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Nucleosides and Nucleotides. 159. Synthesis of Thietane Nucleosides Via the Pummerer Reaction as a Key Step[1]

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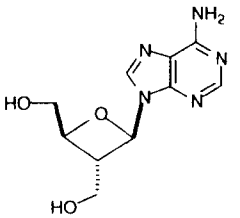
Abstract: New thymine thietane nucleosides **7** and **20** were synthesized via Pummerer rearrangement of the corresponding sulfoxides **5** and **18** in the presence of thymine, TMSOTf, Et_3N, and ZnI_2 as a key step. Copyright © 1996 Elsevier Science Ltd

Oxetanocin A, which was isolated from *Bacillus megaterium NK84-0218*, bears an oxetanose instead of a furanose in the sugar moiety of the nucleoside.[2] Due to this unique structure and its biological activity, including anti-HIV activity, various analogues of oxetanocin A, at both the sugar and base moieties, have been synthesized to improve its chemotherapeutic index.[3] A guanine congenor of oxetanocin A and its carbocyclic analogue have also been shown to have potent antiviral activities against HSV and HBV.[3d] Their 5'-triphosphates were found to be incorporated into DNA molecules and to terminate elongation.[4] Although the sugar moiety of oxetanocin analogues is unique, it is surprising that such nucleosides were recognized as substrates of kinases. Therefore, nucleosides that have been further modified at the sugar moiety may be selectively recognized by less substrate-specific viral kinases without affecting cellular enzymes. In our efforts to find new antiviral nucleosides, we designed thietane analogues of oxetanocins in which the ring oxygen in the sugar moiety is replaced by a sulfur atom. However, the synthesis of thietane nucleosides by the classical condensation of corresponding 2-*O*-acyl thietane derivatives with nucleobases has not been successful.[5] Therefore, a new method should be developed to synthesize such nucleosides. In this paper, we report the first synthesis of thietane nucleosides via the Pummerer reaction as a key step.[6]

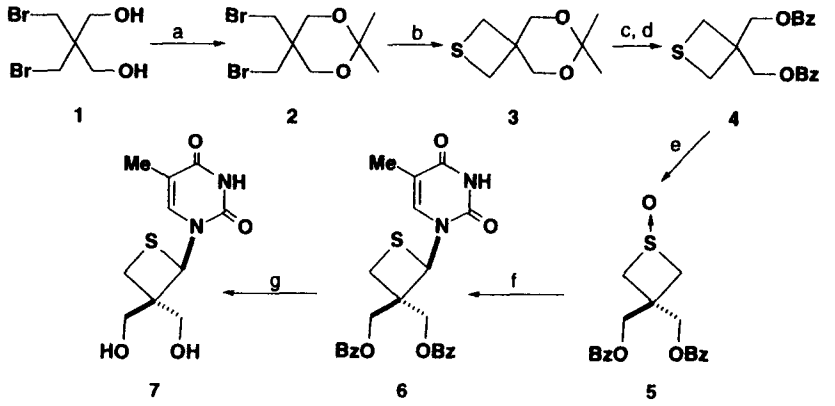


oxetanocin A

We first examined the Pummerer reaction of the readily accessible sulfoxide **5**. The commercially available diol **1** was converted into thietane **3** as shown in Scheme 1. The protecting group in **3** was converted into a benzoyl group to give **4**, which was oxidized by $NaIO_4$ in MeOH to give sulfoxide **5** in a good overall yield. When **5** was subjected to the Pummerer reaction with thymine (1.2 equiv) in the presence of TMSOTf, Et_3N, and ZnI_2 in toluene, the desired racemic **6** was obtained in 31% yield. However, the use

