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## ORIGINAL ARTICLE

# Selective modification of oleuropein, a multifunctional bioactive natural product

Amel Jerbi <sup>a</sup>, Paul Mosset <sup>b,\*</sup>, René Grée <sup>b</sup>, Majed Kammoun <sup>a,\*</sup>

<sup>a</sup> *Université de Sfax, Institut Supérieur de Biotechnologie, Unité de Recherche de Chimie Médicinale et Environnementale, UR-17-ES-40, BP 1175-3038 Sfax, Tunisia*

<sup>b</sup> *Univ Rennes, CNRS, ISCR (Institut des Sciences Chimiques de Rennes), UMR 6226, F-35000 Rennes, France*

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Click chemistry

**Abstract** Oleuropein is the major phenolic compound extracted from olive leaves and it is also present in olive fruits and virgin olive oil. It has already demonstrated a wide range of pharmacological activities, but new derivatives have to be designed in order to obtain useful Structure–Activity Relationships for this family of products, as well as new analogs with improved and/or different biological properties. However, taking into account the multiple OH groups (catechol and sugar) present in oleuropein, the selective modification of this natural product is a challenging problem. In this paper, we present an efficient strategy allowing the selective modification at the primary alcohol position of this natural product. Using appropriate protection/deprotection sequences, we prepared by hemisynthesis several triazoles linked to the oleuropein core, as representative examples for the development of such an approach.

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## 1. Introduction

Natural products are the source of numerous therapeutic agents, as already exemplified in many reviews [1–8] and books [9–11] published on this topic. A recent review by Newman and Cragg [5] indicated that among the 1562 new approved drugs in 1981–2014 by the U.S. FDA (and similar organiza-

tions) classified in eight categories, the second category was natural product derivatives (320, 21%), very close to the largest one which was synthetic products (420, 27%). It is also worthy of note that the three most important medical indications of natural product derivatives are anticancer, followed nearly equally by antibacterial and antiviral.

In this context, we started studies on oleuropein **1** easily obtained from the leaves of olive tree [12], a natural product which is also commercially available. Oleuropein and hydroxytyrosol, its degradation product, are known to be the main phenolic constituents which are also found in olives and in olive oil (Fig. 1). These compounds give to extra-virgin olive oil its bitter, pungent taste. Olive oil is known to be an essential constituent of the Mediterranean diet which has well established beneficial health effects [13–16]. Oleuropein itself was found to have miscellaneous useful pharmacological activities

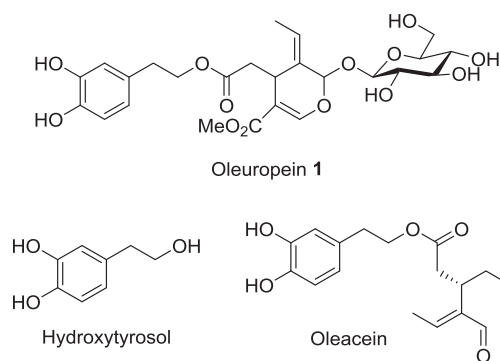
\* Corresponding authors.

E-mail addresses: [paul.mosset.1@univ-rennes1.fr](mailto:paul.mosset.1@univ-rennes1.fr) (P. Mosset), [majed.kammoun@isbs.usf.tn](mailto:majed.kammoun@isbs.usf.tn) (M. Kammoun).

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**Fig. 1** Chemical structures of oleuropein **1**, hydroxytyrosol and oleacein.

including antioxidant, anti-inflammatory, anti-atherogenic, anti-cancer, antimicrobial, antiviral ones, as well as hypolipidemic and hypoglycemic effects [17–23]. Our aim was to transform selectively and efficiently oleuropein **1** into new derivatives, suitable for further biological studies. In 2008 and 2009, Procopio et al. reported peracetylation of oleuropein by acetic anhydride with catalysis by erbium triflate [24,25]. Peracetylated oleuropein (Ac-Ole) was subsequently found to have improved biological properties (antioxidant, antitumor action in thyroid cancer cells, antiproliferative effects on breast cancer cells, prevention of hepatic steatosis, hyperinsulinemia, and weight gain) compared to oleuropein itself [26–28]. Except peracetylation, chemical transformations of **1** were almost exclusively degradative, with cleavage of its carbohydrate moiety [24,25,29–38], such as the one-step hemisynthesis of oleacein [39,40] known as a 5-lipoxygenase inhibitor (Fig. 1) [36]. There was a report on a series of semi-synthetic analogs of oleuropein with modification of the hydroxytyrosol part (substitution and variation of the length of the connecting chain as well as new alkyl esters, amide and thioesters derivatives) while keeping the glucose part, in free or peracetylated form, with good anticancer activity for some of them [41]. In this context, our aim was the selective manipulation of the hydroxyl groups of the glucose part in **1** while keeping its complex structure. Due to the presence of diverse functionalities in **1**, hydroxyls from the sugar and the catechol moieties combined with the esters and the two double bonds, this selective manipulation is a quite challenging problem. Ideally, we aimed to take advantage of the expectedly more reactive primary hydroxyl group.

## 2. Experimental

### 2.1. General

Most NMR spectra were recorded on Bruker spectrometers (Avance I 300 MHz, Avance III 300 MHz, and Avance III 400 MHz) using tetramethylsilane (TMS) as an internal standard. High resolution mass spectra were performed in Electro-spray positive ionization mode (ESI+) on a Thermo Fisher Scientific Q-Exactive spectrometer at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, ScanMAT UMS 2001, Université de Rennes 1). Solvents which were used for

electrospraying were methanol in the case of **1**, **2**, **6**, **8**, **10b**, **10c**, **11a**, **11c**, **11d**, CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>: 90/10 in the case of **3**, **7**, **10a**, CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH: 90/10 in the case of **4** and CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH: 90/10 in the case of **10d**, **11b**.

### 2.2. Materials

Initial experiments were done with oleuropein which was extracted from the roots of olive tree instead of the leaves. Its identity was checked by comparison with reported <sup>1</sup>H and <sup>13</sup>C NMR [42]. Then most experiments were performed with commercial oleuropein (Sigma–Aldrich, ≥80% (HPLC)). All other reagents and solvents were used from commercial sources as received except that for the synthesis of **2**, dichloromethane was distilled from calcium hydride prior to use.

### 2.3. Oleuropein monobenzoate (**2**)

To a solution of oleuropein (17 mg) in dichloromethane (0.5 mL) and pyridine (70 μL, 27 equiv) which was cooled at 0 °C, was added benzoyl cyanide (17 mg, 4 equiv). The reaction flask was flushed under nitrogen and tightly closed and the reaction was allowed to proceed at 0 °C under smooth stirring. The reaction was monitored by TLC (eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1). After about 15 h, the reaction mixture was transferred directly onto silica gel (0.60 g) in a pipette which was rinsed by CH<sub>2</sub>Cl<sub>2</sub>. First, gradient elution by CH<sub>2</sub>Cl<sub>2</sub> followed by 1% MeOH–CH<sub>2</sub>Cl<sub>2</sub> and then 2% MeOH–CH<sub>2</sub>Cl<sub>2</sub> eluted by-products (R<sub>f</sub> = 0.54 to 0.30 with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1), followed by a small amount of slightly less polar impurity. Then pure **2** was eluted with 5% MeOH–CH<sub>2</sub>Cl<sub>2</sub> (R<sub>f</sub> = 0.15 with CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1, 7.2 mg, 36%).

<sup>1</sup>H NMR (CD<sub>3</sub>COCD<sub>3</sub>, 400 MHz): δ 8.07–8.02 (m, 2H), 7.88–7.55 (broad envelope which topped at 7.69 ppm, ca. 1.3H), 7.60 (ddt, *J* = 8.0, 6.9, 1.3 Hz, 1H), 7.50–7.43 (m, 3H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 2.1 Hz, 1H), 6.53 (broad dd, *J* = 8.0, 2.1 Hz [ddt after improving the resolution, *J* = 8.0, 2.1, 0.6 Hz], 1H), 6.01 (qdd, *J* = 7.0, 1.4, 0.5 Hz, 1H), 5.88 (qdd after improving the resolution, *J* = 1.5, 1.4, 0.7 Hz, 1H), 4.91 (d, *J* = 7.8 Hz, 1H), 4.74 (dd, *J* = 11.8, 2.2 Hz, 1H), 4.67–4.33 (envelope which topped at 4.52 ppm, 3H), 4.44 (dd, *J* = 11.8, 7.0 Hz, 1H), 4.13 (dt, *J* = 10.7, 7.3 Hz, 1H), 4.01 (ddd, *J* = 10.7, 7.4, 6.7 Hz, 1H), 3.95 (broad dd, *J* = 9.6, 4.2 Hz [ddt after improving the resolution, *J* = 9.5, 4.2, 0.7 Hz], 1H), 3.78 (ddd, *J* = 9.3, 6.9, 2.1 Hz, 1H), 3.69 (s, 3H), 3.54 (dt, *J* = 12.7, 8.6 Hz, 1H), 3.54 (t, *J* = 2.6 Hz, 1H), 3.47–3.39 (m, 1H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.63 (dd, *J* = 14.3, 4.2 Hz, 1H), 2.23 (dd, *J* = 14.3, 9.6 Hz, 1H), 1.63 (dd, *J* = 7.1, 1.5 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 171.41 (C<sub>quat</sub>), 167.17 (C<sub>quat</sub>), 166.72 (C<sub>quat</sub>), 154.11 (CH), 145.80 (C<sub>quat</sub>), 144.54 (C<sub>quat</sub>), 133.91 (CH), 131.23 (C<sub>quat</sub>), 130.46 (C<sub>quat</sub>), 130.35 (2CH), 130.22 (C<sub>quat</sub>), 129.41 (2CH), 124.26 (CH), 121.15 (CH), 116.80 (CH), 116.15 (CH), 109.35 (C<sub>quat</sub>), 100.68 (CH), 94.57 (CH), 77.84 (CH), 75.43 (CH), 74.59 (CH), 71.61 (CH), 66.03 (CH<sub>2</sub>), 65.01 (CH<sub>2</sub>), 51.51 (CH<sub>3</sub>), 40.89 (CH<sub>2</sub>), 35.08 (CH<sub>2</sub>), 31.50 (CH), 13.51 (CH<sub>3</sub>); HRMS-ESI (*m/z*) [M + Na]<sup>+</sup> calcd for C<sub>32</sub>H<sub>36</sub>NaO<sub>14</sub>: 667.19973, found 667.1998, [M + K]<sup>+</sup> calcd for C<sub>32</sub>H<sub>36</sub>KO<sub>14</sub>: 683.17366, found 683.1733, [M – H + 2Na]<sup>+</sup> calcd for C<sub>32</sub>H<sub>35</sub>Na<sub>2</sub>O<sub>14</sub>: 689.18167, found 689.1814.

