Improved Synthetic Routes to Prostaglandins Utilizing Sulfide-Mediated Oxidation of Primary and Secondary Alcohols

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We have recently reported a new and highly effective method for the synthesis of aldehydes and ketones by oxidation of primary and secondary alcohols which utilizes complexes of a sulfide such as methyl sulfide with chlorine or *N*-chlorosuccinimide.[1] The general process may be outlined as

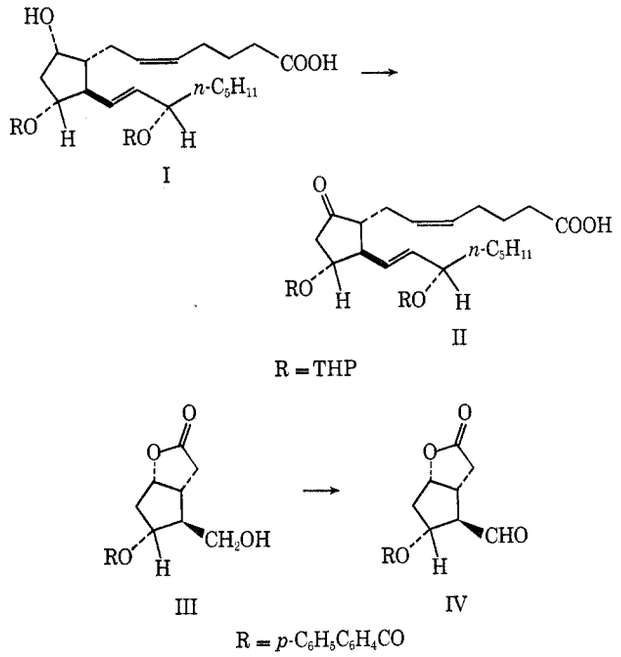
$$R'R''CHOH \xrightarrow[-25°,\ e.g.,\ \text{toluene}]{RS(X)CH_3\ Cl^-} R'R''CHOS(X)CH_3\ Cl^- \xrightarrow[-25°]{Et_3N} R'R''C{=}O + Et_3NHCl + RSCH_3$$

X = Cl or *N*-succinimido

We have now ascertained that this method of oxidation is highly advantageous in the generation of two key intermediates for the synthesis of prostaglandins, the keto acid II (prostaglandin E_2 11,15-bistetrahydropyranyl derivative), and the lactone ester aldehyde IV. In each of these cases the lability of the synthetic intermediates imposes severe restrictions on the reagents and reaction conditions which may be utilized.

The oxidation of the hydroxy acid I to the keto acid II has previously been accomplished using the Jones (CrO_3) reagent[2] at −20° in yields of *ca.* 70%.[3,4] The conditions of the reaction are quite critical, since there are several acid-sensitive units in II (*e.g.*, β-ketal system, tetrahydropyranyl ether system) which become involved to a substantial degree if reaction temperature and time are not carefully controlled. All previously known nonacidic oxidizing agents (*e.g.*, Collins reagent[5]) which were tried originally[3] were found to fail. In contrast, the use of the newly developed methyl sulfide–*N*-chlorosuccinimide reagent[1] under simple, standard conditions allowed the oxidation of I to II in >90% yield. Furthermore, the process is extremely convenient and clearly suitable for use on a multimolar scale.

In order to avoid reaction of the carboxyl function of I with an equivalent of the oxidizing agent, the isopropyldimethylsilyl ester[6] of I was prepared for use *in situ* from equivalent amounts of I, triethylamine, and isopropyldimethylsilyl chloride in toluene. The solution of this ester of I in toluene was then subjected to oxidation using the *N*-chlorosuccinimide–methyl sulfide to afford the silyl ester of II as a chromatographically homogeneous oil, which upon hydrolysis under mildly acidic conditions (pH ~4.5) furnished



the 11,15-bistetrahydropyranyl derivative of prostaglandin E_2.

