Prostaglandins. 2.[1] Synthesis of Prostaglandin $F_{2\alpha}$ in Optically Active Form from Chiral Precursors

Francis Johnson,*[2a,b] K. G. Paul,[2c] Duccio Favara,[2d] Romeo Ciabatti,[2d] and Umberto Guzzi[2d]

Contribution from the Department of Pharmacological Sciences, State University of New York at Stony Brook, Long Island, New York 11794, the New England Laboratory, Dow Chemical Company, Wayland, Massachusetts 01778, and Research Laboratories, Gruppo Lepetit Spa, Milano, Italy. *Received May 21, 1981*

Abstract: A synthetic route to optically active prostaglandins is described which uses chiral starting materials. Acylation of the bis(magnesiobromide) salt of methyl hemimalonate with (*S*)-(−)-2-acetoxysuccinyl chloride led to the unstable dimethyl (*S*)-4-acetoxy-3,6-dioxosuberate (**1b**). Treatment of the latter with basic magnesium carbonate then afforded a 4:1 mixture of methyl (*S*)-(−)-2-[2-(methoxycarbonyl)-3-oxo-5-acetoxycyclopent-1-enyl]acetate (**2b**) and its 4-acetoxy isomer (**2d**), from which the former was easily isolated by recrystallization. Catalytic reduction of **2b** over a palladium-on-barium sulfate catalyst gave [2-(methoxycarbonyl)-3-oxo-5-acetoxycyclopentyl]acetate (**9**). Further reduction of the latter compound with sodium borohydride under conditions of carefully controlled pH afforded the corresponding 3α'-hydroxy derivative **10** as an oil. Basic hydrolysis of **10** with KOH/methanol followed by acidification yielded the bicyclic lactonic acid **12**, or its methyl ester (**11**) if an anhydrous base was used. Proof of structure of these compounds and of the optical integrity of the route was achieved by chemical correlation with a commercially available optically active sample of the related 6-hydroxy compound **14**. In continuing the main synthetic scheme, **12** was converted to **14** by acetylation of the 7-hydroxy group which in turn was transformed into the alcohol **14** by means of sodium borohydride reduction of its acid chloride. Oxidation of **14** with chromium trioxide–pyridine complex followed by treatment of the resulting crude aldehyde **23** with methanolic hydrogen gave the corresponding acetal **24b**. Conversion of **24b** to its 7-*O*-THP derivative **25** was followed by reduction of the lactone group to the hemiacetal **26**. Introduction of the α side chain was accomplished by condensation of the latter with the sodium salt **28** of the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide (**27**). Methylation (diazomethane) and acetylation of the resulting hydroxy acid **29** gave the corresponding 5'-*O*-acetyl methyl ester **30** which underwent diacetalation on mild acid treatment to give the aldehyde **31**. Condensation of crude **31** with the sodium salt of dimethyl (2-oxoheptyl)phosphonate afforded methyl (+)-9α-acetoxy-11α-hydroxy-15-oxoprosta-5(*Z*),13(*E*)-dienoate (**32**). The conversion of **32** to (+)-$PGF_{2\alpha}$ (**33**) followed conventional lines. A total chiral synthesis of (+)-prostaglandin $F_{\alpha\alpha}$ (**33**) was achieved by the condensation of the 11-*O*-THP derivative **43** of **31** with the ylide derived from [(*S*)-2-hydroxyheptyl]triphenylphosphonium iodide (prepared in six steps from D-mannitol), followed by mild acid and then basic hydrolysis. However, the overall yield of **33** from **31** using this method of introducing the β side chain is low.

In 1971 when we first began our investigations aimed at the total synthesis of the prostaglandins, several solutions to the problem had already appeared[3] in print. None of these was particularly short in length or efficient in overall yield. In addition, the final products obtained were racemic, except in those cases where an appropriate intermediate had been resolved.[4,5] At that point in time interest in synthesizing these compounds increased dramatically and a substantial number of new approaches were published.[6] Nevertheless, in those instances where optically active prostaglandins were obtained as the final products, the classical methods of resolution still were used,[7,8] with the usual losses of material attendant on such procedures. With the exception of cases in which optical induction[9,10] or microorganisms[11] were used to introduce chirality, it was not until 1976 that methods were forthcoming that led directly to optically active prostaglandins. Almost simultaneously, two different solutions to the problem appeared both of which utilized chiral starting materials. One of these, due to Stork and Rauscher,[12] used L-rhamnose as the initial compound, whereas the other method[1] which is the subject of this paper, began with (*S*)-(−)-malic acid and D-mannitol.

Synthetic Approach. The heart of the synthetic plan that we envisaged at the outset lay in the generation of the five-membered ring of the prostaglandins via an intramolecular 1,4-diketone condensation, of which the general case is shown below (**1** → **2**). This approach seemed to us to have a number of advantages, viz., (a) if $R_1 = R_2$, **1** becomes symmetrical and thus represents a reasonably easy synthetic target, (b) the presence of the two ester functions in **2** offers a variety of opportunities to introduce the α and β side chains of the target molecules, (c) in the simplest case (**2a**, $R_1 = R_2 = H$) access to 11-deoxyprostaglandins should be feasible, and (d) the possibility existed of using the chiral

(1) Part 1: Paul, K. G.; Johnson, F.; Favara, D. *J. Am. Chem. Soc.* **1976**, *98*, 1285–6.

(2) (a) Apart from the introduction of the optically active β side chain, most of this work was carried out (1971–1974) while F.J. was employed at the Dow Chemical Company, Wayland, MA. (b) State University of New York at Stony Brook. (c) Dow Chemical Co. (d) Research Laboratories, Gruppo Lepetit Spa.

(3) Summaries of these early synthetic approaches have been reviewed by: Bentley, P. H. *Chem. Soc. Rev.* **1973**, *2*, 29.

(4) Corey, E. J.; Vlattas, E.; Harding, K. *J. Am. Chem. Soc.* **1969**, *91*, 535.

(5) Fried, J.; Lin, C. H.; Dalven, P.; Cooper, G. F. *J. Am. Chem. Soc.* **1972**, *94*, 4342.

(6) Summaries of these synthetic approaches have recently been reviewed by: Mitra, A. In "The Synthesis of Prostaglandins"; Wiley: New York, 1977. Garcia, G. A.; Maldonado, L. A.; Crabbé, P. In "Prostaglandin Research"; Academic Press: New York, 1977; 121–221. Bindra, J. S.; Bindra, R. "Prostaglandin Synthesis"; Academic Press: New York, 1977.

(7) (a) Corey, E. J.; Moinet, G. *J. Am. Chem. Soc.* **1973**, *95*, 6831. (b) Corey, E. J.; Mann, J. *Ibid.* **1973**, *95*, 6832. (c) Bindra, J. S.; Grodski, A.; Schaaf, T. K.; Corey, E. J. *Ibid.* **1973**, *95*, 7522. (d) Woodward, R. B.; Gostell, J.; Ernest, I.; Friary, R. J.; Nestler, G.; Raman, H.; Sitrin, R.; Suter, Ch.; Whitesell, J. K. *Ibid.* **1973**, *95*, 6853. (e) Fried, J.; Lin, C. H.; Sih, J. C.; Dalven, P.; Cooper, G. F. *Ibid.* **1972**, *94*, 4342. (f) Miyano, M.; Mueller, R. A.; Dorn, R. A. *Intra-Sci. Chem. Rept.* **1972**, *6*, 43. (g) Taub, D. *Ibid.* **1972**, *6*, 99. (h) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397. (i) Corey, E. J.; Vlattas, I.; Harding, K. *Ibid.* **1969**, *91*, 535.

(8) (a) Oda, O.; Sakai, K. *Tetrahedron Lett.* **1975**, 3705. (b) Oda, O.; Kojima, K.; Sakai, K. *Ibid.* **1975**, 3709. (c) Sakai, K.; Ide, J.; Oda, O. *Ibid.* **1975**, 3021.

(9) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 7171.

(10) (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. (b) Fishli, A.; Klaus, M.; Mayer, H.; Schonholzer, P.; Ruegg, R. *Helv. Chim. Acta* **1975**, *58*, 564.

(11) (a) Heather, J. B.; Sood, R.; Price, P.; Peruzzotti, G. P.; Lee, S. S.; Hsu Lee, L. F.; Sih, C. J. *Tetrahedron Lett.* **1973**, 2313. (b) Sih, C. J.; Heather, H. B.; Sood, R.; Price, P.; Peruzzotti, G. P.; Lee, S. S.; Hsu Lee, S. F. *J. Am. Chem. Soc.* **1975**, *97*, 865. (c) Takano, S.; Tanigawa, K.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.* **1976**, 189.

(12) Stork, G.; Raucher, S. *J. Am. Chem. Soc.* **1976**, *98*, 1583. See also: Stork, G.; Takahashi, T. *Ibid.* **1977**, *99*, 1275. Stork, G.; Takahashi, T.; Kawamoto, I.; Suzuki, T. *Ibid.* **1978**, *100*, 8272.

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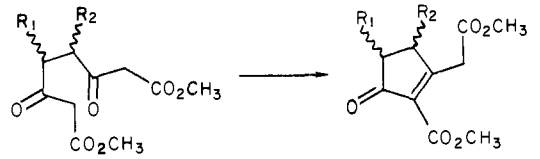
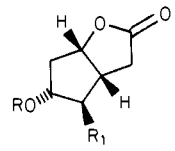


1a, $R_1 = R_2 = H$
b, $R_1 = H$, $R_2 = OAc$
c, $R_1 = R_2 = OAc$

2a, $R_1 = R_2 = H$
b, $R_1 = H$, $R_2 = OAc$
c, $R_1 = R_2 = OAc$
d, $R_1 = OAc$, $R_2 = H$)



3, $R_1 = CH_2OH$, CHO, CO_2H, etc.

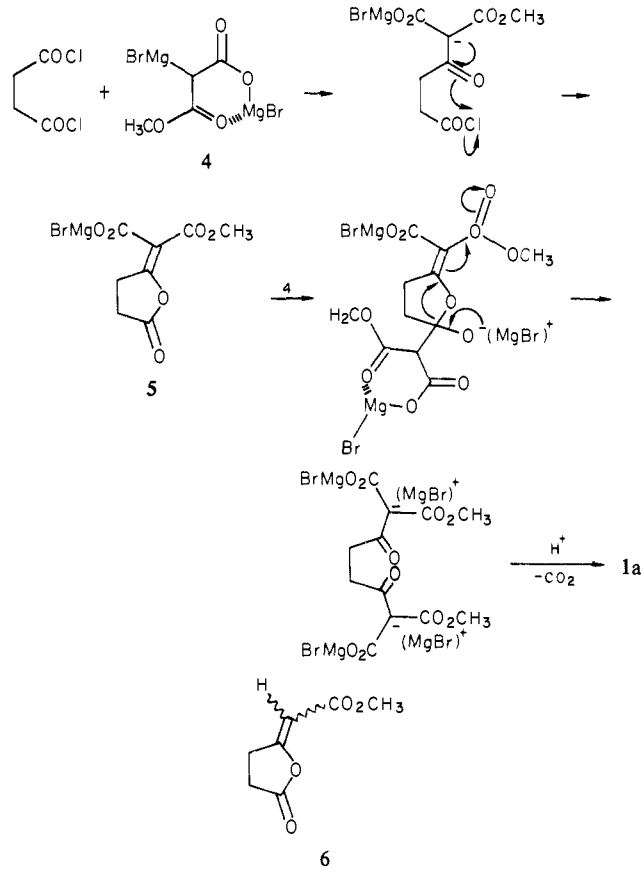
precursors, malic acid or tartaric acid, in a synthesis of a substance in the Corey lactone class (represented generally by **3**) via **2b** or **2c**, since both of the latter have the correct array of carbon and oxygen substituents on the five-membered ring.

