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Synthesis of Hexahydrocyclopentimidazol-2-(1*H*)-one Derivatives Displaying Selective DP-Receptor Agonist Properties

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Abstract—The rationale for investigating conformationally restricted analogues of BW245C as DP-receptor ligands and the syntheses of three such racemic bicyclic imidazolidinone analogues are described. Compounds **7** (BW587C), **8** (BW480C85), and **9** (BW572C85) were found to be potent inhibitors of human platelet aggregation and selective DP-receptor agonists in washed platelet and jugular vein isolated tissue assays.

Introduction

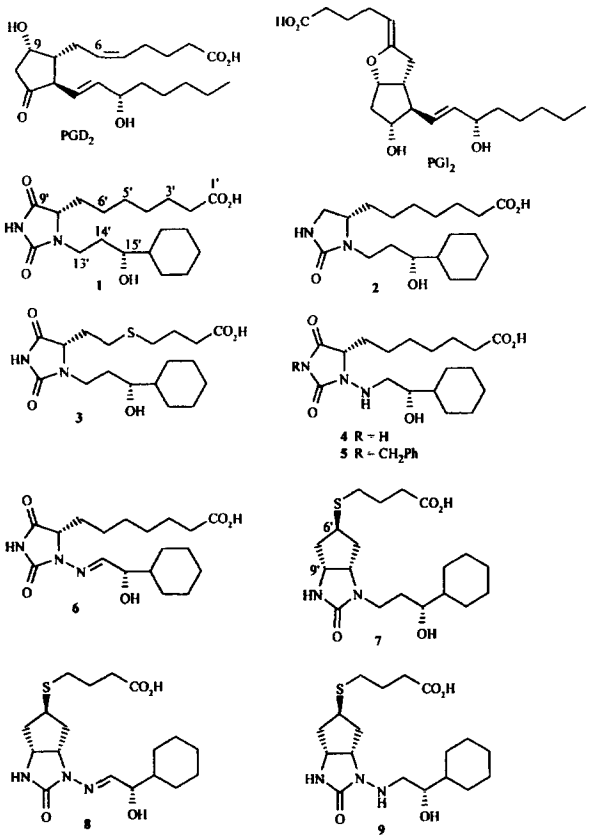
Blood platelets play a key role in the pathophysiology of arterial thrombosis. Both prostaglandin (PG) I_2 and PGD_2 are potent inhibitors of human platelet aggregation although they act via different receptors[1,2] (IP and DP respectively). Indeed, PGI_2 (Flolan, epoprostenol sodium) has been marketed for use as an antithrombotic agent.[3] The DP-receptor agonist, BW245C (**1**), has also been studied[4] in human volunteers. The major limitation to the clinical use of these agents as antithrombotics has been their short duration of action and their vasodepressor side effects. In view of their favourable antithrombotic profile, the identification of platelet-selective agonists, devoid of effects on vascular receptors is therefore an attractive goal.

DP-selective ligands are required to determine whether DP-receptors on human platelets and vascular smooth muscle are of the same type. DP-receptor properties are known to vary between species[5,6] and animal models are therefore of limited value for assessing vasodilatation side effects which manifest as facial flushing and headache. The hypothesis that selective DP-agonists will display potent platelet effects with minimal vascular actions can therefore probably only be tested in man.

As a first step towards testing this hypothesis we obviously required a selective DP-receptor agonist. The DP-agonist **1**[7] was taken as the lead compound for optimisation. Studies of the structure–activity relationships (SARs) of BW245C have shown[8] that when the 9′-carbonyl group of **1** is replaced by CH_2 (to give **2**) the inhibitory effects on human platelet aggregation are retained. Similarly, replacement of the 5′-6′ CH_2CH_2 moiety of **1** by CH_2S (to give **3**) leads to only a small variation in potency with respect to inhibition of platelet aggregation.[9] The 13′-aza analogues **4** and **6** are more potent inhibitors of platelet aggregation than **1** and their effects are of longer duration in vivo.[10] Compounds **1–4** and **6** are non-selective DP-receptor agonists, but which display additional agonist effects at other prostanoid (possibly EP_2) vascular receptors. Nevertheless, replacement of the N-10 H of **4** by a benzyl group, to give **5** (BWA868C), leads to a highly selective DP-receptor antagonist[7] that is, reduction of efficacy at the DP-receptor in addition to a complete loss of affinity at the other vascular receptor.

As a result of our SAR and modelling studies[9] we speculated that the DP-receptor-bound conformations of PGD_2 and BW245C are ones in which C-6 (and C-6′, PG numbering) is folded back toward the main ring. We therefore designed the heterobicyclic analogues of BW245C, **7-9**, in which C-6′ is tethered by a stable methylene linked to the ring at C-9′. Bicycles **7-9** cannot adopt the fully extended α-ω-parallel conformation ('Hairpin')[11] of $PGF_{2\alpha}$, but are capable of adopting conformations similar to the C-6 folded crystal conformation[12] of PGE_2 reasonably well. It seemed possible, therefore, that these conformationally restricted analogues might display selective DP-receptor agonism especially if extended conformations[13,14] are a prerequisite for agonism at other PG receptors.

Although analogues **7-9** are more rigid than **1** they are more flexible than PGI_2. Nonetheless, our main



concern with these conformational restraints was that the broad structural similarity between these analogues and PGI_2 might lead to effects at IP-receptors.

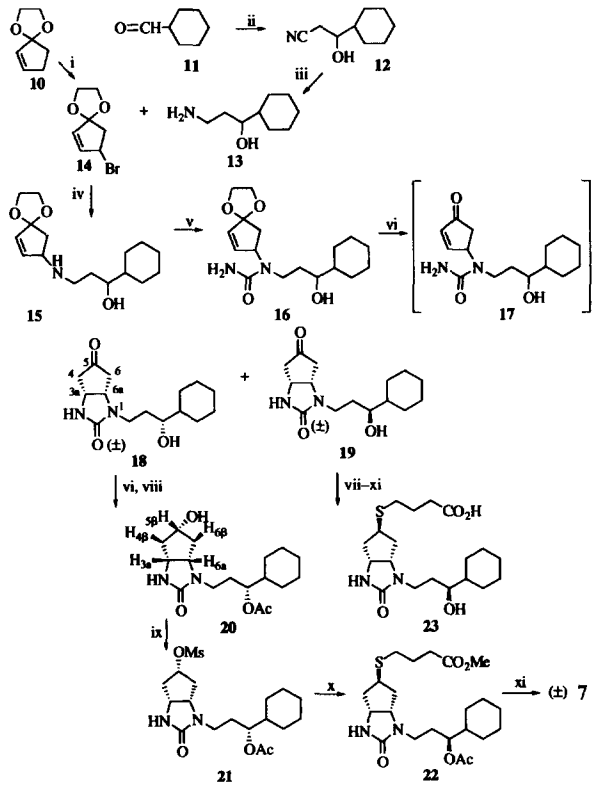
Synthesis

The eleven step synthesis of racemic **7**, from the unstable bromide **14**[15] and nitrile **12**[16,17] is shown in Scheme 1. The key step is the in situ generation of enone **17** and subsequent conversion into bicycles **18** and **19** via an intramolecular Michael type addition. Diastereomers **18** and **19** are readily separated by flash chromatography.[18] Their relative stereochemistries were determined by converting each diastereomer into the corresponding prostanoid. Since **7** displayed far more potent (>100×) PG mimetic activity than its 15′-epimer **23**, **7** and **18** (1 (R*) 3aα, 6aα) were assigned the same configurations as PGD_2. The reduction of the O-acetate of **18** with $NaBH_4$ gave a single alcohol epimer which was assigned as **20** (i.e., the 5-α configuration) on the basis of NOE experiments.[19] Reaction of mesylate **21** with $NaS(CH_2)_3CO_2Me$[20] was also stereospecific and gave, as expected, diester **22** with the inverted 5-β configuration.[21]

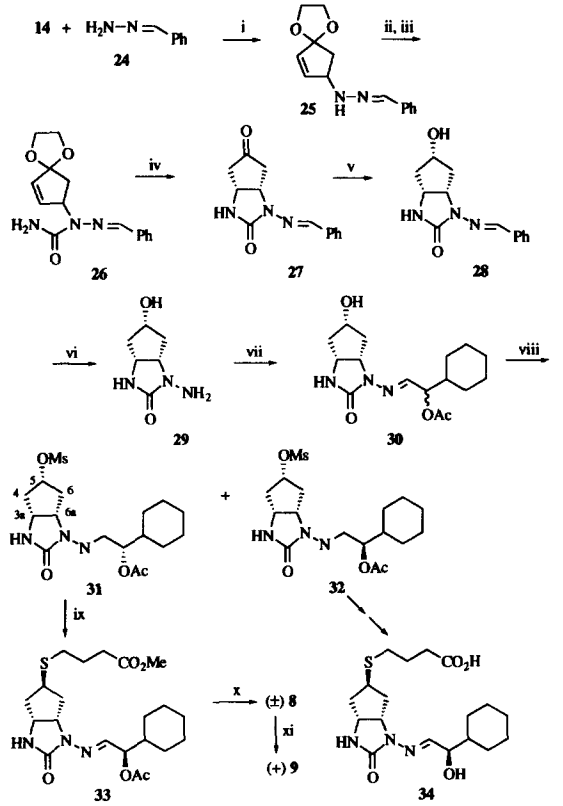
The 13′-aza analogues (±)-**8** and **9** were obtained from bromide **14**[15] and benzaldehyde hydrazone **24**[22] by the route shown in Scheme 2. Stereochemical assignments[23] were analogous to those of the 13′-carbo series. Thus, hydrazone **27** was converted into the bicyclic N-amino imidazolidinone **29** and then to alcohol **30**. Since this alcohol could not be stored satisfactorily for more than a few days separation of the diastereomers was carried out[24] on the mesylate intermediates **31** and **32**. Conversion of (±)-**14** into (±)-**8** was achieved in 2.4 overall yield,[25] compared with 0.6% of (±)-**7** from (±)-**14**.[26]

