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A Highly Stereocontrolled Synthesis of *(S)*-(-)-3-(4-*tert*-Butyl)phenyl-1-N-(*cis*-2,6-dimethyl)morpholinyl-2-methylpropane *via* Asymmetric Mannich Reaction

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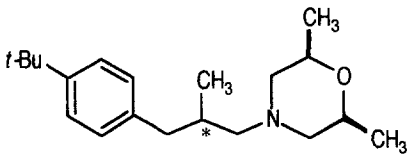
Abstract: By employing *cis*-2,6-dimethylmorpholinemethylene immonium tetrachloroaluminate (**5**) enamines **9** and **10**, prepared from 4-*tert*-butylpropiophenone and propiophenone with *(R)*-(-)-2-(methoxymethyl)pyrrolidine (**8**), were converted to chiral Mannich bases **11,12** with nearly 100% ee; optical purity of these β-amino ketones drops significantly during isolation. Two-step reduction of the keto group in **11,12** afforded *(S)*-(-)-3-(4-*tert*-Butyl)phenyl-1-N-(*cis*-2,6-dimethyl)morpholinyl-2-methylpropane (**1**), *(S)*-enantiomer of racemic systemic fungicide, generic name fenpropimorph, and its congener **13** with 95.1% and 90.7% ee, respectively. A mechanistic model for asymmetric induction in the diastereoselective step is proposed.

Chiral variants of well known synthetic reactions provide an opportunity for linking their synthetic power with efficient creation of a new chiral center.[1] These reactions are among the most powerful building tools available since they increase structural and stereochemical complexity of the substrate. Recently, Risch *et al.*[2] have reported a chiral variant of the Mannich reaction that comprises low-temperature reaction between methylene immonium tetrachloroaluminates and chiral enamines. It is based on asymmetric induction by the chiral center from the incorporated *sec.* amine, derivative of L-proline. The reported enantioselectivities for β-amino ketones (30-60% ee) were not encouraging, however. They were deduced from ^{1}H NMR data in the presence of chiral shift reagents, determined for corresponding β-amino alcohols, obtained on reduction of the *isolated* β-amino ketones. Since the authors have refrained from more accurate direct determination of ee's of chiral β-amino ketones by chromatography on the columns with chiral support, and also in view of our experience with this method for various groups of chiral structures,[3] we entered the project of application of this chiral variant of the Mannich reaction in the key step of the enantioselective synthesis of *(S)*-(-)-3-(4-*tert*-Butyl)phenyl-1-N-(*cis*-2,6-dimethyl)morpholinyl-2-methylpropane (***S*-1**). Racemic **1** is registered as a systemic fungicide under the generic name fenpropimorph, its *(S)*-(-)-enantiomer possess more specific fungicidal activity than the *(R)*-enantiomer.[4-6]



