A Novel Approach to Dual-Acting Thromboxane Receptor Antagonist/Synthase Inhibitors Based on the Link of 1,3-Dioxane–Thromboxane Receptor Antagonists and –Thromboxane Synthase Inhibitors

Norman Ackerley, Andrew G. Brewster, George R. Brown,* David S. Clarke, Alan J. Foubister, Stephen J. Griffin, Julian A. Hudson, Michael J. Smithers, and Paul R. O. Whittamore

Cardiovascular and Metabolism Department, ZENECA Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.

Received January 10, 1995®

A new class of dual-acting racemic thromboxane receptor antagonist/thromboxane synthase inhibitors is reported, based on the novel approach of linking the known thromboxane synthase inhibitors (TXSI) dazoxiben (**2**) or isbogrel (**11**) (separately) to thromboxane receptor antagonists (TXRA) from the 1,3-dioxane series, such as ICI 192605 (**10**). Dual activity was observed *in vitro* with inhibition of human microsomal thromboxane synthase in the range IC_{50} = 0.01–1.0 μM and receptor antagonist activity by inhibition of U46619-induced human platelet aggregation in the range pA_2 = 5.5–7.0. The *in vitro* results also showed that very large groups could be tolerated at the selected substitution positions of the TXRA and TXSI components. Oral activity was observed in *ex vivo* tests in both rats and dogs at a dose of 10 mg/kg. Thus, (*E*)-7-[4-[[4-[(2*SR*,4*SR*,5*RS*)-5-[(*Z*)-5-carboxypent-2-enyl]-4-(2-hydroxyphenyl)-1,3-dioxan-2-yl]-benzyl]oxy]phenyl]-7-(3-pyridyl)hept-6-enoic acid (**110**) was both an antagonist (pA_2 = 6.7) and a synthase inhibitor (IC_{50} = 0.02 μM). On oral dosing (10 mg/kg) to rats and dogs, **110** showed significant TXRA activity [concentration ratio >64 (rat, 3 h) and >59 ± 11.3 (dog, 2 h) *vs ex vivo* U46619-induced platelet aggregation]. Inhibition of thromboxane synthase at the respective time points in these experiments was 81 ± 4.4% (rat) and 69 ± 4.8% (dog).

Arachidonic acid is converted by the enzyme cyclooxygenase to the unstable cyclic endoperoxide PGH_2, which in turn acts as the precursor to a further series of metabolites displaying a variety of biological properties.[1] In particular, thromboxane A_2 (TXA_2) is a potent vasoconstrictor and platelet aggregating agent, whereas prostacyclin (PGI_2) behaves as a vasodilator and platelet antiaggregatory agent. The recognition that PGH_2 is also an agonist at the TXA_2 receptor led to the hypothesis[2] that a combined TXA_2 receptor antagonist (TXRA) and thromboxane synthase inhibitor (TXSI) compound might have beneficial effects in thrombotic disease. Thus while the receptor actions of both TXA_2 and PGH_2 would be blocked by the receptor antagonist component, the inhibition of thromboxane synthase may additionally lead to an increased amount of PGH_2 and permit redirection of PGH_2 to beneficial PGI_2. Work[3] with a combination of the TXRA sulotroban (**1**; Chart 1) and the TXSI dazoxiben (**2**) supports this view in both animals and human volunteers, but a single chemical entity possessing both properties would be much more attractive for drug development. Two compounds, ridogrel (**3**) and picotamide (**4**), have been claimed[4] to show dual activity, but neither compound expresses both activities potently *in vitro*. Several analogues (**5**–**7**) of **1** have been reported[5,6] which possess both TXRA and TXSI properties, and compounds (**8** and **9**) that more closely resemble prostaglandin structures have also been described.[7] Recently structural variation of the TXSI **3** has afforded dual-acting compounds.[8] Reviews[9,10] of dual-acting TXA_2 receptor antagonist/synthase inhibitors show that in general the design of these agents has been based on structural modification of one of the two potential component structures (TXRA or TXSI), so that known SAR features of the other component may be incorporated. By contrast we have examined the feasibility of a novel approach to the design of these dual-acting agents, namely, the covalent linking of known TXSI and TXRA compounds. In order for this approach to lead to dual-acting compounds, a number of issues have to be considered. Thus, the linked compounds have to be able to act separately at both the enzyme and receptor sites without preventing inhibitor or antagonist effects at the other site; in addition, in *in vivo* situations the compound has to have access to the receptor site on the cell surface and be able to cross the cell membrane to reach the intracellular enzyme site; finally, it is desirable that the dual-acting compounds exhibit conventional pharmacokinetic parameters, such as oral availability and duration of pharmacological action. These issues were addressed in the choice of the TXRA and TXSI components and subsequently by analogue synthesis, leading to the variation of linking positions and the nature and length of the tether groups used.

In this paper we describe the design, synthesis, and pharmacology of dual-acting TXRA/TXSI compounds by linking the previously reported[11] 1,3-dioxane series of TXRA compounds to known TXSI compounds, via covalently "tethered" alkyl- and aryl-containing fragments.

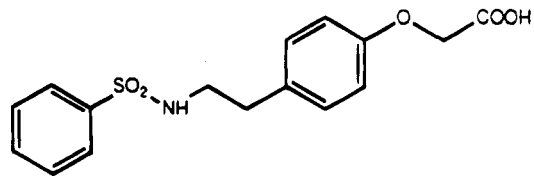
Design of TXRA/TXSI Compounds

In order to formulate a strategy for linking known TXSI compounds to 1,3-dioxane-based TXRA compounds, it was first necessary to consider the structural requirements for biological activity within each area independently.

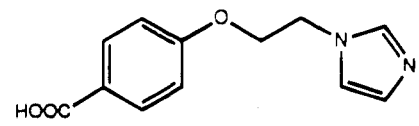
® Abstract published in *Advance ACS Abstracts,* April 15, 1995.

0022-2623/95/1838-1608$09.00/0

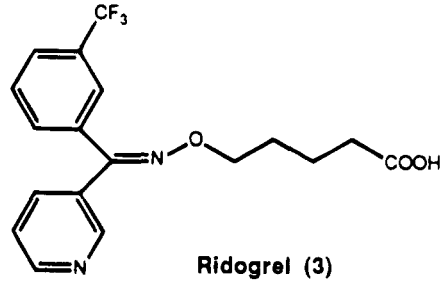
Chart 1



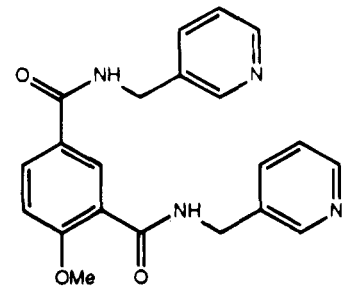
Sulotroban (1)



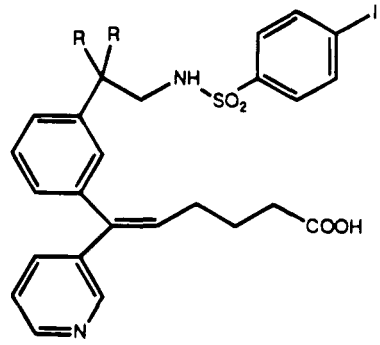
Dazoxiben (2)



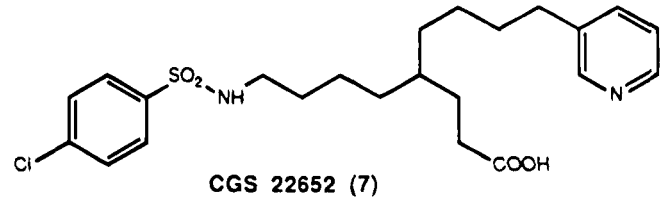
Ridogrel (3)



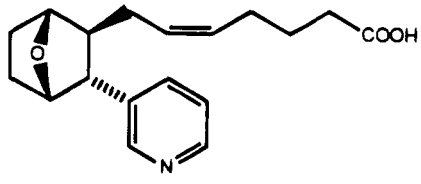
Picotamide (4)



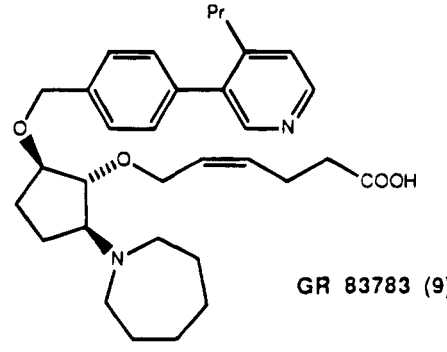
R=H GR 85305 (5)
R=Me GR 108774 (6)



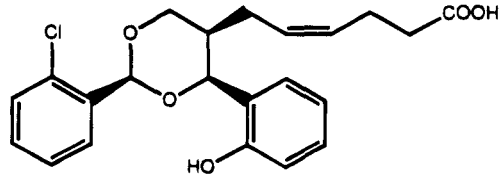
CGS 22652 (7)



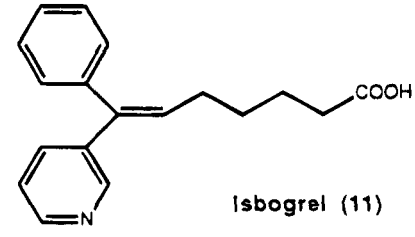
(8)



GR 83783 (9)



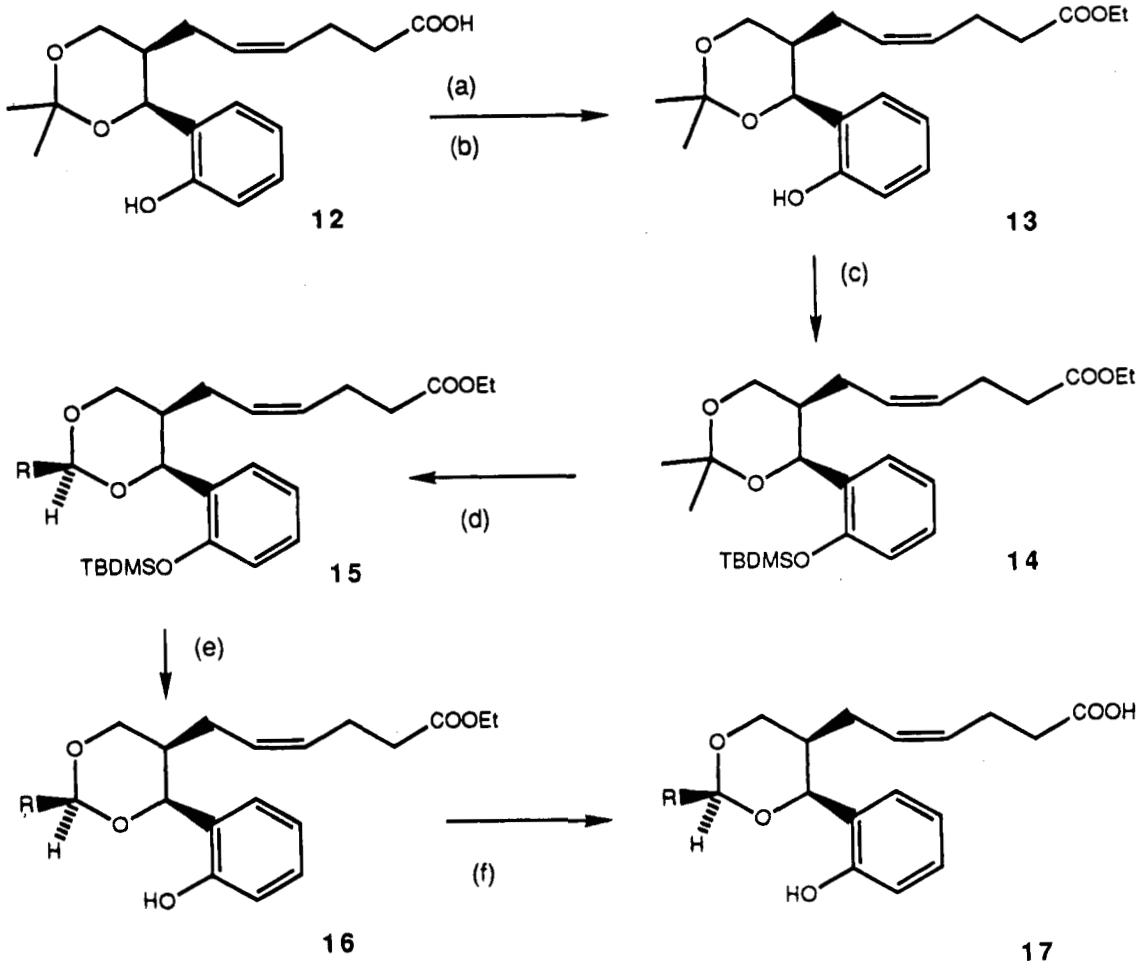
ICI 192605 (10)



Isbogrel (11)

The previously reported[11] orally active compound ICI 192605 (**10**) is a very potent example of a 1,3-dioxane-containing TXRA compound, and it had been demonstrated[12] that a relatively wide range of substituents could be tolerated on the phenyl ring at C2 of the dioxane ring without adversely affecting TXRA activity. It was therefore decided that the most promising link position for the TXSI fragment to the 1,3-dioxane–TXRA compound would be through the C2-position of the dioxane ring. An additional attraction of this

Scheme 1. General Synthetic Method[a]



[a] (a) $KHCO_3$, aqueous EtOH; (b) EtI, DMPU; (c) TBDMSCl, imidazole; (d) *p*-TSA, RCHO; (e) TBAF; (f) NaOH, H_2O.

approach was that variation of the C2 substituent could be readily accomplished chemically *via* acid-catalyzed acetal exchange reactions.

When considering the choice of TXSI, it was known[13] that potent and selective TXSI compounds generally contain a carboxylic acid group and either an imidazole (e.g., **2**) or a pyridine ring (e.g., **11**). Additionally it has been suggested that the nitrogen atom of the heterocycle binds to a haem iron atom in the enzyme.[13] In selecting the best way to join the TXSI element to the 1,3-dioxane–TXRA, it was noted that published evidence[14] suggested that increased steric hindrance near to the haem-ligating nitrogen atom of the heterocycle resulted in a decrease in TXSI potency for a wide range of TXSI series. However, it was not considered possible to predict the extent to which the proximity of the 1,3-dioxane fragment to either the heterocycle or to the carboxylic acid of the TXSI would be deleterious. It was therefore decided to initially join the 1,3-dioxane to the TXSI at a range of positions, in order to define an optimum linking position. As representative examples of the two main classes of TXSI, we chose the clinically tested compounds dazoxiben (**2**) and isbogrel (**11**), which contain imidazole and pyridine rings, respectively.

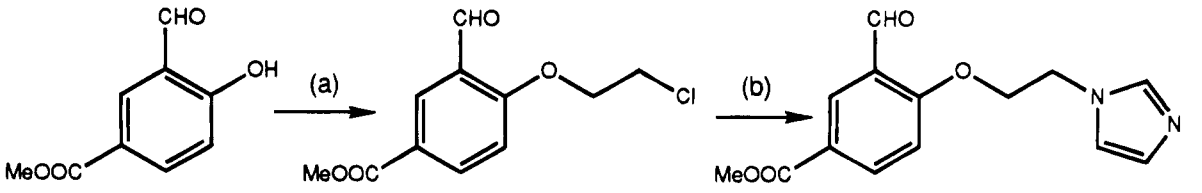
In the first instance, compounds were prepared as the more readily accessible racemates, although a true dual-acting TXRA/TXSI compound should display both activities in a single enantiomer.

Chemistry

Compounds with a substituted 1,3-dioxane linked to dazoxiben (**2**) or isbogrel (**11**), which are described in Tables 2–4, were all prepared by the general method in Scheme 1. Thus the TXSI carboxyl group was protected as an alkyl ester and a tether group bearing a terminal aldehyde group attached. This aldehyde was then reacted in an acetal exchange reaction in the presence of *p*-toluenesulfonic acid with the protected *tert*-butyldimethylsilyldioxane ester **14**. (**14** was prepared from the acid **12**[11] by alkylation with ethyl iodide to give **13** and then reaction with *tert*-butyldimethylsilyl chloride.) This gave a protected target compound **15** with the thermodynamically favored cis stereochemistry for the 2-substituent in the 1,3-dioxane ring, for which there is precedent[11] supported by X-ray crystal structure evidence,[15] trans material was not detected (2,4-substituent interaction in the 1,3-dioxane ring minimized). The silyl protective group was removed by tetra-*n*-butylammonium fluoride (TBAF) to give a phenol **16**, and aqueous base treatment removed both of the ester groups to give the tabulated products **17**. The various aldehyde-tethered TXSIs derived from the standard synthase inhibitor compounds (**2** and **11**) were prepared as follows, and characteristic data on the final compounds are reported in Table 5.

Reaction of 3-(methoxycarbonyl)-6-hydroxybenzaldehyde (**18**) and 2-chloroethyl *p*-toluenesulfonate (**19**)

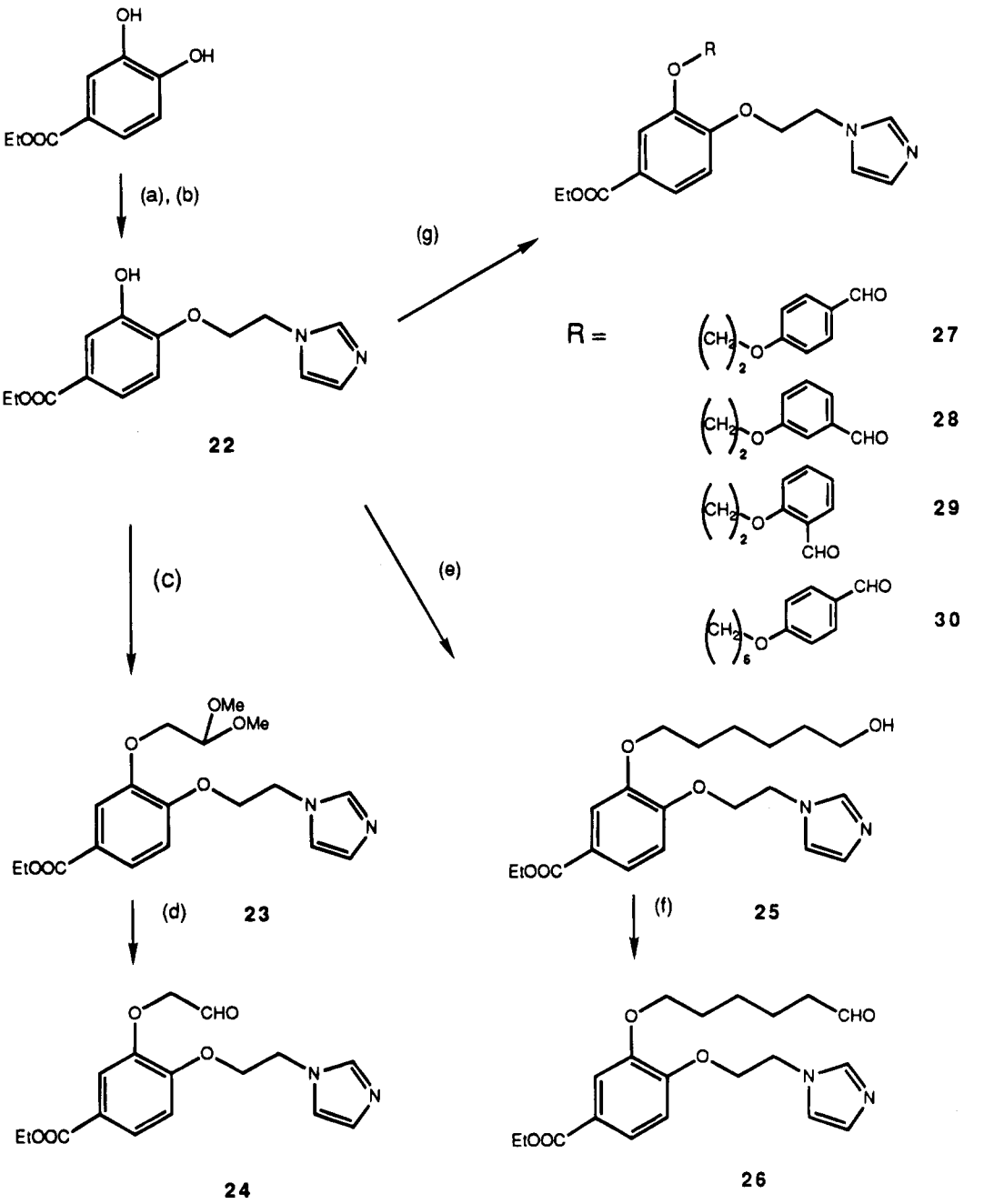
Scheme 2[a]



18 **20** **21**

[a] (a) K_2CO_3, *p*-TosOCH_2CH_2Cl (**19**), MeCOEt; (b) NaH, imidazole, DMF.

