received epinephrine (3 μM) plus the phosphodiesterase inhibitor methylisobutylxanthine (10 μM). Test compounds were dissolved in Me_2SO or water to a concentration of 20 mM, and 40 μL was added to the buffer plus cells in the counting vials. The final compound concentration for routine screening was 200 μM (final concentration of Me_2SO = 1%).

The cells were incubated for 1 h at 37 °C under a 95:5 O_2/CO_2 atmosphere. The incubation was stopped by placing the vials in crushed ice. The cells and the medium were transferred to test tubes and centrifuged, and the cell layer was removed by aspiration. The aqueous phase was assayed for glycerol using the enzyme glycerol dehydrogenase.

The glycerol dehydrogenase assay for glycerol depends on the enzyme-catalyzed conversion of glycerol to glyceraldehyde and NAD to NADH. The assay can detect as little as 5–10 nmol of glycerol. The aqueous phase, following removal of the cells, usually contained about 50–80 nmol of glycerol/300 μL of assayed samples if no inhibitory activity was present. Samples from the control tubes (no agonist) usually contained 0–5 nmol of glycerol/300 μL of sample.

Registry No. 1, 20842-55-1; 2, 100926-71-4; 3, 100926-72-5; 4, 100926-73-6; 5, 20842-55-1; 6, 100926-71-4; 7, 100926-72-5; 8, 100926-76-9; 9, 59741-09-2; 10, 100926-77-0; 11, 99541-10-3; 12, 99541-11-4; 13, 104531-64-8; 14, 59741-07-0; 15, 100926-78-1; 16, 14628-09-2; 17, 14628-08-1; 18, 14628-13-8; 19, 100926-79-2; 20, 99541-00-1; 21, 99541-01-2; 22, 14577-73-2; 23, 100926-80-5; 24, 14628-11-6; 25, 100926-81-6; 26, 59741-06-9; 27, 99541-02-3; 28, 99541-03-4; 29, 6329-08-4; 30, 14577-80-1; 31, 20843-96-3; 32, 99541-04-5; 33, 99541-05-6; 34, 99541-14-7; 35, 83685-83-0; 36, 99541-15-8; 37, 99541-06-7; 38, 99541-07-8; 39, 100926-82-7; 40, 99541-08-9; 41, 99541-09-0; 42, 104531-65-9; 43, 28507-33-7; 44, 94242-00-9; 45, 94242-03-2; 4-$MeOC_6H_4NCO$, 5416-93-3; 2-$MeOC_6H_4NCO$, 700-87-8; 3-$MeOC_6H_4NCO$, 18908-07-1; 4-$EtOCOC_6H_4NCO$, 30806-83-8; 2-ClC_6H_4NCO, 3320-83-0; 2-$CH_3C_6H_4NCO$, 614-68-6; 2-$F_3CC_6H_4NCO$, 2285-12-3; 4-$MeOC_6H_4CH_2NCO$, 56651-60-6; 4-$MeOC_6H_4(CH_2)_2NCO$, 52634-59-0; (S)-$PhCH(CH_3)NCO$, 14649-03-7; (R)-$PhCH(CH_3)NCO$, 33375-06-3; 4-$MeOC_6H_4OH$, 150-76-5; 2-$MeOC_6H_4OH$, 90-05-1; 4-$ClCH_2CONHC_6H_4OMe$, 22303-36-2; 4-$MeOC_6H_4NH_2$, 104-94-9; $ClCH_2COCl$, 79-04-9; 4-$MeOC_6H_4CH_2COCl$, 4693-91-8; 4-$MeOC_6H_4COCl$, 100-07-2; 8-hydroxyquinoline, 148-24-3; 7-hydroxyquinoline, 580-20-1; 6-hydroxyquinoline, 580-16-5; 5-hydroxyquinoline, 578-67-6; 2,4-dimethoxyphenylisocyanate, 33904-03-9; 8-hydroxy-2-methylquinoline, 826-81-3; 8-aminoquinoline, 578-66-5; phosgene, 75-44-5; 8-quinoline carbamoyl chloride, 99541-17-0; 8-hydroxyquinoline-5-sulfonic acid triethylamine salt, 104531-67-1; 2-vanillin, 148-53-8; ethyl chloroacetate, 105-39-5; 7-methoxybenzofuran-2-carboxylic acid, 4790-79-8; 7-methoxybenzofuran, 7168-85-6; 7-hydroxybenzofuran, 4790-81-2; 2-aminoresorcinol, 3163-15-3; triethylorthoformate, 122-51-0; 4-hydroxybenzoxazole, 89590-22-7.

