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Enantioselective Synthesis of (*S*)- and (*R*)-Tolterodine by Asymmetric Hydrogenation of a Coumarin Derivative Obtained by a Heck Reaction

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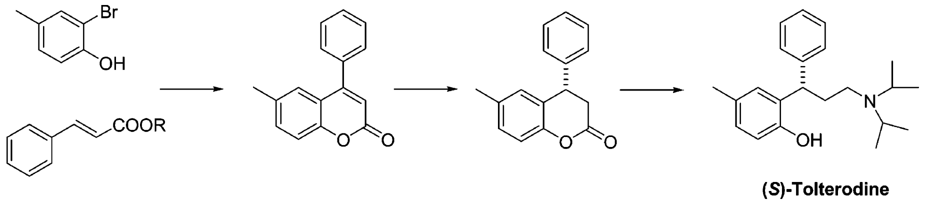

An efficient and short enantioselective synthesis of (*S*)- and (*R*)-tolterodine was performed by asymmetric hydrogenation of a coumarin intermediate, easily obtained by a Heck reaction from inexpensive and commercially available starting materials.

In this paper, we describe the enantioselective synthesis of (*R*)-tolterodine (*R*-tol), a potent and competitive muscarinic antagonist used for the treatment of urinary urge incontinence and other overactive bladder disorders,[1] and (*S*)-tolterodine (*S*-tol), which has a non-cholinergic spasmolytic activity and a weak sedative effect. Being practically devoid of anticholinergic activity,[2] (*S*)-tol does not have any of the anticholinergic side effects that reside in (*R*)-tol such as dry mouth, tachycardia, etc. While (*R*)-tol provides medical treatment in patients with urinary incontinence that arises from muscarinic hyperactivity, (*S*)-tol provides spasmolytic activity against urinary disorders and intestinal spasms caused by various non-cholinergic mechanisms or where antimuscarinc effects are not acceptable. Some different approaches have been published for the racemic and asymmetric synthesis of tolterodine.[3] We thought that an alternative and simple way to obtain the target enantiopure tolterodine would have been through the asymmetric hydrogenation of coumarin intermediate **3**, easily obtained by a Heck reaction between the inexpensive commercially available starting materials 2-bromo-4-methylphenol (**1**) and the *trans*-cinnamate derivative (**2**) (Scheme 1).[4] This simple way of obtaining the coumarin intermediate could permit the synthesis of different important coumarin derivatives. In fact, because of their wide biological activity,[5] and their properties as luminescent probes,[6] photostable laser dyes,[7] and triplet sensitizers,[8] coumarin

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(9) Subsequently to our Italian Patent MI2003A001354, 2003, another example of this approach was published: Battistuzzi, G.; Cacchi, S.; De Salve, I.; Fabrizi, G.; Parisi, L. M. *Adv. Synth. Catal.* **2005**, *347*, 308.

