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]

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(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).

E. J. Corey,* Sem M. Albonico, Urs Koelliker
Thomas K. Schaaf, Ravi K. Varma
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138
Received December 17, 1970

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-

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(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.

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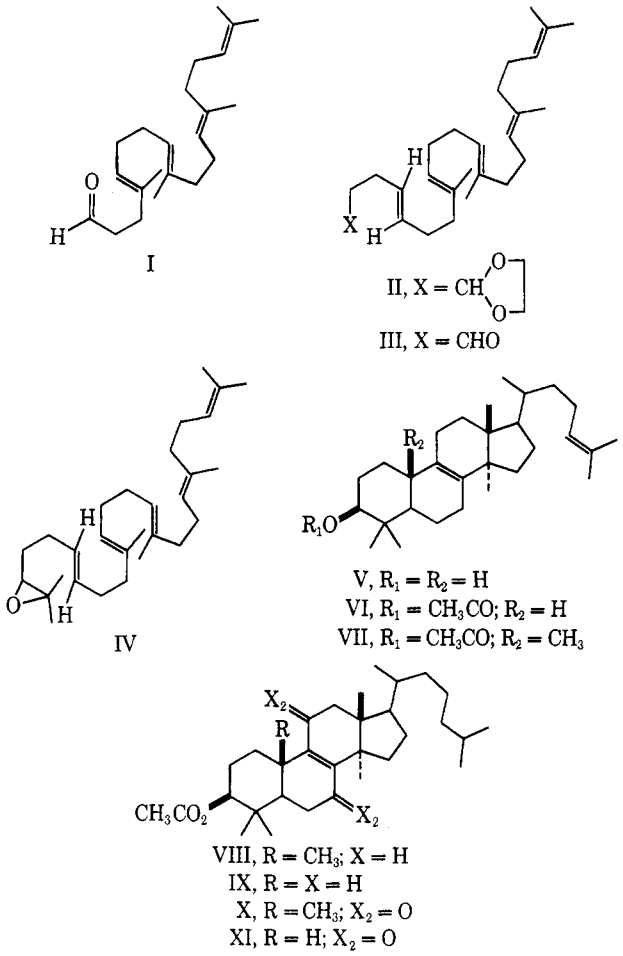

matographically indistinguishable from lanosterol (*e.g.*, R_f 0.21 with silica gel and chloroform for development), afforded an acetyl derivative VI with excess acetic anhydride–pyridine, giving essentially identical R_f values as lanosteryl acetate using silica gel or silica gel impregnated with silver nitrate as adsorbent (evidence for monoacetylation).

The mass spectrum of the acetate VI (purified by tlc) was obtained using a mass spectrometer (LKB Instrument Co.) coupled to a vapor-phase chromatographic (vpc) apparatus fitted with an OV-1 column,[12] and that of lanosteryl acetate (VII) was measured under the same conditions for comparison. In agreement with structure VI for the enzymically derived acetate, the molecular ion was observed at *m/e* 454 (M^+ for VII, 468). Further, major fragments from VI (in the range *m/e* >180) occurred at *m/e* 439, 379, 325, 283, 241, and 189, and those from VII were found at 453, 393, 325, 283, 255, and 189, that is, either displaced by *m/e* 14 or of the same value. Catalytic reduction of the acetate VI using a platinum catalyst in ethyl acetate with 1 atm of hydrogen, conditions which afford 24,25-dihydrolanosteryl acetate (VIII) from VII, led to selective formation of the dihydro derivative IX. The R_f values observed for VIII, IX, and VII using silver nitrate impregnated silica gel with chloroform–hexane, 3:7, for development were 0.36, 0.36, and 0.30, respectively. Oxidation of dihydrolanosteryl acetate (VIII) and the labeled acetate IX using dipyridine–chromium trioxide complex in methylene chloride at 25° for 9 hr led (*ca.* 50% yield) to the enedione derivatives X and XI, respectively. The mass spectra (LKB instrument as above) of these enediones fully support the assigned structures; for XI found (*m/e*): 484 (M^+), 469, 424, 381, 329, 302, 269, 241, 187; and for X found (*m/e*): 498, 483, 438, 395, 343, 302, 283, 255, 187. The major fragments found for X and XI differ, as expected, by either 14 or 0 *m/e* units.

The dihydro acetates VIII and IX also exhibited parallel behavior toward ruthenium tetroxide, both undergoing conversion to seco-diketo acetates.

Anaerobic incubation of labeled IV with the sterol cyclase in the presence of a 200-fold *M* amount of unlabeled 2,3-oxidosqualene results in only a 2.4% conversion of IV to the sterol V under the same conditions which lead to a 60% conversion in the absence of 2,3-oxidosqualene. This experiment indicates that the sterol cyclase is responsible for the transformation of IV to V.[13]

From the structural information outlined above, we conclude that des-6-methyl-2,3-oxidosqualene (IV) is an excellent substrate for the sterol cyclase enzyme and undergoes conversion to 19-norlanosterol (V).

In view of the findings of the dispensability with regard to enzymic cyclization of each of the methyl groups in 2,3-oxidosqualene which become angular methyl substituents on the sterol nucleus, it would be interesting to see whether the 2,3-oxidosqualene analog lacking methyl groups at C-6, C-10, *and* C-15 would be converted to a sterol which is completely devoid of angular methyl groups, and such an experiment is planned.

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(12) We are indebted to Dr. James Orr, Massachusetts General Hospital, for the use of this apparatus.

(13) Thermally (70°, 4 min) denatured sterol cyclase is ineffective for the generation of V from IV.

E. J. Corey,* Alain Krief, Hisashi Yamamoto
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138
Received December 22, 1970

Stereochemistry of Acetoxypalladation of Cyclohexene[1]

Sir:

The addition of the elements of Pd(II) or Pt(II) and nucleophiles across the double bonds of diolefins to give stable adducts has been found to have trans stereochemistry.[2] In contrast, the stereochemistry of the addition to monoolefins is usually considered to be cis[3] because the kinetics of the oxidation of olefins to aldehydes and ketones suggest the initial step is the cis addition of Pd(II)–OH to the double bond.[4,5]

(1) Hercules Research Center Contribution No. 1545.

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