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Synthesis of 3α-hydroxy-21-(1′-imidazolyl)-3β-methoxyl-methyl-5α-pregnan-20-one via lithium imidazole with 17α-acetylbromopregnanone

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ABSTRACT

The synthesis of biologically active 3α-hydroxyl-21-(1′-imidazolyl)-3β-methoxymethyl-5α-pregnan-20-one (**11**) was accomplished in six steps. The key steps were the improvement of stereoselectivity for acetyl isomers in C-17 and the introduction of imidazole into the core structure by use of lithium imidazole. This latter key step provided the desired product **11** in 82% yield without the formation of 1,3-disubstituted imidazolium salt as impurity, which is generally observed in traditional method.

1. Introduction

Steroid compounds attract much attention because of their special biological activity [1]. They can regulate a variety of biological processes and thus be developed as drugs for the treatment of disease including autoimmune diseases, brain tumors, breast cancer, cardiovascular, prostate cancer, osteoarthritis [2,3]. Except for the naturally-occuring substances, most of steroidal pharmaceuticals were semi-synthetic compounds prepared by connecting a special functionality to the core structure of a steroid [4].

The azole moiety often shows some special biological activity when it is introduced to some biological active compounds [5]. However, it is unusual that a steroid contains an azole moiety at C-21 position [6]. The basicity and hydrophilicity of an azole in theory might alter the biological function of a steroid. Moreover, the azole might interact with some enzymes, e.g. cytochrome P. 450, as a part of the whole

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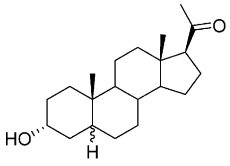
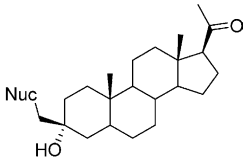
pharmaceutical [7–10]. The naturally-occurring neuroactive steroid 3α-hydroxyl-5α-pregnan-20-one (**1**), its 5β-epimer (**2**) and 3β-substituted derivatives of **1** and **2** (**3**) are potent allosteric modulators of the GABA-$_A$ receptor [11,12]. As a result, we designed a new steroidal derivative, 3α-hydroxyl-21-(1′-imidazolyl)-3β-methoxymethyl-5α-pregnan-20-one (**11**). It possesses an imidazole group in C-21 [12] and was found in preliminary studies to enhance the ability of the inhibitory neurotransmitter, gamma aminobutyric acid (GABA) to activate a type of receptors known as GABA-$_A$ receptors. Therefore, we planned to develop a process for the synthesis of compound for future investigation of its detailed biological activity and toxicity.



1 (5α–H), **2** (5β–H)



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The key features for the synthesis of **11** involved the improvement of the ratio for acetyl isomers in C-17 in the ring opening reaction and the introduction of an imidazole moiety into the core structure. The usual method of direct heating of α-bromoketone with imidazole, however, always provides a di-alkylated product as major impurity and is not suitable for scale up. In this work, we report the reaction of lithium imidazole with 21-bromo-3α-hydroxy-3β-methoxymethyl-5α-pregnan-20-one (**10**) to provide 3α-hydroxyl-21-(1′-imidazolyl)-3β-methoxymethyl-5α-pregnan-20-one (**11**) in high yield without the formation of the 1,3-disubstituted imidazolium salt dimer.

2. Experimental

2.1. General procedure

Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254), purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Varian Unity-400 (400 MHz) or a Bruker-300 (400 MHz) spectrometer by use of $CDCl_3$ and *d6*-DMSO as solvent. Carbon-13 NMR spectra were obtained on a Varian Unity-400 (100 MHz) spectrometer or a Bruker-400 (100 MHz) spectrometer by used of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer. Purity of all products was >99% from the results of HPLC analysis.

