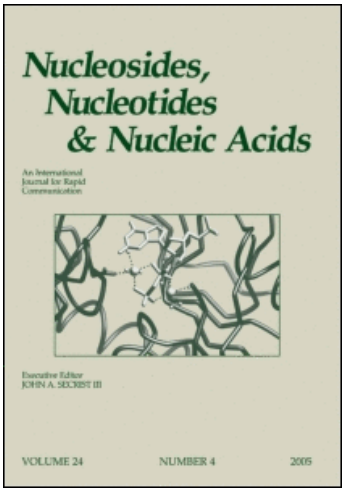

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A Practical and Stereospecific Approach to the Synthesis of 3'-Deoxy-2',3'-didehydrothymidine (D_4T)

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A Practical and Stereospecific Approach to the Synthesis of 3'-Deoxy-2',3'-didehydrothymidine (D_4T) .

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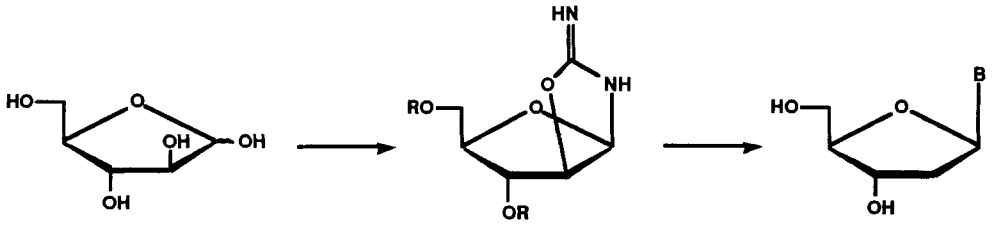
Abstract: *Starting with D-glucose, 5-t-butyldimethylsilyl-3-deoxy-D-arabinose (**5**) was prepared. Condensation of **5** with cyanamide followed by reaction of the resulting oxazoline **6** with methyl-2-formylpropionate furnished the anhydronucleoside **7**. t-Butoxide elimination of **7** gave the target compound in moderate yields due to concomitant 1',2'-double bond formation. However, phenylselenolate and phenylthiolate opened **7** regiospecifically to the corresponding seleno and thio compounds, **10** and **11**, respectively. Oxidative elimination of **10** and the pivaloyl derivative **12** gave 5'-t-butyldimethylsilyl (**8**) and 5'-pivaloyl (**13**) D_4T in excellent yield.*

The introduction of AZT as a clinically useful anti HIV drug[1] has spurred interest in discovering other sugar-modified deoxynucleosides. 3'-Deoxythymidine (D_2T)[2], 3'-deoxy-2',3'-didehydrothymidine (D_4T)[3], 2',3'-dideoxy-3'-azidouridine (ddAZU)[4], 2',3'-dideoxycytidine (ddC)[5], and more recently, 4'-azidothymidine (ADRT)[6] are examples of such pyrimidine nucleosides with potential utility.

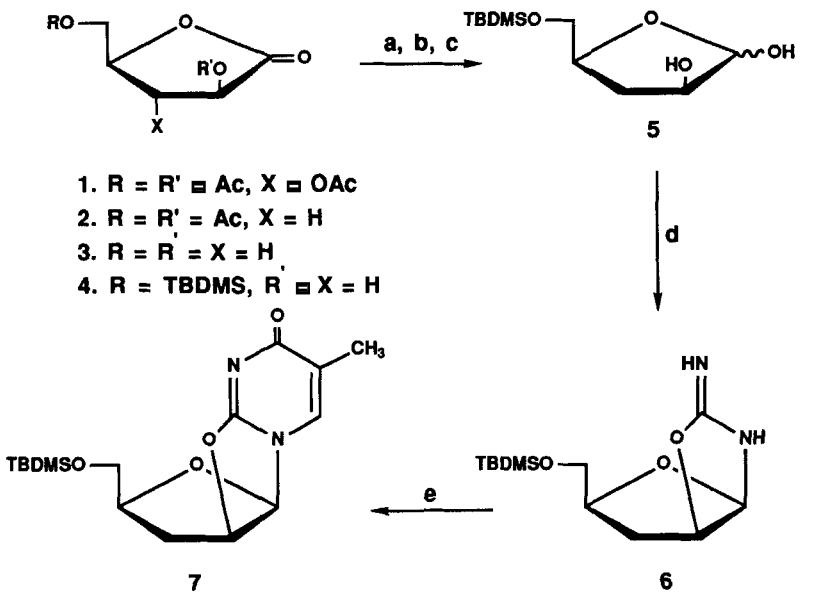
The relative inaccessibility of 2-deoxypentofuranoses and the formation of α,β-mixtures during glycosylation[7] have resulted in dependence on naturally occurring deoxynucleosides as starting materials. Consequently, efforts have been directed at developing alternate synthetic routes to prepare these compounds. There are literature reports using 2-deoxypentofuranoses where formation of β- over α-anomers is preferred. The use of copper iodide, for example, resulted in a β/α ratio of 9:1.[8] Furthermore, a 3-α-O-2-methylsulfinylethyl group was shown to participate in a glycosylation reaction favoring β-attack by the heterocycle resulting in predominant formation of the β-anomer.[9]

