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Synthesis and antioxidant properties of novel α-tocopherol glycoconjugates

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ABSTRACT

Glycoconjugates of α-tocopherol (**1**), synthesized using click chemistry between α-tocopherol-azide and glyco-alkynes are solids, have enhanced water solubility and exhibit radical-scavenging activities comparable to **1**, as determined by DPPH and lipid peroxidation assay methods.

α-Tocopherol form of vitamin E, ((2*R*,4′*R*,8′*R*)-6-hydroxy-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chromane, (**1**) is a well-known antioxidant/radioprotective compound, which inhibits lipid peroxidation and other free radical-mediated reactions in biological systems.[1] It finds applications in prevention and treatment of many oxidative stress-induced diseases as well as in cosmetics and food preservation.[1,2] The antioxidant/radioprotective activity of **1** is thought to be associated with its ability to scavenge reactive oxygen species via its phenolic group.[3] However, the largely hydrophobic character of **1** makes it poorly soluble in aqueous media, which in some cases limits its therapeutic efficacy and this has a strong influence on its pharmacokinetic and pharmacodynamic properties. Efforts have been made to ameliorate these shortcomings of **1** by developing its water-soluble stable analogs, excellent accounts of which are available in the literature.[4] Thus, attempts have been made to prepare vitamin E analogs with enhanced amphiphilicity by attaching hydrophilic moieties like polyethylene glycol to the phenolic group of **1** via ester linkage[5] or by linking carbohydrate moieties to the phenolic group of **1** via ether linkage.[6–10] However, it is known that such ether-linked O-glycosides are resistant to enzymatic hydrolysis.[8] This can limit the bio-availability of phenolic group, crucial for the antioxidant/radioprotective activity of **1**. Attempts have also been directed towards design and synthesis of *C*-glycosyl compounds of vitamin E as amphiphilic antioxidants.[11–13]

Herein, we report the preparation and antioxidant properties of glycosyl compounds of **1** in which the carbohydrate moiety is attached away from its phenolic group at C-5a position. The novelty of the synthetic approach lies in the use of glyco-alkynes and tocopherol-azide to obtain the glycoconjugates under the click condition.[14] Glycoconjugates thus prepared are solid and show significant water solubility. These are biologically interesting and show radical-scavenging activity comparable to **1**. The solid nature and the enhanced water solubility together with the observed radical-scavenging activity make these glycoconjugates potentially useful antioxidant/radioprotective agents. Thus, this work presents a nice use of click, with good potential to offer simple methodology to design and access a wide variety of vitamin E compounds. It also presents a mechanism of increasing water solubility and stability of derivatives of therapeutically important **1**.

Towards our goal of designing solid vitamin E compounds, which are also water soluble and have good radical-scavenging activity, we first attempted the synthesis of glycoconjugates **11** and **12** (Scheme 1) in which the glycosyl moiety is attached via a triazole linker directly at the C-5 phenyl carbon atom of **1**. However, these glycoconjugates could not be obtained as their synthetic precursors **9** and **10**, respectively, turned out to be unstable. For the synthesis of compounds **9** and **10**, we employed the click chemistry between tocopherol-alkyne (**6**, 6-*O*-methyl-5-ethynyl-γ-tocopherol) and sugar-azides **7** and **8**. Tocopherol-alkyne (**6**) was synthesized from **1** in five steps. First, 6-*O*-acetyl-5-formyl-γ-tocopherol (**3**) was prepared from 6-*O*-acetyl-5a-bromo-α-tocopherol (**2**) as described in the literature[15], with slight modification of the reaction mixture work-up and product isolation. Thus, after the completion of the reaction between **2** and *N*-methyl morpholine *N*-oxide in acetonitrile, the solvent was removed from the reaction mixture under reduced pressure.

