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ASYMMETRIC TOTAL SYNTHESIS OF AZASUGARS BRANCHED AT C-5

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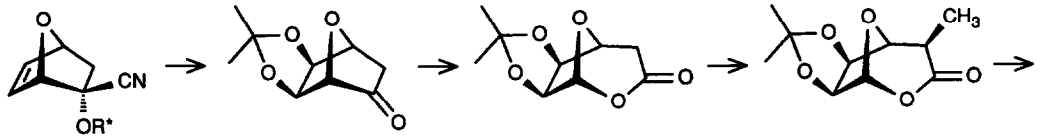
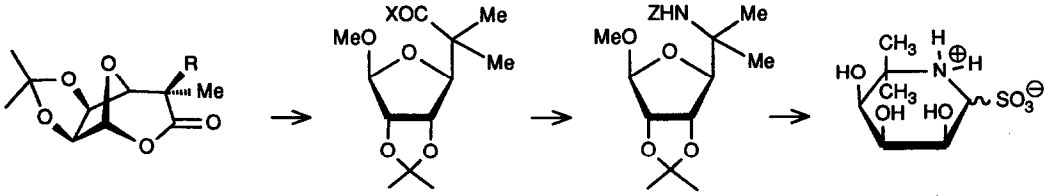
Summary: *The new azasugars (5-ammonio-1,5-N-anhydro-5,6-dideoxy-5-C-methyl-αβ-L-ribo-hexitol)-1-sulfonate and (5-ammonio-1,5-N-anhydro-5-deoxy-5-C-methyl-αβ-D-talo-hexitol)-1-sulfonate have been derived from (1S,2R,4S)-2-cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl (1R')-camphanate.*

Because some azasugar derivatives have exhibited AIDS anti-viral activity,[1] there has been recently a large effort in the search of new nojirimycine analogues (5-amino-5-deoxy-hexoses).[2] We report here the first synthesis of azasugars branched at C(5) starting from the *Diels-Alder* adduct **1** (a "naked sugar"[3]) of furan and (+)-(1-cyano-vinyl)-(1R)-camphanate.



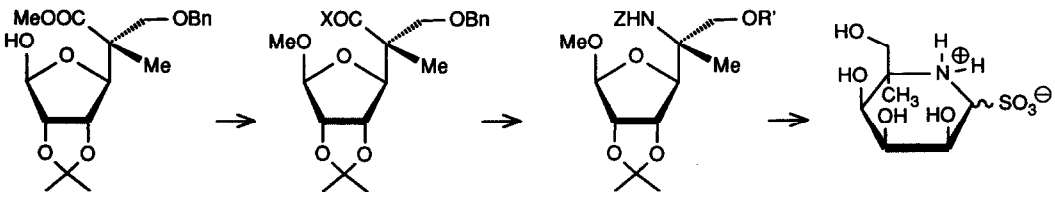
1 R*=(1R)-camphanoyl (-)-**2** (+)-**3** (+)-**4**



(+)-**5** R=Me (+)-**6** X=OMe **8** X=OCO_2Et (+)-**10** Z=CO_2Bn (+)-**12**
(+)-**13** R=CH_2OBn (+)-**7** X=OH **9** X=N_3 (+)-**11** Z=H

Double hydroxylation of **1** and protection of the glycol as an acetonide followed by saponification gives (-)-**2** (60%) and (1R)-camphanic acid (recovery of the chiral auxiliary). *Baeyer-Villiger* oxidation of (-)-**2** gives (+)-**3** (98%), as already described.[4] Treatment of (+)-**3** with $(Me_3Si)_2NLi$ in THF (-65°C), and then with MeI (-65°C to -20°C, 20 min) afforded (+)-**4** (98%). The same process applied to (+)-**4** furnished (+)-**5** (86%).[5] Methanolysis of (+)-**5** ($HC(OMe)_3$, CCl_4, Nafion 117, 20°C, 9 d) gave the methyl furanosiduronate (+)-**6** (70%, oil, $[\alpha]_D^{25}$ = +59 (c = 0.65, CH_2Cl_2)) whose saponification (KOH/THF/H_2O, 20°C, 36 h) afforded acid (+)-**7** (100%, oil, $[\alpha]_D^{25}$ = +50 (c = 1.2, CH_2Cl_2)). Treatment with $ClCO_2Et/Et_3N$ in acetone (0°C, 20 min) led to the unstable mixed anhydride **8** which reacted with NaN_3/H_2O (0°C, 10 min) to give **9**. Heating **9** with $PhCH_2OH$ (4 eq.) and Et_3N (1 eq.) in benzene for 2 days gave (+)-**10** (89%, m.p. 55.5-56°C, $[\alpha]_D^{25}$ = +18 (c = 1.6, CH_2Cl_2)). Catalytical hydrogenolysis of (+)-**10** furnished (+)-**11** (91%).[6] Bubbling of SO_2 into an aqueous solution of (+)-**11** heated to 55°C for 5 days afforded after addition of EtOH (0°C) crystalline sulfonate (+)-**12** (62%, m.p. 120°C (dec.), $[\alpha]_D^{25}$ = +6.8 (c = 0.96, H_2O); 2:1 mixture of α/β-anomer).

