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Asymmetric synthesis of 5-arylmethylpyrrolidin-2-ones and 2-arylmethylpyrrolidines

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Abstract—An efficient methodology for the enantioselective synthesis of 5-arylmethylpyrrolidin-2-ones and 2-arylmethylpyrrolidines has been devised. The key step is the stereoselective hydrogenation of the *N*-acylhydrazonium salts obtained from the corresponding arylmethylene hydrazides. These highly conjugated compounds are readily prepared by reacting a chiral succinimide with a variety of arylmethyl Grignard reagents. Removal of the chiral auxiliary and subsequent reduction complete the synthesis of the title compounds.

1. Introduction

The 2-arylmethylpyrrolidine ring system and its lactam pyrrolidinone analogue (and potential precursor) are structural features frequently encountered in a wide array of natural and biologically active compounds. Thus the 2-benzylpyrrolidine framework is embedded in a variety of phenanthroindolizidine alkaloids as typified by tylocrebine **1**, tylophorine **2** and antofine **3** (Fig. 1). In the biological domain many derivatives, e.g. **4**, **5**, have been used for the treatment of central nervous system disorders and changes in blood pressure and/or pain states.[1,2] It has been demonstrated also that bis-(benzylpyrrolidine) derivatives, e.g. **6**, are potent, selective and orally active dopamine analogs with hypotensive and diuretic activities.[3] In addition the 5-benzylpyrrolidinone lactam scaffold is present in compounds displaying nanomolar potency against HIV protease,[4] while some fluorobenzylpyrrolidinone derivatives, e.g. **7**, have shown anticonvulsant, hypnotic and central nervous activities comparable with currently marketed drugs.[5]

The common structural feature shared by all these compounds is the presence of a stereogenic center adjacent to the nitrogen in the heteroring unit and it is vital that synthetic chemists embarking on the assembly of such models address the problem of stereocontrol at this center. Groups that have tackled this challenge have adopted anion or cation methodology as well as radical chemistry. Thus, cation methodologies rely

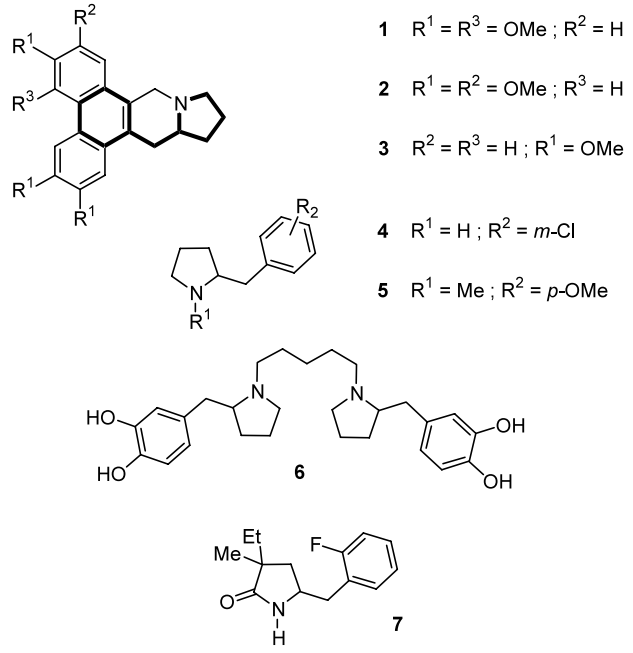

Figure 1.

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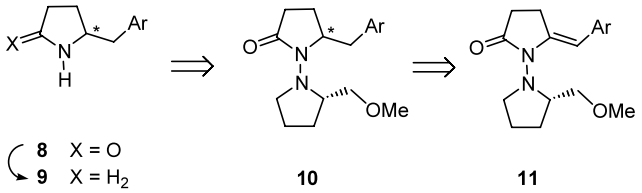
mainly upon the interception of prochiral iminium ions by a hydride source[6] or by achiral nucleophiles.[7] These cationic species may be generated either from the corresponding hydroxy derivatives[8] or by the opening of chiral cyclic sulfamates[7] or bicyclic lactams.[6,9] The chiral auxiliary may be connected to the nitrogen atom or to the adjacent carbon atom either by making use of suitably configured prolinol derivatives or by employing chiral phenylglycinol. In some instances it may also be present at different positions of the heterocyclic framework[10] but this strategy is rather cumbersome owing to the supplementary steps required to strip off the chiral auxiliary.[11] This carbocationic approach has been recently complemented by radical chemistry involving preliminary conversion of the previously evoked hydroxylactams into their phenylsulfamyl derivatives and subsequent treatment to produce the carbon radical adjacent to nitrogen.[12] However, despite the presence of the chiral auxiliary which has been used successfully in the carbocationic process, yields and enantiomeric excesses are extremely low.

Finally, the carbanionic approach hinges upon the asymmetric replacement of a prochiral hydrogen adjacent to the nitrogen in a chiral ligand-mediated asymmetric lithiation–substitution sequence.[13] Alternatively, the generation of the asymmetric center α to N may also be achieved by stoichiometric chirality transfer from a chiral precursor[14] but this approach has been mainly confined to pyrrolidines bearing a formamidine chiral activating group on the nitrogen atom.[15] More limited methods based upon the annulation of the heteroring unit starting from an appropriate prochiral amino acid[16] or an aminoalcohol[17] or upon the generation of a benzylic carbon–carbon bond under the agency of a Friedel–Crafts reaction involving a chiral *N*-protected prolyl chloride[18] have also appeared.

However, most of the reported methods which rely on the introduction of an alkyl group directly onto the pyrrolidine or pyrrolidinone ring system exhibit modest enantiomeric excesses, lack versatility and suffer low yields or a combination of these. On the other hand, application of the carbanionic approach to the stereoselective incorporation of arylmethyl groups via their halides or trifluoromethanesulfonate derivatives has been mainly confined to open or annulated *N*-activated benzylamines.[13b,19] Herein we describe an efficient asymmetric synthesis of 5-arylmethylpyrrolidin-2-ones **8** and 2-arylmethylpyrrolidines **9** that should find general applicability to a variety of modern synthetic challenges.

