Tetrahedron 67 (2011) 358–363

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of thietane nucleoside with an anomeric hydroxymethyl group

Naozumi Nishizono *, Yuji Akama, Masayuki Agata, Michiyasu Sugo, Yuki Yamaguchi, Kazuaki Oda *

Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan

ARTICLE INFO

Article history:
Received 7 September 2010
Received in revised form 8 November 2010
Accepted 8 November 2010
Available online 13 November 2010

Keywords:
Thietane nucleoside
Pummerer reaction
Thymine
Hydroxy(tosyloxy)iodobenzene
Ring-expansion reaction

ABSTRACT

Thietane nucleoside **5** with an anomeric hydroxymethyl group was synthesized via the Pummerer reaction. The stereochemistry of the sulfoxide and the nature of the protecting group had no significant effect on the yield of the reaction. When a hypervalent iodine reagent was used, sulfide **16** with *O*-benzoyl protecting groups gave the ring-expanded nucleoside **21**. Unfortunately, synthesized compound **6** did not exhibit anti-HSV activity.

1. Introduction

The nucleosides of DNA and RNA are composed of a sugar moiety (2-deoxyribose and ribose, respectively) linked to a purine or pyrimidine base through a β-*N*-glycosidic bond. In addition to the nucleosides of DNA and RNA, many other naturally occurring nucleosides have been isolated, and their biological activity has been evaluated.[1] Examples of these nucleosides are shown in Fig. 1. Among these compounds, bredinin[2] and Ara-A[3] are clinically used as an immunosuppressant agent and anti-herpes agent, respectively.

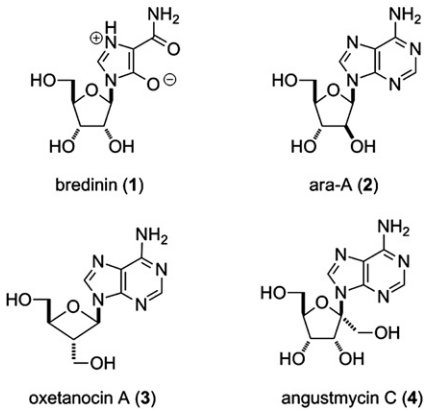
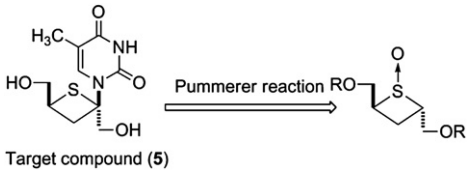


Fig. 1. Nucleoside antibiotics.

Oxetanocin A (**3**) has an unusual structure with an unstable oxetane ring in the sugar moiety; this compound possesses potent antiviral activity against various viruses, such as HIV and HSV.[4,5] Accordingly, many derivatives of oxetanocin A have been synthesized, and their antiviral activity has been investigated.[6] Among these compounds, carbocyclic oxetanocin G exhibits potent antiviral activity against VZV,[7] and the thietane nucleoside with a cytosine base shows antiviral activity against HIV.[8] Furthermore, angustmycin C (**4**), which has a hydroxymethyl group at the anomeric position, possesses attractive antiviral and antimicrobial properties.[9]

Aiming to develop a new antiviral agent, we designed a thietane nucleoside (**5**) having the structural features of both oxetanocin A and angustmycin C. We selected thymine as the nucleobase because some thietane nucleosides with a pyrimidine base have been found to have interesting antiviral activity. We hypothesized that target compound **5** could be synthesized by the Pummerer reaction[10] of a sulfoxide and silylated thymine (Scheme 1).



Scheme 1.

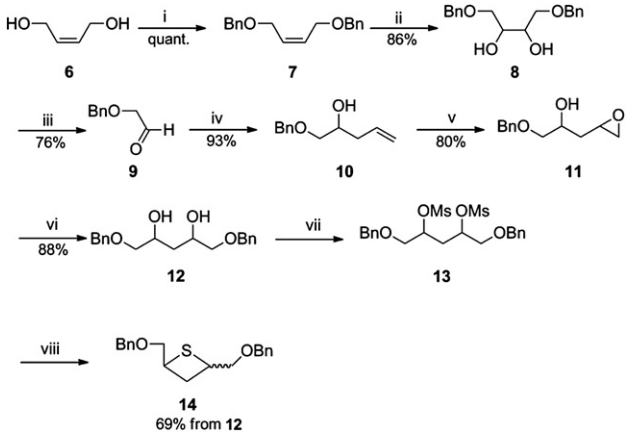
2. Results and discussion

First, sulfide **14** was synthesized from *cis*-2-butene-1,4-diol (**6**; Scheme 2). This diol was protected with *O*-benzyl groups by

* Corresponding authors. E-mail address: nishizon@hoku-iryo-u.ac.jp (N. Nishizono).

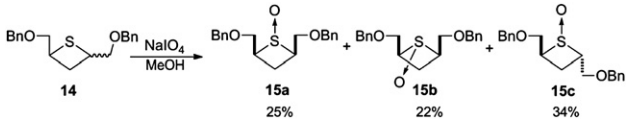
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.11.038

treatment with benzyl bromide in the presence of sodium hydride in DMF to give **7** (quantitative yield). The dihydroxylation of **7** with catalytic OsO_4 and NMO as co-oxidant gave **8**, which was then treated with $NaIO_4$ to give 2-(benzyloxy)acetaldehyde (**9**) in 65% yield from **7**. The treatment of **9** with allylmagnesium chloride in THF gave **10** in 93% yield. The epoxidation of **10** with *m*-CPBA gave **11**, which was treated with sodium benzyloxide to afford **12**[11] as a 1:1 diastereomeric mixture (70% from **10**). The diastereomeric mixture of **12** was treated with mesyl chloride in pyridine to give **13**, which was then treated with sodium sulfide in DMF at 100 °C to give thietane **14** as a 1:1 diastereomeric mixture (69% from **12**).