(±)**1** Fenpropimorph

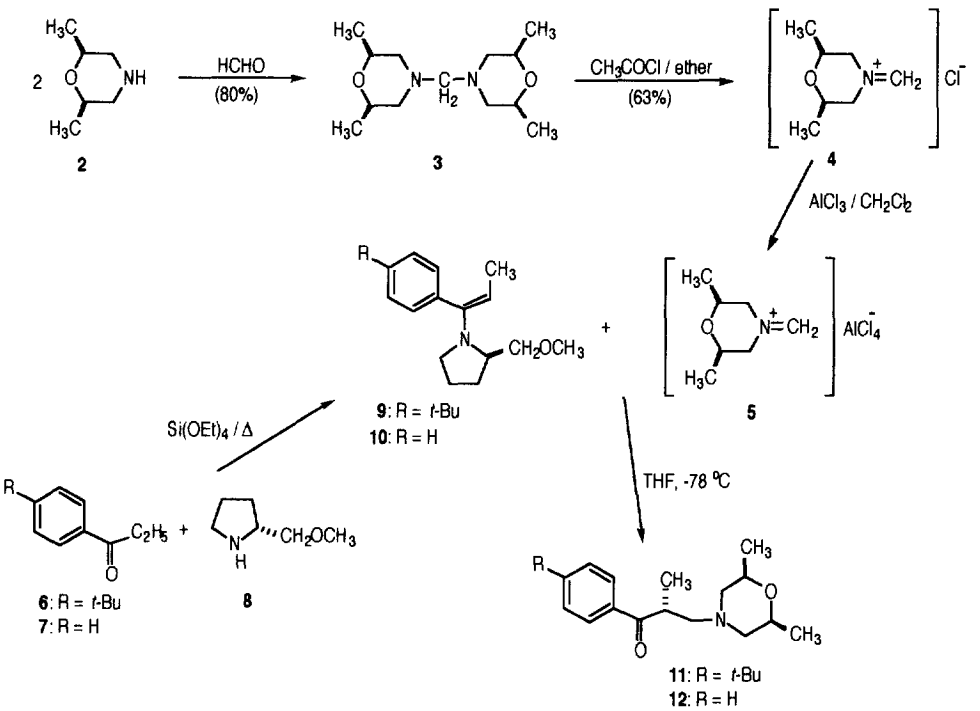
Although the racemic mixture is presently commercialized, the importance of stereoselective synthesis of *(S)*-(-)-enantiomer is obvious in view of the recent trend toward "racemic switch" to replace biologically active racemic mixtures with their more active enantiomer.[7-9] We have recently reported two chemoenzymatic syntheses of the title compound; *via* lipase catalyzed kinetic resolution of racemic 3-(4-*tert*-butylphenyl)-2-methylpropionic acid ethyl ester,[10] and by enantioselective acylation of prochiral 2-(4-*tert*-butylbenzyl)-1,3-propanediol, catalyzed by lipases in organic solvent.[11] Both biocatalytic approaches afforded optically active intermediates which were in a few steps transformed into *(S)*-(-)-fenpropimorph. In view of the generally recognized limitations in the scale-up of biocatalytic reactions, we entered the study of chemical stereocontrolled approaches to the title compound. Central to our objective was the question of whether or not a chiral variant of the Mannich reaction can be completed with practically acceptable diastereoselectivity, to afford final product with ee well over 90%. Herewith we describe the successful completion of this objective.

RESULTS AND DISCUSSION

cis-2,6-Dimethylmorpholynemethylene immonium tetrachloroaluminate (**5**) was prepared by the known procedure.[12] It is most convenient to prepare the tetrachloroaluminate salt just before use from the immonium chloride **4**, which under anhydrous conditions can be preserved for a long time.[13] Chiral enamines **9** and **10**, the reactive counterparts of **5**, have been prepared by incorporation of *(R)*-(-)-2-(methoxymethyl)pyrrolidine (**8**) as the chiral auxiliary,[14] Scheme 1. Preparation of enamines rendered notable difficulties; when ketone **6** was refluxed with a five fold excess of **8** for 20 hours in toluene in the presence of *p*-toluenesulfonic acid, under a column of P_2O_5 on an inert support,[15] only ~60% conversion to enamine **9** was achieved. Purification of the crude product either by extraction with water, by chromatography or by kugelrohr distillation, results in decomposition to the starting ketone. All attempts to trap water in high-boiling solvents in the presence of an acid catalyst, using molecular sieves,[16] alumina,[17] or anhydrous $TiCl_4$ that irreversibly binds water,[18] failed. Substantial enhancement of the yield of enamines **9** and **10** was achieved using tetraethoxysilane as a dehydrating agent; ethanol is formed as the side-product and can suitably be eliminated by evaporation.[19] ^{13}C NMR spectra of these products did not reveal any trace of the *Z* isomer. This could be explained by the strong conjugative interaction of pyrrolidine with the alkene group,[20] making the amine group coplanar. This interaction requires twisting of the phenyl group out of the plane of the double bond, leading to the preferred geometrical isomer with the methyl and phenyl groups on the same side of the double bond.[21] Complete conversion to enamines was confirmed by the ^{13}C NMR spectra, kugelrohr distillation at very low pressure (0.0005 mbar) led to their extensive decomposition. Therefore crude **9** and **10** were used in the next stereoselective Mannich reaction. This reaction was performed at -78 °C in THF under anhydrous conditions and argon atmosphere, affording 1-(4-*tert*-butyl)phenyl-3-N-(2,6-dimethyl)morpholinyl -2-methyl-1-propanone (**11**) and 3-N-(2,6-dimethyl)morpholinyl-2-methyl-1-phenyl-1-propanone (**12**).

