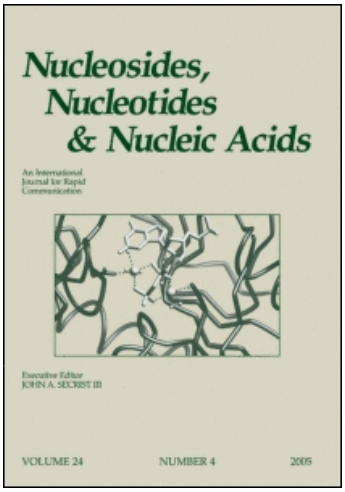

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A Highly Efficient and Selective Synthesis of 1,2,3-Triazole Linked Saccharide Nucleosides Via "Click Chemistry"

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A HIGHLY EFFICIENT AND SELECTIVE SYNTHESIS OF 1,2,3-TRIAZOLE LINKED SACCHARIDE NUCLEOSIDES VIA "CLICK CHEMISTRY"

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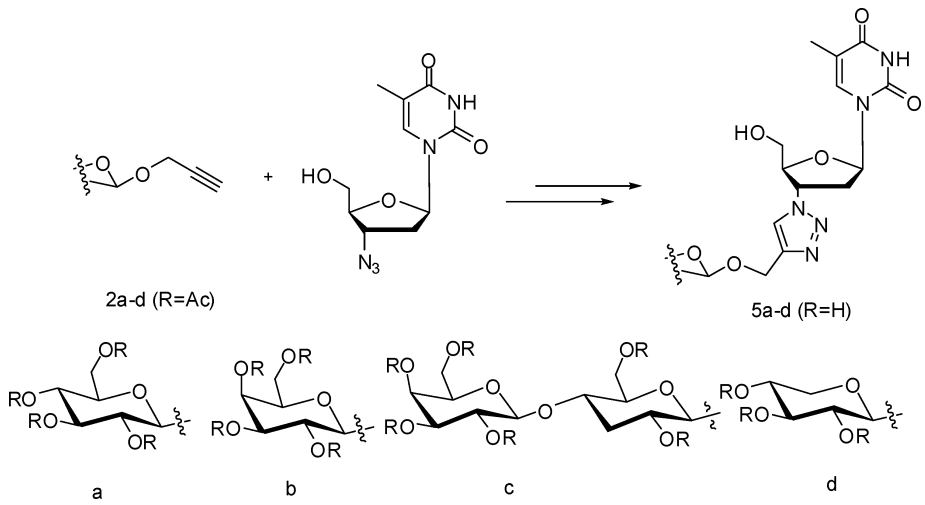
□ *A series of 1,2,3-triazole linked saccharide nucleosides were synthesized in high yield and selectivity via "click chemistry" of the 3′-azido-2′-deoxythymidine and the propargyl carbohydrates.*



Keywords 1,2,3-Triazole; "click chemistry"; saccharides, antiviral compounds

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INTRODUCTION

In our long-standing search the antiviral compounds, a number of nucleosides with sufficient structural diversity need to be synthesized for structure-activity relationship (SAR) studies. However, the synthesis of a nucleoside is not an easy procedure, especially when the ribose motif needs to be modified.[1] A persistent technical challenge facing the synthesis is harsh catalysis and stereoselectivity not being fully selective, which leads to a tedious column separation of the synthesized product. As a result, it is difficult to obtain a vast pool of potentially active compounds through usual synthesis methods in a relative short period.[2,3] Due to the above reasons, a new strategy is highly needed.

