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PAPER

Design and synthesis of bile acid–peptide conjugates linked *via* triazole moiety†

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A conjugation of bile acids with peptides *via* Cu(I)-catalyzed click chemistry has been described. Novel bile acid–peptide conjugates linked *via* a 1,2,3-triazole moiety based on cholic, deoxycholic and lithocholic acid derivatives were synthesized using Cu(I)-catalyzed 1,3-dipolar cycloaddition ("click" reaction). It was shown that up to three peptide fragments can be attached to a central steroid core, thus forming complex three-dimensional polyconjugate structures, which can find important applications in biochemistry, medicinal chemistry, and coordination chemistry.

Introduction

In recent years bile acids and their derivatives have become increasingly important in a number of fields such as medicine, pharmacology, coordination and supramolecular chemistry, materials chemistry, and also in nanotechnology.[1] Bile acids are a group of steroids formed during the catabolism of cholesterol in the hepatocytes. The primary bile acids produced by living organisms are usually conjugated with the amino acids glycine and taurine.[2] Bile acids play various physiological roles, such as the digestion and absorption of lipids, cholesterol and lipid-soluble vitamins, and influence intestinal and colonic epithelial function and integrity. One of the most efficient processes in the human body is the enterohepatic circulation of bile acids, which is carried out by transport proteins.[3] Synthesis and design of new pharmacologically active hybrid molecules and prodrugs based on bile acids are very important from the viewpoint of improving intestinal absorption and increasing the metabolic stability of pharmaceuticals specifically targeting enterohepatic circulation.[4]

Examples of bile acid–peptide conjugates linked *via* amide bonds have been reported in the literature.[5] However, in all these approaches classical methods of peptide chemistry have been used.

Herein, we disclose a conjugation of bile acids and peptides *via* a 1,2,3-triazole moiety using copper-catalyzed Huisgen 1,3-dipolar cycloaddition ("click" reaction) of alkynes and azides.[6]

1,2,3-Triazole moieties are ideal linkers, because they are stable under typical physiological conditions and form hydrogen bonds.[7] Moreover, the ability of 1,2,3-triazoles to mimic topological and electronic features of the amide bond can be used for design of peptidomimetics with improved medicinal properties.[8]

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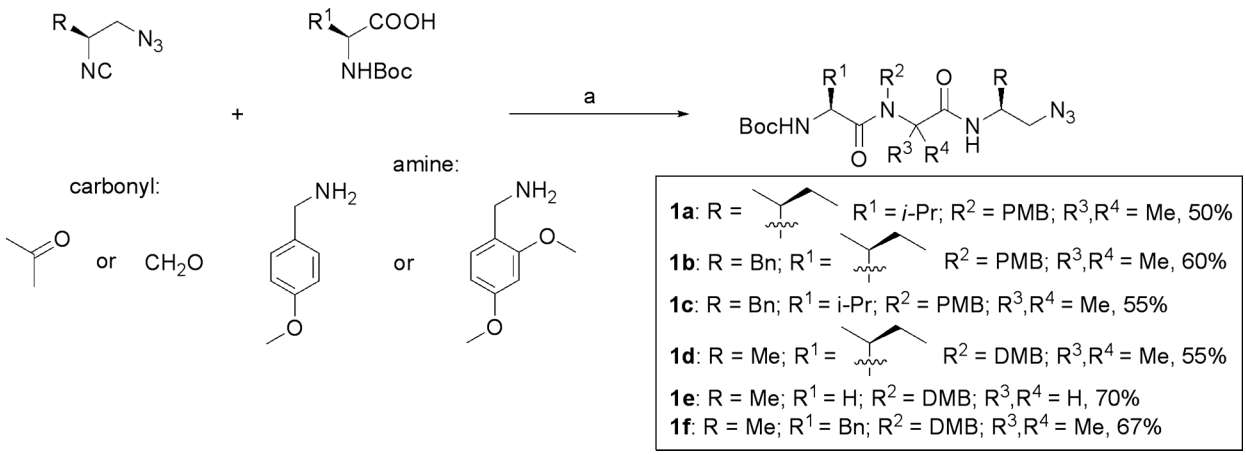
The Ugi MCR is an efficient method for the construction of peptides and peptide-like molecules in one step.[9] Recently, we leveraged on this multicomponent reaction for a straightforward synthesis of "clickable" azidopeptides, starting from novel isocyanoazides. We also demonstrated that the Ugi/click strategy is a powerful method for the decoration of biologically active molecules with peptide residues.[10]

