9,11-Epoxy-9-homo-14-oxaprosta-5-enoic Acid Derivatives. Novel Inhibitors of Fatty Acid Cyclooxygenase

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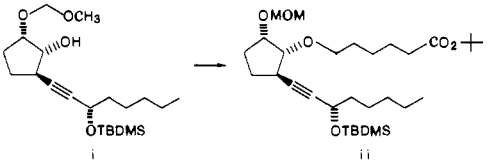
A novel bicyclic prostaglandin analogue, [1*R*-[1α,2β(5*Z*),3β,4α]]-7-[3-[(hexyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid (1), and cogeners were found to be potent inhibitors of fatty acid cyclooxygenase. Compound 1 was the only stereoisomer out of eight possible structures that was active. Ether 1 was 20 times more potent than indomethacin (IND) in inhibiting arachidonic acid (AA) induced aggregation of human platelet-rich plasma. Compound 1 was also more potent than IND in several in vivo assays, AA-induced sudden death in the conscious mouse (2 times) and AA-induced bronchoconstriction in the anesthetized guinea pig (16–45 times).

Pharmacological manipulation of the arachidonic acid (AA) cascade, along both the cyclooxygenase and lipoxygenase pathways, continues to be an area of intense activity. Although 7-oxabicyclo[2.2.1]heptane derivatives have previously been reported to be either agonists or antagonists at the thromboxane A_2 (TXA_2), PGD_2, or prostacyclin (PGI_2) receptors,[1-10] ether analogue 1 exemplifies the first class of these bicyclic compounds that significantly inhibits AA metabolism at the enzymatic level. (See Scheme I.)

This discovery emerged from our continuing program to develop specific TXA_2 antagonists with use of the natural product TXA_2 as a template. We have prepared a number of 7-oxabicycloheptane derivatives in which heteroatom chains were employed as surrogates for the allylic alcohol moiety of TXA_2.[11] Among these analogues, ether 1 was identified as a potent inhibitor of AA-induced aggregation of human platelet-rich plasma (PRP).[12] Further investigation revealed, however, that 1 was not acting at any of these receptors, but rather was a potent inhibitor of prostaglandin (PG) synthetase.[13,14]

Chemistry

At the outset, the synthesis of this simple ether and its diastereomeric relatives appeared to be straightforward given the availability of alcohols **5** and **6**. These intermediates were prepared from the exo and endo Diels–Alder adducts of furan and maleic anhydride as described by Sprague et al.[15] Conversion of alcohols **5–8** to their respective ethers 1 and **9–11** proved, however, to be somewhat elusive. Attempts to prepare ether 1 by using a number of "standard" etherification reactions afforded only low yields of the desired product.[16] For example, reaction of alcohol **5** with hexyl iodide using either KO-*t*-Bu in THF/HMPA (3:1, v/v; 15 h at room temperature → 9 h under reflux) or KH in DMF (26 h at 80–100 °C) afforded none of the desired ether but rather a plethora of unidentified byproducts. Alternatively, treatment of **5** with NaH and either hexyl bromide or hexyl iodide afforded the desired ether in only 5% and 15% yields, respectively. Likewise, treatment of **5** with 4 equiv of powdered KOH (hexyl iodide, Me_2SO, room temperature) provided a meager 17% yield of 1 as its hexyl ester. Following the phase-transfer method reported by Freedman and DuBois,[17] treatment of **5** with 0.27 equiv of n-Bu_4NHSO_4 in THF/50% NaOH/hexyl bromide (1:1:1, v/v/v) afforded 1 as a mixture of hexyl (27%) and methyl (22%) esters. The yield of this alkylation could be improved by increasing the amount of phase-transfer catalyst (PTC). Thus, alkylation of **5** with octyl bromide using 1.0 equiv of PTC provided a 72% yield of **12**. (See Scheme II.)



(1) Sprague, P. W.; Heikes, J. E.; Harris, D. N.; Greenberg, R. In *Advances in Prostaglandin and Thromboxane Research*; Samuelsson, B., Ramwell, P., Paoletti, R., Eds.; Raven: New York, 1980; Vol. 6, p 493.
(2) Harris, D. N.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Sprague, P. W.; Antonaccio, M. J. *Prostaglandins* **1981**, 22, 295.
(3) Harris, D. N.; Phillips, M. B.; Michel, I. M.; Sprague, P. W.; Antonaccio, M. J. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1980**, *39*, 392.
(4) 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.
(5) Greenberg, R.; Steinbacher, T. E.; Harris, D. N.; Haslanger, M. F. *Eur. J. Pharmacol.* **1984**, *103*, 19.
(6) Haslanger, M. F.; Sprague, P. W.; Snitman, D.; Vu, T.; Harris, D. N.; Greenberg, R.; Powell, J. In *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*; Samuelsson B., Paoletti, R., Ramwell, P., Eds.; Raven: New York, 1983; Vol. 11, p 293.
(7) (a) Sprague, P. W.; Heikes, J. E.; Harris, D. N.; Greenberg, R. In *Advances in Prostaglandin and Thromboxane Research*; Samuelsson, B., Ramwell, P., Paoletti, R., Eds.; Raven: New York, 1983; Vol. 11, p 337. (b) Ogletree, M. L.; Harris, D. N.; Greenberg, R.; Haslanger, M. F.; Nakane, M. *J. Pharmacol. Exp. Ther.* **1985**, *234*, 435.
(8) Greenberg, R.; Steinbacher, T. E.; O'Keefe, E. H.; Seaman, K.; Antonaccio, M. J. *Pharmacologist* **1981**, *23*, 208.
(9) Phillips, M. B.; Harris, D. N.; Michel, I. M.; Goldenberg, H. J.; Haslanger, M. F. *Pharmacologist* **1983**, *25*, 204.
(10) Harris, D. N.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Heikes, J. E.; Sprague, P. W.; Anatonaccio, M. J. *Thromb. Haemostasis* **1981**, *46*, 27.
(11) Nakane, M.; Reid, J.; Haslanger, M. F.; Garber, D. P.; Harris, D. N.; Ogletree, M. L.; Greenberg, R. In *Advances in Prostaglandin and Thromboxane Research*; Samuelsson, B., Paoletti, R., Ramwell, P., Eds.; Raven: New York, 1985; Vol. 15, p 291.
(12) Arachidonic acid (800 μM) induced platelet aggregation in platelet-rich plasma as described in ref 2.
(13) Half-maximal inhibition of bovine seminal vesicle cyclooxygenase occurred at a 6.4-μM concentration of 1. This value was determined with use of the methods described in ref 2.
(14) A preliminary communication of these findings has been published: Harris, D. N.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Steinbacher, J. E.; Ogletree, M. L.; Hall, S. E. *Thromb. Haemostasis* **1985**, *54*, 18.
(15) Sprague, P. W.; Heikes, J. E.; Gougoutas, J. Z.; Malley, M. F.; Harris, D. N.; Greenberg, R. *J. Med. Chem.* **1985**, *28*, 1580.
(16) This problem is not unique to these compounds. For example, Matthews et al. were able to obtain a 60% yield of ether ii only after *extensive* optimization of reaction conditions: Matthews, R. S.; Mihelich, E. D.; McGowan, L. S.; Daniels, K. *J. Org. Chem.* **1983**, *48*, 409.
(17) (a) Freedman, H. H.; DuBois, R. A. *Tetrahedron Lett.* **1975**, 3251. (b) DiCesare, P.; Gross, B. *Synthesis* **1979**, 458.

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Scheme I. Activities of 7-Oxabicycloheptane Analogues

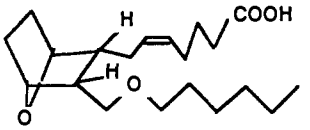
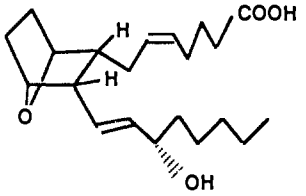
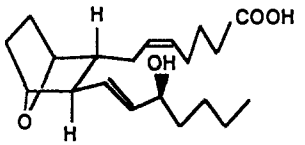
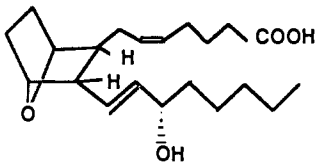
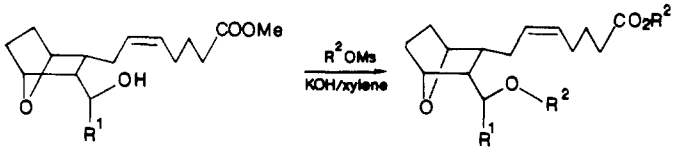
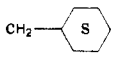
No.	Compound	Pharmacological Profile	AAIPA I_{50}(μM)	ADPIPA I_{50}(μM)
1		cyclooxygenase inhibitor	0.5	>1000
2		TXA_2 antagonist	6.0	300
3		TXA_2-mimic	Ac_{50}=2.5μM	---
4		PGI_2/PGD_2 mimic	0.3	1.6

Table I. Synthesis of Unsymmetrical *O*-Ethers



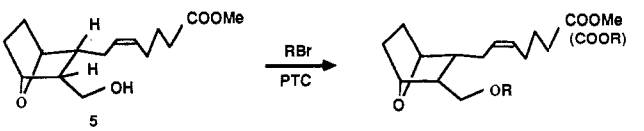
no.	R^1	R^2	amount, equiv R^2OMs	amount, equiv KOH	reaction time, h	yield, %
14	H	$(CH_2)_5CH_3$	5.0	9.0	1.2	79
15	H	$(CH_2)_3Ph$	5.0	7.0	1.0	81
16	H		11.5	9.0	5.0	93
17	H	(*E*)-$CH_2CH{=}CHC_3H_7$	9.0	9.0	3.0	74
18	H	(*Z*)-$CH_2CH{=}CHC_3H_7$	8.0	9.0	2.3	73
19	H	$CH_2C{\equiv}CC_3H_7$	6.0	9.0	0.5	68
20	H	(*Z*)-$(CH_2)_2CH{=}CHC_2H_5$	10.0	9.0	1.5	60
21	H	$CH_2CH(CH_3)C_4H_9$	5.0	8.0	2.5	58[a]
22a,b	H	$CH(CH_3)C_5H_{11}$	5.0	9.0	4.7	36[b]
23	CH_3	$(CH_2)_5CH_3$	5.8	10.3	4.5	51[c]
24	H	$CH_2CH{=}CH_2$				62[d]
25	H	CH_3				*e*

[a] A 19% yield of the hexyl ether was also obtained due to the presence of *n*-hexyl alcohol in the commercial 2-methylhexanol. [b] A 40% yield of **5** was recovered. [c] An 18% yield of **5** was recovered. [d] This compound was prepared via PTC alkylation. [e] Obtained as a byproduct in the preparation of **5**.

The limitations of this methodology were quickly realized as this reaction failed completely when 3-phenylpropyl bromide was employed as the alkylating agent (due to elimination and subsequent polymerization). Thus, our search for an efficient etherification method continued.

Further perusal of the literature uncovered another O-alkylation method used routinely by lipid chemists. This method, developed by Mangold,[18] involved alkylation of the alcohol in xylene with KOH as the base and mesylates as the alkylating agents. Indeed, treatment of **5** with 9 equiv of powdered KOH in refluxing xylene followed by the addition of hexyl mesylate (5 equiv) afforded **1** in 79%

Scheme II. Phase-Transfer Alkylation

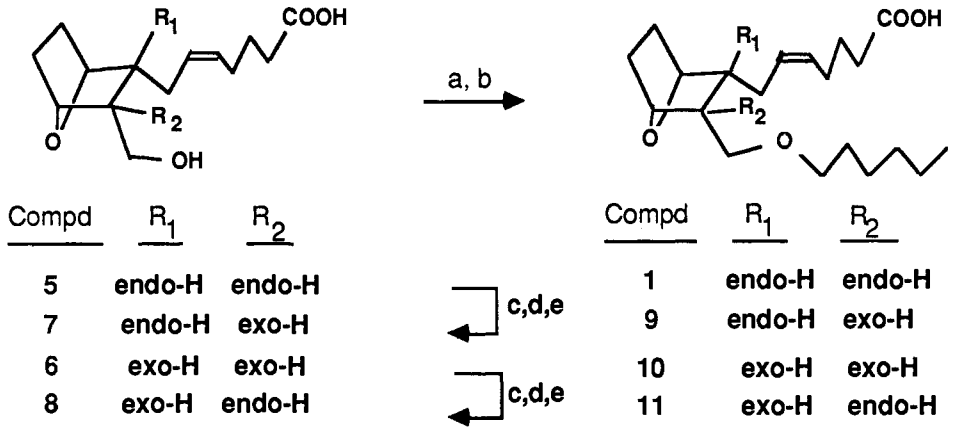


Bu_4NHSO_4

No.	eq	R	Yield
1	0.27	hexyl	49%
12	1.0	octyl	72%
13	0.5	$-(CH_2)_3Ph$	0%

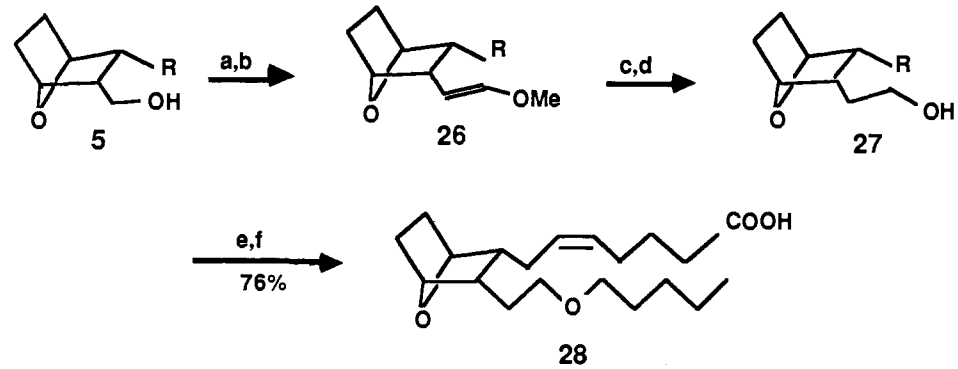
(18) (a) Baumann, N. J.; Mangold, H. K. *J. Org. Chem.* **1966**, *31*, 498. (b) Mangold, H. K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 493. (c) This method was cited in a recent review (ref 18b) as the best procedure for the preparation of alkoxylipids, yet it has gone essentially unreferenced in synthetic organic chemistry.

