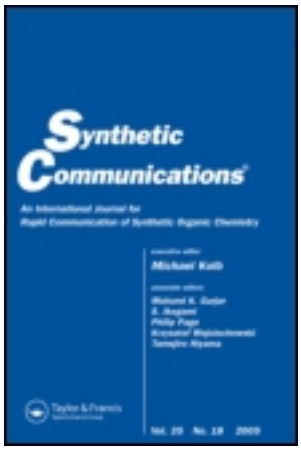

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SYNTHESIS OF LINEAR AND CYCLIC DIMERIC ESTER DERIVATIVES FROM BILE ACIDS AND GLYCINE

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ABSTRACT

Two novel taylor-made linear and cyclic dimers were synthesized from the inexpensive steroid bile acids and amino acid glycine. The structures and stereochemistry of all intermediates and dimers were determined by means of spectroscopic analyses.

The unique features of the bile acids, such as cholic acid **1** (Sch. 1), in terms of their chiral, rigid framework and chemically different hydroxyl groups, have made them well-established 'engineering components' for supramolecular chemistry.[1,2] As a result, considerable efforts have been

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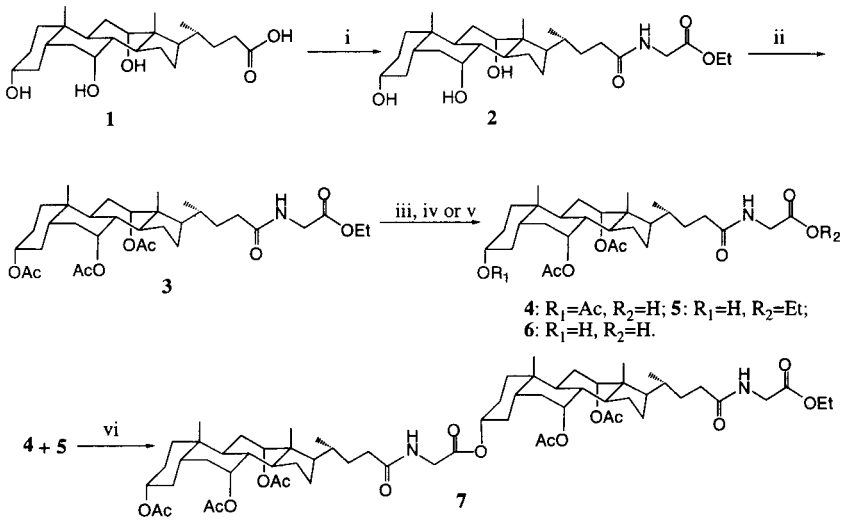


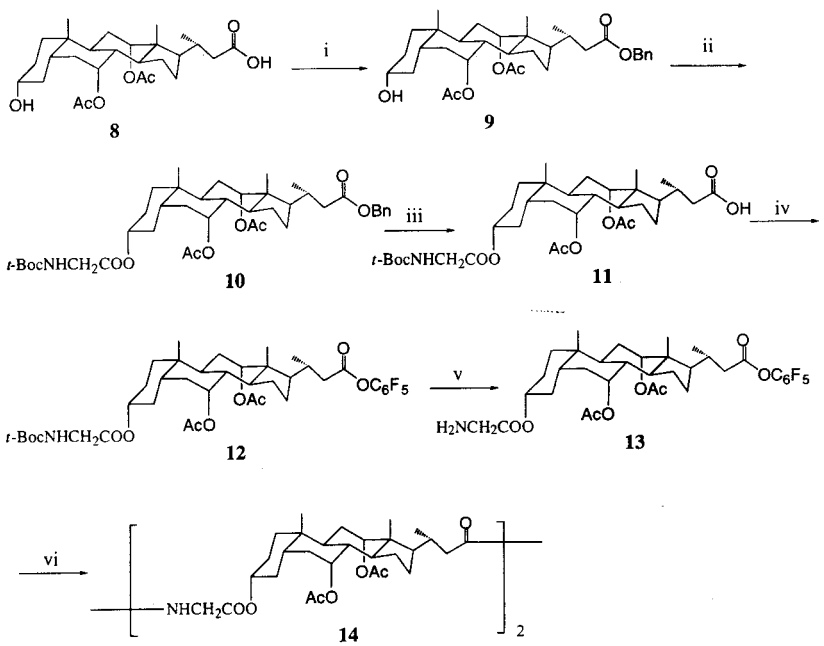
Scheme 1. Reagents and conditions: i. EEDQ, $H_2NCH_2CO_2Et$ HCl, Et_3N, EtOAc, reflux, 24 h, **2**: 73%; ii. Ac_2O, pyridine, DMAP, 23°C, 2 h, **3**: 86%; iii. 10% K_2CO_3/H_2O, EtOH, 23°C, 13 h, **4**: 93%; iv. NaOEt/EtOH (1.0 M), 23°C, 1 h, **5**: 75%; v. $LiOCH_3/H_2O$ (0.2 N), THF, 23°C, 6 h, **6**: 93%; vi. DCBC, DMAP, toluene, reflux, 48 h, **7**: 57%.

