Stereoselective conversion of 2′,3′-dideoxydidehydro carbocyclic nucleosides into 2′-deoxy carbocyclic nucleosides

James V. Barkley,[a] Anupma Dhanda,[a] Lars J. S. Knutsen,[b]†‡ May-Britt Nielsen,[a] Stanley M. Roberts*[a]§ and David R. Varley[c]

[a] *Department of Chemistry, Liverpool University, Liverpool, UK L69 7ZD*
[b] *Novo-Nordisk A/S, Novo Nordisk Park, DK-2760, Malov, Denmark*
[c] *Department of Chemistry, Exeter University, Exeter, Devon, UK EX4 4QD*

Treatment of 2′,3′-dideoxydidehydro carbocyclic nucleosides 5–9 with *N*-bromoacetamide in AcOH gives bromoesters 10–14 with good stereocontrol: debromination and hydrolysis furnishes 2′-deoxy carbocyclic nucleosides, *e.g.* 22.

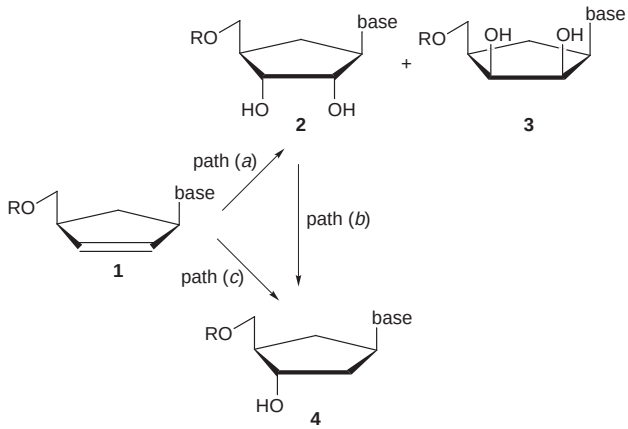
The preparation of 2′,3′-dideoxydidehydro carbocyclic nucleosides **1** (Scheme 1) has been the subject of a great deal of attention, owing to the biological activity of carbovir and related compounds.[1] The conversion of the readily-available alkenes of general stucture **1** into structurally more complex carbocyclic nucleosides **2** and 2′-deoxy carbocyclic nucleosides **4** has been fraught with difficulty. For example, bis-hydroxylation of compounds **1** tends to give an equimolar mixture of isomers corresponding to *ribo*- and *lyxo*-sugars **2** and **3**.[2] The preference for the formation of the carbocyclic *ribo*nucleoside on steric grounds is countered by a stabilizing Cieplak effect which favours formation of the *lyxo* analogues.[3]

Conversion of *ribo*-carbocyclic nucleosides **2** into 2′-deoxy *ribo*-carbocyclic nucleosides **4** [path (*b*)] through reaction of the diol with AcBr in MeCN and subsequent hydrodehalogenation is marred by the formation of the desired bromohyrins corresponding to the *ara*- and isomeric *xylo*-bromohydrins in an unfavourable 1 : 5 ratio.[4]

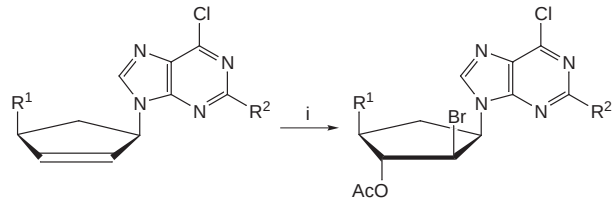
Direct conversion of carbocyclic nucleosides of type **1** into deoxy *ribo* systems of type **4** [path (*c*)] by hydroboration was investigated by Deardorff *et al.*;[5] unfortunately the 3′-hydroxy and the 2′-hydroxy compounds were both obtained, in a 2 : 1 ratio.

Herein we report a novel stereoselective method for the transformation of alkenes **1** into the corresponding alcohols **4**.

Most of the starting materials for this study (**5**, **6**, **8** and **9**) were prepared from (±)-*cis*-1-acetoxy-2-(acetoxymethyl)-cyclopent-4-ene; a typical procedure is described below. Compound **7** was prepared from compound **5**.¶



Scheme 1



5	$R^1 = CH_2OAc$, $R^2 = NH_2$	**10**
6	$R^1 = CH_2OAc$, $R^2 = H$	**11**
7	$R^1 = CH_2OAc$, $R^2 = Cl$	**12**
8	$R^1 = CH_2OCPh_3$, $R^2 = NH_2$	**13**
9	$R^1 = CH(OAc)CH_2OAc$, $R^2 = NH_2$	**14**

Scheme 2 *Reagents and conditions*: i, NBS or *N*-bromoacetamide, AgOAc, AcOH, 18 h, room temp.

