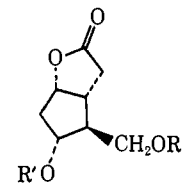
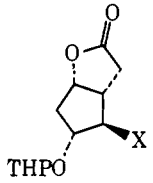
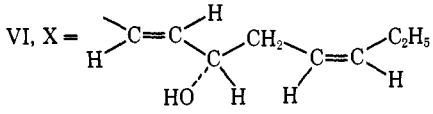
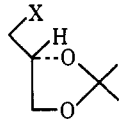


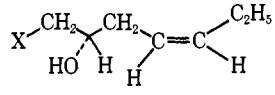
I, R = $CH_2C_6H_5$; R′ = H
II, R = $CH_2C_6H_5$; R′ = THP
III, R = H; R′ = THP
IV, R = H; R′ = H



V, X = CHO

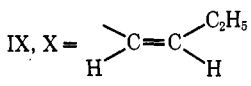


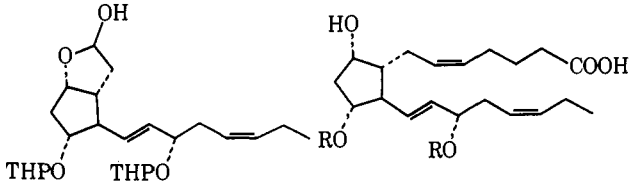




VII, X = CH_2OH
VIII, X = CHO

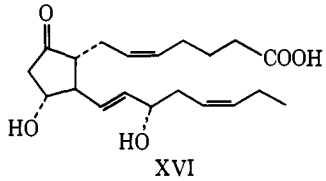
X, X = OH
XI, X = I
XII, X = $(C_6H_5)_3P^+$





XIII

XIV, R = THP
XV, R = H



XVI

chloride in pyridine at −20° for 5 hr and 0° for 12 hr and thence to the iodo alcohol XI[3] (NaI in acetone, 96% yield), $[\alpha]^{25}D$ +12.4° (*c* 1.0, $CHCl_3$). Prolonged reaction of XI with 2 equiv of triphenylphosphine in benzene at 40–45° (8–20 days) afforded cleanly the (*S*)-(+)-phosphonium iodide XII[3] as a solid foam, $[\alpha]^{25}D$ +45.8° (*c* 1.0, $CHCl_3$).

Reaction of the allylic alcohol VI with dihydropyran as described for II yielded the corresponding bis-THP derivative,[3] $[\alpha]^{25}D$ −40.5° (*c* 0.84, methanol), which was transformed in >98% yield to the lactol XIII[3a] by exposure to 2 equiv of diisobutylaluminum hydride in toluene at −60° for 20 min; $[\alpha]^{25}D$ −35.9° (*c* 1.06, $CHCl_3$). Treatment of the lactol XIII with the Wittig reagent derived from 5-triphenylphosphonovaleric acid[5] in dimethyl sulfoxide[9] produced stereospecifically the 11,15-bistetrahydropyranyl derivative of prostaglandin $F_{3\alpha}$ (XIV),[3a] $[\alpha]^{25}D$ −4.9° (*c* 0.82, $CHCl_3$), in 66% yield. This derivative was converted by hydrolysis in acetic acid–water–tetrahydrofuran, 19:11:3, at 45° for 1 hr into prostaglandin $F_{3\alpha}$ (XV),[3] $[\alpha]^{26}D$ +29.6° (*c* 0.54, tetrahydrofuran), homogeneous in five different solvent systems[10,11] on silica gel and silica gel–silver nitrate. Oxidation of XIV with 1.1 equiv of chromic acid–acetone (Jones) reagent at −10° for 25 min followed by removal of the tetrahydropyranyl groups and chromatography on silica gel using 10% methanol–chloroform led to prostaglandin E_3 (XVI),[3] $[\alpha]^{24}D$ −48.9° (*c* 1.2, tetrahydrofuran), spectroscopically and chromatographically identical with prostaglandin E_3 of natural origin.[12] The mass spectrum of the methyl ester diacetate methoxy oxime of XVI provided additional confirmation of structure.[13]

All of the known primary prostaglandins have now been prepared by chemical synthesis in biologically active, naturally occurring form, and our original objective of the synthesis of these substances from a common intermediate has been achieved.

