alumina chromatography (hexane), colorless crystals, 40% yield, mp 86–88°.

Anal. Calcd for $C_{18}H_{13}F$: C, 87.1; H, 5.3. Found: C, 87.3; H, 5.2.

trans-**1-(1-Fluoro-3-naphthyl)-2-(*o*-iodophenyl)ethylene (4b)**.—Using the above procedure with *o*-iodobenzaldehyde, colorless needles were obtained, mp 85.5–86.5°.

Anal. Calcd for $C_{18}H_{12}FI$: C, 57.8; H, 3.2. Found: C, 57.5; H, 3.3.

5-Fluorobenzo[*c*]phenanthrene (2).—Photolysis of **4b** in cyclohexane in a Pyrex reaction vessel gave the desired product after 3 hr, the solution having acquired a pink iodine color. The product was purified by chromatography on neutral alumina (cyclohexane–benzene, 3:1) and recrystallized from hexane, yield 80%, mp 57–59°.

Anal. Calcd for $C_{18}H_{11}F$: C, 87.7; H, 4.5. Found: C, 87.3; H, 4.8.

Photolysis of a solution of 4 mg of **4a** in 100 ml of cyclohexane in a Pyrex reaction vessel gave a uv spectrum indicating that the photodehydrogenation reaction had occurred and that compound **2** was formed.

All uv spectra were run on a Unicam SP.800 spectrophotometer. The parameters used for the MO calculations were[23] $\alpha_F = \alpha_C + 2.3\beta$; $\alpha_{C'} = \alpha_C + 0.1\beta$; $\alpha_{CF} = 0.7\beta_{CC}$.

Registry No.—**1**, 34236-47-0; **2**, 34236-48-1; **3a**, 34280-38-1; **3b**, 34236-49-2; **4a**, 34236-50-5; **4b**, 34236-51-6; **5d**, 34236-52-7; **5e**, 34236-53-8; **24**, 34236-54-9; **25**, 34236-55-0; 3-fluoro-2-naphthoic acid, 712-70-9.

Acknowledgment.—Thanks are due to Dr. Jochanan Blum for his interest and for his discussions of some of the synthetic procedures. We also wish to thank Dr. A. Y. Meyer for carrying out the MO calculations.

[23] H. Berthod, personal communication.

Prostaglandins. IV.[1] A Synthesis of F-Type Prostaglandins. A Total Synthesis of Prostaglandin $F_{1\alpha}$

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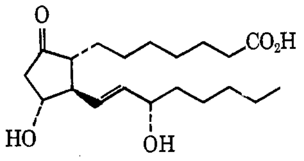
Received December 2, 1971

A seven-step total synthesis of eight racemic modifications of prostaglandin F_1 (**12** and **13**) is described in Chart I. The key steps are condensation of 3-oxoundecan-1,11-dioic acid with styrylglyoxal (**5**) to 9,12-dioxo-11-hydroxy-14-phenyltetradeca-13-enoic acid (**6**), cyclodehydration to **7**, cleavage of the side chain to **8**, selective reduction of the double bond to **9**, and the Wittig reaction to **10** and **11**. Borohydride reduction of **10** gives rise to *dl*-$PGF_{1\alpha}$ (**12a**), *dl*-$PGF_{1\beta}$ (**12c**), and their 15 epimers (**12b** and **d**), whereas borohydride reduction of **11** affords 11-epi-PGF_1s (**13a–d**). The stereochemistry of the four 11-epi-PGF_1 isomers was determined.

The prostaglandins,[2a–e] a family of oxygenated C_{20} fatty acids of widespread occurrence in animal tissues, exhibit a broad range of biological activities and presumably play an important role in sereral key processes.[2c,3] At present, the unavailability of a suitable natural source coupled with their potential drug utility has focused considerable attention toward the synthesis of these compounds and related analogs.



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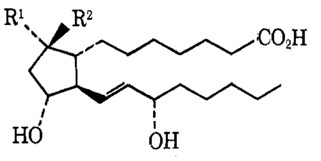


2, $R^1 = OH$; $R^2 = H$
3, $R^1 = H$; $R^2 = OH$

Prostaglandin $F_{1\alpha}$ (**2**, $PGF_{1\alpha}$) can be obtained along with $PGF_{1\beta}$ (**3**, a slightly predominant product) by borohydride reduction[4a,b] of natural PGE_1 (**1**). Similarly, *dl*-$PGF_{1\alpha}$ and *dl*-$PGF_{1\beta}$ were prepared[5a] by the borohydride reduction of racemic PGE_1, the latter having been synthesized by several independent methods.[5–9] Synthesis of the natural forms of **1** and **2** has been recorded by Corey and coworkers.[5c,e] The first direct total synthesis of *dl*-$PGF_{1\alpha}$ was reported by Just and Simonovitch[10] in 1967. Experimental details were not given in this communication, the pure compound was not isolated, and the reproducibility of these results was shortly thereafter questioned by Holden, *et al.*[11a] Subsequently, however, Just[11b] and Simonovitch, in colloboration with investigators from the Upjohn Co., described the experimental details for the isolation of the pure methyl esters of *dl*-$PGF_{1\alpha}$, $PGF_{1\beta}$, 8-epi-$PGF_{1\alpha}$, and 8-epi-$PGF_{1\beta}$. An efficient modification of this procedure with increased yield was reported by the Upjohn group.[7a,b]

(1) (a) Part III: M. Miyano, *J. Org. Chem.*, **35**, 2314 (1970). (b) A portion of this work was disclosed in preliminary form: M. Miyano and C. R. Dorn, *Tetrahedron Lett.*, 1615 (1969).

(2) (a) P. W. Ramwell, J. E. Shaw, G. B. Clarke, M. R. Grostic, D. G. Kaiser, and J. E. Pike, *Progr. Chem. Fats Other Lipids*, **9**, Part 2, 231 (1968); (b) S. Bergström, *Science*, **157**, 382 (1967); (c) S. Berström, L. A. Carlson, and J. R. Weeks, *Pharmacol. Rev.*, **20**, 1 (1968); (d) V. R. Pickles, *Nature (London)*, **224**, 221 (1969); (e) J. F. Bagli, *Annu. Rep. Med. Chem.*, 170 (1970).

(3) *Brit. Med. J.*, **4**, No. 5730, 253 (1970).

(4) (a) S. Bergström, L. Krabisch, B. Samuelsson, and J. Sjövall, *Acta Chem. Scand.*, **16**, 969 (1962); (b) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).

(5) (a) E. J. Corey, N. H. Andersen; R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. Winter, *J. Amer. Chem. Soc.*, **90**, 3245 (1968); (b) E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *ibid.*, **90**, 3247 (1968); (c) E. J. Corey, I. Vlattas, and K. Harding, *ibid.*, **91**, 535 (1969); (d) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *ibid.*, **91**, 5675 (1969); (e) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *ibid.*, **92**, 397 (1970); (f) E. J. Corey, R. Noyori, and T. K. Schaaf, *ibid.*, **92**, 2586 (1970); (g) E. J. Corey, U. Koelliker, and J. Neuffer, *ibid.*, **93**, 1489 (1971); (h) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971); (i) E. J. Corey, T. Ravindranathan, and S. Terashima, *ibid.*, **93**, 4326 (1971).

(6) H. Nugteren, H. Vonkeman, and D. A. van Dorp, *Recl. Trav. Chim. Pays-Bas*, **86**, 1237 (1967).

(7) (a) W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *J. Amer. Chem. Soc.*, **90**, 5895 (1968); (b) *ibid.*, **91**, 5372 (1969); (c) U. Axen, F. H. Lincoln, and J. L. Thompson, *Chem. Commun.*, 303 (1969).

