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Reductive decyanation of N-protected 6-Amino-3-aza-bicyclo[3.1.0]hexanecarbonitriles

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Abstract

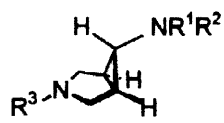
The cyano moiety in dibenzylamino-3-azabicyclo[3.1.0]hexane-6-carbonitriles **14c,d** can be removed reductively by alkali metals: sodium in liquid ammonia at low temperatures causes a reaction with retention of configuration whilst lithium in an ethylamine - ammonia mixture at 0°C leads predominantly to inversion of configuration. The analogous diallylamino species **14e** is less suitable for reductive decyanation. It can be used, however, for the synthesis of a 3-azabicyclo[3.2.0]heptane diamine **22**. The solid state conformation of an N(3)-unsubstituted 3-azabicyclohexane skeleton is determined by an X-ray structural analysis. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: **Bicyclic heterocyclic compounds; Diamines; Antibacterials; Reduction**

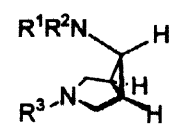
1. Introduction

6α-6-Amino-3-azabicyclo[3.1.0]hexane (**1b**) represents the diamino building block in trovafloxacin (**1a**), a new, strongly active, Gyrase inhibitor [1] (Figure 1). Several syntheses

Figure 1



1



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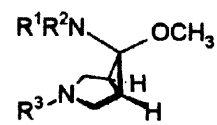
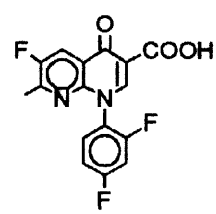


3d,e

a: $R^1 = R^2 = H$; $R^3 =$ 

b: $R^1 = R^2 = R^3 = H$

c: $R^1 = R^2 = Bn$; $R^3 = H$

d: $R^1 = R^2 = R^3 = Bn$

e: $R^1 = R^2 = All$; $R^3 = Bn$

f: $R^1 = R^2 = H$; $R^3 = Bn$

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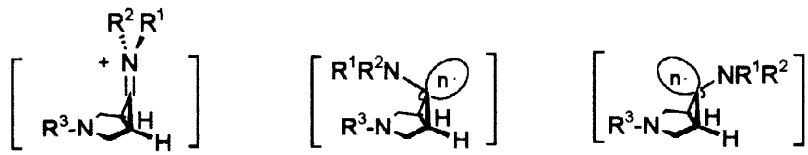
were developed in the meantime for compound **1b** (see references cited in ref. [2]). The nucleophilic substitution at a suitable cyclopropane precursor such as **3d,e** was investigated as a potential basis for the trovafloxacin diamino component, too [2]. It turned out, however, that this method leads to N-protected endo-amino derivatives **2** which could be used [2] for the synthesis of trovafloxacin 6β-diastereomer **2a**. Iminium ion **4** represents the intermediate in the nucleophilic displacement of the methoxy moiety in **3** by the hydride. The strong steric "inside shielding" at the planar iminium unit in **4** causes indeed a high stereoselectivity in 6β-diamine formation but - on the other hand - it complicates an access to the 6α-isomer. A bent, and most probably configurational stable, geometry should be found in the corresponding aminocyclopropyl-radical **5/7** or the aminocyclopropyl-anion **6/8** analogues [3]. These species could be regarded as interesting candidates for a selective generation of both diasteromers of aminocyclopropane derivatives **1** and **2** (Figure 2).

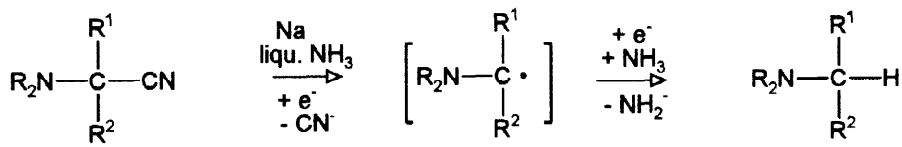
Figure 2



4 **5:** n = 1 **6:** n = 2 **7:** n = 1 **8:** n = 2

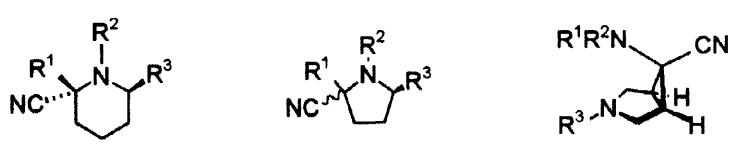
Aminoalkyl radicals or anions are described as intermediates in the reductive decyanation of α-aminocarbonitriles **9** with sodium [4-15] or lithium [16-19] in liquid ammonia to give amines **11** (Scheme 1). This substitution reaction is characterized by the sequence of the following steps: Initial transfer of an electron to **9** with formation of a radical anion, generation of radical **10** by

