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A new and efficient method for the synthesis of Ulipristal acetate

Xu Cheng [1], Xiaocen Li [1], Yanjun Duan, Yongguo Yu, Li Hai *, Yong Wu *

Key Laboratory of Drug-Targeting of Education Ministry and Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, PR China

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ABSTRACT

In this study, we describe another new and efficient route for preparing Ulipristal acetate. The 1,4-addition compound **5** was greatly improved after the starting material ketone **1** was underwent epoxidation, cyanation, hydroxyl group protection and Grignard addition. The synthetic procedure is only 6 steps and the total yield is about 27.4%, which is much suitable for industrial process.

1. Introduction

A large number of 11β-substituted norpregna compounds were reported, which have shown antiprogestational and/or antiglucocorticoid activity [1–5]. Among them, 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 and more specifically 19-norprogesterone and a selective progesterone receptor modulator (SPRM) which efficiently binds and inhibits progesterone receptor (PR) in progesterone target tissues [1]. Ulipristal acetate is well characterized for its anti-fertility potency in variety of in vivo and in vitro assays, but to have less antiglucocorticoid activity than the most well-known SPRM mifepristone as a result of differences in their active metabolites. Because of Ulipristal acetate's reduced anti-glucocorticoid activity, its clinical applicability is wider, and more potential to employed in the gynecological field, also exhibit benefits for endometriosis treatment, as well as ovarian and breast cancer therapies [6].

As a consequence several methods have been developed so far for the synthesis of Ulipristal acetate in the literature. Cook et al. [5] processed one route about 9 steps to get out Ulipristal acetate with unsatisfactory total yield of about 0.62% and relatively complex process. Dancsi et al. [7] obtained Ulipristal acetate also via 9 steps with 14% total yield. But, in this route the proportion of the 3,3,20,20-bis(ethylene-dioxy)-17α-hydroxy-5α,10α-epoxy-19-norpregn-9(11)-ene and 3,3,20,20-bis(ethylene-dioxy)-17α-hydroxy-5β,10β-epoxy-19-norpregn-9(11)-ene in the epoxidized biketal was about 55:45, which wasted 45% of material. Kim et al. [8] yielded target product via 7 steps about 12.5% yield, which was also relatively complex. Afterwards, Kim et al. [9] supplied another route to increase the total yield to about 19.5%. However, the starting material was extremely expensive. Therefore, most of the routes reported were relatively complex and multisteps process and lacked generality, needed use of toxic and expensive reagents, and suffered from complex purification and unsatisfactory yield. Previously, we had published our work describing a synthetic route to Ulipristal acetate [10]. In fact, this route was rather simple and convenient in lab scale. But, when we transferred this method to a large scale in the factory, we found that phenylsulfenyl chloride had a quite unpleasant smell and was unfriendly to environment.

Thus, there is a demand for finding an alternative and convenient synthetic route to synthesize Ulipristal. In this letter, we present another new efficient and concise synthetic method with only 6 steps and the yield of 27.4% (Scheme 1). Compared with our previously published route, it avoided the use of phenylsulfenyl chloride and was shorter and simpler, although the yield was almost similar.

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 &

* Corresponding authors. Tel.: +86 028 85503235 (L. Hai), +86 028 85503666 (Y. Wu).
E-mail addresses: smile@scu.edu.cn (L. Hai), wyong@scu.edu.cn (Y. Wu).
[1] These authors contributed equally to this work.

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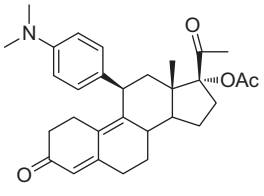


Fig. 1. The structures of Ulipristal acetate.