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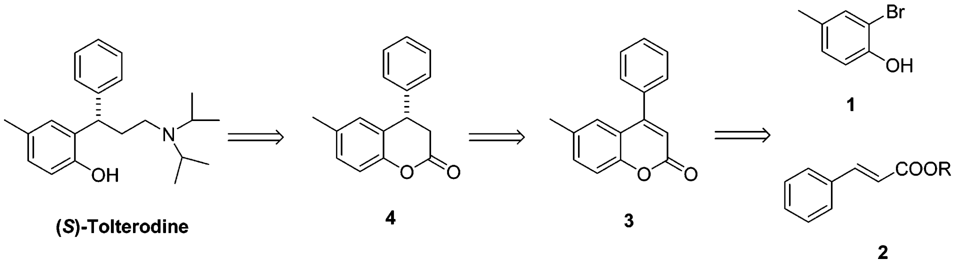
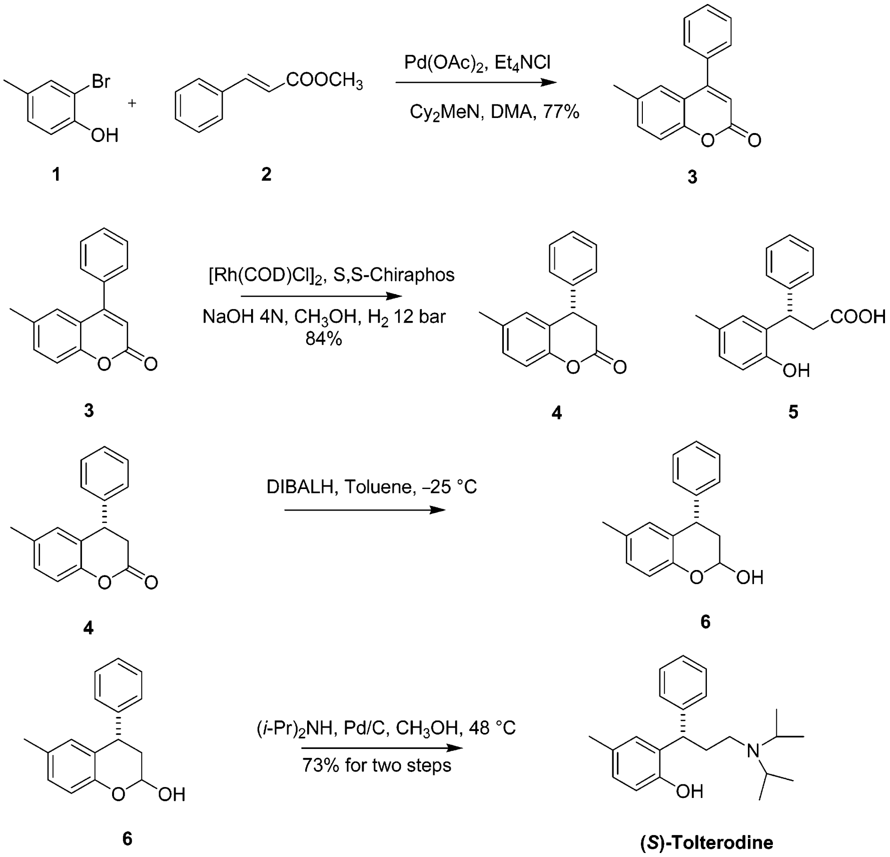
SCHEME 1. Retrosynthetic Analysis of (*S*)-Tolterodine



SCHEME 2. Synthesis of (*S*)-Tolterodine



derivatives are themselves important synthetic targets. For this reason, the very simple coumarin synthesis described here represents another important goal of this work.[9]

Starting from **1** and **2** (R = CH_3) (Scheme 2), the Heck reaction was performed in dimethylacetamide (DMA) with $Pd(OAc)_2$, Et_4NCl, and $Cy_2(Me)N$ at 95 °C for 48 h, to give coumarin **3** as the only product in 77% isolated yield.[10] The Heck reaction was carried out also using as starting materials *trans*-cinnamic acid (R = H)[11a−c] or *N*,*N*-diisopropylcinnamamide (R = $(i\text{-Pr})_2N$))[11d−g] in the same reaction conditions, to explore different synthetic strategies with the aim of going directly to tolterodine. Direct reduction of the amide intermediate would make the synthesis shorter, but unfortunately, the reaction did not work in either case.[12]

Subsequent asymmetric hydrogenation of coumarin intermediate **3**,[13] performed with $[Rh(COD)Cl]_2$ and (*S*,*S*)-Chiraphos as the chiral ligand in a stainless steel autoclave under a H_2 pressure of 12 bar in CH_3OH and with 4 N NaOH,[14] gives the hydrogenated adduct enantiomers (*S*)/(*R*) in 84% isolated yield[15] and 90:10 enantiomeric ratio, 80% ee, as a mixture of closed **4**

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(10) For an industrial application, flash chromatography could be avoided, purifying the product only by crystallization.

(11) For examples of a Heck reaction on α,β-unsaturated acids, see: (a) Zhao, S. F.; Zhou, R. X.; Zheng, X. M. *J. Mol. Catal., A* **2004**, *211*, 139. (b) Arvela, R. K.; Leadbeater, N. E. *J. Org. Chem.* **2005**, *70*, 1786. (c) Zhang, Z.; Zha, Z.; Gan, C.; Pan, C.; Zhou, Y.; Wang, Z.; Zhou, M.-M. *J. Org. Chem.* **2006**, *71*, 4339. On amides, see: (d) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949. (e) Dankwardt, J. W.; Flippin, L. A. *J. Org. Chem.* **1995**, *60*, 2312. (f) Pinho, P.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 259. (g) McDermott, M. C.; Stephenson, G. R.; Huges, D. L.; Walkington, A. J. *Org. Lett.* **2006**, *8*, 2917.