Herein, we apply our Ugi/click strategy to the conjugation of azidopeptides with different bile acid derivatives. We believe that due to cooperative interactions of flexible and functionalized peptide chains bile acid–peptide conjugates containing free amine functions together with 1,2,3-triazole moieties may play an important role in biochemistry, and medicinal chemistry, as well as in coordination chemistry, because of their "tweezer-like" structure.[11] For example, they can find applications in "click-to-chelate" approach to the preparation of ligand systems suitable for complexation of metals[12] and can be useful in finding of new receptors for the selective recognition of anions.[13]

Results and discussion

Starting azidopeptides **1a–f** were synthesized using chiral isocyanoazides, recently developed in our group.[10] By reacting different Boc-protected amino acids with chiral isocyanoazides we prepared a series of novel azidopeptides **1** (Scheme 1). Advantageously, 2,4-dimethoxybenzyl or 4-methoxybenzyl protecting groups, were introduced *via* their corresponding amines. Formaldehyde and acetone were used as carbonyl components to form the central amino acid fragment of the azidopeptide skeleton. As a result, azidopeptides **1** containing both natural and unnatural amino acid residues were successfully synthesized. Therefore, we have demonstrated that the Ugi reaction with isocyanoazides is a convenient route for the introduction of orthogonal protecting groups in the peptides **1**.

Acetylenic derivatives of deoxycholic **2a–c**, lithocholic **2d**, and cholic **2e** acids containing one, two or three terminal alkyne



Scheme 1 Reagents and conditions: (a) MeOH, rt, 24 h.

groups were prepared *via* acylation of cholic acids with acyl chlorides containing terminal alkynyl group using a modified literature procedure.[14] For this, the methyl and propargyl esters of bile acids were treated with propargyloxyacetyl chloride or 4-(propargyloxy)benzoyl chloride in the presence of different bases to provide the required bile acid derivatives **2a–e** in good yields.[15]

We envisioned that the geometry of peptide chains in the target molecules can be controlled by the structure of starting deoxycholic, lithocholic and cholic acids containing one, two or three acetylenic fragments. In bile acids, the *cis*-coupled rings A and B assume chair conformation, wherein the hydroxy group in the 3-position takes an equatorial and the 7-hydroxy takes an axial conformation, both pointing in the same direction. Thus, a conjugation of peptide residues is likely to maintain an U-shaped spatial arrangement.

Having the corresponding sets of alkynylated bile acids and azidopeptides in hand we investigated a combinatorial approach towards the conjugates. In a first series, deoxycholic acid derivative **2a** bearing a monoacetylenic functionality on the C-3 position was reacted with azidopeptides **1a–c** (Scheme 2).

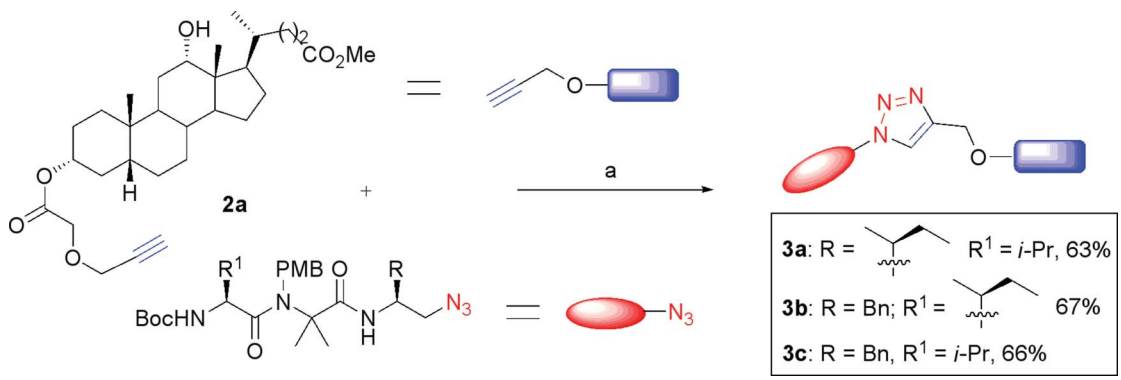
The click reaction proceeded regioselectively in good yields to afford conjugates **3a–c**. The optimal reaction conditions were found to be EtOH–H_2O (5 : 1)/10% of $CuSO_4 \cdot 5H_2O$/40% of sodium ascorbate for 12 h at 60 °C.

