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Synthesis of L-Oxetanocin

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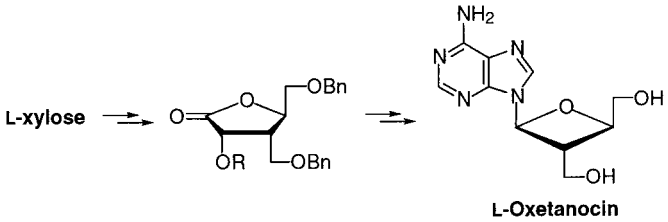
ABSTRACT



Hitherto unknown L-oxetanocin has been synthesized from L-xylose in 16 steps via a ribonolactone derivative.

Oxetanocin (Figure 1) was first isolated from the culture of a strain of *Bacillus megaterium*.[1] It has demonstrated good antibacterial, antitumor, and antiviral activity.[1,2]

As a result of its unusual structure, characterized by the presence of an oxetane ring, oxetanocin has been the subject of numerous synthetic studies,[3,4] which led to the synthesis of analogues where the adenine moiety is replaced by other heterocyclic bases. Biologically, the most interesting compound seems to be the thymine derivative, A-73209 (Figure 1), which shows potent in vitro and in vivo activity against several thymidine kinase positive strains of VZV, HSV-1, and HSV-2.[5]

As in all natural nucleosides, the absolute configuration of the glycosyl moiety in oxetanocin is D. During the past 10 years, the interesting biological activities of several "unnatural" L-nucleosides have been discovered.[6,7]

The most notable example regards oxathiolane analogues, wherein 3TC (the L-isomer) is more potent and less toxic than its D-counterpart [(+)-BCH-189].[7] These findings, together with the promising activity of the oxetanocin nucleosides, prompted us to synthesize the L-isomer of oxetanocin **1** (Figure 1).

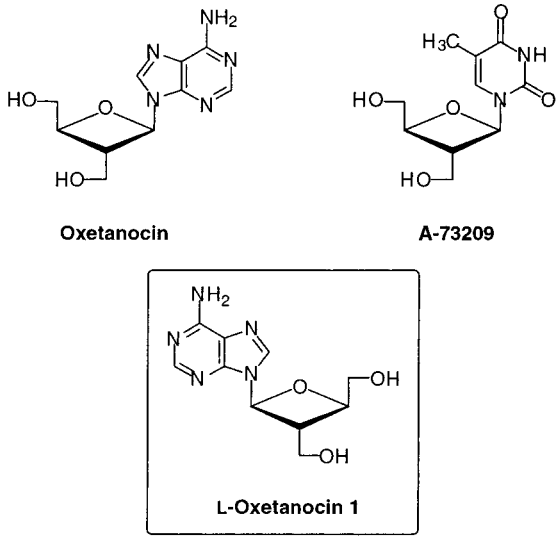


Figure 1. Structures of D- and L-oxetanocin analogues.

