Synthesis of 2′,3′-Didehydro-2′,3′-dideoxy Nucleosides from 2′,2′-Bis(phenylthio) Nucleoside Analogs

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2′,3′-Didehydro-2′,3′-dideoxy nucleosides were synthesized from 2′,2′-bis(phenylthio) nucleoside analogs via five-step reactions. The sulfonyl group of the intermediate was removed by a treatment with sodium amalgam.

In recent years, 2′,3′-didehydro -2′,3′-dideoxy nucleosides (**1**) have been studied concerning their activities against retroviruses, such as HIV.[1] Though natural ribonucleosides[2] or 2′-deoxyribonucleosides[3] can be converted to **1**, access to the starting materials, especially deoxyribonucleosides, is limited.

We have been studying the synthesis of unnatural sugars as well as their coupling reactions with nucleic bases as a preparation method of nucleoside analogs.[4] We have already synthesized nucleoside analogs (**2**) having two phenylthio groups at the 2′-position, and converted them to 2′,3′-dideoxy nucleosides.[4d] In this paper we report the conversion of **2** to **1** in order to demonstrate its usefulness in the synthesis of nucleoside analogs (Scheme 1).

The conversion of dithioacetals **2** to vinyl sulfides **3** was accomplished by two steps involving the oxidation of one of the two phenylthio groups to a phenylsulfinyl group, and a thermal elimination of the resulting phenylsulfinyl group. The oxidation was performed with one equivalent of *m*-chloroperbenzoic acid (mCPBA) in dichloromethane. The phenylsulfinyl group was eliminated under basic conditions. A base was necessary to neutralize the liberated sulfenic acid that causes decomposition of product **3**. It is noteworthy that the elimination occurred in a regiospecific manner to form a double bond only between the 2′- and 3′-positions. Although the intermediate sulfoxide was a mixture of four diasteremers, they showed little difference in reactivity in the elimination. The sulfides **3** were separated from their anomers, which could not be separated by column chromatography when **2** were prepared.

The phenylthio group of **3** should be converted to a phenylsulfonyl group to obtain **4**, because direct desulfurization has failed. Oxidation of the phenylthio group of **3** proceeded smoothly with two equivalents of mCPBA, and sulfone **4** were obtained in excellent yields. If the reaction was not complete, the intermediates of sulfoxides could be completely converted to **4** by an additional treatment with mCPBA.

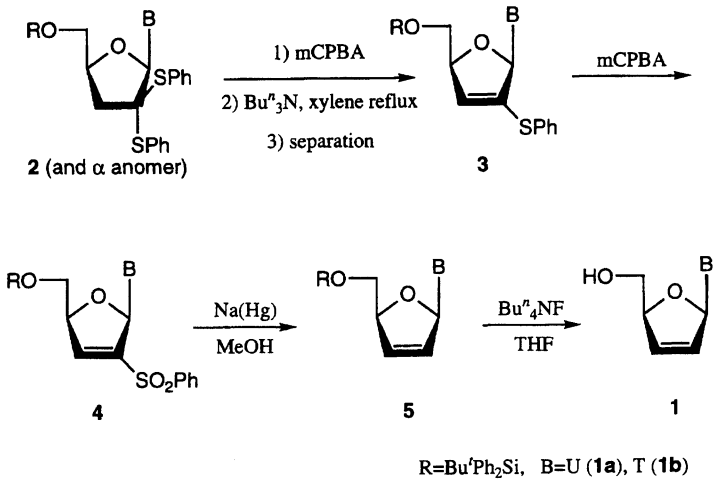
Removal of the sulfonyl group was achieved by treating **4** with sodium amalgam in methanol to produce the protected nucleoside analog **5**. The presence of a phosphate buffer[5] and low temperature are necessary to minimize the decomposition of **4** caused by the basicity of the sodium amalgam. The deprotection of **5** was accomplished by the usual treatment with tetrabutylammonium fluoride in tetrahydrofuran to give 2′,3′-didehydro-2′,3′-dideoxy nucleosides (**1**).

In summary, 2′,3′-didehydro-2′,3′-dideoxy nucleosides were synthesized from nucleoside analogs **2**. The overall yield was about 30% in these five-step reactions. It gives us a new synthetic approach to 2′,3′-didehydro-2′,3′-dideoxy nucleosides.

Experimental

The optical rotations were recorded on a JASCO DIP-370 polarimeter. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC-300P spectrometer. The chemical shifts are given in ppm (δ) relative to tetramethylsilane for ^{1}H NMR and relative to $CDCl_3$ (77.0 ppm) for ^{13}C NMR. The Infrared (IR) spectra were recorded on a JASCO FT/IR-5000 spectrophotometer. The ultraviolet (UV) spectra were recorded on a Beckman DU-65 spectrophotometer. FL 100D (Fuji Silicia Co., Ltd.) was used for silica-gel column chromatography.

