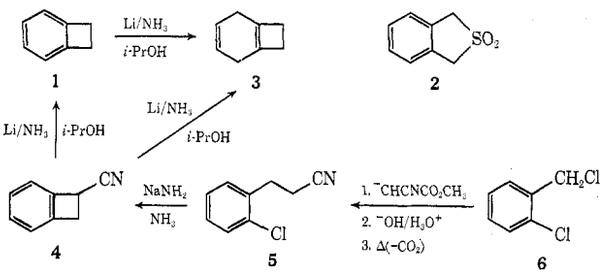
veloped a simple new synthetic route to both **1** and **3** which is of acceptable yield and amenable to large-scale production.

1 is prepared in 83% yield from 1-cyanobenzocyclobutene[4] (**4**) *via* reduction with Li in liquid ammonia. This is a useful example of the unusual reductive cleavage of a benzylic nitrile.[5] The nitrile **4** is readily prepared by the method of Bunnett and Skorcz as outlined above from *o*-chlorobenzyl chloride. We routinely effect the **6** → **5** → **4** conversion in 48% overall yield starting with as much as 1 kg of **6**.



While **3** is a known compound[6] it was prepared *via* an involved route. The Birch reduction of **1** has never been reported and we find that it proceeds to give **3** in excellent yield (98%). In fact, one can proceed directly from **4** to **3** without isolating **1** simply by adding the appropriate additional amounts of Li and isopropyl alcohol.

There are several dihydrobenzocyclobutene double bond isomers that could have resulted as products from the Birch reduction of **1**. In fact, the unusual chemical nature of carbocyclic four-membered rings does not permit one to predict the product with any great certainty. It is interesting that this reaction proceeds so easily and cleanly to give the double bond arrangement as in **3**. This new synthesis of benzocyclobutene and its subsequent Birch reduction to **3** may provide a ready access to some potentially new and interesting compounds.

Experimental Section

Preparation of Benzocyclobutene from 1-Cyanobenzocyclobutene (1).—A 3-l. three-necked flask, equipped with mechanical stirrer and gas inlet and outlet, was flame dried under a vigorous nitrogen flow. Ammonia (*ca.* 1.75 l.) was condensed and a solution of 1-cyanobenzocyclobutene (77.4 g, 0.6 mol) and isopropyl alcohol (72 g, 1.2 mol) in diethyl ether (300 ml) was added. The temperature was maintained at −40 to −45° and lithium wire (7.91 g, 1.14 mol) was added over a 30-min period. When all the lithium has reacted, ammonium chloride (64.0 g, 1.2 mol) was added while the temperature was kept below the boiling point of ammonia with a Dry Ice–acetone bath. The ammonia was evaporated overnight and water (1.5 l.) was added to the residue. The organic products were extracted with diethyl ether (4 × 300 ml), and this solution was washed successively with water (1 l.), 3 *N* hydrochloric acid (500 ml), saturated sodium bicarbonate solution (200 ml), and saturated sodium chloride solution (200 ml) and dried over magnesium sulfate. After filtration and concentration, distillation of the residue afforded benzocyclobutene (41.0 g), bp 79–83° (95 mm), 82.5% based on recovered starting material, and 1-cyanobenzocyclobutene (15.7 g), bp 75–78° (1 mm). Integration of the nmr spectrum showed the benzocyclobutene to be contaminated with bicyclo[4.2.0]octa-1(6),3-diene only to the extent of 3%: nmr (CCl_4) τ 6.88 (s, 4 H), 3.0 (A_2B_2, 4 H).

Preparation of Bicyclo[4.2.0]octa-1(6),3-diene from Benzocyclobutene (3).—A 1-l. three-necked flask was equipped with a Dry Ice condenser, mechanical stirrer, and gas inlets and outlet and was flame dried under a vigorous nitrogen flow. Ammonia (400 ml) was condensed. A solution of benzocyclobutene (13.0 g, 0.125 mol), isopropyl alcohol (15 ml), and tetrahydrofuran (50 ml, freshly distilled from lithium aluminum hydride) was added. Lithium wire (2.5 g, 0.36 mol) was added over a period of 2 hr. At this point the nmr of an aliquot showed no remaining aromatic protons. Ammonium chloride (18.7 g, 0.36 mol) was added cautiously and the ammonia was evaporated. Water (100 ml) was added to the residue and the organic product was extracted with diethyl ether (3 × 100 ml).

