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Synthesis of Four Stereoisomers of 5-Amino-2,5-dideoxy-heptono-1,5-lactams

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Abstract: The reaction of 2-trimethylsilyloxyfuran with a glyceraldehyde derived nitrone is examined under different reaction conditions. The four intermediates, tetrahydrofuro[2,3-d]isoxazol-5(2H)ones, were separated by combined chromatographic-crystallisation techniques. The synthetic versatility of tetrahydrofuro[2,3-d]isoxazol-5(2H)ones is demonstrated by a direct high yielding conversion into 5-amino-2,5-dideoxy-heptono-1,5-lactams upon simple hydrogenolysis in the presence of Pearlman catalyst. © 1997 Elsevier Science Ltd.

Pyrrolidine or piperidine azasugars as well as their 2-deoxy derivatives have found an extraordinary attention in medicinal chemistry in the last decade due to an outstanding biological activity as glycosidase inhibitors which makes them unique candidates for pharmacological treatment of bacterial and viral infections, including AIDS.[1] After the isolation of naturally occurring azasugars, a variety of synthetic congeners have been prepared and tested for biological activity, in some cases with superior inhibition properties.[2]

Among natural and synthetic monocyclic azasugars, at our knowledge, very few cases of higher sugars have been reported; among them 1,5-dideoxy-1,5-iminooctitols,[3] 1,5-dideoxy-1,5-iminoheptitols[4], and 2,6-dideoxy-2,6-iminoheptitols have been synthesized or isolated from living organisms.[5]

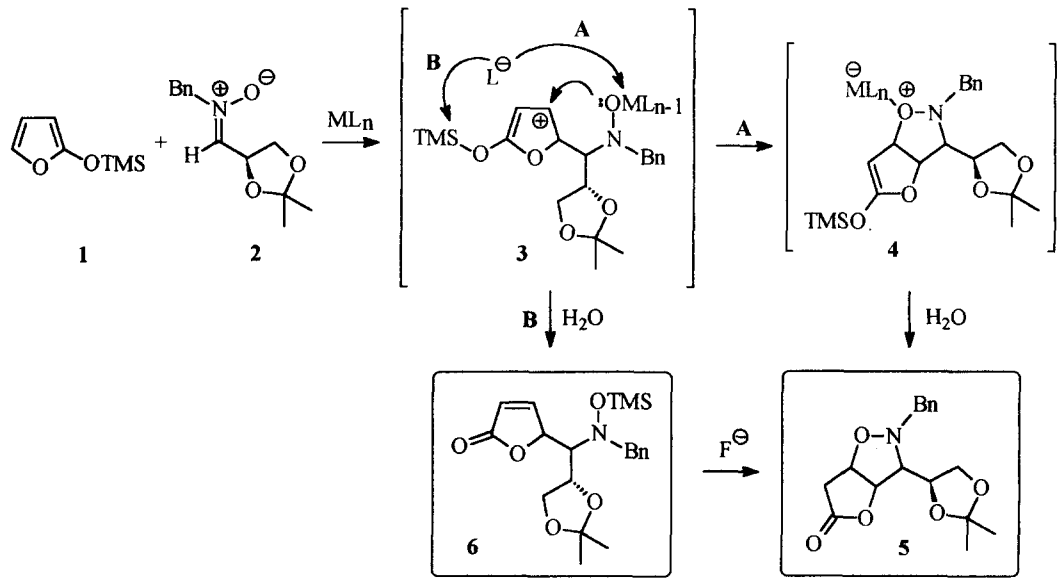
Within this context, we wish to apply a general protocol for the condensation of 2-trimethylsilyloxyfuran with nitrones to a synthesis of 5-amino-heptonic acids which can be considered immediate precursors of 7-carbon piperidine azasugars.

Results and Discussion

The use of 2-trimethylsilyloxyfuran (**1**) as a four carbon homologating agent in reactions with electrophiles has been extensively studied for the synthesis of higher carbon sugars and azasugars.[6] We

recently reported the Lewis acid promoted addition of **1** to prochiral[7] and chiral nitrones[8] which allowed us an easy entry to tetrahydrofuro[2,3-d]isoxazol-5(2H)ones.

Here we wish to examine the reaction of **1** with the *N*-benzylnitrone **2** deriving from D-glyceraldehyde under different reaction conditions and to demonstrate the synthetic versatility of the intermediates tetrahydrofuro[2,3-d]isoxazol-5(2H)ones. A number of experiments carried out in the presence of both catalytic and stoichiometric amount of Lewis acid are collected in Table 1. Let's first consider the use of a stoichiometric amount of promoter (runs 3,5-8). Depending on the Lewis acid two different mechanistic pathways are possible, as depicted in Scheme 1.



