Chemistry of Natural Compounds and Bioorganic Chemistry

Stereoselective synthesis of 2,6-dideoxy-α-L-*arabino*-hexopyranoside of glycyrrhetic acid in the presence of iodine-containing promoters

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Glycosylation of methyl glycyrrhetate with L-rhamnal acetate in the presence of iodine-containing promoters and subsequent hydrogenolysis yield 2,6-dideoxy-α-L-*arabino*-hexopyranoside of glycyrrhetic acid, an analog of glycyrrhizic acid, the natural glycoside of licorice root extract.

Key words: methyl glycyrrhetate, L-rhamnal acetate, stereoselective glycosylation, *N*-iodosuccinimide, iodonium dicollidine perchlorate, 2,6-dideoxy-2-iodo-α-L-manno-pyranoside, 2,6-dideoxy-α-L-*arabino*-hexopyranoside.

Previously,[1,2] we reported the stereoselective synthesis of 2-deoxy-α-D-*arabino*-hexopyranosides of glycyrrhetic acid, which are analogs of the natural glycoside, glycyrrhizic acid, the main component of licorice root extract (*Glycyrrhiza glabra* and *Gl. uralensis*). In a continuation of these works, we carried out stereoselective glycosylation of methyl glycyrrhetate[3] (**1**) with di-*O*-acetyl-L-rhamnal (**2**) in the presence of iodine-containing promoters, *viz.*, *N*-iodosuccinimide (NIS) and iodonium dicollidine perchlorate (IDCP) (Scheme 1). It is known that the L-rhamnose residue as a constituent of *O*-glycosides determines their higher biological acivity in comparison to other carbohydrates.[4]

Glycosylation in the presence of NIS or IDCP was carried out under anhydrous conditions with equimolar amounts of triterpene alcohol **1** and glycal **2**. With NIS as a promoter in CH_2Cl_2—MeCN, 2,6-dideoxy-2-iodo-α-L-glycoside (**3**) is formed stereoselectively in 70 h in a 65% yield. Replacement of NIS by IDCP (in CH_2Cl_2) allowed us to reduce the reaction time to 4 h and to increase the yield of product **3** to 84%. The physicochemical properties and the spectral data (IR, UV, NMR) for the glycosides synthesized using NIS and IDCP, coincide completely. The lower yield of glycoside **3** obtained by the action of NIS can apparently be explained by the formation of *N*-glycoside (**4**), which is an adduct of *N*-iodosuccinimide and L-rhamnal acetate, as it has been observed previously in glycosylation of steroids with glycals.[5]

Hydrogenolysis of 2,6-dideoxy-2-iodo-α-L-glycoside **3** in MeOH in the presence of 10% Pd/C yielded the acetylated 2,6-dideoxy-α-L-glycoside of methyl glycyrrhetate (**5**) in a high yield. Mild deacetylation of glycoside **5** gave glycoside (**6**).