A second series of conjugates was prepared starting from deoxycholic acid derivative **2b** bearing two alkyne appendages and excess of azidopeptides **1a,d–f** (Scheme 3). After careful optimization, heating the starting materials with Cu(II)/sodium ascorbate in a biphasic mixture of CH_2Cl_2–H_2O provided the desired products **4a–d** in good to excellent yields. An analogous series of conjugates **5a–c** replacing the 4-propargyloxy benzoate linker with an propargyloxy glycolate linker was prepared (Scheme 3).

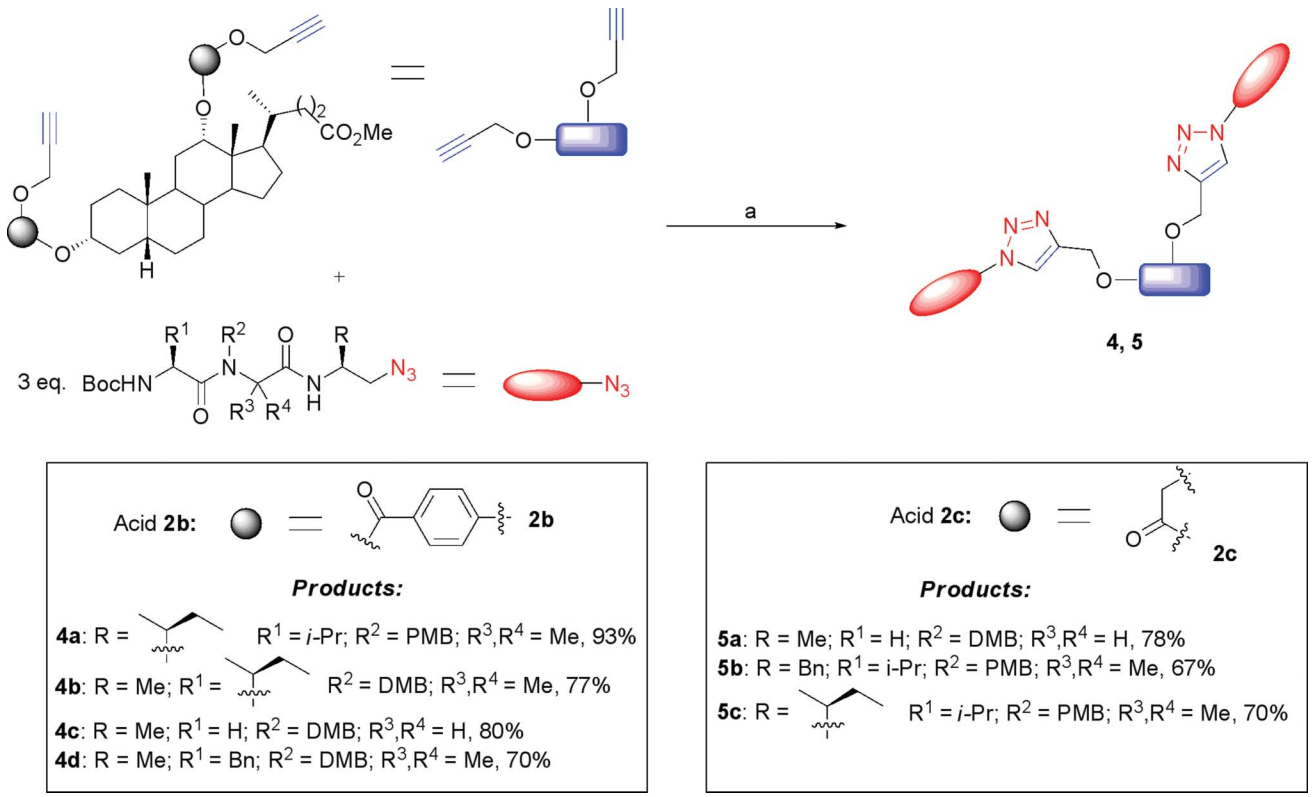
Additionally, a series of bisconjugated derivatives was prepared. Lithocholic acid derivative **2d** containing two terminal alkyne groups was reacted with azidopeptides **1a,d,e** under the same conditions afforded the corresponding conjugates **6a–c** in high yields (Scheme 4). In contrast to the compounds from series **4** and **5**, which present an angular geometry, compounds **6a–c** show a linear arrangement.

