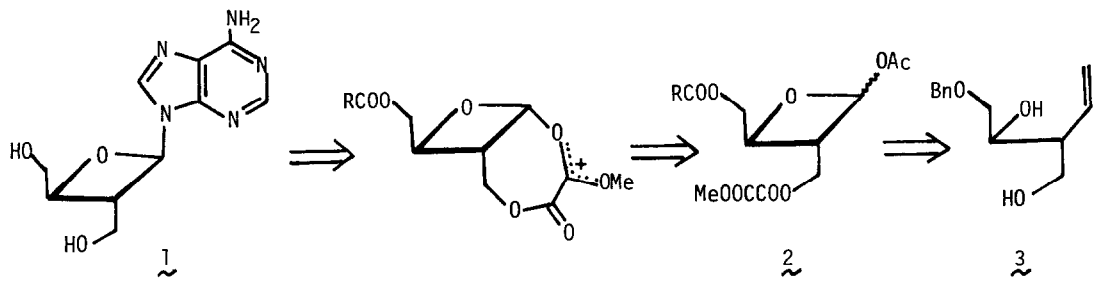
Tetrahedron Letters,Vol.29,No.37,pp 4743-4746,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A TOTAL SYNTHESIS OF OXETANOCIN, A NOVEL NUCLEOSIDE WITH AN OXETANE RING

Shigeru Nishiyama, Shosuke Yamamura,* Kuniki Kato,+ and Tomohisa Takita+
Department of Chemistry, Faculty of Science and Technology, Keio University
Hiyoshi, Yokohama, Japan
+ Research Laboratories, Pharmaceutical Groups, Nippon Kayaku Co. Ltd., 3-31-12 Shimo,
Kita-ku, Tokyo 115, Japan

Summary: Oxetanocin has been synthesized starting from cis-2-buten-1,4-diol through α- or β-D-oxetanosyl acetate as an important intermediate which has an α-(methyl oxalyloxy)methyl group at C_2-position.

As described in the preceding paper,[1] oxetanocin with antiviral, antitumor and antibacterial activities is regarded as the first oxetanosyl-N-glycoside,[2] and its synthesis has been accomplished by Niitsuma et al.[3] However, their synthetic method is only limited to oxetanocin (1). We describe herein a general method to synthesize oxetanocin and related nucleosides. In the light of our important results,[4] retrosynthesis of oxetanocin (1) is shown in Scheme 1, wherein an α-(methyl oxalyloxy)methyl group at C_2-position operates to yield a favorable intermediate with a seven-membered ring on treatment of 2 with Lewis acid.

