Support Studies for the Conversion of Actinobolin into Bactobolin

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Strategies for the final steps in a synthesis of bactobolin have been examined on substrates obtained by retrograde transformations of actinobilin. It is shown that α-acetamido ketones react with $LiCHCl_2$ from the *Re* face thereby generating the C-5 configuration required for bactobolin. However, the transformations involved are highly substrate specific. The reasons for this sensitivity are not apparent, but they indicate the need for caution in laying plans for the finals steps of a synthesis.

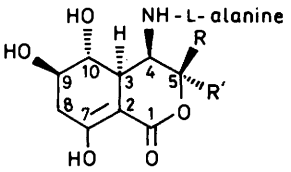
Actinobolin (**1a**) and bactobolin (**1b**) are an interesting pair of antibiotics.† In spite of their structural similarities, they are not congeners, their natural sources being *Streptomyces griseoviridis*[1] and *pseudomonas*,[2] respectively. Nor are their biological activities similar. The former displays weak antibiotic activity,[3] and recent interest surrounds its potential as an agent for arresting tooth decay owing to its ability to bind to the calcium ions in human tooth enamel.[4] Bactobolin displays anti-tumor activity.[5]

Five syntheses[5-9] of actinobolin have been reported, and it would seem logical to retool those synthetic strategies to accommodate the unique C-5 stereocentre of bactolin. Indeed, Weinreb has recently achieved this objective in reporting the first total synthesis of bactobolin.[10] Difficulties reported with earlier attempts[6b,9b] may be attributed to the idiosyncratic behaviour of these unusual molecules, an aspect that became clear during the structural elucidation studies of Munk and Haskell.[11] Our own synthetic[8] and retrograde studies[12] convinced us of the need for caution in planning any chemical transformations. Accordingly, we have carried out studies aimed at uncovering a suitable strategy, especially for the final stages of converting actinobolin into bactobolin.

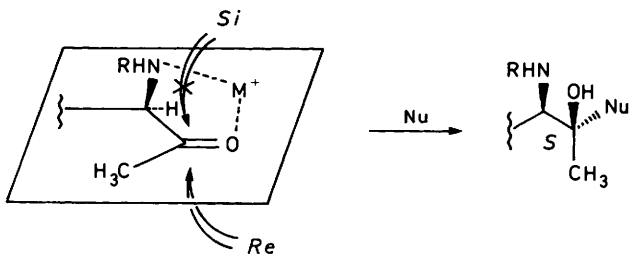
The C-5 centre of bactobolin (**1b**), is clearly a major challenge, the stereoselectivity of its formation being an obvious first requirement. As exemplified in Ohno's studies,[6b] a logical procedure for creating this C-5 stereocentre involves addition of the dichloromethyl anion to a methyl ketone. We assumed that with the proper choice of the counterion a chelated intermediate, (**I**), would exist which would show a preference for addition to the *Re*-face, leading to the desired *S*-configuration in (**II**).

We decided to test the strategy by using compound (**2a**) Scheme 1, which we had prepared earlier both by total synthesis[8] and by transformations of actinobolin.[12] Prolonged acetylation led to the triacetate (**2b**). Opening of the pyranolactone to provide access to the secondary 5-OH was required, but previous studies in our laboratory[12] and Danishefsky's,[9] had shown that achieving this goal in these molecules was not a simple matter. In keeping with this history, reduction of (**2b**) with sodium borohydride in isopropyl alcohol gave a complex mixture; but conditions were developed whereby *in situ* glycosidation could be achieved by quenching with ion exchange resin and diluting with methanol, whereby the methyl pyranoside (**3a**) was produced as the main component.

The di-*O*-benzyl ether (**3c**) was prepared, and opening of the lactol ring was addressed. However, attempts at acid catalysed hydrolysis led to intractable material. Noting that these unsaturated compounds were reminiscent of hex-2-enopyranosides such as (**IIIa**), we took advantage of earlier work in our



(**1**) **a**; R = CH_3, R' = H actinobolin
b; R = $CHCl_2$, R' = CH_3 bactobolin



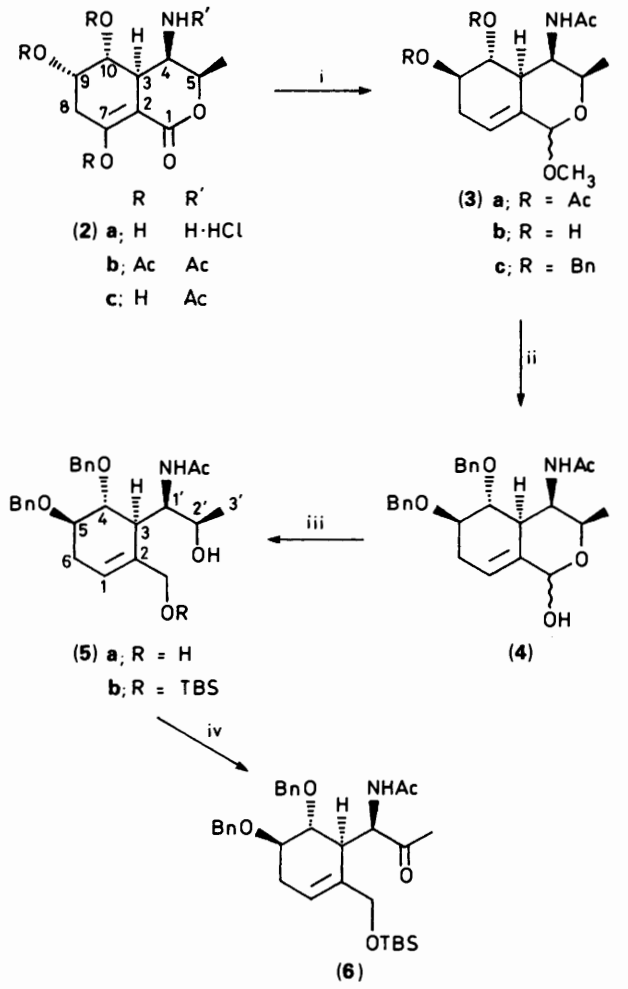
(**I**) (**II**)

laboratory that had shown that these activated glycosides could be hydrolysed by boiling water.[13]

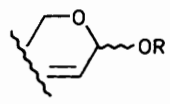
Accordingly, treatment of (**3c**) with boiling aqueous dioxane afforded the hemiacetal (**4**), which then succumbed to reductive cleavage with sodium borohydride under Luche conditions,[14] affording the diol (**5a**). After silylation of the primary hydroxy group, the secondary alcohol (**5b**) was oxidized with pyridinium chlorochromate to give the ketone (**6**).

Treatment of (**6**) with butyl-lithium–CH_2Cl_2 in tetrahydrofuran at −100 °C[15] for 2 h afforded a single product, whose C-5 configuration was assignable, as shown in (**7**) (Scheme 2), on the basis of subsequent transformations. In preparation for the relactonization, attempts were made to effect desilylation with tetrabutylammonium fluoride. These led to the aldehyde (**9**), which was presumably formed *via* the chloro epoxide (**8**). On the other hand, protodesilylation with aqueous acetic acid worked smoothly to give the diol (**10**). Selective oxidation under Swern conditions was not without surprises. Thus, if the reaction mixture was processed

† For the sake of simplicity, the numbering sequence shown in (**1**) and (**2**) is used. For a numbering system that includes the side-chain, see reference 4*b*.



Scheme 1. *Reagents and conditions:* i, $NaBH_4$–Pr^iOH–CH_3OH, ii, dioxane, water, reflux, 1.5 h; iii, $NaBH_4$, $CeCl_3$; iv, PCC.



(III) **a**; R = H
b; R = Me

at −30 °C, the desired hemiacetal (**11**) was obtained. However, processing at −10 °C led to the diene (**12**).

Although compound (**12**) was a single compound and (**11**) was a mixture of hemiacetals, that latter proved to be more amenable to difference NOE experiments. This technique allowed the *syn*-relationship of 3-H and 5-CH_3 to be established unequivocally, thereby confirming that *Re* addition of the dichloromethide anion to ketone (**6**) had indeed occurred as depicted in (**I**).

Although compound (**11**) seemed to be a promising intermediate, it lacked the C-7 oxygen and all attempts to oxygenate the material or its derivatives proved unavailing. For example, attempted hydroboration of (**11**) regenerated the diol (**10**), whereas with the corresponding diacetate (**13**), the acetamide entity was reduced, giving the *N*-ethylamine (**14**).

The C-7 oxygen had been removed from actinobolin during the formation of (**3**), and we therefore turned our attention to preparation of a derivative of actinobolin that would retain the C-7 oxygen. Acetonation of (**2a**) gave the known acetonide (**15a**),[11,12] which was protected as the enol ether (**15b**) and then processed to give the methyl ketone (**16b**) using the same procedure as described above for converting (**2b**) into (**6**) (Scheme 1). However, reaction with $LiCHCl_2$ led to a complex mixture.

In the belief that the poor result with (**16b**) was somehow connected with the strain imposed by the *trans*-fused isopropylidene ring, the trismethoxymethyl derivative (**17**) was prepared (Scheme 3), and a similar reaction sequence as described above was applied to obtain the methyl ketone (**18c**). Under optimized conditions, a single adduct (**19a**) was obtained, which was subjected to protodesilylation to afford the diol (**19b**).

