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]

MASATERU MIYANO* AND CLIFFORD R. DORN

*Chemical Research Division, G. D. Searle & Company, Chicago, Illinois 60680*

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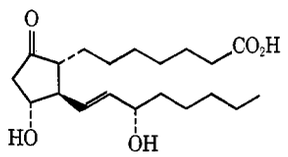
The facile synthesis of the new prostaglandin analogs, *dl*-$\Delta^{8(12)}$-dehydroprostaglandin $E_1$ (**5**) and its 15 epimer **6** is described (Chart I) which consists of a Wittig condensation of **3** with **19** to produce **4** followed by the selective reduction of the 15 ketone with borohydride. 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$_1$.




**1**

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 m$\mu$ are consistent[8] with the observed value of 278 m$\mu$ for the known 11-deoxy analog, prostaglandin $B_1$ (**12**).[9] Secondly, the adsorption at 276 m$\mu$ is in good agreement with the calculated value[10a,c,d] of 272 m$\mu$, but at variance with the theoretical value of 299 m$\mu$ 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**

(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).

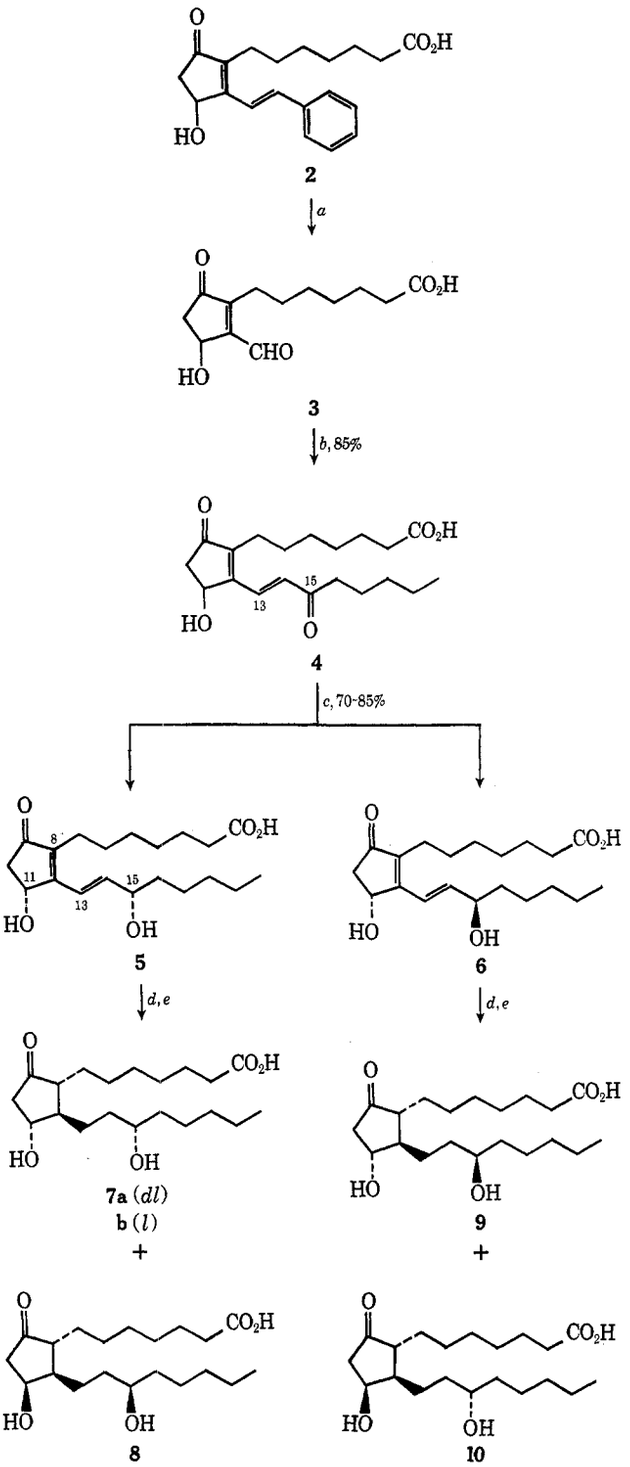
(8) The 11-hydroxy group exhibits a hypsochromic shift; see Table III of M. Miyano, *J. Org. Chem.*, **35**, 2314 (1970).

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

(10) (a) 202 (five-membered enone) + 30 ($\gamma,\delta$ double bond) + 10 ($\alpha$ substituent) + 12 ($\beta$ substituent) + 18 ($\delta$ substituent) = 272; (b) 215 (aliphatic enone) + 30 ($\gamma,\delta$ double bond) + 18 ($\gamma$ substituent) + 36 (two $\delta$ 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.