Deprotonation of (+)-**4** with $(Me_3Si)_2NLi$ (THF, -60°C) followed by addition of $BrCH_2OBn$ (-60°C to



14 (+)-**15** X=OMe **17** X=OCO_2Et (+)-**19** R'=Bn, Z=CO_2Bn (+)-**21**
(+)-**16** X=OH **18** X=N_3 (+)-**20** R'=Z=H

-10°C, 30 min) gave (+)-**13** (97%)[4] whose methanolysis (MeOH, K_2CO_3, 20°C, 2h) furnished the furanose **14** which was then treated with $HC(OMe)_3$ and Amberlyst 15 (CCl_4, 20°C, 24 h) to yield (+)-**15** (87%, oil, $[\alpha]_D^{25}$ = +42 (c = 0.85, CH_2Cl_2), β-anomer) and 4% of its α-anomer. Saponification of (+)-**15** (KOH/MeOH/ THF/H_2O, 50°C, 24 h) gave acid (+)-**16** (100%, oil) whose mixed anhydride **17** (90%, obtained as **8**) underwent reaction with NaN_3 (giving the unstable azide **18**) and *Curtius* rearrangement into the protected azasugar (+)-**19** (72%, yellowish oil, $[\alpha]_D^{25}$ = +12 (c = 2.2, CH_2Cl_2)). Debenzylation (H_2, 10% Pd/C, THF/H_2O, 20°C, 3 d) gave (+)-**20** (99%).[7] Treatment of (+)-**20** with SO_2 afforded (+)-**21** (53%, m.p. 115-116°C (dec.), $[\alpha]_D^{25}$ = +12 (c = 0.70, H_2O); 1:1 mixture of α- and β-anomer).[8]

Since the "naked sugars" can be obtained readily in both enantiomeric forms and considering the possibility of substituing C(5) and C(6) of **1** by other groups than *exo*-hydroxy moieties,[3] our approach should allow one to prepare a large variety of yet unknown azasugars and analogues.

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5. For a preliminary report on these stereoselective alkylations, see: Wagner, J.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **1989**, 1634.
6. Data of (+)-**11**: oil, $[\alpha]_D^{25}$ +48 (c =1.2, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H 4.92 (s, HC(1)); 4.74 (dd, J=6.2, 2.0, HC(3)); 4.49 (d, J=6.2, HC(2)); 3.93 (d, J=2.0, HC(4)); 3.36 (s, MeO); 1.62 (s, NH_2); 1.44, 1.27, 1.13, 1.08 (4s, 4Me); MS (CI, NH_3) m/z 232 ($M^{+\cdot}$+1, 100), 200 (63).
7. Data of (+)-**20**: m.p. 82.5-83.5°C; $[\alpha]_D^{25}$ = +37 (c = 0.7, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H 5.0 (s, HC(1)); 4.87 (dd, J=6.2, 2.0, HC(3)); 4.54 (d, J=6.2, HC(2)); 4.16 (d, J=2.0, HC(4)); 3.48, 3.38 (2d, ^{2}J=10.8, H_2C(6)); 3.41 (s, MeO); 1.91 (s, NH_2); 1.49, 1.33, 1.08 (3s, 3Me); IR (KBr) ν 3340, 3280, 3160, 2970, 2950, 2910, 2840, 1590; MS (CI, NH_3) m/z 248 ($M^{+\cdot}$+1, 100), 216 (18).
8. All the compounds described here were fully characterized by their spectral data and elemental analyses.

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