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Thromboxane receptor active analogues based on the 6-oxabicyclo[3.2.1]octane ring system

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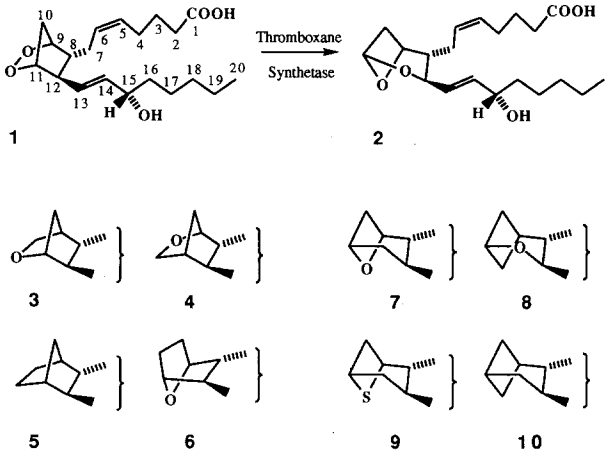
Summary — Prostanoid analogues with a 6-oxabicyclo[3.2.1]octane ring and 3 different types of ω-chain have been synthesized and evaluated for biological activity on thromboxane A_2 (TXA_2) receptors and prostaglandin I_2 (PGI_2) receptors. The standard ω-chain analogue **34b** is a TXA_2 receptor agonist approximately 10-fold less potent than U46619 **3**, the standard agonist. The *O*-diphenylmethyloximino-ω'-chain analogue **32** gives a PGI_2-like agonist ≈ 5-fold less active than EP 157, the most active molecule in this class. Conversely, 4-arylsemicarbazone ω-chain analogues **35a** and **35b** show TXA_2 antagonism comparable to that obtained with bicyclo[2.2.2]octane and bicyclo[2.2.1]heptane systems containing this type of ω-chain (*eg* EP 092).

6-oxabicyclo[3.2.1]octanes / thromboxane receptors / prostaglandin I_2 receptors

Introduction

Thromboxane A_2 (TXA_2) **2** and its biosynthetic precursor prostaglandin H_2 (PGH_2) **1** (scheme 1) both activate cell surface thromboxane receptors to induce platelet aggregation, vasoconstriction and bronchoconstriction (see [1–3] for review of chemistry and basic biology and [4] for a review of TXA_2 active drugs). However, the instability of these natural agents presents considerable problems in experiments designed to characterise thromboxane receptor subtypes. Consequently a number of stable analogues which retain a rigid bicyclic ring system have been synthesised. The most widely used agent, 11,9-epoxymethano-PGH_2 (U-46619) **3**, is a potent full agonist with a reasonably high specificity for thromboxane receptors [5,6]. The 7-oxabicyclo[2.2.1]heptane analogue **6** is also a potent full agonist [7, 8]. Other analogues are partial agonists (9,11-epoxymethano-PGH_2 **4**, 9,11-ethano-PGH_2 **5**, 9,11, 11*a*-dicarba-TXA_2 (CTA_2) **10** [9, 10]) and/or stimulants of the adenylate cyclase system in human platelets (9,11-thia-11*a*-carba-TXA_2 (STA_2) 9, CTA_2 **10** [8, 10]). The latter action results in inhibition of platelet aggregation induced by a variety of agents including U-46619, ADP and PAF, although it has not been determined whether PGI_2 or PGD_2 receptors are involved. It is therefore difficult to analyse the true thromboxane-like activity of STA_2 and CTA_2 on human platelets.



Scheme 1. Biosynthesis of TXA_2 **2** from PGH_2 **1** and structures of some stable analogues. The bracket indicates that the α- and ω-chains are the same as in the natural compounds. The conventional prostanoid numbering is shown in **1**.

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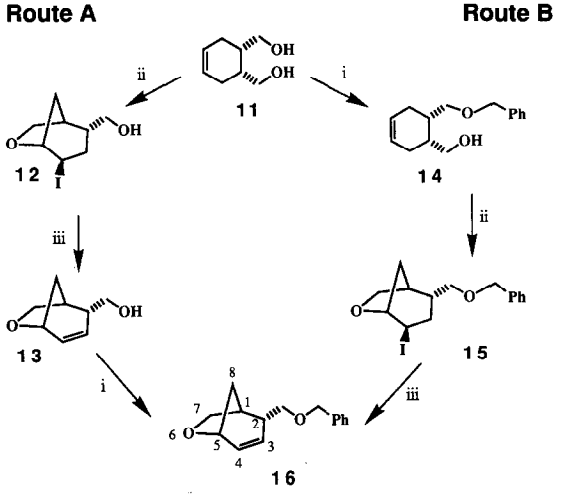
With the intention of producing additional potent and specific full agonists for thromboxane receptors, we decided to synthesise compound **34b**, which is a *carba-homo* analogue of both PGH_2 and TXA_2. In this molecule an α-orientated ring oxygen is present in a more flexible ring system. However, we were by no means confident of high biological activity for **34b** since the 11*a*-carba-analogue of TXA_2 **7** has been reported to be devoid of agonist (and antagonist) activity on rat aorta and human platelets [11]. The isomeric 9,11-carba-TXA_2 **8** has also been synthesised, but surprisingly no biological data have been published [12].

We have also prepared **35a** and **35b**, in which the natural ω-chain of **34b** has been replaced by 4-(*p*-methoxyphenyl)-semicarbazone and 4-(*p*-methoxyphenyl)-thiosemicarbazone units respectively. The intention was to obtain potent thromboxane receptor antagonists with greater water solubility than previous antagonists with bicyclo[2.2.1]heptane and bicyclo-[2.2.2]octane ring systems [8–10]. Finally the ω-chain of **34b** has been replaced by a diphenylmethoxime unit to determine whether this compound **32** has the PGI_2-like activity shown by corresponding bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane ring analogues (EP 035 and EP 157) [13].

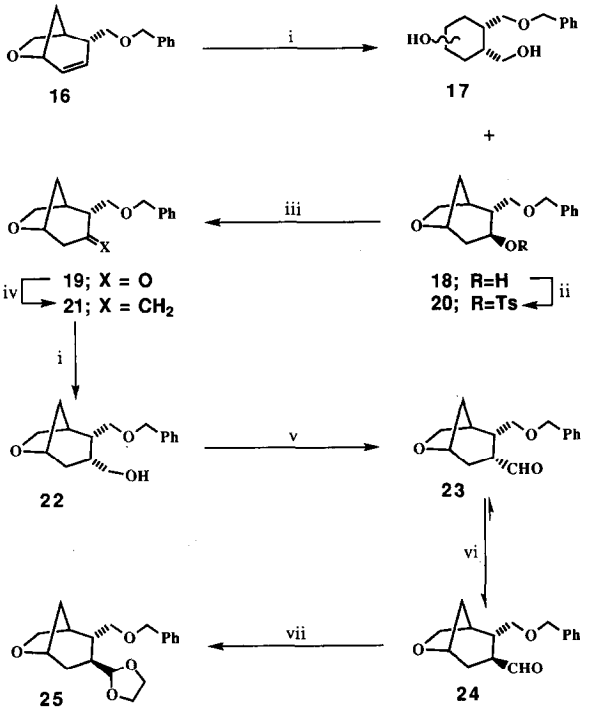
Chemistry

The starting material, diol **11**, was readily obtained by lithium tetrahydroaluminate reduction of the commercially available *cis*-1,2,3,6-tetrahydrophthalic anhydride. Diol **11** (scheme 2) was monobenzylated (Route B) and cycloetherified using iodine [14, 15]. Dehydroiodination then gave olefin **16**.



Scheme 2. Reagents: i: NaH/DMF/$PhCH_2Cl$; ii: I_2/KI $NaHCO_3$/H_2O; iii: DBU.

The cyclisation and dehydroiodination steps can advantageously be performed before benzylation (scheme 2, Route A). Attempts to carbonylate olefin **16** with 9-borabicyclo[3.3.1]nonane (9-BBN)/carbon monoxide gave very poor yields of aldehydic material. Treatment of **16** (scheme 3) with 9-BBN followed by alkaline hydrogen peroxide likewise gave low yields of alcohol **18**, showing that the 9-BBN reaction was hindered but regio- and stereo-selective. Complete hydroboration of **16** was easily achieved by borane itself. Oxidation then gave **18** in 50–60% yields, but other alcoholic products were apparent (scheme 3). The less selective borane can attack at the 4-position of **16** leading, with excess hydroborating species, to ring opening and ultimately the mixture of diols **17**. The definitive work of Zweifel and Plamondon [16] provides a precedent for this reaction. The general structures of diols **17** were inferred from gas chromatography–mass spectrometry data of the trimethylsilyl ether derivatives. The desired alcohol **18** was easily separated from diols **17** by column chromatography. Since the major product **18** is formed and not its epimer the hoped-for directive effects due to association of the borane reagent(s) with the ether oxygen atoms in **16**, did not significantly feature in the reaction, and the selectivity was



Scheme 3. Reagents: i: $BH_3THF/H_2O_2/THF$; ii: TsCl/DMAP/pyridine; iii: Jones [O]; iv: $TiCl_4/Zn/CH_2Br_2/THF$; v: PCC/CH_2Cl_2; vi: $DBU/CHCl_3$; vii: glycol/H^+.

mainly controlled by steric factors. The structure of **18** was determined by X-ray crystallographic analysis of the tosylate ester **20** (fig 1).

Jones oxidation of **18** gave ketone **19**, from which the *exo*-cyclic olefin derivative **21** was obtained in good yield using a zinc/titanium tetrachloride/dibromomethane reagent [17, 18]. A further hydroboration–oxidation sequence gave aldehyde **23**, which epimerised almost totally to aldehyde **24**. This epimerisation step is similar to that previously performed in this laboratory in the synthesis of 7-oxabicyclo[2.2.1]heptane prostanoid analogues **6** [19]. The homologation on ketone **19** using standard methoxymethylenation Wittig methods [20, 21] proved to be much less efficient in this system. The glycol acetal **25**, derived from **24**, was debenzylated by sodium/liquid ammonia to alcohol **26** (scheme 4). Chain extension *via* tosylation, cyanation and dibal reduction gave aldehyde **29** [22]. The normal 2-series prostanoid α-chain (see [1] for nomenclature details) was then elaborated on aldehyde **29**, by standard methods [22] to give the key synthon **30**. Removal of the acetal protecting group from portions of **30** gave aldehyde **31** to which were added the several classes of ω-chain. This allowed synthesis of final molecules **32**, **34a**, **b** and **35a**, **b** [19, 22].

