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Stereoselective synthesis of novel five-membered homoazasugars. A convenient route to all-*cis* tetrasubstituted pyrrolidines

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Abstract—We present a highly stereoselective procedure for the preparation of (2*S* and 2*R*,3*S*,4*R*,5*S*)-5-methyl-3,4-dihydroxy-2-ethoxycarbonylmethylpyrrolidines based on conjugate addition of ammonia to unsaturated aldonic esters derived from D-ribose followed by tandem cyclization. Derivatisation of these compounds to 2-hydroxyethyl-, benzymidazolylmethyl-, biphenyl-1-aminoethyl and naphthalene-l-aminoethyl-pyrrolidines is also presented.

Hydroxylated pyrrolidines, which constitute one type of azasugars or iminosugars, have attracted considerable interest in recent years due to their therapeutic potential. This is due to their inhibitory activity towards carbohydrate processing enzymes such as glycosidases and glycosyltransferases.[1] Recently, they have also attracted attention because of their application as catalysts,[2] chiral ligands for asymmetric catalysis and chiral auxiliaries.[3]

Among the iminosugars, those having a carbon chain linked to the carbon adjacent to nitrogen, the so-called homoazasugars (aza-*C*-glycosides) have achieved special importance due to their stability towards chemical and enzymatic degradation, maintaining their biological activity.[4] Homoazasugars bearing a hydroxymethyl group or 1,2-dihydroxyethylene group as side chains have been recently described.[5] With regard to their enzymatic inhibitory activity, it has been reported that some homoanalogues of 1,4-dideoxy-1,4-iminoalditol derivatives are more active than the parent compounds.[6] It has been also claimed that hydrophobic groups attached to the iminosugar improve their inhibitory activity through unspecific contributions to the binding to the enzyme.[7] We and other authors have reported that the attachment of aromatic moieties to the pyrrolidine framework greatly improves the activity and selectivity towards glycosidases.[8–10] We have recently reported a stereoselective route to (2*S*,3*S*,4*R*,5*S*)-5-methylpyrrolidine-3,4-diol-2-carbaldehyde (**1**) having *fuco*-configuration and explored its use in the preparation of highly selective α-L-fucosidase inhibitors, such as benzymidazolyl derivative **2** with inhibitory activity in the nM range (Fig. 1).[10d]

In this letter, we report a stereoselective synthesis of several homoanalogue derivatives of compound **1** (**3**–**5**) and the transformation of **3** into an imino-*C*-heterocycle and aryl aminoethyl pyrrolidines (Fig. 2).

Compounds **3**, **5**–**8** are tetrasubstituted all-*cis* pyrrolidines. As far as we are aware, a small number of pyrrolidine derivatives with this stereochemical arrangement have been described.[11]

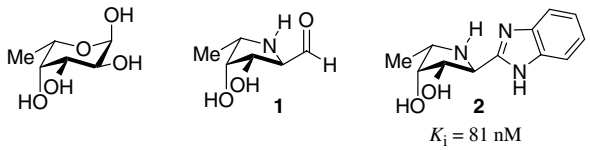

Figure 1.

Keywords: Pyrrolidines; Azasugars; Iminosugars; Imino-*C*-glycosides; Homoazasugars; Glycosidase inhibitors.
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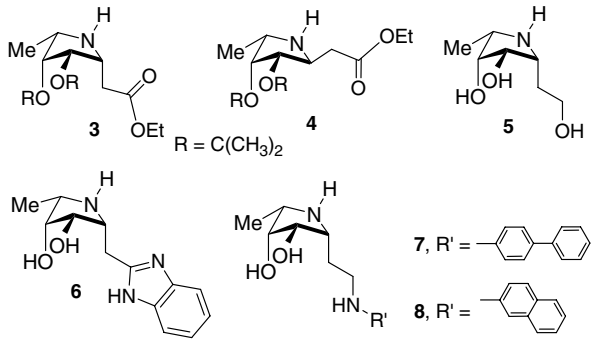
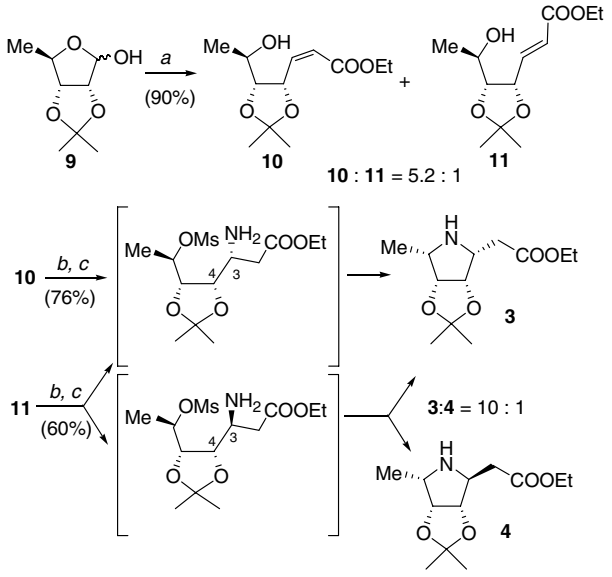


Figure 2.