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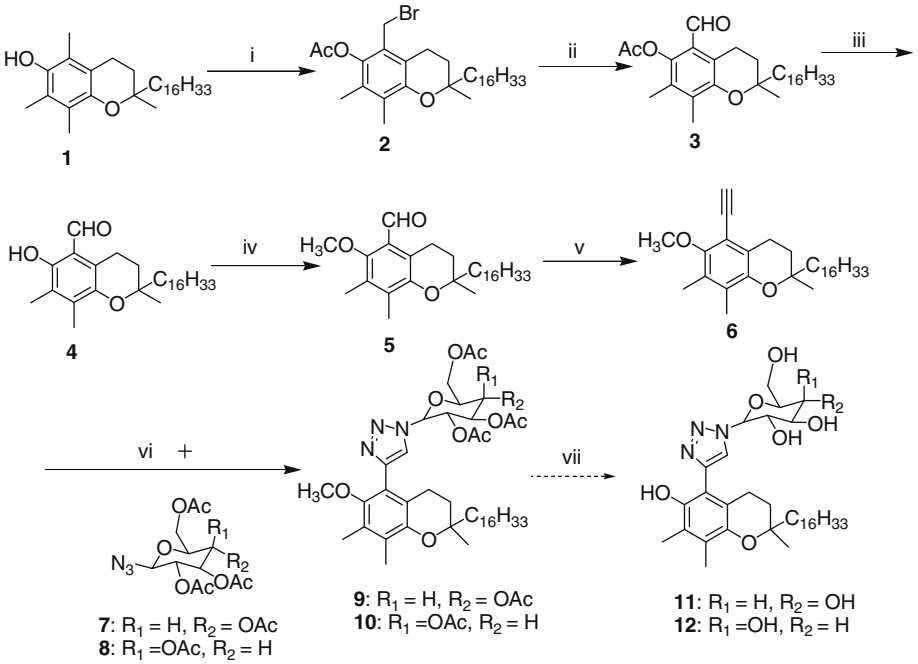


Scheme 1. Reagents and conditions: (i) (a) Br_2, *n*-hexane, rt, 3 h, (b) Ac_2O, AcOH, H_2SO_4, 78%; (ii) *N*-methyl morpholine *N*-oxide, MeCN, rt, 5 h, 98%; (iii) SiO_2, (100–200 mesh) column elution, 90%; (iv) 20% NaOH, Me_2SO_4, 40 °C, 3 h, 90%; (v) Bestmann–Ohira reagent [$(CH_3COCN_2P(O)(OEt)_2$], K_2CO_3, rt, 24 h, 40%; (vi) $CuSO_4{\cdot}5H_2O$, 1 mol %, sodium ascorbate 5 mol %, *t*-BuOH/H_2O, 1:1; (vii) $BBr_3{\cdot}OEt_2$, NaOMe–MeOH.

The viscous material obtained was then dissolved in petroleum ether (60–80 °C fraction) when *N*-methylmorpholine crystallized out leaving **3** in the mother liquor. The removal of petroleum ether from the mother liquor under reduced pressure yielded **3**. Aldehyde **3** was then placed on a silica gel column (100–200 mesh) and was slowly eluted with 1% EtOAc–petroleum ether (60–80 °C fraction) when 5-formyl-γ-tocopherol (**4**) was obtained due to hydrolysis of **3** on the silica column. Treatment of **4** with 20% NaOH/Me_2SO_4 mixture yielded 6-*O*-methyl-5-formyl-γ-tocopherol (**5**). For the synthesis of tocopherol-alkyne (**6**) from aldehyde **5**, we followed a general procedure described in the literature[16] for the preparation of alkynes from aldehydes using Bestmann–Ohira reagent[17] [$(CH_3COCN_2P(O)(OEt)_2$], which in turn was prepared as described elsewhere.[16,18] However, aldehydes **3** and **4** did not react with Bestman–Ohira reagent to give the corresponding alkynes.