Scheme III[a]



[a] (a) KOH, hexyl mesylate, xylene, Δ; (b) 1 N LiOH, H_2O, THF, room temperature; (c) PCC, NaOAc, CH_2Cl_2, room temperature; (d) cat. NaOMe, MeOH, 0 → 23 °C; (e) $NaBH_4$, CH_3OH, 0 °C.

Scheme IV[a]



R=-CH_2-CH=CH-$(CH_2)_3$-CO_2CH_3

[a] (a) PCC; (b) $Ph_3P^+CH_2OMeBr^-$, KO-*t*-Am, THF; (c) 20% TFA, THF; (d) $NaBH_4$, CH_3OH, $CeCl_3$; (e) pentyl mesylate, KOH, xylene, Δ; (f) 1 N LiOH, THF, H_2O.

yield. Alkylation of the other three diastereomeric alcohols, **6–8**, proceeded smoothly to give **9–11** in 82%, 76%, and 65% yields, respectively. (See Scheme III.)

As shown in Table I, these conditions proved to be of general applicability, producing the desired ethers in good to excellent yield. Particularly noteworthy was the success of this method using 3-phenylpropyl mesylate (entry 2), in sharp contrast to the failure observed with the PTC reaction.

Despite their propensity for elimination, secondary and allylic mesylates could be used as well; however, the rate of alkylation with secondary mesylates was, as expected, considerably slower. Unlike the phase-transfer procedure,[17] this method works well for the alkylation of secondary alcohols. Although the yields of ethers from secondary alcohols were modest, significant amounts of starting alcohol ester were recovered as well. It should be emphasized that the yields listed in Table I are unoptimized and are the results of single experiments.[19]

A priori, was not obvious what effect translocation of the oxygen atom might have with regard to cyclooxygenase inhibition. As such, we were interested in analogues of **1** wherein the 15-oxygen (PG numbering) had been shifted to either the 14 or 16 position. The synthesis of the 16-oxa analogue proceeded in a straightforward manner from alcohol **5** as outlined in Scheme IV.

(19) We are currently investigating the scope and limitations of this methodology. These results will be reported in a separate account.

Table II. Inhibition of Platelet Aggregation[a,b]

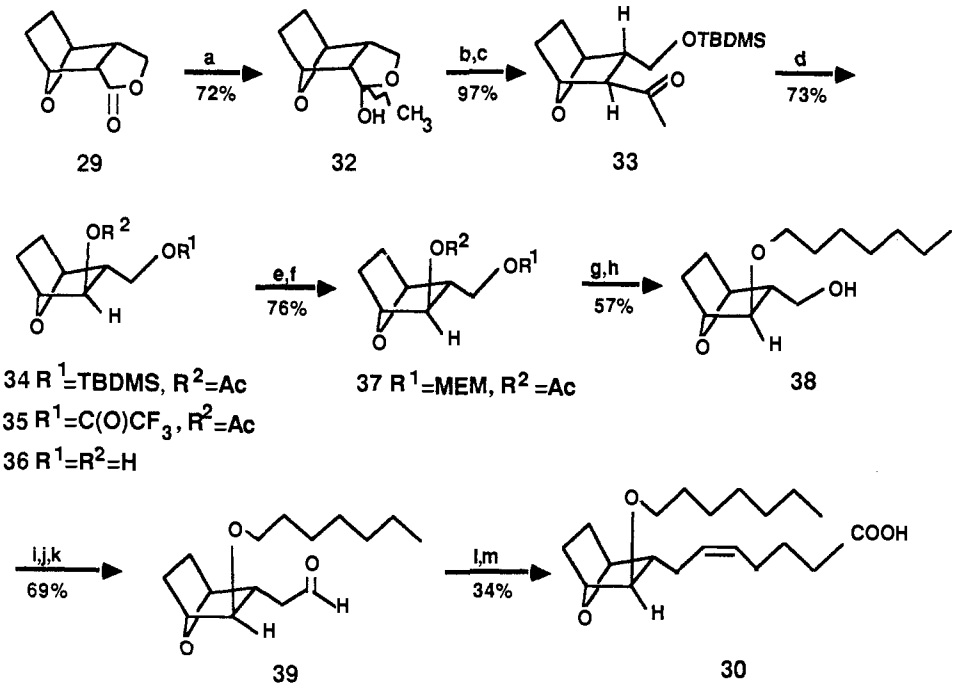
no.	I_{50}, μM	no.	I_{50}, μM
1	0.5	**20**	0.5
9	25.0	**21**	7.4
10	10.0	**22-FMI**	3.2
11	18.0	**22-SMI**	23
12	32	**23**	14
15	26	**24**	6.0
16	165	**25**[c]	22
17	0.3	**28**	105
18	3.3	**30**	120
19	0.2	**31**	340
indomethacin	4.0	**44**[d]	>1000
aspirin	185	**47**[c]	0.2

[a] For details of the methods used, see ref 3; none of the compounds were effective in inhibiting ADP-induced PA; the I_{50} values are the results of single determinations. [b] All compounds were viscous oils and were prepared as racemates unless otherwise indicated. [c] Prepared as a single enantiomer (1*R*). [d] Mp 102–103 °C.

Oxidation of alcohol **5** with pyridinium chlorochromate[20] followed by condensation of the resultant aldehyde with (methoxymethylene)triphenylphosphorane provided vinyl ether **26** in 80% overall yield. Hydrolysis of the vinyl ether followed by hydride reduction afforded alcohol **27** in 40% yield. Alkylation of **27** with KOH/pentyl mesylate proceeded without incident to provide an 83% yield of **28** as its pentyl ester. Subsequent hydrolysis gave the target acid **28** in 92% yield. The synthesis of the 14-oxa analogue

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

Scheme V[a]



[a] (a) CH_3Li, THF, −78 °C, 30 min; (b) TBDMSCl, imidazole, DMF, room temperature, 21 h; (c) cat. $NaOCH_3$, CH_3OH, room temperature, 22 h; (d) 3.9 equiv CF_3CO_3H, CH_2Cl_2, 0 °C, 5.5 h; (e) THF, sat. $NaHCO_3$, room temperature, 8 h; (f) MEM-Cl, *i*-Pr_2EtN, CH_2Cl_2, room temperature, 21 h; (g) KOH, xylene, heptyl mesylate, Δ; (h) $TiCl_4$, CH_2Cl_2, 0 °C, 30 min; (i) PCC, NaOAc, CH_2Cl_2, 90 min; (j) $Ph_3P^+CH_2OCH_3Br^-$, THF, KO-*t*-Am, 0 → 23 °C, 3 h; (k) 20% TFA, THF, 3 h; (l) $Ph_3P^+(CH_2)_4CO_2HBr^-$, KO-*t*-Am, THF, 0 → 23 °C, 22 h; (m) 1 N LiOH, THF, H_2O, room temperature, 8 h.

could not, unfortunately, derive from alcohol **5**, due to the sensitivity of the 5,6-olefinic linkage to oxidative procedures. As a result, we chose the readily available[15] lactone **29** as the starting material for these analogues. The synthesis of the cis and trans isomers **30** and **31** followed somewhat different routes as summarized in Schemes V and VI.

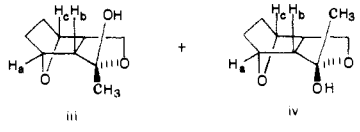
Addition of methyllithium to lactone **29** proceeded without incident to afford hemiketal **32**. It is interesting to note that the major isomer resulted from addition to the more hindered, convex face,[21] suggesting that the oxa bridge is directing addition. Silylation[22] of this intermediate afforded the protected hydroxy ketone,[23] which underwent facile epimerization on treatment with catalytic NaOMe in methanol to give **33**.[24] We anticipated that Baeyer–Villiger oxidation of this intermediate might be problematic due to the severe steric congestion about the carbonyl moiety.

Indeed, treatment of **33** with either MCPBA or 40% peracetic acid was without effect. The desired transformation, however, could be accomplished by using trifluoroperacetic acid (3.9 equiv, 0 °C, 5.5 h) as the oxidant. In the latter reaction, the use of buffer (Na_2HPO_4)[25] was ineffective in preventing cleavage of the silyl ether. This resulted in isolation of the product as a mixture of C(1)-protected derivatives as well as a small amount of diol **36**. Manipulation of protecting groups provided acetate **37**, which was converted, in one reaction, to its respective heptyl ether in 72% yield.[26] Removal of the MEM group[27] with $TiCl_4$ proceeded at 0 °C to give alcohol **38**. Oxidation[20] and homologation of the α-chain using standard Wittig methodology[28] afforded the desired acid, **30**. Thus,

(21) The ratio of the two addition products was ≈3:2 as measured by integration of the 400-MHz ^1H NMR spectrum of the crude reaction product. The relative stereochemistry of iii and iv was assigned on the basis of relative chemical shifts as shown below.

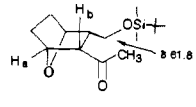
^1H (^{13}C) chemical shifts

isomer	H_a	H_b	CH_3
iii	4.56	2.35	1.56 (23.7)
iv	4.65	2.29	1.52 (25.6)

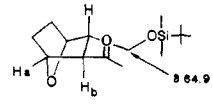


(22) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(23) The stereochemistry of the two side chains was clearly cis–exo as evidenced by the resonance multiplicities observed for H_a (δ 4.60, d, J = 5 Hz) and H_b (δ 2.76, d, J = 9 Hz). These two protons are not coupled to one another since the dihedral angle is ≈90°.



(24) The stereochemistry of the two side chains must be trans as evidenced by the resonance multiplicities observed for H_a (δ 4.72, t, J = 5 Hz) and H_b (δ 2.65, t, J = 4 Hz). In addition, the carbinol methylene showed the expected downfield shift in the ^{13}C NMR spectra due to release of steric compression present in the cis isomer.



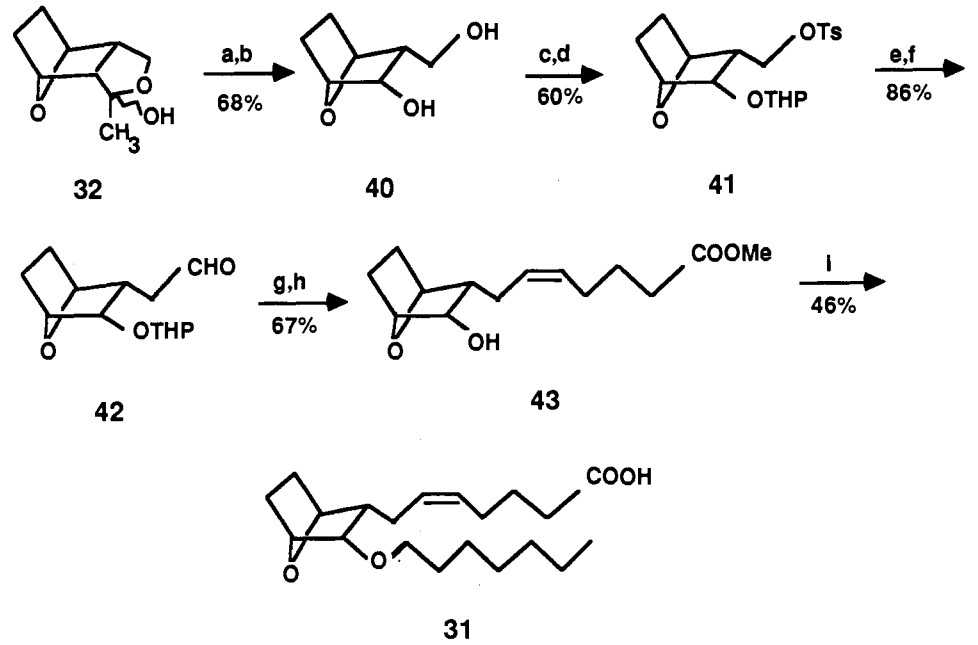
(25) (a) Emmons, W. D.; Lucas, G. B. *J. Am. Chem. Soc.* **1955**, *77*, 2287. (b) Smissman, E. B.; Muren, J. F.; Dahle, N. A. *J. Org. Chem.* **1964**, *29*, 3517.

(26) The yield in this reaction demonstrates the usefulness of this methodology for the alkylation of hindered alcohols and in our hands is superior to any other method.

(27) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

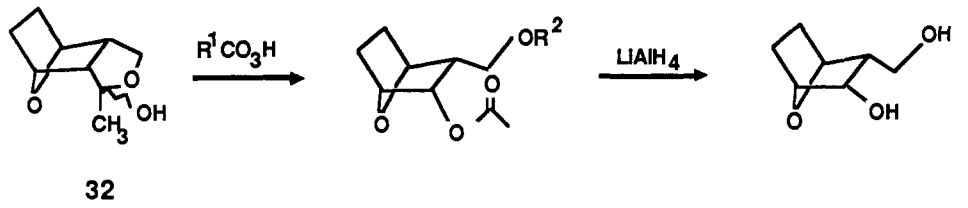
(28) The phosphonium salt is commercially available from several sources (Aldrich, Fluka).

