The "Triamino-analogue" of Methyl Cholate; A Practical, Large-Scale Synthesis

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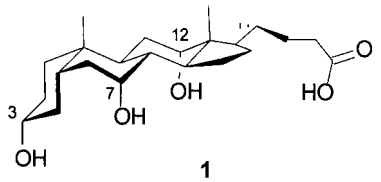
Abstract: The triamino steroids **2** are in demand as facial amphiphiles and starting materials for supramolecular chemistry. **2** (R = Me) is now available from cholic acid **1** in substantial quantities via a new, high-yielding procedure.

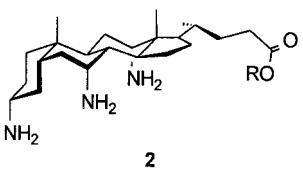
Key words: bile acids, scaffold, supramolecular chemistry, facial amphiphile, oxime reduction

As part of our programme on cholic acid **1** as a building block for supramolecular chemistry,[1] we have recently become interested in the replacement of -OH with -NH_2 at the steroidal 3, 7 and 12 positions. Amino groups can be derivatised efficiently in various ways, most of which give functionality capable of strong and specific non-covalent interactions. Aminocholanoates have been used to synthesize cyclooligomeric hosts,[2] and also monomeric receptors capable of binding inorganic anions,[3] amino acid derivatives[4] and DNA.[5] They also have potential as facial amphiphiles,[6] and as scaffolds for library synthesis in combinatorial chemistry.[4a,7]



1

The "virtues" of aminocholanoates are expressed most fully in compounds **2**, containing the tris-deoxa-tris-aza analogue of the cholic acid nucleus. **2** (R = Me) has been used to prepare the unusually potent electroneutral anionophore **3**,[3] and undoubtedly has many other applications in supramolecular chemistry. However its value to date has been limited by a lengthy and somewhat unwieldy synthesis from **1**, requiring 17 steps and proceeding in ≤1.4% overall yield.[6a] We now report an improved procedure which is shorter, more efficient, and allows multigram production of 2 (R = Me) on a routine basis.



