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A simple and convenient synthetic route to Ulipristal acetate

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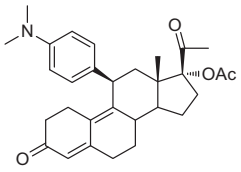
ABSTRACT

We set out to describe a new and efficient route for preparing Ulipristal acetate with a good yield. The selected epoxidization conditions gave out 80% of 5α,10α-epoxide **2a** in the two diastereoisomers which greatly improved the yield of 11β-substituted isomer **4a**. And phenyl–sulfinyl compound **6** was synthesized from ketone **5** directly treated with phenylsulfenyl chloride in the presence of triethylamine. These synthetic procedures is only 8 steps, less than currently reported in the literature, but more suitable for industrial process.

1. Introduction

A great number of 11β-substituted norpregna compounds with antiprogestational and/or antiglucocorticoid activity were synthesized by Teutsch's method [1–5]. Among them, 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione, represented by formula **I**, is a well-known steroid and more specifically 19-norprogesterone, which possesses appropriate antiprogestational and antiglucocorticoidal activity as progesterone receptor blocker/antagonist [1].



I

In 2010, the acetate form of Ulipristal was approved by FDA as emergency contraceptive pill, with the trade name Ella to be used for pregnancy prevention within 120 h after unprotected sex or known or suspected contraceptive failure. As a selective progesterone receptor modulator (SPRM), *in vivo*, Ulipristal has much weaker antiglucocorticoid activity than mifepristone as a result of differences in their active metabolites. Compared with the most commonly used emergency contraceptive levonorgestrel, its clinical applicability is wider, and more potential to prevent unwanted pregnancies [6].

Cook CE, et al. [1] used 3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene as the starting material, and processed about 9 steps to give Ulipristal acetate with total yield of about 0.62%. However, this route introduced osmium tetroxide which is not only expensive but also highly toxic and hazardous from the point of environment protection. Thus this route is not suitable for industrial process. Kim HK, et al. [7] used 3-ethylendioxy-17β-cyano-17α-hydroxy-5(10),9(11)-diene as the starting material via 7 steps yield about 12.5%. But the synthesis of the starting material must use the highly toxic KCN or acetone cyanohydrin. Kim group. [8] started with 17α-hydroxy-19-norpregnen-4,9-diene-3,20-dione to yield the total yield of about 19.5%. Unfortunately, the starting material was expensive, in part because the synthesis of the starting material must even use the highly toxic osmium tetroxide or KCN or acetone cyanohydrins. Dancsi L, et al. [9] used 3-(ethylene-dioxy)-estra-5(10),9(11)-diene-17-one as the starting material. This route is 9 steps with 14% total yield. And the proportion of the 5α,10α and 5β,10β in the epoxidized biketal is about 55/45, which led to up to 45% waste of isomer.

The above four routes currently reported in the literature gave unsatisfactory yield and relatively complex process. Therefore this study aim at a simple and convenient synthetic route (Scheme 1)

3-Ethylenedioxy-estra-5(10),9(11)-diene-17-one **1** was epoxidized with hydrogen peroxide to give two diastereoisomers, 3-ethylene-dioxy-estra-5α,10α-epoxy-9(11)-ene-17-one **2a** and 3-(ethylene-dioxy)-estra-5β,10β-epoxy-9(11)-ene-17-one **2b** (**2a**/**2b** = 80/20)

