New Synthesis of 2′,3′-Didehydro-2′,3′-dideoxynucleosides

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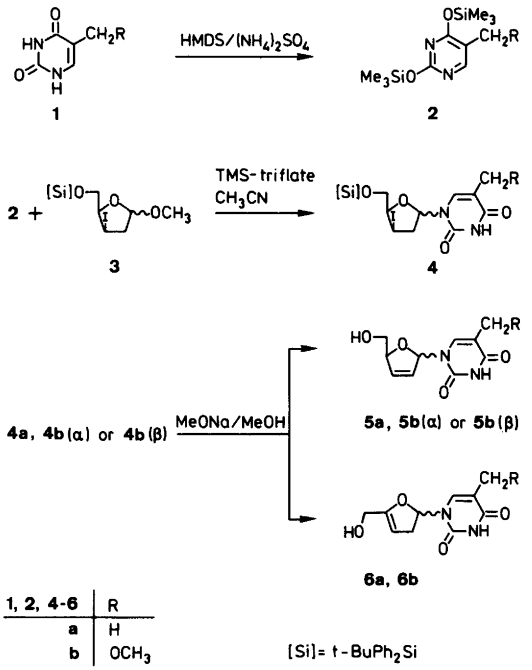
The 3′-iodonucleoside **4** and the 3′-*O*-methylsulfonylthymidine **9** have been synthesized by condensation of silylated uracils **2** with methyl 5-*O*-*tert*-butyldiphensilyl-2,3-dideoxy-3-iodo-D-*threo*-pentofuranoside (**3**) and methyl 5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-3-methylsulfonyl-D-*erythro*-pentofuranoside (**8**), respectively. The nucleoside **4** and **9** produced the correspnding 2′,3′-didehydro-2′,3′-dideoxynucleosides **5** in an elimination reaction on treatment with sodium methoxide. The compounds **5b** showed no antiviral activity against HIV-1.

Convergent syntheses have been developed in which nucleobases and 2,3-dideoxy sugars are independently synthesized and condensed to give nucleoside analogues of 3′-azido-3′-deoxythymidine (AZT), 2′-3′-dideoxycytidine (DDC) and 3′-deoxy-3′-fluorothymidine (DFT). These syntheses have recently been reviewed[1] because of their increasing importance in the synthesis of compounds with potential activity against human immunodeficiency virus (HIV). In spite of the fact that 2′,3′-didehydro-3′-deoxythymidine (D4T) is also an important lead for compounds with activity against HIV,[2] no such convergent synthesis has yet been developed for this type of compound. D4T analogues have always been prepared from the corresponding uridine or 2′-deoxyuridine derivatives in a linear approach in which the normal nucleoside is first prepared by standard methods. In the present investigation it is demonstrated that appropriately substituted 2,3-dideoxypentofuranoses may be useful substrates for a convergent synthesis of D4T analogues. The potential of this approach is exemplified by the synthesis of a D4T analogue with an unnatural nucleobase.

Results and discussion

5-Methoxymethyluracil (**1b**) was prepared by reaction of 5-hydroxymethyluracil[3] with methanol. Silylation of thymine (**1a**) and the methoxy derivative (**1b**) with 1,1,1,3,3,3-hexamthyldisilazane (HMDS)[4] was carried out prior to nucleoside coupling with methyl 5-*O*-tert-butyldiphenylsilyl-2,3-dideoxy-3-iode-D-*threo*-pentofuranoside (**3**)[5] using the trimethylsilyl trifluoromethanesulfonate (TMS-triflate) method of Vorbrüggen[6] to give a 1:1 (α/β) anomeric mixture of protected nucleoside (**4a,b**) in 67–70 % yields. The α- and β-anomers of **4b** were separated by chromatography on silica gel and reacted with sodium methoxide in methanol under reflux to give the corresponding anomers of the elimination products **5b** and **6b** in 51–53 % and 14–20 % yields, respectively, as pure compounds after separation by reversed phase chromatography. Correspondingly, it was not possible to separate the anomers of **4a**. Treatment with sodium methoxide in methanol similarly gave the D4T anomers **5a** (27 %) which were also inseparable by reversed phase and silica chromatography. In the latter reaction the 3,4-elimination product **6a** was likewise isolated in 18 % yield.



