RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Synthesis of Some Novel Steroidal 1,2,4,5-Tetraoxanes

Archana M. Das*and Manash P. Hazarika

Natural Products Chemistry Division
CSIR-North East Institute of Science & Technology
Jorhat – 785 006, Assam, India.

ABSTRACT

A facile synthesis of A-ring manipulated C-20 methyl carboxylate steroid derivative with unsymmetrical dispiro 1,2,4,5 tetraoxanes has been focused herein via acid catalyzed cyclocondensation of bis-epidioxy ketone. To develop the novel stable unsymmetrical steroidal based spirocycloalkane 1,2,4,5 tetraoxane **8** starting from 3β-acetoxy – pregn -5(6), 16(17) – diene -20 –one (16-dehydropregnenolone acetate, ie. 16-DPA) **1** via metal-mediated halogenation as a key reaction.

Keywords : 16-dehydropregnenolone acetate, C-20 methyl carboxylate steroid, bis-epidioxy, spiroalkane, tetraoxane.

* Corresponding author :
Email : archanads2@gmail.com

1. Introduction

Tetroxanes are cyclic peroxides having considerable attention towards the clinical practice as an antimalarial and antimicrobial drug. Many literatures reported that tetroxanes have similar antimalarial mode of action compared to the naturally occurring peroxides such as artemisinin and its derivatives [1-3]. In the past few decades, chemists and researchers put their attention to develop the organic peroxides in the field of drug design due to certain representatives of these compounds exhibit antimalarial [4-9] and antitumor [10-14] activities. This has stimulated the development of several molecules of these types as depicted in various literatures. It is pertinent to note that, cyclic compounds like tetraoxanes and trioxanes are considered as the most promising synthetic peroxides having activities like antimalarial and antimicrobial. Some of which exhibit high antimalarial activity [15-18] comparae to the natural peroxide artemisinin, a potent antimalarial drug and antibacterial activity [19]. Based on the design of explosives of cyclic peroxides has been particular interest nowadays. Besides these, synthesis of unsymmetrical tetroxane has become one of the promising areas towards the development of antimalarial drugs [20]. Synthesis of peroxides (tetroxanes) are mainly based on the cyclocondensation reaction of ketones / aldehydes with steroids and its intermediates [13,20] or alicyclic gem-bishydroperoxides [21], aliphatic / alicyclic gembishydroperoxides [15,22] etc.

Malaria has been considered as a serious threat to the health and economic prosperity of the human race in recent year. It is estimated that approximately 300 million clinical cases were observed and more than 2.5 million people die from this disease each year. Due to resistance of the vector (Anopheles mosquito) to insecticides and ongoing spread of the drug-resistant strains of *Plasmodium falciparum* against chloroquine and

other clinically used drugs, exploration is going considerable interest worldwide for new effective anti-malarial drug development [23-25].

Symmetric tetraoxanes are limited in number and non-symmetric tetraoxanes would offer more opportunity for selective incorporation of various functional groups on the tetraoxanes scaffold. Several factors have been depends on the synthesis of 1,2,4,5 tetroxanes, like the structure of ketones, temperature, solvent, pH and the catalyst concentration of the substrate of the bis peroxides etc.