#### 2.4. Benzoylation of oleuropein. Synthesis of (3)

In a flame-dried flask under vacuum, oleuropein (100 mg, 0.185 mmol, 1.0 equiv) and cesium carbonate (271 mg, 0.83 mmol, 4.5 equiv) were introduced. Then acetonitrile (3.7 mL) followed by benzyl bromide (142 mg, 0.83 mmol, 4.5 equiv) were added. The reaction flask was flushed under nitrogen and tightly stoppered. After stirring for 16 h at 35 °C, water was added. Extraction with ethyl acetate, drying ( $\text{Na}_2\text{SO}_4$ ), concentration and chromatography of the remaining yellow oil on a column of silica gel (1.72 g, loaded with  $\text{CH}_2\text{Cl}_2$ ) with gradient elution with  $\text{CH}_2\text{Cl}_2$  + 1 to 2% MeOH afforded dibenzyl ether **3** (123 mg, 92%,  $R_f$  = 0.46 with  $\text{CH}_2\text{Cl}_2$ /MeOH 9:1 vs. 0.14 for oleuropein, white foam).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.45 (broad s, 1H), 7.45–7.37 (m centered at 7.42 ppm, 4H), 7.35–7.24 (m, 6H), 6.83 (d,  $J$  = 8.2 Hz, 1H), 6.81 (d,  $J$  = 2.0 Hz, 1H), 6.69 (dd,  $J$  = 8.2, 2.0 Hz, 1H), 6.02 (broad q,  $J$  = 7 Hz, 1H), 5.75 (broad s, 1H), 5.11 (s, 2H), 5.09 (s, 2H), 5.04–4.8 (envelope, 1H), 4.81 (broad d,  $J$  = 7.7 Hz, 1H), 4.72–4.43 (envelope which topped at 4.57 ppm, 1H), 4.19 (dt,  $J$  = 10.8, 7.1 Hz, 1H), 4.05 (dt,  $J$  = 10.8, 7.3 Hz, 1H), 3.92 (broad dd,  $J$  = 9.0, 4.5 Hz, 1H), 3.84 (very broad dd,  $J$  = 12, 2 Hz, 1H), 3.75 (very broad dd,  $J$  = 12, 4 Hz, 1H), 3.69–3.59 (m, 1H), 3.65 (s, 3H), 3.54 (broad t,  $J$  = 9.1 Hz, 1H), 3.49 (broad t,  $J$  = 8.5 Hz), 3.44–3.36 (m, 1H), 2.78 (t,  $J$  = 7.1 Hz, 2H), 2.74 (dd,  $J$  = 13.8, 4.2 Hz, 1H), 2.35 (dd,  $J$  = 13.8, 9.4 Hz, 1H), 1.60 (dd,  $J$  = 7.1, 1.2 Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.58 ( $\text{C}_{\text{quat}}$ ), 166.74 ( $\text{C}_{\text{quat}}$ ), 153.59 (CH), 148.97 ( $\text{C}_{\text{quat}}$ ), 147.76 ( $\text{C}_{\text{quat}}$ ), 137.35 ( $\text{C}_{\text{quat}}$ ), 137.29 ( $\text{C}_{\text{quat}}$ ), 130.98 ( $\text{C}_{\text{quat}}$ ), 128.58 ( $\text{C}_{\text{quat}}$ ), 128.44 (4CH), 127.78 (CH), 127.75 (CH), 127.40 (2CH), 127.31 (2CH), 124.41 (CH), 121.82 (CH), 116.04 (CH), 115.36 (CH), 108.37 ( $\text{C}_{\text{quat}}$ ), 100.06 (CH), 94.82 (CH), 76.19 (2CH), 73.22 (CH), 71.42 ( $\text{CH}_2$ ), 71.35 ( $\text{CH}_2$ ), 69.86 (CH), 65.49 ( $\text{CH}_2$ ), 61.78 ( $\text{CH}_2$ ), 51.46 ( $\text{OCH}_3$ ), 40.32 ( $\text{CH}_2$ ), 34.45 ( $\text{CH}_2$ ), 30.63 (CH), 13.32 ( $\text{CH}_3$ ); HRMS-ESI ( $m/z$ ) [ $\text{M} + \text{Na}$ ] $^+$  calcd for  $\text{C}_{39}\text{H}_{44}\text{NaO}_{13}$ : 743.26741, found 743.2675.

#### 2.5. 4-Nitrobenzoylation of oleuropein. Synthesis of (4)

In a flame-dried flask under vacuum, oleuropein (100 mg, 0.185 mmol, 1.0 equiv) and cesium carbonate (232 mg, 0.71 mmol, 3.84 equiv) were introduced. Then acetonitrile (3.7 mL) followed by 4-nitrobenzyl bromide (139.3 mg, 0.625 mmol, 3.38 equiv) were added. The reaction flask was flushed under nitrogen and tightly stoppered. After stirring for 15.5 h at 30 °C, water and ethyl acetate were added and the resulting mixture was sonicated for a few seconds. Partitioning, drying of the yellow organic layer ( $\text{Na}_2\text{SO}_4$ ), concentration and chromatography on a column of silica gel (1.70 g, loaded with  $\text{CH}_2\text{Cl}_2$ ) with gradient elution with  $\text{CH}_2\text{Cl}_2$  + 2–4% MeOH afforded di(4-nitrobenzyl) ether **4** (122.4 mg, 82%,  $R_f$  = 0.38 with  $\text{CH}_2\text{Cl}_2$ /MeOH 92:8 vs. 0.12 for oleuropein, yellow foam). Compound **4** eluted mostly with  $\text{CH}_2\text{Cl}_2$  + 3% MeOH and additionally 14.2 mg impure **4** was obtained.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  8.22 (half part of an  $\text{A}_2\text{X}_2$  system, 2H), 8.19 (half part of an  $\text{A}_2\text{X}_2$  system, 2H), 7.63 (half

part of an  $\text{A}_2\text{X}_2$  system with further small coupling with  $\text{CH}_2$ , 2H), 7.59 (half part of an  $\text{A}_2\text{X}_2$  system with further small coupling with  $\text{CH}_2$ , 2H), 7.44 (broad s, 1H), 6.84 (d,  $J$  = 8.3 Hz, 1H), 6.83 (d,  $J$  = 2.0 Hz, 1H), 6.76 (broad dd,  $J$  = 8.3, 2.0 Hz, 1H), 6.00 (broad q,  $J$  = 7 Hz [qdd after improving the resolution,  $J$  = 7.1, 1.4, 0.6 Hz], 1H), 5.74 (dq after improving the resolution,  $J$  = 1.7, 1.5, 0.6 Hz, 1H), 5.25 (s, 2H), 5.22 (s, 2H), 4.80 (d,  $J$  = 7.6 Hz, 1H), 4.40–4.15 (broad envelope which topped at 4.27 ppm, 1H), 4.21 (dt,  $J$  = 10.8, 6.8 Hz, 1H), 4.05 (dt,  $J$  = 10.8, 7.1 Hz, 1H), 4.05–3.93 (broad envelope which topped at 3.99 ppm, 1H), 3.88 (broad dd,  $J$  = 9.1, 4.1 Hz, 1H), 3.84 (superimposed envelope with signals of H-5 from about 3.9–3.81 ppm, 1H), 3.75 (broad envelope starting at 3.81 ppm and which topped at 3.76 ppm, 1H), 3.75–3.64 (m, 1H), 3.68 (s, 3H), 3.65–3.37 (m, 4H), 3.28–3.11 (broad envelope which topped at 3.20 ppm, 1H), 2.81 (t,  $J$  = 6.9 Hz, 2H), 2.74 (dd,  $J$  = 13.8, 4.3 Hz, 1H), 2.34 (dd,  $J$  = 13.8, 9.4 Hz, 1H), 1.54 (dd,  $J$  = 7.1, 1.4 Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.51 ( $\text{C}_{\text{quat}}$ ), 166.73 ( $\text{C}_{\text{quat}}$ ), 153.59 (CH), 148.35 ( $\text{C}_{\text{quat}}$ ), 147.57 (2 $\text{C}_{\text{quat}}$ ), 147.02 ( $\text{C}_{\text{quat}}$ ), 144.69 ( $\text{C}_{\text{quat}}$ ), 144.67 ( $\text{C}_{\text{quat}}$ ), 131.85 ( $\text{C}_{\text{quat}}$ ), 128.66 ( $\text{C}_{\text{quat}}$ ), 127.58 (2CH), 127.55 (2CH), 124.32 (CH), 123.79 (2CH), 123.78 (2CH), 122.45 (CH), 115.84 (CH), 115.18 (CH), 108.32 ( $\text{C}_{\text{quat}}$ ), 100.11 (CH), 94.82 (CH), 76.26 (CH), 76.24 (CH), 73.29 (CH), 70.09 ( $\text{CH}_2$ ), 70.02 ( $\text{CH}_2$ ), 69.97 (CH), 65.31 ( $\text{CH}_2$ ), 61.90 ( $\text{CH}_2$ ), 51.45 ( $\text{OCH}_3$ ), 40.29 ( $\text{CH}_2$ ), 34.44 ( $\text{CH}_2$ ), 30.65 (CH), 13.23 ( $\text{CH}_3$ ); HRMS-ESI ( $m/z$ ) [ $\text{M} + \text{Na}$ ] $^+$  calcd for  $\text{C}_{39}\text{H}_{42}\text{N}_2\text{NaO}_{17}$ : 833.23757, found 833.2374, [ $\text{M} + \text{K}$ ] $^+$  calcd for  $\text{C}_{39}\text{H}_{42}\text{KN}_2\text{O}_{17}$ : 849.21151, found 849.2108, [ $\text{M} - \text{H} + 2\text{Na}$ ] $^+$  calcd for  $\text{C}_{39}\text{H}_{41}\text{N}_2\text{Na}_2\text{O}_{17}$ : 855.21951, found 855.2187.

#### 2.6. Tosylation of (3). Synthesis of (5)

To dibenzyl ether **3** (115.5 mg, 0.16 mmol, 1.0 equiv) was added *p*-toluenesulfonyl chloride (62 mg, 0.32 mmol, 2.0 equiv), pyridine (77 mg, 0.96 mmol, 6.0 equiv) and  $\text{CH}_2\text{Cl}_2$  (1.82 mL, distilled over  $\text{CaH}_2$ ). The reaction flask was flushed under nitrogen and tightly stoppered. It was left aside in a refrigerator at ca. –5 °C for 63 h. After concentration, the remaining colorless oil was purified by chromatography on a column of silica gel (1.5 g, loaded with  $\text{CH}_2\text{Cl}_2$ ) with gradient elution with  $\text{CH}_2\text{Cl}_2$  + 0–2% MeOH afforded tosylate **5** (64.3 mg, 46%,  $R_f$  = 0.50 with  $\text{CH}_2\text{Cl}_2$ /MeOH 92:8 vs. 0.39 for **3**, white foam). Then elution with  $\text{CH}_2\text{Cl}_2$  + 4% MeOH afforded starting **3** (29.8 mg, 26% recovered **3**).