The comparable activity of D_4T to that of AZT[10] has generated interest in developing synthetic routes to this and other 2',3'-dideoxypyrimidines. Starting with thymidine, 5'-methoxytrityl, 5'-pivaloyl,[11] and 5'-trityl[12]-3'-deoxy-3'-phenylselenothymidines were prepared. Oxidative elimination followed by deprotection furnished D_4T in good yields. The high cost of thymidine has prompted the search for alternate efficient routes to these compounds. Mansuri *et al.,* have developed general methods to prepare the title compounds by reductive elimination of vicinal 2',3'-functionalities in ribosides.[13] Chu *et al.,* have also introduced 2',3'-double bonds by reductive elimination of xanthates.[14] There are also three recent reports which capitalized on the β-directing effect of 2-phenylseleno[15] and 2-phenylthio[16] groups in 5-protected-2,3-dideoxy-1-O-acetyl-D-ribofuranosides during glycosylation with persilylated thymine. The reactions proceeded with high stereoselectivity and in good yields. However, there is still a need for non-thymidine based syntheses for this type of compound. In this paper, a practical approach to D_4T is described. Stereospecificity, high yields, and the low cost of starting material are the attractive features of the work.

The use of sugar chirality to direct nucleoside bond formation in pyrimidine deoxynucleosides is an ongoing program in our laboratory. We have recently described an approach for the regiospecific formation of these compounds using the chirality at C-4 in methyl-2-deoxyribofuranosides.[17] The chirality at C-2 in D-arabinose has also been successfully used to prepare β-purine and uridine nucleosides.[18] Reaction of D-arabinose with cyanamide furnished an intermediate bicyclic oxazoline from which the uridine ring was built using propiolate and other related synthons. This method was recently extended to prepare thymine nucleosides using β-oxidized methacrylate esters.[19]



B = Purines and Pyrimidines
R = TBDMS, TMS

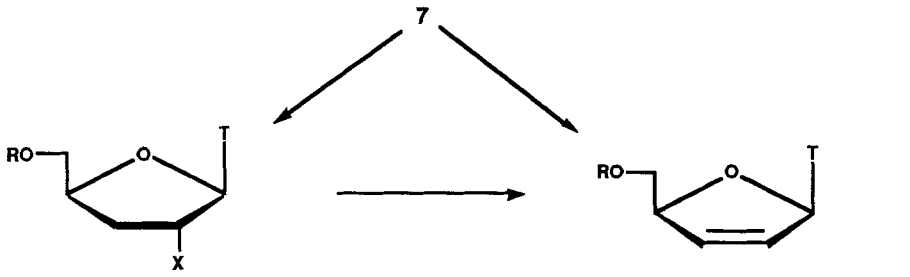


a. $NaOCH_3$/MeOH, rt; b. TBDMSCl, triethylamine, DMAP, THF, rt; c. DIBALH, toluene, -78 °C; d. NC-NH_2, NH_3, MeOH, 60 °C; e. $CH_3CH(CHO)CO_2CH_3$, C_6H_6, Δ.

Scheme 1

The use of 3-deoxypentofuranosides in nucleoside synthesis is not as common as their 2-deoxy counterparts. Should 3-deoxy-D-arabinose undergo a similar condensation with cyanamide, a practical and regiospecific route to the title compounds might be feasible. This proved to be the case as is shown in **Scheme 1**.

