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Original article

Novel 2-aryl-3,4,5-trihydroxypiperidines: Synthesis and glycosidase inhibition

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ABSTRACT

Three pairs of novel 2-aryl-3,4,5-trihydroxypiperidines (**6**–**8** and their enantiomers), the piperidine analogues of the pyrrolidine alkaloids radicamine A and radicamine B, were prepared from six-membered cyclic nitrones through a concise two-step procedure, *i.e.*, Grignard reagent addition and deprotection. These novel polyhydroxylated piperidine iminosugars were assayed against 10 types of enzymes. Only compound **8** exhibited weak inhibition (IC_{50} 1080 μmol/L) against β-galactosidase from rat intestinal lactases.

1. Introduction

Iminosugars, also referred to as azasugars, iminocyclitols, or polyhydroxylated alkaloids, have attracted considerable attention due to their intriguing biological properties [1]. These "nitrogen-in-the-ring" analogues of pyranoses and furanoses are potent inhibitors of glycosidases and other glycosyl processing enzymes, and have potential as pharmaceuticals [1,2]. Polyhydroxylated pyrrolidines carrying an aromatic substituent on the iminosugar ring are a rare class of iminosugars found in nature (Fig. 1) [3]; these alkaloids exhibit antihypertensive pharmacological activity without influencing the central nervous system in animal tests. Many methods have been developed to access these alkaloids [4a], and a number of derivatives have been synthesized [5]. In contrast, 2-aryl polyhydroxylated piperidines have not yet been isolated from nature; in view of this, this paper reports the synthesis and glycosidase inhibition profile of a number of aryl piperidine analogues.

Nitrones have been shown as very versatile synthetic intermediates for the construction of structurally complex molecules [5g,6,7] because they are capable of undergoing a variety of synthetically useful transformations, such as 1,3-dipolar cycloadditions [8], nucleophilic additions [9,10], and pinacol-type coupling reactions [11].

In the context of our interest in the synthesis of bioactive azasugars [4k,12], we have developed a practical method to synthesize a series of five- and six-membered polyhydroxylated cyclic nitrones on a large scale [13], which are versatile synthons in the construction of novel iminosugars [14]. As a part of our continuing interest in the synthesis of iminosugar analogues, herein we report the synthesis of 2-aryl polyhydroxylated piperidine iminosugars (compounds **6**–**8**, and *ent*-(**6**–**8**), Fig. 2) from a pair of enantiomeric six-membered polyhydroxylated cyclic nitrones **12** and *ent*-**12**, and their glycosidase inhibitory activity.

2. Experimental

*General procedure for the synthesis compounds **6**–**8** and ent-(**6**–**8**)*: A solution of the cyclic six-membered nitrone **12** or *ent*-**12** (1.0 mmol) in THF (10 mL) was cooled to 0 °C and aryl Grignard reagents (5.0 mmol) in THF (5 mL) was added under an inert N_2 atmosphere. The mixture was kept at this temperature for 2 h, and then quenched by adding saturated aqueous NH_4Cl solution (15 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), the combined extracts were dried ($MgSO_4$) and concentrated under

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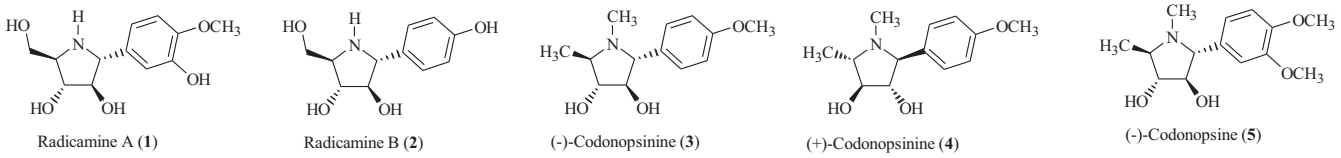

Fig. 1. Radicamines and related natural compounds.

reduced pressure. The residue was purified by flash column chromatography (silica gel, petroleum ether/EtOAc = 15/1) to give the addition compound. Aqueous HCl (6 mol/L, 1.0 mL) was added to the suspension of the addition product (0.23 mmol) and Pd/C (40 mg) in CH_3OH (20 mL), then the mixture was subjected to hydrogenation under H_2 atmosphere for 24 h. The catalyst was filtered and washed with methanol (5 mL). The filtrate was neutralized by adding $NH_3{\cdot}H_2O$, then concentrated, the residue was purified by ion exchange resin to give the target product **6**–**8** or *ent*-(**6**–**8**).

