Development, Synthesis, and Biological Evaluation of (−)-*trans*-(2*S*,5*S*)-2-[3-[(2-Oxopropyl)sulfonyl]-4-*n*-propoxy-5-(3-hydroxypropoxy)-phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran, a Potent Orally Active Platelet-Activating Factor (PAF) Antagonist and Its Water-Soluble Prodrug Phosphate Ester

N. N. Girotra,* T. Biftu,* M. M. Ponpipom,* J. J. Acton, A. W. Alberts, T. N. Bach, R. G. Ball, R. L. Bugianesi, W. H. Parsons,* J. C. Chabala, P. Davies, T. W. Doebber, J. Doherty, D. W. Graham, S-B. Hwang, C. H. Kuo, M-H. Lam, S. Luell, D. E. MacIntyre, R. Meurer, C. D. Roberts, S. P. Sahoo, and M. S. Wu

Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065. *Received February 27, 1992*

(−)-*trans*-(2*S*,5*S*)-2-[3-[(2-Oxopropyl)sulfonyl]-4-*n*-propoxy-5-(3-hydroxypropoxy)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (**10**) is one of the most potent platelet-activating factor (PAF) antagonists in vitro and in vivo developed to date. This diaryltetrahydrofuran derivative evolved from modifications of MK 0287 which has been evaluated in clinical studies for asthma. Two structural modifications of MK 0287 were made: (1) elaboration of the 3′-[(hydroxyethyl)sulfonyl] group to a β-keto propylsulfonyl, and (2) replacement of the 5′-methyl ether by a 3-hydroxypropyl ether. Compound **10** potently and specifically inhibits the binding of [^{3}H]-C_{18}-PAF to human platelet membranes (K_i 1.85 nM) and PMN membranes (K_i 2.89 nM). In vivo, **10** inhibits PAF-induced plasma extravasation and elevated *N*-acetyl-β-D-glucosaminidase (NAGA) levels in male rats with ED_{50} values of 60 μg/kg, po and 4 μg/kg, iv respectively, and inhibits PAF-induced bronchoconstriction in guinea pigs with an ED_{50} value of 15 μg/kg after intraduodenal administration. Compound **15**, a water-soluble phosphate ester prodrug derivative of **10** is at least equipotent to **10** in the in vivo models. Compound **19*S***, the primary and major metabolite of **10** and **15**, is equipotent in in vitro and in vivo models.

Introduction

Platelet-activating factor (PAF), primarily 1-*O*-hexadecyl- and 1-*O*-octadecyl-2-*O*-acetyl-*sn*-*glycero*-3-phosphocholine, is a potent endogenous lipid mediator found in a variety of cells implicated in inflammatory processes, including platelets, neutrophils, basophils, eosinophils, macrophages, mast cells, and endothelial cells.[1,2] PAF elicits its biological responses by interaction with specific receptors that have been found in cell and tissue preparations from many animal species, including human platelets, polymorphonuclear leukocytes (PMN), eosinophils, endothelial cells (EC), and lung preparations.[3-5] The binding of PAF to its receptors results in phosphatidylinositol turnover, intracellular Ca^{+2} mobilization, Ca^{+2} influx, and cell activation (including sensitization of cells to other stimuli) of PAF synthesis, degranulation, and/or secretion of cell contents. PAF also induces cell aggregation and adhesion of circulating leukocytes and platelets to vascular endothelium. Specific PAF-receptor antagonists have been shown to inhibit these cellular responses to PAF.

In vivo studies with PAF and PAF antagonists in animal models suggest pathophysiological roles for PAF in systemic anaphylaxis,[6,7] nephritis,[8,9] organ transplant rejection,[10-12] ischemia reperfusion,[13,14] embryonic development,[15,16] and asthma.[17]

In animal models of allergic asthma, PAF-receptor antagonists have been shown to block PAF-induced late-phase bronchoconstriction and delayed hyperresponsiveness.[17] The mounting evidence suggesting that PAF may be a key mediator in asthma has prompted the search for potent specific PAF antagonists.

To assess the role of PAF in various pathophysiological states, medicinal chemical research efforts have resulted in the identification of a number of potent, structurally diverse classes of PAF antagonists, and several are reported to be undergoing clinical evaluation. Notable classes of PAF antagonists include PAF-like,[18] ginkgolide,[19] thienotriazolo[1,4]diazepine,[20] pyrrolothiazole,[21] 5-aryl-2,3-dihydroimidazoisoquinoline,[22] and dihydropyridine derivatives.[23]

In 1982, a screening program was initiated at Merck to identify novel chemical entities that exhibit PAF-antago-

* To whom correspondence should be addressed.

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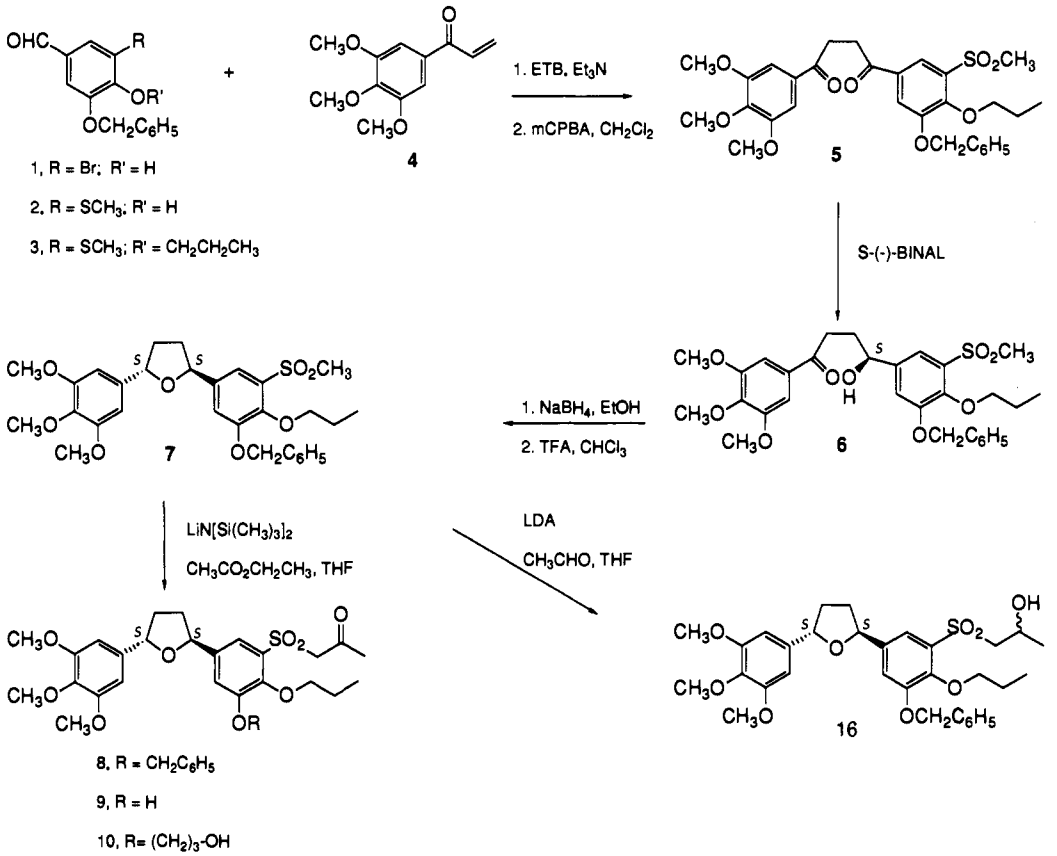
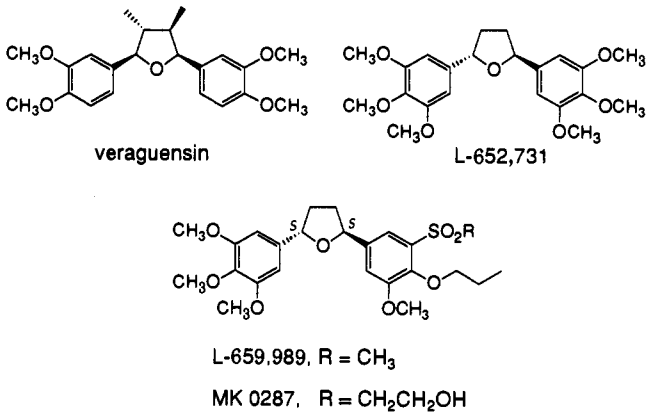
Scheme I



nist activity. This screening program was based upon an assay that measured the inhibition of binding of [^{3}H]PAF to rabbit platelet membrane preparations[3] and resulted in the discovery of the natural products kadsurenone[24,25] and veraguensin.[26] Chemical elaboration of veraguensin



(IC_{50} rabbit platelet membranes = 1000 nM) provided successively L-652,731 (K_i human platelet membranes = 103 nM),[27] L-659,989 (K_i human platelet membranes = 9.0 nM),[28] and culminating with MK 0287 (K_i human platelet

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membranes = 6.1 nM), which has been investigated in Phase IIa clinical trials.[29]

An objective of the Merck PAF program has been to identify modifications of the diaryltetrahydrofuran template that further improve in vivo potency and drug characteristics. MK 0287 possesses gender-dependent efficacy in rodent models in vivo. This phenomenon is attributable to an increased rate of microsomal metabolism in male rats relative to females.[30] Furthermore, MK 0287 is poorly water soluble (<10 μg/mL), which makes formulation for intravenous administration difficult. A breakthrough was achieved when chemistry was devised to modify the 5′-methoxy group. When the 5′-methyl ether group of MK 0287 was replaced with a 5′-(2-oxopropyl) ether, the gender-dependent metabolism in rats was significantly attenuated and potency in in vivo guinea pig and rat models was improved 5–10-fold.[31] This paper describes the development of the third generation tetrahydrofuran derivative **10**, which exhibits significantly enhanced in vivo potency and minimal gender-dependent potency in vivo. Furthermore, this paper discloses a water-soluble phosphate ester prodrug derivative **15** which is equipotent to **10** in vivo.

