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First synthesis and characterization for the stereoisomers of Ulipristal acetate

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ABSTRACT

The three stereoisomers, 11α,17α-isomer **I**, 11α,17β-isomer **II** and 11β,17β-isomer **III** are related substances of the selective progesterone receptor modulator Ulipristal acetate. Herein, we presented an efficient and practical synthesis approach to deliver these three stereoisomers for the first time, and also confirmed the structure of the key intermediate **5a** by single-crystal X-ray analysis. Our research will be of immense help for organic chemists to study the impurity profile of Ulipristal acetate.

1. Introduction

The presence of impurities, especially chiral impurities in an active pharmaceutical ingredient (API) has a significant impact on the quality and safety of the drug products. Therefore, it is necessary to study the impurity profiles of any API and try to control it during the manufacturing of a drug product. As per the International Conference on Harmonization (ICH) guidelines any impurities, which are forming at a level of ⩾0.10% with respect to the API, should be identified, synthesized and characterized thoroughly [1,2].

17α-Acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (Ulipristal, Ella®, VA-2914 or CDB-2914, Fig. 1) is a well-known, more specific 19-norprogesterone and a selective progesterone receptor modulator (SPRM) which efficiently binds and inhibits progesterone receptor (PR) in progesterone target tissues [3]. Ulipristal acetate is well characterized for its anti-fertility potency in several of in vivo and in vitro assays. Different from the active metabolites, Ulipristal acetate expresses less antiglucocorticoid activity compared with the most well-known SPRM and mifepristone Besides, it also exhibits benefits for endometriosis treatment, as well as ovarian and breast cancer therapies [4].

Therefore, several methods have been developed so far for the synthesis of Ulipristal acetate [5–9]. However, two chiral centers in the Ulipristal acetate molecule from the starting materials can give rise to four stereoisomers including Ulipristal acetate (Fig. 2) [5,8,9]. Thus, the synthesis of the final product with the required stereochemistry is a significant challenge. Furthermore, these stereoisomers play essential roles for the preparation of Ulipristal acetate and also for the quality control of bulk drugs and drug formulations. In this report, we have designed and synthesized the stereoisomers of Ulipristal acetate. More importantly, the configuration of each isomer was also confirmed.

2. Experimental

All reactions were carried out under an argon atmosphere. Most chemicals and solvents were analytical grade and used without further purification. TLC was performed using precoated silica gel GF254 (0.2 mm), while column chromatography was performed using silica gel (100–200 mesh). The melting point was measured on an YRT-3 melting point apparatus (Shantou Keyi instrument & Equipment Co. Ltd., Shantou, China). IR spectra were obtained on a Perkin Elmer 983 (Perkin Elmer, Norwalk, CT, USA). ^{1}H NMR spectra were taken on a Varian INOVA 400 (Varian, Palo Alto, CA, USA) using $CDCl_3$, d-DMSO and D_2O as solvent. Chemical shifts are expressed in δ (ppm), with tetramethylsilane (TMS) functioning as the internal reference, and coupling constants (J) were expressed in Hz. Mass

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spectra were recorded on an Agilent 1946B ESI-MS instrument (Agilent, Palo Alto, CA, USA).

(1) Synthesis of the key intermediate **5**:

