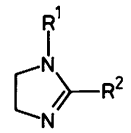
2-Methyl-4,5-dihydroimidazole as a Doubly Nucleophilic Unit: Preparation of Dihydroimidazole Azaprostanoids

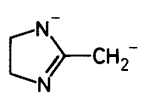
Raymond C. F. Jones * and Julie Schofield
Department of Chemistry, The University, Nottingham, NG7 2RD

2-Methyl-4,5-dihydroimidazole is incorporated as a doubly nucleophilic synthon, by successive alkylations at N-1 and C-2(Me), into monocyclic 9,12- and 8,11-diazaprostanoids containing the dihydroimidazole moiety. 2-Methyl-3a,4,7,7a-tetrahydrobenzimidazole is prepared (from 1,2,3,6-tetrahydrophthalic anhydride) and elaborated in the same way into a diazaprostacyclin precursor.

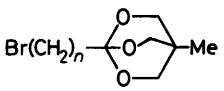
The elaboration of simple heterocycles is a long-standing goal of organic chemists. As part of a programme to develop methods patterned on the biological processes involving 4,5-dihydroimidazoles (2-imidazolines), we have described some chemistry consequent upon the deprotonation of 1-benzyl-2-methyl-4,5-dihydroimidazole (**1a**) to produce the lithio-derivative (**1b**).[1] The biological activity exhibited by many compounds containing the 4,5-dihydroimidazole ring was an added incentive for our investigations.[2] The potential nucleophilicity of N-1 presents the possibility of incorporating the 2-methyl-4,5-dihydroimidazole unit into target molecules as the doubly nucleophilic synthon (**2**), and we report herein the realisation of this objective as demonstrated by the synthesis of some monocyclic azaprostanoids, the first analogues of the primary prostaglandins to contain the 4,5-dihydroimidazole moiety.[3] This work also illustrates the reactivity of the lithio-dihydroimidazole (**1b**) towards some bifunctional electrophiles. We also report the application of this methodology to the elaboration of 2-methyl-3a,4,7,7a-tetrahydrobenzimidazole (prepared from 1,2,3,6-tetrahydrophthalic anhydride) into a potential precursor to diazaprostacyclins containing the 4,5-dihydroimidazole unit.



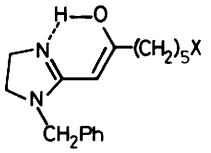
(**1**) **a**; $R^1 = CH_2Ph$, $R^2 = Me$
b; $R^1 = CH_2Ph$, $R^2 = CH_2Li$
c; $R^1 = H$, $R^2 = Me$



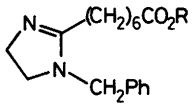
(**2**)



(**3**) **a**; $n = 5$
b; $n = 6$
c; $n = 3$



(**5**) **a**; X = Br
b; X = I

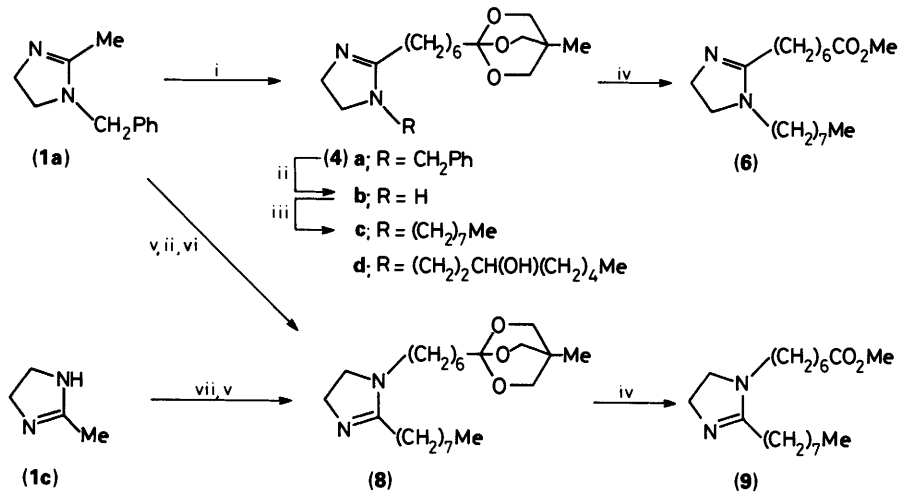


(**7**) **a**; $R = CH_2C(Me)(CH_2OH)_2$
b; R = Me

Results and Discussion

Attempts to form the dianion (**2**) directly by double deprotonation of 2-methyl-4,5-dihydroimidazole (**1c**) with butyl-lithium [2.2 mol equiv., tetrahydrofuran (THF), −78 °C] were unsuccessful, quenching with benzyl bromide affording only the *N*-benzylated (**1a**) (78%);[4] similar results were obtained with t-butyl-lithium as base. *N*-Alkylation of such cyclic amidines usually leads to mixtures containing some quaternary salt, so that this finding taken with our earlier work with the lithio-derivative (**1b**)[1] suggested the sequential use of the nucleophilic reactivities at N-1 and C-2(Me). The methodology is illustrated by the synthesis of the first analogues of the primary prostaglandins to contain the 4,5-dihydroimidazole moiety.[3] The incorporation of a variety of heterocycles is a well established approach to novel derivatives of these bioactive metabolites.[5]

The preparation of simple 9,12-diazaprostanoids proceeded (Scheme 1) *via* lithiation of a 1-benzyl-2-methyl-4,5-dihydroimidazole (**1a**) (butyl-lithium, THF, −78 °C)[1] and *C*-alkylation with 1-(5-bromopentyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane (**3a**) to elaborate the α-side-chain, affording (**4a**) (73%). The bromo-orthoesters (**3a**), and the homologues (**3b,c**) (see below), were prepared from boron trifluoride-mediated rearrangement of the ester formed between the corresponding ω-bromo-acid and 3-methyl-3-(hydroxymethyl)oxetane.[6] The trioxabicyclo-octane (OBO)[7] orthoester (**3a**) was chosen as the masked carboxylic acid derivative after attempted *C*-alkylation of (**1a**) with methyl 6-bromo- or 6-iodo-hexanoate resulted in competing *C*-acylation[1] to afford the halides (**5a**) and (**5b**), respectively. Unusually for a *C*-acylation product of a 2-methyl-4,5-dihydroimidazole,[1] the iodide (**5b**) existed in solution in chloroform as a mixture (1:1) of enol and keto tautomers. Debenzylation of (**4a**) with sodium in liquid ammonia–ethanol (−33 ⟶ 0 °C) unmasked N-1 to afford (**4b**) (78%) and subsequent *N*-alkylation with 1-iodo-octane (butyl-lithium, THF, 0 °C) gave the OBO orthoester (**4c**) (70%), which was smoothly converted into the methyl ester (**6**) (61%) by acidic methanolysis (MeOH, H_2SO_4) followed by basification with potassium carbonate; the dihydroimidazole ring is unaffected by these conditions.[1] Methanolysis of this and other OBO orthoesters prepared in our programme required modification of the reported conditions.[8] Increased acid concentrations and extended reaction times were necessary (see Experimental section), otherwise the intermediate 2,2-bis(hydroxymethyl)-propyl esters were isolated in good yield; this was exemplified by the isolation of either dihydroxyester (**7a**) (67%) or methyl ester (**7b**) (61%) from the treatment of the dihydroimidazole

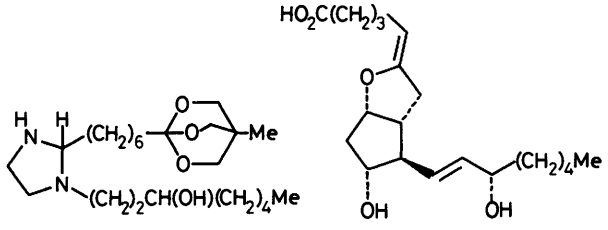


Scheme 1. *Reagents:* i, BuLi, −78 °C, (**3a**); ii, Na–NH_3(l), EtOH; iii, BuLi, 0 °C, $Me(CH_2)_7I$; iv, MeOH, H_2SO_4; then K_2CO_3; v, BuLi, −78 °C, $Me(CH_2)_6I$; vi, BuLi, 0 °C, (**3b**); vii, BuLi, 20 °C, (**3b**).

(**4a**) with H_2SO_4–MeOH, then K_2CO_3, depending on the exact conditions employed.

The 8,11-diazaprostanoids were also prepared from (**1a**) (Scheme 1) in an analogous fashion. Successive *C*-alkylation with 1-iodoheptane (87%), debenzylation (57%), and *N*-alkylation (this time at 20 °C) using 1-(6-bromohexyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**3b**) (53%) afforded the OBO orthoester (**8**). Conversion into the methyl ester (**9**) was performed as above. The orthoester (**8**) was also assembled by reversal of the order of utilisation of the nucleophilic reactivities (Scheme 1). Thus the dihydroimidazole (**1c**) was first *N*-alkylated at 20 °C with the bromo-orthoester (**3b**) (73%) and then *C*-alkylated with 1-iodoheptane (51%) to afford the orthoester (**8**) in an improved overall yield.

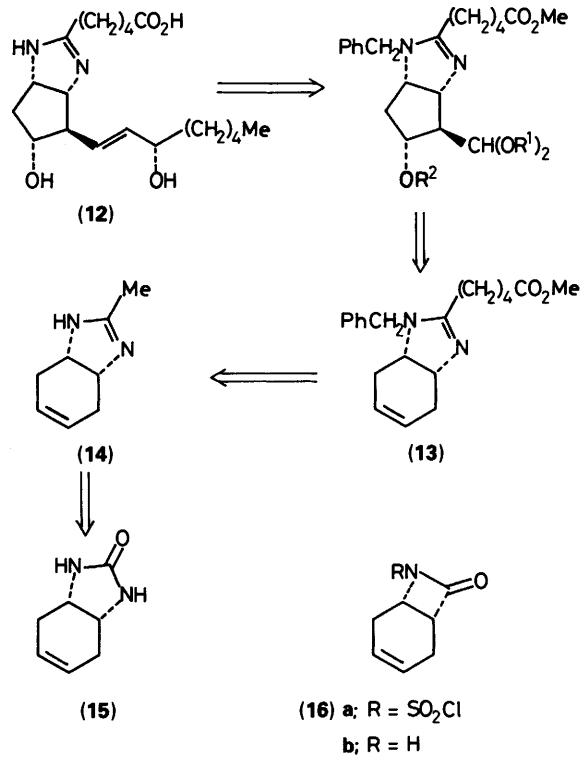
A functionalised β-side-chain was introduced into a 9,12-diazaprostanoid by reaction of the dihydroimidazole orthoester (**4b**) with oct-1-en-3-one (neat, 70 °C, 4 h) followed by reduction of the adduct without further purification; treatment at 0 °C in ethanol with $NaBH_4$ afforded the tetrahydroimidazole (**10**) (40%), whilst the use of $LiBH_4$ gave the dihydroimidazole (**4d**) after chromatography.