made in recent years towards the synthesis of taylor-made dimeric and oligomeric steroids.[3,4] The macrocyclic polyesters-'cyclocholates'-formed by head to tail cyclization of cholic acid derivatives, in general, composed principally of dimers to pentamers can be prepared by Yamaguchi macrolactonization[5] of 7,12-protected monomeric hydroxy acids using 2,6-dichlorobenzoyl chloride as the coupling reagent.[6] The size of ring produced was found to depend on both the steric bulk of protecting groups on the 7,12-axial hydroxyl groups[7] and the length of 17-side chain of monomers.[8] Recently, a steroidal cyclopeptide where two molecules of the pseudoamino acid (3α-amino-lithocholic acid) form with two or four phenylalanines a cyclopeptide with a lipophilic steroid cavity has been reported.[9,10] However, to our knowledge, taylor-made either linear or cyclic dimer system form with amino acids has not yet been synthesized. We report here a synthesis of first linear chola-peptide **7** and cyclic cholapeptide **14** where two molecules of the bile acid form with two molecules of glycine.

Glycine conjugate **2** was obtained by refluxing ethyl glycinate hydrochloride (1.4 eq.), *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ, 1.4 eq.), cholic acid (1 eq.), and triethylamine in ethyl acetate

solution overnight (Sch. 1).[11] The triacetylation of compound **2** at 3α-, 7α- and 12α-positions was carried out in acetic anhydride with pyridine as the solvent using dimethylaminopyridine (DMAP) a catalyst. The ethyl ester of compound **3** were selectively hydrolyzed in ethanol and aqueous 10% potassium carbonate for 17 h to obtain compound **4** in 93% yield. Because the rate of hydrolysis of three acetate groups in decreasing order is $3\alpha \gg 7\alpha > 12\alpha$ (*vida infra*),[12] selective removal of the 3α-acetoxy group was achieved using EtONa/THF (1.0 M) in 75% yield after column chromatography. We also employed lithium methoxide aqueous solution (0.2 N) regioselectively hydrolyzed both 3α-acetoxy and ethyl ester groups in compound **3** to obtain compound **6** in 93% yield. The final dimerization was accomplished from monomers **4** and **5** by Yamaguchi esterification in 57% yield.[5]

The synthesis of cyclic chola-peptide **14**, from 24-norcholic acid (**8**)[8] with a shorter 17-side chain, is outlined in Sch. 2. The carbonyl group of



Scheme 2. Reagents and conditions: i. BnOH, DCC, DMAP, CH_2Cl_2, 23°C, 24 h, **9**; ii. *t*-$BocNHCH_2CO_2H$, DCC, DMAP, DMF, 23°C, 15 h, **10**: 94% over two steps; iii. H_2, 10% Pd/C, THF, 23°C, 17 h, **11**: 965; iv. C_6F_5OH, DCC, CH_2Cl_2, 23°C, 17 h, **12**; v. CH_2Cl_2, TFA, 23°C, 1 h, **13**; vi. Na_2HPO_4, DMAP, CH_2Cl_2, 23°C, 5 days, **14**: 17% over three steps.

