Click Chemistry: An Efficient Synthesis of Heterocycles Substituted with Steroids, Saponins, and Digitalis Analogues

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Abstract: The copper-catalyzed azide-alkyne cycloaddition (CuAAC) has been used for the construction of 1,2,3-triazole containing steroids in good to excellent yields. Combination of propargylic glycosides and steroidal azides as reaction partner allowed the synthesis of a privileged class of natural product analogues. The versatility of this protocol makes this chemistry a useful attractive approach for the synthesis of target molecules.

Key words: click chemistry, 1,2,3-triazole, sugars, steroids, saponins, digitalis

Steroidal glycosides constitute a structurally and biologically diverse class of molecules, which has been isolated from a wide variety of both plant and animal species.[1] Members of this class of biomolecules have demonstrated cardiotonic activity and therapeutic potential as antiviral and antitumoral agents.[2] The Chinese folk medicine contains steroidal glycosides as major components, which are gylcoconjugate templates in drug design and development.[3] Thus, taking inspiration from bioactive compounds isolated from nature, many glycoconjugate derivatives have been prepared and evaluated as drug candidates.[4] The replacement of the glycosidic bond with different linkers provides steroidal glycoside mimics with improved stability and enlarges molecular length.[5]

In this context, 1,2,3-triazole scaffolds are attractive linker units, because they are stable regarding metabolic degradation. Furthermore these heterocyclic compounds are able to form hydrogen bonds, which are important in binding bimolecular targets and to increase their solubility. The unique chemistry behavior of this moiety aroused the chemist's interest, ranging from a synthetic point of view to the context of biological and pharmacological applications.[6] The 1,3-dipolar cycloaddition reaction is a powerful synthetic protocol for the synthesis of 1,2,3-triazoles.[7] In 2002, Sharpless and Meldal independently discovered the copper-catalyzed azide–alkyne cycloaddition (CuAAC) for the synthesis of five-membered heterocycles.[8] These click chemistry protocols have shown to be regioselective and compatible with a wide range of reaction partners, for example, peptides, proteins, nucleosides, steroids, and carbohydrates.[9] Recently, Li's group reported the synthesis of 1,2,3-triazolic heterocycles containing lithocholic acid and their application as inhibitors of α-2,3-sialyltransferase.[10] Additionally, there are only two specific examples, which described the application of click chemistry for binding a steroid with a carbohydrate by an 1,2,3-triazole scaffold.[11] For example, Chang and co-workers have synthesized cyclopamine derivatives and applied them as lead compounds in anticancer drug discovery.[11b] Therefore, it remains the necessity for a deep study on the combinations between the reaction partners for the synthesis of saponins and digitalic analogues.

Herein, we describe our contribution to the application of the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction for the synthesis of 1,2,3-triazoles containing a steroidal moiety. In order to get the best reaction conditions for the 1,3-dipolar cycloaddition of phenylacetylene with the azidocholesterol **1a**[12] the reaction was carried out in a mixture of THF–H_2O (1:1) in the presence of 10 mol% $Cu(OAc)_2 \cdot H_2O$ and sodium ascorbate (20 mol%). To our delight the desired product **3a** was obtained in quantitative yield (Table 1, entry 1). The experimental procedure involves the in situ generation of Cu(I) species by reducing $Cu(OAc)_2 \cdot H_2O$ with sodium ascorbate in aqueous solution.[13] When the reaction time was decreased from 12 to 6 hours the chemical yield was dramatically dropped to 56% (Table 1, entry 1 vs 2). The use of different amounts of copper salt and sodium ascorbate were also studied. Decreasing the copper catalyst loading to 5 mol% along with 10 mol% of sodium ascorbate the 1,2,3-triazole **3a** was obtained in 65% yield (entry 3). Using 5 mol% of $Cu(OAc)_2 \cdot H_2O$ with 20 mol% of sodium ascorbate the triazole **3a** was obtained in a reasonable chemical yield of 82% (entry 4). By changing the copper acetate to $CuBr_2$ (10 mol%) the cholesterol containing the triazole ring was obtained in 45% yield (entry 5).

The additional parameters were also analyzed including change of the solvent and temperature. A mixture of ethanol–water (1:1) gave the desired product in 25% yield (entry 6). When the reaction was run in PEG 400–H_2O or [BMIM]BF_4–H_2O at room temperature for 12 hours the triazole **3a** was obtained with 28% and 35% yield, respectively (entries 7 and 8).

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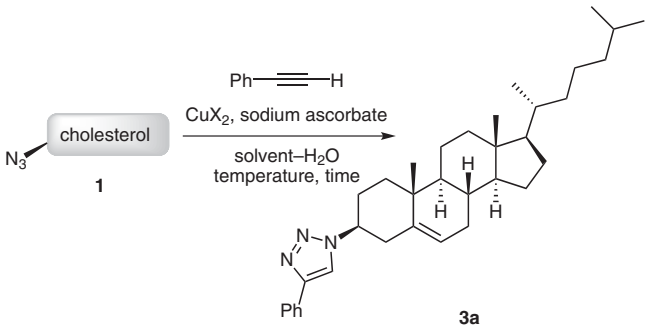
Table 1 Optimization Studies of the Copper-Catalyzed 1,3-Dipolar Cycloaddition of 3-β-azidocholesterol (**1a**) with Phenylacetylene



