Synthesis of Nucleoside Conjugates as Potential Inhibitors of Glycogen Phosphorylase

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Abstract: Click chemistry has been successfully used for the synthesis of novel nucleoside conjugates between uridine and *N*-acetylglucosamine or oleanolic acid derivatives. These molecules displayed micromolar inhibition towards glycogen phosphorylase.

Key words: bioorganic chemistry, carbohydrates, click chemistry, inhibitors, nucleosides

Nucleosides are components of nucleic acids. They also exist in other natural compounds like complex nucleoside antibiotics.[1] Synthesis of modified nucleosides as well as of their conjugates is of interest for medical, biochemical, and physiological applications. For example, nucleoside conjugates with sugars,[2] sterols,[3] lipids,[4] amino acids,[5] and pleuromutilin[6] have been designed and synthesized for various biological applications.

Glycogen phosphorylase (GP) is the enzyme responsible for glycogen breakdown to produce glucose and related metabolites to supply energy.[7] Due to the key role of GP in the modulation of glycogen metabolism, inhibition of GP has been regarded as an effective therapeutic approach for the treatment of diseases caused by abnormalities in glycogen metabolism, such as type 2 diabetes, myocardial ischemia, and tumors. Most notably, GP inhibitors lower glucose in diabetic animal models, both acutely and chronically, and demonstrate potential for a beneficial effect on cardiovascular risk factors.[8] This information has bolstered interest and promise in glycogen phosphorylase inhibitors as potential new hypoglycaemic agents for the treatment of type 2 diabetes mellitus. Several classes of GP inhibitor have been reported, including glucose and derivatives, iminosugars, hydantocidins, caffeine, flavopiridol, etc.[9] We have recently reported that oleanolic acid and related pentacyclic triterpenes represented a new class of inhibitors of glycogen phosphorylases.[10] GP is an allosteric enzyme that exists in two interconvertible forms, GPa (the phosphorylated form, high activity, high substrate affinity) and GPb (the nonphosphorylated form, low activity, low substrate affinity). Screening of our previously synthesized sugar–nucleoside conjugates[11] showed that compounds **1** and **2** displayed moderate inhibition towards GPa (Figure 1). To the best of our knowledge, uridine derivatives have not been reported as GP inhibitors. As an ongoing program on the research of novel GP inhibitors,[12] we decided to synthesize novel uridine conjugates with *N*-acetylglucosamine or oleanolic acid derivatives, by employing the very efficient click chemistry.[13]

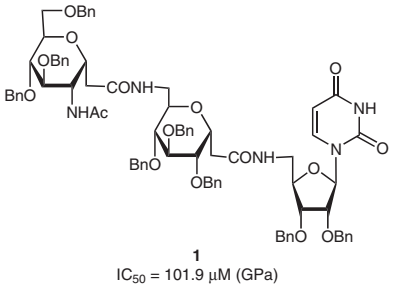

Figure 1 Structure of sugar–nucleoside conjugates

To prepare uridine conjugates with click chemistry, we chose to introduce either an alkyne or an azide group at the 5′-position of uridine. Both isopropylidene- or benzyl-protected uridine derivatives have been used as starting materials. Compound **3** was prepared according to known procedures.[14] The perbenzylated uridine **7**[15] was converted into 5′-*O*-propargyl derivative **8** by treatment with propargyl bromide and sodium hydride in 63% yield (Scheme 1). Click reaction of alkynes **3** or **8** with azido derivative of *N*-acetylglucosamine **4**[2b] led to the corresponding conjugates **5** and **9** in 75% and 60% yields, respectively. Deprotection of the isopropylidene group in **5** by trifluoroacetic acid in dichloromethane afforded com-

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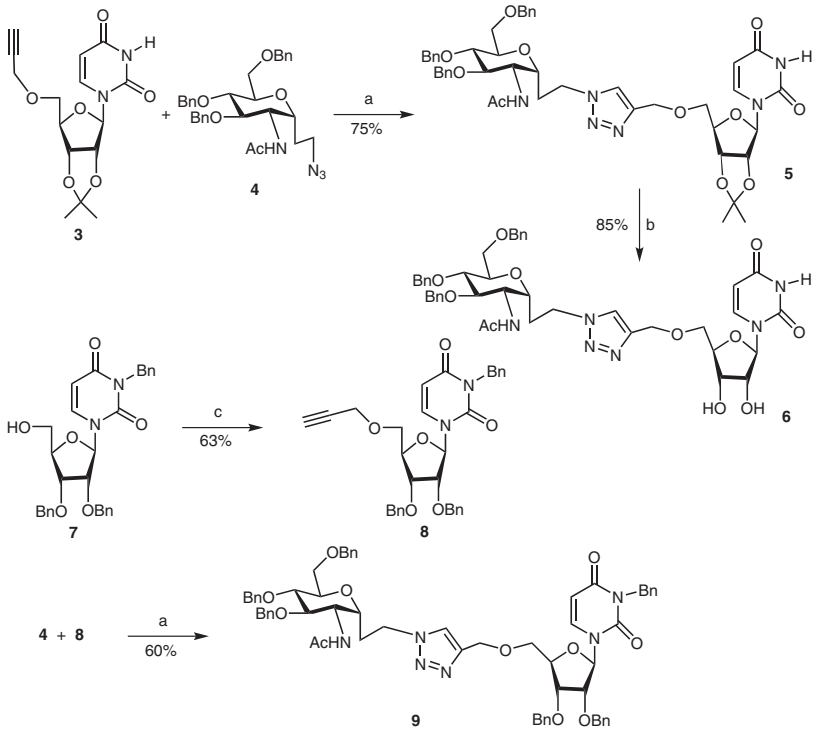


