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Studies on the synthesis and unusual behavior of vinyl sulfone-modified hexenopyranosylthymines

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Abstract—Although vinyl sulfone-modified- (VSM) pent-2′-enofuranosyl nucleosides **2** and hex-2-enopyranosyl glycoside **4** are easily synthesized from the corresponding mesylated sulfones **1c** and **3c**, respectively, via an oxidation–mesylation–elimination route, the 3′-*C*-sulfonyl-hex-2′-enopyranosylthymine **11** is not obtained from **10** and a glycal derivative **12** is formed instead. On the other hand, 3′-*C*-sulfonyl-hex-3′-enopyranosylthymine **20** is easily synthesized from the mesylated sulfone **19**. Again unlike the reaction patterns of VSM-pent-2′-enofuranosyl nucleosides **2** and hex-2-enopyranosyl glycosides **4** as Michael acceptors, the reactions of nucleophiles with 3′-*C*-sulfonyl-hex-3′-enopyranosylthymine **20** yielded a rearranged product **21** instead of Michael adducts.

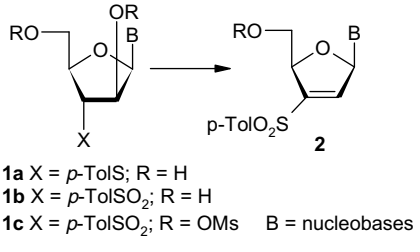
Keywords: Hexopyranosyl nucleosides; Vinyl sulfone-modified nucleosides; Unsaturated nucleosides; Michael addition; Glycal

1. Introduction

The selective reverse transcriptase inhibitory properties of the unsaturated nucleoside, 2′,3′-didehydro-2′,3′-dideoxythymidine (d_4T, stavudine), have triggered the designing of a plethora of unsaturated furanosyl nucleosides having variations at either or both of the 2′- and 3′-positions.[1] Attempts are also currently underway to synthesize and study the biological properties of a wide range of unsaturated pyranosyl nucleosides.[2–4]

As part of a program on the synthesis of modified nucleosides,[5–8] we functionalized furanosyl nucleosides with electron-rich double bonds such as those of enamines[6] as well as with electron-deficient double bonds such as those of vinyl sulfones.[7] Although the vinyl sulfone moiety was identified as a biologically important functional group long ago, in recent times vinyl sulfone-containing dipeptides are shown to be efficient cysteine protease inhibitors through covalent bond formation with the enzymes.[9] In fact a wide range of vinyl sulfone-modified (VSM) organic molecules have been subjected to extensive biological studies.[9] Surprisingly, no biological data on any VSM carbohydrates and nucleosides are available in the literature to date.[9]

Our interest in developing methodologies for the functionalization of hexopyranosyl nucleosides[8] at the 2′, 3′, or 4′ positions for the generation of new six-membered nucleosides prompted us to initiate a study for the designing of VSM pyranosyl nucleosides. As VSM-pent-2′-enofuranosyl nucleosides **2** synthesized from **1a** via **1b** and **1c** (Scheme 1) were used as efficient Michael



Scheme 1. Reported[10] synthesis of vinyl sulfone-modified nucleosides **2**.

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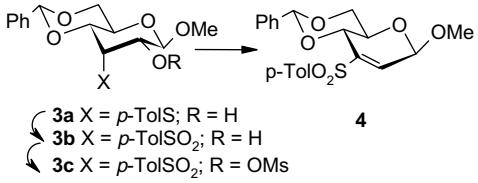
acceptors for the generation of a range of amino- and branched-chain nucleosides,[10] we presumed that VSM hexopyranosyl nucleosides, in addition to their potential biological properties,[9] would also act as useful intermediates for the functionalization of the sugar moiety of pyranosyl nucleosides.

