Highly Diastereoselective Addition of *N*-Boc-pyrrolidin-2-yllithium to Optically Active Ketimines − Synthesis of Enantiomerically Pure 1,3-Imidazolidin-2-ones and Diamines[‡]

Nikolai Graf v. Keyserlingk[a] and Jürgen Martens*[a]

Keywords: Schiff bases / Nitrogen heterocycles / Diastereoselectivity / C−C coupling / Ligand design

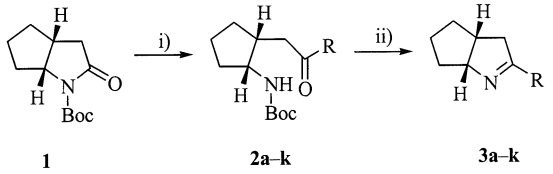
A highly diastereoselective addition of chiral *N*-Boc-pyrrolidin-2-yllithium to optically active bicyclic ketimines has been developed. For this purpose alkyl- and aryl-substituted chiral *N*-Boc-amino ketones **2** have been synthesized by addition of various Grignard reagents to an *N*-Boc-protected lactam **1**. The resulting *N*-Boc-amino ketones **2** have been converted into bicyclic ketimines **3** after deprotection and intramolecular cyclization. A kinetic resolution of the racemic organolithium compound by the chiral substrate is discussed based on X-ray crystal structure analysis and experimental results. The influence of the substituent of the ketimine has been studied. Some of the obtained tetracyclic 1,3-imidazolidin-2-ones **4** have been converted into tetracyclic aminals **5** and these compounds have been hydrolysed to the desired diamines **6**.

Introduction

Because of their widespread utility in different fields of chemistry, for example medicinal chemistry and especially as catalysts and chiral auxiliaries in stereoselective syntheses, optically active vicinal diamines are of great importance and interest.[1] Thus, different routes have been developed in order to synthesize these compounds. One of them, among others, is the addition of organometallic reagents to chiral 1,2-bisimines derived from glyoxal.[2−4] Another possible method is the use of α-amino carbanions as organometallic agents in the nucleophilic addition to prochiral imines, and subsequent hydrolysis of the initially obtained 1,3-imidazolidin-2-ones to the corresponding diamines.[5] Beak et al. found that this methodology could be performed in an enantioselective manner by the use of (−)-sparteine in the deprotonation of the *N*-Boc-protected benzylamine derivative.[6] Katritzky has described very recently the reaction of a benzotriazole-stabilized *N*-Boc-protected benzylmethylamine carbanion to give prochiral aldimines.[7] The addition of dipole-stabilized α-amino carbanions to chiral ketimines has not been reported so far although this synthetic pathway would give the possibility of forming vicinal diamines with a nitrogen-substituted quaternary stereogenic carbon centre.[8] In this paper we wish to report the addition of *N*-Boc-pyrrolidin-2-yllithium to optically active chiral bicyclic ketimines.

Results and Discussion

The requisite ketimines **3a**−**k** for this study were synthesized starting from the bicyclic *N*-Boc-protected lactam **1** by addition of aliphatic or aromatic Grignard reagents and subsequent intramolecular dehydration of the resulting amino ketones **2a**−**k** after deprotection with trifluoroacetic acid, in a similar manner to a procedure described in the literature (Scheme 1).[9] Lactam **1** is available in three steps from the enantiomerically pure unnatural α-amino acid octahydrocyclopenta[*b*]pyrrol-2-carboxylic acid,[10,11] and its synthesis has already been described elsewhere.[12]



Scheme 1. i) RMgX, THF, room temperature; ii) 1. trifluoroacetic acid, CH_2Cl_2, room temperature; 2. NaOH; for yields see Exp. Sect. and for description of the substituents **a**−**k** see Table 1

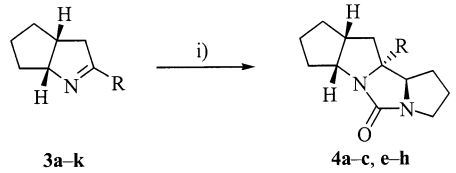
With these ketimines **3a**−**k** at hand we next studied their behaviour in the reaction with *N*-Boc-pyrrolidin-2-yllithium (Scheme 2).

Reaction of one equivalent of *N*-Boc-pyrrolidin-2-yllithium, generated by deprotonation with *sec*-butyllithium in the presence of TMEDA at −78 °C, with chiral ketimine **3a** for 12 h at −78 °C gave, after extractive and chromatographic workup, the expected tetracyclic 1,3-imidazolidin-2-one **4a** (Table 1, entry 1). The ^{1}H NMR spectrum of the crude product showed the absence of other diastereomers.

[‡] Utilization of Industrial Waste Materials, 21. − Part 20: Ref.[12]

[a] Universität Oldenburg, Fachbereich Chemie,
Carl-von-Ossietzky-Str. 9−11, 26129 Oldenburg, Germany
E-Mail: juergen.martens@uni-oldenburg.de

  1434−193X/02/0102−0301 $ 17.50+.50/0



Scheme 2. i) *N*-Boc-pyrrolidine, diamine, *sec*-butyllithium, Et_2O, −78 °C, 12 h; for yields and description of the substituents **a**−**k** see Table 1

This result is amazing as the organometallic compound was formed as a racemate and therefore it appeared that only one enantiomer of the racemic *N*-Boc-pyrrolidin-2-yllithium had reacted with the enantiomerically pure imine **3a** in the nucleophilic addition reaction. To confirm this theory we carried out a further experiment. Use of the Beak procedure[13,14] for deprotonation of the *N*-Boc-pyrrolidine [*sec*-butyllithium and (−)-sparteine as the chelating diamine], which is known to produce the 2-substituted *N*-Boc-pyrrolidines in high *ee*'s up to 96% after addition of an electrophile and subsequent hydrolysis, increased the yield of **4a** to 31% (entry 2). As shown by comparison of the spectroscopic and analytical data of the two products the same 1,3-imidazolidin-2-one was produced in both reactions. The use of a slight excess of *N*-Boc-pyrrolidin-2-yllithium [generated in the presence of (−)-sparteine] resulted in an improved yield of 48% (entry 3). In the case of the 4-methylphenylketimine **4b** reaction of the imine with a twofold excess of *N*-Boc-pyrrolidinyl-2-lithium gave 27% yield in the presence of TMEDA as chelating agent (entry 4); despite a reduction of the substrate/nucleophile ratio to 1:1.16, the use of (−)-sparteine for the deprotonation also increased the yield to 47% (entry 5).

From 1,3-imidazolidin-2-one (**4b**) we were able to get suitable crystals for an X-ray-crystal structure analysis.[15] As shown in Figure 1, the newly generated stereogenic centres both have an (*R*)-configuration, meaning that the dipole-stabilized α-amino carbanion that has added to the C=N double bond must have been (*S*)-configured. This intermediate was reported by Beak et al. as being generated almost exclusively upon deprotonation of *N*-Boc-pyrrolidine with *sec*-butyllithium in the presence of (−)-sparteine.[14] With this information we were able to make some mechanistic considerations about the stereochemical results of the reaction (Figure 2).

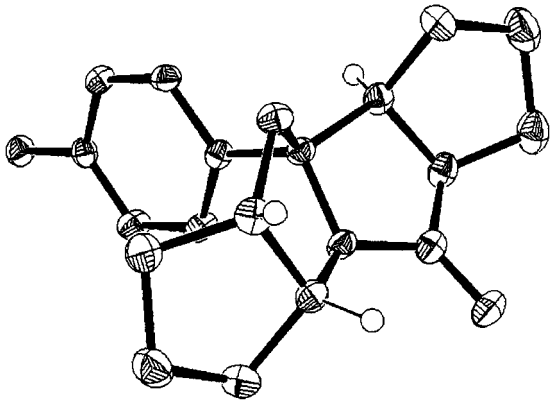


Figure 1. ORTEP diagram of **4b**

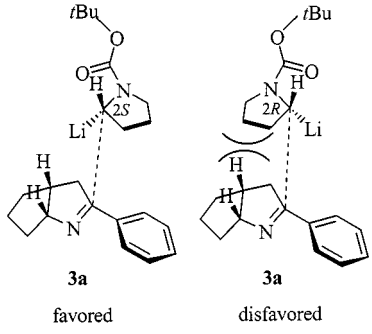


Figure 2. Possible interactions between optically active ketimine **3a** and the two enantiomeric forms of *N*-Boc-pyrrolidin-2-yllithium

A nucleophilic attack from the bottom side of the bicyclic ketimine **3a** is less probable because of strong shielding by the second five-membered ring. More plausible is the addition of the nucleophile from the sterically less-crowded top

Table 1. Results of the addition of N-Boc-pyrrolidin-2-yllithium to optically active ketimines 3a−k; all reactions were carried out with a substrate/N-Boc-pyrrolidine ratio of 1:1.16

