Synthesis of Potentially Biologically Active Cyclopropane- and Spirocyclopropane-annelated Oligoazaheterocycles

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To my parents

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A. INTRODUCTION

Heterocyclic compounds containing nitrogen are not only widely distributed in nature, but naturally occurring and synthetic ones also have an enormous range of applications. They are used as optical brightening agents, as antioxidants, as pigments and many of these compounds display important biological activities.[1] A large number of natural and synthetic *N*-heterocyclic compounds have found applications as pharmaceuticals and agrochemicals. Their synthesis, therefore, has attracted much interest and a large variety of synthetic methodologies have been developed.[1]

A central concept in pharmaceutical chemistry is that of the pharmacophore, a specific three-dimensional arrangement of essential chemical groups common to active molecules, which is recognized by a single receptor. Sheridan[2] has proposed that the essential groups in a pharmacophore are: a cationic center (e. g. a protonated sp^3-hybridized nitrogen), an electronegative atom capable of forming a hydrogen bond, and an atom or a point that, together with the electronegative atom, defines a line along which the hydrogen bond may form. The cationic and the electronegative centers are often represented by N-atoms, while the third group can be defined by a π-system (such as an aromatic ring). Therefore, the interest in N-containing compounds has primarily been focusing on the inter-nitrogen (N–N) distances in the supposed binding conformation of the ligand.[3]

Over the years, many new structures have been found in natural products, which have shown biological activity, but many of these proved to be toxic. Thus, the chemist has been encouraged to synthesize structurally related analogues in the search for ligands which show a higher specificity and are, therefore, less toxic.

Current interest in neuronal nicotinic acetylcholine receptors, for which nicotine **1** (Figure 1) is a selective ligand, and their potential as therapeutic targets is considerable. The

development of pharmacophores for the nicotinic receptors requires the study of the structure-activity relationships and a geometrical approach in the introduction of functional groups which may influence the conformation.[2,3]

The attention of many organic chemists was drawn to the area of nicotine analogues in 1992 by the discovery of the natural product epibatidine **2** (Figure 1),[4] the skeleton of which is a 7-azabicyclo[2.2.1]heptane ring system.[5] The alkaloid **2** contains a 6-chloro-3-pyridyl unit as the hydrogen bond acceptor component in the general pharmacophore model, and it has powerful analgesic effects. This has stimulated a remarkable level of interest in spite of its toxicity.[4] Another compound containing the 6-chloro-3-pyridyl fragment is imidacloprid (**3**, Figure 1), widely used for treatment of soil and green plants.[6] The latter, being an agonist of the nicotinic acetylcholine receptor, is nowadays one of the most active insecticides. Barlocco[7] reported that the epibatidine analogue diazabicyclo[3.2.1]octane derivative **4** has similar analgesic properties and a similar mechanism of action as **2**. Key features of **4** are the 4-chloropyridazinyl system connected to one nitrogen atom and the rigid conformation of the molecule.

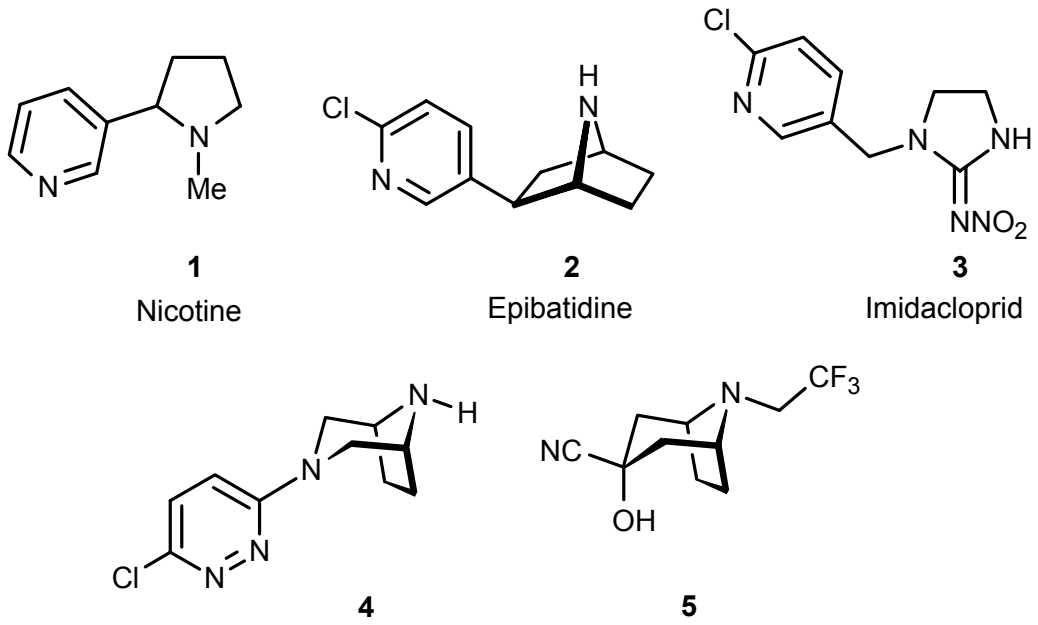
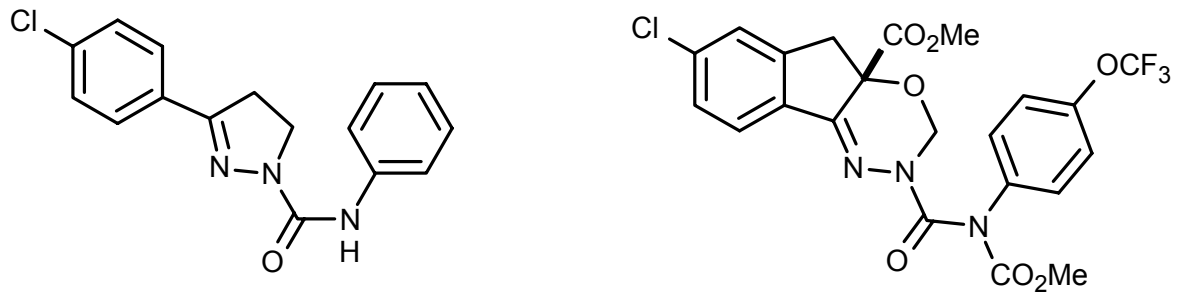


Figure 1. Structures of selected biologically active N-containing compounds.

With the development of new computational methods and more powerful computers it is nowadays possible to investigate the interaction between binding sites and substrates. Molecular modelling demonstrated that in substrates for the nicotine receptor, the N–N distances and the orientation of the chloroaromatic substituents play an important role in their affinity for the receptor itself. Thus, organic chemists were stimulated to synthesize new compounds with rigidified structures bearing two or more nitrogen atoms held at a well-defined distance between the pharmacophore groups.[7] An example for the successful application of this approach is the synthetic trifluoromethyl-tropanone cyanohydrine **5** (Figure 1)[8] which has high activity as a ligand for the nicotinic receptor.

The discovery of insecto-acaricides with novel modes of action is very important because of insect resistances to compounds which have been in use for several decades, such as carbamate classes of cholinesterase-inhibiting insecticides.[9] Pyrazoline systems, for example, were reported by Salgado[10] to act by blocking the sodium channel of neurons, a novel insecticidal mode of action. The first commercially available compounds of this class were reported by Philips-Duphar,[11] e. g. PH 60–41 **6** (Figure 2). Recently, DuPont reported the highly active and less toxic oxadiazine analogue indoxacarb **7** (Figure 2), [9] which presents a combination of chloro- and trifluoromethoxy-substituted phenyl groups and a formal urea function as biologically active moieties.

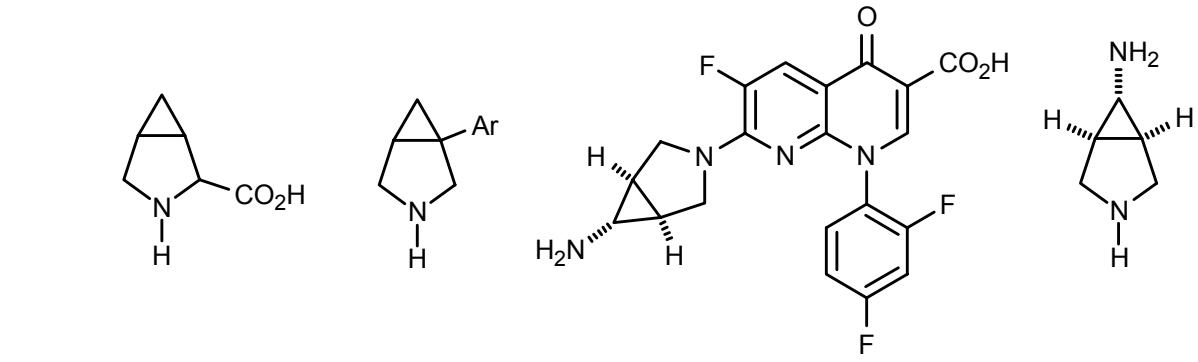


6 PH 60–41

7 Indoxacarb

Figure 2. Structure of PH 60–41 (Philips-Duphar) and Indoxacarb (DuPont).

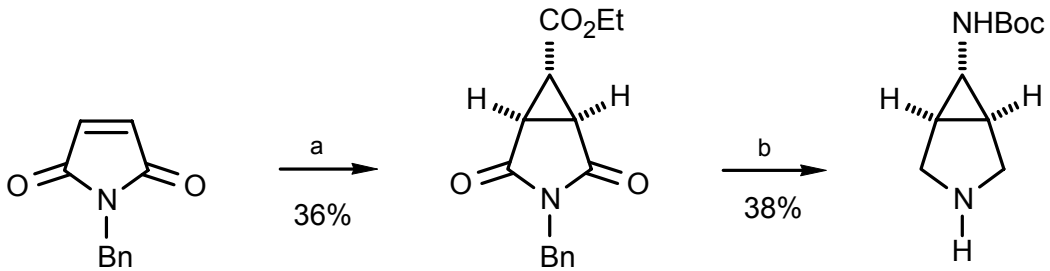
In the last 30 years specific interest has been directed towards the cyclopropyl group as a special substituent in biologically active molecules. Natural and synthetic molecules bearing a cyclopropyl moiety are endowed with a large spectrum of biological properties.[12] In addition, the rigidity of the three-membered ring makes this group a unique structural unit for the preparation of molecules with defined orientation of pendant functional groups.[13] An interesting example of this class of molecules is the 3-azabicyclo[3.1.0]hexane ring system, which contains a fused cyclopropyl group and is also common to a number of biologically active compounds. Some examples of molecules containing this skeleton are 3,4-methanoproline **8**, which displays gametocidic activity in cereals, bicifadine **9**, which shows analgetic and antidepressant activity and the highly active antibiotic trovafloxacin **10**,[14] which has a potent activity against Gram-negative, Gram-positive and anaerobic bacteria, and against penicillin-resistant *Streptococcus pneumoniae*. Trovafloxacin **10** contains as a substituent on C-7 of the naphthyridinon moiety the 3-azabicyclo[3.1.0]hex-6-ylamine (**11**), which is interesting as a rigid scaffold with two nitrogen atoms held at a well-defined distance (Figure 3).



8 3,4-Methanoproline **9** Bicifadine **10** Trovafloxacin **11**

Figure 3. Structures containing the 3-azabicyclo[3.1.0]hexane ring system.

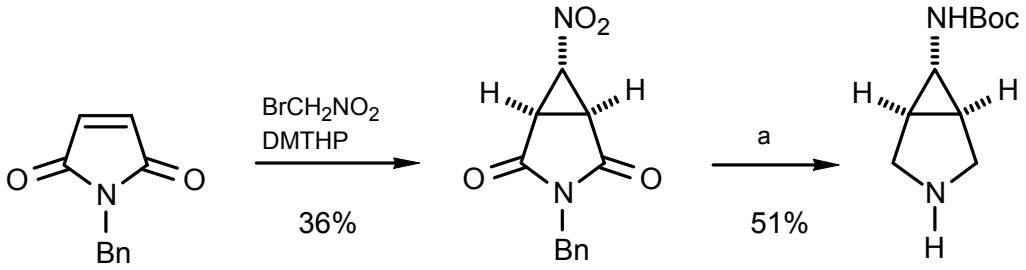
In view of the biological activity of compounds containing **11**, its synthesis has attracted some attention. A few methods have been reported for the synthesis of **14**, the *N*-*tert*-butoxy-carbonyl-protected form of **11**.[15] The rhodium acetate-catalyzed addition of ethyl diazoacetate to *N*-protected pyrroline is known to give a 2/1 mixture of *exo* : *endo* bicyclic carboxylic esters.[14c] Brighty[14d] reported that the uncatalyzed addition of ethyl diazoacetate to *N*-benzylmaleimide **12** afforded *exo*-3-azabicyclo[3.1.0]hexane **13** as a single diastereomer in 36% yield (Schema 1). Amine **14** was prepared from imide **13** by a sequence of steps in which a modified Curtius rearrangement was involved.



12 **13** **14**

Schema 1. Synthesis of *exo*-3-azabicyclo[3.1.0]hex-6-ylamine **14** accroding to Brighty et al.[14d] a) i. $EtOOCCHN_2$, ii. heat; b) i. $LiAlH_4$, ii. H_2, Pd/C, iii. CbzCl, iv. CrO_3, v. $(PhO)_2PON_3$, *t*BuOH, vi. H_2, Pd/C.

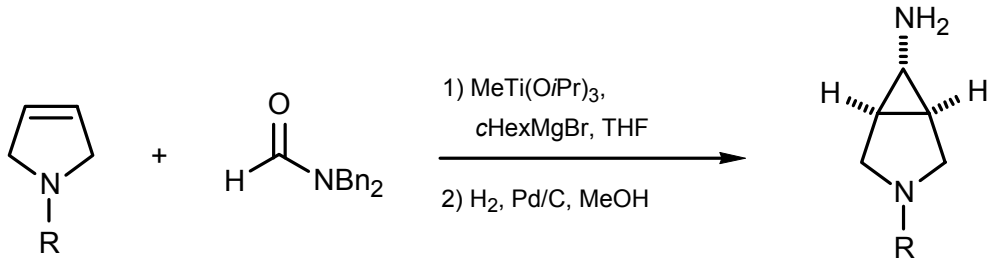
An alternative preparation of amine **14** was reported by Braish[16] in which the treatment of *N*-benzylmaleimide (**12**) with bromonitromethane and dimethyl-1,3,4,5-tetrahydropyrimidine (DMTHP) gave *exo*-**15** as the only product in 36% yield (Scheme 2). The two carbonyl groups in **15** were then reduced prior to selective reduction of the nitro group, otherwise opening of the cyclopropane ring occurred.



Scheme 2. Synthesis of *exo*-3-azabicyclo[3.1.0]hex-6-ylamine **14** according to Braish et al.[16] a) i. BH_3, ii. H_2, Pt/C, iii. Boc_2O, iv. H_2, Pd/C.

Recently, a synthetically useful reaction in which a titanacyclopropane intermediate acts in a formal sense as a 1,2-dicarbanionic equivalent, and thus leads to the formation of two new carbon-carbon bonds, has been developed by Kulinkovich,[17] allowing the conversion of esters to cyclopropanols. A very useful adaptation of the original protocol has been developed by de Meijere[18] for the highly versatile preparation of cyclopropylamines with such titanium 1,2-dicarbanionic equivalents.

By application of this method, the unprotected *exo*-3-azabicyclo[3.1.0]hex-6-ylamines (**11**) and the mono-*tert*-butoxycarbonyl-protected derivative **19** have been prepared in only two steps from *N*-protected pyrrolines **16** as well as **17** and *N*,*N*-dibenzylformamide (**18**) in 87 and 85% yield, respectively (Scheme 3).[19,20]



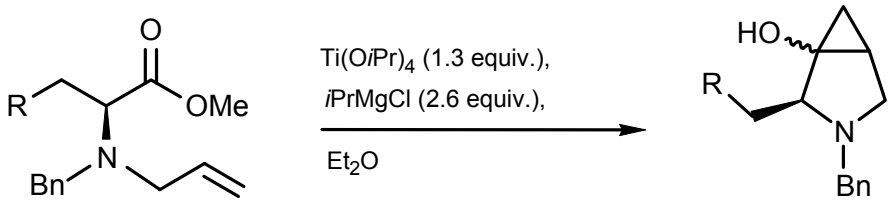
16 R = Bn
17 R = Boc

18

11 R = H (87%)
19 R = Boc (85%)

Scheme 3. Synthesis of the *exo*-3-azabicyclo[3.1.0]hex-6-ylamine (**11**) and its 3-*tert*-butoxycarbonyl derivative **19** according to de Meijere.[20]

Cha[21] and Sato[22] independently reported the olefin exchange-mediated intramolecular Kulinkovich hydroxycyclopropanation of ω-vinyl-substituted carboxylates and carboxamides which leads to the formation of bi- and tricyclic cyclopropane-annelated systems. Sato,[22a] moreover, applied this method for the preparation of 1-hydroxy-3-azabicyclo[3.1.0]hexanes **22** and **23** by intramolecular cyclopropanation of *N*-(2-alkenyl)amino esters **20** and **21** with titanium tetraisopropoxide and isopropylmagnesium chloride (Scheme 4).

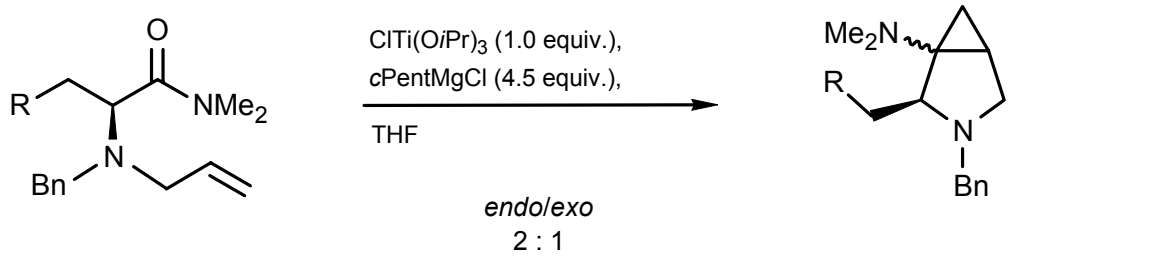


20 R = Ph
21 R = TBDMSO

22 R = Ph (75%, d. r. 73 : 27)
23 R = TBDMSO (86%, d. r. 75 : 25)

Scheme 4. Ti-mediated intramolecular cyclopropanation of esters **20** and **21** (TBDMSO = *tert*-butyldimethylsilyloxy).

The synthesis of 1-amino-3-azabicyclo[3.1.0]hexane, structurally related to the amine **11**, was reported by Joullié et al,[23] as an application of the intramolecular reductive cyclopropanation of *N*-allyl-α-aminocarboxylic acid *N*,*N*-dimethylamides. Some derivatives (**26** and **27**, Scheme 5) were prepared as a mixture of *endo*- and *exo*-diastereomers in a ratio of 2 : 1 by treatment of amides **24** and **25** with chlorotitanium triisopropoxide and cyclopentylmagnesium chloride in good yields (Scheme 5).

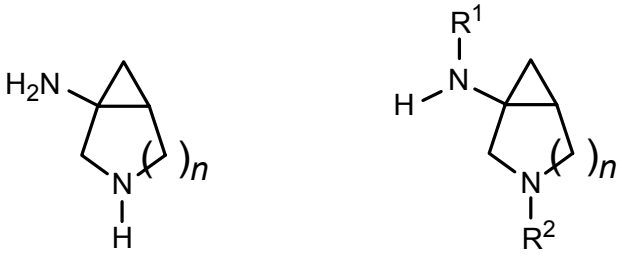


24 R = Ph
25 R = 4-TBDMSO-C_6H_4

26 R = Ph (83%)
27 R = 4-TBDMSO-C_6H_4 (85%)

Scheme 5. Ti-mediated intramolecular cyclopropanation of amides **24** and **25**.

1-Amino-3-azabicyclo[3.1.0]hexane (**28**), as an isomer of **11**, and 1-amino-3-azabicyclo-[3.1.0]heptane (**29**) (Figure 4) could be interesting structures from a pharmaceutical point of view. Due to the position of the substituents, the distance between the nitrogen atoms in **28** and **29** is different from that one in diamine **11**. Thus, the isomers **28** and **29** are likely to display altered biological activities. In order to be able to utilize these scaffolds in combinatorial approaches to libraries of compounds **30–33** containing at least two different aromatic or heteroaromatic substituents and alkyl substituents on the two nitrogen atoms, the latter would have to be chemically addressable individually and selectively.

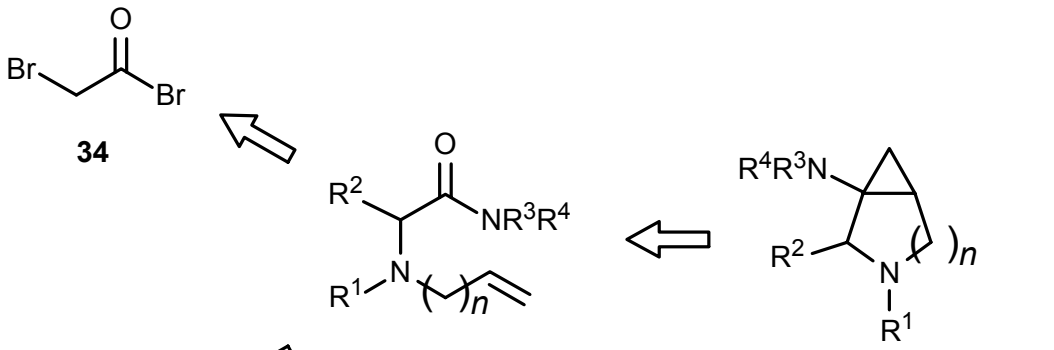


28 n = 1
29 n = 2

30 n = 1, R^1 = alkyl, R^2 = aryl
31 n = 2, R^1 = alkyl, R^2 = aryl
32 n = 1, R^1 = aryl, R^2 = alkyl
33 n = 2, R^1 = aryl, R^2 = alkyl

Figure 4. 1-Amino-3-azabicyclo[3.1.0]hexane (**28**), 3-azabicyclo[4.1.0]heptane (**29**) and their derivatives.

Accordingly, a synthetic protocol ought to be developed, which would allow one to prepare a variety of tri- and monoprotected derivatives with the 3-azabicyclo-[3.1.0]hexane **39** and the homologous 3-azabicyclo[4.1.0]heptane **40** skeleton by intramolecular cyclopropanation of *N*-allyl and *N*-homoallyl alkylamides of types **35**–**38** (Scheme 6). The latter ought to be accessable from natural amino acids or, in the case of glycine derivatives, simply from bromoacetyl bromide (**34**).

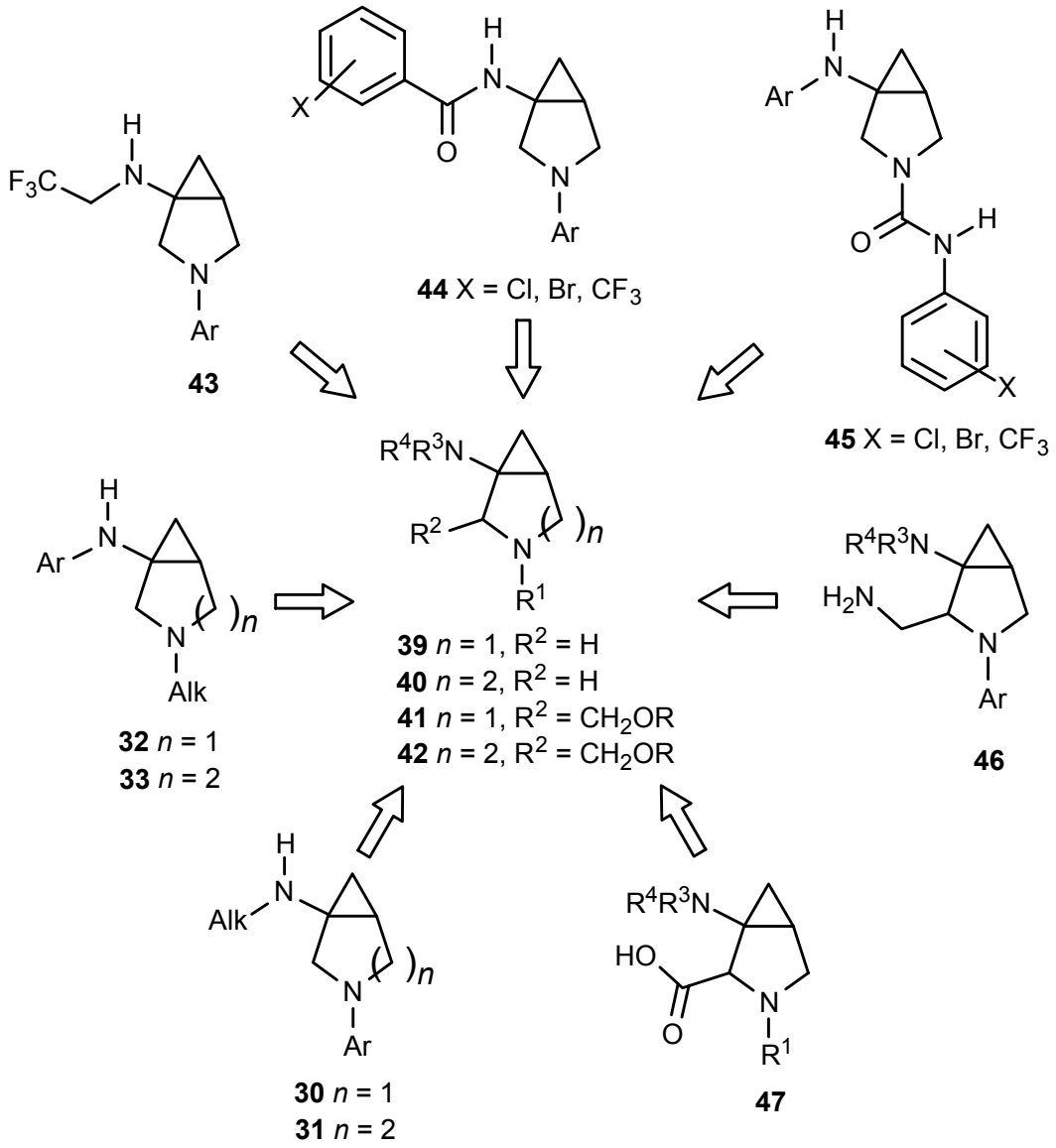


35 n = 1, R^2 = H
36 n = 2, R^2 = H
37 n = 1, R^2 = CH_2OR
38 n = 2, R^2 = CH_2OR

39 n = 1, R^2 = H
40 n = 2, R^2 = H
41 n = 1, R^2 = CH_2OR
42 n = 2, R^2 = CH_2OR

Scheme 6. Strategy for the synthesis of 1-amino-3-azabicyclo[3.1.0]hexanes and homologues **39**–**42**.

The *O*-protected 2-hydroxymethyl-1-amino-3-azabicyclo[3.1.0]hexane derivative **41**, which has an interesting additional functionality for further elaboration, ought to be accessable along this route from the natural amino acid L-serine. Oxidation of the liberated hydroxy function in **41**, for example, may give amino-substituted analogues **47** of the natural 3,4-methanoproline **8**. Moreover, it should be possible to attach aromatic and heteroaromatic substituents to compounds **28** and **29** in order to obtain new ligands for the nicotinic receptors (e. g. **30–33** and **43**) and new analogues such as **44** and **45** of indoxacarb (**7**).



Scheme 7. Strategies for the further elaboration of the 3-azabicyclo[3.1.0]hexane and the 3-azabicyclo-[3.1.0]heptane skeletons.

The aims of this project can be summarized as follows:

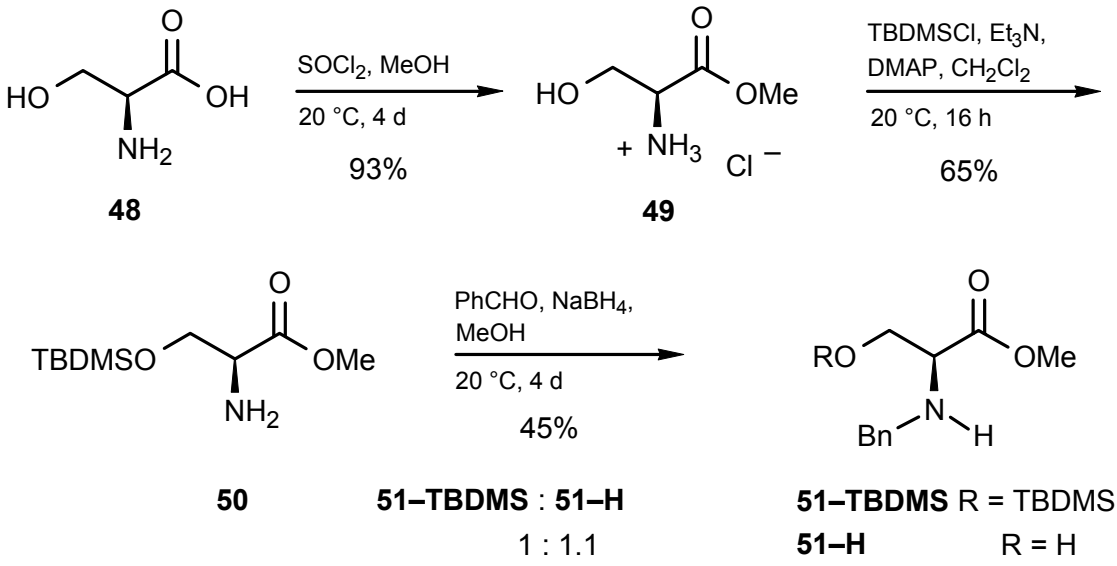
- Synthesis of 2-hydroxymethyl-3-azabicyclo[3.1.0]hex-1-ylamine **41** and further elaboration of the hydroxy function.
- Synthesis of 1-amino-3-azabicyclo[3.1.0]hexane (**28**) and 1-amino-3-azabicyclo[4.1.0]-heptane (**29**) and study of their reactivity in nucleophilic aromatic substitution.
- Investigation of intramolecular reductive cyclopropanations for the synthesis of oligocyclic compounds with the 3-azabicyclo[3.1.0]hexane skeleton.
- Synthesis of trifluoromethyl derivatives of type **43** as analogues of compound **5**.
- Synthesis of indoxacarb analogues of types **44** and **45**.
- Study on the 1,3-dipolar cycloaddition of nitrones to highly strained alkenes and subsequent thermal rearrangement of the resulting cycloadducts for the synthesis of spirocyclopropane-annelated azaheterocycles.

B. MAIN PART

1. Synthesis of 3-Azabicyclo[3.1.0]hex-1-ylamines by Ti-Mediated Intramolecular Reductive Cyclopropanation

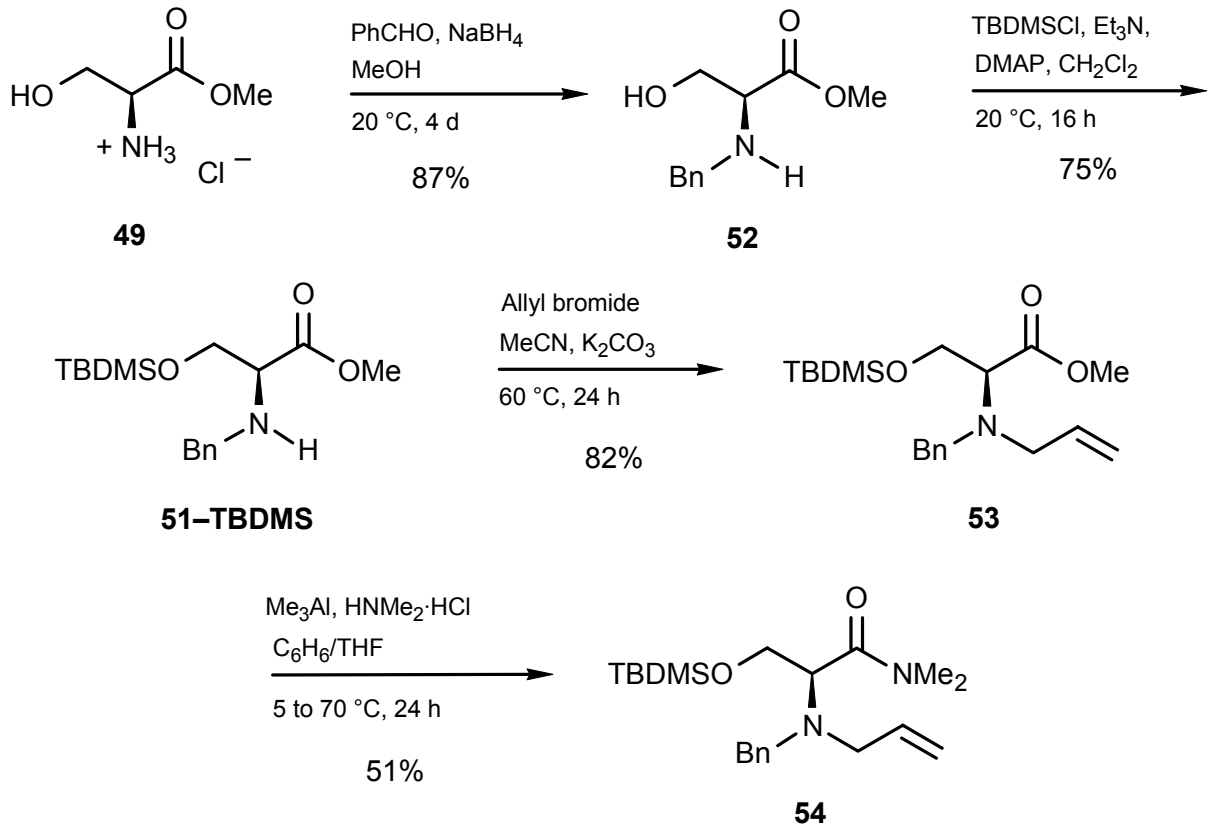
1.1. Synthesis of N,N-dialkylamides from L-serine

The first aim of this project was the development of a synthetic method for the synthesis of 3-azabicyclo[3.2.1]hexane and 3-azabicyclo[4.2.1]heptane derivatives by Ti-mediated intramolecular reductive cyclopropanation, which may be applied to different types of substrates. Initially this transformation was investigated with the natural amino acid L-serine (**48**) as the starting material for the synthesis of the corresponding amides, precursors for the intramolecular cyclopropanation. L-Serine (**48**) was transformed into its methyl ester (**49**, 93%)[24], and this protected as the *tert*-butyldimethylsilyl ether[25] **50** by treatment with *tert*-butyldimethylsilyl chloride (TBDMSCl), *N*,*N*-dimethylaminopyridine (DMAP) and Et_3N in 65% yield (Scheme 8).



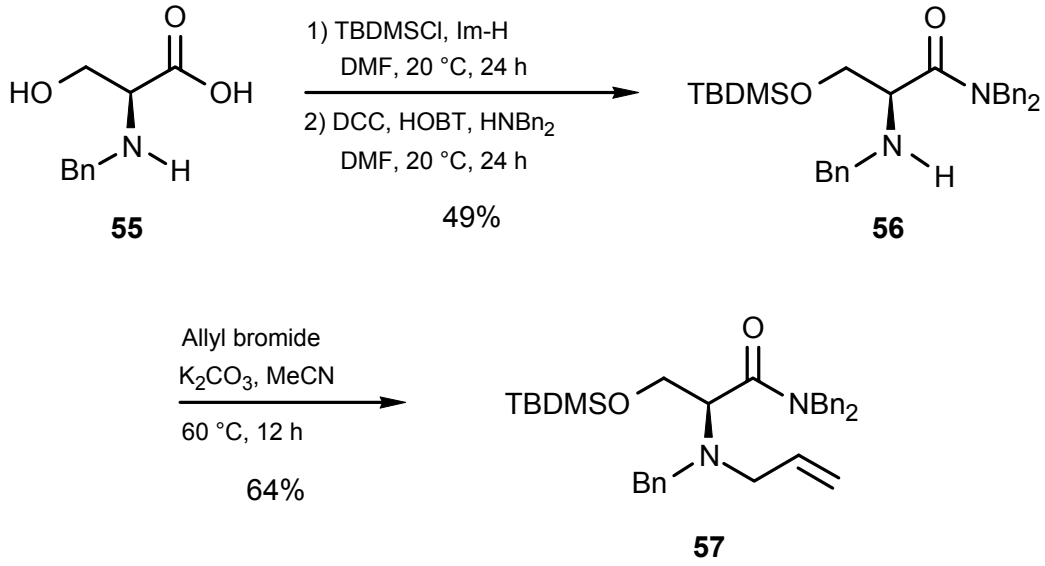
Scheme 8. Transformations of L-serine.

When compound **50** was treated with PhCHO and $NaBH_4$ in MeOH,[26] the *N*-benzyl derivative **51-TBDMS** and the *O*-deprotected derivative **51-H** were obtained in a ratio of 1 : 1.1. The alcohol **51-H** could be removed by column chromatography, but its formation as the major product limited the use of this method. The problem of the partial deprotection of compound **51** was solved by performing the reductive *N*-alkylation on serine methyl ester hydrochloride (**49**), followed by TBDMS protection (Scheme 9). The hydrochloride **49** was converted into the *N*-benzyl derivative **52** in 87% yield.[26] Protection of the hydroxy function was carried out by treatment with TBDMSCl, Et_3N/DMAP in CH_2Cl_2 to give compound **51-TBDMS** in 75% yield.[25] The latter was transformed into the *N*-allyl-*N*-benzyl derivative **53** in 82% yield, when allyl bromide and K_2CO_3 in MeCN were used.[27] The methyl ester **53** was then converted into the corresponding *N*,*N*-dimethyl amide **54** by treatment with $AlMe_3$, $HNMe_2$·HCl in benzene/THF[23] in 51% yield (Scheme 9).



Scheme 9. Synthesis of *N*,*N*-dimethylamide **54**.

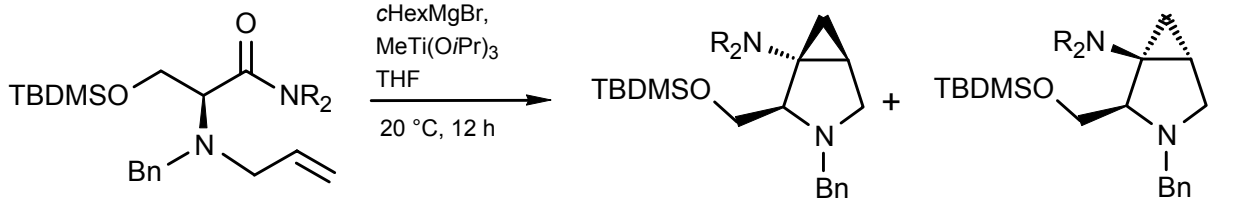
The possibility to prepare *N*,*N*-dibenzyl derivatives was also considered, in order to be able to deprotect the amino group after intramolecular cyclopropanation of the corresponding amide. The synthesis of such derivatives required a different set of reactions than was used for the *N*,*N*-dimethylamides (Scheme 10). *N*,*N*-dibenzylamide **56** was prepared starting from *N*-benzylserine (**55**) in a "one-pot" synthesis by treatment with TBDMSCl and imidazole (Im-H) in DMF at ambient temperature for 24 h,[28] followed by treatment with dicyclohexylcarbodiimide (DCC), hydroxybenzotriazole (HOBT) and $HNBn_2$[29] at ambient temperature for 24 h in 49% overall yield. The desired *N*-allyl derivative **57** was obtained from the *N*,*N*-dibenzylamide **56** in 64% yield using allyl bromide and K_2CO_3 in MeCN (Scheme 10).[27]



Scheme 10. Synthesis of (*S*)-2-(allylbenzylamino)-*N*,*N*-dibenzyl-3-(*tert*-butyldimethyl-silyloxy)propionamide **57**.

1.2. Synthesis of endo- and exo-(2R)-N,N-dialkyl-3-benzyl-2-(tert-butyldimethylsilyloxy-methyl)-3-azabicyclo[3.1.0]hex-1-ylamines

Under the conditions published by Joullié[23] for the reductive intramolecular cyclopropanation of α-substituted *N*-allylglycine *N*,*N*-dimethylamides [4.50 equiv. *c*PentMgCl, 1.00 equiv. ClTi(O*i*Pr)$_3$, THF, 20 °C, see Section A], the serine *N*,*N*-dimethyl-amide **54** and the *N*,*N*-dibenzylamide **57** did not cyclize to the corresponding bicyclic diamines. However, the target 1-amino-3-azabicyclo[3.1.0]hexane derivatives **58** and **59** were obtained from the amides **54** and **57** applying a slightly different protocol [1.50 equiv. methyltitanium triisopropoxide, MeTi(O*i*Pr)$_3$, instead of ClTi(O*i*Pr)$_3$ and 5.00 equiv. Of cyclohexylmagnesium bromide, *c*HexMgBr, instead of *c*PentMgCl] in 89 and 83% yield, respectively (Scheme 11). The observed diastereoselectivity was *endo*-**58** : *exo*-**58** = 2 : 1 and *endo*-**59** : *exo*-**59** = 2.5 : 1.



54 R = Me
57 R = Bn

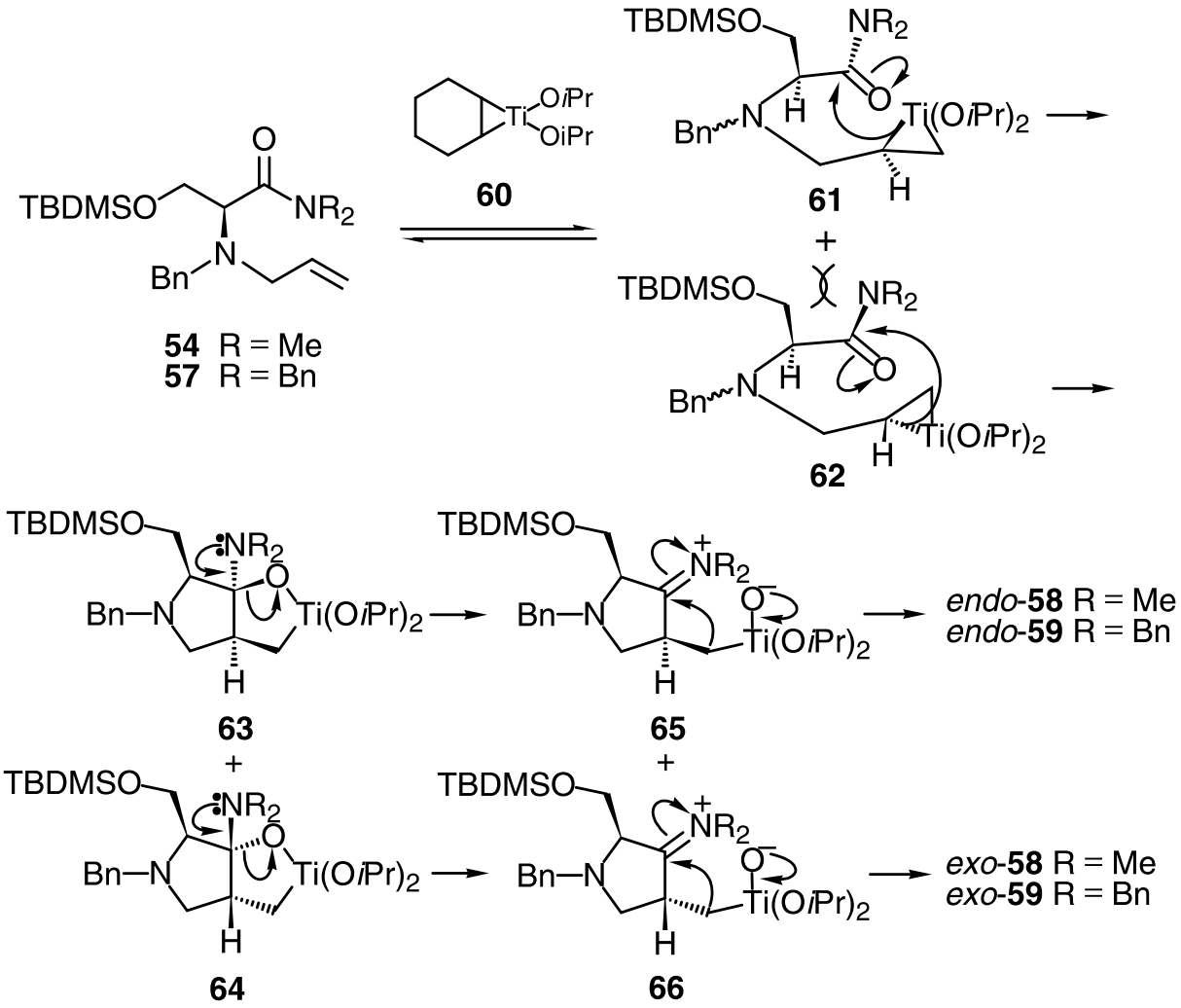
endo-**58,59** *exo*-**58,59**

R	Product	Yield (%)	*endo* : *exo*
Me	**58**	89	2.0 : 1
Bn	**59**	83	2.5 : 1

Scheme 11. Intramolecular reductive cyclopropanation of *N*-allyl-*N*-benzyl aminoserine *N*,*N*-dialkylcarboxamides **54** and **57**.

Earlier experiments[30] had disclosed that $MeTi(OiPr)_3$ gave consistently better yields of cyclopropylamines from *N*,*N*-dialkylcarboxamides. This was confirmed for the conversion of esters to cyclopropanols when ligand exchange was involved in the generation of the reactive titanium intermediate.[31] Cyclohexylmagnesium bromide also gave better yields and purer products than cyclopentylmagnesium halides (bromide or chloride).[20b]

The formation of the *endo*- and *exo*-isomers can be explained on the basis of the following mechanism (Scheme 12).[23]



Scheme 12. Mechanism and explanation of diastereoselectivity in the Ti-mediated intramolecular cyclopropanation of amide **54** and **57**.

The titanacyclopropane intermediate **60**, formed in the reaction between $MeTi(OiPr)_4$ and *c*HexMgBr, undergoes ligand exchange with the allyl moiety of **54** and **57** to give the titanacyclopropane intermediate **61** and **62**. The latter undergo titanacyclopropane ring expansion by insertion of the amide carbonyl group between titanium and the most highly substituted carbon atom. The more favorable conformation **61** has the hydroxymethyl group *anti* to the hydrogen of the most highly substituted carbon atom of the titanacyclopropane and to the NR_2 group. The titanacyclopropane ring expansion in the intermediate **61** may lead to the formation of a titanaoxacyclopentane of type **63** which, through the intermediate iminium ion **65**, leads to the *endo*-isomer as the major product. In the case of *N*,*N*-dibenzyl derivatives the more severe steric interaction in the intermediate of type **62**, which leads to the formation of the *exo*-isomer, may explain the diastereoselectivity observed.

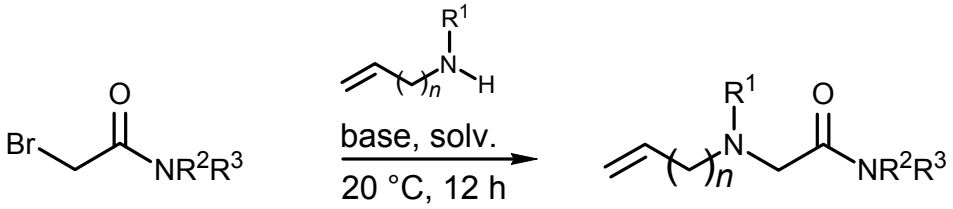
2. Synthesis of 1-Amino-3-azabicyclo[3.1.0]hexanes and 1-Amino-3-azabicyclo[4.1.0]heptanes

2.1. Synthesis of N,N-dialkylamides from bromoacetyl bromide

The results obtained in Section 1 stimulated the application of the intramolecular cyclopropanation towards the synthesis of the bicyclic amines **28** and **29** (see Section A).

The *N*-allylglycine *N*,*N*-dialkylamides **70–73** were prepared from 2-bromoacetamides **67** and **68** by nucleophilic substitution[32,33] with the appropriately *N*-substituted allyl- or homoallylamine in good yields (Table 1).

Table 1. Synthesis of amides **70–73**.

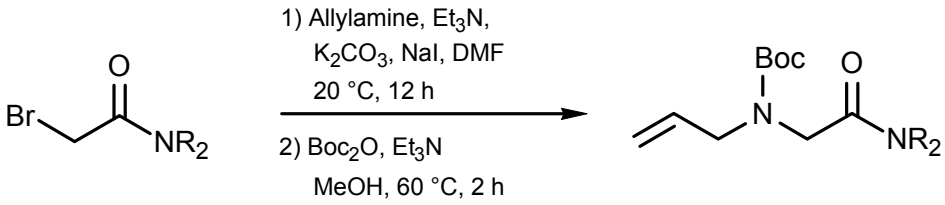


67 $R^2 = R^3 = Bn$
68 $R^2 = Bn$, $R^3 = Me$
69 $R^2 = R^3 = Ph$

70–75

R^1	R^2,R^3	*n*	Base	Solv.	Product	Yield (%)
Bn	Bn,Bn	1	Et_3N	THF	**70**	98
Bn	Bn,Me	1	Et_3N	THF	**71**	85
Me	Bn,Bn	1	Et_3N	THF	**72**	93
Bn	Bn,Bn	2	NaH	DMF	**73**	76
Boc	Bn,Bn	1	Et_3N	THF	**74**	—
Boc	Ph,Ph	1	Et_3N	THF	**75**	—

The preparation of amides **74** and **75** containing the *N*-*tert*-butoxycarbonyl (Boc) group required a different synthetic approach, because the *N*-allyl-*N*-*tert*-butoxycarbonylamine reacted sluggish in the nucleophylic substitution with bromoacetamides **67** and **69** (Table 1). Compounds **74** and **75** were obtained by treating 2-bromoacetamides **67** as well as **69** with allylamine in THF followed by *N*-Boc-protection of the amino group in 57 and 54% yield, respectively (Scheme 13).[34]



67 R = Bn
69 R = Ph

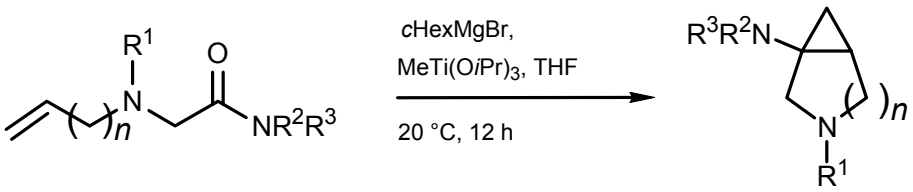
74 R = Bn (57%)
75 R = Ph (54%)

Scheme 13. Synthesis of *N*-Boc-protected amides **74** and **75**.

2.2. Ti-mediated reductive intramolecular cyclopropanation of N,N-dialkylamides

The amides **70**–**75** were subjected to the optimized conditions for the reductive intramolecular cyclopropanation of serine derivatives. The targets 1-amino-3-azabicyclo[3.1.0]hexane and 1-amino-3-azabicyclo[4.1.0]heptane derivatives **76**–**81** were obtained from the corresponding amides in moderate to good yields, when $MeTi(OiPr)_3$ (1.50 equiv.) and *c*HexMgBr (5.00 equiv.) were used (Table 2). Only in the case of compound **75** the formation of the desired product **81** was not observed.

Table 2. Intramolecular cyclopropanation of amides **70–75**.



70–75 **76–81**

R^1	R^2,R^3	*n*	Product	Yield (%)
Bn	Bn,Bn	1	**76**	56
Bn	Bn,Me	1	**77**	51
Me	Bn,Bn	1	**78**	66
Bn	Bn,Bn	2	**79**	59
Boc	Bn,Bn	1	**80**	43
Boc	Ph,Ph	1	**81**	—

The structural features of the homologous *N*,*N*,3-tribenzyl-3-azabicyclo[3.1.0]hex-1-ylamine (**76**) and *N*,*N*,3-tribenzyl-3-azabicyclo[4.1.0]hept-1-ylamine (**79**) were established by X-ray crystal structure analyses (Figure 5). The structural parameters of the two compounds are very similar, and in both cases the two phenyl rings of the dibenzylamino fragment are orthogonal with respect to each other. The *N*-benzyl group on the heterocycle in both cases adopts an equatorial position bending the envelope of the azacyclopentane moiety in **76** and the chair of the azacyclohexane in **79** in such a way that the whole azabicyclo[3.1.0]hexane and azabicyclo[4.1.0]heptane systems adopt boat conformations.

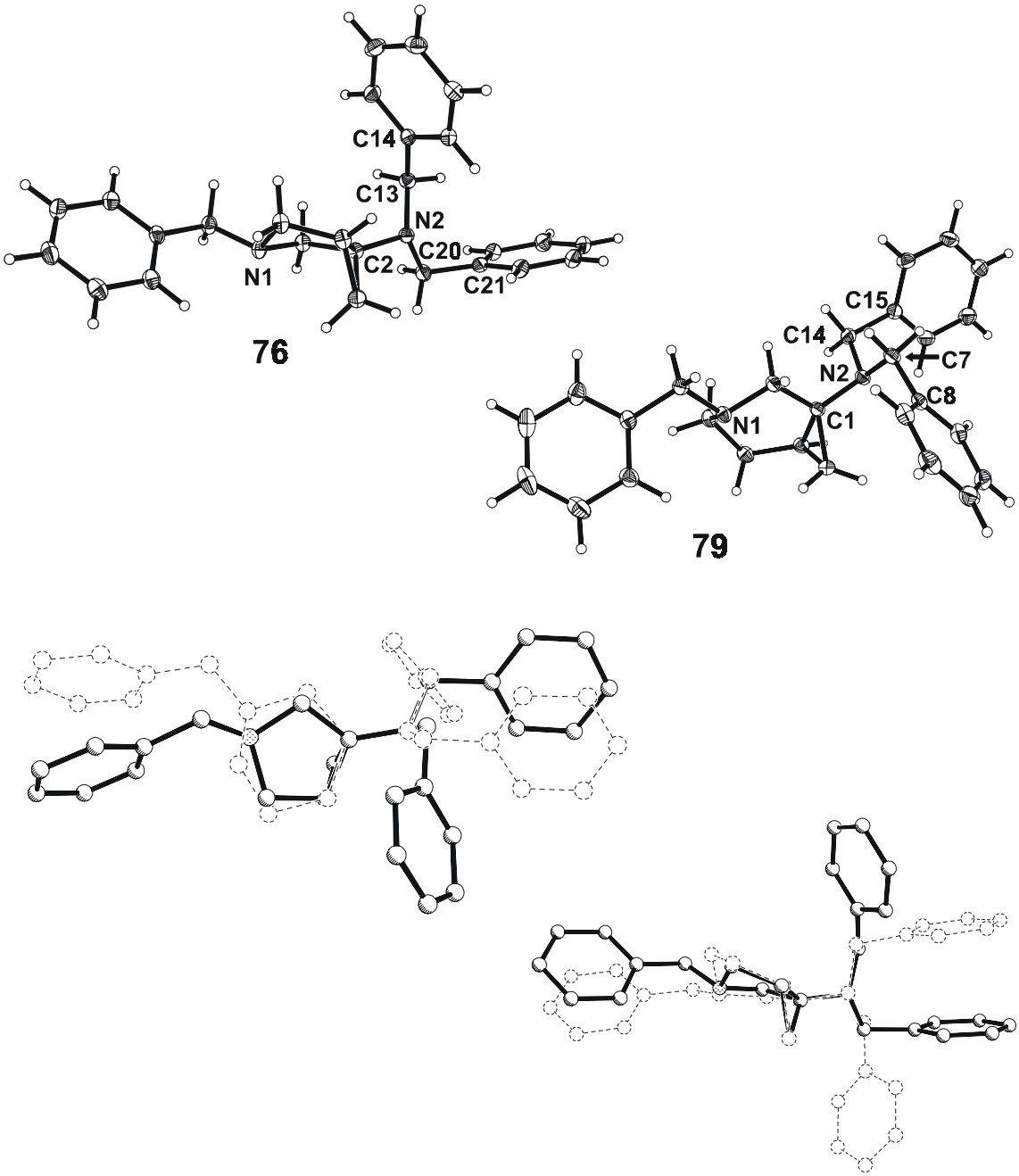


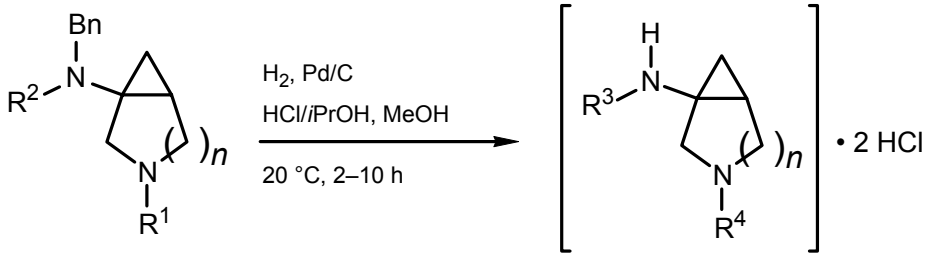
Figure 5. Molecular structures of *N*,*N*,3-tribenzyl-3-azabicyclo[3.1.0]hex-1-ylamine **76** and *N*,*N*,3-tribenzyl-3-azabicyclo[4.1.0]hept-1-ylamine **79** in the crystal (top) and their superpositions (bottom).

Both compounds are racemates and therefore crystallized in a centrosymmetric space group. The geometry of the molecules and their packing in the crystals are quite similar, however the conformations of the molecules are different, as demonstrated by the superpositions of

molecules with their 3-membered ring carbon and their nitrogen atoms of the dibenzylamino groups held at the same places (Figure 5). Molecule **76** has an *ap* orientation (with respect to the heterocycle) of the quasi-equatorial N2-C20 bond [dihedral angle C2-N2-C20-C21 = –163.0(1)°] and an *sc* orientation of the quasi-axial N2-C13 bond [angle C2-N2-C13-C14 = 69.7(1)°]. In contrast, molecule **79** has an *ap* orientation of the quasi-axial bond N2-C14 and an *sc* orientation of the quasi-equatorial bond N2-C7 [dihedral angles C1-N2-C14-C15 = –169.9(1)° and C1-N2-C7-C8 = 66.0(1)°, respectively].

The unprotected diamine hydrochlorides **28-HCl**, **29-HCl** and partially unprotected diamine hydrochlorides **82-HCl, 83-HCl** and **84** were obtained from the corresponding amines **76–80** by catalytic hydrogenation in the presence of an HCl/*i*PrOH solution in MeOH (Table 3).

Table 3. Deprotection of the benzyl-protected 3-azabicyclo[3.1.0]hex-1-ylamines **76**, **77**, **78**, **80** and *N*,*N*,3-tribenzyl-3-azabicyclo[4.1.0]hept-1-ylamine (**79**).



76–80 **28**, **29**, **82–84**

R^1	R^2	R^3	R^4	*n*	Product	Yield (%)
Bn	Bn	H	H	1	**28-HCl**	91
Bn	Me	Me	H	1	**82-HCl**	96
Me	Bn	H	Me	1	**83-HCl**	95
Bn	Bn	H	H	2	**29-HCl**	99
Boc	Bn	H	Boc	1	**84**[a]	76

[a]Compound **84** was obtained as a free base.

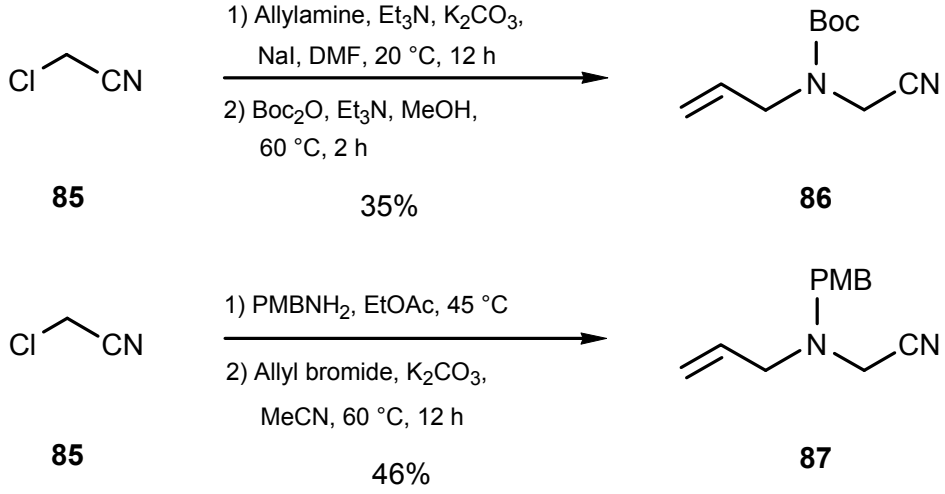
3. Ti-Mediated Intramolecular Reductive Cyclopropanation of Carbonitriles

3.1. Considerations

The derivatives discussed in Section 2 still do not allow one to fully control the introduction of potential aryl substituents on the primary amino group. The best way to solve this problem would be by way of a one-step preparation of the bicyclic diamines with a protected secondary and an unprotected primary amino group which, according to the logic of the titanium-mediated transformation, might be achieved using nitriles as starting materials. Early attempts to convert aliphatic nitriles into primary cyclopropylamines under the action of Grignard reagents and $Ti(O\textit{i}Pr)_4$ were met only with very moderate success.[35] Szymoniak et al., however, found that nitriles do react with *in situ* generated titanacyclopropane intermediates to form remarkably stable azatitanacyclopentane intermediates which only upon activation by an added Lewis acid (LA) like boron trifluoride etherate ($BF_3 \cdot Et_2O$) eventually undergo ring contraction to the Lewis acid-complexed primary cyclopropylamines. Aqueous work-up under basic conditions then furnished the primary cyclopropylamines in moderate to good yields.[36] In an independent development it was found that in particular aromatic nitriles could be converted to primary cyclopropylamines by treatment with dialkylzinc reagents in the presence of $Ti(O\textit{i}Pr)_4$ and addition of lithium isopropoxide ($LiO\textit{i}Pr$) or lithium iodide (LiI).[37]

3.2. Synthesis of 2-allylaminoacetonitriles

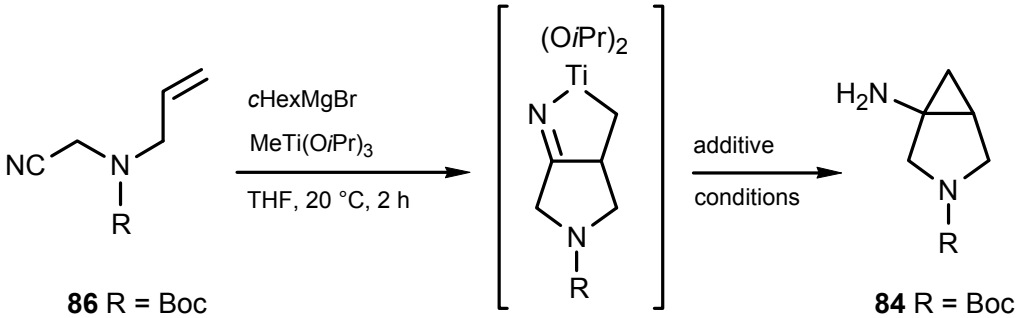
Some nitriles for an intramolecular application of this protocol were synthesized. Treatment of chloroacetonitrile (**85**) with allylamine, Et_3N and K_2CO_3 in DMF followed by protection with Boc_2O and Et_3N in MeOH afforded the nitrile **86** in 35% overall yield (Scheme 14).[38] Compound **87** was prepared from chloroacetonitrile (**85**) by initial amination using 4-methoxybenzylamine ($PMBNH_2$) in EtOAc, followed by treatment with allyl bromide and K_2CO_3 in MeCN in 46% overall yield. *N*-Allyl-*N*-benzylacetonitrile (**88**) was prepared according to a published procedure.[39]



Scheme 14. Synthesis of nitriles **86** and **87**.

3.3. Synthesis of 3-substituted 3-azabicyclo[3.1.0]hex-1-ylamines from 2-allylamino-acetonitriles

The intramolecular reductive cyclopropanation of nitriles **86–88** upon treatment with MeTi(O*i*Pr)$_3$ (1.10 equiv.) and *c*HexMgBr (2.00 equiv.) with subsequent addition of a Lewis acid did indeed provide the 3-*tert*-butoxycarbonyl-3-azabicyclo[3.1.0]hex-1-ylamine (**84**), 3-(4-methoxybenzyl)-3-azabicyclo[3.1.0]hex-1-ylamine (**90**) and 3-benzyl-3-azabicyclo-[3.1.0]hex-1-ylamine (**91**), albeit in moderate yields (Table 4).



86 R = Boc
87 R = PMB
88 R = Bn

89

84 R = Boc
90 R = PMB
91 R = Bn

Product	R	Additive	*T* [°C]	*t* [h]	Yield (%)
91	Bn	$BF_3{\cdot}Et_2O$	20	1	trace
91	Bn	$BF_3{\cdot}Et_2O$	70	2	46
91	Bn	LiI	70	3	48
91	Bn	LiI	70	16	43
91	Bn	NaI	70	3	28
84	Boc	LiI	70	14	trace
84	Boc	LiI	70	3	41
90	PMB	LiI	70	3	48

Table 4. Intramolecular reductive cyclopropanation of *N*-allylaminocarbonitriles **86–88**.

While only traces of the product **91** were detected under the conditions developed by Szymoniak et al. to accelerate the ring contraction of the intermediate azatitanacyclopentene

89, *i. e.* addition of $BF_3 \cdot OEt_2$ as a Lewis acid at ambient temperature, compound **91** could be obtained by heating the reaction mixture at 70 °C for 2 h. The reaction, however, proceeded more cleanly and gave the bicyclic diamine **91** in 48% yield, when the reaction mixture was heated at 70 °C for 3 h after addition of 2 equivalents of lithium iodide. No by-products could be isolated except for unidentified oligomeric materials. The structure of the diamine **91** was confirmed by an X-ray crystal structure analysis of its hemihydrochloride **91**·0.5 HCl (Figure 6).

The structure of **91**·0.5 HCl is another example of the conformational flexibility of this class of compounds. The unit cell contains two independent molecules, both are partially disordered. The independent molecules are different conformers. The dihedral angle C6-N5-C7-C8, describing the conformation of the benzyl group relative to the bicyclic system, is 172.5(2)° in one independent molecule and –72.8(2)° in the second one. Molecules in crystals of **91**·0.5 HCl are linked to each other by a network of hydrogen bonds of N–H···Cl and N–H···N types, forming a layered structure (Figure 6).

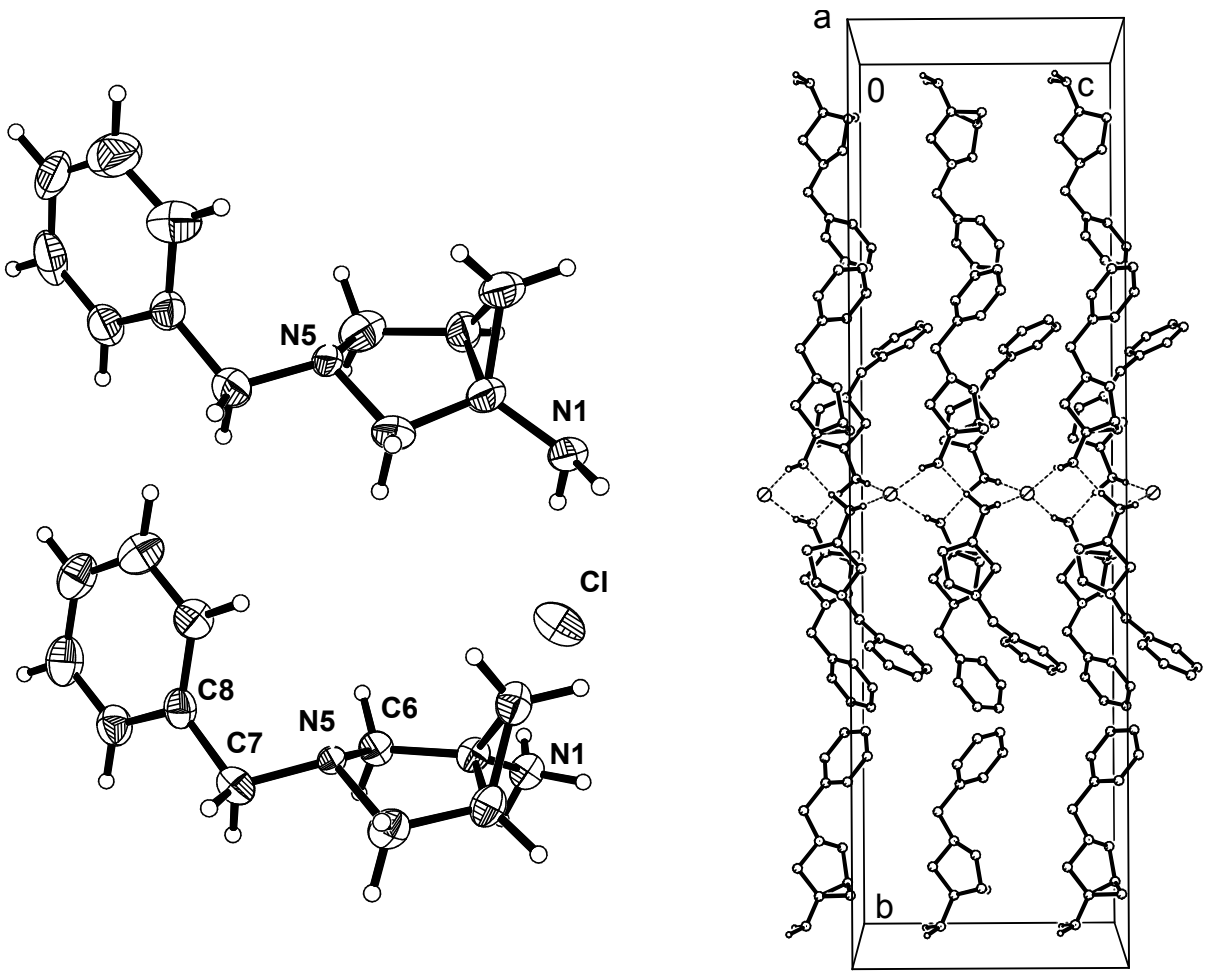
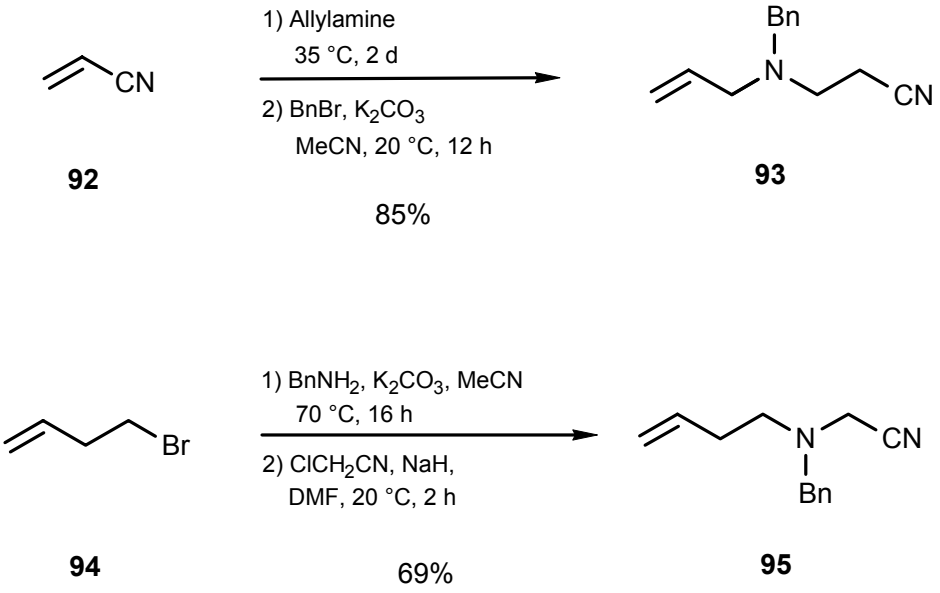


Figure 6. Molecular structure (left) and packing (right) of the 3-benzyl-3-azabicyclo[3.1.0]hex-1-ylamine hemihydrochloride **91**·0.5 HCl in the crystal (displacement ellipsoids are shown at the 50% probability level).

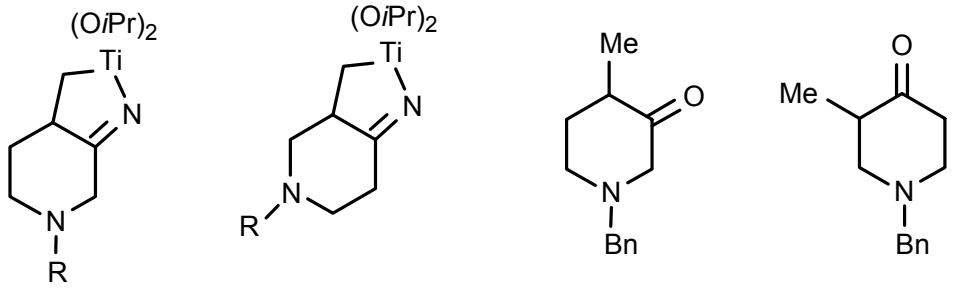
3.4. Attempted synthesis of 3-azabicyclo[4.1.0]heptane systems from nitrile derivatives

In contrast to the behavior of nitriles **86–88**, the homologous *N*-allyl-*N*-benzyl-3-aminopropionitrile (**93**) and *N*-homoallyl-*N*-benzyl-2-aminoacetonitrile (**95**), the synthesis of which is described in Scheme 15, gave predominantly the 1-benzyl-4-methylpiperidin-3-one (**98**)[40] (45%) and 1-benzyl-3-methylpiperidin-4-one (**99**)[41] (35%) resulting from hydrolysis of the intermediate azatitanacyclopentenes **96** and **97**, respectively. Apparently the

intermediates **96** and **97** are particularly stable under the used reaction conditions, and only traces of the corresponding 3-azabicyclo[4.1.0]heptane derivatives were obtained (Scheme 16).



Scheme 15. Synthesis of *N*-allyl-*N*-benzyl-3-aminopropionitrile (**93**) and *N*-homoallyl-*N*-benzyl-2-aminoacetonitrile (**95**)



Scheme 16. Intermediate azatitanacyclopentenes **96** and **97** and their hydrolysis products **98** and **99**.

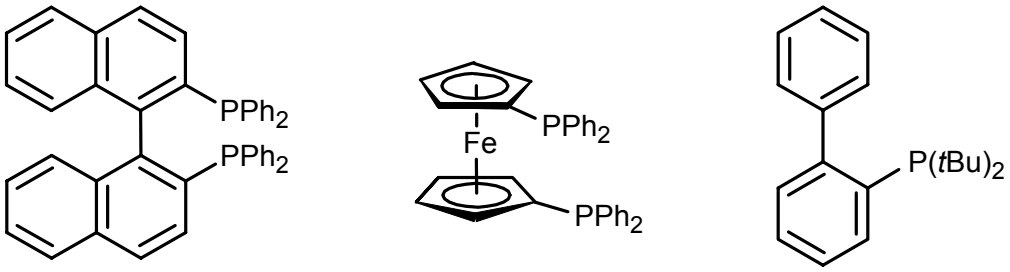
4. Synthesis of 3-Aryl-3-azabicyclo[3.1.0]hex-1-ylamine Derivatives

4.1. Introduction

Aromatic amines play an important role in many areas including pharmaceuticals, agrochemicals, photography, pigments and electronic materials.[42] In the last 25 years the advent of Pd-catalyzed cross-coupling reactions introduced a new concept of carbon-carbon bond formation. The strategies developed by Kumada, Stille, Suzuki, Negishi, Heck and Sonogashira are now widely used.[43]

The Pd-catalyzed cross-coupling reactions were applied for the first time to the formation of carbon–heteroatom bonds by Kosugi and Migita in 1983.[44] They reported that *N*,*N*-diethylanilines can be prepared from the $PdCl_2[P(o\text{-tolyl})_3]_2$-catalyzed reaction of aryl bromides and *N*,*N*-diethylaminotributylstannane. During the following 10 years no example of such reactions was reported, until Buchwald et al. and Hartwig et al. started their investigations in this field. They demonstrated that using $Pd(dba)_2$ and $P(o\text{-tolyl})_3$ in the presence of a base such as sodium *tert*-butoxide (NaO*t*Bu) the reaction proceeds without the use of stannanes.[45] However, such conditions presented problems in the reaction of primary amines and were of limited use in the synthesis of aminopyridines. The latter are important compounds, they have been used as acyl transfer reagents in organic chemistry[46], as ligands in organometallic chemistry[47], as fluorescent dyes[48] and as central nervous system stimulants.[49] The current methods for the preparation of aminopyridines are based on nucleophilic aromatic substitution of halopyridines. However, this process usually gives low yields and requires activated substrates and high temperatures.[50] Attempts to apply Pd(0) complexes in the cross-coupling reaction of bromopyridines have been unsuccessful.[50] It has been shown that these pyridines inhibit the $Pd(0)/P(o\text{-tolyl})_3$-catalyzed amination of aryl

bromides by displacing a P(*o*-tolyl)$_3$ ligand, forming inactive *trans*-bis(pyridyl)palladium complexes.[51] Buchwald et al. found that using chelating bisphosphines, 3-bromopyridines could be converted to their aminated derivatives in good yields, even in the presence of primary amines.[52] They showed that chelating bisphosphines do not undergo ligand exchange with pyridines (thus preventing deactivation of the catalyst) and inhibit side reactions such as β-hydride elimination from an amidopalladium intermediate. Several examples[53] have been reported which show the catalyst generated from $Pd_2(dba)_3$ and (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(±)–BINAP, **100**, Figure 7] to be the most general system for the cross-coupling reaction of a wide variety of substrates including 3-bromopyridines and primary amines.



100 (±)–BINAP

101 dppf

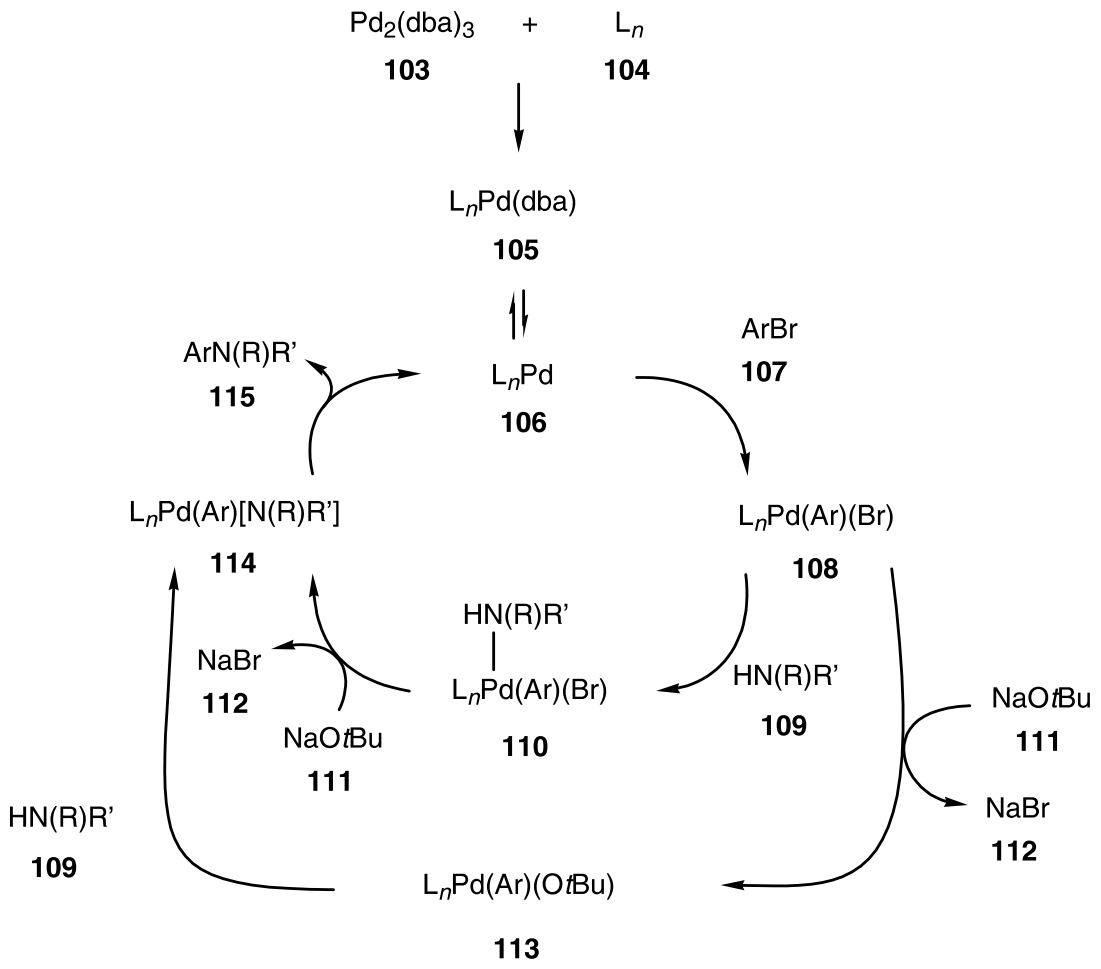
102 2-(di-*tert*-butylphosphino)-biphenyl

Figure 7. Ligands for Pd-catalyzed cross-coupling aminations.