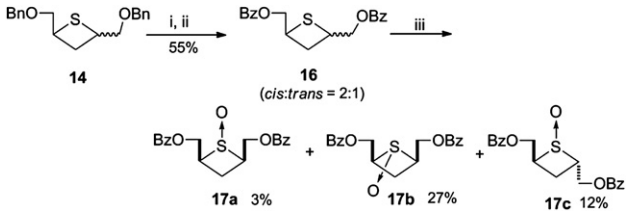
Scheme 2. Reagents and conditions: (i) BnBr, NaH, DMF, 0 °C to rt; (ii) OsO_4, NMO, acetone/H_2O; (iii) $NaIO_4$, MeOH, 0 °C to rt; (iv) allylmagnesium chloride, THF, 0 °C to rt; (v) *m*-CPBA, CH_2Cl_2, −20 °C to rt; (vi) NaOBn, BnOH; (vii) MsCl, pyridine, 0 °C to rt; (viii) Na_2S, DMF, 100 °C.

Sulfoxide **15a**–**c** was obtained by oxidation of diastereomeric mixture **14** with $NaIO_4$ in methanol (Scheme 3). The configuration of each diastereomer, **15a** and **15b**, was assigned on the basis of solvent- and Eu(fod)$_3$-induced shifts in their ^{1}H NMR spectra following the procedure reported by Folli et al.[12]



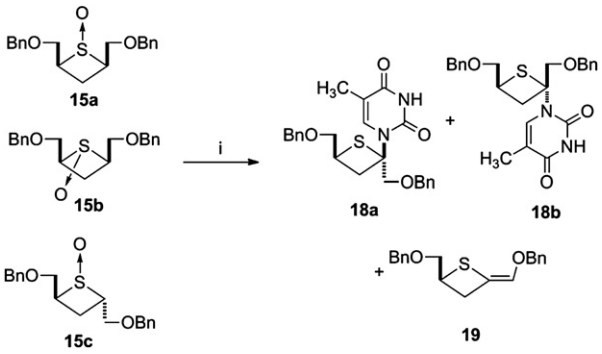
Scheme 3.

Sulfoxide **17**, the hydroxy groups of which were protected with benzoyl groups, was also prepared (Scheme 4). The configuration of each diastereomer, **17a** and **17b**, as also assigned on the basis of solvent- and Eu(fod)$_3$-induced shifts in their ^{1}H NMR spectra.



Scheme 4. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, 0 °C to rt; (ii) BzCl, pyridine, 0 °C to rt; (iii) $NaIO_4$, MeOH, 0 °C to rt.

We first examined the Pummerer reaction of sulfoxide **15c**, the hydroxy groups of which were protected with benzyl groups (Scheme 5). A solution of **15c** in toluene was added to a solution of silylated thymine in toluene at 0 °C under an argon atmosphere. Trimethylsilyl triflate and then triethylamine were added to the



Scheme 5. Reagents and conditions: (i) silylated thymine, TMSOTf, Et_3N, toluene, 0 °C to rt.

mixture at 0 °C. After stirring the mixture for 24 h at room temperature, the desired thietane nucleoside **18** (52%) was obtained as a 1:1 anomeric mixture along with alkene **19** (36%). Medium pressure liquid chromatography allowed the separation of the anomeric mixture to give **18a** and **18b**. The structure of the less polar compound **18b** was assigned to the α-anomer on the basis of its ^{1}H, ^{13}C NMR, and NOESY spectra. NOE correlation was observed between H-6 of the thymine and H-3′-α, as well as between H-3′-α and H-4′ (Fig. 2).

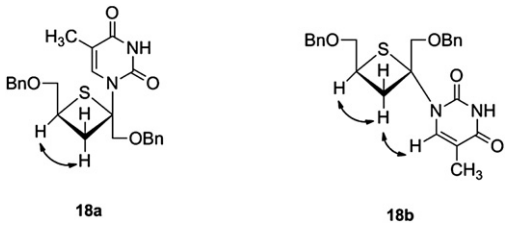
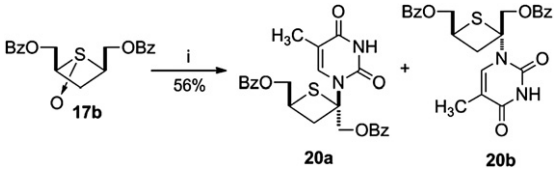


Fig. 2. Selected NOEs observed for **18a** and **18b**.

The Pummerer reaction was performed under the same condition using sulfoxides **15a** and **15b** (Scheme 5). The Pummerer reaction of **15a** gave **18** (47%) as a 1:1 diastereomeric mixture and **19** (41%). Sulfoxide **15b** also coupled with silylated thymine to give **18** (52%) as a 1:1 diastereomeric mixture and **19** (39%). Although the yield of the Pummerer reaction has been found to depend on the stereochemistry of the sulfoxide,[13] no significant effect of stereochemistry was observed for the present sulfoxides.

Next, *O*-benzoyl protected sulfoxide **17b** was used in the Pummerer reaction. Similar to the case of **16**, the reaction of **17b** with silylated thymine gave thietane nucleoside **20** as a 1:1 diastereomeric mixture in 56% yield (Scheme 6). The nature of the protecting group also had no significant effect on the yield for these sulfoxides.

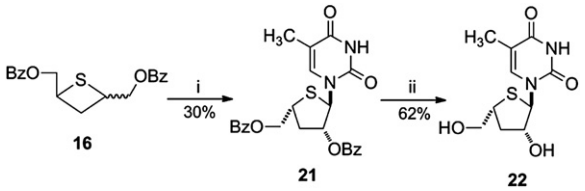


Scheme 6. Reagents and conditions: (i) silylated thymine, TMSOTf, Et_3N, toluene, 0 °C to rt.

We recently reported a novel method for synthesizing 4′-thionucleosides via the condensation of a thiofuranoid and silylated nucleobase in the presence of a hypervalent iodine compound.[14,15] To investigate the scope of this method, it was adopted for the synthesis of the thietane nucleoside. The reaction of thymine and **14** in the presence of PhI=O was examined. Although PhI=O gave the best result in the case of the thymine nucleoside, the present reaction resulted in a complex mixture with no detectable amount of

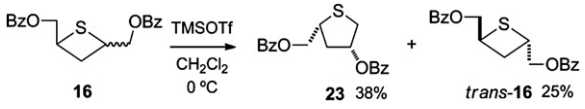
the desired compound. Similarly, the thietane nucleoside was not obtained from the reaction with other hypervalent iodine reagents.