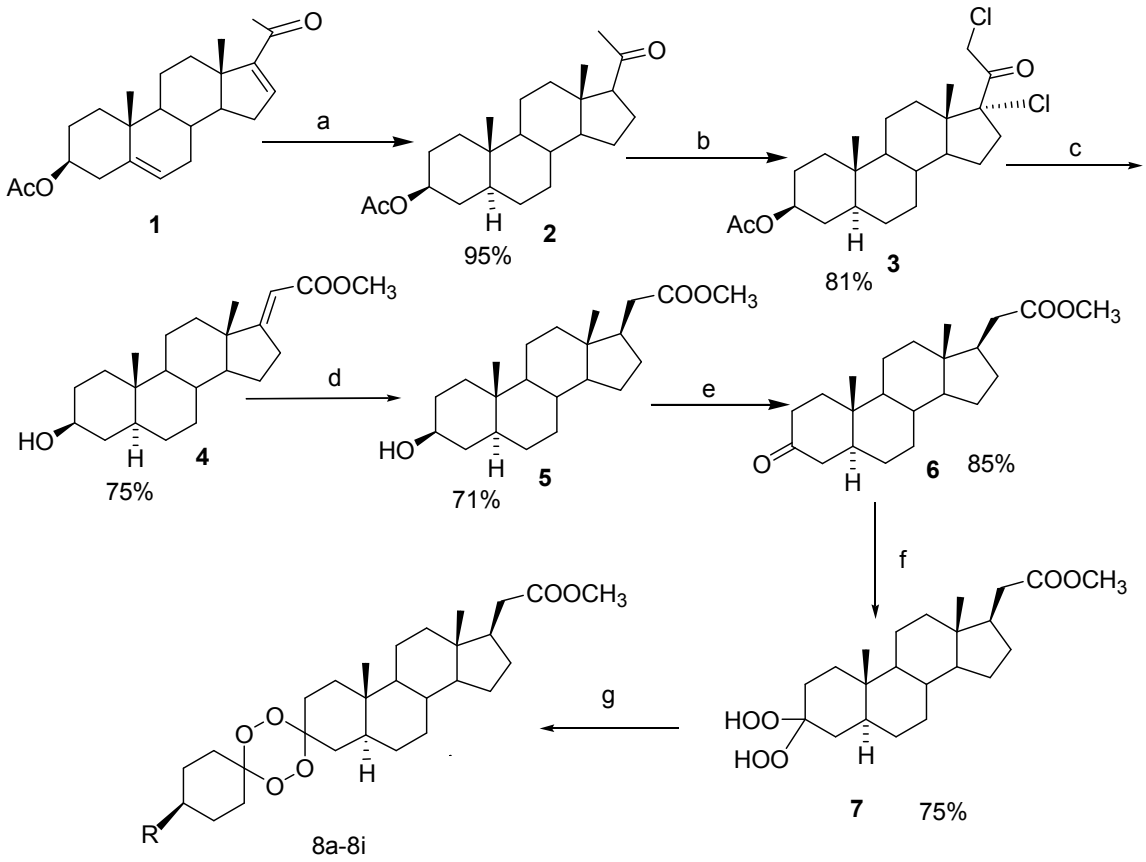
In continuation of our work on steroid transformations [26], we developed a potential method of metal mediated halogenation of 16-DPA and its relatives using the reagents like MnO_2-TMSCl-AcOH etc. This reaction has been utilized to introduce C-20 methyl carboxylate group in a steroid molecule [Scheme 1].

Our effort has been given to introduce spirocycloalkane 1,2,4,5 tetroxanes that possess significantly higher stability than that of their 1,2,4-trioxane or 1,2,4-trioxolane counterparts [27-28]. It is pertinent to note that, so far no reports on the tetroxane in pregnane-like structure are available except some of in cholestane like structure [14] only. In the synthetic route, we have utilized our metal mediated halogenation technique [26] to construct the C-20 methyl carboxylate side chain in D-ring and its derivatives and also minimize the side effect associated with this class of compounds, to make it soft drug like structure.

2. Results and Discussion

As depict in Scheme 1, 16-DPA was hydrogenated in presence of Pd-C to furnish the product **2** which was subjected to metal mediated helogenation reaction using MnO_2-TMSCl-AcOH system to furnish 17α, 21-dichloro 20-oxopregnane **3** in high yield. The

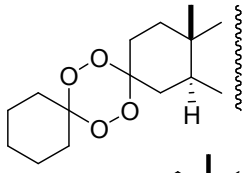
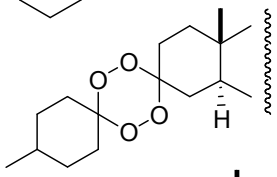
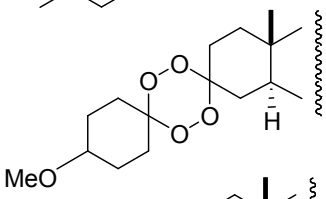
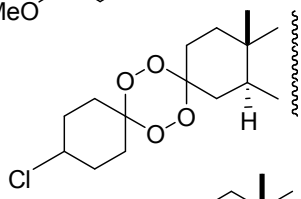
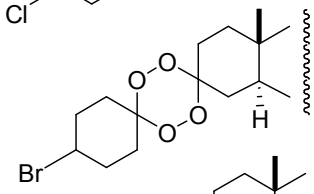
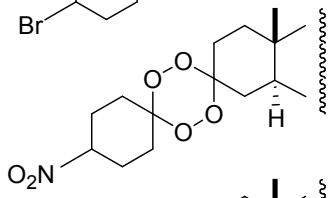
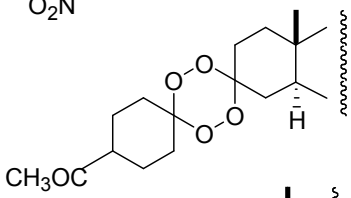
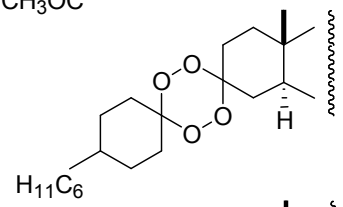
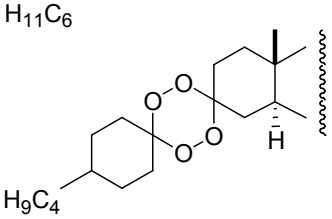
product was characterized by direct comparison with the authentic materials [26, 28-29]. This compound **3** on the treatment with alkaline methanolic solution to gave the 3β-hydroxy Favorskii rearrangement product **4** [30-31]. Catalytic hydrogenation of **4** in the presence of Pd/C provided the hydrogenated compound **5** in high yield. PCC oxidation of **5** in methylene chloride gave the corresponding 3-oxosteroid **6**. Conversion of the compound 3-oxoandrostan **6** to bishydroperoxy androstan **7** was carried out by using 30% H_2O_2 in acetonitrile at 0 ^{0}C [14] and the reaction **7** was carried out with cyclohexanone/substituted cyclohexanone in the presence of conc.H_2SO_4 in CH_3CN afforded the target compounds **8a-8i**.