In the same period Hartwig et al. reported on the use of 1,1'-bis(diphenylphosphino)ferrocene (dppf, **101**) as a chelating ligand for Pd-catalyzed amination of aryl halides.[54] Complexes of **101** and Pd(0) prefer reductive elimination over β-hydride elimination. It is assumed that this preference[55] results from chelation and a large bite angle rather than from steric effects.

In 1999 Buchwald et al. reported the development of catalysts of the third generation, such as 2-(di-*tert*-butylphosphino)-biphenyl (**102**) which, in combination with $Pd(OAc)_2$, is able to effect even the amination of chloropyridines in high yields.[56]

The catalytic cycle for the Pd-catalyzed cross-coupling amination for $Pd_2(dba)_3$ and ligand L is believed to be similar to that postulated for many Pd-catalyzed C-C bond forming processes (Scheme 17).[53]



Scheme 17. Catalytic cycle for the Pd-catalyzed cross-coupling amination.

The initial reaction of $Pd_2(dba)_3$ (**103**) and L_n (**104**) leads to the formation of the complex **105** which probably undergoes dissociation of a dba ligand to complex **106**. Oxidative addition of an aryl bromide **107** to **106** gives complex **108**. Coordination of the amine **109** to **108**,

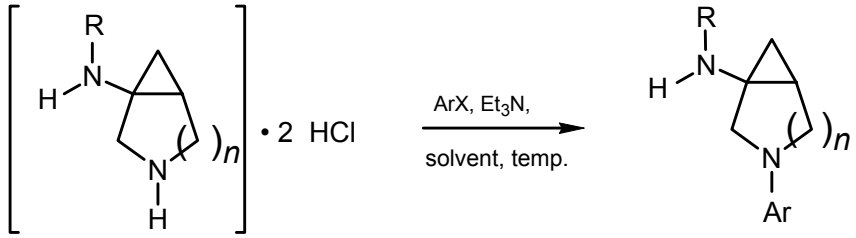
followed by deprotonation induced by NaO*t*Bu as a base, may form amido complex **114**, which undergoes reductive elimination to form the target compound **115** and to regenerate the Pd(0) catalyst. Alternatively, Hartwig et al. have demonstrated that by addition of the amine **109** to (L_n)Pd(Ar)(O*t*Bu) (**113**, L_n = dppf), the aryl amine is formed via intermediate **114**.[55] Thus, it can be postulated that the reaction proceeds via complex **113** when NaO*t*Bu (**111**) is used as a base.

4.2. Nucleophilic aromatic substitution with 3-azabicyclo[3.1.0]hex-1-ylamine

Belov[57] observed that *exo*-6-*tert*-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane underwent nucleophilic aromatic substitution with highly active heteroaromatic chlorides under thermal conditions in good yields.

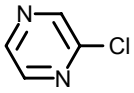
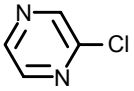
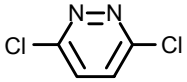
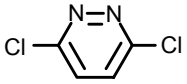
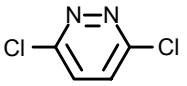
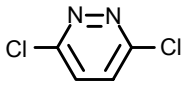
In this project, the reactivity toward nucleophilic aromatic substitution was studied with the 3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**28-HCl**), its partially protected derivatives **82-HCl**–**84-HCl** and the 3-azabicyclo[4.1.0]hept-1-ylamine dihydrochloride (**29-HCl**). Nucleophilic aromatic substitution of amine **28-HCl** may lead to a mixture of mono-, di- and triarylsubstituted products. Indeed, reaction of amine **28-HCl** with 2-chloropyrazine as well as 3,6-dichloropyridazine in MeCN, in a sealed tube at 80 °C for 1 d (entries 1 and 3, Table 5), gave products **116** and **117** in 16 and 35% yield, respectively, after aqueous work up and chromatographic purification. The 3-aryl-3-azabicyclo[3.1.0]hex-1-ylamines were formed as the sole products and no traces of 1-aryl amino derivatives were observed.

Table 5. Nucleophilic aromatic substitution with **28**-**HCl**, **82**-**HCl** and **29**-**HCl**.



28-**HCl** R = H n = 1
82-**HCl** R = Me n = 1
29-**HCl** R = H n = 2

116–119

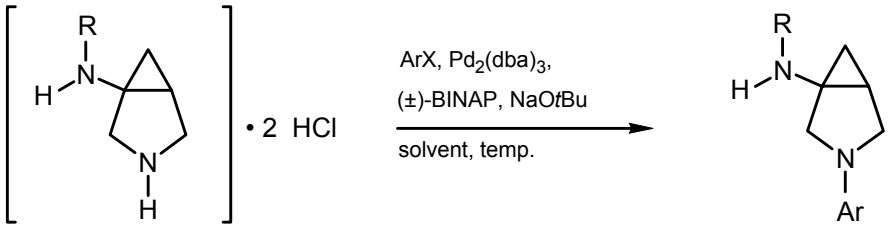
Entry	Amine	ArX	*n*	Solvent	T [°C]	Time	Product	Yield (%)
1	**28**-**HCl**		1	MeCN	80	1 d	**116**	16
2	**28**-**HCl**		1	DMAA	130	3 h	**116**	36
3	**28**-**HCl**		1	MeCN	80	1 d	**117**	35
4	**28**-**HCl**		1	DMAA	130	3 h	**117**	64
5	**82**-**HCl**		1	DMAA	130	3 h	**118**	65
6	**29**-**HCl**		2	DMAA	130	4 h	**119**	57

Upon heating in *N*,*N*-dimethylacetamide (DMAA) at 130 °C for 3 h and performing a simple filtration without aqueous work up, better yields were observed. Due to the significantly shorter reaction times, extensive decomposition of starting material is prevented, and no product was lost in the aqueous phase during the work up. Even in the case of *N*-methyl-3-azabicyclo[3.1.0]hex-1-ylamine hydrochloride (**82**-**HCl**) (entry 5, Table 5), in which the presence of two secondary amines should give a competitive nucleophilic substitution, the exclusive formation of the 3-aryl derivative **118** was detected.

4.3. Pd-catalyzed cross coupling of 3-azabicyclo[3.1.0]hex-1-ylamines

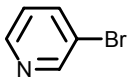
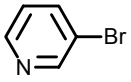
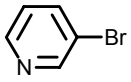
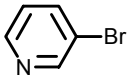
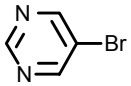
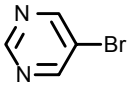
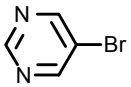
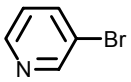
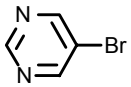
The introduction of a pyrid-3-yl function was of great interest in order to synthesize new possible nicotinic receptor ligands (see Section A). As reported in Section 4.1, the aromatic substitution of 3-halopyridines requires Pd-catalysis. It was considered first to apply Buchwald's protocol[53] to the reaction of **82-HCl** with 3-bromopyridine as well as 5-bromopyrimidine in the presence of NaO*t*Bu (3.50 equiv.) and a mixture of $Pd_2(dba)_3$ (2 mol%) and (±)–BINAP (4 mol%) as a catalyst in toluene (Table 6).

Table 6. Pd-catalyzed cross-coupling reactions of **28-HCl** and **82-HCl**.



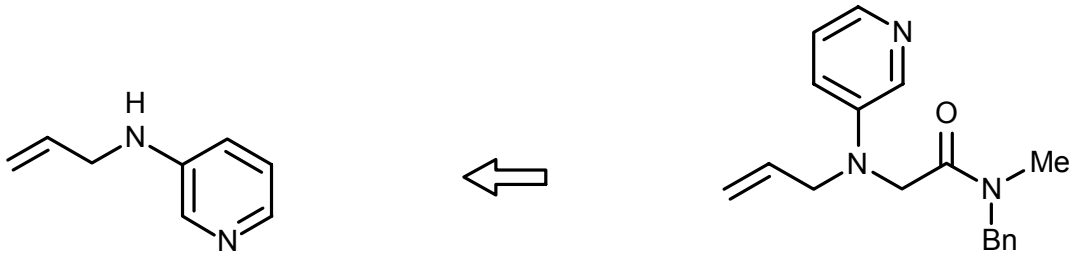
28-HCl R = H
82-HCl R = Me

120–123

Amine	ArX	Solvent	Time	T [°C]	Product	Yield (%)
82-HCl		toluene	3 h	80	**120**	37
82-HCl		THF	2 h	70	**120**	32
82-HCl		toluene/DMF	1 d	100	**120**	53
82-HCl		DME	1 d	80	**120**	67
82-HCl		toluene	3 h	80	**121**	26
82-HCl		toluene/DMF	1 d	100	**121**	45
82-HCl		DME	1 d	80	**121**	61
28-HCl		toluene/DMF	16 h	100	**122**	40
28-HCl		DME	10 h	80	**123**	63

The reaction was complete within 3 h at 80 °C (TLC control), and the target molecules **120** and **121** were obtained in 37 and 26% yield, respectively (Table 6). Change of the solvent improved the yield and **120**, **121** and **123** were obtained in 67, 61 and 63% yield, respectively, when 1,2-dimethoxyethane (DME) and a catalyst mixture of $Pd_2(dba)_3$ (5 mol%) and (±)-BINAP (10 mol%) were used. Also in this case, the 3-substituted arylamines were obtained as the sole products.

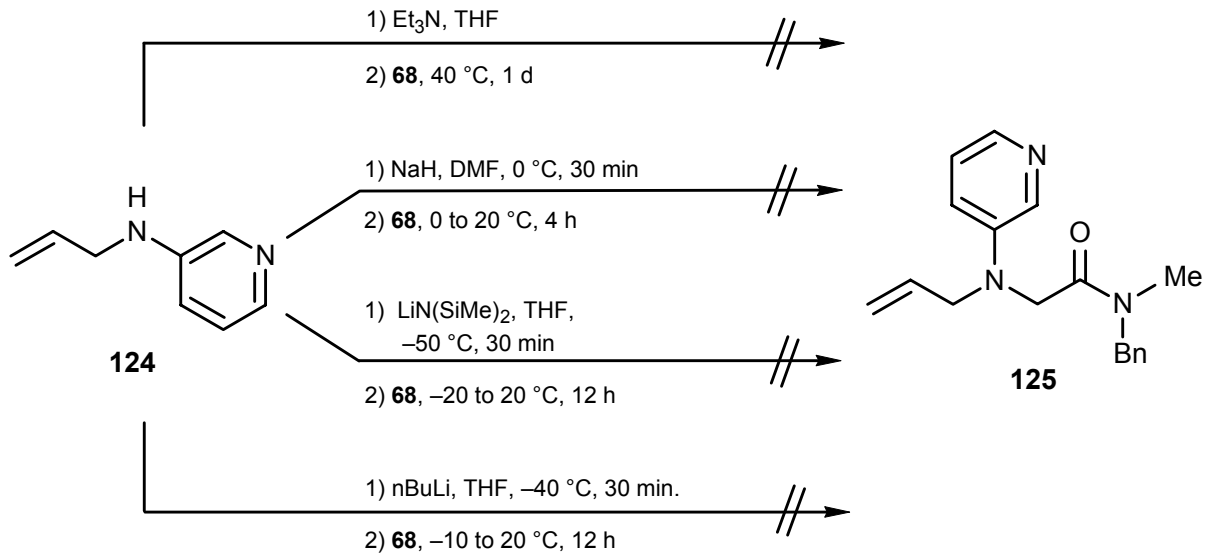
An alternative approach to compound of **120** would be to introduce the pyridin-3-yl substituent directly in the amide **125**, as the starting material for the Ti-mediated intramolecular reductive cyclopropanation (Scheme 18).



124 **125**

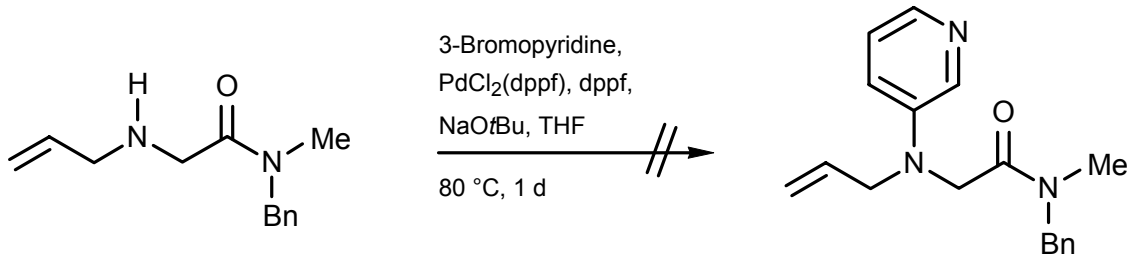
Scheme 18. A strategy for the synthesis of the amide **125**.

Compound **124** was synthesized according to Putman et al.[58] in a Pd-catalyzed cross-coupling of allylamine and 3-bromopyridine, which involved $PdCl_2$(dppf)/dppf as a catalyst system, in 65% yield. Alkylation of amine **124** with *N*-benzyl-*N*-methylbromoacetamide (**68**) was attempted by treatment with Et_3N in THF, but heating at 40 °C for 1 d only led to quantitative recovery of starting materials. Initially this poor reactivity was thought to be a result of the reduced acidity of the NH proton in **124**. However, the use of stronger bases such as NaH, *n*BuLi and $LiN(SiMe)_2$ did not give the desired product either (Scheme 19).



Scheme 19. Attempted synthesis of the amide **125**.

Another possible approach was the use of amine **126** in the Pd-catalyzed crosscoupling of 3-bromopyridine, but even in this case the reaction did not take place, and unreacted starting materials were recovered (Scheme 20).

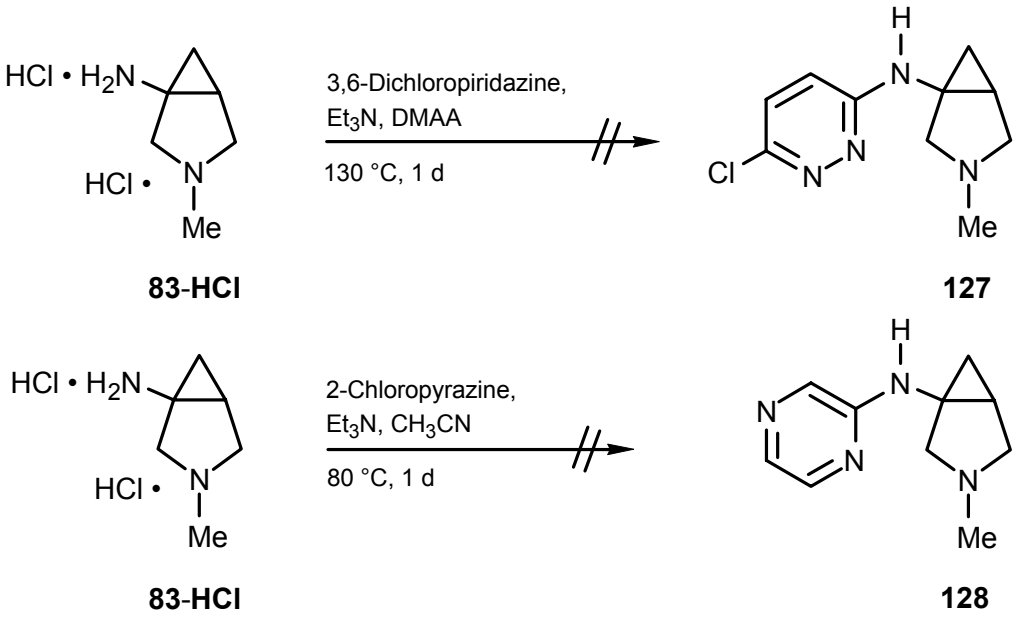


126 **125**

Scheme 20. Attempted synthesis of amide **125** from amine **126**.

4.4. Pd-catalyzed aromatic substitution of 3-methyl-3-azabicyclo[3.1.0]hex-1-ylamine hydrochloride

The high selectivity observed in the arylations in Sections 4.2 and 4.3 indicated that this approach did not allow the synthesis of 1-arylamino derivatives. In fact, the primary amine **83-HCl** did not react with 2-chloropyrazine as well as 3,6-dichloropyridazine to give compounds **127** and **128**, respectively (Scheme 21).



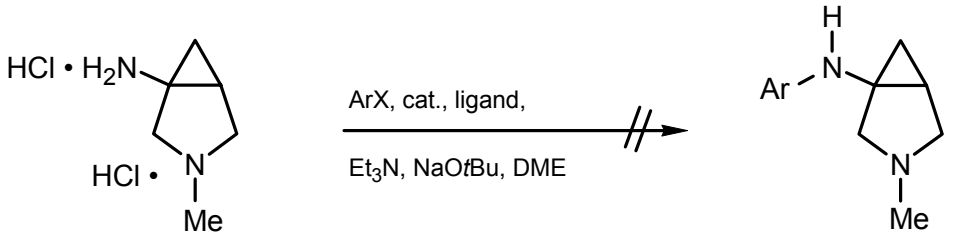
83-HCl **127**

83-HCl **128**

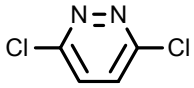
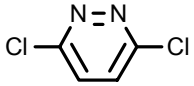
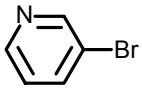
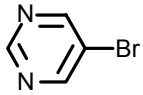
Scheme 21. Attempted synthesis of compounds **127** and **128**.

Thus, the next idea was to perform the Pd-catalyzed cross coupling with highly reactive heterocycles, in analogy to the results reported in Section 4.3. However, the reaction with 3-bromopyridine, 5-bromopyrimidine and 3,6-dichloropyridazine, using $Pd_2(dba)_3$/**100** as a catalytic system, did not proceed and the formation of any desired products was not observed (Table 7).

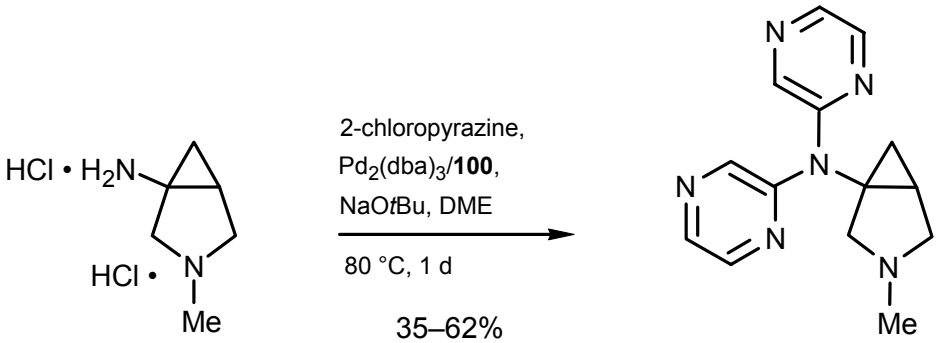
Table 7. Attempted Pd-catalyzed amination of **83**-**HCl**.



83-**HCl** **127**,**129**,**130**

ArX	Cat.	Ligand	Product
	$Pd_2(dba)_3$	**100**	**127**
	$Pd(OAc)_2$	**102**	**127**
	$Pd_2(dba)_3$	**100**	**129**
	$Pd_2(dba)_3$	**100**	**130**

Unfortunately, this approach did not lead to the target compounds even when a combination of $Pd(OAc)_2$/**102** and the highly reactive 3,6-dichloropyridazine was employed. Amine **83**-**HCl** underwent twofold substitution only in the presence of $Pd_2(dba)_3$/**100** with 6-chloropyrazine, and compound **131** was isolated in 35% yield (Scheme 22). In line with this unexpected result, compound **131** was obtained in 62% yield as a crystalline solid when 2 equivalents of 6-chloropyrazine were used.



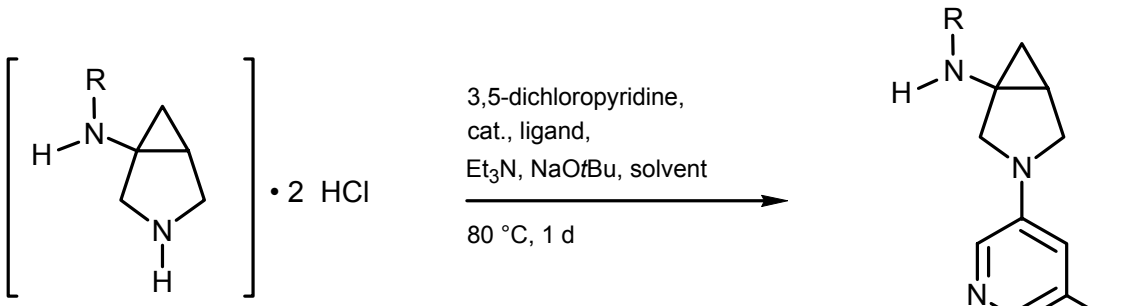
83-**HCl** **131**

Scheme 22. Synthesis of 3-methyl-*N*,*N*-di(pyrazin-2-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**131**).

4.5. Synthesis of 5-chloropyridin-3-yl derivatives

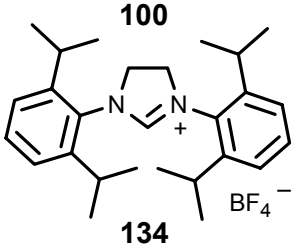
It is known that 3-chloro- and 3,5-dichloropyridines do not undergo nucleophilic aromatic substitution with amines.[53,54] Therefore, these pyridines appeared to be good candidates to be employed in a Pd-catalyzed cross-coupling reactions as described by Buchwald et al. and Hartwig et al..

Table 8. Pd-catalyzed amination of 3,5–dichloropyridine.



28-**HCl** R = H
82-**HCl** R = Me

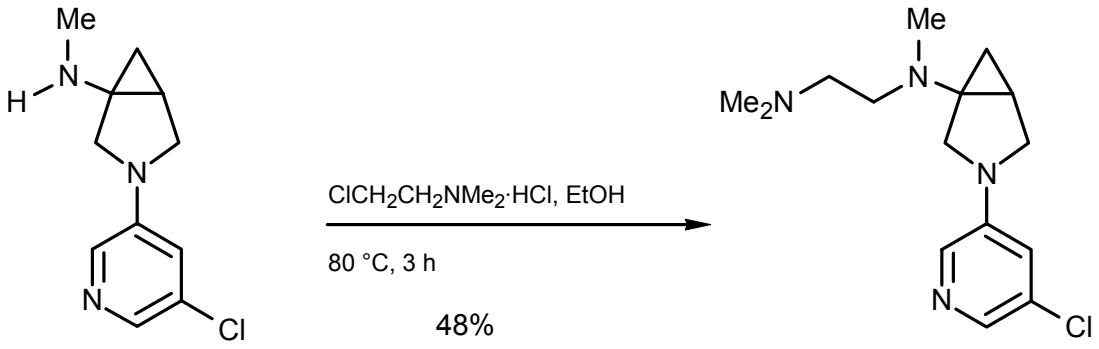
132,**133**

Amine	Cat.	Ligand	Solvent	Product	Yield [%]
28-**HCl**	$Pd_2(dba)_3$	**100**	DME	**132**	—
82-**HCl**	$Pd_2(dba)_3$	 **134**	DME	**133**	—
82-**HCl**	$Pd_2(dba)_3$	**100**	nBu$_4$NCl	**133**	—
82-**HCl**	$Pd(OAc)_2$	**102**	DME	**133**	38
28-**HCl**	$Pd(OAc)_2$	**102**	DME	**132**	41

Amines **28**-**HCl** and **82**-**HCl** were heated with 3,5-dichloropyridine at 80 °C in the presence of $Pd_2(dba)_3$/**100**, but the desired products **132** and **133** were not formed, even when the phase transfer catalyst nBu$_4$NCl was added. Hartwig et al.[59] reported that the saturated carbene ligands, used by Grubbs et al. in ruthenium complexes for olefin metathesis,[60] led to fast reactions in the Pd-catalyzed coupling of aryl chlorides with amines. But even when ligand **134** was used in combination with $Pd_2(dba)_3$, the desired reaction did not take place (Table 8).

The desired results were obtained when $Pd(OAc)_2$ was used in combination with 2-(di-*tert*-butylphosphino)-biphenyl (**102**) to provide the 3-substituted amines **132** and **133** in 38 and 40% yield, respectively (Table 8).

Amine **133** was further elaborated by introduction of an additional amino substituent to provide a fourth nitrogen atom in the molecule. After heating the amine **133** and 1-chloro-2-dimethylaminoethane hydrochloride in EtOH for 3 h at 80 °C, compound **135** was isolated in 48% yield (Scheme 23).



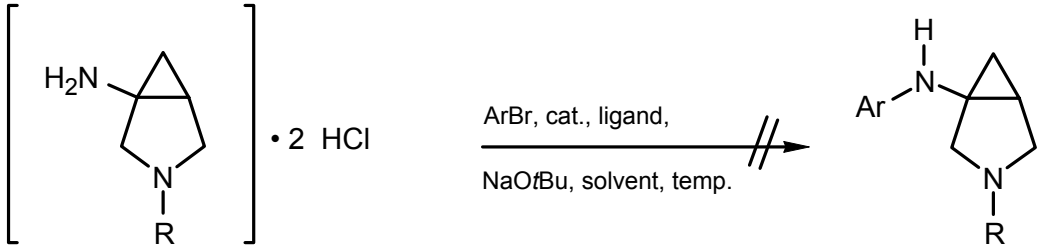
133 **135**

Scheme 23. Synthesis of *N*-(2-dimethylaminoethyl)-*N*-methyl-3-(5-chloropyridin-3-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**135**).

4.6. Attempted synthesis of aniline derivatives

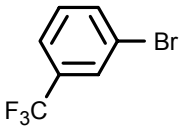
In this context the Pd-catalyzed cross coupling of aryl bromides with amines **83**-**HCl** and **84**, using NaO*t*Bu (1.40 equiv.) and a variety of catalytic systems in toluene at 110 °C was also investigated. Again, the primary amine proved to be inert under any catalytic conditions, and the desired products were not obtained.

Table 9. Pd-catalyzed cross-coupling of aryl bromides.



83-**HCl** R = Me
84 R = Boc (free base)

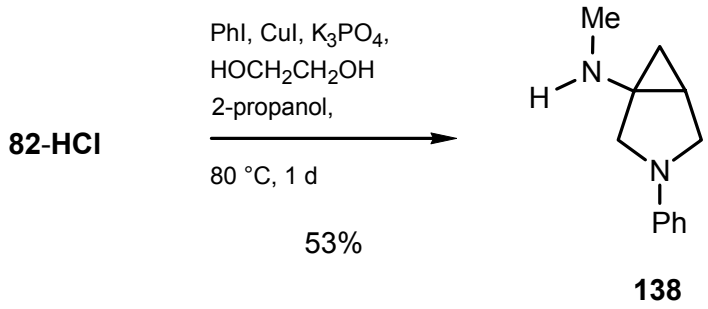
136, **137**

Amine	ArX	Cat.	Ligand	Solvent	T [°C]	Product
83-**HCl**		$Pd_2(dba)_3$	**100**	toluene	110	**136**
83-**HCl**		$Pd(OAc)_2$	**100**	toluene	110	**136**
84		$Pd(OAc)_2$	**102**	DME	80	**137**

This lack of reactivity must be attributed to the bulk of the bicyclic system, which may retard the insertion of the palladium species to yield intermediate **110** (Scheme 17) and interrupt the catalytic cycle.

Buchwald et al. have recently reported that aryl iodides can undergo copper-catalyzed coupling with alkylamines in the presence of diols.[61]

Amine **82**-**HCl** did indeed react with iodobenzene upon treatment with CuI (5 mol%), K_3PO_4 (2.00 equiv.) and 1,2-propanediol (2.00 equiv.) in 2-propanol at 80 °C to yield phenylamine **139** in 53% yield (Scheme 24).



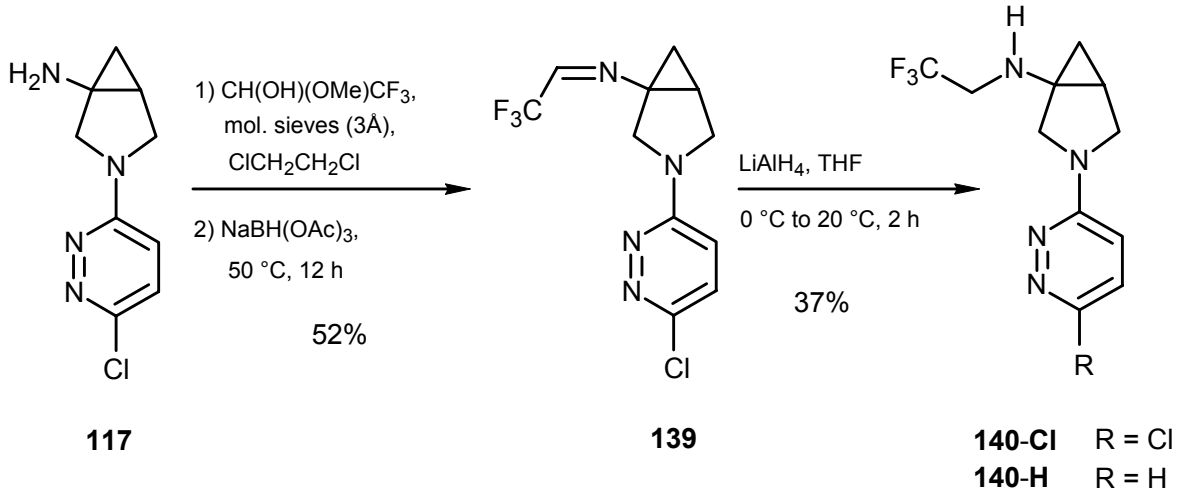
Scheme 24. Cu-catalyzed amination with amine **82-HCl**.

5. Elaboration of the 3-Aryl-3-azabicyclo[3.1.0]hex-1-ylamine Skeleton

5.1. Synthesis of trifluoroethyl derivatives

Further elaboration of the primary amines **116**, **117**, **122** and **123** was studied in order to obtain compounds bearing a combination of trifluoroethyl and aryl substituent on the amino functions, as analogs of compound **5** (see Section A). Direct alkylation of **117** with alkyl bromides may give dialkylated compounds as major or unique products. Belov[57] observed that reductive alkylation of *exo*-6-amino-3-azabicyclo[3.1.0]hexane with aliphatic carbonyl compounds in the presence of sodium triacetoxyborohydride [$NaBH(OAc)_3$] and molecular sieves (3 Å), led to monoalkylated derivatives in good yields.

In the next approach it was decided to apply the same conditions to amine **117**. The latter was treated with trifluoroacetaldehyde methyl hemiacetal (commercially available equivalent and source of trifluoroacetaldehyde) and molecular sieves (3 Å) in 1,2-dichloroethane at ambient temperature for 30 min, then with $NaBH(OAc)_3$ at 50 °C for 12 h (Scheme 25).

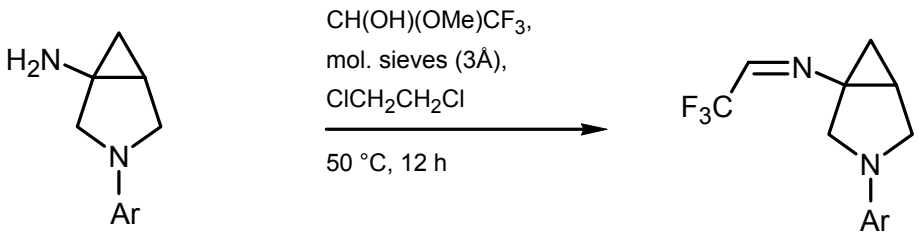


117 **139** **140-Cl** R = Cl
140-H R = H

Scheme 25. Synthesis of trifluoroethyl derivative **140-H**.

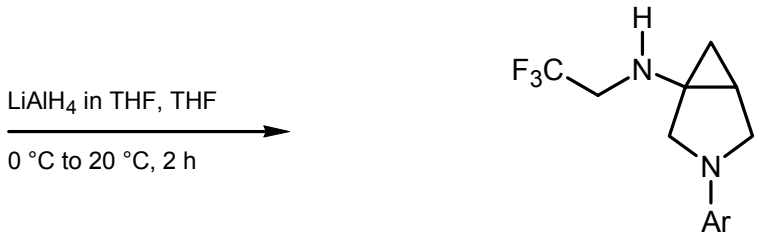
Instead of the desired compound **140-Cl**, the imine **139** was isolated in 52% yield. The imine function in **139** was then reduced with $LiAlH_4$ in THF with concomitant reduction of the aryl chloride to give compound **140-H** in 37% yield (Scheme 25).

The synthesis of trifluoroethyl derivatives could be achieved in a two-step process: first formation of the imine at 50 °C, then reduction by adding a suspension of $LiAlH_4$ in THF carefully at 0 °C to the imine (Scheme 26).



116 Ar = pyrazin-2-yl
117 Ar = 6-chloropyridazin-3-yl
122 Ar = pyrid-3-yl
123 Ar = pyrimidin-5-yl

139 Ar = 6-chloropyridazin-3-yl (92%)
141 Ar = pyrid-3-yl (78%)
142 Ar = pyrimidin-5-yl (70%)
143 Ar = pyrazin-2-yl (72%)



140-Cl Ar = 6-chloropyridazin-3-yl (79%)
144 Ar = pyrid-3-yl (56%)
145 Ar = pyrimidin-5-yl (55%)
146 Ar = pyrazin-2-yl (73%)

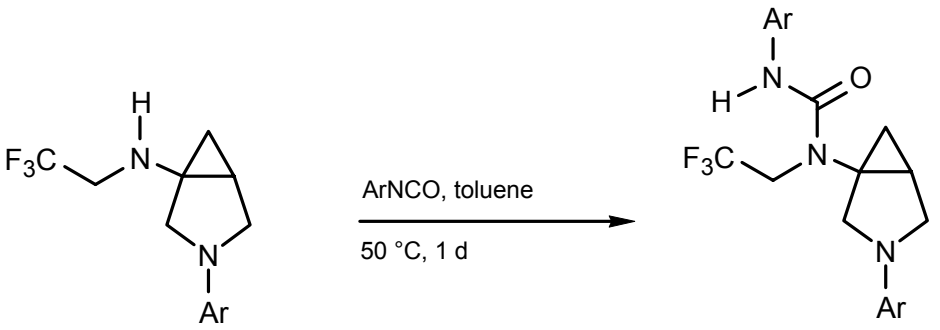
Scheme 26. Synthesis of trifluoroethyl derivatives **140-Cl**, **144**–**146**.

Such conditions prevented the loss of the chlorine substituent from the aryl moiety in compound **140** and improved the yields. The imines **139**, **141**, **142** and **143** were used directly in the next step without further purification to provide compounds **140-Cl**, **144**, **145** and **146** in 73, 44, 39 and 53% overall yield, respectively.

5.2. Synthesis of urea derivatives

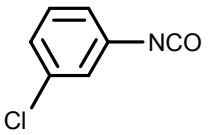
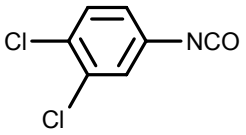
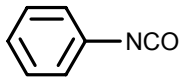
Preparation of indoxacarb analogs (see Section A) of type **147–149** was achieved by treatment of amines **140–Cl**, and **146** with the corresponding isocyanate in toluene at 50 °C. The products, isolated as crystals, were purified by chromatography or by recrystallization and were obtained in excellent yields.

Table 10. Synthesis of urea derivatives **147–149**.



140-Cl
146

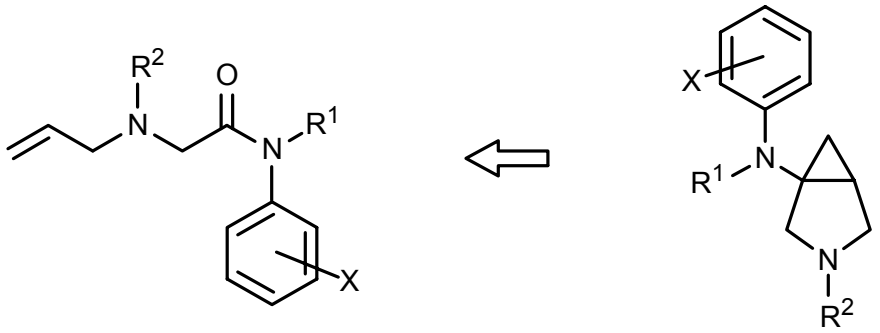
147–149

Amine	ArNCO	Product	Yield (%)
140-Cl		**147**	quant.
140-Cl		**148**	92
146		**149**	98

Amine **116**, **117**, **122**, **123**, **132** have been used in combinatorial chemistry with 48 types of isocyanates for the synthesis of a library of compounds, the biological tests of which are currently in progress.

5.3. Synthesis of N-methyl-N-aryl-3-azabicyclo[3.1.0]hex-1-ylamines

One possible way to attach an aryl group onto the 1-amino group of the 3-azabicyclo[3.1.0]hexane is to synthesize an amide precursor of type **150** (Scheme 27).



150 **151**

Scheme 27. Strategy for the synthesis of 3-azabicyclo[3.1.0]hex-1-ylamines of type **151**.

Amides **154**–**156** were synthesized according to the procedure reported in Section 2.1 from 2-bromoacetylamides **152** and **153** in 35, 50 and 38% overall yield, respectively (Scheme 28).

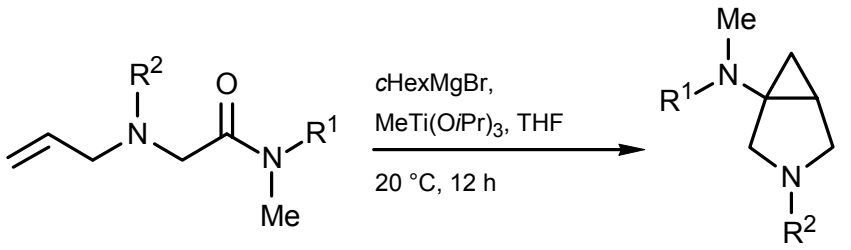
152 $R^1 = C_6H_5$
153 $R^1 = 4\text{-}ClC_6H_4$

154 $R^1 = C_6H_5$, R^2 = Boc (35%)
155 $R^1 = 4\text{-}ClC_6H_4$, R^2 = Boc (50%)
156 $R^1 = 4\text{-}ClC_6H_4$, R^2 = PMB (38%)

Scheme 28. Synthesis of amides **154**–**156** (PMB = *p*-methoxybenzyl).

Ti-mediated intramolecular reductive cyclopropanation of amides **154** and **155** was not successful, and unreacted starting materials were partially recovered. Only the reaction of amide **156** gave the desired product **159** in 54% yield (Table 11).

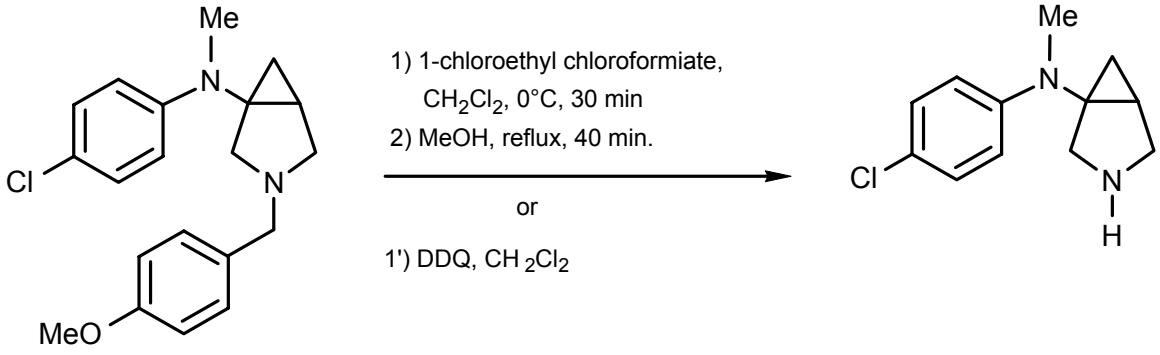
Table 11. Ti-mediated reductive cyclopropanation of amides **154**–**156**.



154–156 **157–159**

Amide	R^1	R^2	*n*	Product	Yield (%)
154	C_6H_5	Boc	1	**157**	—
155	4-ClC_6H_4	Boc	1	**158**	—
156	4-ClC_6H_4	PMB	1	**159**	54

Removal of the PMB group in the 3-azabicyclo[3.1.0]hex-1-ylamine **159** was investigated in order to obtain a target molecule which could be further elaborated. Amine **160** was obtained in 10% yield when 1-chloroethyl chloroformate in CH_2Cl_2 was used, and in 22% yield upon treatment with dichlorodicyanodihydroquinone (DDQ) in CH_2Cl_2 (Scheme 29).[62]



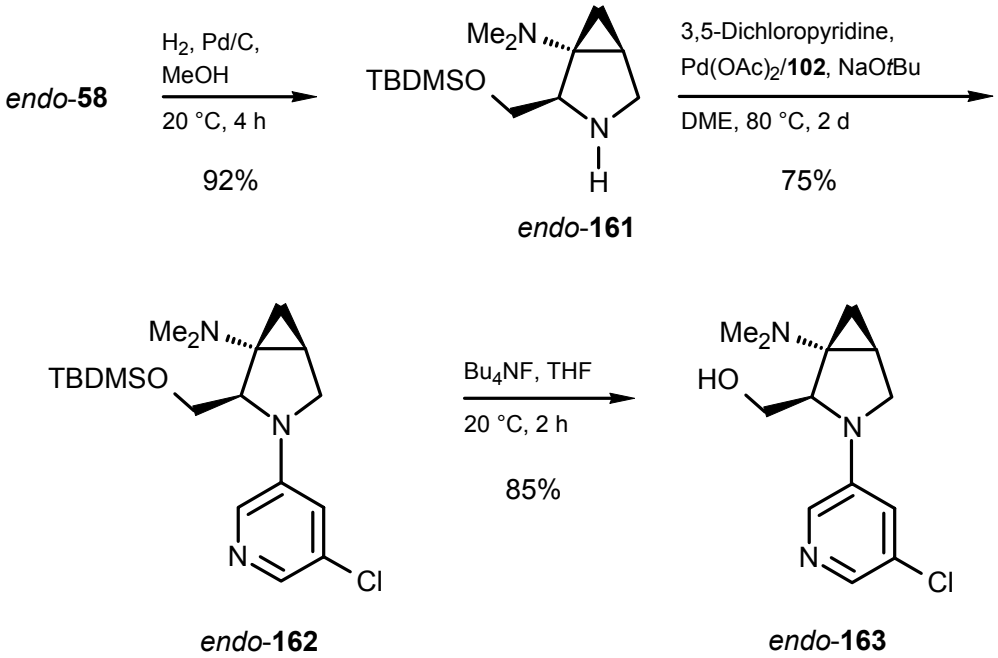
159 **160**

Scheme 29. Deprotection of the 3-azabicyclo[3.1.0]hex-1-ylamine **159**.

6. Elaboration of *endo*- and *exo*-(2*R*)-*N*,*N*-Dialkyl-3-benzyl-2-(*tert*-butyldimethylsilyloxymethyl)-3-azabicyclo[3.1.0]hex-1-ylamines

6.1. Attempted synthesis of endo-(2R)-2-(aminomethyl)-3-(5-chloropyrid-3-yl)-N,N-dimethyl-3-azabicyclo[3.1.0]hex-1-ylamine hydrochloride

In line with the aim of this project, the skeleton of compound **58** appeared to be a good candidate for the introduction of a combination of a further amino function and a chloropyrid-3-yl residue in order to increase the ligand capacity of such structures (see Section A).



Scheme 30. Synthesis of *endo*-(2*R*)-3-(5-chloropyrid-3-yl)-2-(hydroxymethyl)-*N*,*N*-dimethyl-3-azabicyclo[3.1.0]hex-1-ylamine (*endo*-**163**).

Amine *endo*-**58** was debenzylated by catalytic hydrogenation in 92% yield, and the resulting secondary amine underwent Pd-catalyzed cross coupling with 3,5-dichloropyridine under the optimized conditions reported in Section 4.5 [$Pd(OAc)_2$/2-(di-*tert*-butylphosphino)biphenyl (**102**) and NaO*t*Bu in DME], to give compound *endo*-**162** in 75% yield. The latter was

deprotected by treatment with Bu_4NF in THF at ambient temperature for 2 h to furnish the alcohol *endo*-**163** in 85% yield (Scheme 30). The structure of compound *endo*-**163** was confirmed by an X-ray crystal structure analysis (Figure 8).

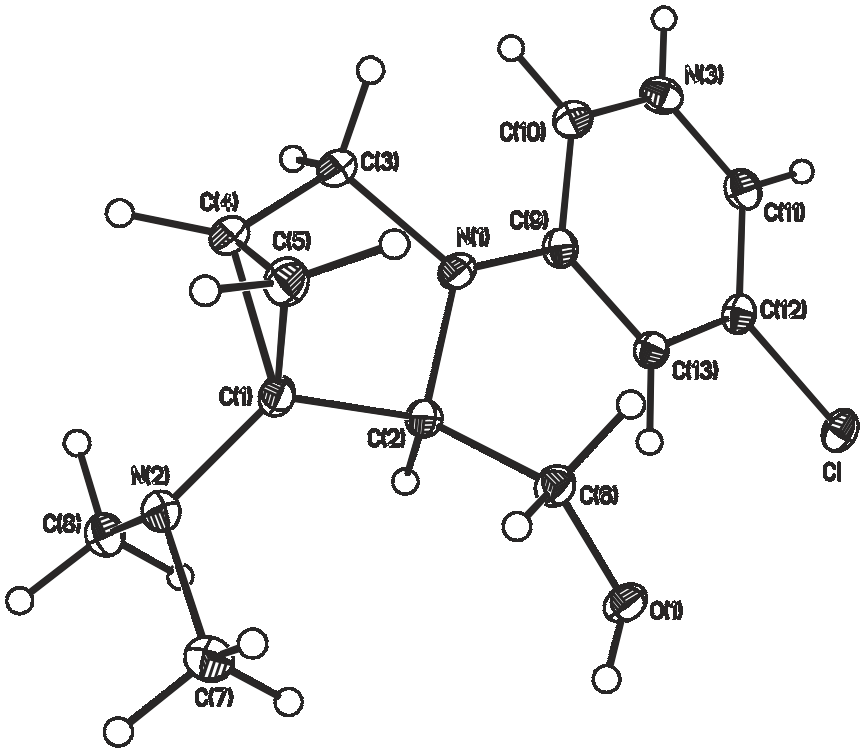
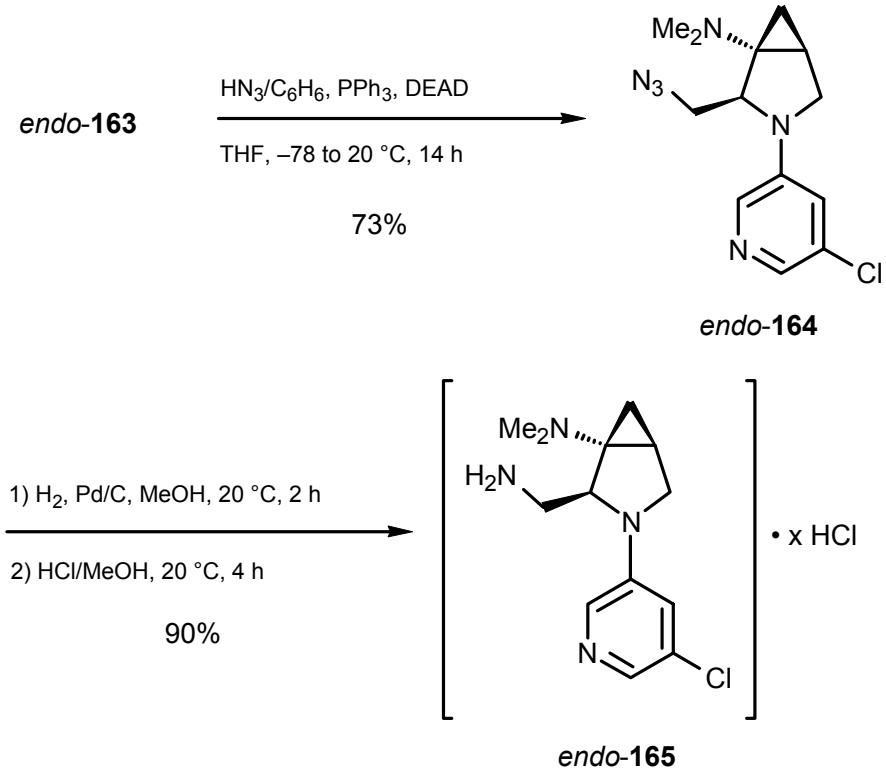


Figure 8. Molecular structure of *endo*-(2*R*)-3-(5-chloropyrid-3-yl)-2-(hydroxymethyl)-*N*,*N*-dimethyl-3-azabicyclo[3.1.0]hex-1-ylamine (*endo*-**163**) in the crystal.

Alcohol *endo*-**163** was transformed into the azide *endo*-**164** according to a Mitsunobu protocol[63] (HN_3/C_6H_6, PPh_3 and DEAD in THF) in 73% yield (Scheme 31). The latter was reduced by catalytic hydrogenation in the presence of HCl/MeOH to give the bicyclic amine hydrochloride *endo*-**165**. The latter was obtained as a yellow oil, which, after being exposed to the air for only a few hours, became dark, and the attempted purification failed. The ^{1}H-NMR spectrum (CD_3OD) showed only broad signals and also in the ^{13}C-NMR spectrum a

complex system of signals was observed. Only the mass-spectrometric-analysis revealed the molecular peak belonging to the desired product.

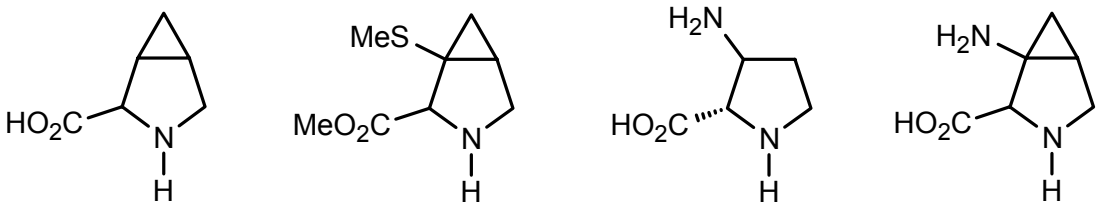


Scheme 31. Attempted synthesis of the tetraaza derivative *endo*-**165**.

6.2. Attempted synthesis of natural amino acid analogues

6.2.1. Considerations

Natural cyclopropane amino acids bearing a bicyclic structure are known (see Section A). 3,4-Methanoproline **8**[64] was extracted from the seeds of *Aesculus parviflora* and its synthesis was reported by Sasaki et al.[65] and by Witkop et al..[66] Recently, Krass[67] reported the synthesis of the related structure **166**. (2*S*)-3-Aminoproline (**167**) is another interesting amino acid and was isolated by Hatanaka et al.[68] from *Morchella esculenta* and related species (Figure 9). Its total synthesis has been reported by Baldwin et al..[69]



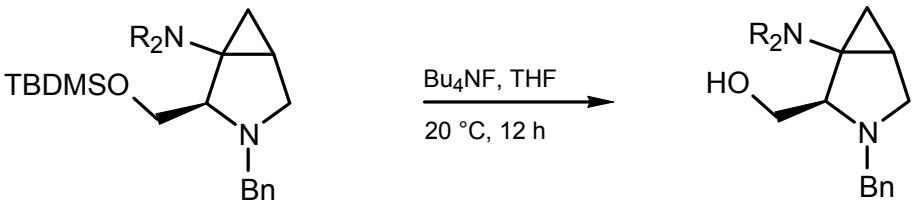
8 **166** **167** **168**

Figure 9. Structure of amino acids structurally related to **168**.

The bicyclic skeletons **58** and **59** obtained by Ti-mediated intramolecular cyclopropanation (see Section 1.2) appeared to be good candidates for the synthesis of analogues of type **168** of such amino acids, bearing simultaneously a cyclopropane moiety and an amino group in position 3 (proline numbering).

6.2.2. Attempted oxidation of the hydroxy function in endo- and exo-(2R)-N,N-dialkyl-3-benzyl-2-(hydroxymethyl)-3-azabicyclo[3.1.0]hex-1-ylamines

Deprotection of the hydroxy function in compounds *exo*-**58**, *endo*-**59** and *exo*-**59** was carried out by treatment with Bu_4NF in THF at ambient temperature, and the desired products *exo*-**169**, *endo*-**170** and *exo*-**170** were isolated in 90, 95 and 78% yield, respectively (Scheme 32).



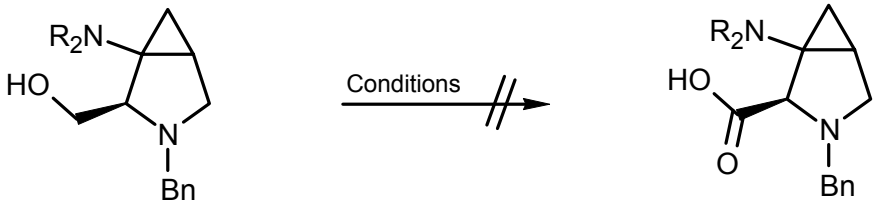
exo-**58** R = Me
endo-**59** R = Bn
exo-**59** R = Bn

exo-**169** R = Me (90%)
endo-**170** R = Bn (95%)
exo-**170** R = Bn (78%)

Scheme 32. Deprotection of the trialkylsilyl-protected hydroxy function in *exo*-**58**, *endo*-**59** and *exo*-**59**.

In the first attempt to perform an oxidation of the primary alcohol, the method reported by Kordes for the synthesis of an α-cyclopropylamino acid was applied.[70] By treatment of compound *exo*-**169** with $KMnO_4$ and NaOH in *tert*-butyl alcohol and water at ambient temperature for 12 h, a complex mixture of products was obtained and the ^{1}H-NMR spectrum showed no cyclopropyl proton signals. Even attempted oxidation with Jones reagent (Table 12) at ambient temperature[71] or at 0 °C[72] did not lead to the desired product (Table 12). In all cases even the formation of the corresponding aldehyde was not detected.

Table 12. Attempted synthesis of amino acids from alcohols **169** and **170**.



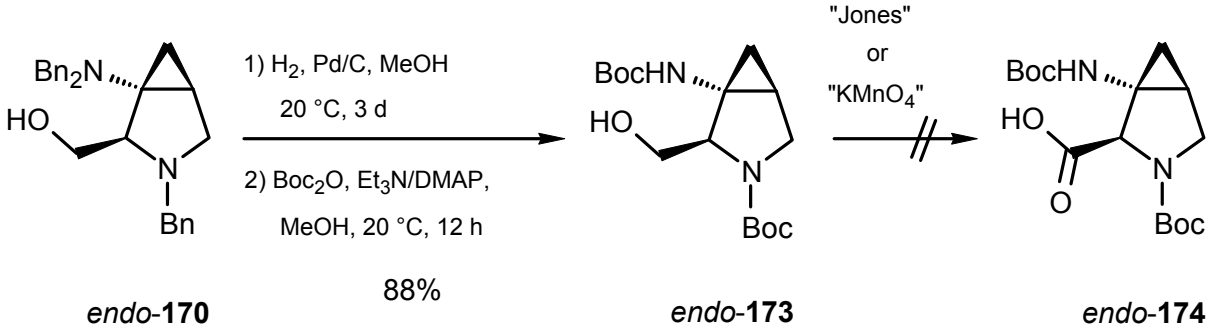
exo-**169** R = Me
endo-**170** R = Bn
exo-**170** R = Bn

exo-**171** R = Me
endo-**172** R = Bn
exo-**172** R = Bn

Compound	R	Conditions
exo-**169**	Me	$KMnO_4$, NaOH, *tert*BuOH/H_2O, 20 °C, 12 h
endo-**170**	Bn	Jones reagent, Me_2CO, 20 °C, 1 h
endo-**170**	Bn	Jones reagent, Me_2CO, 0°C to 20 °C, 5 h
exo-**170**	Bn	$KMnO_4$, NaOH, *tert*BuOH/H_2O, 20 °C, 12 h

To assure that the steric or electronic effects of the *N*-benzyl group were not the cause of the problematic oxidation of the alcohol function, oxidation of a differently substituted structure was attempted.

Thus, compound *endo*-**170** was deprotected by catalytic hydrogenolysis and protected as the bis-*tert*-butoxycarbonylamino derivative *endo*-**173** (Scheme 33).[72] Even in this case, the attempted oxidation with $KMnO_4$ or the Jones reagent did not give the desired product *endo*-**174**, and unreacted starting material was recovered.



endo-**170** *endo*-**173** *endo*-**174**

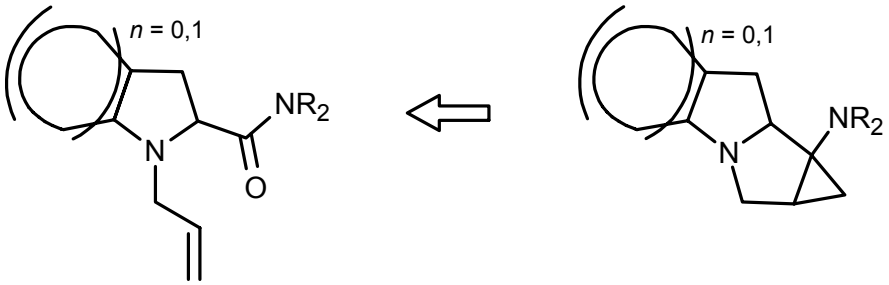
Scheme 33. Attempted synthesis of the *N*-Boc-protected amino acid *endo*-**174**.

7. Synthesis of Tri- and Tetracyclic Azaheterocycles by Ti-Mediated Intramolecular Reductive Cyclopropanation

7.1. Considerations

As reported in Sections 1 and 2, a variety of azabicyclo[3.1.0]hexane and azabicyclo[4.1.0]heptane systems can be synthesized by Ti-mediated intramolecular reductive cyclopropanation of *N*,*N*-dialkylamides, readily available from natural amino acids or bromoacetyl bromide with simple transformations.

Sato et al.[22a] reported that pyrrole- and indole-2-carboxylic esters underwent intramolecular cyclopropanation to give tri- and tetracyclic cyclopropanols. Consequently, it was tried to apply such a transformation to a suitable *N*,*N*-dialkylamide of type **175** which would lead to tricyclic and even tetracyclic systems of type **176** in a few steps (Scheme 34).



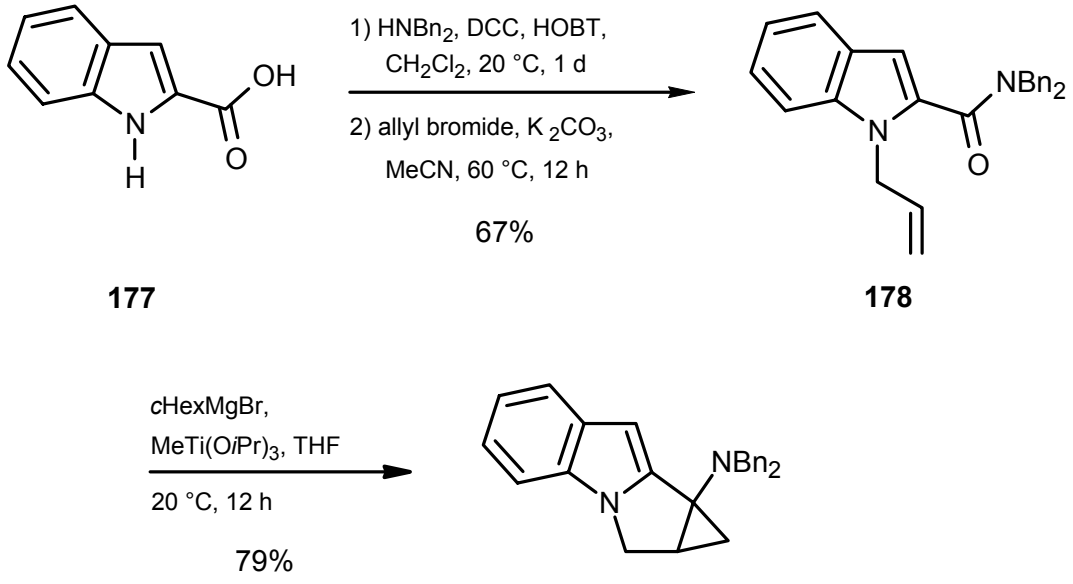
175 **176**

Scheme 34. Strategy for the synthesis of oligocyclic azabicyclo[3.1.0]hexane systems.

7.2. Synthesis of tetracyclic derivatives

7.2.1. Synthesis of N,N-dibenzyl-indolo[1,2-a]cyclopropa[1,2-c]pyrrolidin-8b-amine

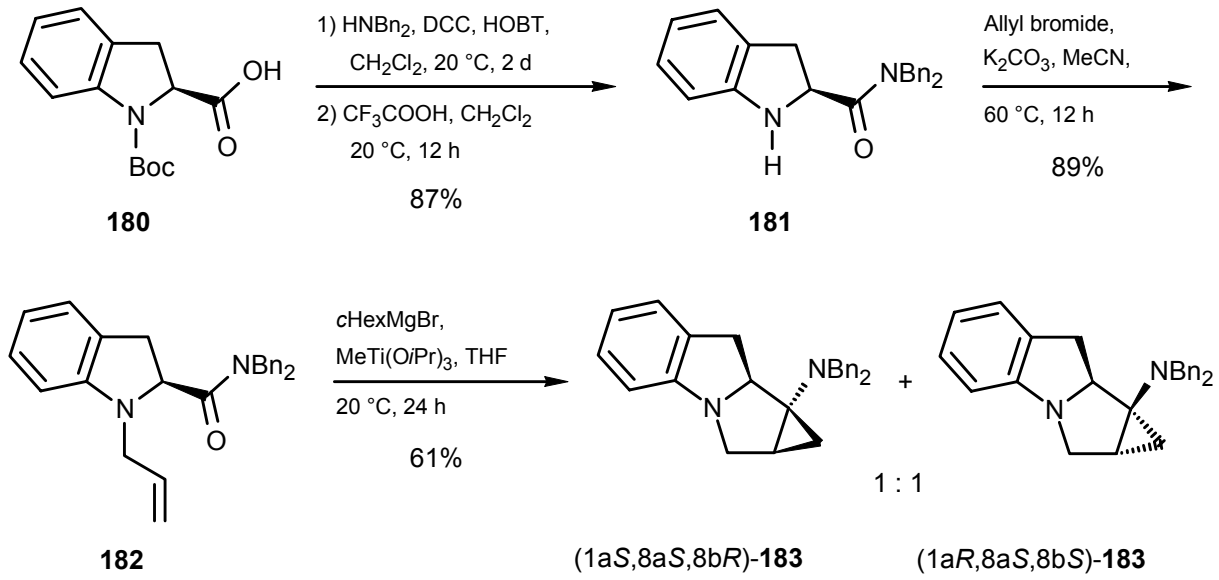
The first investigation concerned the synthesis of the tetracyclic compound **179** from amino acid **177**. The amide **178** was prepared from indole-2-carboxylic acid (**177**) by treatment with $HNBn_2$, DCC and HOBT, and then with allyl bromide and K_2CO_3 in 67% yield. Intramolecular cyclopropanation of amide **178** under the optimized conditions [1.50 equiv. $MeTi(OiPr)_3$ and 5.00 equiv. *c*HexMgBr] gave the desired product **179** in 79% yield (Scheme 35).



Scheme 35. Synthesis of *N*,*N*-dibenzyl-indolo[1,2-*a*]cyclopropa[1,2-*c*]pyrrolidin-8b-amine (**179**).

7.2.2. Synthesis of (8aS)-N,N-dibenzyl-8,8a-dihydroindolo[1,2-a]cyclopropa[1,2-c]-pyrrolidin-8b-amine

These results triggered the idea to apply such a protocol to an indoline derivative of type **182** in order to synthesize enantiopure compounds and to study the diastereoselectivity of the cyclopropanation process. Sato et al. [22a] reported that the proline methyl ester derivative did not undergo intramolecular cyclopropanation. This was attributed to a disfavoring of the transition state for ring closure because of a preference for the ester and *N*-allyl group to be aligned *anti*. The idea that a fused aromatic ring might favor the ring closure suggested to attempt the intramolecular cyclopropanation of the amide **182**, derived from *N*-*tert*-butoxycarbonyl-indoline-2-carboxylic acid (**180**). Applying the established set of reactions to the acid **180**, the bicyclic compounds (1a*S*,8a*S*,8b*R*)-**183** and (1a*R*,8a*S*,8b*S*)-**183** obtained in 61% yield as a 1 : 1 mixture which was separated by column chromatography (Scheme 36).



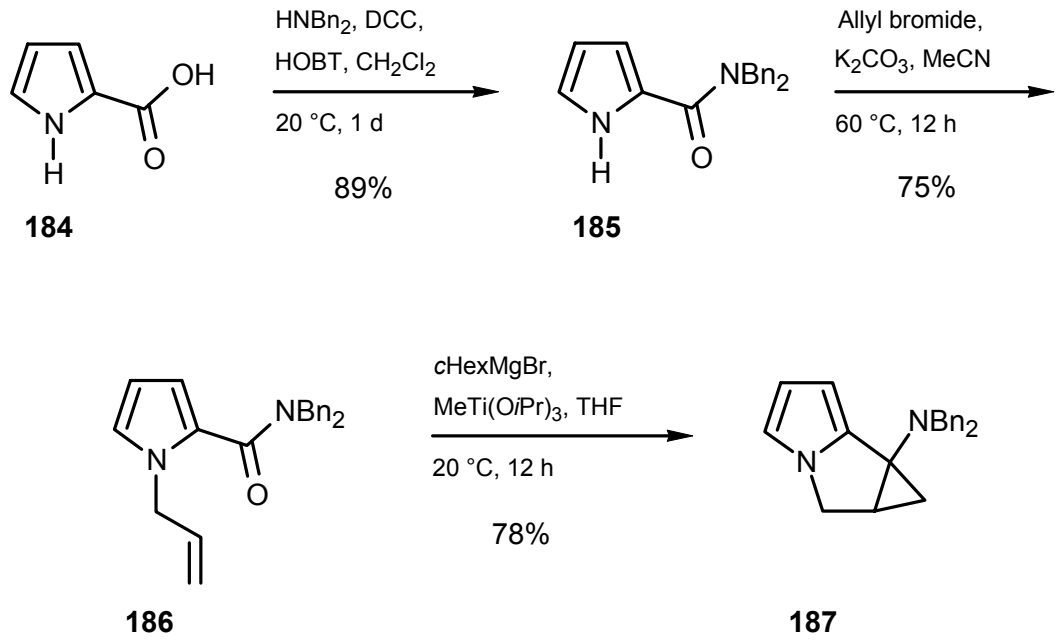
Scheme 36. Synthesis of (8a*S*)-*N*,*N*-dibenzyl-8,8a-dihydroindolo[1,2-*a*]cyclopropa[1,2-*c*]-pyrrolidin-8b-amine (**183**).

7.3. Synthesis of tricyclic derivatives

7.3.1. Synthesis of N,N-dibenzyl-1,1a,2,6b-tetrahydrocyclopropa[1,2-a]pyrrolizin-6b-amine

For the synthesis of tricyclic compounds the same set of transformations was investigated with pyrrole and proline derivatives.

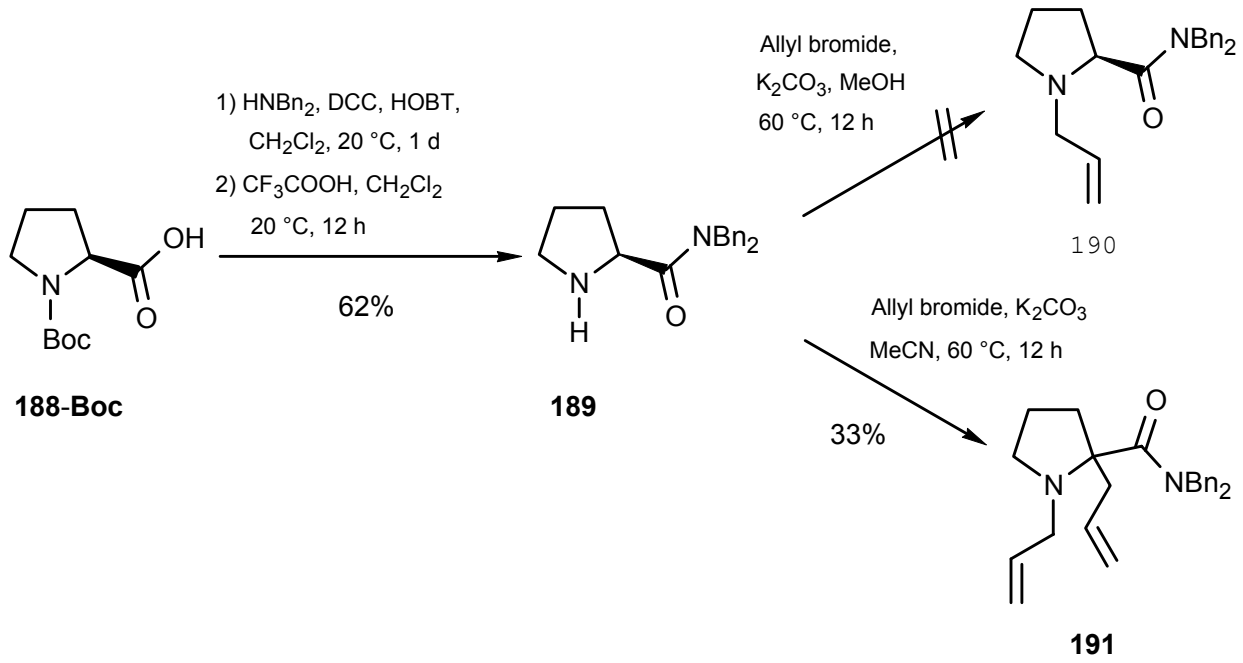
Pyrrole-2-carboxylic acid (**184)** was converted to the *N*,*N*-dibenzylamide **185** by treatment with $HNBn_2$, DCC and HOBT in 89% yield, then to compound **186** by *N*-alkylation with allyl bromide and K_2CO_3 in 75% yield. Intramolecular cyclopropanation of amide the **186** under the optimized conditions [1.50 equiv. $MeTi(OiPr)_3$ and 5.00 equiv. *c*HexMgBr] gave the desired product **187** in 78% yield (Scheme 37).



Scheme 37. Synthesis of *N*,*N*-dibenzyl-1,1a,2,6b-tetrahydrocyclopropa[1,2-*a*]pyrrolizin-6b-amine (**187**).

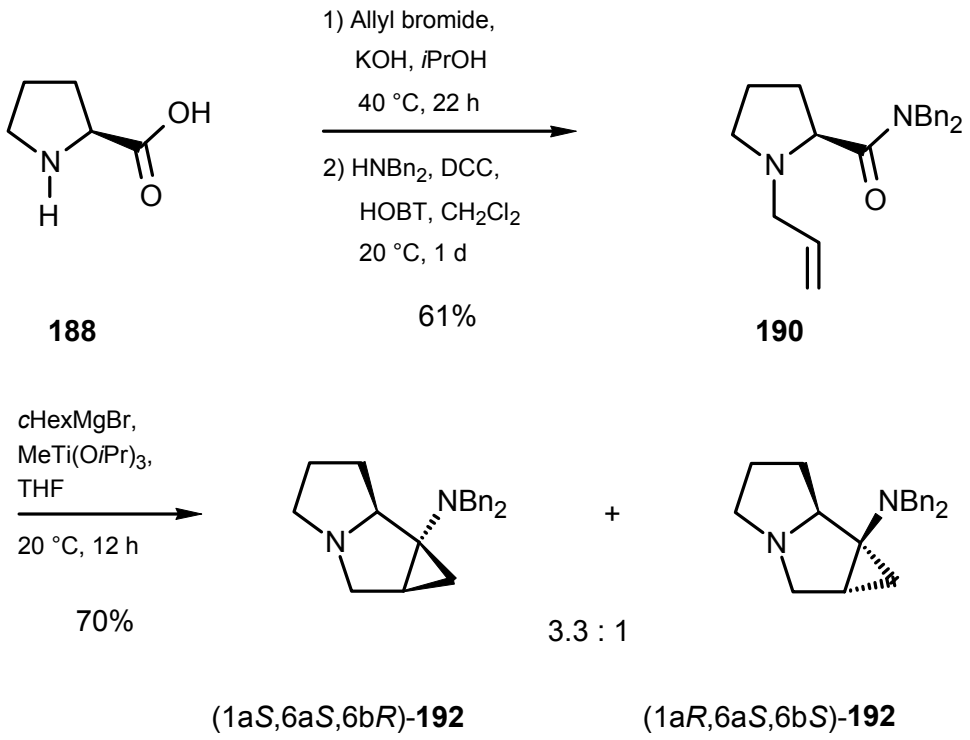
7.3.2. Synthesis of (6aS)-N,N-dibenzyl-perhydrocyclopropa[1,2-a]pyrrolizin-6b-amine

The result obtained in the cyclopropanation of the indoline derivative **182** initiated the idea to study the behavior of the corresponding proline derivative. Treatment of L-(*N-tert*-butoxy-carbonyl)proline (**188)** with $HNBn_2$, DCC and HOBT, followed by deprotection with TFA gave the amine **189** in 62% overall yield. When the latter was treated with allyl bromide and K_2CO_3, the doubly alkylated compound **191** was obtained instead of the desired compound **190** (Scheme 38). The deprotection in position 2 occurred quantitatively under the reaction conditions employing K_2CO_3 as a base at 60 °C, with racemization at C-2, as revealed from the optical activity measurement $[\alpha]_D^{20} = 0.0$ ($c = 1.0$, $CHCl_3$), and no traces of compound **190** were detected. The NMR spectra revealed signals for the two different allyl groups, and in the APT spectrum a C_{quat} signal for C-2 was observed instead of the CH-signal. This result was surprising, since it is well documented literature that the deprotection of position 2 of proline derivatives requires much stronger bases, such as lithium diisopropylamide.[73]



Scheme 38. Attempted synthesis of the amide **190**.

Compound **190** was then synthesized performing another set of transformations. By treatment of L-proline (**188)** with allyl bromide and KOH in *i*PrOH,[74] then with $HNBn_2$, DCC and HOBT, the amide **190** was obtained in 61% overall yield. Ti-mediated intramolecular reductive cyclopropanation of the latter afforded compounds (1a*S*,6a*S*,6b*R*)-**192** and (1a*R*,6a*S*,6b*S*)-**192** in 70% yield as a 3.3 : 1 mixture which was separated by column chromatography (Scheme 39).



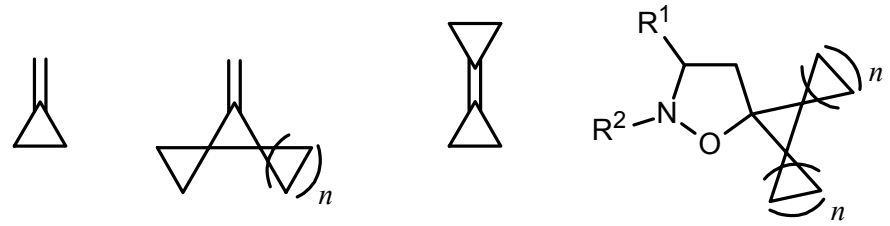
Scheme 39. Synthesis of (6a*S*)-*N*,*N*-dibenzyl-perhydrocyclopropa[1,2-*a*]pyrrolizin-6b-amine (**192**).

The pyrrolizidine system is common in a variety of natural compounds, some of which have also a benzo-fused ring, and their synthesis has been widely reported in the literature.[75] The intramolecular reductive cyclopropanation of amides **178**, **182**, **186** and **190** provides an easy access to analogues of such systems, with an additional annelated-cyclopropane, even in enantiomerically pure form.

8. 1,3-Dipolar Cycloadditions of Nitrones to Bicyclopropylidenes

8.1. Introduction

1,3-Dipolar cycloadditions constitute the most general method for the synthesis of five-membered heterocycles.[76a] Among the large variety of 1,3-dipolar cycloadditions of nitrones to double bonds, cycloadditions to methylenecyclopropane (**193**, Figure 10)[76b], its spirocyclo-propanated analogs (**194**, **195**)[77] and bicyclopropylidene (**196**)[78] have been of special interest in the last 15 years. Nitrones add to such alkenes (**193**–**195**) regioselectively forming mainly cycloadducts of type **197** in which the oxygen atom is attached to a carbon atom of a cyclopropane ring.



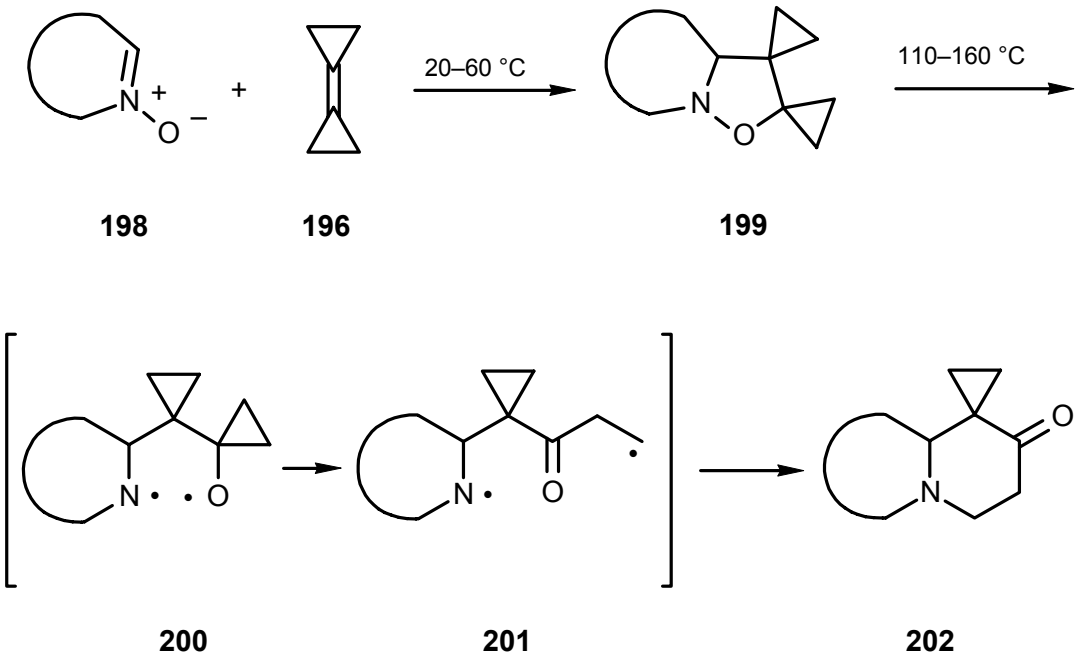
193 **194** *n*=0 **195** *n*=1 **196** **197**

Figure 10. Structures of alkenes **193–196** and cycloadducts **197**.

Bicyclopropylidene (**196**) is a uniquely strained tetrasubstituted alkene[79], which has shown an unusually high reactivity towards electron-deficient cycloaddends.[80] Bicyclopropylidene (**196**) is easily available on a large scale from methyl cyclopropanecarboxylate by the synthesis optimized by de Meijere et al.,[81] which applies the Ti-mediated cyclopropanation, developed by Kulinkovich[82], as the key step.

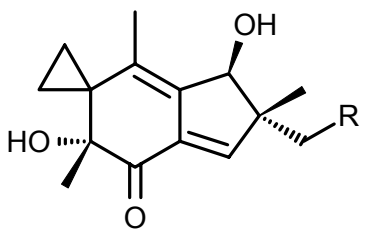
It is known[83] that tetraalkyl-substituted alkenes do not cycloadd nitrones at all and isobutene and its derivatives react slowly. Various nitrones **198** indeed react with bicyclopropylidene

(**196**)[80] at ambient or slightly elevated temperature to furnish bis(spirocyclo-propane)-annelated isoxazolidines of type **199** in high yield (Scheme 40). The cycloadducts of type **199** are prone to undergo thermal rearrangement (so called Brandi-Guarna reaction[84]) by homolytic cleavage of the N–O bond, followed by opening of the adjacent cyclopropane ring and eventual reclosure of the resulting diradical. This type of transformation provides a large variety of oligospirocyclopropane-annelated azaheterocycles of type **202** (Scheme 40).[80,85]



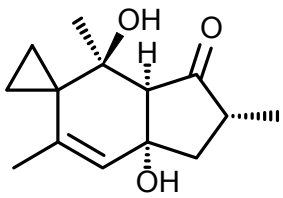
Scheme 40. 1,3-Dipolar cycloaddition and subsequent thermal rearrangement sequence.

