pounds X and **20** were better resolved on column III at 100°, giving retention times of 38.9 and 39.3 min, respectively.

Kinetic Measurements. A. Anhydrous Acetic Acid.[40]—Anhydrous acetic acid was prepared by refluxing reagent grade glacial acetic acid with 10% acetic anhydride and a catalytic amount of concentrated sulfuric acid. After having been refluxed for 12 hr, the acetic acid was distilled through a 30-plate perforated-glass column and collected over the range 117–117.5°. The acetic acid was stored in a flask equipped with a siphon-type arrangement so that it could be removed using a positive pressure of dry nitrogen without exposing it to air.

B. Titrations.—Titrations of acetic acid solutions of *p*-toluenesulfonic acid with sodium acetate in acetic acid were accomplished potentiometrically on a Potentiograph E 336 (Metrohm Ltd., Herisau, Switzerland). The sodium acetate solution, approximately 0.05 *M*, was obtained by dissolving anhydrous, reagent grade sodium acetate in anhydrous glacial acetic acid and making the solution up to volume. The sodium acetate solution was standardized against 0.0527 *M* perchloric acid in acetic acid.

C. Rate Measurements.—Solutions 0.05 *M* in the compounds to be solvolyzed were made up at room temperature in a volumetric flask from a weighed portion of the tosylate and anhydrous acetic acid. About 3-ml portions of the solutions were sealed in 10 ml color-break ampoules (Kimble Neutraglas) under nitrogen and immersed in a 100° oil thermostat. The exact temperature of the bath was obtained from a Beckman thermometer which had been previously calibrated with a quartz thermometer (Hewlett-Packard, Inc., Quartz Thermometer No. 2801A). At suitable times an ampoule was removed and placed in a dewar of Dry Ice–isopropyl alcohol until all samples could be titrated together. Approximately 12 samples were taken during each run, spaced evenly over the first two to four half-lives. An additional one to three samples were taken for infinity points. The samples were brought to room temperature and opened. A 2-ml aliquot was removed with a Chaney syringe adjusted to deliver a constant volume. The 2-ml volume was standardized by weighing the volume of distilled water delivered by the syringe. Each aliquot was diluted to approximately 15 ml with glacial acetic acid and titrated potentiometrically.

Rate constants were obtained using a nonlinear least-squares computer program LSKIN1[41] which calculates the best value of the first-order rate constant. The infinity titer was treated as a fixed parameter. The standard deviations of the rate constants, as calculated by the computer, showed the precision of the measurements to be good, the error limits obtained generally being less than ±3% of the observed rate constants. Results are presented in Table III.

(40) The procedure was adapted from the Ph.D. thesis of H. A. Hammond, "Studies of Acetolysis Rates of Arylmethyl *p*-Toluenesulfonates," University of California, Berkeley, Calif., 1966.

(41) D. F. DeTar and C. E. DeTar, "Computer Programs for Chemistry," Vol. I, W. A. Benjamin, New York, N. Y., 1969.

Registry No.—**1**, 22489-58-3; **2**, 34217-23-7; **3**-*d*, 34217-24-8; **4**, 34217-25-9; **6**, 34217-26-0; **8**, 34217-27-1; **9**, 34217-28-2; **10** ketal alcohol, 34217-29-3; **12**, 34217-30-6; **14**, 34217-31-7; **18**, 21789-58-2; **19**, 22489-59-4; **19** DNP, 34217-34-0; **19** semicarbazone, 34217-35-1; **20**, 22489-60-7; **22**, 34217-37-3; **23**, 34217-38-4; **24**, 34217-39-5; **25** (trans), 21370-71-8; **26**, 34217-41-9; **27**, 34217-42-0; **30**, 13031-01-1; **31** (trans), 5365-38-8; **32**, 34217-44-2; **33**, 22460-14-6; **37**, 15674-93-8; **54** DNP, 22460-13-5.

Acknowledgments.—We gratefully acknowledge financial assistance by the National Science Foundation and the Committee on Research, Berkeley Division, University of California. We also thank Mr. Clayton Quinn for technical assistance and Professor Donald Noyce for several stimulating discussions on the subject.

