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SYNTHETIC STUDIES ON NEW SUGAR OXETANOSE: SYNTHESIS OF D-ERYTHROOXETANOSE AND ITS REACTION WITH SILYLATED ADENINE DERIVATIVE

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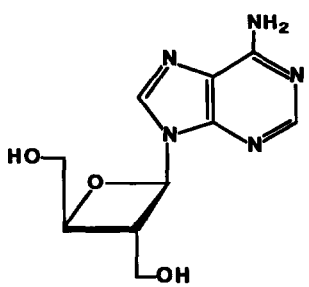
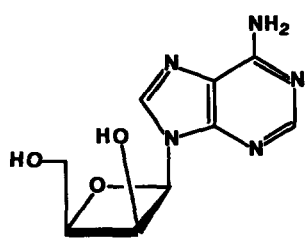
Summary: Related to antiviral antibiotic oxetanocin, 1-O-acetyl-β-D-erythrooxetanose was synthesized in two different methods, and coupling reaction with silylated adenine provided α- and β-L-threofuranosyl adenines via an unusual neighboring group participation.

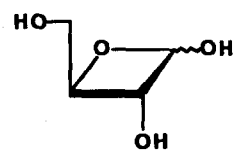
In connection with oxetanocin (1) possessing prominent antiviral activities as well as a novel nucleoside structure,[1] our extensive investigation[2] has also been focussed on developments of an oxetanose (four membered ring sugar) chemistry. Up to now, only few informations have been known about chemical features of this new sugar series. During chemical modifications of oxetanocin by Nippon Kayaku group, epinor-oxetanocin (2) carrying β-D-threooxetanoside as a sugar moiety has been found to exhibit more potent antiviral activities than 1.[3] This observation prompted us to start syntheses of oxetanoses and evaluate their effect to biological activities. Along this line we have synthesized a representative D-erythrooxetanose, however its glycosidation with silylated adenine derivative did not afford an expected oxetanosyl adenine, but furanosyl adenines were obtained via an unusual acyloxy group participation. We describe herein our synthetic process.



OXETANOCIN (1)

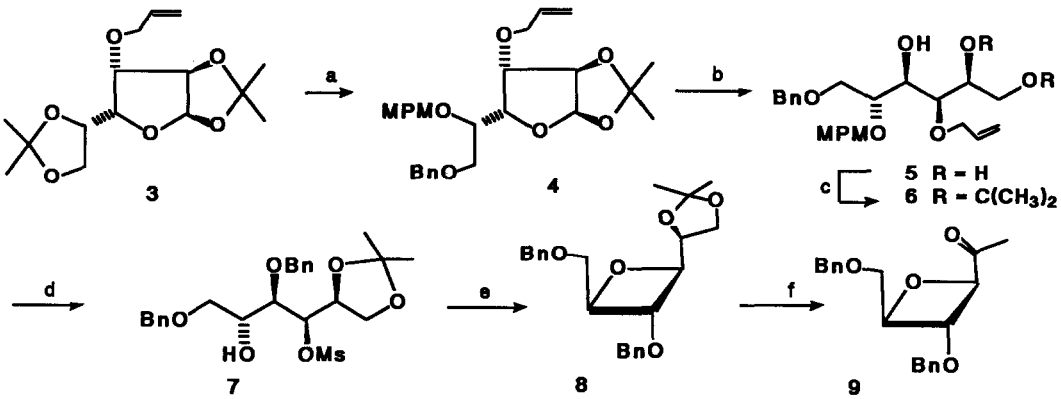


EPINOR-OXETANOCIN



ERYTHROOXETANOSE

The known diacetonide (3)[4] was partially hydrolized, and again protected in two steps to 4,[5] which was further converted to the corresponding D-glucitol derivative (5). Selective protection of the three OH groups in 5 afforded an alcohol (6)[5] in over 90% yield. This acyclic compound was further derivatized in four steps to afford a mesyl ester (7).[5] Cyclization of 7 took place in the desired direction to an oxetane derivative (8)[5] in 38% yield. In

