travenous injection and the time course of the response was followed for at least 1 h.

Acknowledgment. The authors gratefully acknowledge the contributions made to this work by Dr. J. C. Emmett, S. J. Bakewell, and N. E. Sore.

Registry No. 5, 107549-65-5; 6, 107549-69-9; 7, 126725-00-6; 8, 126725-01-7; 9, 107549-66-6; (*R**,*R**)-10, 126725-02-8; (*R**,*S**)-10, 126725-06-2; 11, 107549-68-8; 12, 107549-70-2; (*R**,*R**)-13, 126725-03-9; (*R**,*S**)-13, 126725-07-3; 15·2HCl, 21702-05-6; 16·2HCl, 107549-76-8; 17, 34555-41-4; 18, 107549-77-9; 19, 107549-74-6; 20, 126725-04-0; 21, 107549-80-4; 22, 107549-81-5; 23·HCl, 126725-05-1; 24, 107549-83-7; 25, 36725-27-6; 26, 86798-59-6; 27, 52240-83-2; 28·HCl, 126725-08-4; 29, 21394-91-2; 30, 84243-58-3; 31·HCl, 54557-93-6; 32, 1017-06-7; 33, 54558-04-2; 34, 24912-35-4; 35, 107549-84-8; 4-AcC_6H_4Ac, 1009-61-6; 3-AcC_6H_4Ac, 6781-42-6; 4-AcC_6H_4-4-C_6H_4Ac, 787-69-9; $OHCCO_2H$, 298-12-4; 4-$H_3CCH_2COC_6H_4COCH_2CH_3$, 17558-64-4; 4-$AcC_6H_4(CH_2)_2CH_3$, 2932-65-2; 4-$H_3CCHBrCOC_6H_4COCHBrCH_3$, 7709-84-4; $H_2NNHC(S)OCH_3$, 19692-07-0; 2,5-diacetylthiophene, 4927-10-0.

9,11-Epoxy-9-homoprosta-5-enoic Acid Analogues as Thromboxane A_2 Receptor Antagonists

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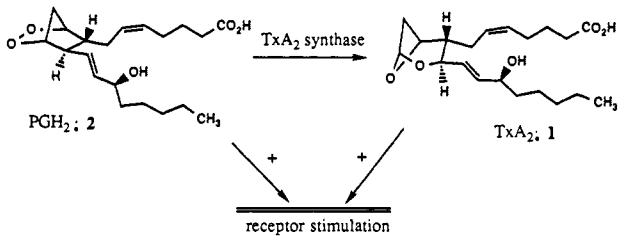
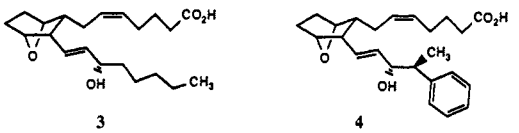
A novel bicyclic prostaglandin analogue, (1*S*)-[1α,2α(*Z*),3α(1*E*,3*S**,4*R**),4α]-7-[3-(3-hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (4), was found to be a potent and selective thromboxane A_2 (TxA_2) receptor antagonist. Alcohol 4 was the only member in a series of allylic alcohols which did not display direct contractile activity in the rat stomach strip model. Alcohol 4 was effective in the inhibition of (a) arachidonic acid induced platelet aggregation of human platelet-rich plasma (I_{50} = 0.65 ± 0.1 μM); (b) 11,9-epoxymethano-PGH_2 induced contraction of guinea pig trachea (pA_2 = 8.0 ± 0.2) or rat aorta (pA_2 = 8.1 ± 0.2); and (c) arachidonic acid induced bronchoconstriction in the anesthetized guinea pig (1 mg/kg iv). A radioiodinated analogue of 4 bound in a specific and saturable manner to human platelet membranes with a K_d = 2.3 ± 0.9 nM. Modification of the α-chain, in an attempt to minimize in vivo metabolism, resulted in TxA_2 receptor antagonists of reduced in vitro potency.

The pursuit of pharmacological agents that modulate the synthesis or actions of thromboxane A_2 (TxA_2, 1)[1] has been an area of intense effort over the past decade.[2] TxA_2, as well as its biosynthetic precursor PGH_2 (2), are potent stimulators of platelet aggregation and mediate vascular and pulmonary smooth muscle contraction (Scheme I). Earlier studies[3] from these laboratories have described a series of 7-oxabicyclo[2.2.1]heptane analogues related to 3 which were found to antagonize TxA_2 at the receptor level. These analogues were TxA_2 receptor antagonists in the platelet preparations but displayed direct contractile activity in smooth muscle preparations. In addition, 3 was not specific in that it inhibited platelet aggregation by both TxA_2 and non-TxA_2 dependent mechanisms. In this report, we describe the modification of the ω-chain terminus which led to a highly selective TxA_2 receptor antagonist, 4 (Scheme II). Alteration of the α-chain in an attempt to limit in vivo degradation of 4 by β-oxidation led to TxA_2 receptor antagonists of reduced potency.

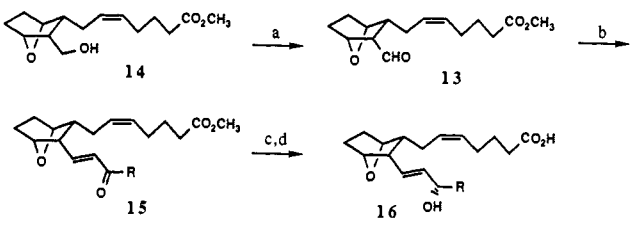
Scheme I



Scheme II



Scheme III[a]



[a] (a) PCC, Celite, NaOAc, CH_2Cl_2, 23 °C; (b) $(H_3CO)_2POCH_2COR$, NaH, DME, 23 °C; (c) $NaBH_4$, $CeCl_3$, CH_3OH, 0 °C; (d) LiOH, H_2O, THF, 23 °C.

Chemistry

Allylic alcohols 4–12 (Table I), which possess the natural 5(*Z*)-heptenoic acid α-chain, were prepared by using the straightforward sequence outlined in Scheme III. These analogues derived from the common precursor, aldehyde 13, which was previously synthesized from alcohol ester 14 via a Collins oxidation[3a] but was more conveniently prepared with pyridinium chlorochromate. Aldehyde 13 was extremely sensitive to epimerization during the Horner–Emmons condensation but this side reaction could be prevented as long as complete consumption of the NaH had occurred.[4] A more convenient procedure employed the $LiCl/R_3N$ methodology described by Masamune and Roush.[5] In addition to the lack of epimerization, the latter method afforded less of the *cis*-enone isomers. Reduction[6] using $NaBH_4/CeCl_3$ followed by hydrolysis afforded the target allylic alcohols. Separation of the C(15) alcohol

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(1) Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994. For the total synthesis of TxA_2 and its characterization, see: (b) Bhagwat, S. S.; Hamann, P. R.; Still, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 6372. (c) Bhagwat, S. S.; Hamann, P. R.; Still, W. C.; Bunting, S.; Fitzpatrick, F. A. *Nature (London)* **1985**, *315*, 511.

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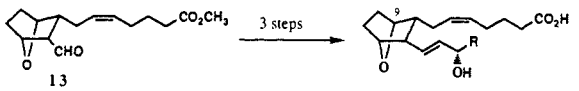
Table I. Synthesis and in Vitro Activity of Allylic Alcohols

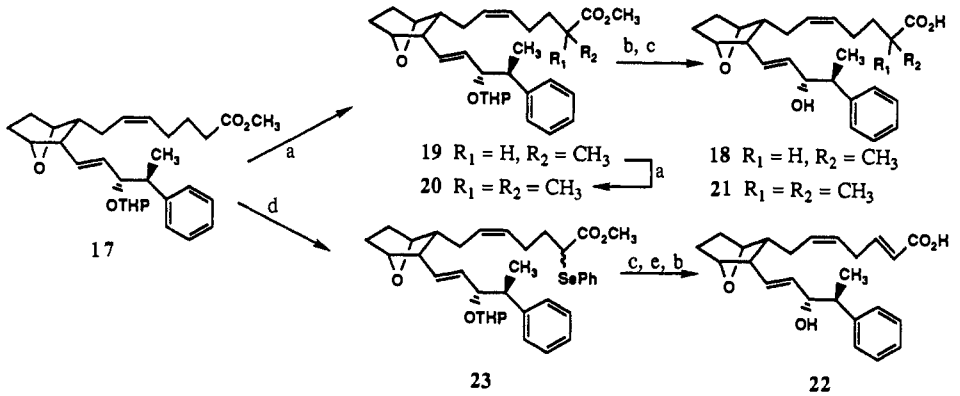


13

no.	R	overall % yield[a]	method[b]	configuration at C(9)	formula[c]	mp, °C	in vitro pharmacology: I_{50}, μM AA-IPA[e]	ADP-IPA[f]	contraction of rat stomach[g] A_{50}, μM
3	C_5H_{11}			see ref 3			1.7	300	0.4 ± 0.2
5	$C(CH_3)_2C_4H_9$		A	*R, S*	$C_{23}H_{38}O_4 \cdot 0.3H_2O$	oil	1.1	>1000	
6	*c*-C_6H_{12}	45	A	*S*	$C_{22}H_{34}O_4$	79–81	0.4	0.9	9% (30 μM)
7	CH_2CH_2Ph	17	A	*R, S*	$C_{24}H_{32}O_4$	oil	1.2	>1000	3.7 ± 1.6
8	CH_2OPh	26	A	*R, S*	$C_{23}H_{30}O_5 \cdot 0.2H_2O$	oil	A_{50} = 6 μM		
4	(*S*)-$CH(CH_3)Ph$	60	A	*S*	$C_{24}H_{32}O_4$	71–72	0.65 ± 0.1	>1000	0%
9	(*R*)-$CH(CH_3)Ph$	45	A	*S*	$C_{24}H_{32}O_4$	oil	3.1	>1000	0%
10	(*R*)-$CH(CH_3)Ph$	25[h]	B	*R*	$C_{24}H_{32}O_4$	oil	730	>100	
11	(*S*)-$CH(CH_3)$-4-OHPh	33	B	*S*	$C_{24}H_{32}O_5$	116–118	0.24	950	21% (0.1 μM)
12	(*S*)-$CH(CH_3)$-4-OH-3-IPh	46[d]	B	*S*	$C_{24}H_{31}O_5I$	foam	0.93	>1000	

