Complementary Ways to Diastereomers of Bridged Aminopiperidine Derivatives – A Stereochemical Challenge [1])

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Dedicated to Prof. Dr. R. W. Saalfrank on the Occasion of his 60th Birthday

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Abstract. Routes to diastereomers of constrained 4-aminopiperidines – a common pharmaceutically used diaminic building block – are realized mainly on the basis of *CN*-double bond species or their radicalic or anionic analogues. Kinetically controlled reactions on the one hand and thermodynamic control of reactions, reversible introduction of a repulsive group, direction of a reactant by intramolecular complexation, or involvement of radicalic or anionic intermediates with strong isomerization tendency on the other hand are the tools for a complementary accessibility of both diastereomers.

Contents

1. Introduction

4-Aminopiperidine is found as diaminic component in various active compounds. Fig. 1 shows presently commercially available drugs containing a 4-aminopiperidine building block. The amino moiety in 4-position is functionalized in different ways. It may be a simple heterocycle, a part of a spiro compound, an acylated or alkylated arylamine or a simple amide. The spectrum of activity is widespread. In most cases, the substituent R at *N*(1) [1] plays the main role for the corresponding activity. Investigations of structure activity relationship, however, have demonstrated the advantage of 4-aminopiperidine as diaminic component in these active compounds. In some cases, the aminopiperidine system behaves as a real pharmacophoric group; this applies to the antihistaminics Bamipine **5** and Thenalidine **6** in which only a methyl group is bond to *N*(1).

The 4-aminopiperidine moiety **26** adopts a chair conformation. Two chair conformers, however, are to be considered due to a ring inversion and an *N*-inversion as dynamic processes: the arrangement of the 4-amino group in an axial or equatorial manner corresponds to a *cis* and *trans* isomer, respectively (Fig. 2).

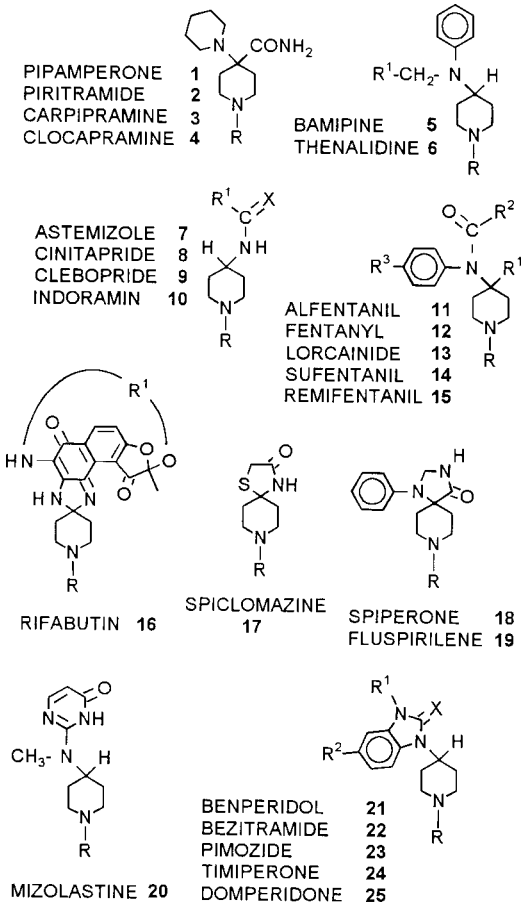

Fig. 1

[1]) Presented in part at the Fourth Conference on Iminium Salts, Stimpfach-Rechenberg (Germany), September 14–16, 1999

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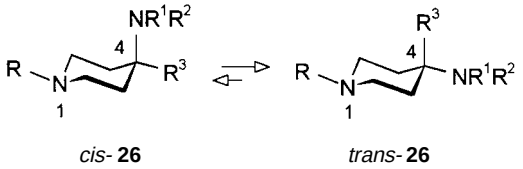


Fig. 2

2. Diastereomers of Constrained Aminopiperidine Derivatives as Target Molecules

It is to be expected that the two conformers of **26** as well as the thereof derived *N*(1)-protonated species have different affinities to the receptor. The biological activity, therefore, will decrease if the suitable conformer is disfavored energetically. Constraining of the piperidine ring in **26** by bridging prohibits the interconversion of both conformers. This allows the creation of models **27** and **28** for the non-isolable conformational isomers. The model substances **27** and **28** should give an insight into the sterical requirements of the receptor concerning the geometry of the 4-aminopiperidine system and could allow a design of activity (Fig. 3). The presence

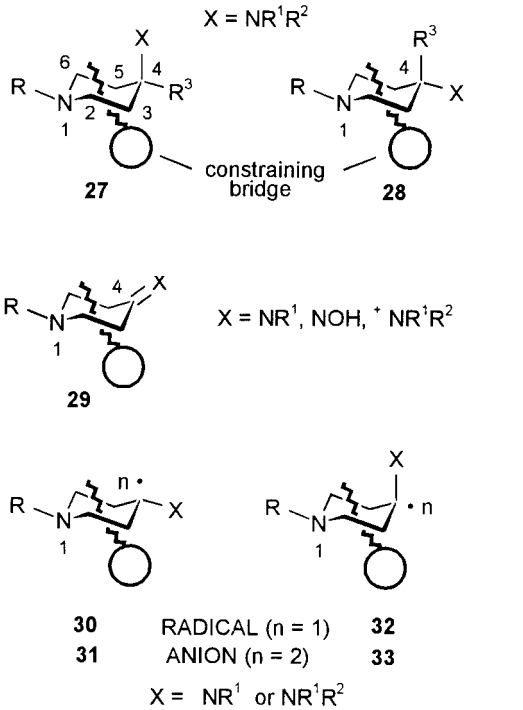


Fig. 3

of defined substituents at *N*(1) and *C*(4) in the active compounds excludes an involvement of these centers in bridging. The remaining possibilities for constraining allow a bridging of the positions 2 and 3, 2 and 5, 2 and 6 or 3 and 5. The subsequent review covers stereoselective syntheses of diastereomers **27** and **28** on the basis of compounds **29** with a prostereogenic *CN*-double bond or a stereogenic *CN*-intermediate of a radical type **30**, **32** or an anion type **31**, **33**. The main goal in this context should be the presentation of complementary synthetic tools for a highly selective accessibility of each of the two diastereomers of type **27** and **28**. General information about reactions of *CN*-double bonds, *CN*-radicals and α-aminocarbanions is found in ref. [2–6], [7] and [8], respectively; a consideration of the subject of complementary routes to diastereomers, however, is missing there. A comprehensive survey of the chemistry of cyclopropaniminium ions is given in reference [9]. The newest recommendations [10] of the Chemical Abstracts were used for assignment of diastereomers of type **27** and **28**.