White solid becomes pasty at 50 °C and melts at about 85 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.73 (half-part of  $\text{A}_2\text{X}_2$  system, 2H), 7.47–7.39 (m, 5H), 7.38–7.22 (m, 8H), 6.85 (d,  $J$  = 8.2 Hz, 1H), 6.82 (d,  $J$  = 2.0 Hz, 1H), 6.70 (dd,  $J$  = 8.2, 2.0 Hz, 1H), 6.02 (qdd after improving the resolution,  $J$  = 7.1, 1.4, 0.7 Hz, 1H), 5.72 (qdd after improving the resolution,  $J$  = 1.6, 1.6, 0.5 Hz, 1H), 5.12 (s, 2H), 5.11 (s, 2H), 4.77 (d,  $J$  = 7.7 Hz, 1H), 4.34–4.22 (m, 2H), 4.19 (dt,  $J$  = 10.8, 7.2 Hz, 1H), 4.12 (dt,  $J$  = 10.8, 7.2 Hz, 1H), 3.97 (broad dd,  $J$  = 8.8, 4.4 Hz [ddt after improving the resolution,  $J$  = 8.9, 4.5, 0.7 Hz], 1H), 3.69 (s, 3H), 3.63–3.41 (m, 5H with 1H dd at 3.46 ppm,  $J$  = 8.8, 7.8 Hz), 3.4–3.05 (broad envelope, 1H), 2.79 (t,  $J$  = 7.2 Hz, 2H), 2.70 (dd,  $J$  = 14.6, 4.4 Hz, 1H), 2.38 (dd,  $J$  = 14.5, 8.9 Hz, 1H), 2.37 (s, 3H),

1.68 (dd,  $J = 7.1, 1.5$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.17 ( $\text{C}_{\text{quat}}$ ), 166.81 ( $\text{C}_{\text{quat}}$ ), 153.22 (CH), 148.95 ( $\text{C}_{\text{quat}}$ ), 147.68 ( $\text{C}_{\text{quat}}$ ), 145.05 ( $\text{C}_{\text{quat}}$ ), 137.39 ( $\text{C}_{\text{quat}}$ ), 137.30 ( $\text{C}_{\text{quat}}$ ), 132.57 ( $\text{C}_{\text{quat}}$ ), 131.18 ( $\text{C}_{\text{quat}}$ ), 129.93 (2CH), 128.49 ( $\text{C}_{\text{quat}}$ ), 128.45 (4CH), 127.92 (2CH), 127.78 (CH), 127.75 (CH), 127.40 (2CH), 127.31 (2CH), 124.63 (CH), 121.88 (CH), 115.99 (CH), 115.35 (CH), 108.55 ( $\text{C}_{\text{quat}}$ ), 99.48 (CH), 94.43 (CH), 75.91 (CH), 73.92 (CH), 73.09 (CH), 71.43 ( $\text{CH}_2$ ), 71.33 ( $\text{CH}_2$ ), 69.26 (CH), 68.53 ( $\text{CH}_2$ ), 65.29 ( $\text{CH}_2$ ), 51.46 ( $\text{CH}_3$ ), 40.06 ( $\text{CH}_2$ ), 34.48 ( $\text{CH}_2$ ), 30.19 (CH), 21.62 ( $\text{CH}_3$ ), 13.43 ( $\text{CH}_3$ ); HRMS–ESI ( $m/z$ ) [ $\text{M} + \text{Na}$ ] $^+$  calcd for  $\text{C}_{46}\text{H}_{50}\text{NaO}_{15}\text{S}$ : 897.27626, found 897.2760; Anal. calcd. for  $\text{C}_{46}\text{H}_{50}\text{O}_{15}\text{S}$ : C, 63.15; H, 5.76; N, 0.00; S, 3.66; found: C, 62.60; H, 5.66; N, 0.00; S, 3.56.

### 2.7. Tosylation of (4). Synthesis of (6)

To di(4-nitrobenzyl) ether **4** (105.4 mg, 0.13 mmol, 1.0 equiv) was added *p*-toluenesulfonyl chloride (63.2 mg, 0.325 mmol, 2.5 equiv), pyridine (63 mg, 0.78 mmol, 6.0 equiv) and  $\text{CH}_2\text{Cl}_2$  (0.85 mL, distilled over  $\text{CaH}_2$ ). The reaction flask was flushed under nitrogen and tightly stoppered. It was left aside in a refrigerator at ca.  $-5^\circ\text{C}$  for 87 h. After concentration, the remaining residue was purified by chromatography on a column of silica gel (1.36 g, loaded with  $\text{CH}_2\text{Cl}_2$ ) with gradient elution with  $\text{CH}_2\text{Cl}_2 + 0$ –1% MeOH afforded tosylate **6** (70.5 mg, 56%,  $R_f = 0.47$  with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  92:8 vs. 0.38 for **4**, white foam). Then elution with  $\text{CH}_2\text{Cl}_2 + 2$ –4% MeOH afforded starting **3** (32 mg, 30% recovered **3**).

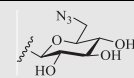
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.22 (half-part of  $\text{A}_2\text{X}_2$  system, 2H), 8.21 (half-part of  $\text{A}_2\text{X}_2$  system, 2H), 7.75 (half-part of  $\text{A}_2\text{X}_2$  system, 2H), 7.65–7.57 (two half-parts of  $\text{A}_2\text{X}_2$  system coupled with  $\text{CH}_2$  at 7.62 and 7.59 ppm, 4H), 7.45 (broad t, [t after improving the resolution,  $J = 0.6$  Hz], 1H), 7.33–7.27 (m centered at 7.30 ppm, 2H), 6.85 (d,  $J = 8.2$  Hz, 1H), 6.85 (d,  $J = 1.9$  Hz, 1H), 6.77 (dd,  $J = 8.2, 1.9$  Hz, 1H), 6.00 (qdd after improving the resolution,  $J = 7.1, 1.5, 0.7$  Hz, 1H), 5.72 (dq after improving the resolution,  $J = 1.6, 1.5, 0.4$  Hz, 1H), 5.24 (s, 2H), 5.22 (s, 2H), 4.77 (d,  $J = 7.7$  Hz, 1H), 4.32 (dd,  $J = 11.1, 0.5$  Hz, 1H), 4.25 (dd,  $J = 11.1, 4.0$  Hz, 1H), 4.22 (dt,  $J = 10.8, 7.0$  Hz, 1H), 4.14 (dt,  $J = 10.8, 7.2$  Hz, 1H), 3.94 (broad dd,  $J = 8.9, 4.3$  Hz [ddt after improving the resolution,  $J = 9.0, 4.5, 0.6$  Hz], 1H), 3.71 (s, 3H), 3.63–3.41 (m, 4H with 1H dd at 3.45 ppm,  $J = 8.8, 7.8$  Hz), 3.35–2.8 (broad envelope, 3H), 2.83 (t,  $J = 7.1$  Hz, 2H), 2.71 (dd,  $J = 14.5, 4.4$  Hz, 1H), 2.38 (dd,  $J = 14.5, 9.0$  Hz, 1H), 2.41 (s, 3H), 1.63 (dd,  $J = 7.1, 1.5$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.09 ( $\text{C}_{\text{quat}}$ ), 166.78 ( $\text{C}_{\text{quat}}$ ), 153.17 (CH), 148.33 ( $\text{C}_{\text{quat}}$ ), 147.57 ( $\text{C}_{\text{quat}}$ ), 146.87 ( $\text{C}_{\text{quat}}$ ), 145.15 ( $\text{C}_{\text{quat}}$ ), 144.71 ( $\text{C}_{\text{quat}}$ ), 144.67 ( $\text{C}_{\text{quat}}$ ), 132.63 ( $\text{C}_{\text{quat}}$ ), 132.12 ( $\text{C}_{\text{quat}}$ ), 129.96 (2CH), 128.48 ( $\text{C}_{\text{quat}}$ ), 127.95 (2CH), 127.54 (2CH), 127.51 (2CH), 124.60 (CH), 123.82 (2CH), 123.79 (2CH), 122.48 (CH), 115.72 (CH), 115.15 (CH), 108.52 ( $\text{C}_{\text{quat}}$ ), 99.49 (CH), 94.35 (CH), 75.98 (CH), 73.91 (CH), 73.16 (CH), 70.10 ( $\text{CH}_2$ ), 69.95 ( $\text{CH}_2$ ), 69.26 (CH), 68.46 ( $\text{CH}_2$ ), 65.09 ( $\text{CH}_2$ ), 51.46 ( $\text{CH}_3$ ), 39.96 ( $\text{CH}_2$ ), 34.49 ( $\text{CH}_2$ ), 30.19 (CH), 21.67 ( $\text{CH}_3$ ), 13.36 ( $\text{CH}_3$ ); HRMS–ESI ( $m/z$ ) [ $\text{M} + \text{Na}$ ] $^+$  calcd for  $\text{C}_{46}\text{H}_{48}\text{N}_2\text{NaO}_{19}\text{S}$ : 987.24642, found 987.2463, [ $\text{M} + \text{K}$ ] $^+$  calcd for  $\text{C}_{46}\text{H}_{48}\text{KN}_2\text{O}_{19}\text{S}$ : 1003.22036, found 1003.2192, [ $\text{M} - 2\text{O}_2\text{NC}_6\text{H}_4\text{CH}_2 + \text{Na}$ ] $^+$  calcd for  $\text{C}_{32}\text{H}_{36}\text{NaO}_{15}\text{S}$ : 715.16671, found 715.1669.

### 2.8. Synthesis of catechol-protected azide (7)

To tosylate **5** (66.5 mg, 0.076 mmol, 1.0 equiv) was added sodium azide (20 mg, 0.304 mmol, 4.0 equiv) and DMSO (0.66 mL). The reaction flask was flushed under nitrogen and tightly stoppered. After stirring for 17 h at  $70^\circ\text{C}$  and cooling down, water was added and the resulting mixture was extracted 3 times with ethyl acetate. Each organic extract was washed with water and the resulting aqueous phase was combined with the foregoing one before a subsequent extraction. After drying ( $\text{Na}_2\text{SO}_4$ ) and concentration, the remaining residue was purified by chromatography on a column of silica gel (1 g, loaded with  $\text{CH}_2\text{Cl}_2$ ) with gradient elution with  $\text{CH}_2\text{Cl}_2 + 0$ –2% MeOH afforded azide **7** (39.5 mg, 70%,  $R_f = 0.44$  with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  92:8, colorless oil).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.47 (s, 1H), 7.46–7.40 (m, 4H), 7.38–7.26 (m, 6H), 6.86 (d,  $J = 8.2$  Hz, 1H), 6.81 (d,  $J = 2.0$  Hz, 1H), 6.71 (dd,  $J = 8.2, 2.0$  Hz, 1H), 6.03 (broad qd,  $J = 7.0, 1.0$  Hz, 1H), 5.76 (broad t,  $J = 1.3$  Hz, 1H), 5.13 (s, 2H), 5.12 (s, 2H), 4.82 (d,  $J = 7.7$  Hz, 1H), 4.18 (dt,  $J = 10.8, 7.3$  Hz, 1H), 4.12 (dt,  $J = 10.8, 7.3$  Hz, 1H), 3.98 (broad dd,  $J = 8.9, 4.3$  Hz, 1H), 3.69 (s, 3H), 3.64–3.38 (m, 6H), 3.14 (broad envelope from 3.25 to 3.02 ppm, 2H), 2.80 (t,  $J = 7.2$  Hz, 2H), 2.70 (dd,  $J = 14.7, 4.4$  Hz, 1H), 2.37 (dd,  $J = 14.7, 9.0$  Hz, 1H), 1.74 (broad envelope from 1.90 to 1.58 ppm, 1 OH + water), 1.69 (dd,  $J = 7.1, 1.3$  Hz [dd,  $J = 7.1, 1.5$  Hz after improving the resolution], 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.17 ( $\text{C}_{\text{quat}}$ ), 166.81 ( $\text{C}_{\text{quat}}$ ), 153.13 (CH), 148.93 ( $\text{C}_{\text{quat}}$ ), 147.67 ( $\text{C}_{\text{quat}}$ ), 137.36 ( $\text{C}_{\text{quat}}$ ), 137.27 ( $\text{C}_{\text{quat}}$ ), 131.15 ( $\text{C}_{\text{quat}}$ ), 128.51 ( $\text{C}_{\text{quat}}$ ), 128.46 (4CH), 127.81 (CH), 127.77 (CH), 127.39 (2CH), 127.32 (2CH), 124.62 (CH), 121.84 (CH), 115.96 (CH), 115.34 (CH), 108.70 ( $\text{C}_{\text{quat}}$ ), 99.49 (CH), 94.54 (CH), 76.10 (CH), 75.80 (CH), 73.31 (CH), 71.45 ( $\text{CH}_2$ ), 71.35 ( $\text{CH}_2$ ), 70.59 (CH), 65.23 ( $\text{CH}_2$ ), 51.51 ( $\text{CH}_3$ ), 51.11 ( $\text{CH}_2$ ), 39.99 ( $\text{CH}_2$ ), 34.50 ( $\text{CH}_2$ ), 30.18 (CH), 13.46 ( $\text{CH}_3$ ); HRMS–ESI ( $m/z$ ) [ $\text{M} + \text{Na}$ ] $^+$  calcd for  $\text{C}_{39}\text{H}_{43}\text{N}_3\text{NaO}_{12}$ : 768.27389, found 768.2739, [ $\text{M} + \text{K}$ ] $^+$  calcd for  $\text{C}_{39}\text{H}_{43}\text{KN}_3\text{O}_{12}$ : 784.24783, found 784.2480, [ $\text{M} + \text{NH}_4$ ] $^+$  calcd for  $\text{C}_{39}\text{H}_{47}\text{N}_4\text{O}_{12}$ : 763.3185, found 763.3191, [ $\text{M} - \text{C}_6\text{H}_{10}\text{N}_3\text{O}_4 + \text{H} + \text{Na}$ ] $^+$  calcd for  $\text{C}_{33}\text{H}_{34}\text{NaO}_8$ : 581.21459, found 581.2148.