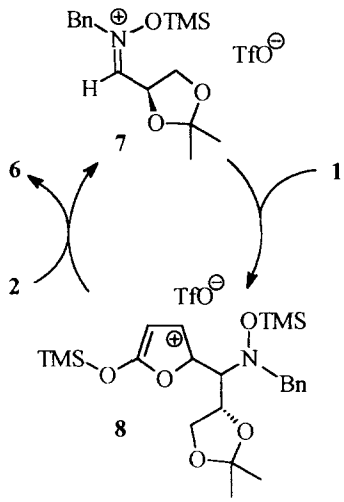
Scheme 1

The delocalised carbonium ion **3** undergoes ring closure to tetrahydrofuro[2,3-d]isoxazol-5(2H)one **5** via **4**, according to path **A**, when a strong association of L^- and M occurs leaving a formal negative charge on the OML_n group. This is observed in the case of $BF_3{\cdot}Et_2O$ (run 6), dicyclohexylboron triflate (Chx_2BOTf) (run 5), Et_2AlCl (run 8) and $ZnCl_2$ (run 7). When TMSOTf is used (run 3), the intermediate **3** undergoes desilylation by triflate anion (path **B**) leading to γ-substituted butenolide **6**. In any case, treatment of **6** with Bu_4NF in THF quantitatively converts **6** into **5**. On the other hand, when the Lewis acid is used in catalytic amount (runs 1, 2, 4), intermediate **3** undergoes desilylation by a molecule of nitrone; the resulting *N*-silyloxyiminium ion **7** promotes the catalytic cycle shown in Scheme 2. In runs producing butenolides **6**, no attempt was made to purify them, and the crude extracts were treated with Bu_4NF in THF in order to directly get tetrahydrofuro[2,3-d]isoxazol-5(2H)ones **5 a-d** (Figure 1).

Table 1. Synthesis of Tetrahydrofuro[2,3-d]isoxazol-5(2H)ones **5a-d**.

Run	ML_n (%)	T(°C)	t(h)	Yield[a] (%)	**5a** (%)	**5b** (%)	**5c** (%)	**5d** (%)	**5a+5c/ 5b+5d**	**5a+5d/ 5b+5c**
1	TMSOTf (10)	-78	3	80[b]	30	23	31	16	61/39	46/54
2	TMSOTf (10)	-20	1.5	85[b]	25	27	35	13	60/40	38/62
3	TMSOTf (100)	-78	2	88[b]	18	27	48	7	66/34	25/75
4	Chx_2BOTf (10)	-20	2	76[b]	43	19	27	11	70/30	54/46
5	Chx_2BOTf (100)	-20	0.5	78	65	15	9	11	74/26	76/24
6	BF_3OEt_2 (100)	-20	5	40	51	-	-	49	51/49	>99/1
7	ZnI_2 (100)	20	30	15	59	6	6	29	65/35	88/12
8	Et_2AlCl (100)	0	8	10	61	-	16	23	77/23	84/16

[a] Overall isolated yield. [b] Overall isolated yield of the two-step condensation/cyclisation sequence.



Scheme 2

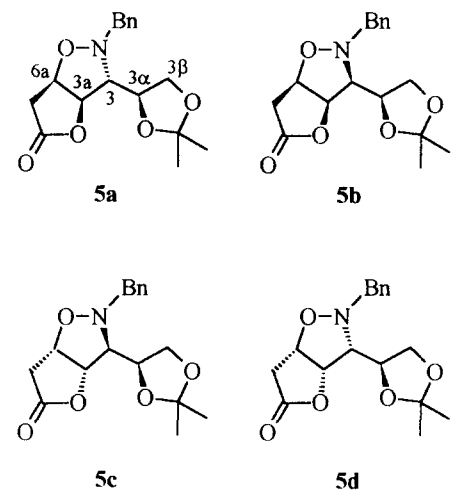


Figure 1

The last column of Table 1 estimates the extent of facial selectivity (*syn/anti* C-3/C-3α relationship), the last but one column the simple diastereoselectivity (*syn/anti* C-3/C-3a relationship). Simple diastereoselectivity, with the only exception of run 6, favours the *anti* C-3/C-3a products, as previously observed when *N*-benzylnitrones are involved.[7,8]

Facial selectivity depends on the Lewis acid chelating properties. Monodentate TMSOTf slightly favours the *syn* C-3/C-3α products, as expected by the conformation **A** in Figure 2 (Houk model)[9] while

bidentate Lewis acids (runs 6-8) strongly favour the *anti* C-3/C-3α stereorelationship, according to the β-chelated conformation **B** (Figure 2).

