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Synthesis of [(2*S*,3*S*,4*R*)-3,4-Dihydroxypyrrolidin-2-yl]-5-methylfuran-4-carboxylic Acid Derivatives: New Leads as Selective β-Galactosidase Inhibitors

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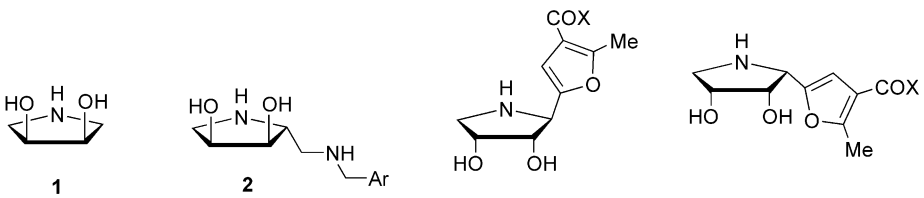
Abstract—The preparation of [(2*S*,3*S*,4*R*)-3,4-dihydroxypyrrolidin-2-yl]furan derivatives in a stereoselective route starting from D-glucose and ethyl acetoacetate is presented. Ethyl ester (**6**), *N,N*-diethylamide (**7**) and *N*-isopropylamide (**8**) have been tested towards 25 glycosidases. Ester (**6**) is a selective inhibitor of β-galactosidases. The new compounds represent a new type of imino-*C*-nucleoside analogues. © 2002 Published by Elsevier Science Ltd.

Cell sociology involves a language based on molecular recognition between cell-surface carbohydrates and proteins.[1] The biosynthesis of the surface oligosaccharides uses glycosyltransferases and glycosidases as catalysts. Inhibitors of these enzymes[2] are important molecular tools for glycobiology, and can be used to modulate cellular functions. They are also potential drugs in new therapeutic strategies.[3] Among the most potent glycosidase inhibitors are polyhydroxypiperidines (1,5-dideoxy-1,5-iminoalditols) that are mimics of the glycosyl cation intermediates liberated during the enzyme-catalyzed hydrolytic processes.[4,5] Derivatives of 3,4-dihydroxypyrrolidines (1,4-dideoxy-1,4-iminoalditols) also emerge as an important class of glycosidase[4a,6,7] and glycosyltransferase inhibitors.[7] Simple *meso*-3,4-dihydroxypyrrolidine (**1**) is a non-selective, weak inhibitor of several glycosidases.[8] We have found that derivatives **2** with (2*R*)-iminomethyl side chains can be highly selective and competitive inhibitors of α-mannosidases, especially for Ar = phenyl or thiophenyl.[8]

We have also found that [(2*R*,3*S*,4*R*)-3,4-dihydroxypyrrolidin-2-yl]furan derivatives **3**–**5** are selective and competitive inhibitors of α-L-fucosidases.[9]



