Available online at www.sciencedirect.com
ScienceDirect
Carbohydrate Research 342 (2007) 1151–1158
Carbohydrate RESEARCH

Novel chalcogenides of thymidine and uridine: synthesis, properties and applications

Kirubakaran Sivapriya, Perumal Suguna, S. Shubashree, Perali Ramu Sridhar and Srinivasan Chandrasekaran*

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

Received 1 November 2006; received in revised form 19 February 2007; accepted 10 March 2007
Available online 4 March 2007

Abstract—A facile and efficient methodology has been developed for the synthesis of dithymidine and di-uridine derived disulfides using benzyltriethylammonium tetrathiomolybdate as a sulfur transfer reagent. However, a similar reaction of thymidine derivative with tetraethylammonium tetraselenotungstate as a selenium transfer reagent resulted in the formation of an unexpected cyclic diselenide. The disulfide derivatives of nucleosides have been used as precursors in a tandem disulfide cleavage-Michael addition/ring opening reactions to construct aminoacid and carbocyclic derivatives of nucleosides.

Keywords: Nucleosides; Tetrathiomolybdate; Tetraselenotungstate; X-ray crystallography

1. Introduction

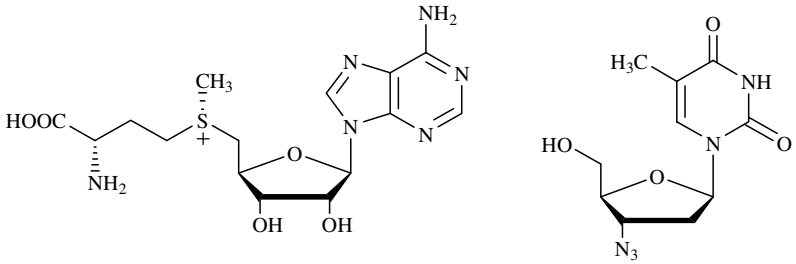
In the past few years modified nucleosides especially thio- and seleno-substituted nucleosides have gained much attention. This is because the sulfur or selenium functionalities present in sugar precursors play a pivotal role in directing β-selective coupling reactions with bases. These functionalities can be removed easily either thermally or reductively to produce dideoxynucleosides.[1] Many modified deoxynucleosides have been shown to exhibit antiretroviral and anticancer activities of varying potency.[2] Selenols derived from deoxynucleosides are known for their susceptibility to oxidation. Nucleoside analogues like 3′-azido-3′-deoxythymidine (**AZT**) and 2′-fluoro-5′-thio analogues have been demonstrated to have anti-HIV and antitumor activity.[3] The important role of *S*-adenosyl-L-methionine (**SAM**) in biological methylation reactions[4a–c] has attracted considerable interest in the synthesis of thionucleoside analogues[5a–g] (Chart 1).

The chemical stability of the 5′-bridging sulfur atom makes it a good candidate for use as a physical and mechanistic probe for specific protein or metal interactions involving this position in DNA[6a] and heavy metal labelled 5′-thiooligonucleotides are interesting substrates in the study of DNA-binding proteins by X-ray crystallography.[6b] The 5′-disulfide derivatives and other 5′-thionucleosides were mainly synthesized involving the use of their respective thiols produced in situ[7a,b] and the diselenide derivatives from selenols and selenocyanides.[8]

In this paper we report a facile and efficient route to the synthesis of 5′-thio and 5′-seleno derivatives of thymidine and uridine. The synthesis of disulfides of thymidine and uridine has been accomplished using our efficient sulfur transfer reagent, benzyltriethylammonium tetrathiomolybdate, $[BnEt_3N]_2MoS_4$ **1**.[9] The disulfides derived from thymidine and uridine have been effectively used in tandem disulfide cleavage-Michael addition/ring opening reactions to form amino acid and carbocyclic derivatives of nucleosides. Interestingly, the selenium transfer reaction of thymidine with

* Corresponding author. Address: Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur, Bangalore, India. Tel.: +91 80 2293 2404; fax: +91 80 2360 2423; e-mail: scn@orgchem.iisc.ernet.in

0008-6215/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2007.02.035



SAM **AZT**

Chart 1.

tetraselenotungstate, $[Et_4N]_2WSe_4$ **2**[10] led to the formation of an unexpected cyclic diselenide **9**.

2. Results and discussion

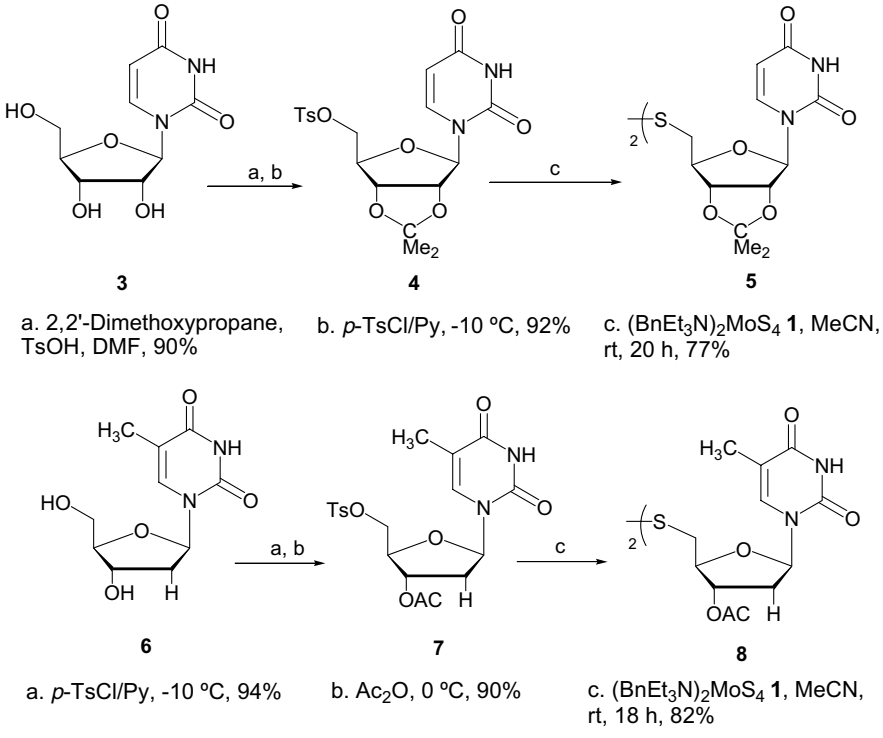
2.1. Synthesis of thymidine and uridine derived disulfides

