Diastereoselective preparation of (S)-(1,4,4-trimethylpyrrolidin-3-yl)amine, a new chiral 1,2-diamine for thiourea-type organocatalysts

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Abstract

The enantioselective synthesis of the title compound, its conversion into a thiourea-type organocatalyst and the behavior of this organocatalyst in several enantioselective Michael reactions are described.

1. INTRODUCTION

(*R*)-Pantolactone (*R*)-**1** (Fig. 1) is a widely used chiral auxiliary.[1] Several years ago, we prepared an improved and easily available closely related chiral auxiliary, 3-hydroxy-4,4-dimethyl-1-phenylpyrrolidin-2-one (*N*-phenylpantolactam), **2** (Fig. 1), in both enantiomeric forms.[2] Compounds (*R*)- and (*S*)-**2** were used as chiral auxiliaries in different diastereoselective reactions, such as the deracemization of α -arylpropionic acids, Diels–Alder reactions and dynamic kinetic resolutions of α-haloesters, and as resolution agents.[1,3] We also synthesized different aminopantolactams, such as (*S*)-**3**,[4] which was used as a chiral auxiliary in Michael reactions, and (*S)*-**4**,[5] as a ligand for organometallic catalysis

Inspired by the work of Pedrosa et al.[6,7] on the use of N-[3,5-bis(trifluoromethyl)phenyl]-*N*'-[2-(dimethylamino)alkyl]thioureas as organocatalysts in Michael reactions and in the desymmetrization of meso-cyclic anhydrides, we planned the preparation of the related aminopyrrolidine thiourea (*S*)-**16** (Scheme 2) to study its properties as a novel organocatalyst in different transformations. We selected aminopyrrolidine (*S*)-**10** as a key intermediate for the preparation of (*S*)-**16** (Scheme 2).

2. RESULTS AND DISCUSSION

At first, we carried out the synthesis of racemic aminopyrrolidine *rac*-**10**, as shown in Scheme 1. Pantolactam *rac*-**5** was prepared in 48% yield by reaction of *rac*-pantolactone rac-**1** with 40% aqueous methylamine under *p*-TsOH·H_2O catalysis at 250 °C and 75 atm, as previously described.[8] Chromic acid oxidation[9] of *rac*-**5** gave in high yield the corresponding ketolactam **6**. The same transformation was also carried out, albeit in lower yield, by oxidation with RuO_4, generated from a catalytic amount of $RuCl_3 \cdot 3H_2O$ and trichloroisocyanuric acid as the stoichiometric oxidant.[10]

The reaction of ketolactam **6** with benzylamine in toluene at reflux, in the absence of an acidic catalyst, with azeotropic elimination of water quantitatively afforded imine **7**, which was reduced to benzylaminopantolactam *rac*-**8** with $NaBH_3CN$ and then subjected to catalytic hydrogenation to give aminopantolactam *rac*-**9** in high yield. Reduction of *rac*-**9** with the $BH_3 \cdot THF$ complex in THF gave the highly volatile aminopyrrolidine *rac*-**10**, which was isolated as its dihydrochloride salt in 60% yield.

Next, we synthesized (*S*)-**10** as shown in Scheme 2. The reaction of ketolactam **6** with (*R*)-1-phenylethylamine in toluene at reflux with azeotropic distillation of water in the absence of any acidic catalyst quantitatively afforded imine (*R*)-**12**. Reduction of this imine with $NaBH_3CN$ afforded a diastereomeric mixture of aminopantolactams (3*S*,1'*R*)-**13** and (3*R*,1'*R*)-**14** in an 80:20 ratio, established on the basis of the quartet signal of the CH3CH proton of each diastereomer [δ3.91 ppm for (3*S*,1'*R*)-**13** and 4.31 ppm for (3*R*,1'*R*)-**14**]. The above mixture was separated by crystallization as salts of (*S*)-(+)-mandelic acid; both salts were fully characterized. The absolute configuration of the (*S*)-mandelate of the minor aminolactam (3*R*,1'*R*)-**14** was established by X-ray diffraction analysis (Fig. 2).[11] Consequently, the absolute configuration of the major aminolactam must be (3*S*,1'*R*)-**13**. Aminolactams (3*S*,1'*R*)-**13** and (3*R*,1'*R*)-**14** were liberated from their (*S*)-mandelate salts and (3*S*,1'*R*)-**13** was hydrogenated to give aminopantolactam (*S*)-**9** in high yield as an oil, which was also characterized as its solid mono-*O*,*O*-di-*p*-toluoyl (2*R*,3*R*)-tartrate. The reduction of (*S*)-**9** with $BH_3 \cdot THF$ complex, followed by treatment with an excess of HCl/MeOH as before for *rac*-**9**, gave aminopyrrolidine (*S*)-**10**·2HCl. A sample of free amine

(*S*)-**10** was isolated from its dihydrochloride for characterization purposes. The reaction of (*S*)-**10**·2HCl with 3,5-bis(trifluoromethyl)phenylisothiocyanate,[7] **15**, in CH_2Cl_2 in the presence of K_2CO_3 gave thiourea (*S*)-**16** in good yield.

Following the optimized experimental conditions described by Pedrosa et al., [6] we studied the enantioselective Michael reactions of acetylacetone **18a** (R = Me), dimethyl malonate **18b** (R = OMe), and diethyl malonate **18c** (R = OEt), with t*rans*-β-nitrostyrene, **17**, catalyzed by (*S*)-**16** (Table 1). Reaction times were similar to those described. The fastest reaction, which used **18a** as the dicarbonyl compound, took place in about 4 h, while reactions using **18b** and **18c** required approximately 24 and 48 h, respectively. Good isolated yields but modest enantioselectivities were observed in all cases (**19a**: 82%, 49% ee; **19b**: 94%, 35% ee; **19c**: 88%, 18% ee). To establish the chiral HPLC conditions, racemic products **19a**, **19b** and **19c** were prepared by using the known[12] achiral organocatalyst **21** (Fig. 3) under similar reaction conditions. The configuration of the main stereoisomers in these reactions was established as (*S*) in all cases, by comparison of the specific rotation of the obtained mixtures with the described data (see Section 4). It should be noted that when using Pedrosa's catalyst (*S*)-**20** (Fig. 3), we were able to reproduce the results of Pedrosa et al.[6] on these enantioselective Michael reactions, thus establishing that the main enantiomers obtained in our case were the same, that is, those of an (*S*)-configuration.

The new organocatalyst (*S*)-**16** can be considered as a cyclic analog of (*S*)-**20**, the best catalyst described by Pedrosa et al.[6] formally derived from it by dehydrogenation with formation of the five-membered ring of (*S*)-**16**, as shown in Fig. 3. Very recently, related thioureas derived from (*S*)-(1,2-dimethyl-3,5-diphenylpyrrolidin- 3-yl)amine proved to be completely inefficient as organocatalysts in the Michael addition of diethyl malonate to b-nitrostyrene.[12] It is usually assumed that the transition-state complex in thiourea organocatalyzed reactions implies several hydrogen bonds in which the thiourea N–H groups and the tertiary amine of the catalyst are involved.[7,13] The modest enantioselectivities obtained with catalyst (*S*)-**16** in the Michael reactions studied must be related to a reduced ability of this catalyst to form the required hydrogen bonds due to the restricted conformational mobility of the cyclic tertiary amine.[14]

3. CONCLUSION

In conclusion, we have synthesized (*S*)-(1,4,4-trimethylpyrrolidin-3-yl)amine, (*S*)-**10**, in a diastereoselective manner, using (*R*)-1-phenylethylamine as a chiral auxiliary. The absolute configuration of (*S*)-**10** has been unambiguously established by X-ray diffraction of the (*S*)-mandelate of (3*R*,1'*R*)-**14**, diastereomer of (3*S*,1'*R*)-**13**, precursor (*S*)-**10**. Amine (*S*)-**10** has been transformed into organocatalyst (*S*)-**16** by reaction with 3,5-bis(trifluoromethyl) phenylisothiocyanate, which in a preliminary study, has shown modest enantioselectivities in the Michael addition of 1,3-dicarbonyl compounds to trans-b-nitrostyrene.

