

A New Efficient Route to Tolterodine

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Abstract:

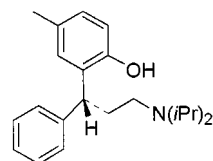
Tolterodine, an important urological drug, can be conveniently prepared starting from 1-[2-hydroxy-5-methylphenyl]-1-phenylethylene, accessible in high yield by alumina-promoted ortho alkenylation of *p*-cresol with phenylacetylene. The hydroformylation of this olefin, catalyzed by rhodium complexes both in homogeneous or in aqueous biphasic system, affords the desired linear aldehyde in about 80–90% yield. The reductive amination of this aldehyde, in the presence of HN-(*i*Pr)₂ and Pd/C (5%) as the catalytic precursor at 4 atm H₂ and 48 °C, produces directly tolterodine in more than 90% yield. Some experiments of enantioselective hydroformylation of 1-[2-hydroxy-5-methylphenyl]-1-phenylethylene catalyzed by Rh(CO)₂acac/(*S,R*)-Binaphos and other enantiopure ferrocenyldiphosphines afforded only low yields of the expected chiral aldehyde; unfortunately, the achieved ee did not exceed 8%.

Introduction

Urinary incontinence is a condition affecting more than 10% of the adult population and can represent an embarrassing problem for many people, negatively influencing their normal way of life.¹ As the mean age of the worldwide population begins to rise, one can speculate that such a pathology is fated to increase its relevance as a health problem.

In the search for new drugs with improved side effect profiles to treat an overactive bladder, a family of phenylpropylamines as muscarinic receptor antagonists has been investigated, and very recently, (+)(*R*)-tolterodine **1** (Figure 1) (brand names Detrol or Detrusitol) was launched and marketed worldwide with success as the (*R,R*)-tartaric acid salt.^{1,2} The annual consumption increment is estimated about 20%. The bulk production in 15 most industrialized countries in the world in 1999 was 450 kg.³

The original synthetic approaches to this molecule⁴ are characterized by numerous steps (more than six), some of



(+)(*R*)-Tolterodine (**1**)

Figure 1.

which involve the use of toxic or hazardous reagents and solvents, give only fair yields, or both. A classical resolution via the formation of diastereomeric salts with (*R,R*)-tartaric acid is used to achieve the enantiomerically pure molecule; even if the racemization and the recycle of the unwanted (*S*)-enantiomer does not seem particularly difficult to accomplish, it requires additional costs; hence, it is strongly desirable to eliminate it from the productive process. Also, a recently published asymmetric approach⁵ to **1** appears quite costly for industrial application.

Recently, a more efficient synthesis involving a lower step number has been claimed in a U.S. patent to obtain (*R,S*)-tolterodine; this is characterized by the preparation of the hemiacetalic compound 3,6-dihydro-6-methyl-4-phenyl-2H-benzopyran-2-ol (**3a**) as a key intermediate.⁶

Another more recent patent⁷ reported a multistep synthetic route to **3a** enriched in the (*R*)-enantiomer. This fact documents the remarkable interest in finding asymmetric processes leading to (+)(*R*)-tolterodine suitable for industrial application.

Before these patents were published, we presented at international symposia^{8–10} a synthetic approach to hemiacetal **3a** following a quite different strategy, namely the regioselective rhodium–carbonyl complex-catalyzed hydroformylation of 1-[(2-hydroxy-5-methyl)-1-phenylethene (**2a**). We based this approach on previous experiences^{11–14} in the production of several compounds endowed with interesting

