by silica gel (Sigma Sil B-200) column chromatography and elution with 2.5% methanol in $CHCl_3$ gave (175 μCi (24% yield); sp act. 59 mCi/mmol) pure [^{125}I]-**9**, which cochromatographed with unlabeled **9** on TLC (25% MeOH in $CHCl_3$).

Radiochemical Synthesis of [^{125}I]-11, [^{125}I]-12, and [^{125}I]-13. The commercial sample of iodine-125 (21.8 mCi) was received in 0.1 N NaOH and was first neutralized with a hydrofluoric acid (HF) solution (prepared by diluting 48% aqueous HF with methanol). A solution of iodine (one atom equivalent of the substrate, 12.7 mg) in methanol (2 mL) was added to the radioiodide solution. The resulting solution was made homogeneous and added to a cold (ice–water bath) stirred suspension of finely powdered 4-(aminophenyl)mercuric acetate (0.1 mmol). An instantaneous reaction with iodine color discharge was observed. The reaction mixture was stirred for 5–10 min, diluted with water (25 mL), and extracted with ethyl ether. The ether portion was washed with 10% aqueous sodium bisulfite solution followed by water and dried (Na_2SO_4). Evaporation of ether provided 4-[^{125}I]iodoaniline (15.8 mCi, 73% radiochemical yield) with a specific activity of 218 mCi/mmol. Further purification could be achieved by silica gel column chromatography by elution with $CHCl_3$ without significant loss of the product. The 4-[^{125}I]iodoaniline prepared by this method was characterized by comparing with an authentic unlabeled sample[21] of **11**. The [^{125}I]-**11** (15.8 mCi) and the succinimidyl ester **4** (27 mg, 0.075 mmol) were dissolved in DMF (1 mL). The solution was stirred for 4 h and applied to a 16 × 1.2 cm column packed with silica gel (Sigma Sil B-200) in $CHCl_3$. Elution of the column with $CHCl_3$ provided unreacted [^{125}I]-**11** (5.52 mCi). Further elution with 20% MeOH in $CHCl_3$ (v/v) gave [^{125}I]-**12** (5.67 mCi, 35.8% radiochemical yield) in 70% yield with a specific activity of 137 mCi/mmol on the basis of recovered [^{125}I]-**11**. The [^{125}I]-**12** was reduced into [^{125}I]-**13** in an argon atmosphere, using $NaHCO_3$ (25 mg) and $Na_2S_2O_4$ (35 mg) as described for [^{125}I]-**9** in 13% (719 μCi) radiochemical yield.

Acknowledgment. This research was sponsored by the Office of Health and Environmental Research, U.S. Department of Energy, under Contract DE-AC05-840R21400 with Martin Marietta Energy Systems, Inc. The authors thank A. P. Callahan, B. A. Owen, and E. B. Cunningham for technical assistance and L. S. Ailey for typing the manuscript.

Registry No. **1**, 59-67-6; **2**, 6066-82-6; **3**, 78348-28-4; **4**, 97807-17-5; **5**, 97807-18-6; **6**, 97807-19-7; **7**, 97807-20-0; **8**, 97807-21-1; [^{125}I]-**8**, 97807-22-2; **9**, 97807-23-3; [^{125}I]-**9**, 97807-24-4; **10**, 6283-24-5; [^{125}I]-**11**, 77718-00-4; **12**, 97807-25-5; [^{125}I]-**12**, 97807-26-6; **13**, 97807-27-7; [^{125}I]-**13**, 97807-28-8; *p*-$H_2NC_6H_4(CH_2)_2NH_2$, 13472-00-9; $NHEt_2$, 109-89-7; piperidine, 110-89-4; **11**, 540-37-4; 1-methyl-3-[*N*-(2-phenylethyl)carbamoyl]pyridinium iodide, 84254-38-6.

Synthesis and in Vitro Pharmacology of 7-Oxabicyclo[2.2.1]heptane Analogues of Thromboxane A_2/PGH_2

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Departments of Chemistry-Cardiopulmonary Agents, Pharmacology, and Science Information, E. R. Squibb & Sons, Princeton, New Jersey 08540. *Received August 3, 1984*

A series of chemically stable TXA_2/PGH_2 analogues modeled after the structure of the natural products was prepared in search of useful inhibitors of TXA_2/PGH_2-mediated pathophysiology. Each of the 16 isomers implied in structure **1** was prepared in chiral form and evaluated for activity in vitro in platelets and smooth muscle. Depending on relative side chain and carbinol stereochemistry, TXA_2/PGH_2 agonist and antagonist and, surprisingly, PGD_2/PGI_2 agonist activities were observed. The enantiomers possessing the α heterocycle shown in **1** were generally more potent than their mirror-image isomers.

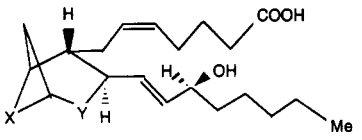
The adversary relationship between prostacyclin and thromboxane-A_2 (TXA_2), which modulates coronary blood vessel caliber[1] and platelet aggregation,[2] presents a novel opportunity for therapeutic intervention in cardiovascular events. Substances that inhibit TXA_2 synthetase or interfere at the TXA_2 receptor would be expected to normalize pathological events caused by oversynthesis of TXA_2. Thus, the synthesis of compounds modeled after TXA_2 has been the goal of our research group since publication of its structure in 1975.[3]

Topologically, TXA_2 and its biosynthetic precursor PGH_2 can be represented by three areas of polar functionality (carboxyl, heterocycle, carbinol) connected by linkages of precise length and stereochemistry. Medicinally useful agents modeled after TXA_2 or PGH_2 will require structural modifications in each area to overcome the chemical and metabolic instability and undesired activity inherent in the nature products. Currently, active research is directed toward identifying advantageous replacement functionality in each area. However, the major emphasis has centered on the chemically labile dioxabicyclo[3.1.1]heptane ring system. Stable surrogate ring systems in which oxygen is replaced by carbon,[4,7,8] nitrogen,[5] or

(1) Sivakoff, M.; Pure, E.; Hsueh, W.; Needleman, P. *Fed. Proc.* **1979**, *38*, 78–82.
(2) Gorman, R. R. *Fed. Proc.* **1979**, *38*, 83–88.
(3) Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994–2998.
(4) (a) Ohuchida, S.; Hamanaka, N.; Hayashi, M. *Tetrahedron Lett.* **1979**, 3661–3664. (b) Nicolaou, K. C.; Magolda, R. L.; Smith, J. B.; Aharony, D.; Lefer, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2566–2570. (c) Wilson, N. H.; Peesapati, V.; Jones, R. L.; Hamilton, K. *J. Med. Chem.* **1982**, *25*, 495–500.
(5) Kosuge, S.; Hayashi, M.; Hamanaka, N. *Tetrahedron Lett.* **1982**, *23*, 4027–4030.
(6) (a) Kosuge, S.; Hamanaka, N.; Hayashi, M. *Tetrahedron Lett.* **1981**, *22*, 1345–1348. (b) Uhuchida, S.; Hamanaka, N.; Hayashi, M. *Tetrahedron Lett.* **1981**, *22*, 1349–1352. (c) Ibid. *J. Am. Chem. Soc.* **1981**, *103*, 4597–4599. (d) Uhuchida, S.; Hamanaka, N.; Hashimoto, S.; Hayashi, M. *Tetrahedron Lett.* **1982**, *23*, 2883–2886.
(7) (a) Maxey, K. M.; Bundy, G. L. *Tetrahedron Lett.* **1980**, *21*, 445–448. (b) Gorman, R. R.; Maxey, K. M.; Bundy, G. L. *Biochem. Biophys. Res. Commun.* **1981**, *100*, 184–190.
(8) Corey, E. J.; Ponder, J. M.; Ulrich, P. *Tetrahedron Lett.* **1980**, *21*, 137–140.
(9) Ansell, M. F.; Caton, M. P.; Mason, J. S. *Tetrahedron Lett.* **1981**, *22*, 1141–1142.
(10) Schaaf, T. K.; Bussolotti, D. L.; Parry, M. J.; Corey, E. J. *J. Am. Chem. Soc.* **1981**, *103*, 6502–6505.
(11) Barraclough, P. *Tetrahedron Lett.* **1980**, *21*, 1897–1900.
(12) Corey, E. J.; Shibasaki, M.; Nicolaou, K. C.; Malmsten, C. L.; Samuelsson, B. *Tetrahedron Lett.* **1976**, *734*–741.
(13) Corey, E. J.; Niwa, H.; Bloom, M.; Ramwell, P. W. *Tetrahedron Lett.* **1979**, 671–674.

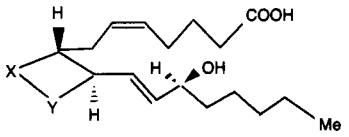
0022-2623/85/1828-1580$01.50/0

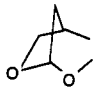
Table I. Bicyclo[3.1.1]heptane Thromboxane A_2 Analogues



No.	X	Y	Classification	Reference
I	C	C	agonist	4a
II	Me_2C	C	antagonist	4b,c
III	C	S	agonist	6a
IV	S	C	agonist	6b
V	S	O	agonist	6d
VI	C	N	agonist	5
VII	S	S	agonist	6c
VIII	O	C	antagonist	7a,b
IX	C	O	unknown	8

Table II. Bicyclic Thromboxane A_2/PGH_2 Analogues[a]

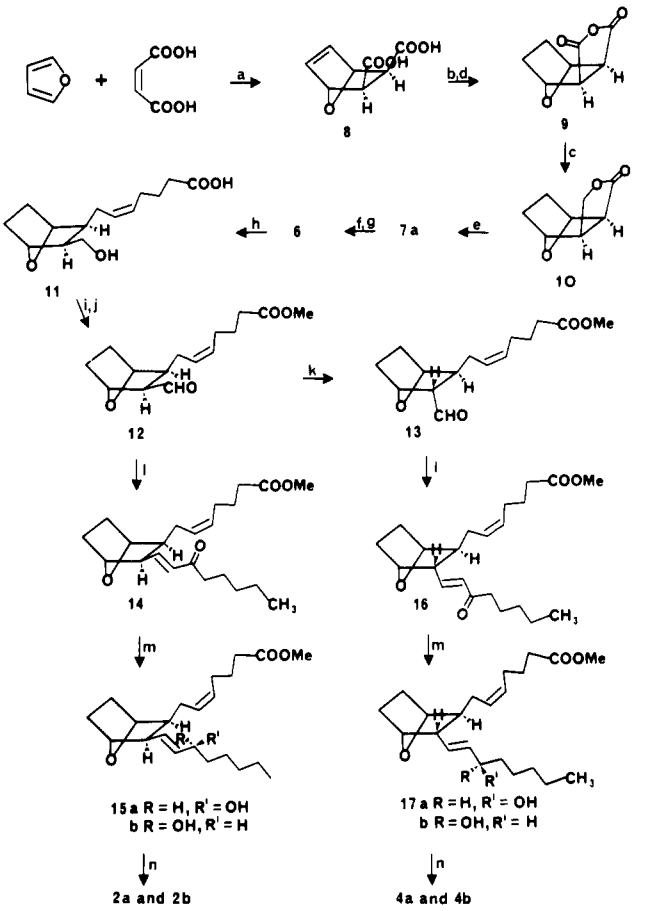


X—Y	Classification	Reference
	weak agonist	9
	weak agonist	10
	unknown	11
	agonist	4e
	weak agonist	12
	agonist	4c
	TXA_2 Synth. Inhibitor	13

[a] For a discussion of prostaglandin endoperoxide analogues prepared before 1979, see ref 14.

sulfur[6] have been reported by several groups (Table I). Alternatively, stability has been achieved by enlargement

Scheme I[a]

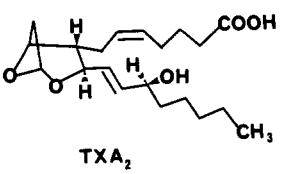


[a] Key: a, 25 °C; b, H_3CCOCl; c, $NaBH_4$, THF; d, H_2, Pd/C; e, DIBAL; f, $Ph_3P{=}CHOCH_3$; g, F_3CCO_2H; h, $Ph_3P{=}CH(CH_2)_3CO_2^-Na^+$; i, CH_2N_2; j, CrO_3, pyridine; k, NaOMe, MeOH; l, $(MeO)_2POCH^-COC_5H_{11}Na^+$; m, $CeCl_3$, $NaBH_4$; n, LiOH, HOH, THF.

