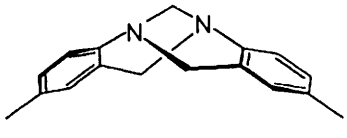
# Asymmetric synthesis of steroidal Tröger's base analogues. X-Ray molecular structure of methyl 3α,12α-{6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-2,8-bisacetoxy}-5β-cholan-24-oate †

**Uday Maitra,*[a] Braja Gopal Bag,[a] Photon Rao[a] and Douglas Powell‡[b]**
[a] *Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India*
[b] *Department of Chemistry, University of Wisconsin, Madison, WI 53706, USA*

Cyclization of compound **5c** in trifluoroacetic acid/hexamethylenetetramine produces Tröger's base analogue **6c** in 75% yield with 70% diastereoselectivity.

## Introduction

First synthesized by Julius Tröger in 1887 from *p*-toluidine and formaldehyde, the unique structure of Tröger's base[1] **1** and its mechanism of formation has attracted the attention of organic chemists during the past six decades. The correct structure of Tröger's base was first proposed by Spielman in 1935.[2] Subsequently, Prelog and Wieland successfully resolved compound **1** using chiral column chromatography.[3] The absolute configuration of the (+)-enantiomer was proposed to be *S*,*S* by Cervinka.[4] This was revised to *R*,*R* by Mason *et al.*, through circular dichroism (CD) analysis,[5] which recently has been corrected to *S*,*S* by Wilen *et al.*, through the X-ray analysis of a diastereoisomeric salt.[6] The mechanism of formation of this base has been investigated by Wagner,[7] and by Farrer.[8] The rigid, sharply folded, V-shaped geometry of Tröger's base has made this molecule attractive in the design of molecular receptors, chiral solvating agents and inclusion complexes. Wilcox and co-workers have elegantly used this as a structural module in the construction of cyclic as well as acyclic molecular receptors.[9] Wilen *et al.* have reported the use of Tröger's base **1** as a chiral solvating agent.[6] Quaternized Tröger's base salts have been shown to form inclusion complexes with aliphatic and aromatic solvents by Weber *et al.*,[10] and by Bond and Scott.[11] A recent paper has described a phenanthroline-derived Tröger's base analogue which interacts with DNA.[12] Heterocycle-substituted Tröger's base analogues have recently been synthesized.[13]



**1**

Even though compound **1** has been resolved *via* a second-order asymmetric transformation,[6] a general asymmetric synthesis of the chiral methanodibenzodiazocine unit was not known at the time this work was initiated.§ We recently reported the first asymmetric synthesis of a *symmetrical* Tröger's base analogue (**8a**/**9a** from diamine **5a**) in moderate chemical and optical yields by using 7-deoxycholic acid as a chiral template.[14] Since the C-3 and the C-12 hydroxy groups have different reactivities (3 ≫ 12),[15] it was apparent that these two handles could be utilized to synthesize *unsymmetrical* Tröger's base analogues as well.¶ During this work we have been able to improve significantly the diastereoselectivity in the cyclization through fine tuning of the spacer lengths which link the two aniline fragments to the steroid. Five new Tröger's base analogues have been synthesized by systematic variation of the spacer lengths. We have also carried out X-ray structural analysis of a previously synthesized steroidal Tröger's base analogue.

## Results and discussion

As shown in Scheme 1, the precursors (**4c–4f**) of *unsymmetrical* Tröger's base analogues were easily synthesized in two steps starting from methyl 7-deoxycholate **2**. Selective esterification of the 3-hydroxy group to give mono(*p*-nitroarylalkanoyl) deviatives **3a-3c** was accomplished by stirring methyl deoxycholate at low temp. with the appropriate acid chloride in toluene in the presence of pyridine. Oppenauer esterification[16].‖ was used for the subsequent acylation of the hindered 12-hydroxy group, as well as for the synthesis of the precursors for symmetrical (**4a, 4b**) Tröger's base analogues. Reduction with $SnCl_2 \cdot 2H_2O$[17] allowed a clean conversion into the corresponding bis-anilines **5** ready for cyclization.

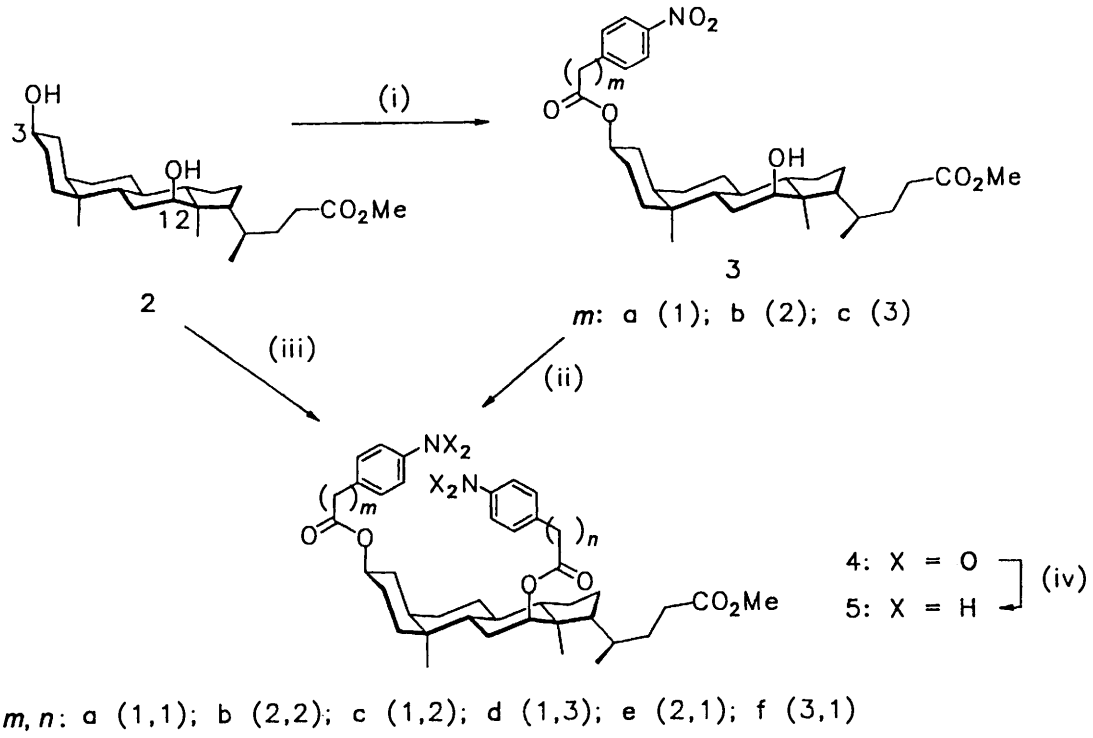
The cyclization of the steroidal bis-anilines **5** has been investigated under two different cyclization conditions, (i) in trifluoroacetic acid (TFA) in the presence of hexamethylenetetramine[9c] ('TFA/HMT') and (ii) using our own[14] reagent system of dimethoxymethane–methanesulfonic acid ('DMM/MsOH') (Scheme 2). In all cases the reaction products were analysed by high-field NMR spectroscopy to determine the ratio of the two diastereoisomers from the integrated intensities of steroidal 12-H. When ≥ 10% selectivity was observed by NMR spectroscopy, the diastereoisomeric mixtures were reduced with lithium aluminium hydride (LAH) to detach the steroidal unit and then were acetylated. The isolated Tröger's base analogues were characterized using a combination of spectroscopic techniques, and the enantiomeric excess (ee)/absolute configurations were established from the optical rotation and CD data.[14]

It is interesting to note from Table 1 that the symmetrically substituted esters **5a** and **5b** did not show any significant