The high-field ^{1}H-NMR, used to confirm key structures, displayed interesting phenomena. The methylene hydrogens adjacent to the benzyloxy group in **15**, **18** and **24** are non-equivalent. In the iodo-ether **15** the signals appear as a close doublet of doublets (d x d) at δ 3.3, but in the 3-hydroxy-benzylether **18** the signals are well separated (δ 3.64; 3.48). Again the d x d signals were clearly defined. Both **15** and **18** are single conformers, presumably due to the large iodine atom, and intramolecular H-bonding respectively. However, in the 3β-formyl-benzylether **24** these methylene resonances are more complex, showing along with several other resonances at least 2 contributing conformers. This is in contrast to bicyclo-[2.2.1]heptane **5** [22] and 7-oxabicyclo[2.2.1]-heptane analogues **6** [19], which are more strained (see also the *Discussion* section below).

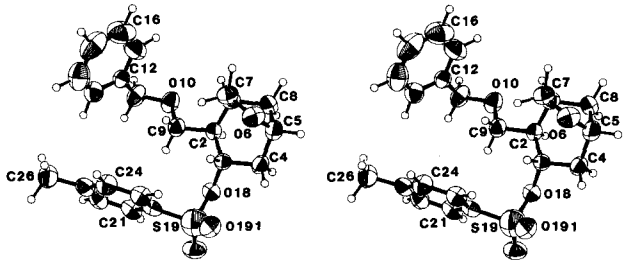
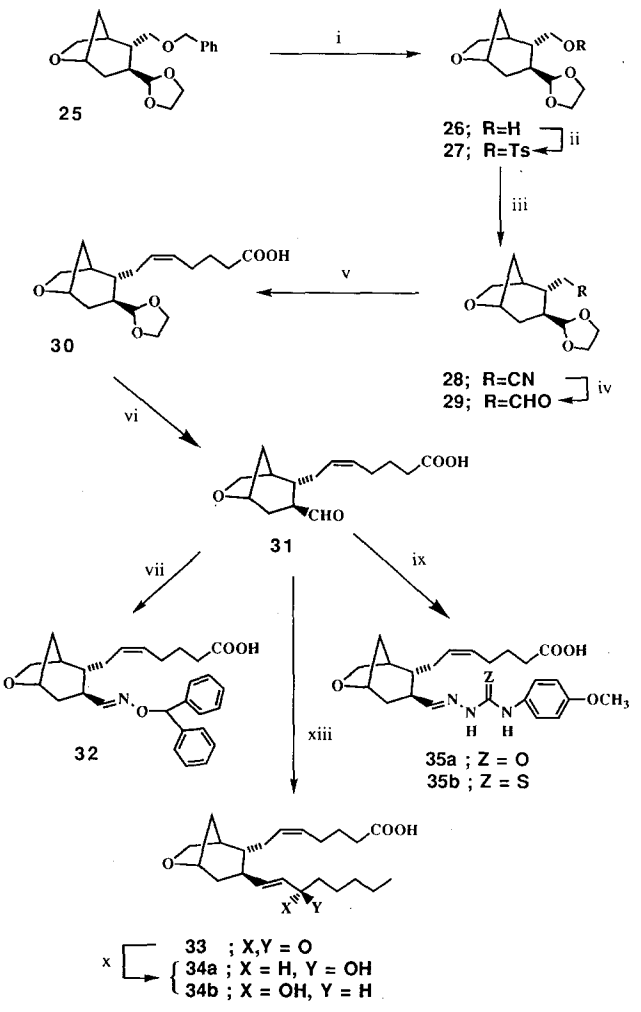


Fig 1. A stereo-diagram of structure **20**. Non-hydrogen atoms are shown as 50% probability thermal ellipsoids. The numbering of the hydrogens is after the atoms to which they are attached: H2 is attached to C2, H91, H92 are attached to C9 etc.

Biology

Compound **34b** showed thromboxane-like activity on human platelet-rich plasma, rabbit aorta, rat aorta and guinea-pig trachea (table I). However, **34b** was only a full agonist on the rabbit aorta (7-fold less active than the standard agonist U-46619).



Scheme 4. Reagents: i: Na/NH_3; ii: TsCl/DMAP/pyridine; iii: KCN/DMSO; iv: *i*-Bu_2AlH; v: $Ph_3PCH(CH_2)_3COOH$/DMSO; vi: H^+/H_2O/dioxane; vii: Ph_2CHONH_2/pyridine; viii: *p*-Y-Ar-NHC(Z)$NHNH_2$ dioxane; ix: $(CH_3O)_2P(O)$-$CH_2COC_5H_{11}$/base/THF; x: (*i*-PrO)$_3$Al/*i*-PrOH/Tol.

Table I. Comparison of the thromboxane-like activity of U-46619, **34a** and **34b.**

Preparation	*U-46619*	*34a*		*34b*	
	EC_{50} (nM)	*EC_{50} (nM)*	*Maximum (%)*	*EC_{50} (nM)*	*Maximum (%)*
Human platelet-rich plasma	110	> 10 000	0	2300	81
Rabbit aorta	5.4	5300	≥ 75*	38	100
Rat aorta	20	–	–	156	82
Guinea-pig trachea	7.8	–	–	286	85

EC_{50} values relate to the compound's own maximum response; *highest concentration tested: 10 μM.

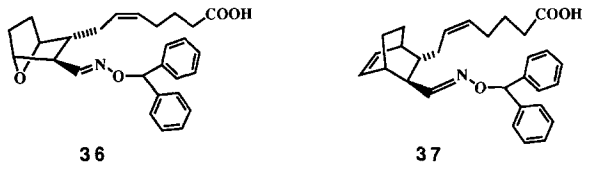
In the other preparations a maximum response could not be achieved and **34b** appeared to behave as partial agonist on the thromboxane-sensitive system for the following reasons.

In the presence of a high concentration (5 μM) of the thromboxane receptor antagonist EP 092, platelet aggregation induced by PAF (40 nM) was unaffected by **34b** up to a concentration of 10 μM. This implies that **34b** has minimal PGI_2- or PGD_2-like inhibitory activity on the human platelet and hence the lower maximum response is not due to its ability to act as a physiological antagonist. Similarly in the guinea-pig trachea preparation, 3 μM **34b** in the presence of 5 μM EP092 did not oppose the contractile actions of either histamine or 17-phenyl-ω-trinor PGE_2. The latter prostanoid is a selective agonist for the PGE receptor-mediating contraction of the trachea [23].

The isomeric **34a** was ≈ 140-fold less potent than **34b** on the rabbit aorta and did not aggregate human platelets over the concentration range 1–30 μM.

Compounds **35a** and **35b** (0.25–6.25 μM) blocked the contractile action of U-46619 on the guinea-pig trachea with the log concentration–response curves being displaced to the right in a parallel manner. Competitive antagonism at thromboxane receptors was further supported by Schild plots with slopes not significantly different from unity: 1.07 ± 0.20 and 1.05 ± 0.23 (95% confidence limits), $P > 0.05$ (Student's t-test). The pA_2 values for **35a** and **35b** were 7.0 and 7.1 respectively.

Finally, compound **32** inhibited aggregation in human platelet-rich plasma induced by U-46619 (300 nM), ADP (2 μM) and PAF (40 nM) with IC_{50} values of 0.81 ± 0.07, 1.67 ± 0.67 and 4.02 ± 0.5 μM (SE mean, n = 4) respectively. The 7-oxabicyclo-[2.2.1]heptane analogue **36** (EP 202 depicted in fig 2) showed very weak inhibitory effects against PAF-induced aggregation (IC_{50} = 11.0, 12.3, 14.0 μM, 3 separate experiments).



36 37

Fig 2. Chemical structure of EP 202 (**36**) and EP 157 (**37**).

In plasma-free suspensions of human platelets **32** produced modest increases in cyclic AMP levels as shown in figure 3. The log concentration–response curve for the specific PGI_2 analogue cicaprost [24] is also shown.

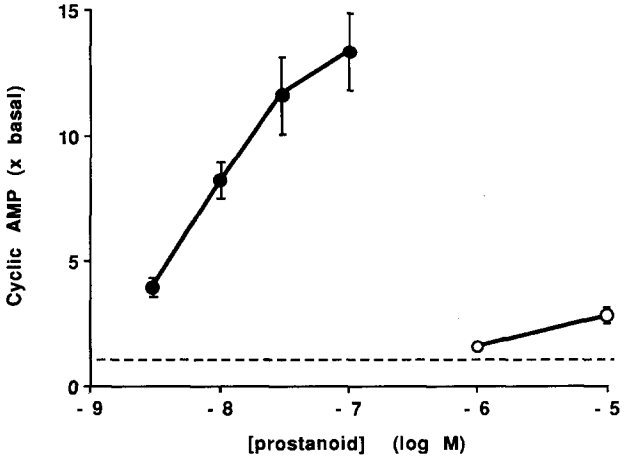


Fig 3. Effect of cicaprost (●) and compound **32** (○) on cyclic-AMP levels in a suspension of human washed platelets. The broken line indicates the basal level of 14 + 2 pmol ml^{-1}. Each point is the mean + SE mean of 4 determinations.

Discussion

Part of our initial aim has been achieved in that compound **34b** is a thromboxane receptor agonist devoid of non-specific inhibitory effects on human platelets. However, its efficacy is sufficiently low to make it a partial agonist on 3 of the 4 preparations examined and this makes it less than ideal for comparing thromboxane receptors in different preparations. On the rat aorta, threshold contractile responses to **34a** are seen at concentrations of 50 nM and in the rabbit aorta, where **34b** is a full agonist, at concentrations of 10–20 nM; this moderate thromboxane agonist potency only serves to highlight the inconsistency of the available structure–activity data for thromboxane agonists. 11*a*-Carba-TXA_2 **7** (scheme 1), which is structurally closer to TXA_2 than **34b**, appears to have no thromboxane-like activity [11]. Furthermore, STA_2, **9** in which a sulphur atom replaces the 9,11-oxygen in 11*a*-carba-TXA_2, is highly active, producing threshold effects in rat and rabbit aortae at 0.2 and 1 nM respectively [6]. At present we can offer no explanation for this puzzling situation.

In our extensive studies of thromboxane receptor antagonists with *N*-substituted iminomethyl and 1-iminoethyl ω-chains arranged *trans* to the α-chain, we have found that 4-(*p*-methoxyphenyl)-semicarbazone and 4-(*p*-methoxyphenyl)-thiosemicarbazone moities impart high binding affinity. Thus the 4-(*p*-methoxyphenyl)-semicarbazone-bicyclo[2.2.1]octane analogue EP 116 has a pA_2 of 8.8 in guinea-pig trachea [25]. However, the 2 analogues reported here, **35a** and **35b**, are only moderately potent thromboxane receptor antagonists (pA_2 7.0 and 7.1 respectively), and it is clear that in the series under study the 6-oxabicyclo[3.2.1]octane ring system offers no advantage over the bicyclo[2.2.1]heptane or bicyclo[2.2.1]octane analogue rings in terms of potency or ease of synthesis.

