Contribution to the Stereoselective Synthesis of (3′*S*)-3′-Isothiocyanato-3′-*C*-vinyl-3′-deoxyuridine and its Derivatives

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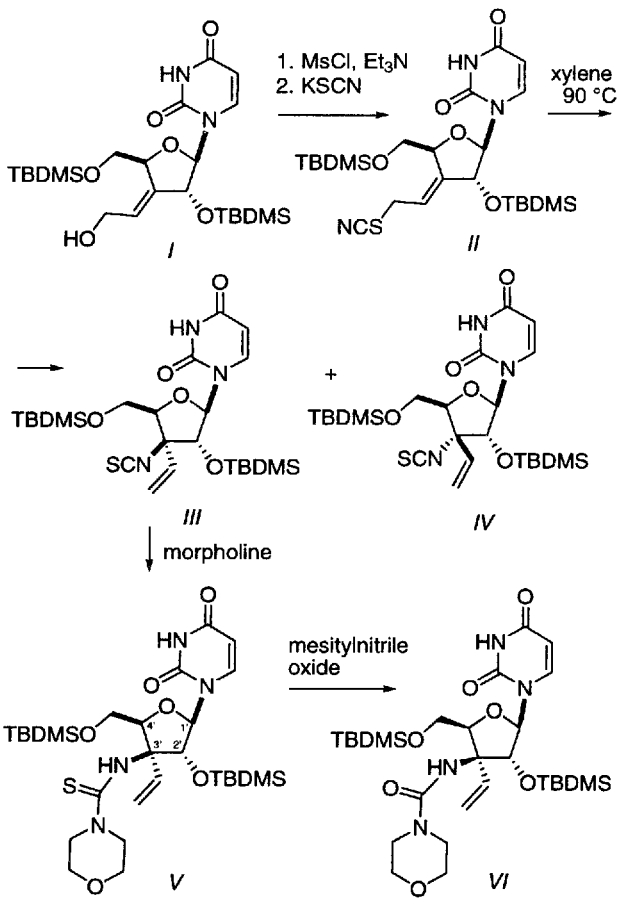
A stereoselective synthesis of the (3′S)-3′-isothiocyanato-3′-*C*-vinyl-3′-deoxyuridine *via* (3,3)-sigmatropic rearrangement of allylic thiocyanate derived from protected uridine was investigated.

Modified nucleosides represent important synthetic targets of significant biological activity. These types of compounds have been employed mainly as antiviral, anticancer agents [1], but modified nucleosides are also components of a broad range of natural products with antibiotic activity [2]. The discovery of various 2′,3′-dideoxynucleosides as powerful selective inhibitors of HIV-reverse transcriptase [3, 4] such as 3′-azido-3′-deoxythymidine (AZT) and also 3′-deoxynucleosides has led to the design and synthesis of the new types of modified nucleoside analogues. Due to the interesting biological properties [5—7] of these compounds, many synthetic approaches to such structures have been reported [8—10].

In the previous communication [11] we published the stereoselective synthesis of the branched-chain sugar (3*S*)-3-isothiocyanato-3-*C*-vinyl-3-deoxyglucose as a suitable precursor for the synthesis of natural compounds and where 1,2-*O*-isopropylidene group is a decisive factor for the stereocontrol in the aza-Claisen rearrangement of allylic thiocyanates.

In the further phase of our investigation we decided to study stereoselectivity of (3,3)-sigmatropic rearrangement of allylic thiocyanate *II* (Scheme 1) with 1-uridyl moiety at C-1′ and bulky 2′,5′-di-*O*-(*tert*-butyldimethylsilyl) protecting groups and presented the short stereoselective synthesis of new modified 3′-deoxynucleosides. As the starting material we have chosen allylic alcohol *I* [12—14], which is accessible from uridine. By the mesylation of the corresponding allylic alcohol *I* with $MsCl/NEt_3$ in methylene chloride and S_N2 displacement of *O*-mesyl group in mesylate by thiocyanate group (KSCN/MeCN) the corresponding thiocyanate *II* was prepared. The thermal rearrangement of *II* was carried out at 90 °C in xylene under N_2 for 24 h to give good yield of the isothiocyanates with a relatively low stereoselectivity ($n(III):n(IV)$