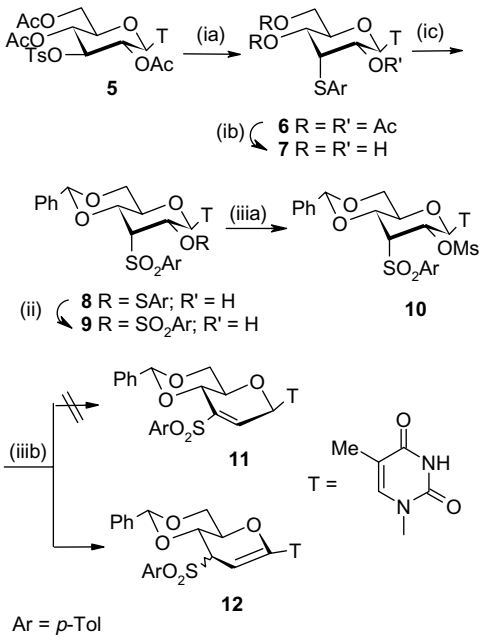
2. Results and discussion

2.1. Attempted synthesis of 3′-*C*-sulfonyl-hex-2′-enopyranosylthymine (11)

In connection with VSM carbohydrates, we have demonstrated that the β-anomeric derivative **4** was easily accessible from **3a** via **3b** and **3c** (Scheme 2).[11] We therefore decided to apply a similar strategy to synthesize VSM pyranosyl nucleosides. Our synthesis started from 1-(2,4,6-tri-*O*-acetyl-3-*O*-tosyl-β-D-glucopyranosyl)thymine (**5**), which was converted to a mixture of **6** and partially deacetylated compounds earlier reported by us (Scheme 3).[8] Complete deacetylation of the mixture was achieved by NaOMe in methanol. Triol **7** thus obtained was benzylidenated yielding the partially protected alcohol **8**. Compound **8** was oxidized with magnesium monoperoxypthalate (MMPP) in MeOH to produce the sulfonylated nucleoside **9**. Crude **9** was mesylated using the standard conditions, and product **10** was subsequently treated with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU). Although oxidation–mesylation–base treatment is a standard route that was used earlier for the synthesis of VSM-nucleosides (Scheme 1) and carbohydrates (Scheme 2), to our surprise in this case the desired compound **11** was not produced. In the ^{1}H NMR spectrum, the H-2′ proton of nucleoside **2** (B = U) appeared[10] at δ 6.56, and the H-2 olefinic proton of the carbohydrate **4** appeared[11] at δ 6.94 (1H, m). The absence of any such peak around this region and the unusual chemical shift values of the other protons in the ^{1}H NMR spectrum of the product of mesylate **10** indicated the absence of a vinyl sulfone group. The isolated product was identified as 1-[2,3-deoxy-(4,6-*O*-benzylidene)-(3-*C*-*p*-toluenesulfonyl)-*erythro*-β-D-hex-1-*eno*-pyranosyl]- thymine **12** as follows: The signal of the H-2′ alkene proton for **12** appeared (^{1}H–^{1}H COSY) as a doublet at δ 5.40. The peak position of quaternary C-1′ was established to be δ 149.0 on the basis of its correlations with two β protons, H-3′ (δ 4.20) and H-6 (δ 7.13) in the heteronuclear multiple bond correlation (HMBC) spectrum. The identification of C-1′ as a quaternary carbon and the presence of the olefinic proton at a higher field (δ 5.40 as opposed to $>\delta$ 6.50) established the position of the double bond between C-1′ and C-2′. Since the hex-1-enopyranosyl nucleoside **12** was not the desired product, no attempt was made further to unambiguously establish the configuration of the C-3′ center of this compound (Scheme 3).

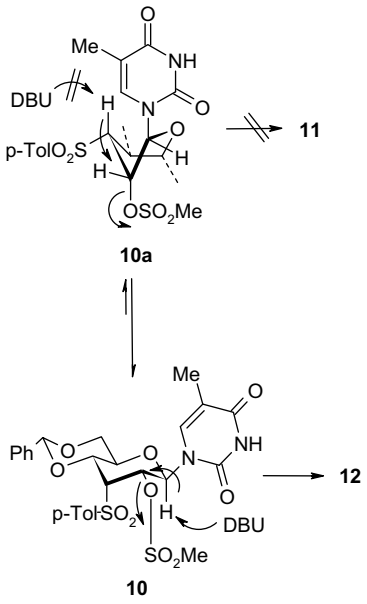


Scheme 2. Reported[11] synthesis of vinyl sulfone-modified carbohydrate **4**.



Scheme 3. Reagents and conditions: (i) (a) *p*-TolSH, NaOMe, DMF, 90 °C, 10 h; (b) NaOMe, MeOH, rt, 6 h; (c) $PhCH(OCH_3)_2$, TsOH, DMF, 100 °C, 1 h, 66% (from **5**); (ii) MMPP, MeOH, rt, 3–3.5 h; (iii) (a) MsCl, pyridine, 0–4 °C, overnight; (b) DBU, DCM, rt, 5 h, 52% (from **8**).