2.2. Hydrogenation reaction

3β-Hydroxy-5α-pregnan-20-one (5) [13]: To a THF solution (800 mL) containing 3β-hydroxypregn-5-en-20-one (**4**, pregnenolone, 100 g, 315 mmol, 1.0 equiv.) and 10% Pd/C (8.0 g) was added glacial acetic acid (28 mL). The reaction mixture was hydrogenated under a constant H_2 pressure of 60 psi at 50–60 °C for 8.0 h. The solution was filtered through Celite and the Celite bed was washed with hot THF. The filtrate was concentrated under reduced pressure and the residue was washed with hexanes (800 mL×2) to give **5** (90 g, 283 mmol) as a white solid in 90%: m.p. (recrystallized from toluene/hexanes) 194–196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.62 (s, 3 H, 19-CH_3), 0.83 (s, 3 H, 18-CH_3), 0.63–1.09 (m, 3 H), 1.19–1.49 (m, 10 H), 1.60–2.16 (m, 9 H), 2.51 (s, 3 H, 21-CH_3), 2.24 (t, 3 H, J = 8.8 Hz, 17α-CH), 3.61 (m, 1 H, 3α-CH); MS *m*/*z* (relative intensity) 319 (M^+, 31), 301 (43), 154 (100), 149 (43), 137 (84), 107 (40), 95 (26), 91 (37), 89 (27), 77 (33); HRMS calcd for $C_{21}H_{34}O_2$ 318.2559, found 318.2554.

2.3. Oxidation reaction

5α-Pregnane-3,20-dione (6) [14,15]: To 3β-hydroxy-5α-pregnan-20-one (**5**, 100 g, 318 mmol, 1.0 equiv.) in glacial acetic acid (1.5 L) was added dropwise an aqueous NaOCl solution (12%, 510 mmol, 317 mL) containing sodium bromide (3.27 g, 3.18 mmol, 0.10 equiv.) under 38 °C. The biphasic reaction mixture was stirred vigorously at room temperature for 2.0 h. The reaction mixture was quenched with water (850 mL) and the resultant solids were collected by filtration and washed with water (100 mL×2). The solids were dried under vacuum for 12 h and purified by recrystallization from ethyl acetate to give pure **6** (79.6 g, 252 mmol) as a white solid in 79% yield: m.p. 200–202 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.64 (s, 3 H, 19-CH_3), 1.01 (s, 3 H, 18-CH_3), 0.95–1.00 (m, 2 H), 1.10–1.79 (m, 13 H), 2.02–2.46 (m, 7 H), 2.23 (s, 3 H, 21-CH_3), 2.53 (t, 3 H, J = 8.8 Hz, 17α-CH); IR (diffuse reflectance) 3380 (m), 2937 (s), 1708 (m, C=O), 1434 (m), 1385 (m), 1354 (m), 1231 (m), 1206 (m), 1147 (m), 1040 (m), 1004 (m), 947 (m), 866 (m), 804 (m), 722 (m), 569 (m), 502 (m) cm^{-1}; MS *m*/*z* (relative intensity) 317 (M^+, 100), 176 (42), 154 (80), 149 (55), 137 (75), 107 (30), 95 91 (29), 89 (20), 81 (21), 77 (29), HRMS calcd for $C_{21}H_{32}O_2$ 316.2402, found 316.2408.

2.4. Epoxidation reactions

(3R)-Spiro[oxirane-2′,5α-pregnan]-20-one (7) [11]: A stirred solution of trimethylsulfoxonium iodide (32.0 g, 144 mmol, 1.5 equiv.) and potassium *tert*-butoxide (17.2 g, 154 mmol, 1.6 equiv.) in DMSO (500 mL) was heated at 55–60 °C for 1.0 h under N_2. 5α-Pregnane-3,20-dione (**6**, 30.4 g, 96.1 mmol, 1.0 equiv.) was added to the reaction mixture and stirred at room temperature for 5.0 h. After the reaction was completed, the reaction mixture was quenched and precipitated by water (500 mL) in ice-bath. The resultant precipitate was collected by filtration, washed with water (200 mL×2), and dried in vacuum oven at below 50 °C for 12 h. The residue was purified by recrystallization from MeOH/acetone (**4**/**1**) to give pure **7** (23.8 g, 72.1 mmol) as a white powder in 75% yield: m.p. 204–206 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.62 (s, 3 H, 19–CH_3), 0.85 (s, 3 H,

18-CH_3), 0.83–1.08 (m, 2 H), 1.10–1.56 (m, 10 H), 1.57–1.83 (m, 7 H), 1.84–2.28 (m, 3 H), 2.16 (s, 3 H, 21–CH_3), 2.53 (t, 3 H, J = 8.8 Hz, 17α-CH), 2.62 (s, 2 H, –OCH_2); IR (diffuse reflectance) 3375 (m), 2930 (s), 1702 (m, C=O), 1440 (m), 1381 (m), 1358 (m), 1280 (m), 1211 (m), 1166 (m), 958 (m), 916 (m), 901 (m), 835 (m), 792 (m), 700 (m), 594 (m) cm^{-1}; MS m/z (relative intensity) 331 (M^+, 57), 149 (100), 137 (82), 107 (64), 95 (79), 91 (91), 81 (70), 77 (63), 55 (73), 43 (93); HRMS calcd for $C_{22}H_{34}O_2$ 330.2559, found 330.2565.