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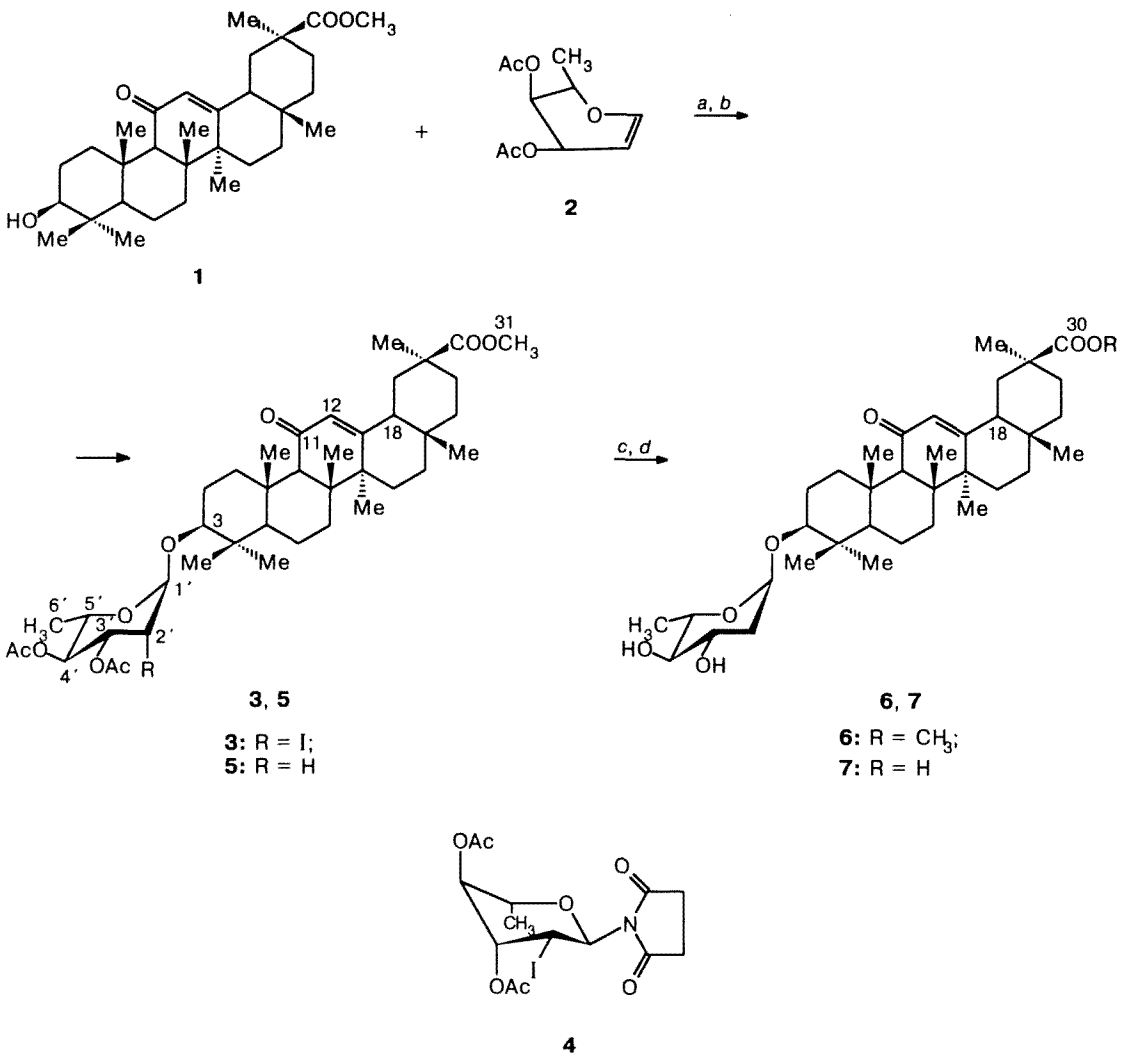
Scheme 1



Reagents and conditions: *a*. NIS (CH_2Cl_2—MeCN) or IDCP (CH_2Cl_2); *b*. H_2, 10% Pd/C, MeOH; *c*. 5% KOH/MeOH; *d*. 5% KOH/EtOH—H_2O (1 : 1).

Refluxing of glycoside **5** in a solution of KOH in aqueous EtOH yielded compound **7**.

The structure of compounds **3**, **5**—**7** was established by analysis of their NMR spectra and a comparison with the published data for glycyrrhetic acid[6] and the carbohydrate unit.[5] The ^{13}C NMR spectra of aglycones of the glycosides synthesized were similar to the spectrum of methyl glycyrrhetate. The signal of the C(3) atom in glycoside **3** is at δ 89.7. The paramagnetic shift of this signal by *ca.* 11.4 ppm in comparison to the C(3) signal in the spectrum of **1** is due to the formation of an *O*-glycosidic bond. The introduction of a carbohydrate fragment into the molecule of methyl glycyrrhetate also results in an upfield shift of the signal of the β-carbon of aglycone, C(2), by *ca.* 5 ppm. The signal of the anomeric atom C(1′) in glycoside **3** is observed at δ 103.5, which is close to the chemical shifts of natural triterpene *O*-α-L-rhamnosides.[7,8] The α-configuration of the *O*-glycosidic bond and the axial position of the aglycone in glycoside **3** are confirmed by the value of the coupling constant $J_{C(1'),H(1')}$ = 170 Hz in the ^{13}C NMR spectrum recorded in the GATED mode.[9] In the ^1H NMR spectrum of glycoside **3**, the H(1′) proton resonates in the lower field at δ 5.16 as a doublet with $J_{1',2'}$ = 1.4 Hz, and the H(2′) proton gives the doublet of doublets at δ 4.54 having $J_{1',2'}$ = 1.4 Hz and $J_{2',3'}$ = 4.4 Hz. The values of the coupling constants $J_{2',3'}$ = 4.4 Hz and $J_{3',4'}$ = 9.2 Hz of the H(3′) proton (δ 4.57) and $J_{3',4'}$ = $J_{4',5'}$ = 9.2 Hz proton H(4′) (δ 5.12) demonstrate their axial orientation and the equatorial position of the H(2′) proton. Therefore, the NMR spectral data show that 2,6-dideoxy-2-iodo-L-glycoside **3** has the α-L-*manno*-configuration of the carbohydrate ring in the $^1C_4$(L)-conformation.

