Synthesis of 5'-Halo-2',3'-*lyxo*-epoxy and 2',3'-Unsaturated Thieno[3,2-*d*]pyrimidine Nucleosides

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A series of thieno[3,2-*d*]pyrimidine-2,4-dione nucleosides modified in the carbohydrate moiety has been synthesized. In the first part, synthetic routes are described for the replacement of 5'-hydroxyl group in preformed 1-(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione **I** by fluoro, iodo or chloro atoms. Reduction of the 5'-iodo substituent of **VI** was then carried out catalytically using palladium on carbon as catalyst to give the expected 5'-deoxy derivative **VIII**. The *lyxo*-epoxide derivative **XII** was then synthesized by sequential treatment of the 5'-deoxy-5'-chloro derivative **X** with methanesulfonyl chloride and with sodium hydroxide. In the second part, most of attention has been devoted to apply different methods reported in the literature that allow access to 2',3'-olefinic derivatives from the corresponding 2',3'-dihydroxy precursor. The 5'-*O*-silyl protected bisxanthate **XIV** either on reduction with tri-*n*-butyltin hydride or by reductive elimination of the haloacetate **XVI** afforded the free 2',3'-olefin nucleoside after removal of the 5'-protecting group. However none of the compounds in this series exhibited significant antiviral activity against HIV at the doses tested.

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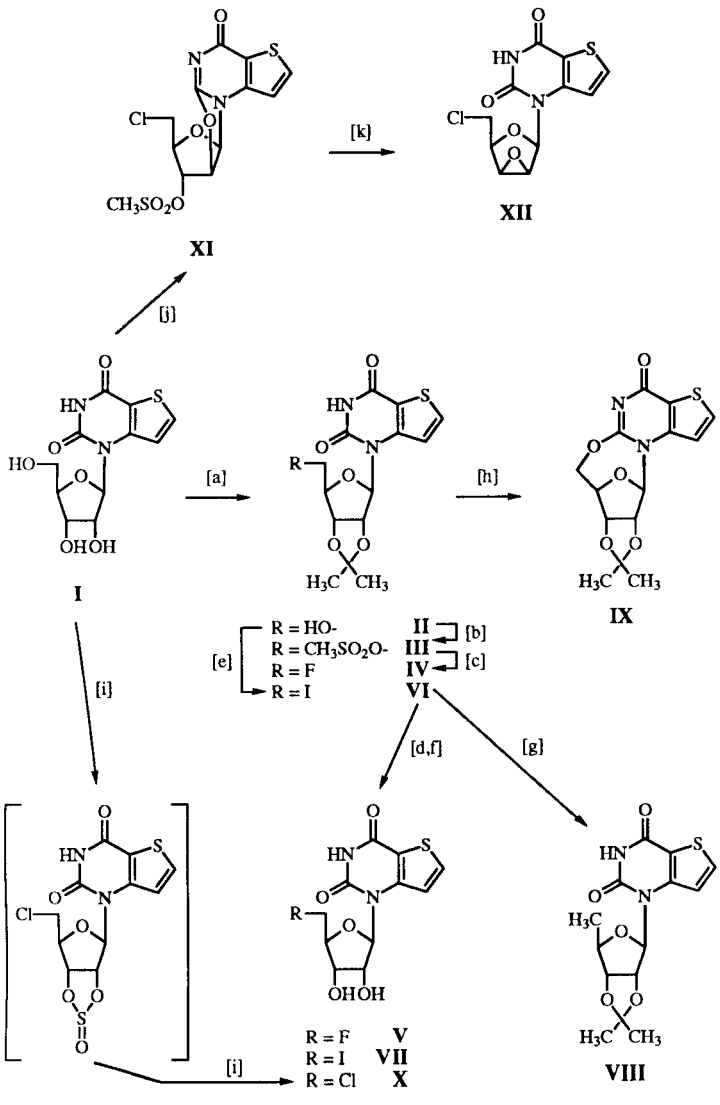
A large number of 5'-deoxynucleosides have been synthesized in recent years. The resulting halo sugar nucleosides are versatile starting materials for the preparation of unusual deoxynucleosides [1,2,3], 4',5'-unsaturated nucleosides [4] and anhydro nucleosides [3]. The general strategy in this work was to employ preformed 1-(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione as starting material. The replacement of specific 5'-hydroxyl group by fluoro or iodo functions was realized after conversion of 2' and 3' hydroxyl groups into their isopropylidene derivative as protecting group. The 5'-chloro derivative was obtained *via* a 2',3'-*O*-sulfinyl intermediate. We have then initiated the synthesis of 2',3'-*lyxo*-epoxy compound so that the epoxide function could undergo a cleavage to afford either an arabinonucleoside or a xylonucleoside. Finally, it was of particular interest to apply well known methods to access 2',3'-olefinic nucleoside analogues, since the unsaturated compounds such as 1-(2,3-dideoxy-β-D-glyceropent-2-enofuranosyl)thymine (d4T) and 1-(2,3-dideoxy-β-D-glyceropent-2-enofuranosyl)cytosine (d4C) are currently undergoing clinical trials in patients with AIDS [5].

The synthesis of 5'-deoxynucleosides led us to employ preformed 1-(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione **I** described in a previous report as starting material [6]. After conversion of **I** into its 2',3'-*O*-isopropylidene derivative **II** by a standard procedure [7], reaction of **II** with methanesulfonyl chloride afforded 5'-*O*-mesyl-2',3'-*O*-isopropylidene compound **III** (Scheme A). Treatment of **III** with silver fluoride in refluxing pyridine led to 5'-deoxy-5'-fluoro-2',3'-*O*-isopropylidene derivative **IV** [8], which was purified by column chromatography on silica gel (34%). Removal of the isopropylidene group was carried out using 80% trifluoroacetic acid to afford 1-(5-deoxy-5-fluoro-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione **V** as crystals in an overall yield of 15% from **I**. The characteristic ^{13}C nmr spectrum of **V** with large fluorine couplings (J $C_{5'}$-F = 167.0 Hz, J $C_{4'}$-F = 17.6 Hz, J $C_{3'}$-F = 5.9 Hz) was readily apparent.

The reaction of iodination of the primary 5'-hydroxyl group of **II** was also realized with methyltriphenoxyphosphonium iodide in *N,N*-dimethylformamide to give the corresponding 5'-deoxy-5'-iodo-2',3'-*O*-isopropylidene nucleoside **VI** (53%) after silica gel preparative tlc [9]. This reaction was conducted at room temperature in order to avoid starting material damage. Removal of the 2',3'-*O*-isopropylidene group was achieved using acetic acid at reflux and 1-(5-deoxy-5-iodo-β-D-ribofuranosyl)thieno-[3,2-*d*]pyrimidine-2,4-dione **VII** was obtained in an overall yield of 44% from **I**. Reduction of the 5'-iodo derivative **VI** was then carried out using palladium on carbon as hydrogenation catalyst to yield the 5'-deoxy nucleoside **VIII** (28%). We then attempted to convert **VI** to the corresponding 4',5'-olefin using potassium *tert*-butoxide in dimethyl sulfoxide as reported by Verheyden and Moffatt [10]. This method was unsuccessful probably due to the steric hindrance caused by the bulky 2',3'-protecting group. Such a result was nevertheless interesting in view of the fact that this treatment provided the 2,5'-anhydro-2',3'-*O*-isopropylidene nucleoside **IX** identified by comparison with an authentic sample. In fact the most convenient route to provide this compound proceeded by treatment of the 2',3'-*O*-isopropylidene-5'-*O*-mesyl nucleoside **III** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile (50%). That prompted us to confirm the pref-

Scheme A



[a] $(CH_3)_2C(OCH_3)_2$, *p*-toluenesulfonic acid in acetone Δ for **II** (94%). [b] CH_3SO_2Cl in pyridine for **III** (85%). [c] AgF in pyridine Δ for **IV** (34%). [d] **IV** to **V**: TFA/H_2O (57%). [e] $CH_3P^+(OC_6H_5)_3I^-$ in DMF for **VI** (53%). [f] **VI** to **VII**: acetic acid Δ (88%). [g] **VI** to **VIII**: H_2-Pd/C-TEA in methanol (28%). [h] **III** to **IX**: DBU in CH_3CN Δ (50%); **VI** to **IX**: KOtBu in DMSO (19%). [i] $SOCl_2$/pyridine in CH_3CN and NH_3-CH_3OH-H_2O for **X** (28%). [j] $SOCl_2$/pyridine in CH_3CN Δ and CH_3SO_2Cl in pyridine for **XI** (30%). [k] 1 *N* NaOH in EtOH Δ for **XII** (50%).

erential formation of the 2,5'-cyclonucleoside due to the tendency of the 2',3'-*O*-isopropylidene derivative to undergo intramolecular cyclization reaction involving $C_{5'}$.

