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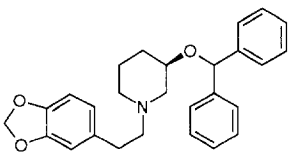
A SHORT AND EFFICIENT SYNTHESIS OF ZAMIFENACIN A MUSCARINIC M_3 RECEPTOR ANTAGONIST

Janine Cossy*, Cécile Dumas, Domingo Gomez Pardo*

Laboratoire de Chimie Organique, Associé au CNRS,
ESPCI, 10 rue Vauquelin - 75231 PARIS Cedex France

Abstract : A short synthesis of zamifenacin is described by using a ring enlargement of a L-prolinol derivative. © 1997 Elsevier Science Ltd.

Muscarinic M_3 receptor antagonists have therapeutic potential for the treatment of disorders associated with altered smooth muscle contractility or tone. These include irritable bowel syndrome, chronic obstructive airways disease and urinary incontinence. Zamifenacin[1] [(3R)-(+)-diphenylmethoxy-1-(3,4)-methylenedioxyphenethyl)piperidine] has been shown to antagonise selectively muscarinic M_3 receptors over muscarinic M_2 receptors *in vitro*[2] and *in vivo*[3,4], inhibiting gastrointestinal motility in dogs at doses that do not effect heart rate or pupil diameter[5]. In man, zamifenacin has been shown to inhibit small bowel and colonic motility in a dose-dependent fashion with little or no side effects[4]. Zamifenacin was in Phase III Clinical Trial[6].



Zamifenacin

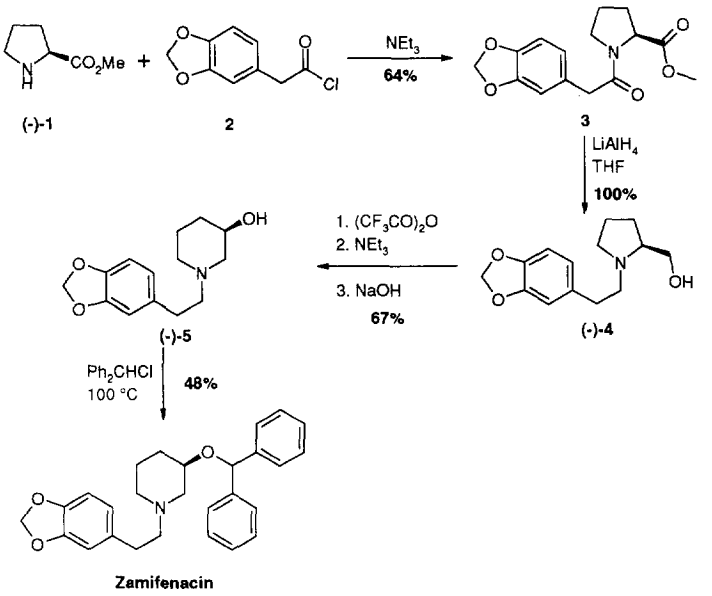
Here in, we would like to report a very short and efficient synthesis of zamifenacin starting from the commercial available L-proline methyl ester (-)-**1** (ee = 98%) and 1,3-benzodioxole-5-acetic acid.

Conversion of the commercially available 1,3-benzodioxole-5-acetic acid to the acid chloride **2** by treatment of the acid with oxalyl chloride[7], followed by addition of the L-proline methyl ester in the presence of NEt_3 gave the amido derivative **3** in good yield (64%). The reduction compound of **3** with $LiAlH_4$ in THF afforded the prolinol derivative (-)-**4**[8] quantitatively. Treatment of prolinol (-)-**4** with trifluoroacetic anhydride in THF followed by the addition of NEt_3 and then by the addition of an aqueous solution of NaOH (3.75 M)[9] gave piperidin-3-ol (-)-**5**[10] (yield = 67%; $[\alpha]_D^{20}$ = -1, *c* = 0.68, EtOH). Piperidin-3-ol (-)-**5** was then heated neat at 100 °C with diphenyl methyl chloride to produce, after 2h, zamifenacin[11] (yield = 48%; ee > 90%[12]; $[\alpha]_D^{20}$ = +20, *c* = 0.26, EtOH).

Zamifenacin was synthesized from L-proline methyl ester in 4 steps with an overall yield of 20% by using a ring enlargement of a L-proline derivative.