In reviewing this approach one of our concerns was that molecules such as **1b** and **1c** might easily undergo an elimination reaction to produce a 4-ene-3,6-dione. This fear proved well-founded in the case of **1b**, but the difficulty was avoidable. On the other hand, the possibility that such an elimination might occur in the cases of **2b** and **2c** did not seem likely, because the products would be the thermodynamically less stable cyclopentadienones. Although the lack of molecular symmetry in the case of **1b** suggested that this might make **2b** a more difficult synthetic target, this did not subsequently prove to be the case.

Synthesis of the Corey Lactone in Optically Active Form. The initial goal of our synthetic work then reduced itself to the development of a general method for the preparation of dimethyl 3,6-dioxosuberates (**1**). Willstätter and Pfannenstiehl[13] had previously prepared **1a** (as the ethyl ester) in 12% yield by electrolysis of ethyl potassium 2-oxopropane-1,3-dicarboxylate. This they found underwent cyclization in good yield to the ethyl ester homologue of **2a** in aqueous sodium hydroxide. However, the yield in the initial step discouraged us from pursuing this route further, and we looked for an alternate method. A number of approaches[14,15] were examined but the method which proved really successful was based on a report by Ireland and Marshall,[16] who showed that methyl β-keto esters can be synthesized by the acylation[17] of the bis(bromomagnesium) salt **4** of methyl hemimalonate. When this reaction was applied to succinyl chloride, the desired dioxosuberate **1a** was obtained in good yield, but in this case even better results (~75% yield) were obtained when the mixed salt, potassium bromomagnesium methyl hemimalonate, was used in place of **4**.

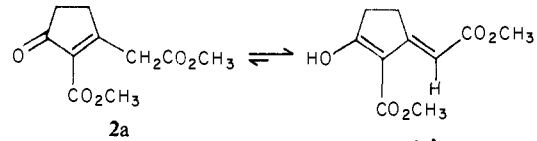
The reaction pathway probably involves the sequence shown in Scheme I. However, the isolation of the enol-lactone **6** from an incomplete reaction and the evolution[18] of some CO_2 as the reaction progresses suggests that the mechanism is more complex. The cyclization[13] of crude **1a** in our hands then gave **2a** in 84%

Scheme I



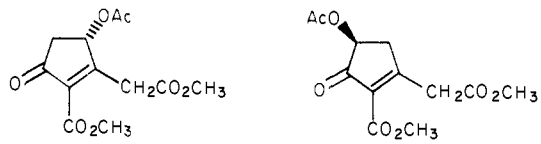
4 **5** **6**

yield. The latter can be obtained in the keto or enol form depending on the solvent of crystallization.



2a **2a'**

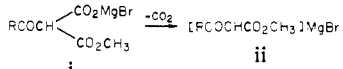
The (*S*)-(−)-2-acetoxysuccinyl chloride[20a] (**7**) required for the initial step in the synthesis of **1b** was prepared by the treatment of optically active 2-acetoxysuccinic anhydride[21] with dichloromethyl methyl ether in the presence of zinc chloride. When this acid chloride was allowed to react with **4** in the Ireland–Marshall procedure,[17] the desired product **1b** was obtained in 73% yield. Because **1b** is an unstable oil that undergoes a slow elimination of acetic acid on standing, it was used immediately in the subsequent cyclization step. Although a number of basic reagents accomplished this reaction, the best results were obtained when basic magnesium carbonate was employed. This appears to be linked to the ability of the latter material to keep the pH of the aqueous phase at 6.0–6.5. Under these conditions crude **2b** was



2b **2d**

obtained largely as the magnesium salt from which it was liberated by acidification. Isolated in this way, it was obvious, from its NMR spectrum, that the crude crystalline product constituted **2b** together with its regioisomer **2d** in a ratio of 4:1, proportions

(13) Willstätter, R.; Pfannenstiehl, A. *Justus Liebigs Ann. Chem.* **1920**, *422*, 1.
(14) Stiles, M.; Finkbeiner, H. L. *J. Am. Chem. Soc.* **1959**, *81*, 505.
(15) Crombie, L.; Hemesley, P.; Pattenden, G. *J. Chem. Soc. C* **1969**, *1016*.
(16) Ireland, R. E.; Marshall, J. A. *J. Am. Chem. Soc.* **1959**, *81*, 2907.
(17) For a discussion of the difficulties of acylating malonate esters see: Taylor, E. C.; McKillop, A. *Tetrahedron* **1967**, *23*, 897.
(18) The immediate decarboxylation of the acylated hemimalonate salt i

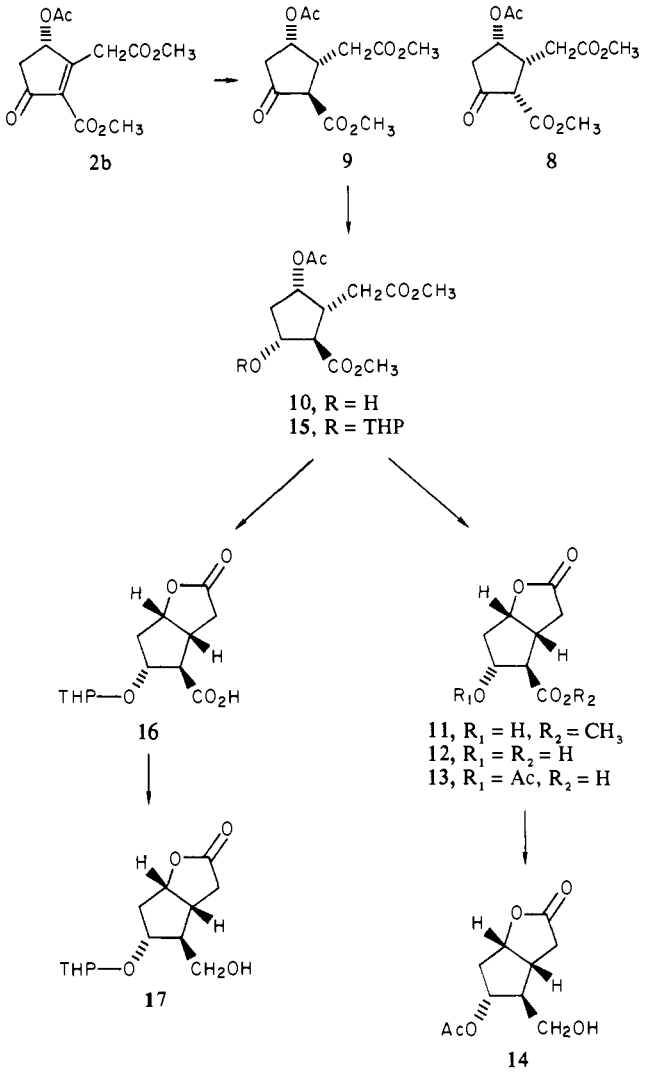


i ii

to give the salt of an α-substituted acetoacetic ester ii might be expected on thermodynamic grounds, since the bromomagnesium salts of acetoacetic esters generally do not undergo carboxylation by carbon dioxide, under the conditions used (unpublished work, F. Johnson).

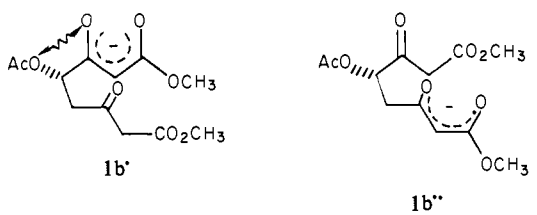
(19) This will be the subject of a separate publication.
(20) (a) Freudenberg, K.; Lux, A. *Chem. Ber.* **1928**, *61*, 1083. (b) Rieche, A.; Gross, H. *Ibid.* **1959**, *92*, 83.
(21) Anschutz, R. *Chem. Ber.* **1881**, *14*, 2791.

Scheme II



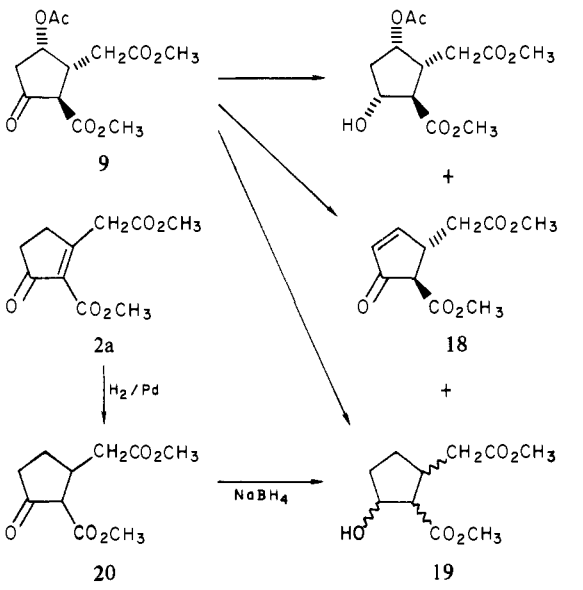
which are unaffected by the nature of the cyclizing catalyst. It did not prove possible to separate **2d** easily from **2b** chromatographically, so that the former remains uncharacterized. Purification of **2b**, however, was easily accomplished by a single recrystallization from carbon tetrachloride, the overall yield from the acid chloride **7** being 51%. It exists almost entirely in the keto form (NMR data) but does, however, give a deep blue color in the ferric chloride test.

Although the regioselectivity expressed in the cyclization reaction deserves comment, the precise reason for the observed preference is not evident, because it is not known if the reaction sequence is under thermodynamic or kinetic control. One possible explanation is that the anion **1b′** is less stable than **1b″** because



of the steric interaction[22] in the former, that exists between the two oxygen atoms in the conformation, which leads to cyclization. Alternatively the results may reflect the intrinsic differences in the basicities of the two keto groups and thus the product ratio may be a result of the thermodynamically determined ratio of

Scheme III



1b″/**1b′** assuming the kinetics of ring closure to be the same in each case. One other point that deserves mention concerns the optical rotation of **2b**. It was found to be $\sim -11°$ ($[\alpha]^{25}_{D}$), but we had no way of knowing if any loss of optical activity had taken place. However, being aware of the relative difficulty[23] of deprotonating a carbon atom bearing both a ketonic and an ether group [i.e., RCH(OR′)CO–] and considering the mildness of the reaction conditions that we had employed, we proceeded with some confidence to the next phase of the synthesis, namely, the conversion of **2b** to known substances related to the Corey lactone **3**. The essential details of this work are shown in Scheme II.