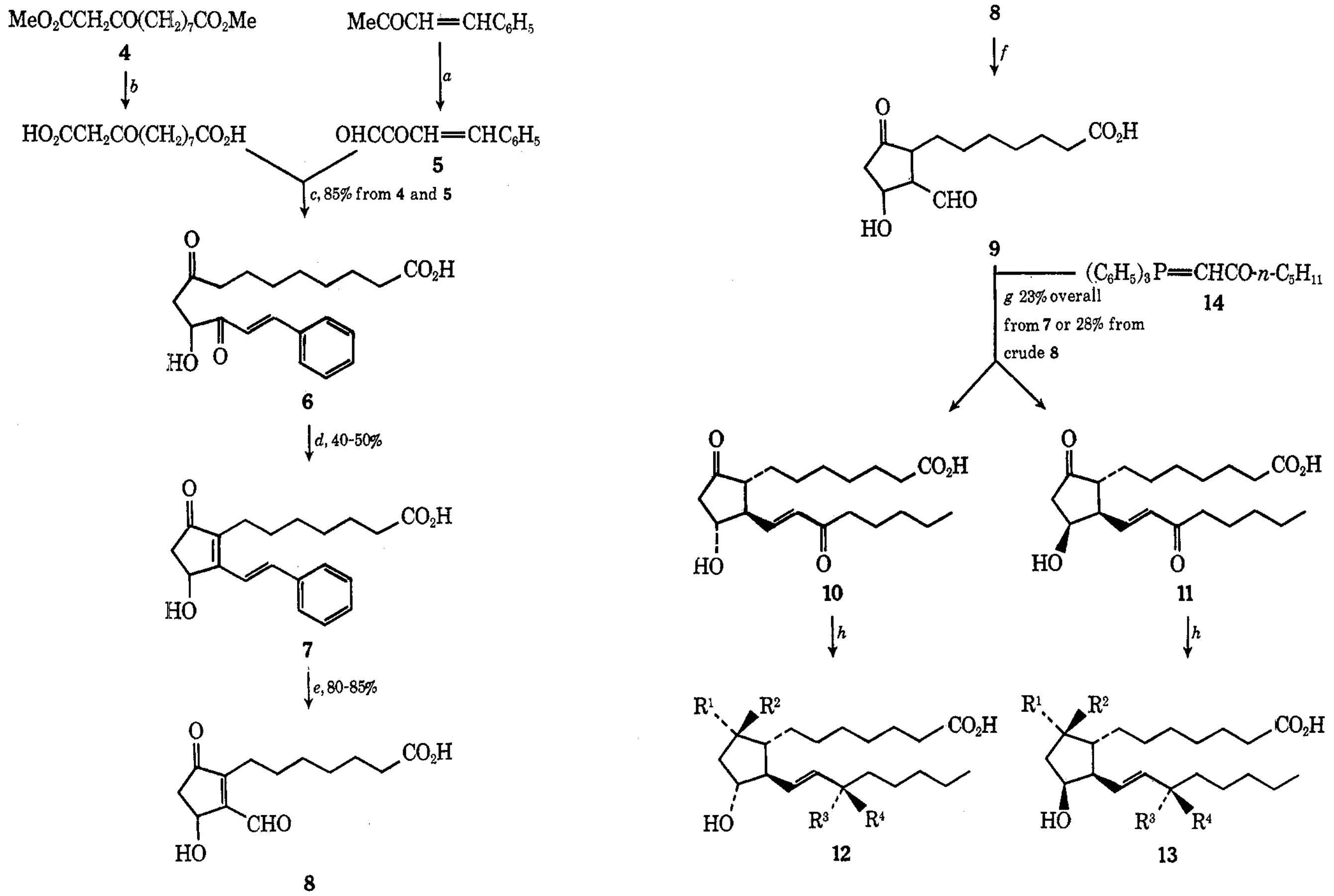
(8) N. Finch and J. J. Fitt, *Tetrahedron Lett.*, 4639 (1969).

(9) D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, Z. S. Zelawski, and N. L. Wendler, *Chem. Commun.*, 1258 (1970).

(10) G. Just and C. Simonovitch, *Tetrahedron Lett.*, 2093 (1967).

(11) (a) K. G. Holden, B. Hwang, K. R. Williams, J. Weinstock, M. Harman, and J. A. Weisbach, *Tetrahedron Lett.*, 1569 (1968). (b) G. Just, C. Simonovitch, F. H. Lincoln, W. P. Schneider, U. Axen, G. B. Spero, and J. E. Pike, *J. Amer. Chem. Soc.*, **91**, 5364 (1969).

CHART I

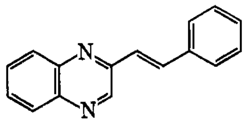


a, $R^1 = R^3 = OH; R^2 = R^4 = H$
b, $R^1 = R^4 = OH; R^2 = R^3 = H$
c, $R^2 = R^3 = OH; R^1 = R^4 = H$
d, $R^2 = R^4 = OH; R^1 = R^3 = H$

[a] Selenous acid in refluxing aqueous dioxane. [b] KOH in water at 5° for 72 hr. [c] Aqueous citrate buffer of pH 4.5-5.0 at room temperature. [d] Dilute KOH at room temperature. [e] 2 $NaIO_4$ in the presence of a catalytic amount of OsO_4 in aqueous dioxane. [f] Zinc powder in 2% acetic acid at 0° or in 8% phosphate buffer of pH 3.5 at 0°. [g] Two moles of n-hexanoylmethylene triphenylphosphorane in refluxing benzene containing dioxane. [h] Sodium borohydride in citrate buffer at 0°.

The object of this work was not merely the preparation of F_1 type prostaglandins, but also to develop an efficient general synthesis of new prostaglandin analogs having more selective biological activities. A sufficiently flexible synthetic route was sought which would afford the various PGF_1s (**12** and **13**) and might be extended to the synthesis of other important prostaglandins such as PGE_1 (1)[12] or dihydro-PGE_1.[13] A novel aspect of our seven-step scheme outlined in Chart I utilizes no protecting groups, but instead relies on a few carefully chosen reagents designed to achieve selective reactions in the presence of other reactive functional groups. Another unique feature of this scheme is that the relative stereochemistry at C-8, C-11, and C-12 of the final products (15-dehydro-PGE_1,[14a] PGE_1,[14a,c] and PGF_1[14b,c]) can be controlled by a single step, that is, reduction of **8** to **9**. This special situation offers an unusual opportunity to effect a stereospecific total synthesis of natural prostaglandins by modifying[12] the reduction step. All synthetic compounds described in this paper are racemic.

Synthesis and Determination of the Stereochemistry of the *dl*-15-Dehydro-PGE$_1$s (10, 11, and 18).—The starting material, styrylglyoxal (**5**), was readily prepared by the selenous acid oxidation of benzalacetone. Although the nmr spectrum of **5** revealed only a weak aldehyde proton signal (possibly due to the presence of polymeric forms), the structure was confirmed by the formation of styrylquinoxaline[15] (**15**) on brief treatment with *O*-phenylenediamine. Mild saponification of the dimethyl ester **4**[16] furnished 3-ketoundecan-1,11-dioic acid, which was condensed[17] with **5** in aqueous



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[12] This has been acieved in these laboratories for the racemic substance and will be published in a subsequent paper.

[13] This was accomplished and is the subject of the accompanying communication: M. Miyano and C. R. Dorn, *J. Org. Chem.*, **37**, 1818 (1972).

[14] (a) The 8,12-cis forms can be isomerized to the trans isomers (see ref 4b and 25). (b) The configuration at C-15 of undesired isomers can be reversed by recycling either by formolysis and saponification (see ref 4b) or selective oxidation and reduction (see ref 5c). (c) See ref 5h for stereoselective reduction of 15 ketone.

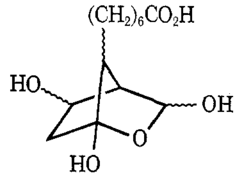
[15] (a) W. Ried and S. Hinsching, *Justus Liebigs Ann. Chem.*, **600**, 54 (1959); (b) J. K. Landquist and G. J. Stacey, *J. Chem. Soc.*, 2827 (1953).

[16] K. E. Arosenius, G. Ställberg, E. Stenhagen, and B. Tägtström-Eketorp, *Ark. Kemi, Mineral. Geol.*, **26A**, No. 19, 20 (1948).

[17] A similar condensation between pyruvic aldehyde and several 3-keto acids is well documented: M. S. Schechter, N. Green, and F. B. LaForge, *J. Amer. Chem. Soc.*, **71**, 3165 (1949).

buffer (pH 4.5–5.0) to afford the crystalline acid **6** in *ca.* 85% yield from the crude starting materials. The crystalline half potassium salt of **6** spontaneously precipitated from the reaction mixture as the condensation proceeded. It was absolutely necessary to *depolymerize* **5** (for instance, by briefly heating a methanolic solution to 60°) in order to obtain a satisfactory yield of **6**. Treatement of the hydroxy diketone **6** with dilute alkali effected cyclodehydration to the crystalline cyclopentenone derivative **7** in 40–50% yield. Periodate cleavage[18] of **7** in the presence of a catalytic amount of osmium tetroxide gave an 85% yield of the oily aldehyde **8**, which was characterized as the crystalline aldoxime and dioxime. The unsaturated aldehyde **8** was reduced to **9** with zinc in cold 2% aqueous acetic acid or in cold phosphate buffer of pH 3.5.

Since the nmr spectrum of **9** (mixture of stereoisomers) in deuteriochloroform or in deuteriodimethyl sulfoxide did not show the aldehydic proton, the aldehyde group is conceivably masked as hydrated lactol forms such as **16** or polymeric forms like **17**. The hydrated form **16** is unlikely to be the predominant species, since little water was formed in the subsequent Wittig condensation. In any event, compound **9** was too unstable to be fully purified and was used immediately in the next step. Apparently the saturated aldehyde derived some stabilization when mixed with (*n*-hexanoylmethylene)triphenylphosphorane (**14**)[19] and the Wittig reaction[20] produced oily 15-dehydro-PGE$_1$ (**10**, $\sim$12% from **7**), crystalline 11-epi-15-dehydro-PGE$_1$ (**11**, $\sim$12% from **7**), crystalline 12-epi-15-dehydro-PGE$_1$ (**18**, $\sim$1.2%), and an oily dehydration product (**19**, $\sim$12%). The product ratio is determined by the conditions of the zinc reduction rather than by the subsequent Wittig condensation. Thus, by zinc reduction of **8** in 2% acetic acid, **19** became one of the major products and **18** diminished to a negligible amount, while reduction in 8% phosphate buffer yielded little **19**.



