Highly Stereoselective Conversion of Prostaglandin A_2 to the 10,11α-Oxido Derivative Using a Remotely Placed Exogenous Directing Group

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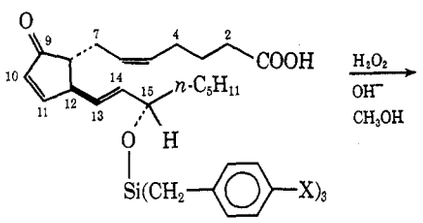
Attachment of the tri-*p*-xylylsilyl group to the 15-hydroxyl function of prostaglandin A_2 has been used to control the stereochemistry of epoxidation at the $\Delta^{10,11}$ bond using alkaline peroxide in methanol at −40°. The controller group allows formation of the 10,11α-oxide with 94% stereoselectivity. A lower degree of control (87.5% α-oxide) is observed under the same conditions using the tribenzylsilyl group as the control unit. Utilizing these exogenous controlling groups, convenient, efficient, and highly stereoselective conversion of A prostaglandins to E prostaglandins becomes possible.

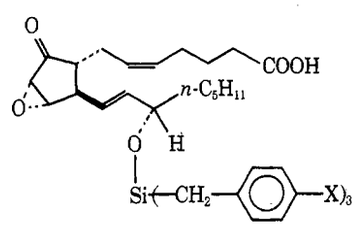
We have recently been concerned with the development of a process for stereocontrolled epoxidation of prostaglandin A_2 at the $\Delta^{10,11}$ linkage for several reasons. First, quantities of very pure 10,11α- and 10,11β-oxido derivatives were required for studies of enzymic transformations of prostaglandin A_2 in blood.[1] Additionally, two simple and stereocontrolled synthetic routes to prostaglandins have been developed lately in these laboratories[2] which lead with high efficiency to A type prostaglandins; these syntheses would become general for all primary prostaglandins with the realization of a process for stereocontrolled *10,11α-epoxidation* of the PGA's. Although our studies of the directed α-epoxidation are not yet complete, we have at this point in time succeeded in effecting epoxidation essentially quantitatively with a ratio of 10,11α-epoxide to 10,11β-epoxide (referred to herein as α/β ratio) of 94:6. Previously described epoxidations of PGA_2 derivatives,[3] including those in a very recent communication,[4] have favored only moderately the α isomer. Our plan depends on the attachment of a controller group at the 15-hydroxyl group so designed as to block the approach of a reagent to the β face of C-11 in the five-membered ring of PGA_2. In this connection it should be noted that a technique has recently been devised in this laboratory which permits highly stereoselective generation of the 15*S* configuration of the natural prostaglandins by reduction of 15-ketones bearing an appropriate controlling group at C-11.[5] Taken together, the present studies and previous work[5] illustrate the use of a controller group at C-15 to direct stereochemistry at C-11 and also the reverse, *i.e.*, the regulation of configuration at C-15 by the presence of a suitable control element at C-11.

The epoxidation of the $\Delta^{10,11}$ linkage of the A prostaglandins can be effected by the alkaline hydrogen peroxide method.[3,6,7] Two attractive candidates as



1, X = H

2, X = CH_3



3, X = H

4, X = CH_3

substrates designed to favor 10,11α-epoxidation appeared to be the 15-tribenzylsilyl ether of PGA_2 (**1**) and the 15-tri-*p*-xylylsilyl ether **2**. Figure 1 shows a view of **2** in what appears to be the energetically favorable molecular conformation.[8] The strong shielding of the β face of the cyclopentenoid unit in **2** by one of the benzenoid units of the controller is apparent. Although this shielding can be decreased to some degree by rotation about the Si–CH_2Ar bonds and/or O–Si bond, the obstruction to nucleophilic attack at the β face of C-11 remains substantial.

Reaction of prostaglandin A_2 with tribenzylsilyl chloride[9] (3.5 equiv) (prepared from benzylmagnesium chloride and silicon tetrachloride in ether, mp 140°) in dimethylformamide in the presence of 2,6-lutidine (3.5 equiv) at −20° for 24–36 hr followed by aqueous work-up and chromatography of the crude product on silica gel afforded the 15-tribenzylsilyl derivative of PGA_2 (**1**) as a colorless oil, homogeneous by tlc analysis on silica gel using ether for development (R_f 0.58), and free of PGB_2 tribenzylsilyl ether (R_f 0.23), the most

(1) E. J. Corey, H. E. Ensley, L. Levine, and R. H. Abeles, in progress.