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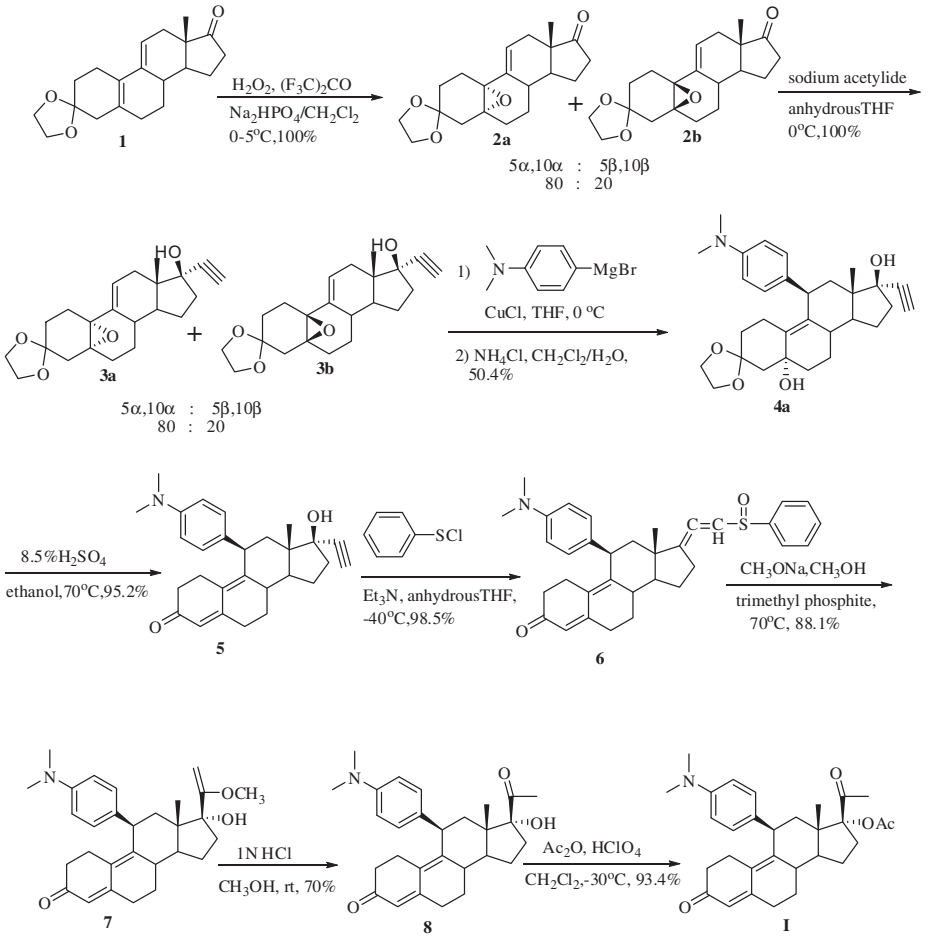


Scheme 1. Synthesis of Ulipristal acetate.

in dichloromethane. The above mixture without separation was reacted with sodium acetylide in anhydrous THF to afford 3-ethylenedioxy-estra-5α,10α-epoxy-17α-ethynyl-17β-hydroxy-9(11)-ene **3a** and 3-(ethylene-dioxy)-estra-5β,10β-epoxy-17α-ethynyl-17β-hydroxy -9(11)-ene **3b** (**3a**/**3b** = 80/20). Both of them underwent copper catalyzed Grignard addition to get out 3-ethylenedioxy-estra-5α-hydroxy-11β-(4-N,N-dimethylaminophenyl)-17α-ethynyl-17β-hydroxy-9-ene **4** at 0 °C. Treatment of this compound with a 10:1 mixture of ethanol and 8.5 vol% sulfuric acid solution at 70 °C yielded 11β-(4-N,N-dimetnylaminophenyl)-17α-ethynyl-17β-hydroxy-estra-4,9-diene-3-one **5**. The ketone **5** was then reacted with phenylsulfenyl chloride in the presence of triethylamine in anhydrous THF at −78 °C to form 11β-(4-N,N-dimetnylaminophenyl)-21-(phenyl-sulfinyl)-19-norpregna-4,9,17(20),20-tetraene-3-one **6**. The compound **6** is coupled with sodium methoxide in methanol, then treated with trimethyl phosphate at 70 °C to provide 11β-(4-N,N-dimetnylaminophenyl)-17α-hydroxy-20-methoxy-19-norpregna-4,9,20-triene-3-one 7, which was hydrolyzed in the presence of diluted HCl in methanol at room temperature to give 11β-(4-N,N-dimetnylaminophenyl)-17α-hydroxy-19-norpregna-4,9-diene-3,20-dione **8**. To the mixture of acetic acid and perchloric acid, a solution of the above dione **8** in methylene chloride is added with a slow speed at −30 °C to give the desired Ulipristal Acetate **I**. All the route is about 8 steps and the crude yield is about 27.2%.

