COMMUNICATION

A novel stereo-controlled nucleobase exchange process for the synthesis of 2′-*C*-branched nucleosides

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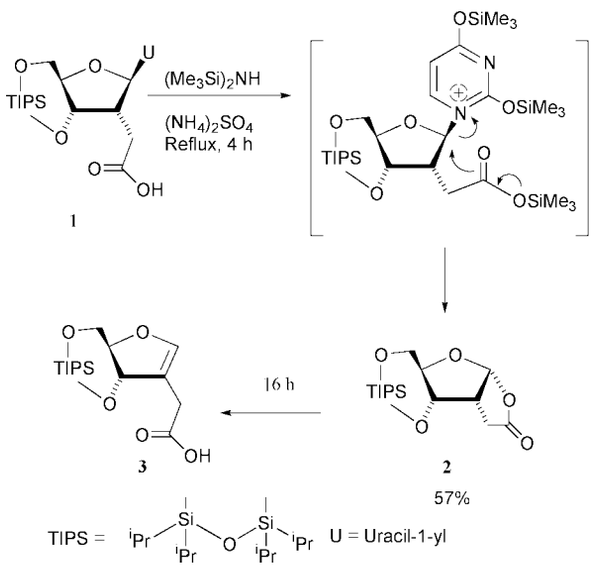
A novel stereo-controlled process is described which enables the uracil base on a 2′-deoxy-2′-α-*C*-carboxymethyl-uridine nucleoside to be exchanged for either a purine or another pyrimidine base, *via* the intermediacy of an isolable pentofuranosyl butyrolactone.

The development of methods for the stereo-controlled synthesis of β-nucleosides is of fundamental importance in the search for new antiviral and anticancer drugs.[1] In the case of ribonucleoside synthesis, stereochemistry at the anomeric centre can generally be controlled by neighbouring group participation (NGP) influenced through an acyloxy protecting group at the 2-position of the ribofuranoside moiety.[1,2] In comparison, the synthesis of deoxy- and dideoxy-ribonucleosides usually presents synthetic chemists with a considerably greater challenge as there is no general means of controlling anomeric configuration. Perversely though, it is the deoxy- and dideoxy-nucleosides which commonly show more potent biological activity, especially with regard to antiviral properties.[1,3] However, in recent years a number of innovative strategies for the preparation of the β-anomers of deoxy- and dideoxy-ribonucleosides have emerged. In one approach, the stereo-controlled delivery of the nucleobase is achieved by tethering it to the β-face of the sugar.[4] Other strategies have relied upon NGP by derivatising the ribose moiety with either a non-traceable substituent at the 2-position[5] or a suitable protecting group at the 3-position.[6] Very recently Lim and Kim[7] have shown that *C*-branched nucleosides can be prepared by ring opening of cyclopropanated sugars, although this procedure was not applicable to cytosine or purine bases.

We now wish to report a novel process which enables the uracil base on a 2′-α-*C*-carboxymethyl-2′-deoxyuridine nucleoside[8] to be exchanged, *via* the intermediacy of an isolable pentofuranosyl butyrolactone (**2**), for either a purine, or another pyrimidine base in a stereocontrolled manner. Given that a variety of *C*-branched nucleosides have been shown to exhibit potent antiviral activity[9] and that the 2′-*C*-carboxymethyl group can be readily manipulated, this base exchange procedure provides an efficient and divergent approach to a variety of potentially very interesting nucleoside analogues.

Previous work by Larson *et al.*[10] has established a facile route to furanoid glycals by elimination of the nucleobase from thymidine in a reaction that is induced by treatment with hexamethyldisilazane (HMDS), and essentially equates to the reverse of nucleoside synthesis. Based on this result, it was anticipated that treatment of 2′-deoxy-2′-α-*C*-carboxymethyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxy)uridine (**1**), under similar conditions, should lead to displacement of uracil by the carboxymethyl group resulting in the *cis*-fused pentofuranosyl butyrolactone (**2**) (as shown in Scheme 1). Opening of this lactone from the β-face by another nucleobase would then provide access to a variety of β-nucleosides.