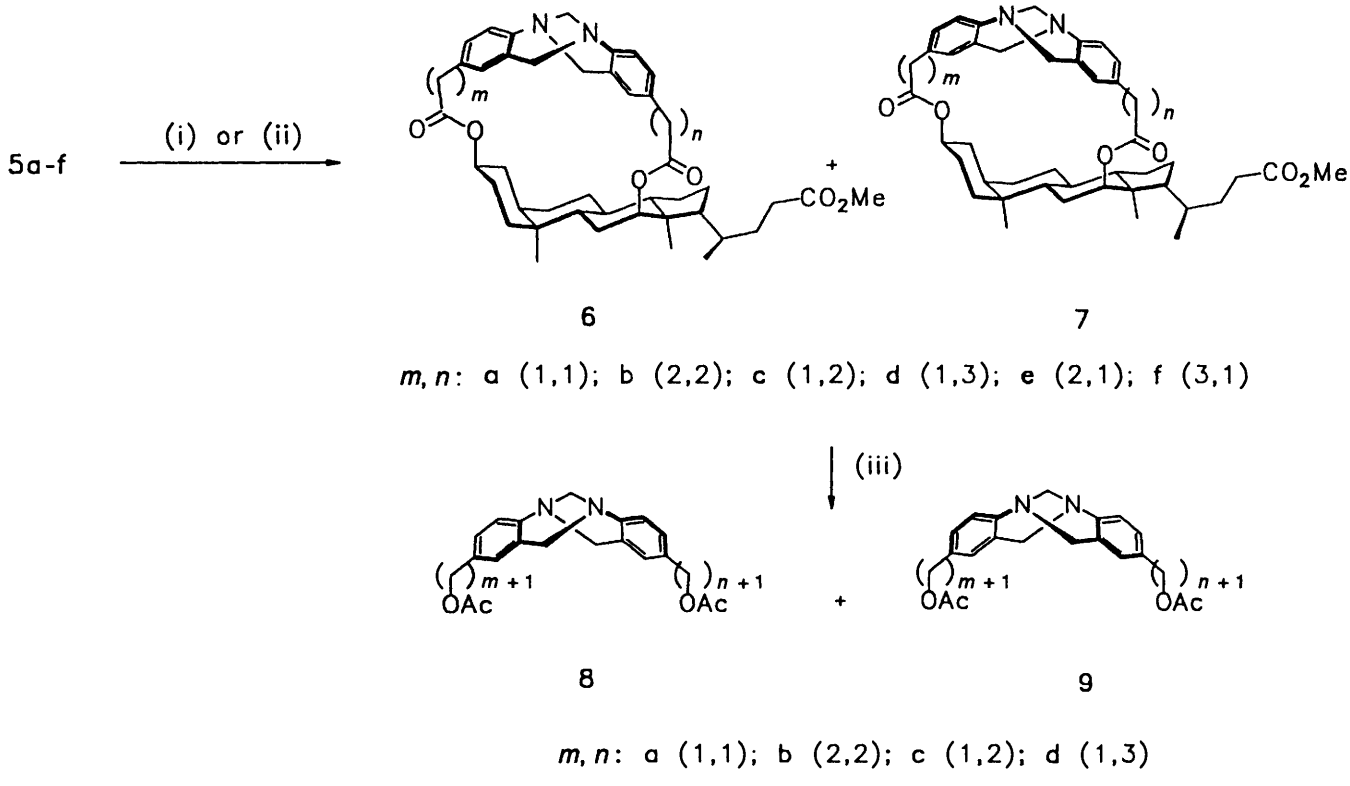
† Bile Acids in Asymmetric Synthesis, Part 5. For Part 4, see ref. 24.
‡ Author to whom correspondence regarding crystal structure analysis should be sent.
§ See ref. 14, footnote 5.

¶ The Tröger's base analogues with non-identical substituents at the C-2 and C-8 positions are termed *unsymmetrical*.

‖ $PhCH_2\overset{+}{N}Et_3\ Cl^-$ was used instead of $Bu_4N^+\ I^-$.




**Scheme 1** *Reagents and conditions:* i, $Ar[CH_2]_mCOCl$, pyr., toluene, −5 °C; ii, $Ar[CH_2]_nCOCl$, $CaH_2$, toluene, $BnEt_3\overset{+}{N}Cl^-$, 80 °C; iii, $Ar[CH_2]_mCOCl$, $CaH_2$, toluene, $BnEt_3\overset{+}{N}Cl^-$, 80 °C; iv, $SnCl_2{\cdot}2H_2O$, EtOAc, 70 °C




**Scheme 2** *Reagents and conditions:* i, TFA, HMT, 70 °C; ii, DMM, MsOH, reflux; iii, $LiAlH_4$, THF, reflux; then $Ac_2O$, pyr., room temp.

stereoselectivity in the cyclization under TFA–HMT conditions. However, elongation of the 12-substituent by one carbon (**5c**) led to the formation of the *S,S* stereoisomer in 75% yield and with 70% diastereoselectivity (**6c** in excess). Elongation by one more carbon (compound **5d**), on the other hand, led to a *reversal* of the selectivity (10% in favour of the *R,R* diastereoisomer **7d**). A similar pattern emerges from an examination of entries 5 and 6 as well. Increasing the chain length from C-3 by one carbon (**5e**) yielded *R,R*-diastereoisomer **7e** with 22% de, but the two-carbon elongated precursor (**5f**)

**Table 1** Cyclization of compounds **5a–5f** with TFA–HMT

| Entry | Compound | Yield (%) | Product | Product (cleaved) | Product ratio |
|---|---|---|---|---|---|
| 1 | **5a** | 77 | **6a/7a** | **8a/9a** | ~50:50 |
| 2 | **5b** | 56 | **6b/7b** | **8b/9b** | ~50:50 |
| 3 | **5c** | 77 | **6c/7c** | **8c/9c** | 85:15 |
| 4 | **5d** | 40 | **6d/7d** | **8d/9d** | 45:55 |
| 5 | **5e** | 41 | **6e/7e** | **8c/9c** | 44:56 |
| 6 | **5f** | 33 | **6f/7f** | **8d/9d** | 63:37 |

**Table 2** Cyclization in DMM–MsOH

| Entry | Compound | Yield (%) | Product | Product (cleaved) | Product ratio |
|---|---|---|---|---|---|
| 1 | **5a** | 25–35 | **6a/7a** | **8a/9a** | 70:30 |
| 2 | **5b** | 14 | **6b/7b** | **8b/9b** | 75:25 |
| 3 | **5c** | 25–50 | **6c/7c** | **8c/9c** | 70:30 to 85:15 |

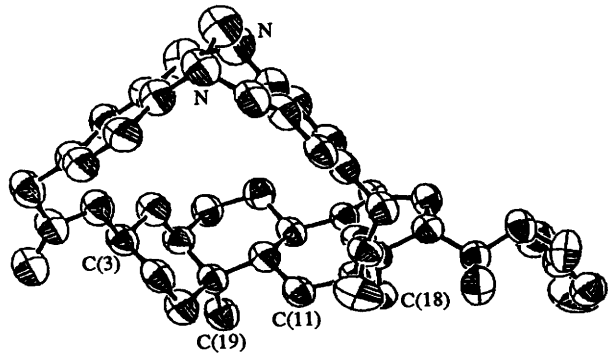



**Fig. 1** ORTEP diagram of compound **7a**

gave *S,S*-diastereoisomer **6f** with 26% de. This switching of the selectivities with increase in the carbon chain length is possibly related to the general odd/even effect observed elsewhere.[18]

Under DMM–MsOH-mediated cyclization conditions the yields were low to moderate, and reproducibility difficult to achieve. However, as Table 2 shows, the results of cyclizations under these conditions revealed that both compound **5a**[14] as well as the bis(propionate) analogue **5b** cyclized to yield the *S,S*-diastereoisomer with 40–50% selectivity. The cyclization of compound **5c**, on the other hand, resulted in variable yields and variable stereoselectivities.

## X-Ray structural analysis

In our previous study,[14] we were able to isolate compound **7a** (the minor diastereoisomer formed in the cyclization) in analytically pure form by careful crystallization. X-Ray structural analysis of a single crystal has been carried out, which confirmed our earlier stereochemical assignment (*R,R* at nitrogen). An ORTEP diagram is shown in Fig. 1. The bond distances and angles are in good agreement with expected values for dibenzodiazocine and methyl deoxycholate groups.