(2) (a) E. J. Corey and J. Mann and (b) E. J. Corey and G. Moinet, Symposium on Prostaglandins (Canadian Institute of Chemistry), Montreal, Canada, June 5, 1973.

(3) (a) W. P. Schneider, R. D. Hamilton, and L. E. Rhuland, *J. Amer. Chem. Soc.*, **94**, 2122 (1972); (b) G. L. Bundy, W. P. Schneider, F. H. Lincoln, and J. E. Pike, *ibid.*, **94**, 2123 (1972); (c) G. L. Bundy, E. G. Daniels, F. H. Lincoln, and J. E. Pike, *ibid.*, **94**, 2124 (1972).

(4) W. P. Schneider, G. L. Bundy, and F. H. Lincoln, *J. Chem. Soc., Chem. Commun.*, 254 (1973). Strictly quantitative measurements of α/β epoxide ratios are not available in this or previous papers.

(5) E. J. Corey, K. B. Becker, and R. K. Varma, *J. Amer. Chem. Soc.*, **94**, 8616 (1972).

(6) The epoxidation of prostaglandin A_1 using alkaline hydrogen peroxide [for method see E. Klein and G. Ohloff, *Tetrahedron*, **19**, 1091 (1963)] was studied first in these laboratories: E. J. Corey and N. H. Anderson, unpublished results, 1968. Such direct epoxidation of the A prostaglandins is relatively nonstereoselective in protic solvents and affords a mixture of diastereomers, typically with an α/β ratio of 60:40.

(7) The epoxidation of prostaglandin A_2 methyl ester by the procedure of N. C. Yang and R. A. Finnegan, *J. Amer. Chem. Soc.*, **80**, 5845 (1958) (*tert*-butyl hydroperoxide–Triton B in aprotic medium) shows a preference opposite to the alkaline epoxidation in protic media (E. J. Corey and R. A. Ruden, unpublished experiments, 1972); for example, an α/β ratio of 25:75 is observed in benzene solution at 25°. This appears to be the method of choice at present for the preparation of 10,11β-oxido PGA's.

(8) In this conformation the two side chains are extended to avoid torsional or eclipsing interactions, and the tri-*p*-xylylsilyl group is arranged so as to minimize nonbonded intramolecular repulsions. Other conformations generated by rotation about the C-15–O bond appear to involve a major increase in steric repulsion.

(9) G. Martin and F. S. Kipping, *J. Chem. Soc.*, **95**, 302 (1909).

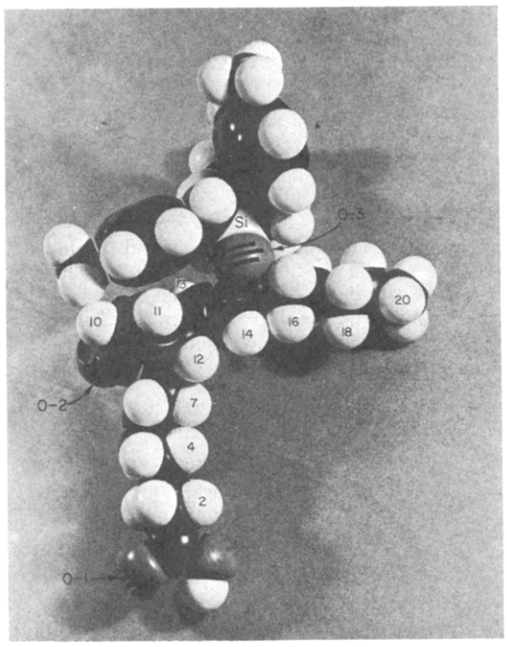


Figure 1.—CPK model of 2. Numbers on hydrogens correspond to the carbons to which they are attached. O-1 is carboxyl oxygen, O-2 carbonyl at C-9 and O-3 oxy at C-15. The lower and upper faces of the cyclopentane unit are α and β, respectively.