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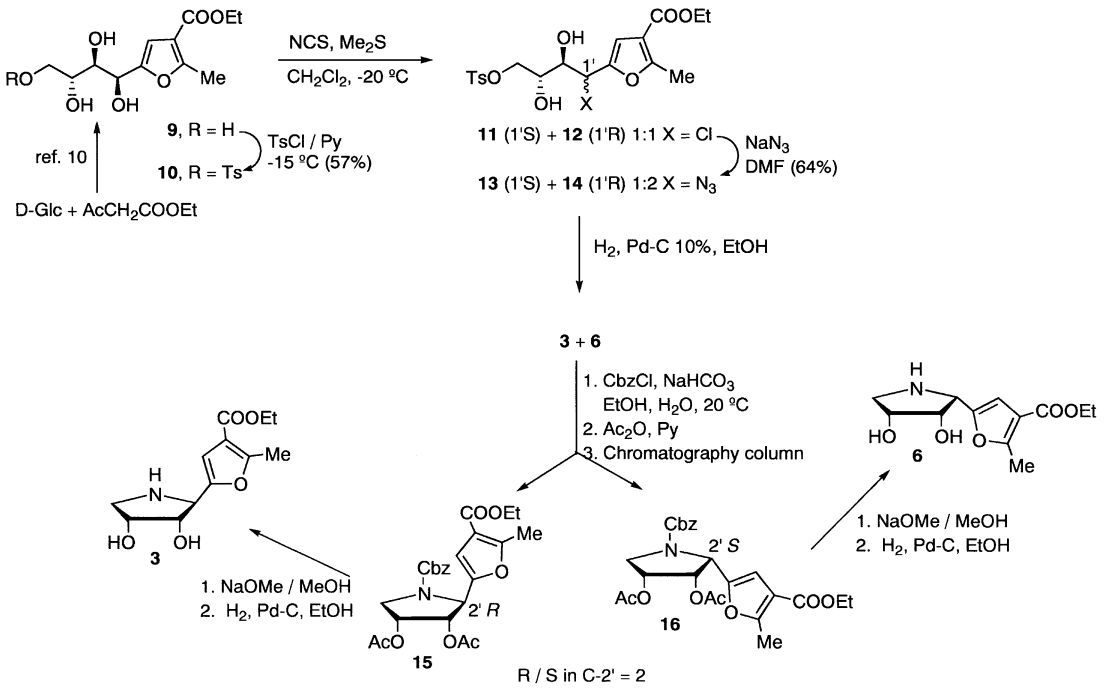
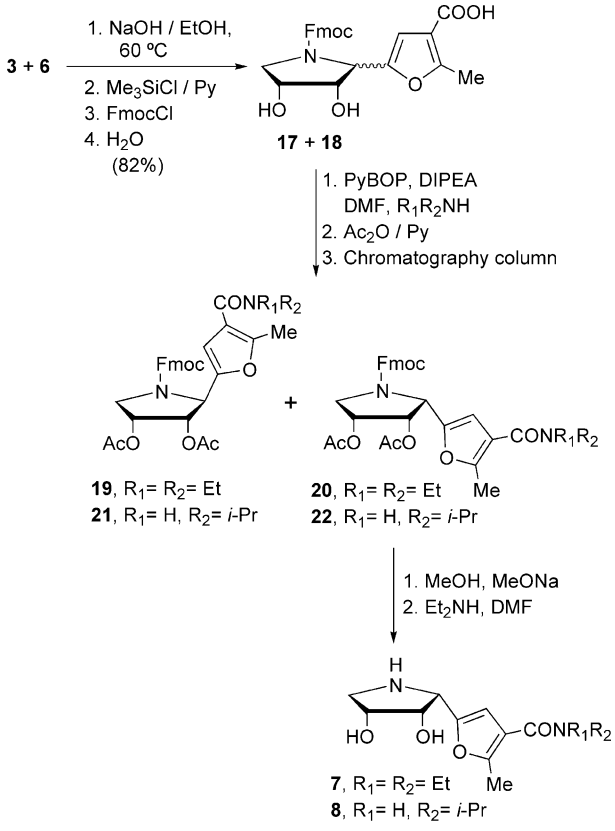


Scheme 1.

We now report on the synthesis of their (2*S*)-stereoisomers **6**–**8** and their evaluation as glycosidase inhibitors. It is worth mentioning that we have found the latter compounds to be selective inhibitors of β-galactosidases, the highest inhibitory activity being observed for ester **6**.