The oxidation of the hydroxy lactone III using the methyl sulfide–*N*-chlorosuccinimide reagent in toluene–methylene chloride solution produced the aldehyde IV contaminated by variable amounts of the starting alcohol III even when an excess of oxidizing agent was employed, perhaps because of insolubility of the sulfoxonium intermediate. Much better results were obtained, however, using as reagent the 1:1 complex of chlorine with methyl phenyl sulfide in carbon tetrachloride–methylene chloride mixture. Using essentially the standard procedure,[1] the aldehyde IV[4] could be isolated simply in crystalline form in >90% yield. The original[3,4] preparation of IV from III, which involved the use of Collins reagent,[5] afforded IV in 90% yield, but suffered from the disadvantage of being difficult to carry out on a multimolar or even molar scale.[7]

Experimental Section

Oxidation of I to II.—To a stirred solution of 56 mg (0.11 mmol) of the 11,15-bistetrahydropyranyl derivative of prostaglandin $F_{2\alpha}$ (I) in 0.5 ml of dry toluene and 0.11 ml of a 1.0 *M* solution of isopropyldimethylsilyl chloride in toluene was added dropwise at 0° 0.11 ml of a 1.0 *M* solution of triethylamine in toluene *via* syringe under an argon atmosphere. The reaction mixture was used immediately for oxidation.

To a solution of 64 mg (0.50 mmol) of *N*-chlorosuccinimide in 2 ml of toluene was added at 0° 45 μl (0.6 mmol) of methyl sulfide *via* microsyringe under an argon atmosphere. The stirred mixture was cooled to −25° (carbon tetrachloride–Dry Ice), and the

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(7) The oxidation of III and IV has also been carried out in very good yield by Dr. N. M. Weinshenker and coworkers at the Alza Co. (personal communication) using Moffatt's method [K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5661 (1965); **88**, 1762 (1966)] with *N,N'*-diethylcarbodimide–dimethyl sulfoxide.

above-described solution of the silyl ester of I in toluene was added dropwise by syringe. Stirring was continued for 2 hr at −25°, and then a solution of 100 mg (0.99 mmol) of triethylamine in 0.2 ml of pentane was added dropwise. The cooling bath was removed, and after 5 min 5 ml of ether was added. The organic layer was washed with 2 ml of ice-cold 1% aqueous hydrochloric acid and twice with 3 ml of cold water. Removal of dried (magnesium sulfate) solvents under vacuum produced 59 mg (92%) of the silyl ester of II as a colorless oil (homogeneous by tlc; R_f 0.40, silica gel–methylene chloride): ir max (neat) 2970 (m), 1745 (s), 1710 (s), and 1150 cm^{-1} (br s).

To a solution of 246 mg (3.00 mmol) of sodium acetate in 3 ml of acetone and 1 ml of water was added 180 mg (3.00 mmol) of acetic acid to give a standard solution of pH 4.5. To a solution of 59 mg of above-described silyl ester of II in 1 ml of acetone and 0.3 ml of water was added at 0° 0.4 ml of sodium acetate–acetic acid standard solution, and the mixture was stirred for 45 min. After warming to 25°, stirring was continued for 30 min, at which time tlc analysis indicated the absence of silyl ester. The solution was poured into 2 ml of ice–water and extracted with three 5-ml portions of ether. Removal of dried (magnesium sulfate) solvents under reduced pressure produced 48 mg (91% yield based on I) of the 11,15-bistetrahydropyranyl ether of prostaglandin E_2, chromatographically identical with authentic material. The infrared and nmr spectra were also identical with those of an authentic sample which had been prepared previously in this laboratory.[3,4]

Oxidation of III to IV.—To a solution of 21.3 mg (0.30 mmol) of chlorine in 1.5 ml of carbon tetrachloride was added at −10° a solution of 37.2 mg (0.30 mmol) of thioanisole in 0.5 ml of methylene chloride under argon. A white precipitate appeared immediately after addition of the sulfide. The mixture was cooled to −25°, and a solution of 56 mg (0.16 mmol) of the lactone alcohol III in 1 ml of methylene chloride was added dropwise. Stirring was continued for 90 min at −25°, and then a solution of 60.6 mg (0.60 mmol) of triethylamine in 0.5 ml of methylene chloride was added dropwise. The cooling bath was removed, and after 5 min 5 ml of ether was added. The organic layer was washed with 1 ml of ice-cold 1% aqueous hydrochloric acid. Removal of dried (magnesium sulfate) solvents produced a white solid which was washed twice with 3 ml of cold pentane to give 52 mg (93%) of IV as colorless crystals (R_f 0.25, silica gel–chloroform): nmr ($CDCl_3$) δ 2.0–3.6 (m, 6 H), 5.20 (br t, J = 5 cps, 1 H), 5.6–5.8 (m, 1 H), 7.3–8.4 (m, 9 H, aromatic protons), 9.89 (s, 1 H, aldehyde); ir ($CHCl_3$) 2950 (m), 2850 (m), 1775 (s), 1725 (s), 1720 (s), 1610 (m), 1270 (s), 1100 (br), 910 cm^{-1} (s). The chromatographic and spectral data agreed with those obtained for IV which had been prepared by Collins oxidation. The product IV could be used for the synthesis of prostaglandins as previously described[3,4] without further purification.

