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Enantioselective total synthesis of pyrroloquinolone as a potent PDE5 inhibitor

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ABSTRACT

A concise enantioselective strategy for the synthesis of key PDE5 inhibitor **2** was developed in **5** and **6** steps using asymmetric hydrogenation and one-pot chiral auxiliary approaches, respectively. The synthesis features the use of imine **6** obtained through Bischler–Napieralsky reaction from amide **5**. Absolute *R* configuration was introduced in (+)-**7** by asymmetric transfer-hydrogenation reaction with Ru(II) catalyst followed by establishing the tricyclic pyrroloquinalone core using the Winterfeldt oxidation. Another alternative synthetic approach for the introduction of chirality in the molecule employed imine **6** and chloroformates of different chiral auxiliaries, which achieved *N*-acyliminium ion intermediates that were reduced in situ using $PdCl_2/Et_3SiH$ protocol. These synthetic routes were applied in the total synthesis of promising male erectile dysfunction (MED) PDE5 inhibitor **1**.

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Nowadays, Sildenafil is the main drug employed for male erectile dysfunction (MED). Through several mechanistic considerations about the mode of action of these classes of compounds, Sildenafil and its analogues showed inhibition of the phosphodiesterase type 5 (PDE5) enzyme but not in a specific manner.[1] This class of compounds was initially studied for the treatment of angina, and then it showned its effectiveness in treating erectile dysfunction (ED).[2] Although its success, accumulation of clinical data suggested that several side effects were observed when sildenafil was used, which are headache, nausea, cutaneous flushing, and visual disturbances.[3] Herein, sildenafil and other PDE5 inhibitors are contraindicated for patients taking nitrates or NO^- donors due to abrupt synergistic decrease of blood pressure observed after co-administration of these agents.[4] Recently, a wide variety of PDE5 inhibitors were synthesized by Jiang group and evaluated for their biological profiles, which included the lead compound RWJ387273 (**1**)[5] as shown in Figure 1.

Chirality in molecules plays an enormous role in areas ranging from medicine to material science. However, after great developments in synthetic organic chemistry, there are still few methodologies that allow the stereoselective construction of predetermined moieties in some classes of compounds. In this context, particular attention in efficient synthetic routes for novel chemotypes is already pursued when stereoselectivity is required.

As part of our efforts in the field of biologically relevant β-carbolines, we turned our attention toward an alternative synthetic route for PDE5 inhibitors, figured out through key intermediate (−)-**2**. Recently, we reported an enantioselective total syntheses of arborescidine alkaloids and (−)-quinolactacin B antibiotic.[6] Structurally, **1** comprises a tricyclic framework attributing a common pyrroloquinolone core. The retrosynthetic analysis for the basic framework of **2** was depicted in Figure 2, and features the Noyori asymmetric hydrogen-transfer reaction and chiral-auxiliary

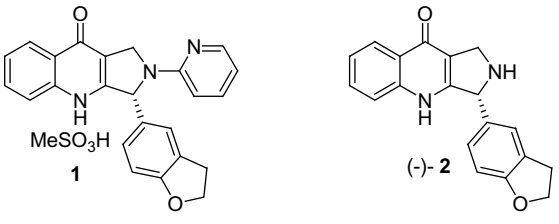

Figure 1. Optically active potential PDE5 inhibitor **1** (RWJ387273) and its important intermediate (−)-**2**.

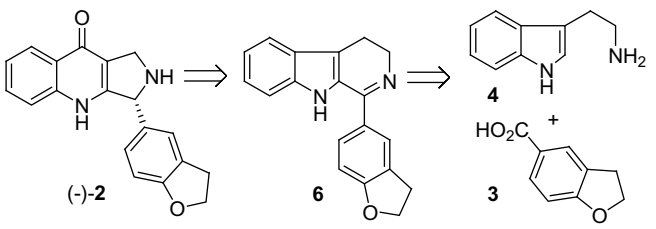

Figure 2. Retrosynthetic analysis of key pyrroloquinolone (PDE5) inhibitor intermediate **2**.

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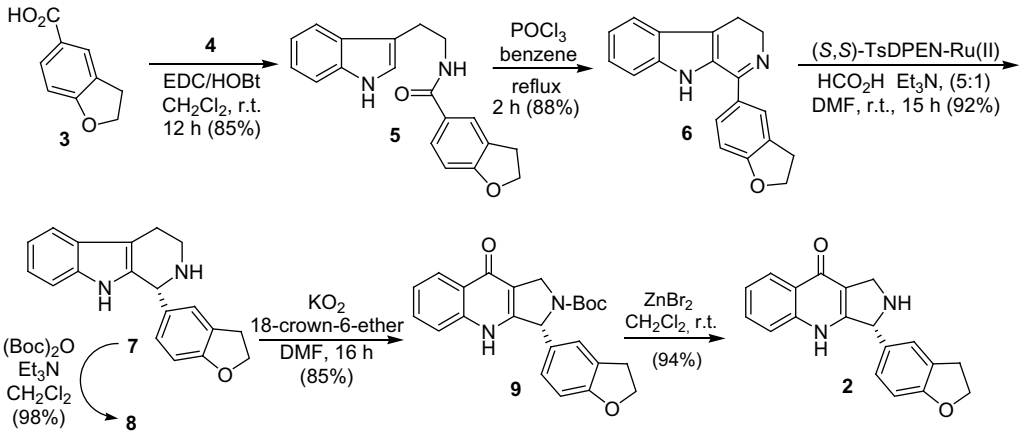


Scheme 1. Asymmetric hydrogen-transfer with (*S*,*S*)-TsDPEN-Ru(II) followed by Winterfeldt reaction for key PDE5 inhibitor **2** intermediate.