Compounds **11** and **12** were obtained in 51%, and in 48% overall yield, resp., based on **6** and **7** as starting compounds. Isolation of the optically active β–amino ketones was performed by chromatography on silica gel, attempting to avoid racemization of the unstable stereogenic center on the carbon atom α– to the carbonyl group.

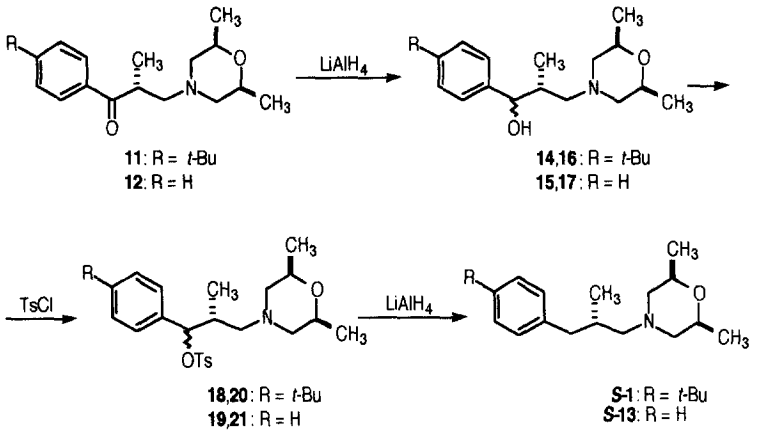
Scheme 1



To determine the enantiomeric purity of these ketones two different chiral columns were used, Chiralcel OD and Chiralcel OD–R, both based on modified cellulose.[22] Ketone **12** could be resolved in the normal phase mode on the Chiralcel OD column, whereas ketone **11** was resolved in the reverse-phase mode on a Chiralcel OD–R column, Table 1. The isolated **11** and **12** exhibited 82% and 47% ee, respectively, indicating various degrees of racemization during isolation. This was confirmed by substantially higher optical purity of the final products **1** and **13** obtained from crude β-amino ketones. The ee's of β–amino ketones **11** and **12** are, however, in the range found by Risch for their congeners (30-60%) using a less accurate NMR method.[2]

All attempts to reduce **11** and **12** directly to the final products **1** and **13** failed. Catalytic hydrogenation and hydride reduction afforded diastereomeric mixtures of alcohols **14**,**16** and **15**,**17**. Catalytic hydrogenation in ethanol on Pd/C predominantly afforded one isomer and only traces of the other. Instead, reduction with $LiAlH_4$ or reduction with W-7 Raney-Nickel in boiling aqueous ethanol, indicated in the literature as particularly suitable for reduction of α-aryl ketones to hydrocarbons,[23,24] afforded *ca.* 1:1 mixture of *threo*/*erythro* isomeric alcohols.

Scheme 2



To complete the stereocontrolled synthesis of **1**, alcohols **14,16**, were tosylated, then a mixture of their respective tosylates **18,20** was reduced with $LiAlH_4$ to target molecule **1**, Scheme 2. Enantiomeric purity of **1** was only 82% when ketone **11** was isolated; when the same synthesis was performed without isolation of ketone **11**, final product exhibited 95.1% ee, as determined for its hydrochloride by HPLC on Chiral–AGP column[25] in the reverse–phase mode, Table 1. By the same procedure **13** was obtained from crude β-amino ketone **12** with 90.7% ee.

Table 1. Results, Conditions and Properties of Chiral HPLC analyses for compounds **11**, **12**, ***S*–1** and ***S*–13**.