[a] Overall yield from aldehyde 13. [b] Base used for Horner–Emmons reaction: A = NaH, B = Et_3N, LiBr. [c] C, H, and I (if applicable) analysis were within ±0.4% of calculated values. [d] Overall yield from the methyl ester of 11. [e] I_{50} vs 800 μM arachidonic acid in human platelet-rich plasma (PRP); values represent single determinations unless otherwise noted. For details of the methods used see ref 8. For comparison, AAIPA I_{50} = 38.5 ± 3.5 μM for 33 (Scheme VIII); AAIPA I_{50} = 0.012 ± 0.005 μM for 34 (Scheme VIII). [f] Adenosine diphosphate (ADP, 20 μM) induced aggregation of human PRP. [g] Concentration of test compound required to elicit 50% of the maximal contraction induced by 3.0×10^{-7} M serotonin; when given as a percentage, this is the maximum contraction observed at the indicated concentration; $n = 8$ for all compounds tested. [h] Prepared by condensation of the enantiomer of 13 with racemic phosphonate and separation of the diastereomeric products.

Scheme IV[a]

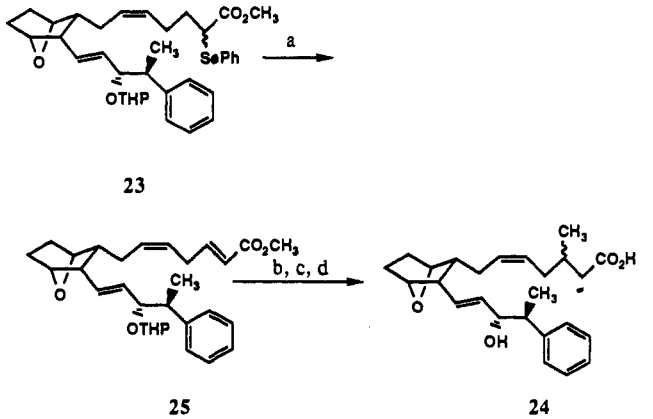


23 22

[a] (a) LDA, THF, CH_3I, −78 °C; (b) THF, 2 N HCl; (c) THF, 1 N LiOH; (d) LDA, THF, $(PhSe)_2$, −78 °C; (e) THF, 30% H_2O_2, 0–5 °C.

epimers was effected at the ester stage and the stereochemical assignments were, for the most part, based on their relative mobility on straight-phase TLC.[7] The stereochemical assignments of 4 and 9 were confirmed by synthesis of the compounds using the optically pure ketophosphonates.

Scheme V[a]



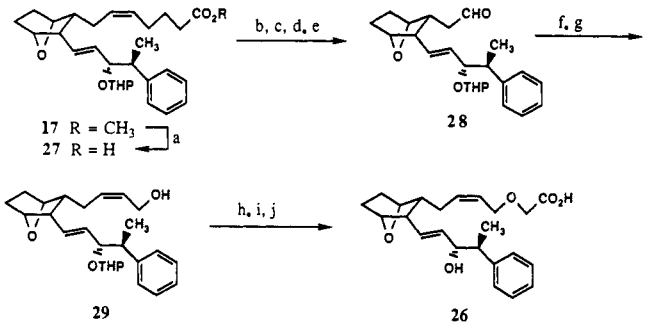
23 25 24

[a] (a) EtOAc, CH_3OH, 30% H_2O_2; (b) $(H_3C)_2CuLi$, Et_2O, −20 °C; (c) amberlyst-15 resin, CH_3OH; (d) THF, 1 N LiOH.

Preparation of α-chain modified analogues of 4 were limited to modifications that would offer protection to β-oxidative cleavage. The methyl ester of 4 was converted to THP ether 17, which served as the starting material for

(2) For a recent review of TxA_2 synthetase inhibitors and TxA_2 receptor antagonists, see: Cross, P. E.; Dickinson, R. P. in *Annual Report in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic Press: New York, 1987; Vol. 22, p 95.
(3) (a) Sprague, P. W.; Heikes, J. E.; Gougoutas, J. Z.; Malley, M. F.; Harris, D. N.; Greenberg, R. *J. Med. Chem.* **1985**, *28*, 1580. For a review of the pharmacology of 7-oxabicycloheptane analogues, see: (b) Harris, D. N.; Hall, S. E.; Hedberg, A.; Ogletree, M. L. *Drugs Future* **1988**, *13*, 153.
(4) The oxabicycloheptane bridgehead protons are diagnostic for the stereochemistry of the two side chains; in the desired cis-exo product these resonances appear at δ 4.23 (d, J = 4.7 Hz) and 4.18 (d, J = 4.7 Hz) as opposed to δ 4.38 (t, J = 4.7 Hz) and 4.19 (d, J = 4.7 Hz) in the epimerized enone.
(5) Blanchette, M. A.; Choy, W.; Davis, J. T.; Esenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(6) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(7) The fast-moving and the slow-moving alcohol epimers were tentatively assigned the 15*S* and 15*R* configuration, respectively, on the basis of their TLC mobilities compared to those of the natural prostaglandins and previous 7-oxabicycloheptyl prostaglandin analogues.[3]

Scheme VI[a]

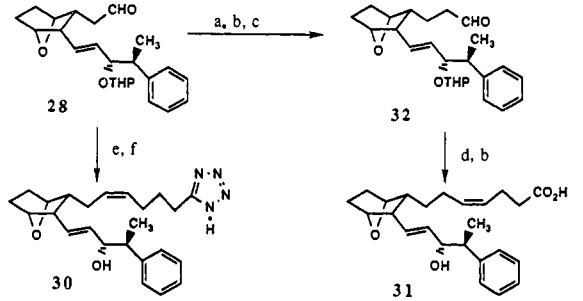


[a] (a) THF, 1 N LiOH; (b) THF, H_2O, $NaHCO_3$, I_2, 0–5 °C; (c) CH_3OH, 1 N LiOH; (d) Et_2O, CH_2N_2; (e) CH_3OH, H_2O, $NaIO_4$; (f) CH_3OH, $Ph_3P{=}CHCOOCH_3$; (g) DIBAL-H, toluene, THF, −78 °C; (h) $BrCH_2COO$-*t*-Bu, THF, 50% NaOH, *n*-Bu_4NHSO_4; (i) amberlyst-15 resin, CH_3OH; (j) THF, 50% NaOH.

these α-chain analogues. For the synthesis of 2-methyl analogue **18**, the ester enolate of **16** was allowed to react with iodomethane to form an epimeric mixture of 2-methyl adducts **19**, which on aqueous acid hydrolysis and subsequent saponification afforded **18** (Scheme IV). Further alkylation of **19** with iodomethane under similar conditions provided **20**, which after deprotection of THP ether and saponification afforded 2,2-dimethyl derivative **21** (Scheme IV). For the preparation of 2,3-dehydro adduct **22**, the ester enolate from **17** was treated with diphenyldiselenide to form an epimeric mixture of 2-phenylseleno adducts **23**. Acidic hydrolysis followed by treatment with 30% H_2O_2 in aqueous THF and subsequent basic hydrolysis of the ester group provided **22** (Scheme IV). The 2-phenylseleno adduct **23** also served as an intermediate for the synthesis of 3-methyl analogue **24** (Scheme V). Accordingly, **23** was transformed to α,β-unsaturated ester **25**, which on reaction with dimethyl cuprate in ether formed exclusively a single 3-methyl epimer (mixture of epimers at the anomeric tetrahydropyran carbon) which was then converted to acid **24** under standard conditions. Although the cuprate addition was stereospecific, we were unable to determine the absolute stereochemistry at the newly formed C-3 center from proton and carbon NMR spectra.