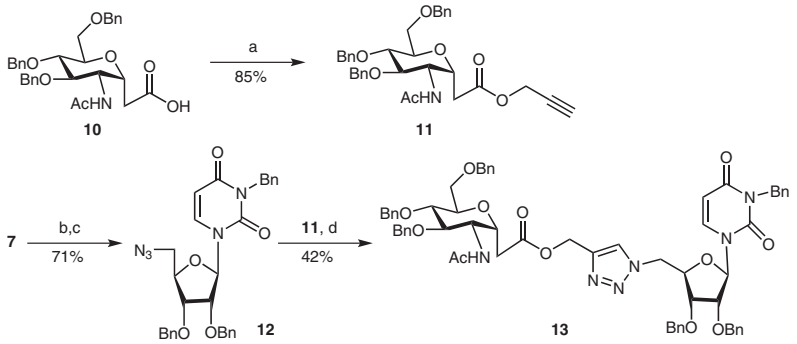
Scheme 1 *Reagents and conditions:* (a) sodium ascorbate, $CuSO_4$, CH_2Cl_2, H_2O; (b) TFA, CH_2Cl_2; (c) propargyl bromide, NaH, THF.

pound **6**. However, debenzylation of **5**, **6**, and **9** under catalytic hydrogenation conditions failed.

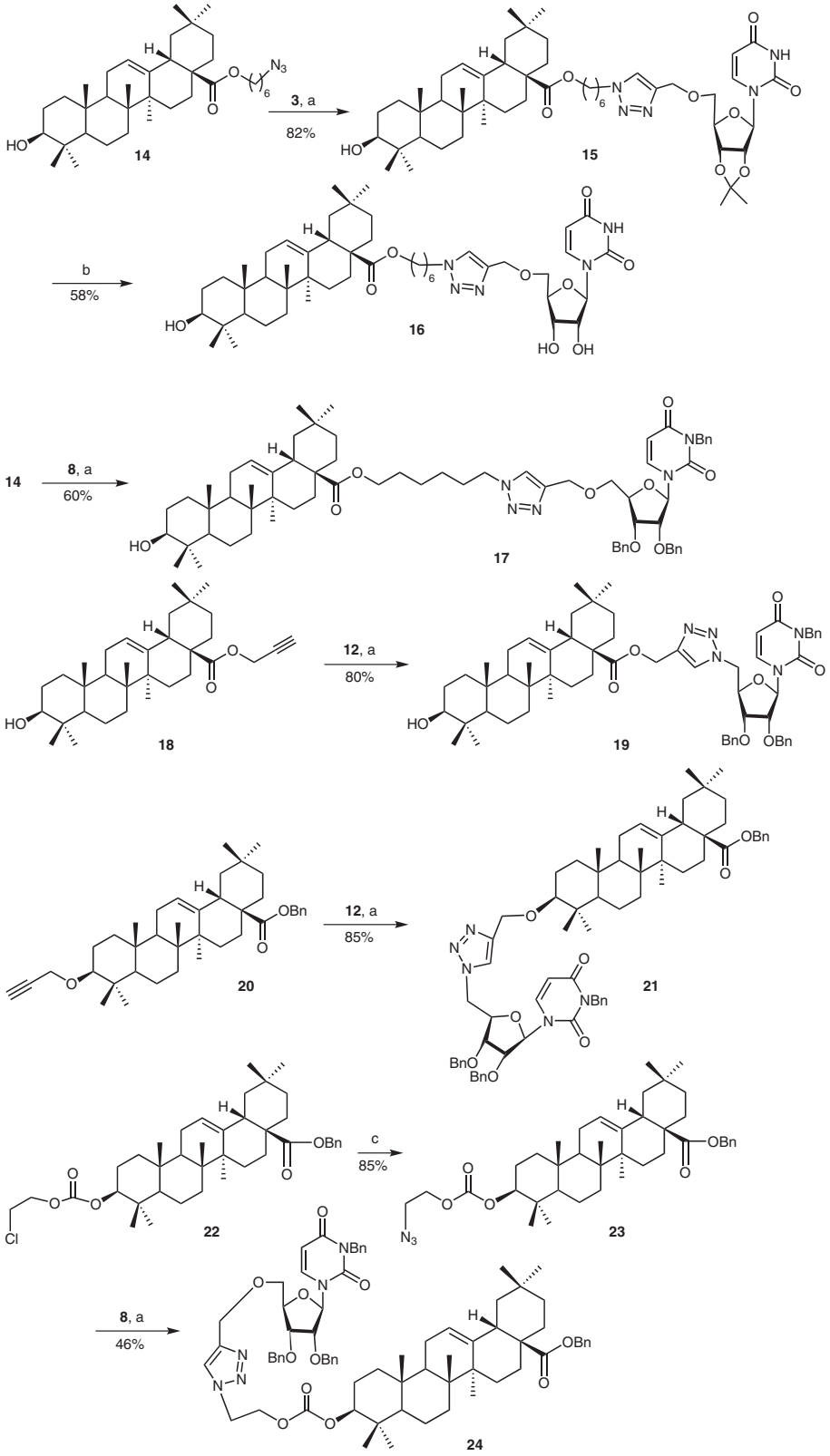
We have also prepared sugar–nucleoside conjugate **13** with an ester linkage (Scheme 2). For this synthesis, the known carboxylic acid **10**[11] was converted into propargyl ester **11** in 85% yield. Uridine **7** was transformed into its azido derivative **12** through activation as the mesylate followed by nucleophilic substitution with sodium azide. Copper(I)-catalyzed Huisgen cycloaddition between **11** and **12** led to the desired compound **13** in 42% yield. Once again, we failed to debenzylate the nucleoside conjugate **13**.

For the synthesis of uridine–oleanolic acid conjugates, the azido derivative of oleanolic acid **14**[12] was reacted with alkyne **3** catalyzed by sodium ascorbate/copper sulfate to afford the conjugate **15** in 82% yield (Scheme 3). Deprotection under acidic condition led to the fully deprotected compound **16**. Click reaction of **14** with perbenzylated alkyne **8** gave the conjugate **17**. We have also prepared compound **19** with a shorter linker between uridine and oleanolic acid, by treating propargyl ester **18**[12] with azide **12**. Reaction of **12** with 3-*O*-propargyloleanoate **20**[12] led to the conjugate **21** linked at the 3-position of oleanolic acid. The carbonate derivative of oleanolic acid **22**[12] has been converted into its azido derivative **23** with sodium azide. Cycloaddition reaction between **23** and **8** allowed the synthesis of the conjugate **24**.