Entry	1,3-Imidazolidin-2-one	R	Chelating diamine	Yield [%]
1	**4a**	Phenyl	TMEDA	16[a]
2	**4a**	Phenyl	(−)-Sparteine	31[a]
3	**4a**	Phenyl	(−)-Sparteine	48
4	**4b**	4-Methylphenyl	TMEDA	27[b]
5	**4b**	4-Methylphenyl	(−)-Sparteine	47
6	**4c**	3-Methylphenyl	(−)-Sparteine	26
7	**4d**	2-Methylphenyl	(−)-Sparteine	[c]
8	**4e**	4-Methoxyphenyl	(−)-Sparteine	6
9	**4f**	3-Methoxyphenyl	(−)-Sparteine	56
10	**4g**	2-Methoxyphenyl	(−)-Sparteine	42
11	**4h**	2-Naphthyl	(−)-Sparteine	14
12	**4i**	1-Naphthyl	(−)-Sparteine	[c]
13	**4j**	Methyl	(−)-Sparteine	[c]
14	**4k**	*tert*-Butyl	(−)-Sparteine	[c]

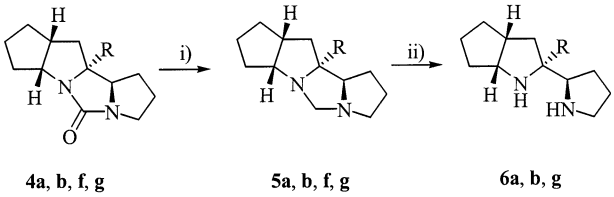
[a] Substrate/N-Boc-pyrrolidine ratio of 1:1.16. [b] Substrate/N-Boc-pyrrolidine ratio of 1:1.16. [c] No reaction.

side of the bicyclic molecule, in accordance with the results of the X-ray crystal structure analysis. For this direction of nucleophilic attack different diastereomeric interactions of the optically active imine **4a** with the two enantiomeric organolithium compounds are possible. For the (*R*)-configured *N*-Boc-pyrrolidin-2-yllithium strong interactions with the exposed bridgehead hydrogen atoms of the bicyclic system can be expected. Because there is no possibility for nucleophilic attack to the C=N double bond, side-reactions such as enolisation and metalloenamine formation can occur, resulting in recovery of the starting material after hydrolysis.[16] These interactions and complications are avoided by the use of the (*S*)-configured organolithium compound, which is manifested in the higher yields of the reaction.

After this preliminary work on optimization of the reaction conditions we tested different substituted bicyclic ketimines **3c**−**k** as substrates for the nucleophilic addition reaction in order to get more information about the scope and limitation of this synthetic procedure (entry 6−14). The methyl- and the *tert*-butyl-substituted ketimines **3j** and **3k** gave no reaction at all, probably because of formation of the corresponding metalloenamine with the methylimine and the steric bulkiness of the *tert*-butyl derivative; only the starting materials could be isolated from the reaction mixture. In order to avoid enolisation, and for increased reactivity of the C=N double bond, $BF_3{\cdot}Et_2O$ was added.[17] However, no positive effect of the Lewis acid was detected. Similar results were observed with the 2-methylphenyl ketimine **3d** and the ketimine **3i** with a sterically demanding 1-naphthyl subunit as substrate. The other aromatic-substituted ketimines reacted with *N*-Boc-pyrrolidin-2-yllithium with isolated yields of between 6 and 56%. In all cases where an addition of the nucleophile took place, only one diastereomer was detected by NMR spectroscopy of the crude reaction products.

The substitution pattern of the aromatic ring system seems to have an important influence on the yields obtained with aromatic ketimines **3a**−**i**. The experimental results, if compared to each other, cannot be explained only by steric factors without taking into account mesomeric canonical structures and inductive field effects of the substituents in the aromatic ring. For example, the addition of *N*-Boc-pyrrolidine-2-yllithium to the 4-methoxyphenyl-ketimine **3e** takes place in a low yield of only 6%, compared to the 47% obtained with the 4-methylphenyl ketimine **3b**. Similar observations were made with the 2-methylphenyl-substituted imine **3d**, where no reaction was achieved, and the 2-methoxyphenyl imine **3g**, which gave 42% of the expected 1,3-imidazolidin-2-one **4g**.

The next step to be examined was the conversion of the 1,3-imidazolidin-2-one system **4** into the desired diamines **6**. Simple hydrolysis of **4a** under acidic[18] or basic[19] conditions either at room temperature or with heating was unsuccessful. We therefore decided to convert the 1,3-imidazolidin-2-ones **4a**,**b**,**f**,**g** into a compound that could be hydrolysed more easily. Reduction of the 1,3-imidazolidin-2-ones **4a**,**b** and **4f**,**g** with $LiAlH_4$ in refluxing THF furnished, after 12 h, the aminals **5a**,**b** and **5f**,**g** in good yields (86−89%). Treatment with dilute aqueous hydrochloric acid at room temperature or at reflux gave the desired diamines **6a**,**b** and **6g** (Scheme 3). In the case of the 3-methoxyphenyl-substituted aminal **5f** total decomposition of the starting material was observed, giving a complex mixture that could not be separated into single compounds.



Scheme 3. i) $LiAlH_4$, THF, reflux, 12 h, yields: 86−89%; ii) 3 M HCl, room temperature or reflux, yields: 72−96%

Conclusion

A highly diastereoselective addition of *N*-Boc-pyrrolidin-2-yllithium to optically active ketimines **3** was demonstrated. A kinetic resolution of the racemic organometallic compound by the optically active substrate during the reaction was observed, as confirmed by an X-ray crystal structure analysis of 1,3-imidazolidin-2-one (**4b**) and variation of the reaction conditions of the addition of the chiral organolithium reagent to the ketimines **3a** and **3b**. The conversion into diamines **6a**,**b** and **6g** was achieved by reduction of the tetracyclic 1,3-imidazolidin-2-ones **4a**,**b** and **4f**,**g** to the aminals **5a**,**b** and **5f**,**g** with $LiAlH_4$ and subsequent hydrolysis with dilute HCl. Further investigations on the use of the synthesized diamines in enantioselective catalysis are in progress.

Experimental Section

General Remarks: Experiments involving organometallic reagents were carried out in oven-dried, evacuated glassware under a positive pressure of dry argon. THF and Et_2O were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium chloride. Analytical thin layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} aluminium sheets. TLC spots were detected with UV light and iodine. Column chromatography was performed using silica gel 60 (particle size 0.040−0.063 mm) from Merck. Melting points (uncorrected) were determined in open capillaries using an apparatus according to Dr. Lindström. Infrared spectra were recorded using a Beckman IR 4220 spectrometer as KBr discs for solids or as films between NaCl plates for liquids. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 or a Bruker ARX 500 spectrometer. The chemical shifts are reported in ppm relative to residual nondeuterated solvent or tetramethylsilane (TMS) in $CDCl_3$ as solvent. Coupling constants, *J*, are given in Hz. Optical rotations were measured with a Perkin−Elmer polarimeter 241 MC and mass spectra were measured with a Finnigan-MAT 212 (datasystem SS 300) spectrometer. Elemental analyses were performed with a C,H,N Analyser EA 1108 from Fisons Instruments.

Typical Procedure for the Synthesis of the *N*-Boc-amino Ketones 2: A solution of the *N*-Boc-protected lactam **1**[12] (5.62 g, 25 mmol) in THF (90 mL) at room temperature was added to a solution of the appropriate Grignard reagent, prepared from the alkyl or aryl halide (27 mmol) and Mg (30 mmol) in THF (90 mL). The mixture was stirred until TLC showed no more starting material (normally 24 to 72 h). After hydrolysis with satd. NH_4Cl (50 mL) at 0 °C the phases were separated and the aqueous layer was extracted with ether (3 × 30 mL). After washing the combined organic extracts with brine (50 mL) the organic layer was dried ($MgSO_4$) and concentrated in vacuo. The resulting crude Boc-protected amino ketones **2** were obtained as yellow viscous oils and were purified by column chromatography.

(*all-R*)-*tert*-Butyl-2-(2-oxo-2-phenylethyl)cyclopentyl Carbamate (2a): Purification by column chromatography (*n*-hexane/ethyl acetate 6:1) gave 3.18 g (42%) of **2a** as a colourless oil. $[\alpha]_D^{20}$ = +16.7 (*c* = 1.00, CH_2Cl_2). IR (NaCl): $\tilde{\nu}$ = 3450, 2990, 1690, 750 cm^{-1}. ^1H NMR: δ = 1.15−2.01 (m, 6 H), 1.45 (s, 9 H), 2.51 (m, 1 H), 2.72 (m, 1 H), 3.21 (m, 1 H), 4.05 (m, 1 H), 4.45 (s, 1 H), 7.33−7.49 (m, 3 H), 7.99 (d, *J* = 7.7 Hz, 2 H). ^{13}C NMR: δ = 21.7, 27.9, 28.2, 29.1, 31.9, 38.9, 54.2, 79.0, 127.5, 128.0, 132.7, 137.0, 155.5, 199.8. MS (CI, *i*-butane): *m*/*z* (%) = 304 (80), 248 (100). $C_{18}H_{25}NO_3$ (303.2): calcd. C 71.26, H 8.31, N 4.62; found C 71.01, H 8.25, N 4.34.