Scheme 1



9 **10** **11**

Figure 3



12 **13** **14**

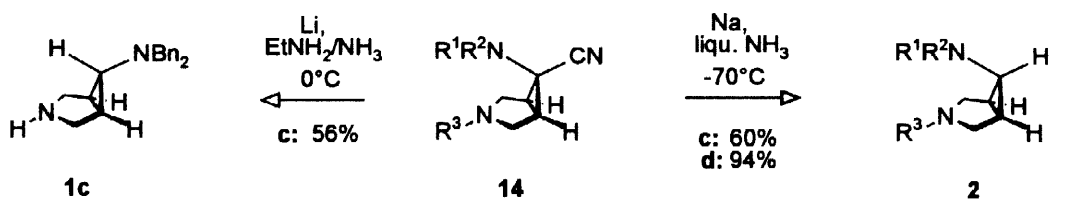
splitting off the cyanide, further reduction of **10** and finally, protonation of the resulting anion by ammonia. The stereochemistry was studied with five- and six-membered ring systems (Figure 3). A displacement of the cyano group with complete retention of configuration was reported for the reaction of **12** with sodium at lower temperatures in liquid ammonia [8] (further examples see ref. [8,9,11-15]). Reduction of compound **13** by lithium in liquid ammonia, THF and ethanol at -40°C provided the thermodynamically favored products [16,17] (further examples see ref. [17,18]).

To our knowledge, nothing is known about the applicability[1] of this reaction to an aminocyclopropanecarbonitrile derivative. We studied, therefore, the reaction of compounds **14** with an alkali metal in liquid ammonia. Model compounds **14c-e** with protected amino moieties were first used for these investigations as a potential further access to the diamino building block of target molecules **1a** and **2a**.

2. Reductive decyanation of 6β-dibenzylaminocarbonitriles 14c,d

Treatment of 6β-dibenzylamino-3-azabicyclohexanecarbonitriles **14c** and **14d** with a "solution" of sodium in liquid ammonia at -70°C gave decyanated diamines **2c** and **2d** which were isolated in 60% and 94% yield, respectively (Scheme 2). The configuration, thereby, remained unchanged. No products **1c** or **1d** from an inversion process could be observed in the ^{1}H NMR spectra of the crude reaction products. The applied concentration of sodium in liquid ammonia (about 0.3 M) corresponds to a solution with "salt-like characteristics" [20].

Scheme 2



1c **14** **2**

The potential realization of a reductive decyanation with inversion of configuration was investigated with compound **14c**. Running the reaction at 0°C in a mixture of ethylamine and ammonia and the use of lithium turned out to be optimal conditions in this context. Ammonia was added in order to facilitate the dissolution of the metal. Lithium as reducing agent gave a 4:1 mixture of **1c** and **2c** in 89% yield. Subsequent crystallization from pentane provided pure 6α-dibenzylamino isomer **1c** in 56% overall yield (Scheme 2). Sodium proved to be less suitable than lithium due to decreasing stereoselectivity (formation of **1c/2c** in a 3:2 ratio).

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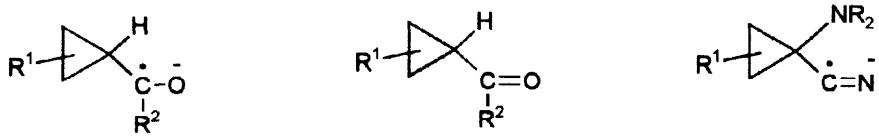
[1] A computer assisted search in the literature gave one example of a reductive decyanation of a cyclopropane carbonitrile species: 1-butylcyclopropanecarbonitrile was transformed to 1-butylcyclopropane by interaction with potassium in HMPT/ether at 0°C [21].

Cyclopropylmethyl radicals are known for undergoing a very fast ring opening reaction [3]. A three-membered ring, however, is less influenced by an adjacent radical anion. A slow and reversible ring opening is observed for a cyclopropyl ketyl species **15** if it is generated electrochemically and if an unsubstituted or alkyl-substituted three-membered ring is present [22]. A different behaviour [23-26], however, is found when **15** is generated by alkali metals in liquid ammonia upon reduction of cyclopropyl ketones **16**: A ring opening of **16** can only be avoided [27] if the reaction is run and quenched below -70°C. In the case of the analogous reactions of nitriles **14**, a fast displacement of the cyanide ion obviously prevents a considerable ring opening reaction of the radical anion **17** (Figure 4).