(5*Z*)-7-(2,2-Dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic Acid: A Specific Thromboxane A_2 Receptor Antagonist

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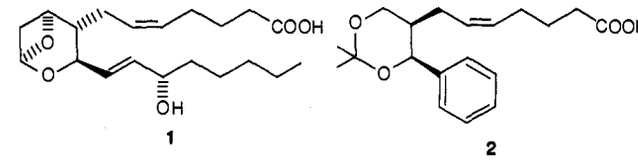
(5*Z*)-7-(2,2-Dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (**2**) was found to be a specific, competitive thromboxane A_2 receptor antagonist that acts at platelet, vascular, and pulmonary receptors. No antagonism was detected at receptors for prostacyclin, SRSA, norepinephrine, and serotonin. The synthesis of a series of analogues is described; activity at the thromboxane receptor was observed in cis-substituted compounds but not in their trans counterparts. Compound **2** inhibited the bronchoconstriction induced by a stable thromboxane mimetic in the anesthetized guinea pig.

The short-lived arachidonic acid metabolite thromboxane A_2[1] (TxA_2, **1**) has been shown to be a potent inducer of platelet aggregation[2] and of vascular[3] and pulmonary[4] smooth muscle contraction. The possibility that an abnormal production of TxA_2 may be involved in a number of disease processes is now well-recognized,[5] and in recent years considerable effort has been devoted to the development of new therapeutic agents that have as their mode of action either the inhibition of the enzyme thromboxane synthase[6] or the antagonism of TxA_2 at the receptor level.[7]

The latter approach is particularly attractive because it has been established that several prostanoids, including PGH_2 and PGD_2, exert an effect via the thromboxane receptor;[8] thus an agent that modifies TxA_2 receptor binding could also inhibit the potentially deleterious effect of a variety of prostanoids in certain tissues, e.g., the lung. It follows that a thromboxane antagonist could be of value in the treatment of asthma.



1 **2**

In an attempt to design a thromboxane antagonist, we decided to retain certain structural features of TxA_2, no-

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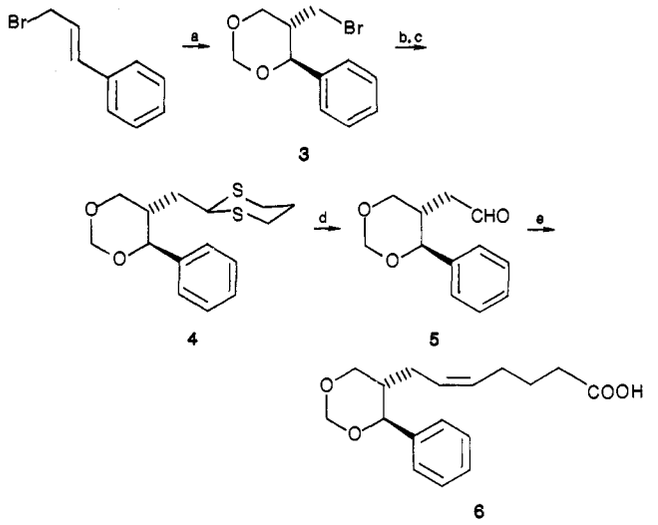
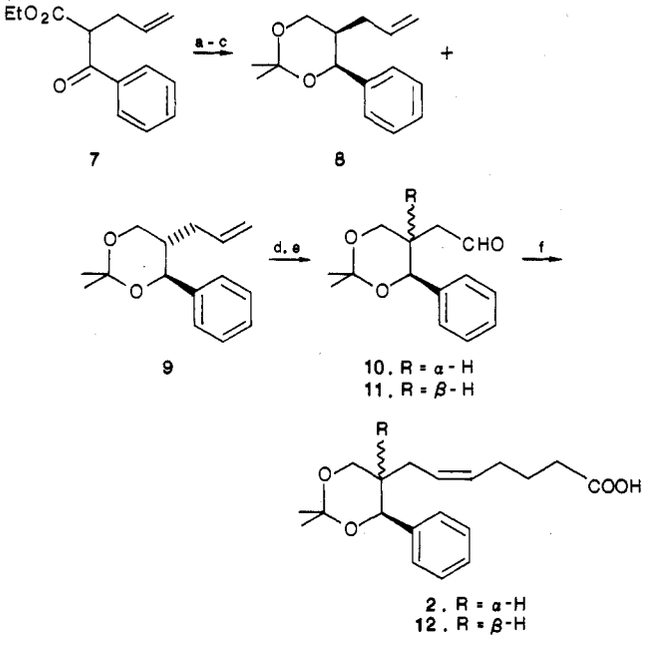
Scheme I[a]