Treatment of the cyclopentene derivative **5** with NBS or *N*-bromoacetamide and AgOAc in AcOH afforded bromoacetate **10** as the sole product in 68% yield (Scheme 2). This bromoester was recrystallized and the stereochemistry confirmed by X-ray crystallography (Fig. 1).‖

Similarly, compounds **6**–**8** produced the corresponding haloesters **11**–**13** in 47–69% yield.** In the latter case the NMR spectrum of the crude product, besides the major product **13**, gave evidence of a few percent of an isomeric product, in too small an amount to isolate. Treatment of the diester **9** under the standard reaction conditions afforded the expected product **14** (49%) [with spectroscopic properties in accord with the assignments for compounds **10**–**13** and an isomeric substance (13%)]. We tentatively assign a 2′-acetoxy-3′-bromo structure to the minor product on the basis of NMR spectroscopy.

The conversion of the alkenes **5**–**9** into the bromoesters **10**–**14** is reminiscent of the conversion of the cyclopentene

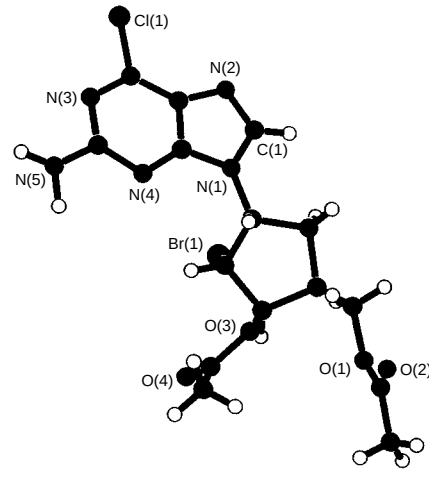
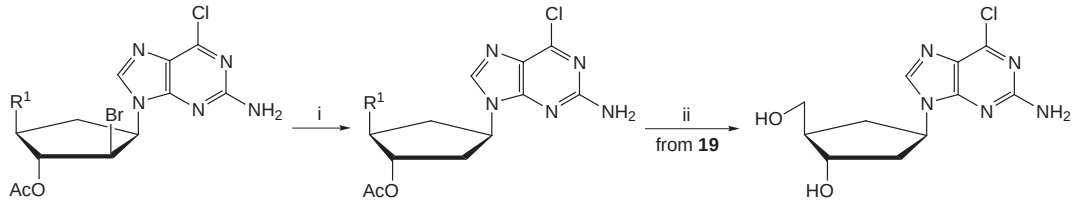


Fig. 1 X-Ray structure of compound **10**

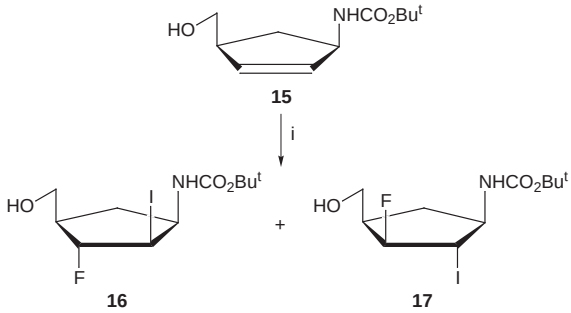


10 $R^1 = CH_2OAc$ **19**
14 $R^1 = CH(OAc)CH_2OAc$ **20**
18 $R^1 = CH_2OH$ **21**

22

Scheme 4 *Reagents and conditions*: i, Bu^n_3SnH, AIBN, THF, heat, 3–7 h (68–92%); ii, K_2CO_3, MeOH, 2 h (96%)

derivative **15** into the dihalides **16** and **17** (ratio 8 : 1) (Scheme 3), in that in both cases the major product is formed *via* the intermediacy of a *syn*-halonium ion.[6] However, the preferential formation of compound **16** was explained by a proposed stabilisation of the *syn*-iodonium ion by the adjacent hydroxy group, a phenomenon which is clearly impossible in our cases. Instead we believe that the formation of the *syn*- and *anti*-bromonium ions are reversible processes and only on formation of the *syn*-bromonium ion is attack by the nucleophile possible, from the more exposed face and distant from the heteroatom bonded to C-1′.



Scheme 3 *Reagents and conditions*: i, *N*-iodosuccinimide, tetrabutylammonium dihydrogen trifluoride, CH_2Cl_2

Detritylation of bromoester **13** was accomplished using aq. AcOH to furnish the alcohol **18** in 66% yield. Treatment of compounds **10**, **14** and **18** with tri-*n*-butyltin hydride in hot THF furnished the nucleoside analogues **19**–**21** (Scheme 4).‡‡ Methanolysis of the diester **19** provided the 2′-deoxycarbocyclic nucleoside in almost quantitative yield.