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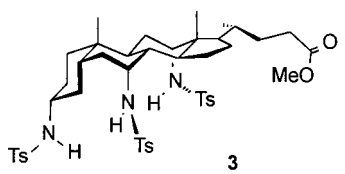
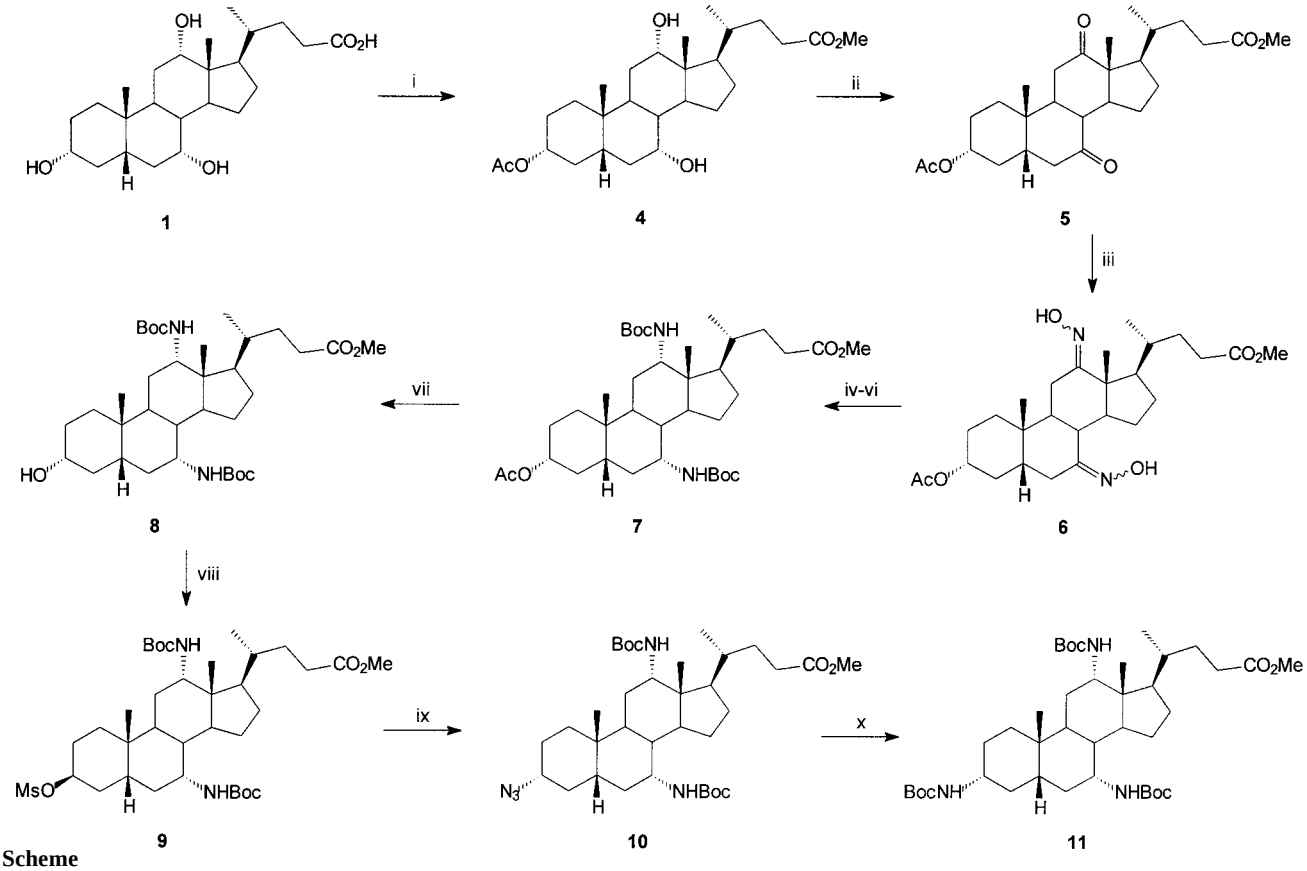


3

The conversion of hydroxyl to amino groups may be achieved by nucleophilic displacement, or by oxidation followed by reductive amination. In our initial synthesis we used the former strategy where possible, to ensure the correct stereochemical outcome and minimise the need for potentially difficult separations of diastereomeric polyamine derivatives. Unfortunately this required that each secondary hydroxyl be given individual attention, resulting in a synthesis which was "safe" but impractical for routine preparation of **2**. In subsequent work, we have developed a reductive amination protocol which is reliable, high-yielding, and shows excellent selectivity for the α-product at both C7 and C12.[8] The application of this method simultaneously to both positions forms the basis for the new preparation described herein.[9]

The synthetic route to tris-carbamate **11**, immediate precursor of **2** (R = Me), is summarised in the Scheme. Acetoxydiol **4** was available in 83% yield through a one-pot esterification and selective 3α-acetylation of **1**, employing MeOAc as source of both methoxy and acetyl groups.[10] Oxidation with potassium chromate gave the acetoxy-dione **5** in 98% yield.[11] Both **4** and **5** could be purified by crystallisation; alternatively the crystallisation of **4** could be omitted without a drop in overall yield. The amino groups on C7 and C12 were introduced by oximation[12] to acetoxydioxime **6** (99% yield) followed by catalytic hydrogenation to give mainly the corresponding bis-hydroxylamine, and treatment with Zn/AcOH to give the diamine.[8,13] Protection with di-*t*-butyl dicarbonate, followed by crystallisation, gave acetoxydicarbamate **7** in 92% yield from **6**.[13] **7** was stereochemically homogeneous by ^{1}H and ^{13}C NMR,[14] and could be prepared in batches of 40 g using normal laboratory equipment.