Chemistry

Methylsulfone intermediate **7** was synthesized enantioselectively as outlined in Scheme I. 1-[3-(Methylsulfonyl)-4-*n*-propoxy-5-(benzyloxy)phenyl]-4-(3,4,5-trimethoxyphenyl)butane-1,4-dione (**5**) was prepared from 3-bromo-4-hydroxy-5-(benzyloxy)benzaldehyde[41] (**1**) by modification of methodology previously developed for the syntheses of L-659,989[28,32] and MK 0287.[29] The four-step sequence to prepare crystalline **5** from **1** can be accomplished on a kilogram scale in 40% overall yield. Diketone **5** was converted to (−)-*trans*-(2*S*,5*S*)-2-[3-(methylsulfonyl)-4-*n*-propoxy-5-(benzyloxy)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (**7**) by methodology that was previously described by Sahoo et al. for the enantioselective synthesis of MK 0287.[29] In the event, regio- and enantioselective reduction of diketone **5** to (1*S*)-isomer **6** was accomplished in 73% yield using (*S*)-BINAL-H as the reducing agent.[33] Reduction of **6** with $NaBH_4$ followed by cyclization with 5% trifluoroacetic acid (TFA) in chloroform provided chirally pure trans tetrahydrofuran (THF) derivative **7** and its cis isomer. This cyclization provides approximately 55% of the trans isomer and approximately 20% of the cis isomer.[32] More trans isomer can be obtained by equilibration of the cis isomer in TFA and chloroform.[32]

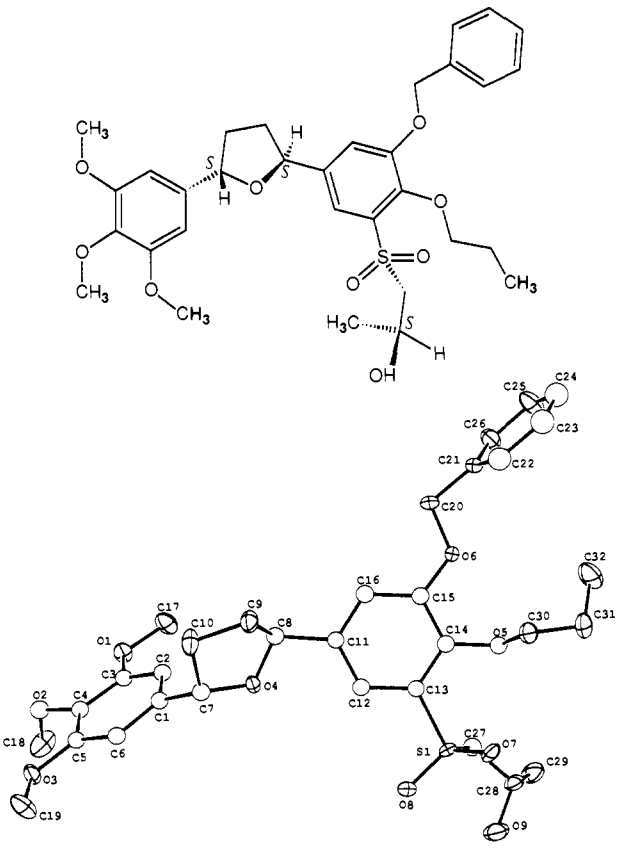

Figure 1. X-ray structure of (−)-*trans*-(2*S*,5*S*)-2-[3-[(2*S*)-(2-hydroxypropyl)sulfonyl]-4-*n*-propoxy-5-(benzyloxy)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (**16*S***).

Reaction of methylsulfone **7** with lithium bis(trimethylsilyl)amide ($LiN[Si(CH_3)_3]_2$) in THF at −78 °C and then with ethyl acetate provided (2-oxopropyl)sulfone **8**. Hydrogenolysis of **8** followed by alkylation with 3-bromopropanol provided **10**. This three-step sequence can be accomplished in 72% yield. Deprotonation of methylsulfone **7** with $LiN[Si(CH_3)_3]_2$ at −78 °C followed by addition of acetaldehyde provided (2-hydroxypropyl)-sulfone **16** as a mixture of diastereomers in 75% yield after crystallization. The diastereomeric alcohols were resolved by chromatographic separation of their (−)-(*R*)-*O*-methylmandelate esters which were prepared by standard esterification procedures (DCC, DMAP). The absolute stereochemistry for each diastereomer was assigned by examination of NMR chemical shifts using the Mosher model depicted in an extended Newman projection.[32,34,35] By this projection, the NMR of the more mobile isomer

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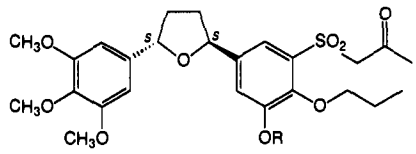
Chart I



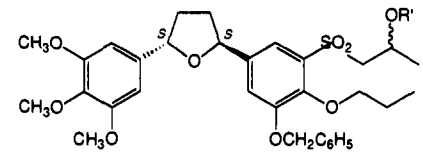
11, R = $(CH_2)_3$-Br

12, R = $(CH_2)_3$-N(imidazolyl)

13, R = $(CH_2)_3$-N(morpholino)

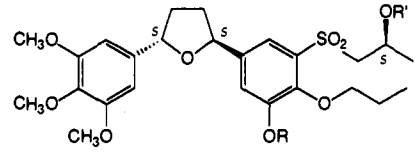
14, R = $(CH_2)_3$-$OPO(OCH_2C_6H_5)_2$

15, R = $(CH_2)_3OPO(OH)O^-K^+$



16, R = H

17, R = $\overset{R}{COCH(OCH_3)C_6H_5}$

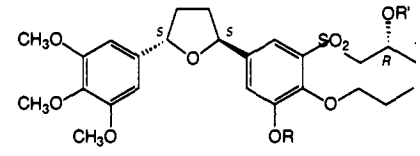


16S, R' = H; R = $\overset{R}{CH_2C_6H_5}$

17S, R' = $\overset{R}{COCH(OCH_3)C_6H_5}$; R = $CH_2C_6H_5$

18S, R' = R = H

19S, R' = H; R = $(CH_2)_3$-OH



16R, R' = H; R = $\overset{R}{CH_2C_6H_5}$

17R, R' = $\overset{R}{COCH(OCH_3)C_6H_5}$; R = $CH_2C_6H_5$

18R, R' = R = H

19R, R' = H; R = $(CH_2)_3$-OH

reveals that the methyl group α to the chiral alcohol (δ = 1.37) resonates downfield relative to that for the less mobile isomer (δ = 1.14) which is shielded by the phenyl group. The corresponding α-methylene protons for the more mobile isomer which are shielded by the phenyl group (δ = 3.51 and 3.71) are shifted upfield relative to the less mobile isomer (δ = 3.54 and 3.79). By the Mosher model, the more mobile and less mobile isomers were assigned the respective **17*R*** and **17*S*** stereochemistries (see Chart I). Reduction of **17*R*** and **17*S*** ($LiAlH_4$, THF, 0 °C) provided the corresponding hydroxy derivatives **16*S*** and **16*R***. The absolute stereochemistry of **16*S*** was unambiguously determined to be *S*,*S*,*S* by an X-ray structure determination as depicted in Figure 1.

Hydrogenolysis (H_2, Pd/C 10%, 40 psi) of **16*S*** and **16*R*** gave the respective phenols **18*S*** and **18*R*** which were then reacted with 3-bromopropanol and K_2CO_3 in acetone to give the 3-hydroxypropyl ether derivatives **19*S*** and **19*R***, respectively, in approximately 79% yield for the two steps.