[a] Reagents: a, HCHO, H_2SO_4, AcOH, 60 °C; b, NaI, CH_3COCH_3; c, lithium 1,3-dithiane; d, $(NH_4)_2Ce(NO_3)_6$; e, $Ph_3P{=}CH(CH_2)_3COO^-$.

Scheme II[a]



[a] Reagents: a, $LiAlH_4$; b, $(MeO)_2CMe_2$, H^+; c, separate isomers; d, O_3; e, Ph_3P; f, $Ph_3P{=}CH(CH_2)_3COO^-$.

tably the 1,3-dioxane ring and the α-heptenoic acid side chain, and to vary the nature and stereochemistry of the substituent formally corresponding to the ω-octenol side chain. In the course of these studies we discovered that (5*Z*)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (**2**) is a specific, competitive antagonist that blocks the action at the thromboxane receptor not only of TxA_2 and a thromboxane mimetic (U46619)[9] but also of certain other prostanoids. Compound **2** provides a useful prototype of a novel series of thromboxane antagonists with therapeutic potential in asthma and cardiovascular diseases. The chemical synthesis and biological properties of **2** and some close structural analogues are described below.

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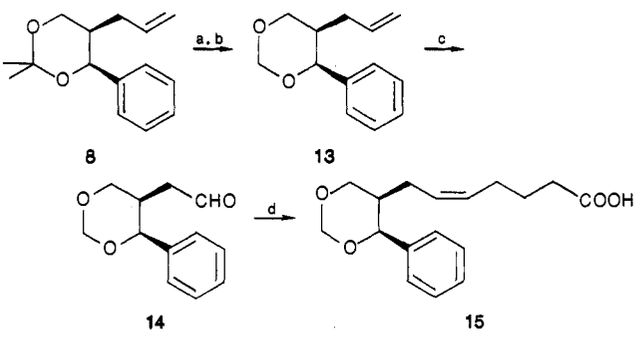
Scheme III[a]



[a] Reagents: a, H_2O, THF, HCl; b, NaH, CH_2Br_2; c, OsO_4, $NaIO_4$; d, $Ph_3P{=}CH(CH_2)_3COO^-$.

Table I

compound	pA_2 vs. U46619 (rabbit aorta)
2	6.30 ± 0.1 (n = 4)
6	<4.7
12	<4.7
15	6.30 ± 0.1 (n = 4)

Chemistry

Compound **2** and three structural analogues, **6**, **12**, and **15**, were prepared as shown in Schemes I–III. Thus the reaction of *trans*-cinnamyl bromide under Prins-type conditions[10] gave **3** which was converted by standard methods to **6** (Scheme I).

A more flexible approach that provides access to cis-substituted dioxanes as well as permitting substitution at C(2) of the dioxane ring is shown in Scheme II.

Reduction of **7** was performed with either zinc borohydride[11] followed by lithium aluminum hydride to give exclusively the *cis*-dioxane **8** or lithium aluminum hydride alone to give both **8** and **9** (55:45). Separation of these isomers by chromatography followed by ozonolytic cleavage of the alkene and Wittig olefination gave the desired dioxanes **2** and **12**.