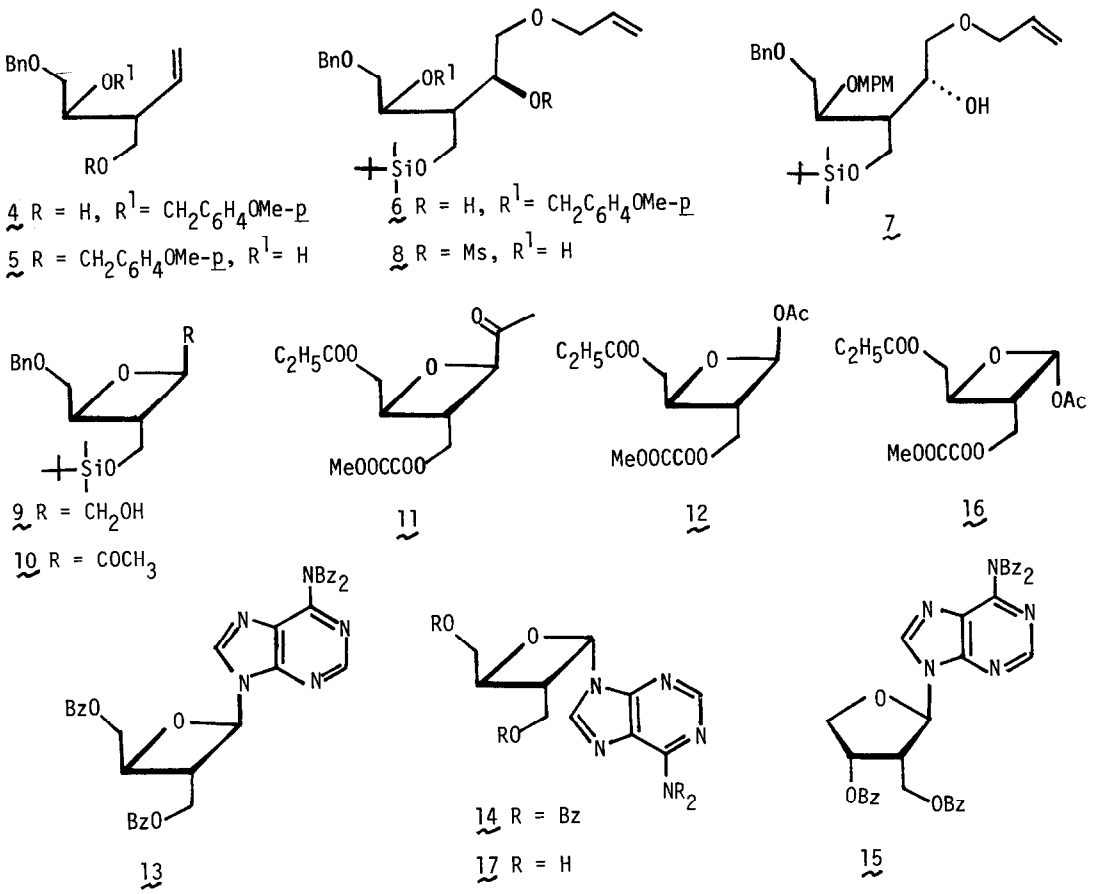


1 2 3

R : Me, Et, Bu^t and phenyl groups

Scheme 1. Retrosynthesis of oxetanocin.

The known diol (3),[5] derived from cis-2-buten-1,4-diol, was readily converted into two monohydroxy compounds (4 and 5)[6] in 2 steps [1) p-$MeOC_6H_4CHO$ - TsOH, benzene (refluxing temp., 3 h); 2) DIBAL-H, toluene (room temp., 3 h) (85% overall yield (4/5 = 2))]. The latter was reconverted into the original diol (3) using DDQ, whereas 4 was further treated with (Bu^t)Me_2SiCl - imidazole in DMF (room temp., 1.5 h) to afford a silyl ether, in 91% yield, which was directly converted into two epimers (6 and 7)[6] in 2 steps [1) OsO_4 (cat) - NMMO, acetone - H_2O - Bu^{t}OH (room temp., 2 days); 2) CH_2=$CHCH_2Br$ - NaH, THF (room temp., 15 h) (58% overall yield (6/7 = 1/3))]. On Mitsunobu reaction followed by hydrolysis [1) PhCOOH - Ph_3P - DEAD, THF (room temp., 20 h); 2) K_2CO_3, MeOH (room temp., 15 h)], the latter was converted



into 6 in 47% yield. Therefore, the total yield of 6 from 4 was 32%. The compound (6) so far obtained was treated with MsCl - Et_3N in CH_2Cl_2 (room temp., 3 h) and then deprotected with DDQ in CH_2Cl_2 - H_2O (room temp., 3 h) to afford the corresponding mesylate (8),[6] in 65% overall yield, from which an oxetane (9)[6] was produced in 3 steps [1) 60% NaH (1.6 equiv), THF (room temp., overnight) (84%); 2) $RhCl(Ph_3P)_3$ - DABCO (refluxing temp., 6 h); 3) HgO - $HgCl_2$, acetone (room temp., 2 h) (65% in 2 steps)].

As described in the preceding paper,[1] in the next step, the oxetane (9) was readily converted into a methyl ketone (10)[6] in 3 steps [1) $(COCl)_2$ - DMSO - Et_3N, CH_2Cl_2 (-45 °C, 30 min); 2) MeMgI, Et_2O (0 °C, 2 h) (87% in 2 steps); 3) DCC - DMSO - pyridine -TFA, benzene (room temp., overnight) (51%)]. This ketone was further converted into an oxetane (11)[6] with the desired two different functional groups, in 4 steps [1) $(Bu^n)_4NF$, THF (0 °C, 1 h) (69%); 2) MeOOCCOCl - pyridine, CH_2Cl_2 (-23 - 10 °C, 2.5 h) (95%); 3) H_2/Pd-black, THF (room temp., 20 min); 4) C_2H_5COCl - pyridine, CH_2Cl_2 (0 °C, 1 h) (66% in 2 steps)]. Baeyer-Villiger oxidation of 11 was carried out using mCPBA in CH_2Cl_2 (4 °C, overnight) to afford the corresponding β-D-oxetanosyl acetate (12)[6] in quantitative yield.