(**10**) (**11**)

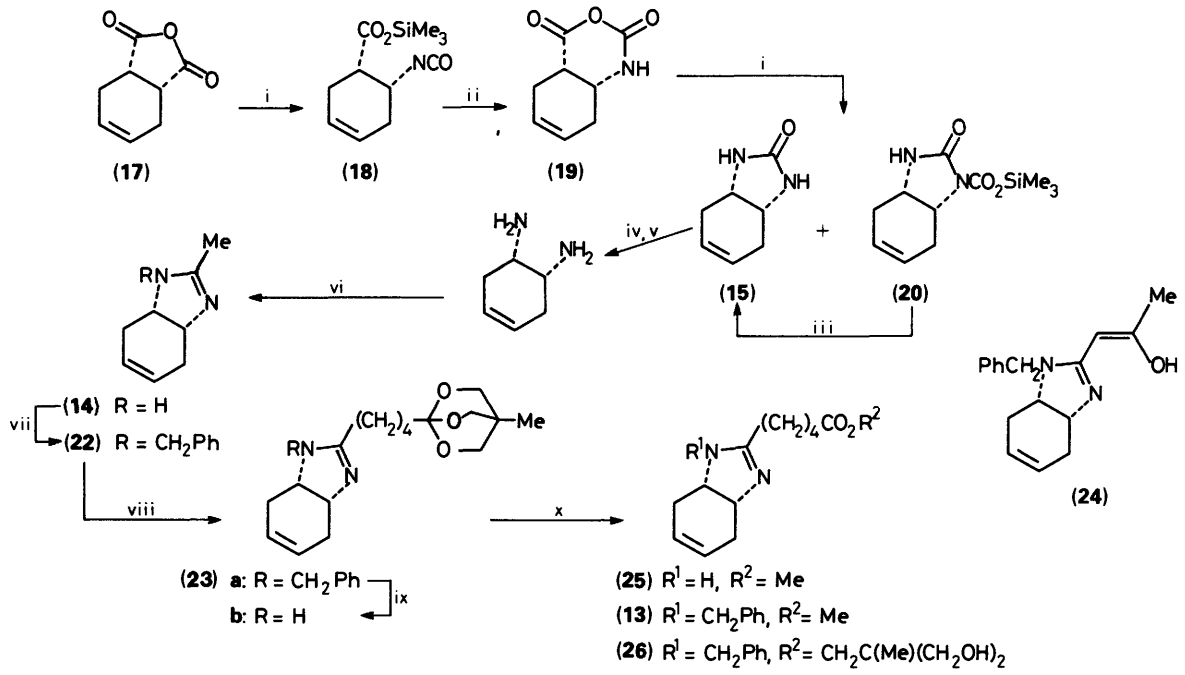
This methodology is readily adaptable for the elaboration of other dihydroimidazoles. We have illustrated this by the construction of a tetrahydrobenzimidazole as a precursor for a diazaprostacyclin containing a 4,5-dihydroimidazole unit.

The inhibition of platelet aggregation exhibited by prostacyclin (PGI_2) (**11**), combined with the chemical instability of this metabolite at physiological pH, has led to the search for stable agonists for possible application in antithrombotic therapy.[9] Despite this interest the 4,5-dihydroimidazole moiety does not yet appear to have been incorporated into a bicyclic PGI_2 analogue.[3] Our retrosynthetic analysis for the dihydroimidazole analogue (**12**) is shown in Scheme 2. The use of a cyclohexene as source of the cyclopentane unit is well precedented.[10] We report here the synthesis of the key intermediate (**13**) in the proposed sequence by elaboration, using the methodology developed above, of 2-methyl-3a,4,7,7a-tetrahydrobenzimidazole (**14**), itself prepared from the cyclic urea (**15**).



Scheme 2.

We first proposed to generate the urea (**15**) by Curtius rearrangement from the β-lactams (**16a,b**).[11] Although the latter were readily accessed by monocycloaddition of *N*-chlorosulphonyl isocyanate to cyclohexa-1,4-diene,[12] attempts to cleave the four-membered ring with azide reagents were unsuccessful. Instead, an alternative route from *cis*-1,2,3,6-tetrahydrophthalic anhydride (**17**) was developed (Scheme 3). Treatment of freshly purified anhydride (**17**) with trimethylsilyl azide in dioxane (70 ⟶ 100 °C) produced an acyl azide that



Scheme 3. *Reagents:* i, Me_3SiN_3, 70–100 °C; ii, H_2O, 0 °C; iii, $Bu_4N^+F^-$, SiO_2; iv, $Ba(OH)_2$ aq., 140 °C; then CO_2, H_2SO_4 aq.; v, NH_3–$CHCl_3$; vi, $MeC(OEt)=NH_2^+Cl^-$; vii, BuLi, 0 °C, $PhCH_2Br$; viii, BuLi, −78 °C, (**3c**); ix, Na–NH_3(l), EtOH; x, MeOH, H_2SO_4; then K_2CO_3.

underwent thermolysis and Curtius rearrangement *in situ* to afford the isocyanate (**18**) (89%), from which the isatoic anhydride (**19**) was obtained (85%) by silyl ester cleavage–cyclisation in water (0 °C, 2 days).[13] The reaction of trimethylsilyl azide with the anhydride (**19**) as above led to a second Curtius rearrangement and the production of mixtures of the required cyclic urea (**15**) (30–40%) and its *N*-trimethylsilyloxycarbonyl precursor (**20**). After much investigation, our optimised protocol for the production of the imidazolone (**15**) involved chromatographic separation at this stage; subsequent exposure of the silyloxycarbonyl urea (**20**) to tetrabutylammonium fluoride on silica gel[14] promoted desilylation–decarboxylation to afford a second batch of the urea (**15**); the combined yield was 76%.

The urea (**15**), which was stable towards 10M aqueous sodium hydroxide at reflux, was hydrolysed under the harsher conditions[15] of excess barium hydroxide at 140 °C for 19.5 h. The resulting *cis*-4,5-diaminocyclohexene (**21**) was isolated as the monosulphate (72%) from which the hygroscopic free base could be obtained [87%; 63% from urea (**15**)] by treatment with ammoniacal chloroform (Scheme 3). Condensation of the diamine with ethyl acetimidate hydrochloride (ethanol, reflux)[1] afforded 2-methyl-3a,4,7,7a-tetrahydrobenzimidazole (**14**) as the hydrochloride salt (93%). Basification with ammoniacal chloroform and distillation afforded the dihydroimidazole (**14**) in 65% yield from the diamine (**21**); purification by distillation at this stage was crucial to the success of subsequent operations.

Elaboration of (**14**) was achieved by the methodology developed above. Thus, *N*-alkylation with benzyl bromide (butyl-lithium, THF, 0 °C) gave a dihydroimidazole (**22**) (77%) that was *C*-alkylated in the usual way with the C_4-bromo-orthoester (**3c**) to afford, along with some unchanged heterocycle (**22**) (18%), the OBO orthoester (**23a**) (62% based on starting material converted). Interestingly, *C*-acylation of the dihydroimidazole (**22**) can compete with alkylation; the *C*-acetylated compound (**24**) was isolated in 25% yield from one experiment carried out with the bromo-orthoester (**3c**) contaminated with ethyl acetate. Debenzylation of the orthoester (**23a**) with sodium–liquid ammonia–ethanol gave the heterobicycle (**23b**) (56%) from which the methyl ester (**25**) was obtained in 61% yield by the acidic methanol–potassium carbonate sequence (see above); alternatively, the orthoester (**23a**) could be converted by this methanolysis protocol, *via* an isolable dihydroxyester (**26**), into the methyl ester (**13**) (73%), a suitable intermediate along with OBO orthoester (**23a**) for elaboration towards the dihydroimidazole PGI_2 analogue (**12**).

Experimental

M.p.s were measured on a Reichert–Kofler microhotstage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 710B or a Pye-Unicam SP3-100 spectrometer, either as solutions ($CHCl_3$ or $CHBr_3$), Nujol mulls, or liquid films as indicated. NMR spectra were determined in deuteriochloroform solution (tetramethylsilane as internal standard); ^1H NMR spectra were recorded using JEOL MH-100, Perkin-Elmer R32, or Bruker WM 250 spectrometers at 100, 90, and 250 MHz, respectively, whilst ^{13}C NMR spectra were recorded using the Bruker WM 250 instrument at 62.5 MHz. Mass spectra were obtained using A.E.I. MS 902 or VG 7070F spectrometers. Column chromatographic purifications were achieved on silica gel (Merck Kieselgel 60 Art. 7729, 7734), or on flash column[16] silica gel (Art. 9385) as indicated. TLC analysis was performed using plastic-backed silica gel plates (Camlab Polygram Sil G/UV_{254}) eluting with appropriate solvent mixtures, generally chloroform–2-aminopropane, and visualising with UV light, $KMnO_4$ spray, or iodoplatinic acid spray.[17] Butyl-lithium solutions were standardised by the diphenylacetic acid method.[18] Ether refers to diethyl ether and light petroleum to that fraction of b.p. 40–60 °C. THF was distilled from $LiAlH_4$ prior to use, with triphenylmethane as indicator; dichloromethane was distilled from $CaCl_2$; ethanol and methanol were dried over magnesium; and toluene, benzene, and 1,4-dioxane over sodium wire.

Attempted Dialkylation of 2-Methyl-4,5-dihydroimidazole (**1c**).—Commercial 2-methyl-4,5-dihydroimidazole (**1c**) was dried azeotropically (toluene). This compound (538 mg, 6.4

mmol) was stirred in THF (50 ml) at −78 °C under nitrogen and treated with butyl-lithium (8.81 ml, 1.6M solution in hexane, 14.1 mmol). The mixture was stirred for 1 h, and to the resulting suspension was added dropwise predistilled benzyl bromide (2.41 g, 14.1 mmol). The mixture was allowed to warm to 25 °C and stirred for 24 h, after which time the solvents were evaporated under reduced pressure, the residue was partitioned between water (50 ml) and chloroform (50 ml) and the aqueous phase was further extracted with chloroform (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave a residue that was chromatographed on silica gel (Art. 7734, 80 g) eluting with chloroform–2-aminopropane (95:5 v/v) to afford 1-benzyl-2-methyl-4,5-dihydroimidazole (**1a**) (883 mg, 78%) as the only alkylated product, identical with an authentic sample,[1] b.p. 99–102 °C at 0.4 mmHg (lit.,[1] b.p. 102–106 °C at 1 mmHg).