In a final series, we even prepared cholic acid derivatives bearing three peptide moieties. Thus, 1,3-dipolar cycloaddition between the triynic cholic acid derivative **2e** and excess of peptides **1a,c,e** afforded triplex conjugates **7a–c** in high yields under standard conditions (Scheme 5).

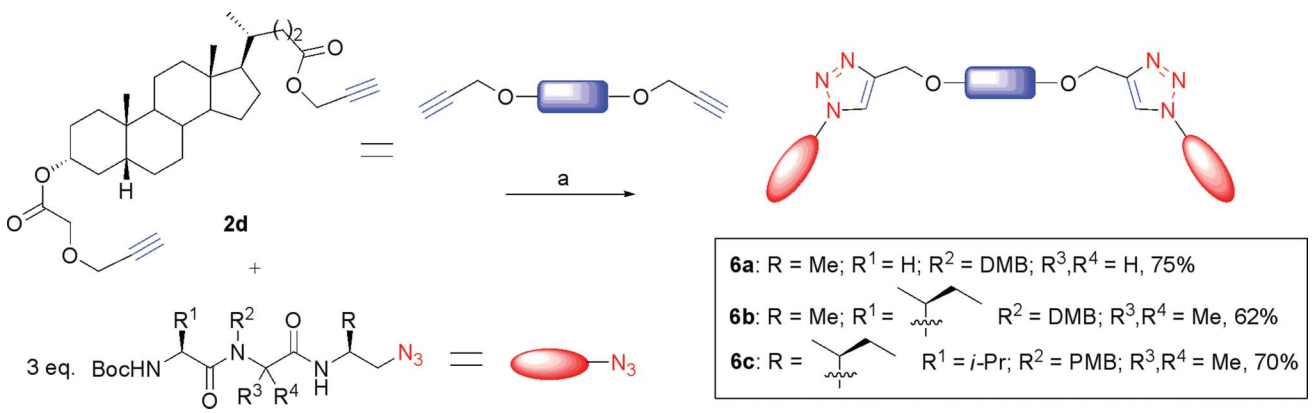
Both protecting groups of the amide and the amine functions can be easily removed from the target conjugates, either in an orthogonal mode under mildly acidic conditions or in one step under more forcing conditions.[16] As an example, heating of the conjugate **6b** in TFA led to the product **8** containing free amide and amine groups in good yield (Scheme 6).



Scheme 2 Reagents and conditions: (a) sodium ascorbate (40%), $CuSO_4 \cdot 5H_2O$ (10%), EtOH–H_2O (5 : 1), 60 °C, 12 h.



Scheme 3 Reagents and conditions: (a) sodium ascorbate (80%), $CuSO_4 \cdot 5H_2O$ (20%), CH_2Cl_2–H_2O (10 : 1), 40 °C, 10 h.



