volume readings were made. The volume of gas evolved at infinite time (V_∞) was determined by removing the reaction flask from the cooling bath, warming it to room temperature, and allowing it to remain there for some time (15–30 min). The flask was then recooled to the temperature of the experiment and the gas volume read. Plots of the log ($V_\infty - V$) *vs.* time were made and slopes were determined by a least-squares treatment of the data. A typical first-order rate plot is shown in Figure 2. Most runs were followed for about 2 half-lives and all were followed at least 1 half-life. In the experiments where the amount of initial adduct was quite small, due to decomposition during the warm-up of the adduct flask to the temperature of the experiment, it was found that the slope of the line changed somewhat at the end of the run. These points were neglected when calculating the rate constants. Temperature control in all cases was better than $\pm 1°$ and in most cases better than $\pm 0.5°$

Determination of Transition-State Parameters. Rate constants for the decomposition of the triphenyl phosphite–ozone adduct were determined at five different temperatures using methylene chloride as solvent. A summary of the results of these experiments appears in Table I. An Arrhenius plot of log k *vs.* $1/T°K$ was treated by least squares to determine the slope, the intercept, and the probable error in the slope. From these were calculated the energy of activation (E_a) and the transition-state parameters for the decomposition of the adduct. These results are tabulated in Table II.

Effect of Solvent. Rate constants for the decomposition of the triphenyl phosphite–ozone adduct were determined at $-24°$ in a variety of solvents. These results are collected in Table III.

Acknowledgment. We wish to acknowledge helpful discussions with Dr. A. M. Trozzolo.

A Synthesis of Prostaglandin $F_{1\alpha}$ and Related Substances

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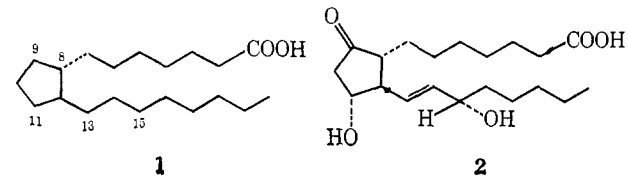
Abstract: The synthesis of prostaglandins $F_{1\alpha}$, $F_{1\beta}$, and a number of related products is described. The key step of the syntheses involves the acid-catalyzed opening and rearrangement of epoxybicyclo[3.1.0]hexanes of the type **28**.

The prostaglandins consist of a family of C_{20} acids of widespread occurrences in animal tissues and of varied, extremely potent, biological activities. Several recent reviews[2] adequately summarize the extensive literature on this important class of natural products. Syntheses of compounds containing the prostanoic acid carbon skeleton (**1**) have been accomplished,[3] and three groups[4] have reported syntheses of racemates of naturally occurring prostaglandins or their derivatives. The first of these reported[4a] a multistep synthesis of the ethyl ester of 13,14-dihydroprostaglandin E_1, a metabolite of prostaglandin E_1 (PGE_1) (**2**). The second[4b] carried out the autoxidation of 8,11,14-eicosatrienoic acid, which was reported to give a 0.1% yield of noncrystalline PGE_1. Crystalline racemic PGE_1, $PGF_{1\alpha}$, and $PGF_{1\beta}$ (as well as several other members of the prostaglandin family) have recently been made by Corey and his group at Harvard.[4c]



1 **2**

In this paper, we give details of a synthesis of prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$), prostaglandin $F_{1\beta}$ ($PGF_{1\beta}$), and several other prostaglandins isomeric with these, *via* bicyclo[3.1.0]hexane derivatives. A portion of this work has been published in a preliminary fashion.[5a,b] Recently, another group has reported[5c] failure to obtain PGE_1 or $PGF_{1\alpha}$ by this route or modifications of it.

3-Cyclopentenol[6] (**3**) was converted to its tetrahydropyranyl ether (**4**), which was then treated[7] with ethyl diazoacetate in the presence of copper powder (Chart I). Two major products were formed in 75% total yield which were assigned the *exo* structures **5a** and **6a**. Treatment of the mixture with methanolic sodium methoxide to isomerize *endo* isomers, if present, to *exo* also resulted in ester exchange to give the two methyl esters, **5b** and **6b**. That these differed only in configuration at the carbinolic carbon was shown by removal of the tetra-

(1) (a) McGill University; (b) The Upjohn Co.

(2) S. Bergström, *Science*, **157**, 382 (1967); S. Bergström, L. A. Carlson, and J. R. Weeks, *Pharmacol. Rev.*, **20**, 1 (1968); "Nobel Symposium 2, Prostaglandins," S. Bergström and B. Samuelsson, Ed., Almqvist and Wiksell, Stockholm, Sweden, 1967; V. R. Pickles, *Biol. Rev.*, **42**, 614 (1967); U. S. von Euler and E. Eliasson, "Medicinal Chemical Monographs," Vol. 8, Academic Press, New York, N. Y., 1967, p 1; J. W. Hinman, *Bioscience*, **17**, 779 (1967).

(3) (a) B. Samuelsson and G. Stallberg, *Acta Chem. Scand.*, **17**, 810 (1963); (b) J. F. Bagli, T. Bogri, R. Degenghi, and K. Wiesner, *Tetrahedron Lett.*, 465 (1966); J. F. Bagli and T. Bogri, *ibid.*, 5 (1967); J. F. Bagli, 10th Annual Medicinal Chemistry Symposium, Bloomington, Ind., June 1966.

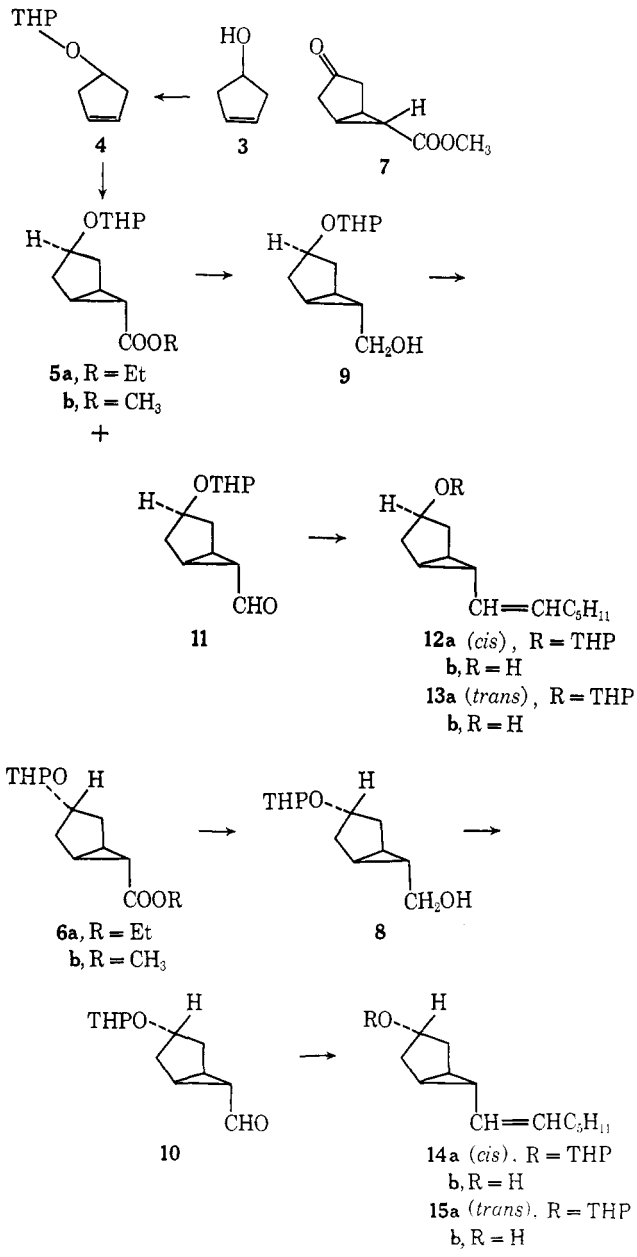
(4) (a) P. F. Beal, J. C. Babcock, and F. H. Lincoln, *J. Am. Chem. Soc.*, **88**, 3131 (1966); (b) D. H. Nugteren, H. Vonkeman, and D. A. van Dorp, *Rec. Trav. Chim.*, **86**, 1 (1967). (c) Following the completion of this work, two other total syntheses of *dl*-prostaglandins were described: E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968); E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *ibid.*, **90**, 3247 (1968).