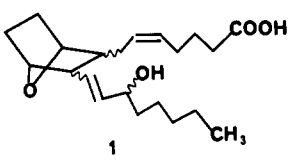
of the TXA_2 oxetane ring (Table II).

Our understanding of the effect on biological activity of these structural variations is mixed. Several PGH_2 mimics (Table II) and a few TXA_2 analogues (Table I, see II and VIII) have been extensively characterized. In most other cases, however, only a rough classification as agonists or antagonists of TXA_2 and/or TXA_2 synthetase inhibitors is possible.

In this work we employed the 7-oxabicyclo[2.2.1.]heptane ring system as a chemically stable surrogate for the TXA_2 heterocycle and chose compounds of general structure 1 as our primary targets.



TXA_2



1

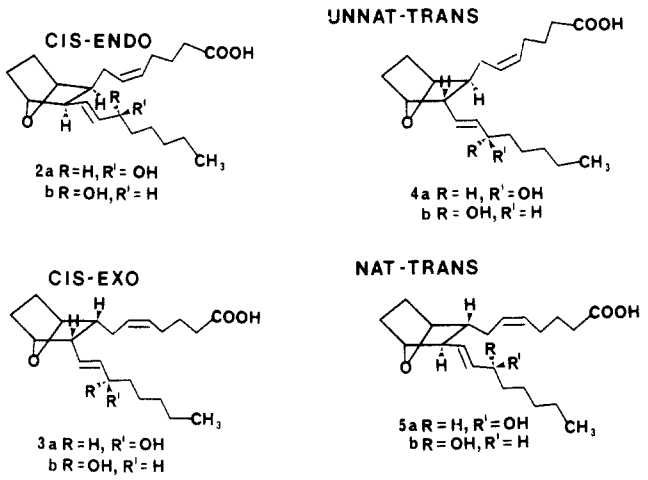
Previous experience with derivatives of PGE_2[15] suggested prostaglandin activity is sensitive to isomerism at the 15-carbinol and side chain ring junctions. Anticipating TXA_2 agonist activity for the "natural" trans stereochemistry (α side chain exo), we felt isomers with alternate ring side chain stereochemistry could have different activity and

(14) Nicolaou, K. C.; Gasic, G. P.; Barnett, W. E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293–312.
(15) Usardi, M. M.; Ceserani, R.; Doria, C.; Gandolfi, C.; Turba, C. *Pharm. Res. Commun.* **1974**, *6*, 437–444.

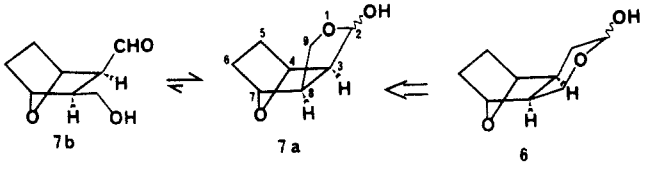
might behave as antagonists. We are plased to report that this hypothesis has proven to be true. Our results indicate that three different activity profiles can be distinguished among the isomers of **1** *depending on side chain stereochemistry.* We will also present evidence suggesting both the heterocyclic ring oxygen and side chain carbinol strongly effect the activity of these compounds.

Results

Chemistry. For definitive structure–activity correlations to be made, biological evaluation of each isomer implied by structure **1** was necessary. Of the five asymmetric carbon atoms in **1**, two share the bridge oxygen atom. The compound can therefore exist in 16 isomeric forms; the eight diastereomers shown below and their mirror-image enantiomers. Construction of the acid and allylic alcohol side chains in compounds such as **1** can be carried out by using Wittig-type chemistry already well established by Corey[16] and others.[14] The synthetic challenge presented by structure **1** centers on controlling the functionality and stereochemistry at positions 3 and 8 on a chiral 7-oxabicyclo[2.2.1]heptane starting material.



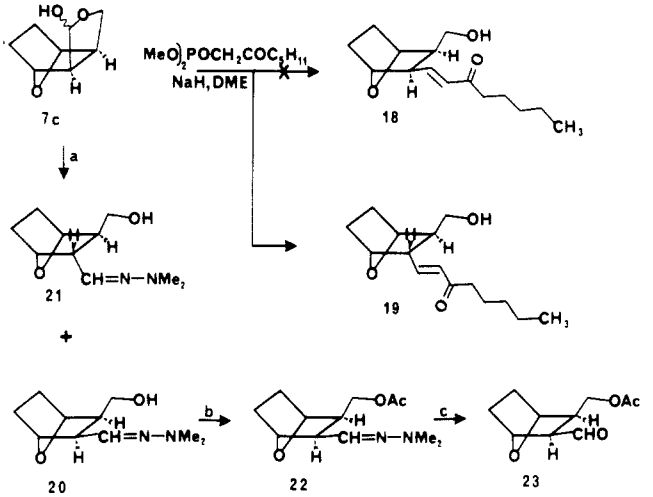
Hemiacetal **6** contains the necessary functionality and stereochemistry to make synthesis of **2a** and **2b** possible.



In a retrosynthetic sense, **6** is available from hemiacetal **7a** by homologation. Compound **7a** in turn is available from furan and maleic acid[17] as shown in Scheme I. Reaction of **7a** with (methoxymethylene)triphenylphosphorane followed by hydrolysis of the intermediate enol ether mixture gave hemiacetal **6**. Exposure of **6** to (carboxybutylene)triphenylphosphorane gave **11** which, after esterification, was oxidized to endo aldehyde **12**. Treatment of this compound with the anion of dimethyl (2-oxoheptyl)phosphonate followed by reduction of the ketone function, chromatographic separation of the epimers of **15**, and hydrolysis of the ester function led to compounds **2a** and **2b**.

The hemiacetal **7a** can also serve as starting material for preparation of **4a**, **4b**, **5a**, and **5b**. Both substituents

Scheme II[a]



[a] Key: a, H_2NNMe_2, CH_2Cl_2; b, Et_3N, Ac_2O, DMAP; c, $CuCl_2 \cdot 2H_2O$, THF, H_2O, pH 7.

in **7a** are endo and therefore in a hindered steric environment. Epimerization at either position 3 or 8 should be facile and synthetically useful, provided ring-opened forms of **7a** can be generated. Epimerization at position 8 leading to compounds with the unnat-trans type stereochemistry found in **4a** and **4b** becomes possible after cyclic hemiacetal **6** is converted to the ring-opened derivative **12** as shown in Scheme I. Aldehyde **12** is epimerized completely to trans aldehyde **13** by exposure to a catalytic amount of NaOMe in methanol for 1 h. Syntheses of examples **4a** and **4b** are then completed using standard methodology.

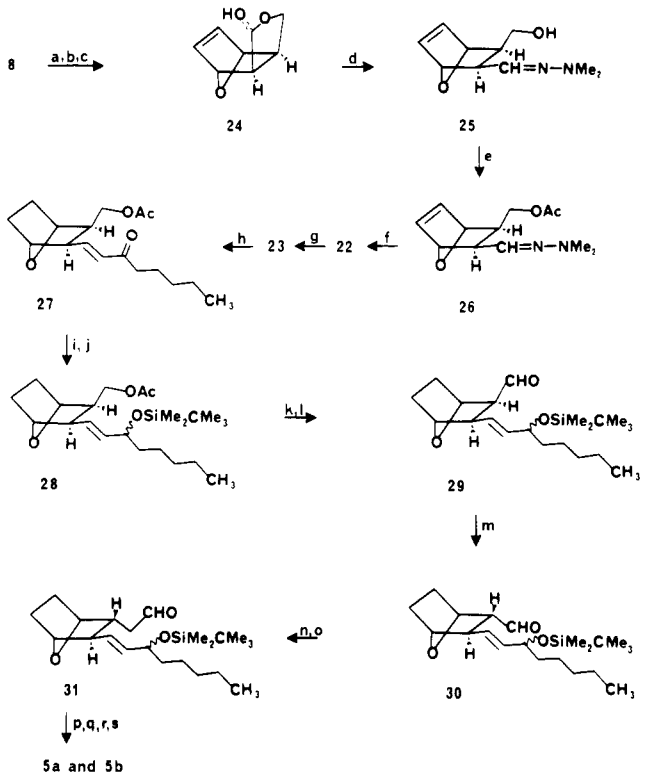
The nat-trans stereochemistry exemplified by **5a** and **5b** should theoretically be available by reversal of the side chain construction sequence. Reaction of the Wadsworth–Emmons reagent with hemiacetal **7c** as shown in Scheme II should produce hydroxy enone **18** in which the stage is set for oxidation and epimerization of the carbinol function at C-3. Unfortunately, the Wadsworth–Emmons reagent was sufficiently basic to cause epimerization of **7c** before coupling which led to **19** as the only enone product in this reaction. We reasoned that this problem might be overcome if the equilibrium exemplified by **7a**–**7b** could be prevented. To arrange for this, we prepared hydrazone **20** which could be acetylated and hydrolyzed to aldehyde **23**. Reaction of hemiacetal **7c** with unsymmetrical dimethylhydrazine gave a mixture of cis and trans hydrazones **20** and **21** in a ratio of 2.3 to 1. Although this ratio was in favor of the desired stereochemistry, neither the alcohols **20** or **21** nor their acetates could be separated in a practical way.

While the experiments outlined in Scheme II were not synthetically useful, they did emphasize the importance of steric considerations in controlling the ratio of cis and trans products. Removal of the endo hydrogen atoms at C-5 and C-6 would be expected to decrease the steric requirements of **7c** and perhaps lead to a more favorable cis–trans product ratio. As shown in Scheme III, this tactic was successful and hydrazone **25** was obtained with less than 5% of the trans isomer present. We were gratified to find that aldehyde **23**, obtained by reduction of the olefinic double bond and hydrolysis of the hydrazone function in **26**, was reactive enough in the Wadsworth–Emmons reaction to give enone **27** uncontaminated by the acetate of isomeric compound **19**. Manipulation of the functional groups in **27** gave aldehyde **29** which, on epimerization to **30**, provided an intermediate suitable for

(16) (a) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675. (b) Corey, E. J.; Noyori, R.; Schaaf, T. K. *J. Am. Chem. Soc.* **1970**, *92*, 2586.

(17) (a) Eggelte, T. A.; DeKoning, H.; Huisman, H. O. *Tetrahedron* **1973**, *29*, 2491–2493. (b) *Ibid.* 2445–2447.

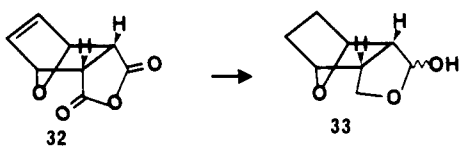
Scheme III[a]



[a] Key: a, pyridine, $(H_3CCO)_2O$; b, $NaBH_4$, THF; c, DIBAL; d, H_2NNMe_2; e, $(H_3CCO)_2O$, DMAP, Et_3N; f, H_2, Pd/C; g, Cu^{2+}, HOH; h, $(MeO)_2POCH^-COC_5H_{11}Na^+$; i, $CeCl_3$, $NaBH_4$; j, *t*-$BuMe_2SiCl$, imidazole, DMF; k, Na_2CO_3, MeOH; l, CrO_3, pyridine; m, NaOMe, MeOH; n, $Ph_3P{=}CHOCH_3$; o, $Hg(OCOCH_3)_2$, KI; p, $Ph_3P{=}CH(CH_2)_3CO_2^-Na^+$; q, CH_2N_2; r, HF, H_3CCN; s, LiOH, HOH, THF.

conversion by standard methods to target nat-trans compounds **5a** and **5b**.

