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A Trifunctional Steroid-Based Scaffold for Combinatorial Chemistry

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Abstract: The steroid **3**, with three independently-addressable, rigidly-positioned functional groups, has been synthesized in an efficient, multi-gram sequence from inexpensive cholic acid **1**. Compound **3** should prove valuable as a starting point for combinatorial libraries with preorganised, co-directed arrays of substituents. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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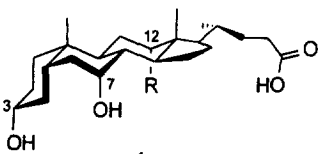
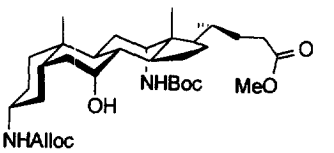
Combinatorial chemistry, in conjunction with solid phase synthesis, is proving a powerful tool for the discovery of biologically active molecules,[1] receptors[2] and catalysts.[2b] Although there are many transformations which have now been effected on the solid phase,[3] the simple derivatisations (e.g. amine acylations) which dominated early work are still the most convenient to perform. A valuable contribution can therefore be made by "scaffolds" with independently-addressable functional groups in well-defined relative positions.[4] Such molecules can extend the structural diversity provided by straightforward derivatisations at the cost of relatively little experimental effort. As noted by several groups,[4a-e] the steroid nucleus has special attractions as a starting point for scaffold design and synthesis. It is rigid, readily accessible, versatile in terms of substitution patterns, and has been intensively studied by synthetic chemists over many years. The bile acids, such as cholic acid **1** or deoxycholic acid **2**, are especially interesting. Their co-directed



1 R = OH
2 R = H



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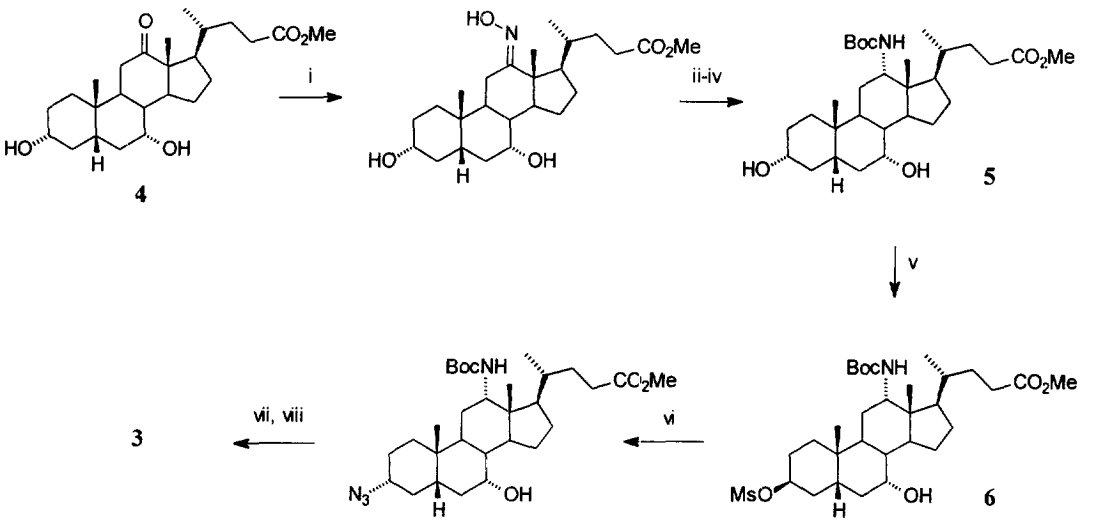
functionality suggests the presentation of arrays of structural units to protein surfaces, binding sites or substrates (in case of receptors/catalysts), while the side-chain provides a natural point of attachment to the solid phase.

The exploitation of bile acids as scaffolds requires the differentiation of their secondary hydroxyl groups, preferably by replacement or elaboration to give more reactive units. Previous efforts have generally employed **2** as a starting point, giving bis-functionalised library precursors.[4a-c,5] We now describe a practical synthesis of the differentially protected diamino alcohol **3**. With three centres for elaboration, two of which are masked amino groups, this molecule should serve as a convenient source of "preorganised diversity". The spacing of the functional groups permits cooperative action on a central substrate,[6] suggesting particular value for the discovery of receptors and catalysts.

Our synthesis of **3** is summarised in the Scheme. The starting ketodiol **4**[7] is available from **1** routinely in 50-60% yield (4 steps). Oxime formation was followed by a 2-step reduction, firstly with H_2/PtO_2 to give mainly the corresponding hydroxylamine, and then with Zn/AcOH to the amine. Reaction with di-*t*-butyl dicarbonate then gave **5**, in 80% overall yield from **4**. The assignment of C12 stereochemistry in **5** (epimeric ratio >24:1) was made on the basis of NMR comparisons with earlier work,[4e] and confirmed by X-ray crystallography (*vide infra*). The oxime reduction could also be performed with $NaBH_3CN$/MeOH, followed again by Zn/AcOH, although this procedure gave a somewhat lower overall yield. Treatment of **5** with Ph_3P/DEAD/$MeSO_3H$, employing a modification[8] of a procedure published earlier from one of our laboratories,[9] gave β-mesylate **6**. Displacement of the mesylate with azide, reduction and N-protection as allyloxycarbonyl gave **3** in 61% overall yield from **5**. The yield from cholic acid **1** through to **3** is around 27%, for a process which is operable on a multi-gram scale using ordinary laboratory equipment.