Deiodination by catalytic hydrogenolysis followed by deacetylation resulted in an upfield shift of the signals of the anomeric carbons C(1′) in glycosides **5** and **6** by 3.4—4 ppm and of the C(3) atoms by *ca.* 1 ppm, and, on the other hand, the C(2′) signals of the pyranose rings undergo paramagnetic shifts by 4.5—7.3 ppm. Catalytic hydrogenolysis does not result in changes in the aglycone part of glycoside **5** (C=O and C=C), which was confirmed by preservation of the characteristic absorption in the IR spectrum (ν 1650 cm^{-1}, C=O) and the absorption maximum at λ 246.8 nm in the UV spectrum, which is characteristic of the 12-ene-11-one system in the aglycone.[10] In the ^{13}C NMR spectrum of glycoside **5**, the C(12) carbon atom resonates at δ 128.6, as in the case of glycyrrhizic acid,[11] and in its ^1H NMR spectrum, the signal of H(12), characteristic of triterpenes of the olean-12-ene series, persists at δ 5.66. The signal of proton H(1′) appears at δ 4.91 as a doublet of doublets with $J_{1',2'e}$ = 1.4 Hz and $J_{1',2'a}$ = 3.8 Hz, which indicates its equatorial position and confirms the formation of the α-glycosidic bond. The coupling constants $J_{2'e,3'}$ = 5.2 Hz, $J_{2'a,3'}$ = 11.5 Hz, and $J_{3',4'}$ = $J_{4',5'}$ = 9.6 Hz indicate the axial orientation of the H(3′), H(4′), and H(5′) protons in accordance with the 2,6-dideoxy-α-L-*arabino*-configuration of the carbohydrate ring.

The ester group in the aglycone of glycoside **6** is stable towards treatment of glycoside **5** with 5% methanolic KOH (signals of C(30) at δ 177.1 and C(31) at δ 51.9 in the ^{13}C NMR spectrum and the proton signals of the OCH_3 group at δ 3.69 in the ^1H NMR spectrum). After refluxing of glycoside **5** in a 5% solution of KOH in aqueous EtOH, a downfield shift of the C(30) signal to δ 181.3 is observed in the ^{13}C NMR spectrum of glycoside **7**, and the signals of the C(31) carbon atom and the corresponding protons disappear. A similar signal of C(30) of the carboxyl group was observed in the spectrum of glycyrrhizic acid.[12] Refluxing for 2 h under alkaline conditions does not change the configuration of the proton at C(18) of the aglycone (δ 48.3), as has been observed previously.[13]

Experimental

TLC was carried out on Silufol plates (Chemapol, Czech Republic) in the following solvent systems: dichloromethane—methanol, 10 : 1 (*A*), ethyl acetate—light petroleum, 2 : 1 (*B*), benzene—methanol, 1 : 3 (*C*). The spots were visualized by spraying the plates with a 20% ethanolic solution of phosphotungstic acid followed by heating at 100—120 °C for 2—3 min. Column chromatography was carried out on silica gel L (40/100 mm, Chemapol, Czech Republic).

The IR spectra were recorded with a Specord M-80 spectrometer for suspensions in nujol. The UV spectra were recorded with a Specord M-40 spectrophotometer in methanol. The ^{13}C and ^1H NMR spectra were recorded with a Bruker AM-300 spectrometer (75.5 and 300 MHz, respectively) in $CDCl_3$ or Py-d_5, and tetramethylsilane was used as the internal standard.