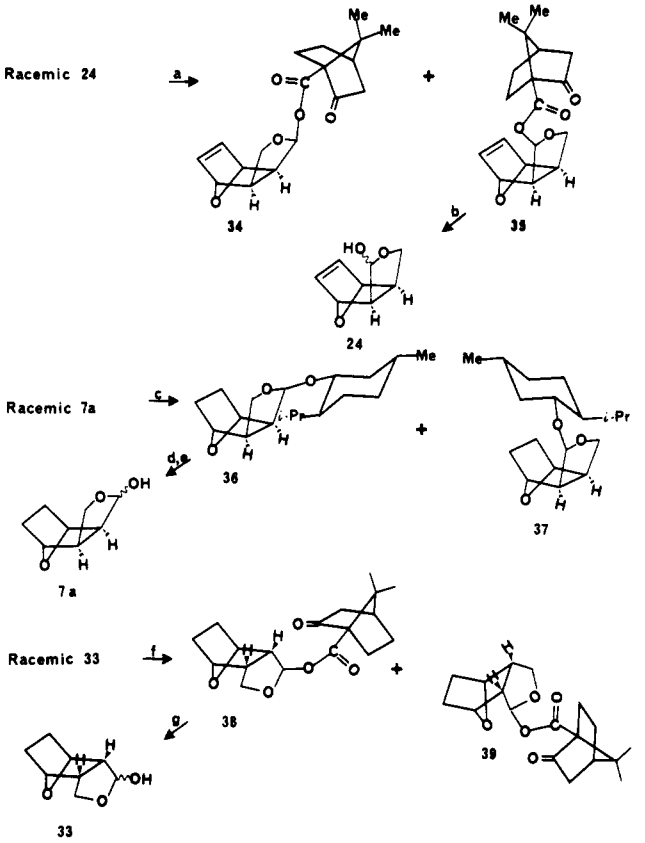
The remaining cis-exo side chain arrangement exemplified by compounds **3a** and **3b** was available by application of the chemistry outlined in Scheme I to the exo hemiacetal **33**. This substance was readily available from the well-known Diels–Alder adduct **32**[18]



The methods described above were applied in the same way to prepare the eight enantiomeric isomers **2–5c,d** using hemiacetal starting materials of appropriate chirality (see below).

This work required a source of chiral hemiacetals **7**, **24**, and **33**. Since hemiacetal **7a** can be generated from the enantiomer of **24** by hydrogenation, resolution of **24** and **33** are sufficient to produce starting materials for all 16 isomers of **1**. Two resolving agents, (−)-menthol and (+)- or (−)-ketopinic acid were used in this work. Of these, ketopinic acid[19] was the most useful primarily because both (+) and (−) acids are now available in over 60% yield from commercially available (+)- and (−)-camphorsulfonic acid.[20] No less important was the observation that ketopinic acid

Scheme IV[a]



[a] Key: a, (+)-ketopinic acid, DMAP, DCC, CH_2Cl_2; b, LiOH, H_2O_2, THF, H_2O; c, (−)-menthol, H^+; d, benzyl alcohol, H^+; e, H_2, Pd/C; f, (−)-ketopinic acid, DMAP, DCC, CH_2Cl_2; g, NaOH, H_2O.

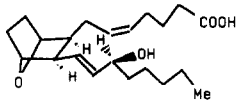
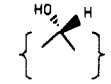
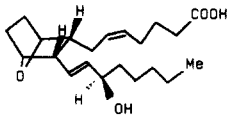
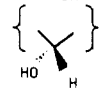
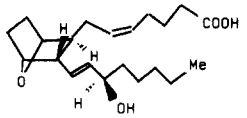
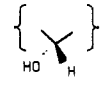
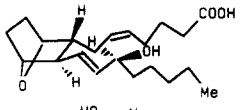
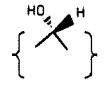
could be attached and removed efficiently under conditions that did not degrade the heterocyclic portion of the molecule. Racemic **24** was esterified as shown in Scheme IV with (+)-ketopinic acid, giving a diastereomeric mixture from which the less soluble isomer **35** could be separated by recrystallization from isopropyl ether. Hydrolysis of the pure diastereomer gave chiral **24**. Although the enantiomer of **24** was convertible to saturated **7a** by reduction over palladium, direct resolution of racemic **7a** using (−)-menthol as the resolving agent was used to provide large quantities of **7a**. This method was attractive because diastereomers **36** and **37** have such different solubilities that complete separation is effected by a single crystallization from methanol. Moreover, diastereomers **36** and **37** have distinctly different CMR spectra, providing a check other than rotation on the degree of resolution attained. (−)-Ketopinic acid was used as shown in Scheme IV to resolve racemic **33**.

Stereochemical Assignments. The absolute configuration of **36** was established by X-ray crystallography. This assignment establishes the absolute stereochemistry of **7a** and also **24** because of the chemical link between **24** and **7c**. The absolute configuration of **33** was established by X-ray crystallography of diastereomer **38**, which was prepared from racemic **33** and (−)-ketopinic acid. Thus, the stereochemistry about the heterocyclic portion of compounds **2–5** is based on X-ray data of diastereomers in which molecules of known absolute configuration have been incorporated. The remaining asymmetric center on the allylic alcohol side chain was assigned in the following way.

Stereochemistry at the allylic alcohol position in prostaglandins and analogue has often been assigned by TLC

(18) Diels, O.; Alder, K. *Ber.* **1929**, *62*, 557.
(19) Bartlett, P. D.; Knox, L. H. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 689.
(20) Haslanger, M. F.; Heikes, J. *Synth.* **1981**, 801.

Table III

No.	Structure	Platelet Aggregation* (I_{50}, μM) AA	ADP	EPI-1°	EPI-2°	TXA**	Cyclo***	Smooth Muscle**** GPT(I_{50}, μM) Hist.	AZO	RSS (A_{50}, μM)
2a		9.2	>1000	>1000	0.6	>1000		>10	2.1	0.22
2b		360	>1000	>1000	130	>1000		>10	>10	>10
3a		Stimulates A_{50} = 2.0 μM				1000		>10	>10	0.0015
3b		0.6	310	670	7.5	1000	>1000	>10	0.12	0.4
4a		4.2	150	>1000	10	770		>10	65	0.51
4b		0.3	1.6	2.2	4.2	1000	>1000	2.4	0.34	2.9
5a		Stimulates A_{50} = 0.26 μM				71% inhib. @ 1000 μM		>10	2.2	0.0009
5b		9.5	>1000	>1000	0.7	>1000	>1000	>10	4.9	0.88

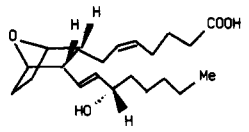
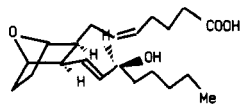
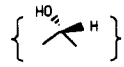
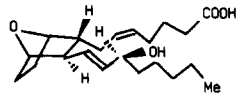
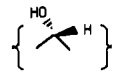
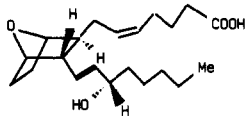
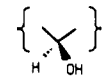
* Inhibition of aggregation of human platelets induced by arachidonic acid (AA), adenosine diphosphate (ADP) and epinephrine (EPI).
** Inhibition of human platelet thromboxane synthetase.
*** Inhibition of sheep seminal vesicle prostaglandin synthetase.
**** GPT = guinea pig trachea stimulated with histamine (HIST) or 9,11-AZO-PGH_2; RSS = rat stomach strip.

behavior arguments that are based on chemical degradation experiments by Samuelsson[21] and others[22] and on the X-ray work done with PGE_2.[23] For compounds structurally very closely related to the natural prostaglandins, these arguments are probably valid. However, we decided to adopt a more rigorous approach to this assignment and used a derivation of the procedures mentioned above. Samples of compounds **2a**, **3b**, **4d**, and **5c** were converted to their methyl ester acetates and degraded by ozonolysis. From the reaction mixture it was possible to isolate chiral 2-hydroxyheptanoic acid as the major product. This was converted without further purification to a methyl ester and then to a menthyl carbonate derivative that, depending on the chirality of the acid, had a characteristic GC retention time. Comparison of this material with derivatives of authentic (+)-, (−) and (±)-2-hydroxyheptanoic acid allowed assignment of the stereochemistry at the alcohol function. This method proved to be reliable for samples as small as 20 mg. Since enantiomeric and diastereomeric relationships exist between the four isomers of each side chain arrangement, these experiments were sufficient to establish the alcohol configurations of all 16 isomers. A recently described degradative method[24] in which aldehydes produced by reductive workup of the ozonolysis reaction are converted to oxazolidines with *l*-ephedrine was employed as a check on our assignments. The same assignments were obtained with either method.

Biology. Platelet Effects. Compounds **2–5** and their enantiomers were evaluated in vitro against platelet aggregation (PA) induced in human platelets (platelet rich plasma) by arachidonic acid (AA), adenosine diphosphate (ADP), and epinephrine (EPI) and against TXA_2 synthetase (from human platelet membranes). The test methods have been described previously,[25] and the results of these tests are presented in Tables III and IV. Two general conclusions become possible on inspection of these platelet data. First, these molecules as a class are active inhibitors of platelet aggregation but ineffective against TXA_2 synthetase and thus, by inference, platelet cyclooxygenase. Isomers **3b**, **4b**, and **5b** were also found inactive as inhibitors of sheep seminal vesicle cyclooxygenase.[25] Second, enantiomers in which the heterocyclic oxygen is α (Table III) are usually more active than their isomers (Table IV). More specifically, these data reveal differences in activity profiles among isomers, depending on their relative chain stereochemistry. The cis-exo isomer **3b**

(21) Nugteren, D. H.; Van Dorp, D. A.; Bergstrom, S.; Hamburg, M.; Samuelsson, B. *Nature* **1966**, *212*, 38.
(22) Hauser, F. M.; Coleman, M. L.; Huffman, R. C.; Carroll, F. I. *J. Org. Chem.* **1974**, *39*, 3426.
(23) Abrahamsson, S. *Acta Crystallogr.* **1963**, *16*, 409.
(24) Just, G.; Oh, H. *Tetrahedron Lett.* **1980**, *21*, 3667–3668.
(25) (a) Harris, D. N.; Phillips, M. B.; Michel, I. M.; Sprague, P. W.; Antonaccio, M. J. *Fed. Proc.* **1980**, *39*, 392. (b) Harris, D. M.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Heikes, J. E.; Sprague, P. W.; Antonaccio, M. J. *Prostaglandins* **1981**, *22*, 295–307.
(26) Vane, J. R. *B. J. Pharmacol.* **1957**, *12*, 344.

Table IV

No.	Structure	Platelet Aggregation* (I_{50}, μM)				TXA**
		AA	ADP	EPI-1°	EPI-2°	
2c		310	>1000	>1000	6	>1000
2d		140	>1000			560
3c		Stimulates A_{50} = 20μM				>1000
3d		93	>1000	>1000	170	>1000
4c		23	>1000	>1000	56	>1000
4d		1000	>1000	670	140	470
5c		Stimulates A_{50} = 30μM				1000
5d		95	>1000	>1000	52	>1000

* Inhibition of aggregation of human platelets induced by arachidonic acid (AA), adenosine diphosphate (ADP) and epinephrine (EPI).

** Inhibition of human platelet thromboxane synthetase.

inhibits PA induced by all the agents tested but is much more potent against AA and the second phase of EPI-induced aggregation. This suggests specificity against TXA_2/PGH_2-mediated events. By contrast, the 15-epimer **3a** is a potent stimulator of PA.

Cis-endo isomer **2a** shows similar specificity as a TXA_2/PGH_2 antagonist although it is 10-fold less potent than **3b**. In this example, epimerization at C-15 (**2b**) does not lead to TXA_2/PGH_2 agonism activity.

Compound **4b** is the most active of the unnat-trans isomers. This molecule, in contrast to any other isomer, causes potent inhibition of aggregation regardless of the inducing agent employed.