2,3,5-Tri-O-acetyl-D-arabinolactone was prepared from D-glucose[20] and was converted to the diacetate **2** by catalytic hydrogenation.[21] Base hydrolysis of **2** to **3** followed by selective silylation furnished lactone **4** in overall yield of 30% starting from D-glucose. DIBALH reduction of **4** gave lactol **5** which was reacted with cyanamide, following published procedures,[18a] to provide the bicyclic oxazoline **6** in 70% yield. When **6** was condensed with either 3-methoxy-2-methyl or methyl 3-bromo-2-methylacrylate, as previously reported,[19] no thymine formation could be detected. Similar results were obtained with methyl-3,3-dimethoxy-2-methylpropionate. However, when methyl-2-formylpropionate[22] was heated with **6** in refluxing benzene, the corresponding 2,2'-anhydronucleoside **7** was isolated in 65% yield. ^1H NMR



10. R = TBDMS, X = PhSe
11. R = TBDMS, X = PhS
12. R = $(CH_3)_3CCO$, X = PhS

8. R = TBDMS
9. R = H
13. R = $(CH_3)_3CCO$

Scheme 2

analysis of **7** showed characteristic signals supporting the assigned structure. A methyl doublet at δ 1.94 ppm (J = 1.2 Hz) coupled to a proton at δ 7.17 ppm is characteristic of thymines. A one proton doublet (J = 6 Hz) at δ 6.1 ppm belongs to the anomeric proton.

Having obtained **7**, we looked for suitable methods to introduce the 2',3'-double bond **Scheme 2**. Treatment of **7** with KOtBu in DMSO[1a] led to the formation of D_4T (**9**) in 50% yield. Two other products were isolated in 5 and 35% yield, respectively. The former was 5'-silylated D_4T (**8**) and the latter proved to be the 1',2'-unsaturated isomer. Similar 1',2'-eliminations have been reported.[23]

Eliminations involving 2'-phenylseleno[14] and 2'-phenylthio[15] compounds have been reported to undergo exclusive formation of the 2',3'-double bond. Efforts were, therefore, directed at introducing either of these groups at the 2'-position. Schinazi and Cosford have recently reported a regiospecific opening of 2,3'-anhydro-1-(2-deoxy-5-O-trityl-β-D-pentofuranosyl)thymine with phenylselenolate.[12] When the same conditions were applied to **7**, it underwent a clean and facile ring opening to give **10** in quantitative yield. Oxidative elimination of **10** followed published reports,[12] and proceeded smoothly in acetic acid but not in pyridine to give **8**. Application of the same reaction conditions using phenylthiolate ($Ph_2S_2/LiAlH_4$) generated **11** in comparable yields. However, oxidative elimination of **11** did not furnish **8**. Instead a mixture of products were obtained. The failure of this reaction can

only be attributed to the nature of the substituent at C-5', since the same reaction was successfully performed on an identical compound having a TBDPS, instead of TBDMS, group at C-5'.[16] This problem was solved by replacing the TBDMS with a pivaloyl group. Thus, desilylation of **11** followed by *in situ* acylation with pivaloyl chloride provided **12** in quantitative yield. Oxidative elimination furnished pivaloyl D_4T **13** in excellent yield.

In conclusion, starting from D-arabinolactone, an alternate synthetic sequence for D_4T has been established which proceeds in 21% overall yield. It should be emphasized that further improvement in this sequence is feasible by optimizing lower yielding reactions, combining steps, and using alternate reagents to reduce **2** directly to **5**. The same can be said about D_2T which can be equally prepared by reduction of the 2'-phenylseleno or 2'-phenylthio group in **10** and **11**, respectively.[12]

Experimental

^1H NMR spectra were recorded on either a Varian EM-390 and/or Bruker 300 MHz spectrometer using $CDCl_3$ as the solvent. Chemical shifts are expressed in parts per million with respect to TMS. Optical rotations were measured on a Perkin-Elmer Model-141 digital readout polarimeter. Silica gel (Merck grade 60, 230-400 mesh, 60Å) suitable for column chromatography was purchased from Aldrich. All solvent proportions are by volume unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

