epialexine, that bypasses the need for protecting group manipulation of the hydroxyl functionality. The retrosynthesis is outlined in Scheme 1. The highly functionalized pyrrolizidine skeleton was envisioned to arise from an intramolecular bis-reductive amination reaction of a nonprotected tetrahydroxylated keto-aldehyde, which sets the stereocenter corresponding to C-3.[7] This keto-aldehyde would be generated from a stereospecific enzymatic aldol reaction between dihydroxyacetone phoshpate (DHAP, available in four steps)[8]

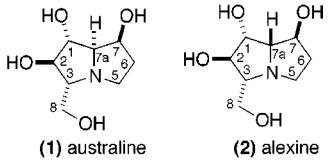
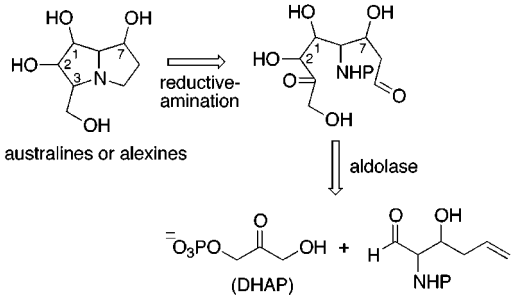


Figure 1.

Scheme 1. Retrosynthetic Analysis of Austrialines and Alexines



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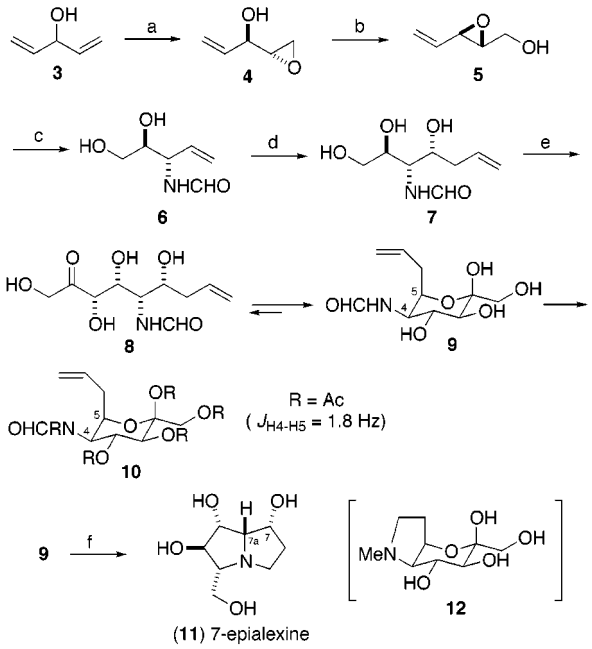
Scheme 2[a]

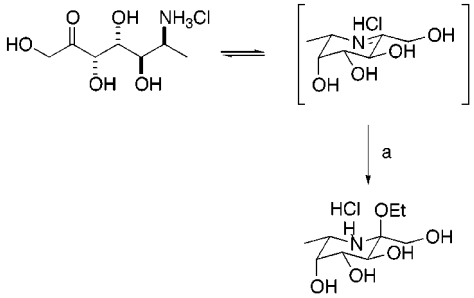


[a] Conditions: (a) (−)-DIPT, cumene hydroperoxide, CH_3Cl_3, −45 °C, 86%, >99% ee; (b) 0.5 N NaOH, 98%; (c) 30% NH_4OH, rt, then ethylformate, EtOH, 90 °C, 95%; (d) O_3, MeOH, −78 °C, then In, allyl bromide, H_2O, rt, 56% (after separation of diastereomers); (e) $NaIO_4$, H_2O, then DHAP, FDPA, then Pase, 25%; (f) O_3, MeOH−H_2O, −78 °C, then H_2 Pd/C, then HCl and H_2 Pd/C, 66%. DIPT = diisopropyl tartrate, DHAP = dihydroxyacetone phosphate, FDPA = fructose-1,6-diphosphate aldolase, Pase = acid phosphate.

and an appropriate aldehyde to contruct the stereocenters corresponding to C-1 and C-2 of australines and alexines.[9] Since the final two sequences do not require protection of the hyroxyl groups, we planned a synthesis of the required aldehyde that would be amenable to this non-protecting group strategy.