The diphenylmethoxime analogue **32** still exhibits the PGI_2-like inhibitory action on human platelets previously reported for the corresponding bicyclo-[2.21]heptane (EP 035) and bicyclo[2.2.2]octane **37** (figs 2, 6; EP 157) analogues [13, 26]. However, its ability to raise cyclic AMP levels in the human platelet is limited and far less impressive than that of EP 157 [13] (10–15 x basal at 1 μM). Nevertheless, as we have previously commented [26], a rise in cyclic AMP of 50% as produced by 1 μM **32** is sufficient to produce a marked inhibition of platelet aggregation. We have also raised the possibility that the efficacy of EP 157 may be less than that of PGI_2 analogues such as cicaprost and iloprost [26]. This may also apply to compound **32**. However, it must be borne in mind that the human platelet contains a PGE receptor negatively linked to adenylate cyclase, which when activated potentiates aggregation induced by ADP, PAF or U-46619 [27]. A weak agonistic action by **32** at this receptor could easily counteract its ability to activate adenylate cyclase *via* the prostacyclin receptor. Further studies are in progress to evaluate this possibility.

The very weak PGI_2-like activity of the 7-oxabicyclo[2.2.1]-heptane analogue **36** (fig 2), shows that ring structure is more critical for this particular agonist action, since **36** is virtually inactive (Jones and Wilson, unpublished observations). Structure **27** (fig 4) is the closest crystalline material to the final 6-oxabicyclo[3.2.1]octane products for which we have X-ray crystallographic data, and we have used this as the basis of a comparison of the disposition of the substituents on the bicyclo-heptane and bicyclooctane nuclei. The comparison was carried out with an Evans and Sutherland ESV20 molecular graphics workstation using the program FRODO [28]. The molecules which we have superimposed on PGI_2 are **32**, EP157, and the 7-oxabicyclo[2.2.1]heptane analogue **36**. The crystal structures of these molecules were not immediately available, and it was therefore necessary to model the structures starting from fragments obtained from the Cambridge Crystallographic Database [29]. It is important to stress that the torsional angles adopted by the extended chains may not be those most prevalent in solution. We have chosen to superimpose the various molecules in such a way as to maximise the overlap of the 5,6-double bonds, adopting the α-chain with its carboxyl as a primary locating group. The remainder of the molecular system was then adjusted to try various superpositions (see fig 5). This analysis shows that the oxygen atom of the oxime in the bicyclo[2.2.1]heptane, bicyclo[2.2.2]-octane and **32** analogues, having the prostanoid absolute configuration, can occupy the same space as the 11-hydroxyl oxygen in PGI_2 and its close structural analogue carbacyclin **42** (fig 7). This is not true for the 7-oxabicyclo[2.2.1]heptane system **36**. In this last case the bridged ring is much more strained, with the oxime moiety and the α-chain extended quasi-axially

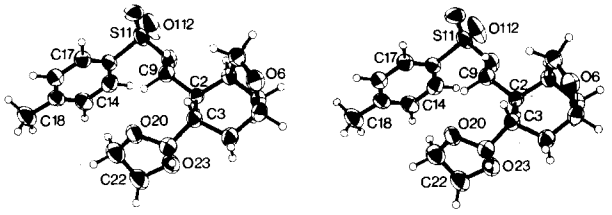


Fig 4. A stereo diagram of structure **27**. Non-hydrogen atoms are shown as 50% probability thermal ellipsoids. Numbering of the bicyclic ring moiety, and of the atoms attached to C2 and C3 is the same as in structure **20** (fig 1). Hydrogen atoms are also numbered in a similar manner to those in **20**.

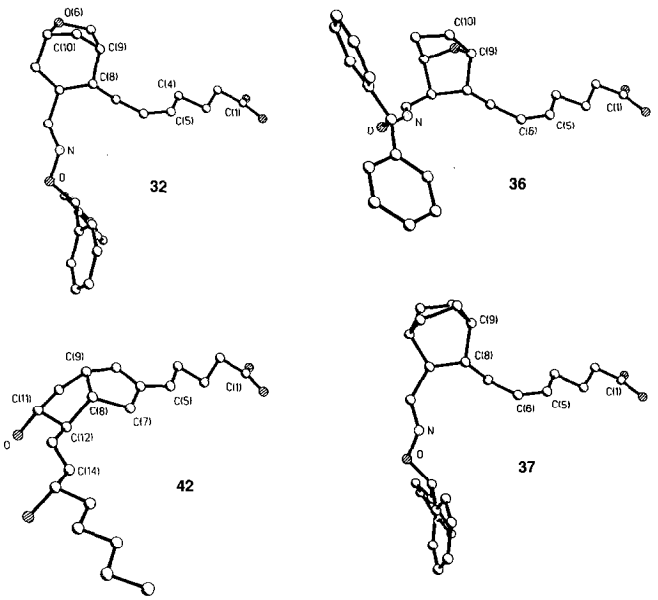


Fig 5. Molecular graphic representation of 6-oxabicyclo[3.2.1]analogue **32**, EP 157 **37**, EP 202 **36** and carbacyclin **42**. The orientations are consistent, showing the α-chains in alignment. Only in **36** is it impossible to achieve an approximate superposition of the oxime oxygen atom with the 11-hydroxyl in carbacyclin **42**. The oxime oxygens (and the adjacent nitrogens) are indicated in the diagram.

from it. Figure 2 is therefore merely a structural outline and is a poor model of the real situation. Figure 5 reflects the true structure more accurately. In the bioactive analogues the ring systems are, in general, more flexible, and more significantly, the side-chains are deployed in a quasi-equatorial manner. Furthermore, the 11-position oxygen function (PG numbering) is known to be essential to high agonist potency in PGI_2 analogues (Jones and Wilson, unpublished observations). However, if the oxime oxygen moiety is able to mimic this, as suggested by the molecular graphics, the ω-chain seems to have been replaced by part of a phenyl group.

Further PGI_2 agonist mimetics whose structures suggest that they interact with the receptor in a similar way to **32**, **37** etc, have recently been reported. The first example was octimibate **38** (fig 6) based on a central imidazole ling [30]. This has been followed by several papers employing a selection of heterocyclic 5-membered rings [31–33]. These analogues incorporate many of the structural elements of **32**, **37** and **38** (see fig 6 which illustrates the structural relationships).

The potency of **39** is of the same order as **37**; however, the latter cannot be altered in structure much before PGI_2 activity is reduced or lost. The molecular

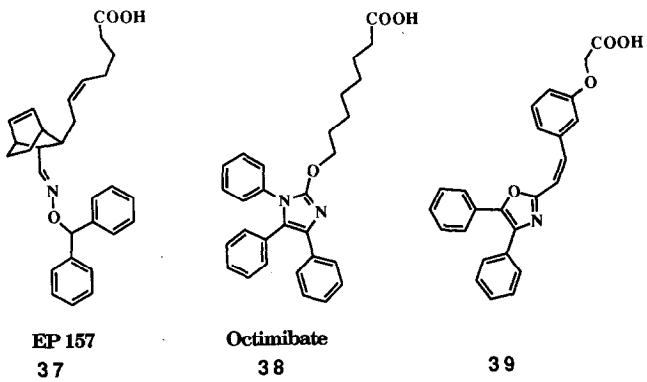


Fig 6. Structures of analogues active at PGI_2 receptors.

modelling discussed in the structure activity study [32, 33], is in essential agreement with the above hypothesis derived from modelling studies with **32**-type analogues. These proposals are further adumbrated by results obtained on diphenylmethylazine analogues [34] such as **40** and **41** (fig 7). The partially planar nature of many of these molecules is a common feature. Even in **41**, where the aromatic system orbitals extend into a conjugated chain as far as position-13 (PG numbering) appreciable activity is observed. A minimum of 2 benzenoid rings are required in both analogue types for a reasonable level of PGI_2 activity.

Experimental protocols

Chemisty

Chemicals and reagents were purchased from Aldrich Chemical Co Ltd, Gillingham, UK, and solvents from Rathburn Chemical Ltd, Walkerburn, Scotland, UK. Silicic acid Sil-A-200, Florisil (magnesium silicate for chromatography) from Sigma Chemical Co Ltd, Poole, UK and silica gel

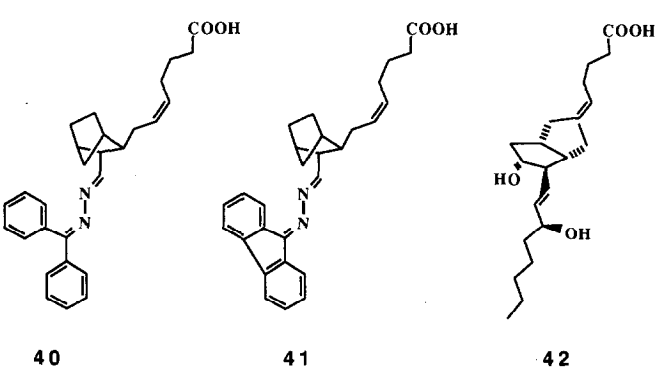


Fig 7. Structures of diphenylmethylazine analogues and carbacyclin (close structural analogue of PGI_2).

thin layer plates, Merck 5714, were used for chromatography. Lipidex partition chromatography was employed for purification of final target molecules as described by Brash and Jones [35]. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Perkin–Elmer R32 (90 MHz) spectrometer unless otherwise stated, in which case a Brucker WH-360 (360 MHz) instrument was used. Tetramethylsilane was used as internal standard and chemical shifts are given as δ values (ppm). Elemental analyses were generally performed on crystalline compounds by the Edinburgh University chemistry department analysis service. Composition values quoted were within ± 0.4%. The composition of other compounds, mostly viscous gums, were ascertained by gas chromatography–mass spectroscopy, and high-resolution mass spectroscopy performed on a VG Micromass 70-70F instrument. Gas chromatographic analysis was effected on a Pye-Unicam 204 instrument, temperature-programmed from 100°C at 2° per min using helium (5 ml/min, ≈ 150°C) as carrier gas, fitted with a 15-m long 0.53-mm id DB1 Megabore column (J and W Scientific Inc), and connected to the mass spectrometer. Trimethylsilyl (TMS) ether derivatives, suitable for gas chromatography, were prepared from hydroxy compounds by heating them for 15 min at 65°C with bis(trimethylsilyl)trifluoroacetamide. IR spectra were recorded as neat films on a Perkin–Elmer 237 instrument. UV spectra were run in ethanol on a Cary 118 spectrophotometer. Molecular parameters were examined on an Evans and Sutherland PS330 molecular graphics system.