Finally, the acetate (12)[7] so far obtained was subjected to condensation reaction with

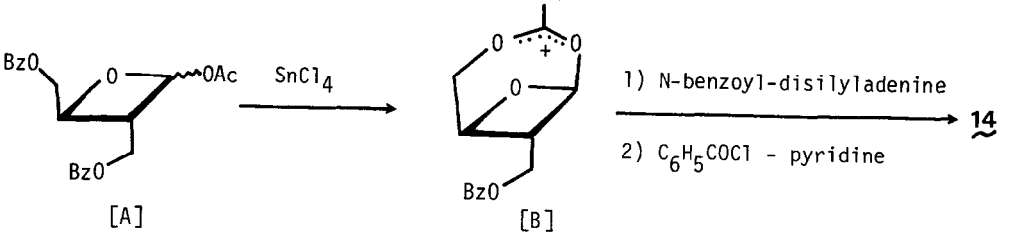
N-benzoyl-disilyladenine in 1,2-dichloroethane (room temp., 30 min) using $SnCl_4$ as Lewis acid, followed by hydrolysis [0.15N NaOMe, MeOH (room temp., 4.5 h)][8] and then benzoylation [BzCl - pyridine, CH_2Cl_2 (room temp., overnight)] to afford three condensation products (13, 14 and 15) in 16, 10 and 6.3% overall yields, respectively. The first one was completely identical with the dibenzoate (13)[6] derived from natural oxetanocin (1) in all respects of spectral data, whereas the second one was N,N-dibenzoylepioxetanocin dibenzoate (14).[6] The stereostructure (15) of the remaining product is based on its spectral data.[9] Clearly, the four-membered ring of the oxetanose is cleaved and then recyclized to afford the corresponding furanoside (15).

According to essentially the same synthetic procedure as described above, we also synthesized an α-D-oxetanosyl acetate (16)[6] from 7. This acetate (16) was also treated successively with N-benzoyl-disilyladenine - $SnCl_4$, 0.15N NaOMe and then benzoyl chloride - pyridine to give both 13 and 14 in 26 and 8.7% overall yields, respectively. On hydrolysis with 0.1N NaOMe in MeOH (room temp., overnight), these two dibenzoates (13 and 14) were readily converted into oxetanocin (1) and epioxetanocin (17)[10] in 81 and 77% yields, respectively.

Further synthetic studies on other nucleosides related to oxetanocin are in progress.

References

1. Submitted to Tetrahedron Letters.
2. N. Shimada, S. Hasegawa, T. Harada, T. Tomisawa, A. Fujii, and T. Takita, J. Antibiot., 39, 1623 (1986); H. Nakamura, S. Hasegawa, N. Shimada, A. Fujii, T. Takita, and Y. Iitaka, ibid., 39, 1629 (1986).
3. S. Niitsuma, Y. Ichikawa, K. Kato, and T. Takita, Tetrahedron Lett., 28, 1967, 4713 (1987).
4. In the case of the dibenzoate [A],[1] only α-N-glycoside (14) has been produced through a favorable intermediate [B] with a seven-membered ring, as shown below.