The initial step of the sequence, namely, the conversion of **2b** to **9**, was examined in some detail, and after considerable experimentation it was established that for optimal stereoselective results (90–95% yields) the catalytic reduction was best carried out in benzene in the presence of a mild catalyst (5% $Pd/BaSO_4$). Inspection of structure **2b** shows that the cyclopentenone ring is practically planar with the 5-acetoxy group oriented substantially out of this plane. It was expected therefore that the addition of hydrogen would take place in a cis manner on the least hindered side to yield **8** initially. From a practical point of view, however, it seems likely that the isolated product has the stereochemistry represented in **9**, that is, the thermodynamically more stable form, because of the facile keto–enol tautomerism associated with β-keto esters. Again considering the geometry of **9**, it appeared that the more stable conformer would be the one in which the substituents at positions **1** and **2** were ψ equatorially oriented and the acetoxy at C-5 were ψ axially oriented. Thus it seemed that once again the acetoxy group might play a major role this time in directing the reduction of the keto group of **9** to give **10** the next compound desired. Nevertheless, this reduction proved to be very troublesome to control. Most of the work centered around sodium borohydride, other complex metal hydrides proving to be less satisfactory in preliminary experiments.

Reduction of **9** with sodium borohydride at pH 7 yielded only a minor amount (28%) of the desired **10**. A GC/MS investigation of the reaction mixture quickly revealed that the major, but undesired, components were **18** (15%) and its further reduction products **19** (two isomers, 51%). These result from reduction after the elimination of acetic acid. The isomers (as the mixture) were identified by comparison with authentic samples prepared from **2a** as shown in Scheme III, but their stereochemistry was not proven rigorously. Small amounts (6%) of two isomers **21** and **22** of **10** were also shown to be present by GC/MS, but due to the fact that they could not be separated easily by preparative TLC, they remain incompletely characterized.

(22) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(23) Stork, G.; Schultz, R. *J. Am. Chem. Soc.* **1971**, *93*, 4074.

Table I. Effect of pH on the Reduction of 10 with Sodium Borohydride

	pH[a]							
	4	4.5	5	5.25	5.5	6	6.5	7
	mass balance (% recovery)							
% yield[b]	92	89	98	99	100	97	91	88
10	35	36	67	79	68	51.5	47	28
18[c]	40	40	15		1-2		11	15
19	5	5		7	13	31	32	51
21	19	10	11	9.5	8	9	5	3
22		9	7	4.5	5	8	5	3

[a] pH was controlled by the use of citrate or phosphate buffers. [b] Yields were determined by GC [10% OV225 (Hewlett-Packard) at 200 °C]. [c] 18 partially isomerizes to 2a under the conditions of GC or TLC. Analysis by NMR, however, indicates the absence of 2a from the initial mixture of reduction products.

In an effort to prevent the elimination of acetic acid from **10**, a study was made of the effect of pH on the course of the reaction. The results are shown in Table I and demonstrate that pH is indeed a critical factor. The best yields of the desired product (**10**) occur in the pH range 5–5.5 with a maximum at pH 5.25. Reduction at the latter pH was repeated several times, and the results were found to be quite reproducible. A further point worth mentioning is that at a pH <5, **18** is not further reduced, presumably because the rate of decomposition of the borohydride ion exceeds the reduction rate. Purification of **10**, which is an oil, is possible by chromatography over silica gel, which removes **19** but not **21** or **22**. Nevertheless, this was not an impediment since the use of crude **10** in the preparation of either **11** or **12** led easily to pure crystalline products.

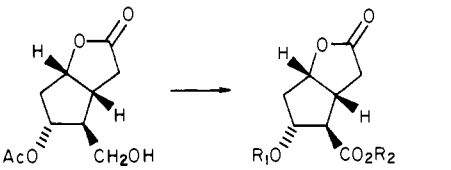
The direct reduction of **2b**, using the optimal pH conditions, was also examined. The resulting mixture was found to comprise **10** (62%), **19** (2%), **21** (10%), and **22** (26%) and thus represents an inferior procedure in comparison with the two-step method described above.

At this point it became important to demonstrate both that **10** had the desired stereochemistry and that the synthesis had proceeded with maintenance of optical integrity. Proof of the cis relationship, in **10**, of the acetoxy and the methyl acetate residue was deduced from the fact that treatment of this compound with anhydrous potassium carbonate or sodium methoxide in dry methanol led to **11** (34% overall yield from **1**). The IR spectrum of **11** showed bands indicative not only of ester (1735, 1745 cm^{-1}) and hydroxyl (3480 cm^{-1}) groups but also of an unstrained (1760 cm^{-1}) five-membered lactone ring. Treatment of **10** with potassium hydroxide in methanol, followed by acidification, led to the acid **12** (corresponding to the ester **11**) whose infrared spectrum showed a band again corresponding to an unstrained five-membered ring lactone.

At this stage, further demonstration of the postulated stereochemistry of **10**, **11**, and **12** and of their optical purity was forthcoming chemically from the series of transformations shown in Scheme IV, starting with a commercially available[24] sample of optically pure **14**. Jones oxidation of **14** led to **13** which when treated with methanolic potassium hydroxide followed by acidification furnished the lactonic acid **12**. Treatment of **12** with diazomethane afforded **11**. Both of the latter compounds were identical in all respects, including optical activity, with those prepared according to our own synthetic sequence, thus not only confirming the structures but also demonstrating the optical integrity of the route.

Returning now to Scheme II, for purposes of further synthetic work, **12** was converted by normal acetylation procedures to **13** and the carboxyl group of the latter was then reduced[25] to the carbinol **14** by the action of sodium borohydride on the corresponding acid chloride. We also synthesized the related 7-O-THP

Scheme IV



14 **11**, $R_1 = H$, $R_2 = CH_3$; **12**, $R_1 = R_2 = H$; **13**, $R_1 = CH_3CO$, $R_2 = H$

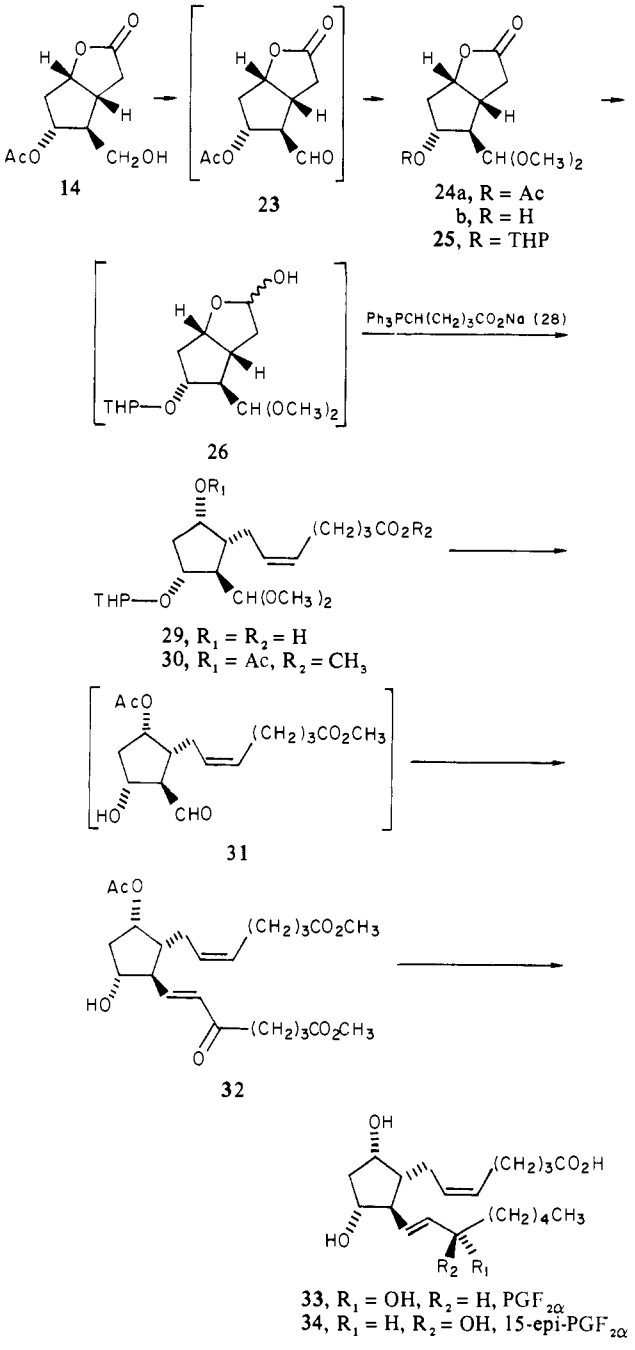
Corey intermediate, namely, **17** by similar procedures although in this case the mixed ethyl carbonic anhydride proved much superior to the acid chloride. Treatment of **10** with dihydropyran afforded **15** which on saponification followed by careful acidification led to **16**. The order of these two steps could be reversed, without loss in yield. Conversion of **16** to **17** was accomplished by sodium borohydride reduction of the mixed ethyl carbonic anhydride. However, further experiments[26] with **17** did not prove to be as successful as those with the related carbinol **14**, and virtually all of the research concerned with the introduction of the α and β side chains was carried out with the latter substance.

Introduction of the Side Chains. For synthetic purposes the Corey intermediate **14** proved to be the more valuable from our point of view because from it, via **23**, we were able to evolve a route to the final compounds in which the α side chain was introduced first.[27] This particular approach allows **30** to be used as a staging point for the introduction of a variety of β side chains (one of the objectives of our program) as a penultimate step.[28] The key compound, **25**, in the synthetic plan (Scheme V) was obtained by selective oxidation of **14** to the aldehyde **23** which, without isolation, was treated with a large excess of methanolic hydrogen chloride to give the lactonic acetal **24b**, concomitant deacetylation also having occurred. (If a limited amount of the latter reagent were used, the acetoxyacetal **24a** was obtained. This, however, was not as useful a substrate as **25** for the introduction of the α side chain.) Treatment of the **24b** with dihydropyran in the presence of an acid catalyst then afforded **25** in good (~81%) yield. Attempts to prepare **25** from **17** via oxidation to the aldehyde followed by treatment with acidic methanol led to loss of the tetrahydropyranyl group with the formation of **24b**, thus making this route to **25** less economical. Reduction of lactone **25** to the lactol **26** was easily accomplished[29] in 75% yield using sodium bis(2-methoxyethoxy)aluminum hydride at −78 °C. The lactol without further purification was then allowed to react with the sodium salt **28** derived from (4-carboxybutyl)triphenylphosphonium bromide[30] (**27**) by treatment with the sodium salt of dimethyl sulfoxide. This led to the crude coupled product **29** which after column chromatography was obtained pure in 48% overall yield. Methylation of **29** by diazomethane followed by treatment with acetic anhydride and pyridine then afforded a 90% yield of the fully protected ester **30**. Mild acidic hydrolysis of **30** cleaved both of the acetal linkages, yielding the hydroxyaldehyde **31** which was used without purification in the subsequent condensation reaction that introduces the β side chain.