Scheme 1.

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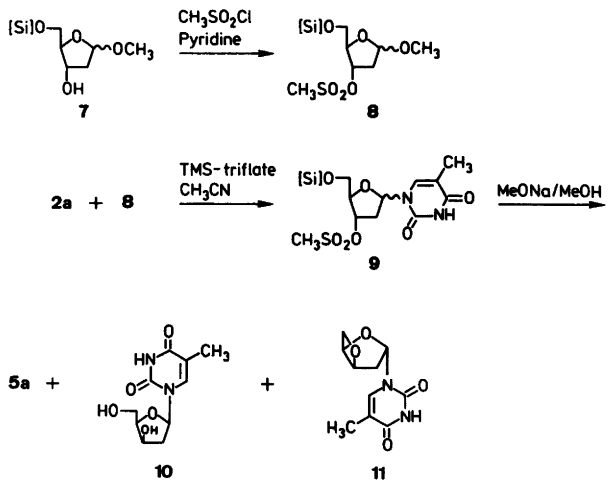

Scheme 2.

The iodosugar **3** used as starting material was prepared from the silylated methyl 2-deoxy-D-furanoside **7** which in turn was prepared in two steps from 2-deoxy-D-ribose by treatment with methanolic hydrogen chloride and subsequently with *tert*-butyl(chloro)diphenyl silane in *N,N*-dimethylformamide in the presence of imidazole. Since the yield of the iodosugar **3** has been reported to be as low as 40 and 56 % for the α- and β-anomers, respectively, it was of interest to find another sugar derivative useful for the nucleoside coupling reaction and subsequent 2',3'-elimination reaction to give nucleosides of the D4T type. One attractive possibility was mesylation of the silylated methyl 2-deoxy-D-furanoside **7** by treatment with methanesulfonyl chloride in dry pyridine. Indeed, the reaction at 0 °C for 2 h afforded the 3-*O*-methanefulfonyl sugar **8** in 90 % yield after chromatographic work-up.

The silylated thymine was condensed with **8** in dry acetonitrile using TMS-triflate as a catalyst to give 1-(5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-3-*O*-methanesulfonyl-D-*erythro*-pentofuranosyl)thymine (**9**) in 82 % yield (α:β = 1:2). For proper characterization of the pure anomers they were separated on an analytical scale by reversed phase chromatography. Treatment of **9** with 10 equivs. of sodium methoxide in methanol under reflux gave D4T anomers **5a** (35 %), the *threo*-nucleoside **10** (28 %) and the 3,5'-anhydronucleoside **11** (20 %).

The ^1H and ^{13}C NMR data for compound **5a**,[7,8] **6a**[9] and **10**[10] are in close agreement with data previously reported. This also proves the configurations of the compounds **5b** and **6b**.

The compounds **5b**(α) and **5b**(β) were tested for antiviral activity against HIV-1 in MT-4 cell culture, but no activity was found at non-toxic concentrations.

Experimental

*1-(5'-*O*-tert-Butyldiphenylsilyl-2',3'-dideoxy-3'-iodo-*D*-threo-pentofuranosyl)uracil derivatives* (**4a,b**). The silylated uracil (**2a,b**) (13 mmol) was dissolved in MeCN (70 ml), the solution was cooled to −10 °C and TMS-triflate (2.35 ml, 13 mmol) in 5 ml of MeCN was slowly added. The iodo furanoside **3** (4.96 g, 10 mmol) dissolved in 10 ml of MeCN was added dropwise (20 min) at −10 °C. After 0.5 h, the cooling bath was removed and the stirring continued for 1–4 h. The reaction mixture was diluted with CH_2Cl_2 (200 ml) and neutralized with cooled aqueous $NaHCO_3$. The organic phase was separated, dried over Na_2SO_4, and evaporated *in vacuo* to give a crude yellow product which after silica-gel column chromatography gave **4a** [petroleum ether (b.p. 60–80 °C)–Et_2O = 8:2], yield 4.14 g (70 %), and **4b** (CH_2Cl_2–MeOH = 97:3), yield 4.13 g (67 %). Some of the anomeric mixture (2.3 g) of **4b** was separated on a silica-gel column ($CHCl_3$–MeOH = 98:2) to give 0.75 g of α-anomer and 0.88 g of β-anomer.