Gratifyingly, reaction of the carboxymethyl nucleoside **1** with HMDS at reflux for 4 h, in the presence of ammonium sulfate, did indeed give the desired lactone **2** in 57% yield, following chromatography. The identity of this compound was confirmed by spectroscopic analysis. Importantly, compound **2** was shown



Scheme 1

to have a characteristic carbonyl stretch IR absorption (1785 cm^{-1}) whilst the ^1H NMR spectrum revealed that the 1-H proton was present as the expected doublet (5.97 ppm) and the ^{13}C NMR DEPT spectrum disclosed that the C2 possessed the required proton. Interestingly, prolonged reaction (16 h) converted the lactone into the isomeric unsaturated carboxylic acid **3**. In particular, the 1-H proton of compound **3** was shown to be a singlet (6.41 ppm) in the ^1H NMR spectrum.

We initially chose to examine the silyl variant of the Hilbert–Johnson method[11] for nucleoside synthesis developed by Vorbrüggen and Bennua,[12] as this procedure routinely uses glycosyl donors which are structurally analogous to lactone **2**. Bases were silylated by heating with HMDS in the presence of a catalytic quantity of ammonium sulfate. After removal of excess HMDS, an excess (~5 equiv.) of the silylated base was dissolved in acetonitrile and introduced into a solution of lactone **2**. Following addition of a Lewis acid the reaction mixture was stirred, under argon, at room temperature for 18–48 h. Although a variety of Lewis acids [$BF_3{\cdot}OEt_2$, $ZnCl_2$, $SnCl_4$, trimethylsilyl triflate (TMSOTf)] were investigated, significant quantities of nucleoside product were only obtained using tin(IV) chloride. Thus, nucleoside syntheses were performed with 2 equivalents of tin(IV) chloride, as described for Method A (Scheme 2). Yields using this procedure ranged from 69% for reaction with thymine (entry 2, Table 1) down to 17% for *N*-4-benzoylcytosine (entry 5).

In order to increase both the simplicity of the procedure and yield of the reaction, the widely used *in situ* silylation strategy[13] was investigated and once again a variety of Lewis acids were employed. Whilst the use of tin(IV) chloride gave yields that were comparable with Method A, the use of trimethylsilyl triflate both simplified product isolation and unexpectedly gave much improved yields. Thus, using this simplified procedure as

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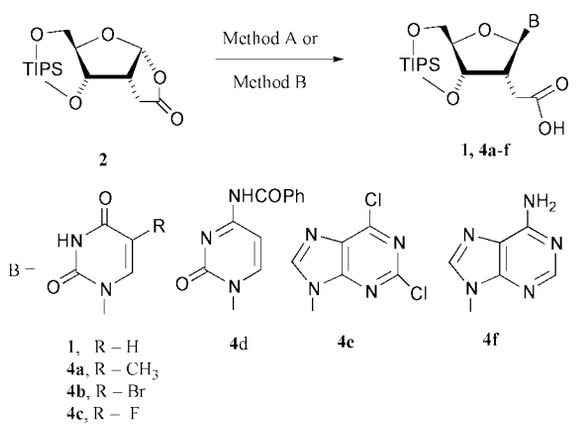
Table 1 Yields and reaction times for nucleoside syntheses

Entry	Nucleobase used	Method A		Method B	
		Time/h	Yield (%)	Yield (%)	Compound
1	Uracil	48	48	64	**1**
2	Thymine	48	69	79	**4a**
3	5-Bromouracil	48	46	69	**4b**
4	5-Fluorouracil	—	—	47	**4c**
5	*N*-4-Benzoylcytosine	48	17	58	**4d**
6	2,6-Dichloropurine	18	47	62	**4e**
7	Adenine	18	21	37	**4f**



Scheme 2 *Reagents and conditions*: Method A, CH_3CN, bis(trimethylsilylated) nucleobase (5 equiv.), $SnCl_4$ (2.3 equiv.), rt; Method B (see Experimental), CH_3CN, nucleobase (1.3 equiv.), HMDS (1.2 equiv.), TMSCl (1.2 equiv.), TMSOTf (3.3 equiv.), 0 °C to rt, 18 h.

described under Method B (Scheme 2 and Experimental) a wide range of nucleobases could be used to open the lactone in yields of up to 79% (Table 1).