The formation of uridine and thymidine derived disulfides **5** and **8** from their respective bases in good yields is depicted in Scheme 1. Uridine **3** was protected as its acetal using standard procedure, which on treatment with *p*-toluenesulfonyl chloride in pyridine furnished the tosylate **4** in 92% yield.[11] Similarly, 5-*O*-tosyl-3-*O*-acetyl thymidine **7** was synthesized (90%) from thymidine **6** by tosylation[12] (*p*-TsCl/Py, −10 °C, 8 h) followed by acetylation (Ac_2O, 0 °C, 3 h) in one pot. The tosylates **4** and **7** when treated with tetrathiomolybdate **1** (1.1 equiv, MeCN, 28 °C, 18–20 h) gave the corresponding disulfides **5** and **8**, respectively, in good yields (77–82%). Attempts at the introduction of sulfur at the 2′ and/or 3′-positions of the nucleosides (adenosine, guanosine and thymidine) using the present methodology were not satisfactory and the starting materials were recovered unchanged.

Thymidine derived disulfide **8** was found to be a crystalline solid and its molecular structure was confirmed by X-ray crystallography (Fig. 1).

2.2. Synthesis of thymidine and uridine derived diselenides

When thymidine derived tosylate **7** was treated with tetraselenotungstate **2** (1.1 equiv, MeCN, 28 °C, 22 h) an unexpected cyclic diselenide **9** with an inverted configuration at C-3 was obtained in good yield (82%) (Scheme 2). Compound **9** showed two peaks (δ 301 for Se1 and δ



Scheme 1.

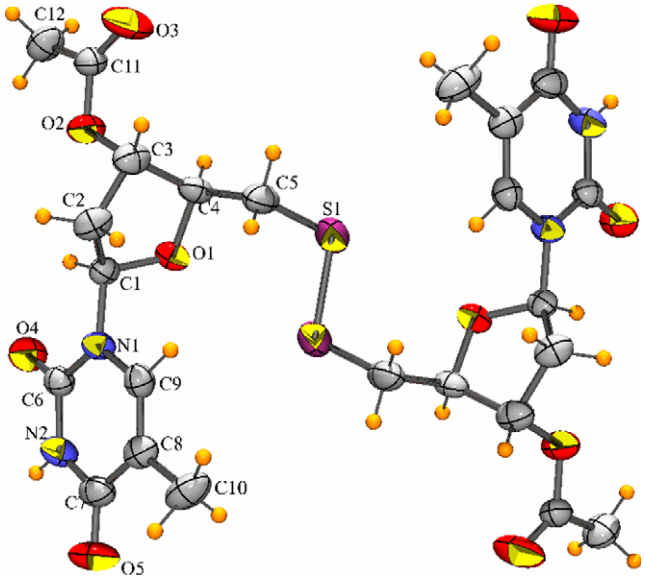
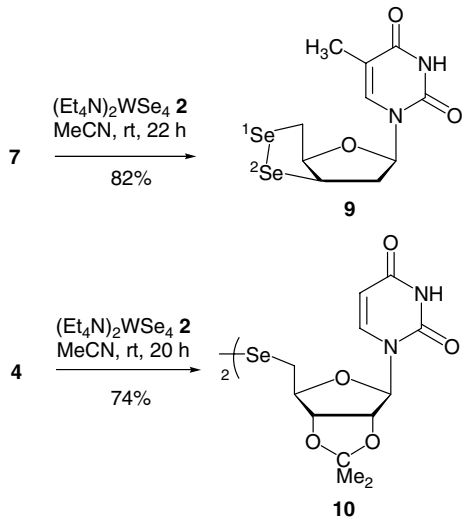


Figure 1. ORTEP diagram of **8** (the other half of the molecule was not labelled for clarity).



Scheme 2.

502 for Se2) in the ^{77}Se NMR spectrum. The molecular structure of **9** was confirmed by single crystal X-ray analysis (Fig. 2). Similar cyclic diselenides were reported previously but the synthesis involved longer routes giving lower yields.[13] The neighbouring group participation reaction to end up with an inverted configuration at C-3 has been reported earlier in the synthesis of 3′-azido-2′,3′-dideoxyadenosine.[14] Interestingly, when uridine derived tosylate **4** was treated with tetraselenotungstate **2** (1.1 equiv, MeCN, 28 °C, 20 h) the corresponding uridine derived diselenide **10**[8] was obtained in 74% yield and the presence of cyclic diselenide was not detected (Scheme 2). The ^{77}Se NMR of compound **10** shows a single peak at δ 291 as expected.

