Monatshefte für Chemie 137, 117–124 (2006)
DOI 10.1007/s00706-005-0402-z

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

New Acyclic Dimers of Cholic Acid with Oxamide and Hydrazide Spacers

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Received March 15, 2005; accepted (revised) April 25, 2005
Published online December 13, 2005

Summary. Three new acyclic dimers of cholic acid with oxamide and isomeric hydrazide (*N,N′*-diacylhydrazine) spacers were obtained. The oxamide spacers bind two identical steroidal subunits through position 3 (head-to-head dimer) or position 23 (tail-to-tail dimer). In the case of a third dimer the hydrazine moiety binds two molecules of cholic acid through position 24 (tail-to-tail dimer).

Keywords. Bile acids; Hydrazides; Oxamides; Steroids; Supramolecular chemistry.

Introduction

Bile acids are versatile building blocks for the design and synthesis of molecular receptors, enzyme models, and transporters, *e.g.*, drugs across phospholipid membranes [1, 2]. There are many kinds of acyclic structures based on bile acids, among which the most interesting are: cleft type structures [3], molecular tweezers [4], ionophores [5], molecular umbrellas [6], dendrons [7], gelling agents [8], and inclusion compounds (clathrates) [9]. On the other hand, the oxamide moiety is an important component of many products with specific biological activity. Some of them have found application as plant growth regulators [10], cephalosporin bactericides [11], HIV-1 protease inhibitors [12], and pesticides [13].

In this paper we report the synthesis of three new cleft-type dimers of cholic acid with oxamide (dimers **9** and **15**) and isomeric hydrazide (dimer **17**) spacers (Scheme 1).

Results and Discussion

Dimer **9** was prepared from cholic acid (**1**) according to Scheme 2. The key step of this synthesis appeared to be the removal of the protecting ester groups of **8**. The treatment of this dimer with $LiAlH_4$ in *THF* at room temperature for two days caused complete reduction of the two methyl esters in the side chains and only