A stereoselective method was found[9] to convert the readily available ethyl furancarboxylate **9**[10] into **3**–**5**. We have now found conditions under which their (2*S*)-stereoisomers can also be obtained. Regioselective tosylation of tetritol **9** with ClTs and pyridine at −15 °C generated tosylate **10** in 57% yield. Chlorination[11] of the benzylic position with *N*-chlorosuccinimide and dimethylsulfide at −20 °C afforded a 1:1 mixture of furfuryl chlorides **11** and **12** that were not separated. This mixture was directly reacted with an excess of NaN_3 in DMF at rt to give a 1:2 mixture of azides **13** and **14** in 64% overall yield. This result can be interpreted in terms of competing S_N1 and S_N2 azidolysis. The existence of epoxide intermediates by participation of adjacent hydroxy group to the chlorine atom cannot be excluded. Hydrogenation (10% Pd/C, EtOH, 20 °C) of the mixtures of azides **13** and **14** gave corresponding primary amines that underwent fast intramolecular displacements of the primary tosylates, leading to a 1:2 mixture of (2*S*)- and (2*R*)-pyrrolidin-2-yl derivatives that was not resolvable. Protection of the amine functions of **3** and **6** as benzylcarbamate and acetylation of the diols provided a 2:1 mixture of **15** and **16** (60% overall yield) that could be separated by chromatography on silica gel. The structures of **15**[12] and **16**[13] were established unambiguously by their spectral data, and confirmed by NOE experiments. Compound **16** showed an NOE between proton pairs H-2′/H-3′ that was not observed in **15**. Alkaline methanolysis of **15** and **16**, followed by hydrogenolysis, gave **3** (100%) and **6** (92%), respectively (Scheme 1).

Saponification of a 2:1 mixture of **3** and **6**, followed by silylation of the diol moieties with Me_3SiCl/pyridine



Scheme 2.

and Fmoc-protection of the pyrrolidines units,[14] gave a 2:1 mixture of carboxylic acids **17** and**18** after aqueous workup. They were not purified but directly submitted to their amidification with Et_2NH or *i*-$PrNH_2$ (activation with PyBOP and Hünig's base in DMF) to give the corresponding mixture of amides **19** + **20** and **21** + **22**, that were separated by flash chromatography on silica gel. Alkaline methanolysis of **20**, followed by treatment with Et_2NH in DMF, liberated pure **7**[15] (66% yield).[16] In a similar way, **22** rendered compound **8**[16] in 60% yield (Scheme 2).

Pyrrolidine derivatives **6**–**8** were tested for their enzymatic inhibitory activities towards 25 commercially available glycosidases.[17] At 1 mM concentration, no inhibition was detected for α-galactosidases from *Aspergillus niger* and from *Escherichia coli*, for α-glucosidases (maltase) from yeast and from rice, for α-glucosidase (isomaltase) from Baker's yeast, for β-glucosidases from almond and from *Caldocellum saccharolyticum*, for β-mannosidase from *Helix pomatia*, for β-xylosidase from *Aspergillus niger*, from α-*N*-acetylgalactosaminidase from chicken liver and for β-*N*-acetylglucosaminidases from jack bean, bovine epididymis A and from bovine epididymis B. Results of other glycosidases are summarized in the table. The inhibition constants (K_i) and the type of inhibition (competitive, non-competitive, mixed) were determined from Lineweaver–Burk plots.[17] For each plot, a blank and two concentrations of inhibitor were used corresponding to IC_{50} and $IC_{50}/2$.

Except for a weak inhibitory activity towards α-mannosidases from jack bean and from almond, ester **6** appears to be a selective inhibitor of β-galactosidases. Competitive inhibition was established only for β-galactosidases from *E. coli*. Non-competitive inhibition was found with β-galactosidases from *A. niger*, and mixed-type inhibition was observed with the other β-galactosidases. Amides **7** and **8** showed a similar spectrum of inhibitory activity, but with less potency, the *N*-isopropylamide **8** being a much weaker inhibitor than diethylamido derivative **7** and ethyl ester **6**. Thus, activity and selectivity towards β-galactosidases are

Table 1. Inhibitory activity of pyrrolidine derivatives: percentage of inhibition at 1 mM (IC_{50} and K_i in μM, except when indicated mM)