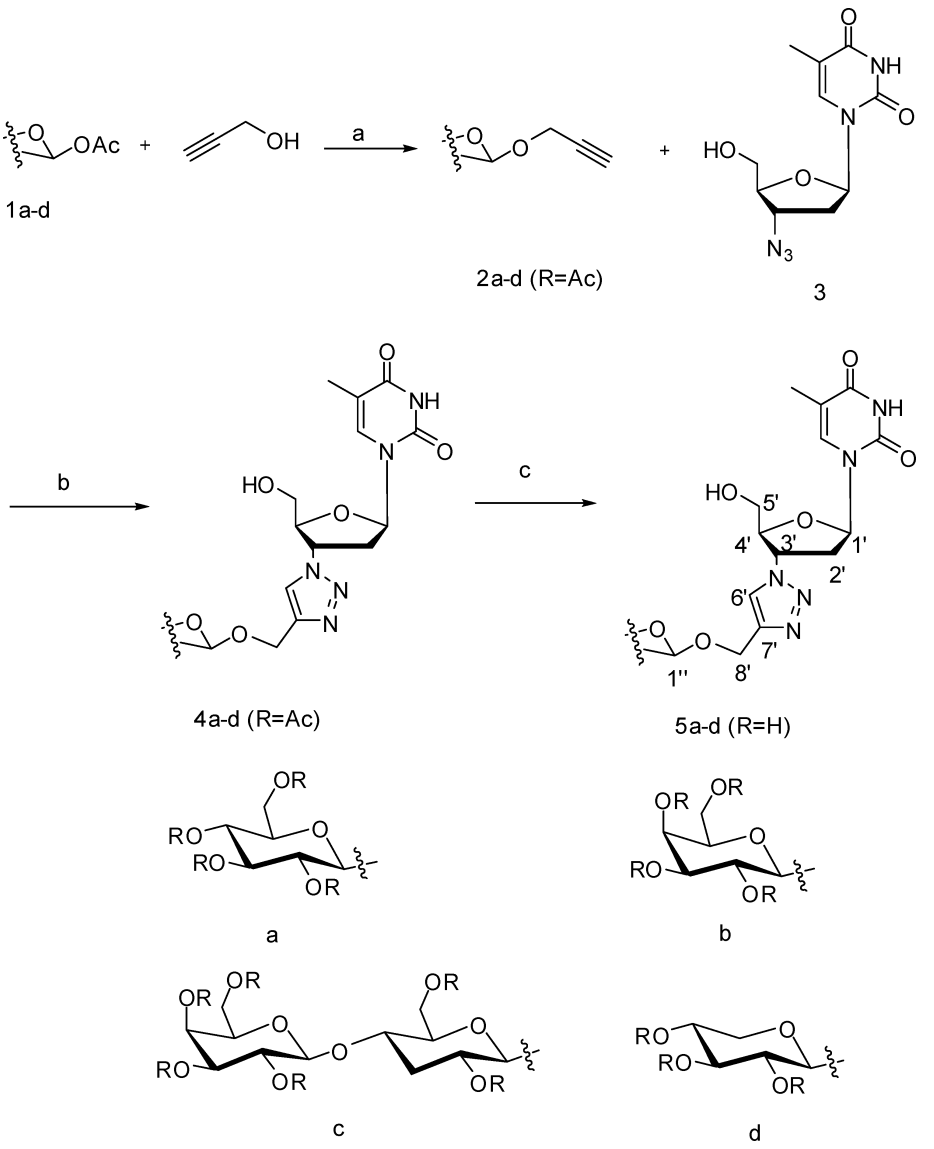
The emerging field of "click chemistry" may offer a powerful weapon to tackle this bottleneck. According to Sharpless's definition of "click chemistry," which is a set of powerful, highly reliable, and selective reactions, one of the most powerful reactions is the Cu^{I}-catalyzed Huisgen's [2+3] cycloaddition of azides and alkynes to afford the 1,2,3-triazoles.[4,5] Because of benign reaction conditions and simple workups, a wide molecular diversity can be constructed through the use of corresponding reactive modular building blocks. Many amazing applications of "click chemistry" have been reported in recent years, such as constructing fluorescent oligonucleotides for DNA sequencing,[6] labeling enzymes in vitro and in vivo, synthesizing a GDP-triazole library as inhibitor of fucosyltransferases,[7] and functionalizing surfaces coated with self-assembled monolayer,[8,9] among others.

During our extended program for synthesizing new derivatives of nucleosides, various monosaccharide and oligosaccharide may be conjugated to the bioactive nucleoside. Carbohydrates residues, appended to pharmaceutical compounds, are known to influence drug solubility, pharmacology, target recognition, toxicity, and mechanism of action.[10–13] These are important factors for improving the bioactivities of potential drug candidates.