5. M. A. Tius and H. Fauq, J. Org. Chem., 48, 4132 (1983).
6. The spectral data for the new compounds are in accord with the structures assigned, and only selected data are cited: 4: $C_{21}H_{26}O_4$ [m/z 342.1817(M^+)]; IR (film) 3400 and 1610 cm^{-1}; δ ($CDCl_3$) 2.51(1H, m), 3.53(1H, dd, J= 5, 10 Hz), 3.63(3H, complex), 3.79(3H, s), 4.50(1H, d, J= 11 Hz), 4.52(2H, s), 4.66(1H, d, J= 11 Hz), 5.15(2H, complex), 5.81(1H, m), 6.86(2H, d, J= 8.8 Hz), 7.25(2H, d, J= 8.8 Hz) and 7.33(5H, complex). 5: $C_{21}H_{26}O_4$ [m/z 342.1833(M^+)]; δ ($CDCl_3$) 2.50(1H, m), 3.4 - 3.5(2H, complex), 3.53(1H, dd, J= 5, 9 Hz), 3.61(1H, dd, J= 6.3, 9 Hz), 3.79(3H, s), 4.05(1H, m), 4.43(2H, s), 4.50(1H, d, J= 12 Hz), 4.53(1H, d, J= 12 Hz), 5.15(2H, complex), 5.88(1H, m), 6.86(2H, d, J= 8 Hz), 7.22(2H, d, J= 8 Hz) and 7.32(5H, complex). 6: $C_{30}H_{46}O_6Si$ [m/z 530.3046(M^+)]; IR (film) 3520 cm^{-1}; δ ($CDCl_3$) 0.87(9H, s), 2.00(1H, m), 3.77(3H, s), 3.4 - 3.85(6H, complex), 3.97(3H, complex), 4.10(1H, m), 4.47(1H, d, J= 9 Hz), 4.52(2H, s), 4.67(1H, d, J= 9 Hz), 5.0 - 5.3(2H, complex), 5.76(1H, m), 6.82(2H, d, J= 9 Hz), 7.23(2H, d, J= 9 Hz) and 7.30(5H, s). 7: $C_{30}H_{46}O_6Si$ [m/z 530.3056(M^+)]; IR (film) 3500 cm^{-1}; δ ($CDCl_3$) 0.80(9H, s), 1.98(1H, m), 3.4 - 3.7(6H, complex), 3.83(3H, s), 3.93(4H, complex), 4.42(1H, d, J= 12 Hz), 4.47(2H, s), 4.62(1H, d, J= 12 Hz), 5.0 - 5.3(2H, complex), 5.80(1H, m), 6.78(2H, d, J= 9 Hz), 7.22(2H, d, J= 9 Hz) and 7.27(5H, s). 8: $C_{23}H_{40}O_7SSi$ [m/z 488.2254(M^+)]; IR (film) 3550 and 1645

cm^{-1}; $\delta(CDCl_3)$ 0.83(9H, s), 2.03(1H, m), 3.03(3H, s), 3.4 - 4.0(9H, complex), 4.50(2H, s), 5.1 - 5.3(3H, complex), 5.83(1H, m) and 7.28(5H, br.s). 9: $C_{19}H_{33}O_4Si$ [m/z 353.2140 ($M^+ + 1$)]; IR (film) 3450 cm^{-1}; $\delta(CDCl_3)$ 0.04(6H, s), 0.88(9H, s), 3.27(1H, m, overlapped with 1H signal), 3.53(1H, dd, J= 3.4, 11.2 Hz), 3.5 - 3.6(1H, m), 3.70(1H, dd, J= 2.9, 11.2 Hz), 3.73(2H, d, J= 5.9 Hz), 3.82(1H, m), 4.58(1H, d, J= 12 Hz), 4.65(1H, d, J= 12 Hz, overlapped with 2H signals) and 7.35(5H, complex). 10: $C_{20}H_{32}O_4Si$ [m/z 364.2064(M^+)]; IR (film) 1715 cm^{-1}; $\delta(CDCl_3)$ 2.24(3H, s) and 4.76(1H, d, J= 6.8 Hz). 11: $C_{11}H_{15}O_7$ [m/z 259.0798(M^+ - CH_3CO)]; IR (film) 1770 and 1750 cm^{-1}; $\delta(CDCl_3)$ 1.12 (3H, t, J= 7.5 Hz), 2.25(3H, s), 2.35(2H, q, J= 7.5 Hz), 3.20(1H, m), 3.88(3H, s), 4.18 (2H, complex), 4.50(2H, d, J= 6 Hz) and 4.70(1H, d, J= 6 Hz), overlapped with 1H signal). 12: $C_{11}H_{15}O_7$ [m/z 259.0799(M^+ - CH_3COO)]; IR (film) 1775 and 1750 cm^{-1}; $\delta(CDCl_3)$ 1.15 (3H, t, J= 7.5 Hz), 2.08(3H, s), 2.38(2H, q, J= 7.5 Hz), 3.12(1H, m), 3.90(3H, s), 4.27 (2H, complex), 4.50(2H, d, J= 6 Hz, overlapped with 1H signal) and 6.22(1H, d, J= 3 Hz). 13: $C_{31}H_{24}N_5O_6$ [m/z 562.1707(M^+ - Bz)]; $[\alpha]_D^{26}$ -35.8° (c 0.63, $CHCl_3$); IR (film) 1710, 1595, 1570 and 1490 cm^{-1}; $\delta(CDCl_3)$ 4.36(1H, m), 4.64(1H, dd, J= 4.9, 12.2 Hz), 4.70 (1H, dd, J= 5.4, 12.2 Hz), 4.84(1H, dd, J= 3.9, 12.7 Hz), 4.92(1H, dd, J= 5.4, 12.7 Hz), 5.07(1H, m), 6.61(1H, d, J= 5.9 Hz), 7.35(4H, complex), 7.45(6H, complex), 7.58(2H, complex), 7.85(4H, complex), 8.03(4H, complex), 8.32(1H, s) and 8.57(1H, s). 14: $C_{31}H_{24}N_5O_6$ [m/z 562.1708(M^+ - Bz)]; $[\alpha]_D^{24}$ -19.3° (c 0.46, $CHCl_3$); IR (film) 1725, 1600, 1580 and 1490 cm^{-1}; $\delta(CDCl_3)$ 3.64(1H, m), 4.50(1H, dd, J= 3, 11 Hz), 4.56(1H, dd, J= 5, 11 Hz), 4.68(1H, dd, J= 3, 11 Hz), 4.80(1H, dd, J= 5.5, 11.7 Hz), 5.64(1H, m), 6.45(1H, d, J= 2.9 Hz), 7.33(4H, complex), 7.46(6H, complex), 7.59(2H, complex), 7.85(6H, complex), 8.02(2H, complex), 8.38(1H, s) and 8.51(1H, s). 16: $\delta(CDCl_3)$ 1.15(3H, t, J= 7.5 Hz), 2.12(3H, s), 2.38(2H, q, J= 7.5 Hz), 3.43(1H, m), 3.88(3H, s), 4.26(2H, complex), 4.57 (2H, d, J= 7.5 Hz), 4.82(1H, m) and 6.47(1H, d, J= 6 Hz).