troublesome potential contaminant at this stage. Epoxidation of **1** was effected by reaction with a large excess of hydrogen peroxide in methanol at $-40°$ with the addition of 0.6-equiv portions of 3 *N* sodium hydroxide after 0.1, 4, 12, and 30 hr. Addition of saturated aqueous ammonium chloride, concentration at $<20°$ to remove methanol, and extraction afforded 10,11-epoxide almost quantitatively. Analysis of the product, carried out using a Waters Associates ALC-202 high-pressure liquid chromatographic unit using an ultraviolet (254 nm) detector,[10] revealed the product to be 87.5% α-oxide **3** and 12.5% of the epimer.[11] As expected, the α/β ratio was lower when the reaction was conducted at higher temperature (*e.g.*, 84.5:15.5 at $-18°$), and in addition, the epoxidation was considerably faster (*ca.* 4 hr required).

The 15-tri-*p*-xylylsilyl ether of PGA_2 (**2**)[12] upon epoxidation as described above at $-40°$ afforded 94% of the 10,11α-oxide **4** and 6% of the β-oxide. At $-20°$ epoxidation led to a product of α/β ratio of 89.5:10.5.

The epoxides **3** and **4** were converted smoothly by desilylation [acetic acid–tetrahydrofuran–water (3:1:1) 26°, 9 hr] and reduction with aluminum amalgam to prostaglandin E_2, identical in all respects with an authentic sample. Since the rate of the aluminum amalgam reduction of the 10,11α-oxide of PGA_2 is considerably faster than that of the isomeric 10,11β-oxide, it is probable that by proper choice of reaction time pure crystalline prostaglandin E_2 can be prepared efficiently from the 94:6 α,β-oxide mixture simply by use of an appropriate reaction time followed by recrystallization of the resulting PGE_2. Thus a highly stereoselective and convenient process is available for the conversion of A to E prostaglandins.[13]

These studies are continuing. It is of great interest that the replacement of hydrogen in **1** by para methyl as in **2** results in a substantial increase in the directive influence of the remote controller group. The effect is not surprising based upon the considerations outlined above; it points the way for further research.[14]

Experimental Section

15-Tri-*p*-xylylsilyloxy-PGA_2 (2).—A mixture of 201 mg (0.60 mmol) of PGA_2 (purity 70–80%) and 710 mg (1.88 mmol) of tri-*p*-xylylsilyl chloride[9,12] was dissolved in 3 ml of DMF. The slurry was cooled to $-25°$, and 80 mg (0.75 mmol) of 2,6-lutidine was added. The solution was stirred at $-25°$ for 12 hr and then another 80 mg (0.75 mmol) of 2,6-lutidine was added and the solution was stirred for another 24 hr. The solution was diluted with 15 ml of methylene chloride and extracted twice with saturated brine. After drying (Na_2SO_4) and evaporation of the solvent, the residue was chromatographed on silica gel to give 283 mg (0.42 mmol, 90–100%) of the pure 15-silyl ether of PGA_2: nmr ($CDCl_3$) δ 7.6–7.2 (multiplet, 1 H, C_{11} H), 6.9 (singlet, 12 H, ArH), 6.4–6.1 (multiplet, 1 H, C_{10} H), 5.5–5.2 (multiplet, 4 H, olefinic), 4.25–3.95 (multiplet, 1 H, C_{15} H), 3.35–0.7 (multiplet, 36 H); ir (CH_2Cl_2) 3480, 1740, 1705, 1510 cm^{-1}; mass spectrum (70 eV) *m/e* 676 (M^+).

10,11-Epoxy-15-tri-*p*-xylylsilyloxy-PGA_2 (4).—To a solution of 174.3 mg (0.26 mmol) of 15-tri-*p*-xylylsilyloxy-PGA_2 dissolved in 10 ml of methanol at $-45°$ was added 150 μl of 2 *N* NaOH and 0.5 ml (*ca.* 2 mmol) of 30% H_2O_2. The homogeneous mixture was stirred at $-45°$ for 12 hr. Another 150 μl of 2 *N* NaOH and 0.5 ml of 30% H_2O_2 were added, and the solution was stirred for 24 hr at $-45°$. The solution was added to 5 ml of saturated ammonium chloride, and the methanol was evaporated under reduced pressure. The aqueous residue was extracted twice with methylene chloride. The organic layers were washed with saturated ammonium chloride and then saturated sodium chloride solution. After drying and evaporation of the solvent, there was obtained 180 mg (102%) of the oily epoxide: nmr ($CDCl_3$) δ 6.94 (singlet, 12 H, ArH), 5.55–5.20 (multiplet, 1 H, C_{15} H), 3.67–3.51 (multiplet), 1 H, C_{10} H), 3.49–3.30 (multiplet, 1 H, C_{11} H), 3.0–0.7 (multiplet, 36 H); ir (CH_2Cl_2) 3480, 1770, 1720, 1510 cm^{-1}; mass spectrum (70 eV) *m/e* 692 (M^+).