Reaction of 1-*Benzyl*-2-*methyl*-4,5-*dihydroimidazole* (**1a**) *with Methyl* 6-*Halohexanoates*.—1-Benzyl-2-methyl-4,5-dihydroimidazole[1] (0.91 mg, 5.2 mmol) in THF (15 ml), stirred at −78 °C under nitrogen, was treated with butyl-lithium (3.59 ml, 1.6M solution in hexane, 5.74 mmol) to give an orange–yellow solution that was stirred for 30 min at this temperature before addition of methyl 6-bromohexanoate (1.2 g, 5.74 mmol). The mixture was allowed to warm to 25 °C and stirred for 17 h, the solvents were then evaporated under reduced pressure, the residue was partitioned between chloroform (25 ml) and water (25 ml), and the aqueous phase was further extracted with chloroform (3 × 25 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford a residue that was chromatographed on silica gel (Merck Art. 7729) eluting with chloroform–methanol (97:3 v/v) to give the *C*-acylated material 1-*benzyl*-2-(7-*bromo*-2-*hydroxyhept*-1-*enyl*)-4,5-*dihydroimidazole* (**5a**) (0.27 g, 33%) (Found: M^+, 350.100. $C_{17}H_{23}N_2O^{79}Br$ requires *M*, 350.099); $\nu_{max}(CHCl_3)$ 3 600–2 700, 1 600, 1 530, 1 455, and 1 140 cm^{-1}; δ(90 MHz) 1.30–2.05 [6 H, m, $(CH_2)_3CH_2Br$], 2.30 (2 H, t, CH_2COH), 3.25–3.80 (6 H, m and t, NCH_2CH_2N and CH_2Br), 4.40 (2 H, s, benzyl CH_2), 4.85 (1 H, s, vinyl CH), 7.40 (5 H, s, Ph), and 9.45 (1 H, br s, OH); *m*/*z* 352 and 350 (M^+), 271 (27%), 270 (19), 216 (16), 201 (42), 174 (18), 173 (23), 91 (100), and 74 (10).

Reaction of 1-benzyl-2-methyl-4,5-dihydroimidazole (**1a**) (1 g, 5.8 mmol) with methyl 6-iodohexanoate (1.58 g, 6.17 mmol; b.p. 85 °C at 1.5 mmHg), as described above for the bromo-compound, gave after chromatography the *C*-alkylated material 1-*benzyl*-2-(6-*methoxycarbonylhexyl*)-4,5-*dihydroimidazole* (0.14 g, 9%); $\nu_{max}(CHCl_3)$ 2 935, 2 850, 1 725, 1 605, 1 430, and 1 360 cm^{-1}; δ(90 MHz) 1.10–1.85 [8 H, m, $(CH_2)_4CH_2CO_2$], 2.15–2.65 (4 H, m, $N{=}CCH_2$ and CH_2CO_2), 3.10–3.80 (7 H, m, NCH_2CH_2N and CO_2CH_3), 4.30 (2 H, s, benzyl CH_2), and 7.15–7.50 (5 H, m, Ph); and the C-*acylated compound* (**5b**) (0.2 g, 15%) that existed in solution as a 1:1 mixture of enol and keto tautomers; $\nu_{max}(CHCl_3)$ 3 600–2 800, 1 730, 1 600, 1 530, 1 460, and 1 375 cm^{-1}; δ(90 MHz) 1.20–1.90 [6 H, m, $(CH_2)_3CH_2I$], 2.10–2.40 (2 H, 2 × t, CH_2CO and $CH_2C{=}C$), 3.00–3.90 (7 H, m, NCH_2CH_2N, CH_2CO, and CH_2I), 4.27 and 4.30 (2 H, 2 × s, benzyl CH_2), 4.80 (0.5 H, s, vinyl CH), 7.10–7.50 (5 H, m, Ph), and 9.45 (0.5 H, br s, OH); also isolated were unchanged starting material (**1a**) (0.11 g, 11%) and some mixed fractions.

1-(5-*Bromopentyl*)-4-*methyl*-2,6,7-*trioxabicyclo*[2.2.2]*octane* (**3a**).—To a solution of 3-methyl-3-(hydroxymethyl)oxetane[6] (24.92 g, 0.24 mol) and pyridine (25.12 g, 0.32 mol) in dichloromethane (100 ml) at 0 °C under nitrogen was added dropwise 6-bromohexanoyl chloride (51.25 g, 0.24 mol). An exothermic reaction ensued, with precipitation of pyridinium hydrochloride. The solution was stirred at 0 °C for 90 min then added to water (400 ml) and extracted with dichloromethane (3 × 250 ml). The combined organic extracts were washed with phosphate buffer solution (pH6, 250 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil (76.90 g). Purification by flash column chromatography on silica gel (Merck Art. 9385), eluting with ethyl acetate–light petroleum (50:50 v/v), gave (3-*methyl*-3-*oxetanyl*)*methyl* 6-*bromohexanoate* as a pale yellow oil (48.2 g, 72%). The crude product was purified by reduced pressure distillation (40.10 g, 60%), b.p. 132 °C at 1.5 mmHg [Found: $(M - CH_2O)^+$, 248.0404. $C_{11}H_{19}O_3{}^{79}Br$ requires $(M - CH_2O)$, 248.0411]; ν_{max}(film) 2 970, 2 945, 1 740 (CO), 645, and 565 (CH_2Br) cm^{-1}; δ(250 MHz) 1.35 (3 H, s, CCH_3), 1.4–2.2 [6 H, m, $BrCH_2(CH_2)_3CH_2$], 2.40 (2 H, t, $CH_2CO_2CH_2$), 3.45 (2 H, t, CH_2Br), 4.2 (2 H, s, CO_2CH_2C), and 4.52 (4 H, 2 × d, AB, 2 × ring CH_2); *m*/*z* 250 and 248 $(M - CH_2O)^+$, 179 (45%), 177 (43), 69 (100), and 55 (28).

To a solution of the oxetane ester (3-methyl-3-oxetanyl)-methyl 6-bromohexanoate (40 g, 0.14 mol) in dry dichloromethane (250 ml) at −15 °C was added, with stirring, boron trifluoride etherate (5.09 g, 0.036 mol). After being stirred at −15 °C for 2 h, the solution was stored at −15 °C for 12 h, whereby solidification occurred. The reaction mixture was quenched by the addition of triethylamine (18.20 g, 0.18 mol), then diluted with ether (250 ml) and filtered to remove the amine–BF_3 complex. The filtrate was concentrated by evaporation under reduced pressure to give a yellow oil (41 g). Purification by flash column chromatography on silica gel (Merck Art. 9385), eluting with light petroleum–ethyl acetate (5:2 v/v) containing 1% triethylamine, gave the *title compound* (**3a**) as a colourless oil (25.80 g, 66%) [Found: C, 47.6; H, 6.5%; $(M - H)^+$, 277.0460. $C_{11}H_{19}O_3Br$ requires C, 47.3; H, 6.8%; (*M* − H), 277.0439]; ν_{max}(film) 2 960, 2 915, 2 870, 1 455, 1 395, 1 350, 1 275, 1 190, 1 055, and 990 cm^{-1}; δ(90 MHz) 0.8 (3 H, s, CCH_3), 1.2–1.95 [8 H, m, $BrCH_2(CH_2)_4$], 3.36 (2 H, t, CH_2Br), and 3.85 (6 H, s, 3 × OCH_2); *m*/*z* 277 $(M - H)^+$, 250 (14%), 248 (15), 178 (62), 176 (62), 72 (23), 69 (100), and 55 (13).

1-(6-*Bromohexyl*)-4-*methyl*-2,6,7-*trioxabicyclo*[2.2.2]*octane* (**3b**).—This compound was prepared as above from 3-methyl-3-(hydroxymethyl)oxetane (12.08 g, 0.118 mol), pyridine (12.12 g, 0.153 mol), and 7-bromoheptanoyl chloride (31 g, 0.136 mol). After 1.5 h at 0 °C, the reaction mixture was worked up to afford a liquid that was purified by reduced pressure distillation to give (3-*methyl*-3-*oxetanyl*)*methyl* 7-*bromoheptanoate* as a colourless liquid (20.26 g, 97%), b.p. 144 °C at 0.4 mmHg [Found: C, 48.92; H, 7.39%; $(M - CH_2O)^+$, 262.0574; $(M - Br)^+$, 213.1489. $C_{12}H_{21}O_3Br$ requires C, 49.16; H, 7.22%; (*M* − CH_2O), 262.0567; (*M* − Br), 213.1489]; ν_{max}(film) 2 945, 2 880, 1 735, 1 460, 1 245, 1 180, and 985 cm^{-1}; δ(90 MHz) 1.2–2.1 [11 H, m, CCH_3 and $BrCH_2(CH_2)_4CH_2$], 2.40 (2 H, t, CH_2CO_2), 3.43 (2 H, t, CH_2Br), 4.20 (2 H, s, CO_2CH_2), and 4.50 (4 H, AB, 2 × ring CH_2); *m*/*z* 264 and 262 $(M - CH_2O)^+$, 213 $[(M - Br)^+, 20\%]$, 194, 193 (99), 191 (100), 144 (30), 111 (34), 83 (93), and 55 (65).

Treatment of (3-methyl-3-oxetanyl)methyl 7-bromoheptanoate (20.25 g, 0.069 mol) with boron trifluoride etherate (2.45 g, 0.017 mol) as above gave, after stirring at −15 °C for 2 h and storing at −15 °C for 15 h, a mixture that was worked up to afford a liquid. This was purified by flash column chromatography on silica gel (Merck Art. 9385, 130 g), eluting with ethyl acetate–triethylamine (99:1 v/v), to give the *title compound* (**3b**) as a colourless liquid (17 g, 84%) [Found: C, 49.19; H, 7.43%; $(M - CH_2O)^+$, 262.0557; $(M - Br)^+$, 213.1482. $C_{12}H_{21}BrO_3$ requires C, 49.16; H, 7.22%; (*M* − CH_2O), 262.0567; (*M* − Br), 213.1489]; ν_{max}(film) 2 935, 2 875 (sh), 1 465, 1 400, 1 355, 1 270, 1 190, 1 060, and 990 cm^{-1}; δ(90 MHz) 0.80 (3 H, s, CCH_3), 1.2–2.1 [10 H, m, $BrCH_2(CH_2)_5$], 3.41 (2 H, t, CH_2Br), and 3.92 (6 H, s, 3 × OCH_2); *m*/*z* 264 (14%) and 262 (16), 213 (10), 193 (97), 191 (100), 144, 111, 83 (72), 72 (33), and 55 (60).