The phenyl rings of the Tröger's base moiety are approximately at right angles to each other. The dihedral angles between the phenyl rings in compounds with Tröger's base groups show a great deal of flexibility, lying in the range 79.0–104.0 °.[10,11,19] The deoxycholate group of the compound reported here places the dihedral angle of the dibenzodiazocine group in the middle of this range with a value of 88.9(4) °. The N–$CH_2$–N angle for compound **7a** is 111.9(5) °. The same angle in similar neutral Tröger's base compounds ranges from 110.2 to 112.6 °.[10,11,19] For Tröger's base compounds with one quaternary nitrogen the methylene group bridging the nitrogens has angles of 109.3 and 109.5 °.[6,10]

The rings of the deoxycholate group have the same conformation as seen in 3α,12α-diacetoxycholan-24-oic acid methyl ester and methyl deoxycholate methanol clathrate.[20] The hydrophobic region of the deoxycholate group is on the outside of the molecule. The long side-chain at C(17) is in an equatorial position extending away from the rest of the molecule. The side chain was disordered. The molecules pack with pairs of molecules extending their long side-chains towards each other. The polar N–$CH_2$–N bridgeheads of the dibenzodiazocine groups of two other molecules are near the polar regions of the pair of side chains.

## Conclusions

We have developed an efficient methodology to construct both symmetrical and unsymmetrical Tröger's base analogues using deoxycholic acid as a chiral template. Our systematic alteration of the spacer lengths has provided a precursor (**5c**) which cyclized under TFA–HMT conditions to give the unsymmetrical product in high chemical and optical yields. Furthermore, this work illustrates that optimum geometric control, and not merely a short distance between the existing and the newly formed stereogenic centres, is responsible for the observed stereoselectivity. *It is to be noted that the template method is the only efficient procedure to synthesize unsymmetrical analogues.* Attempts to reverse the stereoselectivity through structural modifications in precursor diamines **5a** and **5b** are in progress. We believe that further work on the molecular design of suitable precursors of bile acid derivatives will lead to the application of this class of compounds to other facets of template-mediated asymmetric synthesis.

## Experimental

### General comments

All reactions were conducted under dry nitrogen and mixtures were stirred magnetically unless otherwise stated. When anhydrous conditions were required, the glassware was heated under high vacuum and then filled with dry nitrogen while cooling. Reaction temperatures refer to external or bath temperatures, unless indicated otherwise. Analytical TLC was performed on precoated (0.25 mm) silica gel 60F-254 plates purchased from E. Merck. Visualization was done under UV (254 nm) radiation or by dipping the plates in 5% ethanolic

phosphomolybdic acid solution and heating. Columns for chromatography were made from 100–200 mesh silica gel. All solvents were purified and distilled before use. Toluene and THF were distilled from sodium/benzophenone ketyl. Methanol and acetic anhydride were distilled from magnesium methoxide and phosphorus pentaoxide, respectively. Pyridine and triethylamine were stored over KOH and distilled from $CaH_2$. Thionyl dichloride was distilled before use. Mps were recorded in open capillaries and are uncorrected. Optical rotations were measured at 589 nm in a 0.2 $cm^3$ cell at the specified temperature on a JASCO DIP-370 polarimeter, and $[\alpha]_D$-values are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. IR spectra were recorded on a Hitachi 270-50 spectrophotometer using NaCl cells, and are reported in $cm^{-1}$. NMR spectra were recorded on a JEOL FX-90Q (90 MHz), or on 200, 270 and 400 MHz Bruker instruments for $CDCl_3$ solutions with $SiMe_4$ as the internal standard. Chemical shifts are reported in $\delta$ values and coupling constants in Hz.

### Crystal structure analysis

**Crystal data for compound 7a.** $C_{44}H_{56}N_2O_6$, M = 708.91. Orthorhombic, $a$ = 8.708(2), $b$ = 15.502(2), $c$ = 28.398(3) Å, $V$ = 3833.5(11) Å$^3$ (by least-squares refinement of diffractometer angles for 15 centred peaks in the range $22 < 2\theta < 33°$, 243 K, Cu–K$\alpha$ radiation, $\lambda$ = 1.541 78 Å), space group $P2_12_12_1$, $Z$ = 4, $D_x$ = 1.228 g $cm^{-3}$, $F$(000) = 1528. Prisms, crystal dimensions 0.4 × 0.3 × 0.3 mm, $\mu$(Cu–K$\alpha$) = 0.643 $mm^{-1}$.

**Data collection and processing.** Siemens P4 diffractometer on a rotating-anode source with graphite-monochromatized Cu-K$\alpha$ radiation was used for all measurements. All data in the range $4 \leqslant 2\theta \leqslant 114°$, $+h$ $+k$ $+l$ and Friedel-related data were collected using $\omega$-scan method with scan speeds between 3 and 60° $min^{-1}$ in a scan range of 1.60°. Of the 6213 data collected, 5161 were unique [$R$(int) = 0.0265] and used in refinement. Data were corrected for Lorentz and polarization effects but not absorption. Three standard peaks which were remeasured after every 100 data showed only statistical fluctuations.

**Structural analysis and refinement.** The structure was solved by direct methods using the program SHELXS86.[21] The coordinates and anisotropic thermal parameters for the non-hydrogen atoms were refined by a full-matrix least-squares procedure based on $F^2$ with weights $w = 1/[\sigma^2(F_o^2) + (0.1693* P)^2 + 3.10* P]$, $P = [\mathrm{Max}(F_o^2, 0) + 2* F_c^2]/3$.[22] The positions of the hydrogen atoms were initially calculated and refined assuming a riding model; hydrogen thermal parameters were assigned values of 1.2* $U_{eq}$(C). A secondary extinction correction was applied [coefficient = 0.0150(13)]. At convergence, $R1$ = 0.0885 for [$I > 2\sigma(I)$], $wR2$ = 0.2556 (for all data), $S$ = 1.035, data/parameter = 10.96, max shift/esd = 0.032, residual electron density −0.369 to 0.409 e Å$^{-3}$. The Flack enantiopole [0.4(6)] could not be used to determine uniquely the handedness of the molecule. Complex, neutral atom-scattering factors were taken from ref. 23. All calculations were carried out on a Silicon Graphics Indigo computer.**

### Methyl 12α-hydroxy-3α-[(4-nitrophenyl)acetoxy]-5β-cholan-24-oate 3a

*p*-Nitrophenylacetic acid (0.101 g, 0.56 mmol) was heated with thionyl dichloride (1.5 $cm^3$, 21 mmol) at 45–52 °C for 12 h. Volatiles were removed under reduced pressure. The crude acid chloride and methyl 7-deoxycholate (0.194 g, 0.47 mmol) were dissolved in dry toluene (6 $cm^3$), placed in a cold bath (−4.2 °C), stirred with pyridine (0.072 g, 0.91 mmol) at this temperature for 17 h, and diluted with a mixture of distilled water (10 $cm^3$) and ethyl acetate (50 $cm^3$). The organic layer was separated, and washed successively with 7% aq. $NaHCO_3$ (20 $cm^3$ × 3) and 25% aq. NaCl and dried over anhydrous $Na_2SO_4$. Volatiles were removed under reduced pressure and the crude product was purified column chromatography (Si-gel, 100–200 mesh; 12 g; 20.4 cm × 1.4 cm). Elution with 2–3% of EtOAc–$CHCl_3$ yielded the title product (0.19 g, 70%), $R_f$ 0.34 [(5%) EtOAc–$CHCl_3$]; $\delta_H$(90 MHz; $CDCl_3$) 8.7 (2 H, d, $J$ 8.4), 7.44 (2 H, d, $J$ 8.4), 4.74 (1 H, br m, $w_{\frac{1}{2}}$ 17.9), 3.9 (1 H, br s), 3.69 (3 H, s), 2.44–1.06 (br m), 1.1 (3 H, d, $J$ 6.4), 0.94 (3 H, s) and 0.69 (3 H, s); $\delta_C$(22.5 MHz; $CDCl_3$) 174.7, 169.7, 147.0, 141.7, 130.2, 123.6, 75.4, 72.9, 51.5, 48.2, 47.2, 46.5, 41.8, 41.4, 35.9, 35.1, 34.8, 34.0, 33.6, 32.1, 30.9, 28.7, 27.4, 26.9, 26.4, 26.0, 23.6, 23.1, 17.2 and 12.7; $\nu_{max}$(neat)/$cm^{-1}$ 3484w, 2866s, 1923w, 1725s, 1605m, 1515s, 1449s, 1347s, 1218s, 1089m and 1017m; $[\alpha]_D$ = +43.3 ($c$ 1.64, $CHCl_3$).