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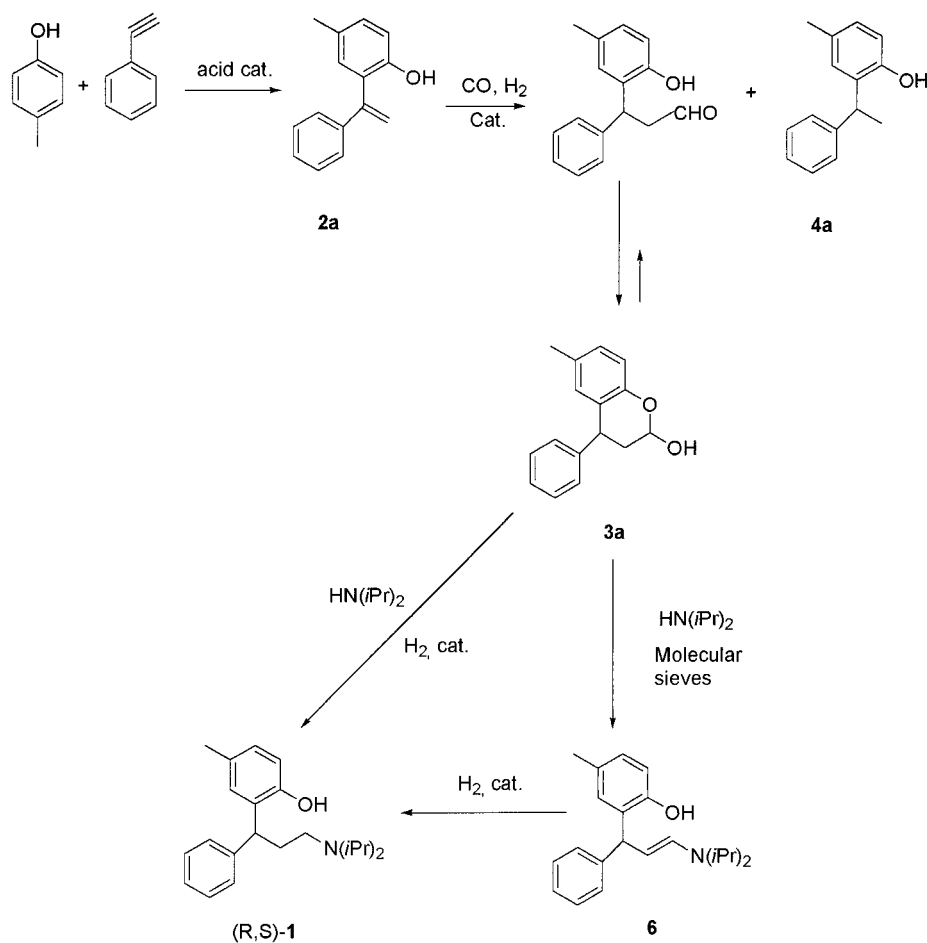
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Scheme 1



therapeutic activity and containing a 3,3-diarylpropyl- or a 4,4-diarylbutylamine moiety. The idea was to use a synthetic scheme involving catalytic processes with high atom utilization and low salt waste. Indeed, the synthetic route outlined in the patent⁶ is afflicted by a serious drawback, namely the use of DIBAL as the reduction agent, which works in stoichiometric amount with respect to the lactone at low temperature; in addition, it is sensitive to air and moisture.

Furthermore, our synthetic approach, involving the hydroformylation process could be developed in an enantioselective way to produce the key intermediate, hemiacetal **3a**, enriched in the desired diastereomer.

Results and Discussion

The synthetic route to (R,S)-tolterodine proposed by us is depicted in Scheme 1.

This short route not only could offer better overall yields and significant improvement in terms of cost reduction, but could also, in principle, permit the formation of a nonracemic chiral center by using rhodium complexes modified with

enantioselectively pure ligands as catalysts in the hydroformylation step.

The olefinic substrate **2a** to be subjected to the oxo reaction was prepared by ortho alkenylation of *p*-cresol with phenylacetylene, both easily available in the industrial market, according to an experimental procedure described by Sartori et al.¹⁵ and suitably modified by us. In fact, while the zeolite catalysts employed by these authors, in our hands, did not give the expected selectivity, much better results were obtained using acidic Al₂O₃ activated by calcination at 500 °C for 5 h; almost complete chemoselectivity and yields up to 90% were achieved. Even if the alumina was used in a large amount (47 wt % with respect to *p*-cresol), this does not represent a serious drawback, owing to its low cost and the possibility to recover and to reactivate it.

The hydroformylation of olefin **2a** to the corresponding linear aldehyde, mostly in the hemiacetalic form **3a**, is conveniently carried out either in the biphasic water/toluene system or in organic solvent as, for instance, toluene, in the presence of an appropriate catalytic precursor (see Table 1).