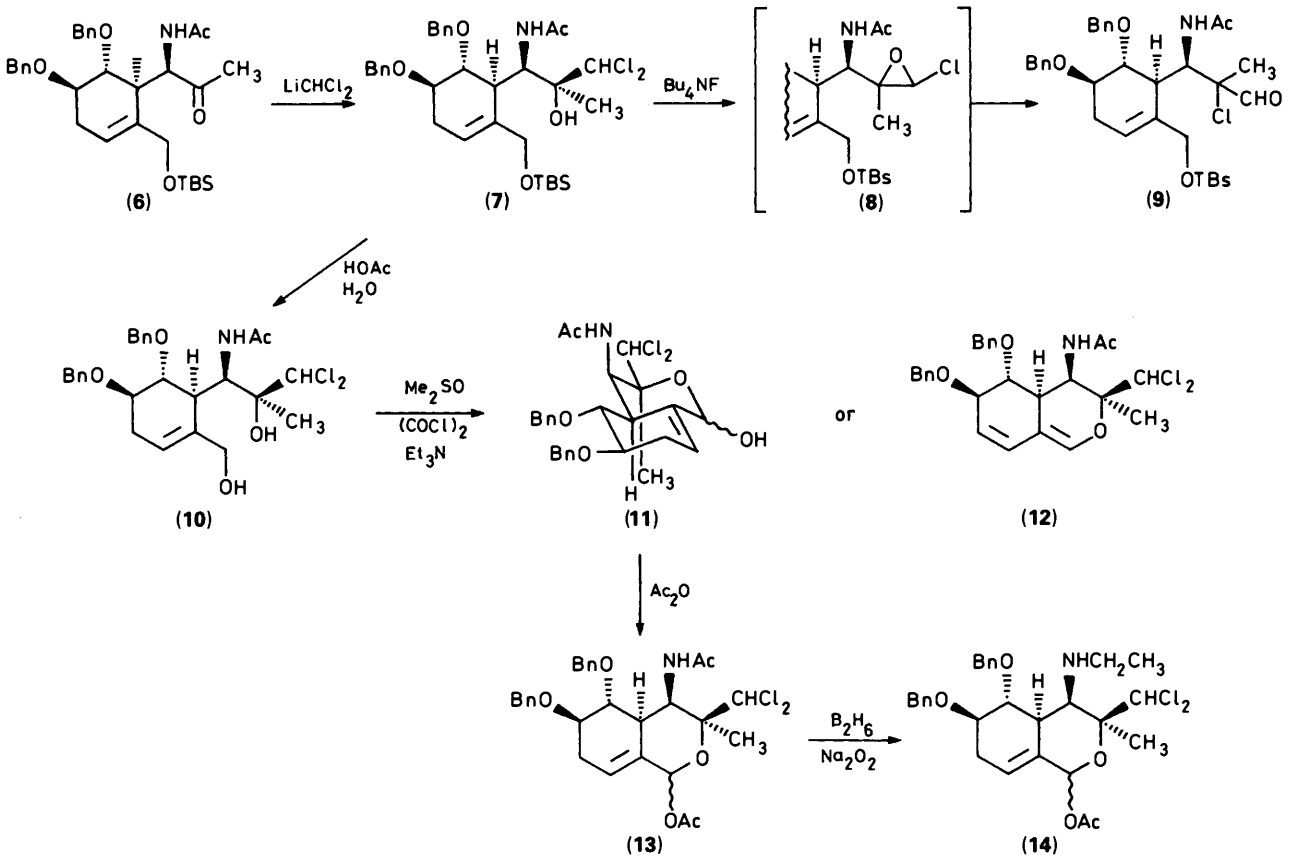
Manganese dioxide oxidation of (**19b**) led to the diene (**21**) (Scheme 4), whereas pyridinium dichromate oxidation in the presence of acetic anhydride,[16] led to the vinylogous lactone (**23**). The hemiacetals (**20**) and (**22**), were logical intermediates that underwent 1,4- and 1,2-eliminations, respectively, to give the observed products. A strong difference in NOE was observed between 3-H and CH_3 of (**23**), thereby establishing that the C-5 configuration was as desired.

These studies confirm earlier observations,[6,10] that *Re*-face addition in chelates such as (**I**) is indeed realizable, as witnessed by the formation of (**7**) and (**19**). However, there appears to be subtle structural requirements for the ketone precursors. This is amply demonstrated by the results for (**16**) and (**18**), where the remote acetonide ring evidently affects the outcome of the reaction. This information is being incorporated in a synthesis of bactobolin that is currently being carried out in our laboratory.

Experimental

Column chromatography was carried out on Kieselgel (230–400 mesh) with the eluant specified in each case. All reactions requiring anhydrous conditions were conducted in oven-dried apparatus under a static atmosphere of argon. Organic extracts were dried over $MgSO_4$ and evaporated at aspirator pressure using a rotary evaporator, unless otherwise stated. Light petroleum refers to the fraction boiling in the range 35–60 °C. Dichloromethane, pyridine, and *N*,*N*-dimethylformamide (DMF) were dried and distilled before use using standard methods.[17] Chemical shifts are reported in δ values relative to tetramethylsilane or chloroform as an internal standard. ^1H NMR spectra were recorded in deuteriochloroform on a Varian XL-300 spectrometer. IR were recorded in chloroform on a Perkin-Elmer 297 instrument. Optical rotations were measured for chloroform solutions using a Perkin-Elmer 241 instrument. Mass spectra were recorded on a Hewlett-Packard 59-88A GCMS by chemical ionisation (with methane–ammonia as the reagent gas). Accurate mass determinations were recorded on a VG-705 by chemical ionisation (with ammonia as the reagent gas, an accelerating voltage of 8 kV, and *ca.* 10 000 resolution). TLC was conducted on precoated Kieselgel 60 F254 (Art. 5554; Merck) and spots visualised using a mixture of ammonium molybdate(VI) tetrahydrate and cerium(IV) sulphate tetrahydrate in 10% aqueous sulphuric acid. M.p.s were recorded with a Buchi 510 apparatus and are uncorrected. Elemental combustion analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

(3R)-(3α,4,4aβ,5β,6α)-N-(5,6,8-*Triacetoxy*-3,4,4a,5,6,7-*hexahydro*-3-*methyl*-1-*oxo*-1H-2-*benzopyran*-4-*yl*)*acetamide* (**2b**).—To a stirred solution of the amine hydrochloride (**2a**)[12] (6.129 g, 24.18 mmol) in dry pyridine (40 ml) at room temperature under argon, was added acetic anhydride (18.3 ml, 193.6 mmol). After 22 h, the solvents were evaporated, and the