1-(3-*Bromopropyl*)-4-*methyl*-2,6,7-*trioxabicyclo*[2.2.2]*octane* (**3c**).—This compound was prepared as above from 3-methyl-3-(hydroxymethyl)oxetane (8.6 g, 0.084 mol), pyridine (8.64 g, 0.109 mol), and 4-bromobutanoyl chloride (17.98 g, 0.097 mol). After 2 h at 0 °C, the reaction mixture was worked up to afford a pale yellow liquid that was purified by reduced pressure distillation to give (3-*methyl*-3-*oxetanyl*)*methyl* 4-*bromobutanoate* as a colourless liquid (17.50 g, 83%), b.p. 114 °C at 0.45 mmHg [Found: C, 42.91; H, 6.07%; $(M - CH_2O)^+$, 220.0084. $C_9H_{15}O_3Br$ requires C, 43.05; H, 6.02%; ($M - CH_2O$), 220.0098]; ν_{max}(film) 2 970, 2 880, 1 730, 1 454, 1 380, 1 200, 1 170, 1 132, 984, and 838 cm^{-1}; δ(90 MHz) 1.30 (3 H, s, CCH_3), 2.20 (2 H, quintet, $CH_2CH_2CH_2$), 2.55 (2 H, t, CH_2CO_2), 3.50 (2 H, t, CH_2Br), 4.20 (2 H, s, CO_2CH_2), and 4.16 (4 H, AB, 2 × CH_2O); *m/z* 222 and 220 $(M - CH_2O)^+$, 168 (17%), 166 (14), 150 (100), 148 (100), 144 (24), 122 (29), 120 (31), 72 (94), and 55 (47).

Treatment of (3-methyl-3-oxetanyl)methyl 4-bromobutanoate (17.25 g, 0.069 mol) with boron trifluoride etherate (2.44 g, 0.017 mol) as above gave, after stirring at −15 °C for 30 min and storing at −15 °C for 17 h, a reaction mixture which was worked up to afford a liquid. This was purified by flash column chromatography on silica gel (Merck Art. 9385, 140 g), eluting with light petroleum–ethyl acetate (5:2 v/v), to give the *title compound* (**3c**) as a colourless liquid (12 g, 70%) [Found: C, 42.62; H, 6.16%; $(M - CH_2O)^+$, 222.0082 and 220.0096. $C_9H_{15}O_3Br$ requires C, 43.05; H, 6.02%; ($M - CH_2O$), 222.0079 and 220.0098]; ν_{max}(film) 2 965, 2 935, 2 880, 1 460, 1 400, 1 380, 1 250, 1 060, 995, and 900 cm^{-1}; δ(90 MHz) 0.80 (3 H, s, CCH_3), 1.60–2.20 (4 H, m, $BrCH_2CH_2CH_2$), 3.42 (2 H, t, $BrCH_2$), and 3.77 (6 H, s, 3 × OCH_2); *m/z* 222 (17%), 150 (89), 148 (100), 72 (53), and 55 (27).

1-*Benzyl*-2-[6-(4-*methyl*-2,6,7-*trioxabicyclo*[2.2.2]*oct*-1-*yl*)*hexyl*]-4,5-*dihydroimidazole* (**4a**).—To 1-benzyl-2-methyl-4,5-dihydroimidazole (**1a**) (1 g, 5.75 mmol) in dry THF at −78 °C was added butyl-lithium (5.1 ml, 1.24M solution in hexanes, 6.32 mmol) and the reaction mixture stirred for 40 min. The C_6 bromo-orthoester (**3a**) (1.76 g, 6.32 mmol), in THF (2 ml), was added at −78 °C and the solution stirred for 20 h, warming slowly to 25 °C. The solvent was removed under reduced pressure and after the usual work-up, the residue was purified by column chromatography on silica gel (Merck Art. 7734, 200 g), eluting with chloroform–hexane (98:2 v/v), to afford the *title compound* (**4a**) as an orange oil (1.55 g, 73%) (Found: C, 70.62; H, 8.87; N, 7.35%; M^+, 372.2395. $C_{22}H_{32}N_2O_3$ requires C, 70.94; H, 8.66; N, 7.52%; *M*, 372.2401); ν_{max}(film) 2 930, 2 870, 1 605, 1 505, 1 395, 1 305, 1 050, and 990 cm^{-1}; δ(90 MHz) 0.80 (3 H, s, CCH_3), 1.20–1.90 [10 H, m, $(CH_2)_5CO$], 2.33 (2 H, t, $N{=}CCH_2$), 3.25 (2 H, t, $NCH_2CH_2N{=}C$), 3.75 (2 H, t, $NCH_2CH_2N{=}C$), 3.95 (6 H, s, 3 × OCH_2), 4.35 (2 H, s, NCH_2Ph), and 7.20–7.60 (5 H, m, $PhCH_2$); *m/z* 372 (M^+), 371, 357, 229, 187 (69%), 174 (89), 173 (62), 91 (100), and 56 (12).

2-[6-(4-*Methyl*-2,6,7-*trioxabicyclo*[2.2.2]*oct*-1-*yl*)*hexyl*]-4,5-*dihydroimidazole* (**4b**).—Sodium (400 mg, 4 equiv.) was dissolved in liquid ammonia (40 ml) and to this blue solution was added the 1-benzyldihydroimidazole orthoester (**4a**) (1.51 g, 4.03 mmol), in absolute ethanol (1.85 ml). As the blue colour disappeared, more sodium was added (778 mg total, *ca.* 8 mol equiv.). After being stirred for 1 h, the ammonia was allowed to evaporate. Dichloromethane (30 ml) was added to the resulting white solid, the mixture stirred for 20 min, and water (30 ml) added. The aqueous phase was extracted with dichloromethane (3 × 30 ml), the combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The white solid was purified by column chromatography on silica gel (Merck Art. 7734, 100 g), eluting with chloroform–2-aminopropane (95:5 v/v), to give the *title compound* (**4b**) as white crystals (880 mg, 78%), m.p. 91–92 °C (Found: C, 63.51; H, 8.95; N, 9.68%; M^+, 282.1962. $C_{15}H_{26}N_2O_3$ requires C, 63.80; H, 9.28; N, 9.92%; *M*, 282.1943); ν_{max}($CHBr_3$) 3 430, 2 900(br), 1 625, 1 400, 1 050, 995, and 980 cm^{-1}; δ(90 MHz) 0.80 (3 H, s, CCH_3), 1.20–1.90 [10 H, m, $N{=}CCH_2(CH_2)_5$], 2.28 (2 H, t, $N{=}CCH_2$), 3.62 (4 H, s, NCH_2CH_2N), 3.90 (6 H, s, 3 × OCH_2), and 4.77 (1 H, br s, NH); *m/z* 282 (M^+), 281, 251 (19%), 139 (22), 112 (18), 97 (53), 84 (100), and 55 (13).

2-[6-(4-*Methyl*-2,6,7-*trioxabicyclo*[2.2.2]*oct*-1-*yl*)*hexyl*]-1-*octyl*-4,5-*dihydroimidazole* (**4c**).—To the dihydroimidazole orthoester (**4b**) (500 mg, 1.77 mmol) in dry THF (15 ml) at 0 °C was added butyl-lithium (1.39 ml, 1.53M solution in hexane, 2.12 mmol) dropwise. After being stirred for 50 min at 0 °C, 1-iodo-octane (0.51 g, 2.12 mmol) was added and the mixture stirred at 0 ⟶ 25 °C over 20 h. The solvent was removed under reduced pressure, then the residue was partitioned between dichloromethane (25 ml) and water (25 ml), and worked up in the usual fashion. The residue was purified by flash column chromatography (Merck Art. 9385), eluting with chloroform–2-aminopropane (97:3 v/v), to afford the *title compound* (**4c**) (519 mg, 70%) as an oil, b.p. 250 °C at 0.3 mmHg (Found: C, 68.88; H, 10.96; N, 6.79%; M^+, 394.3190. $C_{23}H_{42}N_2O_3 \cdot 0.5H_2O$ requires C, 68.45; H, 10.74; N, 6.94%; *M*, 394.3194); ν_{max}(film) 3 370 (water), 2 920, 2 860, 1 610, 1 460, 1 400, 1 260, 1 200, 1 060, and 995 cm^{-1}; δ(250 MHz) 0.80 (3 H, s, CCH_3), 0.88 (3 H, br t, CH_2CH_3), 1.20–1.90 [22 H, m, $CH_3(CH_2)_6$ and $N{=}CCH_2(CH_2)_5$], 2.14 (2 H, t, $N{=}CCH_2$), 3.00 (2 H, t, $NCH_2CH_2CH_2$), 3.24 (2 H, t, $NCH_2CH_2N{=}C$), 3.64 (2 H, t, $NCH_2CH_2N{=}C$), and 3.89 (6 H, s, 3 × OCH_2); *m/z* 394 (M^+), 393, 392, 366, 363, 351, 323, 251 (24%), 209 (90), 196 (60), 98 (100), 84 (36), and 56 (47).

2-(6-*Methoxycarbonylhexyl*)-1-*octyl*-4,5-*dihydroimidazole* (**6**).—A solution of concentrated sulphuric acid (4 drops) in dry methanol (5 ml) was prepared. To this solution was added the orthoester (**4c**) (58 mg, 0.19 mmol) at 0 °C and the solution was stirred for 4.5 h. Potassium carbonate (100 mg) was added and the solution stirred at 20 °C for 5 h. TLC analysis indicated a component corresponding to the dihydroxyester intermediate. A further portion of K_2CO_3 was added (100 mg) and the reaction mixture stirred at 20 °C for 16 h. After filtration, the solvent was removed under reduced pressure and the residue purified by flash column chromatography on silica gel (Merck Art. 9385), eluting with chloroform–2-aminopropane (96:4 v/v), to afford the *title compound* (**6**) (27 mg, 61%) (Found: C, 69.15; H, 11.44; N, 8.3%; M^+, 324.2771. $C_{19}H_{36}N_2O_2 \cdot 0.2H_2O$ requires C, 69.55; H, 11.18; N, 8.54%; *M*, 324.2801); ν_{max}(film) 3 380 (water), 2 930, 2 855, 1 735, 1 600, 1 430, 1 250, 1 200, and 1 170 cm^{-1}; δ(250 MHz) 0.88 (3 H, br t, CH_3CH_2), 1.20–1.75 [20 H, m, $(CH_2)_6CH_3$ and $(CH_2)_4CH_2CO_2Me$], 2.12 (2 H, t, $N{=}CCH_2$), 2.27 (2 H, t, $CH_2CO_2CH_3$), 3.00 (2 H, t, $NCH_2CH_2CH_2$), 3.22 (2 H, t, $NCH_2CH_2N{=}C$), and 3.62 (5 H, s and t, CO_2CH_3 and $NCH_2CH_2N{=}C$); *m/z* 324 (M^+) 323 (15%), 293 (26), 251 (99), 209 (52), 196 (41), 125 (45), 98 (100), 84 (40), and 56 (49).

