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FUNCTIONALIZED CHLOROENAMINES IN AMINOCYCLOPROPANE SYNTHESIS - X.[1] AMINO-AZABICYCLO[3.1.0]HEXANE DIASTEREOMERS FROM CHLOROENAMINES AND - ORGANOMETALLIC COMPOUNDS

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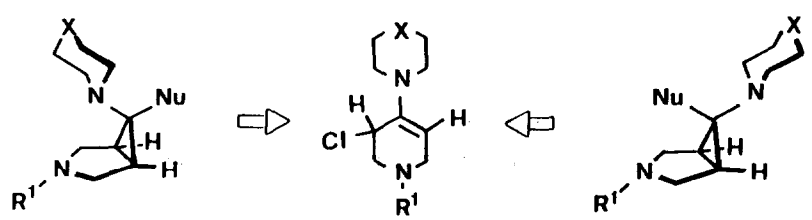
Abstract: Morpholino-chlorotetrahydro-N-methyl-pyridine **4** reacted with Grignard reagents **5** or diorganyl-magnesium compounds **6** to give a mixture of azabicyclo[3.1.0]hexane diastereomers **10** and **11** besides the monocyclic ketones **12**. The latter were obtained as the sole products from chloroenamine **4** and dimethylzinc **7a** or lithium dimethylcopper **8a**. Organolithium compounds **9a,c** or Grignard reagents **5a-c** in the presence of TMEDA transferred **4** exclusively to endo-morpholino isomers **10**. exo-Amines **11** could be obtained with high stereoselectivity from **4** via the N,O-acetal **13** and by the substitution of the methoxy moiety by a Grignard reagent **5**. The stereochemical result of this substitution reaction can be explained by an intermediate complexation of the pyrrolidine N-atom in **13** by the Grignard reagent **5**. An N-benzyl chloroenamine **14** instead of the N-methyl compound **4** showed a different reaction behavior with methylmagnesium bromide **5a** leading only to endo-amine **15** which could be used as a precursor of the parent bicyclic system **16**. The configurations of the bicyclic diamines **10**, **11** and **15** were determined via ^{1}H NMR data.

Azaannulated aminocyclopropanes **1** and **3** could be synthesized from chloroenamines **2** by the reaction with cyanide[2,3] or hydride[4] as a nucleophile. Two different ways,[2-4] thereby, were found for a stereoselective access to **1** and **3**. Diamines **1** and **3** represent relatively rigid compounds; this should lead to definite N,N-distances and to differences in the biological activity.

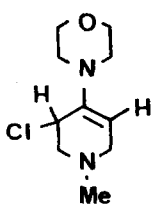


1 **2** **3**

We were interested, therefore, in the synthesis of further compounds of type **1** and **3**. This paper reports on the reaction of chloroenamines **2** with organometallic compounds. In the case of morpholino-chlorotetrahydropyridine **4** as starting material stereoselective preparations of alkyl or aryl substituted azaannulated aminocyclopropanes **1** and **3** are pointed out.

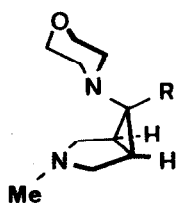
REACTION OF CHLOROENAMINES 4 WITH ORGANOMETALLIC COMPOUNDS

Reaction of methylmagnesium bromide (**5a**) with chloroenamine **4** gave a nearly equimolar mixture of diastereomeric bicyclic diamines **10a** and **11a** besides 10% of monocyclic ketone **12a**. The latter is resulting from a direct displacement of the chloro moiety by the Grignard reagent and a subsequent hydrolytic cleavage of the enamine function upon aqueous working up. Phenylmagnesium bromide (**5c**) as well as dimethylmagnesium (**6a**) or diphenylmagnesium (**6c**) showed a similar behaviour to give a mixture of products **10** - **12** from chloroenamine **4**. Only butylmagnesium bromide (**5b**) led to a significant stereoselection producing a threefold excess of **11b** with respect to **10b**.