Starting from D-ribose, the known hemiacetal **9** was obtained by applying Bols's procedure.[12] Reaction of lactol **9** with methyl triphenylphosphoranylidene acetate in dichloromethane under reflux afforded a mixture of alkenes **10** and **11** in a 90% yield and a ratio $Z{:}E = 5.2{:}1$. The stereoselectivity in the Wittig reaction is in accordance with that described in the literature for other *ribo*-lactols.[13] Mesylation of the free OH group in **10** and **11** followed by treatment with ammonia in ethanol furnished the corresponding pyrrolidines through tandem conjugate addition-internal S_N2 displacement. Starting from *Z*-alkene, pyrrolidine **3** was obtained as the unique stereoisomer in a 76% overall yield, whereas the same procedure applied to *E*-alkene afforded a mixture of **3** and **4** in a 60% overall yield, and a ratio, **3**:**4** = 10:1 (Scheme 1).

The structure of **3** and **4** was based on spectroscopic and analytical data.[14] NOESY spectrum of **3** showed NOEs between proton signals H3($\delta = 3.14$)/H4($\delta = 4.62$) and H3/H6($\delta = 2.86$), and between pair of protons H5($\delta =$ 4.47)/H6(δ=2.86), thus indicating an all-*cis* configuration between the corresponding protons. NOESY spectrum of **4** showed NOEs between H4,H5($\delta =$ 4.48)/H2a,H2b($\delta = 2.41$, 2.33) and between H6($\delta =$ 3.07)/H2a,H2b($\delta = 2.41$, 2.33), indicating a *trans* relationship between H3/H4 and H3/H6. The stereochemical account of the reaction indicates a selectivity towards the 3,4-*syn* adduct in the conjugate addition. Subsequent intramolecular displacement led to pyrrolidine **3** as the major compound. This is in accordance with that described for other sugar derived α,β-unsaturated esters.[15] A Felkin type transition state model may account for the results for the *E*-isomer, whereas in the case of the *Z*-alkene, the strong interaction in that conformation with the acetal ring suggests an alternative transition state resembling the Conforth model and model B_1 of Felkin.[16]

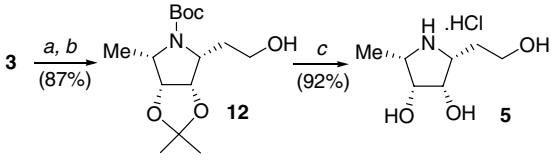


Scheme 1. Synthesis of pyrrolidines **3** and **4**. Reagents and conditions: (a) $Ph_3P{=}CH_2COOEt$, DCM reflux; (b) MsCl, Py and (c) NH_3, EtOH.

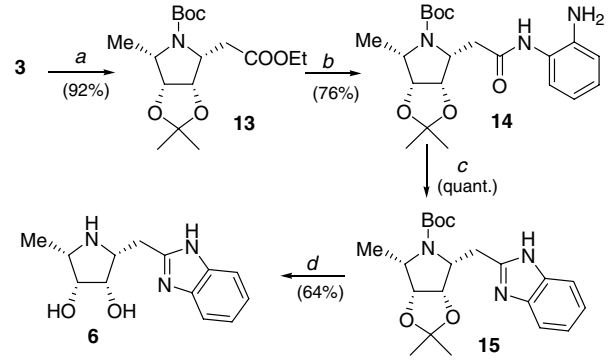
The preparation of hydroxyethyl-dihydroxypyrrolidine **5** was carried out starting from all-*cis*-pyrrolidine **3**. *N*-Boc protection, reduction with $LiBH_4$ and subsequent acidic deprotection furnished **5** in a 80% overall yield (Scheme 2).

The preparation of benzymidazolyl derivative **6** started from pyrrolidine **3** that was protected as *t*-butyl carbamate **13**. Saponification gave the corresponding carboxylic acid that was made to react with *o*-phenylenediamine in the presence of PyBOP and DIPEA to give amide **14** in a 70% overall yield. Heating in AcOH at 55–60 °C followed by acidic deprotection afforded benzymidazolyl pyrrolidine derivative **6** in a good yield (Scheme 3).

