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Asymmetric Synthesis of Anisodine

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Abstract: Anisodine was synthesized from 3α-hydroxy-6β-acetyltropine in 11 steps. Laevorotary isomer of anisodine was prepared from the asymmetric dihydroxylation of compound **10** *via* the osmium catalyzed process employing *p*-chlorobenzoyl dihydroquinidine as the chiral ligands.

Keywords: Anisodine, tropine alkaloid, total synthesis.

Tropane alkaloids such as atropine, scopolamine and anisodamine have been widely used in clinical therapy for a long time. Anisodine[1] **11** is another of the tropane alkaloids which was isolated from the plant *Anisodus tanguticus*. It had many valuable pharmacological activities, such as for the treatment of motion sickness, migraine, and vascular spasm of fundus occuli. Due to its low content in *Anisodus tanguticus* and its difficulties of total synthesis, anisodine has not been used in clinical widely despite it has various valuable pharmacological activities. Researchers[2-4] have tried a lot to find an effective synthetic method of anisodine but the results were not satisfactory.

The synthetic route we reported here is outlined in **Scheme 1**. 3α-Hydroxy-6β-acetyltropine was reacted with acetic anhydride to give 3α,6β-diacetyltropine **1** in 95% yield, which was then hydrolyzed with 1% NaOH solution in 0℃ to give the corresponding compound **2**. Before reaction solution was evaporated under reduced pressure, it must be neutralized to pH 7 at 0℃ otherwise the two acetic esters would hydrolyze simultaneously and 3α,6β-dihydroxytropine could be obtained. If it was neutralized at 0℃, the selective hydrolyzed of acetic esters could be achieved in good yield.

The hydroxyl group of compound **2** was then protected with THP in CH_2Cl_2 at ice cooling in the existence of toluenesulfonic acid at pH 3 to give compound **3** with 84% yield, which was reacted with chloroformic acid ethyl ester to give compound **4** [5]. The THP group of compound **4** was removed by PPTS in ethanol at 55℃, after 5 h TLC showed that the reaction was accomplished and the solution was evaporated under reduced pressure and the residue was dissolved in chloroform and ether was added to the solution, after filtration, the mother liquid was evaporated to dry under reduced pressure and get the corresponding compound **5** in 88% yield. Compound **5** reacted with methanesulfonyl chloride in anhydrous pyridine at 0℃ for 1 h and then stirred at room

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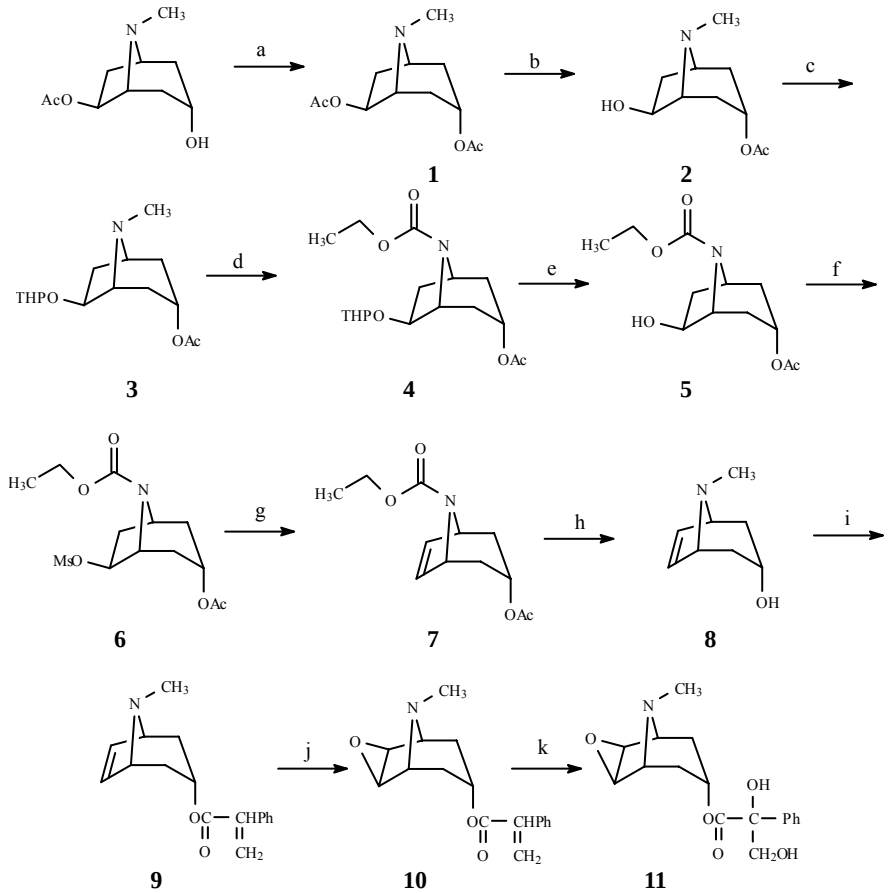
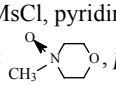
temperature overnight, after workup to give compound **6** in 60% yield, which was refluxed with DBU in 2,4,6-collidine to get the corresponding alkene compound **7** in 75.2%. Reduction of compound **7** was carried with $LiAlH_4$ in THF at room temperature for 6 h gave the 6,7-dehydrotropine **8** in 80% yield , after esterification with the corresponding acyl chloride to give oil compound **9**. Selective oxidation of the 6(7) double bond in cycle with hydrogen peroxide in the existence of V_2O_5 give the corresponding compound **10**, which was dihydroxylated with OsO_4 and N-methylmorpholine N-oxide (NMO) to give the racemic target compound in 65% yield as a white crystal, mp 199.5-200℃.

Scheme 1 The synthetic route of anisodine



a: $(CH_3CO)_2$, pyridine; b: 1% NaOH-EtOH; c: DHP, $TsOH,CH_2Cl_2$; d: ClCOOEt, C_6H_6, reflux; e: EtOH, PPTs; f: MsCl, pyridine; g: DBU, collidine, reflux; h: $LiAlH_4$, THF; i: pyridine, Ph–CHCOCl (CH$_2$OAc); j: H_2O_2, V_2O_5; k:  , *p*-chlorobenzoyl dihydroquinidin, OsO_4.

We used the *p*-chlorobenzoyldihydroquinidine as the chiral ligands，*via* the osmium-catalyzed asymmetric dihydroxylation process [6] of compound **10** to achieve the enantioselective synthesis of anisodine. The reaction was conducted in the mixture

solution of acetone and water at 0℃ for 5 hours and then 8 hours at room temperature, after workup to give the (−)-anisodine of 84% ee, in 28% yield, $[\alpha]_D^{25}$−22.2(c 2.88, H_2O), mp 199.5-200℃.

In summary, anisodine was synthesized in eleven steps and the (−)-anisodine was obtained *via* asymmetric dihydroxylation. All the starting materials and reagents used are commercially available. In this communication, we report chemical synthesis of anisodine, which not only afford the possible route for industrial preparation, but also provide a synthetic methodology which will allow subsequently access to analogs of the parent structures, and its quaternary ammonius salts will be the potential use as anticholinergic bronchodilators.

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