Preparation of the fourth analogue, **15**, could be effected via conversion of intermediate **8** to **13** by using the procedure of Liptâk[12] et al. (Scheme III). Oxidative cleavage of **13** was performed with sodium periodate and osmium tetraoxide rather than ozone, in order to avoid potential problems arising from ozone insertion into the axial C(2)–H bond of the dioxane.[13]

Results and Discussion

Test compounds were evaluated for their ability to inhibit U46619[9]-induced contraction of isolated strips of rabbit thoracic aorta, and this ability was taken as a measure of thromboxane receptor antagonism.[14] Results are expressed as pA_2 values (Table I). It can be seen that inhibitory effect is shown by the two cis-substituted compounds, **2** and **15**, whereas the trans isomers are ineffective.

In order to define the character and specificity of the receptor blockade, the biological properties of **2** were ex-

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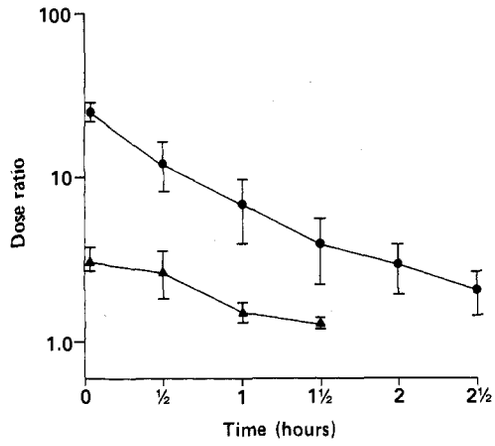

Figure 1. Effect of **2** 5 mg/kg iv ((●) $n = 4$) and 1 mg/kg iv ((▲) $n = 3$) on U46619-induced bronchoconstriction in the guinea pig.

amined in more detail: The TxA_2 antagonism was shown to be competitive (Schild[15] analysis, slope = 1.1, $n = 12$) and specific (serotonin- and norepinephrine-induced contractions of rabbit aorta were not affected at antagonist concentrations up to 2×10^{-5} M). Similar results were obtained on rat aorta (pA_2 vs. U46619 = 6.84 ± 0.03, $n = 4$; pA_2 vs. norepinephrine < 4.7, $n = 4$) and on the guinea pig tracheal chain (pA_2 vs. U46619 = 6.58 ± 0.04, $n = 4$; pA_2 vs. histamine < 4.7, $n = 4$). On human platelets compound **2** inhibited the aggregation induced by arachidonic acid ($K_B = 1.42 (\pm 0.42) \times 10^{-5}$, $n = 4$) and collagen ($K_B = 9.12 (\pm 2.88) \times 10^{-6}$, $n = 12$). However, on tissue preferentially sensitive to PGE_2 (guinea pig ileum)[8] the response to PGE_2 was not inhibited by prior administration of compound **2** ($pA_2 < 4.7$). Similarly, on tissue preferentially sensitive to $PGF_{2\alpha}$ (rat colon),[16] compound **2** did not attenuate the response to $PGF_{2\alpha}$ ($pA_2 < 4.7$). Although inactive against PGE_2 and $PGF_{2\alpha}$ in tissues that do not respond to TxA_2, compound **2** inhibited the contractile effect of these prostaglandins on rabbit aorta (PGE_2, $pA_2 = 5.17 \pm 0.12$, $n = 4$; $PGF_{2\alpha}$, $pA_2 = 5.79 \pm 0.12$, $n = 4$) and guinea pig trachea (PGE_2, $pA_2 = 4.98 \pm 0.05$, $n = 4$; $PGF_{2\alpha}$; $pA_2 = 4.95 \pm 0.1$, $n = 4$). Furthermore, the contractile effect of PGD_2 on rat aorta was also inhibited by compound **2** ($pA_2 = 5.71 \pm 0.19$, $n = 3$). The relaxant effect of PGE_2 on guinea pig trachea was not inhibited by **2** ($pA_2 < 4.7$, $n = 4$). These observations are consistent with the suggestion that there exist in certain tissues up to three types of prostanoid receptor: thromboxane- and PGE-sensitive systems mediating contraction and a PGE-sensitive system mediating relaxation.[17] Our results indicate that both contractile receptor types are present in rabbit aorta; Jones was unable to demonstrate this using EPO45, an alternative thromboxane antagonist.[17]

Other products and pathways of arachidonic acid metabolism were not affected by **2**; thus no inhibition of the cyclooxygenase or TxA_2 synthase enzymes was observed at concentrations of 50 μg/mL[18] and **2** did not antagonize the actions of crude SRSA on guinea pig ileum ($pA_2 < 4.7$). Furthermore **2**, at a final concentration of 1×10^{-4} M in human platelet-rich plasma did not modify PGI_2 inhibition of ADP-induced aggregation.

