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A Simple Efficient Process for the Synthesis of 16-Dehydropregnenolone Acetate (16-DPA) – A Key Steroid Drug Intermediate from Diosgenin

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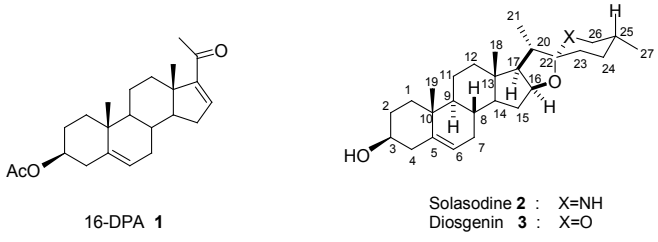
Abstract

A three step efficient synthesis for the commercial production of 16-dehydropregnenolone acetate (16-DPA)- a potent steroid drug intermediate, from diosgenin, in an overall yield of 60%, has been developed, through generation of acetylonium ion ($CH_3C^+=O$) in optimum concentration from acetic anhydride using in the molar ratio of 1:3.5(diosgenin:Ac_2O) in a pressure reactor in a medium of a hydrocarbon solvent at a temperature in the range of 200°C with the corresponding in-built pressure of 5-6kg/cm² (Step 1) and an ultra sound irradiated (35 KHz) oxidation reaction (Step 2).

Keywords: Diosgenin; 16-dehydropregnenolone acetate (16-DPA); Steroid drug intermediate; Corticosteroids; Soft corticosteroids; Steroid-peptide conjugates; Hormones; Acetylonium ion

Introduction

Steroids play a vital role in human physiology and medicine. Although steroidal drugs have several side effects, these are still regarded as potent life saving drugs. Currently work on the synthesis of the modified steroid molecules to minimize their side effects in our body is gaining considerable importance. Development of such soft corticosteroids having less systemic side effects is therefore becoming important in steroid drug industry [1-3]. It is pertinent to note that, most of these steroid drugs including corticosteroids or soft corticosteroids, anabolic steroids, sex hormones and oral contraceptives etc. are synthesized from 16-dehydropregnenolone acetate (16-DPA) 1, barring a few which are obtained by total synthesis. The plant origin compounds solasodine 2 and its oxygen analogue diosgenin 3 (Figure 1) are the two main ingredients from which 16-DPA is generally synthesized [4-15]. Due to the favorable climatic condition of North East region of India, diosgenin yielding *dioscorea* species of plants, *viz*., *D. compositae* and *D. floribunda* grow abundantly in the region which led us to investigate commercial exploitation of these plants through large scale production of 16-DPA starting from diosgenin. Here we report a commercially viable three-step synthesis of 16-DPA 1 (Figure 2) starting from diosgenin 3 applying innovative synthetic strategies which involves the use of neither any high boiling solvents nor any toxic and costly catalyst in the crucial first step of acetolysis [16,17]. The hydrocarbon solvent used (commercial xylene: mixture of o-, p- & m-isomers: bp.138.5°C) in the step was also recovered fully for subsequent use.



16-DPA **1**

Solasodine **2** : X=NH
Diosgenin **3** : X=O

Figure 1:

Synthesis of 16-dehydropregnenolone acetate (16-DPA) 1 from solasodine 2 and diosgenin 3 has been reported by several workers in various literatures [4-15]. For the conversion of this spirostanic compound, diosgenin (22-iso-5-spirostane-3β-ol) into 16-DPA (3β-acetoxy-pregn-5,16-diene-20-one) 1, it must be isomerized first to furostenol derivative pseudodiosgenin diacetate (3β,26-diacetoxy-furosta-5,20(22)- diene) 4, through acetolysis (Figure 2), which on subsequent oxidation of the 20(22) enolic double bond followed by hydrolytic degradation furnishes 16-DPA [4-15]. Chemical transformations of spirostanic compounds also find importance towards the synthesis of plant growth promoting substances including ecdysteroids and some furostenols having significant phytotoxicity [18]. Marker's degradation is the earliest known process for converting diosgenin into 16-DPA [5-7].

