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Asymmetric total synthesis of natural pyrrolizidine alkaloid, (+)-alexine

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Abstract

The total synthesis of the potent glycosidase inhibitor (+)-alexine with five contiguous stereogenic centres [(1*R*,2*R*,3*R*,7*S*,7*aS*)-3-hydroxymethyl-1,2,7-trihydroxypyrrolizidine alkaloid] is described featuring the efficient and stereodefined novel elaboration of the functionalized homochiral lactam derived from 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose.

Keywords: pyrrolizidine alkaloid; alexine; stereoselective reduction; chiral lactam; D-arabinofuranose.

Structurally complex alkaloidal sugar mimics with a nitrogen in the ring have been isolated from plants and microorganisms and inhibit various glycosidases in a reversible and competitive manner.[1] Since such glycosidase inhibitors proved to have the potential to produce antiviral, insect antifeedant, antidiabetic, and anticancer effects, as well as immune modulatory properties, they have held considerable interest in the context of the synthesis of nitrogen-containing natural products. Noteworthy members among this class of compounds are alexine (**1**),[2] australine (**2**),[3] and casuarine (**3**) (Fig. 1).[4] These display powerful glycosidase inhibitory properties and, in addition, exhibit viral and retroviral[5] including anti-HIV activity.[6] These are also a unique subset of pyrrolizidine alkaloids possessing five contiguous stereogenic centres,

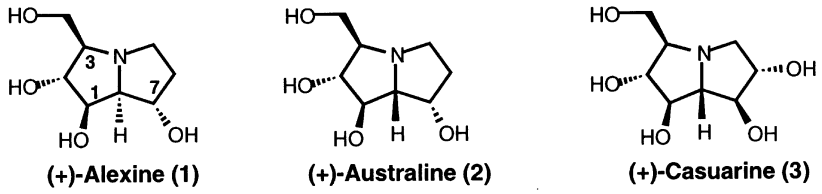

Figure 1.

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and the presence of a hydroxymethyl group adjacent to the ring nitrogen [C(3)] distinguishes this group from the larger class of necine bases, which contain carbon substituents at C(1).

The diverse array of potentially useful activities make them inviting targets for synthesis. In particular, the preparation of unnatural epimers and other structural analogs of these compounds has generated much interest since the biological activity of these molecules varies substantially with the number, position and stereochemistry of the hydroxy groups into the pyrrolizidine skeleton.[7] However, despite interesting pharmacological activity and unique structural features, to our knowledge, only one approach to the total synthesis of the parent alkaloid **1** of alexines has been reported to date based on an optical resolution method.[8] With these considerations in mind, we wish to communicate herein a novel and efficient asymmetric synthesis of **1** by means of requisite stereoselective elaboration of the functionalized homochiral lactam (II) through a pyrrolidine intermediate (III) derived from D-arabinofuranose (I) (Fig. 2).