compound **8** was protected as the corresponding benzyl ester via reaction with benzyl alcohol using DCC and DMAP.[13] *N*-Boc-protected glycine was easily attached to **9** by same strategy. Cleaving the benzyl group via catalytic hydrogenation[14] gave compound **11**. The free carboxylic acid is then converted to the pentafluorophenolester which cyclized to the cholapeptide **14** after removal of the *t*-Boc group.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR (proton decoupled) spectra were recorded on 250 MHz and 63 MHz (Bruker), respectively, in $CDCl_3$ as solvent and with TMS as internal standard. The following abbreviations indicate signal multiplicity, s = singlet, d = doublet, t = triplet, q = quartet, sx = sextet, m = multiplet. ^{13}C NMR assignments in spectra of cholic acid derivatives were made by comparison with reference values.[15,16] In ^{1}H NMR spectra, overlapping steroidal backbone resonances are not quoted. Fast atom bombardment (FAB) mass spectra were obtained using a *m*-nitrobenzyl alcohol matrix on a Autospec-Ultima ETOF instrument. Thin layer chromatography (TLC) was carried out on Fisher 250 micron silica gel G (5 × 20 cm) TLC plates. Visualization was done by either spraying the plates with 5% phosphomolybdic acid in ethanol and briefly heating or keeping the plates in an iodine bottle. Flash column chromatography was carried out using Grade 62 (60–200 mesh) silica gel and eluted by a *n*-hexane–ethyl acetate solvent system. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Materials were obtained from commercial suppliers and used without further purification.

Ethyl 3α,7α,12α-triacetoxy-5β-glycocholate (3): To a cooled (0°C) solution of **2**[11] (13 g, 26.4 mmol) in acetic anhydride (21 mL, 222 mmol, 8.43 eq.) and pyridine (31 mL), DMAP (1.9 g, 15.5 mmol, 0.6 eq.) was added. The reaction mixture was stirred at 23°C for 2 h. The solvent was concentrated in vacuo, the residue was poured into 1.0 M HCl (1000 mL) aqueous and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed by $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford foamy solid **3** (14 g, 86%). ^{1}H NMR ($CDCl_3$): 0.73 (s, 3H, 18-H_3); 0.82 (d, 3H, 21-H_3); 0.93 (s, 3H, 19-H_3); 1.40 (t, 3H, CH_2CH_3); 2.06 (s, 3H, 3α-OAc); 2.09 (s, 3H, 7α-OAc); 2.14 (s, 3H, 12α-OAc); 4.00 (bs, 2H, NH$\underline{CH_2}$COOEt); 4.20 (q, 2H, CH_2CH_3); 4.57 (bs, 1H, 3β-H); 4.90 (s, 1H, 7β-H); 5.09 (s, 1H, 12β-H); 6.44 (bs, 1H, $\underline{NH}CH_2COOEt$). MS (FAB): 620.3 $[M+1]^+$, 500.2 $[M\text{-}2HOAc+1]^+$, 440.2 $[M\text{-}3HOAc+1]^+$, 337.1, 154.0, 136.0, 107.0, 95.0, 69.0, 55.0.

3α,7α,12α-Triacetoxy-5β-glycocholic acid (4): To a solution of compound **3** (14 g, 22 mmol) in ethanol (50 mL), 10% K_2CO_3 (100 mL) aqueous solution was added slowly. The resulted solution was stirred at 23°C for 17 h, neutralized with 1.0 M HCl aqueous solution and extracted with ethyl acetate. The combined organic layers were washed by $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford foamy solid **4** (12.5 g, 93%) ^{1}H NMR ($CDCl_3$): 0.73 (s, 3H, 18-H_3); 0.81 (d, 3H, 21-H_3); 0.93 (s, 3H, 19-H_3); 2.06 (s, 3H, 3α-OAc); 2.10 (s, 3H, 7α-OAc); 2.15 (s, 3H, 12α-OAc); 4.03 (bs, 2H, NH$\underline{CH_2}$COOH); 4.57 (bs, 1H, 3β-H); 4.91 (s, 1H, 7β-H); 5.09 (s, 1H, 12β-H); 6.73 (bs, 1H, $\underline{NH}CH_2COOH$); 10.30 (s, 1H, COOH). MS (FAB): 592.2 $[M+1]^+$, 472.3 $[M\text{-}2HOAc+1]^+$, 440.3, 412.3 $[M\text{-}3HOAc+1]^+$.

