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Synthesis of cholic acid amino analogues by oxime reduction with $TiCl_3$–$NaBH_3CN$

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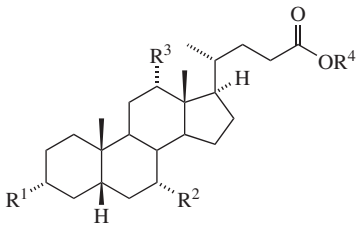
Amino analogues of cholic acid have been synthesized by reduction of the corresponding oximes with titanium(III) chloride in the presence of sodium cyanoborohydride.

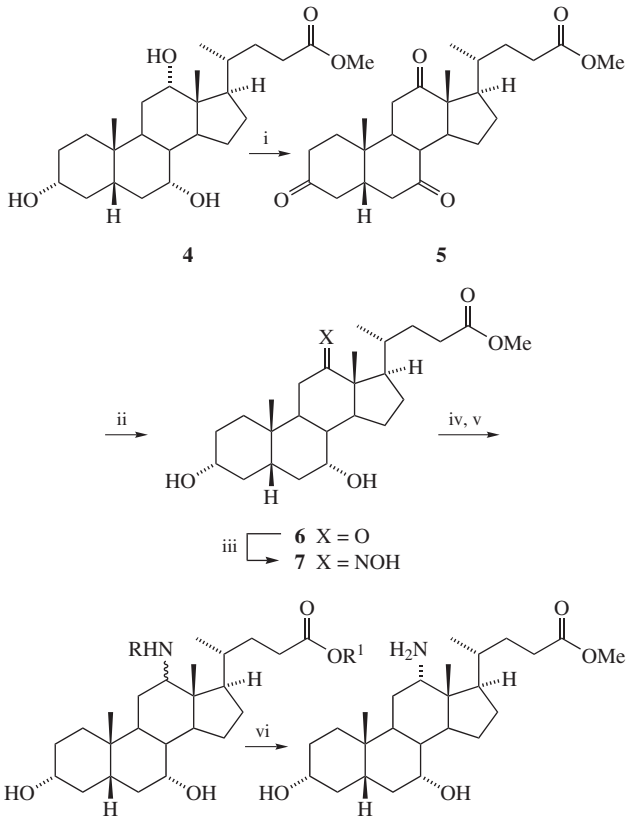
Cholic acid **1** has a special place among steroid molecules due to its rigid tetracyclic hydrocarbon framework and unilateral orientation of the three hydroxy groups. This spatial distribution of hydroxy groups endows the molecule with unique amphiphilic properties. Synthetic receptors of organic molecules[1,2] and ions,[3–5] new chiral substrates for efficient separation of enantiomers,[6] as well as various conjugates with biologically active compounds[7,8] and anti-tumour agents[9,10] were created based on cholic acid. Owing to amphiphilicity, bile acid derivatives can mediate specific transport of ions,[11,12] covalently bound ATP molecules,[13] peptides[14] and oligonucleotides[15] through biological membranes.

Charged derivatives of cholic acid and other bile acids are of interest as delivery systems for nucleic acids in gene therapy[16] and as antimicrobial agents.[17–20] The design of charged amphiphiles based on cholic acid is primarily directed on incorporation of cationic or anionic substituents at the functional groups of a molecule. In order to enhance the amphiphilicity of cholic acid, its triamino analogues (aminocholates), in which hydroxy groups are replaced by amino groups, have been obtained.[21–23] Aminocholates were used as substrates to create combinatorial libraries or steroid antibiotics.[24,25] Furthermore, these compounds enhanced the efficiency of nucleic acid delivery into eukaryotic cells.[26]



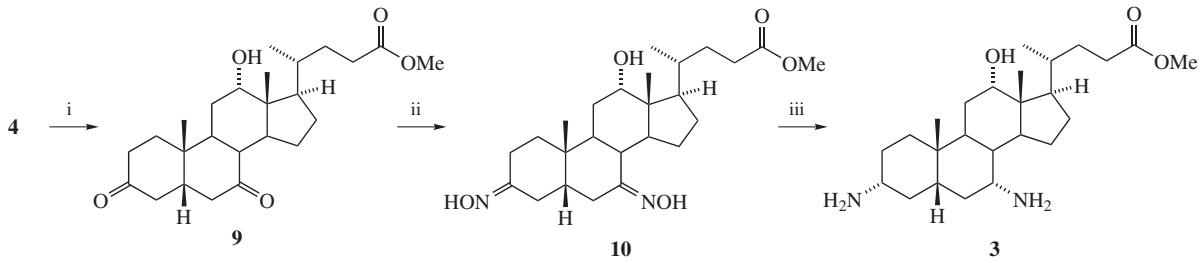
1 $R^1 = R^2 = R^3 = OH$, $R^4 = H$
2 $R^1 = R^2 = OH$, $R^3 = NH_2$, $R^4 = Me$
3 $R^1 = R^2 = NH_2$, $R^3 = OH$, $R^4 = Me$