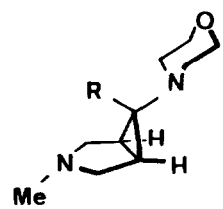


4

1. $R_n$metal 5 - 9
2. H^+ / H_2O
3. OH^-



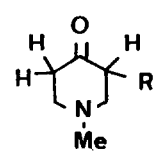
10



11

$R_n$metal	
5:	R - Mg - Br
6:	R - Mg - R
7:	R - Zn - R
8:	Li^+ [R - Cu - R]$^-$
9:	R - Li

5 - 12, 26, 27	
a:	Me
b:	n-Bu
c:	Ph



12

Dimethylzinc (**7a**) or lithium dimethylcopper (**8a**) proved not to be suitable for the cyclopropanation process; these organometallic compounds exclusively gave the direct substitution products **12**. (s. Table 1, Method A).

Table 1 Reactions of organometallic compounds **5-8** with chloroenamine **4**; yields of the products **10, 11** and **12**

Method	Starting material	Organo-metallic compound R_n-metal	Molar excess of R_n-metal	Reaction products[a] 10 [%, (g)]	11 [%, (g)]	12 [%, (g)]
A	4	5a	5	37(0.73)	31(0.62)	10(0.13)
A	4	5b	5	14(0.33)	44(1.05)	-
A	4	5c	5	28(0.72)	19(0.49)	43(0.81)
A	4	6a	5	27(0.53)	26(0.51)	15(0.19)
A	4	6c	5	31(0.80)	8(0.21)	49(0.93)
A	4	7a	2	-	-	62(0.79)
A	4	8a	2	-	-	72(0.92)

[a] Yields in g correspond to the experimental instructions (s. Experimental Part)

STEREOSELECTIVE SYNTHESES OF ALKYL- OR ARYL-AZABICYCLO[3.1.0]HEXYL-MORPHOLINES 10 AND 11

The undesired direct substitution and the missing stereoselectivity in the cyclopropane forming process disappeared if methyllithium (**9a**), phenyllithium (**9c**) or organomagnesium bromide **5a-c** - TMEDA mixtures were used. Pure **endo-amines 10** were the sole products from these reactions with chloroenamine **4**. endo-Amine **10b** as the only detectable bicyclic product was found for the reaction with butyllithium (**9b**), too; the monocyclic compound **12b**, however, was the main product in this special case (s. Table 2 Methods B and C).

A highly stereoselective way to **exo-amine diastereomers 11** was found by the reaction of bicyclic N,O-acetal **13** with methyl- or phenylmagnesium bromide (**5a,c**) (Table 2 Method D). Grignard reagents **5** react more slowly with N,O-acetal **13** than with chloroenamine **4**. Compounds **5** were used, therefore, in a larger molar excess for the former reactions. It was clearly shown by the reaction of **5c** with **4** (5:1 and 20:1 molar ratio) that an increase of the molar ratio of the both components has no influence on the stereochemical result. The stereoselectivity for the exo-amine formation totally could be changed by running the reaction of **13** with **5c** in the presence of TMEDA (Table 2, Method E). Starting material **13** was obtained easily in 71% yield[5] by the interaction of enamine **4** with sodium methoxide in methanol.