Next, sulfide **16** was used instead of **14**. Surprisingly, the condensation reaction of **16** with thymine gave not the desired thietane nucleoside but rather ring-expanded compound **21** in 30% yield (Scheme 7). The deprotection of **21** gave **22** in 62% yield. The structure of **22** was determined by comparison with an authentic synthetic sample.[16]



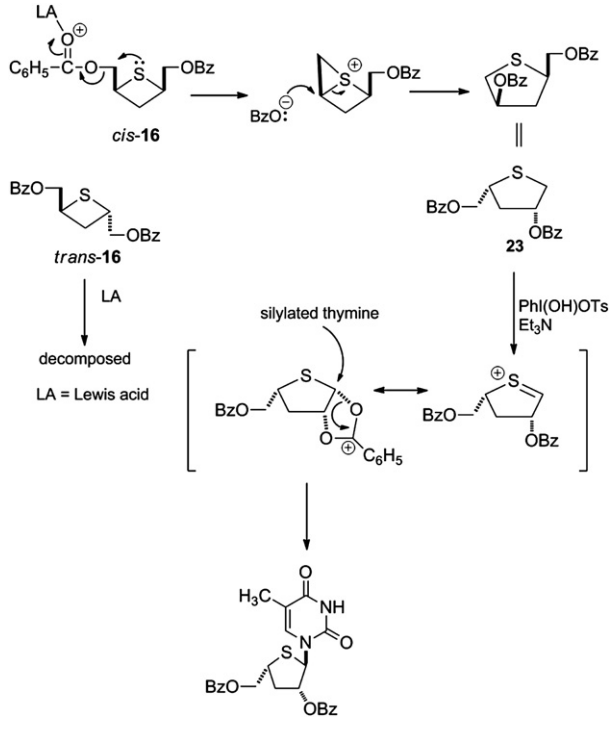
Scheme 7. Reagents and conditions: (i) thymine, TMSOTf, Et_3N, PhI(OH)OTs, CH_2Cl_2, 0 °C to rt; (ii) NaOMe, 0 °C to rt.

To investigate this reaction in further detail, TMSOTf was added to a solution of **16** (*cis*/*trans*=2:1) in CH_2Cl_2 (Scheme 8). After stirring for 30 min, only *cis*-**16** was consumed and the newly formed tetrahydrothiophene derivative **23** was obtained along with unreacted *trans*-**16** (Scheme 8). Although *trans*-**16** was consumed when the reaction time was extended, the yield of **23** did not change. This ring expansion is considered to involve intramolecular nucleophilic attack by the sulfur atom.[17]



Scheme 8.

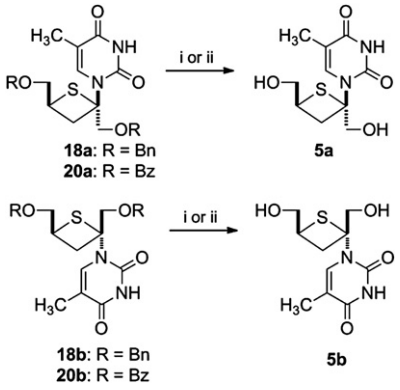
The leaving ability of the benzoyl group is enhanced by the coordination of the carbonyl oxygen to a Lewis acid; thereby, the intramolecular nucleophilic attack of the sulfur atom can easily proceed to afford the bicycle[2.1.0]episulphonium intermediate. Then, regiospecific bridgehead attack by benzoate ion leads to the thermodynamic product (**23**; Scheme 9).



Scheme 9.

This result suggests that **21** was formed via the reaction of silylated thymine with **23**, which was initially formed from *cis*-**16** as a result of Lewis acid activation. Thus, the use of the sulfide with *O*-benzoyl protecting groups gave the interesting result of forming the ring-expanded nucleoside.

Finally, the target compound **5** was obtained by deprotection of **18** and **20** (Scheme 10).



Scheme 10. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, 0 °C (70% from **18a**, 72% from **18b**); (ii) NH_3/MeOH, rt (**20a**: 78% from **20a**, 78% from **20b**).

3. Conclusion

In summary, the thietane nucleoside was synthesized by condensation of the sulfide and silylated thymine. The stereochemistry of the sulfoxide and the nature of the protecting group had no significant effect on the yield of the reaction. When a hypervalent iodine reagent was used, the sulfide with *O*-benzoyl protecting groups gave the ring-expanded nucleoside. Unfortunately, synthesized compound **6** did not exhibit anti-HSV activity, even at 50 μM.

4. Experimental section

4.1. General

All melting points were determined on a Yamato melting point apparatus (model MP-J3) and were uncorrected. The NMR spectra were recorded on a JEOL JNM-ECA-500 spectrometer. The chemical shifts are reported in parts per million (δ) relative to TMS (0.0 ppm) as the internal standard, and the signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). The values of the coupling constant *J* are given in hertz. The MS spectra were obtained on JEOL JMS-HX110, JEOL JMS-700TZ, and JEOL AccuTOF LC-plus systems. TLC was performed on Merck silica gel 60 F_{254} plates. Column chromatography was conducted using silica gel 60 N (Kanto, 100–210 μm) or silica gel 60 (Kanto, 40–50 μm).

*4.1.1. (Z)-1,4-Bis(benzyloxy)but-2-ene (**7**).* To a suspension of 55% NaH (13.0 g, 298 mmol) in DMF (250 mL), a solution of **6** (10.0 g, 114 mmol) in DMF (50 mL) was added at 0 °C. After the mixture was stirred at room temperature for 1 h, benzyl bromide (35.3 mL, 398 mmol) was added dropwise to the mixture. The resulting mixture was stirred for 4 h at room temperature. The reaction was then quenched by addition of saturated aqueous NH_4Cl solution, diluted with ether, and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=8:1) to give **7** (30.2 g, 99%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.25 (m, 10H), 5.82–5.76 (m, 2H), 4.49 (s, 4H), 4.06 (d, 4H, *J*=4.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.3, 129.6, 128.3, 127.9, 127.8, 72.4, 65.9. FAB-LRMS *m*/*z*: 269 (MH^+). FAB-HRMS *m*/*z*: 269.1550 (calcd for $C_{18}H_{21}O_2$: 269.1542).