### Methyl 12α-hydroxy-3α-[3-(4-nitrophenyl)propanoyloxy]-5β-cholan-24-oate 3b

This was synthesized in a similar manner to its lower homologue **3a** in 40% isolated yield; $\delta_H$(90 MHz; $CDCl_3$) 8.2 (2 H, d, $J$ 9.6), 7.4 (2 H, d, $J$ 9.6), 4.7 (br m), 4.0 (br s), 3.7 (3 H, s), 3.0 (2 H, d, $J$ 6.9), 2.7 (2 H, d, $J$ 6.9), 2.2 (m), 0.8–2.0 (br m), 1.0 (s) and 0.7 (s); $\delta_C$(22.5 MHz; $CDCl_3$) 174.6, 171.6, 148.3, 129.2, 123.6, 77.1, 74.7, 51.5, 48.3, 47.3, 46.5, 41.8, 36.0, 35.4, 35.0, 34.8, 34.0, 33.6, 32.1, 31.0, 28.7, 27.4, 26.9, 26.4, 26.0, 23.6, 23.0, 17.4 and 12.7; $\nu_{max}$(neat)/$cm^{-1}$ 3490m, 2866s, 1719s, 1602m, 1515m, 1446m, 1344s, 1170s, 1092m, 1017, 849, 747 and 693; $m/z$ (CI) 566 [($M^+$ − 18, 0.6%)], 548 (2.7) and 255 (100).

### Methyl 12α-hydroxy-3-[4-(4-nitrophenyl)butanoyloxy]-5β-cholan-24-oate 3c

This was synthesized in a similar way in 40% isolated yield; $\delta_H$(90 MHz; $CDCl_3$) 8.2 (2 H, d, $J$ 8.4), 7.3 (2 H, d, $J$ 8.4), 4.6 (1 H, br s), 4.0 (1 H, br s), 3.65 (3 H, s), 2.75 (2 H, t, $J$ 7.2), 2.2–2.5 (4 H, m), 1.1–2.1 (br m), 1.0 (6 H, s) and 0.7 (3 H, s); $\delta_C$(22.5 MHz; $CDCl_3$) 174.6, 172.5, 149.4, 129.3, 123.6, 77.0, 74.4, 51.5, 48.3, 47.3, 46.5, 41.8, 36.0, 35.0, 34.1, 33.6, 32.2, 31.0, 28.7, 27.4, 26.9, 26.5, 26.0, 23.6, 23.1, 17.4 and 12.7; $\nu_{max}$(neat)/$cm^{-1}$ 3460m, 2860s, 1722s, 1602m, 1512m, 1446m, 1344s, 1182s, 1017, 849, 732 and 696; $m/z$ (CI) 580 [($M^+$ − 17, 0.4%)], 579 (0.6), 568 (0.4), 567 (0.9), 544 (10.0) and 255 (100).

### Methyl 3α,12α-bis-[3-(4-nitrophenyl)propanoyloxy]-5β-cholan-24-oate 4b

3-(*p*-Nitrophenyl)propanoyl chloride (0.964 g, 4.51 mmol) was prepared from the corresponding acid by heating it with freshly distilled thionyl dichloride at 47–57 °C for 12.25 h. Volatiles were removed and the residue was mixed with methyl deoxycholate (0.768 g, 1.88 mmol), toluene (8 $cm^3$), calcium hydride (0.51 g, 12.11 mmol) and benzyltriethylammonium chloride (0.069 g, 0.25 mmol). The magnetically stirred mixture was heated at 86–93 °C for 7 h before being cooled to room temperature, diluted with ethyl acetate (30 $cm^3$) and filtered through a Celite bed; washing of the residue was done by ethyl acetate (10 $cm^3$ × 3). The combined filtrate was washed successively with 10% aq. $NaHCO_3$ (20 $cm^3$ × 4) and brine (20 $cm^3$ × 2) and dried over anhydrous sodium sulfate. Volatiles were removed under reduced pressure and the crude product was purified by column chromatography (silica gel, 100–200 mesh; 45 g, 27.8 cm long) with 1–3% EtOAc–$CHCl_3$ to give the title product (1.07 g, 75%). This was crystallized from a mixture of ethanol and ethyl acetate and had mp 120–122 °C; $R_f$ 0.33 [(2%) EtOAc–$CHCl_3$]; $\delta_H$(200 MHz; $CDCl_3$) 8.14 (2 H, d, $J$ 8.6), 8.14 (2 H, d, $J$ 8.7), 7.41 (2 H, d, $J$ 8.7), 7.35 (2 H, d, $J$ 8.7), 5.08 (1 H, s), 4.68 (1 H, br m, $w_{\frac{1}{2}}$ 16), 3.66 (3 H, s), 3.08 (2 H, t, $J$

** *Supplementary publication* (see Instructions for Authors, January issue): Tables of atomic coordinates, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Centre.

7.5), 3.04 (2 H, t, *J* 7.5), 2.74 (2 H, t, *J* 7.2), 2.63 (2 H, t, *J* 7.5), 2.37–2.03 (m), 1.97–0.8 (m), 0.88 (3 H, s), 0.69 (3 H, s) and 0.66 (3 H, d, *J* 6.1); $\delta_C$($CDCl_3$; 50 MHz) 174.3, 171.4, 171.1, 148.1, 146.3, 128.9, 123.4, 58.1, 51.3, 49.1, 47.3, 44.7, 41.4, 35.3, 35.0, 34.8, 34.4, 34.1, 33.7, 31.9, 30.4, 27.1, 26.5, 25.6, 25.3, 23.1, 22.7, 18.1, 17.1 and 12.0; $\nu_{max}$(neat)/$cm^{-1}$ 2920s, 1728s, 1602m, 1515s, 1449m, 1380m, 1344s, 1254s, 1176s, 1107m and 1014m; $[\alpha]_D^{23}$ + 56.9 (*c* 1.58, $CHCl_3$); *m/z* (FAB neg. ion) 760 ($M^+$, 100%).

**Methyl 3α-[(4-nitrophenyl)acetoxy]-12α-[3-(4-nitrophenyl)-propanoyloxy]-5β-cholan-24-oate 4c**

3-(4-Nitrophenyl)propanoic acid was heated with an excess (10 mol equiv.) of thionyl dichloride at 52–53 °C for 12 h. Volatiles were removed under reduced pressure and the crude acid chloride (0.337 g, 1.58 mmol) and compound **3a** (0.69 g, 1.21 mmol) were dissolved in dry toluene (5 $cm^3$). Calcium hydride (0.56 g, 13.3 mmol) and benzyltriethylammonium chloride (0.052 g, 0.19 mmol) were added. The mixture was initially stirred at room temp. for 5 min and then it was heated in an oil-bath at 100 °C for 15.5 h. The reaction mixture was cooled to room temp., diluted with chloroform (50 $cm^3$), and filtered through a Celite bed. The filtrate was washed successively with 7% aq. $NaHCO_3$ (20 $cm^3$ × 2) and 25% aq. NaCl (20 $cm^3$ × 2) and dried over anhydrous $Na_2SO_4$. Volatiles were removed under reduced pressure and the crude product was purified by column chromatography (silica gel, 100–200 mesh; 24 g; 19.7 cm × 2 cm) with 10–20% of ethyl acetate–hexanes as the eluent. The title product was isolated (0.82 g, 90%) and was crystallized from a mixture of EtOH and EtOAc to give *needle-shaped crystals*, mp 94–97 °C; $R_f$ 0.24 ($CHCl_3$); $\delta_H$(200 MHz; $CDCl_3$) 8.17 (2 H, d, *J* 8.8), 8.16 (2 H, d, *J* 8.8), 7.45 (2 H, d, *J* 8.6), 7.41 (2 H, d, *J* 8.7), 5.08 (1 H, s), 4.73 (1 H, br m, $w_{\frac{1}{2}}$ 22), 3.71 (2 H, s), 3.67 (3 H, s), 3.09 (2 H, t, *J* 7.1), 2.75 (2 H, t, *J* 7.1), 2.35–2.04 (m), 1.9–1.0 (br m), 0.89 (3 H, s), 0.69 (3 H, s) and 0.65 (3 H, d, *J* 6.1); $\delta_C$(100 MHz; $CDCl_3$) 174.5, 171.3, 169.6, 148.5, 147.1, 146.6, 141.7, 130.3, 129.3, 123.7, 123.6, 76.4, 75.3, 51.5, 49.3, 47.6, 45.0, 41.8, 41.2, 35.6, 34.9, 34.7, 34.4, 34.0, 32.1, 30.9, 30.5, 27.4, 26.8, 26.6, 25.8, 25.6, 23.4, 23.0, 17.4 and 12.3; $\nu_{max}$(neat)/$cm^{-1}$ 2920s, 1728s, 1605m, 1515s, 1449s, 1380s, 1344s, 1254s, 1221s, 1164s, 1107m and 1008m; $[\alpha]_D^{23}$ + 71.4 (*c* 1.57, $CHCl_3$); *m/z* (FAB neg. ion) 746 ($M^+$, 100%) (Found: C, 67.4; H, 7.4; N, 3.35. $C_{42}H_{54}N_2O_6$ requires C, 67.54;H, 7.29, N, 3.75%).