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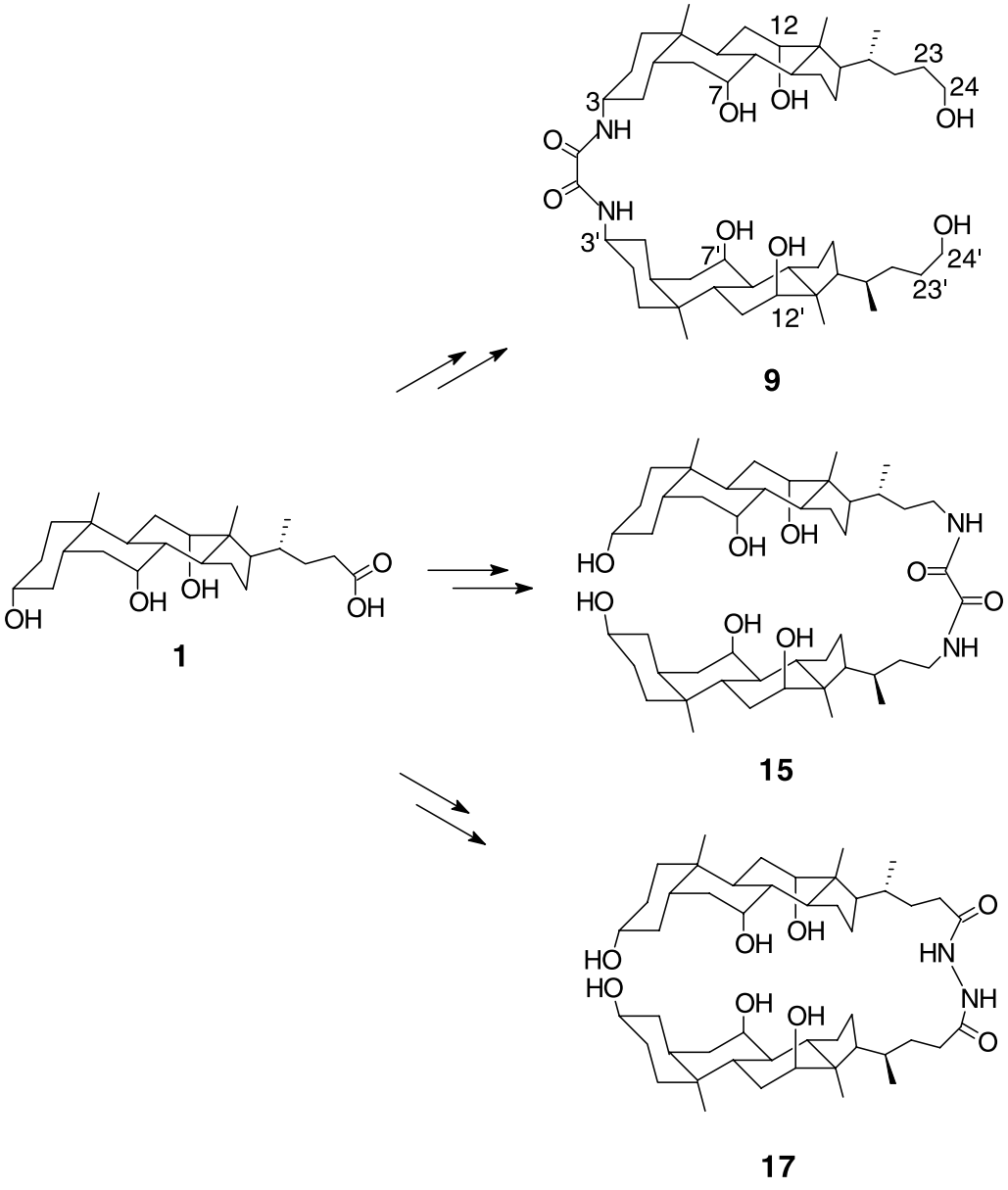
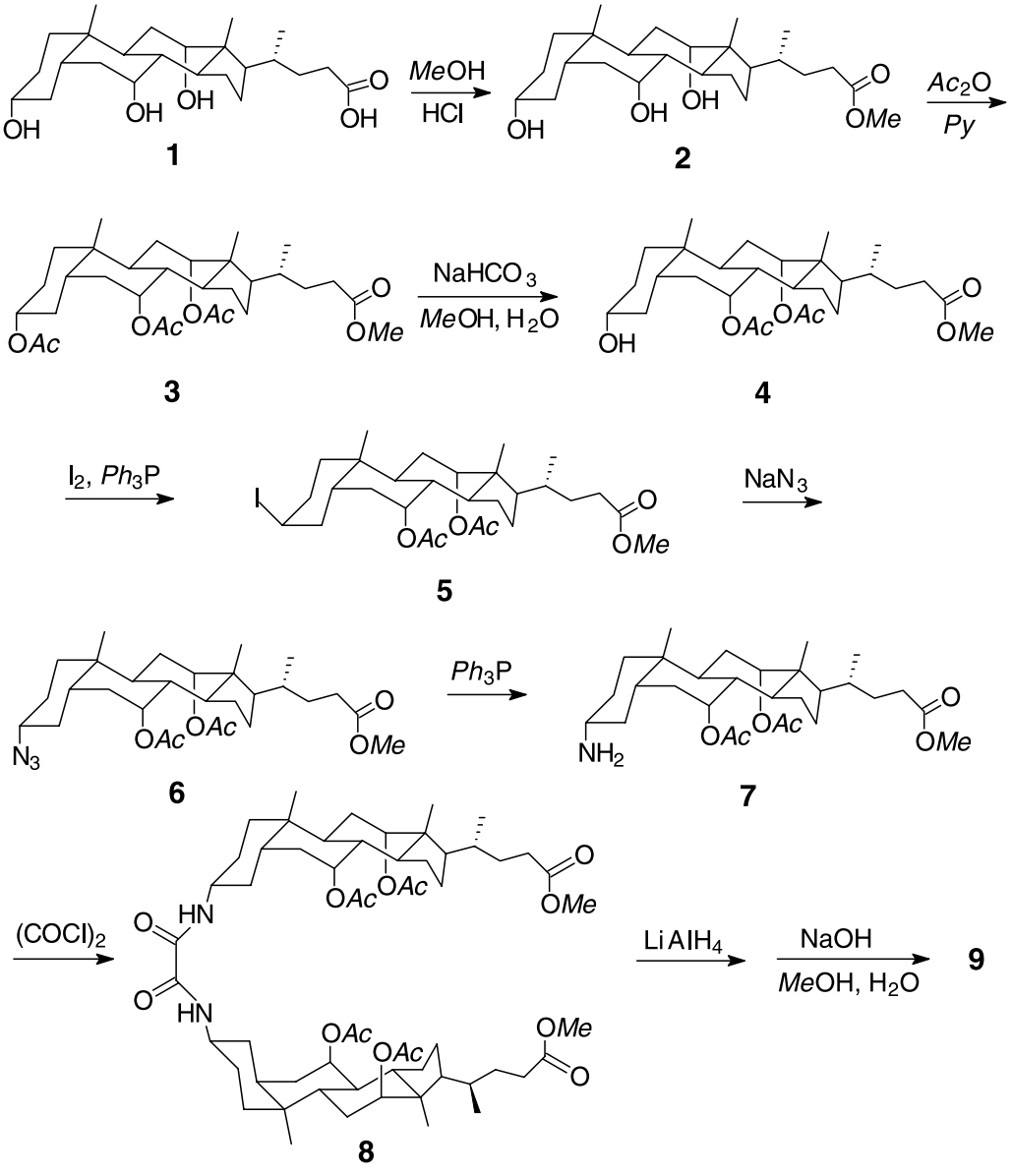