To study the role of the base in the formation of the cyclic diselenide like **9**, a simple 2-deoxy sugar **11** was used as the substrate. The tosylate **12** was synthesized in 91% yield in one pot by stirring the deoxy sugar **11**[15] with *p*-TsCl/Py at −10 °C for 5 h followed by the addition of Ac_2O (0 °C, 2 h) (Scheme 3). Treatment of **12** with tetraselenotungstate **2** (1.1 equiv, MeCN, 28 °C, 10 h) afforded the cyclic diselenide **13** (88%). As expected **13** exhibited two peaks (δ 290 for Se1 and δ 430 for Se2) in the ^{77}Se NMR spectrum. The structure

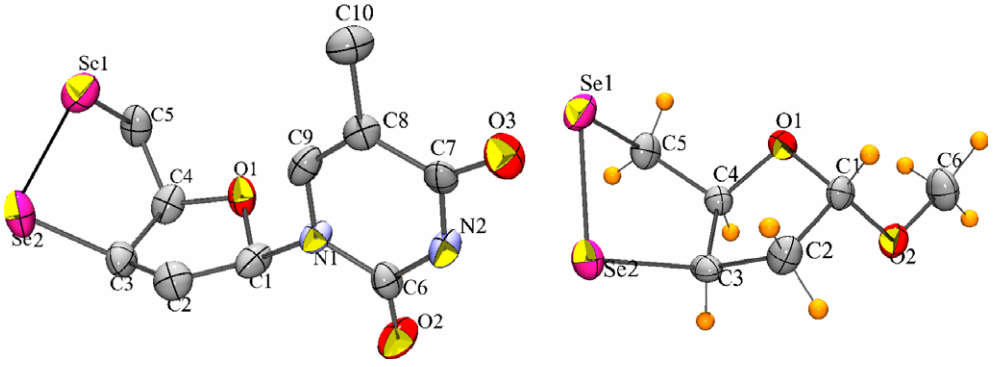
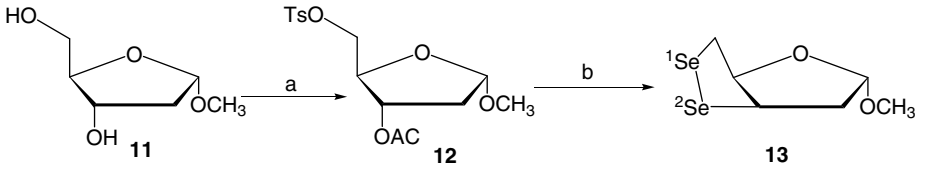


Figure 2. ORTEP diagram of **9** (hydrogens are not shown for clarity) and **13**.



a. i. *p*-TsCl/ Py, -10 °C, 99% ii. Ac_2O, 0 °C b. $(Et_4N)_2WSe_4$ **2**, MeCN, rt, 10 h, 88%

Scheme 3.

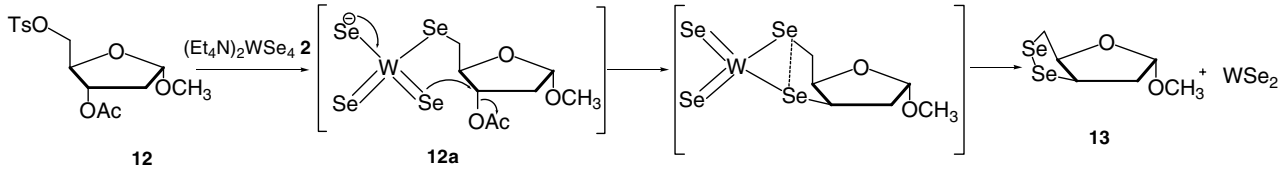
of the product of **13** was further confirmed by X-ray crystallography (Fig. 2).