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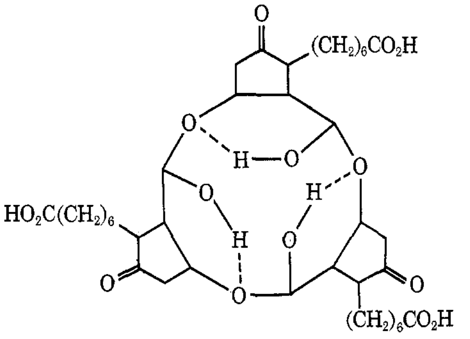

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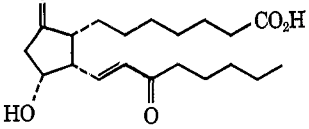

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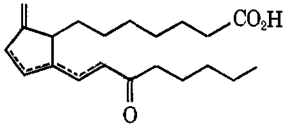

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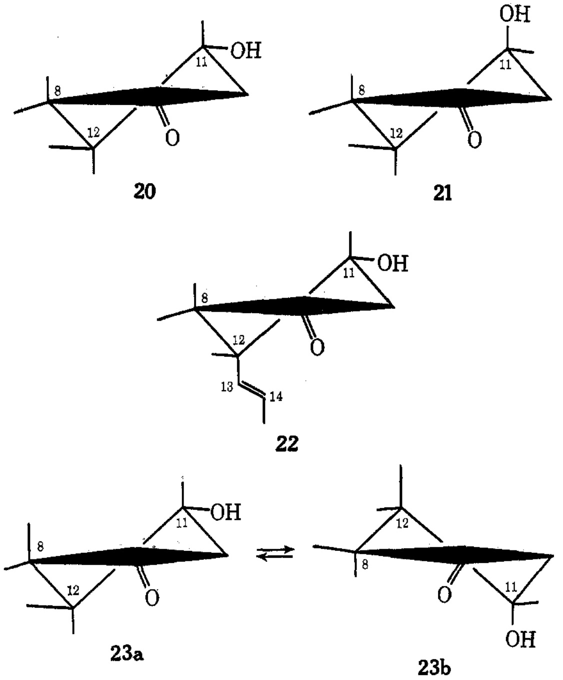
The configurations of the 15-dehydro-PGE$_1$ stereoisomers were determined by nmr spectroscopy, mild base-catalyzed epimerizations, and further chemical transformations to the PGF$_1$s. The most stable conformation for **10**, **11**, **18**, and the fourth isomer, 8-epi-15-dehydro-PGE$_1$, is shown in Chart II with the carbonyl group placed at the least puckered carbon[21-23] to minimize torsional energy and the half-chair conformation of the cyclopentanone ring taken to be more favorable than the envelope form.[22] It was also assumed that large equatorial substituents on the cyclopentanone ring are generally, but not necessarily, more stable than the corresponding axial orientations. For compounds **10**, **11**, and **18**, only one conformation (**20**, **21**, and **22**, respectively) is far more stable than the others; however, two equally plausible structures (**23a** and **23b**) may be written for the 8 epimer. The nmr signals of H-11 for **10** (higher field with larger coupling constants, typical for axial H), **11** (lower field with smaller coupling constants, suggesting equatorial H), and **18** (larger coupling constants, but lower field due to deshielding probably by the C-13–C-14 double bond) given in Table I are in good agreement with the conformations shown in Chart II. Furthermore, the olefinic proton signals (H-13,14) and the carbinol proton signal

CHART II
THE MOST STABLE CONFORMATION OF "NATURAL" (**20**), 11-EPI- (**21**), 12-EPI- (**22**), AND 8-EPI-15-DEHYDRO-PGE$_1$ (**23**)



20 **21** **22** **23a** **23b**

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[18] R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1958).

[19] P. F. Beal, III, J. C. Babcock, and F. H. Lincoln, *J. Amer. Chem. Soc.*, **88**, 3131 (1966).

[20] It was claimed that the tri-*n*-butylphosphorane gave better results (see ref 8) in a similar reaction.

[21] C. Altona, H. R. Buys, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 973 (1966).

[22] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, p 200.

[23] O. Korver, *Recl. Trav. Chim. Pays-Bas*, **88**, 1070 (1969).

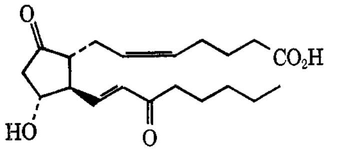
TABLE I

NMR SPECTRA OF **10**, **11**, **18**, AND **24** IN DEUTERIOCHLOROFORM (60 MHz)

Compd	H-11, τ	H-13,[a] τ	$J_{12,13}$, Hz	H-14,[a] τ	$J_{13,14}$, Hz
24	5.56[b] 5.67 5.82 5.95	2.97 3.10 3.23 3.36	7.5	3.58 3.85	16
10	5.57[b] 5.70 5.84 5.96	2.97 3.10 3.23 3.37	7.5	3.57 3.84	16
11	5.46[c] 8.5 Hz[d]	2.77 2.88 3.03 3.14	7.0	3.58 3.85	16
18	5.40[c] *ca.* 24 Hz[d]	3.05 3.22 3.30 3.48	10.0	3.59 3.85	15.5

[a] H-14, H-13, and H-12 constituted an ABX pattern. [b] Broadened quartet. [c] Multiplet centered at value given. [d] Width between outer peaks.

(H-11) for **10** were indistinguishable from those of 15-dehydro-PGE$_2$ (**24**) prepared by a known procedure[24] from natural PGE$_2$. Final confirmation of the "natural" configuration for **10** was accomplished by reduction to *dl*-PGF$_{1\alpha}$ (**12a**) and *dl*-PGF$_{1\beta}$ (**12c**). In line with the 8,12-trans configuration, neither **10** nor **11** was epimerized by treatment with excess potassium acetate, the condition[4b,25] known to isomerize 8-epi-PGE$_1$ (8,12-cis) into PGE$_1$ (8,12-trans). On the other hand, mild treatment of **18** (8,12-cis) effected almost complete epimerization at C-8[26] to produce **11**, thus unequivocally establishing the configurations of **11** and **18**. Evidence for the absence of epimerization of the C-11 hydroxyl group (by reversed aldol followed by aldol cyclization) and of the C-12 hydrogen was demonstrated in these laboratories by deuterium exchange experiments which will be published elsewhere. To the best of our knowledge, **18** is the first compound of the 12-epi prostanoic acid series to be described in the literature.



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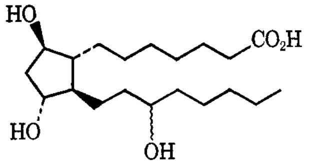
Synthesis of *dl*-PGF$_{1\alpha}$ (12a), *dl*-PGF$_{1\beta}$ (12c), and Their 15 Epimers (12b,d).—The borohydride reduction of **10** was greatly dependent upon conditions; for example, sodium borohydride in cold methanol gave a significant amount of dihydro-PGF$_1$ compounds[27] along with the desired products (**12a–d**). The dihydro-PGF$_1$s were the major products from the tetraethylammonium borohydride reduction in methylene chloride, whereas only small amounts of these dihydro compounds were formed using potassium borohydride in aqueous buffer. In all cases, the crude reduction product was separated into two fractions by reversed phase partition chromatography.[4a] Rechromatography of the earlier fractions (mainly 9,11-trans glycols) on SilicAR CC-4[28] afforded pure *dl*-PGF$_{1\beta}$ (**12c**), mp 116° (lit.[5a,11b] mp 116.6 and 113–115°), and pure *dl*-15-epi-PGF$_{1\beta}$ (**12d**, glass[29]). Esterification of **12c** with diazomethane yielded *dl*-PGF$_{1\beta}$ methyl ester, mp 103–104° (lit.[7a,11b] mp 101–102°). The latter fractions (predominantly 9,11-cis glycols) from the partition column were chromatographed again to afford pure *dl*-15-epi-PGF$_{1\alpha}$ (**12b**), mp 61–62°,[29] and partially crystalline PGF$_{1\alpha}$ (**12a**) contaminated with **12d**. Crude **12a** was freed from impurities by boric acid impregnated dry column chromatography[30a,b] to furnish *dl*-PGF$_{1\alpha}$, mp 81° (lit.[5a] mp 81°), which was found[31] to be 48.6% as active on the smooth muscle of the rabbit duodenum as natural PGF$_{1\alpha}$ kindly provided by the Upjohn Co. The nmr spectra of synthetic **12a** and **12c** in deuteriomethanol were identical with the nmr spectra of natural PGF$_{1\alpha}$ and PGF$_{1\beta}$ prepared by a known procedure.[4a]

Synthesis and Stereochemistry of the Four 11-Epi-PGF$_1$s (13a–d).—Reduction of **11** with potassium borohydride afforded the desired products (**13a–d**) accompanied by dihydro 11-epi-PGF$_1$ isomers. The crude reduction mixture was separated by the reversed phase partition column[4a] followed by adsorption chromatography on SilicAR CC-4 to yield the pure isomers (**13a–d**), of which three are crystalline[29] (see Table V).

