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Synthesis and Glycosidase Inhibition of Australine and Its Fluorinated Derivatives

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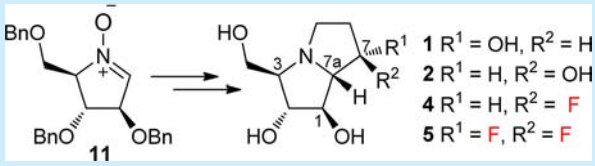
Supporting Information

ABSTRACT: Australine (**1**), 7-*epi*-australine (**2**), and their C-7-fluorinated derivatives **4** and **5** have been synthesized efficiently from D-arabinose-derived cyclic nitrone **11**. Fluorination at the C-7 position enhanced the inhibition against *A. niger* α-glucosidase, and this constitutes the first example of fluorination substitution for a hydroxyl increasing the inhibition of any glycosidases. The enantiomers synthesized from nitrone ***ent*-11** showed no inhibition of the corresponding enzymes.



Australine (**1**) was isolated from seeds of *Castanospermum australe* in 1988[1] and can be viewed as a conformationally fixed 2,5-dideoxy-2,5-imino-D-mannitol (DMDP, **6**) analogue. As one of the most investigated iminosugars, australine (**1**) is a potent inhibitor of α-glucosidase,[2] a competitive inhibitor of amyloglucosidase,[1,3] and the first polyhydroxylated pyrrolizidine inhibiting glycoprotein processing enzyme glucosidase I,[3b] which also displays antiviral[4] and anti-HIV activity.[5] Compared to DMDP (**6**),[6] the glycosidase inhibition profile of australine (**1**) was believed to arise from the locked bicyclic structure which abolished the C_{2v} symmetry of the system.[6d,7] In the context of our continuing interest in the synthesis and biological activities of DMDP-related iminosugars,[8] we became interested in the synthesis and structure−activity relationship study of australine and its derivatives, especially C-7-fluorinated derivatives (Figure 1).

Fluorination is a powerful tool in structure−activity relationship studies.[8d,9] The importance of the C-6 hydroxyl group of DMDP in glycosidase inhibition had been reported by Stütz and co-workers.[9b] Study of the role of the C-7 hydroxyl of the bicyclic system of australine could prove insightful, since the C-7 hydroxyl of australine corresponds to the C-6 hydroxyl of DMDP. In this regard, fluorination of iminosugar hydroxyls usually decreases glycosidase inhibition except for a few examples.[9e]

The synthesis and glycosidase inhibition evaluation of 7-deoxy-7-fluoro-australine (**3**), 7-deoxy-7-fluoro-7-*epi*-australine (**4**), and 7,7-difluoro-7-deoxyaustraline (**5**) could help us to understand the SAR of australine and that of the DMDP-related iminosugars. Moreover, synthetic enantiomers of some naturally occurring iminosugars are more potent glycosidase inhibitors.[10] For example, L-DMDP (***ent*-6**) is a more powerful and specific α-glucosidase inhibitor than DMDP (**6**).[8d,10a,f] Therefore, the synthesis and glycosidase inhibition evaluation of enantiomers of australine (***ent*-1**) and its derivatives (***ent*-2**)-(***ent*-5**) could help to provide a better understanding of the SAR of australine and DMDP-related iminosugars.

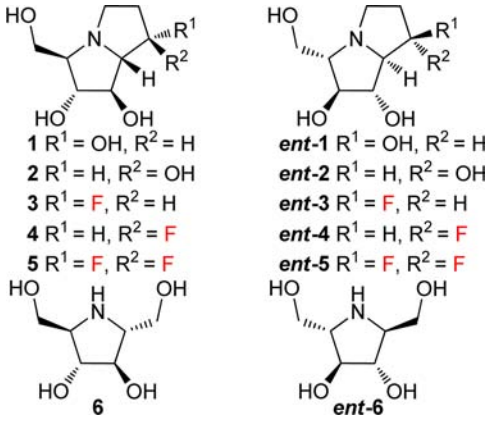


Figure 1. Iminosugars related to australine.

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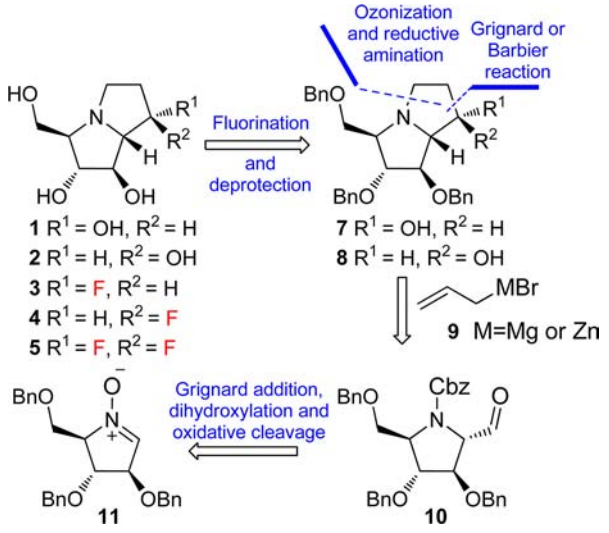
Synthetic methods for accessing australine or its derivatives have been well documented in the literature via a range of approaches.[11] Our strategy was based on the sugar-derived nitrone **11**[12] which can be easily converted to aldehyde **10**, establishing the bicyclic structure in an efficient way (Scheme 1).[8d,12h] The aldehyde can then be converted to australine