The "natural" side chain isomers (nat-trans) **5a** and **5b** are similar in profile to the cis-exo isomers **3a** and **3b**. Thus, TXA_2/PGH_2 agonism (**5a**) or antagonism (**5b**) depends on C-15 stereochemistry. Compound **5a**, which is stereochemically identical with TXA_2, is the most potent agonist in the series.

Smooth Muscle Effects. The compounds in Table III were also tested for direct effects on a rat stomach strip preparation (RSS)[26] and for selectivity as TXA_2/PGH_2 antagonists against histamine and 9,11-AZO-PGH_2-induced contractions of guinea pig trachea (GPT)[27]. The RSS preparation, known to contract in response to all prostanoids except PGA_2 and PGD_2,[28] provides a measure of prostaglandin-like agonist activity. The most active compounds in this test are **3a** and **5a**, which cause contraction of the tissue at nanomolar concentrations. This result, combined with the platelet effects, supports our hypothesis that **3a** and **5a** are TXA_2/PGH_2 agonists. The weak agonist activity shown by carbinol epimers **3b** and **5b** may be due to trace contamination (1%) by **3a** and **5a**.

In the GPT preparation, compounds **2a**, **3b**, **5a**, and **5b** antagonize contractions induced by 9, 11-AZO-PGH_2 but not those caused by histamine. Thus, these compounds are selective TXA_2/PGH_2 antagonists in this tissue. In contrast, **4b** effectively blocks both agents in agreement with the nonspecific activity found for this isomer in the platelet.

Discussion

We have shown that these 7-oxabicyclo[2.2.1]heptane TXA_2/PGH_2 analogues demonstrate three distinct types of biological activity depending on the relative stereochemistry of the side chains and the cabinol function. Inspection of space-filling molecular models of these compounds reveals structural elements in common with the natural products that may be partly responsible for the activities observed. For example, because of constraints imposed by the cis-exo side chain arrangement in **3a**, the hydroxyl group in this molecule occupies the same region in space as does that of the trans-configured **5a** and PGH_2. Thus, **3a** and **5a**, carbinol epimers where **3a** possesses the "unnatural" *R* configuration, are both agonists of TXA_2. These models also show that the cis side chain orientation in **2** and **3** makes these compounds relatively rigid compared to the trans isomers. It is possible that these differences in side chain rigidity play a major role in deter-

(27) Patterson, R. J. *Allergy* **1958**, *29*, 165–172.
(28) Whittle, B. J. R.; Mugridge, K. G.; Moncada, S. *Eur. J. Pharmacol.* **1979**, *53*, 167–172.

mining the degree and kind of activity expressed for each isomer.

Compound **4b**, the only nonselective inhibitor in this series, requires an additional comment. The behavior of **4b** in the platelet and on smooth muscle along with the observation that this compound elevates platelet cAMP[25b] suggests this molecule acts as PGI_2 or PGD_2 receptor agonist. The reason why this isomer alone should function as a PGI_2/PGD_2 agonist is unclear but again points to the importance of side chain stereochemistry for activity.

While our work with 7-oxabicyclo[2.2.1]heptane TXA_2/PGH_2 analogues was in progress,[29] groups in The Netherlands[30] and in Japan[31] were also pursuing stable analogues based on this heterocycle. The Dutch group, employing a similar synthetic method, synthesized racemic examples of **3–5** processing saturated α side chains. The Japanese have limited their investigations to the preparation of racemic **5a** and **5b**, which are reported to be, respectively, an inducer of PA and "inactive".[31]

The Gist–Brocades group have presented data on the effects of racemic 5,6-dihydro derivatives of **3–5** on smooth muscle, in vivo bronchoconstriction in guinea pigs and ADP-induced platelet aggregation in rats.[32] Since their emphasis was on agonist properties of these compounds rather than antagonism of the effects of TXA_2, our results are not directly comparable to theirs. Nevertheless, it is apparent that there are large differences in activity between our compounds and those evaluated by Hall, Funcke, and Jaitly. Part of the difference between our data may be due to the absence of the Δ^5 double bond in the GBR compounds, and experiments are under way in our laboratories to investigate this point. There are also probable differences in our assay procedures that contribute to the disparity among our data. However, we believe most of the discrepancy is due to misassignment of the C-15 carbinol stereochemistry in the GBR compounds.[33]

(29) Presented in part at: International Conference on Prostaglandins, Washington, DC, **1978**; "Advances in Prostaglandin and Thromboxane Research"; Ramwell, P. W., Paoletti, R., Eds.; Raven Press: New York, 1980; Vol. 6, pp 493–496. International Conference on Prostaglandins, Florence, Italy, 1982; "Advances in Prostaglandin and Thromboxane Research"; Samuelsson, B., Paoletti, R., Ramwell, P., Eds.; Raven Press: New York, 1983; Vol. 11, pp 337–343.

(30) Eggelte, T. A.; DeKoning, H.; Huisman, H. O. *J. Chem. Soc., Perkin Trans. 1* **1977**, 980–989.

(31) Kametani, T.; Suzuki, T.; Tomino, A.; Kamada, S.; Unno, K. *Chem. Pharm. Bull.* **1982**, *30*, 796–801.

(32) Hall, D. W. R.; Funcke, A. B. H.; Jaitly, K. D. *Prostaglandins* **1979**, *18*, 317–330.

(33) Diels, O.; Alder, K. *Ann.* **1931**, *240*, 252.

(34) Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1948** *70*, 1161–1166.

(35) We have shown that most of the activity of racemic compounds in this series resides with the enantiomers in which the ring oxygen is α. Assuming the C-15 stereochemistry assignments used by Hall et al. are based on the TLC assignments of DeKoning et al., the active enantiomers in GBR-30726-GBR-30731 possesses C-15 carbinol stereochemistry opposite to that shown in the paper. We believe, for example, the active enantiomers of GBR-30726 and GBR-30727 are 5,6-dihydro-**3a** and 5,6-dihydro-**3b**. Our results with **3a** and **3b** show these isomers contract *RSS* in agreement to the Gist–Brocades results with GBR-30726 and GBR-30727. However, our data show a 260-fold difference in potency between **3a** and **3b**, and our results with **5a** and **5b** (5,6-dihydro derivatives of the active enantiomers in GBR-30729 and GBR-30728) suggest that GBR-30729 should contract *RSS* 1000 times more effectively than GBR-30728. The Gist–Brocade data show these compounds are all nearly equipotent.

Experimental Section

Introduction. All flash chromatography experiments were carried out on a Whatman LPS-1 silica gel using 10–20 psi nitrogen column pressure. Melting points were obtained on a standard Thomas-Hoover apparatus and are uncorrected. CMR spectra were run on a JEOL FX-60Q spectrometer.

***endo,cis*-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Acid (8).** A mixture of maleic acid (982 g, 8.5 mol) and furan (618 mL, 8.5 mol) in water (2100 mL) was stirred at 25 °C for 48 h in a three-neck flask sealed by a greased stopper retained by a rubber band. A small amount of unreacted furan was separated and the aqueous layer clarified by treatment with Norite-A. The solution was chilled to 5 °C and seeded, causing precipitation of 8 (250 g), which was collected by filtration and dried over P_2O_5: mp 149–150 °C (lit.[17] mp 148–149 °C); ^{13}C NMR (D_2O) δ 174.1 (s), 135.1 (d), 79.9 (d), 47.4 (d). Anal. ($C_8H_8O_5$) C, H.

***endo*-1,3,3a,4,7,7a-Hexahydro-4,7-epoxyisobenzofuran-1-ol (24) and *endo*-3a,4,7,7a-Tetrahydro-4,7-epoxyisobenzofuran-1,3-dione (8a).** Compound 8 (200 g, 1.09 mol) was added to a mixture of pyridine (160 mL) and acetic anhydride (200 mL) at −5 °C (ice–salt bath) and the resultant mixture stirred rapidly for 10 min. The mixture was diluted with ether–pentane (1:9, 4 L) and the resulting precipitate separated by filtration: ^{13}C NMR (D_3CCN) δ 170.2 (s), 136.6 (d), 80.8 (d), 48.5 (d). This substance was reduced to lactone **8b** directly as follows.

***endo*-3a,4,7,7a-Tetrahydro-4,7-epoxyisobenzofuran-1(3*H*)-one (8b).** The above anhydride was added to a mixture of sodium borohydride (44 g, 1.16 mol) in THF (3.2 L) at 0 °C and the resultant mixture stirred under a calcium chloride drying tube for 4 h. The solvent was removed under vacuum and the solid residue added slowly with stirring to ice. The resulting mixture was acidified to pH 3 with concentrated HCl and extracted with methylene chloride (6 × 300 mL). The combined extracts were dried ($MgSO_4$) and concentrated to yield **8b**: 100 g (60%), recrystallized from benzene–pentane; mp 121 °C; ^{13}C NMR ($CDCl_3$) δ 174.9 (s), 136.5 (d), 134.0 (d), 80.5 (d), 79.4 (d), 67.8 (t), 47.9 (d), 40.3 (d).

Anal. ($C_8H_8O_3$) C, H. Lactone **8b** was reduced to hemiacetal **24** by the procedure used in preparation of hemiacetal **7a**: 75% from **8b**, recrystallized from benzene–pentane; mp 108–110 °C; ^{13}C NMR ($CDCl_3$) δ 134.2 (d), 97.6 (d), 80.1 (d), 78.9 (d), 66.6 (t), 55.1 (d), 45.6 (d). Anal. ($C_8H_{10}O_3$) C, H.

***endo*-Hexahydro-4,7-epoxyisobenzofuran-1,3-dione (9) and *endo,cis*-7-Oxabicyclo[2.2.1]heptane-2,3-dicarboxylic Acid (8c).** A mixture of 8 (80 g, 0.43 mol) and 10% Pd/C (5 g) in ethanol (800 mL) was stirred on an atmospheric hydrogenation apparatus until uptake of hydrogen ceased (1 h, 9739 mL). The catalyst was removed by filtration and the solvent removed under vacuum to give 80 g of **8c**, which was recrystallized from ethyl acetate–pentane: mp 169–170 °C (lit.[34] mp 168–169 °C); ^{13}C NMR (D_3CCN) δ 174.4 (s), 79.9 (d), 49.4 (d), 26.5 (t). Anal. ($C_8H_{10}O_5$) C, H.

A slurry of **8c** (8.4 g, 0.045 mol) in acetyl chloride (80 mL) was heated at reflux for 30 min. Removal of the acetyl chloride under vacuum and recrystallization of the residue from benzene gave **9**: 6 g (79%); mp 156–158 °C (lit.[35] mp 158–159 °C); ^{13}C NMR ($CDCl_3$) δ 169.2 (s), 78.3 (d), 52.8 (d), 26.2 (d). Anal. ($C_8H_8O_4$) C, H.

***endo*-Hexahydro-4,7-epoxyisobenzofuran-1(3*H*)-one (10).** Anhydride **9** (183 g, 1.09 mol) was converted to **10** by the method used in the synthesis of **8b**: 120 g (71%), recrystallized from heptane; mp 153–155 °C; ^{13}C NMR ($CDCl_3$) δ 176.1 (s), 79.5 (d), 78.2 (d), 66.8 (t), 49.9 (d), 45.1 (d), 27.0 (t), 22.9 (t). Anal. ($C_8H_{10}O_3$) C, H.

(−)-*endo*-Octahydro-4,7-epoxyisobenzofuran-1-ol (7a). Racemic 7a. A solution of **10** (45 g, 0.28 mol) in toluene was cooled to −78 °C and treated with DIBAL (390 mL, 25% in toluene, 0.59 mol) over 10 min. Stirring at −78 °C was continued 30 min when the reaction was quenched with acetic acid (37 g in 200 mL of toluene, 0.62 mol). The mixture was allowed to warm to −30 °C and treated carefully with 10% HCl (300 mL), allowing the reaction temperature to rise to 0 °C (exothermic reaction). The aqueous phase was separated and extracted with $CHCl_3$ (10 × 300 mL). The combined extracts were washed with 5% $NaHCO_3$ (200 mL), dried ($MgSO_4$), and concentrated, yielding

racemic **7a**: 43 g (98%), recrystallized from benzene–cyclohexane; mp 132–133 °C; ^{13}C NMR ($CDCl_3$) δ 97.5 (d), 79.5 (d), 78.0 (d) 65.3 (t), 56.2 (d), 47.3 (d), 25.6 (t), 24.2 (t). Anal. ($C_8H_{12}O_3$) C, H.