6: $[\alpha]_D^{20}$ + 18.06 (*c* 1.55, CH_3OH); mp: 204–205 °C; IR (KBr, cm^{-1}): 3472 (m), 3426 (s), 3356 (s), 3279 (vs), 2959 (m), 2922 (m), 2905 (m), 2883 (m), 1613 (m), 1517 (vs), 1384 (m), 1249 (s), 1057 (s), 1030 (vs), 820 (m), 742 (m); ^{1}H NMR (300 MHz, D_2O): δ 7.28 (d, 2H, *J* = 8.31 Hz, Ph–), 6.94 (d, 2H, *J* = 8.34 Hz, Ph–), 3.99–4.01 (m, 1H, H-5), 3.78 (t, 1H, *J* = 9.75 Hz, H-3), 3.76 (s, 3H, CH_3O–), 3.57 (dd, 1H, J_1 = 2.79 Hz, J_2 = 9.42 Hz, H-4), 3.35 (d, 1H, *J* = 9.99 Hz, H-2), 2.96 (d, 1H, *J* = 14.29 Hz, H-6e), 2.80 (d, 1H, *J* = 14.30 Hz, H-6a); ^{13}C NMR (75 MHz, D_2O): δ 158.5, 132.1, 129.2, 114.3 (Ph–C), 74.6 (C-4), 72.1 (C-3), 69.3 (C-5), 64.1 (C-2), 55.4 (CH_3O–), 49.0 (C-6); HRMS (ESI-MS), *m*/*z* 240.12302 $[M+H]^+$ ($C_{12}H_{18}NO_4$ calcd. 240.12303).

7: $[\alpha]_D^{20}$ + 20.74 (*c* 1.35, CH_3OH); mp: 233–234 °C; IR (KBr, cm^{-1}): 3366 (br s), 2918 (m), 1637 (m), 1496 (m), 1455 (m), 1145 (m), 1091 (s), 866 (m), 761 (s), 701 (m); ^{1}H NMR (300 MHz, D_2O): δ 7.16 (d, 2H, *J* = 8.06 Hz, Ph–), 6.77 (d, 2H, *J* = 8.07 Hz, Ph–), 3.97 (s, 1H, H-5), 3.76 (t, 1H, *J* = 9.67 Hz, H-3), 3.53 (dd, 1H, J_1 = 2.78 Hz, J_2 = 9.43 Hz, H-4), 3.30 (d, 1H, *J* = 9.99 Hz, H-2), 2.93 (d, 1H, *J* = 14.08 Hz, H-6e), 2.76 (d, 1H, *J* = 14.17 Hz, H-6a); ^{13}C NMR (75 MHz, D_2O): δ 155.8, 130.4, 129.4, 115.8 (Ph–C), 74.4 (C-4), 71.7 (C-3), 69.0 (C-5), 64.0 (C-2), 48.8 (C-6); HRMS (ESI-MS), *m*/*z* 226.10719 $[M+H]^+$ ($C_{11}H_{16}NO_4$ calcd. 226.10738).

8: $[\alpha]_D^{20}$ + 25.33 (*c* 1.45, CH_3OH); mp: 106–107 °C; IR (KBr, cm^{-1}): 3366 (br s), 2918 (m), 1640 (m), 1496 (m), 1453 (m), 1145 (m), 1091 (s), 761 (s), 701 (s); ^{1}H NMR (300 MHz, D_2O): δ 7.23–7.38 (m, 5H, Ph–), 3.98 (m, 1H, H-5), 3.78 (t, 1H, *J* = 9.76 Hz, H-3), 3.55 (dd, 1H, J_1 = 2.93 Hz, J_2 = 9.46 Hz, H-4), 3.34 (d, 1H, *J* = 10.00 Hz, H-2), 2.93 (dd, 1H, J_1 = 1.91 Hz, J_2 = 14.35 Hz, H-6e), 2.76 (d, 1H, *J* = 14.17 Hz, H-6a); ^{13}C NMR (75 MHz, D_2O): δ 139.2, 128.9, 128.2, 127.9 (Ph–C), 74.5 (C-4), 72.0 (C-3), 69.2 (C-5), 64.7 (C-2), 49.0 (C-6); HRMS (EI), *m*/*z*, 210.11245; $[M+H]^+$ ($C_{11}H_{16}NO_3$ calcd. 210.11247).