**Methyl 3α-[(4-nitrophenyl)acetoxy]-12α-[4-(4-nitrophenyl)-butanoyloxy]-5β-cholan-24-oate 4d**

Compound **4d** was synthesized from the alcohol **3a** in a similar manner to its lower homologue **4c** in 68% isolated yield; $\delta_H$(90 MHz; $CDCl_3$) 8.20 (4 H, d, *J* 8.4), 7.40 (4 H, d, *J* 8.4), 5.10 (br s), 4.70 (br s), 3.70 (5 H, s, $CO_2Me$ and $ArCH_2$), 2.80 (2 H, t, *J* 7.2), 2.50 (m), 1.00–2.00 (br m), 0.90 (3 H, s, 19-$H_3$) and 0.70 (3 H, s, 18-$H_3$); $\delta_C$(22.5 MHz; $CDCl_3$) 174.3, 172.1, 169.5, 149.1, 146.9, 146.4, 141.5, 130.1, 129.2, 123.6, 76.0, 75.2, 51.4, 49.4, 47.5, 45.0, 41.7, 41.1, 35.5, 34.6, 33.9, 33.6, 32.1, 30.8, 27.3, 26.6, 26.0, 25.6, 23.3, 23.0, 17.5 and 12.3; $\nu_{max}$(neat)/$cm^{-1}$ 2866s, 1722, 1599m, 1512s, 1443, 1344s, 1218, 1167, 1008, 849 and 747; $[\alpha]_D^{23}$ + 57.1 (*c* 14.6, $CHCl_3$); *m/z* (EI) 730 [($M^+$ − NO), 3%] and 371 (100).

**Methyl 12α-[(4-nitrophenyl)acetyloxy]-3α-[3-(4-nitrophenyl)-propanoyloxy]-5β-cholan-24-oate 4e**

Compound **4e** was synthesized from alcohol **3b** (similar to the synthesis of compound **4c**) in 78% isolated yield; $\delta_H$(90 MHz; $CDCl_3$) 8.2 (2 H, d, *J* 8.0), 8.16 (2 H, d, *J* 8.0), 7.5 (2 H, d, *J* 8.0), 7.32 (2 H, d, *J* 8.0), 5.12 (br s), 4.64 (br m), 3.78 (2 H, s), 3.7 (3 H, s, $CO_2Me$), 3.1 (2 H, t, *J* 7.2), 2.74 (2 H, t, *J* 7.2), 1.0–2.0 (br m), 0.92 (3 H, s, 19-$H_3$) and 0.74 (3 H, s, 18-$H_3$); $\delta_C$(22.5 MHz; $CDCl_3$) 174.2, 171.6, 168.8, 148.5, 147.0, 146.5, 141.7, 130.3, 129.3, 123.7, 78.7, 76.9, 75.8, 74.5, 51.5, 49.2, 47.5, 45.1, 41.7, 35.5, 35.1, 34.5, 34.1, 32.3, 30.7, 26.8, 26.0, 25.5, 23.0, 17.4 and 12.2; $\nu_{max}$(neat)/$cm^{-1}$ 2908s, 1725s, 1602m, 1515s, 1443, 1344s, 1254m, 1167, 1008m, 849 and 750; $[\alpha]_D^{23}$ + 55.4 (*c* 3.18, $CHCl_3$); *m/z* (EI) 716 [($M^+$ − NO), 3%] and 255 (100).

**Methyl 12α-[(4-nitrophenyl)acetoxy]-3α-[4-(4-nitrophenyl)-butanoyloxy]-5β-cholan-24-oate 4f**

Compound **4f** was synthesized from alcohol **3c** in a similar way to its homologue **4c**, in 66% isolated yield; $\delta_H$(90 MHz; $CDCl_3$) 8.24 (2 H, d, *J* 8.9), 8.12 (2 H, d, *J* 8.9), 7.5 (2 H, d, *J* 8.9), 7.36 (2 H, d, *J* 8.9), 5.12 (br s), 4.7 (br s), 3.8 (2 H, s, $ArCH_2$), 3.7 (3 H, s, $CO_2Me$), 2.8 (2 H, t, *J* 7.2), 2.4 (2 H, t, *J* 7.2), 2.1 (m), 1.0–2.0 (br m), 0.92 (3 H, s, 19-$H_3$) and 0.7 (3 H, s, 18-$H_3$); $\delta_C$(22.5 MHz; $CDCl_3$) 174.3, 172.5, 168.9, 149.5, 147.1, 146.4, 141.7, 130.3, 129.3, 123.6, 78.7, 76.9, 75.7, 74.2, 51.5, 49.3, 47.5, 45.1, 41.8, 35.5, 34.6, 34.1, 33.6, 32.3, 30.8, 27.3, 26.8, 26.1, 25.5, 23.4, 23.1, 17.4 and 12.2; $\nu_{max}$(neat)/$cm^{-1}$ 2930s, 2860, 1720s, 1600m, 1515s and 1340s; $[\alpha]_D^{23}$ + 54.2 (*c* 2.33, $CHCl_3$); *m/z* (EI) 730 [($M^+$ − NO), 1.8%] and 371 (100).

**Methyl 3α,12α-{6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine-2,8-bispropanoyloxy}-5β-cholan-24-oate 6b/7b (TFA–HMT conditions)**

A mixture of compound **4b** (0.033 g, 0.04 mmol), $SnCl_2 \cdot 2H_2O$ (0.203 g, 0.89 mmol) and ethyl acetate (1 $cm^3$) was heated at 65–66 °C for 2.5 h under dry nitrogen. The mixture was cooled to room temp., diluted with ethyl acetate (20 $cm^3$), and made alkaline with 7% aq. $NaHCO_3$ (7 $cm^3$). The organic layer was separated after equilibration and the aqueous layer was extracted with ethyl acetate (10 $cm^3$ × 3). The combined organic layer was washed successively with 7% aq. $NaHCO_3$ (15 $cm^3$) and 25% NaCl (15 $cm^3$ × 3) and dried over anhydrous $Na_2SO_4$. Volatiles were removed and the crude product was dissolved in TFA (2 $cm^3$), treated with HMT (0.0099 g, 0.07 mmol) and heated at 50–53 °C for 23 h under dry nitrogen. The reaction mixture was cooled to room temp., diluted with ethyl acetate (20 $cm^3$), and neutralized with conc. aq. $NH_3$ (6 $cm^3$). The organic layer was separated after equilibration and the aqueous layer was extracted with ethyl acetate (10 $cm^3$). The combined organic layer was washed with 25% aq. NaCl (10 $cm^3$ × 2) and dried over anhydrous $Na_2SO_4$. Volatiles were removed and the crude product was purified by column chromatography (Si-gel, 100–200 mesh; 3 g; 12.2 × 0.8 cm) using 25% EtOAc–$CHCl_3$ as eluent. The title product was isolated (0.022 g, 70%).