Although VSM-nucleoside **2** and the carbohydrate **4** were easily synthesized from the mesylates **1c** (Scheme 1) and **3c** (Scheme 2), respectively,the failure of the same reaction sequence to afford the VSM hexopyranosyl nucleosides **11** was a surprising result. The unexpected result may be partially explained by considering the fact that the presence of a better electron-withdrawing and sterically bulkier nucleobase at the anomeric position of the mesylate **10** as opposed to the methoxy group of **3c** tripped the balance in favor of the C-1′–C-2′ elimination product **12** instead of desired **11**. However, as mentioned above, the VSM-nucleoside **2** was easily synthesized following a similar route. Therefore, to settle the anomaly, we argued that for the *trans*-elimination required for the bond formation between C-2′ and C-3′, the H-3′ and C-4′-OMs should be antiperiplanar (diaxial). In that case the mesylated compound **10** needed to flip to a twist-boat conformation **10a**, which

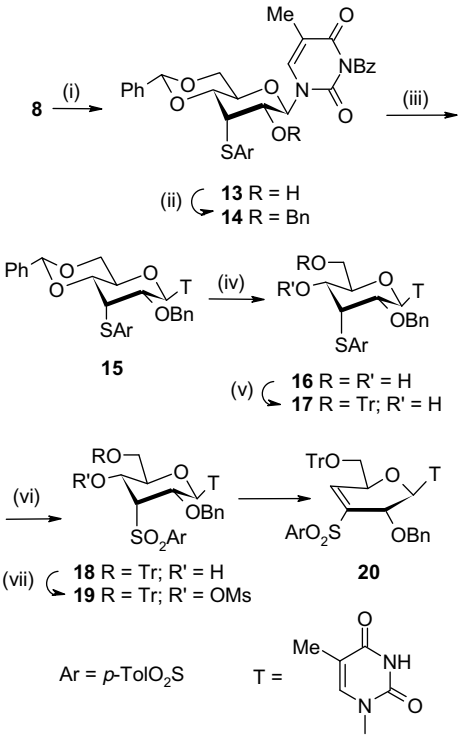


Scheme 4. Probable mechanism of formation of the undesired glycal **12**.

would have created severe 1,3-diaxial interaction between the bulky nucleobase and H-3′ proton (Scheme 4).[12a] Under the circumstances, the acidity of H-1′ as well as the stability of C-1′–C-2′ olefin via conjugation of the ring oxygen would favor the formation of compound **12**. It should be noted that the steric hindrance mentioned in Scheme 4 would be minimal in the case of the carbohydrate-derived mesylate **3c** because of the much smaller bulk of OMe and also because of the fact that the methyl group attached to oxygen was 'removed somewhat'[12b] from the ring. It is noteworthy that the synthesis of the vinyl nitro analogue 1-(4,6-*O*-benzylidene-2,3-didehydro-2,3-dideoxy-3-nitro-β-D-hexopyranosyl)uracil was also difficult because the compound was 'too unstable'.[13] However, it was possible to generate this compound in situ, and the Michael addition product was isolated although the authors suggested the involvement of a 'boat-like *aci*-nitro intermediate' in the product formation process.[13] It is probable that the different structural as well as electronic features of the $-NO_2$ and the $-SO_2Ar$ groups also contributed significantly to the stability of one vinyl derivative over the other. However, it is also probable that the vinyl sulfone derivative **11** formed first via the elimination and then underwent rearrangement to yield glycal **12**.

2.2. Synthesis of 3′-*C*-sulfonyl-hex-3′-enopyranosylthymine (20)

With the non-availability of one required VSM-nucleoside **11**, we decided to explore the possibility of synthesizing 3′-*C*-sulfonyl-hex-3′-enopyranosylthymine **20** (Scheme 5), which was expected to be useful for the



Scheme 5. Reagents and conditions: (i) (a) TMSCl, pyridine, 1 h; BzCl, pyridine, rt, 1 h; (b) 0.25% TFA, CH_2Cl_2, MeOH, 20 min; (ii) BnBr, NaH, DMF, rt, overnight; (iii) NaOMe, MeOH, rt, 3–5 h; (iv) aq TFA (80%), rt, 30–45 min; (v) TrCl, pyridine, reflux, 3 h; (vi) MMPP, MeOH, rt, 3–3.5 h; (vii) MsCl, pyridine, 0–4 °C, overnight.

functionalization of the C-4′ position. Because of its easy accessibility, we started our synthesis from thionucleoside **8**. Our intention was to deprotect **15**, protect the primary alcohol selectively, and then mesylate the C-4′ hydroxyl group. However, for this strategy it was necessary to mask the C-2′ hydroxyl group. The instability of ester groups under nucleophilic reaction conditions to be used later prompted us to benzylate the C-2′ hydroxyl group. It was therefore necessary to protect the nucleobase prior to the protection of the C-2′ hydroxyl group to avoid any alkylation of the nucleobase. Thus, alcohol **8** was treated with chlorotrimethylsilane in pyridine at 0 °C, followed by benzoyl chloride in a one-pot fashion. The product, after usual work-up, was treated with 0.25% TFA in 1:1 MeOH–CH_2Cl_2 for a few minutes to produce the N^3-benzoylated derivative **13**. Compound **13** was benzylated using excess of benzyl bromide and NaH in anhydrous DMF. After purification, compound **14** was treated with NaOMe in MeOH to afford nucleoside **15**. Compound **15** was treated with 4:1 TFA–water for a brief period to remove the benzylidene protecting group. The primary C-6′ hydroxyl group of **16**, thus obtained, was protected with trityl group to produce **17**. Compound **17** was oxidized to sulfone nucleoside **18**. Sulfone **18** was mesylated in pyridine, and the reaction condition was basic enough to initiate an elimination reaction to afford the desired