RESULTS AND DISCUSSION

In this article, a series of 1,2,3-triazole linked oligosaccharide nucleosides was synthesized using "click chemistry." The starting nucleoside is 3′-azido-2′-deoxythymidine **3**, known as Retrovir (AZT), which was the first drug approved for the treatment of HIV. It is a nucleoside reverse transcriptase inhibitor, which blocks the reverse transcriptase enzyme during the process of transcript virus RNA into the form of DNA.[14] We reasoned that it should remain as a nucleoside reverse transcriptase inhibitor after its conjugation with the saccharide, and may be useful for exploring new anti-HIV drugs.

The synthetic route is shown as Scheme 1. At first, the propargyl carbohydrates **2a-d** were synthesized. There are many approaches available,



SCHEME 1 Synthesis of 1,2,3-triazole linked oligosaccharide nucleosides via "click chemistry." Reagents and reaction conditions: a) $BF_3{\cdot}Et_2O$, CH_2Cl_2; b) $CuSO_4$ (5%), sodium ascorbate (10%), $THF/H_2O(1:1)$; c) saturated NH_3 in MeOH.

such as the classic Koenigs-Knorr reaction, glycosyl trichloroacetimidate, and thioglycoside approaches.[15] We use the glycosyl peracetates as donors, which were inexpensive, and either commercially available or easily synthesized in one step from the corresponding free sugars in high yields. As result, the propargyl carbohydrates **2a-d** were synthesized from the corresponding peracetate carbohydrate and propargyl alcohol in the presence of excess Lewis acid catalyst (BF3·Et2O) in dichloromethane

at room temperature.[16] After workup, purification was carried out by recrystallization from absolute ethanol. The glycosylation reaction is very efficient and highly β-selective. Its scale could be easily enlarged into 100 mmol.

In the next "click chemistry," the propargyl β-D-peracetyl glycoside **2a-d** (glucose, galactose, lactose, and xylose) were conjugated to AZT to produce the targeted compounds. To verify whether this reaction could be applied to the targeted compounds, we first used the reported Cu(I)-catalyzed click chemistry in DMF:H_2O system. The Cu(I) species was generated in situ using L-ascorbic acid sodium and $CuSO_4$. The reaction rate was quite slow and the starting material cannot be consumed completely. During the course of our endeavors, the THF:H_2O (1:1) solvent system was found to be more suitable for this reaction. After workup, the targeted compounds were obtained in over 80% yield. The 1,4-disubstituted 1,2,3-triazoles **4a-d** were obtained in complete selectivity. The characteristic proton H-6′ of 1,2,3-triazole was a single peak at about 7.67 ppm in the ^{1}H NMR spectrum. At last, the acetyl protecting group was removed by saturated ammonia in methanol in almost quantitive yield.

In conclusion, a series of 1,2,3-triazole linked oligosaccharide nucleosides were synthesized in high yield and selectivity. The Cu^I-catalyzed Huisgen [2+3] cycloaddition of azides and alkynes was demonstrated to be a powerful tool for constructing a nucleoside library.[17,18] We are approaching more diversity of nucleoside compounds using this "click chemistry."

EXPERIMENTAL

All chemicals were purchased from Sigma-Aldrich in China unless specified. NMR spectra: Bruker 400 MHz spectrometer; δ values in ppm relative to Me_4Si as internal standard, J values are in Hz. ESI mass spectra were acquired using a Bruker Esquire-LC ion trap mass spectrometer operated in positive ion mode.

General Procedure for the Synthesis of 4a-d via "Click Chemistry"

3′-Azido-2′-deoxythymine (0.134 g, 0.5 mmol) and the corresponding propargyl β-D-peracetyl-glycoside (0.5 mmol) were dissolved in THF (2 mL). The reaction mixture was stirred at room temperature for 10 minute while $CuSO_4 \cdot 5H_2O$ water solution (1.0 mL, 5%) and L-ascorbic acid sodium salt water solution (1.0 mL, 10%) were added. The reaction mixture was stirred until complete consumption of the starting material indicated by TLC analysis (24 hours). The solution was extracted with dichloromethane solution (3 × 50 mL). The organic phase was washed with saturated NaCl

(2 × 30 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to dryness in vacuo to give the product as white foam.