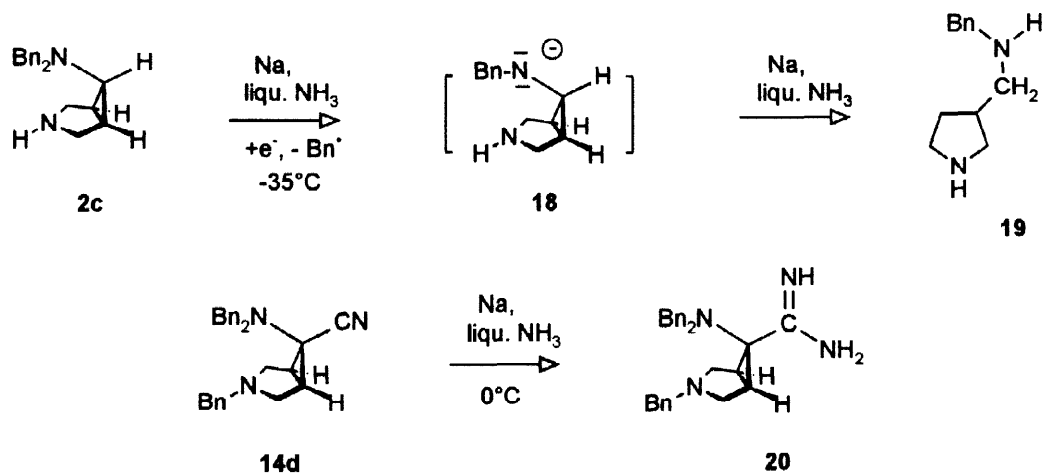
Figure 4



15 **16** **17**

In spite of this fact, some details must be considered for minimization of formation of side products in the preparation of compounds **1c** and **2c,d**: Aromatic systems such as the benzyl moiety are accessible to a Birch reduction [28] under these conditions: Higher concentrations of sodium than 0.3 mol/l at low temperatures and the appearance of a blue color in the ethylamine-ammonia-lithium system at 0°C should be excluded in order to avoid a Birch reduction. „Birch-products" are indicated in the ^{1}H NMR spectrum by signals between δ = 5.0 and δ = 5.5 ppm. Additionally, small amounts of dibenzylamine are formed in the reaction; they should result from a ring opening process. A way for potential inhibition of this amine formation was not found.

Scheme 3



2c **18** **19**

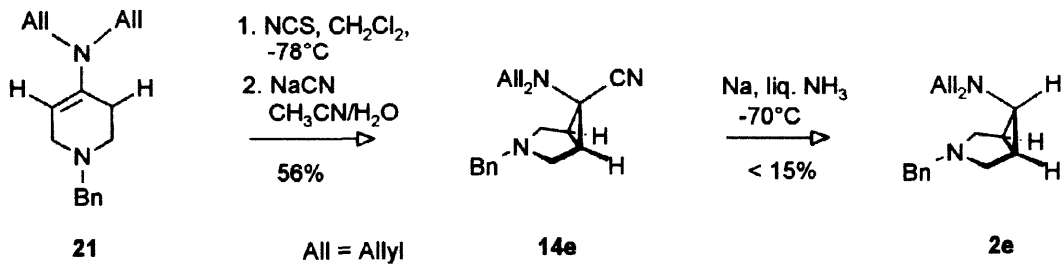
14d **20**

Too long reaction time causes a reductive monodebenzylation of **2c** leading to benzylaminomethylpyrrolidine **19** (Scheme 3). This side reaction can be used for an easy preparation of **19** by treatment of azabicyclohexane **2c** with sodium in ammonia at -35° for 8 h. The formation of **19** can be interpreted as transfer of an electron to one of the phenyl rings, N-C-bond cleavage, ring opening of the thereby formed aminyl radical or amine anion **18** and subsequent reduction. Increasing temperature and the presence of alkali amide finally favors the formation of an amidine as shown by the transfer of **14d** to **20** with sodium amide in liquid ammonia at 0°C (Scheme 3, formation of amidines from nitriles in liquid ammonia see ref. [29]).

