

An Efficient Synthesis of Racemic Tolterodine

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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 M₂ and M₃ subtypes of muscarinic receptors whereas other antimuscarinic treatment (eg. oxybutynin) for overactive bladder only acts on M₃ 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 requires 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

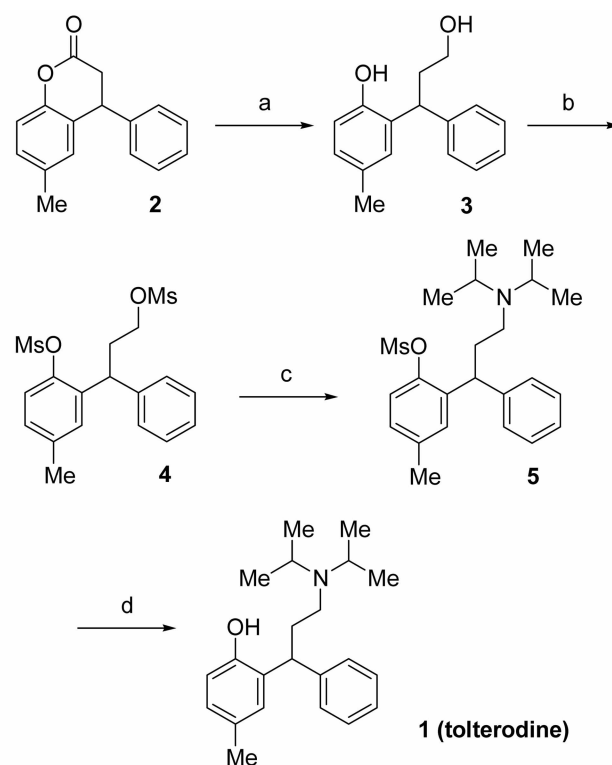
The synthetic route to (±)-tolterodine (**1**) proposed by us is depicted in Scheme 1. Commercially available 6-methyl-4-chroman-2-one (**2**) as a starting material was reduced with LiBH₄ to afford a diol **3** in 93% yield, which was treated with 2.2 equiv of CH₃SO₂Cl in the presence of triethylamine 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-H₂O provided (±)-tolterodine (**1**) in quantitative yield.

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) LiBH₄ (1.0 equiv), THF, 0 °C to rt, overnight, 93%; (b) CH₃SO₂Cl (2.2 equiv), TEA (2.5 equiv), CH₂Cl₂, 0 °C to rt, 1 h, 99%; (c) KI (1.5 equiv), CH₃CN, reflux, 6 h, and then *N,N*-diisopropylamine (10.5 equiv), rt to 70 °C, 24 h, 99%; (d) NaOH (5.0 equiv), MeOH/H₂O (2:1), 85 °C, 10 h, 99%.

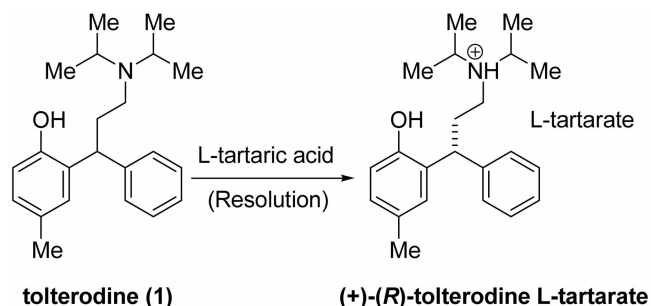


Figure 1. Resolution of racemic tolterodine.

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 MgSO₄, and concentrated *in vacuo* to afford **3** as a white solid (35.4 g, 93%); mp 111–113 °C; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 CH₂Cl₂ (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 MgSO₄, and concentrated *in vacuo* to provide **4** (29.7 g, 99%) as a brown oil; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 MgSO₄, and concentrated *in vacuo* to afford **5** (30.0 g, 99%) as a yellowish oil; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 CH₃OH and H₂O (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 MgSO₄ and concentrated *in vacuo* to give (±)-tolterodine (**1**, 40.0 g, 99%) as an oil; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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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