The synthesis begins with Sharpless asymmetric epoxidation of divinylcarbinol (**3**) to furnished epoxide **4** in excellent yield with high enantiomeric purity (86%, >99% ee)[10] (Scheme 2). In our attempts to repeat and optimize the known literature procedure for the epoxidation of this substrate,[11a−c] we discovered that substituting cumene hydroperoxide[11c] for *tert*-butyl hydroperoxide produced better results. Base-induced rearrangement of epoxide **4** followed by regioselective nucleophilic opening with ammonia[11d] and protection of the resulting amine with ethyl formate gave the formamide **6**.[12] Attempts at selective ring opening of the epoxide **5** using either NaN_3 or $TMSN_3$ failed, since only a mixture of regioisomeric azides was obtained. Ozonolysis of **6** afforded a mixture of hemiacetals that were directly subjected to allyl bromide and indium,[13] which generated triol **7** as a 3:1 mixture of diastereomers.[14] The major isomer was separated and submitted to sodium periodate cleavage followed by aldol addition reaction with DHAP mediated by fructose-1,6-diphosphate aldolase (FDPA, obtained from rabbit muscle). Enzymatic cleavage of the phosphate group with acid phosphatase (Pase) led to **8** in 25% yield.[15]

Scheme 3[a]



[a] Conditions: (a) EtOH, 65%.

The NMR spectrum of **8** showed an ∼7:1 mixture of the pyranose **9** and ketone **8**. COSY and ^1H NMR analysis of the peracetate **10** established the cis orientation between substituents at C-4 and C-5 (J_{H4-H5} = 1.8 Hz) and thus established formation of syn product **7** as the major stereoisomer resulting from the allyl indium addition reaction.

A key feature in the successful enzymatic aldol reaction was the mild generation of a sensitive α-*N*-formyl aldehyde through the use of $NaIO_4$ in water.[16] In addition, the choice of the *N*-formyl protecting group was instrumental, since the enzymatic aldol reaction between DHAP and the analogous *N*-Cbz-protected aldehyde failed to give any desired aldol product.

The final bis-reductive amination sequence was accomplished by ozonolysis of **9**, followed by a reductive workup of the ozonide with Pd/C and hydrogen. Cleavage of the formamide with HCl in the presence of Pd/C and hydrogen resulted in concomitant reduction of the intermediate iminium ion affording 7-epialexine (**11**) (66%) as a 8:1 mixture of stereoisomers.[17,18] Concentration of the reaction mixture was required after the ozonolysis step in order to avoid the N-methylated side product **12**, arising from competitive intermolecular reductive amination with formaldehyde.

In a related example (Scheme 3), while studying the reactivity of highly functionalized iminium ions, we observed that in the absence of a hydride source, protic solvents (i.e., MeOH and EtOH) serve as nucleophiles to give the mixed N,O-ketals in moderate yields. When

(9) All four possible stereoisomers can be obtained depending on the choice of aldolase enzyme, see ref 6a and: Zannetti, M. T.; Knorst, M; Fessner, W.-D. *Chem. Eur. J.* **1999**, *5*, 1882−1890.

(10) For comparison of optical rotation with known literature values, see ref 11a−c.

(11) (a) Jager, V.; Schroter, D.; Koppenhoefer, B. *Tetrahedron* **1991**, *47*, 2195−2210. (b) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525−1529. (c) Katsuki, T.; Martin, V. S. *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1996; Vol. 48, pp 1−300. (d) Jager, V.; Stahl, U.; Hummer, W. *Synthesis* **1991**, 776−782.

(12) Other formylating conditions (i.e., acetic anhydride and formic acid) gave low yields.