2. Results and discussion

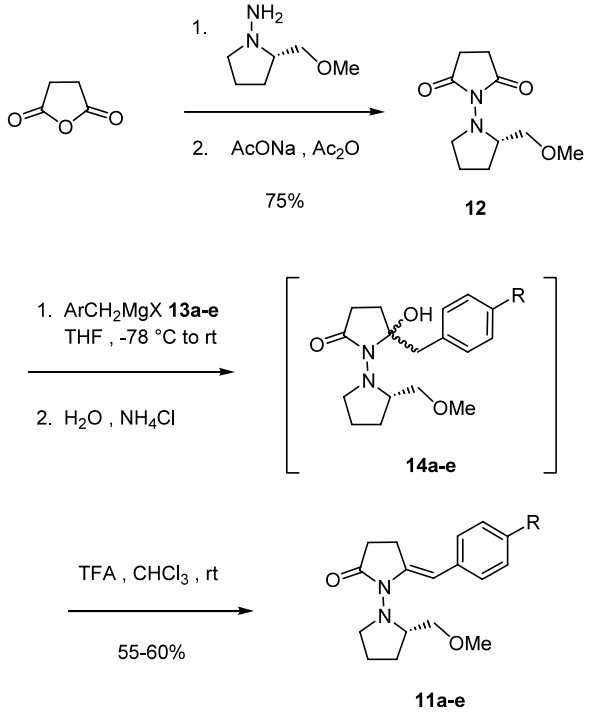
Our conceptually new synthetic approach, which is depicted in the retrosynthetic Scheme 1, hinges in the key step upon the asymmetric reduction of an enehydrazide **11** equipped with an enantiopure pyrrolidine as the chiral inductor.[20] The N–N bond cleavage to trigger off the release of the chiral auxiliary from the saturated compounds **10** should then result in the formation of



Scheme 1.

the enantiopure lactamic heterocycles **8** and thus ultimately to the 2-arylmethylpyrrolidines **9**.

Scheme 2 portrays the overall three-step sequence which provides the parent 5-arylmethylenepyrrolidin-2-ones **11a–e**. The first facet of the synthesis was the assemblage of the cyclic imide **12** bearing the stereocontrolling group, i.e. the (*S*)-2-methoxymethylpyrrolidin-1-yl (SMP) group.[21] This chiral auxiliary has been elegantly and skilfully used by Enders in the area of hydrazine and hydrazide chemistry[22] and has proved to be more advantageous than the C_2 symmetric disubstituted pyrrolidines[7b] or the α-methylbenzyl group[23] in related systems. This operation was readily performed by treatment of succinic anhydride with (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP).



Scheme 2.

Once installation of the stereocontrolling agent on the succinimide unit had been achieved, the resulting succinhydrazide **12** was then allowed to react with a variety of arylmethyl Grignard reagents **13a–e**. Usual work up delivered the 5-hydroxypyrrolidinone derivatives

Table 1.

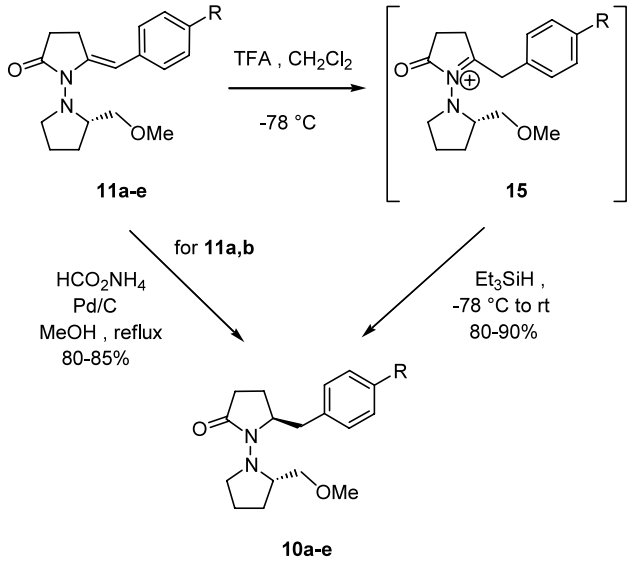
Entry	9–11, 13	R	11	10		8		9	
			Yield (%)	Yield (%)	De	Yield (%)	Ee	Yield (%)	Ee
1	**a**	H	55	90[a]	92	95	92[c]	85	92[c]
2				85[b]	80				
3	**b**	Me	60	82[a]	>96	93	>96[c]	80	>96[c]
4				90[b]	85				
5	**c**	OMe	51	80[a]	>96	93	>96[c]		
6	**d**	Cl	55	88[a]	>96	95	>96[c]		
7	**e**	F	59	85[a]	>96	91	>96[c]		

[a] Reaction conditions: Et_3SiH/TFA.
[b] Reaction conditions: Pd on C/HCO_2NH_4.
[c] In correlation with the de value of the corresponding hydrazides **10a–e** assuming that the deprotecting step takes place without detectable racemization.[26b]

14a–e which were subsequently treated without purification with trifluoroacetic acid. Owing to the high degree of conjugation in the final models the enehydrazides **11a–e** were thus formed and isolated in very satisfactory yields over the last two steps (Table 1). These enelactamic compounds were invariably obtained as the *E*-isomers and the stereochemistry of the exocyclic double bond followed unambiguously from the ^1H NMR data.[†]

With a reliable route to these enehydrazides in hand, studies addressing the enantioselective preparation of the substituted pyrrolidinones and pyrrolidines, **8** and **9** respectively, were initiated. Based upon the efficient method developed by Kibayashi et al. for enantioselective nucleophilic additions to chiral *N*-acyliminium ions,[7b] we anticipated that a high level of diastereoselectivity in the asymmetric hydrogenation of the unsaturated compounds **11a–e** could be ensured by interception of their *N*-acylhydrazonium salts **15** with a hydride source.