3-Oxa analogue **26** was prepared from **17** (Scheme VI) through the following transformations: (i) basic hydrolysis to form **27**; (ii) iodolactonization of **27** followed by treatment of crude iodolactone with LiOH in aqueous methanol and subsequent treatment with ethereal diazomethane to give a 5,6-diol ester, which underwent oxidative cleavage with sodium metaperiodate in aqueous methanol to afford aldehyde **28**; (iii) reaction of the aldehyde with methyl(triphenylphosphoranylidine)acetate in methanol to form a 1:1 mixture of (*Z*)- and (*E*)-esters which could be separated by silica gel chromatography; (iv) DIBAL-H reduction of the (*Z*)-ester to (*Z*)-allylic alcohol **29**; (v) O-alkylation with *tert*-butyl bromoacetate under phase-transfer conditions followed by THP ether hydrolysis and methyl ester hydrolysis to produce the target acid **26**. Aldehyde **28** also served as the precursor to both tetrazole adduct **30** and 4,5-olefin **31** (Scheme VII). Synthesis of the former was accomplished by condensation of **28** with [4-(5-tetrazoyl)butyl]triphenylphosphonium bromide under standard Wittig conditions and deprotection of the resulting THP ether to afford tetrazole **30**. Alternatively, one-carbon homologation of aldehyde **28** under standard conditions produced aldehyde **32**, which was treated with (carboxypropyl)triphenylphosphonium iodide under Wittig conditions to afford **31** following deprotection of the THP ether.

Scheme VII[a]



[a] (a) $Ph_3P^+CH_2OCH_3Cl^-$, THF, KO-*t*-amylate; (b) THF, 2 N HCl; (c) CH_2Cl_2, DHP, *p*-TsOH; (d) THF, KO-*t*-amylate, $Ph_3P^+I^-(CH_2)_3CO_2H$; (e) THF, KO-*t*-amylate, [4-(5-tetrazolyl)butyl]triphenylphosphonium bromide; (f) amberlyst-15, CH_3OH.

Pharmacology

In Vitro. All of the allylic alcohols were evaluated for their ability to inhibit aggregation of human platelet-rich plasma (PRP) induced by either arachidonic acid (AA) or adenosine diphosphate (ADP).[8] The results for the ω-chain analogues are summarized in Table I. Our initial goal was to identify an analogue of **3** which was a specific thromboxane receptor antagonist for use as a pharmacological tool in order to assess the role of TxA_2 in disease. As previously reported,[3,8] **3** inhibited platelet aggregation induced by AA or at higher concentrations primary aggregation induced by ADP. The latter activity was due to the ability of **3** to enhance cAMP levels in the platelet (albeit, at high concentrations, >300 μM) perhaps through stimulation of an antiaggregatory prostaglandin receptor. Clearly, this dual activity would hamper efforts to define the pharmacology of a TxA_2 receptor antagonist. We were thus most interested in identifying an analogue of **3** which lacked this additional antiplatelet activity. Initial analogue work focused on the modification of the ω-chain to take advantage of advanced synthetic intermediates. Alteration of the allylic alcohol group led to profound effects on activity. Regardless of the structure of the allylic alcohol substituent, increased lipophilicity resulted in increased antiaggregatory activity. Replacement of the *n*-pentyl residue with a cyclohexyl group resulted in a compound (**6**) which was nearly equally effective in inhibiting both AA- and ADP-induced aggregation.[9] In contrast, the *gem*-dimethylpentyl and phenethyl groups produced specific TxA_2 receptor antagonists (**5**, **7**) as evidenced by their lack of effect on ADP-induced aggregation. Unlike all other allylic alcohols, phenoxymethyl analogue **8** stimulated platelet aggregation[10] with an A_{50} = 6 μM. Although analogues **5** and **7** had profiles as specific TxA_2 receptor antagonists in the platelet, these compounds displayed direct agonist activity in vitro (rat stomach strip[11]) or in

(8) Arachidonic acid (800 μM) and ADP (20 μM) induced platelet aggregation in platelet-rich plasma as described previously: Harris, D. N.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Sprague, P. W.; Antonaccio, M. J. *Prostaglandins* **1981**, *22*, 295.

(9) A similar effect was observed when R = cyclopentyl or cycloheptyl (data not shown).

(10) Analogues of **8** in which the ω-chain is in the endo orientation have recently been described and are the most potent PGH_2/TxA_2 mimetics identified to date; synthesis and pharmacology of the *p*-fluoro derivative: Wilson, N. H.; Jones, R. L.; Marr, C. G.; Muir, G. *Eur. J. Med. Chem.* **1988**, *23*, 359. Pharmacology of the *p*-iodo derivative: Morinelli, T. A.; Oatis, J. E., Jr.; Okwu, A. K.; Mais, D. E.; Mayeux, P. R.; Masuda, A.; Knapp, D. R.; Halushka, P. V. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 557.

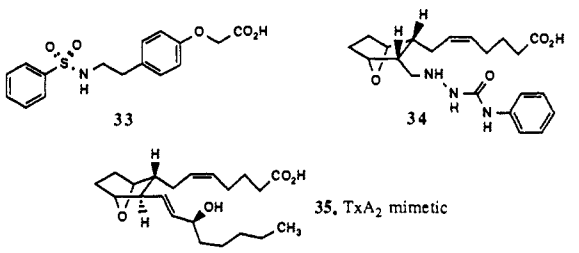
Table II. Activity of Thromboxane Antagonists in Smooth Muscle Preparations[a]

no.	tissue	agonist	I_{50}/pA_2	K_B,[f] nM
4	guinea pig trachea	9,11-azo-PGH_2[b]	1.98 ± 0.15 μM	
33[c]	guinea pig trachea	9,11-azo-PGH_2[b]	>100 μM[d]	
4	guinea pig trachea	11,9-epoxymethano-PGH_2	8.0 ± 0.2	12.1 ± 2.2
34[e]	guinea pig trachea	11,9-epoxymethano-PGH_2	9.2 ± 0.2	1.3 ± 0.2
4	rat aorta	11,9-epoxymethano-PGH_2	8.0 ± 0.2	13.5 ± 2.4
34	rat aorta	11,9-epoxymethano-PGH_2	9.4 ± 0.2	0.66 ± 0.06

[a] For details of the methods used, see ref 12. None of the compounds inhibited contraction induced by histamine (1 μg/mL). [b] Concentration of 0.1 μg/mL. [c] 4-[2-(Benzenesulfonamido)ethyl]phenoxyacetic acid. See ref 15. [d] Maximal inhibition at 100 μM = 43%. [e] [1S-[1α,2α(Z),3α,4α]]-7-[3-[[2-[(Phenylamino)carbonyl]hydrazino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid. See ref 14a. [f] Slopes of the Schild plots were not significantly different from −1 ± 0.1, supporting competitive antagonism of 11,9-epoxymethano-PGH_2-induced contraction of smooth muscle.

Scheme VIII. Reference Structures

TxA_2 Receptor Antagonists

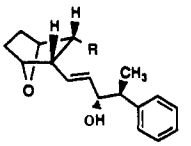


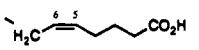
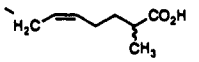
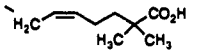
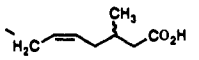
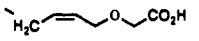
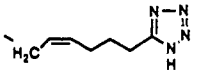
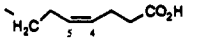
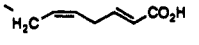
vivo (guinea pig bronchoconstriction[12]). This profile of agonistic activity in smooth muscle tissue is not unusual and has been observed with a number of TxA_2 receptor antagonists.[13]

Unfortunately, the contractile activity of allylic alcohols such as **5** was found to be general for a number of additional analogues (data not shown). Unique among these analogues, however, were 2-phenethyl epimers **4** and **9**. Neither compound displayed contractile activity in the rat stomach with the former isomer being a more potent TxA_2 receptor antagonist in the platelet. Activity was stereospecific as the enantiomer of **4** was essentially inactive (1000-fold less potent). Due to its specificity of action, **4** was selected for further development.

Alcohol **4** was also shown to be an competitive TxA_2 receptor antagonist in several smooth muscle preparations[11] (Table II). Compound **4** was more potent than a nonprostanoid analog, **33**[14] (BM 13.177, Scheme VIII), but somewhat less potent than the widely studied semicarbazide **34**[15] (SQ 29,548, Scheme VIII) in both the rat aorta and guinea pig trachea.

Table III. α-Chain Analogues of Alcohol **4**[a]



no.	R	formula[b]	AAIPA[c] I_{50}, μM
4		$C_{24}H_{32}O_4$	0.65 ± 0.1
18		$C_{25}H_{34}O_4$	25
21		$C_{26}H_{36}O_4$	260
24		$C_{25}H_{34}O_4$	12
26		$C_{23}H_{30}O_5 \cdot 0.5H_2O$	3.4
30		$C_{24}H_{32}N_4O_2 \cdot 0.25H_2O$	3.2
31		$C_{24}H_{32}O_4$	25
22		$C_{24}H_{30}O_4 \cdot 0.2H_2O$	3.8

[a] All compounds were viscous oils and were prepared as a single enantiomer. [b] All compounds were analyzed for C, H, and N (if applicable) and the analytical values were within ±0.4% of calculated values. [c] None of the compounds were effective in inhibiting ADP (20 μM) induced aggregation of human platelet-rich plasma. All values are the result of a single determination unless otherwise indicated.