The cis,trans relationships between the C-9 and C-11 hydroxyl groups could be established by either nmr analysis or boric acid complex formation (see Tables II–IV and discussion below). A discussion of the nmr spectra of the dihydro compounds **25** and **26** (by-products from the aforementioned borohydride reduction of **10** and **11**, respectively) is informative, since the same general argument can be made for F-type prostaglandins. Complications arise from the nmr analysis of the PGF$_1$s, because these compounds do not assume "fixed" conformations, but exist as rapidly interconverting (pseudorotation[21]) conformational mixtures. Thus, compound **25** presumably pseudorotates rapidly among half-chair conformations such as **27**, **28**, and **29** and envelope conformations like **30** and **31** (X = H, Y = OH) (Chart III). From these conformations, it is readily seen that the carbinol H-9 and H-11 protons of **25** are predominantly axial, whereas H-9 and H-11 of



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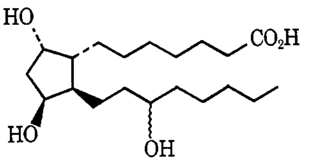

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(24) E. Änggard and B. Samuelsson, *J. Biol. Chem.*, **239**, 4097 (1964).

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

(26) Since we are dealing with a racemic substance, 8,12-bisepi isomer is equivalent to the 11 epimer.

(27) A similar reduction of the $\Delta^{13(14)}$ bond has been recorded; see ref 5a.

(28) N. H. Andersen, *J. Lipid Res.*, **10**, 316 (1969).

(29) No melting point has been recorded in the literature.

(30) (a) This technique, developed in our laboratory, appears especially useful for separation of 9,11-*cis*- from 9,11-*trans*-hydroxy prostaglandin. (b) The methyl ester of *dl*-PGF$_{1\alpha}$ could be purified by boric acid impregnated thick layer chromatography (see ref 11b, p 5371). The crude *dl*-PGF$_{1\alpha}$ obtained by our synthesis could not be purified by the latter technique.

(31) Evaluated by Dr. J. H. Sanner of the Biology Department.

TABLE II

NMR SPECTRA OF **12a–d** IN DEUTERIOMETHANOL (60 MHz)

Compd	$J_{9,10}$ and $J_{10,11}$, Hz	H-9, τ	H-10, τ	H-11, τ	H-15, τ	Diagnosis of cis, trans: By nmr	Diagnosis of cis, trans: By boric acid complex
12a	Unequal	5.92^{c}	*a*	$6.12^{b,d}$	5.92	cis	cis
12b	Unequal	5.93^{c}	*a*	$6.17^{b,d}$	5.93	cis	cis
12c	6.5–7.0	6.00^{d}	8.13^{e} (triplet)	6.00^{d}	6.14^{b}	trans	trans
12d	6.5–7.0	6.05^{d}	8.18^{e} (triplet)	6.05^{d}	6.17^{b}	trans	trans

[a] Could not be located. [b] Approximate chemical shift; because of overlapping signals the exact position could not be located. [c] Quasiequatorial proton. [d] Quasiaxial proton. [e] Two protons were "equivalent."

TABLE III

NMR SPECTRA OF **13a–d** IN DEUTERIOMETHANOL (60 MHz)

Compd	$J_{9,10}$ and $J_{10,11}$, Hz	H-9, τ	H-10, τ	H-11, τ	H-15, τ	Diagnosis of cis, trans: By nmr	Diagnosis of cis, trans: By boric acid complex
13a	4.5	5.75^{c}	8.00^{d} (triplet)	5.75^{c}	5.97	trans	trans
13b	4.5	5.75^{c}	8.00^{d} (triplet)	5.75^{c}	5.92	trans	trans
13c	Unequal	6.20^{b}	*a*	5.95^{c}	5.95	cis	cis
13d	Unequal	6.25^{b}	*a*	6.00^{c}	6.00	cis	cis

[a] Could not be located. [b] Quasiaxial. [c] Quasiequatorial. [d] Two protons were "equivalent."

TABLE IV

NMR SPECTRA OF **25** AND **26** IN DEUTERIOMETHANOL (60 MHz)

Compd	$J_{9,10} = J_{10,11}$, Hz	H-9, τ	H-10, τ	H-11, τ	H-15, τ	Diagnosis of cis, trans: By nmr	Diagnosis of cis, trans: By boric acid complex
25	6–6.5	5.95^{a}	8.20^{c}	5.95^{a}	6.47	trans	trans
26	4.5	5.73^{b}	8.02^{c}	5.73^{b}	6.43	trans	trans

[a] Quasiaxial. [b] Quasiequatorial. [c] Triplet; the two protons were "equivalent."

26 are essentially equatorial. As a consequence of this rapid pseudorotation, the H-10α and H-10β protons of **25** were equivalent by nmr spectrometry; they exhibited no geminal coupling and appeared as a triplet[32] due to equal couplings with H-9 and H-11 (see Table IV). Likewise, the H-10α and H-10β hydrogens of **26** also displayed "equivalence" and appeared as a triplet (Figure 1a). Upon irradiation of the H-9 and H-11 signals at τ 5.73, the H-10α and H-10β protons were decoupled to form a singlet (Figure 1b), while irradiation of the C-10 protons at τ 8.02 transformed the multiplet of H-9 and H-11 into a singlet ($W_{1/2}$ = 4 Hz, Figure 2). A careful examination of the nmr chart of **26** disclosed small coupling constants for $J_{8,9}$ and $J_{11,12}$ (0–2 Hz), suggesting a cis relationship for H-8 and H-9, as well as H-11 and H-12. Since H-10α and H-10β are "equivalent," the C-9 and H-11 hydroxyl groups must be trans, and this was confirmed by negative boric acid complex formation (Table IV). The "equivalence" of H-9 and H-11 (Figures 1 and 2, Table IV) dictates that the C-8 and C-12 side chains must also be trans, thus providing additional and independent evidence for the configuration of **11**.

TABLE V

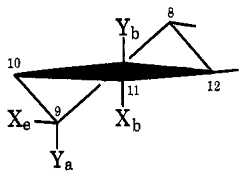
MELTING POINTS, IR SPECTRA, AND ELEMENTARY ANALYSES OF **12a–d**, **13a–d**, **25**, AND **26**

	Mp, °C	Found, %: C	Found, %: H	Ir (KBr), cm^{-1}: OH	Ir (KBr), cm^{-1}: C=O	Ir (KBr), cm^{-1}: C=C
dl-PGF$_{1\alpha}$ (**12a**)	81^{d}	67.52	10.13^{a}	3330	1716	967
12b	62^{e}	67.85	10.25^{a}	3400	1712	975
dl-PGF$_{1\beta}$ (**12c**)	116^{f}	67.67	10.07^{a}	3285	1720	978
12d	Glass^{e}	67.41	10.17^{a}	3330	1712	971^{c}
13a	127.5^{e}	67.11	10.25^{a}	3300	1713	970
13b	108.5^{e}	67.37	10.28^{a}	3480 3300	1713	982
13c	Glass^{e}	67.26	10.34^{a}	3360	1712	972^{c}
13d	67.5^{e}	67.72	10.05^{a}	3350	1719	974
25	Glass^{e}	67.15	10.59^{b}			
26	100.5^{e}	67.03	10.78^{b}	3405 3330	1705	None

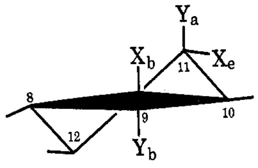
[a] Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. [b] Calcd for $C_{20}H_{38}O_5$: C, 67.00; H, 10.68. [c] Neat. [d] Lit.[5a] mp 81°. [e] To the best of our knowledge, no melting point has been given in the literature. [f] Lit.[5a,11b] mp 116.4–116.8, 113.5°.

CHART III

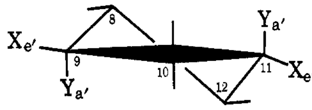
STABLE CONFORMATIONS OF DIHYDRO-PGF$_{1\beta}$ (**25**, X = OH, Y = H) and 11-EPIDIHYDRO-PGF$_{1\alpha}$ (**26**, X = H, Y = OH)[a]



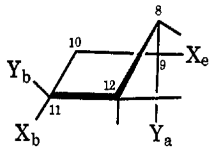
27



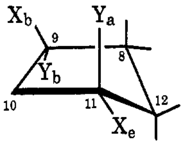
28



29



30



31

[a] a, axial; b, bisectional; e, equatorial.