Ethyl 7α,12α-diacetoxy-3α-hydroxy-5β-glycocholate (5): To a solution of compound **3** (23 g, 37 mmol) in THF (400 mL), EtONa (1.0 M in EtOH, 50 mL) was added. The resulted solution was stirred at 23°C for 2 h and the solvent was concentrated in vacuo. The residue was poured into 1.0 M HCl (1000 mL) aqueous and extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed by $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was flash chromatographed on a silica gel column to afford foamy solid **5** (16 g, 75%). ^{1}H NMR ($CDCl_3$): 0.73 (s, 3H, 18-H_3); 0.82 (d, 3H, 21-H_3); 0.91 (s, 3H, 19-H_3); 1.29 (t, 3H, $CH_2\underline{CH_3}$); 2.09 (s, 3H, 7α-OAc); 2.13 (s, 3H, 12α-OAc); 3.50 (bs, 1H, 3β-H); 4.03 (bs, 2H, NH$\underline{CH_2}$COOEt); 4.22 (q, 2H, $CH_2\underline{CH_3}$); 4.90 (s, 1H, 7β-H); 5.10 (s, 1H, 12β-H); 6.34 (bs, 1H, $\underline{NH}CH_2COOEt$). MS (EI) *m*/*z* (rel intensity): 577.4 $[M]^+$ (8), 440.2 (25), 412.2 (10), 337.2 (19), 253.1 (27), 227.1 (15), 136.0 (33), 107.0 (42), 104.0 (48), 95.0 (53), 81.0 (57), 69.0 (68), 55 (100).

7α,12α-Diacetoxy-3α-hydroxy-5β-glycocholic acid (6): To a solution of compound **3** (4.5 g, 7.8 mmol) in THF (155 mL) at 23°C, $LiOCH_3$ (0.2 N, 155 mL) aqueous solution was added. The resulted solution was continued to stirred at the same temperature for 6 h, neutralized with 1.0 M HCl aqueous solution and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed by $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford foamy solid **6** (3.98 g, 93%). ^{1}H NMR ($CDCl_3$): 0.72 (s, 3H, 18-H_3); 0.81 (d, 3H, 21-H_3); 0.91 (s, 3H, 19-H_3); 2.09 (s, 3H, 7α-OAc); 2.13 (s, 3H, 12α-OAc); 3.53 (bs, 1H, 3β-H); 4.02 (bs, 2H, NH$\underline{CH_2}$COOH); 4.89 (s, 1H, 7β-H); 5.08 (s, 1H, 12β-H); 6.68 (bs, 1H, $\underline{NH}CH_2COOH$); 7.64 (s, 1H, COOH). MS (FAB): 550.3 $[M+1]^+$, 548.3 $[M-1]^+$, 430.3 $[M\text{-}2HOAc+1]^+$, 412.3 $[M\text{-}2HOAc\text{-}H_2O+1]^+$.