Pharmacological Results and Discussion

The PG mimetic activities of analogues **1-9** were determined by previously described methods[5,27] and are shown in Table 1. Bicyclic sulphides **7–9** are more potent inhibitors of platelet aggregation than sulphide **3** but only the 13′-aza analogue **9** was found to be much more potent than BW245C. Thus, structural changes (conformational restriction, loss of carbonyl, and replacement of 13′-CH_2 by NH) in going from **3**→**7**→**9** lead to improved potency of platelet effects. Analogue **7** displays much weaker vasodilatory actions than **3**, **8**, or **9**. Interestingly, the duration of the hypotensive effects of **8** are greater than those of **9** or **7**, whereas **4** is longer acting than **6**. Further work will be required to determine if their metabolic deactivation occurs by different pathways.



Scheme 1. Reagents: (i) NBS, AIBN, CCl_4 [ref. 15]; (ii) *n*-BuLi, CH_3CN, −78 °C (52%); (iii) $LiAlH_4$, Et_2O, 25 °C (58%); (iv) Toluene, 25 °C for 24 h; 40 °C for 3 h; NEt_3 (32%); (v) KCNO, 1 N HCl, EtOH–H_2O (85%); (vi) 2 N HCl, THF, 25 °C, 2 h (45% of **18**; 40% of **19**); (vii) Ac_2O, C_5H_5N, rt, 18 h (84%); (viii) $NaBH_4$, EtOH (54%); (ix) $MeSO_2Cl$, C_5H_5N, 0–5 °C, 24 h (50%); (x) Thiobutyrolactone, NaOMe, MeOH; DMSO (63%); and (xi) 2 N NaOH, MeOH (88%).



Scheme 2. Reagents: (i) Toluene −40 °C→0 °C; NEt_3, reflux 2 h (55%); (ii) $COCl_2$, C_5H_5N, toluene 0 °C; (iii) aqueous NH_3 (d 0.88) (90% overall); (iv) Camphor sulphonic acid, Me_2CO (55%); (v) $NaBH_4$, EtOH (85%); (vi) H_2, 10% Pd–C, EtOH, AcOH, 70 °C, 90 atmos (90%); (vii) $C_6H_{11}CH(OAc)CHO$ [ref. 30], NaOAc, MeOH, 50 °C, 3 h (75%); (viii) $MeSO_2Cl$, C_5H_5N, CH_2Cl_2 (35% of **31**, 36% of **32**); (ix) Thiobutyrolactone, NaOMe, MeOH; DMSO (50%); (x) LiOH, H_2O–MeOH (86%); (xi) $Na(CN)BH_3$, AcOH, MeOH (90%).

The sulphide **7** proved to be a potent and selective DP-receptor agonist (Table 2). In the washed human platelet assay[7] it was found to be a full agonist at the DP-receptor. It behaves as a partial agonist at the DP-receptor in the rabbit jugular vein assay[7] and shows greater selectivity than compound **1** since the effects of **7** could be completely antagonised by BWA868C, which is selective for DP-receptors, with no evidence of actions at other PG receptors. The 13′-aza analogues BW480C85 (**8**) and BW572C85 (**9**) also proved to be selective DP-receptor agonists and behaved as full agonists in the platelet assay. In the jugular vein assay both **8** and **9** behaved as partial agonists, with increased potencies relative to those of **7**. As with **7** the compounds did not activate a second vascular receptor mediating relaxation. EP_2- and IP-receptor mediated relaxations and TP-receptor mediated constrictions in jugular vein were unaffected by these compounds.[28] Also they did not effect IP- or TP-receptor mediated actions on platelet aggregation or smooth muscle contraction at FP- or EP_1-receptors.[28] The DP-receptor selectivity of these bicycles is probably a reflection of their restricted conformations. A better understanding of any unique features of DP-receptor bound ligands would be facilitated by detailed studies of structure–activity relationships,[29] crystallographic investigations, and development of other selective IP- and EP_2-receptor ligands. Unfortunately, selective antagonists for IP- and EP-receptors are not available at present so the sub-type of PG-receptor mediating the DP-antagonist insensitive effects of BW245C cannot be assigned.

In summary bicycles **7–9** should find utility in PG-receptor classification studies[28] as selective DP-agonists. Investigations of the dose–response relationships for inhibition of platelet aggregation and vasodilatation in

Table 1. Pharmacological activities of BW245C and analogues

Compound	Inhibition of ADP-induced human platelet aggregation		Blood pressure lowering activity in rat	
	Relative potencies[a]		Relative potency[b]	
	$PGD_2=1$	($PGI_2=1$)	($PGI_2=1$)	$t_{1/2}$ (min)[c]
1 BW245C	8	(0.20)	0.06	4
2	6	(0.14)	0.01	3
3	4.4	(0.1)	0.15	3
4 BW361C	24	(0.6)	0.02	28
5 BWA868C	no agonism		d	
6 BW68C	12	(0.3)	0.04	17
7 BW587C	10	(0.26)	<0.001	1
8 BW480C85	9.6	(0.24)	0.01	25
9 BW572C85	29	(0.72)	0.07	7

[a]Potencies relative to PGD_2 are approximate. BW245C is approximately 8 and 0.2 times as potent as PGD_2 and PGI_2, respectively. The relative potencies were calculated from the IC_{50} values of the compounds. IC_{50} is the concentration required to reduce the aggregation to 50% of its control amplitude. Compounds **1**, **4**, **6**, **7**, **8** and **9** have IC_{50} values (ng mL^{-1}) of 1.5 ± 0.1 (10), 0.50 ± 0.06 (8), 1.1 ± 0.2 (6), 1.2 ± 0.26 (5), 1.25 ± 0.2 (6), and 0.41 ± 0.04 (8) respectively for (n) experiments. Inactive compounds have IC_{50}'s > 200 ng mL^{-1}. All compounds were incubated with human platelet rich plasma (PRP) for 1 min. PGI_2 was used as a standard for each batch of PRP. Relative potencies were confirmed by comparing the effects of groups of analogues (up to 5 per experiment) with BW245C and PGI_2 on the same batch of PRP.

[b] Values are relative to prostacyclin in the same anaesthetized animal, $n \geq 3$.

[c]Half-life (standard error mean ± 20%) of hypotensive effects at a dose that causes a fall in systemic arterial blood pressure of 20 mmHg.

[d]Tachycardia and some blood pressure lowering is observed in conscious rats.

Table 2. DP-receptor effects of BW245C and analogues

Compound	pA_{50}[a]		pK_A[d]		Agonist/Antagonist[e]		DP-selectivity[f]
	Platelet[b]	Jugular[c]	Platelet[b]	Jugular[c]	Platelet	Jugular	
1 BW245C	8.24	7.09	n.d.[g]	n.d.[g]	F	F	No
5 BWA868C	—	—	9.25[h]	8.7	Ant.	Ant.	Yes
7 BW587C	6.53	5.29	n.d.[g]	n.d.[g]	F	P (0.5)	Yes
8 BW480C	8.00	7.37	6.69	6.75	F	P (0.6)	Yes
9 BW572C	8.43	7.34	7.21	6.63	F	P (0.7)	Yes

[a]Parameter describing potency of agonist response. $pA_{50} = -\log_{10} A_{50}$ where A_{50} is the concentration of compound that produces 50% of the maximum agonist response. Typical error: **9**, 8.43 ± 0.15 (n = 4).

[b]Agonists inhibit the aggregation of human washed platelets induced by 50 μM ADP.

[c]Agonists produce relaxation of tone in rabbit jugular vein ring segments after prior contraction with 1 μM histamine.

[d]Parameter describing affinity of compound for DP-receptor. $pK_A = -\log_{10} K_A$ is the dissociation constant for the agonist at the DP-receptor. Typical errors: **9**, 7.21 ± 0.29; 6.63 ± 0.13: **8**, 6.69 ± 0.40, 6.75 ± 0.15. Values are the average of 3–6 estimates.