$\text{C}_6\text{H}_{10}\text{N}_3\text{O}_4$ :



### 2.9. Synthesis of catechol-unprotected azide (8)

As described for **7**, tosylate **6** (61 mg, 0.063 mmol, 1.0 equiv) was reacted with sodium azide (15 mg, 0.23 mmol, 3.65 equiv) in DMSO  $d_6$  (0.643 mL) for 17.5 h at  $60^\circ\text{C}$ . The use of a deuterated solvent prevented having any trace of DMSO disturbing NMR analysis of the product. Chromatography of the crude brown foam on a column of silica gel (1.6 g, loaded with  $\text{CH}_2\text{Cl}_2$ ) with gradient elution with  $\text{CH}_2\text{Cl}_2 + 0$ –5% MeOH afforded azide **8** (14 mg, 39%,  $R_f = 0.18$  with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  92:8, yellow oil).

$^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  7.81–7.69 (m which topped at 7.74 ppm, 2H), 7.48 (t,  $J = 0.7$  Hz, 1H), 6.75 (d,  $J = 8.0$  Hz, 1H), 6.75 (d,  $J = 2.1$  Hz, 1H), 6.58 (ddt,



$J = 8.0, 2.1, 0.6$  Hz, 1H), 6.05 (qdd,  $J = 7.1, 1.5, 0.7$  Hz, 1H), 5.89 (qdd after improving the resolution,  $J = 1.5, 1.5, 0.6$  Hz, 1H), 4.91 (d,  $J = 7.6$  Hz, 1H), 4.56 (broad d,  $J = 3.8$  Hz, 1H), 4.47 (broad d,  $J = 4.5$  Hz, 1H), 4.44 (very broad d,  $J = 3.4$  Hz, 1H), 4.17 (dt,  $J = 10.7, 7.2$  Hz, 1H), 4.10 (dt,  $J = 10.7, 7.2$  Hz, 1H), 3.99 (ddt,  $J = 9.5, 4.2, 0.7$  Hz, 1H), 3.69 (s, 3H), 3.63 (dt,  $J = 9.5, 4.7$  Hz, 1H), 3.55–3.45 (m, 3H), 3.44–3.31 (m, 2H), 2.76 (t,  $J = 7.2$  Hz, 2H), 2.70 (dd,  $J = 14.6, 4.2$  Hz, 1H), 2.37 (dd,  $J = 14.6, 9.5$  Hz, 1H), 1.70 (dd,  $J = 7.1, 1.5$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  171.48 ( $\text{C}_{\text{quat}}$ ), 167.21 ( $\text{C}_{\text{quat}}$ ), 154.08 (CH), 145.87 ( $\text{C}_{\text{quat}}$ ), 144.55 ( $\text{C}_{\text{quat}}$ ), 130.45 ( $\text{C}_{\text{quat}}$ ), 130.30 ( $\text{C}_{\text{quat}}$ ), 124.26 (CH), 121.09 (CH), 116.80 (CH), 116.11 (CH), 109.40 ( $\text{C}_{\text{quat}}$ ), 100.47 (CH), 94.54 (CH), 77.52 (CH), 77.15 (CH), 74.57 (CH), 72.00 (CH), 66.04 ( $\text{CH}_2$ ), 52.30 ( $\text{CH}_2$ ), 51.55 ( $\text{CH}_3$ ), 40.76 ( $\text{CH}_2$ ), 35.09 ( $\text{CH}_2$ ), 31.36 (CH), 13.61 ( $\text{CH}_3$ ); HRMS–ESI ( $m/z$ )  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{25}\text{H}_{31}\text{N}_3\text{NaO}_{12}$ : 588.17999, found 588.1800,  $[\text{M} + \text{K}]^+$  calcd for  $\text{C}_{25}\text{H}_{31}\text{KN}_3\text{O}_{12}$ : 604.15393, found 604.1539,  $[\text{M} - \text{H} + 2\text{Na}]^+$  calcd for  $\text{C}_{25}\text{H}_{30}\text{N}_3\text{Na}_2\text{O}_{12}$ : 610.16194, found 610.1621,  $[\text{M} - \text{N}_2 + \text{Na}]^+$  calcd for  $\text{C}_{25}\text{H}_{31}\text{NNaO}_{12}$ : 560.17385, found 560.1741,  $[\text{M} - \text{C}_6\text{H}_{10}\text{N}_3\text{O}_4 + \text{H} + \text{Na}]^+$  calcd for  $\text{C}_{19}\text{H}_{22}\text{NaO}_8$ : 401.12069, found 401.1211,  $[\text{M} - \text{C}_6\text{H}_{10}\text{N}_3\text{O}_4 + \text{H} - \text{H}_2\text{O} + \text{Na}]^+$  calcd for  $\text{C}_{19}\text{H}_{20}\text{NaO}_7$ : 383.11012, found 383.1105,  $[\text{M} - \text{C}_6\text{H}_{10}\text{N}_3\text{O}_4 + \text{H} - \text{CH}_3\text{OH} + \text{Na}]^+$  calcd for  $\text{C}_{18}\text{H}_{18}\text{O}_7\text{Na}$ : 369.09447, found 369.0949,  $[(\text{HO})_2\text{C}_6\text{H}_3\text{CH}_2\text{CH}_2]^+$  calcd for  $\text{C}_8\text{H}_9\text{O}_2$ : 137.05970, found 137.0594.

### 2.10. General procedure for the “click reaction” (CuAAC). Synthesis of 1,2,3-triazoles (10a–d)

To a stirred solution of azide **7** (37.3 mg, 0.05 mmol) and alkyne (0.075 mmol for **9a** or **9b**, 0.15 mmol for **9c** or **9d**) in *tert*-butanol (0.25 mL) and water (0.25 mL) was added copper(II) sulfate pentahydrate (4.2 mg, 0.33 equiv) and sodium ascorbate (7.3 mg, 0.73 equiv). After stirring for 16 h at 40 °C, TLC monitoring (elution with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  92:8) showed a complete reaction. Aqueous ammonium hydroxide and ethyl acetate were added to the reaction mixture. After partitioning, drying of the organic phase ( $\text{Na}_2\text{SO}_4$ ), and concentration under vacuum, the remaining residue was purified by chromatography on silica gel with gradient elution using a  $\text{CH}_2\text{Cl}_2/(0\text{--}3\%)$  MeOH solvent system (up to 8% MeOH in the case of **10d**) to afford triazole **10a–d**.

#### 2.10.1. 1,2,3-Triazole (10a) made by condensation of azide **7** with phenylacetylene

Colorless oil. Yield: 94%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.96 (s, 1H), 7.72 (broad dd,  $J = 7.8, 1.3$  Hz, 2H), 7.45–7.37 (m, 4H), 7.37–7.14 (m, 10H), 6.83 (d,  $J = 8.2$  Hz, 1H), 6.80 (d,  $J = 1.9$  Hz, 1H), 6.67 (dd,  $J = 8.2, 1.9$  Hz, 1H), 5.98 (broad q,  $J = 7.0$  Hz, 1H), 5.66 (broad s, 1H), 5.09 (s, 4H), 4.83 (d,  $J = 7.7$  Hz, 1H), 4.75 (very broad d,  $J = 14.5$  Hz, 1H), 4.66 (very broad dd,  $J = 14.4, 5.0$  Hz, 1H), 4.21 (dt,  $J = 10.7, 7.1$  Hz, 1H), 4.01 (dt,  $J = 10.4, 7.3$  Hz, 1H), 3.89 (dd,  $J = 9.8, 4.3$  Hz, 1H), 3.81–3.72 (m, 1H), 3.70 (broad t,  $J = 9.0$  Hz, 1H), 3.62 (s, 3H), 3.43 (dd,  $J = 8.8, 8.0$  Hz, 1H), 3.26 (t,  $J = 9.2$  Hz, 2H), 3.50–2.97 (broad envelope, 5H), 2.79 (t,  $J = 7.1$  Hz, 2H), 2.71 (dd,  $J = 13.3, 4.3$  Hz, 1H), 2.15 (dd,  $J = 13.3, 10.0$  Hz, 1H), 1.55 (dd,  $J = 7.0, 1.1$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.10 ( $\text{C}_{\text{quat}}$ ), 166.64

( $\text{C}_{\text{quat}}$ ), 153.57 (CH), 148.96 ( $\text{C}_{\text{quat}}$ ), 147.72 ( $\text{C}_{\text{quat}}$ ), 147.44 ( $\text{C}_{\text{quat}}$ ), 137.30 ( $\text{C}_{\text{quat}}$ ), 137.23 ( $\text{C}_{\text{quat}}$ ), 130.94 ( $\text{C}_{\text{quat}}$ ), 129.99 ( $\text{C}_{\text{quat}}$ ), 128.72 (2CH), 128.45 (2CH), 128.44 (2CH), 128.37 ( $\text{C}_{\text{quat}}$ ), 128.23 (CH), 127.79 (CH), 127.77 (CH), 127.37 (2CH), 127.29 (2CH), 125.73 (2CH), 124.06 (CH), 122.57 (CH), 121.78 (CH), 115.95 (CH), 115.32 (CH), 108.17 ( $\text{C}_{\text{quat}}$ ), 99.54 (CH), 94.02 (CH), 75.91 (CH), 73.99 (CH), 73.08 (CH), 71.38 ( $\text{CH}_2$ ), 71.29 ( $\text{CH}_2$ ), 70.13 (CH), 65.33 ( $\text{CH}_2$ ), 51.36 ( $\text{CH}_3$ ), 50.60 ( $\text{CH}_2$ ), 40.59 ( $\text{CH}_2$ ), 34.50 ( $\text{CH}_2$ ), 30.83 (CH), 13.24 ( $\text{CH}_3$ ); HRMS–ESI ( $m/z$ )  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{47}\text{H}_{49}\text{N}_3\text{NaO}_{12}$ : 870.32084, found 870.3207,  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{47}\text{H}_{50}\text{N}_3\text{O}_{12}$ : 848.33890, found 848.3393,  $[\text{M} + \text{K}]^+$  calcd for  $\text{C}_{47}\text{H}_{49}\text{KN}_3\text{O}_{12}$ : 886.29478, found 886.2936.