2. Experimental

All reactions were carried out under a 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 a YRT-3 melting point apparatus (Shantou Keyi instrument & Equipment Co. Ltd., Shantou, China). IR spectra were obtained on a Perkin Elmer983 (Perkin Elmer, Norwalk, CT, USA). ^{1}H NMR spectra were taken on a Varian INOVA400 (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 spectra were recorded on an Agilent 1946B ESI–MS instrument (Agilent, Palo Alto, CA, USA).

*2.1. 3-(ethylene-dioxy)-estra-5α,10α-epoxy-9(11)-ene-17-one(**2a**) and 3-(ethylene-dioxy)-estra-5β,10β-epoxy-9(11)-ene-17-one(**2b**)*

Hexafluoroacetone (0.4 ml, 0.0032 mol) and 30% aqueous hydrogen peroxide (1.6 ml 0.0541 mol) and sodium phosphate dibasic dodecahydrate (11.5 g, 0.0321 mol) were added to a solution of **1** (10 g, 0.0318 mol) in methylene chloride (100 ml) at 0 °C. The reaction mixture was stirred for 18 h at the same temperature. Then, it was poured into a mixture of methylene chloride (140 ml) and ice (160 g). A solution of sodium thiosulphate (31.6 g, 0.2 mol) in water (140 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 sulphate. The solvent was removed in vacuo to give 10.6 g (100%) of product, which was a 80:20 mixture of the 5α,10α- and 5β,10β-epoxides showed by HPLC. The obtained crude

mixture of epoxides was used in the next step without further purification. (**2a**/**2b**) MS(*m*/*z*): 331.42 (M+H), Analysis calculated for $C_{20}H_{26}O_4$: C 72.70, H 7.93; found: C 72.58, H 7.88. ^{1}H NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.874 (s, 3H, CH_3), 1.214–2.509 (m, 18H), 3.876–3.966 (m, 4H), 5β,10β: 5.860 (d, 1H, *J* = 2.8,=CH), 5α,10α: 6.054 (d, 1H, *J* = 2.8,=CH).

2.2. 3-(ethylene-dioxy)-estra-5α,10α-epoxy-17α-ethynyl-17β-hydroxy-9(11)-ene(**3a**) and 3-(ethylene-dioxy)-estra-5β,10β-epoxy-17α-ethynyl-17β-hydroxy -9(11)-ene (**3b**)

Under nitrogen the mixture of **2a** and **2b** (10.5 g, 0.031 mol) was dissolved in dry tetrahydrofuran (160 ml) at 0 °C, and sodium acetylide (3 g, 0.0636 mol) was added. The mixture was stirred for 1 h. Saturated ammonium chloride solution (75 ml) and water (200 ml) were added and the reaction mixture was stirred for 10 min. Then the reaction mixture was concentrated to a volume of 200 ml. The residue was stirred for 3 h at 0 °C. The precipitated crystals were filtered off and dried at 50 °C to yield 11.3 g (100%) of the title compound. (**3a**/**3b**) MS(*m*/*z*): 379.48 (M+Na), Analysis calculated for $C_{22}H_{28}O_4$: C 74.13, H 7.92; found: C 74.08, H 7.80. ^{1}H NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.846 (s, 3H, CH_3), 1.149–2.663 (m, 17H), 2.557 (s, 1H, acetylenic hydrogen), 3.878–3.943(m, 4H, O–CH_2), 5β,10β: 5.574 (t, 1H, *J* = 5.27,=CH), 5α,10α: 5.751 (t, 1H, *J* = 5.27,=CH).