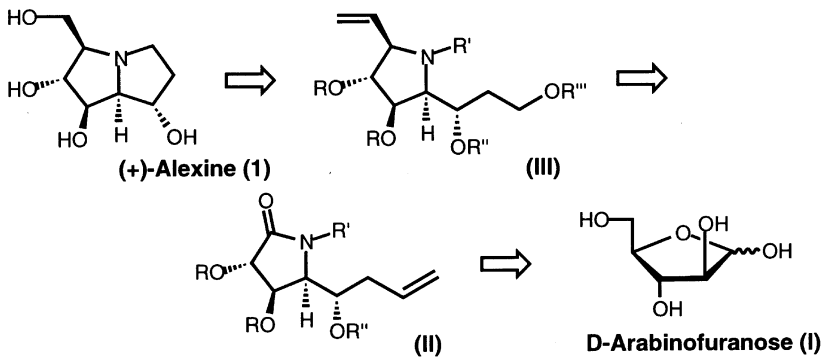
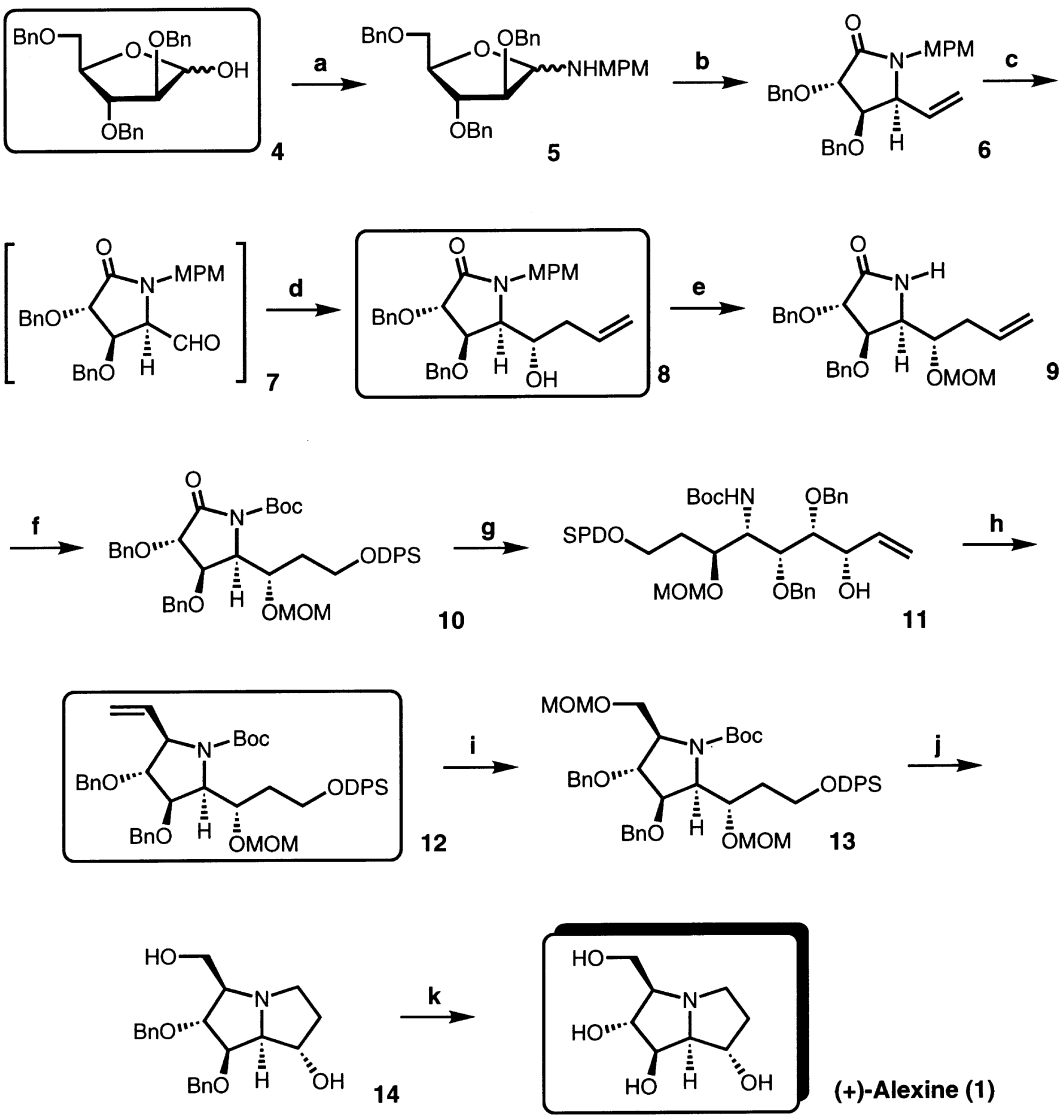


Figure 2.

As shown in Scheme 1, the functionalized homochiral lactam **6** (>99% d.e.) was obtained from nucleophilic addition of vinylmagnesium bromide to the furanosylamine **4**, followed by oxidative degradation with PCC[9] in high yield. The olefinic part in **6** was then cleaved via dihydroxylation to give the aldehyde intermediate **7**, which was in turn subjected to $BF_3{\cdot}OEt_2$-induced allylation at low temperature, leading to the corresponding desired allyl alcohol **8**[10] predominantly (97:3)[11] in 80% yield (three steps) through attack on the carbonyl group from the less hindered face. After removal of the *N*-MPM moiety and protection of the hydroxyl group in **8** with MOMCl, **9** thus obtained was submitted to oxidative cleavage again followed by reduction to the corresponding alcohol, which was stepwisely treated with DPSCl and $(Boc)_2O$ to give the *N*-Boc lactam **10** in an 81% five steps yield from **9**. Then, the second vinyl-Grignard addition to **10** easily afforded the labile quaternary α-hydroxypyrrolidine intermediate,[12] which was subsequently effected by reduction with $NaBH_4$ in the presence of $CeCl_3$ to provide the desired stereoisomer **11**[12b,c] with five contiguous stereogenic centres as a sole product[13] (determined by ^{13}C NMR and chiral HPLC analysis).