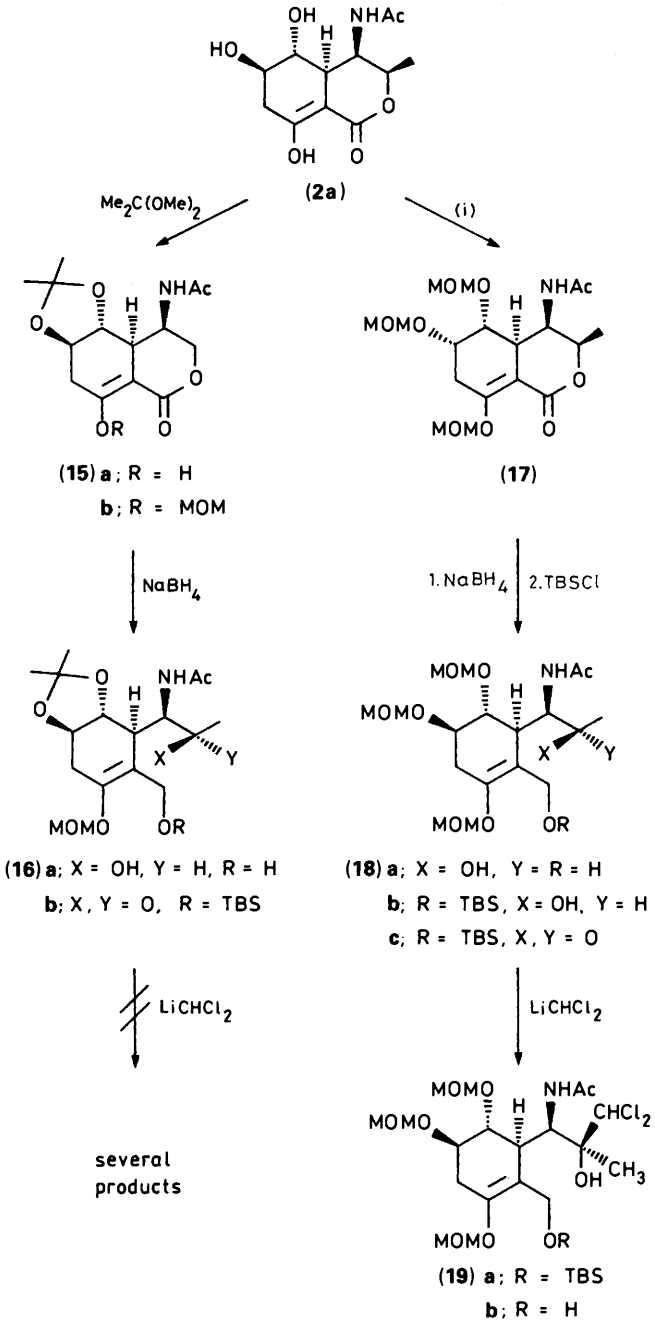
Scheme 2

resulting syrup was azeotroped with toluene, to afford crude material which was chromatographed in 55% ethyl acetate–light petroleum to give (**2b**) (6.2 g, 64.5%) as a clear syrup, $[\alpha]_D$ +25.11° ($CHCl_3$, *c* 1.37); ν_{max} 3 250 (NH) and 1 630–1 750 cm^{-1} (CO, *N*-acetyl, *O*-acetyl, lactone); δ_H 1.30 (d, 3 H, 6-CH_3, $J_{CH_3,5}$ 6.3 Hz), 2.00 (s, 3 H, acetyl CH_3), 2.05 (s, 3 H, acetyl CH_3), 2.10 (s, 3 H, acetyl CH_3), 2.25 (s, 3 H, acetyl CH_3), 2.40–2.55 (m, 1 H, 8-H), 2.98 (br dd, 1 H, 8′-H, $J_{8',8}$ 20 Hz, $J_{8',9}$ 5 Hz), 3.07–3.15 (m, 1 H, 3-H), 4.51–4.60 (m, 2 H, 4-H, 5-H), 5.09–5.19 (m, 2 H, 9-H, 10-H), and 5.98 (d, 1 H, NH, $J_{NH,4}$ 10.2 Hz) (Found: C, 54.25; H, 5.95. $C_{18}H_{23}NO_9$ requires C 54.41; H, 5.83%).

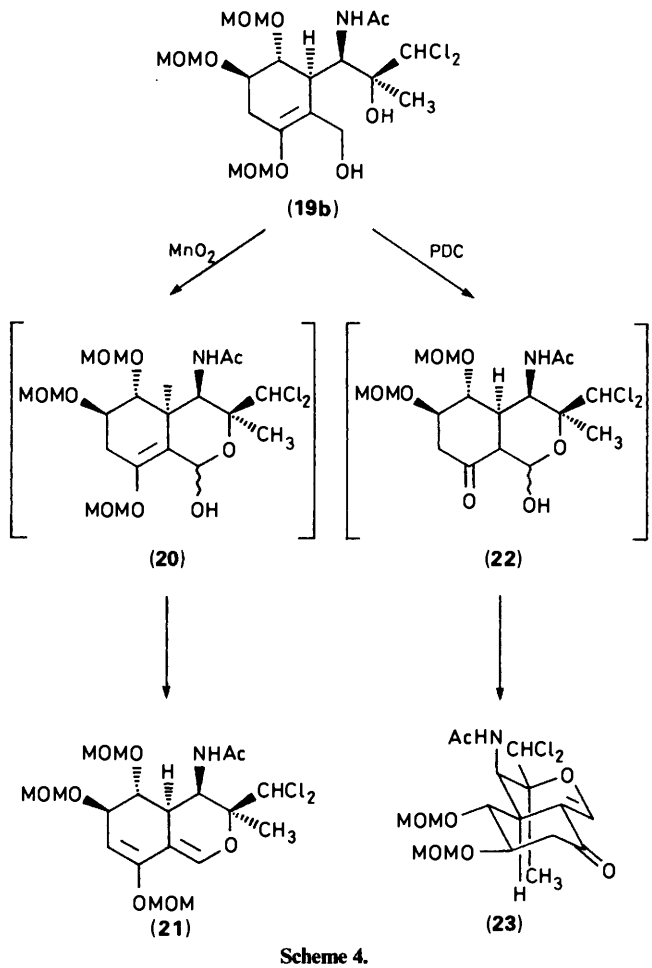
(3R)-(3α,4α,4aβ,5β,6a)-N-(5,6-*Diacetoxy*-3,4,4a,5,6,7-*hexahydro*-1-*methoxy*-3-*methyl*-1H-2-*benzopyran*-4-*yl*)*acetamide* (**3a**).—The lactone (**2b**) (6.05 g, 15.22 mmol) was dissolved in isopropyl alcohol (195 ml) and cooled to 0 °C under argon. Sodium borohydride (2.017 g, 53.32 mmol) was added, and the cloudy solution stirred at room temperature for 48 h. The solution was cooled to 0 °C, brought to pH 5 with Dowex 50 × 2-200 ion exchange resin, and stirred for 15 min at 0 °C. Dry methanol (40 ml) was added and the solution was filtered immediately, and the resin washed with methanol (150 ml). The solvents were evaporated and azeotroped with toluene to afford crude material which was chromatographed in 3% methanol in ethyl acetate to give (**3a**) as the major component: $[\alpha]_D$ +84.73° ($CHCl_3$, *c* 1.29), m.p. 123–125 °C; ν_{max} 3 375 (NH), 3 025 (alkene CH), 1 740 (CO, *O*-acetyl), and 1 680 cm^{-1} (CO, *N*-acetyl); δ_H 1.15 (d, 3 H, 6-CH_3, $J_{CH_3,5}$ 6 Hz), 2.00 (s, 3 H, acetyl CH_3), 2.04 (s, 3 H, acetyl CH_3), 2.08 (s, 3 H, acetyl CH_3), 2.23–2.34 (m, 1 H, 8-H), 2.59–2.69 (m, 1 H, 8′-H), 2.98–3.08 (m, 1 H, 3-H), 3.35 (s, 3 H, OCH_3), 4.18 (q, 1 H, 5-H, J_{5,CH_3} 6.4 Hz), 4.28 (dd, 1 H, 4-H, $J_{4,NH}$ 9-10 Hz, $J_{4,3}$ 4 Hz), 4.81 (s, 1 H, 1-H), 5.02–5.10 (m, 2, 9-H, 10-H), 5.45 (d, 1 H, NH, $J_{NH,4}$ 10.2 Hz), and 5.68–5.74 (m, 1 H, 7-H) (Found: C, 57.6; H, 7.0. $C_{17}H_{25}NO_7$ requires C, 57.45; H, 7.09%).

(3R)-(3α,4α,4aβ,5β,6α)-N-(3,4,4a,5,6,7-*Hexahydro*-5,6-*dihydroxy*-1-*methoxy*-3-*methyl*-1H-2-*benzopyran*-4-*yl*)*acetamide* (**3b**).—The triacetate (**3a**) (9.5 mg, 0.027 mmol) was dissolved in a mixture of methanol–water–triethylamine (5:4:1; 1.0 ml) and after 2 h at room temperature, the solvents were evaporated and the resulting white semisolid was azeotroped with toluene. The crude material was chromatographed in 5% methanol–ethyl acetate to give (**3b**) (5.5 mg, 75.1%) as a white semisolid; $[\alpha]_D$ + 81.64° (MeOH, *c* 1.28); ν_{max} 3 300–3 500 (OH, NH) and 1 660 cm^{-1} (CO, *N*-acetyl); δ_H 1.20 (d, 3 H, 6-CH_3, $J_{CH_3,5}$ 6.59 Hz), 2.05–2.15 (m, 1 H, 8-H), 2.09 (s, 3 H, *N*-acetyl CH_3), 2.50–2.65 (m, 2 H, 8′-H, 3-H), 3.18 (t, 1 H, 10-H, *J* 9.43 Hz), 3.36 (s, 3 H, OCH_3), 3.80–3.89 (m, 1 H, 9-H), 4.13 (br dd, 1 H, 4-H, $J_{NH,4}$ 9.25 Hz, $J_{4,3}$ 4.91 Hz), 4.26 (q, 1 H, 5-H, J_{5,CH_3} 6.89 Hz), 4.50 (br s, 1 H, OH), 4.79 (s, 1 H, 1-H), 5.64–5.66 (m, 1 H, 7-H), 5.88 (d, 1 H, NH, $J_{NH,4}$ 8.65 Hz) (Found: C, 57.5; H, 7.8. $C_{13}H_{21}NO_5$ requires C, 57.55; H, 7.80%).