Synthesis of 5- and 6-Fluorobenzo[c]phenanthrene by Photocyclization

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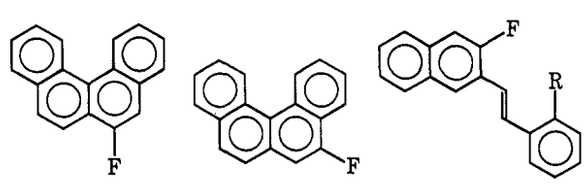
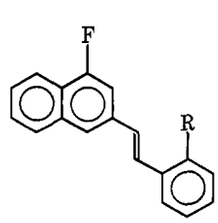
5- and 6-fluorobenzo[c]phenanthrene (**1**, **2**) were synthesized by photocyclization of the appropriately substituted 1-naphthyl-2-phenylethylenes. Various synthetic schemes for obtaining 1,3-disubstituted naphthalenes have been studied. The uv spectra of key compounds are tabulated.

Interest in fluoro analogs of polycyclic aromatic compounds stems from the hope that they may help evolve a model of chemically induced carcinogenicity.[1] We have synthesized the title compounds by photocyclization of the appropriately fluorinated diarylethylenes.[2-4]

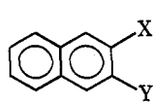
An intrinsic expectation of the synthetic approach to **1** and **2** was that the photodehydrogenation or photocyclization step would occur on the 4 carbon of the naphthalene moiety. This expectation was bolstered by the statement[5] that the formation of phenanthrene moieties from stilbenelike compounds is possible if the sum of the free valence numbers in the first excited state (Σ Fr*) of the appropriate carbon is greater than 1.0.



1 **2** **3a**, R = H; **b**, R = I



4a, R = H; **b**, R = I



5a, X = NH_2; Y = CO_2H
b, X = NH_2; Y = CO_2Me
c, X = F; Y = CO_2Me
d, X = F; Y = CH_2OH
e, X = F; Y = CH_2Br

(1) E. D. Bergmann and J. Blum, *J. Org. Chem.*, **27**, 527 (1962).
(2) J. Blum, F. Grauer, and E. D. Bergmann, *Tetrahedron*, **25**, 3501 (1969).
(3) S. M. Kupchan and H. C. Warmser, *Tetrahedron Lett.*, 3792 (1965); *J. Org. Chem.*, **30**, 3792 (1965).
(4) T. Sata, S. Shimada, and K. Hata, *Bull. Chem. Soc. Jap.*, **42**, 766 (1969).
(5) W. H. Laarhoven, T. J. Cuppen, and R. J. Nivard, *Recl. Trav. Chim. Pays-Bas*, **87**, 687 (1968).

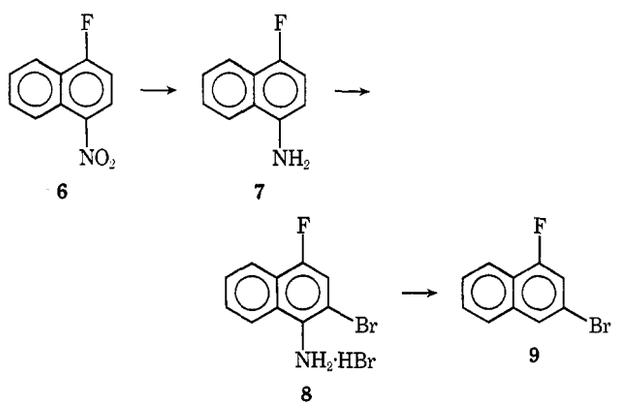
Such calculations were carried out and gave values of Σ Fr* = 1.169 (**3a**) and 1.173 (**4a**).