As mentioned earlier, acetolysis or isomerization (Step 1) is the crucial step in the process to get high yield of the final product. The condition of the isomerization reaction of diosgenin 3 as reported by Marker et al. involved the direct use of acetic anhydride at an elevated temperature and pressure in a sealed tube, while the use of high boiling anhydrides as solvent led to lower yield of the isomerized product pseudodiosgenin diacetate 4 [5-7].

Afterwards several modifications have been made including catalytic conversion to effect this isomerization process [9-13]. Gould et al. [9] observed that the conversion could be achieved at the boiling point of acetic anhydride in the presence of acetyl chloride or anhydrous $AlCl_3$. Similar conditions using acetyl chloride also have

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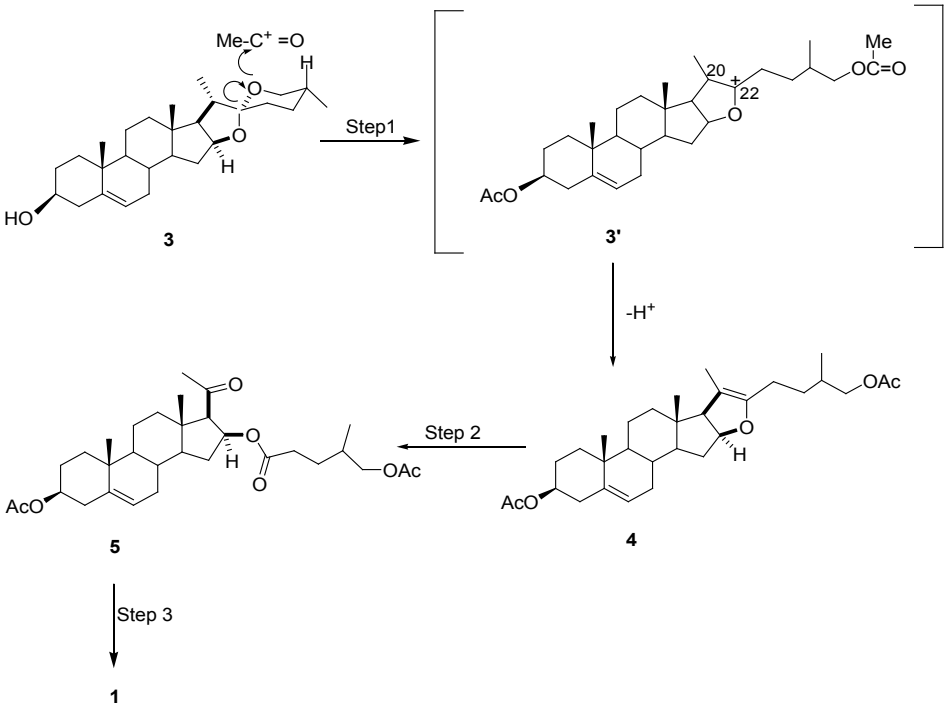

Figure 2: Reagents and Conditions: Step 1: Ac_2O, xylene, 200°C, 5-6Kg/cm^2, 91%; Step 2: CrO_3, CH_3COOH- H_2O, 0-15°C, sonication, 70%; Step 3: CH_3COOH, reflux, 90%.

been used for the transformation of $\Delta^{4,6}$-22-isospirostadiene-3-one to the corresponding 3β-acetoxy-3,5,7- triene [11].

The poor yield of the desired isomerized product pseudosapogenine diacetate (33-40%) is the main disadvantage of all these methods [5-7].To improve the yield of the isomerized product for its eventual conversion to this central steroid drug intermediate,16-DPA and its relatives several other workers have reported the isomerization of spirostanic compounds to furostenols in 70-84% yield by using various catalysts like pyridine and ammonium chloride, pyridinium hydrochloride, anhydrous titanium tetrachloride or aluminum chloride or p-toluenesulphonic acid etc. and also through the application of high boiling solvent like n-octanoic acid in the process [9-13]. Earlier we reported the application of magnesium iodide-diethyl ether and chlorotrimethylsilane as catalysts in this isomerization process giving fairly good yield of the isomerized product 4 [19]. For commercial production of 16-DPA from diosgenin, the use of both high boiling solvents and toxic & costly catalysts are not desirable and hence alternative methods to eliminate all these drawbacks are still sought after in steroid drug industry.