(5) (a) G. Just and C. Siminovitch, *Tetrahedron Lett.*, 2093 (1967); *Chem. Canada*, **19** (1), 41 (1967); (b) W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *J. Am. Chem. Soc.*, **90**, 5895 (1968); (c) K. G. Holden, B. Hwang, K. R. Williams, J. Weinstock, M. Harman, and J. A. Weisbach, *Tetrahedron Lett.*, 1569 (1968). It is difficult for us to evaluate this report or compare results with ours since intermediate isomeric mixtures were not separated, and melting points of the crystalline products obtained in the attempted PGF synthesis were not given.

(6) E. L. Allred, J. Sonnenberg, and S. Winstein, *J. Org. Chem.*, **25**, 26 (1960).

(7) J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Am. Chem. Soc.*, **85**, 582 (1963).

Chart I



hydropyranyl ethers and oxidation to a single crystalline keto ester (**7**), mp 59–60°. Reduction of a mixture of **5b** and **6b** with lithium aluminum hydride followed by silica gel chromatography gave the easily separable isomeric ether alcohols **8** and **9**. The chemical shift of the *endo*-cyclopropyl hydrogen was definitive in assigning structures, the more polar isomer **8** showing this hydrogen as a doublet of triplets, $J = 7$ and 3 cps, centered at δ 0.77. In the other isomer **9**, all three cyclopropyl hydrogens absorbed below δ 1.0, due to the proximity of the *syn* ether oxygen function to the *endo*-cyclopropyl hydrogen.[8] The proton at C_3 of isomer **8** was shifted upfield *ca.* δ 0.5 compared to that of isomer **9**.

Each of these isomers (**8**, **9**) was oxidized to aldehydes (**10**, **11**) by Jones reagent[9] at −10° in 84% yield. The aldehydes were spectrally distinct and were characterized by the crystalline 2,4-dinitrophenylhydrazones of the corresponding 3-alcohols, mp 220–223 and 215–218°, respectively.

Reaction of aldehyde **10** with the ylide from *n*-hexyltriphenylphosphonium bromide gave a mixture of the *cis*- and *trans*-olefins **14a** and **15a**, and in the same way aldehyde **11** gave **12a** and **13a**. After acid hydrolysis of the tetrahydropyranyl ethers, **12b** and **13b** were separated by chromatography on silica gel, and the **14b**, **15b** pair were separated on a silver nitrate impregnated silica gel[10] column. In each case the ratio of *cis* and *trans* olefins was 80–85% *cis* to 15–20% *trans* when the reaction was carried out in benzene–hexane[11] and nearly 1:1 in tetrahydrofuran. The two isomeric alcohols **12b** and **14b** gave the same ketone (**16**) after oxidation with Jones reagent. Similarly, alcohols **13b** and **15b** gave **17**. As a usual practice, the isomeric bicyclohexanes **5** and **6** were not separated, but were carried through as mixtures of isomers at C-3 until after oxidation to the 3-ketones **16** and **17**, which were then separated on silver nitrate impregnated silica gel. The *cis–trans* assignments of the double bond in **16** and **17** were evident from spectral data, **17** showing a band at 960 cm^{-1} in the infrared, and $J = 15$ cps for the olefinic protons in the nmr; **16** had no absorption near 980 cm^{-1} and $J = 11$ cps. In addition, **17** was eluted first from silver nitrate impregnated absorbants. The combined yield of ketones **16** and **17** from cyclopentenol, without separation of intermediate isomers, was about 30%.

Because of the symmetry of ketones **16** and **17**, two racemic pairs of monoalkylated products are to be expected from each, *e.g.*, **18** and **19** from *cis*-ketone **16**, and **20**, **21** from *trans*-ketone **17** (Chart II). When ketone **16** was treated with methyl ω-iodoheptanoate and potassium *t*-butoxide in dimethoxyethane[12] at reflux as described earlier,[5a] vpc indicated that the amounts of starting ketone and mono-, and dialkylated products did not change appreciably after 30 min, but that peaks due to further condensation reactions of excess iodo ester continued to increase in amount. Under these conditions the two monoalkylated products, **18** and **19**, could be separated by chromatography in yields of about 10 and 25%, respectively. Dialkylated material was formed in yields of 20% or more, and about the same amount of unalkylated ketone **16** was recovered. When the alkylation was carried out at 0° with slow addition of 1.25 *M* of potassium *t*-butoxide, the ratio of **18** and **19** could be changed to favor, slightly, the α-alkylated isomer **18**. Equilibration of each pure monoalkylated product **18** and **19** in dimethoxyethane was very rapid when a trace of potassium *t*-butoxide was added, giving the same mixture, consisting of 35% **18** and 65% **19**. *trans*-Ketone **17** behaved analogously, giving comparable yields of the two monoalkylated products **20** and **21**. Configurations of C_2 in these products were tentatively assigned on the basis of polarity on adsorbants, and were confirmed in subsequent products.

Table I gives some relevant nmr data for the alkylated ketones **18–21**. While the data are consistent with that given by Bergqvist and Norin[13a] for the similarly iso-

(8) See S. Winstein, E. C. Friedrich, B. Baker, and Y. Lin, *Tetrahedron Suppl.*, **8**, II, 621 (1966).

(9) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

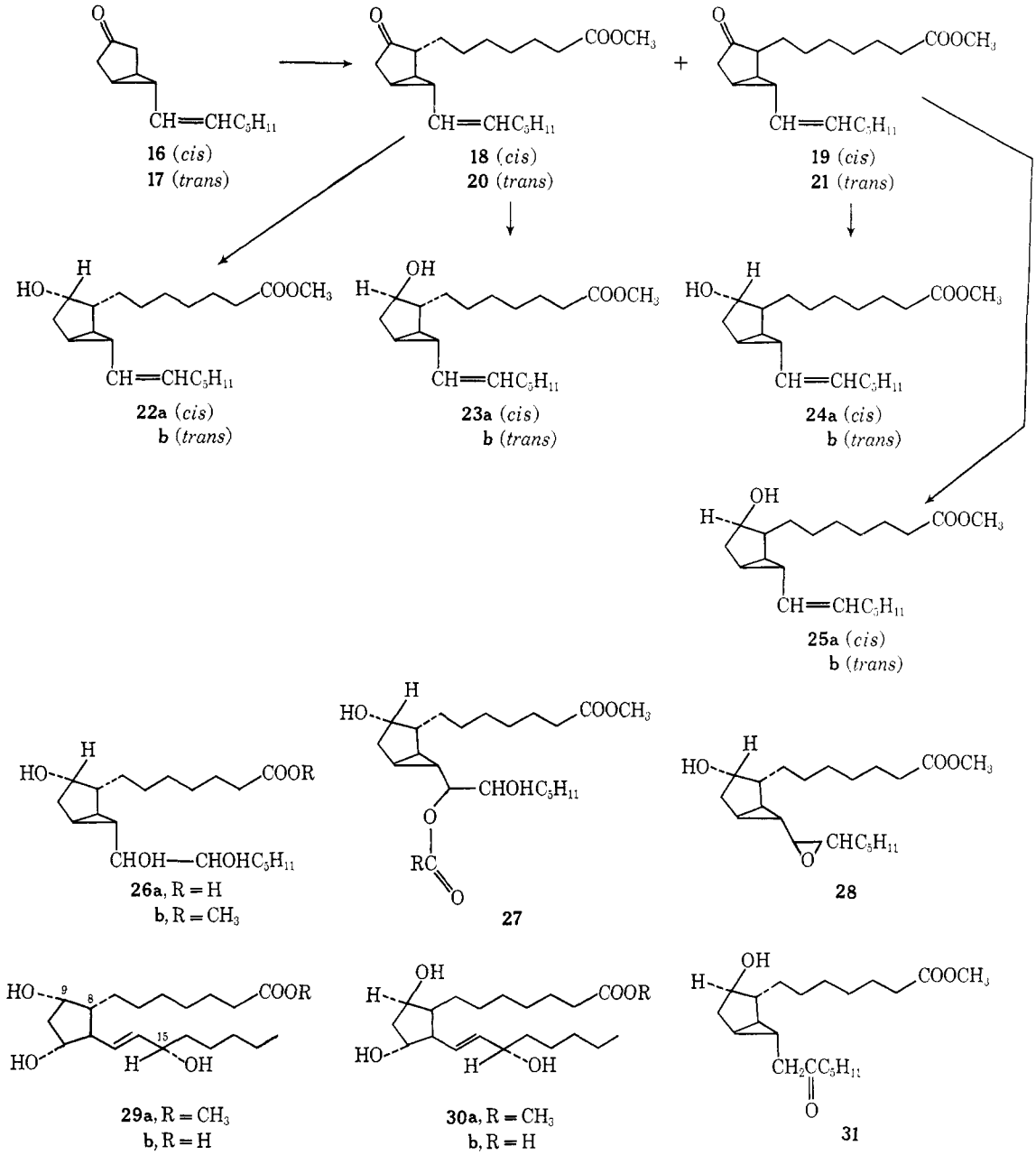
(10) L. J. Morris, *J. Lipid Res.*, **7**, 717 (1966), and references therein.