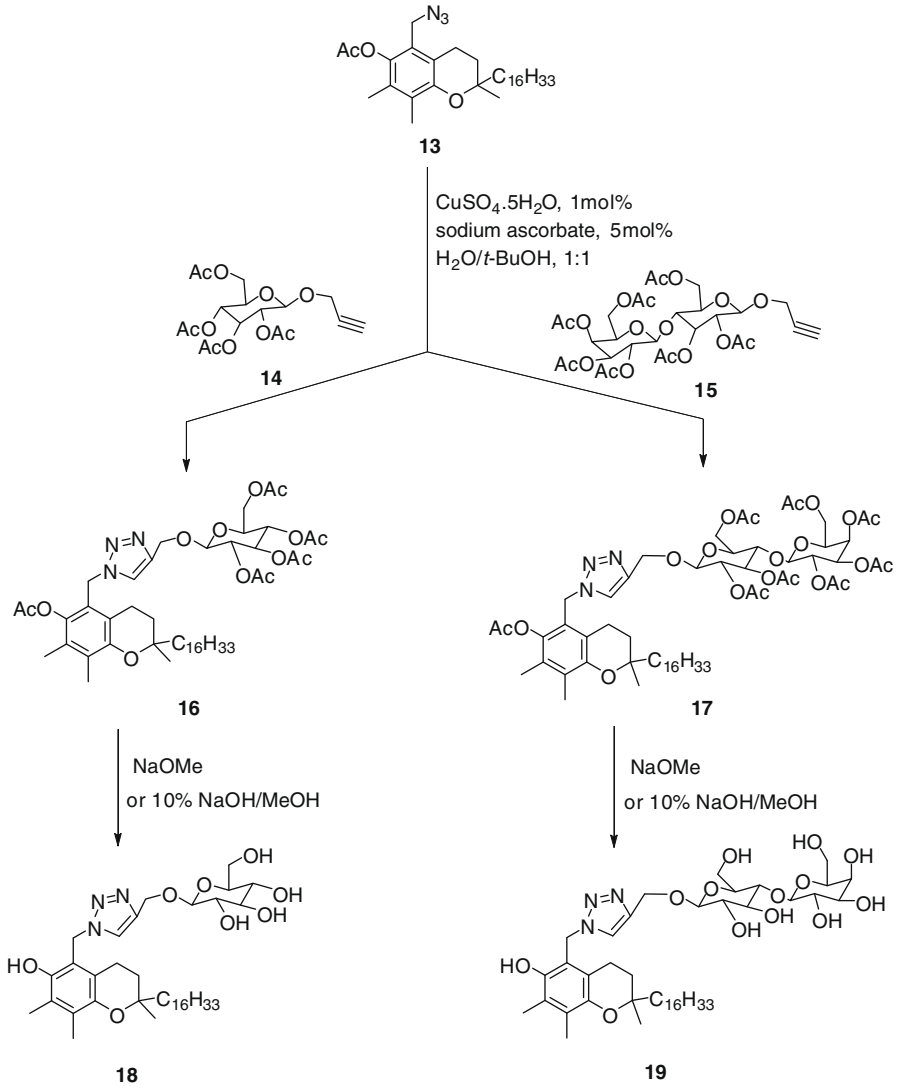
The preparation of glycoconjugates **9** and **10** was attempted through copper(I)-catalyzed cycloaddition process between azides and alkynes as described in the literature.[19] Thus, tocopherol-alkyne **6** was reacted with sugar-azides **7** and **8**, which in turn were synthesized according to the literature procedure.[20] ^1H and ^{13}C NMR and mass spectral analysis of the product obtained immediately after work-up showed the formation of **9**, which was found to be highly air sensitive and unstable. TLC of the reaction mixture showed the formation of **10**; however, it decomposed during its isolation from the reaction mixture. Therefore, demethylation and deacetylation of unstable **9** and **10** were not pursued.

In view of the observed instability of glycoconjugates prepared from sugar-azides and tocopherol-alkyne, in which the triazole unit is attached directly to the phenyl group of **1**, we attempted the synthesis of glycoconjugates by reacting glyco-alkynes with tocopherol-azide in which the triazole unit containing the glycosyl moiety is not directly linked to the phenyl ring of **1** but is linked to its C-5a methyl carbon atom. Thus, the reaction between tocopherol-azide (**13**) and glyco-alkynes (**14** and **15**) was performed by following known method[19], when the stable glycoconjugates (**16** and **17**) were obtained in high yields (Scheme 2).[21] Azide **13** was prepared by following the literature method.[22] Similarly, glyco-alkynes **14** and **15** were prepared as reported elsewhere.[23] 1,2,3-Triazole derivatives of vitamin E have earlier been synthesized via cycloaddition reaction between simple alkynes (up to 2.2 equiv) and tocopherol-azide under reflux condition in toluene.[22] In the present work, the triazole unit is introduced in **1** via Cu(I)-catalyzed click reaction between equimolar glyco-alkynes and tocopherol-azide at ambient temperature.