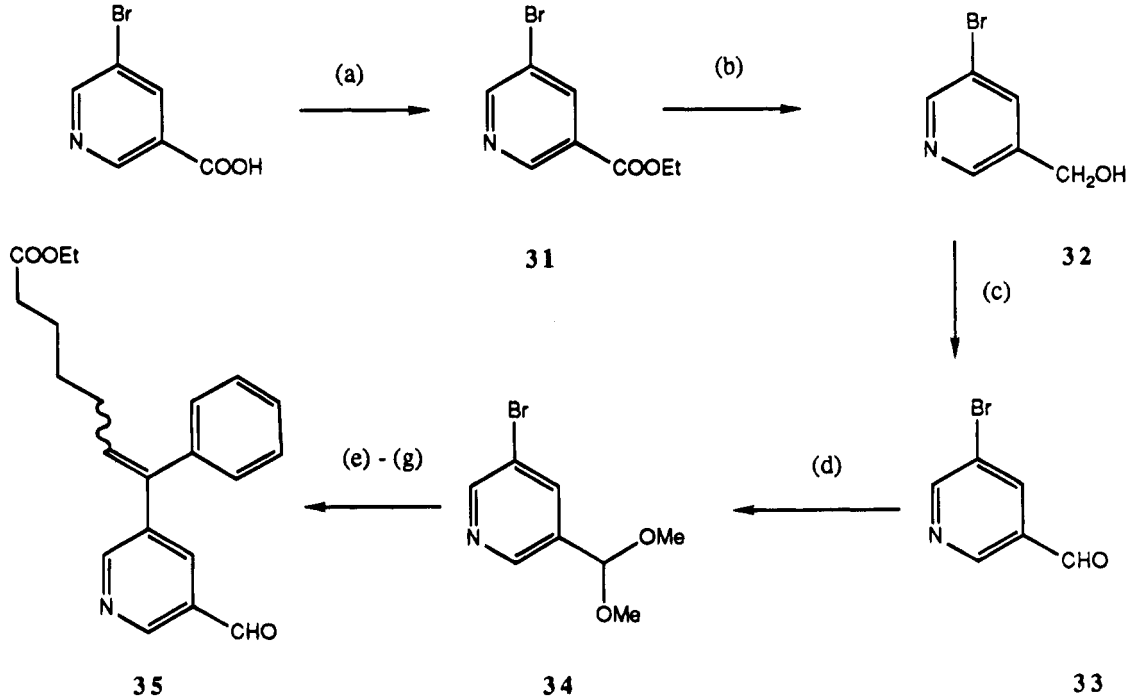
Scheme 3[a]



[a] (a) K_2CO_3, *p*-TosOCH_2CH_2Cl, MeCOEt; (b) NaH, imidazole, DMF; (c) K_2CO_3, $BrCH_2CH(OMe)_2$, MeCOEt; (d) 1 M HCl, aqueous THF; (e) K_2CO_3, HO$(CH_2)_6Cl$, MeCOEt; (f) $(COCl)_2$, DMSO, −78 °C; NEt_3; (g) NaH, DMF, *p*-TosO$(CH_2)_6OC_6H_4CHO$ or Cl$(CH_2)_2OC_6H_4CHO$.

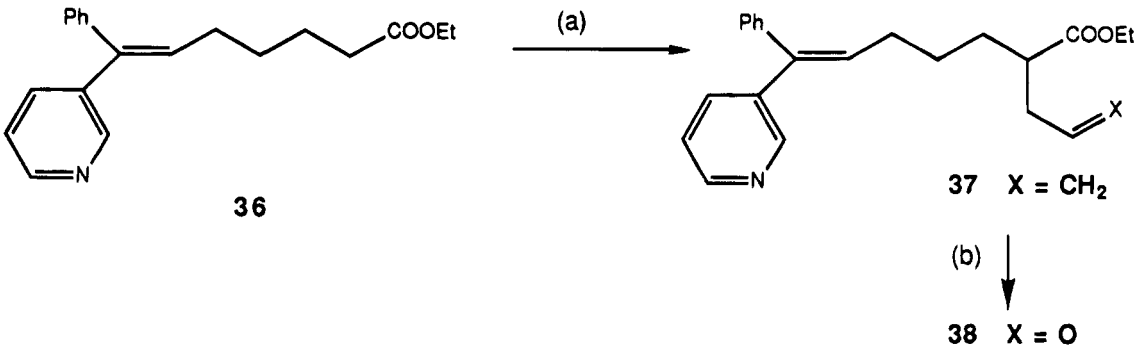
(Scheme 2), afforded the (chloroethoxy)benzaldehyde **20**, which subsequently was converted to **21** with imidazole in the presence of NaH. Scheme 3, elaborates the synthesis of dazoxiben-derived aldehydes **24** and **26**–**30**. Ethyl 3,4-dihydroxybenzoate and 2-chloroethyl *p*-toluenesulfonate gave a chloroethyl derivative which reacted *in situ* with imidazole, in the presence of NaH to give only the phenol **22** (the assigned structure was

Scheme 4[a]



[a] (a) *p*-TSA, EtOH; (b) $NaBH_4$, MeOH; (c) PCC, CH_2Cl_2; (d) MeOH, $(MeO)_3CH$, *p*-TSA; (e) *n*-BuLi, THF, −78 °C; $PhCON(Me)_2$; (f) $Br^-Ph_3P^+(CH_2)_5COOH$, KO^tBu, THF; (g) HCl, aqueous EtOH.

Scheme 5[a]



[a] (a) LDA, THF, −78 °C; $BrCH_2CH{=}CH_2$; (b) OsO_4, $NaIO_4$

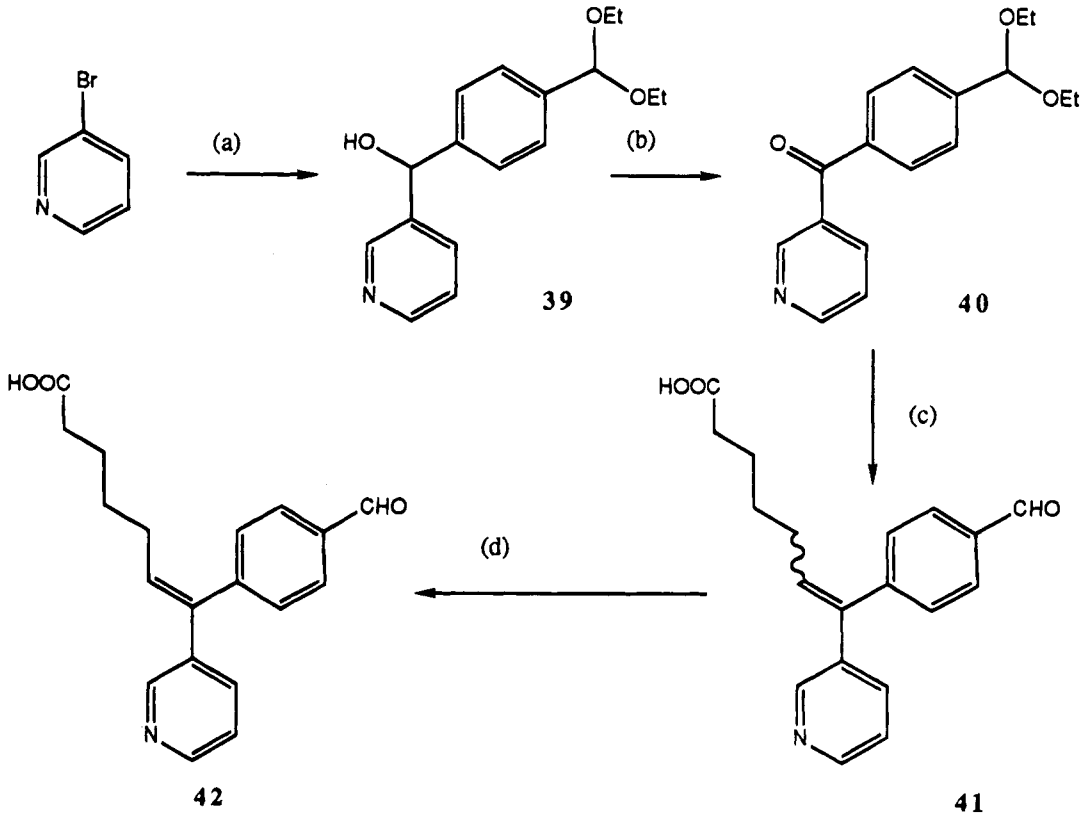
consistent with the ^1H- and ^{13}C-NMR spectra and precedent[16]). Alkylation of **22** with 1-bromo-2,2-dimethoxyethane in the presence of K_2CO_3 gave **23**, which was hydrolyzed with HCl to the aldehyde **24**. Similar alkylation of **22** with 6-chlorohexanol afforded an alcohol intermediate **25** which upon Swern oxidation afforded the aldehyde **26**. Four aldehydes (**27**–**30**) were prepared by the direct alkylation of **22** with appropriate halo- or (tosyloxy)alkoxybenzaldehydes in the presence of NaH in DMF.

Reduction of the ester **31** (Scheme 4) with $NaBH_4$/MeOH gave the alcohol **32** which was oxidized with PCC/CH_2Cl_2 to 3-bromopyridine-5-carboxaldehyde (**33**). The aldehyde was protected as the acetal **34** with trimethyl orthoformate. Reaction with *N*,*N*-dimethylbenzamide in the presence of ^{n}BuLi/THF followed by stereoselective Wittig reaction (KO^tBu) and deprotection with HCl gave the aldehyde **35**.

The ethyl ester (**36**)[13] of isbogrel (**11**) (Scheme 5) was alkylated with allyl bromide in the presence of LDA/THF to give **37**, which was selectively oxidized to the aldehyde **38** with $NaIO_4/OsO_4$. Aldehyde **42** was prepared as shown in Scheme 6 by reaction of 3-bromopyridine, terephthaldehyde mono(diethyl acetal), and ^{n}BuLi in THF. Swern oxidation gave **40**, which after Wittig reaction using KO^tBu/THF gave a mixture of aldehydes **41** which were separated by HPLC to give the (*E*)-aldehyde **42**. The *E*-stereochemistry was assigned for **42** (and related compounds, e.g., **54**) by comparison of the ^1H-NMR spectrum with published[13] data on isbogrel analogues.

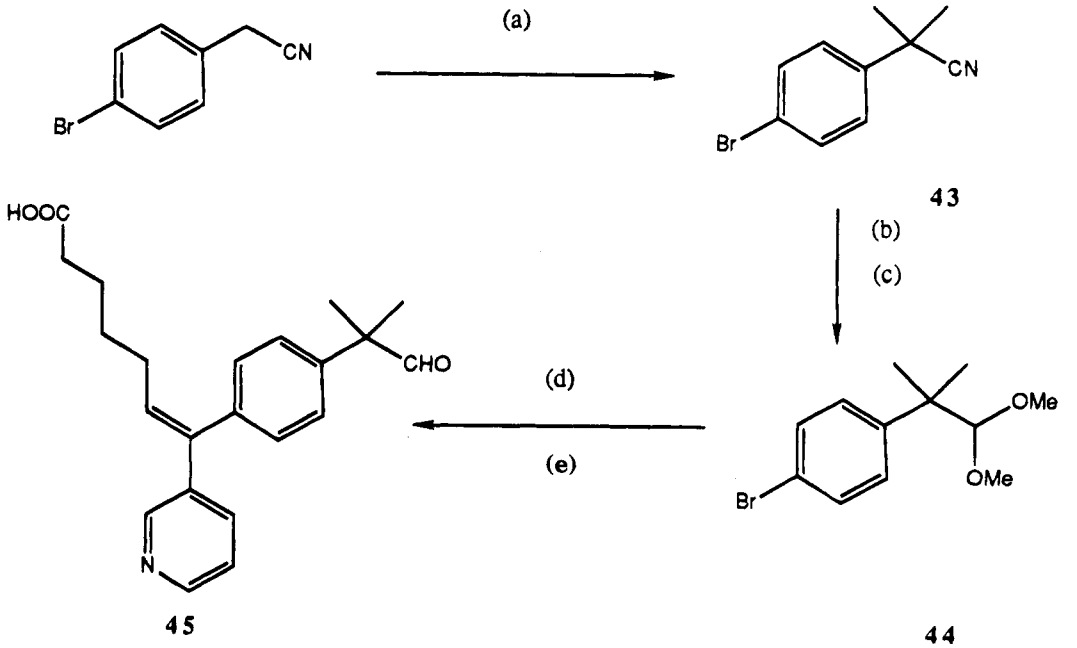
Scheme 7 shows the alkylation of (4-bromophenyl)-acetonitrile to give **43**, which was reduced with DIBAL at −20 °C and the resulting aldehyde converted to the acetal **44**. Reaction with *N*,*N*-diethylpyridine-3-carboxamide in the presence of ^{n}BuLi/THF at −70 °C, followed by Wittig reaction, led to the aldehyde **45**. The 2-naphthyl derivative **100** (Table 4) was synthesized (Scheme 8) by Swern oxidation of **46**, deprotection of **47**, and protection of the aldehyde **48** as the cyclic acetal **49**. A further Swern oxidation afforded the aldehyde **50** which was reacted with 3-bromopyridine in the presence of ^{n}BuLi to give the alcohol **51**. Swern oxida-

Scheme 6[a]



[a] (a) *n*-BuLi, THF, −78 °C; $OHCC_6H_4CH(OEt)_2$; (b) $(COCl)_2$, DMSO, −78 °C; NEt_3; (c) $Br^-Ph_3P^+(CH_2)_5COOH$, KO^{t}Bu, THF; (d) HPLC.

Scheme 7[a]

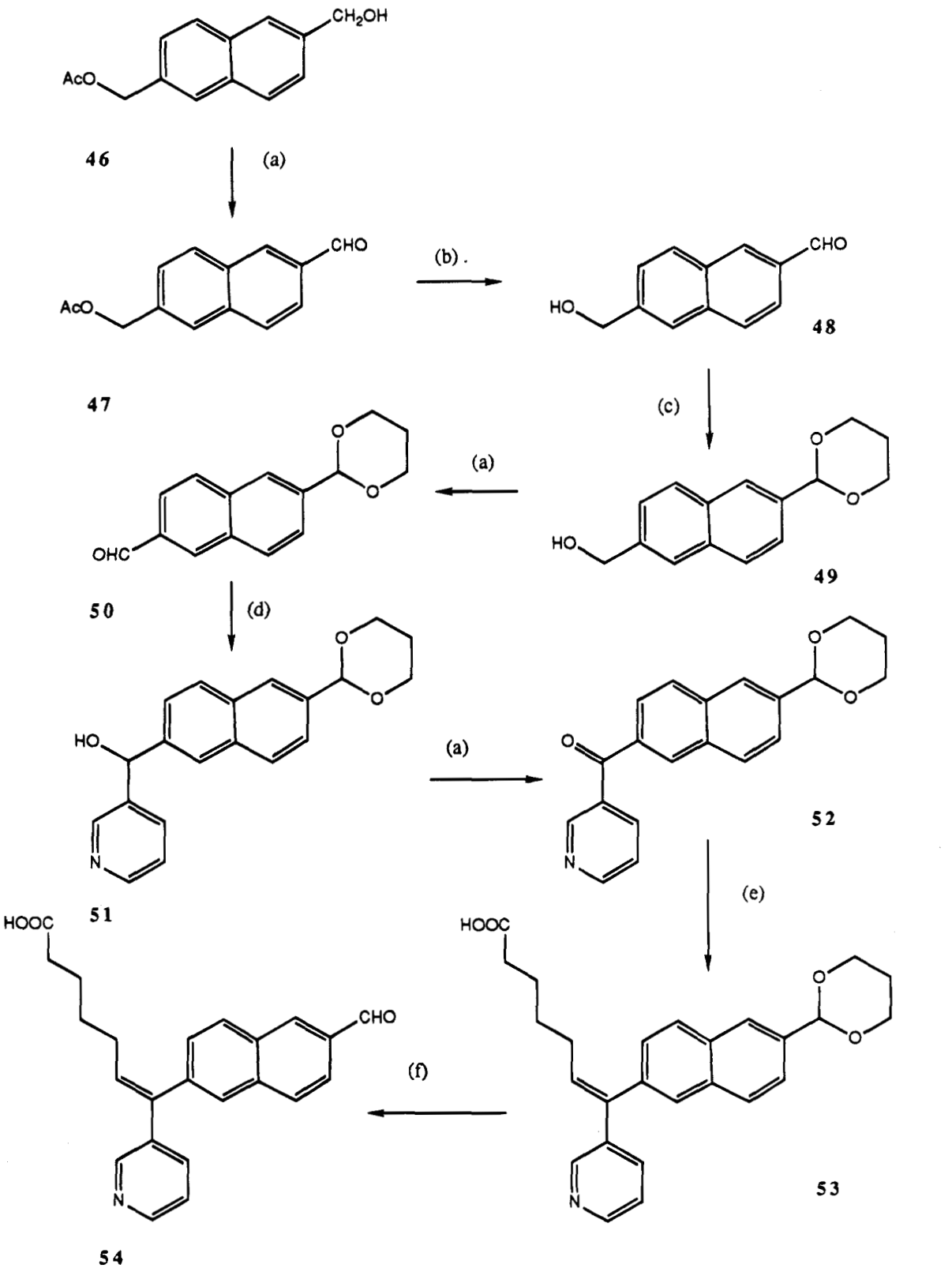


[a] (a) NaH, MeI, DMF; (b) DIBAL, THF/Tol, −20 °C; (c) MeOH, *p*-TosOH, $HC(OMe)_3$; (d) *n*-BuLi, THF, −78 °C; 3-Me(MeO)NCO-py, −78 °C to 0 °C; (e) $Br^-Ph_3P^+(CH_2)_5COOH$, KO^{t}Bu, THF

tion (**52**), Wittig reaction with KO^{t}Bu (**53**), and acetal hydrolysis with HCl gave the intermediate aldehyde **54**.

Alkyl-linked compounds in Table 4 were prepared as shown in Scheme 9 from the alcohol **55** derived from 3-lithiopyridine and *p*-anisaldehyde (for the general procedure, see **51**). Swern oxidation (**56**; for the general procedure, see **50**) followed by a Wittig reaction gave an *E*/*Z* mixture of heptenoic acids (**57**). The purified *E* isomer was demethylated with HBr and esterified with $SOCl_2$/EtOH to the phenol **58**. Reaction of **58** with an appropriate alkyl halide RX and NaH gave intermediates **59**–**62**, which were either hydrolyzed with HCl or hydrolyzed and oxidized prior to acetal exchange with the dioxane **14**. The alkylating agents RX (**64**–**66**) were prepared as shown by protection of alkanols, with excess of dihydropyran and *p*-toluenesulfonic acid.