4α,5α-Dihydroxymethylcyclohex-1-ene ***11*** *[36]*
A solution of *cis*-1,2,3,6-tetrahydrophthalic anhydride (30 g; 197 mmol) in dry tetrahydrofuran (THF) (150 ml) was added slowly to a stirred suspension of lithium aluminium hydride (11.3 g, 297 mmol) in dry ether (200 ml) under nitrogen. The addition rate was such as to maintain steady reflux of solvent. The mixture was boiled a further 2 h after addition was complete. The reaction mixture was quenched by v/v 1:1 THF water. An aqueous 1 M NaOH solution (10 ml) was then added to precipitate the inorganic salts which were filtered off through a funnel containing anhydrous $MgSO_4$. The residue was leached with dichloromethane (300 ml). The combined organic liquors were evaporated to give the product as a colourless oil, yield: 26.2 g (93%). ^{1}H-NMR ($CDCl_3$): δ 5.60 (s, 2H, olefinic); 4.37 (broad, 2H, OH); 3.78–3.43 (m, 4H, CH_2-O-); 2.4 (m, 6H, aliphatic ring). This oil was used directly in the next step(s).

4α-Benzyloxymethyl-5α-hydroxymethylcyclohex-1-ene ***14***
A 500-ml flask was charged with sodium hydride (7.0 g of 60% NaH in protective oil). The oil was removed by washing with 2 x 50 ml dry light petroleum under nitrogen. The sodium hydride was resuspended in 200 ml dry freshly distilled dimethylformamide (DMF), and a solution of diol **11** (25.0 g; 176 mmol) in 50 ml DMF was added dropwise so that there was a steady evolution of hydrogen. The mixture was stirred a further 2 h, by which time gas evolution had ceased. Benzyl chloride (24.5 g; 194 mmol) in 25 ml DMF was slowly added and an exothermic reaction occurred, the mixture reaching ≈ 70°C. After the addition the mixture was maintained at 80°C for 2 h. About 3/4 of the solvent was removed by distillation under 15 mm vacuum, and the cooled slurry was quenched with a minimum of water and product extracted with 3 x 150 ml ethyl acetate. The combined organic layers were washed with water then brine and dried over $MgSO_4$. The oil obtained on evaporation of solvent was distilled under vacuum. A large central fraction gave the title compound as a colourless oil. Yield: 25.9 g (65%); bp: 130–134°C at 0.1 mm.

2α-Benzyloxymethyl-4β-iodo-6-oxabicyclo[3.2.1]octane ***15***
The benzyl ether **14** (23.2 g; 100 mmol) was suspended in 600 ml of 1 M aqueous sodium bicarbonate solution with vigorous stirring. An aqueous solution (1000 ml) containing iodine (27.9 g; 110 mmol), and potassium iodide (56.4 g; 340 mmol) was added over 1 h. The dark mixture was then stirred overnight at room temperature, before being exhaustively extracted with dichloromethane (4 x 300 ml). The combined organic phases were washed with saturated sodium thiosulphate solution to remove the excess iodine and water. After drying ($MgSO_4$), filtering and removal of solvent, the product was obtained as a light yellow oil. Purification by chromatography on Florisil in hexane/toluene gave a colourless oil, found to be homogeneous by thin-layer chromatography (TLC). Yield: 31.1 g (87%). High resolution MS calc for $C_{15}H_{19}O_2I$ = 358.043; found: *m/e* 358.042, other major ions at 267 (M-91), 237 (M-121), 231 (M-127), 183 (?), 139 (M-91-127), 91 (base peak, $PhCH_2$). ^{1}H-NMR (360 MHz) ($CDCl_3$) δ 7.30 (m, 5H, aromatic); 4.50 (d, 1H, benzylic, J = 12.0 Hz); 4.45 (d, 1H, benzylic, J = 12.0 Hz); 4.34 (d x d, 1H, CH-I, J = 5.8; 4.1 Hz); 4.29 (m, 1H, CH-O-); 3.89 (d, 1H, CH_2-O-, J = 8.5 Hz); 3.75 (d x d, 1H, CH_2-O-, J = 8.5; 4.4 Hz); 3.30 (m, 2H, CH_2-O-Bn); 2.60 (d, 1H, CH_2 bridge, J = 12.0 Hz); 2.44 (m, 1H, CH at bridge junction, 1-position, adjacent to carbon atoms); 2.33 (m, 1H, CH-CH_2-O-Bn); 1.94 (m, 3H, aliphatic).

2α-Benzyloxymethyl-6-oxabicyclo[3.2.1]oct-3-ene ***16***
A solution of the iodo-benzyl ether **15** (15.0 g; 42 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), (7.95 g; 52.5 mmol) in dry dioxane (150 ml) was heated and stirred overnight at reflux temperature under nitrogen. After cooling the precipitated DBU-hydroiodide was filtered off and washed with 100 ml ether. The mother liquor was washed with 150 ml water and the aqueous phase extracted with 2 x 100 ml portions of ether. The organic layers were combined and washed successively with dilute hydrochloric acid, saturated sodium bicarbonate and finally brine before drying over magnesium sulphate. On evaporation of solvent the product was obtained as a pale yellow oil. Purification was carried out by chromatography on silica gel in hexane with increasing amounts of toluene. The product was obtained as a colourless oil. Yield: 7.6 g (78%). Subsequent larger batches were purified by vacuum distillation, bp: 143–147°C at 0.25 mm. High resolution MS $C_{15}H_{18}O_2$ calc: 230.131; found: 230.122 (± 10 ppm) other major ions *m/e* 199 (M-31); 139 (M-91); 121 (CH_2OCH_2Ph); 91 (CH_2Ph) (base peak). ^{1}H-NMR ($CDCl_3$) δ 7.3 (s, (broad), 5H, aromatic); 5.9 (m, 1H, olefinic); 5.5 (m, 1H, olefinic); 4.45 (s, 2H, O-CH_2Ph); 4.25 (m, 1H, CH-O); 3.8 (m, 2H, CH_2-O (ring)); 3.4 (m, 2H, CH_2-O-Bn); 2.9 (m, 1H, aliphatic); 2.6 (m, 1H, aliphatic); 1.9 (m, 2H, aliphatic).

2α-Hydroxymethyl-4β-iodo-6-oxabicyclo[3.2.1]octane ***12***
A solution of the diol **11** (60 g; 422 mmol) in 1200 ml 1 M aqueous sodium bicarbonate was stirred vigorously at 23°C, while 1500 ml of an aqueous solution containing iodine (118 g; 444 mmol) and potassium iodide (238 g; 1.44 mol) was slowly added dropwise. The resulting reaction mixture was stirred overnight before being subjected to the same extraction process as for **15**. The desired iodo-alcohol, found to be homogeneous by TLC, was the sole product. Yield: 110 g (97%) of pale yellow oil which was used without further purification. The GC-MS of the TMS derivative exhibited a single GC peak with MS *m/e* 340 (M^+); 245 (M-45); 213 (M-127); 167 (M-127-46); 123 (M-90-127); 103 (CH_2OTMS) (base peak). ^{1}H-NMR

($CDCl_3$) δ 4.3 (m, 2H, CH-O; CH-I); 3.85 (m, 2H, CH_2-O (ring)); 3.45 (d, 2H, CH_2-O); 2.75–1.7 (m, 6H, aliphatic); 2.2 (broad, 1H, OH). The corresponding bromo-compound is known [37].

2α-Hydroxymethyl-6-oxabicyclo[3.2.1]oct-3-ene ***13***
A solution of the iodo-alcohol **12** (110 g; 410 mmol) in dioxane 750 ml was treated with DBU (78.0 g; 513 mmol) and then boiled under nitrogen for 20 h. After this period 3/4 of the dioxane solvent was removed by distillation and the residue taken up in 750 ml ethyl acetate. The DBU salt was filtered off and the filtrate treated as in the isolation of **16**. The olefinic product was obtained as a pale yellow viscous oil found to be of high purity by TLC. Yield: 52.6 g (91.5%). GC-MS (TMS derivative) gave a single GC peak, *m/e* 212 (M^+); 123 (M-89). ^{1}H-NMR ($CDCl_3$) δ 5.95 (m, 1H, olefinic); 5.6 (m, 1H, olefinic); 4.3 (m, 1H, CH-O); 3.9 (m, 2H, CH_2-O (ring)); 3.6 (d (fine structure discernible), 2H, CH_2-O); 3.1 (broad, 1H, OH); 2.65 (m, 2H, aliphatic); 1.95 (m, 2H, aliphatic).

2α-Benzyloxymetyl-6-oxabicyclo[3.2.1]oct-3-ene ***16***
This synthesis (scheme 2, Route A) of the benzyl ether has the advantage that only monobenzylation is possible. The reaction details are similar to that described previously. Sodium hydride (16.3 g of a 60% suspension in oil, 409 mmol) was washed with 2 x 75 ml portions of dry petroleum spirit under nitrogen and resuspended in 400 ml dry DMF. A solution of the alcohol **13** (52 g; 371 mmol) in 100 ml DMF was added to provide a steady evolution of hydrogen (1.5–2 h). The mixture was stirred at room temperature for a further 1 h before heating at 60–70°C for 2 h to ensure complete alkoxide formation. After cooling, a solution of benzyl chloride (56.4 g; 448 mmol) in 100 ml DMF was added dropwise. An exothermic reaction was noted and the reaction mixture was allowed to reach 80°C. After the addition, the mixture was heated at this temperature for 2 h before being allowed to cool overnight. Most of the DMF was removed by rotary evaporator, and the residue taken up by ethyl acetate. Sufficient water was added to dissolve the precipitated salts and the aqueous phase extracted with more ethyl acetate. The combined organic phases were washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent gave the crude benzyl ether as a yellow oil identical to **16** obtained previously. Vacuum distillation gave a pure colourless product, bp: 143–147°C at 0.25 mm. Yield: 80.7 g (94%).

2α-Benzyloxymethyl-3β-hydroxy-6-oxabicyclo[3.2.1]octane ***18***
A solution of the olefin **16** (20.0 g; 87 mmol) in 150 ml dry THF was chilled under nitrogen to –78°C in a dry-ice/acetone bath. The solution was then treated with a 1 M solution of borane in THF (90 ml) in a dropwise manner. On completion of the addition, the mixture was stirred for a further 3 h while allowing the temperature to slowly reach 20°C. The solution was recooled to 0°C and a 3 M aqueous solution of sodium hydroxide (33 ml; 100 mmol) was carefully added so that the vigorous effervescence was not excessive. After 15 min a 30% solution of hydrogen peroxide (31 ml; 274 mmol) was added such that the temperature did not rise above 5°C. The mixture was left to reach room temperature and was stirred for a further 2 h before pouring into water and extracting 3 times with copious quantities of ether. The ether phase was washed with water, saturated aqueous sodium sulphite (which removes any unreacted peroxide) and finally with brine. After drying ($MgSO_4$), the ethereal solution was filtered and the solvent evaporated to give a colourless oil (20.3 g). TLC run in toluene/ethyl acetate, v/v 10:90, showed that the product was a mixture of 3 components. Similarly, GC-MS of the TMS derivative showed 3 GC peaks in a ratio of 3:1:1. The first component possessed a fragmentation pattern consistent with the desired alcohol **18**, while the other 2 peaks gave essentially identical mass spectra (M^+ = 394; TMS derivative consistent with alcohols **17**). The mixture was chromatographed on Florisil in toluene, which eluted the least polar major alcohol **18**, the other alcohols **17** being eluted as a mixture with increasing amounts of ethyl acetate. The desired alcohol **18** was thus obtained in a very pure state. Yield: 12.3 g (57%). High-resolution MS (TMS derivative) $C_{18}H_{28}O_3Si$ calc: 320.1808; found: 320.180, (± 10 ppm); other major ions at *m/e* 290 (M-30); 230/231 (M-89/90); 229/230 (M-90/91); 213 (M-107; 199 (M-121); 181; 145; 139 (M-90-91); 91 (CH_2Ph)(base peak). The absolute structure of **18** follows from the X-ray crystallographic analysis of the tosylate ester **20** whose synthesis is given below.