[e]Classification of compound as agonist or antagonist. F = Full agonist; P = partial agonist; Ant. = antagonist. In the platelet assay all agonists gave a maximal response (100% inhibition of aggregation). BW245C was the only agonist to give a maximal response (100% relaxation) in the rabbit jugular vein. For partial agonists the approximate mean efficacy is given in brackets. Thus compound **8** ($\alpha = 0.6$) gives $61 \pm 25\%$ (n = 3) of the response observed for BW245C.

[f]Inferred from experiments with the selective DP-antagonist, **5**. If the effects of the agonist were totally blocked in the presence of 10 μM **5** the agonist was assumed to be DP-selective. Non-selective agonists show a response which is partly resistant to BWA868C antagonism. The DP-receptor selectivity of compounds **7–9** was confirmed by their absence of effects at other prostanoid receptors. All experiments ($n \geq 2$) were performed in the presence of 10 μm BWA858C to prevent binding to the DP-receptor. None of the compounds, at concentrations up to 10 μm, exerted any effect on baseline tone in the rabbit jugular vein preparation nor on histamine (1 μm)-induced tone in this assay. It has previously been shown[7] that this jugular vein preparation contains TP-receptors which mediate vasoconstriction, IP-receptors and EP_2-receptors which mediate vasorelaxation. Also, in guinea-pig ileum and rat fundus preparations, which contain respectively EP_1-receptors[2] and FP-receptors[31] mediating smooth muscle contraction, compounds **7–9** were without effect at concentrations up to 10 μM. In the platelet assay neither IP-receptor-mediated inhibition of aggregation (by PGI_2, PGE_1 and carbacyclin) nor TP-receptor-mediated aggregation (by U46619) was affected by concentrations up to 10 μm.

[g]n.d. = not determined. PGD_2 and BW245C elicit non-DP-receptor effects (e.g., vasorelaxation through presumed EP_2-receptors). Displacements of agonist-concentration effect curves may also be confounded by slowing of agonist responses in the presence of BWA868C.

[h]pK_B value of the antagonist. pK_B is the dissociation constant of the antagonist.

man will allow a test of the hypothesis that selective inhibition of platelet aggregation by DP-receptor ligands is possible.

Experimental

Mps were taken in open capillary tubes and are uncorrected. ^{1}H NMR spectra were obtained on Bruker HFX90, AM-200, or WM-360 spectrometers. Ei mass spectra were obtained on an A.E.I. MS 902 spectrometer, interfaced to a VG MULTISPEC data system at 70 eV. Fast atom bombardment mass spectrometry (FABMS) were obtained from a Kratos MS50 mass spectrometer equipped with an RF magnet. The instrument was calibrated to 2,000 amu with caesium iodide. The samples were admixed with thioglycerol on the probe tip, introduced via the vacuum lock to the source on the mass spectrometer, and bombarded with fast Xe atoms. Thin-layer chromatograms (TLC) were performed on Merck silica gel 60 F_{254} and developed with iodine or phosphomolybdic acid, gravity column chromatography with Merck silica gel (60–120 mesh), and flash chromatography with Merck silica gel (230–400 mesh).

Several of the intermediates prepared which are described as oils, syrups or waxes may be crystalline solids when analytically pure. Crystallisation of many pure compounds was often very slow and inhibited by small amounts of occluded solvents. Melting points of the bicycles were often of poor diagnostic value since they appeared to vary with heating rate and trace impurities. Compounds in this series are probably capable of existing in several interconvertible crystalline forms. **Hazard**: Bioactive compounds should be handled with care since absorption on skin may cause facial flushing.

(±)-3-Cyclohexyl-3-hydroxypropylamine (13). A solution of 3-cyclohexyl-3-hydroxyproprionitrile (**12**)[16,17] (40.8 g, 0.27 mol) in dry ether (360 mL) was added dropwise, over 45 min, to a stirred solution of lithium aluminium hydride (10.4 g, 0.27 mol) in dry ether (450 mL) at 0 °C under N_2. The mixture was stirred at rt for 2 h, a saturated aqueous solution of Na_2SO_4 added slowly followed by $CHCl_3$ (1500 mL). Inorganic material was removed by filtration and washed with more $CHCl_3$. Evaporation of the filtrate gave a pale yellow oil. Purification by distillation yielded 24.6 g (58%) of **13**, bp 82–92 °C/0.3 mmHg, as a colourless syrup which solidified to a wax on cooling. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.80–2.08 (13H, complex m, aliphatic H), 2.40 (2H, brs, NH_2, exchang.) 2.64–3.20 (2H, m, NCH_2), 3.30–3.75 (1H, m, OCH). FABMS *m/z* 158 ($M^+ + H$). Anal. calcd for $C_9H_{19}NO$ requires C, 68.7; H, 12.2; N, 8.9. Found C, 68.5; H, 12.4; N, 8.7%.

[1(*R*,*S*)-N(*R,*S**)]-N-(3-Cyclohexyl-3-hydroxypropyl)-4,4-ethylenedioxycyclopent-2-enamine (15).** 5-Bromo-

3-ethylenedioxycyclopent-2-ene (**14**) was prepared from the ketal **10** (15.0 g, 0.12 mol) by the method of DePuy[15] and dissolved in dry toluene (150 mL). The solution was added dropwise with stirring to the amine **13** (15.0 g, 0.096 mol) in dry toluene (240 mL) at −25 °C. The brown solution was stirred for 26 h at rt then at 40 °C for 3.5 h then triethylamine (18.0 g) was added. The resulting cloudy solution was washed with three portions of water, then dried ($MgSO_4$) and the solvent evaporated in vacuo giving a brown oil. Purification by column chromatography (silica, chloroform: methanol, 100:7) gave the mixture of diastereomers of **15** as a pale red oil. Yield 8.58 g (32%) ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.80–2.02 (14H, complex m, aliphatics + ring C<u>H</u>), 2.14–2.56 (1H, m, ring CH<u>H</u>), 2.60–3.58 (5H, complex m, $NHCH_2$ + CHOH, 2H exchang.), 3.64–3.90 (1H, m, CHN), 3.92 (4H, s, OCH_2CH_2O), 5.56–5.80 (1H, m, olefinic H), 5.86–6.10 (1H, m, olefinic H). FABMS *m/z* 282 ($M^+ + H$).

[1(*R),3aα,6aα]-(±)-1-(3-Cyclohexyl-3-hydropropyl)-tetrahydro-2,5(1*H*,3*H*)-cyclopentimidazoledione (18) and [1(*S**),3aα,6aα]-(±)-1-(3-Cyclohexyl-3-hydroxypropyl)tetrahydro-2,5(1*H*,3*H*)-cyclopentimidazoledione (19).** The amine **15** (6.60 g, 23.4 mmol) in ethanol (140 mL) was treated with potassium cyanate (2.86 g, 35.4 mmol) in water (15 mL) at 0–5 °C and then 1 N aqueous hydrochloric acid (20 mL, 20 mmol). The mixture was stirred at 0–5 °C for 2 h and then at rt. After 18 h, the solvent was evaporated, the residue diluted with water and extracted with chloroform. The extract was dried then decolourised and the solvent was removed in vacuo to give crude N-(3-cyclohexyl-3-hydroxypropyl)-*N*-(4.4-ethylenedioxycyclopent-2-enyl)-urea (**16**) as a tan glass (6.45 g ca. 85%). This material was dissolved in tetrahydrofuran (90 mL) and 2.0 N aqueous hydrochloric acid (75 mL) and the solution stirred at rt for 2 h. The solvent was removed in vacuo, the residue diluted with water and the oily mixture extracted with $CHCl_3$ (2×). The combined extracts were dried ($MgSO_4$) and evaporated to give a tan oil. This material was purified and separated into its diastereomers by column chromatography on silica. Elution with MeOH:EtOAc (1:9) gave 1.26 g (45%) of the less polar diastereomer **18** as a pale yellow glass. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.90–1.48 (7H, complex m, aliphatic H), 1.58–1.92 (6 H, complex m, aliphatic H), 2.32–2.70 (4H, complex m, CH_2 $C(O)CH_2$), 2.85–2.95 (1H, m NC<u>H</u>H), 3.17–3.27 (1H, m, OCH), 3.56 (1H, d, *J* = 6Hz, OH, exchang.), 3.67–3.80 (1H, m, NCH<u>H</u>), 4.28–4.42 (2H, m, NCHCHN), 5.85 (1H, s, NH, exchang.). FABMS m/z 281 ($M^+ + H$) R_f 0.3 (silica, EtOAc:MeOH, 9:1). 1.11 g (40%) of the more polar diastereomer **19** was also obtained as a pale yellow glass ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.90–1.48 (7H, complex m, aliphatic H), 1.58–1.92 (6H, complex m, aliphatic H), 2.34–2.70 (4H, complex m, $CH_2C(O)CH_2$), 3.18–3.28 (1H, m, NC<u>H</u>H), 3.40–3.62 (2H, m, NCH<u>H</u> + OCH), 3.80 (1H, brs, OH, exchang.), 4.32–4.45 (2H, m, NCHCHN), 6.16 (1H, s, NH, exchang.). FABMS *m/z* 281 ($M^+ + H$), R_f 0.2 (silica, EtOAc:MeOH, 9:1).