Scheme VI[a]

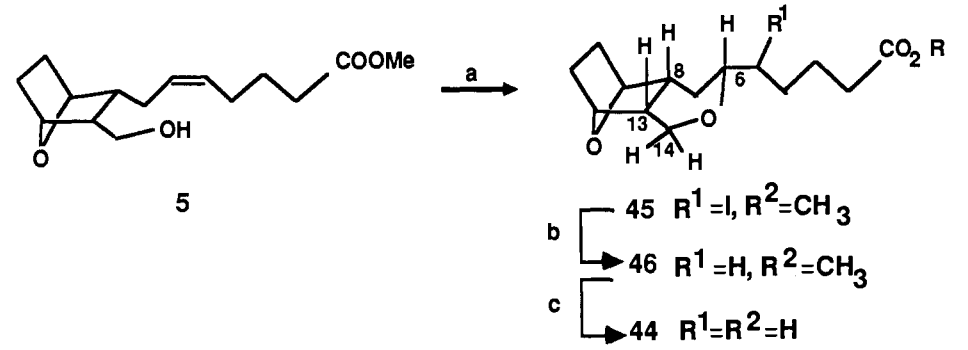


[a] (a) 5 equiv CF_3CO_3H, CH_2Cl_2, 0 → 23 °C, 60 h; (b) $LiAlH_4$, ether, Δ; (c) TsCl, pyridine, CH_2Cl_2, −20 → 5 °C, 4 days; (d) DHP, CH_2Cl_2, cat. *p*-TsOH; (e) NaCN, Me_2SO, 95 °C, 4 h; (f) Dibal, toluene, −20 → 15 °C, 3.5 h; (g) $Ph_3P^+(CH_2)_4CO_2HBr^-$, KO-*t*-Am, THF/toluene, room temperature, 15 h; then CH_2N_2; (h) crushed Amberlyst 15, MeOH, room temperature, 4 h; (i) KOH, xylene, heptyl mesylate, Δ, 30 min.

Scheme VII



Scheme VIII[a]



[a] (a) I_2, ether, aqueous $NaHCO_3$, 0 °C; (b) (n-Bu)$_3$SnH, toluene, Δ; (c) 1 N LiOH, H_2O, THF.

30 was prepared in 13 steps from lactone **29** in 5.4% overall yield.

As outlined in Scheme VI, hemiketal **32** was also used in the synthesis of cis ether **31**.

With the knowledge that the Baeyer–Villiger oxidation would likely produce a mixture of protected diol analogues, it was necessary to modify our scheme for the synthesis of **31**. We decided to attempt the Baeyer–Villiger oxidation on **32** itself; subsequent treatment of the crude product with $LiAlH_4$ would convert the expected mixture of acetates to a common intermediate, diol **40**. (See Scheme VII.)

After several attempts, we were gratified to observe that direct peracid oxidation of **32** with 5 equiv of CF_3CO_3H (0 → 23 °C, 60 h) followed by $LiAlH_4$ reduction of the crude oxidation product afforded diol **40** in 68% overall yield. Selective tosylation (−20 → 5 °C, 4 days) and subsequent protection of the secondary alcohol provided **41**. Displacement of the tosylate with NaCN proceeded efficiently to provide the requisite nitrile in 86% overall yield from **41**. Reduction with excess Dibal afforded aldehyde **42**.[29] Homologation of the α-chain followed by O-alkylation afforded the desired ether **31**.[30] The synthesis of

(29) A convenient nonaqueous workup was employed. The reaction mixture was treated sequentially with SiO_2, H_2O, and acetic acid. The silica gel is removed by filtration and the filtrate is concentrated to afford the desired aldehyde. This is a modification of a method developed by J. E. Heikes at these laboratories. For details see the Experimental Section.

31 was thus accomplished in only 10 steps from lactone 29 in 6.9% overall yield.

In order to further develop our structure–activity relationships, we were interested in preparing examples of conformationally restricted ethers. The synthesis of one such example is outlined in Scheme VIII. Iodoetherification[31] of 5 proceeded in excellent yield to afford iodide 45. Subsequent reduction with n-Bu_3SnH afforded ester 46, which on hydrolysis provided cyclic ether 44. Examination of ^1H and ^{13}C spectral data for 44 supported the assumption that the initial reaction proceeded stereospecifically to produce a single diastereomer at C(6).[32]

Pharmacology

In Vitro. All of the ethers were evaluated for their ability to inhibit both arachidonic acid and adenosine diphosphate induced platelet aggregation (AAIPA and ADPIPA, respectively) of human platelet-rich plasma (PRP). These results are summarized in Table II.

Initial evaluation of the four isomeric ethers 1 and 9–11 established that only the cis-exo isomer possessed significant activity. Identification of 1 as a potent inhibitor of AA-induced platelet aggregation (I_{50} = 0.5 μM) prompted further investigation into its mechanism of action. It was determined that 1 had no effect on platelet aggregation induced by either ADP or the stable TXA_2 mimics, 9,11-azo-PGH_2 or U-46619. Thus, 1 was neither a TXA_2 antagonist nor a common pathway inhibitor (i.e., 1 did not elevate cAMP levels in the platelet). Incubation of 1 with platelet lysate, however, caused a dose-dependent inhibition of AA conversion to both TXA_2 (I_{50} = 6.3 μM) and PGE_2 (I_{50} = 3.8 μM). In addition, 1 also inhibited the biosynthesis of PGE_2 (I_{50} = 6.3 μM) from AA in bovine seminal vesicle microsomes. These results are consistent with the proposition that 1 inhibits AA-induced platelet aggregation solely by blocking cyclooxygenase (CO).

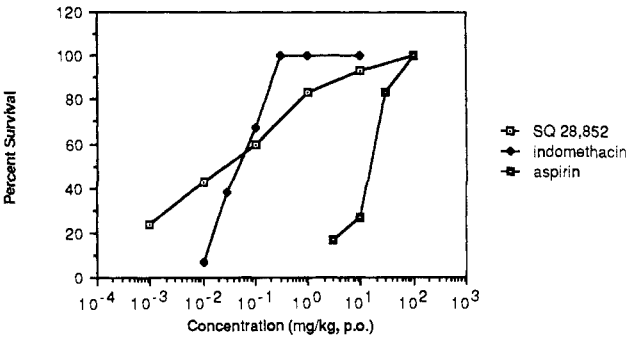
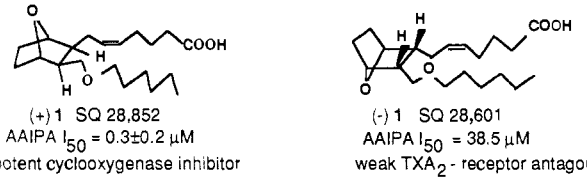


Figure 1. Effects of SQ 28,852, indomethacin, and aspirin on arachidonic acid induced lethality in mice. All points represent an n = 30 except SQ 28,852 (0.001 mg/kg, n = 33), IND (0.03 mg/kg, n = 40), IND (1.0 mg/kg, n = 20), and IND (10 mg/kg, n = 20).

Scheme IX



The modest activity of 9 and 11 may be due to TXA_2 synthetase inhibition since PGE_2 synthesis was stimulated at the concentrations of 9 and 11 required to inhibit TXB_2 production.[34]

Further examination of the activities listed in Table II revealed that this inhibition was exquisitely sensitive to the position of the ether oxygen and the nature of the ω side chain. Translocation of the oxygen atom from position 15 (1) to either 14 (31) or 16 (28) resulted in a 200-fold drop in activity. Cyclic ether 44, a conformationally restricted 15-oxa analogue, was completely without effect on PA (0% inhibition at 1000 μM) despite the modest activity of methyl ether 25. That the lack of activity was not a consequence of the loss of the 5,6-double bond was shown by the excellent activity of 5,6-dihydro-1, 47, (AAIPA; I_{50} = 0.2 μM).

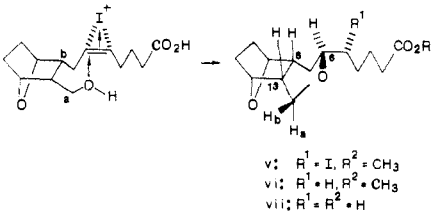
Modification of the ether side chain led, in general, to compounds of reduced potency. Replacement of the alkyl residue with either an aryl (15) or cycloalkyl (16) moiety led to dramatic decreases in activity. The introduction of steric bulk in the vicinity of oxygen-15 led to similar decreases in activity. In fact, the only alteration that could be tolerated was the introduction of unsaturation in the alkyl residue, i.e., 17–20 and 24.

Given the sensitivity of CO inhibition to the stereochemistry of the side chains, it was necessary to evaluate the individual enantiomers[35] of 1. As shown in Scheme IX, the active enantiomer possessed the 1R configuration. The modest activity of its antipode was determined to be the result of TXA_2 antagonism as opposed to CO inhibition. With ether (+)-1 established as our initial lead

(30) The yield of this alkylation reaction was considerably higher, but this number represents the amount of pure material obtained after a single column purification. Additional ether could have been obtained by rechromatography of the impure fractions.

(31) Whittaker, N. *Tetrahedron Lett.* **1977**, 2805.

(32) Due to the limited rotational freedom about bonds a and b, we anticipated that iodoetherification would provide, as the major product, ether v. Extensive NMR studies were performed on acid vii to confirm our hypothesis. The stereochemical consequence of this ring closure would be to put the α-chain in an equatorial position on the tetrahydropyran ring, itself constrained to be in a boatlike conformation. In addition to a series of homonuclear decoupling experiments, selective population transfer (SPT)[33] experiments were used to assign the proton resonances of interest. Consistent with the assigned structure, H(8) and H(13) appeared at similar chemical shifts with nearly identical multiplicities: H(8), δ 1.96, ddd, J = 6.6, 8.4, 12.5 Hz; H(13), δ 2.08, ddd, J = 6.6, 8.4, 11.4 Hz. Additional support for the stereochemical assignment came from NOE experiments. Simultaneous irradiation at both H(14b) and H(6), which unfortunately overlapped at 400 MHz, resulted in significant NOE's to H(14a), 3.4%; H(13), 3.4%; and H(8), 2.2%. Since both the protons on C(14) are more than 3.5 Å from H(8), the NOE observed for H(8) must derive from H(6). Taken together, these results are *only* consistent with H(8) and H(6) occupying axial positions on a boatlike tetrahydropyran ring.

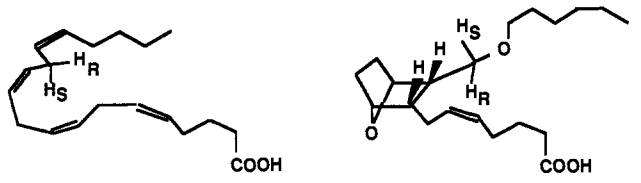


(33) Anderson, N. H.; Eaton, H. L.; Nguyen, K. T. *Tetrahedron Lett.* **1985**, 5259.

(34) In the lysed platelet preparation, both 9 and 11 at a concentration of 1 μM inhibited TXB_2 production (45% and 21%, respectively) while stimulating PGE_2 production (37% and 28%, respectively). This suggests that 9 and 11 may have weak inhibitory activity against TXA_2-synthetase.

(35) The absolute configuration of these ethers was determined by correlation with alcohol 5; see ref 7a, 15.

Scheme X



48 (+)1

compound, we were interested in evaluating this compound for in vivo activity.

In Vivo. Kohler et al.[36] and Myers et al.[37] have reported that AA-induced sudden death in the mouse is due primarily to TXA_2 generation by platelets. As such, this is a useful model for evaluating compounds that block the cyclooxygenase pathway (i.e., synthesis of TXA_2) or antagonize the effects of TXA_2 at the receptor level. Oral administration of (+)-1 or indomethacin (IND) at a dose of 10 mg/kg afforded virtually complete protection from AA-induced lethality. The complete dose–response curves for SQ 28,852 ((+)-1), IND, and aspirin (ASA) are depicted in Figure 1. Although the slopes of the IND and ASA curves appear to be similar, the slope of the SQ 28,852 curve is clearly more shallow. The reason for this difference is at present unknown.

Despite its outstanding potency, the duration of action of (+)-1 was considerably less than that of ASA or IND.[38] In analogy to the catabolism of the natural eicosanoids, it is likely that β-oxidation is a major pathway for the in vivo degradation of (+)-1, a result that would explain its reduced duration of action.[39]

Ether (+)-1 was also effective in inhibiting AA-induced changes in lung mechanics in the anesthetized guinea pig.[40] At doses of 0.01–1.0 mg/kg iv, (+)-1 inhibited AA-induced bronchoconstriction (BC) and systemic hypertension for at least 60 min. Ether (+)-1 was clearly more potent than indomethacin in this model (16–45 times as potent as IND at 3 and 60 min after treatment). Consistent with its mechanism of action, (+)-1 did not significantly inhibit bronchoconstriction induced by histamine or 9,11-azo-PGH_2.

Discussion

A number of authors have attempted to construct a working model for the active site of fatty acid cyclooxygenase with use of the structural similarities (pattern recognition) of known inhibitors as well as conformational energy minimizations of the natural substrate, arachidonic acid. One of these proposals, put forth by Gund and Shen[41] in 1977, had the advantage that it could "explain" the stereochemical outcome of the oxygenase reaction. Evaluation of CPK models of both (+)-1 and the bioactive conformation of arachidonic acid 48 as proposed by Gund and Shen reveals striking similarities (see Scheme X). In particular, it is interesting that H_R of 1 can occupy the same region of space as H_S of arachidonic acid 48. In the transformation of arachidonic acid to PGH_2, it is of course H_S that is abstracted by the cyclooxygenase enzyme. Whether this structural coincidence has any connection to the mode of action of ethers such as 1 remains to be determined.

Regardless of the exact mechanism of action of ethers such as (+)-1, SQ 28,852 and its analogues are the first cyclooxygenase inhibitors[42] that bear an obvious resemblance to the product (and/or the transition state) of the cyclooxygenase reaction and possess potencies 2–50 times that of indomethacin. Further biological evaluation of these novel cyclooxygenase inhibitors and synthesis of related analogues are in progress. In addition, experiments are planned to elucidate the exact mechanism of inhibition.