2.3. Proposed mechanism for the formation of cyclic diselenide 13

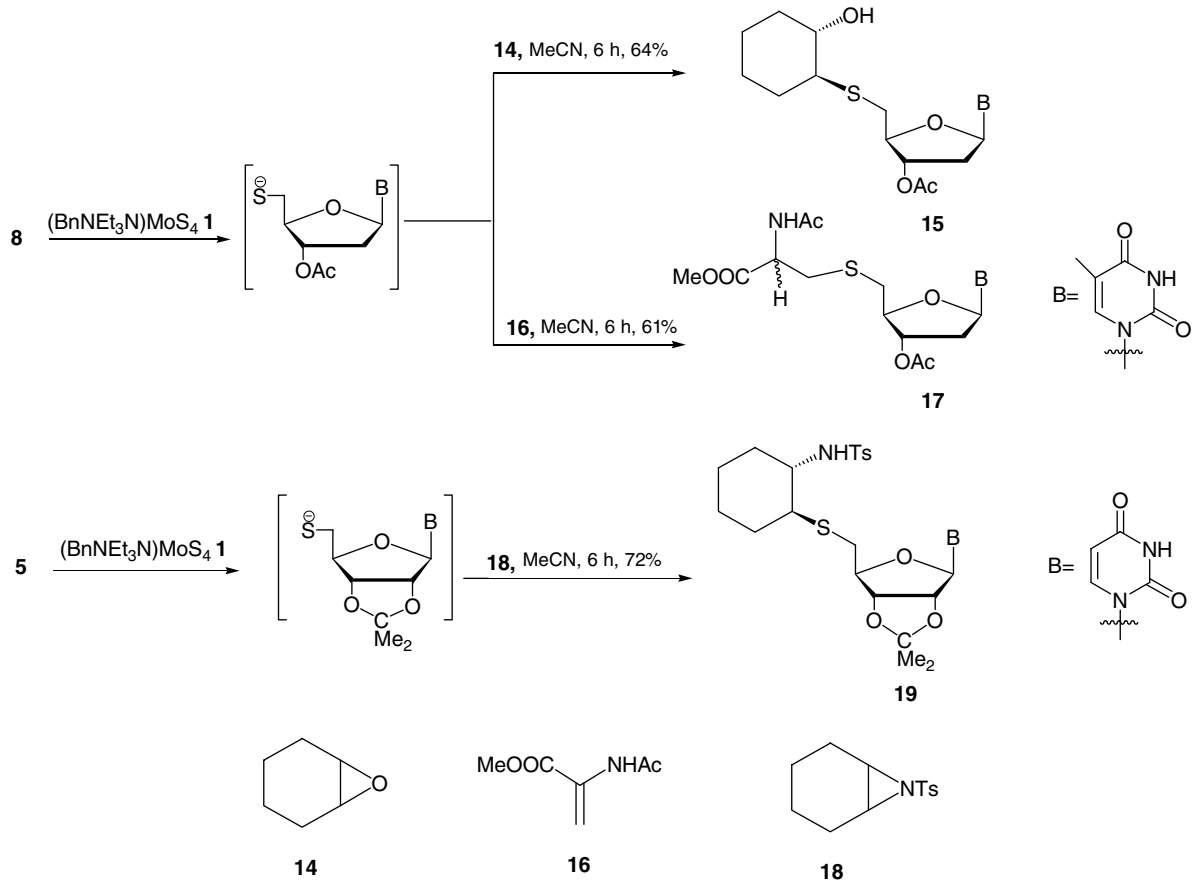
The proposed mechanism for the formation of the diselenide **13** is shown in Scheme 4. The first step is the nucleophillic attack of tetraselenotungstate **2** on tosylate **12**, which will give the alkylated intermediate **12a**. The intermediate **12a** on intramolecular displacement of acetate by selenium followed by the diselenide formation in an internal redox process[16a–d] furnishes the cyclic diselenide **13**. However, it should be pointed that the reaction of 3′,5′-ditosyl derivatives of thymidine **6** and 2-deoxy sugar **11** with tetraselenotungstate **2** (1.1 equiv, MeCN, 28 °C) gave a mixture of products along with the cyclic diselenides **9** and **13**, respectively, which were difficult to purify.

2.4. Application of disulfides 5 and 8 in the modification of nucleosides

The next step was the application of disulfides **5** and **8** in the modification of nucleosides. Accordingly thymidine derived disulfide **8** was allowed to react with tetrathiomolybdate **1** in the presence of epoxide **14** (MeCN, 6 h, 28 °C). The β-hydroxy sulfide derivative **15** was isolated as a 1:1 mixture of diastereomers in reasonable yield (64%). In this reaction in the first step tetrathiomolybdate **1** cleaves the disulfide bond[17] to give the corresponding thiolate in situ, which immediately opens the epoxide **14** to give the product **15**. Similarly, when the reaction of **8** was carried out with **1** in the presence of a Michael acceptor like **16** (MeCN, 6 h, 28 °C) the nucleoside derived amino acid **17** was obtained in 61% yield and it was found to be racemic (Scheme 5). The sulfides similar to **17** were previously prepared from



Scheme 4.



Scheme 5.

the 5′-tosyl intermediates through reactions with the corresponding thiols.[5c] But the 5′-tosyl intermediates were found to be not very stable and generally gave a lower yield of the sulfides.[18]

Treatment of uridine derived disulfide **5** with tetrathiomolybdate **1** (1.1 equiv, MeCN, 3 h) in the presence of aziridine **18** (1.2 equiv, 28 °C, 6 h) resulted in the formation of β-amino sulfide derivative **19** in 72% yield (Scheme 5). By the use of these reactions a nucleoside can be attached through a 5′-sulfide linkage to a carbocycle or an amino acid by choosing the right donor and acceptor.

2.5. Structural studies

Molecular packing of disulfide **8** shows strong NH···O and CH···O interactions (Fig. 3). The distances and the angles are given in Table 1. There is only one strong NH···O hydrogen bonding with a distance (D···H) 2.00 Å. But this NH···O hydrogen bonding is not similar to the base pair interaction, which is commonly found in nucleosides. The oxygen of the carbonyl of 2-acetyl group participates in this strong interaction rather than the pyrimidine carbonyl group. It is apparent that the CH···O interactions overcome the NH···O interactions. There are three strong CH···O interactions that are found in this molecule (Table 1).

However, the molecular packing of cyclic diselenide **9** shows a dimeric packing pattern, which is found in all nucleoside bases (Fig. 4).[19] The packing is due to strong NH···O and CH···O interactions. The NH of one base interacts with the carbonyl of the adjacent base. This strong NH···O interaction with a distance of 2.34 Å allows the molecule to pack in a dimeric fashion. Apart from NH···O interaction, the carbonyl of the base interacts with the hydrogen (H-3) of the deoxysugar moiety. The distances and the angles are given in Table 2.

Table 1. C–H···O and N–H···O intermolecular interactions of **8**

D–H···A	Distance H···A (Å)	Distance D···A (Å)	Angle D–H···A (°)
C(4)–H(4)···O(5)^{i}	2.58(5)	3.418(7)	153(4)
C(12)–H(12A)···O(4)^{ii}	2.49(8)	3.185(6)	135(7)
C(2)–H(2B)···O(1)^{iii}	2.21(5)	3.347(5)	159(4)
N(2)–H(2)···O(3)^{iv}	2.00(5)	2.849(6)	176(5)

Symmetry codes: (i) $1/2 + x$, $-1/2 + y$, z, (ii) $1/2 - x$, $1/2 + y$, $-z$, (iii) x, $1 + y$, z, (iv) $-1/2 + x$, $-1/2 + y$, z.