Preservation of the natural α-stereo configuration in the cholic acid molecule on replacement of hydroxy groups by amino groups can be reached by sequential double inversion of configuration at each chiral centre, which implies an expensive synthesis involving multiple stages.[21] In an alternative approach, oximes were reduced with sodium borohydride in the presence of titanium(IV) chloride,[23] sodium in an alcohol[24] or by hydrogenolysis on platinum(IV) oxide.[22] Reduction with sodium borohydride in the presence of titanium(IV) chloride[23] resulted in a triamino analogue of cholic acid in 33% yield, but this combination of reagents proved to be unsuccessful in a synthesis of a forskolin amino analogue.[27] Reduction with sodium metal preferentially gives the 7β-isomer; furthermore, it cannot be used if the starting molecule bears sodium-sensitive groups.[24] Platinum oxide-catalyzed hydrogenolysis, although being effective, takes a long time.[22] Therefore, it would be interesting to find more convenient approaches to incorporate amino groups into steroid polycyclic system using accessible



4 **5**
6 X = O
7 X = NOH
8a α-isomer R = Boc, R^1 = Me
8b β-isomer R = H, R^1 = Me
8c α-isomer R = Boc, R^1 = H
2

Scheme 1 *Reagents and conditions*: i, IBX, DMSO, 25 °C, 94 h; ii, $NaBH_4$, MeOH, 0 °C, 20 min; iii, 50% aq. NH_2OH, MeOH, reflux, 17 h; iv, $NaBH_3CN$, $TiCl_3$, $AcONH_4$, MeOH, 25 °C, 24 h; v, Boc_2O, Et_3N, 25 °C, 5 h; vi, 4 N HCl, dioxane, 24 °C, 30 min.



Scheme 2 *Reagents and conditions*: i, IBX, DMSO, 24 °C, 20 h; ii, 50% aq. NH_2OH, MeOH, 24 °C, 24 h; iii, $NaBH_3CN$, $TiCl_3$, $AcONH_4$, MeOH, 24 °C, 4 h.

inexpensive reducing agents. Here, we have accessed mono- and diamino derivatives of cholic acid **2** and **3** (Schemes 1 and 2), involving reduction of methyl cholate oximes with titanium(III) chloride–sodium cyanoborohydride system at the key stage.

The starting methyl cholate **4** was obtained in 99% yield by H_2SO_4-assisted esterification of cholic acid **1** with methanol (Scheme 1). Oxidation of ester **4** with 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide[28] (IBX) in DMSO afforded 3,7,12-trioxo derivative **5** in 84% yield. To provide the reaction completeness, a 1.5-fold excess of IBX per hydroxy group was used. The ^{13}C NMR spectrum of compound **5** contained signals of carbon atoms with chemical shifts δ 208.80, 209.15 and 213.03 ppm that are typical of carbonyl carbons.

Keto diol **6** can be synthesized in ~50% yield using a reactions sequence based on regioselective acetylation of hydroxy groups at C-3 and C-7 atoms of methyl cholate with acetic anhydride, followed by oxidation of the remaining OH group at C-12 and removal of acetyl protection.[29] Enzyme-assisted synthesis allows 12-oxocholic acid to be obtained in 85% yield.[30] Chenodeoxycholic acid was synthesized by regio- and stereoselective reduction of 3,7,12-trioxocholate (dehydrocholic acid) with sodium borohydride at 0 °C to give 3α,7α-dihydroxy-12-oxocholane acid in 62% yield.[31] In our synthesis, reduction of compound **5** with an equimolar amount of sodium borohydride at 0 °C preferentially led to methyl 3α,7α-dihydroxy-12-oxocholate **6** in 76% yield.† Minor amounts of methyl cholate **4** and other regio- and stereoisomers of compound **6** were formed as side products; we did not study their structures because of the small amounts of these compounds. The regio- and stereoselectivity of reduction were confirmed by ^1H and ^{13}C NMR spectra.† The subsequent reaction of compound **6** with hydroxylamine in methanol under reflux gave oxime **7** in 91% yield after chromatographic purification.