Derivatives of **10** that possess improved water solubility are depicted in Chart I. 3-(1-Imidazolyl)propyl and 3-(1-morpholino)propyl ethers **12** and **13** were prepared via a two-step process. Alkylation of **9** with 1,3-dibromopropane (K_2CO_3, THF) afforded 3-bromopropyl ether **11** (65%) which was then allowed to react with imidazole or morpholine and K_2CO_3 in acetone under reflux to provide compounds **12** and **13**, respectively. Phosphate prodrug **15** as its potassium salt was prepared in two steps by first allowing **10** to react with dibenzyl phosphate under Mitsunobu conditions to give dibenzyl phosphate ester **14** (83%) followed by hydrogenolysis in the presence of $KHCO_3$ to provide **15** in near quantitative yields. Compound **14** can also be prepared directly from phenol **9** in 85% yield by alkylation with preformed dibenzyl 3-bromopropyl phosphate and K_2CO_3 in acetone.

Results and Discussion

Structure–activity studies at the 5′-position of the diaryl-THF template revealed that when the methyl group of MK 0287 was replaced by a 3-hydroxypropyl group, there was a significant improvement in in vitro and in vivo potency and appreciably reduced gender-dependent efficacy. Lower and higher homologs are nearly as potent. Meanwhile, studies at the 3′-position revealed that simple elaboration of the 3′-[(2-hydroxyethyl)sulfonyl] group of MK 0287 into a 3′-[(2-hydroxypropyl)sulfonyl] group led to improved in vivo potency, and, in some cases, to improved in vitro activity as well. Table I compares the in vitro activities of compounds **19*S*** and **19*R*** which are hybrid compositions of the 5′-(3-hydroxypropyl) ether and resolved 3′-[(2-hydroxypropyl)sulfonyl] groups. It is noteworthy that the stereochemistry at the secondary hydroxyl position has only a minimal effect on inhibition of the binding of [^{3}H]PAF to human platelet membranes (HPM) or human PMN membranes. The structurally simpler β-keto sulfone derivative **10** was prepared and found to be marginally more potent in vitro than **19*S*** or **19*R*** and 2–3-fold more potent than MK 0287, exhibiting K_i values of 1.85 and 2.89 nM, respectively, in the HPM and PMN receptor binding assays. Compounds **19*S*** and **10** are saturable and reversible inhibitors of the binding of [^{3}H]-C_{18}-PAF to its receptors in human platelet membranes (data not shown).

In metabolism studies in rats and in incubation studies with rat and human microsomal preparations, it was found that compound **10** is converted specifically and enantios-

Table I. In Vitro PAF Antagonist Activity

assay	MK 0287	19*S*	19*R*	10
binding assays (K_i, nM)[a]				
human PM	6.3	3.72	2.86	1.85
human PMN	3.2	5.26	3.70	2.89
human platelet aggregation (IC_{50}, nM)[b]				
PRP	55	13.2	–	32
WP	1.5	0.9	–	0.8

[a] Inhibition of the specific binding of [^{3}H]-C_{18}-PAF to human platelet or PMN membrane preparations. [b] Inhibition of PAF-induced aggregation of platelets suspended in plasma (PRP) or in buffer [washed platelets (WP)]. The concentration of PAF used is that which induced 70–80% maximum aggregation.

Table II. In Vivo PAF Antagonist Activity

assay	MK 0287	19S	10
Rat NAGA/Extravasation (ED_{50}, mg/kg)[a]			
iv			
males	0.1	0.0055	0.004
po			
males	2.3	–	0.06
females	0.1	–	0.01
PAF-Induced Guinea Pig Bronchoconstriction (ID_{50}, mg/kg)[b]			
males	0.18	0.01	0.015

[a] Inhibition of 5.5 μg/kg PAF-induced increases in plasma N-acetyl-β-D-glucosaminidase activity and hematocrit (n = 3 rats per point). SEM ≤ 10% of the mean for all values. [b] Inhibition of PAF-induced bronchoconstriction in guinea pigs. Compounds were administered intraduodenally.

electively to (2S)-(2-hydroxypropyl)sulfone **19S**.[36] Table II compares the in vivo profiles of compounds **19S** and **10** relative to MK 0287. Intravenous infusion of PAF (5.5 μg/kg) into rats induces a 70% increase in hematocrit (plasma extravasation) and in the plasma level of N-acetyl-β-D-glucosaminidase (NAGA). Compound **19S** was equipotent to compound **10** in inhibiting these PAF-induced responses in male rats with ED_{50} values of 5.5 μg/kg upon intravenous administration, and **10** exhibits an ED_{50} value of 60 μg/kg upon oral dosing. Thus in male rats, these derivatives are approximately 40- and 25-fold more potent than MK 0287 by the oral or intravenous routes, respectively. Whereas the difference in gender-dependent efficacy for MK 0287 upon oral administration to rats is approximately 23-fold, the differential with **10** is substantially reduced (only 6-fold). In male guinea pigs, compounds **19S** and **10** inhibited 100 ng/kg PAF-induced bronchoconstriction with ED_{50} values of 10 and 15 μg/kg, respectively, after intraduodenal administration and were 1 order of magnitude more potent than MK 0287.

A remaining objective was to improve on the poor water solubility of **10** which is less than 100 μg/mL. To address this, the 5′-(3-hydroxypropyl) ether group of **10** was derivatized with a variety of potential water-solubilizing groups. Acidic and very basic amino substituents significantly diminished potency in vitro, but hydroxyl group replacements that contained amino groups with reduced basicity were identified which maintained potency. In particular, imidazole and morpholine derivatives **12** and **13** retain much of the inherent potency of **10**.

An alternate approach for improving the water solubility of **10** is by prodrug formulation. Decadron phosphate, a disodium phosphate ester of the water-insoluble dexamethasone had been previously developed in these laboratories for intravenous formulation.[37] In a similar manner, conversion of **10** to provide **15** dramatically boosts water solubility to greater than 30 mg/mL.

The biological activities for water-soluble derivatives **12**, **13**, and **15** are compared with **10** and MK 0287 in Table III. Compounds **12** and **13** maintain the potency of **10** in inhibiting the binding of [^{3}H]-C_{18}-PAF to human platelet membranes. Although **15** is 50-fold less potent than **10**, the K_i value of crystalline phosphate ester **15** as its potassium salt is dependent on incubation time and is sensitive to the presence of vanadate, a phosphatase inhibitor, suggesting that **15** is indeed a prodrug form of **10** which can be liberated in vivo by endogenous phosphatases that

Table III. In Vitro and in Vivo Profiles of Water-Soluble Derivatives of Compound 10

assay	MK 0287	10	15	13	12
Binding Assays (nM)[a]					
HPM	6.3	1.85*	110*	2.5	3
PMN	3.2	2.9*	174*		
Human Platelet Aggregation (IC_{50}, nM)[b]					
PRP	55	32	5300	19	26.6
WP	1.5	0.8	515	1	0.9
Rat NAGA/Extravasation (ED_{50}, mg/kg)[c]					
po					
males	2.3	0.06	0.055	0.15	0.20
females	0.1	0.01	0.01	0.20	
iv					
males	0.1	0.0043	0.0065	0.037	0.08
PAF-Induced Guinea Pig Bronchoconstriction (ID_{50}, mg/kg)[d]					
males	0.19	0.015	0.013	0.06	0.26
females	–	–	0.01	0.04	0.09
iv	–	–	0.013	–	–
Water Solubility [mg/mL (pH)][e]					
	~0.002	~0.10	>30 (7.4)	5.4 (5)	5.5 (5)
				0.9 (6)	0.8 (6)

[a] Inhibition of the specific binding of [^{3}H]-C_{18}-PAF to human platelet or PMN membrane preparations. The results are reported as IC_{50} or K_i* (nM). [b] Inhibition of PAF-induced aggregation of platelets suspended in plasma (PRP) or in buffer [washed platelets (WP)]. The concentration of PAF used is that which induced 70–80% maximum aggregation. [c] Inhibition of 5.5 μg/kg PAF-induced increases in plasma N-acetyl-β-D-glucosaminidase activity and hematocrit. (n = 3 rats per point). SEM ≤ 10% of the mean for all values. [d] Inhibition of PAF-induced bronchoconstriction in guinea pigs. Compounds were administered intraduodenally. [e] Solubilities were determined by comparison by UV (with standards of known concentration) of aliquots of compound that had been combined with buffered solutions, sonicated, shaken for 1 h, and then filtered.

are located in blood.[38] Using concentrations of PAF that induce 70–80% of maximum aggregation, compounds **10**, **12**, and **13** were found to be twice as effective as MK 0287 in dose-dependently inhibiting platelet aggregation in human platelet rich plasma (PRP). The increased potency of these compounds in human washed platelet (WP) preparations may reflect the effects of protein binding of these compounds in PRP. Prodrug derivative **15** is much less active in these assays.