*2.1. 3,3-(Ethylene-dioxy)-5β,10β-epoxyestr-9(11)-ene-17-one(**2b**)*

Hexachloroacetone (14.5 mL, 0.0954 mol), 30% aqueous hydrogen peroxide (14.1 mL, 0.477 mol) and sodium phosphate dibasic dodecahydrate (34.5 g, 0.0964 mol) were added to methylene chloride (300 mL) at 0 °C. The mixture was stirred for 1 h at the same temperature. The material **1** (30 g, 0.0954 mol) was added to above mixture. The reaction mixture was stirred for another 18 h at the same temperature. Then, it was poured into a mixture of methylene chloride (200 mL) and ice (160 g). A solution of sodium thiosulfate (79 g, 0.5 mol) in water (300 mL) was added dropwise to the mixture to destroy the excess of hydrogen peroxide. After separation, the organic fraction was washed with water (2 × 100 mL) and dried on sodium sulfate. The solvent was removed in vacuo to give 32 g (100%) of product, which was a 65:35 mixture of the 5α,10α- and 5β,10β-epoxides showed by HPLC. The obtained crude mixture of epoxides was recrystallized with petroleum ether/ethyl acetate (5:1) to get 12.8 g (40%) white solid **2a**. The filtrate was concentrated in vacuo to yield 19.2 g (60%) of a 42:58 mixture of the 5α,10α- and 5β,10β-epoxides. Then the mixture was purified via column chromatography (petroleum ether/ethyl acetate 10:1) to give 6.91 g (36%) white solid **2b**. mp: 158–160 °C, MS (*m*/*z*): 331.42 $[M+H]^+$, Analysis calculated for $C_{20}H_{26}O_4$: C 72.70, H 7.93; found: C 72.80, H 7.89. ^{1}H NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.861 (s, 3H, CH_3), 1.201–2.511 (m, 18H), 3.796–3.961 (m, 4H, O—CH_2), 5.851 (d, 1H, *J* = 2.8, =CH).

*2.2. 3,3-(Ethylene-dioxy)-17α-ethynyl-17β-hydroxy-5β,10β-epoxyestr-9(11)-ene (**3b**)*

Under argon, **2b** (6.8 g, 0.02 mol) was dissolved in dry tetrahydrofuran (70 mL) at 0 °C, and sodium acetylide (1.9 g, 0.04 mol) was added. The mixture was stirred for 1 h. Saturated ammonium chloride solution (50 mL) and water (50 mL) were added, then, the reaction mixture was stirred for 10 min. Then the reaction mixture was concentrated to a volume of 80 mL. The residue was stirred for 3 h at 0 °C. The precipitated crystals were filtered off and dried at 50 °C to yield 7.3 g (100%) of the title compound **3b**, mp: 154–156 °C, MS (*m*/*z*): 379.48 $[M+Na]^+$, Analysis calculated for $C_{22}H_{28}O_4$: C 74.13, H 7.92; found: C 74.21, H 7.89. ^{1}H NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.825 (s, 3H, CH_3), 1.081–2.627 (m, 18H), 2.557 (s, 1H, acetylenic hydrogen), 3.867–3.946(m, 4H, O—CH_2), 5.890 (t, 1H, *J* = 4.4, =CH).

*2.3. 3,3-(Ethylene-dioxy)-5β,17β-dihydroxy-11α-(4-N,N-dimethylaminophenyl)-19-nor-17α-pregn-9-ene-21-ethyne(**4b**)*

Under anhydrous conditions, a portion (2 mL) of a solution of 4-bromo-N,N-dimethylaniline (12 g, 0.06 mol) in dry tetrahydrofuran (50 mL) and one crystal of iodine was added to the mixture of magnesium (1.7 g, 0.07 mol) in dry tetrahydrofuran (5 mL) at 50 °C. After evidence of reaction was observed, the entire amount of the reagent was added dropwise. The reaction mixture was stirred for an additional 2 h while it was cooling to room temperature. The mixture was then added dropwise to a suspension of **3b** (7.0 g, 0.02 mol) and copper (**I**) chloride (0.6 g, 0.002 mol) in dry tetrahydrofuran (70 mL) at 0 °C. The reaction mixture was stirred for 1 h, then, it was poured into 10% ammonium chloride (70 mL) solution and extracted with methylene chloride (3 × 50 mL). The combined organic fractions were washed with water (4 × 50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to give a black oil (21.1 g). The oil was purified via column chromatography (petroleum ether–ethyl acetate 10:1) to yield 5.23 g (55%) light blue solid. mp: 162–164 °C, MS (*m*/*z*): 478.62 $[M+H]^+$, Analysis calculated for $C_{30}H_{39}NO_4$: C 75.44, H 8.23, N 2.93; found: C 75.55, H 8.28, N 2.75. ^{1}H NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.970 (s, 3H, CH_3), 0.842–2.332 (m, 18H), 2.474 (s, 1H, acetylenic hydrogen), 2.923 (s, 6H, N—CH_3), 3.716 (t, 1H, *J* = 6.4, CH), 3.820–4.022(m, 4H, O—CH_2), 6.680(d, 2H, *J* = 8.4, Ar—H), 7.048 (d, 2H, *J* = 8.4, Ar—H).

