Pergamon

Tetrahedron Letters, Vol. 36, No. 36, pp. 6433-6436, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01293-1

D- and L- Purpurosamine C Type Glycosyl Donors Starting from D- Glucosamine**

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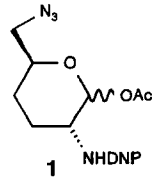
Summary: New D- purpurosamine C type glycosyl donors (**1**, **2**) are prepared from D-glucosamine in 26% (25%) total yield after 11 (8) steps. Access to the L-2-*epi*-donor **3** is opened through selective enzyme catalysed acetylation, ring opening and epimerisation in 7% total yield after 20 steps.

For the total synthesis of binuclear aminoglycoside antibiotics, natural (D) as well as non-natural (L) purpurosamine type glycosyl donors are wanted[1]. The synthetic procedures worked out for D-purpurosamines and purpurosaminides (starting from D-glucose, cellulose, neamine, D-glucosamine, D-amino acids, from L-alanine and L-malic acid) generally do not provide glycosyl donors which are appropriate for modified Koenigs-Knorr glycosylation[1,2]. Our recently reported route starting from racemic acrolein dimer had opened the way to D- as well as L- donors[2]; a drawback, however, is the time consuming and costly resolution of the racemic starting material[2].

In this letter we present the results of a project which was directed at a more efficient access to the D-purpurosamine C type glycosyl donors **1**, **2** and to the 2-*epi*-L-donor **3** with D-glucosamine as common starting



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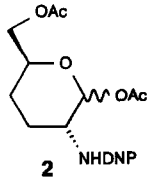

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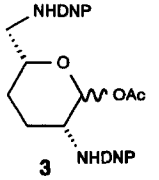

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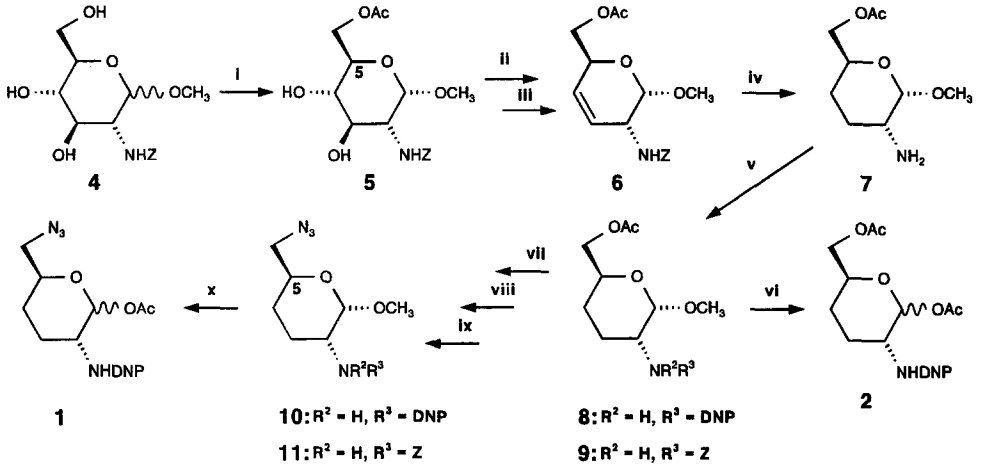
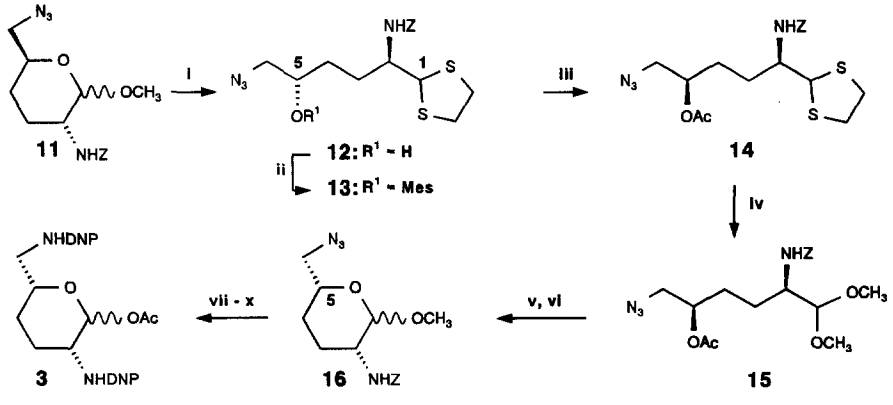
material. The synthetic sequence followed to prepare D-donors is a variation of an earlier approach to D-6-N-methyl-2,6-di(N-benzyloxycarbonyl)purpurosamine C [2,6-di(benzyloxycarbonylamino)-6-methylamino-2,3,4,6-tetradeoxy-α/β-D-erythro-hexopyranose] reported by Ito[3].