*4.1.2. meso-1,4-Bis(benzyloxy)butane-2,3-diol (**8**).* To a solution of **7** (10.0 g, 38 mmol) in acetone (150 mL) and water (150 mL), NMO (4.8 g, 41 mmol) and a 0.02 M solution of OsO_4 in *t*-BuOH (2 mL, 0.04 mmol) were added at room temperature, and the resulting mixture was stirred at room temperature for 12 h. The mixture was diluted with ethyl acetate and washed with saturated aqueous $Na_2S_2O_4$ solution, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=1:1) to give **8** (9.3 g, 86%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.28 (m, 10H), 4.54 (s, 4H), 3.85–3.82 (m, 2H), 3.69–3.60 (m, 4H), 2.67 (d, 2H, *J*=5.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.7, 128.4, 127.8, 127.7, 73.5, 71.4, 71.1. EI-LRMS *m*/*z*: 302 (M^+). EI-HRMS *m*/*z*: 302.1518 (calcd for $C_{18}H_{22}O_4$: 302.1518).

*4.1.3. 2-Benzyloxyacetaldehyde (**9**).* To a solution of **8** (22.3 g, 74 mmol) in methanol (200 mL), $NaIO_4$ (23.7 g, 111 mmol) was added at 0 °C, and the resulting mixture was stirred at room temperature for 8 h. The formed precipitate was removed by filtration. Most of the solvent was removed by a rotary evaporator and the residual oil was distilled under reduced pressure to give **9** (16.9 g, 76%) as a colorless oil, bp 120 °C at 13 mm Hg.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.69 (s, 1H), 7.38–7.34 (m, 5H), 4.61 (s, 2H), 4.08 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.4, 137.0, 128.7, 128.3, 128.1, 75.4, 73.7. EI-LRMS *m*/*z*: 150 (M^+). EI-HRMS *m*/*z*: 150.0680 (calcd for $C_9H_{10}O_2$: 150.0681).

*4.1.4. 1-(Benzyloxy)pent-4-en-2-ol (**10**).* To a 2.0 M solution of allylmagnesium chloride in THF (100 mL, 200 mmol), a solution of **9** (10.0 g, 66 mmol) in THF (100 mL) was added at 0 °C under an argon atmosphere, and the mixture was stirred at room temperature for 15 min. The reaction was quenched by addition of saturated aqueous NH_4Cl solution, diluted with ethyl acetate, and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=4:1) to give **10** (11.8 g, 93%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.26 (m, 5H), 5.83 (m, 1H), 5.15–5.08 (m, 2H), 4.56 (s, 2H), 3.88 (m, 1H), 3.52 (dd, 1H, *J*=3.5 and 9.5 Hz), 3.38 (dd, 1H, *J*=6.8 and 9.5 Hz), 2.37 (d, 1H, *J*=3.5 Hz), 2.26 (t, 2H, *J*=6.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.9, 134.2, 128.4, 127.7, 127.6, 117.5, 73.8, 73.3, 69.6, 37.8. EI-LRMS *m*/*z*: 192 (M^+). EI-HRMS *m*/*z*: 192.1136 (calcd for $C_{12}H_{16}O_2$: 192.1150).

*4.1.5. 1-(Benzyloxy)-3-(oxiran-2-yl)propan-2-ol (**11**).* To a solution of **10** (10.8 g, 56 mmol) in CH_2Cl_2 (500 mL), *m*-CPBA (14.6 g, 85 mmol) was added at −20 °C under an argon atmosphere, and the mixture was stirred at room temperature for 18 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution, diluted with chloroform, and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=1:1) to give **11** (9.4 g, 80%, 1:1 diastereomeric mixture) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.29 (m, 10/2H), 4.57 (s, 4/2H), 4.08–4.04 (m, 2/2H), 3.58–3.51 (m, 2/2H), 3.47 (m, 1/2H), 3.38 (dd, 1/2H, *J*=7.4 and 9.4 Hz), 3.14–3.08 (m, 2/2H), 2.82–2.77 (m, 2/2H), 2.61–2.58 (m, 2/2H), 2.56–2.50 (m, 2/2H), 1.91–1.81 (m, 2/2H), 1.65 (m, 1/2H), 1.51 (ddd, 1/2H, *J*=4.2, 7.2, and 14.3 Hz). FAB-LRMS *m*/*z*: 209 (MH^+). EI-HRMS *m*/*z*: 209.1190 (calcd for $C_{12}H_{17}O_3$: 209.1177).

*4.1.6. 1,5-Bis(benzyloxy)pentane-2,4-diol (**12**).* To 50 mL of stirred benzyl alcohol, 0.5 g of finely cut sodium metal (23 mmol) was added, and the mixture was then stirred under nitrogen for 3 h. With stirring, a solution of **11** (2.4 g, 12 mmol) in benzyl alcohol (20 mL) was added to the reaction mixture and stirring at room temperature was continued for 16 h. To quench the reaction, the mixture was poured into 100 mL of water. The aqueous mixture was extracted with ethyl acetate (200 mL). The separated organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=1:1) to give **12** (3.2 g, 88% (1:1 diastereomixture)) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36–7.27 (m, 20/2H), 4.55 (s, 8/2H), 4.14–4.04 (m, 4/2H), 3.52–3.38 (m, 8/2H), 3.19 (d, 2/2H, *J*=2.3 Hz), 2.78 (d, 2/2H, *J*=3.4 Hz), 1.61–1.55 (m, 4/2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.9, 128.5, 128.4, 127.7, 127.6, 126.9, 74.4, 74.2, 73.3, 70.4, 67.6, 65.3, 36.0, 35.8. EI-LRMS *m*/*z*: 316 (M^+). EI-HRMS *m*/*z*: 316.1667 (calcd for $C_{19}H_{24}O_4$: 316.1674).

