Synthesis of macrocyclic diazanedicarboxylate and diazenedicarboxylate esters containing a steroid skeleton: an unusual oxidation of bromide to bromine by a strained diazenedicarboxylate ester. X-Ray molecular structure of 3α-(3-hydroxypropyl)-24-nor-5β-cholan-7α-ol diazane-1,2-dicarboxylate cyclic diester

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A series of diazanedicarboxylates **23**–**26** bridged by steroidal moieties obtained from 3α-hydroxyethyl or 3α-hydroxypropyl derivatives of 12α-hydroxy-24-norcholane or 7α-hydroxy-24-norcholane were synthesized. NMR studies showed that these diazanedicarboxylates were rapidly oxidized to the corresponding diazenedicarboxylate esters with *N*-bromosuccinimide (or *N*-chlorosuccinimide) and pyridine. Upon storage the diazenedicarboxylate esters are slowly reduced back to the diazanedicarboxylate esters with concomitant oxidation of bromide to bromine, which could be trapped with cyclohexene. Although diazenedicarboxylate **27** could be trapped by Diels–Alder reaction with cyclopentadiene to give the expected diastereoisomeric adducts **30a** and **30b**, aqueous work-up regenerated diazanedicarboxylate **25** and traces of ring-opened compounds including compound **29**. The crystal structure of 3α-hydroxypropyl-24-nor-3β-cholan-7α-ol diazanedicarboxylate diester **26** was determined.

Introduction

Our interest in the generation of chiral dialkyl diazene-1,2-dicarboxylates†[1,2] stems from their utility as reagents for Mitsunobu reactions,[3–5] electrophilic aminations,[6–12] and electrocyclic processes such as Diels–Alder[13] or ene reactions.[14] In the accompanying paper,[1] we report that various chiral dialkyl (bornyl, isobornyl and menthyl) diazenedicarboxylates show little or no stereoselectivity in amination reactions with achiral enolates of esters and *N*,*N*-dimethylamides. The failure of these simple chiral diazenedicarboxylate esters to influence amination stereochemistry could be due to conformational mobility and the equal accessibility of both faces of the azo moiety to electrophilic attack. Hence, the present study investigates the preparation of cyclic diazanedicarboxylate esters wherein one face is shielded by frameworks derived from deoxycholic acid and chenodeoxycholic acid. The geometry of one of these compounds was determined by X-ray crystallographic analysis. Oxidation of these diazanedicarboxylate esters to the corresponding diazenedicarboxylate esters proceeds readily, but the latter show an unprecedented tendency to be reduced back to the diazane form, apparently because of strain imposed by the rigid steroidal skeleton.

Results and discussion

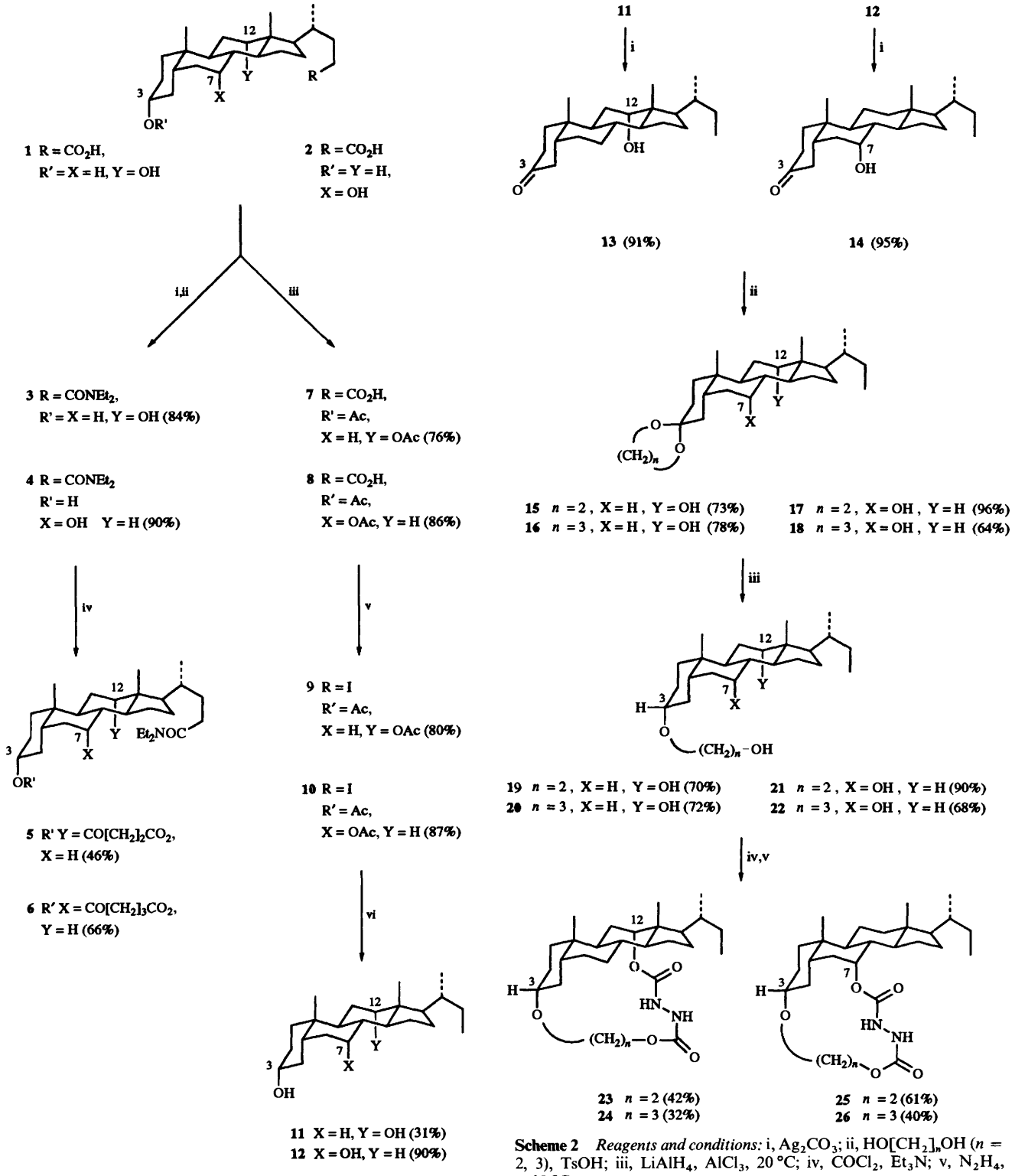
Deoxycholic acid **1** and chenodeoxycholic acid **2** are relatively inexpensive and commercially available sources of chiral auxiliaries.[15] In preliminary experiments to determine the feasibility of bridging the hydroxy groups, substrates **1** and **2** were converted into their *N*,*N*-diethylamides **3** and **4**, respectively, and treated with various diacyl chlorides (Scheme 1). Succinyl dichloride readily links the 3α and 12α hydroxy groups of compound **3** to generate cyclic diester **5** (46%), whereas glutaryl dichloride bridges the 3α and 7α hydroxy groups of the chenodeoxycholic amide **4** to afford compound **6** (66%) (yields not optimized). To eliminate possible interference by the side-chain carbonyl at C-24 in subsequent reactions, this carbon was removed from both substrates **1** and **2** as shown in Scheme 1 to produce the norcholane diols **11** and **12**, respectively. Reaction of these diols with phosgene produced chloroformates, but all attempts to form an intramolecular bridge using hydrazine failed, presumably because of the additional conformational constraints induced by the planar amide (hydrazide) groups. Thus, homologation of the diols is clearly required.

To lengthen the chains, the 24-nor-5β-cholane-3α,12α-diol **11** was selectively oxidized to 12α-hydroxynorcholan-3-one **13**, which was converted into either the 5-membered ring acetal **15** or its 6-membered analogue **16** (Scheme 2). Reductive acetal cleavage with lithium aluminium hydride (LAH) in the presence of aluminium chloride proceeds selectively to give the 3α-ethers **19** or **20** bearing the carbon chain with a terminal hydroxy group. Reaction of compounds **19** or **20** with phosgene produces the corresponding bis-chloroformates, which upon treatment with hydrazine afford the desired cyclic diazanedicarboxylates **23** or **24**, respectively. The 24-nor-5β-cholane-3α,7α-diol **12** was transformed similarly *via* the sequence: ketone **14** ⟶ acetal **17** (or acetal **18**) ⟶ 7α-hydroxy-3α-ether **21** (or 7α-hydroxy-3α-ether **22**) ⟶ bis-chloroformate ⟶ diazane-1,2-dicarboxylate **25** (or diazanedicarboxylate **26**). The structure of the 3α,7α-bridged diazanedicarboxylate **26** was determined by X-ray crystallographic analysis (Fig. 1).‡

We were surprised to find that our initial attempts to obtain the corresponding diazenedicarboxylate esters from the bridged diazanedicarboxylates **23**–**26**, by oxidation using the standard conditions of *N*-bromosuccinimide (NBS) and pyridine,[16] followed by aqueous work-up, resulted only in isolation of the starting diazanedicarboxylate and traces of ring-opened compounds such as **29**, derived from compound **27** (Scheme 3). In each case the oxidizing agent is rapidly consumed by the

† Previously called azodicarboxylates.