For this purpose we envisaged adopting the rarely employed synthetic tactic[25] depicted in Scheme 3. Thus, enehydrazides **11a–e** were first treated with trifluoroacetic acid and then with triethylsilane in sequence. This protocol delivered the arylmethylhydrazides **10a–e** with high yields and excellent diastereoselectivities (Table 1). According to Kibayashi's assumptions,[7b] the high stereoselectivities observed upon hydride trapping of the reactive intermediate **15** may be tentatively ascribed to the preferred transition conformer I (Fig. 2) where the N–C2 bond adopts a perpendicular position to the plane of the azomethine double bond. Due to the pyramidal character of the trivalent pyrrolidine nitrogen the ring methylene group C5 is placed *syn* to the carbonyl group and consequently an antiperiplanar approach of the hydride source can preferentially occur from the sterically less demanding face, thus leading to (5*S*)-isomers. Interestingly, a slight decrease in terms of diastereoselectivity was observed by performing the asymmetric hydrogenation under catalytic conditions. Thus the use of Pd on C with ammonium formate decreased the diastereoselectivity to some extent as in this case the de was lowered to 80–85% (Scheme 3, Table 1, entries 2 and 4).



Scheme 3.

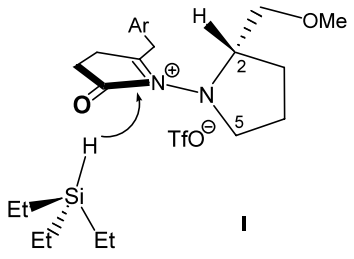
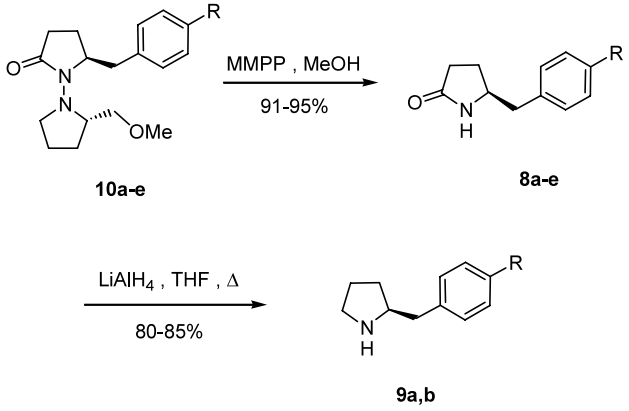


Figure 2.

[†] In contrast to structurally similar *Z*-configured enelactams[24] no NOE effect could be detected on the allylic proton at C4 upon irradiation of the vinylic proton.

Removal of the pyrrolidine chiral auxiliary was readily achieved by homolytic oxidative cleavage promoted by magnesium monoperoxyphthalate[26] (Scheme 4). This deamination method efficiently afforded the enantioenriched 5-arylmethypyrrolidin-2-ones **8a**–**e** released from the stereocontrolling protecting group. The absolute configuration of **8a**–**e** was inferred by comparison of the specific rotation with the literature data, e.g. $[\alpha]_D^{20} = -38.5$ for (*S*)-**8a** (ethanol), lit.[16b] +39.6 for (*R*)-**8a** (ethanol). Additionally the stereochemistry of the pyrrolidinones was also assigned in this manner once they had been converted to their corresponding pyrrolidines (Scheme 4). Typically pyrrolidinones **8a**,**b** were treated with lithium aluminum hydride, a mild reducing agent sparing the stereogenic center,[6,16b] to afford almost quantitatively the enantiomerically enriched (2*S*)-arylmethylpyrrolidines **9a**,**b** (Table 1).



Scheme 4.

To summarize, an efficient and simple procedure has been devised for the preparation of 5-arylmethylpyrrolidin-2-ones and 2-arylmethylpyrrolidines in high enantiomeric purity. This work demonstrates that chiral *N*-acylhydrazonium ions are an efficient means of producing a high degree of asymmetric induction at the stereogenic center vicinal to nitrogen via nucleophilic addition. The methodology is synthetically attractive and we believe that it could be utilized in a general procedure for preparing enantiomerically pure derivatives of pyrrolidin(one)s that might find application in the synthesis of natural chiral alkaloids and bioactive compounds.

3. Experimental

3.1. General

Mps were determined on a Reichert–Thermopan apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AM 300 spectrometer and were referenced against internal tetramethylsilane. Coupling constants (*J*) are given in Hz and rounded to the nearest 0.1 Hz. Elemental analyses were determined by the CNRS microanalysis center. TLC was performed with plates coated with Kieselgel G (Merck). The plates were developed with petroleum ether (PE)–ethyl acetate (EA). The silica gel used for flash column chromatography was Merck Kieselgel of 0.040–0.063 mm particle size. Dry glassware was obtained by oven-drying and assembly under Ar. Ar was used as the inert atmosphere and was passed through a drying tube to remove moisture. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl under argon, immediately before use. Benzylmagnesium chloride **13a** is commercially available (2 M in THF). Arylmethyl Grignard reagents **13b**–**e** were prepared in diethyl ether by a literature method.[27]