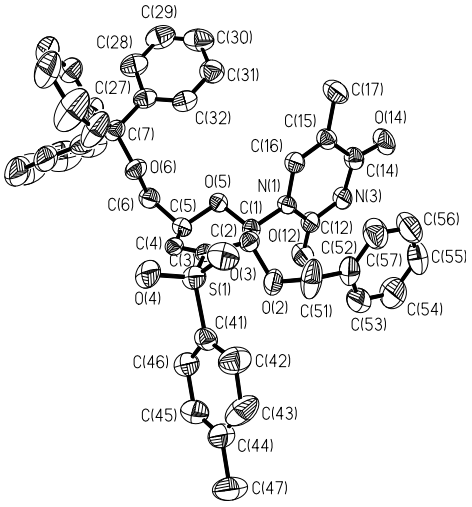


Figure 1. ORTEP of compound **20**.

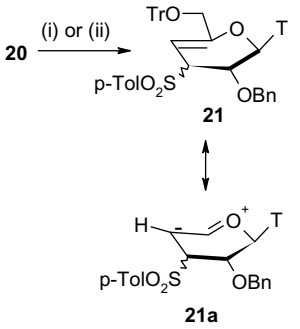
1-[2-*O*-benzyl-3,4-deoxy-(3-*C*-*p*-toluenesulfonyl)-6-*O*-trityl-*erythro*-β-D-hex-3-*eno*-pyranosyl]thymine **20**. The characteristic peak of the vinyl proton of the vinyl sulfone group was identified at δ 7.10–7.43. However, the structure of **20** was established unambiguously with the help of X-ray crystallography (Fig. 1); notably the C-3′–C-4′ bond length was 1.31 Å, which was less than the average C–C single bond length.

Compound **20** was easily synthesized from **19** because, in this case the six-membered ring could easily flip to the required conformation to place the H-3′ and the C-4′-OMs in the antiperiplanar positions. It is important to note that even a strong base like DBU could not facilitate the formation of vinyl sulfone **11** from **10** (Scheme 3), whereas under the conditions employed for mesylation, **19** was transformed to **20** by pyridine at +4 °C.

2.3. Reactions of 3′-*C*-sulfonyl-hex-3′-enopyranosyl-thymine (20)

Michael acceptor **20** was treated with several amines and carbon nucleophiles generated from nitromethane or dimethyl malonate. Only benzylamine and piperidine in a nonpolar solvent like 1,2-dichloroethane (EDC) afforded an isomerized single product **21**, which was identified as having a C-4′–C-5′ double bond to give the more stable product, namely, 1-[2-*O*-benzyl-3,4-dideoxy-(3-*C*-*p*-toluenesulfonyl)-6-*O*-trityl-*erythro*-β-D-hex-4-*eno*-pyranosyl]thymine (**21**) in 50–55% yield (Scheme 6). The peak at δ 5.84 (^{1}H NMR) for compound **21** was identified as the H-1′ proton, and the rest of the protons were assigned using the correlation spectrum.

Notably the absence of H-5′-proton, simplified the splitting patterns of H-6′ and H-6″ protons that appeared at δ 3.44–3.55. The peak position of quaternary C-5′ was established at δ 156.1 on the basis of its correlations with two α protons, H-4′ (δ 5.10) and



Scheme 6. Reagents and conditions: (i) benzylamine, EDC, rt, 48 h, 55%; (ii) piperadine, EDC, rt, 5 h, 50%.

H-6′, H-6″ (δ 3.50) in the HMBC spectrum. Identification of C-5′ as a quaternary carbon and the presence of the olefinic proton H-4′ at a higher field (δ 5.10 as opposed to $>\delta$ 6.50 for vinyl sulfones **2** and **4**) devoid of any coupling with H-5′, established the position of the double bond between C-4′ and C-5′. Almost all the other reactions produced inseparable mixtures of products (Table 1). In this case also no attempt was made to establish the configuration at the C-3′ position.