The results obtained in the aqueous biphasic hydroformylation are particularly attractive in the perspective of a semi-industrial application due to the use of an environmentally benign solvent and to the easy separation of the products and nearly quantitative recovery of the expensive rhodium

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Table 1. Rhodium-catalyzed hydroformylation of olefin **2a**^a

entry	catalytic system	<i>t</i> (h)	conv. (%) ^b	aldehyde yield (%) ^b	hydrog. product (%) ^b
1 ^c	[Rh(COD)Cl] ₂	72	96.0	94.4	1.6
2 ^{c,d}	HRh(CO)(PPh ₃) ₃	48	32.3	27.1	5.4
3 ^c	HRh(CO)(PPh ₃) ₃	48	95.2	91.6	3.6
4 ^c	Rh(CO) ₂ acac/PPh ₃	72	51.3	42.6	8.7
5 ^c	Rh(CO) ₂ acac/DPPB	72	83.0	74.5	8.5
6 ^c	Rh(CO) ₂ acac/Xantphos	24	10.3	6.0	4.3
7 ^c	Rh(CO) ₂ acac/Xantphos	72	90.3	83.5	6.8
8 ^{c,e}	Rh(CO) ₂ acac/Xantphos	72	26.2	7.9	18.3
9 ^f	[Rh(COD)Cl] ₂ /TPPTS	48	99.1	99.1	-
10 ^f	[Rh(COD)Cl] ₂ /TPPTS	24	80.0	80.0	-
11 ^f	[Rh(COD)Cl] ₂ /Xantphos(SO ₃ Na) ₂ ^g	24	37.7	33.9	3.8

^a Experimental conditions: *P* = 100 atm (CO/H₂ = 1); temp. = 100 °C; substrate/Rh (molar ratio) = 250/1; ligand/Rh (molar ratio) = 1.1/1; water soluble ligand /Rh (molar ratio) = 3/1; DPPB = 1,4-bis(diphenylphosphino)butane; TPPTS = triphenylphosphine-3,3',3''-trisulfonic acid trisodium salt; Xantphos(SO₃Na)₂ = 2,7-bis(SO₃Na)Xantphos. ^b Determined by GC. ^c Solvent = toluene. ^d Experiment carried out at 80 °C. ^e Ligand/Rh (molar ratio) = 2.2/1. ^f Solvent = H₂O/toluene. ^g Catalyst preformed in water at 20 atm (CO/H₂ = 1) and 100 °C for 4 h.

catalyst; as a matter of fact, we observed, after five recycles of the catalytic solution, a very small efficiency loss (<5%). Generally, the only byproduct is compound **4a** derived from the olefinic double bond hydrogenation; sometimes we noticed that this compound was the main product when commercial catalytic precursors such as HRh(CO)(PPh₃)₃ and [Rh(COD)Cl]₂ were employed. When these rhodium complexes are carefully prepared and purified according to well-known procedures,^{16,17} the chemoselectivity of the oxo reaction is fairly good.

The data reported in Table 1 also show the effect of the phosphine ligands on the reaction; contrary to the results usually observed in the hydroformylation catalyzed by rhodium/phosphine complexes,¹⁸ in several cases we noticed a detrimental influence of the ligand on both reaction rate and chemoselectivity (entries 2, 4–8); when this catalytic process was carried out in the more economically convenient and environmentally friendly aqueous biphasic system catalyzed by [Rh(COD)Cl]₂/TPPTS, we obtained a good reaction rate and an almost quantitative chemoselectivity (entries 9 and 10).¹⁹ When Xantphos(SO₃Na)₂ was used as the hydrosoluble ligand, both the reaction rate and the chemoselectivity of the process remarkably decreased (entry 11; see also Figure 2).

Some experiments to prepare (*R,S*)-tolterodine by reductive amination of the hemiacetal **3a** in the presence of PtO₂ as the catalyst and diisopropylamine at 76 atm of H₂ and 120 °C for 24 h, following a well-described procedure²⁰ that demonstrated good success in our previous works,^{11,12} gave unsatisfactory results in this case. However, the catalytic reduction of the corresponding enamine **6**, prepared by treatment with diisopropylamine in the presence of molecular sieves, afforded the target compound in an efficient way:

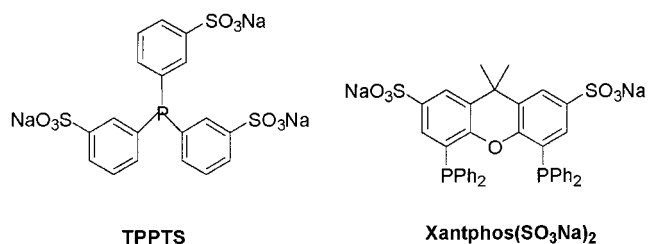
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**Figure 2.**