#### 2.10.2. 1,2,3-Triazole (10b) made by condensation of azide **7** with 1-octyne

Colorless oil. Yield: 75%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.46–7.42 (m, 5H), 7.41 (almost broad s with several weak couplings, 1H), 7.38–7.26 (m, 6H), 6.86 (d,  $J = 8.2$  Hz, 1H), 6.83 (d,  $J = 2.0$  Hz, 1H), 6.71 (dd,  $J = 8.2, 2.0$  Hz, 1H), 6.03 (broad qd,  $J = 7.1, 0.8$  Hz [qdd after improving the resolution,  $J = 7.1, 1.5, 0.7$  Hz], 1H), 5.66 (broad t,  $J = 1.3$  Hz, 1H), 5.13 (s, 2H), 5.11 (s, 2H), 4.79 (d,  $J = 7.8$  Hz, 1H), 4.67 (dd,  $J = 14.6, 2.8$  Hz, 1H), 4.61 (dd,  $J = 14.6, 5.1$  Hz, 1H), 4.49–4.33 (broad envelope which topped at 4.41 ppm, 1H), 4.25 (dt,  $J = 10.8, 7.0$  Hz, 1H), 4.31–4.14 (broad envelope which superimposed to signals of H-1'b, 1H), 4.08 (dt,  $J = 10.8, 7.2$  Hz, 1H), 3.97 (broad dd,  $J = 9.7, 4.2$  Hz, 1H), 3.70 (s, 3H), 3.74–3.59 (m, 2H), 3.38 (dd after improving the resolution,  $J = 9.0, 8.0$  Hz, 1H), 3.34–3.22 (broad envelope which topped at 3.28 ppm, 1H), 3.14 (broad dd,  $J = 9.3, 8.5$  Hz, 1H), 2.86 (dd,  $J = 13.7, 4.3$  Hz, 1H), 2.83 (dd,  $J = 7.2, 6.9$  Hz, 2H), 2.62 (broad dd,  $J = 7.9, 7.5$  Hz, 2H), 2.28 (dd,  $J = 13.7, 9.9$  Hz, 1H), 1.84–1.69 (broad envelope which topped at 1.74 ppm, 4H), 1.64 (dd,  $J = 7.1, 1.5$  Hz, 3H), 1.62–1.54 (m, 2H), 1.34–1.18 (m, 6H), 0.84 (pseudo t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.99 ( $\text{C}_{\text{quat}}$ ), 166.68 ( $\text{C}_{\text{quat}}$ ), 153.41 (CH), 149.06 ( $\text{C}_{\text{quat}}$ ), 148.42 ( $\text{C}_{\text{quat}}$ ), 147.86 ( $\text{C}_{\text{quat}}$ ), 137.32 ( $\text{C}_{\text{quat}}$ ), 137.27 ( $\text{C}_{\text{quat}}$ ), 131.00 ( $\text{C}_{\text{quat}}$ ), 128.51 ( $\text{C}_{\text{quat}}$ ), 128.47 (4CH), 127.83 (CH), 127.80 (CH), 127.40 (2CH), 127.32 (2CH), 124.26 (CH), 123.28 (CH), 121.81 (CH), 116.11 (CH), 115.43 (CH), 108.39 ( $\text{C}_{\text{quat}}$ ), 99.73 (CH), 94.31 (CH), 75.92 (CH), 74.30 (CH), 73.16 (CH), 71.47 ( $\text{CH}_2$ ), 71.45 ( $\text{CH}_2$ ), 69.99 (CH), 65.31 ( $\text{CH}_2$ ), 51.46 ( $\text{CH}_3$ ), 50.27 ( $\text{CH}_2$ ), 40.58 ( $\text{CH}_2$ ), 34.58 ( $\text{CH}_2$ ), 31.54 ( $\text{CH}_2$ ), 30.70 (CH), 29.45 ( $\text{CH}_2$ ), 28.96 ( $\text{CH}_2$ ), 25.55 ( $\text{CH}_2$ ), 22.57 ( $\text{CH}_2$ ), 14.07 ( $\text{CH}_3$ ), 13.34 ( $\text{CH}_3$ ); HRMS–ESI ( $m/z$ )  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{47}\text{H}_{57}\text{N}_3\text{NaO}_{12}$ : 878.38344, found 878.3832,  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{47}\text{H}_{58}\text{N}_3\text{O}_{12}$ : 856.40150, found 856.4018,  $[\text{M} + \text{K}]^+$  calcd for  $\text{C}_{47}\text{H}_{57}\text{KN}_3\text{O}_{12}$ : 894.35738, found 894.3559,  $[\text{M} + 2\text{Na}]^{2+}$  calcd for  $\text{C}_{47}\text{H}_{57}\text{N}_3\text{Na}_2\text{O}_{12}$ : 450.68633 ( $z = 2$ ), found 450.6865.

#### 2.10.3. 2,3-Triazole (10c) made by condensation of azide **7** with ethyl propiolate

White solid with pasty melting at about 80 °C. Yield: 80%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.21 (s, 1H), 7.47–7.39 (m, 5H), 7.37–7.27 (m, 6H), 6.85 (d,  $J = 8.2$  Hz, 1H), 6.84 (d,  $J = 2.0$  Hz, 1H), 6.72 (dd,  $J = 8.2, 2.0$  Hz [ddt after improving the resolution,  $J = 8.2, 1.5, 0.6$  Hz], 1H), 5.99 (qdd after improving the resolution,  $J = 7.1, 2.0, 0.6$  Hz,

1H), 5.66 (qdd after improving the resolution,  $J = 1.5, 1.5, 0.6$  Hz, 1H), 5.13 (s, 2H), 5.10 (s, 2H), 4.78 (d,  $J = 7.8$  Hz, 1H), 4.88–4.67 (m, 2H), 4.7–4.55 (broad envelope which topped at 4.64 ppm and partly superimposed with the neighboring multiplet, 1H), 4.30 (q,  $J = 7.1$  Hz, 2H), 4.42–4.20 (presumably broad envelope which completely superimposed to other signals, 1H), 4.25 (dt,  $J = 10.8, 7.1$  Hz, 1H), 4.11 (dt,  $J = 10.8, 7.1$  Hz, 1H), 3.95 (broad dd,  $J = 9.6, 4.3$  Hz, 1H), 3.78–3.65 (m, 1H), 3.69 (s, 3H), 3.64 (broad dd,  $J = 9.7, 9.0$  Hz, 1H), 3.59–3.47 (broad envelope which topped at 3.55 ppm and partly superimposed with the neighboring signals, 1H), 3.38 (broad dd,  $J = 8.7, 8.3$  Hz, 1H), 3.15 (broad dd,  $J = 9.8, 8.7$  Hz, 1H), 2.83 (dd which mostly superimposed with resonance of the other dd,  $J = 13.6, 4.9$  Hz, 1H), 2.83 (dd,  $J = 7.4, 6.8$  Hz, 2H), 2.33 (dd,  $J = 13.6, 9.8$  Hz, 1H), 1.95–1.76 (broad envelope which topped at 1.86 ppm, 4H), 1.65 (dd,  $J = 7.1, 1.5$  Hz, 3H), 1.29 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.18 ( $\text{C}_{\text{quat}}$ ), 166.68 ( $\text{C}_{\text{quat}}$ ), 160.62 ( $\text{C}_{\text{quat}}$ ), 153.36 (CH), 149.06 ( $\text{C}_{\text{quat}}$ ), 147.83 ( $\text{C}_{\text{quat}}$ ), 140.01 ( $\text{C}_{\text{quat}}$ ), 137.37 ( $\text{C}_{\text{quat}}$ ), 137.32 ( $\text{C}_{\text{quat}}$ ), 131.21 ( $\text{C}_{\text{quat}}$ ), 129.69 (CH), 128.63 ( $\text{C}_{\text{quat}}$ ), 128.46 (4CH), 127.82 (CH), 127.80 (CH), 127.44 (2CH), 127.34 (2CH), 124.35 (CH), 121.90 (CH), 116.24 (CH), 115.49 (CH), 108.54 ( $\text{C}_{\text{quat}}$ ), 100.29 (CH), 95.03 (CH), 75.90 (CH), 73.64 (CH), 73.02 (CH), 71.52 ( $\text{CH}_2$ ), 71.49 ( $\text{CH}_2$ ), 69.77 (CH), 65.32 ( $\text{CH}_2$ ), 61.38 ( $\text{CH}_2$ ), 51.44 ( $\text{CH}_3$ ), 50.57 ( $\text{CH}_2$ ), 40.57 ( $\text{CH}_2$ ), 34.55 ( $\text{CH}_2$ ), 30.77 (CH), 14.28 ( $\text{CH}_3$ ), 13.28 ( $\text{CH}_3$ ); HRMS–ESI ( $m/z$ )  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{44}\text{H}_{49}\text{N}_3\text{NaO}_{14}$ : 866.31067, found 866.3108,  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{44}\text{H}_{50}\text{N}_3\text{O}_{14}$ : 844.32873, found 844.3293,  $[\text{M} + \text{K}]^+$  calcd for  $\text{C}_{44}\text{H}_{49}\text{KN}_3\text{O}_{14}$ : 882.28461, found 882.2838,  $[\text{M} - 2\text{PhCH}_2 + \text{Na}]^+$  calcd for  $\text{C}_{30}\text{H}_{35}\text{N}_3\text{NaO}_{14}$ : 684.20112, found 684.2016.