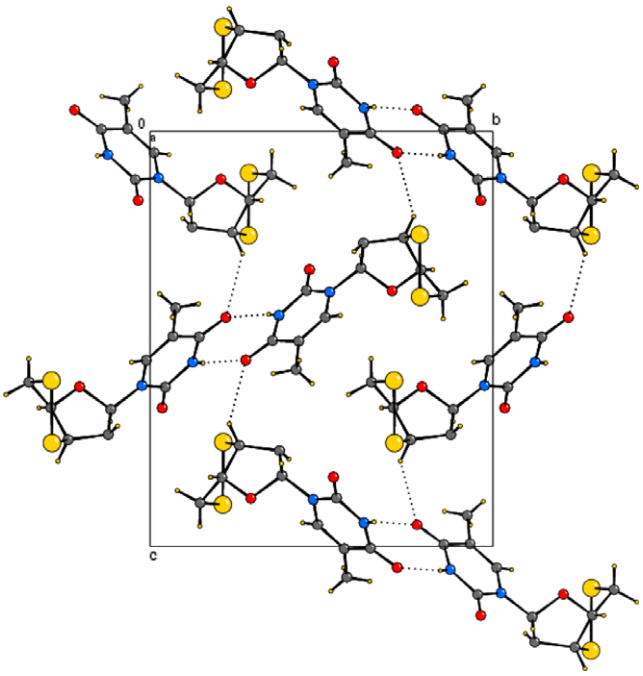


Figure 4. Packing diagram of **9** indicating C–H···O and N–H···O interactions.

In conclusion, we provide an efficient and simple method to synthesize disulfides and diselenides of thymidine and uridine derivatives. The molecular structures and

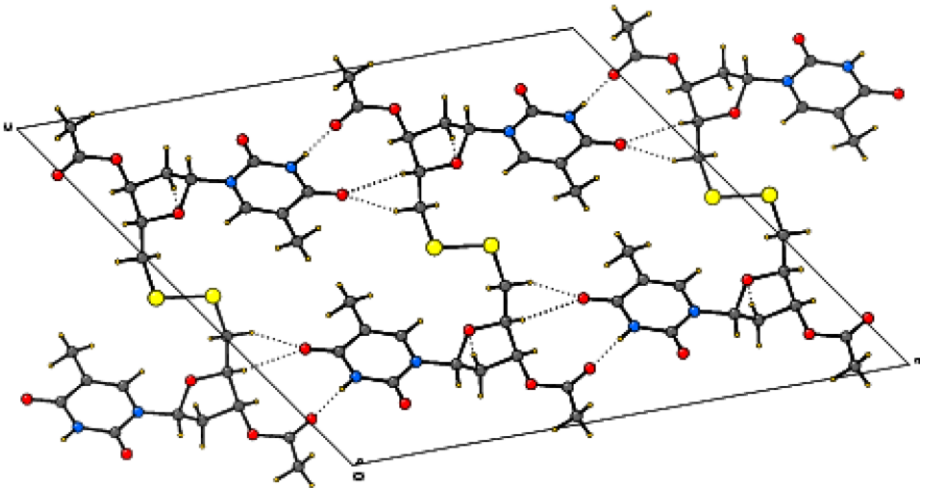


Figure 3. Packing diagram of **8** indicating C–H···O and N–H···O interactions.

Table 2. Intermolecular hydrogen bonding geometry and interactions of **9**

D–H···A	Distance H···A (Å)	Distance D···A (Å)	Angle D–H···A (°)
N(2)–H(10)···O(3)^{i}	2.34(5)	2.954(8)	172(7)
C(3)–H(3)···O(3)^{ii}	2.45(5)	3.207(9)	135(4)

Symmetry codes: (i) $-1/2+x, -1/2-y, -z$; (ii) $1/2-x, -y, 1/2+z$.

the interaction patterns of the new cyclic diselenide and thymidine disulfide derivatives were studied by X-ray crystallography. The utility of these disulfides in various ring opening reactions as well in Michael addition reactions has been demonstrated. By these simple and efficient reactions a nucleoside can be attached to an amino acid or a carbocyclic system effectively through a sulfur linkage.

3. Experimental

3.1. General methods

Melting points reported are recorded in Büchi B540 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL—300 and 75 MHz spectrometer, respectively. Chemical shifts are reported in parts per million downfield from the internal reference, tetramethylsilane. Coupling constants are reported wherever it is necessary in Hertz (Hz). Flash column chromatography was performed on (230–400 mesh) silica gel. Mass spectra were recorded on a Q-TOF electrospray instrument. $[\alpha]_D$ values were recorded in a JASCO P-1020 polarimeter. X-ray data collections were recorded on a BRUKER-SMART APEX CCD-Single Crystal Diffractometer.

3.2. General procedure for the synthesis of disulfides 5 and 8

To a stirred soln of the tosylates **4**[11] or **7**[12] (0.1 g, 0.23 mmol) in MeCN (3 ml), benzyltriethylammonium tetrathiomolybdate **1** (0.15 g, 0.25 mmol) was added and the reaction mixture was stirred for 18 h at 28 °C. After the disappearance of the starting material (TLC), the solvent was removed under diminished pressure and the black residue was extracted with MeOH–CH_2Cl_2 (1:9, 5 × 20 ml) and filtered through a Celite pad. The filtrate was concentrated and the crude products were purified by flash column chromatography on silica gel (230–400 mesh, elution with 1:9 MeOH–$CHCl_3$) to furnish compounds **5** or **8**.