(3R)-(3α,4α,4aβ,5β,6α)-N-(3,4,4a,5,6,7-*Hexahydro*-1-*methoxy*-3-*methyl*-5,6-*dibenzyloxy*-1H-2-*benzopyran*-4-*yl*)*acetamide* (**3c**).—The diol (**3b**) (0.350 g, 1.29 mmol) was dissolved in dry *N*,*N*-dimethylformamide (5 ml) and cooled to 0 °C under argon. Sodium hydride (0.350 g, 8.75 mmol) was washed several times with light petroleum and added along with tetrabutylammonium iodide (catalytic amount). The solution was stirred for 5 min at 0 °C and then benzyl bromide (0.460 ml, 3.87 mmol, 3.0 equiv.) was added. After 30 min at 0 °C, the reaction was quenched with methanol, water was added and the mixture extracted with diethyl ether. The organic



Scheme 3. i, Ac_2O, Et_3N; $MeOCH_2Cl$, Pr^i_2NEt



Scheme 4.

extracts were combined and washed with saturated brine, dried (Na_2SO_4), and evaporated. The crude material was chromatographed in 35% ethyl acetate–light petroleum to give (**3c**) (0.318 g, 54.3%) as a white solid, $[\alpha]_D$ +90.08° ($CHCl_3$, *c* 1.19), m.p. 128–130 °C; ν_{max}(Nujol) 3 300 (NH) and 1 640 cm^{-1} (CO, *N*-acetyl); δ_H 1.16 (d, 3 H, 6-CH_3, $J_{CH_3,5}$ 6.48 Hz), 2.07 (s, 3 H, *N*-acetyl CH_3), 2.10–2.19 (m, 1 H, 8-H), 2.52 (ddt, 1 H, 8′-H, $J_{8',8}$ 17.48 Hz, *J* 1.44 Hz, *J* 5.67 Hz), 2.82–2.90 (m, 1 H, 3-H), 3.35 (s, 3 H, OMe), 3.46 (t, 1 H, 10-H, *J* 8.7 Hz), 3.71–3.78 (m, 1, 9-H), 4.17 (q, 1 H, 5-H, J_{5,CH_3} 6.41 Hz), 4.50 (dd, 1, 4-H, $J_{4,3}$ 3.63 Hz, $J_{NH,4}$ 10.47 Hz), 4.71 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 11.75 Hz, δv 9.97 Hz), 4.79 (s, 1 H, 1-H), 4.82 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 9.89 Hz, δv 93.6 Hz), 5.58 (d, 1 H, NH, $J_{NH,4}$ 10.5 Hz), 5.69–5.71 (m, 1 H, 7-H), and 7.25–7.50 (m, 10 H, aromatic) (Found: C, 71.75; H, 7.15. $C_{27}H_{33}NO_5$ requires C, 71.82; H, 7.37%) (Found: *m/z* 452.2437. MH^+ requires 452.2443).

(3R)-(3α,4α,4aβ,5β,6α)-N-(3,4,4a,5,6,7-*Hexahydro*-1-*hydroxy*-3-*methyl*-5,6-*dibenzyloxy*-1H-2-*benzopyran*-4-*yl*)*acetamide* (**4**).—The glycoside (**3c**) (0.318 g, 0.70 mmol) was dissolved in dioxane (3 ml) and brought to reflux. Water was added until the solution was turbid, and reflux was continued for 1.5 h. The solvents were then evaporated, the residual syrup was azeotroped with toluene, and the crude material was then chromatographed in 60% ethyl acetate/light petroleum to give the anomeric mixture of (**4**) (0.266 g, 87.1%) as a clear syrup: ν_{max}(neat): 3 450 (OH), 3 600 (NH), and 1 680 cm^{-1} (CO, *N*-acetyl); δ_H 1.15 (d, 3 H, 6-CH_3, $J_{CH_3,5}$ 6.3 Hz; major), 1.21 (d, 3 H, 6-CH_3, $J_{CH_3,5}$ 6.3 Hz; minor), 2.06 (s, 3 H, *N*-acetyl CH_3; minor), 2.07 (s, 3 H, *N*-acetyl CH_3; major), 2.05–2.18 (m, 1 H, 8-H), 2.49–2.58 (m, 1 H, 8′-H), 2.64 (d, 1 H, OH, $J_{OH,1}$ 2.4 Hz), 2.90–2.95 (m, 1 H, 3-H), 3.45–3.56 (m, 1 H, 10-H), 3.66–3.80 (m, 1 H, 9-H), 4.41 (q, 1 H, 5-H, J_{5,CH_3} 6.2 Hz), 4.52 (br dd, 1 H, 4-H, $J_{4,NH}$ 9.9 Hz, $J_{4,3}$ 3.3 Hz), 4.73 (s, 2 H, $OCH_2C_6H_5$; major), 4.72 (s, 2 H, $OCH_2C_6H_5$; minor), 4.83 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 9.75 Hz, δv 95.05 Hz), 5.35 (br d, 1 H, 1-H, $J_{1,OH}$ 2.7 Hz), 5.56 (d, 1 H, NH, $J_{NH,4}$ 10.9 Hz), 5.69–5.72 (m, 1 H, 7-H; major), 5.97–5.98 (m, 1 H, 7-H; minor), and 7.15–7.52 (m, 10 H, aromatic) (Found: C, 71.15; H, 6.95. $C_{26}H_{31}NO_5$ requires C, 71.37; H, 7.14%).

(3R)-(3α,1R*,2R*),4α,5β-N-[2-*Hydroxy*-1-(2-*hydroxymethyl*-4,5-*dibenzyloxycyclohex*-1-*en*-3-*yl*)*propyl*]*acetamide* (**5a**).—The hemiacetal (**4**) (0.1325 g, 0.31 mmol) was dissolved in dry methanol (6 ml) and cooled to 0 °C under argon. Cerium chloride (0.298 g, 0.80 mmol) was added, followed by sodium borohydride (0.329 g, 8.70 mmol) slowly over 5 min. A vigorous evolution of gases occurred. After 15 min at 0 °C, the reaction

was brought to pH 5 with Dowex 50 × 2-200 ion exchange resin. The solution was stirred for 15 min at 0 °C, after which the resin was filtered off and washed with methanol. The solvent was evaporated and the residue was azeotroped with toluene and then taken up in 1M hydrochloric acid and extracted with diethyl ether. The organic extracts were dried (Na_2SO_4) and evaporated, and the crude material was chromatographed in ethyl acetate to give (**5a**) (0.0956 g, 71%) as a clear syrup; $[\alpha]_D$ −23.21° ($CHCl_3$, *c* 1.09); ν_{max}(neat) 3 200–3 450 (NH, OH) and 1 640 cm^{-1} (CO, *N*-acetyl); δ_H 1.08 (d, 1 H, 6-CH_3, $J_{CH_3,5}$ 6.3 Hz), 1.75 (s, 3 H, *N*-acetyl CH_3), 2.10–2.25 (m, 1 H, 8-H), 2.77 (br s, 1 H, OH), 2.82–2.86 (m, 1 H, 3-H), 3.33 (d, 1 H, OH, *J* 4.8 Hz), 3.73 (br q, 1 H, 9-H, *J* 6.1 Hz), 3.84–4.0 (m, 3 H, 1-, 5-, 10-H), 4.11–4.20 (m, 2 H, 1′-, 4-H), 4.56 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 11.7 Hz, δν 37.83 Hz), 4.68 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 11.55 Hz, δν 76.08 Hz), 5.67 (br s, 1 H, 7-H), 6.53 (d, 1 H, NH, $J_{NH,4}$ 8.1 Hz), and 7.22–7.35 (m, 10 H, ArH) (Found: 70.95; H, 7.5. $C_{26}H_{33}NO_5$ requires C, 71.05; H, 7.57%) 440.2437 (MH^+ requires 440.2431).

(3R)-[3α(1R*,2R*),4α,5β]-N-(1-{2-[(*t-Butyldimethylsilyloxy)methyl*]-4,5-*dibenzyloxycyclohex*-1-*en*-3-*yl*}-2-*hydroxypropyl*)*acetamide* (**5b**).—The diol (**5a**) (0.1330 g, 0.30 mmol) was dissolved in dry methylene dichloride (5 ml), and triethylamine (0.13 ml, 0.93 mmol), a catalytic amount of *N*,*N*-dimethylaminopyridine, and t-butyldimethylsilyl chloride (68.4 mg, 0.45 mmol) were added. After 7 h, the solution was diluted with methylene dichloride and washed with aqueous sodium hydrogencarbonate and brine. The organic layer was dried (Na_2SO_4) and evaporated, and the crude material was chromatographed in 25% ethyl acetate–light petroleum to give (**5b**) (0.1298 g, 76%) as a clear syrup; $[\alpha]_D$ −22.96° ($CHCl_3$, *c* 0.85); ν_{max}(neat) 3 250–3 500 (OH, NH), 1 640 (CO, *N*-acetyl), and 1 260 cm^{-1} ($SiCH_3$); δ_H 0.03 [s, 6 H, $Si(CH_3)_2$], 0.85 (s, 9 H, $SiBu^t$), 1.09 (d, 3 H, 6-CH_3, $J_{CH_3,5}$ 6.3 Hz), 1.75 (s, 3 H, *N*-$COCH_3$), 2.12–2.21 (m, 1 H, 8-H), 2.38–2.49 (m, 1 H, 8′-H), 2.66 (br s, 1 H, 3-H), 3.37 (d, 1 H, OH, $J_{OH,5}$ 4.8 Hz), 3.68 br q, 1 H, 9-H, *J* 6.2 Hz), 3.78–3.87 (m, 2 H, 5-H, 10-H), 4.03 (ABq, 2 H, 1-H, 1′-H, J_{AB} 13.65 Hz, δν 27.55 Hz), 4.11–4.16 (m, 1 H, 4-H), 4.57 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 11.7 Hz, δν 28.60 Hz), 4.71 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 11.7 Hz, δν 81.06 Hz), 5.68 (br s, 1 H, 7-H), 6.56 (d, 1 H, NH, $J_{4\text{-}NH}$ 8.4 Hz), and 7.29 (m, 10 H, aromatic) (Found: C, 69.9; H, 8.3. $C_{33}H_{47}NO_5Si$ requires C, 70.05; H, 8.37%).