It is known that in the basic medium, 1,2,3-triazole derivatives of vitamin E break down to the corresponding NH-triazole and spiro-dimeric vitamin E.[22] Therefore, the base stability of 1,4-triazoles synthesized in this work was examined. Thus, glycoconjugates **16** and **17** were treated with freshly prepared NaOMe in methanol as well as with 10% methanolic NaOH at ambient temperature when the corresponding glycoconjugates **18** and **19** formed[24] (Scheme 2). Glycoconjugate **18** is a pale yellow solid in dry condition but it turns into a sticky yellow solid in the presence of air and moisture. Glycoconjugate **19** is an off-white solid and remains stable under ambient conditions.

Water solubility of **1** and glycoconjugate **19** was measured according to the literature procedure,[25] with a slight modification wherein saturated solutions of the test compounds were prepared in HPLC grade water by sonication at ambient temperature. For every addition of 100 μL of water, absorbance at 292 nm for **1** and 305.5 nm for **19** was measured. Plot of absorbance versus volume of water added gives the maximum volume of water required for solubilization. It is noted that in contrast to **1**, which showed water solubility of 20.8 mg/L (lit.[25] 20.9 mg/L), glycoconjugate **19** showed enhanced water solubility of 1.87 g/L.

The antiradical activities of **1** and glycoconjugates **18** and **19** were examined by their ability to quench the stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical[26] and by 2,2′-azobis(2-methylpropinonitrile) (AIBN)-induced lipid peroxidation methods.[27] DPPH radical shows a strong absorption at 517 nm but it pairs off in the presence of free radical scavenger and shows a significant reduction in the absorption peak. In lipid peroxidation method, the methyl linoleate oxidation at 55 °C (formation of conjugated diene)



Scheme 2.

in the presence of antioxidant is monitored periodically by the increase in absorbance at 233 nm. Spontaneous autoxidation of lipids is also monitored at the same temperature. The difference in the absorption spectra obtained (i.e., lipid oxidized in the presence of antioxidant—autoxidized lipid) is used for the determination of conjugated diene concentration, taking $\varepsilon = 25{,}200\ M^{-1}\ cm^{-1}$. Employing these two methods, we have also examined the antiradical activities of known hydrophilic antioxidants like Trolox and L-ascorbic acid and lipophilic antioxidants like **1** and butylated hydroxytoluene (BHT) and have compared the observed activities with the antiradical activities of compounds **18** and **19**.

The IC_{50} values as determined by employing DPPH method (Fig. 1) and the time lag to produce conjugated diene as measured by plotting incubation time versus concentration of conjugated diene formed (Fig. 2) are presented in Table 1. It is observed that the order of antiradical activity as measured by DPPH procedure is generally similar to the reports in the literature.[28] It is further observed that towards DPPH radical scavenging, glycoconjugates **18** and **19** show antiradical activities similar to those of the L-ascorbic acid; however, these are about five times less active as compared to Trolox. As compared to lipophilic BHT, these glycoconjugates are more active. Towards lipid peroxidation, glycoconjugates **18** and **19** show better antiradical ability than

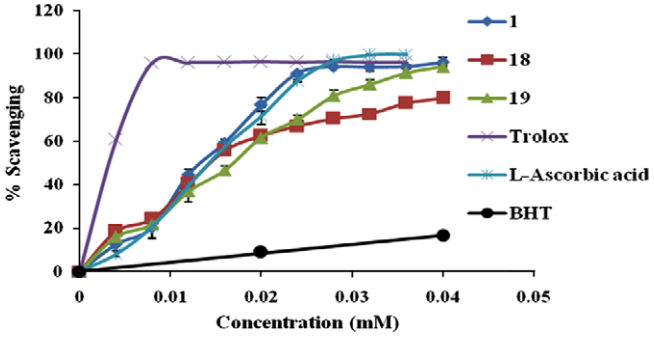


Figure 1. Antioxidant activity of different concentrations (0.004, 0.008, 0.012, 0.016 up to 0.04 mM) of **1**, **18**, **19**, Trolox, L-ascorbic acid and BHT as measured by DPPH (0.05 mM) radical scavenging assay at 25 °C.