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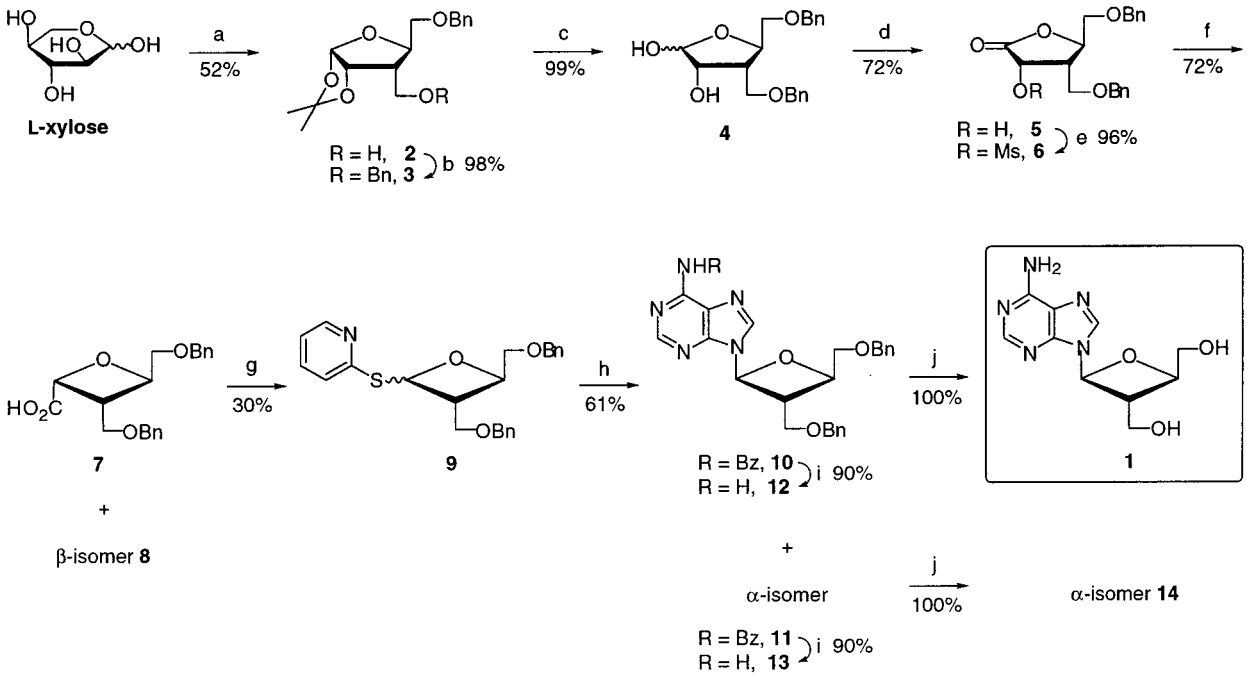
Scheme 1. Synthesis of L-Oxetanocin **1**



[a] Reagents and conditions: (a) seven steps, ref 10; (b) NaH, THF, then TBAI, BnBr; (c) 10% HCl, 1,4-dioxane; (d) Br_2, $BaCO_3$, 3:1 H_2O/1,4-dioxane; (e) MsCl, Py, CH_2Cl_2; (f) 1 N NaOH, MeOH; (g) *i*-BuOC(O)Cl, *N*-methylmorpholine, THF, then 2-mercaptopyridine-*N*-oxide, Et_3N, then *hν*; (h) N^6-benzoyladenine, Br_2, 4 Å molecular sieves, DMF; (i) MeONa, MeOH; (j) H_2, Pd black, EtOH.

From a review of the current literature, none of the synthetic schemes for the synthesis of natural oxetanocin published so far seemed conveniently applicable to the synthesis of L-oxetanocin. The first reported total synthesis of D-oxetanocin,[3] starting from D-ribose, led to the final product in 19 steps with an overall yield of 0.008% and was not applicable to the synthesis of other analogues. In another approach,[4a] oxetanocin and its analogues were prepared in 26 steps from D-glucose with 0.15% overall yield. In this procedure, the starting material was converted to an acyclic structure that, eventually, was recyclized to afford the four-membered ring.

Among the reported syntheses of D-oxetanocin, the method that utilizes adenosine appears to be the most efficient, in which adenosine was converted to oxetanocin in 12 steps, with an overall yield of approximately 7%.[4b] By varying the starting nucleoside, a series of analogues was successfully obtained.[4c] The main advantage of this approach is that the five-membered ring is contracted to an oxetane when it is already bound to the base, thereby bypassing a difficult condensation step involving an oxetane derivative. On the other hand, this procedure seems to be less convenient in the case of analogues bearing "unnatural" heterocyclic moieties, as well as L-nucleosides, as a natural starting material is not readily available.

In devising our scheme, we had to consider the reactivity of oxetane systems. These are highly strained and tend to open, particularly in the presence of acids, to give acyclic compounds or, in the presence of particular substituents, oxolane-type rearrangement products.[8] This explains the low yields observed in the early syntheses,[3,4a] where the base and the sugar were coupled in the presence of a Lewis acid as the catalyst. One way to avoid the use of an acidic catalyst is to condense the base, free or activated as an anion, with an oxetane substituted at the anomeric position with a good leaving group. Unfortunately, such derivatives proved to be very unstable, as reported in another low yield synthetic procedure.[4d]

Our approach was based on some interesting syntheses in which a base is coupled to a sugar, activated as thioglycoside.[8,9] In most cases, the reaction is catalyzed by a Lewis acid; however, in certain cases, a protected adenine is reacted with a thiopyridyloxetane in the presence of bromine to give the coupled product in good yield.[8]

As the starting material of our synthesis (Scheme 1), we used protected 3-deoxy-3-(hydroxymethyl)-L-ribofuranose **2**, previously prepared from L-xylose in our laboratory.[10]