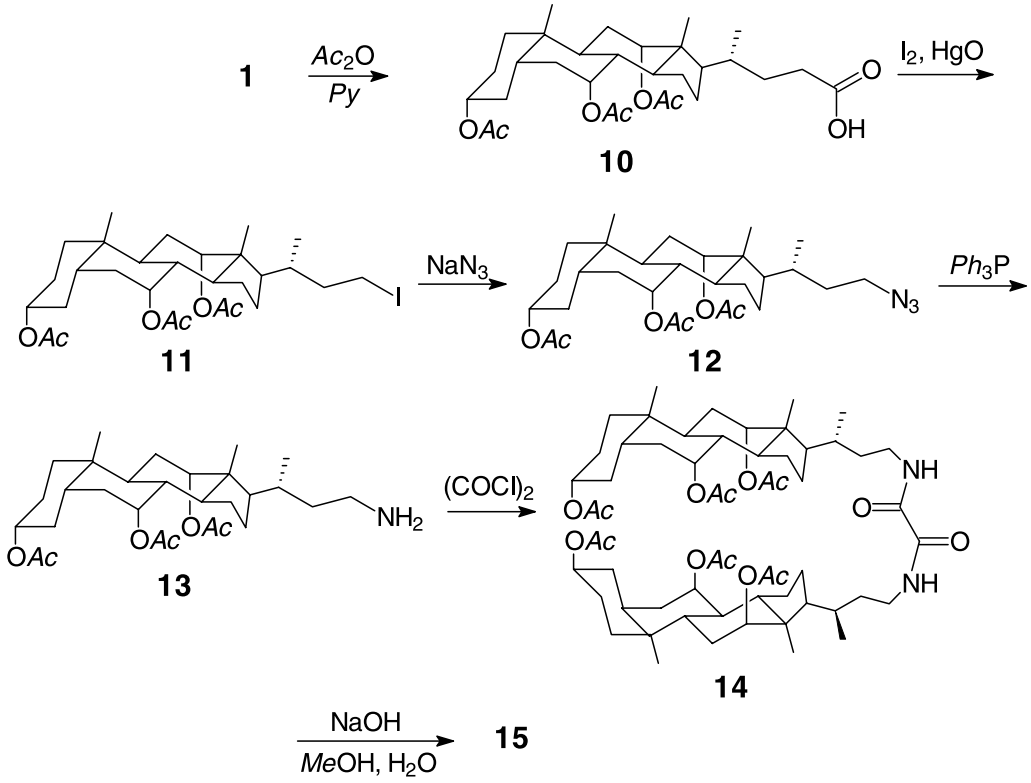
Scheme 1

partial reduction of the acetyl groups (TLC showed formation of a number of more polar products, among which the dimer **9** was present in only about 10%). Neither additional portions of the reducing agent nor prolonged reaction time forced the reaction to reach completion; what is even worse, small amounts of very polar compounds appeared, probably as the result of the reduction of the oxamide moiety. Therefore it was decided to carry out a two step procedure: $LiAlH_4$ reduction of the carbomethoxy groups followed by NaOH/*Me*OH–H_2O hydrolysis of the acetyl groups resistant to reduction. In this way the yield of dimer **9** rised to about 85%.