In vivo activity was demonstrated by using the anesthetised guinea pig pulmonary model of Konzett and Rossler,[19] in which a single dose of **2** (5 mg/kg iv) significantly inhibited the bronchoconstriction induced by U46619 for a period exceeding 2 h[20] (Figure 1).

Conclusions

Compound **2** is a specific, competitive TxA_2 receptor antagonist that acts at platelet, vascular, and pulmonary receptors. No antagonism was detected at receptors for prostacyclin, SRSA, norepinephrine, and serotonin. This type of agent may be therapeutically useful not only in diseases involving elevated TxA_2 levels but also in situations where increased production of other contractile prostanoids (e.g., PGD_2, $PGF_{2\alpha}$) occurs.

Experimental Section

All flash chromatography experiments were carried out with Merck Kieselgel (Art, 9385) under 4–6 psi of air pressure. Other chromatography was performed on Merck Kieselgel (Art. 7734). Melting points were obtained on a Büchi apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ on either a JEOL-FX90 Q spectrometer or where indicated (*) a Bruker AM20 machine. Mass measurements were made with an AEI MS902S spectrometer.

(4-Phenyl-1,3-dioxan-*trans*-5-yl)bromomethane (3). A stirred solution of paraformaldehyde (7.0 g) in 1,2-dichloroethane (30 mL) containing concentrated H_2SO_4 (2 mL) at 60 °C was treated with a solution of cinnamyl bromide (15.0 g, 0.076 mol) in CH_2ClCH_2Cl (30 mL), and the mixture was stirred at 60 °C for 3 h. The cooled reaction was poured into H_2O (200 mL) and this mixture was extracted with $CHCl_3$ (3 × 100 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to an oil. Flash column chromatography, eluting with toluene, gave (4-phenyl-1,3-dioxan-*trans*-5-yl) bromoethane (**3**) (5.4 g, 28%) as an oil: NMR * δ 2.15–2.40 (1 H, m), 2.9–3.2 (2 H, m), 3.70–3.85 (1 H, t, $J = 11.2$ Hz), 4.25–4.4 (1 H, dd, $J = 5.0$, 11.2 Hz), 4.5 (1 H, d, $J = 9.6$ Hz), 4.85 (1 H, d, $J = 6.6$ Hz), 5.2 (1 H, d, $J = 6.6$ Hz), 7.3–7.5 (5 H, m).

2-[(4-Phenyl-1,3-dioxan-*trans*-5-yl)methyl]-1,3-dithiane (4). A mixture of **3** (3.50 g, 0.014 mol), sodium iodide (2.5 g, 0.017 mol), and acetone (100 mL) was stirred at 25 °C for 15 h. The solvent was evaporated in vacuo and the residue was partitioned between H_2O (100 mL) and Et_2O (100 mL). The organic phase was washed sequentially with saturated $Na_2S_2O_3$ and saturated NaCl, dried, ($MgSO_4$), filtered, and concentrated in vacuo to give an oil (A, 4.0 g).