Tetrahydropyridones of type **202** are interesting compounds, which, when appropriately transformed, are known to undergo ring expansion of the cyclopropyl group.[86] Certain derivatives have also been extensively studied with respect to their properties of being aza-analogues of the Illudine **203**[87] and Ptaquilosin (**204**)[88] sesquiterpenes, and they have shown interesting biological activities in being able to cleave a DNA plasmid (Figure 11).[89]



203-OH Illudine S (R = OH)

203-H Illudine M (R = H)



204

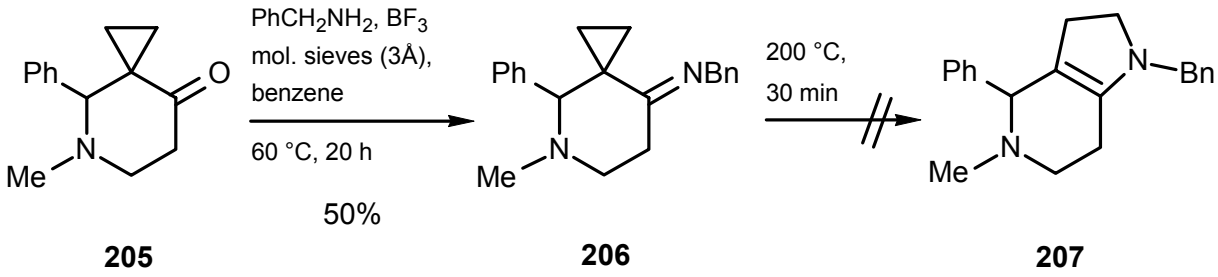
Figure 11. Structure of Illudines **203** and Ptaquilosin **204**.

8.2. Attempted synthesis of perhydropyrrolo[2,3-c]pyridine derivatives

Funke[86b] reported that spirocyclopropane-annelated azaheterocycles bearing a ketimine function α to the cyclopropane ring undergo rearrangement at high temperature under vacuum.

In this context it was of interest to investigate whether the tetrahydropyridone **205**, synthesized according to the published procedure,[80] when converted to the imine **206**, would undergo such a transformation which ought to lead to perhydropyrrolo[2,3-*c*]pyridine systems of type **210**.

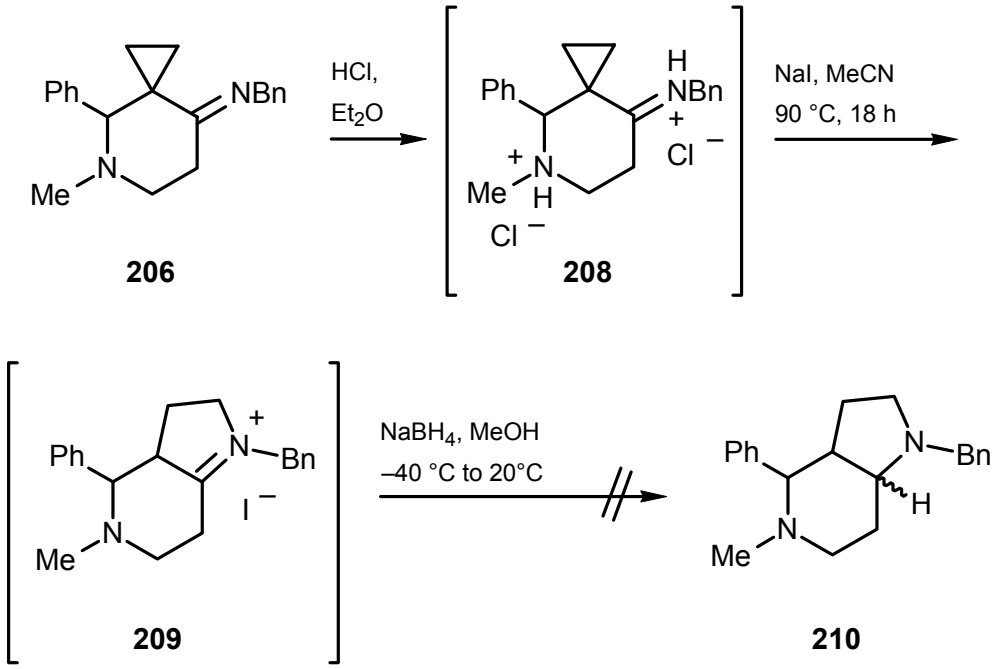
Therefore, compound **205** was heated with $BnNH_2$ and $BF_3{\cdot}Et_2O$ in benzene, in the presence of molecular sieves (3 Å), at 60 °C for 20 h to yield the imine **206** in 50% yield (Scheme 41).[90] The latter immediately turned dark when heated at 200 °C, and its polymerization took place already at atmospheric pressure without formation of compound **207**.



205 **206** **207**

Scheme 41. Attempted synthesis of the pyrrolo[2,3-*c*]pyridine system **207**.

De Meijere et al.[91] reported that the cyclopropylimine moiety of spirocyclopropane-annelated 1-cyclopropyl-2-azaazulenes underwent nucleophilic attack by iodide and subsequent borohydride reduction of the resulting iminium-eneammonium salts to give hexahydrospiro[cyclohepta[a]pyrrolizine-5,1'-cyclopropane] systems. Compound **206** appeared to be a good candidate for such a transformation, so it was transformed into the hydrochloride **208** by treatment with HCl/Et_2O. The latter was treated with NaI in MeCN at 90 °C for 18 h to give compound **209**, which was directly treated with $NaBH_4$ in MeOH at – 40 °C, but after stirring at ambient temperature for 12 h, a complex mixture of products was obtained, and this could not be separated by column chromatography, so that the assignment of their structures was not possible (Scheme 42).



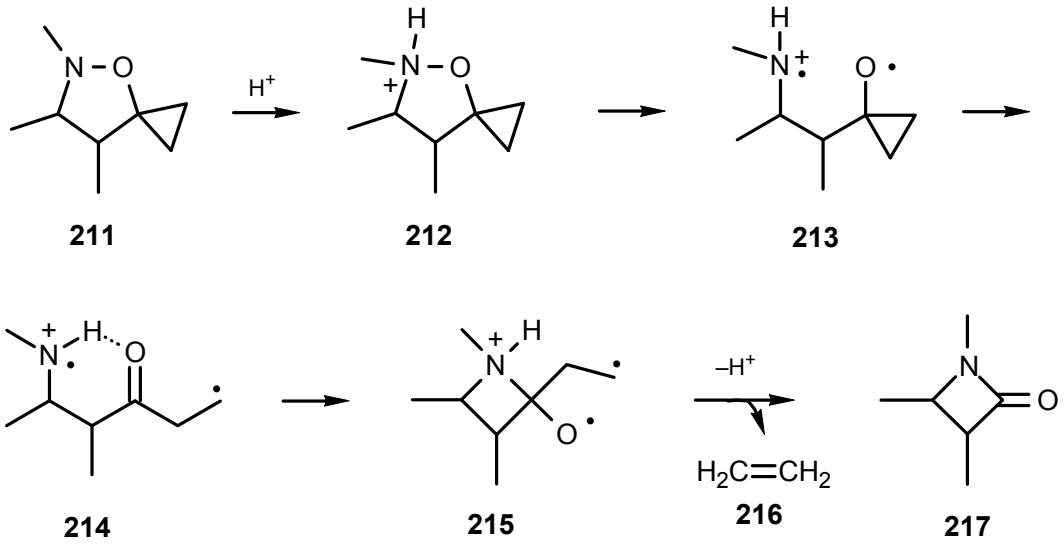
Scheme 42. Attempted synthesis of the perhydropyrrolo[2,3-*c*]pyridine system **210**.

8.3. Synthesis of spirocyclopropane-annelated β-lactams

8.3.1. Considerations

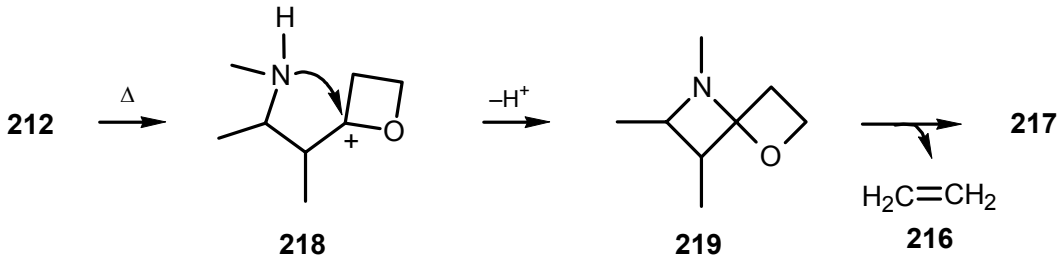
β-Lactams are important structures present in such important natural compounds as penicillins and cephalosporines.[92] Recently Brandi et al. reported a new synthesis of *β*-lactams based on ring contraction of 5-spirocyclopropane-annelated isoxazolidines of type **211** in the presence of protic acids.[93] This process occurs with elimination of ethylene, analogous to the enzymatic conversion of 1-aminocyclopropanecarboxylic acid into ethylene during the plant growth regulation and the maturation of fruits.[12b] The proposed mechanism is believed to proceed in analogy with the Hofmann–Löffler reaction[94] of protonated chloro amines.[93] Initially an N–O bond homolysis in the protonated isoxazolidine **212** may lead to the diradical cation **213**. The latter could rearrange to the protonated amino ketone **214**, stabilized by a

strong intramolecular hydrogen bond, which prevents the intramolecular diradical coupling or 1,5-hydrogen shift which usually occur in such systems.[95] Ring closure may lead to azetidin **215**, and then to ethylene (**216**) and the *β*-lactam **217** through a radical fragmentation (Scheme 43).



Scheme 43. First proposed mechanism for the *β*-lactam formation.[93]

In case the N–O bond cleavage occurs in a heterolytic manner, **212** may rearrange through a cyclopropane ring enlargement to **218**, analogous to the cyclopropylcarbinyl cation behavior. The resulting azaoxaspiroheptane **219** may lead to the formation of **216** and **217** by a formal retro–Paterno–Büchi reaction (Scheme 44).[96]

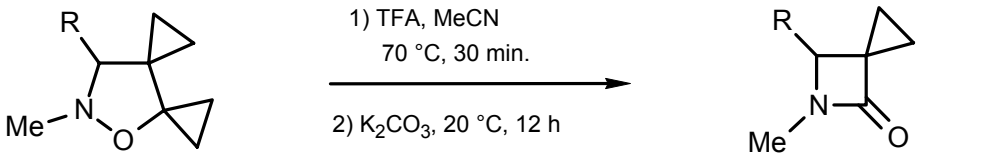


Scheme 44. Second proposed mechanism for the *β*-lactam formation.[93]

8.3.2 Syntheses of 5-methyl-6-phenyl-5-azaspiro[2.3]hexan-4-one and 5-methyl-6-(pyrid-2-yl)-5-azaspiro[2.3]hexan-4-one

Only a few synthesis of spirocyclopropane-annelated *β*-lactams are known, based, for example, on [2 + 2] cycloadditions between ketene imines and isocyanates.[97] Some examples of 6-spirocyclopropane-annelated penicillins have also been reported.[98]

In this context the transformation reported by Brandi et al.[93] was investigated with the isoxazolidines **220** and **221**, derived from the 1,3-dipolar cycloaddition of benzylidenemethylamine oxide and methylpyridin-2-ylmethyleneamine oxide to bicyclopropylidene (**196**).[80] Treatment of compounds **220** and **221** with trifluoroacetic acid (TFA) in MeCN at 70 °C for 40 min, followed by stirring for 12 h in the presence of K_2CO_3, gave lactams **222** and **223** in 96 and 98% yield, respectively (Scheme 45).



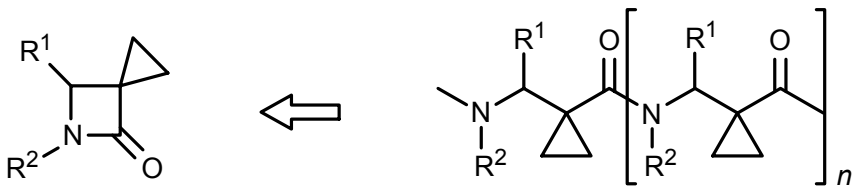
220 R = C_6H_5
221 R = pyrid-2-yl

222 R = C_6H_5 (96%)
223 R = pyrid-2-yl (98%)

Scheme 45. Syntheses of 5-methyl-6-phenyl-5-azaspiro[2.3]hexan-4-one (**222**) and 5-methyl-6-(pyrid-2-yl)-5-azaspiro[2.3]hexan-4-one (**223**).

The structures of compounds **222** and **223** were established by spectroscopic analyses. Particularly significant were the absorptions of the C=O moieties in the IR spectrum (1751 cm^{-1} for both compounds) and the presence of four cyclopropyl proton signals in the ^{1}H-NMR spectrum.

Spirocyclopropane-annelated β-lactams of types **222** and **223** could be interesting systems as precursors to β-amino acids and β-peptides bearing a 1,1-disubstituted cyclopropane ring in position 2. Such β-peptides in which R^1 = H have recently been reported by Seebach et al.[99] (Scheme 46).



222, **223** **224**

Scheme 46. Spiropropane-annelated β-lactams as potential precursor of interesting β-peptides.

8.4. 1,3-Dipolar cycloadditions of nitrones to cyclopropylidenespiropentane and 7-cyclopropylidenedispiro[2.0.2.1]heptane and subsequent thermal rearrangement

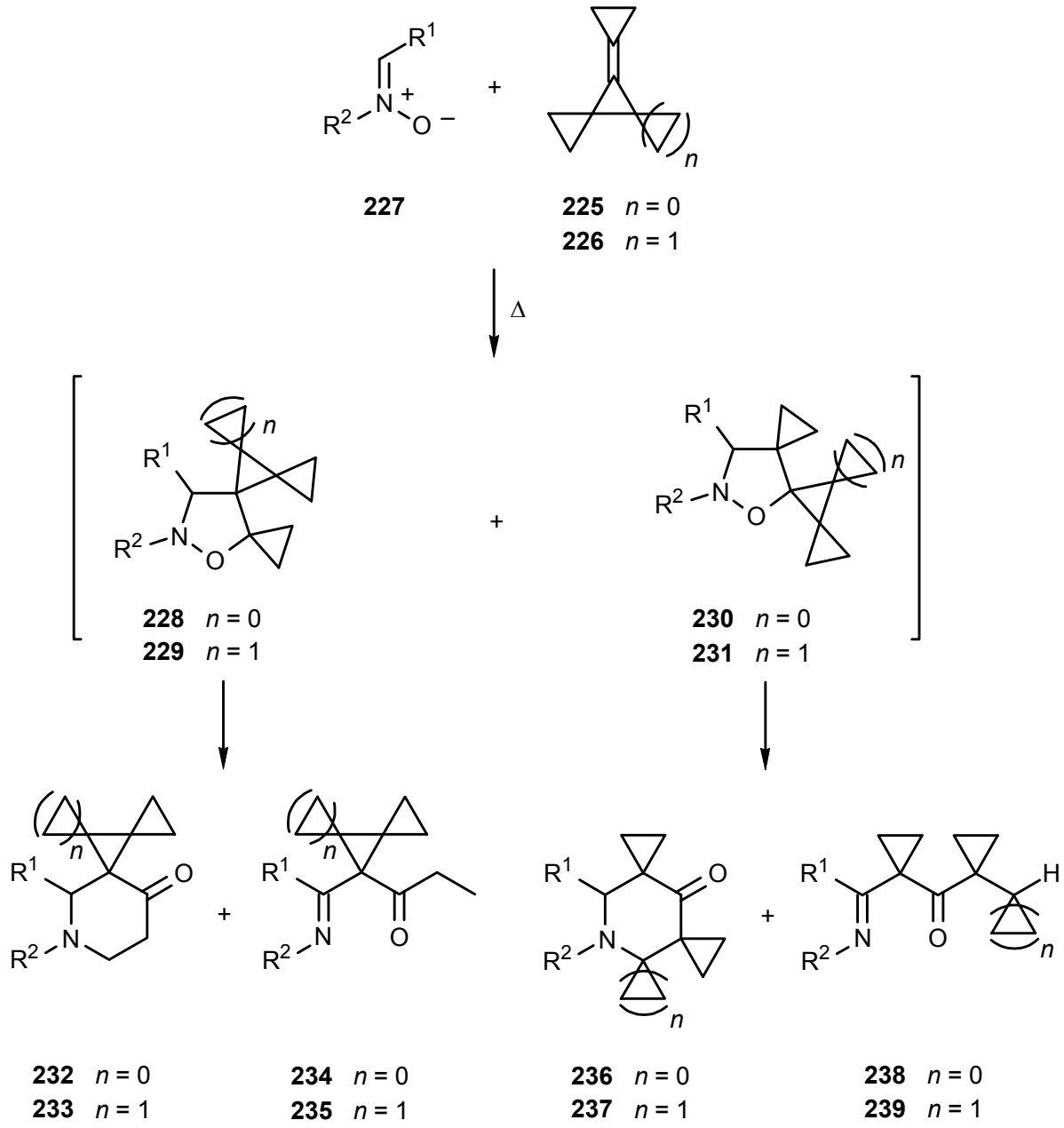
8.4.1. Considerations

The 1,3-dipolar cycloaddition of various nitrones to the highly strained cyclopropylidene-spiropentane (**225**) and 7-cyclopropylidenedispiro[2.0.2.1]heptane (**226**)[100,101] (Figure 12) and the thermal rearrangement of the intermediate isoxazolidines has been studied in this project in order to investigate the influence of an additional spirocyclopropane ring on bicyclopropylidene (**196**) upon the selectivity of cycloaddition. This reaction also could lead to the formation of new tetrahydropyridinone derivatives with up to three spiroannelated cyclopropane rings, which can be of interest as analogues of Illudines **203** and Ptaquilosin (**204**, Figure 11).[102]

225 **226**

Figure 12. Structures of cyclopropylidenespiropentane (**225**) and 7-cyclopropylidenedispiro-[2.0.2.1]heptane (**226**).

The reaction of bicyclopropylidenes **225** and **226** with nitrones of type **227** might result in the formation of several products **232**–**239**, as shown in Scheme 47.



227 **225** $n = 0$; **226** $n = 1$

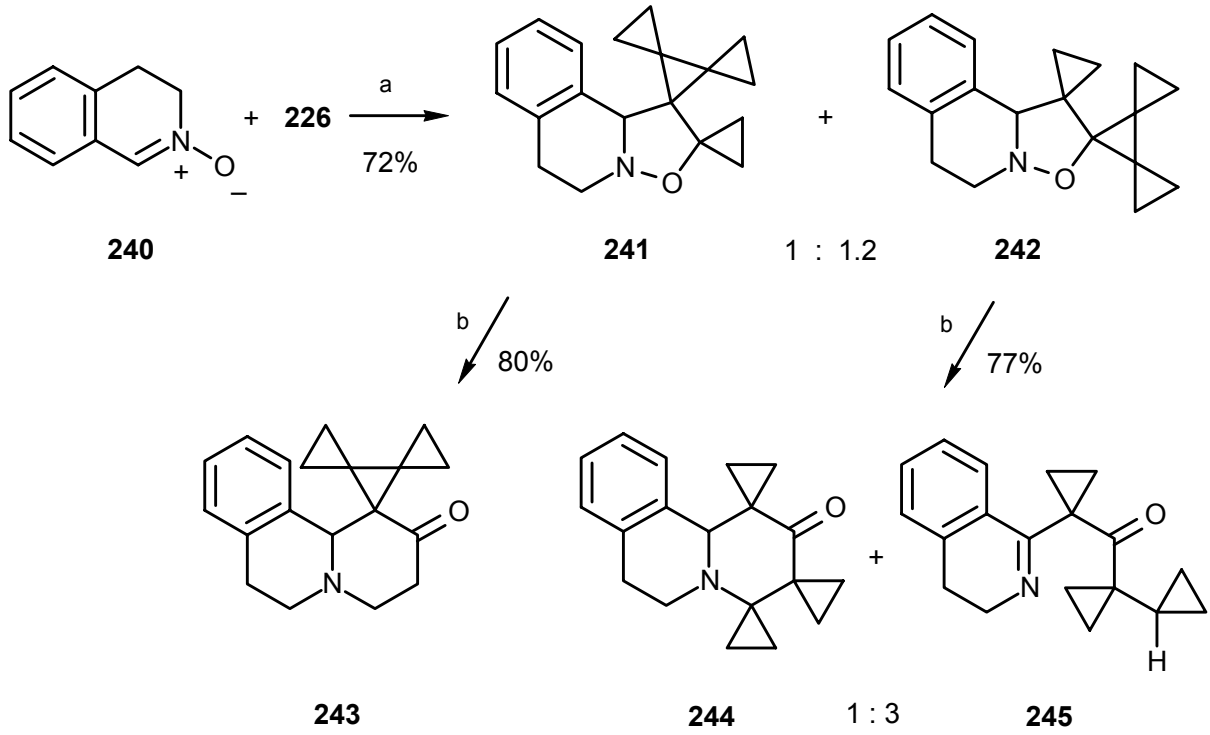
228 $n = 0$; **229** $n = 1$ + **230** $n = 0$; **231** $n = 1$

232 $n = 0$; **233** $n = 1$ + **234** $n = 0$; **235** $n = 1$ + **236** $n = 0$; **237** $n = 1$ + **238** $n = 0$; **239** $n = 1$

Scheme 47. 1,3-Dipolar cycloadditions of nitrone **227** to cyclopropylidenespiropentane (**225**) and 7-cyclopropylidenedispiro[2.0.2.1]heptane (**226**), and the thermal rearrangement of the formed isoxazolidines **228**–**231**.

8.4.2. 1,3-Dipolar cycloaddition of 3,4-dihydroisoquinoline N-oxide and 7-cyclopropylidene-dispiro[2.0.2.1]heptane

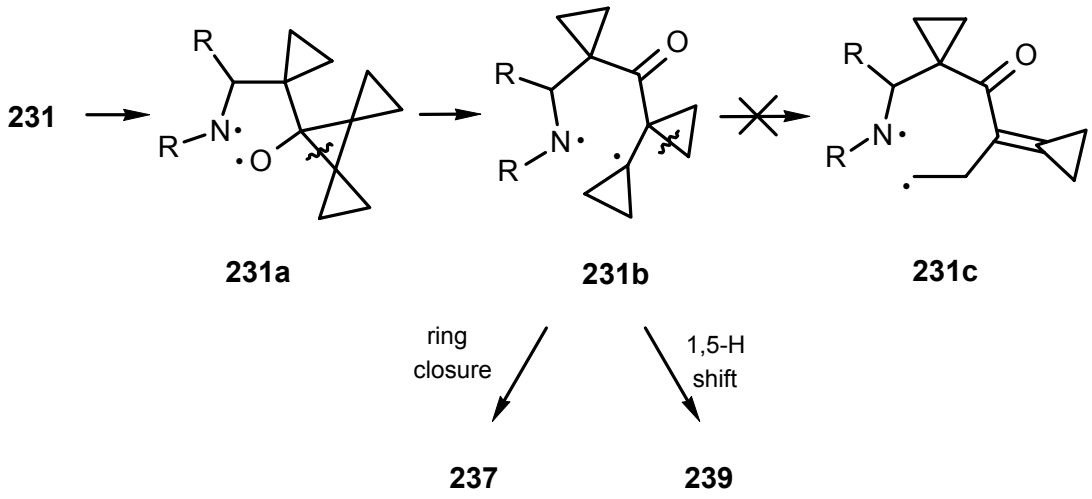
Initially, the 1,3-dipolar cycloaddition of nitrone **240** to 7-cyclopropylidenedispiro-[2.0.2.1]heptane (**226**) was investigated. The reaction was performed at ambient temperature within 7 days and resulted in the formation of cycloadducts **241** and **242** in a ratio of **241**/**242** = 1 : 1.2 (1 : 1.1 after chromatographic separation) (Scheme 48).



Scheme 48. a) C_6H_6, 20 °C, 7 d; b) *p*-xylene, 140 °C, 5 h.

The slight predominance of cycloadduct **242** is in line with the previously published results for the alkenes **193**–**195**[89b], but the regioselectivity in this current case is relatively poor, as a comparable quantity of the isomer **241** was also obtained. Upon heating the perspirocyclopropanated isoxazolidine **241** in *p*-xylene at 140 °C for 5 h, it rearranged cleanly to the pyridinone **243** (80% yield), the structure of which was proved by X-ray diffraction (Figure 1). The isomeric compound **242** under these conditions gave a mixture of the

trispirocyclopropanated benzoquinolizinone **244** and the non-cyclized dihydroisoquinoline derivative **245** (77% yield, ratio 1 : 3). The latter apparently arose by a 1,5-hydrogen shift of the hydrogen adjacent to the nitrogen atom in the intermediate diradical of type **231b** (Scheme 49)[103].



Scheme 49. Rearrangement of isoxazolidine **231**.

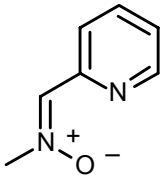
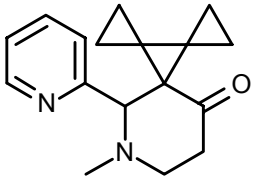
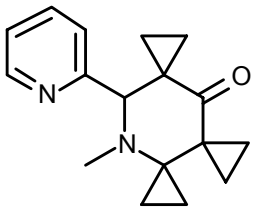
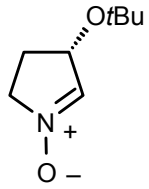
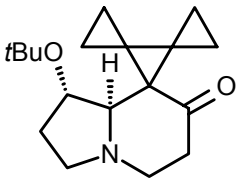
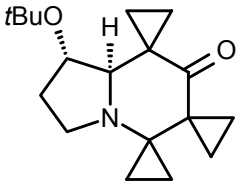
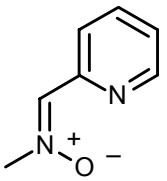
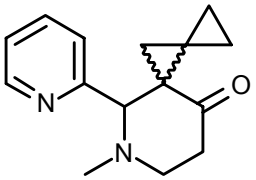
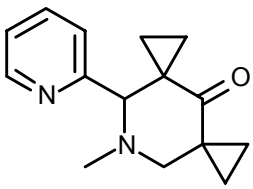
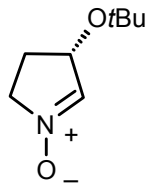
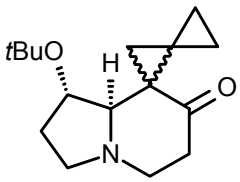
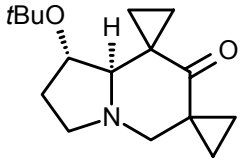
Spirocyclopropanated isoxazolidines of type **231** are known to undergo a highly chemo- and regioselective sequence of ring openings.[104] The initially formed diradical intermediate **231a** (Scheme 49) as an oxygen-analogue of a cyclopropylmethyl radical immediately undergoes the well-known rapid rearrangement[105] to a buten-4-yl radical forming the diradical of type **231b**. This, in turn, intramolecularly recombines to give the trispirocyclopropanated skeleton of type **237**. A diradical of type **231b** would also be capable to rearrange further leading to a diradical of type **231c**. Cyclization of the latter would form an azepinone derivatives.[106] However, such a product was not detected in the rearrangement of the isoxazolidine of type **231**. This indicates that intramolecular radical recombination in **231b** is faster than the second cyclopropylmethyl to homoallyl radical ring opening.

8.4.3. One-pot 1,3-dipolar cycloaddition and subsequent thermal rearrangement

The one-pot reaction of nitrone **240** and bicyclopropylidene **226** (120 °C, 1 d) furnished a mixture of products **243**–**245**, from which **243** was isolated in 28% yield (Table 13). Unfortunately, compounds **244** and **245** could not be separated completely, and their yields were estimated from NMR spectra of enriched fractions to be 11 and 32% yield, respectively. The formation of byproducts of type **235** (Scheme 47) was not observed.

Further cycloaddition of nitrones **246** and **249**[107] to bicyclopropylidene derivatives **225** and **226** with subsequent thermal rearrangement was carried out as one-pot reactions in order to increase the overall yield of the final products and to avoid cycloreversion of the intermediate isoxazolidines.[76a] The results are presented in Table 13.

Table 13. One-pot 1,3-dipolar cycloaddition and subsequent thermal rearrangement sequence.

Alkene	Nitrone	Product (Yield %)		Total Yield (%)
226	**240**	**243** (28)	**244** (11) + **245** (32)	71
226	 **246**	 **247** (14)	+  **248** (54)	68
226	 **249**	 **250** (47)	+  **251** (30)	77
225	 **246**	 (*cis* and *trans*)-**252** (53)	+  **253** (21)	74
225	 **249**	 (*cis* and *trans*)-**254** (53)	+  **255** (27)	80

The reactions of nitrones **246** and **249** were carried out in *o*-xylene at 120 °C for 1 d. The products were obtained as mixtures of isomers, which were easily separated by chromatography on silica gel and isolated in 68, 77, 74 and 80% total yield, respectively (Table 1). No open-chain isomers were observed for compounds **246** and **249**. Compounds **252** and **254** were obtained as a mixture of two diastereoisomers due to the stereogenicity of

C-3 (piperidinone numbering). The molecular structure of compounds **243**, **248** and *trans*-**252** were rigorously proved by X-ray crystal structure analysis (Figure 13).

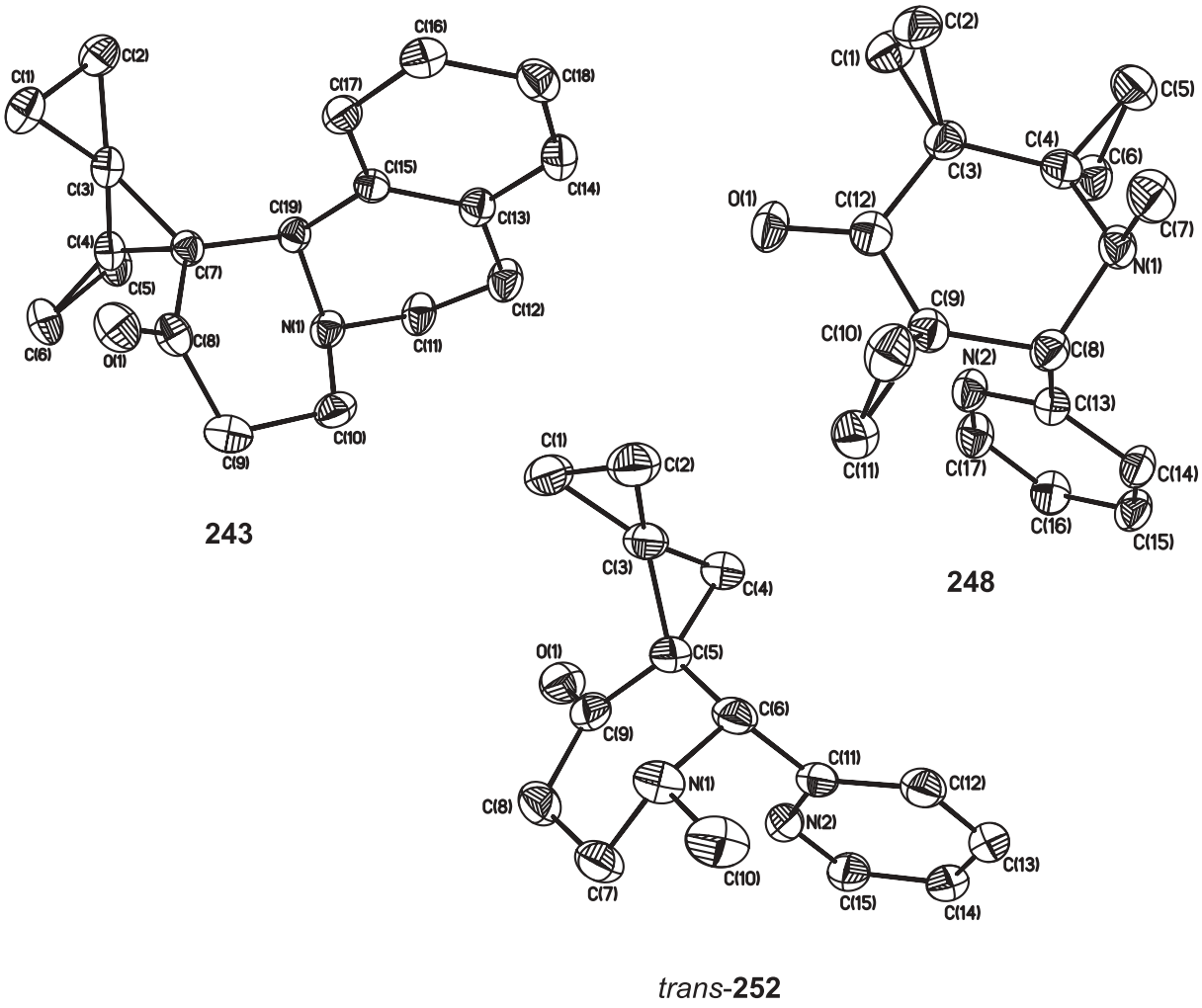


Figure 13. Molecular structures of compounds **243**, **248** and *trans*-**252** in the crystals.

The previously observed regioselectivity in 1,3-dipolar cycloadditions of nitrones to methylenecyclopropane and its spirocyclopropanated analogues to predominantly yield oxazolidines of type **197**, in which the oxygen atom is attached to a cyclopropane ring, can be rationalized on the basis of steric as well as electronic effects. The long-lasting controversial debate about whether 1,3-dipolar cycloadditions occur stepwise via dipolar intermediates[108]

or in a concerted fashion,[109] has now been solved in favor of a more or less concerted reaction mode.[110] The degree of concertedness undoubtedly depends on the nature and the pattern of substituents on both the 1,3-dipole and the alkene substrate. In case of the particularly nucleophilic methylenecyclopropane and bicyclopropylidene[100] it is reasonable to assume that the nitrone approaches the alkene faster and thus more closely at any time with its electrophilic end and leading to a dipolar transition structure of types **I** or **II** (Figure 14).

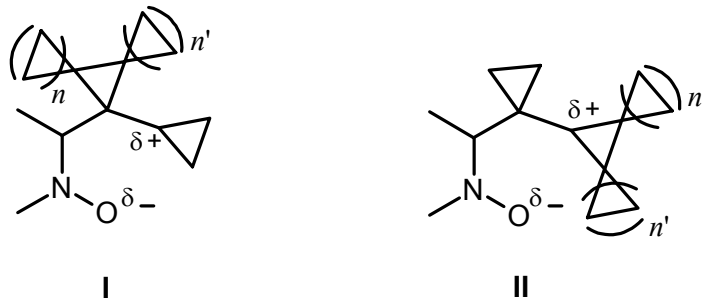


Figure 14. Separate charges in transition states in the initial *electrophilic addition*.

According to experimental and computational results on the bromination of spirocyclopropanated methylenecyclopropanes **193**, **194**, **195** and bicyclopropylidenes **196**, **225**, **226**[111] and the relative stabilities of spirocyclopropanated cyclopropyl cations,[112] a transition structure of type **II** ought to be favored. However, the outcome of the nitrone cycloaddition to **225** and **226** is quite surprising: while the adducts of nitrones **240** and **246** to **226** are formed with the thus expected regioselectivity (Scheme 48), those of **249** to **226** as well as **246** and **249** to **225** are formed with a reversed regioselectivity. Even the fact that the cycloadducts **241** and **242** from **240** and **226** are obtained in almost equal amounts, is noteworthy, as the significant steric bulk of the dispiroheptyl moiety should also favor the transition structure **II**. Both the electronic as well as the steric arguments should also hold for

the last three examples in Table 13, yet the experimental results are just opposite. The high diastereoselectivities in the addition of the enantiomerically pure nitrone **249** to **225** and **226** is due to the *anti* approach of the alkenes towards the nitrone which leads to the *cis* relationship of the *tert*-butoxy group and the bridgehead hydrogen in the final products **250**/**251** and **254**/**255**.

C. EXPERIMENTAL PART

1. General Notes

IR: Bruker IFS 66 (FT-IR). – ^{1}H-NMR: Bruker AM 250 (250 MHz), Varian UNITY-300 (300 MHz); δ (ppm) = 0.00 for tetramethylsilane, 2.50 for [D_6]-dimethylsulfoxide, 4.78 for [D_4]-methanol, 7.26 for deuterochloroform. The signals were characterized: s = singlet, bs = broad singlet, d = doublet, t = triplet, ps t = pseudo triplet, q = quartet, dd = double of doublets, ddd = double of dd, dt = double of triplets, m = multiplet, *c*Pr-H = cyclopropyl proton, Ar-H = aromatic proton, * = the assignment is exchangeable. – ^{13}C-NMR: Bruker AM 250 (62.9 MHz), Varian UNITY-300 (75.5 MHz); δ (ppm) = 0 for tetramethylsilane, 39.5 for [D_6]-dimethylsulfoxide, 49.0 for [D_4]-methanol, 77.0 for deuterochloroform. The characterization was performed with the help of DEPT (Distortionless Enhancement by Polarization Transfer) or APT (Attached Proton Test), where + = primary or tertiary (positive-DEPT signal), – = secondary (negative DEPT-signal), C_{quat} = quaternary carbon atom (zero DEPT-signal) or + = primary or tertiary (positive APT-signal), – = secondary or quaternary carbon atom (negative APT-signal). The signals were characterized: *c*Pr-C = cyclopropyl carbon, Ar-C = aromatic carbon, * = the assignment is exchangeable. – MS: Varian MAT 731, MAT CH 7. – High resolution MS (HRMS): Varian MAT 311, INCOS 50 with Varian 34000 (GC-MS) using preselected ion peak matching at R = 10000 to be within ± 2 ppm. – Thin layer chromatography (TLC): Macherey-Nagel Alugram® SIL G/UV_{254} 0.25 mm silica gel with fluorescent indicator. – Developer: molybdenum phosphoric acid solution (10% in ethanol) or ninhydrine (300 mg ninhydrine, 3.00 g acetic acid, 100 mL *n*-butanol). – Column chromatography: Merck Silica gel 60 (0.063–0.200 mm, 70–230 mesh

ASTM). – Melting point: melting point instrument according to Dr. Tottoli (Büchi); all measured values are uncorrected. – Elemental analysis: the Mikroanalytisches Laboratorium des Instituts für Organische Chemie der Universität Göttingen. – X-Ray structure analysis of compounds **76**, **79** and **91** were measured with Brucker CCD SMART 1 K and SMART 6000 diffractometers, measurement made by Dr. D. S. Yufit, University of Duram, Duhram, South Rd. DM1 3LE, UK. X-Ray structure analysis of compounds *endo*-**163**, **243**, **248** and *trans*-**252** were measured with IPDS II diffractometer, measurement made by D. Vidović, Instituts für Anorganische Chemie der Universität Göttingen, Göttingen, DE. – Solvents were dried and purified according to the conventional methods of the laboratory under nitrogen atmosphere. All the reactions, which were performed not in an aqueous solution, were carried out under Argon atmosphere. Unless specified otherwise, solutions of NH_4Cl, $NaHCO_3$ and NaCl were saturated aqueous solutions. All chemicals were used as commercially available, unless otherwise noted. – Abbreviations: Ac = acetate, Ar = aryl, (±)-BINAP = (±)-2,2'-bis-(diphenyl-phosphino)1,1'-binaphthyl, Bn = benzyl, Boc = *tert*-butoxycarbonyl, $ClTi(OiPr)_3$ = chlorotitanium triisopropoxyde, dba = dibenzylideneacetone, DCC = dicyclohexylcarbodi-imide, DCE = 1,2-dichloroethane, DEAD = diethylazodicarboxylate, DMAA = *N*,*N*-di-methylacetamide, DMAP = *N*,*N*-dimethylaminopyridine, DMF = dimethylformamide, DPPF = 1,1'-bis-(diphenylphosphino)ferrocene, *c*HexMgBr = cyclohexylmagnesium bromide, HOBT = hydroxybenzotriazole, Im-H = imidazole, Me = methyl, MeCN = acetonitrile, $MeTi(OiPr)_3$ = methyltitanium triisopropoxyde, *c*PentMgCl = cyclopentylmagnesium chloride, Ph = phenyl, PMB = 4-methoxybenzyl, *t*Bu = *tert*-butyl, THF = tetrahydrofuran, TBAF = tetrabutyl-ammonium fluoride, TBDMS = *tert*-butyldimethysilyl,

The following substances were prepared according to literature: $MeTi(OiPr)_3$ according to methyl (*S*)-2-amino-3-hydroxypropionate hydrochloride (**49**) according to Giacomelli et al.,[24] methyl (*S*)-2-amino-3-(*tert*-butyldimethylsilyloxy)propionate (**50**) according to Reez,[113] Baldwing et al.,[25] methyl (*S*)-2-benzylamino-3-hydroxypropionate (**52**) according to Green et al.,[26] 2-bromoacetamides **67–69** according to Ohta et al.,[32a] *N*-allyl-*N*-benzylamine according to Sigano et al.,[32b] *N*-benzylbut-3-enylamine according to Pandit et al.,[33a] *N*-allyl-*N*-benzylacetonitrile (**88**) according to Zecchi et al.,[39] 5-methyl-4-phenyl-5-azaspiro[2.5]octan-8-one (**205**) and 8-methyl-9-phenyl-7-aza-8-azadispiro-[2.0.2.3]nonane (**220**) according to Brandi and de Meijere,[80] cyclopropylidene-spiropentane (**225**) and 7-cyclopropylidenedispiro[2.0.2.1]heptane (**226**) according to de Meijere,[101] 3,4-dihydroisoquinoline *N*-oxide (**240**) according to Murahashi,[114] methyl-pyridin-2-yl-methylene-amine oxide (**246**) according to Brandi and de Meijere,[106] (4*S*)-4-(*tert*-butoxy)-3,4-dihydro-2*H*-pyrrole-*N*-oxide (**249**) according to Brandi.[108]

2. Procedures for the Synthesis and Spectral Data of the Compounds

2.1. General procedures

Preparation of 2-(allylbenzylamino)propionic acid derivatives. General Procedure 1 (GP 1): Allyl bromide (1.40 equiv.) was added dropwise at 0 °C to a suspension of the corresponding 2-(benzylamino)propionic acid derivative (1.00 equiv.) and K_2CO_3 (2.00 equiv.) in anhydrous MeCN (8.0 mL). After the addition was complete, the reaction mixture was stirred at 60 °C for 16 h. EtOAc (8.0 mL) and a sat. aq. $NaHCO_3$ solution (8.0 mL) were added, the organic phase was separated, washed with brine (10 mL) and dried over $MgSO_4$. After evaporation of

the solvent under reduced pressure the crude product was purified by column chromatography on silica gel.

Preparation of 2-(alkylallylamino)-N-alkyl-N-benzylacetamides. General Procedure 2 (GP 2): Triethylamine (2.00 equiv.) and alkylbenzylamine (1.10 equiv.) were added dropwise at 0 °C to a solution of *N*-alkyl-*N*-benzylbromoacetamides (1.00 equiv.) in anhydrous THF (25 mL). After the addition was complete, the reaction mixture was stirred at ambient temperature for an additional 20 h. Water (10 mL) and EtOAc (10 mL) were added, the organic phase was separated, washed with sat. aq. $NaHCO_3$ solution (20 mL), brine (30 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure the crude product was purified by column chromatography on silica gel.

Preparation of 3-azabicyclo[3.1.0]hex-1-ylamine and 3-azabicyclo[4.1.0]hept-1-ylamine. General Procedure 3 (GP 3): Cyclohexylmagnesium bromide (5.00 equiv.) was added dropwise at ambient temperature to a well-stirred solution of *N*,*N*-dialkylpropionamide (1.00 equiv.) and $MeTi(O\textit{i}Pr)_3$ (1.50 equiv.) in anhydrous THF (30 mL). After the addition was complete, the mixture was stirred for 12 h, then poured into ice-cold water (10 mL), and stirred for an additional 1 h. The mixture was filtered through Celite®, the aqueous phase was extracted with Et_2O (3 × 50 mL) and the combined ethereal phases were washed with sat. aq. $NaHCO_3$ solution (50 mL), brine (50 mL) and dried over $MgSO_4$. The solvent was removed and the residue was purified by column chromatography on silica gel.

Preparation of 3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride. General Procedure 4 (GP 4): A solution of *N*-benzyl-protected 3-azabicyclo[3.1.0]hex-1-ylamine (1.00 equiv.) and HCl (6.00 equiv., 5.0 M solution in *i*PrOH) in MeOH (15 mL) was stirred under hydrogen atmosphere (1 bar) and Pd/C catalysis at 20 °C. The reaction mixture was filtered through Celite® and concentrated under reduced pressure. The product was obtained as a colorless solid and purified by recrystallization from MeOH/Et_2O 2 : 1.

Preparation of 3-azabicyclo[3.1.0]hex-1-ylamines from nitriles. General Procedure 5 (GP 5): Cyclohexylmagnesium bromide (2.00 equiv.) was added dropwise at ambient temperature to a well-stirred solution of allylaminoacetonitrile (1.00 equiv.) and $MeTi(O\textit{i}Pr)_3$ (1.10 equiv.) in anhydrous THF (40 mL). After the addition was complete, the reaction was stirred at 20 °C for 2 h, then LiI (2.00 equiv.) was added in one portion. The mixture was stirred at 70 °C for an additional 3 h, cooled to 0 °C, quenched with 10% aq. NaOH solution (5.0 mL) and the mixture was filtered through Celite®. The aqueous phase was extracted with Et_2O (3 × 20 mL), the combined organic phases were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

Preparation of 3-hydroxymethylderivatives. General Procedure 6 (GP 6): Tetrabutyl-ammonium fluoride hydrate (4.00 equiv.) was added to a solution of *tert*-butyldimethyl-silylalcohol (1.00 equiv.) in THF (10 mL) and the mixture was stirred at ambient temperature for 2 h. EtOAc (10 mL) and water (10 mL) were added, the aqueous layer was separated and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

Preparation of 3-aryl-3-azabicyclo[3.1.0]hex-1-ylamine by nucleophylic substitution. General Procedure 7 (GP 7): 3-Azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (1.10 equiv.), heterocycle (1.00 equiv.) and Et_3N (4.00 equiv.) in DMAA (4.0 mL) were heated at 130 °C for 3 h. The reaction mixture was filtered through Celite® and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

Preparation of 3-aryl-3-azabicyclo[3.1.0]hex-1-ylamine by Pd-catalyzed cross-coupling. General Procedure 8 (GP 8): 3-Azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (1.10 equiv.), heterocycle (1.00 equiv.), $Pd_2(dba)_3$ (5 mol%), (±)–BINAP (10 mol%), Et_3N (4.00 equiv) and NaO*t*Bu (3.50 equiv.) in DME (8.0 mL), were heated at 80 °C for 1 d. The reaction mixture was filtered through Celite® and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

Preparation of 3-(5-chloropyrid-3-yl)-azabicyclo[3.1.0]hex-1-ylamine. General Procedure 9 (GP 9): 3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (1.10 equiv.), 3,5-dichloropyridine (1.00 equiv.), $Pd(OAc)_2$ (5 mol%), 2-(di-*tert*-butylphosphino)-biphenyl (10 mol%), Et_3N (3.00 equiv.) and NaO*t*Bu (1.40 equiv.) in anhydrous DME (4.0 mL) were heated at 80 °C for 1 d. The reaction mixture was filtered through Celite® and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

Preparation of dibenzylamides from the corresponding carboxylic acid derivatives. General Procedure 10 (GP 10): Dibenzylamine (2.50 equiv.) was added dropwise to a suspension of DCC (2.50 equiv.), HOBT (1.00 equiv.) and carboxylic acid (1.00 equiv.) in anhydrous CH_2Cl_2 (10 mL). The mixture was stirred at ambient temperature for 2 d. EtOAc (10 mL) was added, the mixture was filtered through Celite®, and the solvent was removed under reduced

pressure. EtOAc (10 mL) was added, the organic phase was washed with aq. 5% HCl solution (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

Deprotection of N-tert-butoxycarbonyl derivatives. General Procedure 11 (GP 11): TFA (5.00 equiv.) was added to a well-stirred solution of *N-tert*-butoxycarbonyl derivative (1.00 equiv.) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at ambient temperature for 12 h, cooled in ice-bath and a sat. aq. $NaHCO_3$ solution (20 mL) was carefully added. The organic phase was separated, washed with $NaHCO_3$ (2 × 20 mL), brine (20 mL) and dried over $MgSO_4$. The product was used without further purification.

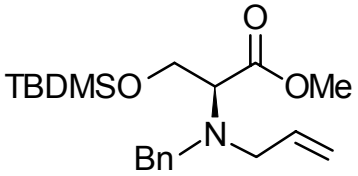
Preparation of N-trifluoroethyl derivatives. General Procedure 12 (GP 12): Trifluoro-acetaldehyde monomethylacetale (5.00 equiv.) and molecular sieves (3 Å) were added at ambient temperature to a solution of amine (1.00 equiv.) in DCE (10 mL). The reaction mixture was heated at 50 °C for 12 h, filtered through Celite® and concentrated under reduced pressure. The residue was dissolved in anhydrous THF (20 mL), cooled to 0°C, and $LiAlH_4$ (1.10 equiv., solution in THF) was added. The reaction mixture was stirred at ambient temperature for 1 d, then quenched carefully with an aq. 3 M NaOH solution (10 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), the organic phase washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

One-pot 1,3-dipolar cycloaddition/thermal rearrangement process. General Procedure 13 (GP 13): A solution of nitrone (1.00 equiv.) and alkene (1.20 equiv.) in *o*-xylene (4.0 mL) was heated at 120 °C for 1 d. The solvent was removed by elution with petroleum ether through a pad of silica gel, and the residue was recovered by eluition with MeOH and the solvent was removed. The crude oil was purified by chromatography on silica gel.

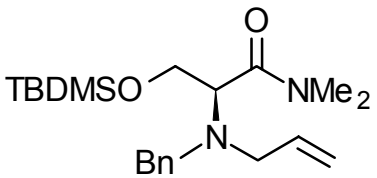
Preparation of N-allyl-N-(tert-butoxycarbonyl)glycine derivatives. General Procedure 14 (GP 14): Allyl amine (1.00 equiv.) first, then 2-bromoacetamide (1.00 equiv.) were added dropwise at 0 °C to a suspension of K_2CO_3 (2.00 equiv.), NaI (2.00 equiv.) and Et_3N (24.0 mmol) in anhydrous DMF (30 mL). The reaction mixture was stirred at ambient temperature for 16 h, Celite® was added and the mixture was filtered. Water (30 mL), and Et_2O (30 mL) were added to the filtrate. The aqueous layer was separated, cooled to 0 °C, saturated with NaCl and extracted with EtOAc (5 × 30 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed. A solution of the resulting amine (1.00 equiv.), Et_3N (1.40 equiv.) and Boc_2O (1.20 equiv.) in MeOH (50 mL) was heated for 4 h at 60 °C, the solvent was removed and water (20 mL) was added. The aqueous layer was extracted with EtOAc (3×30 mL), the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

2.2. Synthesis of 3-azabicyclo[3.1.0]hex-1-ylamines by Ti-mediated intramolecular reductive cyclopropanation of L-serine derivatives

Methyl (S)-2-(Allylbenzylamino)-3-(tert-butyldimethylsilyloxy)propionate (**53**): The ester **53** (1.14 g, 82%) was obtained from methyl (*S*)-2-benzyl-amino-3-(*tert*-butyldimethylsilyloxy) propionate (**51-TBDMS**, 1.11 g, 3.71 mmol), K_2CO_3 (1.03 g, 7.42 mmol) and allyl bromide (0.5 mL, 5.40 mmol) according to GP 1 as a colorless oil. R_f (Et_2O/hexane 1 : 10) = 0.50. – IR (film): ν = 3064 cm^{-1}, 2953, 2884, 1739, 1472, 1257, 1106. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.01 [s, 6 H, $Si(CH_3)_2$], 0.85 [s, 9 H, $SiC(CH_3)_3$], 3.16 (dd, ^2J = 14.5, ^3J = 7.3 Hz, 1 H, C*H*$_2$CH=CH_2), 3.33–3.35 (m, 1 H, C*H*$_2$CH=CH_2), 3.60–3.68 (m, 2 H, CH_2Ph, 2-H), 3.72 (s, 3 H, OCH_3), 3.81–3.99 (m, 3 H, CH_2Ph, 3-H), 5.09–5.25 (m, 2 H, CH=C*H*$_2$), 5.79–5.81 (m, 1 H, C*H*=CH_2), 7.22–7.38 (m, 5 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = –5.2 [+, 2 C, $Si(CH_3)_2$], 18.1 [C_{quat}, Si*C*$(CH_3)_3$], 25.7 [+, 3 C, $SiC(CH_3)_3$], 51.1 (+, OCH_3), 54.5 (–, *C*H_2CH=CH_2*), 55.1 (–, CH_2Ph*), 62.7 (–, C-3), 63.6 (+, C-2), 117.1 (–, CH=*C*H_2), 126.8 (+, Ar-C), 128.1 (+, 2 C, Ar-C), 128.5 (+, 2 C, Ar-C), 136.6 (+, *C*H=CH_2), 140.1 (C_{quat}, Ar-C), 172.2 (C_{quat}, C=O).

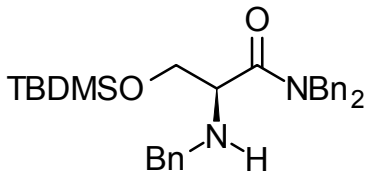


(S)-2-(Allylbenzylamino)-3-(tert-butyldimethylsilyloxy)-N,N-dimethylpropionamide (**54**): Trimethylalluminium (12.2 mL, 24.4 mmol, 2.0 M solution in hexane) was added at 5 °C over a period of 1 h to a solution of Me_2NH·HCl (2.00 g, 24.5 mmol) in anhydrous benzene (10 mL). The solution was stirred at 20 °C for 2 h and transferred to a solution (precooled to



5 °C) of methyl (*S*)-2-(allylbenzylamino)-3-(*tert*-butyldimethylsilyloxy)-propionate (**53**, 1.11 g, 3.06 mmol) in a mixture of anhydrous benzene (50 mL) and anhydrous THF (15 mL). After the addition was complete, the reaction mixture was stirred at 70 °C for 2 d, then cooled in an ice bath and carefully quenched with an aq. 10% NaOH solution (50 mL). EtOAc (10 mL) was added, the organic phase was washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue gave the amide **54** (587 mg, 51%) as a colorless oil. R_f (Et_2O/hexane 1 : 1) = 0.58. – $[\alpha]_D^{20}$ = –11.4 (*c* = 1.0, $CHCl_3$). – IR (film): ν = 3063 cm^{-1}, 2928, 1699, 1494, 1361, 1257, 1102. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.04 [s, 3 H, $Si(CH_3)_2$], 0.07 [s, 3 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $SiC(CH_3)_3$], 2.88 (s, 3 H, NCH_3), 2.90 (s, 3 H, NCH_3), 3.23–3.33 (m, 2 H, $CH_2CH{=}CH_2$), 3.75–4.02 (m, 5 H, CH_2Ph, 2-H, 3-H), 5.06–5.21 (m, 2 H, $CH{=}CH_2$), 5.73–5.86 (m, 1 H, $CH{=}CH_2$), 7.17–7.34 (m, 5 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = –5.4 [+, 2 C, $Si(CH_3)_2$], 18.1 [C_{quat}, $SiC(CH_3)_3$], 25.8 [+, 3 C, $SiC(CH_3)_3$], 35.4 (+, NCH_3), 37.2 (+, NCH_3), 54.2 (–, $CH_2CH{=}CH_2$*), 54.6 (–, CH_2Ph*), 59.4 (+, C-2), 62.1 (–, C-3), 116.9 (–, $CH{=}CH_2$), 126.6 (+, Ar-C), 128.0 (+, 2 C, Ar-C), 128.6 (+, 2 C, Ar-C), 136.9 (+, $CH{=}CH_2$), 140.2 (C_{quat}, Ar-C), 172.1 (C_{quat}, C=O). – MS (CI, 70 eV), *m*/*z* (%): 377 (100) [M^+ + H], 337 (3), 287 (5), 232 (3). – HRMS (EI) calcd. for $C_{21}H_{36}N_2O_2Si$ [M^+] 376.2546, found 376.2546.

(S)-2-Benzylamino-N,N-dibenzyl-3-(tert-butyldimethylsilyloxy)propionamide (**56**): *Tert*-butyldimethylsilylchloride (300 mg, 1.10 mmol, 55% solution in toluene) was added dropwise at 0 °C to a suspension of (*S*)-2-benzylamino-3-hydroxypropionic acid (**55**, 390 mg, 2.00 mmol) and Im-H (150 mg, 2.20 mmol) in DMF (10 mL). After the addition



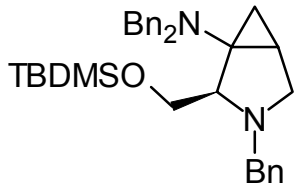
was complete, the mixture was stirred at ambient temperature for 2 d to give crude (*S*)-2-benzylamino-3-(*tert*-butyldimethyl-silyloxy)propionic acid. DCC (310 mg, 1.50 mmol), HOBT (150 mg, 1.10 mmol), and $HNBn_2$ (0.30 mL, 1.50 mmol) were then added, and stirring was continued for an additional 16 h. EtOAc (10 mL) was added, the mixture was filtered through Celite®, and the solvent was removed under reduced pressure. EtOAc (10 mL) was again added, and the organic phase was washed with $NaHCO_3$ (5 mL), H_2O (5 mL), brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue gave (*S*)-2-benzylamino-*N*,*N*-dibenzyl-3-(*tert*-butyldimethyl-silyloxy)propionamide (**56**, 236 mg, 48%) as a colorless oil. R_f (Et_2O/hexane 1 : 1) = 0.60. – $[\alpha]_D^{20}$ = –12.0 (*c* = 0.50, $CHCl_3$). – IR (film): ν = 3032 cm^{-1}, 2929, 2856, 1656, 1453, 1115, 785. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.05 [s, 3 H, $Si(CH_3)_2$], 0.09 [s, 3 H, $Si(CH_3)_2$], 0.90 [s, 9 H, $SiC(CH_3)_3$], 2.52 (br s, 1 H, NH), 3.50 (d, ^2J = 12.5 Hz, 1 H, CH_2Ph), 3.75–3.97 (m, 4 H, CH_2Ph, 2,3-H), 4.15 (d, ^2J = 14.7 Hz, 1 H, CH_2Ph), 4.26 (d, ^2J = 17.4 Hz, 1 H, CH_2Ph), 5.00 (d, ^2J = 17.4 Hz, 1 H, CH_2Ph), 5.33 (d, ^2J = 14.7 Hz, 1 H, CH_2Ph), 7.19–7.41 (m, 15 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = –5.5 [+, 2 C, $Si(CH_3)_2$], 18.3 [C_{quat}, $SiC(CH_3)_3$], 25.9 [+, 3 C, $SiC(CH_3)_3$], 48.9 (–, CH_2Ph), 49.4 (–, CH_2Ph), 51.9 (–, CH_2Ph), 59.0 (+, C-2), 66.0 (–, C-3), 126.6 (+, Ar-C), 127.0 (+, Ar-C), 127.4 (+, Ar-C), 127.6 (+, Ar-C), 128.1 (+, Ar-C), 128.3 (+, Ar-C), 128.4 (+, 3 C, Ar-C), 128.6 (+, 2 C, Ar-C), 128.9 (+, 2 C, Ar-C), 129.1 (+, 2 C, Ar-C), 136.9 (C_{quat}, Ar-C), 137.1 (C_{quat}, Ar-C), 139.9 (C_{quat}, Ar-C), 174.7 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 488 (26) [M^+], 473 (71), 343 (18), 264 (100), 91 (44) [$C_7H_7^+$]. – $C_{30}H_{40}N_2O_2Si$ (488.75): calcd. C 73.72, H 8.25, N 5.73; found C 73.58, H 8.33, N 5.54.

(S)-2-(Allylbenzylamino)-N,N-dibenzyl-3-(tert-butyldimethylsilyloxy)propionamide (**57**): The amide **57** (139 mg, 64%) was obtained from (*S*)-*N,N*-dibenzyl-2-benzylamino-3-(*tert*-butyldimethylsilyloxy)-propionamide (**56**, 200 mg, 410 µmol), K_2CO_3 (113 mg, 820 µmol) and allyl bromide (50 µL, 570 µmol) according to GP 1 as a colorless oil. R_f (Et_2O/hexane 1 : 5) = 0.60. – $[\alpha]_D^{20}$ = –2.0 (*c* = 0.90, $CHCl_3$). – IR (film): ν = 3028 cm^{-1}, 2927, 2855, 1652, 1452, 1256, 1099. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.10 [s, 3 H, $Si(CH_3)_2$], 0.12 [s, 3 H, $Si(CH_3)_2$], 0.94 [s, 9 H, $SiC(CH_3)_3$], 3.25 (dd, ^2J = 14.0, ^3J = 7.7 Hz, 1 H, $CH_2CH{=}CH_2$), 3.44 (dd, ^2J = 14.0, ^3J = 5.2 Hz, 1 H, $CH_2CH{=}CH_2$), 3.71 (d, ^2J = 13.8 Hz, 1 H, CH_2Ph), 3.87 (dd, ^3J = 5.4, ^3J = 7.2 Hz, 1 H, 2-H), 3.95 (d, ^2J = 14.8 Hz, 1 H, CH_2Ph), 4.02–4.24 (m, 4 H, 3-H, CH_2Ph), 4.66 (d, ^2J = 17.2 Hz, 1 H, CH_2Ph), 5.03–5.21 (m, 3 H, CH_2Ph, $CH{=}CH_2$), 5.70–5.86 (m, 1 H, $CH{=}CH_2$), 7.08–7.39 (m, 15 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = –5.4 [+, 2 C, $Si(CH_3)_2$], 18.3 [C_{quat}, $SiC(CH_3)_3$], 25.9 [+, 3 C, $SiC(CH_3)_3$], 47.8 (–, CH_2Ph), 49.0 (–, CH_2Ph), 53.9 (–, CH_2Ph*), 54.5 (–, $CH_2CH{=}CH_2$*), 59.7 (–, C-3), 60.1 (+, C-2), 117.8 (–, $CH{=}CH_2$), 126.6 (+, 2 C, Ar-C), 126.9 (+, Ar-C), 127.2 (+, Ar-C), 128.1 (+, 5 C, Ar-C), 128.5 (+, 2 C, Ar-C), 128.6 (+, 2 C, Ar-C), 128.9 (+, 2 C, Ar-C), 136.2 (C_{quat}, Ar-C), 136.9 (+, $CH{=}CH_2$), 137.4 (C_{quat}, Ar-C), 139.6 (C_{quat}, Ar-C), 171.8 (C_{quat}, C=O). – MS (EI, 70 eV): *m*/*z* (%) = 528 (15) [M^+], 513 (35), 437 (33) [$M^+ - C_7H_7$], 383 (12), 304 (100), 91 (25) [$C_7H_7^+$]. – $C_{33}H_{44}N_2O_2Si$ (528.81): calcd. C 74.95, H 8.39, N 5.30; found C 75.08, H 8.22, N 5.21.

endo- and exo-(2R)-3-Benzyl-2-(tert-butyldimethylsilyloxymethyl)-N,N-dimethyl-3-azabicyclo[3.1.0]hex-1-ylamine (**58**): The amines **58** (1.83 g, 89%) were obtained from the *N*,*N*-dimethylamide **54** (2.15 g, 5.70 mmol), $MeTi(OiPr)_3$ (2.06 g, 8.60 mmol) and *c*HexMgBr (35 mL, 34.0 mmol, 1.0 M solution in Et_2O) according to GP 3 in an *endo*/*exo* ratio of 2 : 1. *Endo*-**58**: Colorless oil, R_f (hexane/Et_2O 2 : 1) = 0.29. – $[\alpha]_D^{20}$ = +13.8 (*c* = 1.0, $CHCl_3$). – IR (film): ν = 2927 cm^{-1}, 2855, 1453, 1257, 1100. – ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.07 [s, 6 H, $Si(CH_3)_2$], 0.61 (dd, ^2J = 4.3, ^3J = 8.6 Hz, 1 H, *c*Pr-H), 0.91 [s, 9 H, $SiC(CH_3)_3$], 1.04 (ps t, ^2J = 4.0, ^3J =4.0 Hz, 1 H, *c*Pr-H), 1.26–1.33 (m, 1 H, *c*Pr-H), 2.35 (dd, ^2J = 9.0, ^3J = 4.0 Hz, 1 H, 4-H), 2.47 [s, 6 H, $N(CH_3)_2$], 2.71 (d, ^2J = 9.0 Hz, 1 H, 4-H), 3.02 (t, ^3J = 4.5 Hz, 1 H, 2-H), 3.30 (d, ^2J = 13.5 Hz, 1 H, CH_2Ph), 3.70 (dd, ^2J = 10.5, ^3J = 4.5 Hz, 1 H, CH_2O), 3.89 (dd, ^2J = 10.5, ^3J = 4.5 Hz, 1 H, CH_2O), 4.21 (d, ^2J = 13.5 Hz, 1 H, CH_2Ph), 7.18–7.28 (m, 5 H, Ar-H). – ^{13}C-NMR (75.5 MHz, $CDCl_3$, additional DEPT): δ = –5.4 [+, 2 C, $Si(CH_3)_2$], 14.7 (–, *c*Pr-C), 18.3 [C_{quat}, $SiC(CH_3)_3$], 23.3 (+, *c*Pr-C), 26.0 [+, 3 C, $SiC(CH_3)_3$], 42.0 [+, 2 C, $N(CH_3)_2$], 54.2 (–, C-4), 54.3 (C_{quat}, *c*Pr-C), 58.7 (–, CH_2Ph), 62.5 (+, C-2), 65.3 (–, CH_2O), 128.0 (+, Ar-C), 128.5 (+, 2 C, Ar-C), 128.7 (+, 2 C, Ar-C), 139.8 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 360 (12) [M^+], 316 (66), 229 (79), 215 (100), 123 (11), 91 (21) [$C_7H_7^+$]. – HRMS (EI) calcd. for $C_{21}H_{36}N_2OSi$ [M^+] 360.2597, found 360.2597. *exo*-**58**: Colorless oil, R_f (hexane/Et_2O 2 : 1) = 0.77. – $[\alpha]_D^{20}$ = +34.9 (*c* = 1.0, $CHCl_3$). – IR (film): ν = 3027 cm^{-1}, 2925, 1461, 1254, 1042. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.07 [s, 3 H, $Si(CH_3)_2$], 0.08 [s, 3 H, $Si(CH_3)_2$], 0.66 (dd, ^2J = 3.5, ^3J = 8.5 Hz, 1 H, *c*Pr-H), 0.85–0.89 (m, 1 H, *c*Pr-H), 0.94 [s, 9 H, $SiC(CH_3)_3$], 1.57–1.64 (m, 1 H, *c*Pr-H), 2.21 [s, 6 H, $N(CH_3)_2$], 2.61 (d, ^2J = 7.8 Hz, 1 H, 4-H), 3.01–3.06 (m, 2 H, 2,4-H), 3.78 (d, ^2J = 13.4 Hz, 1 H,

CH_2Ph), 3.85–3.88 (m, 2 H, CH_2O), 4.00 (d, ^2J = 13.4 Hz, 1 H, CH_2Ph), 7.30–7.22 (m, 5 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = –5.5 [+, 2 C, $Si(CH_3)_2$], 14.1 (–, *c*Pr-C), 18.1 [C_{quat}, $SiC(CH_3)_3$], 22.9 (+, *c*Pr-C), 26.9 [+, 3 C, $SiC(CH_3)_3$], 43.3 [+, 2 C, $N(CH_3)_2$], 52.5 (C_{quat}, *c*Pr-C), 53.4 (–, C-4), 54.4 (–, CH_2Ph), 61.0 (+, C-2), 64.5 (–, CH_2O), 126.4 (+, Ar-C), 128.0 (+, 3 C, Ar-C), 128.1 (+, Ar-C), 139.6 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 360 (6) [M^+], 316 (25), 229 (53), 215 (100), 123 (26), 110 (29), 91 (21) [$C_7H_7^+$]. – HRMS (EI) calcd. for $C_{21}H_{36}N_2OSi$ [M^+] 360.2597, found 360.2597.

endo- and exo-(2R)-N,N,3-Tribenzyl-2-(tert-butyldimethylsilyloxymethyl)-3-azabicyclo-[3.1.0]hex-1-ylamine (**59**): The amines **59** (265 mg, 83%) were obtained from *N*,*N*-dibenzylamide **57** (330 mg, 620 μmol), $MeTi(OiPr)_3$ (206 mg, 858 μmol) and *c*HexMgBr (3.5 mL, 2.87 mmol, 0.80 M solution in Et_2O) according to GP 3 in an *endo*/*exo* ratio of 2.5 : 1.



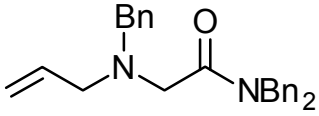
endo-**59**: Colorless oil, R_f (hexane/Et_2O 10 : 1) = 0.20. – $[\alpha]_D^{20}$ = +3.6 (*c* = 0.50, $CHCl_3$). – IR (film): ν = 3027 cm^{-1}, 2927, 1453, 1256, 873, 698. – ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 0.15 [s, 3 H, $Si(CH_3)_2$], 0.17 [s, 3 H, $Si(CH_3)_2$], 0.53 (dd, ^3J = 4.0, ^2J = 8.5 Hz, 1 H, *c*Pr-H), 0.85–0.91 (m, 2 H, *c*Pr-H), 1.02 [s, 9 H, $SiC(CH_3)_3$], 1.86 (dd, ^3J = 3.5, ^3J = 8.5 Hz, 1 H, 4-H), 2.46 (d, ^3J = 8.5 Hz, 1 H, 4-H), 3.25 (t, ^3J = 5.0 Hz, 1 H, 2-H), 3.37 (d, ^2J = 13.5 Hz, 1 H, CH_2Ph), 3.75 (dd, ^2J = 10.5, ^3J = 4.5 Hz, 1 H, CH_2O), 3.84 (s, 2 H, CH_2Ph), 3.85 (s, 2 H, CH_2Ph), 3.92 (dd, ^2J = 10.5, ^3J = 5.0 Hz, 1 H, CH_2O), 4.06 (d, ^2J = 13.5 Hz, 1 H, CH_2Ph), 7.18–7.32 (m, 15 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = –5.2 [+, 2 C, $Si(CH_3)_2$], 13.9 (–, *c*Pr-C), 18.4 [C_{quat}, $SiC(CH_3)_3$], 25.4 (+, *c*Pr-C), 26.1 (+, 3 C, $SiC(CH_3)_3$], 53.1 (–, C-4), 53.2 (C_{quat}, *c*Pr-C), 56.8 (–, 2 C, CH_2Ph),

58.1 (–, CH_2Ph), 62.5 (+, C-2), 64.8 (–, CH_2O), 126.6 (+, Ar-C), 126.7 (+, 2 C, Ar-C), 127.9 (+, 5 C, Ar-C), 128.0 (+, 2 C, Ar-C), 128.9 (+, 5 C, Ar-C), 131.8 (C_{quat}, Ar-C), 139.1 (C_{quat}, Ar-C), 140.6 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 512 (6) [M^+], 421 (40) [$M^+ – C_7H_7$], 381 (100), 367 (39), 316 (25), 276 (19), 91 (44) [$C_7H_7^+$]. – $C_{33}H_{44}N_2OSi$ (512.81): calcd. C 77.29, H 8.65, N 5.46; found C 77.12, H 8.55, N 5.51.

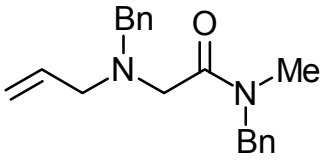
exo-**59**: Colorless solid, R_f (hexane/Et_2O 10 : 1) = 0.32, m.p. 54–56 °C. – $[\alpha]_D^{20}$ = +17.0 (*c* = 0.50, $CHCl_3$). – IR (KBr): ν = 3027 cm^{-1}, 2926, 1452, 1255, 1099, 697. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.06 [s, 3 H, $Si(CH_3)_2$], 0.12 [s, 3 H, $Si(CH_3)_2$], 0.78–0.84 (m, 2 H, *c*Pr-H), 0.89 [s, 9 H, $SiC(CH_3)_3$], 1.60–1.66 (m, 1 H, *c*Pr-H), 2.50 (d, ^3J = 8.1 Hz, 1 H, 4-H), 2.81 (t, ^3J = 3.4 Hz, 1 H, 4-H), 2.86 (dd, ^3J = 3.4, ^3J = 8.1 Hz, 1 H, 2-H), 3.60–3.84 (m, 6 H, CH_2O, CH_2Ph), 3.90–3.97 (m, 2 H, CH_2Ph), 7.15–7.37 (m, 15 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = –5.3 [+, 2 C, $Si(CH_3)_2$], 14.6 (–, *c*Pr-C), 18.0 [C_{quat}, $SiC(CH_3)_3$], 24.3 (+, *c*Pr-C), 26.1 [+, 3 C, $SiC(CH_3)_3$], 26.9 (–, C-4), 30.2 (–, CH_2Ph), 51.7 (C_{quat}, *c*Pr-C), 52.1 (–, CH_2Ph), 54.6 (–, CH_2Ph), 61.7 (–, CH_2O), 65.9 (+, C-2), 126.3 (+, 2 C, Ar-C), 126.7 (+, Ar-C), 127.9 (+, 6 C, Ar-C), 128.1 (+, 5 C, Ar-C), 129.5 (+, Ar-C), 138.1 (C_{quat}, Ar-C), 140.9 (C_{quat}, 2 C, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 512 (3) [M^+], 421 (50) [$M^+ – C_7H_7$], 381 (100), 367 (51), 316 (27), 276 (33), 91 (9) [$C_7H_7^+$]. – $C_{33}H_{44}N_2OSi$ (512.81): calcd. C 77.29, H 8.65, N 5.46; found C 77.07, H 8.42, N 5.55.

2.3. Synthesis of 3-azabicyclo[3.1.0]hex-1-ylamines by Ti-mediated intramolecular reductive cyclopropanation of glycine derivatives

2-(Allylbenzylamino)-N,N-dibenzylacetamide (**70**): The amide **70** (37.9 g, 93%) was obtained from the *N*,*N*-dibenzylamide **67** (33.7 g, 106 mmol), Et_3N (28 mL, 202 mmol) and allylbenzylamine (17.3 g, 117 mmol) according to GP 2 as a colorless oil. R_f (hexane/Et_2O 2 : 1) = 0.33. – IR (film): ν = 3028 cm^{-1}, 2922, 1650, 1494, 1451, 1213, 1076, 734. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.27 (d, ^3J = 6.5 Hz, 2 H, CH_2CH=CH_2), 3.40 (s, 2 H, 2-H), 3.77 (s, 2 H, CH_2Ph), 4.49 (s, 2 H, CH_2Ph), 4.60 (s, 2 H, CH_2Ph), 5.13–5.26 (m, 2 H, CH=CH_2), 5.88 (ddt, ^3J = 6.6, ^3J =10.2, ^3J =17.1 Hz, 1 H, C*H*=CH_2), 7.06–7.38 (m, 15 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 47.6 (–, *C*H_2CH=CH_2), 49.3 (–, C-2), 55.7 (–, CH_2Ph), 57.0 (–, CH_2Ph), 58.1 (–, CH_2Ph), 118.7 (–, CH=*C*H_2), 126.5 (+, 2 C, Ar-C), 127.0 (+, Ar-C), 127.3 (+, 2 C, Ar-C), 128.1 (+, 4 C, Ar-C), 128.5 (+, 2 C, Ar-C), 128.6 (+, 2 C, Ar-C), 129.1 (+, 2 C, Ar-C), 135.0 (+, *C*H=CH_2), 136.6 (C_{quat}, Ar-C), 137.2 (C_{quat}, Ar-C), 138.3 (C_{quat}, Ar-C), 171.0 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 384 (6) [M^+], 343 (14), 293 (48) [$M^+ – C_7H_7$], 160 (78), 91 (100) [$C_7H_7^+$]. – $C_{26}H_{28}N_2O$ (384.52): calcd. C 81.21, H 7.34, N 7.28; found C 81.04, H 7.11, N 7.09.

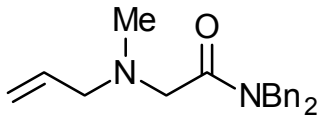


2-(Allylbenzylamino)-N-benzyl-N-methylacetamide (**71**): The amide **71** (3.15 g, 85%) was obtained from the *N*-benzyl-*N*-methylamide **68** (2.90 g, 12.0 mmol), Et_3N (0.10 mL, 24.0 mmol) and allylbenzylamine (1.95 g, 13.2 mmol) according to GP 2 as a colorless oil. R_f (hexane/Et_2O 1 : 1) = 0.39. – IR (film): ν = 3028 cm^{-1}, 2920, 2836, 1646, 1452, 1261,



1103, 699. – ^{1}H-NMR (250 MHz, $CDCl_3$, observed as a major rotamer/minor rotamer ratio of 1.5 : 1): δ = 2.86 (s, 3 H, minor, NCH_3), 2.88 (s, 3 H, major, NCH_3), 3.20–3.23 (m, 2 H, C*H*$_2$CH=CH$_2$), 3.33 (s, 2 H, 2-H), 3.69 (s, 2 H, minor, CH_2Ph), 3.74 (s, 2 H, major, CH_2Ph), 4.54 (s, 2 H, minor, CH_2Ph), 4.56 (s, 2 H, major, CH_2Ph), 5.12–5.26 (m, 2 H, CH=C*H*$_2$), 5.77–5.95 (m, 1 H, C*H*=CH$_2$), 7.05–7.38 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT, observed as a major rotamer/minor rotamer ratio of 1.5 : 1): δ = 33.6 (+, minor, NCH_3), 34.6 (+, major, NCH_3), 50.8 (–, major, *C*H$_2$CH=CH$_2$), 52.8 (–, minor, *C*H$_2$CH=CH$_2$), 55.8 (–, major, C-2), 56.0 (–, minor, C-2), 57.1 (–, major, CH_2Ph), 57.3 (–, minor, CH_2Ph), 58.1 (–, major, CH_2Ph), 58.2 (–, minor, CH_2Ph), 118.3 (–, minor, CH=*C*H$_2$), 118.4 (–, major, CH=*C*H$_2$), 126.5 (+, Ar-C), 127.0 (+, Ar-C), 127.2 (+, Ar-C), 128.2 (+, 2 C, Ar-C), 128.5 (+, 2 C, Ar-C), 128.7 (+, Ar-C), 129.2 (+, 2 C, Ar-C), 135.2 (+, minor, *C*H=CH$_2$), 135.3 (+, major, *C*H=CH$_2$), 136.9 (C_{quat}, minor, Ar-C), 137.3 (C_{quat}, major, Ar-C), 138.5 (C_{quat}, minor, Ar-C), 138.7 (C_{quat}, major, Ar-C), 170.7 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 308 (7) [M^+], 267 (14), 217 (48) [$M^+ - C_7H_7$], 160 (88), 91 (100) [$C_7H_7^+$]. – $C_{20}H_{24}N_2O$ (308.43): calcd. C 77.88, H 7.84, N 9.08; found C 77.99, H 7.97, N 8.89.

2-(Allylmethylamino)-N,N-dibenzylacetamide (**72**): The amide **72** (19.0 g, 98%) was obtained from the *N*,*N*-dibenzylamide **67** (20.0 g, 63.0 mmol), Et_3N (17 mL, 126 mmol) and allylmethylamine (6.57 mL, 69.0 mmol) according to GP 2 as a colorless oil. R_f (hexane/Et_2O 1 : 2) = 0.28. – IR (film): ν = 3029 cm^{-1}, 2919, 2788, 1649, 1451, 1233, 699. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, NCH_3), 3.10 (d, ^3J = 6.6 Hz, 2 H, C*H*$_2$CH=CH$_2$), 3.29

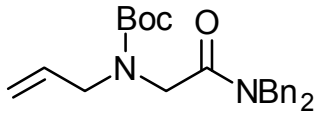


(s, 2 H, 2-H), 4.57 (s, 2 H, CH_2Ph), 4.60 (s, 2 H, CH_2Ph), 5.08–5.20 (m, 2 H, CH=CH_2), 5.82 (ddt, ^3J = 6.5, ^3J = 10.3, ^3J = 17.0 Hz, 1 H, C*H*=CH_2), 7.15–7.39 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 42.6 (+, NCH_3), 47.8 (–, *C*H_2CH=CH_2), 49.5 (–, C-2), 59.7 (–, CH_2Ph), 60.8 (–, CH_2Ph), 118.3 (–, CH=*C*H_2), 126.7 (+, 2 C, Ar-C), 127.4 (+, Ar-C), 127.5 (+, Ar-C), 128.3 (+, 2 C, Ar-C), 128.6 (+, 2 C, Ar-C), 128.9 (+, 2 C, Ar-C), 135.0 (+, *C*H=CH_2), 136.8 (C_{quat}, Ar-C), 137.3 (C_{quat}, Ar-C), 170.7 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 308 (7) [M^+], 279 (11), 217 (3) [$M^+ - C_7H_7$], 91 (26) [$C_7H_7^+$], 84 (100). – $C_{20}H_{24}N_2O$ (308.43): calcd. C 77.88, H 7.84, N 9.08; found C 77.59, H 7.61, N 8.97.

