Synthesis of New Carbocyclic Analogues of 3′-Azido- and 3′-Amino-2′,3′-dideoxynucleosides

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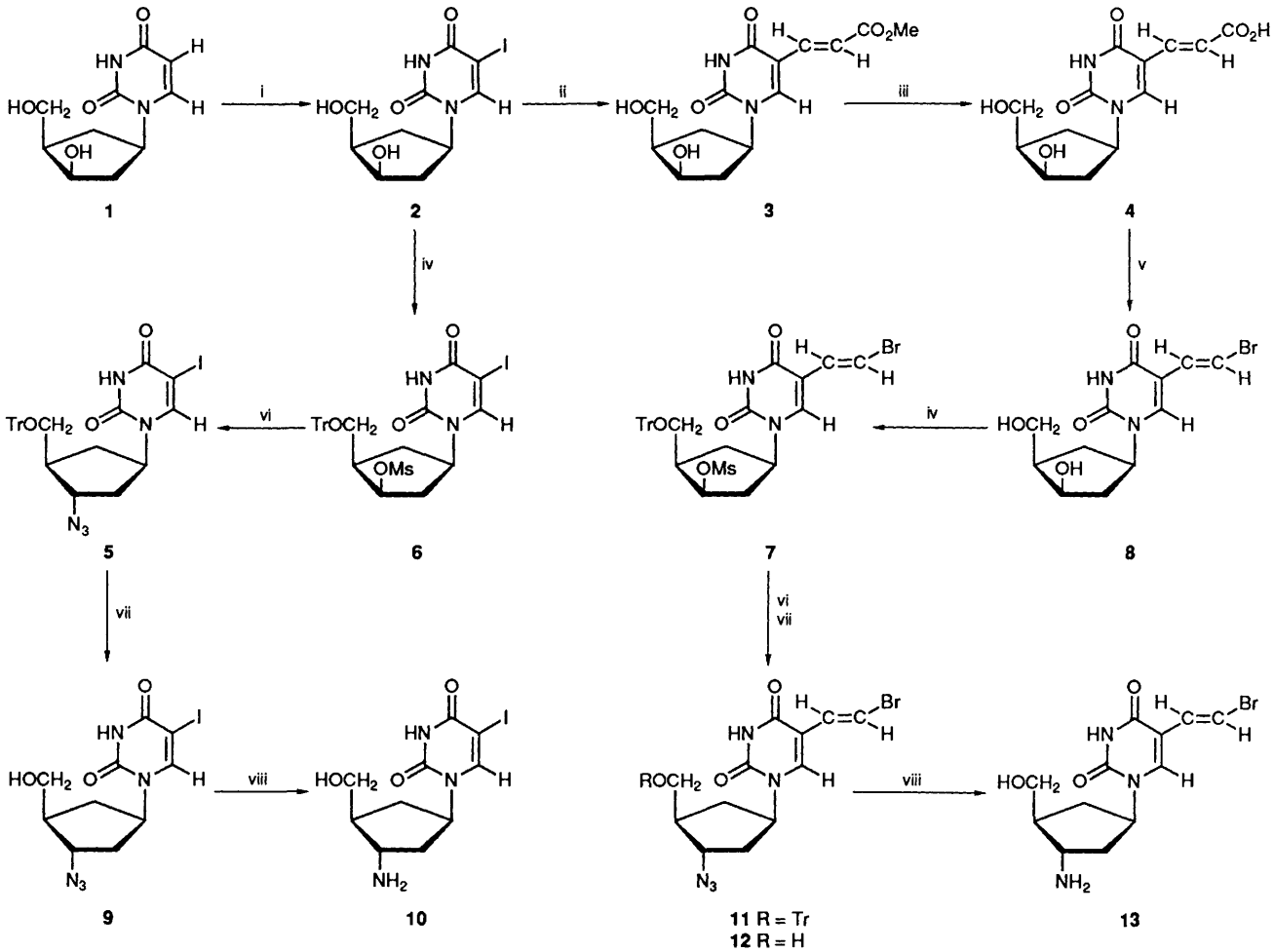
A route is described for the synthesis of cyclopentane analogues of 1-(3′-azido- and 3′-amino-2′,3′-dideoxy-β-*erythro*-pentofuranosyl)-5-iodouracil and -(*E*)-5-(2-bromovinyl)uracil, compounds of interest as potential antiviral and/or antitumour agents.

In a previous publication[1] we have described regiospecific routes for the preparation of cyclopentane analogues of (2′- and 3′-deoxy-*threo*-pentofuranosyl)nucleosides. Subsequently an alternative route for the preparation of the 2′-deoxy analogues was described[2] and applied to the synthesis of enantiomerically pure carbocyclic analogues.[3] This latter approach involves an enzymatic resolution of the racemate of one of the synthetic intermediates.[4] We have used (±)-1-[(1β,3β,4β)-3-hydroxy-4-(hydroxymethyl)cyclopentyl]-(1*H*,3*H*)-pyrimidine-2,4-dione **1**, prepared by our regiospecific route,[1] in the synthesis of novel carbocyclic analogues of nucleosides, in which an iodo or 2-bromovinyl group at the 5-position of the pyrimidine base and an amino or azido group at the 3′-position of the cyclopentane ring, were incorporated.



