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A Synthesis of (+)-7-Epiaustraline and (-)-7-Epialexine

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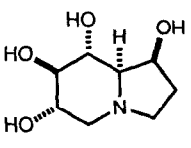
Key Words. (+)-7-Epiaustraline; (-)-7-epialexine; glycosidase inhibitors; polyhydroxylated pyrrolizidine alkaloids; epoxide

Abstract: *Reductive cyclization of the azido epoxides 19α and 19β followed by deprotection afforded the HIV inhibitor (+)-7-epiaustraline 7 and (-)-7-epialexine 9. The formation of 7 proceeded with an unusual inversion of configuration at C-7.*

Polyhydroxylated indolizidine alkaloids such as castanospermine **1** and swainsonine **2** have attracted considerable interest in recent years due to their ability to inhibit glycosidases.[1] In addition to their use in the study of glycoprotein-processing enzymes, such alkaloids are promising anticancer and antiretroviral agents. More recently, polyhydroxylated pyrrolizidine alkaloids with similar biological activities have emerged from the independent investigations of research teams in the U.K. and the U.S.A. The isolation of alexine **3** from *Alexa leiopetala* was reported in 1988.[2] The isolation of similar alkaloids from *Castanospermum australe* quickly followed, including 3,7a-diepialexine (or 3-epiaustraline) **4**,[3,4] australine **5**,[5] 1-epiaustraline (or 1,7a-diepialexine) **6**,[6,7] and 7,7a-diepialexine (or 7-epiaustraline) **7**.[7] While alexine **3** and 3-epiaustraline **4** are generally poor inhibitors of glucosidases and galactosidases,[2,4] they display amyloglucosidase inhibition which is on par with that of castanospermine,[7] and alexine is an effective thioglucosidase inhibitor.[8] Compounds **5-7** are also good amyloglucosidase inhibitors.[5,7,9] Australine **5** inhibits glucosidase I, but not glucosidase II,[9] and has recently been shown to exhibit antiviral activity.[10] Modest glucosidase I, β-glucosidase, and α-mannosidase inhibition was observed for 1-epiaustraline **6**,[6] but it displayed good activity in a mouse gut digestive α-glucosidase assay, as did 7-epiaustraline **7**.[7,11] An exciting recent report shows that australine **5**, 1-epiaustraline **6**, and 7-epiaustraline **7** inhibit HIV-induced syncytia formation in JM cells.[11] The potential of the polyhydroxylated pyrrolizidine alkaloids as selective glycosidase inhibitors and as antiviral and antiretroviral agents makes them attractive targets for synthesis. In particular, the ability to prepare alternative stereoisomers of these alkaloids would be desirable, since the biological activity of these compounds varies substantially with their stereochemistry. We wish to report our initial efforts in this area, which have led to the synthesis of the naturally occurring alkaloid (+)-7-epiaustraline **7** (also known as 7,7a-diepialexine) which shows anti-HIV



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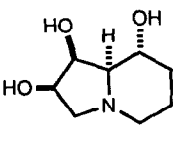

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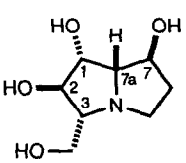

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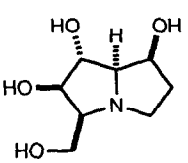

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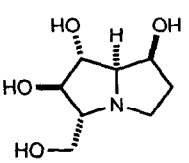

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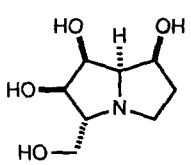

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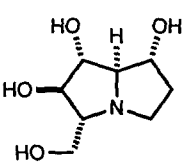

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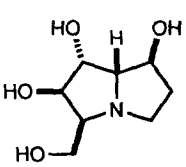

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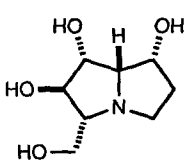

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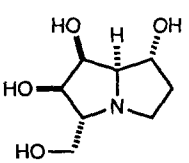

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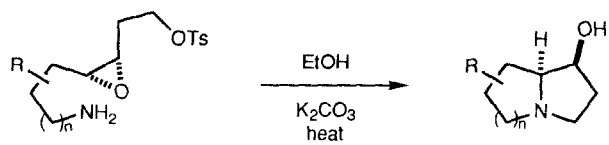
activity,[11] and the non-natural compound (-)-7-epialexine **9**.[12] Our synthesis of **7** confirms its absolute configuration.[7]

Synthetic efforts on the polyhydroxylated pyrrolizidine alkaloids have been sparse to date.[13] In 1988, Fleet reported the synthesis of alexine **3** and the two non-natural alkaloids 3-epialexine **8** and 7-epialexine **9** from glucose.[12] Fleet has now completed the synthesis of **6** and the non-natural alkaloid 1,7,7a-triepialexine (or 1,7-diepiaustraline) **10**.[14] Syntheses of related pyrrolizidine alkaloids without the 3-hydroxymethyl group have also been reported.[15,16]