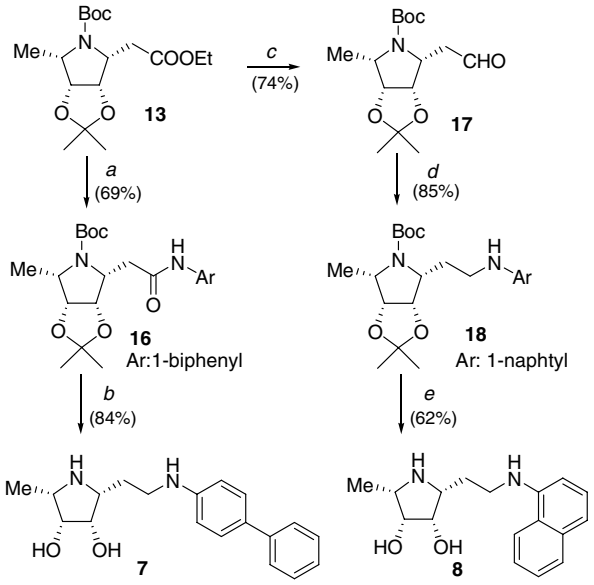
The synthesis of biphenylaminoethyl pyrrolidine **7** has been carried out starting from ethyl ester **13**. Saponification and reaction with biphenyl-4-amine in the presence of PyBOP and DIPEA gave amide **16** in a 69% yield.



Scheme 2. Synthesis of hydroxyethyl pyrrolidine **5**. Reagents and conditions: (a) Boc_2O/Py; (b) $LiBH_4$, THF and (c) HCl (1 N), THF.



Scheme 3. Synthesis of benzymidazolyl pyrrolidine **6**. Reagents and conditions: (a) Boc_2O/Py; (b) (1) NaOH, EtOH; (2) *o*-phenylenediamine, PyBOP, DIPEA, DMF; (c) AcOH, 55–65 °C and (d) (1) HCl 1 N, THF; (2) NH_4OH.



Scheme 4. Synthesis of aryl aminoethyl pyrrolidines **7** and **8**. Reagents and conditions: (a) (1) NaOH, EtOH; (2) biphenyl-4-amine, PyBOP, DIPEA, DMF; (b) (1) BH_3, SMe_2, THF; (2) HCl, THF; (3) NH_4OH; (c) DIBALH, CH_2Cl_2, −78 °C; (d) naphthalene-1-amine, $NaBH(OAc)_3$, $(CH_2Cl)_2$ and (e) (1) HCl, THF; (2) NH_4OH.

Reduction with $BH_3{\cdot}SMe_2$ followed by acidic deprotection gave **7** in a 84% overall yield. The same procedure applied to the preparation of **8** gave a poor yield. Thus, compound **8** was obtained by the reductive amination of aldehyde **17** with naphthalene-1-amine (85%) followed by acidic deprotection. Carbaldehyde **17** was obtained from **13** by reduction with DIBALH in a 74% yield (Scheme 4).

In summary, we have presented a highly stereoselective procedure for the preparation of (2*S* and 2*R*,3*S*,4*R*,5*S*)-5-methyl-3,4-dihydroxy-2-ethoxycarbonylmethylpyrrolidines based on the conjugate addition of ammonia to unsaturated aldonic esters derived from D-ribose and tandem cyclization. Derivatisation of these compounds to hydroxyethyl-pyrrolidine **5**, benzymidazolyl-pyrrolidine **6** and biphenyl- and naphthalene-l-aminoethyl-pyrrolidines **7** and **8** is also presented.

The new compounds presented in this letter show the introduction of several structural modifications to our reported pyrrolidine derivatives[10d] such as, the spacer between the *N* of the pyrrolidine ring and the aminoalkyl side chain, the configuration of the pyrrolidine moiety at C-2, and the nature of the substituent attached to the pyrrolidine framework (CH_2CH_2OH, CH_2CH_2NHAr, CH_2Ar). This diversity will hopefully provide useful information on the structure/activity relationships in glycosidase inhibition assays. These studies will be reported in due time.