*2.4. 11α-(4-N,N-dimethylaminophenyl)-17α-ethynyl-17β-hydroxyestr-4,9-diene-3-one(**5**)*

To a solution of potassium bisulfate (3.7 g, 0.027 mol) in water (50 mL) was added compound **4b** (5 g, 0.01 mol) at 0 °C. The mixture was stirred for 5 h and almost became clear. Then, saturated sodium bicarbonate was added to the above mixture to adjust pH to 7–8. The precipitated crystals were filtered off and dried at 50 °C to yield 2.7 g (65%) of the title compound **5**. mp: 134–136 °C, MS (*m*/*z*): 416.58 $[M+H]^+$, Analysis calculated for $C_{28}H_{33}NO_2$: C 80.93, H 8.00, N 3.37; found: C 80.85, H 8.18, N3.28. ^{1}H NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}: 1.005 (s, 3H, CH_3), 1.396–2.628 (m, 16H), 2.476 (s, 1H, acetylenic hydrogen), 2.920 (s, 6H, N—CH_3), 3.899 (t, 1H, *J* = 8.8, CH), 5.664 (s, 1H, =CH), 6.680 (d, 2H, *J* = 8.4, Ar—H), 6.952 (d, 2H, *J* = 8.4, Ar—H).

(2) Synthesis of 11α,17α-isomer **I**:

*2.5. 11α-(4-N,N-dimethylaminophenyl)-21-(phenyl-sulfinyl)-19-norpregna-4,9,17(20),20-tetraene-3-one (**6**)*

To a suspension of compound **5** (1.5 g, 0.0036 mol), triethylamine (2.2 mL, 0.0152 mol) in dry tetrahydrofuran (20 mL), a solution of phenylsulfenyl chloride (0.9 g, 0.0062 mol) in dry tetrahydrofuran (15 mL) was added dropwise while keeping the temperature between −70 and −78 °C. The reaction mixture was stirred for 4 h at −78 °C, then water (20 mL) and methanol (20 mL) was added. The reaction mixture was stirred for 10 min and extracted with methylene chloride (3 × 40 mL). The combined organic fractions were washed with water (4 × 20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to get 2.5 g of a reddish brown oil. The oil was purified via column chromatography (petroleum ether–ethyl acetate 5:1) to yield 1.18 g (62.5%) of white solid. mp: 151–155 °C. MS (*m*/*z*): 546.78 $[M+Na]^+$, Analysis calculated for $C_{34}H_{37}NO_2S$: C77.97, H 7.12, N 2.67, S 6.12; found: C 77.84, H 7.21, N 2.75, S 6.18. ^{1}H NMR {400 MHz, CDCl3 (TMS), δ (ppm)}: 1.042 (s, 3H, CH_3), 1.213–2.767 (m, 16H), 2.900 (s, 6H, N—CH_3), 3.967 (t, 1H, *J* = 8.8, CH), 5.681 (s, 1H, =CH), 6.075 (s, 1H, =CH), 6.634 (d, 2H, *J* = 8.4, Ar—H), 6.888 (d, 2H, *J* = 8.4, Ar—H), 7.460–7.539 (m, 3H, Ar—H), 7.626 (d, 2H, *J* = 7.2, Ar—H).

*2.6. 11α-(4-N,N-dimethylaminophenyl)-17α-hydroxy-19-norpregna-4,9-diene-3,20-dione(**7**)*

Compound **6** (1.1 g, 0.0021 mol) was added to a solution of sodium methoxide (0.11 g, 0.0021 mol) in methanol (20 mL). The reaction mixture was stirred at 50 °C for 1 h, then trimethyl

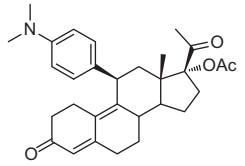

Fig. 1. The structures of Ulipristal acetate.