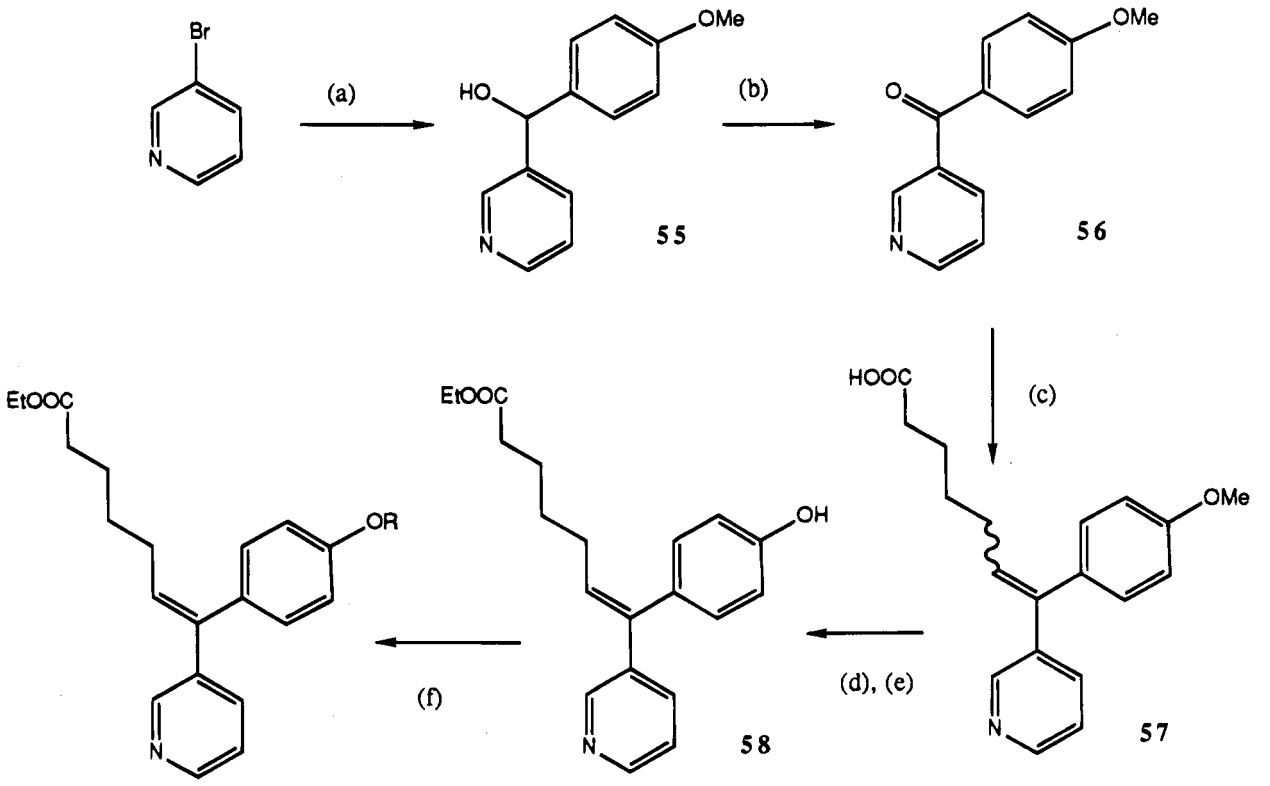
Scheme 8[a]

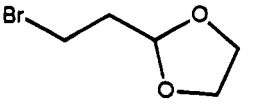


[a] (a) $(COCl)_2$, DMSO, −78 °C; NEt_3; (b) K_2CO_3, MeOH; (c) $HO(CH_2)_3OH$, *p*-TSA, Tol; (d) 3-Br-py + *n*-BuLi, THF, −78 °C; (e) $Br^-Ph_3P^+(CH_2)_5COOH$, KO^tBu, THF; (f) HCl(aq).

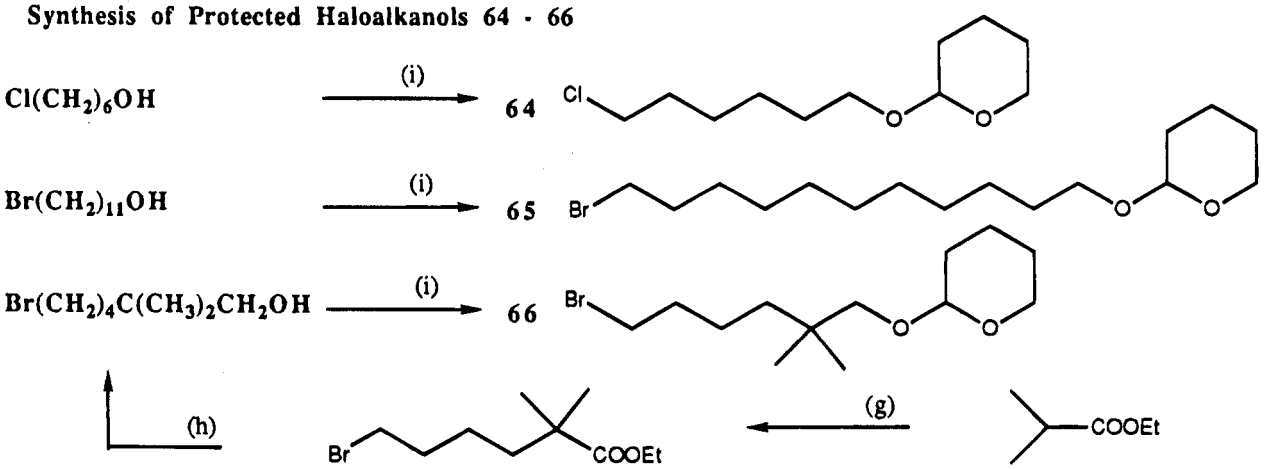
A Wittig reaction (KO^tBu) between the acid **67** and terephthaldehyde mono(diethyl acetal) followed by esterification with EtOH/HCl gave the aldehyde **68**, (Scheme 10). Reaction with ^{n}BuLi and 3-bromopyridine and sequential reduction with H_2/Pd−C and then $LiAlH_4$/THF afforded the diol **69**. A double Swern oxidation (for the general procedure, see **50**) led to the ketoaldehyde **70**, which underwent selective acetal exchange with the dioxane **14**. The silyl protective group of the ketone **71** was removed with TBAF (for the general procedure, see **88**) prior to a second Wittig reaction (for the general procedure, see **54**) to give the intermediate **72**, which required ester hydrolysis with NaOH to afford the product **105** (Table 4).

Scheme 9[a]



59 R = $(CH_2)_2CH(OCH_2CH_2O)$	**62** R = $(CH_2)_4C(CH_3)_2CH_2OTHP$
60 R = $(CH_2)_6OTHP$	**63** 
61 R = $(CH_2)_{11}OTHP$	

Synthesis of Protected Haloalkanols 64 - 66

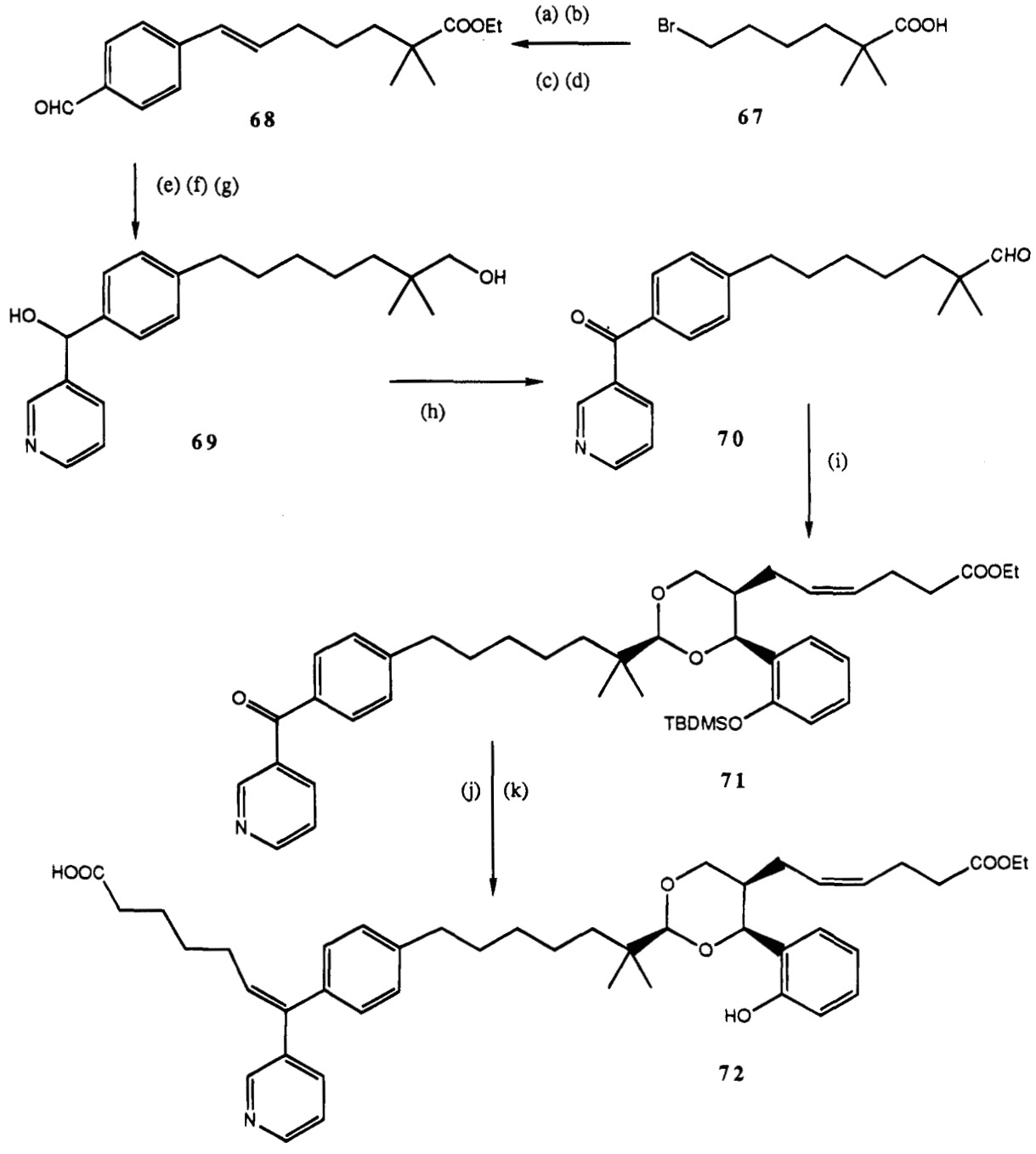


[a] (a) *n*-BuLi, THF, −78 °C; $OHCC_6H_4OMe$; (b) $(COCl)_2$, DMSO, −78 °C; NEt_3; (c) $Br^-Ph_3P^+(CH_2)_5COOH$, KO^tBu, THF; (d) HBr; (e) $SOCl_2$, EtOH; (f) NaH, RX; (g) LDA, $Br(CH_2)_4Br$; (h) DIBAL (i) DHP, *p*-TosOH.

The synthesis of analogues **106–109** (Table 4) is elaborated in Scheme 11, with the para-linked compound **108** shown as a typical example. Alkylation of 4-hydroxybenzaldehyde with 2-chloroethyl *p*-toluenesulfonate gave the aldehyde **73**, which reacted with the isbogrel derivative **58** in the presence of NaH/DMF to give **74**.

Scheme 12 displays the synthesis of the alcohols required for the preparation of compounds **110–112**, together with an example of the final synthetic steps to the aldehyde intermediates. Thus reduction of terephthaldehyde mono(diethyl acetal) gave after acetal cleavage the alcohol **75**. 2-(4-Bromophenyl)ethanol was protected as a tetrahydropyranyl ether and the product **76** lithiated with ^{n}BuLi/THF before reaction with DMF to afford **77**. Acetal formation with 1,3-dihydroxypro-

Scheme 10[a]



[a] (a) Ph_3P, toluene, Δ; (b) NaH, DMSO; terephthaldehyde diethyl acetal; (c) HCl; (d) HCl, EtOH, Δ; (e) *n*-BuLi, py-3-Br, Et_2O, −78 °C; (f) 10% Pd/C, H_2; (g) $LiAlH_4$, THF; (h) $(COCl)_2$, DMSO, −78 °C; NEt_3; (i) **14**, *p*-TSA, CH_2Cl_2; (j) TBAF, THF; (k) $Br^-Ph_3P^+(CH_2)_5COOH$, KO^tBu, THF.

pane gave **78**. 3-Bromobenzaldehyde was protected as a cyclic acetal, lithiated with ^{n}BuLi/THF, reacted with DMF, and reduced to the alcohol **79**. Mitsunobu reaction with intermediate **58** and hydrolysis gave the intermediate aldehyde **80**. In a similar manner the aldehyde **81** (Scheme 14) was prepared from 4-bromobenzaldehyde. Hydrolysis of **81** with NaOH afforded the acid **82**.

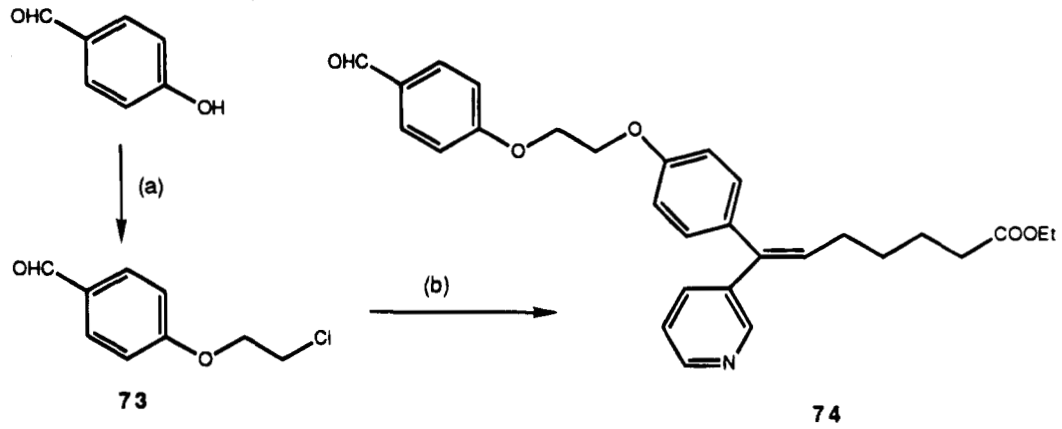
The preparation of ester **83** (Scheme 13) was identical to that for the isomeric phenol **58** (Scheme 9) except that *m*-anisaldehyde was used as starting material. Reaction of **83** with the diethyl acetal of alcohol **75** under Mitsunobu conditions, followed by acid hydrolysis, gave **84**.

The three esters **85**−**87** (Scheme 14) were derived from **14** with an appropriate aldehyde exchange reaction in the presence of *p*-toluenesulfonic acid and removal of the silyl protective group with TBAF. In particular, **85** was prepared via the disilyl derivative **14c**.

Pharmacology

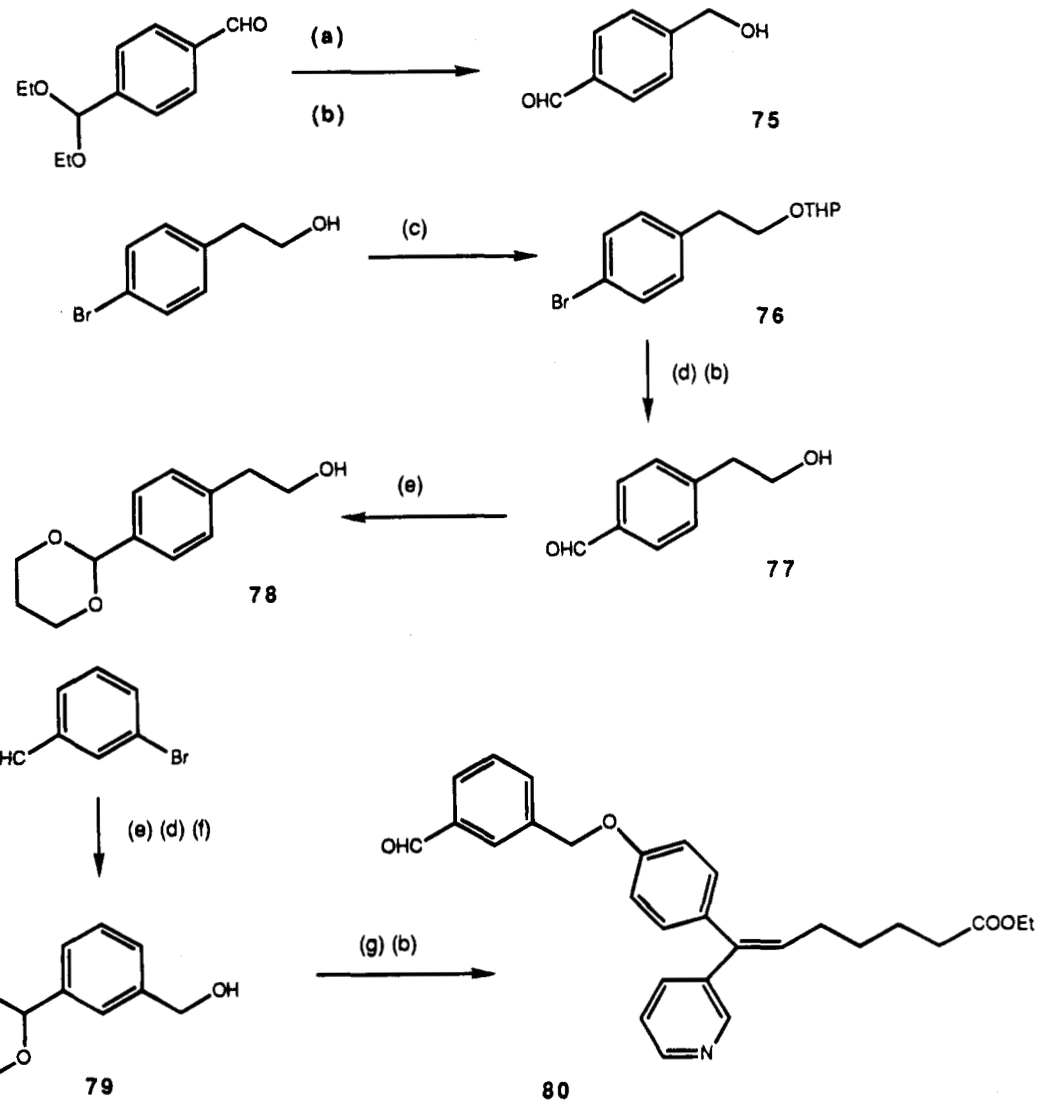
Test compounds were evaluated as in previously reported tests.[17,18] The *in vitro* antagonist potencies of compounds in the tables were measured[17] at human platelet TXA_2 receptor sites ($n = 2$). Venous blood from volunteers was taken into 3.2% (w/v) trisodium citrate and centrifuged at 200 g for 10 min. The platelet-rich plasma was aggregated with 15(*S*)-hydroxy-11α,9α-

Scheme 11[a]



[a] (a) $ClCH_2CH_2OTos$, K_2CO_3, butan-2-one; (b) NaH, THF, **58**.