Liquid–liquid chromatography[10] showed the mixture to consist of 94.5% α-epoxide and 5.5% β-epoxide.

10,11-Epoxy-PGA_2.—A solution of 180 mg (0.26 mmol) of 15-tri-*p*-xylylsilyloxy-PGA_2 epoxide in 12 ml of HOAc, 4 ml of H_2O, and 4 ml of THF was stirred for 6 hr at *ca.* 26°. Then the temperature was raised to 45° for 3 hr. After evaporation of the solvent there was obtained 184 mg of a mixture of trixylylsilanol and PGA_2 epoxide. The PGA_2 epoxide could not be purified by extraction into pH 8 buffer and then acidification to pH 3.5; however, it was easily purified by filtration through silica gel. Thus 87 mg of the mixture of trixylylsilanol and PGA_2 epoxide was filtered through 5 g of silica gel in ether. The silanol was eluted rapidly and then a trace of acetic acid was added to the ether. The A_2 epoxide (37 mg, 85%) was eluted rapidly: nmr ($CDCl_3$) δ 6.00–5.20 (multiplet, 6 H, olefinic, CO_2H and OH), 4.17 (broad singlet, 1 H, C_{15} H), 3.87–3.62 (multiplet, 1 H, C_{10} H), 3.55–3.38 (multiplet, 1 H, C_9 H), 3.20 (multiplet, 21 H); ir (CCl_4) 3350, 1741, 1709 cm^{-1}.

PGE_2.—To a solution of 2.75 ml of THF, 1.5 ml of H_2O, 0.1 ml of saturated sodium bicarbonate, 1 ml of ethanol, and 15 mg (0.043 mmol) of PGA_2 epoxide was added aluminum amalgam (freshly prepared from 250 mg of aluminum foil). The reaction

(10) Although the 10,11α- and 10,11β-epoxides are not cleanly separated by thin layer chromatography using a wide variety of solvent systems (*cf.* ref 3 and 4), the isomers were easily and completely resolved by the ALC-202 instrument using a 5 ft × 0.125 in. Porasil T column with 0.5% acetic acid in methylene chloride as eluent. Using a flow rate of 1 ml/min, retention times of 12 and 16 min were observed for the β- and α-epoxides, respectively. The strong ultraviolet absorbance of the controller group allowed analyses to be performed on submilligram amounts with a precision of better than 0.5%.

(11) Satisfactory infrared, nuclear magnetic resonance, and mass spectral data were obtained for all new substances reported herein.

(12) The ether **2** was prepared by the procedure used for **1** using tri-*p*-xylylsilyl chloride, mp 69°, which in turn was made by the Grignard–silicon tetrachloride method.[9]

(13) Although this development can be regarded as additional incentive to exploit the marine source of PGA_2, the soft coral *Plexaura homomalla*,[3,4] the authors urge against such exploitation as potentially damaging or disastrous to the beautiful and irreplaceable reefs of the Caribbean.

(14) This work was assisted financially by the National Institutes of Health, the National Science Foundation, and the Chas. Pfizer Co.

was allowed to proceed for 1.5 hr at 4°. The reaction mixture was centrifuged, and the aqueous THF was decanted. The alumina residue was washed twice with 10 ml of ethyl acetate containing 1% acetic acid, and the washings were combined with the THF solution. The solution was acidified with acetic acid and extracted with 10 ml of saturated sodium chloride solution. Drying (Na_2SO_4) and evaporation of the solvent gave 16.1 mg of material which was almost entirely PGE_2 with some PGA_2 and starting material (no detectable epi-PGE_2).