4. EXPERIMENTAL

4.1. General

Melting points were determined in open capillary tubes. Unless otherwise stated, NMR spectra were recorded at 25 °C in $CDCl_3$: ^1H NMR (400 MHz), ^{13}C NMR (100.6 MHz). All chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) related to internal standard ($CHCl_3$ at δ_H = 7.26 ppm, δ_C = 77.0 ppm). Assignments given for the NMR spectra are based on DEPT sequence, $^1H/^1H$ COSY, $^1H/^{13}C$ HETCOR (HSQC sequence) and $^1H/^1H$ NOESY experiments for selected compounds. Coupling constants *J* are given in Hertz (Hz). Mass spectra were recorded on a LC/MSD-TOF (2006, Agilent technologies), using electrospray (ESI-MS, positive mode, capillary: 3.5 kV, fragmentor: 215 V). Unless otherwise stated, IR spectra were performed with the attenuated total reflection (ATR) technique and the absorption values are given as wavenumbers (cm^{-1}). Elemental analyses were done at the Microanalysis Service of the IIQAB (CSIC, Barcelona, Spain). Optical rotations were determined on a polarimeter using a 1-dm cell. Column chromatography was performed on silica gel 60 A C.C. (35–70 mesh). For the thin layer chromatography (TLC), aluminum-backed sheets with silica gel 60 F_{254} or aluminum oxide ALOX N/UV_{254} were used and spots were visualized with UV light and/or 1% aqueous $KMnO_4$. Chiral HPLC analysis was performed at 20 °C using Perkin Elmer Series 200 pump equipped with UV detector and using a Daicel® Chiralpak IC column (250 x 4.6 mm). UV detection was monitored at different wavelengths. The resolution (Rs) of the two enantiomers was determined by the equation: $Rs = 1.18\ (t_2 - t_1)\cdot(W_{50(1)} + W_{50(2)})^{-1}$ where $t1$ and $t2$ are the retention times of the first and second eluted peaks, respectively; $W_{50(1)}$ and $W_{50(2)}$ are the corresponding peak widths at the half peak height.

152 **4.2. 1,4,4-Trimethylpyrrolidine-2,3-dione 6**

153 To a cooled (0 °C) solution of *rac*-**5** (330 mg, 2.30 mmol) in AcOH (18 mL) a
154 solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (380 mg, 1.28 mmol) in H_2SO_4 (20% aqueous solution, 3.5
155 mL) was added dropwise and the mixture was stirred for 30 min at room temperature. Water
156 (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined
157 organic phases were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (15 mL).
158 The organic phase was dried (anhydrous $MgSO_4$) and concentrated under reduced pressure
159 to give **6** (300 mg, 93% yield) as a white solid. An analytical sample was obtained by
160 crystallization from EtOAc (3 mL). Mp 116–117 °C (EtOAc); IR 2974, 2935, 2874, 1751
161 and 1705 (CO), 1492, 1473, 1436, 1406, 1384, 1327, 1269, 1216, 1101, 1038, 938, 738 cm^{-1};
162 ^1H NMR 1.22 [s, 6H, 4-$(CH_3)_2$], 3.09 (s, 3H, *N*-CH_3), 3.41 (s, 2H, 5-H_2); ^{13}C NMR 23.7
163 [CH_3, 4-$(CH_3)_2$], 31.7 (CH_3, *N*-CH_3), 39.7 (C, C4), 58.4 (CH_2, C5), 159.4 (C, C2), 203.5
164 (C, C3). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.72; H, 7.89;
165 N, 9.96. HRMS (ESI): Calcd for ($[M+H]^+$): 142.0863; found 142.0863.

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168 **4.3. 3-(Benzylimino)-1,4,4-trimethylpyrrolidin-2-one 7**

169 A solution of 1,4,4-trimethylpyrrolidine-2,3-dione, **6** (5.00 g, 35.4 mmol), and
170 benzylamine (3.90 mL, 3.82 g, 35.7 mmol) in toluene (150 mL) was heated at reflux for 24
171 h in a Dean–Stark equipment. Evaporation of the solvent under reduced pressure gave **7**
172 (8.90 g, quantitative yield) as an orange oil. IR (NaCl) 3062, 3028, 2962, 2927, 2869, 1692
173 (CO), 1496, 1466, 1453, 1431, 1404, 1322, 1277, 1210, 1108, 753, 733, 698 cm^{-1}; H NMR
174 1.25 [s, 6H, 4-$(CH_3)_2$], 2.97 (s, 3H, *N*–CH_3), 3.28 (s, 2H, 5-H_2), 5.48 (s, 2H, CH_2–Ph), 7.22
175 (t, J = 7.4 Hz, 1H, Ar–H_{para}), 7.32 (tm, J = 7.6 Hz, 2H, Ar–H_{meta}), 7.39 (d, J = 7.6 Hz, 2H,
176 Ar–H_{ortho}); ^{13}C NMR 26.5 [CH_3, 4-$(CH_3)_2$], 30.5 (CH_3, *N*–CH_3), 37.7 (C, C_4), 53.4 (CH_2,
177 CH_2–Ph), 59.7 (CH_2, C5), 126.3 (CH, Ar–C_{para}), 127.7 (CH, Ar–C_{ortho}), 128.2 (CH, Ar–
178 C_{meta}), 140.8 (C, Ar–C_{ipso}), 161.0 (C, C2), 166.6 (C, C3). Anal. Calcd for

$C_{14}H_{18}N_2O \cdot 0.25H_2O$: C, 71.61; H, 7.94; N, 11.93. Found: C, 71.30; H, 7.87; N, 11.68. HRMS (ESI): Calcd for ($[M+H]^+$): 231.1492; found 231.1496.

4.4. *rac*-3-Benzylamino-1,4,4-trimethylpyrrolidin-2-one r*ac*-8

To a solution of **7** (6.00 g, 26.0 mmol) in anhydrous MeOH (100 mL), a solution of $NaBH_3CN$ (95% content, 3.50 g, 52.9 mmol) and AcOH (1.80 mL, 1.89 g, 31.4 mmol) were added and the reaction mixture was stirred at room temperature for 4 h. Next, more $NaBH_3CN$ (95% content, 1.00 g, 15.1 mmol) was added and stirring was continued for another 45 min. Water (50 mL) was added and the organic solvent was evaporated under reduced pressure. The remaining aqueous phase was treated with aqueous 2 M NaOH until pH 12–13 and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give rac-**8** (5.81 g, 96% yield) as a pale yellow oil. IR (NaCl) 3500 and 3314 (NH), 3061, 3028, 2957, 2925, 2868, 1697 (CO), 1496, 1454, 1438, 1405, 1385, 1368, 1319, 1268, 1149, 1094, 1028, 997, 739, 699 cm^{-1}; H NMR (300 MHz) 1.02 (s, 3H) and 1.12 (s, 3H) [4-$(CH_3)_2$], 1.93 (br s, 1H, *N*–H), 2.83 (s, 3H, *N*–CH_3), 2.86 (d, *J* = 9.6 Hz, 1H) and 3.035 (d, *J* = 9.6 Hz, 1H) (5-H2), 3.036 (s, 1H, 3-H), 3.95 (d, J = 13.5 Hz, 1H) and 4.00 (d, *J* = 13.5 Hz, 1H) (CH2–Ph), 7.21–7.40 (complex signal, 5H, Ar–H); ^{13}C NMR (75.4 MHz) 21.5 (CH_3) and 26.0 (CH_3) [4-$(CH_3)_2$], 29.9 (CH_3, *N*–CH_3), 38.6 (C, C4), 53.5 (CH_2, *N*–CH_2), 59.9 (CH_2, C5), 67.3 (CH, C3), 126.8 (CH), 128.1 (CH) and 128.2 (CH) (Ar–C*ortho*, Ar–C*meta* and Ar–C*para*), 140.3 (C, Ar–C*ipso*), 174.6 (C, C2). Anal. Calcd for $C_{14}H_{20}N_2O \cdot 0.25H_2O$: C, 71.00; H, 8.72; N, 11.83. Found: C, 71.26; H, 8.65; N, 11.80. HRMS (ESI): Calcd for ($[M+H]^+$): 233.1648; found 233.1652.

4.5. *rac*-3-Amino-1,4,4-trimethylpyrrolidin-2-one *rac*-9

A mixture of *rac*-**8** (4.51 g, 19.4 mmol), concentrated HCl (6.20 mL), and 5% Pd/C (16.7 g) in MeOH (150 mL) was hydrogenated at 1 atm and room temperature for 24 h. The mixture was filtered through a pad of Celite®, washing the filter with MeOH (50 mL). The filtrate was basified with aqueous 5 M NaOH (20 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried (anhydrous MgSO4) and concentrated under reduced pressure to give *rac*-**9** (2.65 g, 96% yield) as a colorless oil. IR 3313 and 3297 (NH), 2957, 2938, 2869, 2830, 2784, 1661 (CO), 1453, 1431, 1313, 1295, 1268, 1208, 1177, 1094, 1076, 1035, 855, 709 cm^{-1}; For the ^{1}H and ^{13}C NMR data, see (S)- 9. Anal. Calcd for $C_7H_{14}N_2O \cdot 2/3H_2O$: C, 54.52; H, 10.02; N, 18.17. Found: C, 54.51; H, 9.60; N, 17.85. HRMS (ESI): Calcd for ($[M+H]^+$): 143.1179; found 143.1181.