In in vivo rat models, prodrug **15** was equipotent to parent **10** and was 3-fold more potent than **12** and **13** after oral administration. When administered intravenously, both **10** and **15** exhibited very potent ED_{50} values of 4.3 and 6.5 μg/kg, respectively, and were 5–6-fold more potent than compound **13**. The gender-dependent oral potency found with MK 0287 is significantly diminished with **13** and **15**, and both compounds exhibited prolonged duration of action in male and female rats. Six hours after a single 1 mg/kg oral dose of **15**, the level of PAF-induced increased NAGA and extravasation was inhibited 90% and 70%, respectively, in female and male rats. Using the same protocols, compounds **10**, **12**, and **13** maintained inhibition levels of 80%, 45%, and 60%, respectively, in male rats.

When compounds **10** and **15** were administered intraduodenally to male guinea pigs, they inhibited 100 ng/kg PAF-induced bronchoconstriction nearly equipotently with ED_{50} values of 15 and 13 μg/kg, respectively, and are 1 order of magnitude more potent than MK 0287, **12**, and **13**. Furthermore, compound **15** is equally effective whether it was administered intravenously or intraduodenally. The efficacy of derivatives **10**, **12**, **13**, and **15** are nearly inde-

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pendent of gender in this species.

As seen in Table III, compounds **12**, **13**, and **15** are significantly more soluble than MK 0287. Most significant is the solubility of phosphate ester **15** which in water or phosphate-buffered saline (PBS) is greater than 30 mg/mL and is not pH dependent. The solubilities of the hydrochloride salts of **12** and **13** are pH dependent and increase when the pH is lowered. The decreased solubility as demonstrated by derivatives **12** and **13** at pH greater than 6 is a result of the surprisingly low pK_a values of their protonated forms, approximately 5.5, for both derivatives.

As a measure of specificity, PAF antagonists **10**, **12**, **13**, **15**, and **19S**, were evaluated in a battery of receptor assays. At concentrations of 1–10 μM, these compounds exhibited no effects on the binding of the relevant radioligands to the following receptors: C5a (human PMN), LTB_4 (human PMN), the inflammatory peptide formyl-Met-Leu-Phe (fMLP) (human PMN), LTD_4 (guinea pig lung), α_1, α_2 (bovine cerebral cortex), β_1, β_2 (bovine aorta)), and angiotensin II (rabbit aorta). On a cellular level, these compounds at concentrations (1 μM or greater) that abolish PAF-induced aggregation of human platelets have little or no inhibitory effects on aggregation induced by ADP, vasopressin, or U44069, a thromboxane A_2 mimetic.

Conclusions

Diaryltetrahydrofuran derivative **10** and its phosphate ester prodrug form **15** represent the third generation of this class of PAF antagonists. Compound **15** is one of the most potent PAF antagonists, in vivo, reported to date, exhibiting ED_{50} values of 55 μg/kg, po and 6.5 μg/kg, iv in rats and 13 μg/kg, id and iv in guinea pigs in models employing exogenously administered PAF. Furthermore, the intrinsic water solubility of **15** makes it suitable for intravenous administration. Further studies with compound **15** will be the subject of future publications.

Experimental Section

Biological Assays. Receptor binding assays and calculation of K_i values were carried out according to methods reported by Hwang.[27] The effect of PAF antagonists on PAF-induced platelet aggregation was determined according to procedures described by Hwang.[39]

In vivo studies in rats were carried out according to procedures described by Doebber et al.[40] In vivo studies in guinea pigs were performed according to procedures described by Hwang.[39]

Chemistry. General Methods. ^1H NMR were recorded on a Varian XL200 pulsed Fourier transform instrument. Unless specified, NMR spectra were recorded at ambient temperature in $CDCl_3$ and chemical shifts (δ) are reported relative to TMS as an internal standard. Mass spectra were recorded on a Finnigan-MAT 731 mass spectrometer.

Microanalyses were within ±0.4% of the calculated values. Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on GF254 (Analtech) plates, and silica gel glass-backed plates. Routine column chromatography was conducted using silica gel 60 (70–230 mesh ASTM). Unless otherwise noted, high pressure liquid chromatography (HPLC) was performed with a Waters Associates Prep LC/System 500 and using PrepPak 500 silica columns.

3-Bromo-4-hydroxy-5-(benzyloxy)benzaldehyde (1). A solution of 4-hydroxy-5-(benzyloxy)benzaldehyde[41] (930 g, 4.1 mol) in acetic acid (7.5 L) was warmed to 50 °C. To this solution was added sodium acetate (373 g), and the mixture was cooled to 30 °C. To the reaction mixture was added over 1.5 h a solution of bromine (233 mL, 4.5 mol) in acetic acid (930 mL). After the addition was complete, the mixture was stirred for an additional 45 min, after which time water (1.9 L) was added. The precipitate was filtered, air-dried, and washed with water and hexane (8 L). The residue was dried at 40 °C overnight under high vacuum to yield 1.3 kg of the title compound: mp 160–162 °C. Anal. ($C_{14}H_{11}BrO_3$) C, H, Br.

3-(Methylthio)-4-hydroxy-5-(benzyloxy)benzaldehyde (2). A mixture of **1** (1.3 kg, 4.3 mol), copper powder (1.07 kg, 16.8 mol), and dimethyl disulfide (1.07 kg, 11.4 mol) in pyridine (23 L) was heated at 95 °C with stirring for 16 h. The reaction mixture was filtered, and the filtered cake was washed with dichloromethane (30 L). The filtrates were combined and evaporated in vacuo to leave a black residue, and the product was extracted with the dichloromethane. The combined organic extracts were washed with 2 N HCl until they became light brown and the acidic aqueous layer was clear. The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was evaporated to dryness. Crystallization from dichloromethane–hexane afforded **2** (900 g, 76%): mp 117–119 °C; NMR δ 2.50 (s, SCH_3), 5.20 (s, OCH_2Ar), 6.72 (s, OH), 7.34–7.46 (m, ArH), 9.78 (s, ArCHO). Anal. ($C_{15}H_{14}O_3S$) C, H, S.

3-(Methylthio)-4-*n*-propoxy-5-(benzyloxy)benzaldehyde (3). A mixture of **2** (900 g, 3.3 mol), 1-bromopropane (450 mL, 4.94 mol), and K_2CO_3 (500 g, 3.6 mol) in DMF (1 L) was heated with stirring at 75 °C overnight. The reaction mixture was cooled, and to it was added ethyl acetate (1 L). The solid was removed by filtration, and the filtrate was evaporated to provide the title compound (1.04 kg) which was used without further purification in the preparation of **5**: NMR δ 1.02 (t, $CH_2CH_2CH_3$), 1.82 (m, $CH_2CH_2CH_3$), 2.48 (s, SCH_3), 4.12 (t, $OCH_2CH_2CH_3$), 5.18 (s, OCH_2Ar), 7.26–7.52 (m, ArH), 9.86 (s, ArCHO).

1-(3,4,5-Trimethoxyphenyl)prop-2-en-1-one (4). To a stirred mixture of 3,4,5-trimethoxyacetophenone (210 g, 1 mol), dimethylamine hydrochloride (81 g, 1 mol), and paraformaldehyde (45 g, 1.5 mol) in ethanol (300 mL) was added concentrated hydrochloric acid (1 mL). The reaction mixture was heated under reflux for 1 h. A second portion of paraformaldehyde (30 g, 1 mol) was added, and the heating was continued for another 2 h. The hot reaction mixture was poured with vigorous stirring into acetone (2.4 L), and the slurry was heated at 60 °C for 15 min, cooled, and filtered. The solid was washed with acetone and dried to provide the hydrochloride salt of 3-(*N*,*N*-dimethylamino)-1-(3,4,5-trimethoxyphenyl)propan-1-one (196 g, 65%): mp 175 °C. A mixture of the hydrochloride salt (148 g, 0.48 mol) and aqueous NaOH (1 N, 750 mL) was shaken with ethyl acetate (4 × 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated in vacuo to give 3-(*N*,*N*-dimethylamino)-1-(3,4,5-trimethoxyphenyl)propan-1-one (126 g, 97%): mp 45–47 °C. A solution of the free amine (242 g, 0.91 mol) and methyl iodide (83 mL, 1.27 mol) in ethyl ether (1.6 L) was stirred under nitrogen at room temperature for 2 h. The solid was filtered and dried in vacuo overnight at room temperature to provide 3-(*N*,*N*,*N*-trimethylammonium)-1-(3,4,5-trimethoxyphenyl)-propan-1-one iodide (356 g, 96%) which was suspended in water (3.56 L) and ethyl acetate (2.54 L) and heated under reflux with rapid stirring for 3 h. The mixture was cooled, and the pale yellow organic layer was removed. Fresh ethyl acetate (2 L) was added, the mixture was again heated under reflux for 1 h, and the process was repeated once again. The organic extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to a yellow oil which was crystallized from hexanes–ethyl ether to afford **4** (179 g, 93%): mp 46–47 °C; NMR δ 3.94 (s, 3 OCH_3), 5.92 (2 d, J = 1.5 and 9.0 Hz, $CH{=}CH_2$), 6.44 (2 d, J = 1.5 and 16 Hz, $CH{=}CH_2$), 7.18 (2 d, J = 9.0 and 16 Hz, $CH{=}CH_2$), 7.28 (m, ArH).