The acetoxy group on C3 was easily removed with sodium carbonate to yield **8** in quantitative yield. The third amino group was then introduced through double nucleophilic displacement. A Mitsunobu reaction with methanesulfonate as nucleophile, employing a modification of conditions published earlier from our laboratory,[15] gave mesylate **9**.[16] Treatment of **9** with NaN_3 gave azide **10** in 72% yield from **8**.[16] Finally, reduction/*N*-protection with H_2/Pd/$(Boc)_2O$[17] gave tris-carbamate **11** in 85% crystalline yield, 45% overall from cholic acid. Although chromatography was required for the purification of **9** and **10**, the preparation of **11** could be conducted in 8 gram batches without inconvenience. Deprotection of **11** with



Scheme

Reagents and conditions: (i) *p*-TsOH, AcOMe, 23 h, reflux; (ii) K_2CrO_4, AcOH, 48 h, rt; (iii) $H_2NOH{\cdot}HCl$, AcONa, MeOH, 4.5 h, reflux; (iv) H_2, $PtO_2{\cdot}xH_2O$, AcOH, 6 d, rt; (v) Zn, AcOH, 12 h, rt; (vi) $(Boc)_2O$, $NaHCO_3$ aq., THF, 3 d, rt; (vii) Na_2CO_3, MeOH, 12 h, rt; (viii) Ph_3P, Et_3N, $MeSO_3H$, DEAD, THF, 1 d, 45 °C; (ix) NaN_3, DMF, 2 d, 45 °C; (x) H_2, Pd/C (10%), $(Boc)_2O$, EtOH, 24 h, rt.

TFA in dichloromethane occurs cleanly to give **2** (R = Me), as its tris-TFA salt, in apparently quantitative yield.

In conclusion, we have presented a new route to the "triaza-analogue" of the cholic acid nucleus. This new synthesis is high-yielding and can be performed on a multigram scale with normal laboratory equipment. Ready access to **2** will allow us to explore further applications in the design and synthesis of receptors, facial amphiphiles, and scaffolds for combinatorial chemistry. Intermediate **7**, moreover, is exceptionally convenient to prepare, and may itself find uses in these areas.