Acknowledgment. This research was assisted financially by a grant from the National Institutes of Health.

(9) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).
(10) N. H. Andersen, *J. Lipid Res.*, 10, 316 (1969).
(11) K. Gréen and B. Samuelsson, *ibid.*, **5**, 117 (1964).
(12) We are indebted to Dr. Bengt Samuelsson, Department of Medical Chemistry, Royal Veterinary College, Stockholm, and Dr. John Pike the Upjohn Co., for reference samples of naturally derived prostaglandin E_3.
(13) K. Gréen, *Chem. Phys. Lipid*, **3**, 254 (1969).

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Received December 17, 1970

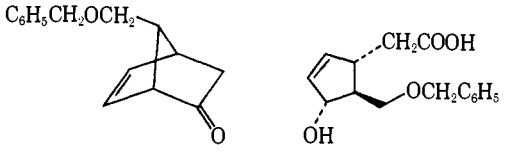
New Reagents for Stereoselective Carbonyl Reduction. An Improved Synthetic Route to the Primary Prostaglandins

Sir:

This communication describes three significant improvements in the previously described synthesis[1] of primary prostaglandins, including the application of a new reagent for stereoselective carbonyl reduction. Successive alkylation of cyclopentadiene with chloromethyl benzyl ether using the thallium method,[2] cupric fluoroborate catalyzed addition of 2-chloroacrylonitrile,[2] and hydrolysis using potassium hydroxide in dimethyl sulfoxide[2] afforded the bicyclic ketone I.[3] Crude I was subjected to reaction with *m*-chloroperbenzoic acid–sodium bicarbonate in methylene chloride at 0 to −10° to form a lactone[1] which was directly

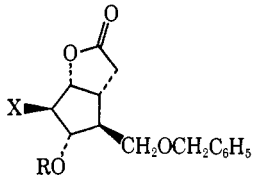
(1) (a) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969); (b) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *ibid.*, **92**, 397 (1970).
(2) E. J. Corey, U. Koelliker, and J. Neuffer, *ibid.*, **93**, 1489 (1971).
(3) The only purification step involved was the filtration of I through a fivefold amount of silica gel.

converted into the hydroxy acid II by base-catalyzed hydrolysis. The acid II was isolated and purified as the crystalline (racemic) ammonium salt (formed by addition of anhydrous ammonia to a solution of II in ether at 0°), mp 134–135°[4] (40–50% yield overall from thallous cyclopentadienide).[5] The hydroxy acid II was resolved (60–70% yield) by recrystallization of the (+)-amphetamine salt; found for the resolved salt,[4] mp 112.5–113.5°, $[\alpha]^{25}D$ +17° (*c* 1.5, methanol).

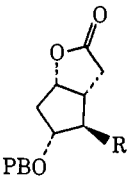


I

II

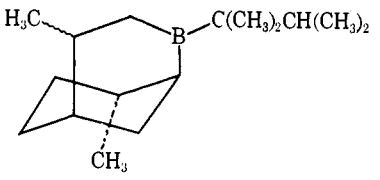


III, X = I; R = H
IV, X = I; R = PB
V, X = H; R = PB



VI, R = CH_2OH
VII, R = CH=O
VIII, R = $CH=\overset{t}{C}HCO\text{-}n\text{-}C_5H_{11}$
IX, R = $CH=CH-\overset{15}{C}(HO,H)\text{-}n\text{-}C_5H_{11}$
X, R = $CH=CH-\overset{15}{C}(HO,H)\text{-}n\text{-}C_5H_{11}$