[1(*R),3aα,5α,6aα]-(±)-1-[3-Acetyloxy)-3-cyclohexyl-propyl]hexahydro-5-hydroxy-2(1*H*)-cyclopentimidazolone (20).** The keto-alcohol **18** (less polar isomer) (1.18 g) was dissolved in pyridine (6.0 mL) and acetic anhydride (6.0 mL) and stirred at rt for 18 h. The solution was evaporated, the residue diluted with chloroform and washed with water, N hydrochloric acid, aqueous sodium bicarbonate solution, then finally water. After drying ($MgSO_4$) the organic layer the solvent was removed in vacuo to give 1.14 g (84%) of [1(*R**),3aα,6aα]-(±)-1-[3-acetoxy-3-cyclohexylpropyl]-tetrahydro-2,5(1*H*,3*H*)-cyclopentimidazoledione as a yellow glass. This keto-ester (1.14 g, 3.5 mmol) in ethanol (50 mL) was treated at +5 °C with sodium borohydride (250 mg, 6.6 mmol) with stirring. After 4 h at rt the ethanol was removed in vacuo, the residue diluted with water, and the product extracted into ether. The extract was dried ($MgSO_4$), the solvent removed in vacuo and the residue chromatographed on silica. Elution with EtOAc:MeOH (19:1) gave 619 mg (54%) of **20** as a colourless oil. ^{1}H NMR (360MHz, $CDCl_3$) δ: 0.90–2.04 (17 H, complex m, aliphatic H), 2.05 (3H, s, CH_3), 2.48 (1H, brd, *J* = 6 Hz, OH, exchang.), 2.88–3.68 (2H, m, NCH_2), 4.05–4.30 (2H, m, NCHCHN), 4.32–4.48 (1H, m, C<u>H</u>OH), 4.60 (1H, brs, NH, exchang.), 4.70–5.08 (1H, m, C<u>H</u>OAc). FABMS *m/z* 325 ($M^+ + H$).

The relative stereochemistry of alcohol **20** was established by a full NMR analysis of the *O*-Tosyl derivative **35** which was prepared by an analogous series of reactions. Details of the preparation and assignments are given below.

[1(*R),3aα,5α,6aα]-(±-1-[3-(Acetyloxy octyl) hexahydro-5-(4-methyl phenyl sulphonyloxy)-2(1*H*)-cyclopentimidazolone (35).** [1(*R**), 3aα,5α,6aα]-(±)-1-[3-(Acetyloxy octyl)hexahydro-5-hydroxy-2(1*H*) cyclopentimidazolone (**36**), (312 mg) in dry pyridine (2.4 mL) was treated at rt with *p*-toluenesulphonyl chloride (240 mg). The orange solution was set aside at rt for 24 h then diluted with chloroform and washed with excess 2 N hydrochloric acid. The organic extract was dried ($MgSO_4$) and the solvent removed in vacuo and the residual gum purified by column chromatography (silica, elution with ether:methanol, 23:2) giving 0.28 g (60%) of the *O*-Tosyl derivative **35** as colourless crystals, mp 51–52 °C (from ether:hexane). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz, aliphatic CH_3), 1.20–1.36 (6H, m, 3 × CH_2), 1.50–1.61 (2H, m, CH_2), 1.70–1.80 (2H, m, N-C-CH_2), 1.85–1.97 (1H, m, $J_{6\alpha,6\beta}$ = 15.0, $J_{6a,6\beta}$ = 6.6, $J_{5\beta,6\beta}$ = 5.3 Hz, H-6β), 1.98–2.10 (2H, m, $H_{4\alpha}$, $H_{4\beta}$), 2.22–2.30 (1H, m, $J_{6\alpha,6\beta}$ = 15.0, $J_{5\beta,6\alpha}$ = 2.6, $J_{6a,6\alpha}$ = $J_{4\alpha,6\alpha}$ = 2 Hz, H6α), 2.44 (3H, s, $ArCH_3$), 2.77–2.86 (1H, m, NC<u>H</u>H), 3.42–3.53 (1H, m, NCH<u>H</u>), 4.09–4.17 (1H, m, $J_{3a,6a}$ = 8.8, $J_{3a,4\beta}$ = 6.6 Hz, $J_{3a,4\alpha}$ = 2 Hz, H-3a), 4.22–4.30 (2H, m, $J_{3a,6a}$ = 8.8, $J_{6a,6\beta}$ = 6.6, $J_{6a,6\alpha}$ = 2 Hz, H-6a + NH, exchang.), 4.84 (1H, quintet, J = 6.3 Hz, CHOAc), 5.13–5.19 (1H, m, $J_{4\beta,5\beta}$ = $J_{5\beta,6\beta}$ = 5.3 Hz, $J_{4\alpha,5\beta}$ = $J_{5\beta,6\alpha}$ = 2.6 Hz, H-5β), 7.34 (2H, d, *J* = 8.2 Hz, aromatics), 7.70 (2H, d, *J* = 8.2 Hz, aromatics).

NOE experiments: irradiation of the δ 4.13 signal (H-3a) gave enhancements of the δ 4.27 (H-6a) and δ 1.98–2.10 ($H_{4\alpha,4\beta}$) signals; irradiation of the δ 4.27 signal (H-6a) gave enhancements of the δ 4.13 (H-3a), 2.26 (H-6α), 1.90 (H-6β), 1.74 (N-C-CH_2), 3.48 (NCHH and 4.84 (CHOAc) signals; irradiation of the δ 5.15 (H-5β) signal gave enhancements of the δ 1.98–2.10 ($H_{4\alpha}$,$H_{4\beta}$), 2.26 (H-6α), 1.90 (H-6β), and 7.70 (aromatic) signals; irradiation of the δ 1.90 (H-6β) signal gave enhancements of the δ 2.26 (H-6α), 4.27 (H-6a) and 5.15 (H-5β) signals; irradiation of the δ 1.98–2.10 (H-4) signals gave enhancements of the δ 4.13 (H-3a) and 5.15 (H-5β) signals; irradiation of the δ 2.26 (H-6α) signal gave enhancements of the δ 1.90 (H-6β), 2.82 (NCHH) and 5.15 (H-5β signals).

Spin decoupling expts: irradiation of the δ 3.48 (NCHH) signal simplified the multiplets at δ 2.82 (NCHH) and 1.74 (N-C-CH_2); irradiation of the δ 4.13 (H-3a) signal simplified the multiplets at δ 1.98–2.10 (H-4) and 1.90 (H-6β); irradiation of the δ 4.84 (CHOAc) signal simplified the δ 1.74 (N-C-CH_2) signal; irradiation of the δ 5.15 (H-5β) signal simplified the δ 2.26 (H-6α, dt, J=15, 2, 2Hz) and δ 1.90 (H-6β, dd, J=15, 6.6 Hz) signals; irradiation of the δ 1.98–2.10 (H-4) signals simplified the δ 2.26 (H-6α, dt, J=15.0, 2, 2 Hz) and 4.13 (H-3a, dt, J=8.8, 2, 2 Hz); irradiation of the δ 2.26 (H-6α) signal simplified the δ 1.90 (H-6β) and 4.27 (H-6a) signals. FABMS *m/z* 467 (M^++H). Anal. cald for $C_{23}H_{34}N_2O_6S$ requires C, 59.2; H, 7.34; N, 6.02. Found C, 59.0; H, 7.52; N, 5.81%.

[1(*R),3aα,5α,6aα]-(±)-1-(3-Acetyloxy-3-cyclohexylpropyl) hexahydro-5-methanesulphonyloxy-2(1*H*)-cyclopentimidazolone (21).** Methanesulphonyl chloride (0.70 mL, 9.0 mmol, redistilled) was added dropwise to a stirred solution of acetoxy-alcohol (**20**) (1.10 g, 3.4 mmol) in dry dichloromethane (20 mL) and dry pyridine (0.70 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h, set aside at +5 °C for 16 h, and then ice-water (50 mL) added. The mixture was extracted with CH_2Cl_2 (3×), the extracts washed with brine, 5% hydrochloric acid, 5% $NaHCO_3$ solution, and finally brine. After drying ($MgSO_4$) the solvent was removed in vacuo and the residual oil chromatographed on silica. Elution with EtOAc:MeOH (9:1) and crystallisation from EtOAc-Et_2O yielded 0.68 g (50%) of **21**, mp 125 °C ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.85–2.68 (17H, complex m, aliphatic H), 2.06 (3H, s, C—CH_3), 2.72–3.14 (1H, m, NCHH), 2.97 (3H, s, SCH_3), 3.24–3.52 (1H, m, NCHH), 4.03–4.36 (2H, m, NCHCHN), 4.50–4.84 (1H, m, CHOAc), 5.01–5.36 (2H, m, CHOMes+NH, 1H exchang.). FABMS *m/z* 403 (M^++H). Anal. cald for $C_{18}H_{30}N_2O_6S$ requires C, 53.7; H, 7.51; N, 6.96. Found C, 53.5; H, 7.68; N, 6.76%.