2.3. 3-(ethylene-dioxy)-estra-5α-hydroxy-11β-(4-N,N-dimethylaminophenyl)-17α-ethynyl-17β-hydroxy-9-ene(**4a**)

Under anhydrous conditions, to the mixture of magnesium (3.1 g, 0.1272 mol) in dry tetrahydrofuran (10 ml), a portion (4 ml) of a solution of 4-bromo-N,N-dimethylaniline (22.3 g, 0.1113 mol) in dry tetrahydrofuran (100 ml) and one crystal of iodine was added 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 **3** (11.3 g, 0.03181 mol) and copper (I) chloride (0.96 g, 0.0032 mol) in dry tetrahydrofuran (110 ml) at 0 °C. The reaction mixture was stirred for 1 h, and then, it was poured into 10% ammonium chloride (70 ml) solution and extracted with methylene chloride (3 × 100 ml). The combined organic fractions were washed with water (4 × 70 ml), dried over sodium sulfate, filtered, and concentrated in vacuo to give a black oil (31.2 g). Diisopropyl ether was added to the residue, and the mixture was stirred for 3 h at room temperature. The precipitated crystals were filtered off and dried at 50 °C to yield light blue solid (14.4 g). The solid was crystallized in n-hexane/dioxane (3:1) to give 7.66 g (50.4%) of the title compound. mp: 181–183 °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 75.48, H 8.30, N 2.87. ^{1}H NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.969 (s, 3H, CH_3), 0.855–2.795 (m, 19H,), 2.475 (s, 1H, acetylenic hydrogen), 2.928 (s, 6H, N–CH_3), 3.688 (br, 1H, OH), 3.809–4.475 (m, 4H, O–CH_2), 4.475 (d, 1H, *J* = 6.4), 6.758 (d, 2H, *J* = 8.4), 7.044 (d, 2H, *J* = 8.4).

2.4. 11β-(4-N,N-dimetnylaminophenyl)-17α-ethynyl-17β-hydroxy-estra-4,9-diene-3-one(**5**)

8.5% aqueous sulfuric acid (3.8 ml) was added to a solution of compound **4** in ethanol (70 ml) under a nitrogen atmosphere. The reaction mixture was stirred for 2 h at 70 °C. After neutralizing with saturated sodium bicarbonate, the mixture was diluted with water (200 ml). The precipitated crystals were filtered off and dried at 50 °C to yield 6.34 g (95.2%) light white solid. The obtained crude product was used in the next step without further purification. mp: 120–123 °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 80.89, H 7.98, N 3.35. ^{1}H NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.555 (s, 3H, CH_3), 0.789–2.778 (m, 16H), 2.636 (s, 1H, acetylenic hydrogen), 2.937 (s, 6H, N–CH_3), 4.376 (d, 1H, J = 6.4), 5.760 (s, 1H, C=CH), 6.669 (d, 2H, J = 7.6), 7.039 (d, 2H, J = 7.6).

2.5. 11β-(4-N,N-dimetnylaminophenyl)-21-(phenyl-sulfinyl)-19-norpregna-4,9,17(20),20-tetr aene-3-one (6)

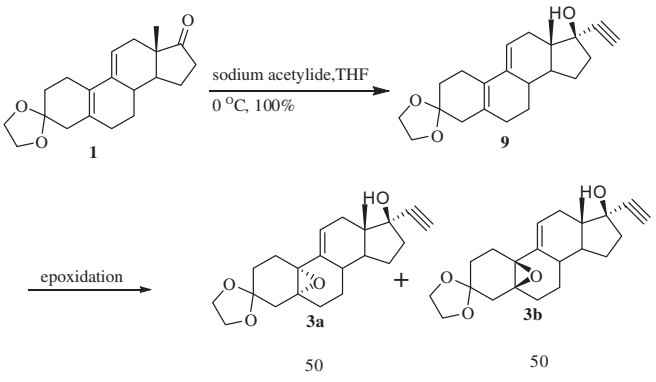
To a suspension of compound **5** (6.34 g, 0.0152 mol), triethylamine (8.8 ml, 0.0608 mol) in dry tetrahydrofuran (60 ml), a solution of phenylsulfenyl chloride (3.76 g, 0.026 mol) in dry tetrahydrofuran (30 ml) was added dropwise while keeping the temperature between −70 and −78 °C. The reaction mixture was stirred for 2 h at −78 °C, then water (100 ml) and methanol (50 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 × 70 ml), dried over sodium sulfate, filtered, and concentrated in vacuo to give 7.87 g(98.5%) of a reddish brown oil. 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 77.95, H 7.05, N 2.70, S 6.08. ^{1}H NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.618 (s, 3H, CH_3), 0.828–2.816 (m, 16H), 2.953 (s, 6H, N–CH_3), 4.272 (d, 1H, *J* = 6.8), 5.753 (s, 1H, C=CH), 6.152 (m, 1H), 6.695 (d, 2H, *J* = 7.6), 7.000 (d, 2H, *J* = 7.6), 7.475–7.576 (m, 3H), 7.644 (t, 2H, *J* = 7.6).