The latter reaction was carried out by using the standard method,[30] namely, condensation of **31** with the sodium salt of

(24) Supplied by Fuji Chemical Industries Ltd., Tokyo, Japan.
(25) A direct reduction of the acid **13** to the carbinol **14** by diborane has been reported by Peel, J.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1974**, 151.
(26) The 6-aldehyde corresponding to **17**, however, has found use in several synthetic sequences. (a) Corey, E. J.; Shirahama, H.; Yamamoto, H.; Terashima, S.; Venkateswarlu, A.; Schaaf, T. K. *J. Am. Chem. Soc.* **1971**, *93*, 1490. (b) van Hooland, J.; De Clercq, P.; Vandervalle, M. *Tetrahedron Lett.* **1974**, 4343.
(27) Other examples using Corey intermediates where the β side chain is introduced last include: (a) Schaff, T. K.; Corey, E. J. *J. Org. Chem.* **1972**, *37*, 2921. (b) Doria, G.; Gaio, P.; Gandolfi, C. *Tetrahedron Lett.* **1972**, 4307.
(28) Alternate syntheses of compounds **24b**, **25**, **26**, and **29** have been published in communication form by research workers at ICI Ltd. but no physical data were recorded. Mallin, K. B.; Walker, E. R. H. *Synth. Commun.* **1975**, *5*, 221. For preliminary work see: Brown, E. D.; Clarkson, R.; Leeney, T. J.; Robinson, G. E. *J. Chem. Soc., Chem. Commun.* **1974**, 642.
(29) Doria, G.; Gaio, P.; Gandolfi, C. *Tetrahedron Lett.* **1972**, 4307.
(30) (a) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654. (b) Corey, E. J.; Hamanaka, E. *Ibid.* **1967**, *89*, 2758. (c) Grieco, P. A.; Pogonowski, Ch. *Ibid.* **1973**, *95*, 3071.

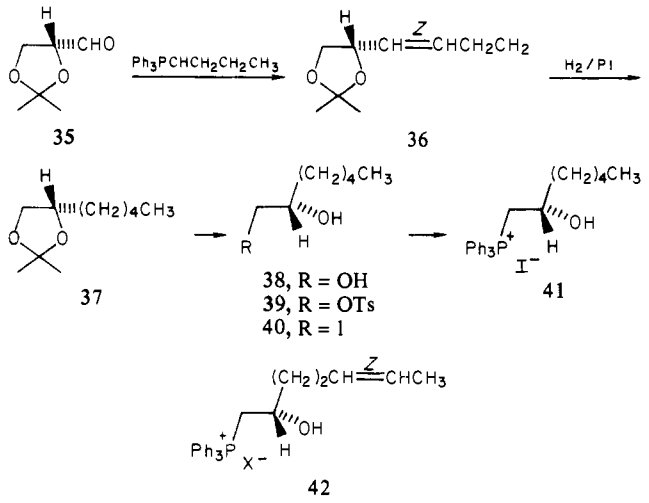
Scheme V



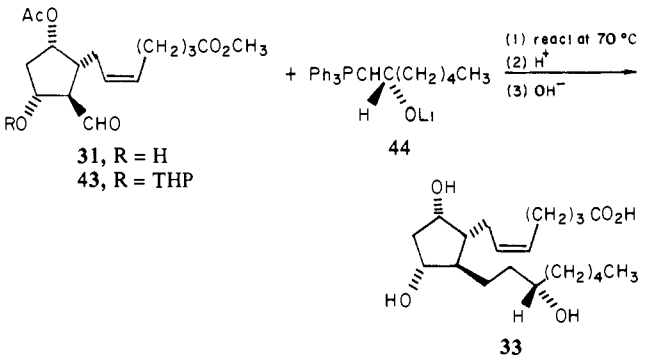
dimethyl (2-oxoheptyl)phosphonate. This led to **32** in 66% yield. Completion of the synthesis of $PGF_{2\alpha}$ was then effected by the two-step procedure involving sodium borohydride reduction[31] of the 15-ketone followed by simple basic hydrolysis of the ester group. This afforded $PGF_{2\alpha}$ (**33**) which was separated by preparative TLC. The synthetic $PGF_{2\alpha}$ prepared in this way proved to be identical, in all its physical properties, with an authentic specimen.[24] The overall yield of $PGF_{2\alpha}$ from (*S*)-(−)-2-acetoxysuccinyl chloride is 1%.

In order to complete the synthesis of $PGF_{2\alpha}$ purely from optically active precursors, we synthesized the appropriate β side chain derivative in optically active form according to the method shown in Scheme VI.

Scheme VI



The synthesis of **35** from the (1-O,2-O) (5-O,6-O)-bisacetonide of D-mannitol was carried out according to Fischer and Baer.[33] Conversion of the latter to **41** then followed procedures similar to those used by Corey et al.[26a] for the synthesis of the corresponding unsaturated derivative (**42**). Condensation of the



phosphonium ylide **44**, derived from **41**, with the crude 7-*O*-THP (**43**) derivative of **31** then led, after hydrolysis of the crude product, to a mixture of compounds including $PGF_{2\alpha}$. Separation of the desired $PGF_{2\alpha}$ (**33**) was achieved by preparative TLC (other compounds were not characterized), but the overall yield (12%) was poor in comparison with the method shown in Scheme V. After further purification, the substance showed an optical rotation, $[\alpha]^{25}_D$ +24.3° [lit.[7f] +23.5°], essentially identical with that of an authentic specimen, thus completing our objective, namely, *the direct synthesis of an optically active prostaglandin from the readily available chiral precursors,* D-*mannitol and* (*S*)-(−)-*malic acid.*

Experimental Section

Methyl 2-[2-(Methoxycarbonyl)-3-oxocyclopent-1-enyl]acetate (2a). In a dry 5-L flask equipped with a mechanical stirrer there was prepared, under N_2, a Grignard reagent from isopropyl bromide (123 g, 1 mol) and magnesium (25 g, 1.05 mol) in dry tetrahydrofuran (600 mL). The solution was then diluted with the same solvent (2 L), and dry potassium methyl malonate[34] (156 g, 1 mol) was added during 20 min via a funnel for solids. The slurry was refluxed until gas evolution ceased (1–2 h) and then cooled to room temperature. Succinyl chloride (38.75 g, 0.25 mol) was added dropwise during 15 min, and stirring was then continued for 15 h. The reaction mixture was then teemed, with vigorous stirring, into a solution of sulfuric acid (70 mL) in ice water (700 mL). The organic layer was separated, and the residual aqueous phase was extracted with

(31) Slates, H. L.; Zelawski, Z. L.; Taub, D.; Wendler, N. L. *J. Chem. Soc., Chem. Commun.* **1972**, *304*; *Tetrahedron* **1974**, *30*, 819.
(32) Bundy, G. L.; Schneider, W. P.; Lindoln, F. H.; Pike, J. E. *J. Am. Chem. Soc.* **1972**, *94*, 2123. Schneider, W. P.; Bundy, G. L.; Lincoln, F. H.; Daniels, E. G.; Pike, J. E. *Ibid.* **1977**, *99*, 1222.
(33) Fischer, H. O. L.; Baer, E. *Helv. Chim. Acta* **1934**, *17*, 622.

(34) Melting points were taken on a Buchi capillary melting point apparatus and are uncorrected. Infrared spectra were recorded by using a Perkin-Elmer 421 spectrophotometer. NMR spectra were obtained with a Varian A60 or CFT-20 spectrometer using $(CH_3)_4Si$ as the internal standard. Low-resolution mass spectra were obtained with a Hitachi RMU-6L mass spectrometer at 70 eV using the direct insertion system and an ion-source temperature of 200 °C. GLC–MS data were recorded by means of a Perkin-Elmer 270 spectrometer.

ether (3 × 200 mL). These extracts and the organic layer were combined, washed successively with saturated sodium bicarbonate solution and brine, and then dried ($MgSO_4$). Evaporation of the solvents afforded dimethyl 3,6-dioxosuberate (**1a**) as an oil (44 g, 76.5%): IR ($CHCl_3$) 1750–1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.92 (4 H, s, CH_2CH_2), 3.60 (4 H, s, $COCH_2CO_2CH_3$), 3.76 (6 H, s, OCH_3). The substance gives a brilliant deep red color with ferric chloride solution.

Without further purification the crude dimethyl 3,6-dioxosuberate (43.8 g, 0.19 mol) was added with stirring to sodium hydroxide solution (1 N, 195 mL, 0.195 mol) at 0 °C over 30 min. The ice bath was then removed, and stirring was continued for 30 min. The mixture was poured into water (100 mL) and the pH of the solution adjusted to 3 by using 2 N hydrochloric acid. The isolation of the desired methyl 2-[2-(methoxycarbonyl)-3-oxocyclopent-1-enyl]acetate (**1a**) as a crystalline solid (39.2 g, 89%) followed a routine extraction procedure with ethyl acetate (3 × 200 mL). Recrystallization from ether/hexane yielded pure **1a** (35.4 g) as needles: mp 59–60 °C [enol form (lit.[13] mp 59.5–60 °C)] or 81–82 °C (keto form); IR ($CHCl_3$) 3200–2800, 1700, 1650, 1615, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ (enol form) 2.6–3.3 (4 H, m), 3.70 (3 H, s), 3.90 (3 H, s), 6.23 (1 H, t, J = 3 Hz) ~10 (1 H, s); δ(keto form) 2.4–3.0 (4 H, m), 3.72 (3 H, s), 3.80 (3 H, s), 3.85 (2 H, s). It gives a deep blue color with ferric chloride.

Anal. ($C_{10}H_{12}O_5$) C, H.

(*S*)-(−)-2-Acetoxysuccinyl Chloride (7). (*S*)-(−)-malic acid (50 g, 0.38 mol) was heated under reflux, with acetyl chloride (70 mL) until complete dissolution had taken place (~1.2 h). The solution of 2-acetoxysuccinic anhydride was cooled, and 1,1-dichloromethyl methyl ether (100 g, 0.8 mol) was added together with zinc chloride (0.5 g). The mixture was heated at reflux for 4 hours, cooled, and diluted with benzene (500 mL). The solution was then decanted from a small amount of an insoluble dark oil (~1 g) and after filtration was concentrated to remove the volatile organic materials. The residual liquid was distilled at 0.05mmHg to give (*S*)-2-acetoxysuccinyl chloride (64 g, 80%): bp 80–81 °C (0.05mmHg); $[\alpha]^{25}_D$ − 10° ($CHCl_3$, c 1.0% [lit.[20a] bp 118 °C (14mmHg); $[\alpha]^{22}_D$ −13°]; IR (neat) 1800, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (3 H, s), 3.2 (2 H, d, J = 3 Hz), 5.43 (1 H, t, J = 3 Hz).

