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Enantiopure Purpurosamine C Type Glycosyl Donors
An Improved Access from *rac*-Acrolein Dimer - Biocatalytic Resolution

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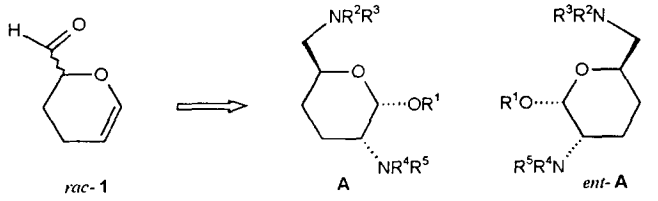
Summary. An improved synthetic access to a suitably "protected" purpurosamine C type glycosyl donor (**11**, analogously *ent*-**11**) starting from racemic 3,4-dihydro-2*H*-pyran-2-carbaldehyde (*rac*-**1**, acrolein dimer) implies an "indirect aziridination protocol" and a biocatalytic resolution step (acetate hydrolysis, ee > 98). The latter's stereochemical course is confirmed by a highly α-selective glycosylation with an acceptor of known absolute configuration. © 1997 Elsevier Science Ltd.

As part of our activities directed toward the total synthesis of binuclear aminoglycoside antibiotics[1], the search for serviceable routes to the respective glycosyl donors in enantiomerically pure natural and non-natural form is a constant topic on our agenda[2,3]. A shorter, more efficient route to suitably "protected" purpurosamine C type donors **A** (and *ent*-**A**) starting once again from cheap acrolein dimer *rac*-**1**[4] and including a biocatalytic resolution is presented in this communication[5].

Scheme 1

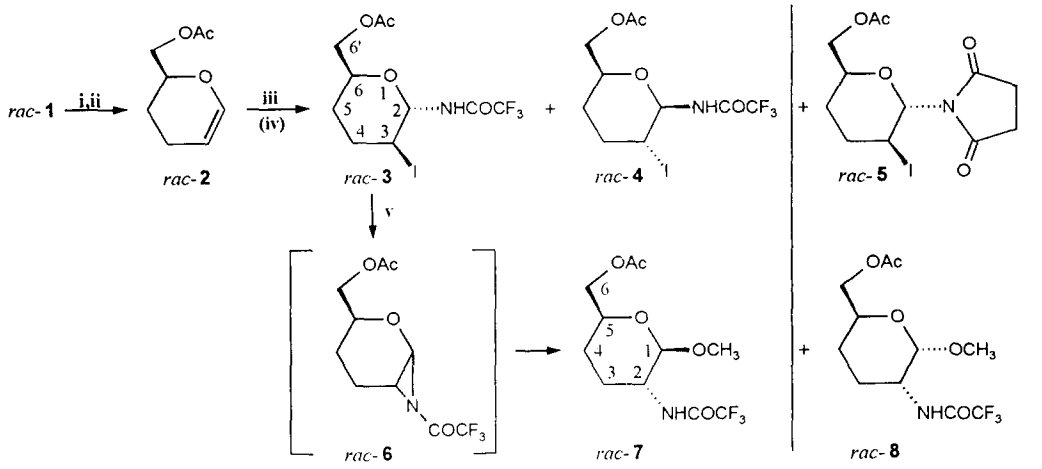


rac-**1** **A** *ent*-**A**

Prior attempts to harmonize the installation of the 3α-amino functionality into the pyran ring with the glycosylation procedure had deficiencies in stereo- and regioselectivity[6,7]. The results reported recently by Danishefsky[8] for the "indirect aziridination protocol" as applied to the synthesis of β-glycosides was the impetus to utilize this methodology for the preparation of protected donors of type **A** and thus for the construction of the aspired α-glycosides.

