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De novo Syntheses of Enantiopure Glycosyl Donors of *D*-/*L*-Azapurpurosamine C Type - Enzymatic Asymmetrizations

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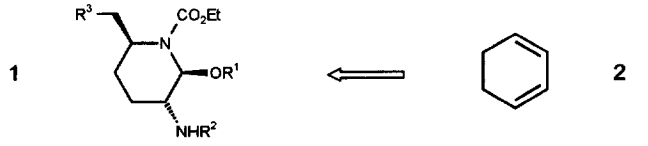
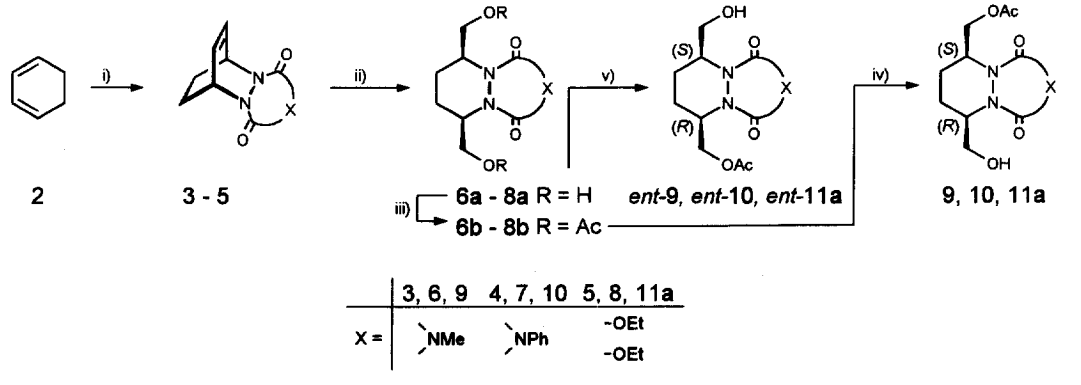
Summary: Glycosyl donors of type **1** are synthesized starting from known cycloadducts of 1,3-cyclohexadiene with azo dienophiles and by utilizing biocatalytic asymmetrizations as access to the pure antipodes.

In the context of total syntheses in the Astromycin area[1], *D*- and *L*-azapurpurosamine C glycosyl donors of type **1** were needed. In this letter we detail *de novo* syntheses based on the proven cycloaddition of azo dienophiles to 1,3-cyclohexadienes[2] and with the biocatalytic asymmetrization of *meso*-diols and *meso*-diacetates[3] as access to the optically pure antipodes.



The diazabicyclo[2.2.2]octenes **3** - **5** are available in high yields, along partially modified protocols[4], through addition of 4-methyl-1,2,4-triazoline-3,5-dione (MTAD), 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) and diethyl azodicarboxylate (DEAD) to 1,3-cyclohexadiene **2** (Scheme 1). After ozonolysis of the C=C double bond and reduction ($NaBH_4$) the *meso*-diols **6a** - **8a** (85%) and their acetates **6b** - **8b** were obtained[5]. Asymmetrization was explored with a set of lipases earlier applied successfully in similar cases[6]. The transesterification experiments with the diols **6a** - **8a** were performed in vinyl acetate as solvent, the hydrolyses of **6b** - **8b** in a two phase system (water/

