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SYNTHETIC STUDIES ON OXETANOCIN ANALOGS: SYNTHESIS OF OXETANOSYL C-NUCLEOSIDE, 2-DEOXY-2-HYDROXYMETHYL-β-D-ERYTHROOXETANOSYL MALEIMIDE

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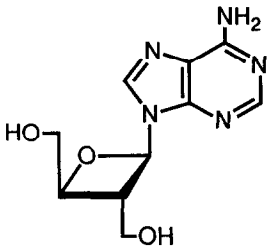
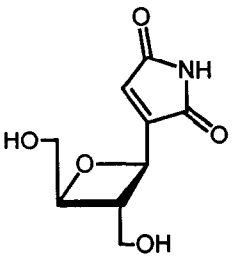
Summary: Synthesis of oxetanosyl C-nucleoside similar to showdomycin, 2-deoxy-2-hydroxymethyl-β-D-erythrooxetanosyl maleimide has successfully been carried out starting from the potent intermediate of oxetanocin synthesis.

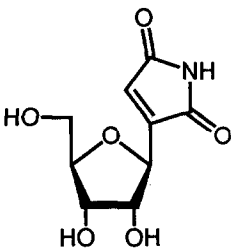
Related to a novel antiviral antibiotic oxetanocin (**1**),[1] our attention was focused on synthesis of its analogs and their biological activities. As a part of this investigation, we synthesized showdomycin-type C-nucleoside[2] carrying a four-membered ring sugar, oxetanose. We disclose herein our synthetic process of 2-deoxy-2-hydroxy-methyl-β-D-erythrooxetanosyl maleimide (**2**).



1 (OXETANOCIN)

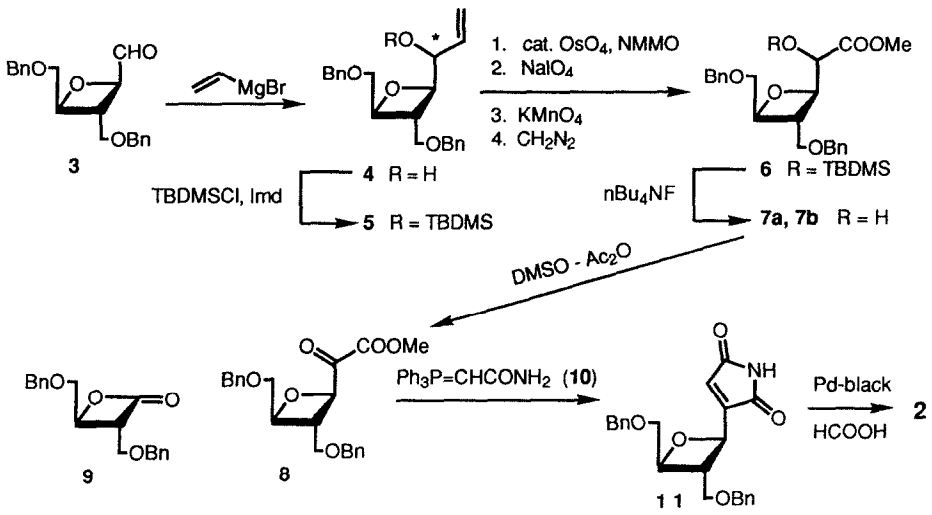


2



SHOWDOMYCIN

When the known oxetane derivative (**3**)[3] was submitted to Grignard reaction (vinylmagnesium bromide, -50°C→ room temp.), the corresponding allyl alcohols (**4**) were obtained as ca. 2:1 mixture in 53% yield. The OH group in **4** was protected as *tert*-butyldimethylsiloxy ether (TBDMSCl, Imd.) to give **5**, which was converted into a mixture of methyl ester (**6**) in four steps. (1. cat. OsO_4, 96%: 2. $NaIO_4$, 83%: 3. $KMnO_4$, : 4. CH_2N_2, 54% in two steps) Removal of the TBDMS group (nBu_4NF in THF, 83%) provided chromatographically separable alcohols (**7a** and **7b**) in quantitative yields, respectively. Oxidation of either alcohol with DMSO - Ac_2O afforded the same α-keto ester (**8**)[4] in high yield. However, on using tetrapropylammonium perruthenate (TPAP)[5]as oxidizing reagent, the reaction proceeded in entirely different way to afford a β-lactone (**9**) in 44% yield. Compound **8** thus obtained was treated with a phosphorane (**10**)[6] in $CHCl_3$ (room temp., 40



min) to yield a maleimide (**11**)[4] in 24% yield[7] *via* a simultaneous cyclization. In the final step, successful debenzylation of **11** by a hydrogen transfer method (Pd-black in HCOOH- MeOH) provided the target **2**[4] in 28% yield.[7] To the best of our knowledge, this is the first synthesis of oxetanosyl C-nucleoside.

Bioassay data concerning antiviral activities will be published elsewhere.

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4. **8**: IR (film) 1740 cm^{-1}; ^1H NMR (CDCl3) δ 5.44 (1H, d, J= 7 Hz). **11**: $[\alpha]_D^{29}$ +41.2° (*c* 0.78, $CHCl_3$); IR (film) 3250, 1780 (sh.), 1730, and 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10 (1H, m), 3.57 (1H, dd, J= 4.2, 11.5 Hz), 3.64 - 3.69 (2H, complex), 3.74 (1H, dd, J= 5.9, 10 Hz), 4.54 - 4.62 (4H, complex), 4.91 (1H, m), 5.42 (1H, dd, J= 2.0, 6.8 Hz), 6.61 (1H, t, J= 2.0 Hz), 7.10 (1H, broad s), and 7.33 (10H, complex). **2**: ^1H NMR (CD_3OD) δ 2.92 (1H, m), 3.61 (1H, dd, J= 4.6, 12.9 Hz), 3.69 (1H, dd, J= 3.1, 12.9 Hz), 3.76 (1H, dd, J= 4.6, 11.6 Hz), 3.82 (1H, dd, J= 5.6, 11.6 Hz), 4.75 (1H, m), 5.38 (1H, dd, J= 2.0, 7.1 Hz), and 6.63 (1H, d, J= 2.0 Hz).
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7. The reaction condition has not yet been optimized.

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