Synthesis and X-Ray Crystal Structure of a New 'Cholaphane' with Externally Directed Functionality

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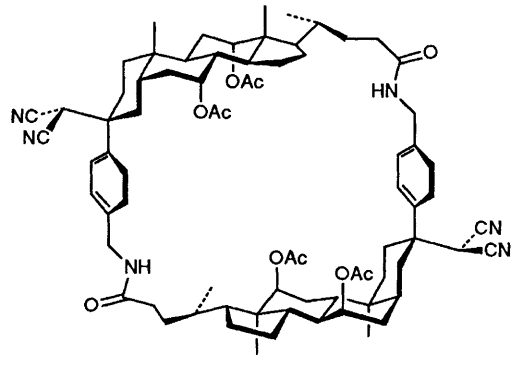
The 'cholaphane' **1** was synthesized in 26% overall yield from cholic acid and its structure determined by X-ray crystallography; the molecule adopts an open conformation and is able to surround two molecules of tetrahydrofuran.

A recent communication from the Dublin laboratory described the synthesis of a number of 'cholaphanes,' macrocyclic dimers derived from the inexpensive steroid cholic acid.[1] It was argued that the framework on which these molecules were based had unusual potential in molecular recognition and enzyme mimicry, because of its ease of access and synthetic flexibility. Subsequently, it was shown that two of them could act as receptors for an organic-soluble carbohydrate derivative.[2]

We now report the synthesis of a new cholaphane **1**. This molecule is based on an alternative framework which is also readily accessible, has greater rigidity than that employed in previous work and bears externally directed functionality which is potentially useful for immobilisation or water-solubilisation. We also report the crystal structure of **1**, which is the first of a cholaphane and confirms the accessibility of an open conformation.



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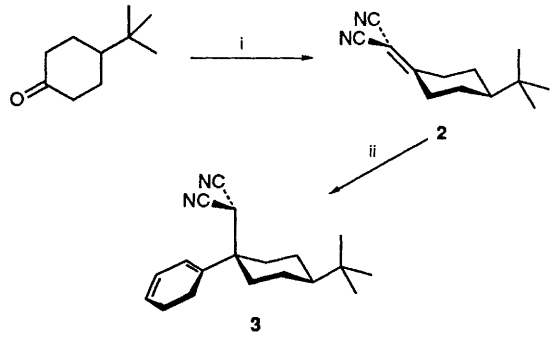
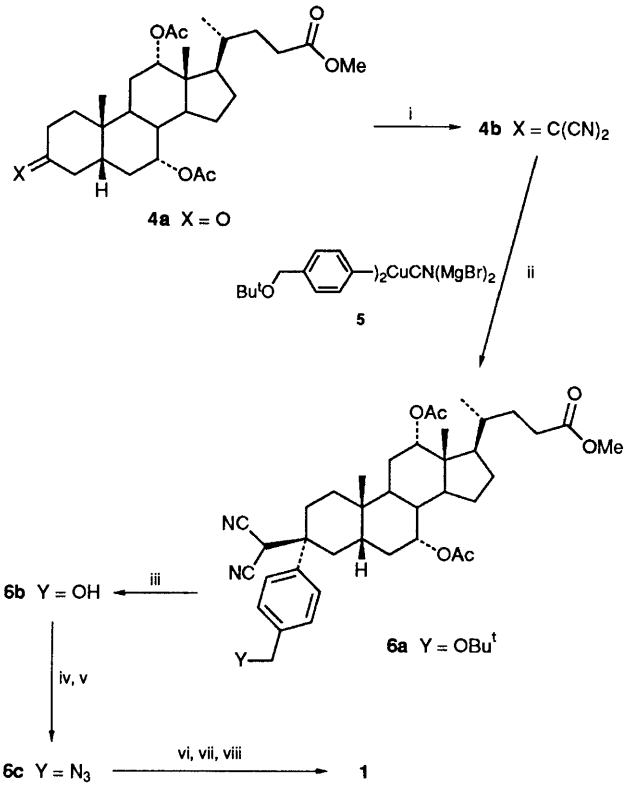
The design of **1** was motivated largely by our ultimate goal of water-soluble cholaphanes capable of hydrophobic binding and the realistic mimicry of enzyme reaction mechanisms. In the construction of such molecules, it seemed desirable that the introduction of an aromatic 'spacer' group in the 3α position of the steroid nucleus be accompanied by the generation of a 3β substituent which is (*i*) bulky and (*ii*) convertible to a water-solubilising functionality. The former criterion arose from the desire to fix the conformation of the aromatic rings so that they face into the centre of the