The approach outlined in Scheme 2[9] starts with the standard transformation of *rac*-**1** into acetate *rac*-**2** (in toto 84%). In the latter, offering little stereochemical guidance, the installation of the 2α,3β,-functionalities of *rac*-**3** was tested under strictly anhydrous conditions with the combinations N-iodosuccinimide (NIS, 1.2 equiv.) / F_3CONH_2/CH_3CN and $[I(sym\text{-}Coll)_2]ClO_4$ (1.5 equiv.)/CF_3CONH_2/CH_2Cl_2. Under the former set of conditions

besides 62% of the desired 3β-iodo-2α-trifluoroacetamide *rac*-**3** ($J_{2,3}$ = 7.9, $J_{2,NH}$ = 6.4, $J_{6',6'}$ = 8.6 Hz; 2e,3e,6a-chair preferred conformation), 32% of the 2α-succinimide *rac*-**5** ($J_{2,3}$ = 10.7 Hz),[10] and only traces (< 1%, collected from several runs, 5 g scale) of the 3α-iodo-2β-trifluoroacetamide *rac*-**4** ($J_{2,3}$ = $J_{2,NH}$ = 10.1 Hz) were chromatographically isolated. This product distribution was practically temperature invariant; succinimide set free during the reaction evidently is an efficient competitor for the intermediate iodonium ion. Under the second set of conditions (not opti-



Scheme 2: i.) $NaBH_4$, EtOH, r.t., 6 h, 89%.- ii.) Ac_2O, pyridine, r.t., 4 h, 94%.- iii.) NIS (1.2 equiv), CF_3CONH_2, CH_3CN, 0°C, 1.5 h, 62%.- iv) [I(*sym*-Coll)$_2$]ClO_4 (1.5 equiv.)/CF_3CONH_2/CH_2Cl_2, 70-72%.- v.) NEt_3, MeOH, DMF (1:2), r.t., 24 h, 84%.

mized) - the perchlorate was added to the mixture of the other components at 0°C - monitoring the reaction (TLC, cyclohexane/ethyl acetate/$CHCl_3$, 5:5:1) showed the generation of *rac*-**3** (R_f = 0.46) as major component separated after total conversion in 70-72% yield from ca. 6% of *rac*-**4** (R_f = 0.53) and ca. 5% of a mixture of at least two non-identified components (R_f = 0.7). Treatment of *rac*-**3** with triethylamine in CH_3OH/DMF (1:2) at room temperature provided selectively the β-glycoside *rac*-**7** (m.p. 152°C, 84% isolated, $J_{1,2}$ = 7.9 Hz) via the intermediate aziridine *rac*-**6**; up to 10% of the 1α-isomer *rac*-**8** (m.p. 77°C, $J_{1,2}$ = 3.7 Hz) are evidence for the intervention of an alternative reaction channel.

For the resolution of acetate *rac*-**7**[3,11] a good number of enzymes has been tested[12] - with notably very slow conversion only occurring with PPL and PSL (Table 1). With the former at limited conversion (ca. 40%) the formed

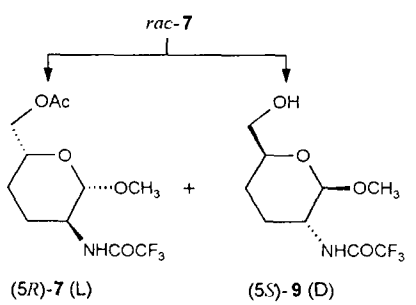


Table 1: Biocatalytic separation of *rac*-**7**
(ee determined by ^{1}H NMR, Eu(hfc)$_3$).