N,N-Dibenzyl-2-[(benzyl)(but-3-enyl)amino]acetamide (**73**): A solution of *N*-benzyl-but-3-enylamine (322 mg, 2.00 mmol) in anhydrous DMF (3.0 mL) was added at 0 °C to a suspension of NaH (104 mg, 2.60 mmol, 60% suspension in mineral oil) in anhydrous DMF (4.0 mL). The reaction mixture was stirred for 10 min at 0 °C, the *N*,*N*-dibenzylamide **67** (732 mg, 2.30 mmol) was then added in one portion, and stirring was continued at ambient temperature for an additional 2 h. The reaction mixture was cooled with an ice-bath, and a 2 : 1 mixture of sat. aq. NH_4Cl solution and 25% aq. NH_4OH solution (6 mL) was added. The aqueous layer was extracted with Et_2O (3 × 15 mL), the combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica gel to give the amide **72** (605 mg, 76%) as a yellow oil. R_f (hexane/Et_2O 2 : 1) = 0.37. – IR (film): ν = 3062 cm^{-1}, 3028, 2921, 1650, 1451, 1211, 698. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.20–2.29 (m, 2 H, 2'-H), 2.71 (ps t, ^3J = 7.2 Hz, 2 H, 1'-H), 3.37 (s, 2 H, 2-H), 3.72 (s, 2 H, CH_2Ph), 4.50 (s, 2 H, CH_2Ph),

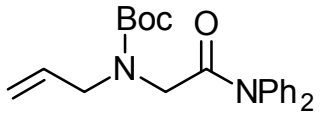
4.56 (s, 2 H, CH_2Ph), 4.92–5.02 (m, 2 H, CH=CH_2), 5.82 (ddt, ^3J = 6.7, ^3J = 10.2, ^3J = 17.1 Hz, 1 H, CH=CH_2), 7.05–7.39 (m, 15 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 31.4 (–, C-2'), 47.8 (–, C-1'), 49.3 (–, C-2), 53.6 (–, CH_2Ph), 56.8 (–, CH_2Ph), 58.4 (–, CH_2Ph), 115.8 (–, CH=CH$_2$), 126.4 (+, 2 C, Ar-C), 127.2 (+, Ar-C), 127.3 (+, Ar-C), 127.4 (+, Ar-C), 128.2 (+, 2 C, Ar-C), 128.3 (+, 2 C, Ar-C), 128.6 (+, 2 C, Ar-C), 128.8 (+, 2 C, Ar-C), 129.2 (+, 2 C, Ar-C), 136.5 (C_{quat}, Ar-C), 136.7 (+, CH=CH_2), 137.2 (C_{quat}, Ar-C), 138.4 (C_{quat}, Ar-C), 171.1 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 398 (3) [M^+], 357 (37), 174 (82), 91 (100) [$C_7H_7^+$]. – HRMS (EI) calcd. for $C_{27}H_{30}N_2O$ [M^+] 398.2358, found 398.2358.

2-[(Allyl)(tert-butoxycarbonyl)amino)-N,N-dibenzylacetamide (**74**): Triethylamine (1.3 mL, 9.10 mmol) and allyl amine (286 mg, 5.01 mmol) were added dropwise at 0 °C to a solution of the *N*,*N*-dibenzylamide **67** (1.45 g, 4.56 mmol) in anhydrous THF (15 mL). After the addition was complete, the reaction mixture was stirred at ambient temperature for an additional 12 h. Sat. aq. $NaHCO_3$ solution (10 mL) and EtOAc (10 mL) were added, the organic phase was separated, washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give an oil which was used without further purification. This oil was taken up in a mixture of H_2O (7 mL) and dioxane (15 mL), and to this solution were added a solution of NaOH (160 mg, 4.00 mmol) in H_2O (7.0 mL) and Boc_2O (1.09 g, 5.00 mmol). The mixture was stirred for 2 d, concentrated to about 50% of its original volume, and extracted with Et_2O (3 × 15 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue gave the amide **74** (1.02 g, 57%) as a colorless oil. R_f (Et_2O/hexane 2 : 1) = 0.59. – IR (film):

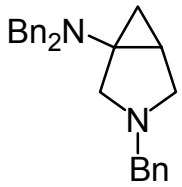


ν = 3031 cm^{-1}, 2978, 1700, 1652, 1448, 1172. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.40 [s, 9 H, $C(CH_3)_3$], 3.64–3.70 (m, 2 H, $CH_2CH{=}CH_2$), 3.88 (s, 2 H, 2-H), 4.47 (s, 2 H, CH_2Ph), 4.58 (s, 2 H, CH_2Ph), 5.04–5.19 (m, 2 H, $CH{=}CH_2$), 6.85 (m, 1 H, $CH{=}CH_2$), 7.05–7.32 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 28.3 [+, 3 C, $C(CH_3)_3$], 43.0 (–, $CH_2CH{=}CH_2$), 48.4 (–, C-2), 50.7 (–, CH_2Ph), 60.3 (–, CH_2Ph), 79.1 [C_{quat}, $C(CH_3)_3$], 115.5 (–, $CH{=}CH_2$), 126.4 (+, 2 C, Ar-C), 127.6 (+, Ar-C), 127.9 (+, Ar-C), 128.0 (+, 2 C, Ar-C), 128.6 (+, 2 C, Ar-C), 129.0 (+, 2 C, Ar-C), 135.0 (+, $CH{=}CH_2$), 135.7 (C_{quat}, Ar-C), 136.4 (C_{quat}, Ar-C), 155.8 (C_{quat}, C=O), 167.4 (C_{quat}, C=O).

2-(Allyl-tert-butoxycarbonylamino)-N,N-diphenylacetamide (**75**): The amide **75** (6.00 g, 54%) was obtained from K_2CO_3 (8.15 g, 58.7 mmol), NaI (9.00 g, 60.0 mmol), Et_3N (16.0 mL, 117 mmol), allyl amine (2.25 mL, 30.0 mmol), *N,N*-diphenylamide **69** (8.07 g, 30.0 mmol) and Boc_2O (7.20 g, 33.0 mmol) according to GP 14 as a colorless oil. R_f (Et_2O/hexane 2 : 1) = 0.80. – ^{1}H-NMR (250 MHz, $CDCl_3$, observed as a major rotamer/minor rotamer ratio of 1.1 : 1): δ = 1.45 [s, 9 H, major, $C(CH_3)_3$], 1.49 [s, 9 H, minor, $C(CH_3)_3$], 3.80 (s, 2 H, 2-H), 3.91–4.00 (m, 2 H, $CH_2CH{=}CH_2$), 5.06–5.16 (m, 2 H, $CH{=}CH_2$), 5.70–5.81 (m, 1 H, $CH{=}CH_2$), 7.24–7.31 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT, observed as a major rotamer/minor rotamer ratio of 1.1 : 1): δ = 28.4 [+, 3 C, $C(CH_3)_3$], 49.0 (–, major, $CH_2CH{=}CH_2$), 49.3 (–, minor, $CH_2CH{=}CH_2$), 50.5 (–, minor, C-2), 50.8 (–, major, C-2), 80.0 [C_{quat}, $C(CH_3)_3$], 116.4 (–, major, $CH{=}CH_2$), 117.2 (–, minor, $CH{=}CH_2$), 126.1 (+, 4 C, Ar-C), 128.5 (+, 2 C, Ar-C), 129.7 (+, 4 C, Ar-C), 134.2 (+, $CH{=}CH_2$), 134.6 (C_{quat}, 2 C, Ar-C), 155.8 (C_{quat}, C=O), 168.6 (C_{quat}, C=O).

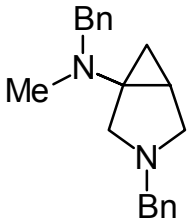


N,N,3-Tribenzyl-3-azabicyclo[3.1.0]hex-1-ylamine (**76**): The amine **76** (32.0 g, 58%) was obtained from the *N,N*-dibenzylamide **70** (57.0 g, 150 mmol), $MeTi(OiPr)_3$ (54.1 g, 225 mmol) and *c*HexMgBr (930 mL, 750 mmol, 0.80 M solution in Et_2O) according to GP 3 as a colorless solid.



R_f (hexane/Et_2O 2 : 1) = 0.56, m.p. 76–79 °C. – IR (KBr): ν = 3022 cm^{-1}, 2929, 2793, 1493, 1454, 1210, 735. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.56–0.60 (m, 1 H, *c*Pr-H), 0.97–1.04 (m, 2 H, *c*Pr-H), 2.20 (dd, ^2J = 8.5, ^3J = 2.7 Hz, 1 H, 4-H), 2.71 (d, ^2J = 13.1 Hz, 1 H, 2-H), 2.74 (d, ^2J = 12.7 Hz, 1 H, 2-H), 2.96 (d, ^2J = 8.2 Hz, 1 H, 4-H), 3.65 (s, 2 H, CH_2Ph), 3.75 (d, ^2J = 13.2 Hz, 2 H, CH_2Ph), 3.85 (d, ^2J = 13.2 Hz, 2 H, CH_2Ph), 7.23–7.41 (m, 15 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 16.5 (–, *c*Pr-C), 24.4 (+, *c*Pr-C), 49.8 (C_{quat}, *c*Pr-C), 50.8 (–, C-2*), 54.2 (–, C-4*), 56.9 (–, 2 C, CH_2Ph), 59.4 (–, CH_2Ph), 126.7 (+, 3 C, Ar-C), 127.9 (+, 4 C, Ar-C), 128.1 (+, 2 C, Ar-C), 128.5 (+, 2 C, Ar-C), 128.9 (+, 4 C, Ar-C), 139.2 (C_{quat}, Ar-C), 140.1 (C_{quat}, 2 C, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 368 (18) [M^+], 277 (100) [$M^+ - C_7H_7$], 158 (16), 91 (67) [$C_7H_7^+$]. – $C_{26}H_{28}N_2$ (368.52): calcd. C 84.74, H 7.66, N 7.60; found C 84.70, H 7.51, N 7.50.

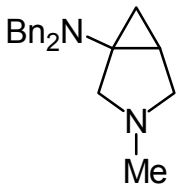
N,3-Dibenzyl-N-methyl-3-azabicyclo[3.1.0]hex-1-ylamine (**77**): The amine **77** (10.3 g, 56%) was obtained from the *N*-benzyl-*N*-methylamide **71** (19.4 g, 63.0 mmol), $MeTi(OiPr)_3$ (23.0 g, 96.0 mmol) and *c*HexMgBr (308 mL, 315 mmol, 1.0 M solution in Et_2O) according to GP 3 as a colorless oil.



R_f (hexane/Et_2O 2 : 1) = 0.45. – IR (film): ν = 3026 cm^{-1}, 2896, 2787, 1452, 1378, 1027. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.71 (dd, ^2J = 3.7, ^3J = 8.5 Hz, 1 H, *c*Pr-H), 1.16 (ps t, ^2J = 3.9, ^3J = 3.9 Hz, 1 H, *c*Pr-H), 1.35–1.41 (m, 1 H, *c*Pr-H), 2.30 (s, 3 H,

NCH_3), 2.44 (dd, ^2J = 8.6, ^3J = 3.5 Hz, 1 H, 4-H), 2.61 (d, ^2J = 8.2 Hz, 1 H, 2-H), 2.84 (d, ^2J = 8.6 Hz, 1 H, 4-H), 2.93 (d, ^2J = 8.2 Hz, 1 H, 2-H), 3.56–3.70 (m, 3 H, CH_2Ph), 3.80 (d, ^2J = 13.0 Hz, 1 H, CH_2Ph), 7.21–7.34 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 17.0 (–, *c*Pr-C), 24.2 (+, *c*Pr-C), 39.2 (+, NCH_3), 50.3 (–, C-4*), 52.1 (C_{quat}, *c*Pr-C), 54.8 (–, C-2*), 59.6 (–, CH_2Ph), 59.8 (–, CH_2Ph), 126.8 (+, Ar-C), 128.1 (+, 4 C, Ar-C), 128.5 (+, 2 C, Ar-C), 128.8 (+, 3 C, Ar-C), 139.5 (C_{quat}, Ar-C), 139.7 (C_{quat}, Ar-C). – MS (EI), *m*/*z* (%): 292 (39) [M^+], 201 (40) [$M^+ - C_7H_7$], 173 (46), 158 (43), 91 (100) [$C_7H_7^+$]. – $C_{20}H_{24}N_2$ (292.43): calcd. C 82.15, H 8.27, N 9.58; found C 81.91, H 8.06, N 9.37.

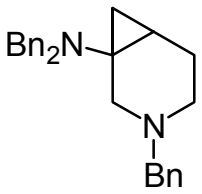
N,N-Dibenzyl-3-methyl-3-azabicyclo[3.1.0.]hex-1-ylamine (**78**): The amine **78** (193 mg, 66%) was obtained from the *N*,*N*-dibenzylamide **72** (308 mg, 1.00 mmol), $MeTi(OiPr)_3$ (351 mg, 1.46 mmol) and *c*HexMgBr (5.0 mL, 5.00 mmol, 1.0 M solution in Et_2O) according to GP 3 as a colorless oil.



R_f (CH_2Cl_2/MeOH 15 : 1 + 1%NH_3) = 0.50. – IR (film): ν = 3027 cm^{-1}, 2885, 2776, 1453, 1198, 748. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.53 (dd, ^2J = 4.0, ^3J = 8.3 Hz, 1 H, *c*Pr-H), 0.88 (ps t, ^2J = 4.3 , ^3J = 4.3 Hz, 1 H, *c*Pr-H), 1.05–0.98 (m, 1 H, *c*Pr-H), 2.11 (dd, ^2J = 8.8 , ^3J = 3.5, Hz, 1 H, 4-H), 2.29 (s, 3 H, NCH_3), 2.61 (d, ^2J = 8.4 Hz, 1 H, 2-H), 2.94 (d, ^2J = 8.4 Hz, 1 H, 2-H), 2.70 (d, ^2J = 8.8 Hz, 1 H, 4-H), 3.76 (s, 2 H, CH_2Ph), 3.78 (s, 2 H, CH_2Ph), 7.19–7.34 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 16.8 (–, *c*Pr-C), 24.8 (+, *c*Pr-C), 42.0 (+, NCH_3), 50.5 (C_{quat}, *c*Pr-C), 53.2 (–, C-2*), 56.7 (–, C-4*), 56.8 (–, 2 C, CH_2Ph), 126.8 (+, 2 C, Ar-C), 127.9 (+, 4 C, Ar-C), 128.9 (+, 4 C, Ar-C), 139.9 (C_{quat}, 2 C, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 292 (13) [M^+], 201 (100) [M^+ –

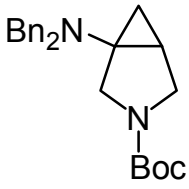
C_7H_7], 158 (14), 91 (44) [$C_7H_7^+$]. – HRMS (EI) calcd for $C_{20}H_{24}N_2$ [M^+] 292.1939, found 292.1939.

N,N,3-Tribenzyl-3-azabicyclo[4.1.0]hept-1-ylamine (**79**): The amine **79** (1.10 g, 59%) was obtained from the *N,N*-dibenzylamide **73** (1.94 g, 4.87 mmol), MeTi(O*i*Pr)$_3$ (1.76 g, 7.33 mmol) and *c*HexMgBr (19.5 mL, 19.5 mmol, 1.0 M solution in Et_2O) according to GP 3 as a colorless solid.



R_f (hexane/Et_2O 5 : 1) = 0.52, m.p. = 82–84 °C. – IR (KBr): ν = 3027 cm^{-1}, 2912, 2770, 1452, 1124, 753. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.49 (dd, ^2J = 3.9, ^3J = 6.3 Hz, 1 H, *c*Pr-H), 0.57 (dd, ^2J = 3.8, ^3J = 9.8 Hz, 1 H, *c*Pr-H), 0.73–0.82 (m, 1 H, *c*Pr-H), 1.49–1.60 (m, 1 H, 4-H*), 1.67–1.80 (m, 1 H, 4-H*), 1.99–2.06 (m, 1 H, 5-H*), 2.15–2.24 (m, 1 H, 5-H*), 2.62 (d, ^2J = 11.1 Hz, 1 H, 2-H), 3.04 (d, ^2J = 11.2 Hz, 1 H, 2-H), 3.51 (s, 2 H, CH_2Ph), 3.74 (s, 4 H, CH_2Ph), 7.16–7.53 (m, 15 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 19.8 (+, *c*Pr-C), 19.9 (–, *c*Pr-C), 24.3 (–, C-5), 42.8 (C_{quat}, *c*Pr-C), 49.5 (–, C-4), 52.9 (–, C-2), 55.9 (–, 2 C, CH_2Ph), 63.0 (–, CH_2Ph), 126.6 (+, 2 C, Ar-C), 126.7 (+, Ar-C), 127.9 (+, 4 C, Ar-C), 128.2 (+, 2 C, Ar-C), 128.7 (+, 2 C, Ar-C), 129.2 (+, 4 C, Ar-C), 139.3 (C_{quat}, Ar-C), 140.4 (C_{quat}, 2 C, Ar-C). – MS (EI, 70 eV), *m/z* (%): 382 (15) [M^+], 291 (22) [$M^+ – C_7H_7$], 210 (24), 166 (12), 91 (100) [$C_7H_7^+$].

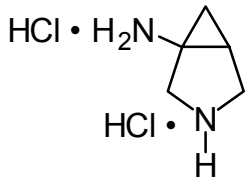
N,N-Dibenzyl-3-(tert-butoxycarbonyl)-3-azabicyclo[3.1.0]hex-1-ylamine (**80**): The amine **80** (262 mg, 43%) was obtained from the *N,N*-dibenzylamide **74** (635 mg, 1.61 mmol), MeTi(O*i*Pr)$_3$ (581 mg, 2.42 mmol) and *c*HexMgBr (10 mL, 8.00 mmol, 0.8 M solution in Et_2O) according to GP 3 as a colorless oil,



R_f (hexane/Et_2O 2 : 1) = 0.56. – IR (film): ν = 3027 cm^{-1}, 2978, 2862, 1692, 1401, 1116. –

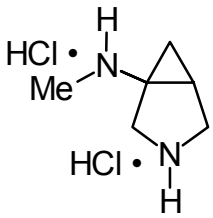
^{1}H-NMR (250 MHz, $CDCl_3$, observed as a major rotamer/minor rotamer ratio of 1.2 : 1): δ = 0.35 (ps t, ^2J = 4.7, ^3J = 4.7 Hz, 1 H, *c*Pr-H), 0.78–0.83 (m, 1 H, *c*Pr-H), 1.00–1.03 (m, 1 H, *c*Pr-H), 1.45 [s, 9 H, major, $C(CH_3)_3$], 1.49 [s, 9 H, minor, $C(CH_3)_3$], 3.08–3.12 (m, 1 H, 4-H), 3.19 (d, ^2J = 10.6 Hz, 1 H, major, 2-H), 3.27 (d, ^2J = 10.6 Hz, 1 H, minor, 2-H), 3.40 (d, ^2J = 10.4 Hz, 1 H, minor, 2-H), 3.54 (d, ^2J = 10.5 Hz, 1 H, major, 2-H), 3.58–3.87 (m, 5 H, 4-H, CH_2Ph), 7.22–7.32 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT, observed as a major rotamer/minor rotamer ratio of 1.2 : 1): δ = 18.7 (–, minor, *c*Pr-C), 18.9 (–, major, *c*Pr-C), 24.3 (+, minor, *c*Pr-C), 24.7 (+, major, *c*Pr-C), 28.4 [+, 3 C, major, $C(CH_3)_3$], 28.5 [+, 3 C, minor, $C(CH_3)_3$], 44.6 (–, major, C-4), 44.9 (–, minor, C-4), 47.6 (–, minor, C-2), 48.0 (–, major, C-2), 50.0 (C_{quat}, *c*Pr-C), 56.8 (–, minor, CH_2Ph), 56.9 (–, major, CH_2Ph), 79.3 [C_{quat}, $C(CH_3)_3$], 127.0 (+, 2 C, Ar-C), 128.1 (+, 4 C, Ar-C), 129.0 (+, 4 C, Ar-C), 139.5 (C_{quat}, 2 C, Ar-C), 155.1 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 378 (23) [M^+], 287 (38) [$M^+ - C_7H_7$], 231 (100), 187 (23), 91 (59) [$C_7H_7^+$], 57 (62).

3-Azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**28-HCl**): The dihydrochloride **28-HCl** (156 mg, 91%) was obtained from the 3-azabicyclo[3.1.0]hexane **76** (368 mg, 1.00 mmol) and HCl (1.2 mL, 6.00 mmol, 5.0 M solution in *i*PrOH) by use of 5% Pd/C (184 mg) according to GP 4 as a colorless solid. M.p. 200–203 °C. – IR (KBr): ν = 3441 cm^{-1}, 2882, 2534, 1588, 1452, 1217. – ^{1}H-NMR (250 MHz, CD_3OD): δ = 1.20–1.26 (m, 1 H, *c*Pr-H), 1.41 (ps t, ^2J = 8.2, ^3J = 8.2 Hz, 1 H, *c*Pr-H), 2.15–2.22 (m, 1 H, *c*Pr-H), 3.34 (d, ^2J = 11.7 Hz, 1 H, 2-H*), 3.56–3.68 (m, 3 H, 2,4-H*). – ^{13}C-NMR (62.9 MHz, CD_3OD, additional DEPT): δ = 14.3 (–, *c*Pr-C), 22.4 (+, *c*Pr-C), 40.6 (C_{quat}, *c*Pr-C), 49.6 (–, 2 C, C-2,4). – MS (CI, 70 eV): *m*/*z*



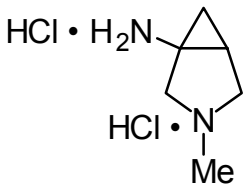
(%) = 197 (10) [$2M^+ + H$], 116 (33) [$M^+ + 18$], 99 (100) [$M^+ + H$]. – $C_5H_{10}N_2 \cdot 2$ HCl (171.07): calcd. C 35.11, H 7.07, N 16.38; found C 35.20, H 6.97, N 16.67.

N-Methyl-3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**82**-**HCl**): The dihydrochloride **82**-**HCl** (3.91 g, 96%) was obtained from the 3-azabicyclo[3.1.0]hexane **77** (6.44 g, 22.0 mmol) and HCl (22 mL, 130 mmol, 6.0 M solution in *i*PrOH) by use of 5% Pd/C (3.22 g) according to GP 4 as a colorless solid



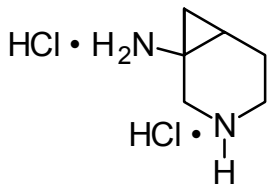
M.p. 192–195 °C. – IR (KBr): ν = 3423 cm^{-1}, 2924, 2680, 2550, 1580, 1411. – ^{1}H-NMR (300 MHz, D_2O): δ = 1.15 (dd, ^2J = 5.0, ^3J = 8.5 Hz, 1 H, *c*Pr-H), 1.55 (dt, ^2J = 2.0, ^3J = 8.9, ^3J = 8.9 Hz, 1 H, *c*Pr-H), 2.36 (m, 1 H, *c*Pr-H), 2.76 (s, 3 H, NCH_3), 3.41 (d, ^2J = 11.5 Hz, 1 H, 4-H), 3.63 (dd, ^2J = 11.5, ^3J = 4.5, Hz, 1 H, 4-H), 3.69 (d, ^2J = 11.5 Hz, 1 H, 2-H), 3.78 (d, ^2J = 11.5 Hz, 1 H, 2-H). – ^{13}C-NMR (62.9 MHz, D_2O, additional DEPT): δ = 14.3 (–, *c*Pr-C), 22.8 (+, *c*Pr-C), 34.4 (+, NCH_3), 47.7 (C_{quat}, *c*Pr-C), 48.2 (–, C-2*), 49.6 (–, C-4*). – MS (EI, 70 eV), *m*/*z* (%): 112 (4) [M^+], 97 (2), 83 (100), 68 (21). – $C_6H_{12}N_2 \cdot 2$ HCl (185.09): calcd. C 38.93, H 7.62, N 15.13; found C 38.74, H 7.51, N 14.96.

3-Methyl-3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**83**-**HCl**): The dihydrochloride **83**-**HCl** (2.60 g, 95%) was obtained from the 3-azabicyclo-[3.1.0]hexane **78** (4.30 g, 14.7 mmol) and HCl (7.6 mL, 45.6 mmol, 6.0 M solution in *i*PrOH) by use of 5% Pd/C (2.16 g) according to GP 4 (6 h reaction time) as a colorless solid. M.p. 227–230 °C. – IR (KBr): ν = 3437 cm^{-1}, 2868, 2654, 1456, 1158. – ^{1}H-NMR (300 MHz, [D_6]-DMSO): δ = 1.37 (ps t, ^2J = 8.0, ^3J = 8.0 Hz, 1 H, *c*Pr-H), 1.68 (dd, ^2J = 6.8, ^3J = 5.3 Hz, 1 H, *c*Pr-H), 2.13–2.19 (m, 1 H, *c*Pr-H), 2.76 (s, 3 H, NCH_3), 3.28 (br s, 2 H, NH_2), 3.38–3.50 (m, 2 H, 4-H), 3.55 (d,



^2J = 11.3 Hz, 1 H, 2-H), 3.73 (d, ^2J = 11.3 Hz, 1 H, 2-H). – ^{13}C-NMR (75.5 MHz, [D_6]-DMSO, additional DEPT): δ = 11.7 (–, *c*Pr-C), 19.4 (+, *c*Pr-C), 38.6 (C_{quat}, *c*Pr-C), 39.5 (+, NCH_3), 55.7 (–, 2 C, C-2,4). – MS (EI, 70 eV), *m*/*z* (%): 112 (15) [M^+], 82 (9), 69 (100), 44 (15). – $C_6H_{12}N_2$·2 HCl (185.09): calcd. C 38.93, H 7.62, N 15.13; found C 38.88, H 7.51, N 15.18.

3-Azabicyclo[4.1.0]hept-1-ylamine dihydrochloride (**29-HCl**)*:* The dihydrochloride **29-HCl** (407 mg, 99%) was obtained from the 3-azabicyclo[4.1.0]heptane **79** (850 mg, 2.22 mmol) and HCl (2.5 mL, 15.0 mmol, 6.0 M solution in *i*PrOH) by use of 5% Pd/C (425 mg) according to GP 4 (14 h reaction time) as a colorless solid. M.p. 175–177 °C. – IR (KBr): ν = 3430 cm^{-1}, 2956, 1616, 1471, 1046. – ^{1}H-NMR (300 MHz, CD_3OD): δ = 1.12–1.21 (m, 1 H, *c*Pr-H), 1.37 (dt, ^2J = 2.5, ^3J = 7.0 Hz, 1 H, *c*Pr-H), 1.70–1.78 (m, 1 H, *c*Pr-H), 1.95 (dt, ^3J = 4.5, ^3J = 4.5, ^4J = 1.5 Hz, 1 H, 5-H), 2.42 (m, 1 H, 5-H), 2.88 (dq, ^3J = 4.5, ^4J = 1.5 Hz, 1 H, 4-H), 3.18–3.24 (m, 1 H, 4-H), 3.32 (br s, 2 H, NH_2), 3.57 (dd, ^2J = 19.0, ^4J = 1.5 Hz, 1 H, 2-H), 3.72 (d, ^2J = 19.0 Hz, 1 H, 2-H). – ^{13}C-NMR (75.5 MHz, CD_3OD, additional APT): δ = 15.2 (+, *c*Pr-C), 15.9 (–, *c*Pr-C), 19.7 (–, C-5), 30.1 (C_{quat}, *c*Pr-C), 39.7 (–, C-4*), 45.2 (–, C-2*). – MS (CI, 70 eV), *m*/*z* (%): 112 (11) [M^+], 95 (19), 82 (100), 71 (43), 42 (38). – HRMS (EI) calcd for $C_6H_{12}N_2$ [M^+] 112.1000, found 112.1000. – $C_6H_{12}N_2$·2 HCl (185.09): calcd. C 38.93, H 7.62; found C 39.04, H 7.40.



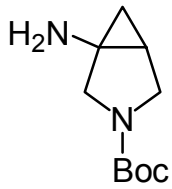
2.4. Synthesis of 3-azabicyclo[3.1.0]hex-1-ylamines by Ti-mediated intramolecular reductive cyclopropanation of nitriles

[(Allyl)(tert-butoxycarbonyl)amino]acetonitrile (**86**): Chloroacetonitrile (**85**, 1.90 g, 25.0 mmol) and allyl amine (1.90 mL, 25.0 mmol) were added dropwise at 0 °C to a suspension of K_2CO_3 (7.00 g, 51.0 mmol), NaI (7.50 g, 50.0 mmol), Et_3N (14 mL, 100 mmol) in anhydrous DMF (50 mL). After the addition was complete, the reaction mixture was stirred at ambient temperature for 20 h. Et_2O (30 mL) and Celite® (1.00 g) were added, and the solid was filtered off. Ice-cold water (30 mL) was added to the filtrate, the aqueous layer was separated, cooled to 0 °C, saturated with NaCl and extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over $MgSO_4$, and removal of the solvent gave (*N*-allylamino)acetonitrile as a brown oil pure enough to be used without further purification. Et_3N (5.0 mL, 36.0 mmol) and a solution of Boc_2O (6.00 g, 27.5 mmol) in MeOH (50 mL) were added at 0 °C to a solution of (*N*-allylamino)acetonitrile in MeOH (50 mL). The resulting mixture was stirred at 60 °C for 2 h and the solvent was removed. Water (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue gave the nitrile **86** (1.70 g, 35%) as a colorless oil. R_f (Et_2O/hexane 2 : 1) = 0.33. – IR (film): ν = 2980 cm^{-1}, 2249, 1699, 1401, 1250, 1168. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.40 [s, 9 H, $C(CH_3)_3$], 3.88–4.19 (m, 4 H, 2-H, $CH_2CH{=}CH_2$), 5.23–5.29 (m, 2 H, $CH{=}CH_2$), 6.68–6.85 (m, 1 H, $CH{=}CH_2$). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 28.1 [+, 3 C, $C(CH_3)_3$], 33.5 (–, $CH_2CH{=}CH_2$*), 48.7 (–, C-2*), 81.8 [C_{quat}, $C(CH_3)_3$], 115.9 (–, $CH{=}CH_2$), 119.2 (C_{quat},

C≡N), 132.1 (+, *C*H=CH_2), 158.5 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 196 (2) [M^+], 140 (25), 123 (12), 57 (100), 41 (46). – HRMS (EI) calcd. for $C_{10}H_{16}N_2O_2$ [M^+] 196.1212, found 196.1212.

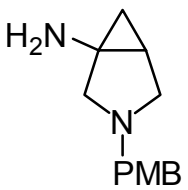
[N-Allyl-N-(4-methoxybenzyl)-amino]acetonitrile (**87**): A solution of chloroacetonitrile (**85**, 1.84 g, 50.0 mmol) and $PMBNH_2$ (13.7 g, 100 mmol) in EtOAc (15 mL) was heated for 1 d at 45 °C. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was solved in CH_2Cl_2 (100 mL), Et_3N (7.6 mL, 55.0 mmol) and allyl bromide (4.3 mL, 50.0 mmol) were added to this solution and the reaction was heated for 1 d at 45 °C. EtOAc (50 mL) and a sat. aq. $NaHCO_3$ solution (50 mL) were added, the organic phase was separated, washed with brine (50 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and purification by column chromatography gave the nitrile **87** (8.42 g, 78%) as a colorless oil. R_f (hexane/Et_2O 2 : 1) = 0.41. – IR (film): ν = 2935 cm^{-1}, 2836, 2245, 1612, 1513, 1248, 1035. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.22 (m, 2 H, C*H*$_2$CH=CH_2), 3.41 (s, 2 H, 2-H), 3.60 (s, 2 H, CH_2Ph), 3.79 (s, 3 H, OCH_3), 5.23–5.89 (m, 2 H, CH=C*H*$_2$), 5.78–5.89 (m, 1 H, C*H*=CH_2), 6.88–6.92 (m, 2 H, Ar-H), 7.24–7.30 (m, 2 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 40.5 (–, C-2), 55.2 (–, *C*H_2CH=CH_2), 57.1 (+, OCH_3), 57.5 (–, CH_2Ph), 113.9 (–, CH=*C*H_2), 114.7 (C_{quat}, C≡N), 119.4 (+, 2 C, Ar-C), 129.0 (C_{quat}, Ar-C), 130.2 (+, 2 C, Ar-C), 134.2 (+, *C*H=CH_2), 157.5 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 216 (13) [M^+], 135 (68), 121 (100), 77 (20). – $C_{13}H_{16}N_2O$ (216.10): calcd. C 72.19, H 7.46; found C 72.32, H 7.47.

3-tert-Butoxycarbonyl-3-azabicyclo[3.1.0]hex-1-ylamine (**84**): The amine **84** (162 mg, 41%) was obtained from the nitrile **86** (393 mg, 2.00 mmol), MeTi(O*i*Pr)$_3$ (721 mg, 3.00 mmol), *c*HexMgBr (4.0 mL, 4.00 mmol, 1.0 M solution in Et_2O) and LiI (535 mg, 4.00 mmol) according to GP 5 as a colorless solid.



Alternatively, the amine **84** (100 mg, 76%) was prepared from 3-azabicyclo[3.1.0]hexane **80** (250 mg, 0.660 mmol) by use of 5% Pd/C (125 mg) according to GP 4 as a colorless solid. R_f (CH_2Cl_2/MeOH 8 : 1 + 1%NH_3) = 0.33, m.p. 57–59 °C. – IR (KBr): ν = 3505 cm^{-1}, 2973, 2881, 1684, 1411, 1172. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.46 (ps t, ^2J = 4.7, ^3J = 4.7 Hz, 1 H, *c*Pr-H), 0.88–0.94 (m, 1 H, *c*Pr-H), 1.32–1.35 (m, 1 H, *c*Pr-H), 1.40 [s, 9 H, C(CH_3)$_3$], 1.62 (br s, 2 H, NH_2), 3.17–3.21 (m, 1 H, 2-H*), 3.43 (m, 2 H, 2,4-H*), 3.63–3.76 (m, 1 H, 4-H*). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT, observed as a major rotamer/minor rotamer ratio of 2 : 1): δ = 17.4 (–, *c*Pr-C), 23.4 (+, minor, *c*Pr-C), 23.9 (+, major, *c*Pr-C), 28.4 [+, 3 C, C(*C*H$_3$)$_3$], 40.8 (C_{quat}, major, *c*Pr-C), 41.2 (C_{quat}, minor, *c*Pr-C), 48.1 (–, major, C-2*), 48.5 (–, minor, C-2*), 54.0 (–, minor, C-4*), 54.4 (–, major, C-4*), 79.2 [C_{quat}, minor, *C*(CH_3)$_3$], 79.4 [C_{quat}, major, *C*(CH_3)$_3$], 154.6 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 198 (3) [M$^+$], 142 (30), 125 (14), 69 (100), 57 (48). – HRMS (EI) calcd. for $C_{10}H_{18}N_2O_2$ [M$^+$] 198.1368, found 198.1368.

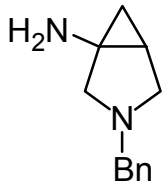
3-(4-methoxybenzyl)-3-azabicyclo[3.1.0]hex-1-ylamine (**90**): The amine **90** (181 mg, 48%) was obtained from the nitrile **87** (372 mg, 2.00 mmol), MeTi(O*i*Pr)$_3$ (530 mg, 2.20 mmol), *c*HexMgBr (4.0 mL, 4.00 mmol, 1.0 M solution in Et_2O) and LiI (535 mg, 4.00 mmol) according to GP 5 as a colorless oil.



R_f (CH_2Cl_2/MeOH 8 : 1 + 1%NH_3) = 0.25. – IR (film): ν = 2925 cm^{-1}, 2853, 1513, 1250, 1032. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.14–1.19 (m, 1 H, *c*Pr-H), 1.51 (ps t, ^2J = 4.4,

^3J = 4.4 Hz, 1 H, *c*Pr-H), 1.70–1.76 (m, 1 H, *c*Pr-H), 2.55 (dd, ^2J = 8.3, ^3J = 3.6 Hz, 1 H, 4-H*), 2.73 (d, ^2J = 8.1 Hz, 1 H, 4-H*), 2.97 (d, ^2J = 8.7 Hz, 1 H, 2-H*), 3.19 (d, ^2J = 8.2 Hz, 1 H, 2-H*), 3.62 (s, 2 H, CH_2Ph), 3.80 (s, 3 H, OCH_3), 6.84 (m, 2 H, Ar-H), 7.21–7.25 (m, 1 H, Ar-H), 7.60–7.63 (m, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 25.8 (–, *c*Pr-C), 29.7 (+, *c*Pr-C), 46.9 (C_{quat}, *c*Pr-C), 53.2 (–, C-4*), 54.3 (–, C-2*), 55.3 (–, CH_2Ph), 113.5 (+, 2 C, Ph-C), 113.9 (+, 2 C, Ph-C), 129.1 (C_{quat}, Ph-C), 129.8 (C_{quat}, Ph-C). – MS (EI, 70 eV), *m*/*z* (%): 218 (13) [M^+], 150 (8), 121 (100) 69 (17).

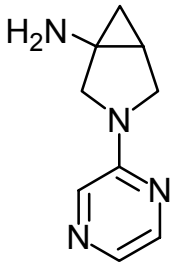
3-Benzyl-3-azabicyclo[3.1.0]hex-1-ylamine (**91**): The amine **91** (181 mg, 48%) was obtained from the nitrile **88** (372 mg, 2.00 mmol), MeTi(O*i*Pr)$_3$ (721 mg, 3.00 mmol), *c*HexMgBr (4.0 mL, 4.00 mmol, 1.0 M solution in Et_2O) and LiI (535 mg, 4.00 mmol) according to GP 5 as a colorless oil. R_f (CH_2Cl_2/MeOH 8 : 1 + 1%NH_3) = 0.25. – IR (film): ν = 3278 cm^{-1}, 3061, 2925, 2787, 1452, 1156. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.64 (m, 1 H, *c*Pr-H), 1.09 (ps t, ^2J = 4.2, ^3J = 4.2 Hz, 1 H, *c*Pr-H), 1.16–1.21 (m, 1 H, *c*Pr-H), 2.28 (br s, 2 H, NH_2), 2.32 (d, ^2J = 8.3 Hz, 1 H, 2-H), 2.49 (dd, ^2J = 8.6, ^3J = 3.6 Hz, 1 H, 4-H), 2.83 (d, ^2J = 8.6 Hz, 1 H, 4-H), 3.00 (d, ^2J = 8.3 Hz, 1 H, 2-H), 3.58 (s, 2 H, CH_2Ph), 7.20–7.28 (m, 5 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 15.4 (–, *c*Pr-C), 23.7 (+, *c*Pr-C), 40.7 (C_{quat}, *c*Pr-C), 54.7 (–, C-2*), 59.1 (–, C-4*), 61.2 (–, CH_2Ph), 126.8 (+, Ar-C), 128.1 (+, 2 C, Ar-C), 128.6 (+, 2 C, Ar-C), 139.0 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 188 (24) [M^+], 120 (32), 97 (17) [M^+ – C_7H_7], 91 (100) [$C_7H_7^+$], 69 (86). – HRMS (EI) calcd. for $C_{12}H_{16}N_2$ [M^+] 188.1313, found 188.1302.



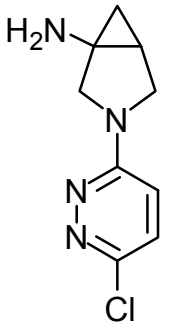
(N-Allyl-N-benzylamino)propionitrile (**93**): Allyl amine (7.5 mL, 100 mol) and 3-butenenitrile (**93**, 10 mL, 150 mmol) were heated for 2 d at 35 °C. Removal of the volatile reagents under vacuum gave (*N*-allylamino)propionitrile (10.0 g, 90%) as a colorless oil. K_2CO_3 (7.50 g, 54.0 mmol) and benzyl bromide (4.7 mL, 39.6 mmol) were added to a solution of (*N*-allylamino)propionitrile (4.00 g, 36.0 mmol) in MeCN (150 mL). The reaction mixture was stirred for 12 h at ambient temperature, a sat. aq. $NaHCO_3$ solution (50 mL) and EtOAc (50 mL) were added. The organic phase was separated, was washed with brine (50 mL) and dried over $MgSO_4$. The residue was purified by chromatography and the nitrile **93** (6.10 g, 85%) was obtained as a colorless oil. R_f (hexane/Et_2O 2 : 1) = 0.41. – IR (film): ν = 3016 cm^{-1}, 2811, 2248, 1453, 1129, 741. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.42 (t, ^3J = 7.0, ^3J = 7.0 Hz, 2 H, 2-H), 2.81 (t, ^3J = 7.0, ^3J = 7.0 Hz, 2 H, 3-H), 3.14–3.17 (m, 2 H, CH_2CH=CH_2), 3.65 (s, 2 H, CH_2Ph), 5.18–5.29 (m, 2 H, CH=CH_2), 5.88 (ddt, ^2J = 17.0, ^3J = 10.0, ^4J = 6.0 Hz, 1 H, C*H*=CH_2), 7.24–7.39 (m, 5 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 16.4 (–, C-2), 48.7 (–, C-3*), 56.8 (–, *C*H_2CH=CH_2*), 58.2 (–, CH_2Ph), 118.1 (–, CH=*C*H_2), 118.9 (C_{quat}, C≡N), 127.3 (+, Ar-C), 128.4 (+, 2 C, Ar-C), 128.7 (+, 2 C, Ar-C), 135.1 (+, *C*H=CH_2), 138.6 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 200 (6) [M^+], 160 (68), 91 (100), 41 (8). – $C_{13}H_{16}N_2$ (200.10): calcd. C 77.96, H 8.05; found C 77.69, H 8.06.

2.5. Synthesis of 3-aryl-3-azabicyclo[3.1.0]hex-1-ylamines by nucleophilic aromatic substitution

3-(Pyrazin-2-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**116**): The amine **116** (698 mg, 36%) was obtained from 3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**28-Cl**, 1.90 g, 11.0 mmol), 2-chloropyrazine (1.0 mL, 11.0 mmol) and Et_3N (9.10 mL, 66.0 mmol) according to GP 7 as a colorless oil. R_f (CH_2Cl_2/MeOH 10 : 1 + 1%NH_3) = 0.26. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.58 (ps t, ^2J = 4.7, ^2J = 4.7 Hz, 1 H, *c*Pr-H), 1.05 (ddd, ^3J = 1.5, ^3J =5.0, ^3J =8.6 Hz, 1 H, *c*Pr-H), 1.53–1.60 (m, 1 H, *c*Pr-H), 2.06 (br s, 2 H, NH_2), 3.34 (d, ^2J = 9.8 Hz, 1 H, 4-H), 3.56–3.58 (m, 2 H, 2,4-H), 3.90 (d, ^2J = 9.8 Hz, 1 H, 2-H), 7.77–7.81 (m, 2 H, Ar-H), 7.98–8.00 (m, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.8 (–, *c*Pr-C), 24.0 (+, *c*Pr-C), 41.4 (C_{quat}, *c*Pr-C), 49.2 (–, C-4), 55.1 (–, C-2), 130.6 (+, Ar-C), 132.0 (+, Ar-C), 142.0 (+, Ar-C), 153.3 (C_{quat}, Ar-C).

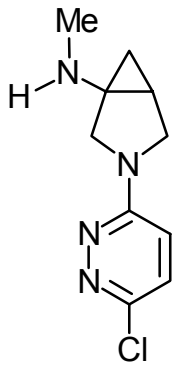


3-(6-Chloropyridazin-3-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**117**): The amine **117** (270 mg, 64%) was obtained from 3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**28-Cl**, 350 mg, 2.06 mmol), 3,6-dichloropyridazine (298 mg, 2.06 mmol) and Et_3N (1.1 mL, 8.24 mmol) according to GP 7 as a yellow solid. R_f (CH_2Cl_2/MeOH 10 : 1 + 1%NH_3) = 0.33, m.p. 138–141 °C. – IR (KBr): ν = 3365 cm^{-1}, 3051, 2853, 1594, 1471, 1165, 836. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.50 (ps t, ^2J = 4.7, ^3J = 4.7 Hz, 1 H, *c*Pr-H), 1.02–0.97 (m, 1 H, *c*Pr-H), 1.49–1.53 (m, 1 H, *c*Pr-H), 1.90 (br s, 2 H, NH_2), 3.33 (dd, ^2J = 10.0, ^3J = 1.4 Hz, 1 H, 4-H), 3.52–3.53 (m, 2 H, 2,4-H), 3.86 (d, ^2J = 10.2 Hz, 1 H, 2-H), 6.53 (d, ^3J = 9.4 Hz, 1 H, Ar-H), 7.08

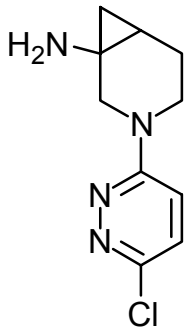


(d, ^3J = 9.4 Hz, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.6 (–, *c*Pr-C), 23.8 (+, *c*Pr-C), 41.3 (C_{quat}, *c*Pr-C), 49.6 (–, C-4), 55.3 (–, C-2), 114.6 (+, Ar-C), 128.3 (+, Ar-C), 145.6 (C_{quat}, Ar-C), 157.0 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 212/210 (9/27) [M^+], 196/194 (10/32), 175 (28) [M^+ – Cl], 169 (100), 107 (25), 69 (37). – $C_9H_{11}N_4Cl$ (210.64): calcd. C 51.31, H 5.26, N 26.60; found C 51.04, H 5.11, N 26.46.

3-(6-Chloropyridazin-3-yl)-N-methyl-3-azabicyclo[3.1.0]hex-1-ylamine (**118**): The amine **118** (110 mg, 49%) was obtained from *N*-methyl-3-azabicyclo-[3.1.0]hex-1-ylamine dihydrochloride (**82**-**HCl**, 256 mg, 1.40 mmol), 3,6-dichloropyridazine (209 mg, 1.40 mmol) and Et_3N (1.2 mL, 8.50 mmol) according to GP 7 as a colorless oil R_f (CH_2Cl_2/MeOH 15 : 1 + 1%NH_3) = 0.22. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.54 (ps t, ^2J = 4.7, ^3J = 4.7 Hz, 1 H, *c*Pr-H), 1.01 (ddd, ^3J = 1.4, ^3J =5.0, ^3J =8.6 Hz, 1 H, *c*Pr-H), 1.61–1.66 (m, 1 H, *c*Pr-H), 1.89 (br s, 1 H, NH), 2.47 (s, 3 H, NCH_3), 3.46–3.55 (m, 3 H, 2,4-H), 3.87 (d, ^2J = 10.0 Hz, 1 H, 2-H), 6.56 (d, ^3J = 9.4 Hz, 1 H, Ar-H), 7.10 (d, ^3J = 9.4 Hz, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.5 (–, *c*Pr-C), 22.6 (+, *c*Pr-C), 33.3 (+, NCH_3), 47.4 (C_{quat}, *c*Pr-C), 49.6 (–, C-4), 51.3 (–, C-2), 114.7 (+, Ar-C), 128.4 (+, Ar-C), 145.7 (C_{quat}, Ar-C), 156.3 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 226/224 (11/37) [M^+], 210/208 (9/28) [M^+ – CH_3], 189 (38) [M^+ – Cl], 142 (20), 95 (36), 82 (100).



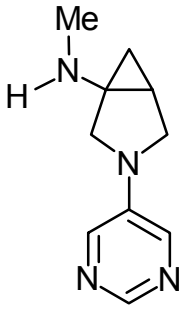
3-(6-chloropyridazin-3-yl)-3-azabicyclo[3.1.0]hept-1-ylamine (**119**): The amine **119** (90.0 mg, 57%) was obtained from 3-azabicyclo[4.1.0]hept-1-ylamine dihydrochloride (**29-HCl**, 160 mg, 700 μmol), 3,6-dichloropyridazine (149 mg, 1.00 mmol) and Et_3N (700 μL, 5.00 mmol) according to GP 7 as a colorless oil. R_f (CH_2Cl_2/MeOH 10 : 1 + 1%NH_3 = 0.23. – IR (film): ν = 3310 cm^{-1}, 2930, 1662, 1442, 1265, 735. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.45 (ps t, ^2J = 5.4, ^3J = 5.4 Hz, 1 H, *c*Pr-H), 0.69 (dd, ^3J = 5.2, ^3J =9.4 Hz, 1 H, *c*Pr-H), 1.12–1.21 (m, 1 H, *c*Pr-H), 1.75–1.94 (m, 3 H, 5-H, NH_2), 2.05–2.16 (m, 1 H, 5-H), 3.15–3.26 (m, 1 H, 4-H), 3.42–3.49 (m, 1 H, 4-H), 3.52 (d, ^2J = 12.7 Hz, 1 H, 2-H), 4.22 (d, ^2J = 12.9 Hz, 1 H, 2-H), 6.75 (d, ^3J = 9.5 Hz, 1 H, Ar-H), 7.14 (d, ^3J = 9.5 Hz, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 16.4 (–, *c*Pr-C), 18.5 (+, *c*Pr-C), 22.2 (–, C-5), 33.1 (C_{quat}, *c*Pr-C), 41.7 (–, C-4), 49.9 (–, C-2), 114.5 (+, Ar-C), 128.6 (+, Ar-C), 145.7 (C_{quat}, Ar-C), 158.3 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 226/224 (20/58) [M^+], 189 (100) [M^+ – Cl], 142 (33), 82 (86). – HRMS (EI) calcd. for $C_{10}H_{13}N_4Cl$ [M^+] 224.0829, found 224.0829.



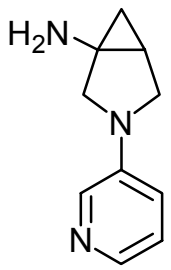
2.6. Synthesis of 3-aryl-3-azabicyclo[3.1.0]hex-1-ylamines by Pd-catalyzed cross-coupling

N-Methyl-3-(pyrid-3-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**120**): The amine **120** (100 mg, 53%) was obtained from *N*-methyl-3-azabicyclo-[3.1.0]hex-1-ylamine dihydrochloride (**82**-**HCl**, 201 mg, 1.10 mmol), 5-bromopyridine (0.10 mL, 1.00 mmol), $Pd_2(dba)_3$ (46.0 mg, 50.0 μmol, 5 mol%), (±)-BINAP (62.3 mg, 100 μmol, 10 mol%), Et_3N (0.30 mL, 2.20 mmol) and NaO*t*Bu (288 mg, 3.00 mmol) in toluene (5.0 mL) and DMF (5.0 mL) according to GP 8 as a yellow oil. R_f (CH_2Cl_2/MeOH 15 : 1 + 1%NH_3) = 0.21. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.62 (ps t, ^2J = 4.6, ^3J = 4.6 Hz, 1 H, *c*Pr-H), 0.97 (ddd, ^2J = 3.8, ^3J = 8.6, ^4J = 1.1, Hz, 1 H, *c*Pr-H), 1.57–1.64 (m, 1 H, *c*Pr-H), 1.96 (br s, 1 H, NH), 2.48 (s, 3 H, NCH_3), 3.22 (d, ^3J = 8.7 Hz, 1 H, 4-H), 3.25–3.40 (m, 2 H, 2,4-H), 3.65 (d, ^2J = 8.6 Hz, 1 H, 2-H), 6.72–6.77 (m, 1 H, Ar-H), 7.02–7.08 (m, 1 H, Ar-H), 7.90–7.92 (m, 2 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.3 (–, *c*Pr-C), 22.7 (+, *c*Pr-C), 33.4 (+, NCH_3), 47.5 (C_{quat}, *c*Pr-C), 50.0 (–, C-4), 51.8 (–, C-2), 118.0 (+, Ar-C), 123.4 (+, Ar-C), 134.3 (+, Ar-C), 137.6 (+, Ar-C), 143.9 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 189 (28) [M^+], 174 (4) [$M^+ - CH_3$], 82 (100), 49 (32). – HRMS (EI) calcd. for $C_{11}H_{15}N_3$ [M^+] 189.1266, found 189.1266.

N-Methyl-3-(pyrimidin-5-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**121**): The amine **121** (115 mg, 61%) was obtained from *N*-methyl-3-azabicyclo-[3.1.0]hex-1-ylamine dihydrochloride (**82**-**HCl**, 200 mg, 1.10 mmol), 5-bromopyrimidine (159 mg, 1.00 mmol), $Pd_2(dba)_3$ (46.0 mg, 50.0 µmol, 5 mol%), (±)-BINAP (62.3 mg, 100 µmol, 10 mol%), Et_3N (0.30 mL, 2.20 mmol) and NaO*t*Bu (288 mg, 3.00 mmol) according to GP 8 as a yellow oil. R_f (CH_2Cl_2/MeOH 8 : 1 + 1%NH_3) = 0.21. – IR (film): ν = 3304 cm^{-1}, 3045, 2851, 1573, 1200, 723. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.54 (ps t, ^2J = 4.7, ^3J = 4.7 Hz, 1 H, *c*Pr-H), 0.95 (ddd, ^3J = 5.0, ^3J = 8.7, ^4J = 1.3 Hz, 1 H, *c*Pr-H), 1.55–1.62 (m, 1 H, *c*Pr-H), 2.22 (br s, 1 H, NH), 2.42 (s, 3 H, NCH_3), 3.22 (dd, ^2J = 8.7, ^4J = 1.1 Hz, 1 H, 4-H*), 3.31–3.33 (m, 2 H, 2,4-H), 3.58 (d, ^2J = 8.7 Hz, 1 H, 2-H*), 7.91 (s, 2 H, Ar-H), 8.45 (s, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.5 (–, *c*Pr-C), 22.6 (+, *c*Pr-C), 33.4 (+, NCH_3), 47.6 (C_{quat}, *c*Pr-C), 49.7 (–, C-4), 51.4 (–, C-2), 139.6 (+, 2 C, Ar-C), 141.4 (C_{quat}, Ar-C), 147.4 (+, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 190 (40) [M^+], 175 (5) [$M^+ - CH_3$], 108 (7), 82 (100). – $C_{10}H_{14}N_4$ (190.14): calcd. C 63.13, H 7.42, N 29.45; found C 62.90, H 7.18, N 29.20.

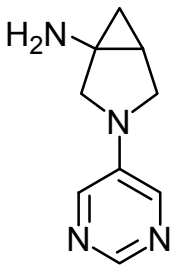


3-(Pyrid-3-yl)-azabicyclo[3.1.0]hex-1-ylamine (**122**): The amine **122** (222 mg, 63%) was obtained from 3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**28**-**HCl**, 350 mg, 2.06 mmol), 5-bromopyridine (286 mg, 1.87 mmol), $Pd_2(dba)_3$ (85.6 mg, 93.0 µmol, 5 mol%), (±)-BINAP (116.4 mg, 190 µmol, 10 mol%), Et_3N (0.60 mL, 4.12 mmol) and NaO*t*Bu (630 mg, 6.55 mmol) according to GP 8 as a yellow oil. R_f (CH_2Cl_2/MeOH 10 : 1 + 1%NH_3) = 0.22. – ^{1}H-NMR (250 MHz,



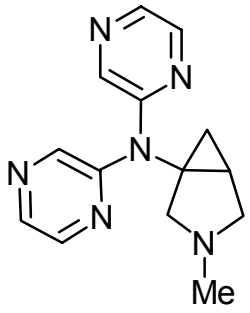
$CDCl_3$): δ = 0.64 (ps t, ^2J = 4.6, ^3J = 4.6 Hz, 1 H, *c*Pr-H), 1.00 (ddd, ^3J = 4.9, ^3J = 8.6, ^4J = 1.2 Hz, 1 H, *c*Pr-H), 1.51–1.56 (m, 1 H, *c*Pr-H), 2.18 (br s, 2 H, NH_2), 3.14 (d, ^3J = 8.6 Hz, 1 H, 4-H*), 3.34–3.44 (m, 2 H, 2,4-H), 3.69 (d, ^2J = 8.6 Hz, 1 H, 2-H*), 6.74–6.77 (m, 1 H, Ar-H), 7.04–7.09 (m, 1 H, Ar-H), 7.91–7.94 (m, 2 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.6 (–, *c*Pr-C), 24.1 (+, *c*Pr-C), 41.5 (C_{quat}, *c*Pr-C), 50.2 (–, C-4), 56.2 (–, C-2), 118.2 (+, Ar-C), 123.5 (+, Ar-C), 134.4 (+, Ar-C), 137.7 (+, Ar-C), 143.9 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 175 (40) [M^+], 107 (100) [M^+ – CH_3], 86 (42), 69 (52).

3-(Pyrimidin-5-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**123**): The amine **123** (222 mg, 63%) was obtained from 3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**28**·**HCl**, 350 mg, 2.06 mmol), 5-bromopyrimidine (286 mg, 1.87 mmol), $Pd_2(dba)_3$ (85.6 mg, 93.0 μmol, 5 mol%), (±)-BINAP (116.4 mg, 190 μmol, 10 mol%), Et_3N (0.60 mL, 4.12 mmol) and NaO*t*Bu (630 mg, 6.55 mmol)

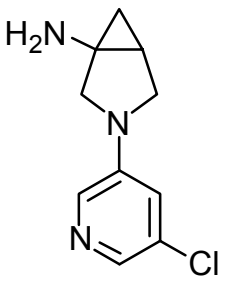


according to GP 8 as a yellow oil. R_f (CH_2Cl_2/MeOH 10 : 1 + 1%NH_3) = 0.22. – IR (film): ν = 3274 cm^{-1}, 3042, 2844, 1573, 1445, 1197, 723. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.65 (ps t, ^2J = 4.7, ^3J = 4.7 Hz, 1 H, *c*Pr-H), 1.06 (ddd, ^2J = 5.0, ^3J = 8.6, ^4J = 1.1 Hz, 1 H, *c*Pr-H), 1.56–1.63 (m, 1 H, *c*Pr-H), 1.96 (br s, 2 H, NH_2), 3.20 (dd, ^2J = 8.7, ^4J = 1.1 Hz, 1 H, 4-H), 3.41–3.43 (m, 2 H, 2,4-H), 3.71 (d, ^2J = 8.7 Hz, 1 H, 2-H), 8.01 (s, 2 H, Ar-H), 8.57 (s, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.8 (–, *c*Pr-C), 24.1 (+, *c*Pr-C), 41.6 (C_{quat}, *c*Pr-C), 49.9 (–, C-4), 55.8 (–, C-2), 139.8 (+, 2 C, Ar-C), 141.4 (C_{quat}, Ar-C), 147.5 (+, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 176 (23) [M^+], 135 (14), 108 (13), 95 (13), 69 (100). – $C_9H_{12}N_4$ (176.22): calcd. C 61.34, H 6.86, N 31.79; found C 61.42, H 6.68, N 31.99.

3-Methyl-N,N-di(pyrazin-2-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**131**): The amine **131** (166 mg, 62%) was obtained from 3-methyl-3-azabicyclo-[3.1.0]hex-1-ylamine dihydrochloride (**83**-**HCl**, 204 mg, 1.10 mmol), 2-chloropyrazine (0.20 mL, 2.00 mmol), $Pd_2(dba)_3$ (46.0 mg, 50.0 μmol, 5 mol%), (±)-BINAP (62.3 mg, 100 μmol, 10 mol%), Et_3N (0.30 mL, 2.20 mmol) and NaO*t*Bu (336 mg, 3.50 mmol) according to GP 8 as a yellow solid. R_f (CH_2Cl_2/MeOH 10 : 1 + 1%NH_3) = 0.38, m. p. 209–211 °C. – IR (KBr): ν = 3066 cm^{-1}, 2876, 2766, 1576, 1416, 1162, 1002, 833. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.86 (dd, ^2J = 4.9, ^3J = 8.7 Hz, 1 H, *c*Pr-H), 1.61 (ps t, ^2J = 5.0, ^3J = 5.0 Hz, 1 H, *c*Pr-H), 1.78–1.84 (m, 1 H, *c*Pr-H), 2.38 (s, 3 H, NCH_3), 2.78–2.83 (m, 2 H, 2,4-H*), 3.01 (d, ^2J = 8.9 Hz, 1 H, 2-H*), 3.38 (d, ^2J = 8.5 Hz, 1 H, 4-H*), 8.19–8.25 (m, 4 H, Ar-H), 8.71 (s, 2 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 17.8 (–, *c*Pr-C), 26.9 (+, *c*Pr-C), 41.3 (+, NCH_3), 45.3 (C_{quat}, *c*Pr-C), 56.1 (–, C-4*), 57.3 (–, C-2*), 138.1 (+, 2 C, Ar-C), 138.2 (+, 2 C, Ar-C), 141.9 (+, 2 C, Ar-C), 158.3 (C_{quat}, 2 C, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 268 (60) [M^+], 224 (36), 198 (61), 175 (40) [$M^+ - CH_3 - C_4H_3N_2$], 94 (100), 79 (36). – HRMS (EI) calcd. for $C_{14}H_{16}N_6$ [M^+] 268.1436, found 268.1436.

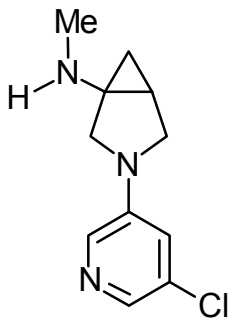


3-(5-Chloropyrid-3-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**132**): The amine **132** (172.0 mg, 41%) was obtained from 3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**28**-**HCl**, 340 mg, 2.20 mmol), 3,5-dichloropyridine (296 mg, 2.00 mmol), $Pd(OAc)_2$, (22.4 mg, 100 μmol, 5 mol%), 2-(di-*tert*-butylphosphino)biphenyl (60.0 mg, 200 μmol, 10 mol%), Et_3N (0.80 mL, 6.00 mmol) and NaO*t*Bu (270 mg, 2.80 mmol) according to GP 9 as a colorless oil. R_f (CH_2Cl_2/MeOH 15 : 1 + 1%NH_3) = 0.36. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.56 (ps t,



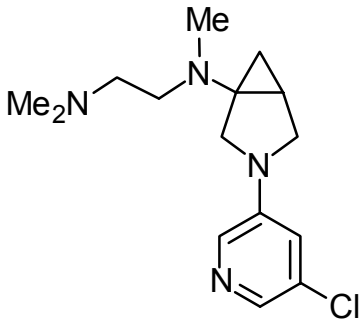
^2J = 4.6, ^3J = 4.6 Hz, 1 H, *c*Pr-H), 0.98–1.05 (m, 1 H, *c*Pr-H), 1.41–1.51 (m, 1 H, *c*Pr-H), 2.01 (br s, 2 H, NH_2), 3.20 (d, ^2J = 8.6 Hz, 1 H, 4-H*), 3.20–3.38 (m, 2 H, 2,4-H), 3.59 (d, ^2J = 8.6 Hz, 1 H, 2-H*), 6.70–6.72 (m, 1 H, Ar-H), 7.70–7.73 (m, 1 H, Ar-H), 7.79–7.83 (m, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.8 (–, *c*Pr-C), 24.1 (+, *c*Pr-C), 41.5 (C_{quat}, *c*Pr-C), 50.3 (–, C-4*), 56.2 (–, C-2*), 117.7 (+, Ar-C), 132.0 (C_{quat}, Ar-C), 132.3 (+, Ar-C), 135.9 (+, Ar-C), 144.5 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 211/209 (12/38) [M^+], 168 (10) [M^+ – Cl], 141 (28), 94 (46), 69 (100). – HRMS (EI) calcd. for $C_{10}H_{12}N_3Cl$ [M^+] 209.0720, found 209.0720.

3-(5-Chloropyrid-3-yl)-N-methyl-3-azabicyclo[3.1.0]hex-1-ylamine (**133**): The amine **133** (75.0 mg, 34%) was obtained from *N*-methyl-3-azabicyclo-[3.1.0]hex-1-ylamine dihydrochloride (**82**-**HCl**, 204 mg, 1.10 mmol), 3,5-dichloropyridine (148 mg, 1.00 mmol), $Pd(OAc)_2$, (11.2 mg, 50.0 µmol, 5 mol%), 2-(di-*tert*-butylphosphino)biphenyl (30.0 mg, 100 µmol, 10 mol%), Et_3N (0.40 mL, 3.00 mmol) and NaO*t*Bu (135 mg, 1.40 mmol) according to GP 9 as a colorless oil. R_f (CH_2Cl_2/MeOH 10 : 1 + 1%NH_3) = 0.43. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.59 (ps t, ^2J = 4.6, ^3J = 4.6 Hz, 1 H, *c*Pr-H), 1.00 (ddd, ^2J = 4.9, ^3J = 8.6, ^4J = 1.1 Hz, 1 H, *c*Pr-H), 1.59–1.65 (m, 1 H, *c*Pr-H), 1.88 (br s, 1 H, NH), 2.49 (s, 3 H, NCH_3), 3.26 (d, ^2J = 8.7 Hz, 1 H, 4-H*), 3.27–3.29 (m, 2 H, 2,4-H), 3.61 (d, ^2J = 8.7 Hz, 1 H, 2-H*), 6.71–6.73 (m, 1 H, Ar-H), 7.77–7.85 (m, 2 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.6 (–, *c*Pr-C), 22.7 (+, *c*Pr-C), 33.5 (+, NCH_3), 47.6 (C_{quat}, *c*Pr-C), 50.2 (–, C-4*), 52.0 (–, C-2*), 117.6 (+, Ar-C), 132.0 (C_{quat}, Ar-C), 132.3 (+, Ar-C), 135.9 (+, Ar-C), 144.5 (C_{quat}, Ar-C). – MS (EI, 70 eV),



m/*z* (%): 225/223 (13/33) [M^+], 141 (9), 82 (100). – HRMS (EI) calcd. for $C_{11}H_{14}N_3Cl$ [M^+] 223.0876, found 223.0876.

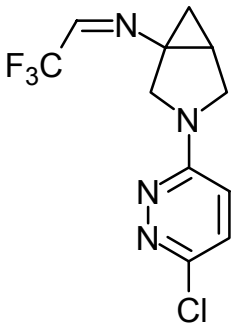
N-(2'-Dimethylaminoethyl)-N-methyl-3-(5-chloropyrid-3-yl)-3-azabicyclo[3.1.0]hex-1-yl-amine (**135**): A solution of the amine **133** (72.0 mg, 320 μmol), 1-chloro-2-dimethylaminoethane hydrochloride (54.0 mg, 370 μmol) and K_2CO_3 (89.0 mg, 640 μmol) in EtOH (4.0 mL) was heated at 80°C for 3 h. The mixture was filtered through Celite® and the solvent was removed under reduced pressure. Column chromatography of the residue gave compound **135** (41.0 mg, 44%) as a colorless oil. R_f (CH_2Cl_2/MeOH 10 : 1 + 1%NH_3) = 0.34. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.64 (ps t, ^2J = 4.5, ^3J = 4.5 Hz, 1 H, *c*Pr-H), 1.08–1.14 (m, 1 H, *c*Pr-H), 1.70–1.76 (m, 1 H, *c*Pr-H), 2.24 (s, 6 H, $N(CH_3)_2$), 2.28–2.44 (m, 2 H, 1'-H*), 2.45 (s, 3 H, NCH_3), 2.65–2.86 (m, 2 H, 2'-H*), 3.32–3.46 (m, 4 H, 2,4-H), 6.75–6.77 (m, 1 H, Ar-H), 7.80–7.88 (m, 2 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 20.7 (–, *c*Pr-C), 24.0 (+, *c*Pr-C), 40.0 (+, NCH_3), 45.6 (–, C-1'*), 45.8 (+, 2 C, $N(CH_3)_2$), 49.9 (–, C-2'*), 52.6 (C_{quat}, *c*Pr-C), 53.3 (–, C-4), 57.7 (–, C-2), 117.6 (+, Ar-C), 132.0 (C_{quat}, Ar-C), 132.4 (+, Ar-C), 136.0 (+, Ar-C), 144.7 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 296/294 (<1/2) [M^+], 238/236 (<1/6), 191 (3), 154 (2), 58 (100).



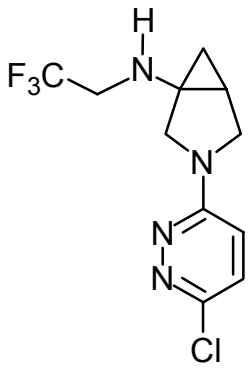
N-Methyl-3-phenyl-3-azabicyclo[3.1.0]hex-1-ylamine (**138**): A mixture of *N*-methyl-3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**28-HCl**, 200 mg, 1.10 mmol), iodobenzene (0.10 mL, 1.00 mmol), Et_3N (0.3 mL, 2.20 mmol), CuI (10.4 mg, 55.0 μmol, 5 mol%), ethyleneglycol (0.10 mL, 2.00 mmol) and K_3PO_4 (424 mg, 2.00 mmol) in 2-propanol (2.0 mL) was heated at 80 °C for 20 h. The reaction mixture was filtered and concentrated under reduced pressure. Column chromatography on silica gel of the residue gave the amine **138** (100 mg, 53%) as a colorless oil. R_f (CH_2Cl_2/MeOH 10 : 1 + 1%NH_3) = 0.43. – IR (film): ν = 3319 cm^{-1}, 3058, 2949, 1670, 1599, 1364, 752. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.69 (ps t, ^2J = 4.5, ^3J = 4.5 Hz, 1 H, *c*Pr-H), 0.97 (dd, ^2J = 4.6, ^3J = 8.5 Hz, 1 H, *c*Pr-H), 1.60–1.66 (m, 1 H, *c*Pr-H), 1.82 (br s, 1 H, NH), 2.53 (s, 3 H, NCH_3), 3.26 (d, ^2J = 8.5 Hz, 1 H, 4-H), 3.33 (dd, ^2J = 8.5, ^3J = 8.9 Hz, 1 H, 4-H), 3.43 (d, ^3J = 8.9 Hz, 1 H, 2-H), 3.70 (d, ^3J = 8.6 Hz, 1 H, 2-H), 6.54–6.57 (m, 2 H, Ar-H), 6.67–6.72 (m, 2 H, Ar-H), 7.19–7.25 (m, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.3 (–, *c*Pr-C), 20.9 (+, *c*Pr-C), 33.8 (+, NCH_3), 50.3 (C_{quat}, *c*Pr-C), 60.9 (–, C-4), 66.1 (–, C-2), 111.8 (+, 2 C, Ph-C), 116.3 (+, Ph-C), 129.1 (+, 2 C, Ph-C), 153.1 (C_{quat}, Ph-C). – MS (EI, 70 eV), *m*/*z* (%): 188 (55) [M^+], 173 (5) [$M^+ - CH_3$], 82 (100), 77 (21). – HRMS (EI) calcd. for $C_{12}H_{16}N_2$ [M^+] 188.1313, found 188.1313.

2.7. Synthesis of trifluoroethyl derivatives

[3-(6-Chloropyridazin-3-yl)-3-azabicyclo[3.1.0]hex-1-yl]-2,2,2-trifluoro-1-ethanimine (**139**): The imine **139** (717 mg, 95%) was obtained from the amine **117** (547 mg, 2.60 mmol), trifluoroacetaldehyde methyl hemiacetale (1.70 g, 13.0 mmol) and molecular sieves (3 Å) according to GP 12 as a colorless oil. R_f (CH_2Cl_2/MeOH 15 : 1) = 0.49. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.26 (ps t, ^2J = 4.6, ^3J = 4.6 Hz, 1 H, *c*Pr-H), 1.69–1.78 (m, 1 H, *c*Pr-H), 2.28–2.37 (m, 1 H, *c*Pr-H), 3.56–3.64 (m, 1 H, 4-H), 3.68–3.76 (m, 1 H, 4-H), 3.82 (d, ^2J = 11.0 Hz, 1 H, 2-H), 4.07 (d, ^2J = 11.1 Hz, 1 H, 2-H), 6.79 (d, ^3J = 11.2 Hz, 1 H, Ar-H), 7.34 (d, ^3J = 11.2 Hz, 1 H, Ar-H), 7.62 (q, $^3J_{H,F}$ = 3.7 Hz, N=C*H*CF_3). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 21.5 (–, *c*Pr-C), 27.7 (+, *c*Pr-C), 48.4 (–, C-4), 48.6 (–, C-2), 52.6 (C_{quat}, *c*Pr-C), 114.9 (+, Ar-C), 119.0 (C_{quat}, q, $^1J_{C,F}$ = 274 Hz, N=CH*C*F_3), 128.6 (+, Ar-C), 145.9 (+, q, $^2J_{C,F}$ = 38.7 Hz, N=*C*HCF_3), 146.4 (C_{quat}, Ar-C), 157.3 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 292/290 (25/74) [M^+], 251/249 (34/100), 196/194 (25/80), 142 (21), 40 (32).

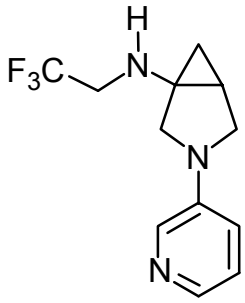


N-(2',2',2'-Trifluoroethyl)-3-(6-chloropyridazin-3-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**140-Cl**): The amine **140-Cl** (570 mg, 79%) was obtained from the imine **139** (717 mg, 2.47 mmol) and $LiAlH_4$ (3.7 mL of a 0.70 M solution in THF, 2.60 mmol) according to GP 12 as a colorless oil. R_f (CH_2Cl_2/MeOH 40 : 1 + 1%NH_3) = 0.20. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.26 (ps t, ^2J = 4.6, ^3J = 4.6 Hz, 1 H, *c*Pr-H), 1.69–1.78 (m, 1 H, *c*Pr-H), 2.28–2.37 (m, 1 H, *c*Pr-H), 3.29 (q, $^3J_{H,F}$ = 9.4 Hz, 2 H, NCH_2CF_3), 3.43 (d,



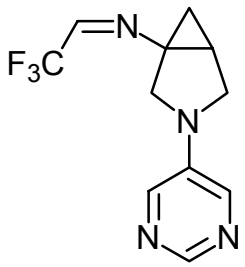
^2J = 10.0 Hz, 1 H, 4-H), 3.58 (s, 2 H, 2,4-H), 3.94 (d, ^2J = 10.0 Hz, 1 H, 2-H), 6.58 (d, ^3J = 9.4 Hz, 1 H, Ar-H), 7.16 (d, ^3J = 9.4 Hz, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.8 (–, *c*Pr-C), 24.3 (+, *c*Pr-C), 46.3 (–, C-4), 48.8 (–, q, $^2J_{C,F}$ = 39.1 Hz, N*C*H$_2$CF$_3$), 49.4 (–, C-2), 52.4 (C$_{quat}$, *c*Pr-C), 114.7 (+, Ar-C), 120.4 (C$_{quat}$, q, $^1J_{C,F}$ = 281.1 Hz, NCH$_2$*C*F$_3$), 128.6 (+, Ar-C), 146.1 (C$_{quat}$, Ar-C), 157.2 (C$_{quat}$, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 294/292 (15/48) [M$^+$], 253/251 (20/63), 222 (25), 142 (48), 41 (100).

N-(2',2',2'-trifluoroethyl)-3-(pyrid-3-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**144**): First the imine **141** (150 mg, 78%) was obtained from the amine **122** (130 mg, 740 µmol), trifluoroacetaldehyde methyl hemiacetale (483 mg, 3.70 mmol) and molecular sieves (3 Å) as a colorless oil which was used without further purification. The amine **144** (72.0 mg, 58%) was obtained from the imine **141** (150 mg, 500 µmol) and $LiAlH_4$ (23.0 mg, 500 µmol) according to GP 12 as a colorless oil. R_f (CH_2Cl_2/MeOH 40 : 1 + 1%NH_3) = 0.32. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.73 (ps t, ^2J = 4.6, ^3J = 4.6 Hz, 1 H, *c*Pr-H), 1.08 (ddd, ^2J = 4.8, ^3J = 8.7, ^4J = 1.3 Hz, 1 H, *c*Pr-H), 1.69–1.75 (m, 1 H, *c*Pr-H), 3.21–3.45 (m, 6 H, 2,4-H, NCH_2CF_3, NH), 3.71 (d, ^2J = 8.7 Hz, 1 H, 2-H), 6.78–6.83 (m, 1 H, Ar-H), 7.09–7.14 (m, 1 H, Ar-H), 7.94–7.98 (m, 2 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.6 (–, *c*Pr-C), 24.4 (+, *c*Pr-C), 46.3 (C$_{quat}$, *c*Pr-C), 49.1 (–, q, $^2J_{C,F}$ = 28.2 Hz, N*C*H$_2$CF$_3$), 49.8 (–, C-4), 53.0 (–, C-2), 118.5 (+, Ar-C), 123.7 (+, Ar-C), 124.2 (C$_{quat}$, q, $^1J_{C,F}$ = 278.3 Hz, NCH$_2$*C*F$_3$), 134.0 (+, Ar-C), 137.6 (+,



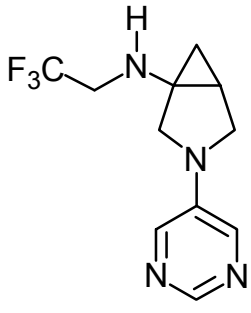
Ar-C), 142.3 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 257 (52) [M^+], 216 (8), 176 (18), 150 (31), 107 (100).

[3-(pyrimidin-5-yl)-3-azabicyclo[3.1.0]hex-1-yl]-2,2,2-trifluoro-1-ethanimine (**142**): The imine **142** (184 mg, 72%) was obtained from the amine **123** (173 mg, 1.00 mmol), trifluoroacetaldehyde methyl hemiacetale (640 mg, 5.00 mmol) and molecular sieves (3 Å, 1.50 g) according to GP 12 as a colorless oil. R_f (CH_2Cl_2/MeOH 15 : 1 + 1%NH_3) = 0.59. –



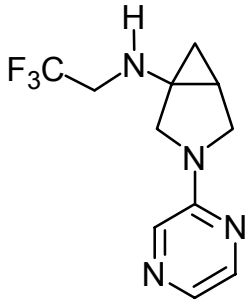
^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.30 (ps t, ^2J = 5.3, ^3J = 5.3 Hz, 1 H, *c*Pr-H), 1.66–1.71 (m, 1 H, *c*Pr-H), 2.24–2.32 (m, 1 H, *c*Pr-H), 3.47 (dd, ^2J = 9.1, ^3J = 4.2 Hz, 1 H, 4-H), 3.54–3.63 (m, 2 H, 2,4-H), 3.79 (d, ^2J = 8.6 Hz, 1 H, 2-H), 7.63 (q, $^3J_{H,F}$ = 3.3 Hz, N=C*H*CF_3), 8.09 (s, 2 H, Ar-H), 8.61 (s, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 21.5 (–, *c*Pr-C), 27.9 (+, *c*Pr-C), 43.4 (–, C-4), 48.9 (–, C-2), 55.0 (C_{quat}, *c*Pr-C), 119.8 (C_{quat}, q, $^1J_{C,F}$ = 278 Hz, N=CH*C*F_3), 140.1 (+, 2 C, Ar-C), 141.5 (C_{quat}, Ar-C), 146.0 (+, q, $^2J_{C,F}$ = 38.7 Hz, N=*C*HCF_3), 147.9 (+, Ar-C).

N-(2',2',2'-trifluoroethyl)-3-(pyrimidin-5-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**145**): The amine **145** (102 mg, 55%) was obtained from the imine **142** (185 mg, 720 µmol) and $LiAlH_4$ (28.0 mg, 720 µmol) according to GP 12 as a colorless oil. R_f (CH_2Cl_2/MeOH 40 : 1 + 1%NH_3) = 0.30. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.67 (ps t, ^2J = 4.7, ^3J = 4.7 Hz, 1 H, *c*Pr-H), 1.06–1.10 (m, 1 H, *c*Pr-H), 1.68–1.72 (m, 1 H, *c*Pr-H), 2.03 (s, 1 H, NH), 3.21–3.38 (m, 5 H, 2,4-H, NCH_2CF_3), 3.67 (d, ^2J = 8.8 Hz, 1 H, 2-H), 7.97 (s, 2 H,

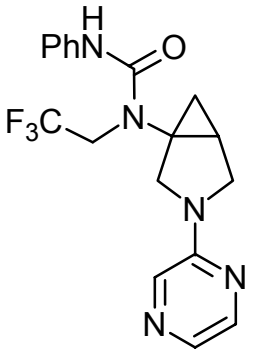


Ar-H), 8.54 (s, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.6 (–, *c*Pr-C), 24.3 (+, *c*Pr-C), 46.3 (C_{quat}, *c*Pr-C), 48.7 (–, q, $^2J_{C,F}$ = 32.1 Hz, N*C*H$_2$CF$_3$), 49.5 (–, C-4), 52.5 (–, C-2), 124.2 (C_{quat}, q, $^1J_{C,F}$ = 278 Hz, NCH$_2$*C*F$_3$), 139.8 (+, 2 C, Ar-C), 141.3 (C_{quat}, Ar-C), 147.6 (+, Ar-C). – MS (EI, 70 eV), *m/z* (%): 258 (54) [M$^+$], 217 (14), 151 (74), 95 (27), 84 (100). – HRMS (EI) calcd. for $C_{11}H_{13}N_4F_3$ [M$^+$] 258.1092, found 258.1092.