Scheme 4 Reagents and conditions: (a) sodium ascorbate (80%), $CuSO_4 \cdot 5H_2O$ (20%), CH_2Cl_2–H_2O (10 : 1), 40 °C, 10 h.

In general, "clickable" peptides based on chiral isocyanoazides are promising candidates for bioconjugation reactions and synthesis of hybrid peptide molecules with improved medicinal properties.

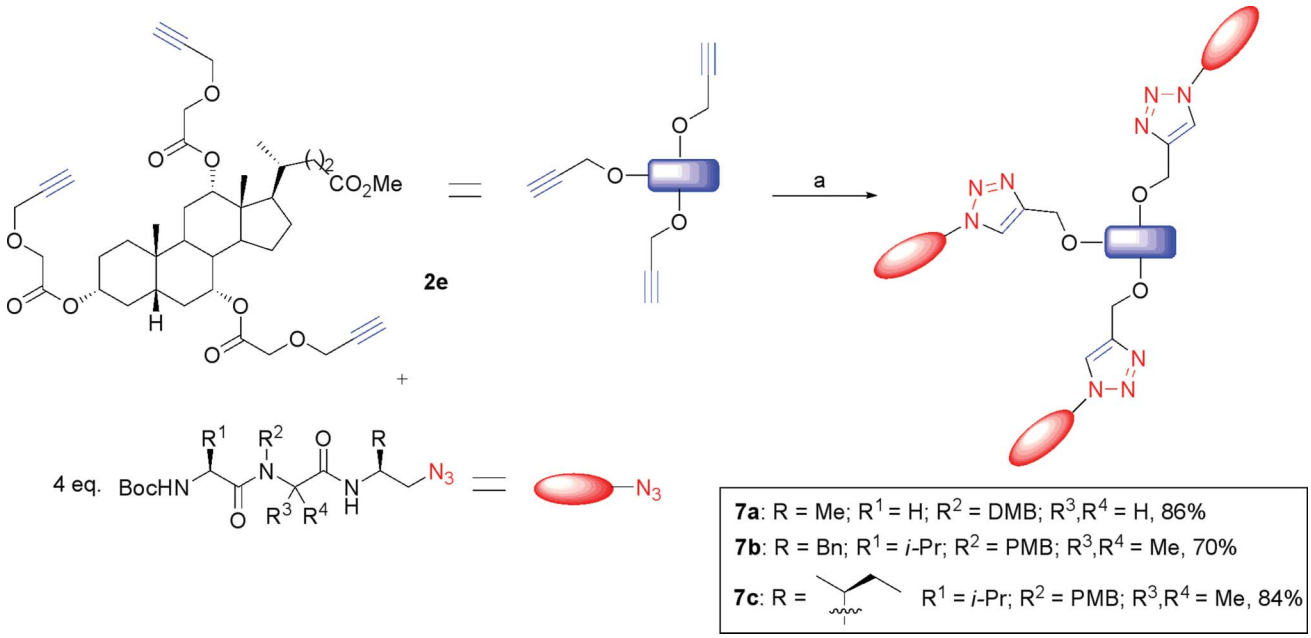
Conclusions

In conclusion, we described the conjugation of azidopeptides **1** with alkyne functionalized bile acids **2** *via* the Cu(I) catalyzed Huisgen cycloaddition reaction. 1,2,3-Triazole formation proceeded smoothly "clicking" up to three alkyne moieties attached to the steroid core. After straightforward deprotection, series of mono-, duplex- and triplex-peptidyl bile acid conjugates may play an important role in biochemistry, and medicinal chemistry, as well as in coordination chemistry, because of their "tweezer-like" structure and hydrogen bond forming potential.