(11) C. F. Hauser, T. W. Brooks, M. L. Miles, M. A. Raymond, and G. B. Butler, *J. Org. Chem.*, **28**, 376 (1963).

(12) H. O. House and B. M. Trost, *ibid.*, **30**, 1341 (1965); H. O. House and V. Kramer, *ibid.*, **28**, 3362 (1963).

(13) (a) M. S. Bergqvist and T. Norin, *Arkiv Kemi*, **22**, 137 (1964); (b) K. Tori, *Chem. Pharm. Bull* (Tokyo)., **12**, 1439 (1964); (c) H. E. Smith, J. C. D. Brand, E. H. Massey, and L. J. Durham, *J. Org. Chem.*,

Chart II



meric alkylated [3.1.0]bicyclohexanones thujone and isothujone, we do not feel that it is sufficiently distinctive to prove the configuration at C-2 in the alkylated ketones.

Other alkylation procedures, including alkylation of enamines,[14] the Stork–Dowd imine–alkylation modification,[15] and the Fauvarque[16] alkylation of bromomagnesium enolates in hexamethylphosphoramide, were less successful in our hands.

The thermodynamically more stable β-alkylated isomers **19** and **21** contain the bulky carbomethoxyalkyl side chain *cis* to the substituted cyclopropane ring. However, there have been frequent references[13] to the probable preference of the bicyclo[3.1.0]hexane system for a boatlike conformation, and in such a conformation, the β-oriented side chain at C_2 would assume an equatorial position, minimizing the nonbonded interactions.

Reduction of ketone **18** with sodium borohydride produced two alcohols, **22a** and **23a**, in a ratio of 1:9, and in the same manner, ketone **19** gave **24a** and **25a**, ratio 58:42. The corresponding *trans*-ketones **20** and **21** gave a completely analogous series of four alcohols, **22b–25b**. On adsorbants, **24a** was the most polar and **25a** the least polar of the four *cis*-alcohols. The observed ratios of alcohols formed from borohydride reduction of these ketones and the chemical shifts and coupling constants observed for their carbinolic protons in the nmr (Table II) show a remarkable resemblance to the corresponding data reported by Bergqvist and Norin[13] for the four thujyl alcohols. Thus, **22** is stereochemically analogous to (−)-thujyl alcohol, **23** to (−)-neothujyl alcohol, **24** to (+)-isothujyl alcohol, and **25** to (+)-neoisothujyl alcohol.

Treatment of alcohol **22a** with hydrogen peroxide in buffered formic acid,[5a,b] followed by hydrolysis of esters,

31, 690 (1966); (d) A. Diefferbacker and W. von Philipsborn, *Helv. Chem. Acta*, **49**, 897 (1966); and also ref 8.

(14) J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).

(15) G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).

(16) J. Fauvarque and J. F. Fauvarque, *Compt. Rend.*, **263**, 488 (1966).

Table I[a]

Compd	H	Chemical shift, δ ($CDCl_3$)	J, cps	
20	4β	2.03 (d)	4α,4β	[18.5]
	4α	2.55 (d-d)	4α,5α	4.5
	6β	0.83 (m)	4α,1α	~1
	1′	4.92 (d-d)	2β,CH_2	7
	2′	5.42 (d-t)	6β,1′	7
			1′,2′	15
			2′,3′	6
			6β,5α	3.5
18	1′	4.88 (d-d)	1′,2′	11
	2′	5.32 (d-t)	2′,3′	7
		Others similar to 20	6β,1′	9
			1′,3′	1.5
19	4β	2.13 (d)	4α,4β	[18.5]
	4α	2.62 (d-q)	4α,5α	5
	6β	0.95 (m)	4α,1α	~1.5
	1′	4.88 (d-d)	2α,CH_2	7
	2′	5.33 (d-t)	6β,1′	9
			1′,2′	11.5
			2′,3′	7
			1′,3′	1.5
21	1′	4.95 (d-d)	6β,5α	3.5
	2′	5.42 (d-t)	2′,1′	15
		Others similar to **19**	6β,1′	6.5
			2′,3′	6

[a] Abbreviations are as follows: d = doublet; t = triplet; q = quartet; m = multiplet.

Table II. Nmr Data[a] for the 3-Proton in [3.1.0]Bicyclohexanes

	δ	$J_{2\alpha,3}$, cps	$J_{2\beta,3}$, cps	$J_{3,4}$, cps
(−)-Thujyl alcohol	3.85	9.4	7.4	6.5
Alcohol **22**	3.94	~9	7.5	~7
(−)-Neothujyl alcohol	3.81	~0	6.4	~0
Alcohol **23**	3.90	~0	6.0	~0
(+)-Isothujyl alcohol	3.21	8.4	7.0	7
Alcohol **24**	3.45	~8	7	7
(+)-Neoisothujyl alcohol	4.03	~0	5.8	6
Alcohol **25**	4.18	~0	5.5	~6

[a] The data for the thujyl alcohols are from Bergqvist and Norin.[13a] The general shapes of the multiplets arising from the 3-proton are strikingly similar for each pair of compounds.

gave as the main products a mixture of isomeric glycols of structure **26a**.[17] A small amount (less than 1% yield)[18] of material having the same thin layer mobility and color reactions as $PGF_{1\alpha}$ (both as the acid **29b** and as the methyl ester **29a**) was found. This material was biologically active (smooth muscle assay), but was noncrystalline and was not further investigated. By the same method, **23** gave about 2% yield of partially crystalline material which corresponded to $PGF_{1\beta}$ (epimeric to $PGF_{1\alpha}$ at C-9) in thin layer behavior and mass spectrum of its methyl ester. Again, the major products were unrearranged *vic*-glycols.

Better results were obtained by first epoxidizing the side chain double bond and then separately treating with acids. Epoxidation of **22** with *m*-chloroperbenzoic acid under usual conditions gave, however, largely a mixture of monoacylated glycol **27** and glycol **26b**, showing the greatly enhanced reactivity of the C–O bond adjacent to the cyclopropyl ring. Under especially mild reaction and work-up conditions, however, 75–80% yields of epoxide **28** could be obtained. Alcohols **23**, **24**, and **25** were also converted to their corresponding epoxides. Although two isomeric epoxides were undoubtedly formed in each case, these were not separated, although in some cases evidence of their presence was seen on thin layer chromatograms.

When epoxides[19] **28** were treated with formic acid at room temperature or trifluoroacetic acid at 40° a deep purple color slowly developed. After removal of solvent *in vacuo*, hydrolysis with sodium carbonate cleaved the formate or trifluoroacetate esters. The resulting methyl esters consisted, again, mainly of unrearranged *vic*-glycols of structure **26b**, but chromatography separated in addition two products having the prostanoic acid skeleton. The less polar of these, obtained in about 2.5% yield, was *dl*-15-isoprostaglandin $F_{1\alpha}$ methyl ester, identical in tlc mobility, infrared, nmr, and mass spectra with authentic material prepared[20] from natural $PGF_{1\alpha}$. The more polar material, corresponding in tlc mobility to $PGF_{1\alpha}$ methyl ester, required repeated chromatography, finally on boric acid treated silica gel[21] to separate it from a similar, but biologically inactive, contaminant. This material, isolated in about 2.5% yield, was crystalline, mp 70–73°, and was identical with natural $PGF_{1\alpha}$ methyl ester in thin layer chromatographic mobility on four systems, infrared, nmr, and mass spectra, and showed more than 50% of the biological activity of authentic material in two different systems.[22]

In the same way, the epoxides obtained from alcohol **23** were treated with trifluoroacetic acid, and from the products was isolated somewhat more than 10% yield of *dl*-prostaglandin $F_{1\beta}$ methyl ester, mp 101–102°. Its identity was established by the same criteria as above. Again, approximately an equal amount of *dl*-15-*i*-$PGF_{1\beta}$ was isolated, and the major products were unrearranged *vic*-glycols.