3.2. (2′*S*)-2′-Methoxymethyl[1,1′]bipyrrolidinyl-2,5-dione 12

(*S*)-1-Amino-2-methoxymethylpyrrolidine (SAMP, 5.2 g, 0.04 mol) was added to a suspension of succinic anhydride (4 g, 0.04 mol) in CH_2Cl_2 (50 ml). The mixture was stirred at room temperature for 1 h. Acetic anhydride (5.6 ml, 0.06 mol) and a catalytic amount of sodium acetate (30 mg) were subsequently added and the mixture was refluxed for 5 h. The reaction mixture was cooled to 0°C and stirred with a 5% aqueous $NaHCO_3$ solution (50 ml) for 30 min. The aqueous layer was separated and extracted with $CHCl_3$ (3×30 ml). The combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash chromatography on silica gel using EA (ethyl acetate)/PE (petroleum ether, boiling range 40–60°C) (50:50) as eluent and finally recrystallized from hexane to afford **12** (6.36 g, 75%). Mp 43–44°C; $[\alpha]_D^{25} = +5.6$ (*c* 1.36, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.44–1.53 (m, 1H, H_{smp}), 1.75–1.94 (m, 3H, H_{smp}), 2.51 (s, 4H, $H_{pyrrolidine}$), 3.04–3.13 (m, 4H, OCH_3+1H_{smp}), 3.21–3.29 (m, 2H, H_{smp}), 3.32–3.40 (dd, J=16.2, 8.2, 1H, H_{smp}), 3.63–3.70 (m, 1H, H_{smp}). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.1 (CH_2), 26.4 (2 $CH_{2pyrrolidine}$), 26.6 (CH_2), 51.3 (NCH_2), 58.9 (OCH_3), 59.8 (NCH), 76.3 (CH_2O), 175.9 (C=O). IR ($CHCl_3$) cm^{-1}: 2986, 1781, 1709, 1454, 1379, 1209, 1105. Anal. calcd for $C_{10}H_{16}N_2O_3$ (212) C, 56.59; H, 7.60; N, 13.20. Found C, 56.76; H, 7.82; N, 13.34.

3.3. General procedure for the preparation of 5-arylmethylenepyrrolidin-2-ones 11a–e

A solution of the appropriate arylmethyl Grignard reagent **13a**–**e** (1.3 equiv., 6.14 mmol) in THF or diethyl ether was added dropwise under argon to a cold (−78°C) solution of succinhydrazide **12** (1 g, 4.72 mmol) in THF (30 ml). The reaction mixture was stirred at this temperature for 2 h and progressively warmed to room temperature. A saturated aqueous solution of NH_4Cl (10 ml) was then added and the aqueous layer was extracted with AcOEt (3×40 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum to furnish the crude hemiaminals **14** which were immediately dissolved in $CHCl_3$ (30 ml). Trifluoroacetic acid (10 ml) was then added

and the mixture was stirred under argon at room temperature for 2 h. The solution was neutralized using a saturated $NaHCO_3$ solution (30 ml) and extracted with Et_2O (3×40 ml). The extracts were combined, washed with water and brine, and dried over $MgSO_4$. Concentration under vacuum left a residue which was purified by flash chromatography on silica gel using EA/PE (50:50) as eluent followed by recrystallization from hexane–toluene to give the arylmethylenehydrazide **11a–e**.

3.3.1. (2′*S*)-5-Benzylidene-2′-methoxymethyl-[1,1′]-bipyrrolidinyl-2-one 11a. Mp 110–111°C; $[\alpha]_D^{25}=+15.3$ (*c* 1.37, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.64–2.18 (m, 4H, H_{smp}), 2.46–2.51 (m, 2H, $H_{pyrrolidine}$), 2.95–3.00 (m, 2H, $H_{pyrrolidine}$), 3.16–3.21 (m, 1H, H_{smp}), 3.25–3.36 (m, 5H, OCH_3+2H_{smp}), 3.41–3.48 (m, 1H, H_{smp}), 3.89–3.96 (m, 1H, H_{smp}), 6.37 (s, 1H, H_{vinyl}), 7.20–7.32 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.2 (CH_2), 22.8 (CH_2), 27.3 (CH_2), 28.0 (CH_2), 50.4 (NCH_2), 59.0 (OCH_3), 59.9 (NCH), 75.3 (CH_2O), 102.7 (CH_{vinyl}), 125.1 (CH_{arom}), 127.5 (2 CH_{arom}), 128.5 (2 CH_{arom}), 130.9 (C_q), 141.3 (C_q), 172.9 (C=O). IR (KBr) cm^{-1}: 2875, 1704, 1649, 1389, 1281, 1113, 867. Anal. calcd for $C_{17}H_{22}N_2O_2$ (286) C, 71.30; H, 7.74; N, 9.78. Found C, 71.42; H, 7.94; N, 9.83.

3.3.2. (2′*S*)-2′-Methoxymethyl-5-(4-methylbenzylidene)-[1,1′]bipyrrolidinyl-2-one 11b. Mp 114–115°C; $[\alpha]_D^{25}=+14.0$ (*c* 0.32, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.66–2.20 (m, 4H, H_{smp}), 2.31 (s, 3H, CH_3), 2.43–2.50 (m, 2H, $H_{pyrrolidine}$), 2.91–2.98 (m, 2H, $H_{pyrrolidine}$), 3.15–3.19 (m, 1H, H_{smp}), 3.26 (s, 3H, OCH_3), 3.27–3.35 (m, 2H, H_{smp}), 3.43–3.52 (m, 1H, H_{smp}), 3.88–3.97 (m, 1H, H_{smp}), 6.35 (s, 1H, H_{vinyl}), 7.15–7.28 (m, 4H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.1 (CH_3), 22.2 (CH_2), 22.9 (CH_2), 27.3 (CH_2), 28.1 (CH_2), 50.4 (NCH_2), 59.0 (OCH_3), 60.0 (NCH), 75.4 (CH_2O), 102.7 (CH_{vinyl}), 127.1 (2 CH_{arom}), 127.4 (C_q), 129.2 (2 CH_{arom}), 133.4 (C_q), 141.0 (C_q), 172.8 (C=O). IR (KBr) cm^{-1}: 2868, 1710, 1649, 1386, 1283, 1104, 865. Anal. calcd for $C_{18}H_{24}N_2O_2$ (300) C, 71.97; H, 8.05; N, 9.33. Found C, 72.05; H, 8.10; N, 9.21.