Experimental Section

^1H NMR spectra were measured at 270 MHz on a JEOL FX-270 and at 400 MHz on a JEOL GX-400 instrument. ^{13}C NMR spectra were measured at 15 MHz on a JEOL FX-60 and at 67.5 MHz on a JEOL FX-270 instrument. 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 use of 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 structures 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 atmospheres of argon. 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 et al.[43] with use of J. T. Baker "Flash" grade silica gel.

General Procedure for the Synthesis of *O*-Ethers. The synthesis of *O*-ethers followed the procedure described below for 1 except for the variation in conditions as noted in Table I.

[1*R*-[1α,2β(*Z*),3β,4α]]-7-[3-[(Hexyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (1). A mixture of powdered KOH (0.93 g) in 25 mL of dry xylene was heated to

(36) Kohler, G.; Wooding, N.; Ellenbogen, L. *Thromb. Res.* **1976**, *9*, 67.

(37) Myers, A.; Penhos, J.; Ramey, E.; Ramwell, P. *J. Pharmacol. Exp. Ther.* **1983**, *224*, 369.

(38) Although (+)-1 and IND possessed similar duration of action when the mice were dosed at 300 mg/kg po, dosing at 10 mg/kg po revealed a significant difference between these two compounds. The times after dosing at which (+)-1 and IND still afforded a 50% survival rate were ca. 3 h and 52 h, respectively.

(39) Standard modification of the α-chain in an attempt to block β-oxidation has led to the discovery of a more potent analogue of (+)-1. This compound has duration of action that equals or exceeds that of IND. The detailed pharmacology of this compound will be reported in due course.

(40) (a) Amdur, M. O.; Mead, J. *Am. J. Physiol.* **1958**, *192*, 364. Giles, R. E.; Williams, J. C.; Finkel, M. P. *J. Pharmacol. Exp. Ther.* **1973**, *186*, 472. (c) Steinbacher, T. C.; Ogletree, M. L. *Pharmacologist* **1985**, *27*, 214.

(41) (a) Gund, P.; Shen, T. Y. *J. Med. Chem.* **1977**, *20*, 1146. (b) Appleton, R. A.; Brown, K. *Prostaglandins* **1979**, *18*, 29. (c) Salvetti, F.; Buttononi, A.; Ceserani, R.; Tosi, C. *Eur. J. Med. Chem.-Chim. Ther.* **1981**, *16*, 81. For a more complete list of references, see the following: Gund, P.; Jensen, N. P. In *Quantitative Structure–Activity Relationship of Drugs*; Topliss, J. G., Ed.; Academic: New York, 1983; p 285.

(42) Several publications have appeared over the years in which prostanoid-type structures were purported to be cyclooxygenase inhibitors. In general, these derivatives were not very potent. (a) McDonald-Gibson, R. G.; Flack, J. D.; Ramwell, P. W. *Biochem. J.* **1973**, *132*, 117. (b) Fried, J.; Lin, C.; Mehra, M.; Kao, W.; Dalven, P. *Ann. N.Y. Acad. Sci.* **1971**, *180*, 38. (c) Ohki, S.; Ogino, N.; Yamamoto, S.; Hayaiski, O.; Yamamoto, H.; Miyake, H.; Hayashi, M. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *79*, 144. (d) Wlodawer, P.; Samuelsson, B.; Albonico, S. M.; Corey, E. J. *J. Am. Chem. Soc.* **1971**, *93*, 2815. (e) Leeney, T. J.; Marsham, P. R.; Ritchie, G. A.; Senior, M. W. *Prostaglandins* **1976**, *11*, 953. (f) Ghali, N. I.; Venton, D. L.; Hung, S. C.; LeBreton, G. C. *J. Med. Chem.* **1983**, *26*, 1056.

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

reflux under an argon atmosphere, and 12 mL of xylene was removed by distillation. To this mixture was added a solution of 500 mg (1.86 mmol) of alcohol methyl ester **5** in 16 mL of dry xylene. The volume of the reaction mixture was reduced 12 mL by distillative removal of xylene. To the reaction mixture was then added a solution of 1.68 g (9.30 mmol) of hexyl mesylate in 16 mL of dry xylene. This mixture was refluxed for 1.25 h. The cooled reaction mixture was diluted with 100 mL of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 extracts were washed with brine (1 × 200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification was effected by flash chromatography on 46 g of silica gel 60 with 5:1 hexane/ether as eluant. This gave 0.62 g of the hexyl ester of **1** (79%) as a colorless oil. TLC: silica gel, 2% CH_3OH/CH_2Cl_2, R_f 0.80, iodine.

To a stirred solution of 517 mg (1.125 mmol) of the above ester, 55 mL of distilled THF, 4.40 mL of CH_3OH, and 7.20 mL of H_2O under argon was added 13.50 mL of 1 N aqueous lithium hydroxide solution. This mixture was purged with argon vigorously for 30 min and stirred at room temperature for 15 h. The reaction mixture was acidified to pH 3 by the addition of 1 N aqueous HCl solution. The resulting solution was poured into 120 mL of saturated NaCl solution and was saturated with solid NaCl. The aqueous layer was extracted with EtOAc (4 × 150 mL). The combined EtOAc extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. This was chromatographed on 40 g of silica gel 60 with 4% CH_3OH in CH_2Cl_2 as eluant to give the desired product contaminated with a small amount of hexyl alcohol. The product was pumped under high vacuum for ≈60 h at room temperature to give 350 mg (85%) of pure acid **1**. TLC: silica gel, 4% CH_3OH/CH_2Cl_2, R_f 0.42, iodine. $[\alpha]_D$: 1.1 ± 0.5° (CH_3OH). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.36 (m, H_5, H_6), 4.41 (br d, J = 4 Hz, 1 H), 4.19 (br d, J = 4 Hz, 1 H), 3.45–3.26 (m, 4 H), 2.33 (t, J = 7.6 Hz, 2 H), 2.1–1.97 (m, 4 H), 1.82 (dd, J = 8.4, 14.8 Hz, 1 H), 0.86 (t, J = 7 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.8, 130.1, 129.4, 80.0, 79.3, 71.2, 69.8, 46.8, 46.4, 33.4, 31.6, 29.6, 29.5, 29.4, 26.6, 25.8, 25.7, 24.5, 22.5, 13.9. Anal. ($C_{20}H_{34}O_4$) C, H.

[1β,2α(Z),3β,4β]-7-[3-[(Hexyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (9). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.48–5.30 (m, 2 H), 4.53 (t, J = 5 Hz, 1 H), 4.13 (d, J = 5 Hz, 1 H), 3.62–3.46 (dd, J = 8, 11 Hz, 1 H), 3.45–3.31 (m, 2 H), 3.30–3.21 (t, J = 10 Hz, 1 H), 2.36 (t, J = 7 Hz, 2 H), 0.90 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.7, 129.9, 128.7, 80.6, 79.1, 71.6, 71.2, 49.1, 47.8, 33.4, 32.6, 31.7, 29.9, 29.5, 26.6, 25.8, 24.6, 23.8, 22.6, 13.9. Anal. ($C_{20}H_{34}O_4$) C, H.

[1α,2α(Z),3α,4α]-7-[3-[(Hexyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (10). ^1H NMR ($CDCl_3$, 270 MHz): δ, 5.32 (m, 2 H), 4.54 (t, J = 5 Hz, 1 H), 4.43 (t, J = 5 Hz, 1 H), 3.5–3.2 (m, 4 H), 2.35 (t, J = 7.4 Hz, 2 H), 0.88 (t, J = 6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.3, 129.2, 129.0, 80.2, 79.9, 71.4, 68.8, 42.4, 41.8, 33.3, 31.6, 29.6, 26.7, 25.9, 24.5, 24.4, 23.5, 22.6, 14.0. Anal. ($C_{20}H_{34}O_4$) C, H.

[1β,2β(Z),3α,4β]-7-[3-[(Hexyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (11). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.43–5.31 (m, 2 H), 4.41–4.32 (m, 2 H), 3.43–3.36 (m, 2 H), 3.24–3.13 (m, 2 H), 2.38 (t, J = 7 Hz, 2 H), 0.88 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.8, 129.2, 128.8, 79.2, 73.4, 71.2, 50.4, 46.08 33.3, 31.6, 29.7, 29.5, 28.8, 26.6, 25.8, 24.5, 23.8, 22.6, 13.9. Anal. ($C_{20}H_{34}O_4$) C, H.

[1β,2α(5Z),3α,4β]-7-[3-[(Octyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (12). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.44–5.33 (m, 2 H), 4.40 (d, J = 5 Hz, 1 H), 4.19 (d, J = 5 Hz, 1 H), 3.47–3.28 (m, 4 H), 2.35 (t, J = 7 Hz, 2 H), 0.88 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.7, 130.2, 129.5, 80.1, 79.4, 71.3, 69.9, 46.9, 46.4, 33.4, 31.8, 29.7, 29.5, 29.5, 29.3, 26.7, 26.2, 25.8, 24.6, 22.6, 14.0. Anal. ($C_{22}H_{38}O_4$) C, H.

[1β,2α(Z),3α,4β]-7-[3-[(3-Phenylpropoxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (15). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.23 (m, 3 H), 7.29 (d, J = 10 Hz, 2 H), 5.42–5.35 (m, 2 H), 4.43 (d, J = 5 Hz, 1 H), 4.21 (d, J = 5 Hz, 1 H), 3.49–3.30 (m, 4 H), 2.70 (t, J = 7 Hz, 2 H), 2.35 (t, J = 7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ, 178.7, 141.9, 130.1, 129.5, 128.4, 128.4, 128.4, 128.4, 125.7, 80.1, 79.3, 70.2, 69.9, 46.8, 46.3, 33.4, 32.3, 31.2, 29.5, 29.5, 26.6, 25.7, 24.5. Anal. ($C_{23}H_{32}O_4$) C, H.

[1β,2α(Z),3α,4β]-7-[3-[(Cyclohexylmethoxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (16). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.50–5.30 (m, 2 H), 4.40 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H), 3.48–3.09 (m, 4 H), 2.35 (t, J = 7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.8, 130.2, 129.5, 80.1, 79.4, 46.9, 46.4, 37.9, 33.4, 30.2, 30.2, 29.5, 29.5, 26.7, 26.7, 25.9, 25.9, 24.6. Anal. ($C_{21}H_{34}O_4$) C, H.

[1β,2α(Z),3α(E),4β]-7-[3-[(2-Hexenyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (17). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.75–5.49 (m, 2 H), 5.45–5.33 (m, 2 H), 4.42 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H), 3.40 (d, J = 8 Hz, 2 H), 3.43–3.29 (m, 2 H), 2.38 (t, J = 7 Hz, 2 H), 0.91 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.8, 134.6, 130.1, 129.5, 126.4, 80.1, 79.4, 71.9, 69.1, 46.9, 46.4, 34.3, 33.4, 29.5, 29.5, 26.7, 25.8, 24.5, 22.2, 13.6. Anal. ($C_{20}H3_2O_4$) C, H.

[1β,2α(Z),3α(Z),4β]-7-[3-[(2-Hexenyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (18). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.63–5.50 (m, 2 H), 5.43–5.34 (m, 2 H), 4.41 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H), 4.02 (d, J = 7 Hz, 2 H), 3.44–3.29 (m, 2 H), 2.38 (t, J = 7 Hz, 2 H), 0.91 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.8, 133.5, 130.1, 129.5, 126.2, 117.5, 80.1, 79.4, 69.3, 66.6, 46.9, 46.4, 33.4, 29.5, 29.5, 26.7, 25.8, 24.5, 22.6, 13.7. Anal. ($C_{20}H_{32}O_4$) C, H.

[1α,2β(Z),3β,4α]-7-[3-[(2-Hexynyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (19). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.37 (m, 2 H), 4.42 (br d, J = 4 Hz, 1 H), 4.19 (br d, J = 4 Hz, 1 H), 4.10 (br d, J = 2 Hz, 2 H), 3.49 (dd, J = 5.8, 9 Hz, 1 H), 3.38 (t, J = 9.2 Hz, 1 H), 2.34 (t, J = 7.4 Hz), 0.96 (t, J = 7.4 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 178.9, 130.1, 129.5, 86.8, 80.1, 79.4, 76.1, 69.0, 58.8, 46.7, 46.4, 33.4, 29.5, 29.4, 26.7, 25.8, 24.5, 22.0, 20.8, 13.4. Anal. ($C_{20}H_{30}O_4$) C, H.

[1β,2α(Z),3α(Z),4β]-7-[3-[(3-Hexenyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (20). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.50–5.26 (m, 4 H, CH=CH), 4.41 (br s, 1 H), 4.20 (br s, 1 H), 3.48–3.23 (m, 4 H), 0.93 (t, J = Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.9, 133.6, 130.1, 129.5, 124.8, 80.1, 79.3, 70.8, 69.8, 46.7, 46.3, 33.4, 29.4, 29.4, 27.7, 26.6, 25.6, 24.5, 20.6, 14.2. Anal. ($C_{20}H_{32}O_4$) C, H.

[1α,2β(Z),3β,4α]-7-[3-[[(2-Methylhexyl)oxy]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (21). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.38 (m, 2 H), 4.41 (br s, 1 H), 4.21 (br s, 1 H), 3.3–3.1 (m, 4 H), 2.34 (t, J = 7 Hz, 2 H), 0.90 (m, 6 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.1, 130.3, 129.6, 80.2, 79.5, 76.9, 70.1, 47.0, 46.6, 33.5, 29.7, 29.6, 29.3, 26.8, 25.9, 24.7, 23.1, 17.3, 14.2. Anal. ($C_{21}H_{36}O_4$) C, H.

[1α,2β(Z),3β,4α]-7-[3-[(2-Heptyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid, Fast-Moving Isomer (22a). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.43–5.50 (m, 2 H), 4.43 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H), 3.60 (dd, J = 8, 10 Hz, 1 H), 3.40 (m, 1 H), 3.21 (t, J = 11 Hz, 1 H), 2.32 (t, J = 7 Hz, 2 H), 1.10 (d, J = 8 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.8, 130.2, 129.4, 80.1, 79.5, 75.9, 67.5, 47.1, 46.4, 36.7, 33.4, 31.9, 29.5, 29.5, 26.7, 25.7, 25.3, 24.6, 22.6, 19.7, 14.0. Anal. ($C_{21}H_{36}O_4$) C, H.