The 2β-alkylated bicyclo[3.1.0]hexanols **24** and **25** were also epoxidized and the mixed epoxides treated with formic acid. From **24** was isolated *dl*-8-*i*-$PGF_{1\alpha}$ methyl ester, mp 83–84°, and from **25** was obtained *dl*-8-*i*-$PGF_{1\beta}$ methyl ester, mp 93–94°. The latter had the same mobility on silica gel thin layer plates as $PGF_{1\alpha}$ methyl ester, but spectral data were clearly different. These two synthetic prostaglandins were identical in spectral properties and thin layer mobilities to the two borohydride reduction products of the methyl ester of 8-isoprostaglandin E_1, a new prostaglandin isomer recently isolated[23] from enzymatic conversions of *all-cis*-8,11,14-eicosatrienoic acid.

(17) There are four racemates possible having the unrearranged *vic*-glycol structure (*i.e.*, **26**) from each unsaturated alcohol (*i.e.*, **25**). We have found that epoxide opening in this type of compound is not stereospecifically a *trans* opening, but instead results in two *erythro* and two *threo* racemates. The preparation of such pure isomers will be included in a forthcoming paper.

(18) The yield of amorphous $PGF_{1\alpha}$ given in ref 5a was of material of undetermined purity, prepared from a mixture of starting materials probably containing **22–25** and their *trans*-olefinic analogs of unknown composition, and we (Just and Simonovitch) now realize to have been unduly optimistic.

(19) Although all eight isomers of structures **22–25a** and **b** were isolated in pure form, subsequent reactions of epoxidation and acid-catalyzed ring opening were usually carried out on four separate pairs of *cis–trans* isomers, **22a,b**; **23a,b**; **24a,b**; **25a,b**, where the *cis*:*trans* ratio in each was about 80:20.

(20) The preparation of 15(*R*)-$PGF_{1\alpha}$ and other 15(*R*)-prostaglandins from the natural 15(*S*) isomers is effected by epimerization at C_{15} in formic acid: J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, in press.

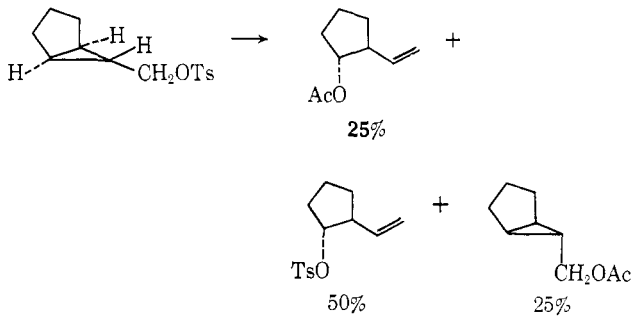
(21) L. J. Morris, *Lipids*, **1**, 41 (1966); *J. Chromatog.*, **12**, 321 (1963).

(22) Effects on smooth muscle (gerbil colon) and blood pressure in rats were measured in the laboratory of Dr. J. R. Weeks, Pharmacology Research, The Upjohn Co.

(23) E. G. Daniels, W. C. Krueger, F. P. Kupiecki, J. E. Pike, and W. P. Schneider, *J. Am. Chem. Soc.*, **90**, 5894 (1968).

Reaction of the above epoxides with strong acids in less nucleophilic solvents, such as boron trifluoride or perchloric acid in tetrahydrofuran, or trifluoroacetic acid in methylene chloride, gave up to 50% of ketonic products, *e.g.*, **31**, arising by hydride transfer.

The relatively small extent of reaction of the cyclopropylcarbinyl systems above which occurs *with ring opening* is at variance with the experience of Wiberg and Ashe.[24] In the similar bicyclohexane system below they found solvolysis to give 75% of ring-opened products. References to most of the other work on cyclopropylcarbinyl systems dating from that of Winstein and Roberts in the 1950's has been listed recently by Schleyer.[25] It seems generally agreed that there is extensive charge delocalization in the cyclopropylcarbinyl cation. However, Tsuji, *et al.*,[26] conclude from solvolysis rates of substituted cyclopropylcarbinyl systems that the unusual reactivity of such systems does not necessarily result from *participation* of the cyclopropane ring.



In the epoxides we have studied, *i.e.*, **28**, and in other derivatives to be reported later, it seems clear that there is substantially increased reactivity at the site adjacent to the cyclopropyl ring, but that at least 75% of the products result from nucleophilic attack at that site, without participation of the ring. It seems difficult, from models, to account for this preference on purely steric grounds. Also, the potential gain in energy due to relief of strain in going from a bicyclo[3.1.0]hexane system to a vinylcyclopentane seems not to affect the major reaction pathway. We would suggest that in these compounds the oxygen function adjacent to the developing cyclopropylcarbinyl cation acts to stabilize the charge on that carbon atom, decreasing the extent of delocalization into the cyclopropane ring, and so decreasing the extent of nucleophilic attack on the ring.

Experimental Section

The nmr spectra were obtained on a Varian Associates A-60 spectrometer in deuteriochloroform with tetramethylsilane as internal standard unless otherwise specified. Infrared spectra of crystalline materials were as Nujol mulls, of noncrystalline materials as neat liquids between glass plates, unless a solvent is specified.

All totally synthetic asymmetric substances described here are racemic mixtures; the prefix *dl* is usually omitted. Where substituents are described as α or β, we mean below or above the plane of the molecule, respectively, as written; the enantiomeric material is assumed to be present in the case of all racemates.

Tetrahydropyranyl Ether of Δ^3-Cyclopentenol (4). A mixture of Δ^3-cyclopentenol[5] (3.29 g) and dihydropyran (3.39 g) was cooled to 0° and two drops of phosphorus oxychloride was added. The mixture was stirred 1 hr at 0° and 3 hr at 25°, then washed with 10% aqueous potassium hydroxide, and dried over magnesium sulfate. Chromatography on alumina (activity II–III) gave **4**, bp 120° (1 mm), 46° (0.05 mm), in nearly quantitative yield: $n^{21.5}$D 1.4709; ν 3030, 1625, 1140, 1070 cm^{-1}. The nmr spectrum showed two protons centered at δ 5.42 (olefinic), four allylic protons, δ 2.24, three protons on the carbon bearing oxygen at δ 3.5, and one proton, δ 4.45, on the carbon bearing two oxygens.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.32; H, 9.59. Found: C, 71.59; H, 9.27.

6-Carbethoxybicyclo[3.1.0]hexan-3-ol 3-Tetrahydropyranyl Ether (5a, 6a). A mixture of 26.54 g of Δ^3-cyclopentenol tetrahydropyranyl ether and 3 g of copper powder was heated to 95–100° (bath temperature). While vigorously stirring at this temperature, it was treated with 97 g of ethyl diazoacetate, added slowly over a period of 4 hr. When gas evolution was complete, it was cooled, diluted with ether, and filtered through Celite filter aid. Removal of ether left 84.7 g of red oil which was chromatographed on 2000 g of silica gel. Starting material (**4**), 6.22 g, was eluted with methylene chloride, and 23 g (75%) of a mixture of **5a** and **6a** was obtained from 10% ethyl acetate–Skellysolve B eluates. This showed two major peaks on vpc of retention times 11 and 13 min (6 ft, 10% silicone rubber at 200°).

6-Carbomethoxybicyclo[3.1.0]hexan-3-ol 3-Tetrahydropyranyl Ether (5b, 6b). To 2.8 g of the mixture of **5a** and **6a** above in 50 ml of methanol was added 150 mg of sodium methoxide and the mixture was heated under reflux for 4 hr. Most of the methanol was evaporated; the residue was extracted with ether which was washed with water, dried, and evaporated to leave a residue consisting of two products (**5b** and **6b**), retention times 10 and 12 min (Apieson L column at 210°). The mixture was distilled at 133° (1.1 mm), ν 3100, 3070, 3030, 1725, 1272, 1140, 1020 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.68; H, 8.42.

6-*exo*-Carbomethoxybicyclo[3.1.0]hexan-3-one (7). A solution of 2.5 g of mixed **5b** and **6b** and 100 mg of oxalic acid in 50 ml of methanol was refluxed for 20 min. The methanol was removed at reduced pressure, and the residue was dissolved in 60 ml of acetone. It was cooled in an ice–salt bath and treated with 2.5 ml of Jones reagent[9] in 2.5 ml of acetone over 15 min. Isopropyl alcohol (4 ml) was added, followed by water, and the products were extracted with ether. The extracts were washed, dried, and evaporated to leave a residue which was chromatographed on silica gel. Elution with 25% ethyl acetate in Skellysolve B gave 495 mg (31%) of crystalline **7**, mp 59–60°.

Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 61.85; H, 6.66.