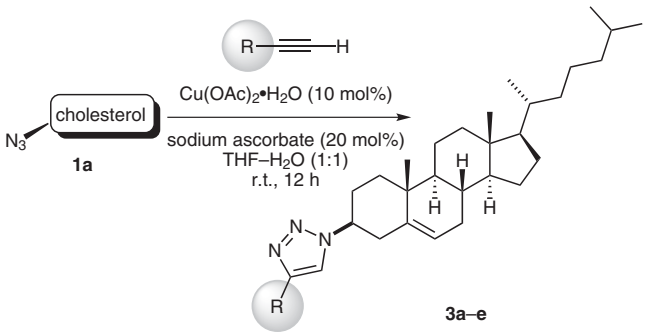
Entry	Copper salt	Solvent–H_2O (1:1)	Temp °C)	Yield (%)[a]
1	$Cu(OAc)_2·H_2O$ 10 mol%	THF	r.t.	100
2[b]	$Cu(OAc)_2·H_2O$ 10 mol%	THF	r.t.	56
3[c]	$Cu(OAc)_2·H_2O$ 5 mol%	THF	r.t.	65
4	$Cu(OAc)_2·H_2O$ 5 mol%	THF	r.t.	82
5	$CuBr_2$ 10 mol%	THF	r.t.	45
6	$Cu(OAc)_2·H_2O$ 10 mol%	EtOH	r.t.	25
7	$Cu(OAc)_2·H_2O$ 10 mol%	PEG 400	r.t.	28
8	$Cu(OAc)_2·H_2O$ 10 mol%	$[BMIM]BF_4$	r.t.	35
9[b]	$Cu(OAc)_2·H_2O$ 10 mol%	THF	80	90
10[b]	$Cu(OAc)_2·H_2O$ 10 mol%	THF	100	70
11[d,e]	$Cu(OAc)_2·H_2O$ 10 mol%	THF	60	66
12[d,e]	$Cu(OAc)_2·H_2O$ 10 mol%	THF	80	40
13[d,f]	$Cu(OAc)_2·H_2O$ 10 mol%	THF	100	75
14[d,g]	$Cu(OAc)_2·H_2O$ 10 mol%	THF	100	75

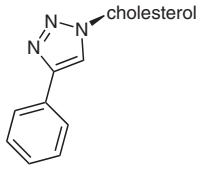
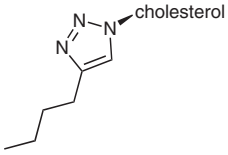
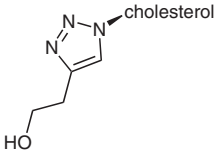
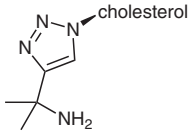
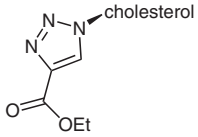
[a] Unless otherwise noted, all reactions were carried out on a 0.3 mmol scale using 1 mL of solvent for 12 h, 20 mol% of sodium ascorbate. All yields are given for isolated products after column chromatography.
[b] Reaction time of 6 h.
[c] 10 mol% of sodium ascorbate was used.
[d] Reaction was carried out under microwave irradiation using 100 W as maximum potency.
[e] Reaction time of 30 min.
[f] Reaction time of 20 min.
[g] Reaction time of 40 min.

Moreover, investigation of the temperature effects on the reaction revealed that raising the temperature had no significant influence on the yield although the reaction time could be decreased to six hours (see entries 1, 9, and 10). On the other hand moderate yields were obtained under microwave irradiation using 100 W as maximum potency at different temperatures (entries 11–14).

Once the optimal conditions were obtained, we examined the possibilities and limitation of this cycloaddition reaction by varying the nature of the terminal alkyne

Table 2 Substrate Scope of CuAAC: Variation of the Alkyne Partner



Entry	Product	Yield (%)[a]
1	 **3a**	100
2	 **3b**	96
3	 **3c**	92
4	 **3d**	87
5	 **3e**	88

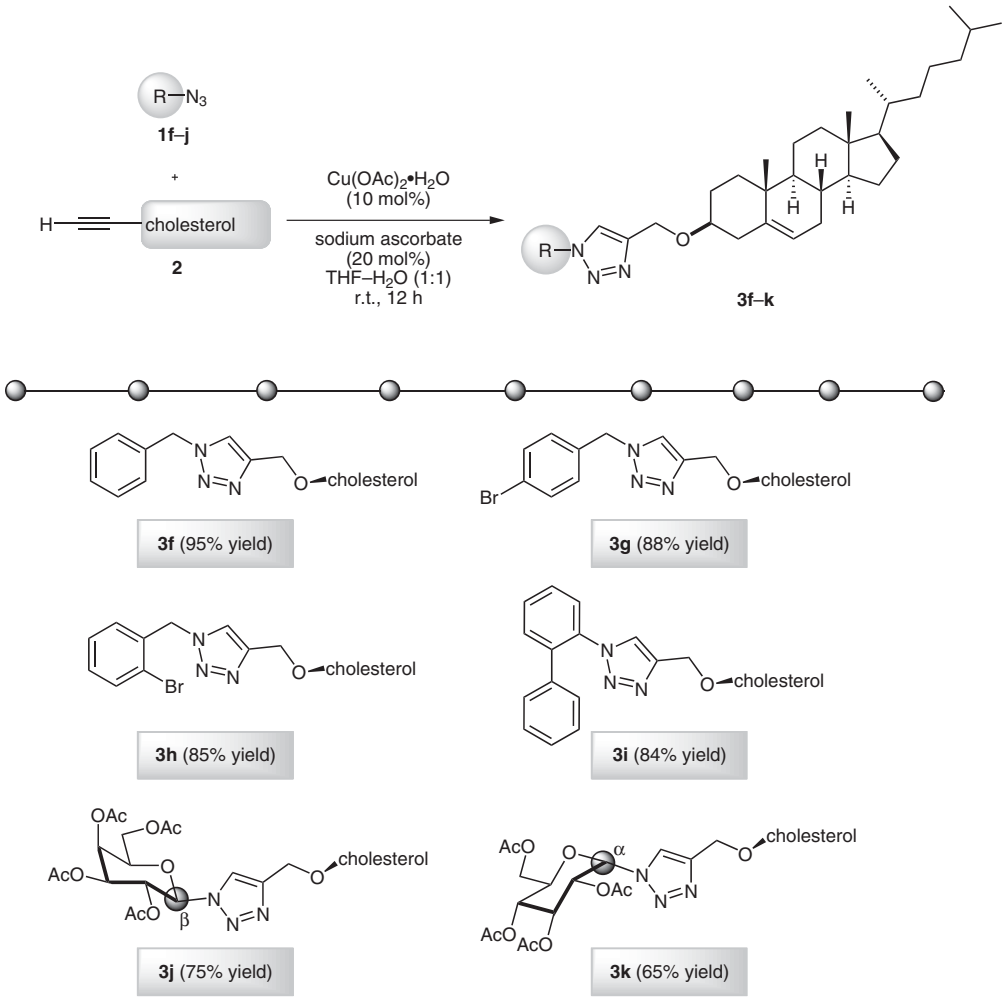
[a] Unless otherwise noted, all reactions were carried out on a 0.3 mmol scale using 1 mL of solvent for 12 h. All yields are given for isolated products after column chromatography.