(13) Paquette, L. A.; Bennett, G. D.; Isaac, M. B.; Chatriwalla, A. *J. Org. Chem.* **1998**, *63*, 1836−1845.

(14) The use of other allylating reagents and conditions (i.e., allyltributylstannane) gave lower selectivity.

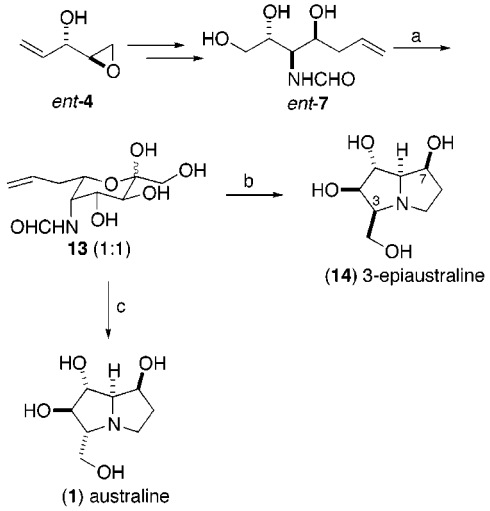
(15) We detected ∼10−15% of a third stereoisomer, tentatively assigned as the product arising from epimerization of the starting aldehyde.

(16) Other oxidative or reducing stategies to generate this aldehyde would most likely lead to facile epimerization. For a review on optically active *N*-protected α-amino aldehydes, see: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149−164.

(17) The major stereoisomer was assigned as 7-epialexine upon comparison of physical and spectral data to literature values, see refs 5a and 18.

(18) Fleet, G. W.; Haraldsson, M.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1988**, *29*, 5441−5444.

Scheme 4[a]



[a] Conditions: (a) $NaIO_4$, H_2O, DHAP, FDPA, then Pase, 30%; (b) O_3, MeOH−H_2O, −78 °C, then H_2 Pd/C, then HCl and H_2 Pd/C, 70%; (c) O_3, MeOH−H_2O, −78 °C, then HCl, rt, then NaOAc, $NaCNBH_3$, AcOH, 52%. DHAP = dihydroxyacetone phosphate, FDPA = fructose-1,6-diphosphate aldolase, Pase = acid phosphatase.

employing anhydrous MeOH and shorter reaction times in the reductive amination leading to **11**, similar mixed N,O-ketals products were detected. This observation may provide a new route to iminocyclitols containing a leaving group as inhibitors of glycosidase.

ent-**7** was prepared using similar methods starting from *ent*-**4** and submitted to sodium periodate cleavage and enzymatic aldol reaction as described for **7** (Scheme 4). Pyranose **13** was obtained as a 1:1 mixture of anomeric stereoisomers in 30% yield.[15] Ozonolysis of this mixture and intramolecular bis-reductive amination produced 3-epiaustraline (**14**) in 70% yield as a single isomer.[20,21]

The demonstrated facial selectivity of the reductions leading to 7-epialexine (**11**) and 3-epiaustraline (**14**) was consistent with related reductions of iminium ions, leading to simple *cis*-pyrrolizidines.[22] Surprisingly, when the reductive amination of **13** was carried out with $NaCNBH_3$, australine (**1**) was produced as the major stereoisomer (8:1) in 52% yield.[20] It is possible that the inversion in facial selectivity arises from a hydroxyl-directed iminium ion reduction, where the reducing agent is a soluble hydride source.[7]

In summary, a short chemoenzymatic method utilizing a stereospecific aldol reaction coupled with selective bis-reductive amination have been applied toward the total synthesis of tetrahydroxylated pyrrolizidines, 3-epiaustraline, australine, and 7-epialexine. This strategy can be potentially be used to access other stereoisomers and analogues related to the hydroxylated pyrrolizidine class of alkaloids. Additionally, an improved epoxidation of divinyl carbinol **3** was described leading to a concise synthesis of the required triol **7** and *ent*-**7**.