[1(*R),3aα,5β,6aα]-(±)-Methyl-4-[[1-(3-Acetyloxy 3-cyclohexylpropyl)octahydro-2-oxo-5-cyclopentimidazolyl]thio]butanoate (22).** Thiobutyrolactone (326 mg, 3.2 mmol) was dissolved in methanolic sodium methoxide [from sodium (75 mg, 3.3 g.a.) and dry methanol (7.0 mL)] and set aside at rt for 2 h. The solvent was removed in vacuo and the residue dissolved in dry dimethylsulphoxide (7.0 mL). The mesylate **21** (0.60 g, 1.5 mmol) in dimethylsulphoxide (3.0 mL) was added in one portion to the thiolate solution prepared[20] above and the mixture set aside at rt for 18 h. The solution was then diluted with 0.5% aqueous sodium dihydrogen phosphate solution (45 mL) and the product extracted into ethyl acetate. The extract was washed with water, dried ($MgSO_4$), the solvent removed in vacuo and the product purified by column chromatography (silica, elution with methanol:ether, 3:100) giving 0.41 g (63%) of **22** as a colourless syrup. ^{1}H NMR [200 MHz, $CDCl_3$] δ: 0.80–2.20 (19 H, complex m, aliphatic H), 2.03 (3H, s, C-CH_3), 2.28–2.80 (4H, complex m, $CH_2C(O)$, CH_2S), 2.85–3.87 (3H, m, NCH_2+CHS), 3.66 (3H, s, OCH_3), 4.08–4.35 (2H, m, NCHCHN), 4.63–5.04 (2H, m, CHOAc+NH, 1H exchang.). FABMS *m/z* 441 (M^++H).

[1(*R),3aα,5β,6aα]-(±)-4-[[1-(3-Cyclohexyl-3-hydroxypropyl)octahydro-2-oxo-5-cyclopentimidazolyl]-thio]butanoic acid (7).** The ester **22** (0.40 g, 0.90 mmol) in methanol (8.5 mL) was treated with 2 N aqueous sodium hydroxide (5.2 mL, 10.4 mmol) and set aside at rt for 2 h. The solution was diluted with water, washed with ether, and the aqueous phase acidified to pH 3 with dilute hydrochloric acid. The product was extracted into chloroform, the extract dried ($MgSO_4$), the solvent removed in vacuo and the residue recrystallized from chloroform:ether giving 0.30 g (88%) of acid **7** as colourless prisms, mp 148–149.5 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.90–1.98 (17H, complex m, aliphatics), 2.12–2.19 (1H, m, H-4α), 2.21–2.28 (1H, m, H-6α), 2.42 (2H, t, J=7.0 Hz, CH_2CO), 2.60 (2H, t, J=7.0 Hz, CH_2S), 2.90–3.13 (NCHH), 3.19–3.32 (2H, m, CHS+OCH), 3.60–3.78 (1H, m, NCHH), 4.07–4.28 (2H, m, H-3a, H-6a), 4.3–5.2 (2H, rise in baseline, 2×OH, exchang.), 5.80 (1H, brs, NH, exchang).

NOE experiments: irradiation of the δ 2.90–3.13 (NCHH) signal gave an enhancement of the δ 3.60–3.78 (NCHH), and δ 2.21–2.28 (H-6α) signals and vice-versa; irradiation of the δ 5.80 (NH) signal gave an enhancement of the δ 4.24 (H-3a) and δ 2.12–2.19 (H-4α) signals.

COSY2D and spin decoupling experiments allowed the following assignments: δ: 1.55 (H-6β), 1.68 (H-4β), 2.16 (H-4α), 2.24 (H-6α), 3.27 (H-5α), 4.17 (H-6a), 4.24 (H-3a); J values 3a-N1=1, 4α-6α=1.8, 4α-4β=13.5, 6α-6β=13.7, 4α-5α=6.0, 4β-5α=6.0, 4β-5α=11.3, 5α-6α=6.0, 5α-6β=11.5, 3a-4α=1, 3a-4β=6.2, 6a-6α=1, 6a-6β=6.2, 3a-6a=8.7 Hz. Anal. cald for $C_{19}H_{32}N_2O_4S$ requires C, 59.4; H, 8.39; N, 7.29. Found C, 59.2; H, 8.53; N, 7.09%

[1(*S),3aα,5β,6aα]-(±)-4-[1-(3-Cyclohexyl-3-hydroxypropyl)octahydro-2-oxo-5-cyclopentimidazolyl-thio]butanoic acid (23).** It was found that the sequence of reactions described above for the synthesis

of acid **7** could be carried out on the mixture of diastereomeric ketones **18** and **19** utilising only a purification of the mesylate intermediates (**21** and epimer) and final acid products. This gave a 36% overall yield mixture of **7** and **23**, which were separated by column chromatography (silica 100 × wt. of mixture, $CHCl_3$:MeOH:HOAc, 93:3.5:3.5). The seperation of these acid diastereomers proved more difficult than that for ketone intermediates **18** and **19**. Nevertheless this procedure gave a 6% overall yield of **23** as a colourless glass ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.90–1.98 (17H, complex m, aliphatics), 2.06–2.15 (1H, m, H-4α), 2.16–2.22 (1H, m, H-6α), 2.40 (2H, t, J=7.0 Hz, CH_2CO), 2.60 (2H, t, J=7.0 Hz, CH_2S), 3.13–3.29 (2H, m, NCHH+H-5α), 3.30–3.42 (1H, m, NCHH), 3.50–3.62 (1H, m, CHOH), 4.13–4.24 (2H, m, H-3a, H-6a), 6.10 (1H, brs, NH, exchang), 6.5–7.5 (2H, vbr peak, 2 × OH, exchang.).

NOE, COSY and spin decoupling experiments permitted the following assignments: δ 1.58 (H-6β), 1.66 (H-4β), 2.11 (H-4α), 2.18 (H-6α), 3.24 (H-5α); J 4α-6α=1.8, 4α-4β=6α-6β=13.5, 4α-5α=6.0, 4β-5α=11.1, 5α-6α=6.0, 5α-6β=11.1, 3a-4α=1, 3a-4β=6.0, 6a-6α=1, 6a-6β=6.0. R_f 0.30 (Silica, $CHCl_3$:MeOH:HOAc, 93:3.5:3.5). Epimer **7** could more readily be obtained from the mixture of **7** and **23** by seeding it with pure **7** in ether and recrystallisation yield 12% of **7**, mp 147–149 °C, R_f 0.32 (silica, $CHCl_3$:MeOH:HOAc), 93:3.5:3.5). The relative stereochemistry of **7** was confirmed by analogy with that of acid **37**, obtained by a similar sequence of reactions.[26] This compound was more amenable to a full NMR analysis.

[1(*R),3aα,5β,6aα]-(±)-4-[1-(3-Hydroxyoctyl)octahydro-2-oxo-5-cyclopentimidazolyl]thio]butanoic acid (37).** Mp 79–80 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=6.8 Hz, CH_3), 1.22–1.38 (8H, m, 4 × CH_2), 1.40–1.60 (2H, N-C-CHH, H-6β), 1.62–1.74 (2H, m, N-C-CHH, H-4β), 1.83–2.02 (2H, m, S-C-CH_2-C-CO_2), 2.17 (1H, br dd, $J_{4\alpha,4\beta}$=13.5, $J_{4\alpha,5\alpha}$=5.8, $J_{3a,4\alpha}$ ca. 1, $J_{4\alpha,6\alpha}$ ca 2 Hz, H-4α), 2.25 (1H, br dd, $J_{6\alpha,6\beta}$=13.5, $J_{5,6\alpha}$ 5.8, $J_{6a,6\alpha}$ ca. 1, $J_{4\alpha,6\alpha}$ ca. 2 Hz, H-6α), 2.38–2.54 (2H, m, CH_2CO_2), 2.63 (2H, t, J=7.0 Hz, SCH_2), 2.94–3.03 (1H, m, NCHH), 3.23–3.34 (1H, 7 line m, $J_{4\beta,5\alpha}$=$J_{5\alpha,6\beta}$=11.6, $J_{4\alpha,5\alpha}$=$J_{5\alpha,6\alpha}$=5.8 Hz, H-5α), 3.48–3.56 (1H, m, OCH), 3.62–3.74 (1H, m, NCHH), 4.19 (1H, br dd, $J_{3a,6a}$=8.8, $J_{6a,6\beta}$=6.2, $J_{6a,6\alpha}$ ca 1Hz, H-6a), 4.25 (1H, br dd, $J_{3a,6a}$=8.8 $J_{3a,4\beta}$=6.2, $J_{3a,4\alpha}$ ca. 1Hz), 5.5–6.0 (2H, vbr peak, NH, OH, exchang.).