Selective acetylation[4] of 6-OH in the known triol 4[5] by making use of CAL (Novozym 435) in vinyl acetate/pyridine (r.t., 5[6], 93 %) was followed by mesylation, deoxygenation (NaI/DMF[7] rflx., 6, 65 %), and catalytic hydrogenation to give methyl 6-O-acetyl-2-amino-2,3,4-trideoxy-α-D-erythro-hexopyranoside 7. Protection with DNP-F (8) or Z-Cl (9), hydrolysis of the acetate, mesylation (100%), and substitution by azide (NaN_3/DMF) led to the D-methyl glycosides 10 (99%) and 11 (92%), resp. After treatment of 10 and 8 with Ac_2O/H_2SO_4(cat.)[8], the D-glycosyl donors 1 (98%, α:β ratio 6:1) and 2 (97%, α:β ratio 4:1) were isolated as yellowish solids in total yields of 26% (11 steps) and 25% (8 steps), respectively, based on D-glucosamine.



Scheme 1. i) Novozym 435, vinyl acetate/pyridine, 93%; ii) MesCl /Et_3N, 96%; iii) NaI/DMF rflx., 67%; iv/v) H_2/Pd-C/MeOH; DNP-F/$NaHCO_3$/acetone:H_2O 1:1 (**8**, 90%) or Z-Cl/$NaHCO_3$/acetone:H_2O 1:1 (**9**, 99%); vi) Ac_2O/H_2SO_4(cat.)/CH_2Cl_2, 97%; vii) K_2CO_3/MeOH, 100%; viii) MesCl/Et_3N, 100%; ix) NaN_3/DMF rflx., 99%; x) Ac_2O/H_2SO_4(cat.)/CH_2Cl_2, 98%.

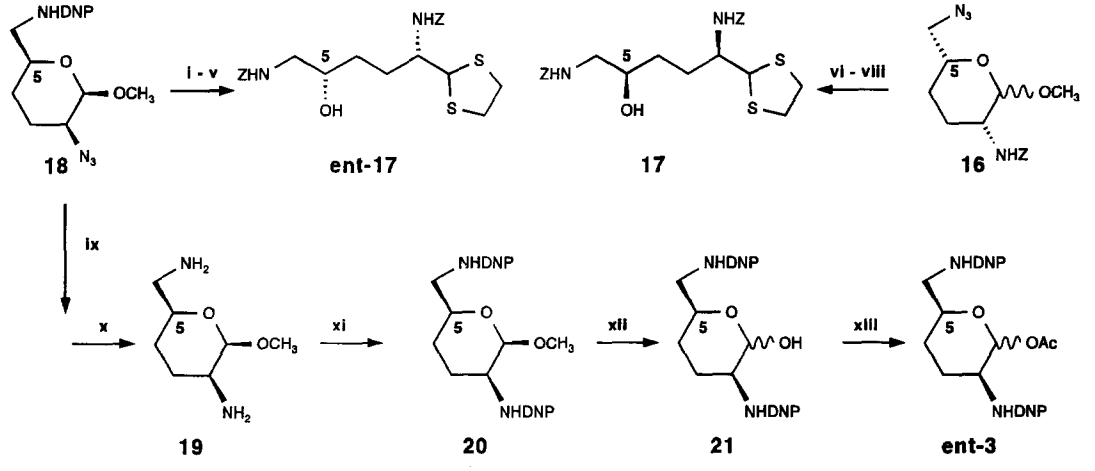
The 2-*epi*-L-donor 3 was approached starting from 11 (Scheme 2). The latter's transformation into linear