8a : R = H
8b : R = 4-Me
8c : R = 4-MeO
8d R = 4-Cl
8e : R = 4-Br
8f : R = 4-NO_2
8g : R = -$COCH_3$
8h : R = -C_6H_{11}
8i : R = -C_4H_9

Scheme 1 : Synthetic route for the synthesis of 1,2,4,5-tetraoxane derivatives

Reagent and conditions used : (a) H_2, Pd/C (b)TMSCL, MnO_2, Acetic acid, r.t (c) Favorskii rearrangement (3% KOH, r.t) (d) H_2, Pd/C (e) PCC, CH_2Cl_2, r.t (f) 30% H_2O_2, CH_3CN, 0˚C (g) Cyclohexanone, CH_3CN, H_2SO_4, 0˚C.

Sl.No.	R	Products	Yield (%)
8a	R = H		67%
8b	R = 4-Me		59%
8c	R = 4-MeO		63%
8d	R = 4-Cl		61%
8e	R = 4-Br		56%
8f	R = 4-NO_2		62%
8g	R = -$COCH_3$		66%
8h	R = -C_6H_{11}		53%
8i	R = -C_4H_9		64%

95

3. Conclusion

A facile and novel route towards the synthesis of 1,2,4,5 tetroxane 8a-8i from 16-dehydropregenolone acetate ie., 16-DPA **1** using acid catalyzed cyclocondation of bis-epidioxy tetraoxanes also with a C-20 methyl carboxylate side chain in ring D was developed. The method affords the target compounds with good yield, 53-67%. Here also, the acid acts both as catalyst as well as cosolvent, which influence both the formation of tetraoxanes and the stability of the peroxides during the experiment.

4. Experimental

4.1. General remarks

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 F254. Melting points were measured with a Buchi B-540 melting point apparatus and are uncorrected. 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 (300 MHz) spectrometer using $CDCl_3$ or DMSO-d_6 as solvent with tetramethylsilane (TMS) as internal standard on ppm scale (d). 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 (Perkin-Elmer 2400 II)

4.2. Experimental methodology and Chemistry

4.2.1. 3β-Acetoxy-5α-pregnan-20-one (2)

1 gm of 16 –DPA (**1**) was dissolved in 50 mL of ethanol and hydrogenated at 45 psi using 200 mg of 5% Pd/C for a period of 12 hr. The reaction mixture was filtered and alcohol was distilled under reduced pressure to get the crude hydrogenated product. The product was purified by column chromatography over silica gel using 1:10 ethyl acetate and hexane as eluent. The product obtained was pregnenolone acetate **2.**

Yield: 950 mg (95%); Melting point (mp.) 172˚C. The observed ^{1}H and ^{13}C NMR data (300 MHz, $CDCl_3$) agree well with the literature values [26]. IR ($CHCl_3$) : 1735, 1700, 1450, 1200 cm^{-1}; MS (ESI) m/z : 360 $(M)^{+}$; Anal. Calcd. for $C_{23}H_{36}O_3$: C, 77.66; H, 10.00. Found : C, 77.49; H 9.65.

4.2.2. 3β-Acetoxy-17α, 21- dichloro-5α-pregnan-20-one (3)

To a solution of 500 mg (1.4 mmol) of compound (**2**) was dissolved in 10 mL of glacial acetic acid, added 450 mg of activated MnO_2 (5 mmol) and 4 mL of TMSCl (trimethyl chlorosilane). The reaction mixture was kept at room temperature for 24 hours and then poured into 500 ml of water and extracted with chloroform (5 X 100 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to get the solid crude product. The product was purified by column chromatography to get the desired pure product **3** over silica gel using 1: 40:: ethyl acetate and hexane as eluent.

Yield: 405 mg (81%); mp. 160˚C. The observed ^{1}H and ^{13}C NMR data (300 MHz, $CDCl_3$) agree well with the literature values [26]. IR ($CHCl_3$) : 1730, 1710, 1445, 1200 cm^{-}

141 [1]; MS (ESI) m/z : 428 $(M)^+$; Anal. Calcd. for $C_{23}H_{34}O_3Cl_2$: C, 64.49; H, 7.94. Found : C,
142 64.46; H, 7.8; α D = + 35° ($CHCl_3$, 22°C and 0.1).