3. 6β-Diallylaminocarbonitrile 14e as basis for reductive decyanation

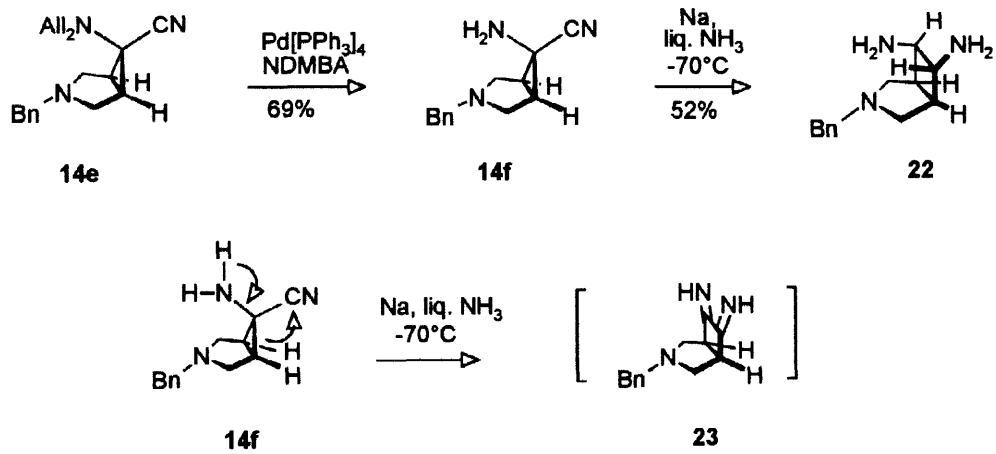
Carbonitrile **14e** as starting material for the decyanation was synthesized easily from enamine [2] **21** and subsequent reaction with N-chlorosuccinimide and cyanide (56% yield). Treatment of **14e** with sodium in liquid ammonia at -70°C, however, showed that diallyl protecting groups are less useful for the preparation of 6-amino-3-azabicyclohexane derivatives: 6β-Diamine **2e** was generated only as side product in less than 15% amount as determined by ^{1}H NMR spectroscopy (Scheme 4) (^{1}H NMR data of **2e** in ref. [2]).

Scheme 4



21 All = Allyl **14e** **2e**

Scheme 5



14e **14f** **22**

14f **23**

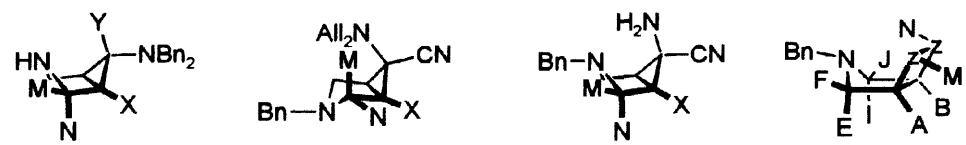
Deallylation of **14e** prior to the decyanation proved to be no suitable alternative to this route. The diallyl amino moiety in carbonitrile **14e** could be deprotected to give nitrile **14f** by treatment with N,N'-dimethylbarbituric acid in the presence of tetrakis(triphenylphosphine)palladium [2,30]. This easy removal of the allyl groups in **14e** contrasts strongly with the unsuccessful attempts [31] of deblocking the 6-dibenzylamino moiety in the analogous derivative **14d**. Decyanation of nitrile **14f** gave a product in 52% yield which was established rather as 3-azabicyclo[3.2.0]heptane derivative **22** than as the expected 3-azabicyclo[3.1.0]hexane **2f**. The formation of **22** can be understood by initial deprotonation of the amino moiety in **14f** followed by a ring enlargement to **23** and subsequent reduction of the two vicinal imino moieties (Scheme 5).

4. Structure of the 3-azabicycloalkane derivatives

C(6)-Configuration of the prepared 3-azabicyclo[3.1.0]hexane derivatives **1/2** is established by the $^3J_{HH}$-coupling of the bridge head hydrogen atoms with C(6)-H (see ref. [2]: **1c**: 2.25 Hz; **2c**: 6.9 Hz; **2d**: 6.7 Hz). The exo-position of the cyano moiety in **14f** (and consequently in **14e**) is deduced by its $^3J_{CH}$-coupling [32,33] which is determined in the ^{13}C NMR spectrum (**14f**: $^3J_{CH}$ = 5.0 Hz). The relative configuration of triamine **22** follows from the observance of six ^{13}C NMR signals for the bicyclic skeleton (2 triplets and 4 doublets) indicating the absence of a plane of symmetry and thus the trans arrangement of the two amino groups in the C_2-bridge.