Reduction of the oxime group into amino one was the key reaction in the synthesis. We used titanium(III) chloride in the presence of sodium cyanoborohydride to reduce oxime **7**; this combination was successfully employed before in stereoselective syntheses of compounds with complex structures.[27,32] To assess the preparative value of this method, we compared its results with catalytic hydrogenation of oxime **7** in the presence of platinum(IV).[22] In order to improve the separation efficiency of the reduction products, the amino group formed was blocked *in situ* by *tert*-butoxycarbonyl (Boc) protection. Reduction with $TiCl_3$–$NaBH_3CN$ followed by incorporation of a Boc group furnished compound **8a** in 51% yield.‡ The structure of compound **8a** was characterised by elemental analysis and mass spectrometry, as well as ^1H and ^{13}C NMR spectroscopy.‡

Using column chromatography, compounds **8b** and **8c** were also isolated from the reaction mixture in 5% and 3% yields, respectively; their structures were determined by NMR spectroscopy and mass spectrometry. β-Isomer **8b** did not react with Boc_2O, apparently due to a spatial inaccessibility of its amino group. Furthermore, the methyl ester underwent partial hydrolysis to give acid **8c**.

Hydrogenolysis of oxime **7** on platinum(IV) oxide was faster (4.5 h); compound **8a** was isolated in 59% yield after introduction of Boc protection. Compounds **8b** and **8c** were also obtained in 5% and 13% yields, respectively. Thus, the two methods for the reduction of oxime **7** are comparable both in yields and stereoselectivity.

At the final stage, the amino group in compound **8a** was deblocked by treatment with 4 N HCl in dioxane. Amine **2** was obtained in 81% yield; its structure was confirmed by ^1H, ^{13}C NMR and mass spectra.§

Analogously, the 3,7-diamino derivative **3** was obtained (Scheme 2) *via* the step of preparation of 3,7-dioxo derivative **9**. It is known that the susceptibility of hydroxy groups in the cholic acid molecule towards oxidation decreases in the rank C-7 > C-12 > C-3. The hydroxy group at C-7 readily undergoes oxidation with CrO_3 in acetic acid[33] or with *N*-bromosuccinimide.[34] The use of excess oxidants results in the formation of the corresponding 3,7,12-trioxo derivatives.[34,35] Regioselective

† *Synthesis of methyl 3α,7α-dihydroxy-12-oxo-5β-cholan-24-oate* **6**. $NaBH_4$ (0.044 g, 1.15 mmol) was added to a cooled to 0 °C solution of compound **5** (0.48 g, 1.15 mmol) in methanol (20 ml) and stirred at 0 °C for 30 min. The reaction was quenched with acetone (1 ml) and warmed to 25 °C, water (0.5 ml) was added, and after 20 min the solvents were removed under diminished pressure. Flash chromatography on silica gel ($CHCl_3$–MeOH, 60:1) gave compound **6** (0.366 g, 76%), mp 154–156 °C (lit.,[37] 154.5–161.5 °C), $[\alpha]_D^{20}$ +62 (*c* 1.0, $CHCl_3$). ^1H NMR (Bruker DPX-300, 300.13 MHz, $CDCl_3$, TMS) δ: 0.79 (d, 3H, 21-Me, *J* 6.6 Hz), 0.93 (s, 3H, 18-Me), 0.96 (s, 3H, 19-Me), 0.87–2.45 (m, 24H, steroid protons), 3.31–3.44 (m, 1H, 3β-H), 3.59 (s, 3H, OMe), 3.85–3.90 (m, 1H, 7β-H). ^{13}C NMR (75 MHz) δ: 11.70, 18.68, 22.28, 23.95, 27.63, 30.65, 31.40, 35.10, 35.49, 35.74, 35.94, 37.02, 37.81, 39.48, 39.84, 41.26, 46.50, 51.50, 53.34, 57.20, 68.16, 71.82, 174.81, 213.01. MS (Bruker Ultraflex, MALDI-TOF), *m/z*: 420.1 $[M]^+$.