Results and Discussions

We argued that the isomerization of the isospirostane (diosgenin) 3 to furostenol (pseudodiosgenin diacetate) 4 is possibly due to the attack on the nucleophillic pyran oxygen of 3, by the highly reactive acetylonium ion (Me-C$^+$=O) generated *in situ* from acetic anhydride under different reaction conditions [19-23]. We further argued that in the case of Marker's degradation, the low yield of isomerized product 4 might be due to extensive decomposition of the starting material because of the indiscriminate formation of this highly reactive species under reaction condition, viz., heating diosgenin directly with acetic anhydride at 200°C in a sealed tube [5-7]. Considering this fact, we hit the idea of generating this acetylonium ion in an optimum concentration by heating diosgenin in a pressure reactor dissolving it in commercial grade of xylene containing low concentration of acetic anhydride (diosgenin: Ac_2O:: 1mol:3.5mol) at a temperature of 200°C to react selectively on the pyran oxygen of diosgenin 3 with concomitant acetylation of 3β- hydroxyl group [24] [Figure 1]. The opening of the spiroketal ring by acetylonium ion forms a carbonium ion at C-22 [intermediate 3] which undergoes favorable proton elimination from C-20 position to furnish the desired compound 4.The heating was continued for 10 h during which time the in-built pressure inside the reactor reached to a magnitude of around 5-6 kg/cm^2. Under this condition the yield of pseudodiosgenin diacetate 4 from diosgenin 3 was found to be more than 90% in a very clean reaction, a method so far not reported by any worker. In its ^{1}H NMR spectrum, the generation of the C-20(22) double bond was indicated by the presence of a singlet for the methyl on the double bond at 1.7 ppm while a broad singlet at 2.1ppm was appeared for C-3 & C-26 acetate protons. IR spectrum displayed the characteristic absorption band at 1735 cm^{-1} for the acetate functionalities. ^{13}C NMR and microanalyses were in conformity with its molecular structure and formula $C_{31}H_{46}O_5$. It is pertinent to note that the reaction proceeded without the aid of any catalyst. Moreover, the low cost aromatic hydrocarbon solvent i.e. xylene (commercial) used in the process could be recovered fully for reuse.

Oxidation of pseudodiosgenin diacetate 4 to Diosone 5 (Step 2) was performed by using chromium trioxide in a biphasic solvent medium containing acetic acid and water at a temperature in the range of (-) 10 to (+) 10°C and under ultrasound irradiation at a frequency in the range of 30-40 KHz [25]. Application of ultrasound irradiation reduced the amount of the oxidizing agent by about 40-60% than that required

under normal oxidation condition. In its ^{1}H NMR spectrum, the compound 5 exhibited the newly generated C-20 methyl ketone signal at 2.2 ppm as a singlet. IR spectrum exhibited a band at 1715 cm^{-1} for this newly generated carbonyl functionality. ^{13}C NMR & microanalyses were in conformity with its molecular structure and formula $C_{31}H_{46}O_{7}$. Although some literature reveal the application of other oxidant like hydrogen peroxide in presence of catalyst/phase transfer catalysts etc [14]. CrO_3 is still regarded as an oxidant of choice, because of its high efficacy and low cost. The main advantage of carrying out oxidation under ultrasound irradiation is to minimize of the amount of chromium trioxide by about 40-60% as compared to normal oxidation process. Besides, the catalysts used with other oxidants could not be recovered for reuse making the process non-economical. Conversion of Cr (VI) to Cr (III) state by simply alcohol addition is another advantage of this oxidant for easy disposal through proper effluent treatment. Further work on complete replacement of chromium reagent in the oxidation process is in progress.