Scheme 1 *Reagents and conditions*: i, $CH_2(CN)_2$, $NH_4^+OAc^-$, AcOH, C_6H_6; ii, $(PhMgBr)_2CuCN$, Et_2O, 1,2-dimethoxyethane



Scheme 2 *Reagents and conditions*: i, $CH_2(CN)_2$, $NH_4^+OAc^-$, AcOH, C_6H_6; ii, THF; iii, CF_3CO_2H; iv, $MeSO_2Cl$, $EtPr^i_2N$, THF; v, tetramethylguanidinium azide, $CHCl_3$; vi, Ph_3P, H_2O, THF; vii, LiOH, MeOH, H_2O, THF; viii, $(EtO)_2POCN$, $CHCl_3$, dimethylformamide, K_2HPO_4

macrocycle. This should maximise the hydrophobic surface of the cavity and, according to studies with Corey–Pauling–Koltun (CPK) models, limit the ability of the steroid nuclei to fold towards each other. Clearly, it was also important that the reaction used to attach the spacer group be stereoselective, favouring the equatorial introduction of the aromatic ring.

The addition of an aryl organometallic reagent to a steroidal 3-dicyanomethylene derivative seemed a promising strategy. Dicyanomethylene derivatives can be formed from ketones under mild conditions [$CH_2(CN)_2$, $NH_4^+AcO^-$, AcOH, C_6H_6][3] and react cleanly with various organometallic reagents to give 1,4-addition products.[4] There was literature precedent for equatorial attack of an organocopper reagent on an exocyclic electron-deficient double bond.[5] Finally, various possibilities exist for conversion of the dicyanomethyl group in the products into bulky, water-solubilising functionality.[6]

Initially the methodology was tested on 4-t-butylcyclohexanone as a model for the 3-ketosteroid. As shown in Scheme 1, the ketone was first converted to its dicyanomethylene derivative **2** in 82% yield and then treated with a higher-order cuprate[7] derived from PhMgBr (2 equiv.) and CuCN (1 equiv.). The addition proved to be both high-yielding and stereoselective, only one product **3** being detected. X-Ray crystallography confirmed that the stereochemistry was as expected, with the conformation as indicated in the formula.

A similar sequence was then applied to ketone **4a**, readily available from cholic acid in *ca.* 90% yield. However, this time the organometallic reagent bore a 4-t-butoxymethyl substituent, so that the addition product could be further elaborated and eventually cyclised. Thus, as shown in Scheme 2, the dicyanomethylene derivative **4b** was obtained in 93% yield and treated with organocuprate **5** to give **6a**. Again, the reaction appeared to be completely stereoselective.

The t-butyl group was removed by treatment with trifluoroacetic acid (TFA) to give alcohol **6b** (90% yield from **4b**).