(12) With the cinnamamide, all the starting materials were detected as unreacted by GC-MS, also after 3 days at 125 °C. With the acid, we detected the starting materials and only trace amounts of product **4**.

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(14) Addition of 4 N NaOH was necessary to hydrolyze the coumarin **3**. In fact, the hydrogenation reaction did not work on the closed lactone but only on the more flexible open compound according to ref 13.

(15) For an industrial application, it is possible to avoid flash chromatography by purifying the product by crystallization or, since the yield of the reaction, detected by GC-MS, is almost quantitative (96 %), by purifying the tolterodine only on the reductive amination step.

TABLE 1. Results of Hydrogenation Reaction with Respect to Catalysts and Ligands

entry	ML*	S/C	*T* (°C)	*P* (bar)	*t* (h)	GC yields (%)	*S*/*R*	ee (%)
a	$[Rh(COD)Cl]_2$(*S*,*S*)-Chiraphos	20:1	50	12	24	96	90:10	80
b	$[Rh(COD)Cl]_2$(*S*,*S*)-Chiraphos	200:1	50	12	24	70	90:10	80
c	$[Rh(COD)Cl]_2$(*S*,*S*)-Chiraphos	2000:1	50	12	24	36	90:10	80
d	$[Rh(nbd)BF_4]$(*S*,*S*)-Chiraphos	1000:1	50	12	24	11	60:40	20
e	$[Rh(COD)Cl]_2$(*R*)-Prophos	100:1	50	12	24	99	50:50	0
f	$[Ru(II)(S)\text{-}BINAP(OAc)_2]$	100:1	50	12	24	22	72:28	44
g	$[Ru(TFA)_2(+)TMBTP]$	100:1	50	12	24	96	90:10	80

and open **5** derivatives (Scheme 2). The products **4** and **5** were obtained in different ratios varying from 80:20 to 20:80 for different reactions. The open product **5** cyclizes spontaneously by standing or by refluxing in toluene with *p*TsOH or when injected in the GC-MS instrument. In fact, no open product was detected by GC-MS.

The ee of the hydrogenated intermediate **4**, determined by chiral GC and confirmed by ^{1}H NMR experiments with a europium(III) camphorate derivative, was strongly dependent on the cleanliness of the glass cylinder in which the reaction was carried out. For this reason, it was necessary to wash the cylinder very carefully several times with 3 N HCl before the reaction. The hydrogenation reaction was studied with different catalysts of Rh and Ru and different chiral ligands (Table 1). The best results were obtained by using $[Rh(COD)Cl]_2$ with (*S*,*S*)-Chiraphos (Table 1, entry a) and $[Ru(TFA)_2(+)\text{-}TMBTP]$ (Table 1, entry g); in both cases, the yield was around 96% and the ee 80%.

Interestingly, when dissolving a crude mixture of the hydrogenated lactone in warm CH_3OH and then cooling, a few milligrams (20% yield) of white crystals of the *S* enantiomer were obtained with ee >98%,[16] as determined by chiral GC analysis. The hydrogenated lactone (*S*)-**4** with ee 80% was then reduced to lactol **6** with DIBALH in toluene at –25 °C. The reaction was followed by GC-MS and was quenched when 89% of lactol **6** was observed together with 4% of the over-reduction product and 7% of the starting material. The crude product **6** was then submitted to reductive amination with $(i\text{-}Pr)_2NH$, Pd/C in CH_3OH, to give (*S*)-tol in 73% isolated yield for the two steps as a colorless oil. The desired product was so obtained in 47% overall isolated yield and 80% ee. Following the same procedure but using (*R*,*R*)-Chiraphos as the chiral ligand, (*R*)-tol was obtained in 45% overall yield and 81% ee. The (*S*)-tol was converted to D-tartrate salt, and the $[\alpha]_D$ was measured to assign the absolute configuration by comparing the obtained value with the data reported in the literature.[1] The $[\alpha]_D$ of the (*S*)-tol D-tartrate salt recovered was in accordance with literature reported data for the product with ee >98%.

In conclusion, we have developed a short and efficient four-step enantioselective synthesis of (*S*)- and (*R*)-tol that could easily be used on an industrial scale. The target products were obtained in high yield and enantioselectively by an asymmetric hydrogenation of a coumarin intermediate, easily synthesized by a Heck reaction from inexpensive commercially available starting materials. Moreover, we also realized a very simple synthesis of a coumarin derivative that represent a useful and short approach to the synthesis of many other coumarins.

