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Development of a Scalable Process for a Key Intermediate of Rocuronium Bromide: A Neuromuscular Blocking Agent¶

NETI SRINIVASAN†, VIJAYAVITTHAL T. MATHAD, VURIMINDI HIMABINDU†
and JAYDEEPKUMAR LILAKAR*
Dr. Reddy's Laboratories Ltd., Integrated Product Development
Innovation Plaza, Bachupalli, Qutubullapur, RR District-500 072, India
Fax: (91)(40)44346285 ; Tel: (91)(40)44346000
E-mail: jaydeepkumar@drreddys.com

Rocuronium bromide **1** is an amino steroid non-depolarizing neuro muscular blocker or muscle relaxant used in modern anesthesia. An economical process has been developed for large-scale synthesis of key intermediate diepoxide **6** of rocuronium bromide.

Key Words: Rocuronium bromide, (3b, 5a)-3-tosyloxy-androstan-17-one,5a-androst-2-en-17-one,2a,3a,16a,17a-diepoxy-5a-androstan-17b-yl-aetate, Epoxidation.

INTRODUCTION

Rocuronium bromide[1] (Fig. 1) has rapid onset and intermediate of action. It binds competitively to cholinergic receptors on motor end plate to an antagonize action of acetylcholine, resulting in block of neuromuscular transmission[2]. As an adjunct to general anesthesia to facilitate both rapid sequence and routine tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

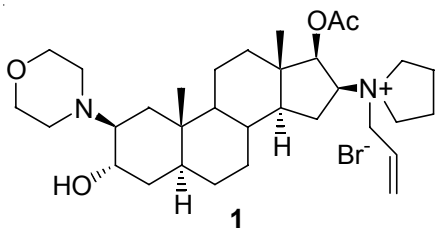

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Fig. 1. Chemical structure of rocuronium bromide

Magni *et al.*[3] accomplished the synthesis of **6**, where in the tosylation of epiandrosterone **2** to yield **3**, followed by olefination to yield **4**, which on *keto-enol* tautomerism afforded the enolic product **5**. It was subjected to epoxidation resulted

†Centre for Environmental Sciences, JNT University, Kukatpally, Hyderabad-500 072, India.
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the desired diepoxy compound **6**. This process has the obstacles for the large scale production, because of poor yields of **4**, operational difficulty and lack of consistency in the reaction of **5**, much emulsion formation in the workup resulting low yield of **6** and the longer reaction time cycles. This process was found to be expensive because of the low yields and poor quality and requires further purifications.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded in $CDCl_3$, on a Varian Gemini 400 MHz FT NMR spectrometer and the chemical shifts are reported in δ ppm relative to TMS. Mass spectra (70 eV) were recorded on HP-5989 A LCMS spectrometer. The solvents and reagents were used without further purification.

(3b,5a)-3-Tosyloxy-androstan-17-one (3): *p*-Toluenesulfonyl chloride (25.0 g, 131.2 mol) was added to the mixture of **1** (25.0 g, 86.2 mol) and pyridine (37.5 mL, 465.6 mol) at 10-15 °C. The reaction was allowed to maintain at 30 °C and stirred for 5 h. The reaction mass was poured in chilled water (375 mL), stirred for 1 h. Filtered the solid, washed with water (375 mL). Dried the solid at 55 °C for 5 h to reach the water content below to 1.0 %; yield: % 98.3; ^{1}H NMR ($CDCl_3$, δ): 7.7 (d, 2H, *J* = 4.8 Hz), 7.3 (d, 2H, *J* = 8 Hz), 2.4 (m, 4H), 2.1 (m, 2H), 1.8 (m, 12H), 1.4 (m, 4H), 0.9 ppm (m, 6H). MS m/z 444. Anal. Calcd. for $C_{26}H_{36}O_4S$; $[\alpha]^{20}_D$: + 43.8° (C = 1.0 $CHCl_3$).

5a-Androst-2-en-17-one (4): (a) To a mixture of acetic acid (45 mL, 78 mol) and sodium acetate (2.77 g, 33.7 mol), compound **3** (15.0 g, 33.7 mol) was added and the reaction mixture was refluxed for **3** h. The reaction mixture was cooled to 30 °C and add water (45 mL) and dichloromethane (2 × 75 mL), stirred for 15 min. The combined organic layer was evaporated under reduced pressure at below 50 °C. 10 % Aqueous methanol (88.5 L) and potassium hydroxide (3.0 kg, 53.5 mol) were added to the resultant crude and refluxed for 45 min to get homogeneity. Then cool down the solution to 10-15 °C, maintained at the same temperature for 2 h. Filtered the solid and washed with chilled methanol (5.25 mL). Dried the compound at 60 °C to attain the moisture content to below 0.5 %; yield: 57.1 %; ^{1}H NMR ($CDCl_3$, δ): 5.5 (q, 2H, *J* = 2.8 Hz), 2.0 (m, 8H), 1.8 (m, 3H), 1.3 (m, 9H), 0.9 ppm (m, 6H). MS m/z 272. Anal. Calcd. for $C_{19}H_{28}O$; $[\alpha]^{20}_D$: +144.6° (C = 1.0 EtOH).