The aforementioned nmr analysis of **25** and **26** can be applied to determine the cis,trans relationship of the C-9 and C-11 hydroxyl groups of **12a–d** as well as **13a–d**. In the trans glycols (**12c**, **12d**, **13a**, and **13b**) H-10α and H-10β appeared as triplets, whereas in the cis glycols (**12a**, **12b**, **13c**, and **13d**) they exhibited more complex patterns. In addition, the 9,11 cis,trans orientation could be ascertained by tlc; that is, the R_f values of the cis glycols are significantly increased on silica gel plates pretreated with boric acid, owing to transient formation of the boric acid complexes.[33] As

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(32) For a similar example, see N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "High Resolution NMR Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963, p 469.

(33) For a similar observation, see (a) ref 11b, p 5371; (b) L. J. Morris, *Lipids*, **1**, 41 (1966); (c) *J. Chromatogr.*, **12**, 321 (1963).

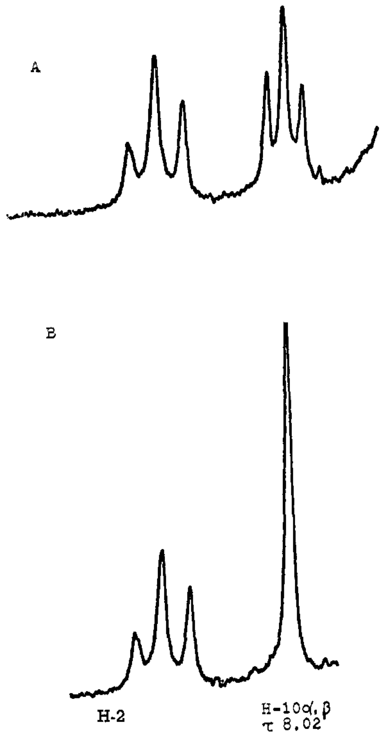


Figure 1.—Nmr signal (100 MHz, CD_3OD) of H-10α and H-10β of **26** before (A) and after (B) irradiating H-9 and H-11.

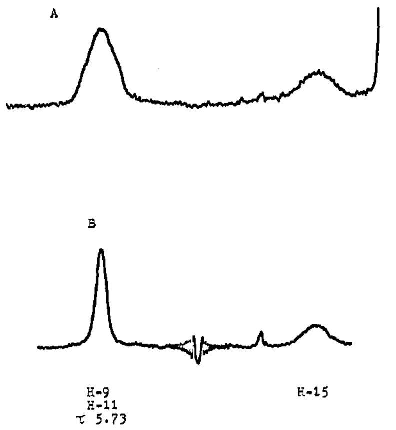
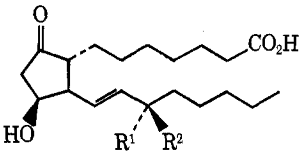


Figure 2.—Nmr signal (100 MHz, CD_3OD) of H-9 and H-11 of **26** before (A) and after (B) irradiating H-10.

summarized in Tables II–IV, the nmr diagnosis is in good agreement with the boric acid complexing ability.

Finally, the stereochemistry at C-15 of **13a–d** was determined chemically by sodium borohydride reduction of *dl*-11-epi-PGE$_1$ (**32**)[5a,34] and *dl*-11,15-bisepi-PGE$_1$ (**33**).[5a,34] Reduction of **32** afforded **13a** and **13c**, which must possess the "natural" configuration at C-15, whereas the isomer **33** produced the 15-epi compounds **13b** and **13d**.



32, $R^1 = OH; R^2 = H$
33, $R^1 = H; R^2 = OH$

All four 11-epi-PGF$_1$s (**13a–d**) have been mentioned in the literature.[28] Unfortunately, the method of preparation was not given. Furthermore, the only property described for these compounds was their relative mobilities on tlc and these were not consistent with our findings (**12b** > **13d** = **13b** > **12d** > **13c** > **12a** > **13a** > **12c**). We were therefore unable to compare our compounds with those previously reported.

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt in open capillaries and were not corrected. The nmr spectra were recorded at 60 MHz on a Varian A-60 and at 100 MHz on a Varian HA-100 nmr spectrometer in either $CDCl_3$ or CD_3OD, using TMS as an internal reference (τ 10.00). $W_{1/2}$ denotes peak width (hertz) at half-height. All uv spectra were determined in 1 mg % methanol solution.

Styrylglyoxal (5).—A solution of 106 g of benzalacetone and 100 g of selenous acid in 20 ml of water and 200 ml of dioxane in a 1-l. round-bottom flask was refluxed vigorously for 20 min. The reaction mixture was decanted while it was warm, concentrated, and distilled quickly to give 64.2–77.2 g (55–66%) of yellow crystalline **5**, bp 110–120° (2.5 mm), uv (MeOH) 295 mμ (ε 17,400).

2-Styrylquinoxaline (15).—A solution of 5.0 g of **5** and 3.4 g of *o*-phenylenediamine in 20 ml of ethanol was warmed on a steam bath and set aside overnight. Crystals (5.0 g, mp 106°) were collected and recrystallized from ethanol to give light brown needles, mp 106.5°.[15]

14-Phenyl-11-hydroxy-9,12-diketotetradeca-13-enoic Acid (6).—A cold solution of 38.2 g of dimethyl 3-oxoundecan-1,11-dioate (90–95% pure)[16] in 200 ml of 10% potassium hydroxide was refrigerated for 3 days. The alkaline solution was filtered through a wet filter to remove unsaponifiable oil (mostly dimethyl azelate contaminated in the starting β-keto ester), neutralized with concentrated citric acid to pH 4.9, and treated with 30 ml of 1.0 *M* citrate buffer (pH 4.8 prepared from citric acid and potassium hydroxide). To the undecanoate solution was added a solution of freshly depolymerized glyoxal, prepared by heating a mixture of 21.9 g of **5** in 50 ml of 50% aqueous methanol at 65–75° for 20 min and then diluting with 75 ml of methanol. The mixture was stirred at room temperature for 3 hr. The slightly exothermic reaction proceeded with evolution of carbon dioxide and the final pH of the reaction mixture was 6. Crystals were collected by suction, washed with water, and dried to give 37.6 g (76% based upon **5**) of the half potassium salt of **6**, mp 105°. The pure half potassium salt for analysis was obtained by recrystallization from methanol, mp 107.5°, uv (MeOH) 294 mμ (ε 22,500).

Anal. Calcd for $C_{40}H_{51}O_{10}K$: C, 65.73; H, 7.03. Found: C, 65.65; H, 7.01.

The ether extract of the mother liquor was washed with water, dried over sodium sulfate, and concentrated to yield 19.9 g of residue which gave rise to crystalline **6**. The latter was also obtained from the half potassium salt by shaking with ether and aqueous hydrochloric acid. Recrystallization from chloroform–ether afforded pure **6**: mp 81.5–83°; uv (MeOH) 294.5 mμ (ε 22,300); ir ($CHCl_3$) 2.84 (OH), 5.82 (C=O), 6.20 μ (C=O or C=C); nmr ($CDCl_3$) τ 2.19 (d, 1, J = 16 Hz), 2.97 (d, 1, J = 16 Hz,), 5.20 (t, 3, J = 5.5 Hz), 7.10 (d, 2, J = 6 Hz).

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.34; H, 7.65.

2-Styryl-3-hydroxy-5-oxo-1-cyclopentene-1-heptanoic Acid (7).—To a stirred solution (21°) of 6.7 g of potassium hydroxide in 3 l. of distilled water was added a solution of 10.4 g of **6** in 125 ml of chloroform during 2.5 hr at 21–23°. The mixture was stirred at 23–25° for another 2 hr, 200 ml of saturated salt solution was added, and the reaction mixture was acidified with 10 g of oxalic acid dihydrate. The chloroform extract (total 1.2 l.) was washed with dilute salt solution, dried over sodium sulfate, and concentrated and the residue was recrystallized from benzene to give 4.1 g (42%) of **7**, mp 117°. An additional amount of **7** was obtained by chromatographing the mother liquor (4.3 g) on silica gel using benzene containing 2% acetic acid and increasing amounts (up to 60%) of ethyl acetate. The analytical sample was obtained by recrystallization from chloroform–ether: mp 118°; ir ($CHCl_3$) 2.66, 2.74, 2.82 (OH), 5.86 (C=O), 6.14 μ (C=O) or C=C); uv (MeOH) 325 mμ (ε 36,400); nmr ($CDCl_3$)

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(34) Prepared in these laboratories together with *dl*-PGE$_1$ (ref 12).

τ 4.76 (d of d, 1, $J = 2$ and 6 Hz), 7.11 (d of d, 1, $J = 19$ and 6 Hz), 7.65 (d of d, 1 $J = 19$ and 2 Hz).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.20; H, 7.57.