Anal. ($C_6H_6Cl_2O_4$) C, H, Cl.

Dimethyl (*S*)-4-Acetoxy-3,6-dioxosuberate (1b). A solution of ethylmagnesium bromide in tetrahydrofuran (1 L) was prepared, under N_2 in a 5-L flask, by using magnesium (72 g, 3.0 mol) and ethyl bromide (350 g, 3.3 mol), the temperature being kept at 30–35 °C and all the usual precautions being observed. When visible reaction had subsided, the mixture was heated under reflux for 1 h, and immediately thereafter, dry N_2 gas was passed through the solution (no heat; no condenser) for 10 min to remove excess ethyl bromide. The resulting reagent was cooled to −15 °C and diluted with dry tetrahydrofuran (2.5 L). While the temperature of the Grignard reagent was maintained below −10 °C, methyl hydrogen malonate (177 g, 1.5 mol) in dry tetrahydrofuran (0.5 L) was added slowly (0.5 h), and the mixture, thereafter, was boiled until ethane ceased to be evolved (~1 h). The solution was cooled to 20 °C, and (*S*)-(−)-2-acetoxysuccinyl chloride (63.6 g, 0.3 mol) was added dropwise and the mixture allowed to stand overnight. Thereafter it was poured with stirring into cold hydrochloric acid (1 N, 1.8 L). Hexane (~0.5 L) was added to aid separation of the layers, and the organic phase was then removed and washed with a phosphate buffer (2 × 0.5 L) containing 1 mol/L each of KH_2PO_4 and K_2HPO_4 to remove methyl hydrogen malonate. The organic layer was then dried ($MgSO_4$), and the solvents were removed under reduced pressure (25 °C) to give the desired crude dimethyl (*S*)-4-acetoxy-3,6-dioxosuberate as a pale yellow oil (70 g): IR (neat) 1750–1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (3 H, s, CH_3COO), δ 3.1–3.9 (6 H, m, CH_2), 3.69 (6 H, s, CO_2CH_3), 5.46 (1 H, t, J = 3.5 Hz, C*H*OAc). Because the product slowly loses acetic acid on standing, it was used immediately in the following reaction.

Methyl (*S*)-(−)-2-[2-(Methoxycarbonyl)-3-oxo-5-acetoxycyclopent-1-enyl]acetate (2b). A solution of crude dimethyl (*S*)-4-acetoxy-3,6-dioxosuberate (70 g) in ether (0.5 L) was added to a stirred suspension of basic magnesium carbonate (30 g, $4MgCO_3$, $Mg(OH)_2 \cdot nH_2O$) in water (1 L). [Note: the pH should be 6–6.5, and some magnesium carbonate should always remained out of solution.] After 30 min the mixture was filtered and the ether layer separated and washed once with a phosphate buffer (200 mL, pH 7). The buffer extract, the aqueous phase from the reaction, and the solid removed by filtration were then combined and acidified with hydrochloric acid (3 N). This solution was extracted with ethyl acetate (3 × 0.5 L), and the combined extracts were dried ($MgSO_4$). Evaporation of the solvent afforded an oil (55 g) which solidified almost immediately and which on recrystallization from carbon tetrachloride gave crystals of **2b** (41 g; yield, 51% from *o*-acetylmalyl chloride), mp 97–99 °C. An analytical sample obtained by recrystallization from ether had the following properties: mp 99–100 °C; IR (Nujol) 1720–1750, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (3 H, s, CH_3CO_2), 2.40 (1 H, d of d, J_{AB} = 18 Hz, J_{AX} = 2.5 Hz), 3.03 (1 H, d of d, J_{BA} = 18 Hz, J_{BX} = 6.5 Hz), 3.72 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 3.70–3.90 (2 H, m, CH_2CO_2), 5.94 (1 H, d of d, J_{AX} = 2.5 Hz, J_{BX} = 6.5 Hz, CHOAc); UV (CH_3OH) λ_{max} (ϵ) 223 (8515), 328 (6430), 300 (shldr) pK_A (H_2O/Me_2SO) 5.2; mass spectrum, m/z 270 (M^+); $[\alpha]^{25}_D$ −10.7° ($CHCl_3$, c 2.15%). It gives a deep blue color with ferric chloride solution.

Anal. ($C_{12}H_{14}O_7$) C, H.

Methyl (1*R*,2*R*,5*S*)-(−)-2-[2-(Methoxycarbonyl)-3-oxo-5-acetoxycyclopentyl]acetate (9). A solution of the cyclopentenyl compound (**2b**, 9.5 g) in benzene (180 mL) was hydrogenated over a 5% Pd-on-$BaSO_4$ catalyst (0.5 g) at 1 atm and 25 °C. Gas absorption (840 mL) ceased after 16 h, and the solution was then filtered and evaporated under reduced pressure to give essentially pure **9** (9 g, 95% yield). A sample recrystallized from ether had the following properties: mp 54 °C; IR (neat) 1740–1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (3 H, s, AcO), 2.5–2.7 (4 H, m), 3.15–3.35 (2 H, m), 3.68 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 5.5–5.7 (1 H, m, CHOAc): mass spectrum, m/z 272 (M^+); $[A]^{25}_D$ −17.8° ($CHCl_3$, c 1.02%).

Anal. ($C_{12}H_{16}O_7$) C, H.

Methyl (1*R*,2*R*,3*R*,5*S*)-(+)-2-[2-(Methoxycarbonyl)-3-hydroxy-5-acetoxycyclopentyl]acetate (10). A solution of **9** (1 g), in methanol (25 mL, was added dropwise as 0 °C to an aqueous buffer (pH 5.25) prepared from potassium dihydrogen phosphate solution (0.067 M, 120 mL) and disodium hydrogen phosphate solution (0.067 M, 2.44 mL). A solution of sodium borohydride (70 mg) in water (7 mL) was then added dropwise at 0 °C. After a further 2 h at 10–15 °C sodium chloride was added until the solution was saturated and the mixture was extracted with ethyl acetate (4 × 30 mL). The combined extracts were dried ($MgSO_4$) and evaporated to give crude **10** as an oil (0.97 g) whose purity was estimated by GLC analysis to be 80% (yield, 79%). This material could be purified only partially (~90%) by preparative TLC using ether as the eluting solvent, and the data reported below are for material of this quality: IR (neat) 3450, 1730, 1725, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (3 H, s, CH_3CO), 1.55–3.0 (7 H, m; centered at δ 1.6 and 1.9 are two quartets whose assignment is unclear), 3.6 (3 H, s, OCH_3), 3.7 (3 H, s, OCH_3), 4.4 (1 H, m, CHOH), 5.2 (1 H, m, CHOAc); mass spectrum, m/z 275 ($M^+ + 1$), 231, 201, 186, 183, 165, 154 (100%), 141, 127, 113, 95, 59; $[\alpha]^{25}_D$ +49° ($CHCl_3$, c 1.0%).

Anal. ($C_{12}H_{18}O_7$) C, H.

Borohydride Reduction of 9 in Unbuffered Solution. Isolation of 18 and 19. A solution of **9** (0.2 g) in 2-propanol at 0 °C was treated with sodium borohydride (0.1 g). The mixture was stirred at this temperature for 2 h, then excess reagent was destroyed with 1% hydrochloric acid. Isolation using ether led to an oily mixture (0.17 g) which was chromatographed over silica gel (5 g) using first ethyl ether/hexane (1:1) and then ethyl ether to yield three major oily fractions. The least polar fraction (25 mg) was identified as **18**: ^1H NMR ($CDCl_3$) δ 2.3–2.9 (2 H, m, CH_2CO), 3.22 (1 H, d, J_{CH-CH} = 3 Hz, CO*CH*CO), 3.6–4.0 (1 H, m, *CH*CH_2), 3.75 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 6.23 (1 H, d of d, J_{AB} = 6 Hz, J_{AX} = 2.5 Hz, CH=C*H*CO), 7.81 (1 H, d of d, J_{BA} = 6 Hz, J_{BX} = 2.5 Hz, C*H*=CHCO); mass spectrum, m/z 212 (M^+); $[\alpha]^{25}_D$ +120° ($CHCl_3$; c 2.02%).

Anal. ($C_{10}H_{12}O_5$) C, H.

The intermediate fractions yielded a mixture of the two hydroxy epimers of **19** as an oil (20 mg): IR (neat) 3400–3500 (OH), 1725 (esters) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–3.2 (8 H, m), 3.65 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), 4.35, 4.6 (1 H, m, C*H*OH); mass spectrum, m/z, M^+ is absent, 188, 185, 167, 156, 139, 127, 115 This material proved to be spectroscopically identical with a sample prepared by the reduction of methyl *rac-trans*-2-[2-(methoxycarbonyl)-3-oxocyclopentyl]acetate (**20**) as described below. The later fraction from the column contained **10** together with small quantities of its isomers **21** and **22**. Both of the latter show mass spectra almost identical with that of **10**, but no attempts were made to characterize these substances further.

Methyl *rac-trans*-2-[2-(Methoxycarbonyl)-3-oxocyclopentyl]acetate (20). A solution of **2a** (5.0 g) in ethyl acetate (60 mL) was hydrogenated over a 5% palladium-on-charcoal catalyst (0.5 g) until gas absorption ceased (20 min). After the catalyst and solvent were removed, the residual oil was distilled to give **20** as a colorless oil (5 g): bp 98–101 °C (0.2mmHg); IR 1760, 1740 cm^{-1}; ^1H NMR ($CHCl_3$) δ 2.3–3.3 (8 H, m), 3.38 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3).

Anal. ($C_{10}H_{14}O_5$) C, H.

Reduction of 20 to an Epimeric Mixture of Alcohols (19). A sample of **20** (0.1 g) in methanol (5 mL) was reduced with sodium borohydride (10 mg) in water (1 mL) at 0 °C under the buffered conditions (pH 5), described for the preparation of **10**. Isolation of the product in the usual way led to an oily mixture of the epimeric alcohols **19** whose spectroscopic properties were identical with those observed for the diester alcohols isolated from the reduction of **9** as described above.

Anal. ($C_{10}H_{16}O_5$) C, H.