(*all-R*)-*tert*-Butyl-2-[2-(4-methylphenyl)ethyl-2-oxo]cyclopentyl Carbamate (2b): Purification by column chromatography (*n*-hexane/ethyl acetate 9:1) gave 1.32 g (42%) of **2b** as a colourless solid from 2.25 g of lactam **1**. M.p. 65−69 °C. $[\alpha]_D^{20}$ = +15.8 (*c* = 3.69, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3450, 2950, 1760, 1660, 750 cm^{-1}. ^1H NMR: δ = 1.19−2.09 (m, 6 H), 1.43 (s, 9 H), 2.39 (s, 3 H), 2.62 (m, 1 H), 2.68 (m, 1 H), 3.29 (d, *J* = 14.7 Hz, 1 H), 4.10 (m, 1 H), 4.46 (s, 1 H), 7.21 (d, *J* = 7.9 Hz, 2 H), 7.82 (d, *J* = 7.9 Hz, 2 H). ^{13}C NMR: δ = 21.7, 21.8, 28.0, 29.2, 32.1, 38.9, 39.4, 54.4, 79.3, 128.3, 129.2, 134.7, 143.6, 155.6, 199.6. MS (CI, *i*-butane): *m*/*z* (%) = 262 (100), 318 (75). $C_{19}H_{27}NO_3$ (317.2): calcd. C 71.89, H 8.57, N 4.41; found C 71.85, H 8.61, N 4.21.

(*all-R*)-*tert*-Butyl-2-[2-(3-methylphenyl)ethyl-2-oxo]cyclopentyl Carbamate (2c): Purification by column chromatography (*n*-hexane/ethyl acetate 9:1, with 1% Et_3N) gave 4.50 g (57%) of **2c** as a colourless viscous oil which solidified on standing in a refrigerator. M.p. slow melting at room temperature. $[\alpha]_D^{20}$ = +18.9 (*c* = 0.87, CH_2Cl_2). IR (NaCl): $\tilde{\nu}$ = 3400, 2950, 1680, 750 cm^{-1}. ^1H NMR: δ = 1.19−2.05 (m, 6 H), 1.44 (s, 9 H), 2.39 (s, 3 H), 2.65 (m, 1 H), 2.74 (m, 1 H), 3.32 (m, 1 H), 4.11 (m, 1 H), 4.50 (s, 1 H), 7.32 (m, 2 H), 7.82 (m, 2 H). ^{13}C NMR: δ = 21.2, 21.7, 28.3, 29.1, 32.0, 38.9, 39.3, 54.3, 79.1, 125.3, 128.3, 128.6, 133.5, 137.2, 138.2, 155.6, 199.9. MS (CI, *i*-butane): *m*/*z* (%) = 318 (80), 262 (100). $C_{19}H_{27}NO_3$ (317.2): calcd. C 71.89, H 8.57, N 4.41; found C 71.65, H 8.63, N 4.32.

(*all-R*)-*tert*-Butyl-2-[2-(2-methylphenyl)ethyl-2-oxo]cyclopentyl Carbamate (2d): Purification by column chromatography (*n*-hexane/ethyl acetate 4:1, with 2% Et_3N) gave 2.80 g (35%) of **2d** as a colourless oil which solidified on standing. M.p. 60−61 °C. $[\alpha]_D^{20}$ = +8.0 (*c* = 1.28, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3370, 2950, 1750, 1680, 750 cm^{-1}. ^1H NMR: δ = 1.21−2.09 (m, 6 H), 1.41 (s, 9 H), 2.49 (s, 3 H), 2.53 (m, 1 H), 2.71 (dd, *J* = 17.5, *J* = 8.8, 1 H), 3.19 (dd, *J* = 17.5, 5.1 Hz, 1 H), 4.09 (m, 1 H), 4.48 (s, 1 H), 7.18−7.39 (m, 3 H), 7.61 (d, *J* = 7.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 21.0, 21.7, 28.2, 29.2, 32.1, 39.2, 41.9, 54.0, 79.0, 125.5, 128.3, 130.9, 131.7, 137.8, 138.3, 155.5, 203.9. MS (CI, *i*-butane): *m*/*z* (%) = 318 (65), 262 (100). $C_{19}H_{27}NO_3$ (317.2): calcd. C 71.89, H 8.57, N 4.41; found C 71.76, H 8.51, N 4.37.

(*all-R*)-*tert*-Butyl-2-[2-(4-methoxyphenyl)ethyl-2-oxo]cyclopentyl Carbamate (2e): Purification by column chromatography (*n*-hexane/ethyl acetate 4:1, with 2% Et_3N) gave 4.56 g (54%) of **2e** as a colourless solid. M.p. 74−75 °C. $[\alpha]_D^{20}$ = +23.9 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3380, 2950, 1680, 1280, 830 cm^{-1}. ^1H NMR: δ = 1.21−2.05 (m, 6 H), 1.40 (s, 9 H), 2.52 (m, 1 H), 2.67 (m, 1 H), 3.29 (d, *J* = 17.0 Hz, 1 H), 3.85 (s, 3 H), 4.09 (m, 1 H), 4.61 (s, 1 H), 6.89 (d, *J* = 7.9 Hz, 2 H), 7.92 (d, *J* = 7.9 Hz, 2 H). ^{13}C NMR: δ = 21.7, 28.3, 29.2, 32.0, 38.5, 39.4, 54.3, 55.3, 79.0, 113.6, 130.2, 130.3, 155.6, 163.2, 198.5. MS (CI, *i*-butane): *m*/*z* (%) = 278 (100), 234 (43), 334 (59). $C_{19}H_{27}NO_4$ (333.2): calcd. C 68.44, H 8.16, N 4.20; found C 68.39, H 8.20, N 4.13.

(*all-R*)-*tert*-Butyl-2-[2-(3-methoxyphenyl)ethyl-2-oxo]cyclopentyl Carbamate (2f): Purification by column chromatography (*n*-hexane/ethyl acetate 4:1, with 2% Et_3N) gave 4.84 g (58%) of **2e** as a colourless solid. M.p. 52−53 °C. $[\alpha]_D^{20}$ = +18.0 (*c* = 1.57, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3350, 2950, 1760, 1660, 780 cm^{-1}. ^1H NMR: δ = 1.21−2.08 (m, 6 H), 1.39 (s, 9 H), 2.52 (m, 1 H), 2.72 (m, 1 H), 3.29 (d, *J* = 14.7 Hz, 1 H), 3.84 (s, 3 H), 4.09 (m, 1 H), 4.49 (s, 1 H), 7.08 (d, *J* = 9.8 Hz, 1 H), 7.31 (m, 1 H), 7.51 (m, 2 H). ^{13}C NMR: δ = 21.7, 28.3, 29.2, 32.1, 39.0, 39.3, 54.3, 55.4, 79.1, 112.3, 119.4, 120.7, 129.4, 138.5, 155.6, 159.8, 199.6. MS (CI, *i*-butane): *m*/*z* (%) = 234 (100), 278 (86), 334 (25). $C_{19}H_{27}NO_4$ (333.2): calcd. C 68.44, H 8.16, N 4.20; found C 68.35, H 8.22, N 4.15.

(*all-R*)-*tert*-Butyl-2-[2-(2-methoxyphenyl)ethyl-2-oxo]cyclopentyl Carbamate (2g): Workup by column chromatography (*n*-hexane/ethyl acetate 4:1, with 1% Et_3N) gave 5.30 g (64%) of **2g** as an impure colourless solid, which was used without characterization in the next step.

(*all-R*)-*tert*-Butyl-2-[2-(2-naphthyl)ethyl-2-oxo]cyclopentyl Carbamate (2h): Purification by column chromatography (*n*-hexane/ethyl acetate 4:1, with 1% Et_3N) gave 5.24 g (59%) of **2h** as a colourless crystalline solid. M.p. 126 °C. $[\alpha]_D^{20}$ = +34.8 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3400, 2950, 1700, 850, 760 cm^{-1}. ^1H NMR: δ = 1.19−2.09 (m, 6 H), 1.48 (s, 9 H), 2.59 (m, 1 H), 2.81 (m, 1 H), 3.45 (m, 1 H), 4.15 (m, 1 H), 4.52 (s, 1 H), 7.52, 7.72−8.01 (2m, 6 H), 8.46 (s, 1 H). ^{13}C NMR: δ = 21.8, 28.3, 29.10, 32.0, 39.0, 39.5, 54.3, 79.1, 123.9, 126.6, 127.7, 128.3, 129.5, 129.7, 132.5, 134.4, 135.4, 155.6, 199.8. MS (CI, *i*-butane): *m*/*z* (%) = 254 (100). $C_{22}H_{27}NO_3$ (353.2): calcd. C 74.76, H 7.70, N 3.96; found C 74.81, H 7.62, N 3.85.

