Asymmetric Total Synthesis of (+)-Tolterodine, a New Muscarinic Receptor Antagonist, via Copper-Assisted Asymmetric Conjugate Addition of Aryl Grignard Reagents to 3-Phenyl-prop-2-enoyl-oxazolidinones

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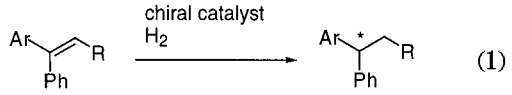
Introduction

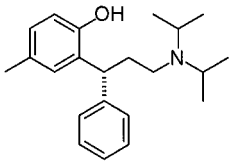
Tolterodine (Figure 1) is a new and potent competitive muscarinic receptor antagonist. The drug is intended for the treatment of urinary urge incontinence and other symptoms of bladder overactivity.[1] It has been shown that Tolterodine has a more pronounced action on the urinary bladder than on salivary glands in vivo in the anaesthetised cat.[2] This selectivity also seems to occur in humans as demonstrated in clinical trials.[3] However, this favorable profile cannot be attributed to selectivity for a single muscarinic receptor subtype.

The structural element with two aryl groups attached to a chiral center, as in Tolterodine, which has the R configuration, is unusual, and few reports in the chemical literature deal with asymmetric synthesis of these types of diaryl compounds.[4] Retrosynthetically, there are several ways to approach this problem. One attractive way would be catalytic asymmetric hydrogenation of a double bond, as pictured in eq 1, using some chiral-ligand−metal complex. However, this requires control of the double bond configuration in the preceding steps, which is not a trivial problem.



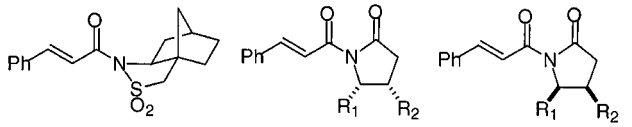
(1)

On the other hand, conjugate additions of various nucleophiles to α,β-unsaturated acid derivatives attached to a chiral auxiliary is a well-known methodology in asymmetric synthesis (eq 2). Oxazolidinones, for example, have been extensively used in this context and are also easily obtained.[5] Thus, by choosing this approach we could use readily available starting materials and reliable synthetic routes for the preparation of the desired substrates.



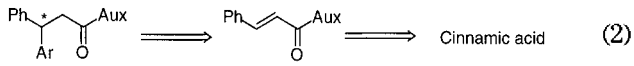
Tolterodine

Figure 1.



1 **2a**: R_1 = *i*-Pr, R_2 = H **3a**: R_1 = Me, R_2 = Ph
2b: $R_1 = R_2$ = *i*-Pr **3b**: R_1 = Ph, R_2 = H
3c: $R_1 = R_2$ = Ph

Figure 2.



(2)

Results and Discussion

To find a suitable chiral auxiliary for the asymmetric 1,4-addition to the cinnamic unit, a number of substrates were prepared and evaluated. The substrates used (Figure 2), camphorsultam **1**[6] or the oxazolidinones **2a,**[7] **2b**[8] or **3a**,[6] **3b**,[9] **3c**,[8] were prepared from cinnamoyl chloride, and the corresponding chiral auxiliary was prepared using literature procedures.

Several aryl−magnesium and aryl−copper reagents were evaluated in the 1,4-addition to the camphorsultam **1** (Scheme 1). It was found that none of the aryl grignards (alone or copper-catalyzed), not homocuprates nor arylcopper reagents, led to any reaction. On the other hand, the reagent derived from phenylmagnesium bromide and CuBr−Me_2S (PhMgBr/Cu 2:1) smoothly underwent a highly regioselective 1,4-addition to the camphorsultam and gave **4a** in a quantitative yield. When the aryl group was changed from phenyl to 2-methoxy-5-methylphenyl, the adduct **4b** was formed in 74% chemical yield but with a disappointingly low diastereomeric excess[10] (50%).

To improve the diastereoselectivity of the reactions with 2-methoxy-5-methylphenyl, the sultam was replaced by chiral oxazolidinones **2a**−**b** and **3a**−**c**. These substrates also underwent highly regioselective 1,4-additions when they were treated with 2-methoxy-5-methylphenylmagnesium bromide and CuBr·Me_2S, as shown in Scheme 2 and Table 1.