4a: 96% yield; IR (KBr) ν**:** 3463, 2111, 1757, 1695, 1472, 1372, 1230, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H, H-3), 7.67 (s, 1H, H-6′), 7.43 (s, H, H-6), 6.19 (t, J = 6.4 Hz, 1H, H-1′), 5.41–5.38 (m, 1H, H-3′), 5.15 (t, J = 9.5 Hz, 1H), 5.04 (t, J = 9.6 Hz, 1H), 4.94 (t, J = 8.7 Hz, 1H), 4.87 (d, J = 12.5 Hz, 1H, H-8a′), 4.78 (d, J = 12.5 Hz, 1H, H-8b′), 4.64 (d, J = 7.9 Hz, 1H, H-1″), 4.36 (m, 1H,H-4′), 4.10–4.21 (m, 2H, H-5′), 3.94 (d, J = 11.0Hz, 1H), 3.74–3.67 (m, 3H), 2.90 (m, 2H, H-2′), 2.03, 1.97, 1.95, 1.94 (4 × CH_3), 1.86 (s, 3H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.29, 169.70, 169.00, 168.96 (4 × C = O), 163.36 (C-4), 150.00 (C-2), 144.11 (C-7′), 137.17 (C-6), 122.67 (C-6′), 110.72 (C-5), 99.74 (C-1″), 87.81 (C-1′), 84.67 (C-4′), 72.20, 71.47, 70.76, 67.86, 62.61(C-8′), 61.32, 60.98 (C-5′), 58.82 (C-3′), 37.06 (C-2′), 20.26, 20.18, 20.07, 19.55 (4 × CH_3), 11.92 (C-7); MS (ES^+) m/z: 676 $[M+Na]^+$.

4b: 87.5% yield; IR (KBr) ν**:** 3449, 2114, 1751, 1698, 1473 × 1372, 1229, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H, H-3), 7.70 (s, 1H, H-6′), 7.48 (s, 1H, H-6), 6.23 (t, J = 6,4 Hz, 1H, H-1′), 5.42–5.38 (m, 1H, H-3′), 5.35 (d, J = 3.1 Hz, 1H), 5.15 (t, J = 8.0 Hz, 1H), 4.98 (dd, J = 3.3 Hz, J = 3.4 Hz, 1H), 4.91 (d, J = 12.5 Hz, 1H, H-8a′), 4.75 (d, J = 12.5 Hz, 1H, H-8b′), 4.61 (d, J = 8.0 Hz, 1H, H-1″), 4.35 (m, 1H, H-4′), 4.08–4.02 (m, 2H, H-5′), 3.95–3.90 (m, 3H), 3.74–3.72 (m, 1H), 2.89–2.87 (m, 2H, H-2′), 1.99, 1.98, 1.95, 1.92 (4 × CH_3), 1.84 (s, 3H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.57, 169.24, 169.13, 168.69 (4 × C = O), 163.06 (C-4), 149.61 (C-2), 143.60 (C-7′), 136.63 (C-6), 122.10 (C-6′), 110.20 (C-5), 99.59 (C-1″), 87.02 (C-1′), 84.19 (C-4′), 69.92, 69.81, 67.87, 66.13, 61.87 (C-8′), 60.45, 60.33 (C-5′), 58.37 (C-3′), 36.62 (C-2′), 19.78, 19.69, 19.63, 19.55 (4×CH_3), 11.41 (C-7); MS (ES^+) m/z: 676 $[M+Na]^+$.

4c: 43.5% yield; IR (KBr) ν**:** 3475, 2117, 1752, 1699, 1437, 1372, 1233, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H, H-3), 7.64 (s, 1H, H-6′), 7.40 (s, 1H, H-6), 6.18 (t, J = 6.3 Hz, 1H, H-1′), 5.37 (m, 1H, H-3′), 5.28 (d, J = 3.1 Hz, 1H), 5.13 (t, J = 9.3 Hz, 1H), 5.04 (t, J = 8.0 Hz, 1H), 4.91 (dd, J = 3.3 Hz, J = 3.3 Hz, 1H), 4.84 (t, J = 8.4 Hz, H), 4.83–4.79 (m, 1H), 4.57 (d, J = 7.9 Hz, 1H), 4.50 (d, J = 11.6 Hz, 1H, CHC$\underline{H_2}$O), 4.45 (d, J = 7.9 Hz, 1H, H-1″), 4.38–4.34 (m, 1H, H-4′), 4.08–3.98 (m, 4H), 3.94 (d, J = 11.5 Hz, 1H, H-8′), 3.83 (t, J = 6.8 Hz, 1H), 3.78–3.74 (m, 2H), 3.59–3.57 (m, H), 2.90 (t, J = 6.4 Hz, 2H, H-2′), 2.09, 2.06, 1.99, 1.98, 1.95, 1.90 (7 × CH_3), 1.87(s, 3H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.08, 169.89, 169.65, 169.60, 169.26, 169.26, 168.68 (7 × C = O), 163.15 (C-4), 149.91 (C-2), 144.20 (C-7′), 137.23 (C-6), 122.64 (C-6′), 110.76 (C-5), 100.49, 99.69 (C-1″), 88.06 (C-1′), 84.68 (C-4′), 75.49, 72.42, 72.18, 71.08, 70.44, 70.18, 68.67, 66.14, 62.82, 61.17 (C-8′), 61.10, 60.29 (C-5′), 58.83 (C-3′), 37.00 (C-2′), 20.54, 20.44, 20.28, 20.24, 20.13, 20.13, 20.02 (7 × CH_3), 11.94 (C-7); MS (ES^+) m/z: 964 $[M+Na]^+$.