Tr = Ph_3C; Ms = $MeSO_2$

Scheme 1 *Reagents and conditions*: i, I_2, HNO_3, 1,4-dioxane, 100 °C, 1 h (**2**, m.p. 172–173 °C, 90%); ii, palladium(II) acetate, Ph_3P, Et_3N, 1,4-dioxane, methyl acrylate, 85 °C, 4 h (**3**, m.p. 200–202 °C, 64%); iii, 2 mol dm^{-3} KOH, room temp., 9 h, 4 °C, 24 h, acidified with conc. HCl to pH 2.0 {**4**, R_f 0.50 [8:1:1 (v/v/v) ethyl acetate–methanol–acetic acid], 71%}; iv, Ph_3CCl, pyridine, 80 °C, 2.5 h, cooled with an ice-bath and added methanesulphonyl chloride, room temp., 29 h {**6**, R_f 0.32 [3:2 (v/v) toluene–ethyl acetate], 90%, **7**, R_f 0.28 [2:1 (v/v) toluene–ethyl acetate], 80%}; v, DMF, $KHCO_3$, *N*-bromosuccinimide, room temp., 90 min (**8**, m.p. 183–185 °C decomp., 62%); vi, NaN_3, DMF, 85 °C, 2 h {**5**, R_f 0.35 [4:1 (v/v) toluene–ethyl acetate], 76%, **11**, R_f 0.46 [4:1 (v/v) toluene–ethyl acetate], 78%}; vii, 80% aqueous acetic acid, steam bath, 15 min {**9**, colourless, glassy solid, R_f 0.27 [2:3 (v/v) toluene–ethyl acetate], 83%, **12**, glassy solid, R_f 0.28 [1:1 (v/v) toluene–ethyl acetate], 89%}; viii, Ph_3P, pyridine, room temp., 6 h, then added 15 mol dm^{-3} ammonia, 4 °C overnight {**10**, m.p. 188–191 °C, decomp., 60%, **13**, white solid, R_f 0.46 [3:1:1 (v/v/v) acetonitrile–propan-2-ol–15 mol dm^{-3} ammonia], 94%}

Similar compounds having the pentofuranosyl ring, such as (*E*)-5-(2-bromovinyl)-3′-amino-2′,3′-dideoxyuridine, exhibit significant antiherpes activity,[5] and the 3′-azido derivative of 5-iodo-2′-deoxyuridine was shown recently to have significant antiviral activity against HIV (EC_{50} of 1.1 μmol dm^{-3}).[6] In addition, the carbocyclic analogue of (*E*)-5-(2-bromovinyl)-2′-deoxyuridine was shown to be a potent antiherpes agent.[7]

Compound **1** was converted first into the 5-iodo derivative **2**, in 90% yield, which in turn was transformed into the methyl acrylate derivative **3**, in the route towards the 2-bromovinyl compounds, using the procedure described by Herdewijn and coworkers.[8] Hydrolysis of **3** in 2 mol dm^{-3} KOH followed by acidification gave **4**, in 71% yield, which on treatment with *N*-bromosuccinimide in *N*,*N*-dimethylformamide (DMF) afforded the 2-bromovinyl compound **8** in 62% yield.

The 3′-position of **8**, and of **2**, were derivatized by similar methods. Treatment of **2** or **8** with trityl chloride in pyridine followed by addition of methanesulphonyl chloride provided **6** or **7** (in one-pot reactions) in 90 and 80% yield, respectively. Displacement of the methanesulphonyloxy group using sodium azide in DMF gave **5** or **11** in 76 and 78% yield, respectively. These intermediates were deprotected in 80% aqueous acetic acid to provide the 3′-azido analogues **9** and **12** in 83 and 89% yield, respectively. The azido group in each case was then reduced using triphenylphosphine in pyridine followed by treatment with ammonium hydroxide to give the 3′-amino compounds **10** and **13** in 60 and 93% yield, respectively.

All of the analyses on the above compounds, including NMR and UV absorption spectroscopy and elemental analyses, were consistent with the structures provided in Scheme 1. The above compounds are currently being investigated for antiviral and antitumour activities.

Our regiospecific syntheses[1] provide convenient approaches to useful intermediates such as compound **1**, utilizing readily available substrates and reagents. These compounds can be used in the preparation of the carbocyclic analogues of a wide variety of potentially interesting 3′-substituted-2′,3′-dideoxynucleosides utilizing the general synthetic approaches described in this communication.

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References

1 L. J. J. Hronowski and W. A. Szarek, *Can. J. Chem.*, 1985, **63**, 2787.
2 M. Bodenteich and H. Griengl, *Tetrahedron Lett.*, 1986, **27**, 4291.
3 M. Bodenteich, K. Faber, G. Penn and H. Griengl, *Nucleosides Nucleotides*, 1987, **6**, 233.
4 G. Eichberger, G. Penn, K. Faber and H. Griengl, *Tetrahedron Lett.*, 1986, **27**, 2843.
5 R. Busson, L. Colla, H. Vanderhaeghe and E. De Clercq, *Nucleic Acids Res. Symposium Ser.*, 1981, **9**, 49.
6 T.-S. Lin, J.-Y. Gao, R. F. Schinazi, C. K. Chu, J.-N. Xiang and W. H. Prusoff, *J. Med. Chem.*, 1988, **31**, 336.
7 R. C. Cookson, P. J. Dudfield, R. F. Newton, P. Ravenscroft, D. I. C. Scopes and J. M. Cameron, *Eur. J. Med. Chem.-Chim. Ther.*, 1985, **20**, 375.
8 P. Herdewijn, E. De Clercq, J. Balzarini and H. Vanderhaeghe, *J. Med. Chem.*, 1985, **28**, 550, and references therein.