# Expeditious Synthesis of Aminocyclopentitols from D-Ribose *via* Intramolecular Nitrone Cycloaddition[1]

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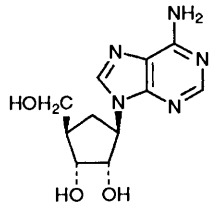
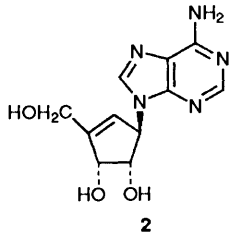
The synthesis of 4α-aminocyclopentane-1α,2β,3β-triol (a key-intermediate in the preparation of carbocyclic nucleosides) and its *N*-substituted derivatives, has been achieved by the intramolecular nitrone cycloadditions of a γ-unsaturated aldehyde, easily accessible from D-ribose, followed by reductive N–O bond cleavage in the resulting bicyclic oxazanes.

Modified nucleosides have received considerable attention over the last few years due to their remarkable antiviral and antitumour activities.[2] Among them, the carbocyclic nucleosides aristeromycin **1** and neplanocin A **2** have become the subject of many synthetic efforts.[2b,c] Furthermore, the synthetic analogue, noraristeromycin **3**, has recently been prepared and its strong antiviral properties evaluated.[3]



**1**



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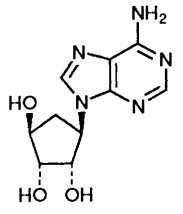

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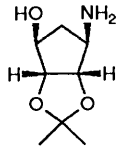


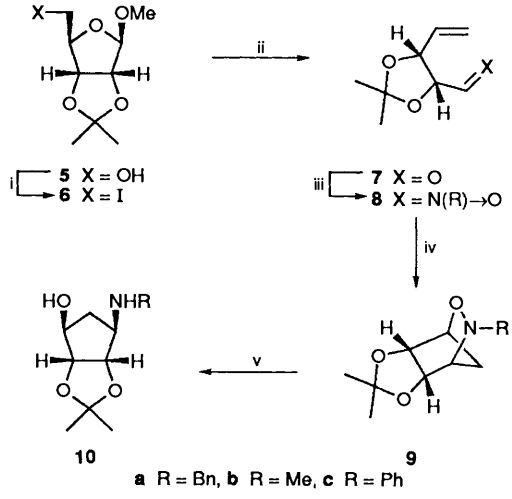
**4**

An important synthetic intermediate used in the synthesis of both noraristeromycin **3**[3] and neplanocin A **2**,[4] as well as other related purine carbocyclic nucleosides,[3] is the 2,3-*O*-isopropylidene derivative of 4-α-aminocyclopentane-1α,2β,3β-triol **4**. (±)-Neplanocin A **2** was first prepared in ten steps from the racemic compound **4** in 11% overall yield,[4] while (±)-noraristeromycin **3**[3] was synthesized in three steps from compound (±)-**4**. However, the amine **4** was not known in its enantiomerically pure form and this led other research groups to investigate alternative routes for the construction of the carbocyclic ring in optically pure form as well as the synthesis of a number of related carbocyclic nucleosides.[5] In one of these recent papers, (−)-neplanocin A **2** was prepared from the 2,3-*O*-isopropylidene derivatives of (−)-noraristeromycin **3**.[5e]

We report herein a concise synthesis of (−)-**4** in the correct enantiomeric form, which could further be used for the synthesis of several optically pure carbocyclic nucleosides, including (−)-neplanocin A **2** and (−)-noraristeromycin **3**, along with other *N*-substituted derivatives of compound **4**. Aminocyclopentitols are of considerable importance not only because of their structural similarity to carbocyclic nucleosides, but also because of their biological activity as glycosidase inhibitors.[6]

Since the amine **4** was prepared in its racemic form from (±)-**9** (R = H), our efforts focused on the synthesis of enantiomerically pure **9**, which could also be prepared from the correct enantiomer of the unsaturated aldehyde **7** by intramolecular nitrone cycloaddition.[7] It is known[8] that the desired, unprotected enantiomer of compound **7** is a degradation product of coenzyme $B_{12}$ and that the other stereoisomers of compound **7** are also known.[9]

The aldehyde **7** was easily prepared from the iodoribose derivative **6** utilizing the method developed by Vasella,[7a] by refluxing an ethanolic solution of compound **6** with activated zinc. After removal of the solids by filtration, the selected *N*-substituted hydroxylamine was added to give the respective nitrone **8**. No further cyclisation was observed by prolonged refluxing of the ethanolic solution of compound **8**, while poor yields of the desired product **9** were obtained when the solvent was replaced by refluxing xylene. Finally, the cyclisation was achieved in high yields by refluxing the nitrone **8** in chlorobenzene to yield the products **9a–c** which were isolated as single enantiomers.† Special care should be given to the activation of zinc, since this can dramatically affect the yields.[7a]




**Scheme 1** *Reagents and conditions:* i, $Ph_3P$, $I_2$, toluene, reflux, 1 h, 80%; ii, Zn, EtOH (95%), reflux, 1 h; iii, RNHOH, EtOH (95%), 15 min; iv, chlorobenzene, reflux, 30 min, 33–70% overall yields from **6**; v, Zn, $MeCO_2H$, diethyl ether, room temp., 48 h, 78–99%.