83% yield of tolterodine was obtained after 24 h at 120 °C and 80 atm H₂ using PtO₂ as the catalyst.²⁰

Finally, following the experimental procedure recently described in a patent,⁶ (*R,S*)-tolterodine was obtained by reductive amination of **3a** after 10 h at 4 atm H₂ and 48 °C in methanol, in the presence of Pd/C (5%): the yield reached 96%. This latter method is strongly preferable because of the lower cost of the catalyst, the remarkably milder reaction conditions, and the higher chemical yield obtained.

As only the (+)-(*R*)-enantiomer of tolterodine displays the desired pharmacological activity, we devised a way to prepare this chiral drug by enantioselective hydroformylation of olefin **2a** and subsequent transformation of the enantiomerically enriched *oxo*-aldehyde obtained. Indeed, the results obtained in the hydroformylation of this substrate catalyzed by rhodium carbonyl complexes modified with phosphorus external ligand did not appear very promising (see Table 1); however, we hoped that a high enantioselectivity could counterbalance a low chemical yield. The catalyst of choice to perform the oxo process was the system Rh(CO)₂acac/(*S,R*)-Binaphos (1:4 molar ratio), thus far the most active catalyst in the enantioselective hydroformylation of various alkenes.²¹ This reaction, carried out on substrate **2a** in toluene at 60 °C and 80 atm (CO/H₂ = 1) and with a substrate-to-rhodium molar ratio of 250 to 1, gave compound **4a** as the only reaction product.

Therefore, we thought to study the behavior towards hydroformylation of substrate **2b**, in which the hydroxy group was protected as acetoxy derivative, in the aim of improving the yield of the desired *oxo*-aldehyde when the oxo process was catalyzed by rhodium-carbonyl complexes modified with external phosphorus ligands.

Compound **2b** was conveniently prepared in 90% yield by reacting olefin **2a** with acetyl chloride in wet toluene for 2 h at room temperature in the presence of NaOH and the phase-transfer catalyst tetrabutylammonium hydrogensulfate.²²

When **2b** was used, the reaction catalyzed by Rh(CO)₂acac/(*S,R*)-Binaphos^{21,23} ran again very sluggishly, and no more than 51% of conversion was achieved after 168 h at 60 °C and 80 atm (Table 2, entry 1). The chemoselectivity was also very disappointing, about 27% of olefin hydrogenation product **4b** being detected in the reaction mixture. The chiral nonracemic aldehyde obtained showed an enantiomeric excess of only 8%. This value was determined by aldehyde

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Scheme 2

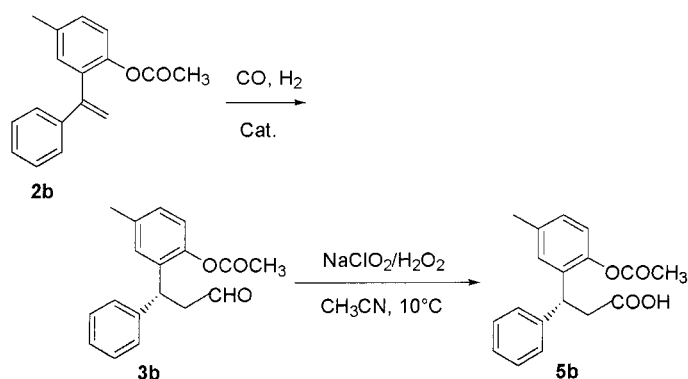


Table 2. Enantioselective rhodium-catalyzed hydroformylation of olefin 2b^a

entry	ligand	substrate/ catalyst	<i>t</i> (h)	conv. (%) ^b	aldehyde yield (%) ^b	hydrog. product (%) ^b	ee (%) ^c
1 ^d	Binaphos	250/1	168	51.4	24.7	26.7	8
2	L ₁	307/1	216	>99	61.9	25.5	1
3	L ₁	250/1	216	>99	37.6	59.0	-
4	L ₂	250/1	216	66.2	22.0	44.2	-
5	L ₃	250/1	144	58.7	17.6	41.1	-

^a Experimental conditions: cat. = Rh(CO)₂acac; ligand/Rh = 4/1 (molar ratio); *P* = 100 atm (CO/H₂ = 1); Temp = 100 °C; solvent = toluene. ^b Determined by GC. ^c Determined by HPLC (see Experimental Section). ^d Experiments carried out at 80 atm (CO/H₂ = 1) and 60 °C.

