Synthesis of (1*R*, 2*R*, 4*S*, 5*R*)-2,4-Dihydroxy-5-hydroxymethylcyclopentylamine and its Conversion to an Analogue of Aristeromycin

Atanu Roy, Ranjan Patra, Basudeb Achari and Sukhendu B. Mandal*

Indian Institute Of Chemical Biology, 4 Raja S. C. Mullick Road, Calcutta 700 032, India

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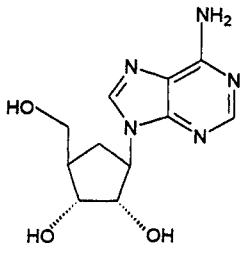
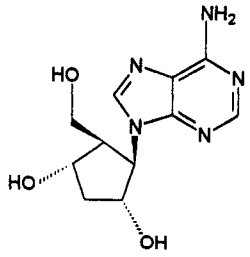
Abstract: Isoaristeromycin (**1**), an isomer of the nucleoside antibiotic aristeromycin, has been synthesized in twelve steps from D-glucose.

The use of carbohydrates and their derivatives as chiral building blocks for the synthesis of enantiomerically pure "non-carbohydrate" compounds continues to be an area of active investigation, particularly for preparing enzyme inhibitors,[1] antibiotics[2] or bio-active carbocyclic nucleosides.[3] Recently we have reported the use of intramolecular nitrone cycloaddition (INC) for converting D-glucose into functionalized carbocycles,[4] and consequently into nucleosides having a carbocycle or heterocycle fused to the ribose ring.[5] Herein we disclose the usefulness of the methodology to allow an efficient synthesis of a chiral trihydroxy aminocyclopentane (**5**) and of the aristeromycin analogue (**1**) also; aristeromycin itself is a naturally occurring antitumor agent.[6]



Aristeromycin



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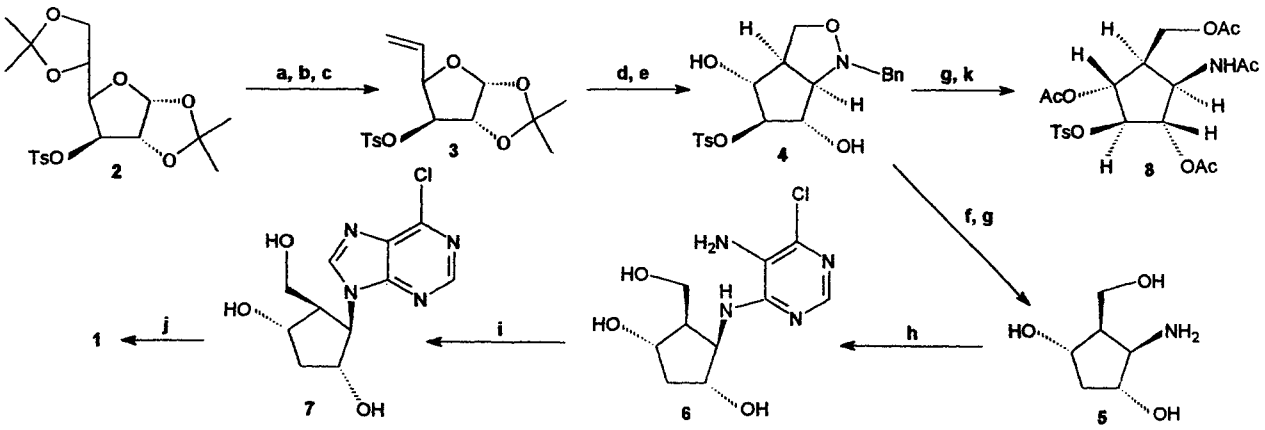
The tosyl derivative of 1:2,5:6-di-*O*-isopropylidene-D-glucofuranose (**2**) was converted to the olefinic compound **3**[7](in 66% yield) through selective opening of 5,6-*O*-isopropylidene group by HOAc followed by vicinal diol cleavage and Wittig reaction (**Scheme 1**). Deprotection of the acetal group in **3** with dil.H_2SO_4 and subsequent INC reaction between the *N*-benzyl nitrone of the masked aldehyde at C-1 and the olefin at C-5 afforded isoxazolidine **4**[8] (74% yield). Reductive elimination of the tosyl group of **4** by $LiAlH_4$ and cleavage of the isoxazolidine ring employing transfer hydrogenation furnished aminocyclopentane **5**, a key precursor of the nucleoside, in 91% yield. Reaction between aminotriol **5** and 5-amino-4,6-dichloropyrimidine yielded **6** (43% yield), $[\alpha]_D$ -41.7°(*c* 0.35, MeOH), mp 131-132°C, which was cyclized to the chloronucleoside derivative **7**[9] (44% yield), $[\alpha]_D$ -27.8°(*c* 0.51, MeOH), mp 119-120°C, with triethyl orthoformate / p-toluenesulphonic acid in DMF. Finally the compound **7** was converted to the target isoaristeromycin (**1**)[10] by heating with a solution of ammonia in MeOH (80% yield).