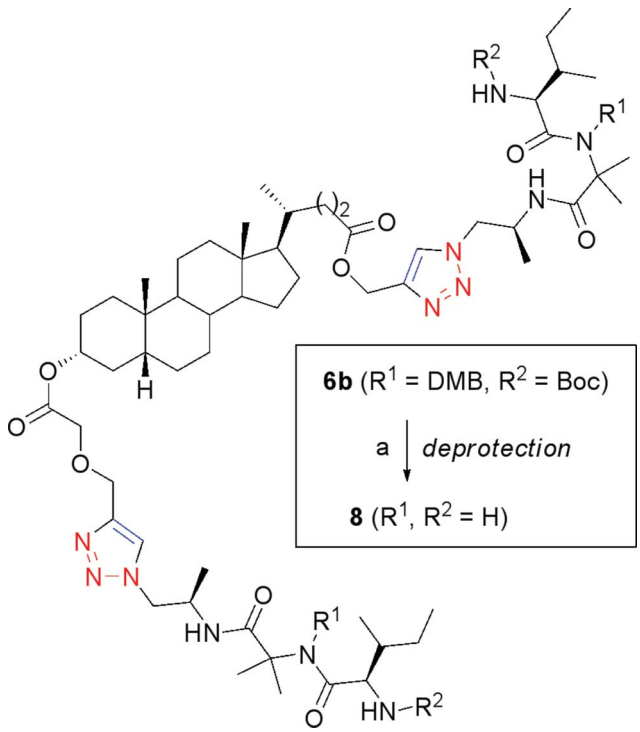
Experimental

General information

^1H and ^{13}C NMR spectra were recorded in deuterated solvents on a Bruker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) or δ values downfield from TMS as internal standard. Deuterated solvent peaks were used as internal references: $CDCl_3$ at 7.25 and 77.00 ppm. Analytical thin layer chromatography (TLC) was performed using DC-Alufolien Kieselgel 60 F254 (Merck). The developed chromatogram was analyzed by UV light and aqueous potassium



Scheme 5 Reagents and conditions: (a) sodium ascorbate (90%), $CuSO_4 \cdot 5H_2O$ (30%), CH_2Cl_2–H_2O (10 : 1), 40 °C, 12 h.



Scheme 6 Reagents and conditions: (a) TFA, reflux, 7 h, 60%.

permanganate ($KMnO_4$). Liquid chromatography was performed using Fluka Silica gel 60 (0.063–0.200 mm). Infrared (IR) spectra were recorded on a Nicolet IR2000 (Thermo Scientific). Optical rotations were measured on a Perkin–Elmer 341 polarimeter at 589 nm. Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. High-resolution mass spectra (HRMS) were measured on a Micr OTOF II (Bruker Daltonics) spectrometer. All commercial solvents were distilled prior to use.

General procedure for Ugi-4CC. Synthesis of peptides 1a–f

The corresponding amine (1 mmol) and acetone or CH_2O (40% in H_2O) (1 mmol) were dissolved in 5 mL of MeOH and *N*-Boc protected amino acid (1 mmol) and isocyanide (1 mmol) were added at room temperature. The mixture was stirred for 24 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (hexanes–ethyl acetate 2 : 1).

***N*-(*tert*-butoxycarbonyl)-L-valyl-N^1-[(1*S*,2*S*)-1-(azidomethyl)-2-methylbutyl]-N^2-(4-methoxybenzyl)-2-methylalaninamide (1a).** According to the general procedure for Ugi-4CC, **1a** was obtained from *p*-methoxybenzylamine, acetone, *N*-Boc-L-valine and (2*S*,3*S*)-1-azido-2-isocyano-3-methylpentane. White solid, mp 78–78.8 °C, 50% yield; R_f (hexanes–ethyl acetate 1 : 1) 0.6; $[\alpha]_D$ −48.8 (*c* 1.0, MeOH, 25 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86–0.92 (m, 12H), 1.10–1.17 (m, 1H), 1.28–1.35 (m, 1H), 1.39 (s, 3H), 1.43 (s, 9H), 1.47 (s, 3H), 1.54–1.61 (m, 1H), 1.91–1.99 (m, 1H), 3.30–3.40 (m, 2H), 3.79 (s, 3H), 3.82–3.87 (m, 1H), 4.42–4.48 (m, 1H), 4.59 (d, $J_{AA'}$ = 17.7 Hz, 1H), 4.73 (d, $J_{AA'}$ = 17.7 Hz, 1H), 5.16 (d, J = 8.8 Hz, 1H), 5.59 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 15.4, 17.2, 19.5, 24.0, 24.4, 25.2, 28.2, 32.2, 35.7, 46.9, 52.4, 55.3, 56.1, 63.3, 79.4, 114.4, 127.8, 130.1, 155.4, 159.1, 173.1, 174.0; IR (film, cm^{-1}) 2108, 1710, 1682, 1640; Anal. Calcd for $C_{28}H_{46}N_6O_5$ (546.70): C, 61.51; H, 8.48; N, 15.37; found: C, 61.35; H, 8.51; N, 15.20%.