(1*S*,5*R*,6*R*,7*R*)-(−)-2-Oxa-6-(methoxycarbonyl)-7-hydroxybicyclo[3.3.0]octan-3-one (11). Method A. Anhydrous potassium carbonate (69 mg) was added to a solution of **10** (274 mg, 80% pure) in dry methanol (30 mL). The mixture was stirred for 45 min, citric acid (105 mg) was added, and the solvent was removed under reduced pressure. Water (15 mL) was added to the residue, and the mixture was extracted with ethyl acetate (2 × 10 mL). Isolation from this organic extract in the usual way then led to **11** (160 mg) which crystallized on standing and which was pure by TLC analysis. Recrystallization from ether afforded **11** (140 mg); mp 103 °C; IR (Nujol) 3480 (OH), 1760 (lactone CO), 1745, 1735 (ester CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (7 H, m, includes 7-OH), 3.72 (3 H, s, OCH_3), 4.55 (1 H, q, H at C-7), 5.1 (1 H, m, H at C-1), mass spectrum, m/z 200 (M^+); $[\alpha]^{25}_D$ −15.9° ($CHCl_3$; c 1.95%).

Anal. ($C_9H_{12}O_5$) C, H.

Method B. A solution of **10** (0.5 g, 80% pure) in anhydrous methanol (5 mL) was added dropwise to a solution of sodium methoxide (prepared from 80 mg of Na) in dry methanol (10 mL) under N_2. After being left standing at 10–20 °C for 90 min, the solution was poured rapidly into a solution of citric acid (0.84 g) in water (10 mL). Sodium chloride was added, and the mixture was extracted with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated to dryness to give crude **11** (318 mg). Thick-layer chromatography using ether, or direct crystallization from ether of 250 mg of this material, led to pure **11** (150 mg), mp 103 °C, identical with the sample prepared by method A.

(1*S*,5*R*,6*R*,7*R*)-(−)-2-Oxa-6-carboxy-7-hydroxybicyclo[3.3.0]octan-3-one (12). To a solution of **10** (0.5 g, 80% pure) in methanol (3 mL) at 0 °C was added dropwise a solution of potassium hydroxide (1.0 g) in methanol (7 mL). After 5 h at 0 °C methanol (30 mL) and an acidic resin (Amberlite CG 120, British Drug Houses, 7 g) were added with vigorous stirring. After 10 min the resin was removed by filtration and the solvent removed under reduced pressure below 50 °C. The residue was crystallized from ethyl acetate to give pure **12** (192 mg): mp 152 °C; IR (Nujol) 3500 (OH), 3500–2500 (CO_2H), 1750, 1725 cm^{-1}; ^1H NMR (Me_2SO) δ 2.1–3.5 (6 H, m), 4.51 (1 H, m, H at C-7), 5.05 (1 H, m, H at C-1) $[\alpha]^{25}_D$ −53° (pyridine; c 0.85%).

Anal. ($C_8H_{10}O_5$) C, H.

Structure Proof of 10. A commercial sample (Fuji Chemical Industries Limited) of (1*S*,5*S*,6*R*,7*R*)-(−)-2-oxa-6-(hydroxymethyl)-7-acetoxybicyclo[3.3.0]octan-3-one (**14**, 1.07 g) was dissolved in acetone (7.5 mL), and the resulting solution was treated dropwise over 30 min, at 15 °C, with Jones's reagent (3.5 mL). The mixture was allowed to stand for 1 h, and then water (10 mL) was added followed by ammonium sulfate to saturation. The solution was then extracted five times with a 3:2 mixture of ethyl acetate/*tert*-butyl alcohol (10 mL). The combined extracts were washed with saturated ammonium sulfate solution, dried ($MgSO_4$), and, after the addition of benzene (100 mL), evaporated to dryness below 50 °C. Crystallization of the residue from water or ethyl acetate afforded (1*S*,5*R*,6*R*,7*R*)-(−)-2-oxa-6-carboxy-7-acetoxybicyclo[3.3.0]octan-3-one (**13**, 0.8 g, 70%): mp 206 °C; IR (Nujol) 3300–3500, 1740, 1720 cm^{-1}; ^1H NMR (pyridine) δ 1.97 (3 H, s, CH_3CO_2), 2.3–3.8 (6 H, m), 5.18 (1 H, m), 5.83 (1 H, m), 13.68 (1 H, s, CO_2H); $[\alpha]^{25}_D$ −90.1° (pyridine, c 1.1%).

Anal. ($C_{10}H_{12}O_6$) C, H.

A suspension of **13** (0.31 g) in methanol (3 mL) was treated at 0 °C with a cold solution of potassium hydroxide (0.46 g) in methanol (3 mL). After 30 min the clear solution was diluted with methanol (6 mL), and Amberlite CG 120 (2.4 g, British Drug Houses) was added. The mixture was stirred for 5 min, the resin was removed by filtration, and the methanol was evaporated under reduced pressure. Crystallization of the residue from tetrahydrofuran/ethyl acetate afforded pure **12**: mp 152 °C; $[\alpha]^{25}_D$ −52.5° (pyridine, c 1.0%). Mixed melting point with a specimen of **12** prepared via the synthetic procedures described earlier showed no depression, mixed mp 152 °C.

Treatment of a suspension of **12** (38 mg) in ether with excess diazomethane followed by crystallization from ether afforded **11** (35 mg): mp 102 °C; $[\alpha]^{25}_D$ −16° ($CHCl_3$, c 2.0%). Mixed melting point with a specimen of **11**, prepared as described previously, showed no depression, mixed mp 102 °C.

(1*S*,5*R*,6*R*,7*R*)-(−)-2-Oxa-6-carboxy-7-acetoxybicyclo[3.3.0]octan-3-one (13). A sample (112 mg) of **12** was stirred for 40 min with acetyl chloride (1 mL). Excess reagent was removed under reduced pressure, and residual traces were chased by evaporation with benzene (5 mL). The residue was crystallized from ethyl acetate to give pure **13** (104 mg, yield 94%), mp 208 °C, which showed no depression in melting point (207 °C) when mixed with a sample of **13** prepared, as noted above, by oxidation of a commercial specimen of **14**.

(1*S*,5*R*,6*R*,7*R*)-2-Oxa-6-(hydroxymethyl)-7-acetoxybicyclo[3.3.0]-octan-3-one (14). A sample (342 mg) of **13**, dichloromethyl methyl ether (1 mL), and a trace of zinc chloride were heated gently at reflux until complete dissolution had taken place (5 min). Excess reagent was removed under reduced pressure, and the oily residue was dissolved in methylene chloride and added dropwise under nitrogen to a solution of sodium borohydride (170 mg) in ethanol (10 mL) kept at −30 °C. After 30 min, the temperature was allowed to rise to −10 °C and the mixture was poured into a solution of monosodium citrate (1 g) in water (15 mL). Sodium chloride was added to saturation, and the solution was extracted with ethyl acetate (4 × 30 mL). The combined extracts were washed once with brine and dried ($MgSO_4$), and the solvent was removed in vacuo to give pure **14** (316 mg, 98%): mp and mixed mp 55 °C; IR (Nujol) 3400, 1750, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (3 H, s, CH_3CO_2), 1.93–3.0 (7 H, m), 3.5–3.8 (2 H, m, CH_2OH), 5.02 (2 H, m, H at C-1 and C-7); $[\alpha]^{25}_D$ −48.2° ($CHCl_3$, c 1.91%) spectroscopically identical with an authentic specimen. The authentic sample had $[\alpha]^{25}_D$ −44.2° ($CHCl_3$; c 1.88%) (lit.[7h] $[\alpha]^{26}_D$ −40.3°).

(1*S*,5*R*,6*R*,7*R*)-(−)-2-Oxa-6-(dimethoxymethyl)-7-hydroxybicyclo[3.3.0]octan-3-one (24b) and Its Acetate (24a). To a solution of chromium trioxide–dipyridine complex (150 g) in anhydrous methylene chloride (1.2 L), containing dry diatomaceous earth (120 g; Celite) in suspension, was added at 0 °C with stirring under N_2 a solution of **14** (20 g) in methylene chloride (50 mL). After 20 min the mixture was filtered, diluted with methanol (2000 mL), and treated with a saturated solution (500 mL) of hydrogen chloride in methanol. After the solution was left standing overnight at 20 °C, solid sodium carbonate was added, and, when neutralization was complete, the solution was filtered and concentrated at reduced pressure. Water (200 mL) was added to the residue, and the mixture was extracted with ethyl acetate (5 × 150 mL). The combined extracts were dried (Mg_2SO_4) and worked up in the usual way to give the crude oily acetal[28] **24b** (11.9 g). This was purified by column chromatography over silica gel (100 g) using increasing quantities of ethyl ether in low boiling (30–68 °C) petroleum as the eluents. This afforded pure **24b** as an oil (10.4 g, 50%); IR (neat) 3500, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8–3.0 (6 H, m), 3.37 (3 H, s, OCH_3), 3.39 (3 H, s, OCH_3), 3.9–4.4 (1 H, m), 4.25 (1 H, d, J = 7.0 Hz), 4.6–5.0 (1 H, m); $[\alpha]^{25}_D$ −20.7° ($CHCl_3$, c 1.16%).

Anal. ($C_{10}H_{16}O_5$) C, H.

When the reaction described above was carried out by using a lesser quantity (150 mL) of hydrogen chloride in methanol for a shorter period (3 h), the principal product was the acetate (**24a**, 51% yield). Purified by chromatography over silica gel (ether/petroleum ether), it was obtained as an oil: IR (Nujol) 1760, 1725, 1230, 1175, 1130, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (3 H, s, $OCOCH_3$), 2.1–3.2 (6 H, m), 3.36 (3 H, s, OCH_3), 3.38 (3 H, s, OCH_3), 4.23 (1 H, d, J = 5 Hz), 4.8–5.3 (2 H, m); $[\alpha]^{25}_D$ −59° ($CHCl_3$, c 1.1%).

Anal. ($C_{12}H_{18}O_6$) C, H.

(1*S*,5*R*,6*R*,7*R*)-(−)-2-Oxa-6-(dimethoxymethyl)-7-(tetrahydropyranyloxy)bicyclo[3.3.0]octan-3-one (25). To a solution of the alcohol **24b** (10 g) in anhydrous benzene was added freshly distilled dihydropyran (13.25 g) and thereafter a solution of anhydrous TsOH (0.25 g) in benzene (10 mL). The mixture was maintained at 20 °C for 30 min and then quenched by the addition of saturated $NaHCO_3$ solution. Workup in the usual way afforded an oil (21.8 g) which was subjected to column chromatography (SiO_2, 100 g). Elution with petroleum ether (bp 30–60 °C) containing increasing quantities of ether led to pure **25** (11.2 g, 80.6% yield; eluant petroleum ether/ether, 6:4) as an oil:[28] IR (neat) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–3.1 (12 H, m), 3.38 (3 H, s, OCH_3), 3.39 (3 H, s, OCH_3), 3.3–4.4 (4 H, m), 4.6–5.3 (2 H, m); $[\alpha]^{25}_D$ −32° ($CDCl_3$, c 1.1%).

Anal. ($C_{15}H_{24}O_6$) C, H.

