Tandem Ring-Closing Metathesis Transannular Cyclization as a Route to Hydroxylated Pyrrolizidines. Asymmetric Synthesis of (+)-Australine

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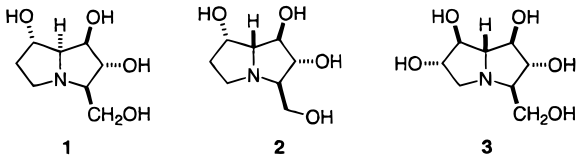
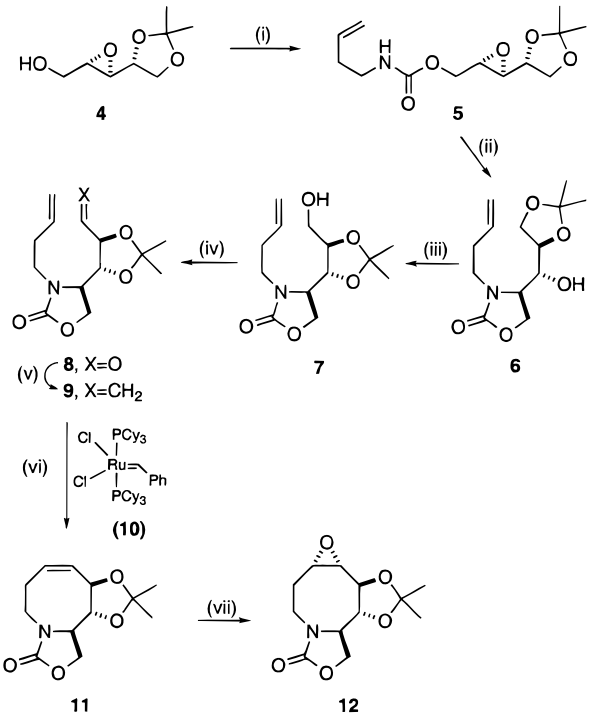
The family of pyrrolizidine alkaloids continues to provide novel structures with interesting and potentially valuable biological properties.[1] The alexines,[2] represented by the parent alkaloid (**1**), australine (**2**),[3] and the pentahydroxypyrrolizidine casuarine (**3**),[4] are powerful inhibitors of glucosidase and exhibit antiviral[5] including anti-HIV activity.[6] Although a variety of *de novo* approaches to the construction of simple pyrrolizidines is available,[7] none is directly applicable to the asymmetric synthesis of structures such as **1**−**3**. Indeed, pathways to these systems have



generally pursued routes involving transmutation of carbohydrates from the chiral pool.[8] Herein we describe a new synthesis of pyrrolizidines based on ring-closing metathesis in conjunction with transannular cyclization. The method is potentially applicable not only to polyhydroxylated pyrrolizidines such as **1**−**3** but to important indolizidines, such as swainsonine[9] and castanospermine,[10] as well.

Ring-closing metathesis (RCM) has established itself as a valuable method for the elaboration of medium-sized rings,[11] including heterocyclic variants.[12] In tandem with transannular cyclization (TC),[13] RCM affords convenient access to a fused bicyclic system from an acyclic precursor. The practicality of a RCM-TC strategy is illustrated here by its application to an efficient stereocontrolled synthesis of (+)-australine (**2**),[14] a tetrahydroxypyrrolizidine isolated from the rainforest tree *Castanospermum australe*.[3]

Scheme 1[a]



[a] Key: (i) CH_2═$CH(CH_2)_2NCO$, *i*-Pr_2NEt, C_6H_6, Δ, 93%; (ii) *t*-BuOK, THF, 0 °C, 96%; (iii) Amberlyst−15, Me_2CO, rt, 62% (98% based on recovered **6**); (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 90%; (v) Ph_3P^+Me Br^-, KHMDS, THF, −78 °C → rt, 76%; (vi) **10**, CH_2Cl_2, rt, 97%; (vii) *m*-CPBA, CH_2Cl_2, rt, 82%.

The known epoxy alcohol **4**[15] was reacted with 4-butenyl isocyanate, prepared from 4-pentenoic acid via Curtius rearrangement of the corresponding azide and used in situ, to give the urethane **5** (Scheme 1). Exposure of **5** to potassium *tert*-butoxide afforded the oxazolidinone **6** which readily underwent acetonide migration in the presence of Amberlyst resin to give the internal ketal **7**. Swern oxidation of primary alcohol **7** followed by a Wittig reaction of the resultant aldehyde **8** with methylenetriphenylphosphorane furnished diene **9**.

Ring-closing metathesis of **9** with Grubbs catalyst **10** produced the azacyclooctene derivative **11** in virtually quantitative yield. Conformational analysis of **11** using an AM1 algorithm led to the prediction that epoxidation of this olefin should occur with high stereoselectivity at the face opposite the transannular alkyl substituent, and when **11** was treated with *m*-chloroperoxybenzoic acid (*m*-CPBA) , a single epoxide was the result. An X-ray crystallographic analysis revealed the configuration of this epoxide to be as shown in **12**. Although an azacyclooctane could be liberated from oxazolidinone **12**, intramolecular attack by nitrogen at the epoxide to form a pyrrolizidine was impeded by the transfused acetonide in this structure. Unfortunately, attempts to