4.6. *rac*-1,4,4-Trimethylpyrrolidin-3-amine dihydrochloride *rac*-10·2HCl

To a cold (0 °C) solution of BH3THF complex (1 M in THF, 37.0 mL, 37.0 mmol), a solution of *rac*-**9** (1.57, 11.0 mmol) in anhydrous THF (50 mL) was added dropwise and the solution was heated at reflux for 1 h. The solution was cooled to room temperature, was treated with aqueous 5 M HCl (30 mL) and stirred for 30 min, until gas evolution ceased. The solution was concentrated to dryness under reduced pressure. The residue was taken in MeOH (100 mL), after which anhydrous Na_2CO_3 (10 g) was added and the mixture was heated at reflux for 16 h. The solution was cooled to room temperature, basified with KOH pellets (85% content) until pH 12–13 and distilled at atmospheric pressure (63 °C). The distillate was treated with 2 M methanolic HCl (6.0 mL) and concentrated under reduced pressure to give *rac*-**10**·2HCl (1.56 g) as a yellow solid, that was crystallized from a mixture of EtOAc/MeOH 5:1 (12 mL) to give *rac*-**10**·2HCl (1.33 g, 60% yield) as a white solid. Mp 272–274 °C (dec.) (EtOAc/MeOH 5:1); IR 3100–2300 (max. at 2957, 2897, 2624, 2501, 2353) (CH and NH), 1583, 1526, 1462, 1357, 1331, 1230, 1175, 1130, 1099, 1061, 744, 731 cm^{-1}; for the ^{1}H and ^{13}C NMR data, see (*S*)-**10**·2HCl. Anal. Calcd for

234 $C_7H_{16}N_2 \cdot 2.1HCl \cdot 0.4H_2O$: C, 39.66; H, 8.99; N, 13.21; Cl, 35.12. Found: C, 39.65; H, 9.30;
235 N, 13.04; Cl, 35.35.

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238 **4.7. (*R*)-1,4,4-Trimethyl-3-[(1-phenylethyl)imino]pyrrolidin-2-one (*R*)-12**

239 A solution of 1,4,4-trimethylpyrrolidine-2,3-dione, **6** (878 mg, 6.22 mmol), and (*R*)-
240 1-phenylethylamine, (*R*)-**11** (800 lL, 752 mg, 6.22 mmol) in toluene (30 mL) was heated at
241 reflux for 20 h in a Dean–Stark equipment. Evaporation of the solvent under reduced
242 pressure gave a crude product (1.63 g) that was crystallized from EtOAc (6 mL) to give (*R*)-
243 **12** (1.52 g, quantitative yield) as a yellow solid. Mp 89–90 °C (from EtOAc); $[\alpha]_D^{24}$ = + 62
244 (c 0.81, CH_2Cl_2); IR 2973, 2958, 2921, 2862, 1687 and 1674 (CO), 1489, 1448, 1397, 1322,
245 1279, 1204, 1120, 1095, 1068, 907, 763, 698 cm^{-1}; ^1H NMR 1.21 (s, 3H) and 1.26 (s, 3H)
246 [4-$(CH_3)_2$], 1.44 (d, *J* = 6.8 Hz, 3H, C*H*$_3$–CH), 2.94 (s, 3H, *N*–CH_3), 3.24 (s, 2H, 5-H_2),
247 6.55 (q, *J* = 6.8 Hz, 1H, CH_3–CH), 7.19 (tm, *J* = 7.6 Hz, 1H, Ar–H*para*), 7.30 (tm, *J* = 7.6
248 Hz, 2H, Ar–H*meta*), 7.47 (d, *J* = 7.6 Hz, 2H, Ar–H*ortho*); ^{13}C NMR 25.3 (CH_3), 26.2 (CH_3)
249 and 26.9 (CH_3) [4-$(CH_3)_2$ and CH_3–CH], 30.5 (CH_3, *N*–CH_3), 37.5 (C, C4), 55.9 (CH,
250 CH_3–CH), 59.7 (CH_2, C5), 126.3 (CH, Ar–C*para*), 126.6 (CH, Ar–C*ortho*), 128.1 (CH, Ar–
251 C*meta*), 146.5 (C, Ar–C*ipso*), 160.8 (C, C3), 164.2 (C, C2); Anal. Calcd for $C_{15}H_{20}N_2O$: C,
252 73.74; H, 8.25; N, 11.47. Found: C, 73.70; H, 8.38; N, 11.37. HRMS (ESI): Calcd for
253 ($[M+H]^+$) 245.1648; found 245.1646.

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256 **4.8. Mixture of (3S, 1'*R*)- and (3R, 1'*R*) - 1,4,4 – trimethyl - 3- [(1-phenylethyl) amino]**
257 **pyrrolidine – 2 - one, (3S, 1'*R*) - 13 and (3*R*, 1'*R*) - 14**

258 To a cold (-78 °C) solution of (*R*)-**12** (703 g, 2.88 mmol) in anhydrous MeOH (80
259 mL), a solution of $NaBH_3CN$ (95% content, 600 mg, 9.08 mmol) and AcOH (200 μL, 210
260 mg, 3.49 mmol) in anhydrous MeOH (5 mL) was added dropwise and the reaction mixture

was stirred at this temperature for 4 h. Then more $NaBH_3CN$ (95% content, 600 mg, 9.08 mmol) was added and the mixture was stirred for another 45 min. The mixture was allowed to warm to room temperature, after which water (100 mL) was added and the organic solvent was evaporated under reduced pressure. The remaining aqueous phase was treated with aqueous 2 M NaOH until pH 12–13 and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give a diastereomeric mixture of (3S,1'*R*)-**13** and (3*R*,1'*R*)-**14** (610 mg, 87% yield) in a ratio of 80:20 (^{1}H NMR) as a colorless oil.

4.9. Isolation of (3S,1'*R*)-13·(*S*)-mandelate and (3*R*,1'*R*)-14·(*S*)-mandelate

An 80:20 mixture of (3*S*,1'*R*)-**13** and (3*R*,1'*R*)-**14** (5.05 g, 20.5 mmol) was taken in MeOH (10 mL), treated with a solution of (*S*)-(+)-mandelic acid (3.12 g, 20.5 mmol) in MeOH (20 mL), and the mixture was concentrated to dryness in vacuo. The solid obtained was taken in a mixture of i-PrOH/Et_2O/hexane 2:2:3 (17 mL) and was cooled to 5 °C for 24 h. The precipitated solid was collected by filtration and washed with Et2O (10 mL) to give, after drying, (3*R*,1'*R*)-**14**·(*S*)-mandelate (1.21 g, 15% yield) as a white solid. Hexane (3 mL) was added to the mother liquors and the solution was kept at -20 °C for 48 h precipitating an equimolar mixture of the (*S*)-mandelate salts of (3*S*,1'*R*)-**13** and (3*R*,1'*R*)-**14** (820 mg, 10% yield). The mother liquors were concentrated to dryness in vacuo obtaining the (*S*)-mandelate of the major amine (3*S*,*1'R*)-**13** (5.40 g, 66% yield) as a foamy white solid. An analytical sample of (3*S*,1'*R*)-**13**·(*S*)-mandelate was obtained by crystallization from a mixture of i-PrOH/Et_2O/hexane 2:2:3. (3*S*,1'*R*)-**13**·(*S*)-mandelate: mp 110–112 °C (i-PrOH/Et_2O/hexane 2:2:3); $[\alpha]_D^{22}$ = + 171 (c 0.65, MeOH); IR (KBr) 3600–2100 (max. at 3439, 2959, 2875, OH, $^+$NH and CH), 1705 and 1693 (CO), 1619, 1590, 1516, 1499, 1467, 1450, 1442, 1430, 1395, 1377, 1352, 1320, 1274, 1243, 1183, 1092, 1069, 1060, 769, 736, 706, 698 cm^{-1}; ^{1}H NMR (CD_3OD) 1.05 (s, 3H) and 1.19 (s, 3H) [4-$(CH_3)_2$], 1.43 (d, *J* = 6.6 Hz, 3H, CH_3–C*H*), 2.80 (s, 3H, *N*–CH_3), 2.94 (d, *J* = 10.0 Hz, 1H) and 3.08 (d, *J* = 10.0 Hz, 1H) (5-H_2), 3.22 (s, 1H, 3-H), 4.17 (q, *J* = 6.6 Hz, 1H, CH_3–C*H*), 4.87 (br s, 4H, mobile H),