3.3.3. (2′*S*)-5-(4-Methoxybenzylidene)-2′-methoxymethyl[1,1′]bipyrrolidinyl-2-one 11c. Mp 83–84°C; $[\alpha]_D^{25}=+17.7$ (*c* 0.68, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.68–2.19 (m, 4H, H_{smp}), 2.41–2.48 (m, 2H, $H_{pyrrolidine}$), 2.85–2.93 (m, 2H, $H_{pyrrolidine}$), 3.14–3.22 (m, 1H, H_{smp}), 3.25–3.33 (m, 5H, OCH_3+2H_{smp}), 3.42–3.51 (m, 1H, H_{smp}), 3.80 (s, 3H, OCH_3), 3.89–3.98 (m, 1H, H_{smp}), 6.31 (s, 1H, H_{vinyl}), 6.86 (d, $J=8.5$, 2H, H_{arom}), 7.20 (d, $J=8.5$, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.1 (CH_2), 22.9 (CH_2), 27.3 (CH_2), 28.1 (CH_2), 50.3 (NCH_2), 55.3 (OCH_3), 59.0 (OCH_3), 59.9 (NCH), 75.3 (CH_2O), 102.2 (CH_{vinyl}), 114.0 (2 CH_{arom}), 127.4 (C_q), 128.6 (2 CH_{arom}), 141.1 (C_q), 157.7 (C-OMe), 173.1 (C=O). IR (KBr) cm^{-1}: 2885, 1709, 1648, 1385, 1284, 1111, 882. Anal. calcd for $C_{18}H_{24}N_2O_3$ (316) C, 68.33; H, 7.65; N, 8.85. Found C, 68.12; H, 7.82; N, 8.60.

3.3.4. (2′*S*)-5-(4-Chlorobenzylidene)-2′-methoxymethyl-[1,1′]bipyrrolidinyl-2-one 11d. Mp 98–99°C; $[\alpha]_D^{25}=+17.8$ (*c* 0.62, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.65–2.11 (m, 4H, H_{smp}), 2.42–2.51 (m, 2H, $H_{pyrrolidine}$), 2.88–2.95 (m, 2H, $H_{pyrrolidine}$), 3.11–3.19 (m, 1H, H_{smp}), 3.23–3.35 (m, 5H, OCH_3+2H_{smp}), 3.41–3.50 (m, 1H, H_{smp}), 3.86–3.95 (m, 1H, H_{smp}), 6.35 (s, 1H, H_{vinyl}), 7.15–7.25 (m, 4H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.2 (CH_2), 22.9 (CH_2), 27.3 (CH_2), 28.1 (CH_2), 50.4 (NCH_2), 59.0 (OCH_3), 59.9 (NCH), 75.3 (CH_2O), 101.6 (CH_{vinyl}), 128.2 (C_q), 128.5 (2 CH_{arom}), 128.7 (2 CH_{arom}), 135.7 (C_q), 142.3 (C_q), 173.0 (C=O). IR (KBr) cm^{-1}: 2881, 1705, 1649, 1384, 1282, 1119, 882. Anal. calcd for $C_{17}H_{21}ClN_2O_2$ (320) C, 63.65; H, 6.60; N, 8.73. Found C, 63.80; H, 6.68; N, 8.81.

3.3.5. (2′*S*)-5-(4-Fluorobenzylidene)-2′-methoxymethyl-[1,1′]bipyrrolidinyl-2-one 11e. Mp 102–103°C; $[\alpha]_D^{25}=+15.6$ (*c* 0.68, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.69–2.18 (m, 4H, H_{smp}), 2.44–2.55 (m, 2H, $H_{pyrrolidine}$), 2.90–2.95 (m, 2H, $H_{pyrrolidine}$), 3.14–3.20 (m, 1H, H_{smp}), 3.24–3.35 (m, 5H, OCH_3+2H_{smp}), 3.38–3.51 (m, 1H, H_{smp}), 3.90–3.99 (m, 1H, H_{smp}), 6.32 (s, 1H, H_{vinyl}), 6.99 (t, $J=8.8$, 2H, H_{arom}), 7.20 (t, $J=8.8$, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.0 (CH_2), 22.8 (CH_2), 27.2 (CH_2), 27.9 (CH_2), 50.4 (NCH_2), 59.0 (OCH_3), 59.9 (NCH), 75.3 (CH_2O), 106.6 (CH_{vinyl}), 115.3 (d, $J=21.2$, 2 CH_{arom}), 128.8 (d, $J=7.3$, 2 CH_{arom}), 133.2 (d, $J=3.6$, C_q), 141.4 (C_q), 160.5 (d, $J=243.8$, C-F), 172.9 (C=O). IR (KBr) cm^{-1}: 2880, 1707, 1646, 1386, 1263, 1113, 876. Anal. calcd for $C_{17}H_{21}FN_2O_2$ (304) C, 67.09; H, 6.95; N, 9.20. Found C, 66.99; H, 6.81; N, 9.31.

3.4. General procedure for the preparation of 5-arylmethylhydrazides 10a–e

3.4.1. Reduction with Et_3SiH/TFA. Trifluoroacetic acid (3 ml) was added under argon to a cooled (−78°C) solution of arylmethylenehydrazide **11a–e** (1.5 mmol) in CH_2Cl_2 (30 ml). The solution was stirred at −78°C for 5 min and then treated with triethylsilane (3 mmol, 0.5 ml). After stirring at this temperature for 30 min, the reaction mixture was allowed to come to room temperature over 1 h and further stirred for 12 h. The mixture was then poured into ice water and a saturated aqueous $NaHCO_3$ solution (50 ml) was added. The aqueous layer was extracted with Et_2O (2×50 ml) and the combined organic layers were dried over $MgSO_4$. Concentration in vacuum followed by chromatography on silica gel using EA/PE (60:40) as eluent afforded compound **10a–e**.

3.4.2. Reduction with Pd on C/HCO_2NH_4. A suspension of compound **11a**,**b** (2 mmol) in methanol (30 ml) was stirred with activated Pd/C (10%, 30 mg) and a solution of HCO_2NH_4 (500 mg, 8 mmol) in distilled water (5 ml) was then added. The reaction mixture was refluxed for 4 h, filtered on Celite and diluted with water. Extraction with CH_2Cl_2 (3×20 ml), drying over $MgSO_4$ and concentration under vacuum left an oily product which was purified by chromatography on silica gel using EA/PE (60:40) as eluent to give **10a**,**b**.