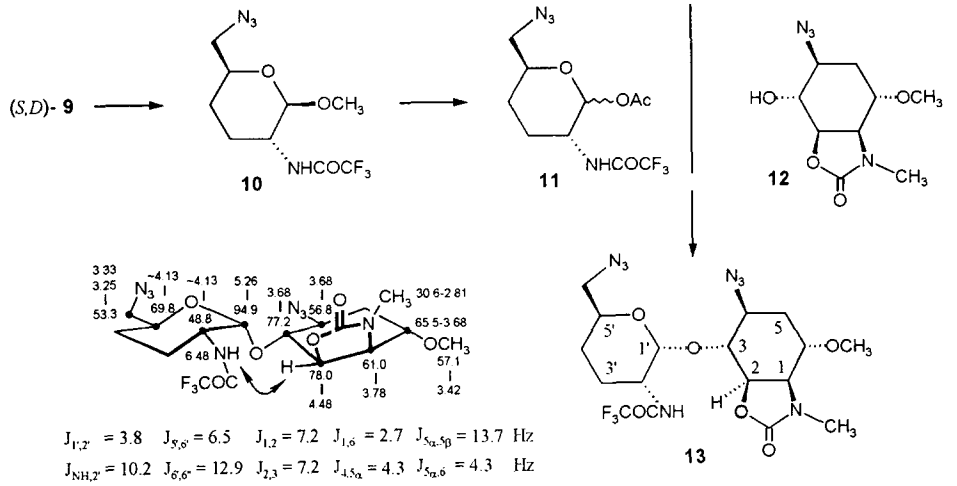
lip.	*conv.*	(5*S*)-**9** (D)	(5*R*)-**7** (L)
PPL	38%	$[\alpha]_D^{25}$ = -42.0, ee >98	
PPL	70%		$[\alpha]_D^{25}$ = + 43.6, ee > 98
PPL	50%	$[\alpha]_D^{25}$ = -27.2, ee = 59	$[\alpha]_D^{25}$ = +14.6, ee = 31
PSL	36%	$[\alpha]_D^{25}$ = -35.7, ee = 79	
PSL	69%		$[\alpha]_D^{25}$ = + 44.3, ee > 98

alcohol (5*S*)-**9** (D), after ca. 70% conversion the remaining acetate (5*R*)-**7** (L) was isolated in very high optical purity (ee > 98). With PSL, though, under comparable conditions only for (5*R*)-**7** a similarly satisfactory result was noted.

Standard mesylation of (5*S*)-**9** (CH_3SO_2Cl/pyridine/CH_2Cl_2/0°C) and substitution by azide (NaN_3/DMF/80°C/ 24 h) provided in toto 92% of the methyl glycoside **10** (m.p. 78°C; $[\alpha]_D^{25}$ = -50.6). By exposing the latter to a mixture of Ac_2O/H_2SO_4 (1.5 h) in CH_2Cl_2 at 0°C, the "protected" donor **11** was obtained (89%) in form of a colorless, crystalline, chromatographically separable α/β mixture (12:1, **11**α: m.p. 63°C; $[\alpha]_D^{25}$ = +57.6).

Starting from *ent*-**7** ($[\alpha]_D^{25}$ = +44.3) by an analogous reaction sequence, implying the PLE catalyzed hydrolysis of the acetate (5*R*)-**7**, via *ent*-**9** ($[\alpha]_D^{25}$ = +42.9) the enantiomeric donor *ent*-**11** ($[\alpha]_D^{25}$ = -59.8) was prepared.

With donor **11** (0.1 mmol) and the optically pure sannamine type acceptor **12** (0.11 mmol) of known absolute configuration[13] an exemplary glycosylation was performed under modified Koenigs-Knorr conditions (BF_3/OEt_2/ CH_2Cl_2, 0.11 mmol). The α-glycoside **13** selectively formed (ca. 80%) besides several small components (TLC, ^1H NMR; no β-glycoside) was isolated chromatographically as a pure colorless oil (TLC, ^1H NMR, ^{13}C NMR, MS (FAB, Nba): 515(16) $[M+Na]^+$, 493(16) $[M+H]^+$, 251(3) $[C_8H_{10}N_4O_2F_3]^+$, 241(42) $[C_9H_{13}N_4O_4]^+$, 139(68) $[C_6H_9N_3O]^+$).



Scheme 3

The absolute configuration of the enantiomers **9** - **11** as shown was first derived from the 5S selectivity of PPL established for the hydrolysis of the *rac*-2-hydroxymethyl-3,4-dihydro-2*H*-pyran acetate[3,11] and was confirmed for the glycoside **13** by the NOE measured between the amide NH at C2' and 2-H[1].

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