The ethereal solution was washed with water (2 × 100 ml) and saturated sodium chloride solution (2 × 50 ml), dried over magnesium sulfate, filtered, and concentrated. Distillation of the residue gave 12.78 g (98%) of the bicyclo[4.2.0]octa-1(6),3-diene: bp 78–79° (90 mm); nmr (CCl_4) τ 4.33 (s, 2 H), 7.50 (s, 8 H).

Acknowledgment.—This investigation was supported by a Public Health Service Research Career Development Award (GM-70,394-01) from the Institute of General Medical Sciences.

Registry No.—**1**, 694-87-1; **3**, 38325-66-5; **4**, 6809-91-2.

(4) J. Skorcz, *et al.*, *J. Med. Chem.*, **9**, 656 (1966).
(5) P. Arapakos, M. Scott, and F. Huber, Jr., *J. Amer. Chem. Soc.*, **91**, 2059 (1969).
(6) J. Garrett and G. Fonken, *Tetrahedron Lett.*, 191 (1969).

Prostaglandins. A Total Synthesis of (±)-11,15-Dideoxy-PGE$_2$ and (±)-11-Deoxy-PGE$_2$ Methyl Ester

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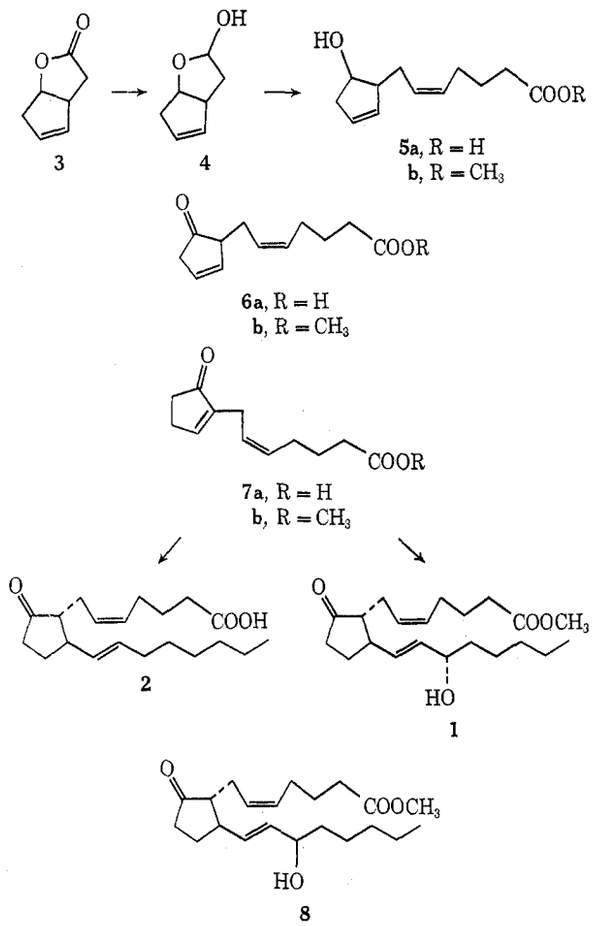
Received April 30, 1973

The synthesis of deoxyprostaglandins which represent potential intermediates for conversion into the naturally occurring prostaglandins *via* microbiological hydroxylation has recently been the subject of considerable synthetic effort. During the course of our work, a number of alternate 11-deoxy-PGE$_2$ syntheses have been developed.[1] We wish to report practical syntheses of (±)-11,15-dideoxyprostaglandin E$_2$ (**2**) and (±)-11-deoxyprostaglandin E$_2$ methyl ester (**1**).