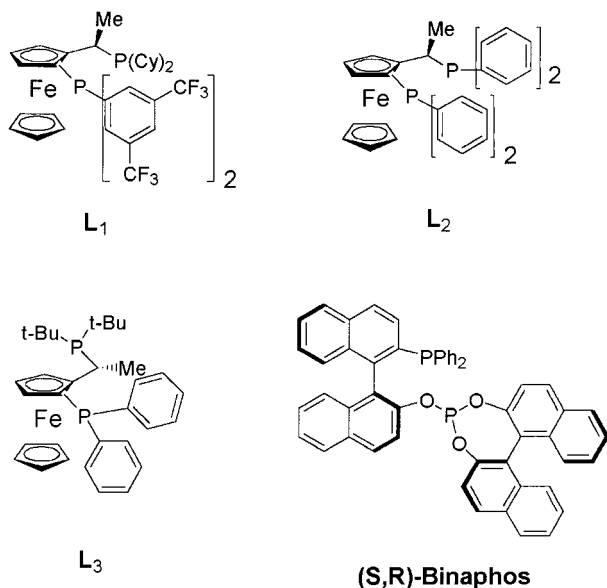


Figure 3.

3b oxidation to the corresponding acid²⁴ **5b** and enantioselective HPLC using the chiral column Chiralcel OD (Scheme 2).

Since enantiopure ferrocenylphosphines were seldomly employed as ligands in enantioselective hydroformylation,^{25,26} we carried out some oxo experiments on olefin **2b** using the diphosphines L₁-L₃ depicted in Figure 3 to modify the

carbonyl complex Rh(CO)₂acac (Table 2). Only in one case (Table 2, entry 2) we obtained a sufficiently high yield (about 62%) to isolate from the reaction mixture and to purify the aldehyde **3b**; this showed negligible ee.

Conclusions

In conclusion, we were able to carry out an efficient route to (*R,S*)-tolterodine with an overall yield up to 60%. This preparative scheme, in our opinion, could be convenient for an industrial scale-up; however, all the steps of the preparative route proposed by us and, in particular, that of the hydroformylation step, are under investigation in our laboratory for further improvements. Unfortunately, the asymmetric hydroformylation will hardly be successfully employed for the synthesis of enantiomerically enriched (+)-(*R*)-tolterodine, but other more promising enantioselective catalytic processes are currently under study by us.

Experimental Section

General Methods. The rhodium complexes HRh(CO)-(PPh₃)₃¹⁶ and [Rh(COD)Cl]₂¹⁷ were prepared following well-known procedures. Rh(CO)₂acac and palladium, 5 wt % on activated carbon, were purchased from Aldrich. Acid Al₂O₃ (S, 0.063 mm, Riedel-De Haen AG) was activated by calcination at 550 °C for 5 h before use. Phenylacetylene was filtered through a short column of alumina and then distilled at reduced pressure (bp 75 °C/80 mmHg). Molecular sieves (Aldrich, 4 Å, 1.6 nm) were heated in vacuo at 250 °C for 24 h. (*S,R*)-Binaphos was prepared following a described procedure.²⁷ Merck silica gel 60 (240–400 mesh) was used for column chromatography. NMR spectra were measured for solutions in CDCl₃ using a Bruker AC 200 spectrometer operating at 200 MHz. Solvents were purified following well-known procedures.²⁸

1-[(2-Hydroxy-5-methylphenyl)-1-phenylethylene (2a).

A mixture of *p*-cresol (2.16 g, 20 mmol), phenylacetylene (2.2 mL, 200 mmol) and 1 g (47 wt %) of activated acid alumina S (0.063 mm) in anhydrous 1,2-dichlorobenzene (12 mL) was heated at reflux for 72 h, after which was cooled to room temperature. The alumina was filtered off and washed several times with diisopropyl ether. Removal of the solvent in vacuo left a crude oil, which was purified by

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distillation at reduced pressure (81 °C/32 mmHg), so furnishing olefin **2a** as a colorless oil (3.8 g, 90% yield). ¹H NMR δ 7.41–6.85 (m, 8H), 5.88–5.86 (d, *J* = 1.21 Hz, 1H), 5.44–5.42 (d, *J* = 1.21 Hz, 1H), 5.02 (s, 1H), 2.31 (s, 3H). MS: *m/e* 210 (M⁺, 57), 209 (100), 195 (39), 165 (21), 77 (12). Anal. Calcd for C₁₅H₁₄O: C, 85.68; H, 6.71. Found: C, 85.42; H, 6.68.