Experimental Section

For general experimental procedures, see the Supporting Information.

6-Methyl-4-phenylchromen-2-one (3). 2-Bromo-4-methylphenol (**1**) (2.38 mL, 19.71 mmol), Et_4NCl (2.18 g, 13.14 mmol), $Cy_2(Me)N$ (4.22 mL, 19.71 mmol), and $Pd(OAc)_2$ (59 mg 0.26 mmol) were added under nitrogen at room temperature to a solution of methyl *trans*-cinnamate (**2**) (2.131 g, 13.14 mmol) in DMA (40 mL). The reaction mixture was stirred at 95 °C for 48 h, then cooled and filtered through celite. A GC-MS of the solution showed that the Heck adduct was obtained in 94% yield. The solution was then diluted with Et_2O and washed 3 times with H_2O. The organic phase was dried over Na_2SO_4, and the solvent was evaporated under vacuum. The crude product was purified by crystallization from Et_2O/*n*-hexane, and the crystallization residue was purified by flash chromatography (SiO_2, *n*-hexane/Et_2O 7:3). The pure product **3** was obtained as pale yellow crystals (2.40 g, 77% yield): mp = 132−134 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.56 (m, 3H), 7.44−7.47 (m, 2H), 7.25−7.38 (m, 3H), 6.36 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 155.9, 152.6, 135.6, 134.1, 133.2, 129.8, 129.1, 128.7, 126.9, 118.9, 117.3, 115.4, 21.2; MS: *m*/*z* 236 (M^+, 100); Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.36; H, 5.15.

(*S*)-6-Methyl-4-phenylchroman-2-one (4). A glass cylinder placed in a stainless steel autoclave was charged with 6-methyl-4-phenylchromen-2-one (**3**) (1 g, 4.2 mmol), $[Rh(COD)Cl]_2$ (10.45 mg, 0.2 mmol), *S*,*S*-Chiraphos (18.08 mg, 0.4 mmol), CH_3OH (10 mL), and 4 N NaOH (2.1 mL). The autoclave was pressurized to 12 bar with hydrogen, the reaction mixture was stirred at 50 °C for 24 h and then was cooled to room temperature, and the residual gas was released. The solvent was removed under vacuum, and the crude product dissolved in H_2O was acidified to pH = 1−2 with a solution of 6 N HCl and extracted with CH_2Cl_2 (30 mL × 3). The organic phases were dried over Na_2SO_4 and filtered through celite, and the solvent was removed under vacuum. Chiral GC of the crude product (DetTBuSilβCDX 25 m column, carrier gas N_2, $T_1 = 100$ °C, initial isotherm time = 1, heating rate = 2, $T_{final} = 200$ °C, final isotherm time = 10, flow = 2, N_2 pressure = 30 psi) showed that the hydrogenated product was obtained in 96% yield and that the enantiomeric ratio *S*/*R* 90:10, 80% ee, was enriched in the enantiomer which has the lower retention time, and to which the absolute *S* configuration was attributed (*S* enantiomer, retention time = 46.12 min; *R* enantiomer, retention time = 48.55 min; retention time of 6-methyl-4-phenylchromen-2-one = 53.05 min). The ^{1}H NMR $CDCl_3$ of the crude product showed a mixture of closed and open reaction products **4** and **5**. The open form **5** was cyclized either by standing or by refluxing for 4 h in toluene in the presence of a catalytic amount of *p*TsOH acid. After complete cyclization of **5** to **4**, the crude product mixture was purified by flash chromatography (SiO_2, hexane/Et_2O 7:3) to give 850 mg of **4** as a white solid (84% yield). The crude mixture of products **4** and **5** was dissolved in warm CH_3OH and then cooled to give 170 mg (20% yield) of white needles of product *S*, with ee >98% (retention time = 46.12 min), as determined by chiral GC analysis: $[\alpha]_D^{20}$ −2.8 (*c* 1.44, $CHCl_3$), mp = 103−105 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.28 (m, 3H), 7.18−7.00 (m, 4H),6.78 (bs, 1H), 4.30 (t, $J = 6.4$ Hz, 1H),

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[16] Yield of the highly enantiomerically pure hydrogenated product (ee >98%) could be improved by studying the crystallization conditions also according to: Mughal, R. K.; Davey, R. J.; Black, S. N. *Cryst. Growth Des.* **2007**, *7*, 225.