Resolution of 7a. A mixture of racemic **7a** (26.6 g, 0.17 mol), *l*-menthol (26.6 g, 0.17 mol), and *p*-toluenesulfonic acid (trace) was heated at reflux in benzene (1.4 L) for 18 h under N_2 in a flask equipped with a condenser and Dean–Stark trap. The mixture was cooled, washed with 5% $NaHCO_3$ (500 mL), and concentrated under vacuum. The crystalline residue was recrystallized from methanol (900 mL), yielding 20.5 g of **36** as a first crop and, after concentration of the filtrate to 500 mL, an additional 2 g was obtained: total 22.5 g (45%); mp 160–162 °C; $[\alpha]^{25}_D$ −193° (*c* 1, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 98.9 (d), 79.5 (d), 78.0 (d), 73.9 (d), 65.1 (t), 55.6 (d), 47.8 (d), 47.5 (d), 39.8 (t), 34.4 (t), 31.3 (d), 25.6 (t), 25.2 (t), 24.2 (t), 22.9 (t), 22.1 (q), 20.9 (q), 15.2 (q).

Subsequent concentration of the filtrate by 50-mL increments (to 350 mL) removed all but 5% of **36** as estimated by ^{13}C NMR. The volume of the filtrate was then reduced to 125 mL whereupon 17.8 g of **37** crystallized from the solution: 36%; mp 88–90 °C; $[\alpha]^{25}_D$ +60° (*c* 2, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 104.8 (d), 79.5 (d), 78.0 (d), 64.8 (t), 55.8 (d), 48.6 (d), 47.3 (d), 43.4 (t), 34.3 (d), 31.6 (d), 25.6 (d and t), 24.2 (t), 23.4 (t), 22.1 (q), 21.0 (q), 16.3 (q).

Acetal Exchange. A mixture of **36** (10 g, 0.034 mol) and *p*-toluenesulfonic acid (trace) was heated in benzyl alcohol (100 mL) at 120 °C for 4 h. The mixture was cooled and partitioned between water and hexane. The hexane layer was washed with water (4 × 500 mL), decolorized with Norite-A, dried ($MgSO_4$), and concentrated, giving the benzyl mixed acetal **36a** of **7a**: 8.3 g (99%); mp 108–110 °C, recrystallized from ethyl acetate; $[\alpha]^{25}_D$ −158° (*c* 10 mg/mL, MeOH); ^{13}C NMR ($CDCl_3$) δ 137.7 (s), 128.2 (d), 127.7 (d), 127.4 (d), 102.1 (d), 79.3 (d), 77.7 (d), 68.4 (t), 65.1 (t), 55.5 (d), 47.2 (d) 25.6 (t), 24.1 (t).

Reduction. A mixture of **36a** (18.0 g, 0.073 mol) and 10% Pd/C (1.8 g) in ethyl acetate (200 mL) was hydrogenated at atmospheric pressure until 1 mol of H_2 was consumed (1 h, 1641 mL). The mixture was filtered and concentrated, yielding **7a**: 11.5 g (89%), recrystallized from cyclohexane–benzene; mp 132 °C; $[\alpha]^{25}_D$ −79° (*c* 10 mg/mL, MeOH).

(−)-*endo*-Octahydro-5,8-epoxy-1*H*-benzopyran-3-ol (6). A slurry of (methoxymethylene)triphenylphosphonium chloride (33.1 g, 0.097 mol) in toluene (800 mL) was treated under argon with a solution of LDA (prepared at −78 °C from 1.6 M *n*-butyllithium (60.05 mL, 0.096 mol) and diisopropylamine (20.5 mL, 0.146 mol) in THF (20 mL)) and stirred at 0 °C for 20 min. Powdered **7a** (5.0 g, 0.032 mol) was added and the mixture stirred at 25 °C for 72 h and then quenched at 0 °C with acetic acid (6.0 g in 50 mL of ether). The mixture was poured into saturated NH_4Cl (250 mL) and extracted with ether (6 × 100 mL). The ether was removed under vacuum and the residue dissolved in warm isopropyl ether. On standing, nearly all the triphenylphosphine oxide precipitated and was removed by filtration. Concentration of the filtrate and purification of the residue by flash chromatography gave a mixture of enol ethers (^{13}C NMR ($CDCl_3$) δ 149.8 (d), 148.4 (d), 100.8 (d), 97.5 (d), 81.3 (d), 80.2 (d), 79.4 (d), 77.9 (d), 60.9 (t), 59.5 (t), 56.3 (q), 45.8 (d), 45.5 (d), 41.5 (d), 37.4 (d), 24.1 (t)) which was dissolved in 20% trifluoroacetic acid–water (38 mL) under argon and stirred at 25 °C for 2 h. The pH was adjusted to 8 with solid $NaHCO_3$ and the solution saturated with salt and extracted with methylene chloride (6 × 200 mL). Concentration gave a mixture that was subjected to a second TFA treatment and workup. The product was purified by flash chromatography, yielding **6**: 2.68 g (55%) from **7a**; $[\alpha]^{25}_D$ −15.6° (*c* 19.2 mg/mL, MeOH); ^{13}C NMR ($CDCl_3$) δ 92.0 (d), 90.4 (d), 80.1 (d), 79.6 (d), 77.5 (d), 59.4 (t), 40.6 (d), 37.6 (d), 35.8 (d), 32.9 (d), 28.4 (t), 26.4 (t), 25.4 (t), 24.8 (t), 24.1 (t).

[1*S*-(1α,2α(*Z*),3α,4α)]-7-[3-(Hydroxymethyl)-7-oxabicyclo[2.2.1]heptan-1-yl]-5-heptenoic Acid (11). A solution of **6** (3.75 g, 0.022 mol) in Me_2SO (10 mL) was added to a mixture of ylide prepared from triphenyl(carboxybutylene)phosphonium bromide (29.3 g, 0.066 mol) and freshly prepared dimsyl in Me_2SO (60 mL) at 25 °C and the reaction mixture stirred at 25 °C under argon for 2 h. The reaction was quenched (0.066 mol of acetic acid in 5 mL of ether) poured into brine (1 L) and extracted with ethyl acetate (4 × 300 mL). The extracts were dried ($MgSO_4$) and concentrated, and the residue was extracted with saturated $NaHCO_3$ solution. The aqueous solution was separated from granular triphenylphosphine oxide and extracted with benzene (3 × 100 mL) followed by ethyl acetate (3 × 300 mL). Acidification (to pH 2 with concentrated HCl) followed by extraction with ether (6 × 200 mL) gave crude **11** from which an additional contaminate crystallized on chilling (0 °C) for 24 h. The filtrate was concentrated, giving 4.0 g of acid **11**: ^{13}C NMR ($CDCl_3$) δ 178.0 (s), 129.2 (d), 128.8 (d), 80.2 (d), 79.7 (d), 60.1 (t), 43.9 (d), 42.1 (d), 33.0 (t), 26.4 (t), 24.3 (t), 23.9 (t), 23.3 (t), 20.5 (t). It was esterified (excess diazomethane in ether) and purified by flash chromatography (elution sequence hexane–ether (1:1) 1 L, ether 2 L) giving **11a**: 2.91 g (49%); $[\alpha]^{25}_{Hg365}$ −23° (*c* 12.5 mg/mL, MeOH); ^{13}C NMR ($CDCl_3$) δ 173.8 (s), 129.2 (d), 128.9 (d), 80.1 (d), 79.5 (d), 60.2 (t), 51.3 (q), 44.2 (t), 42.2 (d), 33.2 (t), 26.5 (t), 24.5 (t), 24.0 (t), 23.3 (t).

[1*S*-(1α,2α(5*Z*),3α,4α)]-7-[3-Formyl-7-oxabicyclo[2.2.1]-heptan-1-yl]-5-heptenoic Acid Methyl Ester (12). A mixture of chromium oxide (6.48 g, 6.4 mmol) and pyridine (10.4 mL, 0.13 mol) in methylene chloride (340 mL) was prepared and stirred at 25 °C under argon for 30 min. Dry Celite (18 g) was added followed by **11a** (2.91 g, 10.8 mmol) dissolved in methylene chloride (15 mL), and stirring was continued for 30 min. The mixture was filtered and the filtrate washed with 5% $NaHCO_3$ (3 × 100 mL), 5% $NaHSO_4$ (2 × 250 mL), and 5% $NaHCO_3$ (200 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in ether, treated with Norite-A, filtered, and concentrated, giving **12**: 2.6 g (90%); ^{13}C NMR ($CDCl_3$) δ 203.1 (d), 173.6 (s), 130.3 (d), 127.8 (d), 80.3 (d), 78.6 (d), 54.8 (d), 51.3 (q), 44.3 (d), 33.2 (t), 26.7 (t), 25.2 (t), 24.5 (t), 23.6 (t). This compound was used in the next reaction without further purification.

[1*S*-(1α,2α(5*Z*),3β,4α)]-7-[3-Formyl-7-oxabicyclo[2.2.1]-hepten-1-yl]-5-heptenoic Acid Methyl Ester (13). A solution of **12** (1.3 g, 4.9 mmol) and NaOMe (commercial preparation, 100 mg) was prepared in MeOH (20 mL) at 0 °C and stirred at 25 °C for 2 h. The mixture was poured into saturated NH_4Cl solution (1 L) and extracted with ether (4 × 100 mL), and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated, giving **13** (1.3 g, quantitative yield). The degree of epimerization was estimated by ^{13}C NMR and judged complete when the aldehyde peak at 203.1 ppm had disappeared (the chemical shift for this atom in **12** is 203.1 ppm and in **13** is 200.6 ppm): ^{13}C NMR ($CDCl_3$) δ 200.6 (d), 173.4 (s), 129.8 (d), 127.3 (d), 78.9 (d), 77.3 (d), 61.6 (d), 51.0 (q), 43.4 (d), 32.8 (t), 29.5 (t), 28.1 (t), 26.3 (t), 24.3 (t), 23.6 (t). This compound was used in the next reaction without further purification.

[1*S*-(1α,2α(5*Z*),3α(1*E*),4α)]-7-[3-(3-Oxo-1-octenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid Methyl Ester (14). A mixture of the anion of dimethyl (2-oxoheptyl)phosphonate (1.11 g, 5.0 mmol) was prepared by reaction with NaH (202 mg, 59% in oil, 4.95 mmol) in dimethoxyethane (100 mL) at 25 °C under argon. After the mixture was stirred for 1 h, **12** (1.3 g, 4.9 mmol) dissolved in dimethoxyethane (10 mL) was added and stirring continued 3 h more. The reaction was quenched with acetic acid (4.95 mmol), and the solvents were removed at 30 °C under vacuum. The residue was dissolved in saturated $NaHCO_3$ and extracted with ether (3 × 100 mL). The combined extracts were washed with water (300 mL and brine (300 mL), dried ($MgSO_4$), and concentrated, giving crude **14** (1.61 g). This was purified by flash chromatography using 9:1 ethyl acetate–hexane as the eluent: yield of trans enone **14** 1.14 g (63%); $[\alpha]^{25}_{Hg365}$ −12° (*c* 14.5 mg/mL, MeOH); ^{13}C NMR ($CDCl_3$) δ 199.0 (s), 173.2 (s), 143.0 (d), 132.7 (d), 129.3 (d), 128.0 (d), 80.9 (d), 79.9 (d), 50.9 (q), 46.2 (d), 45.2 (d), 40.5 (t), 32.9 (t), 31.0 (t), 26.4 (t), 24.8 (t), 24.5 (t), 24.3 (t), 23.4 (t), 22.1 (t), 13.5 (q).