2α-Benzyloxymethyl-3β-tosyloxy-6-oxabicyclo[3.2.1]octane ***20***
To a solution of *p*-toluenesulphonyl chloride (3.5 g; 18.4 mmol) in 25 ml dry pyridine at 0°C was added, with stirring, a solution of the alcohol **13** (3.3 g; 13.3 mmol) in 10 ml dry pyridine followed by a catalytic quantity (20 mg) of 4-dimethylaminopyridine (DMAP). The resulting solution was left overnight at 5°C, whereupon crystals of pyridinium hydrochloride were deposited. Isolation of the title compound was performed by pouring the mixture into ice/water and extracting the resultant emulsion with ether. The organic phase was washed with water and brine before drying $MgSO_4$. Filtration and evaporation of solvent at < 20°C gave the crude tosylate **20** as an off-white solid. Recrystallisation from ether/petroleum spirit at low temperatures produced pure white crystals, mp: 95.5–96.5°C, yield: 3.7 g (70%). Anal $C_{22}H_{26}O_5S$ (C, H). ^{1}H-NMR ($CDCl_3$) δ 7.75 (d, 2H, aromatic (tosyl)); 7.3 (m, 5H, C_6H_5); 7.2 partially obscured (d, 2H, aromatic (tosyl)); 4.6 (m, 1H, CH-OTs); 4.3 (s, 2H, benzylic); 4.2 (m, 1H, CH-O- ring bridge junction); 3.9 (m, 1H, CH_2-O- ring); 3.6–3.1 (m, 3H, aliphatic); 2.75 (m (broad), 1H, aliphatic); 2.4 (s, 3H, CH_3-); 2.3–1.3 (m, 5H, aliphatic).

2α-Benzyloxymethyl-6-oxabicyclo[3.2.1]octan-3-one ***19***
To a solution of alcohol **17** (12.0 g; 48 mmol) in 150 ml analytical grade acetone at –15°C was added, dropwise, 27.2 ml, 1.5 molar excess of Jones reagent (prepared as a 2.6 M solution, by dissolving 26 g chromic anhydride in 23 ml conc sulphuric acid and diluting to 100 ml with water). After addition was complete (30 min) the solution remained an orange colour. A further 15 min stirring gave a TLC analysis showing complete absence of starting material. The mixture was poured into water (150 ml) and the product extracted with 3 x 100 ml portions of diethyl ether. The ether phase was washed with water and brine before drying ($MgSO_4$). Filtration and evaporation of solvent gave the desired ketone as an oil of very high purity by TLC, GC and NMR. Yield: 11.4 g (96%). IR ν_{max} (C=O) 1705 cm^{-1} (thin film). High resolution MS $C_{15}H_{18}O_3$ calc: 246.1256; found: 246.126 (± 10 ppm). ^{1}H-NMR ($CDCl_3$) δ 7.3 (s, 5H, C_6H_5); 4.5 (s (broad), 2H, benzylic); 4.5 obscured (m, 1H, CH-O- ring bridge junction); 4.1–3.3 (m, 4H, aliphatic); 3.0–1.9 (m, 6H, aliphatic).

2α-Benzyloxymethyl-3-methylene-6-oxabicyclo[3.2.1]octane ***21***
The titanium–methylene complex was prepared by the addition of dibromomethane (16 ml, 39.6 g; 228 mmol) to a stirred suspension of activated zinc dust (44.4 g; 683 mmol) in 500 ml dry THF under argon at – 40°C. (The zinc was activated by

stirring in 5% HCl for 2 min then washing with water and acetone and drying *in vacuo*.) After 10 min titanium tetrachloride (17.9 ml, 30.9 g; 163 mmol) was added slowly over 20 min. The resulting grey slurry was allowed to reach 5–10°C, whereupon it was stored under argon for a period of 3 d at this temperature. The olive-green slurry was then ready for use, and was cooled to 0°C before the dropwise addition of a 100 ml THF solution containing ketone **19** (20.0 g; 81.3 mmol) over 20 min. Analysis by TLC (toluene:ethyl acetate, v/v 90:10) on silica gel plates showed the reaction to be virtually instantaneous; however, the mixture was stirred a further 30 min to ensure completion. The mixture was quenched by pouring into 1000 ml saturated aqueous sodium bicarbonate solution (paying attention to effervescence). Diethyl ether (750 ml) was added and the biphasic system was stirred vigorously for 30 min. The liquid phases were decanted from the granular precipitate which was leached further with 3 x 250-ml portions of ether. The liquid phases were separated and the ether layer volume reduced by 50% before washing with sodium bicarbonate solution, brine, followed by drying ($MgSO_4$). Evaporation of solvent gave the crude product which was passed through a short Florisil column in hexane. Increasing amounts of toluene eluted the exo-cyclic olefin as a pure colourless oil. Yield: 16.6 g (84%). High resolution MS $C_{16}H_{20}O_2$ calc: 244.1463; found: 244.147 (± 10 ppm); ^{1}H-NMR ($CHCl_3$) δ 7.3 (s, 5H, C_6H_5); 4.9 (m, 1H, olefinic); 4.75 (m, 1H, olefinic); 4.5 (s, 2H, benzylic); 4.3 (m, 1H, CH-O- ring bridge junction); 3.9–3.3 (m, 4H, aliphatic); 2.8–1.7 (m, 6H, aliphatic).

2α-Benzyloxymethyl-3α-hydroxymethyl-6-oxabicyclo[3.2.1]-octane ***22***

A 1 M solution of diborane (BH_3:THF) in THF (61.5 ml; 61.5 mmol) was added to a stirred solution of olefin **21** (15.0 g; 61.5 mmol) in 250 ml dry THF at –20°C under argon over 1 h. After a further 1 h at this temperature the solution was allowed to warm to 0°C. Water (5 ml) was added to discharge excess reagent, followed by 3 M aqueous sodium hydroxide (22.5 ml; 67.6 mmol). After 15 min an aqueous solution of 30% hydrogen peroxide (20.9 ml; 184.4 mmol) was added at such a rate that the temperature was kept below 15°C. On completion of the addition the reaction mixture was allowed to reach room temperature and was then stirred for a further 2 h. Brine (100 ml) was added and the organic layer separated. The aqueous layer was further extracted with 2 x 150 ml diethyl ether. The combined organic phases were washed consecutively with 100 ml amounts of water, saturated sodium thiosulphate and brine. The solution was dried ($MgSO_4$) and the solvent evaporated to give the product alcohol **22** in a clean state, whereupon it was taken directly to the next step. Yield: 15.8 g (98%). High resolution MS $C_{16}H_{22}O_3$ calc: 262.1569; found: 262.157 (± 10 ppm); IR ν_{max} (OH) 3360 cm^{-1} (broad); ^{1}H-NMR ($CDCl_3$) δ 7.3 (s, 5H, C_6H_5); 4.5 (s, 2H, benzylic) 4.35 (m, 1H, CH-O- ring bridge junction); 3.9 (m, 1H, CH_2OH(D)); 3.6 (m, 6H, aliphatic); 2.9 (s (broad), 1H, OH); 2.5–1.5 (m, 7H, aliphatic).

2α-benzyloxymethyl-3α-formyl-6-oxabicyclo[3.2.1]octane ***23*** *and 2α-benzyloxymethyl-3β-formyl-6-oxabicyclo[3.2.1]octane* ***24***

To a vigorously stirred suspension of freshly prepared pyridinium chlorochromate (PCC) (30.6 g; 143 mmol) and anhydrous sodium acetate (1.5 g; 18.3 mmol) in dichloromethane (150 ml) was added dropwise, a solution of alcohol **22** (15.0 g; 57.2 mmol) in 75 ml dichloromethane. The addition took ≈ 20 min. After 2 h, 200 ml diethyl ether was added and stirring continued for 15 min. The mixture was filtered through a Celite plug to remove the granular precipitate. The residue remaining in the flask was triturated with 2 x 50 ml portions of ether and these were washed through Celite. The ether solution was washed with water, 5% sodium hydroxide solution (to remove chromium complexes) and brine before drying ($MgSO_4$). Evaporation of solvent afforded aldehyde **23** as the sole product, yield: 14.0 g (94%). This was redissolved in 150 ml chloroform and stirred with 1,8-diazabicyclo[5.4.0]-undecane (DBU) (0.5 g; 2.7 mmol) at 35°C to epimerise the formyl group. The reaction was conveniently followed by NMR, and was complete after 60 min. The solution was washed first with water (pH 5), to remove the DBU, and then with brine before workup as above. The product was chromatographed briefly on a Florisil column in toluene with increasing amounts of diethyl ether to give the aldehydes **24** and **23** in a ratio > 95:5 by NMR, yield: 13.4 g (90% overall). The following physical data refers to the more stable epimer **24**. High-resolution MS, $C_{16}H_{20}O_3$ calc: 260.141; found: 260.140 (± 10 ppm). IR ν_{max} (C=O) 1720 cm^{-1} (thin film). ^{1}H-NMR (360 MHz) ($CDCl_3$) δ 9.6 (d, 1H, CHO, J = 3.2 Hz); 7.3 (m, 5H, C_6H_5); 4.5 (d x d, 1H, benzylic J_{gem} = 12.0 Hz; J_{vic} = 1.8 Hz); 4.4 (d, 1H, benzylic, J = 12.0 Hz); 4.35 (m, 1H, CH-O- ring bridge junction); 3.9 (d x d, 1H; CH_2-O- ring, J_{gem} = 8.5 Hz; J_{vic} = 4.0 Hz); 3.7 (m, 1H, CH_2-O- ring); 3.35 (m, 2H, (CH_2OBn); 2.55–1.35 (m, 7H, aliphatic, showing 2 conformers). The formyl signal of **23** occured at δ 9.7 (d, 1H, CHO, J = < 1 Hz).