6-*exo*-Hydroxymethylbicyclo[3.1.0]hexan-3α- and -3β-ol 3-Tetrahydropyranyl Ethers (8 and 9). A solution of 40 g of mixed **5b** and **6b** in 1 l. of ether was added dropwise to a stirred suspension of 8 g of lithium aluminum hydride in 640 ml of ether. After 1 further hr of stirring, water was slowly added, and the ether layer was separated, washed, dried, and evaporated. The 32 g of residue was chromatographed on 3 kg of silica gel. Elution with 30% ethyl acetate in Skellysolve B gave 15.5 g (44%) of **9** and 13.6 (39%) of **8**, retention times 25 and 31 min (6 ft 10% silicone rubber, 160°). The infrared spectra for the two products were similar, ν 3400, 3030, 1040, 1020 cm^{-1}, but the nmr spectra were quite distinct. Compound **9** showed three cyclopropyl hydrogens at δ 1.0–1.25, two carbinol protons, doublet, at δ 3.3, one carbinol proton, multiplet, at δ 4.22, and one proton, δ 4.53, O–CHO. Compound **8** showed one cyclopropyl proton as multiplet which seemed to consist of overlapping triplets centered at δ 0.77, two carbinol protons, doublet, at δ 3.22 (J = 7 cps), and one proton O–CHO at δ 4.51. The C_3 carbinolic proton was in the δ 3.3–4.0 envelope, unlike that of **9**.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found for **8**: C, 67.58; H, 9.61. Found for **9**: C, 68.21; H, 9.59.

6-*exo*-Hydroxymethylbicyclo[3.1.0]hexan-3α- and -β-ol. Removal of the tetrahydropyranyl ether from **9** at room temperature in acidified (HCl) isopropyl alcohol for 1 hr resulted in a crystalline diol, mp 77–78°, from methylene chloride. The nmr showed the 3-proton at δ 4.37 (triplet, J = 6 cps with long-range coupling), the 6-hydroxymethyl group at δ 3.33 (doublet, J = 6 cps), the ring methylenes centered at δ 1.82 (multiplet, J_{gem} = 14 cps), the 6-cyclopropyl hydrogen at δ 1.25–1.6 (multiplet), and the 1 and 5 protons centered at δ 1.18 (multiplet).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.46; H, 9.60.

Hydrolysis of the tetrahydropyranyl ether of **8** also gave a crystalline diol, mp 63–65°, nmr showing the 3-proton as a multiplet, δ 3.7–4.2, the 6-hydroxymethyl group at δ 3.28, doublet, J = 6.5 cps, C_1

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(26) T. Tsuji, I. Moritani, S. Nishida, and G. Tadokoro, *Bull. Chem. Soc. Japan*, **40**, 2344 (1967).

and C_5 protons, multiplet centered at δ 1.1, and the C_6 proton, multiplet at δ 0.6–1.0; mass ion peaks at 128, 110, 97, and 95.

Anal. Found: C, 65.81: H, 9.58.

3β-Hydroxybicyclo[3.1.0]hexane-6-*exo*-carboxaldehyde 3-Tetrahydropyranyl Ether (11). A solution of 12 g of **9** in 400 ml of acetone at −10° was treated with 24 ml of Jones reagent[9] over a period of 10 min with stirring. After an additional 15 min at −10°, 14 ml of isopropyl alcohol was added, and the mixture was diluted with water and extracted with ether. The ether was washed with bicarbonate, dried, and evaporated to give 10 g (84%) of colorless oil showing one vpc peak, retention time 23 min (6 ft, 10% silicone rubber at 160°). It formed a 2,3-dinitrophenylhydrazone with concomitant hydrolysis of the tetrahydropyranyl ether, mp 215–218°.

Anal. Calcd for $C_{13}H_{14}N_4O_5$: C, 50.98; H, 4.61; N, 18.29. Found: C, 50.99; H, 4.75; N, 18.20.

3α-Hydroxybicyclo[3.1.0]hexane-6-*exo*-carboxaldehyde 3-Tetrahydropyranyl Ether (10). Oxidation of **8** in the same manner as above gave **10**, characterized by its 2,4-dinitrophenylhydrazone formed with hydrolysis of the tetrahydropyranyl ether, mp 220–223°.

Anal. Calcd for $C_{13}H_{14}N_4O_5$: C, 50.98; H, 4.61; N, 18.29. Found: C, 51.10; H, 4.91; H, 18.39.

Oxidation of mixed isomers **8** and **9** in the same way gave a mixture of **10** and **11** which could be distilled at 100–110° (0.02 mm).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.38; H, 8.65.

This mixture of aldehydes formed the same two 2,4-dinitrophenylhydrazones as described above for the separate isomers, which could be separated by silica gel chromatography, the one derived from **10** being the more polar.

***n*-Hexyltriphenylphosphonium Bromide.** A mixture of 100 g of 1-bromohexane and 158.5 g of triphenylphosphine in 300 ml of toluene was refluxed 8 hr, cooled, and filtered to give 54% yield of nicely crystalline product, mp 197° (lit.[11] mp 198–200°).

6-*exo*-(*cis*- and *trans*-1′-Heptenyl)bicyclo[3.1.0]hexan-3β-ol (12b, 13b). To a stirred mixture of 31 g of *n*-hexyltriphenylphosphonium bromide in 400 ml of benzene under nitrogen was added 45 ml of a 15.15% solution of *n*-butyllithium in hexane. After 15 min, 9.6 g of **11** in 70 ml of benzene was added dropwise. The mixture was heated for 3 hr at 60–70°, cooled, and filtered; the filtrate was washed with water, dried, and concentrated to about 100 ml. It was diluted with an equal volume of Skellysolve B and filtered through silica gel. Evaporation of the eluates gave 9.4 g of oil which seemed to be a mixture of **12a,b**, and **13a,b** by vpc. This crude mixture was hydrolyzed by refluxing in 300 ml of methanol containing 600 mg of oxalic acid for 1 hr. The methanol was removed *in vacuo;* the residue was dissolved in ether, washed with bicarbonate, water, dried, and evaporated. The residue was chromatographed on silica gel. Elution with 5% ethyl acetate in Skellysolve B gave 3.3 g (38%) of *cis*-alcohol **12b** and 0.7 g (8%) of *trans*-alcohol **13b**. Retention times on a 6 ft, 10% silicone rubber column at 170° were 9 min for **12b** and 11 min for **13b**. For nmr spectra, see Figures 1a and b. The ir spectrum of **13b** shows a band at 955 cm^{-1} not present in **12b**.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found for **12b**: C, 80.22; H, 11.26. For **13b**: C, 79.98; H, 11.44.

6-*exo*-(*cis*- and *trans*-1′-Heptenyl)bicyclo[3.1.0]hexan-3α-ol (14b, 15b). In the same manner as the preceding experiment, 4.5 g of aldehyde **10** was converted to a mixture of **14b** and **15b**. These were separated on a silver nitrate impregnated silica gel column (silica gel stirred with 50% aqueous silver nitrate on the steam bath, filtered by suction, and dried at 110°). Elution with 15 and 20% ethyl acetate in Skellysolve B gave 0.44 g (11%) of the *trans*-alcohol **15b** and 1.93 g (47%) of the *cis*-alcohol **14b**. Retention times on a 6 ft 10% silicone rubber column at 175° were 10 min for **14b** and 12 min for **15b**. The ir spectrum of **15b** showed a sharp peak at 970 cm^{-1} for the *trans*-double bond not seen in the spectrum of **14b**. The complex olefinic proton absorption in the nmr of **15b** was shifted downfield with respect to **14b** (see Figures 1c and d).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found for **15b**: C, 80.70; H, 11.65. For **14b**: C, 80.11; H, 11.39.

6-*exo*-(*cis*-1′-Heptenyl)bicyclo[3.1.0]hexan-3-one (16). A solution of 4.8 g of **12b** in 200 ml of acetone was cooled to −10° and 12 ml of Jones reagent was added over 10 min. After stirring a further 15 min, 15 ml of isopropyl alcohol was added, followed by water, and the product extracted with methylene chloride. This was washed, dried, and evaporated; the resulting oil was chromatographed on silica gel. Elution with 40% methylene chloride in Skellysolve B gave 3.5 g (75%) of **16**. The ir spectrum showed a carbonyl absorption at 1745 cm^{-1}. The olefinic proton adsorption in the nmr was factorable into overlapping triplets (J = 11 cps) centered at δ 5.27 (C-8 proton) and two doublets (J = 11 cps) centered δ 4.78 (C-7 proton). The cyclopropyl proton was partially obscured by the terminal methyl signal.