3.4.3. (2′*S*,5*S*)-5-Benzyl-2′-methoxymethyl-[1,1′]-bipyrrolidinyl-2-one 10a. Oil; $[\alpha]_D^{25}=-64.4$ (*c* 0.57, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.60–1.93 (m, 5H, $4H_{pyrrolidine}+1H_{smp}$), 2.07–2.45 (m, 4H, $3H_{smp}+1H$ CH_2Ar), 3.15–3.21 (m, 1H, H_{smp}), 3.33–3.42 (m, 7H, $OCH_3+2H_{smp}+NCH+1H$ CH_2Ar), 3.63–3.69 (m, 1H, H_{smp}), 4.00–4.08 (m, 1H, H_{smp}), 7.18–7.32 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.6 (CH_2), 23.3 (CH_2), 27.1 (CH_2), 29.4 (CH_2), 40.5 (CH_2Ar), 50.6 (NCH_2), 58.8 (OCH_3), 59.5 (NCH), 60.4 (NCH), 75.1 (CH_2O), 126.4 (CH_{arom}), 128.5 (2 CH_{arom}), 129.1 (2 CH_{arom}), 138.0 (C_q), 173.9 (C=O). IR ($CHCl_3$) cm^{-1}: 2950, 1689, 1511, 1223, 1100. Anal. calcd for $C_{17}H_{24}N_2O_2$ (288) C, 70.80; H, 8.39; N, 9.71. Found C, 70.98; H, 8.16; N, 9.96.

3.4.4. (2′*S*,5*S*)-2′-Methoxymethyl-5-(4-methylbenzyl)-[1,1′]bipyrrolidinyl-2-one 10b. Oil; $[\alpha]_D^{25}=-21.1$ (*c* 0.30, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.59–1.91 (m, 5H, $4H_{pyrrolidine}+1H_{smp}$), 2.05–2.42 (m, 7 H, $CH_3+3H_{smp}+1H$ CH_2Ar), 3.17–3.23 (m, 1H, H_{smp}), 3.28–3.44 (m, 7H, $OCH_3+2H_{smp}+NCH+1H$ CH_2Ar), 3.63–3.72 (m, 1H, H_{smp}), 3.98–4.07 (m, 1H, H_{smp}), 7.05–7.13 (m, 4H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.0 (CH_3), 22.6 (CH_2), 23.3 (CH_2), 27.0 (CH_2), 29.4 (CH_2), 40.1 (CH_2Ar), 50.7 (NCH_2), 58.9 (OCH_3), 59.4 (NCH), 60.5 (NCH), 75.2 (CH_2O), 129.0 (2 CH_{arom}), 129.2 (2 CH_{arom}), 134.8 (C_q), 135.9 (C_q), 174.0 (C=O). IR ($CHCl_3$) cm^{-1}: 2962, 1688, 1515, 1215, 1097. Anal. calcd for $C_{18}H_{26}N_2O_2$ (302) C, 71.49; H, 8.67; N, 9.26. Found C, 71.69; H, 8.45; N, 9.43.

3.4.5. (2′*S*,5*S*)-5-(4-Methoxybenzyl)-2′-methoxymethyl-[1,1′]bipyrrolidinyl-2-one 10c. Oil; $[\alpha]_D^{25}=-38.2$ (*c* 0.97, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.53–1.85 (m, 5H, $4H_{pyrrolidine}+1H_{smp}$), 2.09–2.34 (m, 4H, $3H_{smp}+1H$ CH_2Ar), 3.12–3.21 (m, 1H, H_{smp}), 3.28–3.37 (m, 7 H, $OCH_3+2H_{smp}+NCH+1H$ CH_2Ar), 3.56–3.68 (m, 1H, H_{smp}), 3.76 (s, 3H, OCH_3), 3.93–4.04 (m, 1H, H_{smp}), 6.81 (d, $J=8.5$, 2H, H_{arom}), 7.09 (d, $J=8.5$, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.6 (CH_2), 23.2 (CH_2), 27.0 (CH_2), 29.6 (CH_2), 39.6 (CH_2Ar), 50.7 (NCH_2), 55.2 (OCH_3), 58.9 (OCH_3), 59.4 (NCH), 60.6 (NCH), 75.1 (CH_2O), 113.9 (2 CH_{arom}), 130.1 (2 CH_{arom}), 158.2 (C-OMe), 174.0 (C=O). IR ($CHCl_3$) cm^{-1}: 2952, 1687, 1510, 1245, 1109. Anal. calcd for $C_{18}H_{26}N_2O_3$ (318) C, 67.90; H, 8.23; N, 8.80. Found C, 67.80; H, 8.42; N, 8.65.

3.4.6. (2′*S*,5*S*)-5-(4-Chlorobenzyl)-2′-methoxymethyl-[1,1′]bipyrrolidinyl-2-one 10d. Oil; $[\alpha]_D^{25}=-66.6$ (*c* 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.51–1.88 (m, 5H, $4H_{pyrrolidine}+1H_{smp}$), 1.99–2.35 (m, 4H, $3H_{smp}+1H$ CH_2Ar), 3.13–3.17 (m, 1H, H_{smp}), 3.24–3.33 (m, 7H, $OCH_3+2H_{smp}+NCH+1H$ CH_2Ar), 3.59–3.64 (m, 1H, H_{smp}), 3.98–4.04 (m, 1H, H_{smp}), 7.09 (d, $J=8.3$, 2H, H_{arom}), 7.21 (d, $J=8.3$, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.6 (CH_2), 23.3 (CH_2), 27.0 (CH_2), 29.3 (CH_2), 39.8 (CH_2Ar), 50.6 (NCH_2), 58.9 (OCH_3), 59.4 (NCH), 60.3 (NCH), 75.0 (CH_2O), 128.6 (2 CH_{arom}), 130.4 (2 CH_{arom}), 132.2 (C_q), 136.5 (C-Cl), 173.8 (C=O). IR ($CHCl_3$) cm^{-1}: 2930, 1688, 1513, 1215, 1102. Anal. calcd for $C_{17}H_{23}ClN_2O_2$ (322) C, 63.25; H, 7.18; N, 8.68. Found C, 63.08; H, 7.32; N, 8.89.