A −20 °C solution of 1,3-dithiane (2.0 g, 16.6 mmol) in THF (50 mL) was treated with *n*-butyllithium (10 mL, 1.6 M solution in hexane), and the mixture was stirred at −20 °C for 45 min. The solution was cooled to −70 °C and a solution of A (4.0 g) in THF (50 mL) was added over 10 min. The reaction mixture was allowed to warm to 25 °C and then stirred for a further 18 h. The solvent was evaporated in vacuo and the residue partitioned between Et_2O (3 × 100 mL) and H_2O (150 mL). The combined ethereal solutions were washed with saturated NaCl, dried, (Mg_2SO_4), filtered, and concentrated in vacuo to give an oil. Chromatography eluting with 40% Et_2O–petroleum ether (bp 60–80 °C) gave 2-[(4-phenyl-1,3-dioxan-*trans*-5-yl)methyl]-1,3-dithiane (**4**) (2.3 g, 57%) as a colorless oil, which solidified on standing: NMR * δ 1.2–2.1 (4 H, m), 2.3–2.8 (5 H, m), 3.4–3.6 (2 H, m), 4.15 (1 H, d, $J = 9.6$ Hz), 4.2–4.4 (1 H, dd, $J = 5.0$, 11.2 Hz), 4.8 (1 H, d, $J = 6.6$ Hz), 5.2 (1 H, d, $J = 6.6$ Hz), 7.3–7.5 (5 H, m).

(4-Phenyl-1,3-dioxan-*trans*-5-yl)acetaldehyde (5). A stirred solution of **4** (2.3 g, 7.8 mmol) in CH_3CN (80 mL) at 20 °C was treated with a solution of ceric ammonium nitrate (9.2 g, 16.7 mmol) in water (20 mL), and the mixture was stirred for 5 min. Water (100 mL) was added and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined extracts were washed

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with water (2 × 50 mL) and saturated brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo to an oil. Chromatography, eluting with toluene/ethyl acetate (19:1, v/v) gave (4-phenyl-1,3-dioxan-*trans*-5-yl)acetaldehyde (**5**) as a colorless oil (510 mg, 32%): NMR * δ 1.9–2.3 (2 H, m), 2.5–2.8 (1 H, m), 3.45–3.60 (1 H, t, J = 11.2 Hz), 4.2–4.4 (2 H, m), 4.85 (1 H, d, J = 6.6 Hz), 5.2 (1 H, d, J = 6.6 Hz), 7.25–7.50 (5 H, m), 9.4 (1 H, t, J = 1.6 Hz); mass spectrum, m/e 206.0931 ($C_{12}H_{14}O_3$ requires 206.0943). Anal. ($C_{12}H_{14}O_3$) C; H: calcd, 6.8; found, 7.3.

(5*Z*)-7-(4-Phenyl-1,3-dioxan-*trans*-5-yl)heptenoic Acid (6). A mixture of (4-carboxybutyl)triphenylphosphonium bromide (3.33 g, 7.5 mmol), potassium *tert*-butoxide (1.60 g, 14 mmol), and THF (70 mL) was stirred at 0 °C under argon for 1 h. A solution of **5** (500 mg, 2.4 mmol) in THF (5 mL) was added, and the reaction mixture was stirred for a further 3 h. H_2O (200 mL) was added, and the mixture was extracted with Et_2O (2 × 100 mL). The combined extracts were discarded, and the aqueous layer was acidified to pH 4–5 (2 N HCl). The acidified aqueous solution was extracted with Et_2O (3 × 100 mL), and the combined extracts were washed with saturated NaCl (100 mL), dried ($MgSO_4$), filtered, and concentrated to give an oil. Chromatography, eluting with toluene/ethyl acetate/acetic acid (80:20:2, v/v) gave (5*Z*)-7-(4-phenyl-1,3-dioxan-*trans*-5-yl)heptenoic acid (**6**) (510 mg, 73%) as a colorless oil: NMR δ 1.5–2.4 (9 H, m), 3.2–3.6 (1 H, t, J = 11.2 Hz), 4.0–4.4 (2 H, m), 4.7–4.8 (1 H, d, J = 6.6 Hz), 5.0–5.5 (3 H, m), 7.2–7.5 (5 H, m).