2.5. *Ring opening reactions*

3α-Hydroxy-3β-methoxymethyl-5α,17α-pregnan-20-one (8) and 3α-hydroxy-3β-methoxymethyl-5α,17β-pregnan-20-one (9) [11]: Sodium hydroxide (7.70 g, 192 mmol, 2.0 equiv.) was dissolved in MeOH (300 mL) and heated at reflux for 30 min under N_2. Compound **7** (31.7 g, 96.0 mmol, 1.0 equiv.) was slowly added to the methanolic solution at room temperature under N_2 and the solution was heated at 35–40 °C for 8.0–10 h. The reaction mixture was quenched and precipitated by water (500 mL) in ice-bath. The resultant precipitate was filtrated, washed with water (100 mL×2), and dried in vacuum oven at below 50 °C for 12 h to give diastereomers **8** and **9** (34.1 g, 94.1 mmol) as light yellow solids in 98% total yield. The mixture was purified by recrystallization from ethyl acetate/hexanes (**1/1**) to give pure **8** (23.8 g, 75.3 mmol) as a white powder in 80% yield. The residual solution was concentrated under reduced pressure and purified by column chromatography on silica gel (30% EtOAc in hexanes as eluant) to give a pure **9** as a light yellow powder.

For compound **8**: m.p. 167–169 °C; TLC R_f 0.35 (30% EtOAc in hexanes as eluant); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.62 (s, 3 H, 19-CH_3), 0.77 (s, 3 H, 18-CH_3), 0.75–1.08 (m, 3 H), 1.12–1.80 (m, 17 H), 1.91–2.13 (m, 2 H), 2.16 (s, 3 H, 21-CH_3), 2.54 (t, 3 H, J = 8.8 Hz, 17α-CH), 3.12 (s, 2 H, –OCH_3), 3.39 (s, 3 H, –OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.21, 13.46, 20.80, 22.80, 24.40, 28.43, 30.24, 31.51, 31.93, 33.35, .5.54, 36.04, 37.13, 39.13, 40.23, 44.27, 54.03, 56.78, 59.42, 63.85, 71.05, 81.96, 209.69; IR (diffuse reflectance) 3515 (s), 3385 (s), 2910 (s), 1708 (m, C=O), 1435 (m), 1385 (m), 1352 (m), 1235 (m), 1207 (m), 1070 (m), 968 (m), 946 (m), 860 (m), 804 (m), 602 (m), 514 (m) cm^{-1}; MS m/z (relative intensity) 363 (M^+, 28), 345 (100), 313 (51), 154 (77), 137 (82), 119 (44), 107 (62), 95 (86), 93 (55), 91 (77), 81 (70), 77 (50), 71 (50), 67 (47), 55 (60), 43 (64); HRMS calcd for $C_{23}H_{38}O_3$ 362.2821, found 362.2827.

For compound **9**: m.p. 154–156 °C; TLC R_f 0.30 (30% EtOAc in hexanes as eluant); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.74 (s, 3 H, 19-CH_3), 091 (s, 3 H, 18-CH_3), 0.98–2.12 (m, 21 H), 2.12 (s, 3 H, 21-CH_3), 2.78 (t, 3 H, J = 6.0 Hz, 17β-CH), 3.17 (s, 2 H, –OCH_2), 3.38 (s, 3 H, –OCH_3); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 11.15, 20.92, 20.95, 24.27, 25.89, 28.50, 30.21, 32.20, 32.70, 35.39, 35.77, 35.99, 37.13, 40.07, 45.79, 50.36, 53.41, 59.41, 61.44, 70.97, 82.00, 212.59; MS m/z (relative intensity) 363 (M^+, 9), 345 (100), 327 (45), 313 (60), 311 (19), 154 (21), 147 (24), 143 (10), 137 (28), 133 (19), 119 (29), 107 (35), 95 (41), 93 (33), 91 (42), 85 (19), 81 (32), 77 (23), 71 (27), 55 (19), 43 (30); HRMS calcd for $C_{23}H_{38}O_3$ 362.2821, found 362.2818.