The readily available cyclopentenone **7b** (*vide infra*) plus the recently reported capabilities of appropriately functionalized organocopper reagents to undergo smooth 1,4 conjugate addition to cyclopentenones[2] have allowed us to develop a short route to the deoxyprostaglandins of the E$_2$ series. Previous approaches to (±)-11-deoxy-PGE$_2$ methyl ester have constructed the C$_8$ side chain from dimethyl 2-oxoheptylphosphonate,[3] which was originally introduced by Corey.[4]

We now describe the synthetic sequence. Reduction

(1) P. Crabbé and A. Guzman, *Tetrahedron Lett.*, 115 (1972); J. Bagli and T. Bogri, *ibid.*, 3815 (1972); K. F. Bernady and M. J. Weiss, *ibid.*, 4083 (1972).
(2) (a) C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey, *J. Amer. Chem. Soc.*, **94**, 3643 (1972); (b) A. F. Kluge, K. G. Untch, and J. H. Fried, *ibid.*, **94**, 7827 (1972).
(3) For a versatile synthesis of dimethyl 2-oxoalkylphosphonates see P. A. Grieco and C. S. Pogonowski, *J. Amer. Chem. Soc.*, **95**, 3071 (1973).
(4) E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *J. Amer. Chem. Soc.*, **90**, 3247 (1968).



of lactone **3**[5] with dissobutylaluminum hydride in toluene as previously described[6] affords a quantitative yield of hemiacetal **4**. The cis double bond in **5a** was introduced in 80% yield by treatment of hemiacetal **4** with the ylide derived from 5-triphenylphosphoniopentanoic acid and sodio methylsulfinylmethide in dimethyl sulfoxide.[7] The resulting acid **5a** was characterized as its methyl ester **5b** (ethereal diazomethane). Alcohol **5a** was oxidized with Jones reagent at 0° in acetone to afford a 98% yield of the corresponding Δ^3-cyclopentenone **6a** which was immediately isomerized in 85% yield to the more stable α,β-unsaturated ketone **7a** by treatment with 95% ethanol–1 *N* NaOH (1:1) at 35–40° for 1 hr. Esterification with diazomethane produced ester **7b**. Treatment of **7b** with 3-(α-ethoxy)ethoxy-1-lithio-*trans*-oct-1-ene in the presence of tri-*n*-butylphosphine–copper(I) iodide complex at −78° in ether for 1 hr followed by warming to 0° afforded after removal of the C-15 protecting group (HOAc–THF–H_2O) two *dl* pairs in approximately equal amounts. The stereochemistry at C-8 and C-12 was anticipated as a result of protonation of the resultant enolate to give the thermodynamically more stable trans arrangements of alkyl and vinyl groups. Separation by preparative thin layer chromatography afforded pure (±)-11-deoxy-PGE_2 methyl ester (**1**) which exhibited satisfactory nmr, ir, and mass spectral data. In addition it showed identical tlc behavior in several solvent systems with an authentic sample. There was obtained also (±)-11-deoxy-15-epi-PGE_2 methyl ester (**8**).

Similarly, when **7b** was treated with 2 molar equiv of 1-lithio-*trans*-oct-1-ene in the presence of 1 molar equiv of tri-*n*-butylphosphine–copper(I) iodide complex, there was obtained after ester hydrolysis (±)-11,15-dideoxy-PGE_2 (**2**) which exhibited identical tlc behavior with an authentic sample.

(5) E. J. Corey, Z. Arnold, and J. Hutton, *Tetrahedron Lett.*, 307 (1970).
(6) P. A. Grieco, *J. Org. Chem.*, **37**, 2363 (1972).
(7) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963); E. Hamanaka, Ph.D. Thesis, Harvard University, 1967. The cis geometry for the double bond in V is indicated by the absence of the absorption characteristic of trans CH=CH at 10.3–10.4 μ.

Experimental Section

Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Precoated plc silica gel F-254 Merck plates were used for preparative tlc. The following spectrometers were used: nmr, Varian A-60D and T-60; ir, Perkin-Elmer Model 247; mass spectrum, LKB-9.