Oxazolidinone **2a**, derived from L-valine, smoothly underwent the 1,4-addition and furnished (*S*)-**5** after deprotection of the chiral auxiliary.[11] The enantiomeric

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(1) Registration applications have been filed in EU and US.
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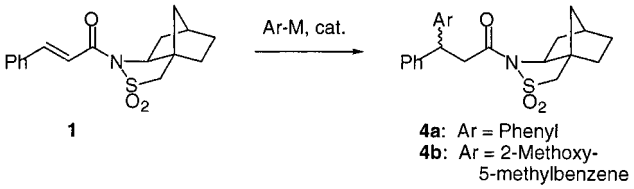
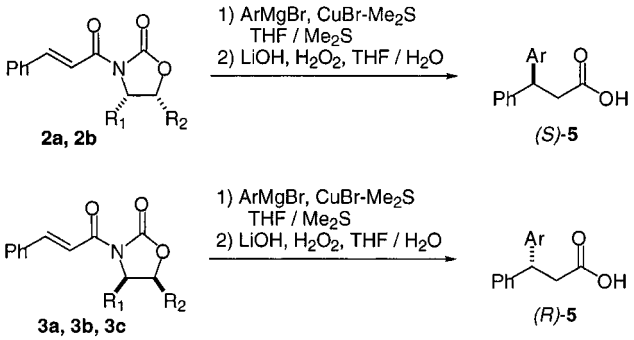
Table 1. Cu-Catalyzed Conjugate Addition to Substrates 2a,b and 3a−c

entry	substrate	R_1	R_2	yield (%)	de (%)	config
1	**2a**	*i*-Pr	H	68	60	S
2	**2b**	*i*-Pr	*i*-Pr	84	99	S
3	**3a**	Me	Ph	75	50	R
4	**3b**	Ph	H	78	98	R
5	**3c**	Ph	Ph	81	99	R

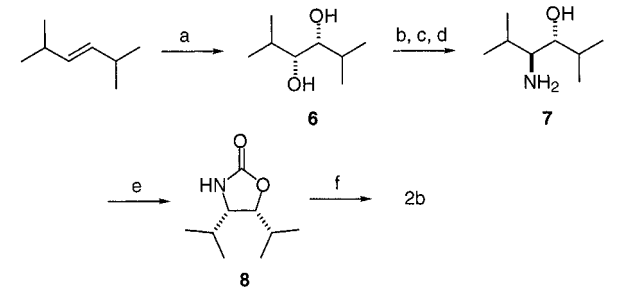
Scheme 1



Scheme 2



Scheme 3



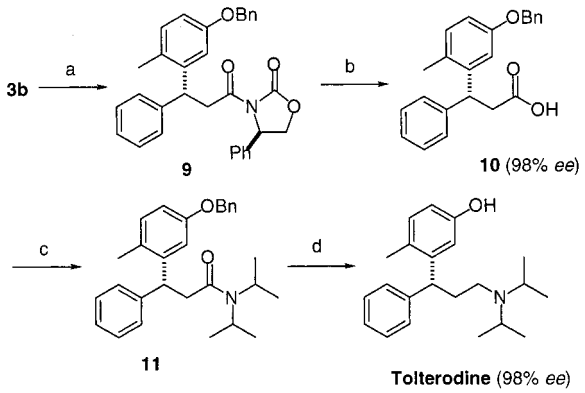
[a] $(DHQD)_2$-PHAL, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH-H_2O, 95%. [b] *i*) $CH_3C(OMe)_3$, PPTS, CH_2Cl_2, *ii*) AcBr, CH_2Cl_2, *iii*) NaOH, Et_2O, MeOH. [c] LiN_3, DMF. [d] Pd/C, H_2, EtOH, 80% from **6**. [e] $COCl_2$, Et_3N, CH_2Cl_2, 94%. [f] BuLi, Cinnamoyl chloride, THF, 85%.

excess was determined by chiral HPLC and revealed that the acid had been obtained in 60% ee.