Scheme 2. i) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2/CH_2Cl_2$, 85%; ii) MesCl/pyridine/DMAP/CH_2Cl_2, 100%; iii) TMAA/AcOH/CH_3CN rflx., 78-82%; iv) $(CF_3CO_2)_2IPh$, $MeOH_{abs}$, 94%; v) Na_2CO_3/MeOH, 88%; vi) $ZnCl_2/CH_2Cl_2$, 87% α- and β-glycoside (α:β ratio: 2:1); vii/viii) H_2/Pd-C/MeOH, DNP-F/$NaHCO_3$/acetone:H_2O 1:1, 83%; ix/x) 2n HCl/AcOH/CH_3NO_2, Ac_2O/pyridine, 78%, α:β ratio 1:1).

thioacetal **12** with 1,2-ethanedithiol/$BF_3{\cdot}OEt_2$[9] was, when taken to completion, severely hampered by side reactions. With the conversion limited to ca. 70%, yields up to 85% of dithiolane **12** were achieved. After mesylation of **12** to **13** (quantitative), the S_N2 substitution **13** → **14** was found to be problematic due to competing elimination. With tetramethylammonium acetate (TMAA) in CH_3CN in the presence of AcOH, elimination could be reduced to trace amounts; however, formation of still unknown side products could not be avoided (78 - 82% **14**). After treatment of **14** with $(CF_3CO_2)_2IPh$[10] in MeOH, the dimethylacetal **15** was recovered in nearly quantitative yield; hydrolysis (Na_2CO_3/MeOH, 88%) and direct cyclisation led to oily, colorless methyl L-2-*epi*-purpurosaminide **16** (87%, α:β ratio 2:1, 16 steps from D-glucosamine, 11% total yield). Catalytic hydrogenation followed by derivatisation of the resulting amino groups with DNP-F (83%), hydrolysis[2] of the methylglycoside, and acetylation of the pyranose led to a 1:1 mixture of anomers of the desired L-2-*epi*-glycosyl donor **3** (78%, 2 steps, 7% total yield after 20 steps starting from D-glucosamine), which could easily be separated by column chromatography (silica gel, acetone/CH_2Cl_2 1:15, R_f (3α) = 0.59, R_f (3β) = 0.38), $[\alpha]_D^{25}$: **3α** = – 99.0, c = 0.14, CH_2Cl_2; **3β** = – 89.5, c = 0.12, CH_2Cl_2).

The stereochemistry at C-5 was established beyond doubt by ^{1}H-NMR comparison of **16α** with **11α**[6], by comparison of **17** with **ent-17** ($[\alpha]_D^{25}$ **17** = + 14.9, **ent-17** = – 13.0) synthesized from **16** and known **18**[2] (Scheme 3), respectively, and of **ent-3** (from **18**[2], Scheme 3, $[\alpha]_D^{25}$: **ent-3α** = + 102.5, c = 0.06, CH_2Cl_2; **ent-3β** = + 89.1, c = 0.10, CH_2Cl_2) with **3**.



Scheme 3. i,ix) Amberlite IRA-400 (OH^-); ii,iv,vii) Z-Cl, $NaHCO_3$; iii,vi,x) H_2/Pd-C; v,viii) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$; x/xi) H_2/Pd-C, DNP-F/$NaHCO_3$/acetone:H_2O 1:1; xii/xiii) 2n HCl/AcOH/CH_3NO_2, Ac_2O/pyridine (α:β ratio 1:1).