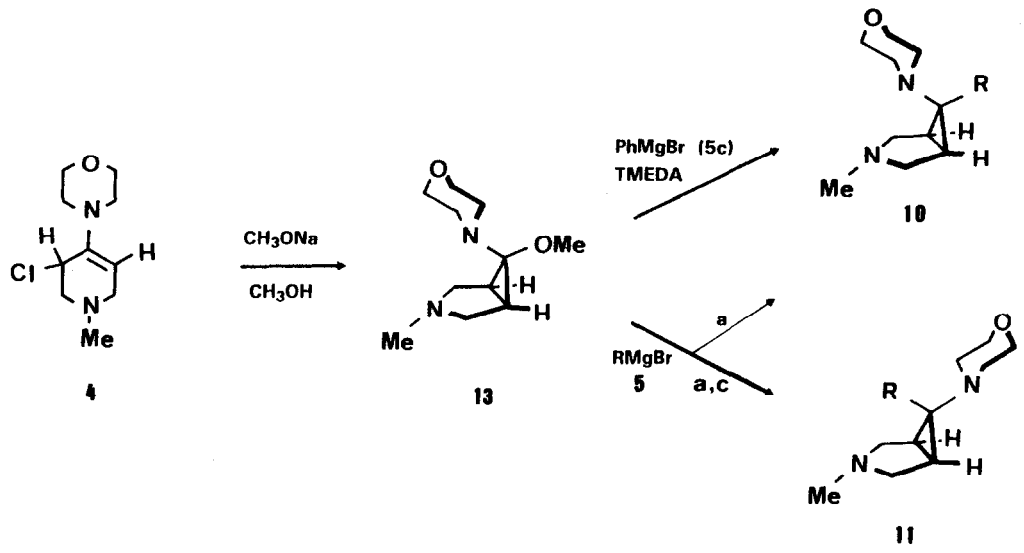


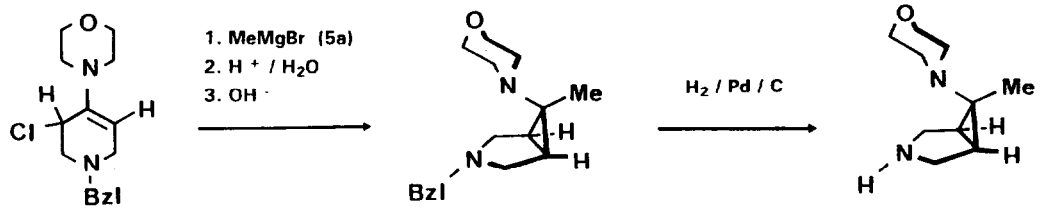
Table 2 Reactions of organometallic compounds **5**/TMEDA or **9** with chloroenamine **4** and reactions of organometallic compounds **5** or **5**/TMEDA with N,O-acetal **13**; yields of the products **10**, **11** and **12**

Method	Starting material	Organo-metallic compound R_n-metal	Molar excess of R_n-metal	Reaction products[a]		
				10 [%, (g)]	**11** [%, (g)]	**12** [%, (g)]
B	**4**	**5a**/TMEDA	3	68(1.33)	-	-
B	**4**	**5b**/TMEDA	5	32(0.76)	-	-
B	**4**	**5c**/TMEDA	5	38(0.98)	-	-
C	**4**	**9a**	2	55(1.08)	-	-
C	**4**	**9b**	2	14(0.33)	-	27(0.46)
C	**4**	**9c**	3	46(1.19)	-	-
D	**13**	**5a**	20	5(0.02)	54(0.21)	-
D	**13**	**5c**	20	-	81(0.42)	-
E	**13**	**5c**/TMEDA	20	73(0.19)	-	-

[a] Yields in g correspond to the experimental instructions (s. Experimental Part)

Thus, chloroenamine **4** acts as suitable starting material for selective syntheses of the two diastereomeric amines **10** and **11**, respectively. **10**, thereby, can be prepared directly from **4** and organolithium compunds **9** or a Grignard reagent **5** - TMEDA mixture. exo-Amine isomers **11** are preferentially synthesized from **4** by a two step sequence using N,O-acetal **13** as intermediate product and its subsequent reaction with Grignard reagents **5**. Both ways are complementary to each other.

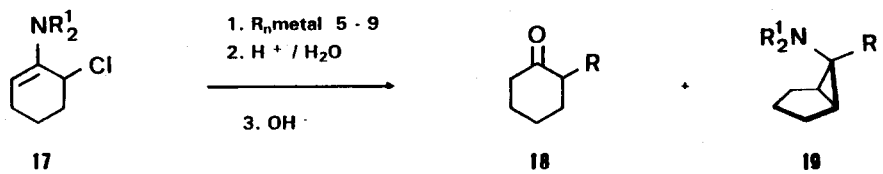
Contrarily, N-benzyl-chloroenamine **14** gave bicyclic amine **15** in 53% yield upon the interaction with methylmagnesium bromide (**5a**) (5 molar excess) without any ^1H NMR spectroscopic detectable amount of an exo-amine isomer or a direct substitution product. The N-benzyl moiety in **15** could be removed by hydrogenolysis in methanol with palladium as catalyst leading to the parent amine **16**.