*1-(5-*O*-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-*D*-threo-pentofuranosyl)thymine* (**4a**). ^1H NMR ($CDCl_3$): δ 1.08 and 1.09 (2×s, 9 H, *t*-Bu), 1.78 and 1.93 (2×s, 3 H, CH_3), 2.59–2.69 (m, 2'-H), 2.73–3.26 (m, 2'-H), 3.55 [m, 1 H, 4'-H (β)], 3.76–4.05 [m, 3 H, 4'-H (α), 5'-H], 4.46–4.58 (m, 1 H, 3'-H), 6.10–6.19 (m, 1 H, 1'-H), 7.12–7.74 (m, 11 H, ArH and 6-H), 9.32 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 12.21 and 12.46 (Me), 19.05 and 19.13 (Me_3C), 21.60 and 23.08 (C-3'), 26.71 and 26.80 (Me_3C), 43.9 and 44.9 (C-2'), 68.54 (C-5'), 81.81 and 83.19 (C-4'), 84.77 and 87.71 (C-1'), 110.29 and 110.76 (C-5), 127.81, 129.79, 129.87, 132.88, 135.51 and 136.02 (Aryl and C-6), 149.96 and 150.29 (C-2), 163.79 (C-4).

*1-(5-*O*-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-α-D-threo-pentofuranosyl)-5-(methoxymethyl)uracil* [**4b**(α)]. ^1H NMR ($CDCl_3$): δ 1.08 (s, 9 H, *t*-Bu), 2.80 (m, 1 H, 2'-H), 3.10 (m, 1 H, 2'-H), 3.42 (s, 3 H, OMe), 3.78 (dd, J = 4.5 and 10.4 Hz, 1 H, 5'-H), 3.91 (q, J = 4.5 Hz, 1 H, 4'-H), 4.01 (dd, J = 4.5 and 10.4 Hz, 1 H, 5'-H), 4.21 (dd, J = 4.5 and 0.8 Hz, 2 H, CH_2O), 4.54 (m, 1 H, 3'-H), 6.18 (t, J = 6.1, 1 H, 1'-H), 7.3–7.8 (m, 11 H, ArH and 6-H), 9.43 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 19.02 (Me_3C), 22.72 (C-3'), 26.68 (*Me*C), 44.86 (C-2'), 58.65 (OMe), 66.50 (C-5'), 68.56 (CH_2O), 83.23 (C-4'), 87.99 (C-1'), 111.57 (C-5), 127.67, 129.76, 132.75, 135.50 (Aryl), 137.41 (C-6), 149.74 (C-2), 162.53 (C-4).

*1-(5-*O*-tert-Butyldiphenylsilyl-2,3-dideoxy-3-iodo-β-D-threo-pentofuranosyl)-5-(methoxymethyl)uracil* [**4b**(β)]. ^1H NMR ($CDCl_3$): δ 1.08 (s, 9 H, *t*-Bu), 2.69 (m, 1 H, 2'-H), 3.20–3.44 (m, 4 H, 2'-H and OMe) 3.48 (m, 1 H, 4'-H), 3.83 (dd, J = 5.7 and 10.7 Hz, 1 H, 5'-H), 4.02 (dd, J = 5.5 and 10.7 Hz, 1 H, 5'-H), 4.14 (s, 2 H, CH_2O), 4.49 (m, 1 H, 3'-H), 6.10 (dd, J = 3.6 and 7.4 Hz, 1'-H), 7.3–7.8 (m, 10 H, Aryl) 7.84 (s, 1 H, 6-H), 9.50 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 19.21 (Me_3C), 22.51 (C-3'), 26.90 (Me_3C), 44.35 (C-2'), 58.54 (OCH_3), 66.73 (C-5'), 68.57 (CH_2O), 82.42 (C-4'), 85.36 (C-1'), 110.99 (C-5), 127.83, 129.96, 132.88, 132.95, 135.56 and 135.61 (Aryl), 138.73 (C-6), 150.22 (C-2), 162.80 (C-4).