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(14) (a) A synthesis by Pearson targeted at australine was reported as a synthesis of (+)-7-epiaustraline (Pearson, W. H.; Hines, J. V. *Tetrahedron Lett*. **1991**, *32*, 5513) due to erroneous NMR data in the literature. The errors have now been corrected (Wormald, M. R.; Nash, R. J.; Hrnciar, P.; White, J. D.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, in press), and it has been confirmed that Pearson's synthesis is indeed that of (+)-australine. (b) A different synthesis of **2** has been reported utilizing ring contraction of castanospermine (Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C. *Tetrahedron* **1994**, *50*, 2131).
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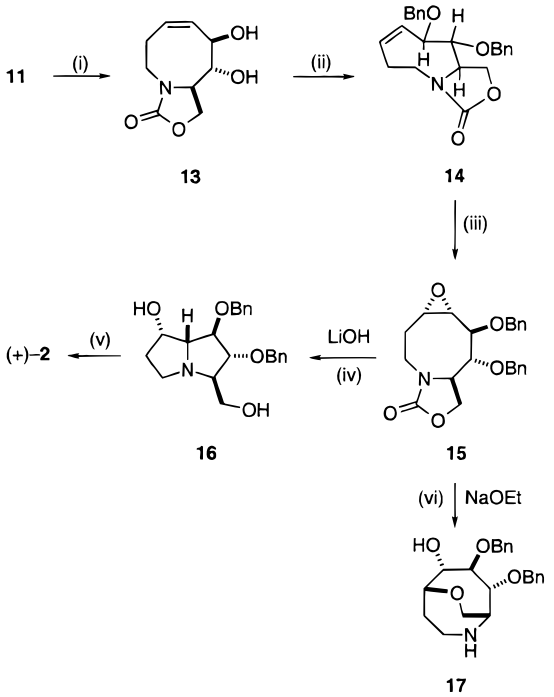
Scheme 2[a]



[a] Key: (i) HBr, MeCN, rt, 99%; (ii) NaH, BnBr, $Bu_4N^+ I^-$, THF, 60 °C, 84%; (iii) *m*-CPBA, CH_2Cl_2, rt, 75%; (iv) LiOH, EtOH−H_2O (1:1), 95 °C, 99%; (v) H_2, 20% $Pd(OH)_2$/C, MeOH, rt, 99%; (vi) NaOEt, EtOH, 70 °C, 40%.

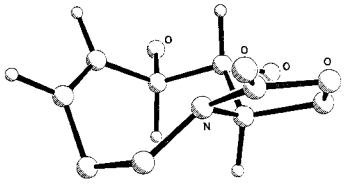


Figure 1. Optimized geometry of **14** using an AM1 algorithm (the benzyl groups were omitted to facilitate computation).

remove the acetonide from **12** led to destruction of the epoxide. The problem was conveniently solved by deleting the acetonide from **11** and protecting the resultant diol **13** as its dibenzyl ether **14** (Scheme 2). Again, conformational analysis of **14** (Figure 1) suggested an optimized geometry in which all substituents on the eight-membered ring are in a pseudoequatorial orientation, leading to a prediction of high stereoselectivity in the epoxidation of the alkene moiety from the α face. In the event, reaction of **14** with *m*-chloroperoxybenzoic acid yielded a single epoxide assigned

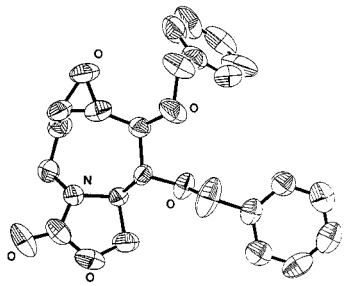


Figure 2. ORTEP diagram of **15**. Ellipsoids are drawn at the 50% probability level.

structure **15** on the basis of an X-ray crystallographic analysis (Figure 2).[16] Treatment of **15** with a hot aqueous solution of lithium hydroxide resulted in cleavage of the oxazolidinone followed by immediate TC to give dibenzylaustraline (**16**) in quantitative yield. Hydrogenolysis of the latter produced australine (**2**), identical by comparison of spectral data with those of natural material provided by Professor G. W. J. Fleet (Oxford University). Interestingly, when **15** was exposed to hot concentrated sodium ethoxide in ethanol, a different mode of transannular cyclization predominated, resulting in a compound assigned the bridged bicyclic structure **17** on the basis of a careful analysis of its COSY spectrum.

In summary, RCM-TC has been shown to be an efficient strategy for assembling the polyhydroxylated pyrrolizidine australine from simple precursors (11 steps, 35% overall yield). Application of this approach to other members of the alexine family of alkaloids can be foreseen by relatively straightforward modification of the route described above.

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Supporting Information Available: Characterization data, NMR spectra, and X-ray crystallographic details (24 pages, print/PDF). An X-ray crystallographic file, in CIF format, is available via the Web only. See any current masthead page for ordering information and Web access instructions.

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(16) Crystal data for **15**: mp 139−140 °C (hexanes−EtOAc), $C_{23}H_{25}NO_5$, MW = 395.44, colorless parallelepiped 0.1 × 0.4 × 0.5 mm^3 in size, monoclinic $P2_1$ (No. 4), a = 12.786(1) Å, b = 8.207 (1) Å, c = 19.320(1) Å, β = 91.68(1)°, V = 2026.5(1) $Å^3$, Z = 4 (2 unique molecules per asymmetric unit). R1 = 0.0475 and wR2 = 0.1116 with GOF = 1.051 for 590 parameters refined against all 5305 unique reflections and 228 restraints (R1 = 0.0418 and wR2 = 0.1061 for 4817 reflections with $I > 2\sigma(I)$).