3. Complementary Syntheses Based on Prostereogenic or Stereogenic *CN*-Units in

3.1 the Tropane and Granatane System

2,6-Constrained compounds **34**/**35** correspond to tropylamines for z = CH_2 and to granatylamines for z = $(CH_2)_2$; isomers **34** are designated as 3-*endo*-amines and isomers **35** as 3-*exo*-amines (Fig. 4). In the literature the names pseudotropylamine (ψ-tropylamine), pseudogranatylamine (ψ-granatylamine) or 3β-amines are found for the latter. The 3-*endo*-amino isomers **34a,b** then were simply called as tropylamine, granatylamine or 3α-amines.

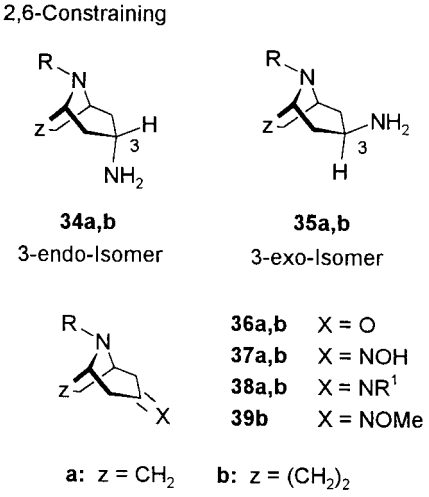
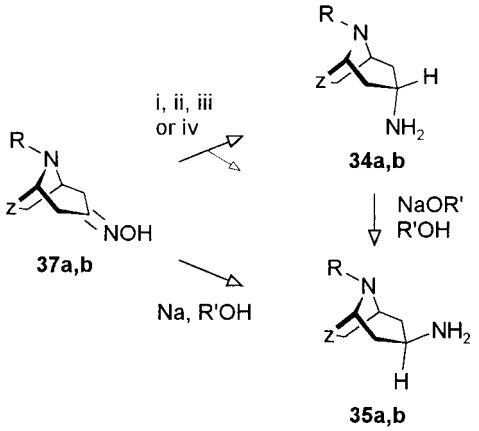


Fig. 4

Complementary ways to the tropylamine diastereomers **34a** and **35a** (R = CH_3) were first described already in 1898 by Willstätter and Müller [11]. Reaction of oxime **37a** with sodium in pentanol led to pure *exo*-amine **35a** in almost quantitative yield whilst the treatment of **37a** with sodium amalgam in acetic acid provided mainly *endo*-amin **34a** (Scheme 1). The same

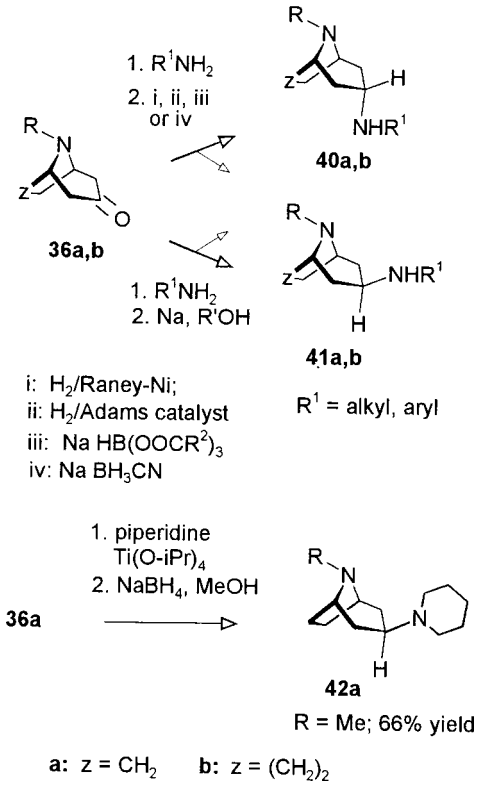
procedures were applied successfully one year later for the synthesis of the granatane analogues **34b** and **35b** by Piccinini together with Quartaroli [12] and Cortese [13]. 3-*endo*-Amines **34a**,**b** could be isomerized to the more stable 3-*exo*-compounds **35a**,**b** by heating in a pentanolic solution of sodium pentanolate; this reaction was used for structural assignment of **34a**/**35a** in this early investigation [11].

The reduction of the oximes **37a**,**b** with sodium in alcohol is – apart from some variation of the alcohol [14–17] – till now the procedure of choice for the synthesis of 3-*exo*-amines **35a** and **35b** [17–22]. Several variations and improvements were reported in the literature for the preparation of 3-*endo*-amines **34**: Sodium amalgam was replaced as reducing agent by hydrogen and Raney nickel (**37a** → 70–80% **34a** and 20–30% **35a** [18]; **37b** → 90% **34b** [22]) [18, 22, 23] or Adams catalyst [14–16] or by lithium aluminum hydride [22, 24, 25] (Scheme 1). The combination of a methoxime as **39b** (R = Bn or 4-F–C_6H_4-CH_2) and of borane/THF as reducing agent seems to be unfavorable from a stereochemical point of view due to lacking stereoselectivity [26].



Scheme 1 Reduction of oximes of tropinone and pseudopelletierine

These complementary routes could be transferred also to imines **38a**,**b** of tropanone **36a** or pseudopelletierine **36b** to give *N*-substituted 3-amines (Scheme 2). A slight shift in the stereoselectivity, thereby, is resulting with respect to the analogous reactions of oximes **37**: Again, hydrogenation with Adam's catalyst or Raney Nickel produced the 3-*endo*-amines **40** [14, 22, 27–33] but now as almost pure stereoisomers. Lithium aluminum hydride showed a similar [14] and sodium borohydride a



Scheme 2 Reduction of imines and iminium species of tropinone and pseudopelletierine

lower stereoselectivity [22]. A decrease of stereoselectivity is observed, on the other hand, for the reduction of imines **38a**,**b** with sodium and alcohol still favoring the formation of 3-*exo*-isomers **41** [14, 22, 32–34]. An increasing amount of 3-*endo*-isomers **40** as side products was indicated especially in the case of *N*-phenyltropanonimines **38a** (R^1 = Ph) [32, 34] or pseudopelletierinimines **38b** [14, 22, 33] as starting materials. A successful hydrogenation of an enamine of tropinone **36a** was described without determination of the configuration of the resulting amine [35].