ent-**6**: $[\alpha]_D^{20}$ – 17.14 (*c* 1.05, CH_3OH); mp: 198–199 °C; IR (KBr, cm^{-1}): 3352, 3278 (br s), 2954 (m), 2882 (m), 1516 (s), 1249 (vs), 1184 (m), 1070 (s), 1031 (m), 820 (m), 742 (m); ^{1}H NMR (300 MHz, D_2O): δ 7.27 (d, 2H, *J* = 8.40 Hz, Ph–), 6.93 (d, 2H, *J* = 8.40 Hz, Ph–), 3.96–4.03 (m, 1H, H-5), 3.75–3.82 (m, 4H, H-3, CH_3O–), 3.56 (dd, 1H, J_1 = 3.30 Hz, J_2 = 9.60 Hz, H-4), 3.30 (d, 1H, *J* = 9.90 Hz, H-$_2$), 2.94 (d, 1H, *J* = 14.41 Hz, H-6e), 2.76 (d, 1H, *J* = 13.80 Hz, H-6a); ^{13}C NMR (75 MHz, D_2O): δ 158.5, 132.2, 129.1, 114.2 (Ph–C), 74.6 (C-4), 72.1 (C-3), 69.4 (C-5), 64.1 (C-2), 55.4 (CH_3O–), 49.0 (C-6); HRMS (ESI-MS): *m*/*z* 240.12302 $[M+H]^+$ ($C_{12}H_{18}NO_4$ requires: 240.12303).

ent-**7**: $[\alpha]_D^{20}$ – 22.5 (*c* 0.80, CH_3OH), mp: 227–228 °C, IR (KBr, cm^{-1}): 3293 (br s), 1614 (s), 1599 (m), 1520 (vs), 1447 (s), 1407 (s), 1256 (s), 1179 (m), 1134 (m), 1084 (s), 833 (m); ^{1}H NMR (300 MHz, D_2O): δ 7.19 (d, 2H, *J* = 7.80 Hz, Ph–), 6.80 (d, 2H, *J* = 7.80 Hz, Ph–), 3.95–4.03 (m, 1H, H-5), 3.78 (t, 1H, *J* = 9.60 Hz, H-3), 3.57 (d, 1H, *J* = 7.20 Hz, H-4), 3.33 (d, 1H, *J* = 9.90 Hz, H-2), 2.96 (d, 1H, *J* = 13.80 Hz, H-6e), 2.79 (d, 1H, *J* = 13.80 Hz, H-6a); ^{13}C NMR (75 MHz, D_2O): δ 155.8, 130.4, 129.4, 115.8 (Ph–C), 74.4 (C-4), 71.7 (C-3), 69.0 (C-5), 64.0 (C-2), 48.8 (C-6); HRMS (ESI-MS): *m*/*z* 226.10748 $[M+H]^+$ ($C_{11}H_{16}NO_4$ calcd. 226.10738).