2-(Methyl-*cis*-hept-2-en-7-oate)cyclopent-3-en-1-ol (5b).—Triphenylphosphoniopentanoic acid, 13.5 g (30.5 mmol) (prepared from 5-bromopentanoic acid and triphenylphosphine in acetonitrile), was dried at 75° (0.1 mm) for 1 hr. The acid was then dissolved in 60 ml of dimethyl sulfoxide (DMSO, freshly distilled from CaH_2). To this solution under an atmosphere of nitrogen was added 46.0 mmol of sodium methylsulfinylmethide which was prepared from 1.94 g (46.0 mmol) of sodium hydride dispersion (57%) and 40 ml of dry DMSO. To the resultant ylide solution was added 1.50 g (11.8 mmol) of pure hemiacetal **4** in 3 ml of dry DMSO. Stirring at room temperature was continued for 2.5 hr, after which time the DMSO was removed under reduced pressure and the residue was taken up in 100 ml of water. The resultant aqueous solution was extracted with ether–ethyl acetate (1:1) to remove any neutral compounds, acidified to pH 2.0, and extracted several times with pentane–ether (1:1). The combined organic layers were washed with brine and separated and the solvent was removed under reduced pressure to leave 2.40 g (90%). The acid **5a** was characterized as its methyl ester **5b** (ethereal diazomethane). The crude ester was evaporatively distilled, 106–110° (0.01 mm), affording 1.88 g (71%) of a homogeneous material: ν_{max} ($CHCl_3$) 1735 cm^{-1}; nmr (CCl_4) δ 5.8–5.2 (m, 4 H), 4.5–4.15 (m, 1 H), 3.6 (s, 3 H); *m/e* 224.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.43; H, 9.01.

2-(Methyl-*cis*-hept-2-en-7-oate)-2-cyclopentenone (7b).—A solution of 1.0 g of alcohol **5a** in 35 ml of acetone was cooled to 0° and treated dropwise with 2.6 ml of standard Jones reagent. After 5 min, the reaction was quenched with isopropyl alcohol and the acetone was removed under reduced pressure. The resultant residue was taken up in water and extracted with ether several times. The combined ethereal extracts were washed with water, and saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* afforded 1.00 g (99% yield) of Δ^3-cyclopentenone (**6a**) [ν_{max} ($CHCl_3$) 3600–2400, 1740 (C=O), 1705 cm^{-1} (COOH)], which was characterized as its methyl ester **6b** (diazomethane) [ν_{max} ($CHCl_3$) 1740 cm^{-1}; nmr (CCl_4) δ 3.64 (s, 3 H), 5.40 (m, 2 H), 6.08 (s, 2 H); *m/e* 222].

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.32; H, 8.08.

The Δ^3-cyclopentenonecarboxylic acid **6a** was dissolved in 50 ml of 95% ethanol. To this solution was added 70 ml of 1 *N* NaOH and the resultant homogeneous solution was heated at 35°. After 2.5 hr, the reaction mixture was concentrated *in vacuo* and the crude product was dissolved in 25 ml of water. The resultant aqueous solution was extracted with ethyl acetate and acidified with 1 *N* HCl, and the product was isolated by extraction with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure afforded 1.0 g of crude acid **7a** which was esterified with diazomethane, producing 970 mg (92%) of pure enone ester **7b** [ν_{max} ($CHCl_3$) 1725, 1695, 1630 cm^{-1}; nmr (CCl_4) δ 7.15 (m, 1 H), 5.41 (m, 2 H), 3.60 (s, 3 H); *m/e* 222].

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.94; H, 7.81.