Reductive amination of tropinone **36a** with primary amines and an acyloxyborohydride seems also to be a suitable way to 3-*endo*-tropylamines **40a** [36–38]; *endo*/*exo* ratios of 4:1 up to > 50:1 were reported (Scheme 2). Sodium cyanoborohydride (Borch method) or borohydride exchange resin as hydride reagent decreased the stereoselectivity (*endo/exo* ratio of ≈ 2:1 [36, 39] or ≈ 1:1 [40]). No stereoselectivity was observed in the reductive amination of tropinone **36a** with triacetoxyborohydride and a secondary amine such as piperidine [37]. Other diastereomer ratios resulted, however, by changing the conditions of the reductive amination [37, 41]: Thus, reacting tropinone **36a** first with piperidine and titanium tetraisopropoxide to a semi-*N*,*O*-acetal and reducing it then with sodium borohydride allowed the preparation of pure *exo*-amine **42a** in 66% yield (crude

product *exo/endo* ratio of 7:1) [37]; a higher diastereomer ratio (15:1) was found for the analogous reaction with piperazine [41]. Both the formation of sole 3-*endo*-isomers **40b** [42] and of mixtures **40b**/**41b** (*endo*/*exo* ≈ 2:1) [39] were reported for the reductive amination of a pseudopelletierine **36b** with sodium cyanoborohydride and various amines. Catalytic hydrogenation of in situ generated imine **38a** (R^1 = H) and oxime **37b** serves for commercial syntheses of *endo*-3-tropylamine **34a** and *endo*-3-granatylamine **34b** on an industrial scale, respectively [43].

The preferred formation of the 3-*endo*-amines **34**/**40** can be understood by the favored attack of hydrogen or a hydride from the less hindered *exo*-side to the *CN*-double bond in **37a**,**b**–**39a**,**b** (Fig. 5).The steric hin-

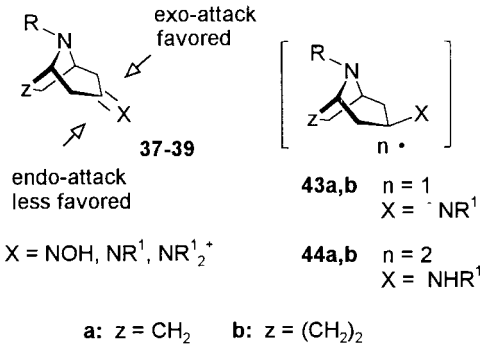
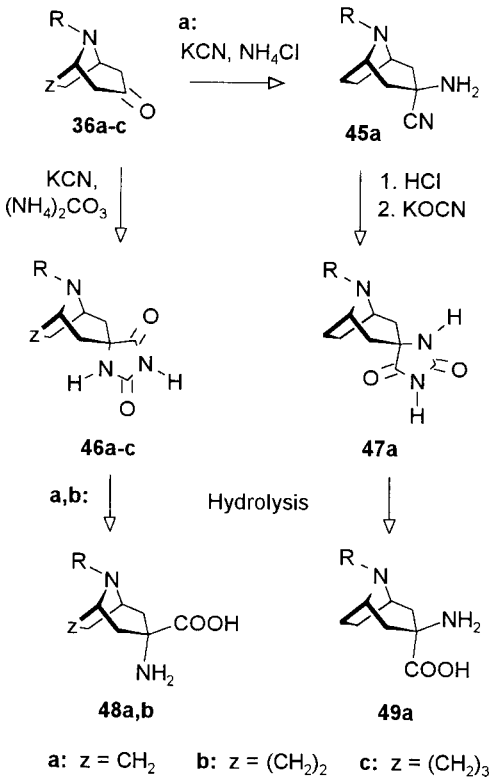


Fig. 5

drance, thereby, is more effective in the granatane **b** than in the tropane compounds **a**. The influence of the bulkiness of the amine in the reductive amination of tropinone **36a** on the *exo/endo*-ratio was discussed in terms of the Exterior Frontier Orbital Extension Model [44]. The system sodium in an alcohol should pass radical anions and carbanions with a strong tendency to invert to most stable isomers **43a**,**b**/**44a**,**b** and to give the thermodynamically favored 3-*exo*-amines **35**/**41**. The possibility of a thermodynamically controlled isomerization of a primarily formed 3-*endo*-amine **34**/**40** *via* an anion **44** should be taken in account, too [11]. The creation of radical anions is also expected in the first step of the reduction of oximes **37a**,**b** with sodium amalgam. It is not clear, however, if the lower reaction temperature or the presence of acetic acid for a faster protonation of the corresponding carbanion is responsible for the formation of the 3α-amines **34a**,**b** in this special case.

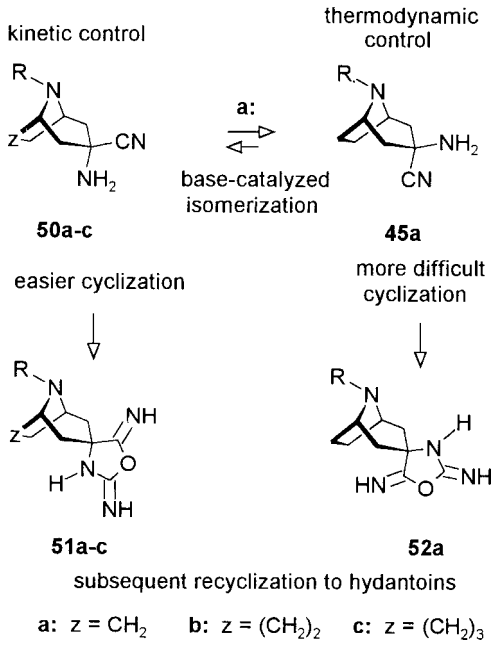
Elegant complementary routes to 3-aminotropanecarboxylic acids **48a** and **49a** were found by González Trigo and his group by application of a Bucherer-Bergs reaction on the one hand or a Strecker synthesis on the other hand to tropinone **36a** (Scheme 3) [45–49]. **36a** was transferred exclusively to 3-*exo*-aminonitrile **45a**



Scheme 3 2,6-Bridged piperidones as starting material in the Bucherer-Bergs reaction and in the Strecker synthesis

upon interaction with KCN and NH_4Cl; the subsequent cyclization of **45a** with KOCN in acidic medium led to 3-*exo*-spirohydantoin **47a** [45, 48, 49]. The isomeric 3-*endo*-spirohydantoin **46a** was formed directly from **36a**, KCN and $(NH_4)_2CO_3$ as the only reaction product [45, 46]. Hydantoins **46a** and **47a** were hydrolyzed with sulfuric acid to give amino acids **48a** and **49a** in excellent yields, respectively [50]. Treatment of **45a** with KCN and NH_4Cl in the presence of CS_2 provided a 3-*exo*-spirodithiohydantoin [51]. 3-*endo*-Amino acid **48a** and 3-*exo*-aminonitrile **45a** were used as starting materials for the synthesis of various 3-*endo*- and 3-*exo*-spiroheterocycles [47–49, 50, 52, 53]. Only 3-*endo*-hydantoin derivatives **46b,c** [54–56] or the 3-*endo*-aminoacid **48b** [57], however, could be obtained with the granatane or homogranatane skeleton.