143 *4.2.3. Methyl (E)–3β–Hydroxy-5α-pregn-17-ylideneacetate (**4**)*

144 500 mg of substrate, 3β-Acetoxy-17α, 21- dichloro-5α-pregnan-20-one (**3**) was
145 allowed to stir with 3% KOH in MeOH –H_2O (85:15) at room temperature for a period
146 of 6 hours. The reaction was monitored on TLC. Then the reaction mixture was poured
147 into cold water (300 mL), acidified with 30 % citric acid solution and extracted with
148 chloroform (5 X 100 mL). The organic layer was dried over anhydrous sodium sulfate
149 and evaporated under reduced pressure to get the solid crude product. The product was
150 purified by column chromatography to get the desired pure product **4** over silica gel using
151 1: 2:: ethyl acetate and hexane as eluent.

152 Yield: 375 mg (75%); mp. 165°C; IR (cm^{-1}): 3400, 1730, 1250. The observed ^1H
153 and ^{13}C NMR data (300 MHz, $CDCl_3$) agree well with the literature values [26]. MS (ESI)
154 m/z : 346 $[M]^+$; Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.30; H, 9.83; found: C, 76.21; H, 9.76.

155 *4.2.4. Methyl 3β-Hydroxy-5α-pregnan-17β-acetate (**5**)*

156 400 mg of compound (**4**) was dissolved in 20 mL of ethanol and hydrogenated at
157 45 psi using about 80 mg of 5% Pd/C for a period of 2 hr. The reaction mixture was
158 filtered and alcohol was distilled under reduced pressure to get the crude hydrogenated
159 product. The product was purified by column chromatography to get the desired pure
160 product **5** over silica gel using 1: 3:: ethyl acetate and hexane as eluent.

161 Yield: 284 mg (71%); mp. 172°C; ^1H NMR ($CDCl_3$): 0.8 (s, 3H, Me), 1.2 (s, 3H,
162 Me), 0.9–2.1 (m, 23H, –CH and $–CH_2$), 2.2 (m, 1H, 3-OH), 3.4 (s, 3H, OMe), 3.5 (m, 1H,
163 H-3), 2.3 (s, 1H, H-20); ^{13}C NMR: δ 15.2, 16.4, 21.4, 27.7, 29.7, 31.5, 32.0, 32.2, 36.6,

36.9, 37.8, 40.6, 46.3, 49.9, 56.8, 65.0, 73.8, 170.5; IR (cm^{-1}): 3400 (b), 1735, 1450, 1250; MS (ESI) m/z : 348 $[M]^+$; Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.86; H, 10.34; found: C, 75.60; H, 10.18.

*4.2.5. Methyl 3-Oxo-5α- pregnan-17β-acetate (**6**)*

200 mg of PCC was suspended in methylene chloride and then 200 mg of compound **(5)** was rapidly added to it at room temperature. The reaction mixture was allowed to stir at room temperature. The progress of the reaction was monitored by TLC using 1:5:: ethyl acetate: hexane. After completion of the reaction (2 hours), reaction mixture was diluted with 5 volumes of anhydrous ether and allowed to pass through neutral alumina. The ether was distilled under reduced pressure to get the crude product. The product was purified by column chromatography to get the desired pure product **6** over silica gel using 1: 5:: ethyl acetate and hexane as eluent.

Yield: 170 mg (85%); mp. 267˚C; IR (cm^{-1}): 1735, 1715, 1450, 1250; ^{1}H NMR ($CDCl_3$): δ 0.8 (s, 3H, Me), 1.0 (s, 3H, Me), 0.9–2.1 (m, 23H and $–CH_2$), 3.4 (s, 3H, Me), 2.3 (s, 1H, H-20); ^{13}CNMR : δ 13.4, 16.4, 18.8,19.3, 20.6, 21.4, 27.7, 30.7, 31.5, 31.9, 32.1, 36.7, 36.9, 37.8, 38.0, 40.6, 46.3, 49.9, 56.9, 64.9, 170.6, 205.2; MS (ESI) m/z : 346 $[M]^+$; Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.3; H, 9.82; found: C, 76.01; H, 9.79.

4.2.6. Methyl (3,3-Bishydroperoxy)-5α-pregnan-17β-acetate (7)

100 mg of compound (**6)** was dissolved in acetonitrile, 30% H_2O_2 was added at 0˚C. After completion of the reaction (4 hours), reaction mixture was poured into cold water (300 mL) and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to get the crude

product. The product was purified by column chromatography to get the desired pure product **7** over silica gel using 1: 2:: ethyl acetate and hexane as eluent.