General procedure for the synthesis of 3a–c

The propargyl ester of bile acid derivative **2a** (1 mmol), $CuSO_4 \cdot 5H_2O$ (0.1 mmol) in 0.5 ml of H_2O and sodium ascorbate (0.4 mmol) in 0.5 ml of H_2O were added successively to a solution of the corresponding peptide (1 mmol) in 5 mL of EtOH. The reaction mixture was stirred at 60 °C for 12 h. The solvent

was removed *in vacuo* and the residue was purified by column chromatography (hexanes–ethyl acetate 1 : 1).

Compound 3a. White solid, mp 77–79 °C, 63% yield; R_f (ethyl acetate) 0.7; $[\alpha]_D$ +10.5 (*c* 1.5, MeOH, 25 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.63 (s, 3H), 0.82–0.85 (m, 6H), 0.89–0.92 (m, 6H), 0.95 (d, J = 5.8 Hz, 3H), 1.01 (d, J = 6.3 Hz, 3H), 1.15–1.40 (m, 26H), 1.46–1.58 (m, 8H), 1.64–1.93 (m, 9H), 2.17–2.27 (m, 1H), 2.30–2.39 (m, 1H), 3.64 (s, 3H), 3.78 (s, 3H), 3.94 (br s, 1H), 4.01–4.12 (m, 2H), 4.13–4.23 (m, 1H), 4.40–4.61 (m, 4H), 4.66–4.81 (m, 4H), 5.20 (d, J = 9.3 Hz, 1H), 5.72 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 8.1 Hz, 2H), 7.23–7.25 (m, 2H), 7.75 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.0, 12.6, 15.5, 17.2, 19.4, 23.0, 23.6, 23.9, 24.1, 24.9, 25.9, 26.5, 26.9, 27.4, 28.2, 28.6, 29.6, 30.9, 31.0, 32.1, 32.2, 33.6, 34.1, 34.8, 35.1, 35.9, 41.8, 46.4, 47.0, 47.1, 47.9, 51.2, 51.5, 55.3, 55.2, 55.8, 62.9, 64.5, 67.4, 72.9, 75.0, 79.5, 114.2, 124.1, 127.9, 130.0, 144.2, 155.5, 159.0, 169.7, 173.0, 174.4, 174.7; HRMS (ESI) calcd for $C_{58}H_{92}N_6O_{11}$ $[M + Na]^+$ 1071.6722, found 1071.6690.

General procedure for the synthesis of 4–7

The corresponding peptide (3 mmol for **2b–d** and 4 mmol for **2e**), $CuSO_4 \cdot 5H_2O$ (0.2 mmol for **2b–d** and 0.3 mmol for **2e**) in 0.5 ml of H_2O and sodium ascorbate (0.8 mmol for **2b–d** and 0.9 mmol for **2e**) in 0.5 ml of H_2O were added successively to a solution of the corresponding propargyl ester of bile acid derivative (1 mmol) in 10 mL of CH_2Cl_2. The reaction mixture was stirred at 40 °C for 10 h for **4**, **5**, **6** and 12 h for **7**. The solvent was removed *in vacuo* and the residue was purified by column chromatography (ethyl acetate or CH_2Cl_2–MeOH 10 : 1).