The formation of compound **21** may be considered as a simple migration of a double bond that was facilitated by the abstraction of the C-5′ proton, followed by the stability imparted by the delocalization of the lone pairs of the ring oxygen. Although **20** did not react as a Michael acceptor, there are several reports on the addition of nucleophiles at the C-4 position of pyranosyl Michael acceptors, such as the addition of azide to methyl 6-*O*-benzoyl-3,4-dideoxy-α-D-*glycero*-hex-3-enopyranosid-2-ulose,[14] functionalization of C-4 of methyl 3,4-dideoxy-6-*O*-(l-ethoxyethyl)-α-D-*glycero*-hex-3-enopyranosid-2-ulose with a methyl group,[15] and most notably, the reaction of benzylamine with phenyl 4,6-di-*O*-acetyl-2-*O*-benzyl-3-deoxy-3-nitro-β-D-glucopyranoside to afford the corresponding Michael adduct in 77% yield via the in situ generated vinyl nitro derivative.[16]

Table 1. Reactions of **20** under various conditions[a]

Sl. no.	Reaction conditions	Products
1	Benzylamine (5 equiv) in EDC; 48 h	55% **21**
2	Piperidine (5 equiv) in EDC; 5 h	50% **21**
3	Isobutylamine (neat); 8–10 h	Inseparable mixture
4	$EtNH_2$ aq (70%, excess) in dioxane; 1 h	Inseparable mixture
5	NH_3 aq (excess) in dioxane; rt; 1 h	Inseparable mixture
6	Nitromethane–NaOMe in MeOH; rt; 10–12 h	Inseparable mixture
7	Dimethyl malonate–NaH in THF; rt; 24 h	Inseparable mixture

[a] All reactions were carried out at room temperature.

In summary, on one hand the presence of a nucleobase at the anomeric position of a VSM hexopyranoside drastically altered its properties, which led to the formation of glycal derivative **12** instead of 3′-*C*-sulfonyl-hex-2′-enopyranosylthymine **11**; this is an unexpected deviation from the known pattern of reactions of mesylated sulfones, such as **1c** and **3c** under basic conditions. On the other hand, in spite of the reported reactions of vinylnitro-modified hex-3-enopyranosides and related Michael acceptors with nucleophiles, 3′-*C*-sulfonyl-hex-3′-enopyranosylthymine (**20**) uncharacteristically underwent isomerization instead of the expected Michael addition reactions.

3. Experimental

3.1. General methods

Melting points were determined in open-end capillary tubes and are uncorrected. Carbohydrates and other fine chemicals were obtained from commercial suppliers and were used without purification. Solvents were dried and distilled following the standard procedures. TLC was carried out on precoated plates (E. Merck Silica Gel 60, F_{254}), and the zones were visualized with UV light or by charring the plates dipped in 5% H_2SO_4–MeOH or 5% H_2SO_4–vanillin–EtOH. Column chromatography was performed on silica gel (60–120 or 230–400 mesh). ^{1}H and ^{13}C NMR spectra for most of the compounds were recorded at 200 and 50.3 MHz, respectively, in $CDCl_3$ unless stated otherwise. Optical rotations were recorded at 589 nm.

3.2. 1-(4,6-*O*-Phenylmethylene-3-deoxy-3-*S*-tolyl-β-D-allopyranosyl)thymine (8)

To a solution of 4-methylbenzenethiol (*p*-toluenethiol, 0.87 g, 7 mmol) in DMF (5 mL), NaOMe (0.27 g, 5 mmol) was added. The reaction mixture was stirred at rt for 0.5 h. Compound **5** (0.57 g, 1.0 mmol) was added, and the reaction mixture was heated at 90 °C for 10 h. The reaction mixture was allowed to cool to rt, and DMF was evaporated under reduced pressure. To a methanolic solution (10 mL) of the reaction mixture, NaOMe (0.17 g, 3 mmol) was added. After 6 h at rt, the reaction mixture was neutralized with Dowex H^+ (50 × 8) and filtered. All volatiles were removed under reduced pressure, and the crude residue was purified over silica gel to get **7**. To a mixture of the unprotected thio nucleoside **7** (0.32 g, 0.81 mmol) and benzaldehyde dimethyl acetal (0.18 g, 1.21 mmol) in DMF (25 mL), a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) was added. The reaction mixture was heated at 100 °C under vacuum for 1 h. After cooling the mixture at rt, DMF was evaporated under reduced pressure. The residue was diluted with EtOAc (50 mL), and the solution was washed with satd aq $NaHCO_3$ (2 × 25 mL). The organic layer was dried over anhyd Na_2SO_4, and filtered, and the filtrate was concentrated. The crude product was purified over a silica gel column to afford **8**. (Eluent: 3:2 EtOAc–petroleum ether.) The compound was crystallized from a $CHCl_3$–petroleum ether mixture to give **8** as white crystals: 0.32 g, (66%) from **5**. Mp: 220 °C. $[\alpha]_D^{25}$ −73.0 (*c* 1.20, $CHCl_3$). IR (Nujol): 1686 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.94 (s, 3H), 2.29 (s, 3H), 3.71–4.10 (m, 5H), 4.37 (dd, $J = 4.8$, 10.2 Hz, 1H), 5.62 (s, 1H), 5.69 (d, $J = 8.8$ Hz, 1H), 7.03 (d, $J = 7.9$ Hz, 2H), 7.12 (s, 1H), 7.37–7.51 (m, 7H, aromatic), 9.26 (s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$):δ 12.3, 20.8, 59.0, 67.6, 68.5 (CH_2), 69.0, 78.0, 82.3, 101.4, 111.5, 126.2, 128.1, 129.0, 129.7, 131.2, 133.3, 135.0, 136.9, 137.8, 151.0, and 163.5. Anal. Calcd for $C_{25}H_{26}N_2O_6S{\cdot}0.5H_2O$: C, 61.09; H, 5.54. Found: C, 61.35; H, 5.44.