‡ See Experimental section for crystal data for compound **26**. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Note to Authors, Issue No. 1.



Scheme 1 *Reagents and conditions:* i, $ClCO_2Et$; ii, Et_3N, Et_2NH; iii, Ac_2O, pyr; iv, $[CH_2]_n(CH_2COCl)_2$ (n = 0, 1); v, $Pb(OAc)_4$, I_2, *hv*; vi, $LiBEt_3H$, 25 °C, 20 h

Scheme 2 *Reagents and conditions:* i, Ag_2CO_3; ii, $HO[CH_2]_nOH$ (n = 2, 3), TsOH; iii, $LiAlH_4$, $AlCl_3$, 20 °C; iv, $COCl_2$, Et_3N; v, N_2H_4, −98 °C

diazanedicarboxylate at 0 °C, with appearance of a yellow colour which is characteristic of a diazenedicarboxylate moiety. These observations prompted investigation of the reaction by ^1H NMR spectrometry. Upon addition of 1 mole equivalent of NBS to equimolar quantities of diazanedicarboxylate **25** and pyridine in CD_2Cl_2, the solution immediately becomes yellow and the ^1H NMR spectrum suggests complete conversion of the diazanedicarboxylate ester into a species which has lost both NH protons, but which has retained the conformationally restricted macrocyclic ring. The NMR spectra of such compounds generally show four non-equivalent methylene hydrogens for the bridging ethylenedioxy chain. This compound appears unchanged for a period of *ca.* 45 min. However, over a period of 4 days, a gradual but complete reappearance of the starting diazanedicarboxylate ester **25** is observed. This reverse reaction is much slower than the formation of diazenedicarboxylate ester, which proceeds very rapidly.

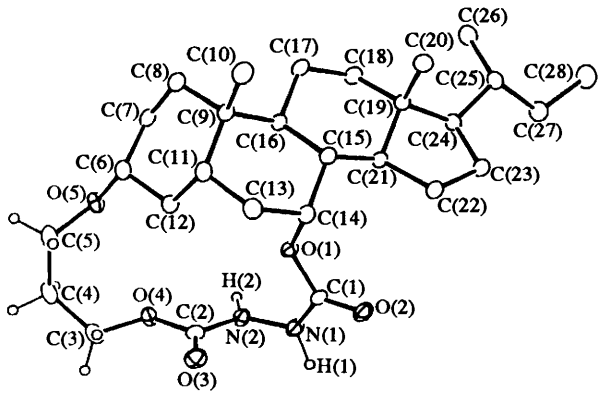
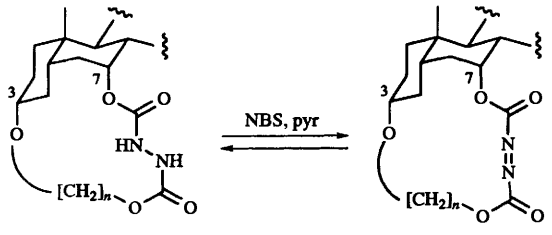


Fig. 1 Perspective view of the crystal conformation of diazanedicarboxylate **26** ($C_{28}H_{46}N_2O_5$). The torsion angle about the N–N bond (*i.e.* C–N–N–C) is 73.2(4)°. Crystallographic numbering scheme is shown.

Clearly the reduction is not due to simple reversibility of the oxidation process. In order to establish that the initial product formed on addition of NBS was indeed the diazenedicarboxylate ester **27**, it was trapped with cyclopentadiene. On addition of the diene, the yellow solution immediately turned colourless, and the two stable Diels–Alder products **30a** and **30b** could be isolated by silica gel chromatography (Scheme 3). Simple

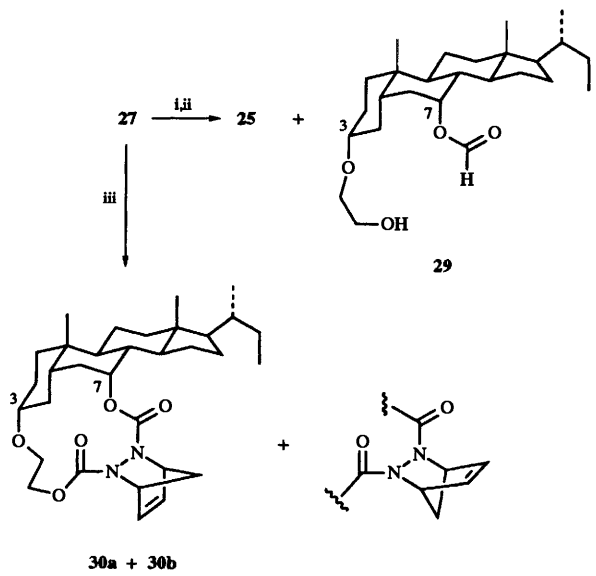


25 $n = 2$
26 $n = 3$

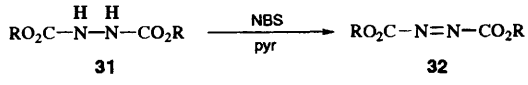
27 $n = 2$
28 $n = 3$

unbridged dialkyl diazenedicarboxylates (*e.g.*, dimenthyl diazenedicarboxylate **32**) are readily formed by analogous NBS oxidation (*e.g.*, of diester **31**), but are not re-reduced, remain unchanged in the initial mixture over several weeks, and can be isolated readily as described previously.[1,2] The more flexible steroidal diazanedicarboxylate ester **26** having a three-carbon ether linkage is rapidly oxidized to the diazenedicarboxylate ester **28**, but shows a significantly slower reduction back to the diazanedicarboxylate ester, with only 50% conversion after 4 days.

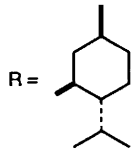
The addition of 3 mole equivalents of pyridine has no significant effect on the rate of either the oxidation of the hydrazine **25** or the subsequent reduction of the diazene **27**. No transformation of pyridine or succinimide (a product of the oxidation reaction) could be detected during the diazenedicarboxylate-reduction process, based on gas chromatographic (GC) and ^{1}H NMR analysis of the reaction mixture. Addition of methanol to the reaction mixture after ~40% of the material had been reduced back to diazanedicarboxylate ester greatly increased the rate of the reduction, suggesting that protic solvent assists this process. This is in accord with the high recovery of reduced diazanedicarboxylate **25** after aqueous work-up. Interestingly, the use of triethylamine (1 mole equivalent) in place of pyridine invoked a much more rapid reversal of the oxidation, but the base again appeared to remain unchanged. After 55 min, diazenedicarboxylate ester **27** was completely converted into the diazane analogue **25** under the latter conditions. More NBS could be added to regenerated



Scheme 3 *Reagents:* i, water; ii, silica; iii, cyclopentadiene



31 **32**



diazanedicarboxylate **25** to reoxidize to the same azo compound **27**, and the whole process can be repeated several times with no differences observable by ^{1}H NMR spectroscopy.

The lack of detectable transformation of the base, of succinimide, or of the steroid nucleus during reduction of the azo moiety suggests that bromide is oxidized *via* the macrocyclic diazenedicarboxylate. To test this, cyclohexene was added to the mixture immediately after formation of the diazenedicarboxylate ester **27**. As in the previous experiments, diazanedicarboxylate ester **25** is detectable after *ca.* 45 min, and after 4 h comprises ~30% of the steroidal material. However, additional peaks at δ 2.5 and 4.4 arise concurrently in the ^{1}H NMR spectrum. Comparison of this spectrum with that of *trans*-1,2-dibromocyclohexane, independently generated by the addition of bromine to a solution of cyclohexene in CD_2Cl_2 and pyridine, confirmed that dibromocyclohexane was produced at the same rate as diazanedicarboxylate ester. After 2 days, 50% of the material had been reduced and an equivalent amount of dibromocyclohexane had been formed. In this experiment, the ratio of diazenedicarboxylate **27** to diazanedicarboxylate ester **25** did not change thereafter (for $\geqslant$5 days). This is expected since there is only 1 mol equiv. of Br present in the reaction mixture, and once this has been removed as dibromocyclohexane the reduction can proceed no further.