[1α,2β(Z),3β,4α]-7-[3-[(2-Heptyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid, Slow-Moving Isomer (22b). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.41–5.30 (m, 2 H), 4.40 (br s, 1 H), 4.80 (br s, 1 H), 3.75 (m, 1 H), 3.34 (m, 3 H), 2.50 (t, J = 7 Hz, 2 H), 1.10 (d, J = 8 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.6, 130.2, 129.4, 80.1, 79.6, 75.7, 67.4, 47.0, 46.4, 36.6, 33.4, 31.9, 29.5, 29.5, 26.7, 25.8, 25.3, 24.6, 22.6, 19.6, 14.0. Anal. ($C_{21}H_{36}O_4$) C, H.

[1β,2α(Z),3α,4β]-7-[3-[1-(Hexyloxy)ethyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid, Fast-Moving Isomer (23). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.50–5.30 (m, 2 H), 4.71 (d, J = 5 Hz, 1 H), 4.23 (d, J = 5 Hz, 1 H), 3.74 (m, 2 H), 3.55 (dt, J = 8, 4 Hz, 1 H), 3.40 (m, 2 H), 2.35 (t, J = 7 Hz, 2 H), 1.15 (d, J = 8 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.9, 130.1, 129.7, 79.7, 79.1, 73.2, 68.9, 53.8, 46.9, 33.4, 31.7, 30.8, 30.0, 28.4, 26.7, 26.2, 25.9, 24.5, 22.6, 20.8, 14.0. Anal. ($C_{21}H_{36}O_4$) C, H.

[1β,2α(Z),3α,4β]-7-[3-[(2-Propenyloxy)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (24). To a stirred solution of 310 mg (1.16 mmol) of ester alcohol **5** in 1.34 mL of distilled THF were added, in order, 1.34 mL (15.5 mmol) of allyl bromide, 107 mg (0.31 mmol) of tetrabutylammonium hydrogen sulfate,

and 1.34 mL of 50% aqueous sodium hydroxide solution. This mixture was stirred at room temperature in darkness for 23 h. The reaction mixture was poured into 30 mL of saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification was effected by flash chromatography on 35 g of silica gel, 1:1 hexane/ether, R_f 0.4, iodine. To a stirred solution of 220 mg (0.71 mmol) of this ester, a small amount of hydroquinone, 36 mL of distilled THF, and 6.0 mL of H_2O under argon was added 7.0 mL of 1 N aqueous lithium hydroxide solution. This mixture was purged with argon vigorously for 30 min and stirred at room temperatue for 5.5 h. The reaction mixture was acidified to pH 3 by the addition of 1 N aqueous HCl solution. The resulting solution was poured into 80 mL of saturated NaCl solution and was saturated with solid NaCl. The aqueous layer was extracted with EtOAc (4 × 125 mL). The combined EtOAc extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. This was chromatographed on 30 g of silica gel 60 with 4% CH_3OH/CH_2Cl_2 as eluant to give 190 mg (90%) of acid **24**. TLC: silica gel, 1:1 hexane/ether, R_f 0.15, iodine. ^1H NMR ($CDCl_3$, 270 MHz): δ 6.00–5.82 (m, 1 H), 5.96–5.10 (m, 3 H), 4.43 (br s, 1 H), 4.19 (br s, 1 H), 3.94 (d, J = 8 Hz, 2 H), 3.43–3.39 (m, 2 H), 2.33 (t, J = 7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.9, 134.7, 130.0, 129.5, 117.0, 80.1, 79.3, 72.0, 69.3, 46.7, 46.3, 33.4, 29.4, 26.6, 25.7, 24.5. Anal. ($C_{17}H_{26}O_4$) C, H.

[1*R*-[1α,2β(*Z*),3β,4α]]-7-[3-(Methoxymethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (25). $[\alpha]_D$: +10.4° (*c* 2.21, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.37 (m, 2 H), 4.40 (d, J = 4 Hz, 1 H), 4.19 (d, J = 4 Hz, 1 H), 3.32 (s, 3 H), 2.33 (t, J = 7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.3, 129.8, 129.5, 79.9, 79.1, 71.7, 58.5, 46.5, 46.2, 33.2, 29.3, 26.5, 25.5, 24.4. Anal. ($C_{15}H_{24}O_4$) C, H.

Methyl [1β,2α(*Z*),3α,4β]-7-[3-(Formylmethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (49). To a stirred solution of 3.83 g (11.2 mmol) of $Ph_3P^+CH_2OCH_3Cl^-$ in 70 mL of dry toluene was added under argon at 0 °C 5.24 mL (8.39 mmol) of 1.60 M KO-*tert*-Am over 15 min. This mixture was stirred at 0 °C for 35 min, at which time a solution of 1.49 g (5.60 mmol) of aldehyde (prepared by PCC oxidation of **5**[15]) in 18 mL of dry toluene was added dropwise over 40 min. The reaction mixture was stirred at 0 °C for another 12 min and quenched by dropwise addition of a solution of 1.36 g (23.8 mmol) of glacial acetic acid in 6.0 mL of ether. The quenched reaction mixture was immediately poured into 70 mL of saturated NH_4Cl solution and extracted with ether (4 × 50 mL). The combined ether extracts were washed with brine (1 × 100 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in vacuo, and the residue (purple) was triturated in ether. the decanted ether solution was concentrated in vacuo and chromatographed on 126 g of silica gel 60 with 1% CH_3OH/CH_2Cl_2 as eluant to give 1.26 g of vinyl ether **26** (80%) as an oil. TLC: silica gel, 1% CH_3OH/CH_2Cl_2, R_f 0.24, I_2.

To a stirred solution of 1.26 g of **26** (4.50 mmol) in 25 mL of distilled THF at room temperature was added 100 mL of 20% aqueous TFA solution. The resulting two-phase reaction mixture was stirred vigorously for 4 h and then neutralized to pH 7 by the addition of solid $NaHCO_3$. The reaction mixture was concentrated in vacuo to remove all the THF and then diluted with 80 mL of water. The resulting solution was extracted with CH_2Cl_2 (4 × 100 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 0.72 g (57%) of aldehyde **49**. This was used immediately in the next step without purification. TLC: silica gel, 4% CH_3OH/CH_2Cl_2, R_f 0.6, I_2. ^1H NMR ($CDCl_3$, 270 MHz): δ 9.83 (s, 1 H), 5.38 (m, 2 H), 4.16 (m, 2 H), 3.67 (s, 3 H), 2.56 (m, 2 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 201.9, 173.8, 130.0, 129.4, 81.5, 80.0, 51.4, 46.4, 44.1, 40.4, 33.4, 29.4, 29.4, 27.3, 26.8, 24.7.

Methyl [1β,2α(*Z*),3α,4β]-7-[3-(2-Hydroxyethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (27). To a stirred solution of 0.72 g (2.57 mmol) of aldehyde **49** and 1.03 g of $CeCl_3 \cdot 7.6H_2O$ in 42 mL of methanol at 0 °C under argon was added 102 mg of$NaBH_4$. This mixture was stirred for 30 min at 0 °C and then poured into 180 mL of saturated NH_4Cl solution. The resulting solution was extracted with EtOAc (5 × 100 mL). The combined EtOAc extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was chromatographed on 40 g of silica gel 60 with 3% CH_3OH/CH_2Cl_2 as eluant to give 0.50 g (69%) of alcohol **27** as an oil. TLC: silica gel, 4% CH_3OH/CH_2Cl_2, R_f 0.50, PMA. ^1H NMR ($CDCl_3$, 270 MHz): δ 5.39 (m, 2 H), 4.28 (br d, J = 5 Hz, 1 H), 4.18 (br d, J = 5 Hz, 1 H), 3.67 (s in m, 5 H), 2.38,(t, J = 8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 174.0, 130.1, 129.5, 80.4, 80.0, 62.3, 51.4, 47.2, 43.4, 33.4, 33.3, 31.7, 29.6, 29.5, 26.7, 26.7, 24.7.

[1β,2α(*Z*),3α,4β]-7-[3-[2-(Pentyloxy)ethyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid (28). ^1H NMR ($CDCl_3$, 270 MHz): δ 5.48–5.32 (m, 2 H), 4.29 (d, J = 5 Hz, 1 H), 4.20 (d, J = 5 Hz, 1 H), 3.53–3.33 (m, 4 H), 2.37 (t, J = 7 Hz, 2 H), 0.90 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 178.5, 129.5, 130.2, 80.4, 79.9, 71.0, 70.2, 47.2, 43.7, 33.4, 29.7, 29.4, 29.3, 28.6, 28.6, 28.3, 26.6, 24.5, 22.4, 13.9. Anal. ($C_{20}H_{34}O_4$) C, H.

[1β,2α,3α,4β]-3-Acetyl-2-(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane, Hemiketal (32). To a stirred solution of 5.0 g (32.5 mmol) of (3aα, 4α, 7α, 7aα)-hexahydro-4,7-epoxyisobenzofuran-1(3*H*)-one (**29**) (prepared as described in U.S. Patent 4143054; see also ref 15) in 360 mL of dry THF under argon at −78 °C was added dropwise 22 mL of 1.5 M methyllithium solution over a period of 15 min. The reaction mixture was stirred at −78 °C for 35 min and then quenched with 8 mL of acetone. The reaction mixture was concentrated in vacuo to approximately 100 mL and diluted with 300 mL of EtOAc and 300 mL of saturated NH_4Cl solution. The aqueous layer was saturated with NaCl and extracted with EtOAc (2 × 300 mL). The combined EtOAc extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 3.82 g (72%) of hemiketal **32**. TLC: silica gel, 4% CH_3OH/CH_2Cl_2, R_f 0.54, $Ce(SO_4)_2$. Major diastereomer; mp 118–122 °C. ^1H NMR ($CDCl_3$, 270 MHz): δ 4.50 (d, J = 6 Hz, 1 H), 4.35 (d, J = 6 Hz, 1 H), 4.02 (dd, J = 9, 7 Hz, 1 H), 3.76 (dd, J = 9, 2 Hz, 1 H), 2.48 (m, 2 H), 2.28 (d, J = 8 Hz, 1 H), 1.52 (s, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 106.0, 81.9, 77.2, 71.2, 57.8, 48.3, 28.7, 28.4, 23.8. Anal. ($C_9H_{14}O_3$) C, H.

[1β,2α,3α,4β]-3-Acetyl-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-7-oxabicyclo[2.2.1]heptane (50). To a stirred solution of 15 g (88.2 mmol) of hemiketal **32** in 267 mL of dry DMF under argon was added 35.5 g (521 mmol) of imidazole. To this mixture was then added 31.4 g (208 mmol) of *tert*-butyldimethylsilyl chloride. The reaction mixture was stirred at room temperature for 21 h. The reaction mixture was partitioned between 1.4 L of ether and 1.4 L of H_2O. The aqueous layer was extracted with ether (2 × 1.4 L). The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The resultant oil was chromatographed on 180 g of silica gel 60 with 2:1 hexane/ether as eluant to give 25.0 g (99%) of silyl ether **50**. TLC: silica gel, 1:1 hexane/ether, R_f 0.56, $Ce(SO_4)_2$. ^1H NMR ($CDCl_3$, 270 MHz): δ 4.60 (d, J = 6 Hz, 1 H), 4.40 (d, J = 6 Hz, 1 H), 3.38 (m, 2 H), 2.76 (d, J = 9 Hz, 1 H), 2.33 (q, J = 8 Hz, 1 H), 2.15 (s, 3 H), 0.83 (s, 9 H), 0.02 (s, 6 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 207.9, 78.2, 77.5, 61.8, 57.5, 51.6, 31.2, 29.7, 28.8, 25.8, 18.2, −5.5.

[1β,2α,3β,4β]-3-Acetyl-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-7-oxabicyclo[2.2.1]heptane (33). To a stirred solution of 25.0 g (87.8 mmol) of cis ketone **50** in 1.12 L of CH_3OH was added 326 mg (8.15 mmol) of sodium methoxide under argon. The reaction mixture was stirred at room temperature for 22 h. The reaction mixture was concentrated in vacuo to ca. 100 mL and diluted with 700 mL of EtOAc. The resulting solution was washed with saturated $NaHCO_3$ solution (2 × 100 mL) and brine (1 × 150 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to give 24.5 g (98%) of trans ketone **33**. TLC: silica gel, 2% CH_3OH in CH_2Cl_2, R_f 0.78, $Ce(SO_4)_2$. In subsequent runs, the conversion of lactone **39** to ketone **33** was carried out without purification of any of the intermediates in comparable yield. ^1H NMR ($CDCl_3$, 270 MHz): δ 4.72 (t, J = 6 Hz, 1 H), 4.35 (d, J = 6 Hz, 1 H), 3.46 (t, J = 9 Hz, 1 H), 3.25 (dd, J = 10, 7 Hz, 1 H), 2.65 (t, J = 4 Hz, 1 H), 2.35 (m, 1 H), 2.11 (s, 3 H), 0.85 (s, 9 H), 0.00 (s, 6 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 205.9, 79.5, 77.5, 64.9, 60.2, 47.3, 30.5, 29.1, 25.8, 18.2, −5.4.