(*all-R*)-*tert*-Butyl-2-[2-(1-naphthyl)ethyl-2-oxo]cyclopentyl Carbamate (2i): Purification by column chromatography (*n*-hexane/ethyl acetate 15:1, with 1% Et_3N) gave 1.45 g (42%) of **2i** as a colourless solid from 2.21 g of lactam **1**. M.p. 92−95 °C. $[\alpha]_D^{20}$ = +9.9 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3390, 2950, 1690, 780 cm^{-1}. ^1H NMR: δ = 1.33 (s, 9 H), 1.17−1.97 (m, 6 H), 2.58 (m, 1 H), 2.84 (dd, *J* = 16.5, 8.8 Hz, 1 H), 3.35 (dd, *J* = 16.5, 5.5 Hz, 1 H), 4.16 (m, 1 H), 4.54 (s, 1 H), 7.41−7.60 (m, 3 H), 7.84 (m, 2 H), 7.94 (d, *J* = 8.3, 1 H), 8.55 (d, *J* = 8.3 Hz, 1 H). ^{13}C NMR: δ = 21.7, 28.3, 29.2, 32.2, 39.5, 42.6, 54.1, 79.1, 124.3, 125.8, 126.3, 127.2, 127.6, 128.3, 130.1, 132.2, 133.9, 136.4, 155.6, 204.2. MS (*i*-butane): *m*/*z* (%) = 354 (81), 298 (100). $C_{22}H_{27}NO_3$ (353.20): calcd. C 74.76, H 7.70, N 3.96; found C 74.70, H 7.74, N 3.91.

(*all-R*)-*tert*-Butyl-2-[2-methylethyl-2-oxo]cyclopentyl Carbamate (2j): Extractive workup gave 4.79 g (80%) of **2j** as a colourless solid which was used without characterization in the next step.

(*all-R*)-*tert*-Butyl-2-[2-*tert*-butylethyl-2-oxo]cyclopentyl Carbamate (2k): Purification by column chromatography (*n*-hexane/ethyl acetate 5:1, with 1% Et_3N) gave 1.09 g (15%) of **2k** as a colourless solid.

M.p. 74−76 °C. $[\alpha]_D^{20}$ = +13.1 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3350, 2950, 1680 cm^{-1}. ^1H NMR: δ = 1.01−1.97 (m, 6 H), 1.08 (s, 9 H), 1.41 (s, 9 H), 2.33 (m, 2 H), 2.69 (m, 1 H), 4.00 (m, 1 H), 4.40 (s, 1 H). ^{13}C NMR: δ = 21.7, 26.4, 28.3, 29.2, 32.3, 36.7, 38.6, 44.2, 53.9, 77.4, 155.5, 215.2. MS (CI, *i*-butane): *m*/*z* (%) = 228 (100), 284 (72), 184 (29). $C_{16}H_{29}NO_3$ (283.2): calcd. C 67.81, H 10.31, N 4.94; found C 67.70, H 10.25, N 4.81.

Typical Procedure for the Synthesis of the Ketimines 3: Trifluoroacetic acid (30 mL) was added dropwise at 0 °C to a stirred solution of the *N*-Boc-amino ketone **2** (12 mmol) in CH_2Cl_2 (35 mL). After complete addition the reaction mixture was allowed to warm to room temperature and stirring was continued for a further 3 h. The reaction flask was cooled again to 0 °C and the mixture was then basified by addition of aqueous NaOH (35% solution). The phases were separated and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow or brown oils were purified by column chromatography.

(*all-R*)-2-Phenyl-3,3a,4,5,6,6a-hexahydrocyclopenta[*b*]pyrrole (3a):[20] Purification by column chromatography (*n*-hexane/ethyl acetate 4:1, with 2% Et_3N) gave 0.39 g (69%) of **3a** as a pale yellow oil from 0.91 g of amino ketone **2a**. $[\alpha]_D^{20}$ = +35.7 (*c* = 1.00, CH_2Cl_2). IR (NaCl): $\tilde{\nu}$ = 2950, 1610, 750 cm^{-1}. ^1H NMR: δ = 1.24−1.99 (m, 6 H), 2.71 (dd, *J* = 17.1, 5.4 Hz, 1 H), 2.81 (m, 1 H), 3.20 (dd, *J* = 17.1, 9.3 Hz, 1 H), 4.77 (m, 1 H), 7.35 (m, 3 H), 7.81 (m, 2 H). ^{13}C NMR: δ = 24.0, 33.2, 34.9, 39.0, 43.9, 79.4, 127.6, 128.2, 130.1, 134.5, 171.3. MS (*i*-butane): *m*/*z* (%) = 186 (100). $C_{13}H_{15}N$ (185.1): calcd. C 84.28, H 8.16, N 7.56; found C 84.36, H 8.06, N 7.49.

(*all-R*)-2-(4-Methylphenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta-[*b*]pyrrole (3b): Purification by column chromatography (*n*-hexane/ethyl acetate 3:1, with 1% Et_3N) gave 2.72 g (55%) of **3b** as a colourless solid from 6.31 g of crude amino ketone **2b**. M.p. 39−40 °C. $[\alpha]_D^{20}$ = +35.6 (*c* = 1.49, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1620, 800 cm^{-1}. ^1H NMR: δ = 1.32−1.95 (m, 6 H), 2.36 (s, 3 H), 2.69 (dd, *J* = 17.5, 2.8 Hz, 1 H), 2.79 (m, 1 H), 3.19 (dd, *J* = 17.5, 9.9 Hz, 1 H), 4.75 (m, 1 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 7.70 (d, *J* = 7.8 Hz, 2 H). ^{13}C NMR: δ = 21.3, 24.1, 33.3, 34.9, 39.0, 44.0, 79.4, 127.6, 129.0, 131.9, 140.3, 171.1. MS (*i*-butane): *m*/*z* (%) = 200 (100). $C_{14}H_{17}N$ (199.1): calcd. C 84.37, H 8.60, N 7.03; found C 84.12, H 8.72, N 6.95.

(*all-R*)-2-(3-Methylphenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta-[*b*]pyrrole (3c): Purification by column chromatography (*n*-hexane/ethyl acetate 4:1) gave 2.16 g (65%) of **3b** as a yellow oil from 5.32 g of crude amino ketone **2c**. $[\alpha]_D^{20}$ = +29.1 (*c* = 1.48, CH_2Cl_2). IR (NaCl): $\tilde{\nu}$ = 2950, 1620, 750 cm^{-1}. ^1H NMR: δ = 1.31−1.99 (m, 6 H), 2.36 (s, 3 H), 2.70 (dd, *J* = 17.1, 2.5 Hz, 1 H), 2.79 (m, 1 H), 3.28 (dd, *J* = 17.1, 9.7 Hz, 1 H), 4.78 (m, 1 H), 7.22 (m, 2 H), 7.53 (d, *J* = 7.8 Hz, 1 H), 7.68 (s, 1 H). ^{13}C NMR: δ = 22.3, 25.2, 34.4, 36.0, 40.1, 45.1, 80.5, 126.0, 129.26, 129.27, 132.0, 135.6, 139.1, 172.6. MS (*i*-butane): *m*/*z* (%) = 200 (100). $C_{14}H_{17}N$ (199.1): calcd. C 84.37, H 8.60, N 7.03; found C 84.22, H 8.73, N 7.09.

(*all-R*)-2-(2-Methylphenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta-[*b*]pyrrole (3d): Purification by column chromatography (*n*-hexane/ethyl acetate 1:1, with 1% Et_3N) gave 1.40 g (75%) of **3b** as a pale yellow oil from 2.95 g of amino ketone **2d**. $[\alpha]_D^{20}$ = +24.1 (*c* = 0.64, CH_2Cl_2). IR (NaCl): $\tilde{\nu}$ = 2950, 1620, 750 cm^{-1}. ^1H NMR: δ = 1.33−2.01 (m, 6 H), 2.48 (s, 3 H), 2.62 (dd, *J* = 17.6, 2.7 Hz, 1 H), 2.73 (m, 1 H), 3.20 (dd, *J* = 17.6, 9.9 Hz, 1 H), 4.78 (m, 1 H), 7.19 (m, 3 H), 7.32 (d, *J* = 7.7 Hz, 1 H). ^{13}C NMR: δ = 21.2, 24.0, 33.3, 34.9, 38.8, 47.6, 80.0, 125.4, 128.5, 128.7, 131.0, 135.3, 136.7, 173.3. MS (CI, *i*-butane): *m*/*z* (%) = 200 (100). $C_{14}H_{17}N$ (199.1): calcd. C 84.37, H 8.60, N 7.03; found C 84.33, H 8.72, N 6.98.