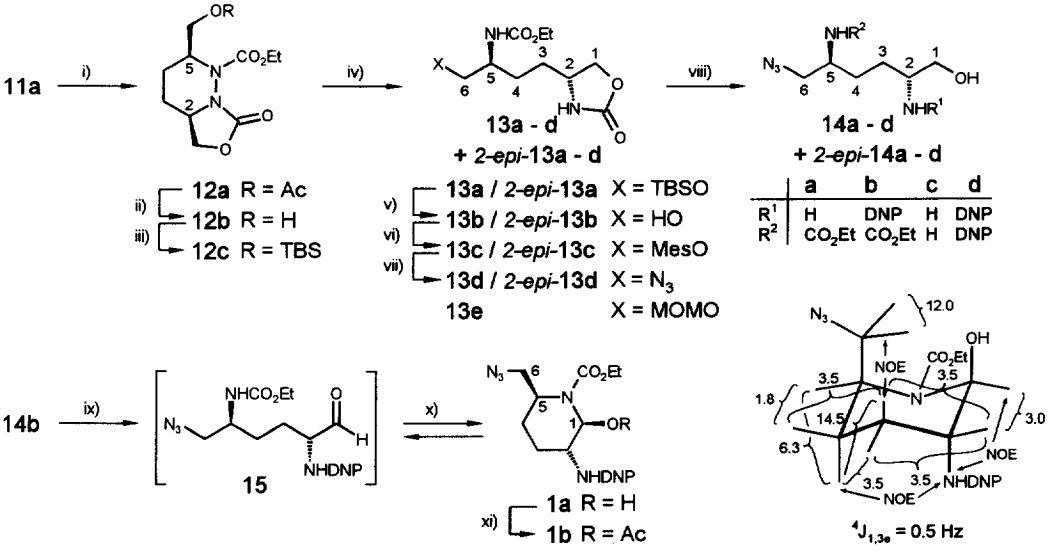


Scheme 1. i) s. lit. 4; ii) O_3/EtOH; then $NaBH_4$, -50 - -40°C, 85%; iii) Ac_2O/pyridine/DMAP, 0°C, 12 h, quant.; iv) phosphate buffer/*n*-hexane, lipase, r.t.; v) vinyl acetate, lipase, r.t.

n-hexane; pH 7 buffer) monitored by TLC and stopped when the monoacetates **9**, **10** and **11a** had reached their maximum concentration. The enantiomeric excess (ee) was determined by ^{1}H NMR spectroscopy in the presence of (*R*)- or (*S*)-TFAE or on esters of **9**, **10**, and **12b** (for **11a**) with (*R*)- and/or (*S*)-MTPA.

This study revealed for the substrates **6** - **8** a remarkable effect of the structural elements X. In the MTAD series acetyl transfer to the diol **6a** with the lipase R-10 yielded monoacetate (-)-**9** nearly quantitatively (97% isolated, absolute configuration unknown) in high optical purity (ee = 94, after recrystallization from light petroleum/ethyl acetate ee > 97, $[\alpha]_D^{25}$ = -10.7 (*c* = 0.6, acetone)), whilst hydrolysis of the diacetate **6b** provided monoacetate (+)-**9** in only moderate yield (67%) and with poor ee (61). Application of enzymes with reversed selectivity (AY, CE) in the acetyl transfer to **6a** significantly raised the yields of (+)-**9** (80 - 85%), but not the ee (ca. 70). After exchange of the methyl by the phenyl group (PTAD series), the rates of transesterifications/hydrolyses were generally too low. In the bisurethanes of the DEAD series Lipozym IM proved as the reagent of choice: Diol **8a** was transformed to the monoacetate (+)-*ent*-**11a** ($[\alpha]_D^{25}$ = +7.3 (*c* = 2.6, acetone)), diacetate **8b** to monoacetate (-)-**11a** ($[\alpha]_D^{25}$ = -6.2 (*c* = 1.8, acetone)) on a decigram scale with only fair to good yields (60 - 80%) but very good optical purities (ee 97 - 95) and isolated in pure form after chromatography. In the pursuit of the program both antipodes were utilized (here only described for **11a**).

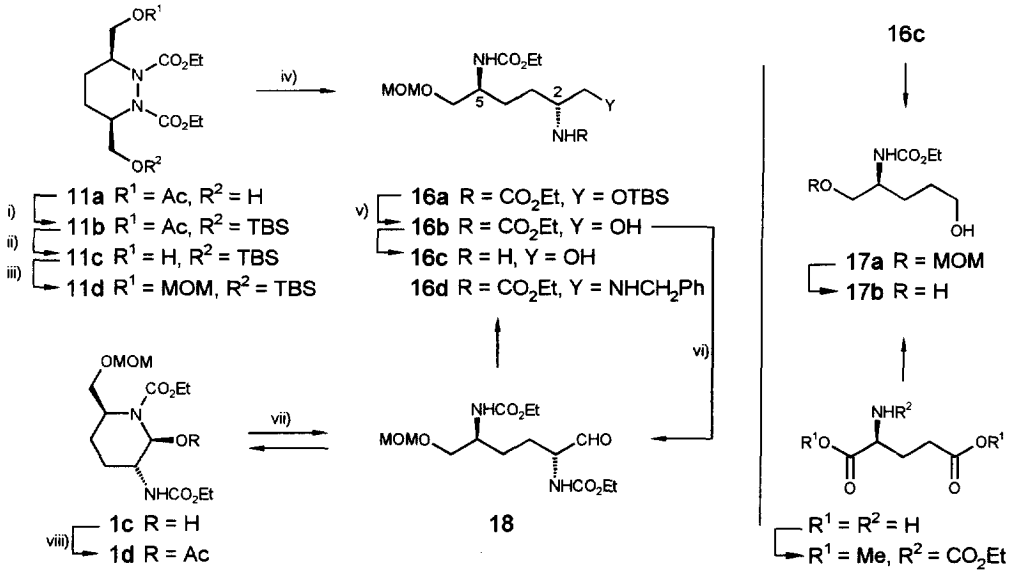
For the subsequent reductive cleavage of the N-N bond under standard conditions[7], protection of ester and alcohol functionalities was necessary (Scheme 2). For **11a** this was conveniently accomplished by lactonization to give **12a** with the use of weak bases (preferably $NaBH_4$, strong ones as e.g. NaH cause partial racemization through deacylation and/or acetyl migration), ammonolysis (**12b**) and silylation (**12c**). N-N cleavage in diacylhydrazine **12c**, possibly without affecting the stereochemistry at C-2 and C-5, was attempted under the conditions successfully applied to chiral alkylacylhydrazines (Li/NH_3/THF, -33°C, 1h; quenching by addition of solid NH_4Cl)[8]. Yet, the