Scheme 12[a]



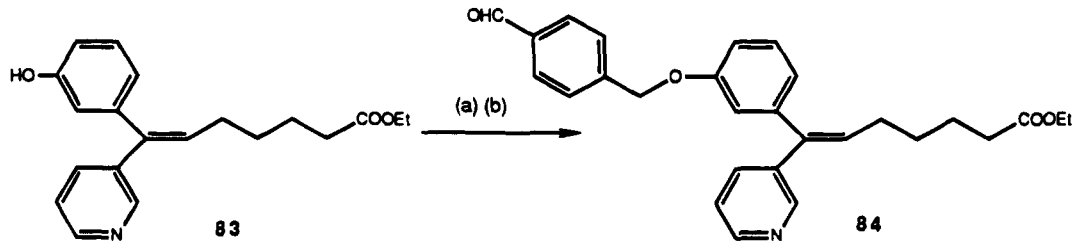
[a] (a) $NaAl(CH_3OCH_2CH_2O)_2H_2$, (b) HCl; (c) DHP, *p*-TSA; (d) *n*-BuLi, THF, −78 °C; DMF; (e) $HO(CH_2)_3OH$, *p*-TSA; (f) $LiAlH_4$, THF; (g) DEAD, Ph_3P, **58**.

(epoxymethano)prosta-5(*Z*),13(*E*)-dienoic acid (U46619) in the presence and absence of different concentrations of putative antagonists to give EC_{50} agonist values from which apparent pA_2 values were derived.

The *in vitro* TXA_2 synthase inhibition was determined[18] with human blood platelet microsomes ($n = 2$). The microsomes were incubated with [1-^{14}C]arachidonic acid in the presence and absence of putative enzyme inhibitors and the extent of conversion to labeled thromboxane B_2 determined by a quantitative radiochromatographic method.

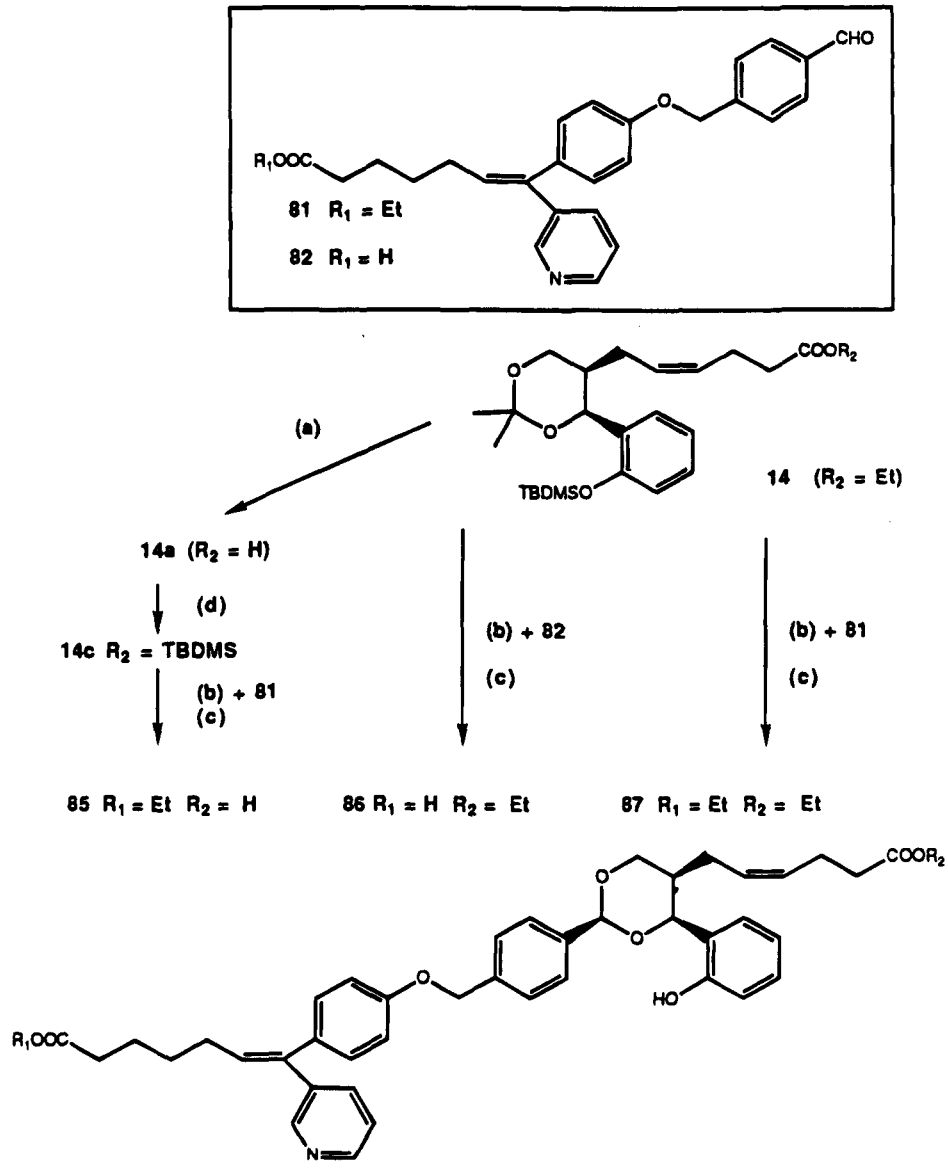
Antagonist and inhibitory properties of test compounds dosed to rats and dogs were found by *ex vivo* methods. Groups of conscious rats ($n = 6$) were gavaged

Scheme 13[a]



[a] (a) $HOCH_2C_6H_4CH(OEt)_2$, DEAD, Ph_3P; (b) HCl.

Scheme 14[a]



[a] (a) NaOH(aq); (b) aldehyde exchange, *p*-TSA; (c) *n*-$Bu_4N^+F^-$,THF; (d) TBDMSCl, imidazole, DMF.

with test compound and anaesthetized, and blood was withdrawn from the abdominal aorta at 3 and 5 h after compound dosing. Platelet-rich plasma was prepared from an aliquot of this blood and platelet aggregation with U46619 compared before and after dosing to give a dose ratio of U46619. A second aliquot was treated with collagen and the TXB_2 produced determined by radioimmunoassay. The dog *ex vivo* test was identical to the rat test, except that blood was taken from the jugular vein of conscious dogs at 2 and 5 h after dosing. The aliquot used in platelet aggregation studies was treated with a predetermined threshold concentration of the platelet aggregation agent adenosine diphosphate (about $(0.4-1.2) \times 10^{-6}$ M) in addition to U46619.

Biological Results and Discussion

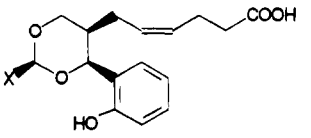
Results for the three component TXRA and TXSI compounds are given in Table 1. These compounds have all undergone clinical evaluation and are known to be very effective agents in either *in vitro* or *ex vivo* test situations. When considering the activity of the potential dual-acting compounds (Tables 2–4), obtaining both

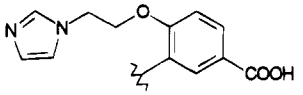
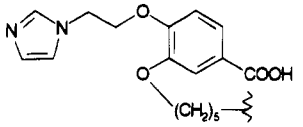
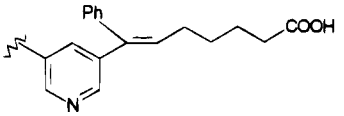
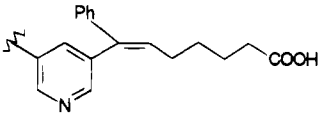
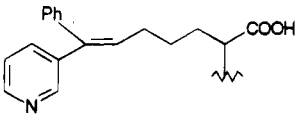
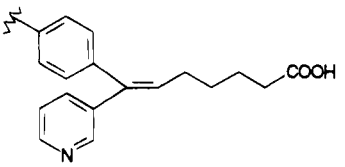
Table 1. Biological Data for Standard TXA_2 Receptor Antagonists and TXA_2 Synthase Inhibitors

compd[a]	formula	pA_2 vs U46619 human platelet-rich plasma	IC_{50} μM TXA_2 synthase human platelet microsomes		conc ratio vs U46619 after oral dose of 10 mg/kg; mean (±SEM) 1 h	3 h	5 h	% inhibition TXA_2 synthase after oral dose of 10 mg/kg; mean (±SEM) 1 h	3 h	5 h
2	$C_{12}H_{12}N_2O_3$	<5.0	0.07	rat	2 ± 0.3	2 ± 0.5		86 ± 2.7	87 ± 4.4	
				dog[b]	1 ± 0.2	1 ± 0.2	1 ± 0.2	73 ± 2.4	91 ± 1.5	77 ± 4.1
10	$C_{22}H_{23}ClO_5$	8.5	>100	rat	15 ± 6	3 ± 0.2	7 ± 2.1			
				dog[c]	93 ± 2.4	121 ± 2.9	93 ± 1.8			
11	$C_{18}H_{19}NO_2$	<5.0	0.02	rat	1 ± 0.2	1.7 ± 0.4		97 ± 0.6	97 ± 0	87 ± 4.5
				dog[b]	1 ± 0.2	1 ± 0.1	1 ± 0.2	93 ± 1.2	83 ± 5.1	82 ± 3.5

[a] The analysis for C, H, and N for all compounds was within ±0.4% of the calculated values. [b] Dosed at 1 mg/kg. [c] Dosed at 0.05 mg/kg.

Table 2. Comparison of the *in vitro* Activity of Compounds with Potential Enzyme Binding Sites Close to and away from the 1,3-Dioxane Fragment



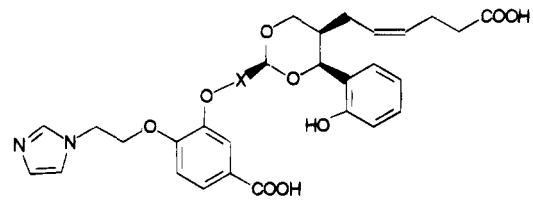
compound[a]	X	formula	mp °C	pA_2 vs. U46619 Human platelet rich plasma	IC_{50} μM TXA_2 synthase Human platelet microsomes
88		$C_{28}H_{30}N_2O_8 \cdot 2\,H_2O$	123-125	5.9	3.8
89		$C_{33}H_{40}N_2O_9$	91-93	5.9	0.06
90		$C_{34}H_{37}NO_7 \cdot 0.5\,H_2O$	Foam	7.4	>10
91		$C_{34}H_{37}NO_7 \cdot 1.5\,H_2O$	75-77	7.6	>10
92		$C_{35}H_{39}NO_7 \cdot 0.5$ EtOAc	Gum	<5.0	0.04
93		$C_{34}H_{37}NO_7 \cdot 1.2\,H_2O$	Gum	7.0	0.04

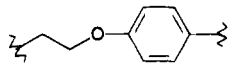
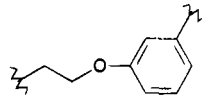
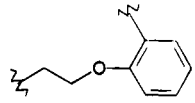
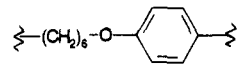
[a] The analysis for C, H, and N for all compounds was within ±0.4% of the calculated values (except **90**).

enzyme inhibition and receptor antagonism in a single compound was regarded as the key issue, so that matching the very high potency of the component compounds (which each only display one of the required activities) was not considered essential for testing the feasibility of the approach.

Initially a small group of compounds was examined (Table 2) to investigate some general *in vitro* structure activity relationships concerning the most appropriate positions for linking the TXSIs to the 1,3-dioxane–TXRA. Thus comparison of **88** and **89** indicated that a tether group was required to obtain good synthase inhibition properties in the "dazoxiben" series and in the "isbogrel" series, whereas links to the inhibitor component in the pyridine ring (**90** and **91**) resulted in diminished synthase inhibition properties. By contrast a link from the TXRA dioxane component adjacent to the carboxyl group of the TXSI component, as in **92**, resulted in a loss of antagonist potency compared to compound **93**. The subsequent more general work

Table 3. *In Vitro* Data for Dual-Action Compounds Containing a Dazoxiben (2) Fragment



compound[a]	X	formula	mp °C	pA_2 vs. U46619 Human platelet rich plasma	IC_{50} μM TXA_2 synthase Human platelet microsomes
94	$-CH_2-$	$C_{29}H_{32}N_2O_9 \cdot H_2O$	96-98	5.5	1.7
95		$C_{36}H_{38}N_2O_{10} \cdot H_2O$	172-175	6.3	0.06
96		$C_{36}H_{38}N_2O_{10} \cdot H_2O$	142-144	6.8	0.03
97		$C_{36}H_{38}N_2O_{10} \cdot H_2O$	114-116	5.9	0.03
98		$C_{40}H_{46}N_2O_{10} \cdot H_2O$	116-118	6.8	0.04

[a] The analysis for C, H, and N for all compounds was within ±0.4% of the calculated values.

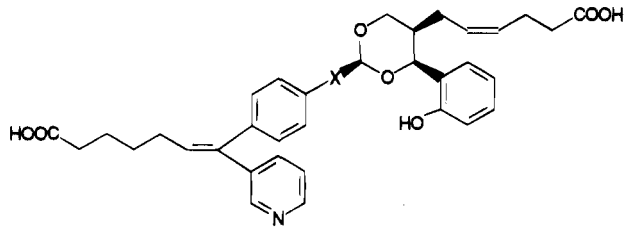
(Tables 3 and 4) was thus concentrated on the synthesis of compounds where the dazoxiben fragment had a tether group to the TXRA, and links to the isbogrel fragment were made to the phenyl ring rather than the pyridyl ring or the carboxylic acid side chain.

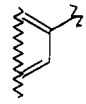
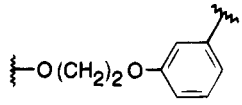
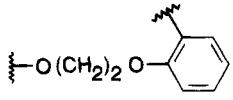
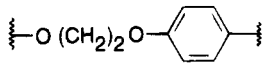
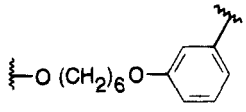
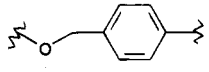
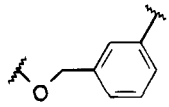
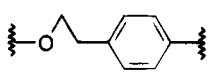
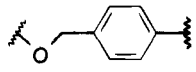
The *in vitro* biological activity of the dazoxiben-containing compounds (Table 3) shows that all compounds were considerably less potent as receptor antagonists than the parent TXRA ICI 192605 (**10**), although significant TXRA activity was retained (pA_2 = 5.5−6.8). On the other hand, TXSI potency comparable to that of the clinically tested TXSI **2** was seen in all compounds (IC_{50} = 30−60 nM), except for those in which the dazoxiben fragment was linked to the 1,3-dioxane ring without a tether group (**88**) or by a particularly short tether (**96**), when TXSI activity decreased considerably. This further indicated that the 1,3-dioxane component and the TXSI needed to be held apart to get dual action.

In general, compounds containing the isbogrel component (Table 3) showed consistent *in vitro* TXRA activity approaching more closely that of the parent 1,3-dioxane, ICI 192605 (**10**). Exceptions to this trend occurred where the carboxylic acid function of the TXSI component was positioned near to the 1,3-dioxane ring (**92**) and where the length of the tether group was particularly great (**103**). Inhibitory potency comparable to that of the TXSI isbogrel was retained in all compounds except those in which the pyridine ring was directly bound to the 1,3-dioxane ring (**90** and **91**) and was, presumably, too hindered to bind to the haem iron of the enzyme. Thus, unlike the dazoxiben-linked compounds (Table 2) the component TXRA and TXSI groups did not need to be apart. In addition, it was shown that this separation of the components could be too great for optimal TXRA activity.

Representative examples of both the imidazole and pyridine series of the dual-acting compounds were tested *ex vivo* in the rat and dog. Receptor antagonism was expressed as a concentration ratio of the amount of the thromboxane mimetic compound U46619 required to cause platelet aggregation in platelet-rich plasma, divided by the amount of U46619 required for aggregation in plasma from control animals. The > symbols used with these concentration ratios reflect the maximum concentration ratio available on the day of the experiment using a maximal U46619 concentration (1×10^{-4} M). Synthase inhibition was expressed as a percentage inhibition of the formation of the TXA_2 metabolite thromboxane B_2. Thus, for example, from the dazoxiben series, **96** and **98** showed modest TXRA activity in the rat (concentration ratios at 5 h after dosing were in the range 1.9−5.0), but neither compound gave any TXSI activity. In the isbogrel series, however, **102** and **109** showed potent TXSI activity in the rat (90−93% inhibition after 5 h) and both compounds gave significant TXRA activity (concentration ratios in the range 2−5).

Table 4. *In Vitro* Data for Dual-Action Compounds Containing an Isbogrel (11) Fragment



compound[a]	X	formula	mp °C	pA_2 vs. U46619 Human platelet rich plasma	IC_{50} μM TXA_2 synthase Human platelet microsomes
99		$C_{37}H_{43}NO_7$	Foam	6.6	0.03
100[b]		$C_{38}H_{39}NO_8$	83-84	6.6	0.05
101	$-O(CH_2)_2-$	$C_{36}H_{41}NO_8 \cdot H_2O$	62-63	6.7	0.03
102	$-O(CH_2)_5-$	$C_{39}H_{47}NO_8 \cdot 0.66$ PhMe	55-57	6.7	0.01
103	$-O(CH_2)_{10}-$	$C_{44}H_{57}NO_8 \cdot 0.5\ H_2O$	50-51	5.6	0.04
104	$-O(CH_2)_4C.Me_2-$	$C_{41}H_{51}NO_8 \cdot 0.75\ H_2O$	68-72	6.6	0.03
105	$-(CH_2)_5C(Me)_2-$	$C_{42}H_{53}NO_7 \cdot 0.5\ H_2O$	Gum	6.3	0.01
106		$C_{42}H_{45}NO_9 \cdot H_2O$	70-71	6.1	0.04
107		$C_{42}H_{45}NO_9 \cdot 0.5\ H_2O$	82-86	6.8	0.03
108		$C_{42}H_{45}NO_9 \cdot 0.33$ EtOAc	72-75	6.2	0.05
109		$C_{46}H_{53}NO_9$	64-66	7.0	0.07
110		$C_{41}H_{43}NO_8 \cdot 0.33$ EtOAc	72-75	6.7	0.02
111		$C_{41}H_{43}NO_8 \cdot 0.5\ H_2O$	87-88	6.7	0.04
112		$C_{42}H_{45}NO_8 \cdot 0.5\ H_2O$	83-84	6.2	0.05
113[c]		$C_{41}H_{43}NO_8 \cdot 1.5\ H_2O$	78-80	7.0	0.01

[a] The analysis for C, H, and N for all compounds was within ±0.4% of the calculated values. [b] I.e., naphthyl. [c] Isomer of compound **110** with a 3-OPh link in the isbogrel fragment rather than the 4-substitution of all other compounds.