Experimental Section

General Methods. The reagents and solvents were reagent grade and used as supplied. Fructose-1,6-diphosphate aldolase (rabbit muscle) and acid phosphatase (sweet potato) were purchased from Sigma. Solvent evaporation was performed under reduced pressure using a rotary evaporator, followed by evacuation (<0.1 mmHg) to constant sample weight. Silica gel 60 (230−240 mesh) or reverse phase silica gel (RP-18, 40−63 mesh)was used in chromatograhpy. Standard conditions using Ac_2O and pyridine were employed for the acetylation reactions.

Modified Procedure for the Preparation of (2*S*,3*R*)-1,2-Epoxy-4-penten-3-ol (4). A mixture of crushed 4 Å molecular sieves (4.0 g) and CH_2Cl_2 (120 mL) was cooled to −35 °C, and titanium tetraisopropoxide (3.5 mL, 11.9 mmol) and (*R*,*R*)-(−)-diisopropyl tartrate (3.3 mL, 15.5 mmol) were added by syringe. After the mixture was stirred at −35 °C for 30 min, divinylcarbinol (10 g, 119 mmol) was added by addition funnel, followed by cumene hydroperoxide (35 mL, 238 mmol). The reaction mixture was stirred at −35 °C for 36 h. Aqueuous saturated Na_2SO_4 (10 mL) was added, and the mixture was diluted with Et_2O (100 mL). After the mixture was stirred at ambient temperature for 3 h, the resulting slurry was filtered through a pad of Celite, and the resulting yellow solution was concentrated. Excess cumene alcohol and cumene hydroperoxide were removed by silica gel chromatography (Hex/EtOAc, 4:1 then 100% Et_2O). Kugelrohr distillation (120 °C, 30 mm/Hg) provided 10.2 g (86%) of **4** as a colorless oil: $[a]^{25}_D$ −53° (*c* 0.73, $CHCl_3$) (lit.[11a] $[\alpha]^{25}_D$ −49° (*c* 0.73, $CHCl_3$)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddd, J = 16.9, 10.6, 6.2 Hz, 1H), 5.38 (br d, J = 17.2 Hz, 1H), 5.25 (d, J = 10.6 Hz, 1H), 4.33 (br s, 1H), 3.09 (dd, J = 6.6, 2.9 Hz, 1H), 2.80−2.74 (m, 2H), 2.05 (br, s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 117.6, 70.1, 53.9, 43.5; LRMS (ESI) *m*/*z* 99 (M − H).

(2*R*,3*R*)-2,3-Epoxy-4-pentenol (5). Epoxide **4** (4.0 g, 40 mmol) was added to 40 mL of 0.5 N NaOH and stirred for 20 min at room temperature. Extraction with CH_2Cl_2 (3 × 100 mL), drying of the combined organic layers (Na_2SO_4), and concentration gave 3.9 g (98%) of **5** as a colorless oil: $[\alpha]^{25}_D$ +50° (*c* 2.0, $CHCl_3$) (lit.[11a] $[\alpha]^{22}_D$ +56° (*c* 2.5, $CHCl_3$)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61−5.54 (m, 1H), 5.49 (dd, J = 17.3, 1.5 Hz, 1H), 5.29 (dd, J = 10.3, 1.5 Hz, 1H), 3.91 (dd, J = 12.9, 1.8 Hz, 1H), 3.65 (dd, J = 12.5, 3.3 Hz, 1H), 3.39 (dd, J = 7.7, 2.2 Hz, 1H), 3.07−3.05 (m, 1H), 2.53 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.6, 120.0, 61.2, 60.1, 55.9; LRMS (ESI) *m*/*z* 99 (M − H).