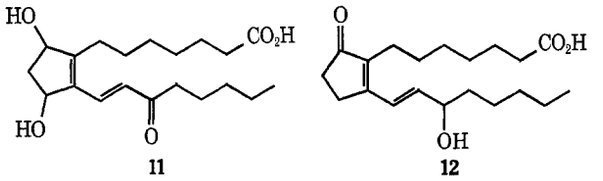
(11) See Experimental Section for **5** and **6**. Separation of 15-dehydro-PGE$_1$ from its 11 epimer (see ref 1) and separation of **7** from **8** as well as **9** from **10** (*vide infra*) were also carried out on the same column with little decomposition. Since the column can separate 2–5 g of 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.

CHART I



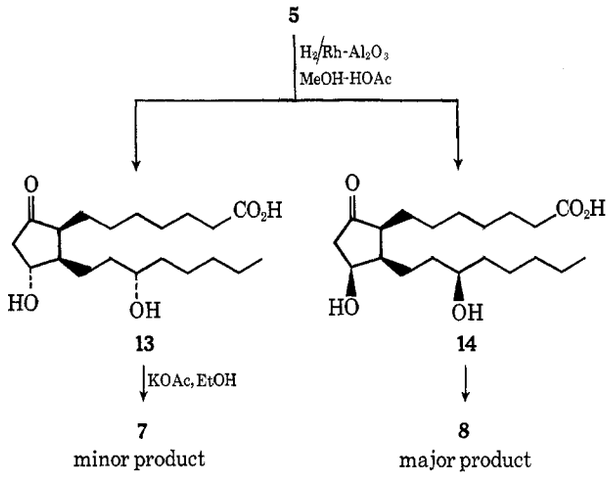

[a] $NaIO_4$, $OsO_4$; see ref 1. [b] $(C_6H_5)_3P{=}CHCO\text{-}n\text{-}C_5H_{11}$ and $Et_3N$ in refluxing benzene. [c] $Et_3N$ and $NaBH_4$ in water. [d] Hydrogenation over rhodium on alumina in methanol containing 0.5% of acetic acid. [e] KOAc in 95% EtOH at 25° for 4 days.

and **6**) were spectroscopically indistinguishable except for a very slight difference in the nmr signals of the olefinic protons, but fortunately they displayed different chromatographic behavior on the partition column[11] (**6** being less polar) or on tlc (**5** being less polar, using silica gel with benzene–ethyl acetate–acetic acid, 25:25:1). Each isomer gave a crystalline oxime having a distinctive melting point and in addition **5** and **6** possessed different biological properties.[12] The stereochemistry of the 11- and 15-hydroxy groups was established by direct comparison of the racemic dihydro-$PGE_1$ (**7a**) obtained from hydrogenation of **5** with authentic dihydro-$PGE_1$ (**7b**) prepared from natural $PGE_2$.




The double bonds of **5** were saturated smoothly over rhodium on alumina in methanol containing acetic acid, whereas hydrogenation over palladium on carbon resulted mainly in hydrogenolysis of the 11-hydroxy group prior to the reduction of the $\Delta^{8(12)}$ double bond. In order to convert the 8,12-cis products into the more stable 8,12-trans isomers, the crude hydrogenation mixture was treated with excess potassium acetate in ethanol to effect epimerization[13] at C-8 to a mixture consisting predominantly of **7a** and **8**. Chromatography on the partition column[11] separated oily **7a** and crystalline **8** satisfactorily. Since the ratio of **7a** to **8** was about 2:5, hydrogenation must have occurred predominantly from the less hindered side of **5**, in other words, opposite the 11-hydroxy group, to afford **14** (8,12-cis), which in turn was isomerized to **8** (8,12-trans (Chart II). The formation of **7** may be rationalized by isomerization of **13**, the hydrogenation product from the more hindered side. Another product isolated from the column was 13,14-dihydro-$PGA_1$ (**15**),[7a] a dehydration product most likely formed during work-up. Likewise, the hydrogenation of **6** followed by the potassium acetate induced isomerization and partition chromatography afforded **10** as the major product together with a smaller quantity of **9**.

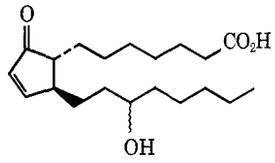
CHART II




The 100-MHz nmr spectra in deuteriochloroform

(12) Acute hypotensive activity on the anesthetized rat and activities of **5–10** on various smooth muscles were evaluate by Drs. L. P. Rozek and J. H. Sanner.

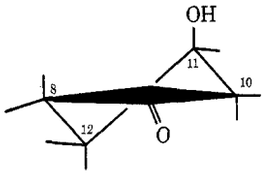
(13) For isomerization of 8-epi-$PGE_1$ (8, 12-cis) to $PGE_1$, see J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969). For isomerization of 12-epi-15-dehydro-$PGE_1$ (8,12-cis) to 11-epi-15-dehydro-$PGE_1$ (8,12-trans), see ref 1.



