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A general asymmetric route for the synthesis of the alexine and australine family of pyrrolizidine alkaloids. The first asymmetric synthesis of 1,2-*diepi*-alexine and 1,2,7-*triepi*-australine

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Abstract—The first asymmetric synthesis of 1,2-*diepi*-alexine and 1,2,7-*triepi*-australine (both are unknown at present) is described, which utilized the regioselective asymmetric aminohydroxylation (RAA) reaction of the achiral olefin **VI**, the cross metathesis (CM) reaction of the terminal olefin **8**, and the formation and subsequent intramolecular double cyclization (DC) reactions of the epoxides **10** and **11**. The C1 stereocenter was diastereoselectively introduced by the reaction of the aldehyde **7** with vinylmagnesium bromide.

Alexine (**1**) and australine (**2**) were isolated from *Alexa leiopetala* and *Castanospermum australe*, respectively, in 1988, and were shown to be potent glycosidase inhibitors.[1] Since glycosidases are involved in many vital biological processes and also believed to be implicated in human diseases such as diabetes,[2] cancers,[3] malaria,[4] and viral infection,[5] a plethora of research activities have been directed to find or prepare the other stereoisomers and derivatives of alexine and australine with such activities.[6] So far, 13 stereoisomers of **1** and **2** (out of 32 possible isomers) are known from natural sources[1,7] and syntheses.[8] These compounds have indeed proved to be selective glycosidase inhibitors,[7] and further some of them have been reported to exhibit antiviral and retroviral activities[9] (Fig. 1).

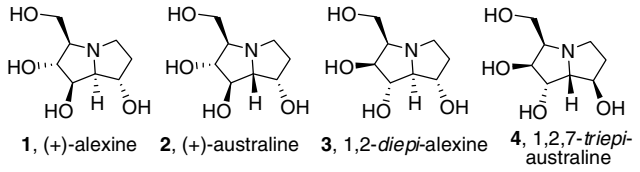

Figure 1. Structure of alexine, australine, 1,2-*diepi*-alexine, and 1,2,7-*triepi*-australine.

Besides their profound biological activities, the alexine and australine family of pyrrolizidine alkaloids represent interesting and challenging synthetic targets. They are densely functionalized by the hydroxyl and amino groups, and have five contiguous stereocenters as well as a pyrrolizidine ring. Thus, both stereoselective installation of the substituents and the stereoselective construction of the pyrrolizidine ring are required for any successful asymmetric synthesis. A number of methodologies have been devised for the asymmetric synthesis of this family, most of which have employed chiral carbohydrates and amino acids as starting materials.[8,10] To the best of our knowledge, only two true asymmetric methodologies have been reported to date, in which achiral starting materials were used and all stereocenters were introduced either by asymmetric induction or enzymatic reaction. Denmark utilized tandem chiral auxiliary based intermolecular [4+2] and inter-/intramolecular [3+2] nitroalkene cycloaddtion reactions followed by a stereoselective dihydroxylation reaction to introduce all five stereocenters.[11] Wong used Sharpless asymmetric epoxidation/enzymatic aldol reaction/bisreductive amination for the stereochemical control in their synthesis.[12] Herein, we report an efficient and highly flexible asymmetric approach for the synthesis of the alexine and australine family of pyrrolizidine

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alkaloids, which not only resulted in the first asymmetric synthesis of 1,2-*diepi*-alexine and 1,2,7-*triepi*-australine (two unknown members of this family until now) from the readily available achiral olefin **VI**, but also implies the potential to synthesize other stereoisomers of this family from the same olefin.

Shown in Figure 2 is the retrosynthetic analysis for the alexine and australine family of pyrrolizidine alkaloids. In designing the synthetic strategy, emphasis has been put on the stereochemical predictability as well as the flexibility and overall efficiency of the synthesis. Thus, the fully functionalized pyrrolizidine ring (**I**) can be derived from the S_N2-type double cyclization (DC)[8f] of the epoxyamine **II**, which itself would be generated through the allylic epoxidation[13] of the alkenylalcohol **III**. The sequential epoxidation and double cylization reactions set the C7a and C7 stereocenters of the alexine and australine family. Compound **III** can be prepared by the cross metathesis (CM) reaction[14] of the terminal olefin **IV**. A nucleophilic addition reaction between the aldehyde **V** and vinyl metals should give **IV**, establishing the C1 stereocenter. Finally, **V** would be prepared through the regioselective asymmetric aminohydroxylation (RAA) reaction[15] of the readily available α,β-unsaturated ester **VI**, which installs the C2 and C3 stereocenters in a *syn*-fashion.