5-O-*tert*-Butyldimethysilyl-3-deoxy-D-*threo*-pentono-1,4-lactone (4). The acetylated lactone **2**[19] (2.36 g, 11 mmol) was added to dry MeOH (50 mL) containing metallic sodium (0.029 g, 1.27 mmol) and the mixture was stirred for an hour at rt. The basic solution was then neutralized with Amberlite IR-120 resin. After filtration of the resin, the filtrate was concentrated under reduced pressure to afford **3** (1.4 g, 97%) as a gummy material which was used without further purification. To a solution of **3** in dry THF (50 mL) was added triethylamine (1.75 mL, 12.7 mmol), DMAP (0.26 g, 2.10 mmol) and TBDMSCl (1.76 g, 11.70 mmol) and the mixture was allowed to stir at rt for 24 h. THF was removed under reduced pressure and the residue was diluted with CH_2Cl_2 (100 mL) and washed successively with water (2 x 50 mL), 5% hydrochloric acid (2 x 25 mL), water (2 x 50 mL) and brine (50 mL), and then dried over anhydrous $MgSO_4$. The viscous material obtained after solvent

removal at reduced pressure was chromatographed on a silica gel column eluting with hexanes-EtOAc (7:3) to give **4** (2.10 g, 80%) as an oil: $[\alpha]_D^{25}$ +8.57° (c 1.155, EtOH); ^{1}H NMR δ 0.10 (s, 6H), 0.87 (s, 9H), 1.87-2.33 (m, 1H), 2.37-2.80 (m, 1H), 3.37-3.97 (m, 3H), 4.20-4.67 (m, 2H). Anal. Calcd for $C_{11}H_{22}SiO_4$: C, 53.63; H 9.00. Found: C, 53.48; H, 8.81.

5-O-*tert*-Butyldimethylsilyl-3-deoxy-D-*threo*-pentofuranose 5. A solution of lactone **4** (1.66 g, 6.70 mmol) in dry toluene (50 mL) was cooled to -78 °C and treated dropwise with 1 M solution of DIBALH in toluene (15 mL, 15 mmol). After 2 h at -78 °C, the reaction was quenched by the slow addition of saturated NH_4Cl solution (25 mL) followed by 25% citric acid (20 mL) and warmed up to rt. The layers were separated and the aqueous phase was extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give an oil. The product was purified by column chromatography on silica gel with 30% EtOAc-hexanes as eluent to afford **5** (1.5 g, 90%): ^{1}H NMR δ 0.1 (s, 6H), 0.85 (s, 9H), 1.37-1.87 (m, 1H), 1.97-2.58 (m, 1H), 3.20-4.43 (m, 6H), 4.80-5.22 (m, 1H). Anal. Calcd for $C_{11}H_{24}SiO_4$: C, 53.19; H, 9.74. Found: C, 53.26; H, 9.59.

2-Amino-5'-O-*tert*-butyldimethylsilyl-β-D-*threo*-pentofurano-[1',2':4,5]-2-oxazoline 6. To a stirred solution of **5** (0.31 g, 1.25 mmol) in MeOH (3 mL) was added concentrated ammonia solution (0.10 mL) and cyanamide (0.105 g, 2.50 mmol) and the resulting mixture was heated at 50-60 °C overnight. MeOH was then removed under reduced pressure and the residue obtained was diluted with CH_2Cl_2 (25 mL), washed with water (15 mL) and brine (15 mL) and dried over $MgSO_4$. The crude product obtained after solvent removal was chromatographed on a silica gel column. Elution with 5% MeOH-EtOAc gave compound **6** (0.238 g, 70%). $[\alpha]_D^{25}$ -15.06° (c 0.77, EtOH); ^{1}H NMR δ 0.09 (s, 6H), 0.83 (s, 9H), 1.87-2.41(m, 2H), 3.04-3.37 (m, 3H), 4.71-5.00 (m, 1H), 5.17-5.61 (bs, 2H, D_2O exchangeable), 5.71 (d, J = 4.5 Hz, 1H). Anal. Calcd for $C_{12}H_{24}N_2SiO_3$: C, 52.91; H 8.88; N, 10.28. Found: C, 52.72; H, 8.61; N, 10.24.

Methyl 2-formylpropionate. 15% Sulfuric acid (2 g) was added with continuous stirring to a suspension of silica gel (20 g) in CH_2Cl_2 (40 mL). After 2-3 min, methyl 3,3-dimethoxy-2-methylpropionate[24] (1 g) was added and the stirring was continued at rt overnight. The mixture was neutralized with $NaHCO_3$ (0.7 g) and the solid phase was separated by filtration and washed

several times with CH_2Cl_2. Evaporation of the solvent under reduced pressure gave the aldehyde (0.57 g, 80%).