15

clearly indicated that both **8** and **10** have the 11-hydroxyl in the $\beta$ orientation (axial OH or equatorial carbonol H, see Chart III), since H-11 appeared at lower

CHART III
THE MOST STABLE CONFORMATION
(A HALF CHAIR) OF **8** AND **10**



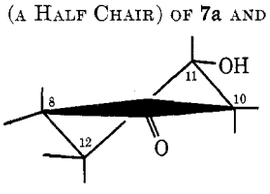
field with smaller coupling constants (narrow multiplets, see Table I). On the other hand, **7a** and **9** exhibited the typical diaxial interaction of H-11 and H-10$\alpha$ (see Chart IV) with the carbinol protons at

TABLE I
100-MHz NMR SPECTRA IN DEUTERIOCHLOROFORM

| Compd | H-11, $\tau$ | $W_{1/2}$, Hz | H-15, $\tau$ | $W_{1/2}$, Hz |
|---|---|---|---|---|
| **7a** (synthetic)[a] | 5.89 | ~17 | 6.35 | 15 |
| **8**[b] | 5.53 | 8.0 | 6.27 | 15 |
| **9**[c] | 5.89 | ~17 | 6.35 | 15 |
| **10**[d] | 5.54 | 8.0 | 6.36 | 15 |
| **7b** (natural)[e] | 5.89 | ~17 | 6.34 | 15 |

[a] Very similar to **9** but strong peak at $\tau$ 8.36. [b] Very similar to **10** but a peak at $\tau$ 8.32. [c] Two weak signals at $\tau$ 8.375 and 8.435 instead of strong peak at $\tau$ 8.36. [d] No peak at $\tau$ 8.32. [e] Identical with synthetic **7a**.

CHART IV
THE MOST STABLE CONFORMATION
(A HALF CHAIR) OF **7a** AND **9**

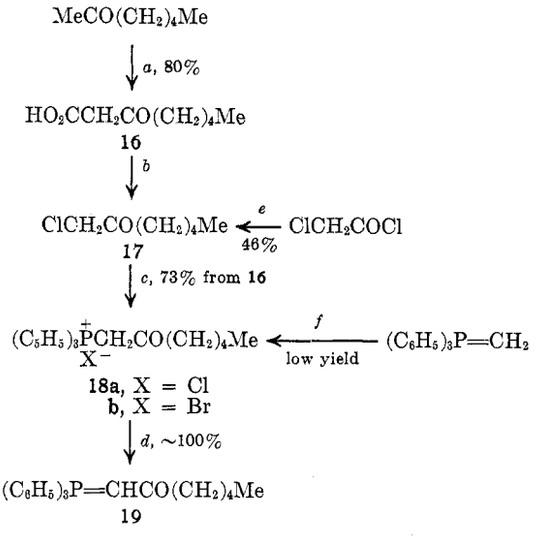


higher field having larger coupling constants (broad multiplets, see Table I). Furthermore, the nmr spectrum of **7a** was similar to that of **9**, but indistinguishable from that of dihydro-PGE$_1$ (**7b**) prepared by hydrogenation of natural PGE$_2$ (see Table I). The chromatographic behavior of the stereoisomers on tlc[14] as well as on the partition column[11] was consistent with[1] the assigned configuration at C-11; that is, the compounds having the axial hydroxyl group (**8** and **10**) migrated faster than the isomers bearing the equatorial hydroxyl group (**7a** and **9**). Lastly, the biological activities[12] of **7a** were in good agreement with the natural stereochemistry.

(14) Silica gel with either benzene–ethyl acetate–acetic acid (25:25:1) or the upper phase of ethyl acetate–acetic acid–2,2,4-trimethylpentane–water (11:2:3:10).

Although the Wittig reagent (*n*-hexanoylmethylene)-triphenylphosphorane (**19**) has been mentioned in the literature,[6] the compound was not characterized and the suggested preparative procedure (addition of *n*-hexanoyl chloride to triphenylphosphine methylene) invariably gave poor yields in our hands. To remedy this, we devised an efficient alternate scheme (see Chart V) for the kilogram-scale preparation of **19**.

CHART V




[a] Known procedure; see ref 15 and 16. [b] Sulfuryl chloride in methylene chloride at 25° followed by distillation. [c] Refluxing with triphenylphosphine in chloroform. [d] Shaking the chloroform solution of the phosphonium halide with aqueous carbonate. [e] *n*-Amylcadmium; see ref 17. [f] Known procedure; see ref 6.

Thus, the chlorination of readily available 3-ketooctanoic acid (**16**)[15,16] with sulfuryl chloride followed by distillation afforded 1-chloro-2-heptanone (**17**) which by displacement with triphenylphosphine was converted into the phosphonium chloride **18a** in 73% overall yield. The less satisfactory alternate route[17] to **17** involved the condensation of di-*n*-amylcadmium (prepared from *n*-amylmagnesium bromide *in situ*) with chloroacetyl chloride. Consistent yields could not be obtained and the **17** obtained by this procedure was contaminated with the corresponding bromo ketone.