Thus, the synthesis of the desired bicyclic oxazanes **9** was achieved from compound **6** in virtually a one-pot procedure with very good overall yields, while the intermediates **7** and **8** need not be isolated and characterized. The isolation of the aldehyde **7** should be avoided since it is volatile.[9a] Compound **6**

† See footnote * on following page.

was readily available from D-ribose in two steps; by its protection to give compound **5**[10] followed by replacement of the primary hydroxy group by iodine. The corresponding bromide[11] (**6**, X = Br), gave lower yields of the desired products.

In the final step, the N–O bond of the bicyclic oxazanes (**9a–c**) was easily cleaved by activated zinc and acetic acid in diethyl ether[4] to give the *N*-substituted aminocyclitols (**10a–c**) in high yields.* The desired unsubstituted aminocyclitol **4** was prepared in 75% from the *N*-benzyloxazane **9a** by reduction with Pd/C (10%) in refluxing methanol for 1 h using ammonium formate as the hydrogen donor.[12] The overall yield from compound **5** to compound **4** was 37.2% in three steps.†

Since other stereoisomers of aldehyde **7** are also readily prepared,[9] the methodology reported here could be used for the synthesis of other stereoisomers of compounds **4** and **10**, including their antipodes.

## Experimental

*General Procedure for the Preparation of Bicyclic Oxazanes* **9** *from Compound* **6**.—To a well stirred solution of compound **6** (628 mg, 2 mmol) in EtOH 95% (10 $cm^3$) was added activated Zn[7a] (1.3 g, 20 mmol) and the mixture was refluxed for 1 h, while the reaction progress was monitored by TLC. The solids were then filtered off, RNHOH (2 mmol) or RNHOH·HCl (2 mmol) with $Na_2CO_3$ (1 g) were added and the mixture was stirred at room temp. for 15 min. The solvent was removed by evaporation and the resulting oil was dissolved in chlorobenzene (10 $cm^3$) and refluxed for 30 min. Column chromatography of the mixture on silica gel using ethyl acetate–hexane 1:2 as the eluent gave the desired compound **9**.*

* All new compounds gave satisfactory microanalyses or exact mass measurements. $[\alpha]_D$ Values are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. Compound **9a**: 62% yield from compound **6**, m.p. 126–128 °C ($CH_2Cl_2$–hexane), $[\alpha]_D$ = +87.7 (*c* 1.22 in $CHCl_3$). Compound **9b**: 70% yield from compound **6**, oil; $[\alpha]_D$ = +82.6 (*c* 0.92 in $CHCl_3$). Compound **9c**: 33% yield from compound **6**, m.p. 115–117 °C ($CH_2Cl_2$–hexane); $[\alpha]_D$ = +49.1 (*c* 1 in $CHCl_3$). Compound **10a**: oil, 78% yield; $[\alpha]_D$ = −2.3 (*c* 0.9 in $CHCl_3$). Compound **10b**: oil, 81% yield; $[\alpha]_D$ = +6.2 (*c* = 1 in $CHCl_3$). Compound **10c**: 99% yield; m.p. 119–121 °C; $[\alpha]_D$ +40 (*c* 1 in $CHCl_3$). Selected $^1H$ NMR data (*J*/Hz). Compound **9a**: $\delta_H(CDCl_3)$ 1.2 (3 H, s), 1.4 (3 H, s), 2.0 (2 H, s), 3.5 (1 H, s), 3.65 (1H, d, *J* 12), 4.05 (1 H, d, *J* 12), 4.2 (2 H, s), 4.4 (1 H, s) and 7.2 (5 H, s). Compound **10a**: $\delta_H(CDCl_3)$ 1.25 (3 H, s), 1.35 (3 H, s), 1.8 (1 H, d, *J* 14), 2.3 (1 H, dt, *J* 14 and 4), 3.25 (3 H br s), 3.75 (1 H, d, *J* 12), 3.8 (1 H, d, *J* 12), 3.9 (1 H, d, *J* 6), 4.2 (1 H, d, *J* 4), 4.45 (1 H, d, *J* 5), 4.65 (1 H, d, *J* 5) and 7.2 (5 H, s).

† Compound (−)**4** had spectra identical with those reported for the racemic one,[4] m.p. 85–88 °C; for (±)-**4**, lit.[4] m.p. 128 °C; $[\alpha]_D$ = −51.5 (*c* 0.33 in $CHCl_3$).

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