Enzyme/compd	**3**	**4**	**5**	**6**	**7**	**8**
α-L-Fucosidase						
Bovine epididymis	84% $IC_{50}=200$ $K_i=9$ (C)	85% $IC_{50}=110$ $K_i=9.1$ (C)	94% $IC_{50}=40$ $K_i=3$ (C)	NI	NI	22%
Human placenta	76% $IC_{50}=300$ $K_i=15$ (C)	91% $IC_{50}=220$ $K_i=20.1$ (C)	93% $IC_{50}=80$ $K_i=5.3$ (C)	ND	ND	39%
α-Galactosidase						
Coffee bean	NI	NI	29%	NI	NI	NI
β-Galactosidase						
Escherichia coli	NI	NI	NI	83% $IC_{50}=90$ $K_i=74$ (C)	33%	NI
Bovine liver	57% $IC_{50}=850$	58%	38%	78% $IC_{50}=250$ $K_i=35$ (M)	90% $IC_{50}=42$ $K_i=13$ (C)	49% $IC_{50}=1$mM
Aspergillus niger	80% $IC_{50}=370$ $K_i=340$ (C)	NI	NI	99% $IC_{50}=7.5$ $K_i=9.8$ (NC)	96% $IC_{50}=28$ $K_i=30$ (NC)	79% $IC_{50}=250$
Aspergillus orizae	45%	NI	NI	98% $IC_{50}=12$ $K_i=6.6$ (M)	93% $IC_{50}=65$ $K_i=13$ (M)	68% $IC_{50}=500$
Jack beans	42%	NI	NI	94% $IC_{50}=12$ $K_i=6.4$ (M)	52% $IC_{50}=1$ mM	22%
Amyloglucosidases						
Aspergillus niger	NI	NI	23%	NI	NI	NI
Rhizopus mold	25%	25%	33%	NI	NI	NI
α-Mannosidases						
Jack beans	38%	27%	NI	49%	37%	NI
Almonds	NI	31%	9%	37%	38%	NI

Inhibitions: (C), competitive; (NC), non-competitive; (M), mixed; NI, no inhibition at 1 mM concentration; ND, not determined.

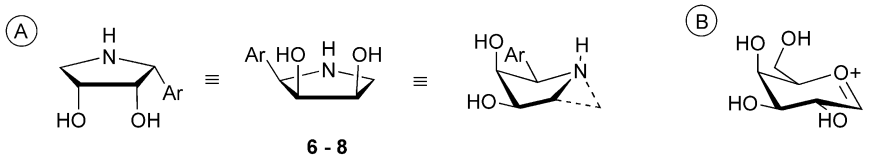


Figure 1. Representation of [(2*S*,3*S*,4*R*)-1-(3,4-dihydroxypyrrolidin-2-yl)]furan derivatives (A) and D-galactopyranosyl cation (B).

highest for ester **6**. In the case of the (2*R*)-stereoisomers **3**–**5**, the trend is the opposite (Table 1) as the highest activity and selectivity towards α-L-fucosidase are for *N*-isopropylamide **5**.

With respect to the inhibitory activity for **6**–**8** towards β-galactosidases and α-mannosidases for non-competitive, and perhaps also for the mixed type of inhibition, the inhibitors do not interact with the active site of the enzymes, but adhere to it and lead to allosteric effects responsible for the inhibitions observed. In the case of competitive inhibitors (**6** for β-galactosidase from *E. coli*, **7** for β-galactosidase from bovine liver) the inhibition can be explained considering actual configuration of these compounds which resembles that of centers C(3,4,5) of D-galactosides (Fig. 1). The weak inhibitory activity towards α-mannosidases can be explained by invoking that these compounds have the same configurations of centers C(2,3,4) of D-mannopyranosides. The pyrrolidine moiety can mimic the transition states of the hydrolysis of galactopyranosides or mannopyranosides but no other enzymes such as amyloglucosidases or glucosidases. This is consistent with the reports that 1,4-dideoxy-1,4-imino-D-lyxitol[18] and 2,5-dideoxy-2,5-imino-D-altritol[19] are potent inhibitors of α- and β-galactosidases and α-mannosidases.