ent-**8**: $[\alpha]_D^{20}$ – 24.52 (*c* 1.55, CH_3OH); mp: 99–100 °C; IR (KBr, cm^{-1}): 3349 (br s), 3060 (w), 2917 (m), 1602 (m), 1454 (m), 1339 (m), 1240 (m), 1091 (s), 865 (s), 761 (m), 701 (s); ^{1}H NMR (300 MHz, D_2O): δ 7.33–7.36 (m, 5H, Ph–), 3.69–3.98 (m, 1H, H-5), 3.77 (t, 1H, *J* = 9.60 Hz, H-3), 3.55 (dd, 1H, J_1 = 3.00 Hz, J_2 = 9.60 Hz, H-4), 3.32 (d, 1H, *J* = 9.90 Hz, H-2), 2.92 (dd, 1H, J_1 = 1.50 Hz, J_2 = 14.41 Hz, H-6e), 2.74 (d, 1H, *J* = 14.41 Hz, H-6a); ^{13}C NMR (75 MHz, D_2O): δ 139.5, 128.9, 128.2, 127.9 (Ph–C), 74.6 (C-4), 72.1 (C-3), 69.3 (C-5), 64.8 (C-2), 49.0 (C-6); HRMS (ESI-MS), *m*/*z* 210.11246 $[M+H]^+$ ($C_{11}H_{16}NO_3$ calcd. 210.11247).

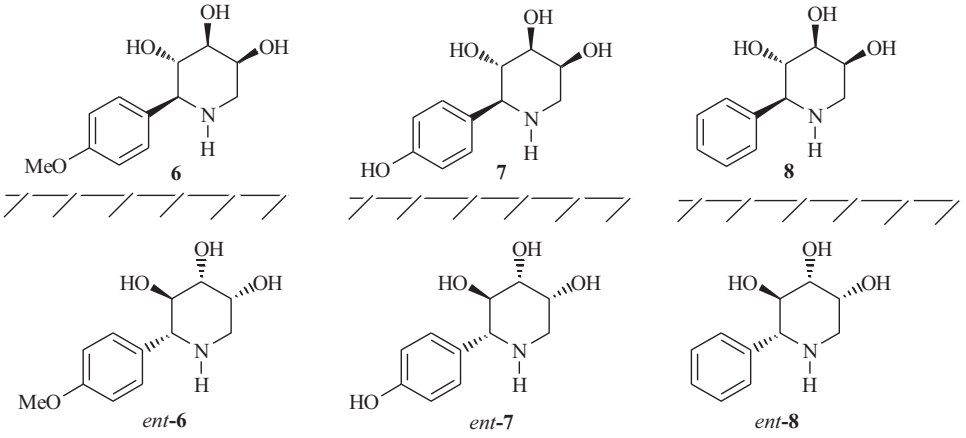

Fig. 2. 2-Aryl polyhydroxylated piperidine iminosugars.

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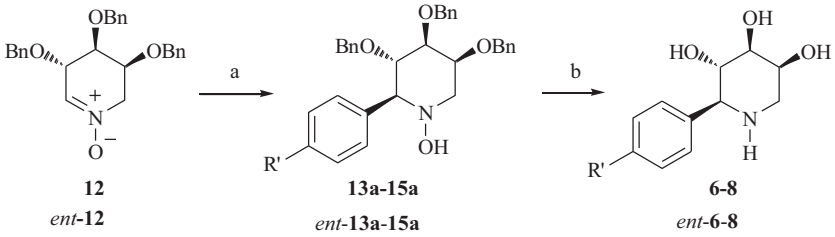
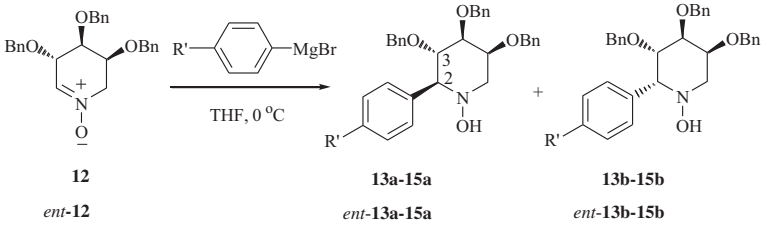


Scheme 1. Reagents and conditions: (a) Grignard reagents, THF, ice-bath, 2 h, 68%–82%; (b) H_2, Pd–C, 6 mol/L HCl, CH_3OH, 89%–97%.