1-[(2-Acetoxy-5-methyl)phenyl]-1-phenylethylene (2b). This olefin was prepared in 90% yield, starting from olefin **2a**, according to a described procedure.²² Bp 175 °C/0.1 mmHg. ¹H NMR δ 7.45–6.85 (m, 8H), 5.88–5.86 (d, *J* = 1.21 Hz, 1H), 5.44–5.42 (d, *J* = 1.21 Hz, 1H), 2.32 (s, 3H), 1.80 (s, 3H). MS: *m/e* 252 (M⁺, 22), 237 (12), 209 (100), 195 (26), 165 (14), 43 (31). Anal. Calcd for C₁₇H₁₆O₂: C, 80.93; H, 6.39. Found: C, 80.65; H, 6.37.

Hydroformylation of 2a. A 150-mL stainless steel reaction vessel was charged under a nitrogen purge with 2 mmol of olefin **2a**, 0.008 mmol of rhodium catalyst and 5 mL of anhydrous toluene. The reactor was then pressurized to 100 atm with syngas (CO/H₂ = 1) and heated at 80–100 °C for 24–72 h (see Table 1). For analytical purposes aldehyde **3a** (hemiacetalic form), a white solid, was recovered from the reaction mixture by flash silica gel chromatography (hexane/ether, 80/20). Mp 82.5 °C. ¹H NMR δ 7.40–6.60 (m, 8H), 5.67 (t, *J* = 3.05, 1H), 4.36–4.28 (m, 1H), 2.34–2.20 (m, 2H), 2.16 (s, 3H). MS: *m/e* 240 (M⁺, 100), 222 (66), 221 (72), 195 (57), 145 (70), 115 (25). Anal. Calcd for C₁₆H₁₆O₂: C, 80.0; H, 6.71. Found: C, 79.76; H, 6.69.

Hydroformylation of 2a in Aqueous Biphasic Medium. In a Schlenk tube [Rh(COD)Cl]₂ (4.0 mg, 0.008 mmol) and TPPTS (27.6 mg, 0.048 mmol) were dissolved under nitrogen in H₂O (2.5 mL); then, a solution of **2a** (0.5 g, 2.0 mmol) in toluene (3 mL) was added. The Schlenk tube containing the two-phase liquid mixture was transferred to a 150-mL stainless steel autoclave under nitrogen, pressurized to 100 atm with syngas (CO/H₂ = 1) and heated at 100 °C for 48 h (see Table 1). The reactor was then cooled to room temperature and the residual gases released. The organic phase was separated and dried on MgSO₄, and toluene was removed in vacuo; the aldehyde **3a** (hemiacetalic form) was recovered and identified as previously described.

Hydroformylation of 2b. A 150-mL stainless steel reaction vessel was charged under a nitrogen purge with 2 mmol of olefin **2b**, 0.008 mmol of rhodium catalyst, 0.0032 mmol of an external ligand, and 5 mL of anhydrous toluene. The reactor was then pressurized to 100 atm with syngas (CO/H₂ = 1) and heated at 80–100 °C for 24–72 h (see Table 2). For analytical purposes aldehyde **3b**, a pale yellow oil, was recovered from the reaction mixture by flash silica gel chromatography (hexane/ether, 80/20). ¹H NMR δ 9.73 (t, *J* = 1.83, 1H), 7.45–6.71 (m, 8H), 4.8–4.68 (t, *J* = 7.32, 1H), 3.26–3.0 (m, 2H), 2.35 (s, 3H), 1.81 (s, 3H). MS: *m/e* 282 (M⁺, 6), 240 (15), 222 (100), 196 (10), 145 (19). Anal. Calcd for C₁₈H₁₈O₃: C, 76.57; H, 6.42. Found: C, 76.37; H, 6.40.