Table 5. Additional Data for Compounds in Tables 2–4; ^{1}H-NMR [(DMSO-d_6),[a] δ, ppm] and MS

88	1.65 (m, 1H), 1.95 (m, 1H), 2.1 (m, 5H), 4.1 (q, 2H), 4.35 (m, 4H), 5.3 (m, 3H), 5.95 (s, 1H), 6.75 (m, 3H), 7.15 (m, 4H), 7.7 (b s, 1H), 7.95 (dd, 1H), 8.2 (d, 1H); FAB-MS *m/z* 523 $(MH)^+$
89	1.5 (m, 5H), 1.7 (m, 5H), 2.1 (m, 4H), 2.4 (m, 1H), 3.9 (m, 4H), 4.3 (m, 4H), 4.8 (m, 1H), 5.2 (m, 3H), 6.8 (m, 2H), 7.0 (m, 2H), 7.2 (m, 2H), 7.5 (m, 3H), 7.8 (m, 1H), 9.5 (m, 1H); FAB-MS *m/z* 609 $(MH)^+$
90	($CDCl_3$) 1.5 (m, 1H), 1.65 (m, 1H), 1.8 (m, 1H), 1.9–2.5 (m, 11H), 2.75 (m, 1H), 3.3–3.8 (m, 3H), 4.2 (q, 2H), 5.25 (m, 1H), 5.4 (m, 2H), 5.75 (s, 1H), 6.17 (t, 1H), 6.85 (m, 2H), 7.0 (m, 1H), 7.15 (m, 3H), 7.35 (m, 3H), 7.85 (t, 1H), 8.35 (d, 1H), 8.55 (d, 1H); FAB-MS *m/z* 572 $(MH)^+$
91	($CDCl_3$) 1.5 (m, 1H), 1.65 (m, 1H), 1.8 (m, 1H), 1.9–2.5 (m, 11H), 2.75 (m, 1H), 3.3–3.8 (m, 3H), 4.2 (q, 2H), 5.2–5.5 (m, 3H), 5.81 (s, 1H), 6.21 (t, 1H), 6.85 (m, 2H), 7.0–7.3 (m, 7H), 7.7 (t, 1H), 8.45 (d, 1H), 8.8 (d, 1H); FAB-MS *m/z* 572 $(MH)^+$
92	($CDCl_3$) 1.4–1.9 (m, 6H), 2.2 (m, 2H), 2.4 (m, 6H), 2.55–2.95 (m, 2H), 3.85 (d, 1H), 4.05 (d, 1H), 4.85 (t, 1H), 5.2 (m, 2H), 5.45 (m, 1H), 6.15 (dt, 1H), 6.8 (m, 2H), 6.9 (m, 1H), 7.05–7.45 (m, 8H), 8.45 (m, 1H), 8.7 (dd, 1H); FAB-MS *m/z* 584 $(M - H)^-$
93	($CDCl_3$) 1.6 (m, 4H), 1.85 (m, 2H), 2.2 (m, 2H), 2.45 (m, 10H), 3.0 (q, 1H), 4.1 (d, 1H), 4.3 (s, 1H), 5.3 (m, 1H), 5.55 (m, 2H), 5.75 (s, 1H), 6.15 (t, 1H), 6.85 (m, 2H), 7.0 (d, 1H), 7.2 (m, 4H), 7.45 (d, 1H), 7.60 (d, 2H), 8.5 (bd, 2H); FAB-MS *m/z* 572 $(MH)^+$
94	1.5 (m, 1H), 1.9 (m, 1H), 2.1 (m, 4H), 2.4 (m, 1H), 4.1 (m, 4H), 4.4 (m, 4H), 5.2 (m, 4H), 5.8 (m, 3H), 7.1 (m, 5H), 7.6 (m, 2H); FAB-MS *m/z* 551 $(M - H)^-$
95	1.55 (m, 1H), 1.95 (m, 1H), 2.15 (m, 4H), 2.5 (m, 1H), 4.4 (m, 10H), 5.25 (m, 3H), 5.7 (s, 1H), 6.8 (m, 3H), 7.1 (m, 5H), 7.2 (m, 1H), 7.5 (m, 5H), 9.6 (m, 1H); FAB-MS *m/z* 659 $(MH)^+$
96	1.6 (m, 1H), 1.9 (m, 1H), 2.2 (m, 4H), 2.5 (m, 1H), 4.0 (m, 2H), 4.3 (m, 8H), 5.3 (m, 3H), 6.0 (s, 1H), 6.7 (m, 3H), 7.1 (m, 7H), 7.4 (m, 1H), 7.5 (m, 2H), 7.7 (m, 1H); FAB-MS *m/z* 659 $(MH)^+$
97	1.6 (m, 1H), 1.9 (m, 1H), 2.2 (m, 4H), 2.5 (m, 1H), 4.0 (b s, 2H), 4.2 (b s, 4H), 4.3 (b s, 4H), 5.3 (m, 3H), 6.0 (s, 1H), 6.8 (m, 3H), 7.1 (m, 6H), 7.4 (m, 1H), 7.6 (m, 4H)
98	1.5 (m, 5H), 1.8 (m, 4H), 1.9 (m, 1H), 2.2 (m, 4H), 2.5 (m, 1H), 4.0 (m, 6H), 4.3 (m, 2H), 4.4 (m, 2H), 5.3 (m, 3H), 5.7 (s, 1H), 7.2 (m, 14H), 7.9 (m, 1H), 9.3 (m, 1H); FAB-MS *m/z* 715 $(MH)^+$
99	($CDCl_3$) 1.4 (d, 6H), 1.6 (m, 6H), 2.25 (m, 8H), 3.85 (d, 1H), 4.1 (d, 1H), 4.6 (s, 1H), 5.15 (m, 2H), 5.35 (m, 1H), 6.2 (t, 1H), 6.8 (m, 3H), 7.15 (m, 3H), 7.35 (m, 3H), 7.6 (m, 1H), 8.5 (m, 2H); FAB-MS *m/z* 612 $(M - H)^-$
100	1.6 (m, 4H), 1.8 (m, 1H), 2.0 (m, 1H), 2.3 (m, 8H), 2.7 (m, 1H), 4.2 (m, 2H), 5.3 (m, 1H), 5.5 (m, 2H), 5.9 (s, 1H), 6.2 (t, 1H), 6.85 (m, 2H), 7.25 (m, 4H), 7.5 (d, 1H), 7.7 (m, 2H), 7.9 (m, 2H), 8.1 (s, 1H), 8.5 (m, 2H); FAB-MS *m/z* 620 $(M - H)^-$
101	1.5 (m, 6H), 1.9 (m, 1H), 2.15 (m, 11H), 2.4 (m, 1H), 3.2 (s, 1H), 3.95 (b s, 2H), 4.15 (m, 3H), 5.0 (t, 1H), 5.2 (m, 2H), 5.3 (m, 1H), 6.1 (t, 1H), 6.8 (m, 3H), 7.0 (m, 5H), 7.3 (m, 2H), 7.5 (m, 1H), 8.4 (b s, 2H), 9.5 (b s, 1H), 11.95 (m, 1H)
102	1.6 (m, 14H), 2.2 (m, 8H), 2.4 (m, 1H), 3.5 (m, 4H), 4.8 (t, 1H), 5.2 (m, 3H), 6.1 (t, 1H), 6.8 (m, 2H), 7.0 (m, 5H), 7.25 (m, 2H), 7.5 (m, 1H), 8.4 (m, 2H), 9.4 (b s, 1H), 11.9 (b s, 2H); CI-MS *m/z* 658 $(MH)^+$
103	1.2–1.5 (m, 22H), 1.6 (m, 1H), 1.7 (m, 1H), 1.82 (m, 1H), 2.1 (m, 8H), 2.3 (m, 2H), 3.85 (s, 2H), 4.0 (t, 2H), 4.8 (t, 1H), 5.1 (d, 1H), 5.25 (m, 2H), 6.1 (t, 1H), 6.8 (m, 2H), 7.0 (m, 5H), 7.25 (m, 2H), 7.5 (dt, 1H), 8.4 (m, 2H), 9.45 (s, 1H), 11.95 (b s, 2H)
104	1.0 (s, 6H), 1.4 (m, 8H), 1.8 (m, 4H), 2.1 (m, 8H), 2.4 (m, 1H), 3.9 (m, 4H), 4.5 (s, 1H), 5.2 (m, 3H), 6.1 (t, 1H), 6.8 (m, 2H), 7.1 (m, 5H), 7.3 (m, 2H), 7.6 (d, 1H), 8.5 (m, 2H), 9.6 (s, 1H), 11.3 (m, 2H); FAB-MS *m/z* 686 $(MH)^+$
105	0.9 (s, 6H), 1.3 (m, 8H), 1.5 (m, 8H), 1.8 (m, 1H), 2.1 (m, 8H), 2.4 (m, 1H), 2.55 (m, 2H), 3.85 (q, 2H), 4.4 (d, 1H), 5.05 (s, 1H), 5.25 (m, 2H), 6.15 (t, 1H), 6.8 (m, 2H), 7.0 (m, 4H), 7.25 (m, 2H), 8.4 (m, 2H), 9.4 (m, 1H), 11.9 (m, 1H)
106	1.5 (m, 4H), 1.8 (b d, 1H), 2.0 (b d, 1H), 2.2 (m, 4H), 2.4 (m, 4H), 2.8 (m, 1H), 4.2 (m, 4H), 4.4 (s, 4H), 5.3 (m, 1H), 5.5 (m, 2H), 5.52 (s, 1H), 6.1 (t, 1H), 6.8 (m, 2H), 7.0 (m, 8H), 7.1 (m, 2H), 7.3 (m, 1H), 7.5 (m, 1H), 8.5 (d, 2H); FAB-MS *m/z* 706 $(M - H)^-$
107	1.5 (m, 5H), 1.9 (m, 1H), 2.1 (m, 8H), 2.6 (m, 1H), 4.0 (s, 2H), 4.4 (m, 4H), 5.2 (m, 1H), 5.4 (m, 2H), 6.05 (s, 1H), 6.10 (t, 1H), 6.8 (m, 2H), 7.1 (m, 8H), 7.3 (m, 2H), 7.5 (m, 1H), 7.65 (dd, 1H), 8.5 (m, 2H), 9.5 (s, 1H), 12.0 (m, 2H); CI-MS *m/z* 708 $(MH)^+$
108	1.5 (m, 5H), 1.95 (m, 1H), 2.2 (m, 8H), 2.5 (m, 1H), 4.1 (m, 2H), 4.4 (s, 4H), 5.3 (m, 3H), 5.7 (s, 1H), 6.1 (t, 1H), 6.8 (m, 2H), 7.1 (m, 7H), 7.3 (m, 2H), 7.5 (m, 3H), 8.4 (m, 2H), 9.6 (m, 1H), 12.0 (m, 2H); FAB-MS *m/z* 708 $(MH)^+$
109	1.5 (m, 9H), 1.8 (m, 4H), 1.9 (m, 1H), 2.1 (m, 8H), 2.5 (m, 1H), 4.1 (m, 6H), 5.2 (m, 1H), 5.3 (m, 2H), 5.7 (s, 1H), 6.1 (t, 1H), 6.9 (m, 2H), 7.0 (m, 8H), 7.3 (m, 3H), 7.5 (m, 1H), 8.5 (m, 2H), 9.5 (s, 1H), 12.0 (b s, 2H); FAB-MS *m/z* 762 $(M - H)^-$
110	($CDCl_3$) 1.7 (m, 6H), 2.3 (m, 8H), 2.9 (m, 1H), 4.2 (m, 2H), 5.2 (m, 3H), 5.5 (m, 2H), 5.7 (s, 1H), 6.1 (t, 1H), 6.9 (m, 7H), 7.2 (m, 2H), 7.4 (d, 2H), 7.56 (d, 2H), 7.63 (dt, 1H), 8.4 (m, 2H); FAB-MS *m/z* 678 $(MH)^+$
111	1.5 (m, 5H), 2.0 (m, 1H), 2.1 (m, 8H), 2.5 (m, 1H), 3.3 (m, 3H), 4.1 (m, 2H), 5.3 (m, 5H), 5.8 (s, 1H), 6.1 (t, 1H), 6.8 (m, 2H), 7.1 (m, 5H), 7.3 (m, 2H), 7.4 (m, 4H), 7.6 (s, 1H), 8.4 (m, 2H); FAB-MS *m/z* 676 $(M - H)^-$
112	1.5 (m, 5H), 2.0 (m, 1H), 2.2 (m, 8H), 2.5 (m, 1H), 3.1 (t, 2H), 4.2 (m, 4H), 5.3 (m, 3H), 5.7 (s, 1H), 6.1 (t, 1H), 6.8 (m, 2H), 7.0 (m, 6H), 7.4 (m, 8H), 8.5 (m, 2H); FAB-MS *m/z* 690 $(M - H)^-$
113	1.5 (m, 5H), 2.1 (m, 9H), 4.1 (q, 2H), 5.1 (s, 2H), 5.3 (m, 3H), 5.8 (s, 1H), 6.23 (t, 1H), 6.75 (m, 4H), 7.05 (m, 2H), 7.2 (d, 1H), 7.45 (m, 6H), 7.7 (m, 1H), 8.5 (b s, 2H), 9.5 (b s, 1H); FAB-MS *m/z* 678 $(MH)^+$

[a] Except where indicated.

The optimal dual activity in the rat for these compounds was seen with **110** which, at 3 and 5 h after oral dosing (at 10 mg/kg), gave TXRA concentration ratios of >64 and >47 together with 81 ± 4.4% and 78 ± 6.1% TXSI activity. Thus in the rat **110** displayed very similar TXRA/TXSI dual activity to that found for the singly acting component TXRAs and TXSIs **2**, **10**, and **11** (Table 1). However, when **110** was dosed orally at 10 mg/kg to the dog, TXSI activity was only apparent at the 2 h time point (69 ± 4.8%) and was <50% at 5 h after dosing. Nevertheless, **110** was active as a TXRA in the dog, giving concentration ratios of >59 ± 11.3 and >22 ± 5.0 at 2 and 5 h, respectively. Examination of **85**, **86**, and **87** (the two monoethyl and the diethyl esters of **110**) as potential prodrugs failed to give any activity in the dog following oral dosing at 10 mg/kg. This lack of activity at 10 mg/kg for the potential prodrugs could be due to a number of reasons but was not investigated further.

TXA_2 synthase is a P450 enzyme, and it was necessary to show that, in modifying the structure of isbogrel to get the dual-acting compound **110**, selectivity for TXA_2 synthase had been retained. Compound **110** was thus examined in a previously described[14] standard test for the inhibition of P450 enzymes, the inhibition of steroid 11β-hydroxylation. The IC_{50} of 3.4 μM found for **110** in this test showed that there was a greater than 150-fold ratio to that found for the inhibition of TXSI and suggested selectivity of enzyme inhibition was retained.

Although it had previously been reported[12] that a range of substituted aryl and alkyl groups could be accommodated in the C2 position of the 1,3-dioxane–TXRAs without adversely affecting TXRA activity, the results in the tables show examples of compounds where a whole drug entity (a TXSI) can be accommodated in this position and TXRA potency retained. Thus, substitution at the C2 position of the 1,3-dioxane ring in these TXRAs appears to allow the substituent group to lie away from the thromboxane receptor site. In a

similar manner the results indicate that potent enzyme inhibition may be found if a very large substituent (a TXRA) is positioned away from the key nitrogen atom and carboxyl binding group of a TXSI. In particular, *in vitro* test results for compounds of the isbogrel-type (Table 4) indicate that the previously postulated[13] enclosed binding region for the phenyl ring of isbogrel (**11**) must be open ended and larger than conceived. The identification of regions in both the TXRA and the TXSI components, which can accept a large substituent without greatly diminishing biological activity, is an essential requirement for the successful discovery of dual-acting compounds by this approach.

Conclusions

We have shown that it is feasible to covalently tether the potent TXSIs dazoxiben or isbogrel to racemic 1,3-dioxane–TXRA compounds, so as to give a new class of agents which express potent dual TXRA/TXSI activity *in vitro*. Inhibition of thromboxane synthase was found which *in vitro* equalled that of the component TXSIs **2** and **11**, whereas receptor antagonist activity, though significant, was below that of the component TXRA ICI 192605. There was evidence that only particularly short or long tether groups were inappropriate, so that a wide range of alkyl and aryl tethers could be employed. The *in vitro* results also showed that very large groups could be tolerated at the selected substitution positions of the TXRA and TXSI components. A compound (**110**) was found which showed good dual activity in orally dosed rat and dog *ex vivo* tests, with a duration of action for both effects of 5 h in the rat and 2 h in the dog. This shorter duration of action found in the dog model may indicate that **110** is not suitable for clinical development for the treatment of chronic diseases by oral dosing, but nevertheless the feasibility of this approach for the identification of TXRA/TXSI dual-acting compounds in *in vivo* situations has been demonstrated.

Experimental Section

Melting points were determined with a Buchi apparatus and are uncorrected. The ^{1}H-NMR spectra were determined with a Bruker AM (200 MHZ) spectrometer (with $SiMe_4$ as an internal standard) and IR spectra recorded on a Perkin-Elmer 157 spectrophotometer. Mass spectra were measured on a MS902 Kratos (AEI) instrument. Reactions were carried out under an atmosphere of argon, and column chromatography was on E. Merck silica gel (Kieselgel 60, 230–400 mesh). Solvents were dried over $MgSO_4$ before evaporation. Sodium hydride was 60% dispersion in mineral oil.

Preparation of the 1,3-Dioxane Intermediate for Acetal Exchange Reactions. Ethyl 4(*Z*)-6-[4-[2-*tert*-Butyldimethylsilyl)oxy]phenyl]-2,2-dimethyl-1,3-dioxan-*cis*-5-yl]hexenoate (14). A solution of $KHCO_3$ (1.0 g, 10 mmol) in H_2O (5 mL) was added to stirred **12** (3.2 g, 10 mmol) in EtOH (20 mL). The mixture was stirred 0.5 h and evaporated to dryness. The residue in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (15 mL) was treated with EtI (1.95 g, 12.5 mmol) for 4 h at 25 °C. H_2O was added and the aqueous phase extracted with Et_2O. The extract was washed with brine, dried, and evaporated to given an oil which was purified by flash-column chromatography on silica gel in hexane–EtOAc (70:30) to give, as a pale yellow oil, **13** (2.81 g, 81%): ^{1}H-NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.62 (m, 7H), 1.82 (m, 1H), 2.28 (m, 4H), 3.67 (m, 1H), 3.83 (q, 1H), 4.10 (m, 3H), 6.86 (m, 3H), 7.15 (m, 1H), 8.47 (s, 1H). Anal. ($C_{20}H_{28}O_5$) C, H. *tert*-Butyldimethylsilyl chloride (340 mg, 2.2 mmol) and imidazole (340 mg, 5 mmol) were added to stirred **13** (696 mg, 2 mmol) in DMF (6 mL). After 16 h, H_2O (50 mL) was added and the mixture extracted with Et_2O. The extract was washed with brine, dried, and evaporated to give an oil which was purified by flash column chromatography on silica gel. Elution with hexane–EtOAc (90:10) gave **14** as a colorless oil (801 mg, 86%): ^{1}H-NMR ($CDCl_3$) δ 0.20 (s, 3H), 0.25 (s, 3H), 1.00 (s, 9H), 1.22 (t, 3H), 1.53 (m, 7H), 1.73 (m, 1H), 2.26 (m, 4H), 2.50 (m, 1H), 3.75 (q, 1H), 4.08 (m, 3H), 5.15 (m, 1H), 5.32 (m, 1H), 5.45 (d, 1H), 6.75 (q, 1H), 6.90 (m, 1H), 7.08 (m, 1H), 7.43 (m, 1H). Anal. ($C_{26}H_{42}OSi$) C, H.