1-[5-(*O*-*t*-Butyldiphenylsilyl)-2,3-dideoxy-2-phenylthio-β-D-*glycero*-pent-2-enofuranosyl]uracil (3a). 1-[5-(*O*-*t*-Butyldiphenylsilyl)-2,3-dideoxy-2,2-bis(phenylthio)-β-D-*glycero*-pentofuranosyl]uracil (**2a**) and its anomer (1.52 g, 2.28 mmol, $\alpha:\beta=24:76$) were dissolved in anhydrous dichloromethane (10 ml) at 0 °C. A solution of mCPBA (85% purity, 0.483 g, 2.38 mmol) in anhydrous dichloromethane (7 ml) was added dropwise. The reaction mixture was stirred for 10 min at 0 °C, poured into saturated aqueous sodium hydrogencarbonate, and extracted with dichloromethane; the organic layer was dried with magnesium sulfate. Removal of the solvent under reduced pressure gave 1-[5-(*O*-*t*-butyldiphenylsilyl)-2,3-dideoxy-2-phenylsulfinyl-2-phenylthio-β-D-*glycero*-pentofuranosyl]uracil and



Scheme 1.

its anomer. This reaction mixture was dissolved in xylenes (15 ml). After tributylamine (1.0 ml, 4.2 mmol) was added the solution was heated under reflux for 2 h in an argon atmosphere. After the solvent was removed under reduced pressure, the residue was chromatographed (hexane : ethyl acetate=2 : 1) to give **3a** (0.897 g, 71%) as a pale-yellow foam, along with its α anomer (0.209 g, 16%) as a pale-yellow foam. $[\alpha]_D^{25}$ +62.9° (*c* 1.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=7.64—7.57 (5H, m), 7.49—7.32 (12H, m), 6.92 (1H, dd, *J*=3.5, 1.6 Hz), 5.85 (1H, t, *J*=1.6 Hz), 5.21 (1H, d, *J*=9.7 Hz), 4.88—4.86 (1H, m), 3.91 (1H, dd, *J*=11.7, 2.9 Hz), 3.76 (1H, dd, *J*=11.7, 3.0 Hz), 1.07 (9H, s); IR (KBr) 1690 (s), 1461 (m), 1259 (m), 1113 (m), 703 (m), 506 cm^{-1} (m). Anal. Found: C, 66.65; H, 5.92; N, 4.96%. Calcd for $C_{31}H_{32}N_2O_4SiS$: C, 66.88; H, 5.79; N, 5.03%.

1-[5-(*O*-*t*-Butyldiphenylsilyl)-2,3-dideoxy-2-phenylthio-β-D-*glycero*-pent-2-enofuranosyl]thymine (3b). In the same maner as described above, **2b** (1.76 g, 2.58 mmol) gave 907 mg (62%) of **3b**, a pale-yellow foam, as an anomeric mixture (α : β=20 : 80). $[\alpha]_D^{24}$ +34.3° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=7.61—7.58 (4H, m), 7.46—7.29 (12H, m), 7.03 (1H, d, *J*=1.2 Hz), 6.89 (1H, dd, *J*=3.7, 1.6 Hz), 5.93 (1H, t, *J*=1.4 Hz), 4.88—4.86 (1H, m), 3.86 (1H, dd, *J*=11.4, 3.6 Hz), 3.79 (1H, dd, *J*=11.4, 4.0 Hz), 1.41 (3H, s), 1.05 (9H, s); IR (KBr) 1690 (s), 1473 (m), 1257 (m), 1116 (m), 702 cm^{-1} (m). Anal. Found: C, 67.38; H, 5.93; N, 4.83%. Calcd for $C_{32}H_{34}N_2O_4SiS$: C, 67.34; H, 6.00; N, 4.91%.