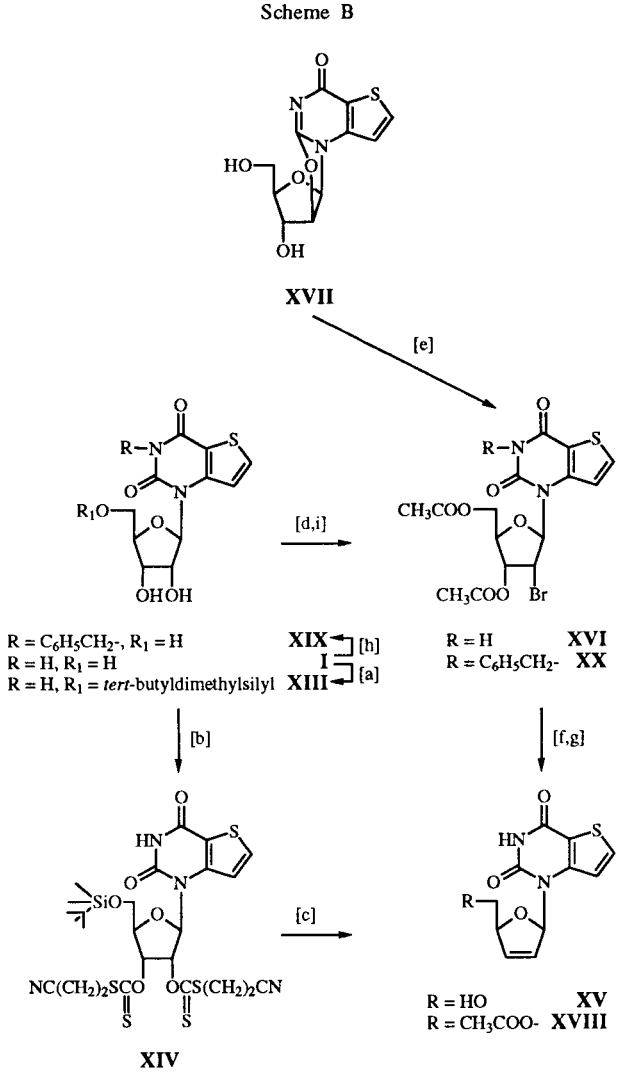
Finally, sequential treatment of **I** with thionyl chloride in the presence of pyridine led to a mixture of the cyclic sulfinate diastereoisomers which on treatment with methanol saturated with ammonia afforded 1-(5-chloro-5-deoxy-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione **X** (28%) [11]. As expected, the replacement of the hydroxyl group on 5'-position by chlorine led to a strong upfield shift of the $C_{5'}$ ($\Delta\delta$ = 16.3 ppm) relative to that in **I**, whereas the introduction of fluorine or iodine atoms involved a roughly deshielding (respectively $\Delta\delta$ = 21.8 ppm and $\Delta\delta$ = 2.2 ppm) in the ^{13}C nmr spectra.

Subsequent reaction of **X** with methanesulfonyl chloride conducted to the 2,2'-anhydro-5'-chloro-5'-deoxy-3'-*O*-mesyl nucleoside **XI** instead of the presumed 2',3'-dimesyl compound [12]. In fact, the nmr data of this material exhibited the presence of a 2,2'-anhydro species rather than the 2,3'-anhydro structure which was furthermore considered to be less likely for steric reasons. Treatment of **XI** with sodium hydroxide afforded the 2',3'-*lyxo*-epoxy compound **XII**. The intramolecular cyclization to epoxide **XII** can be rationalized by a first cleavage of the 2,2'-anhydro bridge followed by an attack of the 2'-hydroxyl group on carbon $C_{3'}$ with elimination of a methanesulfonate group which was evidently facilitated under alkaline conditions.

Since our ultimate goal was the preparation of the 2',3'-unsaturated nucleoside **XV**, we attempted in a second part to apply a few known methods for the conversion of the *cis* vicinal diols of **I** to the 2',3'-olefin (Scheme B). Therefore this conversion should be carried out under mild neutral conditions due to the lability of the derived allylic glycosidic bond to both acidic [13] and basic [5f] conditions. We have investigated the Eastwood procedure [13] (that reported the conversion of 2-methoxy-1,3-dioxolane into the corresponding olefin) and the Corey-Winter reaction [14,15] (that notified the desulfurization of a cyclic thionocarbonate to furnish the desired olefin) which revealed unfortunately unsuccessful. These failures prompted us to investigate an alternative procedure as the Barton reaction that reported the synthesis of olefinic carbohydrates from the corresponding *vic*-diols through their bisxanthates [16]. Protection of the $OH_{5'}$ group of **I** with a *tert*-butyldimethylsilyl moiety and treatment of the protected nucleoside **XIII** with carbon disulfide, followed by alkylation with β-bromopropionitrile (initially used in order to prevent N_3-alkylation) yielded the bisxanthate intermediate **XIV** (28%) after column chromatography (see Scheme B). The bisxanthate **XIV** on sequential treatment with tri-*n*-butyltin hydride in refluxing toluene under an argon atmosphere and with tetra-*n*-butylammonium fluoride in tetrahydrofuran afforded in low yield (7%) the expected 1-(2,3-dideoxy-β-D-glyceropent-2-enofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione **XV**. Its ^1H nmr spectrum exhibited olefinic protons as characteristic low-field doublets at 6.18 and 6.36 ppm and its ^{13}C nmr spectrum two ethylenic signals at 127.9 ($C_{3'}$) and 32.8 ppm ($C_{2'}$).

In order to increase the 2',3'-olefinic nucleoside yield, we have then investigated the Robins procedure that

Scheme B



[a] *tert*-butyldimethylsilyl chloride-imidazole in DMF for **XIII** (77%). [b] **XIII** to **XIV**: CS_2-DMSO- 5 *N* NaOH-$Br(CH_2)_2CN$ in DMF (36%). [c] $n(Bu)_3SnH$-AIBN in toluene Δ and *n*-$Bu_4N^+F^-$ in THF for **XV** (7%). [d] **I** to **XVI**: CH_3COBr in CH_3CN Δ (94%). [e] CH_3COBr in DMF-ethyl acetate Δ for **XVI** (82%). [f] **XVI** to **XVIII**: Zn/Cu couple in DMF-acetic acid (3%). [g] **XVI** to **XV**: Zn/Cu couple-acetic acid in CH_3OH-CH_2Cl_2 and NH_3-CH_3OH (17%). [h] $C_6H_5CH_2Cl$-K_2CO_3 in DMF-acetone Δ for **XIX** (54%). [i] **XIX** to **XX**: CH_3COBr in CH_3CN Δ (73%).