Conformation of the 3-azabicyclic skeleton of the new compounds **1c**, **14e**, **14f** and **22** was studied by ^1H NMR spectroscopy. Simulation of the spectra and determination of the coupling constants was performed with the CALM program [34]. The ^1H NMR signals were analyzed as MM'NN'XX'Y-, MM'NN'XX'- and ABEFIJMN systems for **1c**, **14e,f** and **22**, respectively. The assignment of the hydrogen atoms is shown in Figure 5; chemical identical hydrogen atoms which are indicated by a prime are not drawn. Coupling constants are given in the Experimental Part.

Figure 5



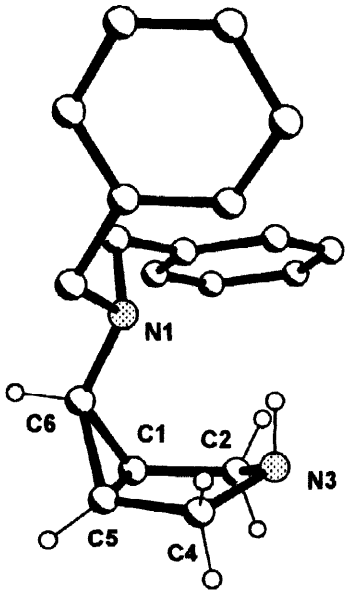
1c B **14e C** **14g B** **22 B**

B = boat C = chair z = C - NH_2

6ß-Amino-3-azabicyclo[3.1.0]hexane derivatives **2** with two tertiary amino units generally adopt a chair conformation due to repulsive effects of the N-lone pairs (X-ray structural analyses [32,33,35]). A boat conformation, however, is present in 6α-derivatives **1**; it is also found in 6β-derivatives **2** with at least one hydrogen atom at one of the two nitrogen atoms [2,31-33,35]. The

absence of a coupling for MX, M'X' or for AF, BJ indicates the adoption of a boat conformation **B** for **1c**, **14f** and also for **22**. **14e**, on the other hand, prefers a chair conformation **C**.

The presence of a boat conformation for a 3-unsubstituted 6β-3-azabicyclo[3.1.0]hexane derivative was established thus far only ^{1}H NMR spectroscopically [2,31-33,35]. Various experiments for crystallization of **1c** and **2c** during this work provided a single crystall of **2c** which allowed the performance of an X-ray structural analysis.



The molecular plot [36] of compound **2c** in Figure 6 shows clearly the inside direction of the lone-pair of the dibenzylamino moiety and the adoption of a bicyclohexane boat conformation with an axial hydrogen atom at N(3). This one and all other hydrogen atoms of the bicyclohexane skeleton could be localized directly. A buckling of the bicyclohexane unit by 65.3° [(angle C(1)C(2)C(4)C(5) // C(1)C(5)C(6)] and 26.9° [angle C(1)C(2)C(4)C(5) // C(2)N(3)C(4)] and a N ··· N distance of 2.958 Å should be mentioned as characteristic structural data of **2c**.

Figure 6 Molecular plot [36] of diamine **2c**

5. Experimental

^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker AMX 400 spectrometer (TMS as internal standard). Microanalyses were performed using a Perkin-Elmer 2400 Elemental Analyzer. Reactions in liquid ammonia or in ethylamine - ammonia mixtures were run with exclusion of moisture (nitrogen atmosphere). A pressure tube and an argon atmosphere were used for the deallylation reaction.

Decyanation of nitriles **14** *with sodium in liquid ammonia - General procedure*: Nitrile **14** (5.1 mmol, **14c** [31]: 1.55 g; **14d** [31]: 2.00 g) was added to a "solution" of sodium (0.7 g, 30 mmol) in liquid ammonia (100 mL) at -70°C. Then the cooling bath was removed and the mixture was stirred until the ammonia evaporated. The residue was triturated with ether (3 x 30 mL) and the extract was distilled in a Kugelrohr apparatus.

1α,5α,6β-6-Dibenzylamino-3-azabicyclo[3.1.0]hexane (**2c**): Distillation at 145°C/0.007 mbar and recrystallization from pentane; yield 0.64 g (60%), identical ^{1}H NMR spectrum with respect

to the published data [2]. Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 82.1; H, 8.1; N, 10.1.

1α,5α,6β-3-Benzyl-6-dibenzylamino-3-azabicyclo[3.1.0]hexane (**2d**): Distillation at 190°C/0.007 mbar; yield 1.76 g (94%), identical ^{1}H NMR spectrum with respect to the published data [2]. Anal. Calcd. for $C_{26}H_{28}N_2$: C, 84.74; H, 7.66; N, 7.60. Found: C, 84.7; H, 7.6; N, 7.9.