This reaction sequence was monitored very carefully by TLC analysis, as too high a concentration of acid afforded the ring opened product; δ(250 MHz) as above, with additional peak at 6.20 (1 H, t, amide NH) plus extra C=O in ^{13}C NMR spectrum.

1-*Benzyl*-2-(6-*methoxycarbonylhexyl*)-4,5-*dihydroimidazole* (**7b**).—A solution of 3mM sulphuric acid–methanol (10 ml) was added to the benzyldihydroimidazole orthoester (**4a**) (190 mg, 0.51 mmol) at 0 °C and stirred for 2.5 h. Potassium carbonate (excess) was added and the mixture stirred at 20 °C for 15 h. Solvent was removed *in vacuo* and the crude material (200 mg) purified by column chromatography on silica gel (Merck Art. 7734, 20 g), eluting with chloroform–2-aminopropane (97:3

v/v), to afford the *dihydroxyester* (**7a**) (132 mg, 67%) (Found: M^+, 390.2527. $C_{22}H_{34}N_2O_4$ requires M, 390.2517); δ(250 MHz) 0.88 (3 H, s, CCH_3), 1.35–1.80 [8 H, m, $(CH_2)_4CH_2CO_2CH_2$], 2.25–2.40 (4 H, 2 × t, $N{=}CCH_2$ and $CH_2CO_2CH_2$), 3.20 (2 H, t, $NCH_2CH_2N{=}C$), 3.60 (4 H, s, 2 × CH_2OH), 3.68 (2 H, t, $NCH_2CH_2N{=}C$), 4.17 (2 H, s, CO_2CH_2C), 4.30 (2 H, s, $PhCH_2$), and 7.20–7.45 (5 H, m, $PhCH_2$); *m/z* 390 (M^+), 271, 229 (21%), 174 (35), 173 (27), 91 (64), 72 (96), and 57 (100).

The above experiment was repeated; treatment with acid at 0 °C was extended to 4 h. TLC analysis indicated the absence of the orthoester but appearance of the dihydroxyester. Potassium carbonate was added; after 24 h at 25 °C TLC showed the formation of some methyl ester but still the presence of dihydroxyester. Addition of excess potassium carbonate and stirring for a further 3.5 h afforded the *methyl ester* (**7b**) (61%) after column chromatography (Found: C, 71.20; H, 9.15; N, 9.06%; M^+, 302.1962. $C_{18}H_{26}N_2O_2$ requires C, 71.49; H, 8.67; N, 9.26%; M, 302.1994); ν_{max}(film) 3 370 (water), 2 937, 2 860, 1 730, 1 610, 1 435, 1 360, 1 250, 1 200, 1 175, 1 000, 740, and 700 cm^{-1}; δ(250 MHz) 1.25–1.80 [8 H, m, $(CH_2)_4CH_2CO_2$], 2.30 (4 H, t, $N{=}CCH_2$ and CH_2CO_2), 3.20 (2 H, t, $NCH_2CH_2N{=}C$), 3.60–3.80 (5 H, t, and s, $NCH_2CH_2N{=}C$ and CO_2CH_3), 4.30 (2 H, s, $PhCH_2N$), and 7.20–7.40 (5 H, m, $PhCH_2$); *m/z* 303, 302 (M^+), 271 (22%), 229 (57), 187 (49), 174 (95), 173 (91), 91 (100), 65 (8), and 56 (7).

1-Benzyl-2-octyl-4,5-dihydroimidazole.—To 1-benzyl-2-methyl-4,5-dihydroimidazole (**1a**) (1 g, 5.75 mmol) in dry THF (30 ml) at −78 °C was added butyl-lithium (5.1 ml, 1.24M solution in hexane, 1.1 mol equiv.), yielding an orange solution. After being stirred for 35 min, 1-iodoheptane (1.43 g, 6.32 mmol) was added and the solution stirred for 23 h, warming to 25 °C. Removal of the solvent under reduced pressure and partitioning of the residue between chloroform (30 ml) and water (30 ml) afforded, after extractive isolation, the product (2.41 g) as an orange oil. Purification by column chromatography (Merck Art. 7734, 200 g), eluting with chloroform–2-aminopropane (98:2 v/v), gave the *dihydroimidazole* (1.36 g, 87%) (Found: C, 74.35; H, 9.78; N, 9.23%; M^+, 272.2254. $C_{18}H_{28}N_2{\cdot}H_2O$ requires C, 74.44; H, 10.41; N, 9.65%; M, 272.2250); ν_{max}(film) 2 900, 2 850, 1 610, 1 510, and 1 460 cm^{-1}; δ(90 MHz) 0.90 (3 H, t, CH_2CH_3), 1.10–1.90 [12 H, m, $(CH_2)_6CH_3$], 3.20 (2 H, t, $NCH_2CH_2N{=}C$), 3.70 (2 H, br t, $NCH_2CH_2N{=}C$), 4.30 (2 H, s, $PhCH_2N$), and 7.20–7.50 (5 H, m, $PhCH_2N$); *m/z* 272 (M^+), 271, 243, 229, 187 (49%), 174 (78), 173 (72), and 91 (100).

2-Octyl-4,5-dihydroimidazole.—Ammonia (50 ml, predried by treatment with sodium) was condensed into a 3-necked flask. Sodium was added portion by portion to give a blue solution. 1-Benzyl-2-octyl-4,5-dihydroimidazole (616 mg, 2.26 mmol) in dry ethanol (1.5 ml) was added dropwise to the solution. The blue colour persisted; if it did not, another small portion of sodium was added. After being stirred for 1.5 h, the ammonia was allowed to evaporate affording a cream solid mixture. Chloroform (20 ml) was added, the solution stirred for 15 min, and the organic phase carefully washed with water (15 ml). The dried solvent was removed under reduced pressure to give a crystalline yellow solid. Purification by column chromatography on silica gel (Merck Art. 7734, 50 g), eluting with chloroform–2-aminopropane (98:2 v/v), afforded the *dihydroimidazole* (235 mg, 57%), m.p. 68 °C, as white crystals (Found: C, 72.22; H, 13.31; N, 14.95%; M^+, 182.1770. $C_{11}H_{22}N_2$ requires C, 72.47; H, 12.16; N, 15.37%; M, 182.1783); ν_{max}(film) 3 400, 2 910, 2 855, 1 620, 1 430, and 1 285 cm^{-1}; δ(90 MHz) 0.85 (3 H, br t, CH_2CH_3), 1.00–1.80 [12 H, m, $(CH_2)_6CH_3$], 2.20 (2 H, t, $N{=}CCH_2$), 3.55 (4 H, s, 2 × ring CH_2), and 4.20 (1 H, br s, NH); *m/z* 182 (M^+), 181, 153, 139 (25%), 98 (27), 97, and 84 (100).

1-[6-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)hexyl]-2-octyl-4,5-dihydroimidazole (**8**).—To the 2-octyldihydroimidazole above (200 mg, 1.1 mmol) in dry THF (40 ml) at room temperature was added butyl-lithium (1.06 ml, 1.24M solution in hexanes, 1.32 mmol) to give a yellow solution. After stirring for 45 min, the C_7 bromo-orthoester (**3b**) (386 mg, 1.32 mmol) was added and the solution stirred for 23 h. Removal of THF under reduced pressure, followed by partitioning of the residue between chloroform (30 ml) and water (30 ml), gave, after chloroform extraction (3 × 30 ml), a yellow oil. Purification by column chromatography on silica gel (Merck Art. 7734, 55 g), eluting with chloroform–2-aminopropane (98:2 v/v), afforded the *title compound* (**8**) as a yellow oil (231 mg, 53%) (Found: C, 70.14; H, 11.04; N, 7.12%; M^+, 394.3167. $C_{23}H_{42}N_2O_3$ requires C, 70.01; H, 10.73; N, 7.10%; M, 394.3195); ν_{max}(film) 3 500–3 100 (water), 1 610, 1 460, 1 355, 1 260, 1 060, and 990 cm^{-1}; δ(250 MHz) 0.80 (3 H, s, CCH_3), 0.90 (3 H, br t, CH_2CH_3), 1.20–1.80 [22 H, m, $CH_3(CH_2)_6$ and $N{=}CCH_2(CH_2)_5$], 2.15 (2 H, t, $N{=}CCH_2$), 3.0 (2 H, t, $NCH_2CH_2CH_2$), 3.25 (2 H, t, $NCH_2CH_2N{=}C$), 3.62 (2 H, t, $NCH_2CH_2N{=}C$), and 3.90 (6 H, s, 3 × OCH_2); *m/z* 394 (M^+), 393 (20%), 251 (37), 209 (71), 196 (48), 139 (23), 125 (35), 112 (27), 111 (25), 98 (100), 84 (37), and 56 (46).

1-(6-Methoxycarbonylhexyl)-2-octyl-4,5-dihydroimidazole (**9**).—This compound was prepared from the corresponding orthoester (**8**), as outlined above for the ester (**6**), to afford the *methyl ester* (**9**) (60 mg, 24%) (Found: C, 68.66; H, 11.46; N, 8.67%; M^+, 324.2758. $C_{19}H_{36}N_2O_2{\cdot}0.3H_2O$ requires C, 69.17; H, 11.18; N, 8.49%; M, 324.2777); ν_{max}(film) 3375 (water), 2 930, 2 850, 1 735, 1 600, 1 430, 1 250, and 1 170 cm^{-1}; δ(90 MHz) 0.88 (3 H, br t, CH_2CH_3), 1.10–1.90 [20 H, m, $(CH_2)_6CH_3$ and $(CH_2)_4CH_2CO_2$], 2.20–2.40 (4 H, 2 × t, $N{=}CCH_2CH_2$ and CH_2CO_2), 3.30 (2 H, t, $NCH_2CH_2N{=}C$), and 3.65 (5 H, t and s, $NCH_2CH_2N{=}C$ and CO_2CH_3); *m/z* 324 (M^+), 323, 311, 213 (21%), 185 (56), 184 (30), 175 (76), 173 (58), 172 (100), 170 (54), 140 (45), 112 (62), 98 (60), 84 (28), 57 (59), 56 (65), and 55 (59).