[1*S*-(1α,2α(5*Z*),3β(1*E*),4α)]-7-[3-(3-Oxo-1-octenyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic Acid Methyl Ester (16). The isomeric trans enone **16** was prepared in 64% yield from aldehyde **13** by using the above procedure. Anal. ($C_{22}H_{34}O_4$) C, H. ^{13}C NMR ($CDCl_3$) δ 200.5 (s), 173.4 (s), 148.5 (d), 129.5 (d), 128.7 (d), 127.8 (d), 81.2 (d), 79.2 (d), 53.4 (d), 51.0 (q), 49.8 (d), 39.4 (t), 33.0 (t), 31.2 (t), 29.8 (t), 28.2 (t), 26.4 (t), 24.4 (t), 23.7 (t), 23.5 (t), 22.1 (t), 13.6 (q).

[1*S*-(1α,2α(5*Z*),3α(1*E*,3*S),4α)]-7-[3-(3-Hydroxy-1-octenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid Methyl Ester (15a) and [1*S*-(1α,2α(5*Z*),3α(1*E*,3*R**),4α)]-7-**

[3-(3-Hydroxy-1-octenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid Methyl Ester (15b). A solution of **14** (1.14 g, 3.1 mmol) in MeOH (30 mL) was treated at 0 °C with $CeCl_3 \cdot 8H_2O$ (1.21 g, 3.1 mmol) followed by $NaBH_4$ (122 mg, 3.2 mmol) added over a 1-min period. The resulting mixture was stirred 7 min, poured into saturated NH_4Cl solution, and extracted with ether (3 × 100 mL). The combined extracts were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated, giving a mixture of **15a** and **15b** (1.1g). The mixture was separated by flash chromatography: (using 7.5% ethyl acetate–hexane to elute the less polar **15b**) 610 mg (55%); $[\alpha]^{25}_D$ −23.7° (*c* 6.4 mg/mL, MeOH); ^{13}C NMR ($CDCl_3$) δ 173.6 (s), 137.5 (d), 129.0 (d), 128.8 (d), 126.8 (d), 81.2 (d), 79.9 (d), 72.1 (d), 51.2 (q), 46.0 (d), 44.3 (d), 37.1 (t), 33.0 (t), 31.5 (t), 26.4 (t), 24.8 (t), 24.4 (t), 23.4 (t), 22.3 (t), 13.7 (q); (using 20% ethyl acetate–hexane to elute **15a** 300 mg (27%); $[\alpha]^{25}_D$ −17.8° (*c* 7.4 mg/mL, MeOH); ^{13}C NMR ($CDCl_3$) δ 173.8 (s), 137.5 (d), 129.0 (d), 127.6 (d), 81.3 (d), 80.2 (d), 72.6 (d), 51.3 (q) 46.3 (d), 44.5 (d), 37.3 (t), 31.7 (t), 26.7 (t), 25.0 (t), 24.7 (t), 23.6 (t), 22.5 (t), 13.9 (q).

[1*S*-(1α,2α(5*Z*),3β(1*E*,3*S),4α)]-7-[3-(3-Hydroxy-1-octenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid Methyl Ester (17b) and [1*S*-(1α,2α(5*Z*),3β(1*E*,3*R**),4α)]-7-[3-(3-Hydroxy-1-octenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid Methyl Ester (17a).** The isomeric esters **17a** and **17b** were prepared from enone **16** by using the above method.

17b: 49%; $[\alpha]^{25}_D$ −31° (*c* 7.2 mg/mL, MeOH); ^{13}C NMR ($CDCl_3$) δ 173.7 (s), 134.1 (d), 132.3 (d), 129.1 (d), 128.5 (d), 82.1 (d), 79.1 (d), 72.4 (d), 53.4 (d), 51.2 (q), 50.3 (d), 37.1 (t), 33.2 (t), 31.5 (t), 30.0 (t), 28.2 (t), 26.4 (t), 24.9 (t), 24.5 (t), 23.4 (t), 22.4 (t), 13.8 (q).

17a: 34%; $[\alpha]^{25}_D$ −38° (*c* 6.1 mg/mL, MeOH); ^{13}C NMR ($CDCl_3$) δ 173.7 (s), 134.3 (d), 132.1 (d), 129.0 (d), 128.5 (d), 81.9 (d), 79.2 (d), 72.5 (d), 53.4 (d), 51.2 (q), 50.4 (d), 37.1 (t), 33.2 (t), 31.5 (t), 30.0 (t), 28.3 (t), 26.5 (t), 24.9 (t), 24.5 (t), 23.4 (t), 22.4 (t), 13.8 (q).

[1*S*-(1α,2α(5*Z*),3α(1*E*,3*S),4α)]-7-[3-(3-Hyroxy-1-octenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid (2a) and [1*S*-(1α,2α(5*Z*),3α(1*E*,3*R**),4α)]-7-[3-(3-Hydroxy-1-octenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid (2b).** A solution of **15b** (610 mg, 1.7 mmol) in THF (90 mL) and water (17 mL) at 0 °C under argon was treated with LiOH (773 mg, 18 mmol) in water (17 mL) and the resulting mixture stirred at 0 °C 1 h followed by 4 h at 25 °C. The mixture was acidified (pH 3) with saturated oxalic acid and poured into water (700 mL). Extraction with ether (3 × 100 mL) followed by washing the combined extracts with water (100 mL) and brine (100 mL), drying ($MgSO_4$), and concentration gave **2a** as an oil. This was purified by chromatography on a short $^1/_2$ in. × 4 in. silica gel column (ether as eluent) and millipore filtering (in 95:5 cyclohexane–ether on 0.4-μm Millipore membrane) to give **2b**: 340 mg (57%); $[\alpha]^{25}_D$ −25° (*c* 6 mg/mL, MeOH). Anal. ($C_{21}H_{34}O_4$) C, H. ^{13}C NMR ($CDCl_3$) δ 177.1 (s), 136.9 (d), 129.3 (d), 129.0 (d), 128.1 (d), 81.2 (d), 80.1 (d), 72.9 (d), 46.3 (d), 44.6 (d), 36.9 (t), 32.7 (t), 26.3 (t), 25.0 (t), 24.7 (t), 24.3 (t), 23.6 (t), 22.4 (t), 13.9 (q).

In the same way **15a** was converted to **2a**: $[\alpha]^{25}_D$ −20° (*c* 4.8 mg/mL, MeOH). Anal. ($C_{21}H_{34}O_4$) C, H. ^{13}C NMR ($CDCl_3$) δ 177.7 (s), 137.0 (d), 129.2 (d), 129.0 (d), 127.4 (d), 81.3 (d), 80.2 (d), 72.6 (d), 46.3 (d), 44.5 (d), 37.1 (t), 33.0 (t), 31.7 (t), 26.5 (t), 25.0 (t), 24.7 (t), 24.3 (t), 23.6 (t), 22.5 (t), 13.9 (q).

The same procedure was used to convert **17a** and **17b** to **4a** and **4b**.

4a: $[\alpha]^{25}_D$ −43° (*c* 8.5 mg/mL, MeOH). Anal. ($C_{21}H_{34}O_4$) C, H. ^{13}C NMR ($CDCl_3$) δ 177.3 (s), 134.9 (d), 131.5 (d), 129.3 (d), 128.4 (d), 81.9 (d), 79.1 (d), 72.9 (d), 53.5 (d), 50.7 (d), 36.9 (t), 32.9 (t), 31.5 (t), 30.8 (t), 28.0 (t), 26.3 (t), 24.9 (t), 24.4 (t), 23.3 (t), 22.4 (t), 13.9 (q).

4b: $[\alpha]^{25}_D$ −31° (*c* 5 mg/mL, MeOH). Anal. ($C_{21}H_{34}O_4$) C, H. ^{13}C NMR ($CDCl_3$) δ 177.7 (s), 134.5 (d), 131.8 (d), 129.2 (d) 128.6 (d), 82.1 (d), 79.3 (d), 72.6 (d), 53.4 (d), 50.6 (d), 36.9 (t), 33.2 (t), 31.6 (t), 30.1 (t), 28.3 (t), 26.5 (t), 25.0 (t) 24.5 (t), 23.5 (t), 22.5 (t), 13.9 (q).

Resolution of 24. A solution of racemic **24** (53.2 g, 0.34 mol), *l*-ketopinoyl chloride (70 g, 0.35 mol), and 4-(dimethylamino)-pyridine (1 g, 8 mmol) in pyridine (500 mL) was stirred at 25 °C for 18 h. The reaction mixture was concentrated under vacuum and the residue diluted with water and extracted with methylene chloride (3 × 300 mL). The combined extracts were dried ($MgSO_4$) and concentrated, yielding a solid mixture of **34** and **35** from which pure **35** was separated by multiple recrystallization (four times from isopropyl ether): yield 19 g; mp 123–125 °C; $[\alpha]^{25}_D$ +58° (*c* 10 mg/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 210.4 (s), 169.1 (s), 134.3 (d) 98.4 (d), 80.2 (d), 78.9 (d), 68.3 (t), 54.3 (d), 49.1 (s), 45.0 (d), 44.4 (d), 43.8 (t), 26.2 (t), 21.3 (q), 19.7 (q). A solution of **35** (6.36 g, 20 mmol), lithium hydroxide (20 mL of 1 N solution, 20 mmol) and hydrogen peroxide (30%, 0.23 mL, 20 mmol) in THF (100 mL) was stirred vigorously in a Morton flask at 25 °C for 2 h. Sodium thiosulfate (5 mL, 5% solution) was added, and the mixture was saturated with NaCl and extracted with $CHCl_3$ (10 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated and the residue recrystallized from benzene–cyclohexane, giving **24**: 3 g; mp 99–100 °C; $[\alpha]^{25}_D$ +67° (*c* 10 mg/mL, $CHCl_3$).

[(1*S*-(1α,2α,3α,4α)]-3-(Hydroxymethyl)-7-oxabicyclo-[2.2.1]hepten-2-ylcarboxaldehyde 1,1-Dimethylhydrazone (25). A solution of **24** (2.8 g, 18 mmol) and 1,1-dimethylhydrazine (2.2 g, 37 mmol) in methylene chloride (50 mL) was stirred at 25 °C for 18 h. The mixture was concentrated under vacuum, giving **25** (3.5 g, 100%) which was used without further purification in the preparation of **26**: ^{13}C NMR ($CDCl_3$) δ 135.1 (d), 134.8 (d), 80.6 (d), 80.3 (d), 61.5 (t), 46.1 (d), 44.1 (d), 42.6 (q).

[1*S*-(1α,2α,3α,4α)]-3-(Acetoxymethyl)-7-oxabicyclo-[2.2.1]hepten-2-ylcarboxaldehyde 1,1-Dimethylhydrazone (26). A solution of **25** (11.5 g, 59 mmol), triethylamine (61 g, 0.6 mol), and 4-(dimethylamino)pyridine (0.46 g, 3.8 mmol) in acetic anhydride (31 g, 0.3 mol) was stirred at 25 °C for 2 h. The mixture was concentrated under vacuum, poured into ice water, and extracted with methylene chloride (2 × 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography (1:1 ether–hexane as eluent), giving **26**: 14 g (100%); ^{13}C NMR ($CDCl_3$) δ 170.4 (s), 135.7 (d), 134.7 (d), 132.8 (d), 80.9 (d), 80.1 (d), 63.9 (t), 44.7 (d), 42.6 (q), 41.8 (q), 20.6 (q).

[1*S*-(1α,2α,3α,4α)]-3-(Acetoxymethyl)-7-oxabicyclo-[2.2.1]heptan-2-ylcarboxaldehyde 1,1-Dimethylhydrazone (22). A mixture of **26** (2.1 g, 8.8 mmol) and 10% Pd/C (200mg) in ethyl acetate (100 mL) was hydrogenated at 1 atm until 1 equiv (197 mL) of hydrogen was absorbed (10 min). The mixture was filtered through Celite and concentrated, giving **22** as an oil: 2.1 g (99%); ^{13}C NMR ($CDCl_3$) δ 169.8 (s), 131.2 (d), 79.5 (d), 78.5 (d), 61.9 (t), 45.2 (d), 42.2 (d), 41.9 (d), 24.3 (t), 23.7 (t), 20.0 (q).