By the introduction of a second substituent on the oxazolidinone, as in **2b** (prepared via Sharpless dihydroxylation of 2,4-dimethyl-3-hexene and subsequent transformation of **6** into its amino alcohol **7**, Scheme 3), the enantiomeric excess of the acid could be raised to 99%.

Since the synthesis of Tolterodine requires the opposite sense of chiral induction in the 1,4-addition, we studied oxazolidinones **3** as chiral auxiliaries. As expected, the use of oxazolidinone **3a** gave rise to the opposite configuration, giving the acid (*R*)-**5** in 50% ee after deprotection of the oxazolidinone. However, the oxazolidinone **3b** derived from (*R*)-phenylglycine, resulted in (*R*)-**5** with 98% ee. This shows that the phenyl group is superior to the isopropyl group in directing the incoming nucleophile. By introduction of a second substituent on the oxazolidinone (**3c**), the ee could be improved to 99%.

Scheme 4



[a] 2-Benzyloxy-5-methylphenylbromide, Mg, CuBr-Me_2S, THF, 84%. [b] LiOH, H_2O_2, THF / H_2O, 90%. [c] *i*) $SOCl_2$, pyridine, benzene *ii*) *i*-Pr_2NH, 81%. [d] *i*) $LiAlH_4$, Et_2O *ii*) Pd/C, H_2, MeOH, 74%.

Since **3b**, derived from commercially available phenyloxazolidinone, gave good yield and high stereoselectivity in the addition reaction, it was used for further elaboration to Tolterodine according to the sequence outlined in Scheme 4.

Changing the phenol protective group of the nucleophile from methyl to the more easily removable benzyl did not affect the stereoselectivity or the yield of the conjugate addition reaction. Reacting **3b** with the aryl Grignard reagent, as described earlier, afforded the diaryl derivative **9** in 84% yield. NMR analysis of the reaction mixture suggested a high diastereomeric excess, >95%. This was confirmed in the next step. Removal of the chiral auxiliary[11] ($LiOH/H_2O_2$ in water/THF) yielded the acid **10**, and HPLC analysis revealed the ee to be 98%. Treating **10** with thionyl chloride followed by diisopropylamine afforded the corresponding diisopropylamide **11**. Subsequent reduction of the amide with lithium aluminum hydride gave *o*-benzyl Tolterodine, which after deprotection (H_2/palladium on carbon) yielded Tolterodine in 98% ee.

Experimental Section

General. For general experimental information, see ref 12. 1-Methoxy-2-bromo-4-methylbenzene[13] and 1-benzyloxy-2-bromo-4-methylbenzene[14] were prepared from commercially available 2-bromo-4-methylphenol and had spectral data in agreement with those reported in the literature. Merck silica gel 60 (240−400 mesh) was used for column chromatography. Chiral HPLC analyses were done on a CHIRAL-AGP 100 × 2 mm column using 2-propanol as the eluent. All reactions except those involving water were performed in flame-dried glass charged with nitrogen. The copper(I) bromide−dimethyl sulfide complex was purchased from Aldrich (art. 23,050−2). Magnesium sulfate was used for drying of organic extracts.

2,5-Dimethyl-3*R*,4*R*-hexadiol, 6. This diol was prepared in 95% yield and 98% ee[15] according to the procedure developed by Sharpless et. al. using $(DHQD)_2$−PHAL as the chiral ligand.[16]

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mp: 78−79 °C. ^{1}H NMR (300 MHz) δ: 3.28 (br s, 2 H), 2.21 (br s, 2 H), 1.78 (app oct, J = 6.5 Hz, 2 H), 0.93 (d, J = 6.5 Hz, 12 H). ^{13}C NMR (75 MHz) δ: 76.3, 31.1, 30.4, 19.5, 17.4. IR: 3640, 2962, 1469, 1388, 993, 908 cm^{-1}. MS: *m/e* (relative intensity) 146 (M^+, 0.2), 129 (0.6), 117 (1.5%), 103 (14), 85 (9), 73 (100), 72 (37). $[\alpha]^{25}_D$: 2.27 (*c* 2.2, EtOH). Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.64; H, 12.47.