The melting points were determined with a Boetius heating stage. The optical rotations were measured with a Perkin—Elmer 241 MC polarimeter in a cell with a 1 dm path length.

Acetonitrile and dichloromethane used in the syntheses were distilled twice over P_2O_5. 4 Å molecular sieves were calcined for 3 h at 180—190 °C (1—5 Torr). Methyl glycyrrhetate was prepared according to the known procedure[3] from β-glycyrrhizic acid (the content of the basic compound in the starting material was *ca.* 95%). Di-*O*-acetyl-L-rhamnal was synthesized according to the previously published procedure[14] from L-rhamnose (Chemapol, Czech Republic). *N*-Iodosuccinimide[15] (iodine content 55.8—56.1%, 98—99% of the theoretical), and iodonium dicollidine perchlorate[16] (iodine content 25.5—27.0%, 94—99% of the theoretical) were prepared according to the known procedures.

Methyl 3-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-2-iodo-α-L-mannopyranosyl)-3β-hydroxy-11-oxo-18β-olean-12-ene-20β-carboxylate (3). ***A.*** Calcined 4 Å molecular sieves (0.43 g) were added to a solution of methyl glycyrrhetate **1** (0.97 g, 2 mmol) and di-*O*-acetyl-L-rhamnal **2** (0.43 g, 2 mmol) in a 1 : 1 (v/v) mixture of dry dichloromethane and acetonitrile (50 mL), the resulting mixture was cooled to 0 °C, and NIS (0.52 g, 2.3 mmol) was added with stirring in the dark. The temperature was increased to *ca.* 20°C and the mixture was stirred for 70 h (TLC control, system *A*).

The sieves were filtered off, the solvent was removed *in vacuo*, the residue was dissolved in dichloromethane (50 mL), and the resuling solution was washed with 10% aqueous $Na_2S_2O_3$ (2×20 mL), dried with Na_2SO_4 and concentrated. The residue (1.57 g) was chromatographed on a column with silica gel, eluting with pentane—ethyl acetate mixtures, 7 : 1, 5 : 1, 3 : 1, 2 : 1, 1 : 1 (v/v). Glycoside **3** (1.07 g, 65.0%), homogeneous according to TLC, was eluted with a 3 : 1 → 2 : 1 gradient mixture as a yellow powder. R_f 0.74 (*A*), 0.81 (*B*), 0.73 (*C*); m.p. 237—239 °C; $[\alpha]_D^{20}$ + 106° (*c* 0.06, $CHCl_3$). Found (%): C, 60.0; H, 7.7; I, 14.9. $C_{41}H_{61}IO_9$. Calculated (%): C, 59.7; H, 7.5; I, 15.4.

B. Calcined 4 Å molecular sieves (0.43 g) were added to a solution of methyl glycyrrhetate **1** (0.97 g) and di-*O*-acetyl-L-rhamnal **2** (0.43 g) in dry dichloromethane (50 mL). The mixture was stirred for 30 min, then IDCP (1 g, 2.13 mmol) was added. The mixture was stirred for 4 h (TLC control, system *A*) and filtered. The filtrate was washed with a 10% solution of $Na_2S_2O_3$ (2×20 mL), dried with $MgSO_4$, and concentrated. The residue (1.84 g) was chromatographed as in procedure *A* to yield glycoside **3** (1.38 g, 84.0%). R_f 0.74 (*A*), 0.80 (*B*), 0.73 (*C*); m.p. 237—240 °C; $[\alpha]_D^{20}$ +108° (*c* 0.07, $CHCl_3$). Found (%): C, 60.1; H, 7.7; I, 15.0. UV, λ_{max}/nm: 246.8 (log ε 4.02). ^1H NMR ($CDCl_3$), δ: 0.81, 0.87, 0.97, 1.14, 1.16, 1.18, and 1.20 (all s, 7 CH_3 of aglycone); 1.36 (d, 3 H, C(6′)H_3); 1.25—2.00 (m, CH_2, CH); 2.03, 2.05 (both s, 6 H, 2 Ac); 2.31 (s, 1 H, H(9)); 2.81 (d, 1 H, H(18), *J* = 13.6 Hz); 3.12 (dd, 1 H, H(3), $J_{3,2e}$ = 4.4 Hz, $J_{3,2a}$ = 11.4 Hz); 3.68 (s, 3 H, OCH_3); 4.06 (dq, 1 H, H(5′), $J_{4',5'}$ = 9.2 Hz, $J_{5',6'}$ = 6.2 Hz); 4.54 (dd, 1 H, H(2′); $J_{1',2'}$ = 1.4 Hz, $J_{2',3'}$ = 4.4 Hz); 4.57 (dd, 1 H, H(3′), $J_{2',3'}$ = 4.4 Hz, $J_{3',4'}$ = 9.2 Hz); 5.12 (t, 1 H, H(4′), $J_{3',4'}$ = $J_{4',5'}$ = 9.2 Hz); 5.16 (d, 1 H, H(1′), $J_{1',2'}$ = 1.4 Hz); 5.65 (br.s, 1 H, H(12)). ^{13}C NMR ($CDCl_3$) δ: 22.3 (C(2)); 89.7 (C(3)); 38.5 (C(4)); 61.9 (C(9)); 36.9 (C(10)); 200.3 (C(11)); 128.6 (C(12)); 169.3 (C(13)); 45.5 (C(14)); 48.4 (C(18)); 44.1 (C(20)); 177.0 (C(30)); 52.0 (CH_3O); 103.5 (C(1′)); 31.1 (C(2′)); 69.5 (C(3′)); 72.8 (C(4′)); 67.2 (C(5′)); 17.4 (C(6′)); 170.1 ($O\underline{C}OCH_3$)); 20.88, 20.91 (CH_3COO).