It is expected, though, that other structural modifications of the aromatic heterocycle moiety, as well as the introduction of hydroxymethyl or 1,2-dihydroxymethyl side chain at C-5′ of the pyrrolidinyl moiety, may lead to higher inhibitory activities. Our work demonstrates that simple systems such as 2,3-dihydroxypyrrolidine, which is neither a potent nor a selective glycosidase inhibitor, can be transformed by adequate substitution at (C-2′) or (C-5′) into new leads for selective inhibition of various types of glycosides. Particularly striking is the observation that enzymatic selectivity of β-galactosidases versus α-fucosidases depends on the configuration of the (C-2′) center of the [(3*S*,4*R*)-3,4-dihydroxypyrrolidin-2-yl]-5-methylfuran-4-carboxylic acid derivatives.

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12. Data for **15**: $[\alpha]_D^{25}$ −1 (*c* 1, CH_2Cl_2); ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C, δ ppm, *J* Hz) δ 7.42–7.21 (m, 5H, H-aromat of Cbz), 6.50 (s, 1H, H-3), 5.42–5.37 (m, 2H, H-3′, H-4′), 5.12, 5.01 (d, 1H each, $^2J_{H,H}$ = 12.7, CH_2 of Cbz), 4.84 (d, 1H, $J_{2',3'}$ = 3.3, H-2′), 4.23 (q, 2H, $^3J_{H,H}$ = 7.1, CH_2CH$_3$), 3.94 (dd, 1H, $J_{4',5'a}$ = 5.6, $J_{5'a,5'b}$ = 11.6, H-5′a), 3.56 (dd, 1H, $J_{4',5'b}$ = 5.1, H-5′b), 2.47 (s, 3H, CH_3), 2.03, 2.02 (s, 3H each, 2 CH_3CO), 1.23 (t, 3H, CH_2CH_3); ^{13}C NMR (75.4 MHz, DMSO-d_6, 90 °C, δ ppm) δ 168.9, 168.7 (2CH_3CO), 162.3 (COOEt), 157.6 (CO of Cbz), 153.4, 148.9 (C-2, C-5), 136.0 (C-1 of Ph), 127.7–126.7 (5C, C-aromat of Cbz), 113.6 (C-4), 107.8 (C-3), 73.9, 69.0 (C-3′, C-4′), 66.0 (CH_2 of Cbz), 59.3 (CH_2CH$_3$), 57.4 (C-2′), 47.8 (C-5′), 19.7 (2CH_3CO), 13.6 (CH_2CH_3), 12.8 (CH_3); CIMS *m*/*z* 474 [30%, $(M+H)^+$]. Analysis calcd for $C_{24}H_{27}NO_9$: C, 60.88; H, 5.75; N, 2.96. Found: C, 60.69; H, 6.11; N, 2.69.
13. Data for **16**: $[\alpha]_D^{25}$ +40 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C, δ ppm, *J* Hz) δ 7.32–7.16 (m, 5H, H-aromat of Cbz), 6.30 (s, 1H, H-3), 5.44 (dd, 1H, $J_{2',3'}$ = 7.2, $J_{3',4'}$ = 4.8, H-3′), 5.39–5.34 (m, 1H, H-4′), 5.14 (d, 1H, H-2′), 5.07, 4.96 (d, 1H each, $^2J_{H,H}$ = 12.7, CH_2 of Cbz), 4.20 (q, 2H, $^3J_{H,H}$ = 7.1, CH_2CH$_3$), 3.88 (dd, 1H, $J_{4',5'a}$ = 5.8, $J_{5'a,5'b}$ = 11.8, H-5′a), 3.54 (dd, 1H, $J_{4',5'b}$ = 3.8, H-5′b), 2.43 (s, 3H, CH_3), 1.93, 1.84 (s, 3H each, 2 CH_3CO), 1.25 (t, 3H, CH_2CH_3); ^{13}C NMR (75.4 MHz, DMSO-d_6, 90 °C, δ ppm) δ 169.3, 