2,5-Dimethyl-3*S*-aminohexan-4*R*-ol, 7. 2,5-Dimethyl-3*R*,4*R*-hexadiol **6** (3.50 g, 23.9 mmol), trimethyl orthoacetate (3.73 g, 31.1 mmol, 1.3 equiv), and pyridinium toluenesulfonic acid (60 mg, 0.24 mmol, 0.01 equiv) were dissolved in dry methylene chloride (40 mL) and stirred at room temperature for 2 h. The reaction mixture was evaporated in vacuo, and dry methylene chloride (40 mL) was added. The resulting solution was cooled to 0 °C, and acetyl bromide (3.82 g, 31.1 mmol, 1.3 equiv) was added. After the addition, the reaction was stirred and allowed to reach ambient temperature overnight. The reaction mixture was evaporated in vacuo, filtered through silica (eluent: 10% EtOAc in hexane), and evaporated to give ca. 6 g of a clear, colorless oil.

The oil was dissolved in dry ether (40 mL) and NaOH (2.10 g, 52.7 mmol, 2.2 equiv), and MeOH (1.53 g, 47.9 mmol, 2.0 equiv) was added. The resulting mixture was then stirred at room temperature for 24 h. Ether (100 mL) was added, and the organic phase was washed with water (50 mL) and brine (25 mL) and dried. The solvent was removed by distillation at atmospheric pressure to yield (2*R*,3*R*)-diisopropyloxirane (ca. 4 g ethereal solution) as a clear, colorless solution, which was used directly in the next step.

(2*R*,3*R*)-Diisopropyloxirane (approximately 22 mmol) and LiN_3 (5.4 g, 110 mmol, 5 equiv) were dissolved in dry DMF (100 mL). The resulting mixture was stirred for 24 h at 110 °C, cooled to room temperature, diluted with water (200 mL), and extracted with ether (4 × 25 mL). The combined organic phases were washed with water (25 mL) and brine (25 mL), dried, and evaporated to give crude 2,5-dimethyl-3*S*-azidohexan-4*R*-ol (3.4 g, 20 mmol).

A slurry of 2,5-dimethyl-3*S*-azidohexan-4*R*-ol (3.4 g, 20 mmol) and Pd/C (5% on carbon, 170 mg) in ethanol (50 mL) was stirred under an atmosphere of H_2 at room temperature for 5 h. The slurry was filtered, and the filtrate evaporated in vacuo to give 2,5-dimethyl-3*S*-aminohexan-4*R*-ol (2.76 g, 19 mmol) as a clear, colorless oil. ^{1}H NMR (300 MHz) δ: 3.28 (dd, J = 4.5, 6.7 Hz, 1 H), 2.61, (dd, J = 3.9, 6.7), 12.05−1.83 (m, 5 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.89 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz) δ: 77.1, 57.9, 29.2, 28.2, 20.9, 20.2, 16.3, 16.1. IR: 3450, 2960, 1686, 1468, 1385, 995 cm^{-1}. MS: *m/e* (relative intensity) 145 (M^+, 0.5), 117 (0.6), 102 (11), 73 (9), 72 (100). $[\alpha]^{25}_D$: +7.07 (*c* 2.05, EtOH). Anal. Calcd for $C_8H_{19}NO$: C, 66.16; H, 13.19; N, 9.64. Found: C, 65.89; H, 13.24; N, 9.45.

(4*S*,5*R*)-Diisopropyl-2-oxazolidinone, 8. 2,5-Dimethyl-3*S*-aminohexan-4*R*-ol, **7** (0.30 g, 2.06 mmol, 1.0 eq.), and triethylamine (0.25 g, 2.47 mmol, 1.2 equiv) were dissolved in CH_2Cl_2 (15 mL) and stirred at 0 °C. To this solution was added slowly phosgene (1.3 mL, 1.93M in toluene, 1.2 equiv). After the addition was complete, the resulting mixture was stirred for 2 h at room temperature. Methylene chloride (25 mL) was added, and the solution was washed with 2 M hydrochloric acid (10 mL), dried, and evaporated to give the product (0.330 g, 1.93 mmol, 94%) as colorless crystals. mp: 139−143 °C. ^{1}H NMR (400 MHz) δ: 5.80 (br. s, 1 H), 4.18 (dd, J = 6.9, 9.1 Hz, 1 H), 3.56 (dd, J = 3.5, 6.9 Hz, 1 H), 2.08 (m, 1 H), 1.99, (m, 1 H), 1.10 (d, J = 6.5 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H), 0.96 (d, J = 6.5 Hz, 3 H), 0.94 (d, J = 6.5 Hz, 3 H). ^{13}C NMR (100 MHz) δ: 160.4, 85.8, 60.6, 27.5, 27.4, 20.6, 19.3, 19.1, 17.0. IR: 3458, 2967, 2878, 1752, 1469, 1396, 1373, 1223, 1029 cm^{-1}. MS: *m/e* (relative intensity) 171 (M^+, 0.8), 129 (8), 128 (100), 127 (28), 119, (4), 86 (24), 84 (56). $[\alpha]^{25}_D$: −16.9 (*c* 0.35, $CHCl_3$). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.32; H, 9.94; N, 8.35.