NOE Experiments: irradiation of the δ 2.17 (H-4α) signal gave an enhancement of the δ 1.69 (H-4_β), δ 3.28 (H-5α) signals and δ 4.25 (H-3a) signals; irradiation of the δ 2.25 (H-6α) signal gave enhancements of the δ 1.55 (H-6_β), 3.28 (H-5α), 4.19 (H-6a) and 2.98 (NCHH) signals; irradiation of the δ 2.63 (SCH_2) signals; irradiation of the δ 4.19 (H-6a) signal gave enhancements of the δ 1.55 (H-6_β), 1.69 (H-4_β), 2.98 (NCHH), and 3.68 (NCHH) signals; irradiation of the δ 4.25 (H-3a) signal gave an enhancement of the δ 1.69 (H-4_β) signal; irradiation of the δ 5.5–6.0 (NH, OH) signal gave enhancements of the δ 4.25 (H-3a), 3.50 (OCH), 3.68 (NCHH) and δ 2.17 (H-4α) signals.

Spin decoupling experiments: irradiation of the δ 2.25 (H-6α) signal simplifies the multiplets at δ 1.55 (H-6_β), 4.19 (H-6a) and 3.28 (td, $J_{5\alpha,6\beta}$=$J_{4\beta,5\alpha}$=11.6, $J_{4\alpha,5\alpha}$= 5.8Hz, H-5α); irradiation of the δ 3.28 (H-5α) signal simplifies the multiplets at δ 1.55 (H-6_β), 1.69 (H-4_β), 2.17 (br d, $J_{4\alpha,4\beta}$=13.5 Hz, H-4α), δ 2.25 (br d, $J_{6\alpha,6\beta}$=13.5 Hz, H-6α); irradiation of the δ 1.69 (H-4_β) signal simplifies the multiplets at δ 2.17 (H-4α), 2.98 (NCHH), 3.28 (H-5α), 3.68 (NCHH) and 4.25 (br d, $J_{3a,6a}$=8.8Hz, H-3a); irradiation of the δ 1.55 signal (H-6_β) simplifies the multiplets at δ 2.25 (br d, $J_{5\alpha,6\alpha}$=5.8Hz, H-6α), 3.28 (H-5α), 3.50 (OCH) and 4.19 (br d, $J_{3a,6a}$=8.8 Hz, H-6a); irradiation of the δ 2.17 (H-4α) signal simplifies the multiplets at δ 1.69 (H-4_β), 3.28 (td, $J_{5\alpha,6\alpha}$=$J_{4\alpha,5\alpha}$=5.8; $J_{5\alpha,6\beta}$=11.6 Hz, H-5α) and 4.25 (H-3a). Anal. cald for $C_{18}H_{32}N_2O_4S$ requires C, 58.0; H, 8.66; N, 7.52. Found C, 57.8; H, 8.72; N, 7.36%.

Benzaldehyde 1,4-dioxaspiro[4.4]non-6-en-8-ylhydrazone (25). The allylic bromide **14**,[15] prepared from ketal **10** (22.5 g, 0.178 mol), was dissolved in toluene (50 mL) and the solution cooled to −40 °C with stirring. Benzaldehyde hydrazone **24**[22] (17.0 g, 0.141 mol) in toluene (50 mL) was added rapidly over 5 min, followed by triethylamine (25 g). The solution was warmed slowly to 15 °C and stirred at this temperature for 16 h. The mixture was then heated to a gentle reflux for a further 5 h. After cooling, the triethylamine hydrobromide formed was filtered off under reduced pressure and the resulting filtrate concentrated in vacuo. The residual dark oil was chromatographed on silica (450 g). Elution with ether-hexane (1:1) and then ether gave 18.9 g (55%) of **25** as a yellow oil. ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.88 (1H, dd, J=14, 5 Hz, C-CHH-C), 2.46 (1H, dd, J=14, 7 Hz, C-CHH-C), 3.84 (4H, s, OCH_2CH_2O), 4.36–4.84 (1H, m, CHN), 5.28 (1H, brs, NH), 5.68–5.92 (1H, m, olefinic H), 5.93–6.20 (1H, m, olefinic H), 7.04–7.82 (5H, m, aromatics), 7.48 (1H, s, CHAr). FABMS *m/z* 245 (M^++H). This compound decomposes on standing at rt for several days, but could be stored satisfactorily at −20 °C for 3 days. It is important to purify the crude product as soon as possible.

(±)-1-Benzylideneamino-tetrahydrocyclopentimidazol-2,5(1*H*,3*H*)-dione (27). The hydrazone **25** (7.42 g, 30.4 mmol) and pyridine (3.0 mL, 37.1 mmol) were added to toluene (175 mL) and the resulting solution cooled to 0 °C. To this stirred mixture, a solution of phosgene in toluene (12%, 40 mL, 44.2 mmol) was rapidly added over 10 min, after which the solution was warmed to 15 °C and stirred for a further 20 min. Aqueous ammonia solution (190 mL, d=0.88) was added to the solution at 0 °C over 10 min and after stirring for a further 30 min, water (200 mL) was

added. The organic layer was separated, dried (sodium sulphate) and evaporated in vacuo to give Benzaldehyde 2-(1,4-dioxaspiro[4.4]non-6-en-8-yl)semicarbazone (**26**) as a brown oil (7.85 g, 90%). An acetone solution (150 mL) of semicarbazone **26** (7.85 g) was stirred at 15 °C while camphorsulphonic acid (0.75 g) was added portionwise over 10 min. The mixture was heated at reflux for 5 h, cooled and concentrated in vacuo. Water (150 mL) and chloroform (100 mL) were added and the organic phase separated. The latter was washed with dilute aqueous $NaHCO_3$ solution (100 mL), dried ($MgSO_4$) and concentrated in vacuo to give a brown oil, (21.0 g). This material was chromatographed on silica (260 g). Elution with $CHCl_3$:MeOH (19:1) gave 3.66 g (55%) of **27**, mp 49–52 °C ^{1}H NMR (200 MHz, $(CD_3)_2SO$) δ: 2.12–2.35 (2H, m, $CH_2C(O)$), 2.65–3.04 (2H, m, $CH_2C(O)$), 4.35–4.49 (1H, m, CHN), 4.73–4.90 (1H, m, CHN), 7.29–7.52 (3H, m, aromatics), 7.62–7.70 (2H, m, aromatics), 7.74 (1H, s, CHPh). FABMS *m/z* 244 ($M^+ + H$). Anal. cald for $C_{13}H_{13}N_3O_2$ requires C, 64.2; H, 5.39; N, 17.3. Found C, 64.4; H, 5.50; N, 17.1%.

[3aα,5α,6aα]-(±)-1-Benzylideneamino-5-hydroxyhexahydrocyclopentimidazol-2(1*H*)-one (28). The ketone **27** (3.60 g, 14.8 mmol) was dissolved in ethanol (60 mL) and the solution cooled to 0 °C while sodium borohydride (0.80 g, 21.1 mmol) was added portionwise over 15 min. When addition was complete the mixture was stirred at rt for 1 h. The solvent was removed in vacuo, water (100 mL) and chloroform (100 mL) added and the organic phase separated. After drying (Na_2SO_4) concentration in vacuo gave the crude product as a brown syrup. This was purified by column chromatography (silica, $CHCl_3$:MeOH, 9:1) to give 3.09 g (85%) of **28** as a yellow solid, mp 206–207 °C. ^{1}H NMR (200 MHz, $(CD_3)_2SO$) δ: 1.62–1.92 (2H, m, C-CH_2-C), 1.90–2.22 (2H, m, C-CH_2-C), 4.02–4.15 (1H, m, CHN), 4.16–4.27 (1H, m, OCH), 4.40–4.52 (1H, m, CHN), 5.60 (1H, d, J=5 Hz, OH, exchang.), 7.26–7.48 (3H, m, aromatics), 7.62–7.73 (3H, m, aromatics+CHPh). FABMS *m/z* 246 ($M^+ + H$). Anal. cald for $C_{13}H_{15}N_3O_2$ requires C, 63.7; H, 6.16; N, 17.1. Found C, 63.5; H, 6.37; N, 16.8%.

[3aα,5α,6aα]-(±)-1-Amino-5-hydroxyhexahydrocyclopentimidazole-2(1*H*)-one (29). The hydrazone **28** (3.00 g, 12.2 mmol) was added to a solution of ethanol (70 mL) and acetic acid (0.7 mL) containing 10% Pd on carbon (1.3 g) and the resulting mixture stirred at 70 °C under 90 atmospheres of hydrogen for 3 days. The catalyst was removed by filtration through Celite and concentration of the filtrate in vacuo gave 1.73 g (90%) of **29** as an unstable yellow oil FABMS *m/z* 158 ($M^+ + H$). This material was utilised for the following reaction as soon as possible—it appears unstable to air and decomposes on standing.