reported the reductive elimination of vicinal acetylated halohydrins which are readily available from vicinal diols with Zn/Cu couple as the reducing agent [17]. This strategy led us to synthesize the 2'-bromo-2'-deoxy-3',5'-di-*O*-acetyl derivative **XVI** obtained in 94% by addition of acetyl bromide to a suspension of **I** in acetonitrile heated at reflux as described in the literature [18]. Moreover, in agreement with Moffatt [19], this reaction involved the intramolecular participation of the O_2 oxygen to give the 2,2'-*O*-anhydro compound subsequently opened by bromide ion to give the corresponding bromoacetate. The existence of this 2,2'-cyclonucleoside intermediate could be proved by treatment of the 2,2'-anhydro-1-(β-D-arabinofuranosyl)thieno[3,2-*d*]pyrimidin-4-one **XVII** described in a previous report [6] by acetyl bromide which afforded the bromoacetate **XVI**. Its ^{13}C nmr spectrum was characteristic with an upfield shift of $C_{2'}$ ($\Delta\delta$ = 22.5 ppm) when compared to **I**. In a second step, **XVI** was directly reduced with the activated Zn/Cu couple in *N,N*-dimethylformamide:acetic acid at room temperature and the expected olefin **XVIII** was yielded in 3% after purification by silica gel column chromatography. A small amount of **XVI** (R_f 0.82 9:1 methylene chloride:methanol) and the 3'-*O*-acetyl and $OH_{3'}$ derivatives of 2,2'-anhydro-(5-*O*-acetyl-β-D-arabinofuranosyl)thieno[3,2-*d*]-pyrimidin-4-one with respectively R_f (0.36 and 0.27) were detected by chromatography as by-products. Several variations in reaction times and choice of solvents were examined in an attempt to optimize the yield of **XVIII**. However, these variations gave either incomplete consumption of starting material or an increase in the amount of the 2,2'-cyclonucleoside formed. The olefination reaction was also carried out in methylene chloride rather than *N,N*-dimethylformamide under an argon atmosphere since the solvent could be removed at lower temperature and consequently the cleavage of the glycosidic bond could be prevented. In a second stage, the 5'-protected olefin without purification was treated with methanol saturated with ammonia at room temperature to give **XV** in 17% yield after purification by silica gel column chromatography (R_f 0.44 9:1 methylene chloride:methanol). A small amount of thieno[3,2-*d*]pyrimidine-2,4-dione (R_f 0.35), arabinonucleoside (R_f 0.31) and 2,2'-cyclonucleoside (R_f 0.13) were detected by chromatography as by-products. Thus, in order to prevent the formation of the 2,2'-anhydro compound, selective protection of the N_3-imide function in the aglycon moiety has attracted considerable attention. Treatment of **I** with benzyl chloride in refluxing *N,N*-dimethylformamide:acetone and potassium carbonate as a base gave the N_3-benzyl nucleoside **XIX** (54%) after chromatography. Its structure was clearly confirmed on the basis of the disappearance of the NH band in its infrared spectrum and on the chemical shift of C_4 in its ^{13}C nmr when compared to **I** which allowed us to assign the N_3-alkylated product and not the *O*-alkylated compound. Subsequent treatment of **XIX** with acetyl bromide gave actually the N_3-benzyl haloacetate **XX** in 73% yield after chromatography. Unfortunately, the reduction of **XX** with activated Zn/Cu couple led only to cleavage of the glycosidic bond. In conclusion, among the methods described for the preparation of 2',3'-olefinic nucleosides, the reductive elimination of bromoacetate was found to be the most efficient process. Therefore the poor overall yield obtained for compound **XV** was due to the lability

of 2'-bromo of the sugar which afforded preferentially the 2,2'-anhydro compound and the glycosidic bond was found unstable to protic solvent due to deglycosylation of N_3-alkylated product.

Antiviral Assays on CEM cl 13 Cells.

Compounds **XV** and **XVII** were tested *in vitro* for cytotoxicity and for their ability to inhibit the cytopathic effect induced by HIV_1 infection. The CEM cl 13 cells, a subclone enriched in CD_4 receptors (5.10^4 cells/ml), were treated with each compound dilution (0 to 30 µg/ml) or PBS alone, and incubated for 1 hour at 37°. Cells were then infected with virus suspension (LAV-Bru strain of HIV_1, 100-200 $CCID_{50}$) and cultured for at least 7 days. Mock-infected cultures were carried out in parallel to determine the cytotoxicity of the compounds. Cells viability was then evaluated by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method [20], but no significant activities were detected.

EXPERIMENTAL

Melting points (mp) were determined on a Kofler apparatus and are uncorrected. Infrared (ir) spectra were obtained on a Philips SP-3 Pye Unicam spectrophotometer with samples in potassium bromide disk. Ultraviolet (uv) spectra were recorded on a Seconam S-1000G spectrometer. Mass spectra (ms) were recorded with a Jeol D-300 instrument using the ionization by electronic impact technique or with a Jeol JMS SX-102 instrument by using the fast-atom bombardment (FAB) technique. Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Jeol FX-200 or a Jeol EX-90 spectrometer and chemical shifts were expressed in δ (ppm) relative to tetramethylsilane (TMS) as an internal standard. Thin layer chromatography (tlc) was performed on silica gel 60F-254 plates purchased from E. Merck and Co. (spots were detected by ultraviolet examination) and column chromatography was performed on silica gel 60 (230-400 mesh, ASTM, Merck).

1-(β-D-Ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (**I**) [6].

Thieno[3,2-*d*]pyrimidine-2,4-dione (1.68 g, 10 mmoles) was silylated with hexamethyldisilazane (HMDS, 40 ml) in the presence of a catalytic amount of ammonium sulfate by heating the solution at reflux temperature for 5 hours with exclusion of moisture. The excess HMDS was removed by vacuum distillation to give the silylated intermediate. 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (5.06 g, 0.01 mole) and stannic chloride (4 ml) were added successively to a solution of the above silylated base in 1,2-dichloroethane (40 ml). The solution was stirred at room temperature for 18 hours. Pyridine (3 ml) was then added to complex the excess of stannic chloride. The reaction mixture was stirred for an additional 1 hour and the precipitate which had formed was collected by filtration. The precipitate was washed with chloroform (2 x 80 ml) and the combined filtrates were then washed successively with a saturated aqueous sodium hydrogencarbonate solution (100 ml) and water (2 x 100 ml). The organic layer was separated, dried (magnesium sulfate) and the solvent was evaporated *in vacuo* to give 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione. A solution of this blocked nucleoside (6 g, 9.79 mmoles) in methanol saturated with ammonia (200 ml) was then stirred at room temperature for 3 days. The solvent was removed *in vacuo* and the residue was co-evaporated several times with methanol to give an oil which was crystallized from methanol after 3 days as a white solid, 2 g (67%), mp 250°; $[\alpha]^D_{20}$ -6° (*N,N*-dimethylformamide); ir (potassium bromide): ν 3400-3300 (OH), 3140 (NH), 1700-1640 (CO), 1495, 1300, 1115, 1045 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.64 (m, 2H, $H_{5'}$), 3.83 (m, 1H, $H_{4'}$), 4.10 (m, 1H, $H_{2'}$), 4.31 (m, 1H, $H_{3'}$), 5.07 (1H, OH, deuterium oxide-exchangeable), 5.13 (1H, OH, deuterium oxide-exchangeable), 5.28 (1H, OH, deuterium oxide-exchangeable), 6.09 (d, J = 6.8 Hz, 1H, $H_{1'}$), 7.69 (d, J = 5.4 Hz, 1H, H_7), 8.09 (d, J = 5.4 Hz, 1H, H_6), 11.63 (1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 60.9 ($C_{5'}$), 68.7 ($C_{3'}$), 69.6 ($C_{2'}$), 84.0 ($C_{4'}$), 88.4 ($C_{1'}$), 114.0 (C_{4a}), 119.4 (C_7), 134.9 (C_6), 144.5 (C_{7a}), 151.1 (C_2), 157.7 (C_4).

Anal. Calcd. for $C_{11}H_{12}N_2O_6S$: C, 44.00; H, 4.03; N, 9.33; S, 10.68. Found: C, 43.72; H, 4.13; N, 9.54; S, 10.40.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (**II**) [7].

2,2-Dimethoxypropane (1.01 g, 9.69 mmoles) and *p*-toluenesulfonic acid monohydrate (200 mg) were added successively to a suspension of **I** (500 mg, 1.68 mmoles) in dry acetone (40 ml). The reaction mixture was heated under reflux for 2 hours, then cooled to room temperature and stirred for an additional 30 minutes. Solid sodium hydrogencarbonate (1 g) was then added and the stirring continued for further 3 hours. The inorganic materials were collected by filtration and washed with acetone (2 x 20 ml). The combined filtrates were evaporated to dryness *in vacuo* to yield **II** as a white crystalline solid, 540 mg (94%), mp 130°; ir (potassium bromide): ν 3520-3320 (OH), 3200 (NH), 1710-1670 (CO), 1480, 1370, 1210, 1100, 770 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.29 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 3.60 (m, 2H, $H_{5'}$), 3.99-4.87-5.13 (m, $H_{2',3',4'}$), 6.14 (d, J = 2.7 Hz, 1H, $H_{1'}$), 7.49 (d, J = 5.4 Hz, 1H, H_7), 8.13 (d, J = 5.4 Hz, 1H, H_6); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 25.0-27.0 (CH_3), 61.0 ($C_{5'}$), 80.2 ($C_{3'}$), 82.1 ($C_{2'}$), 86.4 ($C_{4'}$), 90.5 ($C_{1'}$), 113.6 (C_{4a}), 118.3 (C_7), 129.2 (CCH_3), 135.6 (C_6), 145.1 (C_{7a}), 150.5 (C_2), 157.8 (C_4).

Anal. Calcd. for $C_{14}H_{16}N_2O_6S$: C, 49.41; H, 4.74; N, 8.23; S, 9.42. Found: C, 49.30; H, 5.04; N, 8.27; S, 9.52.