General Procedure for Acetal Exchange with 14 (TXRA Component), Silyl Group Removal, and Ester Hydrolysis. (*Z*)-6-[4-(2-Hydroxyphenyl)-2-[2-[2-(1-imidazolyl)ethyl]oxy]-5-carboxyphenyl]-1,3-dioxan-*cis*-5-yl]-hex-4-enoic Acid (88). The aldehyde **21** (0.15 g, 0.55 mmol), the protected dioxane **14** (0.28 g, 0.61 mmol), and *p*-toluenesulfonic acid (0.19 g, 1.0 mmol) were stirred in CH_2Cl_2 (25 mL) at room temperature for 2 h. The mixture was washed with a saturated $NaHCO_3$ solution and the organic phase dried and evaporated to give an amber oil, which was dissolved in THF (1.5 mL) and added to 1.0 M tetrabutylammonium fluoride in THF (0.6 mL, 0.6 mmol). The solution was stirred for 1 h at room temperature, EtOAc (32 mL) added, the mixture washed with a saturated $NaHCO_3$ solution, and the organic phase dried and evaporated to give an amber oil which was dissolved in MeOH (2 mL), added to a 1 M NaOH solution (1.0 mL), and stirred at 25 °C for 3 h. H_2O (20 mL) and a 1 M HCl solution (1.0 mL) were added, and the separated solid was collected, washed with water, and dried to give **88** (0.06 g, 40%): mp 123–125 °C; ^{1}H-NMR (DMSO-d_6) δ 1.6–1.7 (b s, 1H), 1.9–2.0 (b s, 1H), 2.1–2.2 (m, 5H), 4.0–4.2 (q, 2H), 4.3–4.4 (m, 4H), 5.2–5.3 (m, 2H), 5.4 (s, 1H), 5.95 (s, 1H), 6.7–6.9 (m, 3H), 7.05–7.25 (m, 4H), 7.7 (s, 1H), 7.95 (dd, 1H), 8.2 (d, 1H); CI-MS *m/z* 523 $(M + H)^+$. Anal. ($C_{28}H_{30}N_2O_8$) C, H, N.

Syntheses of TXSI-Tethered Aldehydes for Acetal Exchange Reactions with 14. Methyl 3-Formyl-4-[(2-chloroethyl)oxy]benzoate (20). Methyl 3-formyl-4-hydroxybenzoate (**18**) (2.68 g, 14.9 mmol), 2-chloroethyl *p*-toluenesulfonate (**19**) (3.77 g, 15.7 mmol), and K_2CO_3 (10.3 g, 75.0 mmol) were heated under reflux for 3 h in MeCOEt (100 mL). The mixture was filtered and the filtrate evaporated *in vacuo* to give an amber oil which was purified by chromatography using hexane–EtOAc (80:20) as eluant to give **20** (0.85 g, 24%): ^{1}H-NMR ($CDCl_3$) δ 3.0 (t, 2H), 3.9 (s, 3H), 4.5 (t, 2H), 7.05 (d, 1H), 8.25 (dd, 1H), 8.55 (d, 1H), 10.55 (s, 1H).

Methyl 3-Formyl-4-[[2-(1-imidazolyl)ethyl]oxy]benzoate (21). Imidazole (0.26 g, 3.8 mmol) was added to NaH (0.09 g, 3.8 mmol) in DMF (3 mL) at 0 °C. The mixture was treated with a solution of ester **20** (0.82 g, 3.4 mmol) in DMF (5 mL) and heated at 60 °C for 16 h. The mixture was poured onto H_2O (150 mL), the aqueous phase was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were washed with brine, dried, and evaporated to give an amber oil which was purified by chromatography using EtOAc–MeOH (95:5) as eluant to give **21** (0.15 g, 16%): ^{1}H-NMR ($CDCl_3$) δ 3.9 (s, 1H), 4.4 (m, 4H), 6.95 (d, 1H), 7.1 (m, 2H), 7.6 (s, 1H), 8.2 (m, 1H), 8.5 (d, 1H), 10.4 (s, 1H).

Ethyl 3-Hydroxy-4-[[2-(1-imidazolyl)ethyl]oxy]benzoate (22). Imidazole (6.8 g, 100 mmol) was added to stirred NaH (4.0 g, 100 mmol) in DMF (30 mL) at 5 °C. The chloro compound **19** (23.7 g, 100 mmol) in DMF (40 mL) was added. After 1.25 h, a solution of NaH (4.0 g, 100 mmol) and ethyl 3,4-dihydroxybenzoate (18.2 g, 100 mmol) in DMF (60 mL) was added followed by NaI (1.0 g). The mixture was heated at 100 °C for 12 h and cooled. H_2O (1 L) was added and the aqueous phase extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give a solid which was crystallized from EtOAc to give, as a colorless solid, **22** (4.3 g, 16%): mp 154–6 °C; ^{1}H-NMR (DMSO-d_6) δ 1.28 (t, 3H), 4.30 (m, 6H), 6.86 (m, 1H), 6.97 (m, 1H), 7.28 (s, 1H), 7.38 (m, 2H), 7.72 (s, 1H), 9.47 (m, 1H). Anal. ($C_{14}H_{16}N_2O_4$) C, H, N.

The methyl ester of **22** was prepared in a similar manner: methyl 3-hydroxy-4-[[2-(1-imidazolyl)ethyl]oxy]benzoate, mp 207–209 °C. Anal ($C_{13}H_{14}N_2O_4$), C, H, N.

Ethyl 3-(2,2-Dimethoxyethoxy)-4-[[2-(1-imidazolyl)-ethyl]oxy]benzoate (23). Ester **22** (552 mg, 2 mmol), bromoacetaldehyde dimethyl acetal (572 mg, 3.4 mmol), and

K_2CO_3 (278 mg, 2 mmol) in MeCOEt (10 mL) were heated at reflux for 60 h and cooled. H_2O (200 mL) was added the mixture extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give an oil which was purified by chromatography on silica gel. Elution with $CHCl_3$–EtOH (49:1) gave, as a colorless solid, **23** (360 mg, 49%): mp 80–81 °C; ^{1}H-NMR ($CDCl_3$) δ 1.48 (t, 3H), 3.47 (s, 6H), 4.06 (d, 2H), 4.32 (m, 6H), 4.80 (t, 1H), 6.78 (d, 1H), 7.07 (s, 1H), 7.15 (s, 1H), 7.61 (m, 3H).

Ethyl 3-(Formylmethoxy)-4-[[2-(1-imidazolyl)ethyl]-oxy]benzoate (24). Ester **23** (340 mg, 0.93 mmol) in THF (5 mL) and 1 M HCl (5 mL) was refluxed for 2 h. After cooling, 1 M Na_2CO_3 (50 mL) was added. The solid precipitate was collected, washed (H_2O), and dried to give **24** (190 mg, 64%): mp 92–4 °C; ^{1}H-NMR (DMSO-d_6) δ 1.31 (t, 3H), 4.33 (m, 6H), 4.88 (s, 2H), 6.86 (b s, 1H), 7.05 (m, 1H), 7.28 (b s, 1H), 7.50 (m, 2H), 7.70 (b s, 1H), 9.69 (s, 1H).

Ethyl 3-[(6-Hydroxy-*n*-hexyl)oxy]-4-[[2-(1-imidazolyl)-ethyl]oxy]benzoate (25). A stirred mixture of ester **22** (1.10 g, 4 mmol), K_2CO_3 (560 mg, 4 mmol), 6-chloro-1-hexanol (800 mg, 5.8 mmol), and NaI (600 mg, 4 mmol) in MeCOEt (20 mL) was refluxed for 72 h. H_2O (120 mL) was added and the mixture extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give a solid which was purified by flash column chromatography on silica gel. Elution with CH_2Cl_2–EtOH (90:10) followed by recrystallization from EtOAc–hexane gave, as a colorless solid, **25** (910 mg, 62%): ^{1}H-NMR ($CDCl_3$) δ 1.38 (t, 3H), 1.57 (m, 6H), 1.86 (m, 2H), 2.97 (m, 1H), 3.66 (t, 2H), 4.05 (t, 2H), 4.32 (m, 6H), 6.80 (d, 1H), 7.05 (m, 2H), 7.52 (d, 1H), 7.60 (m, 1H), 7.82 (b s, 1H). Anal. ($C_{20}H_{28}N_2O_5$) C, H, N.

Ethyl 3-[(5-Formyl-*n*-pentyl)oxy]-4-[[2-(1-imidazolyl)-ethyl]oxy]benzoate (26). The alcohol **25** (690 mg, 1.84 mmol) in CH_2Cl_2 (5 mL) was added to a solution of $(COCl)_2$ (250 mg, 2.01 mmol) and DMSO (350 mg, 4.3 mmol) at −60 °C. The mixture was stirred 1 h at −60 °C and 0.5 h at −40 °C. After recooling to −60 °C, Et_3N (930 mg, 9.2 mmol) was added. After 30 min, CH_2Cl_2 (25 mL) was added, the reaction warmed to 25 °C, and H_2O (25 mL) added. The organic phase was separated and the aqueous phase reextracted with CH_2Cl_2. CH_2Cl_2 was washed with brine, dried, and evaporated to give an oil which was purified by flash column chromatography on silica gel. Elution with $CHCl_3$–EtOH (49:1) gave, as a colorless solid, **26** (350 mg, 53%): mp 47–48 °C; ^{1}H-NMR ($CDCl_3$) δ 1.38 (t, 3H), 1.56 (m, 2H), 1.73 (m, 2H), 1.88 (m, 2H), 2.50 (m, 2H), 4.04 (t, 2H), 4.34 (m, 6H), 6.80 (d, 1H), 7.10 (d, 2H), 7.52 (m, 1H), 7.62 (q, 1H), 7.72 (s, 1H), 9.78 (s, 1H). Anal ($C_{20}H_{26}N_2O_5$) C, H, N.

Ethyl 3-[(4-Formylphenoxy)ethoxy]-4-[[2-(1-imidazolyl)-ethyl]oxy]benzoate (27). The ester **22** (276 mg, 1 mmol) was added to NaH (50 mg, 1.25 mmol) in DMF (2 mL) at 0 °C. After 30 min, 4-(2-chloroethoxy)benzaldehyde (230 mg, 1.25 mmol) in DMF (3 mL) and NaI (15 mg, 0.1 mmol) were added. The mixture was heated at 85 °C for 6 h and cooled. H_2O (100 mL) was added and the aqueous phase extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give an oil which was purified by flash column chromatography on silica gel. Elution with CH_2Cl_2–EtOH (95:5) gave, as a colorless solid, **27** (163 mg, 39%); mp 103–106 °C; ^{1}H-NMR (DMSO-d_6) δ 1.30 (t, 3H), 4.34 (m, 10H), 7.45 (m, 10H), 9.85 (s, 1H). Anal. ($C_{23}H_{24}N_2O_6$) C, H, N.

In a similar manner the following esters were prepared: methyl 3-[(3-formylphenoxy)ethoxy]-4-[[2-(1-imidazolyl)ethyl]-oxy]benzoate (**28**; 77%; mp 129–131 °C), methyl 3-[(2-formylphenoxy)ethoxy]-4-[[2-(1-imidazolyl)ethyl]oxy]benzoate (**29**; 70%; mp 100 °C), ethyl 3-[[(4-formylphenoxy)-*n*-hexyl]oxy]-4-[[2-(1-imidazolyl)ethyl]oxy]benzoate (**30**; 75%; mp 68–71 °C).

(5-Bromopyrid-3-yl)methanol (32). $SOCl_2$ (20 mL) was added dropwise over 30 min to a stirred solution of 5-bromonicotinic acid (10 g, 49 mmol) in EtOH (250 mL). The mixture was stirred for 3 days and evaporated to dryness. Aqueous Na_2CO_3 was added and the mixture extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was dissolved in $PhCH_3$ and evaporated to give as a crude solid, **31** (12.6 g). A solution of **31** (45.5 g, 230 mmol) in MeOH (100 mL) was added dropwise to $NaBH_4$ (87 g, 2.3 mol) in MeOH (400 mL). The mixture was maintained at reflux for 2 h and then allowed to cool to 25 °C. H_2O (300mL) was added and the mixture concentrated to 400 mL and extracted with EtOAc. The organic phase was washed with 1 M HCl. The aqueous phase was adjusted to pH 9 with 2 M NaOH and extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give, as a red oil, **32** (17.3 g, 40%): ^{1}H-NMR ($CDCl_3$) δ 4.2 (s, 2H), 7.45 (m, 1H), 8.0 (m, 1H), 8.08 (m, 1H).

5-Bromo-3-formylpyridine (33). Pyridinium chlorochromate (6.0 g, 220 mmol) was added to a stirred solution of **32** (4.0 g, 21 mmol) in CH_2Cl_2 (100 mL). After 1 h, Et_2O (100 mL) was added. After a further 30 min the mixture was filtered through a short column of Fluorisil. The filtrate was evaporated to give, as an oil, **33** (2.0 g, 51%): ^{1}H-NMR ($CDCl_3$) δ 8.3 (m, 1H), 8.9 (m, 1H), 9.0 (m, 1H), 10.08 (s, 1H).

Ethyl (*E*/*Z*)-7-(3-Formylpyridyl)-7-phenylhept-6-enoate (35). *p*-Toluenesulfonic acid (2.7 g, 143 mmol) and trimethyl orthoformate (1.6 mL, 143 mmol) were added to a stirred solution of **33** (2.5 g, 13 mmol) in MeOH (50 mL). The mixture was heated at reflux for 18 h and cooled to 25 °C. Aqueous Na_2CO_3 was added to give pH 8, and the mixture was concentrated by evaporation. H_2O was added and the mixture extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was purified by short-path (Kugelrohr) distillation (0.15 mmHg, oven temperature 140 °C) to give, as a colorless oil, **34** (2.3g, 75%). ^{n}BuLi (1.55 M solution in hexane; 7 mL, 10.85 mmol) was added dropwise over 30 min to a stirred solution of **34** (2.3 g, 10 mmol) in THF (50 mL) at −78 °C. The mixture was stirred at −78 °C for 30 min and a solution of *N*,*N*-dimethylbenzamide (1.42 g, 10 mmol) in THF (20 mL) added dropwise over 10 min. The mixture was stirred at −78 °C for 30 min and (carboxybutyl)-triphenylphosphonium bromide (6.75 g, 15 mmol) added before the mixture was allowed to warm to −10 °C. A solution of KO^{t}Bu (2.24 g, 20 mmol) in THF (60 mL) was added and the mixture stirred at 25 °C for 18 h. Aqueous HCl was added and the mixture extracted with EtOAc. The aqueous phase was adjusted to pH 5 with aqueous Na_2CO_3 and extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give an oil which after esterification (HCl–EtOH) was purified by chromatography on silica gel in hexane–EtOAc–AcOH (50:50:1) to give, as an oil, **35** (0.57 g, 18%); ^{1}H-NMR ($CDCl_3$) δ 1.6 (m, 3H), 2.2 (m, 5H), 6.2 (t, 0.3H, J = 7 Hz, C=CH [*E*]), 6.35 (t, 0.7H, J = 7 Hz, C=CH [*Z*]), 7.1–8.0 (m, 6H), 8.5–8.7 (m, 2H), 10.0 (s, 0.7H, CHO [*Z*]), 10.1 (s, 0.3H, CHO [*E*]).

Ethyl (*E*)-7-(3-Pyridyl)-7-phenyl-2-(prop-2-enyl)hept-6-enoate (37). ^{n}BuLi (1.6 M in hexane; 7.8 mL, 12.48 mmol) was added to a stirred solution of diisopropylamine (8.6 mL, 62 mmol) in THF (75 mL) at −78 °C. The mixture was stirred for 10 min, and a solution of ethyl (*E*)-7-(3-pyridyl)-7-phenylhept-5-enoate (**36**; 10.0 g, 31 mmol) in THF (30 mL) was added over 10 min. The mixture was stirred for 30 min at −78 °C and then a solution of allyl bromide (3.0 mL, 35 mmol) in DMPU (15 mL) was added and the reaction allowed to warm to −30 °C. The mixture was stirred for 15 min at −30 °C and then aqueous 2 M HCl (40 mL) was added and the mixture allowed to warm to 25 °C. Aqueous Na_2CO_3 was added to pH 9 and the mixture extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give an oil that was purified by chromatography on silica gel eluting with hexane–EtOAc–AcOH (from 100:0:1 to 50:50:1) to give, as an oil, **37** (9.6 g, 65%): ^{1}H-NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.48 (m, 4H), 2.18 (m, 2H), 2.35 (m, 2H), 4.13 (q, 2H), 5.2 (t, 2H), 5.71 (m, 2H), 6.09 (t, 1H), 7.17 (m, 3H), 7.37 (m, 4H), 8.45 (m, 1H), 8.51 (m, 1H).

Ethyl (*E*)-7-(3-Pyridyl)-7-phenyl-2-(formylmethyl)hept-6-enoate (38). To a stirred solution of **37** (3.2 g, 9 mmol) in ^{t}BuOH (150 mL) at 50 °C was added a solution of sodium periodate (3.6 g, 16 mmol) in H_2O (60 mL) and *p*-toluenesulfonic acid (1.70 g, 9 mmol), and a solution of OsO_4 in ^{t}BuOH (2.5%, 1.6 mL) was added. The reaction was stirred at 50 °C for 2.5 h and allowed to cool to 25 °C. H_2O was added and the mixture extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give an oil which was purified

by chromatography on silica gel, eluting with $PhCH_3$–EtOAc–AcOH (100:0:1 to 50:50:1) to give, as an oil, **38** (0.45 g, 16%): ^{1}H-NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.48 (m, 2H), 1.65 (m, 2H), 2.16 (m, 2H), 2.5 (m, 2H), 2.85 (m, 2H), 4.14 (q, 2H), 6.08 (t, 1H), 7.15 (m, 3H), 7.37 (m, 4H), 8.45 (m, 1H), 8.5 (s, 1H), 9.75 (s, 1H).

(*E*/*Z*)-7-(3-Pyridyl)-7-(4-formylphenyl)hept-6-enoic Acid (41). A solution of 3-bromopyridine (5 g, 30 mmol) in Et_2O (10 mL) was added dropwise over 30 min to a stirred solution of ^{n}BuLi (1.6 M in hexane; 25 mL, 40 mmol) in Et_2O (40 mL) at −78 °C. The mixture was stirred at −78 °C for 20 min and a solution of 4-(diethoxymethyl)benzaldehyde (6.6 g, 30 mmol) in Et_2O (30 mL) added. The mixture was stirred at −78 °C for 20 min and allowed to warm to 25 °C. H_2O (300 mL) was added and the mixture extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give an oil. The oil was purified by flash chromatography on silica gel, eluting with hexane–EtOAc (from 100:0 to 0:100, by volume) to give, as an oil, **39** (5.4 g, 62%). A solution of DMSO (2.4 mL, 33 mmol) in CH_2Cl_2 (8 mL) was added dropwise over 10 min to a stirred solution of $(COCl)_2$ (1.14 mL, 15 mmol) in CH_2Cl_2 at −78 °C. The mixture was stirred for 15 min and a solution of **39** (4.0 g, 14 mmol) in CH_2Cl_2 (15 mL) added. The mixture was stirred for 15 min at −78 °C, Et_3N (9.8 mL, 90 mmol) added, and the mixture allowed to warm to 25 °C over 18 h. H_2O (50 mL) was added and the mixture extracted with CH_2Cl_2. The extract was dried and evaporated to give, as an oil, **40** (2.8 g, 80%). A solution of **40** (2.8 g, 10 mmol) in THF (20 mL) was added to a stirred mixture of KO^{t}Bu (6 g, 50 mmol) and (carboxypentyl)triphenylphosphonium bromide (11.4 g, 25 mmol) in THF (80 mL) at −10 °C. The mixture was allowed to warm to 25 °C over 18 h and concentrated under reduced pressure. 2 M HCl (350 mL) was added and the mixture stirred for 20 min and then adjusted to pH 5 before extraction with EtOAc. The extract was dried and evaporated to give a gum which was purified by flash chromatography on silica gel eluting with hexane–EtOAc–AcOH (from 90:10:1 to 50:50:1) to give, as an oil, **41** (2.0 g, 71%, *E*/*Z* mixture 1/2): ^{1}H-NMR ($CDCl_3$) δ 1.6 (m, 3H), 2.2 (m, 2H), 2.3 (m, 3H), 6.22 (t, $^1/_3$H*E*), 6.35 (t, $^2/_3$H*Z*), 7.3 (m, 4H), 7.1–7.55 (m, 6H), 7.8 (d, $^2/_3$H), 7.92 (d, $^1/_3$H), 8.48 (d, 1H), 8.59 (m, 1H), 9.99 (s, $^2/_3$H), 10.05 (s, $^1/_3$H).