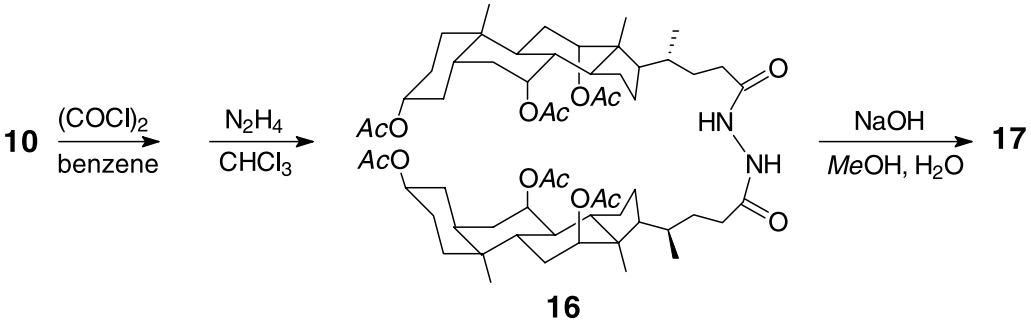


Scheme 2

The two other dimers were obtained from cholic acid in typical procedures as shown in Scheme 3 for dimer **15** and **4** for dimer **17**. Both dimers **15** and **17** were designed as structural isomers to each other, so the synthesis of **15** required to remove one carbon atom from the side chain of **10**; this was achieved by a *Hunsdiecker* type reaction [14] carried out in good yield by means of mercury(II) oxide and iodine in refluxing CCl_4. In the first attempt to obtain **15** the direct conversion carboxylic acid **10** → amine **13** (*Schmidt* reaction) was tried. In addition, the other three methods of this conversion were tested: the acid **10** with NaN_3 in polyphosphoric acid [15a]; **10** in benzene with hydrazoic acid [15b]; **10** in chloroform with NaN_3/conc. H_2SO_4 [15c]. It turned out that all these experiments were



Scheme 3



Scheme 4

unsuccessful due to very poor yields of **13** (the yields of the desired product were lower than 10% regardless of the reaction conditions). The procedure shown in Scheme 3 (*via* iodide **11** and azide **12**) was longer but also more efficient; in this case the total yield of **13** exceeded 40%.

Conclusion

Three new cleft-type dimers **9**, **15**, and **17** based on cholic acid were obtained in good yields in typical procedures shown in Schemes 2–4. All these compounds are

potential supramolecules capable to complex guest molecules or ions. This kind of physicochemical studies is under way.

Experimental

Melting points were determined on a *Kofler* apparatus of the *Boëtius* type. NMR spectra were taken with a Bruker AC 200F spectrometer with *TMS* as internal standard. Infrared spectra were recorded on a Nicolet series II Magna-IR 550 FT-IR spectrometer. Mass spectra were obtained with AMD-604 spectrometer. The reaction products were isolated by column chromatography performed on 70–230 mesh silica gel (J.T. Baker). Thin-layer chromatograms were developed on aluminum TLC sheets precoated with silica gel F_{254} (Merck) and visualized with 50% H_2SO_4 after heating. All solvents were dried and freshly distilled prior to use. Cholic acid (**1**) was purchased from ABCR GmbH & Co. KG and it was used without further purification. Methyl cholate (**2**), 3,7,12-triacetylmethyl cholate (**3**), 7,12-diacetylmethyl cholate (**4**), and 3,7,12-triacetylcholic acid (**10**) were prepared according to known procedures [16].

Methyl 7α,12α-diacetoxy-3β-iodo-5β-chol-24-anoate (**5**, $C_{29}H_{45}IO_6$)
To a solution of 2.94 g **4** (5.81 mmol) in 100 cm^3 benzene/acetonitrile 4/1 mixture 8.40 g triphenylphosphine (32.06 mmol) and 2.30 g imidazole (33.82 mmol) were added. After a few minutes 7.4 g I_2 (29.13 mmol) were added portionwise with vigorous stirring. The reaction was continued for 15 min and then the mixture was poured into H_2O containing a few drops 30% H_2O_2 and extracted with benzene. The combined organic layers were washed with aqu $Na_2S_2O_5$ and dried ($MgSO_4$). The crude product was subjected to column chromatography. Pure iodide **5** was eluted with *n*-hexane/ethyl acetate 8/2 (3.54 g, 99% yield). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.08$ (m, 12β-H), 4.91 (m, 7β-H and 3α-H), 3.66 (s, OCH_3), 2.12 (s, 12α-CH_3CO), 2.09 (s, 7α-CH_3CO), 0.92 (s, 19-CH_3), 0.86 (d, $J = 6.05$ Hz, 21-CH_3), 0.73 (s, 18-CH_3) ppm.