7. The α-(methyl oxalyoxy)methyl group at C_2-position is not always better than other functional groups. For example, there remains a possibility that an eight-membered ring intermediate is more favorable than the seven-membered ring intermediate shown in Scheme 1. Further study on this point is in progress. In addition, pivaloyloxymethyl group was used instead of propionyloxymethyl group at C_3-position. However, any good result has not yet been obtained. Other acyloxymethyl groups at C_3-position are also examined in due course.

8. Both oxetanocin and epioxetanocin were detected on analytical TLC (Kieselgel PF_{254}). At this stage, however, these two epimers were not obtained in a pure state.

9. The molecular ion peak of 15 was not observed in its mass spectrum, but its stereostructure was unambiguously confirmed by the spectral data: $[\alpha]_D^{26}$ -55.7° (c 0.24, $CHCl_3$), IR (film) 1720 cm^{-1}; $\delta(CDCl_3)$ 4.07(1H, m), 4.33(1H, br.d, J= 10.7 Hz), 4.71(1H, dd, J= 7.8, 11 Hz), 4.77(1H, dd, J= 6.4, 11 Hz), 4.85(1H, dd, J= 3.4, 10.7 Hz), 6.05(1H, m), 6.41(1H, d, J= 7.3 Hz), 7.37(6H, complex), 7.49(5H, complex), 7.63(1H, m), 7.68(2H, complex), 7.86(4H, complex), 8.07(2H, complex), 8.20(1H, s) and 8.62(1H, s).

10. The molecular ion peak of 17 has not been observed in its mass spectrum, but its structure is supported by the spectral data: IR (film) 3340, 1630br. and 1575 cm^{-1}; $\delta(DMSO\text{-}d_6)$ 2.72(1H, m), 3.55(2H, complex), 3.92(1H, dd, J= 3, 9 Hz), 4.00(1H, dd, J= 5, 9 Hz), 4.23 (1H, m), 6.05(1H, d, J= 3.9 Hz), 8.15(1H, s) and 8.36(1H, s).

(Received in Japan 21 April 1988; accepted 27 June 1988)