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A short synthesis of bicyclic sugar pyrimidine nucleosides from *C*-glycosides

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Abstract—The *C*-glycosides were prepared from dichloroketene cycloaddition reaction to glycals and converted to bicyclic sugar nucleosides in good yields.

Over recent decades much attention has been focused on the synthesis of nucleoside derivatives. Among them are *C*-branched sugar nucleosides,[1] bicyclic sugar nucleosides,[2] acyclic sugar nucleosides[3] and carbocyclic sugar nucleosides.[4] Many structural modifications on the ribose ring[3] of the nucleoside have been made to find molecules showing enhanced biological activities such as anti-HIV and anti-HBV. In this paper, we wish to present a synthesis of new nucleosides bearing a bicyclic sugar ring.

In the course of the synthesis of *C*-glycoside, we found that [2+2] cycloaddition of dichloroketene to glycal and subsequent chemical modification of the cyclobutanone intermediate would provide a very powerful and efficient protocol for the stereo- and regioselective introduction of functionalized alkyl chain on *C*-1 of glycoside.[5] With respect to the application of this protocol, it was envisioned that the *C*-branched glycoside from dichloroketene cycloaddition could provide a useful moiety of bicyclic sugar ring of nucleoside.

Our synthesis, as outlined in Scheme 1, begins with the preparation of lactol acetates **3**. Tri-*O*-benzyl-D-glucal (**1**) was treated with dichloroketene, generated in situ from a zinc–copper couple and trichloroacetyl chloride in ether, to give a labile dichlorocyclobutanone intermediate. The latter was further treated with zinc in acetic acid to afford dechlorinated cyclobutanone containing *C*-glycoside **2** in 90% for two steps. The cycloaddition of dichloroketene took place from the α face of glucal presumably due to the *C*-3 stereochemistry. Oxidation of **2** with mCPBA–$NaHCO_3$ in CH_2Cl_2 gave lactone, which was then reduced and acetylated to give lactol acetates **3** in 64%. The intermediates **3** were then subjected to *N*-glycosylation conditions[6] (uridine, potassium nonafluoro-1-butanesulfonate, 1,1,1,3,3,3-hexamethyldisilazane, chlorotrimethylsilane in acetonitrile) to afford α and β nucleosides in 34 and 57% yield, respectively. The total isolated yield of glycosylation is excellent, however, the bicyclic ring system and bulky tribenzyl groups did not play an important role in the stereoselectivity during *N*-glycosylation. The two isomers were separated by careful preparative TLC (CH_2Cl_2–ether, 3:1), and the fast moving isomer was found to be the β isomer by NOE. Irradiation of H-2′β (2.07 ppm) gave NOE on H-6 (7.95 ppm) and irradiation of H-2′α (2.59 ppm) did not show NOE on H-6. The stereochemistry was confirmed by irradiation of H-6 to give strong NOE on H-2′β and no NOE H-2′α. The conformational analysis, by NMR and X-ray technology, of ribose and deoxyribose ring of nucleosides has been a subtle subject in nucleoside synthesis.[2d–g,7] Based on relatively small coupling constants between H-1′ and H-2′β (2.1 and 3.1 Hz, respectively), furanose part of our bicyclic sugar in **5** and **6** are unlikely to have *S*-conformation. However, more systematic study is necessary to figure out the major conformation of our bicyclic sugar to understand the relationship between the conformations and activities of **5** and **6**.

The synthesis of bicyclic nucleoside was completed by deblocking (H_2, Pd/C, 1N HCl, MeOH) of three hydroxyl groups to give **6** in 80% yield.[8] Nucleoside **6**

Keywords: *C*-glycoside; dichloroketene cycloaddition; glycal; bicyclic sugar nucleoside.