Radioligand binding studies[16] in human platelet membranes with [^{125}I]-**12** revealed rapid and reversible binding of high affinity (K_d = 2.3 ± 0.9 nM). The binding was saturable and identified one binding site (B_{max} = 5.1 pmol/mg protein). The specific binding of [^{125}I]-**12** was competitively inhibited by both TxA_2 receptor antagonists (**12**; K_d = 4.7 ± 1.3 nM; **4**, K_d = 19 ± 2.2 nM; **34**, K_d = 2.8 ± 0.5 nM) and TxA_2 mimetics (11,9-epoxymethano-PGH_2, K_d = 25 ± 3.3 nM; 9,11-azo-PGH_2, K_d = 7.5 ± 1.1 nM; **35** (SQ 26,655, Scheme VIII); K_d = 2.3 ± 1.1 nM). Additional studies using [^{3}H]-**34** revealed a similar affinity (K_d = 31.9 ± 1.2 nM) for **4**.

One potential problem in the development of prostanoids such as **4** is its rapid in vivo degradation via β-oxidation of the α-chain.[17] As summarized in Table III,

(11) A_{50} determined as the concentration of test compound required to elicit 50% of the maximal contraction of rat fundic stomach strips induced by 3×10^{-7} M serotonin. For details see: (a) Ogletree, M. L.; Harris, D. N.; Greenberg, R.; Haslanger, M. F.; Nakane, M. *J. Pharmacol. Exp. Ther.* **1985**, *234*, 435. (b) Harris, D. N.; Greenberg, R.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Haslanger, M. F.; Steinbacher, T. E. *Eur. J. Pharmacol.* **1984**, *103*, 9. (c) Vane, J. R. *J. Pharmacol.* **1957**, *12*, 344.

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(13) (a) Corey, E. J.; Ponder, J. W.; Ulrich, P. *Tetrahedron Lett.* **1980**, 137. (b) Nicolaou, K. C.; Magolda, R. L.; Claremon, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1404. (c) Nicolaou, K. C.; Magolda, R. L.; Smith, J. B.; Aharony, A.; Smith, E. F.; Lefer, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2566. (d) Wilson, N. H.; Jones, R. L. In *Advances in Prostaglandins and Thromboxane Research*; Samuelsson, B., Paoletti, R., Ramwell, P., Eds.; Raven: New York, 1985; Vol. 14, p 393. (e) Ansell, M. F.; Caton, M. P. C.; Palfreyman, M. N.; Stuttle, K. A. *Tetrahedron Lett.* **1979**, 4497.

(14) Ogletree, M. L.; Harris, D. N.; Greenberg, R.; Haslanger, M. F.; Nakane, M. *J. Pharmacol. Exp. Ther.* **1985**, *234*, 435. For a detailed list of studies with this compound, see ref 3b.

(15) Stegmeier, K.; Pill, J.; Muller-Beckman, B.; Schmidt, F. H.; Witte, C.; Wolff, H. P.; Patscheke, H. *Thromb. Res.* **1984**, *35*, 379.

(16) (a) Hedberg, A.; Hall, S. E.; Ogletree, M. L.; Carpenter, K. S.; Liu, E. C.-K. *Pharmacologist* **1987**, *29*, 167. (b) Hedberg, A.; Hall, S. E.; Ogletree, M. L.; Harris, D. N.; Liu, E. C.-K. *J. Pharmacol. Exp. Ther.* **1988**, *245*, 786. (c) [^{3}H]-34 (SQ 29,548) is now commercially available from New England Nuclear.

(17) β-Oxidation of the α-chain in **4** results in a dramatic loss of activity; AAIPA I_{50} = 135 μM for 2,3-bisnor-**4** and AAIPA I_{50} > 1000 μM for the corresponding tetrakisnor analogue.

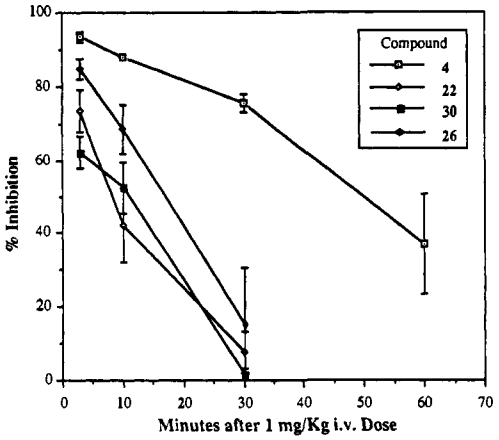

Figure 1. Inhibition of the increased resistance induced by 0.5 mg/kg iv arachidonic acid in the anesthetized guinea pig. Each bar is the mean ±SE of the response in five animals.

modification of the α-chain led, in general, to a significant loss in potency. Introduction of one or two methyl groups in the 2-position resulted in progressive loss of activity. 2-Methyl analogue **18** and 2,2-dimethyl analogue **21** were about 40-fold and 400-fold less active, respectively, than parent compound **4**. Presumably the increased steric congestion around the carboxylic acid function interferes with the binding of these compounds to the TxA_2 receptor.[18] Introduction of the 3-methyl group (**24**) also resulted in a 20-fold loss in potency. The relative position of the olefin linkage in the α-chain proved critical for activity since 4,5-olefin derivative **31** was 40-fold less potent than its 5,6-isomer **4**. 3-Oxa analogue **26**, the tetrazole **30**, and 2,3-dehydro adduct **22**, all of which by virtue of their chemical structures could offer protection against β-oxidation, showed a modest 5-fold loss in potency.

In Vivo. Compound **4** and its congeners were evaluated for their effects on changes in lung mechanics as well as blood pressure induced by AA in the anesthetized guinea pig.[11] Unlike other oxabicycloheptane derivatives,[19] **4** and its α-chain analogues **22**, **26**, and **30** had no direct effects on guinea pig airway tone or systemic blood pressure. As shown in Figure 1, all of these compounds inhibited AA-induced bronchoconstriction and systemic hypertension when dosed at 1 mg/kg iv. However, none of the analogues which should be resistant to β-oxidation (**22, 26, 30**) displayed a duration of action in vivo superior to that of **4**. In addition to its antibronchospastic activity, **4** has previously been shown to be an effective antithrombotic agent[20] in vivo and to prevent the pulmonary hypertension induced by endotoxin administration.[21]

Conclusion

Modification of the nonselective alcohol **3** has led to a more potent and selective TxA_2 antagonist, **4** (SQ 28,668), which displays antithrombotic, antivasospastic, and antibronchospastic activity in vitro and in vivo. Efforts to increase its duration of action in vivo by structural modifications to the α-chain which would prevent or minimize β-oxidation led to compounds of reduced potency in vitro. Toxicological studies showed that **4** was free of any overt toxicity and was advanced to phase I clinical trials.[22] Further development of this compound was suspended as it was superseded by a more potent TxA_2 antagonist[3b,23] (**36**, SQ 30,741; [1*S*-[1α,2α(*Z*),3α,4α]]-7-[3-[[[[(1-oxoheptyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic acid).

Experimental Section

^1H NMR spectra were measured at 270 MHz on a JEOL FX-270 and at 400 MHz on a JEOL GX-400. ^{13}C NMR spectra were measured at 15 MHz on a JEOL FX-60 and at 67.5 MHz on a JEOL FX-270. Unless indicated otherwise, all ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported in δ units relative to internal Me_4Si, $CHCl_3$ assigned at δ 7.24, or $CDCl_3$ at δ 77.0. Infrared spectra were recorded on a Perkin-Elmer Model 983 infrared spectrophotometer and were calibrated with the 1601 cm^{-1} absorption of polystyrene. Mass spectra were measured with an Extranuclear Simulscan or Finnigan TSQ mass spectrometer in either CI or EI mode. High-resolution mass spectra and fast-atom bombardment MS were measured on a VG-ZAB-2F instrument. All new compounds exhibited IR and MS spectra consistent with their assigned structure and for the sake of brevity will not be tabulated here. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

All reactions were conducted in oven-dried glassware under an argon atmosphere. All solvents were purified before use unless otherwise indicated; THF and ether were distilled from sodium benzophenone ketyl, CH_2Cl_2 was distilled from P_2O_5, and toluene and xylene were distilled from sodium and stored over activated 4A molecular sieves. Flash chromatography was performed as described by Still[24] with J. T. Baker "flash" grade silica gel.

Methyl [1α,2α(*Z*),3α,4α]-7-[3-Formyl-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoate (**13**). To a stirred slurry of 1.38 g (6.40 mmol) of pyridinium chlorochromate,[25] 0.10 g (1.22 mmol) of NaOAc, and 1.38 g of Celite in CH_2Cl_2 (7.0 mL) was added a solution of 540 mg (mmol) of alcohol **14** in CH_2Cl_2 (7.0 mL) over approximately 1 min. The reaction mixture was stirred for 1.75 h at room temperature and then diluted with ether (35 mL). The reaction mixture was filtered through a pad of Florisil. The filter cake was rinsed with ether (70 mL). The combined filtrates were concentrated in vacuo to afford 0.52 g of **13** as a nearly colorless oil. Diagnostic ^1H NMR signals include the aldehydic proton, δ 9.60 (d, J = 4.7 Hz), and the oxabicycloheptane bridgehead protons, δ 4.76 (d, J = 4.7 Hz) and 4.34 (d, J = 4.7 Hz). These signals appear at δ 9.71 (d, J = 1.8 Hz) and δ 4.82 (t, J = 4.7 Hz) and 4.30 (d, J = 4.7 Hz), respectively, if epimerization has occurred.