1-(2,3-*O*-Isopropylidene-5-*O*-methanesulfonyl-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (**III**).

A solution of **II** (1 g, 2.94 mmoles) in anhydrous pyridine (25 ml) was cooled to 0° under the exclusion of moisture. Methanesulfonyl chloride (0.27 ml, 3.53 mmoles) was then added drop by drop while the temperature was maintained below 0°. The reaction mixture was stirred at 0° for 2 hours and allowed to warm to room temperature gradually. After evaporation to dryness, the oily residue was dissolved in chloroform (200 ml) and the solution washed with water (200 ml). The organic layer was separated, dried (magnesium sulfate) and evaporated *in vacuo* to yield an oil which was crystallized from ether as a beige solid, 1.05 g (85%), mp 120°; R_f 0.79 (85:15 chloroform:methanol); ir (potassium bromide): ν 3180 (NH), 1720-1630 (CO), 1340-1160 (R-SO_2-O-), 1050, 950 cm^{-1}; ^1H

nmr (dimethyl sulfoxide-d_6): δ 1.31 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.17 (s, 3H, SO_2CH_3), 4.38-4.93-5.30 (m, $H_{2',3',4'}$), 6.14 (1H, $H_{1'}$), 7.52 (d, J = 5.5 Hz, 1H, H_7), 8.15 (d, J = 5.5 Hz, 1H, H_6); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 24.9-26.7 (CH_3), 36.7 (CH_3SO_2O), 69.3 ($C_{5'}$), 80.8 ($C_{3'}$), 83.0 ($C_{2'}$), 84.8 ($C_{4'}$), 92.1 ($C_{1'}$), 117.6 (C_7), 125.4 ($C(CH_3)_2$), 135.8 (C_6), 145.5 (C_{7a}), 150.7 (C_2), 157.8 (C_4); ms: (70 eV, electron impact) m/z 418 (molecular ion).

Anal. Calcd. for $C_{15}H_{18}N_2O_8S_2$: C, 43.06; H, 4.34; N, 6.69; S, 15.32. Found: C, 43.37; H, 4.45; N, 6.44; S, 15.48.

1-(5-Deoxy-2,3-*O*-isopropylidene-5-fluoro-β-D-ribofuranosyl)-thieno[3,2-*d*]pyrimidine-2,4-dione (**IV**).

Silver fluoride (480 mg, 3.82 mmoles) was added portionwise to a solution of **III** (800 mg, 1.91 mmoles) in anhydrous pyridine (20 ml) and the reaction mixture was heated under reflux for 90 minutes. After removal of the solvent under reduced pressure, the residual oil (2.35 g) was purified on a silica gel column prepacked in ethyl acetate:hexane (7:3). Elution of the column with ethyl acetate:hexane (7:3, v/v) gave **IV** as a pale yellow solid, 220 mg (34%), mp 114°; R_f 0.69 (7:3 ethyl acetate: hexane); ir (potassium bromide): ν 3180 (NH), 1740-1630 (CO), 1480, 1370, 1210, 1060 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.31 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 4.26 (m, 1H, $H_{4'}$), 4.62 (m, 2H, $H_{5'}$), 4.91 (t, J = 5.4 Hz, 1H, $H_{3'}$), 5.26 (m, 1H, $H_{2'}$), 6.17 (d, J = 2.0 Hz, 1H, $H_{1'}$), 7.43 (d, J = 5.4 Hz, 1H, H_7), 8.14 (d, J = 5.4 Hz, 1H, H_6), 11.66 (NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 25.0-26.8 (CH_3), 79.7 ($C_{3'}$, $JC_{3'}$-F = 7.5 Hz), 81.8 ($C_{5'}$, $JC_{5'}$-F = 167 Hz), 82.7 ($C_{2'}$), 85.1 ($C_{4'}$, $JC_{4'}$-F = 18.7 Hz), 91.5 ($C_{1'}$), 113.6 (C_{4a}), 117.6 (C_7), 128.6 ($C(CH_3)_2$), 135.8 (C_6), 145.4 (C_{7a}), 150.6 (C_4), 157.8 (C_2); ms: (FAB) m/z 343 (MH^+).

Anal. Calcd. for $C_{14}FH_{15}N_2O_5S$: C, 49.12; H, 4.42; S, 9.36. Found: C, 48.95; H, 4.44; S, 9.59.

1-(5-Deoxy-5-fluoro-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (**V**).

A solution of **IV** (200 mg, 0.58 mmole) in a mixture of trifluoroacetic acid (2.5 ml) and water (0.5 ml) was stirred vigorously at room temperature for 1 hour and then concentrated to dryness *in vacuo*. The residue was then co-evaporated several times with ethanol to yield an oil which was crystallized from ether as a beige crystalline solid, 100 mg (57%), mp >260°; ir (potassium bromide): ν 3500-3100 (OH), 1730-1650 (CO), 1490, 1300, 1100, 770 cm^{-1}; uv (*p*H 1): λ max 298 nm (log ε 3.72); (*p*H 7): λ max 294 nm (log ε 3.70); (*p*H 11): λ max 299 nm (log ε 3.63); ^1H nmr (dimethyl sulfoxide-d_6): δ 4.17 (t, J = 5.9 Hz, 1H, $H_{3'}$), 4.37 (t, J = 6.1 Hz, 1H, $H_{2'}$), 4.53 (m, 1H, $H_{4'}$), 4.77 (m, 2H, $H_{5'}$), 6.04 (d, J = 5.9 Hz, 1H, $H_{1'}$), 7.29 (d, J = 5.4 Hz, 1H, H_7), 8.14 (d, J = 5.4 Hz, 1H, H_6), 11.64 (1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 68.0 ($C_{3'}$, $JC_{3'}$-F = 5.9 Hz), 69.8 ($C_{2'}$), 82.0 ($C_{4'}$, $JC_{4'}$-F = 17.6 Hz), 82.7 ($C_{5'}$, $JC_{5'}$-F = 167.0 Hz), 90.1 ($C_{1'}$), 113.9 (C_{4a}), 117.9 (C_7), 135.6 (C_6), 144.7 (C_{7a}), 150.7 (C_2), 157.6 (C_4).

Anal. Calcd. for $C_{11}FH_{11}N_2O_5S$: C, 43.71; F, 6.29; H, 3.67; S, 10.61. Found: C, 43.39; F, 6.19; H, 3.54; S, 10.34.

1-(5-Deoxy-2,3-*O*-isopropylidene-5-iodo-β-D-ribofuranosyl)-thieno[3,2-*d*]pyrimidine-2,4-dione (**VI**).

A mixture of **II** (500 mg, 1.47 mmoles) and methyltriphenoxyphosphonium iodide (1.2 g, 2.43 mmoles) in anhydrous *N,N*-dimethylformamide (30 ml) was stirred at room temperature for 2 hours. After evaporation to dryness, the residue was dissolved in ethyl acetate (150 ml) and the solution washed successively with an aqueous sodium thiosulfate solution (2 x 100 ml, 10%) and water (100 ml). The organic layer was separated, dried (magnesium sulfate) and concentrated *in vacuo*. A solution of the residual oil in ethyl acetate (10 ml) was applied to a preparative tlc and developed with chloroform:ethyl acetate (8:2) as eluent. Elution of the major band which was detected by ultraviolet examination was performed by using methanol at reflux to yield **VI** as a white crystalline solid, 350 mg (53%), mp 120°; ir (potassium bromide): ν 3220-3160 (NH), 1740-1640 (CO), 1480, 1370, 1080, 1050, 860 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.30 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 3.49 (m, 2H, $H_{5'}$), 4.22 (m, 1H, $H_{4'}$), 4.86 (m, 1H, $H_{3'}$), 5.32 (d, J = 6.4 Hz, 1H, $H_{2'}$), 6.11 (d, 1H, $H_{1'}$), 7.53 (d, J = 5.0 Hz, 1H, H_7), 8.15 (d, J = 5.0 Hz, 1H, H_6), 11.67 (1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 24.9-26.7 (CH_3), 64.8 ($C_{5'}$), 83.6 ($C_{3'}$), 83.7 ($C_{2'}$), 87.6 ($C_{4'}$), 92.3 ($C_{1'}$), 113.1 (C_{4a}), 117.7 (C_7), 129.8 ($C(CH_3)_2$), 136.0 (C_6), 145.7 (C_{7a}), 150.5 (C_4), 157.8 (C_2).