1-[6-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)hexyl]-2-methyl-4,5-dihydroimidazole.—To 2-methyl-4,5-dihydroimidazole (**1c**) (500 mg, 5.95 mmol) in dry THF (20 ml) was added butyl-lithium (5.49 ml, 1.3M solution in hexanes, 7.14 mmol) at room temperature and the mixture stirred for 3 h. To the lithium salt was added the C_7 bromo-orthoester (**3b**) (2.1 g, 7.14 mmol) in dry THF (5 ml) and the reaction mixture was stirred at room temperature for 23 h. THF was removed under reduced pressure, the residue was partitioned between chloroform (30 ml) and water (20 ml), and the aqueous phase was extracted with chloroform (3 × 30 ml). The combined organic extracts were dried ($MgSO_4$) and the solvents removed under reduced pressure to give an orange oil (2.43 g). Purification by column chromatography (Merck Art. 7734, 120 g), eluting with chloroform–2-aminopropane (97:3 v/v), gave the *title compound* (1.29 g, 73%) (Found: C, 63.86; H, 9.55; N, 9.31%; M^+, 296.2100. $C_{16}H_{28}N_2O_3{\cdot}0.25H_2O$ requires C, 63.86; H, 9.55; N, 9.31%; M, 296.2100); ν_{max}(film) 3 280 (water), 2 930, 2 870, 1 610, 1 425, 1 398, 1 272, 1 193, 1 060, 994, 945, and 765 cm^{-1}; δ(90 MHz) 0.87 (3 H, s, CH_2CCH_3), 1.20–1.90 [10 H, m, $(CH_2)_5C$], 1.96 (3 H, s, $N{=}CCH_3$), 3.0–3.90 (6 H, m, NCH_2CH_2N and NCH_2CH_2C), and 3.98 (6 H, s, 3 × OCH_2); *m/z* 296 (M^+), 295 (27%), 267, 265 (19), 168, 125, 111, 98, 97 (100), 84 (14), 56 (77), and 55 (20).

1-[6-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)hexyl]-2-octyl-4,5-dihydroimidazole (**8**).—To the above dihydroimidazole-orthoester (188 mg, 0.64 mmol) in dry THF (40 ml) at −78 °C was added butyl-lithium (615 μl, 1.24M solution in hexane, 0.76 mmol). After being stirred for 1 h, 1-iodoheptane

(179 mg, 0.76 mmol, 1.2 equiv.) was added and the orange solution became yellow. The solution was stirred at −78 ⟶ 25 °C for 21.5 h, solvent removed *in vacuo*, and the residue partitioned between chloroform (30 ml) and water (30 ml). The product was extracted into chloroform and the crude oil purified by column chromatography, eluting with chloroform–2-aminopropane (98:2 v/v). Further purification by Kugelrohr distillation afforded the title compound as a colourless oil (320 mg, 51%), b.p. 240 °C at 0.2 mmHg, identical with a sample prepared by the alternative sequence from (**1a**) (see above).

1-(3-*Hydroxyoctyl*)-2-[6-(4-*methyl*-2,6,7-*trioxabicyclo*-[2.2.2]*oct*-1-*yl*)*hexyl*]-4,5-*dihydroimidazole* (**4d**).—The dihydroimidazole-orthoester (**4b**) (100 mg, 0.35 mmol) and oct-1-en-3-one[19] (54 mg, 0.45 mmol) were heated together without solvent on an oil bath at 70 °C for 4 h. The mixture was cooled to 0 °C, dry ethanol (1 ml) and sodium borohydride (19 mg, 0.49 mmol) were added, and the mixture was stirred for 3 h. The multi-component mixture was purified by column chromatography on silica gel (Merck Art. 7734), eluting with chloroform–2-aminopropane (97:3 v/v), to afford the over-reduced tetrahydroimidazole (**10**) (59 mg, 40%); δ(250 MHz) 0.78 (3 H, s, CCH_3), 0.86 (3 H, br t, CH_2CH_3), 1.18–1.80 [22 H, m, $(CH_2)_6CHN$ and $(CH_2)_4CH(OH)CH_2$], 2.20–2.90 (8 H, m, $NCH_2CH_2NCH_2CH_2CH$, N*H*, and O*H*), 3.00 (1 H, dt, NCHN), 3.77 (1 H, br m, C*H*OH), and 3.90 (6 H, s, 3 × OCH_2).

Repetition of the above experiment but using lithium borohydride as the reducing agent for 1 h at 0 °C afforded, after column chromatography, the *title compound* (**4d**) (42 mg, 21%) (Found: M^+, 410.3130. $C_{23}H_{42}N_2O_4$ requires *M*, 410.3144); δ(250 MHz) 0.80 (3 H, s, CCH_3), 0.88 (3 H, t, CH_2CH_3), 1.20–1.80 [20 H, m, $CH_3(CH_2)_4CH(OH)CH_2$ and $(CH_2)_5CO$], 2.22 (2 H, t, N=CCH_2), 3.20–3.40 (4 H, m, ring $CNCH_2$ and NCH_2CH_2CH), 3.55–3.70 (3 H, m, ring C=NCH_2 and C*H*OH), and 3.90 (6 H, s, 3 × OCH_2); *m/z* 410 (M^+), 409, 382 (12%), 267 (21), 258 (16), 225 (49), 205 (14), 158 (28), 157 (23), 125 (29), 111 (22), 98 (100), 57 (31), 56 (27), 55 (45), 44 (82), and 41 (24).

4a,5,8,8a-*Tetrahydro*-2H-[3,1]*benzoxazine*-2,4(1H)-*dione* (**19**).—Trimethylsilylazide[20] (12 g, 0.10 mol) and 1,2,3,6-tetrahydrophthalic anhydride [11.8 g, 0.08 mol, freshly recrystallised from light petroleum–acetic anhydride, m.p. 100–101 °C (lit.,[13] m.p. 101–102 °C)] were heated in dry dioxane (75 ml) to 70–80 °C. Nitrogen evolution was observed as the anhydride dissolved. The often vigorous reaction was controlled by occasional cooling. After nitrogen evolution had subsided (*ca.* 30 min), the pale yellow solution was heated to boiling for 30 min. Distillation at atmospheric pressure to remove unreacted trimethylsilylazide (b.p. 95–97 °C) and dioxane (b.p. 101 °C) afforded a viscous yellow solution. This was distilled at reduced pressure to afford trimethylsilyl 6-isocyanatocyclohex-3-en-1-carboxylate (**18**) as a colourless liquid (16.62 g, 89%), b.p. 95 °C at 0.6 mmHg (lit.,[13] b.p. 82–84 °C at 0.4 mmHg); ν_{max}(film) 3 025, 2 950, 2 900, 2 275, 1 720, 1 370, 1 340, 1 250, 1 210, 1 075, 1 000, 940, and 840 cm^{-1}; δ(90 MHz) 0.45 (9 H, s, $SiMe_3$), 2.40 (4 H, m, CH_2CH=$CHCH_2$), 2.65 (1 H, m, CH_2CHCO), 4.30 (1 H, t, CH_2CHN), and 5.85 (2 H, t, CH=CH).

A mixture of the β-isocyanatocarboxylic acid trimethylsilyl ester (**18**) (11.84 g, 50 mmol) and diethyl ether (150 ml) was cooled to 0 °C. Water (0.44 ml, 25 mmol) was added and the solution stirred strongly for 10 min. The reaction mixture was left to stand at 0 °C for 2 days. The resulting white crystals were filtered and dried *in vacuo* over P_2O_5. The filtrate was concentrated to one quarter of its original volume by evaporation under reduced pressure whereby a second crop of crystals was obtained (total 7.01 g, 85%), m.p. 116 °C (lit.,[13] m.p. 117–119 °C); ν_{max}(Nujol mull) 3 150, 1 750, 1 667, 1 050, 985, and 940 cm^{-1}; δ(100 MHz) 2.50 (4 H, m, 2 × ring CH_2), 3.25 (1 H, m, CO·C*H*CHN), 3.85 (1 H, m, CO·CHC*H*N), 5.50 (2 H, m, CH=CH), and 7.70 (1 H, br s, NH).

2,3,3a,4,7,7a-*Hexahydro*-1H-*benzimidazol*-2-*one* (**15**).—The isatoic anhydride (**19**) (3 g, 17.94 mmol) was heated with trimethylsilylazide (3.10 ml, 23.32 mmol) in dry dioxane (120 ml) at 70–80 °C for 1.5 h. Nitrogen evolution was observed. The temperature of the oil-bath was increased to 110 °C and heating continued for 4–5 h. The reaction mixture was allowed to cool and solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (Merck Art. 9385, 80 g), eluting with methanol–chloroform (4:96 v/v), to afford the *benzimidazolone* (**15**) (1.03 g, 42%) as a white solid and its trimethylsilyloxycarbonyl derivative (**20**) (2.01 g). This latter material was dissolved in dry dioxane (50 ml), tetrabutylammonium fluoride on silica gel[14] (*ca.* 1 g) was added, and the mixture stirred vigorously at room temperature for 17 h. After filtration, the solvent was removed under reduced pressure and the residue purified as outlined earlier to afford a further portion of the desired *urea* (**15**) [828 mg, 76% conversion from precursor (**20**); 34% from isatoic anhydride (**19**), *i.e.* a total yield of benzimidazolone (**15**) of 76%], m.p. 157–158 °C (Found: C, 60.92; H, 7.39; N, 20.50%; M^+, 138.0785. $C_7H_{10}N_2O$ requires C, 60.85; H, 7.29; N, 20.27%; *M*, 138.0793); ν_{max}($CHBr_3$) 3 450, 3 240, 1 710, 1 430, 1 350, and 1 060 cm^{-1}; δ(90 MHz) 2.10–2.40 (4 H, m, 2 × ring CH_2), 4.05 (2 H, m, NCHCHN), 5.30 (2 H, br s, 2 × NH), and 5.95 (2 H, t, CH=CH); *m/z* 138 (M^+), 94, 85 (51%), 84 (100), 56 (75), and 54 (19).

