An Efficient Synthesis of Racemic Tolterodine

Joo Hi Kang, Jong Hyoup Lee,[†] Young Jun Park,[†] Kyoung Soo Kim,[†,*] and Jae Yeol Lee[*]

Research Institute for Basic Sciences and Department of Chemistry, College of Sciences, Kyung Hee University, Seoul 130-701, Korea. [*]E-mail: ljy@khu.ac.kr
[†]Chirogenix Co., Ltd., Kowoon Institute of Technology Innovation, Suwon University, Whasung, Kyunggi 445-743, Korea
[*]E-mail: kskimpc@chirogenix.com
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Tolterodine, in particular (+)-(*R*)-tolterodine L-tartrate (Detrol®), is a new and potent competitive muscarinic receptor antagonist and is used to treat urinary incontinence (Figure 1).[1] The drug acts on M_2 and M_3 subtypes of muscarinic receptors whereas other antimuscarinic treatment (*eg.* oxybutynin) for overactive bladder only acts on M_3 receptors making them more selective.[2-5] Nonetheless, tolterodine has fewer side effects than other antimuscarinics because tolterodine targets the bladder more than other areas of the body.[6] This means that less drug needs to be given daily (due to efficient targeting of the bladder) and so there are fewer side effects. Therefore, some different approaches have been published for racemic and asymmetric synthesis of tolterodine.[7-14] In the case of racemic tolterodine, a classical resolution by the formation of diastereomeric salt using L-(+)-tartaric acid is used to achieve pure (*R*)-tolterodine, and the racemization of (*S*)-tolterodine for the recycle does not seem particularly difficult to accomplish, even if it require additional cost (Figure 1).[15]

Herein we report an efficient synthetic route of racemic tolterodine suitable for the large-scale commercial production by modifying the reported synthetic routes.[11]

The synthetic route to (±)-tolterodine (**1**) proposed by us is depicted in Scheme 1. Commercially available 6-methyl-4-chroman-2-one (**2**) as a starting material was reduced with $LiBH_4$ to afford a diol **3** in 93% yield, which was treated with 2.2 equiv of CH_3SO_2Cl in the presence of triethylamine to give a dimesylated compound **4** in quantitative yield. A solution of compound **4** in acetonitrile was treated with 1.5 equiv of KI followed by an addition of 10.5 equiv of *N*,*N*-diisopropylamine to provide mono-mesylated amine **5** in quantitative yield. Finally, hydrolysis of **5** with NaOH in MeOH-H_2O provided (±)-tolterodine (**1**) in quantitative yield.

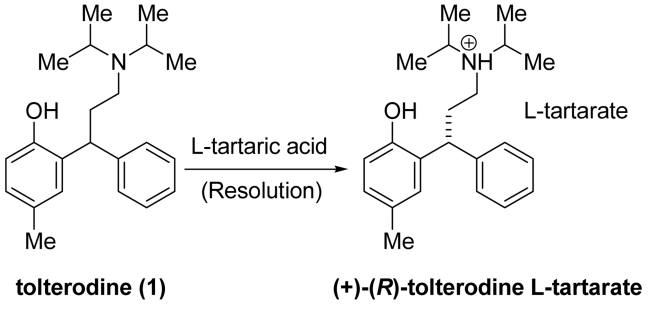
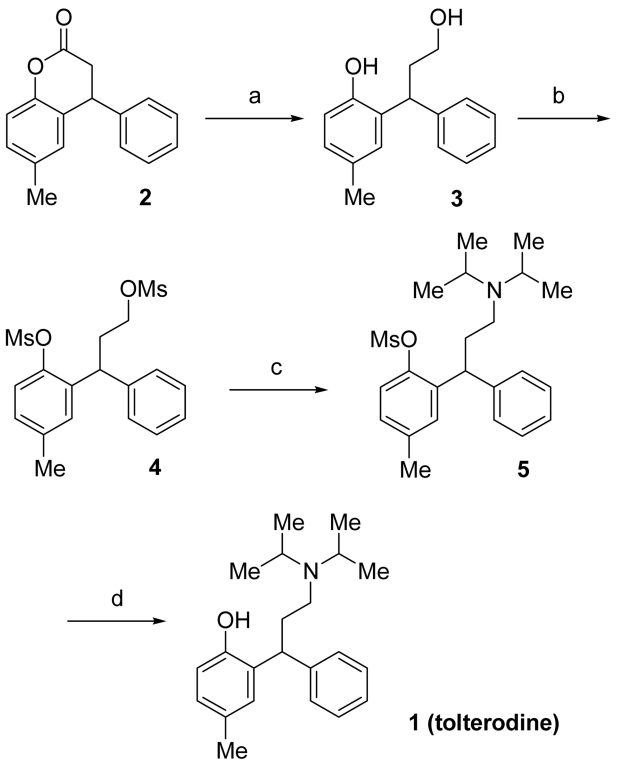


Figure 1. Resolution of racemic tolterodine.

In summary, the synthesis of (±)-tolterodine (**1**), a precursor of (+)-(*R*)-tolterodine, was efficiently performed from 6-methyl-4-chroman-2-one (**2**) *via* 4 steps in high yield. This process is suitable for large-scale commercial production by avoiding hazardous reagents and high pressure of hydrogen gas.