1-[5-(*O*-*t*-Butyldiphenylsilyl)-2,3-dideoxy-2-phenylsulfonyl-β-D-*glycero*-pent-2-enofuranosyl]uracil (4a). A solution of mCPBA (85% purity, 0.267 g, 1.31 mmol) in anhydrous dichloromethane (5 ml) was slowly added to a solution of **3a** (0.336 g, 0.604 mmol) in anhydrous dichloromethane (10 ml) at 0 ° C. The reaction mixture was stirred for 90 min at room temperature, poured into saturated aqueous sodium hydrogencarbonate, and extracted with dichloromethane; the organic layer was dried with magnesium sulfate. After the solvent was removed under reduced pressure, the residue was chromatographed (hexane : ethyl acetate=1 : 1) to give **4a** (0.348 g, 98%) as a white foam. $[\alpha]_D^{28}$ −50.5° (*c* 0.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=9.12 (1H, br.s), 7.90—7.84 (2H, m), 7.68—7.36 (14H, m), 7.28 (1H, t, *J*=1.5 Hz), 7.18 (1H, dd, *J*=3.9, 1.4 Hz), 4.99—4.93 (1H, m), 4.91 (1H, dd, *J*=8.1, 2.0 Hz), 4.04 (1H, dd, *J*=12.1, 2.5 Hz), 3.94 (1H, dd, *J*=12.1, 2.6 Hz), 1.08 (9H, s); ^{13}C NMR ($CDCl_3$) δ=162.67, 150.10, 144.59, 141.30, 139.53, 138.23, 135.49, 135.21, 134.60, 132.30, 131.66, 130.44, 130.21, 129.78, 128.25, 128.16, 128.02, 103.08, 86.41, 85.57, 64.36, 26.98, 19.28; IR (KBr) 1694 (s), 1462 (m), 1328 (m), 1261 (m), 1164 (m), 1137 (m), 1106 (m), 727 (m), 704 (m), 688 (m), 507 cm^{-1} (m); UV ($CHCl_3$) λ_{max} 260 nm (log ε=3.92). Anal. Found: C, 63.14; H, 5.29; N, 4.52%. Calcd for $C_{31}H_{32}N_2O_6SiS$: C, 63.24; H, 5.48; N, 4.76%.

1-[5-(*O*-*t*-Butyldiphenylsilyl)-2,3-dideoxy-2-phenylsulfonyl-β-D-*glycero*-pent-2-enofuranosyl]thymine (4b). In the same maner as described above, **3b** (455 mg, 0.796 mmol) gave 466 mg (97%) of pure **4b** as a white foam. $[\alpha]_D^{26}$ − 53.4° (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=8.67 (1H, br.s), 7.83—7.80 (2H, m), 7.63—7.55 (2H, m), 7.48—7.33 (3H, m), 7.16 (1H, dd, *J*=4.3, 1.3 Hz), 6.74 (1H, d, *J*=1.3 Hz), 4.98—4.96 (1H, m), 3.99 (1H, d, *J*=3.4 Hz), 1.10 (3H, s), 1.08 (9H, s); ^{13}C NMR ($CDCl_3$) δ=163.24, 150.18, 144.80, 141.13, 138.18, 135.16, 134.37, 134.27, 132.85, 132.13, 130.27, 130.11, 129.57, 128.18, 128.04, 127.97, 111.52, 86.43, 85.22, 64.65, 27.07, 19.43, 11.56; IR (KBr) 1696 (s), 1465 (m), 1329 (m), 1259 (m), 1164 (m), 1102 (m), 704 (m), 598 cm^{-1} (m). Anal. Found: C, 63.76; H, 5.75; N, 4.47%. Calcd for $C_{32}H_{34}N_2O_6SiS$: C, 63.76; H, 5.69; N, 4.65%.

1-[5-(*O*-*t*-Butyldiphenylsilyl)-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl]uracil (5a). Anhydrous disodium hydrogenphosphate (obtained by heating the 12 hydrate (0.22 g) to 130 °C for 2 h) and sodium amalgam (5% sodium, 0.35 g) were suspended to anhydrous methanol (3 ml) under an argon atmosphere at −78 °C. To this suspension a solution of **4a** (46 mg, 0.078 mmol) in anhydrous methanol (2 ml) was added; the reaction mixture was then stirred for 3 h at −78 °C. After the solid was filtered, the filtrate was washed with methanol. The solvent was then removed under reduced pressure, and the residue was purified by preparative TLC (hexane : ethyl acetate=1 : 1) to give **5a** (16.6 mg, 47%) as a white foam. $[\alpha]_D^{24}$ −7.6° (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=9.12 (1H, br.s, NH), 7.78—7.60 (5H, m, H-6, aromatic H), 7.55—7.37 (6H, m, aromatic H), 7.03 (1H, t, *J*=1.8 Hz, H-1′), 6.30 (1H, dt, *J*=6.0, 1.6 Hz, H-3′), 5.86 (1H, quasi-d, *J*=5.8 Hz, H-2′), 5.20 (1H, d,