(4*S*,5*R*)-Diisopropyl-3-(3-phenyl-2-(*E*)-propenoyl)-2-oxazolidinone, 2b. (4*S*,5*R*)-Diisopropyl-2-oxazolidinone, **7** (0.33 g, 1.93 mmol, 1.0 equiv), was dissolved in THF (9 mL), in a 25 mL round-bottomed flask, and then cooled to −78 °C. *n*-Butyllithium (1.93 mmol, 1.35 mL, 1.43 M in hexanes, 1.0 equiv) was added dropwise via syringe, and the resulting solution was tirred for 10 min. To this mixture was then added a solution of cinnamoyl chloride (0.353 g, 2.12 mmol, 1.1 equiv) dissolved in THF (2 mL) over 30 min. The resulting yellow slurry was stirred for 1 h at −78 °C, after which the cooling bath was removed and the reaction was allowed to reach ambient temperature. The reaction was quenched with sat. NH_4Cl (25 mL), and the volatiles were evaporated. EtOAc (25 mL) was added, and the organic layer was separated and washed with water (15 mL) and brine (15 mL). The solution was dried and evaporated to give the crude product (0.65 g) as a yellow semicrystalline mixture. Flash chromatography with pentane/ether (90:10, R_f = 0.48) gave the pure product as colorless crystals 0.49 g (1.64 mmol, 85%). mp: 95−98 °C. ^{1}H NMR (400 MHz) δ: 7.97 (d, J = 15.5 Hz, 1 H), 7.85 (d, J = 15.5 Hz, 1 H), 7.63 (m, 2 H), 7.40 (m, 3 H), 4.68 (dd, J = 1.7, 5.9 Hz, 1 H), 4.04 (dd, J = 5.9, 11.0 Hz, 1 H), 2.20 (m, 1 H), 2.14 (m, 1 H), 1.14 (d, J = 6.5 Hz, 3 H), 1.07 (d, J = 6.5 Hz, 3 H), 1.00 (d, J = 6.5 Hz, 3 H), 0.98 (d, J = 6.5 Hz, 3 H). ^{13}C NMR (100 MHz) δ: 165.3, 154.4, 146.2, 134.7, 130.5, 128.8, 128.6, 117.1, 85.7, 60.6, 28.6, 27.0, 22.2, 19.7, 18.5, 17.0. IR: 3010, 2967, 2879, 1782, 1684, 1623, 1469, 1450, 1361, 1342, 1225, 1207, 1176, 1008 cm^{-1}. MS: *m/e* (relative intensity) 301 (M^+, 19), 214 (9), 190 (2), 170 (4), 132 (10), 131 (100). $[\alpha]^{25}_D$: +119.5 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.53; H, 7.47; N, 4.81.

