# AN EFFICIENT SYNTHESIS OF 3α-HYDROXY-5α-PREGNA-9(11),16-DIENE-20-ONE

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## ABSTRACT

3α-Hydroxy-5α-pregna-9(11),16-diene-20-one (6) was synthesized for the first time from the commercially available 16,17α-epoxy-3β-hydroxy-5-pregnen-20-one(1) in several steps. The key step involves a remote chlorination reaction utilizing m-iodobenzoate group as a free-radical guide.

## INTRODUCTION

The direct introduction of a 9(11)-double bond has been achieved only by microbiological fermentation in low yields (1). Recently, Brewlow *et al* reported successful remote chlorination of cholesterol in which a *m*-iodobenzoate was used with a chlorinating reagent (2-6).

We report a convenient synthesis of the 9(11),16-diene 6 in respectable yields from 16,17α-epoxy-3β-hydroxy-5-pregnen-20-one(1) by utilizing the method of Breslow *et al*.

# EXPERIMENTAL

## Materials

All Chemicals purchased were used without further purification : m-iodobenzoic acid and diethyl azodicarboxylate (DEAD) (Waco, Japan), triphenylphosphine and sulfuryl chloride (Aldrich, U.S.A.), benzoyl peroxide (Chon Ya, Taiwan), and 16,17α-epoxy-3β-hydroxy-5-pregnen-20-one (Sigma, U.S.A.). Iodobenzene dichloride was prepared by a published method (7). Merck kieselgel 60FG-254 and 60 (70-230 mesh ASTM) were used for thin layer and column chromatography, respectively.

## Analytical Measurements

Infrared (IR) spectra were recorded on a Perkin-Elmer 283B spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian FT-80A spectrometer in chloroform-d. Melting points (MP) were measured on a Thomas-Hoover Capillary melting point apparatus. Elemental analyses were carried out on a F&M Scientific Corporation C.H.M. Analyzer Model 180.

## Preparation of the m-Iodobenzoate 3 from the Epoxypregnenolone 1

According to the precedure in the literature (8), the ketone 2 was prepared from the enone 1 by catalytic hydrogenation. A solution of the ketone 2 (64 mg, 2.0 mmol), triphenylphosphine (104 mg, 4.0 mmol), and m-iodobenzoic acid (992 mg, 4.0 mmol) in dry tetrahydrofuran (40 ml) was stirred at room temperature under nitrogen. To this was added dropwise a solution of 696 mg (0.630 mmol) diethyl azodicarboxylate (DEAD) in 4 ml tetrahydrofuran. The mixture was stirred for 20h. Kieselgel (6 g) was added to the solution, and then solvent was evaporated off. The resulting powder was poured into the top of a column of kieselgel packed with the aid of hexane-ether mixture (10:1 v/v). Gradient elution with hexane-ether (10:1 v/v) gave 806 mg of the pure ester 3 (76% based on the ketone 2). A sample was recrystallized from methanol giving colorless crystals.

MP : 159-162°C ; $^1$H NMR ($CDCl_3$) δ0.86 (s, 3H, axial $CH_3$), 1.05 (s, 3H, axial $CH_3$), 2.05 (s, 3H, 21-$CH_3$), 3.6 (s, 1H, 16β-H), 5.25 (m, 1H, 3β-H), 7.18 (5, 1H, J=8Hz), 7.9 (m of t, 2H, J=8Hz), 8.3 (m, 1H) ; IR (KBr) ν3000-2950 $cm^{-1}$(aliphatic C-H), 1705 (ester C=O), 1700 (C-20 C=O), 1590 (aromatic C=C), 860 (epoxide C-O) ; Anal for $C_{28}H_{34}IO_4$, Cal C, 59.79 ; H, 6.27%. Found : C, 60.48 ; H, 6.39%.

## Remote Chlorination of the Ester 3 under 300W Hanovia Medium-Pressure Lamp using Iodobenzene Dichloride

A 500 mg (0.9 mmol) amount of the *m*-iodobenzoate 3 was dissolved in 90 ml of redistilled dichloromethane. Iodobenzene dichloride (300 mg, 1.08 mmonl, 1.2 mol-eq) was added. The solution was degassed by a series of freeze-thaw cycles and photolyzed with the Hanovia lamp using a Uranium glass filter for 1h. The solution was kept at a temperature of 10-20°C by use of an ice-water bath. The color changed from green to pink after 45 min. The solution was evaporated to dryness to a brownish oil which was found to consist of the major product 4, unreacted product, a small amount of unidentified polar product, and a trace amount (less than 5%) of a 14 α-chloro compound isolated by kieselgel column chromatagraphy with the aid of hexane-ether mixture (10:1 v/v).