4d: 96.9% yield; IR (KBr) *ν*: 3449, 2108, 1756, 1693, 1471, 1372, 1227, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H, H-3), 7.72 (s, 1H, H-6′), 7.52 (s, 1H, H-6), 6.24 (t, $J = 6.4$ Hz, 1H, H-1′), 5.41–5.39 (m, 1H, H-3′), 5.11 (t, $J = 8.7$ Hz, 1H), 4.83–4.89 (m, 3H), 4.69 (d, $J = 12.4$ Hz, 1H, H-8′), 4.60 (d, $J = 6.8$ Hz, 1H, H-1″), 4.34 (m, 1H, H-4′), 4.08 (dd, $J = 5.1$ Hz, $J = 5.0$ Hz, 2H, H-5′), 3.91 (d, $J = 12.2$ Hz, 1H), 3.74–3.66 (m, 3H), 2.88–2.86 (m, 2H, H-2′), 1.98, 1.97, 1.95 ($3 \times CH_3$), 1.82 (s, 3H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.05, 169.96, 169.68 ($3 \times C=O$), 164.17 (C-4), 150.64 (C-2), 144.50 (C-7′), 137.55 (C-6), 123.06 (C-6′), 111.09 (C-5), 100.01 (C-1″), 87.66 (C-1′), 85.14 (C-4′), 71.35, 70.51, 68.81, 62.38 (C-8′), 62.14, 61.35 (C-5′), 59.35 (C-3′), 37.67 (C-2′), 20.71, 20.67, 20.67 ($3 \times CH_3$),12.38 (C-7); MS (ES^+) m/z: 604 $[M+Na]^+$.

General Procedure for the Deprotection Acetyl Group to Afford 5a-d

The corresponding nucleoside **4a-d** (70 mg) was dissolved in freshly prepared saturated NH_3 in MeOH (5 mL). The solution was stirred at room temperature for 24 hours while starting materials completely consumed. The solvent was evaporated using water pump and then in high vacuum. The compounds **5a-d** were obtained in almost quantitive yield.

5a: ^1H NMR (400 MHz, DMSO) δ 8.32 (s, 1H, H-6′), 7.84 (s, 1H, H-6), 6.43 (t, $J = 6.6$ Hz, 1H, H-1′), 5.41–5.38 (m, 1H, H-3′), 4.90 (d, $J = 12.2$ Hz, 1H, H-8a′), 4.68 (d, $J = 12.2$ Hz, 1H, H-8b′), 4.31 (d, $J = 7.8$ Hz, 1H, H-1″), 4.25–4.22 (m, 1H, H-4′), 3.75–3.72 (m, 2H, H-5′), 3.20–3.16 (m, 2H), 3.08 (t, $J = 9.2$ Hz, 1H), 3.01 (t, $J = 8.4$ Hz, 1H), 2.77–2.67 (m, 2H, H-2′), 1.83 (s, 3H, H-7); ^{13}C NMR (100 MHz, DMSO) δ 163.73 (C-4), 150.38 (C-2), 144.08 (C-7′), 136.21 (6-C), 123.87 (C-6′), 109.63 (C-5), 102.20 (C-1″), 84.42 (C-4′), 83.93 (C-1′), 76.82, 76.53, 73.30, 70.01, 61.54 (C-8′), 61.07, 60.65 (C-5′), 59.15 (C-3′), 37.10 (C-2′), 12.15 (C-7); MS (ES^+) m/z: 508 $[M+Na]^+$.