2-Formyl-3-hydroxy-5-oxo-1-cyclopentene-1-heptanoic Acid (8).—A mixture of 13.0 g of **7**, 17.8 g of sodium metaperiodate, 40 mg of osmium tetroxide, 55 ml of water, and 160 ml of dioxane was stirred in a stoppered flask filled with nitrogen for 4 hr at room temperature. The reaction mixture was diluted with 250 ml of dioxane, filtered to remove inorganic material, diluted with 500 ml of benzene, and extracted six times with 400 ml of 1% sodium chloride solution. The aqueous extracts were washed with 500 ml of benzene (the same benzene being used to wash the six extracts), saturated with sodium chloride, and extracted with ether. The ethereal extracts were combined, dried over sodium sulfate, and concentrated to give 8.3 g (82.5%) of crude **8** which was used for the subsequent step without purification (work-up procedure A): uv (MeOH), 228 mμ (ϵ 10,100); nmr ($CDCl_3$) τ −0.37 (s, 1, aldehyde), 4.76 (d of d, 1, $J = 6$ and 3 Hz), 6.33 (s, 3), 7.09 (d of d, 1, $J = 19$ and 6 Hz), 7.61 (d of d, 1, $J = 19$ and 2.5 Hz).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.49; H, 7.75.

Two other work-up procedures for the above scale are given here. The aqueous extracts (6 × 400 ml of 1% sodium chloride) were concentrated to dryness *in vacuo* and the residue was extracted with ether. The ethereal solution was dried over sodium sulfate and concentrated to afford **8** (work-up procedure B).

The third and most convenient work-up was as follows. The reaction mixture was extracted repeatedly with ether and the ethereal dioxane solution was dried over sodium sulfate, concentrated, and dried at 70° (0.06 mm) for 5 min to remove benzaldehyde. The product obtained by the last procedure was contaminated with a small amount of **7** and benzaldehyde (work-up procedure C).

The dioxime was prepared in the usual manner and recrystallized from methanol–ethyl acetate: mp 184–185°; uv (MeOH) 278 mμ (ϵ 26,000); nmr (CD_3SOCD_3) τ 1.97 (s, 1, CH=N), 5.11 (broad d, 1, $J = 5$ Hz, CHO).

Anal. Calcd for $C_{13}H_{20}O_5N_2$: C, 54.92; H, 7.09; N, 9.85. Found: C, 54.97; H, 7.25; N, 9.27.

The aldoxime was prepared in the usual manner and recrystallized from ethyl acetate–chloroform and then from ether–chloroform: mp 111–112°; uv (MeOH) 273 mμ (ϵ 18,900); nmr (CD_3SOCD_3) τ 1.85 (s, 1, CH=N), 5.01 (broad d, 1, $J = 5.5$ Hz).

Anal. Calcd for $C_{13}H_{19}O_5N$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.68; H, 7.21; N, 5.17.

(*n*-Hexanoylmethylene)triphenylphosphorane (14).—A chloroform solution of the phosphonium chloride[19] was shaken with excess cold potassium carbonate solution, washed with dilute salt solution, dried over sodium sulfate, and concentrated. The residue was dissolved in benzene and the solvent was evaporated *in vacuo*. This was repeated once more to remove traces of chloroform. The residue was used for the subsequent condensations without further purification, nmr ($CDCl_3$) τ 6.41 (s, 1), 7.65 (t, 2, $J = 7$ Hz).

***dl*-15-Dehydro-PGE$_1$ (10), *dl*-11-Epi-15-dehydro-PGE$_1$ (11), and *dl*-12-Epi-15-dehydro-PGE$_1$ (18). A. Aqueous Acetic Acid Procedure 1.**—To a cold (2°) suspension of 20 g of zinc powder in 1.9 l. of 2% acetic acid was added with vigorous stirring 30.6 g of the crude unsaturated aldehyde **8** [prepared from 39 g (0.119 mol) of **7**] in 70 ml of tetrahydrofuran. The mixture was stirred under nitrogen with an additional 15 g of zinc powder for 1.5 hr at 2–3° and at the end of this period 1 l. of ether and 600 g of sodium chloride were added. The reaction mixture was filtered to remove excess zinc, which was washed with 200 ml of tetrahydrofuran. The cold filtrate was acidified with 6 g of tartaric acid and extracted with ether. The ethereal extracts (total of 3 l.) were washed with 1 l. of saturated sodium chloride solution, dried over sodium sulfate, concentrated *in vacuo*, and freed from traces of acetic acid under a nitrogen stream. The residue (26.3 g, crude **9**) was immdediately used for the condensation and refluxed with 90 g of phosphorane **14** in 200 ml of dioxane and 1.5 l. of benzene for 5 hr under nitrogen. The reaction mixture was concentrated *in vacuo*, dissolved in 1.5 l. of cold ether, and washed with 2 l. of cold 2.5% aqueous tartaric acid. Excess phosphorane **14** could be recovered from the tartaric acid washing by treatment with potassium carbonate followed by extraction with benzene. The ethereal solution containing acidic products and triphenylphosphine oxide was extracted repeatedly (5 × 200 ml) with chilled 3.5% potassium bicarbonate solution presaturated with carbon dioxide.[35] The cold bicarbonate extracts (total 1 l.) were acidified with 60 g of citric acid and the acidic product was taken up with ether. The ethereal extract was washed with 1% sodium chloride solution, dried over sodium sulfate, and concentrated *in vacuo* to afford 7.7 g of a mixture of **10**, **11**, and **19**. Repetitions of the bicarbonate extraction (5 × 200 ml) gave an additional 4.8 g. Further repetition of the bicarbonate extraction was very inefficient because the acidic products tended to remain in the ether layer, forming complexes with excess triphenylphosphine oxide. The ethereal mother liquor was then concentrated *in vacuo*, and the residue was dissolved in 30 ml of ether and treated with chilled bicarbonate solution.[35] Triphenylphosphine oxide crystallized out, thus forcing the acidic component to go into the aqueous phase. The chilled mixture was filtered to remove triphenylphosphine oxide, and another 2.9 g of material was obtained from the aqueous phase in the usual manner. Total amount of acidic material was 15.4 g (36% from **7**) which contained comparable amounts of **10**, **11**, and **19**, while 12.5–17 g of crystalline triphenylphosphine oxide was separated.

A mixture of 0.5 l. of Skelly B, 1 l. of benzene, 0.5 l. of methanol, and 0.2 l. of water was shaken and set aside. The lower phase was used to make the stationary phase of a partition column and the upper phase was used for elution. A portion (7.9 g) of the acidic product described above was chromatographed on a partition column made of 900 g of silica gel (Davison 923, 100–200 mesh) and 540 ml of the lower phase. After 2 l. of forerun containing **19** were discarded, fractions of 0.2 l were collected. Fractions 7–12 gave 2.0 g of **11**, fractions 13–18 gave 1.9 g of a mixture of **10** and **11**, and fractions 19–28 gave 1.4 g of **10**. The 11 epimer **11** was recrystallized from ether–pentane: mp 60°; uv max (MeOH) 228.5 mμ (ϵ 11,400); nmr ($CDCl_3$) τ 2.95 (q, 1, $J_{12,13} = 7$ Hz, $J_{13,14} = 16$ Hz, C-13 H), 3.72 (d, 1, $J_{13,14} = 16$ Hz, C-14 H), 5.46 (m, 1, C-11 H).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.08; H, 8.89.

The *dl* natural isomer **10** was an almost colorless glass: uv max (MeOH) 228.5 mμ (ϵ 10,700); nmr ($CDCl_3$) τ 3.17 (q, 1, $J_{12,13} = 7.5$, $J_{13,14} = 16$ Hz, C-13 H), 3.70 (d, 1, $J_{13,14} = 16$ Hz, C-14), 5.77 (m, 1, C-11 H).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.20; H, 9.16.

B. Aqueous Acetic Acid Procedure 2.—Crude aldehyde **8** (21 g, prepared from 27.8 g of **7**) was reduced with zinc and condensed with **14** in the usual manner (see A). After cooling, the reaction mixture was washed with 3 l. of cold 1% tartaric acid, washed with 0.7 l. of 2% sodium chloride, dried over sodium sulfate, and concentrated *in vacuo* to yield 26.2 g of brown gum. A portion (22.4 g) of this product was put on a column of 450 g of silicic acid (Mallinckrodt SilicAR CC-4, 100–200 mesh, packed using benzene), which was eluted with 3.3 l. of 10% ethyl acetate in benzene (dehydrated product **19** followed by triphenylphosphine oxide), 3 l. of 20% ethyl acetate in benzene (remaining triphenylphosphine oxide followed by **11**), and finally with 5 l. of 50% ethyl acetate–benzene (**11** and **10**). Thus 7.9 g (25.6%) of a mixture containing nearly equal amounts of **11** and **10** was obtained. Pure **11** and **10** were prepared by rechromatography of 6 g of the crude mixture on 600 g of SilicAR CC-4 washed with benzene and eluted with increasing amounts (10, 15, 20, 25, and 30%) of ethyl acetate. Pure **11** was obtained from the 25% ethyl acetate fractions while the 30% ethyl acetate fractions afforded a mixture of **11** and **10** followed by pure **10**.

