Synthesis of (*t*-2-Benzyloxymethyl-*t*-3-hydroxy-*r*-1-methoxycarbonyl)-tetrahydrofuran from an *arabino*-Lactone Triflate with K_2CO_3–MeOH

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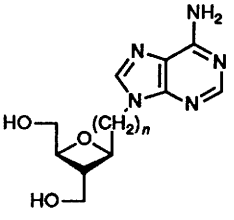
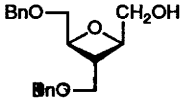
The *arabino*-lactone triflate **4** reacts with K_2CO_3 in MeOH to give the oxetane ester **5** and the tetrahydrofuran ester **6** in a ratio dependent upon the reaction temperature.

Oxetanocin-A **1**,[1] which contains an unprecedented oxetanosyl-*N*-glycoside linkage, inhibits the *in vitro* replication of human immunodeficiency virus (HIV), the causative agent of AIDS. Amongst the many structural types, C-nucleosides are of special interest, since they are not susceptible to degradation *in vivo* by nucleosidases and phosphorylases, and have, therefore, attracted much attention from both a synthetic and a biological viewpoint. As part of continuing studies on the preparation and antiviral evaluation of analogues of **1**, we needed the compound *t*-2, *c*-3-bisbenzyloxymethyl-*r*-1-hydroxymethyloxetane **2** on a large scale in order to make various oxetanosyl homonucleosides **3**, a sort of oxetanosyl C-nucleoside. Two groups have synthesized compound **2** with different approaches.[2,3] Fleet *et al.* reported that the *arabino*-lactone triflate **4** reacted with K_2CO_3 in MeOH at room temperature to give the oxetane ester **5** (57%) as the sole product. In this communication, we report the result of our re-examination of ring transformation reaction of **4**.



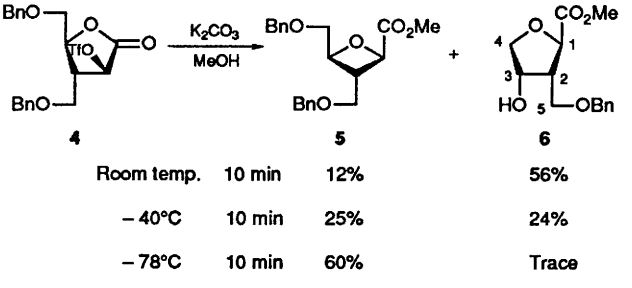
1 $n = 0$
3 $n = 1$



2

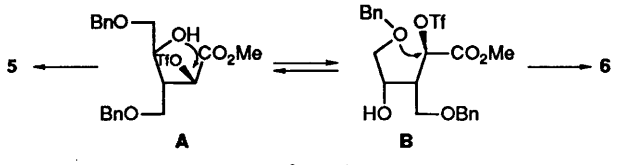
The *arabino*-lactone triflate **4**† when treated with K_2CO_3 in MeOH at room temperature, gave two cyclic compounds, the oxetane ester **5** (12%) and a new compound, the tetrahydrofuran ester **6** (56%).‡ The ratio of the yields of **5** to **6** was markedly dependent upon the reaction temperature (Scheme 1). Thus, when the reaction was conducted at −40 °C, the yields of the two compounds were 25 and 24%, respectively and at −78 °C, **5** predominated (60%). This work demonstrates that intramolecular cyclization to give an oxetane ring occurs *via* transition state **A** at −78 °C and *via* the transition state **B** to give a tetrahydrofuran ring at room temperature (Scheme 2).§

Curiously, however, treatment of the *ribono*-lactone triflate **7**



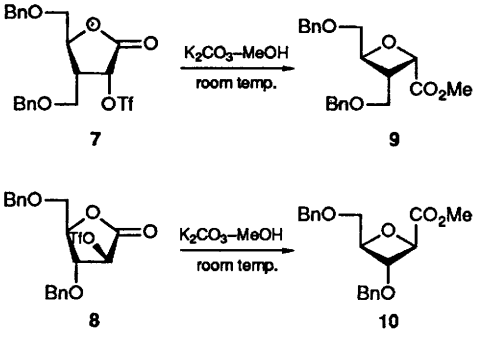
Room temp.	10 min	12%	56%
−40°C	10 min	25%	24%
−78°C	10 min	60%	Trace