A similar experiment in which cyclohexene was added after reduction to diazanedicarboxylate ester **25** was complete gave no detectable dibromocyclohexane. This indicates that although bromine is formed as an intermediate, there must be a second process involving further transformation of bromine, perhaps reaction with solvent to regenerate bromide, for completion of the reduction of the diazenedicarboxylate ester. The process is dependent on the strained diazenedicarboxylate system because various mixtures of the remaining reagents/

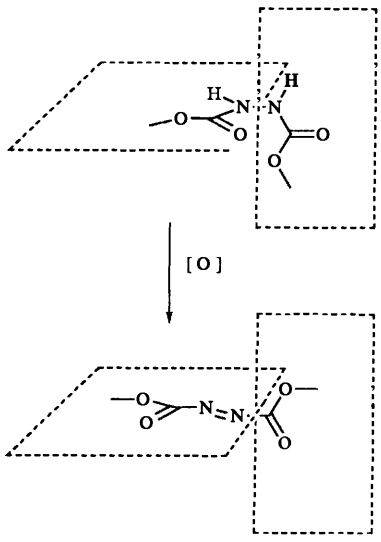
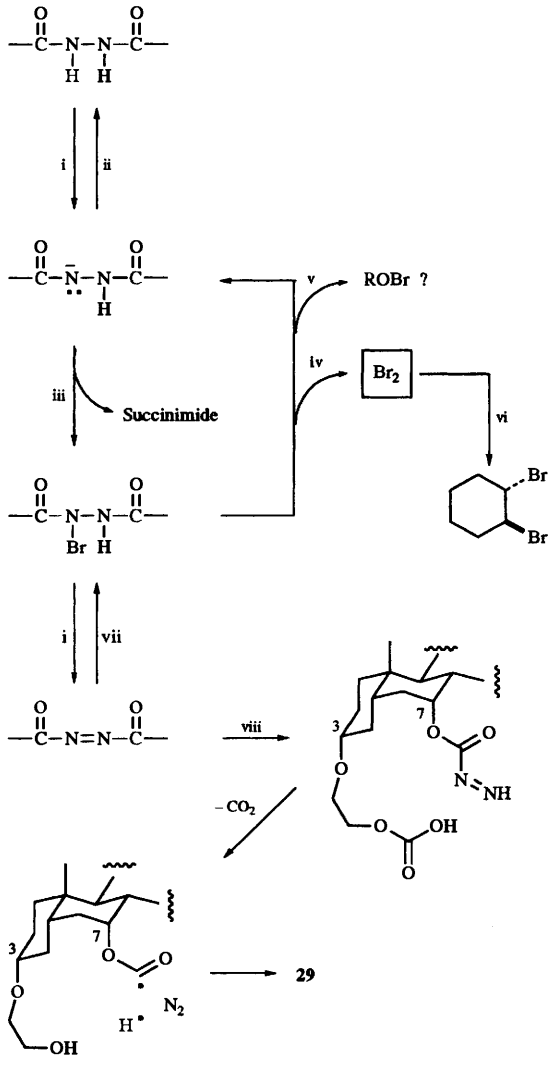


Fig. 2 Comparison of the preferred geometries of diazanedicarboxylates and diazenedicarboxylates based on known crystal structures

products (*i.e.*, pyridine, succinimide, bromine) are not detectably altered (by ^{1}H NMR spectroscopy) after 5 days at room temp. Molecular bromine added to such mixtures without the diazene **27** can be trapped as expected after 5 days with cyclohexene to form *trans*-1,2-dibromocyclohexane.

If *N*-chlorosuccinimide (NCS) was used in place of NBS, the oxidation proceeded more slowly and required more than 6 h before any diazenedicarboxylate **27** was formed. However, after 4 days all of the material was present as diazenedicarboxylate ester. This remained unchanged for at least 7 days, and no reduction to the diazanedicarboxylate ester **25** was observed. Clearly, as expected, chloride is much less readily oxidized than is bromide. Interestingly, addition of Br_2 to a solution of compound **27** made by the NCS route caused reduction to the diazanedicarboxylate ester **25**, as observed by appearance of its resonances (including NH) in the ^{1}H NMR spectrum.

These unusual observations appear to result from the conformational restrictions in the bridged steroidal systems. Examination of the three-dimensional structure of the stable diazanedicarboxylate **26** (Fig. 1) shows that, like acyclic diazanedicarboxylate esters whose X-ray crystallographic structures are known,[17,18] this compound prefers to have a dihedral angle approaching 90° between the two hydrazino N–H bonds. The corresponding diazenedicarboxylate moiety would presumably prefer to assume an arrangement in which the azo group is coplanar with one of the attached carbonyls and where the other carbonyl is orthogonal (Fig. 2), based on the crystal structures of ethyl *N*-(phenylcarbamoyl)azoformate and (1-cyano-1-methylethylazo)formamide.[19] Molecular models suggest that this would introduce additional strain and steric interactions for the oxidized derivative. Relief from this unfavourable geometry may provide the driving force for the unusual oxidation of bromide to bromine. A possible explanation may be that the dehydrohalogenation step to form the azo moiety is reversible, and that the intermediate *N*-bromo species present in undetectable amounts can act as a positive halogenating agent for bromide ion to give bromine (Scheme 4). Protic solvents (*e.g.*, water, methanol) may enhance this process or may themselves accept halogen to form hypobromites which eventually decompose. Formation of the minor product **29** upon hydrolysis probably involves attack by water at the carbonyl attached to the ethylenedioxy bridge of compound **27**, with ensuing decarboxylation and formation of a mono-*N*-acyl azo species. Such an intermediate may easily undergo radical decomposition to give nitrogen and cage recombination of hydrogen and the resulting 7-formyl radical. Although the tendency of these steroidal diazenedicarboxylate esters to revert to starting material and their lack of stability to protic conditions is unique, it limits their usefulness as reagents. Studies on the generation and synthetic use of chiral diazenedicarboxylates bridged on one face by more flexible moieties are underway.



Scheme 4 *Reagents:* i, pyr; ii, H^+; iii, NBS; iv, Br^-; v, ROH; vi, cyclohexene; vii, HBr; viii, water

Experimental

General procedures

The instrumentation and procedures used throughout have been described.[1] All solvents were purified and distilled according to Perrin *et al.*[20] Light petroleum refers to the fraction with distillation range 35–60 °C.

N,N-Diethyldeoxycholamide 3

The procedure of Bellini *et al.* was adapted.[21] A solution of deoxycholic acid **1** (3.93 g, 10.0 mmol) in 1,4-dioxane (50 cm^3), cooled to 10 °C, was treated with tributylamine (2.38 cm^3, 10.0 mmol) followed by ethyl chloroformate (0.956 cm^3, 10.0 mmol). The mixture was stirred at 10 °C for 10 min. Diethylamine (2.59 cm^3, 25.0 mmol) was added, and the mixture was stirred for 15 min at 10 °C and then at room temp. for 2 h before being poured into 5% aq. $KHCO_3$ (50 cm^3) and extracted with ethyl acetate

(3 × 40 cm^3). The organic phase was dried ($MgSO_4$), and concentrated under reduced pressure to give a viscous substance (6.39 g), which was purified on a SiO_2 column [ethyl acetate–MeOH (99:1 to 90:10)] to give *amide* **3** (3.75 g, 84%) as a solid, mp 168–170 °C (from Et_2O) (Found: C, 75.2; H, 10.9; N, 3.1%; M^+, 447.3719. $C_{28}H_{49}NO_3$ requires C, 75.12; H, 11.03; N, 3.13%; *M*, 447.3712); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (OH) and 1626 (C=O); δ_H(400 MHz; $CDCl_3$) 3.99 (1 H, t, *J* 2.5), 3.62 (1 H, m), 3.43–3.25 (4 H, m), 2.35 (1 H, m), 2.21 (1 H, m), 1.94–1.47 (18 H, m), 1.46–1.36 (6 H, m), 1.34–1.22 (2 H, m), 1.17 (3 H, t, *J* 7.0), 1.10 (3 H, t, *J* 7.0), 0.99 (3 H, d, *J* 6.5), 0.91 (3 H, s) and 0.68 (3 H, s); *m/z* (CI-NH_3) 448 (MH^+).