Methyl 3α-azido-7α,12α-diacetoxy-5β-chol-24-anoate (**6**, $C_{29}H_{45}N_3O_6$)
To a solution of 3.50 g **5** (5.68 mmol) in 250 cm^3 *N*-methylpyrrolidone 3 g NaN_3 (46.2 mmol) and 3.5 cm^3 acetic acid (61.25 mmol) were added. The mixture was stirred overnight at room temperature, then poured into aqu $NaHCO_3$ and extracted several times with benzene. The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. The crude product was subjected to column chromatography. Pure azide **6** was eluted with benzene/ethyl acetate 95/5 (2.74 g, 91% yield). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.08$ (m, 12β-H), 4.91 (m, 7β-H), 3.66 (s, OCH_3), 3.14 (m, 3β-H), 2.12 (s, 12α-CH_3CO), 2.09 (s, 7α-CH_3CO), 0.92 (s, 19-CH_3), 0.86 (d, $J = 6.05$ Hz, 21-CH_3), 0.73 (s, 18-CH_3) ppm.

Methyl 3α-amino-7α,12α-diacetoxy-5β-chol-24-anoate (**7**, $C_{29}H_{47}NO_6$)
To a solution of 2.30 g **6** (4.33 mmol) in 80 cm^3 *THF* 3.36 g triphenylphosphine (12.82 mmol) and 2 cm^3 H_2O were added under Ar. The mixture was stirred overnight at room temperature and then evaporated to dryness. The amine **7** was isolated by column chromatography (elution with methanol/$CHCl_3$ 2/8) giving 2.05 g (94%) pure product. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.08$ (m, 12β-H), 4.89 (m, 7β-H), 3.66 (s, OCH_3), 2.62 (m, 3β-H), 2.13 (s, 12α-CH_3CO), 2.08 (s, 7α-CH_3CO), 0.91 (s, 19-CH_3), 0.81 (d, $J = 6.10$ Hz, 21-CH_3), 0.73 (s, 18-CH_3) ppm; IR ($CHCl_3$): $\bar{\nu} = 3368$, 1724, 1256, 1024, 666, 542 cm^{-1}.

N,N′-Di(3α-amino-7α,12α-diacetoxy-5β-cholanoic acid methyl ester)3,3′-oxamide
(**8**, $C_{60}H_{92}N_2O_{14}$)
Amine **7** (2 g, 3.96 mmol) was dissolved in 80 cm^3 anhydrous pyridine and 0.17 cm^3 oxalyl chloride (1.98 mmol) were added dropwise with vigorous stirring within 15 min. Then the reaction mixture was poured into acidified H_2O and the crude product was extracted with CH_2Cl_2. The organic layer was

dried ($MgSO_4$) and the solvent was removed. The dimer **8** was purified by column chromatography (elution with benzene/ethyl acetate 7/3) to afford 1.87 g (89%) pure product. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.37$ (d, $J = 8.51$ Hz, 2N–H), 5.10 (m, 2 12β-H), 4.91 (m, 2 7β-H), 4.15 (m, 2 3β-H), 3.67 (s, 2OCH_3), 2.19 (s, 2 12α-CH_3CO), 2.07 (s, 2 7α-CH_3CO), 0.98 (s, 2 19-CH_3), 0.82 (d, $J = 5.92$ Hz, 2 21-CH_3), 0.74 (s, 2 18-CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 174.5$ (2C), 170.6 (2C), 170.3 (2C), 159.0 (2C), 75.3 (2CH), 70.7 (2CH), 51.5 ($2CH_3$), 50.0 (2CH), 47.3 (2CH), 45.1 (2C), 43.3 (2CH), 41.4 (2CH), 37.7 (2CH), 35.4 ($2CH_2$), 35.3 ($2CH_2$), 34.6 (2CH), 34.3 (2C), 31.3 ($2CH_2$), 30.8 ($2CH_2$), 30.7 ($2CH_2$), 28.9 (2CH), 27.5 ($2CH_2$), 27.1 ($2CH_2$), 25.5 ($2CH_2$), 22.8 ($2CH_2$), 22.7 ($2CH_3$), 21.7 ($2CH_3$), 21.5 ($2CH_3$), 17.5 ($2CH_3$), 12.2 ($2CH_3$) ppm; IR ($CHCl_3$): $\bar{\nu} = 3528$, 3390, 1726, 1670, 1508, 1255, 1021, 682 cm^{-1}; MS (70 eV): $m/z = 1087$ ($M^+ + Na$), 799, 413.

