

RESIN CATALYSED ENE REACTION  
ON 3 $\beta$ -TOLUENE-p-SULFONOXY-(Z)-PREGNA-5,17(20)-DIENE : SYNTHESIS  
OF (20S)-6 $\beta$ -METHOXY-3 $\alpha$ ,5-CYCLO-5 $\alpha$ -PREGNANE-20-CARBOXYALDEHYDE<sup>+</sup>

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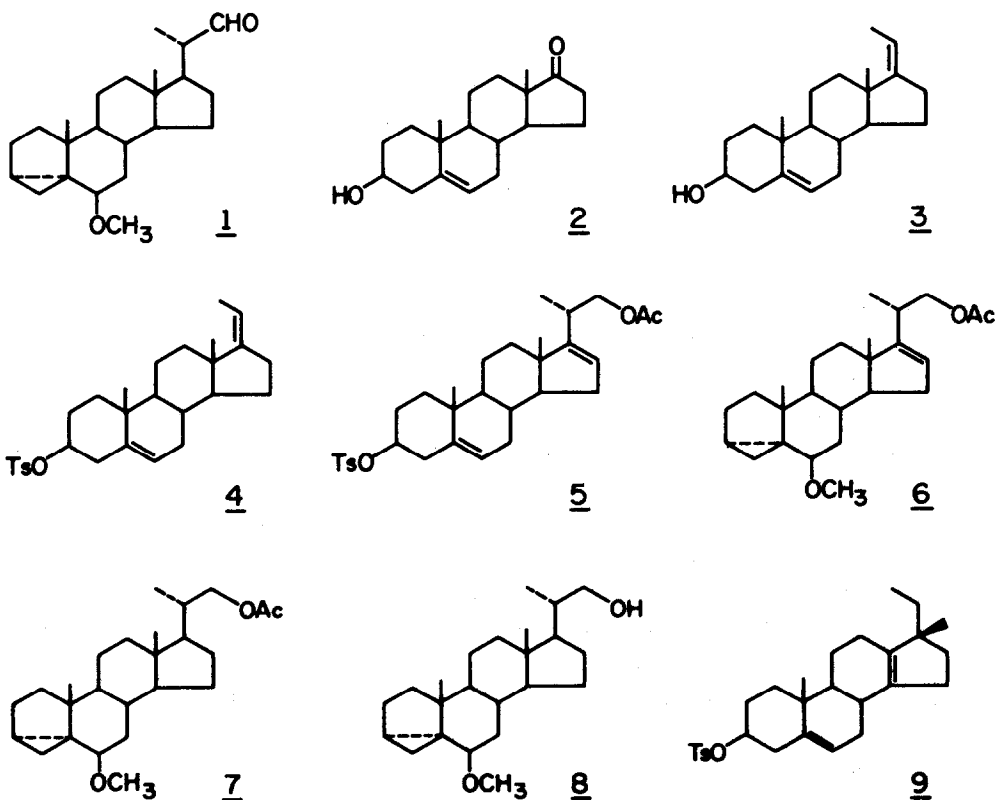
**Abstract:** Conversion of 17-keto steroid 2 in to 17(Z) ethylidene steroid 3 was achieved in high yields using a modified procedure. Ene reaction on 4 with paraformaldehyde in presence of acetic anhydride using various cation exchange resins as catalyst afforded stereospecifically the C-22 acetate 5 in excellent yields. For the first time cation exchange resins have been used as catalysts in ene reaction. Compound 5 was converted to C-22 aldehyde 1 using simple reaction sequence.

In connection with the synthesis of brassinosteroids<sup>1</sup>, we were in need of (20S)-6 $\beta$ -methoxy-3 $\alpha$ ,5-cyclo-5 $\alpha$ -pregnane-20-carboxyaldehyde 1. The aldehyde 1 is also the starting material for the synthesis of a large number of biologically active products<sup>2-8</sup>. Compound 1 has been prepared from stigmasterol in 3 steps<sup>2-5</sup> in varying yields. Herein we wish to report a highly efficient alternative synthesis of this aldehyde 1, starting from 3 $\beta$ -hydroxyandrost-5-en-17-one 2 involving ene reaction with paraformaldehyde on substrate 4. The starting material 2 is readily available via microbial degradation<sup>9</sup> of abundant plant sterols.