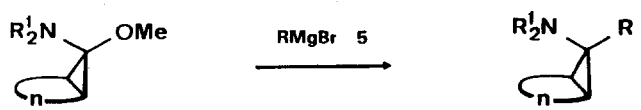
14 **15** **16**

THE STEREOSELECTION - CONSEQUENCE OF AN AMINE METAL COMPLEXATION

The formation of bicyclo[3.1.0]hexylamines **19** from chloroenamines **17**, and organometallic compounds **5**, **6**, **8** or **9** was reported already by Blazejewski, Cantacuzene and Wakselman.[6] Generally they obtained mixtures of **18** and **19**; the resulting bicyclic amines, however, were found to consist of one pure diastereomer to which an endo-amino configuration **19** was assigned.

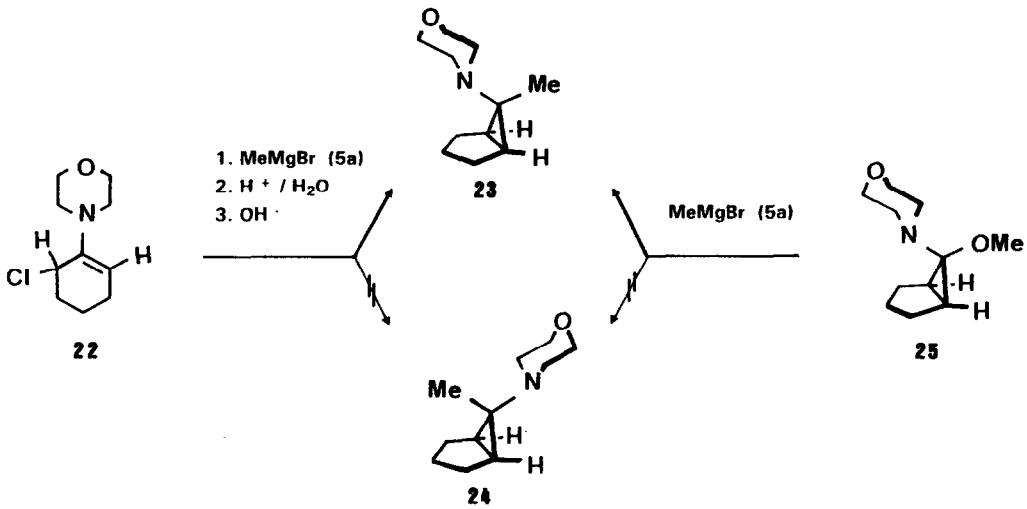


17 **18** **19**

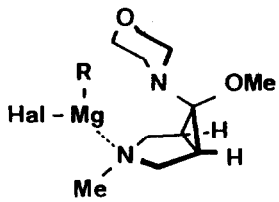


20 **21**

Lithium organocopper compounds **8** gave no cyclopropane formation, only products **18** from a direct substitution process of the chloro substituent in **17** could be isolated.[6] The displacement of the methoxy group in bicyclic N,O-acetals **20** by Grignard reagents **5** to yield alkyl- or arylbicycloalkylamines **21** was described by our group.[7-9] Again, only endo-amine isomers **21** were accessible in all cases. Since both reactions were described neither for morpholinochlorocyclohexene **22** nor for bicyclo[3.1.0]hexanone-N,O-acetal **25**, we investigated additionally both reactions with these special starting materials. Only endo-bicyclo[3.1.0]hexyl-morpholine **23** could be found in both cases (54% yield from **22** and **5a**; 66% yield from **25** and **5a**). No formation of the exo-amine isomer **24** could be detected by ^1H NMR analysis of the reaction mixture.