Yield: 75 mg (75%); mp. 287˚C; IR (cm^{-1}): 1727.3, 1446.3, 1263, 754.6; ^1H NMR ($CDCl_3$): δ 0.8 (s, 3H, Me-19), 1.0 (s, 3H, Me-18), 1.1–2.1 (m, 23H and $–CH_2$), 3.5 (s, 3H, Me), 3.7 (s, methyl ester), 9.6 (broad singlet, -OOH); ^{13}C NMR : δ 12.5, 16.0, 24.4, 28.1, 12.5, 16.0, 24.4, 28.1, 28.8, 31.7, 32.1, 32.2, 35.8, 38.0, 42.1, 46. 6, 51.4, 56.6, 110, 174.6; MS (ESI) m/z : 396 $[M]^+$; Anal. Calcd. for $C_{22}H_{36}O_6$: C, 66.66; H, 9.09; found: C, 66.45; H, 9.03.

*4.2.7. Methyl 3,3-(bis-epidioxycyclohexane)-5α-pregnan-17β-acetate (**8a**)*

300 mg of compound (**7**) was dissolved in 10 mL CH_3CN, then 7.5 mL cyclohexanone/substituted cyclohexanone was added at 0˚C. Conc.H_2SO_4 (0.5 mL) was then added dropwise to the reaction mixture and allowed to stir at 0˚C. After 24 hours TLC indicates the completion of the reaction and neutralized the reaction mixture using base (1% NaOH) and after that acetonitrile was evaporated. The crude reaction mixture was added to 200 mL water and worked up with dichloromethane (300 mL). The organic layer was dried over anhydrous sodium sulphate, evaporated under reduced pressure to get the product **8a**.

Yield: 201 mg (67%); mp. 185˚C; IR (cm^{-1}): 2932, 1711, 1448.3, 1198, 773; ^1H NMR ($CDCl_3$): δ 0.8 (s, 3H, Me-19), 1.2 (s, 3H, Me-18), 0.9 – 2.0 (m, 23H and $–CH_2$), 3.2 (s, 3H, Me), 3.6 (s, methyl ester); ^{13}C NMR: δ 22.1, 22.3, 22.5, 22.7, 23.3, 24.0, 25.1, 26.0, 26.6, 27.1, 27.5, 31.7, 33.7, 37.7, 41.9, 42.1, 58.2, 58.6, 85.0, 97.7, 109.1, 174.0; MS (ESI) m/z : 476 $[M]^+$; Anal. Calcd. for $C_{28}H_{44}O_6$: C, 70.59; H, 9.30; found: C, 70.32; H, 9.11.

*4.2.8. Methyl 3,3-(1,1-epidioxy-4-methylcyclohexane)-5α-pregnan-17β-acetate (**8b**)*

Yield: 177 mg (59%); mp. 172˚C; IR (cm^{-1}) : 2932, 1727, 1448.3, 1250, 773; ^1H NMR ($CDCl_3$): δ 0.8 (s, 3H, Me-19), 1.0 (s, 3H, Me-18), 1.02 (s, 4-methyl), 1.03 – 2.2 (m, 23H and –CH_2), 3.2 (s, 3H, Me), 3.7 (s, methyl ester), 1.5-1.69 (m, CH_2-cyclic ring); ^{13}C NMR: δ 15.2, 15.7, 16.4, 19.3, 20.6, 27.7, 29.7, 31.5, 32.1, 36.7, 36.9, 39.3, 40.6, 49.9, 56.8, 65.0, 89.8, 97.4, 109.2, 170.6; MS (ESI) m/z : 490 $[M]^+$; Anal. Calcd. for $C_{29}H_{46}O_6$: C, 71.02; H, 9.38; found: C, 70.99; H, 9.02.

*4.2.9. Methyl 3,3-(1,1-epidioxy-4-methoxycyclohexane)-5α-pregnan-17β-acetate (**8c**)*

Yield: 189 mg (63%); mp. 202˚C; IR (cm^{-1}): 2932, 2810, 1727, 1448.3, 1250, 773; ^1H NMR ($CDCl_3$): δ 0.8 (s, 3H, Me-19), 1.0 (s, 3H, Me-18), 1.1 – 2.1 (m, 23H and –CH_2), 3.4 (s, 3H, Me), 3.6 (s, methyl ester), 3.3 (s, 4-methyl extended), 1.5-1.6 (m, CH_2-cyclic ring); ^{13}C NMR : δ 15.2, 15.7, 16.4, 20.6, 27.7, 29.7, 31.5, 32.0, 32.2, 36.6, 39.3, 40.6, 46.3, 49.9, 56.8, 65.0, 89.8, 97.4, 109.2, 170.5; MS (ESI) m/z : 506 $[M]^+$; Anal. Calcd. for $C_{29}H_{46}O_7$: C, 68.77; H, 9.09; found: C, 68.51; H, 9.03.