(2*S*,3*S*)-3-*N*-Formylamine-4-pentene-1,2-diol (6). Epoxide **5** (3.9 g, 39 mmol) was added to a 30% solution of ammonium hydroxide (50 mL) at room temperature. After 24 h, the solution was concentrated to give 4.5 g (quantitative) of pure amino diol: $[\alpha]^{25}_D$ −17° (*c* 1.0, MeOH) (lit.[11d] $[\alpha]^{22}_D$ −19° (*c* 1.4, MeOH)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (ddd, J = 17.3, 10.3, 7.3 Hz, 1H), 5.20 (dd, J = 17.3, 10.3 Hz, 2H), 3.65−3.61 (m, 1H), 3.55−3.52 (m, 2H), 3.41−3.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 115.4, 74.3, 63.4, 56.2; LRMS (ESI) *m*/*z* 118 (M + H).

EtOH (10 mL) was added to a mixture of amino diol (4.5 g) and ethyl formate (32 mL, 400 mmol). The homogeneous solution was heated at 90 °C for 18 h. To cleave the formate esters, the solution was concentrated, and MeOH (100 mL) was added. This solution was heated to 80 °C for 12 h. The solution was concentrated, and resulting oil was subjected to silica gel chromatograhy (CH_2Cl_2/MeOH, 7:1) to afford 5.4 g (95%) of formamide **6** as a colorless oil: $[\alpha]^{25}_D$ −15° (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.10 (s, 1H), 5.85 (ddd, J = 17.1, 10.5, 6.6 Hz, 1H), 5.19−5.13 (m, 2H), 4.49 (br t, 1H), 3.59−3.56 (m, 1H), 3.50−3.42 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 163.3, 135.0, 117.9, 74.5, 64.4, 53.9; LRMS (ESI) *m*/*z* 146 (M + H).

(19) Romero, A.; Wong, C.-H. Unpublished results.

(20) 3-Epiaustraline and australine were assigned based upon comparison of physical and spectral data to literature values, see ref 4d.

(21) Each of the two pyranose **13** stereoisomers were partially separated (isomerically enriched to 75%) and submitted to ozonolysis and reductive amination to give **14** as a single isomer, thus providing evidence that pyranose **13** is a mixture of anomeric stereoisomers.

(22) Hesse, M.; Janowitz, A.; Vavrecka, M. *Tetrahedron Lett.* **1991**, *32*, 5543−5546.

(2*S*,3*S*,4*R*)-3-*N*-Formylamine-6-heptene-1,2,4-triol (7). A solution of **6** (2.7 g, 19 mmol) and MeOH (70 mL) was cooled to −78 °C, and a gentle stream of O_3 was bubbled into the solution until a faint blue color appeared. The ozonide was quenched with dimethyl sulfide (2.7 mL, 37 mmol) at −78 °C, and the reaction was allowed to warm to room temperature. The solution was concentrated, and the yellow oil was used in the next step without purification.

Indium powder (2.1 g, 19 mmol) and allyl bromide (3.2 mL, 37 mmol) were added to a solution of aldehyde (prepared above) and H_2O (40 mL). The mixture was stirred vigorously for 12 h, at which point 1 N NaOH was added to bring the reaction mixture to pH 6.5. Celite (1.0 g) was added, and the resulting slurry was filtered and concentrated to produce 3.5 g (98%) of **7** as 3:1 mixture of diastereomers. Purification by silica gel chromatography (CH_2Cl_2/MeOH, 7:1) afforded 2.0 g of **7**: $[\alpha]^{25}_D$ +57° (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 8.12 (s, 1H), 5.78−5.75 (m, 1H), 5.02−4.96 (m, 2H), 4.06−4.04 (m, 1H), 3.84 (d, J = 8.4 Hz, 1H), 3.65−3.63 (m, 1H), 3.57 (dd, J = 11.7, 3.4 Hz, 1H), 3.45 (dd, J = 12.8, 5.9 Hz, 1H), 2.34−2.32 (m, 2H); ^{13}C NMR (150 MHz, CD_3OD) δ164.5, 135.8, 117.8, 72.3, 69.2, 64.6, 53.0, 39.8; HRMS (FAB) *m*/*z* 190.1081 (M + H, 190.1079 calcd for $C_8H_{16}O_4N$).