*1-(2,3-Dideoxy-*D*-glycero-pent-2-enofuranosyl)uracil derivatives* (**5a,b**) *and 1-(5-hydroxymethyl-2,3-dihydrofuran-2-yl)uracil derivatives* (**6a,b**). To a stirred solution of **4a**, **4b**(α) or **4b**(β) (1.4 mmol) dissolved in 5 ml of MeOH was added NaOMe prepared from Na (0.322 g, 14 mmol) in MeOH (25 ml). After 8 h of reflux and cooling to room temp., the reaction mixture was neutralized with NH_4Cl (0.75 g, 14 mmol). The solvent was evaporated. The products from compound **4a** were separated by HPLC with water on a reversed phase column (RP-4, 15–20 μm, 300 A) to give **5a** with the same ^1H and ^{13}C NMR data as previously reported,[6,7] yield 84 mg (27 %), and **6a**, yield 56 mg (18 %). The crude products from **4b**(α) or **4b**(β) were purified on a silica-gel column with 1–10 % MeOH in CH_2Cl_2. **4b**(α) afforded **5b**(α), yield 185 mg (51 %), and **6b**, yield 50 mg (14 %), and **4b**(β) afforded **5b**(β), yield 189 mg (53 %), and **6b**, yield 72 mg (20 %).

1-(5-Hydroxymethyl-2,3-dihydrofuran-2-yl)thymine (**6a**). ^1H NMR (DMSO-d_6): δ 1.78 (s, 3 H, CH_3), 2.63 (br d, J = 16.6 Hz, 1-H, 2′-H), 3.10 (m, 1 H, 2′-H), 4.00 (br s, 2 H, 5′-H), 5.00 (br s, 1 H, 3′-H), 6.59 (br s, 1 H, 1′-H), 7.25 (s, 1 H, 6-H). ^{13}C NMR (DMSO-d_6): δ 12.14 (Me), 35.05 (C-2′), 55.81 (C-5′), 84.30 (C-1′), 95.20 (C-3′), 110.22 (C-5), 135.12 (C-6), 150.06 (C-2), 157.16 (C-4′), 163.61 (C-4).

*1-(2,3-Dideoxy-*α*-*D*-glycero-pent-2-enofuranosyl)-5-(methoxymethyl)uracil* [**5b**(α)]. ^1H NMR ($CDCl_3$): δ 3.39 (s, 3 H, Me), 3.65 (m, 1 H, 5′-H), 3.81 (m, 1 H, 5′-H), 4.18 (s, 2 H, CH_2O), 5.16 (br s, 1 H, 4′-H), 5.92 (d, J = 5.8 Hz, 1 H, 2′-H), 6.37 (d, J = 5.8 Hz, 1 H, 3′-H), 7.08 (d, J = 5.1 Hz, 1′-H), 7.20 (s, 1 H, 6-H), 10.18 (br, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 58.57 (OMe), 63.91 (C-5′), 66.57 (CH_2O), 88.08, 90.60 (C-1′ and C-4′), 112.12 (C-5), 126.35 (C-2′), 134.47 (C-3′), 137.55 (C-6), 150.95 (C-2), 163.10 (C-4).

1-(5-Hydroxymethyl-2,3-dihydrofuran-2-yl)-5-(methoxymethyl)uracil **6b**. ^1H NMR (DMSO-d_6): δ 2.60 (br d, J = 17.1 Hz, 1 H, 2′-H), 3.21 (ddd, J = 17.1, 9.6 and 1.7 Hz, 1 H, 2′-H), 3.38 (s, 3 H, OMe), 4.00 (d, J = 5.4 Hz, 2 H, 5′-H), 4.05 (s, 2 H, CH_2O), 5.02 (br, s, 1 H, 3′-H), 5.22 (t, J = 5.4 Hz, 1 H, OH), 6.58 (dd, J = 3.8 and 9.6 Hz, 1 H, 1′-H), 7.38 (s, 1 H, 6-H), 11.50 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): δ 35.25 (C-2′), 55.64 (C-5′), 57.38 (OCH_3), 66.0 (CH_2O), 84.55 (C-1′), 95.29 (C-3′), 111.11 (C-5), 137.61 (C-6), 149.87 (C-2), 157.15 (C-4′), 162.47 (C-4).

