Carbohydrate Research, 110 (1982) C5–C8
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Preliminary communication

Coupling–elimination reactions of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid: synthesis of 2′-deoxyribo-*C*-nucleosides

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(Received August 10th, 1982; accepted for publication, September 1st, 1982)

2′-Deoxyribo-*C*-nucleosides are of considerable interest as potential antiviral and antitumour agents[1]. However, relatively few examples of this structural type have been reported and the number of direct synthetic procedures remains limited[1,2]. We now report a short, flexible route to a new class of bridgehead-nitrogen 2′-deoxyribo-*C*-nucleosides of general structure **1**. The basis of this synthesis, starting from a *ribosyl* precursor, is a novel coupling–elimination reaction[3] of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid (**2**) with aminoalkyl-substituted heterocycles.

Treatment of **2** with 2-chloro-*N*-methylpyridinium iodide[4] (2 equiv.) in the presence of triethylamine (3.5 equiv.) and 2-aminomethylpyridine (1.5 equiv.), in acetonitrile at room temperature, provided the α,β-unsaturated carboxamide **3** (73%), m.p. 95.5–97.5°, $[\alpha]_D^{21}$ +197° (*c* 1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.17 (d, $J_{3',4'}$ 3 Hz, H-3′). Similarly, when the heterocyclic amines **4**, **5**[5], and **6**[6] were used in place of 2-aminomethylpyridine, the corresponding amides **7** {52%, m.p. 143–144°, $[\alpha]_D^{25}$ +180.5° (*c* 1.6, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.18 (d, $J_{3',4'}$ 3 Hz, H-3′)}; **8** [61%, m.p. 144–145°, ^{1}H-n.m.r. ($CDCl_3$): δ 6.16 (d, $J_{3',4'}$ 3 Hz, H-3′)]; and **9** [51%, gum, ^{1}H-n.m.r. ($CDCl_3$): δ ~6.15 (m, H-3′), mixture of diastereoisomers] were obtained.

Intermediates **3** and **7** are used here to exemplify the synthesis of 2′-deoxyribo-*C*-nucleosides. Thus, hydrogenation (Pd/C, 1 atm., ethyl acetate) of **3** followed by cyclisation using phosphorus oxychloride–pyridine in 1,2-dichloroethane (reflux, 3 h) gave an anomeric mixture (~1:1) of the 3′,5′-dibenzoates **10** (47% from **3**), which were readily separated by a single crystallisation. The α anomer of **10** had m.p. 153–157°, $[\alpha]_D^{21}$ +132° (*c* 2.6, chloroform); the β anomer was a fawn gum, $[\alpha]_D^{21}$ −87° (*c* 2.5, chloroform). Debenzoylation (methanolic ammonia) of each anomer afforded 3-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[1,5-a]pyridine (**11b**; 66%, colourless foam) and the α anomer **11a** (66%, m.p. 133–136°). A similar reaction sequence applied to **7** gave an anomeric mixture (~1:1) of

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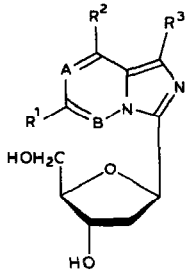
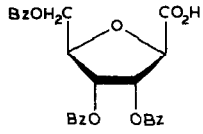


1 A, B = CH, N



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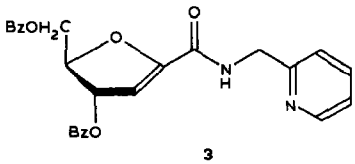

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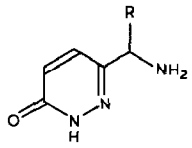
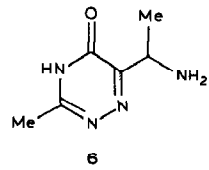