2.6. *Bromination reactions*

21-Bromo-3α-hydroxy-3β-methoxymethyl-5α-pregnan-20-one (10): To a solution of compound **8** (29.0 g, 80.0 mmol, 1.0 equiv.) in MeOH (300 mL) was added three drops of aqueous HBr solution (48%). Bromine (13.5 g, 83.9 mmol, 1.05 equiv.) was dissolved in MeOH solution (200 mL) and added dropwise to the reaction mixture over 1.0 h in the dark. After the reaction was completed, the reaction mixture was quenched and precipitated by water (600 mL). The resultant precipitate was collected by filtration, washed with water (100 mL×2), and dried in vacuum oven at below 40 °C for 12 h. The residue was purified by recrystallization from EtOAc/*n*-hexane (5/95) to give pure **10** (27.4 g, 62.2 mmol) as white powder in 78% yield: m.p. 116–118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.65 (s, 3 H, 19-CH_3), 077 (s, 3 H, 18-CH_3), 0.78–1.10 (m, 2 H), 1.20–2.01 (m, 19 H), 2.15–2.29 (m, 1 H), 2.83 (t, 3 H, J = 8.8 Hz, 17α-CH), 3.20 (s, 2 H, –OCH_2), 3.40 (s, 3 H, –OCH_3), 3.91 (d, 1 H, J = 13.2 Hz, –CHBr), 3.93 (d, 1 H, J = 13.2 Hz, –CHBr); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.20, 13.72, 20.97, 23.71, 24.48, 28.38, 30.23, 31.89, 33.33, 35.58, 36.04, 37.10, 38.98, 40.19, 45.08, 53.93, 56.71, 59.42, 60.55, 71.02, 81.94, 202.12; IR (diffuse reflectance) 3566 (s), 2934 (s), 1709 (s, C=O), 1442 (m), 1384 (m), 1312 (m), 1189 (m), 960 (m), 897 (m), 808 (m), 624 (m), 595 (m), 551 (m), 503 (m) cm^{-1}; MS m/z (relative intensity) 441 (M^+, 8), 423 (89), 391 (95), 175 (24), 161 (25), 159 (27), 154 (29), 147 (32), 145 (30), 137 (51), 133 (35), 121 (46), 105 (71), 95 (100), 91 (82), 81 (65), 79 (62), 77 (43), 71 (29), 67 (36), 45 (36); HRMS calcd for $C_{23}H_{37}BrO_3$ 440.1926, found 440.1931.

2.7. *Substitution reactions*

3α-Hydroxy-21-(1′-imidazolyl)-3β-methoxymethyl-5α-pregnan-20-one (11). Method A: To a solution of imidazole (23.1 g, 217 mmol, 3.0 equiv.) in THF (200 mL) was added lithium hydride (1.79 g, 224 mmol, 3.1 equiv.). The solution was heated at reflux for 30 min under N_2. Compound **10** (31.2 g, 72.8 mmol, 1.0 equiv.) in THF (200 mL) was slowly added to the reaction mixture at −5 to 0 °C over a period of 5 min under N_2. After being stirred at −5 to 0 °C for 30 min, the reaction mixture was quenched by saturated NH_4Cl aqueous solution (500 mL) in ice-bath. The organic layer was separated and concentrated under reduced pressure to give pure **11** (25.3 g, 59.1 mmol) as white powder in 81% isolated yield: m.p. 196–198 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.66 (s, 3 H, 19-CH_3), 076 (s, 3 H, 18-CH_3), 0.78–1.05 (m, 2 H), 1.16–1.71 (m, 18 H), 1.92–1.97 (m, 1 H), 2.14–2.29 (m, 1 H), 2.57 (t, 3 H, J = 9.0 Hz, 17α-CH), 3.18 (s, 2 H, –OCH_2), 3.39 (s, 3 H, –OCH_3), 4.50 (d, 1 H, J = 18.0 Hz, –CHBr), 4.71 (d, 1 H, J = 18.0 Hz, –CHBr), 6.85 (s, 1 H), 7.09 (s, 1 H), 7.41 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.31, 13.88, 21.27, 23.25, 24.49, 28.54, 31.46, 31.98, 35.52, 35.54, 37.03, 38.12, 39.28, 44.84, 45.11, 54.14, 56.49, 56.78, 60.47, 71.06, 119.95, 129.41, 137.79, 203.19; IR (diffuse reflectance) 3483 (s), 2905 (s), 1754 (m, C=O), 1531 (m), 1446 (m), 1372 (m), 1265 (m), 1050 (m), 988 (m), 887 (m), 824 (m), 722 (m), 634 (m), 502 (m) cm^{-1}; MS m/z (relative intensity) 429 (M^+, 100), 427 (31), 413 (15), 411 (22), 383 (22), 137 (28), 105 (13), 93 (12), 82 (37), 69 (39); HRMS calcd for $C_{26}H_{40}N_2O_3$ 428.3039, found 428.3037.