‡ *Synthesis of methyl 12α-(*tert*-butyloxycarbonyl)amino-3α,7α-dihydroxy-5β-cholan-24-oate* **8a**. A solution of compound **7** (137.7 mg, 0.316 mmol), ammonium acetate (280 mg, 3.63 mmol) and sodium cyanoborohydride (61.4 mg, 0.977 mmol) in methanol (5 ml) was cooled to 4 °C and titanium(III) chloride (10 wt% solution in 20–30 wt% aqueous HCl) was dropped for 1 h. After stirring at 25 °C for 24 h the reaction was quenched by addition of acetone (1 ml) and water (0.5 ml). The solvents were evaporated and the residue was dissolved in ethanol and filtered through Celite® 545 pad. After evaporating of ethanol, the residue was dissolved in methanol (5 ml), and then triethylamine (0.482 ml, 3.46 mmol) and Boc_2O were added. The reaction mixture was stirred at 23 °C for 5 h, all solvents were evaporated, and the residue was diluted with dichloromethane (10 ml), washed with 1% aqueous HCl solution. Organic layer was dried with Na_2SO_4, filtered and evaporated. Purification by column chromatography on silica gel [$CHCl_3$–MeOH (45:1) → $CHCl_3$–MeOH–20% aq. NH_3 (10:1:0.01)] gave compound **8a** (83.3 mg, 51%), mp 104–106 °C, $[\alpha]_D^{20}$ +45 (*c* 1.0, $CHCl_3$). ^1H NMR, δ: 0.68 (s, 3H, 18-Me), 0.79 (s, 3H, 19-Me), 0.82 (d, 3H, 21-Me, *J* 6.3 Hz), 0.85–2.33 (m, 24H, steroid protons), 1.35 (s, 9H, Bu^t), 3.23–3.35 (m, 1H, 3β-H), 3.57 (s, 3H, OMe), 3.71–3.75 (m, 1H, 7β-H), 3.82–3.88 (m, 1H, 12β-H). ^{13}C NMR, δ: 13.74, 17.56, 22.86, 23.46, 26.79, 27.49, 27.72, 28.65, 30.40, 30.98, 31.27, 34.83, 35.08, 39.51, 39.73, 41.52, 44.21, 44.83, 48.40, 51.69, 53.19, 68.33, 72.11, 79.07, 155.50, 174.93. MS, *m/z*: 544.2 $[M+Na]^+$ (calc. for $C_{30}H_{51}NNaO_6$: 544.4 $[M+Na]^+$). Found (%): C, 66.86; H, 10.12; N, 2.88. Calc. for $C_{30}H_{51}NO_6 \cdot H_2O$ (%): C, 66.76; H, 9.90; N, 2.60.

oxidation of hydroxy groups at C-3 and C-7 can be reached by the use of potassium permanganate in acidic media[36] or in enzyme-assisted synthesis.[30] We obtained compound **9** by oxidation of methyl cholate **4** with a twofold excess of IBX in 55% yield.

The reaction of diketone **9** with hydroxylamine proceeded under milder conditions than the similar reaction of compound **6**. The yield of dioxime **10** was 51% after chromatographic purification. The reduction of compound **10** was carried out under conditions similar to those for reduction of oxime **7**. The structure of the target diamine **3** (45% yield after chromatographic separation)¶ was determined by NMR spectroscopy [^{1}H, ^{13}C{^{1}H}, ^{13}C-DEPT-135, ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HSQC, ^{1}H,^{13}C-HMBC (*J* 8 Hz) and ^{1}H,^{13}C-HMQC-COSY]. One-dimensional and two-dimensional (^{1}H,^{1}H-COSY) proton spectra are not informative since they contain overlapping groups of signals and cannot be used for unambiguous assignment of proton signals. The use of an advanced ^{1}H,^{13}C-HMQC-COSY technique allowed us to observe cross-peaks between ^{13}C and ^{1}H attached to it, as well as between ^{13}C and ^{1}H which have *J*-coupling with directly attached ^{1}H, and thus, to determine all homonuclear correlations which strongly overlapped in a simple COSY experiment. Assignment of ^{1}H, ^{13}C{^{1}H} spectra of compound **3** revealed that the signals at δ 3.10 (tt, *J* 11.6, 3.8 Hz, width 42.0 Hz) and δ 3.50 (m, width 22.0 Hz) match those of the protons at C-3 and C-7 atoms of the cholane framework. The coupling constant *J* 11.6 Hz of the proton signal at C-3 suggests that it occupies an axial position, while the width of the proton signal at C-7 suggests an equatorial position. Thus, the resulting methyl 3α,7α-diamino-12α-hydroxy-5β-cholan-24-oate **3** has the natural configuration.

In conclusion, we have synthesized mono- and diamino analogues of cholic acid using reduction of oximes on treatment with titanium(III) chloride in the presence of sodium cyanoborohydride. This method is not inferior to the catalytic hydrogenation on platinum(IV) oxide.