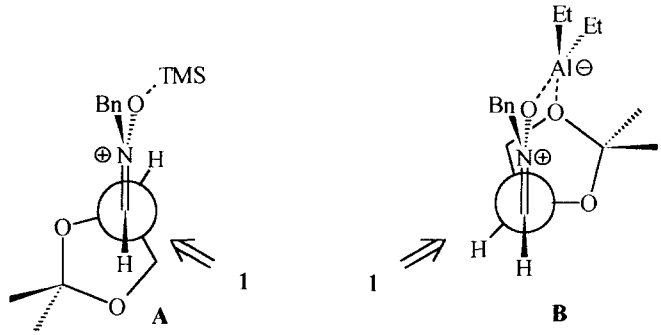
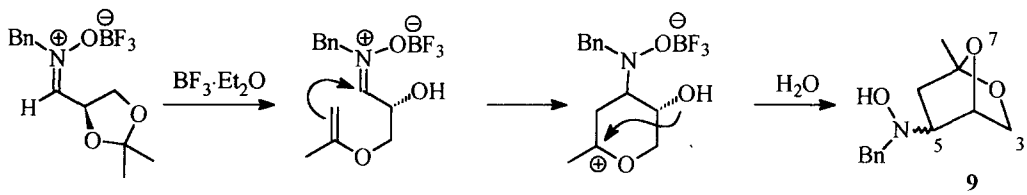


Figure 2

Few comments are deserved to run 6. Not only $BF_3{\cdot}Et_2O$ is interesting by a stereochemical point of view since it displays a complete lack of simple diastereoselectivity and a virtual quantitative facial selectivity, but also by a chemical point of view. In fact, in five replicate reactions overall yields of products **5** never exceeded 44% (mean value 40 ± 4%) but systematically the side bicyclic product **9** was isolated in about 35% yield. A possible rationale for the formation of **9** is proposed in Scheme 3; Lewis acid promoted acetonide ring opening could leave an acetone enolether which undergoes intramolecular Mannich type reaction followed by internal ketalisation to the 2,7-dioxabicyclo[2.2.1]heptane derivative **9**[10].

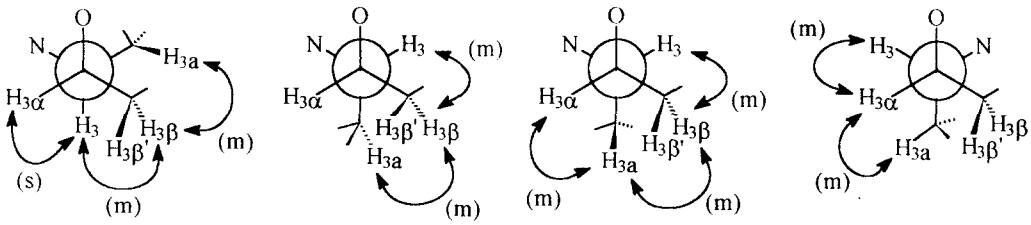


Scheme 3

Separation and characterisation of products **5a-d** was made possible by a careful combination of crystallisation and chromatographic techniques. Isomers **5a** and **5b** display the highest and lowest R_f respectively, and are easily separated by flash chromatography (cyclohexane:ethyl acetate, 1:1); **5b** and **5c** are collected as a mixture from which the former is separated by recrystallisation from petroleum ether and the latter is purified by recrystallisation from diethyl ether.

Stereochemical assignments were made using n.O.e. techniques. *Syn-anti* H-3a/H-3 relationship was established upon irradiation of H-3a; in fact *syn* H-3a/H-3 protons always give strong enhancements (7-9 %) while *anti* H-3a/H-3 give much smaller responses (2-4 %).

Syn-anti H-3α/H-3 relationships in **5** could be established considering the conformational analysis around the C-3/C-3α bond which links the two chiral 1,3-dioxolane and isoxazolidine ring systems. A series of n.O.e. enhancements testify that each member of the family **5a-d** adopts a preferred conformation; since the absolute configuration of C-3α is *S*, the configuration of C-3 ensues. The preferred conformations and the related n.O.e. effects[11] are reported in Figure 3 (for the sake of clarity only essential substituents are reported).