2,2'-Anhydro-1-(3-deoxy-β-D-pentofuranosyl)thymine 7. A benzene solution (5 mL) of compound **6** (0.272 g, 1 mmol) and methyl 2-formyl-propionate (1.16 g, 10 mmol) was refluxed for 16 h. Residual benzene was removed under reduced pressure and the crude product was chromatographed over silica gel (5% MeOH-EtOAc) to obtain **7** (0.22 g, 65%): $[\alpha]_D^{25}$ -74.17° (c 0.1955, EtOH); ^1H NMR δ 0.1 (s, 6H), 0.86 (s, 9H), 1.94 (s, 3H), 2.11-2.61 (m, 2H), 3.14-3.84 (m, 3H), 4.14-4.64 (m, 1H), 5.34-5.57 (m, 1H), 6.1 (d, J = 6Hz, 1H), 7.17 (s, 1H). Anal. Calcd for $C_{16}H_{26}N_2SiO_4$: C, 56.78; H, 7.44; N, 8.28. Found: C, 56.72; H, 7.55; N, 8.24.

Reaction of 7 with *t*-BuOK. To a solution of t-BuOK (0.036 g, 0.323 mmol) in dry DMSO (2 mL) was added compound **7** (0.05 g, 0.147 mmol) and the reaction mixture was stirred for 0.5 h at rt. The basic solution was neutralized with Amberlite-IR 120 resin, filtered and the resin was washed with MeOH. The crude product obtained after solvent removal was chromatographed over silica gel using the following solvents: (EtOAc-hexanes 2:3) afforded compound **8** (0.003 g, 5%), mp 168-170 °C (lit.[14] 169-171 °C); (EtOAc-hexanes 1:1) gave 1-(5-O-*tert*-butyldimethylsilyl-2,3-dideoxy-β-D-*glycero*-pent-1-eno-furanosyl)thymine (0.017 g, 35%); ^1H NMR δ 0.17 (s, 6H), 0.97 (s, 9H), 1.88 (d, J = 1.2 Hz, 3H), 2.05 (dd, J = 14 and 2.5 Hz, 1H), 2.52 (m, 1H), 3.61 (dd, J = 11.2 and 1.5Hz, 1H), 4.0 (dd, J = 11.2 and 1.8 Hz, 1H), 4.35-4.4 (m, 1H), 5.85 (bd, J = 2 Hz, 1H), 7.45 (d, J = 1.2 Hz, 1H), 8.38 (bs, 1H). Anal. Calcd for $C_{16}H_{26}N_2O_4Si$: C, 56.73; H, 7.74; N, 8.27. Found: C, 56.61; H, 7.82; N, 8.17; (EtOAc-MeOH 95:5) gave **9** (0.015 g, 50%), mp 165 °C (lit.[14] 165-166 °C).

1-(5-O-*tert*-Butyldimethylsilyl-2-α-phenylseleno-3-deoxy-β-D-pentofuranosyl)thymine 10. To a stirred THF (5 mL) solution of diphenyldiselenide (0.175 g, 0.56 mmol) at 0 °C and under N_2 atmosphere $LiAlH_4$ (0.016 g, 0.42 mmol) was added carefully. This was gradually allowed to warm to rt and stirring was continued for 1 h. To this clear solution compound **7** (0.118 g, 0.35 mmol) in anhydrous THF (5 mL) was added and the mixture was refluxed for 3 h. The reaction mixture was worked up with saturated NH_4Cl (5 mL) and 2% hydrochloric acid (5 mL), extracted with EtOAc (2 x 20 mL), washed with water (2 x 5 mL) and brine (15 mL) and dried over $MgSO_4$. Evaporation of the solvent afforded a yellow oil which was chromatographed on

a silica gel column eluting with EtOAc-hexanes (1:5) to give **10** (0.15 g, 88%): $[\alpha]_D^{25}$ +30.57° (c 0.35, EtOH); ^{1}H NMR δ 0.1 (s, 6H), 0.89 (s, 9H),1.8 (s, 3H), 1.92-2.62 (m, 2H), 3.29-4.39 (m, 4H), 6.09 (d, J = 7.5 Hz, 1H), 6.8-7.66 (m, 6H), 9.56 (bs, 1H). Anal. Calcd for $C_{22}H_{32}N_2SeSiO_4$: C, 53.32; H, 6.51; N, 5.65. Found: C, 53.23; H, 6.60; N, 5.42.