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§ *Methyl 12α-amino-3α,7α-dihydroxy-5β-cholan-24-oate* **2**: $[\alpha]_D^{20}$ –35 [*c* 1.0, $CHCl_3$–MeOH (1:4)]. ^{1}H NMR, δ: 0.70 (s, 3H, 18-Me), 0.82 (s, 3H, 19-Me), 0.91 (d, 3H, 21-Me, *J* 5.8 Hz), 0.92–1.96 (m, 20H, steroid protons), 2.03–2.38 (m, 4H, steriod protons), 3.30 (br.t, 1H, 12β-H, *J* 3.0 Hz), 3.38 (tt, 1H, 3β-H, *J* 11.4, 4.4 Hz), 3.60 (s, 3H, OMe), 3.72–3.77 (m, 1H, 7β-H). ^{13}C NMR, δ: 13.30, 17.21, 22.19, 23.40, 26.69, 28.01, 30.19, 30.70, 31.30, 34.81, 35.06, 35.24, 35.44, 35.68, 39.61, 39.73, 41.45, 42.00, 45.26, 48.08, 51.79, 55.76, 68.52, 72.08, 174.90. MS, *m*/*z*: 422.029 $[M+H]^+$, 444.015 $[M+Na]^+$. ESI HRMS (Bruker micrOTOF II), m/*z*: 422.3269 (calc. for $C_{25}H_{44}NO_4$: 422.3265 $[M+H]^+$), 444.3091 (calc. for $C_{25}H_{43}NNaO_4$: 444.3084 $[M+Na]^+$).

¶ *Methyl 3α,7α-diamino-12α-hydroxy-5β-cholan-24-oate* **3**: ^{1}H NMR (Bruker Avance-600, 600.13 MHz, CD_3OD) δ: 0.75 (s, 3H, 18-Me), 1.02 (d, 3H, 21-Me, *J* 6.5 Hz), 1.03 (s, 3H, 19-Me), 1.13–1.23 (m, 2H, H_a-1, H_a-15), 1.32–1.41 (m, 2H, H_a-16, H_a-22), 1.41–1.50 (m, 1H, H-20), 1.56–1.62 (m, 1H, H_a-2), 1.63–1.71 (m, 3H, H-5, H_a-11, H_b-11), 1.72–1.93 (m, 7H, H_a-4, H_a-6, H_b-2, H_b-15, H_b-22, H-14, H-17), 1.93–2.04 (m, 4H, H_b-1, H_b-4, H_b-16, H-8), 2.31–2.24 (ddd, 1H, H_a-23, *J* 6.9, 9.3, 15.4 Hz), 2.31–2.37 (m, 2H, H_b-6, H-9), 2.39 (ddd, 1H, H_b-23, *J* 5.3, 9.8, 15.4 Hz), 3.10 (tt, 1H, H-3, *J* 11.8, 3.8 Hz), 3.49–3.52 (m, 1H, H-7), 3.61 (s, 3H, OMe), 3.98 (br.t, 1H, H-12, *J* 3.1 Hz). ^{13}C NMR (150.90 MHz) δ: 12.75 (C-18, +), 17.69 (C-21, +), 22.41 (C-19, +), 23.92 (C-15, –), 26.61 (C-2, –), 28.17 (C-9, +), 28.36 (C-16, –), 28.87 (C-11, –), 31.42 (C-6, –), 31.79 (C-23, –), 32.12 (C-22, –), 41.69 (C-3, +), 34.77 (C-4, +), 35.83 (C-10, –), 35.85 (C-1, –), 36.53 (C-20, +), 37.87 (C-8, +), 41.81 (C-5, +), 42.23 (C-14, +), 47.88 (C-17, +), 48.04 (C-13, –), 51.02 (C-7, +), 52.07 (OMe, +), 52.56 (C-3, +), 73.87 (C-12, +), 176.47 (C-24, +). MS, *m*/*z*: 420.970 $[M]^+$. ESI HRMS (Bruker micrOTOF II), *m*/*z*: 421.3409 (calc. for $C_{25}H_{45}N_2O_3$: 421.3425 $[M+H]^+$), 459.2980 (calc. for $C_{25}H_{44}N_2O_3K$: 459.2984 $[M+K]^+$).

For characteristics of compounds **4**, **5**, **7**, **8b**,**c**, **9** and **10**, see Online Supplementary Materials.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2011.04.007.

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