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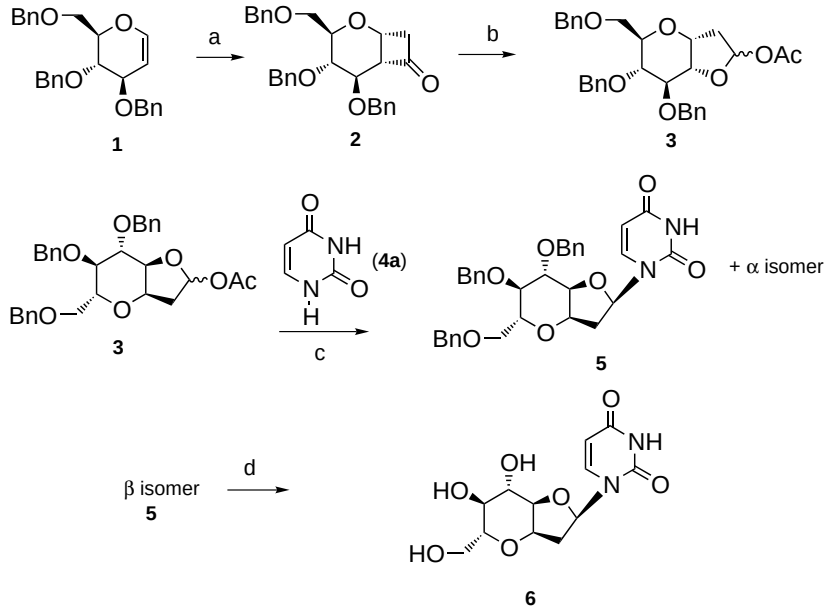

Scheme 1. *Reagents and conditions*: (a) trichloroacetylchloride, Zn(Cu), ether, 0°C, 30 min; Zn, AcOH, 5 h, 90%; (b) mCPBA, $NaHCO_3$, 0°C, N_2, CH_2Cl_2, 1 h; DIBALH, CH_2Cl_2, −78°C, N_2, 15 min; Ac_2O, −78°C to rt, 8 h, 64%; (c) uracil, potassium nonafluoro-1-butanesulfonate, 1,1,1,3,3,3-hexamethyldisilazane, TMSCl, acetonitrile, rt, 30 min; (d) H_2, Pd/C (3%). 1N HCl, MeOH, 6 h, 80%.

Table 1. Summary of *N*-glycosylation yield

	4a	**4b**	**4c**
3	β isomer: 57% α isomer: 34%	98% mixture of α and β	71% mixture of α and β
7	β isomer: 57% α isomer: 31%	β isomer: 44% α isomer: 42%	β isomer: 23% α isomer: 27%

has a unique structure, i.e. a deoxyribose unit bearing a glucose subunit.

As outlined in Table 1, thymine (**4b**) and 5-fluorouracil (**4c**), however, gave an inseparable mixture of two isomers in 98 and 71% yield, respectively. Lactol acetates **7**, prepared from tri-*O*-benzyl-D-galactal following the same procedure for compounds **3** in comparable yields, were also subjected under glycosylation conditions with three bases (**4a**, **4b**, **4c**) to afford bicyclic sugar ring nucleosides bearing galactose stereochemistry on the bicyclic sugar ring moiety in moderate yields and stereoselectivity.

In conclusion, we successfully demonstrated the synthesis of novel bicyclic sugar nucleosides bearing glucose and galactose moieties on the deoxy ribose ring in good yields from *C*-glycosides, which were prepared from dichloroketene cycloaddition to glycals.

Acknowledgements

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8. Selected spectral data for compound **5β**: IR 1694 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) 2.07 (1H, m), 2.59 (1H, m), 3.57 (1H, m), 3.73 (2H, m), 3.95 (2H, m), 4.02 (1H, m), 4.23 (1H, m), 4.20–4.74 (6H, 3×ABq, 3×CH_2), 5.41 (1H, d, $J=8.1$ Hz), 6.22 (1H, dd, $J=2.1$, 8.2 Hz), 7.95 (91H, d, $J=8.1$ Hz), 9.57 (1H, br s, NH). Compound **5α**: IR 1687 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) 2.17 (1H, m), 2.57 (1H, m), 3.59 (2H, m), 3.77 (2H, m), 3.85 (1H, m), 4.53–4.36 (4H, m), 4.85–4.70 (4H, m), 5.73 (1H, dd, $J=$ 2.0, 8.1 Hz), 6.14 (1H, t, $J=6.4$ Hz), 7.36–7.20 (16H, m), 9.34 (1H, br s). Compound **6**: ^1H NMR (300 MHz, D_2O) δ 2.24 (1H, d, $J=15.2$ Hz), 2.281 (1H, m), 3.63 (1H, m), 3.79 (2H, m), 3.95 (2H, m), 4.10 (1H, t, $J=4.5$ Hz), 4.66 (1H, m), 5.92 (1H, d, $J=8.1$ Hz), 6.24 (1H, dd, $J=3.5$, 8.0 Hz), 8.07 (1H, d, $J=8.1$ Hz).