Scheme 1



Scheme 2

and the *arabino*-lactone triflate **8** with K_2CO_3 in MeOH at room temperature *under the same reaction conditions* afforded the oxetane esters **9** (51%) and **10** (57%) but no tetrahydrofuran ester compound (Scheme 3).[5]



Scheme 3

Reduction of **5** thus obtained with $LiAlH_4$ (THF, room temp., 2 h) followed by mesylation (MsCl, Et_3N CH_2Cl_2, room temp., 1 h) gave the mesylate (94%, 2 steps). Subsequent condensation of the latter with the sodium salt of nucleic bases in DMF (80 °C, 20 h) followed by hydrogenolysis using catalytic

† Since compound **4** is not stable at room temperature it should be stored in a refrigerator. In the absence of K_2CO_3 **4** in absolute methanol afforded no detectable product after 1 h at room temperature.

‡ This result is inconsistent with that of the previous paper[3] and the details of the experimental and theoretical aspects of cyclization mode of compounds **4**, **7** and **8** to give the oxetane ester and/or the tetrahydrofuran ester under basic conditions have yet to be clarified.

§ We thank one of the referees for the commenting that although formation of the kinetically preferred tetrahydrofuran ring does not require base, formation of the oxetane ring base does.

hydrogen transfer [20% $Pd(OH)_2$, cyclohexene–EtOH, reflux, 20 h] provided oxetanosyl homonucleosides **3** (B = adenine, guanine, uracil, 5-FU, thymine and cytosine) (24–36%, 2 steps).

Biological Data.—The oxetanosyl homonucleoside analogues were evaluated for activity against representative RNA and DNA viruses in cell cultures. At concentrations < 10 μg cm^{-3} (100 μg cm^{-3} against HIV-1), no inhibition of replication was observed against HSV-1, HSV-2, cytomegalovirus cells and HIV-1. At the concentrations examined, none of the compounds was toxic to the cell monolayer.

Experimental

Synthesis of the Oxetane Ester **5** *and Tetrahydrofuran Ester* **6** *at Room Temperature.*—A solution of the *arabino*-lactone triflate **4** (313 mg, 0.446 mmol) in absolute methanol (distilled

Acetate of **6** (acetic anhydride–pyridine) (Found: C, 62.6; H, 6.3. $C_{16}H_{20}O_6$ requires C, 62.32; H, 6.54%); m/z 308 (M^+); ν_{max}(film)/cm^{-1} 1740 and 1500; δ_H(400 MHz; $CDCl_3$) 1.99 (3 H, s, 3-AcO), 2.80 (1 H, m, 2-H), 3.63–3.72 (2 H, complex, 5-H), 3.74 (3 H, s, 1-CO_2Me), 3.98 (1 H, d, J 10.7, 4-H), 4.17 (1 H, dd, J 10.7 and 3.4, 4-H), 4.45 (1 H, d, J 12.2, PhCH*H*), 4.31 (1 H, d, J 9.8, 1-H), 4.55 (1 H, d, J 12.2, PhCH*H*), 5.45 (1 H, m, 3-H) and 7.32 (5 H, complex, Ph).

Synthesis of **5** *at* −78 °C.—A solution of **4** (4.66 g, 9.83 mmol) in absolute methanol (10 cm^3) was added dropwise to a suspended solution of powdered potassium carbonate (2.0 g, 14.47 mmol) in absolute methanol (60 cm^3) at −78 °C under an argon atmosphere. After being stirred for 30 min, the reaction mixture was poured onto ice–water and extracted with ethyl acetate (50 cm^3 × 3). The extracts were washed, dried