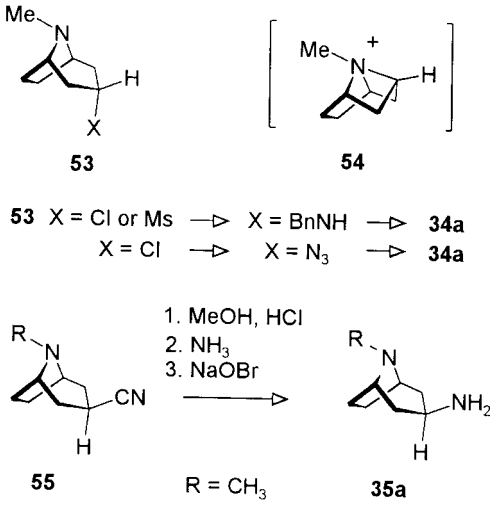
The reason for the highly selective access to **46a** or **47a** depending upon the reaction conditions can be understood on the basis of the fundamental work of Edward and Jitrangsri [58] on the stereochemical course of the Bucherer-Bergs and the Strecker reactions of 4-*tert*-butylcyclohexanone. The compression of the developing C=NH group (attack of $HNCO_2$- to the cyano function), thereby, determines the facility of hydantoin formation. Application of this idea to the tropane system (Scheme 4) expects a stronger compression of the C=NH moiety in **52a** than in **51a** and thus a more diffi-



Scheme 4 Origin of the complementarity of formation of tropinonespirohydantoin diastereomers

cult cyclization for **45a** than for **50a**, the product of a kinetically controlled aminonitrile formation. In the absence of cyanate, **50a** is isomerized by base to the more stable 3-*exo*-aminonitrile **45a** *via* the corresponding imine intermediate **38a** (R^1 = H). Acid prohibits a retro-isomerization of **45a** to **50a** and the subsequent addition of cyanate causes the unfavorable cyclization of **45a** to 3-*exo*-spirohydantoin **47a** via **52a** [47]. The missing isomerization of an initially formed 3-*endo*-aminonitrile **50b** to its more stable 3-*exo*-amino analogue **45b** discriminates the sterically more hindered granatane from the tropane system [57]. The report of only one isomer **46c** [59] of a homogranatane spirohydantoin species in the literature may be the consequence of a similar lack of isomerization of **50c**, too.

Two highly diastereoselective ways to 3-*endo*-tropylamine and 3-*exo*-tropylamine derivatives are not based on *CN*-double bond species as starting materials or intermediates and should be mentioned shortly (Scheme 5). Retention of configuration was observed in nucleophilic substitutions of tropyl chloride **53**, X = Cl or tropyl mesylate **53**, X = Ms due to participation of cationic intermediate **54** [60]; thus 3-*endo*-tropylamine **34a** was synthesized via a benzylamine **53**, X = NHBn or azide **53**, X = N_3 [20, 60]. Tropyl chloride **53**, X = Cl and cyanide led to tropannitrile which was isomerized directly to 3-*exo*-nitrile **55** [60]. **55** (R = CH_3) could be transferred easily to 3-*exo*-tropylamine **35a** *via* Hofmann degradation of the corresponding amide [60]. A route to 3-*exo*-tropylamine also was described by reduction of tropinone **36a** to a mixture of 3-tropanol isomers,



Scheme 5 Alternative routes to 3-tropylamines

subsequent Mitsunobu reaction to a 3-*exo*-azide and its reduction with $LiAlH_4$ [22].

3.2 the 3-Azabicyclo[3.1.0]hexane System

Constraining a 4-aminopiperidine by a 3,5-"zero-bridge" leads to 3-azabicyclo[3.1.0]alk-6-ylamines **56** or **57**. The terms 6α (instead of 6-*exo*) and 6β- (instead of 6-*endo*) have to be used as correct stereodescriptors for the designation of diastereomers **56a**,**b** and **57a**,**b**, respectively (Fig. 6). The more simple name 4-amino-3,5-cyclopiperidine was applied for these compounds, too. Complementary routes to diastereomers **56** and **57** were developed on the basis of cyclopropaniminium intermediates **61** or **62** in the group of Vilsmaier. Their routes to the bicyclic system start from chloroenamines **59** or

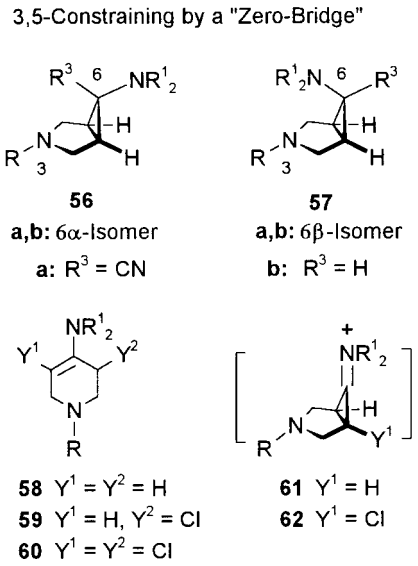
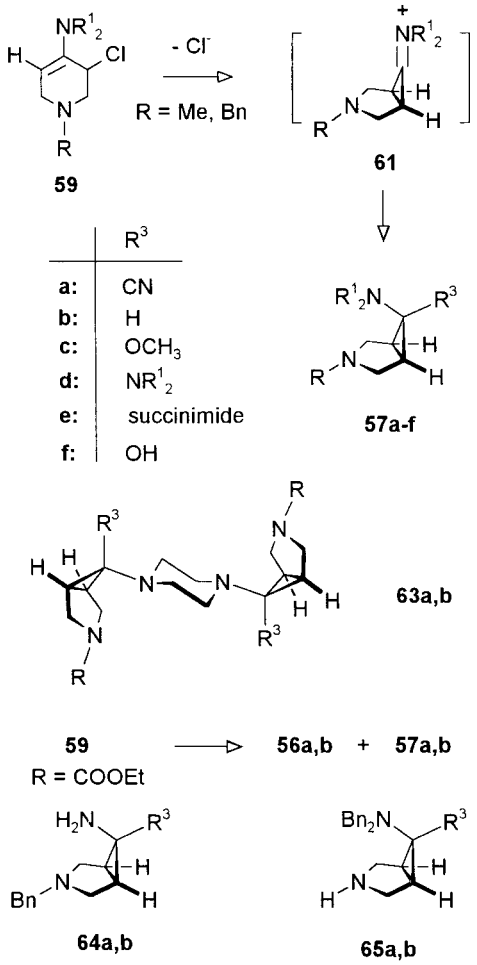


Fig. 6

dichloroenamines **60** which were obtained easily from enamines **58** and one or two equivalents of NCS [61–68] or the NCS–Me_2S complex [62].