Scheme 2. i) $NaBH_4$/dioxane, 60°C, 2 h, 95%; ii) MeOH/H_2O/NH_3, 0°C → r.t., 16 h, 96%; iii) TBSCl/imidazole/DMF, r.t., 2 h, 94%; iv) Li/NH_3/EtOH, -78°C, 1 min, quant.; v) HF/CH_3CN, 0°C, 1 h, 92%; vi) MesCl/Et_3N/CH_2Cl_2, 0°C, 1.5 h then vii) NaN_3/DMF, 80°C, 1.5 h, 84%; viii) KOH/dioxane/H_2O, 60°C, 3 h; then CO_2, DNPF/dioxane/H_2O, 55°C, 40 min, 78%; purification by HPLC; ix) DMSO/oxalyl chloride/CH_2Cl_2/Et_3N, -78°C, 2 h; x) silica gel/CH_3CN, r.t., 3 h, 63%; xi) Ac_2O/pyridine, r.t., 16 h, quant.

quantitatively isolated oily product turned out to be a 2:1 mixture of **13a** and 2-*epi*-**13a** (^{1}H NMR). This ratio could be improved by intensive optimizing efforts to 4:1 (lowering of the reaction temperature to -78°C, addition of ethanol, very quick quenching without raising the temperature; **13a** remained unchanged under the cleavage conditions). After deprotection (**13b**/2-*epi*-**13b**), mesylation (**13c**/2-*epi*-**13c**) and substitution with NaN_3 (DMF), the isolated mixture of azides **13d**/2-*epi*-**13d** (75 - 80%) was exposed to the selective hydrolysis of the oxazolidinone ring, not trivial in the presence of the N-ethylcarbamoyl functionality at C-5. With KOH/dioxane/water at 60°C after total conversion (TLC) a yield of ca. 80% of **14a**/2-*epi*-**14a** was reproducibly achieved (most of the missing material was identified as the diamines **14c**/2-*epi*-**14c**). The DNP-protected mixture **14b**/2-*epi*-**14b** was chromatographically separated from **14d**/2-*epi*-**14d**, pure **14b** secured from preparative HPLC and oxidized with DMSO (Swern)[9]. The linear, not characterized azasugar **15** was quantitatively cyclized through stirring over silica gel/CH_3CN to the oily β-anomer **1a** (63%); it is additionally analyzed as acetate **1b** (glycosyl donor). The chair conformation for **1a**/**1b** with axial substituents at C-1, C-2 and C-5 as ascertained by the $^3J/^4J$ H,H coupling constants and NO effects is in line with expectation[10].

In the sequence **11a** → **1a** the detracting partial epimerization during the N-N cleavage can be avoided - at the expense of a somewhat longer route - through an alternative protection scheme (Scheme 3). To this goal the MOM/TBS protected hexahydropyridazine **11d** was prepared from **11a** by three standard manipulations (85%) and subjected to the analogous N-N cleavage procedure. Besides the protected 2,5-diamino-1,6-diol **16a**, isolated from the crude product (100%) in 85% yield by crystallization, 2-*epi*-**16a** could not be observed. The NMR spectroscopic identification of **16a** was supported by the transformations → **16b** → **13e** → **13b**, the absolute configuration at C-5 (*S*) determined by correlation with *L*-glutamic acid (common derivative **17b**: $[\alpha]_D^{25}$ = -17.3 (*c* = 0.49, CH_3OH) from **16c** vs. $[\alpha]_D^{25}$ = -16.7 (*c* = 0.60, CH_3OH) from *L*-glutamic acid). After desilylation (**16b**, 83%), Swern oxidation[9]