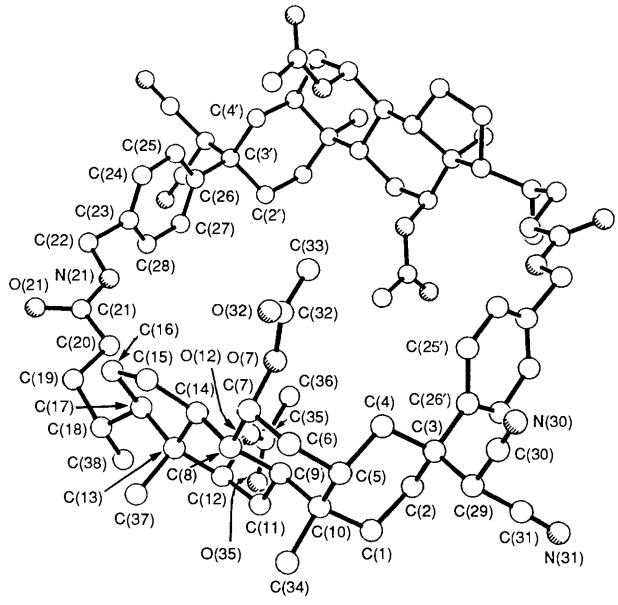


Fig. 1 The molecular structure of **1** showing crystallographic numbering

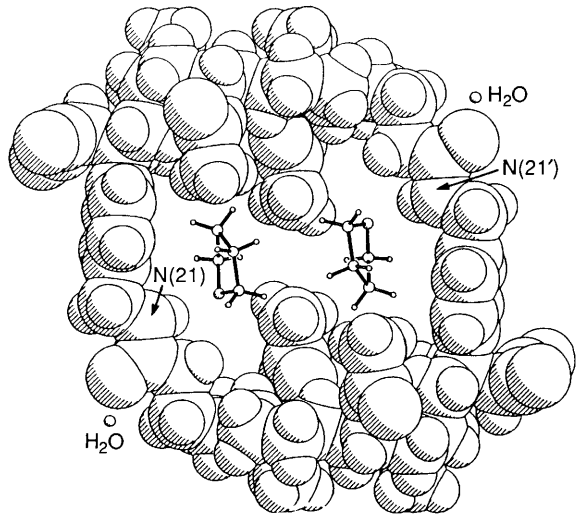


Fig. 2 Space-filling representation of **1** viewed down the crystallographic 2-fold axis showing the macrocyclic cavity and the positions of the included THF molecules. Adjacent macrocycles in the crystal are disposed so as to cap the cavities and encapsulate the guest molecules.

Mesylation followed by treatment with tetramethylguanidinium azide gave **6c** in 93% yield. Finally, reduction of the azide with triphenylphosphine–H_2O–tetrahydrofuran (THF), hydrolysis of the methyl ester and cyclodimerisation according to the procedure described previously[1] gave the macrocycle **1** in 37% crystalline yield. The overall yield of **1** from cholic acid was 26%.

The macrocycle gives well formed crystals from a variety of solvents, including some from THF–MeOH–H_2O which proved suitable for X-ray crystallographic analysis.† The

† *Crystal data* for **1**: $C_{76}H_{98}O_{10}N_6 \cdot 2(C_4H_8O) \cdot H_2O$, M = 1417.9, orthorhombic, a = 13.583(8), b = 17.775(6), c = 33.445(13) Å, V = 8075 Å^3, space group $C222_1$, Z = 4 (the molecule is disposed about a 2-fold axis), D_c = 1.17 g cm^{-3}, μ = 6 cm^{-1}. Data were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and refined anisotropically to give R = 0.083, R_w = 0.075 for 2028 independent observed reflections [$|F_o| > 3\sigma(|F_o|)$, $2\theta \leq 116°$]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

crystal structure (Fig. 1) reveals that the framework is capable of adopting an open conformation with a cavity of quite substantial dimensions. The transannular aromatic–aromatic centroid–centroid distance is 13 Å. The molecule has crystallographic C_2 symmetry with the carbonyl groups of the amide functions and the bulky dicyanomethyl groups directed away from the ring centre. The C-7 and C-12 acetate groups lie principally above and below the ring plane; however, owing to their axial orientation they impinge to some extent on the macrocyclic cavity, producing an appreciable waisting. Despite this, the cavity readily accommodates two molecules of THF (Fig. 2), each being held by an N–H···O hydrogen bond (3.01 Å) to an inwardly directed N–H group. Some difficulty was experienced in obtaining crystals suitable for analysis, and this may reflect the requirement for an included guest to produce an ordered, open geometry for the macrocycle.‡

‡ Molecular mechanics studies on our earlier framework indicated a fair degree of flexibility, arising largely from the steroidal side-chains.[2] Although the current system appears to have fewer conformational options, much of this flexibility is presumably still present.

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