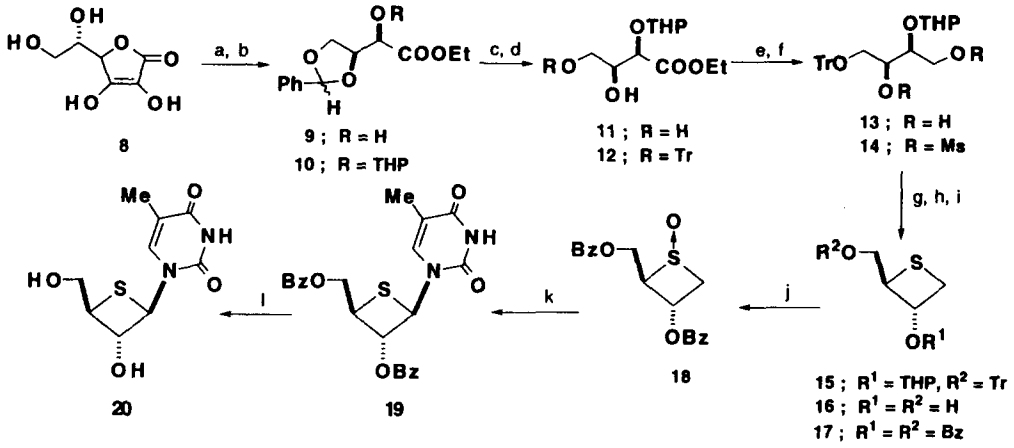
of 2 equiv of thymine and CH_2Cl_2 as a solvent under the same conditions gave **6** in 70% yield.[7] Deprotection of **6** with NaOMe in MeOH furnished **7** in 81% yield.[8] Thus, the Pummerer rearrangement of **5** worked well to give thymine thietane nucleoside **6** in good yield. This is the first example of the synthesis of a thictane nucleoside.

Scheme 1[a]



[a](a) 2,2-dimethoxypropane, TsOH, acetone, rt, 2h, 100%; (b) $Na_2S \cdot 9H_2O$, DMF, 100 °C, 6h, 97%; (c) TsOH, aq. MeOH, rt, 12h; (d) BzCl, Et_3N, MeCN, rt, 3h, 80% from **3**; (e) $NaIO_4$, aq. MeOH, rt, 48h, 72%; (f) thymine, TMSOTf, Et_3N, ZnI_2, CH_2Cl_2, rt, 30h, 70%; (g) NaOMe, MeOH, rt, 1h, 81%.

Scheme 2[a]



[a](a) ref. 9; (b) 3,4-DHP, PPTS, CH_2Cl_2, rt, 19h; (c) H_2, 10% Pd-C, EtOAc, rt, 30h; (d) TrCl, pyridine, rt, 35h; (e) $LiAlH_4$, THF, rt, 20h; (f) MsCl, pyridine, rt, 12h; (g) Na_2S, aq. EtOH, reflux, 24h; (h) TsOH, MeOH, rt, 20h; (i) BzCl, pyridine, rt, 12h; (j) m-CPBA, CH_2Cl_2, 0 °C-rt, 18h; (k) thymine, TMSOTf, Et_3N, ZnI_2, toluene, 0 °C-rt, 30h; (l) NaOMe, MeOH, rt, 1h.

We applied this method to the synthesis of **20**, which is more closely related to the oxetanocins than **7**. Sulfoxide **18** was obtained from L-ascorbic acid (**8**) (Scheme 2). A hydroxyl group in **9**[9] was protected with a THP group to give **10**, which was then debenzylidenated to give diol **11** in 77% yield from **9**. Treatment of **11** with trityl chloride in pyridine gave **12**, which was reduced with $LiAlH_4$ and then mesylated to give **14** in 79% yield from **11**. When **14** was treated with $Na_2S \cdot 9H_2O$ in DMF at 100 °C,[10] the desired thietane product **15** was not obtained. However, the use of EtOH as a solvent gave **15** in 62% yield. It is well known that significant stereoselectivity is generally attained via the neighboring group participation in a glycosidation reaction when the 2-hydroxyl is protected with an acyl group.[11] Thus, **15** was converted into Bz ester **17** (59% yield from **15**). The key intermediate **18**[12] was prepared in 91% yield by oxidation of **17** with m-CPBA in CH_2Cl_2 at 0 °C.

Next, we examined the Pummerer reaction of **18** with thymine as a nucleophile under similar conditions to those described for the synthesis of **6**. The reaction using thymine (2 equiv) and TMSOTf (6 equiv) in the presence of ZnI_2 and Et_3N in toluene gave the desired **19** in 30% yield along with a large amount of **21**. The yield of **19** was decreased when CH_2Cl_2 was used as a solvent. This low yield of **19** is probably due to abstraction of the acidic 3-proton in intermediate **A** to produce **21**. After debenzoylation of **19** with NaOMe in MeOH, the desired (2'*R*,3'*R*,4'*R*)-1-(3-hydroxy-4-hydroxylmethylthiacyclobutan-2-yl)thymine (**20**) was obtained as crystals in 70% yield.[13, 14] The anomeric configuration of **20** was unambiguously confirmed by X-ray crystallographic analysis, which is shown in Figure 1.[15] Since careful TLC and NMR analyses did not show the presence of an α-nucleoside, the desired β-nucleoside would be produced through the participation of the 3-OBz group *via* intermediate **B** in Scheme 3. If this is the case, such neighboring group participation is the first such example in the thietane system.