Pyranose (13). Sodium periodate (1.4 g, 6.4 mmol) was added to a solution of triol *ent*-**7** (1.0 g, 5.3 mmol) and H_2O (13 mL) at room temperature. After 30 min, $BaCl_2$ (647 mg, 2.7 mmol) was added, and the resulting precipitate was filtered through a pad of Celite. Dowex 50W-X8 acidic resin was added to the filtrant until the solution became acidic (pH 1.1). The resin was filtered, and the pH of the solution was adjusted to 6.7 with 2 N NaOH solution. Dihydroxyacetone phosphate (DHAP)[8] (17 mL, 0.37 M in H_2O, 6.4 mmol) was added, and the pH was readjusted to 6.7 with 2 N NaOH. Fructose-1,6-diphosphate-aldolase (500 units, from rabbit muscle) was added, and the mixture was stirred slowly at room temperature. After 72 h, the pH of the mixture was adjusted to 4.7, acid phosphatase (sweet potato) (250 units) was added, and the mixture was incubated at 38 °C for 12 h. The reaction mixture was neutralized to pH 7.0 with 2 N NaOH and concentrated. MeOH (100 mL) was added, and the mixture was filtered though a pad of Celite and concentrated. Silica gel chromatography (CH_2Cl_2/MeOH, 6:1) gave 390 mg (30%) of **13** as a 1:1 mixture of anomeric isomers. Characterization data for the triacetate of each anomeric isomer is provided. Data for the first triacetate off the silica gel column (1:1, CH_2Cl_2/EtOAc): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (s, 1H), 5.89 (d, J = 9.5 Hz, 1H), 5.66 (ddd, J = 17.2, 10.3, 7.3 Hz, 1H), 5.26 (dd, J = 10.6, 4.4 Hz, 1H), 5.13 (d, J = 10.6 Hz), 5.10−5.07 (m, 2H), 4.68 (ddd, J = 4.7, 2.2, 1.5 Hz, 1H), 4.34−4.31 (m, 1H), 4.24 (d, J = 11.7 Hz, 1H), 3.89 (d, J = 11.7 Hz, 1H), 2.34−2.31 (m, 1H), 2.21−2.17 (m, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 170.3, 170.1, 161.5, 132.3, 118.7, 95.8, 69.7, 68.9, 67.8, 66.4, 48.4, 34.8, 20.8, 20.7; HRMS (MALDI-FTMS) *m*/*z* 396.1267 (M + Na^+, 396.1265 calcd for $C_{16}H_{23}O_9NNa$).

Data for second triacetate: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (s, 1H), 5.82−5.77 (m, 1H), 5.74 (d, J = 9.5 Hz, 1H), 5.34 (app t, 1H), 5.11−5.05 (m, 3H), 4.21 (d, J = 11.7 Hz, 1H), 4.16 (app q, J = 10.3 Hz, 1H), 3.97 (d, J = 11.7 Hz, 1H), 3.89 (ddd, J = 10.3, 8.1, 2.2 Hz, 1H), 3.73 (br s, 1H), 2.39−2.36 (m, 1H), 2.29−2.26 (m, 1H), 2.10 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 171.3, 169.6, 160.9, 133.4, 117.7, 95.2, 70.96, 70.93, 70.8, 66.5, 51.9, 35.4, 20.7, 20.69, 20.62; HRMS (MALDI-FTMS) *m*/*z* 396.1267 (M + Na^+, 396.1265 calcd. for $C_{16}H_{23}O_9NNa$).

3-Epiaustraline (14). A 1:1 mixture of anomeric isomers **13** (40 mg, 0.16 mmol) and MeOH (3 mL) was cooled to −78 °C, and a gentle stream of O_3 was bubbled into the solution until a faint blue color appeared. The ozonide was quenched with palladium on carbon (10%) (5 mg) under an atmosphere of H_2 (balloon) at −78 °C, and the reaction was allowed to warm to room temperature. The solution was concentrated, and the colorless oil was used in the next step without purification.