Hydrolytic degradation of diosone 5 to the final product 16-DPA 1 (Step 3) was easily achieved by refluxing it in acetic acid in almost quantitative yield. In its NMR spectrum the compound displayed C-16 olefinic proton at 6.4 ppm as a singlet and the other C-6 olefinic proton appeared at 5.3 ppm as a multiplet while C-3 acetate and C-20 methyl ketone protons appeared as two singlets at 2.0 and 2.2 ppm respectively. In its IR spectrum the band for α,β-unsaturated carbonyl system at C-20 appeared at 1675cm^{-1}. ^{13}C NMR and microanalyses were in conformity with its molecular structure and formula $C_{23}H_{32}O_{3}$. Although the same conversion may be effected by heating with a base such as sodium bicarbonate, sodium carbonate, potassium carbonate, potassium bicarbonate or other similar bases in an alcoholic solvent, use of acetic acid was preferred because of the simplicity of the operation and full recovery of acetic acid for subsequent use. In the process, the overall yield of 16-DPA 1 from diosgenin 3 was found to be more than 60% based on the 85-90% purity of commercial diosgenin.

The whole process was optimized by doing five experiments at 50gm per batch level giving consistent results for its eventual scaling-up to 3 kg per batch level at the pilot plant facilities [27,28] of the institute for commercialization of the process. Table 1 represents the mean, variance and standard deviation on the yield of 16-DPA (%) from diosgenin in 50 gm scale from five experiments while Table 2 represents same for the crop yield (in gm) of 16-DPA from diosgenin in 3 kg per batch level in three experiments.

The comparison of the present process with the existing processes is given in Table 3 which reflects the superiority of the present process with the existing ones.

No of Expts.	Yield of 16-DPA (%)	Mean (%)	Variance	Standard Deviation (%)
Exp. 1	61.2			
Exp. 2	58.3			
Exp. 3	64.4	61.2	4.964	2.228
Exp. 4	59.3			
Exp. 5	62.8			

Table 1: Percentage of Mean, Variance & Standard Deviation on the yield of 16-DPA (%) from Diosgenin in 50 gm scale.

No of Sets	Crop yield (in gm)	Mean (gm)	Variant	Standard Deviation (gm)
1`	1st crop: 911			
2	1st crop: 890	900.667	73.556	8.576
3	1st crop: 901			
1`	2nd crop: 342			
2	2nd crop: 403	372.00	620.667	24.913
3	2nd crop: 371			
1`	3rd crop: 131			
2	3rd crop: 138	132.667	14.889	3.859
3	3rd crop: 129			

Table 2: Variant & Deviation in crop yield (in gm) of 16-DPA from diosgenin in 3 kg per batch level.

Materials and Methods

General methods

Melting points were determined with an electro thermal melting point apparatus and are uncorrected. All the chemicals used were of reagent grade of E. Merck and were used without further purification. The progress of each of the reaction was monitored on Merck thin layer chromatography silica gel 60 F_{254}. IR spectra were recorded with a Perkin-Elmer model 2000 series FT-IR spectrometer for solutions in chloroform. Infrared absorbance is reported in reciprocal centimeters (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX (300MHz) spectrometer with tetramethylsilane (TMS) as internal standard on ppm scale(δ), Multiplicity of the resonance peaks are indicated as singlet(s), broad singlet(bs), doublet(d), triplet(t), quartet (q) and multiplet (m). Mass spectrometric analysis was performed by positive mode electro spray ionization with Bruker Esquire 3000 LC-MS instrument. Elemental analysis was carried out in Varian CHN analyzer.