3.2.1. Bis-(5′-deoxy-2′,3′-*O*-isopropylidene-uridine) 5′,5′-disulfide (5). Starting from **4** (0.1 g, 0.23 mmol); white solid (0.11 g, 77%); mp 175 °C; $[\alpha]_D^{25}$ −2.0 (*c* 1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.63 (s, 1H), 7.28–7.25 (aromatic, 2H), 5.75 (br d, 1H, $J_1 = 1.2$ Hz, $J_2 = 7.8$ Hz), 5.56 (d, 1H, $J = 1.2$ Hz), 5.09 (dd, 1H, $J_1 = 1.5$ Hz, $J_2 = 6.6$ Hz), 4.85 (dd, 1H, $J_1 = 3.9$ Hz, $J_2 = 6.3$ Hz), 4.38 (dd, 1H, $J_1 = 6.6$ Hz, $J_2 = 10.5$ Hz), 3.14–3.05 (m, 2H), 1.57 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 150.0, 143.2, 114.5, 102.7, 95.8, 86.5, 84.5, 83.3, 41.5, 27.1, 25.2; HRESIMS (*m*/*z*): calcd for $C_{24}H_{30}O_{10}N_2S_2$ (M+Na^+): 621.1301, obsd (M+Na^+): 621.1248.

3.2.2. Bis-(3′-*O*-acetyl-5′-deoxy-5′-thiothymidine)-5,5′-disulfide (8). Starting from **7** (0.1 g, 0.23 mmol); white crystalline needles (crystallized from MeOH, 0.11 g, 82%); mp 83 °C; $[\alpha]_D^{25}$ −24 (*c* 1, MeOH); ^{1}H NMR (300 MHz, CD_3COCD_3): δ 7.49 (s, 1H), 6.27 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 7.5$ Hz), 5.24 (br t, 1H, $J_1 = 2.7$ Hz, $J_2 = 6$ Hz), 4.36–4.20 (m, 3H), 2.45–2.32 (m, 2H), 2.07 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3): δ 170.8, 164.3, 151.3, 136.2, 111.2, 85.4, 82.8, 75.0, 64.6, 37.2, 20.8, 12.5; HRESIMS (*m*/*z*): calcd for $C_{24}H_{24}O_{10}N_2S_2$ (M+Na^+): 621.1301, obsd (M+Na^+): 621.1341.

3.3. General procedure for the synthesis of diselenides 9, 10 and 13

To a stirred soln of the tosylates **4**, **7** or **12** in MeCN (2 ml), tetraethylammonium tetraselenotungstate **2** (0.12 g, 0.15 mmol) was added and the reaction mixture was stirred for 22 h at 28 °C. After the disappearance of the starting material (TLC), the solvent was removed under diminished pressure and the black residue was extracted with MeOH–CH_2Cl_2 (1:9, 5 × 20 ml) and filtered through a Celite pad. The filtrate was concentrated and the crude products were purified by flash column chromatography on silica gel (230–400 mesh, elution with MeOH–$CHCl_3$ 1:9) to furnish diselenides **10**, **9** or **13**, respectively.

3.3.1. 1-(2′,3′,5′-Trideoxy-3′,5′-diseleno-β-D-*threo*-pentofuranosyl)thymine (9). Starting from **7** (0.06 g, 0.14 mmol); wine red crystalline solid (crystallized from MeOH, 0.034 g, 0.09 mmol, 82%); mp: 204 °C; $[\alpha]_D^{25}$ 56 (*c* 1, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.61 (s,1H), 6.08 (dd, 1H, $J_1 = 5.99$ Hz, $J_2 = 8.3$ Hz), 5.26 (br t, 1H, $J = 5.8$ Hz), 4.33 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 15.4$ Hz), 3.92 (d, 1H , $J = 12.4$ Hz) 3.37 (dd, 1H, $J_1 = 3.5$ Hz, $J_2 = 12.3$ Hz), 3.05–2.98 (m, 1H), 2.29–2.19 (m, 1H), 1.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.7, 163.3, 150.0, 135.6, 111.5, 88.5, 82.5, 47.7, 42.7, 41.7, 29.7, 22.7, 14.1, 12.7; ^{77}Se NMR (76 MHz, $CDCl_3$): δ 502, 301; HRESIMS: calcd for $C_{10}H_{12}N_2O_3Se_2$ (M+Na^+): 390.9076, obsd: *m*/*z* 390.9083.

3.3.2. Bis-(5′-deoxy-2′,3′-*O*-isopropylidene-uridine)-5′,5′-diselenide (10).[8] Starting from **4** (0.1 g, 0.23 mmol); yellow solid (0.07 g, 74%); mp: 73 °C (decomp); $[\alpha]_D^{25}$

30 (*c* 1, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H), 7.26 (aromatic, 2H), 5.75 (d, 1H, $J = 8.0$ Hz), 5.57 (d, 1H, $J = 1.6$ Hz), 5.09 (dd, 1H, $J_1 = 1.7$ Hz, $J_2 = 6.5$ Hz), 4.84 (dd, 1H, $J_1 = 3.9$ Hz, $J_2 = 6.4$ Hz), 4.39–4.34 (m, 1H), 3.37–3.28 (m, 2H), 1.57 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1, 149.8, 149.2, 115.1, 113.8, 101.5, 94.0, 86.6, 86.5, 83.9, 83.1, 31.1, 26.0, 24.1; ^{77}Se NMR (76 MHz, $CDCl_3$): δ 291; HRESIMS: calcd for ($M+Na^+$): 717.0190, observed: *m*/*z* 717.0189.