PB = *p*-phenylbenzoyl



XI

Iodolactonization of II[6] afforded III,[4] mp 120–122° (from methylene chloride–hexane), $[\alpha]^{25}D$ −34.0° (*c* 1.1, $CHCl_3$) (>97% yield), which was esterified with *p*-phenylbenzoyl chloride (PBCl) in pyridine at 25° for 1 hr to form the ester lactone IV,[4] mp 171.5–172° (from methylene chloride–hexane), $[\alpha]^{25}D$ +0.80° (*c* 1.21, $CHCl_3$) (97% yield), deiodination of which was accomplished using tributyltin hydride in benzene at 55° to give V,[4] mp 97–98° (from methylene chloride–isopropyl ether), $[\alpha]^{25}D$ −85.0° (*c* 1.0, $CHCl_3$) (>98% yield).[7] Debenzylation of V was accomplished by treatment with hydrogen at 45 psi at 25° for 4 hr in 2:1 ethyl acetate–ethanol containing a small amount of hydrochloric acid (*ca.* 0.01 *N*) using 5% palladium/charcoal catalyst to form the alcohol VI,[4] mp 130–131° (from methylene chloride–hexane), $[\alpha]^{25}D$ −87.3° (*c* 1.0, $CHCl_3$) (97% yield). Collins oxidation[6,8] of VI gave the crystalline aldehyde VII which, when treated (without purification) with the sodium salt of dimethyl 2-oxoheptylphosphonate in dimethoxyethane,[6] yielded the crystalline enone VIII,[4] mp 81–82.5° (from isopropyl alcohol–hexane), $[\alpha]^{25}D$ −146° (*c* 0.20, $CHCl_3$) (80% yield from VI).

In previous work the reduction of the ketonic function in enone intermediates such as VIII was effected using zinc borohydride as reagent,[1] which yielded a 1:1 mixture of epimeric 15α and 15β alcohols. Other standard hydride-type reducing agents were found to be less satisfactory (or at best equivalent), since the ratio of 15α to 15β alcohols (prostaglandin numbering used) was never greater than 1:1 and since troublesome by-products, most important of which is the ketone resulting from saturation of the α,β double bond, were usually formed. For example, the reaction of 1 equiv of diisobutylaluminum hydride with VIII in toluene at −80° yielded a complex mixture containing the corresponding saturated ketone and a relatively small amount of the alcohols IX and X in equal proportion. The optically active reagent diisopinocampheylborane, which has been found to reduce saturated ketones of type $RCOCH_3$ to secondary alcohols ($RCHOHCH_3$) of 11–30% optical purity,[9] reacts with VIII in tetrahydrofuran solution (−45°) chiefly (~90%) with reduction of the α,β carbon–carbon double bond. The optically active borohydride ions prepared by the reaction of diisopinocampheylborane with methyl- or *tert*-butyllithium were much more promising, however. These were found to afford 1,2- and 1,4-reduction products in a ratio of 1.5–2.5:1 in tetrahydrofuran at −78°, and it was further observed that the addition of certain Lewis bases dramatically attenuated the 1,4-reduction pathway. The most effective base studied thus far is hexamethylphosphoramide (HPA). Utilizing 4 equiv of a reagent prepared from optically active diisopinocampheylborane[10] and methyllithium (1:1) to which was added 10 equiv of HPA with tetrahydrofuran–ether as solvent under nitrogen at −97 to −100° (pentane–liquid nitrogen bath), the ketone VIII was converted in 5 hr to a product consisting of only 2.8% of the α,β reduction product, 66% of the desired 15α alcohol IX, and 31% of the 15β alcohol X. The corresponding reaction with the reagent diisopinocampheyl-*tert*-butylborohydride afforded slightly better results: 1% of the α,β reduction product, 68% of the desired IX, and 31% X.[11] The alcohols IX and X can be isolated in pure condition by chromatography on silica gel using ether as solvent.[12] The 15α

(4) Satisfactory infrared, nuclear magnetic resonance, and analytical (C, H) data were obtained for this intermediate.

(5) Because of the relative instability of the hydroxy acid II under acidic conditions, its generation and isolation from the salt were carried out by acidification to pH 4.0 at 0° and extraction with ether without delay.

(6) By the procedure outlined in ref 1.

(7) The reaction product was isolated simply by washing the reaction mixture with aqueous sodium carbonate, evaporation of benzene, and trituration with hexane.

(8) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(9) H. C. Brown and D. B. Bigley, *J. Amer. Chem. Soc.*, **83**, 3166 (1961).