3.4.7. (2′*S*,5*S*)-5-(4-Fluorobenzyl)-2′-methoxymethyl-[1,1′]bipyrrolidinyl-2-one 10e. Oil; $[\alpha]_D^{25}=-59.7$ (*c* 1.37, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.58–1.91 (m, 5H, $4H_{pyrrolidine}+1H_{smp}$), 2.05–2.42 (m, 4H, $3H_{smp}+1H$ CH_2Ar), 3.12–3.18 (m, 1H, H_{smp}), 3.23–3.41 (m, 7H, $OCH_3+2H_{smp}+NCH+1H$ CH_2Ar), 3.61–3.68 (m, 1H, H_{smp}), 3.99–4.06 (m, 1H, H_{smp}), 6.96 (t, $J=8.6$, 2H, H_{arom}), 7.14 (t, $J=8.6$, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 22.6 (CH_2), 23.2 (CH_2), 27.0 (CH_2), 29.4 (CH_2), 39.7 (CH_2Ar), 50.6 (NCH_2), 58.8 (OCH_3), 59.4 (NCH), 60.4 (NCH), 75.1 (CH_2O), 115.3 (d, $J=20.8$, 2 CH_{arom}), 130.4 (d, $J=7.9$, 2 CH_{arom}), 133.6 (d, $J=3.0$, C_q), 161.6 (d, $J=242.6$, C-F), 174.0 (C=O). IR ($CHCl_3$) cm^{-1}: 2942, 1687, 1509, 1210, 1104. Anal. calcd for $C_{17}H_{23}FN_2O_2$ (306) C, 66.65; H, 7.57; N, 9.14. Found C, 66.91; H, 7.74; N, 9.24.

3.5. General procedure for the preparation of the 5-arylmethylpyrrolidin-2-ones 8a–e

To a solution of arylmethylhydrazide **10a**–**e** (1 mmol) in methanol (40 ml) was added MMPP (2.5 mmol, 1.24 g). The reaction mixture was stirred at room temperature until no starting material remained (TLC monitoring). The mixture was then poured in CH_2Cl_2 (150 ml) and treated with a saturated $NaHCO_3$ solution (100 ml). The aqueous layer was extracted with CH_2Cl_2 (3×50 ml) and the combined extracts washed successively with water (30 ml), brine (30 ml) and finally dried over $MgSO_4$. Evaporation of the solvent furnished an oily product which was purified by flash column chromatography using EA as eluent. The product was finally recrystallized from diethyl ether to give **8a**–**e**.

3.5.1. (5*S*)-5-Benzylpyrrolidin-2-one 8a. Mp 57–58°C; $[\alpha]_D^{25}=-38.5$ (*c* 0.80, EtOH). ^1H NMR ($CDCl_3$) δ (ppm): 1.71–1.83 (m, 1H, $H_{pyrrolidine}$), 2.12–2.26 (m, 3H, $H_{pyrrolidine}$), 2.75 (d, $J=6.4$, 2H, CH_2Ar), 3.85–3.90 (m, 1H, NCH), 6.87 (brs, 1H, N-H), 7.13–7.25 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 26.5 (CH_2), 30.2 (CH_2), 42.7 (CH_2Ar), 55.7 (OCH_3), 126.7 (CH_{arom}), 128.7 (2 CH_{arom}), 129.1 (2 CH_{arom}), 137.4 (C_q), 178.4 (C=O). IR ($CHCl_3$) cm^{-1}: 3430, 1695, 1510, 1216. Anal. calcd for $C_{11}H_{13}NO$ (175) C, 75.40; H, 7.48; N, 7.99. Found C, 75.12; H, 7.56; N, 7.86.

3.5.2. (5*S*)-5-(4-Methylbenzyl)-pyrrolidin-2-one 8b. Mp 80–81°C; $[\alpha]_D^{25}=-14.5$ (*c* 1.30, EtOH). ^1H NMR ($CDCl_3$) δ (ppm): 1.74–1.84 (m, 1H, $H_{pyrrolidine}$), 2.15–2.24 (m, 3H, $H_{pyrrolidine}$), 2.31 (s, 3H, CH_3), 2.73 (ddd, $J=13.6$, 7.7, 5.8, 2H, CH_2Ar), 3.82–3.87 (m, 1H, NCH), 6.42 (brs, 1H, N-H), 7.04 (d, $J=8.1$, 2H, H_{arom}), 7.10 (d, $J=8.1$, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.0 (CH_3), 26.7 (CH_2), 30.1 (CH_2), 42.4 (CH_2Ar), 55.8 (NCH), 128.9 (2 CH_{arom}), 129.4 (2 CH_{arom}), 134.3 (C_q), 136.3 (C_q), 178.2 (C=O). IR ($CHCl_3$) cm^{-1}: 3426, 1690, 1514, 1215. Anal. calcd for $C_{12}H_{15}NO$ (189) C, 76.16; H, 7.99; N, 7.40. Found C, 76.27; H, 7.85; N, 7.51.

3.5.3. (5*S*)-5-(4-Methoxybenzyl)-pyrrolidin-2-one 8c. Mp 77–78°C; $[\alpha]_D^{25}=-30.2$ (*c* 1.10, EtOH). ^1H NMR ($CDCl_3$) δ (ppm): 1.74–1.88 (m, 1H, $H_{pyrrolidine}$), 2.15–

2.33 (m, 3H, $H_{pyrrolidine}$), 2.72 (ddd, $J=13.6$, 7.6, 5.9, 2H, CH_2Ar), 3.72–3.87 (m, 4H, OCH_3+NCH), 6.06 (brs, 1H, N-H), 6.84 (d, $J=8.8$, 2H, H_{arom}), 7.09 (d, $J=8.8$, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 26.6 (CH_2), 30.0 (CH_2), 41.9 (CH_2Ar), 55.1 (OCH_3), 55.7 (NCH), 114.1 (2 CH_{arom}), 129.4 (C_q), 129.9 (2 CH_{arom}), 158.4 (C-OMe), 177.4 (C=O). IR ($CHCl_3$) cm^{-1}: 3440, 1690, 1506, 1213. Anal. calcd for $C_{12}H_{15}NO_2$ (205) C, 70.22; H, 7.37; N, 6.82. Found C, 70.33; H, 7.50; N, 6.79.