*4.2.10. Methyl 3,3-(1,1-epidioxy-4-chlorocyclohexane)-5α-pregnan-17β-acetate (**8d**)*

Yield: 183 mg (61%); mp. 167˚C; IR (cm^{-1}): 2932, 1727, 1448.3, 1250, 773, 710; ^1H NMR ($CDCl_3$): δ 0.8 (s, 3H, Me-19), 1.2 (s, 3H, Me-18), 1.25 – 2.1 (m, 23H and –CH_2), 3.4 (s, 3H, Me), 3.6 (s, methyl ester), 1.39-68 (m, CH_2-cyclic ring); ^{13}C NMR: δ 15.2, 15.7, 16.4, 20.6, 27.7, 29.7, 31.5, 32.0, 32.2, 36.6, 39.3, 40.6, 46.3, 49.9, 56.8, 65.0, 89.8, 97.4, 109.2, 170.5; MS (ESI) m/z : 510 $[M]^+$; Anal. Calcd. for $C_{28}H_{43}O_6Cl$: C, 65.89; H, 8.43; found: C, 65.52; H, 8.27.

*4.2.11. Methyl 3,3-(1,1-epidioxy-4-bromocyclohexane)-5α-pregnan-17β-acetate (**8e**)*

Yield: 168 mg (56%); mp. 177˚C; IR (cm^{-1}): 2932, 1727, 1448.3, 1250, 773, 645; ^{1}H NMR ($CDCl_3$): δ 0.8 (s, 3H, Me-19), 1.0 (s, 3H, Me-18), 1.1 – 2.2 (m, 23H and –CH_2), 3.6 (s, 3H, Me), 3.7 (s, methyl ester), 1.5-1.6 (m, CH_2-cyclic ring) ; ^{13}C NMR: δ 15.2, 15.7, 16.4, 20.6, 27.7, 29.7, 31.5, 32.1, 36.7, 36.9, 39.3, 40.6, 49.9, 56.8, 65.0, 89.8, 97.4, 109.2, 170.6; MS (ESI) m/z : 554 $[M]^+$; Anal. Calcd. for $C_{28}H_{43}O_6Br$: C, 60.65; H, 7.76; found: C, 60.29; H, 7.38.

*4.2.12. Methyl 3,3-(1,1-epidioxy-4-nitrocyclohexane)-5α-pregnan-17β-acetate (**8f**)*

Yield: 186 mg (62%); mp. 205˚C; IR (cm^{-1}): 2932, 1727, 1448.3, 1250, 1190, 773; ^{1}H NMR ($CDCl_3$): δ 0.8 (s, 3H, Me-19), 1.0 (s, 3H, Me-18), 1.1 – 2.1 (m, 23H and –CH_2), 3.2 (s, 3H, Me), 3.4 (s, methyl ester), 3.1 (m, 1H-extended ring); ^{13}C NMR: δ 15.2, 15.7, 16.4, 20.6, 27.7, 29.7, 31.5, 32.1, 36.7, 36.9, 39.3, 40.6, 49.9, 56.8, 65.0, 89.8, 90.0, 109.7, 170.6; MS (ESI) m/z : 521 $[M]^+$; Anal. Calcd. for $C_{28}H_{43}O_8N$: C, 64.49; H, 8.25, N, 2.69; found: C, 64.15; H, 7.98, N, 2.44 .

*4.2.13. Methyl 3,3-(1,1-epidioxy-4-acetylcyclohexane)-5α-pregnan-17β-acetate (**8g**)*

Yield: 198 mg (66%); mp. 185˚C; IR (cm^{-1}): 2932, 1727, 1745, 1448.3, 1250, 773; ^{1}H NMR ($CDCl_3$): δ 0.8 (s, 3H, Me-19), 1.0 (s, 3H, Me-18), 1.1 – 2.1 (m, 23H, –CH_2, -$COCH_3$), 3.2 (s, 3H, Me), 3.6 (s, methyl ester); ^{13}C NMR: δ 15.2, 15.7, 16.4, 20.6, 29.7, 31.5, 32.1, 36.7, 36.9, 37.8, 38.0, 39.3, 40.6, 49.9, 56.8, 65.0, 89.8, 97.4, 109.6, 170.6, 209.6; MS (ESI) m/z : 518 $[M]^+$; Anal. Calcd. for $C_{30}H_{46}O_7$: C, 69.5; H, 8.88; found: C, 69.35; H, 8.65.

*4.2.14. Methyl 3,3-(1,1-epidioxy-4-hexanecyclohexane)-5α-pregnan-17β-acetate (**8h**)*

Yield: 159 mg (53%); mp. 173˚C; IR (cm^{-1}): 2932, 1727, 1745, 1448.3, 1250, 773; ^1H NMR ($CDCl_3$): δ 0.8 (s, 3H, Me-19), 1.0 (s, 3H, Me-18), 1.1 – 2.1 (m, 23H, – CH_2, -$COCH_3$), 3.4 (s, 3H, Me), 3.6 (s, methyl ester), 5.2 (m, -CH-); ^{13}C NMR: δ 13.8, 14.5, 16.2, 20.7, 27.7, 28.7, 30.2, 31.3, 31.8, 32.0, 36.7, 36.9, 39.7, 40.2, 41.5, 49.9, 56.4, 62.0, 80.8, 97.4, 109.2, 120.7, 170.5; MS (ESI) m/z : 558 $[M]^+$; Anal. Calcd. for $C_{34}H_{54}O_6$: C, 73.10; H, 9.67; found: C, 72.87; H, 9.38.