(3R)-[3α(R*),4α,5β]-N-(1-{2-[(*t-Butyldimethylsilyloxy)methyl*]-4,5-*dibenzyloxycyclohex*-1-*en*-3-*yl*}-2-*oxopropyl*)*acetamide* (**6**).—The alcohol (**5b**) (0.1298 g, 0.23 mmol) was dissolved in dry methylene dichloride (8 ml) at room temperature under argon and a mixture of pyridinium chlorochromate (0.306 g, 1.42 mmol), Celite (0.300 g), Florisil (0.030 g), and sodium acetate (0.117 g, 1.42 mmol) were added. After 4 h, the dark brown solution was diluted with diethyl ether and filtered through a short column of Florisil. The solvents were evaporated and the crude material was chromatographed in 15% ethyl acetate–light petroleum to give (**6**) (0.0894 g, 69.6%) as a clear syrup; $[\alpha]_D$ +27.46° ($CHCl_3$, *c* 2.24); ν_{max}(neat) 3 375 (NH), 3 050 (alkene CH), 1 720 (CO), 1 660 (CO, *N*-acetyl), and 1 260 cm^{-1} ($SiCH_3$); δ_H 0.03 [s, 6 H, $Si(CH_3)_2$], 0.85 (s, 9 H, $SiBu^t$), 1.87 (s, 3 H, *N*-acetyl CH_3), 2.10 (s, 3 H, 6-CH_3), 2.0–2.14 (m, 1 H, 8-H), 2.43 (br dt, 1 H, 8′-H, $J_{8',8}$ 17.1 Hz, *J* 5.78 Hz), 3.09–3.15 (m, 1 H, 3-H), 3.40 (t, 1 H, 10-H, *J* 9.3 Hz), 3.62 (td, 1 H, 9-H, $J_{9,8eq}$ 5.4 Hz, *J* 9.6 Hz), 3.88 (s, 2 H, 1-H, 1′-H), 4.61 (s, 2 H, $OCH_2C_6H_5$), 4.83 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 11.55 Hz, δν 105.42 Hz), 5.04 (dd, 1 H, 4-H, $J_{4,NH}$ 9.9 Hz, $J_{4,3}$ 1.2 Hz), 5.59 (br d, 1 H, 7-H, *J* 6.3 Hz), 6.75 (d, 1 H, NH, $J_{NH,4}$ 9.3 Hz), and 7.15–7.35 (m, 10 H, aromatic) (Found: C, 70.1; H, 8.15. $C_{33}H_{45}NO_5Si$ requires C, 70.30; H, 8.04%); *m*/*z* 552.3145 (MH^+ requires 552.3136).

(3R)-[3α(1R*,2S*)-4α,5β]-N-(3,3-*Dichloro*-1-{2-[*t-butyldimethylsilyloxy)methyl*]-4,5-*dibenzyloxycyclohex*-1-*en*-3-*yl*}-2-*hydroxypropyl*)*acetamide* (**7**).—Dry methylene dichloride (0.50 ml, 7.8 mmol) was added to dry tetrahydrofuran (1.5 ml) and the mixture was cooled to −100 °C (liq. N_2–EtOH) under argon. To the rapidly stirred mixture was added slowly butyllithium (1.6 ml, 4.0 mmol). The resulting grey–white solution of dichloromethyl-lithium was stirred for 15 min at −100 °C after which the ketone (**6**) (0.078 g, 0.14 mmol) dissolved in dry tetrahydrofuran (0.5 ml) was added slowly over 30 min. The reaction mixture was stirred at −100 °C under argon for 2 h and then allowed to warm to −60 °C. At −60 °C, the dark brown solution was quenched with saturated aqueous ammonium chloride and extracted with diethyl ether. The organic layers were dried (Na_2SO_4) and evaporated, and the crude material was chromatographed in 15% ethyl acetate–light petroleum to give (**7**) (0.057 g, 64.3%) as a clear syrup; $[\alpha]_D$ + 4.81° ($CHCl_3$, *c* 1.35); ν_{max}($CHCl_3$) 3 400 (NH, OH) and 1 670 cm^{-1} (CO, *N*-acetyl); δ_H 0.10 [s, 6 H, $Si(CH_3)_2$], 0.90 (s, 9 H, $SiBu^t$), 1.45 (s, 3 H, 6-CH_3), 1.75 (br s, 3 H, *N*-acetyl CH_3), 2.11–2.19 (m, 1, 8-H), 2.53 (br dt, 1 H, 8′-H, $J_{8',8}$ 17.09 Hz, *J* 5.73 Hz), 2.79–2.81 (m, 1 H, 3-H), 3.66 (td, 1 H, 9-H, $J_{9,8eq}$ 5.22 Hz, *J* 8.67 Hz), 4.08–4.24 (m, 3 H, 1-H, 1′-H, 10-H), 4.66 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 11.66 Hz, δν 10.77 Hz), 4.77 (d, 2 H, 4-H, part of ABq of $OCH_2C_6H_5$, *J* 10.5 Hz), 4.93 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 10.60 Hz, δν 96.25 Hz), 5.71 (s, 1 H, $CHCl_2$), 5.72–5.75 (m, 1 H, 7-H), 6.66 (br d, 1 H, NH, $J_{NH,4}$ 8.87 Hz), and 7.29–7.41 (m, 10 H, aromatic) (Found: C, 62.25; H, 7.6; Cl, 11.2. $C_{34}H_{47}Cl_2NO_5Si$ requires C, 62.25; H, 7.44; Cl, 11.14%); *m*/*z* 636.2679 (MH^+ requires 636.2664).

(3R)-[3α(1R*,2S*)-4α,5β]-N-[3,3-*Dichloro*-2-*hydroxy*-1-(2-*hydroxymethyl*-4,5-*dibenzyloxycyclohex*-1-*en*-3-*yl*)-2-*methylpropyl*]*acetamide* (**10**).—The silyl ether (**7**) (0.057 g, 0.090 mmol) was dissolved in a mixture of acetic acid–water–tetrahydrofuran (3:1:1; 5 ml) and the solution was stirred at room temperature for 4 h. It was then quenched with saturated aqueous sodium hydrogencarbonate and the solvents were evaporated. The residue was triturated with ethyl acetate and the organic extract filtered, dried (Na_2SO_4), and evaporated. The crude material was chromatographed in 50% ethyl acetate–light petroleum to give (**10**) (0.0393 g, 83.3%) as a clear syrup; $[\alpha]_D$ +10.5° ($CHCl_3$, *c* 0.60); ν_{max}(solution cell) 3 425 (NH, OH), 3 025 (alkene CH), and 1 660 cm^{-1} (CO, *N*-acetyl); δ_H 1.46 (s, 3 H, 6-CH_3), 1.71 (s, 3 H, *N*-acetyl CH_3), 2.07–2.17 (m, 1 H, 8-H), 2.53 (br dt, 1 H, 8′-H, $J_{8',8}$ 17.33, *J* 5.63 Hz), 2.92 (br d, 1 H, 3-H, *J* 7.27 Hz), 3.65–3.72 (m, 1 H, 9-H), 4.00–4.32 (m, 3 H, 1-H, 1′-H, 10-H), 4.65 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 11.60 Hz, δν 12.79 Hz), 4.72–4.75 (m, 1 H, 4-H), 4.92 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 10.94 Hz, δν 116.44 Hz), 5.64–5.66 (br s, 1 H, 7-H), 5.78 (s, 1 H, $CHCl_2$), 6.69–6.74 (br s, 1 H, NH), and 7.30–7.41 (m, 10 H, aromatic); *m*/*z* 521.1728 (M^+ requires 521.1728).