(b) The methanol filtrate was concentrated to 80 % and cool down to 5 °C, stirred for 1 h. Filtered the solid, dried at 55 °C for 5 h. This solid consists of around 70 % compound **7** and 30 % compound **4**. The second crop material was further tosylated by considering the active component androsterone as 70-75 % and the reagents were added respectively, followed by the same procedure as mentioned in experimental section 1 and 2 (a); yield: % 34.3; Androsterone **7** $[\alpha]^{15}_D$: +87.8° (C=1.5 in dioxane); Epi androsterone **2** $[\alpha]^{20}_D$: +88° (C=1.0 in methanol).

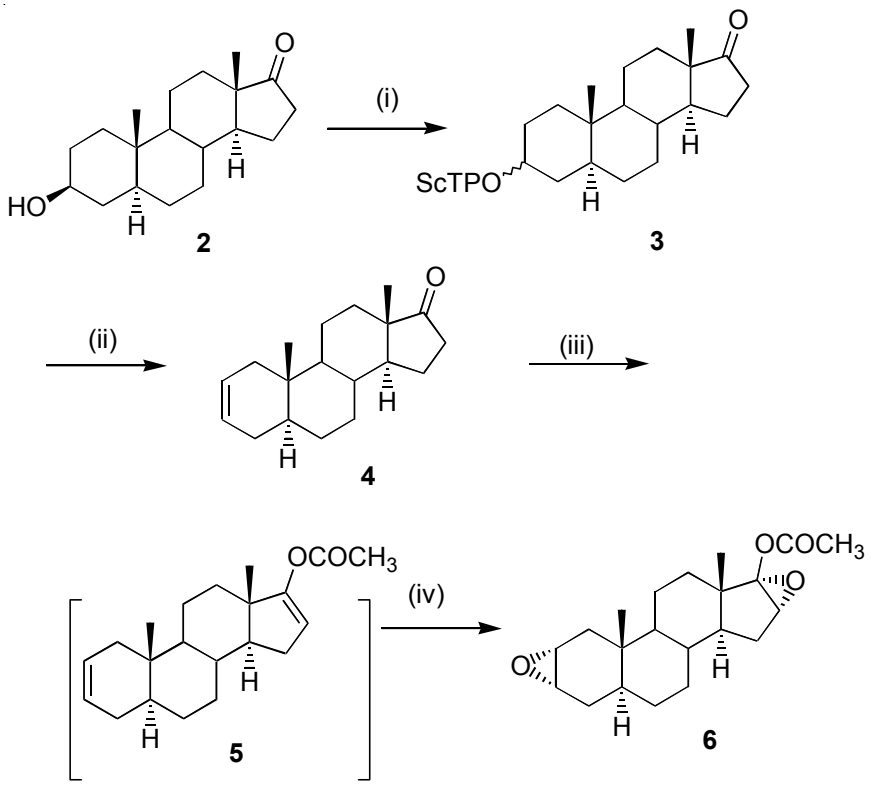
2a,3a,16a,17a-Diepoxy-5a-androstan-17b-yl-aetate (6): A solution of **4** (20 g, 73.5 mol) and isopropenyl acetate (200 mL) was refluxed for 1.5 h under dean-stark attachment (azeotropic reflux mode) added of a mixture of isopropenyl acetate (20

mL) and conc. sulfuric acid (0.96 mL, 18.8 mol) at reflux condition for 1 h and maintained under the same conditions for 2 h under nitrogen atmosphere. The reaction mixture was cooled to 10-20 °C under nitrogen atmosphere. Poured the reaction mass into 10 % sodium carbonate solution (400 mL) under nitrogen atmosphere, separated the organic layer. The acetate extract was washed with water at 10-20 °C. Sodium sulfate (10 kg) was added to the organic layer, stirred for 0.5 h. Filtered the sodium sulfate and washed with isopropenyl acetate (20 mL). Evaporated the organic layer to 80 % of the volume in vacuum. Cool down the resultant crude to 25-35 °C and added cyclohexane (300 mL) and water (200 mL), stirred for 20 min. Filtered the solution through celite, separated the hexane layer. Concentrated the hexane under vacuum below 50 °C afforded **5**. Dissolved the obtained crude **5** in chloroform (200 mL) and cooled to 0-5 °C. A dissolved solution of *meta* chloro perbenzoic acid (40 g, 232.5 mol) and chloroform (200 mL) which was separated from water was added to the above chloroform solution at 0-5 °C, stirred for 8 h at the same temperature. 5 % Sodium hydroxide solution (400 mL) was added to the reaction mass, stirred for 0.5 h and passed through celite pad. The chloroform extract was washed with brine (200 mL), dried over sodium sulfate (5 g) and evaporated. Crystallized the white solid from isopropanol (15 mL), dried at 50 °C for 4 h; yield: % 65.0; ^{1}H NMR ($CDCl_3$, δ): 3.8 (m, 1H), 3.1 (m, 2H), 2.1 (s, 3H), 1.8 (m, 2H), 1.5 (m, 4H), 1.2 (m, 12H), 0.8 ppm (m, 6H). MS m/z 346. Anal. Calcd. for $C_{21}H_{30}O_4$; $[\alpha]^{20}_D$: +20.2° (C = 1.0 $CHCl_3$).