The crude photolysis product was taken up in 10 ml of dioxane and 10 ml of 10% KOH in methanol was added. The solution was refluxed for 2h and diluted with water. The mixture was extracted with dichloromethane, washed with water, dried and evaporated to give 240 mg of nearly colorless oil which solidified on standing. The crude product was purified by kieselgel column chromatography with the oil of hexane-ether mixtrue (1:2 v/v) to give the pure enone 5 (65% based on the ketone 3).

MP : 166-168°C ; $^1$H NMR ($CDCl_3$) δ0.9 (s, 1H, axial $CH_3$), 1.0 (s, 1H, axial $CH_3$), 2.0 (s, 3H, 21-$CH_3$), 3.6 (s, 1H, 16β-H), 4.1 (m, 1H, 3β-H), 5.3 (m, 1H, 11-H) ; IR (KBr) ν3500-3300 cm (3α-OH), 2990-2940 (aliphatic CH), 1700 (C-20 C=O), 860 (epoxide C-O), 825 (C=C).

## Remote Chlorination of the Exter 3 to the Enone 5 using Sulfuryl Chloride under Reflux Condition

A 0.01M solution of the *m*-iodobenzoate 3 in carbon tetrachloride containing 1.2 mol-eq of sulfuryl chloride and 10 mol-eq of benzoyl peroxide was heated at reflux under nitrogen for 5h. Standard workup gave the 9(11)-olefin 5 in 60% yield. Spectral data were identical to those of 5 obtained by photolysis.

Reduction of the Enone 5 to the Dienone 6 with $TiCl_3$-$LiAlH_4$

Lithium aluminum hydride (9.2 mg, 0.23 mmol) in 1 ml of tetrahydrofuran was added in small portion to a stirred slurry of titanium trichloride (85.3 mg, 0.52 mmol) in 3 ml of tetrahydrofuran under nitrogen atmosphere at room temperature. Hydrogen evolution was immediate, and the resulting fine black suspension was stirred for 15 min before use.

A solution of the enone 5 (90 mg, 0.26 mmol) in 3 ml of dry tetrahydrofuran was added to the Ti (II) reagent which was prepared as described above, and the reaction mixture was refluxed for 1.5h. The reaction mixture was then cooled to room temperature and quenched by addition of 3 ml of water. More water was added and diluted with ether. Then the organic layer was separated, washed with water, and brine successively dried with anhydrous magnesium sulfate and concentrated to give the product (58 mg, 80% based on the compound 5). MP : 180-182°C. The product was acetylated by pyridine and acetic anhydride as in the literature (11) to give the acetate.

MP : 148-149°C (lit. 151-2.5 from aq. acetone, 148-50 from methanol) ; $^1H$ NMR ($CDCl_3$) $\delta$0.8 (s, 3H, axial $CH_3$), 0.9 (s, 3H, axial $CH_3$), 2.0 (s, 3H, acetate), 2.2 (s, 3H, 21-$CH_3$), 5.0 (m, 1H, 3β-H), 5.3 (m, 1H, 11-H), 6.76 (m, 1H, 16-H) ; IR (KBr) $\nu$2990-2940 $cm^{-1}$ (aliphatic C-H), 1735 (acetate C=O), 1670 (C-20 C=O), 1595 (conjugate C=C), 825 (C=C).

## RESULTS AND DISCUSSION

With m-iodobenzoic acid, triphenylphosphine, and diethyl azodicarboxylate (DEAD), the compound 2 underwent a convenient inversion-esterification (9) to produce the ester 3. Molecular model suggested that 3α, 5α configuration is suitable for remote chlorination at C-9.

The compound 3 was photolyzed with the 300W Hanovia medium-pressure lamp to give ester 4 as a major product. Aromatic proton peaks are broadened and C-19 angular methyl protons show a signal slightly shifted downfield in the $^1$H NMR spectrum of the major product 4. $^{13}$C NMR spectra of the ester 3 and the major product 4 show many differences between them. The former shows a C-9 peak at 54.4 ppm but the latter shows a signal shifted considerably downfield at 99.5 ppm. The chemical shift of nieghboring carbons to C-9 also vary. Compared with the data given in the literature (4) for the similarly chlorinated 3α-cholestanol, the spectral data can prove the major product 4 to be a chlorinated compound at C-9.