Scheme 3. i) TBSCl/imidazole/DMF, r.t., 2 h, 94%; ii) MeOH/H_2O/NH_3, 0°C, 24 h, 98%; iii) MOMCl/Hünig base/CH_2Cl_2, 0°C, 4 d, 92%; iv) Li/NH_3/THF, -78°C, 15 min, 85%; v) TBAF/THF, r.t., 3 h, 83%; vi) DMSO/oxalyl chloride/CH_2Cl_2/Et_3N, -78°C, 40 min, 80 - 85% after crystallization; vii) silica gel/CH_3CN, r.t., 3 h, 95%; viii) Ac_2O/pyridine, r.t., 16 h, quant.

uniformly gave the crystalline aldehyde **18** (80 - 85%, $[\alpha]_D^{25}$ = -4.1 (*c* = 0.26, CH_3CN)), which proved rather persistent in the solid state and in CD_3CN solution. The stereochemical uniformity of **18** was established NMR spectroscopically after reductive amination with benzylamine/$NaBH_4$ to give the stable derivative **16d**. After stirring for three hours over silica gel in acetonitrile **18** was practically totally cyclized to β-**1c** ($[\alpha]_D^{25}$ = -32.8 (*c* = 3.16, CH_3CN)). The oily product isolated in 95% yield was also characterized as acetate **1d** ($[\alpha]_D^{25}$ = -49.6 (*c* = 0.78, CH_3CN), glycosyl donor). Like for **1a/1b**, the piperidine ring of **1c/1d** is identified NMR spectroscopically as chair with all substituents being axial[10].

It has to be stressed that the synthetic route **2** → **1** in principal allows for multiple chemical modifications and e.g. - in spite of the protecting group manipulations - provided **1d** with a 25% total yield over 11 steps with only one chromatographic purification (gram scale).

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5) All new compounds have been fully characterized (^1H, ^{13}C NMR, MS, IR, elemental analysis). E.g. 1-*O*-Acetyl-2,5-bis-(ethoxycarbonylamino)-6-*O*-methoxymethyl-2,3,4,5-tetradesoxy-β-*D-erythro*-hexopyranose (**1d**): R_f (CH_2Cl_2/CH_3OH 10:1) = 0.63; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.62 (s, 1H), 4.91 (d, br, 1H), 4.64 (d, 1H), 4.62 (d, 1H), 4.31 (m, 1H), 4.19 (q, 2H), 4.13 (q, 2H), 3.94 (m, 1H), 3.69 (t, 1H), 3.52 (dd, 1H), 3.37 (s, 3H), 2.05 (s, 3H), 2.23-1.94 (m, 1H), 1.92-1.73 (m, 2H), 1.65 (m, 1H), 1.27 (t, 3H), 1.26 (t, 3H), $^3J_{2,NH}$ = 7.0, $^2J_{(MOM)}$ = 6.4, $^3J_{(Et)}$ = 7.0, $^2J_{6a,6b}$ = 9.8, $^3J_{5,6a}$ = 9.8, $^3J_{5,6b}$ = 4.8 Hz; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.5 (ester C=O), 155.9, 155.5 (urethane C=O), 96.4 (CH_3OCH_2O), 77.7 (C-1), 67.0 (C-6), 62.5, 61.2 (2 OCH_2CH_3), 55.3 (CH_3OCH_2O), 49.4, 46.8 (C-2, C-5), 21.2 (acetyl CH_3), 18.7, 18.5 (C-3, C-4), 14.55, 14.48 (2 OCH_2CH_3); MS (170eV; CI, NH_3): *m/z* (%): 394 (3) $[M+NH_4]^+$, 334 (100), 317 (47) $[M\text{-}AcO]^+$, 285 (26) $[M\text{-}AcOH\text{-}OCH_3]^+$; $[\alpha]_D^{25}$ = -49.6 (*c* = 0.78, CH_3CN), $[\alpha]_{365}^{25}$ = -152.8 (*c* = 0.78, CH_3CN); HRMS for $(C_{14}H_{24}N_2O_6)^+$ $[M^+\text{-}CH_3CO_2H]$: calc. 316.1634, found 316.1636.

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