General Procedure for the Preparation of Target Acids. The enone intermediates were prepared by using the NaH pro-

(18) The poor activity of the dimethyl analogue **21** contrasts with the potent activity of a nonprostanoid TxA_2 receptor antagonist (L-655,240), which also possesses the 2,2-dimethyl carboxylic acid group; Hall, R. A.; Gillard, J.; Guindon, Y.; Letts, G.; Champion, E.; Ethier, D.; Evans, J.; Ford-Hutchinson, A. W.; Fortin, R.; Jones, T. R.; Lord, A.; Morton, H. E.; Rokach, J.; Yoakim, C. *Eur. J. Pharmacol.* **1987**, *135*, 193.

(19) Hall, S. E.; Han, W.-C.; Harris, D. N.; Hedberg, A.; Ogletree, M. L. *J. Med. Chem.* **1989**, *32*, 974.

(20) (a) Ogletree, M. L.; Harris, D. N.; Heran, C. L.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J. *Eicosanoids* **1988**, *1*, 85. (b) Ogletree, M. L.; Heran, C. L.; Harris, D. N. *Thromb. Haemostasis* **1985**, *54*, 280. (c) Schumacher, W. A.; Goldenberg, H. J.; Harris, D. N.; Ogletree, M. L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1987**, *46(3)*, 423. (d) Ashton, J. H.; Schmitz, J. M.; Campbell, W. B.; Ogletree, M. L.; Raheja, S.; Taylor, A. L.; Fitzgerald, C.; Buja, L. M.; Willerson, J. T. *Circ. Res.* **1986**, *59*, 568. (e) Golino, P.; Buja, M.; Ashton, J. H.; Kulkarni, P.; Taylor, A.; Willerson, J. T. *Circulation* **1988**, *78*, 701. Reference 20a also describes additional in vitro pharmacology with **4**.

(21) Schumacher, W. A.; Adams, H.; Ogletree, M. L. *Pharmacology* **1987**, *34*, 301.

(22) Friedhoff, L. T.; Manning, J.; Funke, P. T.; Ivashkiv, E.; Tu, J.; Cooper, W.; Willard, D. A. *Clin. Pharmacol. Ther.* **1986**, *40*, 634.

(23) Ogletree, M. L.; Harris, D. N.; Hedberg, A.; Nakane, M.; Reid, J. *Pharmacologist* **1986**, *28*, 186. (b) Grover, G.; Schumacher, W. A.; Simon, M.; Parham, C. *J. Cardiovasc. Pharmacol.* **1988**, *12*, 701. (c) Schumacher, W. A.; Steinbacher, T. E.; Allen, G. T.; Olgetree, M. L. *J. Appl. Physiol.* **1989**, *67*, 44. (d) Schumacher, W. A.; Heran, C. L. *J. Cardiovasc. Pharmacol.* **1989**, *13*, 853.

(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(25) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

cedure[3] (method A) or a modification of the Masamune/Roush (LiBr/Et_3N) procedure[5] (method B) as described previously from these laboratories.[26] Conversion of these intermediates to the target acids was accomplished by using the methodology previously described.[26] For a representative procedure, see the preparation of 11.

[1α,2α(*Z*),3α(*E*),4α]-7-[3-(3-Hydroxy-4,4-dimethyl-1-octenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, fast-moving isomer (5): ^{13}C NMR δ 175.7, 133.1, 132.0, 131.3, 130.3, 82.9, 80.1, 79.8, 51.6, 49.5, 39.6, 37.9, 33.6, 30.3, 29.9, 29.0, 27.2, 26.6, 25.5, 24.5, 23.4, 23.4, 14.5. Anal. ($C_{23}H_{38}O_4 \cdot 0.3H_2O$) C, H.

[1*S*-[1α,2α(*Z*),3α(1*E*,3*S),4α]]-7-[3-(3-Cyclohexyl-3-hydroxy-1-propenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (6)**: ^{13}C NMR δ 176.9, 132.4, 132.0, 130.3, 129.3, 81.9, 79.3, 77.5, 50.7, 48.7, 43.4, 32.7, 29.5, 29.1, 28.6, 27.7, 26.3, 26.3, 25.9, 24.3; $[\alpha]_D$ = +51.2° (*c* = 0.85, CH_3OH). Anal. ($C_{22}H_{34}O_4$) C, H.

[1α,2α(*Z*),3α(*E*),4α]-7-[3-(3-Hydroxy-5-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, fast moving isomer (7): ^{13}C NMR δ 177.0, 141.8, 133.4, 132.5, 130.5, 129.4, 128.4, 128.4, 125.8, 82.0, 79.5, 72.6, 50.8, 48.9, 38.7, 32.6, 31.7, 29.7, 29.2, 27.9, 26.3, 24.4. Anal. ($C_{24}H_{32}O_4$) C, H.

[1α,2α(*Z*),3α(*E*),4α]-7-[3-(3-Hydroxy-4-phenoxy-1-butenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, fast-moving isomer (8): NMR δ 175.7, 159.8, 133.7, 131.2, 130.9, 130.4, 130.4, 130.4, 121.7, 115.5, 115.5, 82.7, 80.3, 72.7, 71.3, 51.4, 49.4, 33.5, 30.3, 29.8, 28.9, 27.2, 25.4. Anal. ($C_{23}H_{30}O_5 \cdot 0.2H_2O$) C, H.

[1*S*-[1α,2α(*Z*),3α(1*E*,3*S,4*S**),4α]]-7-[3-(3-Hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (9)**: ^{13}C NMR δ 177.6, 143.4, 132.5, 131.6, 130.4, 129.3, 129.3, 128.1, 126.3, 81.9, 79.4, 77.3, 50.7, 50.7, 48.6, 32.9, 29.6, 29.6, 29.0, 26.4, 24.4, 16.5; $[\alpha]_D$ = +63.5° (*c* = 1.0, $CHCl_3$). Anal. ($C_{24}H_{32}O_4$) C, H.

[1*S*-[1α,2α(*Z*),3α(1*E*,3*S,4*R**),4α]]-7-[3-(3-Hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (4)**: ^{13}C NMR δ 175.5, 145.5, 133.3, 133.3, 131.4, 130.3, 129.1, 129.1, 127.1, 82.8, 80.2, 77.9, 51.5, 49.5, 47.0, 33.5, 30.3, 29.9, 29.0, 27.2, 25.5, 18.2; $[\alpha]_D$ = +63.7° (*c* = 1.5, $CHCl_3$). Anal. ($C_{24}H_{32}O_4$) C, H.

[1*R*-[1α,2α(*Z*),3α(1*E*,3*S,4*R**),4α]]-7-[3-(3-Hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (10).** Acid **10**, as a mixture of methyl epimers, was prepared from the enantiomer of aldehyde **13** and racemic phosphonate by using the procedure described for acid **11**. The crude product was chromatographed on 30 g of silica gel using 2% CH_3OH/CH_2Cl_2 as eluant. Fractions 25–29 afforded 154.8 mg (47%) of acid **10**. Later fractions afforded a mixture of **10** and its methyl epimer **37**. Data for **10**: ^{13}C NMR δ 175.5, 145.5, 133.3, 133.3, 131.4, 130.3, 129.1, 129.1, 127.1, 82.8, 80.2, 77.9, 51.5, 49.5, 47.0, 33.5, 30.3, 29.9, 29.0, 27.2, 25.5, 18.2; $[\alpha]_D$ = −66.4° (*c* = 3.2, $CHCl_3$). Anal. ($C_{24}H_{32}O_4$) C, H. The diagnostic ^1H NMR signal to distinguish the two methyl epimers is the resonance for the methyl group which appears at δ 1.18 in **10** and δ 1.25 in **37**.

Dimethyl [3-[4-(*tert*-butyldimethylsiloxy)phenyl]-2-oxobutyl]phosphonate (38). To a stirred solution of $(MeO)_2P(O)CH_3$ (1.17 mL, 10.8 mmol) in THF (6.0 mL) at −78 °C was added dropwise 1.57 M *n*-BuLi/hexane (5.0 mL, 7.85 mmol) over a period of 10 min. Thirty-five minutes later additional THF (1 mL) was added (to thin out the slurry) followed by the addition of a solution of 0.9 mL of methyl 2-[(4-*tert*-butyldimethylsiloxy)phenyl]propionate in THF (5.0 mL). After 2 h, the reaction had warmed to 0 °C. The reaction was quenched by the addition of HOAc (0.6 mL) in THF (1.0 mL) and stored overnight in the refrigerator. The following day the mixture was concentrated in vacuo. The residue was partitioned between saturated $NaHCO_3$ and ether (40 mL each). The aqueous layer was extracted with ether (30 mL). The combined ether layers were washed with brine (30 mL). The brine layer was then back-extracted with ether (30 mL). The combined ether layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 1.25 g of crude product. Bulb-to-bulb distillation (oven setting = 240 °C, 2–5 mmHg) afforded 0.99 g of phosphonate **38** (84%).