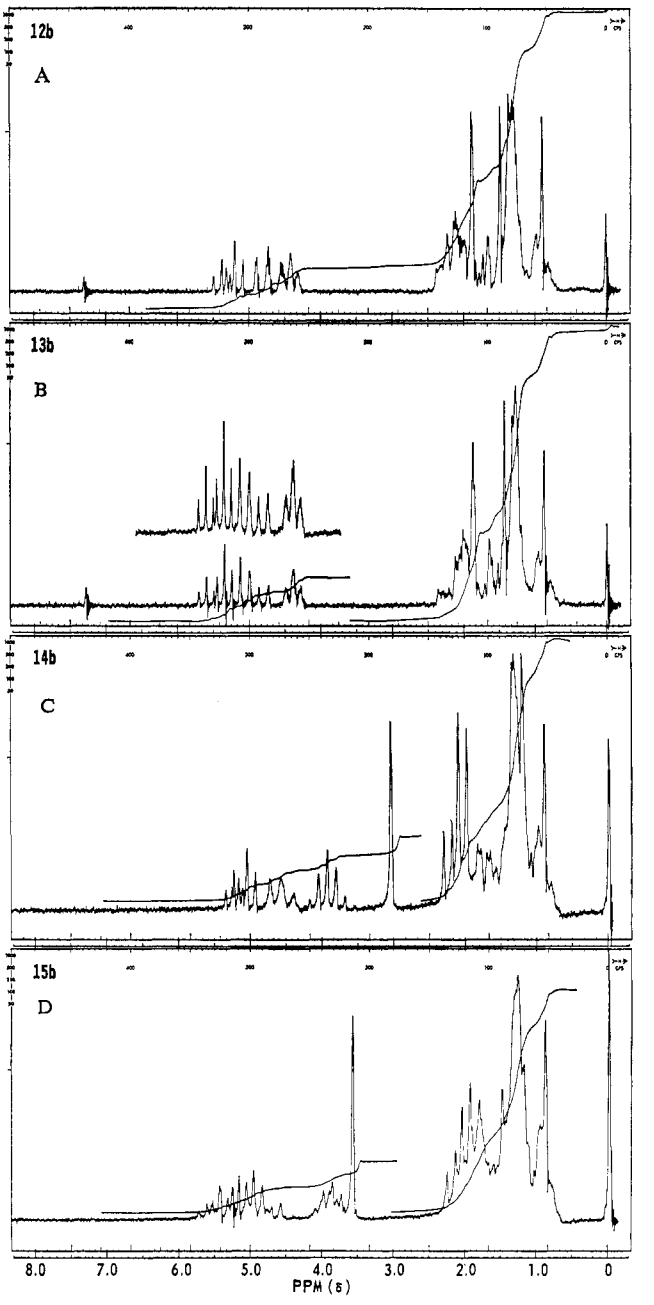

Figure 1.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.96; H, 10.43.

Its 2,4-dinitrophenylhydrazone melted at 94–96° from ethanol.

Anal. Calcd for $C_{19}H_{24}O_4N_4$: C, 61.27; H, 6.48; N, 15.05. Found: C, 61.23; H, 6.69; N, 15.20.

In the same way, **14b** was converted to the same ketone.

6-*exo*-(*trans*-1′-Heptenyl)bicyclo[3.1.0]hexan-3-one (17). In the same manner as above, oxidation of **13b** and **15b** gave the *trans*-ketone **17**. Spectral data were similar to the *cis* isomer except that the *trans*-double bond absorption at 970 cm^{-1} was seen in the ir.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.98; H, 10.57.

Its 2,4-dinitrophenylhydrazone melted at 74–75° from ethanol.

Anal. Calcd for $C_{19}H_{24}O_4N_4$: C, 61.27; H, 6.48; N, 15.05. Found: C, 61.18; H, 6.43; N, 15.04.

Separation of 6-*exo*-(*cis*- and *trans*-1′-Heptenyl)bicyclo[3.1.0]-hexan-3-one (16 and 17). The ketones **16** and **17** were prepared as

above from Δ^3-cyclopentenol without separating isomeric intermediates. The crude product was chromatographed on silver nitrate impregnated[10] silica gel. Elution with 6% ethyl acetate in Skellysolve B gave the *trans*-ketone **17**, and 8% ethyl acetate–Skellysolve B gave the *cis*-ketone **16**. On thin layer plates (Adsorbosil-ADN-2, 25% silver nitrate) developed with 3:1 cyclohexane–ethyl acetate the R_f values were 0.66 and 0.51, respectively, and on vpc retention times were 6 and 7 min (6 ft 10% silicone rubber, 170°).

6-*exo*-(*cis*-1′-Heptenyl)-2-α- and -β-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one (18 and 19). To a stirred solution of 1.02 g of 6-*exo*-(*cis*-1′-heptenyl)bicyclo[3.1.0]hexan-3-one (**16**) and 4.8 g of methyl ω-iodoheptoate in 120 ml of dimethoxyethane (distilled from $LiAlH_4$) under nitrogen was added a solution of 0.75 g of potassium *t*-butoxide (Alfa Inorganics, Inc.) in 60 ml of dimethoxyethane in five equal portions at half-hour intervals. The reaction was followed by vpc (4 ft, 3% silicone rubber column, temperature 160–250°). There was little difference in amounts of two monoalkylated products after the fourth and fifth additions of base, but the amount of dialkylated product continued to increase at the expense of nonalkylated ketone. The mixture was diluted with 60 ml of 5% hydrochloric acid and 120 ml of ethyl acetate, and the organic layer was separated, washed, dried, and evaporated. The residue was heated to 60–65° under vacuum to distill excess methyl iodoheptoate and unalkylated ketone. The residue, 4.1 g, was chromatographed on 100 g of grade II alumina. Elution with increasing ratios of benzene in Skellysolve B gave 326 mg of monoalkylated ketones **18** and **19**, 200 mg of dialkylated material, and the remainder consisted of starting materials and condensation products of methyl ω-iodoheptoate.

The two monoalkylated ketones were separated by further chromatography over silica gel (elution with 5% ethyl acetate in Skellysolve B) to afford 29 mg of pure less polar ketone (**18**), 108 mg of mixture, and 52 mg of more polar ketone (**19**).

A modified procedure involved the slow uniform addition of the potassium *t*-butoxide in purified tetrahydrofuran to an ice-cold solution of the ketone and alkylating agent also in tetrahydrofuran. The same work-up, using a more efficient distillation to remove unreacted unalkylated ketone and alkylating agents and a single chromatogram on silica gel, gave 15% **18**, 17% **19**, and 21% dialkylated product. Compounds **18** and **19** were separately collected from the effluent of the above-mentioned gas chromatogram.

Polarity of the monoalkylated products was reversed on vpc and both **18** and **19** exhibited ions of 334, 303, 302, 292, 274, 245, and 191 mass units in the mass spectrum. The ir spectra showed only a single carbonyl band at 1745 cm^{-1} for both the ring and ester carbonyls. The nmr data are summarized in Table I.

Anal. Calcd for $C_{21}H_{34}O_3$: *m/e* 334.2508. Found: *m/e* 334.2514 (for *cis* **18**), 334.2500 (for *cis* **19**).

6-*exo*-(*trans*-1′-Heptenyl)-2-α- and -β-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-one (20 and 21). In the same manner as above, the *trans*-ketone **17** gave 15% of less polar alkylated product (**20**), 11% of the more polar alkylated product (**21**), and 28% of dialkylated material (modified procedure). Similar spectral data were seen except that the 970-cm^{-1} *trans*-double bond ir absorption peak was evident in these compounds.

Equilibration of Ketones 18 and 19. Samples of the two pure ketones, **18** and **19**, were separately dissolved in dimethoxyethane at concentrations of 12 mg/ml. A 0.5-ml sample of each was added separately to 2 mg of potassium *t*-butoxide in an atmosphere of nitrogen. After 10 min, the red-tan solutions were treated with 2 drops of 3 *N* hydrochloric acid and analyzed by vpc (4 ft 3% silicone rubber column; the sample was introduced at 200° and the column temperature was raised 3°/min). In each case, two peaks were eluted with identical ratios, 35:65 of **18**:**19**. Without the base treatment each of the solutions gave only one of these peaks; **18**, the less polar on silica gel chromatography, was the one having the longer retention time on the vpc column.