5b: ^1H NMR (400 MHz, DMSO) δ 8.26 (s, 1H, H-6′), 7.80 (s, 1H, H-6), 6.40 (t, $J = 6.6$ Hz, 1H, H-1′), 5.35–5.33 (m, 1H, H-3′), 4.84 (d, $J = 12.2$ Hz, 1H, H-8a′), 4.62 (d, $J = 12.2$ Hz, 1H, H-8b′), 4.23–4.19 (m, 2H), 3.70–3.58 (m, 3H), 3.52 (d, $J = 6.1$ Hz, 2H), 3.38 (t, $J = 6.1$ Hz, 1H), 3.29 (m, 2H), 2.71–2.63 (m, 2H, H-2′), 1.79 (s, 3H, H-7); ^{13}C NMR (100 MHz, DMSO) δ 164.61 (C-4), 151.18 (C-2), 145.02 (C-7′), 137.10 (C-6), 124.70 (C-6′), 110.54 (C-5), 103.56 (C-1″), 85.23 (C-4′), 84.82 (C-1′), 76.01, 73.98, 71.18, 68.89, 62.23 (C-8′), 61.44, 61.28 (C-5′), 60.04 (C-3′), 37.91 (C-2′), 12.96 (C-7); MS (ES^+) m/z: 508 $[M+Na]^+$.

5c: ^1H NMR (400 MHz, DMSO) δ 8.26 (s, 1H, H-6′), 7.79 (s, 1H, H-6), 6.40 (t, $J = 6.6$ Hz, 1H, H-1′), 5.35–5.31 (m, 1H, H-3′), 4.86 (d, $J = 12.1$ Hz, 1H, H-8a′), 4.64 (d, $J = 12.2$ Hz, 1H, H-8b′), 4.35 (d, $J = 7.8$ Hz, 1H, H-1″), 4.20 (m, 2H), 3.69–3.60 (m, 5H), 3.50–3.44 (m, 3H), 3.32–3.30 (m, 5H), 3.04 (t, $J = 7.9$ Hz, 1H), 2.71–2.63 (m, 2H, H-2′), 1.79 (s, 3H, H-7); ^{13}C

NMR (100 MHz, DMSO) δ 164.57 (C-4), 151.15 (C-2), 144.79 (C-7′), 137.07 (C-6), 127.70 (C-6′), 110.51 (C-5), 104.47, 102.64 (C-1″), 85.20 (C-4′), 84.80 (C-1′), 81.24, 76.19, 75.62, 75.51, 73.78, 73.72, 71.20, 68.80, 62.42 (C-8′), 61.42, 61.10, 61.10 (C-5′), 60.05 (C-3′), 37.88 (C-2′), 12.93 (C-7); MS (ES^+) m/z: 670 $[M+Na]^+$.

5d: ^1H NMR (400 MHz, DMSO) δ 8.25 (s, 1H, H-6′), 7.80 (s, 1H, H-6), 6.40 (t, J = 6.6 Hz, 1H, H-1′), 5.36–5.34 (m, H, H-3′), 4.79 (d, J = 12.1 Hz, 1H, H-8a′), 4.60 (d, J = 12.1 Hz, 1H, H-8b′), 4.24 (d, J = 7.6 Hz, 1H, H-1″), 4.20 (m, 1H, H-4′), 3.29 (m, 1H), 3.14–3.07 (m, 3H), 2.97 (t, J = 8.3 Hz, 1H), 2.69–2.58 (m, 2H, H-2′), 1.79 (s, 3H, H-7); ^{13}C NMR (100 MHz, DMSO) δ 163.27 (C-4), 149.84 (C-2), 143.41 (C-7′), 135.74 (C-6), 123.29 (C-6′), 109.19 (C-5), 102.24 (C-1″), 83.88 (C-4′), 83.46 (C-1′), 75.69, 72.49, 68.84, 65.03, 60.86 (C-8′), 60.08 (C-5′), 58.72 (C-3′), 36.56 (C-2′), 11.60 (C-7); MS (ES^+) m/z: 478 $[M+Na]^+$.

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