**Steroidal Tröger's base 6b/7b (methylal conditions)**

Compound **4b** (0.496 g, 0.652 mmol) was mixed with $SnCl_2 \cdot 2H_2O$ (1.477 g, 6.545 mmol) and ethanol (5 $cm^3$) in a 10 $cm^3$ flask. The magnetically stirred mixture was heated at 67–72 °C for 2.5 h under nitrogen before being cooled to room temp., diluted and transferred to a conical flask containing 10% aq. $NaHCO_3$ (25 $cm^3$) with the aid of EtOAc (25 $cm^3$). A curd-like mass appeared with the evolution of bubbles. The organic layer was separated and the aqueous layer was extracted with EtOAc (15 $cm^3$ × 3). The combined organic layer was washed successively with 10% aq. $NaHCO_3$ (25 $cm^3$ × 2) and brine (25 $cm^3$ × 2) and dried over anhydrous $Na_2SO_4$. Volatiles were removed and the crude diamine **5b** was treated with dry DMM (64 $cm^3$) and MsOH (0.614 g, 6.39 mmol). The mixture became cloudy and a small, heavier layer was separated. This was heated to reflux under nitrogen for 34 h while being magnetically stirred. The reaction mixture was cooled to room temp., neutralized (pH paper) with conc. aq. $NH_3$, and transferred to a separatory funnel with EtOAc. The organic layer was separated and the aqueous layer was extracted with

EtOAc. The combined organic layer was washed successively with 10% aq. $NaHCO_3$ and brine, and dried over anhydrous $Na_2SO_4$. Volatiles were removed under reduced pressure and the crude product was purified by column chromatography (silica gel, 100–200 mesh; 30 g, 23.2 cm × 2 cm) using 25–30% EtOAc–$CHCl_3$ as eluent. A mixture of *diastereoisomers* **6b/7b** (0.067 g) was isolated in 14% overall yield starting from dinitro compound **4b**, in the ratio 4:1 (12-H of steroid at $\delta$ 5.20 and 5.08 for major and minor isomer, respectively); $R_f$ 0.34 [(25%) EtOAc–$CHCl_3$]; $\delta_H$(200 MHz; $CDCl_3$ for both diastereoisomers) 7.21 (2 H, dd, *J* 8.4 and 1.7), 7.08–6.09 (m), 6.85 (1 H, s), 6.71 (1 H, d, *J* 1.6), 6.69 (1 H, d, *J* 1.6), 5.20 (1 H, s), 5.09 (1 H, s), 4.63 (2 H, d, *J* 16.6), 4.61 (2 H, d, *J* 16.6), 4.31 (2 H, s), 4.28 (2 H, s), 4.06 (2 H, d, *J* 16.3), 4.01 (2 H, d, *J* 16.4), 3.66 (3 H, s), 3.65 (3 H, s), 2.77–0.62 (m), 0.90 (3 H, s), 0.88 (3 H, s), 0.78 (6 H, d, *J* 5.7), 0.72 (3 H, s) and 0.70 (3 H, s); $\delta_C$(100 MHz; $CDCl_3$ for both diastereoisomers) 174.3, 172.9, 172.7, 172.2, 145.9, 145.8, 145.7, 145.6, 137.9, 137.7, 136.8, 136.2, 128.2, 127.9, 127.5, 127.2, 127.0, 126.8, 126.6, 124.8, 124.6, 124.2, 79.7, 76.5, 75.7, 75.3, 74.6, 74.2, 66.9, 58.8, 51.3, 49.3, 48.9, 47.3, 44.9, 42.2, 41.9, 37.1, 36.1, 35.7, 35.6, 34.9, 34.5, 34.4, 34.0, 32.8, 32.5, 30.8, 30.7, 30.6, 30.5, 28.6, 28.5, 27.1, 26.9, 26.7, 26.6, 26.3, 26.1, 25.6, 25.3, 23.4, 23.3, 23.2, 23.1, 17.4, 13.9, 12.4 and 12.2; $\nu_{max}$(neat)/$cm^{-1}$ 2908s, 1725s, 1491m, 1443m, 1347m, 1329m, 1191s, 1113m, 1092m and 1017m; $\lambda_{max}$(2% $CHCl_3$–MeOH)/nm 283.5 and 224.9 ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$ 1730 and 9600); *m/z* (FAB Pos. ion) 737 [(M + 1, 100%)]; $[\alpha]_D^{22}$ 95.1 (*c* 1.03, $CHCl_3$) (Found: $M^+$, 736.4457. $C_{46}H_{60}N_2O_6$ requires M, 736.4454).

### 2,8-Bis(3-acetoxypropyl)-6*H*,12*H*-5,11-methanodibenzo-[*b*,*f*][1,5]diazocine 8b/9b

The mixture of diastereoisomers **6b/7b** (0.049 g, 0.066 mmol) obtained from the methylal reaction was dissolved in dry THF (10 $cm^3$), LAH (0.074 g, 1.95 mmol) was added, and the stirred mixture was refluxed over an oil-bath and under dry nitrogen for 26 h before being cooled to room temp. and diluted with THF (10 $cm^3$). The excess of LAH was quenched by the dropwise addition of ethanol, and the mixture was filtered through a Celite bed with the aid of THF (20 $cm^3$) and ethyl acetate (10 $cm^3$). Volatiles were removed under reduced pressure and the crude product was stirred at room temp. with pyridine (1.06 g, 10.38 mmol) and acetic anhydride (1.16 g, 14.66 mmol) for 12 h under dry nitrogen. Volatiles were removed under reduced pressure and the crude product was diluted with ethyl acetate (40 $cm^3$), washed successively with distilled water (15 $cm^3$ × 2) and 25% aq. NaCl (15 $cm^3$ × 3), and dried over anhydrous $Na_2SO_4$. Volatiles were removed under reduced pressure and the crude product was purified by PTLC (Si-gel, $GF_{254}$) using 25% EtOAc–$CHCl_3$ as the developing solvent. The *title product* was isolated (0.012 g, 43%), $R_f$ 0.20 [(25%) EtOAc–$CHCl_3$]; $\delta_H$(90 MHz; $CDCl_3$) 7.01 (4 H, s), 6.70 (4 H, s), 4.67 (2 H, d, *J* 16.6), 4.29 (2 H, s), 4.11 (2 H, d, *J* 16.6), 4.05 (4 H, t, *J* 6.4), 2.57 (4 H, t, *J* 7.7), 2.02 (6 H, s) and 2.18–1.73 (4 H, m); $\nu_{max}$(neat)/$cm^{-1}$ 2896s, 1734s, 1662s, 1491s, 1437s, 1365s, 1329s, 1242s and 1035s; $\lambda_{max}$(1% $CHCl_3$–MeOH)/nm 284.1 and 219.6 ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$ 1740 and 13 500); CD: $\Delta_\varepsilon$ −3.08 $dm^3$ $mol^{-1}$ $cm^{-1}$ (*c* 1.43 × $10^{-4}$ mol $dm^{-3}$; 1% $CHCl_3$–MeOH); $[\alpha]_D^{23}$ + 94 (*c* 0.606, $CHCl_3$); *m/z* (CI) 422 [($M^+$, 100%)], 335 (35), 130 (40) and 43 (87) (Found: $M^+$, 422.2216. $C_{25}H_{30}N_2O_4$ requires M, 422.2206).

### Authentic (±)-2,8-bis(3-acetoxypropyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine 8b/9b

Methyl 3-(4-nitrophenyl)propanoate on reduction with $SnCl_2$·$2H_2O$ followed by cyclization with DMM–MsOH, gave the corresponding racemic Tröger's base in 42% isolated yield; $R_f$ 0.23 (25% EtOAc–$CHCl_3$); $\delta_H$($CDCl_3$; 90 MHz) 7.00 (4 H, s), 6.72 (2 H, s), 4.65 (2 H, d, *J* 16.6), 4.28 (2 H, s), 4.09 (2 H, d, *J* 16.6), 3.66 (6 H, s), 2.84 (2 H, t, *J* 7.1) and 2.55 (2 H, t, *J* 7.1); $\delta_C$($CDCl_3$; 22.5 MHz) 173.1, 146.3, 136.1, 127.8, 127.2, 126.6, 125.0, 66.8, 58.5, 51.4, 35.5 and 30.3; $\nu_{max}$(neat)/$cm^{-1}$ 2896s, 1731s, 1614m, 1575m, 1491s, 1437s, 1329s, 1200s and 1032s. An authentic sample of racemic diacetates **8b/9b** was prepared from the above racemic mixture of Tröger's base on reduction (LAH–THF, reflux) followed by acetylation ($Ac_2O$–pyridine) as before, in 79% overall yield; $R_f$ 0.24 [(25%) EtOAc–$CHCl_3$]; $\delta_H$(90 MHz; $CDCl_3$) 7.00 (4 H, s), 6.69 (2 H, s), 4.65 (2 H, d, *J* 16.6), 4.28 (2 H, s), 4.09 (2 H, d, *J* 16.6), 4.02 (4 H, t, *J* 6.4), 2.57 (4 H, t, *J* 7.6), 1.99 (6 H, s) and 2.08–1.68 (4 H, m); $\delta_C$(22.5 MHz; $CDCl_3$) 171.0, 145.4, 137.2, 127.5, 126.7, 125.0, 66.9, 63.8, 58.5, 31.7, 30.0 and 20.9; $\nu_{max}$(neat)/$cm^{-1}$ 2914m, 1731s, 1659m, 1575w, 1494s, 1437m, 1368s, 1329m, 1236s, 1113m and 1035 s.