Scheme. *Reagents and conditions*: i, $H_2NOH.HCl$, NaOAc, MeOH, reflux, 6 h; ii, H_2, PtO_2 (~1 mol%), AcOH, 7 d; iii, Zn, AcOH, 3 h; iv, $(Boc)_2O$, THF, aq. KOH; v, Ph_3P, DEAD, $MeSO_3H$, THF-toluene (2:7), 40 °C; vi, NaN_3, THF-DMPU (1:3), 45 °C, 24 h; vii, H_2, Pd/C, EtOAc-MeOH (1:2), 2 h; viii, allyl chloroformate, *i*-Pr_2NEt, CH_2Cl_2, $NaHCO_3$ aq.

Acetylation of the hydroxyl group in **3** with Ac_2O/pyridine gave the acetoxy-bis-carbamate **7**.[10] Crystals of **7** from hexane-CH_2Cl_2 proved suitable for X-ray crystallography, allowing determination of the structure shown in the Figure.[11] The configurations at C3 and (especially) C12 are thus confirmed, as is the nearly parallel, co-directed orientation of the three substituents.

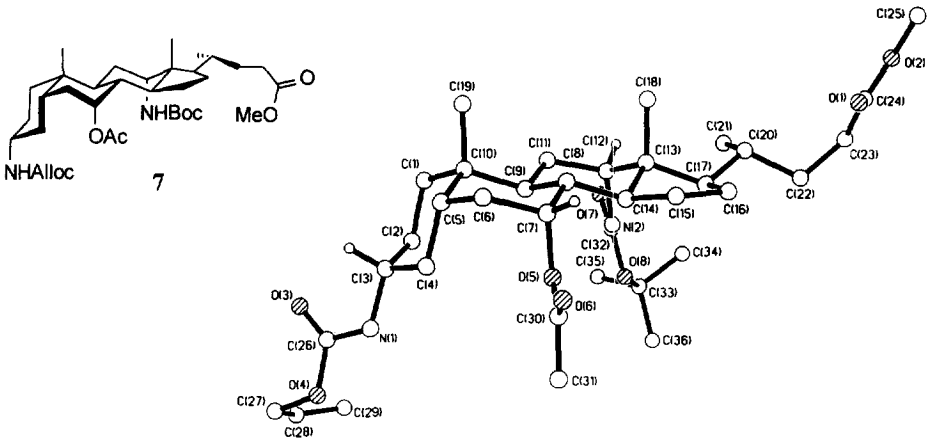


Figure: X-ray crystal structure of **7**

There are two obvious ways in which **3** may be used in combinatorial chemistry. On the one hand, hydrolysis of the C24 ester and attachment to a resin could be followed by solid-phase derivatisation of the 7α-OH, and then by deprotection and elaboration of the other positions in turn. Alternatively, solution-phase transformations of the 7α-OH (such as the acetylation to **7**) might be more practical, to give a suite of scaffolds, each of which could be converted into a distinctive library of tripodal molecules. In work to be reported separately, this has already been achieved for **7** to give a library which is currently being investigated with regard to recognition properties.

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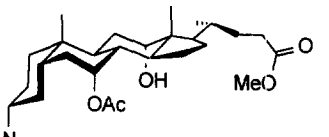
10. Acetate **7** was also prepared *via* a separate route employing azide **8** as an intermediate.



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11. Crystal data for **7**: $C_{36}H_{58}N_2O_8$, M = 646.84, a = 15.4789(18), b = 10.2349(13), c = 23.181(2) Å, β = 101.645(12)°, U = 3596.9(7) Å^3, monoclinic, space group $P2_1$, Z = 4, D_c = 1.194 g cm^{-3}, μ (Cu-Kα) = 0.673 mm^{-1}, $F(000)$ = 1408, colourless crystal, 0.27 × 0.31 × 0.54 mm, T = 160(2) K. 13234 reflections, 12270 unique (R_{int} = 0.0565, $2\theta_{max}$ = 135°) were measured using ω/θ scans with on-line profile fitting[12] on a Stoe-Siemens diffractometer equipped with graphite monochromated Cu-Kα radiation and corrected for absorption using ψ-scans (transmission range 0.761 to 0.948). Unit cell determined from 72 reflections with 20.04°≤ θ ≤ 24.83° measured on both sides of the beam to avoid zero-point errors. Intensity decay of 2% was monitored and corrected with 5 standard reflections measured each hour. Structure solution by direct methods and refinement[13] by full-matrix least-squares on F^2 values with all non-H atoms anisotropic and constrained H-atoms to $wR2$ = 0.1997 for all data, conventional $R1$ = 0.0708 for 9950 data with $F^2 \geq 2\sigma(F^2)$ and 846 parameters. Absolute structure parameter refined: x = 0.3(2). Goodness of fit on F^2 S = 1.038. Two similar molecules in the asymmetric unit with presumed H-bonding *via* NH···O=C giving chains along the crystallographic b direction. No shift/esd > 0.001 in the final least-squares cycle and no peak > ± 0.312 eÅ^{-3} in the final difference map.
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