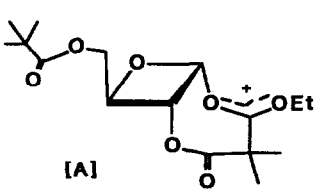


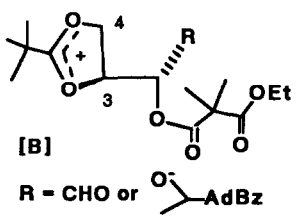
a. i) 2%H_2SO_4, room temp. (98%); ii) nBu_2SnO, then BnCl, nBu_4NBr / PhH, reflux temp.; iii) MPMCl, NaH / DMF, room temp. (82% in two steps). b. i) 4N HCl - THF, room temp., two days; ii) $NaBH_4$ / aq. dioxane, room temp., 15 h (72% in two steps). c. i) 2,2-dimethoxypropane, cat. TsOH, MS 4A / acetone. d. i) BnBr, NaH / PhH, reflux temp., 13 h (98%); ii) $(Ph_3P)_3RhCl$, DABCO / aq. EtOH, reflux temp., 1.5 h, then $HgCl_2$, HgO / aq. acetone, room temp., 20 min (98%); iii) MsCl, pyr. / CH_2Cl_2, room temp., two days (97%); iv) DDQ / CH_2Cl_2 - H_2O,room temp., 2 h (91%). e. NaH / PhMe, reflux temp., 15 min (38%). f. i) 2% H_2SO_4 - dioxane, 50°C, 3 h (98%); ii) Ph_3P, CCl_4 / pyr., 55°C, 75 min (83%); iii) $LiAlH_4$ / Et_2O, 4°C, two days (80%); iv) Swern oxid. (97%).

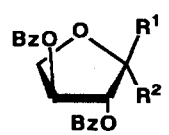
the next stage, the acetonide function in **8** was removed, and then the resulted diol was transformed into a methyl ketone (**9**) in three steps.

This methyl ketone could also be synthesized by a different route which involved the cyclization of an epoxy-alcohol (**13**)[6]. The crystalline dial hydrate (**10**)[7] was treated with ethylidenephosphorane to give a mixture of olefinic products. Without separation, the mixture was submitted to DIBAL reduction to afford **11** (ca. 2 : 1 mixture), and the primary OH group was protected with benzyl group to give **12**. Treatment of **12** with mCPBA effected epoxidation to provide a mixture of epoxy-alcohol (**13**). After alkaline treatment of **13**, the crude product was subjected to Moffatt oxidation to give a mixture of **9**, **14**[5] and **15**[5] (ca. 1 : 1 mixture) in 18, 14 and 25% yields, respectively.[9] Baeyer-Villiger oxidation of **9** so far obtained gave rise to 1-O-acetyl derivative (**16**)[8] in high yield, which was hydrogenated to afford 1-O-acetyl-β-D-erythrooxetanose (**17**).[8]

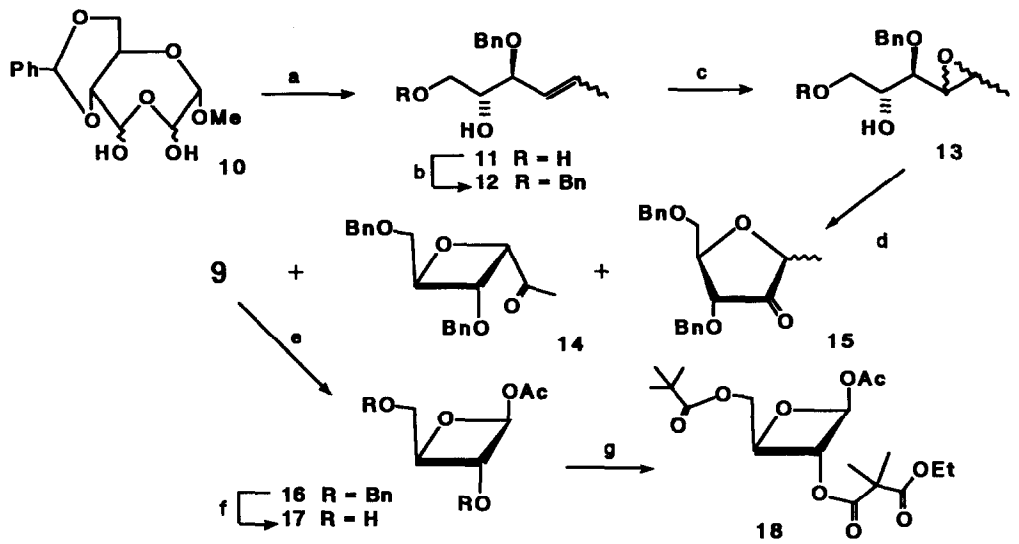
According to our methodology used in the total synthesis of **1**,[2] the erythrooxetanose (**17**) was fully acylated to **18**[8] which might be applicable to the glycosidation via the seven-membered ring participation as depicted in [A]. In Lewis acid ($SnCl_4$)-mediated N-glycosidation with N-benzoyl-bistrimethylsilyladenine, any formation of oxetanosyl adenines could not be monitored on tlc, but a mixture of 9-(L-threofuranosyl)adenines was obtained in 71% yield. The mixture could be separated as their tetrabenzoates (**20**, **21**) in 75 and 17% yields. Their structures were unambiguously confirmed by comparison of the spectral data and optical rotations with an authentic 9-(D-threofuranosyl)adenine tetrabenzoates synthesized by the known procedure.[10] Inversion of the configuration at C_3 position suggested the ring expansion might pass through an acyclic intermediate [B] generated by the acyloxy group participation from C_4 position, followed by recyclization to afford preferentially less strained furanose