Scheme 1. Retrosynthesis of Australine and Its Derivatives

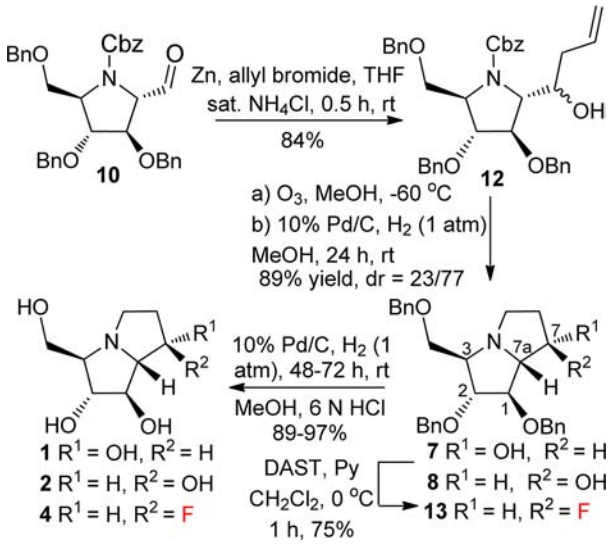


derivatives **7** and **8** by Grignard or Barbier reactions, ozonization, and reductive amination. Direct hydrogenation of **7** and **8** would give australine (**1**) and its C-7 epimer **2**, while fluorination of the suitably protected **7** and **8** and subsequent deprotection would afford fluorinated australine derivatives **3**–**5**.

Thus, the key intermediate, aldehyde **10**, which was prepared via a reported method from nitrone **11** in 81% overall yield within 4 steps,[8d,12h] reacted with allylzinc bromide under Barbier conditions[13] to give **12** as an inseparable mixture of two isomers (dr = 35/65, determined by ^{1}H NMR). Sequential ozonation and reductive amination of **12** afforded tri-*O*-benzylated australine derivatives **7** and **8** in 89% yield (dr = 23/77) which were separated by silica gel chromatography. The configuration of the C-7 hydroxyl was determined by comparing the optical rotation and NMR data of **7** and **8** with those reported for 1,2,8-tri-*O*-benzyl-australine [**7**: $[\alpha]_D^{20}$ +9.0 (*c* 1.11 in CH_2Cl_2); lit. of **7**:[11d] $[\alpha]_D^{25}$ +8.4 (*c* 1.6 in EtOH); **8**: $[\alpha]_D^{20}$ −9.8 (*c* 1.02 in CH_2Cl_2); lit. of **8**:[11l] $[\alpha]_D^{20}$ −27 (*c* 0.33 in $CHCl_3$)]. Further hydrogenolysis of **7** and **8** led to australine (**1**) and 7-*epi*-australine (**2**), respectively, in high yields. The ^{1}H and ^{13}C NMR spectra of compounds **1** and **2** were identical to those reported for australine and 7-*epi*-australine with optical rotations [**1**: $[\alpha]_D^{20}$ +9.0 (*c* 1.12, H_2O); **2**: $[\alpha]_D^{20}$ −12.0 (*c* 1.84, H_2O)] consistent with literature [australine: $[\alpha]_D^{25}$ +8.0 (*c* 0.35, H_2O);[11d] 7-*epi*-australine: $[\alpha]_D^{24}$ −14.1 (*c* 0.22, H_2O),[14a] $[\alpha]_D^{23}$ −13.2 (*c* 1.2, H_2O)[14b]].

Treatment of the alcohols **7** and **8** (Scheme 2) with DAST (diethylaminosulphur trifluoride) unexpectedly gave the *same* fluorinated product **13**. The structure of **13** was determined by spectroscopic data, and its C-7 configuration was determined as an *R*-configuration through a NOESY experiment (**13**: H1 and H7; Supporting Information). Fluorination of **8** with DAST may have occurred via an aziridinium ion intermediate,[11a,15] which opened with a second inversion when attacked by