Method B: A solution containing compound **10** (35.3 g, 80.0 mmol, 1.0 equiv.) and imidazole (10.9 g, 160 mmol, 2.0 equiv.) in THF (400 mL) was heated at reflux for 8.0–10 h under N_2. The reaction mixture was concentrated under reduced pressure and the resultant oil was re-dissolved in CH_2Cl_2 (600 mL). The solution was washed with 5% aqueous $NaHCO_3$ solution (200 mL×2), brine (200 mL×2), and

concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5.0% MeOH in CH_2Cl_2 as eluant) to give **11** (15.5 g, 36.2 mmol) as white solids in 45% yield and **12** (22.4 g, 28.3 mmol) as light yellow solids in 35% yield.

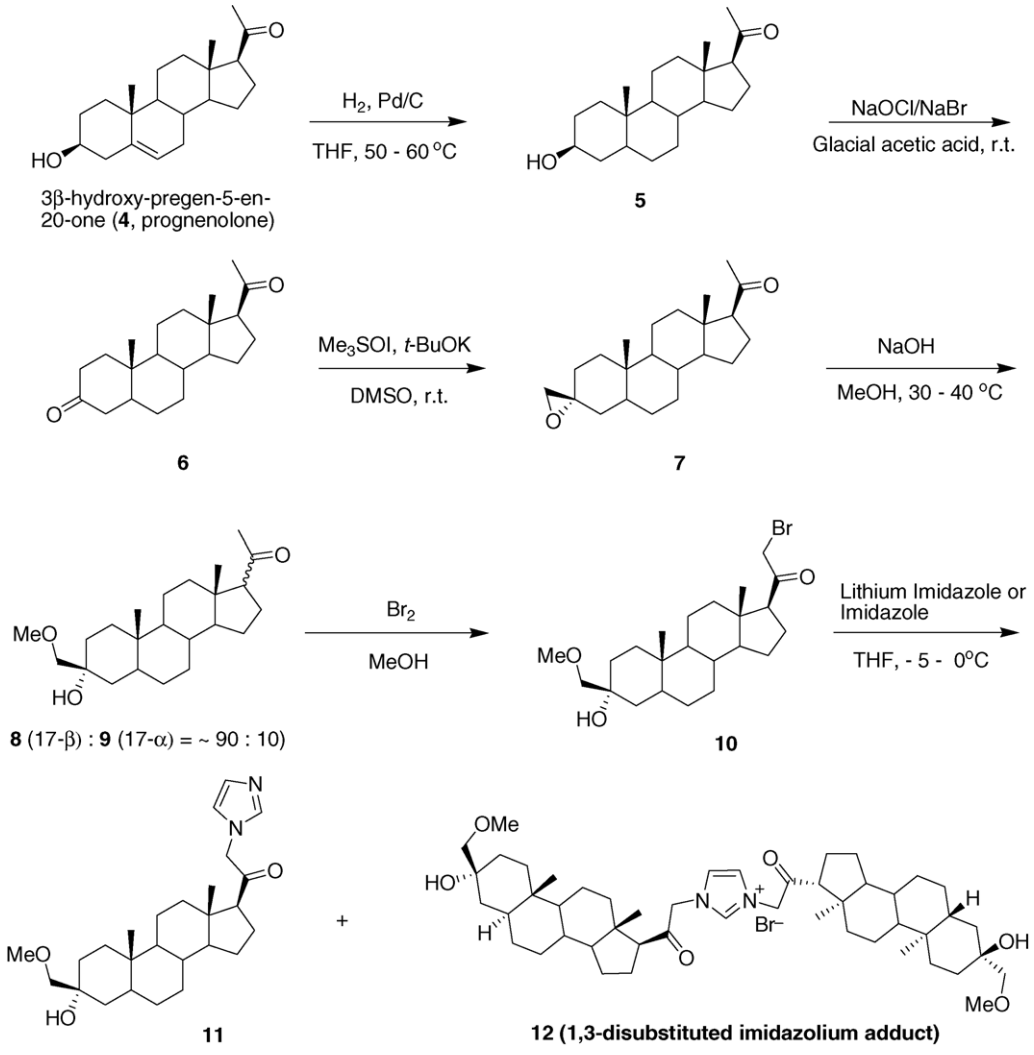
For compound **12**: ^{1}H NMR ($CDCl_3 + CD_3OD$, 400 MHz) δ 0.66 (s, 6 H, 19-CH_3), 0.73 (s, 6 H, 18-CH_3), 0.75–1.09 (m, 4 H), 1.12–1.92 (m, 36 H), 2.01–2.23 (m, 4 H), 2.71 (t, 2 H, J = 8.8 Hz, 17-CH), 3.36 (s, 4 H, –OCH_2), 3.36 (s, 6 H, –OCH_3), 5.19 (d, 2 H, J = 18.4 Hz, –CHBr), 5.49 (d, 2 H, J = 18.4 Hz, –CHBr), 7.28 (s, 1 H), 7.32 (s, 1 H), 9.30 (s, 1 H); IR (diffuse reflectance) 3426 (s), 2931 (s), 1731 (m, C=O), 1632 (m), 1569 (m), 1449 (m), 1385 (m), 1352 (m), 1294 (m), 1172 (m), 1119 (m), 1040 (m), 961 (m), 926 (m), 900 (m), 845 (m), 809 (m), 745 (m), 720 (m), 690 (m), 624 (m) cm^{-1}; MS m/z (relative intensity) 789 (M^+, 100), 773 (14), 744 (12), 497 (17), 429 (31), 442 (20), 149 (14), 81 (11), 73 (23), 69 (12); HRMS calcd for $C_{49}H_{77}N_2O_6$ 789.5776, found 789.5771.