1α,5α,6α-6-Dibenzylamino-3-azabicyclo[3.1.0]hexane (**1c**): Ammonia was bubbled at -78°C into a mixture of ethylamine (20 mL) and lithium (140 mg, 20.0 mmol) unitil a blue color appears. Then the mixture was stirred at -78°C. When the lithium was dissolved totally the cooling bath was removed and the solution was warmed to 0°C during excess ammonia evaporated. Then further ethylamine (40 mL) (disappearance of the blue color) and 6-dibenzylamino-3-azabicyclo[3.1.0]hexane-6-carbonitrile [31] **14c** (1.0 g, 3.3 mmol) were added. The reduction is complete when the resulting red color changes to yellow-green (≈ 10 min.). Excess lithium was removed by addition of ammonium chloride. Evaporation of ethylamine, extraction of the residue with ether (3 x 30 mL) and removal of the ether in vacuo gives crude 6-amine as light yellow oil (0.82 g, 89% yield, **1c/2c** = 4 : 1); crystallization from pentane gave pure **1c**, mp. 51-53°C (0.51 g, 56% yield). ^{1}H NMR ($CDCl_3$): δ 1.31 (H_X, $H_{X'}$, 2H), 1.53 (H_Y, 1H), 2.77 (H_N, $H_{N'}$, 2H), 2.87 (H_M, $H_{M'}$, 2H) (MM'NN'XX'Y-system, $J_{MN} = J_{M'N'} = 11.3$ Hz, $J_{MX} = J_{M'X'} < 0.4$ Hz, $J_{NX} = J_{N'X'} = 3.4$ Hz, $J_{XX'} = 7.4$ Hz , $J_{XY} = J_{X'Y} = 2.25$ Hz), 1.56 (broad, unsplit, 1H, NH), 3.62 (s, 4H), 7.24-7.34 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 138.4 (s), 129.3 (d), 127.9 (d), 126.7 (d), 58.7 (t), 48.5 (t), 43.9 (d, $^1J_{CH} = 167$ Hz), 26.7 (d, $^1J_{CH} = 165$ Hz). Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.8; H, 8.1; N, 10.0.

3-(Benzylaminomethyl)-pyrrolidine (**19**): Dibenzylaminoazabicyclohexane **2c** (0.35 g, 1.26 mmol) was added to a solution of sodium (0.5 g, 21.7 mmol) in liquid ammonia (60 mL) and stirred at -35°C (reflux) for 8h. Then the ammonia was evaporated and the residue was extracted with ether (3 x 30 mL). Distillation in a Kugelrohr apparatus at 110°C/0.007 mbar gave pure diamine **19**; yield 0.21 g (88%); ^{1}H NMR ($CDCl_3$): δ 1.37 (m_c, 1H), 1.70 (s, broad, NH, 2H), 1.91 (m_c, 1H), 2.24 (m_c, 1H), 2.50-2.63 (m, 3H), 2.81-2.95 (m, 2H), 3.04 (m_c, 1H), 3.80 (s, 2H), 7.20-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 140.3 (s), 128.3 (d), 128.0 (d), 126.8 (d), 54.0 (t), 53.5 (t), 51.3 (t), 46.6 (t), 39.6 (d), 30.7 (t). Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.4; H, 9.6; N, 14.4.

1α,5α,6β-3-Benzyl-6-dibenzylamino-3-azabicyclo[3.1.0]hexane-6-carboxamidine (**20**): A solution of sodium (0.1 g, 4.3 mmol) in liquid ammonia (15 mL) was stirred in a pressure tube at 0°C until the blue color disappeared. Then the solution was cooled to -78°C, dibenzylaminocarbonitrile **14d** (0.2 g, 0.51 mmol) was added and the mixture was stirred at 0°C for 2 h. Evaporation of the ammonia and extraction of the residue with ether (2 x 20 mL) gave 0.21 g of a mixture of amidine **20** and starting material **14d** (ratio 2:1). 100 mg of pure amidine **20** could be obtained by crystallization from ether; mp. 134-135°C; ^{1}H NMR ($CDCl_3$): δ 1.89 (H_X, $H_{X'}$, 2H), 2.66 (H_N, $H_{N'}$, 2H), 2.72 (H_M, $H_{M'}$, 2H) (MM'NN'XX'-system, $J_{MN} = J_{M'N'} = 10.0$ Hz, $J_{MX} = J_{M'X'} = 1.6$ Hz, $J_{NX} = J_{N'X'} = 5.0$ Hz, $J_{XX'} = 9.0$ Hz), 3.61 (s, 2H), 3.85 (s, 4H), 7.14-7.39 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 166.5 (s), 139.2 (s), 139.1 (s), 129.3 (d), 129.1 (d),