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1-[3-(Methylsulfonyl)-4-*n*-propoxy-5-(benzyloxy)phenyl]-4-(3,4,5-trimethoxyphenyl)butane-1,4-dione (5). A mixture of **3** (1.04 kg, 3.29 mol), **4** (775 g, 3.5 mol), and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (ETB) (57 g, 0.24 mol) in triethylamine (145 mL, 1.05 mol) was heated with stirring at 90 °C for 2 h. The mixture was cooled and poured slowly into a solution of HCl (2 N, 2 L) in ice–methanol (2 L). Methanol (10 L) was added with stirring, and the solution was allowed to stir for an additional 10 min. The precipitate was isolated by filtration and washed with water, methanol, and hexanes to provide 1-[3-(methylthio)-4-*n*-propoxy-5-(benzyloxy)phenyl]-4-(3,4,5-trimethoxyphenyl)butane-1,4-dione as a tan solid (1.45 kg): NMR δ 1.03 (t, $CH_2CH_2CH_3$), 1.82 (m, $CH_2CH_2CH_3$), 2.50 (s, SCH_3), 3.43 (s, $COCH_2CH_2CO$), 3.94 (s, 3 OCH_3), 4.11 (t, $OCH_2CH_2CH_3$), 5.17 (s, OCH_2Ar), 7.30–7.95 (m, ArH). 3-Chloroperoxybenzoic acid (1.3 kg, 6.48 mol; 86%) was added in portions to a stirred solution of the above compound (1.58 kg, 2.94 mol) in cold dichloromethane (20 L). After stirring for 2 h at room temperature, the mixture was cooled to 0 °C and filtered to remove 3-chlorobenzoic acid, and the filtrate was evaporated in vacuo. The residue was dissolved in ethyl acetate, the solution was washed with aqueous NaOH, water, and brine, dried ($MgSO_4$), and filtered, and the filtrate was evaporated in vacuo. Crystallization from methanol gave **5** (1.1 kg, 65%): mp 115–116 °C; NMR δ 0.99 (t, $CH_2CH_2CH_3$), 1.85 (q, $CH_2CH_2CH_3$), 3.30 (s, SO_2CH_3), 3.45 (s, $COCH_2CH_2CO$), 3.93 (s, 3 OCH_3), 4.26 (t, $OCH_2CH_2CH_3$), 5.20 (s, OCH_2Ar), 7.29 (s, C_4ArH), 7.36–7.48 (m, ArH), 7.92 and 8.25 (2 d, C_1ArH). Anal. ($C_{30}H_{34}O_9S$) C, H, S.

(−)-(1*S*)-1-Hydroxy-1-[3-(methylsulfonyl)-4-*n*-propoxy-5-(benzyloxy)phenyl]-4-(3,4,5-trimethoxyphenyl)butan-4-one (6). A solution of ethanol (48 mL, 0.82 mol) and THF (600 mL) was added dropwise to a stirred solution of lithium aluminum hydride in tetrahydrofuran (1 M, 800 mL). After 10 min, a solution of (*S*)-(−)-binaphthol (229 g, 0.80 mol) in THF (800 mL) was added dropwise over 1 h while keeping the temperature of the milky mixture below 35 °C. After stirring for an additional 30 min at room temperature, the reaction mixture was cooled to −78 °C and to it was added dropwise over 1 h a solution of **5** (200 g, 0.35 mol) in THF (800 mL). The mixture was stirred for an additional 1.5 h, quenched with methanol (240 mL), and the resulting solution was concentrated in vacuo. The residue was dissolved in ethyl acetate, the solution was washed with HCl (1 N), water, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and the filtrate was concentrated in vacuo. Most of the (−)-binaphthol (150 g) was recovered by precipitation with dichloromethane–hexanes (1:1) and filtration. The filtrates were combined, evaporated to a small volume, and chromatographed (silica, 4 kg, hexanes–ethyl acetate, 2:1) to remove the residual (−)-binaphthol. The product was then eluted with hexanes–ethyl acetate (1:1). Evaporation of the desired fractions and crystallization of the residue from ethyl ether gave **6** (147 g, 73%): mp 122–125 °C; $[\alpha]^{25}_D$ −10.6° (*c* 1.0, $CHCl_3$); NMR δ 0.98 (t, $CH_2CH_2CH_3$), 1.82 (m, $CH_2CH_2CH_3$), 2.04–2.24 (m, CH_2CHOH), 3.10 (t, $COCH_2CH_2CHOH$), 3.26 (s, SO_2CH_3), 3.94 (s, 3 OCH_3), 4.16 (t, $OCH_2CH_2CH_3$), 4.85 (m, CH_2CHOH), 5.16 (s, OCH_2Ar), 7.23 (s, C_4ArH), 7.30–7.52 (m, ArH).

(−)-*trans*-(2*S*,5*S*)-2-[3-(Methylsulfonyl)-4-*n*-propoxy-5-(benzyloxy)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (7). To a solution of **6** (113 g, 0.20 mol) in CH_2Cl_2 (400 mL) at room temperature was added dropwise a saturated solution of $NaBH_4$ (4 g) in ethanol (100 mL), and the reaction mixture was stirred for 1 h. The solution was evaporated, and the residue was dissolved in chloroform (200 mL) and cooled to 0 °C. To this solution was carefully added a solution of trifluoroacetic acid and chloroform (600 mL; 1:2), and the mixture was allowed to stand overnight at 4 °C. The reaction mixture was diluted with chloroform (500 mL), washed with aqueous NaOH (1 N) and water, dried ($MgSO_4$), and filtered, and the filtrate was concentrated in vacuo. Crystallization from ethyl ether gave a mixture of cis and trans cyclized derivatives which was separated by HPLC (hexanes–ethyl acetate, 2:1) to provide the trans isomer **7** (50 g) and the cis isomer (25 g). The cis isomer was isomerized with TFA–chloroform (200 mL, 1:2), and the 1:1 mixture was separated as described above. The trans isomer batches were combined and crystallized from ethyl ether to give **7** (60 g, 55%): mp 118–119 °C; $[\alpha]^{25}_D$ −62.4° (*c* 1.0, $CHCl_3$); NMR δ 0.98 (t, $CH_2CH_2CH_3$), 1.82 (m, $CH_2CH_2CH_3$), 1.9–2.6 (m, *H*-3 and *H*-4), 3.27 (s, SO_2CH_3), 3.85 (s, OCH_3), 3.94 (s, 2 OCH_3), 4.16 (t, $OCH_2CH_2CH_3$), 5.17 (s, OCH_2Ar), 5.06–5.28 (m, *H*-2 and *H*-5), 6.61 (s, C_5ArH), 7.28–7.54 (m, ArH).

(−)-*trans*-(2*S*,5*S*)-2-[3-[(2-Oxopropyl)sulfonyl]-4-*n*-propoxy-5-(benzyloxy)phenyl]-5-(3,4,5-trimethoxyphenyl)-tetrahydrofuran (8). To a stirred solution of **7** (60 g, 0.11 mol) in THF (250 mL) at −78 °C under nitrogen was added dropwise a solution of lithium bis(trimethylsilyl)amide (250 mL of a 1 M solution in THF; 0.25 mol). After 20 min at this temperature, ethyl acetate (60 mL) was added, and after an additional 20 min, a solution of saturated ammonium chloride was added. The reaction mixture was warmed to room temperature, and the product was extracted with ethyl acetate. The organic extracts were dried and filtered, and the filtrate was evaporated to a residue which was crystallized from methanol to yield **8** (51.5 g, 80%): mp 90–92 °C; $[\alpha]^{25}_D$ −59.4° (*c* 1.0, $CHCl_3$); NMR δ 0.98 (t, $CH_2CH_2CH_3$), 1.83 (m, $CH_2CH_2CH_3$), 1.9–2.6 (m, *H*-3 and *H*-4), 2.38 (s, CH_3COCH_2), 3.86 (s, OCH_3), 3.88 (s, 2 OCH_3), 4.18 (t, $OCH_2CH_2CH_3$), 4.48 (s, CH_3COCH_2), 5.18 (s, OCH_2Ar), 5.06–5.28 (m, *H*-2 and *H*-5), 6.61 (s, C_5ArH), 7.32–7.54 (m, C_2ArH).