#### 2.10.4. 1,2,3-Triazole (**10d**) made by condensation of azide 7 with 3-butyn-1-ol

White solid. Yield: 71%.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.56 (broad s, 1H), 7.46–7.38 (m, 5H), 7.36–7.30 (m, 4H), 7.30–7.25 (m, 2H), 6.85 (d,  $J = 8.2$  Hz, 1H), 6.83 (d,  $J = 2.0$  Hz, 1H), 6.71 (dd,  $J = 8.2, 2.0$  Hz, 1H), 6.02 (broad q,  $J = 7.0$  Hz, 1H), 5.66 (broad s, 1H), 5.25–5.13 (broad envelope which topped at 5.18 ppm and partly superimposed with the neighboring singlets, 1H), 5.12 (s, 2H), 5.10 (s, 2H), 5.10–4.98 (broad envelope which topped at 5.06 ppm and partly superimposed with the neighboring singlets, 1H), 4.80 (d,  $J = 7.7$  Hz, 1H), 4.69 (broad d,  $J = 13.4$  Hz, 1H), 4.55 (broad dd,  $J = 14.5, 5.3$  Hz, 1H), 4.42–4.25 (broad envelope which topped at 4.31 ppm and partly superimposed with the neighboring signals, 1H), 4.24 (dt,  $J = 10.7, 7.1$  Hz, 1H), 4.06 (dt,  $J = 10.7, 7.2$  Hz, 1H), 3.95 (broad dd,  $J = 9.8, 4.3$  Hz, 1H), 3.89–3.73 (m, 2H), 3.72–3.63 (m, 1H), 3.66 (s, 3H), 3.63–3.53 (m, 1H), 3.55–3.43 (broad envelope which topped at 3.50 ppm and partly superimposed with the neighboring signals, 1H), 3.37 (broad dd,  $J = 8.5, 8.3$  Hz, 1H), 3.13 (very broad t,  $J = 9.5$  Hz, 1H), 2.90–2.76 (m, 5H), 2.27 (dd,  $J = 13.6, 10.0$  Hz, 1H), 2.13–1.87 (broad envelope which topped at 2.00 ppm, 5H), 1.60 (dd,  $J = 7.0, 1.0$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.35 ( $\text{C}_{\text{quat}}$ ), 166.73 ( $\text{C}_{\text{quat}}$ ), 153.55 (CH), 149.06 ( $\text{C}_{\text{quat}}$ ), 147.86 ( $\text{C}_{\text{quat}}$ ), 145.44 ( $\text{C}_{\text{quat}}$ ), 137.35 ( $\text{C}_{\text{quat}}$ ), 137.30 ( $\text{C}_{\text{quat}}$ ), 131.01 ( $\text{C}_{\text{quat}}$ ), 128.53 ( $\text{C}_{\text{quat}}$ ), 128.46 (4CH), 127.81 (CH), 127.79 (CH), 127.42 (2CH), 127.34 (2CH), 124.38 (shoulder of the peak at 124.33 ppm,

CH), 124.33 (CH), 121.86 (CH), 116.18 (CH), 115.48 (CH), 108.34 ( $\text{C}_{\text{quat}}$ ), 99.69 (CH), 94.34 (CH), 75.87 (CH), 74.19 (CH), 73.01 (CH), 71.49 ( $\text{CH}_2$ ), 71.46 ( $\text{CH}_2$ ), 70.14 (CH), 65.46 ( $\text{CH}_2$ ), 61.19 ( $\text{CH}_2$ ), 51.46 ( $\text{CH}_3$ ), 50.56 ( $\text{CH}_2$ ), 40.68 ( $\text{CH}_2$ ), 34.53 ( $\text{CH}_2$ ), 30.70 (CH), 28.58 ( $\text{CH}_2$ ), 13.33 ( $\text{CH}_3$ ); HRMS–ESI ( $m/z$ )  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{43}\text{H}_{49}\text{N}_3\text{NaO}_{13}$ : 838.31576, found 838.3150,  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{43}\text{H}_{50}\text{N}_3\text{O}_{13}$ : 816.33381, found 816.3338,  $[\text{M} - 2\text{PhCH}_2 + \text{Na}]^+$  calcd for  $\text{C}_{29}\text{H}_{35}\text{N}_3\text{NaO}_{13}$ : 656.20621, found 656.2061.

#### 2.11. General procedure for debenylation by CTH. Synthesis of 1,2,3-triazoles (**11a–d**)

To a solution of protected triazole **10a–d** (0.04 mmol for **10a**, 0.025 mmol for **10b** or **10c** or **10d**) in 95% ethanol (0.5 mL) and ethyl acetate (0.5 mL) was added palladium hydroxide on activated charcoal (Pearlman's catalyst, 20% Pd on dry basis, nominally 50% water, 14 mg in the case of **10a**, 6.5 mg in the case of **10b** or **10c** or **10d**) and cyclohexene (330 mg in the case of **10a**, 210 mg in the case of **10b** or **10c** or **10d**, 100 equiv). After stirring for 66 h at 50 °C, TLC (elution with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  92:8) showed a complete reaction. The reaction mixture was concentrated under vacuum and the remaining residue was purified by chromatography on silica gel with gradient elution using a  $\text{CH}_2\text{Cl}_2/(0\text{--}5\%)$  MeOH solvent system (up to 8% MeOH in the case of **11d**) to afford deprotected triazole **11a–d**.

##### 2.11.1. 1,2,3-Triazole (**11a**) made by debenylation of 1,2,3-triazole **10a**

White solid. Yield: 89%.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  8.16 (s, 1H), 7.90–7.86 (broad envelope which topped at 7.88 ppm, 1H), 7.86–7.81 (m, 2H), 7.80–7.75 (broad envelope which topped at 7.77 ppm, 1H), 7.39–7.31 (m, 3H), 7.27 (ddt,  $J = 8.7, 5.9, 1.4$  Hz, 1H), 6.78 (d,  $J = 2.0$  Hz, 1H), 6.76 (d,  $J = 8.0$  Hz, 1H), 6.58 (ddt,  $J = 8.0, 2.1, 0.6$  Hz, 1H), 6.03 (qdd after improving the resolution,  $J = 7.1, 1.5, 0.7$  Hz, 1H), 5.72 (qdd after improving the resolution,  $J = 1.5, 1.5, 0.6$  Hz, 1H), 4.95 (dd,  $J = 14.4, 2.5$  Hz, 1H), 4.84 (d,  $J = 7.8$  Hz, 1H), 4.70 (broad d,  $J = 4.7$  Hz, 1H), 4.59 (dd,  $J = 14.4, 7.9$  Hz, 1H), 4.57 (dt after improving the resolution,  $J = 4.5, 0.6$  Hz, 1H), 4.49 (dt after improving the resolution,  $J = 4.2, 0.5$  Hz, 1H), 4.24 (dt,  $J = 10.7, 7.1$  Hz, 1H), 4.09 (dt,  $J = 10.7, 7.1$  Hz, 1H), 3.91 (ddt after improving the resolution,  $J = 10.0, 4.3, 0.7$  Hz, 1H), 3.80 (broad ddd,  $J = 9.6, 7.9, 2.5$  Hz, 1H), 3.65 (s, 3H), 3.54 (broad td,  $J = 9.0, 4.0$  Hz, 1H), 3.42–3.30 (m, 2H), 2.78 (t,  $J = 7.1$  Hz, 2H), 2.57 (dd,  $J = 13.9, 4.2$  Hz, 1H), 2.13 (dd,  $J = 13.9, 9.9$  Hz, 1H), 1.67 (dd,  $J = 7.1, 1.5$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{COCD}_3$ ):  $\delta$  171.59 ( $\text{C}_{\text{quat}}$ ), 167.05 ( $\text{C}_{\text{quat}}$ ), 154.09 (CH), 147.78 ( $\text{C}_{\text{quat}}$ ), 145.95 ( $\text{C}_{\text{quat}}$ ), 144.62 ( $\text{C}_{\text{quat}}$ ), 132.18 ( $\text{C}_{\text{quat}}$ ), 130.46 ( $\text{C}_{\text{quat}}$ ), 130.19 ( $\text{C}_{\text{quat}}$ ), 129.53 (2CH), 128.57 (CH), 126.39 (2CH), 124.00 (CH), 122.69 (CH), 121.06 (CH), 116.87 (CH), 116.19 (CH), 109.26 ( $\text{C}_{\text{quat}}$ ), 100.24 (CH), 94.02 (CH), 77.57 (CH), 75.77 (CH), 74.53 (CH), 72.22 (CH), 66.12 ( $\text{CH}_2$ ), 51.84 ( $\text{CH}_2$ ), 51.51 ( $\text{CH}_3$ ), 41.10 ( $\text{CH}_2$ ), 35.04 ( $\text{CH}_2$ ), 31.76 (CH), 13.55 ( $\text{CH}_3$ ); HRMS–ESI ( $m/z$ )  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{33}\text{H}_{37}\text{N}_3\text{NaO}_{12}$ : 690.22694, found 690.2268,  $[\text{M} + \text{K}]^+$  calcd for  $\text{C}_{33}\text{H}_{37}\text{KN}_3\text{O}_{12}$ : 706.20088, found 706.2004,  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{33}\text{H}_{38}\text{N}_3\text{O}_{12}$ : 668.24500, found 668.2452.

### 2.11.2. 1,2,3-Triazole (**11b**) made by debenzoylation of 1,2,3-triazole **10b**

Light brown oil which solidified upon prolonged storage in freezer yielding a cream-colored solid. Yield: 82%. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 8.10–7.92 (broad envelope which topped at 8.01 ppm, ca. 0.35H), 7.89–7.72 (broad envelope which topped at 7.78 ppm, ca. 0.4H), 7.57 (s [t after improving the resolution, *J* = 0.7 Hz], 1H), 7.42 (s [t after improving the resolution, *J* = 0.7 Hz], 1H), 6.77 (d, *J* = 2.1 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.57 (ddt after improving the resolution, *J* = 8.0, 2.1, 0.7 Hz, 1H), 6.05 (qdd after improving the resolution, *J* = 7.1, 1.5, 0.7 Hz, 1H), 5.69 (qdd after improving the resolution, *J* = 1.5, 1.5, 0.7 Hz, 1H), 4.87 (dd, *J* = 14.4, 2.3 Hz, 1H), 4.79 (d, *J* = 7.8 Hz, 1H), 4.43 (dd, *J* = 14.4, 8.3 Hz, 1H), 4.27 (dt, *J* = 10.8, 7.0 Hz, 1H), 4.12 (dt, *J* = 10.8, 7.1 Hz, 1H), 4.00 (ddt after improving the resolution, *J* = 10.1, 4.1, 0.7 Hz, 1H), 3.81 (broad s, 1H), 3.70 (ddd, *J* = 9.6, 8.3, 2.3 Hz, 1H), 3.69 (s, 3H), 3.52 (t, *J* = 9.1 Hz, 1H), 3.37 (dd, *J* = 9.1, 7.8 Hz, 1H), 3.30 (dd, *J* = 9.6, 8.8 Hz, 1H), 2.83 (dd, *J* = 14.0, 4.1 Hz, 1H), 2.80 (t, *J* = 7.0 Hz, 2H), 2.62 (td after improving the resolution, *J* = 7.6, 0.6 Hz, 2H), 2.28 (dd, *J* = 14.0, 10.1 Hz, 1H), 1.70 (dd, *J* = 7.1, 1.5 Hz, 3H), 1.64–1.56 (m, 2H), 1.39–1.22 (m, 6H), 0.86 (t, *J* = 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 171.49 (C<sub>quat</sub>), 167.10 (C<sub>quat</sub>), 154.18 (CH), 148.30 (C<sub>quat</sub>), 145.84 (very small, C<sub>quat</sub>), 144.52 (very small, C<sub>quat</sub>), 130.34 (C<sub>quat</sub>), 130.10 (C<sub>quat</sub>), 124.17 (CH), 123.24 (CH), 120.95 (CH), 116.76 (CH), 116.08 (CH), 109.29 (C<sub>quat</sub>), 100.26 (CH), 94.12 (CH), 77.35 (CH), 75.92 (CH), 74.34 (CH), 72.12 (CH), 66.19 (CH<sub>2</sub>), 51.65 (CH<sub>2</sub>), 51.56 (CH<sub>3</sub>), 41.28 (CH<sub>2</sub>), 35.08 (CH<sub>2</sub>), 32.33 (CH<sub>2</sub>), 31.74 (CH), 30.54 (CH<sub>2</sub>), 29.72 (CH<sub>2</sub>), 26.23 (CH<sub>2</sub>), 23.25 (CH<sub>2</sub>), 14.36 (CH<sub>3</sub>), 13.60 (CH<sub>3</sub>); HRMS–ESI (*m/z*) [M+Na]<sup>+</sup> calcd for C<sub>33</sub>H<sub>45</sub>N<sub>3</sub>NaO<sub>12</sub>: 698.28954, found 698.2894, [M+H]<sup>+</sup> calcd for C<sub>33</sub>H<sub>46</sub>N<sub>3</sub>O<sub>12</sub>: 676.30760, found 676.3079.