Registry No.—I, 37786-09-7; II, 38123-52-3; III, 32233-39-9; IV, 32233-41-3.

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The Synthesis of 9-Ketotridecanolide and Related 13- and 16-Membered Ketolactones[1]

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We have shown that keto lactones, including 7-ketoundecanolide, the parent system present in methymycin, can be synthesized by the oxidation of bicyclic enol ethers derived from the acid-catalyzed closure of 2-(ω-hydroxyalkyl)cycloalkanones.[2-4] Previously, six- to eight-membered ring ketones have been utilized. We now demonstrate the further utility of this method in the synthesis of 8-ketododecanolide (**1**), 9-ketotridecanolide (**2**), and 12-ketopentadecanolide (**3**) from cyclooctanone, cyclononanone, and cyclododecanone, respectively, in overall yields of 46, 35, and 19%.

The C-alkylations of carbethoxycyclooctanone (**4**) and cyclononanone (**5**) *via* their sodium enolates with 1-bromo-4-acetaoxybutane (**6**) proceed as previously described for smaller ring ketones[2] to lead to 2-(4′-hydroxybutyl)cyclooctanone (**7**) and the corresponding cyclononanone **8**. Hemiketal formation and dehydration of **7** proceeds readily upon acid catalysis or slow distillation *in vacuo*. The corresponding closure of **8** is more difficult and is best performed by distillation from potassium pyrosulfate.[3]

The oxidation of the resultant bicyclic enol ethers **9** and **10** with excess *m*-chloroperbenzoic acid (MCPBA)[2-4] must be done for a short time period in order to keep Baeyer–Villiger oxidation of the product ketolactone to dilactones as a minor side reaction. The utilization of other oxidation procedures (which avoid dilactone formation but are not as good in yield) such as reaction with *tert*-butylhydroperoxide and molybdenum hexacarbonyl[4b] or lead tetraacetate oxidation of the corresponding glycol[5] was only briefly investigated for these cases.

It is noteworthy that **2** represents the parent system of the erythromycin macrolides.[6]

Finally, **3** is readily synthesized from 2-(3′-hydroxypropyl)cyclododecanone (**12**), which is formed from the pyrrolidine enamine of cyclododecanone (**11**) upon reaction with ethyl acrylate, followed by lithium aluminum hydride reduction.[3,7]

Experimental Section[8]

8-Ketododecanolide (**1**).—Treatment of the sodium enolate of 2-carbethoxycyclooctanone[9] (from **4** and sodium hydride in toluene at reflux for 30 min) with 1-bromo-4-acetoxybutane (**6**, 1.1 equiv) for 2 days at reflux gave crude 2-carbethoxy-2-(4′-acetoxybutyl)cyclooctanone, which was hydrolyzed with potassium hydroxide in aqueous ethanol at reflux for 48 hr to give 2-(4′-hydroxybutyl)cyclooctanone (**7**, 62% yield): bp 127–129°

(1) This investigation was supported by Public Health Service Research Grant AI 07455 from the National Institute of Allergy and Infectious Diseases and by the Eli Lilly Co. This is part 8 of the series, Medium Ring Compounds.

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(8) Infrared spectra were recorded on Perkin-Elmer 257 and Beckman IR-8 spectrophotometers. Nmr spectra were recorded on a Varian A-60A spectrometer with TMS as an internal standard. Melting points were taken on Mel-Temp and Thomas-Hoover apparatus and are corrected while boiling points are uncorrected. Mass spectra were done on Hitachi RMU-6 mass spectrometers at Einstein Medical College, N. Y., and Columbia University. Solvents were dried by distillation from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride. Reactions involving carbanions were conducted under prepurified nitrogen. All vpc columns employed Chromosorb W and were 5 or 10 ft × 0.25 in.

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