Dimerization of compound 4 and 5: A mixture of monomers **4** (6.7 g, 11.3 mmol), **5** (6.5 g, 11.3 mmol), 2,6-dichlorobenzoyl chloride (2 mL,

14 mmol, 1.2 eq.), DMAP (5.5 g, 45 mmol, 3.98 eq.) and anhydrous toluene (366 mL) was refluxed for 48 h. The solvent was concentrated under reduced pressure, the residue was flash chromatographed on a silica gel column and crystalized to afford dimer **7**. M.p. 128–130°C, yield: 57%. ^{1}H NMR ($CDCl_3$): 0.73 (s, 6H, 18-CH_3), 0.82 (d, 6H, 21-CH_3), 0.93 (s, 6H, 19-CH_3), 1.28 (t, 3H, $CH_2\underline{CH_3}$), 2.05–2.14 (m, 15H, 3α-OAc, 7α-OAc, 12α-OAc), 4.00, 4.02 (d, 4H, NH$\underline{CH_2}$COO), 4.20 (q, 2H, $\underline{CH_2}CH_3$), 4.57, 4.62 (db, 2H, 3β-H), 4.91 (bs, 2H, 7β-H), 5.10 (bs, 2H, 12β-H), 6.35 (bs, 2H, $\underline{NH}CH_2COO$). ^{13}C NMR ($CDCl_3$): 34.66 (C-1), 26.78 (C-2), 74.02 (C-3), 34.66 (C-4), 40.84 (C-5), 31.13 (C-6), 70.57, 70.65 (C-7), 37.61 (C-8), 28.80 (C-9), 34.24 (C-10), 25.50 (C-11), 75.34 (C-12), 44.99 (C-13), 43.32 (C-14), 22.75 (C-15), 27.17 (C-16), 47.40 (C-17), 12.19 (C-18), 22.48 (C-19), 34.47 (C-20), 17.51 (C-21), 31.33 (C-22), 32.96 (C-23), 169.67 (C-24), 41.26, 41.50 ($\underline{CH_2}COO$), 173.59 ($CH_2\underline{COO}$), 14.13 ($CH_2\underline{CH_3}$), 61.37 ($\underline{CH_2}CH_3$), 21.43, 21.62 ($\underline{CH_3}COO$), 170.06, 170.41, 170.52 ($CH_3\underline{COO}$). MS (FAB): 1151.3 $[M+1]^+$, 662.2, 578.3, 557.2, 529.25, 440.3, 391.3, 373.3.

Benzyl 3α-hydroxy-7α,12α-diacetoxy-24-nor-5β-cholan-23-oate (9): DCC (6.5 g, 31.5 mmol, 1.2 equiv.) was added to a stirred solution of the acid **8** (12.75 g, 26.7 mmol, 1 equiv.), benzyl alcohol (3.8 mL, 36.7 mmol, 1.37 equiv.) and DMAP (0.9 g, 7.37 mmol, 0.28 equiv.) in anhydrous CH_2Cl_2 (150 mL) at 23°C. After being stirred at same temperature for 24 h, the mixture was diluted with CH_2Cl_2 and filtered. The filtrate was washed with 5% aq. HCl, satd. $NaHCO_3$, brine, dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography to give foamy solid **9** in a quantitative yield. ^{1}H NMR ($CDCl_3$): 0.75 (s, 3H, 18-H_3); 0.86 (d, 3H, 21-H_3); 0.89 (s, 3H, 19-H_3); 2.07 (s, 3H, 7α-OAc); 2.09 (s, 3H, 12α-OAc); 2.42 (d, 2H, 22-H_2); 3.40 (bs, 1H, 3β-H); 4.65 (bs, 1H, 7β-H); 4.87 (bs, 1H, 12β-H); 5.10 (s, 2H, CH_2Ph); 7.33, 7.35 (bs, 5H, CH_2Ph). MS (FAB): 591.2 $[M+Na]^+$, 549.4 $[M-H_2O-1]^+$, 449.2 $[M-2HOAc+1]^+$, 306.2, 225.1, 207.1, 176.0, 154.0, 136.0, 107.0, 95.0, 91.0, 81.0, 55.0.