(Table 2). The results showed that several substituted terminal alkynes coupled efficiently with the 3-β-azidocholesterol (**1a**) to provide the corresponding 1,2,3-triazoles **3a–e** in excellent isolated yields (>87%). When the reaction was carried out using hex-1-yne as a reaction partner the click product was obtained in 96% yield (Table 2, entry 2). Alkylalkynes bearing hydroxy and amino groups were also successfully employed in the 1,3-dipolar cycloaddition reaction (entries 3 and 4). Likewise, when a strong electron-withdrawing group was present in the terminal alkyne, the product was obtained in very good chemical yield (entry 5).

Next, the reactivity of terminal alkynes derived from cholesterol towards different azides was evaluated. Benzylic azides with electron-neutral and electron-deficient substituent react with 3-β-prop-2-ynyloxycholesterol (**2f**) to give the expected 1,2,3-triazoles in good to excellent yields (Scheme 1, products **3f**, **3g**, and **3h**). The hindered *ortho*-biphenyl azide was also used forming **3i** in 84% yield. The use of this methodology has proven that different groups attached to the aryl ring are compatible with this reaction,[14] thus, providing an opportunity for further functionalization of the product. In addition, the 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide (**1j**) also reacted smoothly with 3-β-prop-2-ynyloxycholesterol to give the product **3j** in 75% yield. With regard to stereochemistry on the anomeric carbon of the galactopyranosyl azide, we observed that the stereoconfiguration does not play an important role in determining the degree of chemical yield. For instance, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl azide underwent click coupling with similar level of yield as the β-analogue (**3j** vs **3k**).

To fully explore this transformation, the CuAAC was then successfully applied to the reaction between propargylic glycosides and azido-functionalized steroids. We were able to synthesize a library of saponins and digitalis derivatives containing the triazole moiety.[15] The natural versions of these two classes of compounds are widely recognized for their antifungal, cardiovascular, and antitumor activity.[2]

Effectively, the click chemistry involving 2-propynyl-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside and azidosteroids were performed to give the steroidal glycosides. Different azidosteroids were evaluated and in all the cases the corresponding products were obtained in rather good levels of chemical yield (Table 3, entries 1–4). When the propargylic partner was changed from β-D-glucose pentaacetate to a disaccharide or trisaccharide, the analogues

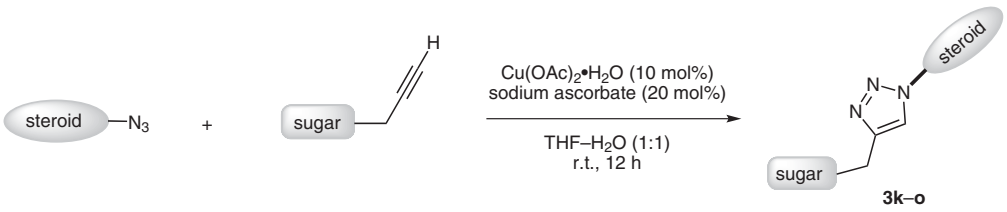


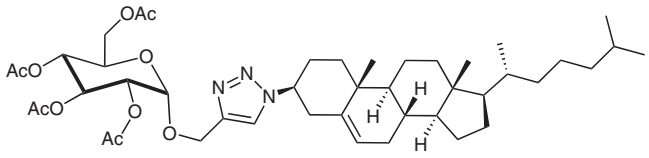
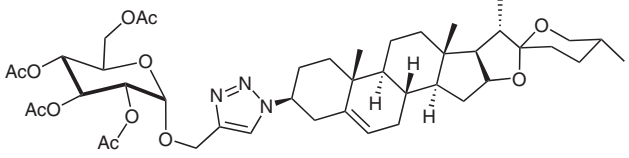
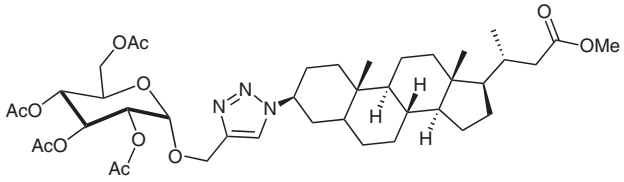
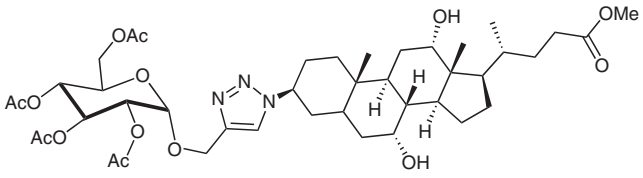
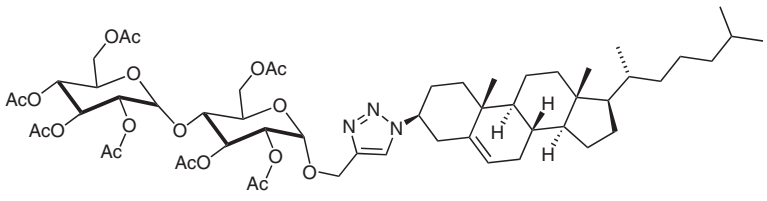
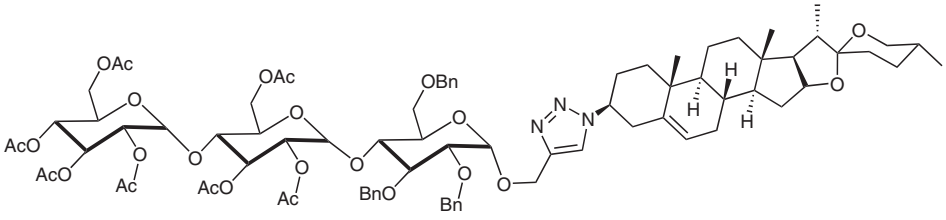
Scheme 1 Scope of the click reaction using alkynylcholesterol building block

of this special class of natural product were also obtained in satisfactory yields (entries 5 and 6).