Methyl 3-*O*-(3,4-di-*O*-acetyl-2,6-dideoxy-α-L-*arabino*-hexopyranosyl)-3β-hydroxy-11-oxo-18β-olean-12-ene-20β-carboxylate (5). Several drops of triethylamine and 10% Pd/C (1.2 g) were added to a solution of glycoside **3** (1.2 g, 1.45 mmol) in methanol (50 mL) and the mixture was hydrogenated for 9 days (p = 1 atm). The catalyst was filtered off, the solvent was removed, and the residue was reprecipitated with light petroleum from solution in chloroform to yield glycoside **5** (0.94 g, 92.3%) as a yellow powder, R_f 0.71 (*A*), 0.79 (*B*); decomp. temp. 220—222 °C; $[\alpha]_D^{20}$ +114° (*c* 0.09, $CHCl_3$). Found (%): C, 70.9; H, 9.2. $C_{41}H_{62}O_9$. Calculated (%): C, 70.5; H, 8.9. UV, λ_{max}/nm: 246.8 (log ε 4.05). IR, ν/cm^{-1}: 1760—1750 (OAc); 1730—1720 ($COOCH_3$); 1650 (C=O). ^{1}H NMR ($CDCl_3$), δ: 0.80, 0.83, 0.91, 1.12, and 1.14 (all s, 7 CH_3 of aglycone); 1.33 (d, 3 H, C(6′)H$_3$); 1.40—1.90 (m, CH_2, CH); 1.98, 2.06 (s, 6 H, 2 Ac); 2.32 (s, 1 H, H(9)); 2.78 (d, 1 H, H(18), J = 13.3 Hz); 3.07 (dd, 1 H, H(3), $J_{3,2e}$ = 5.0 Hz, $J_{3,2a}$ = 10.7 Hz); 3.69 (s, 3 H, OCH_3); 4.02 (dq, 1 H, H(5′), $J_{4',5'}$ = 9.6 Hz, $J_{5',6'}$ = 6.3 Hz); 4.73 (t, 1 H, H(4′), $J_{3',4'} = J_{4',5'}$ = 9.6 Hz); 4.91 (dd, 1 H, H(1′), $J_{1',2'e}$ = 1.4 Hz, $J_{1',2'a}$ = 3.8 Hz); 5.28 (ddd, 1 H, H(3′), $J_{2'e,3'}$ = 5.2 Hz, $J_{2'a,3'}$ = 11.5 Hz, $J_{3',4'}$ = 9.6 Hz); 5.66 (br.s, 1 H, H(12)). ^{13}C NMR ($CDCl_3$), δ: 23.2 (C(2)); 88.8 (C(3)); 38.3 (C(4)); 61.8 (C(9)); 36.8 (C(10)); 200.4 (C(11)); 128.6 (C(12)); 169.3 (C(13)); 45.5 (C(14)); 48.4 (C(18)); 44.1 (C(20)); 176.8 (C(30)); 51.8 (C(31)); 99.5 (C(1′)); 35.6 (C(2′)); 69.3 (C(3′)); 75.1 (C(4′)); 65.7 (C(5′)); 17.4 (C(6′)); 170.4, 170.5 (O<u>C</u>OCH$_3$); 20.89, 20.97 (OCO<u>C</u>H$_3$).