(±)-11,15-Dideoxyprostaglandin E_2 (2).—To a suspension of 393 mg (1 mmol) of tri-*n*-butylphosphine–copper(I) iodide (freshly prepared) in 5 ml of anhydrous ether cooled to −78° under an atmosphere of nitrogen was added with stirring a solution of 1-lithio-*trans*-oct-1-ene in anhydrous ether [prepared by treatment of 1-iodo-*trans*-oct-1-ene (476 mg, 2 mmol) in 3 ml of anhydrous ether cooled to −78° with 2.86 ml of *tert*-butyllithium (1.44 *M* in *n*-pentane) followed by stirring for an additional 2 hr]. The resulting mixture was stirred for approximately 45 min at −78° and then was treated with 220 mg (1 mmol) of cyclopentenone **7b** in 1 ml of ether. After the addition was complete, the reaction was warmed to 0° and stirring at that temperature was continued for 2 hr. The reaction was quenched by the addition of aqueous ammonium sulfate and the product was isolated by extraction with ether. Purification by preparative tlc afforded 154 mg (47%) of (±)-11,15-dideoxy-PGE_2 methyl ether [ν_{max} ($CHCl_3$) 1740, 970 cm^{-1}; nmr (CCl_4) δ 3.62 (s, 3 H, CH_3), 5.20–5.60 (m, 4 H, olefinic); *m/e* 334].

A solution of (±)-11,15-dideoxy-PGE_2 methyl ester (25 mg) in 1.2 ml of THF and 0.5 ml of water containing 1.0 ml of 0.1 *N* NaOH was stirred at room temperature for 24 hr. Work-up afforded 20 mg of pure (±)-11,15-dideoxy-PGE_2 (**2**) which was chromatographically identical in several solvent systems with a sample kindly provided by Dr. M. J. Weiss (Lederle Laboratories).

(±)-11-Deoxyprostaglandin E_2 Methyl Ester (1).—To a mixture of 393 mg (1 mmol) of tri-*n*-butylphosphine–copper(I) iodide in 7 ml of anhydrous ether cooled to −78° maintained under a nitrogen atmosphere was added with stirring a solution of 3-(α-ethoxy)ethoxy-1-lithio-*trans*-oct-1-ene in anhydrous ether [prepared by treatment of 3-(α-ethoxy)ethoxy-1-iodo-*trans*-oct-1-ene[8] (652 mg, 2 mmol) in 5 ml of anhydrous ether cooled to −78° with 2.86 ml of *tert*-butyllithium (1.44 *M* in *n*-pentane); the solution was maintained at −78° for 1.75 hr]. The resulting mixture was stirred at −78° for 60 min and then was treated with 222 mg (1 mmol) of cyclopentenone (**7b**) in 5 ml of anhydrous ether. The reaction mixture was stirred at −78° for an additional 30 min and then warmed to 0°, where stirring was continued for 1.5 hr. The reaction was quenched by the addition of aqueous ammonium sulfate and the product was extracted with ether. The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on silica gel. There was obtained 90 mg (21%) of product plus 30 mg of recovered **7b**.

A solution of the above material (90 mg) in 0.2 ml of THF was added to 1.75 ml of acetic acid–water (65:35). The resulting solution was heated at 39° for 6 hr. After cooling, the product was isolated by extraction with ether. The combined ether layers were washed with saturated sodium bicarbonate solution and water and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure afforded 56 mg of (±)-11-deoxy-PGE_2 methyl ester (**1**) and (±)-11-deoxy-15-epi-PGE_2 methyl ester (**8**), which appeared to be present in equal amounts as indicated by tlc. Chromatography by preparative thin layer with ethyl acetate–hexane (1:2) afforded 18 mg of (±)-11-deoxy-PGE_2 methyl ester [ν_{max} $CHCl_3$ 3610, 3460, 1730, 970 cm^{-1}; nmr (CCl_4) δ 5.20–5.70 (m, 4 H, olefinic), 4.00 (m, 1 H), 3.62 (s, 3 H, OCH_3); *m/e* 350]. (±)-11-Deoxy-PGE_2 methyl ester was chromatographically identical in several solvent systems with a sample kindly provided by Dr. J. F. Bagli (Ayerst Laboratories).

Acknowledgment.—This research was supported by the Health Research and Services Foundation (HRSF), Pittsburgh, Pa. We thank Dr. J. F. Bagli for providing us with a sample of (±)-11-deoxy-PGE_2 methyl ester and Dr. M. J. Weiss for a sample of (±)-11,15-dideoxy-PGE_2.