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(13) The diketone **5** (17.6 g, 38 mmol), sodium acetate (35 g, 430 mmol) and hydroxylamine hydrochloride (9.8 g, 140 mmol) were dissolved in methanol (350 ml) and heated under reflux for 4.5 hours. The reaction mixture was evaporated under reduced pressure, redissolved in DCM, washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was crystallised from chloroform-hexane and filtered to obtain dioxime **6** (18.4 g, 99%) as a white solid.
A mixture of **6** (37.6 g, 70.4 mmol), obtained as above, and platinum oxide hydrate (4.05 g) in glacial AcOH (150 ml) was stirred under H_2 atmosphere for 6 days. The reaction mixture was filtered, washing with glacial acetic acid. The filtrates were concentrated under reduced pressure to *ca*. 200 ml. Zinc powder (75 g) was added. The resulting mixture was stirred overnight at r.t., filtered (washing with glacial AcOH), evaporated under reduced pressure, then redissolved in THF (560 ml) and sat. aq. $NaHCO_3$ (280 ml). Di-*t*-butyl dicarbonate (40 g, 0.18 mol) was added, and the solution stirred for 3 days. The mixture was evaporated under reduced pressure, redissolved in DCM, washed with dilute aq. HCl, dried ($MgSO_4$) and evaporated under reduced pressure. The white foamy crude product crystallised from DCM-hexane to give **7** (46.8 g, 92%) as a white solid.
Selected data for **7**: ^{1}H NMR [400 MHz, $CDCl_3$] δ 0.81 (s, 3H, 18-Me), 0.92 (d, 3H, *J* 6.0, 21-Me), 0.95 (s, 3H, 19-Me), 1.46 (s, 18H, 2 x CMe_3), 2.04 (s, 3H, CH_3COO), 3.70 (broad s, 4H, CO_2CH_3/7β-H), 3.97 (broad m, 1H, 12β-*H*), 4.58 (broad m, 1H, 3β-*H*), 4.94 (broad s, 1H, 7α-NH), 5.12 (broad s, 1H, 12α-NH); ^{13}C NMR [$CDCl_3$] δ 13.5 (C-18), 17.5 (C-21), 21.3 (CH_3COO), 22.8 (C-19), 22.9 , 26.7, 27.1, 27.8, 28.5 (2 x $C(CH_3)_3$), 30.5, 31.8, 32.2, 34.8, 34.9, 35.8, 37.1, 41.4, 44.3, 44.7, 47.2 (C-7), 49.5, 52.3 (CO_2CH_3), 53.3 (12-C), 74.4 (3-C), 155.0 (NCO), 155.5 (NCO), 170.1 ($OCOCH_3$), 174.7 (CO_2CH_3); ν_{max} (Nujol, cm^{-1}) 3386 (NH), 3370 (NH), 1709 (CO), 1246, 1167. Anal. Found: C, 67.19; H, 9.43; N 3.95. $C_{37}H_{62}N_2O_8$ requires C, 67.04; H, 9.43; N 4.23%.
(14) Previous work has shown that the stereoisomers of *N*-Boc aminocholanoate derivatives can be distinguished through their NC*H* chemical shifts and coupling patterns. The configurations at C7 and C12 (and also C3) were further confirmed through the identity of **11**, as prepared in this work, with that synthesised using the earlier procedure.[6a]
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(16) To a solution of compound **8** (4.06 g, 6.54 mmol) and triphenyl phosphine (5.7 g, 21.7 mmol) in dry THF (40 ml) at 0 °C was added triethylamine (1.9 ml, 13 mmol) and methanesulfonic acid (0.90 ml, 13 mmol). The mixture was warmed to 45 °C, and DEAD (3.1 ml, 20 mmol) was added dropwise with stirring. Stirring was maintained for 24 hours, after which the solvent was removed under reduced pressure and the residue partially purified by flash chromatography (hexane-EtOAc, 3:1) to give compound **9** contaminated with DEAD residues. This material was redissolved in DMF (32 ml), sodium azide (2.76 g, 42 mmol) was added with stirring, and stirring was continued for 48 hours at *ca*. 45 °C. Water was added and the resulting mixture extracted with EtOAc. The extract was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography (hexane-EtOAc, 4:1) and crystallisation from DCM-hexane to give **10** as a white powder (3.0 g, 72%).
Selected data for **10**: ^{1}H NMR [400 MHz, $CDCl_3$] δ 0.80 (s, 3H, 18-Me), 0.93 (d, 3H, *J* 5.5, 21-Me), 0.95 (s, 3H, 19-Me), 1.42 (s, 9H, CMe_3), 1.43 (s, 9H, CMe_3), 3.26 (broad m, 1H, 3β-*H*), 3.65 (broad s, 1H, 7β-H), 3.73 (s, 3H, CO_2CH_3), 3.99 (broad m, 1H, 12β-*H*), 5.24 (broad s, 1H, 7α-NH), 5.43 (broad s, 1H, 12α-NH); ^{13}C NMR [$CDCl_3$] δ 13.7 (C-18), 17.4 (C-21), 22.96, 23.02 (C-19), 26.9, 27.0, 27.6, 28.51 ($C(CH_3)_3$), 28.53 ($C(CH_3)_3$), 28.9, 30.7, 31.7, 31.8, 34.8, 35.2, 35.4, 35.5, 37.0, 41.8, 44.6, 44.7, 47.2 (C-7), 49.2, 52.1 (CO_2CH_3), 53.2 (C-12), 61.7 (C-3), 78.9 ($C(CH_3)_3$), 79.0 ($C(CH_3)_3$), 155.5 (2 x NCO), 174.9 (CO_2CH_3).
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