The steric result of the reaction of N,O-acetal **13** with Grignard reagents **5** should be the consequence of a formation of a complex: Indeed, an insoluble solid complex was formed immediately after addition of Grignard reagent **5** to a solution of N,O-acetal **13**; the complexation of the latter should take place with the pyrrolidine nitrogen atom. In this insoluble complex **26** an endo-attack can occur at the stage of the bicyclic iminum ion **27**. According to this no precipitation and no complexation is observed in the analogous reaction of the corresponding N,O-acetal **25** due to the missing aminofunction in the bicyclic system. An intermediate **27** also is not formed from **13** and **5a** in the presence of TMEDA causing the normal exo-attack[10] of the nucleophile to a bicyclic iminium ion (for structures of complexes of Grignard reagents with TMEDA see ref.[11,12]).



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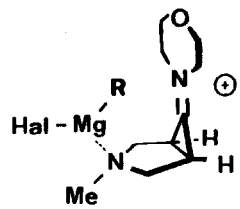

27

The formation of an insoluble complex of the two reacting species seems to be the crucial point even for the stereochemical result of the reaction of chloroenamine **4**. Chloroenamine **4** remained in solution upon the reactions with organolithium compounds **9** or the Grignard reagent **5** - TMEDA complex as detected by ^1H NMR experiments. In solution the same normal stereochemical result was obtained as in the reactions of **4** with nucleophiles as cyanide,[2] hydride[4] or methoxide (see above). The reaction of **4** with organomagnesium compounds **5** and **6** seems to be more complicated. Complexation of N-benzylchloroenamine **14** seemed to be less effective than that of the analogous N-methyl compound **4** as indicated qualitatively by the amount of formed precipitate.

CONFIGURATION OF THE BICYCLIC COMPOUNDS 10, 11, 15 AND 16

Strongly different energies were found for the topomerization process of the two hydrogen atoms of a morpholine methylene moiety in the endo- or exo-position at the C_1-bridge of a bicyclo[3.1.0]hexyl- or bicyclo[4.1.0]heptyl system ($\Delta\Delta G^{\ddagger}$ = 30 - 40 kJ/mol).[7,8,10,13,14] This allowed an easy determination of the configuration of such compounds. Smaller differences of the $\Delta G^{\ddagger}$ - values, however, were observed in the case of a 3-azabicyclo[3.1.0]hexyl skeleton (e.g. **10d**: $\Delta G^{\ddagger}$ = 58.4 - 58.5 kJ/mol,[2] **11d** $\Delta G^{\ddagger}$ = 46.4 kJ/mol,[3]; d: R = CN). Similar magnitudes of hindrance of the dynamics of morpholine were determined for N-methyl compounds **10a-c** and **11a-c** (see Table 3). The availability of both diastereomers **10** and **11** in all cases allowed an unequivocal assignment of the configuration.

Comparing the $\Delta G^{\ddagger}$ value of **10a** with those of **15**, **16** and **23** requires further explanation: The more bulky N-benzyl moiety hinders the morpholine dynamics to the same extand as the less bulky N-methyl group. The small hydrogen atom as N-substituent on the other hand increases the hindrance of the morpholine dynamics. The value of $\Delta G^{\ddagger}$ = 66.0 kJ/mol is of the same magnitude as that of the carbocyclic analogue **23** ($\Delta G^{\ddagger}$ = 67.2 - 67.8 kJ/mol).

Table 3 $\Delta G^{\ddagger}$ - Values of the dynamics of the morpholine ring of the compounds **10a-c**, **11a-c**, **15** and **23** determined on the basis of ^1H NMR data and coalescence temperatures (T_c)

	T [°C]	Group	$H_{A/X}$	$H_{B/Y}$	$^2J_{HH}$ [Hz]	T_c [°C]	$\Delta G^{\ddagger}$ [a] [kJ/mol]
10a[b,d]	-43	OCH_2	3.68	3.47	10.5	13	58.6
		NCH_2	2.43	1.85	11.5	29	59.9
10b[b,e]	-20	OCH_2	3.81	3.62	12.0	40	63.1
		NCH_2	2.80	2.13	12.0	54	62.8
10c[b,d]	-28	OCH_2	3.60	3.47	10.6	20	60.8
11a[c,d]	-63	OCH_2	3.77	3.27	11.0	-40	46.5
11b[c,e]	-63	OCH_2	3.74	3.35	10.3	-33	46.6
		NCH_2	2.70	2.52	10.8	-37	47.2
11c[c,d]	-63	OCH_2	3.59	3.33	11.4	-34	48.3
	-63	NCH_2	2.53	1.98	11.4	-23	49.4
15[b,e]	0	OCH_2	3.66	3.49	12.0	25	60.3
	0	NCH_2	2.43	1.88	12.0	38	60.3
23[b,e]	28	OCH_2	3.62	3.37	10.8	62	67.2
		NCH_2	2.51	2.14	12.0	67	67.8