128.1 (d), 127.9 (d), 126.92 (d), 126.86 (d), 60.3 (t), 57.9 (s), 57.4 (t), 53.2 (t), 31.7 (d, $^1J_{CH}$ = 170 Hz). Anal. Calcd. for $C_{27}H_{30}N_4$: C, 78.99; H, 7.37; N, 13.65. Found: C, 78.8; H, 7.3; N, 13.7.

1α,5α,6β-3-Benzyl-6-diallylamino-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**14e**): A solution of N-chlorosuccinimide (4.64 g, 35.3 mmol) in dichloromethane (100 mL) was dropped under stirring within 1 h at -78°C into a solution of enamine **21** [2] (9.45 g, 35.3 mmol) in dichloromethane (100 mL). Then the cooling bath was removed and stirring was continued for 1.5 h. Evaporation of the solvent and extraction of the residue with pentane (7 x 30 mL) gave crude chloroenamine (9.5 g) which was added to a stirred solution of sodium cyanide (1.7 g, 35 mmol) in water (7 mL) and acetonitrile (70 mL). The mixture was stirred at room temperature for 18 h; then it was extracted in a Kutscher-Steudel apparatus with pentane (40 mL) to give crude nitrile **14e** which was purified by distillation in a Kugelrohr apparatus at 165°C/0.007 mbar. Yield: 5.8 g (56%) of **14e** as a slightly yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.29 (H_{X1}, $H_{X'1}$, 2H), 2.60 (H_{M1}, $H_{M'1}$, 2H), 3.16 (H_{N1}, $H_{N'1}$, 2H) (MM'NN'XX'-system, $J_{MN} = J_{M'N'}$ = 10.4 Hz, $J_{MX} = J_{M'X'}$ = 2.2 Hz, $J_{NX} = J_{N'X'}$ = 5.9 Hz, $J_{XX'}$ = 8.9 Hz), 3.26 (H_Y, 2H), 3.34 (H_{X2}, 2H), 5.20 (H_{M2}, 2H), 5.29 (H_{N2}, 2H), 5.92 (H_A, 2H) (AMNXY-system, J_{AM} = 10.1 Hz, J_{AN} = 17.1 Hz, $J_{AX} = J_{AY}$ = 6.6 Hz, J_{MN} = 1.8 Hz, $J_{MX} = J_{MY}$ = 1.1 Hz, $J_{NX} = J_{NY}$ = 1.5 Hz, H_{X2} and H_Y in beginning coalescence), 3.62 (s, 2H), 7.22-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 138.7 (s), 133.8 (d), 128.1 (d), 128.0 (d), 126.7 (d), 118.8 (s), 118.3 (t), 58.3 (t), 55.7 (t), 51.7 (t), 44.1 (s), 33.8 (d, $^1J_{CH}$ = 173 Hz). Anal. Calcd. for $C_{19}H_{23}N_3$: C, 77.78; H, 7.90; N, 14.32. Found: C, 78.2; H, 8.1; N, 13.8.

1α,5α,6β-6-Amino-3-benzyl-3-azabicyclo[3.1.0]hexane-6-carbonitrile (**14f**): A mixture of tetrakis(triphenylphosphine)palladium (100 mg, 0.095 mmol) and N,N'-dimethylbarbituric acid (4.5 g, 28.5 mmol) was added to a solution of diallylaminocarbonitrile **14e** (1.47 g, 5.0 mmol) in dichloromethane (12 mL) in an argon atmosphere and stirred at 40°C for 2 h. Then the solution was washed with an aqueous solution of sodium hydrogencarbonate (5%, 30 mL). Evaporation of dichloromethane, addition of aqueous hydrochloric acid (5%, 30 mL), extraction of diallylbarbituric acid with ether (30 mL), addition of aqueous sodium hydroxide solution (5 M, till pH 12 was reached) and extraction once more with ether (30 mL) gave almost pure aminonitrile **14f** which was distilled in a Kugelrohr apparatus, bp. 140-150°C/0.007 mbar. Yield: 0.74 g (69%); ^{1}H NMR ($CDCl_3$) δ 2.07 (H_X, $H_{X'}$, 2H), 2.81 (H_N, $H_{N'}$, 2H), 3.09 (H_M, $H_{M'}$, 2H) (MM'NN'XX'-sytem, $J_{MN} = J_{M'N'}$ = 10.2 Hz, $J_{MX} = J_{M'X'} < 0.7$ Hz, $J_{NX} = J_{N'X'}$ = 3.8 Hz, $J_{XX'}$ = 8.3 Hz), 2.15 (broad, unsplit, 2H, NH), 3.60 (s, 2H), 7.19-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 138.0 (s), 128.0 (d), 127.9 (d), 126.8 (d), 121.4 (t, $^3J_{CH}$ = 5.0 Hz), 58.6 (t), 51.5 (t), 31.2 (s), 28.5 (d, $^1J_{CH}$ = 170 Hz). Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.0; H, 7.3; N, 19.4.