(1R)-(1α,3α,4α,4aβ,5β,5α)-N-(3-*Dichloromethyl*-3,4,4a,5,6,7-*hexahydro*-5,6-*dibenzyloxy*-1-*hydroxy*-3-*methyl*-1H-2-*benzopyran*-4-*yl*)*acetamide* (**11**).—Oxalyl chloride (0.11 ml, 1.29 mmol) in dry methylene dichloride (0.5 ml) was cooled to −78 °C under argon, and dimethyl sulphoxide (0.13 ml, 1.86 mmol) was added slowly. The complex was stirred for 15 min at −78 °C, after which the allylic alcohol (**10**) (0.0414 g, 0.079 mmol) dissolved in dry methylene dichloride (0.5 ml) was added. The reaction mixture was stirred at −78 °C for 30 min after which triethylamine (0.52 ml, 3.73 mmol) was added, and the whole warmed slowly to −30 °C. The reaction was then quenched with saturated aqueous sodium hydrogencarbonate and the mixture diluted with methylene dichloride and washed with aqueous sodium hydrogencarbonate. The organic layer

was dried (Na_2SO_4) and evaporated and the resulting crude material was chromatographed in 50% ethyl acetate–light petroleum to give (**11**) (0.019 g, 46.8%) as a clear syrup. The major anomer, (**11a**), had the following physical characteristics: δ_H 1.56 (s, 3 H, 6-CH_3), 2.02 (s, 3 H, *N*-acetyl CH_3), 2.05–2.20 (m, 1 H, 8-H), 2.60 (dt, 1 H, 8′-H, $J_{8',8}$ 17.77 Hz, *J* 5.60 Hz), 2.79–2.81 (m, 1 H, 3-H), 3.38 (t, 1 H, 10-H, *J* 9.06 Hz), 3.71–3.83 (m, 1 H, 9-H), 4.13 (d, 1 H, OH, $J_{OH,1}$ 4.89 Hz), 4.72 (s, 2 H, $OCH_2C_6H_5$), 4.87 (ABq, 2 H, $OCH_2C_6H_5$, J_{AB} 9.77 Hz, δν 54.06 Hz), 4.87 (dd, 1 H, 4-H, $J_{4,3}$ 3.02 Hz, $J_{4,NH}$ 10.65 Hz), 5.53 (br s, 1 H, 1-H), 5.84–5.85 (m, 1 H, 7-H), 5.94 (s, 1 H, $CHCl_2$), 6.34 (d, 1 H, NH, $J_{NH,4}$ 10.74 Hz), and 7.25–7.49 (m, 10 H, aromatic); *m/z* 519.1572 ($C_{27}H_{31}Cl_2O_5H$ requires 519.1572).

(3R)-(3α,4α,4aβ,5β,6α)-N-[3,4,4a,5,6,7-*Hexahydro*-5,6,8-*tris*-(*methoxymethoxy*)-3-*methyl*-1-*oxo*-1H-2-*benzopyran*-4-*yl*]*acetamide* (**17**).—The amine hydrochloride (**2a**) (0.576 g, 2.27 mmol) was dissolved in dry methanol (10 ml) at 0 °C under argon, and triethylamine (5.7 ml, 40.86 mmol), followed by acetic anhydride (1.93 ml, 20.42 mmol) were added. After 30 min at 0 °C, the solvents were evaporated and the residue was azeotroped with toluene to give the crude *N*-acetyl compound (**2c**) as a white solid (0.557 g). This material was suspended in dry methylene dichloride (30 ml) at 0 °C under argon, and dry di-isopropylethylamine (11.2 ml, 64.3 mmol) was added, followed by chloromethyl methyl ether (3.24 ml, 42.66 mmol). The orange–yellow solution was allowed to warm to room temperature and after 24 h it was diluted with methylene dichloride and washed with saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated. The residue in ethyl acetate was chromatographed to give (**17**) (0.186 g, 20.3% over two steps) as a clear syrup; $[\alpha]_D$ +53.27° ($CHCl_3$, *c* 1.13); ν_{max}($CHCl_3$) 3 440 (NH), 2 890 (OCH_2O, OCH_3), 1 710 (CO, lactone), and 1 680 cm^{-1} (CO, *N*-acetyl); δ_H 1.30 (d, 3 H, 6-CH_3, $J_{CH_3,5}$ 6.41 Hz, 2.05 (s, 3 H, *N*-acetyl CH_3), 2.55 (ddd, 1 H, 8-H, $J_{8,8'}$ 17.97 Hz, $J_{8,3}$ 2.98 Hz), 2.84–2.87 (m, 1 H, 3-H), 3.02 (ddd, 1 H, 8′-H, $J_{8',8}$ 18.03 Hz, $J_{8',9}$ 5.90 Hz, $J_{8',3}$ 1.40 Hz), 3.40 (s, 3 H, OCH_2OCH_3), 3.44 (s, 3 H, OCH_2OCH_3), 3.51 (s, 3 H, OCH_2OCH_3), 3.43–3.46 (m, 1 H, 10-H), 3.86 (td, 1 H, 9-H, $J_{9,8'}$ 5.96 Hz, $J_{9,10;9,8}$ 9.0 Hz), 4.51 (qd, 1 H, 5-H, $J_{5,CH3}$ 6.39 Hz, $J_{5,4}$ 1.91 Hz), 4.58–4.63 (m, 1 H, 4-H), 4.75 (ABq, 2 H, OCH_2OCH_3, J_{AB} 6.82 Hz, δν 19.62 Hz), 4.79 (ABq, 2 H, OCH_2OCH_3, J_{AB} 6.13 Hz, δν 22.82 Hz), 5.15 (ABq, 2 H, OCH_2OCH_3, J_{AB} 6.88 Hz, δν 19.80 Hz), and 5.56 (d, 1 H, NH, $J_{NH,4}$ 9.71 Hz) (Found: C, 53.5; H, 7.15. $C_{18}H_{29}NO_9$ requires C, 53.59; H, 7.25%).

(3aR)-(3aα,8β,9β,9aα,9bβ)-N-[4,6,8,9,9a,9b-*Hexahydro*-5-*hydroxy*-8-*methyl*-3aH-1,3-*dioxolo*[4,5-f][2]*benzopyran*-9-*yl*]-*acetamide* (**15a**).—The amine hydrochloride (**2a**) (0.2044 g, 0.81 mmol) was dissolved in dry methanol (5 ml) at 0 °C under argon. To the stirred solution was added triethylamine (0.67 ml, 4.80 mmol) and acetic anhydride (0.23 ml, 2.43 mmol) and the reaction mixture was stirred for 30 min at 0 °C. The solvents were evaporated and the residue was azeotroped with toluene, and then dissolved in dry *N*,*N*-dimethylformamide (5.0 ml). A catalytic amount of pyridinium toluene-*p*-sulphonate and a large excess of 2,2-dimethoxypropane (2.0 ml) were added, and after 14 h, the reaction was quenched with solid sodium hydrogencarbonate. The solvents were removed by the use of a high vacuum pump, and the crude material was chromatographed in ethyl acetate to give (**15a**) (0.100 g, 39% over two steps) as a white semisolid; $[\alpha]_D$ −7.30° ($CHCl_3$, *c* 0.71); ν_{max}($CHCl_3$) 3 375 (NH, OH) and 1 600–1 720 cm^{-1} (CO, *N*-acetyl, lactone); δ_H 1.35 (d, 3 H, 6-CH_3, $J_{CH_3,5}$ 6.4 Hz), 1.43 (s, 3 H, acetonide CH_3), 1.45 (s, 3 H, acetonide CH_3), 2.09 (s, 3 H, *N*-acetyl CH_3), 2.62 (ddd, 1 H, 8-H, $J_{8,3}$ 2.76 Hz, $J_{8,9}$ 11.19 Hz, $J_{8,8'}$ 17.60 Hz), 2.89–2.97 (m, 2 H, 3-H, 8′-H), 3.28 (t, 1 H, 10-H, *J* 9.40 Hz), 3.69–3.78 (m, 1 H, 9-H), 4.62 (qd, 1 H, 5-H, $J_{5,4}$ 1.55 Hz, J_{5,CH_3} 6.42 Hz), 4.77 (br d, 1 H, 4-H, $J_{4,NH}$ 10 Hz), 6.05 (d, 1 H, NH, $J_{NH,4}$ 10.01 Hz) (Found: C, 58.0; H, 6.9. $C_{15}H_{21}NO_6$ requires C, 57.87; H, 6.80%).

(3aR)-(3aα,8β,9β,9aα,9bβ)-N-{4,6,8,9,9a,9b-*Hexahydro*-5-(*methoxymethoxy*)-8-*methyl*-3aH-1,3-*dioxolo*[4,5-f][2]*benzopyran*-9-*yl*}*acetamide* (**15b**).—The enol lactone (**15a**) (0.972 g, 3.12 mmol) was converted into the methoxymethyl ether, as described for (**17**). For (**15b**) $[\alpha]_D$ −41.27° ($CHCl_3$, *c* 0.71); ν_{max}($CHCl_3$) 3 350 (NH), 2 925 (OCH_2O, OCH_3), 1 715, (CO, lactone), and 1 680 cm^{-1} (CO, *N*-acetyl); δ_H 1.30 (d, 3 H, 6-CH_3, $J_{CH_3,5}$ 6.34 Hz), 1.43 (s, 3 H, acetonide CH_3), 1.45 (s, 3 H, acetonide CH_3) 2.08 (s, 3 H, *N*-acetyl CH_3), 2.60 (ddd, 1 H, 8-H, $J_{8,3}$ 3.57 Hz, $J_{8,9}$ 10.85 Hz, $J_{8,8'}$ 16.85 Hz), 2.96–3.02 (m, 1 H, 3-H), 3.12 (ddd, 1 H, 8′-H, $J_{8',3}$ 1.30 Hz, $J_{8',9}$ 5.73 Hz, $J_{8',8}$ 16.79 Hz), 3.30 (t, 1 H, 10-H, *J* 9.40 Hz), 3.52 (s, 3 H, OCH_2OCH_3), 3.68–3.77 (m, 1 H, 9-H), 4.55–4.64 (m, 2 H, 4-H, 5-H), 5.15 (ABq, 2 H, OCH_2OCH_3, J_{AB} 6.88 Hz, δν 20.63 Hz), and 5.65 (d, 1 H, NH, $J_{NH,4}$ 9.71 Hz) (Found: C, 57.2; H, 7.15. $C_{17}H_{25}NO_7$ requires C, 57.45; H, 7.09%).