Compound	**11**	**12**	***S*–1**	***S*–13**
Enantiomeric purity, % ee	82.3	47.1	95.1	90.7
Column	Chiralcel OD–R	Chiralcel OD	Chiral–AGP	Chiral–AGP
Mobile phase	85% MeOH, 15% H_2O	0.5% 2–PrOH, 99.5% hexane	1% 2–PrOH, 99.% 0.5 M NaH_2PO_4	0.3% 2–PrOH, 99.7% 0.5 M NaH_2PO_4
Flow (ml/min)	0.5	0.6	0.7	0.5
Rt_1 (min)	15.1	21.5	11.0	8.3
Rt_2 (min)	16.2	24.7	20.4	11.4
k'_1	2.02	2.58	7.48	4.14
k'_2	2.24	3.12	14.69	6.14
α	1.11	1.21	1.96	1.48
Rs	2.10	4.13	2.19	0.76

Comparison with an authentic sample of ***S*–1**[11] revealed the same absolute configuration of the product obtained in this synthesis. The high optical purity of the final products is a consequence of the two stereoselective steps. In the first one, exclusive formation of the *E* diastereomers of **9** and **10**, in the second step nearly completely diastereoselective formation of ***(R)*–11** and ***(R)*–12** takes place.

The mechanism of the stereoselective Mannich reaction is not elucidated as yet.[26] Based on an early proposal of Seebach[27] and on recent results of Risch,[28] a model depicted in Fig. 1 can be proposed for the transition state of the product with *R*–configuration on the new chiral center.[29] This model takes into account

electrostatic forces between the positively charged nitrogen of the immonium ion and the electronegative heteroatom(s) of the substrate that stabilizes *synclinal* arrangement of the two double bonds. As expected, the configuration at the newly formed chiral center is opposite to that obtained by Risch[2] with *(S)*-(+)-(methoxymethyl)pyrrolidine. This result though is not trivial: the positively charged immonium ion approaches the enamine *from the more hindered* side as the consequence of already mentioned stabilization of the transition state by coulombic interactions.

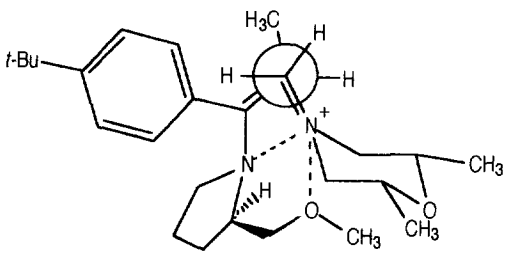


Fig. 1. The proposed transition state of **9** and **5** for chiral Mannich reaction.

In conclusion, we have completed the synthesis of the *(S)*-enantiomer of the commercially important fungicide fenpropimorph with high enantiomeric purity by applying a chiral variant of the Mannich reaction in the key step. This methodology opens the way to other chiral optically pure derivatives of β-aminomethyl aryl-alkyl ketones introduced as racemates in human therapy, and its application is currently underway in our laboratory.

EXPERIMENTAL SECTION

General remarks. IR spectra were obtained using KBr pellets, on a Perkin Elmer M 137 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL FX 90Q FT and Varian XL-GEM 300 spectrometer; shifts are given in ppm downfield from TMS as an internal standard. Optical rotations were measured with an Optical Activity AA-10 polarimeter. Melting points were determined with an Electhrothermal 9100 aparatus. TLC was performed on Merck's DC-alufolien with Kieselgel 60_{254}. HPLC was performed with a Knauer HPLC pump 64 and Knauer Variable wavelength monitor, equipped with an HP 3396A integrator. Analytical chiral columns Chiralcel OD and Chiralcel OD-R (25 cm x 4.6 mm I.D., Daicel, Japan) and Chiral-AGP (10 cm x 4 mm I.D., Chromtech, Sweden) were used.

(R)-(-)-2-(Methoxymethyl)pyrrolidine was prepared from D-prolinol (Fluka) by the procedure described for the same compound with opposite configuration,[14] $[\alpha]^{25}_D$ -2.3° (c 2.0, benzene). Pure *cis*-2,6-dimethylmorpholine (**2**, b.p. 141-143 °C, ≥98% by GC, capillary column HP-17) was obtained by spinning band distillation of the commercially available mixture of isomers (Aldrich, 70:30 *cis/trans*).