Anal. Calcd. for $C_{14}H_{15}IN_2O_5S$: C, 37.35; H, 3.36; I, 28.19. Found: C, 37.21; H, 3.49; I, 28.15.

1-(5-Deoxy-5-iodo-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (**VII**).

A solution of **VI** (250 mg, 0.55 mmole) in acetic acid (40 ml) was heated under reflux for 40 minutes and then concentrated *in vacuo* to afford **VII** as a white crystalline solid, 200 mg (88%), mp 238°; ir (potassium bromide): ν 3460-3280 (OH), 3140 (NH), 1720-1610 (CO), 1490, 1300, 1150, 1120, 1040 cm^{-1}; uv (*p*H 1): λ max 295 nm (log ε 3.74); (*p*H 7): λ max 293 nm (log ε 3.79); (*p*H 11): λ max 298 nm (log ε 3.62); ^1H nmr (dimethyl sulfoxide-d_6): δ 3.62 (m, 2H, $H_{5'}$), 3.79 (m, 1H, $H_{4'}$), 4.03 (t, J = 5.9 Hz, 1H, $H_{3'}$), 4.51 (t, J = 6.0 Hz, 1H, $H_{2'}$), 5.98 (d, J = 5.4 Hz, 1H, $H_{1'}$), 7.35 (d, J = 5.4 Hz, 1H, H_7), 8.13 (d, J = 5.4 Hz, 1H, H_6); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 63.1 ($C_{5'}$), 70.1 ($C_{3'}$), 72.4 ($C_{2'}$), 82.8 ($C_{4'}$), 90.5 ($C_{1'}$), 113.1 (C_{4a}), 118.4 (C_7), 135.5 (C_6), 144.9 (C_{7a}), 150.7 (C_4), 157.8 (C_2).

Anal. Calcd. for $C_{11}H_{11}IN_2O_5S$: C, 32.21; H, 2.70; I, 30.94; S, 7.82. Found: C, 31.97; H, 2.53; I, 30.64; S, 7.51.

1-(5-Deoxy-2,3-*O*-isopropylidene-β-D-ribofuranosyl)thieno-[3,2-*d*]pyrimidine-2,4-dione (**VIII**).

A solution of **VI** (400 mg, 0.89 mmole) in methanol (200 ml) and triethylamine (3 ml) was treated with hydrogen at atmospheric pressure in the presence of palladium on carbon (1.5 g, 5%) for 1 hour at room temperature. The catalyst was removed by filtration and washed with methanol. The combined filtrate and washings were evaporated under reduced pressure to a residual solid which was further purified on a silica gel column prepacked in chloroform:ethyl acetate (8:2, v/v). Elution of the column with chloroform:ethyl acetate (8:2, v/v) gave **VIII** as a white crystalline solid, 80 mg (28%), mp 112°; ir (potassium bromide): ν 3200 (NH), 1745-1650 (CO), 1480, 1380, 1210, 1090 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.28 (s, 3H, $H_{5'}$), 1.30 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 4.04 (m, 1H, $H_{4'}$), 4.69 (m, 1H, $H_{3'}$), 5.18 (m, 1H, $H_{2'}$), 6.08 (s, 1H, $H_{1'}$), 7.32 (d, J = 4.9 Hz, 1H, H_7), 8.09 (d, J = 4.9 Hz, 1H, H_6); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 18.3 ($C_{5'}$), 25.1-27.0 (CH_3), 81.7 ($C_{3'}$), 82.9 ($C_{2'}$), 84.3 ($C_{4'}$), 90.3 ($C_{1'}$), 113.6 (C_{4a}), 117.5 (C_7), 129.1 ($C(CH_3)_2$), 135.2 (C_6), 145.1 (C_{7a}), 151.0 (C_2), 158.4 (C_4).

Anal. Calcd. for $C_{14}H_{16}N_2O_5S$: C, 51.84; H, 4.97; N, 8.64; S, 9.88. Found: C, 51.64; H, 4.97; N, 8.35; S, 9.61.

2,5'-Anhydro-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-thieno[3,2-*d*]pyrimidin-4-one (**IX**).

Method No. 1.

Potassium *tert*-butoxide (390 mg, 3.5 mmoles) was added to a solution of **VI** (600 mg, 1.33 mmoles) in anhydrous dimethyl sulfoxide (8 ml). The reaction mixture was stirred at room temperature for 1 hour, poured into water (20 ml), neutralized with acetic acid and then extracted twice with chloroform (2 x 100 ml). The combined organic layers were washed twice with water (2 x 100 ml), separated, dried (magnesium sulfate) and concentrated to dryness *in vacuo*. The residual oil was triturated with dry ether (80 ml) to afford 80 mg (19%) of **IX** as a white crystalline solid.

Method No. 2.

1,8-Diazabicyclo[5.4.0]undec-7-ene (0.51 ml, 3.42 mmoles) was added to a solution of **III** (1.3 g, 3.11 mmoles) in anhydrous acetonitrile (15 ml) under an argon atmosphere. The reaction mixture was heated at 60° for 5 minutes, kept with stirring at room temperature for 30 minutes. After evaporation to dryness *in vacuo*, the oily residue was dissolved in chloroform (100 ml) and the solution washed with water (100 ml). The organic layer was separated, dried (magnesium sulfate) and evaporated *in vacuo* to yield an oil which was crystallized from ether as a white solid, 500 mg (50%), mp 250°; R_f 0.26 (95:5 methylene chloride:methanol); ir (potassium bromide): ν 1640 (CO), 1580, 1480, 1200, 1040 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.31 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 4.29 (m, 2H, $H_{5'}$), 4.58-4.77-5.07 (m, $H_{2',3',4'}$), 6.20 (1H, $H_{1'}$), 7.90 (d, J = 5.4 Hz, 1H, H_7), 8.17 (d, J = 5.4 Hz, 1H, H_6); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 24.1-25.8 (CH_3), 74.5 ($C_{5'}$), 81.4 ($C_{3'}$), 83.9 ($C_{2'}$), 84.8 ($C_{4'}$), 94.2 ($C_{1'}$), 111.5 (C_{4a}), 117.7 (C_7), 132.2 ($C(CH_3)_2$), 134.8 (C_6), 145.2 (C_{7a}), 157.3 (C_4), 174.4 (C_2); ms: (70 eV, electron impact) m/z 322 (molecular ion).

Anal. Calcd. for $C_{14}H_{14}N_2O_5S$: C, 52.17; H, 4.38; N, 8.69; S, 9.95. Found: C, 52.11; H, 4.37; N, 8.65; S, 9.89.

1-(5-Chloro-5-deoxy-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (**X**).

To a stirred and cooled (0°) solution of **I** (700 mg, 2.33 mmoles) in anhydrous acetonitrile (10 ml), pyridine (0.38 ml, 4.69 mmoles) and thionyl chloride (0.85 ml, 11.67 mmoles) were added drop by drop successively. The reaction mixture was allowed to warm to room temperature and the stirring continued for 4 hours before the solvent was removed *in vacuo*. The residual oil was dissolved in a mixture of water (2.5 ml) and methanol (12 ml) and the solution added with an ammonia solution about 32% (1.4 ml). The reaction mixture was stirred at room temperature for 1 hour and concentrated to dryness *in vacuo* to yield an oil which was crystallized from ether as white crystalline solid, 200 mg (28%), mp >260°; R_f 0.68 (8:2 methylene chloride:methanol); ir (potassium bromide): ν 3360 (NH), 1690-1660 (CO), 1420, 1390, 1120, 1040 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.86 (m, 2H, $H_{5'}$), 3.94-4.15-4.47 (m, $H_{2',3',4'}$), 5.36 (1H, OH, deuterium oxide-exchangeable), 5.99 (d, J = 4.9 Hz, 1H, $H_{1'}$), 7.34 (d, J = 4.9 Hz, 1H, H_7), 8.13 (d, J = 4.9 Hz, 1H, H_6), 10.43 (1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 44.6 ($C_{5'}$), 69.8 ($C_{3'}$), 69.9 ($C_{2'}$), 82.8 ($C_{4'}$), 90.5 ($C_{1'}$), 113.8 (C_{4a}), 118.1 (C_7), 135.4 (C_6), 144.9 (C_{7a}), 150.5 (C_4), 157.6 (C_2).

Anal. Calcd. for $C_{11}ClH_{11}N_2O_5S$: C, 41.45; Cl, 11.12; H, 3.48; N, 8.79. Found: C, 41.63; Cl, 11.35; H, 3.42; N, 8.57.