N,N-Diethylchenodeoxycholamide 4

The above procedure with chenodeoxycholic acid **2** (3.93 g, 10.0 mmol), 1,4-dioxane (50 cm^3), triethylamine (1.39 cm^3, 10.0 mmol), ethyl chloroformate (0.956 cm^3, 10.0 mmol) and diethylamine (2.59 cm^3, 25.0 mmol) gave *amide* **4** (4.05 g, 90%) as a solid, mp 166–170 °C (from ethyl acetate) (Found: C, 75.3; H, 11.0; N, 3.05%; M^+, 447.3711); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420 (OH) and 1626 (C=O); δ_H(360 MHz; $CDCl_3$) 3.86 (1 H, m), 3.46 (1 H, m), 3.40–3.26 (4 H, m), 2.34 (1 H, m), 2.24 (1 H, m), 2.17 (1 H, m), 2.08–1.47 (17 H, m), 1.46–1.24 (8 H, m), 1.20 (3 H, t, *J* 7.0), 1.12 (3 H, t, *J* 7.0), 0.97 (3 H, d, *J* 6.5), 0.92 (3 H, s) and 0.67 (3 H, s); *m/z* (CI-NH_3) 448 (MH^+).

N,N-Diethyl-*O,O'*-succinyldeoxycholamide 5

A solution of the amide **3** (1.52 g, 3.39 mmol) in $CHCl_3$ (20 cm^3) was cooled to 0 °C and treated with pyridine (0.548 cm^3, 6.78 mmol) and succinyl dichloride (0.373 cm^3, 3.39 mmol). The mixture was stirred at 0 °C for 30 min, at 20 °C for 24 h, and then at 55 °C for 4 h. The mixture was cooled to room temp., water (2 cm^3) was added, and the mixture was extracted with $CHCl_3$ (3 × 15 cm^3). The organic phase was washed with 5% aq. $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure to give a black solid (1.64 g). Purification by normal SiO_2 column chromatography [$CHCl_3$–MeOH (100:0 to 90:10)] gave *amide* **5** (0.819 g, 46%) as a solid, mp 120–123 °C (from ethyl acetate) (Found: C, 72.1; H, 9.75; N, 2.6%; MH^+, 530.3822. $C_{32}H_{51}NO_5$ requires C, 72.55; H, 9.70; N, 2.64%; $C_{32}H_{52}NO_5$ requires *m/z* 530.3845); $\nu_{max}(CHCl_3)/cm^{-1}$ 1733 (C=O) and 1640 (C=O); δ_H(300 MHz; $CDCl_3$) 5.15 (1 H, s), 4.78 (1 H, s), 3.35 (4 H, m), 2.64 (3 H, m), 2.35 (1 H, m), 2.18 (1 H, m), 1.86 (4 H, m), 1.64 (9 H, m). 1.45 (5 H, m), 1.30 (7 H, m), 1.20 (3 H, t, *J* 7.0), 1.10 (3 H, t, *J* 7.0), 0.92 (3 H, s), 0.87 (3 H, d, *J* 6.0) and 0.74 (3 H, s); *m/z* (EI) 530 (MH^+).

N,N-Diethyl-*O,O'*-glutarylchenodeoxycholamide 6

The above procedure with amide **4** (1.72 g, 3.85 mmol), $CHCl_3$ (20 cm^3), pyridine (0.623 cm^3, 7.70 mmol) and glutaryl dichloride (0.491 cm^3, 3.85 mmol), followed by purification by flash chromatography [(97:3) CH_2Cl_2–MeOH] gave *amide* **6** (1.38 g, 66%) as a fluffy solid (Found: C, 72.5; H, 9.9; N, 2.6. $C_{33}H_{53}NO_5$ requires C, 72.89; H, 9.82; N, 2.58%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1731 (C=O) and 1640 (C=O); δ_H(300 MHz; $CDCl_3$) 4.89 (1 H, m), 4.60 (1 H, m), 3.34 (4 H, m), 2.49 (1 H, m), 2.34 (3 H, m), 2.15 (2 H, m), 1.87 (9 H, m), 1.43 (16 H, m), 1.18 (3 H, t, *J* 7.0), 1.10 (3 H, t, *J* 7.0), 0.95 (3 H, d, *J* 6.0), 0.92 (3 H, s) and 0.65 (3 H, s); *m/z* (CI-NH_3) 544 (MH^+).

3α,12α-Diacetoxy-5β-cholan-24-oic acid 7

Acetylation of deoxycholic acid **1** (20.0 g, 51.0 mmol) with acetic anhydride (90 cm^3) in pyridine (50 cm^3) employed the procedure of Ahmed *et al.*[22] Purification by flash chromatography [hexane–ethyl acetate (1:1)] gave *diacetate* **7** (18.4 g, 76%) as a solid, mp 84–85 °C [Found: (M^+ – AcOH), 416.2931. $C_{26}H_{40}O_4$ requires *m/z*, 416.2926]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (OH), 1734 (C=O) and 1706 (C=O); δ_H(200 MHz; $CDCl_3$) 5.09 (1 H, s), 4.70 (1 H, m), 2.11 (3 H, s), 2.04 (3 H, s), 2.4–1.0 (26 H, m), 0.90 (3 H, s), 0.81 (3 H, d, *J* 6.0) and 0.73 (3 H, s); *m/z* (FAB$^+$) 477 (MH^+), 417 (MH^+ – AcOH) and 357 (MH^+ – 2 AcOH).

3α,7α-Diacetoxy-5β-cholan-24-oic acid 8

The above procedure with chenodeoxycholic acid **2** (15 g, 38.0 mmol), pyridine (30 cm^3) and acetic anhydride (60 cm^3) gave diacetate **8** (15.7 g, 86%) as a solid, mp 213–216 °C (lit.,[23] 206–208 °C) (Found: C, 70.6; H, 9.45. Calc. for $C_{28}H_{44}O_6$: C, 70.56; H, 9.30%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 (OH), 1734 (C=O) and 1706 (C=O); δ_H(200 MHz; $CDCl_3$) 0.65 (3 H, s), 0.92 (3 H, d, *J* 7.5), 0.94 (3 H, s), 1.0–2.5 (26 H, m), 2.05 (3 H, s), 2.09 (3 H, s), 4.61 (1 H, m) and 4.88 (1 H, d, *J* 4); *m/z* (CI-NH_3) 494 (MNH_4^+).

23-Iodo-24-nor-5β-cholane-3α,12α-diyl diacetate 9

Following the procedure of Ahmed *et al.*[22] the reaction of diacetate **7** (22.3 g, 47.0 mmol) in CCl_4 (190 cm^3) with $Pb(OAc)_4$ (20.78 g, 47.0 mmol) and iodine (11.81 g, 94.0 mmol) in CCl_4 (620 cm^3) gave *iodo diacetate* **9** (20.8 g, 80%) as a solid (Found: C, 58.0; H, 7.7. $C_{27}H_{43}IO_4$ requires C, 58.06; H, 7.76%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1733 (C=O); δ_H(400 MHz; $CDCl_3$) 5.03 (1 H, t, *J* 4), 4.64 (1 H, m), 3.24 (1 H, dq, *J* 8, 4), 3.00 (1 H, q, *J* 8), 2.05 (3 H, s), 1.99 (3 H, s), 2.00–0.90 (24 H, m), 0.86 (3 H, s), 0.72 (3 H, d, *J* 8) and 0.69 (3 H, s); *m/z* (CI-NH_3) 576 (MNH_4^+).

23-Iodo-24-nor-5β-cholane-3α,7α-diyl diacetate 10

The above procedure with diacetate **8** (3.49 g, 8.00 mmol) in CCl_4 (30 cm^3), $Pb(OAc)_4$ (3.55 g, 8.00 mmol) and iodine (2.02 g, 16.0 mmol) in CCl_4 (106 cm^3) gave *iodo diacetate* **10** (3.86 g, 87%) as a solid, mp 184–185 °C (from light petroleum) (Found: C, 58.4; H, 8.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1733 (C=O); δ_H(200 MHz; $CDCl_3$) 4.75 (1 H, d, *J* 4), 4.45 (1 H, m), 3.18 (1 H, dt, *J* 10, 4), 2.95 (1 H, q, *J* 10), 1.95 (3 H, s), 1.92 (3 H, s), 2.05–0.86 (24 H, m), 0.85 (3 H, s), 0.82 (3 H, d, *J* 8) and 0.56 (3 H, s); δ_C(50 MHz; $CDCl_3$) 4.92, 11.65, 17.77, 20.56, 21.42, 21.52, 22.63, 23.43, 26.70, 27.94, 31.22, 33.97, 34.52, 34.71, 34.80, 37.03, 37.78, 39.40, 40.17, 40.84, 42.69, 50.29, 55.55, 71.10, 74.06, 170.27 and 170.47; *m/z* (CI-NH_3) 576 (MNH_4^+).