N,N-Di-(*cis*-2,6-dimethyl)morpholinemethane (3). To the 30% aq. solution of formaldehyde (2.0 g, 20 mmol), cooled at 0 °C, 40% aq. solution of *cis*-2.6-dimethylmorpholine (11.0 g, 40 mmol) is added over 0.5 hour. The mixture was stirred at room temperature overnight, then saturated with solid KOH, and the product extracted with 3 x 10 mL of diisopropyl ether. Organic phase was dried over Na_2SO_4, solvent evaporated and crude product distilled in kugelrohr (15 mbar, 120 °C) to yield 3.63 g (80%) of pure compound **3**; ^{1}H NMR ($CDCl_3$) δ 3.66-3.60 (4H, m), 2.85 (2H, s), 2.83 (4H, dd, J = 11.3 and 1.7 Hz), 1.70 (4H, dd, J = 11.3 and 10.4 Hz), 1.15 (12H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 80.72, 71.22, 57.55, 18.78; IR ν 2960 (s), 2920 (s), 2850 (s), 2770 (s), 1449 (s), 1410 (s), 1369 (s), 1317 (s), 1140 (s), and 1080 (s) cm^{-1}. Anal. Calcd for $C_{13}H_{26}N_2O_2$: C, 64.43; H, 10.81; N, 11.56. Found C, 64.43; H, 10.99; N, 11.61.

***cis*–2,6–Dimethylmorpholinemethylene chloride (4).** To a solution of **3** (0.85 g, 3.5 mmol) in 5 ml of anhydrous diethyl ether (freshly distilled over $LiAlH_4$), cooled at 0 °C under an atmosphere of nitrogen, a solution of acetyl chloride (0.965 g, 10 mmol) in 2 mL of anhydrous diethyl ether was added. The mixture was stirred at room temperature for one hour, then cooled to -20 °C and the etheral solution decanted from the resulting white precipitate. Crude product was washed with 3 x 10 mL of cold (-20 °C) diethyl ether, and traces of the solvent removed in the rotavapor, affording 0.358 g (63%) of *cis*–2,6–dimethylmorpholinemethylene chloride (**4**); ^1H NMR ($CDCl_3$) δ 6.94 (1H, bs),.4.64 (1H, bs), 4.15 (2H, m), 3.36 (2H, m) 2.57 (2H, m), 1.23 (6H, m); IR ν 2985(m), 1450(m). 1375(m), 1120(m) cm^{-1}.

***cis*–2,6–Dimethylmorpholinemethylene immonium tetrachloroaluminate (5).** To a solution of **4** (1.3 g, 7.9 mmol) in 10 mL of anhydrous dichloromethane, under an atmosphere of nitrogen, anhydrous $AlCl_3$ (1.06 g, 7.9 mmol) was added over 15 minutes. The mixture was stirred at room temperature overnight and solvent evaporated affording 2.3 g of white hygroscopic solid. Crude **5** was used in the next step without characterization.

1–(4–*tert*–Butyl)phenyl-1-[*(R)*–2-methoxymethyl–1–pyrrolidyl]–1–propene (9). To the mixture of 4–*tert*–butylpropiophenone (**6**, 0.53 g, 3 mmol) and *(R)*–(–)–2–(methoxymethyl)pyrrolidine (**8**, 0.40 g, 3.5 mmol) tetraethoxysilane (0.74 g, 3.5 mmol, Fluka) was added under an inert atmosphere of argon. Reaction mixture was stirred at 140 °C for 24 hours, then excess of amine evaporated *in vacuo*. ^{13}C NMR spectrum in deuterochloroform of crude **9** exhibited characteristic signals at δ 148.982, 145.395, 134.720, 128.545 (2C), 123.852 (2C), 94.027 (–C=C–N), 73.182, 57.952, 57.797, 48.764, 33.686, 30.595 (3C), 27.737, 22.382, 12.783 (–C=C–CH_3) ppm. Crude product was directly used in the next step.