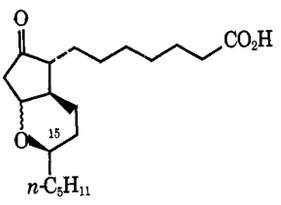
Upon prolonged refrigeration or warming in an isoosmotic phosphate buffer, a portion of **8** and **10** was transformed into **20** and **21**, respectively. It was also found that a mixture of **20** and **21** was formed in quantitative yield by chromatographing **15** (about a 50:50 mixture of 15 epimers) on a silicic acid column impregnated with silver nitrate. The nmr spectrum of **20** exhibited a typical axial H-15 at $\tau$ 6.69 (m, $W_{1/2}$ = 21 Hz) and a narrow multiplet for H-11 at $\tau$ 5.92 ($W_{1/2}$ = 7 Hz) which is consistent with cis conformation **20a**, but incompatible with the other cis conformation **20b** or the trans configuration **20c**. In contrast, the spectrum of 15$\alpha$ ether **21**[17a] revealed a broad multiplet for H-11 at

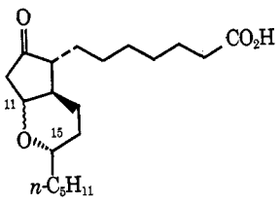
(15) S. B. Soloway and F. B. LaForge, *J. Amer. Chem. Soc.*, **69**, 2678 (1947).

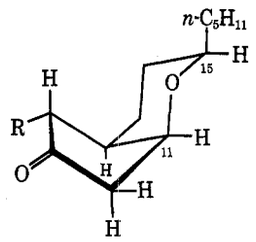
(16) R. Locquin, *Bull. Soc. Chim. Fr.*, **31**, 597 (1904).

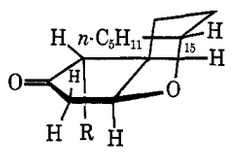
(17) S. Archer, M. J. Jackman Unser, and E. Frollich, *J. Amer. Chem. Soc.*, **78**, 6182 (1956).

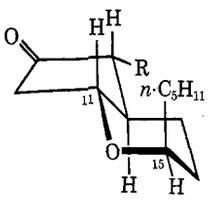
(17a) NOTE ADDED IN PROOF.—After this work had been completed the cyclic ether **21** was described in the literature: R. D. Hoffsommer, D. Taub, and N. L. Wendler, *Tetrahedron Lett.*, 4086 (1971).


20


21


20a


20b


20c

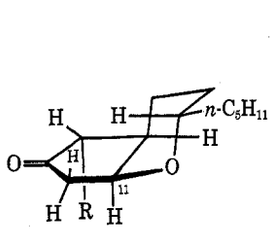
$\tau$ 6.23 ($W_{1/2}$ = 20 Hz) in addition to a somewhat broad multiplet representing H-11 at $\tau$ 5.67 ($W_{1/2}$ = 13 Hz), this pattern being compatible with the cis configuration **21a** or the trans configuration **21c**, but inconsistent with the other cis conformation **21b**. The remarkable downfield shift of protons H-11 and H-15 in compound **21** is more in line with the congested structure **21a** than with **21c**. Similar treatment (prolonged refrigeration) of natural dihydro-PGE$_1$ (**7b**) produced **21** (disregarding optical activity) exclusively, demonstrating that **21** has the 15$\alpha$ configuration. Whereas the nmr spectra of **5**, **7a**, and **8** were very similar to their respective 15 epimers **6**, **9**, and **10**, the nmr spectrum of **20** is quite different from its 15 epimer **21**, thus providing a reliable and probably general method for determining the stereochemistry of C-11 and C-15 in this series of compounds.

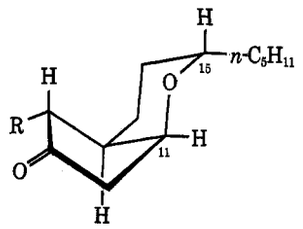
## Experimental Section

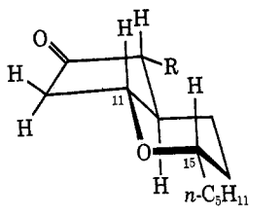
Melting points were taken on a Thomas-Hoover Unimelt in open capillary tubes and were not corrected. The nmr spectra were recorded at 60 MHz on a Varin A-60 and at 100 MHz on a Varian HA-100 nmr spectrometer in $CDCl_3$ using TMS as internal reference ($\tau$ 10.00). $W_{1/2}$ denotes peak width (hertz)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

**Triphenyl 2-Keto-*n*-heptylphosphonium Chloride (18a).**—A solution of 90 g of 3-ketooctanoic acid[15,16] in 360 ml of methylene chloride was treated dropwise at 25° with 82.3 g of sulfuryl chloride in 45 ml of methylene chloride. The mixture was stirred for 5 hr and allowed to stand at room temperature for 65 hr. The solvent was removed by distillation at atmospheric pressure and the residue was further distilled at 20 mm until the temperature of the vapor reached 65°. The pale yellow residue (83 g) contained at least 90% 1-chloro-2-heptanone[17] and was suitable for subsequent modification without further purification.