24-Nor-5β-cholane-3α,12α-diol 11

To a solution of $LiBEt_3H$ [1 mol dm^{-3} in tetrahydrofuran (THF); 281 cm^3, 0.281 mol] under Ar at 25 °C was added, over a period of 30 min, a solution of iodo diacetate **9** (26.11 g, 46.9 mmol) in dry THF (80 cm^3). During addition the temperature was maintained at 25 °C. The reaction mixture was stirred at room temp. overnight and was then cooled in an ice-bath and ethyl acetate (50 cm^3) was added, followed by dropwise addition of water (80 cm^3). The pH of the resulting mixture was adjusted to 1–2 with 1 mol dm^{-3} HCl and the aqueous layer was extracted with CH_2Cl_2 (4 × 200 cm^3). Purification by flash chromatography [hexane–ethyl acetate (10:1)] gave known[22] diol **11** (5.00 g, 31%) as a foam, $\nu_{max}(CHCl_3)/cm^{-1}$ 3350 (OH); δ_H(200 MHz; $CDCl_3$) 3.96 (1 H, t, *J* 2), 3.58 (1 H, m), 1.90–0.99 (24 H, m), 0.91 (3 H, d, *J* 6), 0.88 (3 H, s), 0.81 (3 H, t, *J* 6) and 0.65 (3 H, s); *m/z* (EI) 348 (M^+).

24-Nor-5β-cholane-3α,7α-diol 12

The above procedure with iodo diacetate **10** (28.41 g, 51.0 mmol), $LiBEt_3H$ (1.0 mol dm^3 in THF; 312 cm^3, 0.312 mol) and THF (80 cm^3) gave *diol* **12** (15.93 g, 90%) as a foam (Found: M^+, 348.3026. $C_{23}H_{40}O_2$ requires *M*, 348.3028); $\nu_{max}(CHCl_3)/cm^{-1}$ 3350 (OH); δ_H(200 MHz; $CDCl_3$) 3.86 (1 H, d, *J* 4.0), 3.49 (1 H, m), 2.30–1.00 (24 H, m), 0.93 (3 H, s), 0.92 (3 H, d, *J* 8.0), 0.83 (3 H, t, *J* 8.0) and 0.68 (3 H, s); δ_C(50 MHz, $CDCl_3$) 10.18, 11.75, 18.07, 20.62, 22.82, 23.68, 28.16, 28.26, 30.64, 32.88,

34.64, 35.04, 35.39, 36.92, 39.42, 39.73, 41.56, 42.54, 50.45, 55.60, 68.45 and 71.88; *m/z* (EI) 348 (M^+, 7%), 331 ($M^+ - OH$, 25), 330 ($M^+ - H_2O$, 100) and 312 ($M^+ - 2\,H_2O$, 98).

12α-Hydroxy-24-nor-5β-cholan-3-one 13

To a solution of diol **11** (3.0 g, 8.6 mmol) in freshly distilled toluene (30 cm^3) was added Ag_2CO_3–Celite (9.0 g, 16.0 mmol). The reaction flask was fitted with a Dean–Stark apparatus and heated at reflux for 5 h during which time the reaction colour changed from light green to black. The reaction mixture was filtered and the residue was washed with toluene (20 cm^3) and chloroform (20 cm^3). The combined washings were concentrated under reduced pressure and the resulting residue was purified by flash chromatography [hexane–ethyl acetate (1:1)] to give *ketone* **13** (2.70 g, 91%) as a solid, mp 184–185 °C (Found: C, 79.55; H, 11.05. $C_{23}H_{38}O_2$ requires C, 79.71; H, 11.05%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (OH) and 1706 (C=O); δ_H(200 MHz; $CDCl_3$) 4.04 (1 H, s), 2.72 (1 H, t, *J* 13.6), 2.38 (1 H, dt, *J* 12.5 and 5.5), 2.20–1.0 (23 H, m), 0.99 (3 H, s), 0.93 (3 H, d, *J* 6.5), 0.82 (3 H, t, *J* 7.3) and 0.70 (3 H, s); δ_C(75 MHz; $CDCl_3$) 10.39, 12.61, 17.22, 22.44, 23.62, 25.53, 26.60, 27.44, 28.21, 28.80, 33.94, 34.45, 35.76, 36.63, 36.93, 37.18, 42.39, 44.35, 46.55, 47.50, 48.21, 73.16 and 213.30; *m/z* (CI-NH_3) 364 (MNH_4^+).

7α-Hydroxy-24-nor-5β-cholan-3-one 14

The above procedure with diol **12** (1.00 g, 2.8 mmol), toluene (30 cm^3) and Ag_2CO_3–Celite (3.27 g, 5.7 mmol) gave *ketone* **14** (0.92 g, 95%) as a solid, mp 95–97 °C (Found: M^+, 346.2866. $C_{23}H_{38}O_2$ requires *M*, 346.2872); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (OH) and 1710 (C=O); δ_H(200 MHz; $CDCl_3$) 3.88 (1 H, d, *J* 3.2), 3.39 (1 H, t, *J* 15), 2.40 (1 H, td, *J* 15 and 5), 2.38–1.00 (23 H, m), 0.99 (3 H, s), 0.87 (3 H, d, *J* 6), 0.80 (3 H, t, *J* 8) and 0.65 (3 H, s); δ_C(75 MHz; $CDCl_3$) 10.25, 11.79, 18.04, 20.99, 21.94, 23.72, 28.11, 28.26, 33.33, 33.83, 35.31, 36.83, 36.95, 36.98, 39.40, 39.56, 42.65, 43.22, 45.64, 50.35, 55.60, 68.55 and 213.20; *m/z* (EI) 346 (M^+, 31%), 328 ($M^+ - H_2O$, 100), 313 (14) and 295 (23).

3,3-Ethylenedioxy-24-nor-5β-cholan-12α-ol 15

To a solution of ketone **13** (2.75 g, 7.9 mmol) in benzene (60 cm^3) was added dry ethane-1,2-diol (1.33 g, 21.5 mmol) and toluene-*p*-sulfonic acid (PTSA) (20 mg, 0.012 mmol). The reaction flask was fitted with a Dean–Stark apparatus and heated at reflux overnight under argon. The mixture was then cooled and added to stirred, saturated aq. $NaHCO_3$. The aqueous phase was extracted with diethyl ether (5 × 40 cm^3). The organic phase was then dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography [hexane–ethyl acetate (4:1)] gave *ketal* **15** (2.3 g, 73%), mp 158–160 °C (Found: C, 76.8; H, 10.9. $C_{25}H_{42}O_3$ requires C, 76.87; H, 10.84%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (OH); δ_H(200 MHz; $CDCl_3$) 3.96 (1 H, s), 3.91 (4 H, s), 2.01 (1 H, t, *J* 14), 1.80–1.00 (23 H, m), 0.94 (3 H, d, *J* 7.0), 0.91 (3 H, s), 0.81 (3 H, t, *J* 8.0) and 0.68 (3 H, s); δ_C(75 MHz; $CDCl_3$) 10.41, 12.76, 17.09, 22.91, 23.64, 25.92, 26.71, 27.43, 28.18, 28.79, 29.97, 33.02, 34.03, 34.14, 35.65, 35.88, 36.71, 40.90, 46.45, 47.13, 48.24, 64.04, 64.17, 73.23 and 101.05; *m/z* (CI-NH_3) 391 (MH^+).

3,3-Propane-1,3-diyldioxy-24-nor-5β-cholan-12α-ol 16

The above procedure with ketone **13** (2.5 g, 7.21 mmol), benzene (60 cm^3), propane-1,3-diol (1.09 g, 14.4 mmol) and PTSA (20 mg, 0.012 mmol) gave *ketal* **16** (2.26 g, 78%) (Found: M^+, 404.3288. $C_{26}H_{44}O_3$ requires *M*, 404.3290); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (OH); δ_H(300 MHz; $CDCl_3$) 3.95 (1 H, d, *J* 3.0), 3.88 (2 H, t, *J* 6), 3.80 (2 H, t, *J* 6), 1.98 (1 H, dd, *J* 12 and 0.3), 1.90–0.94 (26 H, m), 0.93 (3 H, d, *J* 6), 0.90 (3 H, s), 0.80 (3 H, t, *J* 7.8) and 0.64 (3 H, s); δ_C(75 MHz; $CDCl_3$) 10.41, 12.74, 17.08, 22.95, 23.63, 25.70, 25.99, 26.76, 27.06, 27.42, 28.18, 28.74, 32.39, 33.08, 34.32, 34.51, 35.92, 36.73, 39.23, 46.44, 47.32, 48.24, 58.98, 59.25, 73.23 and 98.91; *m/z* (EI) 404 (M^+, 20%), 346 ($M^+ - C_3H_6O$, 5), 328 ($M^+ - C_3H_6O - H_2O$, 51) and 271 ($M^+ - C_3H_6O - H_2O - C_4H_9$, 100).