In summary, we have employed the click chemistry concept for the synthesis of 1,2,3-triazole containing steroids. As an application of this approach, combinations of dif-

Table 3 Synthesis of Saponins and Digitalis Derivatives



Entry	Steroidal azide	Product	Yield (%)[a]
1	cholesterol—N_3	 **3l**	85
2	diosgenin—N_3	 **3m**	75
3	lithocholic acid—N_3	 **3n**	70
4	cholic acid—N_3	 **3o**	80
5	cholesterol—N_3	 **3p**	80
6	diosgenin—N_3	 **3q**	68

[a] Unless otherwise noted, all reactions were carried out on a 0.3 mmol scale using 1 mL of solvent for 12 h. All yields are given for isolated products after column chromatography.

ferent saccharides and steroids building blocks have been used and a small library of saponins and digitalis analogues bearing an 1,2,3-triazole moieties as surrogate of the glycosidic linkage, was obtained. The high yields and the feasibility of the method highlights the efficiency of this methodology and prompt us for further extension of this approach, which will be reported in due course.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 (400 and 100 MHz, respectively). Optical rotations were measured with a Perkin-Elmer Polarimeter, Model 241, at 589 nm, 25 °C. High-resolution mass spectra were recorded on a Bruker BioApex 70eV spectrometer. Gas chromatography (GC) was performed using a Varian 3800 gas chromatograph with a Hydrodex β-3P columm. Column chromatography was performed using Merck Silica Gel (230–400 mesh). Thin-layer chromatography (TLC) was performed using Merck Silica Gel GF_{254}, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. Most reactions were monitored by TLC for disappearance of starting material. The following solvents were dried and purified by distillation from the reagents indicated: tetrahydrofuran from sodium with a benzophenone ketyl indicator; dichloromethane from calcium hydride; acetonitrile from phosphorus pentoxide. All other solvents were ACS or HPLC grade unless otherwise noted. Air- and moisture-sensitive reactions were conducted in flame-dried or oven-dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry argon. Reagents and solvents were handled using standard syringe techniques. Temperatures above room temperature were maintained by use of a mineral oil bath with an electrically heated coil connected to a Variac controller.

Triazoles 3a–o; General Click Procedure

To a solution of the desired azido derivative (0.3 mmol) in THF (1.0 mL) were added the respective alkyne (0.33 mmol) and distilled H_2O (0.5 mL). Then a fresh solution of sodium ascorbate (20 mol%, 0.012 g) and $Cu(OAc)_2{\cdot}H_2O$ (10 mol%, 0.006 g) in distilled H_2O (0.5 mL) was added and the mixture stirred under air for 12 h. Brine (3 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, washed with brine (3 mL), and dried ($MgSO_4$). The solvent was removed under vacuum and the product was isolated by column chromatography using hexane–EtOAc as eluent.

3a

Yield: 0.154 g (~100%); white solid; mp 200 °C; $[\alpha]_D$ +12.5 (c = 0.009 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, J = 7.6 Hz, 2 H), 7.78 (s, 1 H), 7.41 (t, J = 7.6 Hz, 2 H), 7.31 (t, J = 7.6 Hz, 1 H), 5.48–5.46 (m, 1 H), 4.46–4.39 (m, 1 H), 2.84–2.77 (m, 1 H), 2.61–2.56 (m, 1 H), 2.16–2.13 (m, 2 H), 2.06–1.99 (m, 4 H), 1.88–1.82 (m, 3 H), 1.63–1.48 (m, 5 H), 1.37–1.23 (m, 8 H), 1.12 (s, 3 H), 1.07–0.99 (m, 4 H), 0.93 (d, J = 6.4 Hz, 3 H), 0.87–0.85 (m, 6 H), 0.70 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.29, 139.21, 130.85, 128.77, 127.96, 125.65, 123.29, 117.36, 60.93, 56.68, 56.15, 50.07, 42.31, 39.69, 39.59, 39.50, 37.84, 36.74, 36.17, 35.77, 31.85, 31.80, 29.35, 28.21, 28.00, 24.25, 23.82, 22.79, 22.53, 21.00, 19.39, 18.71, 11.85.

HRMS (ESI): m/z calcd for $C_{35}H_{51}N_3$ $[M + H]^+$: 514.4083; found: 514.4155.

3b

Yield: 0.143 g (96%); white solid; mp 158 °C; $[\alpha]_D$ –24.2 (c = 3.3 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 1 H), 5.45–5.43 (m, 1 H), 4.37–4.29 (m, 1 H), 3.76–3.73 (m, 1 H), 2.71 (t, J = 8.0 Hz, 3 H), 2.54–2.50 (m, 1 H), 2.09–1.99 (m, 5 H), 1.87–1.83 (m, 2 H), 1.68–1.58 (m, 3 H), 1.55–1.47 (m, 4 H), 1.43–1.32 (m, 4 H), 1.29–1.22 (m, 3 H), 1.19–1.12 (m, 4 H), 1.09 (s, 3 H), 1.06–0.99 (m, 4 H), 0.95–0.91 (m, 6 H), 0.88–0.85 (m, 6 H), 0.69 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.91, 139.36, 123.02, 118.18, 60.60, 56.65, 56.11, 50.03, 42.27, 39.67, 39.56, 39.47, 37.82, 36.70, 36.15, 35.74, 31,82, 31.77, 31.61, 29.29, 28.18, 27.97, 25.44, 24.24, 23.79, 22.77, 22.52, 22.34, 20.96, 19.36, 18.69, 13.80, 11.83.

HRMS (ESI): m/z calcd for $C_{33}H_{55}N_3$ $[M + H]^+$: 494.4396; found: 494.4468.