The above synthesized conjugates were evaluated in the enzyme inhibition assay against rabbit muscle glycogen phosphorylase a (RMGPa) (Table 1), which shared considerable sequence similarity with human liver GPa. As described previously,[16] the activity of rabbit muscle GPa was measured through detecting the release of phosphate from glucose-1-phosphate in the direction of glycogen synthesis. Among the nucleoside derivatives **3**, **7**, **8**, and **12**, the isopropylidene-protected compound **3** exhibited a



Scheme 2 *Reagents and conditions:* (a) propargyl bromide, K_2CO_3, DMF; (b) MsCl, Et_3N, CH_2Cl_2; (c) NaN_3, DMF; (d) sodium ascorbate, $CuSO_4$, CH_2Cl_2, H_2O.



Scheme 3 *Reagents and conditions:* (a) sodium ascorbate, $CuSO_4$, CH_2Cl_2, H_2O; (b) TFA, CH_2Cl_2; (c) NaN_3, DMF.

micromolar inhibition of GPa. However, the corresponding glycoconjugate **5** was less active. Nevertheless, partially deprotected compound **6** was shown to be the most potent inhibitor, with an IC_{50} value of 13.6 μM. The glycoconjugates with ether **9** or ester **13** linkages showed similar inhibitory activities. For the nucleoside–oleanolic acid conjugates, the fully deprotected compound **16** was more potent (IC_{50} = 15.5 μM). No significant difference existed between different conjugates. With the exception

Table 1 IC_{50} Values for RMGPa Inhibition Assay Results

Compd	GPa IC_{50}[a] (μM)	Compd	GPa IC_{50}[a] (μM)
3	55.1	**13**	48.7
5	120.3	**15**	35.7
6	13.6	**16**	15.5
7	na[b]	**17**	85.5
8	na[b]	**19**	65.1
9	55.6	**21**	70.2
11	na[b]	**24**	na[b]
12	na[b]	caffeine	98.5

[a] Values are the mean of 3 experiments.
[b] na = no activity.

of **24**, all these molecules inhibited GPa in the micromolar range.

In summary, sugar–nucleoside and oleanolic acid–nucleoside conjugates have been readily prepared with click chemistry. These novel molecules have been tested as potential glycogen phosphorylase inhibitors. Micromolar inhibition was obtained with most synthetic nucleoside conjugates. These results enlarge the application of nucleoside conjugates in molecular design.

All air-sensitive reactions were carried out under N_2. Column chromatography was performed on E. Merck Silica Gel 60 (230–400 mesh); petroleum ether = PE. Analytical TLC was performed on E. Merck aluminum percolated plates of Silica Gel 60F-254 with detection by UV and by spraying with 3 M H_2SO_4 and heating at 300 °C for ~2 min. NMR spectra were recorded on a Bruker AV-300 or Jeol DX 400 spectrometers in $CDCl_3$. IR spectra were recorded on Shimadzu FTIR-8400S spectrophotometer. Optical rotations were measured using a Jasco P-2000 polarimeter. HRMS were recorded on a MA1212 instrument using standard conditions (ESI, 70 eV).

Click Reaction; General Procedure

To a soln of alkyne (0.28 mmol) and azide (0.28 mmol) in CH_2Cl_2 (2 mL) and H_2O (2 mL) was added $CuSO_4 \cdot 5\ H_2O$ (0.2 mmol) and sodium ascorbate (0.4 mmol). The resulting soln was stirred at r.t. for 8 h. The mixture was extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography.

Sugar–Nucleoside Conjugate 5

Prepared from **3** (90 mg, 0.28 mmol) and **4** (150 mg, 0.28 mmol) according to the general procedure. The residue was purified by column chromatography (CH_2Cl_2–MeOH, 20:1) to afford **5** (180 mg, 75%) as a white solid; R_f = 0.15 (CH_2Cl_2–MeOH, 30:1).

$[\alpha]_D^{22}$ –14.7 (*c* 0.29, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 1.88 (s, 3 H, CH_3), 1.92–2.01 (m, 2 H, CH_2), 3.51 (t, *J* = 1.6 Hz, 1 H, H3″), 3.61–3.75 (m, 4 H, CH_2N, H5′), 3.90 (dd, *J* = 7.8, 10.1 Hz, 1 H, H4″), 3.95–3.98 (m, 1 H, H6″a), 4.18 (m, 1 H, H6″b), 4.28 (t, *J* = 6.9 Hz, 1 H, H4′), 4.38–4.62 (m, 11 H, H1″, H2″, H5″, OCH_2, 3 $PhCH_2$), 4.78 (m, 2 H, H2′, H3′), 5.55 (dd, *J* = 2.1, 8.0 Hz, 1 H, H5), 5.68 (d, *J* = 1.4 Hz, 1 H, H1′), 7.01 (d, *J* = 9.2 Hz, 1 H, NH), 7.20–7.34 (m, 15 H, Ph), 7.43 (d, *J* = 8.2 Hz, 1 H, H6), 7.46 (s, 1 H, NCH-triazole), 9.61 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 23.3, 25.3, 27.2, 32.2, 47.4, 48.0, 65.0, 66.1, 67.4, 70.5, 72.2, 72.3, 73.1, 73.5, 74.0, 74.8, 81.2, 85.5, 86.3, 94.6, 101.4, 113.8, 122.6, 127.7, 127.8, 128.0, 128.3, 128.5, 128.6, 128.7, 137.1, 137.5, 138.1, 141.4, 144.0, 150.1, 163.6, 170.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{46}H_{54}N_6NaO_{11}$: 889.3748; found: 889.3743.