Methyl [1*S*-[1α,2α(*Z*),3α(*E*),4α]]-7-[3-[3-Oxo-4-[4-(*tert*-butyldimethylsiloxy)phenyl]-1-pentenyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoate (39). To a dried flask containing 236 mg (2.71 mmol) of anhydrous LiBr was added a solution of 930 mg (2.41 mmol) of phosphonate **38** in CH_2Cl_2 (5.0 mL). To this stirred slurry was added Et_3N (0.33 mL, 2.38 mmol). This slurry was stirred for 40 min at room temperature and then a solution of 475 mg of optically active aldehyde **13** (1.79 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise over 5 min. The reaction mixture was stirred at room temperature overnight and then partitioned between EtOAc and 0.1 N HCl (25 mL of each). The EtOAc layer was washed with saturated $NaHCO_3$ (25 mL). Separation of the layers was difficult, so additional EtOAc (20 mL) was added. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give 1.12 g of crude enone. Purification was effected by flash chromatography on 40 g of silica gel using 2:1 hexane/ether as eluant. Fractions 23–55 were concentrated in vacuo to give 0.85 g (90%) of enone **39** as an approximate 55:45 mixture of methyl epimers (TLC silica gel, 2% CH_3OH/CH_2Cl_2, R_f = 0.7, $Ce(SO_4)_2$).

Methyl [1*S*-[1α,2α(*Z*),3α(*E*,3*S,4*R**),4α]]-7-[3-[3-Hydroxy-4-[4-(*tert*-butyldimethylsiloxy)phenyl]-1-pentenyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (40).** To a stirred solution of 800 mg of enone **39** (1.52 mmol) in CH_3OH (3.0 mL) and THF (3.0 mL) was added 550 mg of $CeCl_3 \cdot 7H_2O$. This was stirred at room temperature for 10 min and then cooled to −50 °C. To this solution was added 65 mg (1.71 mmol) of $NaBH_4$ in one portion. The reaction mixture was stirred for 2.25 h, allowing the bath temperature to warm to −30 °C. On recooling to −50 °C, the reaction mixture was quenched by the addition of prechilled acetone (2 mL). After stirring an additional 25 min, the mixture was concentrated in vacuo. The residue was partitioned between ether (40 mL) and 1 N HCl (20 mL). The aqueous layer was extracted with ether (20 mL). The combined ether layers were washed with 30 mL of H_2O, dried over $NaHCO_3/MgSO_4$, and concentrated in vacuo to afford 0.75 g of colorless oil. This was chromatographed on 40 g of silica gel using 1% CH_3OH/CH_2Cl_2 as eluant. Fractions 36–39 afforded 160 mg of **40** (fast-moving isomer). Fractions 40–43 gave a mixture of **40** and its methyl epimer **41** (230 mg) [TLC silica gel 2% CH_3OH/CH_2Cl_2, R_f = 0.39 (**40**), 0.33 (**41**)].

[1*S*-[1α,2α(*Z*),3α(1*E*,3*S,4*R**),4α]]-7-[3-[3-Hydroxy-4-(4-hydroxyphenyl)-1-pentenyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (11).** To a stirred solution of 160 mg (0.30 mmol) of alcohol **40** in THF (4.0 mL) and H_2O (1.0 mL) was added 1 N LiOH solution (2.0 mL). The mixture was purged with a stream of argon for 5 min and then stirred at room temperature for 4.5 h. The mixture was diluted with saturated NaCl (10 mL), acidified to pH = 3 with 1 N HCl, and extracted with three portions of ether (20 mL). The combined ether layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was chromatographed on 27 g of silica gel using 6% CH_3OH/CH_2Cl_2 as eluent to afford 90 mg (74%) of acid **11**: TLC silica gel, 6% CH_3OH/CH_2Cl_2, R_f = 0.4, $Ce(SO_4)_2$; ^{13}C NMR δ 177.0, 154.9, 134.4, 133.9, 131.5, 130.5, 129.4, 128.9, 115.6, 82.0, 79.6, 78.3, 50.8, 48.7, 45.1, 32.5, 29.7, 29.1, 27.8, 26.2, 24.3, 18.4; $[\alpha]_D$ = +50.4° (*c* = 1.16, $CHCl_3$). Anal. ($C_{24}H_{32}O_5$) C, H.

[1*S*-[1α,2α(*Z*),3α(*E*,3*S,4*R**),4α]]-7-[3-[3-Hydroxy-4-(4-hydroxy-3-iodophenyl)-1-pentenyl]-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic Acid (12).** To a stirred solution of 210 mg (0.51 mmol) of the methyl ester of **11** (**42**) in CH_3OH (30 mL) was added 0.5 M KH_2PO_4 buffer (70 mL, pH = 7.5). This caused the evolution of some heat so the flask was immersed in an ice bath until the contents were slightly cooled (15–20 °C). To this stirred mixture was added 88 mg (0.59 mmol) of NaI followed by a solution of 436 mg (1.92 mmol) of Chloramine-T hydrate in 0.5 M KH_2PO_4 buffer (50 mL). The mixture was stirred for an additional 90 s and then quenched by the addition of saturated $Na_2S_2O_5$ solution (9 mL). This was extracted with three portions of CH_2Cl_2 (150 mL). The combined CH_2Cl_2 layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude product. Purification was effected by chromatography on 40 g of silica gel using 2% CH_3OH/CH_2Cl_2 as eluant. This gave 184 mg of impure monoiodide **43**, 90 mg of impure diiodide **44**, and 92 mg (44%) of recovered **42** [TLC silica gel, 2% CH_3OH/CH_2Cl_2, R_f = 0.25 (**43**), 0.37 (**44**)].

(26) Das, J.; Vu, T.; Harris, D. N.; Ogletree, M. L. *J. Med. Chem.* **1988**, *31*, 930.

To a stirred solution of 184 mg of impure **43** in THF (4.0 mL) was added H_2O (1.0 mL) followed by 1 N LiOH solution (2.0 mL). This mixture was purged with a stream of argon for 10 min. Analysis of the reaction by TLC showed it to be complete after 3 h. The reaction mixture was partitioned between brine and EtOAc (25 mL of each). The aqueous layer was acidified to pH $\approx$ 3.5 by the addition of 1 N HCl. The aqueous layer was extracted with two portions of EtOAc (35 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification was effected by chromatography on 30 g of silica gel using 4% CH_3OH/CH_2Cl_2 as eluant to afford 88 mg of pure **12** (33% overall from **42**). Another portion of impure **43** (87 mg) was hydrolyzed under the same conditions. Purification of the acid was effected by preparative TLC (20 × 20 cm, 0.5 mm thick) using 4% CH_3OH/CH_2Cl_2. Elution of the compound from the silica gel with EtOAc and 6% CH_3OH/CH_2Cl_2 afforded 36 mg of pure **12**. These two portions were combined. Thus, the overall yield from phenol **42** to monoiodo acid **12** was 46%: TLC silica gel, 4% CH_3OH/CH_2Cl_2, R_f = 0.30, I_2; ^{13}C NMR δ 177.2, 153.9, 137.7, 137.3, 134.0, 131.3, 130.5, 129.5, 129.4, 115.2, 85.4, 82.0, 79.6, 78.0, 50.8, 48.7, 44.7, 32.6, 29.7, 29.1, 27.8, 26.3, 24.3, 18.3; $[\alpha]_D$ = +34.0° (c = 1.0, $CHCl_3$). Anal. ($C_{24}H_{31}O_5I$) C, H, I.

Methyl [1*S*-[1α,2α(*Z*),3α(*E*,3*S,4*R**),4α]]-7-[3-[4-Phenyl-3-(tetrahydropyranyloxy)-1-pentenyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (17).** A solution of the methyl ester of 4 (**45**), 2.16 g, 5.4 mmol) in CH_2Cl_2 (20 mL) was treated with catalytic *p*-toluenesulfonic acid and dihydropyran (0.75 mL, 8.33 mmol) at 0–5 °C. After 40 min, the mixture was poured into aqueous sodium bicarbonate solution. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with ether. The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with 10–15% EtOAc/hexanes as eluents to obtain THP ether **17** (2.43 g, 92%) as a colorless oil.

Methyl [1*S*-[1α,2α(*Z*),3α(*E*,3*S,4*R**),4α]]-2-Methyl-7-[3-[4-phenyl-3-(tetrahydropyranyloxy)-1-pentenyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (19).** A solution of diisopropylamine (1.0 mL, 7.14 mmol) in dry THF (40 mL) was treated dropwise at −78 °C with a 1.57 M solution of *n*-BuLi in hexane (2.46 mL, 3.86 mmol). After 30 min a solution of THP ether **17** (1.7 g, 3.5 mmol) in THF (40 mL) was added. The reaction mixture was stirred for 30 min and iodomethane (1.5 mL, 24.1 mmol) was added. The mixture was stirred at −78 °C for 30 min and was then warmed to −20 °C prior to quenching with saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL, 3×). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on a silica gel column with 15% EtOAc/hexane as eluent to afford an epimeric mixture of 2-methyl adducts **19** (1.45 g, 84%) as an oil.

General Method for the Synthesis of Acids. The carboxylic acids were prepared by following the procedure described below for **18**.