Step 1: Acetolysis (isomerization) of diosgenin 3 to pseudodiosgenin diacetate 4

50 g (0.12 mol) of diosgenin **3** was charged with 40 ml of acetic anhydride (0.4 mol) and 150 ml of xylene in a pressure reactor vessel [24] and heating was started while stirring till the temperature of 250°C and corresponding pressure of 4-6 kg/cm^2 were reached. The reaction was carried for a period of 10 hours after attainment of desired temperature of 250°C. Heating was stopped and was allowed to cool under stirring for a period of one hour and the product was discharged through the discharge tube under positive pressure as the temperature came down to below 100°C. TLC analysis of the sample was carried out which showed the formation of only one major product. Solvent removal was done with a rotary vacuum evaporator under reduced pressure. The recovered solvent was kept for recycle. After the removal of the last traces of the solvent, solid material thus obtained was purified by crystallization from acetone to get pseudodiosgenin diacetate **4** in pure form. Yield: 55g as solid (91%).

Sl. No.	Items	Existing Process	Proposed Process	Comments
1	Raw materials	Diosgenin, Acetic anhydride, Catalysts like Pyridine hydrochloride, Titanium tetrachloride and anhydride Aluminium chloride etc.	Diosgenin, Acetic anhydride, commercial grade Xylene	Methods used by Glaxo and other companies are very old and based on the technology of 1952 but the present technology is developed through modern technology. In the present process acetic anhydride which is a reactant has been used not in large excess along with an aromatic hydrocarbon solvent to give very high yield of pseudodiosgenin acetate. The reaction being homogeneous, its easy to operate. Large excess of acetic anhydride lowers the yield of the above product.
	Catalyst i)Cost			Simple but efficient & cost effective process
	ii) Toxicity			In the present process the use of expensive and environmentally hazardous toxic catalysts has been completely eliminated.
2		Expensive: Pyridine hydrochloride : $200/Kg Titanium tetrachloride:$200/10gm Anhydrous Aluminum Chloride All these catalysts are environmentally hazardous, toxic and corrosive	No catalyst has been used	
	iii) Recovery & cost of catalysts	Catalysts used are not recoverable		
3	Solvent used	High boiling solvent like n-octanoic acid (b.p. 237^{0}C) has been used by Glaxo	Medium boiling low cost aromatic hydrocarbon (b.p.< 150^{0}C) has been used	Doesn't arise In the present process, no high boiling and toxic solvent like n-octanoic acid (corrosive nature) has been used. Besides the recovery of such solvent would be high energy intensive.
4	Yield of pseudodiosgenin diacetate(2)		92%	
5	Oxidation process	Max. 87% (using n-octanoic acid)		Yield under present process is better without using such high boiling solvent
6.				The oxidation has been done in a non toxic solvent which is recoverable
7.	Yield of diosone(3)	Oxidant in acetic acid	Oxidant in solvent	
8	Yield of 16-DPA(over all)			The better yield
		55%	70-75%	Better process
	Effluent generation			
		42-56%	55-62%	
		Step 1: Toxic effluent	Step 1: nil	In the present process the use of ultra-sound in the oxidation step 2 reduces the amount of chromium reagent by about 30-40% which would minimize amount of chromium salts in the effluent.
		Step 2: Chromium salts	Step 2: Chromium salts	

Table 3: Comparison of the present process with the existing processes.

Mp: 98^0 C (lit.[19] mp. 97-98^0);

IR ($CHCl_3$): ν =1735(broad), 1375, 1250, 1025 cm^{-1}

^{1}H NMR(300MHz): δ=0.81(s, 3H, H-18), 0.97(d,3H,J=6.3Hz, H-27), 1.2(s,3H,H-19), 1.7(s,3H,H-21), 2.1(bs, 6H, acetate protons), 3.9(d,2H, J=4.1Hz, H-26), 4.6 (m,2H, H-3 & H-16), 5.4(m,1H, H-6) ppm;

^{13}C NMR : δ= 34.2; 35.1; 78.6(C-3); 39.5; 155.0(C-5); 142.3(C-6); 32.0; 29.0; 46.2; 35.8; 20.9; 39.5; 40.5; 55.4; 34.7; 80.6(C-16); 62.0(C-17); 16.5; 15.2; 41.7; 14.5; 109.3(C-22); 29.4; 28.2; 30.9; 66.9(C-26); 17.1; 21.4(C-CH_3COO); 178.2(C-OCOCH_3) ppm; Mass spectrum (m/z) : 498 (M^+),