3c

Yield: 0.135 g (92%); white solid; mp 110 °C; $[\alpha]_D$ +12.5 (c = 0.004 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 1 H), 5.46–5.44 (m, 1 H), 4.38–4.30 (m, 1 H), 4.12 (q, J = 7.2 Hz, 1 H), 3.96–3.93 (m, 1 H), 2.94 (t, J = 6.0 Hz, 2 H), 2.87 (s, 1 H), 2.78–2.71 (m, 1 H), 2.55–2.50 (m, 1 H), 2.11–1.98 (m, 6 H), 1.87–1.80 (m, 2 H), 1.63–1.47 (m, 4 H), 1.39–1.32 (m, 3 H), 1.29–1.21 (m, 4 H), 1.19–1.12 (m, 3 H), 1.09 (s, 3 H), 1.06–0.97 (m, 4 H), 0.92 (d, J = 6.4 Hz, 3 H), 0.88–0.85 (m, 6 H), 0.69 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.00, 139.19, 123.17, 119.28, 61.64, 60.77, 56.63, 56.09, 50.01, 42.26, 39.64, 39.52, 39.46, 37.78, 36.69, 36.13, 35.74, 31.80, 31.74, 29.23, 28.67, 28.16, 27.97, 24.23, 23.78, 22.77, 22.52, 20.95, 19.33, 18.67, 11.81.

HRMS (ESI): m/z calcd for $C_{31}H_{51}N_3O$ $[M + H]^+$: 482.4032; found: 482.4104.

3d

Yield: 0.129 g (87%); yellow solid; mp 120 °C; $[\alpha]_D$ +12.5 (c = 0.005 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 1 H), 5.45–5.44 (m, 1 H), 4.41–4.33 (m, 1 H), 4.12 (q, J = 7.2 Hz, 2 H), 3.73 (s, 2 H), 3.43 (q, J = 7.2 Hz, 1 H), 2.78–2.71 (m, 1 H), 2.56–2.51 (m, 1 H), 2.36 (s, 6 H), 2.11–2.00 (m, 5 H), 1.87–1.81 (m, 2 H), 1.61–1.47 (m, 4 H), 1.39–1.32 (m, 3 H), 1.27–1.24 (m, 3 H), 1.19–1.12 (m, 3 H), 1.09 (s, 3 H), 1.06–0.99 (m, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 0.87–0.85 (m, 6 H), 0.69 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.17, 139.20, 123.25, 120.93, 60.89, 60.40, 56.67, 56.14, 53.85, 50.05, 44.45, 42.30, 39.68, 39.53, 39.50, 37.80, 36.72, 36.18, 35.78, 31.85, 31.79, 29.26, 28.21, 28.00, 24.27, 23.82, 22.82, 22.57, 20.99, 19.36, 18.72, 11.86.

HRMS (ESI): m/z calcd for $C_{32}H_{54}N_4$ $[M + H]^+$: 495.4348; found: 495.4421.

3e

Yield: 0.132 g (88%); white solid; mp 136 °C; $[\alpha]_D$ +12.9 (c = 0.005 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1 H), 5.49–5.46 (m, 1 H), 4.42 (q, J = 7.2 Hz, 3 H), 2.78–2.71 (m, 1 H), 2.59–2.55 (m, 1 H), 2.17–2.00 (m, 6 H), 1.88–1.79 (m, 2 H), 1.63–1.48 (m, 7 H), 1.43–1.26 (m, 8 H), 1.19–1.01 (m, 9 H), 0.93–0.86 (m, 9 H), 0.69 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.97, 144.77, 138.70, 125.25, 123.74, 61.25, 56.67, 56.16, 50.03, 42.32, 39.74, 39.67, 39.52, 39.46, 37.71, 36.70, 36.19, 35.79, 31.85, 31.79, 29.29, 28.23, 28.03, 24.27, 23.84, 22.84, 22.58, 21.01, 19.36, 18.73, 14.36, 11.87.

HRMS (ESI): m/z calcd for $C_{32}H_{51}N_3O_2$ $[M + H]^+$: 510.3981; found: 510.4054.

3f

Yield: 0.156 g (95%); white solid; mp 121 °C; $[\alpha]_D$ –12.9 (*c* = 0.006 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (s, 1 H), 7.38–7.36 (m, 3 H), 7.28–7.27 (m, 2 H), 5.50 (s, 2 H), 5.35–5.33 (m, 1 H), 4.65 (s, 2 H), 3.33–3.26 (m, 1 H), 2.40–2.36 (m, 1 H), 2.25–2.22 (m, 1 H), 2.17 (s, 1 H), 2.02–1.80 (m, 6 H), 1.58–1.42 (m, 7 H), 1.38–1.25 (m, 4 H), 1.19–1.07 (m, 8 H), 0.98 (s, 3 H), 0.92–0.86 (m, 9 H), 0.67 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.41, 140.67, 134.61, 129.12, 128.76, 128.19, 122.22, 121.83, 79.00, 61.72, 56.78, 56.17, 54.18, 50.17, 42.34, 39.80, 39.54, 39.03, 37.18, 36.86, 36.22, 35.82, 31.95, 31.91, 30.97, 28.30, 28.26, 28.03, 24.32, 23.84, 22.86, 22.60, 21.09, 19.38, 18.76, 11.89.

HRMS (ESI): *m*/*z* calcd for $C_{37}H_{55}N_3O$ [M + H]$^+$: 558.4345; found: 558.4417.

3g

Yield: 0.166 g (88%); white solid; mp 173 °C; $[\alpha]_D$ –10.6 (*c* = 0.005 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.0 Hz, 2 H), 7.46 (s, 1 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 5.46 (s, 2 H), 5.35–5.33 (m, 1 H), 4.66 (s, 1 H), 3.34–3.26 (m, 1 H), 2.40–2.35 (m, 1 H), 2.25–2.18 (m, 1 H), 2.04–1.91 (m, 3 H), 1.88–1.80 (m, 2 H), 1.58–1.42 (m, 8 H), 1.38–1.24 (m, 6 H), 1.18–1.04 (m, 8 H), 0.99 (s, 3 H), 0.91 (d, *J* = 8.0 Hz, 3 H), 0.87–0.85 (m, 6 H), 0.67 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.60, 140.58, 133.59, 132.23, 129.71, 122.87, 122.09, 121.81, 79.01, 61.65, 56.71, 56.11, 53.40, 50.10, 42.27, 39.73, 39.49, 38.98, 37.12, 36.79, 36.15, 35.74, 31.90, 31.84, 28.24, 28.20, 27.97, 24.26, 23.78, 22.79, 22.54, 21.02, 19.32, 18.69, 11.83.