1-(5-O-*tert*-Butyldimethylsilyl-2-α-phenylthio-3-deoxy-β-D-pentofuranosyl)thymine 11. The anhydro compound **7** (0.338 g, 1 mmol) was treated with diphenyldisulfide by following a procedure similar to that described for the preparation of **10** except that the reaction mixture was refluxed overnight instead of 3 h. Workup, followed by silica gel column chromatography eluting with hexanes-EtOAc (5:1) gave pure **11** (0.412 g, 92%): $[\alpha]_D^{25}$ +25.71° (c 0.099, EtOH); ^{1}H NMR δ 0.14 (s, 3H), 0.97 (s, 9H), 1.84 (s, 3H), 1.91-2.64 (m, 2H), 3.4-4.41 (m, 4H), 5.96 (d, J = 6Hz, 1H), 6.94-7.61 (m, 6H), 9.07 (bs, 1H). Anal. Calcd for $C_{22}H_{32}N_2SSiO_4$: C, 58.90; H, 7.19; N, 6.24. Found: C, 59.09; H, 7.16; N, 6.07.

1-(5-O-*tert*-Butyldimethylsilyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine 8. Method I: To a stirred solution of compound **10** (0.04 g, 0.08 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.015 mL) at -50 °C was added 30% H_2O_2 (0.03 mL). The mixture was stirred for 5 min and then allowed to warm to 0 °C for 30 min. After this period, the solvents were removed under reduced pressure and the residue was dissolved in CH_2Cl_2, dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica gel. Elution with EtOAc-hexanes (2:3) afforded **8** (0.01 g, 37%). Further elution with EtOAc-MeOH (95:5) gave **9** as a white solid in 22% yield.

Method II: A THF (2 mL) solution of compound **10** (0.054 g, 0.11 mmol) containing two drops of glacial acetic acid was cooled to 0 °C and 30% H_2O_2 (0.03 mL) was added. The mixture was allowed to stir at 0 °C for 15 min and at rt for 2 h. $NaHCO_3$ and MeOH were added followed by evaporation of the solvents *in vacuo*. The residue was preadsorbed onto silica gel, applied to a silica gel column and eluted with EtOAc-hexanes (2:3) to afford **8** quantitatively.

1-(5-O-Pivaloyl-2-α-phenylthio-3-deoxy-β-D-pentofuranosyl)-thymine 12. To compound **11** (0.18 g, 0.4 mmol) in dry THF (10 mL) under N_2 at rt was added n-Bu_4NF in THF (1 mL, 1 M solution, 1 mmol). After 2 h of stirring, the solution was concentrated under reduced pressure. The residue was dissolved in dry pyridine (4 mL), cooled to -15 °C with ice-salt mixture and

pivaloyl chloride (0.073 mL, 0.59 mmol) was added. After 6 h of stirring at -5 to -15 °C, the solution was concentrated *in vacuo*, applied to a silica gel column and eluted with EtOAc-hexanes (1:3) to give **12** (0.15 g, 92%); $[\alpha]_D^{25}$ +37.38° (c 0.8, EtOH) ^{1}H NMR δ 1.25 (s, 9H), 1.82 (s, 3H), 1.92-2.49 (m, 2H), 3.67 (dd, J = 12 and 9 Hz, 1H), 3.95-4.59 (m, 3H), 5.92 (d, J = 6 Hz, 1H), 6.92 (s, 1H), 7.05-7.62 (m, 5H), 9.35 (bs, 1H). Anal. Calcd for $C_{21}H_{26}N_2SO_5$: C, 60.27; H, 6.26; N, 6.69; S, 7.66. Found: C, 60.34; H, 6.41; N, 6.42; S,7.76.

1-(5-O-Pivaloyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl) thymine 13. A solution of compound **12** (0.06 g, 0.14 mmol) in CH_2Cl_2 (5 mL) was oxidized with m-CPBA (0.044 g, 0.147 mmol, 50-60%) at 0 °C for 3 h. The crude product obtained after the usual work up, was dissolved in dry xylene (5 mL) and DBU (0.025 mL, 0.17 mmol) was added. After refluxing the reaction mixture for 16 h, excess solvent was removed under reduced pressure. Purification of the crude product by chromatography on a silica gel column using EtOAc-hexanes (3:1) yielded **13** as a white solid (0.034 g, 80%), mp 205-206 °C (lit.[11] mp 206-207 °C).

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