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Synthesis of some 2,3′-anhydro and 3′-mesyl nucleosides

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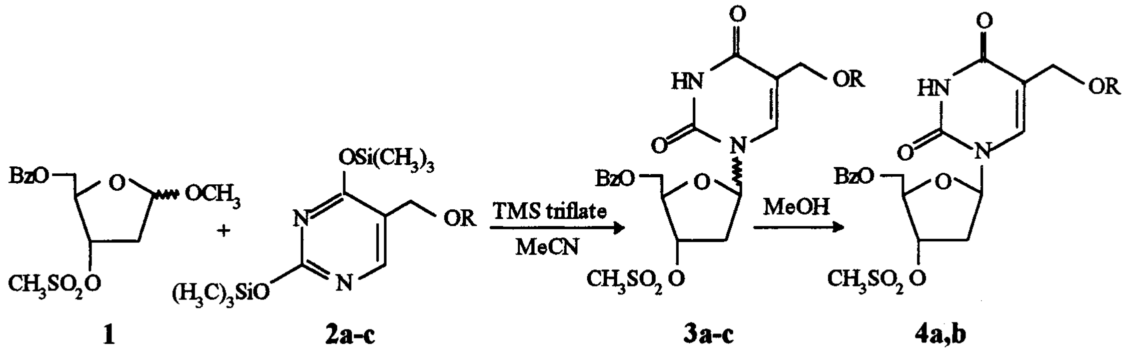
The reaction of sugar **1** with silylated 5-alkoxymethyluracils **2a-c** afforded **3a–c**. Compounds **5a–c, 6a,b, 7a–c** and **8c** were prepared. Treatment of **4a,b** with *tris* (1H-1,2,4-triazole-1-yl) phosphine oxide and subsequent reaction with ammonia in dioxane, then with sodium methoxide yielded **9a,b**.

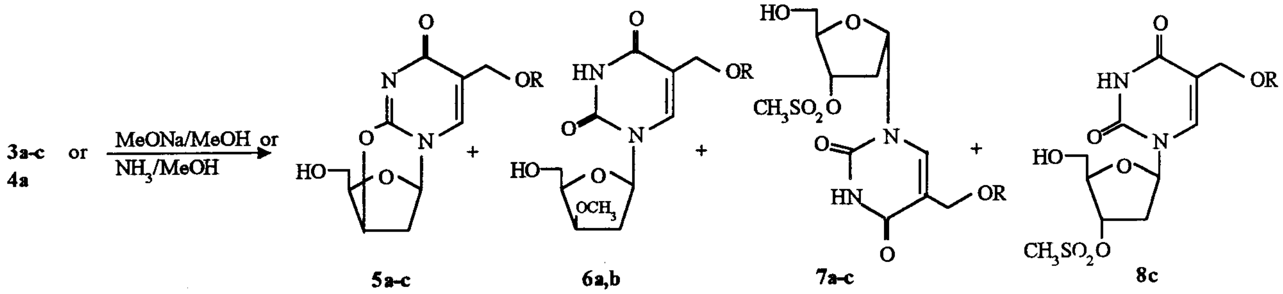
We have recently reported the condensation between methyl 5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-3-*O*-methanesulfonyl-D-erythro-pentofuranoside[7] and silylated thymine gave 1-(2,3-dideoxy-D-glycero-pent-2-enofuranosyl)thymine, 1-(2-deoxy-β-D-threo-pentofuranosyl)thymine and 1-(3,5-anhydro-2-deoxy-α-D-threo-pentofuranosyl)thymine after deprotection by using sodium methoxide in methanol. I decided instead to investigate the possibility of using benzoyl as a 5-*O*-protecting/leaving group. Treatment of 2-deoxy-D-ribose with HCl in methanol[8,9] followed by selective 5-*O*-protection with benzoyl chloride in dry pyridine and finally reaction with methanesulfonyl chloride in dry pyridine[7] to give 5-*O*-benzoyl-2-deoxy-3-*O*-methanesulfonyl-α,β-D-erythro-pentofuranoside **(1)**. In the synthesis of the nucleosides **3a–c**, I used the Friedel-Crafts catalysed Silyl-Hilbert-Johnson reaction as modified by Vorbruggen *et al.*[10] Trimethylsilyl trifluoromethanesulfonate (TMS triflate) was added to a mixture of **1** and the silylated 5-alkoxymethyluracils **2a–c**[11,12] in anhydrous acetonitrile to give an anomeric mixture of the nucleosides **3a–c** in 53-76% yield (α:β=1:3). The β-anomers **4a,b** were obtained by crystallization of **3a,b** from methanol (Scheme 1).