### Methyl 3α,12α-{6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine-2(→3)-acetoxy-8(→12)-propanoyloxy}-5β-cholan-24-oate 6c/7c (TFA–HMT conditions)

*Compounds* **6c/7c** were synthesized from diamine **5c** in 77% yield; $R_f$ 0.27 [(25%) EtOAc–$CHCl_3$]; $\delta_H$(200 MHz; $CDCl_3$ for the major diastereoisomer only) 7.23 (1 H, dd, *J* 8.2 and 1.7), 7.08 (1 H, d, *J* 8.1), 7.01 (1 H, d, *J* 6.7), 6.94 (1 H, d, *J* 8.2), 6.67 (1 H, s), 6.64 (1 H, d, *J* 1.6), 5.03 (1 H, s), 4.85–4.62 (1 H, br m), 4.63 (2 H, d, *J* 16.5), 4.35 (2 H, s), 4.09 (1 H, d, *J* 17.1), 4.06 (1 H, d, *J* 17.3), 3.69 (1 H, d, *J* 15.8), 3.66 (3 H, s), 3.44 (1 H, d, *J* 15.8), 2.95–0.64 (m), 0.88 (3 H, s), 0.75 (3 H, d, *J* 5.9) and 0.67 (3 H, s); $\delta_C$(100 MHz; $CDCl_3$ for the major isomer only) 174.4, 172.4, 170.8, 146.2, 145.4, 137.4, 129.4, 128.3, 128.1, 128.0, 127.2, 126.9, 124.7, 124.2, 74.6, 67.2, 59.2, 59.1, 58.2, 51.3, 48.3, 47.3, 45.0, 42.1, 41.3, 35.7, 34.6, 34.5, 32.3, 30.7, 28.6, 27.2, 26.0, 25.8, 25.6, 23.4, 23.1, 18.2, 17.0 and 12.0; $\nu_{max}$(neat)/$cm^{-1}$ 2908s, 1725s, 1614w, 1494m, 1437m, 1377m, 1329m, 1254s, 1203s, 1152s 1095m and 1008m; $\lambda_{max}$(2% $CHCl_3$–MeOH)/nm 283.3 and 223.4 ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$ 1670 and 10 200); $[\alpha]_D^{23}$ + 126.8 (*c* 0.773, $CHCl_3$); *m/z* (FAB Pos. ion) 723 [(M + 1, 100%)] (Found: $M^+$, 722.4297. $C_{45}H_{58}N_2O_6$ requires M, 722.4294).

### 2-(2-Acetoxyethyl)-8-(3-acetoxypropyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine 8c/9c

*Compounds* **8c/9c** were synthesized from triesters **6c/7c** in a similar method to analogues **8b/9b**, in 66% overall yield; $R_f$ 0.23 [(25%) EtOAc–$CHCl_3$]; $\delta_H$(90 MHz; $CDCl_3$) 7.03 (4 H, s), 6.72 (2 H, s), 4.66 (2 H, d, *J* 16.6), 4.28 (2 H, s), 4.09 (2 H, d, *J* 16.6), 4.04 (4 H, t, *J* 5.9), 2.80 (2 H, t, *J* 6.4), 2.57 (2 H, t, *J* 7.7), 2.20–1.70 (2 H, m), 2.03 (3 H, s) and 2.01 (3 H, s); $\delta_C$(100 MHz; $CDCl_3$) 171.2, 171.0, 146.6, 146.0, 137.0, 133.4, 127.9, 127.7, 127.5, 127.3, 126.7, 125.2, 125.1, 66.9, 64.9, 63.9, 58.7, 34.6, 31.7, 30.1, 21.0 and 20.9; $\nu_{max}$(neat)/$cm^{-1}$ 2896m, 1731s, 1659m, 1575w, 1494s, 1437s, 1365s, 1329s, 1239s, 1113m and 1032s; $\lambda_{max}$(1% $CHCl_3$–MeOH)/nm 283.7 and 219.5 ($\varepsilon$/$dm^3$ $mol^{-1}$ $cm^{-1}$ 1760 and 14 800); $[\alpha]_D^{25}$ + 149.5 (*c* 0.495, $CHCl_3$); CD: $\Delta_\varepsilon$ −3.90 $dm^3$ $mol^{-1}$ $cm^{-1}$ (*c* 1.21 × $10^{-4}$ mol $dm^{-3}$; 1% $CHCl_3$–MeOH); *m/z* (FAB Pos. ion) 409 [(M + 1, 100%)] (Found: $M^+$, 408.2011. $C_{24}H_{28}N_2O_4$ requires M, 408.2049).

### Methyl 3α,12α-{6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine-2(→3)-acetoxy-8(→12)-butanoyloxy}-5β-cholan-24-oate 6d/7d (TFA–HMT conditions)

Compounds **6d/7d** were prepared from diamine **5d** in 40% isolated yield; $\delta_H$(400 MHz; $CDCl_3$ for both diastereoisomers) 7.2–6.6 (ArH), 5.0 (2 s, 12-H), 4.8–4.0 (complex multiplets from Tröger's base methylenes), 3.67 (3 H, $CO_2Me$), 0.87–0.86 (19-$H_3$), 0.74 (d, 21-H) and 0.68–0.67 (18-$H_3$); $\delta_C$(100 MHz; $CDCl_3$) 174.4, 172.7, 170.9, 170.5, 146.5, 146.0, 145.8, 136.1, 135.4, 129.3, 128.9, 128.5, 128.13, 128.05, 127.6, 127.4, 126.6, 126.5, 125.2, 125.0, 124.8, 124.7, 124.6, 73.3, 72.9, 67.5, 67.3, 59.2, 51.3, 49.3, 47.8, 45.3, 41.9, 39.8, 35.9, 34.5, 34.2, 32.7, 32.3, 31.9, 31.6, 31.1, 30.9, 29.6, 27.3, 27.1, 26.5, 25.9, 24.3, 23.0, 21.9,

17.8, 12.4 and 12.3; $\nu_{max}$(neat)/cm$^{-1}$ 2910s, 1720s, 1480, 1430, 1370, 1330, 1240s, 1150s, 1100, 1000, 960, 820 and 770; *m/z* (EI) 737 [($M^+$, 100%)]. From the ratio of signals from the diastereoisomeric Me groups at C-14, the diastereoisomeric excess (de) was calculated to be 11%.

**2-(4-Acetoxybutyl)-8-(2-acetoxyethyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine 8d/9d**

Compounds **8d/9d** were prepared from triesters **6d/7d** in a similar manner to compounds **8b/9b**, in 30% yield; $\delta_H$(90 MHz; $CDCl_3$) 6.8–7.12 (4 H, m), 6.66 (2 H, br s), 4.61 (2 H, d, *J* 16), 4.13 (2 H, d, *J* 16), 4.12 (2 H, s, $NCH_2N$), 3.88–4.04 (4 H, m), 2.74 (2 H, t, *J* 7.2), 2.32–2.6 (2 H, m), 1.96 (6 H, s, OAc) and 1.80–1.44 (4 H, br m); $\lambda_{max}$(2% $CHCl_3$–MeOH)/nm 283 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 1818); $[\alpha]_D^{25}$ −19.6 (*c* 0.82, $CHCl_3$); CD: $\Delta_\varepsilon$ 0.715 dm$^3$ mol$^{-1}$ cm$^{-1}$ (*c* 3.88 × 10$^{-4}$ mol dm$^{-3}$; 2% $CHCl_3$–MeOH) (ee = 12.6%).