(*all-R*)-2-(4-Methoxyphenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta-[*b*]pyrrole (3e): Purification by column chromatography (*n*-hexane/ethyl acetate 2:1, with 1% Et_3N) gave 1.68 g (91%) of **3e** as a colourless solid from 3.00 g of amino ketone **2e**. M.p. 45−46 °C. $[\alpha]_D^{20}$ = +31.1 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1630, 1270, 850 cm^{-1}. ^1H NMR: δ = 1.29−1.95 (m, 6 H), 2.67 (d, *J* = 17.3 Hz, 1 H), 2.76 (m, 1 H), 3.15 (dd, *J* = 17.3, *J* = 9.8, 1 H), 3.79 (s, 3 H), 4.71 (m, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 7.74 (d, *J* = 8.7 Hz, 2 H). ^{13}C NMR: δ = 23.9, 33.2, 34.7, 38.9, 43.7, 55.1, 79.1, 113.4, 127.2, 129.1, 161.0, 170.4. MS (CI, *i*-butane): *m*/*z* (%) = 216 (100). $C_{14}H_{17}NO$ (215.3): calcd. C 78.10, H 7.96, N 6.51; found C 77.96, H 7.88, N 6.47.

(*all-R*)-2-(3-Methoxyphenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta-[*b*]pyrrole (3f): Purification by column chromatography (*n*-hexane/ethyl acetate 1:1) gave 2.23 g (81%) of **3f** as a pale yellow oil from 4.28 g of amino ketone **2f**. $[\alpha]_D^{20}$ = +25.8 (*c* = 0.79, CH_2Cl_2). IR (NaCl): $\tilde{\nu}$ = 2950, 1600, 1260, 750 cm^{-1}. ^1H NMR: δ = 1.32−1.98 (m, 6 H), 2.79 (dd, *J* = 17.7, 2.6 Hz, 1 H), 2.80 (m, 1 H), 3.20 (dd, *J* = 17.7, 9.8 Hz, 1 H), 3.83 (s, 3 H), 4.78 (m, 1 H), 6.95 (d, *J* = 7.9 Hz, 1 H), 7.29 (m, 2 H), 7.52 (s, 1 H). ^{13}C NMR: δ = 24.1, 33.2, 34.9, 39.0, 44.1, 55.3, 79.5, 112.0, 116.7, 120.4, 129.2, 136.0, 159.6, 171.2. MS (CI, *i*-butane): *m*/*z* (%) = 216 (100). $C_{14}H_{17}NO$ (215.3): calcd. C 78.10, H 7.96, N 6.51; found C 78.01, H 7.89, N 6.60.

(*all-R*)-2-(2-Methoxyphenyl)-3,3a,4,5,6,6a-hexahydrocyclopenta-[*b*]pyrrole (3g): Purification by column chromatography (*n*-hexane/ethyl acetate 1:1, with 1% Et_3N) gave 2.30 g (80%) of **3g** as a colourless solid from 4.42 g of amino ketone **2g**. M.p. 45 °C. $[\alpha]_D^{20}$ = +61.1 (*c* = 1.56, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1600, 1230, 760 cm^{-1}. ^1H NMR: δ = 1.30−1.98 (m, 6 H), 2.75 (m, 2 H), 3.25 (dd, *J* = 13.2, 9.8 Hz, 1 H), 3.82 (s, 3 H), 4.67 (m, 1 H), 6.89 (m, 2 H), 7.29 (m, 1 H), 7.71 (d, *J* = 7.7 Hz, 1 H). ^{13}C NMR: δ = 24.0, 33.3, 34.9, 39.4, 47.4, 55.4, 78.2, 111.2, 120.6, 130.0, 130.8, 125.01, 158.0, 172.0. MS (CI, *i*-butane): *m*/*z* (%) = 216 (100). $C_{14}H_{17}NO$ (215.3): calcd. C 78.10, H 7.96, N 6.51; found C 78.03, H 7.71, N 6.42.

(*all-R*)-2-(2-Naphthyl)-3,3a,4,5,6,6a-hexahydrocyclopenta[*b*]pyrrole (3h): Purification by column chromatography (*n*-hexane/ethyl acetate 1:1, with 1% Et_3N) gave 1.52 g (57%) of **3h** as a pale yellow solid from 3.04 g of amino ketone **2h**. M.p. 94−95 °C. $[\alpha]_D^{20}$ = +79.7 (*c* = 0.50, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1600, 820, 750 cm^{-1}. ^1H NMR: δ = 1.30−2.01 (m, 6 H), 2.79 (m, 2 H), 3.29 (dd, *J* = 13.4, 8.7 Hz, 1 H), 4.82 (m, 1 H), 7.46, 7.81, 8.03 (3m, 6 H), 8.10 (s, 1 H). ^{13}C NMR: δ = 24.6, 33.8, 35.4, 39.6, 44.4, 83.1, 125.2, 126.7, 127.4, 128.1, 128.4, 128.5, 129.1, 132.6, 133.4, 134.7, 171.8. MS (CI, *i*-butane): *m*/*z* (%) = 236 (100). $C_{17}H_{17}N$ (235.1): calcd. C 86.77, H 7.28, N 5.95; found C 86.53, H 7.21, N 5.89.

(*all-R*)-2-(1-Naphthyl)-3,3a,4,5,6,6a-hexahydrocyclopenta[*b*]pyrrole (3i): Purification by column chromatography (*n*-hexane/ethyl acetate 1:2) gave 0.73 g (73%) of **3h** as a yellow solid from 1.45 g of amino ketone **2i**. M.p. 58−60 °C. $[\alpha]_D^{20}$ = −28.4 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1600, 750 cm^{-1}. ^1H NMR: δ = 1.39−2.14 (m, 6 H), 2.71 (m, 1 H), 2.78 (dd, *J* = 18.1, 5.5 Hz, 1 H), 3.35 (dd, *J* = 18.1, 10.45 Hz, 1 H), 4.94 (m, 1 H), 7.37−7.59 (m, 4 H), 7.82 (d, *J* = 8.3 Hz, 2 H), 8.88 (d, *J* = 8.3 Hz, 1 H). ^{13}C NMR: δ = 24.1, 33.4, 34.9, 38.5, 47.8, 80.6, 124.6, 125.9, 126.4, 126.88, 126.94, 128.2, 129.9, 131.0, 132.5, 133.9, 172.4. MS (CI, *i*-butane): *m*/*z*

(%) = 236 (100). $C_{17}H_{17}N$ (235.1): calcd. C 86.77, H 7.28, N 5.95; found C 86.65, H 7.22, N 5.86.

(*all-R*)-2-Methyl-3,3a,4,5,6,6a-hexahydrocyclopenta[*b*]pyrrole (3j): Extractive workup gave 1.10 g (45%) of the crude imine **3j** from 4.79 g of amino ketone **2j**. Purification was achieved by distillation with significant loss of product, so the crude imine was used in the next step. B.p. 130 °C (150 mbar). $[\alpha]_D^{20}$ = +116.8 (*c* = 1.50, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1600 cm^{-1}. ^1H NMR: δ = 1.26−1.83 (m, 6 H), 1.97 (s, 3 H), 2.20 (d, *J* = 17.6 Hz, 1 H), 2.66 (m, 1 H), 2.78 (dd, *J* = 17.6, 9.9 Hz, 1 H), 4.51 (m, 1 H). ^{13}C NMR: δ = 19.3, 23.8, 32.9, 34.7, 39.4, 47.8, 78.8, 173.3. MS (CI, *i*-butane): *m*/*z* (%) = 124 (100). $C_8H_{13}N$ (123.1): calcd. C 77.99, H 10.64, N 11.37; found C 77.61, H 10.45, N 11.42.

(*all-R*)-2-*tert*-Butyl-3,3a,4,5,6,6a-hexahydrocyclopenta[*b*]pyrrole (3k): Extractive workup gave 0.37 g (57%) of the crude imine **3k** from 1.23 g of amino ketone **2k**. $[\alpha]_D^{20}$ = +27.0 (*c* = 1.06, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1600 cm^{-1}. ^1H NMR: δ = 1.01−1.82 (m, 6 H), 1.15 (s, 9 H), 2.30 (d, *J* = 17.5 Hz, 1 H), 2.63 (m, 1 H), 2.81 (dd, *J* = 17.5, 9.7 Hz, 1 H), 4.52 (m, 1 H). ^{13}C NMR: δ = 23.9, 28.3, 33.3, 34.9, 35.5, 39.0, 42.3, 78.6, 183.0. MS (CI, *i*-butane): *m*/*z* (%) = 166 (100). $C_{11}H_{19}N$ (165.2): calcd. C 79.94, H 11.59, N 8.47; found C 79.88, H 11.42, N 8.62.