N-(2',2',2'-trifluoroethyl)-3-(pyrazin-2-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**146**): First the imine **143** (152 mg, 72%) was obtained from the amine **116** (144 mg, 820 μmol), trifluoroacetaldehyde methyl hemiacetale (533 mg, 4.10 mmol) and molecular sieves (3 Å) as a colorless oil which was used without further purification. The amine **146** (110 mg, 73%) was obtained from the imine **143** (148 mg, 500 μmol) and $LiAlH_4$ (0.90 mL, 610 μmol, 0.70 M solution in THF) according to GP 12 as a colorless oil. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.63 (ps t, ^2J = 4.5, ^3J = 4.5 Hz, 1 H, *c*Pr-H), 1.08–1.16 (m, 1 H, *c*Pr-H), 1.63–1.77 (m, 1 H, *c*Pr-H), 3.24–3.60 (m, 6 H, 2,4-H, NCH$_2$CF$_3$, NH), 3.91 (d, ^2J = 8.5 Hz, 1 H, 2-H), 7.68–7.82 (m, 2 H, Ar-H), 8.01 (s, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.7 (–, *c*Pr-C), 24.3 (+, *c*Pr-C), 46.5 (C_{quat}, *c*Pr-C), 48.8 (–, q, $^2J_{C,F}$ = 28.2 Hz, N*C*H$_2$CF$_3$), 49.7 (–, C-4), 55.0 (–, C-2), 128.2 (C_{quat}, q, $^1J_{C,F}$ = 278 Hz, NCH$_2$*C*F$_3$), 130.2 (+, Ar-C), 132.5 (+, Ar-C), 145.7 (+, Ar-C), 153.5 (C_{quat}, Ar-C).

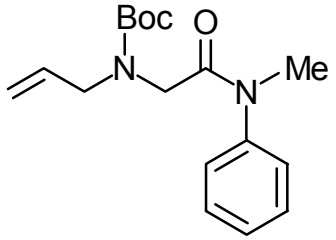


1-[3-(pyrazin-2-yl)-3-azabicyclo[3.1.0]hex-1-yl]-3-phenyl-1-(2',2',2'-trifluoroethyl)-urea (**149**): Phenylisocyanate (50 µL, 450 µmol) was added to a solution of the amine **147** (110 mg, 430 µmol) in toluene (5.0 mL) and the mixture was stirred at 50 °C for 1 d. The solvent was removed and the residue was purified by column chromatography on silica gel. Compound **149** (240 mg, 98%) was obtained as a colorless solid. R_f (CH_2Cl_2/MeOH 50 : 1 + 1%NH_3) = 0.37, m. p. 228–229 °C. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.18–1.24 (m, 1 H, *c*Pr-H), 1.41–1.54 (m, 1 H, *c*Pr-H), 2.24–2.38 (m, 1 H, *c*Pr-H), 3.50–3.82 (m, 5 H, 2',4*-H), 4.10–4.21 (m, 2 H, 2-H*), 7.08–7.29 (m, 5 H, Ar-H), 7.81–7.90 (m, 2 H, Ar-H), 8.04 (s, 1 H, Ar-H). – MS (EI): *m*/*z* (%) = 377 (44) [M^+], 212 (30), 151 (52), 93 (86), 87 (100). The NMR spectra for the urea derivatives **147** and **148** are the same as the correspondent starting amine, except for the aromatic signals.



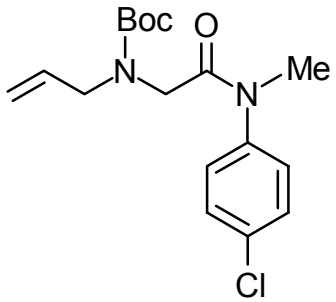
2.8. *Synthesis of N-methyl-N-aryl-3-azabicyclo[3.1.0]hex-1-ylamines by Ti-mediated intramolecular reductive cyclopropanation*

2-(Allyl-tert-butoxycarbonylamino)-N-methyl-N-phenylacetamide (**154**): The amide **154** (602 mg, 33%), was obtained from K_2CO_3 (1.66 g, 12.0 mmol), NaI (1.80 g, 12.0 mmol), Et_3N (3.3 mL, 24.0 mmol), allyl amine (0.30 mL, 6.00 mmol), *N*-methyl-*N*-phenyl(bromoacetyl)amide (**152**, 1.36 g, 6.00 mmol) and Boc_2O (1.57 g, 7.20 mmol) according to GP 14 as a colorless oil. R_f (EtOAc/cyclohexane 2 : 1) = 0.42. – IR (film): ν = 2975 cm^{-1}, 2931, 1700, 1596, 1392, 1246, 1170, 702. – ^{1}H-NMR (250 MHz, $CDCl_3$, observed as a major rotamer/minor rotamer ratio of 2 : 1): δ = 1.43 [s, 9 H, $OC(CH_3)_3$], 3.25



(s, 3 H, major, NCH_3), 3.26 (s, 3 H, minor, NCH_3), 3.57 (s, 2 H, minor, 2-H), 3.69 (s, 2 H, major, 2-H), 3.87 (d, ^3J = 6.8 Hz, 2 H, major, $CH_2CH{=}CH_2$), 3.92 (d, ^3J = 6.6 Hz, 2 H, minor, $CH_2CH{=}CH_2$), 5.05–5.18 (m, 2 H, $CH{=}CH_2$), 5.61–5.76 (m, 1 H, $CH{=}CH_2$), 7.14–7.43 (m, 5 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT, observed as a major rotamer/minor rotamer ratio of 2 : 1): δ = 28.3 [+, 3 C, $OC(CH_3)_3$], 37.5 (+, NCH_3), 48.0 (–, major, $CH_2CH{=}CH_2$), 48.1 (–, minor, $CH_2CH{=}CH_2$), 50.3 (–, minor, C-2), 50.7 (–, major, C-2), 79.9 [C_{quat}, $OC(CH_3)_3$], 116.3 (–, major, $CH{=}CH_2$), 117.0 (–, minor, $CH{=}CH_2$), 127.3 (+, 2 C, Ar-C), 128.1 (+, Ar-C), 130.0 (+, 2 C, Ar-C), 131.9 (+, $CH{=}CH_2$), 134.1 (C_{quat}, Ar-C), 155.1 (C_{quat}, C=O), 168.5 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 304 (3) [M^+], 248 (14) [$M^+ - C_4H_9 - H$], 231 (11), 204 (33), 134 (15), 107 (16), 70 (47), 57 (59) [$C_4H_9^+$], 43 (100). – HRMS (EI) calcd. for $C_{17}H_{24}N_2O_3$ [M^+] 304.1787, found 304.1787. – $C_{17}H_{24}N_2O_3$ (304.30): calcd. C 67.08, H 7.95; found: C 67.00, H 7.85.

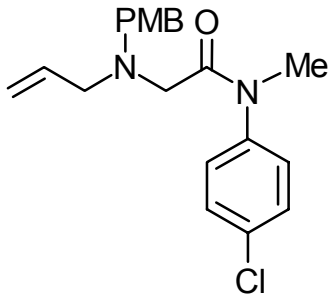
2-(Allyl-tert-butoxycarbonylamino)-N-methyl-N-(4-chlorophenyl)acetamide (**155**): The amide **155** (1.69 g, 50%) was obtained from K_2CO_3 (2.76 g, 20.0 mmol), NaI (3.00 g, 20.0 mmol), Et_3N (5.5 mL, 40.0 mmol), allyl amine (0.75 mL, 10.0 mmol), *N*-methyl-*N*-(4-chlorophenyl)amide **153** (2.62 g, 10.0 mmol) and Boc_2O (2.62 g, 12.0 mmol) according to GP 14 as a colorless oil.



R_f (EtOAc/cyclohexane 2 : 1) = 0.50. – IR (film): ν = 2977 cm^{-1}, 2931, 1683, 1491, 1247, 1170. – ^{1}H-NMR (250 MHz, $CDCl_3$, observed as a major rotamer/minor rotamer ratio of 1.2 : 1): δ = 1.42 [s, 9 H, $C(CH_3)_3$], 3.22 (s, 3 H, major, NCH_3), 3.24 (s, 3 H, minor, NCH_3), 3.56 (s, 2 H, minor, 2-H), 3.67 (s, 2 H, major, 2-H), 3.87–3.91 (m, 2 H, $CH_2CH{=}CH_2$), 5.06–

5.28 (m, 2 H, CH=CH_2), 5.61–5.79 (m, 1 H, CH=CH_2), 7.08–7.19 (m, 2 H, Ar-H), 7.35–7.41 (m, 2 H, Ph-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT, only one rotamer was observed): δ = 28.3 [+, 3 C, C(CH_3)$_3$], 37.5 (+, NCH_3), 47.9 (–, CH_2CH=CH_2), 50.6 (–, C-2), 80.0 [C_{quat}, $C(CH_3)_3$], 116.3 (–, CH=CH_2), 128.7 (+, 2 C, Ar-C), 129.9 (C_{quat}, Ar-C), 130.2 (+, 2 C, Ar-C), 133.9 (+, CH=CH_2), 134.1 (C_{quat}, Ar-C), 154.3 (C_{quat}, C=O), 168.4 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 338/340 (3/<1) [M^+], 282/284 (14/5) [$M^+ - C_4H_6$], 238/240 (33/10), 141 (37), 84 (99), 57 (100).

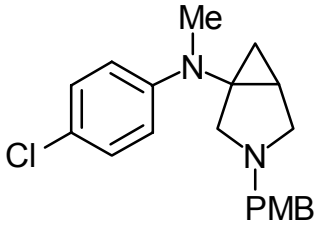
2-(Allyl-4-methoxybenzylamino)-N-methyl-N-(4-chlorophenyl)acetamide (**156**): The amide **156** (1.18 g, 33%) was obtained from K_2CO_3 (2.76 g, 20.0 mmol), NaI (3.00 g, 20.0 mmol), Et_3N (5.5 mL, 40.0 mmol), allyl amine (0.80 mL, 10.0 mmol), *N*-methyl-*N*-(4-chlorophenyl)-amide **153** (2.62 g, 10.0 mmol) and 4-methoxybenzylchloride (1.87 g, 12.0 mmol) according to GP 14 as a colorless oil.



R_f (cyclohexane/EtOAc 1 : 1) = 0.24. Alternatively the amide **156** (1.08 g, 61%) was obtained from *N*-methyl-*N*-(4-chlorophenyl)amide **153** (1.31 g, 5.00 mmol), Et_3N (2.8 mL, 20.0 mmol) and *N*-allyl-*N*-(4-methoxybenzyl)amine (780 mg, 5.00 mmol) according to GP 2. – IR (film): ν = 3069 cm^{-1}, 2934, 2835, 1661, 1512, 1249, 1092, 837. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.24 (s, 3 H, NCH_3), 3.20 (s, 2 H, 2-H), 3.64 (s, 2 H, CH_2Ph), 3.81 (s, 3 H, OCH_3), 5.02–5.21 (m, 2 H, CH=CH_2), 5.64–5.80 (m, 1 H, CH=CH_2), 6.79–7.24 (m, 8 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 37.4 (+, NCH_3), 55.2 (+, OCH_3), 56.8 (–, CH_2CH=CH_2*), 57.1 (–, C-2*), 58.1 (–, CH_2Ph), 117.8 (–, CH=CH_2), 128.2 (+, 2 C, Ar-C), 128.4 (+, Ar-C), 128.6 (+, Ar-C), 129.7 (+, 2 C, Ar-C), 129.9 (+, 2 C, Ar-C), 130.3 (+,

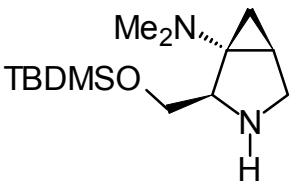
*C*H=CH_2), 131.6 (C_{quat}, Ar-C), 135.6 (C_{quat}, Ar-C), 138.6 (C_{quat}, Ar-C), 141.9 (C_{quat}, Ar-C), 170.5 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 358/360 (14/5) [M^+], 317/319 (5/2), 237/239 (20/6) [$M^+ - CH_2C_6H_4OMe$], 190 (15), 121 (100).

N-(4-Chlorophenyl)-3-(4-methoxybenzyl)-N-methyl-3-azabicyclo[3.1.0]hex-1-ylamine (**159**): The amine **159** (656 mg, 41%) was obtained from the amide **156** (1.90 g, 5.30 mmol), $MeTi(OiPr)_3$ (1.90 g, 7.94 mmol) and *c*HexMgBr (25 mL, 25.0 mmol, 1.0 M solution in Et_2O) according to GP 3 as a colorless oil. R_f (hexane/Et_2O 3 : 1) = 0.36. – IR (film): ν = 2907 cm^{-1}, 2786, 1597, 1496, 1245, 1037. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.81–0.86 (m, 1 H, *c*Pr-H), 1.51 (ps t, ^2J = 4.3, ^3J = 4.3 Hz, 1 H, *c*Pr-H), 1.63–1.69 (m, 1 H, *c*Pr-H), 2.41 (d, ^3J = 4.3 Hz, 1 H, 4-H), 2.64 (dd, ^2J = 8.4, ^3J = 4.1 Hz, 1 H, 4-H), 2.94 (s, 3 H, NCH_3), 2.97–3.01 (m, 1 H, 2-H), 3.07 (d, ^2J = 8.6 Hz, 1 H, 2-H), 3.57 (d, ^2J = 14.6 Hz, 2 H, CH_2Ph), 3.81 (s, 3 H, OCH_3), 6.75–6.87 (m, 4 H, Ar-H), 7.14–7.22 (m, 4 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.3 (–, *c*Pr-C), 26.4 (+, *c*Pr-C), 36.9 (+, OCH_3), 48.0 (C_{quat}, *c*Pr-C), 52.6 (–, C-4), 54.3 (–, C-2), 55.2 (+, NCH_3), 58.6 (–, CH_2Ph), 113.5 (+, 2 C, Ar-C), 114.0 (+, 2 C, Ar-C), 121.4 (C_{quat}, Ar-C), 128.6 (+, 2 C, Ar-C), 129.7 (+, 2 C, Ar-C), 131.1 (C_{quat}, Ar-C), 147.7 (C_{quat}, Ar-C), 158.6 (C_{quat}, Ar-C).

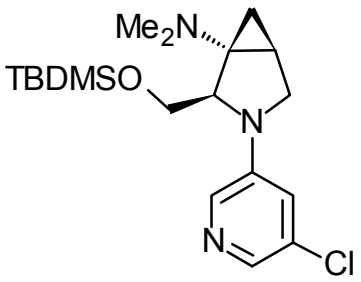


2.9. *Further elaboration of endo- and exo- N,N-dialkyl-3-benzyl-2-(tert-butyldimethyl-silyloxymethyl)-3-aza-bicyclo[3.1.0]hex-1-ylamines*

endo-(2R)-2-(tert-butyldimethylsilyloxymethyl)-N,N-dimethyl-3-azabicyclo[3.1.0]hex-1-yldimethylamine (*endo*-**161**): A solution of the amine *endo*-**58** (360 mg, 1.00 mmol) in MeOH (40 mL) was stirred under hydrogen atmosphere (1 bar) at 20 °C for 4 h under Pd/C (10%) catalysis (180 mg). The reaction mixture was filtered through Celite® and concentrated under reduced pressure. The amine *endo*-**161** (248 mg, 92%) was obtained as a colorless oil. – $[\alpha]_D^{20}$ = –7.2 (*c* = 0.60, $CHCl_3$). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.03 [s, 6 H, $Si(CH_3)_2$], 0.68–0.76 (m, 1 H, *c*Pr-H), 0.86 [s, 9 H, $SiC(CH_3)_3$], 0.96–0.99 (m, 1 H, *c*Pr-H), 1.25–1.32 (m, 1 H, *c*Pr-H), 2.39 [s, 6 H, $N(CH_3)_2$], 2.77 (d, ^2J = 10.8 Hz, 1 H, 4-H), 3.03 (dd, ^2J = 10.8, ^3J = 3.4 Hz, 1 H, 4-H), 3.39–3.42 (m, 1 H, 2-H), 3.70 (dd, ^2J = 10.4, ^3J = 4.8 Hz, 1 H, CH_2O), 3.88 (dd, ^2J = 10.4, ^3J = 3.4 Hz, 1 H, CH_2O). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = –4.3 [+, 2 C, $Si(CH_3)_2$], 13.1 (–, *c*Pr-C), 18.1 [C_{quat}, $SiC(CH_3)_3$], 24.4 (+, *c*Pr-C), 25.8 [+, 3 C, $SiC(CH_3)_3$], 42.0 [+, 2 C, $N(CH_3)_2$], 47.1 (–, C-4), 53.1 (C_{quat}, *c*Pr-C), 57.1 (+, C-2), 63.7 (–, CH_2O).

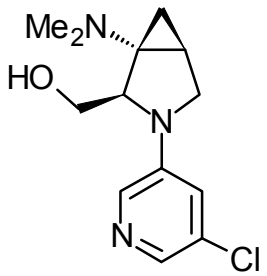


Endo-(2R)-2-(tert-butyldimethylsilyloxymethyl)-3-(5-chloropyridin-3-yl)-N,N-dimethyl-3-aza-bicyclo[3.1.0]hex-1-ylamine (*endo*-**162**): The amine *endo*-**162** (264 mg, 75%) was obtained from the amine *endo*-**161** (250 mg, 580 μmol), $Pd(OAc)_2$ (10.4 mg, 50.0 μmol, 5 mol%), 2-(di-*tert*-butylphosphino)biphenyl (30.0 mg, 100 μmol, 10 mol%) and NaO*t*Bu (125 mg, 1.30 mmol) according to GP 9 as a colorless oil.



R_f (CH_2Cl_2/MeOH 20 : 1 + 1% NH_3) = 0.33. – $[\alpha]_D^{20}$ = +12.0 (*c* = 0.50, $CHCl_3$). – IR (film): ν = 2931 cm^{-1}, 1656, 1462, 1255, 1099. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.07 [s, 6 H, $Si(CH_3)_2$], 0.79–0.82 (m, 1 H, *c*Pr-H), 0.95 [s, 9 H, $SiC(CH_3)_3$], 1.02–1.21 (m, 1 H, *c*Pr-H), 1.66–1.73 (m, 1 H, *c*Pr-H), 2.43 [s, 6 H, $N(CH_3)_2$], 3.24–3.61 (m, 3 H, 2,4-H), 3.78–3.99 (m, 2 H, CH_2O), 7.18 (s, 1 H, Ar-H), 7.90–7.98 (m, 2 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = –5.4 [+, 2 C, $Si(CH_3)_2$], 18.2 (–, *c*Pr-C), 25.4 (+, *c*Pr-C), 25.9 [C_{quat}, $SiC(CH_3)_3$], 26.3 [+, 3 C, $SiC(CH_3)_3$], 42.1 [+, 2 C, $N(CH_3)_2$], 52.6 (–, C-4), 58.9 (C_{quat}, *c*Pr-C), 59.1 (+, C-2), 64.5 (–, CH_2O), 118.9 (+, Ar-C), 133.6 (+, Ar-C), 136.5 (+, Ar-C), 144.8 (C_{quat}, Ar-C), 157.5 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 383/381 (3/9) [M^+ + H], 339/337 (9/22), 314 (43), 257 (100), 236 (44), 201 (46), 183 (70).

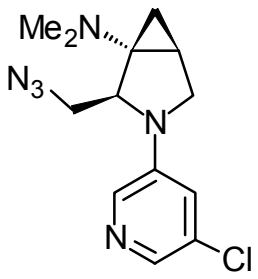
Endo-(2R)-3-(5-chloropyrid-3-yl)-2-(hydroxymethyl)-N,N-dimethyl-3-azabicyclo[3.1.0]hex-1-ylamine (*endo*-**163**): The alcohol *endo*-**163** (95.0 mg, 96%) was obtained from the ether *endo*-**162** (140 mg, 370 µmol) and TBAF (466 mg, 1.48 mmol) according to GP 6. R_f (CH_2Cl_2/MeOH 10 : 1 + 1% NH_3) = 0.30. – $[\alpha]_D^{20}$ = +15.0 (*c* = 0.20, $CHCl_3$). – ^{1}H-NMR



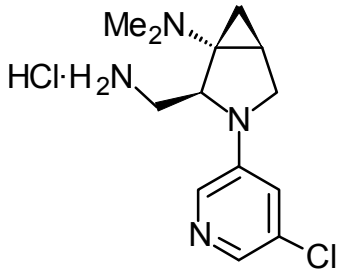
(250 MHz, $CDCl_3$): δ = 0.88–0.99 (m, 1 H, *c*Pr-H), 1.12–1.17 (m, 1 H, *c*Pr-H), 1.71–1.78 (m, 1 H, *c*Pr-H), 2.43 [s, 6 H, $N(CH_3)_2$], 3.33 (dd, ^3J = 5.1, ^3J = 9.1 Hz, 1 H, 4-H), 3.54 (d, ^2J = 9.1 Hz, 1 H, 4-H), 3.74–3.96 (m, 3 H, 2-H, CH_2O), 7.01 (d, ^4J = 2.3 Hz, 1 H, Ar-H), 7.91–7.97 (m, 2 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 18.2 (–, *c*Pr-C), 21.8 (+, *c*Pr-C), 41.9 [+, 2 C, $N(CH_3)_2$], 53.7 (–, C-4), 58.4 (+, C-2), 58.9 (C_{quat}, *c*Pr-C), 63.2 (–, CH_2O), 119.5 (+, Ar-C), 133.8 (+, Ar-C), 136.8 (+, Ar-C), 145.2 (C_{quat},

Ar-C), 157.1 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 269/267 (6/21) [M^+], 238/236 (33/100), 193/191 (11/19), 126 (18), 109 (33).

Endo-(2R)-2-(azidomethyl)-3-(5-chloropyrid-3-yl)-N,N-dimethyl-3-azabicyclo[3.1.0]hex-1-ylamine (*endo*-**164**): A solution of DEAD (433 µmol, 0.10 mL) in THF (2.0 mL), HN_3 (0.40 mL, 440 µmol, 1.1 M solution in benzene) and a solution of the alcohol *endo*-**163** (100 mg, 370 µmol) in anhydrous THF (5.0 mL) were added to a suspension of PPh_3 (116 mg, 444 µmol) in anhydrous THF (8.0 mL), precooled at –78 °C. The reaction mixture was stirred at ambient temperature for 12 h. The solvent was removed, the residue was purified by chromatography, the azide *endo*-**164** (90.0 mg, 73%) was obtained as a colorless oil and was used in the following reaction without further purification. R_f (CH_2Cl_2/MeOH 40 : 1) = 0.31.

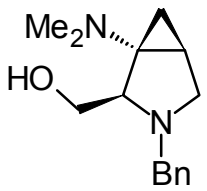


Endo-(2R)-2-(aminomethyl)-3-(5-chloropyrid-3-yl)-N,N-dimethyl-3-azabicyclo-[3.1.0]-hex-1-ylamine hydrochloride (*endo*-**165**): A solution of the azide *endo*-**164** (90.0 mg, 307 µmol) in MeOH (6.0 mL) was stirred under hydrogen atmosphere (1 bar) at 20 °C for 3 h under Pd/C (10%) catalysis (180 mg). The reaction mixture was filtered through Celite® and concentrated until half of the volume. The solution was cooled at 0 °C, HCl (1.0 mL, 6.00 mmol, 6.0 M solution in MeOH) was added and stirring was continued for 30 min. Removal of the solvent under reduced pressure gave 94.0 mg of a yellow oil, which became immediately black. Attempted purification did not give any positive result. The NMR spectra showed a complex system of signals, only the MS



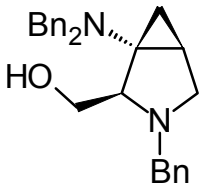
spectrum presented the molecular peak belonging to the amine. – MS (EI): *m*/*z* (%) = 268/266 (1/13) [M^+], 249 (30), 236 (100), 202 (40), 109 (60).

endo-(2R)-N,N,3-Tribenzyl-2-(hydroxymethyl)-3-azabicyclo-[3.1.0]hex-1-ylamine (*endo*-**169**): The alcohol *endo*-**169** (62.0 mg, 90%) was obtained from the amine *endo*-**58** (100 mg, 280 µmol) and TBAF (293 mg, 1.12 mmol) according to GP 6 as a colorless oil. R_f (hexane/Et_2O 1 : 2) = 0.28. –



^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.78–0.81 (m, 1 H, *c*Pr-H), 1.09–1.19 (m, 1 H, *c*Pr-H), 1.29–1.41 (m, 1 H, *c*Pr-H), 2.32 (s, 6 H, NCH_3), 2.38–2.45 (m, 1 H, 4-H), 2.80 (m, 1 H, 4-H), 2.98–3.03 (m, 1 H, 2-H), 3.29 (d, ^2J = 12.5 Hz, 1 H, CH_2Ph), 3.81–3.98 (m, 3 H, CH_2O, CH_2Ph), 7.18–7.30 (m, 5 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 13.1 (–, *c*Pr-C), 17.8 (+, *c*Pr-C), 41.9 (+, 2 C, NCH_3), 54.5 (C_{quat}, *c*Pr-C), 57.6 (–, C-4), 61.8 (–, CH_2Ph), 62.8 (–, CH_2O), 65.8 (+, C-2), 127.0 (+, Ar-C), 128.2 (+, 2 C, Ar-C), 128.5 (+, 2 C, Ar-C), 138.6 (C_{quat}, Ar-C).

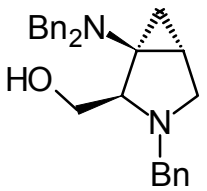
endo-(2R)-N,N,3-Tribenzyl-2-(hydroxymethyl)-3-azabicyclo-[3.1.0]hex-1-ylamine (*endo*-**170**): The alcohol *endo*-**170** (362 mg, 95%) was obtained from the amine *endo*-**59** (490 mg, 960 µmol) and TBAF (1.21 g, 3.84 mmol) according to GP 6 as a colorless solid. R_f (hexane/Et_2O 1 : 2) = 0.43,



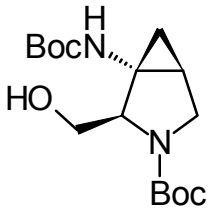
m. p. 56–59 °C. – $[\alpha]_D^{20}$ = –6.2 (*c* = 1.0, $CHCl_3$). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.70–0.81 (m, 1 H, *c*Pr-H), 0.98–1.09 (m, 1 H, *c*Pr-H), 1.99–2.11 (m, 1 H, *c*Pr-H), 2.08–2.15 (m, 1 H, 4-H), 2.62–2.71 (m, 1 H, 2-H), 2.41 (br s, 1 H, OH), 3.18–3.21 (m, 1 H, CH_2O), 3.30–3.41 (m, 1 H, CH_2O), 3.80–4.03 (m, 6 H, CH_2Ph), 7.18–7.32 (m, 15 H, Ar-H). – ^{13}C-NMR

(62.9 MHz, $CDCl_3$, additional DEPT): δ = 14.1 (–, *c*Pr-C), 22.6 (+, *c*Pr-C), 51.8 (C_{quat}, *c*Pr-C), 53.5 (–, C-4), 56.9 (–, 3 C, CH_2Ph), 61.1 (–, CH_2O), 61.9 (+, C-2), 126.6 (+, 2 C, Ar-C), 127.1 (+, Ar-C), 128.1 (+, 4 C, Ar-C), 128.3 (+, 2 C, Ar-C), 128.8 (+, 4 C, Ar-C), 128.9 (+, 2 C, Ar-C), 138.1 (C_{quat}, Ar-C), 140.1 (C_{quat}, 2 C, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 398 (15) [M^+], 307 (74) [$M^+ - C_7H_7$], 277 (27), 202 (16), 91 (100) [$C_7H_7^+$]. – $C_{27}H_{30}N_2O$ (398.54): calcd. C 81.37, H 7.59, N 7.03; found C 81.44, H 7.37, N 6.91.

exo-(2R)-N,N,3-Tribenzyl-2-(hydroxymethyl)-3-azabicyclo-[3.1.0]hex-1-ylamine (*exo*-**170**): The alcohol *exo*-**170** (120 mg, 78%) was obtained from the amine *exo*-**59** (200 mg, 390 μmol) and TBAF (492 mg, 1.56 mmol) according to GP 6 as a colorless solid. R_f (hexane/Et_2O 5 : 1) = 0.48. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.83–0.91 (m, 2 H, *c*Pr-H), 1.18–1.29 (m, 1 H, *c*Pr-H), 2.23–2.35 (m, 2 H, 4-H), 2.68 (m, 1 H, 2-H), 3.46–3.51 (m, 1 H, CH_2O), 3.53–3.61 (m, 1 H, CH_2O), 3.90–4.12 (m, 6 H, CH_2Ph), 7.23–7.42 (m, 15 H, Ar-H).



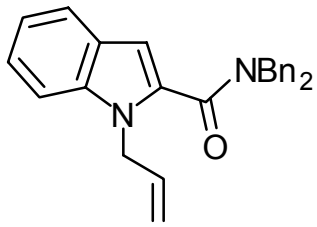
endo-(2R)-N,3-(di-tert-butoxycarbonyl)-2-(hydroxymethyl)-3-azabicyclo-[3.1.0]hex-1-ylamine (*endo*-**173**): A solution of the alcohol *endo*-**170** (475 mg, 1.20 mmol) in MeOH (50 mL) was stirred under hydrogen atmosphere (1 bar) at 20 °C for 3 d under Pd/C (10%) catalysis (238 mg). The reaction mixture was filtered through Celite® and concentrated under reduced pressure. The obtained salt was dissolved in MeOH (15 mL), Et_3N (0.7 mL, 4.76 mmol), DMAP (15.0 mg, 100 μmol) and Boc_2O (780 mg, 3.57 mmol) were added to this solution and the mixture was stirred at ambient temperature for 12 h. EtOAc (20 mL) and a sat. aq. $NaHCO_3$ solution (20 mL), the aqueous layer was separated and extracted with EtOAc



(2 × 20 mL). The combined organic phases were washed with brine (40 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The amine *endo*-**173** (268 mg, 88%) was obtained as a white solid. M. p. 169–171 °C. – $[\alpha]_D^{20}$ = –8.8 (*c* = 0.90, $CHCl_3$). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.75–0.91 (m, 2 H, *c*Pr-H), 1.38 [s, 18 H, $C(CH_3)_3$], 1.58–1.62 (m, 1 H, *c*Pr-H), 2.98 (br s, 1 H, OH), 3.21–3.40 (m, 1 H, 4-H), 3.57–3.70 (m, 2 H, 2,4-H), 3.78–3.91 (m, 2 H, CH_2O). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 14.1 (–, *c*Pr-C), 21.0 (+, *c*Pr-C), 28.2 [+, 6 C, $C(CH_3)_3$], 50.4 (–, C-4), 60.0 (C_{quat}, *c*Pr-C), 64.0 (+, C-2), 65.2 (–, CH_2O), 80.5 [C_{quat}, 2 C, $C(CH_3)_3$], 157.0 (C_{quat}, C=O), 157.1 (C_{quat}, C=O). – MS (DCI, NH_3, 70 eV), *m*/*z* (%): 674 (5) [2M + NH_4^+], 657 (11) [2M + H^+], 346 (64) [M + NH_4^+], 329 (100) [M + H^+].

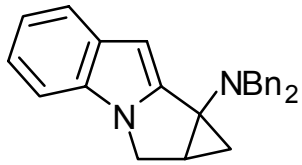
2.10. Synthesis of tetracyclic azaheterocycles by Ti-mediated intramolecular reductive cyclopropanation

1-Allyl-N,N-dibenzyl-1H-indole-2-carboxamide (**178**): *N*,*N*-dibenzyl-*1H*-indole-2-carboxamide was obtained from $HNBn_2$ (1.6 mL, 8.55 mmol), DCC (1.76 g, 8.55 mmol), HOBT (462 mg, 3.42 mmol) and indole-2-carboxylic acid (**177**, 551 mg, 3.42 mmol) in CH_2Cl_2 (30 mL) according to GP 10 as a colorless oil, which was used without further purification. The amide **178** (545 mg, 42%) was obtained from *N*,*N*-dibenzyl-*1H*-indole-2-carboxamide (1.10 g, 3.42 mmol), allyl bromide (0.40 mL, 4.79 mmol) and K_2CO_3 (945 mg, 6.84 mmol) according to GP 1 as a colorless solid. R_f (Et_2O/hexane 1 : 2) = 0.53, m. p. 121–128 °C. – IR (KBr): ν = 3064 cm^{-1}, 3029, 2917, 1630, 1523, 1451, 1244, 962. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 4.73 (s, 4 H, CH_2Ph), 4.91–



5.13 (m, 4 H, CH_2Ph, $CH_2CH{=}CH_2$), 5.94–6.09 (m, 1 H, $CH{=}CH_2$), 6.70 (s, 1 H, 3-H), 7.07–7.56 (m, 14 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 46.6 (–, 2 C, CH_2Ph), 47.0 (–, $CH_2CH{=}CH_2$), 103.7 (+, C-3), 110.3 (+, Ar-C), 116.5 (–, $CH{=}CH_2$), 120.4 (+, 2 C, Ar-C), 121.7 (+, 2 C, Ar-C), 123.5 (+, 2 C, Ar-C), 126.4 (+, 2 C, Ar-C), 127.6 (+, 3 C, Ar-C), 128.8 (C_{quat}, 2 C, Ar-C), 131.0 (C_{quat}, Ar-C), 134.1 (+, 2 C, Ar-C), 136.1 (+, $CH{=}CH_2$), 136.6 (C_{quat}, Ar-C), 137.6 (C_{quat}, Ar-C), 165.1 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 380 (100) [M^+], 196 (17), 184 (81), 157 (55), 91 (62), 56 (29). – $C_{26}H_{24}N_2O$ (380.30): calcd. C 82.07, H 6.36; found: C 81.86, H 6.59.

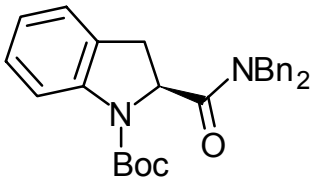
N,N-Dibenzyl-indolo[1,2-a]cyclopropa[1,2-c]pyrrolidin-8b-amine (**179**): The amine **179** (202 mg, 79%) was obtained from the *N*,*N*-dibenzylamide **178** (270 mg, 710 μmol), $MeTi(OiPr)_3$ (256 mg, 1.06 mmol) and *c*HexMgBr (3.5 mL, 3.55 mmol, 1.0 M solution in Et_2O) according to GP 3 as a colorless oil.



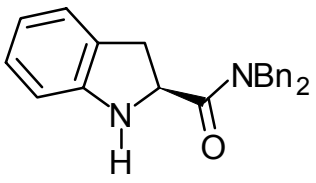
R_f (hexane/Et_2O 10 : 1) = 0.55. – IR (film): ν = 3024 cm^{-1}, 2928, 1510, 1398, 1114. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.85 (ps t, ^2J = 5.0, ^3J = 5.0 Hz, 1 H, *c*Pr-H), 1.32–1.37 (m, 1 H, *c*Pr-H), 1.49–1.59 (m, 1 H, *c*Pr-H), 3.61 (dd, ^2J = 10.0, ^3J = 5.0 Hz, 1 H, NCH_2CH), 3.70 (d, ^2J = 10.1 Hz, 1 H, NCH_2CH), 4.03 (d, ^2J = 13.0 Hz, 2 H, CH_2Ph), 4.15 (d, ^2J = 13.0 Hz, 2 H, CH_2Ph), 6.33 (s, 1 H, Ar-H), 7.12–7.36 (m, 13 H, Ar-H), 7.62–7.66 (m, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 24.2 (–, *c*Pr-C), 30.6 (+, *c*Pr-C), 45.8 (C_{quat}, *c*Pr-C), 49.6 (–, NCH_2CH), 57.8 (–, 2 C, CH_2Ph), 93.4 (+, Ar-C), 108.9 (+, Ar-C), 119.2 (+, Ar-C), 120.4 (+, Ar-C), 120.5 (+, Ar-C), 127.1 (+, 2 C, Ar-C), 128.1 (+, 4 C, Ar-C), 129.2 (+, 4 C, Ar-C), 132.6 (C_{quat}, 2 C, Ar-C), 132.7 (C_{quat}, Ar-C), 139.6 (C_{quat}, 2 C, Ar-C), 143.2 (C_{quat}, Ar-C). – MS (EI): *m*/*z* (%) = 464

(1) [M^+], 273 (100), 168 (6), 91 (32). – $C_{26}H_{24}N_2$ (364.30): calcd. C 85.68, H 6.64; found: C 85.44, H 6.50.

(S)-N,N-Dibenzyl-1-(tert-butoxycarbonyl)-2,3-dihydro-1H-indole-2-carboxamide (**181-Boc**): The amide **181-Boc** (1.50 g, 89%) was obtained from *N*-Boc-indoline-2-carboxilic acid (**180**, 1.00 g, 3.80 mmol), DCC (1.96 g, 9.50 mmol), HOBT (513 mg, 3.80 mmol) and $HNBn_2$ (1.8 mL, 9.50 mmol) according to GP 10 as a colorless oil. R_f (hexane/Et_2O 2 : 1) = 0.35. – ^{1}H-NMR (250 MHz, $CDCl_3$, observed as a major rotamer/minor rotamer ratio of 1.2 : 1): δ = 1.41 [s, 9 H, minor, $C(CH_3)_3$], 1.63 [s, 9 H, major, $C(CH_3)_3$], 2.91–3.25 (m, 2 H, 3-H), 4.41–4.58 (m, 2 H, CH_2Ph), 4.64–4.90 (m, 2 H, CH_2Ph), 5.10–5.28 (m, 1 H, 2-H), 6.80–7.23 (m, 14 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 28.4 [+, 3 C, $C(CH_3)_3$], 49.2 (–, C-3), 49.8 (–, CH_2Ph), 50.1 (–, CH_2Ph), 59.1 (+, C-2), 79.7 [C_{quat}, $C(CH_3)_3$], 114.8 (+, Ar-C), 122.2 (+, Ar-C), 126.8 (+, Ar-C), 127.3 (+, 2 C, Ar-C), 127.7 (+, Ar-C), 128.6 (+, 2 C, Ar-C), 129.0 (+, 2 C, Ar-C), 129.2 (+, 2 C, Ar-C), 129.8 (+, 2 C, Ar-C), 130.2 (C_{quat}, Ar-C), 137.1 (C_{quat}, 2 C, Ar-C), 155.3 (C_{quat}, C=O), 157.2 (C_{quat}, Ar-C), 175.5 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 442 (14) [M^+], 342 (15), 224 (7), 118 (100), 91 (23) [$C_7H_7^+$].

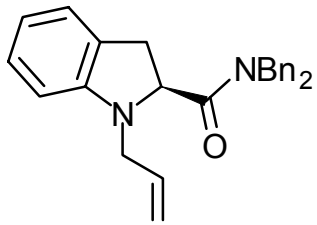


(S)-N,N-Dibenzyl-2,3-dihydro-1H-indole-2-carboxamide (**181**): The amine **181** (1.14 g, 98%) was obtained from the amide **181-Boc** (1.50 g, 3.39 mmol) and TFA (1.3 mL, 17.0 mmol) according to GP 11 as a colorless oil. – $[\alpha]_D^{20}$ = –64.0 (*c* = 1.0, $CHCl_3$). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.25 (dd, ^2J = 15.7, ^3J = 6.4 Hz, 1 H, 3-H), 3.44 (dd, ^2J = 15.7, ^3J = 10.6 Hz,



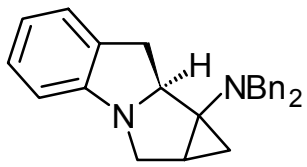
1 H, 3-H), 4.25–4.42 (m, 3 H, NH, CH_2Ph), 4.65–4.75 (m, 2 H, 2-H, CH_2Ph), 4.98 (d, ^2J = 14.6 Hz, 1 H, CH_2Ph), 6.76–6.81 (m, 2 H, Ar-H), 7.12–7.45 (m, 12 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 35.5 (–, C-3), 48.2 (–, CH_2Ph), 49.1 (–, CH_2Ph), 58.2 (+, C-2), 111.5 (+, Ar-C), 119.9 (+, Ar-C), 124.3 (+, Ar-C), 126.7 (+, 2 C, Ar-C), 127.3 (+, Ar-C), 127.6 (+, Ar-C), 127.9 (+, 2 C, Ar-C), 128.4 (+, Ar-C), 128.8 (+, 3 C, Ar-C), 135.7 (C_{quat}, 2 C, Ar-C), 136.9 (+, Ar-C), 156.1(C_{quat}, 2 C, Ar-C), 174.1 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 342 (8) [M^+], 270 (29), 189 (19), 155 (28), 118 (100), 90 (48).

(S)-N,N-Dibenzyl-1-allyl-2,3-dihydro-1H-indole-2-carboxamide (**182**): The amide **182** (1.15 g, 89%) was obtained from the amide **181** (1.10 g, 3.39 mmol), K_2CO_3 (940 mg, 6.78 mmol) and allyl bromide (0.40 mL, 4.75 mmol) according to GP 1 as a colorless oil. R_f (Et_2O/hexane 1 : 2) = 0.31. – $[\alpha]_D^{20}$ = –36.0 (*c* = 0.35, $CHCl_3$). – IR (film): ν = 3030 cm^{-1}, 2925, 1657, 1453, 1208, 747. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 3.04–3.27 (m, 2 H, C*H*$_2$CH=CH_2), 3.73 (dd, ^2J =15.7, ^3J = 7.4 Hz, 1 H, 3-H), 3.98 (dd, ^2J = 15.7, ^3J = 5.0 Hz, 1 H, 3-H), 4.49–4.65 (m, 4 H, 2-H, CH_2Ph), 4.83 (d, ^2J = 14.5 Hz, 1 H, CH_2Ph), 5.10–5.25 (m, 2 H, CH=C*H*$_2$), 5.75–5.91 (m, 1 H, C*H*=CH_2), 6.51–6.68 (m, 2 H, Ar-H), 6.98 (m, 12 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 34.1 (–, C-3), 48.7 (–, *C*H_2CH=CH_2), 49.4 (–, CH_2Ph), 50.1 (–, CH_2Ph), 63.6 (+, C-2), 107.4 (+, Ar-C), 117.9 (–, CH=*C*H_2), 118.3 (+, Ar-C), 124.1 (+, Ar-C), 126.5 (+, Ar-C), 126.6 (+, Ar-C), 127.6 (+, Ar-C), 127.8 (+, 2 C, Ar-C), 128.5 (+, 2 C, Ar-C), 128.7 (+, 2 C, Ar-C), 129.0 (+, 2 C, Ar-C), 133.4 (+, *C*H=CH_2), 136.4 (C_{quat}, Ar-C), 137.2 (C_{quat}, Ar-C),



151.1 (C_{quat}, Ar-C), 156.4 (C_{quat}, Ar-C), 172.9 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 382 (8) [M^+], 270 (10), 158 (100), 117 (20). – $C_{26}H_{26}N_2O$ (382.30): calcd. C 81.64, H 6.85; found C 81.58, H 6.97.

(1aS,8aS,8bR)- and (1aR,8aS,8bS)-N,N-Dibenzyl-8,8a-dihydroindolo[1,2-a]cyclopropa[1,2-c]pyrrolidin-8b-amine (**183**): The amines **183** (223 mg, 61%) were obtained from the amide **182** (382 mg, 1.00 mmol), MeTi(O*i*Pr)$_3$ (361 mg, 1.50 mmol) and *c*HexMgBr (5.0 mL, 5.00 mmol, 1.0 M solution in Et_2O) according to GP 3 in an (1a*S*,8a*S*,8b*R*)-**183**/(1a*R*,8a*S*,8b*S*)-**183** ratio of 1 : 1.

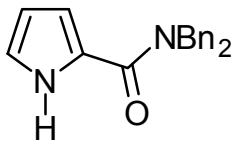


(1a*S*,8a*S*,8b*R*)-**183**: Colorless oil, R_f (Et_2O/hexane 1 : 5) = 0.66. – $[\alpha]_D^{20}$ = –7.7 (*c* = 0.35, $CHCl_3$). – IR (film): ν = 3026 cm^{-1}, 2920, 1480, 1263, 1028, 749. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.18 (ps t, ^2J = 5.0, ^3J = 5.0 Hz, 1 H, *c*Pr-H), 0.58–0.64 (m, 1 H, *c*Pr-H), 0.97–1.03 (m, 1 H, *c*Pr-H), 3.00 (d, ^2J = 11.3 Hz, 1 H, 6-H), 3.15 (dd, ^3J = 11.3, ^3J = 3.5 Hz, 1 H, 6-H), 3.28–3.32 (m, 2 H, 1-H), 3.80 (d, ^2J = 13.5 Hz, 2 H, CH_2Ph), 3.97 (d, ^2J = 13.5 Hz, 2 H, CH_2Ph), 4.74 (ddd, ^3J = 5.2, ^3J = 8.8, ^4J = 1.5 Hz, 1 H, 2-H), 6.34 (d, ^3J = 8.1 Hz, 1 H, Ar-H), 6.65 (t, ^3J = 7.1, ^3J = 7.1 Hz, 1 H, Ar-H), 6.97–7.37 (m, 12 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 14.0 (–, *c*Pr-C), 28.1 (+, *c*Pr-C), 33.1 (–, C-1), 53.1 (–, C-6), 55.3 (C_{quat}, *c*Pr-C), 57.1 (–, 2 C, CH_2Ph), 60.8 (+, C-2), 109.2 (+, Ar-C), 118.5 (+, Ar-C), 124.4 (+, Ar-C), 127.0 (+, 2 C, Ar-C), 127.5 (+, Ar-C), 128.1 (+, 4 C, Ar-C), 128.9 (+, 4 C, Ar-C), 130.1 (C_{quat}, Ar-C), 139.9 (C_{quat}, 2 C, Ar-C), 143.2 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 366 (47) [M^+], 275 (100) [$M^+ – C_7H_7$], 170 (48), 91 (84) [$C_7H_7^+$]. – HRMS (EI) calcd for $C_{26}H_{26}N_2$ [M^+] 366.2096, found 366.2096.

(1a*R*,8a*S*,8b*S*)-**183**: Colorless oil, R_f (Et_2O/hexane 1 : 5) = 0.33, $[\alpha]_D^{20} = -3.3$ (*c* = 0.3, $CHCl_3$). – IR (film): ν = 3016 cm^{-1}, 2919, 1462, 1257, 1027, 769. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.75 (ps t, ^2J = 4.7, ^3J = 4.7 Hz, 1 H, *c*Pr-H), 1.30 (dd, ^2J = 9.1, ^3J = 4.8 Hz, 1 H, *c*Pr-H), 1.82–1.90 (m, 1 H, *c*Pr-H), 2.83 (dd, ^2J = 16.0, ^3J = 9.0 Hz, 1 H, 1-H), 3.22–3.28 (m, 2 H, 6-H), 3.56 (dd, ^2J = 16.0, ^3J = 7.8 Hz, 1 H, 1-H), 3.69 (s, 2 H, 2 CH_2Ph), 3.71 (s, 2 H, CH_2Ph), 3.90 (dd, ^3J = 8.2, ^3J = 8.5 Hz, 1 H, 2-H), 6.69 (d, ^3J = 7.7 Hz, 1 H, Ar-H), 6.87 (t, ^3J = 7.4, ^3J = 7.4 Hz, 1 H, Ar-H), 7.08–7.34 (m, 12 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 21.0 (–, *c*Pr-C), 28.6 (+, *c*Pr-C), 33.1 (–, C-1), 55.0 (C_{quat}, *c*Pr-C), 56.4 (–, C-6), 56.9 (–, 2 C, CH_2Ph), 72.7 (+, C-2), 113.9 (+, Ar-C), 121.2 (+, Ar-C), 124.4 (+, Ar-C), 126.9 (+, 3 C, Ar-C), 127.4 (+, Ar-C), 128.2 (+, 4 C, Ar-C), 128.7 (+, 3 C, Ar-C), 133.1 (C_{quat}, Ar-C), 140.1 (C_{quat}, 2 C, Ar-C), 154.3 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 366 (24) [M^+], 275 (100) [$M^+ - C_7H_7$], 170 (48), 130 (47), 91 (84) [$C_7H_7^+$]. – HRMS (EI) calcd for $C_{26}H_{26}N_2$ [M^+] 366.2096, found 366.2096.

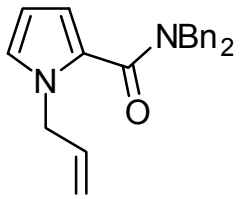
2.11. Synthesis of tricyclic azaheterocycles by Ti-mediated intramolecular reductive cyclopropanation

N,N-Dibenzyl-1H-pyrrole-2-carboxamide (**185**): The amide **185** (1.31 g, 89%) was obtained from pyrrole-2-carboxilic acid (**184**, 556 mg, 5.00 mmol), DCC (2.60 g, 12.5 mmol), HOBT (676 mg, 5.00 mmol) and $HNBn_2$ (2.4 mL, 12.5 mmol) according to GP 10, as a colorless solid. R_f (Et_2O/hexane 1 : 1) = 0.38, m. p. 140–144 °C. – IR (film): ν = 3258 cm^{-1}, 3030, 2905, 1600, 1576, 1424, 1129. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 4.89 (s, 4 H, 2 CH_2Ph), 6.16–6.18 (m, 1 H, 4-H),

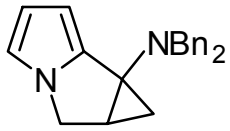


6.48–6.50 (m, 1 H, 3-H), 6.91–6.93 (m, 1 H, 5-H), 7.18–7.48 (m, 10 H, Ar-H), 11.41 (br s, 1 H, NH). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 47.6 (–, 2 C, CH_2Ph), 109.7 (+, Ar-C), 112.7 (+, Ar-C), 122.1 (+, Ar-C), 124.1 (C_{quat}, Ar-C), 126.9 (+, 2 C, Ar-C), 127.5 (+, 4 C, Ar-C), 128.9 (+, Ar-C), 128.9 (+, 3 C, Ar-C), 136.8 (C_{quat}, 2 C, Ar-C), 163.6 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 290 (30) [M^+], 199 (70) [$M^+ – C_7H_7$], 106 (100), 91 (52) [$C_7H_7^+$]. – $C_{19}H_{18}N_2O$ (290.20): calcd. C 78.59, H 6.25; found C 78.38, H 6.42.

1-Allyl-N,N-dibenzyl-1H-pyrrole-2-carboxamide (**186**): The amide **186** (1.11 g, 75%) was obtained from the amine **185** (1.30 g, 4.48 mmol), K_2CO_3 (1.24 g, 8.96 mmol) and allyl bromide (0.50 mL, 6.27 mmol) according to GP 1 as a colorless oil. R_f (Et_2O/hexane 1 : 2) = 0.46. – IR (film): ν = 3029 cm^{-1}, 2925, 1623, 1464, 1240, 987, 734. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 4.74 (s, 4 H, 2 CH_2Ph), 4.91–4.95 (m, 2 H, CH_2CH=CH_2), 5.01–5.20 (m, 2 H, CH=CH_2), 5.97–6.10 (m, 2 H, C*H*=CH_2, 4-H), 6.42 (dd, ^3J = 3.8, ^4J = 1.6 Hz, 1 H, 3-H), 6.80–6.82 (m, 1 H, 5-H), 7.24–7.41 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 49.0 (–, *C*H_2CH=CH_2), 50.7 (–, 2 C, CH_2Ph), 107.1 (+, Ar-C), 112.6 (+, Ar-C), 116.5 (–, CH=*C*H_2), 124.4 (C_{quat}, Ar-C), 125.9 (+, Ar-C), 127.4 (+, 4 C, Ar-C), 128.7 (+, 3 C, Ar-C), 135.3 (+, 3 C, Ar-C), 136.4 (+, *C*H=CH_2), 137.0 (C_{quat}, 2 C, Ar-C), 163.6 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 330 (91) [M^+], 239 (22) [$M^+ – C_7H_7$], 134 (100), 106 (61), 91 (56) [$C_7H_7^+$]. – HRMS (EI) calcd for $C_{22}H_{22}N_2O$ [M^+] 330.1732, found 330.1732.

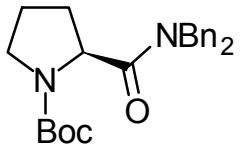


N,N-Dibenzyl-1,1a,2,6b-tetrahydrocyclopropa[1,2-a]pyrrolizin-6b-amine (**187**): The amine **187** (224 mg, 78%) was obtained from the amide **186** (300 mg, 910 μmol), $MeTi(OiPr)_3$ (327 mg, 1.36 mmol) and *c*HexMgBr (4.6 mL, 4.55 mmol, 1.0 M solution in Et_2O) according to GP 3 as a colorless oil.



R_f (hexane/Et_2O 5 : 1) = 0.74. – IR (film): ν = 3028 cm^{-1}, 2924, 1530, 1392, 745. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.72 (ps t, ^2J = 4.6, ^3J = 4.6 Hz, 1 H, *c*Pr-H), 0.84–1.38 (m, 2 H, *c*Pr-H), 3.50–3.59 (m, 2 H, NCH_2CH), 3.96 (d, ^2J = 13.2 Hz, 2 H, CH_2Ph), 4.11 (d, ^2J = 13.2 Hz, 2 H, CH_2Ph), 5.84–5.90 (m, 1 H, Ar-H), 6.20–6.25 (m, 1 H, Ar-H), 6.42–6.50 (m, 1 H, Ar-H), 7.18–7.37 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 23.8 (–, *c*Pr-C), 29.6 (+, *c*Pr-C), 47.9 (–, NCH_2CH), 49.7 (C_{quat}, *c*Pr-C), 57.7 (–, 2 C, CH_2Ph), 99.7 (+, Ar-C), 111.2 (+, Ar-C), 113.5 (+, Ar-C), 126.9 (+, 2 C, Ar-C), 128.1 (+, 4 C, Ar-C), 129.3 (+, 4 C, Ar-C), 131.9 (C_{quat}, Ar-C), 136.0 (C_{quat}, Ar-C), 139.8 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 314 (1) [M^+], 223 (14) [$M^+ – C_7H_7$], 197 (61), 106 (38), 91 (100) [$C_7H_7^+$]. – HRMS (EI) calcd for $C_{22}H_{22}N_2$ [M^+] 314.1783, found 314.1783. – $C_{26}H_{26}N_2O$ (314.30): calcd. C 84.15, H 7.06; found C 84.44, H 7.37.

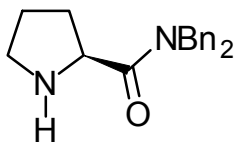
(S)-N,N-Dibenzyl-1-(tert-butoxycarbonyl)-2-pyrrolidinecarboxamide (**189-Boc**): The amide **189-Boc** (2.85 g, 72%) was obtained from *N*-Boc-proline (**188**, 2.15 g, 10.0 mmol), DCC (5.16 g, 25.0 mmol), HOBT (1.35 g, 10.0 mmol) and $HNBn_2$ (4.8 mL, 25.0 mmol) according to GP 10 as a colorless solid.



R_f (Cyclohexane/EtOAc 1 : 1) = 0.42, m. p. 128–131 °C. – $[\alpha]_D^{20}$ = +28.8 (*c* = 1.0, $CHCl_3$). – IR (KBr): ν = 3030 cm^{-1}, 2973, 1684, 1651, 1403, 1164, 706. – ^{1}H-NMR (250 MHz, $CDCl_3$, observed as a major rotamer/minor rotamer ratio of 1.2 : 1): δ = 1.38 [s,

9 H, major, C(CH_3)$_3$], 1.50 [s, 9 H, minor, C(CH_3)$_3$], 1.81–2.04 (m, 4 H, 3,4-H), 3.41–3.66 (m, 2 H, 5-H), 4.40–4.50 (m, 2 H, CH_2Ph), 4.60–4.74 (m, 2 H, CH_2Ph), 4.80–4.89 (m, 1 H, 2-H), 7.20–7.37 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT, observed as a major rotamer/minor rotamer ratio of 1.2 : 1): δ = 23.4 (–, minor, C-4), 24.5 (–, major, C-4), 28.4 [+, minor, C(CH_3)$_3$], 28.5 [+, major, C(CH_3)$_3$], 30.2 (–, major, C-3), 31.5 (–, minor, C-3), 47.0 (–, C-5), 48.8 (–, minor, CH_2Ph), 49.0 (–, major, CH_2Ph), 49.7 (–, minor, CH_2Ph), 50.2 (–, major, CH_2Ph), 56.0 (+, major, C-2), 56.4 (+, minor, C-2), 79.4 [C_{quat}, major, $C(CH_3)_3$], 79.9 [C_{quat}, major, $C(CH_3)_3$], 126.7 (+, 2 C, Ar-C), 126.8 (+, Ar-C), 127.5 (+, Ar-C), 127.9 (+, Ar-C), 128.5 (+, Ar-C), 128.8 (+, 2 C, Ar-C), 128.9 (+, 2 C, Ar-C), 136.5 (C_{quat}, Ar-C), 137.2 (C_{quat}, Ar-C), 155.3 (C_{quat}, C=O), 174.0 (C_{quat}, C=O). – MS (EI, 70 eV), *m/z* (%): 394 (2) [M^+], 303 (21) [$M^+ - C_7H_7$], 170 (36), 114 (100), 91 (83) [$C_7H_7^+$], 70 (96). – $C_{24}H_{30}N_2O_3$ (394.50): calcd. C 73.07, H 7.67; found: C 72.83, H 7.46.

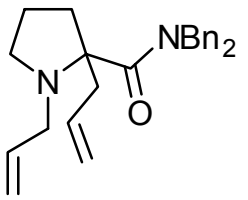
(S)-N,N-Dibenzyl-2-pyrrolidinecarboxamide (**189**): The amine **189** (355 mg, 99%) was obtained from the amide **189-Boc** (501 mg, 1.22 mmol) and TFA (0.50 mL, 6.34 mmol) according to GP 11 as a colorless oil.



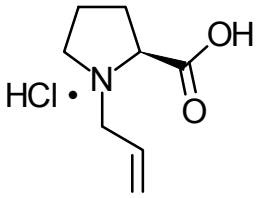
– $[\alpha]_D^{20}$ = –77.0 (*c* = 0.50, $CHCl_3$). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.69–1.84 (m, 3 H, 3,4-H*), 1.98–2.08 (m, 1 H, 3,4-H*), 2.77–2.86 (m, 1 H, 5-H), 2.91 (s, 1 H, NH), 3.19–3.29 (m, 1 H, 5-H), 3.94–3.99 (m, 1 H, 2-H), 4.25 (d, ^2J = 14.8 Hz, 1 H, CH_2Ph), 4.34 (d, ^2J = 23.5 Hz, 1 H, CH_2Ph), 4.58 (d, ^2J = 23.5 Hz, 1 H, CH_2Ph), 4.91 (d, ^2J = 14.8 Hz, 1 H, CH_2Ph), 7.15–7.34 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 26.6 (–, C-4), 31.4 (–, C-3), 47.9 (–, C-5), 48.1 (–, CH_2Ph), 49.1 (–, CH_2Ph), 58.5 (+, C-2), 126.6 (+, 2 C, Ar-C), 127.4 (+, Ar-C), 127.8 (+, Ar-C), 128.1 (+, 2 C,

Ar-C), 128.6 (+, 2 C, Ar-C), 129.0 (+, 2 C, Ar-C), 136.0 (C_{quat}, Ar-C), 137.0 (C_{quat}, Ar-C), 174.8 (C_{quat}, C=O).

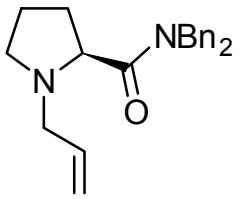
rac-N,N-Dibenzyl-1,2-diallyl-2-pyrrolidinecarboxamide (**191**): Compound **191** (1.32 g, 33%) was obtained from the amine **189** (3.15 g, 10.7 mmol), K_2CO_3 (3.00 g, 21.4 mmol) and allyl bromide (1.40 mL, 16.1 mmol) according to GP 1 as a colorless oil. R_f (hexane/Et_2O 10 : 1) = 0.48. – $[\alpha]_D^{20}$ = 0.0 (*c* = 1.0, $CHCl_3$). – IR (film): ν = 3067 cm^{-1}, 2977, 2812, 1633, 1413, 1190, 916. – ^{1}H-NMR (300 MHz, $C_2D_2Cl_4$ at 100 °C): δ = 1.78–1.84 (m, 2 H, 4-H), 2.03–2.18 (m, 1 H, 3-H), 2.20–2.39 (m, 2 H, 3-H, CC*H*$_2$CH=CH$_2$), 2.61–2.70 (m, 1 H, CC*H*$_2$CH=CH$_2$), 2.90 (dd, ^2J = 13.1, ^3J = 7.3 Hz, 1 H, 5-H), 3.09–3.21 (m, 2 H, 5-H*, NC*H*$_2$CH=CH$_2$), 3.45–3.56 (m, 1 H, NC*H*$_2$CH=CH$_2$*), 4.60 (d, ^2J = 18.5 Hz, 2 H, CH_2Ph), 4.98–5.19 (m, 6 H, CH_2Ph, CCH$_2$CH=C*H*$_2$, NCH$_2$CH=C*H*$_2$), 5.63–5.78 (m, 1 H, NCH$_2$C*H*=CH$_2$), 5.97–6.11 (m, 1 H, NCH$_2$C*H*=CH$_2$), 7.15–7.38 (m, 10 H, Ar-H). – ^{13}C-NMR (75.5 MHz, $C_2D_2Cl_4$ at 100 °C, additional APT): δ = 21.7 (–, C-4), 32.3 (–, C-3), 37.1 (–, C*C*H$_2$CH=CH$_2$), 49.7 (–, N*C*H$_2$CH=CH$_2$), 50.0 (–, CH_2Ph), 51.9 (–, CH_2Ph), 65.2 (C_{quat}, C-2), 115.7 (–, CCH$_2$CH=*C*H$_2$), 116.8 (–, NCH$_2$CH=*C*H$_2$), 126.7 (+, 2 C, Ar-C), 127.2 (+, 4 C, Ar-C), 128.2 (+, 4 C, Ar-C), 136.2 (+, CCH$_2$*C*H=CH$_2$), 136.5 (+, NCH$_2$*C*H=CH$_2$), 137.6 (C_{quat}, 2 C, Ar-C), 174.6 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 374 (<1) [M^+], 150 (100), 91 (14) [$C_7H_7^+$].



(S)-1-Allylproline hydrochloride (**190-OH**)*:* A mixture of L-proline (**192**, 20.0 g, 174 mmol) and KOH (29.2 g, 521 mmol) in *i*PrOH (100 mL) was heated at 40 °C for 30 min, then allyl bromide (18 mL, 208 mmol) was added and the solution stirred at the same temperature for 19 h. HCl (22 mL of a 37% aq. solution) and $CHCl_3$ (100 mL) were added, the mixture stirred for 3 h and then filtered. After removal of the solvent under reduced pressure a yellow solid was obtained and was washed several times with acetone. The hydrochloride **190-OH** (18.3 g, 68%) was obtained as a colorless solid, m. p. 205–209 °C. – $[\alpha]_D^{20} = -60.2$ ($c = 1.0$, MeOH). – IR (KBr): $\nu = 3480\ cm^{-1}$, 3004, 2849, 1734, 1444, 1226, 953. – ^{1}H-NMR (250 MHz, CD_3OD): $\delta = 1.70–2.01$ (m, 3 H, 3,4-H*), 2.24–2.35 (m, 1 H, 3-H*), 2.96–3.08 (m, 1 H, 5-H), 3.42–3.52 (m, 1 H, 5-H), 3.58–3.78 (m, 2 H, C*H*$_2$CH=CH$_2$), 3.94 (dd, $^3J = 6.7$, $^3J = 9.5$ Hz, 1 H, 2-H), 5.26–5.41 (m, 2 H, CH=C*H*$_2$), 5.67–5.84 (m, 1 H, C*H*=CH$_2$). – ^{13}C-NMR (62.9 MHz, CD_3OD, additional DEPT): $\delta = 23.9$ (–, C-4), 29.8 (–, C-3), 55.5 (–, C-5*), 58.3 (–, *C*H$_2$CH=CH$_2$*), 68.1 (+, C-2), 125.8 (–, CH=*C*H$_2$), 128.8 (+, *C*H=CH$_2$), 172.0 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 155 (2) [M^+], 110 (100), 70 (18), 41 (33).

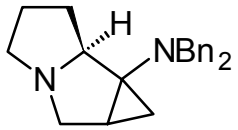


(S)-N,N-Dibenzyl-1-allyl-2-pyrrolidinecarboxamide (**190**): The amide **190** (4.65 g, 89%) was obtained from the acid **190-OH** (3.00 g, 15.6 mmol), DCC (3.40 g, 16.4 mmol), HOBT (2.22 g, 16.4 mmol) and $HNBn_2$ (4.5 mL, 22.8 mmol) according to GP 10 as a colorless oil. R_f (Et_2O) = 0.30. – $[\alpha]_D^{20} = -75.0$ ($c = 1.0$, $CHCl_3$). – IR (film): $\nu = 3030\ cm^{-1}$, 2972, 1651, 1453, 1211, 732. – ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 1.71–1.76$ (m, 1 H, 3-H*), 1.87–2.04 (m, 2 H, 4-H*), 2.25–2.35 (m, 1 H, 3-H*), 3.01 (dd, $^2J = 13.1$, $^3J = 7.3$ Hz, 1 H, 5-H), 3.18–3.25 (m, 1 H,



5-H), 3.34–3.50 (m, 2 H, C*H*$_2$CH=CH$_2$), 4.41–4.49 (m, 4 H, CH$_2$Ph, 2-H) 4.74 (d, ^2J = 14.6 Hz, 1 H, CH$_2$Ph), 4.97–5.16 (m, 2 H, CH=C*H*$_2$), 5.85–5.98 (m, 1 H, C*H*=CH$_2$), 7.12–7.39 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 22.8 (–, C-3*), 29.6 (–, C-4*), 48.1 (–, C-5), 49.0 (–, *C*H$_2$CH=CH$_2$), 53.1 (–, CH$_2$Ph), 57.3 (–, CH$_2$Ph), 63.5 (+, C-2), 116.8 (–, CH=*C*H$_2$), 126.3 (+, 2 C, Ar-C), 127.2 (+, Ar-C), 127.4 (+, Ar-C), 128.3 (+, 2 C, Ar-C), 128.4 (+, 2 C, Ar-C), 128.7 (+, 2 C, Ar-C), 135.8 (+, *C*H=CH$_2$), 136.6 (C$_{quat}$, Ar-C), 137.3 (C$_{quat}$, Ar-C), 173.8 (C$_{quat}$, C=O). – MS (EI, 70 eV), *m*/*z* (%): 334 (2) [M$^+$], 110 (100), 91 (10), 41 (33). – $C_{22}H_{26}N_2O$ (334.20): calcd. C 79.00, H 7.84; found: C 78.89, H 7.64.

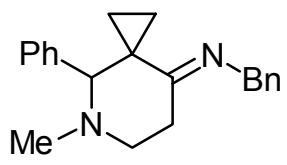
(1aS,6aS,6bR)- and (1aR,6aS,6bS)-N,N-Dibenzyl-perhydrocyclopropa[1,2-a]pyrrolizin-6b-yl-amine (**192**): The amines **192** (224 mg, 70%) were obtained from the amide **190** (334 mg, 1.00 mmol), MeTi(O*i*Pr)$_3$ (370 mg, 1.40 mmol) and *c*HexMgBr (5.0 mL, 5.00 mmol, 1.0 M solution in Et_2O) according to GP 3 in an (1a*S*,6a*S*,6b*R*)-**192**/(1a*R*,6a*S*,6b*S*)-**192** ratio of 3.3 : 1. (1a*R*,6a*S*,6b*S*)-**192**: Colorless oil, R_f (CH_2Cl_2/MeOH 20 : 1) = 0.25. – $[\alpha]_D^{20}$ = –21.6 (*c* = 0.80, $CHCl_3$). – IR (film): ν = 3020 cm^{-1}, 2910, 1465, 1241, 1032. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.59 (ps t, ^2J = 5.3, ^3J = 5.3 Hz, 1 H, *c*Pr-H), 0.94–1.00 (m, 1 H, *c*Pr-H), 1.10–1.17 (m, 1 H, *c*Pr-H), 1.80–1.89 (m, 1 H, 6-H), 2.04–2.50 (m, 4 H, 4,5,6-H), 2.60 (d, ^2J = 12.3 Hz, 1 H, 2-H), 3.40–3.46 (m, 1 H, 2-H), 3.52–3.56 (m, 1 H, 4-H), 3.66 (d, ^2J = 13.3 Hz, 2 H, CH$_2$Ph), 3.83 (d, ^2J = 13.3 Hz, 2 H, CH$_2$Ph), 4.90 (m, 1 H, CHN), 7.15–7.34 (m, 10 H, Ar-H). – ^{13}C-NMR (250 MHz, $CDCl_3$, additional DEPT): δ = 19.3 (–, *c*Pr-C), 27.7 (–, C-5), 29.4 (–, C-6), 30.1 (+, *c*Pr-C), 53.5 (C$_{quat}$, *c*Pr-C), 54.3 (–, C-2), 55.2 (–, C-4), 57.0 (–, 2 C, CH$_2$Ph),



62.4 (+, CHN), 127.1 (+, 2 C, Ar-C), 128.2 (+, 4 C, Ar-C), 128.9 (+, 4 C, Ar-C), 139.4 (C_{quat}, 2 C, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 318 (6) [M^+], 250 (10), 227 (100) [$M^+ – C_7H_7$], 124 (60), 91 (80) [$C_7H_7^+$]. – HRMS (EI) calcd for $C_{22}H_{26}N_2$ [M^+] 318.2096, found 318.2096. – $C_{22}H_{26}N_2$ (318.20): calcd. C 82.97, H 8.23; found: C 82.73, H 8.08. (1a*S*,6a*S*,6b*R*)-**192**: Colorless solid, R_f (CH_2Cl_2/MeOH 20 : 1) = 0.10, m. p. 128–132 °C. – $[\alpha]_D^{20}$ = –40.0 (*c* = 0.25, $CHCl_3$). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.26 (t, ^2J = 4.9, ^3J = 4.9 Hz, 1 H, *c*Pr-H), 0.71–0.80 (m, 1 H, *c*Pr-H), 0.97–1.04 (m, 1 H, *c*Pr-H), 1.57–1.96 (m, 3 H, 5,6-H), 2.12–2.24 (m, 1 H, 5-H), 2.28–2.42 (m, 2 H, 2,4-H), 2.89–3.03 (m, 2 H, 2,4-H), 3.70 (d, ^2J = 13.3 Hz, 2 H, CH_2Ph), 3.79 (d, ^2J = 13.3 Hz, 2 H, CH_2Ph), 4.24 (t, ^2J = 7.3, ^3J = 7.3 Hz, 1 H, CHN), 7.18–7.35 (m, 10 H, Ar-H). – ^{13}C-NMR (250 MHz, $CDCl_3$, additional DEPT): δ = 19.1 (–, *c*Pr-C), 28.0 (–, C-5), 29.8 (–, C-6), 30.5 (+, *c*Pr-C), 54.3 (–, C-2), 55.1 (–, C-4), 57.1 (–, 2 C, CH_2Ph), 57.9 (C_{quat}, *c*Pr-C), 61.4 (+, CHN), 126.8 (+, 2 C, Ar-C), 128.0 (+, 4 C, Ar-C), 128.9 (+, 4 C, Ar-C), 140.1 (C_{quat}, 2 C, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 318 (5) [M^+], 250 (1), 227 (100) [$M^+ – C_7H_7$], 123 (18), 91 (75) [$C_7H_7^+$]. – HRMS (EI) calcd for $C_{22}H_{26}N_2$ [M^+] 318.2096, found 318.2096.

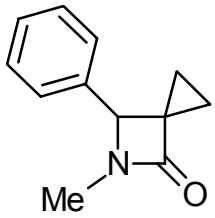
2.12. 1,3-Dipolar cycloadditions of nitrones to bicyclopropylidenes

8-Benzylimino-5-methyl-4-phenyl-5-azaspiro[2.5]octan (**206**): Benzyl amine (1.0 mL, 8.60 mmol) and BF_3 (0.20 mL of a 8.0 M solution in Et_2O, 1.60 mmol) were added to a solution of the tetrahydropiperidone **205** (1.85 g, 8.60 mmol) in benzene (20 mL), in the presence of molecular sieves (3 Å). The mixture was heated at 70 °C for 1 d. The solvent was removed, the residue was purified by column chromatography and the imine **206** (1.31 g, 50%) was



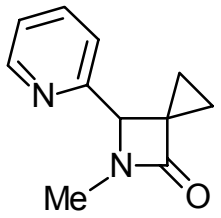
obtained as a colorless oil. R_f (CH_2Cl_2/MeOH 30 : 1) = 0.46. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.41–0.47 (m, 1 H, *c*Pr-H), 0.55–0.61 (m, 1 H, *c*Pr-H), 1.04–1.11 (m, 1 H, *c*Pr-H), 1.15–1.21 (m, 1 H, *c*Pr-H), 2.29 (s, 3 H, NCH_3), 2.68–2.79 (m, 3 H, 6,7-H), 2.96–3.04 (m, 1 H, 6-H), 3.31 (s, 1H, 4-H), 4.57 (s, 2 H, CH_2Ph), 7.38–7.20 (m, 10 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 9.5 (–, *c*Pr-C), 15.3 (–, *c*Pr-C), 28.5 (+, NCH_3), 28.8 (–, C-7), 44.1 (C_{quat}, *c*Pr-C), 50.7 (–, C-6*), 53.6 (–, CH_2Ph*), 73.8 (+, C-4), 126.3 (+, Ar-C), 127.1 (+, Ar-C), 127.4 (+, 2 C, Ar-C), 127.9 (+, 2 C, Ar-C), 128.4 (+, 2 C, Ar-C), 128.7 (+, 2 C, Ar-C), 139.7 (C_{quat}, Ar-C), 140.5 (C_{quat}, Ar-C), 171.4 (C_{quat}, C=N).

5-Methyl-6-phenyl-5-azaspiro[2.3]hexan-4-one (**222**): A solution of the isoxazolidine **220** (150 mg, 700 μmol) and TFA (0.10 mL, 840 μmol) in MeCN (3.0 mL) was heated at 70 °C for 40 min, then K_2CO_3 (140 mg, 1.05 mmol) was added and the mixture was stirred at ambient temperature for 12 h. The mixture was filtrated through a pad of Celite®, the solvent was removed the residue purified by chromatography on silica gel. The β-lactam **222** (128 mg, 98%) was obtained as colorless oil. R_f (CH_2Cl_2/MeOH 30 : 1) = 0.66. – IR (film): ν = 3001 cm^{-1}, 2902, 1751, 1456, 1386, 1172, 1039. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.42 (dt, ^2J = 7.8, ^3J = 7.8, ^3J = 2.6 Hz, 1 H, *c*Pr-H), 1.08–1.18 (m, 2 H, *c*Pr-H), 1.25–1.35 (m, 1 H, *c*Pr-H), 2.86 (s, 3 H, NCH_3), 4.63 (s, 1 H, 6-H), 7.20–7.37 (m, 2 H, Ar-H), 7.38–7.43 (m, 3 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 7.6 (–, *c*Pr-C), 8.6 (–, *c*Pr-C), 27.7 (+, NCH_3), 40.2 (C_{quat}, *c*Pr-C), 64.4 (+, C-6), 127.3 (+, 2 C, Ar-C), 128.9 (+, 3 C, Ar-C), 135.1 (C_{quat}, Ar-C), 175.2 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 187 (59) [M^+], 158 (7) [$M^+ – C_2H_4$],



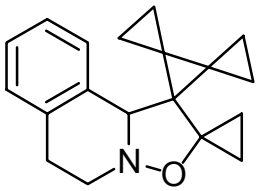
129 (100), 118 (48), 115 (56). – HRMS (EI) calcd. for $C_{12}H_{13}NO$ [M^+] 187.0997, found 187.0997.

5-Methyl-6-(pyrid-2-yl)-5-azaspiro[2.3]hexan-4-one (**223**): A solution of the isoxazolidine **221** (400 mg, 1.85 mmol) and TFA (0.20 mL, 2.22 mmol) in MeCN (5.0 mL) was heated at 70 °C for 40 min, then K_2CO_3 (385 mg, 2.80 mmol) was added and the mixture was stirred at ambient temperature for 12 h. The mixture was filtrated through a pad of Celite®, the solvent was removed the residue purified by chromatography on silica gel. The β-lactam **223** (335 mg, 96%) was obtained as colorless oil. R_f (CH_2Cl_2/MeOH 20 : 1) = 0.38. – IR (film): ν = 3003 cm^{-1}, 2924, 1751 (C=O), 1472, 1291. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.30–0.39 (m, 1 H, *c*Pr-H), 0.98–1.05 (m, 1 H, *c*Pr-H), 1.13–1.31 (m, 2 H, *c*Pr-H), 2.91 (s, 3 H, NCH_3), 4.72 (s, 1 H, 6-H), 7.21–7.27 (m, 1 H, Ar-H), 7.33 (d, ^3J = 7.8 Hz, 1 H, Ar-H), 7.75 (dt, ^3J = 7.8, ^3J = 7.8, ^4J = 1.7 Hz, 1 H, Ar-H), 8.53–8.55 (m, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 6.7 (–, *c*Pr-C), 8.2 (–, *c*Pr-C), 27.8 (+, NCH_3), 40.7 (C_{quat}, *c*Pr-C), 64.7 (+, C-6), 120.6 (+, Ar-C), 123.1 (+, Ar-C), 137.1 (+, Ar-C), 149.5 (+, Ar-C), 157.4 (C_{quat}, Ar-C), 173.0 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 188 (9) [M^+], 159 (54) [$M^+ - C_2H_4$], 145 (16) [$M^+ - CH_3 - C_2H_4$], 130 (100), 119 (19), 78 (27). – $C_{11}H_{12}N_2O$ (188.20): calcd. C 70.20, H 6.43; found: C 70.31, H 6.56.

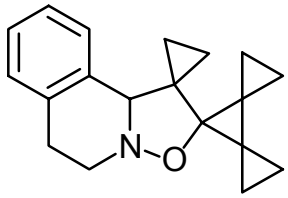


Tetraspiro[cyclopropane-1,1'-cyclopropane-2',1''-cyclopropane-3',1''''-(1'''',5'''',6'''',-10b''''-tetrahydro-2H-isoxazolo[3,2-a]isoquinoline)-1''',2''''-cyclopropane] (**241**) and *tetraspiro-[cyclopropane-1,1''''-(1'''',5'''',6'''',10b''''-tetrahydro-2H-isoxazolo[3,2-a]-isoquinoline)-2',1''-cyclopropane-2'',1'''-cyclopropane-3'',1''''-cyclopropane]* (**242**): A solution of nitrone **240** (206 mg, 1.40 mmol) and alkene **226** (231 mg, 1.75 mmol) in benzene (4.0 mL) was stirred at ambient temperature for 7 d. The solvent was removed and the residue was purified by column chromatography to yield the isoxyzolidines **241** and **242** (281 mg, 72% combined yield) in a **241**/**242** ratio of 1 : 1.1.

241: Colorless solid, R_f (Et_2O/hexane 1 : 1) = 0.55, m.p. 98–101 °C. – IR (KBr): ν = 3106 cm^{-1}, 2982, 2853, 1492, 1454, 1233. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = (–0.39)–(–0.31) (m, 1 H, *c*Pr-H), (–0.02)–0.12 (m, 1 H, *c*Pr-H), 0.26–0.34 (m, 1 H, *c*Pr-H), 0.58–0.91 (m, 7 H, *c*Pr-H), 1.05–1.09 (m, 2 H, *c*Pr-H), 2.77–2.84 (m, 1 H, 6''''-H), 3.04–3.26 (m, 3 H, 5'''',6''''-H), 4.84 (s, 1 H, 10b''''-H), 7.06–7.17 (m, 4 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 2.0 (–, *c*Pr-C), 3.7 (–, *c*Pr-C), 3.8 (–, *c*Pr-C), 4.0 (–, *c*Pr-C), 4.1 (–, *c*Pr-C), 8.1 (–, *c*Pr-C), 17.9 (C_{quat}, *c*Pr-C), 18.6 (C_{quat}, *c*Pr-C), 28.9 (–, C-6''''), 33.8 (C_{quat}, *c*Pr-C), 49.5 (–, C-5''''), 66.4 (C_{quat}, *c*Pr-C), 68.0 (+, C-10b''''), 125.4 (+, Ar-C), 126.7 (+, Ar-C), 127.6 (+, Ar-C), 128.3 (+, Ar-C), 132.6 (C_{quat}, Ar-C), 133.8 (C_{quat}, Ar-C). – MS (EI, 70 eV), *m*/*z* (%): 279 (53) [M^+], 278 (18) [M^+ – H], 250 (68), 222 (84), 130 (76), 91 (100). – HRMS (EI) calcd. for $C_{19}H_{21}NO$ [M^+] 279.1623, found 279.1623. – $C_{19}H_{21}NO$ (279.20): calcd. C 81.73, H 7.58; found C 81.63, H 7.33.