1-[*(R)*–2–Methoxymethyl-1-pyrrolidyl]-1-phenyl-1-propene (10). Enamine **10** was obtained from 0.40 g (3 mmol) of propiophenone according the procedure described for enamine **9**. ^{13}C NMR ($CDCl_3$) of crude **10** exhibited characteristic enamine signals at δ 145.883, 138.115, 129.641 (2C), 127.503 (2C), 126.773, 94.515 (–C=C–N), 73.538, 57.908, 56.419, 49.224, 28.129, 23.078, 13.116 (–C=C–CH_3) ppm.

***(R)*–1–(4–*tert*–Butyl)phenyl-3-N-(*cis*–2,6–dimethyl)morpholinyl-2-methylpropan–1–one (11).** To the solid chloroaluminate **5** (1.31 g, 7 mmol), dried 2 hours at 0.02 mbar in the reaction flask, 10 mL of anhydrous THF (freshly distilled over $LiAlH_4$) was added under an argon atmosphere. Resulting suspension was cooled to -78 °C. In a second flask crude enamine **9** was dissolved in 5 mL of anhydr. THF and cooled to -78 °C. Solution of enamine was added to suspension of aluminate **5** through a long needle over 15 minutes, under argon pressure. The reaction mixture was stirred for 1 hour at -78 °C, then slowly warmed to 0 °C and hydrolyzed by a THF/H_2O mixture (1:1). Resulting solution was extracted with 3 x 20 mL of CH_2Cl_2, dried over Na_2SO_4 and solvent evaporated to afford ketone **11**. Crude product was purified by chromatography on silica gel column with 0→50% CH_2Cl_2 in diisopropyl ether as eluent to afford pure **11**, 0.464 g (51%). Enantiomeric purity (82% ee) was determined by chiral HPLC on Chiralcel OD–R column. ^1H NMR ($CDCl_3$) δ 7.91 (2H, d, J = 8.4 Hz), 7.48 (2H, d, J = 8.4 Hz), 3.76 (2H, m), 3.55 (2H, m), 2.84 (1H, dd, J = 13.6 and 5.0 Hz), 2.70 (2H, t, J = 12.1 Hz), 2.38 (1H, dd, J = 12.5 and 6.4 Hz), 1.78 (2H, m), 1.43 (2H, s), 1.35 (9H, s), 1.19 (3H, d, J = 7.0 Hz), 1.11 (3H, d, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 203.119, 156.515, 134.173, 128.156 (2C), 125.487 (2C), 71.575 (C–2,6 of morph.), 71.505 (C–2,6 of morph.), 61.405 (C–3), 60.113 (C–3,5 of morph.), 59.476 (C–3,5 of morph.), 38.252 (C–2), 35.018 [$(CH_3)_3$–C–], 31.044 [3C, (CH_3)$_3$–C–], 19.040 (2C, CH_3 at morph.), 16.495 (CH_3 at C–2); IR ν 3040 (w), 2965 (s), 2875 (s), 2820 (s), 1682 (s), 1610 (s), 1463 (s), 1234 (s), 980 (s), 710 (m) cm^{-1}. Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.60; H, 9.68; N, 4.48.

***(R)*–3-N-(*cis*–2,6–Dimethyl)morpholinyl–2-methyl-1-phenylpropan-1-one (12).** Ketone **12** was obtained from crude **10** using the same procedure as described for **11**. After chromatography pure **12** was obtained (0.356 g, 48%). Enantiomeric purity (47% ee) of the product was determined by chiral HPLC on Chiralcel OD column. ^1H NMR ($CDCl_3$) δ 7.94 (2H, d, J = 8.6 Hz), 7.53 (1H, d, J = 7.4 Hz), 7.44 (2H, dd, J = 7.6 and 12.7 Hz), 3.73 (1H, m), 3.51 (2H, m), 2.80 (1H, dd, J = 7.7 and 12.5 Hz), 2.66 (2H, m), 2.37 (1H, dd, J = 6.3 and 12.5 Hz), 1.74 (2H, m), 1.18 (3H, d, J = 6.9 Hz), 1.08 (3H, d, J = 6.3 Hz), 1.08 (3H, d, J = 6.3 Hz); ^{13}C NMR