Sugar–Nucleoside Conjugate 6

To a soln of **5** (0.12 g, 0.14 mmol) in CH_2Cl_2 (5 mL) was added dropwise TFA (0.1 mL, 1.4 mmol). After stirring at r.t. for 8 h, the mixture was concentrated. The residue was taken up in EtOAc (20 mL), and washed with H_2O and brine, dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (CH_2Cl_2–MeOH, 18:1) afforded **6** (97 mg, 85%) as a white solid; R_f = 0.48 (CH_2Cl_2–MeOH, 10:1).

$[\alpha]_D^{22}$ –3.1 (*c* 0.65, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (s, 3 H, CH_3), 1.97 (br s, 2 H, CH_2), 3.49 (br s, 1 H, H3″), 3.59–3.64 (m, 3 H, CH_2N, H5′a), 3.75 (d, *J* = 9.6 Hz, 1 H, H5′b), 3.85 (dd, *J* = 7.8, 10.1 Hz, 1 H, H4″), 3.92–3.93 (m, 1 H, H4′), 4.15–4.19 (m, 5 H, H2′, H3′, H2″, H6″), 4.39–4.60 (m, 11 H, 3 $PhCH_2$, CH_2O, H1″, H2″, H5″), 5.53 (d, *J* = 6.9 Hz, 1 H, H5), 5.83 (s, 1 H, H1′), 6.90 (d, *J* = 8.2 Hz, 1 H, NH), 7.18–7.32 (m, 15 H, Ph), 7.58 (s, 1 H, NCH-triazole), 7.73 (d, *J* = 7.8 Hz, 1 H, H6), 10.1 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2, 29.8, 31.8, 47.2, 48.4, 64.4, 66.0, 67.6, 69.5, 71.0, 72.3, 72.4, 73.2, 73.6, 74.3, 74.7, 75.3, 84.1, 90.2, 102.2, 123.4, 127.8, 127.86, 127.91, 128.0, 128.1, 128.3, 128.5, 128.6, 128.7, 137.2, 137.5, 138.0, 140.9, 143.9, 151.3, 164.1, 171.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{43}H_{50}N_6NaO_{11}$: 849.3435; found: 849.3430.

3-Benzyl-2′,3′-di-*O*-benzyl-5′-*O*-propargyluridine (8)

A soln of **7** (1.8 g, 3.5 mmol) in anhyd THF (5 mL) was added dropwise to a suspension of NaH (60%, 280 mg, 7.0 mmol) in anhyd THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then propargyl bromide (0.58 mL, 5.0 mmol) was added and the mixture was stirred at r.t. for 12 h. MeOH (0.3 mL) was added at 0 °C. The mixture was concentrated and diluted with H_2O–EtOAc (1:2, 30 mL). After separation, the organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (EtOAc–PE, 1:4) afforded **8** (1.2 g, 63%) as a yellow oil; R_f = 0.74 (EtOAc–PE, 1:1).

$[\alpha]_D^{22}$ +122.1 (*c* 0.86, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (t, *J* = 2.3 Hz, 1 H, CH≡C), 3.68 (dd, *J* = 1.8, 11.0 Hz, 1 H, H5′a), 3.88–3.91 (m, 2 H, H2′, H5′b), 3.96 (dd, *J* = 4.6, 7.8 Hz, 1 H, H3′), 4.12 (d, *J* = 2.3 Hz, 2 H, CH_2O), 4.30–4.34 (m, 2 H, H4′, PhCH), 4.45 (d, *J* = 11.5 Hz, 1 H, PhCH), 4.80 (d, *J* = 12.4 Hz, 2 H, $PhCH_2$), 5.12 (s, 2 H, $PhCH_2$), 5.67 (d, *J* = 8.3 Hz, 1 H, H5), 6.04 (d, *J* = 1.8 Hz, 1 H, H1′), 7.22–7.52 (m, 15 H, Ph), 7.81 (d, *J* = 8.2 Hz, 1 H, H6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.0 (NCH_2), 58.6 (OCH_2), 67.5 (C5′), 71.5 (OCH_2), 72.3 (OCH_2), 74.3 (C3′), 75.1 (CH≡), 78.6 (C2′), 78.8 (≡C), 81.0 (C4′), 89.0 (C1′), 101.4 (C5), 127.6, 127.7, 127.9, 128.0, 128.4, 128.7, 129.1 (CH-Ph), 136.8, 137.2, 137.3 (C_{ipso}-Ph), 137.8 (C6), 150.8 (C2), 162.7 (C4).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{32}N_2NaO_6$: 575.2158; found: 575.2153.

Sugar–Nucleoside Conjugate 9

Prepared from **4** (100 mg, 0.18 mmol) and **8** (100 mg, 0.18 mmol) according to the general procedure. The residue was purified by column chromatography (CH_2Cl_2–MeOH, 40:1) to afford **9** (120 mg, 60%) as a light yellow solid; R_f = 0.43 (CH_2Cl_2–MeOH, 30:1).

$[\alpha]_D^{22}$ +79.0 (*c* 0.37, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (s, 3 H, CH_3), 2.02–2.03 (m, 2 H, CH_2), 3.54 (t, *J* = 3.7 Hz, 1 H, H3″), 3.63–3.67 (m, 3 H, CH_2N, H5′a), 3.83–3.93 (m, 3 H, H2′, H3′, H5′b), 4.00 (m, 2 H, H4″, H6″a), 4.22–4.32 (m, 3 H, H1″, H2″, H6″b), 4.38–4.63 (m, 12 H, H5″, H4′, OCH_2, 4 $PhCH_2$), 4.78 (d, *J* = 11.9 Hz, 1 H, PhCH), 4.81 (d, *J* = 12.4 Hz, 1 H, PhCH), 5.05 (d, *J* = 14.2 Hz, 1 H, PhCH), 5.08 (d, *J* = 13.8 Hz, 1 H, PhCH), 5.36 (d, *J* = 7.3 Hz, 1 H, H5), 6.00 (s, 1 H, H1′), 6.97 (d, *J* = 9.2 Hz, 1 H, NH), 7.20–7.47 (m, 31 H, NCH-triazole, Ph), 7.87 (d, *J* = 6.9 Hz, 1 H, H6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 21.0, 23.2, 31.5, 43.9, 48.6, 60.4, 66.6, 67.7, 67.8, 71.4, 72.1, 72.6, 72.7, 73.2, 74.2, 75.3, 78.5, 81.2, 89.1, 100.8, 127.5, 127.6, 127.65, 127.7, 127.8, 127.9, 127.92, 128.0, 128.1, 128.2, 128.4, 128.45, 128.5, 128.6, 128.7, 128.9, 136.6, 137.16, 137.19, 137.4, 137.5, 137.9, 138.3, 150.6, 162.8, 170.2, 171.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{64}H_{68}N_6NaO_{11}$: 1119.4844; found: 1119.4838.