2.6. 11β-(4-N,N-dimetnylaminophenyl)-17α-hydroxy-20-methoxy-19-norpregna-4,9,20-triene -3-one(**7**)

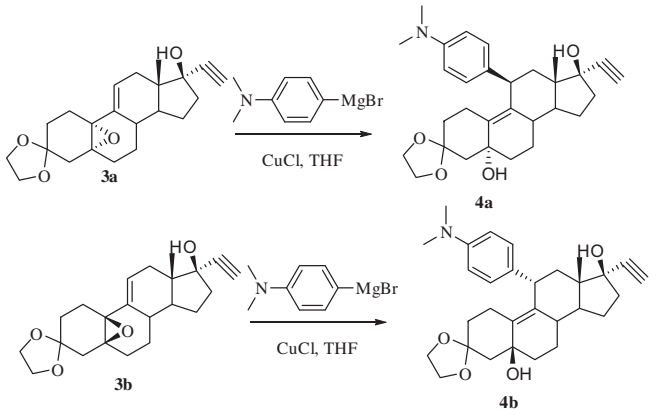
To a solution of sodium methoxide (0.75 g, 0.015 mol) in methanol (70 ml), compound **6** (7.87 g, 0.015 mol) was added. The reaction mixture was stirred at 70 °C for 1 h, then trimethyl phosphite (2.85 g, 0.0226 mol) was added and stirring was continued at 70 °C for 2 h. The reaction mixture was cooled to 20 °C and poured into water (200 ml), then extracted with methylene chloride (3 × 40 ml). The combined organic fractions were dried over sodium sulfate, filtered, and concentrated in vacuo to give 6.72 g (88.1%) of a reddish brown oil. The obtained crude product was used in the next step without further purification. MS(*m*/*z*): 448.62 (M + H), Analysis calculated for $C_{29}H_{37}NO_3$: C77.82, H 8.33, N 3.13; found: C 77.88, H 8.37, N 3.08. ^{1}H NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.359 (s, 3H, CH_3), 1.258–2.795 (m, 16H), 2.913 (s, 6H, N–CH_3), 2.919 (s, 1H, OH), 3.589 (s, 3H, O–CH_3), 4.045 (d, 1H, *J* = 2.8, C=CH_2), 4.206 (d, 1H, *J* = 2.8, C=CH_2), 4.327 (d, 1H, *J* = 6.8), 5.740 (s, 1H, C=CH), 6.665 (d, 2H, *J* = 7.6), 7.016 (d, 2H, *J* = 7.6).

2.7. 11β-(4-N,N-dimetnylaminophenyl)-17α-hydroxy-19-norpregna-4,9-diene-3,20-dione(**8**)

A suspension of compound **7** (6.72 g) in a mixture of 1 N hydrochloric acid (3.3 ml) and methanol (60 ml) was stirred at room temperature for 30 min, then ice water (200 ml) was added. After neutralizing with saturated sodium bicarbonate, the precipitated crystals were filtered off and dried at 50 °C to yield 6.05 g off-white solid. Purification via column chromatography (petroleum ether–ethyl acetate 10:1) gave 4.55 g (70%) off-white solid. mp: 124–127 °C. HPLC: 99.1%; MS(*m*/*z*): 434.58 (M + H), Analysis calculated for $C_{28}H_{35}NO_3$: C 77.56, H 8.14, N 3.23; found: C 77.52, H 8.11, N 3.18. ^{1}H NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.466 (s, 3H, CH_3), 0.827–2.785 (m, 16H), 2.259 (s, 3H, $COCH_3$), 2.911 (s, 6H, N–CH_3), 4.376 (d, 1H, *J* = 6.4), 5.760 (s, 1H, C=CH), 6.669 (d, 2H, *J* = 7.6), 7.039 (d, 2H, *J* = 7.6).