(10) Derived from commercial (+)-α-pinene of *ca.* 93% optical purity (Aldrich Chemical Co., $[\alpha]^{25}D$ + 47.4°); see H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 487 (1961); *Org. React.*, **13**, 1 (1966); and F. H. Thurber and R. C. Thielke, *J. Amer. Chem. Soc.*, **53**, 1030 (1931).

(11) A number of other substituted diisopinocampheylborohydrides (*e.g.*, derived from *sec*-butyl- or phenyllithium) were found to be less satisfactory.

(12) Any α,β reduction product is rapidly eluted, and the 15α epimer precedes the 15β epimer. In our experience the *p*-phenylbenzoyl derivatives IX and X are more easily separated by chromatography than the corresponding esters of other acids studied (approximately 15 in number).

derivative IX,[3] which was obtained as an oil, was readily converted to prostaglandins $F_{2\alpha}$ and E_2 (natural form) by the route previously described.[1] The 15β derivative X[3] was obtained as a crystalline solid, mp 77–78.5°, $[\alpha]^{25}D$ −116° (*c* 0.44, $CHCl_3$). Both IX and X underwent oxidation by manganese dioxide to afford the enone VIII (>97% yield).

An even more satisfactory reagent for the stereoselective conversion of VIII to IX was developed starting with the trialkylborane XI derived from either racemic or (+)-limonene and thexylborane.[13] In our hands the borane XI was not converted smoothly to a borohydride ion by reaction with lithium hydride in tetrahydrofuran. However, reaction with *tert*-butyllithium rapidly gave a borohydride ion presumably by transfer of β hydrogen. When the ketone VIII was treated with this new reagent in the presence of HPA at −120° in tetrahydrofuran, ether, and pentane the desired 15α alcohol IX was found to predominate over the 15β alcohol X by a ratio of 4.5:1 and only small amounts of α,β reduction product could be detected. Thus, the borohydride derived from XI can be seen to be a highly practical reagent for the stereoselective introduction of the 15α-hydroxyl function in prostaglandin synthesis.[14] Interestingly, the hydride of racemic XI appears to be slightly more specific than that of optically active XI.

In summary, three important improvements have now been added to the previously described approach for the chemical synthesis of prostaglandins. The use of the hydride derivative of XI has obvious significance and implications for future advances. The use of the *p*-phenylbenzoyl grouping affords crystalline intermediates which are easily handled, characterized, and purified.[12] The use of benzyl ether rather than methyl ether derivatives in the early stages of the synthesis provides advantages for large-scale operation including the use of catalytic hydrogenation for ether cleavage rather than boron tribromide.[1]

Acknowledgment. This work was assisted financially by grants from the National Institutes of Health, the Chas. Pfizer Co., and the National Science Foundation. We are indebted to Mr. T. J. Daniels and Mr. E. G. Andrews of the Chas. Pfizer Co. for technical assistance.

(13) H. C. Brown and C. D. Pfaffenberger, *J. Amer. Chem. Soc.*, **89**, 5475 (1967).

(14) The use of optically active β-oxidophosphonium ylides to effect the introduction of the 15α-hydroxyl group represents another promising approach. See E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *J. Amer. Chem. Soc.*, **93**, 1490 (1971).

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Conversion of Des-6-methyl-2,3-oxidosqualene to 19-Norlanosterol by 2,3-Oxidosqualene–Sterol Cyclase

Sir:

The enzymic formation of sterol derivatives from artificial substrates differing from the normal sterol precursor, 2,3-oxidosqualene, in various ways has been observed both in the Harvard[1] and Stanford[2] laboratories. The enzymic cyclization has been found to occur with analogs of 2,3-oxidosqualene lacking the methyl substituents at C-10 and C-15,[3] C-15 alone,[4] and C-2.[5,6] The cyclization with these substrates produces sterol derivatives lacking nuclear methyl substituents at three of the four normally methylated carbons. The question of essentiality of the methyl substituent at C-6 of 2,3-oxidosqualene is of special interest, since this methyl resides at the fourth nuclear methyl position after cyclization, *i.e.*, at C-10 of the A–B fusion. A test of this point, based on the study of the action of 2,3-oxidosqualene–sterol cyclase on des-6-methyl-2,3-oxidosqualene (IV), is described herein.