2,2'-Anhydro-1-(5-chloro-5-deoxy-3-*O*-mesyl-β-D-arabinofuranosyl)thieno[3,2-*d*]pyrimidin-4-one (**XI**).

Pyridine (0.5 ml) was added slowly with stirring and ice cooling to thionyl chloride (3 ml). To the resultant complex was added drop by drop at 0° a solution of **I** (1 g, 3.33 mmoles) in anhydrous acetonitrile (5 ml). The reaction mixture was allowed to warm to room temperature and heated under reflux for 1 hour before evaporated *in vacuo* to afford a dark oil which was dissolved in methanol saturated with ammonia (20 ml). The solution was stirred at room temperature for 24 hours and evaporated to dryness *in vacuo*. The crude product was dissolved in anhydrous pyridine (20 ml) at 0° and methanesulfonyl chloride (0.1 ml, 1.19 mmoles) was then added drop by drop. The reaction mixture was stirred at 0° for 2 hours and for an additional 1 hour at room temperature. After evaporation to dryness *in vacuo*, the residue was dissolved in chloroform (100 ml) and the solution washed twice with water (2 x 100 ml). The organic layer was separated, dried (magnesium sulfate) and evaporated *in vacuo* to yield a syrup which was crystallized from dry ether as a beige crystalline solid, 100 mg (30%), R_f 0.21 (9:1 methylene chloride:methanol); ir (potassium bromide): ν 1600 (CO), 1490, 1370, 1170, 970 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.46 (s, 3H, SO_2CH_3), 3.67 (m, 2H, $H_{5'}$), 4.71-5.52 (m, 2H, $H_{3',4'}$), 5.77 (d, J = 5.9 Hz, 1H, $H_{2'}$), 6.82 (d, 1H, $H_{1'}$), 7.42 (d, J = 5.4 Hz, 1H, H_7), 8.21 (d, J = 5.4 Hz, 1H, H_6); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 38.1 (SO_2CH_3), 43.1 ($C_{5'}$), 81.4 ($C_{3'}$), 83.8 ($C_{2'}$), 86.1 ($C_{4'}$), 89.0 ($C_{1'}$), 112.6 (C_{4a}), 116.2 (C_7), 135.5 (C_6), 140.3 (C_{7a}), 159.2 (C_4), 165.1 (C_2).

Anal. Calcd. for $C_{12}ClH_{11}N_2O_6S_2$: C, 38.05; Cl, 9.36; H, 2.93; N, 7.40; S, 16.93. Found: C, 38.32; Cl, 9.52; H, 2.68; N, 7.57; S, 17.16.

1-(5-Chloro-5-deoxy-2,3-epoxy-β-D-lyxofuranosyl)thieno-[3,2-*d*]pyrimidine-2,4-dione (**XII**).

To a solution of **XI** (250 mg, 0.57 mmole) in ethanol (12.5 ml) was added 1 *N* sodium hydroxide in water (5.8 ml) and the mixture was heated at 60° for 1 hour. The reaction mixture was cooled to room temperature, neutralized with acetic acid (80%), poured into water (50 ml) and extracted with methylene chloride (50 ml). The organic layer was washed with water (50 ml), dried (magnesium sulfate) and evaporated to dryness *in vacuo* to yield an oil which was crystallized from dry ether as a white crystalline solid, 80 mg (50%), mp >260°; R_f 0.67 (9:1 methylene chloride:methanol); ir (potassium bromide): ν 3120 (NH), 1680 (CO), 1450, 1070, 1020, 750 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.92 (m, 2H, $H_{5'}$), 4.06-4.12-4.29 (m, $H_{2',3',4'}$), 6.49 (1H, $H_{1'}$), 7.67 (d, J = 5.4 Hz, 1H, H_7), 8.02 (d, J = 5.4 Hz, 1H, H_6), 11.74 (1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 41.6 ($C_{5'}$), 54.1 ($C_{3'}$), 54.5 ($C_{2'}$), 75.6 ($C_{4'}$), 82.3 ($C_{1'}$), 114.3 (C_{4a}), 121.1 (C_7), 134.0 (C_6), 144.1 (C_{7a}), 151.1 (C_2), 157.6 (C_4).

Anal. Calcd. for $C_{11}ClH_9N_2O_4S$: C, 43.94; Cl, 11.79; H, 3.02; N, 9.32. Found: C, 44.15; Cl, 11.92; H, 2.86; N, 9.17.

1-(5-*O*-*tert*-Butyldimethylsilyl-β-D-ribofuranosyl)thieno-[3,2-*d*]pyrimidine-2,4-dione (**XIII**).

To a stirred and cooled (0°) solution of **I** (1.5 g, 4.99 mmoles) in anhydrous *N,N*-dimethylformamide (70 ml) were added successively imidazole (1.1 g, 16.16 mmoles) and *tert*-butyldimethylsilyl chloride (1.2 g, 7.96 mmoles) and the reaction

mixture was stirred with exclusion of moisture at room temperature for 14 hours. After evaporation to dryness *in vacuo*, the oily residue was dissolved in methylene chloride (100 ml) and the solution washed successively with a saturated aqueous sodium hydrogencarbonate solution (150 ml) and water (4 x 100 ml). The organic layer was separated, dried (magnesium sulfate) and evaporated *in vacuo* to yield an oil which was crystallized from a mixture of dry ether-petroleum ether as a beige crystalline solid, 1.6 g (77%), mp 154°; R_f 0.54 (85:15 methylene chloride:methanol); ir (potassium bromide): ν 3380 (OH), 3280 (NH), 1710-1650 (CO), 1500, 1120, 1100, 835 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 0.91 (s, 15H, CH_3), 3.83 (m, 2H, $H_{5'}$), 4.08-4.26 (m, $H_{2',3',4'}$), 5.12-5.34 (2H, OH, deuterium oxide exchangeable), 6.12 (d, J = 6.8 Hz, 1H, $H_{1'}$), 7.57 (d, J = 5.4 Hz, 1H, H_7), 8.03 (d, J = 5.4 Hz, 1H, H_6), 11.65 (1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.9 (CH_3), 25.6 (*t*-Bu), 62.2 ($C_{5'}$), 69.3 ($C_{3'}$), 70.4 ($C_{2'}$), 84.7 ($C_{4'}$), 88.2 ($C_{1'}$), 114.1 (C_{4a}), 118.9 (C_7), 134.8 (C_6), 144.4 (C_{7a}), 150.9 (C_2), 157.6 (C_4).

Anal. Calcd. for $C_{17}H_{26}N_2O_6SSi$: C, 49.25; H, 6.32; N, 6.76; S, 7.73. Found: C, 49.12; H, 6.24; N, 6.52; S, 7.83.

1-(5-*O*-*tert*-Butyldimethylsilyl-2,3-bis-*O*-[[(β-cyanoethyl)thio]-thiocarbonyl]-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (**XIV**).

To a stirred and cooled (0°) solution of **XIII** (1 g, 2.41 mmoles) in anhydrous *N,N*-dimethylformamide (1 ml) containing carbon disulfide (4.8 ml, 81 mmoles), a 5 *N* solution of sodium hydroxide in water (8.5 ml) and dimethyl sulfoxide (4.5 ml) were added drop by drop and the reaction mixture was allowed to stand at room temperature for 20 minutes. The reaction mixture was then added drop by drop with β-bromopropionitrile (6 ml, 73.3 mmoles) and allowed to stand at room temperature for an additional 2 hours. After evaporation to dryness *in vacuo*, the residue was triturated with methylene chloride leaving an insoluble material which was collected by filtration. The organic filtrate was washed twice with water (2 x 100 ml), dried (magnesium sulfate) and evaporated *in vacuo*. The oily residue was dissolved in ethyl acetate (100 ml) and the solution was washed twice with water (2 x 100 ml), dried (magnesium sulfate) and evaporated *in vacuo*. The residual oil was purified on a silica gel column prepacked in methylene chloride. Elution of the column with methylene chloride:methanol (10:0 to 9:1) gave **XIV** as a syrup, 800 mg (36%), R_f 0.66 (95:5 methylene chloride:methanol); ir (potassium bromide): ν 2240 (CN), 1710-1680 (CO), 1480, 1420, 1260, 1110 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 0.93 (s, 15H, CH_3), 3.99 (m, 2H, $H_{5'}$), 4.40-5.02-5.92 (m, $H_{2',3',4'}$), 6.61 (d, J = 4.4 Hz, 1H, $H_{1'}$), 7.43 (d, J = 3.4 Hz, 1H, H_7), 8.05 (d, J = 3.4 Hz, 1H, H_6), 11.70 (1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 17.9 (CH_3), 26.2 (*t*-Bu), 54.2-54.6 ($(CH_2)_2CN$), 61.5 ($C_{5'}$), 82.7-83.1-90.9-92.7 ($C_{1',2',3',4'}$), 114.2 (C_{4a}), 118.5 (C_7), 119.2 (CN), 134.9 (C_6), 144.1 (C_{7a}), 150.5 (C_2), 157.6 (C_4), 212.0 (CS).