2α-Benzyloxymethyl-3β-dioxyethylenemethyl-6-oxabicyclo-[3.2.1]octane ***25***

A mixture of the above aldehyde **24** (13.0 g; 50 mmol), ethane-1,2-diol (7.75 g; 125 mmol) and *p*-toluenesulphonic acid (0.25 g; 2.6 mmol) in 250 ml dry benzene was boiled under nitrogen with azeotropic removal of water using a Dean–Stark trap. The heating was continued until no more water was produced (2–3 h), and then for a further 1 h. The cooled solution was diluted with 100 ml of diethyl ether and saturated aqueous sodium bicarbonate was stirred in vigorously to remove the catalytic amount of toluenesulphonic acid. After 15 min the organic layer was separated and washed successively with water and brine. The solution was dried ($MgSO_4$), filtered and the solvent evaporated to give the crude product. Chromatography on Florisil in v/=v 1:1 hexane/toluene gave pure acetal as a colourless oil. Yield: 14.4 g (95%). ^{1}H-NMR ($CDCl_3$) δ 7.3 (s, 5H, C_6H_5); 4.8 (d, 1H, -O-CH-O-); 4.45 (m, 2H, OCH_2Ph); 4.3 (m, 1H, -CH-O-); 4.05–3.55 (m, 8H, -CH_2-O-); 3.3 (m, 1H, aliphatic); 2.6 (m, 1H, aliphatic); 2.15–1.1 (m, 5H, aliphatic). This compound was taken directly to the next stage.

2α-Hydroxymethyl-3β-dioxyethylenemethyl-6-oxabicyclo-[3.2.1]octane ***26***

The benzyl ether **25** (14.0 g; 46.1 mmol) was dissolved in 100 ml dry diethyl ether and 250 ml of liquid ammonia was added by distillation using a dry-ice/acetone condenser. The stirred solution then received small pieces of freshly cut sodium metal over a period of ≈ 1 h until the blue colour persisted. Solid ammonium chloride was carefully added to quench the reaction and the ammonia was allowed to evaporate. The resulting slurry was treated with enough water to dissolve salts and the layers separated. The aqueous phase was extracted with 2 x 100 ml portions of ethyl acetate and the combined organic layers were washed with water and brine before drying ($MgSO_4$). Filtration and evaporation of solvent gave a pale yellow oil which was chromatographed on Florisil in toluene with increasing amounts of ethyl acetate. The

product alcohol was obtained as a colourless oil. Yield: 8.7 g (88%). ^{1}H-NMR ($CDCl_3$) δ 4.8 (d, 1H, -O-CH-O-, J = 4 Hz); 4.3 (m, 1H, -CH-O-); 3.95–3.3 (m, 8H, CH_2-O); 3.1 (broad, 1H, OH); 2.4 (m, 1H, aliphatic); 2.1–1.1 (m, 6H, aliphatic) was used.

2α-Tosyloxymethyl-3β-dioxyethylenemethyl-6-oxabicyclo-[3.2.1]octane ***27***

The alcohol **26** (8.0 g; 37.4 mmol) in 30 ml dry pyridine was added to a stirred solution of *p*-toluenesulphonyl chloride (9.2 g; 48.6 mmol) in 100 ml dry pyridine at 0°C. Following the addition of a catalytic amount of DMAP (50 mg) the solution was allowed to stand for 20 h at 5°C. During this time pyridinium hydrochloride crystals were deposited. The mixture was poured onto ice-water and shaken vigorously for 20 min. The product was extracted with 3 x 100 ml portions of dichloromethane. Treatment of the combined organic phases in the usual way gave a pale yellow oil which solidified on standing. This material was pure enough for subsequent use; however, an analytically pure sample was obtained after 1 recrystallisation from ether/methylene chloride, mp: 108–109°C. Anal $C_{18}H_{24}O_6S$ (C, H,), yield: 11.1 g (81%). ^{1}H-NMR ($CDCl_3$) δ 7.75 (m, 2H, aromatic); 7.3 (m, 2H, aromatic); 4.6 (d, 1H, -O-CH-O-); 4.5 (d x d, 1H, -CH_2-OTs); 4.3 (m, 1H, -CH-O-); 3.9–3.4 (m, 7H, -CH_2-O-); 2.4 (s, 3H, CH_3); 2.2–1.2 (m, 7H, aliphatic). The X-ray crystal structure of **23** confirmed the above analysis.

2α-Cyanomethyl-3β-dioxyethylenemethyl-6-oxabicyclo[3.2.1]-octane ***28***

A mixture of the tosylate ester **27** (10.0 g; 27.2 mmol) and dry potassium cyanide (2.5 g; 38 mmol) in 150 ml dry distilled dimethyl sulphoxide DMSO was stirred and heated at 60°C under a nitrogen atmosphere for 18 h. On cooling the mixture was poured into 200 ml water and the desired nitrile **28** isolated by extraction with 3 x 100 ml portions of ether. The organic phases were washed with water and brine etc to afford the title compound as an oil found to be homogeneous by TLC. Yield: 5.6 g (96%). IR ν_{max} (CN) 2255 cm^{-1} (thin film). ^{1}H-NMR ($CDCl_3$) δ 4.7 (d, 1H, -O-CH-O-); 4.3 (m, 1H, -CH-O-); 4.1–3.6 (m, 6H, CH_2-O-); 3.0 (m, 1H, aliphatic); 2.6 (m, 1H, aliphatic); 2.4–1.2 (m, 7H, aliphatic).

2α-Formylmethyl-3β-dioxyethylenemethyl-6-oxabicyclo-[3.2.1]octane ***29***

A solution of the nitrile **28** (5.5 g; 24.7 mmol) in 75 ml sodium-dried toluene under nitrogen was cooled to – 60°C. Diisobutylaluminium hydride (19.7 ml of a 1.5 M solution in toluene; 29.6 mmol) was slowly added over a 20-min period. The mixture was allowed to warm gradually to room temperature, and after stirring for a further 1 h, was quenched by careful addition of 20 ml methanol. Chloroform (100 ml) was added to mobilise the resulting heavy slurry, which was filtered and the residual solids washed with chloroform. The filtrate was somewhat reduced in volume before stirring with saturated aqueous sodium hydrogen tartrate (200 ml) at 40°C for 2 h. On cooling, the organic layer was removed and the aqueous layer extracted with 2 x 100 ml portions of chloroform. The combined organic phases were dried ($MgSO_4$), filtered and evaporated to yield a yellow oil. Chromatography on Florisil in toluene gave the aldehyde **29** as a colourless oil. Yield: 4.75 g (85%). IR ν_{max} (C=O) 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 9.7 (t, 1H, CHO, J = < 1 Hz); 4.7 (d, 1H, -O-CH-O-); 4.35 (m, 1H, -CH-O-); 4.0–3.6 (m, 6H, CH_2-O-); 3.0 (m, 1H, aliphatic); 2.4–1.2 (m, 8H, aliphatic). This rather unstable aldehyde was immediately taken to the next stage.

2α-(6'-Carboxyhex-2'Z-enyl)-3β-dioxyethylenemethyl-6-oxabicyclo[3.2.1]octane ***30***

4-Carboxybutyltriphenylphosphonium bromide (22.1 g; 49.8 mmol) was charged to the reaction flask and dried *in vacuo* at 80°C for 2 h. The flask was cooled and the vacuum released to nitrogen. The phosphonium salt was dissolved in 150 ml dry DMSO and then treated dropwise with a solution of *n*-butyllithium (56 ml of 1.6 M in *n*-hexane; 89.6 mmol) over 1.5 h. The mixture was stirred a further 30 min to complete the formation of the bright red ylide. The aldehyde **29** (4.5 g; 19.9 mmol) was slowly added in 50 ml DMSO (20 min) and stirring was continued overnight at room temperature. The bulk of the solvent was removed *in vacuo* and the cooled residue leached out with water. The basic aqueous solution was washed with toluene/ethyl acetate (1:1 v/v) to remove non-acidic material. The aqueous phase was acidified carefully to pH 2–3 with 2 M HCl, and the product extracted into ethyl acetate. The organic layers were washed with brine, dried ($MgSO_4$), filtered and the solvent evaporated. The yellow residue obtained was redissolved in diethyl ether (50 ml) and chilled to crystallise out remaining triphenylphosphine oxide, which was removed by filtration. The filtrate was evaporated to give the product **30** as a yellow oil. This material was purified by chromatography on silicic acid (200 g), in toluene with increasing amounts of ethyl acetate, before storage. Four fractions (25 ml) were collected for each solvent mixture composition, starting in pure toluene and adding 1, 2, 5, 10, 20% v/v ethyl acetate. The desired product was eluted in the last 10% ethyl acetate fraction and the first 20% ethyl acetate fraction. Yield: 4.26 g (69%). High-resolution MS (methyl ester) $C_{18}H_{28}O_5$ calc: 324.194; found: 324.190 (± 10 ppm). ^{1}H-NMR ($CDCl_3$) δ 8.8 (broad, 1H, COOH); 5.4 (m, 2H, olefinic); 4.95 (d, 1H, -O-CH-O-); 4.35 (m, 1H, -CH-O-); 4.0–3.5 (m, 6H, CH_2-O-); 2.5–1.2 (m, 15H, aliphatic).

2α-(6'-Carboxyhex-2'Z-enyl)-3β-formyl-6-oxabicyclo[3.2.1]-octane ***31***

Acetal **30** (500 mg) in chloroform (20 ml) containing 2 ml isopropanol was vortex-stirred with 5 M aqueous hydrochloric acid (20 ml) for 40 min. The chloroform layer was separated and washed acid free with water and brine, before drying ($MgSO_4$), filtering, and evaporating the solvent to give the product in quantitative yield. Aldehyde was obtained by chromatography on silicic acid commencing in toluene as described previously. The product (373 mg; 87%) was eluted with toluene/15% ethyl acetate. High resolution MS (methyl ester, *O-n*-butyloxime derivative) $C_{20}H_{33}NO_4$ calc: 351.241; found: 351.240 (± 10 ppm), other major ions *m/e* 320 (M-31); 294 (M-57); 278 (M-73); 264 (M-83); 236 (M-84-31); 210 (M-141); 128 (base peak): in the GC-MS 2 butyloxime isomers were apparent as expected, both having almost identical fragmentation patterns in MS. ^{1}H-NMR (360 MHz) ($CDCl_3$) δ 9.6 (d, 1H, CHO); 5.4 (m, 2H, olefinic); 4.4 (M, 1H, -CH-O-); 3.9 (m, 1H, CH_2-O-); 3.7 (m, 1H, CH_2-O-); 2.6–1.1 (m, 15H, aliphatic).