5.06 (s, 1H, CH mandelate), 7.25–7.41 (complex signal, 8H) and 7.46 (dm, J = 7.2 Hz, 2H) (Ar–H); ^{13}C NMR (CD_3OD) 21.7 (CH3), 23.1 (CH_3) and 26.0 (CH_3) [4-$(CH_3)_2$ and CH_3–CH], 30.1 (CH_3, N–CH_3), 39.6 (C, C4), 58.4 (CH, CH_3–CH), 60.9 (CH_2, C5), 66.0 (CH, C3), 74.6 (CH, CH mandelate), 127.9 (CH), 128.1 (CH), 129.3 (CH) and 129.8 (CH) (Ar–C$_{ortho}$ and Ar–C$_{meta}$ mandelate and Ar–C$_{ortho}$ and Ar–C$_{meta}$ phenyl), 128.7 (CH) and 128.9 (CH) (Ar–C$_{para}$ mandelate and Ar–C$_{para}$ phenyl), 141.5 (C) and 144.0 (C) (Ar–C$_{ipso}$ mandelate and Ar–C$_{ipso}$ phenyl), 174.7 (C, C2), 176.9 (C, COO mandelate). Anal. Calcd for $C_{15}H_{22}N_2O\cdot_{C8H8O3}$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.25; H, 7.68; N, 6.92. (3*R*,1'*R*)-**14**·(*S*)-mandelate: mp 121– 122 °C (i-PrOH/Et_2O/hexane 2:2:3); $[\alpha]_D^{22}$ = + 148 (c 1.04, MeOH); IR 3600–2100 (max. at 3430, 3036, 2953, 2879; OH, $^+$NH, and CH), 1709 and 1698 (CO), 1610, 1514, 1456, 1339, 1304, 1267, 1249, 1179, 1126, 1112, 751, 694 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) 0.87 (s, 3H) and 1.01 (s, 3H) [4-$(CH_3)2$], 1.48 (d, J = 6.8 Hz, 3H, C*H*$_3$–CH), 2.80 (s, 3H, *N*–CH_3), 2.92 (d, J = 9.6 Hz, 1H) and 3.04 (d, J = 9.6 Hz, 1H) (5-H2), 3.00 (s, 1H, 3-H), 4.59 (q, J = 6.8 Hz, 1H, CH_3–C*H*), 4.88 (br s, 4H, mobile H), 5.04 (s, 1H, CH mandelate), 7.25–7.48 (complex signal, 10H) (Ar–H); ^{13}C NMR (CD_3OD) 21.3 (CH_3), 23.3 (CH_3) and 24.5 (CH_3) [4-$(CH_3)_2$ and CH_3–CH], 30.1 (CH_3, N–CH_3), 38.9 (C, C4), 59.0 (CH, CH_3–CH), 60.7 (CH_2, C5), 66.3 (CH, C3), 74.8 (CH, CH mandelate), 127.9 (CH), 128.7 (CH), 129.3 (CH) and 129.8 (CH) (Ar–C$_{ortho}$ and Ar–C$_{meta}$ mandelate and Ar–C$_{ortho}$ and Ar–C$_{meta}$ phenyl), 128.8 (CH) and 129.1 (CH) (Ar–C$_{para}$ mandelate and Ar–C$_{para}$ phenyl), 141.8 (C) and 143.6 (C) (Ar–C$_{ipso}$ mandelate and Ar–C$_{ipso}$ phenyl), 175.0 (C, C2), 177.2 (C, COO mandelate). Anal. Calcd for $C_{15}H_{22}N_2O\cdot C_8H_8O_3$: C, 69.32; H, 7.59; N, 7.03. Found: C, 68.95; H, 7.51; N, 7.08.

316 **4.10. Isolation of (3*S*,1'*R*)-13 from its (*S*)-mandelate**

317 A solution of (3*S*,1'*R*)-13·(*S*)-mandelate (500 mg, 1.26 mmol) in CH_2Cl_2 (30 mL)
318 was washed with aqueous 2 M NaOH (3 x 10 mL), dried (anhydrous $MgSO_4$) and
319 concentrated in vacuo to give (3S,1'*R*)-13 (310 mg, quantitative yield) as a colorless oil.
320 $[\alpha]_D^{22}$ = + 144 (c 0.74, CH_2Cl_2); IR 3310 (NH), 2961, 2932, 1686 and 1676 (CO), 1604,
321 1528, 1511, 1355, 1303, 1252, 1174, 1052, 1031, 842, 763, 733, 700 cm^{-1}; ^1H NMR (300
322 MHz) 1.02 (s, 3H) and 1.14 (s, 3H) [4-$(CH_3)_2$], 1.36 (d, *J* = 6.6 Hz, 3H, C*H*$_3$–CH), 2.79 (d,
323 *J* = 9.6 Hz, 1H) and 2.94 (d, *J* = 9.6 Hz, 1H) (5-H_2), 2.787 (s, 3H, *N*–CH_3), 2.91 (s, 1H, 3-
324 H), 3.91 (q, *J* = 6.6 Hz, 1H, CH_3–C*H*), 7.19–7.25 (complex signal, 3H, Ar–H$_{para}$ and Ar–
325 H$_{meta}$), 7.32 (m, 2H, Ar–H$_{ortho}$); ^{13}C NMR (75.4 MHz) 21.2 (CH_3), 24.6 (CH_3) and 25.1
326 (CH_3) [4-$(CH_3)_2$ and CH_3–CH], 30.0 (CH_3, *N*–CH_3), 38.2 (C, C4), 57.5 (CH, CH_3–CH),
327 59.7 (CH_2, C5), 66.1 (CH, C3), 126.9 (CH, Ar–C$_{para}$), 127.4 (CH, Ar–C$_{ortho}$), 128.1 (CH,
328 Ar–C$_{meta}$), 145.8 (C, Ar–C$_{ipso}$), 175.8 (C, C2); Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H,
329 9.00; N, 11.37. Found: C, 73.17; H, 9.13; N, 11.34. HRMS (ESI): Calcd for ($[M+H]^+$)
330 247.1805; found 247.1807.

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333 **4.11. Isolation of (3*R*,1'*R*)-14 from its (*S*)-mandelate**

334 A solution of (3*R*,1'*R*)-**14**·(*S*)-mandelate (220 mg, 0.55 mmol) in CH_2Cl_2 (20 mL)
335 was washed with aqueous 2 M NaOH (3 x 10 mL), dried (anhydrous $MgSO_4$) and
336 concentrated in vacuo to give (3*R*,1'*R*)-**14** (135 mg, quantitative yield) as a colorless oil.
337 $[\alpha]_D^{22}$ = + 139 (c 1.10, CH_2Cl_2); IR (NaCl) 3308 (NH), 2959, 2923, 2865, 1682 (CO), 1493,
338 1462, 1450, 1403, 1382, 1367, 1314, 1267, 1148, 1092, 862, 762, 701 cm^{-1}; ^1H NMR 0.77
339 (s, 3H) and 0.89 (s, 3H) [4-$(CH_3)_2$], 1.35 (d, *J* = 6.8 Hz, 3H, C*H*$_3$–CH), 2.74 (d, *J* = 9.6 Hz,
340 1H) and 2.92 (d, *J* = 9.6 Hz, 1H) (5-H2), 2.77 (s, 3H, N–CH_3), 2.78 (s, 1H, 3-H), 4.31 (q, *J*
341 = 6.8 Hz, 1H, CH_3–CH), 7.18 (tm, *J* = 7.6 Hz, 1H, Ar–H$_{para}$), 7.26 (tm, *J* = 7.6 Hz, 2H, Ar–