[1β,2α,3β,4β]-3-Acetoxy-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-7-oxabicyclo[2.2.1]heptane (34) and [1β,2α,3β,4β]-3-Acetoxy-2-[(trifluoroacetoxy)methyl]-7-oxabicyclo[2.2.1]heptane (35). To a stirred slurry of 3.34 mL (138 mmol) of 90% H_2O_2 in 79 mL of dry CH_2Cl_2 at 0 °C was added dropwise 20.9 mL (149 mmol) of distilled trifluoroacetic anhydride

over 20 min. This solution was stirred at 0 °C for 55 min. To a stirred slurry of 10.0 g (35.5 mmol) of ketone **33** and 37.1 g of dry Na_2HPO_4 in 99 mL of dry CH_2Cl_2 at 0 °C was added the above peracid solution dropwise over 80 min. The resulting mixture was stirred at 0 °C for 5.5 h, and then the solid ($NaHPO_4$) was removed by filtration. The filter cake was washed with CH_2Cl_2 (5 × 120 mL). The filtrate was washed with 10% Na_2CO_3 solution (2 × 100 mL) and brine (1 × 200 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. This was chromatographed on 182 g of silica gel 60 with 4:1 hexane/ether as eluant to give 2.96 g (28%) of **34**, 2.46 g (25%) of **35**, and 3.34 g of a mixture that contained the corresponding diol (**36**). TLC: silica, 1:1 hexane/ether, R_f 0.70 (**34**), 0.60 (**35**), $Ce(SO_4)_2$. **34**: ^1H NMR ($CDCl_3$, 270 MHz) δ 4.58 (t, J = 5 Hz, 1 H), 4.38 (m, 1 H), 4.33 (d, J = 5 Hz, 1 H), 3.59 (dd, J = 8, 10 Hz, 1 H), 3.48 (t, J = 10 Hz, 1 H), 2.00 (s, 3 H), 0.84 (s, 9 H), 0.01 (s, 3 H); ^{13}C NMR ($CDCl_3$, 15 MHz) δ 170.7, 78.9, 77.0, 76.2, 63.2, 52.3, 29.1, 25.6, 25.2, 22.8, 20.8, 17.9, -3.6. **35**: ^1H NMR ($CDCl_3$, 270 MHz) δ 4.72 (t, J = 5 Hz, 1 H), 4.53 (m, 2 H), 4.40 (d, J = 5 Hz, 1 H), 4.29 (t, J = 9 Hz, 1 H), 2.08 (s, 3 H). Anal. ($C_{11}H_{13}F_3O_5$) C, H, F. **36**: ^1H NMR ($CDCl_3$, 270 MHz) δ 4.45 (t, J = 5 Hz, 1 H), 4.27 (d, J = 5 Hz, 1 H), 3.93 (m, 1 H), 3.65 (dd, J = 7, 10 Hz, 1 H), 3.52 (dd, J = 7, 10 Hz, 1 H), 2.20 (m, 1 H).

[1β,2α,3β,4β]-3-Acetoxy-2-(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane (51). To a stirred solution of 8.83 g (31.3 mmol) of **35** in 100 mL of freshly distilled THF was added 20 mL of H_2O and 10 mL of saturated $NaHCO_3$ solution. The reaction mixture was stirred at room temperature for 6.3 h, at which time an additional 10 mL of saturated $NaHCO_3$ solution was added. The mixture was stirred for 45 min, and another 10 mL of saturated $NaHCO_3$ solution was added. The mixture was stirred for an additional 25 min and poured into 200 mL of brine. The aqueous layer was saturated with NaCl and extracted with ether (4 × 250 mL). The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 5.41 g of crude alcohol. Purification was effected by flash chromatography on 180 g of silica gel 60 with 3% CH_3OH/CH_2Cl_2 as eluant to give 5.22 g (90%) of alcohol **51** as an oil. TLC: silica gel, 1:1 hexane/ether, R_f 0.24, $Ce(SO_4)_2$. ^1H NMR (270 MHz, $CDCl_3$): δ 4.63 (m, 2 H), 4.37 (d, J = 5 Hz, 1 H), 3.66 (d, J = 7 Hz, 2 H), 2.08 (s, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 171.3, 79.4, 77.1, 76.5, 63.5, 52.3, 29.0, 22.7, 20.8.

[1β,2α,3β,4β]-3-Acetoxy-2-[[(methoxyethoxy)methoxy]methyl]-7-oxabicyclo[2.2.1]heptane (37). To a stirred solution of 3.02 g (16.2 mmol) of alcohol **51** in 25 mL of dry CH_2Cl_2 under argon was added 5.66 mL (32.5 mmol) of diisopropylethylamine, followed by dropwise addition of 2.78 mL (24.4 mmol) of 2-methoxyethoxymethyl chloride. The reaction mixture was stirred at room temperatue for 21 h and then diluted with 300 mL of $CHCl_3$. The organic layer was washed with 1 N HCl solution (2 × 50 mL) and then saturated $NaHCO_3$ solution (1 × 100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification was effected by flash chromatography on 150 g of silica gel 60 with 1% CH_3OH in CH_2Cl_2 as eluant to give 3.78 g (85%) of **37** as an oil. TLC: silica gel, 2% CH_3OH/CH_2Cl_2, R_f 0.25, $Ce(SO_4)_2$. ^1H NMR ($CDCl_3$, 270 MHz): δ 4.70 (s, 2 H), 4.64 (t, J = 6 Hz, 1 H), 4.46 (br t, J = 5 Hz, 1 H), 4.38 (d, J = 6 Hz, 1 H), 3.7–3.5 (m, 6 H), 3.37 (s, 3 H), 2.06 (s, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 170.6, 95.6, 79.2, 77.0, 76.5, 71.7, 68.7, 66.9, 58.9, 49.8, 29.1, 22.7, 20.8.

[1β,2α,3β,4β]-3-(Heptyloxy)-2-[[(methoxyethoxy)methoxy]methyl]-7-oxabicyclo[2.2.1]heptane (52). A mixture of 6.33 g (113 mmol) of powdered KOH in 170 mL of dry xylene was heated to reflux under an argon atmosphere, and 85 mL of xylene was removed by distillation. To this mixture was added a solution of 3.47 g (12.7 mmol) of **37** in 115 mL of dry xylene. The volume of the reaction mixture was reduced 100 mL by distillative removal of xylene. To the reaction mixture was then added a solution of 12.3 g (67.3 mmol) of n-heptyl mesylate in 90 mL of dry xylene. The reaction mixture was refluxed for 3 h. The cooled reaction mixture was diluted with 200 mL of brine and extracted with EtOAc (5 × 200 mL). The combined EtOAc extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. This was chromatographed on 120 g of silica gel 60 with 1:1 hexane/ether as eluant to give 7.08 g of crude ether. Final purification was effected by flash chromatography on 103 g of silica gel 60 with 3:1 hexane/ether as eluant to give 3.0 g (72%) of ether **52**. TLC: silica gel, 1:1 hexane/ether, R_f 0.45, $Ce(SO_4)_2$. ^1H NMR ($CDCl_3$, 270 MHz): δ 4.71 (s, 2 H), 4.48 (t, J = 6 Hz, 1 H), 4.30 (d, J = 6 Hz, 1 H), 3.69 (m, 1 H, A of AB), 3.53 (m, 1 H, B of AB), 3.45 (d, J = 7 Hz, 1 H), 3.38 (s, 3 H), 0.88 (s, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 Hz): δ 95.6, 82.5, 79.5, 77.7, 71.8, 70.3, 69.4, 66.8, 58.9, 50.1, 31.8, 29.8, 29.5, 29.1, 26.1, 22.5, 22.2, 14.0. Anal. ($C_{18}H_{34}O_5$) C, H.

[1β,2α,3β,4β]-3-(Heptyloxy)-2-(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane (38). To a stirred solution of 1.9 g (5.76 mmol) of MEM ether **52** in 25 mL of dry CH_2Cl_2 under argon at 0 °C was added dropwise 3.28 g (17.3 mmol) of $TiCl_4$. The reaction mixture was stirred for 30 min and quenched with 12 mL of concentrated NH_4OH solution. The reaction mixture was diluted with 120 mL of H_2O and extracted with EtOAc (5 × 100 mL). The combined EtOAc extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification was effected by flash chromatography on 80 g of silica gel 60 with 1% CH_3OH in CH_2Cl_2 as eluant to give 1.1 g (79%) of alcohol **38**. TLC: silica gel, 4% CH_3OH/CH_2Cl_2, R_f 0.35, $Ce(SO_4)_2$. ^1H NMR ($CDCl_3$, 270 MHz): δ 4.50 (t, J = 6 Hz, 1 H), 4.34 (d, J = 6 Hz, 1 H), 3.58 (m, 2 H), 3.50 (m, 1 H), 3.33 (m, 2 H), 0.88 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 82.1, 79.5, 77.8, 70.3, 64.2, 52.1, 31.7, 29.8, 29.5, 29.0, 26.0, 22.5, 22.1, 13.9. Anal. ($C_{14}H_{26}O_3$) C, H.

[1β,2α,3β,4β]-2-Formyl-3-(heptyloxy)-7-oxabicyclo[2.2.1]heptane (53). To a stirred mixture of 2.94 g (17.6 mmol) of pyridinium chlorochromate and 0.22 g (2.73 mmol) of NaOAc in 55 mL of dry CH_2Cl_2 under argon at room temperature was added rapidly a solution of 1.32 g (5.45 mmol) of alcohol in 16.5 mL of dry CH_2Cl_2. The reaction mixture was stirred for 1.5 h and diluted with 72 mL of ether. The organic solution was decanted, and the insoluble black residue was washed with ether (2 × 100 mL) until the precipitate became granular. The combined organic solutions were passed through a 3-in. pad of Florisil, which was then washed with ether (3 × 100 mL). The combined filtrates were concentrated in vacuo to give 1.16 g (89%) of aldehyde **53**. TLC: silica gel, 2% CH_3OH/CH_2Cl_2, R_f 0.34, $Ce(SO_4)_2$. ^1H NMR ($CDCl_3$, 270 MHz): δ 9.65 (d, J = 3 Hz, 1 H), 4.76 (d, J = 6 Hz, 1 H), 4.60 (t, J = 6 Hz, 1 H), 4.08 (t, J = 4 Hz, 1 H), 3.39 (m, 2 H), 2.29 (br s, 1 H), 0.88 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 201.2, 85.6, 81.6, 77.9, 70.5, 48.5, 44.2, 31.7, 29.9, 29.7, 29.0, 26.1, 22.5, 21.8, 14.0.

[1β,2α,3β,4β]-3-(Heptyloxy)-2-(methoxyethenyl)-7-oxabicyclo[2.2.1]heptane (54). To a stirred solution of 3.28 g (9.56 mmol) of methoxymethylenetriphenylphosphonium chloride in 45 mL of dry THF under argon at -15 °C was added 4.97 mL (7.11 mmol) of 1.43 M potassium *tert*-amylate solution dropwise over 10 min. To this mixture was added a solution of 1.13 g (4.71 mmol) of aldehyde **53** in 23 mL of dry THF dropwise at 0 °C over 70 min. The reaction mixture was stirred at room temperature for 2 h, cooled in an acetone/ice bath, and then quenched with 20 mL of acetaldehyde. The reaction mixture was diluted with 150 mL of saturated NH_4Cl solution and 50 mL of 1 N aqueous HCl solution and extracted with ether (3 × 270 mL). The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification was effected by flash chromatography on 151 g of silica gel 60 with 7:1 hexane/ether as eluant to give 1.04 g (82%) of vinyl ether **54** as an oil. TLC: silica gel 2:1 hexane/ether, R_f 0.60, $Ce(SO_4)_2$. ^1H NMR ($CDCl_3$, 270 MHz): δ 6.37 (d, J = 15 Hz, E isomer), 5.84 (d, J = 7 Hz, 1 H, Z isomer), 4.81 (dd, J = 9, 15 Hz, 1 H, E isomer), 4.40 (dd, J = 7, 10 Hz, Z isomer), 3.57 (s, 3 H, Z isomer), 3.52 (s, 3 H, E isomer). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 147.1, 145.0, 109.8, 105.8, 87.8, 83.8, 83.6, 77.8, 70.3, 70.0, 59.3, 55.6, 49.4, 45.3, 31.7, 29.7, 29.0, 26.0, 22.5, 22.1, 21.9, 13.9. Anal. ($C_{16}H_{28}O_3$) C, H.

[1β,2α,3β,4β]-2-(Formylmethyl)-3-(heptyloxy)-7-oxabicyclo[2.2.1]heptane (39). To a stirred solution of 740 mg (2.76 mmol) of vinyl ether **54** in 7.4 mL of freshly distilled THF under argon was added 29.6 mL of 20% aqueous trifluoroacetic acid solution. The reaction mixture was stirred at room temperature for 3 h and then neutralized with solid $NaHCO_3$. The mixture was poured into 100 mL of H_2O and extracted with CH_2Cl_2 (4 × 80 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a colorless oil. This compound was dissolved in 30 mL of benzene and concentrated in vacuo to give 670 mg (95%) of aldehyde **39**. TLC: silica gel, 1:1 hexane/ether, R_f 0.34, $Ce(SO_4)_2$. ^1H NMR ($CDCl_3$, 270 MHz):

δ 9.78 (s, 1 H), 4.52 (t, J = 6 Hz, 1 H), 4.13 (d, J = 6 Hz), 3.45 (t, J = 4 Hz, 1 H), 3.32 (dt, J = 4, 7 Hz, 2 H), 2.59 (m, 2 H), 1.38 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 201.2, 85.6, 81.6, 77.9, 70.5, 48.5, 44.2, 31.7, 29.9, 29.7, 29.0, 26.1, 22.5, 21.8, 14.0.