*1-(2,3-Dideoxy-*β*-*D*-glycero-pent-2-enofuranosyl)-5-(methoxymethyl)uracil* [**5b**(β)]. ^1H NMR (DMSO-d_6): δ 3.20 (s, 3 H, OMe), 3.58 (d, J = 3.3 Hz, 2 H, 5′-H), 3.97 (d, J = 11.9 Hz, 1 H, CH_2O), 4.02 (d, J = 11.9 Hz, 1 H, CH_2O), 4.79 (m, 1 H, 4′-H), 5.94 (ddd, J = 6.0, 2.2 and 1.5 Hz, 1 H, 2′-H), 6.42 (dt, J = 6.0 and 1.6 Hz, 1 H, 3′-H), 6.84 (dt, J = 3.2 and 1.5 Hz, 1 H, 1′-H), 7.80 (s, 1 H, 6-H), 11.41 (br, 1 H, NH). ^{13}C NMR (DMSO-d_6): δ 57.28 (OCH_3), 62.16 (C-5′), 66.16 (CH_2O), 87.33, 89.05 (C-1′ and C-4′), 109.92 (C-5), 125.68 (C-2′), 135.13 (C-3′), 139.44 (C-6), 150.58 (C-2), 162.66 (C-4).

*Methyl 5-*O*-(tert-butyldiphenylsilyl)-2-deoxy-3-*O*-methylsulfonyl-*D*-erythro-pentofuranoside* (**8**). **7** (6.0 g, 15.5 mmol) was dissolved in pyridine (150 ml) and cooled to 0 °C. Methanesulfonyl chloride (4.41 g, 38.5 mmol) was added dropwise with stirring. After being stirred for 2 h, the reaction mixture was poured into ice–water (300 ml) and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated to an oil which was purified on a silica gel column with petroleum ether (b.p. 60–80 °C)–Et_2O (8:2) to afford **8** as a yellow oil, yield 6.51 g (90 %). ^1H NMR (DMSO-d_6): δ 1.01 (s, 9 H, *t*-Bu), 2.24–2.49 (m, 2 H, 2-H), 3.22 and 3.23 (2×s, 3 H, Me), 3.24 and 3.30 (2×s, 3 H, OMe), 3.51–3.82 (m, 3 H, 5-H and 3-H), 4.25 (m, 1 H, 4-H), 5.12–5.31 (m, 1 H, 1-H), 7.41–7.69 (m, 10 H, Aryl). ^{13}C NMR (DMSO-d_6): δ 18.68 and 18.73 (CMe_3), 26.47 (CMe_3)], 35.68 and 37.72 (C-2), 38.59 and 38.91 (Me), 54.35 and 54.82 (OMe), 63.26 and 63.68 (C-5), 79.99, 80.74, 83.37 and 83.62 (C-3 and C-4), 104.48 and 104.71 (C-1), 127.85, 129.88, 132.55 and 135.05 (Aryl).

*1-[5-*O*-(tert-Butyldiphenylsilyl)-2-deoxy-3-*O*-methylsulfonyl)-*D*-erythro-pentofuranosyl)*-thymine (**9**). TMS-triflate (1.27 ml, 7.0 mmol) was slowly added to a solution of the silylated thymine (**2a**) (0.9 g, 7 mmol) in MeCN (50 ml) at −30 °C with stirring. **8** (2.79 g, 5 mmol) in MeCN (15 ml) was added dropwise (15 min) at −30 °C. The reaction mixture was left at room temperature for 4 h and diluted with CH_2Cl_2 and quenched with saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4 and evaporated to give an oil which was purified on a silica gel column with CH_2Cl_2 to give **9**, yield 2.29 g (82 %) (α:β, 1:2). The α- and β-anomers of **9** were separated on an analytical scale by HPLC with isocratic 50 % ethanol in water on a reversed phase column (RP-18, 15–20 μm, 300 A).