Anal. Calcd. for C_{31} H_{46} O_5: C, 74.66; H, 9.3; Found: C, 74.34; H, 9.27;

Step 2: Oxidation of pseudodiosgenin diacetate 4 to Diosone 5:

Oxidation under normal condition

Preparation of the oxidant solution:

25 g (0.25 mol) of chromium trioxide (CrO_3) was dissolved in 25 ml of water and 10 ml of glacial acetic acid to get a clean solution which was precooled to 0-5°C.

Addition of oxidant solution:

50 g of Compound 4 (0.1 mol) was dissolved in 100 ml of dichloromethane and 100 ml of glacial acetic acid and 25 ml of water. The mixture was cooled to 0-5°C and the oxidant solution prepared as above was added to it drop wise keeping the temperature of the reaction mixture below 5-7°C till the addition was over. After the addition of the oxidant solution was complete, cooling was discontinued and the temperature of the reaction medium was allowed to rise up to 15°C and stirred at that temperature for a period of another 25 minutes. When the TLC indicated the completion of the reaction, a solution 5 g of sodium chloride in water (200 ml) and methanol (10 ml) were added and the stirring was continued for further 20 minutes.

Keto ester diosone 5 thus formed was extracted from the reaction mixture with 1,2-dichloroethane. The organic layer after separation was subjected to distillation under reduced pressure to recover the solvent. A gummy residue was obtained which was purified by column chromatography using petroleum ether and ethyl acetate as eluent to get pure diosone **5**. Yield: 37.5 g as gum (70%).

IR ($CHCl_3$): ν = 1735(broad), 1715, 1375, 1250, 1100 cm^{-1}

^1H NMR (300 MHz) : δ = 0.81(s,3H, H-18), 0.97(d, 3H,J=6.3Hz, H-27), 1.2(s, 3H,H-19), 2.0(bs, 6H, acetate protons), 2.2 (s, 3H, H-21), 3.9(d,2H, J=4.1Hz, H-26), 4.6 (m,2H, H-3 & H-16), 5.4(m,1H, H-6) ppm;

^{13}C NMR : δ = 34.2; 35.1; 78.6(C-3); 39.5; 155.0(C-5); 142.3(C-6); 32.0; 29.0;46.2; 35.4; 20.9; 39.5; 40.5; 55.4; 34.7; 82.6(C-16); 62.0(C-17); 16.5; 15.2; 217(C-20); 19.2; 173.5(C-22); 29.6; 28.7; 30.3; 71.3(C-26); 177.0(C-$OCOCH_3$); 21.4(C-CH_3COO) ppm.

Mass spectrum (m/z): 530 (M^+).

Anal. Calcd. for $C_{31}H_{46}O_7$: C, 72.06; H, 9.36; Found: C, 72.10; H,9.26;

Oxidation under ultra sound irradiation

Preparation of the oxidant solution

12.5 g (0.125 mol) of chromium trioxide (CrO_3) was dissolved in 25 ml of water and 10 ml of glacial acetic acid to get a clean solution which was precooled to 0-5°C.

Addition of oxidant solution:

50 g (0.1 mol) of compound 4 was dissolved in 100 ml of dichloroethane and 100 ml of glacial acetic acid and 25 ml of water. The mixture was cooled to 0-5°C and the oxidant solution prepared as above was added to it drop wise keeping the temperature of the reaction mixture below 5-7°C till the addition was over. The reaction mixture was sonicated at 35 KHz from the time of addition of chromium trioxide solution. After the addition of the oxidant solution was complete, cooling was discontinued and the temperature of the reaction medium was allowed to rise up to 15°C and stirred at that temperature for a period of another 25 minutes still under sonication. The rest of the operation was same as described in the case of oxidation under normal condition as above.

IR, NMR and Mass spectra of the product were superimposable with those of the compound **5** isolated under normal oxidation condition.