[1(*R,*S**),3aα,5α,6aα]-(±)-5-Hydroxy-1-(2-cyclohexyl-2-acetoxyethylideneamino)-hexahydrocyclopentimidazole-2(1*H*)-one (30).** A solution of the hydrazine **29** (1.73 g, 11.0 mmol) and 2-acetoxy-2-cyclohexylacetaldehyde[30] (2.06 g, 11.2 mmol)) in methanol (175 mL) containing sodium acetate (1.03 g, 12.6 mmol) was stirred at 25 °C under a nitrogen atmosphere for 16 h. The alcohol was removed in vacuo and water (50 mL) and chloroform (100 mL) added. The organic phase was separated and washed with brine (50 mL), then dried (Na_2SO_4). Concentration of the filtrate in vacuo gave a yellow oil. Column chromatography of the crude product (silica, $CHCl_3$:MeOH (12:1) gave 2.71 g (75%) of **30** (mixture of diastereomers) as a colourless gum, FABMS *m/z* 324 ($M^+ + H$). This compound decomposed on standing at rt for a few days.

[1(*R),3aα,5α,6aα]-(±)-5-Methanesulphonyloxy-1-(2-cyclohexyl-2-acetyloxyethylidene-amino) hexahydro-cyclopentimidazole-2 (1*H*)-one (31) and [1(*S**), 3aα, 5α, 6aα]-(±)-5-Methanesulphonyloxy-1-(2-cyclohexyl-2-acetyloxyethylidene-amino) hexahydrocyclopentimidazole-2(1H)-one (32).** To a solution of the acetoxy-alcohol **30** (2.60 g, 8.05 mmol) and pyridine (3.6 g) in dichloromethane (50 mL) at 0 °C under an atmosphere of nitrogen was added methanesulphonyl chloride (1.25 mL, 16.2 mmol). After stirring for 3 days at 25 °C, water (50 mL) was added and the organic layer separated. The latter was washed with 1 N HCl (50 mL) and again separated and dried ($MgSO_4$). Evaporation in vacuo gave 3.16 g of crude product containing both diastereomers as a tan oil. The individual diastereomers, were separated by flash chromatography (silica, EtOAc:MeOH, 9:1) to give 0.56 g (35%) of **31** as white crystals, mp 147–148 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.94–1.38 (5 H, complex m, aliphatics), 1.56–1.90 (6 H, complex m, aliphatics), 1.93–2.18 (2H, m, H-4β, H-6β), 2.08 (3H, s, C-CH_3), 2.41 (1H, dd, $J_{4\alpha,4\beta}$=15, $J_{4\alpha,5\beta}$=2.5 Hz, H-4α), 2.53 (1H, dd, $J_{6\alpha,6\beta}$=15, $J_{5\beta,6\alpha}$=2.5 Hz, H-6α), 2.97 (3H, s, S-CH_3), 4.36 (1H, dd, $J_{3a,6a}$=8.8, $J_{3a,3\beta}$=6.6 Hz, H-3a), 4.54 (1H, dd, $J_{3a,6a}$=8.8, $J_{6a,6\beta}$=6.6 Hz, H-6a), 5.17 (1H, brt, J=5 Hz, CHOAc), 5.26–5.35 (1H, m, $J_{4\beta,5\beta}$=$J_{5\beta,6\beta}$=5, $J_{4\alpha,5\beta}$=$J_{5\beta,6\alpha}$=2.5 Hz, H-5β), 5.92 (1H, s, NH, exchang.), 7.22 (1H, d, J=6 Hz, CH=N).

NOE experiments: irradiation of the δ 2.41 (H-4α) and δ 2.53 (H-6α) signals gave an enhancement of the δ 5.30 (H-5β) signal and vice-versa. FABMS *m/z* 402 ($M^+ + H$). R_f 0.3 (silica, EtOAc:MeOH, 9:1). Anal. cald for $C_{17}H_{27}N_3O_6S$ requires C, 50.9; H, 6.78; N, 10.5. Found C, 50.6; H, 6.89; N, 10.3%.

Also obtained from this experiment were 0.58 g (36%) of **32**, mp 78–82 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.94–1.38 (5H, complex m, aliphatics), 1.56–1.90 (6 H, complex m, aliphatics), 1.95–2.20 (2H, m, H-4β, H-6β), 2.08 (3H, s, C-CH_3), 2.40 (1H, dd, $J_{4\alpha,4\beta}$=15, $J_{4\alpha,5\beta}$=2.5Hz, H-4α), 2.50 (1H, dd, $J_{6\alpha,6\beta}$=15, $J_{5\beta,6\alpha}$=2.5 Hz, H-6α), 2.97 (3H, s, S-CH_3), 4.36 (1H, dd, $J_{3a,6a}$=8.8, $J_{3a,3\beta}$=6.6 Hz, H-3a), 4.54 (1H, dd, $J_{3a,6a}$=8.8, $J_{6a,6\beta}$=6.6 Hz, H-6a), 5.20 (1H, brt, J=6Hz, CHOAc), 5.25–5.36 (1H, m, H-5β), 5.93 (1H, s, NH, exchang.) 7.18 (1H, d, J=6 Hz, CH=N). FABMS *m/z* 402 ($M^+ + H$). R_f 0.2

(silica, EtOAc:MeOH, 9:1). Anal. cald for $C_{17}H_{27}N_3O_6S$ requires C, 50.9; H, 6.78; N, 10.5. Found C, 50.6; H, 6.99; N, 10.2%.

[1(*R),3aα,5β,6aα]-(±)-Methyl-4-1-(2-acetyloxy-2-cyclohexylethylideneamino) octahydro-2-oxo-5-cyclopentimidazolyl]thio]butanoate (33).** Under an atmosphere of nitrogen, thiobutyrolactone (0.26 g, 2.55 mmol) was added to methanolic sodium methoxide (from sodium, 60 mg, 2.61 g.a) in dry methanol (6 mL) at 25 °C and the resulting solution[20] stirred for 2 h. The solvent was removed in vacuo and the residue dissolved in dry dimethylsulphoxide (5 mL) under nitrogen. The mesylate **31** (0.50 g, 1.25 mmol) in dimethylsulphoxide (5 mL) was added in one portion to the thiolate solution and the resulting mixture stirred at 25 °C for 16 h. The solution was diluted with water (100 mL) and the crude product extracted into ether. After drying (Na_2SO_4), the organic extract was concentrated in vacuo to give an oil. Column chromatography (silica, EtOAc:MeOH, 95:5) gave 274 mg (50%) of **33** as a colourless oil ^{1}H NMR (360 MHz, $CDCl_3$ δ: 0.93–1.37 5H, complex m, aliphatics), 1.53–1.99 (10 H, complex m, aliphatics), 2.08 (3H, s, C—CH_3), 2.18 (1H, dd, $J_{4\alpha,4\beta}=13$, $J_{4\alpha,5\alpha}=6$ Hz, H-4α), 2.26 (1H, dd, $J_{6\alpha,6\beta}=13$, $J_{5\alpha,6\alpha}=6$ Hz, H-6α), 2.41 (2H, t, $J=7$ Hz, CH_2CO), 2.60 (2H, t, $J=7$ Hz, SCH_2), 3.15–3.37 (1H, m, H-5α), 3.67 (3H, s, OCH_3), 4.25–4.37 (1H, dd, $J_{3a,6a}=9$, $J_{3a,4\beta}=6$ Hz, H-3a), 4.37–4.51 (1H, dd, $J_{3a,6a}=9$, $J_{6a,6\beta}=6$ Hz, H-6a), 5.21 (1H, t, $J=6$ Hz, CHOAc), 5.52 (1H, brs, NH, exchang.), 7.09 (1H, d, $J=6$ Hz, CH=N). FABMS *m/z* 440 ($M^+ + H$).

[1(*R),3aα,5β,6aα]-(±)-4-[[1-(2-Cyclohexyl-2-hydroxyethylideneamino)octahydro-2-oxo-5-cyclopentimidazolyl]thio]butanoic acid (8).** The ester **33** (0.26 g, 0.60 mmol) was dissolved in methanol:water (2:1, 8 mL) and to the stirred solution was added lithium hydroxide (0.10 g, 2.4 mmol). The resulting mixture was stirred at rt for 3 h. The pH was adjusted to 5.0 with 2 N HCl, water (20 mL) was added and the product was extracted into chloroform (50 mL). After drying (Na_2SO_4) the solvent was removed in vacuo to give 0.19 g (86%) of **8**, mp 176–178 °C (dec) ($CHCl_3$–Et_2O) (1.15 g). ^{1}H NMR (360 MHz, $(CD_3)_2SO$) δ: 0.88–1.87 (15H, complex m, aliphatics), 1.96–2.04 (1H, m, H-4α), 2.08–2.17 (1H, m, H-6α), 2.31 (2H, t, $J=7.0$ Hz, CH_2CO_2), 2.56 (2H, t, $J=7.0$ Hz, CH_2S), 3.02–3.14 (1H, m, H-5α), 3.70–3.78 (1H, m, CHOH), 4.12–4.19 (1H, m, H-3a), 4.40–4.45 (1H, m, H-6a), 4.91 (1H, d, $J=4.5$ Hz, OH, exchang.), 6.83 (1H, d, $J=6.6$ Hz, CH=N), 7.01 (1H, brs, NH, exchang.), 11.8 (1H, brs, CO_2H, exchang.).