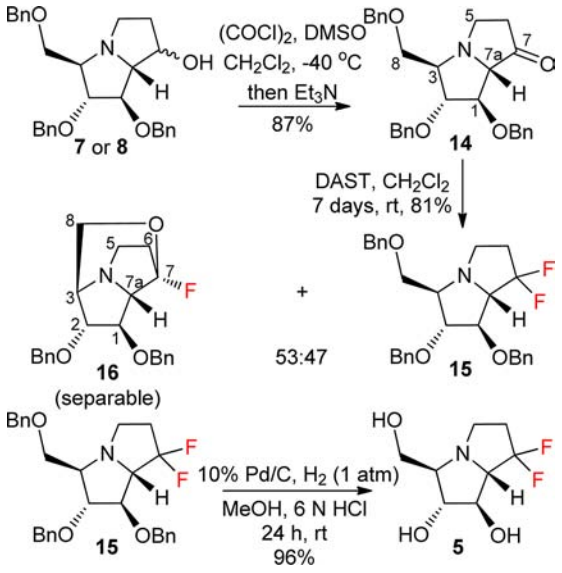
Scheme 2. Synthesis of Australine and Its Derivatives



fluoride, affording the configuration-retained product **13**. As for alcohol **7**, fluorination proceeded in an ordinary S_N2 pattern, giving the configuration-inverted product, i.e., **13**. After hydrogenation of the fluorinated derivative **13**, 7-deoxy-7-fluoro-7-*epi*-australine (**4**) was obtained in high yield.

To prepare the C7-difluorinated derivative of australine, i.e. 7,7-difluoro-7-deoxyaustraline (**5**), the alcohols **7** and **8** were transformed into ketone **14** via Swern oxidation in 87% yield. Treatment of ketone **14** with DAST afforded the desired C-7-difluorinated derivative **15** together with a tricyclic byproduct **16**. Debenzylation of **15** by hydrogenation gave the expected difluorinated product **5** in 96% yield (Scheme 3).

Scheme 3. Synthesis of 7,7-Difluoro-7-deoxyaustraline (5)



A plausible reaction pathway for formation of the C-7 difluorinated product **15** and the tricyclic byproduct **16** is shown in Figure 2. Reaction of ketone **14** with DAST formed the intermediates **17a** and **17b**, where both would give product **15** by an S_N2 attack of fluoride.[16] It is also possible to finish the reaction in another way; that is, an azidirinium system can be formed by losing the leaving group, and the ion is then opened

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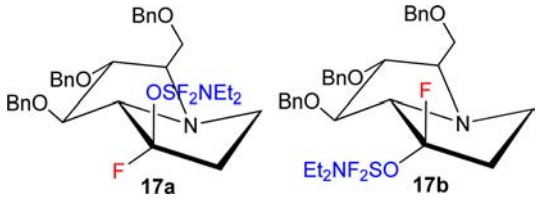

Figure 2. Possible intermediate in formation of **15** and **16**.

by a second fluoride to give product **15**.[11a,15] Since the C-8 benzyloxy group can also act as a nucleophile in **17a** and **17b**, an intramolecular S_N2 reaction in **17b** would furnish the cyclic ether in product **16**,[14b,17] while such a reaction is not favorable in **17a**.

Through similar procedures, the enantiomers of australine (***ent*-1**) and its derivatives ***ent*-2**, ***ent*-4**, and ***ent*-5** were also synthesized from the D-xylose-derived nitrone ***ent*-11** smoothly.

These compounds were then assayed as potential inhibitors for a range of glycosidases (see the Supporting Information). Australine (**1**) and its C-7 diastereomer (**2**) proved to be potent inhibitors of *A. niger* α-glucosidase (IC_{50} = 6.0 and 1.5 μM, respectively) and *A. niger* amyloglucosidase (IC_{50} = 37 and 8.0 μM, respectively). By contrast, ***ent*-1** and ***ent*-2**[18] showed virtually no inhibition of the tested enzymes, which is in sharp contrast to the more potent glycosidase inhibition of L-DMDP (***ent*-6**) than DMDP (**6**).[8d,10a,f] For fluorinated derivatives, compound **4** turned out to be a potent inhibitor of *A. niger* α-glucosidase (IC_{50} = 0.63 μM), which is 10 times better than australine (**1**). Compound **4** also behaved as a moderate inhibitor of porcine kidney trehalase (IC_{50} = 31 μM), while australine (**1**) is only a weak inhibitor of the enzyme (IC_{50} = 175 μM). Difluorinated derivative **5** is not only a potent *A. niger* α-glucosidase inhibitor (IC_{50} = 1.1 μM) but also a good *A. niger* amyloglucosidase inhibitor (IC_{50} = 5.9 μM). In comparison, ***ent*-4** and ***ent*-5** were also completely ineffective toward all tested enzymes.

In summary, we have developed a simple and efficient method for the synthesis of australine (**1**) as well as its C-7-fluorinated and difluorinated derivatives starting from sugar-derived cyclic nitrones. Australine (**1**), 7-*epi*-australine (**2**), and their C-7-fluorinated derivatives **4** and **5** and their enantiomers have been synthesized efficiently by this method. Glycosidase inhibition studies of these compounds showed that C7-fluorination and difluorination of australine considerably enhanced the potency of its inhibition against α-glucosidase. This enriches the few examples that demonstrate fluorination of a hydroxy group increasing rather than seriously decreasing inhibition. These observations are significant to the understanding of the SAR of australine as well as DMDP-related iminosugars and will be helpful for the design and synthesis of more potent α-glucosidase inhibitors based on this kind of compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, ^1H and ^{13}C NMR spectra for all new compounds, ^{19}F NMR spectra and glycosidase inhibition data for australine derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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