6-Fluorobenzo[*c*]phenanthrene (**1**) indeed was formed by the photolysis of either the ethylene **3a** or **3b**. Precursor **3a** gave yields ranging from 52% (without addition of I_2) to 82% (in the presence of the halogen), while **3b** gave >91%. Compounds **3a** and **3b** were obtained from 2-aminonaphthalene-3-carboxylic acid (**5a**), which was sequentially converted to **5e** by straightforward reactions. Horner–Wittig reaction of **5e** with either benzaldehyde or *o*-iodobenzaldehyde gave **3a** or **3b**.

Compound **2** proved to be much more difficult to obtain, since the overall yield in the multistep synthesis of the key compound 1-fluoro-3-bromonaphthalene (**9**) is very low. A number of pathways were explored.

Scheme I involved the reduction of 1-fluoro-4-nitro-

SCHEME I



naphthalene (**6**) to the amine, followed by bromination and deamination,[6] the latter step being particularly unrewarding.

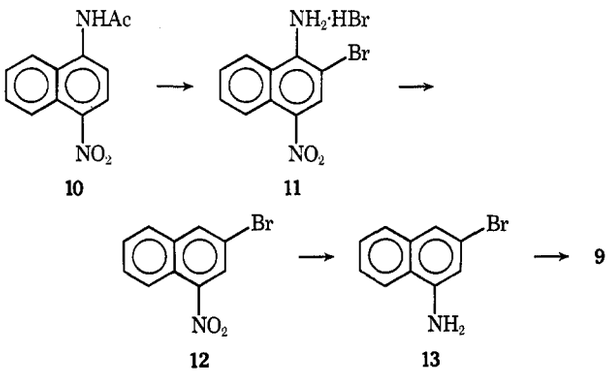
Attempts to deaminate **7** by means of catalytic reduction of the diazonium fluoroborate, using rhodium complexes (RCTP and RCCP) in DMF, were unsuccessful.[7] On the other hand, the reduction of the diazonium fluoroborate of **8** with $NaBH_4$[8] did give **9** although in low yield (5–17%) depending on the solvent.

Scheme II started with the nitration of 1-aminonaphthalene. The 4-nitro *N*-acyl derivative (**10**) was brominated, deaminated, and reduced to 3-bromo-1-nitronaphthalene (**12**).[9–11] In the latter the nitro group was successively replaced by NH_2 (**13**) and F (**9**). The overall yield again was not satisfactory (2–3%).

Alternative syntheses leading to useful 1,3-disubstituted naphthalenes were explored. For example, reaction of 1-fluoro-4-nitronaphthalene (**6**) with NaCN (von Richter reaction)[12–14] gave a complex mixture of products. Ir examination of the many fractions obtained by hydrolysis and silica gel chromatography showed the loss of the NO_2 group and in some cases a new carbonyl band. However, it was not possible to isolate practical amounts of 1-fluoronaphthalene-3-

(6) W. Adcock and M. J. S. Dewar, *J. Amer. Chem. Soc.*, **89**, 386 (1967).
(7) G. S. Marx, *J. Org. Chem.*, **36**, 1725 (1971).
(8) J. B. Hendrikson, *J. Amer. Chem. Soc.*, **83**, 1251 (1961).
(9) H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 1205 (1933).
(10) H. H. Hodgson and D. E. Hathway, *ibid.*, 385, 538 (1944).
(11) H. H. Hodgson and R. L. Elliott, *ibid.*, 1705 (1934).
(12) E. Cullen and Ph. l'Ecuyer, *Can. J. Chem.*, **39**, 382 (1961).
(13) G. T. Roger and T. L. V. Ulbricht, *Tetrahedron Lett.*, 1029 (1968).
(14) J. F. Bunnett and M. M. Rauhut, *J. Org. Chem.*, **21**, 934 (1956).