A solution 83 g of the crude chloro ketone and 180 g of triphenylphosphine in 650 ml of chloroform was refluxed for 3 hr and then allowed to stand overnight at room temperature. The solution was filtered to remove a small amount of insoluble material and the filtrate was concentrated *in vacuo*. The residue


21a


21b


21c

was dissolved in 700 ml of warm acetone, allowed to cool, and refrigerated overnight. Colorless inorganic-looking crystalline **18a** was obtained (170 g, 73%), mp 171°.

*Anal.* Calcd for $C_{25}H_{28}OClP$: C, 73.07; H, 6.87. Found: C, 72.77; H, 6.86.

**Triphenyl 2-Keto-*n*-heptylphosphonium Bromide (18b).**—A suspension of 214 g of methyl triphenylphosphonium *bromide* in 2 l. of ether was cooled in an ice bath and treated with 190 ml of 22% *n*-butyllithium in hexane under nitrogen. The ice bath was removed and the reaction mixture was stirred for 30 min, then poured into a cold stirred solution of 100 g of hexanoyl *chloride* in 500 ml of ether under nitrogen. The solvent was decanted and the residue was dissolved in chloroform washed successively with water, *hydrochloric* acid, and sodium *chloride* solution, dried over sodium sulfate, and concentrated to 600 ml. Crystals (44.9 g, the starting material) were removed by suction and the mother liquor was concentrated *in vacuo*. The residue (116 g) was dissolved in 20 ml of chloroform, diluted with cyclohexane to incipient turbidity, and allowed to stand at room temperature. Crystals (46.4 g, mp 179°) were collected and recrystallized from 30% ethanol, mp 196.5°; ir ($CHCl_3$) 5.84 $\mu$ (C=O).

*Anal.* Calcd for $C_{25}H_{28}OBrP$: C, 65.94; H, 6.20; Br, 17.55. Found: C, 65.84; H, 5.97; Br, 17.64.

***n*-Hexanoylmethylene(triphenyl)phosphorane (19).**—A chloroform solution of the phosphonium chloride or bromide was shaken with excess cold potassium hydroxide[18] solution, washed with dilute salt solution, and dried over sodium sulfate. The solvent was removed and the residue was dissolved in benzene. The solvent was evaporated *in vacuo;* benzene was added; and the evaporation was repeated to remove traces of chloroform. The residue was used for the subsequent condensation without further purification: nmr ($CDCl_3$, 60 MHz) $\tau$ 6.41 (s, 1), 7.65 (t, 2, $J$ = 7 Hz). The compound crystallized on standing at room temperature.

**9,15-Dioxo-11-hydroxyprosta-8(12),13-*trans*-dienoic Acid (4).**—To a solution of **3** prepared from 13 g of **2** (work-up procedure C[1]) in 200 ml of dioxane was added a solution of 4.0 g of triethylamine in benzene. The mixture was concentrated *in vacuo* to remove the excess amine and finally dissolved in 210 ml of dioxane. A solution of **19** (prepared from 18 g of **18b**) in 450 ml of benzene was added and the mixture was refluxed under nitrogen for 18 hr. After cooling, the reaction mixture was concentrated and freed from triphenylphosphine oxide by dry column chromatography on 1.2 kg of silica gel containing 8% water using ethyl acetate as solvent. The desired material (**4**, 9.7 g,71% from **2** or 85% from **3**) migrated faster than triphenylphosphine oxide. The analytical sample was prepared by the second dry column chromatography on silica gel containing 8% water and 3% acetic acid using 4% methanol in benzene as solvent: uv (MeOH) 291 m$\mu$ ($\epsilon$ 21,900); nmr ($CDCl_3$, 60 MHz), $\tau$ 2.46 (d, 1, $J$ = 16 Hz), 3.07 (d, 1, $J$ = 16 Hz), 4.85 (broad d, 1, $J$ = 5.5 Hz).

*Anal.* Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.47; H, 8.69.

For a large scale preparation, the reaction mixture was dissolved in a small amount of ether and shaken vigorously with

(18) Potassium carbonate solution can be used in place of the alkali.

chilled potassium bicarbonate solution. As triphenylphosphine oxide crystallized out, the acidic product was transferred into the aqueous phase; the triphenylphosphine oxide was filtered off and the desired product was recovered from the bicarbonate solution.

The dioxime was prepared in the usual manner and recrystallized from ethanol: mp 211° dec; uv (MeOH) 307 mμ (ε 44,800), 319 (41,000); nmr ($CD_3SOCD_3$, 60 MHz) τ 3.24 (s, 2, olefinic H), 5.06 (d, 1, $J$ = 5.5 Hz, C-11 H).