Propargyl [2-(Acetylamino)-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl]acetate (11)

To a soln of **10** (49 mg, 0.09 mmol) in DMF (0.5 mL) was added K_2CO_3 (27 mg, 0.19 mmol) and propargyl bromide (80% wt% in toluene, 0.22 mL) successively. The mixture was stirred at r.t. for 8 h, 1 M HCl (0.3 mL) was added, and it was diluted with EtOAc (30 mL) and washed successively with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated and then it was purified by flash column chromatography (EtOAc–PE, 3:7) to give **11** (45 mg, 85%) as a light yellow oil; R_f = 0.22 (EtOAc–PE, 3:7).

$[\alpha]_D^{22}$ +5.4 (*c* 0.77, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (s, 3 H, CH_3), 2.39 (t, *J* = 2.3 Hz, 1 H, CH≡), 2.50 (s, 1 H, H2a), 2.52 (d, *J* = 3.2 Hz, 1 H, H2b), 3.63–3.64 (m, 1 H, H3′), 3.68 (m, 1 H, H4′), 3.83–3.88 (m, 2 H, H6′), 4.23–4.26 (m, 2 H, H2′, H5′), 4.60–4.67 (m, 9 H, 3 OCH_2, CO_2CH_2, H1′), 6.70 (d, *J* = 9.6 Hz, 1 H, NH), 7.24–7.36 (m, 15 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 (CH_3), 37.0 (C2), 47.2 (C2′), 52.2 (OCH_2), 65.3 (C1′), 67.9 (C6′), 71.8 (OCH_2), 72.0 (OCH_2), 72.8 (C3′), 73.5 (OCH_2), 74.1 (C4′), 75.0 (CH≡), 75.2 (C5′), 77.7 (≡C), 127.66, 127.7, 127.9, 128.0, 128.2, 128.5, 128.6, 128.7 (CH-Ph), 137.3, 137.5, 138.3 (C_{ipso}-Ph), 170.0 (CO), 170.3 (CO).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{34}H_{37}NNaO_7$: 594.2468; found: 594.2468.

5′-Azido-3-benzyl-2′,3′-di-*O*-benzyl-5′-deoxyuridine (12)

MsCl (0.38 mL, 4.9 mmol) was added to a soln of **7** (1.8 g, 3.5 mmol) and Et_3N (0.88 mL, 6.3 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The ice bath was removed and stirring was continued at r.t. for 14 h. After which MeOH (0.3 mL) was added, the soln was concentrated. The residue was dissolved in EtOAc (50 mL) and washed successively with H_2O, 5% $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give an oil that was used directly for next step without purification. This mesylate was dissolved in DMF (25 mL), NaN_3 (1.14 g, 18 mmol) was added. The mixture was stirred at 90 °C for 12 h and then concentrated. The residue was dissolved in EtOAc (50 mL) and washed successively with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (EtOAc–PE, 1:3) gave **12** (1.35 g, 71%) as a colorless oil; R_f = 0.38 (EtOAc–PE, 1:1).

$[\alpha]_D^{22}$ +127.9 (*c* 0.27, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (dd, *J* = 3.2, 13.7 Hz, 1 H, H5′a), 3.79–3.83 (m, 2 H, H3′, H5′b), 3.92 (dd, *J* = 1.6, 5.3 Hz, 1 H, H2′), 4.26–4.30 (m, 2 H, H4′, PhCH), 4.46 (d, *J* = 11.4 Hz, 1 H, PhCH), 4.78 (s, 2 H, $PhCH_2$), 5.12 (s, 2 H, $PhCH_2$), 5.74 (d, *J* = 8.3 Hz, 1 H, H5), 5.95 (d, *J* = 1.4 Hz, 1 H, H1′), 7.22–7.52 (m, 16 H, H6, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.2 (NCH_2), 50.9 (C5′), 71.8 (OCH_2), 72.5 (OCH_2), 75.1 (C3′), 78.1 (C2′), 79.7 (C4′), 90.1 (C1′), 102.1 (C5), 127.8, 127.9, 128.3, 128.5, 128.6, 128.8, 129.3 (CHPh), 136.7, 137.0, 137.1, 137.4 (C_{ipso}-Ph), 137.4 (C6), 150.7 (C2), 162.5 (C4).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{29}N_5NaO_5$: 562.2066; found: 562.2061.

Sugar–Nucleoside Conjugate 13

Prepared from **11** (100 mg, 0.17 mmol) and **12** (90 mg, 0.17 mmol) according to the general procedure. The residue was purified by column chromatography (CH_2Cl_2–MeOH, 40:1) to afford **13** (80 mg, 42%) as a white solid; R_f = 0.4 (CH_2Cl_2–MeOH, 30:1).