(*E*)-7-(3-Pyridyl)-7-(4-formylphenyl)hept-6-enoic Acid (42). **41** was chromatographed on a Dynamax (30 by 2.5 cm, 5 μm silica) column, eluting with hexane–EtOAc–HOAc (40:60:1) to give as an oil **42**: ^{1}H-NMR ($CDCl_3$) δ 1.65 (m, 4H), 2.19 (m, 2H), 2.35 (m, 2H), 6.2 (t, 1H), 7.1–7.55 (m, 6H), 7.92 (d, 1H), 8.58 (d, 1H), 8.9 (d, 1H), 10.05 (s, 1H). Anal. ($C_{19}H_{19}NO_3$) C, H, N.

(*E*)-7-[4-(1-Formyl-1-methylethyl)phenyl]-7-(3-pyridyl)hept-6-enoic Acid (45). NaH (20 g, 0.5 mol) was added in portions over 1.5 h to a stirred mixture of (*p*-bromophenyl)-acetonitrile (49 g, 0.25 mol) and iodomethane (71 g, 0.5 mol) in DMF (400 mL) at 0 °C. The mixture was allowed to warm to 25 °C over 18 h, poured onto ice/water, and extracted with EtOAc. The extract was dried and evaporated. The residue was purified by short-path (Kugelrohr) distillation (1.2 mmHg; oven temperature 160 °C) to give, as an oil, **43** (41 g, 75%). DIBAL (1.5 M in $PhCH_3$; 170 mL, 260 mmol) was added slowly to a stirred solution of **43** (24 g, 110 mmol) in THF (200 mL). The mixture was warmed to 50 °C for 15 min and cooled to 0 °C. EtOAc (10 mL) was added dropwise. The mixture was poured onto 1 M aqueous HCl (300 mL) and extracted with EtOAc. The extract was dried and evaporated. MeOH (200 mL), trimethyl orthoformate (10 mL, 100 mmol), and *p*-toluenesulfonic acid (0.5 g, 2.5 mmol) were added, and the mixture was heated at reflux for 2 h. The mixture was concentrated, poured onto 1 M $NaHCO_3$, and extracted with EtOAc. The extract was dried and evaporated. The residue was purified by short-path (Kugelrohr) distillation (2 mmHg; oven temperature 150 °C) to give, as an oil, **44** (12.1 g, 40%): ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 6H), 3.4 (s, 6H), 4.1 (s, 1H), 7.3 (d, 2H), 7.5 (d, 2H). ^{n}BuLi (1.55 M in hexane; 26 mL, 40 mmol) was added dropwise over 30 min to a stirred solution of **44** (11 g, 40 mmol) in THF (180 mL) at −78 °C. The mixture was stirred for 30 min and a solution of *N*-methoxy-*N*-methylnicotinamide (6.7 g, 40 mmol) in THF (20 mL) added over 10 min. The mixture was allowed to warm to 25 °C over 18 h, concentrated, poured onto H_2O (50 mL), and extracted with EtOAc. The extract was dried, diluted with an equal volume of $PhCH_3$, and evaporated. The residue was dissolved in THF (200 mL) and added to a stirred mixture of (carboxypentyl)triphenylphosphonium bromide (42 g, 90 mmol) and KO^{t}Bu (20 g, 180 mmol) in THF (1L) at −10 °C. The mixture was allowed to warm to 25 °C over 18 h and concentrated under reduced pressure. 3 M HCl (150 mL) was added and the mixture stirred at 25 °C for 30 min, before extraction with EtOAc. The aqueous phase was adjusted to pH 12, washed with EtOAc, adjusted to pH 5, and extracted with EtOAc. The organic extract was dried and evaporated. The residue was purified by flash chromatography on silica gel eluting with hexane–EtOAc–AcOH (90:10:1 to 60:40:1) to give, as an oil, **45** (6.0 g, 43%, *E*/*Z* 1/2): ^{1}H-NMR ($CDCl_3$) δ 1.5 (d, 6H), 1.6 (m, 4H), 2.3 (m, 4H), 6.2 (t, 1H), 7.2 (m, 2H), 7.5 (m, 2H), 7.7 (m, 2H), 8.5 (m, 2H), 9.5 (s, 1H).

6-(Acetoxymethyl)-2-formylnaphthalene (47). The methanol **46** (7.65 g, 33.4 mmol) in CH_2Cl_2 (150 mL) was added over 30 min to a solution of $(COCl_2)$ (4.77 g, 36.9 mmol) and DMSO (5.7 mL, 80 mmol) at −70 °C. After 30 min Et_3N (28 mL, 198 mmol) was added and stirring continued for 30 min. The reaction was warmed to 25 °C, washed with H_2O and brine, dried, and evaporated. The residue was purified by flash column chromatography on silica gel. Elution with hexane–EtOAc (70:30) gave, as a colorless solid, **47** (6.9 g, 91%): mp 87–90 °C; ^{1}H-NMR ($CDCl_3$) δ 2.18 (s, 3H), 5.3 (s, 2H), 7.56 (dd, 1H), 7.95 (m, 4H), 8.32 (s, 1H), 10.15 (s, 1H). Anal. ($C_{14}H_{12}O_3$) C, H, N.

6-(Hydroxymethyl)-2-formylnaphthalene (48). The aldehyde **47** (6.87 g, 30 mmol) was stirred with K_2CO_3 (4.73 g, 34 mmol) in MeOH (100 mL) and H_2O (5 mL) at 25 °C for 1 h. H_2O (750 mL) was added and the aqueous phase extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give, as a colorless solid, **48** (5.33 g, 96%): mp 83–85 °C.

6-(Hydroxymethyl)-2-(1,3-dioxan-2-yl)naphthalene (49). Aldehyde **48** (5.80 g, 31 mmol) and *p*-toluenesulfonic acid (130 mg, 0.68 mmol) were added to 1,3-dihydroxypropane (2.80 g, 37 mmol) in PhMe (200 mL), and the mixture was heated under reflux for 3 h with continuous Dean and Stark azeotropic distillation. After cooling, EtOAc (200 mL) was added. The mixture was washed with a $NaHCO_3$ solution and brine, dried, and evaporated. Trituration with $PhCH_3$ followed by filtration gave, as a colorless solid, **49** (6.3 g, 86%): mp 93–96 °C; ^{1}H-NMR ($CDCl_3$) δ 1.5 (m, 1H), 2.17 (m, 1H), 4.05 (m, 2H), 4.13 (m, 2H), 4.83 (s, 2H), 5.66 (s, 1H), 7.46 (dd, 1H), 7.60 (dd, 1H), 7.88 (m, 4H). Anal ($C_{15}H_{16}O_3$) C, H.

General Procedure for Swern Oxidation. 6-(1,3-Dioxan-2-yl)-2-formylnaphthalene (50). DMSO (4.47 mL, 62.9 mmol) in CH_2Cl_2 (35 mL) was added slowly to $(COCl)_2$ (3.61 g, 28.4 mmol) in CH_2Cl_2 (50 mL) at −70 °C. After 10 min the alcohol **49** (6.27 g, 26 mmol) in CH_2Cl_2 (150 mL) was added over 10 min at −65 to −70 °C. After stirring at −70 °C for 45 min, Et_3N (21 mL, 151 mmol) was added. The reaction was warmed to 25 °C and the organic phase washed with H_2O and brine. The dried extract was evaporated to give a solid which was recrystallized from EtOAc–hexane to give, as a colorless solid, **50** (4.0 g, 64%): mp 141–144 °C; ^{1}H-NMR ($CDCl_3$) δ 1.55 (m, 1H), 2.30 (m, 1H), 4.07 (m, 2H), 4.35 (m, 2H), 5.70 (s, 1H), 7.70 (m, 1H), 8.02 (m, 4H), 8.33 (d, 1H), 10.18 (s, 1H). Anal. ($C_{15}H_{14}O_3$) C, H.

General Lithiation Procedure. 6-(1,3-Dioxan-2-yl)-2-[1-hydroxy-1-(3-pyridyl)methyl]naphthalene (51). 3-Bromopyridine (2.37 g, 15.0 mmol) in Et_2O (20 mL) was added over 10 min to a stirred solution of ^{n}BuLi (11.5 mL, 1.6 M in hexane; 18.4 mmol) in Et_2O (20 mL) at − 70 °C. Addition of aldehyde **50** (3.67 g, 15.2 mmol) in THF (100 mL) and Et_2O (40 mL) portionwise over 1 h at −70 °C was followed by stirring at −70 °C for 1 h. The reaction was warmed to 25 °C and H_2O (100 mL) added. The aqueous phase was extracted with EtOAc and the extract washed with brine, dried, and evaporated. The residue was recrystallized from EtOAc–hexane to give, as a pale yellow solid, **51** (2.6 g, 55%): mp 151–152 °C; ^{1}H-NMR ($CDCl_3$) δ 1.49 (m, 1H), 2.25 (m, 1H), 2.73 (m, 1H),

4.04 (m, 2H), 4.32 (m, 2H), 5.66 (s, 1H), 6.02 (s, 1H), 7.25 (m, 1H), 7.48 (m, 1H), 7.65 (m, 2H), 7.83 (d, 3H), 7.94 (s, 1H), 8.48 (m, 1H), 8.66 (d, 1H). Anal. ($C_{20}H_{19}NO_3$) C, H, N.

3-Pyridyl-2-[6-(1,3-dioxan-2-yl)naphthyl]methanone (52). The alcohol **51** was oxidized by the method described for the preparation of **50**. The residual oil was purified by chromatography on neutral alumina (Fluka 507C) eluting with EtOAc to give, as a colorless solid, **52** (1.45 g, 56%): mp 105–6 °C; ^{1}H-NMR ($CDCl_3$) δ 1.52 (m, 1H), 2.37 (m, 1H), 4.05 (m, 2H), 4.33 (m, 2H), 5.68 (s, 1H), 7.53 (m, 1H), 7.69 (m, 1H), 7.95 (m, 3H), 8.03 (s, 1H), 8.22 (m, 2H), 8.84 (m, 1H), 9.06 (s, 1H). Anal. ($C_{20}H_{17}NO_3$), C, H, N.

General Procedure for Wittig Reaction. (*E*)-7-(3-Pyridyl)-7-(6-formyl-2-naphthyl)hept-6-enoic Acid (54). To a suspension of carboxypentyltriphenylphosphonium bromide (4.91 g, 10.75 mmol) in THF (50 mL) at −10 °C was added KO^{t}Bu (2.40 g, 21.5 mmol). After 20 min at −10 °C, ketone **52** (1.39 g, 4.3 mmol) in THF (25 mL) was added over 10 min. After 3 h at 25 °C, H_2O (5 mL) was added followed by 2 M HCl (100 mL) and the mixture stirred for 15 min. The solution was washed with EtOAc. The aqueous phase was made alkaline to pH 9 with a Na_2CO_3 solution and washed with Et_2O. The aqueous phase was adjusted to pH 4.5 with HOAc and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The mixture was purified by HPLC on a 30 × 2.5 cm Dynamax silica column eluting with CH_2Cl_2–MeOH–HOAc (100:2:1) to give (RT 11.7 min), as a colorless solid, **54** (380 mg, 24%); mp 153–4 °C; ^{1}H-NMR ($CDCl_3$) δ 1.61 (m, 4H), 2.28 (m, 4H), 3.80 (m, 1H), 6.27 (t, 1H), 7.23 (m, 1H), 7.35 (dd, 1H), 7.42 (dd, 1H), 7.71 (s, 1H), 7.98 (m, 3H), 8.34 (s, 1H), 8.48 (d, 1H), 8.64 (s, 1H), 10.18 (s, 1H); CI-MS *m/z* 359 (M^+). Anal. ($C_{23}H_{21}NO_3$) C, H, N.

(*E*/*Z*)-7-(4-Methoxyphenyl)-7-(3-pyridyl)hept-6-enoic Acid (57). To a suspension of (5-carboxypentyl)triphenylphosphonium bromide (28.56 g, 62.5 mmol) in DMSO (50 mL) was added a solution of 1.5 M dimsylsodium (100 mL, 150 mmol) in DMSO and the resulting solution stirred for 20 min. A solution of ketone **56** (10.65 g, 50 mmol) in DMSO (75 mL) was added slowly. After stirring for 4 h, the mixture was poured onto H_2O (675 mL) and toluene (675 mL) and the organic layer separated. The aqueous layer was washed with Et_2O (200 mL) and acidified to pH 5 with 12 M HCl. The aqueous layer was extracted with EtOAc and the extract washed with brine, dried, and evaporated. The residue was chromatographed on silica gel eluting with EtOAc–hexane (50:50) to give **57** (7.0 g, 45%): ^{1}H-NMR ($CDCl_3$) δ 1.45–1.75 (m, 4H), 2.1–2.4 (m, 4H), 3.8 (d, 3H), 6.1 (t, 1H), 6.75–6.95 (m, 2H), 7.0–7.1 (m, 2H), 7.5 (m, 2H), 8.4–8.6 (m, 2H), 9.0–9.4 (s, 1H).

Ethyl (*E*)-7-(4-Hydroxyphenyl)-7-(3-pyridyl)hept-6-enoate (58). The methyl ether **57** (29.7 g, 95 mmol) was heated under reflux in 48% HBr (150 mL) for 4 h, poured onto H_2O (750 mL), and adjusted to pH 5 with 8 M NaOH. The aqueous layer was extracted with EtOAc, and the extract washed with brine, dried, and evaporated. The residue was added to a solution of $SOCl_2$ (16.0 mL, 220 mmol) in EtOH (160 mL) at −35 °C. The mixture was stirred at room temperature for 3 h and the EtOH evaporated. The residue was dissolved in EtOAc, and the organic layer washed with a $NaHCO_3$ solution and brine, dried, and evaporated. The residue was chromatographed on silica gel eluting with EtOAc–hexane (50:50) to give **58** (14.2 g, 46%): ^{1}H- NMR ($CDCl_3$) δ 1.3 (t, 3H), 1.6 (m, 4H), 2.2 (m, 4H), 4.1 (q, 2H), 6.05 (t, 1H), 6.8 (m, 2H), 6.95 (m, 2H), 7.25 (m, 1H), 7.65 (m, 1H), 8.35 (s, 1H), 8.45 (d, 1H).

Ethyl (*E*)-7-[4-[[(1,3-Dioxolan-2-yl)ethyl]oxy]phenyl]-7-(3-pyridyl)hept-6-enoate (59). To a suspension of NaH (0.17 g, 7 mmol) in DMF (3 mL) was added a solution of the ester **58** (1.63 g, 5 mmol) in DMF (5 mL). After 10 min, 2-(2-bromoethyl)-1,3-dioxolane (**63**; 1.1 g, 6 mmol) was added. The mixture was stirred for 4 h, poured onto H_2O (150 mL), and extracted with EtOAc. The organic extract was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel eluting with EtOAc–hexane (50:50) to give **59** (1.2 g, 54%): ^{1}H-NMR ($CDCl_3$) δ 1.2–1.3 (t, 3H), 1.45–1.7 (m, 4H), 2.1–2.3 (m, 6H), 3.85–4.2 (m, 8H), 5.1 (t, 1H), 6.0 (t, 1H), 6.85–7.1 (dd, 4H), 7.1–7.2 (dd, 1H), 7.4–7.5 (d, 1H), 8.4 (d, 1H), 8.5 (s, 1H).

11-(Tetrahydropyranyloxy)-1-bromoundecane (65). To a solution of 11-bromoundecanol (5.02 g, 20 mmol) and *p*-toluenesulfonic acid (25 mg, 0.13 mmol) in CH_2Cl_2 (50 mL) was added dihydropyran (2.1 g, 25 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, filtered through alumina in CH_2Cl_2, and evaporated to give **65** (5.9 g, 88%): ^{1}H-NMR ($CDCl_3$) δ 1.15–2.0 (m, 24H), 3.3–4.0 (m, 6H), 4.5 (m, 1H).

Ethyl (*E*)-7-[4-[[11-(Tetrahydropyranyloxy)undecyl]-oxy]phenyl]-7-(3-pyridyl)hept-6-enoate (61). To a suspension of NaH (0.24 g, 10 mmol) in DMF (4 mL) was added a solution of the ester **58** (2.6 g, 8 mmol) in DMF (8 mL). After 10 min, the bromo compound **65** (2.95 g, 8.8 mmol) was added. The mixture was stirred for 4 h and poured onto H_2O (220 mL) and the aqueous layer extracted with EtOAc. The organic extract was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel eluting with hexane–EtOAc (60:40) to give **61** (2.8 g, 60%): ^{1}H-NMR ($CDCl_3$) δ 1.2 (t, 3H), 1.3–1.9 (m, 28H), 2.1–2.3 (dt, 4H), 3.3–3.55 (m, 2H), 3.7–3.9 (m, 2H), 3.95 (t, 2H), 4.1 (q, 2H), 4.55 (t, 1H), 6.0 (t, 1H), 6.85–7.05 (dd, 4H), 7.15 (m, 1H), 7.45 (dd, 1H), 8.4 (d, 1H), 8.5 (s, 1H).

Ethyl (*E*/*Z*)-7-(4-Formylphenyl)-2,2-dimethylhept-6-enoate (68). To a solution of diisopropylamine (28.0 mL, 200 mmol) in THF (200 mL) was added ^{n}BuLi (126 mL, 1.6 M in hexane; 200 mmol) at −78 °C. The mixture was stirred for 30 min, and ethyl isobutyrate (28.0 mL, 210 mmol) in THF (40 mL) added at −78 °C. The mixture was stirred for 1 h. To the mixture was added 1,4-dibromobutane (33.8 mL, 280 mmol) at −78 °C, followed by DMPU (30 mL) at −78 °C. The mixture was stirred for 30 min and the THF evaporated. The residue was dissolved in a saturated NH_4Cl solution (1 L) and the aqueous layer extracted with EtOAc. The organic extract was washed with brine, 1 M HCl, and a saturated $NaHCO_3$ solution, dried, and evaporated. The residue was distilled to give ethyl 6-bromo-2,2-dimethylhexanoate (37.8 g, 72%) (bp 0.2 mm Hg, 86 °C), which was heated under reflux in 48% HBr in AcOH (150 mL) for 16 h. The AcOH was evaporated, and the residue taken up in 1 M NaOH (300 mL), and the aqueous layer washed with Et_2O. The aqueous phase was acidified to pH 1 with 12 M HCl and extracted with Et_2O. The organic extract was washed with brine, dried, and evaporated to give **67** (25.2 g, 54%); IR (film, cm^{-1}) 1690 (carbonyl). To a solution of the bromo acid **67** (25.2 g, 113 mmol) in $PhCH_3$ (250 mL) was added Ph_3P (29.6 g, 113 mmol). The mixture was heated under reflux for 16 h and the $PhCH_3$ evaporated. To a suspension of the residual phosphonium salt in DMSO (100 mL) was added a solution of 1.5 M dimsylsodium (180 mL, 270 mmol) in DMSO and the resulting solution stirred for 20 min. A solution of terephthalaladehyde mono(diethyl acetal) (18.72 g, 90 mmol) in DMSO (100 mL) was added slowly. After stirring for 4 h the mixture was poured onto H_2O (1.25 L) and $PhCH_3$ (1.25 L) and the organic layer separated. The aqueous layer was washed with Et_2O (1 L) and acidified to pH 1 with 12 M HCl. The aqueous layer was extracted with EtOAc and the extract washed with brine, dried, and evaporated. The residue was chromatographed on silica gel eluting with EtOAc–hexane (50:50) to give the acid (12.7 g, 49 mmol) which was added to saturated ethanolic HCl (100 mL). The mixture was heated under reflux for 16 h and the EtOH evaporated. The residue was dissolved in EtOAc the organic layer washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated. The residue was chromatographed on silica gel eluting with hexane–EtOAc (98:2) to give **68** (7.9 g, 30%): ^{1}H-NMR ($CDCl_3$) δ 1.2 (s, 6H), 1.5–1.7 (m, 4H), 2.2–2.3 (m, 2H), 6.4 (m, 2H), 7.4–7.8 (dd, 4H), 9.95 (s, 1H).