3,3-Ethylenedioxy-24-nor-5β-cholan-7α-ol 17

The above procedure with ketone **14** (1.10 g, 3.18 mmol), benzene (30 cm^3), ethane-1,2-diol (0.40 g, 7.00 mmol) and PTSA (10 mg, 0.006 mmol) gave ketal **17** (1.19 g, 96%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 (OH); δ_H(200 MHz; $CDCl_3$) 3.82 (4 H, s), 3.72 (1 H, d, *J* 4.9), 2.00–0.90 (24 H, m), 0.86 (3 H, s), 0.80 (3 H, d, *J* 7.4), 0.73 (3 H, t, *J* 7.4) and 0.58 (3 H, s); δ_C(50 MHz; $CDCl_3$) 10.13, 11.71, 17.96, 20.81, 22.44, 23.64, 28.07, 28.17, 29.98, 32.11, 34.04, 34.93, 36.85, 38.46, 39.38, 39.60, 40.16, 50.34, 55.48, 63.61, 63.82, 63.97, 68.35 and 109.66; *m/z* (EI) 391 (MH^+).

3,3-Propane-1,3-diyldioxy-24-nor-5β-cholan-7α-ol 18

The above procedure with ketone **14** (1.01 g, 2.9 mmol), benzene (50 cm^3), propane-1,3-diol (0.68 g, 9.0 mmol) and PTSA (10 mg, 0.006 mmol) gave *ketal* **18** (0.75 g, 64%) (Found: M^+, 404.3299. $C_{26}H_{44}O_3$ requires *M*, 404.3290); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460 (OH); δ_H(200 MHz; $CDCl_3$) 3.88 (1 H, t, *J* 6), 3.79 (4 H, t, *J* 6), 2.25 (1 H, t, *J* 16), 2.01–0.89 (26 H, m), 0.88 (3 H, s), 0.82 (3 H, d, *J* 8), 0.76 (3 H, t, *J* 8) and 0.60 (3 H, s); δ_C(50 MHz; $CDCl_3$) 10.20, 11.71, 17.96, 20.79, 22.51, 23.66, 25.72, 27.63, 28.08, 28.21, 32.22, 32.36, 34.13, 35.35, 36.55, 36.91, 38.56, 39.37, 39.63, 42.54, 50.39, 55.51, 58.97, 59.21, 68.38 and 98.56; *m/z* (EI) 404 (M^+, 7%), 347 ($M^+ - C_3H_5O$, 1), 328 ($M^+ - C_3H_6O - H_2O$, 4), 155 (68) and 113 (100).

3α-(2-Hydroxyethoxy)-24-nor-5β-cholan-12α-ol 19

Aluminium trichloride (5.14 g, 38.4 mmol) was slowly added to an ethereal suspension (70 cm^3) of lithium aluminium hydride (1.46 g, 38.5 mmol) and the mixture was stirred at room temp. for 20 min. A solution of ketal **15** (1.53 g, 3.8 mmol) in diethyl ether (30 cm^3) was added to the stirred slurry at room temp. over a period of 10 min. The mixture was stirred at room temp. overnight and then was cooled in an ice-bath. Ethyl acetate (60 cm^3) was added dropwise, followed by water (20 cm^3). The resulting suspension was then acidified with 6 mol dm^{-3} HCl (40 cm^3) and the solution was stirred for 1 h. The aqueous layer was extracted with diethyl ether (5 × 40 cm^3) and the organic phase was washed with saturated aq. $NaHCO_3$ until neutral (to indicator paper), then was dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane–ethyl acetate (1:1)] to give diol **19** (1.06 g, 70%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3420 (OH); δ_H(300 MHz; $CDCl_3$) 3.94 (1 H, s), 3.66 (2 H, t, *J* 5.6), 3.54 (2 H, m), 3.25 (1 H, m), 2.65 (1 H, br s), 1.89–0.96 (24 H, m), 0.90 (3 H, d, *J* 6.9), 0.88 (3 H, s), 0.79 (3 H, t, *J* 6.9) and 0.64 (3 H, s); δ_C(50 MHz; $CDCl_3$) 10.41, 12.67, 16.99, 23.13, 23.59, 26.01, 26.83, 27.18, 27.38, 28.12, 28.45, 33.17, 33.59, 34.35, 35.05, 35.94, 36.72, 41.97, 46.36, 47.18, 48.17, 61.96, 68.93, 73.11 and 79.41; *m/z* (EI) 392 (M^+), 330 ($M^+ - HO[CH_2]_2OH$, 17%) and 312 ($M^+ - HO[CH_2]_2OH - H_2O$, 100).

3α-(3-Hydroxypropoxy)-24-nor-5β-cholan-12α-ol 20

The above procedure with ketal **16** (1.42 g, 3.50 mmol), lithium aluminium hydride (2.35 g, 61.9 mmol) and aluminium trichloride (8.26 g, 61.9 mmol) in dry diethyl ether (60 cm^3) gave diol **20** (1.03 g, 72%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3470 (OH); δ_H(200 MHz; $CDCl_3$) 3.95 (1 H, t, *J* 0.3), 3.75 (2 H, t, *J* 6), 3.62 (2 H, m), 3.21 (1 H, m), 2.03–0.95 (26 H, m), 0.91 (3 H, s), 0.89 (3 H, d, *J* 7.8), 0.79 (3 H, t, *J* 7.8) and 0.64 (3 H, s); δ_C(75 MHz; $CDCl_3$) 10.42, 12.76, 17.12, 23.24, 23.66, 26.11, 27.05, 27.27, 27.45, 28.20, 28.55, 32.25, 33.18, 33.71, 34.47, 35.17, 36.10,

36.74, 42.15, 46.45, 47.35, 48.23, 62.55, 67.51, 73.27 and 79.65; *m/z* (EI) 406 (M^+).

3α-(2-Hydroxyethoxy)-24-nor-5β-cholan-7α-ol 21

The above procedure with ketal **17** (1.10 g, 2.82 mmol), lithium aluminium hydride (1.18 g, 33.1 mmol) and aluminium trichloride (4.14 g, 31.0 mmol) in dry diethyl ether (90 cm^3) gave diol **21** (0.99 g, 90%) as an oil, $\nu_{max}(CHCl_3)/cm^{-1}$ 3420 (OH); δ_H(200 MHz; $CDCl_3$) 3.83 (1 H, d, *J* 3.2), 3.69 (2 H, t, *J* 4.8), 3.57 (2 H, t, *J* 4.8), 3.16 (1 H, m), 2.28–0.98 (24 H, m), 0.89 (3 H, s), 0.88 (3 H, d, *J* 6.4), 0.82 (3 H, t, *J* 8.0) and 0.67 (3 H, s); δ_C(75 MHz; $CDCl_3$) 10.17, 11.73, 17.99, 20.55, 22.78, 23.64, 27.32, 28.09, 28.22, 32.81, 34.54, 35.26, 35.29, 36.18, 36.89, 39.43, 39.64, 41.45, 42.54, 50.40, 55.54, 62.02, 68.34, 68.95 and 79.69; *m/z* (CI-NH_3) 410 (MNH_4^+) and 393 (MH^+).

3α-(3-Hydroxypropoxy)-24-nor-5β-cholan-7α-ol 22

The above procedure with ketal **18** (0.75 g, 1.86 mmol), lithium aluminium hydride (0.70 g, 18.5 mmol) and aluminium trichloride (2.47 g, 18.5 mmol) in dry diethyl ether (20 cm^3) gave *diol* **22** (0.52 g, 68%) as an oil (Found: M^+, 406.3444. $C_{26}H_{46}O_3$ requires M, 406.3447); $\nu_{max}(CHCl_3)/cm^{-1}$ 3470 (OH); δ_H(200 MHz; $CDCl_3$) 3.78 (1 H, dd, *J* 3.5 and 2.4), 3.71 (2 H, t, *J* 5.8), 3.61 (2 H, dt, *J* 5.8 and 2.5), 3.07 (1 H, m), 2.20–0.90 (26 H, m), 0.88 (3 H, s), 0.85 (3 H, d, *J* 6), 0.79 (3 H, t, *J* 6) and 0.62 (3 H, s); δ_C(75 MHz; $CDCl_3$) 10.22, 11.73, 17.99, 20.56, 22.80, 23.69, 27.28, 28.09, 28.24, 32.24, 32.79, 34.57, 35.28, 35.33, 36.20, 36.95, 39.47, 39.59, 41.49, 42.57, 50.37, 55.55, 62.22, 67.15, 68.41 and 79.73; *m/z* (EI) 406 (M^+), 330 ($M^+ - HO[CH_2]_3$-OH, 14%), 313 ($M^+ - HO[CH_2]_3OH - OH$, 30) and 312 ($M^+ - HO[CH_2]_3OH - H_2O$, 100).