The route presented here to the D-glycosyl donors **1** and **2** is shorter and more efficient than our previous approach to enantiomerically pure D-1-O-acetyl-2,6-bis(N-2,4-dinitrophenyl)purpurosamine C donor[2] (ca. 7%, 12 steps; 3.5% based on racemic acrolein dimer). The route to the 2-*epi*-L-donor **3** (α:β ratio 1:1, 7% total yield after 20 steps starting from D-glucosamine) is lengthy and not completely optimized but should provide sufficient material

of the ultimate astromicin type aminoglycosides with non-naturally configurated glycon parts to allow biological testing.

Acknowledgement: These studies were supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and BASF AG. X. Liang thanks the National Education Committee of P.R. China for financial support. We thank NOVO NORDISK for the generous gift of CAL (NOVOZYM 435).

References and Notes

** This paper is dedicated to Professor Dr. Richard Neidlein on the occasion of his 65th birthday - as an expression of our personal esteem.

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6) The new compounds are characterized by elemental analyses and spectral data (IR, ^{1}H-, ^{13}C-NMR, MS); e.g. **1**: ^{1}H-NMR, δ = 2.21 (s, CH_3); 3.32 (dd, 6-H, J = 4.5, J = 12 Hz); 3.40 (dd, 6-H, J = 5.5, J = 12 Hz); 3.72 - 4.13 (m, 5-,2-H); 5.64 (d, 1-H β-**1**, J = 8.0 Hz); 6.29 (d, 1-H α-**1**, J = 3.0 Hz); **2**:^{1}H-NMR, δ = 2.11 and 2.22 (s, CH_3 α-**2**, β-**2**); 3.74 - 3.90 (m, 2-H β-**2**); 3.91 - 4.23 (m, 2-,6-,6'-H α-**2**, 6-,6'-H β-**2**); 5.66 (d, 1-H β-**2**, J = 8.0 Hz); 6.27 (d, 1-H α-**2**, J = 3.0 Hz); **3**α: ^{1}H-NMR, δ = 2.22 (s, CH_3); 3.45 - 3.69 (m, 6-,6'-H); 3.95 (m, 2-H); 4.34 (m, 5-H); 6.10 (br.s, 1-H), MS (high resolution): calc. for $C_{20}H_{20}N_6O_{11}$: 520.11902, found: 520.1186; **3**β: δ = 2.08 (s, CH_3); 3.50 - 3.73 (m, 6-,6'-H, J = 13.5, 6.0, 4.0, 13.5, 7.0, 4.5 Hz); 4.01 - 4.20 (m, 2-,5-H); 5.93 (d, 1-H, J = 1.8 Hz), MS (high resolution): calc. for $C_{20}H_{20}N_6O_{11}$: 520.11902, found: 520.1180; **11**α: ^{1}H-NMR, δ = 3.16 and 3.29 (dd, 6-,6'-H, J = 12.5, 7.0, 12.5, 3.5 Hz); 3.41 (s, OCH_3); 3.70 - 3.91 (m, 2-, 5-H); 4.65 (d, 1-H, J = 3.0 Hz); **16**α: ^{1}H-NMR, δ = 3.16 and 3.27 (dd, 6-,6'-H, J = 13.0, 7.0, 13.0, 3.5 Hz); 3.41 (s, OCH_3); 3.78 (m, 2-H), 3.94 (m, 5-H); 4.56 (s, 1-H); **17***lent*-**17**: ^{1}H-NMR, δ = 2.60 (br. s, OH); 3.73 (m, 2-H); 3.94 (m, 5-H); 4.67 (d, 1-H, J = 4.0 Hz).

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(*Received in Germany* 30 *June* 1995; *accepted* 7 *July* 1995)