Reaction of chloroenamines **59** possessing an alkyl moiety at N(1) with nucleophiles such as cyanide [61, 64–66, 69] or borohydride [66–68, 70] led to azabicyclohexane derivates as pure stereoisomers **57a**,**b** in sufficient to excellent yields (Scheme 6). Analogous reactions were applied to chloroenamines with a piperazine unit as enamino component to give tetramines **63a**,**b** [63]. Formation of a mixture of diastereomeric amines **56**/**57** was observed to a more or less extent from *N*-ethoxycarbonyl substituted chloroenamines **59** with cyanide or borohydride [61, 70]. Chloroenamines **59** with a diallylamino- [67–69] or dibenzylamino moiety [65, 67, 68] served as starting materials for the synthesis of *C*(6)-*N* protected compounds; a benzyl, an ester or a methyl rest were used as protecting groups for *N*(3). Deprotection was realized by a Palladium catalyzed deallylation [67–69], a hydrogenolytic [64, 65, 68, 71–73] or a chloroformate initiated debenzylation [67, 68],

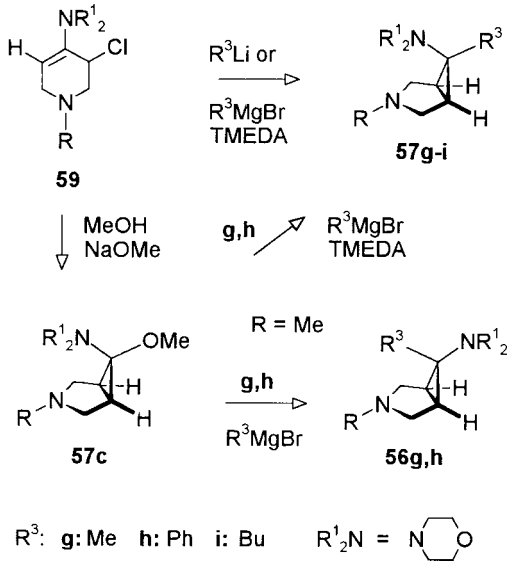


Scheme 6 6β-Amino-3-azabicyclo[3.1.0]hexane derivatives from chloroenamines

a urethane cleavage by trimethylsilyl iodide [64, 67, 68] or a demethylation *via* a Polonovsky reaction [74]. Selectively monoprotected diamines **64a**,**b** and **65a**,**b** were thus obtained.

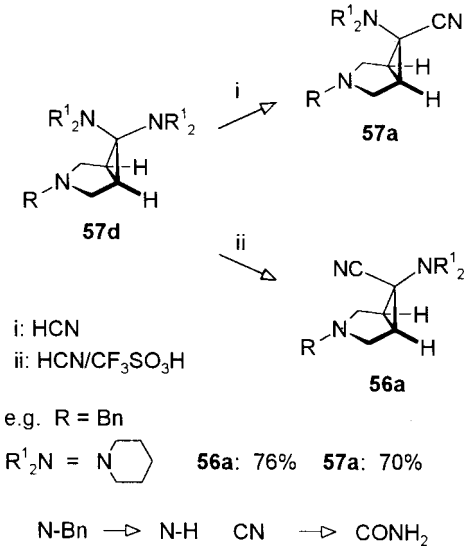
Use of an *O*- or *N*-nucleophile in the synthesis according to Scheme 6 led to *N*,*O*- or *N*,*N*-acetals **57c**–**e** [67, 68, 71, 72, 75, 76] or a semiaminal **57f** [75, 77]; the former could be applied for subsequent substitution reactions. Generally, these S_N-reactions occur with retention of configuration; inversion of configuration, however, can be forced alternatively as outlined in Scheme 7–9.

Reaction of chloroenamines **59** with organolithium compounds or a mixture of Grignard reagents and TMEDA led to the expected 6β-amines **57g**–**i** (Scheme 7) [71]. Preceding preparation of *N*,*O*-acetal **57c** from **59** and subsequent substitution of the methoxy moiety in **57c** by a Grignard reagent provided 6α-amines **56g**,**h** in high diastereoselectivity (d.r. ≥ 10:1) [71]. The *endo*-attack of the carbon nucleophile at the *N*,*O*-acetal **57c** should result from its complexation to *N*(3)-nitrogen atom; inhibition of this complexation by addition of TMEDA to the mixture of **57c** and R^3MgBr gave the 6β-amines **57g**,**h**. Detailed investigations showed that a methyl moiety at *N*(3) is a precondition for a successful complementarity of these routes. Interaction of Grignard reagents with chloroenamines **59** (R = Me) gave mixtures of diastereomers **56g**–**i** and **57g**–**i** besides monocyclic products from a direct substitution [62, 71]; a pure 6β-isomer **57g**, however, was formed in the analogous reaction with an *N*-benzylchloroenamine **59** (R = Bn) [71].



Scheme 7 Grignard reagents as basis for complementary routes to 6α- and 6β-amino-3-azabicyclo[3.1.0]hexane derivatives

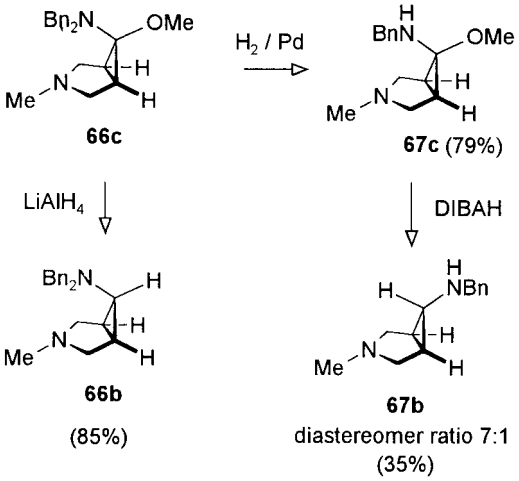
Sterically complementary results could be realized by the cleavage of an *N*,*N*-acetal **57d** (NR^1_2 = piperidine) with hydrocyanic acid (Scheme 8) [72]. Interaction of **57d** with one equivalent of HCN gave 6β-aminonitrile **57a** whilst two equivalents of acid led to diastereomer **56a**. ^{1}H NMR spectroscopic analysis of the crude products showed the formation of pure isomers in each case. Acid catalyzed isomerization of primarily formed **57a** was excluded as reason for the formation of **56a**. The unexpected and complementary route to **56a** should be originated by an inside fixation of the cyanide by protonation of *N*(3) by the excess acid. Isomers **57a** and **56a** were used as basis for the synthesis of further target molecules via hydrogenolytic removal of the benzyl group and saponification of the nitrile moiety [72].