$[\alpha]_D^{22}$ +50.4 (*c* 0.35, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76 (s, 3 H, CH_3), 2.40–2.53 (m, 2 H, CH_2CO_2), 3.56–3.57 (m, 1 H, H3″), 3.64–3.65 (m, 1 H, H4″), 3.75–3.82 (m, 3 H, H6″, H3′), 3.91 (dd, *J* = 2.7, 5.5 Hz, 1 H, H2′), 4.19–4.24 (m, 2 H, H2″, H5″), 4.36–4.70 (m, 14 H, H1″, H4′, H5′, 5 $PhCH_2$), 5.02 (d, *J* = 13.7 Hz, 1 H, PhCH), 5.06 (d, *J* = 13.7 Hz, 1 H, PhCH), 5.18 (d, *J* = 12.8 Hz, 1 H, CO_2CH), 5.19 (d, *J* = 12.8 Hz, 1 H, CO_2CH), 5.63 (d, *J* = 8.3 Hz, 1 H, H5), 5.77 (d, *J* = 2.8 Hz, 1 H, H1′), 6.48 (d, *J* = 8.3 Hz, 1 H, H6), 6.72 (d, *J* = 9.6 Hz, 1 H, NH), 7.14–7.46 (m, 30 H, Ph), 7.54 (s, 1 H, NCH-triazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 36.9, 44.2, 47.2, 50.4, 57.8, 65.2, 68.0, 71.9, 72.1, 72.2, 72.7, 72.9, 73.5, 74.0, 75.3, 76.1, 79.6, 91.6, 102.3, 125.5, 127.7, 127.8, 127.9, 128.0, 128.2, 128.4, 128.49, 128.54, 128.6, 128.7, 129.1, 129.8, 136.6, 136.9, 137.0, 137.3, 137.5, 137.9, 138.2, 143.2, 150.4, 162.2, 170.1, 170.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{64}H_{66}N_6NaO_{12}$: 1133.4636; found: 1133.4632.

Oleanolic Acid–Nucleoside Conjugate 15

Prepared from **3** (60 mg, 0.19 mmol) and **14** (110 mg, 0.19 mmol) according to the general procedure. The residue was purified by column chromatography (CH_2Cl_2–MeOH, 30:1) to afford **15** (140 mg, 82%) as a white solid; R_f = 0.2 (CH_2Cl_2–MeOH, 30:1).

$[\alpha]_D^{22}$ +23.2 (*c* 0.29, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69, 0.75, 0.89, 0.96, 1.10, 1.31, 1.55 (7 s, 21 H, 7 CH_3), 0.87 (s, 6 H, 2 CH_3), 0.69–1.98 (m, 30 H), 2.82–2.84 (m, 1 H, H18″), 3.18–3.21 (m, 1 H, H3″), 3.70–3.81 (m, 2 H, H5′), 3.98 (t, *J* = 6.4 Hz, 2 H, NCH_2), 4.31–4.36 (m, 3 H, H4′, CO_2CH_2), 4.64 (s, 2 H, OCH_2), 4.76 (br s, 2 H, H2′, H3′), 5.25 (br s, 1 H, H12″), 5.64 (d, *J* = 8.2 Hz, 1 H, H5), 5.85 (s, 1 H, H1′), 7.47 (s, 1 H, NCH-triazole), 7.53 (d, *J* = 8.2 Hz, 1 H, H6), 8.78 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 15.4, 15.7, 17.1, 18.4, 23.1, 23.5, 23.7, 25.4, 25.9, 26.3, 27.2, 27.3, 27.7, 28.2, 28.5, 30.3, 30.8, 32.6, 32.8, 33.2, 33.9, 37.1, 38.5, 38.8, 39.4, 41.4, 41.8, 45.9, 46.8, 47.7, 50.4, 55.3, 60.5, 64.0, 64.7, 70.5, 79.1, 81.0, 85.0, 85.7, 93.1, 102.2, 114.3, 122.4, 141.5, 143.9, 150.1, 163.1, 177.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{51}H_{77}N_5NaO_9$: 926.5619; found: 926.5614.

Oleanolic Acid–Nucleoside Conjugate 16

To a soln of **15** (90 mg, 0.10 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.07 mL, 0.9 mmol). The mixture was stirred at r.t. for 8 h and

then concentrated. The residue was taken up in EtOAc (20 mL), and washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (CH_2Cl_2–MeOH, 18:1) afforded **16** (50 mg, 58%) as a white solid; R_f = 0.3 (CH_2Cl_2–MeOH, 10:1).

$[\alpha]_D^{22}$ +28.9 (*c* 0.28, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.69, 0.75, 0.86, 0.88, 0.90, 0.96, 1.10 (7 s, 21 H, 7 CH_3), 0.69–1.98 (m, 30 H), 2.82 (dd, *J* = 4.1, 13.7 Hz, 1 H, H18″), 3.18 (dd, *J* = 4.6, 10.5 Hz, 1 H, H3″), 3.72 (d, *J* = 9.2 Hz, 1 H, H5′a), 3.85 (d, *J* = 9.2 Hz, 1 H, H5′b), 2.97 (t, *J* = 6.4 Hz, 2 H, NCH_2), 4.19–4.22 (m, 3 H, H2′, H3′, H4′), 4.35 (t, *J* = 7.3 Hz, 2 H, CO_2CH_2), 4.67 (s, 2 H, OCH_2), 5.25 (br s, 1 H, H12″), 5.60 (d, *J* = 7.8 Hz, 1 H, H5), 5.87 (s, 1 H, H1′), 7.55 (s, 1 H, NCH-triazole), 7.83 (d, *J* = 8.2 Hz, 1 H, H6), 10.03 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 15.7, 17.1, 18.4, 23.1, 23.5, 23.7, 25.6, 26.0, 26.3, 27.2, 27.7, 28.2, 28.5, 30.3, 30.8, 32.6, 32.8, 33.2, 33.9, 37.1, 38.5, 38.8, 39.4, 41.4, 41.8, 45.9, 46.8, 47.6, 50.5, 55.3, 64.0, 64.5, 69.4, 70.5, 75.3, 79.1, 83.8, 90.2, 102.3, 122.4, 122.6, 140.8, 143.9, 144.1, 151.3, 163.9, 178.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{48}H_{73}N_5NaO_9$: 886.5306; found: 886.5301.

Oleanolic Acid–Nucleoside Conjugate 17

Prepared from **8** (120 mg, 0.21 mmol) and **14** (130 mg, 0.21 mmol) according to the general procedure. The residue was purified by column chromatography (EtOAc–PE, 2:1) to afford **17** (150 mg, 60%) as a white solid; R_f = 0.13 (EtOAc–PE, 1:1).