**Methyl 3α,12α-{6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine 8(→12)-acetoxy-2(→3)-propanoyloxy}-5β-cholan-24-oate 6e/7e (TFA–HMT conditions)**

Compounds **6e/7e** were synthesized from diamine **5e** in 41% isolated yield; $\delta_H$(270 MHz; $CDCl_3$ for both diastereoisomers) 7.11–6.64 (ArH), 5.14–5.31 (12-H), 4.75–3.85 (complex multiplets from Tröger's base methylenes), 3.67–3.66 ($CO_2Me$), 2.95–1.73 (complex multiplets from ethano chain), 0.90–0.88 (19-$H_3$), 0.824 (d, *J* 6.8)–0.800 (d, *J* 6.2, 21-$H_3$) and 0.76–0.72 (s, 18-$H_3$) (From the ratio of signals of the 12-Hs, de = 33%); $\delta_C$(100 MHz; $CDCl_3$ both diastereoisomers) 194.4, 182.5, 174.4, 173.3, 172.7, 170.3, 168.8, 164.2, 158.4, 148.2, 146.2, 136.2, 132.6, 129.3, 128.8, 128.2, 128.0, 127.7, 127.4, 127.1, 127.1, 126.8, 125.2, 124.8, 124.8, 124.5, 123.5, 112.6, 83.0, 77.3, 77.0, 76.1, 75.7, 75.0, 73.7, 67.4, 67.1, 59.6, 59.3, 59.1, 51.4, 49.9, 49.0, 47.7, 45.0, 42.3, 39.7, 39.4, 38.0, 37.8, 36.1, 35.9, 35.4, 34.9, 34.7, 34.5, 34.4, 34.1, 33.2, 32.9, 32.0, 31.1, 30.9, 30.8, 29.6, 27.5, 27.2, 26.9, 26.0, 25.7, 25.3, 23.8, 23.5, 23.4, 17.6, 12.8 and 12.5. From the ratio of the signals from the methyl carbons at $\delta_C$ 12.8 and 12.5, de is 30%; $\nu_{max}$(neat)/cm$^{-1}$ 2940s, 1720s, 1500s, 1450m, 1350m, 1200s, 1020, 980 and 760s; *m/z* (EI) 723 ($M^+$, 100%).

**2-(2-Acetoxyethyl)-8-(3-acetoxypropyl)-6*H*,12*H*-5,11-methanodibenzo [*b*,*f*][1,5]diazocine 8c/9c (alternative preparation)**

Compounds **8c/9c** were synthesized from triesters **6e–7e** in a similar way to analogues **8b/9b**, in 26% isolated yield; $\delta_H$(80 MHz; $CDCl_3$) 7.1–6.75 (4 H, m), 6.65 (2 H, s), 4.6 (2 H, d, *J* 16), 4.13 (2 H, s, $NCH_2N$), 4.1 (2 H, d, *J* 16.0), 4.10–3.85 (4 H, m), 2.7 (2H, t, *J* 8.0), 2.2–2.6 (4 H, t and q merged), 1.95 (3 H, s, OAc) and 1.9 (3 H, s, OAc); $\nu_{max}$(neat)/cm$^{-1}$ 2910s, 2830m, 1730s, 1655m, 1490s, 1430m, 1380m, 1360s, 1325, 1230vs, 1110, 1060, 1030s, 960, 950, 830 and 750; $[\alpha]_D^{24}$ −41.8 (*c* 0.76, $CHCl_3$) (ee 22%); CD: $\Delta_\varepsilon$ +1.24 dm$^3$ mol$^{-1}$ cm$^{-1}$ (*c* 3.31 × 10$^{-4}$ mol dm$^{-3}$; 4% $CHCl_3$–MeOH) (ee = 21.7%); $\lambda_{max}$(4% $CHCl_3$–MeOH)/nm 287 ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 1700); *m/z* (CI) 408 [($M^+$, 89%)] and 348 [($M^+$ − $CH_3CO_2H$, 100%)].

**Methyl 3α,12α-{6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]-diazocine-8(→12)-acetoxy-2(→3)-butanoyloxy}-5β-cholan-24-oate 6f/7f (TFA–HMT conditions)**

Compounds **6f/7f** were synthesized from diamine **5f** in 33% isolated yield; $\delta_H$(270 MHz; $CDCl_3$) 6.66–7.11 (ArH), 5.16 (2 s, 12-Hs *improper resolution*), 4.02–4.69 (complex multiplets from the methylene units of Tröger's base), 3.67 ($CO_2Me$), 1.73–3.86 (complex multiplets from propano chain), 0.90 (19-$H_3$), 0.89 and 0.80 (d, 21-$H_3$) and 0.73 and 0.72 (18-$H_3$); $\delta_C$(22.5 MHz; $CDCl_3$) (both diastereoisomers) 174.5, 173.6, 173.2, 170.9, 146.6, 146.0, 136.2, 129.8, 129.6, 128.6, 128.4, 128.1, 127.7, 127.5, 127.2, 126.7, 126.1, 125.5, 125.3, 124.8, 77.3, 77.0, 76.7, 75.9, 75.7, 75.5, 75.0, 67.4, 67.2, 58.7, 51.4, 49.2, 48.9, 47.8, 45.3, 43.4, 42.1, 41.9, 35.9, 34.9, 34.8, 34.7, 34.4, 34.0, 33.1, 32.63, 32.55, 31.2, 31.0, 29.7, 27.3, 26.7, 26.6, 25.9, 25.4, 24.9, 23.5, 23.3, 23.2, 17.6, 17.5, 12.4 and 12.3; $\nu_{max}$(neat)/cm$^{-1}$ 2866s, 1722s, 1494, 1440, 1314, 1206, 1152, 1005, 747 and 731; *m/z* (CI) 737 [($M^+$, 100%)];

**2-(4-Acetoxybutyl)-8-(2-acetoxyethyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine 8d/9d (alternative preparation)**

Compounds **8d/9d** were synthesized from triesters **6f/7f** in a similar manner to analogues **8b/9b**, in 65% overall yield; $\delta_H$(90 MHz; $CDCl_3$) 6.92–7.82 (4 H, m), 6.68 (2 H, br s), 4.62 (2 H, d, *J* 16), 4.15 (2 H, d, *J* 16), 3.92–4.04 (m), 4.14 (2 H, s, $NCH_2N$), 3.76 (2 H, t, *J* 15.6), 2.32–2.6 (2 H, m), 1.96 (6 H, s, OAc) and 1.4–1.8 (4 H, br m); $\nu_{max}$(neat)/cm$^{-1}$ 2896s, 1728s, 1491, 1437, 1362, 1233, 1032, 951 and 834; $\lambda_{max}$(4% $CHCl_3$–MeOH)/nm 283 nm ($\varepsilon$/dm$^3$ mol$^{-1}$ cm$^{-1}$ 1770); $[\alpha]_D^{23}$ +47.7 (*c* 0.398, $CHCl_3$) (ee = 26%); CD: $\Delta_\varepsilon$ −1.21 dm$^3$ mol$^{-1}$ cm$^{-1}$ (*c* 3.77 × 10$^{-4}$ mol dm$^{-3}$; 4% $CHCl_3$–MeOH) (ee = 21.1%); *m/z* (EI) 422 [($M^+$, 90%)] and 362 [($M^+$ − $CH_3CO_2H$, 100%)].

*Note added in proof:* Since submission of this manuscript, a few more papers on Tröger's base derivatives have been published. Two of which are: (*a*) H. Salcz, A. Wardani, M. Demeunynek, A. Tatibouet and J. Lhomme, *Tetrahedron Lett.*, 1995, **36**, 1271; (*b*) M. J. Crossley, T. W. Hambley, L. G. Mackay, A. C. Try and R. Walton, *J. Chem. Soc., Chem. Commun.*, 1995, 1077.

## Acknowledgements

Financial assistance from the Department of Science and Technology (Grant No. SP/S1/G09/91) is gratefully acknowledged. We thank CSIR for the award of a fellowship to B. G. B. SIF, IISc, Bangalore and RSIC, Lucknow are thanked for recording 400 MHz NMR spectra and FAB-MS respectively. We thank the National Science Foundation (grant CHE-9105497) and the University of Wisconsin for providing funds to purchase the X-ray instrument and computers used in this study. We also thank Professor Samuel H. Gellman, University of Wisconsin at Madison, for help with the X-ray analysis.

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*Paper* 5/00088B
*Received* 5*th January* 1995
*Accepted* 24*th April* 1995