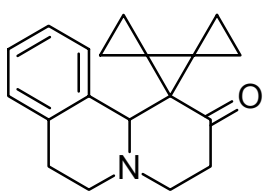
242: Colorless oil, R_f (Et_2O/hexane 1 : 1) = 0.45. – IR (film): ν = 3066 cm^{-1}, 2982, 2852, 1494, 1339, 1008. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = (–0.03)–0.11 (m, 1 H, *c*Pr-H), 0.61–0.96 (m, 11 H, *c*Pr-H), 2.84–2.91 (m, 1 H, 6''''-H), 3.08–3.22 (m, 3 H, 5'''',6''''-H), 4.62 (s, 1 H, 10b''''-H), 6.79–6.82 (m, 1 H, Ar-H), 7.06–7.17 (m, 3 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 2.4 (–, *c*Pr-C), 3.8 (–, *c*Pr-C), 4.7 (–, *c*Pr-C), 5.3 (–, *c*Pr-C), 5.4 (–, *c*Pr-C), 5.5 (–, *c*Pr-C), 17.4 (C_{quat}, *c*Pr-C), 18.8 (C_{quat}, *c*Pr-C), 28.5 (–, C-6''''), 29.9 (C_{quat}, *c*Pr-C), 49.3 (–, C-5''''), 67.6 (+, C-10b''''), 70.6 (C_{quat}, *c*Pr-C), 125.9 (+, Ar-C), 126.0 (+, Ar-C), 127.1 (+, Ar-C), 128.4 (+, Ar-C), 131.9 (C_{quat}, Ar-C), 132.6 (C_{quat}, Ar-C). – $C_{19}H_{21}NO$ (279.20): calcd. C 81.73, H 7.58, N 5.02; found C 81.60, H 7.74, N 5.16.



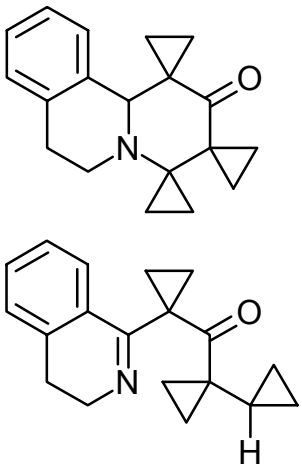
Trispiro[cyclopropane-1,1'-cyclopropane-3',1''-cyclopropane-2',1'''-(1''',3''',4''',6''',7''',11b'''-hexahydro-2H-pyrido[2,1-a]isoquinoline)]-2'''-one (**243**), *trispiro[triscyclopropane-1,1''':1',3''':1'',4'''-(1''',3''',4''',6''',7''',11b'''-hexahydro-2H-pyrido[2,1-a]isoquinoline)]-2-one* (**244**) and *1-cyclopropylcyclopropyl-1-(3,4-dihydro-1-isoquinolinyl)-1-cyclopropylmethanone* (**245**): Compounds **243**, **244** and **245** (298 mg, 71% combined yield) were obtained from nitrone **240** (221 mg, 1.28 mmol) and alkene **226** (248 mg, 1.88 mmol) according to GP 13 in a **243**/**244**/**245** ratio of 2.7 : 1 : 3.

Alternatively, compound **243** (20 mg, 80%) was prepared by heating the isoxazolidine **241** (25.0 mg, 89.0 μmol) in *p*-xylene (1.0 mL) at 140 °C for 5 h. Compounds **244** and **245** (20 mg, 77% combined yield) were obtained as inseparable mixture from the isoxazolidine **242** in a **244**/**245** ratio of 1 : 3, following the same procedure.

243: Colorless solid, R_f (EtOAc/hexane 5 : 1) = 0.42, m.p. 122–124 °C. – IR (KBr): ν = 3093 cm^{-1}, 2983, 2865, 1713, 1485, 1263, 1121. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.48–0.56 (m, 1 H, *c*Pr-H), 0.67–0.98 (m, 4 H, *c*Pr-H), 1.00–1.06 (m, 1 H, *c*Pr-H), 1.39–1.52 (m, 2 H, *c*Pr-H), 2.20–2.36 (m, 2 H, 7'''-H), 2.67–3.09 (m, 5 H, 3''',4''',6'''-H), 3.40–3.53 (m, 1 H, 4'''-H), 4.04 (s, 1 H, 11b'''-H), 6.61 (d, ^3J = 7.2 Hz, 1 H, Ar-H), 7.08–7.20 (m, 3 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 3.8 (–, *c*Pr-C), 4.2 (–, *c*Pr-C), 4.4 (–, *c*Pr-C), 4.6 (–, *c*Pr-C), 22.8 (C_{quat}, *c*Pr-C), 24.6 (–, C-7'''), 30.3 (C_{quat}, *c*Pr-C), 37.7 (C_{quat}, *c*Pr-C), 40.7 (–, C-3'''*), 46.0 (–, C-4'''*), 49.9 (–, C-6'''*), 64.4 (+, C-11b'''*), 126.1 (+, Ar-C), 126.7 (+, Ar-C), 126.9 (+, Ar-C), 128.6 (+, Ar-C), 134.7 (C_{quat}, Ar-C), 135.4 (C_{quat}, Ar-C), 207.4 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 279 (100) [M$^+$], 278 (48) [M$^+$ – H], 250 (25), 158 (83), 145 (40), 132 (37), 105 (23).



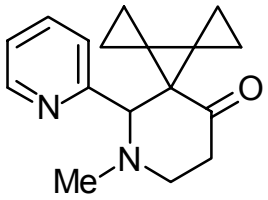
244 and **245**: Colorless oil, R_f (EtOAc/hexane 5 : 1) = 0.29. – IR (film): ν = 3070 cm^{-1}, 3005, 2938, 2898, 1673, 1618, 1334, 1062, 1018. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = (–0.38)–(–0.32) (m, 1 H, *c*Pr-H of **244**), (–0.18)–(–0.12) (m, 2 H, *c*Pr-H of **245**), (–0.02)–0.04 (m, 1 H, *c*Pr-H of **244**), 0.22–1.53 (m, *c*Pr-H), 2.69–2.74 (m, 2 H, 4'''-H of **245**), 3.06–3.24 (m, 4 H, 6''',7'''-H of **244**), 3.63–3.69 (m, 2 H, 3'''-H of **245**), 4.82 (s, 1 H, 11b'''-H of **244**), 7.04–7.53 (m, 8 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 2.0 (–, *c*Pr-C), 3.7 (–, *c*Pr-C), 4.2 (–, 3 C, *c*Pr-C), 8.1 (–, *c*Pr-C), 11.9 (+, *c*Pr-C of **245**), 14.3 (–, 3 C, *c*Pr-C), 14.5 (–, 3 C, *c*Pr-C), 17.8 (C_{quat}, *c*Pr-C), 18.6 (C_{quat}, *c*Pr-C), 25.8 (–, C-7'''), 28.9 (–, C-7'''), 33.1 (C_{quat}, *c*Pr-C), 37.7 (C_{quat}, *c*Pr-C), 47.1 (–, C-6'''), 49.5 (–, C-6'''), 66.4 (+, C-1 of **244**), 67.9 (C_{quat}, *c*Pr-C), 125.4 (+, Ar-C), 125.9 (+, Ar-C), 126.7 (+, Ar-C), 126.9 (+, Ar-C), 127.4 (+, Ar-C), 127.6 (+,



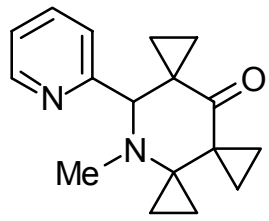
Ar-C), 128.3 (+, Ar-C), 129.7 (C_{quat}, Ar-C), 130.6 (+, Ar-C), 132.5 (C_{quat}, Ar-C), 133.8 (C_{quat}, Ar-C), 137.5 (C_{quat}, Ar-C), 165.2 (C_{quat}, C=N), 207.4 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 279 (16) [M^+], 278 (22) [$M^+ - H$], 250 (100), 222 (14), 170 (14), 115 (6). – HRMS (EI) calcd. for $C_{19}H_{21}NO$ [M^+] 279.1623, found 279.1623. – $C_{19}H_{21}NO$ (279.20): calcd. C 81.73, H 7.58; found C 81.83, H 7.75.

9-Methyl-8-(pyrid-2-yl)-9-azatrispiro[2.0.2^4.0.5^7.0^3]dodecan-12-one (**247**) and *12-methyl-11-(pyrid-2-yl)-12-azatrispiro[2.0.2^4.1.2^8.2^3]dodecan-7-one* (**248**): Compounds **247** and **248** (111 mg, 68% combined yield) were obtained from nitrone **246** (82.3 mg, 610 μmol) and alkene **226** (100 mg, 760 μmol) according to GP 13 in a **247**/**248** ratio of 1 : 3.7.

247: Colorless oil, R_f (CH_2Cl_2/MeOH 20 : 1) = 0.32. – IR (film): ν = 3070 cm^{-1}, 2926, 2804, 1700, 1589, 1435, 1274. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = (–0.40)–(–0.33) (m, 1 H, *c*Pr-H), 0.20–0.28 (m, 1 H, *c*Pr-H), 0.69–0.74 (m, 1 H, *c*Pr-H), 0.79–0.99 (m, 4 H, *c*Pr-H), 1.24–1.33 (m, 1 H, *c*Pr-H), 2.37 (s, 3 H, NCH_3), 2.45–2.71 (m, 3 H, 10,11-H), 2.77–2.82 (m, 1 H, 10-H), 3.88 (s, 1 H, 8-H), 7.05 (d, ^3J = 7.5 Hz, 1 H, Ar-H), 7.11–7.16 (m, 1 H, Ar-H), 7.57–7.64 (m, 1 H, Ar-H), 8.51–8.53 (m, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 2.2 (–, *c*Pr-C), 4.5 (–, *c*Pr-C), 4.9 (–, *c*Pr-C), 5.3 (–, *c*Pr-C), 22.9 (C_{quat}, *c*Pr-C), 33.5 (C_{quat}, *c*Pr-C), 36.9 (C_{quat}, *c*Pr-C), 39.5 (–, C-11), 43.1 (+, NCH_3), 46.8 (–, C-10), 71.5 (+, C-8), 121.8 (+, Ar-C), 123.5 (+, Ar-C), 135.4 (+, Ar-C), 148.8 (+, Ar-C), 157.0 (C_{quat}, Ar-C), 207.4 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 268 (24) [M^+], 267 (50) [$M^+ - H$], 253 (51), 226 (87), 212 (88), 190 (66), 184 (94), 182 (100), 168 (56), 154 (45), 106 (40), 79 (34). – HRMS (EI) calcd. for $C_{17}H_{20}N_2O$ [M^+] 268.1576, found 268.1576 (HRMS).

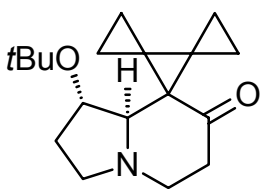


248: Colorless oil, R_f (CH_2Cl_2/MeOH 20 : 1) = 0.49. – IR (film): ν = 3068 cm^{-1}, 2924, 1700, 1579, 1430, 1270. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = (–0.49)–(–0.43) (m, 1 H, *c*Pr-H), (–0.17)–(–0.09) (m, 1 H, *c*Pr-H), (–0.04)–0.16 (m, 2 H, *c*Pr-H), 0.28–0.47 (m, 2 H, *c*Pr-H), 0.95–1.02 (m, 1 H, *c*Pr-H), 1.12–1.30 (m, 3 H, *c*Pr-H), 1.45–1.53 (m, 1 H, *c*Pr-H), 1.73–1.81 (m, 1 H, *c*Pr-H), 2.93 (s, 3 H, NCH_3), 3.86 (s, 1 H, 11-H), 7.13–7.18 (m, 1 H, Ar-H), 7.29–7.33 (m, 1 H, Ar-H), 7.61 (dt, ^3J = 7.7, ^3J = 7.7, ^4J = 1.7 Hz, 1 H, Ar-H), 8.64–8.71 (m, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 6.4 (–, *c*Pr-C), 7.6 (–, *c*Pr-C), 10.7 (–, *c*Pr-C), 17.6 (–, *c*Pr-C), 22.9 (–, *c*Pr-C), 25.7 (–, *c*Pr-C), 25.9 (C_{quat}, *c*Pr-C), 28.5 (C_{quat}, *c*Pr-C), 41.1 (C_{quat}, *c*Pr-C), 41.3 (+, NCH_3), 73.2 (+, C-11), 122.0 (+, Ar-C), 135.7 (+, Ar-C), 149.0 (+, Ar-C), 158.0 (+, Ar-C), 161.2 (C_{quat}, Ar-C), 211.2 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 268 (64) [M^+], 267 (58) [M^+ – H], 253 (47), 239 (90), 200 (22), 190 (100), 174 (17), 130 (33), 117 (14). – HRMS (EI) calcd. for $C_{17}H_{20}N_2O$ [M^+] 268.1576, found 268.1576.

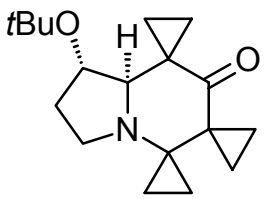


(1'''S,8a'''R)-1'''-tert-Butoxytrispiro[cyclopropane-1,1'-cyclopropane-2',1''-cyclopropane-3',8'''-perhydroindolizine]-7'''-one [**(**1'''*S*,8a'''*R***)-250**] and *(1'''S,8a'''R)-1'''-tert-Butoxytrispiro[triscyclopropane-1,5''':1',6''':1'',8'''-perhydroindolizine]-7'''-one* [**(**1'''*S*,8a'''*R***)-251**]: Compounds **250** and **251** (135 mg, 77% combined yield) were obtained from nitrone **249** (96.0 mg, 610 μmol) and alkene **226** (100 mg, 760 μmol) according to GP 13 in a **250**/**251** ratio of 1.6 : 1.

(1'''*S*,8a'''*R***)-250**: Colorless oil, R_f (CH_2Cl_2/MeOH 20 : 1) = 0.28, $[\alpha]_D^{20}$ = +28.4 (*c* = 0.50, $CHCl_3$). – IR (film):ν = 3065 cm^{-1}, 2976, 2798, 1700, 1473, 1362, 1192, 1046. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.62–0.93 (m, 5 H, *c*Pr-H), 0.98–1.29 (m, 3 H, *c*Pr-H), 1.21 [s, 9 H, $C(CH_3)_3$], 1.76–1.88 (m, 1 H, 2'''-H), 1.96–2.11 (m, 1 H, 2'''-H), 2.29–2.39 (m, 2 H, 6'''-H), 2.61–2.72 (m, 2 H, 3''',5'''-H), 2.82–2.90 (m, 2 H, 8a''',3'''-H), 3.04–3.12 (m, 1 H, 5'''-H), 4.27–4.33 (m, 1 H, 1'''-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 4.1 (–, *c*Pr-C), 5.5 (–, *c*Pr-C), 6.0 (–, *c*Pr-C), 6.9 (–, *c*Pr-C), 23.7 (C_{quat}, *c*Pr-C), 27.6 (C_{quat}, *c*Pr-C), 29.2 [+, 3 C, $C(CH_3)_3$], 34.5 (–, C-2'''). 38.2 (C_{quat}, *c*Pr-C), 39.3 (–, C-6'''), 48.8 (–, C-5'''), 52.3 (–, C-3'''), 70.9 (+, C-8a'''), 72.9 (+, C-1'''), 73.6 [C_{quat}, $C(CH_3)_3$], 208.3 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 289 (3) [M^+], 232 (100) [$M^+ - C_4H_9$], 190 (5), 147 (5), 105 (6), 57 (14) [$C_4H_9^+$]. – HRMS (EI) calcd. for $C_{18}H_{27}NO_2$ [M^+] 289.2042, found 289.2042. – $C_{18}H_{27}NO_2$ (289.20): calcd. C 74.75, H 9.41, N 4.84; found C 74.62, H 9.23, N 4.35.

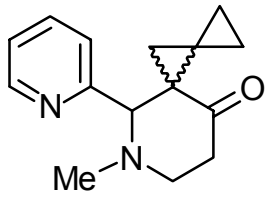


(1'''*S*,8a'''*R***)-251**: Colorless oil, R_f (CH_2Cl_2/MeOH 20 : 1) = 0.50, $[\alpha]_D^{20}$ = –96.0 (*c* = 0.50, $CHCl_3$). – IR (film): ν = 3067 cm^{-1}, 2973, 2929, 1700, 1457, 1363, 1088. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.10–0.19 (m, 1 H, *c*Pr-H), 0.49–0.57 (m, 1 H, *c*Pr-H), 0.61–0.70 (m, 1 H, *c*Pr-H), 0.81–0.90 (m, 4 H, *c*Pr-H), 1.03–1.30 (m, 4 H, *c*Pr-H), 1.22 [s, 9 H, $C(CH_3)_3$], 1.42–1.46 (m, 1 H, *c*Pr-H), 1.58–1.73 (m, 1 H, 2'''-H), 1.96–2.07 (m, 1 H, 2'''-H), 2.85 (d, ^3J = 6.8 Hz, 1 H, 8a'''-H), 2.91–2.99 (m, 1 H, 3'''-H), 3.11–3.21 (m, 1 H, 3'''-H), 3.80–3.89 (m, 1 H, 1'''-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 6.8 (–, *c*Pr-C), 8.0 (–, *c*Pr-C), 10.4 (–, *c*Pr-C), 14.9 (–, *c*Pr-C), 19.1 (–, *c*Pr-C), 20.1 (–, *c*Pr-C), 28.8 [+, 3 C, $C(CH_3)_3$], 30.3 (C_{quat}, *c*Pr-C), 30.9 (C_{quat}, *c*Pr-C), 33.8 (–, C-2'''). 40.4 (C_{quat}, *c*Pr-C), 47.8 (–, C-3'''), 69.9 (+, C-8a'''), 73.9



[C_{quat}, $C(CH_3)_3$], 77.3 (+, C-1'''), 211.1 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 289 (45) [M^+], 232 (98) [$M^+ - C_4H_9$], 204 (71), 100 (33), 57 (100) [$C_4H_9^+$]. – HRMS (EI) calcd. for $C_{18}H_{27}NO_2$ [M^+] 289.2042, found 289.2042.

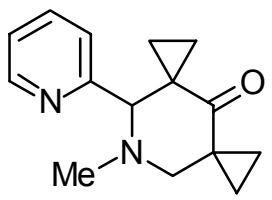
cis- and *trans-7-Methyl-6-(pyrid-2-yl)-7-azatrispiro[2.1.5^5]decan-10-one* (**252**) and *5-Methyl-4-(pyrid-2-yl)-5-azadispiro[2.1.2.3^3]decan-10-one* **(253)**: Compounds **252** and **253** (129 mg, 72% combined yield) were obtained from nitrone **225** (100 mg, 740 µmol) and alkene **246** (98.0 mg, 920 µmol) according to GP 13 in a *trans*-**252**/*cis*-**252**/**253** ratio of 1.3 : 1.3 : 1. *trans*-**252**: Colorless oil, R_f (CH_2Cl_2/MeOH 30 : 1) = 0.53. – IR (film): ν = 3068 cm^{-1}, 2925, 2850, 1700, 1588, 1435, 1276, 1064. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.74–0.93 (m, 4 H, *c*Pr-H), 1.15–1.24 (m, 2 H, *c*Pr-H), 2.32 (s, 3 H, NCH_3), 2.38–2.44 (m, 1 H, 8-H), 2.55–2.73 (m, 2 H, 7,8-H), 2.89–2.99 (m, 1 H, 7-H), 3.67 (s, 1 H, 5-H), 7.10–7.19 (m, 2 H, Ar-H), 7.63 (dt, ^3J = 7.6, ^3J = 7.6, ^4J = 1.8 Hz, 1 H, Ar-H), 8.57–8.59 (m, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 5.3 (–, *c*Pr-C), 5.6 (–, *c*Pr-C), 16.2 (–, *c*Pr-C), 30.7 (C_{quat}, *c*Pr-C), 36.3 (C_{quat}, *c*Pr-C), 39.5 (–, C-8), 43.4 (+, NCH_3), 47.6 (–, C-7), 72.3 (+, C-5), 122.0 (+, Ar-C), 123.4 (+, Ar-C), 135.8 (+, Ar-C), 149.0 (+, Ar-C), 157.8 (C_{quat}, Ar-C), 207.4 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 242 (7) [M^+], 242 (17) [M^+ – H], 227 (22) [$M^+ - CH_3$], 212 (98), 185 (58), 164 (57) [$M^+ - C_5H_4N$], 158 (100), 124 (70), 78 (19) [$C_5H_4N^+$]. – HRMS (EI) calcd. for $C_{15}H_{17}N_2O$ [M^+ – H] 241.1341, found 241.1341.



cis-**252**: Colorless oil, R_f (CH_2Cl_2/MeOH 30 : 1) = 0.32. – IR (film): ν = 3074 cm^{-1}, 3001, 2933, 1676, 1588, 1435, 1074. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.30–0.39 (m, 1 H, *c*Pr-H), 0.62–0.74 (m, 1 H, *c*Pr-H), 0.80–1.19 (m, 2 H, *c*Pr-H), 1.38–1.59 (m, 2 H, *c*Pr-H),

2.38 (s, 3 H, NCH_3), 2.50 (d, ^2J = 10.0 Hz, 1 H, 8-H), 2.97 (d, ^2J = 10.1 Hz, 1 H, 8-H), 3.40–3.49 (m, 1 H, 7-H), 3.62 (d, ^2J = 14.0 Hz, 1 H, 7-H), 3.91 (s, 1 H, 5-H), 7.12–7.20 (m, 2 H, Ar-H), 7.52–7.61 (m, 1 H, Ar-H), 8.55–8.62 (m, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 12.4 (–, *c*Pr-C), 15.1 (–, *c*Pr-C), 23.0 (–, *c*Pr-C), 27.1 (C_{quat}, *c*Pr-C), 30.6 (C_{quat}, *c*Pr-C), 43.8 (+, NCH_3), 47.0 (–, C-8), 57.2 (–, C-7), 73.9 (+, C-5), 123.4 (+, Ar-C), 123.6 (+, Ar-C), 135.8 (+, Ar-C), 148.9 (+, Ar-C), 157.9 (C_{quat}, Ar-C), 207.9 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 242 (16) [M^+], 227 (18) [$M^+ - CH_3$], 214 (100) [$M^+ - C_2H_4$], 172 (51), 164 (78) [$M^+ - C_5H_4N$], 136 (50), 78 (35) [$C_5H_4N^+$]. – HRMS (EI) calcd. for $C_{15}H_{18}N_2O$ [M^+] 242.1419, found 242.1419. – $C_{15}H_{18}N_2O$ (242.20): calcd. C 74.39, H 7.49; found C 74.46, H 7.45.

253: Colorless oil, R_f (CH_2Cl_2/MeOH 30 : 1) = 0.41. – IR (film): ν = 3079 cm^{-1}, 3001, 2925, 1675, 1589, 1436, 1387, 1073. – ^{1}H-NMR (250 MHz, $CDCl_3$):

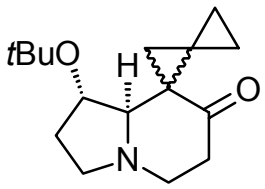


δ = 0.33–0.41 (m, 1 H, *c*Pr-H), 0.65–0.72 (m, 1 H, *c*Pr-H), 0.81–0.94 (m, 2 H, *c*Pr-H), 1.03–1.27 (m, 2 H, *c*Pr-H), 1.47–1.61 (m, 2 H, *c*Pr-H), 2.42 (s, 3 H, NCH_3), 2.53 (d, ^2J = 12.4 Hz, 1 H, 10-H), 2.98 (d, ^2J = 12.4 Hz, 1 H, 10-H), 3.62 (s, 1 H, 8-H), 7.15–7.21 (m, 2 H, Ar-H), 7.66 (dt, ^3J = 7.7, ^3J = 7.7, ^4J = 1.8 Hz, 1 H, Ar-H), 8.57–8.60 (m, 1 H, Ar-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 12.5 (–, *c*Pr-C), 15.2 (–, *c*Pr-C), 22.5 (–, *c*Pr-C), 23.1 (–, *c*Pr-C), 29.6 (C_{quat}, *c*Pr-C), 30.7 (C_{quat}, *c*Pr-C), 43.8 (+, NCH_3), 57.3 (–, C-10), 74.0 (+, C-8), 122.2 (+, Ar-C), 123.5 (+, Ar-C), 135.9 (+, Ar-C), 149.0 (+, Ar-C), 158.0 (C_{quat}, Ar-C), 209.5 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 242 (11) [M^+], 214 (100) [$M^+ - C_2H_4$], 185 (22), 172 (62), 164 (75) [$M^+ - C_5H_4N$], 136 (40), 78 (20) [$C_5H_4N^+$]. – HRMS (EI) calcd. for $C_{15}H_{18}N_2O$ [M^+] 242.1419,

found 242.1419. – $C_{15}H_{18}N_2O$ (242.20): calcd. C 74.39, H 7.49, N 11.57; found C 74.19, H 7.68, N 11.51.

cis-(1"S,8a"R)- and *trans-(1"S,8a"R)-1"-tert-Butoxydispiro[cyclopropane-1,1'-cyclopropane-2',8"-perhydroindo-lizine]-7"-one* [*cis-* and *trans-***254]** and *(1"S,8a"R)-1"-tert-Butoxydispiro-[biscyclopropane-1,6":1',8"-perhydroindolizine]-7"-one* [**(**1"'*S*,8a"'*R***)-255**]: Compounds **254** and **255** (128 mg, 80% combined yield) were obtained from nitrone **249** (100 mg, 610 μmol) and alkene **225** (81.0 mg, 760 μmol) according to GP 13 in a *trans-***254***/**255**/*cis-***254*** ratio of 2 : 1.5 : 1.

*trans-***254***: Colorless oil, R_f (CH_2Cl_2/MeOH 30 : 1) = 0.27. – $[\alpha]_D^{20}$ = –22.0 (*c* = 0.50, $CHCl_3$). – IR (film): ν = 3066 cm^{-1}, 2974, 1717, 1365, 1191, 1113. –

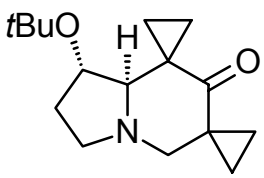


^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.67–0.74 (m, 1 H, *c*Pr-H), 0.79–0.96 (m, 3 H, *c*Pr-H), 1.02–1.07 (m, 1 H, *c*Pr-H), 1.17 [s, 9 H, $C(CH_3)_3$], 1.62 (d, ^3J = 3.8 Hz, 1 H, 2"-H), 1.66–1.77 (m, 1 H, *c*Pr-H), 1.86 (d, ^3J = 3.9 Hz, 1 H, 2"-H), 2.13–2.31 (m, 2 H, 6"-H), 2.46–2.59 (m, 1 H, 3"-H*), 2.66–2.76 (m, 2 H, 3",5"-H*), 2.90–3.01 (m, 2 H, 8a",5"-H*), 3.87–3.97 (m, 1 H, 1"-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 5.7 (–, *c*Pr-C), 6.0 (–, *c*Pr-C), 16.6 (–, *c*Pr-C), 27.7 (C_{quat}, *c*Pr-C), 28.8 [+, 3 C, $C(CH_3)_3$], 33.4 (–, C-2"). 35.0 (C_{quat}, *c*Pr-C), 38.0 (–, C-6"), 47.6 (–, C-3"*), 53.4 (–, C-5"*), 69.2 (+, C-8a"), 73.9 [C_{quat}, $C(CH_3)_3$], 75.5 (+, C-1"), 208.5 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 263 (3) [M^+], 240 (2), 206 (100) [$M^+ - C_4H_9$], 166 (15), 57 (10) [$C_4H_9^+$]. – HRMS (EI) calcd. for $C_{16}H_{25}NO_2$ [M^+] 263.1885, found 263.1885.

*cis-***254***: Colorless oil, R_f (CH_2Cl_2/MeOH 30 : 1) = 0.47. – $[\alpha]_D^{20}$ = +35.4 (*c* = 0.50, $CHCl_3$). – IR (film): ν = 3058 cm^{-1}, 2978, 1716, 1356, 1190, 1109. – ^{1}H-NMR (250 MHz, $CDCl_3$):

δ = 0.47–0.53 (m, 1 H, *c*Pr-H), 0.65–0.73 (m, 1 H, *c*Pr-H), 1.03–1.11 (m, 1 H, *c*Pr-H), 1.18 [s, 9 H, $C(CH_3)_3$], 1.21–1.29 (m, 2 H, *c*Pr-H), 1.43 (d, ^3J = 3.7 Hz, 1 H, 2"-H), 1.69–1.75 (m, 1 H, *c*Pr-H), 1.92 (d, ^3J = 3.7 Hz,, 1 H, 2"-H), 2.07–2.36 (m, 2 H, 6"-H), 2.40–2.54 (m, 2 H, 3"-H*), 2.74 (d, ^3J = 6.9 Hz, 1 H, 5"-H*), 2.96–3.03 (m, 1 H, 5"-H*), 3.14–3.22 (m, 1 H, 8a"-H), 4.24 (dt, ^3J = 3.0, ^3J = 8.4, ^3J = 8.4 Hz, 1 H, 1"-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 3.6 (–, *c*Pr-C), 6.9 (–, *c*Pr-C), 13.4 (–, *c*Pr-C), 25.1 (C_{quat}, *c*Pr-C), 29.1 [+, 3 C, $C(CH_3)_3$], 34.4 (–, C-2"). 35.9 (C_{quat}, *c*Pr-C), 40.2 (–, C-6"), 50.6 (–, C-3"*), 53.1 (–, C-5"*), 71.3 (+, 2 C, 1",8a"-C), 74.2 [C_{quat}, $C(CH_3)_3$], 209.5 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 263 (1) [M^+], 240 (2), 206 (100) [$M^+ - C_4H_9$], 57 (6) [$C_4H_9^+$]. – HRMS (EI) calcd. for $C_{16}H_{25}NO_2$ [M^+] 263.1885, found 263.1885.

(1"*S*,8a"*R*)**-255**: Colorless oil R_f (CH_2Cl_2/MeOH 30 : 1) = 0.37. – $[\alpha]_D^{20}$ = +12.0 (*c* = 1.0, $CHCl_3$). – IR (film): ν = 3062 cm^{-1}, 2973, 2803, 1700, 1457, 1364, 1192. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.61–0.69 (m, 1 H, *c*Pr-H), 0.86–1.15 (m, 4 H, *c*Pr-H), 1.17 [s, 9 H, $C(CH_3)_3$], 1.19–1.54 (m, 3 H, *c*Pr-H), 1.62–1.73 (m, 1 H, 2"-H), 2.15–2.27 (m, 1 H, 2"-H), 2.42–2.53 (m, 1 H, 3"-H), 2.63 (d, ^2J = 11.5 Hz, 1 H, 5"-H), 2.81 (d, ^3J = 7.6 Hz, 1 H, 3"-H), 2.98 (d, ^2J = 11.5 Hz, 1 H, 5"-H), 3.11 (dt, ^3J = 8.8, ^3J = 8.8, ^4J = 2.6 Hz, 1 H, 8a"-H), 3.86 (dt, ^3J = 4.5, ^3J = 8.2, ^3J = 8.2 Hz, 1 H, 1"-H). – ^{13}C-NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 13.4 (–, *c*Pr-C), 13.9 (–, *c*Pr-C), 17.3 (–, *c*Pr-C), 24.7 (–, *c*Pr-C), 27.3 (C_{quat}, *c*Pr-C), 28.8 [+, 3 C, $C(CH_3)_3$], 31.2 (C_{quat}, *c*Pr-C), 33.2 (–, C-2"). 53.3 (–, C-3"*), 59.6 (–, C-5"*), 70.1 (+, C-8a"), 74.2 (+, C-1"), 77.2 [C_{quat}, $C(CH_3)_3$], 212.0 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 263 (3) [M^+], 206 (100) [$M^+ - C_4H_9$], 190 (3), 163 (6), 57 (5) [$C_4H_9^+$]. – HRMS (EI) calcd. for $C_{16}H_{25}NO_2$ [M^+] 263.1885, found 263.1885.



D. SUMMARY

In the first part of this project the Ti-mediated intramolecular reductive cyclopropanations of 2-allylamino-*N*,*N*-dialkylpropionamides were investigated towards the synthesis of 1-amino-3-azabicyclo[3.1.0]hexane and 1-amino-3-azabicyclo[4.1.0]heptane derivatives. The *N*,*N*-dialkylamides **54** and **57** were prepared starting from the natural amino acid L-serine. Such amides underwent the Ti-mediated intramolecular reductive cyclopropanation in the presence of $MeTi(OiPr)_3$ (1.50 equiv) and *c*HexMgBr (5.00 equiv) to yield a mixture of *endo*- and *exo*-(2*R*)-*N*,*N*-dialkyl-3-benzyl-2-(*tert*-butyldimethylsilyloxymethyl)-3-azabicyclo[3.1.0]hex-1-ylamines **58** and **59** in an *endo*-**58**/*exo*-**58** ratio of 2 : 1 and an *endo*-**59**/*exo*-**59** ratio of 2.5 : 1. The *N*,*N*-dialkylpropionamides **70**–**75** were synthesized from bromoacetyl bromide, and their intramolecular cyclopropanations gave the *N*,*N*,3-trialkyl-3-azabicyclo[3.1.0]hex-1-ylamines **76**–**78**, **80** and *N*,*N*,3-tribenzyl-3-azabicyclo[4.1.0]hept-1-ylamine (**79**). The unprotected diamine hydrochlorides **28**-**HCl**, **29**-**HCl** and the partially unprotected diamines **82**-**HCl**, **83**-**HCl** and **84** were obtained from the corresponding amines **76**–**80** by catalytic hydrogenation in isopropanol solution in the presence of hydrogen chloride. The synthesis of such bicyclic diamines with a protected secondary and an unprotected primary amino group was achieved by Ti-mediated intramolecular reductive cyclopropanation of carbonitriles **86**–**88** by treatment with $MeTi(OiPr)_3$ (1.10 equiv) and *c*HexMgBr (2.00 equiv) in the presence of LiI (2.0 equiv) as Lewis acid at 70 °C. Compounds **84**, **90** and **91** were obtained in yields ranging from 41 to 48%. Attempted syntheses of azabicyclo[4.1.0]heptane derivatives starting from *N*-allyl-*N*-benzyl-3-aminopropionitrile and *N*-homoallyl-*N*-benzyl-2-amino-acetonitrile failed. Products **98** and **99** resulting from the hydrolysis of the intermediate azatitanacyclopentenes **96** and **97** could be isolated, and only traces of the azabicyclo[4.1.0]heptane derivatives were obtained.

The possibility of preparing a library of 3-aryl-3-azabicyclo[3.1.0]hex-1-ylamines and 1-aryl-3-azabicyclo[3.1.0]hex-1-ylamines on the basis of the diamine hydrochlorides **28**-**HCl**, **82**-**HCl** and **83**-**HCl** has been studied. The combination of an aza-heteroaromatic substituent and the rigid 3-azabicyclo[3.1.0]hexane system was of interest in view of new potential ligands for the nicotinic receptors. The unique 3-aryl-3-azabicyclo[3.1.0]hex-1-ylamines **116**–**119** were obtained by nucleophylic aromatic substitution with the 3-azabicyclo[3.1.0]hex-1-ylamine hydrochlorides **28**-**HCl**, **82**-**HCl** on highly active halo-substituted heterocycles such as 2-chloropyrazine and 3,6-dichloropyridazine. The introduction of pyridin-3-yl substituents required palladium catalysis. The 3-aryl-3-azabicyclo[3.1.0]hex-1-ylamines **120**–**123** were obtained from the corresponding 3-azabicyclo[3.1.0]hex-1-yl-amine hydrochlorides **28**-**HCl** and **82**-**HCl** and 3-bromopyridines using $Pd_2(dba)_3$/(±)-BINAP as a catalytic system. The synthesis of a 1-aryl-substituted amine was successful only in the case of the amine hydrochloride **83**-**HCl**, and the doubly substituted 3-methyl-*N*,*N*-di-(pyrazin-2-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**131**) was obtained in 62% yield. The introduction of the 5-chloropyridin-3-yl group required the use of the $Pd(OAc)_2$/2-(di-*tert*-butylphosphino)-biphenyl catalyst system, and 3-(5-chloropyrid-3-yl)-3-azabicyclo-[3.1.0]hex-1-ylamine (**132**) as well as 3-(5-chloropyrid-3-yl)-*N*-methyl-3-azabicyclo[3.1.0]-hex-1-ylamine (**133**) were obtained in 38 and 41% yield, respectively.

The trifluoroethylamino derivatives **140, 144**–**146**, analogues of the trifluoromethyltropanone cyanohydrine, were obtained from the 3-aryl-3-azabicyclo[3.1.0]hexane derivatives in a two-step reductive alkylation by use of trifluoroacetaldehyde methyl hemiacetal. The attempted Pd-catalyzed cross-coupling of the amines **83**-**HCl**, **84** with bromoaryl derivatives for the synthesis of 1-aryl-3-azabicyclo[3.1.0]hexane derivatives failed. Thus, the Ti-mediated intramolecular reductive cyclopropanation of an *N*-methyl-*N*-arylpropionamide was tested

and *N*-(4-chlorophenyl)-3-(4-methoxybenzyl)-*N*-methyl-3-azabicyclo[3.1.0]hex-1-ylamine (**159**) was obtained in 54% yield.

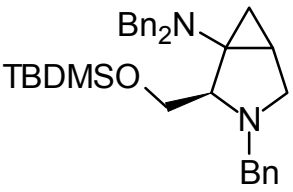
Further elaboration of the *endo*-(2*R*)-*N*,*N*-dimethyl-3-benzyl-2-(*tert*-butyldimethylsilyloxy-methyl)-3-azabicyclo[3.1.0]hex-1-ylamine *endo*-**58** led to the synthesis of the chloropyridyl-substituted bicyclic triamine *endo*-**165** which was unstable and decomposed partially upon exposure to air. Unfortunately, attempted oxidation of the deprotected hydroxymethyl groups in the *endo*- and *exo*-(2*R*)-*N*,*N*-dialkyl-3-benzyl-2-(*tert*-butyl-dimethylsilyloxymethyl)-3-azabicyclo-[3.1.0]hex-1-ylamines **58** and **59** with $KMnO_4$ in *tert*-butyl alcohol and with Jones reagent failed. Even the attempted oxidation of the bis-(*tert*-butoxycarbonyl) derivative *endo*-**173** did not lead to the desired new analogues of some natural amino acids.

The tri- and tetracyclic derivatives **179**, **183**, **187** and **192** containing ring-annelated azabicyclo[3.1.0]hexane systems were prepared from indole, indoline, pyrrole and proline *N*-allyl derivatives by Ti-mediated intramolecular reductive cyclopropanation in yields ranging from 61 to 78%. The *N*-allylindoline derivative and the *N*-allylproline derivative gave mixtures of two diastereomers (1a*S*,8a*S*,8b*R*)-**183** and (1a*R*,8a*S*,8b*S*)-**183** in a ratio of 1 : 1 as well as (1a*S*,6a*S*,6b*R*)-**192** and (1a*R*,6a*S*,6b*S*)-**192** in a ratio of 3.3 : 1.

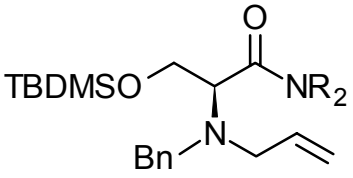
In a second part of this project a new synthesis of spirocyclopropane-annelated β-lactams was studied. By treatment of the isoxazolidines **220** and **221**, synthesized by 1,3-dipolar cycloaddition of benzylidenemethylamine oxide and methylpyridin-2-ylmethyleneamine oxide onto bicyclopropylidene, with trifluoroacetic acid, the β-lactams **222** and **223** were obtained in excellent yields with elimination of ethylene.

Finally, the 1,3-dipolar cycloaddition of various nitrones to the highly strained cyclopropylidenespiropentane and 7-cyclopropylidenedispiro[2.0.2.1]heptane and subsequent thermal rearrangement of the intermediate isoxazolidines was investigated. Such processes led to the formation of new tetrahydropyridone derivatives **243**, **244**, **247**, **248**, **250**–**255** with up to three spirocyclopropane-annelated rings, in yields ranging from 68 to 80%.

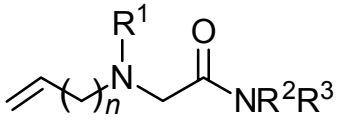
In a collaboration with the Bayer AG company the biological activity tests of compounds **28**–**HCl**, **29**–**HCl**, **76**–**79** and their derivatives are currently in progress.



58 R = Me
59 R = Bn

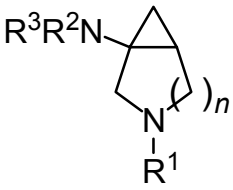


54 R = Me
57 R = Bn



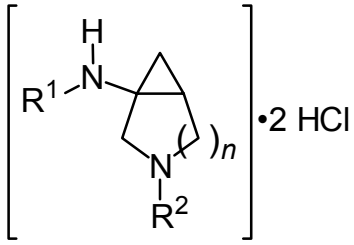
70–**75**

Compound	R^1	R^2,R^3	*n*
70	Bn	Bn,Bn	1
71	Bn	Bn,Me	1
72	Me	Bn,Bn	1
73	Bn	Bn,Bn	2
74	Boc	Bn,Bn	1
75	Boc	Ph,Ph	1



76–**81**

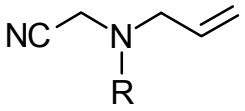
Compound	R^1	R^2,R^3	*n*
76	Bn	Bn,Bn	1
77	Bn	Bn,Me	1
78	Me	Bn,Bn	1
79	Bn	Bn,Bn	2
80	Boc	Bn,Bn	1
81	Boc	Ph,Ph	1



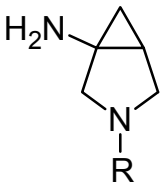
28, **29**, **82**–**84**

Compound	R^1	R^2	*n*
28-HCl	H	H	1
82-HCl	Me	H	1
83-HCl	H	Me	1
29-HCl	H	H	2
84[a]	H	Boc	1

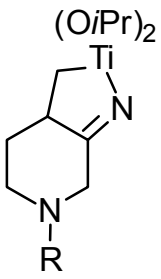
[a]Compound **84** was obtained as a free base.



86 R = Boc
87 R = PMB
88 R = Bn



84 R = Boc
90 R = PMB
91 R = Bn



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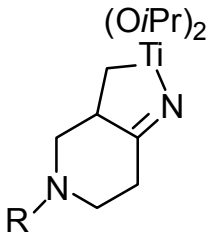

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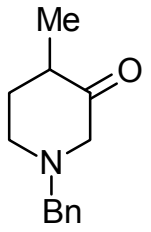

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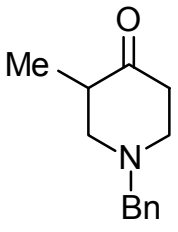

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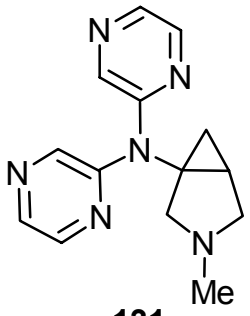

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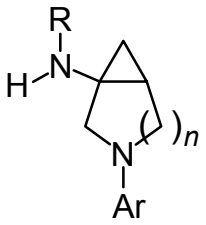
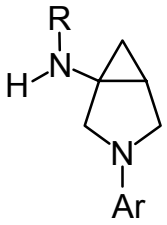
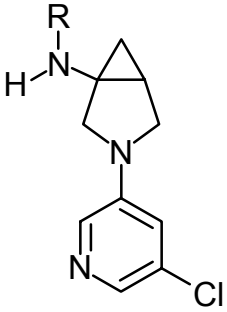


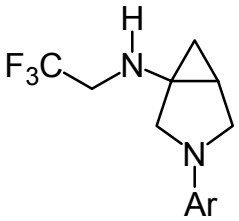
116 R = H, *n* = 1,
Ar = pyrazin-2-yl
117 R = H, *n* = 1,
Ar = 6-chloropyridazin-3-yl
118 R = Me, *n* = 1,
Ar = 6-chloropyridazin-3-yl
119 R = H, *n* = 2,
Ar = 6-chloropyridazin-3-yl



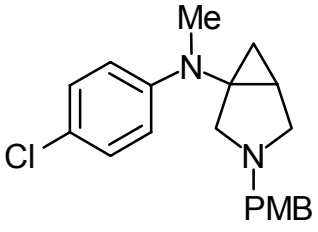
120 R = Me,
Ar = pyridin-3-yl
121 R = Me,
Ar = pyrimidin-5-yl
122 R = H,
Ar = pyridin-3-yl
123 R = H,
Ar = pyridin-3-yl



132 R = H
133 R = Me



140-Cl Ar = 6-chloropyridazin-3-yl
144 Ar = pyrid-3-yl
145 Ar = pyrimidin-5-yl
146 Ar = pyrazin-2-yl



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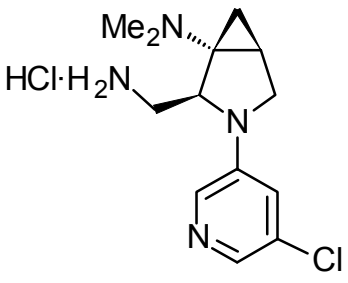
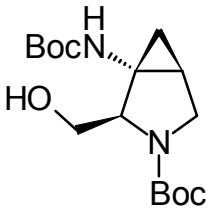
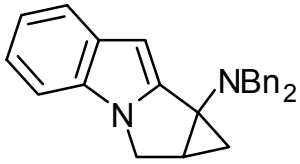


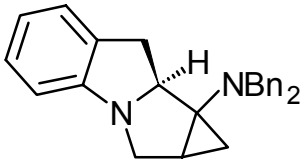
endo-**165**



endo-**173**



179



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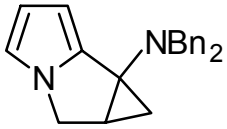

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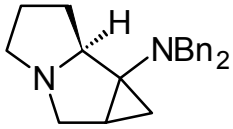

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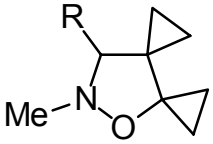

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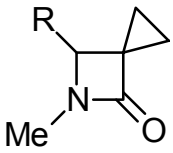

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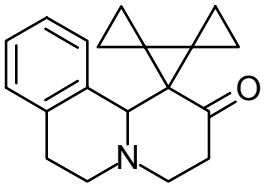

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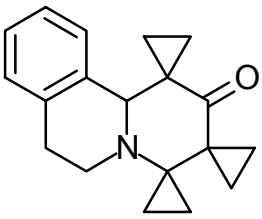

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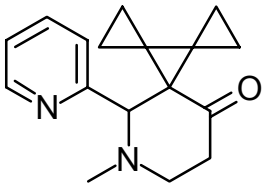

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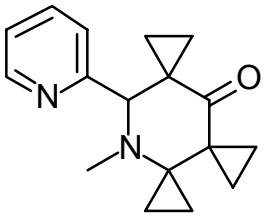

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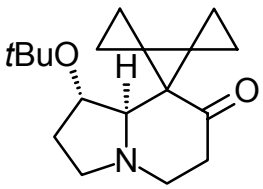

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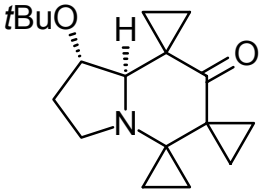

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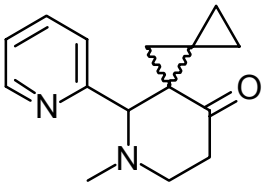

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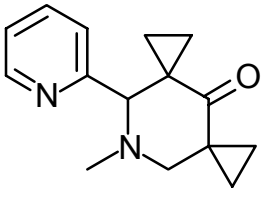

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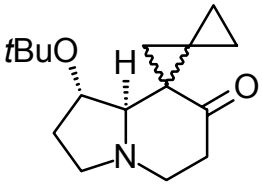

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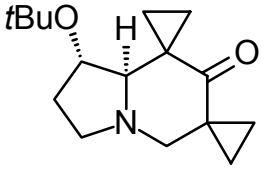

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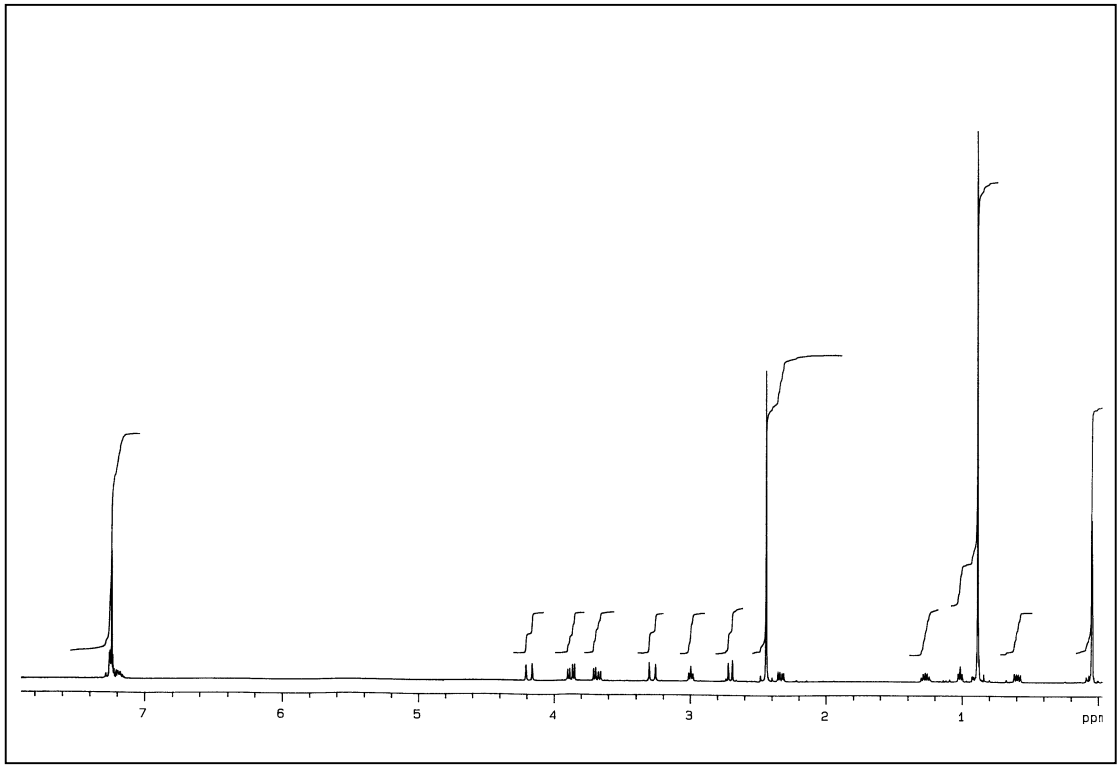
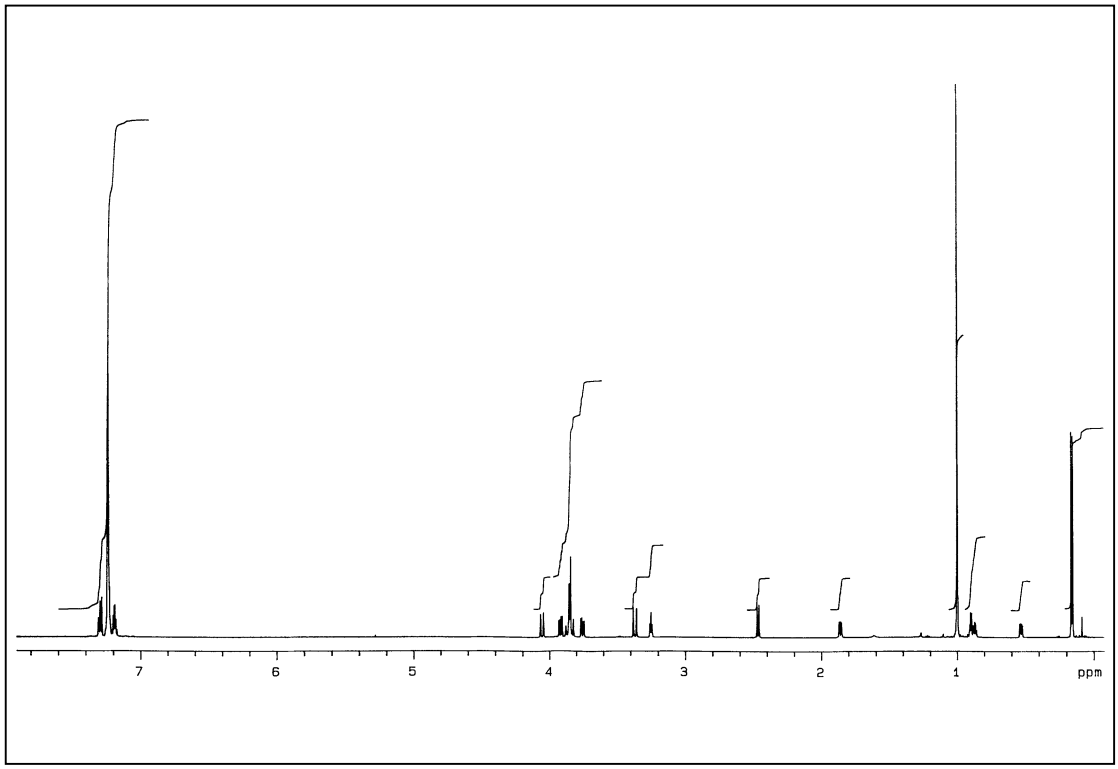
F. SPECTRAL DATA

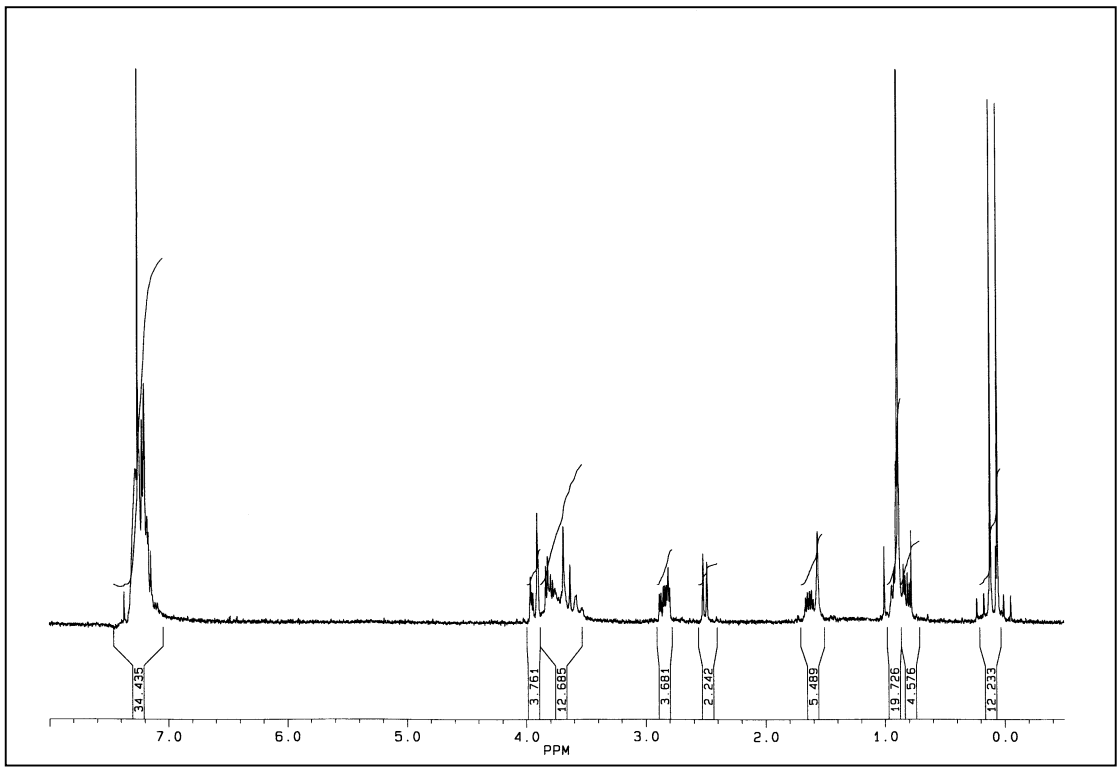
1. ^{1}H-NMR spectra



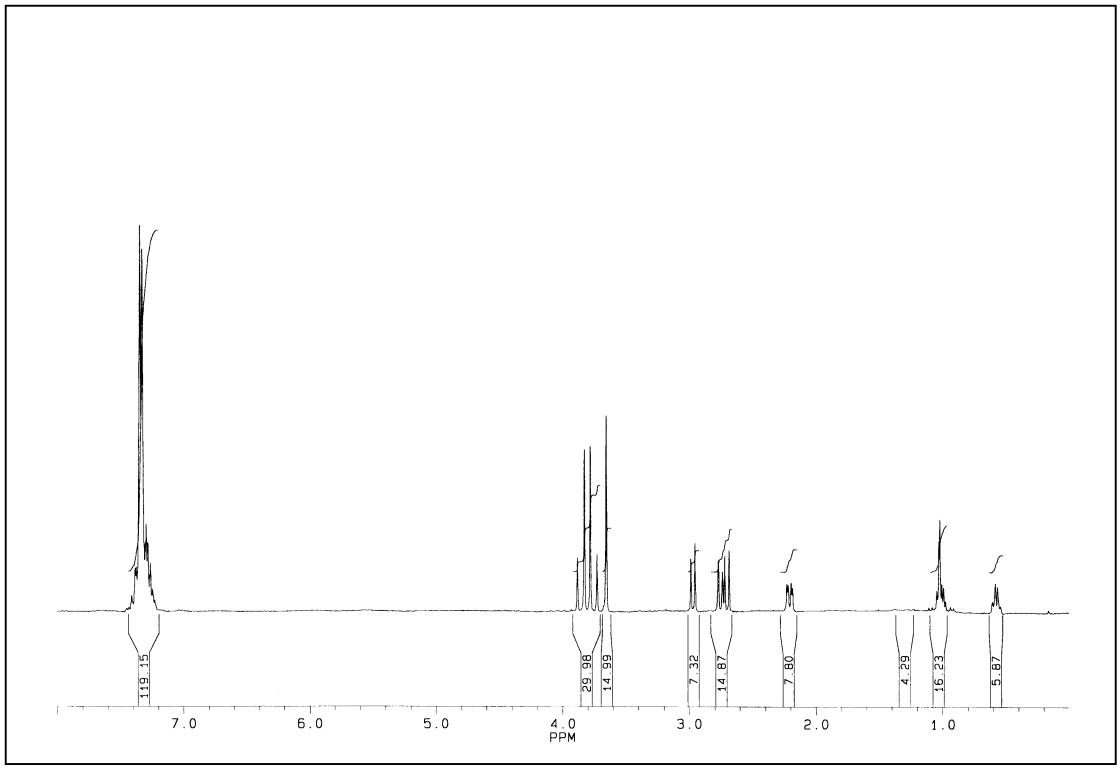
endo-(2*R*)-3-Benzyl-2-(*tert*-butyldimethylsilyloxymethyl)-*N*,*N*-dimethyl-3-azabicyclo[3.1.0]hex-1-ylamine (*endo*-**58**)



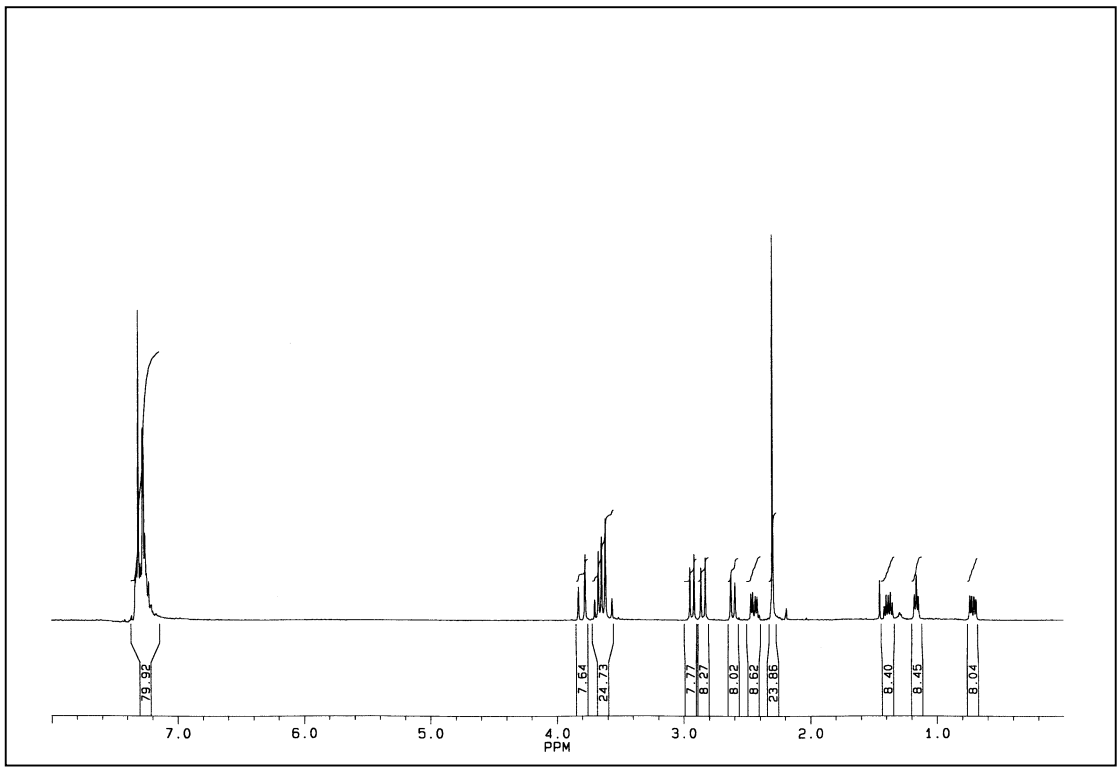
endo-(2*R*)-*N*,*N*,3-Tribenzyl-2-(*tert*-butyldimethylsilyloxymethyl)-3-azabicyclo-[3.1.0]hex-1-ylamine (*endo*-**59**)



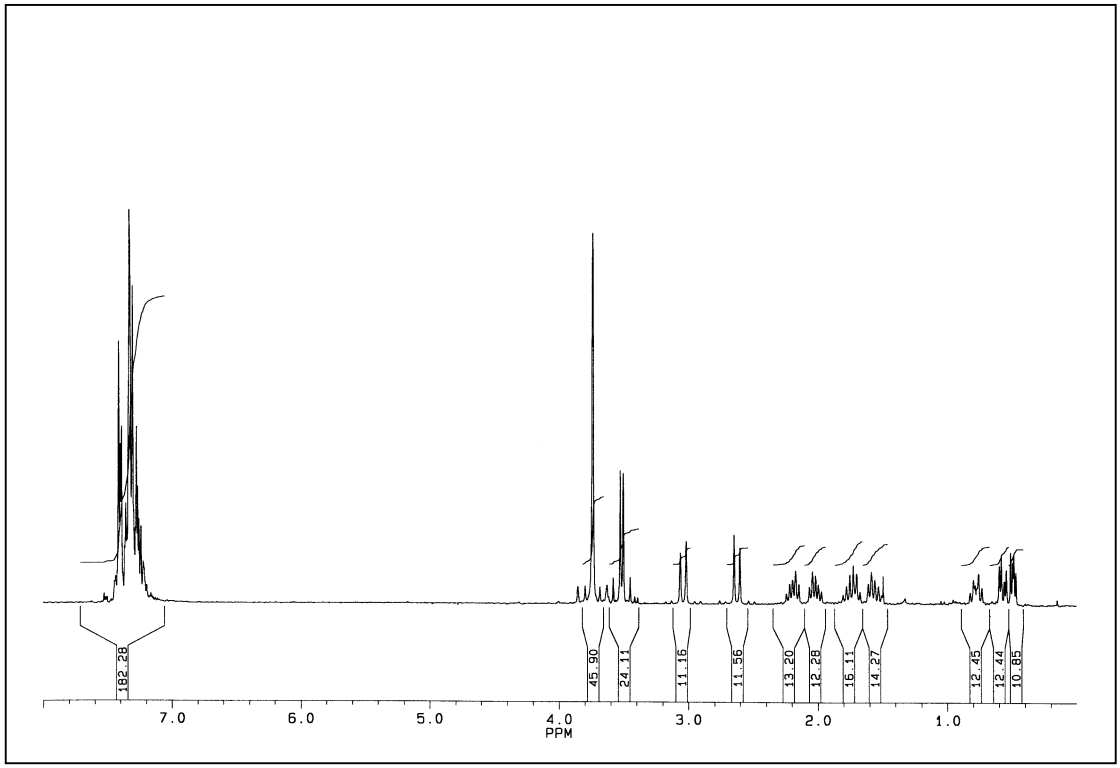
exo-(2*R*)-*N*,*N*,3-Tribenzyl-2-(*tert*-butyldimethylsilyloxymethyl)-3-azabicyclo-[3.1.0]hex-1-ylamine (*exo*-**59**)



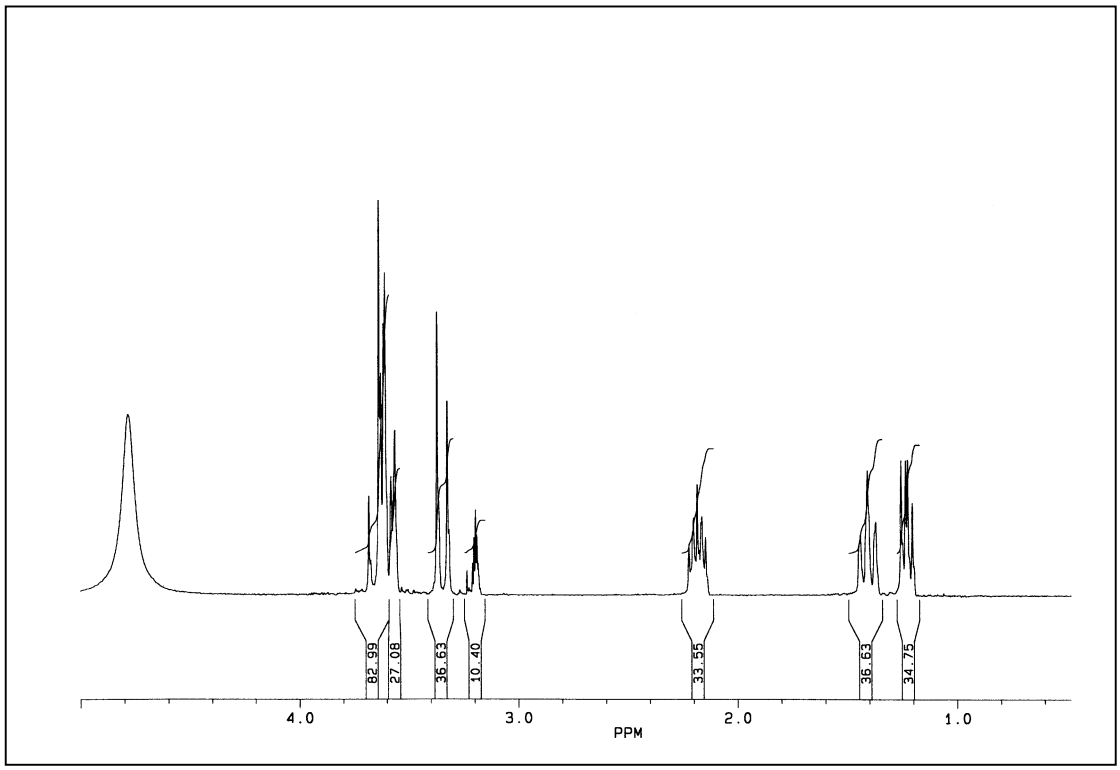
N,*N*,3-Tribenzyl-3-azabicyclo[3.1.0]hex-1-ylamine (**76**)



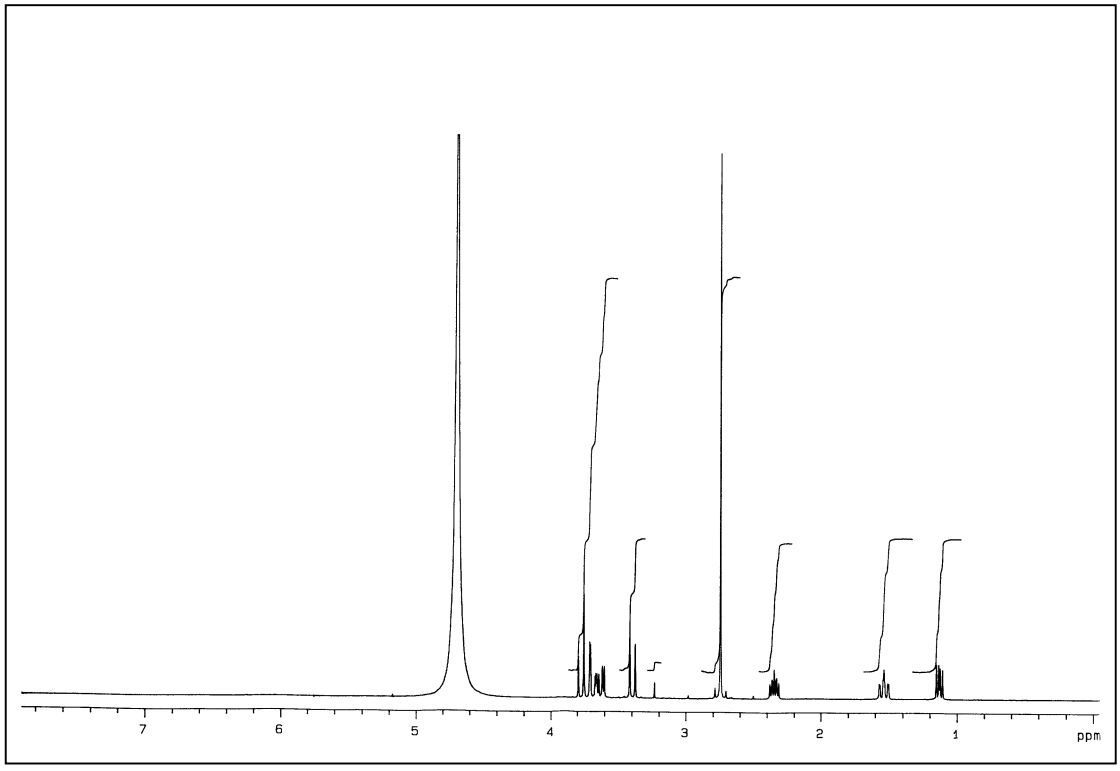
N,3-Dibenzyl-*N*-methyl-3-azabicyclo[3.1.0]hex-1-ylamine (**77**)



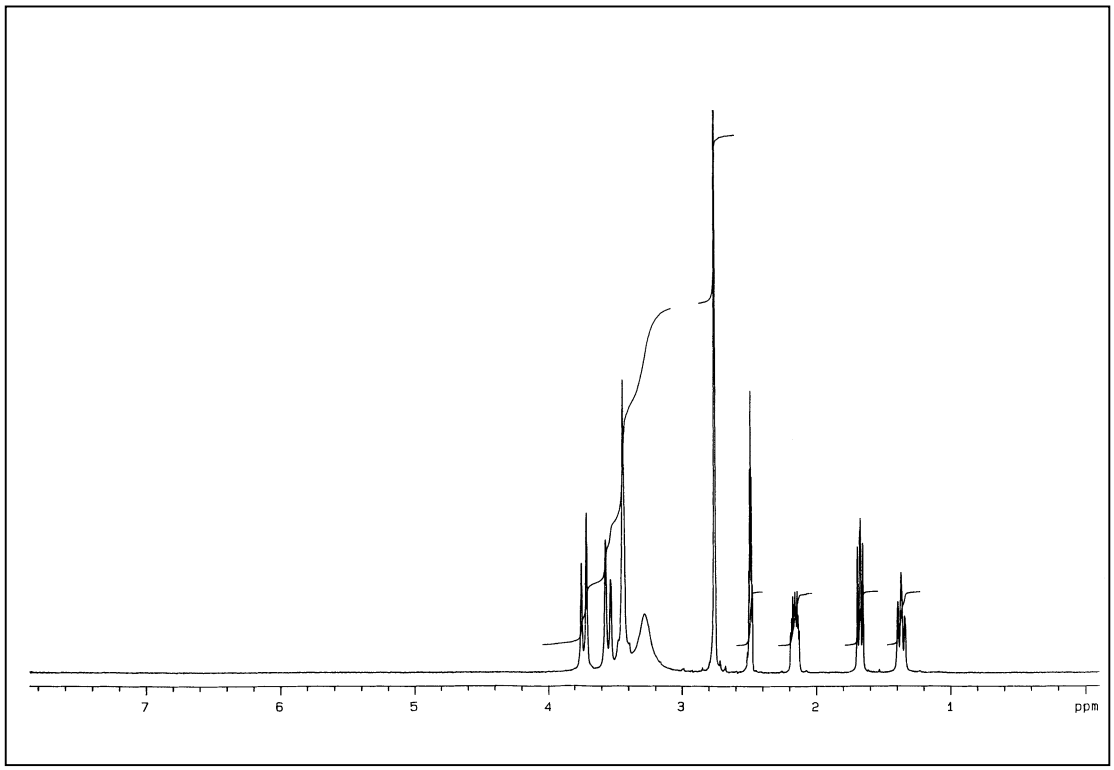
N,*N*,3-Tribenzyl-3-azabicyclo[4.1.0]hept-1-ylamine (**79**)



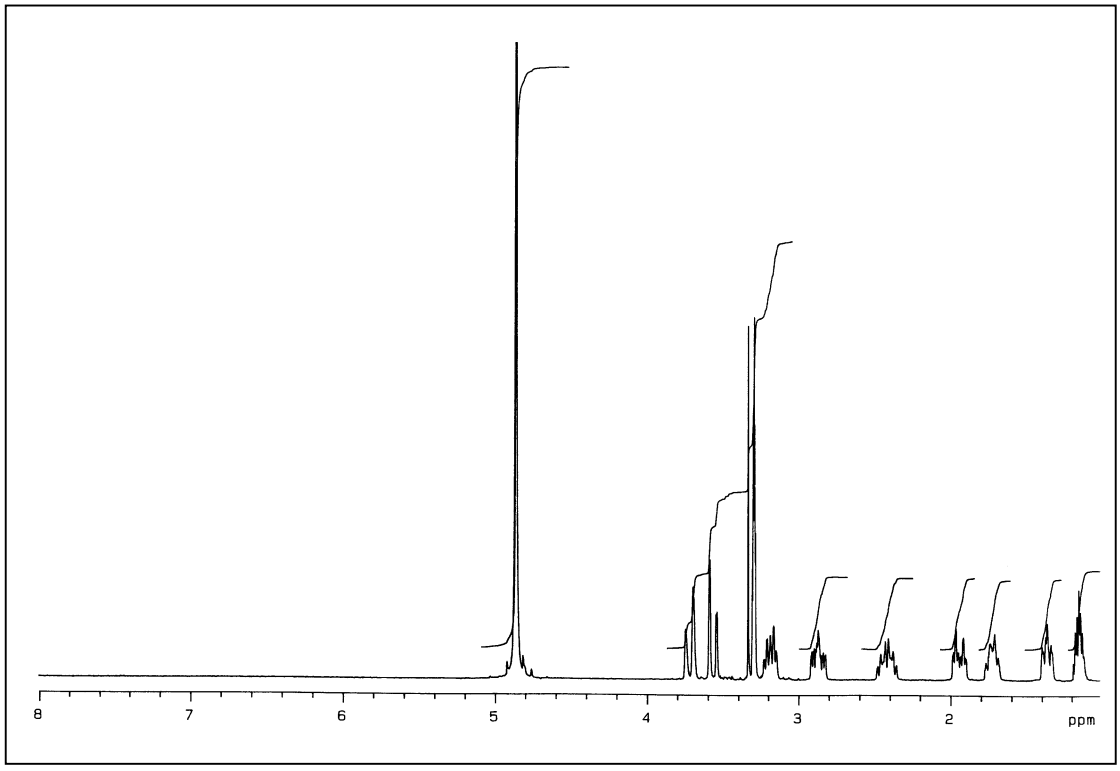
3-Azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**28**-**HCl**)



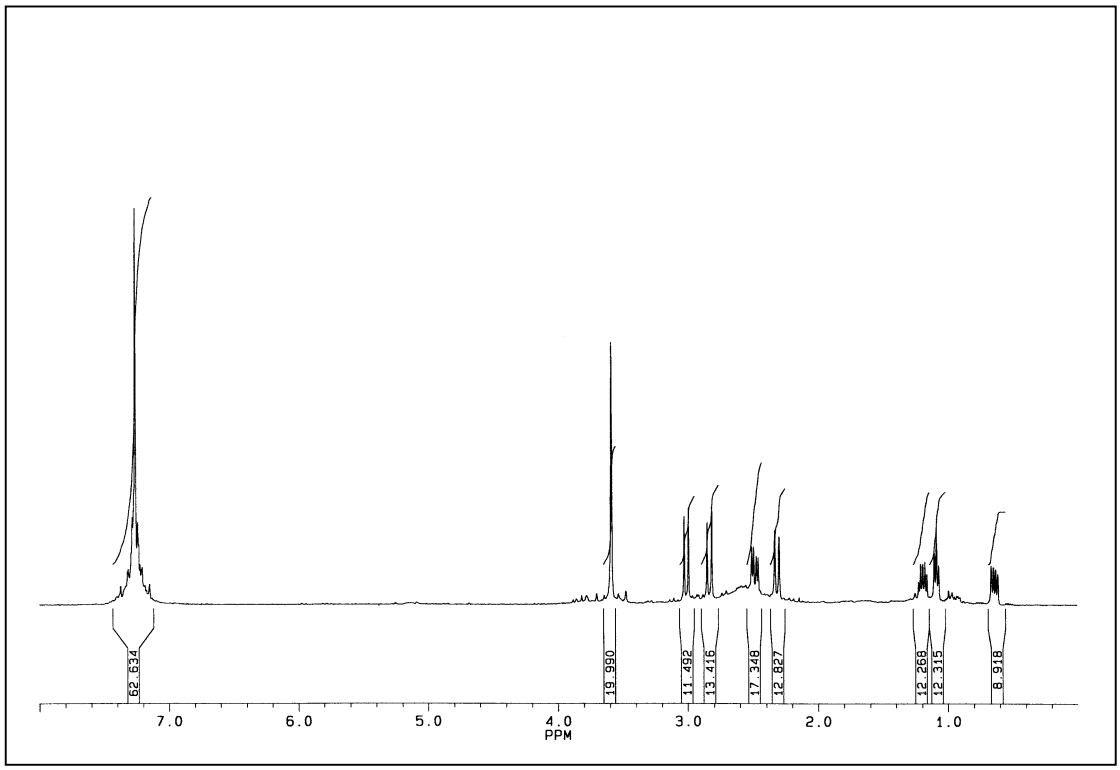
N-Methyl-3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**82**-**HCl**)



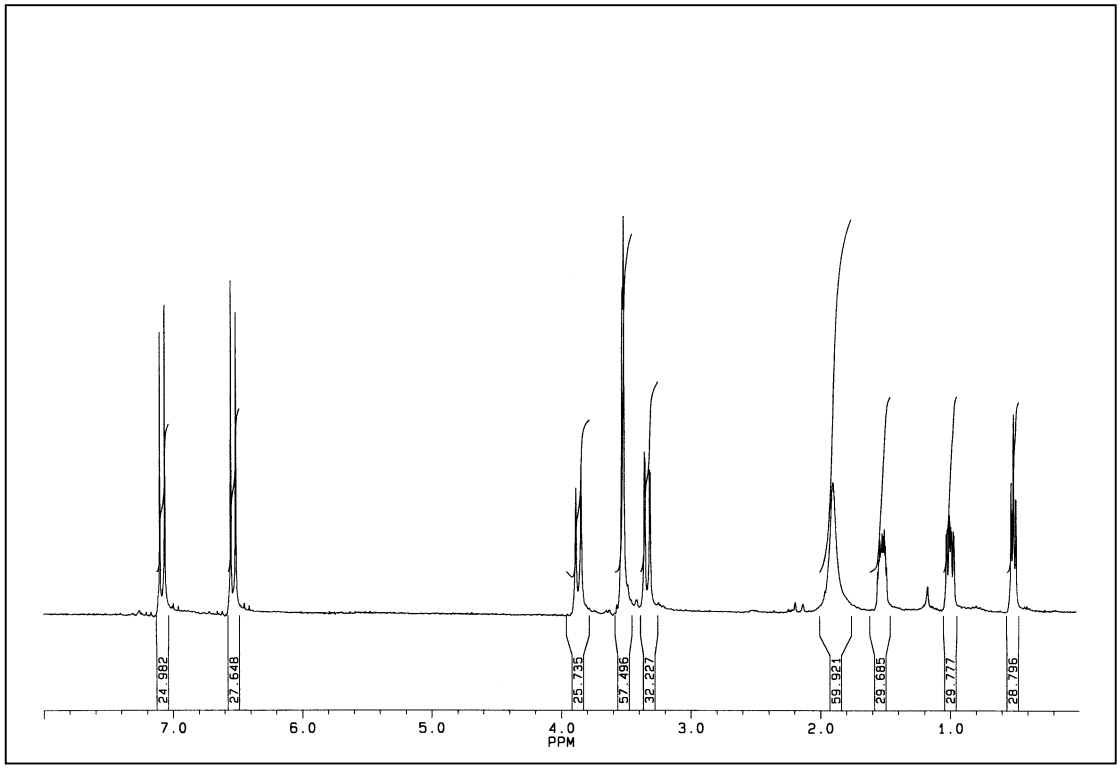
3-Methyl-3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**83**-**HCl**)