3. Result and discussion

The synthetic pathway of the target pharmacological active steroid **11** is depicted in Scheme 1. In the first step, pregnenolone was subjected to hydrogenation in accordance with a reported procedure [13] to give compound **5** in 90% yield. Following the method developed by Kaya et al. [16], the C_3-OH in **5** was oxidized to its corresponding ketone **6** in 79% by use of NaOCl and NaBr in glacial acetic acid. This conversion possesses the advantage of higher reaction rate when compared with traditional methods [17]. The structures of **5** and **6** were characterized by comparison with the data reported in literature [13,14] and their purities were >99% from HPLC analysis.

We then treated compound **6** with trimethylsulfoxonium iodide and potassium *tert*-butoxide in DMSO [18–20]. The corresponding oxiranes **7** was obtained in 75% yield. In this conversion, the selective epoxidation took place only at C-3 carbonyl moiety in **6**. No product containing oxirane functionality at C-17 position was found. When we used trimethylsulfonium ioide under basic conditions instead [21], the reaction gave a mixture of C-3 and C-17 oxiranes.

For the introduction of CH_3OCH_2-group in the steroid skeleton, we tried to use methoxide in methanol to open the oxirane functionality in **7**. The nucleophile would attack the less-hindered exocyclic CH_2 than C-3 in **7** according to the Krasuskii rule [22]. However, it is also reported that the C-17 acetyl group would undergo racemization under strong basic condition [23].



Scheme 1 – The synthetically route of 3α-hydroxyl-21-(1′-imidazolyl)-3β-methoxymethyl-5α-pregnan-20-one.

Table 1 – Ring opening reaction of oxirane 7 in the presence of different equivalent of NaOMe at different temperature in MeOH

Entry	Equivalent of NaOMe	Temperature	Reaction time (h)	Ratio[a] of 8/9
1	1.0	Reflux (~68 °C)	4.0–6.0	78/22
2	2.5	Reflux (~68 °C)	4.0–6.0	79/21
3	5.0	Reflux (~68 °C)	4.0–6.0	79/21
4	2.5	35–40 °C	8.0–10	88/12
5	2.5	20–30 °C	>50	90/10

[a] The ratios of **8/9** (C-17β/C17α) were determined by HPLC on a Hewlett-Packard 1100 Series instrument equipped with Columns (Phenomenex, Luna C18(2), 3 μm particle size, 15 cm (L) × 4.6 mm (i.d.) and mobile phase: MeOH/water (80:20, v/v), flow rate = 0.80 mL/min).