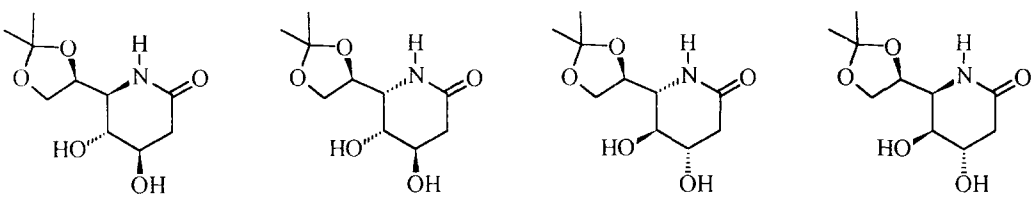


5a **5b** **5c** **5d**

Figure 3

As an example we describe compound **5a**. Upon irradiation of H-3β similar enhancements for both H-3 and H-3a were observed suggesting a blocked conformation around C-3/C-3α bond; a second correlation between H-3 and H-3α was observed indicating a gauche relationship between them; such an arrangement is only possible if C-3 is *R* as shown in conformation **A** relative to **5a**.

The last section of this work refers to a simple manipulation of products **5a-d**. They were individually hydrogenolised (H_2, 45 p.s.i.) in methanol in the presence of Pearlman catalyst; N-O bond hydrogenolysis and reductive *N*-debenzylation are followed by spontaneous cyclisation to give side chain protected tetrahydroxylated heptono-1,5-lactams **10a-d** in 65-87% yield (Figure 4).



10a **10b** **10c** **10d**

Figure 4

Since reduction of lactams to piperidines is a well documented process,[12] lactams **10a-d** may be considered direct precursors of polyhydroxylated piperidines corresponding to the seven carbon azasugars 3,6,7-trideoxy-3,7-imino-heptitols.

Conclusions

We worked out a simple route to tetrahydrofuro[2,3-d]isoxazol-5(2H)ones which makes use of simple reagents such as trimethylsilyloxyfuran and nitrones. Condensation reactions are carried out in the presence of Lewis acids, the most effective one in terms of absolute yield being TMSOTf. Hydrogenolysis of the N-O bond is followed by spontaneous lactamisation. Starting from D-glyceraldehyde, heptono-1,5-lactams **10a-d** are produced in a high yielding short synthetic sequence; these products, together with their reduced derivatives are, in our opinion, interesting candidates for biological activity studies as enzymatic inhibitors.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR Spectra in deuterated solvents were recorded at 300 and 75 MHz, respectively, using a Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm relative to internal standard Me_4Si (δ). ^{1}H-^{13}C NMR (HETCOR) and ^{1}H-^{1}H NMR (COSY) spectra allowed the complete assignments of proton and carbon peaks. IR Spectra were recorded on a Nicolet 205 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Water content of anhydrous solvents used was measured with Karl-Fisher titrator Mettler DL18. Gas chromatographic analyses were performed with HP5890 II instrument (HP-5MS cross-linked 5% phenyl-methyl silicone glass capillary column, 0.25-μm film thickness). The temperature was held at 50°C for the first two minutes and was then ramped to 250°C at 10°Cmin^{-1}. Retention times (t_R) are reported in minutes. Reactions were performed in oven-dried glassware in atmosphere of dry argon. Hydrogenations were performed at 45 p.s.i. on a Parr apparatus. 2-Trimethylsilyloxyfuran and moist 20 % $Pd(OH)_2$ on carbon (Degussa type E101) were purchased from Aldrich, *N*-benzylhydroxylamine hydrochloride from Fluka. Melting points are uncorrected.

(Z,S)-*N*-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methylene]-benzenemethanamine, *N*-oxide (2)

A solution of freshly distilled D-glyceraldehyde acetonide (7.8 g, 60 mmol) in CH_2Cl_2 (40 mL) was added to a solution of *N*-benzylhydroxylamine (8.0 g, 50 mmol, freshly freed from the hydrochloride) in CH_2Cl_2 (100 mL). The reaction mixture was allowed to react at 20°C overnight in the presence of $MgSO_4$ then filtered and evaporated to dryness. Chromatography on silica gel with ethyl acetate-cyclohexane (8:2) as the eluent and recrystallisation from cyclohexane yielded **2** (11 g, 94 %) as a white solid: mp 87-88°C (lit[13] mp 88°C); $[\alpha]_D^{22}$ = +102.9 (c = 0.61 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, s, Me), 1.39 (3H, s, Me), 3.88 (1H, dd, *J* = 5.9,