20 R^1 = $AdBz_2$, R^2 = H
21 R^1 = H, R^2 = $AdBz_2$



a. i) Ph_3PEtBr, nBuLi / THF, -30°C - reflux temp.; ii) DIBAL - H / PhMe, -30°C - room temp. (37% in two steps). b. nBu_2SnO / PhMe, reflux temp., 23 h, then BnBr, nBu_4NBr, 35 h (100%). c. mCPBA / CH_2Cl_2, 4°C, 36 h (100%). d. i) aq. KOH / DMSO, 150°C, 50 min; ii) Moffatt oxid.. e. mCPBA / CH_2Cl_2, 4°C, two days (97%). f. H_2, Pd-black / MeOH, room temp., 5 h (98%). g. i) pivaloyl chloride, pyr., 4°C, 20 h (58%); ii) ethyl 2,2-dimethylmalonyl chloride, pyr. / CH_2Cl_2, room temp., 18 h (73%).

derivative than the corresponding oxetanose, though it was not clear that the process took place before or after the N-glycosidation.[11] This ring opening of the oxetanose has not been observed in usual furanose and pyranose sugars, thus, the chemical feature of the oxetanose may be similar to that of β-lactones. Further synthetic studies on oxetanosyl nucleosides is still going on.

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3. Private communication.
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5. 4: $C_{27}H_{34}O_7$ [m/z 470.2273 (M^+)]; $[\alpha]_D^{28}$ -20.3° (c 0.73, $CHCl_3$); IR (film) 1650, 1610, and 1515 cm^{-1}; δ ($CDCl_3$) 1.30 (3H, s), 1.45 (3H, s), 3.63 (1H, dd, J= 6, 10.5 Hz), 3.77 (3H, s), 4.45 (1H, d, J= 10.5 Hz), 4.57 (4H, br.s), and 4.75 (1H, d, J= 10.5 Hz). 6: $C_{27}H_{36}O_7$ [m/z 472.2459 (M^+)]; $[\alpha]_D^{28}$ -33.9° (c 0.73, $CHCl_3$); IR (film) 3500, 1650, 1610, and 1510 cm^{-1}; δ ($CDCl_3$) 1.36 (3H, s), 1.41 (3H, s), 3.79 (3H, s), 3.84 (1H, dd, J= 2.9, 10.3 Hz), 3.91 (1H, m), 4.03 (1H, dd, J= 6.8, 8.3 Hz), 4.45 (1H, d, J= 11.2 Hz), 4.55 (1H, d, J= 12.2 Hz), 4.59 (1H, d, J= 12.2 Hz), 4.68 (1H, d, J= 11.2 Hz), 5.11 (1H, dd, J= 1.5, 10.7