In light of the above outcome, we turned our attention to the construction of a pyrrolizidine ring system. Thus, cyclization of **11** under basic conditions via mesylation was performed to yield the pyrrolidine derivative **12** in 84% yield. This was then successively effected by reactions of oxidative cleavage, reduction, and MOM-protection to lead to the functionalized *N*-Boc derivative **13**. Construction of the bicyclic pyrrolizidine ring was accomplished under mild basic conditions with K_2CO_3 in MeOH after replacement of the silyl substituent in **13** by the leaving Ts group, followed by simultaneous deprotection of two hydroxyl and amino functions with



Scheme 1. Reagents and conditions: (**a**) **1**, $MPMNH_2$, benzene–$CHCl_3$ (1:1), MS 4A, reflux; quant.; (**b**) **1**, vinylmagnesium bromide, THF, −78 to −40°C; 70%; **2**, PCC, MS 4A, CH_2Cl_2; 68%; (**c**) **1**, OsO_4, NMO, acetone–H_2O (1:1); 98%; **2**, $NaIO_4$, Et_2O–H_2O (2:1); (**d**) allyltrimethylsilane, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 to −20°C; 82% (two steps); (**e**) **1**, CAN, CH_3CN–H_2O (9:1); 71%; **2**, MOMCl, *N*,*N*-diisopropylethylamine, CH_2Cl_2; 75%; (**f**) **1**, OsO_4, NMO, acetone–H_2O (1:1); 91%; **2**, $NaIO_4$, Et_2O–H_2O (2:1); **3**, $NaBH_4$, EtOH; 90% (two steps); **4**, DPSCl, imidazole, DMF; quant.; **5**, $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 99%; (**g**) **1**, vinylmagnesium bromide, THF, −78°C; **2**, $NaBH_4$–$CeCl_3$, MeOH, −45°C; 66% (two steps); (**h**) **1**, MsCl, Et_3N, CH_2Cl_2; **2**, *t*-BuOK, THF; 84% (two steps); (**i**) **1**, OsO_4, NMO, acetone–H_2O (1:1); 92%; **2**, $NaIO_4$, Et_2O–H_2O (2:1); **3**, $NaBH_4$, EtOH; 74% (two steps); **4**, MOMCl, *N*,*N*-diisopropylethylamine, CH_2Cl_2; 99%; (**j**) **1**, Bu_4NF, THF; quant.; **2**, *p*-TsCl, pyridine; 92%; **3**, conc. HCl, MeOH; **4**, K_2CO_3, MeOH; 94% (two steps); (**k**) H_2, 10% Pd/C, EtOH; 70%

conc. HCl, leading to the alexine dibenzyl derivative **14** in an 86% four steps yield. Finally, removal of the benzyl groups in **14** was performed with 10% Pd on carbon to complete the total synthesis of alexine (**1**), ($[\alpha]_D^{27}$ +39.13 (*c* 0.30, H_2O) [lit. $[\alpha]_D^{20}$ +40.0 (*c* 0.25, H_2O)],[2] mp 160–161°C

[lit. 162–163°C][2]) in 70% yield. The spectral data of synthetic **1** were identical to those of the reported natural product.[2]

This work constitutes the first asymmetric synthesis of natural (+)-alexine from the D-arabino-furanose derivative and will be widely applicable to the synthesis of other pyrrolizidine alkaloidal sugar mimics.

Acknowledgements

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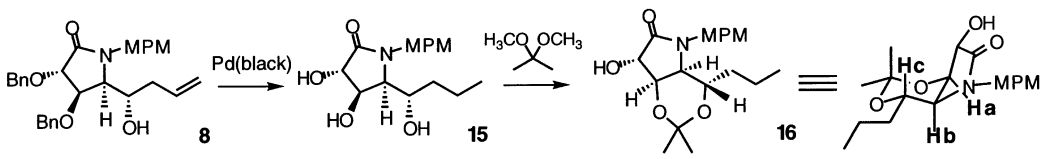
10. The absolute stereochemistry of the newly created carbon centre in **8** was proved to be *S* by the transformation into the acetonide **16** after deprotection as shown below, since the observed vicinal coupling constants ($J_{a,b}$ and $J_{b,c}$) of Ha–Hb and Hb–Hc in **16** were 2.4 and 7.3 Hz, respectively, indicating an equatorial–axial relationship.



11. The ratio of the two diastereomers was easily determined by chromatographic separation after derivatization to *N*-Boc-methoxymethyl ether of **8**.
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13. The absolute configuration of the generated stereogenic centre in **11** was unambiguously assigned to be *S* based on our previous results[12] and the spectral data of synthesized (+)-**1**.