342 H*meta*), 7.36 (dm, 2H, *J* = 7.6 Hz, Ar–H*ortho*); ^{13}C NMR 21.1 (CH3), 24.5 (CH_3) and 25.2
343 (CH_3) [4-(CH_3)2 and CH_3–CH], 29.9 (CH_3, *N*–CH_3), 38.1 (C, C4), 57.4 (CH, CH_3–CH),
344 59.6 (CH_2, C5), 66.1 (CH, C3), 126.8 (CH, Ar–C*para*), 127.4 (CH, Ar–C*ortho*), 128.1 (CH,
345 Ar–C*meta*), 146.0 (C, Ar–C*ipso*), 176.0 (C, C2); HRMS (ESI): Calcd for ($[M+H]^+$) 247.1805;
346 found 247.1809.
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349 **4.12. (*S*)-3-Amino-1,4,4-trimethylpyrrolidin-2-one (*S*)-9**
350 A mixture of (3*S*,1'*R*)-**13** (3.20 g, 13.0 mmol), concentrated HCl (4.10 mL), and 5%
351 Pd/C (11.0 g) in MeOH (150 mL) was hydrogenated at 1 atm and room temperature for 24
352 h. The mixture was filtered through a pad of Celite® washing the solid with MeOH (50 mL).
353 The filtrate was concentrated to dryness under reduced pressure, basified with aqueous 5 M
354 NaOH (25 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts
355 were dried (anhydrous $MgSO_4$) and concentrated under reduced pressure to give (*S*)-9 (1.66
356 g, 90% yield) as a colorless oil. $[\alpha]_D^{22}$ = + 41 (c 0.90, CH_2Cl_2); IR 3364 and 3303 (NH),
357 2954, 2918, 2867, 1686 (CO), 1495, 1463, 1438, 1403, 1383, 1366, 1318, 1272, 1081, 912,
358 871, 816, 782, 720 cm^{-1}; ^{1}H NMR 0.97 (s, 3H) and 1.19 (s, 3H) [4-(CH_3)$_2$], 1.43 (s, 2H,
359 NH_2), 2.86 (s, 3H, N–CH_3), 2.93 (d, J = 9.6 Hz, 1H) and 3.12 (d, J = 9.6 Hz, 1H) (5-H_2),
360 3.13 (s, 1H, 3-H); ^{13}C NMR 20.5 (CH_3) and 25.1 (CH_3) [4-(CH_3)$_2$], 30.0 (CH_3, *N*–CH_3),
361 37.9 (C, C4), 59.9 (CH_2, C5), 62.1 (CH, C3), 175.3 (C, C2); Anal. Calcd for
362 $C_7H_{14}N_2O \cdot 0.1H_2O$: C, 58.39; H, 9.94; N, 19.45. Found: C, 58.40; H, 9.91; N, 19.37. HRMS
363 (ESI): Calcd for ($[M+H]^+$) 143.1179; found 143.1180.
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4.13. (*S*)-3-Amino-1,4,4-trimethylpyrrolidin-2-one mono-O,Odi-p-toluoyl-(2*R*,3*R*)-tartrate (*S*)-9·mono-O,O-di-p-toluoyl-(2*R*,3*R*)-tartrate

To a solution of amine (*S*)-**9** (705 mg, 4.96 mmol) in MeOH (3 mL), a solution of (–)-*O*,*O*-di-p-toluoyl-(2*R*,3*R*)-tartaric acid (97% content, 2.00 g, 5.21 mmol) in MeOH (5 mL) was added. The resulting solution was concentrated to dryness in vacuo and the white solid, thus obtained, was crystallized from a mixture of MeOH/Et_2O 2:3 (17 mL) to give (*S*)-**9**·mono-*O,O*-di-*p*-toluoyl-(2*R*,3*R*)-tartrate (1.94 g, 89% yield). Mp 175–176 °C (MeOH/Et_2O 2:3); $[\alpha]_D^{22}$ = - 106 (c 0.54, MeOH); IR 3200–2500 (max. at 3200, 2924, 2878, 2620, OH, $^+$NH and CH), 1714 and 1667 (CO), 1611, 1533, 1329, 1265, 1173, 1107, 745, 693 cm^{-1}; ^{1}H NMR (CD_3OD) 1.06 (s, 3H) and 1.25 (s, 3H) [4-(CH_3)2], 2.41 (s, 6H, CH_3 *p*-toluoyl), 2.86 (s, 3H, *N*–CH_3), 3.09 (d, *J* = 10.0 Hz, 1H) and 3.28 (d, *J* = 10.0 Hz, 1H) (5-H2), 3.76 (s, 1H, 3-H), 4.91 (s, 4H, mobile H), 5.88 [s, 2H, 2(3)-H tartrate], 7.30 [dm, *J* = 8.0 Hz, 4H, Ar-3(5)-H *p*-toluoyl], 8.02 [d, *J* = 8.0 Hz, 4H, Ar-2(6)-H *p*-toluoyl]; ^{13}C NMR (CD_3OD) 21.3 (CH_3) and 24.8 (CH_3) [4-(CH_3)2], 21.7 (CH_3, CH_3 *p*-toluoyl), 30.2 (CH_3, *N*–CH_3), 37.9 (C, C4), 60.95 (CH, C3), 60.98 (CH2, C5), 74.8 [CH, C2(3) tartrate], 128.4 (C, C1 *p*-toluoyl), 130.1 [CH, Ar-C3(5)], 131.1 [CH, Ar-C2(6)], 145.4 (C, C4 *p*-toluoyl), 167.4 (C, CO *p*-toluoyl), 170.2 (C, C2), 171.5 [C, C1(4) tartrate]. Anal. Calcd for $C_7H_{14}N_2O \cdot C_{20}H_{18}O_8$: C, 61.35; H, 6.10; N, 5.30. Found: C, 61.51; H, 6.20; N, 5.26.

4.14. (*S*)-(1,4,4-Trimethylpyrrolidin-3-yl)amine dihydrochloride (*S*)-10·2HCl

To a cold (0 °C) solution of BH_3·THF complex (1 M in THF, 74.0 mL, 74.0 mmol), a solution of (*S*)-**9** (3.14 g, 22.0 mmol) in anhydrous THF (80 mL) was added dropwise and the solution was heated at reflux for 1 h. The solution was cooled to room temperature, was treated with aqueous 5 MHCl (60 mL) and stirred for about 30 min, until gas evolution ceased. The solution was concentrated to dryness under reduced pressure, the residue was treated with a suspension of anhydrous Na_2CO_3 (20 g) in MeOH (200 mL) and heated at reflux for 15 h. The solution was cooled to room temperature, was basified with KOH pellets

(85% content) until pH 12–13 and was distilled at atmospheric pressure (63 °C). The distillate, a methanolic solution of (*S*)-**10**, was treated with 4 M methanolic HCl (12 mL) and concentrated under reduced pressure to give a residue (3.15 g) which was crystallized from EtOAc/MeOH 5:1 (12 mL) to give (*S*)-**10**·2HCl (2.84 g, 64% yield) as a white solid. Mp 275–276 °C (dec.) (EtOAc/MeOH 5:1); $[\alpha]_D^{22}$ = - 12 (c 1.03, H_2O); IR 3600–2100 (br band, CH and NH), 1584, 1531, 1471, 1421, 1138, 1096, 1061, 971, 954 cm^{-1}; ^1H NMR (D_2O) 1.25 (s, 3H) and 1.29 (s, 3H) [4-$(CH_3)_2$], 3.02 (s, 3H, *N*–CH_3), 3.43 (br d, *J* = 12.0 Hz, 1H) and 3.51 (br d, *J* = 12.0 Hz, 1H) (5-H2), 3.67 (br s, 1H) and 4.02 (br s, 1H) (2-H_2), 3.91 (t, *J* = 7.8 Hz, 1H, 3-H), 4.78 (broad s, mobile H); ^{13}C NMR (D_2O) 22.1 (CH_3) and 26.8 (CH_3) [4-$(CH_3)_2$], 43.6 (CH_3, *N*–CH_3), 45.0 (C, C4), 59.2 (CH, C3), 59.5 (CH_2, C2), 68.5 (CH_2, C5). Anal. Calcd for $C_7H_{16}N_2$·2.3HCl·0.75H_2O: C, 37.27; H, 8.85; N, 12.42; Cl, 36.15. Found: C, 37.14; H, 9.09; N, 12.71; Cl, 36.35.

4.15. (*S*)-(1,4,4-Trimethylpyrrolidin-3-yl)amine (*S*)-10

A suspension of (*S*)-**10**·2HCl (100 mg, 0.50 mmol) in CH_2Cl_2 (3 mL) was treated with aqueous 2 M NaOH (4 mL). The organic phase was dried (anhydrous $MgSO_4$) and carefully concentrated in vacuo at room temperature to give the volatile amine (*S*)-**10** (24.1 mg, 38% yield) as a colorless oil. $[\alpha]_D^{23}$ = - 3 (c 0.73, CH_2Cl_2); ^1H NMR (300 MHz) 0.97 (s, 3H) and 1.05 (s, 3H) [4-$(CH_3)_2$], 1.10–1.40 (br s, 2H, NH_2), 2.30 (s, 3H, *N*–CH_3), 2.36 (d, *J* = 9.3 Hz, 1H) and 2.47 (d, *J* = 9.3 Hz, 1H) (5-H2), 2.20–2.29 (m, 1H) and 2.94–3.04 (m, 2H) (2-H_{cis}, 2-H_{trans} and 3-H); ^{13}C NMR (75.4 MHz) 22.1 (CH_3) and 28.0 (CH_3) [4-$(CH_3)_2$], 40.9 (CH_3, *N*–CH_3), 43.0 (C, C4), 60.8 (CH, C3), 64.5 (CH_2, C2), 70.0 (CH_2, C5).