[1*S*-(1α,2α(1*E*),3α,4α)]-3-(Acetoxymethyl)-2-(3-oxo-1-octenyl)-7-oxabicyclo[2.2.1]heptane (27) and [1*S*-(1α,2α,3α,4α)]-3-(Acetoxymethyl)-7-oxabicyclo[2.2.1]heptan-2-ylcarboxaldehyde (23). A solution of $CuCl_2 \cdot 2H_2O$ (2.98 g, 17.6 mmol) in pH 7 phosphate buffer (140 mL) was added to a solution of **22** (2.1 g, 8.8 mmol) in THF (130 mL) and the mixture stirred at 25 °C for 2 h. The mixture was concentrated to a volume of 150 mL, diluted with methylene chloride (300 mL), and filtered through Celite. The filtrate was washed with 5% $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated under vacuum, giving **23**. Since this compound is easily epimerized, it was converted immediately to **27**. Aldehyde **23** in dimethoxyethane (5 mL) was added to a mixture of dimethyl (2-oxoheptyl)phosphate anion (prepared by stirring dimethyl 2-oxoheptylphosphate (4.0g, 18mmol) in dimethoxyethane (70 mL) with NaH (59% in oil, 676 mg, 16.6 mmol) for 2 h at 25 °C) and the resultant mixture stirred for 2 h at 25 °C. The reaction was quenched with 1 equiv of acetic acid and the mixture concentrated under vacuum. The residue was partitioned between ether and 5% $NaHCO_3$ solution and the ether layer separated, dried ($MgSO_4$) and concentrated, giving crude **27**. This was purified by flash chromatography (1:3 ether–pentane as eluent), giving enone **27**: 1.6 g (62%); $[\alpha]^{25}_D$ +4° (*c* 20 mg/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 199.1 (s), 170.2 (s), 141.0 (d), 133.4 (d), 80.6 (d), 78.9 (d), 61.7 (t), 45.8 (d), 43.6 (d), 40.3 (t), 31.1 (t), 24.6 (t), 24.1 (t), 23.5 (t), 22.1 (t), 20.4 (q), 13.6 (q).

[1*S*-(1α,2α(1*E*),3α,4α)]-3-(Acetoxymethyl)-2-[3-[(*tert*-butyldimethylsilyl)oxy]-1-octenyl]-7-oxabicyclo[2.2.1]heptane (28). A mixture of **27** (1.4 g, 4.8 mmol) and $CeCl_3 \cdot 8H_2O$ (1.86 g, 4.8 mmol) in MeOH (25 mL) was chilled to 0 °C and treated over 30 s with $NaBH_4$ (181 mg, 4.8 mmol). After stirring 7 min, the mixture was poured into saturated NH_4Cl solution and extracted

with ether (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated, giving a mixture of allylic alcohols: 1.4 g (100%); $[\alpha]^{25}_D$ −17° (*c* 30 mg/mL, $CHCl_3$). A solution of this with 4-(dimethylamino)pyridine (57 mg, 0.47 mmol), triethylamine (710 mg, 7 mmol), and *tert*-butyldimethylsilyl chloride (771 mg, 5.1 mmol) in DMF (18 mL) was stirred 2 h at 25 °C. The mixture was poured into water (300 mL) and extracted with ether (3 × 50 mL). The combined extracts were washed (brine), dried ($MgSO_4$), and concentrated, giving **28**: 1.93 g (99%); $[\alpha]^{25}_D$ −8.1° (*c* 20 mg/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 172.6 (s), 141.0 (d), 126.2 (d), 125.9 (d), 83.2 (d), 81.2 (d), 75.2 (d), 74.9 (d), 64.9 (t), 47.7 (d), 44.9 (d), 40.3 (t), 33.7 (t), 27.8 (q), 26.8 (t), 26.0 (t), 24.5 (t), 22.8 (q), 20.2 ns), 16.0 (q), −4.4 (q), −4.8 (q).

[1*S*-(1α,2α,3α(1*E*),4α)]-3-[3-[(*tert*-Butyldimethylsilyl)oxy]-1-octenyl]-7-oxabicyclo[2.2.1]heptan-2-ylcarboxaldehyde (29) and [1*S*-(1α,2α(1*E*),3α,4α)]-2-(3-[(*tert*-Butyldimethylsilyl)oxy]-1-octenyl]-3-(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane (28a). A mixture of **28** (1.8 g, 4.4 mmol) and K_2CO_3 (260 mg, 1.9 mmol) in MeOH (40 mL) was stirred at 25 °C for 1 h. The mixture was poured into water and extracted with ether (3 × 100 mL); the extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (1:3 ether–pentane as eluent), giving carbinol **28a**: 1.46 g (91%); $[\alpha]^{25}_D$ −1.3° (*c* 20 mg/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 138.4 (d), 124.6 (d), 124.3 (d), 81.1 (d), 79.4 (d), 73.0 (d), 72.6 (d), 60.8 (t), 46.3 (d), 45.6 (d), 38.1 (t), 31.6 (t), 25.7 (q), 24.6 (t), 24.4 (t), 23.9 (t), 22.3 (t), 17.9 (s), 13.8 (q), −4.4 (q), −4.8 (q). This compound in methylene chloride (10 mL) was added to a mixture of Collins reagent (prepared by stirring a mixture of pyridine (4.19 mL, 52 mmol) and chromium trioxide (2.6 g, 17 mmol) in methylene chloride (135 mL) at 25 °C for 20 min followed by addition of Celite (10 g)) and stirred at 25 °C for 25 min. The mixture was filtered through Celite, washed with 5% $NaHCO_3$, 5% $KHSO_4$, and water, dried ($MgSO_4$), and concentrated, giving **29**: 1.38 g (95%); $[\alpha]^{25}_D$ +26° (*c* 30 mg/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 202.5 (d), 139.2 (d), 124.6 (d), 124.4 (d), 81.4 (d), 78.3 (d), 72.8 (d), 72.6 (d), 57.2 (d), 46.5 (d), 38.1 (t), 31.7 (t), 25.8 (q), 24.7 (t), 24.5 (t), 22.5 (t), 18.1 (s), 13.9 (q), −4.4 (q), −4.8 (q).

[1*S*-(1α,2β,3α(1*E*),4α)]-3-[3-[(*tert*-Butyldimethylsilyl)oxy]-1-octenyl]-7-oxabicyclo[2.2.1]heptan-2-ylcarboxaldehyde (30). A solution of **29** (1.07 g, 2.9 mmol) and sodium methoxide (36 mg, 0.7 mmol) in methanol (40 mL) was stirred at 25 °C for 1 h. The mixture was poured into saturated NH_4Cl solution and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated, giving **30**: 1.07 g (100%); $[\alpha]^{25}_D$ +39° (*c* 30 mg/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 200.3 (d), 137.5 (d), 126.4 (d), 126.2 (d), 80.2 (d), 77.8 (d) 72.9 (d), 61.5 (d), 46.2 (d), 38.1 (t), 31.7 (t), 29.9 (t), 25.8 (q), 24.8 (t), 24.5 (t), 22.5 (t), 18.2 (s), 13.9 (q), −4.4 (q), −4.8 (q).

[1*S*-(1α,2β(5*Z*),3α(1*E*),4α)]-7-[3-[3-[(*tert*-Butyldimethylsilyl)oxy]-1-octenyl]-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid Methyl Ester (31b). Aldehyde **30** (10.8 g, 29.2 mmol) was converted to a mixture of methyl enol ethers by the procedure used in the preparation of **6**. The enol ether mixture (10.3 g, 90% from **30**, $[\alpha]^{25}_D$ +18° (*c* 30 mg/mL, $CHCl_3$)) in THF/water (70 mL, 10:1) was chilled to 0 °C, treated with solid $Hg(OAc)_2$ (41.6 g, 0.13 mol), and stirred at 0 °C for 1 h. The mercury complex was reduced by pouring the mixture into 10% KI solution (2 L) and shaking until the yellow color was discharged. The mixture was extracted with benzene (3 × 300 mL), and the combined extracts were washed with 10% KI solution, dried ($MgSO_4$), and concentrated, giving crude **31**. This compound in THF (30 mL) was added to a mixture of (4-carboxybutylenetriphenylphosphorane (prepared from (4-carboxybutylene)triphenylphosphonium bromide (46.4 g 0.105 mol) in THF (780 mL) and stirred at 0 °C for 2 h. The reaction was quenched with 1 equiv of acetic acid, concentrated to 100-mL volume, poured into saturated NH_4Cl (2 L), and extracted with ether (4 × 100 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated, giving crude acid **31a**. The accompanying triphenylphosphine oxide was removed by crystallization from a solution of crude **31a** in ether–pentane (1:9). The remaining compound (15 g) was esterified with excess diazomethane and chromatographed as the methyl ester (ether–hexane, 1:9 as eluent), giving **31b**: 11.5 g (82% from **30**); $[\alpha]^{25}_D$ +38° (*c* 20 mg/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 173.8 (s), 136.1 (d), 135.8 (d), 129.7 (d), 128.8 (d), 128.6 (d), 80.9 (d), 80.5 (d), 73.4 (d), 52.6 (d), 51.3 (q), 50.0 (d), 38.2 (t), 33.4 (t), 32.4 (t), 31.7 (t), 30.0 (t), 26.6 (t), 25.8 (q), 24.8 (t), 24.1 (t), 22.5 (t), 18.1 (s), 13.9 (q), −4.4 (q), −4.8 (q).

[1*S*-(1α,2β(5*Z*),3α(1*E*,3*S),4α)]-7-[3-(3-Hydroxy-1-octenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid Methyl Ester (31d) and [1*S*-(1α,2β(5*Z*),3α(1*E*,3*R**),4α)]-7-[3-(3-Hydroxy-1-octenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid Methyl Ester (31e).** A mixture of **31b** (11.5 g, 24 mmol), tetrabutylammonium fluoride (75.4 g, 0.29 mol), acetic acid (57.8 g), and THF (240 mL) was stirred at 50 °C for 16 h. The mixture was concentrated under vacuum, diluted with ether, and poured slowly with stirring into cold 5% $NaHCO_3$. The ether layer was separated and the aqueous layer extracted with additional ether (2 × 100 mL). The combined extracts were washed with brine and concentrated, giving a mixture of isomers epimeric at the carbinol position. This mixture was separated by flash chromatography (ethyl acetate–hexane 1:9 for less polar isomer, 3:7 for more polar isomer). **31c**: 5.2 g; $[\alpha]^{25}_D$ +30° (*c* 10 mg/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 174.0 (s), 135.4 (d), 129.9 (d), 128.6 (d), 80.8 (d), 80.4 (d), 72.5 (d), 52.7 (d), 51.3 (q), 50.2 (d), 37.3 (t), 33.3 (t), 32.3 (t), 31.7 (t), 30.0 (t), 26.6 (t), 25.0 (t), 24.7 (t), 24.2 (t), 22.5 (t), 13.9 (q). **31d**: 2.7 g; $[\alpha]^{25}_D$ +38° (*c* 30 mg/ml, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 173.9 (s), 135.5 (d), 130.2 (d), 129.7 (d), 128.6 (d), 80.9 (d), 80.4 (d), 72.7 (d), 52.8 (d)8 51.3 (q), 50.1 (d), 37.3 (t), 33.4 (t), 32.3 (t), 31.6 (t), 30.0 (t), 26.6 (t), 25.0 (t), 24.8 (t), 24.2 (t), 22.5 (t), 13.9 (q).