3.3. 1-[4,6-*O*-Benzylidene-2,3-deoxy-(3-*C*-*p*-toluenesulfonyl)-*erythro*-β-D-hex-1-*eno*-pyranosyl]thymine (12)

A mixture of compound **8** (0.96 g, 2 mmol) and MMPP (4.94 g, 10 mmol) in MeOH (150 mL) was stirred vigorously at rt for 3–3.5 h. The reaction mixture was passed through a basic alumina column, and the filtrate was evaporated under reduced pressure. A pyridine solution (25 mL) of the resulting product **9** (1.0 g, 1.94 mmol) was cooled to 0 °C in an ice bath. Methanesulfonyl chloride (0.9 mL, 10 mmol) was added dropwise to the reaction mixture. The reaction mixture was kept at +4 °C overnight. The reaction mixture was quenched with ice. Pyridine was evaporated under reduced pressure, and co-evaporated with toluene. The residue was diluted with DCM (75 mL). The organic layer was washed with satd aq $NaHCO_3$ (2 × 10 mL), water (5 mL), and brine (5 mL). The organic layer was dried over anhyd Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure. A solution of the crude mesylated sulfone nucleoside **10** in DCM (40 mL) was cooled to 0 °C in an ice bath. To the reaction mixture was added DBU (0.61 g, 4 mmol), dropwise with constant stirring. The mixture was stirred at rt for 5 h. The volume of the reaction mixture was reduced to one-fifth by evaporation. The solution thus obtained was loaded directly on a silica gel column. (Eluent: 3:2 EtOAc–petroleum ether) Purification afforded compound **12**. The product was crystallized from an EtOAc–petroleum ether mixture to afford **12** as white crystals: 0.46 g, (52% overall from **8**). Mp: 204 °C (dec.); $[\alpha]_D^{27.7}$ +14.6 (*c* 1.60, $CHCl_3$). IR ($CHCl_3$): 1732, 1697.2. ^{1}H NMR (400 MHz, $CDCl_3$) (^{1}H–^{1}H COSY): δ 1.95 (s, 3H, CH_3 thymine), 2.36 (s, 3H, CH_3), 3.84 (t, $J = 10.3$ Hz, 1H, H6″), 4.09 (m, 1H, H5′), 4.20 (m, 2H, H3′, H4′), 4.48 (dd, $J = 5.0$, 10.3 Hz, 1H, H6′), 5.37 (s, 1H, PhCH), 5.40 (d, 1H, H2′), 6.98 (m, 2H, aromatic),

7.13 (s, 1H, H6), 7.24–7.32 (m, 5H, aromatic), 7.82 (d, $J = 8.3$ Hz, 2H, aromatic), 9.00 (s, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$) (^{1}H–^{13}C COSY; HSQC): δ 12.0 (*C*-methyl thymine), 21.5 (*C*-methyl), 63.1 (C-3′), 67.6 (CH_2, C-6′), 69.4 (C-5′), 73.4 (C-4′), 90.3 (C-2′), 100.9 (PhC), 111.2, 125.6, 127.8, 128.7, 129.0, 129.8, 135.3, 135.8, 138.7 (C-6 thymine), 145.3, 149.0, 149.7, 164.0. Anal. Calcd for $C_{25}H_{24}N_2O_7S$: C, 60.47; H, 4.87. Found: C, 60.38; H, 4.49.