N,N′-Di(3α-amino-5β-cholane-7α,12α24-triol)3,3′-oxamide (**9**, $C_{50}H_{84}N_2O_8$)
To a solution of 1.80 g **8** (1.69 mmol) in 100 cm^3 anhydrous *THF* 240 mg $LiAlH_4$ (6.32 mmol) were added portionwise with vigorous stirring under Ar. The progress of the reaction was controlled with TLC. When all of the substrate disappeared (about 0.5 h), the excess of reducing agent was carefully quenched with a few drops H_2O, the precipitate was filtered off, and the solvent was evaporated *in vacuo*. The residue was dissolved in 100 cm^3 methanol, 1.5 cm^3 H_2O and 220 mg NaOH (5.5 mmol) were added, and the reaction mixture was maintained at about 40°C for one week (with TLC control). After this time the solvent was removed and the crude product was subjected to column chromatography to afford 1.21 g (85%) **9** (elution with $CHCl_3$/methanol 95/5). Colorless crystals, mp 303–306°C (methanol); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.63$ (d, $J = 8.71$ Hz, 2N-H), 3.83 (m, 2 12β-H), 3.68 (m, 2 7β-H), 3.46 (m, 2 3β-H), 2.28 (m, 2 C$\underline{H_2}$OH), 0.86 (d, $J = 5.31$ Hz, 2 21-CH_3), 0.79 (s, 2 19-CH_3), 0.55 (s, 2 18-CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 160.1$ (2C), 73.4 (2CH), 68.4 (2CH), 63.1 ($2CH_2$), 50.9 (2CH), 47.7 (2CH), 46.9 (2C), 42.8 (2CH), 42.4 (2CH), 40.3 (2CH), 36.44 (2CH), 36.35 ($4CH_2$), 35.3 (2C), 35.0 ($2CH_2$), 32.6 ($2CH_2$), 29.8 ($2CH_2$), 28.8 ($2CH_2$), 28.2 ($2CH_2$), 27.4 ($2CH_2$), 27.2 (2CH), 23.6 ($2CH_2$), 22.7 ($2CH_3$), 17.6 ($2CH_3$), 12.6 ($2CH_3$) ppm; IR ($CHCl_3$): $\bar{\nu} = 3386$, 1681, 1514, 1084, 1036, 979, 916 cm^{-1}; MS (70 eV): $m/z = 863$ ($M^+ + Na$), 413, 301.

23-Iodo-24-nor-5β-cholane-3α,7α,12α-triol 3,7,12-triacetate (**11**, $C_{29}H_{45}IO_6$)
Compound **10** (4 g, 7.49 mmol) was dissolved in 100 cm^3 CCl_4, 1.9 g red HgO (8.76 mmol) were added, and the mixture was heated at reflux for 2 h. A solution of 1.91 g I_2 (7.52 mmol) in 50 cm^3 CCl_4 was then added portionwise and heating was continued for another 12 h. The cooled reaction mixture was concentrated *in vacuo* and subjected to column chromatography to afford 3 g (65%) iodide **11** (elution with benzene/ethyl acetate 94/6). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.08$ (m, 12β-H), 4.91 (m, 7β-H), 4.56 (m, 3β-H), 3.29 (m, 23-CH), 3.06 (m, 23-CH), 2.12 (s, 12α-CH_3CO), 2.07 (s, 7α-CH_3CO), 2.03 (s, 3α-CH_3CO), 0.91 (s, 19-CH_3), 0.81 (d, $J = 5.94$ Hz, 21-CH_3), 0.74 (s, 18-CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.42$ (C), 170.37 (C), 170.26 (C), 75.3 (CH), 74.0 (CH), 70.6 (CH), 47.2 (CH), 45.1 (C), 43.3 (CH), 40.8 (CH), 40.0 (CH_2), 37.7 (CH), 36.4 (CH), 34.6 (CH_2), 34.5 (CH_2), 34.3 (C), 31.2 (CH_2), 28.8 (CH), 27.1 (CH_2), 26.8 (CH_2), 25.5 (CH_2), 22.7 (CH_2), 22.5 (CH_3), 21.5 (CH_3), 21.43 (CH_3), 21.38 (CH_3), 17.0 (CH_3), 12.2 (CH_3), 4.6 (CH_2) ppm; IR ($CHCl_3$): $\bar{\nu} = 1724$, 1254, 1025 cm^{-1}; MS (70 eV): $m/z = 639$ ($M^+ + Na$), 634, 497, 437.