[a] Calculated with the approximation formula for the coupled case (ref. [15]). [b] $C_6D_5CD_3$ as solvent. [c] CD_2Cl_2 as solvent. [d] 200 MHz. [e] 400 MHz.

Differences in the conformation of compounds **10a** / **15** and **23** can be deduced from these results. Further investigations showed[16] that **10a** and **15** are present preferentially in a chair conformation with an equatorial N-alkyl substituent. **23** is expected to prefer a boat conformation.

EXPERIMENTAL

^1H NMR spectra were obtained with a Bruker AMX 400 or, if noted, with a Bruker WP 200 spectrometer; ^{13}C NMR spectra were recorded with a Bruker AMX 400 spectrometer (TMS as internal standard). IR spectra were measured on a Perkin-Elmer 397 Infrared Spectrophotometer. Microanalyses were performed with a Perkin-Elmer 2400 Elemental Analyzer.

Method A: Reaction of chloroenamine 4 with organomagnesium compounds 5a-c, 6a, 6c, dimethylzinc (7a) or lithium dimethylcopper (8a) - General procedure: Organometallic compounds were dropped as ethereal solutions [organomagnesium compounds **5a-c** or **6a,c**: 25 mL (50 mmol) of a 2 M ethereal solution; dimethylzinc (**7a**): 50 mL of a 0.4 M ethereal solution; lithium dimethylcopper (**8a**)[6,17]: 50 mL of a 0.4 M ethereal solution] to a vigorously stirred solution[2] of **4** (2.16 g, 10 mmol) in 100 mL of ether [**5**, **6** and **7a** at 25°C, **8a**: -20°C]. Stirring was continued at room temperature for 72 h (for **5**, **6** and **7a**) or 5 d (for **8a**). Then the crude mixture (for **5**, **6** or **7a**) or the centrifuged ethereal solution (for **8a**) was cooled to 0°C and slowly hydrolyzed by addition of water (50 mL) and of 20% H_2SO_4 (10 mL). The clear aqueous solution (pH = 1) was washed twice with 50 mL of ether. Subsequent basification of the solution with 20% aqueous NaOH (10 mL) to pH = 9 - 10 and extraction with ether (5 x 50 mL) gave the weaker basic amines **11a-c** and **12a-c**. **11a,c** and **12a,c** could be separated by distillation in a Kugelrohr apparatus and purified by recrystallization; **11b** and **12b** were separated by chromatography (60 cm x 2.5 cm column, basic Al_2O_3; ether/pentane 1/1).

Addition of solid NaOH (10 g, 250 mmol) to the aqueous solution was necessary to allow the extraction of free bases **10a-c** with ether (4 x 50 mL) after removal of the remaining solid by centrifugation. Pure compounds **10** were obtained either by recrystallization from pentane (**10a**) or ether (**10c**) or by chromatography (**10b**, 60 cm x 2.5 cm column, basic Al_2O_3; ether/pentane 1/1).

Method B: Reaction of chloroenamine 4 with Grignard reagents 5a-c in the presence of TMEDA - General procedure: A solution of Grignard reagent (**5a**: 30mmol in 12 mL of ether; **5b,c**: 50mmol in 20 mL of ether) was added to a vigorously stirred solution[2] of **4** (2.16 g, 10mmol) in 30 mL of TMEDA. Stirring was continued for 72h at room temperature; then the solvent was evaporated. The residue was slowly hydrolyzed by addition of water (50 mL) and 90% H_2SO_4 (15 mL). The aqueous layer was washed with ether (2 x 30 mL). Addition of solid NaOH (20 g, 0.5 mol) and extraction of the aqueous phase with ether (5 x 50 mL) gave endo-amines **10** which were purified by recrystallization from ether (**10c**), distillation in a Kugelrohr apparatus (**10a**) or chromatography (**10b**, 60 cm x 2.5 cm column, basic Al_2O_3; ether/pentane 1/1)