The aldehyde I[1a] was treated at −78° (N_2 atmosphere) with the ylide derived from the reaction of phenyllithium (in ether) with 4-triphenylphosphoniobutanal ethylene acetal[7,8] (as the iodide, mp 172–173.5°) in tetrahydrofuran (THF), and the resulting betaine adduct was deprotonated by phenyllithium to form the β-oxido ylide further transformed into the olefinic acetal II[9] in the presence of *tert*-butyl alcohol–potassium *tert*-butoxide at −33°.[10] The newly formed disubstituted olefinic bond in II (purified by preparative thin-layer chromatography (tlc) on silica gel using pentane–ether (9:1) for development) is clearly transoid from the appearance of characteristic strong infrared absorption at 10.35 μ. Hydrolysis of II using 3 *N* aqueous perchloric acid and THF (in a ratio of 1:2.5) at 25° for 1.5 hr gave the aldehyde III[9a] (>90% yield), R_f 0.45 on silica gel using 2% ethyl acetate in benzene. Tritiation of III α to the carbonyl group was accomplished by using tritiated water–triethylamine at 55° for 12 hr; labeled III was obtained thereby with a specific activity of 5.47×10^3 dpm/nmol. Reaction of III with diphenylsulfonium isopropylide[6] in dimethoxyethane at −78° (N_2 atmosphere) produced the desired substrate, des-6-methyl-2,3-oxidosqualene (IV),[9] R_f 0.39 on silica gel with 1:1 benzene–chloroform, purified by tlc (63% yield).

Anaerobic incubation of the labeled oxide IV with a solution of 2,3-oxidosqualene–sterol cyclase[11] at 25° afforded in addition to unchanged oxide a tritiated cyclization product (61% yield) which could be purified by tlc and which is assigned structure V, *i.e.*, 19-norlanosterol. The incubation product, which was chro-

(1) (a) E. J. Corey, K. Lin, and H. Yamamoto, *J. Amer. Chem. Soc.*, 91, 2132 (1969); (b) E. J. Corey and H. Yamamoto, *Tetrahedron Lett.*, 2385 (1970), and previous papers cited therein.

(2) E. E. van Tamelen and J. H. Freed, *J. Amer. Chem. Soc.*, **92**, 7206 (1970), and earlier papers.

(3) E. J. Corey, P. R. Ortiz de Montellano, and H. Yamamoto, *ibid.*, 90, 6254 (1968).

(4) E. E. van Tamelen, R. P. Hanzlik, K. B. Sharpless, R. B. Clayton, W. J. Richter, and A. L. Burlingame, *ibid.*, **90**, 3284 (1968).

(5) R. B. Clayton, E. E. van Tamelen, and R. G. Nadeau, *ibid*, 90, 820 (1968).

(6) E. J. Corey, K. Lin, and M. Jautelat, *ibid.*, 90, 2724 (1968).

(7) E. Bertele and P. Schudel, *Helv. Chim. Acta*, 50, 2445 (1967).

(8) This phosphonium salt was prepared by the sequence: 4-chlorobutanol → 4-chlorobutanal (dipyridine–chromium trioxide complex in CH_2Cl_2 at −5°) → 4-chlorobutanal ethylene acetal (ethylene glycol–*p*-toluenesulfonic acid–benzene at reflux) (52% overall) → 4-iodobutanal ethylene acetal (sodium iodide–calcium carbonate in acetone at reflux) (65%) → phosphonium iodide (triphenylphosphine in benzene at 25° for 5 days) (87%).

(9) (a) The nuclear magnetic resonance and infrared spectra and (b) the mass spectrum were in complete accord with the assigned structure.

(10) M. Schlosser and K. F. Christmann, *Justus Liebigs Ann. Chem.*, 708, 1 (1967).

(11) P. D. G. Dean, P. R. Ortiz de Montellano, K. Bloch, and E. J. Corey, *J. Biol. Chem.*, **242**, 3014 (1967); P. R. Ortiz de Montellano, Ph.D. Thesis, Harvard University, 1968, p 106; S. Yamamoto, K. Lin, and K. Bloch, *Proc. Nat. Acad. Sci. U. S.*, 63, 110 (1969).