Ring opening of lactone **2** with each of the nucleobases proceeded to give a single isolated nucleoside product with the expected β-configuration at the anomeric centre. Anomeric configuration was most readily confirmed by opening of lactone **2** with uracil to reform the original carboxymethyluridine nucleoside **1**. Compound **1** prepared in this fashion was identical to that of an authentic sample[8] and showed a characteristic doublet ($J_{1'\text{-}2'} = 2.5$ Hz) for 1′-H in the ^{1}H NMR spectrum.

With the purine nucleosides there exists the possibility of N7 and N9 regioisomers. N7 and N9 isomers are typically differentiated by characteristic downfield chemical shifts in the anomeric 1′-H and the purine 8-H resonances of the N7 isomer relative to those of the N9 isomer.[14] Whilst exactly the same 2′-carboxymethylpurine nucleosides reported here have not been previously prepared, we were able to compare ^{1}H NMR data for compound **4f** (8-H and 1′-H at 8.11 and 5.99 ppm respectively) with those reported[15] for the analogous 2′-allyl nucleoside (8-H and 1′-H at 8.32 and 5.96 ppm respectively). The very close proximity of the 1′-H chemical shifts and the upfield shift for 8-H in **4f** relative to its position in the allyl derivative are fully consistent with **4f** having the glycosidic bond to N9.

In summary, we have shown that the readily accessible *cis*-fused pentofuranosyl butyrolactone **2** undergoes completely stereoselective ring opening in the presence of nucleobases to give novel 2′-*C*-carboxymethyl β-nucleosides in moderate to high yield. The procedure is applicable to a variety of nucleobases and provides a very useful route to a diverse range of *C*-branched nucleosides.

Experimental

Typical procedure for nucleobase glycosylation using Method B for synthesis of 4a

To a stirred suspension of lactone **2** (0.6 mmol) and a nucleobase (0.9 mmol) in dry acetonitrile (10 ml) at 0 °C were added hexamethyldisilazane (0.72 mmol), chlorotrimethylsilane (0.72 mmol) and trimethylsilyl trifluoromethanesulfonate (2 mmol). The reaction mixture was allowed to warm up to room temperature and was stirred for further 18 hours. Then the clear solution was diluted with ethyl acetate (100 ml) and washed twice with aq. $NaHCO_3$ (30 ml) and brine (30 ml). After drying (Na_2SO_4) of the organic phase the solvent was removed under reduced pressure and the resulting oil was purified by column chromatography (chloroform containing an increasing gradient of methanol from 0–10%) to give the product as an amorphous white solid; R_f 0.42 (chloroform–methanol 9 : 1 v/v); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97–1.09 (28H, m, 4 ^{i}Pr), 1.93 (3H, s, CH_3), 2.46 (1H, dd, $J_{2',6'}$ 11.5, $J_{6',6''}$ 15.0, 6′-H), 2.72–2.78 (2H, m, 2′-H, 6″-H), 3.86 (1H, ddd, $J_{3',4'}$ 7.8, $J_{4',5'}$ 2.9, $J_{4',5''}$ 3.6, 4′-H), 4.03 (dd, 1H, $J_{5',5''}$ 12.9, 5′-H), 4.11 (dd, 1H, 5″-H), 4.51 (dd, 1H, $J_{2',3'}$ 7.8, 3′-H), 5.93 (1H, d, $J_{1',2'}$ 3.4, 1′-H), 7.41 (1H, s, 6-H), 10.88 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.5 (CH_3), 12.6–13.4 (4 *C*H[CH_3]$_2$), 16.9–17.4 (8 CH_3), 31.5 (C-6′), 45.9 (C-2′), 60.4 (C-5′), 69.1 (C-3′), 83.6 (C-4′), 88.4 (C-1′), 111.5 (C-5), 134.9 (C-6), 151.4 (C-2), 164.7 (C-4), 175.0 (C-7′); *m/z* (FAB+): 565 $[M + Na]^+$, 543 $[M + H]^+$. Found HRMS *m/z* $[M + Na]^+$: 565.2373, $C_{24}H_{42}N_2O_8Si_2$ requires $[M + Na]^+$: 565.2377; ε (266 nm) = 9850 in MeOH.

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