Method C: Reaction of chloroenamine 4 with organolithium compounds 9a-c - General procedure: Organolithium compound **9** [**9a**: 12.5 mL (20 mmol) of 1.6 M MeLi/ether solution;

9b: 8.7 mL (20 mmol) of 2.3 M n-BuLi/hexane solution; **9c**: 2.5 g (30 mmol) of PhLi in 40 mL of ether] were added at -50°C to a stirred solution[2] of **4** (2.16g, 10mmol) in 100 mL of ether. Stirring was continued at -50°C for 8h and then 48h at room temperature. In the case of **9a** and **9c** the mixture was centrifuged. The ethereal layer was washed with water (50 mL). Further **10** was obtained by hydrolysis of the solid residue by water (50 mL) / 90% H_2SO_4 (2 mL), addition of solid NaOH (5 g, 125 mmol) and extraction with ether (5 x 50 mL). In the case of **9b** the reaction mixture directly was hydrolyzed without centrifugation and worked up analogously. Distillation in a Kugelrohr apparatus led to pure products **10a-c** and **12b**.

Method D: Reaction of N,O-acetal 13 with Grignard compounds 5a and 5c - General procedure: An ethereal solution of Grignard compound **5** [**5a**: 13.3 mL (40 mmol) 3M MeMgBr/ether-solution; **5c**: 20 mL (40mmol) 2M PhMgBr/ether-solution] was added at 25°C to a solution of **13** (0.424 g, 2.0 mmol) in ether (30 mL). The mixture was stirred at room temperature for 14d and then hydrolyzed with water (30 mL) and 90% H_2SO_4 (2 mL). The aqueous layer was washed with ether (2 x 20 mL) and basified (**5a**: pH = 10; **5c**: pH = 13) by addition of 20% aqueous NaOH (5 - 15 mL). Extraction of the aqueous solution with ether (4 x 20 mL) and evaporation of the ether led to **11a,c** as colorless oils which were purified by recrystallization (**11a**: form pentane; **11c**: from ether). endo-Amine **10a** was obtained by further addition of 50% aqueous NaOH (5 mL) to the water layer, centrifugation and extraction of the water layer with ether (3 x 20 mL). Removing the ether in vacuo gave crude **10a**, which was purified by distillation in a Kugelrohr apparatus.

Method E: Reaction of N,O-acetal 13 with Grignard compound 5c in the presence of TMEDA: An ethereal solution of **5c** [10 mL (20 mmol) of a 2M PhMgBr/ether-solution] was added to a solution of **13** (0.212 g, 1.0 mmol) in TMEDA (10 mL). The mixture was stirred for 3 weeks at room temperature, then the solvent was removed and the residue was hydrolyzed by addition of water (25 mL) and 90% H_2SO_4 (3 mL). The water layer was washed with ether (2 x 20 mL), basified by addition of 50% aqueous NaOH (10 mL) and separated by centrifugation. Extraction of the liquid phase with ether (4 x 20 mL) and of the solid residue with ether (2 x 20 mL) led to crude **10c**, which was purified by recrystallization from pentane.

The yields of the products from the reactions according to **Methods A - E** are given in the Tables 1 and 2.

4-(1α,5α,6β-3,6-Dimethyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (10a): mp 45°C; ^1H NMR ($CDCl_3$) δ 0.99 (s, 3H), 1.58 (H_{X2},$H_{X2'}$, 2H), 2.10 (H_{B2},$H_{B2'}$, 2H), 3.13 (H_{A2},$H_{A2'}$, 2H) (AA'BB'XX'-system; $^2J_{AB}$ = 10.5 Hz), 2.27 (s, 3H), 2.2-2.8 (m, 4H), 3.4-3.9 (m, 4H) (broad, unsplit); ^{13}C NMR ($CDCl_3$) δ 67.2 (t), 54.1 (t), 49.3 (s), 48.4 (t), 40.1 (q), 34.6 (d, $^1J_{CH}$ = 167 Hz), 14.5 (q). Anal. Calcd for $C_{11}H_{20}N_2O$: C, 67.31; H, 10.27; N, 14.27. Found: C, 67.3; H, 10.1; N, 14.2.