($CDCl_3$) δ 203.643, 136.816, 132.684, 128.416 (2C), 127.996 (2C), 71.322 (C–2,6 of morph.), 71.252 (C–2,6 of morph.), 61.263 (C–3), 59.802 (C–3,5 of morph.), 59.293 (C–3,5 of morph.), 38.113 (C–2), 18.683 ($\underline{C}H_3$ at morph.), 18.682 ($\underline{C}H_3$ at morph.), 16.023 ($\underline{C}H_3$ at C–2); IR ν 3055 (m), 2965 (s), 2915 (s), 2860 (s), 2800 (s), 1680 (s), 1445 (s), 1228 (s), 1140 (s), 1080 (s), 1070 (s), 970 (s), 704 (s) cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.27; H, 9.01; N, 5.46.

***(R)*–1-Hydroxy-1-(4-*tert*–butyl)phenyl-3-N-(*cis*–2,6–dimethyl)morpholinyl-2-methylpropanes (14,16).** To achieve the high enantiomeric purity of the final product, ketone **11** was not isolated. The crude product from the previous reaction step was dissolved in 10 mL of anhydrous THF and slowly added to a suspension of $LiAlH_4$ (0.115 g, 3 mmol) in 10 mL of anhydrous THF, cooled at -78 °C. Reaction mixture was stirred for 3 hours at -78 °C and then overnight at room temperature. Excess of $LiAlH_4$ was destroyed by addition of water and reaction mixture extracted with 50 mL of ether. Etheral extract was washed with water (3 x 20 mL), dried over Na_2SO_4 and solvent evaporated to yield crude product. Chromatography on silica gel column with 0→100% CH_2Cl_2 in diisopropyl ether as eluent afforded pure diastereomeric mixture of the alcohols **14,16** (0.312 g, 33% based on 3 mmol of starting 4–*tert*–butylpropiophenone). ^1H NMR ($CDCl_3$) δ 7.15-7.39 (8H, m), 4.77 (1H, bs), 4.37 (1H, d, $\underline{J}$ = 9.1 Hz), 3.72 (4H, m), 3.17 (2H, t, $\underline{J}$ = 10.3 Hz), 2.79 (2H, t, $\underline{J}$ = 10.2 Hz), 1.62-2.57 (12H, m), 1.33 (9H, s), 1.32 (9H, s), 1.12-1.23 (12H, m), 0.72 (3H, d, $\underline{J}$ = 6.7 Hz), 0.57 (3H, d, $\underline{J}$ = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 150.019, 149.473, 140.333, 138.483 126.550 (2C), 126.492 (2C), 124.820 (2C), 124.417 (2C), 82.344, 78.523, 71.494 (2C), 71.316, 71.130, 66.259, 60.858, 60.600, 60.490, 58.662, 58.151, 34.818, 34.078, 33.858, 33.781 (2C), 31.052 (6C), 29.967 (2C), 22.494, 18.726 (3C), 18.605, 15.059, 14.962; IR ν 3140 (s), 2990 (s), 2835 (s), 1770 (m), 1760 (s), 1616 (m) cm^{-1}. Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.19; H, 10.41; N, 4.38. Found: C, 75.16; H, 10.64; N, 4.53.

***(R)*–1–Hydroxy-3-N-(*cis*–2,6–dimethyl)morpholinyl-2-methyl-1-phenylpropanes (15,17).** Reduction of nonisolated ketone **12** was performed as described for **11**, and afforded 0.252 g of diastereomeric alcohols **15,17**. The overall yield of this three–step preparation was 32% based on 3 mmol of starting propiophenone. ^1H NMR ($CDCl_3$) δ 7.28 (10H, m), 4.78 (1H, d, $\underline{J}$ = 3.3 Hz), 4.37 (1H, d, $\underline{J}$ = 9.3 Hz), 3.70 (4H, m), 3.12 (2H, dd, $\underline{J}$ = 17.1 and 11.2 Hz), 1.6-2.8 (14H, m), 1.17 (12H, m), 0.70 (3H, d, $\underline{J}$ = 6.9 Hz), 0.54 (3H, d, $\underline{J}$ = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 143.255, 141.645, 127.823 (2C), 127.412 (2C). 127.132, 126.804 (2C), 126.568 (2C), 125.155, 82.455, 72.934, 71.333 (2C), 71.166, 70.980, 66.083, 60.750, 60.441, 60.297, 58.611, 58.033, 34.919, 33.861, 29.861, 18.615 (2C), 18.497, 14.803, 14.603; IR ν 3120 (s), 2980 (s), 2830 (s), 1760 (m), 1609 cm^{-1}. Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found: C, 72.83; H, 9.73; N, 5.46.