3α-(2-Hydroxyethoxy)-24-nor-5β-cholan-12α-ol diazane-1,2-dicarboxylate cyclic diester 23

A phosgene cylinder with a gas outlet to an aq. ammonia reservoir was connected to a jacketed pressure-equalizing dropping funnel cooled to −78 °C. Condensed phosgene (10 cm^3) was added to stirred THF (20 cm^3). A solution of diol **19** (0.077 g, 0.197 mmol) in dry THF (10 cm^3) was added dropwise to the phosgene solution and the mixture was stirred at room temp. overnight. Excess of argon was bubbled through the reaction mixture and into the aq. ammonia reservoir until ~ 10 cm^3 of the reaction mixture containing bis(chloroformate) remained; $\nu_{max}(CHCl_3)/cm^{-1}$ 3670; δ_H(200 MHz; $CDCl_3$) 5.11 (1 H, t, *J* 2.0), 4.36 (3 H, t, *J* 4.0), 3.67 (2 H, m), 3.21 (1 H, m), 2.00–0.87 (24 H, m), 0.85 (3 H, s), 0.80 (3 H, d, *J* 8.0), 0.78 (3 H, t, *J* 6.0) and 0.65 (3 H, s).

The bis(chloroformate) thus generated (0.077 g, 0.194 mmol) was dissolved in dry THF (10 cm^3). The solution was cooled to −98 °C (MeOH/N_2) and a solution of hydrazine (0.007 g, 0.22 mmol) and triethylamine (112 mg, 1.1 mmol) in THF (1 cm^3) was added dropwise over a period of 30 min. The reaction mixture was allowed to warm to room temp. and stirring was continued overnight. 2% Aq. $NaHCO_3$ was added to the reaction mixture and the aqueous layer was extracted with diethyl ether (4 × 10 cm^3). The organic phase was dried ($MgSO_4$), and concentrated under reduced pressure and the residue was purified by MPLC [hexane–ethyl acetate (1:1)] to give *diazanedicarboxylate* **23** (0.040 g, 42%) as a crystalline solid (Found: C, 68.2; H, 9.6; N, 5.6. $C_{27}H_{44}N_2O_5$ requires C, 68.04; H, 9.30; N, 5.88%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3280 (NH) and 1725 (C=O); δ_H(200 MHz; $CDCl_3$) 6.66 (1 H, m), 6.45 (1 H, br s), 4.92 (1 H, m), 4.64 (1 H, m), 3.88 (2 H, m), 3.58 (2 H, m), 2.10–0.87 (24 H, m), 0.86 (3 H, s), 0.81 (3 H, d, *J* 6.0), 0.79 (3 H, t, *J* 6.0) and 0.71 (3 H, s); δ_C(75 MHz; $CDCl_3$) 10.41, 12.49, 17.39, 22.01, 23.26, 24.72, 25.98, 27.26, 28.13, 32.77, 33.22, 34.57, 34.96, 36.51, 40.64, 45.36, 47.10, 50.17, 61.75, 65.67, 75.08, 79.03, 154.93 and 155.74; *m/z* (FAB^+) 477 (MH^+).

3α-(3-Hydroxypropoxy)-24-nor-5β-cholan-12α-ol diazane-1,2-dicarboxylate cyclic diester 24

The above procedure with diol **20** (0.130 g, 0.32 mmol), triethylamine (1.79 g, 17.6 mmol) and hydrazine (0.115 g, 3.59 mmol) gave *diazanedicarboxylate* **24** (51 mg, 32%) as a crystalline solid, mp 135–137 °C (Found: C, 68.5; H, 9.7; N, 5.5. $C_{28}H_{46}N_2O_5$ requires C, 68.54; H, 9.45; N, 5.71%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3280 (NH) and 1725 (C=O); δ_H(400 MHz; $CDCl_3$) 6.63 (1 H, br s), 6.44 (1 H, br s), 4.89 (1 H, br s), 4.56 (1 H, br s), 4.05 (1 H, br s), 3.66 (2 H, m), 3.52 (2 H, m), 2.02 (2 H, m), 1.90–0.87 (23 H, m), 0.88 (3 H, s), 0.85 (3 H, d, *J* 6), 0.79 (3 H, t, *J* 6) and 0.72 (3 H, s); δ_C($CDCl_3$; 100 MHz) 10.34, 12.40, 17.39, 22.39, 23.37, 23.99, 24.16, 26.25, 26.46, 27.19, 28.12, 29.54, 30.92, 33.52, 35.00, 35.16, 36.37, 41.37, 45.32, 47.21, 49.90, 58.47, 62.23, 77.23, 79.10, 155.23 and 155.94; *m/z* (CI) 491 (MH^+).

3α-(2-Hydroxyethoxy)-24-nor-5β-cholan-7α-ol diazane-1,2-dicarboxylate cyclic diester 25

The above procedure with diol **21** (0.40 g, 1.02 mmol) and phosgene gave the bis(chloroformate); $\nu_{max}(CHCl_3)/cm^{-1}$ 3670; δ_H(200 MHz; $CDCl_3$) 4.94 (1 H, d, *J* 4), 4.42 (3 H, t, *J* 4), 3.74 (2 H, t, *J* 4), 3.19 (1 H, m), 2.3–0.95 (24 H, m), 0.94 (3 H, s), 0.89 (3 H, d, *J* 4.0), 0.84 (3 H, t, *J* 8) and 0.65 (3 H, s). Cyclization of this bis(chloroformate) (0.53 g, 1.02 mmol) by the above procedure with triethylamine (0.5 cm^3) and hydrazine (0.05 g, 1.56 mmol) gave *diazanedicarboxylate* **25** (0.301 g, 61%) as a crystalline solid, mp 254–256 °C (Found: C, 68.1; H, 9.45; N, 5.8. $C_{27}H_{44}N_2O_5$ requires C, 68.04; H, 9.30; N, 5.88%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3290 (NH) and 1730 (C=O); δ_H(300 MHz; $CDCl_3$) 6.71 (1 H, d, *J* 3.7), 6.31 (1 H, d, *J* 3.7), 5.09 (1 H, d, *J* 3.7), 4.40 (1 H, dd, *J* 7.3 and 3.7), 4.19 (1 H, td, *J* 7.3 and 3.7), 3.94 (1 H, td, *J* 7.3 and 3.7), 3.55 (1 H, dd, *J* 7.3 and 3.7), 3.30 (1 H, m), 2.01–0.94 (24 H, m), 0.93 (3 H, s), 0.91, (3 H, d, *J* 7.3), 0.82 (3 H, t, *J* 7.3) and 0.68 (3 H, s); δ_C(75 MHz; $CDCl_3$) 10.30, 11.64, 18.06, 20.63, 22.52, 23.61, 28.03, 28.12, 28.26, 32.33, 33.79, 34.58, 34.83, 34.91, 36.97, 38.13, 39.49, 40.31, 42.85, 50.69, 55.66, 61.94, 65.50, 73.83, 76.60, 155.88 and 155.98; *m/z* (FAB^+) 477 (MH^+).

3α-(3-Hydroxypropoxy)-24-nor-5β-cholan-7α-ol diazane-1,2-dicarboxylate cyclic diester 26

The above procedure with diol **22** (0.30 g, 0.74 mmol), hydrazine (0.026 g, 0.83 mmol) and triethylamine (0.42 g, 4.12 mmol) gave diazanedicarboxylate **26** (0.144 g, 40%) as a crystalline solid, mp 283–285 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3280 (NH) and 1725 (C=O); δ_H(300 MHz; $CDCl_3$) 6.64 (1 H, br s), 6.27 (1 H, br s), 5.12 (1 H, br s), 4.84 (1 H, t, *J* 8), 3.82 (1 H, d, *J* 8), 3.67 (1 H, t, *J* 8), 3.47 (1 H, br s), 3.25 (1 H, m), 2.1–0.87 (26 H, m), 0.89 (3 H, s), 0.88 (3 H, d, *J* 6), 0.80 (3 H, t, *J* 6) and 0.62 (3 H, s); δ_C(75 MHz; $CDCl_3$) 10.31, 11.60, 18.10, 20.49, 22.54, 23.76, 26.61, 28.04, 28.27, 29.57, 32.25, 33.53, 34.19, 34.61, 35.49, 36.95, 38.21, 39.49, 40.77, 42.86, 50.61, 55.55, 62.66, 64.29, 73.49, 78.07, 156.43 and 156.54; *m/z* (FAB^+) 491 (MH^+).