This was dissolved in a small amount of ethyl acetate at *ca.* 40°, and hexane was added until the solution was cloudy. The solution was cooled at −20° for 2 hr, then overnight at −75° to give 11 mg (0.031 mmol, 72.5%): mp 63–66°; nmr ($CDCl_3$, 100 MHz) δ 5.65–5.48 (multiplet, 2 H, olefinic), 5.48–5.25 (multiplet, 2 H, olefinic), 5.17 (broad singlet, 3 H, CO_2H and OH), 4.23–3.83 (multiplet, 2 H, C_{11} H and C_{15} H), 2.80–0.70 (multiplet, 23 H); ir ($CHCl_3$) 3400, 1733, 1704, 967 cm^{-1}. An additional 2 mg of PGE_2 could be obtained from the mother liquor by thin layer chromatography, raising the yield to 85%.

15-Tribenzylsilyloxy-PGA_2 (1).—A mixture of 345 mg (1.03 mmol) of PGA_2 (purity 70–80%) and 1.237 g (3.67 mmol) of tribenzylsilyl chloride was slurried under argon in 5 ml of DMF. The slurry was cooled to −20°, and 113 mg (1.03 mmol) of 2,6-lutidine in 0.5 ml of DMF was added. The solution was stirred for 12 hr at −20° and then another 101 mg (0.94 mmol) of 2,6-lutidine was added and the solution was stirred for 12 hr at −20°. After another 50 mg (0.47 mmol) of 2,6-lutidine and 12 hr at −20°, the silylation was complete. The solution was diluted with 20 ml of methylene chloride and extracted twice with 20 ml of water and then 10 ml of brine. The aqueous layers were extracted with 10 ml of methylene chloride, and the combined methylene chloride solutions were dried (Na_2SO_4). Tlc shows tribenzylsilyl chloride (R_f 0.58, Et_2O) and a small amount of 15-tribenzylsilyloxy-PGB_2 (R_f 0.23, Et_2O) as impurities. Chromatography on silica gel gave 452 mg (0.71 mmol, 88–100%) of 15-tribenzylsilyl-PGA_2 as an oil: nmr ($CDCl_3$) δ 9.8 (1 H, CO_2H), 7.40–6.80 (multiplet, 16 H, ArH and C_{11} H), 6.25–6.05 (multiplet, 1 H, C_{10} H), 5.45–5.15 (multiplet, 4 H, olefinic), 4.20–3.95 (multiplet, 1 H, C_{15} H), 3.22–2.96 (multiplet, 1 H, C_{12} H), 2.50–0.85 (multiplet, 20 H); ir (neat) 2970, 1740, 1720, 1600, 1500, 1450 cm^{-1}; mass spectrum (70 eV) *m/e* 634 (M^+), 527.

10,11-Epoxy-15-tribenzylsilyloxy-PGA_2 (3) and PGE_2.—To a solution of 64 mg (0.10 mmol) in 1 in 5 ml of methanol at −17.5° was added 1 ml (*ca.* 5 mmol) of 30% H_2O_2 followed by 20 μl (0.06 mmol) of 3 *N* NaOH.[6] After 4 hr at −17.5° another 20 μl (0.06 mmol) of 3 *N* NaOH was added and the solution was stirred for 8 hr. Another 25 μl (0.075 mmol) of 3 *N* NaOH was added, and the solution was stirred for another 18 hr. Then 2 ml of saturated NH_4Cl solution was added, and the volume was reduced to *ca.* 5 ml. The residue was diluted with 10 ml of saturated NH_4Cl solution and extracted with 10 ml of CH_2Cl_2 which was washed twice with 5 ml of saturated NH_4Cl solution and then washed with 5 ml of brine. After drying (Na_2SO_4) and evaporation of the solvent, there was obtained 60.7 mg (0.094 mmol, 94%) of a mixture of epoxides: nmr ($CDCl_3$) δ 7.32–6.80 (broad doublet, 15 H, ArH), 5.60–5.10 (multiplet, 4 H, olefinic), 4.20–3.90 (multiplet, 1 H, C_{15} H), 3.56 (doublet, J = 4 Hz, 1 H, C_{10} H), 3.35 (multiplet, 1 H, C_{11} H), 2.80–0.85 (multiplet, 27 H); ir ($CHCl_3$) 3400, 2960, 1760, 1720, 1600, 1500 cm^{-1}; mass spectrum (70 eV) *m/e* 650 (M^+), 541.