***(S)*–1–N–(*cis*–2,6–Dimethyl)morpholinyl–2–methyl–3–phenylpropane (13).** To solution of alcohol **15,17** (79 mg, 0.3 mmol) in anhydrous pyridine (1.0 mL) at 0 °C the freshly recrystallized *p*–toluensulphonyl chloride (63 mg, 0.33 mmol) was added in 5 portions during the period of 5 minutes. The obtained mixture was stored in the refrigerator overnight. Then, anhydrous toluene (10 mL) was added and solvent evaporated *in vacuo* affording crude tosylate **19,21** which was dissolved in anhydrous THF (5 mL). This solution was added over 10 min to a suspension of $LiAlH_4$ (20 mg, 0.5 mmol) and anhydrous THF (10 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature and then the excess of $LiAlH_4$ was destroyed with wet diisopropyl ether and filtered. Organic solution was dried over Na_2SO_4, evaporated and crude product purified on a column of silica gel with diisopropyl ether in n–hexane (0→50%) as eluent. Etheral solution (3 mL) of obtained **13** was treated with gaseous HCl affording 62 mg (72%) of **13** as hydrochloride; mp 192–193 °C. ^1H NMR ($CDCl_3$) δ 12.26 (1H, bs), 7.33–7.23 (3H, m), 7.18 (2H, d, $\underline{J}$ = 7.8 Hz), 4.44 (2H, bd, $\underline{J}$ = 13.9 Hz), 3.29 (2H, dd, $\underline{J}$ = 18.1 and 11.9 Hz), 2.86 (2H, bs), 2.71 (1H, dd, $\underline{J}$ = 13.5 and 6.2 Hz), 2.65 (1H, dd, $\underline{J}$ = 13.5 and 7.1 Hz), 2.33 (2H, m), 1.67 (1H, m), 1.25 (3H, d, $\underline{J}$ = 7.7 Hz), 1.17 (3H, d, $\underline{J}$ = 5.5 Hz), 1.16 (3H, d, $\underline{J}$ = 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 138.534, 129.198 (2C), 128.629 (2C), 126.686, 68.212 (2C, C–2,6 of morph.), 63.569 (C–1), 57.680 (C–3,5 of morph.), 55.844 (C–3,5 of morph.), 41.548 (C–3), 30.483 (C–2), 19.466 ($\underline{C}H_3$ at C–2), 18.321 ($\underline{C}H_3$ at morph.), 18.272 ($\underline{C}H_3$ at morph.); IR (KBr) ν 3012 (w), 2970 (s), 2920 (s), 2430 (s), 1452 (s), 1178 (s), 1090 (s), 743 (s), 704 (s) cm^{-1}. Anal. Calcd for $C_{16}H_{26}NOCl$: C, 67.71; H, 9.23; N, 4.94. Found: C, 67.59; H, 9.27; N, 4.89. Analysis on Chiral–AGP column has revealed 90.7% ee of the second running enantiomer.

(S)*-(−)-3-(4-*tert.*-Butyl)phenyl-1-N-(*cis*-2,6-dimethyl)morpholinyl-2-methylpropane** (S*-1**). Etheral solution of compound **1**, obtained from alcohol **14,16** (92 mg, 0.3 mmol) using the same procedure as described for **13**, was treated with gaseous HCl affording 69 mg (70%) of *(S)*-fenpropimorph as its hydrochloride; mp 173–174 °C. Analysis on Chiral-AGP column has revealed 95.1% ee of the product.

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29. Configurational descriptor changes on going from ***R*-11**, ***R*-12** to ***S*-1**, ***S*-13**, though the same absolute configurations remain.

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