*Anal.* Calcd for $C_{20}H_{32}O_5N_2$: C, 63.13; H, 8.48; N, 7.36. Found: C, 63.47; H, 8.52; N, 7.65.

**9-Oxo-11,15-dihydroxyprosta-8(12),13-*trans*-dienoic Acids (5 and 6).**—Twelve grams of **4** was dissolved in 35 ml of ethanol and treated dropwise in the cold with a solution of 3.0 g of triethylamine in 275 ml of water. The mixture was stirred in an ice bath as 0.32 g of sodium borohydride in 32 ml of water was added dropwise. After stirring at approximately 10° for 25 min, the mixture was poured into excess aqueous citric acid and extracted three times with ether. The combined organic solutions were washed once with water, dried over anhydrous sodium sulfate, and concentrated to an oil (12 g).

A mixture of 1.5 l. of benzene, 0.5 l. of methanol, and 0.2 l. of distilled water was vigorously shaken in a separatory funnel. The stationary phase of the partition column consisted of 250 g of Mallinckrodt SilicAR CC-4 (100–200 mesh) and 250 ml of the lower phase solvent. The upper phase solvent was used for elution. The crude reduction product (2.5 g, mixture of approximately equal amounts of **5** and **6**) was dissolved in 50 ml of the upper phase solvent, placed on the partition column, and eluted. Fractions of 110 ml were collected. Fractions 21–30 contained 0.6 g of **6**, 31–33 gave 0.4 g of crude **6** contaminated by **5**, 34–35 gave 0.4 g of a mixture of **5** and **6**, and 36–42 produced 0.8 g of **5** in addition to a small amount of **6** and other impurities. Impure fractions were chromatographed on the previously used column without recharging. The same column could be used at least 20 times and still gave satisfactory separation. Although ordinary adsorption chromatography (SilicAR CC-4, benzene containing increasing amounts of ethyl acetate) effected partial separation of **5** (eluted first) and **6**, extensive decomposition took place on the column, whereas decomposition on the partition column was minimal. Since the stereoisomers **5** and **6** exhibited very similar ir, uv, and nmr spectra, the most convenient method to distinguish them was tlc (benzene–ethyl acetate–acetic acid, 25:25:1, silica gel plate); compound **5** migrated slightly faster than **6** ($R_f$ 0.23 and 0.21, respectively) and both exhibited a yellow to green color on spraying with phosphomolybdic acid. *dl*-9-Oxo-11α,15α-dihydroxyprosta-8(12),13-*trans*-dienoic acid (**5**) was obtained as a colorless, viscous oil: uv (MeOH) 276 mμ (ε 28,200); nmr ($CDCl_3$, 100 MHz) τ 3.35 (2, broad s, $J$ = 16–17 Hz, can barely be seen), 4.90 (1, broad d, H-11), 5.65 (1, m, H-15).

*Anal.* Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 67.97; H, 9.17.

The oxime was prepared in the usual manner and recrystallized from ethyl acetate: mp 113–115°; uv (MeOH) 276 mμ (ε 32,100); nmr ($CD_3SOCD_3$, 60 MHz) τ 3.65 (2, AB part of ABX), 5.20 (1, m, H-11) 5.90 (1, m, H-15).

*Anal.* Calcd for $C_{20}H_{33}O_5N$: C, 65.37; H, 9.05; N, 3.81. Found: C, 65.39; H, 9.01; N, 3.73.

***dl*-9-Oxo-11α,15β-dihydroxyprosta-8(12),13-*trans*-dienoic acid** (**6**) was also a colorless, viscous oil:[19] uv (MeOH) 276 mμ (ε 26,500); nmr ($CDCl_3$, 100 MHz) τ 3.43 (2, AB portion of ABX pattern, $J_{AB}$ = 16–17 Hz, can barely be seen), 4.89 (1, broad d, H-11), 5.72 (1, m, H-15).

*Anal.* Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 67.52, 67.59; H, 9.03, 9.36.

The oxime was made in the usual manner and recrystallized from methanol–ether: mp 137–138.5°; uv (MeOH) 275.5 mμ (ε 31,600); nmr ($CD_3SOCD_3$ 60 MHz), τ 3.66 (2, AB part of ABX pattern), 5.19 (1, m, H-11), 5.92 (1, m, H-15).

*Anal.* Calcd for $C_{20}H_{33}O_5N$: C, 65.37; H, 9.05; N, 3.81. Found: C, 65.18; H, 9.09; N, 3.69.