Our synthesis of 1,2-*diepi*-alexine and 1,2,7-*triepi*-australine started with the readily available α,β-unsaturated ester **VI** (Scheme 1). The RAA reaction of **VI** using the $(DHQD)_2PHAL$ as a ligand and *N*-bromoacetamide as a nitrogen source/oxidant afforded the *syn*-amino-alcohol **5** with an excellent regio- (>20:1) and enantioselectivity (>99% after one recrystallization from ethyl acetate).[15a,b,c] The protection of the hydroxyl group by benzylchloride and sodium hydride in DMF gave the benzyl ether,[16] the *N*-acetyl group of which was converted to the *N*-Boc group to give the carbamate **6**. The protection group intercoversion was accomplished by employing the Burk's protocol: $(Boc)_2O$, DMAP, then NH_2NH_2.[17] The partial reduction of the ester **6** by slow addition of DIBAL at −78 °C gave the aldehyde

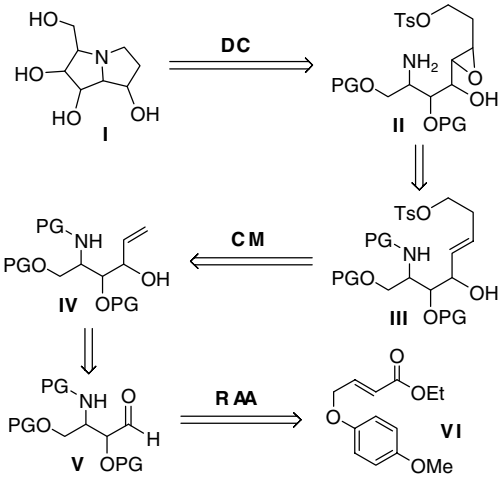
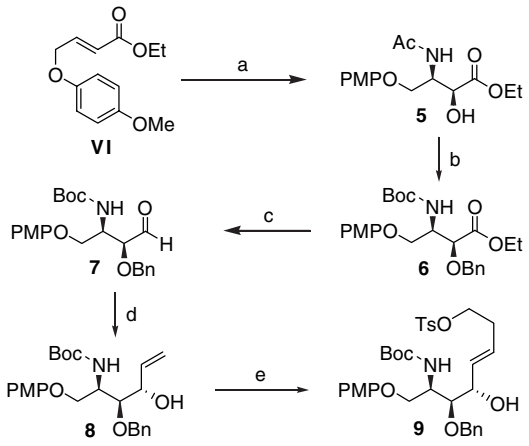


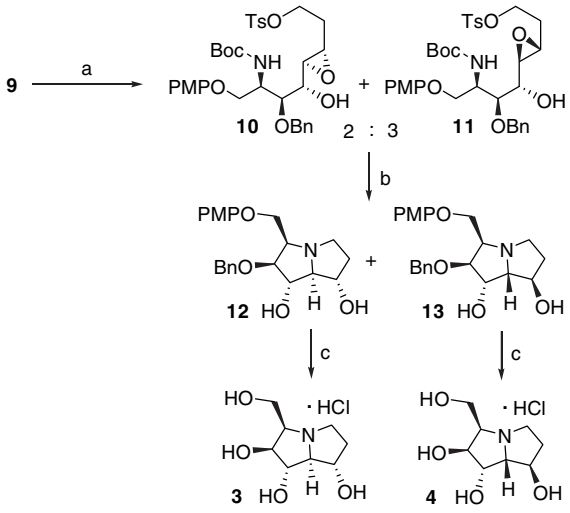
Figure 2. Retrosynthetic analysis of pyrrolizidine alkaloids.



Scheme 1. Reagents and conditions: (a) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2$-PHAL, LiOH, *N*-bromoacetamide, *t*-BuOH–H_2O 2:1, 4 °C, 8 h, 70%; (b) (i) NaH, BnCl, DMF, 0 °C, 10 h; 78%; (ii) $(Boc)_2O$, DMAP, THF, reflux, 4 h, then NH_2NH_2, MeOH, 4 h, 85%; (c) DIBAL, CH_2Cl_2, −78 °C, 3 h, 90%; (d) vinylmagnesium bromide, THF, −50 °C, 1 h then rt, 1 h, 85%; (e) RCM, Grubbs' second generation catalyst, 4-butenol *p*-tolylsulfonate, CH_2Cl_2, 65%.