SCHEME II

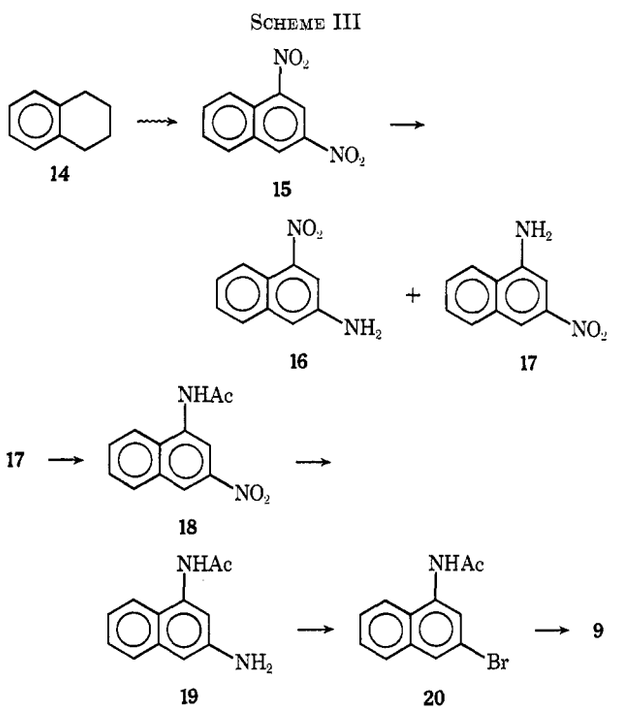


carboxylic acid (**22**). The inability of fluoronitrobenzenes to undergo the von Richter reaction has been remarked on.[10]

Our attempts to duplicate the reported procedure for the synthesis of 1-amino-3-cyanonaphthalene by fusion of sodium 1-aminonaphthalene-3-sulfonate[15] with potassium cyanide gave only traces of **15**.

A further synthesis of **9** was effected by a route starting from tetralin (Scheme III).[16–18] This procedure, too, gave only low yields (overall <1%).

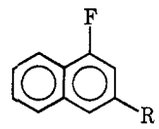
SCHEME III



Altogether, the general unavailability of 1,3-disubstituted naphthalenes makes syntheses based on this type of compound extremely unpromising.

The sequence leading from **9** to compound **25** was similar to that used for the synthesis of **1**, with the exception that the Horner–Wittig reaction had to be replaced by the Michaelis–Arbuzov modification of this reaction. The photolysis of **4a**, when carried out under conditions identical with those for **3a**, gave ambiguous results. Apparently, only a portion of the material

(15) J. Cason, *J. Amer. Chem. Soc.*, **63**, 828 (1941).
(16) G. Schroeter, *Justus Liebigs Ann. Chem.*, **426**, 23 (1921).
(17) S. Vertalier and C. Sannie, *Bull. Soc. Chim. Fr.*, 234 (1954).
(18) H. H. Hodgson and E. R. Ward, *J. Chem. Soc.*, 1187 (1949).



9, R = Br **23**, R = CO_2Me
21, R = CN **24**, R = CH_2OH
22, R = CO_2H **25**, R = CH_2Br

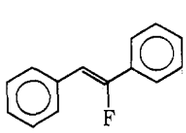
photocyclized to give **2**, as evinced by the uv spectrum. Compound **2** was successfully obtained, however, by the photolysis of **4b** in a Pyrex rather than a quartz vessel. As indicated by the uv spectrum (Table I), a

TABLE I
ULTRAVIOLET ABSORPTION PEAKS IN CYCLOHEXANE

Compd	λ_{max}, mμ ($\epsilon_{max} \times 10^{-4}$)
1	375 (0.068), 357 (0.067), 339 (0.045), sh 325 (0.35), 314 (0.86), 296 (1.2), 282 (4.70), 273 (4.1), sh 264 (2.4), 218 (3.1)
2	374 (0.070), 357 (0.081), sh 325 (0.41), 314 (0.80), 295 (1.2), 282 (4.0), 273 (3.6), sh 264 (2.4), 217 (5.0)
Benzo[c] phenanthrene	371 (0.019), 354 (0.029), 326 (0.45), 314 (1.1), 307 (1.2), 282 (8.2), 272 (6.6), sh 262 (2.6), 230 (2.6), 218 (4.6)
3a	sh 340 (1.4), 331 (3.1), 317 (3.5), sh 306 (2.4), 279 (3.5), 265 (3.5), sh 261 (2.2), 223 (3.0)
3b	sh 337 (0.25), 312 (0.37), sh 277 (0.52), 270 (0.57), 225 (0.85), 218 (0.9)
4a	354 (0.37), 340 (1.0), 327 (2.1), 317 (2.5), sh 305 (2.0), 284 (2.2), 274 (2.1), 253 (1.3), 227 (2.0)
4b	256 (0.68), 345 (0.15), 316 (3.1), 282 (2.7), 275 (2.7), 252 (2.1), 240 (2.2), 227 (3.3)
26	sh 315 (1.8), 300 (2.6), 290 (2.8), 233 (10.0), 226 (14.0), 220 (13.0)