Scheme 1

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= 75:25). The isothiocyanate *III* was converted into thiourea *V* after addition of morpholine. The absolute configuration at C-3′ in thiourea *V* was established by X-ray analysis as (*S*) [15]. Treatment of thiourea *V* with mesitylnitrile oxide in acetonitrile afforded urea *VI* as a suitable synthon for the synthesis of branched-chain nucleosides.

EXPERIMENTAL

Melting points were determined on Kofler block. Optical rotations were measured on a Perkin—Elmer 241 MC polarimeter in chloroform. IR spectra were recorded on a Perkin—Elmer 599 spectrometer in $CHCl_3$ (absorptions in cm^{-1}). NMR spectra were recorded at room temperature on an FT NMR spectrometer Varian UNITY-500 (^1H at 499.8 MHz and ^{13}C at 125.7 MHz in $CDCl_3$). Chemical shifts are referenced either to tetramethylsilane as internal standard (^1H) or to the solvent signal (^{13}C NMR, $\delta(CDCl_3)$ = 77.0). Chemical shifts and coupling constants were obtained by the first-order analysis. All experiments were carried out with freshly distilled and dried solvents under N_2 atmosphere. TLC was performed on Merck 60F-245 silica gel plates and detection of components on TLC was made by UV light absorption at 254 nm and following treatment with 1 % $KMnO_4$ in water. Flash chromatography was carried out on silica gel (Merck, 0.035—0.070 "mesh").

(*E*)-2′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-3′-*C*-(2-thiocyanatoethylidene)-3′-deoxyuridine (*II*)

To a solution of allylic alcohol *I* (1.02 g; 2.05 mmol) in dry CH_2Cl_2 (16 cm^3) Et_3N (0.45 cm^3; 3.07 mmol) and CH_3SO_2Cl (0.19 cm^3; 2.45 mmol) were added at 0 °C. The reaction mixture was stirred for 1 h at the same temperature. Then it was concentrated under reduced pressure. The resulting residue was diluted with diethyl ether (30 cm^3) and solid was removed by filtration. The solvent was evaporated under reduced pressure to afford the crude mesylate. This mesylate was used in the next reaction directly without further purification.