We then investigated the reaction of different equivalent of methoxide in MeOH with **7** under various temperature and time (see Table 1). Under refluxing conditions, the ratios of C-17β/C17α (**8/9**) were similar (~80/20) when different equivalents of methoxide were used. When the reaction temperature was 35–40 °C and the reaction time was 8.0–10 h, the ratio of C-17β/C17α was 88/12 (entry 4 in Table 1). Although the reaction conditions in entry 5 provided the best C-17β/C17α ratio, the reaction time was >50 h and therefore not suitable for synthetic purposes.

For the optimization of the C-17β/C17α (**8/9**) ratio, we tried different soft methoxides including LiOMe, $Mg(OMe)_2$ and $Ca(OMe)_2$; however, they gave poorer C-17β/C17α ratios than using NaOMe (see entries 1–3 in Table 2). When we used LiOH or NaOH in methanol, the reaction provided better C-17β/C17α ratios (see entries 4 and 5 in Table 2). The best result was accomplished by using NaOH in MeOH at reflux for 8.0–10 h. The isomeric ratio of C-17β/C17α (**8/9**) was 91/9 and the yield was 98%. After recrystallization from ethyl acetate/hexanes, compound **8** was obtained as white powder in 80% yield with 99.5% purity. Accordingly, bromoketone 10 was synthesized from the reaction of compound **8** with Br_2 in MeOH in the presence of catalytic amount of HBr [24,25] in 86% yield.

The final step was the key in this synthesis because the usual introduction of imidazole functionality in the α-position of a ketone often provided dimeric products [10]. Supporting evidence comes from our direct treatment of bromoketone **10** with imidazole under reflux. The reaction gave a mixture of the final product **11** in 45% yield and a significant amount of dimeric product **12** in 35% yield. When bromoketone **10** was allowed to react with 1-trimethylsilylimidazole [10] or 1-benzylimidazole at reflux [26], no diminishment of dimeric **12** was found and subsequent latter deprotection procedure was troublesome.

To overcome the low-yield and selectivity of the reaction, we developed lithium imidazole as a new alkylation agent for α-bromoketone. We treated bromoketone **10** with lithium imidazole at −5 to 0 °C for 10 min under N_2 atmosphere. After worked-up, the crude **11** was obtained as a light yellow solid in 91% yield. The crude product was crystallized from MeOH/diisopropyl ether to provide the pure **11** as white solid in 82% yield. In this method, the yield of dimeric **12** was very low and could be easily removed by recrystallization. We believe, this new method would be useful for the future production of compound **11** to study its in vivo activity and toxicology.

In conclusion, we developed a new and more efficient route for the synthesis of 3α-hydroxyl-21-(1′-imidazolyl)-3β-methoxymethyl-5α-pregnan-20-one (**11**). It consisted with six steps and the overall yield was 28%. For the ring opening reaction of oxirane **7**, we found the best reaction condition was the use of NaOH in methanol at reflux. The ratio of **8/9** was 91/9 and the yield was 98%. In the key step of introduction of imidazole group, we developed lithium imidazole as new alkylation agent. The formation of dimeric by-product was very low and it can be easily removed by recrystallization. In this conversion, the yield is high (82%). Consequently, a convenient and efficient method for the introduction of imidazole moiety to α-bromoketone was developed via lithium imidazole with the advantage of high yield and low amount of by-product.

Table 2 – The ring opening reaction of oxirane 7 in the presence of different bases (2.5 equiv.) at 35–40 °C in MeOH

Entry	Base	Reaction time (h)	The ratio[a] of 8/9
1	LiOMe	8.0–10	82/18
2	$Mg(OMe)_2$	>30	76/14[b]
3	$Ca(OMe)_2$	>50	72/18[b]
4	LiOH[c]	8.0–10	85/15
5	NaOH[c]	8.0–10	91/9

[a] The area normalization was focused on **8/9** (C-17β/C17α) ratio and detected by HPLC.
[b] The ring opening reaction did not complete and oxirane **7** was residual in the crude mixture.
[c] Under reflux.

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