3.5.4. (5*S*)-5-(4-Chlorobenzyl)-pyrrolidin-2-one 8d. Mp 96–97°C; $[\alpha]_D^{25}=-22.3$ (*c* 0.75, EtOH). ^1H NMR ($CDCl_3$) δ (ppm): 1.73–1.87 (m, 1H, $H_{pyrrolidine}$), 2.18–2.31 (m, 3H, $H_{pyrrolidine}$), 2.73 (ddd, $J=13.6$, 7.7, 5.8, 2H, CH_2Ar), 3.79–3.88 (m, 1H, NCH), 6.09 (brs, 1H, N-H), 7.09 (d, $J=8.3$, 2H, H_{arom}), 7.27 (d, $J=8.3$, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 26.7 (CH_2), 29.9 (CH_2), 42.2 (CH_2Ar), 55.5 (NCH), 128.9 (2 CH_{arom}), 130.4 (2 CH_{arom}), 132.7 (C_q), 135.8 (C_q), 177.6 (C=O). IR ($CHCl_3$) cm^{-1}: 3429, 1693, 1491, 1215. Anal. calcd for $C_{11}H_{12}ClNO$ (209) C, 63.01; H, 5.77; N, 6.68. Found C, 62.88; H, 5.67; N, 6.57.

3.5.5. (5*S*)-5-(4-Fluorobenzyl)-pyrrolidin-2-one 8e. Mp 64–65°C; $[\alpha]_D^{25}=-40.6$ (*c* 0.50, EtOH). ^1H NMR ($CDCl_3$) δ (ppm): 1.78–1.84 (m, 1H, $H_{pyrrolidine}$), 2.15–2.32 (m, 3H, $H_{pyrrolidine}$), 2.75 (ddd, $J=13.5$, 7.6, 5.7, 2H, CH_2Ar), 3.80–3.86 (m, 1H, NCH), 6.06 (brs, 1H, N-H), 6.99 (t, $J=8.6$, 2H, H_{arom}), 7.12 (t, $J=8.6$, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 26.7 (CH_2), 30.0 (CH_2), 42.1 (CH_2Ar), 55.6 (NCH), 115.6 (d, $J=21.2$, 2 CH_{arom}), 130.5 (d, $J=7.3$, 2 CH_{arom}), 133.1 (C_q), 161.7 (d, $J=242.5$, C-F), 177.9 (C=O). IR ($CHCl_3$) cm^{-1}: 3425, 1687, 1508, 1221. Anal. calcd for $C_{11}H_{12}FNO$ (193) C, 68.38; H, 6.26; N, 9.83. Found C, 68.33; H, 6.43; N, 9.95.

3.6. General procedure for the preparation of the 2-(*S*)-arylmethylpyrrolidines 9a,b

$LiAlH_4$ (80 mg, 2 mmol) was added portionwise at 0°C to a stirred solution of **8a**,**b** (0.5 mmol) in anhydrous THF (20 ml). After stirring at 0°C for 2 h, the reaction mixture was allowed to come to room temperature over 1 h and then refluxed for 4 h. Ethyl acetate (40 ml) was then added and the resulting mixture was filtered on Celite. After drying over $MgSO_4$, the organic layer was concentrated under vacuum and the residue purified by flash chromatography on silica gel using $CHCl_3$/MeOH (80:20) as eluent.

3.6.1. (2*S*)-2-Benzylpyrrolidine 9a. Oil; $[\alpha]_D^{25}=+19.5$ (*c* 0.40, MeOH) {lit.[9b] $[\alpha]_D=+20.0$ (*c* 0.3, MeOH)}. ^1H NMR ($CDCl_3$) δ (ppm): 1.50–1.91 (m, 4H), 2.83 (dd, $J=13.3$, 8.0, 1H), 2.96–3.05 (m, 2H), 3.12–3.18 (m, 1H), 3.40–3.45 (m, 1H), 7.17–7.35 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 24.1 (CH_2), 30.5 (CH_2), 40.1 (CH_2), 45.3 (CH_2Ar), 60.5 (NCH), 126.7 (CH_{arom}), 128.6 (2 CH_{arom}), 129.1 (2 CH_{arom}), 138.2 (C_q). IR ($CHCl_3$) cm^{-1}: 3350, 1630, 1597, 1495, 1445, 1403. Anal. calcd for $C_{11}H_{15}N$ (161) C, 81.94; H, 9.38; N, 8.39. Found C, 82.09; H, 9.65; N, 8.2.

3.6.2. (2*S*)-2-(4-Methylbenzyl)-pyrrolidine 9b. Oil; $[\alpha]_D^{25}=+12.4$ (*c* 0.32, MeOH). ^1H NMR ($CDCl_3$) δ (ppm): 1.45–1.85 (m, 4H), 2.32 (s, 3H, CH_3), 2.86 (dd, $J=13.2$, 8.0, 1H), 3.01–3.09 (m, 2H), 3.06–3.15 (m, 1H), 3.45–3.53 (m, 1H), 7.06 (d, $J=8.0$, 2H, H_{arom}), 7.12 (d, $J=8.0$, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.2 (CH_3), 24.1 (CH_2), 30.7 (CH_2), 39.9 (CH_2), 45.2 (CH_2Ar), 60.4 (NCH), 128.8 (2 CH_{arom}), 129.4 (2 CH_{arom}), 134.1 (C_q), 138.1 (C_q). IR ($CHCl_3$) cm^{-1}: 3343, 1635, 1600, 1436, 1409. Anal. calcd for $C_{12}H_{17}N$ (175) C, 82.23; H, 9.78; N, 7.99. Found C, 82.35; H, 9.57; N, 7.86.

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