RESULTS AND DISCUSSION

In present approach **6** is identified the scalable process to prepare the key intermediate diepoxide compound of rocuronium bromide. Since the reported synthesis is deteriorating wit respect to yields, incompletion of the reactions and difficulties involved in operations, is commercially not feasible for large-scale production.

Present approach (**Scheme-I**) also started with **2**, which was protected with *p*-tolyl sulfonyl chloride (*p*-TsCl) in presence of pyridine to give **3** with 98 %. The olefination of tosyl moiety **3** with acetic acid and sodium acetate furnished **4** in a moderate yield 91 % by established the process of recovered back the compound **4** from methanol filtrate. By employing the azeotropic reflux mode the reaction of the formation of **5** is free from water till the reaction mass has been quenched with the 10 % sodium carbonate solution, the reaction is completed with more product concentration. It is found that the compound **5** is highly unstable upon holding, it was proceeded to further stage directly by taken the crude in chloroform. With the optimized quantities of aqueous sodium hydroxide and brine washings and by employing the filtration passed through celite, we made the process of workup is operational friendly and crystallized the material **6** with a proper polar solvent isopropanol and end up with desired quality material. Further, optimization of time (15 h) and temperature (0-5 °C) enabled the monoepoxy impurity **9** to be controlled to a level of 0.3 % by GC.



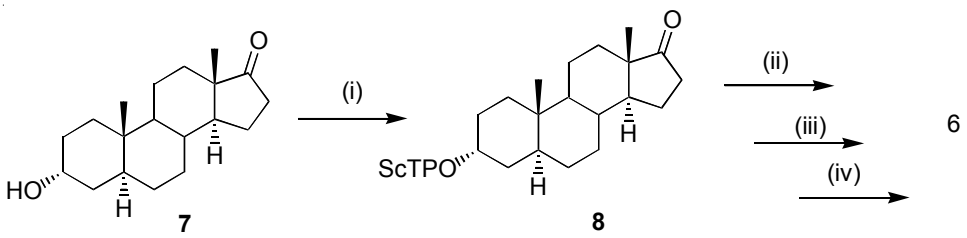
Reagents and conditions: (i) *para*-toluene sulphonyl chloride, pyridine, 5 h, 25-35 °C; (ii) acetic acid, sodium acetate, 3 h, reflux/10 % aq. methanol, KOH, 45 min, reflux; (iii) sulfuric acid, isopropenyl acetate, 2 h, reflux; (iv) *m*-CPBA, chloroform, 8 h, 0-5°C

Scheme-I: Preparation of 2a,3a,16a,17a-diepoxy-5a-androstan-17b-yl-aetate prepared from epiandrosterone

In addition to the above, we have identified a route (**Scheme-II**) commenced from androsterone **7** to achieve the desired **6** by followed the same modified scalable process (experimental section 1-3). It had observed that, in step 2 of **Scheme-I** androsterone **7** is the byproduct and epiandrosterone **2** is the byproduct in step-2 of **Scheme-III** and can be proceeded with any of the byproduct to get the desired compound **6** to overcome the yield drop and to make the process is more economical.

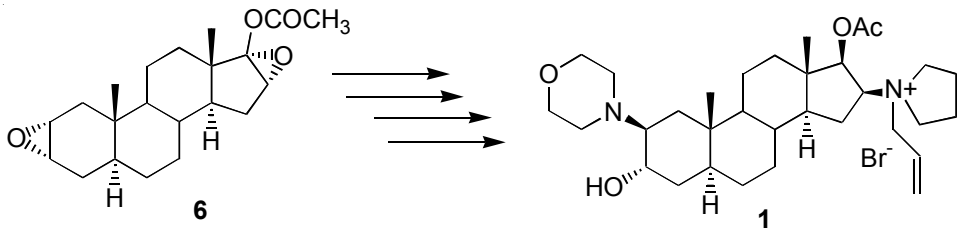
Conclusion

The authors presented an economically competitive synthesis of key intermediate diepoxy compound **6** from epiandrosterone **2** and androsterone **7** with moderate yields and with optimized quantities in a less reaction time cycle. The modified scalable route is well applicable for the **Scheme-III** resulting the same yields and quality with the starting compound androsterone **7**.



Reagents and conditions: (i) *para*-toluene sulphonyl chloride, pyridine, 5 h, 25-35 °C; (ii) acetic acid, sodium acetate, 3 h, reflux/10 % aq. methanol, KOH, 45 min, reflux (iii) sulfuric acid, isopropenyl acetate, 2 h, reflux (iv) *m*-CPBA, chloroform, 8 h, 0-5 °C

Scheme-II: Preparation of 2a,3a,16a,17a-diepoxy-5a-androstan-17b-yl-aetate prepared from androsterone



Scheme-III: Synthesis of rocuronium bromide[4] from diepoxide intermediate **6**

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