Hydrogen chloride (0.04 mL, 4 M in dioxane, 0.18 mmol) was added to a mixture of aldehyde (prepared above), palladium on carbon (10%) (5 mg), and MeOH−H_2O (4 mL, 6:1) under an atmosphere of H_2 (balloon). After 72 h, the mixture was filtered and concentrated to yield 33 mg of crude product. This residue was loaded onto Dowex 50W-X2 ion-exchange resin (200 mg) in H_2O and eluted with H_2O followed by 2 N NH_4OH. After concentration, the yellow residue was submitted to reversed-phase silica gel chromatography (100% H_2O) to afford 21 mg (70%) of 3-epiaustraline (**14**) as a single isomer (white solid): $[\alpha]^{25}_D$ +5.9° (*c* 1.0, MeOH) (lit.[4d] $[\alpha]^{25}_D$ +6.2° (*c* 1.0, MeOH)); ^{1}H NMR (600 MHz, D_2O) δ 4.39 (br t, 1H), 4.27 (t, J = 2.6 Hz, 1H), 4.08 (br t, 1H), 3.91 (dd, J = 12.1, 5.3 Hz, 1H), 3.82 (dd, J = 12.3, 7.4 Hz, 1H), 3.54 (dd, J = 4.6, 2.9 Hz, 1H), 3.43−3.40 (m, 1H), 3.18 (ddd, J = 12.3, 10.0, 6.2 Hz, 1H) 3.02−2.99 (m, 1H), 1.95−1.86 (m, 2H); ^{13}C NMR (150 MHz, D_2O) δ 77.3, 75.1, 73.1, 68.9, 63.5, 55.7, 44.9, 33.9; HRMS (MALDI-FTMS) *m*/*z* 190.1071 (M + H, 190.1074 calcd for $C_8H_{16}O_4N$).

Australine (1). A 1:1 mixture of anomeric isomers **13** (25 mg, 0.10 mmol) and MeOH (2 mL) was cooled to −78 °C, and a gentle stream of O_3 was bubbled into the solution until a faint blue color appeared. The ozonide was quenched with palladium on carbon (10%) (5 mg) under an atmosphere of H_2 (balloon) at −78 °C, and the reaction was allowed to warm to room temperature. The solution was concentrated and the colorless oil was used in the next step without purification.

Hydrogen chloride (0.08 mL, 4 M in dioxane, 0.3 mmol) was added to a solution of aldehyde (prepared above) and MeOH−H_2O (4 mL, 6:1). After 72 h, sodium acetate (25 mg, 0.3 mmol) was added followed by sodium cyanoborohydride (8 mg, 0.12 mmol) and acetic acid (0.03 mL, 0.50 mmol). After the mixture was stirred for 36 h at room temperature, 1 N HCl was added to bring the solution to pH 1.1. The mixture was concentrated, and the residue was loaded onto Dowex 50W-X2 ion-exchange resin (100 mg) in H_2O and eluted with H_2O followed by 2 N NH_4OH. After concentration, the yellow residue was submitted to reversed-phase silica gel chromatography (100% H_2O) to afford 10 mg (52%) of australine (**1**) as a 8:1 stereoisomeric mixture. Data for australine (**1**): ^{1}H NMR (600 MHz, D_2O) δ 4.27 (dt, J = 4.0, 2.2 Hz, 1H), 4.14 (t, J = 7.9 Hz, 1H), 3.80 (dd, J = 9.4, 8.1 Hz, 1H), 3.70 (dd, J = 11.8, 3.5 Hz, 1H), 3.51 (dd, J = 11.6, 6.6 Hz, 1H), 3.09 (dd, J = 7.5, 4.3 Hz, 1H), 3.05 (ddd, J = 9.9, 7.5, 2.2 Hz, 1H), 2.64−2.61 (m, 2H), 1.95−1.92 (m, 1H), 1.87−1.82 (m, 1H); ^{13}C NMR (150 MHz, D_2O) δ 78.0, 72.2, 69.8, 69.7, 68.6, 61.9, 51.0, 34.4; HRMS(MALDI−FTMS) *m*/*z* 190.1073 (M + H, 190.1074 calcd for $C_8H_{16}O_4N$).