### 2.11.3. 1,2,3-Triazole (**11c**) made by debenzoylation of 1,2,3-triazole **10c**

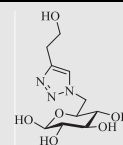
White solid with pasty melting at about 90 °C. Yield: 87%. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 8.36 (s, 1H), 7.76 (broad s, 1H), 7.73 (broad s, 1H), 7.40 (t, *J* = 0.7 Hz, 1H), 6.77 (d, *J* = 2.1 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.58 (ddt, *J* = 8.0, 2.1, 0.6 Hz, 1H), 6.02 (qdd after improving the resolution, *J* = 7.1, 1.5, 0.7 Hz, 1H), 5.72 (qdd after improving the resolution, *J* = 1.5, 1.4, 0.7 Hz, 1H), 4.94 (dd, *J* = 14.3, 2.6 Hz, 1H), 4.83 (d, *J* = 7.8 Hz, 1H), 4.70 (broad d, *J* = 4.7 Hz, 1H), 4.62 (dd, *J* = 14.3, 7.8 Hz, 1H), 4.58 (broad d, *J* = 4.1 Hz, 1H), 4.49 (broad d, *J* = 4.1 Hz, 1H), 4.31 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.26 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.22 (dt, *J* = 10.7, 7.2 Hz, 1H), 4.12 (dt, *J* = 10.7, 7.1 Hz, 1H), 3.96 (ddt after improving the resolution, *J* = 9.8, 4.5, 0.7 Hz, 1H), 3.83 (ddd, *J* = 9.7, 7.8, 2.6 Hz, 1H), 3.69 (s, 3H), 3.54 (broad td, *J* = 9.0, 3.9 Hz, 1H), 3.41–3.25 (m, 2H), 2.78 (t, *J* = 7.1 Hz, 2H), 2.76 (dd, *J* = 13.8, 4.5 Hz, 1H), 2.33 (dd, *J* = 13.8, 9.7 Hz, 1H), 1.70 (dd, *J* = 7.1, 1.5 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 171.56 (C<sub>quat</sub>), 167.16 (C<sub>quat</sub>), 161.39 (C<sub>quat</sub>), 154.14 (CH), 145.88 (C<sub>quat</sub>), 144.55 (C<sub>quat</sub>), 140.47 (C<sub>quat</sub>), 130.50 (C<sub>quat</sub>), 130.35 (C<sub>quat</sub>), 130.23 (CH), 124.02 (CH), 121.09 (CH), 116.87 (CH), 116.14 (CH), 109.37 (C<sub>quat</sub>), 100.72 (CH), 94.68 (CH), 77.50 (CH), 75.25 (CH), 74.44

(CH), 72.14 (CH), 66.11 (CH<sub>2</sub>), 61.24 (CH<sub>2</sub>), 52.03 (CH<sub>2</sub>), 51.54 (CH<sub>3</sub>), 41.25 (CH<sub>2</sub>), 35.05 (CH<sub>2</sub>), 31.83 (CH), 14.63 (CH<sub>3</sub>), 13.53 (CH<sub>3</sub>); HRMS–ESI (*m/z*) [M+Na]<sup>+</sup> calcd for C<sub>30</sub>H<sub>37</sub>N<sub>3</sub>NaO<sub>14</sub>: 686.21677, found 686.2168, [M+K]<sup>+</sup> calcd for C<sub>30</sub>H<sub>37</sub>KN<sub>3</sub>O<sub>14</sub>: 702.19071, found 702.1904, [M–H + 2Na]<sup>+</sup> calcd for C<sub>30</sub>H<sub>36</sub>N<sub>3</sub>Na<sub>2</sub>O<sub>14</sub>: 708.19872, found 708.1984.

### 2.11.4. 1,2,3-Triazole (**11d**) made by debenzoylation of 1,2,3-triazole **10d**

Very small colorless droplets. Yield: 97%. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 8.09 (broad envelope from 8.17 to 8.01 ppm and which topped at 8.09 ppm, 1H), 7.85 (broad envelope from 7.92 to 7.79 ppm and which topped at 7.85 ppm, 1H), 7.63 (s [t after improving the resolution, *J* = 0.7 Hz], 1H), 7.41 (t, *J* = 0.7 Hz, 1H), 6.77 (d, *J* = 2.1 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.57 (ddt, *J* = 8.0, 2.1, 0.6 Hz, 1H), 6.05 (qdd, *J* = 7.1, 1.5, 0.7 Hz, 1H), 5.70 (qdd after improving the resolution, *J* = 1.5, 1.4, 0.7 Hz, 1H), 4.88 (dd, *J* = 14.4, 2.3 Hz, 1H), 4.79 (d, *J* = 7.8 Hz, 1H), 4.72–4.51 (two superimposed broad envelopes which topped at 4.64 and 4.60 ppm, 2H), 4.42 (dd, *J* = 14.4, 8.3 Hz, 1H), 4.27 (dt, *J* = 10.8, 7.0 Hz, 1H), 4.13 (dt, *J* = 10.8, 7.1 Hz, 1H), 3.99 (ddt, *J* = 10.1, 4.2, 0.7 Hz, 1H), 3.94–3.82 (broad envelope which topped at 3.87 ppm, 2H), 3.76 (broad t, *J* = 6.8 Hz, 2H), 3.72–3.66 (m, 1H), 3.69 (s, 3H), 3.52 (broad t, *J* = 8.9 Hz, 1H), 3.43–3.26 (m, 2H), 2.85 (td, *J* = 6.8, 0.7 Hz, 2H), 2.83 (dd, *J* = 14.0, 4.1 Hz, 1H), 2.80 (broad t, *J* = 6.9 Hz, 2H), 2.32 (dd, *J* = 14.0, 10.0 Hz, 1H), 1.70 (dd, *J* = 7.1, 1.5 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>COCD<sub>3</sub>): δ 171.74 (C<sub>quat</sub>), 167.20 (C<sub>quat</sub>), 154.21 (CH), 145.90 (C<sub>quat</sub>), 145.63 (C<sub>quat</sub>), 144.61 (C<sub>quat</sub>), 130.36 (C<sub>quat</sub>), 130.15 (C<sub>quat</sub>), 124.18 (CH), 120.98 (CH), 116.82 (CH), 116.17 (CH), 109.29 (C<sub>quat</sub>), 100.37 (CH), 94.30 (CH), 77.44 (CH), 75.91 (CH), 74.42 (CH), 72.22 (CH), 66.21 (CH<sub>2</sub>), 62.14 (CH<sub>2</sub>), 51.72 (CH<sub>2</sub>), 51.59 (CH<sub>3</sub>), 41.21 (CH<sub>2</sub>), 35.03 (CH<sub>2</sub>), 31.73 (CH), 29.92 (CH<sub>2</sub>), 13.59 (CH<sub>3</sub>); HRMS–ESI (*m/z*) [M+Na]<sup>+</sup> calcd for C<sub>29</sub>H<sub>37</sub>N<sub>3</sub>NaO<sub>13</sub>: 658.22186, found 658.2221, [M+H]<sup>+</sup> calcd for C<sub>29</sub>H<sub>38</sub>N<sub>3</sub>O<sub>13</sub>: 636.23991, found 636.2408, [M+K]<sup>+</sup> calcd for C<sub>29</sub>H<sub>37</sub>KN<sub>3</sub>O<sub>13</sub>: 674.19580, found 674.1958, [M–H + 2Na]<sup>+</sup> calcd for C<sub>29</sub>H<sub>36</sub>N<sub>3</sub>Na<sub>2</sub>O<sub>13</sub>: 680.20380, found 680.2038, [A+Na]<sup>+</sup> calcd for C<sub>10</sub>H<sub>17</sub>N<sub>3</sub>NaO<sub>6</sub>: 298.10096, found 298.1015, [(HO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>]<sup>+</sup> calcd for C<sub>8</sub>H<sub>9</sub>O<sub>2</sub>: 137.05970, found 137.0598.

A:

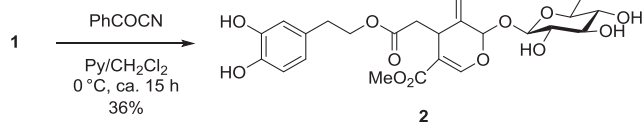


## 3. Results and discussion

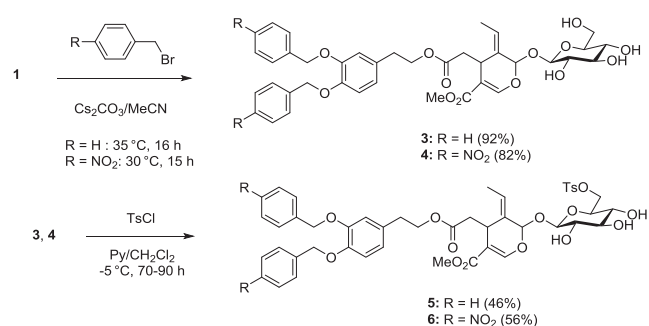
Initial experiments of selective derivatization on the carbohydrate moiety of **1**, without use of protecting groups, led us to investigate benzoylation. Indeed reaction of **1** with benzoyl cyanide (4 equiv) in the presence of excess pyridine (27 equiv) in dichloromethane at 0 °C afforded with a good selectivity and moderate yield (36%) the monobenzoate **2** on the glucose