7-[4-[1-Hydroxy-1-(3-pyridyl)methyl]phenyl)]2,2-dimethylheptan-1-ol (69). To a stirred solution of ^{n}BuLi (21.6 mL, 1.6 M hexane solution, 34.6 mmol) in Et_2O (35 mL) was added a solution of 3-bromopyridine (4.3 g, 27 mmol) in Et_2O (35 mL) at −78 °C. To the mixture was added a solution of the aldehyde **68** (7.85 g, 27 mmol) in Et_2O (70 mL) and THF (7 mL) at −78 °C and stirring was continued at room temperature for 2 h. The mixture was poured onto H_2O and

the organic layer separated. The aqueous layer was extracted with EtOAc, and the extract was combined with the organic layer. The combined extract was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel eluting with EtOAc to give the intermediate olefin (5.2 g, 52%), which was dissolved in EtOH (130 mL) and hydrogenated over 10% Pd–C (0.5 g). After the theoretical amount of hydrogen was absorbed, the catalyst was filtered. The filtrate was evaporated and the residue chromatographed on silica gel eluting with EtOAc to give the hydroxy ester (5.0 g, 96%), which was dissolved in THF (25 mL) and added to a suspension of $LiAlH_4$ (2.0 g, 54 mmol) in THF (200 mL) at 5 °C. After stirring at room temperature for 4 h, H_2O (2.0 mL), 15% NaOH solution (6.0 mL), and H_2O (2.0 mL) were added sequentially. The mixture was filtered and the filtrate evaporated. The residue was chromatographed on silica gel eluting with EtOAc to give **69** (4.5 g, 50%): ^{1}H-NMR ($CDCl_3$) δ 0.85 (s, 6H), 1.2–1.35 (m, 6H), 1.6–1.7 (m, 2H), 2.6 (t, 2H), 3.3 (s, 2H), 5.8 (s, 1H), 7.1–7.25 (dd, 4H), 7.3 (m, 1H), 7.7 (m, 1H), 8.4 (d, 1H), 8.5 (s, 1H).

Ethyl (*E*)-7-(3-Pyridyl)-7-[4-[[2-[(4-formylphenyl)oxy]ethyl]oxy]phenyl]hept-6-enoate (74). To a stirred mixture of 4-hydroxybenzaldehyde (6.10 g, 50 mmol) and NaH (2.0 g, 50 mmol) in DMF (30 mL) at 0 °C was added a solution of 2-chloroethyl *p*-toluenesulfonate (11.80 g, 50 mmol) in DMF (20 mL) over 0.16 h. The mixture was heated at 105 °C for 4 h and cooled to 25 °C. The reaction was poured onto H_2O (400 mL) and extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give an oil which was purified by chromatography on silica gel. Elution with hexane–EtOAc (70:30) gave, as a colorless solid, **73** (6.7 g, 74%): mp 51 °C; ^{1}H-NMR ($CDCl_3$) δ 1.85 (t, 2H), 4.33 (t, 2H), 7.02 (m, 2H), 7.85 (m, 2H), 9.9 (s, 1H). Anal. ($C_9H_9ClO_2$) C, H. Aldehyde **73** (1.25 g, 6.84 mmol) in DMF (15 mL) was added to a stirred suspension of ester **58** (1.47 g, 4.6 mmol) and NaH (0.22 g, 5.5 mmol) in DMF (15 mL) at 0 °C over 10 min. KI (0.75 g, 4.5 mmol) was added and the mixture heated for 18 h at 60 °C and then cooled. H_2O (400 mL) was added and the mixture extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give an oil. Purification by flash chromatography on silica gel eluting with CH_2Cl_2–EtOH (99:1) gave, as a yellow oil, **74** (390 mg, 18%): ^{1}H-NMR ($CDCl_3$) δ 1.24 (t, 3H), 1.56 (m, 4H), 2.20 (m, 4H), 4.11 (q, 2H), 4.43 (m, 4H), 6.08 (t, 1H), 6.96 (m, 2H), 7.08 (m, 4H), 7.19 (m, 1H), 7.51 (m, 1H), 7.86 (m, 2H), 8.57 (m, 2H), 9.91 (s, 1H).

4-(Hydroxymethyl)benzaldehyde (75). To a stirred solution of terephthalaldehyde mono(diethyl acetal) (10.4 g, 50 mmol) in $PhCH_3$ (100 mL) at 0 °C was added sodium bis(2-methoxyethoxy)aluminum hydride (15 mL, 3.4 M solution in $PhCH_3$; 51 mmol) over 15 min. After 1 h, H_2O (50 mL) was added and the mixture stirred for 30 min. The mixture was filtered and the residue washed with H_2O and $PhCH_3$. The organic phase was separated, washed with brine, dried, and evaporated to given an oil (9.7 g), which was used without further purification; IR (film, cm^{-1}) 3400 (hydroxyl) and no absorption at 1650–1750 (carbonyl). The above oil was treated with HCl-saturated ether (70 mL) for 1 h at 25 °C, and the solution was added over 15 min to a saturated $NaHCO_3$ solution (250 mL). The mixture was extracted with EtOAc, and the extracts were washed with brine, dried, and evaporated to give an oil, which was purified by flash chromatography on silica gel eluting with hexane–EtOAc (70:30) to give, as a colorless oil, **75** (6.1 g, 89%); IR (film, cm^{-1}) 3400 (hydroxyl), 1680 (carbonyl).

4-[2-(Tetrahydropyranyloxy)ethyl]bromobenzene (76). To a stirred solution of 4-(2-hydroxyethyl)bromobenzene (4.02 g, 20 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *p*-toluenesulfonic acid (20 mg) and dihydropyran (2.00 g, 23.5 mmol). After 2 h, a $NaHCO_3$ solution (20 mL) was added. The organic phase was dried and evaporated to give an oil which was purified by chromatography on neutral alumina eluting with hexane–EtOAc (80:20) to give **76** (5.8 g, 98%): ^{1}H-NMR ($CDCl_3$) δ 1.40–1.90 (m, 6H), 2.85 (t, 2H), 3.45 (m, 1H), 3.55 (m, 1H), 3.72 (m, 1H), 3.91 (m, 1H), 4.58 (t, 1H), 7.12 (d, 2H), 7.38 (d, 2H).

4-(2-Hydroxyethyl)benzaldehyde (77). ^{n}BuLi (7.9 mL, 1.6 M in hexane; 12.8 mmol) was added to a solution of pyran **76** (3.50 g, 12.5 mmol) in THF (55 mL) at −90 °C over 10 min. After 1 h at −78 °C, DMF (1.88 g, 26 mmol) was added over 15 min and the mixture stirred for 1.5 h. The reaction mixture was quenched with a NH_4Cl solution (100 mL) and extracted with EtOAc. The extracts were washed with brine, dried, and evaporated to give an oil which was purified by flash chromatography on silica gel. Elution with hexane–EtOAc (80:20) gave, as a colorless oil, 4-[2-(tetrahydropyranyloxy)ethyl]-benzaldehyde (1.5 g, 52%): ^{1}H-NMR ($CDCl_3$) δ 1.40–1.90 (m, 6H), 2.98 (t, 2H), 3.43 (m, 1H), 3.66 (m, 2H), 3.97 (m, 1H), 4.58 (t, 1H), 7.41 (d, 2H), 7.80 (d, 2H), 9.70 (s, 1H). The above oil (1.48 g, 6.3 mmol) in $(CH_3)_2CO$ (30 mL) was stirred with 1 M HCl (25 mL) at 5 °C for 1.5 h. A $NaHCO_3$ solution (80 mL) was added and the solution extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated to give an oil. Purification by flash column chromatography eluting with hexane–EtOAc (50:50) gave, as a colorless oil, **77** (0.7 g, 74%): IR (film, cm^{-1}) 3480 (hydroxyl), 1690 (carbonyl); ^{1}H-NMR ($CDCl_3$) δ 2.97 (t, 2H), 3.91 (t, 2H), 7.40 (d, 2H), 7.82 (d, 2H), 9.94 (s, 1H). Anal. ($C_9H_{10}O_2$) C, H.

4-(1,3-Dioxan-2-yl)phenylethanol (78). The aldehyde **77** (1.20 g, 8 mmol), 1,3-dihydroxypropane (2.1 g, 28 mmol), and *p*-toluenesulfonic acid (20 mg) were refluxed in $PhCH_3$ (20 mL) for 1 h. After cooling, $PhCH_3$ (20 mL) was added and the organic phase washed with a saturated $NaHCO_3$ solution, dried, and evaporated to give, as an oil, **78** (1.4 g, 68%): IR (film, cm^{-1}) 3480 (hydroxyl).

2-[3-(Hydroxymethyl)phenyl]-1,3-dioxane (79). A stirred solution of 3-bromobenzaldehyde (9.25 g, 50 mmol), 1,3-dihydroxypropane (4.20 g, 55 mmol), and *p*-toluenesulfonic acid (0.25 g) in $PhCH_3$ (75 mL) was refluxed for 2.5 h with continuous removal of H_2O. After cooling, the organic phase was washed with a $NaHCO_3$ solution, dried, and evaporated to give an oil, which on purification by short-path distillation (Kugelrohr), gave 2-(3-bromophenyl)-1,3-dioxane (12.0 g, 99%): bp 200 °C/0.2 mmHg. The above oil (5.1 g, 21 mmol) in THF (75 mL) was cooled to −100 °C and ^{n}BuLi (15 mL, 1.6 M in hexane; 24 mmol) added. The mixture was stirred for 10 min at −100 °C and for 1.25 h at −78 °C. DMF (2 mL, 25 mmol) was added and the mixture stirred for 1 h at −70 °C. A $NaHCO_3$ solution (100 mL) was added and the reaction warmed to 0 °C and extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give an oil. Purification by flash column chromatography on silica gel and elution with hexane–EtOAc (75:25) gave, as a colorless oil, 2-(3-formylphenyl)-1,3-dioxane (3.34 g, 87%). The above oil (3.30 g, 17 mmol) in Et_2O (60 mL) was treated with $LiAlH_4$ (0.47 g, 12.75 mmol) and stirred 2 h at 0 °C. H_2O (0.5 mL), 15% w/v NaOH (1.5 mL), and then H_2O (1.5 mL) were added. After 30 min, the mixture was filtered and the residue washed with Et_2O. The Et_2O was dried and evaporated to give an oil. Purification by flash column chromatography on silica gel and elution with hexane–EtOAc (65:35) gave, as a colorless oil, **79** (3.1 g, 93%): ^{1}H-NMR ($CDCl_3$) δ 1.45 (m, 1H), 1.95 (s, 1H), 2.25 (m, 1H), 3.84 (m, 2H), 4.27 (m, 2H), 4.63 (s, 2H), 5.50 (s, 1H), 7.40 (m, 4H). Anal. ($C_{11}H_{14}O_3$) C, H.

Ethyl (*E*))-7-[4-[(3-Formylphenyl)methoxy]phenyl]-7-(3-pyridyl)hept-6-enoate (80). To a stirred solution of the ester **58** (5.00 g, 15.4 mmol), the 1,3-dioxane **79** (3.00 g, 15.3 mmol) and Ph_3P (4.45 g, 17 mmol) in THF (70 mL) was added diethyl azodicarboxylate (3.21 g, 18 mmol). After 16 h, 1 M HCl (250 mL) was added and the reaction stirred 30 min. The solution was extracted into EtOAc. The extract was washed with brine, dried, and evaporated to give an oil. Purification by flash chromatography on silica gel and elution with hexane–EtOAc (50:50) gave, as an oil, **80** (2.43 g, 36%): ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, 3H), 1.55 (m, 4H), 2.20 (m, 4H), 4.12 (q, 2H), 5.18 (s, 2H), 6.05 (t, 1H), 6.95 (d, 1H), 7.08 (d, 1H), 7.18 (m, 1H), 7.47 (m, 1H), 7.58 (t, 1H), 7.75 (m, 1H), 7.87 (m, 1H), 7.98 (s, 1H), 8.45 (m, 1H), 8.52 (m, 1H), 10.05 (s, 1H); CI-MS *m/z* 444 $(MH)^+$.

Ethyl (*E*))-7-(3-hydroxyphenyl)-7-(3-pyridyl)hept-6-enoate (83). Compound **83** (Scheme 13) was prepared in a manner similar to **58** (Scheme 9) using 3-methoxybenzaldehyde in place of *p*-anisaldehyde as the starting material to give

83 (32%): ^{1}H-NMR ($CDCl_3$) δ 1.25 (t, 3H), 1.4–1.7 (m, 4H), 2.1–2.4 (m, 4H), 4.1 (q, 2H), 6.0 (t, 1H), 6.6–6.9 (m, 2H), 7.2 (m, 2H), 7.4–7.7 (m, 2H), 8.4 (m, 2H).

Ethyl (*E*))-7-[3-[(4-formylphenyl)methoxy]phenyl]-7-(3-pyridyl)hept-6-enoate (84). To a solution of the ester **83** (1.11 g, 3.4 mmol) in THF (16 mL) was added Ph_3P (0.98 g, 3.7 mmol) and 4-(hydroxymethyl)benzaldehyde diethyl acetal (0.72 g, 3.4 mmol). After 5 min, a solution of diethyl azodicarboxylate (0.54 mL, 3.4 mmol) in THF (4 mL) was added at 5 °C. After stirring at room temperature for 16 h, the mixture was poured onto 1 M HCl (56 mL). After 1 h the mixture was extracted with EtOAc, the organic extract washed with brine, dried, and evaporated. The residue was chromatographed on silica gel eluting with hexane–EtOAc (60:40) to give **84** (0.6 g, 38%): ^{1}H-NMR ($CDCl_3$) δ 1.3 (t, 3H), 1.4–1.7 (m, 4H), 2.1–2.4 (m, 4H), 4.1 (q, 2H), 5.15 (s, 2H), 6.1 (t, 1H), 6.7–6.8 (m, 2H), 6.9–7.0 (dd, 1H), 7.15 (m, 1H), 7.3 (m, 1H), 7.45 (dt, 1H), 7.6–7.9 (dd, 4H), 8.4–8.5 (m, 2H), 10.0 (s, 1H).

Ethyl (*E*))-7-[4-[[4-[(2*RS*,4*RS*,5*SR*)-5-[(*Z*)-5-carboxypent-2-enyl]-4-(2-hydroxyphenyl)-1,3-dioxan-2-yl]benzyl]oxy]-phenyl]-7-(3-pyridyl)hept-6-enoate (85). To a solution of the silyl ether ester **14** (1.5 g, 3.25 mmol) in EtOH (15 mL) was added 1 M NaOH (15 mL) and the mixture stirred at room temperature for 16 h. The EtOH was evaporated and the residue poured onto 1 M HCl (15 mL) and extracted with EtOAc. The organic extract was washed with brine, dried, and evaporated. The residue was dissolved in EtOAc and filtered through a short silica column. Evaporation gave the acid **14a** (1 g). **14a** in DMF (5 mL) was treated with imidazole (1.1 g, 16.3 mmol) and *tert*-butyldimethylsilyl chloride (1.48 g, 9.3 mmol) and the mixture stirred for 16 h. H_2O (100 mL) was added before extraction with EtOAc. EtOAc was washed with brine, dried, and evaporated. Chromatography on silica gel and elution with hexane–EtOAc (80:20) gave as an oil the disilyl-1,3-dioxane **14c** (1.1 g, 59%). To a solution of **14c** (0.98 g, 1.79 mmol) in CH_2Cl_2 (30 mL) was added aldehyde **81** (0.66 g, 1.49 mmol) and *p*-toluenesulfonic acid (0.34 g, 1.79 mmol). The mixture was stirred at room temperature for 3 h and the organic layer washed with saturated $NaHCO_3$, dried, and evaporated. The residue was dissolved in THF (5 mL) and treated with 1 M tetrabutylammonium fluoride in THF (2.5 mL, 2.5 mmol). After 1 h at 25 °C, EtOAc (150 mL) was added and the organic layer washed with brine, dried, and evaporated. The residue was chromatographed on silica gel eluting with $CHCl_3$–EtOH–AcOH (96:4:0.1) to give **85** (0.6 g, 29%): ^{1}H-NMR ($CDCl_3$), δ 1.25 (t, 3H), 1.4–1.9 (m, 6H), 2.1–2.5 (m, 9H), 2.8–3.0 (m, 2H), 4.1–4.2 (m, 4H), 5.15–5.3 (m, 3H), 5.4–5.5 (m, 2H), 5.7 (s, 1H), 6.05 (t, 1H), 6.8–6.9 (m, 2H), 6.9–7.1 (dd, 4H), 7.1–7.3 (m, 3H), 7.4–7.6 (dd, 4H), 7.8 (m, 1H), 8.1 (d, 1H), 8.4 (dd, 1H).

(*E*))-7-[4-[[4-[(2*RS*,4*RS*,5*SR*)-5-[(*Z*)-5-carbethoxypent-2-enyl]-4-(2-hydroxyphenyl)-1,3-dioxan-2-yl]benzyl]oxy]-phenyl]-7-(3-pyridyl)hept-6-enoic Acid (86). To a solution of the silyl ether **14** (0.55 g, 1.2 mmol) in CH_2Cl_2 (25 mL) was added aldehyde **82** (0.45 g, 1.1 mmol) and *p*-toluenesulfonic acid (0.25 g, 1.3 mmol). The mixture was stirred for 3 h and CH_2Cl_2 evaporated. The residue was dissolved in THF (3.5 mL) and treated with 1 M tetrabutylammonium fluoride in THF (1.76 mL, 1.76 mmol). After 1 h the THF was evaporated and the residue chromatographed on silica gel eluting with $CHCl_3$–EtOH–AcOH (96:4:0.1) to give **86** (0.3 g, 39%): ^{1}H-NMR ($CDCl_3$) δ 1.25 (t, 3H), 1.5–2.0 (m, 6H), 2.1–2.5 (m, 8H), 2.6–3.0 (m, 3H), 4.05–4.25 (m, 4H), 5.1 (s, 2H), 5.2–5.5 (m, 3H), 5.7 (s, 1H), 6.1 (t, 1H), 6.8–6.9 (m, 2H), 6.9–7.1 (dd, 4H), 7.1–7.3 (m, 3H), 7.4=7.6 (dd, 4H), 7.6 (m, 1H), 8.4 (m, 1H), 8.6 (m, 1H).

Acknowledgment. We thank our colleagues at Zeneca Pharmaceuticals, Mr. R. Jessup and Mr. M. Wayne, for the biological test results.

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JM940453C