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References and notes

1. (a) *Iminosugars as Glycosidase Inhibitors. Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, Germany, 1999; (b) Goss, P. E.; Baptiste, J.; Fernandes, B.; Baker, M.; Dennis, J. W. *Cancer Res.* **1994**, *54*, 1450–1457; (c) Fiaux, H.; Popowycz, F.; Favre, S.; Schutz, C.; Vogel, P.; Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *J. Med. Chem.* **2005**, *48*, 4237–4246; (d) Robina, I.; Moreno-Vargas, A. J.; Carmona, A. T.; Vogel, P. *Curr. Drug Metabol.* **2004**, *5*, 329–361.
2. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (b) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488–496; (c) Tomioka, K. *Synthesis* **1990**, 541–549.
3. (a) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581–1590; (b) Sweet, J. A.; Cavallari, J. M.; Price, W. A.; Ziller, J. W.; McGrath, D. V. *Tetrahedron: Asymmetry* **1997**, *8*, 207–211; (c) Kim, B. H.; Lee, H. B.; Hwang, J. K.; Kim, Y. G. *Tetrahedron: Asymmetry* **2005**, *16*, 1215–1220; (d) Ni, Y.; Kande, K. D.; Amarsinghe, K. K. D.; Ksebati, B.; Montgomery, J. *Org. Lett.* **2003**, *5*, 3771–3773.
4. Wheatley, J. R.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Butters, T. D.; Muller, M.; Watkin, D. J.; Winkler, D. A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2735–2745.
5. (a) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203–7214; (b) Asiego, C.; Pino-Gonzalez, M. S.; López-Herrera, F. J. *Tetrahedron Lett.* **2004**, *45*, 2611–2613; (c) Cardona, F.; Robina, I.; Vogel, P. *J. Carbohydr. Chem.* **2000**, *19*, 555–571; (d) Marquis, C.; Cardona, F.; Robina, I.; Wurth, G.; Vogel, P. *Heterocycles* **2002**, *56*, 181–208; For a review on aza-disaccharides containing homoazasugar moieties: (e) Robina, I.; Vogel, P. *Synthesis* **2005**, 675–702.
6. (a) Joubert, M.; Defoin, A.; Tarmus, C.; Streith, J. *Synlett* **2000**, 1366–1368; (b) Wong, C.-H.; Provencher, L.; Porco, J. A., Jr.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492–1501; (c) Sifferlen, T.; Defoin, A.; Streith, J.; Le Nouën, D.; Tarnus, C.; Dosbâo, I.; Foglietti, M.-J. *Tetrahedron* **2000**, *56*, 971–978; (d) Chevrier, C.; Le Nouën, D.; Neuburger, M.; Defoin, A.; Tarnus, C. *Tetrahedron Lett.* **2004**, *45*, 5363–5367.
7. (a) Legler, C. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319–384; (b) Charnock, S. J.; Spurway, T. D.; Xie, H.; Beylot, M.-H.; Virden, R.; Warren, R. A. J.; Hazlewood, G. P.; Gilbert, H. J. *J. Biol. Chem.* **1998**, *273*, 32187–32199.
8. For results on α-mannosidases see: (a) Gerber-Lemaire, S.; Popowycz, F.; Rodríguez-García, E.; Carmona Asenjo, A. T.; Robina, I.; Vogel, P. *Chem. BioChem.* **2002**, *3*, 466–470; (b) Gerber-Lemaire, S.; Popowycz, F.; Rodríguez-García, E.; Schuetz, C.; Carmona Asenjo, A. T.; Robina, I.; Vogel, P. *ARKIVOC* **2002**, 23–37; (c) Carmona, A. T.; Popowycz, F.; Gerber-Lemaire, S.; Rodríguez-García, E.; Schutz, C.; Vogel, P.; Robina, I. *Bioorg. Med. Chem.* **2003**, *11*, 4897–4911; (d) Popowycz, F.; Gerber-Lemaire, S.; Schutz, C.; Vogel, P. *Helv. Chim. Acta* **2004**, *87*, 800–810.
9. For results on α-glucosidases, see: (a) Lysek, R.; Vogel, P. *Tetrahedron* **2006**, *62*, 2733–2768; (b) Lysek, R.; Schutz,

C.; Favre, S.; O'Sullivan, A. C.; Pillonel, C.; Kruelle, T.; Jung, P. M. J.; Clotet-Codina, I.; Este, J. A.; Vogel, P. *Bioorg. Med. Chem.* **2006**, *14*, 6255–6282; (c) Lysek, R.; Schutz, C.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3071–3075; (d) Lysek, R.; Schutz, C.; Vogel, P. *Helv. Chim. Acta* **2005**, *88*, 2788–2811; (e) Lysek, R.; Vogel, P. *Helv. Chim. Acta* **2004**, *87*, 3167–3181.