6-*exo*-(*cis*-1′-Heptenyl)-2β-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3-α- and -3β-ol (24a and 25a). To a solution of 640 mg of ketone **19** in 25 ml of isopropyl alcohol at 0° was added a solution of 225 mg of sodium borohydride in 2 ml of water. After 2-hr stirring, 1 ml of acetic acid in 10 ml of water was added; the mixture was concentrated *in vacuo*, extracted with ethyl acetate, washed, dried, and evaporated. The residue was chromatographed on 125 g of Florisil, eluting with increasing concentrations of acetone in Skellysolve B. The first peak eluted, 177 mg (27%), consisted of the 3β-ol, ν 3450, 2990, 1745, 1650, 1190, 1050, 840, 720 cm^{-1}. In the nmr, the 2′ proton was a doublet of triplets, δ 5.26, J = 11 and 7 cps, the 1′ proton a doublet of doublets, δ 4.80, J = 11 and 9 cps, $-OCH_3$ at δ 3.68, and the 3α-hydrogen a doublet of doublets, δ 4.18, J = 5.5 and 6 cps.

The 3α-ol, 243 mg (38%), more polar than the β isomer, had infrared absorptions similar to the β isomer, but in the nmr spectrum the 3β-hydrogen occurred as a multiplet, δ 3.45. On silica gel thin layer plates developed twice with 25% ethyl acetate–cyclohexane; the R_f values of **24a** and **25a** were 0.14 and 0.21, respectively, and both gave similar mass spectra with ions of 336, 318, 305, and 304 mass units.

Anal. Calcd for $C_{21}H_{36}O_3$: *m/e* 336.2664. Found: *m/e* 336.2657 (for **24a**), 336.2643 (for **25a**).

6-*exo*-(*cis*-1′-Heptenyl)-2α-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3α- and -β-ol (22a and 23a). A solution of 175 mg of **18** in 8 ml of isopropyl alcohol was treated with stirring at 0° with a solution of 100 mg of sodium borohydride in 1.5 ml of water. After stirring 2.25 hr in the ice bath, acetone (2 ml) was added, followed by 0.5 ml of acetic acid in 10 ml of water. The mixture was concentrated *in vacuo* and extracted with ethyl acetate, and the extracts were washed, dried, and evaporated. Chromatography of the residue on 25 g of silica gel and elution with increasing concentration of ethyl acetate in Skellysolve B gave first the major product, the 3β-ol **23a** (125 mg, 71%, R_f 0.18 on silica gel plates, developed twice with 25% ethyl acetate–cyclohexane), followed by the minor product (15 mg, 8%, R_f 0.16 on the same tlc system). The infrared and mass spectra of these were similar to those of **24a** and **25a** above, but they could be distinguished by virtue of their differences in nmr spectra, **22a** showing the C_3 proton as a multiplet centered at δ 3.94, J = 9, 7, and 7.5 cps, and in **23a** this proton appeared as a doublet with further fine coupling at δ 3.90, J = 6 cps.

Anal. Calcd for $C_{21}H_{36}O_3$: *m/e* 336.2664. Found: *m/e* 336.2650 (for **23a**), 336.2647 (for **22a**).

6-*exo*-(*trans*-1′-Heptenyl)-2α-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3α- and -3β-ol (22b and 23b). In the same manner as above, ketone **20** gave two epimeric *trans*-alcohols **22b** and **23b** in approximately a 1:9 ratio. The most polar fraction formed waxy crystals on refrigeration. Both samples gave a similar mass spectrum 336, 318 (M − 18), 305 (M − CH_3O), 304 (M − CH_3OH). Infrared spectra were indistinguishable showing strong OH absorption at 3325, a single carbonyl peak at 1740, C–O stretching at 1190, 1160, and 1060, and a *trans*-double bond at 960 cm^{-1}.

6-*exo*-(1′-*trans*-Heptenyl-2α-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3α- and -3β-ol (24b and 25b). In the same manner as above, ketone **21** gave two epimeric *trans*-alcohols corresponding to **24** and **25** in a 45:55 ratio. The most polar epimer formed waxy crystals on refrigeration. Both samples gave similar mass (M^+ 336) and ir spectra, indistinguishable from the corresponding 2α isomers above.

6-*exo*-(1′,2′-Epoxyheptyl)-2α-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3α-ol (28). A solution of 0.71 g of mixed *cis*/*trans* alcohol (**22a** and **b**, approximately 80% **22a**) was cooled in an ice bath and treated while stirring with 0.52 g of *m*-chloroperbenzoic acid. After stirring for 30 min, the mixture was washed in turn with ice-cold solutions of sodium bicarbonate, sodium iodide, and sodium thiosulfate, dried, and evaporated to a colorless oil. A portion (150 mg) was rapidly chromatographed over 10 g of silica gel. Elution with 30% ethyl acetate in cyclohexane afforded 122 mg (80%) of pure epoxide **28** (oil). More polar impurities consisted of hydroxy-*m*-chlorobenzoate (**27**) and glycol (**26b**). The mass spectrum of the epoxide showed a molecular ion at 352 mass units and other fragments at 334 (M − 18), 303 (M − 31), 281 (M − 71), and 263 (281 − 18). Nmr (CCl_4) showed a carbinolic proton multiplet typical of this epimer (Table I) at δ 3.9, a three-hydrogen singlet at δ 3.58 (ester methyl), and a one-hydrogen multiplet at δ 0.58 (cyclopropyl proton).

6-*exo*-(1′,2′-Epoxyheptyl)-2α-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3β-ol. In the same manner as above, mixed *cis*/*trans* alcohol (**23a** and **b**, 80% **23a**) was converted to its corresponding epoxide. In this case the cyclopropyl proton in the nmr spectrum was shifted downfield because of the proximity of the hydroxyl at C-3 and was not seen.[8] The mass spectrum was the same as for the 3α epimer above.

6-*exo*-(1′,2′-Epoxyheptyl)-2β-(6′′-carbomethoxyhexyl)bicyclo[3.1.0]hexan-3α-ol. In the same manner as above mixed *cis*/*trans* alcohol (**24a** and **b**) was converted to the corresponding epoxide. The nmr spectrum showed a three-hydrogen singlet at δ 3.62 (ester methyl), a one-hydrogen multiplet at δ 3.18 (carbinolic proton), and a one-hydrogen multiplet at δ 0.50 (cyclopropyl H). The mass spectrum exhibited a molecular ion at 352 and prominent fragments at 334 (M − 18), 281 (M − 71), and 263 (281 − 18).

6-*exo*-(1′,2′-Epoxyheptyl)-2β-(6′′-carbomethoxyhexyl)bicyclo-[3.1.0]hexan-3β-ol. In the same manner as above mixed *cis/trans* alcohol (**25a** and **b**) was converted to the corresponding epoxide. The nmr spectrum showed a one-hydrogen multiplet at δ 4.08 (carbinolic proton) and a three-hydrogen multiplet at δ 3.62 (ester methyl) but the cyclopropyl proton was partially under the terminal methyl absorption. The mass spectrum was identical with that of the 3α epimer above.