8.7 Hz, CH_2O), 4.39 (1H, dd, J = 7.0, 8.7 Hz, CH_2O), 4.87 (2H, s, NCH_2Ph), 5.15 (1H, m, OCH), 6.84 (1H, d, J = 4.8 Hz, CHN), 7.41 (5H, s, Ar-H); ^{13}C NMR ($CDCl_3$) δ 24.9 (Me), 26.2 (Me), 67.8 (CH_2O), 69.0 (NCH_2Ph), 72.0 (OCH), 109.8 (Me_2C), 129.1, 129.2, 129.4, 132.1, 139.0 (C=N); t_R 16.1; m/z 235 (M^+, 2 %), 220 (9), 177 (97), 101 (76), 91 (100), 73 (30). Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.35; H, 7.29; N, 5.96. Found C, 66.12; H, 7.23; N, 6.15.

Two step synthesis of tetrahydro-2-benzyl-furo[2,3-d]isoxazol-5(2H)ones 5a-d catalysed by TMSOTf (Table 1, run 2)

2-Trimethilsilyloxyfuran (0.4 mL, 2.34 mmol) was added to a solution of **2** (0.5 g, 2.13 mmol) in CH_2Cl_2 (15 mL). The solution was cooled at -20°C, TMSOTf (0.039 mL, 0.21 mmol) was added and the reaction mixture was stirred at -20°C for 1.5 h. The reaction was quenched with aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried and evaporated under vacuum to give a mixture of butenolides **6a-d** (t_R 21.6, 22.1, 22.3 and 22.4) as a yellow oil. To the residue dissolved in THF (15 mL), 1.1 M $Bu_4N^+F^-$ (2.42 mL, 2.67 mmol) was added at 0°C and the solution was stirred for 40 min at room temperature. The reaction was quenched with aq. $NaHCO_3$ and the aqueous layers were extracted with ethyl acetate. The combined organic layers were dried and solvent was removed under vacuum. Chromatography on silica gel with ethyl acetate-cyclohexane (1:1) yielded the compounds **5a-d** in overall 80 % yield.

(3R,3aR,6aR)-Tetrahydro-2-benzyl-3-[(4S)-(2,2-dimethyl-1,3-dioxolan-4-yl)]-furo[2,3-d]isoxazol-5(2H)one **(5a)**[14]

Yellow oil: $[\alpha]_D^{22}$ = +6.4 (c = 0.50 in $CHCl_3$); IR (neat) 3000, 2938, 2882, 1785 (γ-lactone), 1496, 1454, 1370, 1222, 1159, 1053, 857, 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (3H, s, Me), 1.46 (3H, s, Me), 2.72-2.87 (2H, m, H-6), 3.32 (1H, dd, J = 1.7, 5.6 Hz, H-3), 3.63-3.70 (1H, m, H-3β), 4.04-4.10 (4H, m, NCH_2Ph + H-3α + H-3β'), 4.78 (1H, dt, J = 1.9, 5.0 Hz, H-6a), 5.32 (1H, dd, J = 1.7, 5.0 Hz, H-3a), 7.35-7.42 (5H, m, Ar-H); ^{13}C NMR ($CDCl_3$, HETCOR) δ 24.9 (Me), 26.5 (Me), 35.4 (C-6), 62.3 (NCH_2Ph), 67.1 (C-3β), 72.2 (C-3), 73.2 (C-3α), 77.2 (C-6a), 88.6 (C-3a), 109.9 (Me_2C), 127.8, 128.6, 129.1, 136.0, 174.5 (CO); t_R 21.89; m/z 319 (M^+, 4 %), 304 (7), 218 (36), 101 (2), 91 (100). Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.96; H, 6.52; N, 4.45.

(3S,3aR,6aR)-Tetrahydro-2-benzyl-3-[(4S)-(2,2-dimethyl-1,3-dioxolan-4-yl)]-furo[2,3-d]isoxazol-5(2H)one **(5b)**[14]

White solid: mp 104-106°C (petroleum ether); $[\alpha]_D^{22}$ = +139.5 (c = 0.62 in $CHCl_3$); IR (nujol) 1785 (γ-lactone), 1498, 1450, 1375, 1222, 1160, 1053, 857, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (3H, s, Me), 1.47 (3H, s, Me), 2.65-2.80 (2H, m, H-6), 2.84 (1H, dd, J = 4.6, 8.1 Hz, H-3), 3.76 (1H, d, J = 14.9 Hz, NCH_2Ph), 3.87 (1H, dt, J = 1.3, 6.8 Hz, H-3β), 4.29-4.41 (2H, m, H-3α + H-3β'), 4.72 (1H, d, J = 14.9 Hz, NCH_2Ph), 4.87 (1H, ddd, J = 4.6, 6.0, 7.0 Hz, H-6a), 5.17 (1H, dd, J = 4.6, 6.3 Hz, H-3a), 7.30-7.40 (5H, m, Ar-H); ^{13}C NMR