Typical Procedure for the Preparation of the 1,3-Imidazolidin-2-ones 4: *sec*-butyllithium (5.8 mL, 7.54 mmol of a 1.3 M solution in cyclohexane) was added at −78 °C to a stirred solution of *N*-Boc-pyrrolidine (0.99 g, 5.8 mmol) and diamine [(−)-sparteine or TMEDA), 7.54 mmol] in ether (16 mL). The resulting clear, pale-yellow solution was left for 4 h at constant temperature before the ketimine **3** (5 mmol) in ether (4 mL) was added by syringe at −78 °C. After further stirring at constant temperature for 12 h the reaction was allowed to reach −30 °C and was then hydrolysed by addition of water (20 mL). Warming to room temperature was followed by phase separation. The aqueous layer was extracted with ether (3 × 15 mL) and the combined organic extracts were subsequently washed with 2 M HCl (3 × 30 mL), satd. $NaHCO_3$ (2 × 30 mL) and once with brine (30 mL). After drying over $MgSO_4$ the solvent was removed in vacuo and the resulting oil or solid was purified by column chromatography or by recrystallisation.

(3a*R*,7a*R*,7b*R*,8a*R*)-7b-Phenyldecahydro-3b,4a-diazadicyclopenta[*a*,*e*]pentalen-4-one (4a): Purification by column chromatography (*n*-hexane/ethyl acetate 1:1, with 2% Et_3N) gave 0.68 g (48%) of **4a** as a colourless solid from ketimine **3a**. M.p. 159−160 °C. $[\alpha]_D^{20}$ = −2.9 (*c* = 1.06, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1680, 750 cm^{-1}. ^1H NMR: δ = 0.96−2.03 (m, 10 H), 2.20 (dd, *J* = 13.4, 2.6 Hz, 1 H), 2.35 (dd, *J* = 13.4, 9.6 Hz, 1 H), 2.72 (m, 1 H), 2.92 (ddd, *J* = 12.7, 8.9, 3.8 Hz, 1 H); 3.44 (dd, *J* = 9.5, 5.7 Hz, 1 H), 3.72 (ddd, *J* = 12.7, 8.9, 3.8 Hz, 1 H), 4.53 (m, 1 H), 7.21−7.49 (m, 5 H). ^{13}C NMR: δ = 24.5, 25.3, 27.5, 32.0, 33.2, 39.5, 44.2, 44.6, 63.3, 72.5, 72.7, 125.0, 126.7, 128.3, 148.1, 165.8. MS (CI, *i*-butane): *m*/*z* (%) = 283 (100). $C_{18}H_{22}N_2O$ (282.2): calcd. C 76.56, H 7.85, N 9.92; found C 76.49, H 7.83, N 9.90.

(3a*R*,7a*R*,7b*R*,8a*R*)-7b-(4-Methylphenyl)decahydro-3b,4a-diazadicyolopenta[*a*,*e*]pentalen-4-one (4b): Recrystallisation from ethyl acetate/*n*-hexane gave 0.70 g (47%) of **4b** as colourless needles from ketimine **3b**. M.p. 130−132 °C. $[\alpha]_D^{20}$ = −54.2 (*c* = 1.03, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1660, 750 cm^{-1}. ^1H NMR: δ = 0.99−1.98 (m, 10 H), 2.18 (dd, *J* = 13.3, 2.8 Hz, 1 H), 2.32 (dd, *J* = 13.3, 7.3 Hz, 1 H), 2.35 (s, 3 H), 2.72 (m, 1 H), 2.91 (m, 1 H), 3.42 (dd, *J* = 9.7, 5.7 Hz, 1 H), 3.71 (m, 1 H), 4.51 (m,1 H), 7.13 (d, *J* = 7.9 Hz, 2 H), 7.34 (d, *J* = 7.9 Hz, 2 H). ^{13}C NMR: δ = 20.9, 24.7, 25.5, 27.6, 32.2, 33.3, 39.5, 44.3, 44.7, 63.3, 72.6, 72.7, 125.1, 129.1, 136.4, 145.3, 165.9. MS (CI, *i*-butane): *m*/*z* (%) = 297 (100). $C_{19}H_{24}N_2O$ (296.2): calcd. C 76.99, H 8.16, N 9.45; found C 76.87, H 8.12, N 9.34.

(3a*R*,7a*R*,7b*R*,8a*R*)-7b-(3-Methylphenyl)decahydro-3b,4a-diazadicyclopenta[*a*,*e*]pentalen-4-one (4c): Recrystallisation from ethyl acetate/*n*-hexane gave 0.23 g (26%) of **4c** as colourless needles from 0.60 g of ketimine **3c**. M.p. 169−171 °C. $[\alpha]_D^{20}$ = −61.2 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1660, 750 cm^{-1}. ^1H NMR: δ = 0.97−1.99 (m, 10 H), 2.19 (dd, *J* = 13.3, 2.9 Hz, 1 H), 2.32 (dd, *J* = 13.3, 9.5 Hz, 1 H), 2.35 (s, 3 H), 2.74 (m, 1 H), 2.92 (ddd, *J* = 11.3, 9.1, 3.8 Hz, 1 H), 3.49 (dd, *J* = 9.8, 5.6 Hz, 1 H), 3.72 (m, 1 H), 4.51 (m, 1 H), 7.02 (d, *J* = 6.9 Hz, 1 H), 7.25 (m, 3 H). ^{13}C NMR: δ = 21.5, 24.6, 25.4, 27.6, 32.1, 33.2, 39.7, 44.3, 44.7, 63.4, 72.6, 72.7, 122.2, 125.8, 127.5, 128.3, 138.0, 148.3, 166.0. MS (CI, *i*-butane): *m*/*z* (%) = 297 (100). $C_{19}H_{24}N_2O$ (296.2): calcd. C 76.99, H 8.16, N 9.45; found C 76.89, H 8.11, N 9.52.

(3a*R*,7a*R*,7b*R*,8a*R*)-7b-(4-Methoxyphenyl)decahydro-3b,4a-diazadicyclopenta[*a*,*e*]pentalen-4-one (4e): Purification by column chromatography (*n*-hexane/ethyl acetate 1:1, with 2% Et_3N) gave 0.10 g (6%) of **4e** as a yellow viscous oil from **3e**. $[\alpha]_D^{20}$ = −42.4 (*c* = 0.53, CH_2Cl_2). IR (NaCl): $\tilde{\nu}$ = 2950, 1680, 750 cm^{-1}. ^1H NMR: δ = 0.95−1.95 (m, 10 H), 2.18 (dd, *J* = 13.2, 2.6 Hz, 1 H), 2.29 (dd, *J* = 13.2, 9.4 Hz, 1 H), 2.72 (m, 1 H), 2.90 (m, 1 H), 3.40 (dd, *J* = 9.4, 5.3 Hz, 1 H), 3.71 (m, 1 H), 3.79 (s, 3 H), 4.50 (m, 1 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 7.36 (d, *J* = 8.7 Hz, 2 H). ^{13}C NMR: δ = 24.7, 25.4, 27.5, 32.1, 33.3, 39.4, 44.3, 44.6, 55.1, 63.3, 72.4, 72.7, 113.6, 126.2, 140.2, 158.4, 165.9. MS (CI, *i*-butane): *m*/*z* (%) = 313 (100). $C_{19}H_{24}N_2O_2$ (312.2): calcd. C 73.05, H 7.74, N 8.97; found C 72.95, H 7.61, N 9.05.

(3a*R*,7a*R*,7b*R*,8a*R*)-7b-(3-Methoxyphenyl)decahydro-3b,4a-diazadicyclopenta[*a*,*e*]pentalen-4-one (4f): Purification by column chromatography (*n*-hexane/ethyl acetate 1:1, with 2% Et_3N) gave 0.88 g (56%) of **4f** as a colourless oil which solidified on standing. M.p. 110 °C. $[\alpha]_D^{20}$ = −58.1 (*c* = 1.14, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1670, 750 cm^{-1}. ^1H NMR: δ = 0.98−1.97 (m, 10 H), 2.19 (dd, *J* = 13.2, 2.8 Hz, 1 H), 2.32 (dd, *J* = 13.2, 9.3 Hz, 1 H), 2.73 (m, 1 H), 2.93 (ddd, *J* = 11.0, 8.8, 3.3 Hz, 1 H), 3.46 (dd, *J* = 9.9, 5.5 Hz, 1 H), 3.71 (m, 1 H), 3.81 (s, 3 H), 4.53 (m, 1 H), 6.78 (dd, *J* = 7.7, 2.7, 1 H), 7.03, 7.26 (2 m, 3 H). ^{13}C NMR: δ = 24.7, 25.5, 27.6, 32.1, 33.3, 39.5, 44.3, 44.6, 55.2, 63.4, 72.3, 73.0, 111.1, 112.0, 117.5, 129.5, 150.1, 159.7, 166.0. MS (CI, *i*-butane): *m*/*z* (%) = 313 (100). $C_{19}H_{24}N_2O_2$ (312.2): calcd. C 73.05, H 7.74, N 8.97; found C 72.98, H 7.69, N 9.03.