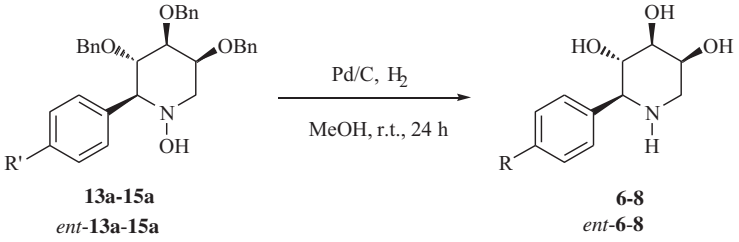
Table 1
The addition of nitrones with aryl Grignard reagents.



Entry	R′	Product	Yield (%)[a]	*Trans*:*cis*[b]
1	MeO–	**13a**	73	90:10
2	BnO–	**14a**	74	92:8
3	H–	**15a**	68	87:13
4	MeO–	*ent*-**13a**	81	89:11
5	BnO–	*ent*-**14a**	77	91:9
6	H–	*ent*-**15a**	82	85:15

[a] Combined isolated yields after column chromatography.
[b] The ratio was determined by isolation of two isomers.

Table 2
Catalytic hydrogenation of the Grignard addition products.



Entry	Reactant	R	Product	Yield (%)[a]
1	**13a**	MeO	**6** (MeO–)	97
2	**14a**	HO	**7** (HO–)	94
3	**15a**	H	**8** (H–)	92
4	*ent*-**13a**	MeO	*ent*-**6** (MeO–)	91
5	*ent*-**14a**	HO	*ent*-**7** (HO–)	89
6	*ent*-**15a**	H	*ent*-**8** (H–)	90

[a] Isolated yield purified by ion exchange resin.

3. Results and discussion

Our synthesis started from the enantiomeric six-membered cyclic nitrones **12** and *ent*-**12** (Scheme 1), prepared from arabinose according to the reported procedures [13]. The addition of aryl Grignard reagents to the nitrone **12** gave compounds **13**–**15** with high 2,3-*trans*-selectivity (Table 1), although not as high as with the corresponding five-membered cyclic nitrones [4k], which gave exclusively *trans*-products. The results are summarized in Table 1. The configurations of the products were determined either by ^{1}H-NMR data (**13a**: $J_{2-3(trans)}$ = 9.69 Hz for example) or by COSY and NOESY spectra (see the Supporting information) (compound **8** for example: the NOE interactions between H-2/H-6a, H-2/H-5, and H-2/H-4, indicated that H-2, H-6a, H-5, and H-4 were on the same side of the ring).

Catalytic hydrogenation of the analogues **13a**, **14a** and **15a** catalyzed by 10% Pd–C afforded the deprotected 2-aryl piperidine iminosugars **6**, **7**, **8** (Table 2).

The three enantiomeric piperidines were obtained similarly; *ent*-**12** was treated with the above three aryl Grignard reagents to

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give the protected addition products *ent*-(**13a**–**15a**), which were converted, as described above, to the targeted compounds *ent*-(**6**–**8**) respectively (Scheme 1, Tables 1 and 2).

The piperidine analogues of radicamine A and B were assayed as potential glycosidase inhibitors against 10 different enzymes. All the compounds tested exhibited weaker inhibition than radicamine A and B [3c] of α-glucosidase in spite of their structural similarities. **8** showed weak glycosidase inhibition of β-galactosidase (IC_{50} 1080 μmol/L) isolated from rat intestinal lactases. The three pairs of compounds had no inhibition of β-mannosidase, while *ent*-(**6**–**8**) had better inhibition of α-L-fucosidase from bovine kidney than compounds **6**–**8**. However, compounds **6**–**8** were more potent than their enantiomers in inhibiting α-galactosidase from coffee beans and β-galactosidase from rat intestinal lactase. To study the effect of the size of the heterocyclic ring on glycosidase inhibitory activity, we will synthesize and survey other related compounds in future work.

4. Conclusion

In summary, we have synthesized three enantiomeric pairs of 2-aryl polyhydroxylated piperidines by the addition of aryl Grignard reagents to six-membered cyclic nitrones. Bioassay results indicated that these compounds exhibited no or only very weak inhibition of any of the glycosidases tested and are a much weaker class of inhibitors than the corresponding pyrrolidines.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2013.06.027.

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