7.[18] The reaction of **7** with vinylmagnesium bromide at −50 °C in THF generated the allylic alcohol **8** with 4:1 diastereoselectivity. Other reaction conditions involving different vinyl anion sources, solvents, and temperatures did not improve diastereoselectivity much. The cross metathesis reaction[14d] of **8** with 4-butenol *p*-tolylsulfonate in the presence of the second generation Grubbs' catalyst {tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]ruthenium (IV) dichloride} provided the *trans*-olefin **9** almost exclusively.

Scheme 2 depicts the latter stage of the synthesis. The allylic alcohol **9** was subjected to the epoxidation conditions involving $VO(acac)_2$/ROOH.[19] After some experi-



Scheme 2. Reagents and conditions: (a) $VO(acac)_2$, TBHP, toluene, 74%; (b) (i) 3 N HCl, MeOH, (ii) K_2CO_3, MeOH, 83%; (c) (i) CAN, CH_3CN–H_2O 4:1, 4 °C; (ii) H_2, Pd/C, MeOH, 72% for **3** and 80% for **4**.

mentations with the $VO(acac)_2$/ROOH/solvent/temperature system, it was found that the reaction conditions using two fold excess of *t*-BuOOH in the presence of 4 mol % of $VO(acac)_2$ in toluene solvent at ambient temperature were optimal for the epoxidation of **9**, which produced an inseparable mixture of the epoxides **10** and **11** in a 2:3 ratio and 74% yield. Treatment of the mixture of **10** and **11** with 3 N HCl in MeOH followed by the addition of solid K_2CO_3 in one pot operation effected the double cyclization to yield the fully functionalized alexine **12** and australine **13**. After column separation, a sequential deprotection of PMP and benzyl group by CAN[20] and hydrogenation, respectively, converted **12** to 1,2-*diepi*-alexine (**3**),[21] which was isolated as a HCl salt. Similarly 1,2,7-*triepi*-australine (**4**)[21] was obtained from **13**, the spectral data (^1H and ^{13}C NMR) of which were consistent with those of its enantiomer in the literature.[8p]

In summary, the first asymmetric synthesis of 1,2-*diepi*-alexine and 1,2,7-*triepi*-australine was accomplished from the simple olefin **VI** in only 10 steps by using the regioselective asymmetric aminohydroxylation, olefin cross metathesis, and double cyclization reactions as key steps. Currently, we are persuing the asymmetric synthesis of the other stereoisomers and derivatives of alexine and australine by modifying the present methodology slightly.

Acknowledgement

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21. Characterization data: 1,2-*diepi*-alexine hydrochloride: $[\alpha]_D$ +33.0 (*c* 0.1, H_2O); ^1H NMR (500 MHz, D_2O): δ 4.62–4.58 (1H, m), 4.37 (1H, br s), 4.32 (1H, br s), 4.12–3.98 (3H, m), 3.80 (1H, d, $J = 5.8$ Hz), 3.75–3.60 (2H, m), 2.51–2.44 (1H, m), 2.04–1.96 (1H, m). ^{13}C NMR (75 MHz, D_2O): δ 81.8, 79.4, 78.9, 74.8, 69.8, 57.6, 50.3, 34.9. 1,2,7-*triepi*-australine hydrochloride: $[\alpha]_D$ +49.0 (*c* 0.1, H_2O); ^1H NMR (500 MHz, D_2O): δ 4.69 (1H, br s), 4.43–4.41 (1H, m), 4.35 (1H, br s), 4.30 (1H, d, $J = 4.8$ Hz), 4.07 (1H, dd, $J = 7.8$ and 4.8 Hz), 4.01 (1H, dd, $J = 12.7$ and 7.8 Hz), 2.42–2.34 (1H, m), 2.15–2.10 (1H, m); ^{13}C NMR (75 MHz, D_2O): δ 80.7, 79.3, 75.6, 72.7, 71.6, 59.8, 54.7, 36.3.