2α-(6'-Carboxyhex-2'Z-enyl)-3β-O-diphenylmethyloximino-methyl-6-oxabicyclo[3.2.1]octane ***32***

The aldehyde **31** (250 mg; 0.94 mmol) and *O*-diphenylmethoxyamine hydrochloride (440 mg; 188 mmol) were allowed to stand overnight in pyridine (10 ml). The solution was then heated at 60°C for 3 h, and the solvent removed by rotary evaporator. The residue was taken into ether and washed with pH 3 water and brine before drying ($MgSO_4$), filtering and evaporating the ether. The crude oxime **32** was obtained in high yield (303 mg). Chromatography on Lipidex LH20/50%N14 in hexane/dichloroethane/ethanol, v/v/v 100:100:2

(+ 0.1% acetic acid) gave a colourless oil which crystallised in fine white prisms from ethanol. Yield: 232 mg (73%), mp: 100–101°C. High-resolution MS (M- $OCHPh_2$) $C_{15}H_{22}NO_3$ calc: 264.160; found: 264.160 (± 10 ppm). The molecular ion was very small in this case and the base peak was the expected *m/e* 167 due to the diphenylmethyl ion. ^{1}H-NMR ($CDCl_3$) δ 8.75 (broad, 1H, COOH); 7.3 (m, 11H, C_6H_5, and -CH=N-); 6.2 (s, 1H, $CHAr_2$); 5.3 (m, 2H, olefinic); 4.3 (m, 1H, -CH-O-); 3.8 (m, 2H, CH_2-O-); 2.5–1.2 (m, 15H, aliphatic). UV λ_{max} = 258 nm (log ε_{max} = 2.85).

2α-(6'-Carboxyhex-2'Z-enyl)-3β-(3"-oxo-oct-1"E-enyl)-6-oxabicyclo[3.2.1]octane ***33***

Dimethyl 2-oxoheptylphosphonate (0.66 g; 3.0 mmol) in 20 ml dry THF was added to a stirred suspension, in 30 ml THF, of sodium hydride (0.105 g of 60% dispersion; 2.6 mmol), at 0°C. After addition the mixture was warmed to 25°C for 1 h to allow the anion to form. The system was recooled to 0°C and aldehyde **31** (300 mg; 1.12 mmol) was added in 5 ml THF. After 1 h at 0°C and 2.5 h at 25°C, the reaction was stopped by addition of glacial acetic acid (2 ml). The product was isolated by pouring the reaction mixture into water and extracting in the usual way with ethyl acetate. The crude enone was chromatographed initially on 5 g silicic acid in toluene, with increasing amounts of ethyl acetate as before, and then on Lipidex LH20/50% N14 run in hexane/dichloroethane/ethanol, v/v/v 100:100:1 (+ 0.1% acetic acid) with a bed volume of 100 ml. Fractions of 5 ml were collected and the desired compound in a quantity of 183 mg (83%) was eluted at 1.5–2.0 bed volumes. High resolution MS (methyl ester, *O-n*-butyloxime derivative) $C_{27}H_{45}NO_4$ calc: 447.335; found: 447.334 (± 10 ppm): both oxime isomers were separable on the GC and had virtually identical mass spectral fragmentation patterns with major ions at *m/e* 416 (M-31); 390 (M-57); 374 (M-73); 306 (M-141) (base peak); 196 (w-chain). ^{1}H-NMR ($CDCl_3$) δ 9.3 (broad, 1H, COOH); 7.65 (d x d, 1H, *trans* olefinic, J_{large} = 16 Hz, J_{small} = 7 Hz); 6.15 (d, 1H, *trans* olefinic, *J* =16 Hz); 5.35 (m, 2H, *cis* olefinic), 4.35 (m, 1H, -CH-O-); 3.8 (m, 2H, $-CH_2$-O-); 2.6–1.1 (m, 23H, aliphatic); 0.9 (t, 3H, CH_3). UV λ_{max} = 229 nm (logε_{max} = 4.06).

2α-(6'-Carboxyhexyl-2"Z-enyl)-3β-(3"-hydroxyoct-1"E-enyl)-6-oxabicyclo[3.2.1]octane ***34a, 34b***

Enone **33** (20 mg; 0.75 mmol) was dissolved in dry toluene (30 ml) and 4 ml of 1 M aluminium isopropoxide in toluene was added along with 4 ml isopropanol. The mixture was boiled gently under a stream of argon (which carried away the acetone formed) for 2–3 h. A further 4 ml isopropanol and 2 ml isopropoxide solution were added and the heating continued for a further 1 h with slow removal of 15–20 ml solvent by distillation. The cooled residue was treated with saturated aqueous sodium hydrogen tartrate and then with more water and ether. The pH was adjusted to 3 and the ether layer separated, washed with brine dried ($MgSO_4$), filtered and evaporated. The product was obtained as an oil, 143 mg (71%) which proved to be a mixture of alcohols **34a** and **34b** in a ratio of ≈ 1:2 respectively. These isomers were separated on Lipidex LH20/25%N14 run in hexane/dichloroethane/ethanol, v/v/v 100:100:2 (+ 0.1% acetic acid) as described for the preceding compound. The less polar isomer **34a** (48 mg; 24%) was eluted first, followed by **34b** (83 mg; 41%). The assignment of the 15-hydroxyl orientation was made on the basis of the TLC polarity of the isomers. Furthermore the more polar isomer **34b** was more biologically active as a TXA_2 agonist in agreement with other analogues [15, 17]. High-resolution MS (methyl ester, trimethylsilyl ether derivative) $C_{26}H_{46}O_4Si$, calc: 450.317; found: 450.320 (± 10 ppm) for both isomers. ^{1}H-NMR ($CDCl_3$) δ 6.4 (broad, 2H, COOH, OH); 5.4 (m, 4H, olefinic); 4.3 (m, 1H, -CH-O- ring); 4.1 (m, 1H, -CHOH); 3.8 (m, 2H, $-CH_2OH$); 2.5–1.0 (m, 33H, aliphatic); 0.9 (t, 3H, CH_3); spectrally the isomers were virtually identical.

2α-(6'-Carboxyhex-2'Z-enyl)-3β-[N-(p-methoxyphenylcarbamoyl)-hydrazonomethyl]-6-oxabicyclo[3.2.1]octane ***35a***

The aldehyde **31** (300 mg; 1.12 mmol) and 4-*p*-methoxyphenylsemicarbazone (400 mg; 2.25 mmol) were heated at 60°C in dioxane (15 ml) under nitrogen for 3 h. The solvent was evaporated and the residue chromatographed on Lipidex LH20/25%N14 in hexane/dichloroethane/ethanol, v/v/v 100:100:2 (+ 0.1% acetic acid) as before. A colourless oil was obtained which crystallised as fine white prisms, mp: 148–150°C from ethanol at – 20°C; yield: 256 mg (53%). High-resolution MS (M - CH_3O-Ph-NCO) $C_{15}H_{24}N_2O_3$ calc: 280.179; found: 280.180 (± 10 ppm); the arylsemicarbazone did not exhibit a molecular ion due to the favoured cleavage of aryl isocyanate. ^{1}H-NMR ($CDCl_3$) δ 10.65 (v, broad, 1H, COOH); 9.8 (s, 1H, -NH-); 7.9 (s, 1H, -NH-); 7.4 (d, 2H, aromatic); 7.1 (d, 1H, -CH=N-); 6.85 (d, 2H, aromatic); 5.4 (m, 2H, olefinic); 4.4 (m, 1H, -CH-O- ring); 3.95 (m, 2H, CH_2-O-); 3.8 (s, 3H, CH_3); 2.5–1.2 (m, 15H, aliphatic). UV λ_{max} = 249 nm (logε_{max} = 4.27)

2α-(6'-Carboxyhex-2'Z-enyl)-3β-[N-(p-methoxyphenylthiocarbamoyl)hydrazonomethyl]-6-oxabicyclo[3.2.1]octane ***35b***

The thio-analogue **35b** was prepared in an identical manner to that described above for **35a**. A yellow gum was obtained which refused to crystallise, but which was found to be pure by TLC and NMR; yield: 192 mg (38%). High-resolution MS (M-CH_3O-Ph-NCS) $C_{15}H_{24}N_2O3$ calc: 280.179; found: 280.180 (± 10 ppm). ^{1}H-NMR ($CDCl_3$) δ 10.55 (s, 1H, -NH-); 8.9 (s, 1H, -NH-); 8.5 (v broad, 1H, COOH); 7.4 (d, 2H, aromatic); 7.25 (d, 1H, -CH=N-); 6.9 (d, 2H, aromatic); 5.5 (m, 2H, olefinic); 4.4 (m, 1H, -CH-O-); 3.85 (m, 2H, CH_2-O-); 3.8 (s, 3H, CH_3); 2.6–1.2 (m, 15H, aliphatic): UV λ_{max} = 275 nm (logε_{max} = 4.46).

Biological measurements

Platelets

Blood was collected into acid/citrate/dextrose (ACD) solution (1 vol: 5 vol blood) from a forearm vein of human volunteers who had not taken non-steroidal anti-inflammatory drugs for at least 7 d previously. Platelet-rich plasma was obtained from the blood by centrifugation at 200 *g* for 20 min at room temperature. Platelet aggregation was measured at 37°C with a Chrono-Log dual channel aggregometer. Each cuvette (siliconised glass) contained 0.2 ml platelet-rich plasma, 0.2 ml Krebs solution and 0.1 ml 0.9% NaCl solution in which potential inhibitors were dissolved. Stirring was effected with a Teflon coated magnetic follower revolving at 1000 rpm. After 2 min equilibration in the aggregometer, the aggregating agent was added in 0.02 ml saline solution. Responses were expressed as percentage of the maximum aggregation response induced by 3 μM U-46619, and approximate log concentration–response curves were plotted from which EC_{50} values were estimated.

Cyclic AMP levels in suspensions of human washed platelets were measured by a protein binding assay as previously described by us [13].

Smooth muscle preparations

Thoracic aortae were obtained from male rats and rabbits and tracheae from male and female guinea pigs killed by stunnung

Table II. Summary of X-ray crystallographic data collection parameters.

Parameters	Molecular number	Molecular number
	20	**27**
Molecular formula	$C_{22}H_{26}O_5S$	$C_{18}H_{24}O_6S$
Molar mass	402.48	368.41
Crystal dimensions / mm	1.0 x 0.3 x 0.15	0.4 x 0.3 x 0.65
Crystal shape	Columnar	Pinacoidal tablet
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/a$ (No. 14)	P1 (No 2)
Temperature (°K)	293	291
Diffractometer used	Seimens - Stoë AED-2	
Reflections to determine lattice parameters (±ω)	8	12
in the range	32 * < θ < 34*	30 * < θ < 34 *
Cell dimensions /Å a	11.9110 (7)	9.709 (5)
" b	12.8832 (10)	10.699 (5)
" c	14.6672 (7)	11.123 (6)
" α	90 *	117.12 (2) *
" β	113.019 (4) *	90.36 (3) *
" γ	90 *	116.06 (3) *
Cell volume / $Å^3$	2071.5	892.5
Z	4	2
D_{calc} ($g.cm^{-3}$)	1.209	1.371
F (000)	856	392
Radiation & monochromator	Mo - Kα graphite	Cu - Kα graphite
Linear absorbtion coefficient (cm^{-1})	1.77	18.41
Transmission coefficient max.	0.6376	0.3005
" min	0.3954	0.1749
Maximum $\sin\theta/\lambda$ ($Å^{-1}$)	0.538	0.558
hkl range h	-12 → 11	-10 → 10
" k	0 → 13	-11 → 11
" l	0 → 15	0 → 12
Drift correction max.	1.066	1.0214
" min.	1.000	0.096
Reflections measured	3026	2478
Reflections for refinement	2430	2200
Parameters refined	283	246
Final R	0.0577	0.0455
Final R_w	0.0682	0.0728
S	4.462	1.308
Weighting scheme from SHELX76	$w^{-1} = \sigma^2(F) + g \cdot F^2$	
g from above equation	0.001000	0.000060 *
Maximum Δ/esd final cycle	0.044	0.018
Final Δ fourier ($e.Å^{-3}$) max	0.22	0.22
" min	-0.31	-0.26

*An empirical extinction correction was applied in this case [40].