3.4. 1-[2-*O*-Benzyl-(4,6-*O*-phenylmethylene)-3-deoxy-3-*S*-(*p*)-tolyl-β-D-*allo*pyranosyl]thymine (15)

To a solution of **8** (0.96 g, 2 mmol) in dry pyridine (10 mL) were added Et_3N (1.01 mL, 10 mmol) and chlorotrimethylsilane (0.4 mL, 3 mmol) under cold conditions. After stirring the reaction mixture for 1 h, it was cooled using an ice bath. Benzoyl chloride (0.35 mL, 3 mmol) was added dropwise and the reaction mixture was stirred at rt for an additional 1 h. The reaction mixture was quenched with a few drops of satd aq $NaHCO_3$. Pyridine was evaporated under reduced pressure, and co-evaporated with toluene. The residue was diluted with EtOAc (50 mL), and the organic layer was washed with satd aq $NaHCO_3$ (3×10 mL), water (5 mL), and brine (5 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure. TFA (0.05 mL) was added to a solution of the crude product in a 1:1 mixture of CH_2Cl_2 and MeOH (20 mL), and the solution was left at rt for 20 min. All volatiles were removed under reduced pressure, and the crude product was purified over a silica gel column (Eluent: 1:1 EtOAc:Hexane) to afford **13** (0.82 g; 70%). A mixture of **13** (1.23 g, 2.1 mmol) and benzyl bromide (2.5 mL, 21 mmol) in DMF (10 mL) was cooled to 0 °C in an ice bath. To the reaction mixture was added NaH (0.092 g, 2.25 mmol, 60% dispersion in oil) in portions with constant stirring. The reaction mixture was stirred overnight at rt. The reaction mixture was diluted with EtOAc (250 mL). The organic layer was washed with brine (3×15 mL). The volatiles were evaporated under reduced pressure. Purification over silica gel column (Eluent: 1:3 EtOAc:Hexane) gave benzyl bromide-free compound **14**. A solution of **14** in MeOH (40 mL), and NaOMe (0.33 g, 6 mmol) was stirred at rt for 3–5 h. Dowex H^+ (50×8) resin was used to neutralize the solution. Silica gel column purification (Eluent: 1:1 EtOAc–petroleum ether) gave the desired compound **15** as a foamy solid: 0.80 g, (66% from **13**). Mp: 108–110 °C; $[\alpha]_D^{27.1}$ −92.9 (*c* 1.40, $CHCl_3$). IR ($CHCl_3$): 1718.5, 1685.7 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78 (s, 3H), 2.31 (s, 2H), 3.62–3.80 (m, 3H), 4.17 (m, 3H), 4.30–4.35 (m, 1H), 4.50 (d, $J = 12.6$ Hz, 1H), 5.55 (s, 1H), 6.09 (bs, 1H), 6.64 (br s, 1H), 7.03–7.56 (m, 14H, aromatic), 8.38 (d, $J = 8.6$ Hz, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.3, 20.9, 53.1, 67.0, 68.4 (CH_2), 69.4 (CH_2), 73.5, 77.8, 79.5, 101.3, 110.9, 126.1, 128.0, 128.2, 128.4, 128.9, 129.4, 131.5, 133.8, 136.0, 136.7, 137.5, 150.5, 163.6. Anal. Calcd for $C_{32}H_{32}N_2O_6S{\cdot}0.25H_2O$: C, 66.59; H, 5.65. Found: C, 66.74; H, 5.54.

3.5. 1-[2-*O*-Benzyl-3,4-deoxy-(3-*C*-*p*-toluenesulfonyl)-6-*O*-trityl-*erythro*-β-D-hex-3-*eno*-pyranosyl]thymine (20)