dilute solution of **4a** also gave the desired compound **2** when irradiated in a quartz vessel.

The possibility of obtaining fluorophenanthrene systems directly by photolysis of suitable fluoro compounds of the stilbene type was attempted on α-fluorostilbene (**26**)[19] as a model. Even after irradiation of a solution



26

of **26** and iodine in cyclohexane with lamp wattages up to 250 V, no evidence of 9-fluorophenanthrene formation was observed.

MO calculations of **26** carried out subsequent to these experiments gave a value of $\Sigma F^* = 0.947$, clearly below the threshold value of 1.0 for successful photodehydrocyclization.[5]

Experimental Section

3-Fluoro-2-naphthoic Acid.—Commercial 3-amino-2-naphthoic acid (Schuchardt) was esterified using $SOCl_2$ and MeOH.[20] Diazotization and decomposition of the diazonium fluoroborate, followed by KOH hydrolysis, gave a 20% yield, mp 194–195°.

Anal. Calcd for $C_{11}H_7O_2F$: C, 69.5; H, 3.7; F, 10.0. Found: C, 70.0; H, 3.8; F, 10.3.

2-Fluoro-3-hydroxymethylnaphthalene (5d).—Esterification of the above acid followed by $LiAlH_4$–THF reduction gave crude **5d** (78% yield). Extraction with hot cyclohexane and recrystallization from CCl_4 gave tan crystals, mp 93–94°.

Anal. Calcd for $C_{11}H_9OF$: C, 75.0; H, 5.1; F, 10.8. Found: C, 75.3; H, 5.2; F, 10.6.

3-Bromomethyl-2-fluoronaphthalene (5e).—Reaction of **5d** with PBr_3 in benzene[2] gave, after chromatography on neutral alumina (benzene) and recrystallization from hexane, light tan needles, mp 87–88°.

Anal. Calcd for $C_{11}H_8FBr$: C, 55.3; H, 3.4. Found: C, 55.6; H, 3.5.

trans-**1-(2-Fluoro-3-naphthyl)-2-phenylethylene (3a).**—Horner–Wittig reaction of **5e** with benzaldehyde[2] gave, after chromatography on neutral alumina (cyclohexane), a 46% yield of **3a**. Recrystallization from hexane gave colorless plates, mp 136.5–138°.

Anal. Calcd for $C_{18}H_{13}F$: C, 87.1; H, 5.3; F, 7.6. Found: C, 87.3; H, 5.3; F, 7.3.

trans-**1-(2-Fluoro-3-naphthyl)-2-(*o*-iodophenyl)ethylene (3b).**—The same procedure as for **3a** gave a 52% yield when *o*-iodobenzaldehyde was used. Recrystallization from hexane gave needles, mp 91–92°.

Anal. Calcd for $C_{18}H_{12}FI$: C, 57.8; H, 3.2. Found: C, 57.6; H, 3.3.

6-Fluorobenzo[c]phenanthrene (1).[2]—A solution of 100 mg of **3b** in 200 ml of cyclohexane in a quartz tube was placed into a Rayonet photochemical reactor, fitted with 16 75-W, 2530-Å ultraviolet lamps. Nitrogen was bubbled through the solution. After 4 hr the reaction was complete (the solution had acquired a characteristic purple iodine color). The solvent was evaporated and the product was chromatographed on alumina (cyclohexane–benzene, 4:1) and recrystallized from hexane, mp 70–71°, yield 91%.