[1*S*-(1α,2β(5*Z*),3α(1*E*,3*S),4α)]-7-[3-(3-Hydroxy-1-octenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid (5a) and [1*S*-(1α,2β(5*Z*),3α(1*E*,3*R**),4α)]-7-[3-(3-Hydroxy-1-octenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid (5b).** Esters **31c** and **31d** were converted to **5b** and **5a** by the same methods employed for **2a** and **2b**, **5b**: 4.8 g (98%); $[\alpha]^{25}_D$ +33° (*c* 10 mg/mL, ether. Anal. ($C_{21}H_{34}O_4$) C, H. ^{13}C NMR ($CDCl_3$) δ 175.8 (s), 136.4 (d), 130.7 (d), 130.6 (d), 129.6 (d), 81.7 (d), 81.2 (d), 73.0 (d), 53.8 (d), 51.0 (d), 38.2 (t), 33.8 (t), 33.1 (t), 32.5 (t), 30.8 (t), 27.3 (t), 25.8 (t), 25.6 (t), 24.9 (t), 23.4 (t), 14.4 (q). **5a**: 2.1 g (81%); $[\alpha]^{25}_D$ +47° (*c* 12 mg/mL, ether). Anal. ($C_{21}H_{34}O_4$) C, H. ^{13}C NMR ($CDCl_3$) δ 175.9 (s), 136.4 (d), 130.7 (d), 129.6 (d), 81.8 (d), 81.2 (d), 73.1 (d), 53.8 (d), 50.9 (d), 38.2 (t), 33.8 (t), 32.5 (t), 30.8 (t), 27.3 (t), 25.9 (t), 25.6 (t), 25.0 (t), 23.4 (t), 14.4 (q).

Resolution of 33. A mixture of racemic **33** (61.7 g, 0.39 mol), *l*-ketopinic acid (72 g, 0.39 mol), 4-(dimethylamino)pyridine (48.3 g, 0.39 mol), and dicyclohexylcarbodiimide (81.5 g, 0.39 mol) in methylene chloride (270 mL) was stirred at 25 °C for 72 h and then filtered. The filtrate was washed with 5% $NaHCO_3$ (100 mL), 10% $KHSO_4$ (100 mL), and water (100 mL) and concentrated and the residue recrystallized three times from ether, giving **38**: 22.5 g (18%); mp 148–150 °C; $[\alpha]^{25}_D$ +48° (*c* 20 mg/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 210.3 (s), 168.8 (s), 103.0 (d), 81.3 (d), 78.2 (d), 67.7 (s), 55.3 (d), 48.8 (s), 46.7 (d), 44.3 (d), 43.6 (t), 28.5 (t), 28.0 (t), 25.9 (t), 21.2 (q), 19.5 (q).

A mixture of **38** (21 g, 0.07 mol) and 1 N NaOH (131 mL) in THF (360 mL) was stirred rapidly in a Morton flask for 18 h. The THF was removed under vacuum and aqueous layer was extracted with chloroform (20 × 100 mL) and the combined extracts were concentrated to give **33**: 10 g (97%); mp 65–67 °C; $[\alpha]^{25}_D$ +46° (*c* 20 mg/mL, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 102.5 (d), 98.6 (d), 81.2 (d), 78.5 (d), 77.9 (d), 77.2 (d), 71.5 (t), 68.8 (t), 56.4 (d), 53.4 (d), 49.0 (d), 47.8 (d), 28.8 (t), 28.6 (t), 28.4 (t), 27.5 (t).

Anhydride **32** was converted to racemic **33** by using the same procedure employed in the preparation of **7a** from **8** (**8** → **8a** → **10** → **7a**).

[1*S*-(1α,2β(5*Z*),3β(1*E*,3*R),4α)]-7-[3-(3-Hydroxy-1-octenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid (3a) and [1*S*-(1α,2β(5*Z*),3β(1*E*,3*S**),4α)]-7-[3-(3-Hydroxy-1-heptenyl)-7-oxabicyclo[2.2.1]heptan-2-yl]-5-heptenoic Acid (3b).** Hemiacetal **33** was converted to **3a** and **3b**, employing the same methodology used in the synthesis of **2a** and **2b**. **3a**: $[\alpha]^{25}_D$ +44° (*c* 20 mg/mL, MeOH). Anal. ($C_{21}H_{34}O_4$) C, H. ^{13}C NMR ($CDCl_3$) δ 177.6 (s), 133.9 (d), 130.8 (d), 130.3 (d), 129.4 (d), 81.8 (d), 79.4 (d), 72.6 (d), 50.5 (d), 48.5 (d), 36.9 (t), 32.9 (t), 31.6 (t), 29.5 (t), 28.0 (t), 26.3 (t), 25.0 (t), 24.3 (t), 22.4 (t), 13.9 (q). **3b**: $[\alpha]^{25}_D$ +47° (*c* 11.4 mg/mL, MeOH). Anal. ($C_{21}H_{34}O_4$) C, H. ^{13}C NMR ($CDCl_3$) δ 177.1 (s), 133.7 (d), 131.7 (d), 130.4 (d), 129.3 (d), 81.9

Table V. Fractional Atomic Coordinates and Their Estimated Errors

36				38			
atom	x	y	z	atom	x	y	z
O1	0.4313 (6)	0.0627 (0)	0.3715 (2)	0.1	−0.6302 (6)	−0.0208 (0)	−0.9470 (4)
O10	−0.0778 (6)	0.03761 (5)	0.4118 (2)	010	−0.9114 (6)	−0.2700 (6)	−0.9863 (3)
O11	0.3110 (5)	0.0757 (5)	0.2424 (2)	011	−0.6219 (6)	0.0761 (5)	−0.7724 (3)
				012	−0.6308 (7)	0.2955 (6)	−0.8560 (4)
				018	−0.6566 (7)	0.2427 (11)	−0.5569 (5)
C2	0.3536 (8)	0.1637 (7)	0.3106 (3)	C2	−0.7394 (9)	0.0141 (9)	−0.8686 (5)
C3	0.1200 (9)	0.2344 (8)	0.3270 (3)	C3	−0.8086 (8)	−0.1266 (8)	−0.8292 (5)
C4	0.1197 (9)	0.3958 (8)	0.3703 (3)	C4	−0.9846 (9)	−0.1925 (8)	−0.9021 (6)
C5	0.3228 (10)	0.4045 (9)	0.4339 (4)	C5	−1.0591 (9)	−0.3171 (9)	−0.8403 (6)
C6	0.2397 (10)	0.2875 (8)	0.4920 (3)	C6	−0.9037 (10)	−0.4321 (8)	−0.8421 (6)
C7	0.0070 (9)	0.2313 (8)	0.4514 (3)	C7	−0.7772 (9)	−0.3547 (9)	−0.9122 (6)
C8	0.0363 (8)	0.1170 (8)	0.3854 (3)	C8	−0.6593 (9)	−0.2395 (8)	−0.8456 (5)
C9	0.2258 (10)	−0.0133 (8)	0.3964 (3)	C9	−0.5336 (9)	−0.1558 (9)	−0.9130 (6)
C12	0.5202 (9)	0.0319 (7)	0.2081 (3)	C12	−0.5716 (8)	0.2181 (8)	−0.7788 (5)
C13	0.5816 (9)	0.1686 (8)	0.1577 (3)	C13	−0.4307 (8)	0.2644 (9)	−0.6814 (5)
C14	0.7880 (9)	0.1289 (8)	0.1153 (3)	C14	−0.3629 (12)	0.4246 (10)	−0.6851 (8)
C15	0.7316 (11)	−0.0255 (9)	0.0691 (3)	C15	−0.1793 (12)	0.4301 (10)	−0.6000 (7)
C16	0.6733 (10)	−0.1634 (8)	0.1195 (3)	C16	−0.1669 (9)	0.2815 (8)	−0.5509 (6)
C17	0.4672 (9)	−0.1248 (7)	0.1648 (3)	C17	−0.3190 (11)	0.2645 (13)	−0.4830 (6)
C18	0.3979 (10)	−0.2679 (9)	0.2146 (3)	C18	−0.4997 (11)	0.2542 (12)	−0.5682 (6)
C19	0.5952 (12)	−0.3237 (10)	0.2709 (4)	C19	−0.2364 (9)	0.1829 (8)	−0.6496 (6)
C20	0.2981 (12)	−0.4062 (9)	0.1644 (4)	C20	−0.2547 (12)	0.0260 (10)	−0.6191 (8)
C21	0.8489 (11)	0.2670 (9)	0.0650 (4)	C21	−0.1230 (11)	0.1882 (15)	−0.7430 (7)

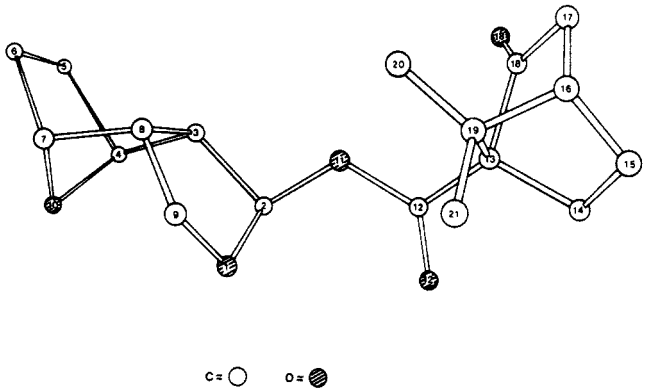


Figure 1. Solid-state conformation of **38**.

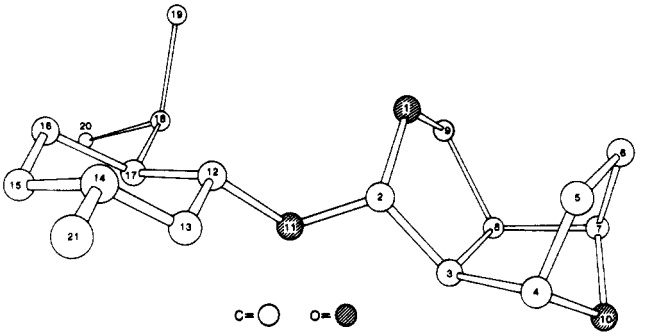


Figure 2. Solid-state conformation of **36**.

(d), 79.4 (d), 73.2 (d), 50.7 (d), 48.8 (d), 36.9 (d), 32.7 (d), 31.6 (d), 29.6 (t), 29.1 (t), 27.8 (t), 26.3 (t), 25.0 (t), 24.3 (t), 22.5 (t), 13.9 (q).

X-ray Analyses of 36 and 38. Both compounds crystallize in monoclinic structures (space group $P2$, $Z = 2$), which were solved by direct methods and refined by least-squares methods assuming anisotropic thermal parameters for all of the non-hydrogen atoms. Hydrogen atoms were introduced at expected positions but were not refined.

Intensities for each structure were collected diffractometrically at ambient temperature using the θ–2θ variable scan rate technique (Cu Kα, $\lambda = 1.5418$ Å, $2\theta_{max} \leq 115°$). Only intensities for which $I \geq 2.5\sigma(I)$ were used in the refinements. Least-squares weights $w = \sigma^{-2}(F_o)$ were assigned assuming $\sigma^2(I) = \epsilon^2 + (pI)^2$ where ϵ is the statistical counting error and $p = 0.02$.

For **38**: $a = 7.220$ (2), $b = 9.219$ (3), $c = 12.406$ (4) Å; $\beta = 100.34$ (3)°; $d_{obsd} = 1.33$, $d_{calcd} = 1.31$ g cm^{-3}; $R = 0.06$ for 826 intensities. For **36**: $a = 5.761$ (1), $b = 8.266$ (2), $c = 17.838$ (7) Å; $\beta = 96.72$ (2)°; $d_{calcd} = 1.16$ g cm^{-3}; $R = 0.05$ for 848 intensities.

Since the absolute configuration of one chiral center in each structure was known at the outset, the X-ray results have defined the absolute configuration of all of the other chiral centers. (Figures 1 and 2). The exo acetal ring of **38** exists in a half-chair conformation while the endo acetal ring of **36** exists in an O1 envelope conformation such that the exocyclic O2–C11 bond in both structures is pseudoaxial. Fractional atomic coordinates are given in Table V.