Scheme 8 Complementary routes to 6α- and 6β-amino-3-azabicyclo[3.1.0]hexanecarbonitriles

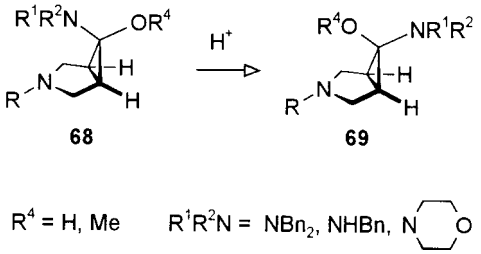
An additional example of complementary routes to 3-azabicyclohexane diastereomers was found in the substitution of the OMe moiety in an *N*,*O*-acetal **66c** or **67c** by a hydrogen atom. Lithium aluminum hydride as hydride reagent transformed **66c** into **66b** with exclusive retention of configuration [67, 68]. Selective hydrogenolytic monodebenzylation of **66c** to **67c** and subsequent introduction of a hydrogen atom with DIBAH provided 6α-amine **67b** in an acceptable diastereomer ratio but only in moderate yield [68, 76] (Scheme 9). Complexation of the DIBAH to the *N*(3)-atom combined with the fact of a missing second substituent at *C*(6)-*N*-atom could explain the preferred access to **67b**.

A thermodynamically controlled isomerization of *N*,*O*-acetals or of semiaminals of type **68** (R^4 = Me, H) to **69** was realized by addition of acid [75, 76] or simple



Scheme 9 Retention and inversion of configuration in reduction of 3-azabicyclo[3.1.0]hexanone-*N*,*O*-acetals

storage at room temperature [77] (Scheme 10). This easy access to **69**, however, is of no preparative interest thus far.

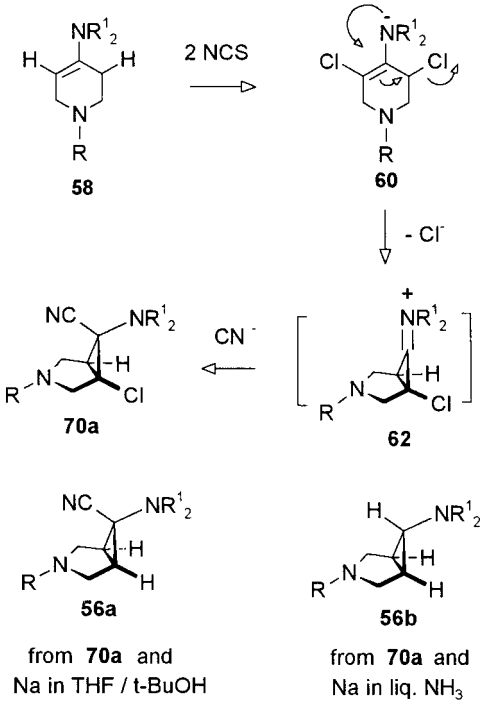


Scheme 10 Isomerization of 3-azabicyclo[3.1.0]hexanone-*N*,*O*-acetals and semiacetals

An unexpected access to 6α-amino compounds **56a** and **56b** was found by the reaction of dichloroenamine **60** with cyanide in an aqueous medium to give 6α-nitriles **70a** as primary products [61]. Very high diastereoselectivities were observed in some cases (*e.g.* **60**: NR_2 = piperidine and R = COOEt provided **70a** in 91% pure yield [64]). Subsequent reductive removal of chloride in **70a** with sodium in *t*-BuOH/THF [78] or of chloride and cyanide with sodium in liquid ammonia [79] provided the 6α-amine derivatives **56a** and **56b**, respectively (Scheme 11). A repulsive effect between the 1α-chloro atom and the nucleophile or a Cieplak type interaction [80–82] of cyanide with the C–Cl-σ*-Orbital can be discussed as reason for the stereochemical result. Thus far, this route is restricted to cyanide as nucleophile and to a solubility of the dichloroenamine in an aqueous solvent at least to a small extent.

The possibilities for direction of the attack of a nucleophile at an iminium ion **61** are summarized in Fig. 7.

Complementarity to formation of compounds with a 6β-amino unit can be realized by the outlined routes which were described in detail in Scheme 7–11.



Scheme 11 Dichloroenamines as access to 6α-amino-3-azabicyclo[3.1.0]hexane derivatives

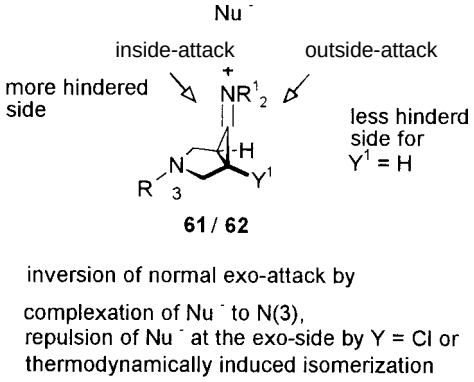


Fig. 7

The reductive removal of the 6β-cyano group in **70a** occurred with exclusive retention of configuration [79]. Application of this reaction to 6α-nitriles could be performed with retention or inversion of configuration depending upon the reaction conditions (Fig. 8) [68, 69]. Thus, pure 6β-amine **65b** was obtained from the corresponding nitrile **65a** and sodium in liquid ammonia at –70 °C; decyanation by lithium in a mixture of ethylamine and ammonia at 0 °C caused mainly an inversion of configuration (**71b**/**65b** = 80:20). Diastereomers **72b** and **73b** were obtained from the corresponding nitrile

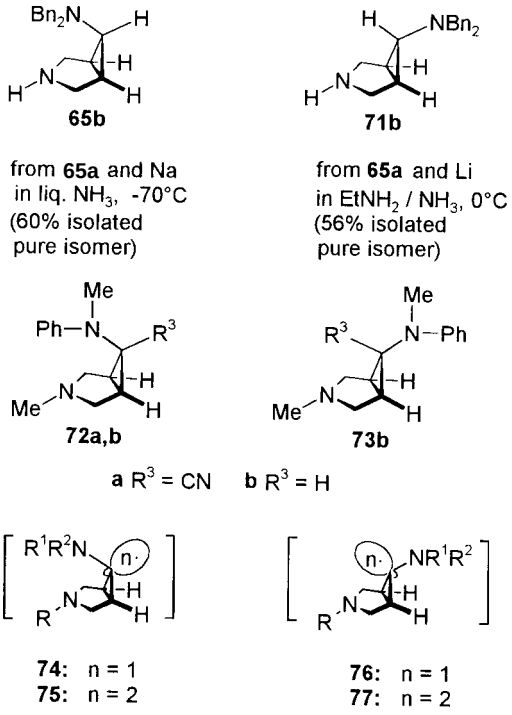


Fig. 8

72a by similar procedures (Na in NH_3 at –70 °C, Li in $EtNH_2$ at 0 °C) in a diastereomer ratio of 80:20 and 20:80 each [83]. Decyanation of the bicyclic nitrile proceeds *via* a radical **74** and the anion **75** which should be configurationally stable at low temperatures but invert to the less hindered analogues **76** and **77** at 0 °C.