Methyl 3-*O*-(2,6-dideoxy-α-L-*arabino*-hexopyranosyl)-3β-hydroxy-11-oxo-18β-olean-12-ene-20β-carboxylate (6). 5% Methanolic KOH (45 mL) was added to a solution of glycoside **5** (1.40 g, 2.0 mmol) in methanol (250 mL) and the resulting mixture was stirred at ambient temperature for 4 h (TLC control, system *A*). The mixture was treated with KU-2-8 cation-exchange resin (H^+-form) and filtered, and the filtrate was diluted with cold water (50 mL) and extracted with chloroform (3×30 mL). The combined extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Reprecipitation of the residue with pentane from a solution in dichloromethane yielded glycoside **6** (1.10 g, 89.8%) as a yellow powder, R_f 0.43 (*A*); decomp. temp. 186—188 °C; $[\alpha]_D^{20}$ +108° (*c* 0.05, $CHCl_3$). Found (%): C, 71.9; H, 9.7. $C_{37}H_{58}O_7$. Calculated (%): C, 72.3; H, 9.5. UV, λ_{max}/nm: 247.0 (log ε 4.32). IR, ν/cm^{-1}: 3600—3200 (OH); 1730—1720 ($COOCH_3$); 1650 (C=O). ^{13}C NMR ($CDCl_3$), δ: 23.5 (C(2)); 88.6 (C(3)); 38.5 (C(4)); 61.9 (C(9)); 36.8 (C(10)); 200.5 (C(11)); 128.5 (C(12)); 169.5 (C(13)); 45.5 (C(14)); 48.4 (C(18)); 44.1 (C(20)); 177.1 (C(30)); 51.9 (C(31)); 99.5 (C(1′)); 38.4 (C(2′)); 69.5 (C(3′)); 78.4 (C(4′)); 67.5 (C(5′)); 17.6 (C(6′)).

3-*O*-(2,6-Dideoxy-α-L-*arabino*-hexopyranosyl)-3β-hydroxy-11-oxo-18β-olean-12-ene-30-oic acid (7). A solution of glycoside **5** (0.35 g, 0.5 mmol) in 5% KOH in 1 : 1 (v/v) aqueous ethanol (13 mL) was kept at ambient the temperature for 10 h and then refluxed for 2 h. The mixture was diluted with water (5 mL), neutralized with KU-2-8 cation-exchange resin (H^+-form), and concentrated to dryness. The residue was chromatographed on a column with silica gel, eluting successively with chloroform—methanol mixtures, 200 : 1, 150 : 1, 100 : 1, 50 : 1, 25 : 1 (v/v). Elution with a 50 : 1 → 25 : 1 gradient mixture yielded glycoside **7** (0.21 g, 71.0%), homogeneous according to TLC, as a yellow powder, R_f 0.29 (*A*), 0.31 (*B*); m.p. 172—175 °C; $[\alpha]_D^{20}$ +134° (*c* 0.15, $CHCl_3$). Found (%): C, 72.3; H, 9.0. $C_{36}H_{56}O_7$. Calculated (%): C, 72.0; H, 9.4. UV, λ_{max}/nm: 247.6 (log ε 4.15). IR, ν/cm^{-1}: 3600—3200 (OH); 1710—1700 (COOH); 1650 (C=O). ^{13}C NMR (Py-d_5), δ: 22.4 (C(2)); 88.6 (C(3)); 38.4 (C(4)); 61.9 (C(9)); 37.0 (C(10)); 200.7 (C(11)); 128.6 (C(12)); 169.6 (C(13)); 45.6 (C(14)); 48.3 (C(18)); 43.3 (C(20)); 181.3 (C(30)); 100.2 (C(1′)); 39.3 (C(2′)); 69.6 (C(3′)); 78.5 (C(4′)); 67.9 (C(5′)); 17.4 (C(6′)).

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