Though the INC reaction could have afforded either a six-membered or a five-membered isoxazolidine (or a mixture of the two) depending upon the mode of cyclization,[4] the structure **4** was preferred due to the location of a triplet at δ 70.0 in the ^{13}C NMR spectrum indicating the presence of -CH_2O- linkage. The stereochemistry of C-2, C-3 and C-4 in **4** are the same as the corresponding carbons in D-glucose since these centers are not disturbed during the reaction sequence, and the *cis* ring juncture is energetically favored in case of bicyclo[3.3.0]octane[11] system, but the relative disposition of H-1 and H-2 could not be settled from the ^1H NMR spectrum due to signal overlap. However, reduction of **4** followed by acetylation afforded **8**, in the NMR spectrum of which the signal at δ 4.42 (td, *J*=10 and 7 Hz) changed on D_2O exchange into a clear triplet of *J*=10 Hz (with disappearance of the doublet of *J*=7 Hz at δ 6.12), showing that it must be due to H-1 with both $J_{1,2}$ and $J_{1,5}$ =10 Hz. The other signals could thereafter be assigned using chemical shift and coupling constant values. Further, attempted vicinal cleavage of derived amino-alcohol **5** with $NaIO_4$ proved unsuccessful, indicating that C_1-NH_2 and C_2-OH must be *trans*. Inspection of a Dreiding model revealed that the compound **8** is likely to assume an envelope conformation with C_2 at the tip; the NHAc, 2-OAc and OTs groups assume the energetically preferred equatorial conformation and the other substituents are in isoclinal position. The coupling constants are then in agreement with the observed dihedral angles.

This synthetic route provides an efficient method for the formation of a single diastereoisomer **4** from INC reaction on an appropriate substrate.



Scheme 1. **a**, HOAc (60%), 55°C, 7h; **b**, $NaIO_4$ (1.3 eq), EtOH, rt, 30 min; **c**, $Ph_3P^+CH_3I^-$ (1.9 eq), *n*-BuLi (1.6 M), -60°C; **d**, H_2SO_4 (4%) in CH_3CN-H_2O, 60-65°C, 2.5 h; **e**, $PhCH_2NHOH$ (1.2 eq), dry EtOH, rt,24h; **f**, $LiAlH_4$ (3.2 eq), THF, reflux, 3h; **g**, Pd/C (10%), cyclohexene, EtOH, 4h; **h**, 5-amino-4, 6-dichloropyrimidine (1.56 eq), Et_3N (4.6 eq), *n*-BuOH, reflux, 18h; **i**, HC(OEt)$_3$, *p*-TSA (1.5 eq), DMF, rt, 24h; **j**, NH_3 (satd.), MeOH,100°C, 48h; **k**, Ac_2O/Py, rt,12h

It is versatile and flexible for synthesizing chiral aminocarbocycles and consequently, nucleoside analogues.

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References and Notes

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7. **3**: mp 72-73°C(Pet. ether); $[\alpha]_D$ -49.9°(*c* 0.46, $CHCl_3$); IR(KBr): 1649, 1596, 745, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.28(s, 3H), 1.47(s, 3H), 2.44(s, 3H), 4.62(dd, 1H, *J*=6.5, 2.7 Hz), 4.69(d, 1H, *J*=3.7 Hz),4.73(d, 1H, *J*=2.9 Hz), 5.17(d, 1H, *J*=10.4 Hz), 5.30(d, 1H, *J*=17.3 Hz), 5.63(ddd, 1H, *J*=17.3, 10.4, 6.5 Hz), 5.93(d, 1H, *J*=3.7 Hz), 7.34 (d, 2H, *J*=8 Hz), 7.76(d, 2H, *J*=8 Hz); EIMS, *m/z*: 324 (M^+-16), 214,155, 91.
8. **4**: mp 142-143°C; $[\alpha]_D$ +12.1°(*c* 1.12, MeOH); IR(KBr): 3492, 1599, 661 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.42(s, 3H), 2.92(m, 1H), 3.37(t-like, 1H), 3.50(brs, 1H), 3.68 (d, 1H, *J*=13 Hz), 3.78 (dd, 1H, *J*=1.8, 9.2 Hz), 4.02(m, 4H), 4.27(t , 1H, *J*=8 Hz), 7.30(m, 7H), 7.81(d, 2H, *J*=8Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.7(q), 59.4(t), 70.0(t), 49.2(d), 70.8(d), 75.6(d), 76.6(d), 89.2(d), 127.6 (d), 128.2 (2xd), 128.5 (2xd), 129.0 (2xd), 130.0 (2xd), 132.0 (s), 136.2(s), 145.4(s); EIMS, *m/z:* 405(M^+), 92.
9. All the new compounds have been well characterized and gave satisfactory elemental analysis.
10. **1**: mp 155-156°C; $[\alpha]_D$ -24.9° (*c* 0.42, MeOH); IR (KBr): 3352 cm^{-1}; ^1H NMR (D_2O, 100 MHz): δ 1.50-1.94(m, 1H), 2.42-2.86(m, 2H), 3.32(d, 2H, *J*=6 Hz), 4.28(brq, 1H, *J*=6 Hz), 4.78-5.14(m, 2H), 8.20(s, 1H), 8.24(s, 1H); ^{13}C NMR (D_2O, 25 MHz): δ 40.8, 50.4, 60.0, 63.1, 71.1, 72.6, 119.1, 142.1, 150.4, 153.1, 156.0; FAB MS, *m/z*: 266(M^++1).
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