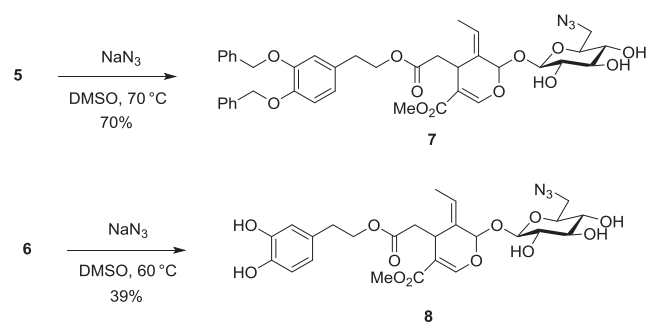
part (Scheme 1). Benzoyl cyanide is known to be the reagent of choice for the selective benzylation of primary alcohols in the presence of secondary ones [43]. However in the case of **1**, pyridine should be employed as the auxiliary base since usual conditions using a catalytic amount of triethylamine led to polybenzylation. On the other hand, attempted tosylation and silylation directly on **1** afforded no evidence of any expected product. Thus, we hypothesized that the catechol moiety impeded such reactions and we protected **1** as benzyl and *p*-nitrobenzyl ethers to afford **3** and **4** by reaction of **1** with benzyl or *p*-nitrobenzyl bromides in the presence of cesium carbonate in acetonitrile at 30 °C (Scheme 2) (yields: **3**: 92%; **4**: 82%) [44]. The preparation of bis-protected oleuropein **4** by *p*-nitrobenzyl ethers was motivated by the fact that a *p*-nitrobenzyl ether was reported to be far easier to cleave than a benzyl one [45]. Next, reaction of tosyl chloride with **3** and **4** in the presence of excess pyridine in dichloromethane at ca. 0 °C afforded primary tosylates **5** and **6** (yields: **5**: 46%; **6**: 56%) (Scheme 2). Remarkably, fully selective reaction was observed on the primary alcohol of the carbohydrate moiety with no reaction on secondary alcohols being detected. Then tosylate substitution by NaN<sub>3</sub> (4 equiv) in DMSO at 70 °C proceeded uneventfully starting with the dibenzyl ether **5** to afford the protected azide **7** in good yield (70%) (Scheme 3). On the other hand, reaction of bis-*p*-nitrobenzyl ether **6** with NaN<sub>3</sub>, even under slightly milder conditions (60 °C), afforded the deprotected azide **8** albeit in low yield (39%) instead of the expected product as the result of simultaneously cleavage of *p*-nitrobenzyl ether groups (Scheme 3). Consequently, the *p*-nitrobenzyl ether protecting group was found to be too labile for our goal. In the next step, protected azide **7** was subjected to the Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition (CuAAC), popularly known as the “click reaction” [46,47], with a set of four alkynes **9a–d** using the classical CuSO<sub>4</sub>/sodium ascorbate protocol [48] to afford the corresponding 1,2,3-triazoles **10a–d** in good yields (**10a**: 94%; **10b**: 75%; **10c**: 80%; **10d**: 71%) (Scheme 4). During the last decade, 1,2,3-triazoles have received increasing attention in medicinal chemistry due to the very useful and widely applicable CuAAC reaction and because the 1,2,3-triazole skeleton is frequently used as a pharmacophore for the modification of known pharmaceuticals [49,50]. To the best of our knowledge, it is the first time that the primary alcohol of a carbohydrate unit was converted to miscellaneous triazoles without the need of a protection (generally peracetylation) – deprotection sequence on the other secondary alcohol groups [51,52]. To complete the synthesis and in order to restore the catechol moiety, the *O*-benzyl groups of triazoles **10a–d** needed to be removed. That was a critical step since the presence of a glycoside linkage and of a catechol moiety excluded any Lewis acid and oxidizing conditions as confirmed by our experiments which were always destructive. As the presence of double bonds also



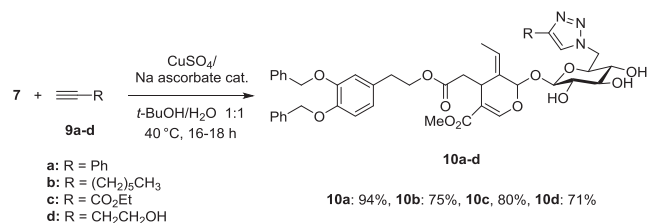
Scheme 1 Selective benzylation of oleuropein **1**.



Scheme 2 Selective tosylation after protection of the catechol moiety.

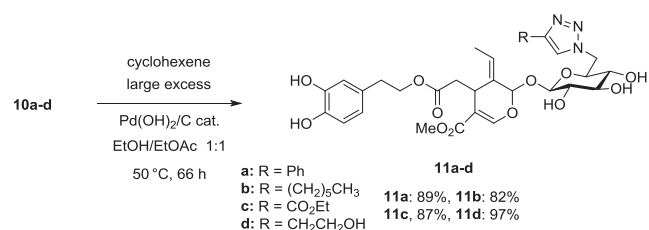


Scheme 3 Compatibility of the protecting groups on the catechol moiety during azidation.



Scheme 4 Synthesis of various protected triazoles by the CuAAC reaction.

exclude any use of hydrogen, we finally found that benzyl groups were efficiently removed by catalytic transfer hydrogenation (CTH) conditions using excess cyclohexene in the presence of palladium hydroxide on carbon in ethyl acetate/ethanol (1:1, v/v) under reflux [53] to afford deprotected triazoles **11a–d** in good yields (**11a**: 89%; **11b**: 82%; **11c**: 87%; **11d**: 97%) (Scheme 5).



Scheme 5 Debonylation in order to restore the catechol moiety and get the targeted triazoles **11a–d**.

**Table 1** Chemical shifts of other carbons than the oleuropein skeleton in **10a–d** and **11a–d**.

Chemical shifts (multiplicities, assignment)	
<b>10a</b>	147.44 (C <sub>quat</sub> , broad and small, triazole), 137.30 (C <sub>quat</sub> , benzyl), 137.23 (C <sub>quat</sub> , benzyl), 129.99 (C <sub>quat</sub> , Ph linked to triazole), 128.72 (2CH <sub>ortho</sub> , Ph linked to triazole), 128.45 (2CH <sub>meta</sub> , benzyl), 128.44 (2CH <sub>meta</sub> , benzyl), 128.23 (CH, CH <sub>para</sub> , Ph linked to triazole), 127.79 (CH <sub>para</sub> , benzyl), 127.77 (CH <sub>para</sub> , benzyl), 127.37 (2CH <sub>ortho</sub> , benzyl), 127.29 (2CH <sub>ortho</sub> , benzyl), 125.73 (2CH <sub>meta</sub> , Ph linked to triazole), 122.57 (CH broad and small, triazole), 71.38 (OCH <sub>2</sub> Ph), 71.29 (OCH <sub>2</sub> Ph)
<b>10b</b>	148.42 (C <sub>quat</sub> , triazole), 137.32 (C <sub>quat</sub> , benzyl), 137.27 (C <sub>quat</sub> , benzyl), 128.47 (4CH <sub>meta</sub> , benzyl), 127.83 (CH <sub>para</sub> , benzyl), 127.80 (CH <sub>para</sub> , benzyl), 127.40 (2CH <sub>ortho</sub> , benzyl), 127.32 (2CH <sub>ortho</sub> , benzyl), 123.28 (CH broad and small, triazole), 71.45 (OCH <sub>2</sub> Ph), 71.47 (OCH <sub>2</sub> Ph), 31.54 (CH <sub>2</sub> ), 29.45 (CH <sub>2</sub> ), 28.96 (CH <sub>2</sub> ), 25.55 (CH <sub>2</sub> ), 22.57 (CH <sub>2</sub> ), 14.07 (CH <sub>3</sub> )
<b>10c</b>	160.62 (C <sub>quat</sub> , CO <sub>2</sub> Et), 140.01 (C <sub>quat</sub> , triazole), 137.37 (C <sub>quat</sub> , benzyl), 137.32 (C <sub>quat</sub> , benzyl), 129.69 (CH broad and small, triazole), 128.46 (4CH <sub>meta</sub> , benzyl), 127.82 (CH <sub>para</sub> , benzyl), 127.80 (CH <sub>para</sub> , benzyl), 127.44 (2CH <sub>ortho</sub> , benzyl), 127.34 (2CH <sub>ortho</sub> , benzyl), 71.52 (OCH <sub>2</sub> Ph), 71.49 (OCH <sub>2</sub> Ph), 61.38 (OCH <sub>2</sub> CH <sub>3</sub> ), 14.28 (OCH <sub>2</sub> CH <sub>3</sub> )
<b>10d</b>	145.44 (C <sub>quat</sub> , triazole), 137.35 (C <sub>quat</sub> , benzyl), 137.30 (C <sub>quat</sub> , benzyl), 128.46 (4CH <sub>meta</sub> , benzyl), 127.81 (CH <sub>para</sub> , benzyl), 127.79 (CH <sub>para</sub> , benzyl), 127.42 (2CH <sub>ortho</sub> , benzyl), 127.34 (2CH <sub>ortho</sub> , benzyl), 124.38 (CH broad and small, triazole), 71.49 (OCH <sub>2</sub> Ph), 71.46 (OCH <sub>2</sub> Ph), 61.19 (CH <sub>2</sub> CH <sub>2</sub> OH), 28.58 (CH <sub>2</sub> CH <sub>2</sub> OH)
<b>11a</b>	147.78 (C <sub>quat</sub> , triazole), 132.18 (C <sub>quat</sub> , Ph linked to triazole), 129.53 (2CH <sub>ortho</sub> , Ph linked to triazole), 128.57 (CH <sub>para</sub> , Ph linked to triazole), 126.39 (2CH <sub>meta</sub> , Ph linked to triazole), 122.69 (CH broad and small, triazole)
<b>11b</b>	148.30 (C <sub>quat</sub> , triazole), 123.24 (CH, triazole), 32.33 (CH <sub>2</sub> ), 30.54 (CH <sub>2</sub> ), 29.72 (CH <sub>2</sub> ), 26.23 (CH <sub>2</sub> ), 23.25 (CH <sub>2</sub> ), 14.36 (CH <sub>3</sub> )
<b>11c</b>	161.39 (C <sub>quat</sub> , CO <sub>2</sub> Et), 140.47 (C <sub>quat</sub> , triazole), 130.23 (CH, triazole), 61.24 (OCH <sub>2</sub> CH <sub>3</sub> ), 14.63 (OCH <sub>2</sub> CH <sub>3</sub> )
<b>11d</b>	145.63 (C <sub>quat</sub> , triazole), 124.18 (CH, triazole), 62.14 (broad and small, CH <sub>2</sub> CH <sub>2</sub> OH), 29.92 (CH <sub>2</sub> CH <sub>2</sub> OH)

All chemical structures were confirmed by <sup>1</sup>H and <sup>13</sup>C NMR spectra for all compounds, as well as by high resolution mass spectroscopy. Extensive studies by 2D NMR (especially COSY and HSQC/HMQC) have been performed for a complete assignment to all protons, even those which were hidden in complex patterns (aromatic signals) in the 1D spectra. For convenience, all chemical shifts of this skeleton were presented in four tables in ESI: two for <sup>1</sup>H and two for <sup>13</sup>C. These NMR data clearly establish that all compounds **1–8**, **10a–d**, **11a–d** have kept the oleuropein skeleton. Indeed it appears that they little vary, except that of the modified primary position of the glucose moiety. Therefore, NMR could be used as an efficient tool to probe quickly the modified position(s) during experiments dealing with the selective functionalization of oleuropein. Chemical shifts of other carbons in **10a–d** and **11a–d** support the structures and are presented in Table 1.

#### 4. Conclusion

In summary, we have described the selective transformation of oleuropein, a natural product from olive tree and oil, to new derivatives by grafting a 1,2,3-triazole as a pharmacophore which could be diversely substituted. The primary hydroxy alcohol of the glucose unit of oleuropein was selectively tosylated in the presence of the unprotected secondary hydroxy groups provided that the catechol moiety was previously protected as benzyl ethers. After classical substitution of tosylate with azide, Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) with four representative alkynes easily afforded the expected 1,2,3-triazoles. Critical debenzylation was efficiently performed using CTH conditions by excess cyclohexene in the presence of palladium hydroxide on carbon in ethyl acetate/ethanol under reflux to afford the desired triazole derivatives of oleuropein.

The selectivity of the tosylation of an unprotected carbohydrate leading to an easy entry to triazole sugars could be emphasized. The good biological profile of oleuropein may be enhanced by the presence of an adjustable pharmacophoric

1,2,3-triazole and these new derivatives will be submitted to biological tests in various areas.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jscs.2019.05.009>.

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