To a solution of the crude mesylate (1.00 g; 1.73 mmol) in CH_3CN (20 cm^3) KSCN (0.20 g; 2.08 mmol) was added. After being stirred for 2 h at room temperature, the solvent was evaporated. The resulting residue was diluted with diethyl ether (25 cm^3) and solid was removed by filtration. The organic phase was concentrated under reduced pressure. Purification by chromatography (ethyl acetate—cyclohexane, volume ratio = 1:3) afforded 0.67 g (71 %) of crystalline compound *II*, m.p. = 146—148 °C, $[\alpha]$(D, 25 °C, ρ = 13 g dm^{-3}, $CHCl_3$) = + 33.6°. For $C_{24}H_{41}N_3O_5SSi_2$ (M_r = 539.83) w_i(calc.): 53.40 % C, 7.66 % H, 7.78 % N; w_i(found): 53.51 % C, 7.75 % H, 7.84 % N. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ: 8.44 (bd, 1H, J(5,NH) = 2.4 Hz, NH), 7.85 (d, 1H, J(6,5) = 8.2 Hz, H-6), 5.88 (dd, 1H, J(2′,1′) = 7.5 Hz, J(5,1′) = 0.6 Hz, H-1′), 5.76 (ddd, 1H, J(6,5) = 8.2 Hz, J(5,NH) = 2.4 Hz, J(5,1′) = 0.6 Hz, H-5), 5.71 (tdd, 1H, $J(7'_a,6')$ = 8.5 Hz, $J(7'_b,6')$ = 8.2 Hz, J(6′,2′) = 2.6 Hz, J(6′,4′) = 1.9 Hz, H-6′), 4.86 (m, 1H, H-4′), 4.66 (dm, 1H, J(2′,1′) = 7.5 Hz, J(6′,2′) = 2.6 Hz, $J(7'_b,2')$ = 1.8 Hz, J(4′,2′) = 1.7 Hz, $J(7'_a,2')$ = 1.2 Hz, H-2′), 3.97 (dd, 1H, $J(5'_a,5'_b)$ = 11.1 Hz, $J(5'_a,4')$ = 2.6 Hz, H-$5'_a$), 3.78 (ddd, 1H, $J(7'_a,7'_b)$ = 12.7 Hz, $J(7'_a,6')$ = 8.5 Hz, $J(7'_a,2')$ = 1.2 Hz, H-$7'_a$), 3.74 (dd, 1H, $J(5'_a,5'_b)$ = 11.1 Hz, $J(5'_b,4')$ = 2.0 Hz, H-$5'_b$), 3.58 (ddd, 1H, $J(7'_a,7'_b)$ = 12.7 Hz, $J(7'_b,6')$ = 8.2 Hz, $J(7'_b,2')$ = 1.8 Hz, H-$7'_b$), 0.92 (s, 9H, $(CH_3)_3C$), 0.90 (s, 9H, $(CH_3)_3C$), 0.12 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), −0.06 (s, 3H, $SiCH_3$). ^{13}C NMR spectrum (125.7 MHz, $CDCl_3$), δ: 162.5 (C=O), 150.1 (C=O), 145.4 (C-3′), 140.0 (C-6), 116.1 (C-6′), 111.0 (SCN), 103.1 (C-5), 86.9 (C-1′), 78.0 (C-4′), 75.6 (C-2′), 65.7 (C-5′), 30.9 (C-7′), 25.9 ($(\underline{C}H_3)_3C$), 25.5 ($(\underline{C}H_3)_3C$), 18.3 (SiC), 17.9 (SiC), −4.9 ($SiCH_3$), −5.0 ($SiCH_3$), −5.5 ($SiCH_3$), −5.5 ($SiCH_3$).

(3′*S*)-2′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-3′-isothiocyanato-3′-*C*-vinyl-3′-deoxyuridine (*III*) and (3′*R*)-2′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-3′-isothiocyanato-3′-*C*-vinyl-3′-deoxyuridine (*IV*)

A solution of thiocyanate *II* (0.67 g; 1.24 mmol) in xylene (10 cm^3) was heated at 90 °C for 24 h under a nitrogen atmosphere. The solvent was evaporated under reduced pressure, the chromatography of the residue on silica gel (ethyl acetate—hexane, volume ratio = 1:5) afforded 0.41 g (61.2 %) of isothiocyanate *III* and 0.14 g (20.9 %) of isothiocyanate *IV*.