[1β,2α(Z),3β,4β]-7-[3-(Heptyloxy)-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic Acid (30). To a stirred solution of 1.96 g (4.43 mmol) of (carboxybutyl)triphenylphosphonium bromide in 35 mL of dry THF under argon at 0 °C was added dropwise 6.23 mL (7.91 mmol) of 1.27 M potassium *tert*-amylate/toluene solution. The mixture was stirred at 0 °C for 1 h. To this homogeneous burgundy-red solution was added dropwise a solution of 670 mg (2.64 mmol) of aldehyde **39** in 56 mL of dry THF over 80 min. The reaction mixture was allowed to warm to room temperature and was stirred for 22 h. The reaction mixture was cooled in an ice bath and quenched with the dropwise addition of 10 mL of glacial acetic acid. The mixture was poured into 100 mL of brine and extracted with EtOAc (4 × 100 mL). The combined EtOAc extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was treated with 300 mL of diazomethane solution, and excess diazomethane was destroyed by addition of HOAc. The mixture was concentrated in vacuo and chromatographed on 40 g of silica gel 60 with 2:1 hexane/ether as eluant to give 900 mg of a mixture of the title methyl ester and the corresponding carboxylic acid. Purification was effected by flash chromatography on 141 g of silica gel 60 with 2:1 hexane/ether as eluant to give 350 mg (38%) of pure methyl ester and 490 mg of a mixture of methyl ester and acid **30**. TLC: silica gel, 1:1 hexane/ether, R_f 0.52, iodine.

To a stirred solution of 350 mg (1.00 mmol) of the above methyl ester in 54 mL of freshly distilled THF and 9.0 mL of H_2O was added 10.0 mL of 1 N aqueous lithium hydroxide solution. The reaction mixture was purged with argon vigorously for 30 min and stirred at room temperature for 8.3 h. The reaction mixture was acidified to pH 3 by the addition of 1 N aqueous HCl solution and poured into 80 mL of brine. The aqueous layer was saturated with NaCl and extracted with EtOAc (4 × 100 mL). The combined EtOAc extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification was effected by flash chromatography on 40 g of silica gel 60 with 2% CH_3OH in CH_2Cl_2 as eluant to give 90 mg of acid and 240 mg of a mixture of acid and ester. The mixture was chromatographed on 24.2 g of silica gel 60 with 2% CH_3OH/CH_2Cl_2 as eluant to give 210 mg of acid. The total yield was 30 mg (89%). TLC: silica gel, 1:1 hexane/ether, R_f 0.40, iodine. ^1H NMR ($CDCl_3$, 270 MHz): δ 5.45–5.30 (m, 2 H, CH=CH), 4.50 (t, J = 4 Hz, 1 H), 4.10 (d, J = 5 Hz, 1 H), 3.45–3.21 (m, 3 H, CH—O—CH_2), 2.35 (t, J = 7 Hz, CH_2COOH, 2 H), 0.88 (t, J = 7 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.9, 129.9, 128.6, 85.8, 81.3, 78.1, 70.3, 50.0, 33.4, 31.8, 31.7, 29.9, 29.8, 29.0, 26.6, 26.1, 24.6, 22.6, 22.0, 14.0. Anal. ($C_{20}H_{34}O_4$) C, H.

[1β,2α,3α,4β]-2-Hydroxy-3-(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane (40). A flask containing 250 mL of dry CH_2Cl_2 was cooled in an ice bath. To this was added 8.8 mL (364 mmol) of 90% H_2O_2. To this stirred slurry was added dropwise 58 mL (411 mmol) of trifluoroacetic anhydride over 40 min. During this time the pot tempterature varied between 2 and 7 °C. The solution was stirred for an additional 25 min at 0 °C. A solution of 8.00 g (47.0 mmol) of crude hemiketal **32** in 280 mL of CH_2Cl_2 was cooled to 0 °C, and then 96.0 g (676 mmol) of anhydrous Na_2HPO_4 was added. To this mechanically stirred slurry was added the above peracid solution in 10-mL portions over 35 min. During the addition, the reaction mixture became thick but then thinned out again. The reaction mixture was stirred at 0–2 °C for an additional 18 h and then allowed to warm to room temperature and stirred for an additional 48 h. At this time the reaction mixture was diluted with 100 mL of CH_2Cl_2 and the solids were removed by filtration. The filter cake was washed with ≈200 mL of ether and enough CH_2Cl_2 to afford ≈1400 mL of filtrate. The filtrate was concentrated in vacuo to afford 18 g of crude oxidation product in the form of a colorless oil. A slurry of 4.6 g (121 mmol) of $LiAlH_4$ in 150 mL of ether under Ar was cooled in an ice bath. To this stirred slurry was added dropwise a solution of 18.0 g of crude oxidation product in 70 mL of ether. After 70 min, an additional 4.1 g (108 mmol) of $LiAlH_4$ was added since the $LiAlH_4$ in the flask had aggregated into a large ball. Thirty minutes later, the addition was complete and the flask was warmed to room temperature. After being stirred for 2.5 h, the reaction mixture was diluted with 200 mL of ether and then cooled in an ice bath. To this vigorously stirred mixture was added 8.5 mL of H_2O dropwise over 30 min, followed by the sequential addition of 8.5 mL of 15% NaOH and 25.5 mL of H_2O. This resulted in the formation of a white granular precipitate. The mixture was diluted with 100 mL of EtOAc and filtered to remove solids. The filter cake was resuspended in 10% CH_3OH in EtOAc (350 mL), stirred, and filtered. This washing procedure was repeated twice. The combined filtrates were concentrated in vacuo to afford 10.5 g of crude diol **40**. A 9.9-g portion of this material was chromatographed on 225 g of silica gel with 4% CH_3OH/CH_2Cl_2 as eluant for fractions 1–60, followed by 500 mL of 6% CH_3OH/CH_2Cl_2 and 600 mL of 8% CH_3OH/CH_2Cl_2. This afforded 3.83 g (56%) of diol **40** and 1.7 g of the monoacetate of the diol. This acetate was subjected to the above $LiAlH_4$ reduction and chromatographed to afford an additional 13% yield of the diol. The total overall yield of **40** from hemiketal **32** was 69%. TLC: silica gel, 4% CH_3OH/CH_2Cl_2, R_f 0.14, iodine. ^1H NMR ($CDCl_3$), 270 MHz): δ 4.36 (d, J = 5 Hz, 1 H), 4.26 (d, J = 4 Hz, 1 H), 4.40 (d, J = 7 Hz, 1 H), 3.76 (m, 2 H), 2.06 (m, 1 H), 1.65 (m, 2 H), 1.38 (m, 2 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 83.0, 78.0, 76.7, 61.6, 50.7, 29.0, 24.4.

[1β,2α,3α,4β]-2-Hydroxy-3-[(p-tosyloxy)methyl]-7-oxabicyclo[2.2.1]heptane (55). A solution of 5.5 g (38.2 mmol) of diol **40**, 20 mL of pyridine, and 10 mL of dry CH_2Cl_2 was cooled to −20 °C under argon. To this stirred solution was added dropwise a solution of 8.23 g (43.2 mmol) of recrystallized TsCl in 25 mL of CH_2Cl_2 over a period of 30 min. The reaction mixture was stirred at −20 °C for 2 h, and then the flask was placed in the refrigerator (3–5 °C) for 4 days. The flask was then allowed to warm to room temperature with stirring. The reaction mixture was partitioned between 300 mL of ether and 200 mL of 1 N HCl. A precipitate began to form in the ether layer so a small amount (50–75 mL each) of EtOAc and MeOH was added, which dissolved the precipitate. The organic layer was washed with 100 mL of 1 N HCl. The combined aqueous layers were then extracted with 150 mL of ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give 11.7 g of white solid. This solid was stirred with ca. 75 mL of ether, and then 25 mL of hexane was added. After this mixture was chilled in the refrigerator for several hours, the white precipitate was collected and dried in vacuo to give 8.4 g (74%) of tosylate **55**, mp 141.5–142 °C. TLC: silica gel, 2% CH_3OH/CH_2Cl_2, R_f 0.31, $Ce(SO_4)_2$. ^1H NMR ($CDCl_3$, 270 MHz): δ 7.79 (d, J = 8 Hz, 2 H), 7.35 (d, J = 8 Hz, 2 H), 4.35 (d, J = 4 Hz, 1 H), 4.30 (d, J = 6 Hz, 1 H), 4.18 (dd, J = 6, 10 Hz, 1 H), 4.00 (t, J = 8 Hz, 2 H), 2.45 (s, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 144.9, 132.3, 129.9, 127.9, 82.6, 77.6, 75.6, 69.0, 48.7, 28.6, 24.2, 21.6. Anal. ($C_{14}H_{18}O_5S$) C, H, S.

[1β,2α,3α,4β]-2-(2-Tetrahydropyranyloxy)-3-[(p-tosyloxy)methyl]-7-oxabicyclo[2.2.1]heptane (41). A solution of 8.2 g (27.5 mmol) of the above tosylate in 130 mL of dry CH_2Cl_2 was cooled to 0 °C. To this rapidly stirred solution was added 0.10 g of p-TsOH followed by dropwise addition of 4.0 mL (43.9 mmol) of dihydropyran. The flask was covered with foil and maintained at 0 °C. After the reaction mixture was stirred for 4 h, it was added to 100 mL of saturated $NaHCO_3$ solution. The aqueous layer was extracted twice with 100 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude product. This was chromatographed on 180 g of silica gel with 4:1 hexane/ether as eluant for fractions 1–40, 2:1 hexane/ether for fractions 40–60, and then ether. This afforded 7.2 g (69%) of 41 along with 1.26 g (12%) of slightly impure **41**. TLC: silica gel, 1:1 hexane/ether, R_f 0.16, 0.24, $Ce(SO_4)_2$.

[1β,2α,3α,4β]-2-(2-Tetrahydropyranyloxy)-3-(cyanomethyl)-7-oxabicyclo[2.2.1]heptane (56). To a stirred solution of 7.0 g (18.3 mmol) of 41 in 70 mL of dry Me_2SO were added 5.95 g (121 mmol) of NaCN (powdered) and 0.12 g of $NaHCO_3$. This mixture was placed in a 95 °C oil bath for 4 h. On cooling, the reaction mixture was partitioned between 500 mL of brine and 400 mL of ether. The aqueous layer was then extracted with three 400-mL portions of ether. The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford

5.4 g of crude product. Flash chromatography on 260 g of silica gel with 3:2 ether/hexane as eluant gave 4.2 g (97%) of nitrile **56**. TLC: silica gel, 1:1 ether/hexane, R_f 0.12, $Ce(SO_4)_2$. ^1H NMR of isomer A ($CDCl_3$, 270 MHz): δ 4.69 (m, 1 H), 4.45 (d, J = 6 Hz, 1 H), 4.38 (d, J = 5 Hz, 1 H), 4.01 (d, J = 7 Hz, 1 H), 3.82 (m, 1 H), 3.50 (m, 1 H). ^1H NMR of isomer B ($CDCl_3$, 270 MHz): δ 4.59 (m, 1 H), 4.56 (d, J 6 Hz, 1 H), 4.23 (d, J = 5 Hz, 1 H), 3.9 (m, 1 H), 3.81 (d, J = 7 Hz, 1 H), 3.50 (m, 1 H). ^{13}C NMR mixture of THP diastereomers ($CDCl_3$, 67.5 MHz); δ 120.3, 119.9, 100.9, 97.1, 81.8, 81.6, 79.3, 79.1, 77.3, 62.7, 62.6, 46.1, 45.9, 30.4, 30.3, 28.5, 28.4, 25.3, 25.2, 24.8, 24.7, 19.3, 16.4, 16.2.

[1β,2α,3α,4β]-2-(2-Tetrahydropyranyloxy)-3-(formylmethyl)-7-oxabicyclo[2.2.1]heptane (42). A solution of 4.2 g (17.7 mmol) of the above nitrile in 50 mL of dry toluene was cooled to 20 °C. To this stirred solution was added dropwise 30 mL of 25% diisobutylaluminum hydride (Dibal) in toluene (44.6 mmol) over a period of 10 min. The bath temperature was maintained at −20 to −15 °C for 3 h. The reaction was then quenched at −20 °C by the addition of 30 mL of acetone and then diluted with 250 mL of toluene. To this was added 100 g of silica gel followed by the dropwise addition of 10 mL of H_2O and 4.0 mL of glacial acetic acid. This slurry was stirred vigorously for 45 min at room temperature. The silica gel was removed and the cake washed with three 300-mL portions of acetone. The combined filtrates were concentrated in vacuo, redissolved in 100 mL of ether, and washed with 80 mL of half-saturated NaCl solution. The aqueous layer was back-extracted with 100 mL of ether. The combined ether layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 3.8 g (89%) of aldehyde **42**. TLC: silica gel, 1:1 hexane/ether, R_f 0.22, $Ce(SO_4)_2$. This was used immediately in the next step without further purification.

Methyl [1β,2α(Z),3α,4β]-7-[3-(2-Tetrahydropyranyloxy)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoate (57). A slurry of 51.75 g (117 mmol) of (carboxybutyl)triphenylphosphonium bromide in 400 mL of THF was cooled in an ice bath under argon. To this stirred slurry was added dropwise 60 mL (84 mmol) of 1.4 M potassium *tert*-amylate/toluene over a period of 48 min. At this point, the reaction mixture was allowed to warm to room temperature. The ylid solution was stirred at room temperature for 5 h, at which time the addition of a solution of 3.7 g (15.4 mmol) of crude aldehyde in 100 mL of THF was begun. The addition was complete after 55 min, and the resulting mixture was stirred at room temperature overnight. The mixture was cooled in an ice bath and quenched by the addition of a solution of 25 mL of HOAc in 25 mL of toluene, followed by dilution with an additional 300 mL of toluene. The precipitate was removed by filtration, and the filtrate was partitioned between 800 mL of half-saturated NaCl and 500 mL of EtOAc (pH of aqueous layer was 3.5). The aqueous layer was then extracted with 3 × 500 mL of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give 12.6 g of crude product. This was triturated with i-Pr_2O/hexane. The filtrate was concentrated in vacuo to afford 8.8 g of crude acid. This was esterified with excess CH_2N_2 at 0 °C. The resultant ester was chromatographed on 180 g of silica gel with 2% CH_3OH in CH_2Cl_2 as eluant. Fractions 46–62 were concentrated to afford 3.80 g of pure methyl ester **57**. Fractions 63–72 were concentrated to give 0.6 g of a mixture of **57** and $Ph_3P{=}O$. TLC: silica gel, 4% CH_3OH/CH_2Cl_2, R_f 0.64, 0.71 (THP diastereomers), iodine. ^{13}C NMR mixture of THP diastereomers ($CDCl_3$, 67.5 MHz): δ 173.9, 130.3, 130.0, 129.4, 100.2, 96.6, 82.1, 81.7, 79.3, 79.0, 78.9, 78.1, 62.4, 62.2, 51.3, 49.6, 49.3, 33.4, 30.6, 30.4, 29.0, 28.9, 26.7, 25.6, 25.4, 25.2, 25.0, 24.8, 19.4, 19.2.