***dl*-Prostaglandin $F_{1\alpha}$ Methyl Ester (29a).** A solution of 400 mg of crude epoxide **28** in 15 ml of recrystallized formic acid stood at 25° for 16 hr, during which time a deep purple color developed. The formic acid was removed *in vacuo* and the residue was stirred under nitrogen in 30 ml of methanol containing 10 ml of water and 3 g of sodium carbonate at 25° for 1.5 hr. The mixture was then acidified with dilute hydrochloric acid, concentrated *in vacuo*, and extracted with methylene chloride. The extracts were washed, dried, evaporated, and chromatographed on 40 g of silica gel. Elution with 60% ethyl acetate in cyclohexane gave 86 mg of a mixture of materials [λ_{max} 233 mμ (ε 5500) and mass peaks at 382 and 366] which was not further investigated. Elution with 80% ethyl acetate gave 85 mg of unrearranged glycol (**26b**), noncrystalline, which had mass spectral peaks similar to those of the crystalline isomer below. This formed a triacetate (nmr evidence) and, on hydrolysis with methanolic sodium hydroxide, gave a crystalline acid, mp 130°, with mass peaks at 338 (M − 18), 320 (M − 36), 302 (M − 54), 255 (glycol cleavage), and 237. Elution with ethyl acetate gave 85 mg of a mixture (by tlc) of *dl*-15-*i*-$PGF_{1\alpha}$ methyl ester and an unrearranged glycol isomeric with the above. The glycol crystallized, mp 54–61°, and had mass peaks at 352, 334, 269, 251, 237, 219, consistent with structure **26b**. The nmr spectrum showed no olefinic protons, and the 6-*endo*-cyclopropyl hydrogen was seen at about δ 1 under the terminal methyl protons. Further elution of the column with 5% methanol in ethyl acetate gave 74 mg of a mixture of the above crystalline glycol and *dl*-$PGF_{1\alpha}$ methyl ester. This was combined with similar material from 200 mg of **28** and rechromatographed on acid-washed silica gel, giving 36 mg of material showing tlc behavior and infrared and nmr spectra essentially like $PGF_{1\alpha}$ methyl ester. However, when tlc plates sprayed with 10% boric acid in methanol and dried at 100° for 1 hr were used, two spots were seen, the less polar of which corresponded to $PGF_{1\alpha}$ methyl ester. This material was separated on four 20 × 20 cm plates treated with boric acid as above, developed twice with ethyl acetate, giving 12 mg of *dl*-$PGF_{1\alpha}$ methyl ester (**30a**) which crystallized from ether–Skellysolve B, mp 70–73°. This material had the same tlc mobility as $PGF_{1\alpha}$ methyl ester on four systems (M-I and A IX,[27] ethyl acetate developed three times, and ethyl acetate containing 10% isopropyl alcohol on silica gel plates). Spectral data was consistent with this structure: ν (CH_2Cl_2) 3400, 1745, 1200, 1175, 1070, 970 cm^{-1}; two-hydrogen multiplet at δ 5.5 (olefinic), broad six-hydrogen multiplet at δ 4.1 (carbinolic and OH protons), three-hydrogen singlet at δ 3.67 (OCH_3), three-hydrogen triplet at δ 0.87 (terminal CH_3); mass peaks at 370 (M^+), 352 (M − 18), 334 (M − 36), 280 (M − 18 − 72).

In the high-resolution mass spectrum, the molecular ion was too weak to quantitate, so the mass of the M − 36 peak was measured.

Anal. Calcd for $C_{21}H_{34}O_3$: 334.2507. Found: *m/e* 334.2524.

The material above containing *dl*-15-*i*-$PGF_{1\alpha}$ methyl ester was treated with excess sodium periodate in methanol and rechromatographed on silica gel as above to give 15 mg of *dl*-15-*i*-$PGF_{1\alpha}$ methyl ester as an oil having tlc behavior identical with authentic material.[20] Ir and nmr data were also consistent with such a structure, being virtually undistinguishable from the data given above for *dl*-$PGF_{1\alpha}$ methyl ester. The mass spectrum of the TMS derivative showed an ion peak at 586 (the molecular ion), but *dl*-$PGF_{1\alpha}$ methyl ester itself did not show an appreciable molecular ion, so the M − 36 peak was measured in the high-resolution spectrum.

Anal. Calcd for $C_{21}H_{34}O_3$: 334.2507. Found: *m/e* 334.2514.

***dl*-Prostaglandin $F_{1\beta}$ Methyl Ester.** A solution of 100 mg of the crude epoxide from *cis/trans* compound **23a** and **23b** was warmed to 40° in 2 ml of trifluoracetic acid for 10 min. The dark solution was concentrated *in vacuo* to a dark oil which was hydrolyzed with sodium carbonate in methanol as described above. The product was chromatographed on 10 g of silica gel as above giving 67 mg of *vic*-glycols, formed by opening of the epoxide without opening of the cyclopropane ring. This was followed by 13 mg (12%) of noncrystalline material having the same tlc mobility as 15-*i*-$PGF_{1\beta}$ methyl ester,[20] and then 17 mg (16%) of partly crystalline *dl*-$PGF_{1\beta}$ methyl ester. This latter material was combined with similar material from other reactions and rechromatographed, resulting in recovery of two-thirds of the material as crystalline fractions which were recrystallized from acetone–Skellysolve B, mp 101–102°. The spectral data were consistent with the $PGF_{1\beta}$ methyl ester structure: ν (CH_2Cl_2) 3350, 1745, 1240, 1200, 1170, 1080, 1030, 970 cm^{-1}; two-hydrogen multiplet at δ 5.55 (olefinic), three-hydrogen broad multiplet at δ 4.0 (carbinolic protons), three-hydrogen singlet at δ 3.68 (OCH_3), three-hydrogen triplet at δ 0.9 (terminal CH_3); mass peaks at 370 (M^+, weak), 352 (M − 18), 334 (M − 36), 280 (M − 18 − 72).

Anal. Calcd for $C_{21}H_{38}O_5$: C, 68.07; H, 10.34. Found: C, 67.68; H, 10.71.

Similar data were given for the *dl*-15-*i*-$PGF_{1\beta}$ methyl ester after rechromatography.

***dl*-Prostaglandin $F_{1\beta}$.** A 15-mg sample of the *dl*-methyl ester was hydrolyzed with aqueous methanolic sodium hydroxide (0.2 *N*) at 50° to afford an oil which crystallized from ether, mp 113–115°. The material exhibited the same mobility as authentic $PGF_{1\beta}$ on two systems (A-IX[27] and ethyl acetate–isopropyl alcohol). The mass spectrum was the same as that seen for authentic $PGF_{1\beta}$.

In the high-resolution mass spectrum, the molecular ion was too weak to quantitate, so the mass of the M − 36 peak was measured.

Anal. Calcd for $C_{20}H_{32}O_3$: *m/e* 320.2351. Found: *m/e* 320.2348.

***dl*-8-Isoprostaglandin $F_{1\alpha}$ Methyl Ester.** Crude epoxide (1.75 g) prepared from *cis/trans* compound **24a** and **b** was treated with 20 ml of recrystallized formic acid and subsequently hydrolyzed as described above for **29**. Chromatography over 100 g of silica gel gave numerous less polar by-products from elution with increasing concentrations of ethyl acetate in cyclohexane. Final elution with 5% methanol in ethyl acetate afforded the most polar product (177 mg, 9.5%) as a waxy crystalline substance which, after recrystallization from acetone–Skellysolve B and then ether, formed colorless plates, mp 83–84°. Mobility on tlc (silica gel, ethyl acetate three times) was between authentic $PGF_{1\alpha}$ and $PGF_{1\beta}$ methyl esters.

Anal. Calcd for $C_{21}H_{38}O_5$: C, 68.07; H, 10.34. Found: C, 67.92; H, 10.25.

The spectral data were consistent with the 8-isoprostaglandin $F_{1\alpha}$ methyl ester structure: $\nu^{(Nujol)}$ 3225, 1745, 1200, 1175, 1095, 1070, 970, 730 cm^{-1}; nmr two-hydrogen multiplet at δ 5.5 (olefinic), three-hydrogen multiplet at δ 4.0 (carbinolic protons), three-hydrogen singlet at δ 3.65 (OCH_3), three-hydrogen multiplet at δ 3.1 (hydroxyl protons), three-hydrogen distorted triplet at δ 2.3 (allylic protons), and three-hydrogen distorted triplet at δ 0.9 (terminal CH_3); mass spectrum peaks at 370 (M^+), 352, 334, and 280.

One of the less polar *vic*-glycol by-products above crystallized after hydrolysis with methanolic sodium hydroxide to the acid: mp 90–92°; mass peaks at 338 (M − 18), 320, 302, 255 (glycol cleavage), and 237.

***dl*-8-Isoprostaglandin $F_{1\beta}$ Methyl Ester.** Crude epoxide (1.53 g) prepared from *cis/trans* compound **25a** and **b** was treated with formic acid, hydrolyzed, and chromatographed as described above for the α epimer. Crystallization of the most polar component (145 mg, 9%) from acetone–Skellysolve B, then ether, afforded colorless plates, mp 93–94°. Mobility on tlc (silica gel with ethyl acetate three times) was nearly the same as $PGF_{1\alpha}$ methyl ester.

Anal. Calcd for $C_{21}H_{38}O_5$: C, 68.07; H, 10.34. Found: C, 67.84; H, 10.42.

The spectral data were consistent with the 8-isoprostaglandin $F_{1\beta}$ methyl ester structure: $\nu^{(Nujol)}$ 3225, 1745, 1320, 1210, 1170, 1040, 1020, 970, 865; nmr (acetone-d_6) three-hydrogen multiplet at δ 5.55 (olefinic), three-hydrogen multiplet at δ 4.2 (carbinolic protons), three-hydrogen singlet at δ 3.6 (OCH_3), three-hydrogen multiplet at δ 2.85 (hydroxyl protons and three-hydrogen distorted triplet at δ 0.9 (terminal CH_3); mass spectrum peaks at 370 (M^+ weak), 352 (M − 18), 334 (M − 36), and 280 (M − 72 − 18).

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