NBS oxidation of 3α-(2-hydroxyethoxy)-24-nor-5β-cholan-7α-ol diazane-1,2-dicarboxylate cyclic diester 25

To a solution of diazanedicarboxylate **25** (0.016 g, 34 μmol) in CH_2Cl_2 (1 cm^3) was added pyridine (4 mm^3, 50 μmol) and the mixture was cooled to 0 °C under Ar. NBS (0.010 g, 58 μmol) was added and the solution immediately turned yellow. The reaction mixture was stirred at room temp. for 20 min. Water (2 cm^3) was added and the organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow oil. ^1H NMR analysis suggested that both product and starting material were present. Purification by flash chromatography [hexane–ethyl acetate (7:3)] gave two minor products, **A** (0.5 mg) and **B** (0.5 mg) and the starting diazanedicarboxyl-

ate **25** (9 mg recovery) which was characterized as above. The yellow material remained bound to the silica gel. Compound **B** was characterized as being the aldehyde **29** which had eliminated nitrogen and carbon monoxide from the diazenedicarboxylate **27**; $\nu_{max}(CHCl_3)/cm^{-1}$ 3439 (OH) and 1719 (C=O); δ_H(360 MHz; $CDCl_3$) 8.07 (1 H, s), 5.09 (1 H, br s), 3.70 (2 H, m), 3.57 (2 H, m), 3.15 (1 H, m), 2.01–0.94 (24 H, m), 0.93 (3 H, s), 0.91 (3 H, d, *J* 6.5), 0.81 (3 H, t, *J* 7.3) and 0.64 (3 H, s); *m/z* (CI-NH_3) 438 (MNH_4^+).

Although not fully characterized, compound **A** also appeared to have eliminated both nitrogen and carbon monoxide.

General procedure for ^{1}H NMR study of the oxidation of diazanedicarboxylate esters

The ^{1}H NMR spectrum of a solution of diazanedicarboxylate **25** (3 mg, 6.3 μmol) in CD_2Cl_2 (0.5 cm^3) containing pyridine (0.5 mm^3, 6.3 μmol) was recorded: δ_H(300 MHz; CD_2Cl_2) 7.12 (1 H, d, *J* 2.6), 6.45 (1 H, d, *J* 2.6), 5.01 (1 H, d, *J* 2.6), 4.37 (1 H, dd, *J* 2.6 and 12.1), 4.14 (1 H, td, *J* 12.2 and 2.6), 3.86 (1 H, td, *J* 12.2 and 3.5), 3.52 (1 H, dd, *J* 12.1 and 3.3), 3.28 (1 H, m), 2.01–0.94 (24 H, m), 0.91 (3 H, s), 0.91 (3 H, d, *J* 6.5), 0.82 (3 H, t, *J* 7.3) and 0.66 (3 H, s). NBS (1.1 mg, 6.3 μmol) was added and the clear solution immediately turned yellow as diazenedicarboxylate **27** was formed: δ_H(300 MHz; CD_2Cl_2) 5.11 (1 H, q, *J* 2.7), 4.42 (1 H, ddd, *J* 11.4, 3.6 and 1.7), 4.33 (1 H, ddd, *J* 11.4, 10.3 and 3.3), 3.92 (1 H, ddd, *J* 12.9, 3.4 and 1.7), 3.61 (1 H, ddd, *J* 12.9, 10.2 and 3.7), 3.21 (1 H, m), 2.06–0.94 (24 H, m), 0.91 (3 H, s), 0.91, (3 H, d, *J* 6.4), 0.83 (3 H, t, *J* 7.3) and 0.69 (3 H, s). On addition of NBS a downfield shift of the pyridine peaks was observed, from δ 8.58 (2 H, m), 7.68 (1 H, tt, *J* 7.7 and 1.9) and 7.28 (2 H, ddd, *J* 7.7, 4.3 and 1.5) to δ 8.66 (2 H, d, *J* 4.7), 7.96 (1 H, m) and 7.53 (2 H, t, *J* 5.9); formation of succinimide [δ 2.72 (4 H, s)] was also observed. The latter remained unchanged throughout the reaction. After 45 min, formation of the starting diazanedicarboxylate **25** became detectable and after a period of 4 days no diazenedicarboxylate remained.

3α-(3-Hydroxypropoxy)-24-nor-5β-cholan-7α-ol diazenedicarboxylate cyclic diester 28. δ_H(300 MHz; CD_2Cl_2) 5.12 (1 H, q, *J* 2.7), 4.48 (1 H, dt, *J* 10.5 and 6.8), 4.38 (1 H, dt, *J* 10.5 and 7.1), 3.58 (2 H, m), 3.07 (1 H, m), 2.07–0.95 (26 H, m), 0.92 (3 H, s), 0.91 (3 H, d, *J* 6.5), 0.82 (3 H, t, *J* 7.3) and 0.69 (3 H, s).

Trapping of diazenedicarboxylate 27 with cyclopentadiene

To a solution of diazanedicarboxylate **25** (5 mg, 10.5 μmol) in CD_2Cl_2 (0.5 cm^3) and pyridine (0.8 mm^3, 10.5 μmol) was added NBS (1.9 mg, 10.5 μmol). The clear solution immediately turned yellow, indicating formation of diazenedicarboxylate **27**. Cyclopentadiene (1.5 mm^3, 23 μmol) was added and the solution immediately went colourless. Purification by flash chromatography [hexane–ethyl acetate (2:3)] gave the two pure *Diels–Alder adducts*, **30a** (1.7 mg, 30%) and **30b** (0.5 mg, 10%), and a mixture of adducts (2.6 mg, 46%) (Found: M^+, 540.3565. $C_{32}H_{48}N_2O_5$ requires M, 540.3563); $\nu_{max}(CHCl_3)/cm^{-1}$ 1702 (C=O); adduct **30a**: δ_H(300 MHz; $CDCl_3$) 6.69 (1 H, m), 6.41 (1 H, m), 5.42 (1 H, m), 5.05 (1 H, d, *J* 1.6), 4.94 (1 H, m), 4.75 (1 H, br m), 3.83 (1 H, br m), 3.67 (1 H, m), 3.64 (1 H, m), 3.39 (1 H, m), 1.96 (2 H, m), 1.76 (4 H, m), 1.70–0.92 (20 H, m), 0.90 (3 H, d, *J* 6.3), 0.88 (3 H, s), 0.80 (3 H, t, *J* 7.3) and 0.63 (3 H, s); adduct **30b**: δ_H(300 MHz; $CDCl_3$) 6.66 (1 H, dt, *J* 5.3 and 1.5), 6.30 (1 H, ddd, *J* 5.5, 3.1 and 1.5), 5.41 (1 H, dd, *J* 2.8 and 1.4), 5.05 (1 H, q, *J* 1.6), 4.80 (2 H, m), 3.93 (1 H, ddd, *J* 14.0, 9.4 and 1.4), 3.84 (1 H, dm, *J* 14.0), 3.67 (1 H, ddd, *J* 15.0, 1.6 and 1.4), 3.40 (1 H, m), 2.20–0.90 (26 H, m), 0.88 (3 H, d, *J* 6.5), 0.86 (3 H, s), 0.81 (3 H, t, *J* 7.4) and 0.60 (3 H, s); *m/z* (EI) 540 (M^+), 496 ($M^+ - CO_2$, 9%), 481 ($M^+ - CO_2 - CH_3$, 15), 430 ($M^+ - CO_2 - C_5H_6$, 16), 415 (481 $- C_5H_6$, 17) and 312 ($C_{23}H_{36}$, 37); *m/z* (CI-NH_3) 558 (MNH_4^+) and 541 (MH^+).

Crystal data for compound 26

Data were acquired on a Rigaku AFC6R diffractometer with a rotating anode generator (12 kW). All intensity measurements were performed using graphite-monochromated Mo-Kα radiation (λ = 0.710 69 Å). Diazanedicarboxylate **26** ($C_{28}H_{46}N_2O_5$) was obtained as monoclinic crystals, $P2_1$, a = 11.700(2), b = 8.316(4), c = 14.444(3) Å, β = 108.01(1)°, V = 1336.4(6) $Å^3$, Z = 2, T = 296 K, D_c = 1.219 g cm^{-3}, μ = 0.77 cm^{-1}. A total of 2669 reflections were collected (2540 unique, R_{int} = 0.028). Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient 0.20747E-05). The structure was solved by direct methods. The final cycle of full-matrix least-squares refinement was based on 1922 observed reflections [$I > 2.00\ \sigma(I)$] and 324 variable parameters, and converged with weighted and unweighted agreement factors R = 0.036 and R_w = 0.040 with a goodness-of-fit indicator of 1.67. Full details as well as atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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