$[\alpha]_D^{22}$ +89.9 (*c* 0.69, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70, 0.76, 0.90, 0.97, 1.11 (5 s, 15 H, 5 CH_3), 0.88 (s, 6 H, 2 CH_3), 0.70–1.98 (m, 30 H), 2.84 (dd, *J* = 3.9, 14.0 Hz, 1 H, H18″), 3.19 (dd, *J* = 4.6, 11.0 Hz, 1 H, H3″), 3.68 (dd, *J* = 2.1, 11.2 Hz, 1 H, H5′a), 3.87 (dd, *J* = 1.6, 4.8 Hz, 1 H, H2′), 3.91–3.99 (m, 4 H, H4′, H5′b, NCH_2), 4.23–4.32 (m, 4 H, H3′, CO_2CH_2, OCH), 4.40 (d, *J* = 11.5 Hz, 1 H, OCH), 4.59 (d, *J* = 12.5 Hz, 1 H, PhCH), 4.61 (d, *J* = 12.4 Hz, 1 H, PhCH), 4.78 (d, *J* = 11.9 Hz, 1 H, PhCH), 4.80 (d, *J* = 12.4 Hz, 1 H, PhCH), 5.10 (s, 2 H, $PhCH_2$), 5.26 (t, *J* = 3.4 Hz, 1 H, H12″), 5.48 (d, *J* = 8.2 Hz, 1 H, H5), 6.01 (d, *J* = 1.4 Hz, 1 H, H1′), 7.20–7.33 (m, 13 H, Ph), 7.34 (s, 1 H, NCH-triazole), 7.48–7.50 (m, 2 H, Ph), 7.80 (d, *J* = 8.2 Hz, 1 H, H6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 15.7, 17.1, 18.4, 23.1, 23.5, 23.7, 25.6, 25.9, 26.3, 27.3, 27.7, 28.2, 28.5, 30.3, 30.8, 32.6, 32.8, 33.2, 34.0, 37.1, 38.5, 38.8, 39.4, 41.4, 41.8, 44.1, 45.9, 46.8, 47.7, 50.4, 55.3, 64.0, 64.7, 68.0, 71.5, 72.2, 74.4, 78.6, 79.1, 81.2, 89.2, 101.4, 122.1, 122.4, 127.7, 127.9, 128.1, 128.5, 128.8, 129.3, 136.9, 137.3, 137.5, 138.0, 143.9, 144.2, 150.8, 162.6, 177.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{69}H_{91}N_5NaO_9$: 1156.6715; found: 1156.6709.

Oleanolic Acid–Nucleoside Conjugate 19

Prepared from **12** (130 mg, 0.24 mmol) and **18** (120 mg, 0.24 mmol) according to the general procedure. The residue was purified by column chromatography (EtOAc–PE, 1:1) to afford **19** (200 mg, 80%) as a white solid; R_f = 0.10 (EtOAc–PE, 1:2).

$[\alpha]_D^{22}$ +85.4 (*c* 0.46, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.54, 0.74, 0.83, 0.84, 0.85, 0.96, 1.08 (7s, 21 H, 7 CH_3), 0.54–1.92 (m, 22 H), 2.78 (dd, *J* = 3.6, 13.7 Hz, 1 H, H18″), 3.18 (dd, *J* = 4.6, 11.0 Hz, 1 H, H3″), 3.74 (dd, *J* = 5.3, 7.6 Hz, 1 H, H3′), 3.93 (dd, *J* = 2.3, 5.0 Hz, 1 H, H2′), 4.36–4.72 (m, 7 H, H4′, H5′, 2 $PhCH_2$), 5.05 (d, *J* = 14.2 Hz, 1 H, PhCH), 5.06 (d, *J* = 14.2 Hz, 1 H, PhCH), 5.09 (s, 2 H, CO_2CH_2), 5.24 (t, *J* = 3.4 Hz, 1 H, H12″), 5.62 (d, *J* = 8.2 Hz, 1 H, H5), 5.77 (d, *J* = 2.3 Hz, 1 H, H1′), 6.49 (d, *J* = 8.2 Hz, 1 H, H6), 7.23–7.46 (m, 15 H, Ph), 7.49 (s, 1 H, NCH-triazole).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 15.7, 16.8, 18.4, 23.0, 23.4, 23.7, 25.9, 27.2, 27.7, 28.2, 30.7, 32.4, 32.7, 33.1, 33.8, 37.1, 38.5, 38.8, 39.4, 41.4, 41.8, 44.2, 45.9, 46.8, 47.6, 50.4, 55.2, 57.3, 72.2, 72.7, 76.3, 79.0, 79.5, 91.9, 102.4, 122.5, 125.7, 127.9, 128.2, 128.4, 128.6, 128.66, 128.70, 128.71, 129.2, 136.6, 136.8, 136.9, 137.8, 143.5, 143.6, 150.4, 162.2, 177.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{63}H_{79}N_5NaO_8$: 1056.5826; found: 1056.5824.

Oleanolic Acid–Nucleoside Conjugate 21

Prepared from **12** (130 mg, 0.24 mmol) and **20** (140 mg, 0.24 mmol) according to the general procedure. The residue was purified by column chromatography (EtOAc–PE, 1:1) to afford **21** (230 mg, 85%) as a white solid; R_f = 0.10 (EtOAc–PE, 1:2).