(−)-*trans*-(2*S*,5*S*)-2-[3-[(2-Oxopropyl)sulfonyl]-4-*n*-propoxy-5-hydroxyphenyl]-5-(3,4,5-trimethoxyphenyl)-tetrahydrofuran (9). A solution of **8** (48.5 g, 0.08 mol) in ethyl acetate (800 mL) was hydrogenated over 10% palladium-on-charcoal (5 g) at 40 psi for 1.5 h. The catalyst was filtered off over Celite, and the filtrate was evaporated in vacuo to give **9** (41.6 g, 100%) which was used without further purification: $[\alpha]^{25}_D$ −71.6° (*c* 1.0, $CHCl_3$); NMR δ 1.10 (t, $CH_2CH_2CH_3$), 1.92 (m, $CH_2CH_2CH_3$), 1.9–2.6 (m, *H*-3 and *H*-4), 2.40 (s, CH_3COCH_2), 3.86 (s, OCH_3), 3.90 (s, 2 OCH_3), 4.12 (t, $OCH_2CH_2CH_3$), 4.42 (s, CH_3COCH_2), 5.10–5.28 (m, *H*-2 and *H*-5), 6.64 (s, C_5ArH), 7.35 and 7.47 (2 d, C_2ArH).

(−)-*trans*-(2*S*,5*S*)-2-[3-[(2-Oxopropyl)sulfonyl]-4-*n*-propoxy-5-(3-hydroxypropoxy)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (10). A mixture of **9** (41 g, 0.08 mol), 3-bromo-1-propanol (8.75 mL, 0.10 mol), and potassium carbonate (16.3 g, 0.12 mol) in acetone (800 mL) was heated with stirring under nitrogen at 56 °C for 42 h. The reaction mixture was cooled and filtered through Celite, and the filtrate was concentrated to a residue which was purified by HPLC (Waters Prep 500, silica, hexanes–ethyl acetate, 1:3). The title compound **10** was isolated as a syrup in 90% yield (41.2 g): $[\alpha]^{25}_D$ −68.3° (*c* 1.0, $CHCl_3$); NMR δ 1.04 (t, $CH_2CH_2CH_3$), 1.80 (m, $CH_2CH_2CH_3$), 2.38 (s, $SO_2CH_2COCH_3$), 4.15 and 4.24 (2 t, OCH_2CH_2), 4.48 (s, $SO_2CH_2COCH_3$); 5.22 (m, *H*-2 and *H*-5), 6.63 (s, C_5ArH), 7.35 and 7.48 (2 d, C_2ArH). Anal. ($C_{28}H_{38}O_{10}S$) C, H, S.

(−)-*trans*-(2*S*,5*S*)-2-[3-[(2-Oxopropyl)sulfonyl]-4-*n*-propoxy-5-(3-bromopropoxy)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (11). To a solution of **9** (1.2 g) in acetone (1.2 L) containing K_2CO_3 (2.0 g) was added 1,3-dibromopropane (2.0 g), and the reaction mixture was stirred for 22 h at 60 °C. The reaction mixture was then cooled and filtered, and the filtrate was evaporated in vacuo. The product was purified by chromatography (silica, hexanes–ethyl acetate, 3:2) to provide 1.04 g (65%) of the title compound: TLC (silica, hexanes–ethyl acetate, 2:1) R_f 0.26; NMR δ 1.1 (t, $CH_2CH_2CH_3$), 1.84 (m, $CH_2CH_2CH_3$), 1.94 (m, $CH_2CH_2CH_2$), 2.0 and 2.49 (2 m, *H*-3 and *H*-4), 2.4 (s, CH_2COCH_3), 3.7 (2 t, CH_2Br), 3.81 (s, OCH_3), 3.86 (s, 2 OCH_3), 4.14 (t, $CH_2CH_2CH_2Br$), 4.25 (t, $CH_2CH_2CH_3$), 4.46 (s, CH_2COCH_3), 5.20 (m, *H*-2 and *H*-5), 6.60 (s, C_5ArH), 7.36 (d, C_2ArH), 7.50 (d, C_2ArH).

(−)-*trans*-(2*S*,5*S*)-2-[3-[(2-Oxopropyl)sulfonyl]-4-*n*-propoxy-5-[3-(1-imidazoyl)-*n*-propoxy]phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (12). A mixture of 11 (70 mg), imidazole (70 mg), and K_2CO_3 (70 mg) in acetone (5 mL) was stirred at 50 °C for 96 h. The reaction mixture was cooled to room temperature and filtered, and the filtrate was evaporated in vacuo. The residue was purified by chromatography (silica, $CHCl_3$–CH_3OH–H_2O, 90:10:1) to give 35 mg (51%) of the title compound: $[\alpha]^{25}_D$ −58° (*c* 1.0, $CHCl_3$); TLC (silica, $CHCl_3$–CH_3OH–H_2O, 90:10:1) R_f 0.4; NMR δ 1.09 (t, 3 H, $CH_2CH_2CH_3$), 1.90 (m, $CH_2CH_2CH_3$), 1.94 (m, $CH_2CH_2CH_2$), 2.0 and 2.49 (m, *H*-3 and *H*-4), 2.3 (m, 2 H), 2.4 (s, CH_2COCH_3), 3.84 and 3.88 (2 s, 3 OCH_3), 4.05 (t, $CH_2CH_2CH_3$), 4.2 (m, $OCH_2CH_2CH_2N$), 4.5

(s, CH_2COCH_3), 5.2 (m, *H*-2 and *H*-5), 6.62 (s, C_5ArH), 6.95, 7.1, 7.55 (3 s, imidazole), 7.23 and 7.5 (2 d, C_2ArH); MS *m/z* 616 (M^+). Anal. ($C_{31}H_{40}N_2O_9S$) C, H, N, S.

(−)-*trans*-(2*S*,5*S*)-2-[3-[(2-Oxopropyl)sulfonyl]-4-*n*-propoxy-5-[3-(1-morpholino)-*n*-propoxy]phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (13). The title compound (2.6 g) was prepared from 11 (3.2 g) and morpholine as described for the preparation of 12. Purification by chromatography (silica, ethyl acetate) provided the title compound as a colorless gum in 80% yield: $[\alpha]^{25}_D$ −57.8° (*c* 1.0, $CHCl_3$); NMR δ 1.06 (t, $CH_2CH_2CH_3$), 1.88 (m, $CH_2CH_2CH_3$), 1.9–2.6 (m, *H*-3, *H*-4), 2.38 (s, 3 H, CH_2COCH_3), 2.40–2.66 [m, 6 H, $CH_2N(CH_2)_2$], 3.75 (br t, CH_2OCH_2), 3.85 (s, OCH_3), 3.88 (s, 2 OCH_3), 4.13 and 4.14 (2 t, $ArOCH_2$), 4.46 (s, CH_3COCH_2), 5.10–5.30 (m, *H*-2, *H*-5), 6.62 (s, C_5ArH), 7.30 and 7.45 (2 d, C_2ArH). Anal. ($C_{32}H_{46}ClNO_{10}S$) C, H, Cl, N.

(−)-*trans*-(2*S*,5*S*)-2-[3-[(2-Oxopropyl)sulfonyl]-4-*n*-propoxy-5-[[[3-(dibenzyloxy)phosphoryl]oxy]propoxy]-phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (14). Compound 14 was prepared by two independent procedures:

(1) Dimethyl azodicarboxylate (11.4 g, 0.08 mol) was added dropwise to a stirred solution of 10 (29.5 g, 0.05 mol), triphenylphosphine (20.48 g, 0.08 mol), and dibenzyl phosphate (21.73 g, 0.08 mol) in THF (200 mL) at 0 °C. The mixture was stirred at room temperature for 2 h and concentrated to a residue which was purified by column chromatography on silica gel (dichloromethane–acetone, 9:1; v/v). The product was isolated as an oil (35 g, 83%) which was crystallized from cold methanol. Recrystallization from 2-propanol afforded pure 14: mp 81–83 °C; $[\alpha]^{25}_D$ −45° (*c* 1.0, $CHCl_3$); NMR δ 1.02 (t, $CH_2CH_2CH_3$), 2.16 (s, $SO_2CH_2COCH_3$), 4.44 (bs, $SO_2CH_2COCH_3$), 5.04 (m, OCH_2Ar), 6.62 (s, C_5ArH) 7.24 and 7.47 (2 d, C_2ArH) and 7.32 (bs, $OCH_2C_6H_5$). Anal. ($C_{42}H_{51}O_{13}PS$) C, H, P.