Experimental Section

2-(3-Hydroxy-1-phenylpropyl)-4-methylphenol (3). To a solution of 6-methyl-4-chroman-2-one (**2**, 37.5 g, 0.16



Scheme 1. Reagents and reaction conditions: (a) $LiBH_4$ (1.0 equiv), THF, 0 °C to rt, overnight, 93%; (b) CH_3SO_2Cl (2.2 equiv), TEA (2.5 equiv), CH_2Cl_2, 0 °C to rt, 1 h, 99%; (c) KI (1.5 equiv), CH_3CN, reflux, 6 h, and then *N*,*N*-diisopropylamine (10.5 equiv), rt to 70 °C, 24 h, 99%; (d) NaOH (5.0 equiv), MeOH/H_2O (2:1), 85 °C, 10 h, 99%.

mol) in tetrahydrofuran (500 mL), was slowly added lithium borohydride (3.60 g, 0.16 mol) at 0 °C. The reaction mixture was stirred at room temperature for 24 h, cooled to 0 °C, and quenched with water (50 mL). After removal of solvent, the resulting residue was adjusted to pH 1 with water (150 mL) and *conc.* HCl (20 mL). The mixture was extracted with ethyl acetate. The extract was washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to afford **3** as a white solid (35.4 g, 93%): mp 111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.18 (m, 5H), 6.84 (dd, J = 8.1, 1.9 Hz, 1H), 6.76 (d, J = 1.7 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 4.56 (m, 1H), 3.82 (br S, 2H), 3.72 (m, 1H), 3.52 (m, 1H), 2.36 (m, 1H), 2.17 (s, 3H), 2.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 144.0, 130.5, 130.2, 129.1, 128.4, 128.2, 127.9, 126.3, 116.0, 60.7, 38.7, 37.0, 20.7.

2-(3-Methanesulfonyloxy-1-phenyl-propyl)-4-methyl-phenyl methanesulfonate (4). To a solution of diol **3** (18.3 g, 75.6 mmol) in CH_2Cl_2 (300 mL) was added triethylamine (26.4 mL, 189.0 mmol, 2.5 equiv.) and methanesulfonyl chloride (12.9 mL, 166.0 mmol, 2.2 equiv.) at 0 °C. After stirring at room temperature for 1 h, the resulting mixture was washed with water (100 mL) and dried over $MgSO_4$, and concentrated *in vacuo* to provide **4** (29.7 g, 99%) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.22 (m, 7H), 7.12 (d, J = 1.9 Hz, 1H), 7.05 (dd, J = 8.3, 1.8 Hz, 1H), 4.56 (t, J = 7.8 Hz, 1H), 4.21-4.16 (m, 2H), 3.01 (s, 3H), 2.93 (s, 3H), 2.47 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 141.8, 137.4, 135.7, 129.2, 128.8, 128.7, 128.1, 127.0, 121.6, 68.0, 39.8, 37.9, 37.3, 34.3, 21.2.

2-(3-*N*,*N*-Diisopropylamino-1-phenylpropyl)-4-methyl-phenyl methanesulfonate (5). A reaction mixture of **4** (29.7 g, 74.5 mmol) and potassium iodide (18.6 g, 111.8 mmol, 1.5 equiv.) in acetonitrile (500 mL) was heated at reflux for 6 h. The reaction mixture was cooled to room temperature and treated with *N*,*N*-diisopropylamine (109.7 mL, 782.6 mmol, 10.5 equiv.). The resulting mixture was further stirred at reflux for 24 h. After cooling to room temperature, the organic solvent was removed under reduced pressure. The residue was extracted with ethyl acetate. The combined organic extract was washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to afford **5** (30.0 g, 99%) as a yellowish oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.22 (m, 6H), 7.14 (m, 1H), 6.99 (dd, J = 8.4, 1.9 Hz, 1H), 4.35 (t, J = 7.5 Hz, 1H), 3.00-2.93 (m, 2H), 2.77 (s, 3H), 2.39-2.33 (m, 2H), 2.30 (s, 3H), 2.15-2.09 (m, 2H), 0.93-0.91 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.6, 143.9, 137.2, 136.9, 129.4, 128.5, 128.2, 128.1, 126.3, 121.5, 120.9, 48.8, 43.7, 41.9, 37.7, 37.4, 37.3, 20.8, 20.6.

(±)-Tolterodine: 2-[3-(*N*,*N*-diisopropylamino)-1-phenyl-propyl]-4-methylphenol (1). To a solution of **5** (51.74 g, 0.13 mol) in mixture of CH_3OH and H_2O (2:1, 500 mL) was added sodium hydroxide (25.6 g, 0.64 mol, 5.0 equiv.). The reaction mixture was heated at 85 °C for 10 h and cooled to room temperature. The volume of reaction mixture was reduced to 1/3 under reduced pressure. The reaction mixture was adjusted to pH 8 with *conc.* HCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give (±)-tolterodine (**1**, 40.0 g, 99%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.18 (m, 5H), 6.81-6.78 (m, 2H), 6.60 (m, 1H), 4.47 (dd, J = 11.1, 4.18 Hz, 1H), 3.25-3.18 (m, 2H), 2.69 (m, 1H), 2.38-2.36 (m, 2H), 2.12 (m, 1H), 2.11 (s, 3H), 1.11 (d, J = 6.7 Hz, 6H), 1.06 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.1, 144.7, 132.2, 129.2, 128.7, 128.5, 128.3, 127.8, 126.1, 117.9, 48.5, 42.6, 39.7, 33.4, 20.8, 19.9, 19.5.

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