Yield: 38 g as gum (70%).

1.2.1.7. Step 3: Hydrolytic Degradation of diosone 5 to 16-DPA 1:

50 g (0.94 mol) of diosone 5 was allowed to reflux directly in 200 ml of glacial acetic acid for a period of 2 hr. The reaction was monitored on TLC. After completion of the reaction acetic acid was recovered by distilling under reduced pressure with a rotary evaporator. The residue was thoroughly washed with cold water and was subjected to exhaustive extraction with petroleum ether (bp. 60-80°C) when a yellow solution of 16-DPA 1 was obtained leaving a black residue. The yellow solution after distillation gave a crude yellow product which on recrystalisation from ethanol (up to 3 crops can be collected) furnished creamy white crystals of 16-DPA 1. The structure of 16-DPA 1 was confirmed by mixed melting point determination and by comparison of ^1H & ^{13}C NMR spectral data (recorded for both authentic & present 16-DPA) with those of the authentic material supplied by M/S Glaxo-India Ltd., Mumbai.

Yield: 30g as solid (90%).

Mp: 172°C (lit.[3-6,9] mp 169-175°);

$[\alpha]_D$: (-) 39.4° (c=1.0, $CHCl_3$) [lit [6,9] $[\alpha]_{D:}$ -37.7to -41.2°(c=1% in $CHCl_3$)];

IR ($CHCl_3$): ν = 1735, 1675, 1375, 1250, 1140, 950 cm^{-1}

^1H NMR (300MHz): δ= 1.0 (s, 3H, H-18), 1.2 (s,3H, H-19), 2.0 (s,3H, acetate protons), 2.2 (s, 3H, H-21), 4.6 (m, 1H, H-3), 5.4 (m, 1H, H-6), 6.4 (m, 1H, H-16) ppm;

^{13}C NMR : δ = 34.2; 35.1; 78.6(C-3); 39.5; 155.0(C-5); 142.3(C-6); 32.0; 29.0; 46.2; 35.4; 20.9; 39.5; 40.5; 55.4; 34.7; 122.9(C-16); 144.5(C-17); 16.7; 15.2; 178.9(C-$OCOCH_3$); 170.5(C-20); 21.3 ppm.

Mass spectrum (m/z): 356(M^+). Anal.Calcd.for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05;

Found: C, 77.41; H, 9.03;

Scaling-up experiments with 3 kg batch level:

Step 1: Acetolysis (isomerization) of diosgenin 3 to pseudodiosgenin diacetate 4:

3 kg of diosgenin 3 (88% pure by GLC) was charged with 2.4 L of Acetic anhydride and 9.0 L of xylene in the Reactor `A' [27]. and heating was started through circulation of hot oil while stirring till the temperature of 250°C and corresponding pressure of 4-6 kg/cm^2 were reached. The reaction was carried for a period of 10 hours after attainment of desired temperature of 250°C. Heating was stopped and was allowed to cool under stirring for a period of one hour and the product was discharged through the discharge tube under positive pressure as the temperature came down to below 100°C. TLC analysis of the sample was carried out which showed the formation of only one major product. Solvent removal was done with a 10 L capacity Buchi Rotavapor under reduced pressure. The recovered solvent was kept for recycle. After the removal of the last traces of

the solvent, solid material thus obtained was directly subjected to the next step of oxidation (Step 2). A small amount of material was purified by preparative TLC (Pet.ether: EtOAc:: 1:12) to get pseudodiosgenin diacetate 4 in pure form. The product was directly compared with that obtained by laboratory scale experiment (TLC, IR, NMR & Mass spectra are superimposable).

Step 2: Oxidation of pseudodiosgenin diacetate 4 to Diosone 5:

Oxidation under normal condition

Preparation of the oxidant solution:

1.5 Kg of chromium trioxide (CrO_3) was dissolved in 1.5 L of water and 600ml of glacial acetic acid to get a clean solution which was precooled to 0-5°C.