[1*S*-[1α,2α(*Z*),3α(*E*,3*S,4*R**),4α]]-7-[3-(3-Hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-2-methyl-5-heptenoic Acid (18).** A solution of **19** (670 mg, 3.5 mmol) in THF (40 mL) was treated dropwise with 2 N HCl solution (10 mL). The mixture was stirred at 25 °C for 18 h and then neutralized by the addition of solid $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2 (40 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by chromatography on a silica gel column with 20% EtOAc/hexane as eluent afforded the intermediate alcohol ester (440 mg, 79%). A solution of the alcohol ester (440 mg, 1.06 mmol) in THF (40 mL) and 1 N LiOH solution (10 mL) was stirred at 25 °C for 4 days. The mixture was concentrated and the residue was diluted with water, acidified to pH 3 with saturated oxalic acid solution, and extracted with Et_2O (40 mL, 3×). The ether extracts were combined, washed with water (20 mL, 2×), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on a silica gel column with a gradient of pentane/ether as eluent to obtain acid **18** (389 mg, 92%) as a 1:1 mixture of epimers at C_2: ^{13}C NMR δ 142.7, 135.0, 130.9, 130.8, 130.3, 129.6, 128.7, 128.0, 126.9, 81.8, 79.4, 78.4, 51.0, 49.1, 48.8, 46.2, 38.6, 38.3, 33.6, 33.5, 29.7, 29.3, 27.7, 25.2, 25.0, 18.7, 17.6; $[\alpha]_D$ = +67.2° (c = 1.0, CH_3OH). Anal. ($C_{25}H_{34}O_4$) C, H.

[1*S*-[1α,2α(*Z*),3α(*E*,3*S,4*R**),4α]]-2,2-Dimethyl-7-[3-(3-hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (21):** ^{13}C NMR δ 142.0, 135.0, 130.7, 129.6, 129.5, 128.8, 128.0, 127.0, 81.8, 79.5, 78.5, 51.1, 49.1, 46.2, 42.2, 40.9, 29.7, 29.3, 27.5, 25.1, 23.7, 18.2; $[\alpha]_D$ = +62.6° (c = 1.0, CH_3OH). Anal. ($C_{26}H_{36}O_4$) C, H.

[1*S*-[1α,2α(2*E*,5*Z*),3α(*E*,3*S,4*R**),4α]]-7-[3-(3-Hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-2,5-heptadienoic Acid (22).** Phenylseleno ester **23** was obtained by alkylation of **17** with diphenyldiselenide using the procedure described for preparation of **19** (81% yield). Hydrolysis of methyl ester **23** using the procedure outlined in the synthesis of **18** formed the corresponding acid **46** in 94% yield. A solution of **46** (423 mg, 0.68 mmol) in THF (10 mL) was treated with 30% aqueous H_2O_2 solution (0.5 mL) at 0–5 °C. The ice bath was then removed and the mixture was stirred at 25 °C for 1 h. The mixture was diluted with ether and washed with water. The organic extract was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on a silica gel column with 20–50% EtOAc/hexanes as eluent to obtain the 2,5-dienoic acid (260 mg, 80%), which was deprotected to afford acid **22** (83%) following the procedure described in the synthesis of **18**: ^{13}C NMR δ 170.7, 149.2, 143.1, 132.6, 132.1, 132.0, 128.4, 128.0, 126.6, 125.0, 121.0, 82.1, 79.5, 77.4, 50.7, 48.3, 46.1, 30.1, 29.5, 29.2, 28.1, 17.7. Anal. ($C_{24}H_{30}O_4 \cdot 0.2H_2O$) C, H.

[1*S*-[1α,2α(*Z*),3α(*E*,3*S,4*R**),4α]]-7-[3-(3-Hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-3-methyl-5-heptenoic Acid (24).** A solution of phenylseleno ester **23** (600 mg, 0.94 mmol) in EtOAc (6 mL) and CH_3OH (4 mL) was treated dropwise at 0–5 °C with a 30% aqueous H_2O_2 solution (1 mL). The mixture was stirred at 0–5 °C for 30 min and at 25 °C for 1 h. It was diluted with ether and water. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. The residue was purified on a silica gel column with 10–20% EtOAc/hexanes as eluent to obtain methyl ester **25** (320 mg, 71%) as an oil.

A suspension of cuprous iodide (673 mg, 3.5 mmol) in dry ether (5 mL) was treated dropwise at 0 °C with a 1.5 M solution of CH_3Li in ether (4.7 mL, 7.1 mmol). After 30 min, the mixture was cooled to −20 °C and a solution of ester **25** (340 mg, 0.7 mmol) in ether (5 mL) was added. After 1 h at −20 °C, the mixture was quenched with saturated aqueous NH_4Cl solution. It was diluted with ether (100 mL) and washed with 1:1 NH_4OH/NH_4Cl solution (20 mL, 3×), water (20 mL, 2×), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on a silica gel column with 10% EtOAc/hexanes as eluent to afford 3-methyl ester **47** (277 mg, 78%).

A solution of **47** (277 mg, 0.55 mmol) in CH_3OH (10 mL) was stirred with Amberlyst-15 resin (150 mg) at 25 °C for 18 h. The mixture was diluted with ether (100 mL) and filtered through Celite. The filtrate was concentrated to obtain a hydroxy ester (220 mg, 96%), which was converted to acid **24** (94%) by using the procedure described for the synthesis of **18**: ^1H NMR δ 7.4–7.2 (m, 5 H), 5.73 (dd, 1 H), 5.47 (m, 2 H), 5.42 (dd, 1 H), 4.30 (d, J = 2.7 Hz, 1 H), 4.20 (d, J = 2.7 Hz, 1 H), 4.14 (t, J = 4.2 Hz, 1 H), 2.8 (q, 1 H), 2.5 (dd, 1 H), 2.17 (m, 3 H), 2.0–1.4 (m, 9 H), 1.22 (d, J = 6.9 Hz, 3 H), 0.97 (d, J = 6.3 Hz, 3 H); ^{13}C NMR δ 176.3, 142.9, 134.2, 131.1, 131.0, 128.6, 128.0, 126.8, 81.9, 79.4, 78.1, 51.0, 48.8, 46.1, 40.6, 33.4, 31.0, 29.7, 29.2, 27.9, 19.6, 18.0; $[\alpha]_D$ = +55.7° (c = 1.0, CH_3OH). Anal. ($C_{25}H_{34}O_4$) C, H.

[1*S*-[1α,2α,3α(*E*,3*S,4*R**),4α]][3-[4-Phenyl-3-(tetrahydropyranyloxy)-1-pentenyl]-7-oxabicyclo[2.2.1]hept-2-yl]acetaldehyde (28).** A solution of acid **27** (8.47 g, 18 mmol), $NaHCO_3$ (17.4 g, 210 mmol), THF (180 mL), and water (90 mL) was stirred vigorously at 0–5 °C in the dark and treated dropwise with a solution of iodine (6.86 g, 27 mmol) in THF (20 mL). The mixture was maintained at 0–5 °C for 24 h and then was poured into aqueous $Na_2S_2O_5$ solution (500 mL). The organic layer was separated and the aqueous layer was extracted with ether. The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated to obtain crude iodolactone **48** (10.25 g) as a yellow oil.

A solution of crude **48** (10.25 g) in CH_3OH (180 mL) and 1 N aqueous LiOH solution (90 mL) was stirred at 25 °C for 24 h. The

mixture was cooled and was acidified to pH 4.5 by the addition of 2 N aqueous HCl solution. The mixture was extracted with CH_2Cl_2 (3×) and Et_2O (3×). The organic extracts were combined, washed with brine, dried ($MgSO_4$), and concentrated. The crude acid was dissolved in Et_2O (100 mL) and treated dropwise with an ethereal CH_2N_2 solution. The mixture was concentrated and the residue was purified by chromatography on a silica gel column with 50% EtOAc/hexanes and EtOAc as eluents to obtain diol ester **49** (6.93 g, 75% overall yield from **17**).

A stirred solution of **49** (1.0 g, 1.9 mmol) in CH_3OH (20 mL) was treated with a solution of sodium metaperiodate (1.0 g, 4.6 mmol) in water (5 mL) at 25 °C. After 2 h, the mixture was extracted with CH_2Cl_2 (20 mL, 3×), dried ($MgSO_4$), filtered, and concentrated to obtain aldehyde **28** (728 mg, 100% crude yield).

[1*S*-[1α,2α(*Z*),3α(*E*,3*S,4*R**),4α]]-[[4-[3-(3-Hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-2-butenyl]oxy]acetic Acid (26).** A solution of aldehyde **28** (1.15 g, 3 mmol) and (carbomethoxymethylene)triphenyl phosphorane (1.77 g, 5 mmol) in CH_3OH (25 mL) was stirred at 25 °C for 5 h. The mixture was concentrated, diluted with Et_2O, cooled in ice-water bath, and the precipitated solid was removed by filtration. The filtrate was concentrated and the residue was purified by chromatography on a silica gel column with 5–10% EtOAc/hexanes to obtain both the (*Z*)-ester (570 mg, 43%) and (*E*)-ester (560 mg, 43%).

A solution of (*Z*)-ester (442 mg, 1 mmol) in THF (5 mL) was treated dropwise at −78 °C with a 1.5 M solution of diisobutylaluminum hydride (2 mL, 3 mmol) in toluene. Two hours later, the reaction was quenched by the addition of excess acetone. The mixture was warmed to 25 °C and silica gel (3 g), followed by a drop of acetic acid, was added. The mixture was stirred for 1 h and filtered. The filtrate was concentrated to obtain (*Z*)-alcohol **29** (388 mg, 94%) as a clear oil.