Hz), 5.20 (1H, m), and 5.87 (1H, m). **7**: $C_{24}H_{32}O_8S$ [m/z 480.1814 (M^+)]; $[\alpha]_D^{25}$ +7.13° (c 0.35, $CHCl_3$); IR (film) 3550, 1500, 1350, and 1170 cm^{-1}; δ ($CDCl_3$) 1.30 (3H, s), 1.43 (3H, s), 3.12 (3H, s), 3.58 (1H, dd, J= 6.8, 8.8 Hz), 3.64 (1H, dd, J= 2.4, 7.8 Hz), 3.96 (1H, m), 4.38 (1H, dd, J= 6.8, 13.7 Hz), 4.50 (1H, d, J= 11.2 Hz), 4.54 (1H, d, J= 11.7 Hz), 4.59 (1H, d, J= 4.4 Hz), 4.62 (1H, d, J= 4.9 Hz), and 4.83 (1H, dd, J= 2.5, 7.3 Hz). **8**: $C_{23}H_{28}O_5$ [m/z 384.1936 (M^+)]; $[\alpha]_D^{24}$ +26.0° (c 0.70, $CHCl_3$); IR (film) 1605 and 1500 cm^{-1}; δ ($CDCl_3$) 1.35 (3H, s), 1.40 (3H, s), 3.49 (1H, dd, J= 4.4, 11.2 Hz), 3.54 (1H, dd, J= 3.9, 11.2 Hz), 3.81 (1H, dd, J= 5.4, 8.8 Hz), 4.05 (1H, dd, J= 6.8, 8.8 Hz), 4.23 (1H, br.q, J= 6.4 Hz), 4.32 (1H, br.t, J= 4.9 Hz), 4.45 (1H, d, J= 11.7 Hz), 4.49 (1H, dd, J= 5.4, 6.8 Hz), 4.55 (2H, d, J= 6.8 Hz), 4.57 (1H, d, J= 12.2 Hz), and 4.70 (1H, br.q, J= 3.3 Hz). **9**: $C_{20}H_{22}O_4$ [m/z 326.1518 (M^+)]; $[\alpha]_D^{25}$ +69.0° (c 1.29, $CHCl_3$); IR (film) 1715, 1600 and 1500 cm^{-1}; δ ($CDCl_3$) 2.25 (3H, s), 3.42 (1H, dd, J= 3.4, 11.7 Hz), 3.57 (1H, dd, J= 2.9, 11.7 Hz), 4.41 (1H, br.t, J= 4.9 Hz), 4.45 (1H, d, J= 11.7 Hz), 4.50 (1H, d, J= 12.2 Hz), 4.57 (1H, d, J= 12.2 Hz), 4.64 (1H, d, J= 11.7 Hz), 4.73 (1H, m), and 4.85 (1H, d, J= 4.9 Hz). **14**: IR (film) 1710 and 1500 cm^{-1}; δ ($CDCl_3$) 2.36 (3H, s), 3.49 (1H, dd, J= 3.9, 11.2 Hz), 3.59 (1H, dd, J= 3.4, 11.2 Hz), 4.38 (1H, d, J= 11.7 Hz), 4.54 (2H, d, J= 11.7 Hz), 4.62 (1H, d, J= 11.7 Hz), 4.68 (1H, dd, J= 4.9, 7.3 Hz), 4.83 (1H, br.q, J= 3.9 Hz), and 5.04 (1H, dd, J= 1, 7.3 Hz). **15**: IR (film) 1770, 1750, 1580, and 1500 cm^{-1}.

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7. R. D. Guthrie, Methods in Carbohydr. Chem., **1**, 445 (1962).
8. **16**: $C_{18}H_{19}O_3$ [m/z 299.1285 (M^+-Ac)]; $[\alpha]_D^{25}$ -2.68° (c 0.75, $CHCl_3$); IR (film) 1750 and 1500 cm^{-1}; δ ($CDCl_3$) 2.03 (3H, s), 3.54 (2H, br.d, J= 4 Hz), and 6.21 (1H, d, J= 3 Hz). **17**: δ ($CDCl_3$) 2.35 (3H, s), 3.63 (1H, dd, J= 2, 11 Hz), 3.85 (1H, dd, J= 1.5, 11 Hz), 4.67 (1H, m), 4.73 (1H, br.t, J= 5 Hz), and 4.96 (1H, d, J= 5.5 Hz). **18**: $C_{16}H_{25}O_7$ [m/z 329.1570 (M^+-OAc)]; $[\alpha]_D^{24}$ -20.4° (c 0.51, $CHCl_3$); IR (film) 1735 cm^{-1}; δ ($CDCl_3$) 1.26 (3H, t, J= 7 Hz), 1.27 (9H, s), 1.47 (6H, br,s), 2.13 (3H, s), 4.19 (2H, q, J= 7 Hz), 4.28 (1H, m), 4.35 (1H, m), 4.51 (1H, m), 5.19 (1H, dd, J= 3, 4.5 Hz), and 6.30 (1H, d, J= 3 Hz).
9. Related to the stereochemistry of each epoxy-alcohol, the ratio of the oxetane to the tetrahydrofuran will be discussed elsewhere. (cf. ref. 6).
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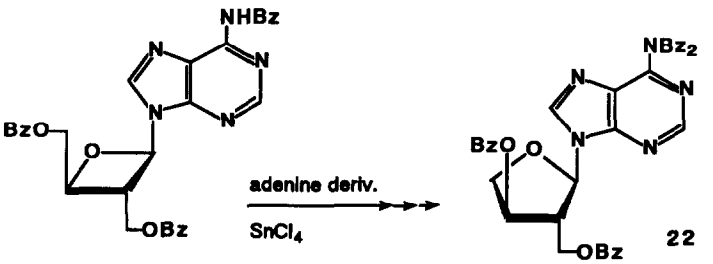
11. Based on this reaction process, ring expansions of acylated **1** might also accompany the inversion at C_3 position. Therefore, the structure of the furanoside derived from **1** (see ref. 2) should be corrected as **22**.



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