*4.1.7. 2,4-Bis(benzyloxymethyl)thietane (**14**).* To a solution of **12** (9.8 g, 31 mmol) in pyridine (200 mL), methanesulfonyl chloride (6.3 mL, 81 mmol) was added at 0 °C, and the resulting mixture was stirred for 2 h at room temperature. The reaction was quenched by addition of ice water. The mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue and $Na_2S\cdot 9H_2O$ (8.2 g, 34 mmol) were dissolved in DMF (300 mL), and the resulting mixture was stirred for 24 h at 100 °C. The mixture was diluted with ether, and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=8:1) to give **14** (6.7 g, 69% (*cis*/*trans*=1:1)) as an yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41–7.36 (m, 20/2H), 4.60 (s, 4/2H), 4.56 (d, 4/2H, *J*=5.1 Hz), 3.85–3.70 (m, 10/2H), 3.62–3.58 (m, 2/2H), 3.01 (q, 1/2H, *J*=8.5 Hz), 2.73 (t, 2/2H, *J*=6.8 Hz), 2.39 (m, 1/2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.3, 128.7, 128.6, 128.4, 127.8, 76.3, 75.8, 73.3, 36.5, 35.7, 33.0, 32.8. EI-LRMS *m*/*z*: 314 (M^+). EI-HRMS *m*/*z*: 314.1340 (calcd for $C_{19}H_{22}O_2S$: 314.1341).

*4.1.8. 2,4-Bis(benzyloxymethyl)thietane 1-oxide (**15**).* To a solution of **14** (2.6 g, 8 mmol) in methanol (80 mL), $NaIO_4$ (2.3 g, 11 mmol) was added at 0 °C, and the mixture was stirred for 8 h at room temperature. The mixture was concentrated in vacuo. The residue was purified by medium pressure chromatography (silica gel; hexane/AcOEt=5:4) to give **15a** (660 mg, 25%) as a yellow oil, **15b** (581 mg, 22%) as a colorless syrup, and **15c** (898 mg, 34%) as an yellow oil.

Compound **15a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.28 (m, 10H), 4.59 (d, 4H, *J*=2.8 Hz), 3.80 (dd, 2H, *J*=4.8 and 10.8 Hz), 3.70 (dd, 2H, *J*=5.7 and 10.8 Hz), 3.49–3.42 (m, 2H), 2.46 (m, 1H), 1.93 (q, 1H, *J*=12.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.8, 128.6, 127.9, 127.7, 73.3, 68.0, 63.3, 16.7. FAB-LRMS *m*/*z*: 331 (MH^+). FAB-HRMS *m*/*z*: 331.1363 (calcd for $C_{19}H_{23}O_3S$: 331.1368).

Compound **15b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.28 (m, 10H), 4.61 (d, 2H, *J*=11.6 Hz), 4.48 (d, 2H, *J*=11.6 Hz), 3.93–3.88 (m, 2H), 3.51–3.44 (m, 4H), 2.79 (m, 1H), 2.49 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.9, 128.6, 127.9, 73.4, 64.5, 51.5, 27.2. FAB-LRMS *m*/*z*: 331 (MH^+). FAB-HRMS *m*/*z*: 331.1364 (calcd for $C_{19}H_{23}O_3S$: 331.1368).

Compound **15c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38–7.28 (m, 10H), 4.64–4.55 (m, 4H), 4.10 (dd, 1H, *J*=7.1 and 10.8 Hz), 3.90 (dd, 1H, *J*=5.7 and 10.8 Hz), 3.81 (m, 1H), 3.68–3.63 (m, 3H), 2.51 (m, 1H), 2.33 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.1, 137.8, 128.6, 128.0, 127.9, 127.8, 73.5, 73.4, 68.3, 65.7, 64.3, 52.9, 19.6. FAB-LRMS *m*/*z*: 331 (MH^+). FAB-HRMS *m*/*z*: 331.1369 (calcd for $C_{19}H_{23}O_3S$: 331.1368).

*4.1.9. 2,4-Bis(benzoyloxymethyl)thietane (**16**).* To a solution of **16** (100 mg, 0.32 mmol) in CH_2Cl_2 (1 mL), a solution of $TiCl_4$ (141 μL,

1.28 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C under nitrogen, and the mixture was stirred for 8 h at room temperature. The mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (10% ethanol in chloroform) to give the crude diol. To a solution of the crude diol in pyridine (1 mL), benzoyl chloride (112 μL, 0.96 mmol) was added at 0 °C under nitrogen, and the mixture was stirred for 8 h at room temperature. The mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=4:1) to give **16** (60 mg, 55%, *cis*/*trans*=2:1) as a colorless solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94–7.79 (m, 6/3H), 7.49–7.46 (m, 3/3H), 7.37–7.34 (m, 6/3H), 4.56 (dd, 1/3H, *J*=6.8 and 11.3 Hz), 4.49 (dd, 2/3H, *J*=6.8 and 11.3 Hz), 4.42 (dd, 1/3H, *J*=6.8 and 11.3 Hz), 4.32 (dd, 2/3H, *J*=6.8 and 11.3 Hz), 3.94–3.83 (m, 3/3H), 3.04 (dt, 1/3H, *J*=6.8 and 14.8 Hz), 2.82 (t, 1/3H, *J*=7.1 Hz), 2.56 (dt, 1/3H, *J*=6.8 and 14.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.2, 166.1, 133.1, 129.7, 129.6, 128.4, 69.4, 68.9, 35.1, 34.2, 32.4, 32.1. FAB-LRMS *m*/*z*: 343 (MH^+). FAB-HRMS *m*/*z*: 343.0986 (calcd for $C_{19}H_{19}O_4S$: 343.1004).