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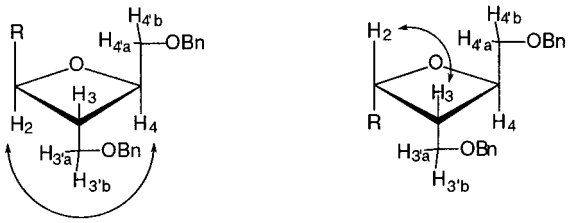
Alcohol **2** was benzylated in the presence of catalytic tetrabutylammonium iodide (TBAI)[11] to give the fully protected derivative **3**, which was deprotected to lactol **4**. The oxidation of **4** to lactone **5**, accomplished by the modification of a reported procedure,[12] required a very accurate control of pH, which needed to be maintained between 4.5 and 4.8 in order to obtain satisfactory yields. Lactone **5** was quantitatively mesylated to compound **6**, which underwent ring contraction, following the procedure reported for the D-isomer,[8] to afford acids **7**[13] and **8**[14] in 3:1 ratio in 73% yield. These acids, purified and characterized separately, were reacted as an epimeric mixture in a three-step, one-pot reaction to afford the epimeric thiopyridyl oxetanes **9** in 30% yield. The epimeric mixture of compounds **9**, not separable by column chromatography, was used in the coupling reaction to yield fully protected oxetanocin derivatives **10** and **11** in 2:3 ratio and 61% overall yield.

Compounds **10** and **11** could be separated by flash chromatography, and each of them was debenzoylated to the corresponding derivatives **12** and **13**, which were in turn catalytically hydrogenated over palladium black to yield oxetanocin **1**[15] and its α-isomer **14**[16] with overall yields of 90%.[17]

Stereochemistry of epimers **7**−**13** has been unequivocally determined by means of 2D-NOESY experiments on both isomers; in all cases (Figure 2), very strong correlations between protons H_2 and H_4 have been observed in the spectra of β-isomers, whereas correlations between H_2 and H_3 characterized the spectra of α-isomers. In most cases, correlations between H_2 and $H_{3'a}$ and/or $H_{3'b}$ and between H_2 and $H_{4'a}$ and/or $H_{4'b}$ were also observed.



R = COOH (**7**, **8**), thiopyridyl (**9**), N^4-benzoyladenine (**10**, **11**), adenine (**12**, **13**)

Figure 2. NOE correlations and stereochemistry of **7**−**13**.

In the case of **9**, these correlations could be clearly observed in the spectra of the epimeric mixture and helped correctly assign ^{1}H signals in each isomer.

In summary, L-oxetanocin has been synthesized from L-xylose in 16 steps and 2.8% overall yield. Our procedure seems more convenient and versatile than the reported total syntheses of D-oxetanocin, because the coupling between the activated oxetane moiety and the nucleobase does not require a Lewis acid, thereby proceeding smoothly and with minimal side reactions. Optimization of the synthesis for other purine and pyrimidine derivatives as well as biological evaluations of L-oxetanocin are in progress.

Preliminary biological evaluation of L-oxetanocin showed no activity up to 100 mM against HIV-1.

Acknowledgment. This research was supported by the U.S. Public Health Service Research Grant AI 32351 from the National Institute of Allergy and Infectious Diseases, NIH. One of the Authors (G.G.) was partially supported by the Italian Department of University and Scientific Research (MURST). We thank Dr. Michael Bartlett of the College of Pharmacy, The University of Georgia for performing the high-resolution mass spectra.

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(13) Colorless oil: R_f 0.14 (95:4.5:0.5 $CHCl_3$/MeOH/AcOH); $[\alpha]^{25}_D$ 11.4 (*c* 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3) δ 7.38−7.26 (m, 10H), 5.08 (d, 1H, J = 9.3 Hz), 4.98 (m, 1H, J = 5.6, 4.1, 2.9), 4.67 (d, 1H, J = 11.9), 4.60 (d, 1H, J = 11.9), 4.54 (d, 1H, J = 11.7), 4.37 (d, 1H, J = 11.7), 3.72 (dd, 1H, J = 11.4, 2.9), 3.66 (dd, 1H, J = 11.4, 4.1), 3.60 (dd, 1H, J = 10.2, 4.2), 3.55 (dd, 1H, J = 10.2, 3.6), 3.43 (m, 1H, J = 9.3, 5.6, 4.2, 3.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.66, 137.79, 137.56, 128.47, 128.37, 127.84, 127.82, 127.74, 127.64, 82.16, 75.68, 73.64, 73.31, 71.32, 66.01, 39.04; HRMS (FAB) *m*/*z* calcd for $C_{20}H_{23}O_5$ $[(M + H)^+]$ 343.1545, found 343.1531. Anal. Calcd for $C_{20}H_{22}O_5$·0.1MeOH: C, 69.86; H, 6.53. Found: C, 69.48; H, 6.54.