*4.2.15. Methyl 3,3-(1,1-epidioxy-4-butanecyclohexane)-5α-pregnan-17β-acetate (**8i**)*

Yield: 192 mg (64%); mp. 155˚C; IR (cm^{-1}): 2932, 1727, 1745, 1448.3, 1250, 773; ^1H NMR ($CDCl_3$): δ 0.8 (s, 3H, Me-19), 0.9 (s, 3H, Me-18), 1.2 – 2.1 (m, 23H, – CH_2, -$COCH_3$), 3.2 (s, 3H, Me), 3.4 (s, methyl ester), 5.5 (m, -CH-); ^{13}C NMR: δ 13.8, 14.5, 16.2, 20.7, 27.7, 28.7, 30.2, 31.3, 31.8, 32.0, 36.7, 36.9, 39.7, 40.2, 41.5, 49.9, 56.4, 62.0, 80.8, 97.4, 170.5; MS (ESI) m/z : 532 $[M]^+$; Anal. Calcd. for $C_{32}H_{52}O_6$: C, 72.18; H, 9.77; found: C, 71.91; H, 9.45.

Acknowledgment

The authors thank the Director CSIR-North East Institute of Science & Technology, Jorhat, Assam for providing facilities and valuable advice and also gratefully acknowledge the financial assistance supported by DST, New Delhi for awarding Fast Track Young Scientist Award, EEOES and CSIR, New Delhi, INDIA.

References

1. Bhattacharjee, A. K.; Carvalho, K. A.; Opsenica, D.; Solaja, B. A. *J. Serb. Chem. Soc.* **2005**, 70, 329–345.
2. Tonmunphean, S.; Wijitkosoom, A.; Tantirungrotechai, Y. *Bioorg. Med. Chem.* **2004**, 12, 2005–2012
3. Amewu, R.; Stachulski, A. V.; Ward, S. A.; Berry, N. G.; Bray, P. G.; Davies, J.; Labat, G.; Vivas, L.; O'Neill, P. M. *Org. Biomol. Chem.* **2006**, 4, 4431-4436.
4. O'Neil, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, 47, 2945–2964.
5. Gelb, M. H. *Curr. Opin. Chem. Biol.* **2007**, 11, 440–445.
6. Jin, H. –X.; Liu, H. –H.; Zhang, Q.; Wu, Y. *Tetrahedron. Lett.* **2005,** 46, 5767–5769.
7. Jin, H. –X.; Zhang, Q.; Kim, H. –S.; Wataya, Y.; Liu, H. –H.; Wu, Y. *Tetrahedron* **2006**, 62, 7699–7711.
8. Najjar, F.; Gorrichon, L.; Baltas, M.; Andre´-Barre`s, C.; Vial, H. *Org. Biomol. Chem.* **2005**, 3, 1612–1614.
9. Ellis, G. L.; Amewu, R.; Hall, C.; Rimmer, K.; Ward, S. A.; O'Neill, P. M. *Bioorg. Med. Chem.Lett.* **2008**, 18, 1720–1724.
10. Dembitsky, V. M.; Gloriozova, T. A.; Poroikov, V. V. Med.Chem. **2007**, 7, 571–589.
11. Dembitsky, V. M. *Eur. J. Med. Chem.* **2008**, 43, 223–251.
12. Terzic,´ N.; Opsenica, D.; Milic,´ D.; Tinant, B.; Smith, K. S.; Milhous, W. K.; S˘olaja, B. A. *J. Med. Chem.* **2007**, 50, 5118–5127.

13. Opsenica, D.; Kyle, D. E.; Milhous, W. K.; S˘olaja, B. A. *J. Serb. Chem. Soc.* **2003**, 68, 291–302.

14. Amewu, R.; Stachulski, A. V.; Ward, S. A.; Berry, N. G.; Bray, P. G.; Davies, J.; Labat, G.; Vivas, L.; O'Neill, P. M. *Org. Biomol. Chem.* **2006**, 4, 4431–4436.

15. Dong, Y.; Tang, Y.; Chollet, J.; Matile, H.; Wittlin, S.; Charman, S. A.; Charman, W. N.; Tomas, J. S.; Scheurer, C.; Snyder, C.; Scorneaux, B.; Bajpai, S.; Alexander, S. A.; Wang, X.; Padmanilayam, M.; Cheruku, S. R.; Brun, R.; Vennerstrom, J. L. *Bioorg. Med. Chem.* **2006**, 14, 6368–6382.