The *silyloxycarbonyl urea* (**20**) isolated above afforded the following data: [Found: $(M - CO_2)^+$, 210.1180. $C_{11}H_{18}N_2O_3Si$ requires $(M - CO_2)$, 210.1188]; ν_{max}(film), 3 240, 3 040, 2 955, 2 900, 1 670, 1 428, 1 408, 1 335, 1 250, 1 122, 845, 753, 705, 676, and 637; δ(90 MHz) 0.20 (9 H, s, $SiMe_3$), 1.80–2.30 (4 H, m, 2 × ring CH_2), 3.40–4.00 (2 H, m, NCHCHN), 5.12 (1 H, br, NH), and 5.75 (2 H, m, CH=CH); *m/z* 210 $(M - CO_2)^+$, 195, 157, 156 (100%), 141 (28), and 73 (25).

cis-4,5-*Diaminocyclohexene* (**21**).—The cyclic urea (**15**) (400 mg, 2.90 mmol), barium hydroxide (8 g, 25 mmol), and water (80 ml) were heated together in a sealed tube at 140 °C for 19.5 h.[15] Carbon dioxide was bubbled through the cooled solution for 15 min; barium carbonate was precipitated. After being filtered through Kieselguhr and very carefully washed with hot water, the filtrate was concentrated under reduced pressure to *ca.* 20 ml. The solution was acidified with 2M sulphuric acid, filtered through Kieselguhr to remove any precipitated barium salt, and the solvent removed under reduced pressure to a volume of *ca.* 5–10 ml. Methanol (50 ml) was added dropwise; crystals of the diamine sulphate salt were observed to precipitate. The mixture was then stored at 0 °C for 15 h, after which time the salt was collected by filtration and dried *in vacuo* over KOH/P_2O_5 to afford white crystal laminae of the *diamine sulphate* (439 mg, 72%), m.p. > 230 °C (Found: C, 33.34; H, 6.82; N, 13.65%. $C_6H_{14}N_2{\cdot}SO_4{\cdot}0.2H_2O$ requires C, 33.7; H, 6.79; N, 13.1%). Liberation of the *cis*-diamine from the salt was achieved by treatment of the salt with dry saturated ammoniacal chloroform (20 ml) for 1 h. The precipitated ammonium sulphate was separated by filtration. The solvent was removed under reduced pressure to give the desired cis-*diamine* (**21**) as a colourless oil [204 mg, 87%; overall yield of 63% from the cyclic urea (**15**)]. The oil was further purified by Kugelrohr distillation, oven temp. 65 °C at 0.7 mmHg (overall 85% from diamine salt) (Found: C, 62.03; H, 11.24; N, 24.66%; M^+, 112.1005. $C_6H_{12}N_2{\cdot}0.2H_2O$ requires C, 62.23; H, 10.80; N, 24.21%; *M*, 112.1001); ν_{max}(film) 3 360, 3 020, 2 905, 1 600, 1 460, 1 430, 1 380, 1 235, 990, and 875 cm^{-1}; δ(90 MHz) 1.24 (4 H, s, 2 × NH_2), 1.75–2.50 (4 H, m, 2 × ring CH_2), 2.98 (2 H, t,

2 × C*H*NH_2), and 5.61 (2 H, s, CH=CH); *m/z* 113, 112 (M^+), 83 (92%), 82 (100), and 58 (40).

2-*Methyl*-3a,4,7,7a-*tetrahydro*-1H-*benzimidazole* (**14**).—The diamine (**21**) (489 mg, 4.37 mmol) and ethylacetimidate hydrochloride[21] (539 mg, 4.37 mmol) were heated together in ethanol at 85 °C for 15 h. The solvent was removed under reduced pressure to afford the imidazoline salt (714 mg, 93%), m.p. 25 °C; δ(90 MHz) 2.20–2.80 (7 H, m, 2 × ring CH_2 and CCH_3), 4.60 (2 H, m, NCHCHN), 6.05 (2 H, m, CH=CH), and 8.50 (2 H, br s, 2 × NH). Treatment of this material with dry saturated ammoniacal chloroform (20 ml) at room temperature for 1 h afforded, after removal of precipitated ammonium chloride by filtration, an orange oil. This was purified by Kugelrohr distillation (oven temp. 130 °C at 0.6 mmHg) to give the *bicyclic dihydroimidazole* (**14**) as white crystals (386 mg, 65% overall from *cis*-diamine), m.p. 99.5–101 °C (Found: C, 70.73; H, 9.17; N, 21.11%; M^+, 136.1002. $C_8H_{12}N_2$ requires C, 70.55; H, 8.88; N, 20.57%; *M*, 136.1001); δ_H(90 MHz) 1.91 (3 H, s, CCH_3), 2.40 (4 H, m, 2 × ring CH_2), 4.20 (2 H, m, NCHCHN), 5.85 (2 H, t, CH=CH), and 6.75 (1 H, br s, NH); δ_C(62.9 MHz) 15.0 (C*C*H_3), 29.0 (C-4, C-7), 60.3 (C-3a, C-7a), 127.7 (C-5, C-6), and 163.1 (C-2); *m/z* 136 (M^+), 135, 121, 95, 94, 82 (100%), and 54.

1-*Benzyl*-2-*methyl*-3a,4,7,7a-*tetrahydro*-1H-*benzimidazole* (**22**).—The bicyclic dihydroimidazole (**14**) (786 mg, 5.78 mmol) was dissolved in dry THF (40 ml) at 0 °C. Butyl-lithium (6.66 ml, 1.3M solution in hexanes, 8.67 mmol) was added dropwise to give a bright yellow opaque solution. After being stirred for 40 min at 0 °C, benzyl bromide (1.02 ml, 8.67 mmol) was added dropwise and the mixture was stirred for 16 h, allowing it to warm to room temperature. The solvent was removed under reduced pressure, followed by the usual work-up, to afford a viscous yellow oil. Purification by column chromatography on silica gel (Merck Art. 7734, 80 g), eluting with chloroform–2-aminopropane (96:4 v/v), afforded the *benzyl dihydroimidazole* (**22**) (1.01 g, 77%) (Found: C, 78.52; H, 8.26; N, 12.23%; M^+, 226.1466. $C_{15}H_{18}N_2 \cdot 0.2H_2O$ requires C, 78.36; H, 8.07; N, 12.18%; *M*, 226.1470); ν_{max}(film) 3 320 (water), 3 020, 2 905, 1 610, 1 590, 1 420, 1 260, 730, and 700 cm^{-1}; δ_H(90 MHz) 1.98 (3 H, s, CCH_3), 2.0–2.5 (4 H, 2 × t, 2 × ring CH_2), 3.82 (1 H, dt, NC*H*CHN=C), 4.10–4.60 (3 H, AB and m, PhCH_2 and NCHC*H*N=C), 5.90 (2 H, 2 × m, CH=CH), and 7.20–7.60 (5 H, m, *Ph*CH_2); δ_C(62.9 MHz) 14.5 (C*C*H_3), 25.6 and 29.2 (C-4, C-7), 47.3 (N*C*H_2Ph), 58.8 and 63.2 (C-3a, C-7a), 126.0 (C-4′), 126.4 and 127.3 (C-5, C-6), 128.4 (C-3′), 129.5 (C-2′), 137.8 (C-1′), and 163.0 (C-2); *m/z* 226 (M^+), 174, 173, 172 (66%), 92, and 91 (100).

1-*Benzyl*-2-[4-(4-*methyl*-2,6,7-*trioxabicyclo*[2.2.0]*oct*-1-*yl*)*butyl*]-3a,4,7,7a-*tetrahydro*-1H-*benzimidazole* (**23a**).—The benzylated bicyclic dihydroimidazole (**22**) (418 mg, 1.85 mmol) was dissolved in dry THF (25 ml) at −78 °C, and butyl-lithium added (2.06 ml, 1.35M solution in hexane, 2.78 mmol) to give an orange solution. After stirring for 45 min at −78 °C, the C_4 bromo-orthoester (**3c**) (557 mg, 2.22 mmol) was added and the mixture stirred for 15 h at −78 ⟶ 20 °C to afford a dark orange solution. Removal of solvent under reduced pressure, followed by addition of chloroform (30 ml) and water (30 ml), extraction with chloroform (3 × 30 ml) and drying ($MgSO_4$) of the organic layers, gave a dark orange oil after removal of solvent under reduced pressure. Purification by column chromatography on silica gel (Merck Art. 7734, 40 g) afforded the starting bicyclic dihydroimidazole (**22**) (76 mg, 18%) and the *title compound* (**23a**) (370 mg, 62% on the basis of consumed starting material) (Found: C, 68.34; H, 8.08; N, 6.74%; M^+, 396.2416. $C_{24}H_{32}N_2O_3 \cdot 1.25H_2O$ requires C, 68.79; H, 8.30; N, 6.69%; *M*, 396.2413); ν_{max}(film) 3 330 (water), 2 930, 2 870, 1 605, 1 590, 1 450, 1 055, 990, and 700 cm^{-1}; δ(250 MHz) 0.88 (3 H, s, CCH_3), 1.40–2.40 [12 H, m, $(CH_2)_4$ and 2 × ring CH_2], 3.70 (1 H, m, NC*H*CHN=C), 3.85 (6 H, s, 3 × OCH_2), 4.10–4.50 (3 H, m and AB, NCHC*H*N=C and N*C*H_2Ph), 5.70–6.00 (2 H, 2 × m, CH=CH), and 7.10–7.40 (5 H, m, *Ph*CH_2); *m/z* 397, 396 (M^+), 366 (17%), 240 (10), 239 (31), 226 (78), 225 (25), 185 (100), 172 (36), and 91 (100).

In one run of this reaction, an interesting by-product was observed, with the formation of the 2-(2-*hydroxyprop*-1-*enyl*)-*dihydroimidazole* (**24**), due to the presence of EtOAc in the orthoester. This was isolated by column chromatography (60 mg, 25%) (Found: C, 70.01; H, 7.12; N, 9.61%; M^+, 268.1577. $C_{17}H_{20}N_2O \cdot 1.2H_2O$ requires C, 70.42, H, 7.78; N, 9.66%; *M*, 268.1576); ν_{max}($CHCl_3$) 3 260, 2 910, 1 650, 1 600, 1 300, 992, and 942 cm^{-1}; δ(250 MHz) 2.00 (3 H, s, CCH_3), 2.05–2.45 (4 H, 2 × m, 2 × ring CH_2), 3.83 (1 H, dt, NC*H*CHN=C), 4.16–4.55 (3 H, AB and m, PhCH_2 and NCHC*H*N=C), 4.67 (1 H, t, N=CC*H*=CCH_3), 5.87 (2 H, 2 × m, CH=CH), 7.20–7.50 (5 H, m, *Ph*CH_2), and 9.42 (1 H, br s, OH); *m/z* 269, 268 (M^+), 214 (11%), 106 (13), 91 (100), and 43 (17).