The functionalized product 4 was directly saponified and dehydrohalogenated by methanolic potassium hydroxide to afford the unsaturated steroidal alcohol 5. The yield of the olefinic compound 5 by photolysis was 66% whereas the yield of the compound 5 by using sulfuryl chloride was 60%. It should be noted that such a preparative method is the first synthesis of the steroid 5 successfully attempted. Furthermore, the photolysis process is of low cost compared to the one by fermentation.

The compound 5 was then converted to the corresponding dienone 6 by $TiCl_3$-$LiAlH_4$ as described in the literature (10,11).

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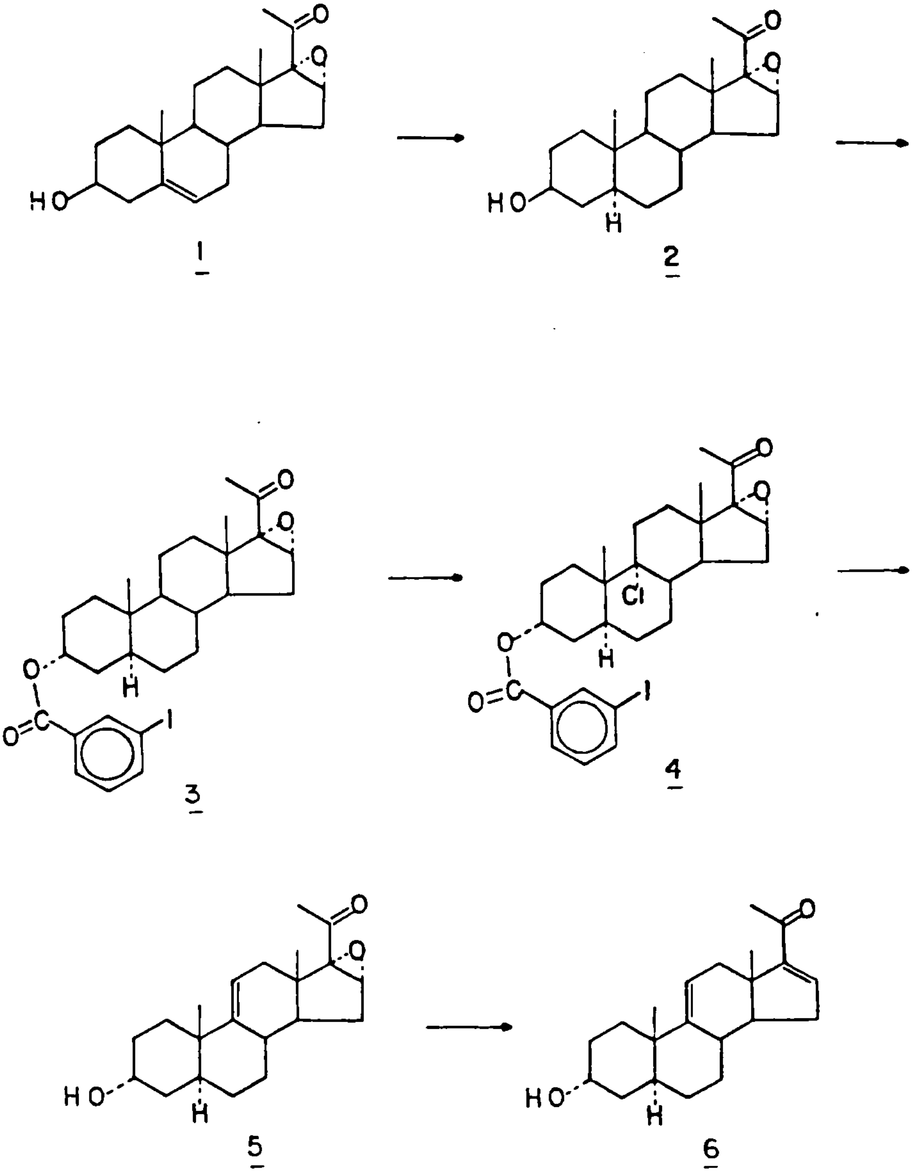
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