(4,5-*cis*)-5-Allyl-2,2-dimethyl-4-phenyl-1,3-dioxane (8) and (4,5-*trans*)-5-Allyl-2,2-dimethyl-4-phenyl-1,3-dioxane (9). A solution of ethyl 2-allyl-3-oxo-3-phenylpropionate (**7**) (10.0 g, 43 mmol) in THF (20 mL) was added over 5 min to a stirred suspension of $LiAlH_4$ (2.0 g, 53 mmol) in THF (130 mL) at −78 °C under argon. The mixture was allowed to warm to 25 °C and was stirred for a further 6 h. Excess reagent was destroyed by cautious addition of EtOAc (25 mL), and saturated NH_4Cl (100 mL) was added. The mixture was filtered and extracted with Et_2O (3 × 150 mL). The combined extracts were washed with saturated NaCl (100 mL), dried ($MgSO_4$), filtered, and concentrated to give an oil (10.0 g). The oil was dissolved in 2,2-dimethoxypropane (250 mL) and *p*-toluenesulfonic acid (25 mg) was added. The resulting solution was allowed to stand for 18 h and then concentrated in vacuo to give an oil. Chromatography, eluting with 50% toluene–hexane, gave, in order of elution, (4,5-*cis*)-5-allyl-2,2-dimethyl-4-phenyl-1,3-dioxane (**8**) (2.1 g, 21%) as a white solid [mp 41–43 °C; NMR δ 1.55 (6 H, s), 1.2–1.6 (3 H, m), 3.8–4.2 (2 H, m), 4.8–5.9 (3 H, m), 5.2 (1 H, d, J = 2.7 Hz), 7.3 (5 H, br s)] and (4,5-*trans*)-5-allyl-2,2-dimethyl-4-phenyl-1,3-dioxane (**9**) (1.8 g, 18%) as an oil, which solidified on standing [mp 31–34 °C; NMR δ 1.4 (3 H, s), 1.5 (3 H, s), 1.3–2.2 (3 H, m), 3.5–4.0 (2 H, m), 4.5 (H, d, J = 10 Hz), 4.7–5.8 (3 H, m), 7.3 (5 H, br s)].

(2,2-Dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde (10). Ozone was bubbled through a solution of **8** (2.1 g, 9.0 mmol) in CH_2Cl_2 (200 mL) at −78 °C until a permanent blue coloration developed. The solution was flushed with argon until colorless. A solution of triphenylphosphine (2.5 g, 9.5 mmol) in CH_2Cl_2 (40 mL) was added, and the mixture was allowed to warm to 25 °C. The solvent was evaporated in vacuo, and the residual gum was purified by chromatography, eluting with 5% EtOAc–$CHCl_3$, to give (2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde (**10**) (2.0 g, 24%) as a white solid: mp 67–69 °C; NMR δ 1.55 (6 H, s), 2.0–3.1 (3 H, m), 3.7–4.4 (2 H, m), 5.2 (1 H, d, J = 2.0 Hz), 7.3 (5 H, br s).

(5*Z*)-7-(2,2-Dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic Acid (2). By the procedure used for **6**, compound **10** (2.0 g, 8.5 mmol) gave (5*Z*)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (**2**) (1.8 g, 66%) as an oil, which solidified on standing: mp 76–78 °C; NMR δ 1.55 (6 H, s), 1.3–2.6 (9 H, m), 3.7–4.3 (2 H, m), 5.1–5.5 (3 H, m), 7.3 (5 H, br s), 9.59 (1 H, s).

(2,2-Dimethyl-4-phenyl-1,3-dioxan-*trans*-5-yl)acetaldehyde (11). By the procedure used for **10**, compound **9** (2.0 g, 8.6 mmol) gave (2,2-dimethyl-4-phenyl-1,3-dioxan-*trans*-5-yl)acetaldehyde (**11**) (1.8 g, 89%) as an oil: NMR δ 1.5 (3 H, s), 1.6 (3 H, s), 1.9–3.0 (3 H, m), 3.7–4.2 (2 H, m), 4.55–4.65 (1 H, d, J = 10.0 Hz), 7.1–7.5 (5 H, m), 9.4 (1 H, t, J = 1.6 Hz).

(5*Z*)-7-(2,2-Dimethyl-4-phenyl-1,3-dioxan-*trans*-5-yl)heptenoic Acid (12). By the procedure used for **6**, compound **11** (1.8 g, 7.7 mmol) gave (5*Z*)-7-(2,2-dimethyl-4-phenyl-1,3-dioxan-*trans*-5-yl)heptenoic acid (**12**) (1.7 g, 69%) as an oil: NMR δ 1.4 (3 H, s), 1.5 (3 H, s), 1.3–2.4 (9 H, m), 3.4–4.1 (2 H, m), 4.40–4.55 (1 H, d, J = 9.6 Hz), 5.0–5.5 (2 H, m) 7.1–7.5 (5 H, m), 9.9–10.4 (1 H, br s).