Scheme 2. Synthesis of the intermediates **3a/3b**.



Scheme 3. Synthesis of 11β(**4a**) and 11α(**4b**)-substituted isomers.

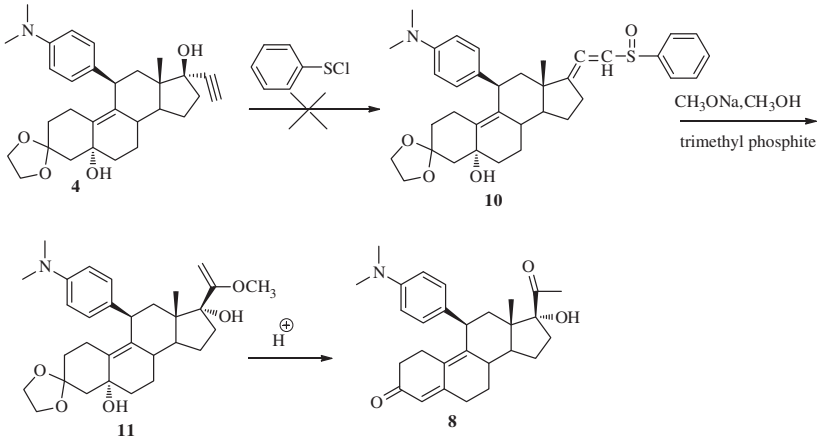
2.8. Ulipristal acetate (*I*)

Acetic anhydride (9.9 ml, 0.105 mol) was cooled to −10 °C and perchloric acid was added (1.5 ml, 0.0171 mol). The so obtained solution was cooled to −30 °C and the solution of compound **8** (4.55 g, 0.0105 mol) in dichloromethane (50 ml) was added at such rate to keep the temperature between −20 and −30 °C, then the reaction mixture was stirred at this temperature for 2 h. The mixture was diluted with dichloromethane (100 ml) and poured into water (100 ml) containing sodium acetate (1.4 g, 0.017 mol). The organic layer was separated, washed with water (3 × 30 ml), dried over sodium sulfate and concentrated under reduced pressure to give 4.66 g (93.4%) off-white syrupy. mp: 183–185 °C. HPLC: 98.9%; FTIR (KBr, diffuse reflectance): γ_{max} 2941; 1733 and 1715 (–C=O); 1663 and 1659 (conjugated –C=O); 1565; 1520; 1438; 1355; 1303; 1254; 1209; 1168; HRMS: calculated for $C_{30}H_{37}NO_4$ 475.6191, found: 475.6189. ^{1}H NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}: 0.355 (s, 3H, CH_3), 1.253–2.857 (m, 16H), 2.099 (s, 3H, $OCOCH_3$), 2.137 (s, 3H, $COCH_3$), 2.913 (s, 6H, N–CH_3), 3.086 (s, 1H, OH), 4.365 (d, 1H, J = 7.2), 5.779 (s, 1H), 6.638 (d, 2H, J = 7.6), 6.982 (d, 2H, J = 7.6); ^{13}C NMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}:21.194; 24.096; 25.699; 26.767; 27.779; 30.160; 30.975; 36.681; 36.768; 38.255; 39.277; 40.489; 46.972; 50.844; 66.992; 96.110; 112.692; 122.859; 127.225; 129.199; 131.406; 145.543; 148.539; 156.487; 170.537; 199.421; 203.719.