Trolox, L-ascorbic acid and BHT. It is also notable that glycoconjugates **18** and **19 s**how DPPH radical-scavenging activity comparable to **1**. However, their ability to retard the formation of conjugated diene is slightly lower than that of **1**.

The solid nature and enhanced water solubility together with the observed radical-scavenging activities make these glycoconju-

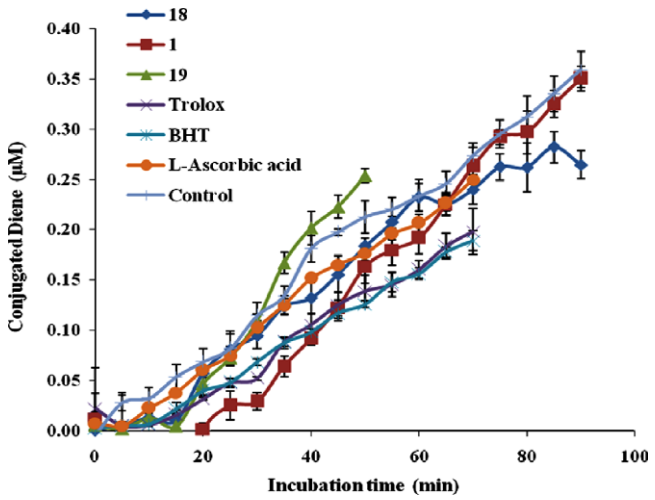


Figure 2. Induction of conjugated diene as monitored at 233 nm at regular time interval by the addition of 0.025 mM acetonitrile solution of AIBN to 0.25 mM acetonitrile solution of methyl linoleate. 0.005 mM solution of **1** in acetonitrile and **18**, **19**, Trolox, L-ascorbic acid and BHT in methanol were added at time zero. Control is methyl linoleate (0.25 mM) and AIBN (0.025 mM) in acetonitrile.

Table 1
IC_{50} and time lag values of **1**, **18**, **19**, Trolox, L-ascorbic acid and BHT

Compound	IC_{50} scavenging[a] (mM)	Time lag[a] (min)
1	0.013 ± 0.0002	18.08 ± 0.1562
18	0.014 ± 0.0136	14.10 ± 0.1002
19	0.016 ± 0.0044	14.52 ± 0.1156
Trolox	0.003 ± 0.0001	9.23 ± 0.4485
L-Ascorbic acid	0.014 ± 0.0011	2.73 ± 0.6391
BHT	0.16 ± 0.0045	7.98 ± 0.6472

[a] Values are mean ± standard deviation of three observations.

gates potentially useful as antioxidant/radioprotective agents. The commercial forms of **1** are usually available as acetate ester. The ester-protected phenolic –OH provides more stability to the compound and it gets deprotected in the biological system by the enzyme action.[29] The aceylated glycoconjugates (**16** and **17**) can be termed as provitamin E, which in biological systems can be activated by deacetylases, which cleave off the acetate group from the phenolic 6-*O* position, thus freeing the crucial phenolic –OH for radical scavenging.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.078.