Although the two epoxides were inseparable by tlc, they were easily separated by llc.[10] This showed a mixture of 84.5:15.5 with the major isomer being the desired epoxide.

When the epoxidation was carried out at −40°, the isomer ratio was 87.5:12.5 and the yield was 95%. However, epoxidation did not occur at −78° even using 90% H_2O_2 instead of 30% H_2O_2.

The conversion of **3** to PGE_2 was carried out by the same procedure described above for the synthesis of PGE_2 from **4**.

Registry No.—**1**, 41366-90-9; **2**, 41366-91-0; **3**, 41366-92-1; PGA_2, 13345-50-1; 10,11-epoxy-PGA_2, 41366-94-3; PGE_2, 363-24-6; tri-*p*-xylylsilyl chloride, 41366-95-4; tribenzylsilyl chloride, 18740-59-5; **4**, 41366-93-2.

A Study of the Scope and Mechanism of Displacement of Halogen from a Saturated Carbon by Organocadmium Reagents[1]

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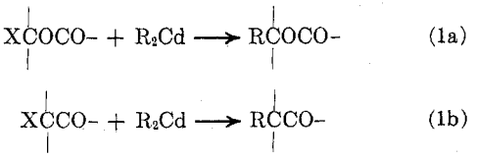
Displacement of halogen with phenylcadmium reagent has been effected in several substrates: ethyl bromoacetate, ethyl α-bromopropionate, ethyl α-bromobutyrate, 3-bromocyclohexene, allyl bromide, benzyl bromide, and chloromethyl methyl ether. Under similar reaction conditions, 1-bromobutane, ethylene bromide, bromoacetaldehyde diethyl acetal, *tert*-butyl chloride, trimethylsilyl chloride, chlorocyanomethane, and 1-chloro-1-nitroethane were unreactive. With α-halo esters, an α hydrogen, as well as halogen, seems to be a minimum requirement for displacement. A carbene intermediate ($R\ddot{C}COOR'$) seems unlikely, inasmuch as none of the expected bicyclo product was found when cyclohexene was added as a carbene trapping agent. The generation of free radicals is evident from the strong esr signal observed initially on mixing of the reactants. The intermediacy of a free-radical intermediate, either by homolysis or electron transfer, is consistent with the fact that the displacement proceeds with racemization, which was established in the formation of (±)-methyl hydratropate from (*R*)-(+)-bromopropionate and phenylcadmium reagent under conditions when the starting ester was optically stable. The interesting observation has been made that the displacement in 3-bromocyclohexene proceeds without the intermediacy of free radicals, as judged by esr spectroscopy.

For some time we have been investigating a fascinating reaction of promising synthetic value, namely, the displacement of substituents—often but not always halogen—in esters, lactones, and ketones with organocadmium reagents.[2] The general reaction is represented in eq 1a and 1b.



While it had already been shown that the displacement from a phthalide[2e] was stereoselective, no such information was at hand concerning the steric course of displacement in α-halo esters[2d] when this present work was undertaken. We found that (*R*)-(+)-methyl α-bromopropionate (**1**) underwent reaction with ethereal phenylcadmium reagent to afford racemic

(1) (a) Taken in part from the Ph.D. thesis of S. J. C., University of New Hampshire, 1972. (b) Presented in part at the 164th National Meeting of the American Chemical Society, New York, N. Y., 1972, ORGN 169.

(2) (a) P. R. Jones and S. L. Congdon, *J. Amer. Chem. Soc.*, **81**, 4291 (1959); (b) P. R. Jones and A. A. Lavigne, *J. Org. Chem.*, **25**, 2020 (1960); (c) P. R. Jones, C. J. Jarboe, and R. Nadeau, *J. Organometal. Chem.*, **8**, 361 (1967); (d) P. R. Jones and J. R. Young, *J. Org. Chem.*, **33**, 1675 (1968); (e) P. R. Jones and C. J. Jarboe, *Tetrahedron Lett.*, 1849 (1969); (f) P. R. Jones and C. J. Jarboe, *J. Organometal. Chem.*, **24**, 555 (1970).