(3a*R*,7a*R*,7b*R*,8a*R*)-7b-(2-Methoxyphenyl)decahydro-3b,4a-diazadicyclopenta[*a*,*e*]pentalen-4-one (4g): Purification by column chromatography (*n*-hexane/ethyl acetate 1:1, with 2% Et_3N) gave 0.97 g (42%) **4g** as colourless crystals from 1.59 g of imine **3g**. M.p. 115−116 °C. $[\alpha]_D^{20}$ = −87.8 (*c* = 1.00, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1660, 750 cm^{-1}. ^1H NMR: δ = 1.12−1.99 (m, 11 H), 2.67 (m, 2 H), 2.89 (ddd, *J* = 11.5, 9.9, 3.3 Hz, 1 H), 3.47 (dd, *J* = 11.0, 4.9 Hz, 1 H), 3.73 (ddd, *J* = 11.5, 8.3, 2.8 Hz, 1 H), 3.85 (s, 3 H), 4.52 (m, 1 H), 6.91 (m, 2 H), 7.25 (dt, *J* = 7.7, 1.7 Hz, 1 H), 7.59 (dd, *J* = 7.7, 1.7 Hz, 1 H). ^{13}C NMR: δ = 23.9, 25.0, 28.0, 32.4, 32.8, 42.2, 44.4, 44.5, 55.1, 63.9, 71.1, 72.3, 110.8, 120.1, 125.1, 128.1, 136.9, 155.7, 166.7. MS (CI, *i*-butane): *m*/*z* (%) = 313 (100). $C_{19}H_{24}N_2O_2$ (312.2): calcd. C 73.05, H 7.74, N 8.97; found C 73.00, H 7.70, N 8.92.

(3a*R*,7a*R*,7b*R*,8a*R*)-7b-(2-Naphthyl)decahydro-3b,4a-diazadicyclopenta[*a*,e]pentalen-4-one (4h): Purification by column chromatography (*n*-hexane/ethyl acetate 1:1) gave 0.46 g (14%) of **4h** as a pale-yellow solid from 2.35 g of imine **3h**. M.p. 121−122 °C. $[\alpha]_D^{20}$ =

−31.8 (c = 1.13, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 1660, 750 cm^{-1}. ^1H NMR: δ = 0.95−2.01 (m, 10 H), 2.28 (dd, J = 13.2, 3.0 Hz, 1 H), 2.41 (dd, J = 13.2, 9.4 Hz, 1 H), 2.75 (m, 1 H), 2.91 (m, 1 H), 3.45 (dd, J = 9.8, 5.7 Hz, 1 H), 3.71 (m, 1 H), 4.57 (m, 1 H), 7.45 (m, 3 H), 7.81 (m, 3 H), 7.92 (s, 1 H). ^{13}C NMR: δ = 24.6, 25.4, 27.6, 32.2, 33.3, 39.6, 44.3, 44.7, 63.5, 72.4, 73.0, 123.3, 124.0, 125.8, 126.2, 127.5, 128.1, 128.5, 132.4, 133.0, 145.4, 166.0. MS (CI, *i*-butane): m/z (%) = 333 (100). $C_{22}H_{24}N_2O$ (332.2): calcd. C 79.48, H 7.28, N 8.43; found C 79.39, H 7.19, N 8.39.

Typical Procedure for the Synthesis of the Tetracyclic Aminals 5: The tetracyclic 1,3-imidazolidin-2-one **4** (1.59 mmol) in THF (10 mL) was added to a suspension of $LiAlH_4$ (0.49 g, 13 mmol) in THF (30 mL). The mixture was refluxed for 12 h until TLC showed no more starting material. For workup the reaction mixture was carefully hydrolysed with aqueous KOH (0.65 mL, 10% solution) and water (0.8 mL). After complete addition stirring was continued for 2 h. After filtration the precipitate was refluxed for 1 h with ethyl acetate (30 mL) and then the solid was filtered off again. The combined filtrates were dried and concentrated in vacuo. The resulting nearly colourless oil was then submitted to column chromatography.

(3a*R*,7a*R*,7b*R*,8a*R*)-7b-Phenyldecahydro-3b,4a-diazadicyclopenta[*a*,*e*]pentalene (5a) Purification by column chromatography (ethyl acetate, with 5% Et_3N) gave 0.38 g (89%) of **5a** as a pale-yellow solid from 0.49 g of 1,3-imidazolidin-2-one **4a**. M.p. 62−63 °C. $[\alpha]_D^{20}$ = +22.5 (c = 1.05, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 750 cm^{-1}. ^1H NMR: δ = 1.18−2.08 (m, 11 H), 2.65 (m, 2 H), 2.94 (m, 1 H), 3.19 (m, 1 H), 3.59 (m, 1 H), 3.74 (m, 1 H), 3.81 (d, J = 9.9 Hz, 1 H), 3.98 (d, J = 9.9 Hz, 1 H), 7.09−7.47 (m, 5 H). ^{13}C NMR: δ = 23.9, 27.0, 29.4, 33.7, 36.2, 43.4, 45.4, 56.1, 73.9, 75.59, 75.64, 79.7, 124.8, 125.8, 128.0, 149.6. MS (CI, *i*-butane): m/z (%) = 269 (100). $C_{18}H_{24}N_2$ (268.2): calcd. C 80.55, H 9.01, N 10.44; found C 80.50, H 8.98, N 10.37.

(3a*R*,7a*R*,7b*R*,8a*R*)-7b-(4-Methylphenyl)decahydro-3b,4a-diazadicyclopenta[*a*,*e*]pentalene (5b): Purification by column chromatography (ethyl acetate, with 5% Et_3N) gave 0.55 g (88%) of **5b** as a colourless oil from 0.70 g of 1,3-imidazolidin-2-one **4b**. $[\alpha]_D^{20}$ = +25.8 (c = 0.68, CH_2Cl_2). IR (NaCl): $\tilde{\nu}$ = 2950, 800 cm^{-1}. ^1H NMR: δ = 1.15−2.09 (m, 11 H), 2.27 (s, 3 H), 2.59 (m, 2 H), 2.92 (m, 1 H), 3.17 (m, 1 H), 3.55 (m, 1 H), 3.74 (m, 1 H), 3.78 (d, J = 9.8 Hz, 1 H), 3.99 (d, J = 9.8 Hz, 1 H), 7.06 (d, J = 7.9 Hz, 2 H), 7.34 (d, J = 7.9 Hz, 2 H). ^{13}C NMR: δ = 20.9, 24.0, 26.9, 29.4, 33.8, 36.2, 43.6, 45.3, 56.0, 74.1, 75.9, 76.0, 79.6, 124.8, 128.7, 135.1, 147.3. MS (CI, *i*-butane): m/z (%) = 283 (100). $C_{19}H_{26}N_2$ (282.2): calcd. C 80.80, H 9.28, N 9.92; found C 80.65, H 9.12, N 9.81.

(3a*R*,7a*R*,7b*R*,8a*R*)-7b-(3-Methoxyphenyl)decahydro-3b,4a-diazadicyclopenta[*a*,*e*]pentalene (5f): Purification by column chromatography (ethyl acetate, with 5% Et_3N) gave 0.62 g (89%) of **5f** as a pale-yellow oil, which solidified on standing, from 0.73 g of 1,3-imidazolidin-2-one **4f**. M.p. 31−32 °C. $[\alpha]_D^{20}$ = +15.3 (c = 1.17, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 800 cm^{-1}. ^1H NMR: δ = 1.18−2.08 (m, 11 H), 2.61 (m, 2 H), 2.94 (m, 1 H), 3.17 (m, 1 H), 3.56 (m, 1 H), 3.76 (m, 2 H), 3.79 (s, 3 H), 4.00 (d, J = 9.4 Hz, 1 H), 6.68 (dd, J = 7.9, 1.5 Hz, 1 H), 6.98 (d, J = 7.9 Hz, 1 H), 7.11 (s, 1 H), 7.17 (m, 1 H). ^{13}C NMR: δ = 24.0, 26.9, 29.3, 33.7, 36.2, 43.7, 45.2, 55.1, 55.9, 74.2, 75.7, 76.0, 79.9, 110.7, 110.9, 117.7, 129.0, 152.2, 159.5. MS (CI, *i*-butane): m/z (%) = 299 (100). $C_{19}H_{26}N_2O$ (298.2): calcd. C 76.47, H 8.78, N 9.39; found C 76.36, H 8.62, N 9.43.