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16. Meffre, P.; Hermann, S.; Durand, P.; Reginato, G.; Riu, A. *Tetrahedron* **2002**, *58*, 5159–5162. 6-*O*-Methyl-5-ethynyl-γ-tocopherol (**6**): Yield, 40%; Yellow dense oil; R_f = 0.29 (petroleum ether); IR (neat, cm^{-1}): *ν* 3604, 3271, 2989, 2934, 2115, 1650, 1456, 1383, 1257, 1056, 999, 896, 773; ^1H NMR (400 MHz, $CDCl_3$): 3.80 (s, 3H), 3.44 (s, 1H), 2.80 (t, *J* = 6.00 Hz, 2H), 2.16 (s, 3H), 2.11 (s, 3H), 1.78 (m, 2H), 1.59–0.83 (m, 36H, $C_{16}H_{33}$ and C (2a)H_3); ^{13}C NMR (100 MHz, $CDCl_3$): 153.5, 147.9, 128.4, 127.8, 121.4, 112.4, 84.5, 79.1, 75.8, 61.1, 40.1, 39.5, 37.7, 37.7, 37.6, 37.6, 33.0, 31.1, 28.1, 25.0, 24.6, 24.1, 22.79, 21.7, 21.2, 19.9, 19.85, 19.78, 12.5, 12.4; MS (ESI): *m/e* 425, 397 (100%), 362, 306, 278, 221.
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21. *Compound* **16**: Yield = 95%; mp = 85–86 °C; R_f = 0.20 (EtOAc/petroleum ether, 4:6); $[\alpha]_D^{20}$ −23.533 (*c* 0.600, $CHCl_3$); IR (KBr cm^{-1}): *ν* 2950, 2923, 2664, 1750, 1621, 1377, 1204, 902; ^1H NMR (400 MHz, $CDCl_3$): 7.34 (s, 1H), 5.37 (br s, 2H), 5.15 (m, 1H), 5.07 (t, *J* = 9.20 Hz, 1H), 4.96 (t, *J* = 8.00 Hz, 1H), 4.84 (d, *J* = 10.40 Hz, 1H), 4.74 (m, 1H), 4.60 (d, *J* = 8.00 Hz, 1H), 4.25 (dd, *J* = 4.20, 12.80 Hz, 1H), 4.10 (d, *J* = 10.40 Hz, 1H), 3.70 (m, 1H), 2.63 (br s, 2H), 2.32 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H), 1.90–0.70 (m, 50H); ^{13}C NMR (100 MHz, $CDCl_3$): 170.8, 170.3, 169.8, 169.5, 150.4, 141.3, 128.4, 128.1, 122.7, 121.3, 118.4, 99.5, 75.9, 73.0, 72.0, 71.3, 68.7, 62.0, 46.1, 40.4, 39.5, 37.5, 32.9, 32.8, 30.7, 28.1, 25.0, 24.6, 23.9, 22.8, 22.8, 21.1, 20.8, 20.7, 19.8, 13.3, 12.4; HRMS (ESI): calcd for $C_{48}H_{74}N_3O_{13}$ $[M+H]^+$ 900.5222, found 900.5182.
Compound **17**: Yield = 93%; mp = 82–83 °C; R_f = 0.20 (EtOAc/petroleum ether, 1:1); $[\alpha]_D^{20}$ −14.640 (*c* 1.00, $CHCl_3$); IR (KBr cm^{-1}): *ν* 2951, 2925, 2850, 1750, 1621, 1459, 1378, 1042, 803; ^1H NMR (400 MHz, $CDCl_3$): 7.33 (s, 1H), 5.45 (br s, 2H), 5.34 (d, *J* = 3.20 Hz, 1H), 5.14 (m, 1H), 4.94 (dd, *J* = 3.20, 10.00 Hz, 1H), 4.85 (m, 2H), 4.69 (m, 1H), 4.56 (d, *J* = 7.20 Hz, 1H), 4.48 (t, *J* = 6.40 Hz, 3H), 4.09 (m, 3H), 3.86 (t, *J* = 6.80 Hz, 1H), 3.78 (t, *J* = 9.20 Hz, 1H), 3.62 (m, 1H), 2.63 (br s, 2H), 2.32 (s, 3H), 2.15 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.02 (s, 3H), 1.97 (s, 3H), 1.90–0.70 (m, 38H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.4, 170.4, 170.2, 170.1, 169.8, 169.7, 169.1, 150.2, 141.5, 128.2, 128.0, 122.6, 121.0, 118.3, 101.1, 76.2, 75.8, 72.9, 72.6, 71.5, 71.0, 70.7, 69.1, 66.6, 61.9, 60.8, 46.0, 40.2, 39.4, 37.4, 37.3, 32.8, 32.7, 30.5, 28.0, 24.8, 24.5, 22.7, 22.6, 20.9, 20.8, 20.7, 20.5, 19.8, 19.8, 19.7, 13.2, 12.3; HRMS (ESI): calcd for $C_{60}H_{90}N_3O_{21}$ $[M+H]^+$ 1188.6067, found 1188.6073.
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24. *Compound* **18**: Yield, 83%; sticky solid; $[\alpha]_D^{20}$ −26.20 (*c* 0.20, MeOH); IR (KBr) cm^{-1}: *ν* 2925, 2868, 1635, 1462, 1377, 1079, 1047, 803, 628; ^1H NMR (400 MHz, CD_3OD): 7.89 (s, 1H), 5.63 (d, *J* = 3.20 Hz, 2H), 4.74 (disd, 2H), 4.56 (d, *J* = 16.00 Hz, 1H), 4.42 (t, *J* = 2.00 Hz, 1H), 4.35 (dd, *J* = 2.00, 8.00 Hz, 1H), 3.86 (m, 1H), 3.64 (m, 2H), 3.26–3.17 (m, 1H), 2.78 (m, 2H), 2.16 (s, 3H), 2.10 (s, 3H), 1.78–0.82 (m, 38H); ^{13}C NMR (100 MHz, CD_3OD): 148.2, 147.8, 128.7, 126.3, 125.8, 119.9, 119.8, 104.3, 78.7, 78.6, 76.8, 76.6, 75.6, 72.3, 63.4, 57.2, 48.0, 41.5, 41.2, 39.3, 39.2, 39.1, 38.9, 34.6, 34.55, 34.49, 34.4, 33.2, 29.8, 26.6, 26.1, 24.7, 23.8, 23.7, 22.6, 21.5, 20.8, 13.5, 13.2; HRMS (ESI): calcd for $C_{38}H_{64}N_3O_8$ $[M+H]^+$ 690.4693, found 690.4705.
Compound **19**: Yield = 90%; mp 164–165 °C (decomp.); R_f = 0.23 (MeOH/$CHCl_3$, 3:7); $[\alpha]_D^{20}$ −4.16 (*c* 0.25, MeOH); IR (KBr cm^{-1}): *ν* 3172, 2954, 1595, 1400, 1264, 1090, 1059, 782, 699, 638; ^1H NMR (300 MHz, DMSO-d_6): 8.13(s, 1H), 7.80 (s, 1H), 5.50 (s, 2H), 4.81 (d, *J* = 11.70 Hz, 1H), 4.56 (d, *J* = 11.70 Hz, 1H), 4.30 (d, *J* = 7.80 Hz, 1H), 4.19 (d, *J* = 6.90 Hz, 1H), 3.79 – 3.20 (m, 16H), 3.01(m, 1H), 2.73 (bm, 2H), 2.4 (t, *J* = 2.40 Hz, 2H), 2.08 (s, 3H), 2.00 (s, 3H), 1.90–0.80

(m, 38H); ^{13}C NMR (75 MHz, DMSO-d_6): 146.2, 144.9, 143.5, 125.4, 123.8, 123.6, 118.7, 117.7, 103.9, 101.9, 80.8, 75.6, 75.0, 74.3, 73.3, 73.1, 70.6, 68.2, 61.7, 60.6, 60.5, 45.1, 36.9, 36.8, 32.2, 30.9, 27.5, 24.3, 23.9, 23.2, 22.5, 20.5, 20.4, 19.6, 19.5, 19.4, 12.9, 12.0; MS (ESI): *m/e* 875, 874 $(M+Na)^+$ (100%), 689, 485, 342, 304, 242, 165, 74; Anal. Calcd for $C_{44}H_{73}N_3O_{13}$: C, 62.02; H, 8.64; N, 4.93; O, 24.21. Found: C, 59.48; H, 8.72; N, 4.67; O, 27.13.

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