HRMS (ESI): *m*/*z* calcd for $C_{37}H_{54}BrN_3O$ [M + H]$^+$: 636.3450; found: 636.3523.

3h

Yield: 0.159 g (85%); white solid; mp 141 °C; $[\alpha]_D$ –14.2 (*c* = 0.005 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.59 (m, 1 H), 7.57 (s, 1 H), 7.34–7.13 (m, 3 H), 5.65 (s, 2 H), 5.35–5.29 (m, 1 H), 4.67 (s, 2 H), 3.39–3.23 (m, 1 H), 2.45–2.34 (m, 2 H), 2.29–2.14 (m, 1 H), 2.04–1.80 (m, 5 H), 1.59–1.32 (m, 9 H), 1.16–0.85 (m, 23 H), 0.67 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.39, 140.69, 134.25, 133.21, 130.44, 130.38, 128.23, 123.51, 122.58, 121.83, 79.02, 61.74, 56.80, 56.20, 53.79, 50.19, 42.36, 39.82, 39.56, 39.07, 37.21, 36.88, 36.24, 35.82, 31.98, 31.92, 28.34, 28.27, 28.05, 24.33, 23.87, 22.86, 22.61, 21.11, 19.40, 18.76, 11.90.

HRMS (ESI): *m*/*z* calcd for $C_{37}H_{54}BrN_3O$ [M + H]$^+$: 636.3450; found: 636.3523.

3i

Yield: 0.158 g (84%): pale yellow solid; mp 154 °C; $[\alpha]_D$ –20.6 (*c* = 0.005 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.61 (m, 1 H), 7.59–7.50 (m, 3 H), 7.28–7.26 (m, 3 H), 7.19 (s, 1 H), 7.11–7.08 (m, 2 H), 5.34–5.32 (m, 1 H), 4.60 (s, 2 H), 3.20–3.12 (m, 1 H), 2.31–2.27 (m, 1 H), 2.18–2.11 (m, 2 H), 2.05–1.94 (m, 2 H), 1.85–1.80 (m, 4 H), 1.68–1.25 (m, 15 H), 1.19–1.08 (m, 6 H), 0.98 (m, 3 H), 0.92–0.91 (m, 3 H), 0.87–0.85 (m, 6 H), 0.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.70, 140.67, 137.11, 131.13, 129.88, 128.71, 128.57, 128.51, 127.99, 126.72, 124.63, 121.82, 78.18, 61.14, 56.83, 56.20, 50.24, 42.36, 39.83, 39.56, 38.96, 37.13, 36.85, 36.24, 35.83, 35.11, 32.00, 31.92, 28.28, 28.22, 28.06, 24.33, 23.87, 22.86, 22.61, 21.11, 19.40, 18.76, 17.70, 11.92.

HRMS (ESI): *m*/*z* calcd for $C_{43}H_{59}N_3O$ [M + H]$^+$: 634.4658; found: 634.4598.

3j

Yield: 0.175 g (75%); white solid; mp 93 °C; $[\alpha]_D$ +99.7 (*c* = 0.006 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1 H), 5.45–5.43 (m, 1 H), 5.25–5.18 (m, 2 H), 5.13–5.07 (m, 2 H), 5.02–4.97 (m, 2 H), 4.93–4.91 (m, 1 H), 4.85–4.78 (m, 2 H), 4.70 (d, *J* = 8.0 Hz, 1 H), 4.40–4.38 (m, 1 H), 4.31–4.28 (m, 2 H), 4.16–4.13 (m, 2 H), 3.75–3.71 (m, 2 H), 2.79–2.72 (m, 1 H), 2.54–2.50 (m, 2 H), 2.12–1.98 (m, 15 H), 1.87–1.82 (m, 1 H), 1.64–1.48 (m, 4 H), 1.37–1.26 (m, 5 H), 1.13–1.01 (m, 8 H), 0.93 (d, *J* = 6.4 Hz, 3 H), 0.89 (d, *J* = 6.4 Hz, 6 H), 0.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.65, 170.20, 169.42, 169.37, 143.59, 139.21, 123.30, 120.74, 99.85, 72.79, 71.90, 71.20, 68.29, 63.34, 61.13, 60.97, 56.65, 56.35, 55.86, 50.03, 42.24, 39.65, 39.59, 39.48, 37.95, 36.70, 36.21, 35.43, 31.74, 31.02, 29.28, 28.33, 27.15, 24.07, 23.11, 22.91, 22.64, 20.98, 20.76, 20.60, 20.15, 19.39, 18.72, 11.92.

HRMS (ESI): *m*/*z* calcd for $C_{44}H_{67}N_3O_{10}$ [M + H]$^+$: 798.4826; found: 798.4899.

3k

Yield: 0.134 g (65%); white solid; mp 155–157 °C; $[\alpha]_D$ +51.0 (*c* = 0.005 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (s, 1 H), 6.33 (d, *J* = 4.0 Hz, 2 H), 6.25 (t, *J* = 8.0 Hz, 1 H), 5.33–5.21 (m, 1 H), 4.69 (s, 2 H), 4.34–4.30 (m, 2 H), 4.25–4.21 (m, 2 H), 4.13–4.06 (m, 2 H), 4.00–3.96 (m, 2 H), 3.34–3.27 (m, 2 H), 2.39–2.34 (m, 2 H), 2.25–2.19 (m, 2 H), 2.04–2.03 (m, 8 H), 2.00 (s, 3 H), 1.97–1.92 (m, 2 H), 1.84 (s, 3 H), 1.57–1.41 (m, 5 H), 1.38–1.29 (m, 3 H), 1.25–1.21 (m, 2 H), 1.14–1.03 (m, 5 H), 0.98 (s, 3 H), 0.89 (d, *J* = 8.0 Hz, 3 H), 0.84–0.83 (m, 6 H), 0.65 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.37, 170.12, 169.64, 169.54, 145.77, 140.49, 124.52, 121.89, 81.30, 79.16, 71.02, 70.45, 69.79, 68.01, 61.44, 61.25, 56.73, 56.13, 50.14, 42.29, 39.74, 39.50, 39.05, 37.15, 36.83, 36.17, 35.76, 31.92, 31.88, 28.30, 28.21, 27.97, 24.28, 23.80, 22.80, 22.56, 21.06, 20.63, 20.58, 20.31, 19.34, 18.71, 14.19, 11.86.