(3a*R*,7a*R*,7b*R*,8a*R*)-7b-(2-Methoxyphenyl)decahydro-3b,4a-diazadicyclopenta[*a*,*e*]pentalene (5g): Purification by column chromatography (ethyl acetate, with 5% Et_3N) gave 0.80 g (86%) of **5g** as a pale-yellow oil, which solidified on standing, from 0.99 g of 1,3-imidazolidin-2-one **4g**. M.p. 55−56 °C. $[\alpha]_D^{20}$ = +18.9 (c = 1.15, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2950, 800 cm^{-1}. ^1H NMR: δ = 1.19−2.11 (m, 11 H), 2.59 (m, 1 H), 2.92 (m, 2 H), 3.17 (m, 1 H), 3.47 (m, 1 H), 3.75 (m, 1 H), 3.78 (s, 3 H), 3.86 (d, J = 10.2 Hz, 1 H), 3.95 (d, J = 10.2 Hz, 1 H), 6.94 (m, 2 H), 7.13 (m, 1 H), 7.69 (d, J = 7.5 Hz, 1 H). ^{13}C NMR: δ = 23.9, 26.9, 29.8, 33.8, 36.3, 43.3, 43.5, 55.0, 56.2, 73.6, 74.7, 74.9, 78.6, 110.7, 120.1, 124.8, 127.0, 138.6, 156.5. MS (CI, *i*-butane): m/z (%) = 299 (100). $C_{19}H_{26}N_2O$ (298.2): calcd. C 76.47, H 8.78, N 9.39; found C 76.38, H 8.69, N 9.29.

Typical Procedure for the Hydrolysis of the Tetracyclic Aminals 5: The aminal **5** (1.4 mmol) was suspended in 3 M HCl (10 mL). The mixture was either stirred without heating until a clear solution was obtained or it was refluxed for 3 h and subsequently stirred for 12 h at room temperature (the exact procedure used is described under the name of each compound). The acidic solution was concentrated to dryness in vacuo and the colourless solid residue was suspended in a mixture of 2 M NaOH (10 mL) and ether (10 mL). After a clear solution had been obtained the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and concentrated in vacuo to give the crude diamine **6** as a pale-yellow oil which was purified by column chromatography.

(*all-R*)-2-Phenyl-2-pyrrolidin-2′-yloctahydrocyclopenta[*b*]pyrrole (6a): The reaction mixture was stirred for 30 min at room temperature. Purification by column chromatography (*n*-hexane/ethyl acetate 1:2, with 3% Et_3N) gave 0.25 g (72%) of **6a** as a pale-yellow oil from 0.38 g of aminal **5a**. $[\alpha]_D^{20}$ = +27.0 (c = 1.00, CH_2Cl_2). IR (NaCl): $\tilde{\nu}$ = 3310, 2950, 750 cm^{-1}. ^1H NMR: δ = 1.31−1.95 (m, 13 H), 2.72 (m, 4 H), 2.61 (m, 1 H), 3.85 (m, 1 H), 7.11−7.46 (m, 5 H). ^{13}C NMR: δ = 23.7, 25.5, 26.9, 33.2, 35.2, 43.1, 44.8, 46.6, 63.9, 66.1, 71.7, 126.1, 127.0, 127.6, 146.5. MS (CI, *i*-butane): m/z (%) = 257 (100). $C_{17}H_{24}N_2$ (256.2): calcd. C 79.64, H 9.44, N 10.93; found C 79.53, H 9.39, N 10.90.

(*all-R*)-2-(4-Methylphenyl)-2-pyrrolidin-2′-yloctahydrocyclopenta[*b*]pyrrole (6b): The reaction mixture was heated for 3 h under reflux and then stirring was continued for 12 h. Purification by column chromatography (ethyl acetate/Et_3N 9:1) gave 0.48 g (96%) of **6b** as a colourless oil from 0.52 g of aminal **5b**. $[\alpha]_D^{20}$ = +24.5 (c = 0.83, CH_2Cl_2). IR (NaCl): $\tilde{\nu}$ = 3300, 2950, 750 cm^{-1}. ^1H NMR: δ = 1.23−1.93 (m, 13 H), 2.32 (s, 3 H), 2.72 (m, 4 H), 3.23 (m, 1 H), 3.84 (m, 1 H), 7.10 (d, J = 7.9 Hz, 2 H), 7.32 (d, J = 7.9 Hz, 2 H). ^{13}C NMR: δ = 20.9, 23.8, 25.6, 27.0, 33.3, 35.2, 43.4, 44.9, 46.8, 64.1, 66.2, 71.7, 127.0, 128.3, 135.6, 143.6. MS (CI, *i*-butane): m/z (%) = 271 (100). $C_{18}H_{26}N_2$ (270.2): calcd. C 79.95, H 9.69, N 10.36; found C 79.83, H 9.52, N 10.25.

(*all-R*)-2-(2-Methoxyphenyl)-2-pyrrolidin-2′-yloctahydrocyclopenta[*b*]pyrrole (6g): The reaction mixture was heated for 3 h under reflux and then stirring was continued for 12 h. Purification by column chromatography (ethyl acetate/ Et_3N 9:1, with 1% MeOH) gave 0.57 g (89%) of **6g** as a colourless oil, which solidified on standing, from 0.67 g of aminal **5g**. M.p. 53−54 °C. $[\alpha]_D^{20}$ = −1.1 (c = 0.82, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 3330, 2950, 750 cm^{-1}. ^1H NMR: δ = 1.18−1.87 (m, 13 H), 2.75 (m, 4 H), 3.52 (m, 1 H), 3.78 (s, 3 H), 3.89 (m, 1 H), 6.83 (d, J = 7.9 Hz, 1 H), 6.90 (m, 1 H), 7.17 (m, 1 H), 7.66 (d, J = 7.5 Hz, 1 H). ^{13}C NMR: δ = 23.6, 25.3, 26.9, 33.6, 36.4, 42.7, 44.1, 46.3, 55.2, 63.4, 65.2, 70.5, 111.1, 120.2, 127.3, 129.0, 136.4, 156.6. MS (CI, *i*-butane): m/z (%) = 287 (100). $C_{18}H_{26}N_2O$ (286.2): calcd. C 75.48, H 9.15, N 9.78; found C 75.39, H 9.09, N 9.80.

[1] D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724−2772; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580−2627 and references cited therein.
[2] K. Bambridge, M. J. Begley, N. S. Simpkins, *Tetrahedron Lett.* **1994**, *35*, 3391−3394.
[3] S. Roland, P. Mangeney, *Eur. J. Org. Chem.* **2000**, 611−616.
[4] G. Alvaro, F. Grepioni, S. Grilli, L. Maini, G. Martelli, D. Savoia, *Synthesis* **2000**, 581−587.
[5] N. Kise, K. Kashiwagi, M. Watanabe, J. Yoshida, *J. Org. Chem.* **1996**, *61*, 428−429.
[6] Y. Park, M. L. Boys, P. Beak, *J. Am. Chem. Soc.* **1996**, *118*, 3757−3758.
[7] A. R. Katritzky, Z. Luo, Y. Fang, P. J. Steel, *J. Org. Chem.* **2001**, *66*, 2858−2861.
[8] A. Steinig, D. M. Spero, *Org. Prep. & Proc. Int.* **2000**, *32*, 205−234 and references cited therein.
[9] A. Giovannini, D. Savoia, A. Umani-Ronchi, *J. Org. Chem.* **1989**, *54*, 228−234.
[10] V. Teetz, R. Geiger, H. Gaul, *Tetrahedron Lett.* **1984**, *25*, 4479−4482.
[11] H. Urbach, R. Henning, *Heterocycles* **1989**, *28*, 957−965.
[12] N. Graf v. Keyserlingk, J. Martens, D. Ostendorff, W. Saak, M. Weidenbruch, *J. Chem. Soc., Perkin Trans. 1* **2001**, 706−710.
[13] S. T. Kerrick, P. Beak, *J. Am. Chem. Soc.* **1991**, *113*, 9708−9710.
[14] P. Beak, T. S. Kerrick, S. Wu, J. Chu, *J. Am. Chem. Soc.* **1994**, *116*, 3231−3239.
[15] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-166061. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
[16] Reaction of the described ketimines **3** with 2-lithiopyridine (generated by metal-bromine exchange with *n*-butyllithium) resulted, besides the formation of the expected addition product, in the isolation of the ketimines alkylated in the 3-position by bromobutane; N. Graf v. Keyserlingk, PhD thesis, Universität Oldenburg, **2001**.
[17] C. N. Meltz, R. A. Volkmann, *Tetrahedron Lett.* **1983**, *24*, 4503−4506.
[18] H. Stetter, V. Löhr, A. Simos, *Justus Liebigs Ann. Chem.* **1977**, 999−1004.
[19] R. Duschinsky, L. A. Dolan, L. O. Randall, *J. Am. Chem. Soc.* **1947**, *69*, 3150−3151.
[20] This compound has been described previously in the literature as a racemate: I. Murakoshi, H. Murata, J. Haginiwa, *Yakugaku Zasshi* **1964**, *84*, 674−679.

Received July 6, 2001
[O01339]