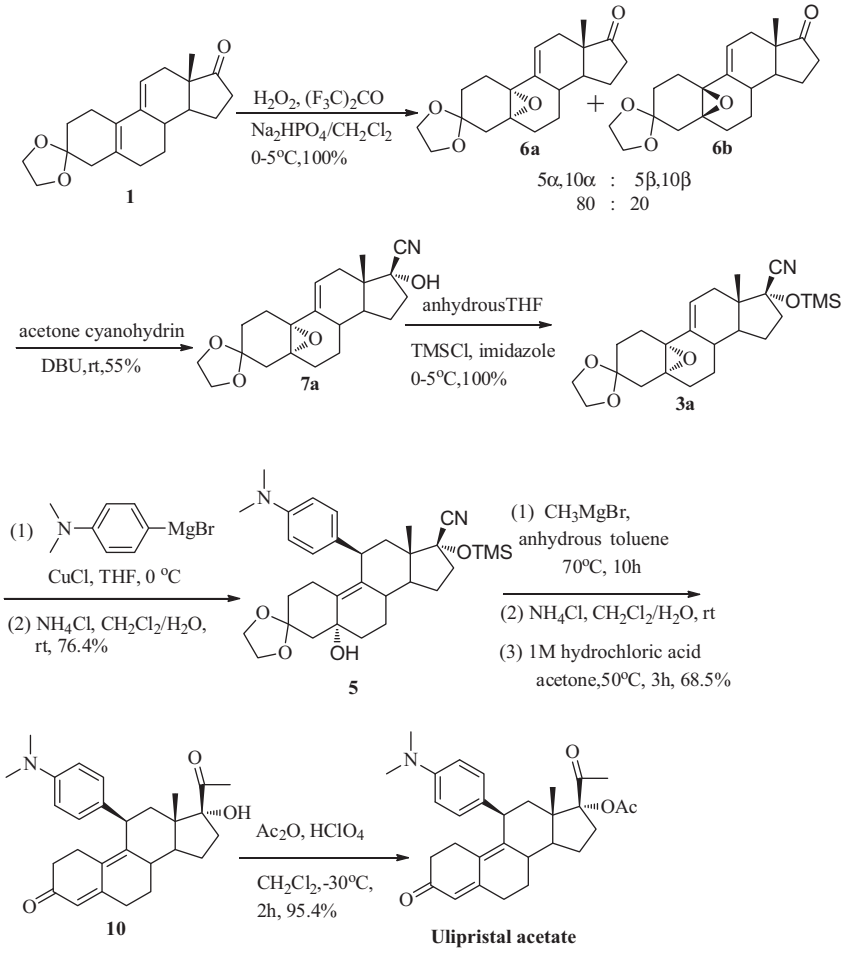
Equipment Co. Ltd, Shantou, China). IR spectra were obtained on a Perkin Elmer983 (Perkin Elmer, Norwalk, CT, USA). ^{1}H NMR spectra were taken on a Varian INOVA400 (Varian, Palo Alto, CA, USA) using $CDCl_3$, d-DMSO and D_2O as solvent. Chemical shifts are expressed in δ (ppm), with tetramethylsilane (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 (**6a**) and 3-(ethylene-dioxy)-estra-5β,10β-epoxy-9(11)-ene-17-one (**6b**)*

Hexafluoroacetone (0.6 ml, 0.0048 mol), 30% aqueous hydrogen peroxide (2.4 ml 0.0811 mol) and sodium phosphate dibasic dodecahydrate (17.25 g, 0.0482 mol) were added to a solution of **1** (15 g, 0.0477 mol) in methylene chloride (150 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 thiosulfate (47.4 g, 0.3 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 sulfate. The solvent was removed in vacuo to give 15.9 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. (**6a**/**6b**) MS (m/z): 331.42 (M+H), ^{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, OCH_2CH_2O), 5β,10β: 5.860 (d, 1H, J = 2.8, =CH), 5α,10α: 6.054 (d, 1H, J = 2.8, =CH).

*2.2. 5α,10α-Epoxy-3,3-[1,2-ethandiyl=bis(oxy)]-17α-hydroxy-5α-oestr-9(11)-en-17β-carbonitrile (**7a**)*

DBU (0.1 ml) was added to a solution of **6a** and **6b** (10 g) in acetone cyanohydrins (20 ml). The reaction mixture was stirred for 24 h at room temperature. A large quantity of white solid was precipitated. Then, isopropyl ether (100 ml) was added to the above reaction mixture and stirred for 30 min. The white solid was filtered and washed with isopropyl ether (2 × 20 ml) and dried at 50 °C to yield 5.95 g (55%) of the compound **7a**. mp: 192–195 °C MS (m/z): 358.19 (M+H), ^{1}HNMR {400 MHz, $CDCl_3$ (TMS), δ (ppm)}:0.935 (s, 3H, CH_3), 1.177–2.520 (m, 18H), 2.609 (s, 1H, OH), 3.882–3.969 (m, 4H, OCH_2CH_2O), 6.081 (t, 1H, J = 2.8, =CH).



Scheme 1. Synthesis of Ulipristal acetate.