Treatment of **3a,b** with a solution of sodium methoxide in methanol under reflux followed by chromatographic purification gave the deprotected 2,2′-anhydro nucleoside **5a** (34%) and **5b** (30%), the threo nucleoside **6a** (20%) and **6b** (25%) and the α-anomer of 3-*O*-methanesulfonyl nucleoside **7a** (15%) and **7b** (11%); whereas similar treatment of the β-anomer **4a** afforded the 2,3′-anhydro nucleoside **5a** (43%) and the threo nucleoside **6a** (33%). Treatment of the anomeric mixture **3c** with a 1:1 mixture of methanol and conc. ammonia at room temperature for 3h followed by chromatographic purification gave 2,2′-anhydro nucleoside **5c** (35%), the α-anomer of 3′-*O*-methanesulfonyl nucleoside **7c** (16%), and the β-anomer of 3′-*O*-methanesulfonyl nucleoside **8c** (11%) (Scheme 2).

4-(1H-1,2,4-triazol-1-yl)pyrimidin-2-one derivatives were prepared by treating **4a,b** with putative *tris*(1H-1,2,4-triazole-1-yl)phosphine oxide[13] in the presence of 1H-1,2,4-triazole and triethylamine in acetonitrile at room temperature.



Scheme 1



Scheme 2

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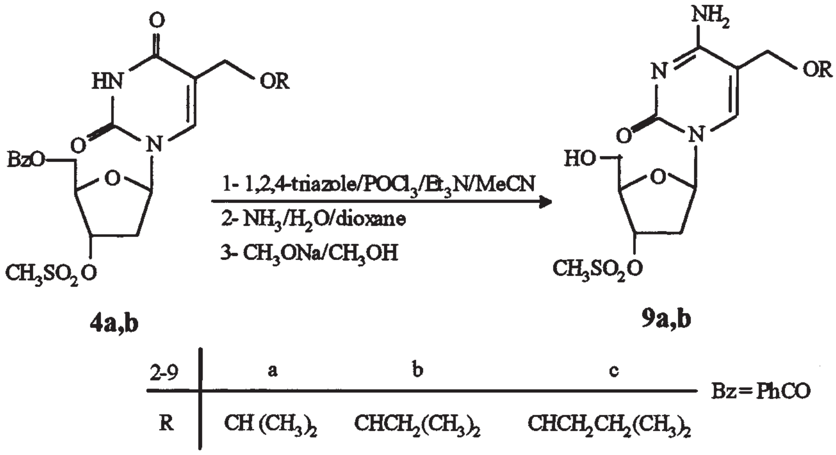
* To receive any correspondence.



Scheme 3

Reaction of the 4-triazol-1-yl derivatives with aqueous ammonia in dioxane solution yielded the cytosine derivatives, subsequent removal of the benzoyl group by treatment with sodium methoxide in methanol at room temperature and followed by chromatographic purification afforded the unprotected cytosine derivatives **9a,b** (34 and 32% from **4a,b**) (Scheme 3).

The β-anomer assignment of compound **3a–c** was made by comparison of ^{1}H and ^{13}C-NMR spectra with ^{1}H and ^{13}C-NMR spectra of 1-[5-*O*-(tert-butyldiphenylsilyl)-2-deoxy-3-*O*-methanesulfonyl-D-erythro-pentofuranosyl]thymine[7] and 1-(3-*O*-mesyl-5-*O*-trityl-2-deoxy-β-D- erythro-pentofuranosyl)-5-ethyluracil.[14] Also the assignment of compounds **5a-c** was made by comparison of ^{1}H-NMR and ^{13}C-NMR spectra with those of 2,3′-anhydro-1-(2-deoxy-β-threo-pentofuranosyluracil.[15] The ^{13}C-NMR spectra of **6a,b** showed the presence of a methoxide group at 55.27 and 55.18 ppm in accordance with the ^{13}C-NMR data reported by Jϕrgensen *et al.*[16]

Techniques used: mp. ^{1}H and ^{13}C NMR, mass spectrometry, microanalysis

References: 16

Schemes: 3

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