3.3.3. Methyl (2,3,5-trideoxy-3,5-diseleno-α-D-*threo*-pentofuranoside (13). Starting from **12** (0.055 g, 0.23 mmol); orange red crystals (crystallized from $CHCl_3$, MeOH mixture, 0.04 g, 88%); mp: 63 °C; $[\alpha]_D^{25}$ 89 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.10 (d, 1H, $J = 4.5$ Hz), 4.34 (dt, 1H, $J_1 = 2.1$ Hz, $J_2 = 6.6$ Hz), 4.19 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = 5.7$ Hz), 3.39 (s, 3H), 3.09 (dd, 2H, $J_1 = 2.1$ Hz, $J_2 = 6.3$ Hz), 2.24–2.16 (m, 1H), 2.06–2.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 105.3, 86.6, 74.8, 54.9, 40.6, 32.7; ^{77}Se NMR (76 MHz, $CDCl_3$): δ 290, 430; HRESIMS: calcd for $C_6H_{10}O_2Se_2$ (M^+): 273.9011, obsd: *m*/*z* 273.9004.

3.4. General procedure for the synthesis of compounds 15, 17 and 19

To a stirred soln of the disulfides **5** or **8** in MeCN (2 ml), benzyltriethylammonium tetrathiomolybdate **1** (0.05 g, 0.08 mmol) was added and the reaction mixture was stirred for 3 h at 28 °C. To this mixture a soln of the epoxide **14** (0.02 g) in MeCN (0.5 ml) or the unsaturated ester **16** (0.02 g in 0.4 ml of MeCN) or aziridine derivative **18** (0.02 g in 0.5 ml of MeCN) was added slowly in drops. After the disappearance of the starting material (TLC), the solvent was removed under diminished pressure and the black residue was extracted with MeOH–CH_2Cl_2 (1:9, 5 × 20 ml) and filtered through a Celite pad. The filtrate was concentrated and the crude product were purified by flash column chromatography on silica gel (230–400 mesh, elution with MeOH–$CHCl_3$ 1:9) to furnish the compounds **15**, **17** or **19**.

3.4.1. 5′-*S*-[(2-Hydroxy)cyclohexylthio]-3′-*O*-acetyl-5′-deoxythymidine 15. Starting from **8** (0.04 g, 0.07 mmol); colourless, gummy solid (0.02 g, 0.04 mmol, 64%); ^1H NMR (300 MHz, $CDCl_3$): δ 8.92 (s, 1H), 7.38 (s, 1H), 6.29–6.24 (m, 1H), 5.35–5.31 (m, 1H), 4.30–4.25 (m, 1H), 3.26–3.16 (m, 3H), 2.62–2.21 (m, 2H), 2.12 (s, 1H), 1.96 (s, 1H), 1.77–1.30 (m, 5H), 1.34–1.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 163.4, 150.2, 135.1, 111.6, 84.7, 83.2, 75.3, 71.4, 58.5, 43.3, 37.2, 34.3, 31.9, 31.8, 26.0, 24.3, 20.9, 12.6. HRESIMS: calcd for $C_{18}H_{26}N_2O_6S$ ($M+Na^+$): 453.1130; obsd: *m*/*z* 453.1138.

3.4.2. 5′-*S*-[(2-Acetamido-2-methoxycarbonyl)ethylthio]-3′-*O*-acetyl-5′-deoxythymidine 17. Starting from **8** (0.04 g, 0.07 mmol); colourless, gummy solid, (0.018 g, 61%); ^1H NMR (300 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.35 (s, 1H), 6.49 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 7.5$ Hz), 6.29–6.21 (m, 1H), 5.30–5.15 (m, 1H), 4.92–4.82 (m, 1H), 4.18–4.14 (m, 1H), 3.79 (s, 1H), 3.19–2.94 (m, 5H), 2.18 (s, 3H), 2.07 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 170.6, 169.9, 163.3, 150.2, 135.1, 111.7, 84.5, 83.4, 75.4, 52.8, 52.3, 37.2, 35.5, 35.4, 23.1, 20.9, 12.6, HRESIMS: calcd for $C_{18}H_{25}N_3O_8S$ ($M+Na^+$): 466.1260, obsd: *m*/*z* 466.1301.

3.4.3. 5′-*S*-[(2-Tolylsulfonylamido)-cyclohexylthio]-5′-deoxy-2′,3′-*O*-isopropylidene-uridine 19. Starting from **5** (0.03 g, 0.04 mmol); colourless, gummy solid (0.017 g, 72%); ^1H NMR (300 MHz, $CDCl_3$): δ 9.24 (s, 1H), 7.83–7.23 (aromatic, 5H), 5.89 (d, 1H, $J = 2.7$ Hz), 5.62–5.57 (m, 1H), 5.43 (dd, 1H, $J_1 = 2.4$ Hz, $J_2 = 6.0$ Hz), 5.11–5.05 (m, 1H), 4.38–4.31 (m, 1H), 3.11–2.97 (m, 2H), 2.44 (s, 3H), 2.20–2.06 (m, 2H), 1.70 (s, 3H), 1.60 (s, 3H), 1.42 (s, 3H), 1.27–1.10 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 163.4, 150.1, 143.3, 137.5, 129.6, 127.2, 114.5, 102.8, 95.9, 88.2, 84.5, 83.5, 82.9, 56.0, 54.8, 53.4, 41.9, 36.9, 27.1, 26.3, 25.2, 23.9, 21.5.

Acknowledgements

The authors thank DST, New Delhi, for CCD X-ray facility and Vijay Thiruvenkatam for his help in solving the molecular structures.