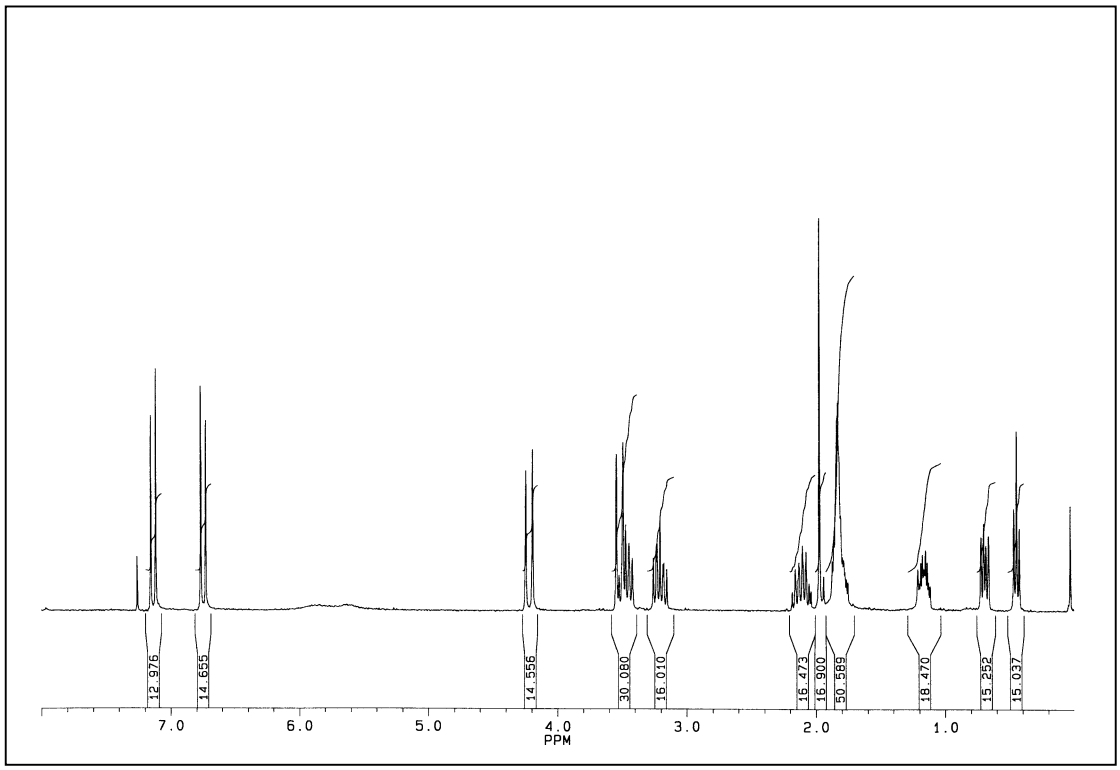
3-Azabicyclo[4.1.0]hept-1-ylamine dihydrochloride (**29**-**HCl**)



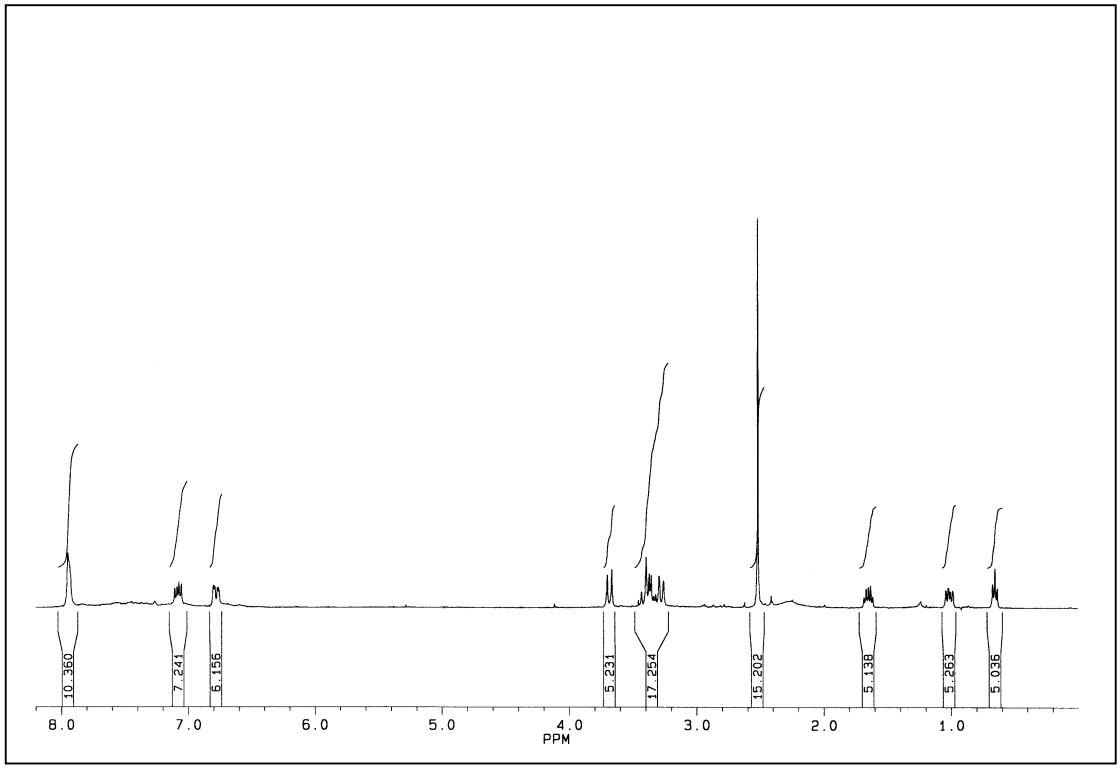
3-Benzyl-3-azabicyclo[3.1.0]hex-1-ylamine (**91**)



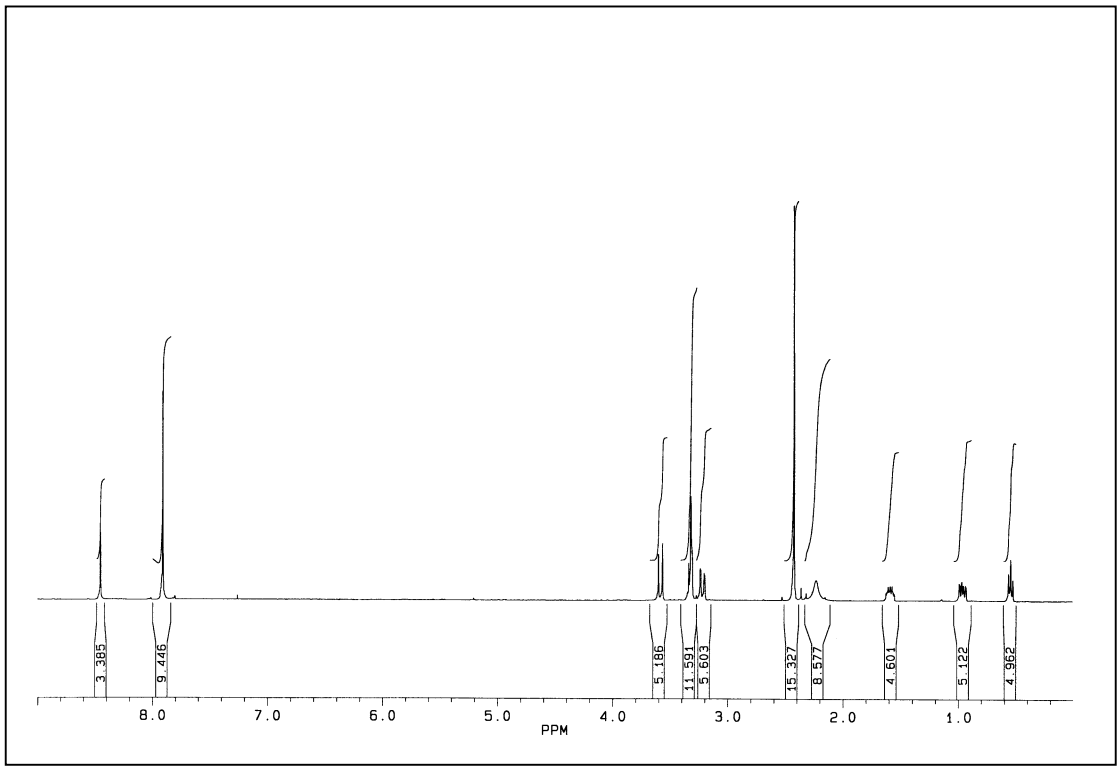
3-(6-Chloropyridazin-3-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**117**)



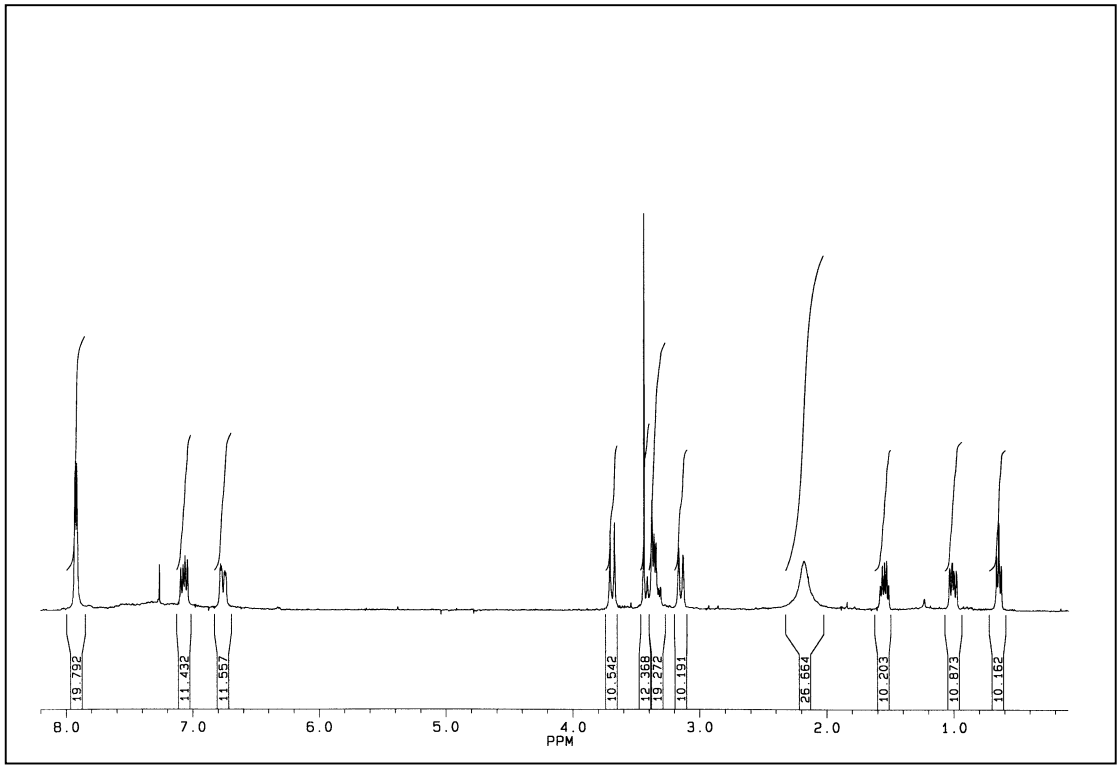
3-(6-Chloropyridazin-3-yl)-3-azabicyclo[4.1.0]hept-1-ylamine (**119**)



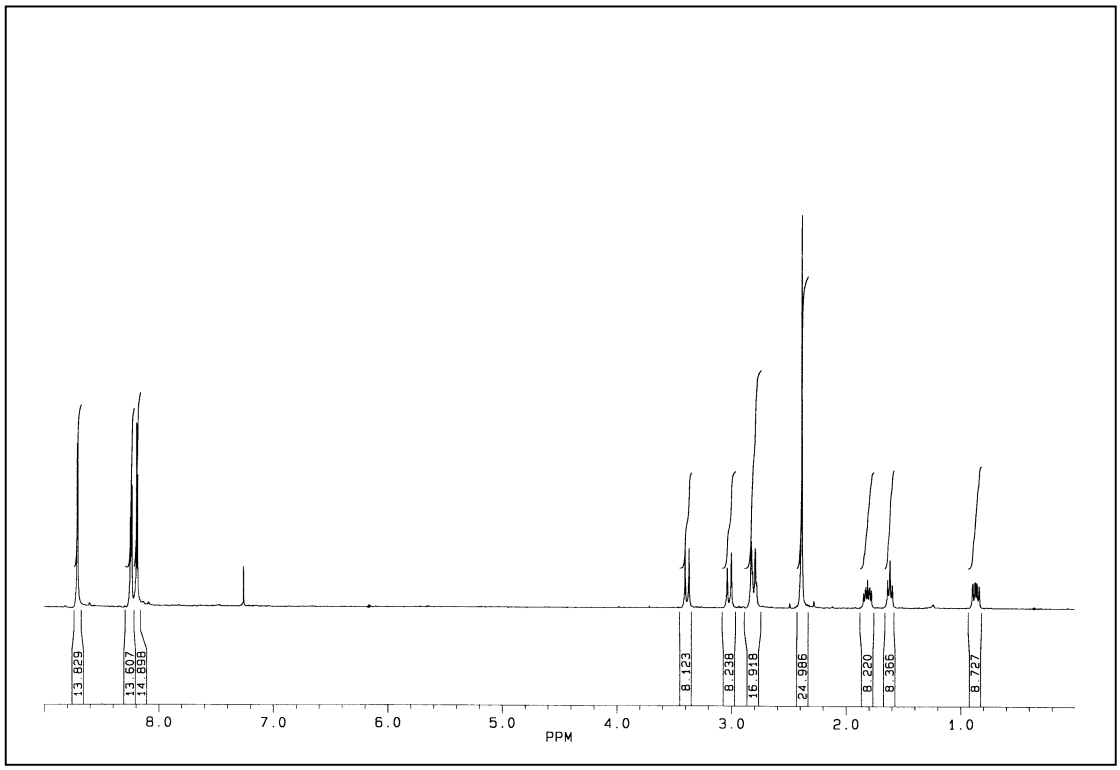
N-Methyl-3-(pyrid-3-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**120**)



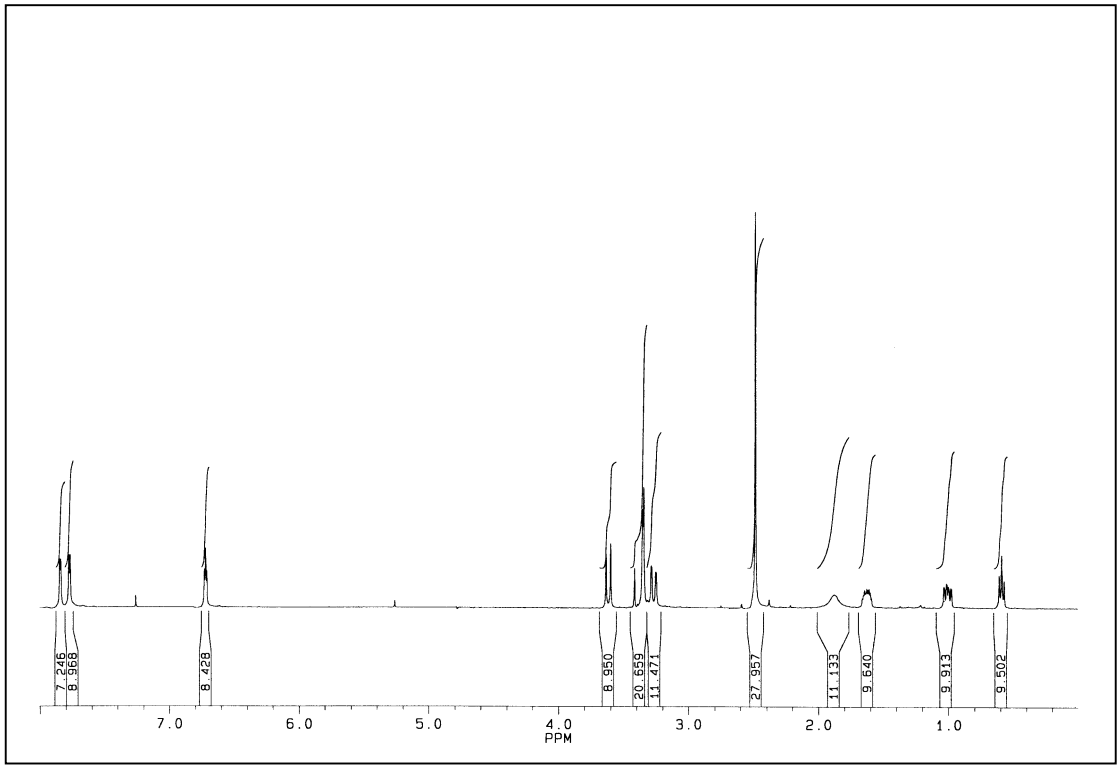
N-Methyl-3-(pyrimidin-5-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**121**)



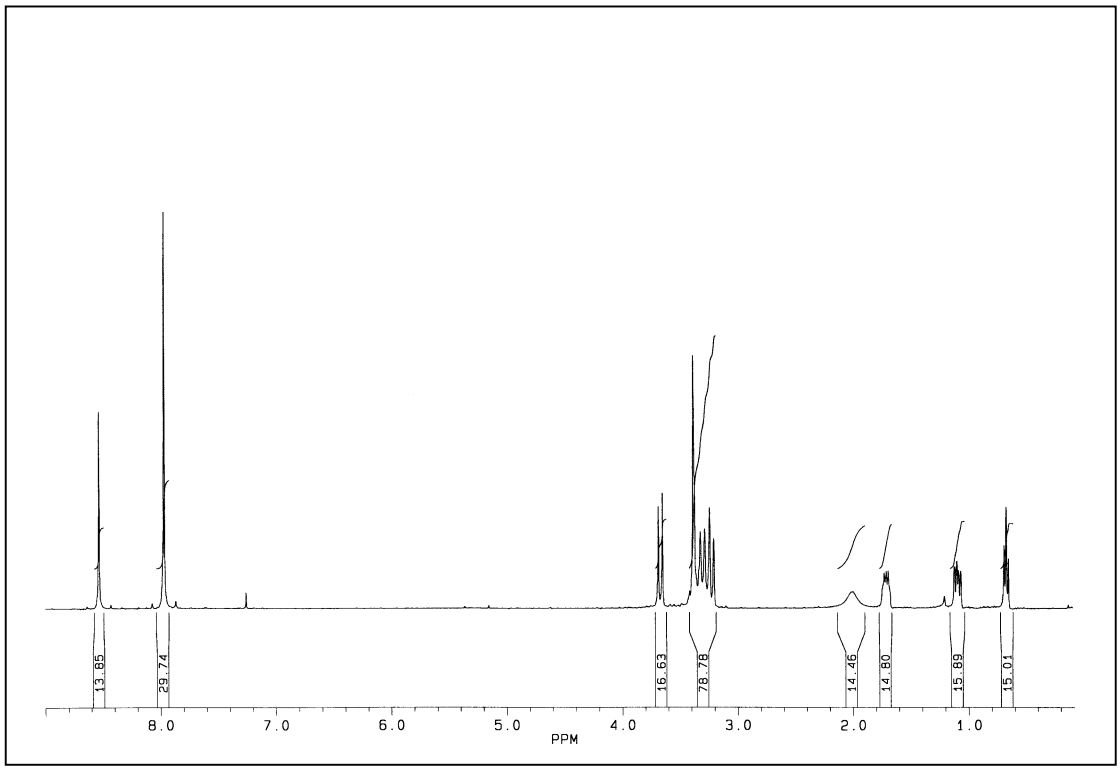
3-(Pyrid-3-yl)-azabicyclo[3.1.0]hex-1-ylamine (**122**)



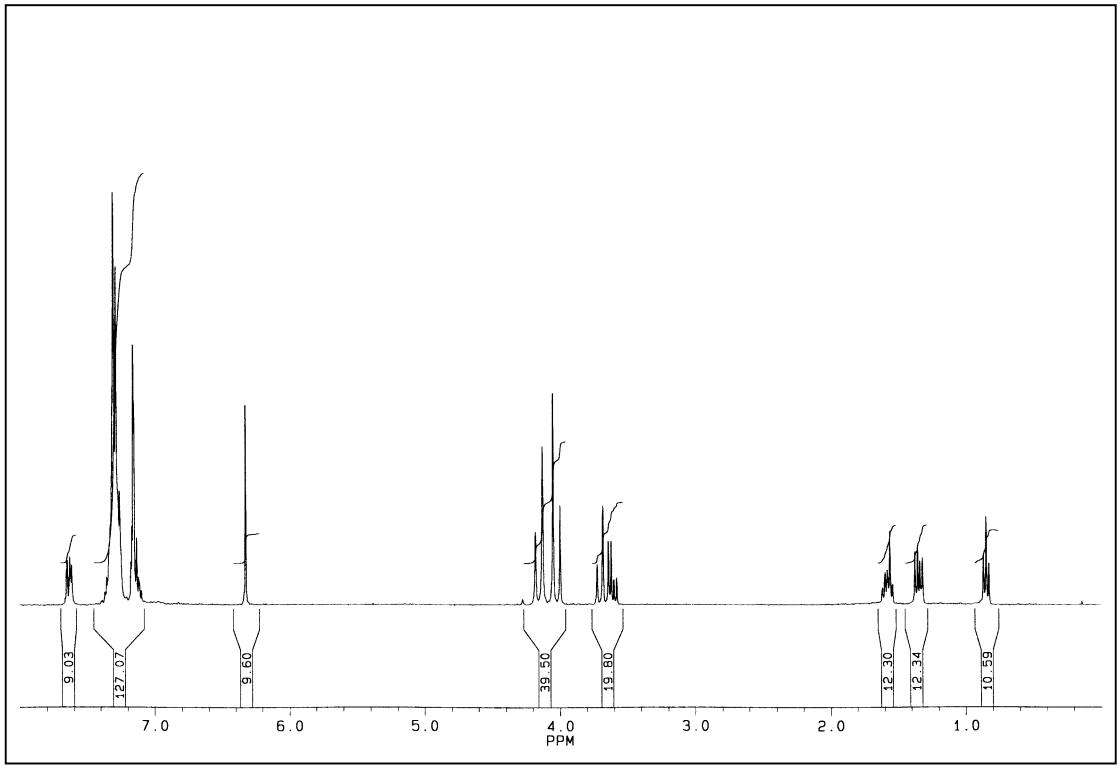
3-Methyl-*N*,*N*-di(pyrazin-2-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**131**)



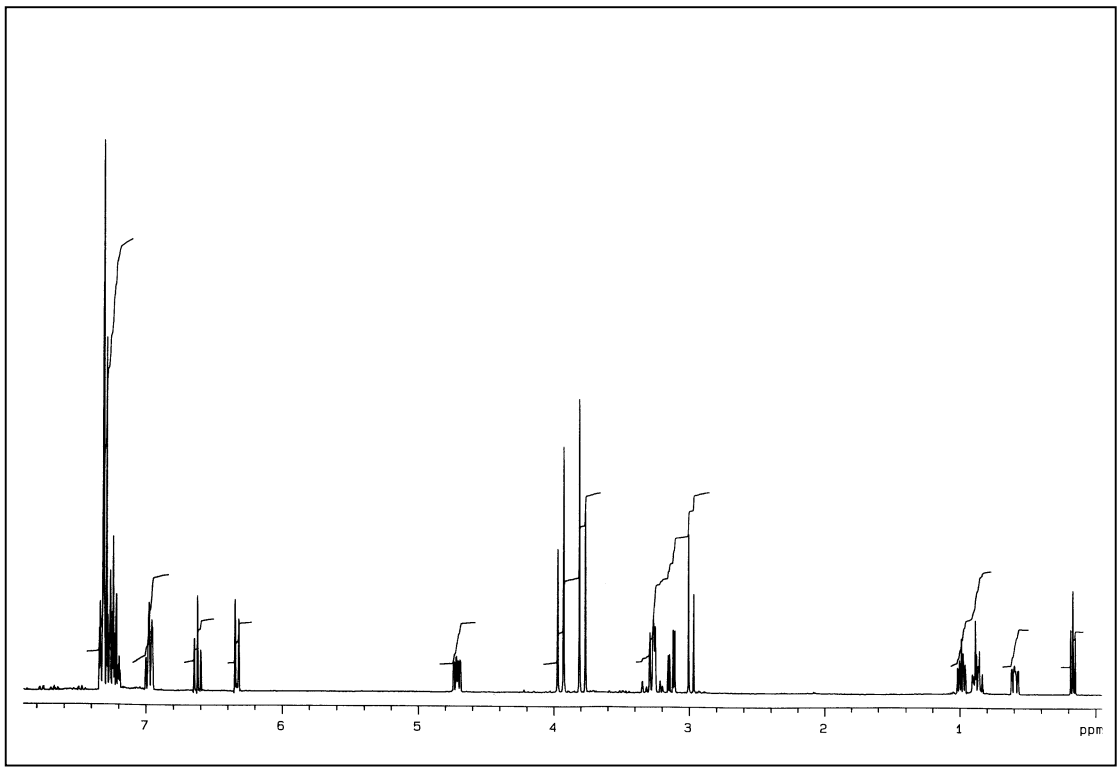
3-(5-Chloropyrid-3-yl)-*N*-methyl-3-azabicyclo[3.1.0]hex-1-ylamine (**133**)



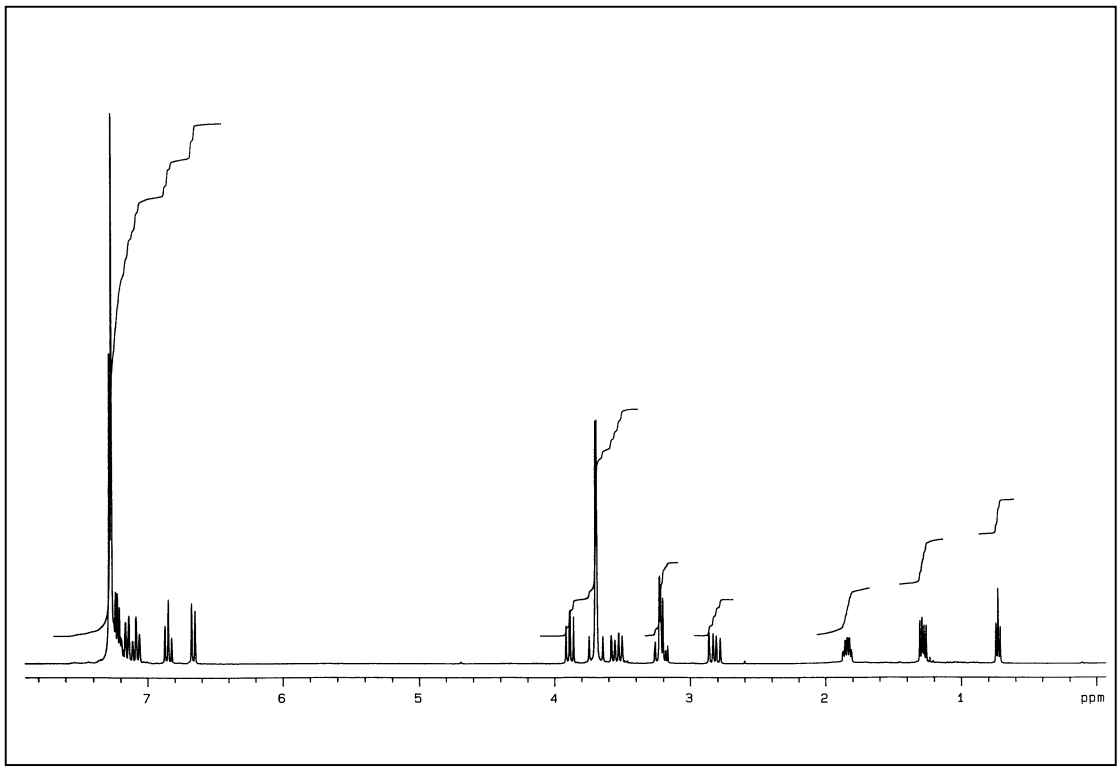
N-(2',2',2'-trifluoroethyl)-3-(pyrimidin-5-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**145**)



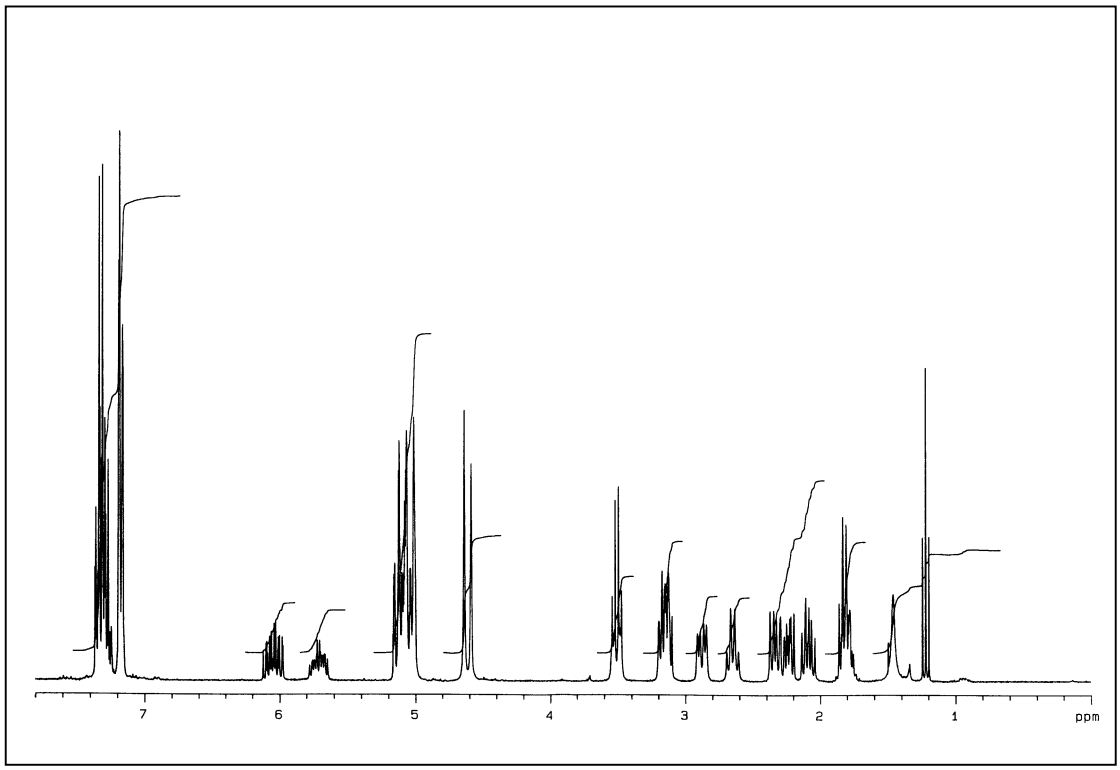
N,*N*-Dibenzyl-indolo[1,2-*a*]cyclopropa[1,2-*c*]pyrrolidin-8b-amine (**179**)



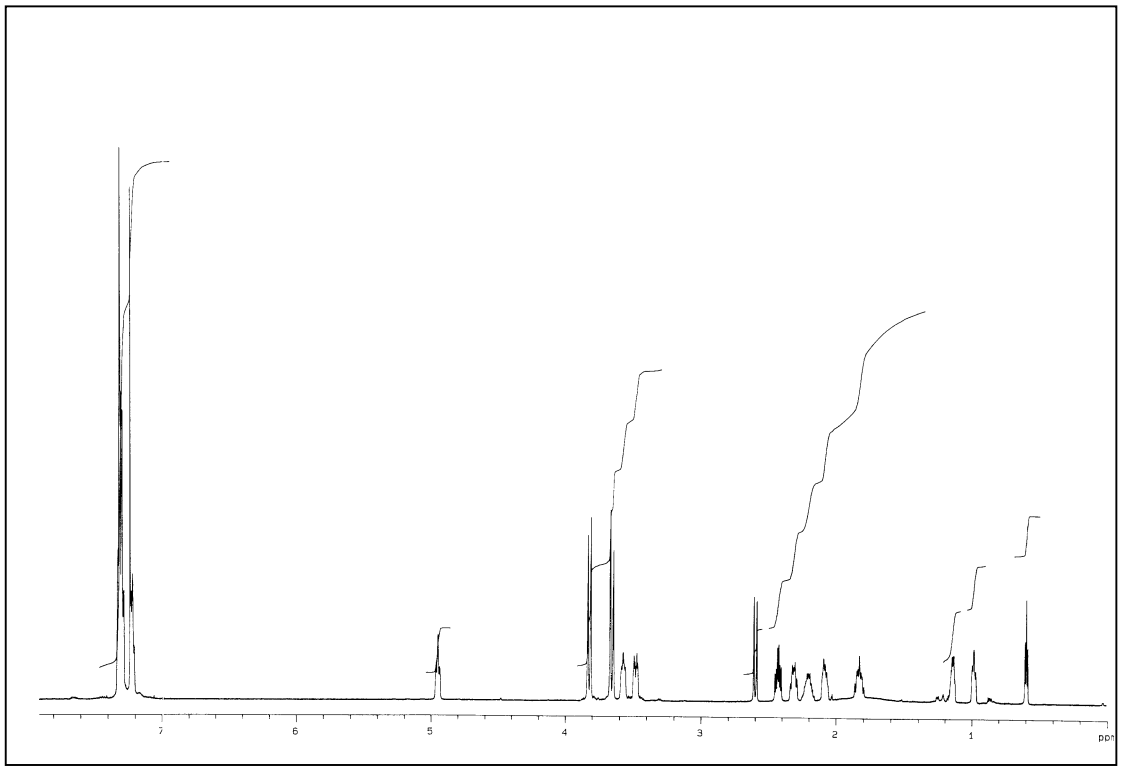
(1a*S*,8a*S*,8b*R)*-*N*,*N*-Dibenzyl-8,8a-dihydroindolo[1,2-*a*]cyclopropa[1,2-*c*]pyrrolidin-8b-amine [(1a*S*,8a*S*,8b*R)*-**183**]



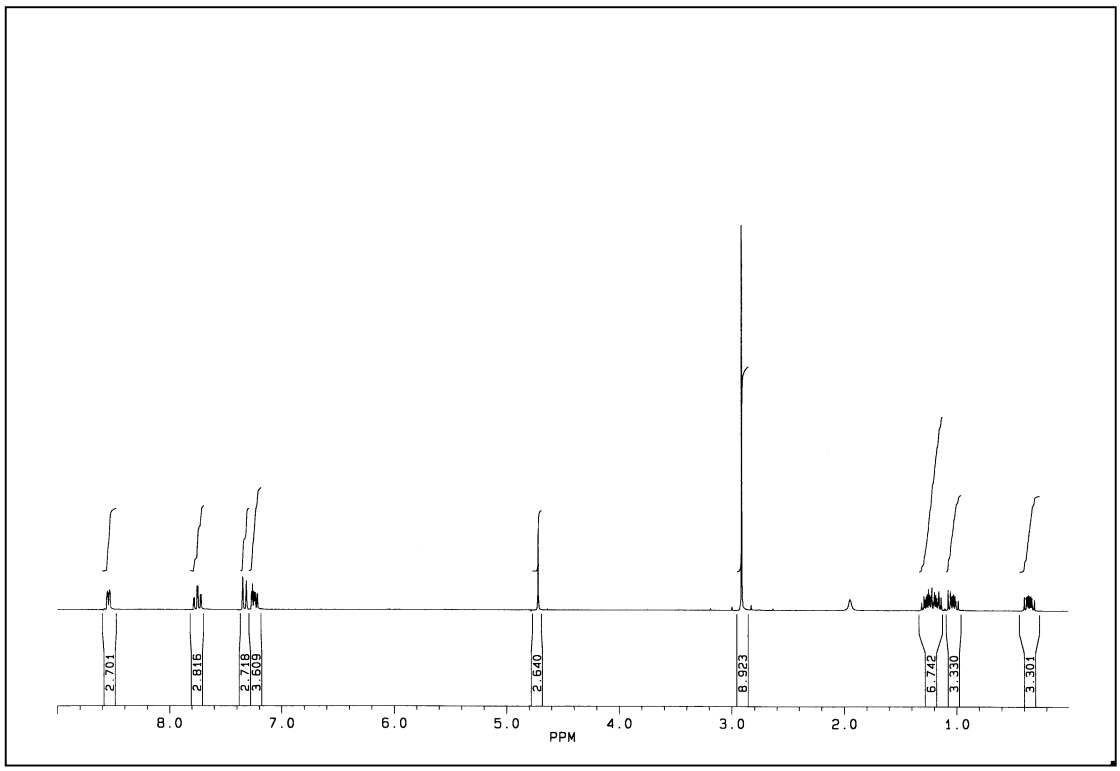
(1a*R*,8a*S*,8b*S)*-*N*,*N*-Dibenzyl-8,8a-dihydroindolo[1,2-*a*]cyclopropa[1,2-*c*]pyrrolidin-8b-amine [(1a*R*,8a*S*,8b*S)*-**183**]



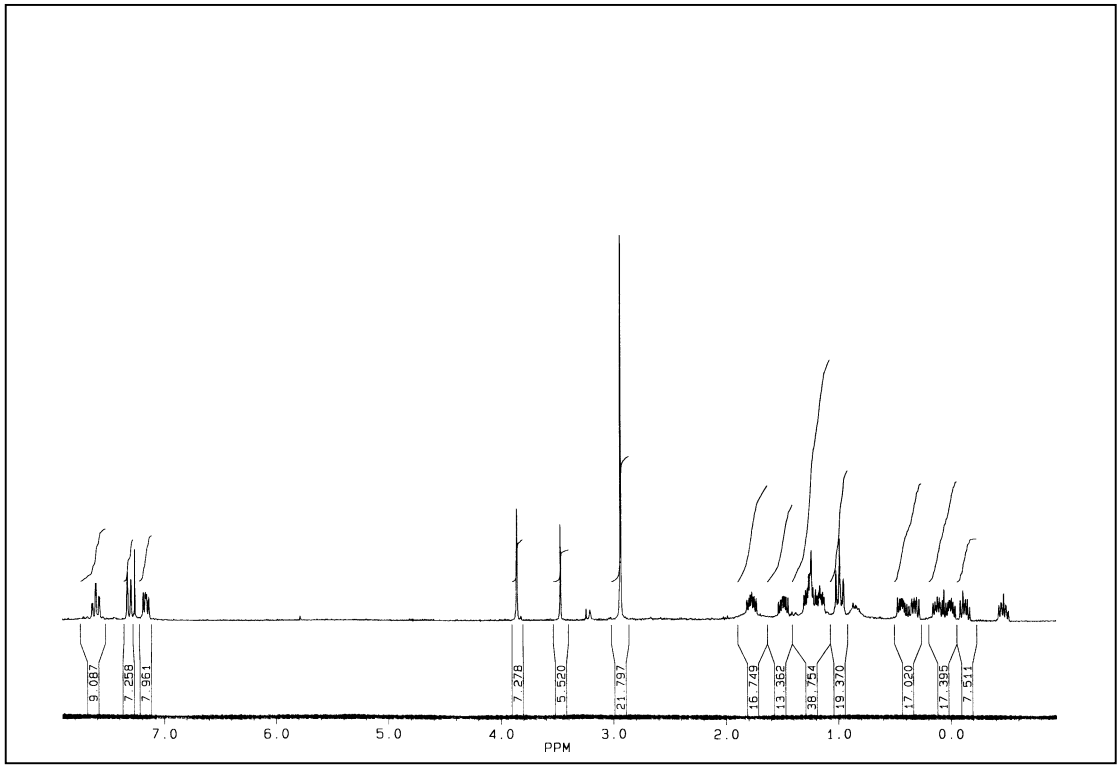
rac-*N*,*N*-Dibenzyl-1,2-diallyl-2-pyrrolidinecarboxamide (**191**)



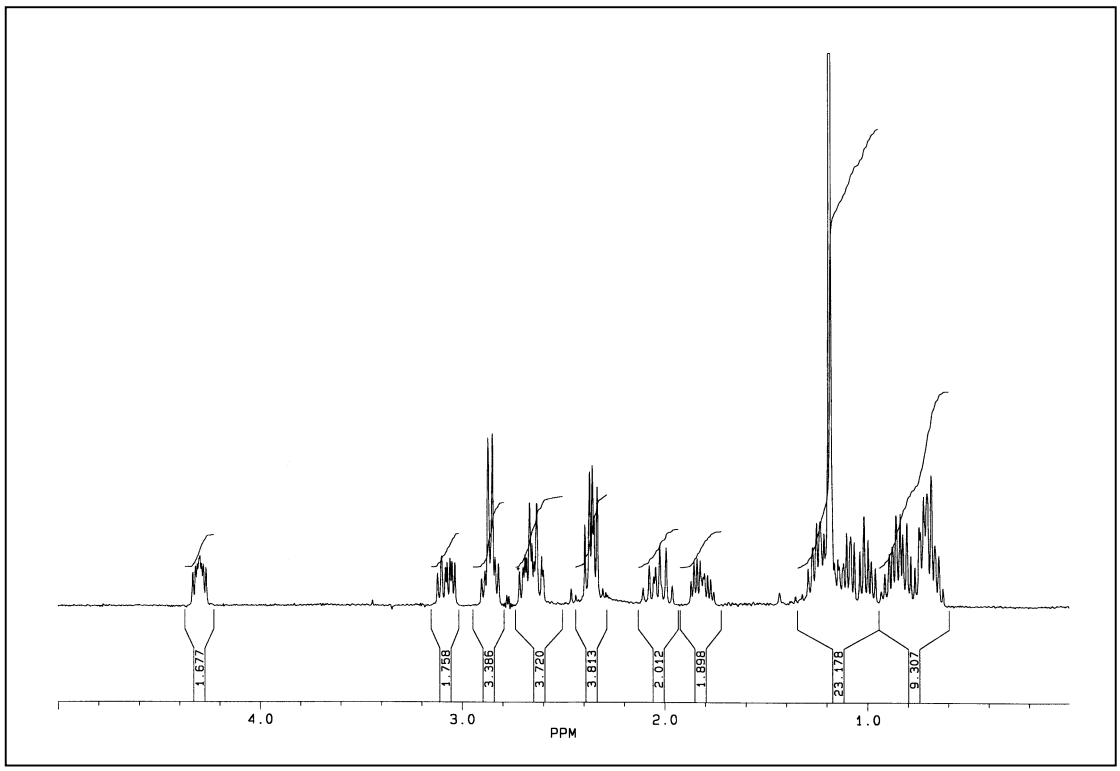
(1a*S*,6a*S*,6b*R)*-*N*,*N*-Dibenzyl-perhydrocyclopropa[1,2-*a*]pyrrolizin-6b-ylamine [(1a*S*,6a*S*,6b*R)*-**192**]



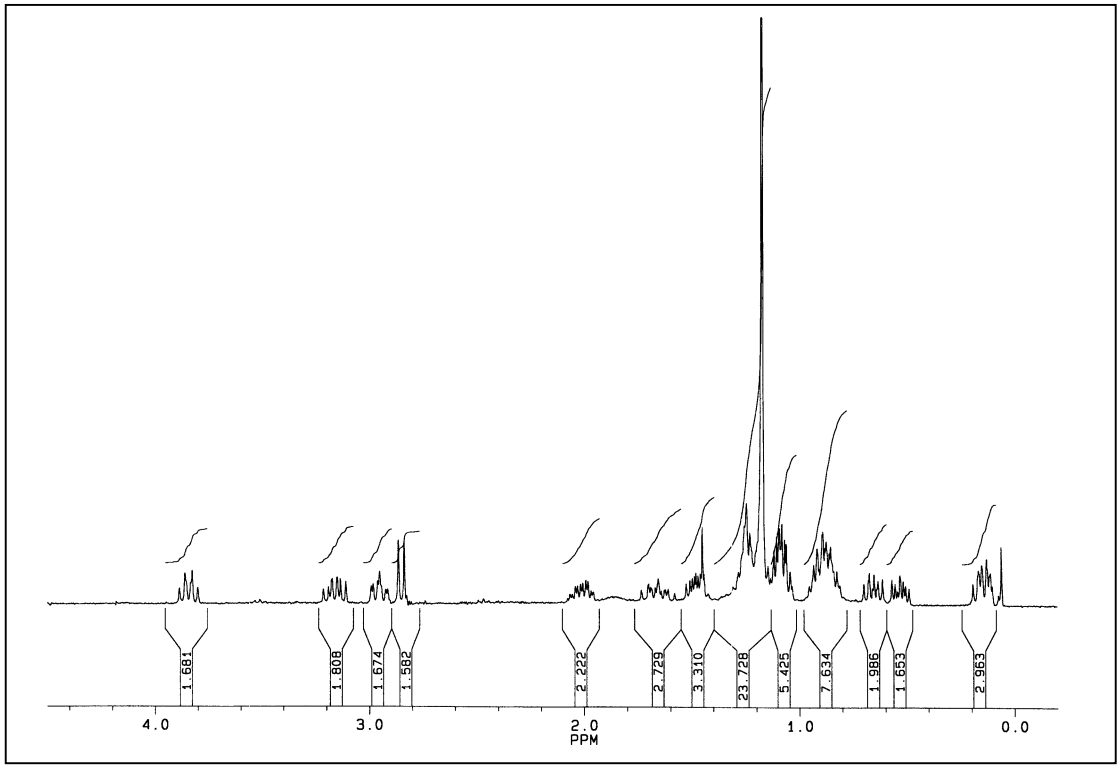
5-Methyl-6-(pyrid-2-yl)-5-azaspiro[2.3]hexan-4-one (**223**)



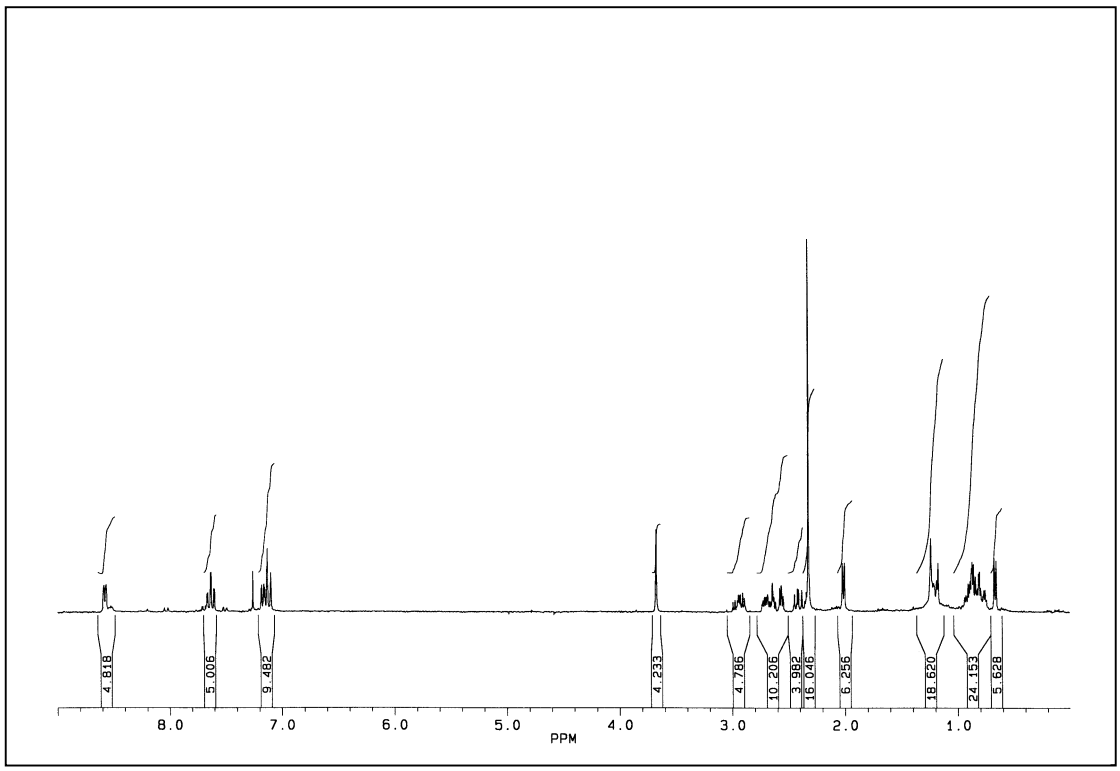
12-methyl-11-(pyrid-2-yl)-12-azatrispiro[2.0.2^{4}.1.2^{8}.2^{3}]dodecan-7-one (**248**)



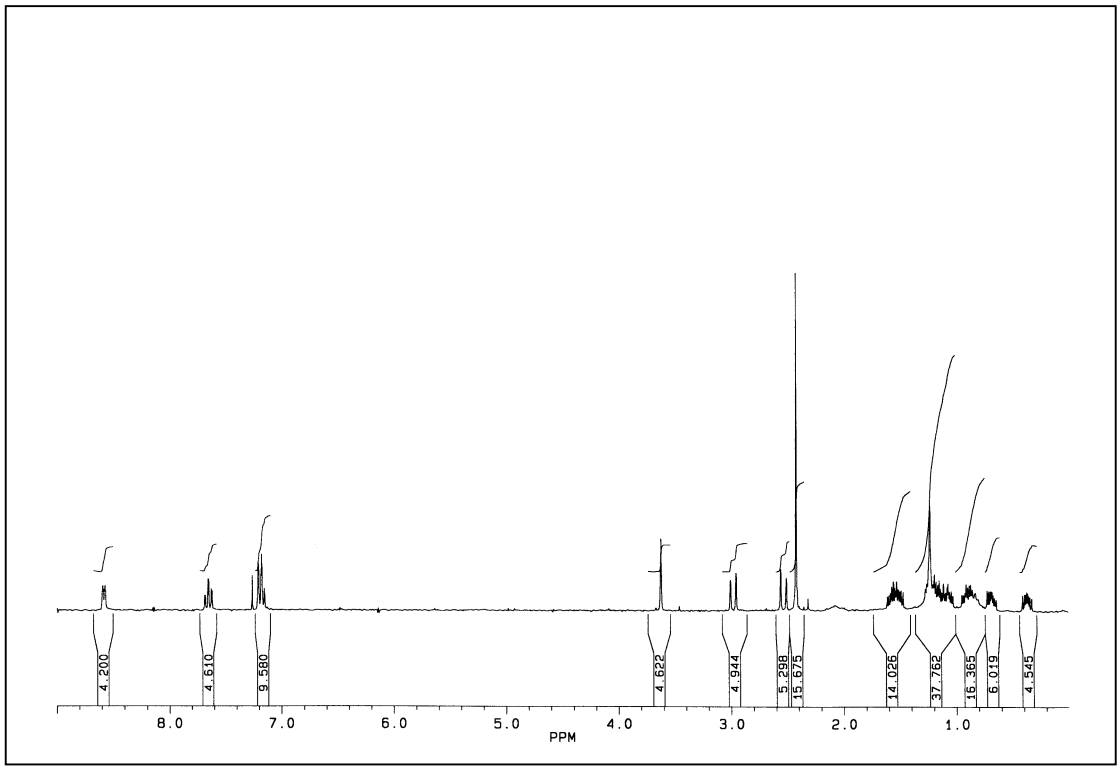
(1'''*S*,8a'''*R*)-1'''-*tert*-Butoxytrispiro[cyclopropane-1,1'-cyclopropane-2',1''-cyclopropane-3',8'''-perhydroindolizine]-7'''-one [(1'''*S*,8a'''*R*)-**250**]



(1'''*S*,8a'''*R*)-1'''-*tert*-Butoxytrispiro[triscyclopropane-1,5''':1',6''':1'',8'''-perhydroindolizine]-7'''-one [(1'''*S*,8a'''*R*)-**251**]

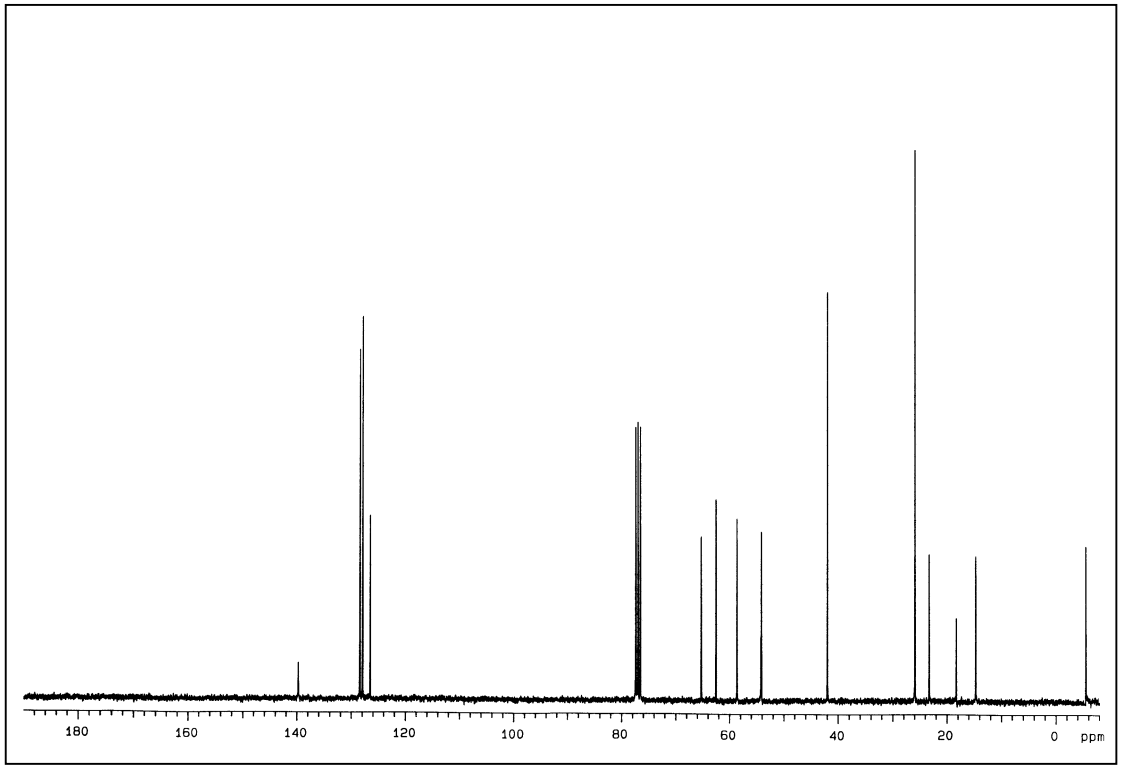


trans-7-Methyl-6-(pyrid-2-yl)-7-azatrispiro[2.1.5^5]decan-10-one (*trans*-**252**)

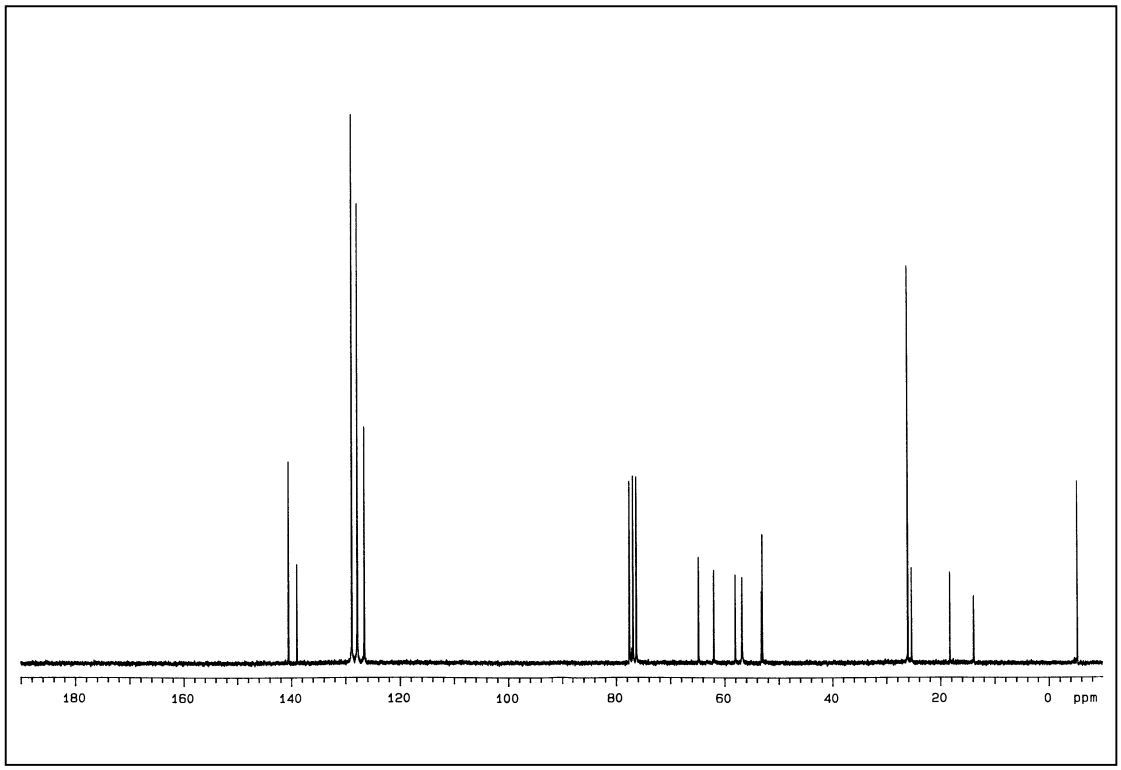


5-Methyl-4-(pyrid-2-yl)-5-azadispiro[2.1.2.3^3]decan-10-one **(253)**

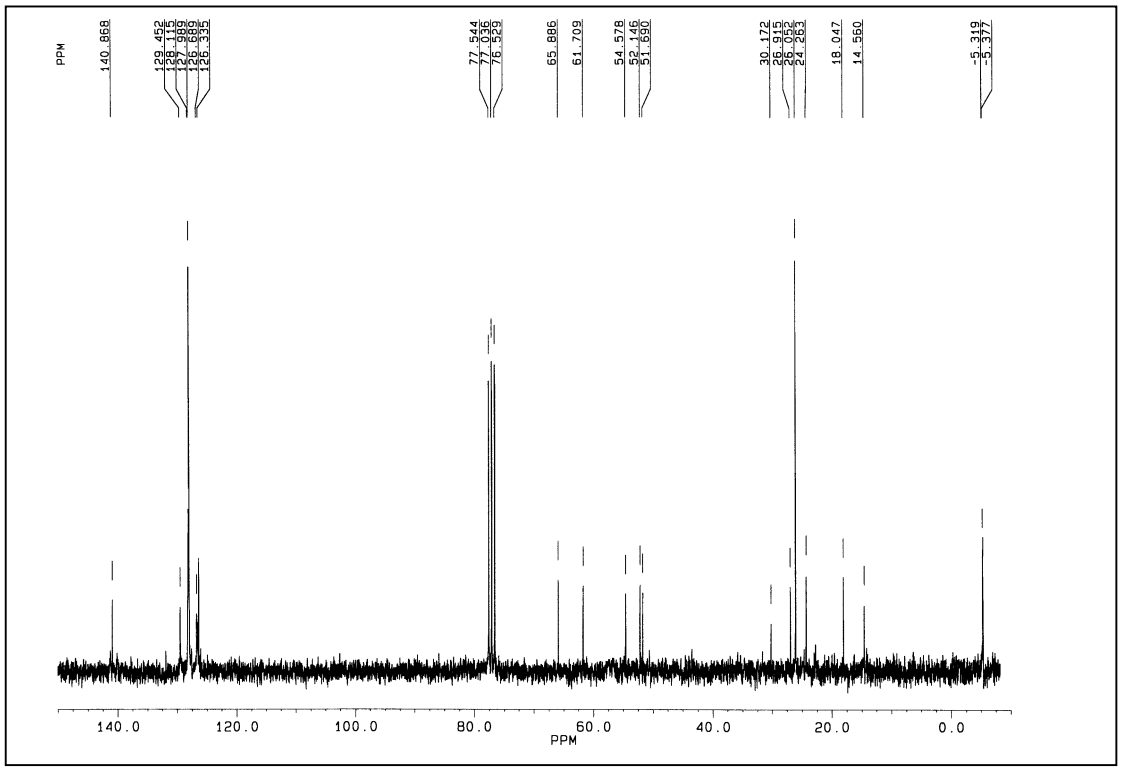
2. ^{13}C-NMR spectra



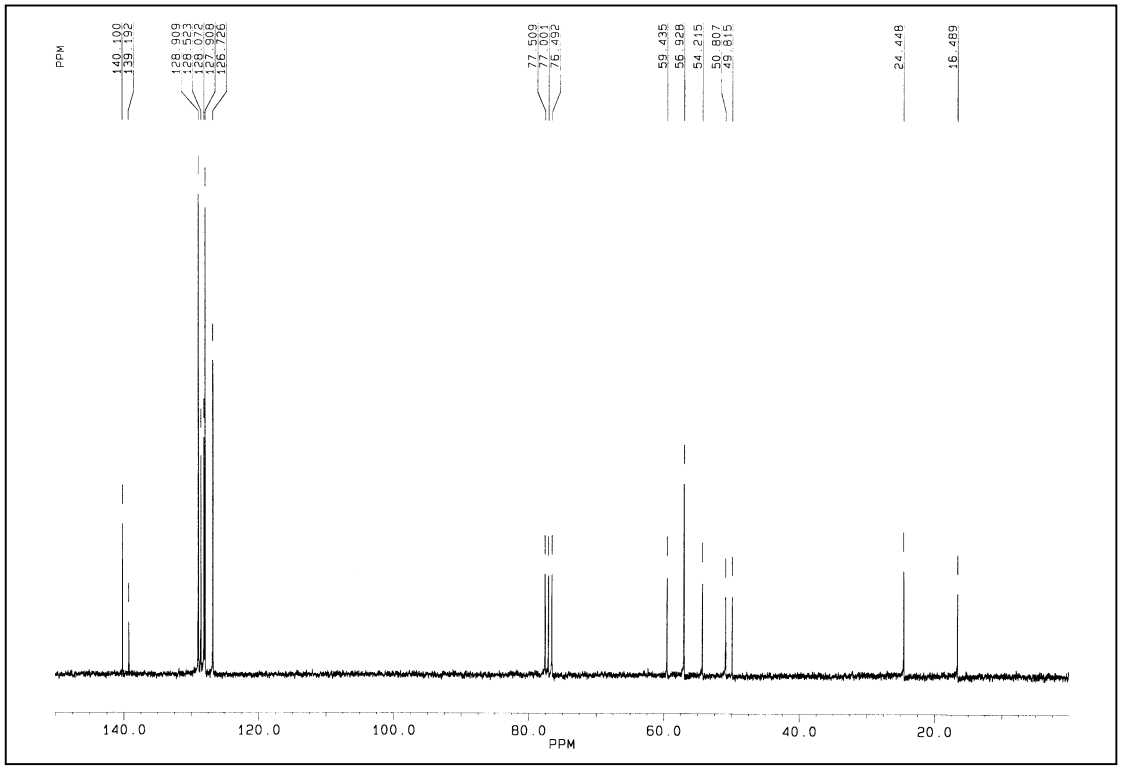
endo-(2*R*)-3-Benzyl-2-(*tert*-butyldimethylsilyloxymethyl)-*N*,*N*-dimethyl-3-azabicyclo[3.1.0]hex-1-ylamine (*endo*-**58**)



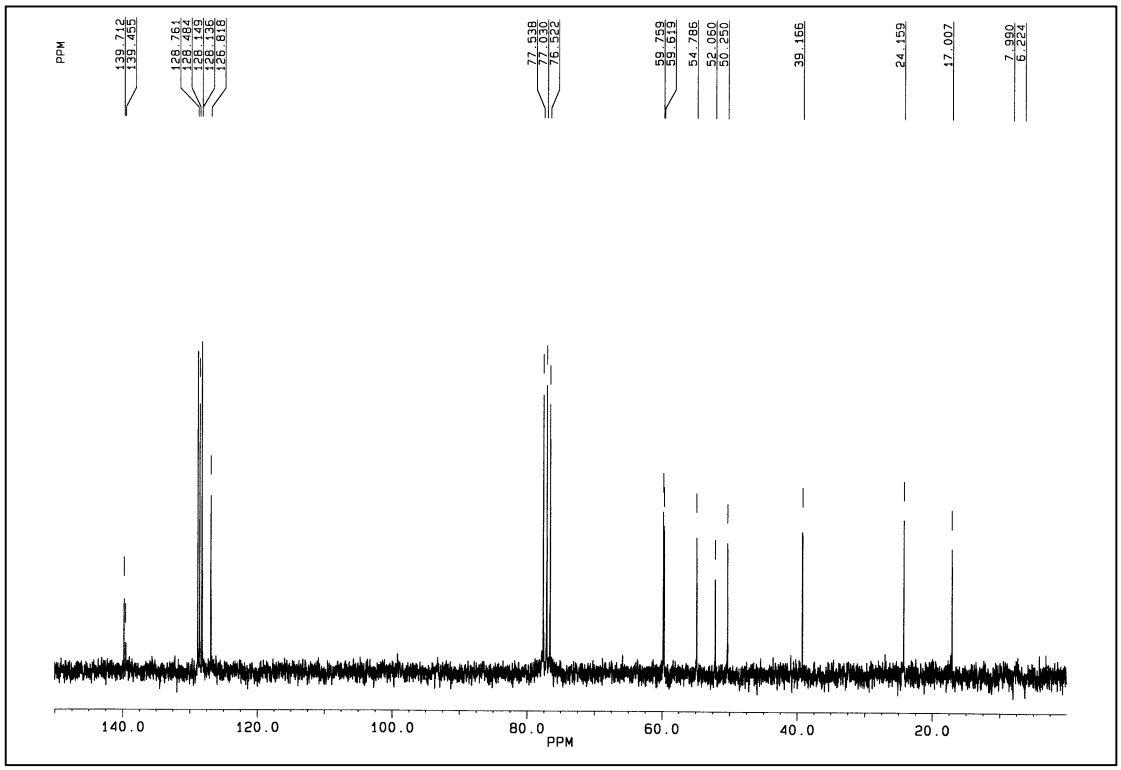
endo-(2*R*)-*N*,*N*,3-Tribenzyl-2-(*tert*-butyldimethylsilyloxymethyl)-3-azabicyclo-[3.1.0]hex-1-ylamine (*endo*-**59**)



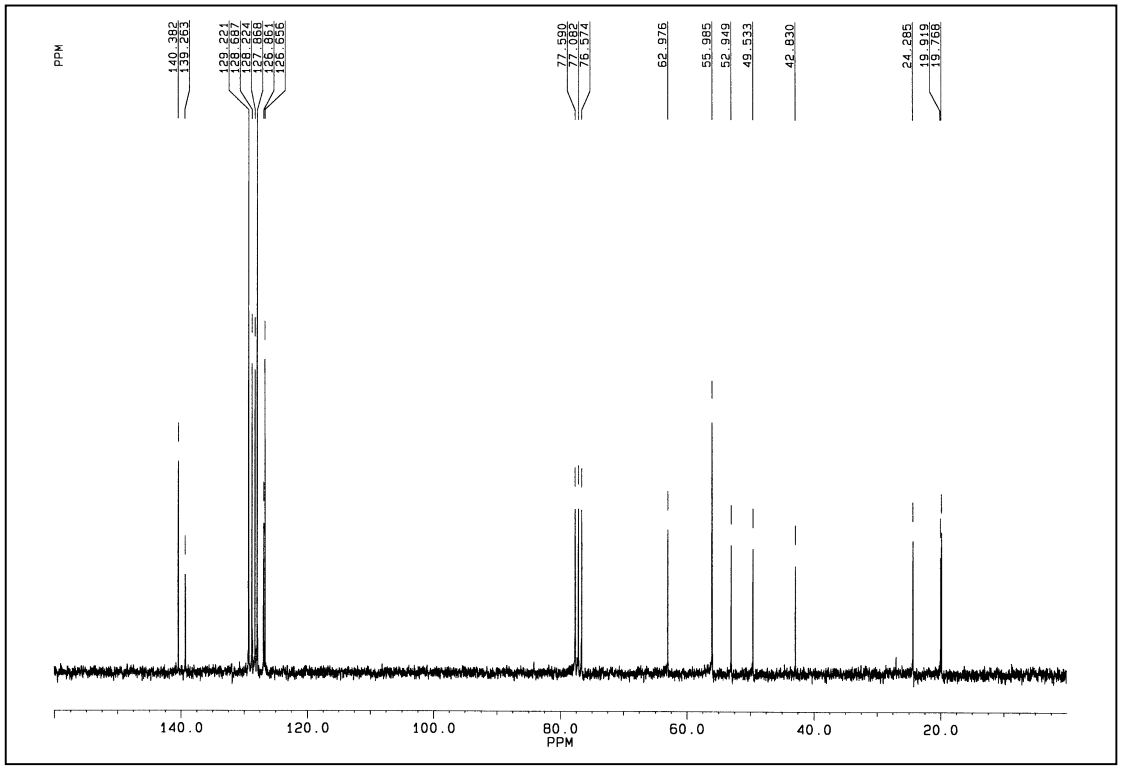
exo-(2*R*)-*N*,*N*,3-Tribenzyl-2-(*tert*-butyldimethylsilyloxymethyl)-3-azabicyclo-[3.1.0]hex-1-ylamine (*exo*-**59**)



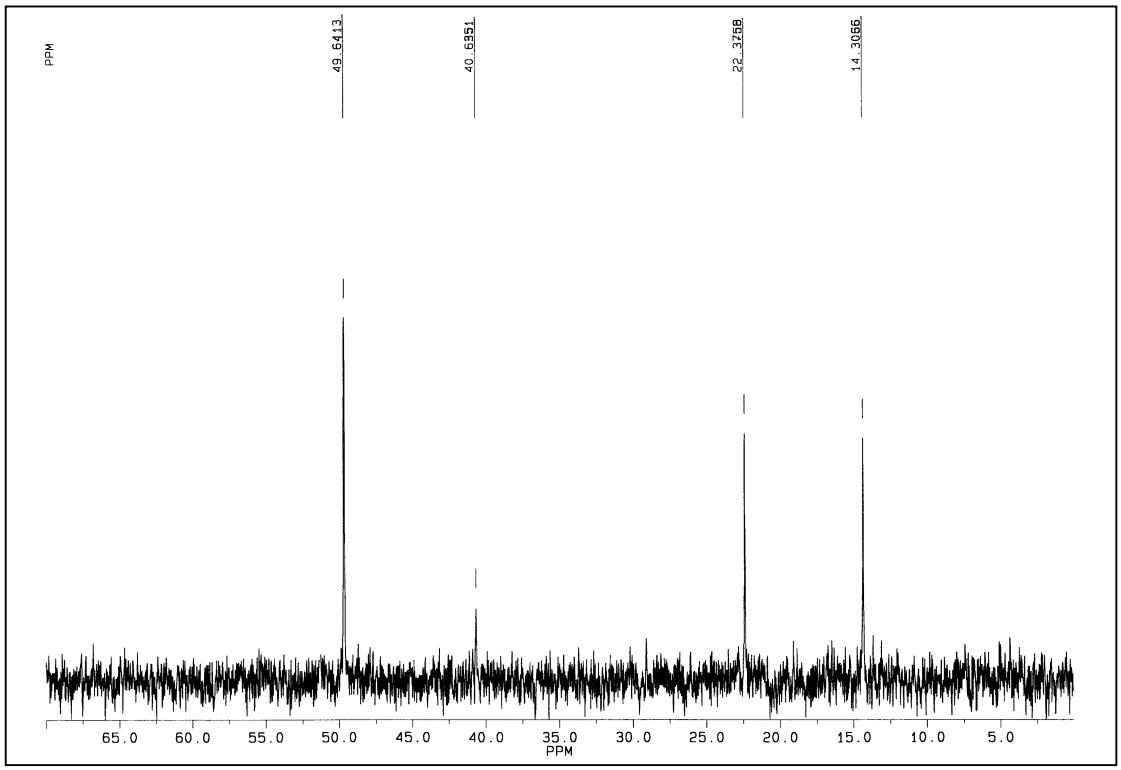
N,*N*,3-Tribenzyl-3-azabicyclo[3.1.0]hex-1-ylamine (**76**)



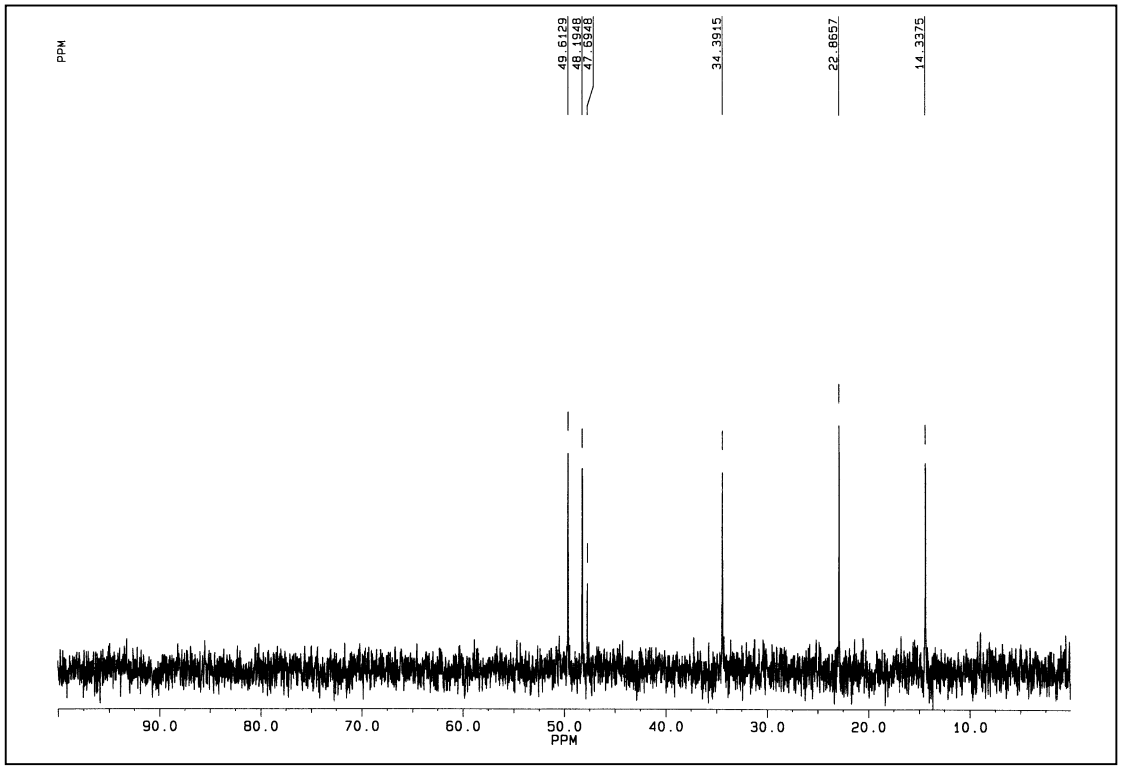
N,3-Dibenzyl-*N*-methyl-3-azabicyclo[3.1.0]hex-1-ylamine (**77**)



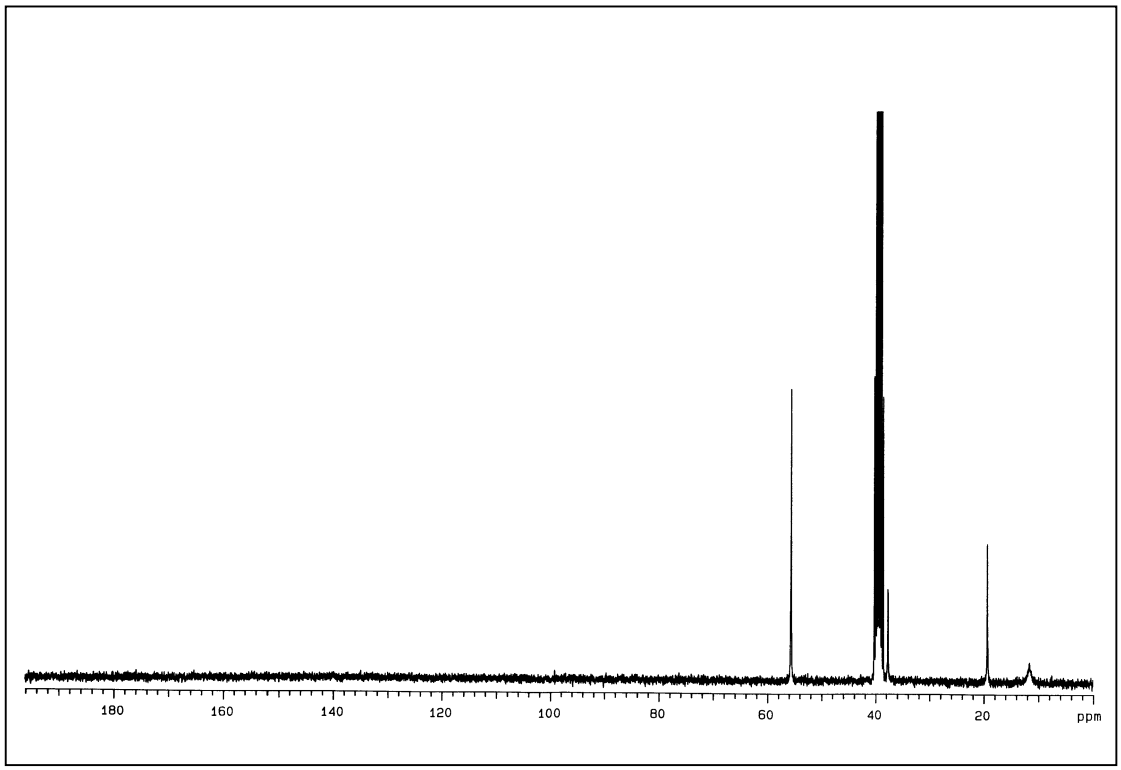
N,*N*,3-Tribenzyl-3-azabicyclo[4.1.0]hept-1-ylamine (**79**)



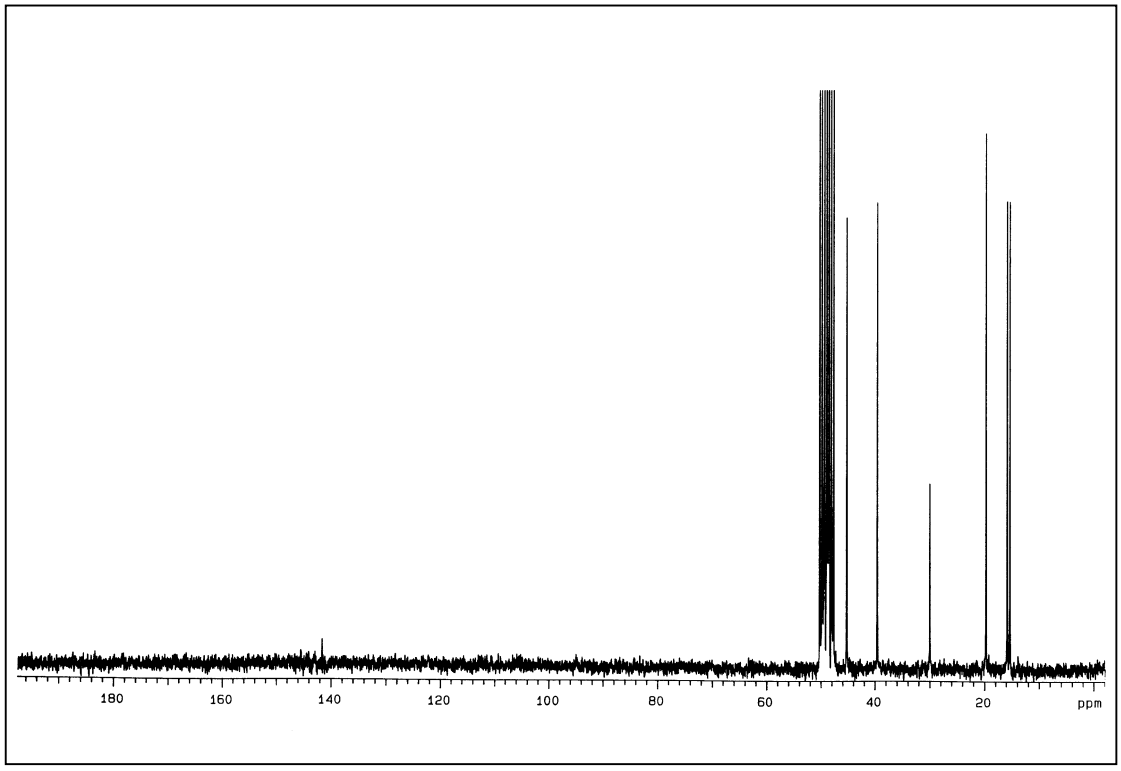
3-Azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**28**-**HCl**)