Anal. Calcd for $C_{18}H_{11}F$: C, 87.7; H, 4.5. Found: C, 87.4; H, 4.5.

Using precursor **3a** with 100 mg of iodine, a yield of 82% was obtained. Without the addition of I_2, the yield dropped to 52%.

3-Bromo-1-fluoronaphthalene (9).—This compound was synthesized as shown in Schemes I–III. The compound was effectively purified by silica gel chromatography (cyclohexane–benzene, 1:1). Tlc on silica gel G using cyclohexane–benzene (5:1) gave a spot, R_f 0.84. Vpc on a 1.5-m 15% DEGS column at 164° gave a well-separated peak after 23 min.

3-Cyano-1-fluoronaphthalene (21) was prepared from the 3-bromo compound[6] by treatment with $Cu(CN)_2$ in *N*-methylpyrrolidone.[2] Chromatography of the crude product on silica gel (benzene) followed by recrystallization in hexane gave colorless needles, yield 60%, mp 120–121° (lit.[6] mp 121–122°).

1-Fluoro-3-hydroxymethylnaphthalene (24).—Hydrolysis of **21** with H_2SO_4–HOAc gave the acid **22**, mp 186–189° (lit.[6] mp 189–191.5°). Esterification with diazomethane was followed by $LiAlH_4$ reduction as described for **5d**. Silica gel chromatography (EtOAc) gave the desired product, which was recrystallized from CCl_4, mp 63.5–64.5°.

Anal. Calcd for $C_{11}H_9OF$: C, 75.0; H, 5.1. Found: C, 74.7; H, 4.75.

3-Bromomethyl-1-fluoronaphthalene (25).—Using the same procedure as for **5e**, colorless crystals were obtained, after recrystallization from hexane, in 44% yield, mp 70–71°.

Anal. Calcd for $C_{11}H_8FBr$: C, 55.3; H, 3.4. Found: C, 55.7; H, 3.2.

trans-**1-(1-Fluoro-3-naphthyl)-2-phenylethylene (4a).**—The Horner–Wittig procedure on **25** gave poor yields of **4a**. Using the Michaelis–Arbuzov adaptation of this reaction,[21,22] 1.6 mmol of $(EtO)_2POH$ was mixed with 2.6 mmol of NaH and refluxed for 1 hr in 5 ml of toluene. The mixture was cooled and, after addition of 2.6 mmol of **25** in 5 ml of toluene, refluxed for 5 hr. Water and ether were added and the organic phase was separated, washed with dilute acetic acid and water, dried over $MgSO_4$, and distilled, bp 180–185° (1.5 mm), yield 54%. Treatment of this compound with equivalent amounts of benzaldehyde and NaOMe in DMF at 110° for 2.5 hr gave, after work-up and neutral

(19) E. D. Bergmann, I. Shahak, and J. Appelbaum, *Israel J. Chem.*, **6**, 73 (1968).

(20) A. Brenner, *Helv. Chim. Acta*, **36**, 1104 (1953).

(21) Houben-Weyl, "Methoden der Organischen Chemie," Vierte Auflage XII/1, Georg Thieme Verlag, Stuttgart, 1963, p 446.

(22) P. C. Crafts and G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **75**, 3379 (1953).

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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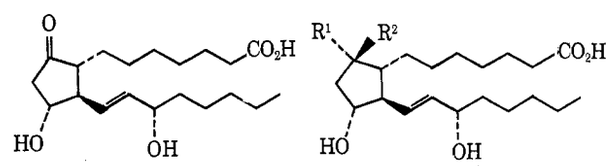
A seven-step total synthesis of eight racemic modifications of prostaglandin F_1 (12 and 13) is described in Chart I. The key steps are condensation of 3-oxoundecan-1,11-dioic acid with styrylglyoxal (5) to 9,12-dioxo-11-hydroxy-14-phenyltetradeca-13-enoic acid (6), cyclodehydration to 7, cleavage of 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.

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

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

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

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