4 R = H

5 R = Me



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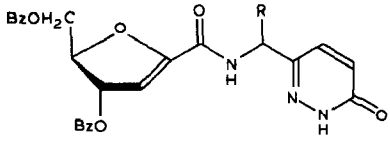
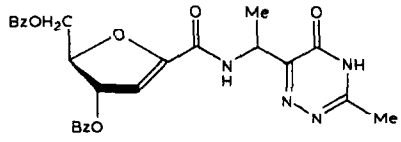


7 R = H

8 R = Me



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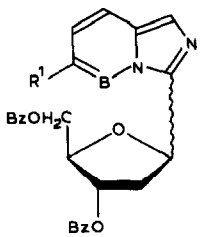
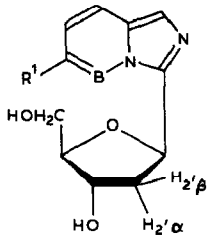
12 (48%). Concomitant chlorination occurred at the cyclisation stage. The mixture was debenzoylated to give 70% of 2-chloro-7-(2-deoxy-α- and -β-D-*erythro*-pentofuranosyl)-imidazo[1,5-b]pyridazines **13a**, m.p. 137–139°, and **13b**, m.p. 106.5–110.5°, which were readily separated by column chromatography on silica gel.



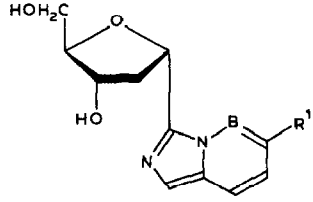
10 R^1 = H, B = CH

12 R^1 = Cl, B = N



11 b R^1 = H, B = CH

13 b R^1 = Cl, B = N



11a R^1 = H, B = CH

13a R^1 = Cl, B = N

Assignment of the anomeric configuration to **11a**, **11b**, **13a**, and **13b** was made on the basis of proton n.O.e. data at 250 MHz, since the differences in chemical shifts and vicinal coupling constants of the 2′-deoxyribosyl protons are not interpretable with certainty (Tables I and II). To our knowledge, this represents the first use of this technique to assign unequivocally anomeric configurations of 2′-deoxyribonucleosides. All new compounds had analytical/m.s. and n.m.r. spectral data consistent with the assigned structures.

TABLE I

N.O.E. DATA[a] FOR IRRADIATION OF H-1′

	11a	11b
H-2′α	6.6%	5%[b]
H-2′β		–
H-3′	3.3%	–
H-4′	–	4%

[a] Using the n.O.e. difference method and a Bruker WM 250 spectrometer. [b] Confirms assignment of H-2′α and H-2′β.

TABLE II

^{1}H-N.M.R. CHEMICAL SHIFTS[a] (δ) AND COUPLING CONSTANTS[b] (Hz)

	H-1′	*H-2′α*	*H-2′β*	*H-3′*	*H-4′*	$J_{1',2'\alpha}$	$J_{1',2'\beta}$	$J_{2'\alpha,3'}$	$J_{2'\beta,3'}$	$J_{3',4'}$
11a	5.52	2.55	2.55	4.27	3.72	6	6	6	6	6
13a	5.60	2.55	2.55	4.19	3.75	6	6	6	6	6
11b	5.55	2.12	2.73	4.35	3.88	6	10	2	5.5	2
13b	5.62	2.12	2.72	4.34	3.85	6	10	2	5.5	2

[a] Recorded at 250 MHz for solutions in $(CD_3)_2SO$. [b] Measured from the spectra.

The methodology described herein can provide easy access to a wide range of novel, imidazo-fused 2′-deoxyribo-*C*-nucleosides of general structure **1**. Since (*i*) the mixtures of α and β anomers are readily separable and (*ii*) α anomers of nucleosides can exhibit interesting biological activity[7], the formation of both anomers is not considered detrimental to the synthetic sequence.

ACKNOWLEDGMENTS

We thank Dr. J. H. Hunt for optical rotations and Mr. S. Krolik for mass spectra.

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