Table III. Fractional coordinates of atoms for **20** with SES.

$$Ueq = \frac{1}{3} \Sigma_i \Sigma_j U_{ij} \cdot a_i^* \cdot a_j^* \cdot a_i \cdot a_j$$

	x	y	z	Ueq
C (1)	-0.0477 (3)	-0.03207 (25)	-0.30998 (24)	0.0581 (22)
C (2)	-0.0541 (3)	0.0351 (23)	-0.22546 (22)	0.0517 (20)
C (3)	0.0737 (3)	0.04541 (24)	-0.14394 (21)	0.0509 (20)
C (4)	0.1395 (3)	-0.05760 (25)	-0.11602 (23)	0.0584 (22)
C (5)	0.1285 (3)	-0.1154 (3)	-0.2094 (3)	0.070 (3)
O (6)	0.16405 (20)	-0.04729 (20)	-0.27198 (17)	0.0739 (18)
C (7)	0.0546 (3)	0.0001 (3)	-0.34206 (25)	0.071 (3)
C (8)	-0.0043 (3)	-0.1408 (3)	-0.2711 (3)	0.0671 (25)
C (9)	-0.1082 (3)	0.14189 (25)	-0.2600 (3)	0.0608 (23)
O (10)	-0.23201 (19)	0.12889 (18)	-0.32768 (18)	0.0700 (17)
C (11)	-0.2881 (3)	0.2251 (3)	-0.3687 (3)	0.076 (3)
C (12)	-0.2362 (3)	0.2730 (3)	-0.43715 (24)	0.0586 (22)
C (13)	-0.2350 (4)	0.2169 (4)	-0.5175 (3)	0.093 (3)
C (14)	-0.1846 (5)	0.2590 (5)	-0.5788 (4)	0.115 (5)
C (15)	-0.1381 (5)	0.3566 (5)	-0.5634 (4)	0.112 (4)
C (16)	-0.1385 (4)	0.4135 (4)	-0.4834 (4)	0.103 (4)
C (17)	-0.1880 (3)	0.3711 (3)	-0.4218 (3)	0.076 (3)
O (18)	0.06006 (18)	0.09004 (16)	-0.05564 (15)	0.0571 (14)
S (19)	0.15528 (7)	0.17434 (7)	0.00665 (6)	0.0579 (6)
O (191)	0.13629 (23)	0.18144 (21)	0.09670 (17)	0.0809 (19)
O (192)	0.27354 (19)	0.14961 (19)	0.00917 (17)	0.0700 (17)
C (20)	0.1042 (3)	0.28905 (24)	-0.06180 (21)	0.0523 (20)
C (21)	0.1625 (3)	0.3269 (3)	-0.11973 (25)	0.0636 (24)
C (22)	0.1214 (3)	0.4188 (3)	-0.1725 (3)	0.069 (3)
C (23)	0.0237 (2)	0.4729 (3)	-0.16744 (25)	0.0633 (24)
C (24)	-0.0340 (3)	0.4319 (3)	-0.1099 (3)	0.069 (3)
C (25)	0.0058 (3)	0.3412 (3)	-0.0564 (3)	0.0652 (25)
C (26)	-0.0174 (4)	0.5747 (3)	-0.2211 (3)	0.086 (3)

and exsanguination. Rings of tissue (3-mm wide) were suspended between stainless steel hooks in 10-ml organ baths. The Krebs bathing solution (NaCl 118, KCl 5,4, $MgSO_4$ 1.0, $CaCl_2$ 2.5, NaH_2PO_4 1.1 $NaHCO_3$ 25, dextrose 10 mmol l^{-1}) was gassed with 95% O_2/5% CO_2 and maintained at 37°C. Tension was recorded with Grass FT03 force displacement transducers linked to a Grass Polygraph. The spontaneous activity of the guinea-pig trachea was abolished by inclusion of 1 μM indomethacin and 20 nM atropine in the bathing fluid. Two cumulative concentration–response curves were obtained to the standard agonist U-46619. For the novel agonists, a further concentration-response was obtained and EC_{50} values and relative maximum responses (U-46619 = 100%) were estimated. Mean values from 4 separate experiments were calculated. For

Table IV. Fractional coordinates of atoms for **27** with SES.

$$Ueq = \frac{1}{3} \Sigma_i \Sigma_j U_{ij} \cdot a_i^* \cdot a_j^* \cdot a_i \cdot a_j$$

	x		y		z		Ueq	
C (1)	0.2117	(3)	0.8122	(3)	0.15401	(24)	0.0603	(21)
C (2)	0.3834	(3)	0.8548	(3)	0.20214	(22)	0.0528	(19)
C (3)	0.4955	(3)	1.0406	(3)	0.28617	(23)	0.0550	(20)
C (4)	0.4592	(3)	1.1242	(3)	0.2188	(3)	0.0689	(23)
C (5)	0.2828	(3)	1.0557	(3)	0.1688	(3)	0.0720	(24)
O (6)	0.20814	(22)	1.05855	(23)	0.28113	(19)	0.0837	(18)
C (7)	0.1565	(3)	0.9068	(4)	0.2733	(3)	0.082	(3)
C (8)	0.2053	(3)	0.8779	(3)	0.05952	(25)	0.0676	(23)
C (9)	0.3927	(3)	0.7766	(3)	0.28338	(24)	0.0606	(21)
O (10)	0.30388	(20)	0.60183	(20)	0.18416	(18)	0.0702	(16)
S (11)	0.29605	(8)	0.48743	(9)	0.23903	(9)	0.0883	(8)
O (111)	0.2586	(3)	0.5389	(3)	0.3720	(3)	0.143	(3)
O (112)	0.19463	(25)	0.32914	(25)	0.1238	(3)	0.1233	(25)
C (12)	0.4903	(3)	0.5198	(3)	0.2644	(3)	0.0624	(21)
C (13)	0.5484	(3)	0.4624	(3)	0.1497	(3)	0.0721	(24)
C (14)	0.6985	(3)	0.4823	(3)	0.1719	(3)	0.0731	(25)
C (15)	0.7878	(3)	0.5512	(3)	0.3054	(3)	0.0653	(22)
C (16)	0.7281	(3)	0.6103	(3)	0.4172	(3)	0.0689	(23)
C (17)	0.5802	(3)	0.5961	(3)	0.3984	(3)	0.0677	(22)
C (18)	0.9444	(3)	0.5569	(4)	0.3259	(4)	0.099	(3)
C (19)	0.6709	(3)	1.0924	(3)	0.3053	(3)	0.0692	(23)
O (20)	0.72614	(20)	1.05201	(22)	0.39333	(17)	0.0722	(16)
C (21)	0.8370	(3)	1.0015	(4)	0.3363	(3)	0.089	(3)
C (22)	0.8491	(4)	1.0239	(5)	0.2122	(3)	0.111	(4)
O (23)	0.70284	(22)	1.0159	(3)	0.17692	(19)	0.1011	(21)

the novel antagonists, 3 preparations were exposed to antagonist at different concentrations (1:5:25 ratio) for 50 min before a further U-46619 curve was obtained. A fourth untreated preparation served as a control. Dose ratios were obtained in 3 or 4 separate experiments, and pA_2 values were calculated for individual dose ratios and the regression of pA_2 on log (antagonist) determined. If the regression coefficient, r, was not statistically different from zero ($P = 0.05$), then the Schild equation for competitive antagonism was obeyed and the best estimate of the pA_2 was the mean value [38]. A slope of best fit for the Schild plot was also determined.

Compounds

U-46619 and 17-phenyl-ω-trinor-PGE2 were purchased from Cayman Chemicals, USA. Cicaprost was a gift from H Vorbruggen of Schering AG, Berlin, Germany.

X-ray crystallography

The crystal structures of **20** and **27** were determined from crystals grown as described. A suitable crystal of each compound was characterised by Weissenberg and precession camera photography before being transferred for data collection to a Seimens-Stoë AED-2 4-circle diffractometer fitted with a graphite monochromator. Unit cell dimensions were determined from a number of reflections measured at ± ω. Intensity control reflections were monitored throughout data collection and showed no significant trend in either case. Corrections for Lorenz and polarisation effects together with a semi-empirical absorption correction [39] were applied yielding data sets with 69% $F > 6.\sigma(F)$ and 96% $F > 4.\sigma(F)$ respectively.

Structure **20** was solved by Patterson and difference Fourier syntheses and refined using SHELX-76 [40]. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms added in their expected positions and refined riding on the atoms to which they were attached, the methyl group of the tosyl being refined as a rigid group. Atomic scattering factors were inlaid [40]. Table II summarises the data collection and refinement with table III giving the coordinates. Figure 1 shows the molecule in an ORTEP representation [41].

Structure **27** was solved by direct methods (SHELX-86) [42], which revealed all non-hydrogen atoms, and refined with SHELX-76. All non-hydrogens were treated anisotropically and all hydrogens added in their calculated positions were refined riding on the atoms to which they were attached. The methyl group of the tosyl group, as before, was treated as a rigid group. Table II summarises the data collection and refinement. Table IV contains coordinates. A diagram of the structure is given in figure 4.

The crystal structures reported here for **20** and **27** are well defined with all bond lengths and angles close to the expected values [43]. Comparing **20** with **27** showed similar *trans* dispositions of the ring substituents on C2 and C3. Both groups are equatorial to the chair conformation of the cyclohexane ring, O6 and C7 being on the same side of this ring as the C3 carbon. The torsion angles about O10–C11/S11 differed by ≈ 120° but despite this, the planes of the 2 phenyl rings were similar. On C3, the attached groups were distinct and so it was not surprising to find the torsion angle C3–O18/C19 decreasing from – 139.4° in **20** to – 67.8° in **27**.

Tables of selected bond lengths and angles derived from the crystallographic data using the program CALC [44] and lists of structure factors and anisotropic thermal parameters have been deposited with the Cambridge Crystallographic Data Centre, available from The British Library Document Supply Centre as Supplementary Publication No SU.

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