*4.1.10. 2,4-Bis(benzoyloxymethyl)thietane 1-oxide(**17**).* To a solution of **16** (38 mg, 0.11 mmol) in methanol (5 mL), $NaIO_4$ (23 mg, 0.11 mmol) was added at 0 °C, and the mixture was stirred for 8 h at room temperature. The mixture was concentrated in vacuo. The residue was purified by medium pressure chromatography (silica gel; hexane/AcOEt=1:4) to give **17a** (1.2 mg, 3%) as a colorless syrup, **17b** (10.7 mg, 27%) as an yellow syrup, and **17c** (4.8 mg, 12%) as a colorless syrup.

Compound **17a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05–8.03 (m, 4H), 7.58–7.55 (m, 2H), 7.46–7.43 (m, 4H), 4.65 (dd, 2H, *J*=9.8 and 12.3 Hz), 4.54 (dd, 2H, *J*=4.1 and 12.3 Hz), 3.70–3.63 (m, 2H), 3.07 (m, 1H), 2.84 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.3, 133.4, 129.9, 129.5, 128.5, 58.8, 49.9, 27.6. EI-LRMS *m*/*z*: 358 (M^+). EI-HRMS *m*/*z*: 358.0877 (calcd for $C_{19}H_{18}O_3S$: 358.0875).

Compound **17b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02–8.00 (m, 4H), 7.57–7.53 (m, 2H), 7.40–7.36 (m, 4H), 4.70 (dd, 2H, *J*=4.5 and 12.5 Hz), 4.58 (dd, 2H, *J*=5.7 and 12.5 Hz), 3.70–3.64 (m, 2H), 2.64 (m, 1H), 1.93 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 166.1, 133.5, 129.8, 129.2, 128.6, 62.4, 62.1, 16.6. EI-LRMS *m*/*z*: 358 (M^+). EI-HRMS *m*/*z*: 358.0880 (calcd for $C_{19}H_{18}O_3S$: 358.0875).

Compound **17c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.06–8.04 (m, 4H), 7.61–7.56 (m, 2H), 7.46–7.43 (m, 4H), 5.01 (dd, 1H, *J*=7.2 and 12.3 Hz), 4.89 (dd, 1H, *J*=5.8 and 12.3 Hz), 4.71 (dd, 1H, *J*=4.5 and 12.5 Hz), 4.61 (dd, 1H, *J*=6.2 and 12.5 Hz), 3.96–3.88 (m, 2H), 2.65 (m, 1H), 2.39 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.4, 166.2, 133.5, 133.4, 129.8, 128.6, 128.5, 63.4, 62.8, 31.0, 19.1. EI-LRMS *m*/*z*: 358 (M^+). EI-HRMS *m*/*z*: 358.0877 (calcd for $C_{19}H_{18}O_3S$: 358.0875).

*4.1.11. 1-[2,4-Bis(benzyloxymethyl)thietan-2-yl]thymine (**18**).* To a solution of **17c** (313 mg, 0.95 mmol) in toluene (5 mL), *O*,*O*′-bis(trimethylsilyl)thymine (487 mg, 1.90 mmol) in toluene (5 mL) and TMSOTf (347 μL, 1.90 mmol) were added at 0 °C. Triethylamine (268 μL, 1.90 mmol) was then added to the mixture, and the resulting mixture was stirred for 24 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution, diluted with ethyl acetate, and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=1:1) to give **18a** (108 mg, 26%) as a yellow syrup, **18b** (108 mg, 26%) as an yellow syrup, and **19** (107 mg, 36%) as a yellow oil.

Compound **18a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.77 (br s, 1H), 7.28–7.12 (m, 10H), 6.93 (d, 1H, *J*=1.1 Hz), 4.45 (s, 2H), 4.44 (s, 2H), 3.96 (d, 1H, *J*=10.2 Hz), 3.90 (dd, 1H, *J*=1.1 and 10.2 Hz), 3.59–3.56 (m, 2H), 3.48 (m, 1H), 3.09 (dd, 1H, *J*=7.4 and 12.5 Hz), 2.79 (dd, 1H, *J*=7.4 and 12.5 Hz), 1.85 (d, 3H, *J*=1.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.0, 149.2, 137.7, 137.6, 137.3, 128.4, 127.9, 127.8, 127.6, 109.1, 74.7, 74.0, 73.4, 73.3, 65.0, 38.1, 34.0, 12.4. FAB-LRMS *m*/*z*: 439 (MH^+). FAB-HRMS *m*/*z*: 439.1681 (calcd for $C_{24}H_{27}N_2O_4S$: 439.1692).

Compound **18b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.86 (br s, 1H), 7.30–7.09 (m, 11H), 4.47 (s, 2H), 4.40 (d, 1H, *J*=12.0 Hz), 4.34 (d, 1H, *J*=12.0 Hz), 3.97 (d, 1H, *J*=9.7 Hz), 3.83 (d, 1H, *J*=9.7 Hz), 3.64–3.51 (m, 3H), 3.26 (dd, 1H, *J*=9.5 and 14.0 Hz), 2.81 (dd, 1H, *J*=4.3 and 14.0 Hz), 1.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.3, 149.4, 138.6, 138.5, 137.8, 137.4, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 108.8, 75.3, 75.2, 74.1, 73.3, 73.2, 67.8, 36.4, 33.1, 12.4. FAB-LRMS *m*/*z*: 439 (MH^+). FAB-HRMS *m*/*z*: 439.1689 (calcd for $C_{24}H_{27}N_2O_4S$: 439.1692).

Compound **19**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.28 (m, 10H), 6.25 (t, 1H, *J*=1.7 Hz), 4.75 (s, 2H), 4.57 (d, 2H, *J*=2.8 Hz), 3.86 (m, 1H), 3.79–3.68 (m, 2H), 3.46 (m, 1H), 3.05 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.1, 137.6, 136.4, 128.5, 128.0, 127.9, 127.8, 127.6, 109.5, 75.2, 73.6, 73.4, 37.8, 35.1. EI-LRMS *m*/*z*: 312 (M^+). EI-HRMS *m*/*z*: 312.1184 (calcd for $C_{19}H_{20}O_2S$: 312.1184).