Anal. Calcd. for $C_{25}H_{32}N_4O_6S_5Si$: C, 44.62; H, 4.79; N, 8.32; S, 23.82; Si, 4.17. Found: C, 44.57; H, 4.52; N, 8.16; S, 23.64; Si, 4.26.

1-(2,3-Dideoxy-β-D-glyceropent-2-enofuranosyl)thieno[3,2-*d*]-pyrimidine-2,4-dione (**XV**).

Method 1.

A solution of tri-*n*-butyltin hydride (1.1 ml, 4.17 mmoles) and 2,2'-azobis-(2-methylpropionitrile) (65 mg, 0.39 mmole) in toluene (5 ml) was added drop by drop to a boiling solution of **XIV** (700 mg, 1.04 mmoles) in anhydrous toluene (10 ml) under an argon atmosphere. The reaction mixture was refluxed for 1 hour and the solvent was removed *in vacuo*. The residue was dissolved in methylene chloride (100 ml) and the solution was washed twice with water (2 x 100 ml). The organic layer was separated, dried (magnesium sulfate) and evaporated *in vacuo*. The residual oil was immediately dissolved in anhydrous tetrahydrofuran (10 ml). The remaining solution was cooled in an ice bath and added with 1 *M* tetra-*n*-butylammonium fluoride in tetrahydrofuran (0.8 ml). The mixture was stirred at room temperature for 1 hour and concentrated *in vacuo* to yield an oil which was crystallized from dry ether as a white solid, 20 mg (7%).

Method 2.

Zn/Cu couple (470 mg, 7.16 mmoles) freshly prepared under an argon atmosphere and acetic acid (1 ml) were added successively portionwise to a solution of **XVI** (800 mg, 1.79 mmoles) in methanol (60 ml) and methylene chloride (5 ml). The heterogeneous reaction mixture was stirred at room temperature for 1 hour (monitored by tlc) until no starting material remained, filtered and the precipitate washed successively with methanol (30 ml) and methylene chloride (30 ml). The combined filtrates were concentrated *in vacuo* and then diluted with methylene chloride (100 ml). The solution was washed successively with a saturated aqueous sodium hydrogencarbonate solution (100 ml) and water (100 ml). The organic layer was separated, dried (magnesium sulfate) and concentrated *in vacuo*. The residual oil (450 mg) was immediately dissolved in methanol saturated with ammonia (70 ml). The reaction mixture was stirred at room temperature for 1 hour. After removal of the solvent under reduced pressure, the residual oil was purified on a silica gel column prepacked in methylene chloride. Elution of the column with methylene chloride:methanol (10:0 to 7:3) yielded **XV** as a white crystalline solid, 80 mg (17%), mp 250°; R_f 0.44 (9:1 methylene chloride:methanol); ir (potassium bromide): ν 1650 (CO), 1220, 1040, 820, 660 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.68 (m, 2H, $H_{5'}$), 4.75 (m, 1H, $H_{4'}$), 6.18-6.36 (doublets, J = 2.0 Hz, $H_{2',3'}$), 7.09 (1H, $H_{1'}$), 7.62 (d, J = 5.4 Hz, 1H, H_7), 8.02 (d, J = 5.4 Hz, 1H, H_6), 11.61 (1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 62.0 ($C_{5'}$), 86.3 ($C_{4'}$), 89.8 ($C_{1'}$), 127.9-132.8 ($C_{2',3'}$), 117.1 (C_{4a}), 119.1 (C_7), 134.5 (C_6), 145.2 (C_{7a}), 151.4 (C_2), 157.6 (C_4).

Anal. Calcd. for $C_{11}H_{10}N_2O_4S$: C, 49.62; H, 3.79. Found: C, 49.34; H, 3.42.

1-(2-Bromo-2-deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)thieno-[3,2-*d*]pyrimidine-2,4-dione (**XVI**).

Method 1.

Acetyl bromide (1.45 ml, 19.42 mmoles) was added drop by drop to a boiling suspension of **I** (1 g, 3.33 mmoles) in anhydrous acetonitrile (20 ml). The reaction mixture was stirred at 80° for 3 minutes and allowed to cool to room temperature. After evaporation to dryness *in vacuo*, the residue was dissolved in methylene chloride (100 ml) and the solution was washed twice with water (2 x 100 ml). The organic layer was separated, dried (magnesium sulfate) and evaporated *in vacuo* to yield an oil which was crystallized from ether as a white solid, 1.4 g (94%).

Method 2.

A solution of **I** (1 g, 3.33 mmoles) in anhydrous acetonitrile (30 ml) was added with a solution of hydrobromic acid about 30 wt% in glacial acetic acid (0.8 ml) and heated at 60° for 2 hours. The reaction mixture was then added drop by drop with acetyl bromide (0.8 ml, 10.9 mmoles) and stirred at 60° for 3 hours. After evaporation to dryness *in vacuo*, the residue was dissolved in ethyl acetate (100 ml) and the solution was washed successively with saturated aqueous sodium hydrogencarbonate solution (100 ml), brine (100 ml) and water (100 ml). The organic layer was separated, dried (magnesium sulfate) and evaporated *in vacuo* to yield a syrup which was crystallized from dry ether as a white solid, 800 mg (54%).

Method 3.

Acetyl bromide (0.4 ml, 5.47 mmoles) was added drop by drop to a solution of **XVII** (500 mg, 1.78 mmoles) in *N,N*-dimethylformamide (45 ml) and ethyl acetate (5 ml). The reaction mixture was refluxed for 90 minutes and evaporated *in vacuo*. The residue was dissolved in ethyl acetate (100 ml) and the solution was washed twice with water (2 x 100 ml). The organic layer was separated, dried (magnesium sulfate) and concentrated *in vacuo* to yield a syrup which crystallized from dry ether as a white solid, 650 mg (82%), mp 220°; ir (potassium bromide): ν 3240 (NH), 1740-1690 (CO), 1260, 1230, 1220, 1070 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.10-2.15 (6H, $COCH_3$), 4.34 (m, 2H, $H_{5'}$), 5.24 (t, J = 6.8 Hz, 1H, $H_{4'}$), 5.36-5.75 (m, $H_{2',3'}$), 6.47 (d, J = 6.8 Hz, 1H, $H_{1'}$), 7.49 (d, J = 5.4 Hz, 1H, H_7), 8.21 (d, J = 5.4 Hz, 1H, H_6), 11.79 (1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.4 (CH_3), 47.1 ($C_{2'}$), 62.5 ($C_{5'}$), 70.2 ($C_{3'}$), 79.0 ($C_{4'}$), 89.8 ($C_{1'}$), 114.2 (C_{4a}), 117.9 (C_7), 135.8 (C_6), 143.9 (C_{7a}), 150.5 (C_2), 157.5 (C_4), 169.3-169.9 (2 CO); ms: (70 eV, electron impact) m/z 446-448 (relative abondance 1:1).

Anal. Calcd. for $BrC_{15}H_{15}N_2O_7S$: Br, 17.87; C, 40.28; H, 3.38; S, 7.17. Found: Br, 17.68; C, 40.31; H, 3.24; S, 7.21.

2,2'-Anhydro-1-(β-D-arabinofuranosyl)thieno[3,2-*d*]pyrimidin-4-one (**XVII**) [6].