Determination of the Enantiomeric Excess. The hydroformylation reaction mixture of **2b** catalyzed by Rh-

(CO)₂acac/(*S,R*)-Binaphos (see Table 2) was oxidized to the corresponding 3-[(2-acetoxy-5-methyl)phenyl]-3-phenylpropanoic acid (**5b**) with NaClO₂, H₂O₂, and NaH₂PO₄ in CH₃CN at 10 °C.²⁴ The enantiomeric excess of **5b** was determined by HPLC analysis using a Chiracel OD 250 mm × 4.6 mm column (*n*-hexane/2-propanol/formic acid = 90/10/1, flux 0.5 mL/min, loop 10 μL, wavenumber 254 nm): ee = 8%. Compound **5b**: ¹H NMR δ 9.71 (s, 1H), 7.45–6.71 (m, 8H), 4.8–4.68 (m, 1H), 3.3–2.98 (m, 2H), 2.35 (s, 3H), 1.80 (s, 3H). MS: *m/e* 298 (M⁺, 1), 280 (1), 238 (100), 220 (30), 195 (57), 165 (11), 91 (4), 77 (5). Anal. Calcd for C₁₈H₁₈O₄: C, 72.47; H, 6.08. Found: C, 72.28; H, 6.06.

(*R,S*)-Tolterodine (1). In a 150-mL stainless steel reaction vessel a solution of **3a** (1 g, 4.2 mmol) in 5 mL methanol was slowly added, under a nitrogen purge, to Pd/C (5%) (0.11 g, 1.03 mmol). Anhydrous *N,N*-diisopropylamine (0.74 mL, 5.3 mmol) was added and the reactor pressurized to 3 atm with H₂. After 16 h at 50 °C the reactor was cooled to room temperature and the residual gas released. The reaction mixture was filtered, and solvent and excess HN(*i*Pr)₂ were distilled off in vacuo; the remaining oil was purified by flash chromatography as described by Andersson et al.⁵ Concentration in vacuo yielded 1.32 g (96.8% yield) of (*R,S*)-tolterodine **1** as a colorless oil. ¹H NMR δ 7.35–6.83 (m, 8H), 6.55 (s, 1H), 4.53–4.46 (m, 1H), 3.24 (q, *J* = 6.71, 2H), 2.77–2.69 (m, 2H), 2.43–2.32 (m, 2H), 2.13 (s, 3H), 1.14 (d, *J* = 6.71, 6H), 1.09 (d, *J* = 6.71, 6H). ¹³C NMR (300 MHz) δ 153.11 (CHOH), 144.6 (ArCHCH), 132.3–125.9 (5C, C₆H₃), 77.45.76.6 (5C, C₆H₅), 48.2 [N(CHCH₃)₂], 42.2 (NCH₂), 39.5 [(Ar)(Ph)CH], 33.2 (CHCH₂CH₂), 20.9 (PhCH₃), 19.8 [CH(CH₃)₂], 19.4 [CH(CH₃)₂]. MS: *m/e* 325 (M⁺, 8), 310 (13), 114 (100), 100 (5). Anal. Calcd for C₁₈H₁₈NO₃: C, 81.18; H, 9.6; N, 4.3. Found: C, 80.94; H, 9.56; N, 4.1.

(*R,S*)-Tolterodine (1) by Hydrogenation of Enamine 6. A solution of hemiacetal **3a** (0.5 g, 2.08 mmol) and anhydrous *N,N*-diisopropylamine (1.05 mL, 7.5 mmol) in 2 mL of anhydrous toluene were slowly stirred, under a nitrogen purge, at 50 °C in the presence of freshly activated 4 Å molecular sieves (2 g). After 72 h the conversion of **3a** to *N,N*-diisopropyl-3-[(2-Hydroxy-5-methyl)phenyl]-3-phenylprop-1-enamine (**6**) was complete; the molecular sieves were filtered off, and the solvent was evaporated at reduced pressure. Compound **6** was characterized by GC/MS; MS: *m/e* 323 (M⁺, 50), 308 (5), 280 (7), 126(100), 84 (94), 71 (91), 43 (59).

The enamine **6**, recovered from the reaction mixture without any further purification, was dissolved in anhydrous toluene (10 mL) and hydrogenated in the presence of PtO₂ (5.0 mg, 0.019 mmol) at 120 °C and 80 atm H₂ for 24 h.²⁰ Tolterodine was obtained in about 90% yield and characterized as described above.

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