3-Benzyl-6,7-trans-diamino-3-aza-bicyclo[3.2.0]heptane (**22**): Aminocarbonitrile **14f** (0.75 g, 3.51 mmol) was added at -70°C to a solution of sodium (0.48 g, 21.1 mmol) in liquid ammonia (50 mL). The cooling bath was removed and the solution was stirred until the ammonia evaporated. Then the residue was triturated with ether (3 x 20 mL) and the extract was distilled in a Kugelrohr apparatus at 120-150°C/0.007 mbar. Redistillation and collection of the fraction of 130-135°C/0.007 mbar gave pure triamine **22**; yield 0.39 g (52%); ^{1}H NMR ($CDCl_3$) δ 2.01

(H_E, H_I, 2H), 2.15 (H_B, 1H), 2.75 (H_A, 1H), 2.83 (H_J, 1H), 2.85 (H_N, 1H), 2.95 (H_F, 1H), 2.96 (H_M, 1H) (ABEFIJMN-system, J_{AB} = 7.55 Hz, J_{AE} = 7.4 Hz, J_{AM} = 8.5 Hz, J_{AN} = 1.0 Hz, J_{BI} = 5.0 Hz, J_{BM} = 1.0 Hz, J_{BN} = 4.0 Hz, J_{EF} = 10.1 Hz, J_{IJ} = 8.8 Hz, J_{MN} = 5.5 Hz), 3.64 (s, 2H), 7.21-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 139.6 (s), 128.3 (d), 128.1 (d), 126.7 (d), 62.5 (d), 59.5 (t), 58.5 (t), 56.5 (d), 52.2 (t), 42.9 (d), 37.2 (d). Anal. Calcd. for $C_{13}H_{19}N_3$: C, 71.85; H, 8.81; N, 19.34. Found: C, 72.2; H, 8.7; N, 18.9.

X-Ray structural analysis of 1α,5α,6β-6-dibenzylamino-3-azabicyclo[3.1.0]hexane (**2c**) [36]: Colorless prisms from cooling of a distilled sample, crystal size 0.35 x 0.25 x 0.15 mm^3, a = 14.001 (3), b = 11.773 (2), c = 9.125 (2) Å, β = 94.640(10)°, V = 1606.3 (5) Å^3, Z = 4, D_{cal} = 1.151 Mg · m^{-3}, μ = 0.068 mm^{-1}, $F_{(000)}$ = 600, monoclinic space group $P2_{(1)}/c$. Graphit monochromated Mo-K_α radiation, Siemens-P4 diffractometer, Θ = 1.36 - 25.00° , temperature: 293K, 3857 reflections, 2822 independent (R_{int} = 0.0228), 2333 observed [I ≥ 2σ(I)]. The structure was solved by direct methods using SHELXTL-PLUS program system [37] and refined by full-matrix least-squares techniques against F^2 with SHELXL-93 [38]. The hydrogen atoms H(1), H(2a), H(2b), H(3), H(4a), H(4b), H(5) and H(6) were localized and refined isotropically; all other hydrogen atoms were placed in calculated positions (d_{C-H} = 0.960Å). All other atoms were refined anisotropically. The final refinement with 268 parameters converged with R1= 0.0617; wR2 = 0.0802 (observed data) and R1 = 0.1558, wR2 = 0.1126 (all data) with w^{-1} = $[\sigma^2(F_o^2) + (0.004P)^2 + 0.4201\ P]$ and P = $[(F_o^2) + 2F_c^2]/3$; residual electron density 124 e · nm^{-3} and -139 e · nm^{-3} ; GOF on F^2 1.052

6. Acknowledgments

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7. References

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