Diphenyl carbonate (0.46 g, 2.15 mmoles) and solid sodium hydrogencarbonate (10 mg) were added successively to a solution of **I** (500 mg, 1.67 mmoles) in *N,N*-dimethylformamide (10 ml). The reaction mixture was heated under reflux for 1 hour, then cooled to room temperature. After evaporation to dryness *in vacuo*, the residual oil was triturated in dry ether to give crystals which were purified on a silica gel column prepacked in methylene chloride. Elution of the column with methylene chloride:methanol (10:0 to 6:4) gave a white crystalline solid, 380 mg (81%), mp 236°; R_f 0.33 (85:15 methylene chloride:methanol); $[\alpha]^D_{20}$ -172° (*N,N*-dimethylformamide); ir (potassium bromide): ν 3280-3380 (OH), 1620 (CO), 1520, 1495, 1075, 1000, 780 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.25 (m, 2H, $H_{5'}$), 4.12 (m, 1H, $H_{4'}$), 4.45 (m, 1H, $H_{3'}$), 4.93 (1H, $OH_{5'}$, deuterium oxide-exchangeable), 5.30 (d, J = 5.9 Hz, 1H, $H_{2'}$), 5.94 (1H, $OH_{3'}$, deuterium oxide-exchangeable), 6.69 (d, J = 5.9 Hz, 1H, $H_{1'}$), 7.37 (d, J = 5.4 Hz, 1H, H_7), 8.15 (d, J = 5.4 Hz, 1H, H_6); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 60.7 ($C_{5'}$), 74.6 ($C_{3'}$), 88.9 ($C_{2'}$), 89.3 ($C_{4'}$), 89.4 ($C_{1'}$), 116.2 (C_{4a}), 118.8 (C_7), 134.8 (C_6), 140.7 (C_{7a}), 159.8 (C_4), 165.2 (C_2).

Anal. Calcd. for $C_{11}H_{10}N_2O_5S$: C, 46.81; H, 3.57; N, 9.92; S, 11.36. Found: C, 46.63; H, 3.37; N, 9.74; S, 11.62.

1-(5-*O*-Acetyl-2,3-didehydro-2,3-dideoxy-β-D-glyceropent-2-enofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (**XVIII**).

Zn/Cu couple (1 g, 15.23 mmoles) freshly prepared [5h] and acetic acid (0.3 ml) were added portionwise successively to a solution of **XVI** (1.5 g, 3.35 mmoles) in anhydrous *N,N*-dimethylformamide (25 ml) under an argon atmosphere. The heterogeneous reaction mixture was stirred at room temperature for 14 hours, filtered and the precipitate washed with *N,N*-dimethylformamide (10 ml). The combined filtrates were neutralized with ammonia and concentrated *in vacuo*. The residual oil was then diluted with chloroform (100 ml) and the mineral salts which precipitated were collected by filtration. The organic filtrate was washed successively with a saturated aqueous sodium hydrogencarbonate solution (100 ml) and water (100 ml). The organic layer was separated, dried (magnesium sulfate) and concentrated *in vacuo*. The residue was then purified on a silica gel column prepacked in methylene chloride. Elution of the column with methylene chloride:methanol (10:0 to 9:1) gave **XVIII** as a white crystalline solid, 30 mg (3%), mp 148°; R_f 0.62 (9:1 methylene chloride:methanol); ir (potassium bromide): ν 1730-1630 (CO), 1480, 1230, 1080, 840 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.02 (s, 3H, CH_3), 4.26 (m, 2H, $H_{5'}$), 4.98 (m, 1H, $H_{4'}$), 6.31 (m, $H_{2',3'}$), 7.06 (1H, $H_{1'}$), 7.47 (d, J = 5.4 Hz, 1H, H_7), 8.11 (d, J = 5.4 Hz, 1H, H_6); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.6 (CH_3), 64.3 ($C_{5'}$), 82.8 ($C_{4'}$), 90.2 ($C_{1'}$), 114.1 (C_{4a}), 118.5 (C_7), 128.9-131.2 ($C_{2',3'}$), 135.0 (C_6), 145.3 (C_{7a}), 151.1 (C_2), 157.7 (C_4), 170.1 (CO); FAB-ms (MH^+) = 309.

Anal. Calcd. for $C_{13}H_{12}N_2O_5S$: C, 50.65; H, 3.92; N, 9.09; S, 10.40. Found: C, 50.36; H, 4.02; N, 8.87; S, 10.73.

3-*N*-Benzyl-1-(β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (**XIX**).

Potassium carbonate (800 mg, 5.67 mmoles) and benzyl chloride (0.6 ml, 5 mmoles) were added successively to a solution of **I** (1 g, 3.33 mmoles) in a mixture of *N,N*-dimethylformamide (8 ml) and acetone (8 ml). The reaction mixture was heated under reflux for 4 hours and acetone was removed *in vacuo*. The reaction mixture was then poured into water (100 ml) and extracted with ethyl acetate (100 ml). The organic layer was separated and washed with water (3 x 100 ml), dried (magnesium sulfate) and concentrated *in vacuo*. The residual oil was purified on a silica gel column prepacked in methylene chloride. Elution of the column with methylene chloride:methanol (10:1 to 7:3) gave **XIX** as a white crystalline solid, 700 mg (54%), mp 255°; R_f 0.32 (9:1 methylene chloride:methanol); ir (potassium bromide): ν 3500-3400 (OH), 1670-1630 (CO), 1470, 1070, 760, 690 cm^{-1}; uv (*p*H 1): λ max 299 nm (log ε 3.97); (*p*H 7): λ max 299 nm (log ε 4.00); (*p*H 11): λ max 299 nm (log ε 3.81); ^1H nmr (dimethyl sulfoxide-d_6): δ 3.64 (m, 2H, $H_{5'}$), 3.83 (1H, $H_{3'}$), 4.12 (1H, $H_{2'}$), 4.32 (1H, $H_{4'}$), 5.11 (m, 2H, benzyl CH_2), 5.28 (1H, OH, deuterium oxide-exchangeable), 6.15 (d, J = 6.8 Hz, 1H, $H_{1'}$), 7.31 (5H, benzyl), 7.72 (d, J = 5.4 Hz, 1H, H_7), 8.14 (d, J = 5.4 Hz, 1H, H_6); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 44.0 (benzyl CH_2), 60.8 ($C_{5'}$), 68.7 ($C_{3'}$), 69.7 ($C_{2'}$), 85.0 ($C_{4'}$), 89.6 ($C_{1'}$), 113.3 (C_{4a}), 119.2 (C_7), 127.0-127.4-128.1-136.6 (benzyl), 135.3 (C_6), 143.1 (C_{7a}), 150.8 (C_2), 157.0 (C_4).

Anal. Calcd. for $C_{18}H_{18}N_2O_6S$: C, 55.38; H, 4.65; N, 7.18; S, 8.21. Found: C, 55.34; H, 4.49; N, 6.87; S, 7.99.

3-*N*-Benzyl-1-(2-bromo-2-deoxy-3,5-di-*O*-acetyl-β-D-ribofuranosyl)thieno[3,2-*d*]pyrimidine-2,4-dione (**XX**).

Acetyl bromide (0.55 ml, 7.48 moles) was added to a refluxing solution of **XIX** (500 mg, 1.28 mmoles) in acetonitrile (20 ml). The reaction mixture was kept under reflux for 3 minutes and allowed to cool to room temperature before concentrated *in vacuo*. The oily residue (700 mg) was dissolved in methylene chloride (100 ml) and the solution was washed twice with water (2 x 100 ml). The organic layer was separated, dried (magnesium sulfate) and concentrated to dryness *in vacuo*. The residual syrup was purified on a silica gel column prepacked in hexane. Elution of the column with hexane:methylene chloride (10:0 to 0:10) and then with methylene chloride:methanol (10:0 to 9:1) yielded **XX** as a white crystalline solid, 500 mg (73%), mp 102°; R_f 0.63 (98:2 methylene chloride:methanol); ir (potassium bromide): ν 1700-1670-1620 (CO), 1450, 1190, 1040, 1000 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.04-2.15 (6H, CH_3), 4.36 (m, 2H, $H_{5'}$), 5.10 (m, 2H, benzyl CH_2), 5.31 (m, $H_{2',3',4'}$), 6.54 (d, J = 6.4 Hz, 1H, $H_{1'}$), 7.30 (5H, benzyl), 7.54 (d, J = 5.4 Hz, 1H, H_7), 8.24 (d, J = 5.4 Hz, 1H, H_6); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.7 (CH_3), 44.0 (benzyl CH_2), 47.4 ($C_{2'}$), 62.9 ($C_{5'}$), 70.0 ($C_{3'}$), 78.9 ($C_{4'}$), 91.3 ($C_{1'}$), 113.5 (C_{4a}), 117.7 (C_7), 127.0-127.2-128.1-136.6 (benzyl), 136.2 (C_6), 142.7 (C_{7a}), 150.3 (C_2), 156.8 (C_4), 169.2-169.8 (2 CO).

Anal. Calcd. for $BrC_{22}H_{21}N_2O_7S$: Br, 14.87; C, 49.17; H, 3.94; N, 5.21. Found: Br, 14.65; C, 49.35; H, 4.12; N, 5.02.

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