Fax: 33.1.40.79.44.25; E-mail: janine.cossy@espci.fr

Scheme : Synthesis of zamifenacin from L-proline methyl ester.



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8. (-)-**4**: $[\alpha]_D^{20}$ = -15 (*c* = 0.87, EtOH). IR (NaCl): 3380, 1610, 1500, 1485, 1440, 1250, 1035 cm^{-1}. NMR ^1H (300 MHz, $CDCl_3$) δ: 1.47-1.78 (m, 4H), 2.14 (dt, ^2J=9.0 Hz, ^3J=9.0 Hz, 1H), 2.26-2.61 (m, 5H), 2.72 (dt, ^2J=11.2 Hz, ^3J=9.0 Hz, 1H), 3.01-3.08 (m, 1H), 3.14 (dd, ^2J=9.9 Hz, ^3J=2.7 Hz, 1H), 3.37 (dd, ^2J=9.9 Hz, ^3J=4.0 Hz, 1H), 5.71 (s, 2H), 6.41-6.57 (m, 3H). NMR ^{13}C (75 MHz, $CDCl_3$) δ: 22.5 (CH_2), 27.5 (CH_2), 35.2 (CH_2), 54.0 (CH_2), 56.1 (CH_2), 61.7 (CH_2), 67.8 (CH), 100.6 (CH_2), 108.0 (CH), 108.9 (CH), 121.2 (CH), 134.0 (C), 145.6 (C), 147.4 (C). MS (EI, 70 eV) *m/z*: 249 ($M^{+\bullet}$, 0.1), 218 (8), 149 (13), 135 (4), 114 (100).
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10. (-)-**5**: $[\alpha]_D^{20}$ = -1 (*c* = 0.68, EtOH). IR (NaCl) ν: 3360, 1505, 1445, 1250 cm^{-1}. NMR ^1H (300 MHz, $CDCl_3$) δ:1.41-1.85 (m, 3H), 1.91-2.08 (m, 1H), 2.72-3.04 (m, 8H), 3.98 (m, 1H), 5.88 (s, 2H), 6.60-6.75 (m, 3H). NMR ^{13}C (75 MHz, $CDCl_3$) δ: 21.8 (CH_2), 31.9 (CH_2), 33.1 (CH_2), 53.5 (CH_2), 60.4 ($2CH_2$), 66.2 (CH), 100.7 (CH_2), 108.1 (CH), 109.0 (CH), 121.3 (CH), 134.0 (C), 145.7 (C), 147.5 (C). MS (EI, 70 eV) *m/z*: 249 ($M^{+\bullet}$, 1), 232 (2), 210 (100), 135 (4), 96 (16).
11. **Zamifenacin**: $[\alpha]_D^{20}$ = +20 (*c* = 0.26, EtOH), [ref. 1 : $[\alpha]_D^{20}$ = +22.5 (*c* = 1.5, EtOH)]. IR (NaCl): 1505, 1490, 1250 cm^{-1}. NMR ^1H (300 MHz, $CDCl_3$) δ: 1.29-1.58 (m, 3H), 1.74-1.80 (m, 1H), 1.98-2.14 (m, 2H), 2.55-2.61 (m, 2H), 2.69-2.73 (m, 2H), 2.81 (dd, ^2J=11.0 Hz, ^3J=1.1 Hz, 1H), 3.11 (dd, ^2J=10.5 Hz, ^3J=3.9 Hz, 1H), 3.54-3.63 (m, 1H), 5.58 (s, 1H), 5.94 (s, 2H), 6.63-6.76 (m, 3H), 7.26-7.37 (m, 10H). NMR ^{13}C (75 MHz, $CDCl_3$) δ: 23.4 (CH_2), 30.7 (CH_2), 33.1 (CH_2), 53.3 (CH_2), 58.6 (CH_2), 60.7 (CH_2), 64.2 (CH), 79.9 (CH), 100.7 (CH_2), 108.1 (CH), 109.1 (CH), 121.4 (CH), 127.1 (CH), 127.4 (CH), 128.0 (2CH), 128.2 (2CH), 128.3 (2CH), 128.4 (2CH), 134.1 (C), 141.0 (C), 142.6 (C), 145.7 (C), 147.5 (C). MS (EI, 70 eV) *m/z*: 415 ($M^{+\bullet}$, 0.1), 280 (4), 168 (14), 167 (100), 165 (8), 152 (5).
12. We have previously shown that the ring enlargement occurs with no racemization, see ref. 9.

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