(14) White solid: mp 80−81 °C; R_f 0.25 (95:4.5:0.5 $CHCl_3$/MeOH/AcOH); $[\alpha]^{25}_D$ −41.3 (*c* 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.28 (m, 10H), 4.93 (d, 1H, J = 6.5 Hz), 4.88 (m, 1H, J = 6.1, 2.3, 1.6), 4.73 (d, 1H, J = 12.0), 4.64 (d, 1H, J = 12.0), 4.57 (d, 1H, J = 12.1), 4.53 (d, 1H, J = 12.1), 3.76 (dd, 1H, J = 11.4, 2.3), 3.68 (dd, 1H, J = 9.8, 5.7), 3.61 (dd, 1H, J = 9.8, 4.3), 3.48 (dd, 1H, J = 11.4, 1.6), 3.31 (m, 1H, J = 6.5, 6.1, 5.7, 4.3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.34, 137.62, 136.39, 128.69, 128.50, 128.34, 128.15, 127.89, 127.67, 81.64, 76.78, 73.77, 73.26, 70.18, 68.19, 39.84; HRMS (FAB) *m*/*z* calcd for C20H23O5 $[(M + H)^+]$ 343.1545, found 343.1530. Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.39; H, 6.80.

(15) White solid: mp 189−190 °C; R_f 0.12 (1:9 MeOH/CH_2Cl_2); $[\alpha]^{27}_D$ 20.38 (*c* 0.36, MeOH); UV (H_2O) λ_{max} 256.0 (ϵ 18950, pH 2), 258.0 (ϵ 19430, pH 7), 258.0 (ϵ 19420, pH 11); ^{1}H NMR (400 MHz, CD_3OD) δ 8.66 (s, 1H), 8.20 (s, 1H), 6.50 (d, 1H, J = 5.3), 4.67 (m, 1H), 3.91 (dd, 1H, J = 13.2, 2.3), 3.82 (m, 3H), 3.77 (dd, 1H, J = 13.2, 3.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.48, 153.86, 150.27, 141.78, 120.26, 83.17, 80.08, 63.97, 60.31, 46.85; HRMS (FAB) *m*/*z* calcd for C10H14N5O3 $[(M + H)^+]$: 252.1097, found: 252.1114. Anal. Calcd for $C_{10}H_{13}N_5O_3$·H2O: C, 44.61; H, 5.62; N, 26.01. Found: C, 44.84; H, 5.62; N, 26.12.

(16) White solid: mp 170−172 °C.; R_f 0.07 (1:9 MeOH/CH_2Cl_2); $[\alpha]^{26}_D$ 14.82 (*c* 0.22, MeOH); UV (H_2O) λ_{max} 257.0 (ϵ 14685, pH 2), 259.0 (ϵ 14738, pH 7), 254.0 (ϵ 14280, pH 11); ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 8.18 (s, 1H), 6.69 (d, 1H, J = 6.2), 4.97 (m, 1H), 3.90 (dd, 1H, J = 12.9, 2.7), 3.78 (dd, 1H, J = 12.9, 3.9), 3.50−3.61 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.33, 153.86, 150.13, 141.14, 120.38, 86.31, 84.77, 64.48, 59.40, 43.72; HRMS (FAB) *m*/*z* calcd for C10H14N5O3 $[(M + H)^+]$ 252.1097, found 252.1092. Anal. Calcd for $C_{10}H_{13}N_5O_3$·0.25CH_2Cl_2: C, 45.18; H, 4.99; N, 25.70. Found: C, 45.30; H, 5.22; N, 25.37.

(17) All the synthesized compounds showed satisfactory analytical and spectroscopic data. When possible, comparison of their data with those of known D-enantiomers confirmed their identity and optical purity.