Methyl [1β,2α(Z),3α,4β]-7-(3-Hydroxy-7-oxabicyclo-[2.2.1]hept-2-yl)-5-heptenoate (43). Each portion of methyl ester **57** was deprotected separately. To a solution of 3.8 g (11.2 mmol) of **57** in 40 mL of CH_3OH was added 600 mg of crushed, dried Amberlyst 15 resin. This mixture was stirred vigorously for 4 h at room temperature. It was then diluted with 100 mL of ether and filtered through a short pad of Celite. The filter cake was washed throughly with ether. The combined filtrates were concentrated in vacuo to afford crude ester **43**. The other portion of methyl ester was deprotected under the same conditions (0.6 g of **57**/5 mL of CH_3OH/120 mg of Amberlyst 15). The crude products from these two deprotections were combined and chromatographed on 110 g of silica gel with 2% CH_3OH/CH_2Cl_2 as eluant. This afforded 2.4 g (61% overall from **42**) of alcohol ester **43**. TLC: silica gel, 4% CH_3OH/CH_2Cl_2, R_f 0.34, iodine. ^1H NMR ($CDCl_3$, 270 MHz): δ 5.40 (m, 2 H), 4.30 (d, J = 6 Hz, 1 H), 4.17 (d, J = 5 Hz, 1 H), 3.87 (m, 1 H), 3.63 (s, 3 H), 2.29 (t, J = 7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 174.0, 129.8, 129.6, 83.1, 79.7, 76.5, 51.4, 49.7, 33.4, 29.2, 26.7, 25.3, 24.7, 24.2. Anal. ($C_{14}H_{22}O_4$) C, H.

[1β,2α(Z),3α,4β]-7-[3-(Heptyloxy)-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic Acid (31). A slurry of 0.42 g (7.5 mmol) of powdered KOH in 20 mL of xylene was heated to reflux under Ar, and ca. 10 mL of xylene was removed by distillation. To this boiling solution were added a solution of 230 mg (0.91 mmol) of alcohol **43**, 1.00 g (5 mmol) of *n*-heptyl mesylate, and 5 mL of xylene. Approximately 3 mL of additional xylene was removed by distillation. TLC analysis after 20 min showed the reaction to be complete. The heat was removed, and the reaction mixture was allowed to cool slowly. On cooling, the reaction mixture was partitioned between 20 mL each of saturated NH_4Cl and EtOAc. The aqueous layer was acidified to pH 3.5 with 1 N HCl and then extracted with 2 × 25 mL of EtOAc. The combined EtOAc extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. Chromatography on 35 g of silica gel with 4% CH_3OH/CH_2Cl_2 as eluant afforded 140 mg (46%) of **31** along with 200 mg of impure **31**. TLC: silica gel, 4% CH_3OH/CH_2Cl_2, R_f 0.31, iodine. ^1H NMR ($CDCl_3$, 270 MHz): δ 5.39 (m, 2 H), 4.45 (d, J = 4 Hz, 1 H), 4.19 (d, J = 4 Hz, 1 H), 3.6–3.4 (m, 2 H), 3.30 (dt, J = 9, 7 Hz, 1 H), 2.35 (t, J = 7 Hz, 2 H), 0.87 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.1, 130.5, 129.2, 83.8, 79.5, 79.1, 70.9, 49.7, 33.4, 31.8, 29.8, 29.1, 26.6, 26.1, 25.2, 24.9, 24.7, 22.6, 14.0. Anal. ($C_{20}H_{34}O_4$) C, H.

Methyl [3α,4aβ,5β,8β,8aβ]-5-(Octahydro-5,8-epoxy-1*H*-2-benzopyran-3-yl)-5-iodopentanoate (45). To a solution of 485 mg (1.81 mmol) of **5** in 20 mL of ether was added 30 mL of saturated aqueous $NaHCO_3$. This mixture was cooled in an ice bath. To this vigorously stirred mixture was added dropwise a solution of 530 mg (2.1 mmol) of I_2 in 28 mL of ether over a period of 90 min. The reaction mixture was stirred at 0 °C for 3.5 h, and then the ice bath was allowed to come to room temperature overnight. The reaction mixture was poured into 50 mL of 10% Na_2SO_3. The aqueous layer was extracted with 50 mL of ether. The combined ether layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to give 0.74 g of crude product. This was chromatographed on 40 g of silica gel with 2:1 ether/hexane as eluant. This gave 0.73 g (99%) of **45**. ^1H NMR ($CDCl_3$, 270 MHz): δ 4.22 (d, J = 3 Hz, 1 H), 4.09 (d, J = 4 Hz, 1 H), 3.94 (m, 1 H), 3.72 (dd, J = 6, 11 Hz, 1 H), 3.65 (s, 3 H), 3.56 (t, J = 11 Hz, 1 H), 2.32 (t, J = 7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 173.0, 80.6, 77.6, 74.5, 62.6, 51.1, 42.8, 40.2, 34.7, 32.7, 29.2, 29.1, 27.5, 24.8.

Methyl [3α,4aβ,5β,8β,8aβ]-5-(Octahydro-5,8-epoxy-1*H*-2-benzopyran-3-yl)pentanoate (46). To a stirred solution of 590 mg (1.50 mmol) of iodo ether **45** in 6 mL of dry toluene under Ar was added 0.45 mL (1.64 mmol) of *n*-Bu_3SnH. This solution was stirred at room temperature for 22 h. An addition 0.45 mL (1.64 mmol) of *n*-Bu_3SnH was added, and the solution was heated to reflux for 7 h. The cooled reaction mixture was concentrated in vacuo. The residue was dissolved in 15 mL of CH_3CN and washed with five 10-mL portions of hexane. The CH_3CN layer was concentrated in vacuo to afford 280 mg (70%) of **46**. The combined hexane layers were extracted once with 10 mL of CH_3CN. This CH_3CN layer was diluted with 10 mL of CH_3CN and washed with 30 mL of hexane. The CH_3CN layer was concentrated in vacuo to give an additional 70 mg (17%) of **46**. ^1H NMR ($CDCl_3$, 270 MHz): δ 4.13 (d, J = 4 Hz, 1 H), 4.07 (d, J = 4 Hz, 1 H), 3.60 (s, 3 H), 3.57 (dd, J = 6, 11 Hz, 1 H), 3.42 (t, J = 11 Hz, 1 H), 2.25 (t, J = 7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 15 MHz): δ 173.8, 80.9, 78.1, 71.6, 61.0, 51.1, 43.0, 40.4, 36.3, 33.7, 29.6, 28.9, 24.7, 24.5.

[3α,4aβ,5β,8β,8aβ]-5-(Octahydro-5,8-epoxy-1*H*-2-benzopyran-3-yl)pentanoic Acid (44). A solution of 270 mg (1.01 mmol) of ester **46** in 3 mL of distilled THF and 0.7 mL of H_2O was purged with Ar. To this stirred solution was added 1.3 mL of 1 N LiOH. After being stirred for 3.5 h, the reaction mixture was diluted with 20 mL of 5% K_2CO_3 and washed once with 20 mL of ether. The aqueous layer was acidified to pH 3.0 with concentrated HCl. It was then saturated with NaCl and extracted

with four 20-mL portions of EtOAc. The combined EtOAc layers were drided over $MgSO_4$, filtered, and concentrated in vacuo to afford 150 mg (59%) of **44**. Two recrystallizations from IPA/IPE/hexane afforded 102 mg of pure **44**, mp 102–103 °C. TLC: silica gel, 1% CH_3OH/CH_2Cl_2, R_f 0.56. ^1H NMR ($CDCl_3$, 400 MHz): δ 4.19 (d, J = 4 Hz, 1 H), 4.12 (d, J = 4 Hz, 1 H), 3.63 (dd, J = 7, 11 Hz, 1 H), 3.63 (m, 1 H), 3.48 (t, J = 11 Hz, 1 H), 2.34 (t, J = 7 Hz, 2 H), 2.08 (m, 1 H, A of AB), 1.96 (m, 1 H, B of AB). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 178.7, 81.2, 78.4, 72.0, 61.1, 43.3, 40.7, 36.5, 33.9, 29.8, 29.2, 24.7. Anal. ($C_{14}H_{22}O_4$) C, H.

[1R-[1α,2β,3β,4α]]-7-[3-[(Hexyloxy)methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]heptanoic Acid (47). To a solution of 120 mg (0.36 mmol) of 1 in 6 mL of EtOAc under Ar was added 24 mg of 10% Pd/carbon. The argon was replaced by hydrogen with several vaccum-fill cycles. The reaction mixture was stirred at room temperature under a slight positive pressure of hydrogen for 14 h. The catalyst was filtered off and the filtrate concentrated in vacuo to give 110 mg of crude product. Analysis of the crude product by 270-MHz ^1H NMR revealed the presence of 5–7% of 1. The material was again subjected to the reaction conditions described above to afford 110 mg of **47**. Purification was effected by flash chromatoraphy on 22 g of silica gel with 2% CH_3OH/CH_2Cl_2 as eluant to afford 105 mg (87%) of **47**. TLC: silica gel, 8% CH_3OH/CH_2Cl_2, R_f 0.74, iodine. $[\alpha]_D$: -3.1° (c 1.37, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz): δ 4.38 (d, J = 5 Hz, 1 H), 4.23 (d, J = 5 Hz, 1 H), 3.3–3.1 (m, 4 H), 2.31 (t, J = 7 Hz, 2 H), 1.89 (m, 1 H), 0.87 (t, J = 7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 179.1, 80.1, 79.1, 71.2, 69.8, 47.0, 46.4, 34.0, 31.6, 29.7, 29.6, 29.3, 29.2, 29.0, 27.6, 25.8, 24.6, 22.6, 14.0. Anal. ($C_{20}H_{36}O_4$) C, H.

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Antiinflammatory and Aldose Reductase Inhibitory Activity of Some Tricyclic Arylacetic Acids[1]

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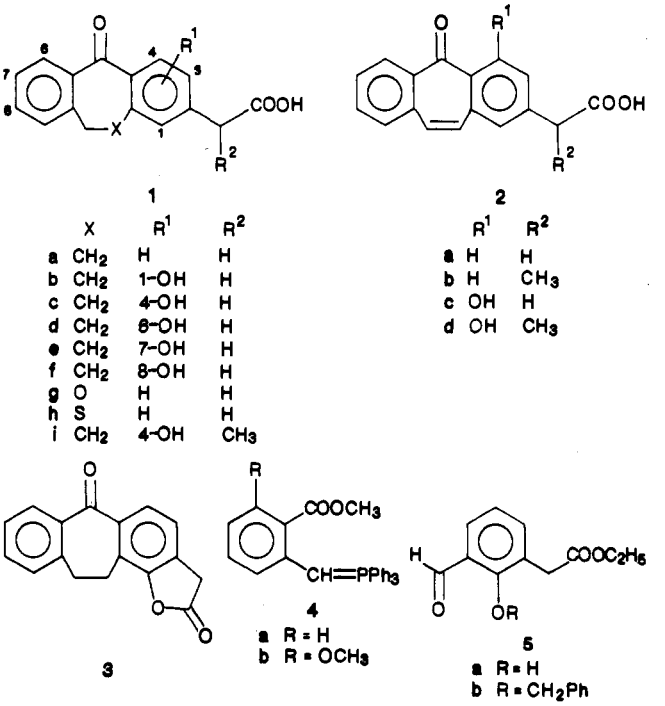
A number of dibenztropone, dibenzsuberone, dibenzoxepin, and dibenzthiepin acetic acids were synthesized and tested for antiinflammatory/analgesic activity and also for their ability to inhibit rabbit lens aldose reductase (AR). It was found that the structural requirements for antiinflammatory/analgesic activity, believed to be mediated by inhibition of cyclooxygenase, were much more stringent than were those for AR inhibition. For example, the introduction of a hydroxyl group into positions 1, 4, 6, 7, or 8 on dibenzsuberone-2-acetic acid (**1a**) had relatively little effect on AR inhibition, but caused wide variations in antiinflammatory/analgesic activity.

The enzyme aldose reductase (AR) catalyzes the formation of sugar alcohols from sugars and has been implicated in the development of cataracts in diabetes and galactosemia[2,3] and in other complications of diabetes such as neuropathy and retinopathy.[4,5] Several compounds of diverse structure are known to inhibit the enzyme aldose reductase.[6-10] Recent reports that certain antiinflammatory drugs such as indomethacin, sulindac,[11-13] and aspirin[14] were inhibitors of the enzyme prompted us to present our findings that certain tricyclic arylacetic acids, in addition to having antiinflammatory and analgesic activity, are also potent inhibitors of the enzyme aldose reductase. The basis of this study was twofold. In the first place there was the possibility that some of the compounds tested may be more effective than the known inhibitors of the enzyme, and the additional activity in preventing prostaglandin synthesis may be useful in diabetic patients.[15,16] Secondly, a comparison could be made between a number of compounds with known antiinflammatory activity and possible aldose reductase inhibitory activity to determine any correlation.

Chemistry. The syntheses of a number of the compounds have been described previously (see Experimental Section). The 1- and 6-hydroxy compounds **1b** and **1d** were obtained by similar syntheses, the key step in each of which was a Wittig reaction between an appropriately substituted (2-carbomethoxybenzylidene)triphenylphosphorane (**4**) and a substituted benzaldehyde. Thus,



reaction between the ylid (**4a**), generated by reaction of the phosphonium bromide with ethanolic sodium ethoxide,

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