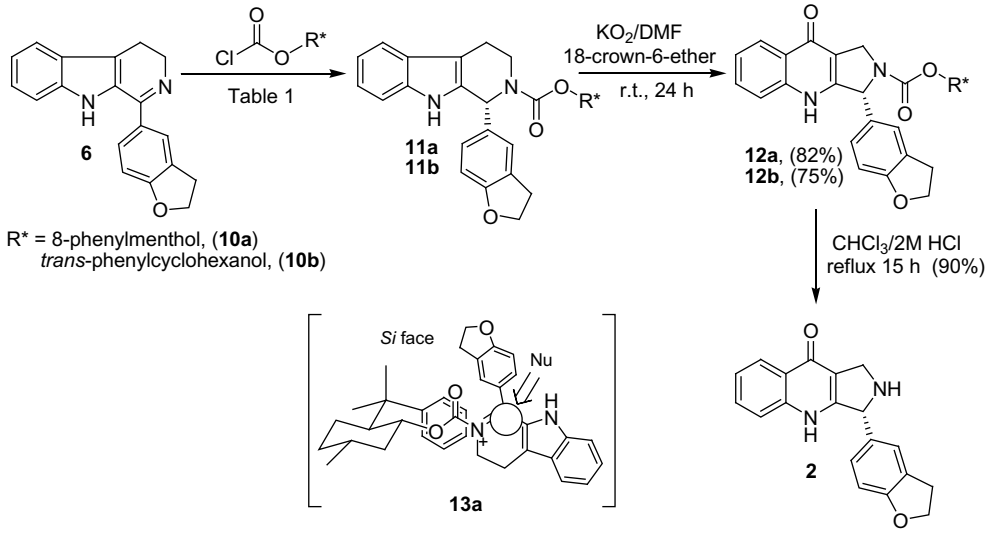
mediated reductions (**6** to **7**/**11**) as key steps. Although demonstrated as a useful synthetic method, these asymmetric reductions remain to be fully explored in the arena of total syntheses of alkaloid natural products.[7,8]

We first explored the Noyori asymmetric hydrogenation (NAH) reaction of the preformed imine **6**. Imine **6** was obtained in 75% overall yield from dihydrobenzo[*b*]furan-5-carboxylic acid (**3**) and tryptamine (**4**) by coupling with EDC/HOBt in CH_2Cl_2 at room temperature, which afforded the corresponding amide **5**. The amide was subjected to Bischler–Napieralsky cyclization affording imine **6**. Having prepared imine **6**, the next stage was set to introduce the required asymmetry through the Noyori asymmetric hydrogen-transfer reaction.[7] In nature, oxidoreductases catalyze remarkably selective transfer hydrogenations of carbonyl compounds to alcohols using co-factors such as NADH or NADPH.[9] Noyori and co-workers have shown that *p*-cymene–Ru(II) complexes of certain chiral 1,2-diamines are highly effective as catalysts for the asymmetric reduction of imines. This method uses a $HCO_2H{-}Et_3N$ azeotropic mixture as the hydrogen source and provides a convenient, general route to natural and unnatural β-carboline alkaloids.

The Noyori hydrogenation of imine **6** was accomplished using the preformed (*S*,*S*)-TsDPEN–Ru(II) complex in DMF, and a $HCO_2H{-}Et_3N$ mixture that afforded amine **7** in 92% yield and >90% ee, as determined by HPLC analysis using a ChiralPack OD column. On the basis of the examples that have been reported by Noyori, the absolute stereochemistry of **7** is expected to be *R*. When it is used (*S*,*S*)-TsDPEN-Ru(II) complex is used in in the hydrogen-transfer, the *Si*-face of imine **6** is expected to be selected for hydrogenation providing (*R*)-**7**. This outcome is consistent with the general model that Noyori had proposed for the asymmetric hydrogen transfer reactions with TsDPEN–Ru(II) complexes,[7] and it was probed by comparing the optical rotation of **7** that agreed in signal to previously described (*R*)-(+)-**7**.[10,11]

Then, amine **7** was protected with Boc using $(Boc)_2O$ and Et_3N in CH_2Cl_2 giving (+)-**8** in 98% yield. A viable method was anticipated to oxidize dihydro-β-carbolines bearing amide functionality into the pyrroloquinolones, the Winterfeldt reaction. It is known that KO_2 is an alternative useful oxygen source for Winterfeldt oxidation reactions.[12,13] Thus, Winterfeldt reaction of (+)-**8** using KO_2 and 18-crown-6-ether gave quinolone (+)-**9** in 85% yield (>90% ee) after 16 h.[6b,14] The enantiomeric excesses were determined by HPLC to assure that no epimerization occurred in the reaction due to basic conditions. The target compound **2** was obtained by treatment of $ZnBr_2$ in 94% yield, as depicted in Scheme 1.

Next, we investigated the scope of reduction of imine **6** mediated by chiral auxiliaries in an one-pot manner. The tested chiral auxiliaries were chloroformate of 8-phenylmenthol (**10a**), and *trans*-phenylcyclohexanol (**10b**), as depicted in Scheme 2. In situ formation of corresponding *N*-acyliminium ions **13a**,**b** from chloro-



Scheme 2. Asymmetric synthesis of PDE5 inhibitor by using chiral auxiliaries followed by Winterfeldt oxidation.

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