10. For results on α-L-fucosidases, see: (a) Robina, I.; Moreno-Vargas, A. J.; Fernández-Bolaños, J. G.; Fuentes, J.; Demange, R.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2555–2559; (b) Moreno-Vargas, A. J.; Demange, R.; Fuentes, J.; Robina, I.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2335–2339; (c) Moreno-Vargas, A. J.; Robina, I.; Demange, R.; Vogel, P. *Helv. Chim. Acta* **2003**, *86*, 1894–1913; (d) Moreno-Vargas, A. J.; Carmona, A. T.; Mora, F.; Vogel, P.; Robina, I. *Chem. Commun.* **2005**, 4949–4951; (e) Laroche, C.; Behr, J.-B.; Szymoniak, J.; Bertus, P.; Schutz, C.; Vogel, P.; Plantier-Royon, R. *Bioorg. Med. Chem.* **2006**, *14*, 4047–4054; For cyclopentitols: (f) Blaser, A.; Reymond, J. L. *Org. Lett.* **2000**, *2*, 1733–1736; For piperidines, (g) Chang, C.-F.; Ho, C.-W.; Wu, C.-Y.; Chao, T.-A.; Wong, C.-H.; Lin, C.-H. *Chem. Biol.* **2004**, *11*, 1301–1306.
11. (a) Thompson, D. K.; Hubert, C. N.; Wightman, R. H. *Tetrahedron* **1993**, *49*, 3827–3840; (b) Sharad, K. V.; Atanes, M. N.; Busto, J. H.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **2002**, *67*, 1314–1318.
12. Jenseb, H. H.; Jensen, A.; Hazell, R. G.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1190–1198.
13. Webb, T. H.; Thomasco, L. M.; Schlachter, S. T.; Gaudino, J. J.; Wilcox, C. S. *Tetrahedron Lett.* **1988**, *29*, 6823–6826.
14. Selected data for **3**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, J Hz) δ 4.62 (dd, 1H, $J_{4,3} = 4.1$, $J_{4,5} = 4.2$, H-4), 4.47 (dd, 1H, $J_{5,6} = 4.0$, H-5), 4.15 (q, 2H, $J_{H,H} = 7.1$, CH_2CH_3), 3.14 (dt, 1H, $J_{3,2a} = J_{3,2b} = 6.6$, H-3) 2.86 (dq, 1H, $J_{6,Me} = 6.6$, $J_{5,6} = 4.0$, H-6), 2.66 (dd, 1H, $J_{2a,2b} = 16.5$, H-2a), 2.57 (dd, 1H, H-2b), 1.88 (br s, 1H, NH) 1.44, 1.30 (2s, 3H each, $C(CH_3)_2$), 1.26 (t, 3H, CH_2CH_3) 1.20 (d, 3H, Me-6). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm) δ 172.1 (C=O), 110.9 ($C(CH_3)_2$), 83.2 (C-5), 82.4 (C-4), 60.7 (CH_2CH_3), 58.8 (C-3), 57.7 (C-6), 33.6 (C-2), 25.8 and 24.3 ($C(CH_3)_2$), 14.3 (Me-6) and 13.4 (CH_2CH_3). CIHRMS m/z Calcd for $C_{12}H_{22}NO_4$: 244.1549. Found 244.1551. Selected data for **4**: ^{1}H NMR: 4.48 (m, 2H, H-4, H-5), 4.16 (q, 2H, $J = 6.9$, CH_2CH_3), 3.59 (t, 1H, $J_{3,2a} = J_{3,2b} = 7.8$, H-3), 3.07 (m, 1H, H-6), 2.41 (dd, 1H, $^{2}J_{2a,2b} = 15.3$ s, H-2a), 2.33 (dd, 1H, H-2b), 1.97 (br s, 1H, NH), 1.46, 1.30 (2s, 3H each, $C(CH_3)_2$), 1.25 (t, 3 H, CH_2CH_3), 1.20 (d, 3H, $J_{6-Me} = 6.6$, Me-6). ^{13}C NMR: 171.5 (C=O), 111.2 ($C(CH_3)_2$), 86.5, 83.2 (C-4, C-5), 61.2 (C-3), 60.7 (CH_2CH_3), 59.2 (C-6), 36.8 (C-2), 26.2, 24.2 ($C(CH_3)_2$), 14.3 (CH_2CH_3), 13.5 (Me-6). CIHRMS m/z Calcd for $C_{12}H_{22}NO_4$: 244.1549. Found 244.1548.
15. Robina, I.; Gearing, R. P.; Buchanan, J. G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2622–2624.
16. McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125–188.