(4,5-*cis*)-5-Allyl-4-phenyl-1,3-dioxane (13). A solution of **8** (10.0 g, 43 mmol) in THF–H_2O (4:1, 125 mL) was treated with dilute HCl (2 N, 1 mL) and heated at 70 °C for 4 h. The solvent was evaporated in vacuo and the residue partitioned between H_2O (100 mL) and EtOAc (100 mL), dried, ($MgSO_4$), filtered, and concentrated to give an oil. The oil was purified by chromatography, eluting with 50% EtOAc–hexane, to give an oil (B, 6.6 g).

A stirred mixture containing B (6.5 g, 34 mmol), powdered KOH (17.5 g, 0.31 mol), and Me_2SO (100 mL) was treated with CH_2Br_2 (12.0 g, 69 mmol) under argon, and stirring was continued for 3 h. Water (200 mL) was added and the mixture was extracted with hexane (3 × 200 mL). The combined extracts were washed sequentially with H_2O (2 × 100 mL) and saturated NaCl (100 mL), dried ($MgSO_4$), filtered, and concentrated to give an oil. The oil was purified by chromatography, eluting with 10% EtOAc–hexane, to give (4,5-*cis*)-5-allyl-4-phenyl-1,3-dioxane (**13**) (1.6 g, 18%) as a colorless oil: NMR * δ 2.0–2.5 (2 H, m), 2.7–3.0 (1 H, m), 3.9–4.3 (2 H, m), 4.90 (1 H, d, J = 6.6 Hz), 4.95 (1 H, br s), 5.2 (1 H, d, J = 6.6 Hz), 7.1–7.5 (5 H, m).

(4-Phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde (14). A solution of **13** (0.9 g, 4.4 mmol) in *tert*-butyl alcohol (10 mL) was added to a solution containing $NaIO_4$ (2.2 g, 10 mmol), H_2O (15 mL), *tert*-butyl alcohol (60 mL), and OsO_4 (10 mg, 0.04 mmol). The mixture was stirred for 4 h. Water (200 mL) was added to dissolve the precipitate and the aqueous solution was extracted with hexane (3 × 150 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to give an oil. The oil was purified by chromatography, eluting with 5% EtOAc–$CHCl_3$, to give (4-phenyl-1,3-dioxan-*cis*-5-yl)acetaldehyde (**14**) (343 mg, 38%) as a colorless oil: NMR δ 2.1–3.2 (3 H, m), 4.1 (2 H, m), 4.9–5.4 (3 H, m), 7.3 (5 H, br s), 9.6 (1 H, br s); mass spectrum, m/e 206.0937 ($C_{12}H_{14}O_3$ requires 206.0943). Anal. ($C_{12}H_{14}O_3$) H; C: calcd, 69.9; found, 69.1.

(5*Z*)-7-(4-Phenyl-1,3-dioxan-*cis*-5-yl)heptenoic Acid (15). By the procedure used for **6**, compound **14** (320 mg, 1.5 mmol) gave (5*Z*)-7-(4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (**15**) (262 mg, 58%) as a colorless oil: NMR δ 1.5–2.6 (9 H, m), 3.7–4.3 (2 H, m), 4.8–5.6 (5 H, m), 7.3 (5 H, br s).

Registry No. **2**, 104693-32-5; **3**, 104693-33-6; **4**, 104693-34-7; **5**, 104693-35-8; **6**, 104693-36-9; **7**, 63202-75-5; **7** (diol), 89424-76-0; **8**, 104693-37-0; **9**, 104693-38-1; **10**, 104693-39-2; **11**, 104693-40-5; **12**, 104693-41-6; **13**, 104693-42-7; **14**, 104693-43-8; **15**, 104693-44-9; (A), 104693-45-0; (B), 98289-97-5; cinnamyl bromide, 4392-24-9; 1,3-dithiane, 505-23-7; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6.