The 17-keto steroid 2 was converted to (Z)-17(20)-ethylidene steroid 3 in 89% yield via the Wittig reaction using 2 equivalents of (C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>PCH<sub>2</sub>CH<sub>3</sub>I and simple work up procedure. Compound 3 was prepared earlier<sup>10</sup> using large excess of (C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>PCH<sub>2</sub>CH<sub>3</sub>Br (6 equivalents), prolonged reaction period and in lesser yield. Compound 3 on treatment with toluene-p-sulfonyl chloride in pyridine furnished the known tosylate 4 in 90% yield. This 4 was subjected to ene reaction with paraformaldehyde as an enophile using 10 mole percent of boron trifluoride etherate in the presence of acetic anhydride to afford a mixture of products from which the required known acetate 5 was isolated in 38% yield. In order to improve the yield of the acetate 5 we have carried out a comprehensive study of the ene reaction using various cation exchange resins and different Lewis acids as catalysts (Table). The use of cation

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exchange resin as a catalyst in the ene reaction has not been reported so far. Diene 4 when treated with paraformaldehyde using different concentrations of Amberlyst-15 (three conditions) in presence of acetic anhydride a mixture of 5 and Wagner-Meerwein rearrangement product 9 were isolated (Table). Structure 9 has been assigned from its spectral data and elemental analysis. Using Tulsion T-42 as a cation exchange resin and continuing the reaction for 20 hrs, the resin was filtered and the reaction mixture was treated with pyridine followed by addition of acetic anhydride; the required acetate 5 was isolated in excellent yield. The filtered catalyst was reused after activation. In a similar manner three more cation exchange resins have been used and the results are listed in the table. The ene reaction carried out using cation exchange resins, stereospecifically generates the natural configuration at C-20. This was confirmed by converting the acetate 5 to the known <sup>2-5</sup> aldehyde 1, having (S)-configuration at C-20 and also by comparison of the spectral data and mixture melting point of 5 with an authentic compound 5 prepared according to earlier <sup>11</sup> report. When various Lewis acids were used as catalysts e.g. AlCl<sub>3</sub>, BF<sub>3</sub>.Et<sub>2</sub>O and SnCl<sub>4</sub> the acetate 5 was isolated in 78 to 95% yields by using the quenching procedure C (Table).



**Table**

**4** + paraformaldehyde + Ac<sub>2</sub>O + Lewis acid / Resin  $\xrightarrow{25 \text{ to } 30^\circ}$  **5** + **9**  
 3 equiv.<sup>a</sup>      2 equiv.

Entry	Lewis Acid /Resin	Conc. <sup>b</sup> parts/mole%	Time hrs.	Quenching <sup>c</sup> condition	% Yield <sup>d</sup>	
					Acetate <b>5</b>	Product <b>9</b>
1	Amberlyst <sup>e</sup> -15	5.0	0.2	A	36	41
		0.5	2.0	A	40	37
		0.3	30.0	A	75	15
2	Indion <sup>f</sup> -130	5.0	1.0	B	41	46
		0.5	7.0	B	47	40
3	Tulsion <sup>g</sup> T-42	5.0	20.0	B	96	-
4	Zeo-Karb <sup>h</sup> -225	5.0	35.0	B	93	-
5	Tulsion <sup>i</sup> CXO-18	5.0	48.0		No Reaction	
6	AlCl <sub>3</sub>	60.0	18.0	C	82	-
7	SnCl <sub>4</sub>	9.0	1.0	C	78	8
8	BF <sub>3</sub> .Et <sub>2</sub> O	10.0	5.0	D	38	-
		10.0	0.75	C	95	-

- a Calculation is based on assuming paraformaldehyde as a trimer.
- b Concentrations of Lewis acids are presented in mole % and concentrations of resins are presented in parts of resin per part of the substrate.
- c Quenching conditions :
- A Catalyst was filtered and the reaction mixture was treated with water and extracted with CH<sub>2</sub>Cl<sub>2</sub>.
- B Catalyst was filtered and to the reaction mixture were added 2 equivalents of pyridine and 1.5 equivalents of AC<sub>2</sub>O.
- C The reaction mixture was quenched with 2 equivalents of pyridine and treated with 1.5 equivalents of AC<sub>2</sub>O.
- D Reaction mixture was treated with water and worked up as usual.
- d Isolated yields, the products were identified by <sup>1</sup>H NMR spectra, mass spectra and elemental analysis.
- e Amberlyst-15 strong acid (20-50 mesh, Fluka AG).
- f Indion-130, strongly acidic cation exchanger [Ion exchange (India)Ltd., Bombay].
- g Tulsion,T-42(H), strongly acidic cation exchanger (Tulsi Fine Chemicals, Pune, India).
- h Zeo-karb-225, strongly acidic cation exchanger [Ion exchange (India) Ltd., Bombay].
- i Tulsion CXO-18, weakly acidic cation exchanger.

Lewis acid mediated ene reaction on (Z)-17(20)steroid olefin to generate natural configuration at C-20 is well documented<sup>11</sup>.

The 22-acetate 5 on treatment with pyridine in anhydrous methanol afforded the 3,5-cyclo compound 6 (89%). This on hydrogenation over Pd/C furnished the saturated compound 7 with natural configuration at C-17 (98%). Hydrolysis of 7 with methanolic KOH afforded the known<sup>12</sup> alcohol 8 (96%). Oxidation of 8 with pyridinium chlorochromate gave the known<sup>2-5</sup> aldehyde 1 in 95% yield. The conversion of 17-keto steroid 2 to the aldehyde 1 in seven steps is achieved in 59% overall yield. This constitutes a new route to this important aldehyde 1 from 17-keto steroid 2.

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