16. Singh, C.; Malik, H.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2004**, 14, 459–462.

17. Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.;, Chollet, J. *Nature*, **2004**, 430, 900–904.

18. O'Neill, P.M.; Barton, V. E.; Ward, S. A. *Molecules* **2010**, 15, 1705–1721.

19. Kumar, N.; Sharma, M.; Rawat, D. S. *Curr. Med. Chem.* **2011**, 18(25), 3889-928.

20. Solaja`, B. A.; Terzic, N.; Pocsfalvi, G.; Genena, L.; Tinant, B.; Opsenica, D.; Milhous, W. K. *J. Med. Chem.* **2002**, 45, 3331–3336.

21. Opsenica, D.; Pocsfalvi, G.; Juranic, Z.; Tinant, B.; Declercq, J-P.; Kyle, D. E.; Milhous, W. K.; Solaja`, B. A. *J. Med. Chem.* **2000**, 43, 3274–3282.

22. Iskra, J.; Bonnet-Delpon, D.; Be´gue´, J-P. *Tetrahedron Lett.* **2003**, 44, 6309–6312.

23. Z´mitek, K.; Stavber, S.; Zupan, M.; Bonnet-Delpon, D.; Iskra, J. *Tetrahedron* **2006**, 62, 1479–1484.

24. Opsenica, I.; Opsenica, D.; Smith, K. S.; Milhous, W. K.; S˘olaja, B. A. *J. Med. Chem.* **2008**, 51, 2261–2266.

25. Terent'ev, A. O.; Kutkin, A. V.; Starikova, Z. A.; Antipin, M. Yu.; Ogibin, Yu. N.; Nikishin, G. I. *Synthesis* **2004**, 65, 2356–2366.

26. Chowdhury, P.; Borah, J. M.; Goswami, P.; Das, A. M. *Steroids* **2011**, 76, 497–501.

27. O'Neill, P. M.; Amewu, R. K.; Nixon, G. L.; Garah, E. L.; Mungthin, M.; Chadwick, J.; Shone, A. E.; Vivas, L.; Lander, H.; Barton, V.; Muangnoicharoen, S.; Bray, P. G.; Davies, J.; Park, B. K.; Wittlin, S.; Brun, R.; Preschel, M.; Zhang, K.; Ward, S. A. *Angew Chem Int Ed*. **2010**, 49, 5693-5697.

28. Ellis, G. L.; Amewu, R.; Sabbani, S.; Stocks, P. A.; Shone, A. E.; Stanford, D.; Gibbons, P.; Davies, J.; Vivas, L.; Charnaud, S.; Bongard, E.; Hall, C.; Rimmer, K.; Maria Jesus, S. L.; Gargallo, D.; Ward, S. A.; O'Neill, P. M. *J Med Chem.* **2008**, 51, 2170-2177.

29. Borah, P.; Ahmed, M.; Chowdhury, P. K. *J. Chem. Res. (S)* **1998**, 236–237.

30. Borah, P.; Ahmed, M.; Chowdhury, P. K. *J Chem Res. (M)* **1998**, 1173-1180.

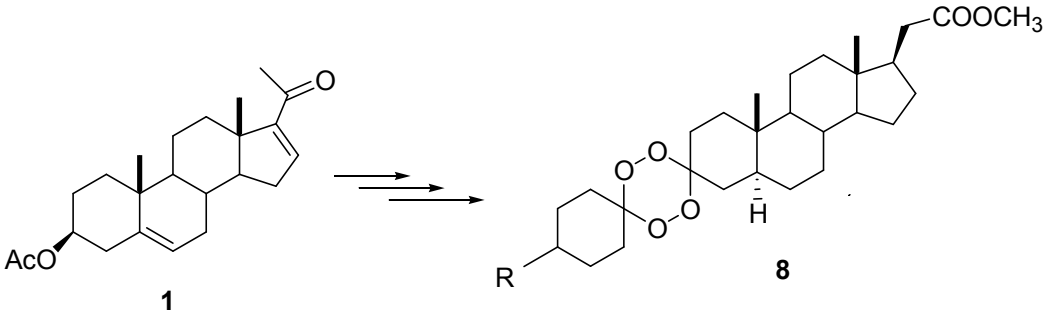
31. Goswami, P.; Hazarika, S.; Das, A. M.; Chowdhury, P. K. *Indian J Chem*. **2004**, 43B, 1275-1281.

356

357

358 **Graphical Abstract**

359



8a : R = H
8b : R = 4-Me
8c : R = 4-MeO
8d : R = 4-Cl
8e : R = 4-Br
8f : R = 4-NO_2
8g : R = -$COCH_3$
8h : R = -C_6H_{11}
8i : R = -C_4H_9

360

361

362