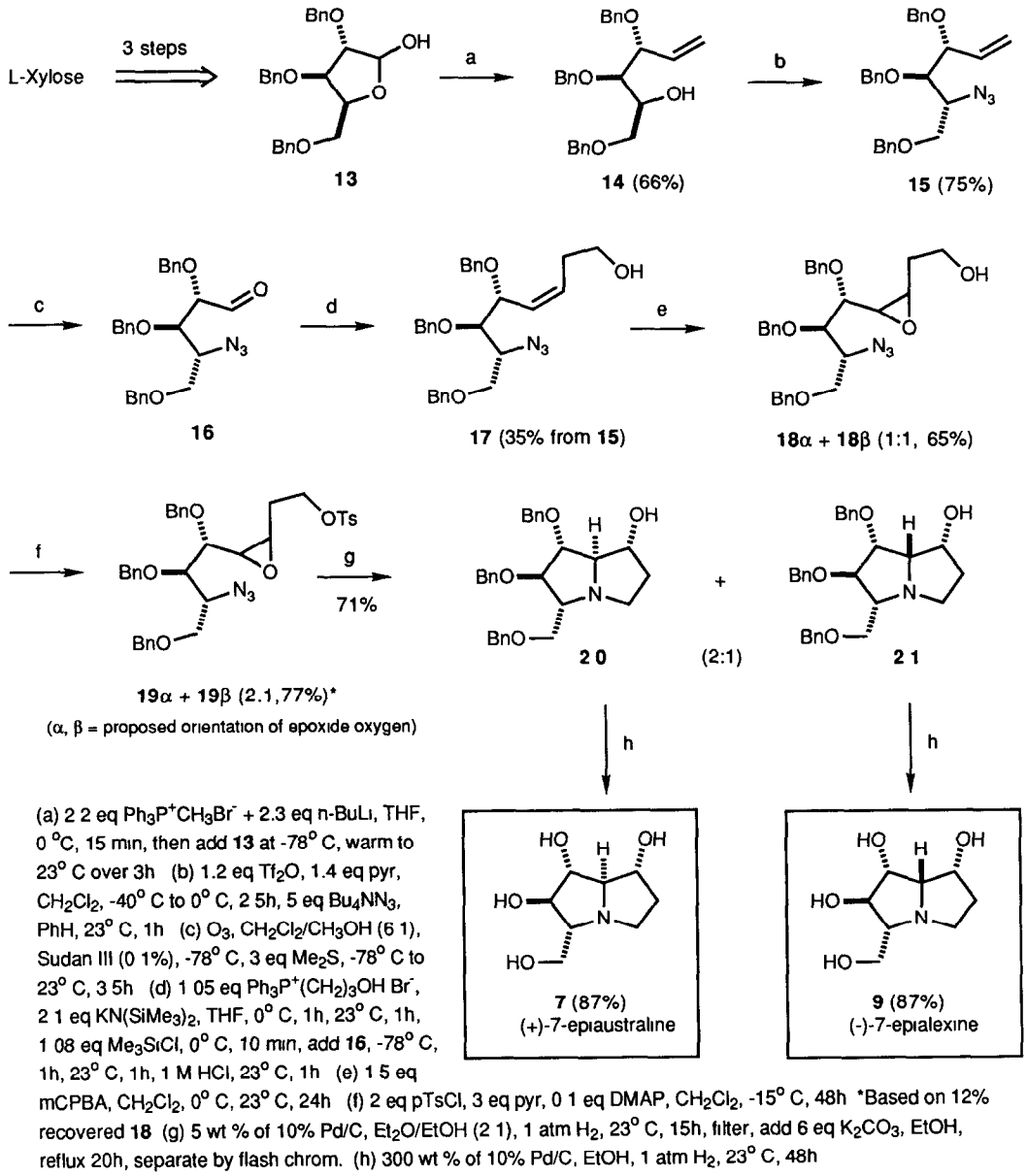
We have recently reported that compounds such as **11** undergo tandem epoxide opening/intramolecular alkylation to produce indolizidines **12** (n=2).[17-19] The relative stereochemistry of the two newly formed stereocenters should be determined ultimately by the geometry of the alkene which is a precursor to **11**. We now report that this strategy is useful for pyrrolizidine synthesis (**12**, n=1), and that the stereochemical outcome of this process is not as straightforward as was predicted.