23-Azido-24-nor-5β-cholane-3α,7α,12α-triol 3,7,12-triacetate (**12**, $C_{29}H_{45}N_3O_6$)
The reaction was carried out according to the procedure described for **6**; 2.56 g azide **12** were obtained from iodide **11** in 99% yield. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.11$ (m, 12β-H), 4.91 (m, 7β-H), 4.59 (m, 3β-H), 3.33 (m, 23-CH), 3.26 (m, 23-CH), 2.14 (s, 12α-CH_3CO), 2.09 (s, 7α-CH_3CO), 2.05 (s, 3α-CH_3CO), 0.93 (s, 19-CH_3), 0.84 (d, $J = 6.33$ Hz, 21-CH_3), 0.75 (s, 18-CH_3) ppm.

23-Amino-24-nor-5β-cholane-3α,7α,12α-triol 3,7,12-triacetate (**13**, $C_{29}H_{47}NO_6$)
Amine **13** (1.52 g, 63% yield) was obtained by reduction of **12** according to the procedure described for **7**. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.10$ (m, 12β-H), 4.91 (m, 7β-H), 4.57 (m, 3β-H), 2.72

(m, 23-CH_2), 2.14 (s, 12α-CH_3CO), 2.08 (s, 7α-CH_3CO), 2.04 (s, 3α-CH_3CO), 0.91 (s, 19-CH_3), 0.81 (d, $J = 5.94$ Hz, 21-CH_3), 0.73 (s, 18-CH_3) ppm; IR ($CHCl_3$): $\bar{\nu} = 1724$, 1254, 1025, 668 cm^{-1}.

N,N′-Di(23-amino-24-nor-5β-cholane-3α,7α,12α-triol 3,7,12-triacetate)23,23′-oxamide (**14**, $C_{60}H_{92}N_2O_{14}$)

The reaction was carried out according to the procedure described for **8**. Thereby 1.12 g of dimer **14** were obtained from amine **13** (82%). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.41$ (d, $J = 5.95$ Hz, 2N–H), 5.09 (m, 2 12β-H), 4.92 (m, 2 7β-H), 4.58 (m, 2 3β-H), 3.32 (m, 2 23-CH), 3.20 (m, 2 23-CH), 2.14 (s, 2 12α-CH_3CO), 2.10 (s, 2 7α-CH_3CO), 2.05 (s, 2 3α-CH_3CO), 0.92 (s, 2 19-CH_3), 0.87 (d, $J = 5.95$ Hz, 2 21-CH_3), 0.73 (s, 2 18-CH_3) ppm; IR ($CHCl_3$): $\bar{\nu} = 3399$, 1724, 1675, 1514, 1254, 1024 cm^{-1}.

N,N′-Di(23-amino-24-nor-5β-cholane-3α,7α,12α-triol)23,23′-oxamide (**15**, $C_{48}H_{80}N_2O_8$)

Dimer **14** (1.1 g, 1.03 mmol) was dissolved in 50 cm^3 methanol, 300 mg NaOH (7.5 mmol) and 1 cm^3 H_2O were added to the flask, and the reaction mixture was heated at 40°C for 4 days. Then the solvent was removed *in vacuo* and the crude product was subjected to column chromatography to afford 650 mg (77%) **15** (elution with $CHCl_3$/methanol 8/2). Colorless crystals, mp 200–203°C (methanol/ethyl acetate); ^{1}H NMR (200 MHz, CD_3OD): $\delta = 8.53$ (d, $J = 5.95$ Hz, 2N–H), 3.95 (m, 2 12β-H), 3.78 (m, 2 7β-H), 3.60 (m, 2 3β-H), 2.27 (m, 2 23-CH_2), 1.06 (d, $J = 6.28$ Hz, 2 21-CH_3), 0.91 (s, 2 19-CH_3), 0.71 (s, 2 18-CH_3) ppm; ^{13}C NMR (50 MHz, CD_3OD): $\delta = 161.3$ (2C), 73.6 (2CH), 72.5 (2CH), 68.6 (2CH), 47.8 (2CH), 47.1 (2C), 42.8 (2CH), 42.6 (2CH), 40.6 (2CH), 40.1 ($2CH_2$), 37.8 ($2CH_2$), 36.1 ($2CH_2$), 36.0 ($2CH_2$), 35.5 ($2CH_2$), 35.1 (2C), 34.7 (2CH), 30.8 ($2CH_2$), 29.2 ($2CH_2$), 28.4 ($2CH_2$), 27.5 (2CH), 23.9 ($2CH_2$), 22.8 ($2CH_3$), 17.6 ($2CH_3$), 12.6 ($2CH_3$) ppm; IR (KBr): $\bar{\nu} = 1667$, 1516, 1246, 1079, 1046, 612.5 cm^{-1}; MS (70 eV): $m/z = 835$ ($M^+ + Na$), 830, 691, 434, 301.