***dl*-Dihydro-PGE$_1$ (7a) and *dl*-11,15-Bisepidihydro-PGE$_1$ (8).**—A solution of 1.815 g of **5** in 226 ml of methanol containing 0.5% acetic acid was hydrogenated in the presence of 680 mg of 5% rhodium on alumina under 60–40 psi hydrogen at room temperature. After 4 hr the hydrogen uptake (120% of the calculated amount) ceased and the product exhibited no uv absorption. To the crude hydrogenation product were added 1.9 g of potassium bircarbonate in 65 ml of water, 31.5 g of potassium acetate, and 1.2 l. of ethanol. The homogeneous solution was set aside for 93 hr. The reaction mixture was concentrated *in vacuo*, dissolved in cold water, acidfied with citric acid to pH 4.0, and extracted with ether. The ethereal solution was washed with iced 1% sodium chloride, dried over sodium sulfate, and concentrated *in vacuo*. The residue was dissolved in 50 ml of ether and the solvent was stripped by a nitrogen stream. This procedure was repeated until the residue became completely free from acetic acid. The residue (1.5 g) was chromatographed on the partition column[11] made from 400 g of SilicAR CC-4 in the usual manner (see for **5** and **6**) and fractions of 100 ml were collected. Fractions 7–9 gave 266 mg of **15**, fractions 16–22 yielded 362 mg of crystalline **8**, fractions 23–24 gave 50 mg of a mixture of **7a** and **8**, and fractions 25–32 afforded 150 mg of **7a**. The *dl*-11,15-bisepidihydro-PGE$_1$ (**8**) thus obtained was free from any impurities and was recrystalized from ethyl acetate–Skelly B, mp 76–77°; for nmr ($CDCl_3$) see Table I.

*Anal.* Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.58; H, 10.25.

The purified *dl*-dihydro-PGE$_1$ (**7a**) thus obtained was chromatographed on 5 g of SilicAR CC-4 using 50% ethyl acetate in benzene. After 25 ml of forerun, fractions containing pure **7a** were collected as a colorless oil, nmr ($CDCl_3$, see Table I) identical with that of natural dihydro-PGE$_1$.

*Anal.* Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.34; H, 10.00.

***dl*-15-Epidihydro-PGE$_1$ (9) and *dl*-11-Epidihydro-PGE$_1$ (10).**—A solution of 1.454 g of **6** in 182 ml of methanol containing 0.5% acetic acid was hydrogenated and worked up in the same manner as for **7a** and **8**. The product (1.3 g) was chromatographed on the partition column[11] made from 400 g of SilicAR CC-4 in the usual manner (as for **5** and **6**). Fractions of 100 ml were collected Fractions 7–9 afforded 251 mg of **15**, 13–21 gave 362 mg of **10**, and 24–31 yielded crude **9**.

The *dl*-11-epidihydro-PGE$_1$ (**10**) thus obtained was essentially pure but was rechromatographed on 50 g of SilicAR CC-4 using 50% ethyl acetate–benzene. After 220 ml of forerun, pure **10** was eluted as a colorless oil; for nmr ($CDCl_3$) see Table I.

*Anal.* Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.66; H, 10.38.

The *dl*-15-epidihydro-PGE$_1$ (**9**) obtained from the partition chromatography was impure and was purified as follows. Fractions 24–26 from the partition chromatography were combined and rechromatographed on 5 g of CC-4 using 50% ethyl acetate–benzene and fractions of 12 ml were collected. Pure **9** (22 mg) was found in fractions 5–8. Fractions 27–31 of the partition chromatography were combined and rechromatographed on 5 g of CC-4 to give 38 mg of **9** as a colorless oil; for nmr ($CDCl_3$) see Table I.

**Cyclic Ether 20.**—A solution of 84 mg of crystalline **8** in 23 ml of isoosmotic phosphate buffer (pH 7.1) was left at 37° for 10 days, acidified with citric acid, and extracted with ether. The ethereal extract was washed with water, dried over sodium sulfate, and concentrated, and the residue was chromatographed on 50 g of SilicAR CC-4 using ethyl acetate–benzene (1:1) to give 67 mg of **20**: mp 33.5–35°; ir ($CHCl_3$) 1742 (C=O), 1713 $cm^{-1}$ ($CO_2H$); nmr ($CDCl_3$, 100 MHz) τ 5.92 (m, 1, $W_{1/2}$ = 7 Hz, H-11), 6.69 (m, 1, $W_{1/2}$ = 21, H-15).

*Anal.* Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 70.97; H, 10.21.

**Cyclic Ether 21. A.**—Oily **10** (161 mg) was left standing for 2 weeks and then chromatographed on 50 g of SilicAR CC-4 using ethyl acetate–benzene (1:1) to give 17 mg of **21**: ir ($CHCl_3$) 1736 (C=O), 1710 $cm^{-1}$ ($CO_2H$); nmr ($CDCl_3$, 100 MHz) τ 5.67 (m, 1, $W_{1/2}$ = 13 Hz, H-11), 6.23 (m, 1, $W_{1/2}$ = 20 Hz, H-15).