(1*R*,2*R*,3*R*,5*S*)-(+)-7-(2-(Dimethoxymethyl)-3-(tetrahydropyranyloxy)-5-hydroxycyclopentyl)hept-5(*Z*)-enoic Acid (29). A. Reduction of 25 to 26. To a solution of the lactone **25** (10 g) in anhydrous toluene (250 mL) cooled to −78 °C was added dropwise under N_2 a solution of 70% sodium bis(2-methoxyethoxy)aluminum hydride (26 mL), diluted with anhydrous toluene (40 mL). When addition was complete, the mixture was stirred for 2 h, and while still at −78 °C, methanol was added cautiously, until gas evolution ceased, to quench excess reagent. The mixture was allowed to warm to room temperature, and, after 30 min, there was added a 10% solution of sodium potassium tartrate (450 mL). Standard isolation procedures then led to the oily lactol[28] (**26**, 7.5 g, 75% yield), homogeneous by TLC (SiO_2, ether), which was employed as such in the second step described below.

B. Coupling of 26 with 28. A mixture of 50% sodium hydride-dispersion-in-oil (13.1 g) and dimethyl sulfoxide (104 mL, freshly distilled over calcium hydride) was stirred under N_2 at 75 °C until gas evolution ceased (1 h). To the resulting solution cooled to ambient temperature was added solid (4-carboxybutyl)triphenylphosphonium bromide (66.5 g). After the deep red liquid had been stirred for a further 20 min, a solution of the lactol **26** (8.0 g) in dimethyl sulfoxide (30 mL) was then added. The temperature was raised to 50 °C, and stirring was continued

for 1 h. The mixture then was poured into ice water (400 mL) and extracted with ethyl acetate. The aqueous phase was retained, acidified with sodium dihydrogen phosphate, and extracted with methylene chloride (4 × 150 mL). The combined extracts were washed with semisaturated sodium chloride solution, dried ($MgSO_4$), and filtered, and the solvent was removed by evaporation. The residue was triturated with ethyl acetate and the solid (4-carboxybutyl)diphenylphosphine oxide removed by filtration. Evaporation of the ethyl acetate then afforded an oil (9.9 g) containing principally **29**. Further purification was achieved by column chromatography over acid-washed silica gel (210 g) using hexane containing increasing quantities of ether. The pure acid (**29**), homogeneous by TLC analysis, was eluted by a 1:1 mixture of these solvents and was obtained as a colorless oil[28] (6.25 g, 48.5% yield): IR (Nujol) 3400 (OH), 3300–2200, and 1710 (CO_2H), 1650 (double bond), 1200–970 (C–O), 905 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3–2.6 (18 H, m), 3.4 (6 H, s, $2OCH_3$), 3.4–4.4 (5 H, m); 4.6–4.8 (1 H, m) 5.1–5.9 (3 H, m, CH=CH, OH); $[\alpha]^{25}_D$ +35° ($CHCl_3$, *c* 2.57%).

Anal. ($C_{20}H_{34}O_7$) C, H.

Methyl (1*R*,2*R*,3*R*,5*S*)-(+)-7-(2-(Dimethoxymethyl)-3-(tetrahydropyranyloxy)-5-acetoxycyclopentyl)hept-5(*Z*)-enoate (30). The hydroxy acid **29** (5.6 g) in dry ether (50 mL) was treated with a slight excess of diazomethane. Evaporation of the ether left an oily residue (5.8 g) of the methyl ester of **29**. Without further characterization, this ester was dissolved in pyridine (10 mL) and treated with acetic anhydride (2 mL) added dropwise at 24 °C with stirring. The temperature was raised to 50 °C for 24 h, cooled to 20 °C, and quenched by addition to water (60 mL). The mixture was extracted with ether (4 × 60 mL), and the combined extracts were washed with water (50 mL), dried (Na_2SO_4), and evaporated to give **30** as an oil (5.8 g, 90.5%). A sample was purified by preparative TLC (SiO_2, ether) to give the analytically pure substance: IR (Nujol) 1730, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20–2.50 (18 H, m), 2.02 (3 H, s, $OCOCH_3$), 3.42 (6 H, 2s, 2-OCH_3), 3.68 (3 H, s, -CO_2CH_3), 3.20–4.0 (4 H, m) 4.50–4.70 (1 H, m) 4.90–5.20 (1 H, m), 5.20–5.55 (2 H, m); $[\alpha]^{25}_D$ +26.5° ($CHCl_3$, *c* 1.02%).

Anal. ($C_{23}H_{38}O_8$) C, H.

Methyl (+)-9α-Acetoxy-11α-hydroxy-15-oxoprosta-5(*Z*),13(*E*)-dienoate (32). A solution of **30** (0.7 g) in aqueous acetic acid (7 mL, 70:30, v/v) was maintained at 50 °C for 1 h. After being cooled to 20 °C, the mixture was neutralized with sodium carbonate and then was extracted with ether (3 × 40 mL). The combined extracts were washed with saturated brine and dried ($MgSO_4$). Removal of the solvent afforded the hydroxy aldehyde **31** (0.59 g), which was used immediately without further purification, as follows.

To a stirred suspension of sodium hydride (57% dispersion-in oil, 172 mg) in 1,2-dimethoxyethane (22 mL) at 0 °C was added a solution of dimethyl (2-oxoheptyl)phosphonate (0.94 g) in the same solvent (6 mL). After stirring at 0 °C for 10 min a solution of the hydroxy aldehyde (**31**, 0.55 g) in 1,2-dimethoxyethane (6 mL) was added. The temperature was allowed to rise to 20 °C, and stirring was continued for 4 h. The reaction was quenched by addition to a saturated solution of sodium dihydrogen phosphate. The resulting mixture was extracted with ether (4 × 50 mL), and the combined extracts were washed with semisaturated brine, dried ($MgSO_4$), and evaporated to give an oily liquid (1.38 g). This was chromatographed on preparative TLC plates (SiO_2, ethyl ether) to give pure **32** as a colorless oil (0.425 g, 65.8% yield): IR (Nujol) 3400 (OH), 1740 (esters), 1675 (ketone), 1630 (double bond), 1240, 1040, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 4.5 Hz, CH_2CH_3) 1.10–2.90 (21 H, m), 2.07 (3 H, s, $OCOCH_3$), 3.67 (3 H, s, CO_2CH_3), 3.80–4.30 (1 H, m, H at C-11), 5.00–5.50 (3 H, m, H at C-5, C-6, and C-9), 6.22 (1 H, d, $J_{H14-H13}$ = 16 Hz, CH=C*H*CO), 6.75 (1 H, d of d, $J_{H13-H14}$ = 16 Hz, $J_{H13-H12}$ = 8 Hz, C*H*=CHCO); $[\alpha]^{25}_D$ +51.2° ($CHCl_3$, *c* 0.90); mass spectrum, *m/z* 408 (M^+).

Anal. ($C_{23}H_{36}O_8$) C, H.

Synthesis of (*S*)-(2-Hydroxyheptyl)triphenylphosphonium Iodide (41). (a) (*S*)-1,2-Hydroxyhept-3(*Z*)-ene Acetonide (36). A solution of *n*-butyltriphenylphosphonium bromide (30.67 g) in dry tetrahydrofuran (307 mL) at 0 °C was treated with methyllithium (1.69 g, 1 equiv) in ether (80 mL), and the mixture was stirred for 3 h. A solution of freshly prepared (*R*)-(+)-glyceraldehyde acetonide **36** (6.5 g, $[\alpha]^{25}_D$ +65°; prepared according to Fisher and Baer[32]) in tetrahydrofuran (50 mL) was then added slowly (1 h), the red color of the ylide vanishing just as the addition was complete. The solvent was removed under reduced pressure, petroleum ether (300 mL, bp 30–60 °C) was added, and triphenylphosphine oxide was then removed by filtration. Removal of the solvent then afforded a yellow oil (6.2 g) which was distilled to give pure **36**: bp 62 °C (5mmHg); ^1H NMR ($CDCl_3$) δ 0.92 (3 H, t, J = 6 Hz, CH_3), 1.4 (6 H, 2s, acetonide CH_3), 1.4 (2 H, m, CH_2) 2.22 (2 H, q, J = 8 Hz), 4.87 (1 H, m), 5.66 (2 H, m); mass spectrum, *m/z* 174 (M^+).

(b) (*S*)-1,2-Dihydroxyheptane Acetonide (37). Hydrogenation of **36** (6.2 g) in benzene (100 mL) over Pt (from 0.6 g of PtO_2) was carried out at NTP. Gas uptake ceased after 45 min, and the solution then was filtered and evaporated to remove solvent. The residue (6.2 g) distilled almost quantitatively at 90–92 °C (30mmHg): ^1H NMR ($CDCl_3$) δ 0.85–1.70 (17 H, m), 3.3–4.2 (3 H, 2m); GC R_f 37 min (QF-1, 150 °C).

Anal. ($C_{10}H_{20}O_2$) C, H.

(c) (*S*)-(+)-1,2-Dihydroxyheptane (38). The acetonide **37** (13.5 g) was added to 1 N hydrochloric acid (100 mL) and methanol (50 mL), and the solution was boiled for 4 h. Methanol was removed under reduced pressure, and the residual aqueous phase was saturated with sodium chloride. Ether extraction (3 × 60 mL) then led to a viscous oil (8.5 g), which on distillation, bp 92–93 °C (0.2mmHg), afforded pure **38** (7.5 g): IR (neat) 3333 (broad) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 6 Hz, CH_3), 1.38 (8 H, m), 3.55 (3 H, m), 4.75 (2 H, s, OH); $[\alpha]^{25}_D$ +15.40° ($CHCl_3$, *c* 1.08) (lit.[35] $[\alpha]^{22}_D$ +16.4°); GC R_f 7.4 min (QF-1, 150 °C).

Anal. ($C_7H_{16}O_2$) C, H.

(d) (*S*)-1-(*p*-Toluenesulfonyloxy)-2-hydroxyheptane (39). To a solution of (*S*)-1,2-dihydroxyheptane (6.38 g) in dry pyridine (64 mL), cooled to −20 °C, was added *p*-toluenesulfonyl chloride (9.2 g). The temperature was maintained at −20 °C for 5 h and then at 5 °C for 20 h. Dilution of the reaction mixture with cold water caused the separation of an oil which was extracted with ether (100 mL). The extract was washed with 1 N hydrochloric acid and then with water. The solution was dried (Na_2SO_4) and concentrated in vacuo to give an oil (13.2 g). TLC indicated the presence of a small amount of ditosylate. Purification of a sample (2.2 g) was easily achieved by preparative TLC (SiO_2, benzene, four elutions). Extraction of the major band with methanol/methylene chloride (1:4) afforded pure monotosylate (1.4 g) as a colorless oil: IR (neat) 3500, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, CH_3), 1.4 (8 H, m), 2.43 (3 H, s, $ArCH_3$), 3.05 (1 H, s, OH), 3.5–4.2 (3 H, 2m, CHOH and $ArSO_2CH_2$).

Anal. ($C_{14}H_{22}O_4S$) C, H, S.