(4*R*,5*S*)-Diphenyl-3-(3-phenyl-2-(*E*)-propenoyl)-2-oxazolidinone, 3c. 3c was prepared in 93% yield from (4*R*,5*S*)-Diphenyl-2-oxazolidinone[17] by following the same procedure as that used for **2b**. mp: 271−274 °C. ^{1}H NMR (400 MHz) δ: 8.05 (d, J = 15.5 Hz, 1 H), 7.83 (d, J = 15.5 Hz, 1 H), 7.64 (m, 2 H), 7.41 (m, 3 H), 7.12 (m, 6 H), 7.01 (m, 2 H), 6.92 (m, 2 H), 5.97 (d, J = 7.5 Hz, 1 H), 5.80 (d, J = 7.5 Hz, 1 H). ^{13}C NMR (100 MHz) δ: 164.6, 153.8, 147.0, 134.49, 134.45, 132.8, 130.8, 128.9, 128.7, 128.4, 128.3, 128.2, 128.1, 126.6, 126.2, 116.8, 80.4, 63.1. IR: 3021, 2972, 2875, 1785, 1681, 1468, 1358, 1227, 1210, 1180, 1010 cm^{-1}. MS: *m/e* (relative intensity) 369 (M^+, 6), 264 (22), 219 (79), 132 (17), 131 (87), 119 (20), 114 (9), 103 (24), 77 (25), 69 (100). $[\alpha]^{25}_D$: −112.5 (*c* 0.48, $CHCl_3$). Anal. Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 78.21; H, 5.05; N, 3.65.

General Procedure for the CuBr-Catalyzed Additions of 2-Methoxy-5-methylphenylmagnesium Bromide to Sultam 1 and Oxazolidinones 2 and 3. CuBr−Me_2S (0.268 g, 1.30 mmol, 1.5 equiv) was placed in a 25 mL dried round-bottomed flask. The solvents, THF (3 mL) and Me_2S (1.5 mL), were added, and the flask cooled to −40 °C. 2-Methoxy-5-methyl-phenylmagnesium bromide (2.7 mL, 0.95 M, 2.61 mmol, 3.0 equiv) was added via syringe, and the temperature was raised to −20 °C over 20 min. The color was dark-green-yellow. The substrate (0.87 mmol, 1.0 equiv) was dissolved in THF (2 mL) and added via syringe during 1 h. The reaction mixture was allowed to reach ambient temperature overnight. The reaction was quenched with sat. NH_4Cl (25 mL), and the volatiles were evaporated. Water (10 mL) and EtOAc (25 mL) were added, and the mixture was filtered through a plug of glass wool, which was rinsed with EtOAc (25 mL). The aqueous layer was separated. The organic layer was washed with 17% NH_4OH (2 × 25 mL), water (30 mL), and brine (30 mL) and dried. Evaporation of the solvent gave the crude product, which was hydrolyzed[7] to give the corresponding acid.

(5*S*)-Phenyl-(3*R*)-(2-benzyloxy-5-methylphenyl)-3-phenylpropanoyl-2-oxazolidinone, 9. Magnesium turnings (84 mg, 3.46 mmol) were placed in a two-neck round-bottomed flask equipped with a reflux condenser. The air in the reaction vessel was evacuated and the flask was placed in an oil bath (75 °C). After 5 min of stirring the magnesium turnings slowly, the system was charged with nitrogen. Using a syringe, a solution of 1-benzyloxy-2-bromo-4-methylbenzene (829 mg, 2.99 mmol) in THF (5 mL) was added to the hot magnesium turnings. After 15 min of reflux, most of the magnesium had been consumed,[18] the oil bath was removed, and the reaction mixture was cooled to room temperature.

(17) Akiba, T.; Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Terashima, S. *Tetrahedron* **1994**, *50*, 3905.

(18) Complete consumption of the aryl halide was confirmed by GC analysis.

Meanwhile, copper bromide−dimethyl sulfide complex (318 mg, 1.55 mmol) was dissolved in THF (4 mL) and dimethyl sulfide (2 mL). The orange solution was cooled to − 50 °C, and then the solution of Grignard reagent (vide supra) was added dropwise over approximately 3 min.