In summary, the stereocontrolled addition of Br/OAc to dideoxydidehydro carbocyclic nucleosides give facile access to 2′-bromo-2′-deoxyribo carbocyclic nucleosides.[7]

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Notes and References

† Present address, Cerebrus Ltd., Oakdene Court, 613 Reading Road, Winnersh, Wokingham, UK RG41 5UA.
‡ E-mail: l.knutsen@cerebrus.ltd.uk
§ E-mail: sj11@liverpool.ac.uk

¶ *Synthesis* of **5**. 2-Amino-6-chloro-9*H*-purine (264 mg, 1.56 mmol) and NaH (60% dispersed in mineral oil, 68 mg, 1.71 mmol) were dissolved in anhydrous DMF (7.0 ml) and stirred for 10 min at room temperature and at 50 °C for 10 min. The reaction mixture was added to a suspension of (±)-(1*R*,2*R*)-1-acetoxy-2-(acetoxymethyl)cyclopent-4-ene (339 mg, 1.71 mmol) and tetrakis(triphenylphosphine)palladium (180 mg, 0.156 mmol) in DMF (7.0 ml) using a cannula, rinsing with anhydrous THF (3 × 2.0 ml). The reaction was excluded from light and stirred for 3 h at 50 °C. The reaction mixture was then cooled to room temperature. Water (25 ml) was added and the mixture was extracted wtih CH_2Cl_2 (4 × 50 ml). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated *in vacuo* to give a crude yellow oil. The oil was purified by column chromatography on silica gel eluting with CH_2Cl_2–EtOH (19 : 1) giving **5** (50% yield) as a clear oil.

Synthesis of **7**. Compound **5** (224 mg, 0.728 mmol) was dissolved in CH_2Cl_2 (8 ml) and the solution was cooled to 0 °C. Me_3SiCl (276 μl, 2.184 mmol) was added followed by isopentyl nitrite (292 μl, 2.184 mmol) which was added slowly to maintain the temperature at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and for 5 h at room temperature. Water (5 ml) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were concentrated *in vacuo* to give a crude yellow oil. The oil was purified by column chromatography on silica gel eluting with EtOAc–light petroleum (2 : 1) giving **7** (60% yield) as a clear oil.

‖ *Crystal data* for **10**: $C_{15}H_{17}BrClN_5O_4$, M = 446.69, colourless prism, monoclinic, $P2_1/n$, 0.15 × 0.20 × 0.25 mm, a = 15.597(5), b = 7.077(2), c = 17.178(2) Å, β = 96.13(2)°, V = 1885.4 Å^3, T = −120 °C, Z = 4, μ(Mo-Kα) = 23.29 cm^{-1}; 3769 reflections measured, 3630 unique, R = 0.055, R_w = 0.080. CCDC 182/834.

** *Selected data* for **11**: δ_H(300 MHz; $CDCl_3$) 2.08 (s, 3 H, C*H*$_3$ of Ac), 2.17 (s, 3 H, C*H*$_3$ of Ac), 2.55 (m, 3 H, 2 × H-6′ and H-4′), 4.35 (m, 2 H, 2 × H-5′), 4.79 (m, 1 H, H-2′), 5.13 (m, 1 H, H-1′), 5.40 (m, 1 H, H-3′), 8.26 (s, 1 H, H-2), 8.70 (s, 1 H, H-8); δ_c(75 MHz; $CDCl_3$) 20.8 (CH_3, *C*H$_3$ of Ac), 20.9 (CH_3, *C*H$_3$ of Ac), 30.1 (CH_2, C-6′), 42.5 (CH, C-4′), 55.1 (CH, C-2′), 56.2 (CH, C-1′), 64.9 (CH_2, C-5′), 80.5 (CH, C-3′), 143.6 (CH), 150.8 (C), 151.6 (C), 152.0 (CH), 169.5 (C, C=O) and 170.7 (C, C=O).

†† *Selected data* for **19**: δ_H(400 MHz; $CDCl_3$) 1.98 (m, 1 H, H-6′), 2.08 (s, 3 H, C*H*$_3$ of Ac), 2.09 (s, 3 H, C*H*$_3$ of Ac), 2.30 (dd, 1 H, *J* 13 and 8, H-6′), 2.52–2.62 (m, 3 H, H-1′ and H-2′), 4.30 (m, 2 H, H-5′), 4.90 (m, 1 H, H-1′), 5.22 (m, 3 H, H-3′ and NH_2), 7.78 (s, 1 H, H-1′); δ_c(100 MHz; $CDCl_3$) 20.8 (CH_3, *C*H$_3$ of Ac), 21.1 (CH_3, *C*H$_3$ of Ac), 33.0 (CH_2, C-6′), 37.3 (CH, C-2′), 43.6 (CH, C-4′), 54.1 (CH, C-1′), 64.8 (CH, C-5′), 75.4 (CH, C-4′), 126.0 (CH, C-5), 140.9 (C, C-8), 151.6 (C, C-4), 153.4 (C, C-6), 158.7 (C, C-2), 170.3 (C, C=O) and 171.0 (C, C=O).

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