(3R)-[3aα(1R*,2R*),4α,6β]-N-{2-*Hydroxy*-3,4,5,6-*tetrahydro*-2-*hydroxymethyl*-1-(*methoxymethoxy*)-1,3-*dioxolo*[4,5-f]-*cyclohex*-1-*en*-3-*ylpropyl*}*acetamide* (**16a**).—The lactone (**15b**) (0.3706 g, 1.04 mmol) was reduced with sodium borohydride in the presence of cerium chloride, as described above for (**5a**). The material (**16a**) was characterized as the diacetate: $[\alpha]_D$ −38.41° ($CHCl_3$, *c* 2.33); ν_{max}($CHCl_3$) 3 500 (NH), 2 950 (OCH_2O, OCH_3), 1 740 cm^{-1} (CO, *O*-acetyl), and 1 680 cm^{-1} (CO, *N*-acetyl); δ_H 1.24 (d, 3 H, 6-CH_3, J_{5,CH_3} 6.34 Hz), 1.42 (s, 3 H, acetonide CH_3), 1.44 (s, 3 H, acetonide CH_3), 2.05 (s, 3 H, acetyl CH_3), 2.06 (s, 3 H, acetyl CH_3), 2.11 (s, 3 H, acetyl CH_3), 2.37–2.48 (m, 1 H, 8-H), 2.65–2.70 (m, 1 H, 3-H), 2.80 (dd, 1 H, 8′-H, $J_{8',9}$ 5.49 Hz, $J_{8',8}$ 15.56 Hz), 3.39 (t, 1 H, 10-H, *J* 9.58 Hz), 3.40 (s, 3 H, OCH_2OCH_3), 3.58–3.67 (m, 1 H, 9-H), 4.45 (br d, 1 H, 4-H, *J* 9.8 Hz), 4.78 (ABq, 2 H, 1-H, 1′-H, J_{AB} 12.56 Hz, δν 46.53 Hz), 4.88 (ABq, 2, OCH_2OCH_3, J_{AB} 6.86 Hz, δν 10.02 Hz, 5.0 (dq, 1 H, 5-H, $J_{5,4}$ 1.47 Hz, J_{5-CH3} 6.34 Hz), and 6.31 (d, 1 H, NH, $J_{NH,4}$ 9.63 Hz) (Found: C, 56.9; H, 7.6. $C_{21}H_{33}NO_9$ requires C, 56.87; H, 7.50%).

(3R)-[3α(R*),4α,5β]-N-{[2-(*t-Butyldimethylsilyloxy*)*methyl*]-3,4,5,6-*tetrahydro*-1-(*methoxymethoxy*)-1,3-*dioxolo*[4,5-f]-*cyclohex*-1-*en*-3-*yl*}-2-*oxopropyl*]*acetamide* (**16b**).—The diol (**16a**) (0.240 g, 0.67 mmol) was monosilylated and oxidized, as described above for compound (**6**) to give (**16b**) (0.1286 g, 73%) as a clear syrup; $[\alpha]_D$ −18.22° ($CHCl_3$, *c* 2.36); ν_{max}($CHCl_3$) 3 650 cm^{-1} (NH), 1 720 (CO, ketone), and 1 680 cm^{-1} (CO, *N*-acetyl); δ_H 0.106 (s, 3 H, $SiCH_3$), 0.112 (s, 3 H, $SiCH_3$), 0.92 (s, 9 H, $SiBu^t$), 1.43 (s, 3 H, acetonide CH_3), 1.44 (s, 3 H, acetonide CH_3), 2.06 (s, 3 H, *N*-acetyl CH_3), 2.22 (s, 3 H, 6-CH_3), 2.37–2.47 (m, 1 H, 8-H), 2.77 (dd, 1 H, 8′-H, $J_{8',9}$ 5.25 Hz, $J_{8',8}$ 15.45 Hz), 3.26 (br s, 1 H, 3-H), 3.29 (t, 1 H, 10-H, *J* 9.96 Hz), 3.42 (s, 3 H, OCH_3OCH_3), 3.61–3.69 (m, 1 H, 9-H), 4.24 (ABq, 2 H, 1-H, 1′-H, J_{AB} 10.84 Hz, δν 141.05 Hz), 4.89 (ABq, 2 H, OCH_2OCH_3), J_{AB} 6.93 Hz, δν 3.71 Hz), 5.04 (dd, 1 H, 4-H, $J_{4,3}$ 1.74 Hz, $J_{4,NH}$ 9.26 Hz), and 7.12 (d, 1 H, NH, $J_{NH,4}$ 9.52 Hz) (Found: C, 58.35; H, 8.65. $C_{23}H_{41}NO_7Si$ requires C, 58.57; H, 8.76%).

(3R)-[3α(1R*,2R*),4α,5β]-N-[2-*Hydroxy*-(2-*hydroxymethyl*-1,4,5-*tris*(*methoxymethoxy*)*cyclohex*-1-*en*-3-*yl*]*propylacetamide* (**18a**).—The lactone (**17**) (0.920 g, 2.28 mmol) was dissolved in dry methanol (30 ml) and cooled to 0 °C under argon. Cerium chloride (2.024 g, 5.43 mmol, 2.38 equiv.) was added to the stirred solution, followed by sodium borohydride

(2.30 g, 60.85 mmol, 26.69 equiv.) added slowly over 5 min. A vigorous evolution of gases occurred. After 2 h at 0 °C, the reaction mixture was brought to pH 6 with HCl–MeOH. The reaction mixture was evaporated, and the white solid was azeotroped with toluene and dried on a high vacuum pump to give the crude diol which was best purified by acetylation. Thus, the material was dissolved in dry pyridine (20 ml) and the solution cooled to 0 °C under argon. To the stirred solution was added excess acetic anhydride and the reaction mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was diluted with methylene dichloride and the organic layer was washed with aqueous sodium hydrogencarbonate and brine, dried (Na_2SO_4), and evaporated to give the crude diacetate. This was dissolved in a mixture of methanol–water–triethylamine (5:4:1; 3.0 ml) and the light yellow solution stirred at room temperature for 14 h. The solvents were then evaporated and the resulting syrup was azeotroped with toluene. The crude material was chromatographed in 5% methanol–ethyl acetate to give (**18a**) (0.2625 g, 28.5% over three steps) as a clear syrup; δ_H 1.17 (d, 3 H, 6-CH_3, $J_{CH3,5}$ 6.40 Hz), 2.01 (s, 3 H, *N*-acetyl CH_3), 2.38 (dd, 1 H, 8-H, $J_{8,8'}$ 16.92 Hz, $J_{8,9}$ 4.98 Hz), 2.57 (dd, 1 H, 8′-H, $J_{8',8}$ 16.72 Hz, $J_{8',9}$ 4.96 Hz), 2.79–2.82 (m, 1 H, 3-H), 3.23–3.30 (m, 1 H, OH), 3.35 (s, 3 H OCH_2OCH_3), 3.38 (s, 3 H, OCH_2OCH_3), 3.44 (s, 3 H, OCH_2OCH_3), 3.71 (d, 1 H, OH, $J_{OH,5}$ 5.13 Hz), 3.86–3.92 (m, 1, 9-H), 3.96–4.05 (m, 2 H, 5-H, 10-H), 4.10–4.20 (m, 2 H, 4-H, 1-H), 4.35 (br d, 1 H, 1′-H, part of ABq, J_{AB} 12.06 Hz), 4.62–4.75 (m, 4 H, 2 × OCH_2OCH_3), 4.86 (s, 2 H, OCH_2OCH_3), and 6.91 (d, 1, NH, $J_{NH,4}$ 8.41 Hz); *m/z* 408.2233 (MH^+; $C_{18}H_{33}NO_9$ requires 408.2227).