(e) (*S*)-(+)-2-Hydroxyheptyl Iodide (40). To a solution of **39** (11 g) in acetone (460 mL) was added sodium iodide (115.5 g), and the mixture was maintained at reflux temperature for 5 h. The acetone was removed under reduced pressure, and the pasty mass was diluted with water (500 mL). The mixture was then extracted with ether (3 × 300 mL), and the combined extracts were washed three times with dilute sodium bisulfite solution and then with 5% sodium carbonate solution. Concentration of the dried (Na_2SO_4) solution at <43 °C afforded a light yellow oil (7.9 g). Distillation then gave pure hydroxy iodide (6.98 g): bp 74–75 °C (0.068mmHg); IR (neat) 3350 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, CH_3), 1.37 (8 H, m) 2.85 (1 H, s, OH), 3.30 (2 H, q, CH_2I), 3.5 (1 H, m, C*H*OH); GC R_f 7.8 min (QF-1, 150 °C); $[\alpha]^{25}_D$ +5.28° ($CHCl_3$, *c* 1.00%).

Anal. ($C_7H_{15}IO$) C, H.

(f) (*S*)-(+)-(2-Hydroxyheptyl)phosphonium Iodide (41). To a solution of the hydroxy iodide **40** (3.5 g) in dry tetrahydrofuran (35 mL) was added triphenylphosphine (7.5 g). The mixture was heated under reflux for 130 h in the absence of oxygen. The solvent was then removed under reduced pressure, and the oily residue was extracted with benzene (4 × 50 mL) to remove excess triphenylphosphine. The residual salt was dried under vacuum to give **41** as a friable froth (6.2 g): IR (Nujol) 3280 (OH), 1590, 1490, 1440, 1106, 995, 742, 715, 687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 6.2 Hz, CH_3) 1.22 (6 H, m, CH_2), 1.95 (2 H, m, CH_2), 3.2–4.4 (3 H, 2m, -$CH_2P^+Ph_3$ and C*H*OH), 7.73 (15 H, m, ArH); $[\alpha]^{25}_D$ +32.0° ($CHCl_3$, *c* 1.0). This material was used without further purification in the experiment described below.

(+)-Prostaglandin $F_{2\alpha}$ (33). (a) By Reduction of 33. To a solution of **32** (0.19 g) in methanol (4 mL) cooled to −10 °C was added a solution of sodium borohydride (38 mg) in ice-cold methanol (2 mL). After 1 h an aqueous solution (20 mL) of saturated sodium hydrogen phosphate was added and the mixture was extracted with ethyl acetate. The extract was dried ($MgSO_4$) and the solvent was removed to yield a colorless glassy residue (0.17 g). The latter was dissolved in methanol (6 mL), and there was added a solution of potassium hydroxide (0.17 g) in methanol (3 mL) and water (1.5 mL). After 12 h at room temperature, Amberlite CG 120 (2 g, acid form) was added, and the mixture was stirred briefly and then filtered. Methanol was removed under reduced pressure. The residual liquid was saturated with ammonium sulfate and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and the solvent removed under reduced pressure to give an oil (0.13 g). This material showed two spots (visualized by spraying with water) when analyzed by TLC (silica gel; ethyl acetate/acetone/acetic acid, 90:10:1). The two compounds were separated by preparative TLC (silica gel; ethyl acetate/methanol, 95:5), and the slower moving band was extracted with methanol. The product isolated by evaporation of the solvent was a colorless oil (0.08 g): IR (neat) 3325, 2642, 1712, 1296, 1250, 1125,

(35) Levine, P. A.; Walti, A. *J. Biol. Chem.* **1932**, *98*, 737.

1085 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 0.90 (3 H, t, CH_3), 1.1-2.45 (20 H, m), 4.05 (3 H, m, CHOH), 5.10 (4 H, s, OH), 5.2-5.7 (4 H, m, olefinic H); mass spectrum, m/z 336 (M - 18), 318, 264; $[\alpha]^{25}D$ +23.8° (THF; c 0.80) [lit.[7f] +23.5° in THF]. This material proved to be in all respects identical with an authentic sample[24] of $PGF_{2\alpha}$.

Characterization of the second compound (the faster running band in the preparative tlc plate) presumably 15-epi-$PGF_{2\alpha}$ was not undertaken.

(b) By Wittig Coupling of 41 with 43. To a solution of **31** (0.3 g; prepared as described above) in methylene chloride (5 mL) was added dihydropyran (1.0 mL) together with anhydrous *p*-toluenesulfonic acid (~10 mg). The mixture was stirred at 20 °C until TLC analysis indicated that no starting material was present (1 h). The solution was then washed with saturated sodium bicarbonate solution and evaporated to dryness to give essentially pure **43** as a viscous oil (0.4 g). TLC analysis (SiO_2; Et_2O; R_f 0.3) showed the presence of only one spot. This material was used as follows.

A solution of the (*S*)-(+)-phosphonium salt **41** (0.8 g) in dry tetrahydrofuran (10 mL) was cooled to -78 °C under N_2 and treated with 2 equiv of butyllithium in ether (2.4 mL solution). The temperature was allowed to rise to -20 °C and then after 30 min was lowered again to -78 °C. To this solution there was added during 7 min a solution of **43** (0.4 g) in tetrahydrofuran (5 mL). The temperature was allowed to rise to 0 °C and, after a further 30 min at room temperature, the solvent was removed under reduced pressure at <20 °C. The residue was treated with 50% aqueous acetic acid (5 mL) and heated to 50 °C for 1 h. Water (15 mL) was then added and the mixture extracted with ethyl acetate (3 × 10 mL). The extract was washed with sodium bicarbonate solution (5 mL) and then dried ($MgSO_4$). For removal of traces of phosphorus compounds, the solution was perolated through a column of silica gel (10 g). The column was washed with additional ethyl acetate (10 mL), and the combined solutions were evaporated to dryness to give a glassy solid (0.37 g). Hydrolysis of this material using potassium hydroxide was accomplished essentially as described in method a except that the neutralization afterward was done by titration with 1 N hydrochloric acid. The material (0.33 g) isolated by ethyl acetate extraction was then subjected to preparative TLC separation (SiO_2; ethyl acetate/methanol/formic acid, 95:4.5:0.5) using authentic (+)-$PGF_{2\alpha}$ as a marker. Much less polar material was present. The band corresponding to $PGF_{2\alpha}$ was extracted to give the crude oily material (56 mg). Further purification was effected via a second preparative TLC. The purified product (42 mg, 12% yield) had $[\alpha]^{25}_D$ +24.3° (THF; c 1.03) and was in all respects identical with the sample prepared as described in method a.

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Registry No. 1a, 58096-39-2; **1b**, 59025-04-6; **2a**, 58096-40-5; **2b**, 59025-05-7; **7**, 59042-97-6; **9**, 58683-43-5; **10**, 59042-99-8; **11**, 58683-45-7; **12**, 59043-00-4; **13**, 58717-38-7; **14**, 26054-65-9; **18**, 80800-64-2; **19**, isomer 1, 80844-93-5; **19**, isomer 2, 80844-94-6; **20**, 67718-97-2; **24a**, 80844-95-7; **24b**, 53275-75-5; **25**, 67842-98-2; **26**, 51638-25-6; **28**, 41723-91-5; **29**, 63162-87-8; **29** methyl ester, 66101-25-5; **30**, 61408-41-1; **31**, 61408-40-0; **32**, 80800-65-3; **33**, 551-11-1; **34**, 37658-84-7; **35**, 15186-48-8; **36**, 78918-73-7; **37**, 61228-99-7; **38**, 61229-00-3; **39**, 80800-66-4; **40**, 80800-67-5; **41**, 80800-68-6; **43**, 61218-06-2; isopropyl bromide, 75-26-3; potassium methyl malonate, 38330-80-2; succinyl chloride, 543-20-4; (*S*)-malic acid, 97-67-6; ethyl bromide, 74-96-4; methyl hydrogen malonate, 16695-14-0; dimethyl (2-oxoheptyl)-phosphonate, 36969-89-8.

Stereoselective Total Synthesis of (±)-Gymnomitrol via Reduction-Alkylation of α-Cyano Ketones

Robert M. Coates,* Shrenik K. Shah, and Robert W. Mason

Contribution from the Department of Chemistry, University of Illinois, 1209 W. California Street, Urbana, Illinois 61801. *Received September 16, 1981*

Abstract: A 16-step total synthesis of the tricyclic sesquiterpene alcohol, gymnomitrol (**1**), from *cis*-tetrahydro-3a,6a-dimethyl-2,5(1*H*,3*H*)-pentalenedione (**8**) is described. Catalytic hydrogenation of the monoenol phosphate of **8** afforded the monoketone, *cis*-hexahydro-3a,6a-dimethyl-2(1*H*)-pentalenone (**7**). Reduction-allylation of the α-(*n*-butylthio)methylene derivative of **7** gave allyl trimethyl ketone **14a** having the allyl substituent in the exo orientation. The stereoisomer (**19**) of **14a** was obtained by reduction-methylation of α-allyl α-cyano ketone **18**. Ring closure was accomplished by conversion of the allyl trimethyl ketones, **14a** and **19**, to keto aldehydes **23** and **6**, aldol cyclizations, and oxidation to give the isomeric bridged diketones **25** and **29**, respectively. A more efficient synthesis of keto aldehyde **6** was based upon a Michael-like condensation of α-cyano ketone **16** with acrolein diethyl acetal which gave rise to α-ethoxyallyl α-cyano ketone **34**. The enol ether in the side chain was converted to an ethylene acetal, the resulting α-cyano ketone (**36**) was subjected to reduction-methylation, and the acetal was hydrolyzed, affording keto aldehyde **6**. Enol lactone **39**, prepared from the corresponding keto acid (**38**), underwent efficient aldol cyclization upon reduction with diisobutylaluminum hydride, and the ketol so obtained was oxidized to bridged diketone **29**. The synthesis of (±)-gymnomitrol was completed by regioselective addition of methyllithium to diketone **29**, dehydration, and hydride reduction.

The isolation of the novel tricylcic sesquiterpenes, (+)-gymnomitrol (**1**), (-)-β-gymnomitrene (**2**), and a number of more highly oxygenated derivatives, from the liverwort *Gymnomitrion obtusum* (Lindb) Pears, and the determination of their structures by chemical degradation and spectroscopic evidence was reported by Connolly, Harding, and Thornton in 1970.[1] Shortly thereafter (-)-β-gymnomitrene (also known as β-barbatene and β-pompene) and its endocyclic isomer were isolated from other species of liverwort in three different laboratories.[2-4] The structure of (+)-α-gymnomitrene (α-pompene) was established firmly by an X-ray crystallographic determination of a diol mono-*p*-bromobenzoate derivative.[3b,d] The only other sesquiterpene known to possess the decahydro-4,8-methanoazulene ring system of gymnomitrol is α-caryophyllene alcohol[5] which has a different methyl

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