Compound 4a. White solid, mp 97–99 °C, 93% yield; R_f (ethyl acetate) 0.7; $[\alpha]_D$ +28.8 (*c* 1.5, MeOH, 25 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79–0.83 (m, 18H), 0.87–0.90 (m, 6H), 0.93 (s, 1H), 0.99–1.04 (m, 6H), 1.12–1.28 (m, 26H), 1.39 (s, 18H), 1.47–1.58 (m, 8H), 1.65–1.89 (m, 10H), 2.06–2.16 (m, 1H), 2.22–2.33 (m, 1H), 3.59 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 4.12–4.24 (m, 2H), 4.33–4.68 (m, 9H), 4.77–4.88 (m, 1H), 5.07–5.17 (m, 5H), 5.33 (br s, 1H), 5.65–5.73 (m, 1H), 5.89–5.99 (m, 1H), 6.87–6.90 (m, 6H), 7.02 (d, J = 8.6 Hz, 2H), 7.22–7.26 (m, 4H), 7.79 (d, J = 8.6 Hz, 2H), 7.85 (s, 1H), 7.87 (s, 1H), 8.03 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.0, 12.5, 14.1, 15.5, 17.2, 17.5, 19.5, 22.9, 23.5, 23.9, 24.1, 24.9, 25.7, 26.0, 26.4, 26.7, 27.4, 28.2, 29.6, 30.8, 31.0, 32.1, 32.2, 33.9, 34.5, 34.7, 35.7, 35.9, 36.1, 41.7, 45.5, 46.8, 47.9, 50.2, 51.0, 51.4, 53.2, 53.3, 55.2, 56.0, 60.3, 61.8, 62.0, 62.9, 74.2, 76.1, 79.4, 114.2, 114.3, 114.5, 123.7, 123.8, 124.1, 127.7, 129.9, 131.4, 143.0, 143.2, 155.3, 159.0, 161.7, 162.0, 165.4, 165.5, 173.1, 174.3, 174.5; HRMS (ESI) calcd for $C_{101}H_{146}N_{12}O_{18}$ $[M + Na]^+$ 1838.0776, found 1838.0696.

Synthesis of compound 8

A solution of **6b** (70 mg, 0.044 mmol) in trifluoroacetic acid (0.5 ml, 6.5 mmol) was refluxed for 7 h. The reaction mixture was diluted with DCM (5 ml) and neutralized with an aqueous saturated solution of sodium bicarbonate until the violet color disappeared. The layers were separated and the aqueous layer was extracted with DCM (2 × 10 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (CH_3CN–NH_3 90 : 1).

White solid, mp 57–58 °C, 60% yield; R_f (CH_3CN–NH_3 9 : 1) 0.3; $[\alpha]_D$ −5.3 (*c* 1.0, CH_2Cl_2, 25 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.61 (s, 3H), 0.87–0.95 (m, 18H), 1.04–1.13 (m, 15H), 1.34–1.49 (m, 24H), 1.62–1.68 (m, 2H), 1.76–1.82 (m, 5H), 1.92–2.03 (m, 4H), 2.17–2.26 (m, 1H), 2.30–2.40 (m, 1H), 3.22–3.25 (m, 2H), 4.11–4.17 (m, 3H), 4.29–4.50 (m, 6H), 4.73–5.00 (m, 4H), 5.18 (br s, 2H), 7.07 (d, J = 5.7 Hz, 1H), 7.13 (d, J = 5.7 Hz, 1H), 7.68–7.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.9, 12.0, 16.1, 17.5, 18.2, 20.8, 23.3, 23.9, 24.1, 24.8, 26.0, 26.3, 26.6, 27.0, 28.2, 30.8, 31.0, 32.2, 34.6, 34.9, 35.3, 35.8, 40.1, 40.4, 41.9, 42.7, 45.2, 45.3, 54.2, 55.9, 56.4, 56.9, 57.4, 58.4, 59.9, 64.6, 67.6, 75.2, 124.6, 125.0, 142.9, 144.1, 169.8, 174.1, 174.3, 174.9, 175.1; HRMS (ESI) calcd for $C_{58}H_{98}N_{12}O_9$ $[M + H]^+$ 1107.7658, found 1107.7639.

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