3.06 (dd, $J = 6.4$, 16.4 Hz, 1H), 2.99 (dd, $J = 6.4$, 16.4 Hz, 1H), 2,26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 149.8, 140.7, 134.5, 129.5, 129.3, 127.8, 127.7, 125.5, 117.1, 41.1, 37.6, 21.2; MS: *m*/*z* 238.2 (M^+, 95); Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.68; H, 5.94.

Following the same procedure, different catalysts and chiral ligands were used. When [Ru(TFA)$_2$(+)-TMBTP)] was used as a catalyst, where TMBTP is 2,2′,5,5′-tetramethyl-3,3′-bisdiphenylphosphine-4,4′-bitiophene, with a substrate/catalyst ratio of 100:1, the hydrogenated product **4** was obtained with a yield >96% and *S*/*R* enantiomeric ratio 90:10, 80% ee.

(*S*)-Tol. To a solution of 6-methyl-4-phenylchroman-2-one **4** (100 mg, 0.42 mmol), with an *S*/*R* enantioselective ratio 90:10, in anhydrous toluene (3 mL) was added dropwise under N_2 at −25 °C a solution of 1 M DIBALH in toluene (440 μL, 0.44 mmol). The reaction monitored by GC-MS was stopped after 5 h when GC-MS showed 89% of product **6**, 7% of the starting material, and 4% of the over-reduction product (3-phenyl-3-(2′-hydroxy-5′-methyl)-phenylpropan-1-ol). The reaction was quenched with ethyl acetate, a solution of citric acid was added, and then the solution was stirred at room temperature overnight. The aqueous phase was extracted with ethyl acetate, the organic phases were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. To a solution of the crude product in CH_3OH (5 mL), placed in a glass cylinder in a stainless steel autoclave, were added Pd/C (20 mg) and (*i*-Pr)$_2$NH (147 μL, 1.05 mmol), and the autoclave was pressurized with 5 atm of H_2. The reaction mixture was stirred for 12 h at 48 °C. The solution was cooled to room temperature, and the autoclave was depressurized. After filtration of the catalyst through celite, GC-MS analysis showed that the product was obtained in 98% yield, 87% overall yield for the two steps. The crude product was purified by flash chromatography (SiO_2, hexane/EtOAc 7:3, hexane/Et_3N 98:2) to give 100 mg of product as a colorless oil (73% yield): $[\alpha]_D^{20}$ −23 (*c* 1.5, CH_3OH), ^{1}H NMR (CD_3OD, 400 MHz) δ 7.31−7.09 (m, 5H), 6.90 (d, $J = 2.3$ Hz, 1H), 6.78 (dd, $J = 2.0$, 8.2 Hz, 1H), 6.63 (d, $J = 7.8$ Hz, 1H), 4.32 (t, $J = 7.6$ Hz, 1H), 2.98−3.10 (m, 2H), 2.45−2.39 (m, 2H), 2.17 (s, 3H), 2.2−2.1 (m, 2H), 0.99 (d, $J = 2$ Hz, 6H), 0.97 (d, $J = 2$ Hz, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 153.7, 146,4, 132.5, 129.4, 129.2, 129.1, 128.3, 126.8, 116.3, 50.7, 48.8, 45.9, 42.7, 37.5, 20.8, 20.3; MS: *m*/*z* 325.2 (M^+, 48); Anal. Calcd for $C_{22}H_{31}NO$: C, 81.18; H, 9.60; N, 4.30. Found: C, 81.20; H, 9.63; N, 4.32.

(*S*)-Tol D-TARTRATE. D-Tartaric acid (34.5 mg, 0.23 mmol) was added to a solution of (*S*)-tol (75 mg, 0.23 mmol) in EtOH (5 mL). The solution was heated to 50 °C for 5 h and then cooled and filtered, to give 100 mg of product as a white solid: mp = 205−207 °C, $[\alpha]_D^{25}$ −37 (*c* 1, CH_3OH). [Literature values for (*S*)-tol D-tartrate: $[\alpha]_D^{25}$ −35.8 (*c* 5%, CH_3OH);[1] (*R*)-tol L-tartrate: mp = 210−211 °C, $[\alpha]_D^{25}$ +27.4 (*c* 1%, CH_3OH),[3b] $[\alpha]_D^{25}$ +36.0 (*c* 5%, CH_3OH)[1].]

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Supporting Information Available: General experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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