*4.1.12. 1-[2,4-Bis(benzoyloxymethyl)thietan-2-yl]thymine (**20**).* Prepared from **17b** (100 mg, 0.3 mmol) using a procedure similar to that described above for compound **19**, **20a** (39 mg, 28%) and **20b** (39 mg, 28%) were obtained as colorless foams.

Compound **20a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.95 (br s, 1H), 7.99–7.97 (m, 2H), 7.91–7.89 (m, 2H), 7.58–7.40 (m, 6H), 7.00 (s, 1H), 4.98 (d, 1H, *J*=12.0 Hz), 4.86 (d, 1H, *J*=11.5 Hz), 4.61 (dd, 1H, *J*=5.8 and 12.0 Hz), 4.37 (m, 1H), 3.95 (m, 1H), 3.38 (dd, 1H, *J*=7.5 and 13.2 Hz), 3.20 (dd, 1H, *J*=8.0 and 13.2 Hz), 1.79 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.3, 165.6, 163.9, 149.4, 136.2, 133.7, 133.5, 129.7, 129.6, 128.7, 128.6, 110.4, 68.1, 67.9, 64.3, 38.2, 33.2, 12.3. FAB-LRMS *m*/*z*: 467 (MH^+). FAB-HRMS *m*/*z*: 467.1272 (calcd for $C_{24}H_{23}N_2O_6S$: 467.1277).

Compound **20b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.14 (br s, 1H), 8.05–8.02 (m, 2H), 7.89–7.40 (m, 8H), 7.25 (s, 1H), 5.03 (d, 1H, *J*=11.3 Hz), 4.81 (d, 1H, *J*=11.3 Hz), 4.69 (dd, 1H, *J*=6.8 and 11.3 Hz), 4.57 (dd, 1H, *J*=6.8 and 11.3 Hz), 3.86 (m, 1H), 3.58 (m, 1H), 3.17 (m, 1H), 1.72 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 166.3, 165.6, 164.1, 133.7, 133.5, 129.8, 129.7, 128.7, 128.6, 110.1, 69.7, 68.1, 51.9, 36.8, 32.1, 12.4. FAB-LRMS *m*/*z*: 467 (MH^+). FAB-HRMS *m*/*z*: 467.1272 (calcd for $C_{24}H_{23}N_2O_6S$: 467.1277).

*4.1.13. 1-(2,5-Di-O-benzoyl-3-deoxy-4-thio-α-arabinofuranosyl)thymine (**21**).* To a suspension of thymine (38 mg, 0.30 mmol) in CH_2Cl_2 (1 mL), TMSOTf (150 μL, 0.90 mmol) and triethylamine (63 μL, 0.90 mmol) were added at 0 °C, and the mixture was stirred for 1 h at room temperature. A solution of **16** (50 mg, 0.15 mmol) in CH_2Cl_2 (10 mL) was added to the mixture at 0 °C, and PhI(OH)OTs (94 mg, 0.24 mmol) was then added in one portion. The mixture was stirred at room temperature for 24 h. The reaction was quenched by addition of ice water, diluted with ethyl acetate, and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=1:1) to give **21** (20 mg, 30%) as a colorless foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.90 (br s, 1H), 8.03–7.98 (m, 4H), 7.58–7.53 (m, 2H), 7.46–7.40 (m, 5H), 6.47 (d, 1H, *J*=6.0 Hz), 5.56 (m, 1H), 4.54 (dd, 1H, *J*=6.6 and 10.9 Hz), 4.42 (dd, 1H, *J*=7.2 and 10.9 Hz), 4.21 (m, 1H), 2.73 (m, 1H), 2.24 (m, 1H), 1.95 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.0, 165.6, 163.3, 150.6, 135.7, 133.7, 133.4, 129.9, 129.7, 129.4, 128.8, 128.6, 128.5, 112.1, 79.4, 67.6, 65.4, 43.6, 35.8, 12.7. ESI-LRMS *m*/*z*: 489 (MNa^+). ESI-HRMS *m*/*z*: 489.1096 (calcd for $C_{24}H_{22}N_2NaO_6S$: 489.1096).

*4.1.14. 1-(3-Deoxy-4-thio-α-arabinofuranosyl)thymine (**22**).* To a solution of **21** (65 mg, 0.13 mmol) in methanol (20 mL), a 0.5 M solution of sodium methoxide in methanol (1.3 mL, 0.62 mmol) was added at 0 °C, and the mixture was stirred for 3 h at room

temperature. The mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (methanol/chloroform=1:9) to give **22** (20 mg, 62%) as a colorless solid, mp 227–229 °C.

^{1}H NMR (500 MHz, methanol-d_4) δ: 7.75 (d, 1H, J=1.2 Hz), 5.98 (d, 1H, J=6.0 Hz), 4.37 (m, 1H), 3.89 (m, 1H), 3.72 (dd, 1H, J=5.2 and 10.9 Hz), 3.58 (dd, 1H, J=6.6 and 10.9 Hz), 2.31 (m, 1H), 1.91 (d, 3H, J=1.2 Hz), 1.84 (m, 1H). ^{13}C NMR (125 MHz, methanol-d_4) δ: 153.0, 138.6, 112.1, 106.2, 79.3, 68.6, 67.1, 48.1, 38.5, 12.5. ESI-LRMS m/z: 281 (MNa^+). ESI-HRMS m/z: 281.5079 (calcd for $C_{10}H_{14}N_2NaO_4S$: 281.5072).