($CDCl_3$, HETCOR) δ 25.5 (Me), 26.7 (Me), 34.7 (C-6), 59.9 (NCH_2Ph), 67.2 (C-3β), 71.6 (C-3), 74.1 (C-3α), 74.7 (C-6a), 86.6 (C-3a), 110.1 (Me_2C), 127.2, 128.2, 128.5, 137.3, 174.8 (CO); t_R 21.96; *m/z* 319 (M^+, 5 %), 304 (7), 218 (38), 101 (3), 91 (100). Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.88; H, 6.71; N, 4.48.

(3S,3aS,6aS)-Tetrahydro-2-benzyl-3-[(4S)-(2,2-dimethyl-1,3-dioxolan-4-yl)]-furo[2,3-d]isoxazol-5(2H)one **(5c)**[14]

White solid: mp 100-103°C (diethyl ether); $[\alpha]_D^{22}$ = +67.0 (c = 0.26 in $CHCl_3$); IR (nujol) 1785 (γ-lactone), 1490, 1455, 1378, 1220, 1163, 1055, 860, 751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (3H, s, Me), 1.48 (3H, s, Me), 2.62-2.76 (2H, m, H-6), 3.18 (1H, dd, *J* = 3.0, 6.8 Hz, H-3), 3.92 (1H, dd, *J* = 6.8, 8.6 Hz, H-3β), 3.96 (1H, d, *J* = 14.0 Hz, NCH_2Ph), 4.13 (1H, dd, *J* = 6.8, 8.6 Hz, H-3β'), 4.23 (1H, q, *J* = 6.8 Hz, H-3α), 4.38 (1H, d, *J* = 14.9 Hz, NCH_2Ph), 4.62 (1H, dt, *J* = 2.0, 4.9 Hz, H-6a), 4.93 (1H, dd, *J* = 3.0, 4.9 Hz, H-3a), 7.30-7.36 (5H, m, Ar-H); ^{13}C NMR ($CDCl_3$, HETCOR) δ 25.1 (Me), 26.5 (Me), 33.9 (C-6), 61.6 (NCH_2Ph), 66.4 (C-3β), 74.1 (C-3), 74.5 (C-3α), 75.9 (C-6a), 88.3 (C-3a), 110.3 (Me_2C), 128.2, 128.3, 128.8, 136.8, 174.3 (CO); t_R 22.00; *m/z* 319 (M^+, 4 %), 304 (10), 218 (35), 101 (3), 91 (100). Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.96; H, 6.75; N, 4.26.

(3R,3aS,6aS)-Tetrahydro-2-benzyl-3-[(4S)-(2,2-dimethyl-1,3-dioxolan-4-yl)]-furo[2,3-d]isoxazol-5(2H)one **(5d)**[14]

White solid: mp 100-101°C (diethyl ether); $[\alpha]_D^{22}$ = -97.0 (c = 1.1 in $CHCl_3$); IR (nujol) 1785 (γ-lactone), 1485, 1450, 1378, 1222, 1161, 1058, 860, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (3H, s, Me), 1.45 (3H, s, Me), 2.64 (1H, dd, *J* = 2.8, 19.0 Hz, H-6), 2.74 (1H, dd, *J* = 7.4, 19.0 Hz, H-6), 3.26 (1H, dd, *J* = 3.0, 4.9 Hz, H-3), 3.79 (1H, d, *J* = 14.3 Hz, NCH_2Ph), 4.02 (1H, dd, *J* = 7.1, 8.4 Hz, H-3β), 4.13 (1H, dd, *J* = 7.1, 8.4 Hz, H-3β'), 4.39 (1H, d, *J* = 14.3 Hz, NCH_2Ph), 4.61 (1H, dt, *J* = 3.0, 7.1 Hz, H-3α), 4.89 (1H, ddd, *J* = 2.9, 6.0, 7.5 Hz, H-6a), 5.30 (1H, dd, *J* = 4.9, 6.0 Hz, H-3a), 7.28-7.34 (5H, m, Ar-H); ^{13}C NMR ($CDCl_3$, HETCOR) δ 24.3 (Me), 26.2 (Me), 34.6 (C-6), 60.9 (NCH_2Ph), 65.3 (C-3β), 69.3 (C-3), 73.1 (C-3α), 74.7 (C-6a), 86.8 (C-3a), 108.1 (Me_2C), 127.4, 128.3, 128.5, 136.9, 174.5 (CO); t_R 22.32; *m/z* 319 (M^+, 5 %), 304 (7), 218 (35), 101 (2), 91 (100). Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.92; H, 6.63; N, 4.39. Found C, 64.07; H, 6.51; N, 4.35.