Isothiocyanate *IV*: colourless oil; $[\alpha]$(D, 25 °C, ρ = 15 g dm^{-3}, $CHCl_3$) = +16.45°. For $C_{24}H_{41}N_3O_5SSi_2$ (M_r = 539.83) w_i(calc.): 53.40 % C, 7.66 % H, 7.78 % N; w_i(found): 53.52 % C, 7.71 % H, 7.87 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}/cm^{-1}$: 2047 ν(NCS). ^1H NMR spectrum (500 MHz, $CDCl_3$), δ: 8.09 (bd, 1H, J(5,NH) = 2.3 Hz, NH), 7.94 (d, 1H, J(6,5) = 8.3 Hz, H-6), 6.22 (dd, 1H, J(2′,1′) = 7.6 Hz, J(5,1′) = 0.5 Hz, H-1′), 5.97 (dd, 1H, $J(7'_{trans},6')$ = 16.8 Hz, $J(7'_{cis},6')$ = 10.5 Hz, H-6′), 5.73 (ddd, 1H, J(6,5) = 8.3 Hz, J(5,NH) = 2.3 Hz, J(5.1′) = 0.5 Hz, H-5), 5.71 (d, 1H, $J(7'_{trans},6')$ = 16.8 Hz, H-$7'_{trans}$), 5.50 (d, 1H, $J(7'_{cis},6')$ = 10.5 Hz, H-$7'_{cis}$), 4.34 (d, 1H, J(2′,1′) = 7.6 Hz, H-2′), 4.12 (m, 1H, H-4′), 3.85 (dd, $J(5'_a,5'_b)$ = 12.0 Hz, $J(5'_a,4')$ = 2.6 Hz, H-$5'_a$), 3.66 (dd, 1H, $J(5'_a,5'_b)$ = 12.0 Hz, $J(5'_b,4')$ = 1.5 Hz, H-$5'_b$), 0.97 (s, 9H, $(CH_3)_3C$), 0.86 (s, 1H, $(CH_3)_3C$), 0.16 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$), −0.06 (s, 3H, $SiCH_3$), −0.10 (s, 3H, $SiCH_3$). ^{13}C NMR spectrum (125.7 MHz, $CDCl_3$), δ: 162.2 (C=O), 150.0 (C=O), 139.9 (C-6), 132.1 (C-6′), 120.2 (C-7′), 103.0 (C-5), 86.1 (C-1′), 86.0 (C-4′), 79.5 (C-2′), 63.0 (C-5′), 29.7 (C-3′), 25.9 ($(\underline{C}H_3)_3C$), 25.4 ($(\underline{C}H_3)_3C$), 18.3

(SiC), 18.3 (SiC), −4.1 ($SiCH_3$), −5.0 ($SiCH_3$), −5.5 ($SiCH_3$), −5.6 ($SiCH_3$).

Isothiocyanate *III*: colourless oil; [α](D, 25 °C, ρ = 23 g dm^{-3}, $CHCl_3$) = + 110.62°. For $C_{24}H_{41}N_3O_5SSi_2$ (M_r = 539.83) w_i(calc.): 53.40 % C, 7.66 % H, 7.78 % N; w_i(found): 53.53 % C, 7.72 % H, 7.89 % N. IR spectrum ($CHCl_3$), $\tilde{\nu}$/cm^{-1}: 2057 ν(NCS). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ: 7.91 (bd, 1H, J(5,NH) = 2.4 Hz, NH), 7.90 (d, 1H, J(6,5) = 8.2 Hz, H-6), 6.01 (dd, 1H, $J(7'_{trans},6')$ = 17.0 Hz, $J(7'_{cis},6')$ = 10.6 Hz, H-6′), 5.77 (dd, 1H, J(6,5) = 8.2 Hz, J(5,NH) = 2.4 Hz, H-5), 5.55 (d, 1H, $J(7'_{trans},6')$ = 17.0 Hz, H-$7'_{trans}$), 5.47 (d, 1H, $J(7'_{cis},6')$ = 10.6 Hz, H-$7'_{cis}$), 5.22 (d, 1H, J(2′,1′) = 2.8 Hz, H-1′), 4.72 (d, 1H, J(2′,1′) = 2.8 Hz, H-2′), 4.25 (dd, 1H, $J(5'_a,4')$ = 4.1 Hz, $J(5'_b,4')$ = 4.0 Hz, H-4′), 3.96 (dd, 1H, $J(5'_a,5'_b)$ = 11.6 Hz, $J(5'_b,4')$ = 4.0 Hz, H-$5'_b$), 3.92 (dd, 1H, $J(5'_a,5'_b)$ = 11.6 Hz, $J(5'_a,4')$ = 4.1 Hz, H-$5'_a$), 0.94 (s, 9H, $(CH_3)_3C$), 0.90 (s, 9H, $(CH_3)_3C$), 0.14 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$). ^{13}C NMR spectrum (125.7 MHz, $CDCl_3$), δ: 162.3 (C=O), 149.9 (C=O), 139.5 (C-6), 137.3 (NCS), 132.4 (C-6′), 118.0 (C-7′), 102.3 (C-5), 90.4 (C-1′), 84.6 (C-4′), 83.7 (C-2′), 72.0 (C-3′), 61.5 (C-5′), 25.9 ($(\underline{C}H_3)_3C$), 25.7 ($(\underline{C}H_3)_3C$), 18.4 (SiC), 18.0 (SiC), −4.8 ($SiCH_3$), −4.9 ($SiCH_3$), −5.3 ($SiCH_3$), −5.6 ($SiCH_3$).