The temperature in the cooling bath was allowed to reach −20 °C, and then a solution of **3b** in THF (2 mL) was slowly added over 35 min, while the temperature was kept between −20 and −25 °C. The orange-red mixture was stirred for 2 h (temp 10 °C) before it was quenched with 10% aqueous NH_4Cl (10 mL). Most of the organic solvents were carefully removed in vacuo. The residue was extracted with ethyl acetate (25 mL then 2 × 10 mL). The combined organic extracts were washed with 17% NH_4OH (3 × 10 mL), water (10 mL), and brine (10 mL) and then dried. Upon concentration in vacuo, 850 mg of a yellow oil was obtained. The crude product was collected on silica and purified by flash chromatography, hexane/EtOAc (80:20 and 70:30) to yield 415 mg (84%) of a colorless oil. $[\alpha]^{25}_D$: −76 (c 1.0, $CHCl_3$). ^{1}H NMR δ: 7.3−7.0 (m, 16 H, Ar), 6.91 (dd, J = 8, 1 Hz, 1 H), 6.70 (d, J = 8 Hz, 1 H), 5.24 (dd, J = 8.5, 3.5 Hz, 1 H), 5.01 (dd, J = 8.5, 6.5 Hz, 1 H), 4.88 (s, 2 H), 4.45 (dd, J = 8.5, 8.5 Hz, 1 H), 4.14 (dd, J = 8.5, 3.5, 1 H), 3.85 (dd, J = 17, 9 Hz, 1 H), 3.62 (dd, J = 17, 6.5 Hz, 1 H), 2.25 (s, 3 H). ^{13}C NMR δ: 170.97, 153.77, 153.72, 143.38, 138.99, 137.26, 131.86, 129.85, 129.03, 128.57, 128.39, 128.31, 128.23, 128.11, 127.78, 127.52, 127.21, 126.06, 125.58, 112.16, 70.14, 69.83, 57.49, 39.98, 39.86, 20.69. IR: 3032, 1788, 1711, 1497, 1454, 1380, 1320, 1241, 1196 cm^{-1}. MS: *m/e* (relative intensity) 491 (M^+, 1.6), 400 (3.8), 328 (2.4), 238 (6.9), 237 (24), 195 (6), 178 (2.7), 92 (7.6), 91 (100), 77 (5.2). Anal. Calcd for $C_{32}H_{29}NO_4$: C, 78.2; H, 5.95; N, 2.85. Found: C, 78.6; H, 5.85; N, 2.9.

(3*R*)-(2-Benzyloxy-5-methylphenyl)-3-phenyl-propanoic Acid, 10. Compound **9** (329 mg, 0.67 mmol) was hydrolyzed according to the general method described by Evans.[11] The crude product was purified by flash chromatography using (hexane/EtOAc (70:30))/AcOH 99:1. The product was obtained as a crystalline solid (209 mg, 90% yield). mp 121−122 °C. $[\alpha]^{25}_D$: +5.5 (*c* 2.1, $CHCl_3$). ^{1}H NMR δ: 10 (br, 1 H), 7.4−7.1 (m, 10 H), 6.99 (d, J = 2 Hz, 1 H), 6.94 (dd, J = 8.5, 2 Hz, 1 H), 6.76 (d, J = 8.5 Hz, 1 H), 4.9 (m, 3 H), 3.08 (m, 2 H), 2.25 (s, 3 H). ^{13}C NMR δ: 177.64, 153.76, 143.08, 137.22, 131.72, 129.92, 128.56, 128.38, 128.25, 127.96 (two carbons), 127.64, 127.20, 126.22, 112.18, 70.13, 40.34, 39.28, 20.71. IR: 3031, 2924, 1712, 1604, 1499, 1453, 1413, 1290, 1241, 1115, 1026 cm^{-1}. MS: *m/e* (relative intensity) 347 (M^+, 1.6), 346 (7.0), 328 (1.7), 255 (3.0), 238 (6.0), 237 (4.0), 195 (11.3), 178 (4.5), 165 (6.3), 92 (7.6), 91 (100), 77 (4.1). Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.7; H, 6.40. Found: C,79.5; H, 6.45.