Spin decoupling experiments: on irradiation of the δ 7.01 (NH) signal the δ 4.17 (H-3a) signal changed to ddd ($J_{3a,6a}=8.2$, $J_{3a,4\beta}=6$, $J_{3a,4\alpha}=1$ Hz); resolution enhancement of the NH signal (δ 7.01) showed it as a d ($J_{3a,NH}=1.5$ Hz): on irradiation of the δ 4.17 (H-3a) signal the δ 3.08 (H-5α) signal changed to dt ($J_{5\alpha,6\beta}=J_{4\beta,5\alpha}=11.3$, $J_{5\alpha,6\alpha}=J_{4\alpha,5\alpha}=5.8$ Hz), the δ 2.01 (H-4α) signal changed to dddd ($J_{4\alpha,4\beta}=13.3$, $J_{4\alpha,5\alpha}=5.8$, $J_{4\alpha,6\alpha}=1.8$ Hz; $J_{3a,4\alpha}=1$ Hz) and the δ 1.622 (H-4β) signal changed to dd ($J_{4\alpha,4\beta}=13.3$, $J_{4\beta,5\alpha}=11.3$ Hz; $J_{3a,4\beta}=6$ Hz); on irradiation of the δ 4.44 (H-6a) signal the δ 2.13 (H-6α) signal changed to dddd ($J_{6\alpha,6\beta}=13.3$, $J_{5\alpha,6\alpha}=5.8$, $J_{4\alpha,6\alpha}=1.8$ Hz; $J_{6a,6\alpha}=1$ Hz) and the δ 1.632 (H-6β) signal changed to dd ($J_{6\alpha,6\beta}=13.3$, $J_{5\alpha,6\beta}=11.3$ Hz; $J_{6a,6\beta}=6.6$ Hz). R_f 0.28 (Silica, $CHCl_3$:MeOH:HOAc, 90:5:5). Anal. cald for $C_{18}H_{29}N_3O_4S$ requires C, 56.4; H, 7.62; N, 11.0. Found C, 56.2; H, 7.86; N, 10.7%.

[1(*S),3aα,5β,6aα]-(±)-4-[[1-(2-Cyclohexyl-2-hydroxyethylideneamino)octahydro-2-oxo-5-cyclopentimidazolyl]thio]butanoic acid (34).** This acid was obtained from mesylate **32** by an identical series of reactions to that used for the preparation of **8**. Compound **34** was obtained in 16% overall yield as a white wax. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 0.97–2.10 (15H, complex m, aliphatics), 2.20–2.40 (2H, m, H-6α, H-4α), 2.45 (2H, t, $J=7$ Hz, CH_2CO), 2.60 (2H, t, $J=7$ Hz, CH_2S), 3.20–3.35 (1H, m, H-5α), 4.08–4.18 (1H, m, OCH), 4.30–4.40 (1H, m, H-3a), 4.42–4.52 (1H, m, H-6a), 7.06 (1H, d, $J=6$ Hz, CH=N). The ^{1}H NMR spectrum of **8** in $CDCl_3$ was identical to the above except for the CH=N (δ 7.12) and OCH signal (δ 4.18–4.27). FABMS *m/z* 384 ($M^+ + H$) *R* 0.28 (Silica, $CHCl_3$:MeOH:HOAc, 90:5:5).

[1(*R),3aα,5β,6aα]-(±)-4[[-1-(2-cyclohexyl-2-hydroxyethylamino)-octahydro-2-oxo-5-cyclopentimidazolyl]thiobutanoic acid (9).** The hydrazone **8** (50 mg; 0.13 mmol) was dissolved in a mixture of methanol (1 mL) and acetic acid (1 mL) at rt and to the stirred solution was added sodium cyanoborohydride (12 mg, 0.19 mmol). After 1 h, the solution was concentrated in vacuo, water and chloroform were added and the organic phase separated. After drying (Na_2SO_4) the solvent was removed in vacuo to give 45 mg (90%) of **9** as a white wax ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.91–2.02 (15H, complex m, aliphatics), 2.05–2.22 (2H, m, H-4α, H-6α), 2.46 (2H, t, $J=7$ Hz, CH_2CO), 2.52–2.76 (3H, m, CH_2S+NCHH), 2.95 (1H, dd, $J=14$, 2 Hz, NCHH), 3.11–3.42 (2H, m, CHS+OCH), 4.11–4.30 (2H, m, NCHCHN), 5.87 (1H, brs, NH, exchang.), 5.0–6.5 (2H, vbr baseline rise, 2×OH, exchang.). FABMS *m/z* 386 ($M^+ + H$). R_f 0.30 (silica, $CHCl_3$:MeOH:HOAc, 90:5:5).

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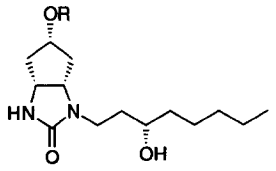
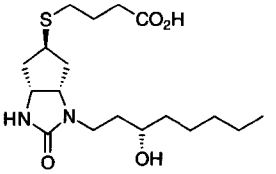
18. The less polar isomer is **18**; the R_fs of **18** and **19** are 0.3 and 0.2 (silica, ethyl acetate:methanol, 9:1) respectively.

19. NOE and spin decoupling experiments helped to provide a detailed analysis of the 360 MHz ^{1}H NMR spectrum ($CDCl_3$) of the 5α-*O*-tosylate **35**. This analogue was prepared by tosylation of **36**, which was obtained by an identical series of reactions to that used for synthesizing **20**. Particularly diagnostic was the enhancement between H-3a and H-4$_\beta$, H-4$_\beta$ and H-5$_\beta$, H-5$_\beta$ and H-6$_\beta$, H-6$_\beta$ and H-6a, and between H-6a and H-3a; δ ppm H-3a (4.13), H-4$_\beta$ (2.01), H-5$_\beta$ (5.15), H-6$_\beta$ (1.90), H-6a (4.27); $J_{3a,4\beta}=J_{6a,6\beta}=6.6$, $J_{4\beta,5\beta}=J_{5\beta,6\beta}=5.3$, $J_{4\alpha,5\beta}=J_{5\beta,6\alpha}=2.6$, $J_{4\alpha,4\beta}=J_{6\alpha,6\beta}=15.0$, J_{3a}, $J_{6a}=8.8$ Hz.



35 R = Tosyl
36 R = H



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21. Based on the nOe, spin decoupling experiments, and analysis of the ^{1}H NMR spectrum of **37**, prepared as for **7**. Enhancements observed between H-3a and H-4$_\beta$, H-6a and H-6$_\beta$, H-5$_\alpha$ and H-6$_\alpha$, H-5$_\alpha$ and H-4$_\alpha$. δ ($CDCl_3$) ppm H-3a (4.25), H-4$_\alpha$(2.17), H-4$_\beta$ (1.69), H-5$_\alpha$ (3.28), H-6a (4.19), H-6$_\alpha$ (2.25), H-6$_\beta$ (1.55); $J_{5\alpha,6\beta}=J_{5\alpha,4\beta}=11.6$, $J_{5\alpha,4\alpha}=J_{5\alpha,6\alpha}=5.8$, $J_{3a,4\beta}=6.2$, $J_{4\alpha,4\beta}=J_{6\alpha,6\beta}=13.5$, $J_{3a,6a}=8.8$Hz.

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23. The ^{1}H NMR spectra of **31** and **33** were analysed in detail as before and the chemical shifts and coupling constants of the cyclopentane ring protons were similar to those of **35** and **7**, respectively.

24. Flash chromatography was employed; the R_fs of **31** and **32** are 0.3 and 0.2 (silica, ethyl acetate:methanol, 19:1).

25. Some preliminary experimental details for Scheme 2 are given in Eur. Pat. Appl. 458 642 (*Chem. Abstr.* 1992, *116*; 106293b).

26. Some preliminary experimental details for Scheme 1 are given in Eur. Pat. Appl. 46 597 (*Chem. Abstr.* **1982**, *97*; 144568w).

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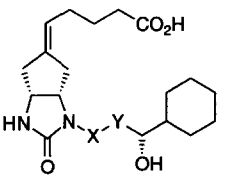
29. Interestingly N-alkyl derivatives of **4**, **8** and **9** display lower efficacy agonism than the parent compound and in the latter two series DP-receptor selectivity is retained. In addition sulphide **37** (mp 79–80 °C) is a much less potent PG mimetic (0.1 × **7**, platelets) than **7**. SAR Studies would be facilitated by the synthesis and pharmacological evaluation of olefins **38** and **39**. To date olefin **38** has only been obtained as a mixture of *E*- and *Z*-isomers (by reaction of **18** with $Ph_3P(CH_2)_4$ CO_2H Br (5 equiv), $KOCMe_3$ (10 equiv), dry benzene, N_2, reflux and purification by the methyl ester). Attempts to obtain **39** by a similar route have so far proved unsuccessful. Preliminary evaluation of **38** indicate it is a weak non-selective DP-agonist.



38 X-Y = CH_2CH_2
39 X-Y = N = CH

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