J=8.3 Hz, H-5), 4.90 (1H, br, H-4′), 3.99 (1H, dd, J=11.5, 3.1 Hz, H-5′), 3.87 (1H, dd, J=11.7, 3.0 Hz, H-5′), 1.07 (9H, s, t-Bu); ^{13}C NMR ($CDCl_3$) δ=163.65 (C-4), 150.84 (C-2), 140.57 (C-6), 135.39 (aromatic C), 135.19 (aromatic C), 134.25 (C-3′), 132.88 (aromatic C), 132.23 (aromatic C), 129.97 (aromatic C), 129.85 (aromatic C), 127.79 (aromatic C), 127.70 (aromatic C), 126.45 (C-2′), 102.45 (C-5), 89.48 (C-1′), 86.93 (C-4′), 64.86 (C-5′), 26.84 (t-Bu), 19.20 (t-Bu); IR (KBr) 1705 (s), 1690 (s), 1460 (m), 1253 (m), 1112 (m), 1083 (m), 1042 (m), 835 (m), 702 cm^{-1} (m); UV ($CHCl_3$) λ_{max} 262 nm (log ϵ=3.88); EI-MS: m/z 391 ($M^+-C_4H_8$), 279 (sugar$-C_4H_8$). Anal. Found: C, 66.86; H, 6.41; N, 6.23%. Calcd for $C_{25}H_{28}N_2O_4Si$: C, 66.94; H, 6.29; N, 6.24%.

1-[5-(*O*-*t*-Butyldiphenylsilyl)-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl]thymine (5b). In the same maner as described above, **4b** (45.3 mg, 0.075 mmol) gave 17.2 mg (50%) of **5b** as a pale-yellow syrup. $[\alpha]_D^{25}$ +4.2° (c 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=9.13 (1H, br.s, NH), 7.68—7.60 (4H, m, aromatic H), 7.45—7.33 (6H, m, aromatic H), 7.16 (1H, d, J=1.1 Hz, H-6), 7.05—7.00 (1H, m, H-1′), 6.35 (1H, dt, J=5.9, 1.6 Hz, H-3′), 5.87 (1H, quasi-d, J=5.9 Hz, H-2′), 4.97—4.90 (1H, m, H-4′), 3.92 (1H, dd, J=11.1, 3.7 Hz, H-5′), 3.88 (1H, dd, J=11.2, 3.9 Hz, H-5′), 1.48 (3H, s, Me), 1.08 (9H, s, t-Bu); ^{13}C NMR ($CDCl_3$) δ=163.70 (C-4), 150.75 (C-2), 135.58 (C-6), 135.43 (aromatic C), 135.34 (aromatic C), 134.66 (C-3′), 133.28 (aromatic C), 132.77 (aromatic C), 130.01 (aromatic C), 129.91 (aromatic C), 127.83 (aromatic C), 127.79 (aromatic C), 126.31 (C-2′), 111.12 (C-5), 89.78 (C-1′), 86.89 (C-4′), 65.51 (C-5′), 26.96 (t-Bu), 19.39 (t-Bu), 11.90 (Me); IR (KBr) 1688 (s), 1466 (m), 1251 (m), 1116 (m), 706 cm^{-1} (m); UV ($CHCl_3$) λ_{max} 266 nm (log ϵ=3.94); EI-MS: m/z 405 ($M^+-C_4H_8$), 279 (sugar$-C_4H_8$).

1-[2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl]-uracil (1a, 2′,3′-Didehydro-2′,3′-dideoxyuridine). After a tetrahydrofuran solution of tetrabutylammonium fluoride (1 mol dm^{-3}, 0.25 ml, 0.25 mmol) was added to a solution of **5a** (99 mg, 0.22 mmol) in tetrahydrofuran (3 ml), the reaction mixture was stirred for 90 min at room temperature. A portion of the cation-exchange resin (Amberlite IR-120B, H^+ form) was added to neutralize the reaction mixture. The resin was filtered off and washed with tetrahydrofuran; the solvent was then removed under reduced pressure and the residue was chromatographed (chloroform : acetone=9 : 1) to give **1a** (44 mg, 95%) as a white crystalline solid from 2-propanol: Mp 152.8—154.2 °C [lit,[6a] 153—154 °C]. The spectral data of **1a** were identical with those previously reported.[6b]

1-[2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl]-thymine (1b, 2′,3′-Didehydro-3′-deoxythymidine). In the same maner as described above, **5b** (105 mg, 0.227 mmol) gave 50.6 mg (100%) of **1b** as a white crystalline solid from 2-propanol: Mp 166.1—167.0 °C [lit,[6a] 165—166 °C]. The spectral data of **1b** were identical with those previously reported.[6c]

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