HRMS (ESI): *m*/*z* calcd for $C_{44}H_{67}N_3O_{10}$ [M + H]$^+$: 798.4905; found: 798.4895.

3l

Yield: 0.199 g (85%); white solid; mp 135 °C; $[\alpha]_D$ –2.9 (*c* = 0.007 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1 H), 5.46–5.44 (m, 1 H), 5.25–5.18 (m, 2 H), 5.13–5.07 (m, 2 H), 5.04–4.99 (m, 2 H), 4.94–4.91 (m, 1 H), 4.84–4.78 (m, 2 H), 4.70 (d, *J* = 8.0 Hz, 1 H), 4.38–4.37 (m, 1 H), 4.30–4.26 (m, 2 H), 4.16–4.13 (m, 2 H), 3.77–3.72 (m, 2 H), 2.79–2.72 (m, 1 H), 2.56–2.50 (m, 2 H), 2.09–1.98 (m, 15 H), 1.87–1.82 (m, 1 H), 1.62–1.47 (m, 4 H), 1.37–1.26 (m, 5 H), 1.14–1.01 (m, 8 H), 0.93 (d, *J* = 6.4 Hz, 3 H), 0.87 (d, *J* = 6.4 Hz, 6 H), 0.70 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.62, 170.17, 169.42, 169.34, 143.58, 139.08, 123.32, 120.64, 99.84, 72.78, 71.85, 71.24, 68.29, 63.06, 61.83, 60.93, 56.65, 56.11, 55.92, 50.03, 42.29, 39.65, 39.52, 39.47, 37.77, 36.70, 36.15, 35.75, 31.84, 31.76, 29.28, 28.20, 27.97, 24.24, 23.79, 22.81, 22.54, 20.98, 20.72, 20.65, 20.56, 19.33, 18.70, 11.84.

HRMS (ESI): *m/z* calcd for $C_{44}H_{67}N_3O_{10}$ [M + H]$^+$: 798.4826; found: 798.4899.

3m

Yield: 0.182 g (75%); white solid; mp 118 °C; $[\alpha]_D$ –56.6 (*c* = 0.006 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (s, 1 H), 5.34–5.31 (m, 1 H), 5.26–5.21 (m, 2 H), 5.12–5.07 (m, 2 H), 5.03–4.98 (m, 2 H), 4.78 (d, *J* = 8.0 Hz, 2 H), 4.43–4.39 (m, 1 H), 4.37–4.36 (m, 3 H), 4.30–4.25 (m, 2 H), 4.16–4.12 (m, 2 H), 3.75–3.71 (m, 2 H), 3.53–3.44 (m, 2 H), 3.39–3.33 (m, 1 H), 2.50–2.49 (m, 2 H), 2.31–2.22 (m, 2 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 1.88–1.81 (m, 2 H), 1.78–1.71 (m, 1 H), 1.67–1.56 (m, 3 H), 1.52–1.43 (m, 2 H), 1.32–1.24 (m, 2 H), 1.20–1.06 (m, 2 H), 1.02 (s, 3 H), 0.96 (d, *J* = 8.0 Hz, 3 H), 0.79–0.77 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.55, 170.14, 169.33, 169.30, 140.76, 121.26, 109.17, 98.02, 80.71, 78.00, 75.46, 72.65, 71.81, 71.53, 70.85, 69.71, 68.19, 66.72, 61.99, 61.66, 56.42, 55.84, 49.95, 42.15, 41.50, 40.16, 39.68, 37.13, 36.54, 31.94, 31.74, 31.49, 31.33, 31.27, 30.18, 28.70, 20.77, 20.63, 20.58, 20.50, 19.32, 17.05, 16.19, 14.43.

HRMS (ESI): *m/z* calcd for $C_{44}H_{63}N_3O_{12}$ [M + H]$^+$: 826.4412; found: 826.4509.

3n

Yield: 0.165 g (70%); yellow oil; $[\alpha]_D$ +27.5 (*c* = 0.012 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 1 H), 3.69 (s, 3 H), 3.68–3.61 (m, 2 H), 2.42–2.35 (m, 2 H), 2.29–2.21 (m, 2 H), 2.01–1.96 (m, 2 H), 1.91–1.77 (m, 6 H), 1.68 (s, 6 H), 1.62–1.51 (m, 4 H), 1.47–1.23 (m, 15 H), 1.20–1.04 (m, 7 H), 1.01–0.98 (m, 1 H), 0.96–0.92 (m, 7 H), 0.67 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.84, 71.93, 77.25, 75.28, 73.23, 56.53, 55.98, 51.52, 42.77, 42.13, 41.91, 40.47, 40.19, 36.49, 35.89, 35.83, 35.41, 35.38, 34.61, 31.10, 31.05, 30.58, 29.74, 28.22, 27.22, 26.45, 24.24, 23.41, 20.87, 18.31, 12.07.

HRMS (ESI): *m/z* calcd for $C_{41}H_{61}N_3O_{12}$ [M + H]$^+$: 788.4255; found: 788.4305.