168.9 (2CH_3CO), 163.1 (COOEt), 157.3 (CO of Cbz), 153.9, 149.3 (C-2, C-5), 136.8 (C-1 of Ph), 128.2–127.3 (5C, C-aromat of Cbz), 113.9 (C-4), 108.6 (C-3), 71.4 (C-3′), 69.9 (C-4′), 66.4 (CH_2 of Cbz), 59.7 (CH_2CH$_3$), 55.3 (C-2′), 49.2 (C-5′), 20.2, 20.0 (2CH_3CO), 14.1 (CH_2CH_3), 13.2 (CH_3); CIMS *m*/*z* 474 [15%, $(M+H)^+$]. Analysis calcd for $C_{24}H_{27}NO_9$: C, 60.88; H, 5.75; N, 2.96. Found: C, 60.71; H, 5.99; N, 2.58.
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15. Data for **7**: $[\alpha]_D^{25}$ −13 (*c* 0.3, CH_3OH). IR ν_{max} 3404 (NH, OH), 2974, 2932, 1661–1542 (CO), 1443, 1383, 1101 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD, δ ppm, *J* Hz) δ 6.55 (s, 1H, H-3), 4.39–4.43 (m, 1H, H-4′), 4.31 (d, 1H, $J_{2',3'}$ = 3.9, H-2′), 4.23 (t, 1H, $J_{3',4'}$ = 3.9, H-3′), 3.52 (bs, 4H, CH_2 of $RNHEt_2$), 3.26 (dd, 1H, $J_{4',5'a}$ = 7.5, $J_{5'a,5'b}$ = 11.5, H-5′a), 3.04 (dd, 1H, $J_{4',5'b}$ = 6.4, H-5′b), 2.36 (s, 3H, CH_3), 1.23 (d, 6H, CH_3 of $RNHEt_2$); ^{13}C NMR (100.5 MHz, CD_3OD, δ ppm) δ 168.1 (CONEt$_2$), 153.5 (C-5), 150.2 (C-2), 118.3 (C-4), 109.6 (C-3), 73.5 (C-3′), 73.3 (C-4′), 60.2 (C-2′), 51.0 (C-5′), 44.6, 40.9 (CH_2 of $RNEt_2$), 14.6, 13.2 (CH_3 of RNEt2), 12.8 (CH_3); CIMS *m*/*z* 282 [15%, $(M)^+$]. HREIMS *m*/*z* obsd 282.1584, calcd for $C_{14}H_{22}N_2O_4$ 282.1579.
16. Data for **8**: $[\alpha]_D^{25}$ −10 (*c* 0.3, CH_3OH). IR ν_{max} 3325 (NH, OH), 2930, 1634 (CO), 1588, 1402, 1101 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD, δ ppm, *J* Hz) δ 6.88 (s, 1H, H-3), 4.50–4.45 (m, 2H, H-2′, H-4′), 4.29 (t, 1H, $J_{3',4'} = J_{2',3'}$ = 3.9, H-3′), 4.18 (hept, 1H, $^3J_{H,H}$ = 6.6, CH of Pr^i), 3.36–3.40 (m, 1H, H-5′a), 3.15 (dd, 1H, $J_{4',5'b}$ = 6.4, $J_{5'a,5'b}$ = 11.6, H-5′b), 2.55 (s, 3H, CH_3), 1.25 (d, 6H, $^3J_{H,H}$ = 6.6, CH_3 of Pr^i). ^{13}C NMR (100.5 MHz, CD_3OD, δ ppm) δ 165.3 (CONHPr^i), 157.7 (C-5), 147.9 (C-2), 118.2 (C-4), 110.1 (C-3), 73.2 (C-3′), 72.8 (C-4′), 59.9 (C-2′), 50.2 (C-5′), 42.5 (CH of *i*-Pr), 22.6 (CH_3 of *i*-Pr), 13.5 (CH_3); CIMS *m*/*z* 269 [8%, (M + H) +]. EIMS *m*/*z* 268 [8%, $(M)^+$]. HREIMS *m*/*z* obsd 268.1429, calcd for $C_{13}H_{20}N_2O_4$ 268.1423.
17. See: (a) Picasso, S.; Chen, Y.; Vogel, P. *Carbohydr. Lett.* **1994**, *1*, 1. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Fignoli, B.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806, and refs 4d, 8 and 9.
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