Pyranose (9). Following the general procedure for the preparation of **13**, triol **7** (690 mg, 3.65 mmol) was submitted to periodate cleavage and aldol condensation to afford 225 mg of **9** (25%) after silica gel chromatography (CH_2Cl_2/MeOH, 7:1). Silica gel TLC R_f 0.6 (CH_2Cl_2/MeOH, 7:1). Existing as a mixture of pyranose and ketone (7:1). Data for pyranose **9**: ^{1}H NMR (600 MHz, D_2O) δ 8.05 (s, 1H), 5.75−5.73 (m, 1H), 5.07−5.02 (m, 2H), 4.41−4.38 (ddd, J = 9.0, 7.2, 2.2 Hz, 1H), 3.94 (br s, 1H), 3.86 (app t, 1H), 3.69 (br d, 1H), 3.65 (d, J = 11.6 Hz, 1H), 3.41 (d, J = 11.6, 1H), 2.24−2.16 (m, 2H); ^{13}C NMR (150 MHz, D_2O) δ 169.9, 132.8, 116.9, 97.2, 68.9, 66.0, 64.8, 63.6, 47.5, 33.8; HRMS (FAB) *m*/*z* 270.0956 (M + Na^+, 270.0954 calcd for $C_9H_{19}O_5NNa$).

Pentaacetate (10): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (s, 1H), 5.75−5.70 (m, 1H), 5.66 (d, J = 8.8 Hz, 1H), 5.56 (app t, J = 8.4 Hz, 1H), 5.04 (dd, J = 16.4 Hz, 1H), 5.01 (d, J = 9.9 Hz, 1H), 4.97 (ddd, J = 6.2, 4.4, 1.8 Hz, 1H), 4.90 (dd, J = 8.4, 1.1 Hz, 1H), 4.82 (d, J = 11.7 Hz, 1H), 4.51 (d, J = 11.7 Hz, 1H), 2.16−1.13 (m, 2H), 2.114 (s, 3H), 2.110 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 170.3, 169.7, 169.4, 169.1, 168.5, 161.9, 133.2, 118.3, 89.9, 74.9, 73.2, 71.1, 66.4, 56.5, 37.0, 21.4, 21.4, 20.7, 20.5; HRMS (FAB) *m*/*z* 480.1478 (M + Na^+, 480.1476 calcd for $C_{20}H_{27}O_{11}NNa$).

7-Epialexine (11). Following the general procedure for the preparation of 3-epiaustraline (**14**), **9** (30 mg, 0.12 mmol) was submitted to ozonolysis followed by reductive amination to give, after reverse phase silica gel chromatography (100%

H_2O), 15 mg of 7-epialexine (**11**) (66%) as a 8:1 mixture of stereoisomers: $[\alpha]^{25}_D$ −7.2° (*c* 0.45, MeOH) (lit.[18] $[\alpha]^{25}_D$ −10.6° (*c* 0.56, H_2O)); ^{1}H NMR (600 MHz, D_2O) δ 4.52−4.50 (m, 1H), 4.25 (t, J = 8.3 Hz, 1H), 3.94−3.92 (m, 2H), 3.91−3.89 (m, 1H), 3.64−3.62 (m, 1H), 3.30−3.26 (m, 1H), 3.12−3.06 (m, 2H), 1.95−1.91 (m, 1H), 1.89−1.85 (m, 1H); ^{13}C NMR (150 MHz, D_2O) δ 76.2, 73.9, 70.9, 65.6, 62.8, 57.9, 45.3, 32.8; HRMS (MALDI-FTMS) *m*/*z* 190.1078 (M + H, 190.1074 calcd for $C_8H_{16}O_4N$).

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Supporting Information Available: Spectral data for the triacetate of **13**. COSY data for **10** and NMR data for compounds **7**, **10**, **11**, **13**, **14**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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