(3′*S*)-2′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-3′-(*N*-morpholinethiocarboxamido)-3′-*C*-vinyl-3′-deoxyuridine (*V*)

To a solution of isothiocyanate *III* (0.13 g; 0.23 mmol) in diethyl ether (5 cm^3) morpholine (0.02 cm^3; 0.25 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the chromatography of residue on silica gel (ethyl acetate—hexane, volume ratio = 1:1) gave 0.12 g (83 %) of thiourea *V* as white solid: m.p. = 88—90 °C, [α](D, 25 °C, ρ = 22 g dm^{-3}, $CHCl_3$) = + 79.76°. For $C_{28}H_{50}N_4O_6SSi_2$ (M_r = 626.95) w_i(calc.): 53.64 % C, 8.04 % H, 8.94 % N; w_i(found): 53.71 % C, 8.16 % H, 9.01 % N. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ: 8.43 (bs, 1H, NH), 7.78 (d, 1H, J(6,5) = 8.2 Hz, H-6), 7.70 (bs, 1H, NH), 6.19 (dd, 1H, $J(7'_{trans},6')$ = 17.7 Hz, $J(7'_{cis},6')$ = 10.8 Hz, H-6′), 5.89 (d, 1H, J(2′,1′) = 1.3 Hz, H-1′), 5.77 (d, 1H, J(2′,1′) = 1.3 Hz, H-2′), 5.61 (d, 1H, J(6,5) = 8.2 Hz, H-5), 5.35 (dd, 1H, $J(7'_{cis},6')$ = 10.8 Hz, $J(7'_{cis},7'_{trans})$ = 0.8 Hz, H-$7'_{cis}$), 5.10 (dd, 1H, $J(7'_{trans},6')$ = 17.7 Hz, $J(7'_{cis},7'_{trans})$ = 0.8 Hz, H-$7'_{trans}$), 4.22 (dd, 1H, $J(5'_a,5'_b)$ = 12.5 Hz, $J(5'_a,4')$ = 3.6 Hz, H-$5'_a$), 4.15 (dd, 1H, $J(5'_a,5'_b)$ = 12.5 Hz, $J(5'_b,4')$ = 0.9 Hz, H-$5'_b$), 4.06 (dd, 1H, $J(5'_a,4')$ = 3.6 Hz, $J(5'_b,4')$ = 0.9 Hz, H-4′), 3.71 (m, 4H, $O(CH_2)_2$), 3.67 (m, 4H, $N(CH_2)_2$), 0.94 (s, 9H, $(CH_3)_3C$), 0.93 (s, 9H, $(CH_3)_3C$), 0.23 (s, 3H, $SiCH_3$), 0.21 (s, 3H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$). ^{13}C NMR spectrum (125.7 MHz, $CDCl_3$), δ: 182.0 (C=S), 162.6 (C=O), 149.8 (C=O), 139.8 (C-6), 133.0 (C-6′), 116.0 (C-7′), 101.0 (C-1′), 81.9 (C-4′), 80.1 (C-2′), 70.6 (C-3′), 66.2 ($O\underline{C}H_2$), 66.2 ($O\underline{C}H_2$), 60.2 (C-5′), 47.6 (NCH_2), 47.6 (NCH_2), 26.0 ($(\underline{C}H_3)_3C$), 25.9 ($(\underline{C}H_3)_3C$), 18.9 (SiC), 18.0 (SiC), −4.1 ($SiCH_3$), −4.6 ($SiCH_3$), −4.7 ($SiCH_3$), −5.6 ($SiCH_3$).