Compound **15** (2.84 g, 5 mmol) was treated with 4:1 TFA–water (3 mL) at rt for 30–45 min. All the volatiles were evaporated under reduced pressure to afford **16**. A solution of crude **16** (2.34 g, 5 mmol) in dry pyridine (20 mL) was reacted with trityl chloride (1.68 g, 6 mmol). The reaction mixture was heated under reflux for 3 h. The reaction mixture was cooled to rt. Pyridine was evaporated under reduced pressure. The reaction mixture was diluted with EtOAc (150 mL), washed with water (10 mL), and brine (5 mL), and the organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated, and the crude product was purified over a neutral alumina column (Eluent: 1:6 EtOAc:Hexane) to afford **17** (3.2 g, 90%). A mixture of **17** (3.47 g, 4.78 mmol) and MMPP (11.82 g, 23.9 mmol) in MeOH (150 mL) was stirred vigorously at rt for 3–3.5 h. The solvent was concentrated to a small volume, and filtered over a column of basic alumina affording a polar compound **18**. A solution of the trityl-protected sulfone nucleoside **18** (3.28 g, 4.42 mmol) in dry pyridine (30 mL) was cooled to 0 °C in ice bath. Methanesulfonyl chloride (1.8 mL, 22.1 mmol) was added dropwise to the reaction mixture. The reaction mixture was kept at +4 °C overnight. The reaction mixture was quenched with ice. Pyridine was evaporated under reduced pressure and co-evaporated with toluene. The residue was diluted with CH_2Cl_2 (75 mL), the organic layer was washed with satd aq $NaHCO_3$ (2×10 mL), water (5 mL), and brine (5 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated, and the product was purified over a neutral alumina column (Eluent: 1:3 EtOAc–petroleum ether) to yield compound **18**. The product was crystallized from a mixture of $CHCl_3$ and petroleum ether to yield **18** as colorless crystals: 2 g, (61% from **15**). Mp: 225–229 °C (dec.). $[\alpha]_D^{28}$ −87.8 (*c* 1.98, $CHCl_3$). IR ($CHCl_3$): 1695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) (^{1}H–^{1}H COSY): δ 1.69 (s, 3H, CH_3 thymine), 2.37 (s, 3H, CH_3), 3.28 (dd, 1H, H6′), 3.36 (dd, 1H, H6″), 4.54–4.63 (m, 3H, H2′, benzylic CH_2), 4.73 (m, 1H, H5′), 5.83 (d, $J_{1',2'} = 7.4$ Hz, 1H, H1′), 6.85 (s, 1H, H6), 7.10–7.43 (m, 23H, aromatic, H4′), 7.69 (d, $J = 8.3$ Hz, 2H, aromatic), 8.49 (s, 1H, NH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.4, 21.5, 64.7 (CH_2), 71.2, 74.2, 74.8 (CH_2), 81.2, 87.0, 111.5, 127.3, 127.9, 128.6, 129.5, 134.1, 136.4, 137.3, 140.6, 141.3, 143.1, 144.4, 150.3, 163.1. Anal. Calcd for

$C_{44}H_{40}N_2O_7S{\cdot}0.25H_2O$: C, 70.90; H, 5.47. Found: C, 70.89; H, 5.37.

3.6. 1-[2-*O*-Benzyl-3,4-deoxy-(3-*C*-*p*-toluenesulfonyl)-6-*O*-trityl-*erythro*-β-D-hex-4-*eno*-pyranosyl]thymine (21)

3.6.1. Reaction A. A mixture of **20** (0.20 g, 0.27 mmol) and benzylamine (0.14 g, 1.35 mmol) in EDC (5 mL) was stirred at rt for 48 h. The reaction mixture was directly loaded onto a silica gel column. (Eluent: 1:3 EtOAc–petroleum ether) The column purification afforded the amine free compound **21**.

3.6.2. Reaction B. A mixture of compound **20** (0.20 g, 0.27 mmol) and piperidine (0.115 g, 1.35 mmol) in EDC (5 mL) was stirred at rt for 5 h. Purification was carried out as above (Eluent: 1:3 EtOAc–petroleum ether), to afford **21** as a white solid: 0.14 g, (55%). Mp: 118–120 °C (dec.). $[\alpha]_D^{28}$ +22.1 (*c* 1.40, $CHCl_3$). IR ($CHCl_3$): 1765, 1716.5 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) (^1H–^1H COSY): δ 1.73 (s, 3H, CH_3, thymine), 2.46 (s, 3H, CH_3), 3.44–3.55 (m, 2H, H6′, H6″), 4.22 (m, 1H, H3′), 4.34 (m, 1H, H2′), 4.63 (d, $J = 11.7$ Hz, 1H, benzylic CH_2), 4.81 (d, $J = 11.7$ Hz, 1H, benzylic CH), 5.10 (bs, 1H, H4′), 5.84 (d, $J_{1',2'} = 9.0$ Hz, 1H, H1′), 6.66 (s, 1H, H6), 7.23–7.35 (m, 22H, aromatic), 7.87 (d, $J = 8.1$ Hz, 2H, aromatic), 8.35 (s, 1H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$) (^1H–^{13}C COSY; HSQC): δ 12.4 (*C*-methyl thymine), 21.7 (*C*-methyl), 61.7 (CH_2, C-6′), 66.9 (C-3′), 71.0 (C-2′), 73.2 (benzylic C), 81.0 (C-1′), 87.2 (Trityl C), 91.2 (C-4′), 111.7, 127.2, 127.9, 128.1, 128.3, 128.4, 128.5, 129.0, 129.9, 133.9, 134.1, 136.4 (C-6), 143.2, 145.3, 150.5, 156.1, 163.2. Anal. Calcd for $C_{44}H_{40}N_2O_7S{\cdot}H_2O$: C, 69.63; H, 5.58. Found: C, 69.25; H, 5.70.

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Supplementary data

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 673335. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK. (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk), and ^1H and ^{13}C NMR spectra of compounds **5**, **8**, **12**, **15**, **20**, and **21**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.02.016.

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