C. Phosphate Buffer and "Magic Column" Procedure.[36]—A solution of 20 g of the crude aldehyde (**8**, prepared from 27 g of **7**) in 45 ml of tetrahydrofuran was added to 2 l. of cold phosphate buffer (8% sodium dihydrogen phosphate solution was acidified with phosphoric acid to pH 3.5) and stirred at 3–5° for 30 min. The zinc dust (35 g) was added portionwise and the mixture was stirred at 3–5° for 45 min. The reaction mixture (the final pH was 4.5) was filtered to remove zinc and the filter cake was washed with 50 ml of tetrahydrofuran. The filtrate was saturated with sodium chloride and extracted with ether (3 × 0.4 l.). The ethereal extracts were washed with saturated salt solution, dried over sodium sulfate and concentrated *in vacuo* to give crude **9** which was used immediately. The Wittig condensation with **14**

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[35] Prepared by adding excess solid carbon dioxide to 3.5% potassium bicarbonate solution.

[36] Carried out by Mr. M. Stealey.

was carried out in the usual manner (see A). After cooling, the reaction mixture was washed with cold tartaric acid (see B) to recover excess **14** and concentrated to leave 22 g of residue which contained very little dehydration product **19** and was separated into **10**, **11**, and **18** by the "magic column" as described below.

A mixture of 1.5 l. of benzene, 0.5 l. of methanol, and 0.2 l. of water was shaken and set aside. The column consisted of 500 g of silicic acid (Mallinckrodt SilicAR CC-4, 100–200 mesh) and 300 ml of the lower phase solvent. This column can be used repeatedly (at least ten times) without recharging. The crude product (22 g) was chromatographed in four portions, each taking 3–4 hr and requiring 2 l. of the upper phase solvent. Triphenylphosphine oxide was eluted first followed by $HOCH_2CH_2OCH_2CH{=}CHCOC_5H_{11}$, **11**, **10**, and **18**, respectively. Mixture fractions were chromatographed once more on the same column, giving ultimately 1.5 g of crude $HOCH_2CH_2OCH_2CH{=}CHCOC_5H_{11}$, 2.3 g of 11 epimer **11**, 1.4 g of a mixture of **11** and **10**, and 3.39 g of **10** containing about 0.5 g of 12 epimer. Total yield of **10**, **11**, and **18** was 7.1 g (23% overall from **7**). The last fraction was chromatographed on 300 g of CC-4. Elution with 33% ethyl acetate in benzene gave 1.34 g of pure **10**, then a mixture of **10** and **18**, and finally 0.50 g of **18**. The latter was recrystallized from ether containing *n*-pentane to give 360 mg of the pure **18**: mp 100–101°; uv max (MeOH) 226 mμ ϵ 12,300); nmr ($CDCl_3$) τ 3.28 (q 1, $J_{13,14} = 16$, $J_{12,13} = 10$ Hz, C-13 H), 3.72 (d, 1 $J_{13,14} = 16$ Hz, C-14 H), 5.40 (m, 1, C-11 H).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.12; H, 9.36.

***dl*-PGF$_{1\alpha}$(12a), *dl*-15-Epi-PGF$_{1\alpha}$ (12b), *dl*-PGF$_{1\beta}$ (12c), and *dl*-15-Epi-PGF$_{1\beta}$ (12d).**—To 300 ml of cold (−5°) 2% aqueous sodium citrate was added a solution of 1.2 g of **10** in 20 ml of methanol. Five grams of potassium borohydride was added in several portions during 40 min while the reaction mixture was stirred at −5° and the pH was kept at about 8 by neutralizing with 10% citric acid. The reaction mixture was stirred for an additional 2 hr at −5° and then warmed to room temperature while the pH was continually adjusted to about 8. After excess borohydride was decomposed with acetone, the reaction mixture was acidified with citric acid to pH 4, saturated with sodium chloride, and extracted with ether. The ethereal extract was washed with dilute hydrochloric acid saturated with sodium chloride, washed with saturated salt solution, dried over sodium sulfate, and concentrated to give 1.5 g of a mixture of **12a–d**.

The reduction product was chromatographed on a reversed phase partition column[4a] consisting of 60 g of hydrophobic Supercel and 60 ml of the stationary phase. After 0.4 l. of forerun, fraction 1 (1.6 l.) containing **12c** and **12d** was obtained, followed by fraction 2 (2.6 l.) containing **12a**, **12b** **25**, and 9-epi-**25**. Fraction 1 was concentrated (0.7 g) and shaken with ether and 0.1% hydrochloric acid saturated with salt. The ethereal extract was washed with saturated salt solution, dried over sodium sulfate concentrated, and chromatographed on 40 g of SilicAR CC-4 (100–200 mesh) using ethyl acetate with increasing amounts of acetone. After a small amount of impurity (**12b**), 15-epi-PGF$_{1\beta}$ (**12d**, 213 mg) was eluted,[37] followed by a mixture fraction (**12a**, **12d**) and finally by crystalline PGF$_{1\beta}$ (**12c**) which was recrystallized from ether to furnish 125 mg of **12c**, mp 116°.[37] A portion (0.5 g) of fraction 2 from the reversed phase partition column was chromatographed on 40 g of SilicAR CC-4 using ethyl acetate containing increasing amounts of acetone. After the removal of fast-moving impurities (dehydration products, **25**[37] and 9-epi-**25**), 85 mg of 15-epi-PGF$_{1\alpha}$ (**12b**) was eluted followed by 52 mg of a mixture fraction (**12b**, **12d**) and finally 201 mg of crude PGF$_{1\alpha}$ (**12a**). The 15-epi-PGF$_{1\alpha}$ (**12b**) thus obtained gave rise to waxy crystals, mp *ca.* 60°, which could be recrystallized from ether at 0° with a significant loss to give needles melting at 62.5°.[37] The 15-epi-PGF$_{1\alpha}$ eluted from a CC-4 column was occasionally contaminated with a trace of **25**, but was readily purified by a silver nitrate impregnated (5%) CC-4 column.

The crude *dl*-PGF$_{1\alpha}$ (**12a**) thus obtained was a sticky, crystalline mass which resisted crystallization, but could be purified by a boric acid impregnated column. Fifty grams of CC-4 was thoroughly mixed with 40 ml of 10% methanolic boric acid, and, after drying on a steam bath, the resulting silicic acid was further dried at 100° under reduced pressure (18 mm). The solvent system was the upper layer of 440 ml of ethyl acetate, 80 ml of acetic acid 60 ml of 2,2,4-trimethylpentane, and 400 ml of water. Crude **12a** (60 mg) in 1 ml of solvent was put on a dry column of 6 g of boric acid impregnated CC-4 and eluted with the same solvent, and fractions of 2 ml were collected. Fractions 4–7 were combined and evaporated under a nitrogen stream, and the residue was taken up in ether. The ethereal solution was washed with saturated salt solution containing a few drops of hydrochloric acid, washed with saturated salt solution, dried over sodium sulfate, and concentrated. Recrystallization of the residue separated 13 mg of pure **12a**, mp 81–82°.[37]

***dl*-11-Epi-PGF$_{1\alpha}$ (13a), *dl*-11,15-Diepi-PGF$_{1\alpha}$ (13b), *dl*-11-Epi-PGF$_{1\beta}$ (13c),[38] *dl*-11,15-Diepi-PGF$_{1\beta}$ (13d),[39] and Dihydro-11-epi-PGF$_1$ (26).**—To 500 ml of chilled (−5–0°) 2% sodium citrate solution was added 1.686 g of **11** in 50 ml of methanol. Potassium borohydride (7 g) was added portionwise during 1 hr while the reaction mixture was stirred at −5 to −3° and kept near pH 8 (phenolphthalein was used as internal indicator) by neutralizing with 10% citric acid. The cold bath was removed and the reaction mixture was stirred for 2 hr at pH 8–8.2. Excess borohydride was decomposed by acetone. The reaction mixture was diluted with ether, acidified with hydrochloric acid to pH 2.5, and saturated with sodium chloride. The ethereal extract was washed with 20% sodium chloride solution, dried over sodium sulfate, and concentrated to leave 1.812 g of colorless glass. Reversed phase partition chromatography[4a] on 100 g of hydrophobic Supercel was carried out and fractions of 100 ml were collected. Isomer **13a** was concentrated in fractions 5–39, isomer **13b** in fractions 26–50, isomer **13c** in fractions 44–56, isomer **13d** in 55–72, and the saturated compound **26** in 51–85. Fractions 9–35, on dissolution in methanol and treatment with acetone in the cold, gave rise to 150 mg of white crystals melting at around 146°. This substance **13a**, containing inorganic material, was dissolved in a small amount of warm methanol and then shaken with ether and saturated sodium chloride solution containing a few drops of hydrochloric acid. The ethereal solution was washed with saturated sodium chloride, dried over sodium sulfate, and concentrated and the residue was recrystallized from ether to afford colorless crystals, mp 126.5–127°.[37] Fractions 36–43, 44–52, 53–60, and 61–72 were chromatographed separately on CC-4 columns using ethyl acetate with increasing amounts of acetone. Fractions enriched with **13b**, **13c**, **13d**, and **26** were collected respectively. Fractions enriched by **13c** were combined and recrystallized from ethyl acetate to give colorless crystals (98 mg), mp 66.5–67.5°.[37] Fractions enriched in **13b** were combined and recrystallized from ether to give colorless crystals (188 mg) which were then recrystallized from ethyl acetate, mp 107.5–108.5°.[37] Fractions enriched with **26** were combined and recrystallized from ethyl acetate to give colorless crystals (117 mg), mp 99.5–100.5°.[37] Fractions enriched by **13d** were combined (102 mg), chromatographed (ethyl acetate) on silver nitrate (5%) impregnated[40] CC-4, and rechromatographed on a boric acid (8%) impregnated dry column of CC-4 to give a colorless glass.[37]