4.16. (*S*) -N - (1, 4, 4 – Trimethylpyrrolidin – 3 - yl) - *N*' - [3, 5 – bis (trifluoromethyl) phenyl] thiourea (*S*)-16

To a mixture of (*S*)-**10**·2HCl (500 mg, 2.49 mmol) and dry CH_2Cl_2 (5 mL) in an argon atmosphere, 3,5-bis(trifluoromethyl) phenylisothiocyanate (475 lL, 2.49 mmol) and solid K_2CO_3 (1.00 g, 9.43 mmol) were added at 0 °C and the mixture was stirred overnight at room temperature. The mixture was filtered, the solid was washed with CH_2Cl_2 (5 mL), the combined filtrate and washing was concentrated in vacuo and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH mixtures) to give (*S*)-**16** as a pale yellow solid (807 mg, 81% yield). The analytical sample of (*S*)-**16** was obtained by crystallization from a mixture of Et_2O/pentane 1:1. Mp 115–117 °C (Et_2O/pentane 1:1); $[\alpha]_D^{25}$ = - 23 (*c* 0.53, CH_2Cl_2). IR (KBr) 3364, 3314, 3154, 3031, 2965, 2898, and 2794 (NH and CH), 1621, 1559, 1512, 1471, 1384, 1353, 1320, 1279, 1193, 1173, 1137, 1124, 1108, 885, 721, 712, 702, 681 cm^{-1}; ^1H NMR (CD_3OD) 1.09 (s, 3H) and 1.26 (s, 3H) [4-$(CH_3)_2$], 2.38 (s, 3H, *N*–CH_3), 2.51 (d, *J* = 9.6 Hz, 1H) and 2.54 (d, *J* = 9.6 Hz, 1H) (5-H_2), superimposed 2.52 (2H, 2-H_2), 3.11 (dd, *J* = 10.2 Hz, 7.4 Hz, 1H, 3-H), 4.86 (s, 2H, mobile H), 7.63 (s, 1H, Ar-4-H), 8.22 [s, 2H, Ar-2(6)-H]; ^{13}C NMR (CD_3OD) 21.5 (CH_3) and 27.0 (CH_3) [4-$(CH_3)_2$], 40.9 (C, C4), 41.2 (CH_3, *N*–CH_3), 59.9 (CH_2, C2), 61.0 (CH, C3), 69.1 (CH_2, C5), 115.8 (CH, Ar-C4), 121.5 [CH, Ar-C2(6)], 122.8 (C, q, J = 271,8 Hz, CF_3), 130.7 [C, q, *J* = 33.5 Hz, Ar-C3(5)], 141.2 (C, Ar-C1), 181.2 (C, C=S). Anal. Calcd for $C_{16}H_{19}F_6N_3S$: C, 48.12; H, 4.19; N, 10.52; F, 28.54; S, 8.03. Found: C, 48.84; H, 4.85; N, 10.14; F, 28.91; S, 7.85. HRMS (ESI): Calcd for ($[M+H]^+$) 400.1277; found 400.1277.

4.17. General procedure for the enantioselective Michael addition of 1,3-dicarbonyl compounds to *trans*-β-nitrostyrene

The conditions described by Pedrosa and co-workers[6] were followed. To a stirred solution of *trans*-β-nitrostyrene, **17** (91 mg, 0.60 mmol) and catalyst (*S*)-**16** (24 mg, 0.06 mmol) in dry toluene (1.2 mL), 1,3-dicarbonyl compound **18** (1.20 mmol) was added at -18 °C under argon. The reaction mixture was stirred until the disappearance of the nitroolefin by TLC (4 h for (*S*)-**19a**, 24 h for (S)-**19b**, 48 h for (*S*)-**19c**). The solvent was removed in vacuo and the residue was purified by flash column chromatography (hexane/AcOEt 4:1) to afford the desired product (*S*)-**19**. The ee was determined by chiral HPLC analysis and the main enantiomer was deduced from the specific rotation of the enantioenriched mixture and comparison with the described data.

4.18. (*S*)-3-(2-Nitro-1-phenylethyl)pentane-2,4-dione (*S*)-19a

White solid. Isolated yield: 82%. $[\alpha]_D^{25}$ = + 97:5 (*c* 1.0, $CHCl_3$, 49% ee) {reported for (R)-19a 95% ee[15] $[\alpha]_D^{25}$ = - 147:6}. HPLC (Chiralpak IC, hexane/*i*-PrOH = 90:10, 1.0 mL/min, λ = 220 nm); t_R = 18.66 min [major, (*S*)], 30.86 min [minor, (*R*)]; Rs = 22.54; α = 1.78.

4.19. Dimethyl (*S*)-2-(2-nitro-1-phenylethyl)malonate (*S*)-19b

White solid. Isolated yield: 94%. $[\alpha]_D^{25}$ = + 2:2 (c 1.0, $CHCl_3$, 35% ee) {reported for (*R*)-**19b** 89% ee[16] $[\alpha]_D^{25}$ = - 6:15}; (Chiralpak IC, hexane/*i*-PrOH = 90:10, 1.0 mL/min, λ = 220 nm); t_R = 16.79 min [major, (*S*)], 23.04 min [minor, (*R*)]; Rs = 15.69; α = 1.46.

4.20. Diethyl (*S*)-2-(2-nitro-1-phenylethyl)malonate (*S*)-19c

White solid. Isolated yield: 88%. $[\alpha]_D^{25}$ = + 2:4 (*c* 1.0, $CHCl_3$, 18% ee); {reported for (*R*)-**19c** 93% ee16 $[\alpha]_D^{25}$ = - 6:0}; HPLC (Chiralpak IC, hexane/*i*-PrOH = 90:10, 1.0 mL/min, k = 220 nm); t_R = 12.88 min [major, (*S*)], 17.72 min [minor, (*R*)]; Rs = 21.07; a = 1.49.

4.21. X-Ray crystal-structure determination of (3*R*,10*R*)-14·(*S*)-mandelate (Table 2)

A prismatic crystal (0.1 x 0.09 x 0.09 mm) was selected and mounted on a MAR345 diffractometer with an image plate detector. Unit-cell parameters were determined from 177 reflections ($3 < \theta < 21°$) and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation. 9768 reflections were measured in the range $2.83 \leq \theta \leq 30.37$, 5260 of which were non-equivalent by symmetry (Rint(on *I*) = 0.034). 4410 reflections were assumed as observed applying the condition I >2σ(I). Lorentz-polarization but no absorption corrections were made.

The structure was solved by Direct methods, using SHELXS computer program[17] and refined by full-matrix least-squares method with SHELX97 computer program,[18] using 9768 reflections (very negative intensities were not assumed). The function minimized was Rw $||Fo|^2 - |Fc|^2|^2$, where $w = [\sigma^2(I) + (0.1058P)^2 + 0.5690P]^{-1}$, and $P = (|Fo|^2 + 2\,|Fc|^2)/3$, *f*, *f*' and *f*" were taken from International Tables of X-ray Crystallography.[19] All H atoms were computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 times the equivalent temperature factor of the atom to which they are linked. The final R(on F) factor was 0.070, wR(on $|F|^2$) = 0.193 and goodness of fit = 1.132 for all observed reflections. Number of refined parameters was 263. Max. shift/esd = 0.00, Mean shift/esd = 0.00. Max. and min. peaks in final difference synthesis was 0.327 and –0.290 $eÅ^{-3}$, respectively.

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11. Crystallographic data (excluding structure factors) for the structure herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 815330 [(3R,10R)-14□(S)-mandelate]. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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14. We also studied the methanolysis of two meso-tricyclic anhydrides (endo-5-norbornene-2,3-dicarboxylic anhydride and exo-7-oxa-5-norbornene-2,3-dicarboxylic anhydride) catalyzed by (S)-16, under conditions similar to those described by Pedrosa and co-workers.7 The reactions were completed in about 36 h, giving essentially racemic methyl hemiesters in high yields, as established by chiral HPLC of the corresponding methyl 4-bromophenyl ester derivatives.

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19. International Tables of X-ray Crystallography; Kinoch Press: Birmingham, 1974; Vol IV, pp 99–100 and 149.