One-pot preparation of tetrahydro-2-benzyl-3-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)-furo[2,3-d]isoxazol-5(2H)ones 5a-d promoted by Chx_2BOTf (Table 1, run 5)

Nitrone **2** (0.5 g, 2.13 mmol) was added at -20°C to a 0.081 M solution of Chx_2BOTf in CH_2Cl_2 (26.5 mL, 2.13 mmol). 2-(Trimethylsilyloxy)-furan (0.36 mL, 2.13 mmol) was added and the reaction mixture was stirred for 30 min at -20°C. The reaction was quenched with aq. $NaHCO_3$, the aqueous layer was extracted with ethyl acetate, dried and evaporated to dryness. Chromatography on silica gel with ethyl acetate-cyclohexane (1:1) as the eluent afforded compounds **5a-d** in overall 76 % yield.

Synthesis of 5-amino-2,5-dideoxy-D-*altro*-heptono-1,5-lactam (10a). General procedure

A mixture of lactone **5a** (0.190 g, 0.6 mmol) and 20% $Pd(OH)_2$ on carbon (0.065 g) in anhydrous methanol (10 mL) was hydrogenated for 12 h. The solution was filtered over Celite, silica gel was added and the solvent was removed under vacuum. Chromatography on silica gel using ethyl acetate-methanol (9:1) as the eluent and recrystallisation from chloroform yielded lactam **10a** (0.09 g, 65 %) as a white solid: mp 132-134°C; $[\alpha]_D^{22}$ = -24.6 (c = 0.71 in $CHCl_3$); IR (nujol) 3388, 3015, 1644 (δ-lactam), 1454, 1222, 1068 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (3H, s, Me), 1.45 (3H, s, Me), 2.61 (1H, d, *J* = 17.6 Hz, H-2), 2.74 (1H, dd, *J* = 5.2, 17.6 Hz, H-2), 3.59 (1H, t, *J* = 6.0 Hz, H-5), 3.91 (1H, dd, *J* = 6.1, 8.5 Hz, H-7), 4.13 (1H, dd, *J* = 6.5, 8.5 Hz, H-7), 4.32-4.39 (2H, m, H-4 + H-6), 4.72 (1H, t, *J* = 5.2 Hz, H-3), ^{13}C NMR ($CDCl_3$, APT) δ 24.9 (Me), 26.4 (Me), 39.0 (C-2), 53.0 (C-5), 65.6 (C-7), 69.4, 75.8, 81.3, 109.5 (Me_2C), 175.0 (C-1). Anal. Calcd. for $C_{10}H_{17}NO_5$: C, 51.92; H, 7.41; N, 6.06. Found C, 51.87; H, 7.55; N, 6.13.

The following isomers were prepared according to the same procedure described for **10a**:

5-Amino-2,5-dideoxy-D-*ido*-heptono-1,5-lactam (10b)

White solid (87 %): mp 147-148°C ($CHCl_3$); $[\alpha]_D^{22}$ = -47.0 (c = 0.40 in MeOH); IR (nujol) 3420, 3015, 1645 (δ-lactam), 1450, 1222, 1060 cm^{-1}; ^1H NMR (CD_3OD) δ 1.24 (3H, s, Me), 1.29 (3H, s, Me), 2.13 (1H, dd, *J* = 3.0, 17.5 Hz, H-2), 2.61 (1H, dd, *J* = 5.0, 17.5 Hz, H-2), 3.43 (1H, dd, *J* = 3.5, 8.4 Hz, H-5), 3.63 (1H, dd, *J* = 3.5, 5.0 Hz, H-4), 3.68 (1H, dd, *J* = 6.1, 8.6 Hz, H-7), 3.92 (1H, dt, *J* = 3.0, 5.0 Hz, H-3), 4.01 (1H, dd, *J* = 6.1, 8.6 Hz, H-7), 4.23 (1H, dt, *J* = 6.1, 8.4 Hz, H-6), ^{13}C NMR (CD_3OD, APT) δ 25.7 (Me), 27.1 (Me), 36.4 (C-2), 56.7 (C-5), 67.1 (C-7), 67.6, 68.0, 76.5, 110.8 (Me_2C), 173.5 (C-1). Anal. Calcd. for $C_{10}H_{17}NO_5$: C, 51.92; H, 7.41; N, 6.06. Found C, 51.98; H, 7.38; N, 5.93.