9(β): ^1H NMR ($CDCl_3$): δ 1.10 (s, 9 H, *t*-Bu), 1.62 (s, 3 H, Me), 2.31 (m, 1 H, 2′-H), 2.63 (m, 1 H, 2′-H), 3.04 (s, 3 H, SO_2Me), 3.97 (m, 2 H, 5′-H), 4.30 (m, 1 H, 4′-H), 5.39 (m, 1 H, 3′-H), 6.40 (m, 1 H, 1′-H), 7.38–7.68 (m, 11 H, 6-H and ArH). ^{13}C NMR ($CDCl_3$): δ 12.04 (CH_3), 19.49 (CMe_3), 27.04 (CMe_3), 38.50 and 38.70 (Me and C-2′), 63.52 (C-5′), 79.49 (C-3′), 84.30, 84.77 (C-1′ and C-4′), 111.75 (C-5), 128.09, 128.17, 129.99, 130.22, 132.66, 134.69, 135.28 and 135.54 (C-6 and Aryl), 150.46 (C-2), 163.73 (C-4).

9(α): ^1H NMR ($CDCl_3$): δ 1.08 (s, 9 H, *t*-Bu), 1.94 (s, 3 H, Me), 2.43 (m, 1 H, 2′-H), 2.80–2.99 (m, 4 H, 2′-H and SO_2Me), 3.78 (m, 2 H, 5′-H), 4.69 (m, 1 H, 4′-H), 5.31 (m, 1 H, 3′-H), 6.30 (dd, J = 2.0 and 7.1 Hz, 1′-H), 7.31 (s, 1 H, 6-H), 7.38–7.67 (m, 10, ArH), 9.41 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ 12.60 (Me), 19.16 (CMe_3), 26.88 (CMe_3), 38.69 and 39.58 (Me and C-2′), 63.91 (C-5′), 80.72 (C-3′), 87.02, 87.21 (C-4′ and C-1′), 110.43 (C-5), 128.01, 130.16, 132.28, 135.27 and 135.55 (C-6 and Aryl), 150.43 (C-2), 164.10 (C-4).

*1-(2,3-Dideoxy-*D*-glycero-pent-2-enofuranosyl)thymine* (**5a**), *1-(2-deoxy-*β*-*D*-threo-pentofuranosyl)thymine* (**10**) *and 1-(3,5-anhydro-2-deoxy-*α*-*D*-threo-pentofuranosyl)thymine* (**11**). A solution of NaOMe [prepared from Na (207 mg, 9 mmol) in methanol (20 ml)] was added to a stirred solution of **9** (0.50 g, 0.9 mmol) in MeOH (5 ml) and refluxed for 24 h. The reaction mixture was neutralized with NH_4Cl (490 mg, 9 mmol) and concentrated *in vacuo*. Column chromatography on silica with 5–10 % methanol in CH_2Cl_2 afforded 70 mg (35 %) of **5a**, 60 mg (28 %) of **10** and 40 mg (20 %) of **11**. ^1H NMR and ^{13}C NMR data of compounds **5a**[6,7] and **10**[9] are in accordance with published values.

11: m.p. 180–182 °C, MS: m/z = 224 (M^+, 30 %). ^1H NMR (DMSO-d_6): δ 1.78 (s, 3 H, Me), 1.96 (m, 1 H, 2′-H), 2.33 (dd, J = 14.3 and 5.6 Hz, 1 H, 2′-H), 4.28 (dd, J = 8.1 and 2.4 Hz, 1 H, 5′-H), 4.71 (dd, 1 H, J = 8.1 and 4.6 Hz, 5′-H), 5.10 (m, 1 H, 4′-H), 5.45 (t, J = 4.3 Hz, 1 H, 3′-H), 6.58 (dd, J = 8.8 and 5.6 Hz, 1 H, 1′-H), 7.54 (s, 1 H, 6-H), 11.36 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): δ 11.81 (Me), 37.08 (C-2′), 76.42, 77.11 (C-3′ and C-5′), 84.49, 85.83 (C-1′ and C-4′), 109.82 (C-5), 136.19 (C-6), 150.27 (C-2), 163.48 (C-4).

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