568 **Table 1** Enantioselective Michael reactions of **17** with 1,3-dicarbonyl compounds **18**
569 catalyzed by (*S*)-**16**[a]

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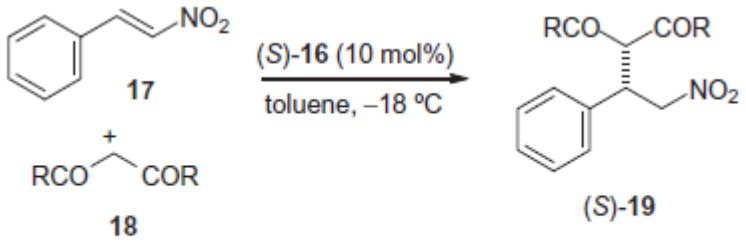

Entry	R	*t* (h)	Yield (%)	Product (ee (%))[b]	(Config.)[c]
1	Me **18a**	4	82	**19a** (49)	(*S*)
2	OMe **18b**	24	94	**19b** (35)	(*S*)
3	OEt **18c**	48	88	**19c** (18)	(*S*)

[a] The reactions were carried out with one equiv of **17** and 2 equiv of **18** in the presence of 10 mol % of (*S*)-**16** at –18 °C.
[b] Enantiomeric excess was determined by HPLC analysis of (*S*)-**19** using the Chiralpack IC chiral column.
[c] The absolute configuration was established by comparison of the specific rotation of (*S*)-**19** with the literature data and the chiral HPLC data of (*S*)-**19** with those obtained using Pedrosa's catalyst (*S*)-**20**.

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573 **Table 2.** Experimental data of the X-ray crystal-structure determination of compound
574 (3*R*,10*R*)-**14**·(*S*)-mandelate

Molecular formula	$C_{23}H_{30}N_2O_4$
Molecular mass weight	398.49
Crystal system	Monoclinic
Space group	C2
Cell parameters	
a (Å)	24.196 (13)
b (Å)	8.924 (4)
c (Å)	10.673 (3)
α (°)	90
ß (°)	101.04 (2)
γ (°)	90
V (Å^3)	2261.9 (17)
Z	4
F (0 0 0)	856
d_{calcd} [Mg m^{-3}]	1.170
Size of crystal (mm)	0.1 × 0.09 × 0.09
Measured reflect	9768
Independent reflect	5260
Observed reflect	4410
μ(Mo Kα) (mm^{-1})[a]	0.080
R	0.034
Rw	0.193
$\Delta\rho_{max}$[b] (e Å^{-3})	0.327
$\Delta\rho_{min}$[c] (e Å^{-3})	−0.290
Refined parameters	263
Max. shift/esd	0.00

[a] μ(Mo Kα) linear absorption coefficient. Radiation Mo Kα (λ = 0.71073 Å).
[b] Maximum peaks in final difference synthesis.
[c] Minimum peaks in final difference synthesis.

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Figures Captions

Figure 1. Structures of pantolactone and several pantolactam derivatives.

Scheme 1. Preparation of aminopyrrolidine dihydrochloride *rac*-**10**·2HCl.

Scheme 2. Preparation of aminopyrrolidine dihydrochloride (*S*)-10·2HCl and thiourea (*S*)-**16.**

Figure 2. ORTEP representation of (3*R*,10*R*)-**14**·(*S*)-mandelate.

Figure 3. Structures of organocatalysts (*S*)-**16**, (*S*)-**20** and **21**.

586 **Figure 1**

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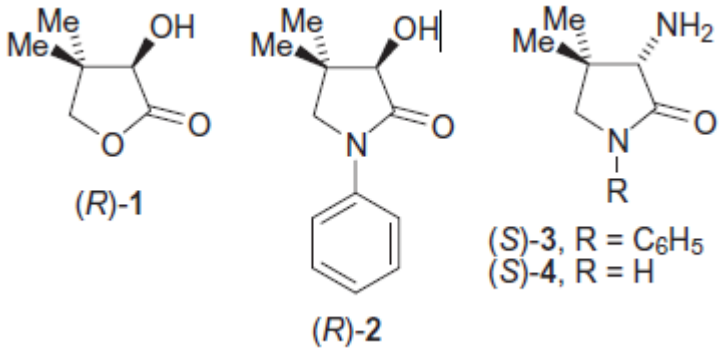

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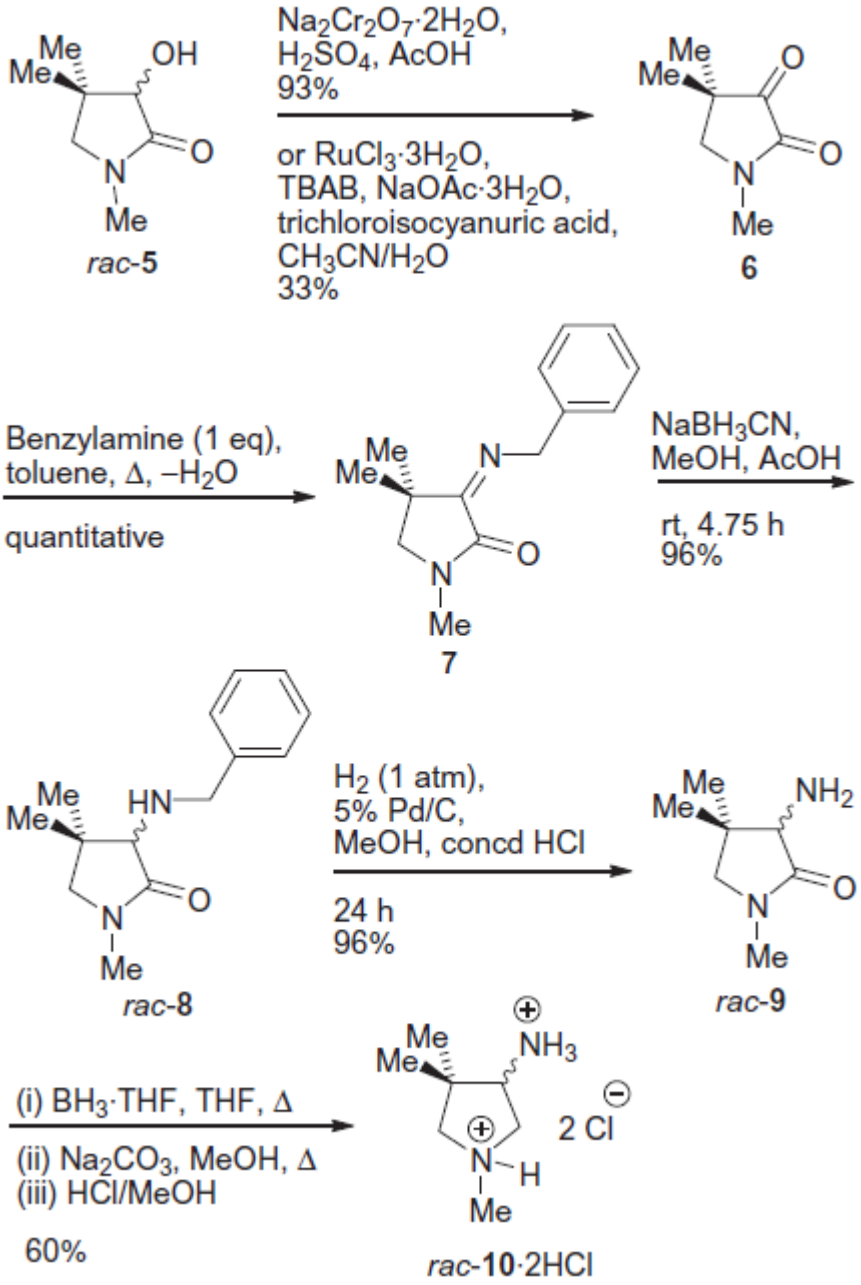
Scheme 1


Me
Me
OH
O
N
Me
rac-5
Na2Cr2O7·2H2O,
H2SO4, AcOH
93%
or RuCl3·3H2O,
TBAB, NaOAc·3H2O,
trichloroisocyanuric acid,
CH3CN/H2O
33%
6
Benzylamine (1 eq),
toluene, Δ, –H2O
quantitative
7
NaBH3CN,
MeOH, AcOH
rt, 4.75 h
96%
HN
rac-8
H2 (1 atm),
5% Pd/C,
MeOH, concd HCl
24 h
96%
NH2
rac-9
(i) BH3·THF, THF, Δ
(ii) Na2CO3, MeOH, Δ
(iii) HCl/MeOH
60%
NH3
2 Cl
H
rac-10·2HCl