5-Amino-2,5-dideoxy-D-*galacto*-heptono-1,5-lactam (10c)

Pale yellow oil (70 %); $[\alpha]_D^{22}$ = -8.7 (c = 0.46 in $CHCl_3$); IR (neat) 3400, 3010, 2987, 2885, 1650 (δ-lactam), 1450, 1215, 1083 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (3H, s, Me), 1.46 (3H, s, Me), 2.62 (1H, d, *J* = 18.0 Hz, H-2), 2.77 (1H, dd, *J* = 4.7, 18.0 Hz, H-2), 3.21 (1H, dd, *J* = 4.3, 8.1 Hz, H-5), 3.79 (1H, dd, *J* = 6.4, 8.5 Hz, H-7), 4.12 (1H, dd, *J* = 6.9, 8.5 Hz, H-7), 4.26 (1H, dd, *J* =4.2, 8.0 Hz, H-4), 4.35 (1H, dt, *J* = 4.2, 6.2 Hz, H-6), 4.67 (1H, broad t, *J*≈4.6 Hz, H-3), ^{13}C NMR ($CDCl_3$, APT) δ 24.8 (Me), 26.2 (Me), 38.3 (C-2), 52.6 (C-5), 66.1 (C-7), 68.3, 75.7, 82.7, 109.3 (Me_2C), 175.6 (C-1). Anal. Calcd. for $C_{10}H_{17}NO_5$: C, 51.92; H, 7.41; N, 6.06. Found C, 51.84; H, 7.47; N, 6.13.

5-Amino-2,5-dideoxy-D-*gluco*-heptono-1,5- lactam (10d)

White solid (81 %): mp 164-166°C (ethyl acetate); $[\alpha]_D^{22}$ = +40.0 (c = 0.30 in MeOH); IR (nujol) 3388, 3010, 1645 (δ-lactam), 1420, 1210, 1067 cm^{-1}; ^1H NMR (CD_3OD) δ 1.14 (3H, s, Me), 1.21 (3H, s, Me), 2.06 (1H, dd, *J* = 2.2, 18.0 Hz, H-2), 2.52 (1H, dd, *J* = 4.1, 18.0 Hz, H-2), 3.64-3.66 (1H, m, H-5), 3.68 (1H, dd, *J* = 6.7, 8.9 Hz, H-7), 3.77-3.79 (2H, m, H-3 + H-4), 3.84 (1H, dd, *J* = 6.7, 8.9 Hz, H-7), 4.10 (1H, dt, *J* = 3.7, 6.7 Hz,

H-6), ^{13}C NMR (CD_3OD, APT) δ 24.1 (Me), 25.7 (Me), 34.4 (C-2), 53.0 (C-5), 64.8 (C-7), 65.5, 66.6, 75.6, 107.5 (Me_2C), 172.2 (C-1). Anal. Calcd. for $C_{10}H_{17}NO_5$: C, 51.92; H, 7.41; N, 6.06. Found C, 52.07; H, 7.49; N, 6.17.

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10. ^{1}H NMR ($CDCl_3$) δ 1.55 (3H, s, Me), 1.90 (1H, d, J = 11.9 Hz, H-6), 2.20 (1H, dd, J = 5.9, 11.9 Hz, H-6), 3.43-3.57 (2H, m, H-3 + H -5), 3.58-3.70 (1H, m, H-4), 3.86 (1H, d, J = 12.7 Hz, NCH_2Ph), 3.93 (1H, dd, J = 5.8, 10.0 Hz, H-2), 4.22 (1H, d, J = 12.7 Hz, NCH_2Ph), 7.27-7.38 (5H, m, Ar-H); ^{13}C NMR ($CDCl_3$, APT) δ 21.2 (Me), 39.1 (C-6), 62.1 (NCH_2Ph), 64.4 (C-5), 65.8 (C-4), 66.3 (C-3), 104.2 (Me_2C), 127.8, 128.6, 129.2; *m/z* 235 (M^+, 4 %), 174 (5), 113 (98), 91 (100), 83(23).
11. Relative values of n.O.e. effects: strong (s) > 7% ; 4 < medium (m) < 7%.
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14. The numbering system used in the NMR assignments for compounds **5a-d** is that reported in Fig. 1. We defined as H-3β' the H-3β proton *syn* to H-3α.

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