(3R)-[3α(1R*,2R*),4α,5β]-N-{[2-(*t-Butyldimethylsilyloxy*)-*methyl*]-1,4,5-*tris*(*methoxymethoxy*)*cyclohex*-1-*en*-3-*yl*]-2-*hydroxypropyl*}*acetamide* (**18b**).—The diol (**18a**) (0.1758 g, 0.43 mmol) was dissolved in dry methylene dichloride (5 ml) at room temperature under argon and to the stirred solution was added triethylamine (0.24 ml, 1.72 mmol), a catalytic amount of *N*,*N*-dimethylaminopyridine, and finally, t-butyldimethylsilyl chloride (0.117 g, 0.78 mmol). After 4 h, the reaction mixture was diluted with methylene dichloride and washed with aqueous sodium hydrogencarbonate and brine. The organic layer was dried (Na_2SO_4) and evaporated, and the crude mixture was chromatographed in ethyl acetate to give (**18b**) (0.129 g, 58%); $[\alpha]_D$ +3.55° ($CHCl_3$, *c* 1.55); ν_{max}(neat) 3 400 (NH, OH), 2 900 (OCH_2O, OCH_3), and 1 660 cm^{-1} (CO, *N*-acetyl); δ_H 0.11 (s, 6 H, $SiMe_2$), 0.92 (s, 9, $SiBu^t$), 1.21 (d, 3 H, 6-CH_3, $J_{CH3,5}$ 6.35 Hz), 1.99 (s, 3 H, *N*-acetyl CH_3), 2.40 (dd, 1 H, 8-H, $J_{8,8'}$ 16.70 Hz, $J_{8,9}$ 6.75 Hz), 2.59 (dd, 1 H, 8′-H, $J_{8',8}$ 17.00 Hz, $J_{8',9}$ 5.04 Hz), 2.75–2.78 (m, 1 H, 3-H), 3.38 (s, 3 H, OCH_2OCH_3), 3.43 (s, 6, 2 × OCH_2OCH_3), 3.82 (q, 1 H, 9-H, *J* 6.18 Hz), 3.92–4.0 (m, 2 H, 10-H, 5-H), 4.25–4.29 (m, 1 H, 4-H), 4.30 (ABq, 2 H, 1-H, 1′-H, J_{AB} 11.50 Hz, δν 51.69 Hz), 4.70 (ABq, 2 H, OCH_2OCH_3, J_{AB} 6.93 Hz, δν 5.16 Hz), 4.77 (ABq, 2 H, OCH_2OCH_3, J_{AB} 6.32 Hz, δν 5.43 Hz), 4.87 (ABq, 2 H, OCH_2OCH_3, J_{AB} 6.67 Hz, δν 12.52 Hz), and 6.68 (d, 1 H, NH, $J_{NH,4}$ 8.79 Hz) (Found: C, 55.15; H, 8.9. $C_{24}H_{47}NO_9Si$ requires C, 55.25; H, 9.08%).

(3R)-[3α(R*),4α,5β]-N-{[2-(*t-Butyldimethylsilyloxy*)-*methyl*]-*tetrahydro*-1,4,5-*tris*(*methoxymethoxy*)*cyclohex*-1-*en*-3-*yl*]-2-*oxopropyl*}*acetamide* (**18c**).—The alcohol (**18b**) (0.1376 g, 0.26 mmol) was oxidized, as described above for (**6**), to give (**18c**) (0.080 g, 57.7%) as a clear syrup; $[\alpha]_D$ +43.36° ($CHCl_3$, *c* 1.10); ν_{max}(neat) 3 350 (NH), 3 900 (OCH_2O, OCH_3), 1 710 (CO, ketone), and 1 680 cm^{-1} (CO, N-acetyl); δ_H 0.10 (s, 6 H, $SiMe_2$), 0.91 (s, 9 H, $SiBu^t$), 2.03 (s, 3 H, *N*-acetyl CH_3), 2.24 (s, 3 H, 6-CH_3), 2.22–2.32 (m, 1 H, 8-H), 2.68 (dd, 1 H, 8′-H, $J_{8,8'}$ 16.73 Hz, $J_{8',9}$ 5.49 Hz), 3.29 (br d, 1 H, 3-H, *J* 6.89 Hz), 3.38 (s, 3 H, OCH_2OCH_3), 3.42 (s, 3 H, OCH_2OCH_3), 3.43–3.45 (m, 1 H, 10-H), 3.47 (s, 3 H, OCH_2OCH_3), 3.76 (td, 1 H, 9-H, $J_{9,10:9,8}$ 8.83 Hz, $J_{9,8'}$ 5.57 Hz), 4.13 (ABq, 2 H, 1-H, 1′-H, J_{AB} 11.01 Hz, δν 150.22 Hz), 4.71 (ABq, 2 H, OCH_2OCH_3, J_{AB} 6.85 Hz, δν 11.72 Hz), 4.85 (s, 2, OCH_2OCH_3), 4.88 (ABq, 2 H, OCH_2OCH_3, J_{AB} 6.81 Hz, δν 5.12 Hz), 5.05 (dd, 1 H, 4-H, $J_{4,NH}$ 9.18 Hz, $J_{4,3}$ 2.05 Hz), and 7.05 (d, 1 H, NH, $J_{NH,4}$ 9.15 Hz) (Found: C, 55.6; H, 8.75. $C_{24}H_{45}NO_9Si$ requires C, 55.47; H, 8.73%).

(3R)-[3α(1R*,2S*),4α,5β]-N-{3,3-*Dichloro*-1-[2-(*t-butyldimethylsilyloxy*)*methyl*-1,4,5-*tris*(*methoxymethoxy*)*cyclohex*-1-*en*-3-*yl*]-2-*hydroxy*-2-*methylpropyl*}*acetamide* (**19a**).—Lithium dichloromethanide (10 equiv.) was prepared and to this was added the ketone (**18c**) (0.041 g, 0.079 mmol) in dry tetrahydrofuran (0.5 ml), as described above for (**7**), to give (**19a**) (0.024 g, 50.6%) as a light yellow syrup; $[\alpha]_D$ +25.80° ($CHCl_3$, *c* 1.12); ν_{max}(neat) 3 300 cm^{-1} (OH, NH), 2 900 (CH_2O, OCH_3), and 1 660 cm^{-1} (CO, *N*-acetyl); δ_H 0.15 (s, 6 H, $SiMe_2$), 0.95 (s, 9 H, $SiBu^t$), 1.49 (s, 3 H, 6-CH_3), 1.94 (s, 3 H, *N*-acetyl CH_3), 2.37 (dd, 1 H, 8-H, $J_{8,8'}$ 17.19 Hz, $J_{8,9}$ 4.74 Hz), 2.58 (dd, 1 H, 8′-H, $J_{8,'8}$ 17.27 Hz, $J_{8',9}$ 5.2 Hz), 2.78 (br s, 1 H, 3-H), 3.37 (s, 3 H, OCH_2OCH_3), 3.41 (s, 3 H, OCH_2OCH_3), 3.43 (s, 3 H, OCH_2OCH_3), 3.89 (q, 1 H, 9-H, *J* 5.27 Hz), 3.97–4.02 (m, 2 H, 10-H, 1-H; part of ABq), 4.13 (br s, 1 H, OH), 4.35 ($\frac{1}{2}$ ABq, 1 H, 1′-H, J_{AB} 9.52 Hz, δν 206.2 Hz), 4.63 (s, 2 H, OCH_2OCH_3), 4.73–4.83 (m, 2 H, 4-H, OCH_2OCH_3), 4.91 (ABq, 2 H, OCH_2OCH_3, J_{AB} 6.83 Hz, δν 20.15 Hz), 5.90 (s, 1 H, $CHCl_2$), and 7.14 (d, 1 H, NH, $J_{NH,4}$ 8.74 Hz); *m/z* 603.2383 (*M*; $C_{25}H_{47}Cl_2NO_9Si$ requires 603.2385).

(3R)-[3α(1R*,2S*),4α,5β]-N-{[3,3-*Dichloro*-2-*hydroxymethyl*-1,4,5-*tris*(*methoxymethoxy*)*cyclohex*-1-*en*-3-*yl*]-2-*hydroxy*-2-*methylpropyl*}*acetamide* (**19b**).—Compound (**19a**) (0.028 g, 0.3 mmol) was desilylated, as described for (**7**), to give the diol (**19b**) (0.085 g). Pyridinium dichromate (0.0123 g, 0.033 mmol) was suspended in dry methylene dichloride (1.0 ml) and the mixture stirred at room temperature under argon. To the suspension was added acetic anhydride (0.006 ml, 0.063 mmol), followed by the diol (**19b**) dissolved in dry methylene dichloride (0.25 ml). After being stirred under reflux for 2.5 h, the solution was allowed to cool to room temperature, when it was diluted with diethyl ether, and filtered through a short column of Florisil. The solvents were evaporated and the crude material was azeotroped with toluene. The residue was chromatographed in ethyl acetate to give (**23**) (0.004 g) as a clear syrup; δ_H 1.58 (s, 3 H, 6-CH_3), 2.05 (s, 3 H, *N*-acetyl CH_3), 2.64 (ddd, 1 H, 8-H, $J_{8,8'}$ 16.75 Hz, $J_{8,9}$ 6.05 Hz, *J* 1.14 Hz), 2.82 (dd, 1 H, 8′-H, $J_{8'8}$ 16.77 Hz, $J_{8',9}$ 3.07 Hz), 3.03–3.07 (m, 1 H, 3-H), 3.34 (s, 3 H, OCH_2OCH_3), 3.43 (s, 3 H, OCH_2OCH_3), 3.64 (t, 1 H, 10-H, *J* 4.33 Hz), 4.10–4.16 (m, 1 H, 9-H), 4.66 (ABq, 2 H, OCH_2OCH_3, J_{AB} 6.74 Hz, δν 15.84 Hz), 4.78 (ABq, 2 H, OCH_2OCH_3, J_{AB} 6.63 Hz, δν 5.79 Hz), 4.88 (dd, 1 H, 4-H, $J_{4,NH}$ 10.16 Hz), $J_{4,3}$ 4.25 Hz), 5.34 (br d, 1 H, NH, $J_{NH,4}$ 9.84 Hz), 5.81 (s, 1 H, $CHCl_2$), 7.50 (d, 1 H, 1-H, $J_{1,3}$ 2.52 Hz); *m/z*: 426.1086 ($C_{17}H_{25}Cl_2NO_7$ requires 426.1090.)

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