Benzyl 7α,12α-diacetoxy-3α-{*N*-[(*tert*-butoxy)carbonyl]-glycyl}-24-nor-5β-cholan-23-oate (10): A solution of **9** (7.4 g, 13 mmol, 1 equiv.) and *t*-Boc-glycine (2.7 g, 15.4 mmol, 1.2 equiv.) in anhydrous DMF was treated with DMAP (0.64 g, 5.2 mmol, 0.4 equiv.) and DCC (3.2 g, 15.5 mmol, 1.2 equiv.) at 23°C. The mixture was stirred 24 h at the same temperature and the solvent was removed in vacuo. The residue was taken up in ethyl acetate (400 mL). The solution was extracted with 1.0 M HCl, saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by column chromatography to afford **10** as a white solid (8.9 g, 94%). M.p. 98–100°C. ^{1}H NMR ($CDCl_3$); 0.76 (s, 3H, 18-H_3); 0.87 (d, 3H, 21-H_3); 0.92 (s, 3H, 19-H_3); 1.44 (s, 9H, $(CH_3)_3C$); 2.08 (s, 3H, 7α-OAc);

2.11 (s, 3H, 12α-OAc); 3.97 (d, 2H, *t*-BocNHCH$_2$COO); 4.63 (m, 1H, 3β-H); 4.90 (bs, 1H, 7β-H); 5.10 (s, 2H, *CH*$_2$Ph); 5.16 (s, 1H, 12β-H); 7.34 (bs, 5H, CH$_2$*Ph*); 7.58 (t, 1H, *t*-BocNHCH$_2$COO). MS (FAB): 724.2 [M−1]$^+$, 551.1, 550.1 [M-*t*-BocNHCH$_2$COOH]$^+$, 540.2, 483.1, 201.0, 157.0, 91.0, 57.0.

7α,12α-Diacetoxy-3α-{*N*-[(*tert*-butoxy)carbonyl]-glycyl}-24-nor-5β-cholan-23-oic acid (11): To a solution of **10** (3.3 g, 4.55 mmol, 1 equiv.) in THF (50 mL), 10% Pd-C (500 mg) was added. The mixture was stirred in a H_2 atmosphere for 20 h at 23°C. The catalyst was filtered and the filtrate was evaporated in vacuo to yield compound **11** as a foamy solid (2.78 g, 96%). ^{1}H NMR ($CDCl_3$): 0.78 (s, 3H, 18-H_3); 0.93 (bs, 6H, 19-H_3, 21-H_3); 1.45 (s, 9H, $(CH_3)_3C$); 2.10 (s, 3H, 7α-OAc); 2.15 (s, 3H, 12α-OAc); 3.98 (d, 2H, *t*-BocNHCH$_2$COO): 4.63 (bs, 1H, 3β-H); 4.92 (bs, 1H, 7β-H); 5.10 (s, 1H, 12β-H); 7.58 (t, 1H, *t*-BocNHCH$_2$COO). MS (FAB): 635.5 [M] $^+$, 539.4, 514.2 [M-2HOAc-1]$^+$, 460.3 [M-*t*-BocNHCH$_2$COOH]$^+$, 382.4, 326.3, 258.2, 201.2, 183.2, 157.2, 98.1.

Pentafluorophenyl 7α,12α-Diacetoxy-3α-{*N*-[(*tert*-butoxy)carbonyl]-glycyl}-24-nor-5β-cholan-23-oate (12): Compound **11** (7.8 g, 12.3 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (150 mL) with pentafluorophenol (3.4 g, 18.4 mmol, 1.5 equiv.) and cooled to 0°C under an inert atmosphere. DCC (3.8 g, 18.5 mmol, 1.5 equiv.) was added in one portion. The mixture was left stirring overnight and filtered. The filtrate was extracted with aqueous $NaHCO_3$, 1.0 M HCl, brine and dried over Na_2SO_4. The solvent was removed in vacuo to give compound **12** as a glass in a quantitative crude yield. This product was used without further purification. ^{1}H NMR ($CDCl_3$): 0.81 (s, 3H, 18-H_3); 0.94 (s, 3Hbs, 19-H_3); 1.15 (d, 3H, 21-H_3); 2.10 (s, 3H, 7α-OAc); 2.15 (s, 3H, 12α-OAc); 4.00 (d, 2H, NHCH$_2$COO); 4.92 (bs, 1H, 3β-H); 5.11 (bs, 1H, 7β-H); 5.44 (s, 1H, 12β-H); 7.51 (t, 1H, *t*-BocNHCH$_2$COO). MS (FAB): 824.2 [M+Na]$^+$, 626.1 [M-*t*-BocNHCH$_2$COOH]$^-$, 507.1 [M-*t*-BocNHCH$_2$COOH-2HOAc+1]$^+$, 431.3, 404.2, 382.2, 326.2, 307.0, 225.2, 201.1, 154.0, 136.0, 95.1, 83.1, 69.1, 57.1.