Working in 3-azabicyclo[3.1.0]hexane area increased strongly with the development of the highly active antibiotic Trovafloxazin **79**/Alatrofloxazin **80** [84]. The efforts were directed towards the synthesis of the 6α-amine **78** (Fig. 9). Cyclopropanation of a pyrroline compound **81** or **82** by a C_1-unit (bromonitromethane, base and **81** [85, 86], ethyl diazoacetate and **81** [87] or **82**/rhodium acetate [87, 88], dibenzylformamide, titanium

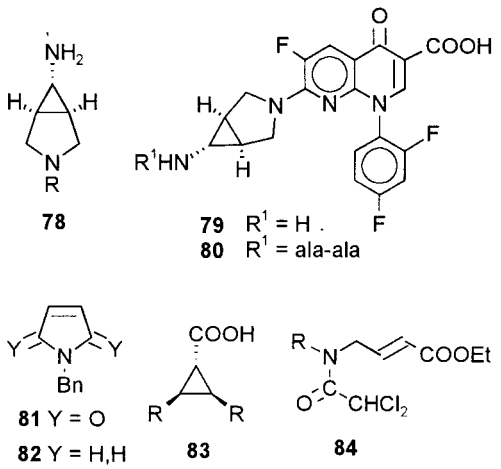


Fig. 9

tetraisopropoxide, isopropylmagnesium bromide and **82** [89]) or aza-annulation of derivatives of type **83** [90, 91] served as access to the azabicyclohexane skeleton. Compounds with a 6α-functionality were exclusively obtained in these sequences (exception ref. [87, 88] 6α/6β ratio ≈ 1:2). Subsequent reduction of the nitro group or application of a Curtius rearrangement were used for generation of the amino function. A potential precursor for diamine **78** was synthesized *via* a base catalyzed Tandem cyclization of **84** [92]. A very special formation of an azabicyclohexane derivative with a very particular pattern of substituents was reported in ref. [93].

3.3 Other Bridged Piperidine Systems

Syntheses for constrained aminopiperidines with other types of bridging were less effective with respect to stereoselectivity and complementarity of the routes.

3.3.1 the Norcamphidine System and Homologues

The 3-azabicyclo[3.2.1]skeleton in **85a** and **86a** corresponds to norcamphidine; it is derived from bridging piperidine in 3,5-position with an ethylene unit. Diamines **85a**,**b** and **86a**,**b** are designated as *syn*- and *anti*-isomer, respectively (Fig. 10). Reductive amination of **87a** (R = 2-phenylethyl) with substituted anilines and sodium cyanoborohydride was reported to give pure *syn*-derivatives **85a** [94] (Scheme 12). Further syntheses of compounds **85a**,**b** and **86a**,**b** were described mainly in the patent literature. Only minor stereoselection was found for the reduction of oxime **88a** with $LiAlH_4$ (→ **85a**/**86a** 60:40) and **88b** with sodium in pentanol (→ **85b**/**86b** 35:65) [95]. The diastereomer ratios refer to yields of isolated and chromatographically separated products of a subsequent acylation of the obtained amines. In the other references a detailed information about the stereoselection of the used processes for the preparation of amines **85** and **86** is not given [96, 97]. Bucherer-Bergs reaction of bicyclic ketone **87a** gave only *syn*-derivative **89a** [98] whilst the homologous

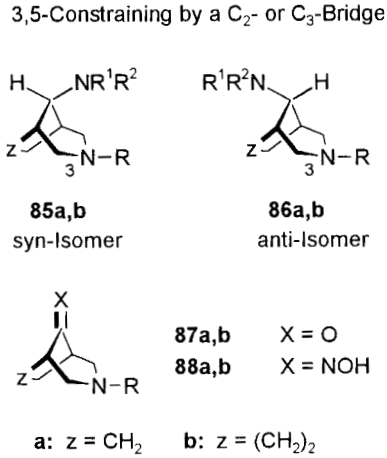
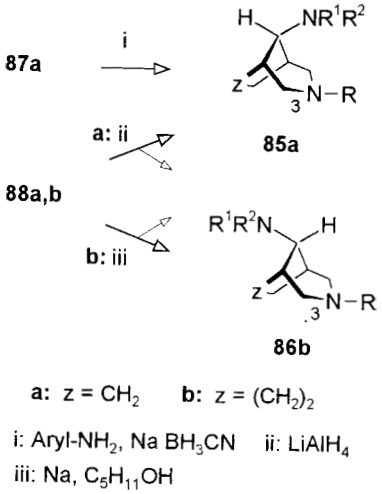


Fig. 10



Scheme 12 Diastereoselective routes to amines of norcamphidine and its homologue

ketones **87b**,**c** led exclusively to spirohydantoines **90b**,**c** [98, 99] (Fig. 11). The contrary stereoselection was explained by the change of bulkiness of the $(CH_2)_n$-chain in **91** depending on n [99]. Application of the Strecker

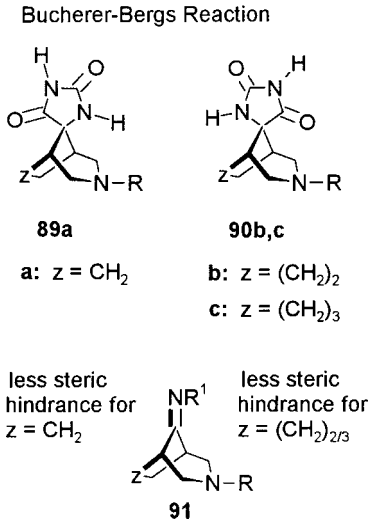


Fig. 11

synthesis to ketone **87a** as a complementary route was ineffective in this case; the obtained 8-aminonitrile had also a *syn*-conformation and it was isolated in only 5% yield besides 75% of the corresponding hydroxynitrile [100].

3.3.2 the Isoquinuclidine and the 2-Azanorbornane System

Bridging a piperidine ring in 2,5-position by a C_2-unit leads to an isoquinuclidine system; analogous compounds with a C_1-bridge correspond to an azanorborn-

ane unit. The two 5-amino diastereomers **92a**,**b** and **93a**,**b** are designated correctly as isomers with a (1*R*,4*R*,5*S*)-rel and (1*R*,4*R*,5*R*)-rel configuration, respectively (Fig. 12). The terms 5α- or 5-*exo*- (for **92**) and 5β-or 5-*endo* (for **39**) were applied in the literature, too. Though,