$[\alpha]_D^{22}$ +94.9 (*c* 0.63, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.59, 0.73, 0.87, 0.88, 0.90, 0.92, 1.11 (7 s, 21 H, 7 CH_3), 0.59–1.98 (m, 22 H), 2.88–2.97 (m, 2 H, H3″, H18″), 3.79 (dd, *J* = 5.5, 7.3 Hz, 1 H, H3′), 3.88 (dd, *J* = 2.7, 5.5 Hz, 1 H, H2′), 4.40–4.52 (m, 4 H, H4′, H5′a, OCH_2), 4.58–4.74 (m, 5 H, H5′b, 2 $PhCH_2$), 5.06 (m, 4 H, 2 $PhCH_2$), 5.29 (t, *J* = 3.4 Hz, 1 H, H12″), 5.59 (d, *J* = 8.2 Hz, 1 H, H5), 5.82 (d, *J* = 2.7 Hz, 1 H, H1′), 6.38 (d, *J* = 8.2 Hz, 1 H, H6), 7.24–7.37 (m, 18 H, Ph), 7.43 (s, 1 H, NCH-triazole), 7.46–7.48 (m, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 16.5, 16.9, 18.2, 22.7, 23.0, 23.4, 23.7, 25.9, 26.9, 27.6, 28.2, 30.7, 32.4, 32.7, 33.1, 33.9, 37.0, 38.3, 38.7, 39.3, 41.4, 41.7, 44.1, 45.9, 46.7, 47.6, 50.1, 55.6, 63.1, 65.9, 72.1, 72.7, 76.1, 79.5, 86.9, 91.3, 102.3, 122.5, 124.0, 127.7, 127.9, 128.0, 128.1, 128.3, 128.40, 128.44, 128.5, 128.6, 129.1, 136.4, 136.5, 136.8, 136.9, 137.5, 143.7, 146.7, 150.4, 162.1, 177.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{70}H_{85}N_5NaO_8$: 1146.6296; found: 1146.6293.

Benzyl 3β-*O*-[(2-Azidoethoxy)carbonyl]olean-12-en-28-oate (23)

To a soln of **22** (260 mg, 0.4 mmol) in DMF (2 mL), was added NaN_3 (250 mg, 4 mmol). The mixture was stirred at 80 °C for 8 h and then it was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography (EtOAc–PE, 1:60) to give **23** (230 mg, 85%) as a white solid; R_f = 0.36 (EtOAc–PE, 1:20).

IR (KBr): 3439, 2943, 2103, 1738, 1258 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.60, 0.87, 0.92, 0.94, 1.13 (5 s, 15 H, 5 CH_3), 0.90 (s, 6 H, 2 CH_3), 0.60–1.98 (m, 22 H), 2.91 (dd, *J* = 3.7, 13.5 Hz, 1 H, H18), 3.52 (t, *J* = 5.2 Hz, 2 H, N_3CH_2), 4.28 (t, *J* = 5.2 Hz, 2 H, CO_2CH_2), 4.35 (t, *J* = 8.1 Hz, 1 H, H3), 5.06 (d, *J* = 12.5 Hz, 1 H, $PhCH_2$), 5.08 (d, *J* = 12.5 Hz, 1 H, $PhCH_2$), 5.29 (t, *J* = 3.2 Hz, 1 H, H12), 7.30–7.35 (m, 5 H, Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 16.5, 16.9, 18.1, 23.0, 23.4, 23.5, 23.6, 25.8, 27.6, 27.9, 30.7, 32.3, 32.6, 33.1, 33.8, 36.9, 37.9, 38.1, 39.3, 41.4, 41.7, 45.9, 46.7, 47.5, 49.7, 55.3, 65.7, 65.9, 86.0, 122.3, 127.9, 128.0, 128.4, 136.4, 143.7, 154.9, 177.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{40}H_{57}N_3NaO_5$: 682.4196; found: 682.4190.

Oleanolic Acid–Nucleoside Conjugate 24

Prepared from **8** (120 g, 0.21 mmol) and **23** (140 mg, 0.21 mmol) according to the general procedure. The residue was purified by column chromatography (EtOAc–PE, 1:1) to afford **24** (120 mg, 46%) as a white solid; R_f = 0.18 (EtOAc–PE, 1:1).

$[\alpha]_D^{22}$ +89.7 (*c* 0.64, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.58, 0.80, 0.89, 0.91, 1.10 (5 s, 15 H, 5 CH_3), 0.86 (s, 6 H, 2 CH_3), 0.58–1.96 (m, 22 H), 2.89 (dd, *J* = 3.9, 13.5 Hz, 1 H, H18″), 3.67 (dd, *J* = 2.1, 11.2 Hz, 1 H, H5′a), 3.87–3.97 (m, 3 H, H5′b, H2′, H3″), 4.23 (d, *J* = 11.9 Hz, 1 H, OCH), 4.28–4.32 (m, 2 H, H3′, H4′), 4.40 (d, *J* = 11.4 Hz, 1 H, OCH), 4.47 (t, *J* = 5.3 Hz, 2 H, CO_2CH_2), 4.55–4.64 (m, 4 H, $PhCH_2$, NCH_2), 4.79 (d, *J* = 12.4 Hz, 1 H, PhCH), 4.80 (d, *J* = 11.9 Hz, 1 H, PhCH), 5.05 (d, *J* = 12.4 Hz, 1 H, PhCH), 5.07 (d, *J* = 12.4 Hz, 1 H, PhCH), 5.10 (s, 2 H, $PhCH_2$), 5.27 (t, *J* = 3.4 Hz, 1 H, H12″), 5.53 (d, *J* = 8.2 Hz, 1 H, H5), 6.02 (d, *J* = 1.8 Hz, 1 H, H1′), 7.20–7.35 (m, 18 H, Ph), 7.47 (s, 1 H, NCH-triazole), 7.48–7.50 (m, 2 H, Ph), 7.80 (d, *J* = 7.8 Hz, 1 H, H6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.4, 16.7, 16.9, 18.2, 23.1, 23.5, 23.7, 25.9, 27.7, 28.0, 30.8, 32.4, 32.7, 33.2, 33.9, 36.9, 38.0, 38.1, 39.4, 41.5, 41.8, 44.1, 45.9, 46.8, 47.6, 49.2, 55.3, 64.6, 65.4, 66.0, 68.0, 71.5, 72.2, 74.4, 78.6, 81.2, 86.4, 89.2, 101.4, 122.4, 123.2, 127.7, 127.8, 128.0, 128.1, 128.5, 128.7, 129.2, 136.5, 136.9, 137.3, 137.5, 138.0, 143.8, 144.4, 150.9, 154.6, 162.7, 177.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{73}H_{89}N_5NaO_{11}$: 1234.6456; found: 1234.6454.

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