Scheme 2

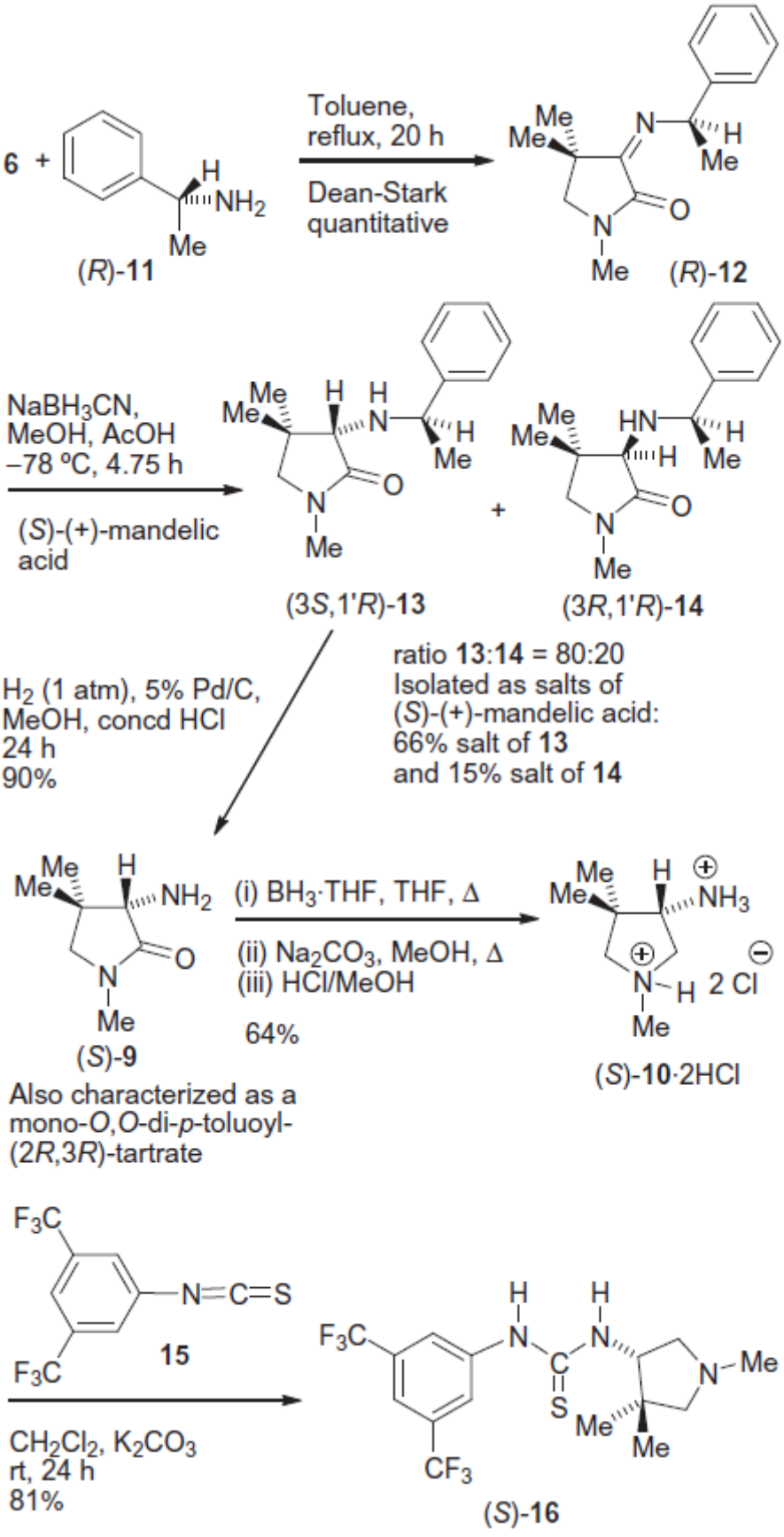
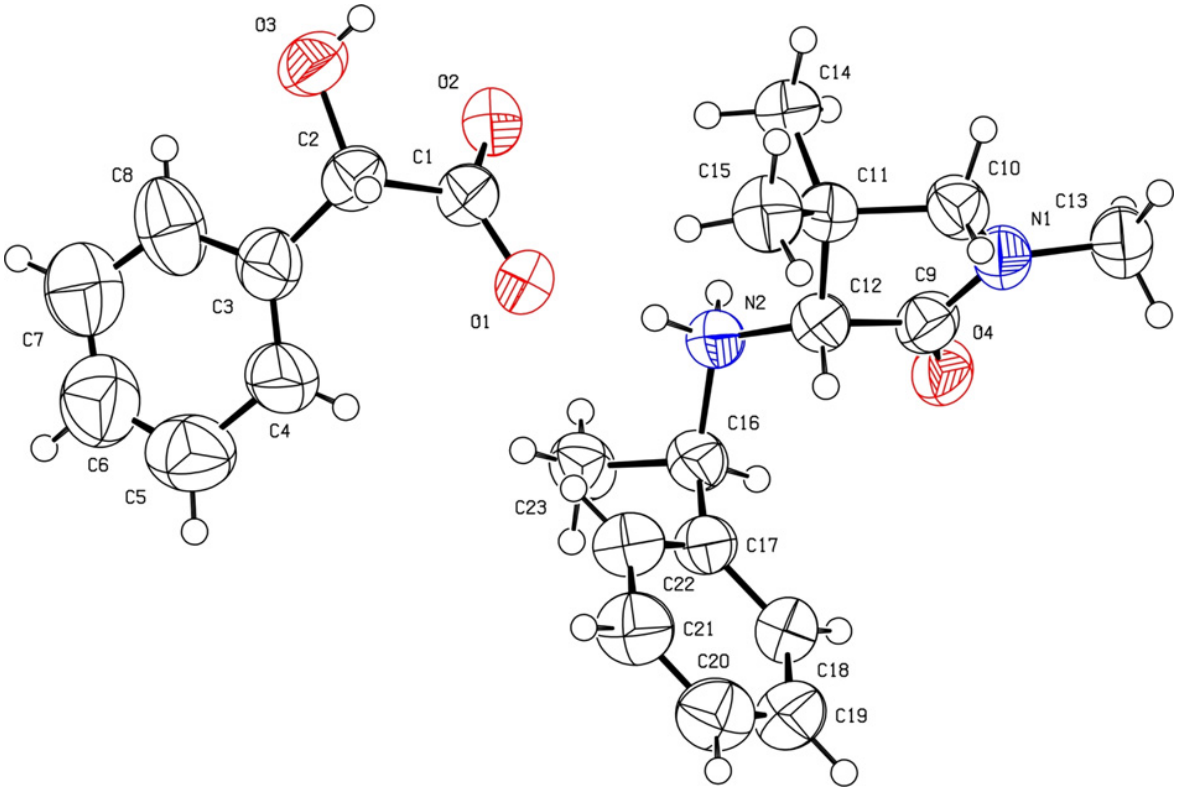

6 +
(R)-11
Toluene,
reflux, 20 h
Dean-Stark
quantitative
(R)-12
NaBH3CN,
MeOH, AcOH
–78 °C, 4.75 h
(S)-(+)-mandelic
acid
(3S,1'R)-13
(3R,1'R)-14
ratio 13:14 = 80:20
Isolated as salts of
(S)-(+)-mandelic acid:
66% salt of 13
and 15% salt of 14
H2 (1 atm), 5% Pd/C,
MeOH, concd HCl
24 h
90%
(i) BH3·THF, THF, Δ
(ii) Na2CO3, MeOH, Δ
(iii) HCl/MeOH
64%
(S)-9
Also characterized as a
mono-O,O-di-p-toluoyl-
(2R,3R)-tartrate
(S)-10·2HCl
15
CH2Cl2, K2CO3
rt, 24 h
81%
(S)-16

Figure 2


O3
O2
C2
C1
C8
C3
O1
C7
C4
C6
C5
C14
C15
C11
C10
N1
C13
C12
C9
N2
O4
C16
C23
C17
C22
C21
C20
C18
C19

634 **Figure 3**

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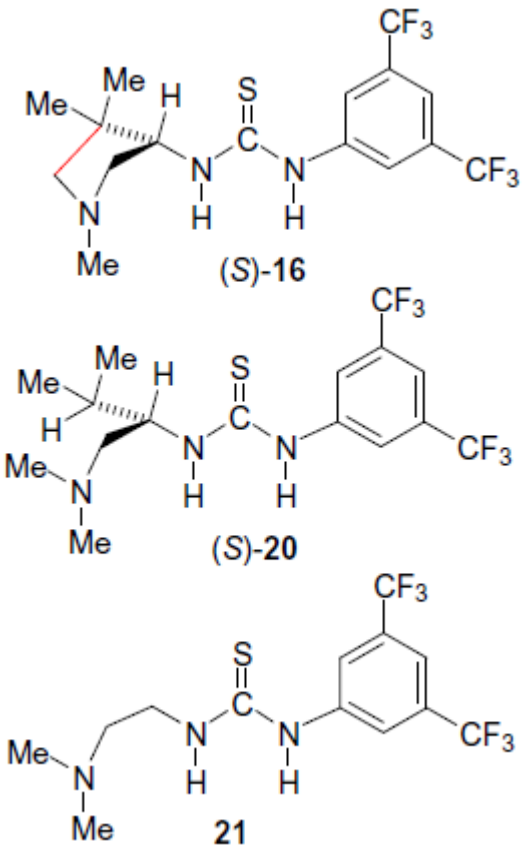

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