A solution of (*Z*)-alcohol **29** (388 mg, 0.94 mmol), *n*-Bu_4NHSO_4 (500 mg, 1.64 mmol), *tert*-butyl bromoacetate (1.8 g, 9.4 mmol) in THF (5.5 mL) and 50% aqueous NaOH solution (5.5 mL) was stirred at 25 °C for 5 h. The mixture was diluted with Et_2O (100 mL) and washed with water (20 mL, 3×). The organic extract was dried ($MgSO_4$), filtered, and concentrated. The residue was purified on a silica gel column with 10% EtOAc/hexanes as eluent to obtain the *tert*-butyl ester (335 mg, 67%), which was converted to acid **26** (57% in two steps) by the method described for the preparation of **24**: ^1H NMR δ 7.36–7.23 (m, 5 H), 5.65–5.44 (m, 6 H), 4.30 (d, 1 H), 4.21 (d, 1 H), 4.16 (t, *J* = 7.9 Hz, 1 H), 4.10 (d, *J* = 3.2 Hz, 1 H), 4.07 (d, *J* = 3.2 Hz, 1 H), 4.03 (s, 2 H), 2.8 (q, 1 H), 2.54 (dd, 1 H), 2.2–1.5 (m, 7 H), 1.22 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR δ 172.6, 142.8, 136.2, 134.1, 131.4, 128.7, 128.0, 126.9, 124.8, 82.0, 79.4, 78.2, 66.3, 65.8, 51.0, 48.6, 46.0, 29.6, 29.2, 28.2, 18.0; $[\alpha]_D$ = +78.5° (*c* = 1.0, CH_3OH). Anal. ($C_{23}H_{30}O_5 \cdot 0.5H_2O$) C, H.

[1*S*-[1α,2α(*Z*),3α(*E*,3*S,4*R**),4α]]-5-[6-[3-(3-Hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-4-hexenyl]-1*H*-tetrazole (30).** A stirred suspension of [4-(tetrazol-5-yl)butyl]triphenylphosphonium bromide (2.67 g, 5.8 mmol) in dry THF (40 mL) at 0 °C was treated dropwise with a 1.7 M solution of potassium *tert*-amylate (3.3 mL, 5.8 mmol) in toluene. After 1 h, a solution of aldehyde **28** (445 mg, 1.16 mmol) in THF (10 mL) was added. The mixture was warmed to 25 °C, stirred for 1 h, and then quenched by the addition of glacial acetic acid. The mixture was concentrated and the residue was poured into brine solution (200 mL) and extracted with Et_2O (50 mL, 3×). The ether extract was dried ($MgSO_4$), filtered, and concentrated. The residue was diluted with 10% NaOH solution (30 mL) and extracted with 1:1:4 Et_2O/CH_2Cl_2/hexanes (40 mL, 3×). The aqueous layer was acidified to pH 3 with concentrated HCl and extracted with CH_2Cl_2 (50 mL, 5×). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography on a CC-7 silica gel column with a gradient of pentane/ether as eluent to obtain the tetrazole adduct (414 mg, 73%), which was transformed to **30** (89%) by the method described for the preparation of **24**: ^1H NMR δ 7.31–7.16 (m, 5H), 5.60 (dd, 1 H), 5.49 (dd, 1 H), 5.34 (m, 2 H), 4.28 (b s, 2 H), 4.22 (t, 1 H), 2.87 (m, 3 H), 2.52 (t, 1 H), 2.00–1.42 (m, 12 H), 1.22 (d, *J* = 6.9 Hz); ^{13}C NMR δ 156.5, 143.0, 133.1, 132.0, 130.5, 129.2, 128.6, 128.0, 126.8, 82.4, 79.6, 77.8, 50.6, 48.4, 48.2, 29.4, 29.35, 27.9, 27.1, 26.0, 22.6, 18.1; $[\alpha]_D$ = +63.8° (*c* = 1.0, CH_3OH). Anal. ($C_{24}H_{32}N_4O_2 \cdot 0.25\ H_2O$) C, H, N.

[1*S*-[1α,2α(*Z*),3α(*E*,3*S,4*R**),4α]]-7-[3-(3-Hydroxy-4-phenyl-1-pentenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-4-heptenoic Acid (31).** A stirred solution of methoxymethyltriphenylphosphonium chloride (2.1 g, 5.5 mmol) in THF (40 mL) at 0 °C was treated dropwise with a 1.27 M solution of potassium *tert*-amylate (4.4 mL, 6.1 mmol). The solution was allowed to warm to room temperature and stirred for 1 h. It was then cooled to 0 °C and a solution of aldehyde **28** (730 mg, 1.9 mmol) in THF (5 mL) was added. The mixture was warmed to room temperature, stirred for 1 h, and then quenched with glacial acetic acid. The mixture was poured into saturated brine solution (200 mL) and extracted with EtOAc (50 mL, 3×). The EtOAc extracts were combined, dried ($MgSO_4$), filtered, and concentrated. The crude residue was chromatographed on a silica gel column and eluted with EtOAc/hexanes (1:9) to obtain an enol ether (500 mg), which was dissolved in THF (40 mL) and treated with 2 N HCl solution (10 mL). The mixture was stirred for 2 h and was then treated with solid $NaHCO_3$. It was extracted with CH_2Cl_2 (20 mL, 3×). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated to obtain aldehyde **32** (360 mg, 48% yield) as an oil.

Aldehyde **32** was converted to acid **31** (32% yield in two steps) following the procedure used in the synthesis of tetrazole **30** except using (3-carboxypropyl)triphenylphosphonium iodide in place of [4-(tetrazol-5-yl)butyl]triphenylphosphonium bromide: ^1H NMR δ 7.36–7.23 (m, 5 H), 5.67 (dd, 1 H), 5.46 (dd, 1 H), 5.40 (m, 2 H), 4.30 (b s, 1 H), 4.19 (b s, 1 H), 4.13 (t, 1 H), 2.82 (q, 1 H), 2.50 (t, 1 H), 2.40–1.35 (m, 10 H), 1.3–1.1 (m, 3 H), 1.23 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR δ 177.0, 143.0, 134.1, 131.3, 131.0, 128.5, 128.0, 127.7, 126.7, 82.0, 80.0, 78.0, 51.2, 48.1, 46.2, 34.1, 30.4, 29.8, 29.1, 26.7, 22.8, 18.0; $[\alpha]_D$ = +19.0° (*c* = 1.0, $CHCl_3$). Anal. ($C_{24}H_{32}O_4$) C, H.

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Registry No. 1, 57576-52-0; 4, 123048-11-3; (±)-**5**, 126451-80-7; **6**, 93060-40-3; (±)-7, 85873-60-5; (±)-**8**, 85873-62-7; **9**, 126451-81-8; **10**, 126451-82-9; 11, 107024-77-1; **12**, 107024-82-8; **13**, 94903-80-7; (9*R*)-**13**, 70120-35-3; (±)-**13**, 104596-33-0; (±)-**14**, 104596-10-3; **17**, 101399-94-4; 18 (isomer 1), 126295-59-8; 18 (isomer 2), 126451-86-3; 18 (methyl ester, isomer 1), 126295-67-8; 18 (methyl ester, isomer 2), 126451-87-4; **19** (isomer 1), 126295-60-1; **19** (isomer 2), 126451-85-2; **20**, 126295-61-2; **21**, 126295-62-3; **22**, 100827-74-5; **22** (THP ether), 100827-73-4; **23** (isomer 1), 126451-83-0; **23** (isomer 2), 126451-90-9; **24**, 126295-63-4; **24** (methyl ester), 126295-72-5; **25**, 100827-69-8; **26**, 104101-55-5; **26** (*tert*-butyl ester), 104101-54-4; **27**, 126451-94-3; **28**, 126451-84-1; **29**, 104153-89-1; **29** (acid, methyl ester), 126451-91-0; (*E*)-**29** (acid, methyl ester), 126451-92-1; **30**, 126295-64-5; **30** (THP ether), 126295-70-3; **31**, 126295-65-6; **32**, 126295-66-7; **32** (methyl enol ether), 126295-71-4; **37**, 126451-88-5; (±)-**38**, 126295-68-9; **39** (isomer 1), 126327-47-7; **39** (isomer 2), 126452-97-9; **40**, 107024-81-7; 41, 107080-60-4; **42**, 107024-83-9; **43**, 107024-85-1; 44, 107024-84-0; **45**, 101399-92-2; **46** (isomer 1), 126451-89-6; **46** (isomer 2), 126451-93-2; 47, 126295-69-0; **48**, 104101-46-4; **49**, 104101-47-5; $(MeO)_2P(O)CH_3$, 756-79-6; (±)-$CH_3OCOCH(CH_3)C_6H_4$-4-$OSiMe_2Bu$-*t*, 126295-58-7; $Ph_3P{=}CHCOOCH_3$, 2605-67-6; $BrCH_2COOBu$-*t*, 5292-43-3; $Ph_3P^+CH_2OCH_3\ Cl^-$, 4009-98-7; $Ph_3P^+(CH_2)CO_2H\ I^-$, 67640-73-7; [4-(5-tetrazolyl)butyl]triphenylphosphonium bromide, 42743-15-7.