(2) Dimethyl azodicarboxylate (4.38 g, 0.03 mol) was added dropwise to a stirred solution 3-bromo-1-propanol (2.78 g, 0.02 mol), triphenylphosphine (7.87 g, 0.03 mol), and dibenzyl phosphate (8.35 g, 0.03 mol) in THF (80 mL) at 0 °C. After 2 h the reaction mixture was concentrated in vacuo, and the residue was chromatographed on silica gel (hexanes–ethyl acetate, 3:2) to afford 6.53 g (82%) of 3-bromopropyl dibenzyl phosphate as a colorless oil: NMR δ 2.12 (m, $OCH_2CH_2CH_2Br$), 3.42 (t, $OCH_2CH_2CH_2Br$), 4.13 (broad q, $OCH_2CH_2CH_2Br$), 5.08 (m, OCH_2Ar), 7.38 (s, $OCH_2C_6H_5$). A mixture of this material (120 mg, 0.3 mmol), **9** (102 mg, 0.2 mmol), and K_2CO_3 (42 mg, 0.3 mmol) in acetone (3 mL) was heated with stirring under nitrogen at 55 °C for 48 h. The reaction mixture was cooled and filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by preparative TLC (hexanes–ethyl acetate, 3:7) to afford 140 mg (85%) of 14 identical to the material obtained via 10.

(−)-*trans*-(2*S*,5*S*)-2-[3-[(2-Oxopropyl)sulfonyl]-4-*n*-propoxy-5-[3-(phosphonooxy)propoxy]phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran Monopotassium Salt (15). Compound 15 was prepared by two independent procedures:

(1) A solution of 14 (5 g, 6.05 mmol) in ethyl acetate (80 mL) and triethylamine (1.85 mL, 13.4 mmol) was hydrogenated over 10% palladium-on-charcoal (1.0 g) at 40 psi for 1 h. The catalyst was filtered off through Celite, and the filtrate was concentrated to dryness. The resulting oil was taken up in methanol–water (1:1, v/v), and the solution was placed on a column of Dowex AG 50W resin (K^+ form; 200 mL) and eluted with the same solvent system. Fractions containing the desired compound were combined, evaporated to a small volume, and lyophilized to give 15 (3.3 g, 80%): $[\alpha]^{25}_D$ −53° (*c* 1.0, MeOH); NMR (CD_3OD) δ 0.98 (t, $CH_2CH_2CH_3$), 2.31 (s, $SO_2CH_2COCH_3$), 4.42 (s, $SO_2CH_2COCH_3$), 5.16 (m, *H*-2 and *H*-5), 6.6 (s, C_5ArH), 7.28 and 7.44 (d, C_2ArH). Anal. ($C_{28}H_{38}KO_{13}PS\cdot H_2O$) C, H, K, P.

(2) A solution of 14 (10.75 g, 1.3 mmoles) in methanol (200 mL) containing solid $KHCO_3$ (1.3 g, 1.3 mmoles) in 4 mL of H_2O was hydrogenated over 10% Pd/C (1.2 g.) at 40 psi for 1 h. The solid was filtered through Celite and washed with water. The filtrates were combined and concentrated to a small volume which was lyophilized to provide 15 (8.7 g, 98%).

(−)-*trans*-(2*S*,5*S*)-2-[3-[((2*R*,*S*)-2-Hydroxypropyl)-sulfonyl]-4-*n*-propoxy-5-(benzyloxy)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (16). To a solution of 7 (3.0 g, 5.4 mmol) and LDA (6.5 mL of 1.5 M in cyclohexane, 9.8 mmol) in THF (30 mL) at −70 °C under nitrogen was added acetaldehyde (1.85 mL, 33.2 mmol). The reaction mixture was stirred at this temperature for 10 min and allowed to warm to room temperature. Dichloromethane was added, and the solution was washed with aqueous NH_4Cl, dried, and filtered, and the filtrate was evaporated in vacuo. The residue was purified by chromatography (silica gel, hexanes–ethyl acetate, 2:1 followed by 3:2, v/v) to give the title compound as a crystalline solid. Recrystallization from dichloromethane–diethyl ether afforded pure 16 (2.43 g, 75%): R_f 0.26 (hexanes–ethyl acetate, 3:2); mp 121–122 °C; $[\alpha]^{25}_D$ −58.1° (*c* 1.2, $CHCl_3$). Anal. ($C_{32}H_{40}O_9S$) C, H, S.

Mandelate Esters 17*S* and 17*R*. To a solution of 16 (2.35 g, 3.9 mmol), (−)-(*R*)-*O*-methylmandelic acid (1.9 g, 11.4 mmol), and 4-(dimethylamino)pyridine (0.16 g, 1.3 mmol) in dry dichloromethane (40 mL) at room temperature under nitrogen was added 1,3-dicyclohexylcarbodiimide (2.35 g, 11.4 mmol), and the mixture was stirred for 3 h. The urea byproduct was removed by filtration, and the filtrate was evaporated to a residue which was purified by flash column chromatography (hexanes–ethyl acetate, 3:1) to give a 1:1 mixture of the diastereomeric mandelate esters (2.7 g). The mixture was repurified by flash column chromatography (silica, CH_2Cl_2–hexanes–EtOAc, 50:35:15), and the two mandelate esters were separated by MPLC (silica, CH_2Cl_2–hexanes–EtOAc, 50:35:15). The absolute stereochemistry of the two compounds was assigned by NMR using the Mosher model depicted in the extended Newman projection. The more mobile compound 17*R* and the less mobile compound 17*S* (total yield = 2.1 g, 72%) had the respective (2*S*,5*S*)-2-[3-[((2*R*)-2-hydroxypropyl)sulfonyl]phenyl]tetrahydrofuran and (2*S*,5*S*)-2-[3-[((2*S*)-2-hydroxypropyl)sulfonyl]phenyl]tetrahydrofuran stereochemistry at the three chiral centers. Compound 17*R* (top spot): NMR δ 0.94 (t, *J* = 7.5 Hz, $CH_2CH_2CH_3$), 1.37 (d, *J* = 6.5 Hz, $CHCHOMCH_3$), 1.77 (m, $CH_2CH_2CH_3$), 3.39 (s, $COCH(OCH_3)Ph$), 3.51 (2 d, *J* = 6.0 and 13.5 Hz, $SO_2CH_AH_B$), 3.71 (2 d, *J* = 5.5 and 13.5 Hz, $SO_2CH_AH_B$), 3.86 (s, OCH_3), 3.88 (s, 2 OCH_3), 4.12 (t, *J* = 6.5 Hz, $CH_2CH_2CH_3$), 4.67 (s, $COCH(OCH_3)Ph$), 5.15 (s, OCH_2Ph), 6.61 (s, C_5ArH). Compound 17*S* (bottom spot): NMR δ 0.98 (t, *J* = 7.0 Hz, $CH_2CH_2CH_3$), 1.14 (d, *J* = 6.0 Hz, $CHCHOMCH_3$), 1.82 (m, $CH_2CH_2CH_3$), 3.36 (s, $COCH(OCH_3)Ph$), 3.54 (2 d, *J* = 4.0 and 14.5 Hz, $SO_2CH_AH_B$), 3.79 (2 d, *J* = 7.5 and 14.5 Hz, $SO_2CH_AH_B$), 3.86 (s, OCH_3), 3.88 (s, 2 OCH_3), 4.17 (t, *J* = 6.5 Hz, $CH_2CH_2CH_3$), 4.49 (s, $COCH(OCH_3)Ph$), 5.18 (s, OCH_2Ph), 6.62 (s, C_5ArH).

(−)-*trans*-(2*S*,5*S*)-2-[3-[((2*S*)-2-Hydroxypropyl)-sulfonyl]-4-*n*-propoxy-5-(benzyloxy)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (16*S*). Lithium aluminum hydride (0.49 mL, 0.49 mmol; 1.0 M solution in THF) was added under nitrogen to a solution of 17*S* (727 mg, 0.97 mmol) in dry THF (25 mL) at 0–5 °C. The reaction mixture was warmed to room temperature, stirred for 2 h, and then cooled and treated dropwise with glacial acetic acid (15 drops) until the reaction mixture became neutral. Dichloromethane was added, the solution was washed with cold 2 N HCl and brine, dried ($MgSO_4$), filtered, and the filtrate was evaporated in vacuo. The mixture was purified by flash column chromatography (hexanes–ethyl acetate, 2:1) to provide the title compound as a crystalline mass and some unreacted starting material (37 mg). Slow recrystallization of the product from methanol afforded pure 16*S* (470 mg, 85% based on the used starting material): mp 117–118 °C; $[\alpha]^{25}_D$ −42.2° (*c* 1.2, $CHCl_3$); NMR δ 0.98 (t, *J* = 7.0 Hz, $CH_2CH_2CH_3$), 1.25 (d, *J* = 6.0 Hz, $CHCHOHCH_3$, 1.83 (m, $CH_2CH_2CH_3$), 1.89–2.09 and 2.38–2.57 (2 m, *H*-3 and *H*-4), 3.41 (2 d, *J* = 9.0 and 14.0 Hz, $SO_2CH_AH_B$), 3.62 (2 d, *J* = 1.5 and 14.0 Hz, $SO_2CH_AH_B$), 3.86 (s, OCH_3), 3.90 (s, 2 OCH_3), 5.18 (s, OCH_2Ph), 5.10–5.30 (m, *H*-2 and *H*-5), 6.62 (s, C_5ArH), 7.34–7.46 (m, ArH). The absolute stereochemistry of 16*S* was unambiguously confirmed by X-ray analysis as follows.