Registry No.—**1**, 35120-22-0; **2**, 40098-57-5; **4**, 34638-26-1; **5a**, 40899-59-0; **5b**, 40899-60-3; **6a**, 40899-61-4; **6b**, 40899-62-5; **7a**, 40899-63-6; **7b**, 38698-54-3; triphenylphosphoniopentanoic acid, 39968-97-3; 1-lithio-*trans*-oct-1-ene, 37730-25-9; 3-(α-ethoxy)ethoxy-1-lithio-*trans*-oct-1-ene, 38380-59-5.

(8) Prepared by treatment of *trans*-1-iodo-1-octen-3-ol[2b] in methylene chloride containing a catalytic amount of *p*-toluenesulfonic acid at 0° with a slight excess of freshly distilled ethyl vinyl ether.

Biosynthesis of Phenazines. II. Incorporation of [6-^{14}C]-D-Shikimic Acid into Phenazine-1-carboxylic Acid and Iodinin[1]

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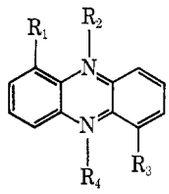
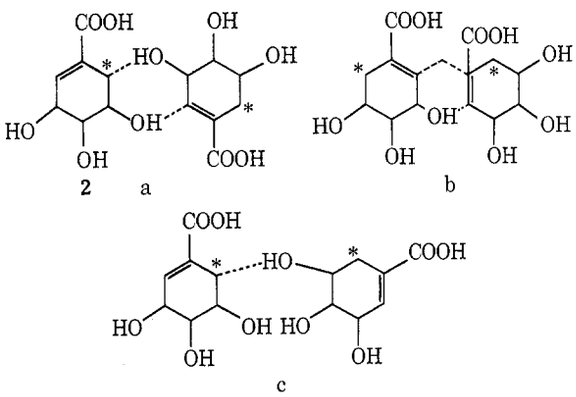
Received April 12, 1973

Previously[1] we have shown that shikimic acid is incorporated into phenazine-1-carboxylic acid (**1a**) and into pyocyanine (**1b**). Degradation of these metabolites[1] from feeding with [G-^{14}C]shikimic acid (**2**) was in agreement with incorporation of the intact shikimic acid molecule. Results from [1,6-^{14}C]shikimic acid feedings narrowed the number of pairing possibilities of two shikimic acid molecules down to four.[1]



1a, R_1 = COOH; R_2 = R_4 = lone pair; R_3 = H
b, R_1 = O^-; R_2 = lone pair; R_3 = H; R_4 = $^+CH_3$
c, R_1 = R_3 = OH; R_2 = R_4 = →O

We have now obtained a sample of [6-^{14}C]-D-shikimic acid,[2] which allowed us to narrow down the number of possible pairing schemes. Feeding of this precursor to *Pseudomonas aureofaciens* led to a 36% incorporation into phenazine-1-carboxylic acid. The labeling data, as shown in Table I, further narrow the number of pairing schemes of two shikimic acid molecules from four to two, *viz.*, d and e. It was hoped that feeding with [$^{14}C_6$]-D-shikimic acid would also allow us to distinguish between the pairing schemes proposed for iodinin by Gerber[3] (a), Holliman[4] (b), and us[1] (c),



since our previous data[1] were not in agreement with the pairing schemes suggested in ref 3 and 4.

The three pairing schemes a–c can be distinguished by 6-monolabeled shikimic acid (Table II). This was

(1) Part I: U. Hollstein and L. G. Marshall, *J. Org. Chem.*, **37**, 3510 (1972).
(2) K. H. Scharf and M. H. Zenk, *J. Label. Compounds*, **7**, 525 (1971).
(3) M. Podojil and N. N. Gerber, *Biochemistry*, **9**, 4616 (1970).
(4) R. B. Herbert, F. G. Holliman, and D. N. Ibberson, *J. Chem. Soc., Chem. Commun.*, 355 (1972).