**B.**—Oily natural dihydro-PGE$_1$ (**7**) was refrigerated for 60 days and then chromatographed on CC-4 giving **21**, which was indistinguishable by nmr, ir, and tlc (benzene–ethyl acetate–acetic acid, 25:25:1, on silica gel) from **21** obtained *via* **10**.

**Cyclic Ethers 20 and 21.**—Crude **15**, obtained as a by-product of **7a**, **8**, **9**, and **10**, was combined (550 mg) and chromatographed on 55 g of silver nitrate (5%) impregnated SilicAR CC-4 using 20% ethyl acetate in benzene. The eluate was concentrated and rechromatographed on 50 g of plain SilicAR CC-4 using ethyl acetate–benzene (1:1) to give 250 mg of an approximately 1:1 mixture of **20** and **21**. The nmr spectrum ($CDCl_3$, 100 MHz)

(19) The optically active forms are crystalline. See ref 2.

indicated that no other cyclic ether stereoisomeric to **20** and **21** was formed in significant quantity.

*Anal.* Calcd for $C_{20}H_{34}O_4$: C, 70.93; H, 10.13. Found: C, 71.01; H, 10.25.

**Registry No.**—**4**, 32925-93-2; **4** dioxime, 34388-66-4; **5**, 32925-94-3; **5** oxime, 34388-96-0; **6**, 32946-04-6; **6** oxime, 34388-98-2; **7a**, 28896-13-1; **8**, 34389-00-9; **9**, 34389-01-0; **10**, 34389-02-1; **18a**, 34407-51-7; **18b**, 34407-52-8; **19**, 33803-58-6; **20**, 34389-03-2; **21**, 34389-04-3.

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# Notes

## Leguminosae Alkaloids. VIII. Development of an Improved Synthesis of Anagyrine as a Potential Route to Other Lupin Alkaloids[1]

STANLEY I. GOLDBERG* AND ALAN H. LIPKIN

*Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122*

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The newer lupin alkaloids multiflorine (**1**)[2] and nuttalline (**2**)[3] are related to the longer known plant base anagyrine (**3**)[4] by the common stereochemistry of the C/D ring fusion and by similar oxidation states of ring A. A total synthesis of anagyrine was developed by van Tamelen and Baran,[6] which, with suitable modification, appeared as an attractive potential route for synthesis of **1** and **2**. We report now on work which has provided substantial material improvements in the van Tamelen–Baran anagyrine synthesis, enhancing its potential role as a more general sequence.

Our modification of the van Tamelen–Baran synthesis consists of a more direct and more economical means of reaching the intermediate, *r*-(1*R*,3*S*,10*S*)-1-hydroxymethyl-3-(2-pyridyl)quinolizidine[7] (**4**). This key compound is converted to anagyrine *via* quaternization of the bromide **5**, followed by oxidation of the resulting quaternary salt **6**.

The present reaction sequence leading to **4** may be conveniently compared with the earlier one, since both start from α-methylpyridine. van Tamelen and Baran[6] reached **4** with a reaction sequence that required five isolation stages and gave **4** in an overall yield of 2.4%. In addition, that synthesis required the use of α-tripiperideine, a reagent obtained in only moderate yield and with some difficulty from piperidine.[8] The present synthesis is much more advantageous. The amino alcohol **4** is obtained in 23% overall yield from α-methylpyridine with only four isolation stages. The ancillary preparation of α-tripiperideine is not required.

In 1936, Clemo, Morgan, and Raper[9] found that treatment of ethyl (2-pyridyl)acetate (**7**, R = ethyl) with ethyl orthoformate in boiling acetic anhydride gave the quinolizone **8** quite efficiently. While utilization of **8**

(1) Work done at the University of South Carolina.

(2) S. I. Goldberg and R. F. Moates, *J. Org. Chem.*, **32**, 1832 (1967).

(3) S. I. Goldberg and V. M. Balthis, *J. Chem. Soc. D*, 660 (1969).

(4) Naturally occurring anagyrine is levorotatory. Its absolute configuration[5] is actually the mirror image of that shown in structure **3**. (−)-Multiflorine and (+)-nuttalline possess the absolute configurations shown in **1** and **2**, respectively.

(5) S. Okuda, H. Kataoka, and K. Tsuda, *Chem. Pharm. Bull.*, **13**, 487, 491 (1965).

(6) E. E. van Tamelen and J. S. Baran, *J. Amer. Chem. Soc.*, **80**, 4659 (1958).

(7) IUPAC convention for specification of relative configurations. See Rule E-5. 10.-(G), *J. Org. Chem.*, **35**, 2849 (1970).

(8) C. Schöpf, A. Komzak, F. Brquh, and E. Jacobi, *Justus Liebigs Ann. Chem.*, **559**, 1 (1948).

(9) G. R. Clemo, W. M. Morgan, and R. Raper, *J. Chem. Soc.*, 1025 (1936).