3o

Yield: 0.165 g (80%); colorless oil; $[\alpha]_D$ +5.2 (*c* = 0.006 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (s, 1 H), 5.22–5.17 (m, 1 H), 5.12–5.07 (m, 1 H), 5.03–4.98 (m, 1 H), 4.91–4.78 (m, 2 H), 4.72 (d, *J* = 8.0 Hz, 1 H), 4.35–4.30 (m, 1 H), 4.28–4.24 (m, 1 H), 4.16–4.09 (m, 2 H), 4.00 (s, 1 H), 4.88 (s, 1 H), 3.79–3.74 (m, 1 H), 3.66 (s, 3 H), 2.88 (s, 1 H), 2.77–2.67 (m, 1 H), 2.41–2.34 (m, 2 H), 2.30–2.22 (m, 2 H), 2.08 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.99 (s, 3 H), 1.97 (s, 3 H), 1.97–1.71 (m, 6 H), 1.63–1.58 (m, 4 H), 1.44–1.30 (m, 2 H), 1.27–1.24 (m, 2 H), 1.20–1.11 (m, 2 H), 0.99–0.97 (m, 6 H), 0.71 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.68, 170.78, 170.13, 169.39, 143.20, 120.85, 99.88, 72.87, 71.70, 71.22, 68.38, 67.96, 63.07, 62.02, 61.00, 60.31, 53.49, 51.42, 47.14, 46.55, 41.98, 41.88, 39.45, 36.55, 35.59, 35.29, 34.80, 34.30, 31.07, 30.82, 28.24, 28.05, 27.46, 26.67, 23.13, 22.50, 20.70, 20.61, 20.52, 17.24, 14.15, 12.50.

HRMS (ESI): *m/z* calcd for $C_{42}H_{63}N_3O_{14}$ [M + H]$^+$: 834.4388; found: 834.4412.

3p

Yield: 0.261 g (80%); yellowish solid; mp 120 °C; $[\alpha]_D$ +39.6 (*c* = 0.010 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (s, 1 H), 5.47–5.16 (m, 5 H), 4.99 (t, *J* = 8.0 Hz, 2 H), 4.91–4.74 (m, 4 H), 4.65 (d, *J* = 8.0 Hz, 1 H), 4.49–4.28 (m, 3 H), 4.21–4.13 (m, 3 H), 4.05 (q, *J* = 8.0 Hz, 1 H), 4.00–3.87 (m, 3 H), 3.68–3.64 (m, 1 H), 2.74–2.67 (m, 1 H), 2.50–2.46 (m, 1 H), 2.16 (s, 1 H), 2.07 (s, 3 H), 2.03 (s, 6 H), 1.97 (s, 6 H), 1.96 (s, 6 H), 1.94 (s, 3 H), 1.93 (s, 3 H), 1.91 (s, 3 H), 1.55–1.41 (m, 4 H), 1.29–1.17 (m, 4 H), 1.08–0.97 (m, 6 H), 0.86 (d, *J* = 6.4 Hz, 3 H), 0.81–0.79 (m, 6 H), 0.63 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.49, 170.46, 170.34, 170.05, 169.63, 169.36, 138.86, 123.44, 121.17, 99.56, 95.44, 88.75, 75.20, 72.49, 72.26, 72.17, 71.92, 71.69, 69.93, 69.63, 69.23, 68.39, 67.92, 67.82, 62.70, 62.50, 61.41, 61.35, 61.21, 56.58, 56.06, 49.95, 42.23, 39.59, 39.42, 39.32, 37.66, 36.64, 36.09, 35.69, 31.77, 31.71, 29.12, 28.13, 27.93, 24.19, 23.74, 22.74, 22.49, 20.92, 20.82, 20.60, 20.51, 19.26, 18.65, 11.78.

HRMS (ESI): m/z calcd for $C_{56}H_{83}N_3O_{18}$ [M + H]$^+$: 1086.5672; found: 1086.5594.

3q

Yield: 0.309 g (68%); white solid; mp 95 °C; $[\alpha]_D$ –80.0 (*c* = 0.004 g/mL, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.34 (m, 3 H), 7.31 (s, 1 H), 7.26–7.15 (m, 2 H), 6.78–6.63 (m, 5 H), 6.51–6.37 (m, 5 H), 5.45–5.42 (m, 2 H), 4.58–4.50 (m, 2 H), 4.45–4.40 (m, 3 H), 3.51–3.48 (m, 2 H), 3.42–3.36 (m, 3 H), 3.30–3.28 (m, 1 H), 3.04 (s, 5 H), 2.56–2.51 (m, 3 H), 2.08–1.97 (m, 6 H), 1.94–1.85 (m, 5 H), 1.83–1.73 (m, 8 H), 1.70–1.60 (m, 10 H), 1.57–1.44 (m, 8 H), 1.35–1.27 (m, 3 H), 1.21–1.12 (m, 5 H), 1.09 (s, 3H), 1.06 (s, 6 H), 1.00–0.98 (m, 6 H), 0.85 (s, 1 H), 0.82–0.80 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.72, 128.96, 128.58, 127.92, 127.49, 126.94, 123.59, 109.35, 82.02, 80.90, 80.80, 77.27, 73.68, 73.15. 72.60, 71.77, 67.62, 66.88, 62.20, 62.08, 56.54, 56.40, 56.34, 50.07, 49.87, 47.76, 43.02, 42.27, 41.63, 40.69, 40.28, 39.82, 39.67, 39.37, 39.16, 38.81, 37.29, 37.24, 37.10, 36.88, 36.67, 36.54, 33.17, 32.63, 32.05, 31.83, 31.77, 3.63, 31.47, 31.40, 31.35, 30.30, 29.49, 28.98, 28.82, 25.00, 24.25, 22.93, 22.51, 20.84, 20.30, 20.02, 19.75, 19.45, 19.25, 17.17, 16.66, 16.31, 14.55, 11.64.

HRMS (ESI): *m/z* calcd for $C_{83}H_{107}N_3O_{25}$ [M + H]$^+$: 1546.7194; found: 1546.7209.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(15) During the reviewing process of this manuscript, Rivera and co-workers reported a similar work on 'click' synthesis of triazole linkage as surrogate of the glycosidic bond. However, the authors only described the application of spirostanic analogues in the click process. See: Pérez-Labrada, K.; Brovard, I.; Morera, C.; Estevez, I.; Bermejo, J.; Rivera, D. G. *Tetrahedron* **2011**, *67*, 7713.