Pentafluorophenyl 7α,12α-Diacetoxy-3α-glycyl-24-nor-5β-cholan-23-oate (13). Crude compound **12** (assumed 12.3 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (100 mL) followed by addition of trifluoroacetic acid (15 mL). The mixture was stirred at 23°C for 1 h and evaporated to dryness. The residue was take up in CH_2Cl_2 (200 mL), washed with $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4) and evaporated to yield **13** of sufficient purity for further elaboration. A portion of the crude product (0.1 g) was purified by flash chromatography using $CHCl_3$-MeOH (9:1) as eluent to yield pure **13** (0.07 g). ^{1}H NMR ($CDCl_3$): 0.76 (s, 3H, 18-H_3); 0.92 (s, 6H, 19-H_3, 21-H_3); 2.02 (s, 3H, 7α-OAc); 2.07 (s, 3H, 12α-OAc); 3.97 (s, 2H, NH_2CH_2COO); 4.64 (bs, 1H, 3β-H); 4.81 (bs, 1H, 7β-H); 5.01 (s, 1H, 12β-H); 8.21 (bs, 2H, NH_2CH_2COO).

Dimerization of compound 13: To a solution of compound **13** (assumed 12.3 mmol), in CH_2Cl_2 (3075 mL) was added DMAP (3.0 g, 24.6 mmol, 2 equiv.), and Na_2HPO_4 (7.0 g, 49.3 mmol, 4 equiv.). After 5 days of stirring at 23°C, the mixture was filtered and evaporated to dryness. The residue was purified by chromatography on silica gel (CH_2Cl_2–MeOH: 9 : 1) to afford compound **14** as a foamy solid (1.07 g, 17% over three steps). ^{1}H NMR ($CDCl_3$): 0.77 (s, 6H, 18-CH_3), 0.85 d, 6H, 21-CH_3), 0.94 (s, 6H, 19-CH_3), 2.09 (s, 6H, 7α-OAc), 2.13 (s, 6H, 12α-OAc), 4.07 (s, 4H, NH$\underline{CH_2}$COO), 4.66 (s, 2H, 3β-H), 4.91 (bs, 2H, 7β-H), 5.10 (bs, 2H, 12β-H), 8.08 (bs, 2H, $\underline{NH}CH_2COO$). ^{13}C NMR ($CDCl_3$): 34.43 (C-1), 26.67 (C-2), 75.30 (C-3), 34.24 (C-4), 41.61 (C-5), 31.17 (C-6), 70.69 (C-7), 37.69 (C-8), 28.76 (C-9), 34.24 (C-10), 25.27 (C-11), 75.81 (C-12), 45.14 (C-13), 43.94 (C-14), 22.79 (C-15), 27.33 (C-16), 48.21 (C-17), 12.27 (C-18), 22.44 (C-19), 32.33 (C-20), 18.40 (C-21), 40.80 (C-22), 167.73 (C-23), 43.32, 43.94 ($\underline{CH_2}$COO), 170.56 ($CH_2\underline{COO}$), 21.04, 21.27, 21.47 ($\underline{CH_3}$COO), 171.84 ($CH_3\underline{COO}$). MS (FAB): 1056.4 $[M+Na\text{-}1]^+$, 929.3, 892.3, 851.3, 768.3, 711.2, 656.2, 599.2, 169.9, 151.9, 124.9.

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