Registry No.—**5**, 6784-05-0; **6**, 34407-34-6; **6** (1/2K salt), 34405-35-1; **7**, 34388-78-8; **8**, 34388-79-9; **8** dioxime, 34388-80-2; **8** aldoxime, 34388-81-3; **10**, 34402-60-3; **11**, 34388-82-4; **12a**, 17066-90-9; **12b**, 34388-84-6; **12c**, 20348-60-1; **12d**, 34402-61-4; **13a**, 34388-86-8; **13b**, 34388-87-9; **13c**, 34437-28-0; **13d**, 34388-89-1; **18**, 34388-90-4; **24**, 34388-91-5; **25**, 34388-92-6; **26**, 34388-93-7.

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[37] See Tables II–V for ir (KBr), nmr (CD_3OD), and elementary analyses.

[38] Equal to *dl*-9,11-diepi-PGF$_{1\alpha}$.

[39] Equal to *dl*-9,11,15-triepi-PGF$_{1\alpha}$.

[40] See purification of *dl*-PGF$_{1\alpha}$ (**12a**).

competent execution of column chromatographies, to Mr. B. Smith for preparative tlc, to the Special Synthesis group under the direction of Drs. W. M. Hoehn and J. Witt for some starting materials, and to Mr. M. H. Stealey for his skillful technical assistance. Thanks are due to Dr. F. B. Colton for helpful discussion on this work and revision of the manuscript. Styryl glyoxal (5) for large-scale preparation of compound 6 and 7 has been supplied by Dr. M. Scott, G. D. Searle & Co., High Wycombe, England, to whom thanks are due.

Prostaglandins. V.[1] Synthesis of *dl*-Dihydroprostaglandin E_1 and $\Delta^{8(12)}$-Dehydroprostaglandin E_1[2]

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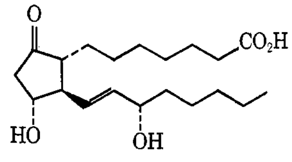
The facile synthesis of the new prostaglandin analogs, *dl*-$\Delta^{8(12)}$-dehydroprostaglandin E_1 (**5**) and its 15 epimer **6** is described (Chart I) which consists of a Wittig condensation of **3** with **19** to produce **4** followed by the selective reduction of the 15 ketone with borohydride. Hydrogenation of **5** afforded *dl*-dihydro-PGE$_1$ (**7a**) and *dl*-11,15-bisepidihydro-PGE$_1$ (**8**), while **6** gave rise to *dl*-15-epidihydro-PGE$_1$ (**9**) and *dl*-11-epidihydro-PGE$_1$ (**10**). Evidence concerning the stereochemical assignments for the above compounds is also presented. In addition, a new procedure for the large-scale preparation of the Wittig reagent, *n*-hexanoylmethylene triphenylphosphorane (**19**), is disclosed (Chart III). The key step is chlorination–decarboxylation of 3-oxooctanoic acid (**16**) to **17**.

The prostaglandins[3] are characterized as a family of C_{20} fatty acids, and one of its members, dihydroprostaglandin E_1 (**7b**, dihydro-PGE$_1$), occurs naturally[4] as a biologically active metabolite[5] of prostaglandin E_1 (**1**, PGE$_1$). Beal, *et al.*,[6] prepared the ethyl ester of a diastereomeric mixture of the various racemic dihydro-PGE$_1$s. More recently two other research teams independently reported[7] the synthesis of a biologically active mixture (presumably **7a**, **8**, **9**, and **10**) of stereoisomers of dihydro-PGE$_1$.



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In this paper we report the synthesis of *dl*-$\Delta^{8(12)}$-dehydro-PGE$_1$ (**5**), *dl*-15-epi-$\Delta^{8(12)}$-dehydro-PGE$_1$ (**6**), and each of the four racemic modifications of dihydro-PGE$_1$ (**7a**, **8**, **9**, and **10**). This synthesis, an extension of our earlier work,[1] is outlined in Chart I. Unless specifically stated to the contrary, all compounds described in this paper are racemic.

The readily available unsaturated aldehyde (**3**)[1] reacted smoothly with the Wittig reagent (**19**)[6] in the presence of an equivalent amount of triethylamine to afford the dienedione **4** in 85% yield. It was evident that the newly formed double bond was trans, as is the case in the natural series, owing to the coupling constant (16.5 Hz) of H-13 and H-14.

Selective reduction of the 15 ketone was accomplished by excess sodium borohydride in aqueous media to produce an approximately 1:1 mixture of **5** and **6** in 70–85% yield. Evidence for the selective reduction of the 15 ketone was deduced from spectral data. First of all, the uv maxima of **5** and **6** at 276 mμ are consistent[8] with the observed value of 278 mμ for the known 11-deoxy analog, prostaglandin B_1 (**12**).[9] Secondly, the adsorption at 276 mμ is in good agreement with the calculated value[10a,c,d] of 272 mμ, but at variance with the theoretical value of 299 mμ for the alternative structure (**11**).[10b–d] The expected coupling between the olefinic protons of either **5** or **6** was not observed using a 60-MHz instrument and could barely be detected (about 16.5 Hz) in 100-MHz nmr spectra, probably due to the fact that H-13 and H-14 happened to exhibit almost identical chemical shifts. In sharp contrast, all of the *trans*-$\Delta^{13(14)}$-15-keto prostaglandins (with or without $\Delta^{8(12)}$ double bond) synthesized in these laboratories showed the typical A,B pattern ($J_{13,14}$ = 16–16.5 Hz) for the olefinic proton signals. It was very difficult to effect large-scale separation of **5** from **6** by conventional adsorption column chromatography because of the unexpected instability of these substances. However, it was discovered that partition column chromatography[11] using SilicAR CC-4 with a benzene–methanol–water system effected fairly good separation with little decomposition. The two stereoisomers (**5**

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[1] Part IV: M. Miyano, C. R. Dorn, and R. A. Mueller, *J. Org. Chem.*, **37**, 1810 (1972).

[2] A portion of this work was disclosed in the preliminary communication: M. Miyano, C. R. Dorn, F. B. Colton, and W. R. Marsheck, *Chem. Commun.*, 425 (1971).

[3] For the review articles, see footnote 2 of part IV of this series.[1]

[4] E. Änggard and B. Samuelsson, *J. Biol. Chem.*, **239**, 4097 (1964).

[5] E. Änggard, *Acta Physiol. Scand.*, **66**, 509 (1966).

[6] P. F. Beal, III, J. C. Babcock, and F. H. Lincoln, *J. Amer. Chem. Soc.*, **88**, 3131 (1966).

[7] (a) D. P. Strike and H. Smith, *Tetrahedron Lett.*, 4393 (1970); (b) R. Klok, H. J. J. Pabon, and D. A. Van Dorp, *Recl. Trav. Chim. Pays-Bas*, **89**, 1043 (1970).

[8] The 11-hydroxy group exhibits a hypsochromic shift; see Table III of M. Miyano, *J. Org. Chem.*, **35**, 2314 (1970).

[9] S. Bergström, R. Ryhage, B. Samuelsson, and J. Sjövall, *J. Biol. Chem.*, **238**, 3555 (1964).

[10] (a) 202 (five-membered enone) + 30 (γ,δ double bond) + 10 (α substituent) + 12 (β substituent) + 18 (δ substituent) = 272; (b) 215 (aliphatic enone) + 30 (γ,δ double bond) + 18 (γ substituent) + 36 (two δ substituents) = 299; (c) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Macmillan, New York, N. Y., 1964, p 58; (d) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 19.

[11] See Experimental Section for **5** and **6**. Separation of 15-dehydro-PGE$_1$ from its 11 epimer (see ref 1) and separation of **7** from **8** as well as **9** from **10** (*vide infra*) were also carried out on the same column with little decomposition. Since the column can separate 2–5 g of a mixture in 4–5 hr, it may be considered a work-up procedure rather than a classical chromatography. The used column could be reused repeatedly without deterioration for as long as 6 months.