*4.1.15. 1,4-Anhydro-2,5-di-O-benzoyl-3-deoxy-4-thio-α-arabinofuranose (**23**).* To a solution of **16** (100 mg, 0.34 mmol) in CH_2Cl_2 (5 mL), TMSOTf (0.25 μL, 1.36 mmol) was added at 0 °C, and mixture was stirred for 30 min at room temperature. The mixture was diluted with ethyl acetate, and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=8:1) to give **23** (38 mg, 38%) as a colorless foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.06–8.03 (m, 4H), 7.59–7.54 (m, 2H), 7.47–7.42 (m, 4H), 5.74 (m, 1H), 4.54 (dd, 1H, J=8.0 and 10.9 Hz), 4.49 (dd, 1H, J=7.5 and 10.9 Hz), 3.91–3.86 (m, 1H), 3.33 (dd, 1H, J=5.4 and 12.0 Hz), 3.15 (ddd, 1H, J=0.9, 3.7 and 12.0 Hz), 2.44 (m, 1H), 2.40 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.1, 165.9, 133.3, 133.1, 129.9, 129.8, 129.7, 128.5, 128.4, 77.4, 68.5, 43.9, 37.9, 36.9. ESI-LRMS m/z: 365 (MNa^+). ESI-HRMS m/z: 365.0814 (calcd for $C_{19}H_{18}NaO_4S$: 365.0824).

4.1.16. 1-[(2R,4R*)-2,4-Bis(hydroxymethyl)thietan-2-yl]thymine (**5a**).* From **18a**: to a solution of **18a** (192 mg, 0.4 mmol) in CH_2Cl_2 (2 mL), a solution $TiCl_4$ (176 μL, 1.6 mmol) in CH_2Cl_2 (2 mL) was added at 0 °C under N_2, and the mixture was stirred for 1 h at 0 °C. The mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (ethanol/chloroform=1:9) to give **5a** (73 mg, 70%) as a colorless solid, mp 217–218 °C.

From **20a**: **20a** (15 mg, 0.03 mmol) was dissolved in 5 mL of methanolic ammonia. The solution was allowed to stand for 24 h at room temperature. The reaction mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (ethanol/chloroform=1:9) to give **5a** (6 mg, 78%) as a colorless foam, mp 217–218 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 11.3 (s, 1H), 7.22 (d, 1H, J=1.1 Hz), 5.42 (t, 1H, J=6.4 Hz), 4.90 (t, 1H, J=5.4 Hz), 3.85 (m, 1H), 3.79 (dd, 1H, J=6.4 and 11.6 Hz), 3.55 (m, 1H), 3.49–3.40 (m, 2H), 2.96 (m, 1H), 2.70 (m, 1H), 1.78 (d, 3H, J=1.1 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 164.2, 149.5, 137.7, 107.7, 66.4, 65.6, 64.6, 36.6, 12.1. FAB-LRMS m/z: 259 (MH^+). FAB-HRMS m/z: 259.0768 (calcd for $C_{10}H_{15}N_2O_4S$: 259.0753).

4.1.17. 1-[(2S,4R*)-2,4-Bis(hydroxymethyl)thietan-2-yl]thymine (**5b**).* From **18b**: prepared from **18b** (100 mg, 0.2 mmol) using a procedure similar to that described above for compound **5a**, **5b** (37 mg, 72%) was obtained as a colorless solid, mp 224–225 °C.

From **20b**: prepared from **20b** (15 mg, 0.03 mmol) using a procedure similar to that described above for compound **5a**, **5b** (6 mg, 78%) was obtained as a colorless solid, mp 224–225 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 11.2 (s, 1H), 7.33 (s, 1H), 5.33 (t, 1H, J=6.2 Hz), 4.99 (t, 1H, J=5.4 Hz), 3.82–3.75 (m, 2H), 3.65 (m, 1H), 3.57 (m, 1H), 3.32–3.19 (m, 2H), 2.69 (dd, 1H, J=4.0 and 13.6 Hz), 1.77 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 164.2, 149.6, 138.3, 107.2, 67.5, 67.4, 66.1, 34.7, 34.6, 12.1. FAB-LRMS m/z: 259 (MH^+). FAB-HRMS m/z: 259.0765 (calcd for $C_{10}H_{15}N_2O_4S$: 259.0753).

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.11.038. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Nakamura, S.; Kondo, H. *Heterocycles* **1977**, *8*, 583–607.
2. Mizuno, K.; Tsujino, M.; Takada, M.; Hayashi, M.; Atsumi, K. *J. Antibiot.* **1974**, *27*, 775–782.
3. Lee, W. W.; Benitez, A.; Goodman, L.; Baker, B. R. *J. Am. Chem. Soc.* **1960**, *82*, 2648–2649.
4. Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, T. *J. Antibiot.* **1986**, *39*, 1623–1625.
5. Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. *J. Antibiot.* **1987**, *40*, 1077–1078.
6. Ichikawa, E.; Kato, K. *Synthesis* **2002**, 1–28.
7. Maruyama, T.; Hanai, Y.; Sato, Y.; Snoeck, R.; Andrei, G.; Hosoya, M.; Balzarini, J.; DeClercq, E. *Chem. Pharm. Bull.* **1993**, *41*, 516–521.
8. Choo, H.; Chen, X.; Yadav, V.; Wang, J.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2006**, *49*, 1635–1647.
9. Sakai, H.; Yuntsen, H.; Ishikawa, F. *J. Antibiot.* **1954**, *7*, 116–119.
10. O'Neil, I. A.; Hamilton, K. M. *Synlett* **1992**, 791–792.
11. Harada, T.; Sakamoto, K.; Ikemura, Y.; Oku, A. *Tetrahedron Lett.* **1988**, *29*, 3097–3100.
12. Folli, U.; Irossi, D.; Taddei, F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 933–936.
13. Naka, T.; Minakawa, N.; Abe, H.; Kaga, D.; Matsuda, A. *J. Am. Chem. Soc.* **2000**, *122*, 7233–7243.
14. Nishizono, N.; Baba, R.; Nakamura, C.; Oda, K.; Machida, M. *Org. Biomol. Chem.* **2003**, *1*, 3692–3697.
15. Nishizono, N.; Soma, K.; Baba, R.; Machida, M.; Oda, K. *Heterocycles* **2008**, *75*, 619–634.
16. See Supplementary data.
17. A related situation has been reported: (a) Jeong, L. S.; Nicklaus, M. C.; George, C.; Marquez, V. E. *Tetrahedron Lett.* **1994**, *35*, 7573–7576; (b) Miller, J. A.; Pugh, A. W.; Ullah, G. M. *Nucleosides Nucleotides Nucleic Acids* **2000**, *19*, 1475–1486.