(3′*S*)-2′,5′-Bis(*O*-*tert*-butyldimethylsilyl)-3′-*N*-morpholinecarboxamido-3′-*C*-vinyl-3′-deoxyuridine (*VI*)

To a solution of corresponding thiourea *V* (0.07 g; 0.12 mmol) in dry CH_3CN (2 cm^3) mesitylnitrile oxide (0.02 g; 0.13 mmol) was added. The reaction mixture was stirred at room temperature for 3 h, acetonitrile was evaporated under reduced pressure. The chromatography of residue on silica gel (ethyl acetate—hexane, volume ratio = 1:1) afforded 0.05 g (76 %) of urea *VI* as white solid: m.p. = 84—86 °C, [α](D, 25 °C, ρ = 34 g dm^{-3}, $CHCl_3$) = +111.65°. For $C_{28}H_{50}N_4O_7SSi_2$ (M_r = 610.89) w_i(calc.): 53.84 % C, 8.23 % H, 8.98 % N; w_i(found): 53.93 % C, 8.34 % H, 9.08 % N. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ: 8.04 (bd, 1H, J(5,NH) = 2.4 Hz, NH), 7.98 (d, 1H, J(6,5) = 8.2 Hz, H-6), 6.72 (bs, 1H, NH), 6.13 (dd, 1H, $J(7'_{trans},6')$ = 17.5 Hz, $J(7'_{cis},6')$ = 10.8 Hz, H-6′), 5.72 (bs, 1H, H-1′), 5.58 (dd, 1H, J(6,5) = 8.2 Hz, J(5,NH) = 2.4 Hz, H-5), 5.35 (dd, 1H, $J(7'_{cis},6')$ = 10.8 Hz, $J(7'_{cis},7'_{trans})$ = 0.9 Hz, H-$7'_{cis}$), 5.16 (dd, 1H, $J(7'_{trans},6')$ = 17.5 Hz, $J(7'_{cis},7'_{trans})$ = 0.9 Hz, H-$7'_{trans}$), 5.13 (bs, 1H, H-2′), 4.23 (dd, 1H, $J(5'_a,5'_b)$ = 12.4 Hz, $J(5'_a,4')$ = 3.6 Hz, H-$5'_a$), 4.08 (dd, 1H, $J(5'_a,4')$ = 3.6 Hz, $J(5'_b,4')$ = 0.8 Hz, H-4′), 4.02 (dd, 1H, $J(5'_a,5'_b)$ = 12.4 Hz, $J(5'_b,4')$ = 0.8 Hz, H-$5'_b$), 3.61 (m, 4H, $O(CH_2)_2$), 3.25 (m, 4H, $N(CH_2)_2$), 0.95 (s, 9H, $(CH_3)_3C$), 0.93 (s, 9H, $(CH_3)_3C$), 0.23 (s, 3H, $SiCH_3$), 0.20 (s, 3H, $SiCH_3$), 0.19 (s, 3H, $SiCH_3$), 0.15 (s, 3H, $SiCH_3$). ^{13}C NMR spectrum (125.7 MHz, $CDCl_3$), δ: 162.6 (C=O), 156.1 (C=O), 149.6 (C=O), 140.3 (C-6), 133.8 (C-6′), 116.1 (C-7′), 100.3 (C-5), 92.3 (C-1′), 82.0 (C-4′), 80.0 (C-2′), 67.9 (C-3′), 66.5 ($O\underline{C}H_2$), 66.5 ($O\underline{C}H_2$), 60.4 (C-5′), 44.0 ($N\underline{C}H_2$), 44.0 ($N\underline{C}H_2$), 26.0 ($(\underline{C}H_3)_3C$), 25.9 ($(\underline{C}H_3)_3C$), 18.9 (SiC), 18.0 (SiC), −4.6 ($SiCH_3$), −4.7 ($SiCH_3$), −4.8 ($SiCH_3$), −5.7 ($SiCH_3$).

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