***N*,*N*-Diispropyl-(3*R*)-(2-benzyloxy-5-methylphenyl)-3-phenylpropane Amide, 11.** The acid **10** (173 mg, 0.50 mmol) was dissolved in benzene (2.5 mL). To the solution was added pyridine (1 drop) followed by $SOCl_2$ (0.20 mL, 2.76 mmol). The mixture was stirred at 50 °C for 50 min and then concentrated in vacuo. The residue was dissolved in benzene (2 mL) and concentrated in vacuo. To the semisolid residue was added ether (1 mL), and the resulting mixture was filtered through a glass wool plug. The plug was rinsed with ether (4 mL), and then the solution was concentrated in vacuo. This gave 180 mg of a yellow solid. This product was dissolved in dry ether, and at room temperature, diisopropylamine (0.70 mL, 5.0 mmol) was added over a period of 3 min. The mixture was stirred at ambient temperature for 1.5 h and then filtered through a cotton plug, which was rinsed with ether (6 mL). The ether solution was washed with 1 M aqueous HCl (5 × 1 mL). The combined aqueous phases were reextracted with ether (3 mL). The organic extracts were pooled, washed with brine (2 mL), and dried. Filtration followed by concentration in vacuo afforded a crude oil, 196 mg. Purification by flash chromatography (hexane/EtAOc 80:20) gave **11** as a pale-yellow oil, 174 mg (81%). $[\alpha]^{25}_D$:−8.3 (c 1.5, $CHCl_3$). ^{1}H NMR δ: 7.35−7.05 (m, 10 H), 7.02 (d, J = 2 Hz, 1 H), 6.93 (dd, J = 8, 2 Hz, 1 H), 6.75 (d, J = 8 Hz, 1 H), 4.9 (m, 3 H), 3.95 (m, 1 H), 3.30 (m, 1 H), 2.99 (m, 2 H), 2.25 (s, 3 H), 1.25 (m, 6 H), 1.00 (m, 6 H). ^{13}C NMR δ: 170.22, 154.01, 144.19, 137.32, 132.66, 129.58, 129.20, 129.14, 128.28, 128.23, 128.10, 128.05, 127.93, 127.76, 127.55, 127.36, 125.74, 111.98, 69.99, 48.58, 45.63, 41.9, 39.61, 20.7. IR: 2966, 1638, 1499, 1453, 1438, 1369, 1337, 1216, 1133, 1043, 1026 cm^{-1}. MS: *m/e* (relative intensity) 429 (M^+, 7.5), 339 (11.2), 338 (35.9), 237 (7.6), 209 (6.0), 195 (17.6), 165 (6.0), 128 (17), 91 (100), 86 (58.8).

(+)-Tolterodine, 1. To a slurry of $LiAlH_4$ (30 mg, 0.79 mmol) in ether (1 mL) was added a solution of **11** in ether (1 mL). The mixture was stirred at ambient temperature overnight. The reaction was quenched by dropwise addition of 1 M NaOH(aq) until evolution of gas ceased. A small spoon of $MgSO_4$ was added, and after 1 min of stirring, the mixture was filtered. Concentration in vacuo afforded 115 mg of a colorless oil. The oil was dissolved in methanol (2 mL), and 10% Pd/C (59 mg, 0.055 mmol Pd) was added. Hydrogen atmosphere (1 atm) was applied, and the mixture was stirred at room temperature overnight. The mixture was filtered, and the resulting solution was concentrated in vacuo. The remaining oil was purified by flash chromatography, (hexane/EtOAc (70:30))/Et_3N-98:2, through a short silica plug. Concentration in vacuo yielded 79 mg (74%) of Tolteriodine as a colorless oil.

The amount of the obtained product was too small to allow for a reliable determination of the optical rotation. The absolute configuration was determined by HPLC on a chiral column by comparing retention times with a sample of (+)-Tolterodine reference standard. By the same method the ee was determined to be 98%. ^{1}H NMR δ: 7.35−7.15 (m, 5 H, Ar), 6.84 (dd, J = 8, 2 Hz, 1 H, Ar), 6.79 (d, J = 8 Hz, 1 H, Ar), 6.54 (d, J = 2 Hz, 1 H, Ar), 4.47 (dd, J = 10, 3.5 Hz, 1 H, C*H*Ph), 3.21 (m, 2 H, 2 × C*H*Me$_2$), 2.70 (m, 1 H, CH_2), 2.35 (m, 2 H, CH_2), 2.10 (s and m, 4 H, ArC H_3 + CH_2), 1.10 (m, 12 H, 4 × Me). ^{13}C NMR δ: 153.18, 144.77, 132.40, 129.35, 128.62, 128.49, 128.25, 127.70, 126.09, 118.12, 47.88, 42.13, 39.37, 33.38, 20.72, 19.94, 19.59.

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