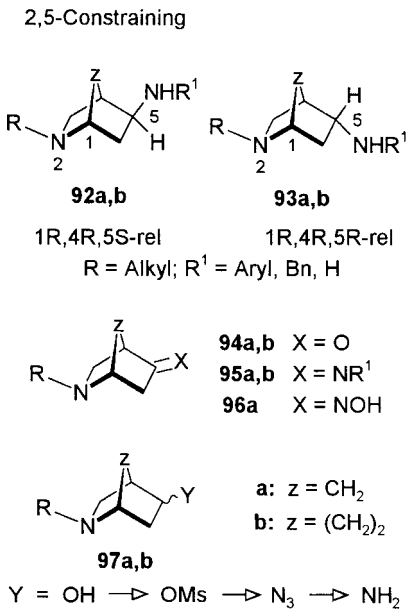


Fig. 12

5-amino-2-azanorbornanes and 5-aminoisoquinuclidines were used recently as diaminic components in active compounds, really selective routes to both diastereomers **92a**,**b** and **93a**,**b** are lacking thus far. Reduction of imines **95b** were performed with Red-Al (→ 5*S*/5*R* ratio ≈ 1:1) [101], sodium in ethanol (→5*S*/5*R* ratio ≈ 2:1) [101] and sodium cyanoborohydride (→ 5*S*/5*R* ratio ≈ 2:1) [102]. Reduction of oxime **96a** with hydrogen or reductive amination of **94a** with sodium cyanoborohydride gave mixtures of isomeric amines **92a**/**93a** (no diastereomer ratio given) [40]. A further access to a mixture of diastereomeric amines **92a**,**b**/**93a**,**b** – not based on an *CN*-double bond species – was found by transforming an alcohol **97a**,**b** (Y = OH) *via* a mesylate to an azide and reduction of the latter (Fig. 12) [103]. Isomers **92a**,**b**/**93a**,**b** were separated by chromatography of the amines [40, 101, 102] or of products from a subsequent reaction [101, 103, 104–106].

3.3.3 the trans-Decahydroquinoline System

Trans-connection of the two rings in decahydroquinoline – a 2,3-bridged piperidine – creates a rigid system; the two diastereomers of 4-amino-*trans*-decahydroquinoline **98** and **99** are designated as (4*R*,4a*R*,8a*R*)-rel- and (4*R*,4a*R*,8a*S*)-rel-isomer, respectively (R = H) (Fig. 13). Preparation of imine **101** from ketone **100** and subsequent reaction with various hydride reagents gave a mixture of **98** and **99** which was separated by chromatography [107, 108]. The isomer **98** was predominant in each case (*e.g.* Ar = Ph, diastereomer ratio **98**/**99**: $NaBH_4$ 2:1, $LiAlH_4$ 8:1, $NaAlH_2(OCH_2CH_2OCH_3)_2$ 15:1). This seems to be the only investigation in this area.

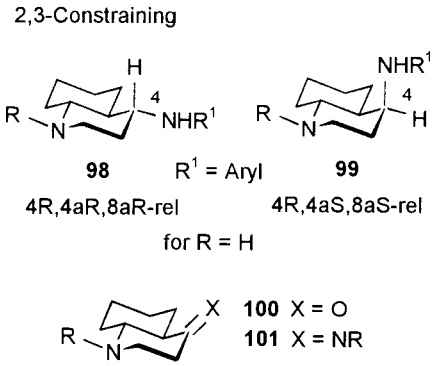


Fig. 13

4. Conclusion and Perspectives

Constrained analogues of various aminopiperidine derivatives were prepared thus far and studies of activity showed the influence of the geometric arrangement of the functional groups. Examples were the best suitable diastereomer did not exceed the activity of the aminopiperidine derivative include analogues of the analgesic fentanyl **12** (decahydroquinoline type [108], isoquinuclidine type [101, 109], tropane type [110], granatane type [111] and norcamphidine type [94]), of the neuroleptic Pipamperone **1** (azabicyclohexane type [64]) or of the analgesic piritramide **2** (azabicyclohexane type [72]). A clear improvement of activity, however, was performed with the substances **102** (analogue of bamipine **6** and 15 times more active [76, 83]), **103** (analogue of Clebopride **9** and 30 times more active [26])

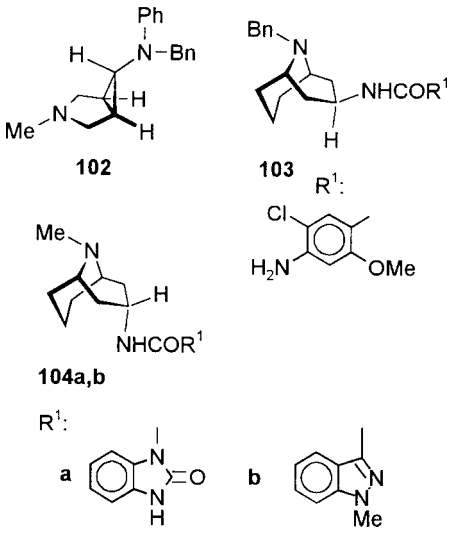


Fig. 14

and **104a** (300 times more active than the analogous aminopiperidine derivative [27]) (Fig. 14). Stereoisomers of **102**, **103** and **104a** were less active or nearly inactive with respect to the corresponding unbridged piperidine compounds. A slightly changed derivative of **104a**, was launched as Granisetrone **104b** in the meantime as remedy against emesis and nausea.

Basis for these investigations was the development of complementary routes to diastereomers of constrained aminopiperidines which were applied in the case of the tropane-, granatane- and 3-azabicyclo[3.1.0]hexane system. Kinetically controlled reactions on the one hand and thermodynamic control of reactions, reversible introduction of a repulsive group, direction of a reactant by intramolecular complexation, or involvement of radicalic or anionic intermediates with strong isomerization tendency on the other hand are the tools for a complementary accessibility of both diastereomeric species. The above possibilities have not been widely used thus far as compared to the other systems discussed here in spite of an increasing interest in constrained aminopiperidines as building blocks in pharmaceutical chemistry.

At this point, I want to thank very much my coworkers; their names are listed in the corresponding references. Their encouraging interest especially in the beginning of the 3-azabicyclo[3.1.0]hexane work was essential for the success. I am grateful to Prof. Dr. M. Psiorz, Boehringer Ingelheim and Dr. H. Heydt, Universität Kaiserslautern for their help in providing me with some very special literature data. I also wish to thank the colleagues Prof. Dr. A. Buschauer and Priv. Doz. Dr. S. Dove, Universität Regensburg, Prof. Dr. T. Wanner, Universität München, Prof. Dr. G. Maas, Universität Ulm and Prof. Dr. W. Frank, Universität Düsseldorf for their effective cooperation. Finally, the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft and the Land Rheinland-Pfalz are gratefully acknowledged for financial support of our work.

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[1] For information about the groups R, R^1 and R^2 of compounds **1**–**25** see Organic-chemical drugs and their synonyms, M. Negwer, 7th ed., Akademie Verlag Berlin 1994. Fig. 1 covers compounds with no substituents at C(2), C(3), C(5) and C(6). The antineoplastic aminopiperidine derivative irinotecan is not considered in Fig. 1; in this case the actual active substance is generated by removement of the aminopiperidine moiety in the first step of metabolism
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