2-[4-(4-*Methyl*-2,6,7-*trioxabicyclo*[2.2.0]*oct*-1-*yl*)*butyl*]-3a,4,7,7a-*tetrahydro*-1H-*benzimidazole* (**23b**).—This compound was prepared according to the method described earlier for the preparation of (**4b**), from dihydroimidazole (**23a**) (180 mg, 0.45 mmol) in dry ethanol (1.5 ml) and sodium (*ca.* 200 mg) in liquid ammonia (25 ml). After being stirred for 2 h at room temperature the reaction mixture was worked up to afford a yellow solid. This was purified by flash column chromatography on silica gel (Merck Art. 9385), eluting with chloroform–2-aminopropane (96:4 v/v), to afford the *title compound* (**23b**) as a white solid (77 mg, 56%), m.p. 178.5–179.5 °C (Found: C, 66.16; H, 8.88; N, 8.67%; M^+, 306.1938. $C_{17}H_{26}N_2O_3 \cdot 0.2H_2O$ requires C, 65.87; H, 8.58; N, 9.04%; *M*, 306.1944); ν_{max}($CHCl_3$) 3 500–3 000 (water), 2 920, 2 880, 1 630, 1 460, 1 050, and 995 cm^{-1}; δ(250 MHz) 0.80 (3 H, s, CCH_3), 1.40–1.75 [6 H, m, $(CH_2)_3CO$], 2.20–2.25 (6 H, m, 2 × ring CH_2 and N=CCH_2), 3.88 (6 H, s, 3 × OCH_2), 4.11 (2 H, br, NCHCHN), and 5.87 (2 H, m, CH=CH); *m/z* 307, 306 (M^+), 276 (13%), 275 (27), 252, 221 (32), 171, 163, 149 (35), 136 (100), 95 (78), 82 (93), and 55.

2-(4-*Methoxycarbonylbutyl*)-3a,4,7,7a-*tetrahydro*-1H-*benzimidazole* (**25**).—A solution of concentrated sulphuric acid (4 drops) in dry methanol (5 ml) was prepared and this solution was added to compound (**23b**) (57 mg) at 0 °C and the solution stirred for 4.5 h. Potassium carbonate (100 mg) was added, the mixture stirred at room temperature for 5 h and the reaction monitored by TLC analysis. Evidence of the intermediate dihydroxyester was still visible on TLC analysis after 5 h, so a further portion of potassium carbonate (100 mg) was added and the mixture stirred for 16 h. The solid was removed by filtration and the solvent removed by evaporation under reduced pressure. The residue was carefully purified by flash column chromatography on silica gel (Merck Art. 9385), eluting with chloroform–2-aminopropane (96:4 v/v), to afford the *title compound* (**25**) (27 mg, 61%) as a pale yellow oil. (Found: M^+, 236.1523. $C_{13}H_{20}N_2O_2$ requires *M*, 236.1525); δ(250 MHz) 1.60–1.75 (4 H, m, CH_2CH_2CH_2CO_2), 2.20–2.40 (8 H, m, N=CCH_2, CH_2CO_2, and 2 × ring CH_2), 3.50 (1 H, br, NH), 3.67 (3 H, s, CO_2CH_3), 4.20 (2 H, m, NCHCHN), and 5.80 (2 H, 2 × m, CH=CH); *m/z* 236 (M^+), 205 (34%), 182 (67), 136 (37), 96 (48), 95 (100), 82 (67), 81 (20), 67 (10), and 54 (12).

1-*Benzyl*-2-(4-*methoxycarbonylbutyl*)-3a,4,7,7a-*tetrahydro*-1H-*benzimidazole* (**13**).—A solution of concentrated sulphuric acid (10 drops) in dry methanol (10 ml) was prepared and added to the orthoester (**23a**) (256 mg, 0.65 mmol) at 0 °C. After being

stirred for 2 h, TLC analysis indicated the absence of starting material, potassium carbonate (300 mg) was added and the solution was stirred at room temperature for 36 h. TLC analysis indicated that the desired product had been formed, along with the dihydroxyester intermediate. At this stage, the reaction mixture was worked up and the residue purified by flash column chromatography on silica gel (Merck Art. 9385), eluting with chloroform–2-aminopropane (97:3 v/v), to afford the desired *methyl ester* (**13**) (53 mg, 25%) and the *dihydroxyester* (**26**) (171 mg). This latter was treated as above; after stirring for 17 h at room temperature, flash column chromatography afforded a second batch of the *title compound* (**13**) (102 mg, 48%; *i.e.* overall 73% yield) (Found: C, 73.61; H, 8.65; N, 8.79%; M^+, 326.1996. $C_{20}H_{26}N_2O_2$ requires C, 73.59; H, 8.03; N, 8.58%; *M*, 326.1994); δ(250 MHz) 1.40–2.45 [12 H, m, $(CH_2)_4$ and 2 × ring CH_2], 3.64 (3 H, s, CO_2CH_3), 3.80 (1 H, m, NC*H*CHN=C), 4.05–4.50 (3 H, m and AB, NCHC*H*N=C and PhCH_2N), 5.70–6.0 (2 H, 2 × m, CH=CH), and 7.10–7.50 (5 H, m, *Ph*CH_2N); *m/z* 326 (M^+) 295 (10%), 272 (9), 226 (19), 185 (76), 172 (22), and 91 (100). The *dihydroxyester intermediate* (**26**), isolated from column chromatographic purification, was characterised as follows: (Found: M^+, 414.2523. $C_{24}H_{34}N_2O_4$ requires *M*, 414.2518); ν_{max}(film) 3 360, 2 920, 1 725, 1 600, 1 450, 1 250, 1 051, 755, and 700 cm^{-1}; δ(90 MHz) 0.90 (3 H, s, CCH_3), 1.55–2.50 [12 H, m, $(CH_2)_4$ and 2 × ring CH_2], 3.58 (4 H, s, 2 × CH_2OH), 3.85 (1 H, m, NC*H*CHN=C), 4.00–4.45 (5 H, m and AB, 2 × OH, NCHC*H*N=C, and NCH_2Ph), 4.15 (2 H, s, CO_2CH_2C), 5.70–6.05 (2 H, 2 × m, CH=CH), and 7.10–7.50 (5 H, m, *Ph*CH_2N); *m/z* 415, 414 (M^+), 360 (13%), 295 (13), 279 (26), 226 (39), 186 (22), 185 (98), 172 (21), 149 (94), 113 (21), 91 (100), 72 (39), 71 (33), and 57 (46).

Acknowledgements

We thank Drs. E. W. Collington and P. Hallett for helpful discussions, and the SERC and Glaxo Group Research for a CASE studentship (J. S.).

References

1 M. W. Anderson, R. C. F. Jones, and J. Saunders, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1995, 205; M. W. Anderson, M. J. Begley, R. C. F. Jones, and J. Saunders, *ibid.*, 1984, 2599.
2 See, *e.g.*, R. J. Grout in 'The Chemistry of Amidines and Imidates,' ed. S. Patai, Wiley, London, 1975, p. 255.
3 Some 2-(alkylthio)-2-imidazolines have been reported as monocyclic PGI_2 (prostacyclin) analogues: W. Bartmann, G. Beck, H. H. Lau, and G. Wess, *Tetrahedron Lett.*, 1984, **25**, 733. Azaprostanoids containing the imidazole and 2-oxotetrahydroimidazole units have been reported: M. Pailer and H. Gutwillinger, *Monatsh. Chem.*, 1977, **108**, 653, 1099, and S. Saijo, W. Wada, J. Wada, J. Himizu, and A. Ishida, *Chem. Pharm. Bull.*, 1980, **28**, 1459, respectively.
4 *cf.* J. V. Hay, D. E. Portlock, and J. F. Wolfe, *J. Org. Chem.*, 1979, **38**, 4379.
5 See, *eg.*, S. M. F. Lai and P. W. Manley, *Nat. Prod. Rep.*, 1984, **1**, 409, and earlier reviews in this series.
6 E. J. Corey and N. Raju, *Tetrahedron Lett.*, 1983, **24**, 5571.
7 E. J. Corey and B. De, *J. Am. Chem. Soc.*, 1984, **106**, 2735.
8 E. J. Corey, C. Shih, N.-Y. Shih, and K. Shimoji, *Tetrahedron Lett.*, 1984, **25**, 5013.
9 See, *e.g.*, W. Bartmann and G. Beck, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 751.
10 For a recent example see: H.-J. Gais and K. L. Lukas, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 511; H.-J. Gais, T. Lied, and K. L. Lukas, *ibid.*, p. 511.
11 *cf.* A. Fliri and K. Hohenlohe-Oehringen, *Chem. Ber.*, 1980, **113**, 607; M. Jouany, S. Constal, F. Frappier, and A. Marquet, *J. Chem. Res. (S)*, 1982, 114.
12 L. A. Paquette, T. Kakihana, J. F. Hansen, and J. C. Philips, *J. Am. Chem. Soc.*, 1971, **93**, 152.
13 H. R. Kricheldorf, *Makromol. Chem.*, 1973, **173**, 13.
14 J. H. Clark, *J. Chem. Soc., Chem. Commun.*, 1978, 789.
15 K. Hoffmann, D. B. Melville, and V. du Vigneaud, *J. Biol. Chem.*, 1941, **141**, 207; S.-H. Jung and H. Kohn, *Tetrahedron Lett.*, 1984, **25**, 399.
16 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
17 E. Schlitter and J. Hohl, *Helv. Chim. Acta*, 1952, **35**, 29; D. Waldi, *J. Chromatogr.*, 1961, **6**, 61.
18 W. G. Kofron and L. M. Baclawski, *J. Org. Chem.*, 1976, **41**, 1879.
19 M. L. Roumestant, M. Malacria, and J. Goré, *Synthesis*, 1976, **11**, 755.
20 S. S. Washburne and W. R. Peterson, *J. Organomet. Chem.*, 1971, **33**, 153.
21 S. R. Sandler and W. Karo, 'Organic Functional Group Preparations,' Academic Press, New York, 1972, vol. 3, p. 276.

Paper 9/02944C
Received 11*th July* 1989
Accepted 2*nd August* 1989