Addition of oxidant solution:

Entire amount of pseudodiosgenin diacetate 4 obtained in Step 1 was transferred to the Reactor `B' along with 6.5L of dichloroethane, 6.5L of glacial acetic acid and 1.5 L of water [28]. The mixture was cooled to 0-5°C by circulating ice cold water through outer jacket of the reactor. The oxidant solution prepared as above was added to it drop wise keeping the temperature of the reaction mixture below 5-7°C till the addition was over. After the addition of the oxidant solution was complete, cooling was discontinued and the temperature of the reaction medium was allowed to rise up to 15°C and stirred at that temperature for a period of another 30 minutes. A solution 300 g of sodium chloride in water (10 L) and methanol (500 ml) were added and the stirring was continued for further 30 minutes.

Keto ester diosone 5 thus formed was extracted with 1,2-dichloroethane (10L) by transferring the material to a separating unit (a 7 ft long glass column having a diameter measuring 10 inches). The organic layer after separation was subjected to distillation under reduced pressure using a rotavapor as described earlier to recover the solvent. A gummy residue thus obtained was directly subjected to the next step of hydrolytic degradation (Step 3). A small amount of the product was purified by preparative TLC (Pet.ether:EtOAc::1:4) to get the keto ester 5 in pure form. The product was directly compared with that obtained in laboratory scale experiment (TLC, IR, NMR & Mass spectra were superimposable).

1.3.3. Step 3: Hydrolytic Degradation of diosone 5 to 16-DPA 1

Crude diosone 5 obtained in Step 2 was dissolved in 10 L of commercial grade acetic acid and was transferred to the Reactor `A' [27]. The reaction mixture was heated to reflux by circulating hot oil through the outer jacket of the reactor for a period of 3 hrs. The reaction mixture was cooled by stopping heating and acetic acid was recovered through distillation under reduced pressure using a rotavapor for reuse. The residue was thoroughly washed with cold water and was subjected to exhaustive extraction with 7L of petroleum ether (bp.60-80°C) when a yellow solution containing 16-DPA 1 was obtained leaving a black residue. The yellow solution after distillation under reduced pressure furnished a crude yellow product which on recrystallization from ethanol furnished creamy white crystals of 16-DPA 1. From mother liquor another 2 crops of pure 16-DPA could be collected.

First crop: 911 gms (98% purity by GLC).

Second crop: 341 gms (95% purity by GLC).

Third crop: 130 gms (92% purity by GLC).

Overall yield > 60% (based on 85-90% purity of commercial diosgenin).

The product obtained was directly compared with 16-DPA obtained by laboratory scale experiment (TLC, IR, NMR & Mass spectra were superimposable). Mixed melting point remained undepressed.

Conclusion

The present work provides a simple efficient way to synthesize 16-DPA from diosgenin. 16-DPA is still regarded as a potent intermediate for the synthesis of various life saving steroidal drugs and hormones including steroid- peptide conjugates having unique biological properties [26]. Other diosgenin related sapogenins, *viz*., sarsasapogenin etc. could also be converted to the relatives of 16-DPA using same route as reported here. Further Step 2 and Step 3 (Figure 2) could be performed in the same vessel after completely decomposing the excess oxidant with alcohol. Economic viability is also another advantage of the process to have a high potential for its commercial production.

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24. Pressure reactor: Make: Berghof (with attached pressure gauge & temperature meter), Eningen, Germany: Art No. 570014, Serial No.86, 265, 12, Input: 220V, 50Hz, 1800 W

25. Ultrasonic Bath: Model: Powersonic 405 Bath Size (mm) : 300x155x150D Power output: 350W

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27. Reactor `A' for Acetolysis (Step 1): 25 L capacity SS Reactor Vessel with an outer Jacket for hot oil circulation and Stirrer. Mak.

28. Reactor `B' for Oxidation (Step 2):50 L capacity Glass Lined Reactor Vessel with an outer Jacket for cold water circulation and Stirrer: Make : Gujrat Machinery Manufacturing Ltd. India.