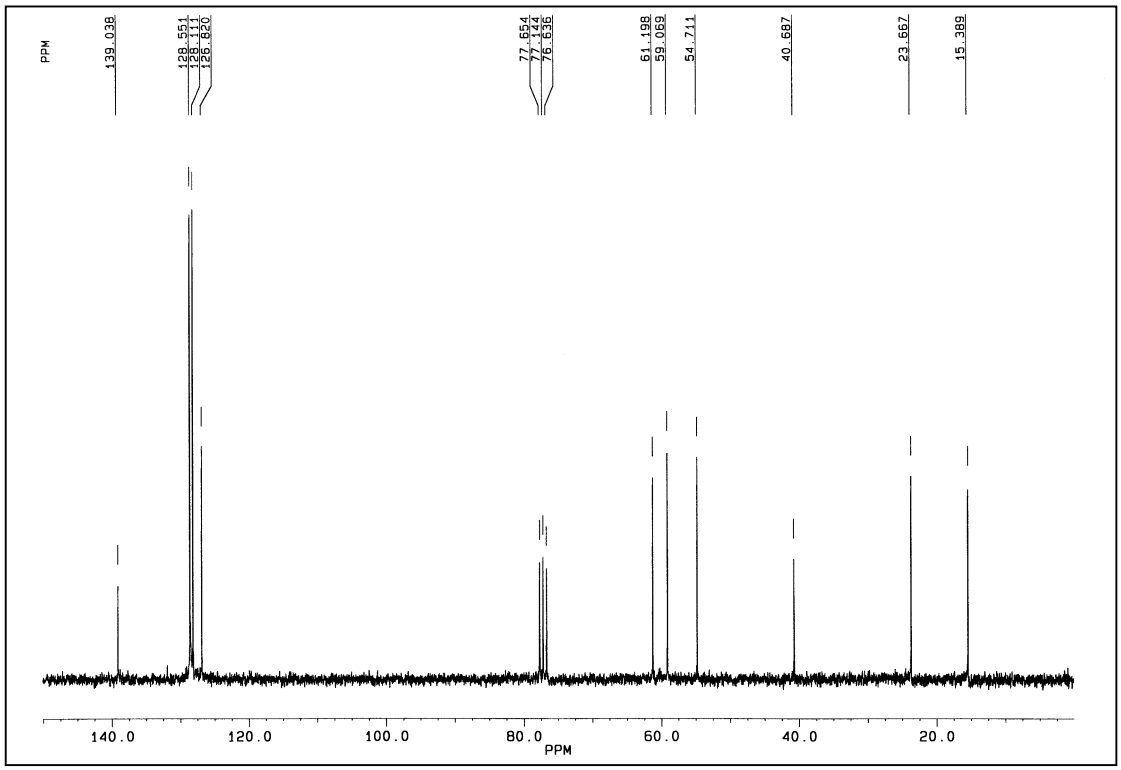
N-Methyl-3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**82**-**HCl**)



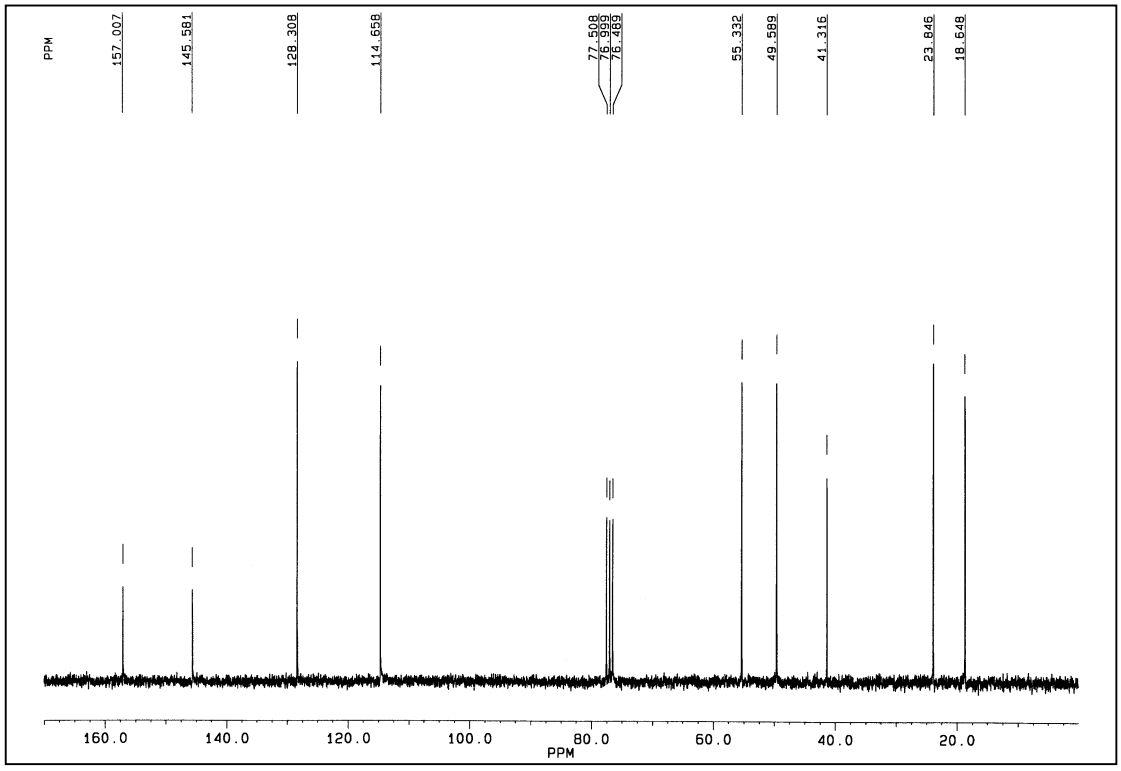
3-Methyl-3-azabicyclo[3.1.0]hex-1-ylamine dihydrochloride (**83**-**HCl**)



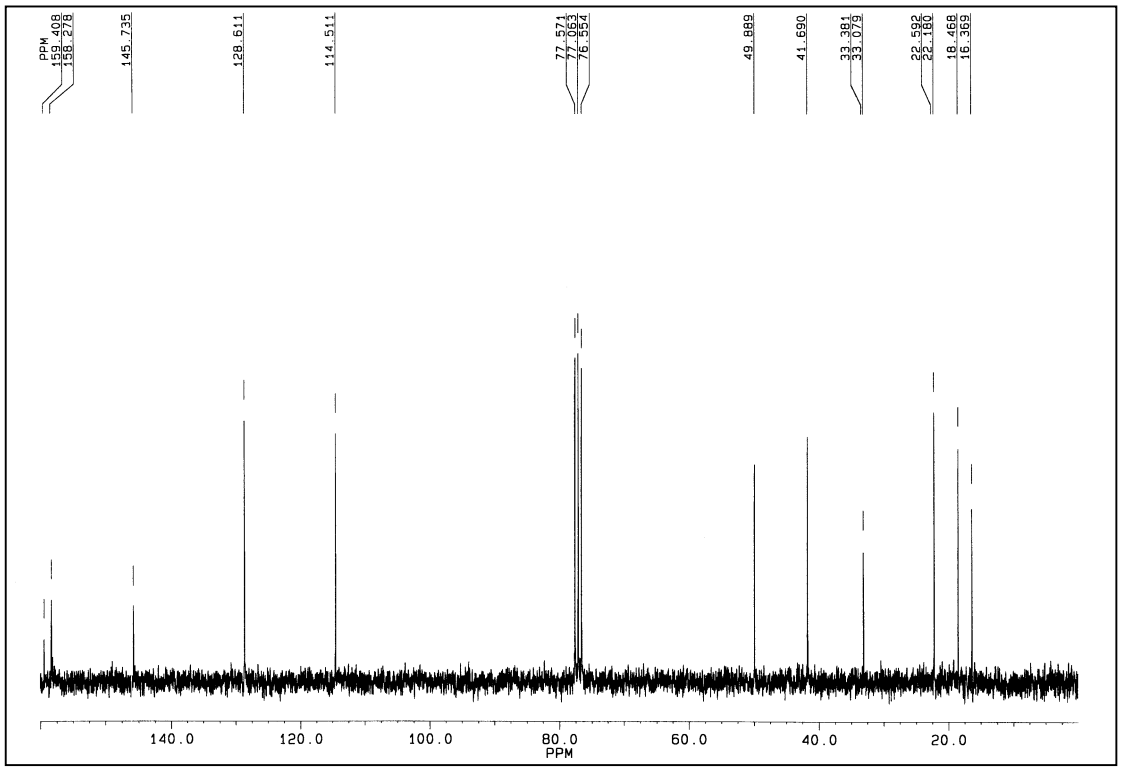
3-Azabicyclo[4.1.0]hept-1-ylamine dihydrochloride (**29**-**HCl**)



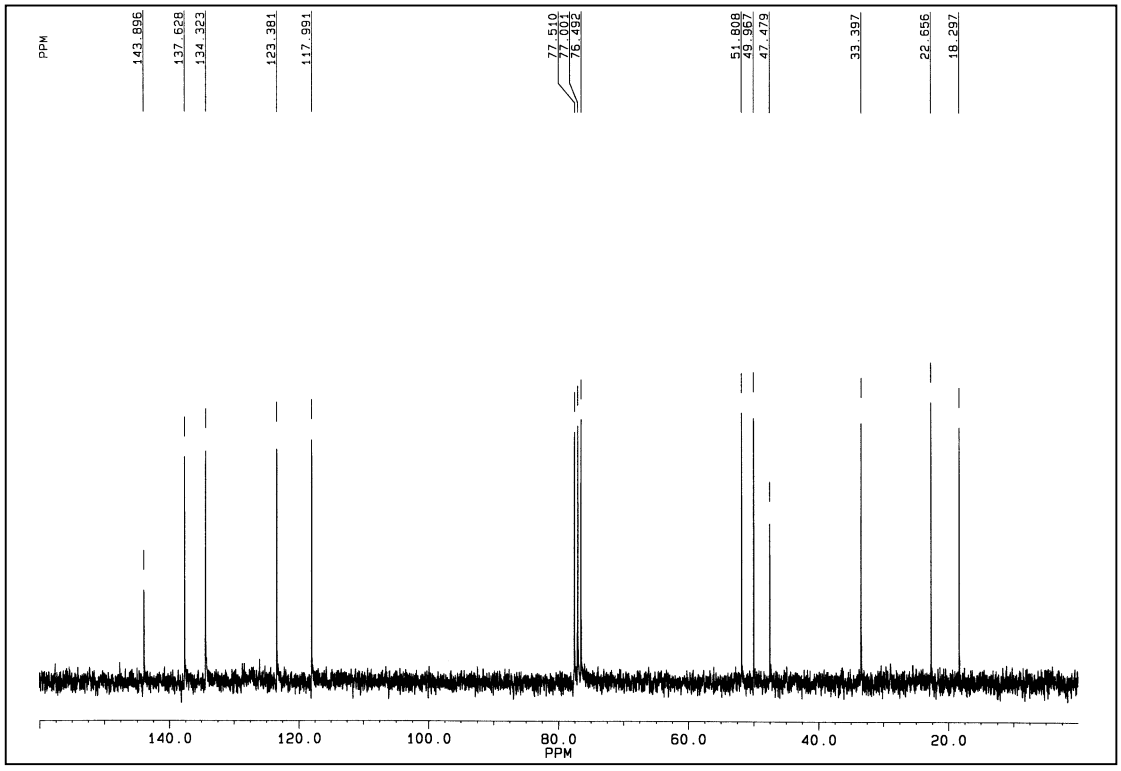
3-Benzyl-3-azabicyclo[3.1.0]hex-1-ylamine (**91**)



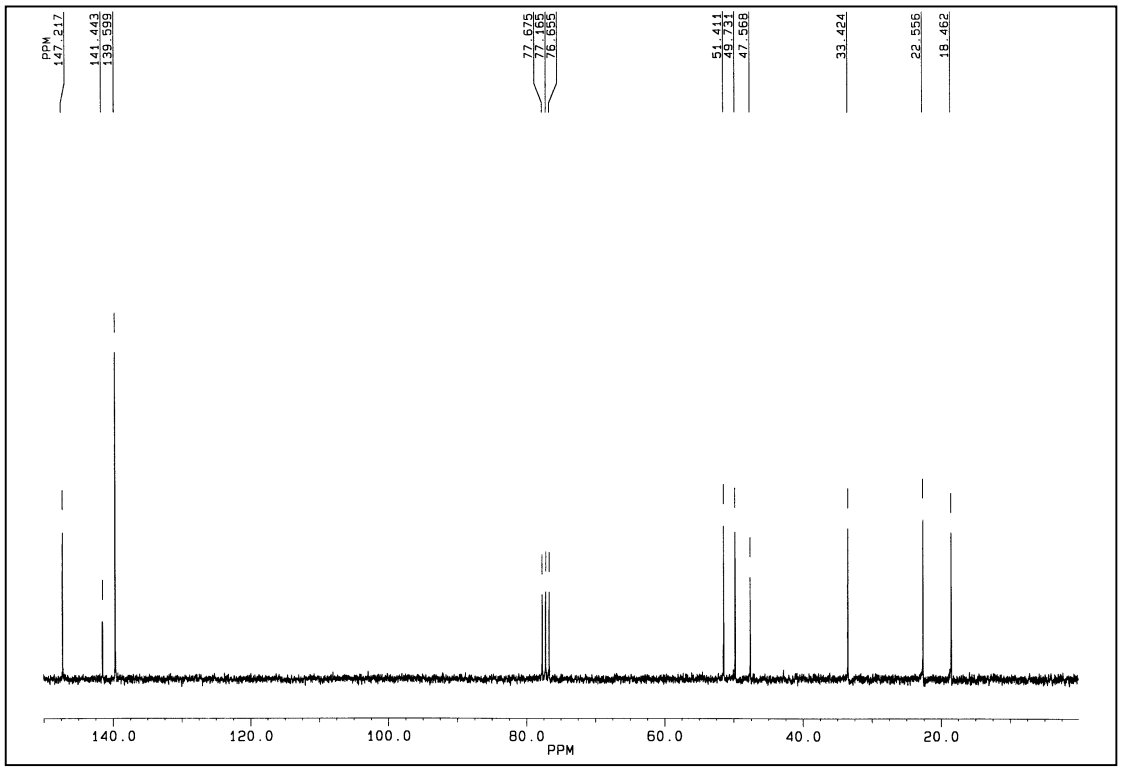
3-(6-Chloropyridazin-3-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**117**)



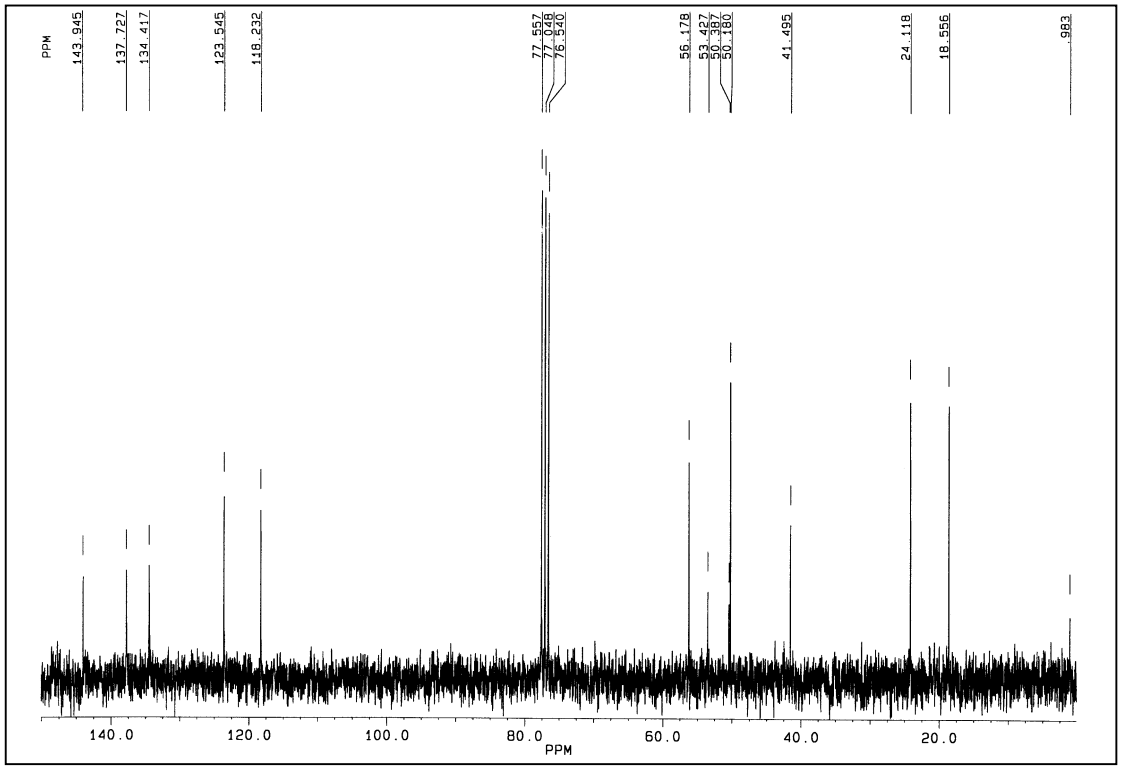
3-(6-Chloropyridazin-3-yl)-3-azabicyclo[4.1.0]hept-1-ylamine (**119**)



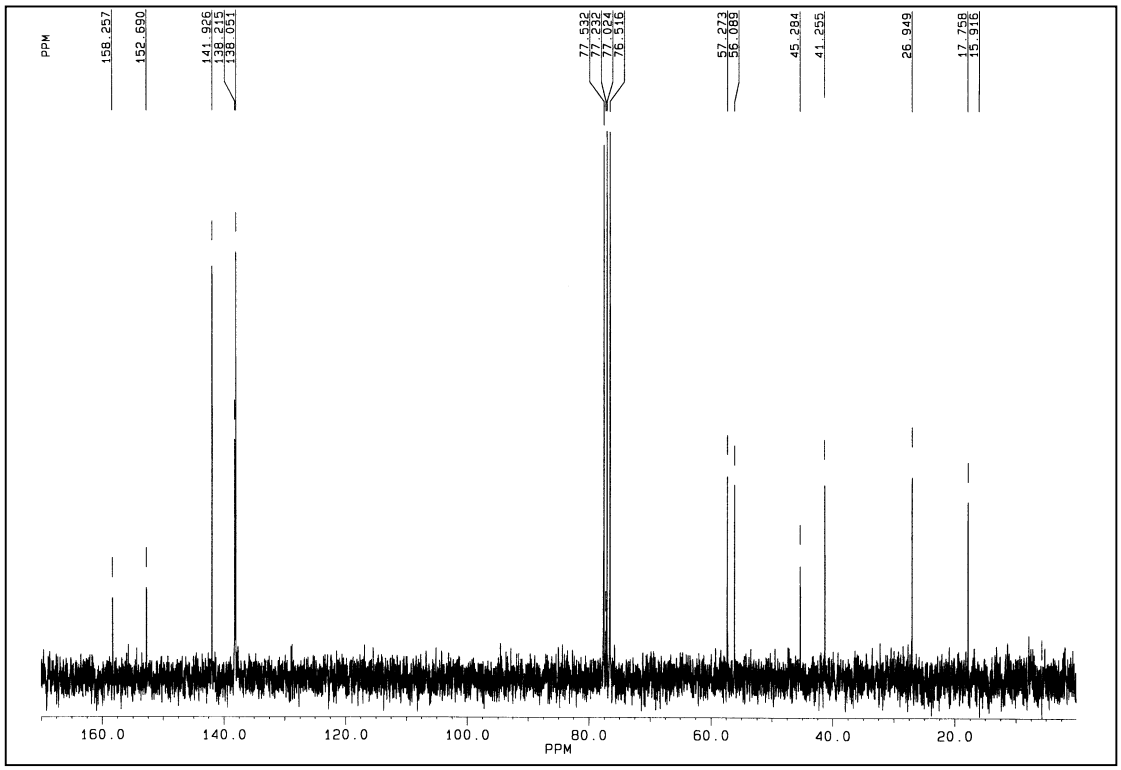
N-Methyl-3-(pyrid-3-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**120**)



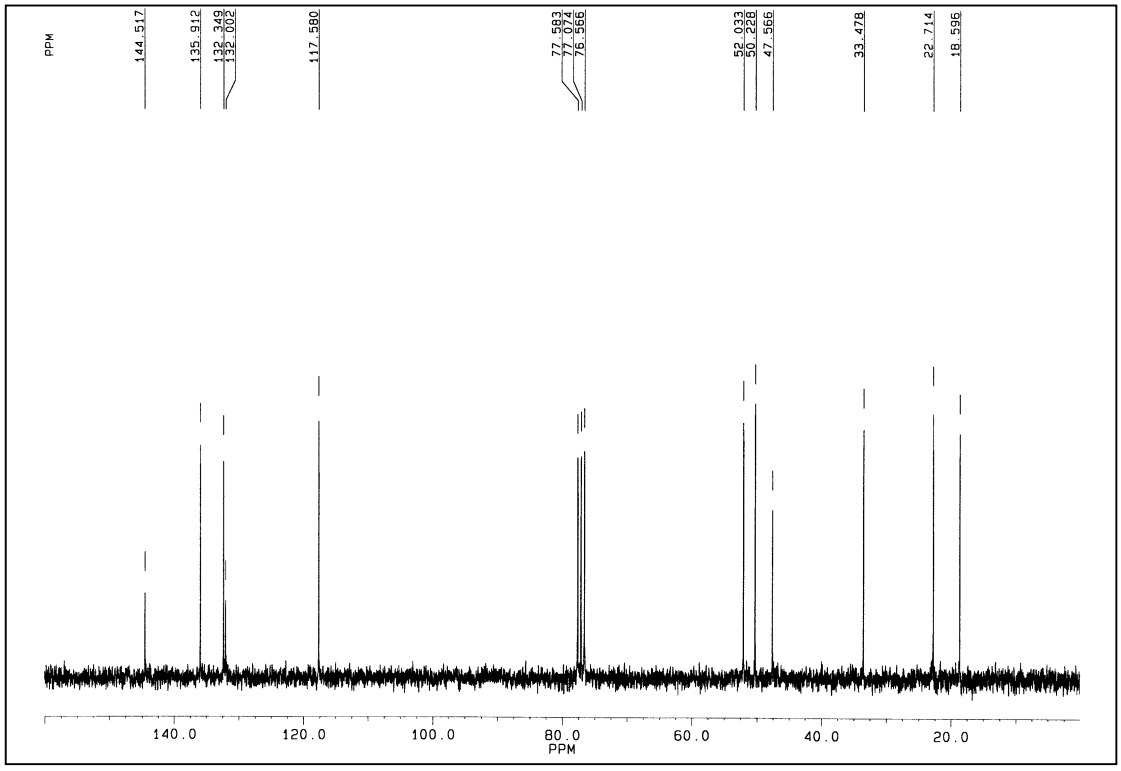
N-Methyl-3-(pyrimidin-5-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**121**)



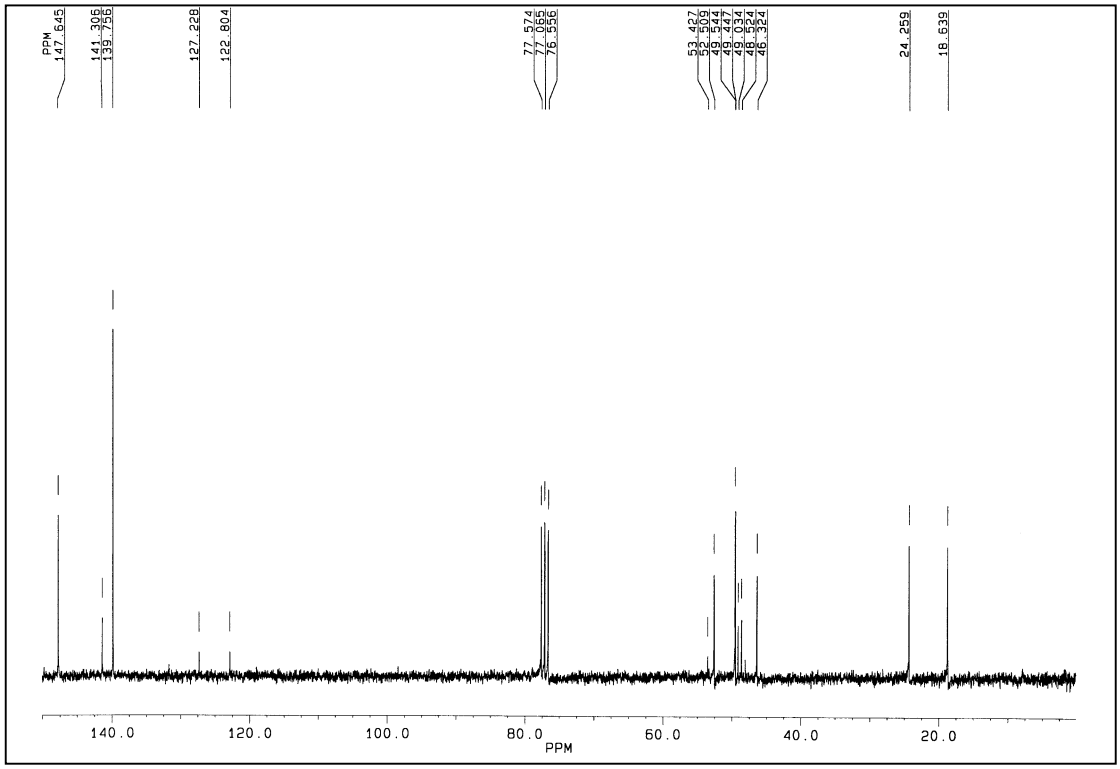
3-(Pyrid-3-yl)-azabicyclo[3.1.0]hex-1-ylamine (**122**)



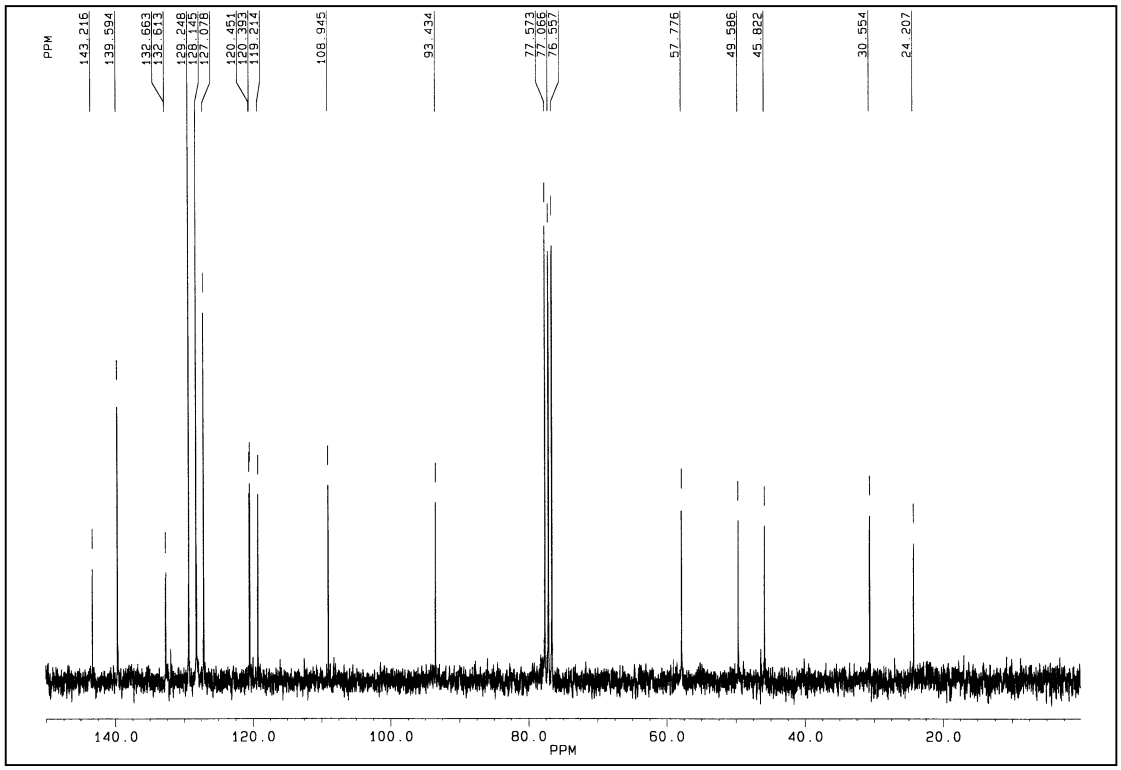
3-Methyl-*N*,*N*-di(pyrazin-2-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**131**)



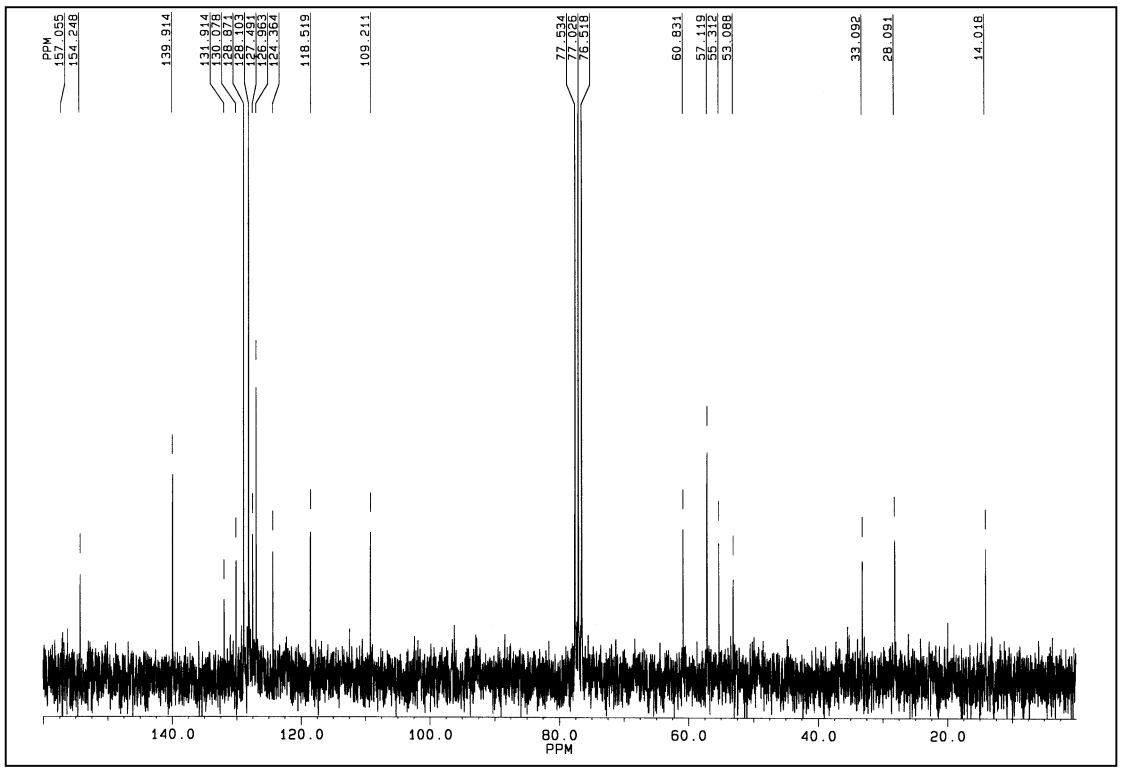
3-(5-Chloropyrid-3-yl)-*N*-methyl-3-azabicyclo[3.1.0]hex-1-ylamine (**133**)



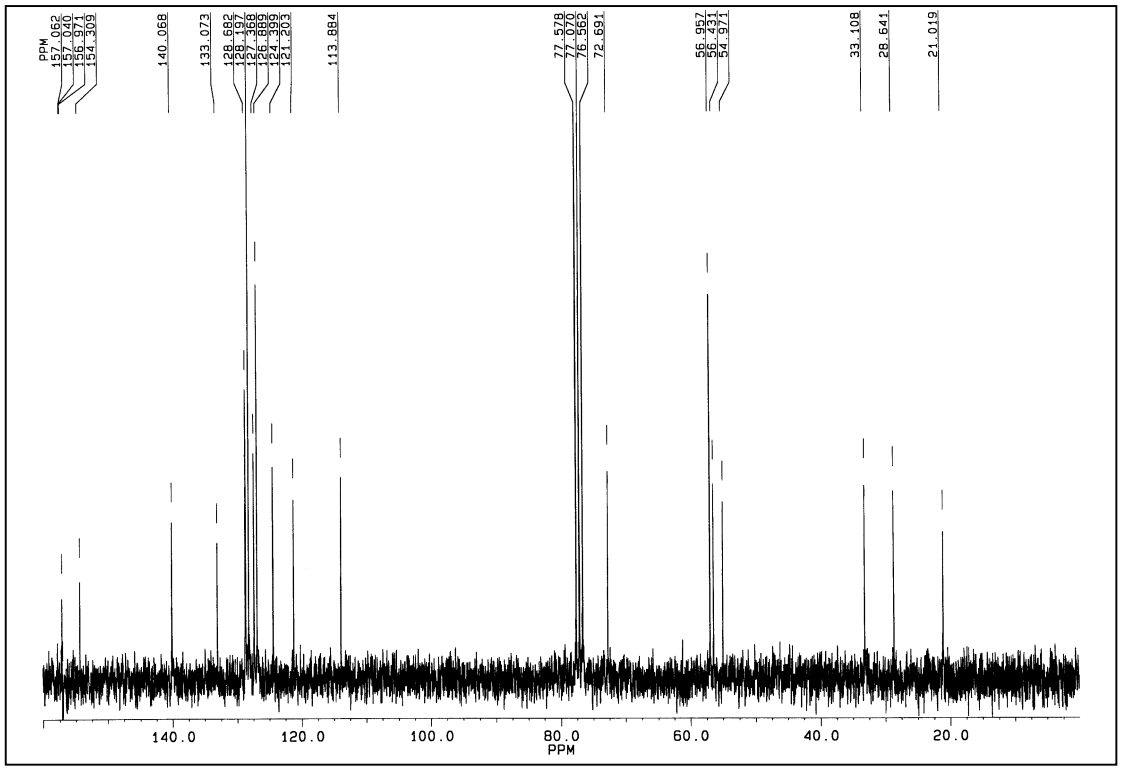
N-(2',2',2'-trifluoroethyl)-3-(pyrimid-5-yl)-3-azabicyclo[3.1.0]hex-1-ylamine (**145**)



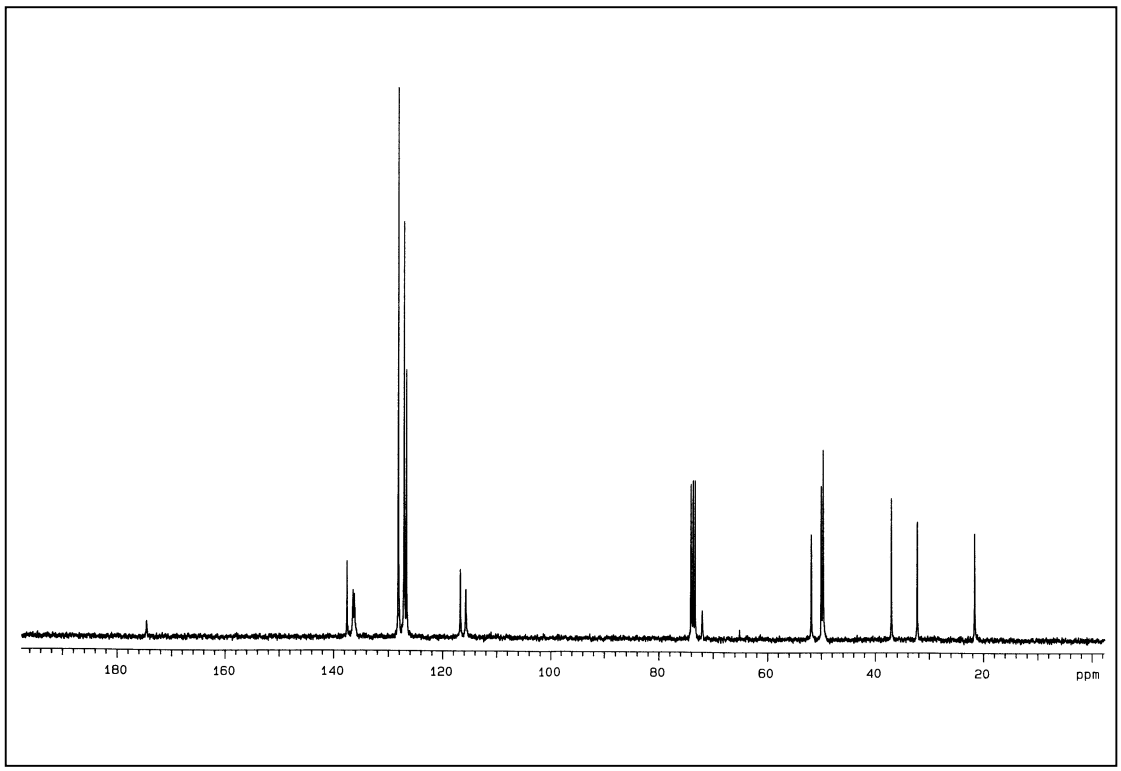
N,*N*-Dibenzyl-indolo[1,2-*a*]cyclopropa[1,2-*c*]pyrrolidin-8b-amine (**179**)



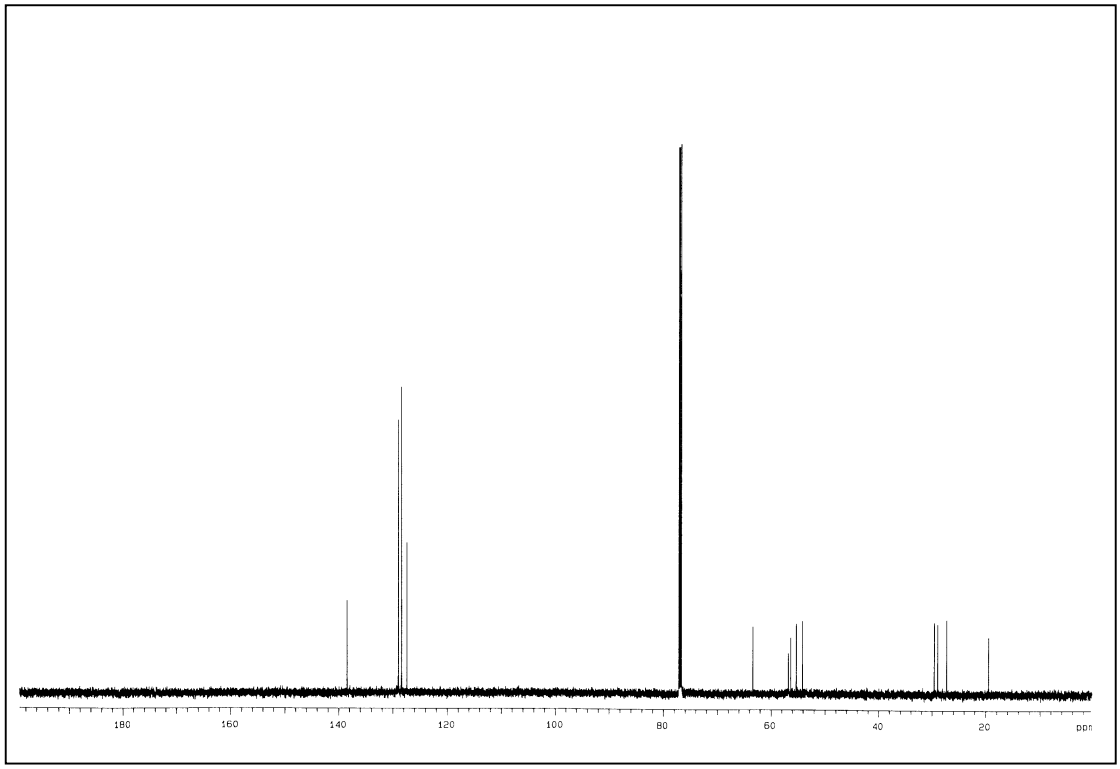
(1a*S*,8a*S*,8b*R)*-*N*,*N*-Dibenzyl-8,8a-dihydroindolo[1,2-*a*]cyclopropa[1,2-*c*]pyrrolidin-8b-amine [(1a*S*,8a*S*,8b*R)*-**183**]



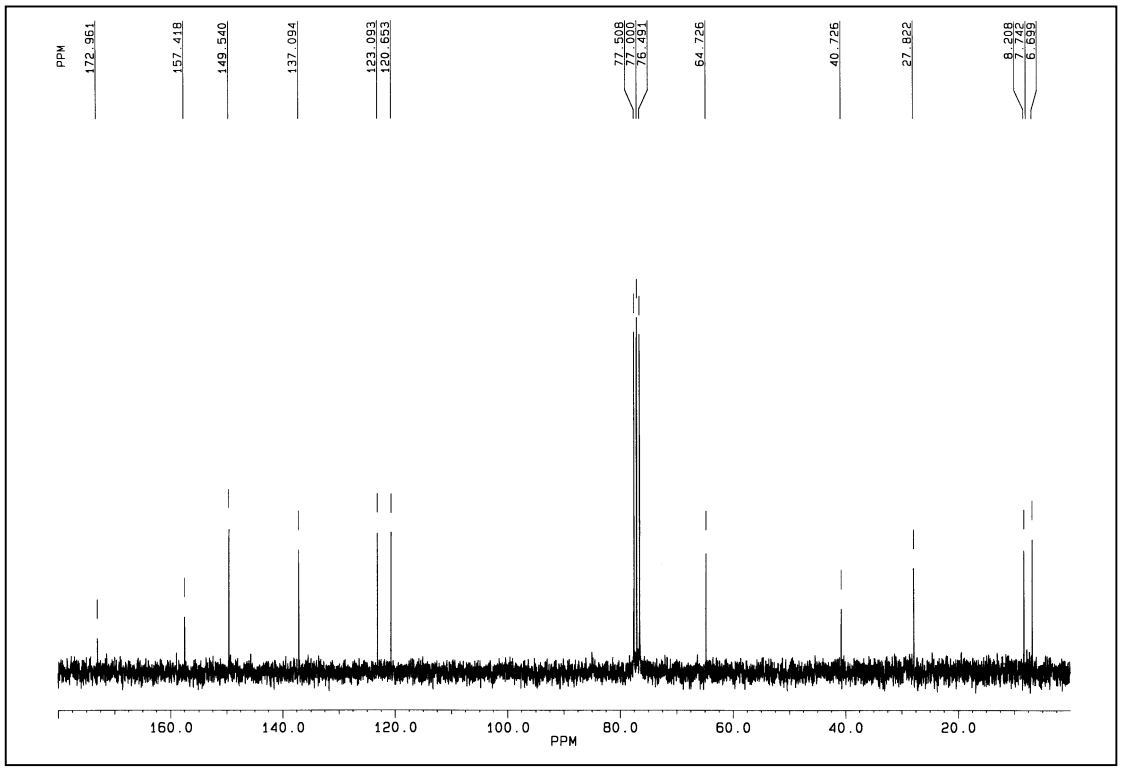
(1a*R*,8a*S*,8b*S)*-*N*,*N*-Dibenzyl-8,8a-dihydroindolo[1,2-*a*]cyclopropa[1,2-*c*]pyrrolidin-8b-amine [(1a*R*,8a*S*,8b*S)*-**183**]



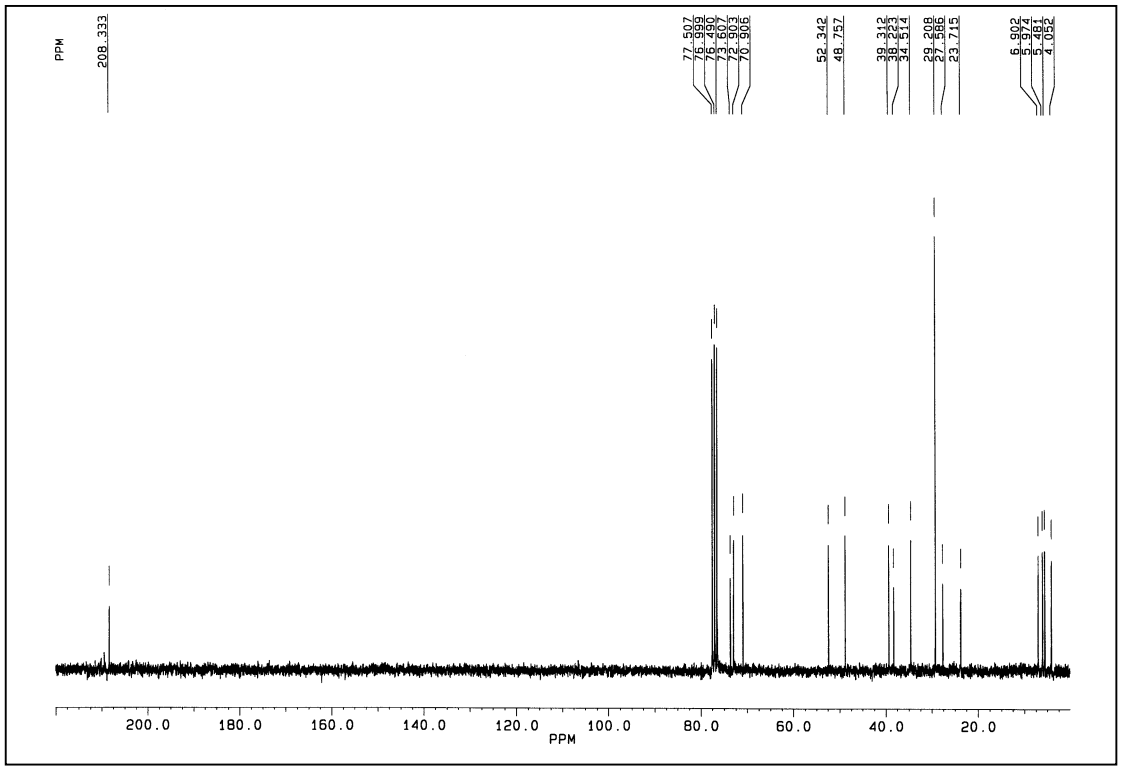
rac-*N*,*N*-Dibenzyl-1,2-diallyl-2-pyrrolidinecarboxamide (**191**)



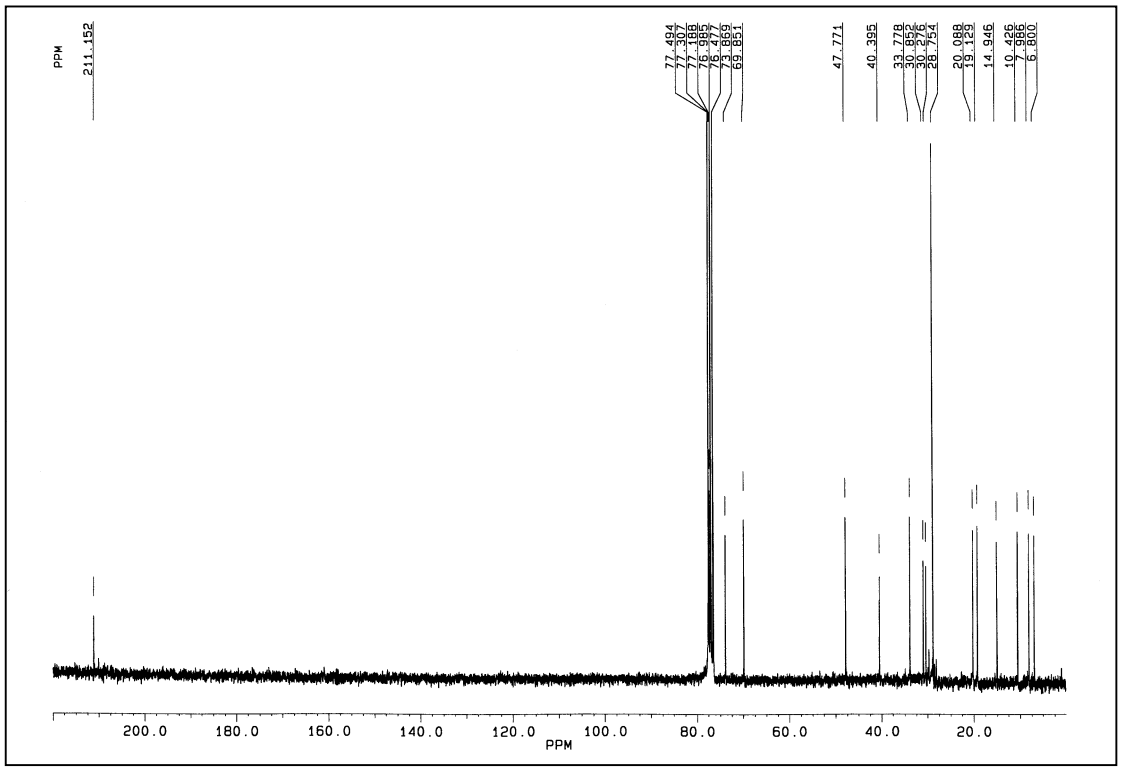
(1a*S*,6a*S*,6b*R)*-*N*,*N*-Dibenzyl-perhydrocyclopropa[1,2-*a*]pyrrolizin-6b-ylamine [(1a*S*,6a*S*,6b*R)*-**192**]



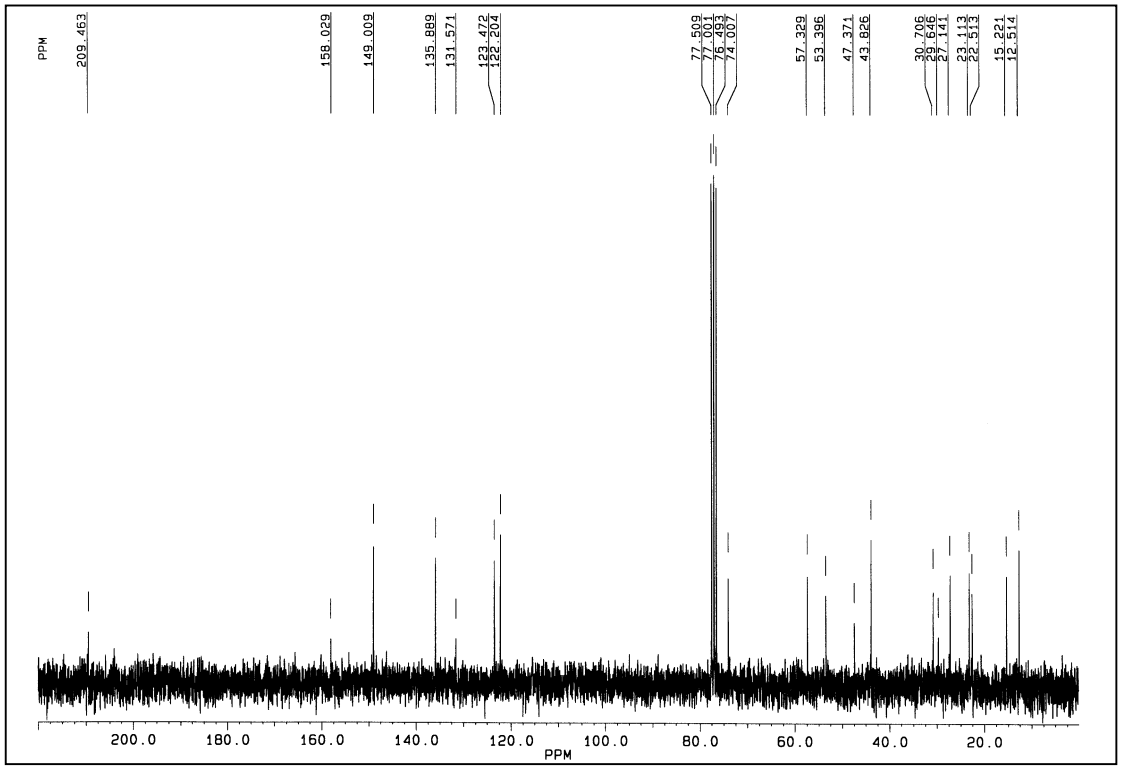
5-Methyl-6-(pyrid-2-yl)-5-azaspiro[2.3]hexan-4-one (**223**)



(1'''*S*,8a'''*R*)-1'''-*tert*-Butoxytrispiro[cyclopropane-1,1'-cyclopropane-2',1''-cyclopropane-3',8'''-perhydroindolizine]-7'''-one [(1'''*S*,8a'''*R*)-**250**]

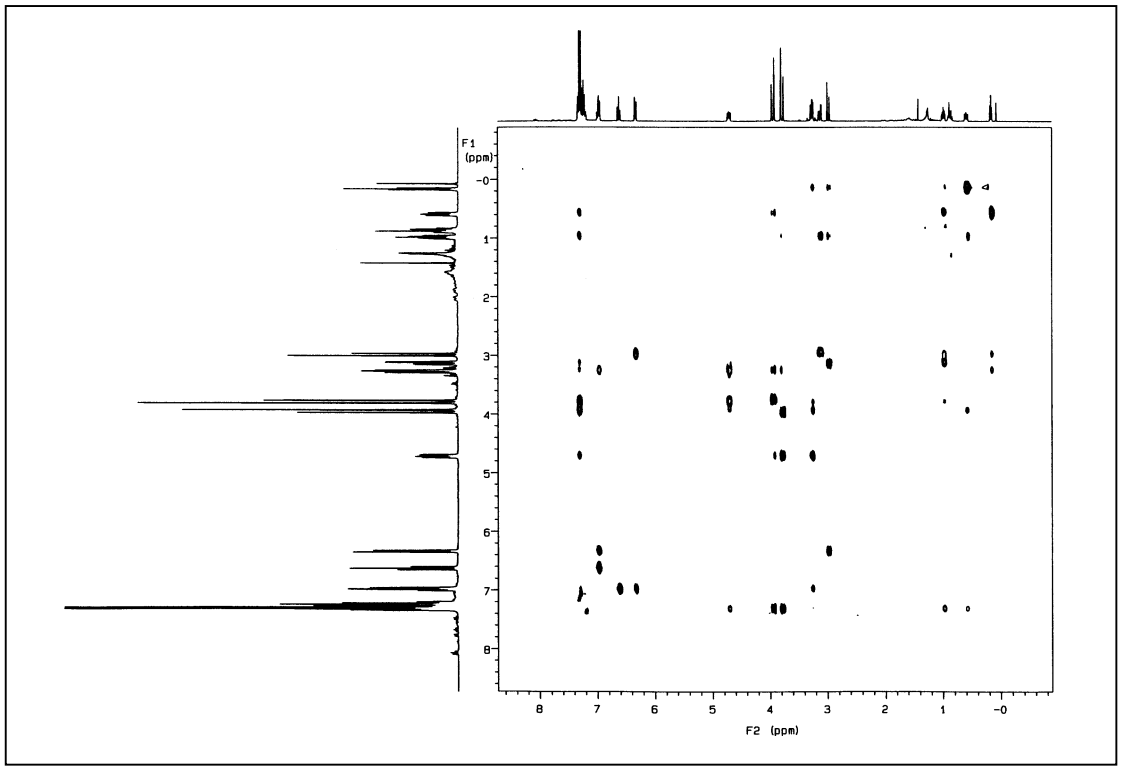


(1'''*S*,8a'''*R*)-1'''-*tert*-Butoxytrispiro[triscyclopropane-1,5''':1',6''':1'',8'''-perhydroindolizine]-7'''-one [(1'''*S*,8a'''*R*)-**251**]

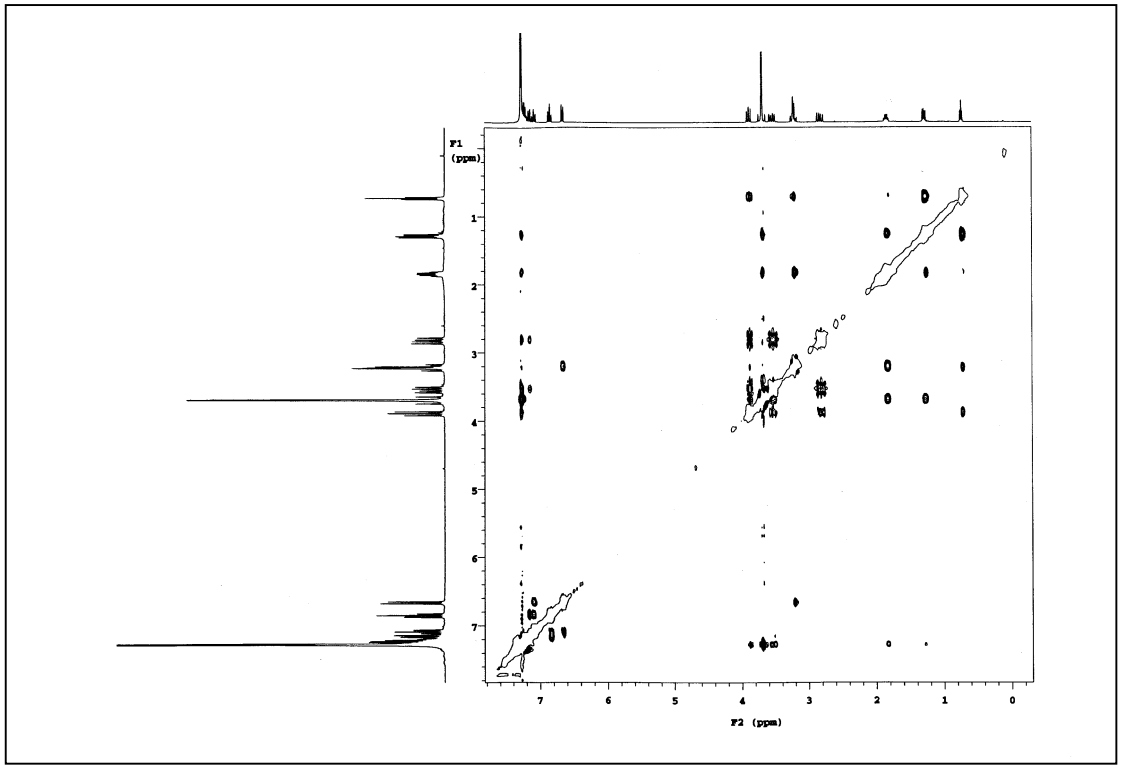


5-Methyl-4-(pyrid-2-yl)-5-azadispiro[2.1.2.3^3]decan-10-one **(253)**

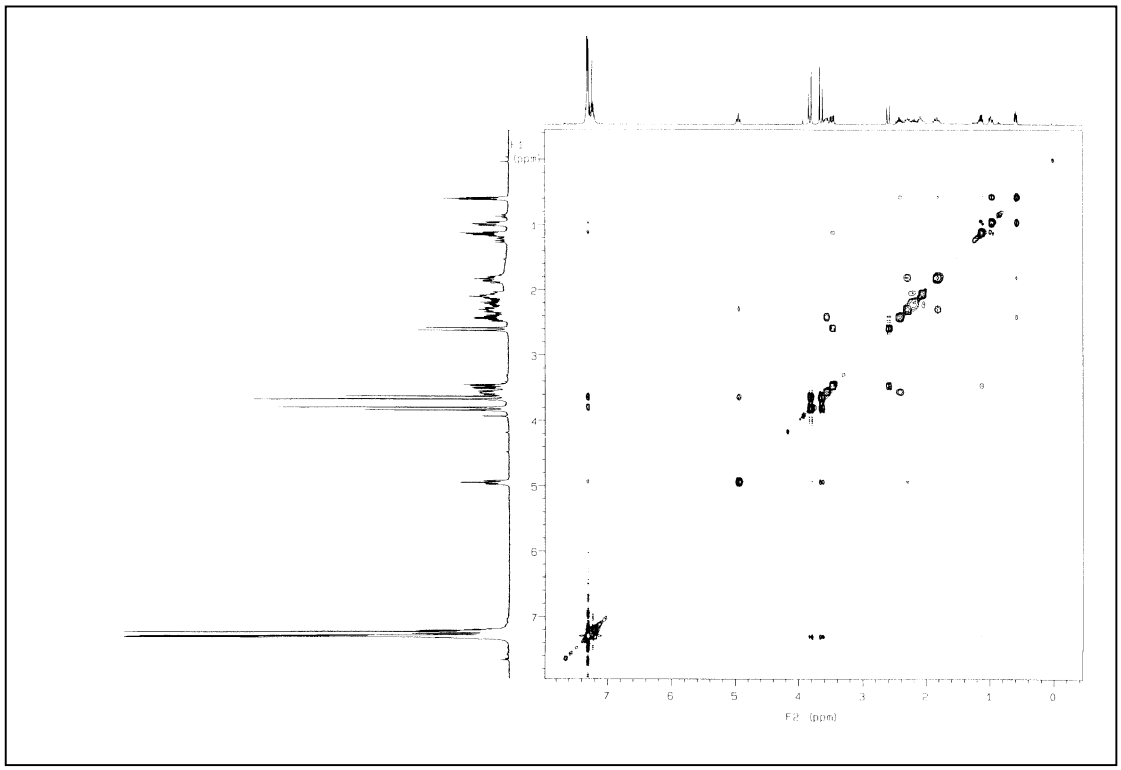
3. NOESY spectra



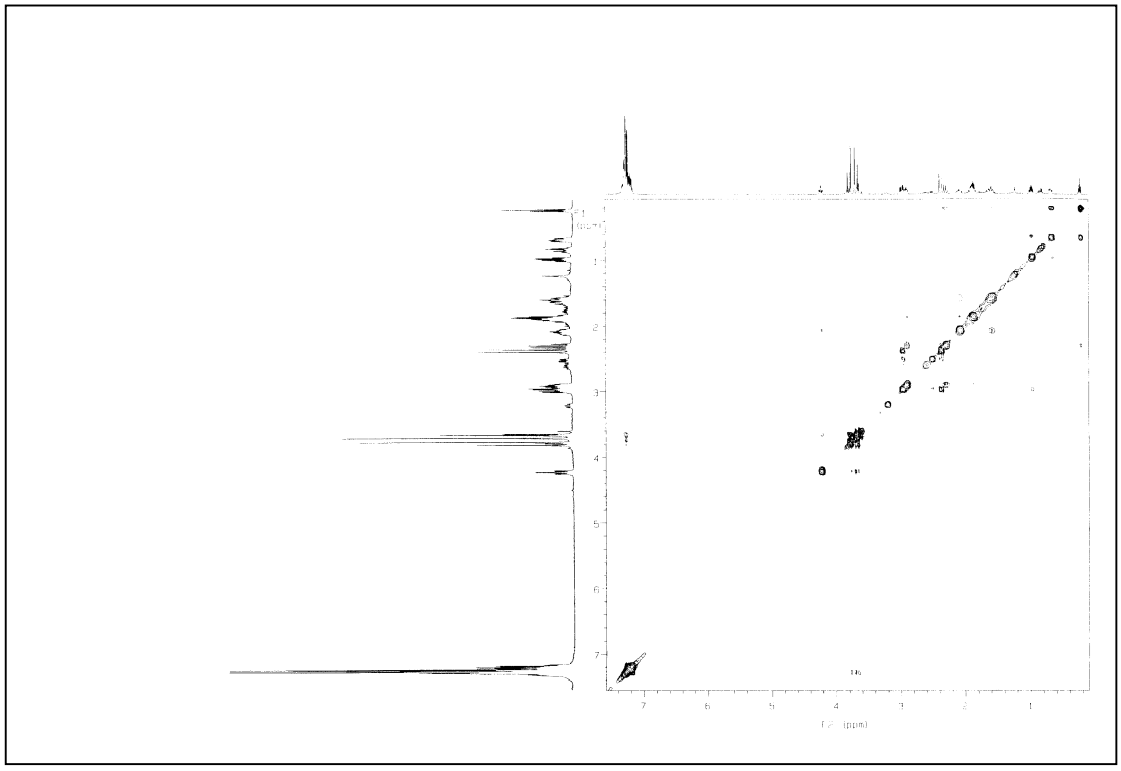
(1a*S*,8a*S*,8b*R)*-*N*,*N*-Dibenzyl-8,8a-dihydroindolo[1,2-*a*]cyclopropa[1,2-*c*]pyrrolidin-8b-amine [(1a*S*,8a*S*,8b*R)*-**183**]



(1a*R*,8a*S*,8b*S)*-*N*,*N*-Dibenzyl-8,8a-dihydroindolo[1,2-*a*]cyclopropa[1,2-*c*]pyrrolidin-8b-amine [(1a*R*,8a*S*,8b*S)*-**183**]



(1a*S*,6a*S*,6b*R)*-*N*,*N*-Dibenzyl-perhydrocyclopropa[1,2-*a*]pyrrolizin-6b-ylamine [(1a*S*,6a*S*,6b*R)*-**192**]



(1a*R*,6a*S*,6b*S)*-*N*,*N*-Dibenzyl-perhydrocyclopropa[1,2-*a*]pyrrolizin-6b-ylamine [(1a*R*,6a*S*,6b*S)*-**192**]

G. CRYSTAL DATA

1. *endo*-(2*R*)-3-(5-Chloropyrid-3-yl)-2-(hydroxymethyl)-*N*,*N*-dimethyl-3-azabicyclo-[3.1.0]hex-1-ylamine (*endo*-**163**)

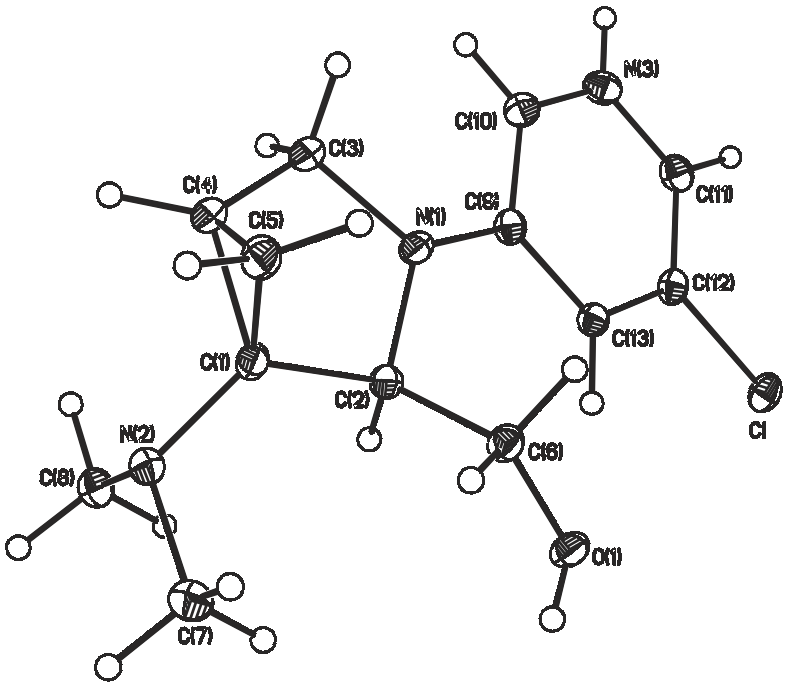


Table 1. Crystal data and structure refinement for *endo*-**163**.

Empirical formula	C13 H19 Cl N3 O
Formula weight	268.76
Temperature	133(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, P 2(1)
Unit cell dimensions	a = 8.6507(10) Å α = 90 deg.
	b = 7.2148(5) Å β = 107.121(9) deg.
	c = 10.8359(13) Å γ = 90 deg.
Volume	646.33(12) $Å^3$
Z, Calculated density	2, 1.381 Mg/m^3
Absorption coefficient	0.288 mm^{-1}
F(000)	286
Theta range for data collection	1.97 to 24.70 deg.
Index ranges	–10<=h<=10, -8<=k<=8, –12<=l<=10
Reflections collected / unique	7346 / 2164 [R(int) = 0.0330]
Observed reflections	2100 [I>2sigma(I)]
Completeness to θ = 24.70	99.5%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2164 / 1 / 167
Goodness-of-fit on F^2	1.035
Final R indices [I>2sigma(I)]	R1 = 0.0253, wR2 = 0.0660
R indices (all data)	R1 = 0.0262, wR2 = 0.0665
Absolute structure parameter	0.03(5)
Largest diff. peak and hole	0.203 and –0.347 $eÅ^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (A^2) for *endo*-**163**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
Cl	0.2431(1)	0.5466(1)	0.8112(1)	0.02721(12)
O(1)	0.5134(2)	0.4326(2)	0.5117(1)	0.0255(3)
N(1)	0.1177(2)	0.4703(2)	0.3183(1)	0.0224(3)
N(2)	0.3723(2)	0.6304(2)	0.1226(1)	0.0231(3)
N(3)	-0.1524(2)	0.4624(2)	0.5221(2)	0.0264(3)
C(1)	0.2718(2)	0.5140(2)	0.1742(1)	0.0212(4)
C(2)	0.2859(2)	0.5102(2)	0.3188(2)	0.0199(4)
C(3)	-0.0021(2)	0.4916(3)	0.1910(2)	0.0254(4)
C(4)	0.0972(2)	0.4928(2)	0.0985(2)	0.0250(4)
C(5)	0.2127(2)	0.3334(3)	0.1050(2)	0.0273(4)
C(6)	0.4060(2)	0.3620(2)	0.3953(2)	0.0226(4)
C(7)	0.5446(2)	0.5898(3)	0.1755(2)	0.0305(4)
C(8)	0.3402(2)	0.8278(2)	0.1339(2)	0.0273(4)
C(9)	0.0692(2)	0.4773(2)	0.4285(2)	0.0211(3)
C(10)	-0.0963(2)	0.4593(3)	0.4205(2)	0.0239(4)
C(11)	-0.0485(2)	0.4845(2)	0.6400(2)	0.0251(4)
C(12)	0.1149(2)	0.5067(2)	0.6556(2)	0.0225(4)
C(13)	0.1778(2)	0.5019(2)	0.5524(2)	0.0207(3)

Table 3. Bond lengths [pm] and angles [deg] for *endo*-**163**.

Cl-C(12)	174.8(2)	C(1)-C(4)	149.9(2)
O(1)-C(6)	142.2(2)	C(1)-C(5)	151.5(2)
N(1)-C(9)	137.7(2)	C(1)-C(2)	153.7(2)
N(1)-C(3)	146.9(2)	C(2)-C(6)	155.0(2)
N(1)-C(2)	148.2(2)	C(3)-C(4)	150.0(2)
N(2)-C(1)	143.5(2)	C(4)-C(5)	151.1(3)
N(2)-C(7)	146.1(2)	C(9)-C(13)	140.5(2)
N(2)-C(8)	146.3(2)	C(9)-C(10)	141.5(2)
N(3)-C(10)	132.7(2)	C(11)-C(12)	138.3(2)
N(3)-C(11)	133.8(2)	C(12)-C(13)	138.1(2)

C(9)-N(1)-C(3)	119.96(14)	C(1)-C(2)-C(6)	113.38(13)
C(9)-N(1)-C(2)	122.59(13)	N(1)-C(3)-C(4)	104.10(13)
C(3)-N(1)-C(2)	113.81(13)	C(1)-C(4)-C(3)	108.57(13)
C(1)-N(2)-C(7)	113.26(13)	C(1)-C(4)-C(5)	60.43(11)
C(1)-N(2)-C(8)	112.67(13)	C(3)-C(4)-C(5)	117.74(15)
C(7)-N(2)-C(8)	111.05(14)	C(4)-C(5)-C(1)	59.40(11)
C(10)-N(3)-C(11)	119.17(15)	O(1)-C(6)-C(2)	112.77(14)
N(2)-C(1)-C(4)	118.35(14)	N(1)-C(9)-C(13)	122.97(15)
N(2)-C(1)-C(5)	117.74(14)	N(1)-C(9)-C(10)	120.31(15)
C(4)-C(1)-C(5)	60.17(11)	C(13)-C(9)-C(10)	116.73(15)
N(2)-C(1)-C(2)	122.20(13)	N(3)-C(10)-C(9)	123.96(16)
C(4)-C(1)-C(2)	108.68(13)	N(3)-C(11)-C(12)	120.38(15)
C(5)-C(1)-C(2)	113.79(14)	C(13)-C(12)-C(11)	122.03(16)
N(1)-C(2)-C(1)	102.54(12)	C(13)-C(12)-Cl	119.76(13)
N(1)-C(2)-C(6)	111.79(13)	C(11)-C(12)-Cl	118.21(13)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2) *endo*-**163**.

The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$h^2 a^{*2}$ U11 + ... + 2 h k a* b* U12]

Atom	U11	U22	U33	U23	U13	U12
Cl	0.0299(2)	0.0335(2)	0.01775(19)	0.00054(18)	0.00623(14)	0.00517(18)
O(1)	0.0188(6)	0.0375(7)	0.0186(6)	-0.0001(5)	0.0030(5)	0.0012(5)
N(1)	0.0185(6)	0.0298(8)	0.0174(7)	0.0009(6)	0.0031(5)	-0.0013(6)
N(2)	0.0217(7)	0.0272(8)	0.0209(7)	0.0028(6)	0.0069(5)	-0.0005(6)
N(3)	0.0214(7)	0.0272(8)	0.0325(8)	-0.0015(7)	0.0109(6)	-0.0008(6)
C(1)	0.0230(8)	0.0222(11)	0.0166(7)	0.0016(6)	0.0031(6)	-0.0003(6)
C(2)	0.0199(7)	0.0227(10)	0.0172(7)	-0.0004(6)	0.0058(6)	-0.0011(6)
C(3)	0.0226(7)	0.0313(10)	0.0196(8)	0.0006(7)	0.0019(6)	-0.0047(7)
C(4)	0.0231(8)	0.0315(10)	0.0176(8)	0.0005(7)	0.0018(6)	-0.0057(7)
C(5)	0.0330(9)	0.0288(9)	0.0192(8)	-0.0031(7)	0.0065(7)	-0.0049(8)
C(6)	0.0233(8)	0.0233(8)	0.0194(8)	-0.0003(7)	0.0034(7)	-0.0010(7)
C(7)	0.0246(8)	0.0346(11)	0.0332(9)	0.0032(8)	0.0101(7)	-0.0008(7)
C(8)	0.0288(9)	0.0243(9)	0.0278(9)	0.0050(7)	0.0068(7)	-0.0024(7)
C(9)	0.0237(8)	0.0186(8)	0.0214(8)	0.0014(6)	0.0071(6)	0.0012(6)
C(10)	0.0215(8)	0.0251(9)	0.0244(9)	-0.0004(7)	0.0059(6)	0.0007(7)
C(11)	0.0279(8)	0.0257(9)	0.0256(8)	0.0009(7)	0.0137(7)	0.0012(7)
C(12)	0.0265(8)	0.0199(9)	0.0203(8)	0.0012(6)	0.0058(6)	0.0029(6)
C(13)	0.0204(7)	0.0197(8)	0.0217(8)	0.0018(6)	0.0058(6)	0.0013(6)

Table 5. Hydrogen coordinates and isotropic displacement parameters (A^2) for *endo*-**163**.

Atom	x	y	z	U(eq)
H(1O)	0.598(3)	0.440(4)	0.502(2)	0.047(8)
H(3A)	-0.2566	0.4501	0.5119	0.032
H(2A)	0.3188	0.6353	0.3573	0.024
H(3B)	-0.0629	0.6090	0.1860	0.030
H(3C)	-0.0796	0.3869	0.1727	0.030
H(4A)	0.0556	0.5620	0.0154	0.030
H(5A)	0.2445	0.3047	0.0265	0.033
H(5B)	0.2038	0.2246	0.1581	0.033
H(6A)	0.3442	0.2573	0.4163	0.027
H(6B)	0.4700	0.3137	0.3401	0.027
H(7A)	0.5629	0.4570	0.1667	0.046
H(7B)	0.5811	0.6243	0.2670	0.046
H(7C)	0.6055	0.6607	0.1282	0.046
H(8A)	0.2241	0.8514	0.0978	0.041
H(8B)	0.3998	0.9003	0.0865	0.041
H(8C)	0.3753	0.8639	0.2252	0.041
H(10A)	-0.1719	0.4442	0.3375	0.029
H(11A)	-0.0873	0.4849	0.7134	0.030
H(13A)	0.2907	0.5147	0.5647	0.025

The crystal data (without structure factors) for the structures **76**, **79**, **91**, **243**, **248** and *trans*-**252** which are reported in this work are available as "supplementary pubblication no. CCDC-178102 (**76**), CCDC-178103 (**79**), CCDC-178104 (**91**), CCDC-199272 (**243**), CCDC-199270 (**248**), CCDC-199271 (*trans*-**252**)". Copies of these data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk.

Table 6: Crystal data and structure refinement for compounds **76**, **79** and **91**.

Structure	**76**	**79**	**91**
Empirical formula	$C_{26}H_{28}N_2$	$C_{27}H_{30}N_2$	$C_{12}H_{16}N_2 \times 0.5HCl$
Formula weight	368.50	382.53	206.50
Temperature [K]	100.0(2)	100(2)	120(2)
Wavelength	0.71073	0.71073	0.71073
Crystal system	Triclinic	Triclinic	Orthorhombic
Space group	P –1	P –1	Aba2
a [Å]	5.9783(2)	6.0829(4)	10.2447(3)
b [Å]	10.6105(4)	9.8909(6)	39.482(1)
c [Å]	16.7535(7)	18.028(1)	11.5005(3)
α [°]	84.071(2)	96.586(2)	90
β [°]	87.981(2)	90.077(2)	90
γ [°]	76.457(2)	91.642(2)	90
Volume [$Å^3$]	1027.58(7)	1077.0(1)	4651.7(2)
Z	2	2	16
Density [Mg/m^3]	1.191	1.180	1.179
μ [mm^{-1}]	0.069	0.068	0.181
F(000)	396	412	1776
Crystal size [mm^3]	0.42 × 0.30 × 0.22	0.42 × 0.28 × 0.06	0.55 × 0.54 × 0.04
θ range for data [°]	1.98 to 30.40	2.07 to 29.50	2.06 to 27.50
Reflections collected	12029	12494	15492
Ind. Reflectons	5541	5730	5318
Final R indice	0.0409	0.0475	0.0421

Table 7: Crystal data and structure refinement for compounds **243**, **248** and *trans*-**252**.

Structure	**243**	**248**	*trans*-**252**
Empirical formula	$C_{19}H_{21}NO$	$C_{34}H_{40}N_4O_2$	$C_{15}H_{19}N_2O$
Formula weight	279.37	536.70	243.32
Temperature [K]	133(2)	133(2)	133(2)
Wavelength	0.71073	0.71073	0.71073
Crystal system	Triclinic	Triclinic	Monoclinic
Space group	P –1	P –1	P2(1)/c
a [Å]	7.6835(15)	9.7459(19)	9.0831(18)
b [Å]	9.960(2)	10.996(2)	9.5608(19)
c [Å]	10.877(2)	13.920(3)	15.107(3)
α [°]	102.94(3)	93.50(3)	90
β [°]	109.76(3)	99.88(3)	93.22
γ [°]	99.29(3)	90.36(3)	90
Volume [$Å^3$]	737.5(3)	1466.7(5)	1309.8(5)
Z	2	2	4
Density [Mg/m^3]	1.258	1.215	1.234
μ [mm^{-1}]	0.077	0.076	0.078
F(000)	300	576	524
θ range for data [°]	2.09 to 24.75	2.37 to 24.61	2.52 to 24.75
Reflections collected	8158	7181	7340
Ind. Reflectons	1803	4341	1629
Final R indices	0.0451	0.0509	0.0447

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Lebenslauf

Am 30. März 1975 wurde ich als zweites Kind von Giuliana, geb. Olivieri, und Sergio Gensini in Florenz (Italien) geboren.
Von September 1981 bis Juli 1986 besuchte ich die Don Minzoni Grundschule in Florenz und wechselte dann im September 1986 zur Guicciardini Mittelschule in Florenz, wo ich bis Juli 1989 verblieb. Von September 1989 bis Juli 1994 besuchte ich das humanistische Liceo Ginnasio Galileo in Florenz, wo ich im Juli 1994 das Abitur bestand.

Im Oktober 1994 nahm ich das Studium der Chemie an der Universitá degli Studi di Firenze in Florenz auf.

Unter der wissenschaftlichen Leitung von Herrn Prof. Dr. A. Brandi fertigte ich meine Diplomarbeit zu dem Thema "*Sintesi di alcaloidi indolizidinici con controllo della stereochimica relativa ed assoluta*" an. Am 20 Dezember 1999 wurde mir der akademische Grad Diplom-Chemikerin zuerkannt.

Seit April 2000 arbeite ich im Arbeitkreis von Herrn Prof. Dr. A. de Meijere an meiner Dissertation zum Thema "*Synthesis of Potentially Biologically Active Cyclopropane- and Spirocyclopropane-annelated Oligoazaheterocycles*".

Von Februar bis April 2002 arbeitete ich als Werks-Student, in Rahmen meiner Doktorarbeit, bei dem Pflanzenschutz Landwirtschaftszentrum der Firma Bayer AG in Monheim.

Von Oktober 2001 bis Januar 2002 war ich als wissenschaftliche Angestellte zur Betreuung im Chemischen Praktikum für Mediziner- und Zahnmediziner beschäftigt.
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