11 **12**

Our synthesis began with 2,3,5-tri-*O*-benzyl-L-xylofuranose **13**,[20a] which was prepared from L-xylose in 3 steps.[20b] Wittig olefination produced **14**, which was converted to azide **15** by displacement of a triflate with azide ion. The azide **15** was quite unstable, and underwent an intramolecular 1,3-dipolar cycloaddition upon standing at room temperature. Hence, it was best to carry **15** to the next step without delay. Ozonolysis of **15** afforded the aldehyde **16**, which was not purified due to its sensitivity, but was directly converted to the *Z*-alkene **17** by a very stereoselective Wittig reaction with a silyloxy-substituted ylide.[21] Again, intramolecular 1,3-dipolar cycloaddition was observed if this azidoalkene was allowed to stand at room temperature. Epoxidation of the **17** with mCPBA produced a 1.1 mixture of epoxides **18**α and **18**β, which were not separated.[22] Tosylation of **18**α/β gave **19**α/β as a 2.1 mixture of isomers, since one of the isomers of **18** underwent tosylation faster than the other, and the reaction could not be driven to completion. Reduction of **19**α/β without debenzylation was possible by hydrogenolysis. The resultant amine was not isolated but was directly heated in refluxing EtOH containing K_2CO_3, affording a 2·1 mixture of two pyrrolizidines **20** and **21** which were easily separated by flash chromatography. At this point, the stereochemistry of **20** and **21** was unknown, but it was assumed that the methine hydrogens at C-7 and C-7a were *cis* in both isomers due to their *cis* relationship in alkene **17** and epoxides **18** and **19**. Hydrogenolysis of the benzyl ethers of the separated pyrrolizidines **20** and **21** using a greater amount of palladium catalyst afforded two tetrahydroxypyrrolizidines, which were found to be (+)-7-epiaustraline **7** and (-)-7-epialexine **9** by comparison of their physical and spectral data to literature values, including optical rotation.[7,12] The formation of **7** was unexpected, since the methine hydrogens at C-7 and C-7a were *trans* rather than *cis*. We had expected australine **4** to result from the cyclization of **19**α. Isomerization of the alkene **17** or the epoxides **18** and **19** from *cis* to *trans* during their manipulation was ruled out by ^{1}H NMR spectroscopy. Given that the stereochemistry of the centers at C1-C3 is based on L-xylose, there are only four possible structures that may arise upon cyclization of the aminoepoxides **19**. **3**, **5**, **7**, and **9**. Since the structures of **3**, **5**, and **9** have been established by X-ray crystallography[2,5,12] and since our data for **7** are not consistent with these structures, it appears that the assignment of **7** must be as shown. The literature assignment of **7** rests on NOE experiments and comparison with known structures.[7] The absolute stereochemistry was not determined, but was proposed to be as shown. The unusual inversion of configuration at C-7 which occurs in the formation of **7** is currently under investigation.

In summary, a relatively short route to (+)-7-epiaustraline **7** and (-)-7-epialexine **9** has been developed. The absolute stereochemistry of the anti-HIV alkaloid **7** has been confirmed to be as shown based on the stereochemistry of L-xylose. While the use of the tandem aminoepoxide opening/intramolecular alkylation approach is efficient, caution must be used in predicting the stereochemical outcome of this reaction.



(a) 2 2 eq $Ph_3P^+CH_3Br^-$ + 2.3 eq n-BuLi, THF, 0 °C, 15 min, then add **13** at -78° C, warm to 23° C over 3h (b) 1.2 eq Tf_2O, 1.4 eq pyr, CH_2Cl_2, -40° C to 0° C, 2 5h, 5 eq Bu_4NN_3, PhH, 23° C, 1h (c) O_3, CH_2Cl_2/CH_3OH (6 1), Sudan III (0 1%), -78° C, 3 eq Me_2S, -78° C to 23° C, 3 5h (d) 1 05 eq $Ph_3P^+(CH_2)_3OH\ Br^-$, 2 1 eq $KN(SiMe_3)_2$, THF, 0° C, 1h, 23° C, 1h, 1 08 eq Me_3SiCl, 0° C, 10 min, add **16**, -78° C, 1h, 23° C, 1h, 1 M HCl, 23° C, 1h (e) 1 5 eq mCPBA, CH_2Cl_2, 0° C, 23° C, 24h (f) 2 eq pTsCl, 3 eq pyr, 0 1 eq DMAP, CH_2Cl_2, -15° C, 48h *Based on 12% recovered **18** (g) 5 wt % of 10% Pd/C, Et_2O/EtOH (2 1), 1 atm H_2, 23° C, 15h, filter, add 6 eq K_2CO_3, EtOH, reflux 20h, separate by flash chrom. (h) 300 wt % of 10% Pd/C, EtOH, 1 atm H_2, 23° C, 48h

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