Scheme 3

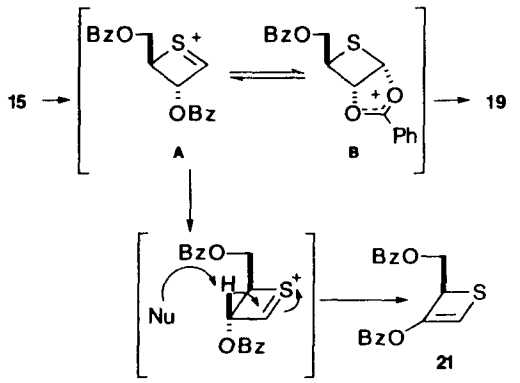
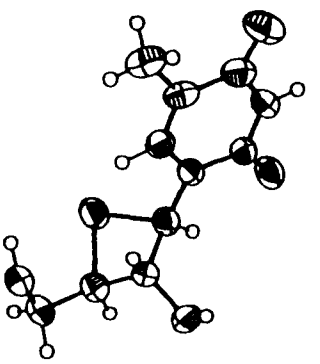


Fig. 1. ORTEP drawing of **20**.



In summary, we have synthesized for the first time a thietane-containing thymine nucleoside via the Pummerer reaction. We are now applying this method to other nucleobases and other thietane systems.

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7) A typical experimental procedure is as follows: Triethylamine (0.6 mmol) and TMSOTf (0.6 mmol) were added to a suspension of thymine (0.2 mmol) in CH_2Cl_2 (2 mL) at 0 ℃. The resulting solution was vigorously stirred for 30 min at room temperature. The solution was then cooled in an ice-water bath and a solution of sulfoxide **5** (0.1 mmol) in CH_2Cl_2 (1 mL) and ZnI_2 (0.03 mmol) were added. After being stirred for 24 h at room temperature, the reaction was quenched by adding saturated aqueous $NaHCO_3$ and then extracted with EtOAc. Usual workup and separation by silica gel column chromatography gave **6**.
8) **7**: ^{1}H-NMR (DMSO-d_6) δ 9.50 (br s, 1 H, NH), 8.18 (s, 1 H), 5.85 (s, 1 H), 4.98 (dd, 1 H, J = 5.4, 5.7 Hz, OH), 4.64 (dd, 1 H, J = 4.5, 4.6 Hz, OH), 3.59 (dd, 1 H, J = 5.7, 10.8 Hz), 3.48-3.32 (m, 3 H), 2.87 (d, 1 H, J = 8.9 Hz), 2.79 (d, 1 H, J = 8.9 Hz), 1.85 (s, 3 H). HRMS *m/z* Calcd for $C_{10}H_{14}N_2O_4S$ 258.0674. Found 258.0685. Anal. Calcd for $C_{10}H_{14}N_2O_4S$ C, 46.50; H, 5.46; N, 10.85; S, 12.41. Found C, 46.40; H, 5.44; N, 10.77; S, 12.42. Mp. 204-209 ℃.
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12) Sulfoxide **18** was obtained as a diastereomixture.
13) **20**: ^{1}H-NMR (DMSO-d_6) δ 9.31 (br s, 1 H, NH), 7.89 (s, 1 H), 6.26 (d, 1 H, J = 7.7 Hz), 5.89 (d, 1 H, J = 7.2 Hz), 4.99 (m, 1 H, OH), 4.47 (m, 1 H), 3.77 (m, 1 H), 3.63 (m, 1 H), 3.42 (ddd, 1 H, J = 7.0, 7.2, and 11.7 Hz), 1.84 (s, 3 H). HRMS *m/z* Calcd for $C_9H_{13}N_2O_4S$ 245.0596. Found 245.0584. Mp. 211-212 ℃.
14) Compounds **7** and **20** were evaluated for anti-herpes simplex virus type-1 and -2, and -varicella-zoster virus activity *in vitro*. However, no significant activities were detected.
15) Crystal data of **20**: $C_9H_{12}N_2O_4S$, Monoclinic, $P2_1$, a = 5.3106 (7), b = 10.695 (1), c = 9.6769 (7) Å, β = 100.083 (8)°, V = 541.1 (1) Å^3, Z = 2, D_c = 1.499 μg m^{-3}. A total of 708 independent reflections were collected and used for the structure analysis. The final R value was 0.0360.

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