X-ray Crystallography of 16*S*. Colorless crystals of 16*S* were grown from methanol. The crystal chosen for data collection (approximate dimensions 0.06 × 0.20 × 0.35 mm) was mounted in a nonspecific orientation of an Enraf-Nonius CAD4F diffractometer. The crystal data and experimental conditions are the following: formula = $C_{32}H_{40}O_9S$, M_r = 600.73, monoclinic space group $P2_1$, *a* = 11.2230 (7), *b* = 8.659 (2), *c* = 35.550 (2) Å, β = 92.464 (5)°, *V* = 3160.3 Å^3, *Z* = 4, D_{calc} = 1.262 g cm^{-3}, μ(Cu Kα) = 1.30 mm^{-1}, *F*(000) = 1280, *T* = 296 K. Data were collected[42]

with Cu K_α monochromatized radiation (λ = 1.54184 Å) to a 2θ limit of 150° yielding 9160 measured reflections (including Bijvoet pairs for $2\theta < 80°$). Scan type is ω with a range of $0.70 + 0.14\tan\theta$ and variable speed of 1.8–10.1 deg min^{-1}. The data set was corrected for Lorentz, polarization, and background effects. Monitoring standard reflections (three every 1 h of exposure time) showed no decay correction necessary. Averaging equivalent reflections (R_{int} = 0.015) gave a unique data set of 8693 reflections with 5833 observed data (at the $I \geq 3\sigma(I)$ level). No absorption correction was calculated. Structure was solved using SHELXS-86[43] and refined[44] using full-matrix least-squares on F with a weighting scheme of $1/\sigma^2(F)$. Included in the refined parameters is a secondary extinction coefficient of 1.46×10^{-6}. The final agreement statistics are the following: R = 0.056, ωR = 0.056, S = 3.00, $(\Delta/\sigma)_{max}$ = 0.02. There is no structural significance to the maximum peak height in a final difference Fourier (0.54 (6) eÅ^{-3}).

The final model has all the non-hydrogen atoms of both independent molecules along with all the H atoms except those of the hydroxyl oxygens (O9 and O9′). These hydrogens were included at their calculated positions and constrained to ride with their parent atom. In order to minimize the number of variables, only those atoms with the largest anisotropic thermal motion are allowed to refine anisotropically in the final cycles. Two calculations were done to ensure the correct absolute configuration was assigned: (1) refinement of the model with the identities of the hydroxyl and methyl groups on C28 switched gave significantly increased R-factors and poor thermal parameters for these atoms, (2) the enantiomorphic structure was fully refined and this gave an R-factor for this refinement which was significantly greater than the first refinement (0.065 vs 0.056). Thus we conclude that the original model with the S,S,S absolute configuration for the three centers is correct. Additional support for the present assignment of the identity of the hydroxyl and methyl groups on C28 comes from the intermolecular distances between molecules in a unit cell. There is one short contact, indicative of a hydrogen bond, between O9 and O1 but no such contacts for C29.

Tables of crystallographic coordinates, thermal parameters, and geometrical quantities have been included in the supplementary material.

(−)-*trans*-(2*S*,5*S*)-2-[3-[((2*R*)-2-Hydroxypropyl)sulfonyl]-4-*n*-propoxy-5-(benzyloxy)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (16*R*). This compound was prepared from 17*R* similarly as described for 17*S*: mp 123–125 °C; $[\alpha]^{25}_D$ −68.8° (*c* 1.1, $CHCl_3$); NMR δ 0.98 (t, *J* = 7.5 Hz, $CH_2CH_2CH_3$), 1.24 (d, *J* = 6.5 Hz, $CHCHOHCH_3$), 1.82 (m, 2H, $CH_2CH_2CH_3$), 3.40 (2 d, *J* = 9.0 and 14.0 Hz, $SO_2CH_AH_B$), 3.60 (2 d, *J* = 1.5 and 14.0 Hz, $SO_2CH_AH_B$), 3.86 (s, OCH_3), 3.89 (s, 2 OCH_3), 5.17 (s, OCH_2Ph), 6.62 (s, C_5ArH).

(−)-*trans*-(2*S*,5*S*)-2-[3-[((2*S*)-2-Hydroxypropyl)sulfonyl]-4-*n*-propoxy-5-(3-hydroxypropoxy)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (19*S*). A solution of 16*S* (470 mg, 0.78 mmol) in ethyl acetate (5 mL) was hydrogenated over 10% palladium-on-charcoal (94 mg) for 1 h. The catalyst was removed by filtration and washed with ethyl acetate. The combined filtrates were evaporated to give 18*S* as a syrup (371 mg, 93%) which was used without further purification. This compound had R_f 0.09 (hexane–ethyl acetate, 3:2); NMR δ 1.09 (t, *J* = 7.5 Hz, $CH_2CH_2CH_3$), 1.25 (d, *J* = 6.5 Hz, $CHCHOHCH_3$), 3.86 (s, OCH_3), 3.89 (s, 2 OCH_3), 5.13–5.28 (m, H-2 and H-5), 5.75 (s, OH), 6.62 (s, C_5ArH), 7.34 and 7.48 (2 d, *J* = 2.0 Hz each, C_2ArH). A mixture of 18*S* (371 mg, 0.73 mmol), 3-bromo-1-propanol (0.12 mL, 1.3 mmol), and potassium carbonate (180 mg, 1.3 mmol) in DMF (3 mL) was heated with stirring under nitrogen at 75 °C for 1.5 h. The reaction mixture was cooled and partitioned between ethyl ether and water. The aqueous layer was extracted twice with Et_2O. The combined ethereal extracts were dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was purified by flash column chromatography (hexane–ethyl acetate, 1:1 to 1:2, v/v) to afford the title compound as a syrup (351 mg, 85%): $[\alpha]^{25}_D$ −46.8° (*c* 1.7, $CHCl_3$); MS *m/z* 568 ($M^{\cdot+}$); NMR δ 1.04 (t, *J* = 7.5 Hz, $CH_2CH_2CH_3$), 1.24 (d, *J* = 6.5 Hz, $CHCHOHCH_3$), 3.40 (2 d, *J* = 9.0 and 14.0 Hz, $SO_2CH_AH_B$), 3.58 (2 d, *J* = 2.0 and 14.0 Hz, $SO_2CH_AH_B$), 3.85 (s, OCH_3), 3.88 (s, 2 OCH_3), 4.11 (m, $CH_2CH_2CH_3$), 4.22 (m, $CH_2CH_2CH_2OH$), 5.14–5.29 (m, *H*-2 and *H*-5), 6.62 (s, C_5ArH), 7.32 and 7.48 (2 d, *J* = 2.0 each, C_2ArH). Anal. ($C_{28}H_{40}O_{10}S$) C, H, S.

(−)-*trans*-(2*S*,5*S*)-2-[3-[((2*R*)-2-Hydroxypropyl)sulfonyl]-4-*n*-propoxy-5-(3-hydroxypropoxy)phenyl]-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (19*R*). This compound was prepared from 16*R* similarly as described for the preparation of 19*S*: $[\alpha]^{25}_D$ −66.2° (*c* 1.8, $CHCl_3$); MS *m/z* 568 ($M^{\cdot+}$); NMR δ 1.04 (t, *J* = 7.5 Hz, $CH_2CH_2CH_3$), 1.25 (d, *J* = 6.5 Hz, $CHCHOHCH_3$), 3.41 (2 d, *J* = 9.0 and 14.0 Hz, $SO_2CH_AH_B$), 3.58 (2 d, *J* = 2.0 and 14.0 Hz, $SO_2CH_AH_B$), 3.85 (s, OCH_3), 3.88 (s, 2 OCH_3), 4.11 (m, $CH_2CH_2CH_3$), 4.22 (m, $CH_2CH_2CH_2OH$), 5.14–5.29 (m, H-2 and H-5), 6.62 (s, C_5ArH), 7.29 and 7.50 (2 d, *J* = 2.0 each, C_2ArH).

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Supplementary Material Available: Positional and thermal parameters for the non-hydrogen atoms, derived positional and thermal parameters for hydrogen atoms, selected interatomic distances, and selected interatomic angles for compound 16*S* (8 pages). Ordering information is given on any current masthead page.

(42) The diffractometer control programs are those supplied by Enraf-Nonius for operating the CAD4F diffractometer.

(43) Sheldrick, G. M. SHELX-86. Crystallographic Computing 3. Sheldrick, G. M., Kr/ger, C., Goddard, R., Eds.; Oxford University Press, 1985; 175–189.

(44) Structure Determination Package Version 3. Enraf-Nonius, Deflt. The Netherlands (1985) implemented on a Sun Microsystems workstation.