3. Discussion

The synthesis of the drug substance was based on the very efficient 1,4-addition in the presence of copper(I) catalyst such as copper (I) chloride (Scheme 1). To the best of our knowledge, when the 5α,10α-epoxide (**3a**) was presented a higher proportion, the 11β-addition ingredient (**4a**) was provided in higher yield [11]. In order to improve the ratio of **3a**, the starting material was first reacted with sodium acetylide to give the compound **9**, and then processed epoxidation to yield **3a/3b** (Scheme 2). Unfortunately, it was found the ratio of the 5α,10α-**3a** and 5β,10β-epoxides **3b** was about 50:50. Even if hexachloroacetone was used as the catalyst, mCPBA was used as epoxidation reagents, or lowering the reaction temperature, the ratio of 5α,10α-**3a** epoxide was still not improved. At last, it was found if epoxidation firstly, the ketone **1** can give out a 65:35 mixture of the 5α,10α-(**2a**) and 5β,10β-(**2b**) epoxides. And when the temperature was reduced to 0–5 °C and the reaction time was prolonged for 24 h, the 5α,10α-epoxide was up to 80%. However, if the catalyst was changed to hexachloroacetone, the 5α,10α-epoxide was lowered to 55%. Even the temperature was lowered, the ratio of 5α,10α-epoxide was about 60% and the starting materials was remained much. At last, the best optimized condition was selected, using 30% hydrogen peroxide as epoxidation reagent, hexafluoroacetone as catalyst at 0–5 °C for 24 h.

The 5α,10α-isomer **3a** got out 11β-substituted isomer (**4a**) while the 5β,10β-epoxide **3b** afforded 11α-substituted isomer (**4b**) (Scheme 3). In order to remove the 11α-substituted isomer (**4b**), the mixture of 5α,10α-**3a** and 5β,10β-epoxides **3b** was attempted to recrystallize to remove the 5β,10β-epoxide, then underwent Grignard addition to get out 11β-substituted isomer (**4a**) only. But the yield of recrystallization of **3a** and **3b** was about



Scheme 4. Synthesis of the intermediate **8**.

55%, and 62% of **4a** was obtained after Grignard addition and purification. Thus, the total yield of **4a** was about 34% after above processes. It was well known that 5β,10β-epoxide reacted more slowly than the 5α,10α-isome, and required more copper (I) chloride, Grignard reagent(2.0 equiv) [10]. Therefore the obtained crude mixture of 5α,10α-(**3a**) and 5β,10β-(**3b**) epoxides was used in the next step without further purificaton [12]. Using above reaction conditions, it was found the starting materials remained much. The reason was the existence of 17-hydroxyl group consumed the Grignard (1.0 equiv). After the Grignard reagent was increased to 3.5 equiv, the materials was completely reacted including the 5β,10β-epoxide. After complete reaction and treatment, the crude residue was stirred in isopropyl ether and the precipitated product was filtered off, then crystallized in n-hexane/dioxane to yield the compound **4a** with 50.4% yield. And under this recrystallization conditions the impurities, including the 11α-substituted isomer (**4b**), can be removed.

At the beginning, we had tried to synthesize the compound **8** from the compound **4** listed in Scheme 4. Firstly, diol **4** was directly reacted with phenylsulfenyl chioride in the presence of acetic acid and triethylamine[9] to prepare the compound **10**. Unfortunately, the reaction products were complicated with no main products monitored by TLC. Then the acetic acid was removed in above conditions, but the reaction was still not ideal. The reason was supposed that the 5α-hydroxyl group might affect the reaction. And the following reactions confirmed the speculation, after removal of hydroxyl group, ketone **8** was smoothly obtained (Scheme 1).

4. Conclusion

We have succeeded in finding a new and efficient route for preparing Ulipristal acetate with a good yield. The ratio of the 5α,10α-**3a** and 5β,10β-epoxides **3b** was improved to 80:20, and the yield of **4a** was greatly improved. In the presence of triethylamine, the phenyl-sulfinyl compound 6 was successfully synthesized from ketone **5** directly reacted with phenylsulfenyl chloride. These synthetic procedures is only 8 steps, less than currently reported in the literature, but more suitable for industrial process.

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