N,N′-Di(3,7,12-triacetylcholyl)hydrazine (**16**, $C_{60}H_{92}N_2O_{14}$)

To a solution of 520 mg **10** (0.97 mmol) in 20 cm^3 anhydrous benzene 1 cm^3 oxalyl chloride (11.6 mmol) was added dropwise with vigorous stirring and the reaction mixture was heated to 60°C for 15 min. Then the solvent and excess of oxalyl chloride were removed *in vacuo*, the residue was dissolved in anhydrous and ethanol-free $CHCl_3$, and 1 cm^3 hydrazine (1 mmol, 1 *M* solution in *THF*, Aldrich) was added slowly with stirring to the flask. When the addition was completed the reaction mixture was stirred for additional 15 min, poured into acidified H_2O, and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and the solvent was removed. Crude product was subjected to column chromatography (elution with benzene/ethyl acetate 3/1) to afford 325 mg (63%) pure dimer **16**. Colorless crystals, mp 153–156°C (*n*-hexane/CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.64$ (s, 2N–H), 5.07 (m, 2 12β-H), 4.98 (m, 2 7β-H), 4.56 (m, 2 3β-H), 2.12 (s, 2 12α-CH_3CO), 2.08 (s, 2 7α-CH_3CO), 2.04 (s, 2 3α-CH_3CO), 0.90 (s, 2 19-CH_3), 0.80 (d, $J = 5.56$ Hz, 2 21-CH_3), 0.71 (s, 2 18-CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.5$ (2C), 170.4 (2C), 170.3 (2C), 170.2 (2C), 75.3 (2CH), 74.0 (CH), 70.6 (2CH), 47.4 (2CH), 43.3 (2CH), 45.0 (2C), 40.9 (2CH), 37.7 (2CH), 34.7 (2CH), 34.64 ($2CH_2$), 34.57 ($2CH_2$), 34.3 (2C), 31.2 ($2CH_2$), 31.1 ($2CH_2$), 30.9 ($2CH_2$), 28.8 (2CH), 27.2 ($2CH_2$), 26.8 ($2CH_2$), 25.5 ($2CH_2$), 22.7 ($2CH_2$), 22.5 ($2CH_3$), 21.6 ($2CH_3$), 21.43 ($2CH_3$), 21.39 ($2CH_3$), 17.5 ($2CH_3$), 12.2 ($2CH_3$) ppm; IR ($CHCl_3$): $\bar{\nu} = 3411$, 1724, 1634, 1254, 1025 cm^{-1}; MS (70 eV): $m/z = 1087$ ($M^+ + Na$).

N,N′-Dicholylhydrazine (**17**, $C_{48}H_{80}N_2O_8$)

The reaction was carried out as described for **15** and thereby 180 mg **17** were obtained from **16** in 84% yield. Colorless crystals, mp > 350°C ($CHCl_3$/methanol); ^{1}H NMR (200 MHz, CD_3OD): $\delta = 3.94$ (m, 2 12β-H), 3.80 (m, 2 7β-H), 3.62 (m, 2 3β-H), 1.01 (d, $J = 5.91$ Hz, 2 21-CH_3), 0.89 (s, 2 19-CH_3), 0.69 (s, 2 18-CH_3) ppm; a N–H singlet is observed at 9.63 ppm in *DMSO*-d_6 as the solvent; ^{13}C NMR (50 MHz, CD_3OD): $\delta = 171.7$ (2C), 71.2 (2CH), 70.5 (2CH), 66.3 (2CH), 46.3 (2CH), 45.8 (2C), 41.6 (2CH), 41.5 (2CH), 40.2 ($2CH_2$), 39.4 (2CH), 39.3 ($2CH_2$), 35.4 ($2CH_2$), 35.2 (2CH), 35.0 ($2CH_2$),

34.5 (2C), 30.45 ($2CH_2$), 30.39 ($2CH_2$), 28.6 ($2CH_2$), 27.4 ($2CH_2$), 26.3 (2CH), 23.0 ($2CH_2$), 22.7 ($2CH_3$), 17.2 ($2CH_3$), 12.5 ($2CH_3$) ppm; IR (KBr): $\bar{\nu} = 3398$, 1630.5, 1075, 607 cm^{-1}; MS (70 eV): $m/z = 835$ ($M^+ + Na$).

Acknowledgements

The authors gratefully acknowledge financial support from the State Committee for Scientific Research, Poland (Grant No. 3 T09A 01427). We also thank professor *J.W. Morzycki* for discussions.

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