Supplementary data

Characterization data (^1H, ^{13}C, HRESIMS) for **5**, **8**, **9**, **10**, **13**, **15**, **17** and ^{77}Se NMR for **9**, **10** and **13**. Crystallographic information file (CIF) for the compounds **8**, **9** and **13**, can be found in the online version of this article. Crystallographic data for **8**, **9** and **13** have been deposited with the Cambridge crystallographic data centre as supplementary publication nos. [a] Compound-**8** CCDC-623425, [b] Compound-**9** CCDC-606051, [c] Compound-**13** CCDC-606052. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, +44 1223 336408; e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.02.035.

References

1. Wnuk, S. F. *Tetrahedron* **1993**, *49*, 9877–9936, references cited therein.

2. Schinazi, R. F. *Perspect. Drug Discovery Des.* **1993**, *1*, 151–180.
3. Herdewijn, P.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. *J. Med. Chem.* **1987**, *30*, 1270–1278.
4. (a) *The Biochemistry of S-Adenosylmethionine and Related Compounds*; Usdin, E., Borchardt, R. T., Creveling, C. R., Eds.; Macmillan Press: London, 1982; (b) Bacchi, C. J.; Sufrin, J. R.; Nathan, H. C.; Spiess, A. J.; Hannan, T.; Garofalo, J.; Alecia, K.; Katz, L.; Yarlett, N. *Antimicrob. Agents Chemother.* **1991**, *35*, 1315–1320; (c) Montgomery, J. A.; Shortnacy, A. T.; Thomas, H. J. *J. Med. Chem.* **1974**, *17*, 1197–1207.
5. (a) Agrofoglio, L. A.; Girard, F.; Fleury, F.; Léonce, S. *Nucleosides Nucleotides* **1999**, *18*, 599–600; (b) Dabkowski, W.; Michalska, M.; Tworowska, I. *Nucleosides Nucleotides* **1998**, *17*, 1635–1637; (c) Pignot, M.; Pljevaljcic, G.; Weinhold, E. *Eur. J. Org. Chem.* **2000**, 549–555, and references cited therein; (d) Metelev, V. G.; Borisova, O. A.; Volkov, E. M.; Oretskaya, T. S.; Dolinnaya, N. G. *Nucleic Acids Res.* **2001**, *29*, 4062–4069; (e) Addo, J. K.; Buolamwini, J. K. *Bioconjugate Chem.* **2004**, *15*, 536–540; (f) Wnuk, S. F.; Lewandowska, E.; Companioni, D. R.; Garcia, P. I., Jr.; Secrist, J. A., III. *Org. Biomol. Chem.* **2004**, *2*, 120–126; (g) Zheng, F.; Zhang, X.-H.; Qiu, X.-L.; Zhang, X.; Qing, F.-L. *Org. Lett.* **2006**, *8*, 6083–6086, and references cited therein.
6. (a) Xu, Y.; Kool, E. T. *Nucleic Acids Res.* **1998**, *26*, 3159–3164; (b) Sproat, B. S.; Beijer, B.; Rider, P.; Neuner, P. *Nucleic Acids Res.* **1987**, *15*, 4837–4848.
7. (a) Anderson, G. L.; Bussolotti, D. L.; Coward, J. K. *J. Med. Chem.* **1981**, *24*, 1271–1277; (b) Guillerm, G.; Muzard, M.; Glapski, C.; Pilard, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5803–5807, and references cited therein.
8. Belostotskii, A. M.; Keren-Yeshuah, H.; Lexner, J.; Hassner, A. *Nucleosides Nucleotides Nucleic Acids* **2001**, *20*, 93–101, and references cited therein.
9. Prabhu, K. R.; Devan, M. N.; Chandrasekaran, S. *Synlett* **2002**, 1762–1778.
10. Saravanan, V.; Porhiel, E.; Chandrasekaran, S. *Tetrahedron Lett.* **2003**, *44*, 2257–2260.
11. Winans, K. A.; Bertozzi, C. R. *Chem. Biol.* **2002**, *9*, 113–129.
12. Reist, E. J.; Benitez, A.; Goodman, L. *J. Org. Chem.* **1964**, *29*, 554–558.
13. Adiwidjaja, G.; Schulze, O.; Voss, J.; Wirsching, J. *Carbohydr. Res.* **2000**, *325*, 107–119.
14. Herdewijn, P. A. M. *J. Org. Chem.* **1988**, *53*, 5050–5053.
15. Bozó, É.; Boros, S.; Kuszmann, J. *Carbohydr. Res.* **1999**, *321*, 52–66.
16. (a) Pan, W. H.; Harmer, M. A.; Halbert, T. R.; Stiefel, E. I. *J. Am. Chem. Soc.* **1984**, *106*, 459–460; (b) Coyle, C. L.; Harmer, M. A.; George, G. N.; Daage, M.; Stiefel, E. I. *Inorg. Chem.* **1990**, *29*, 14–19; (c) Boorman, P. M.; Wang, M.; Parvez, M. *J. Chem. Soc., Chem. Commun.* **1995**, 999–1000; (d) Kruhkak, N. L.; Wang, M.; Boorman, P. M.; Parvez, M. *Inorg. Chem.* **2001**, *40*, 3141–3148.
17. Devan, N.; Sridhar, P. R.; Prabhu, K. R.; Chandrasekaran, S. *J. Org. Chem.* **2002**, *67*, 9417–9420.
18. Borchardt, T.; Huber, J. A.; Wu, Y. S. *J. Org. Chem.* **1976**, *41*, 565–567.
19. Pochan, F.; Michelson, A. M. *Biochim. Biophys. Acta* **1969**, *182*, 17–23.