4-(1α,5α,6β-6-Butyl-3-methyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (10b): bp 86°C/5 x 10^{-3} Torr; ^{1}H NMR ($CDCl_3$) δ 0.85-0.93 (m, 3H), 1.19-1.25 (m, 4H), 1.44-1.48 (m, 2H), 1.68 (H_{X2},$H_{X2'}$, 2H), 2.11 (H_{B2},$H_{B2'}$, 2H), 3.14 (H_{A2},$H_{A2'}$, 2H) (AA'BB'XX'-system; $^2J_{AB}$ = 8.5 Hz), 2.28 (s,3H), 2.25-2.95 (m, 4H), 3.50-3.85 (m, 4H) (broad, unsplit); ^{13}C NMR ($CDCl_3$) δ 67.9 (t), 54.8 (t), 53.7 (s), 49.6 (t), 40.5 (q), 33.4 (d, $^1J_{CH}$ = 168 Hz), 30.5 (t), 29.5 (t), 23.7 (t), 14.2 (q). Anal. Calcd for $C_{14}H_{26}N_2O$: C, 70.58; H, 10.92; N, 11.76. Found: C, 70.3; H, 10.8; N, 11.6.

4-(1α,5α,6β-3-Methyl-6-phenyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (10c): mp 123°C; IR (KBr, cm^{-1}) 1600 (C=C); ^{1}H NMR ($CDCl_3$) δ 2.08 (H_{X2},$H_{X2'}$, 2H), 2.34 (H_{B2},$H_{B2'}$, 2H), 3.30 (H_{A2},$H_{A2'}$, 2H) (AA'BB'XX'-system), 2.35 (s, 3H), 2.23-2.60 (m, 4H), 3.5-3.8 (m, 4H), 7.16-7.30 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 137.2 (s), 130.7 (d), 127.7 (d), 127.3 (d), 67.2 (t), 58.6 (s), 54.2 (t), 49.4 (t), 40.3 (q), 33.6 (d, $^1J_{CH}$ = 169 Hz). Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.3; H, 8.5; N, 11.1.

4-(1α,5α,6α-3,6-Dimethyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (11a): mp 25°C, bp 60°C/10^{-3} Torr; ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 3H), 1.46 (H_{X2},$H_{X2'}$, 2H), 2.63 (H_{B2},$H_{B2'}$, 2H), 2.75 (H_{A2},$H_{A2'}$, 2H) (AA'BB'XX'-system; $^2J_{AB}$ = 9.8 Hz), 2.25 (s, 3H), 2.56 (H_{X1},$H_{X1'}$, 4H), 3.63 (H_{A1},$H_{A1'}$, 4H) (AA'XX'-system); ^{13}C NMR ($CDCl_3$) δ 67.4 (t), 55.0 (t), 48.7 (t), 47.4 (s), 41.6 (q), 31.1 (d, $^1J_{CH}$ = 169 Hz), 3.8 (q). Anal. Calcd for $C_{11}H_{20}N_2O$: C, 67.31; H, 10.27; N, 14.27. Found: C, 67.4; H, 10.2; N, 14.2.

4-(1α,5α,6α-6-Butyl-3-methyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (11b): bp 90°C/10^{-3} Torr; ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 3H), 1.28 (m, 2H), 1.43 (m, 2H), 1.45 (H_{X2},$H_{X2'}$, 2H), 2.56 (H_{B2},$H_{B2'}$, 2H), 2.79 (H_{A2},$H_{A2'}$, 2H) (AA'BB'XX'-system; $^2J_{AB}$= 10.6 Hz), 1.68 (m, 2H), 2.21 (s, 3H), 2.63 (H_{X1},$H_{X1'}$, 4H), 3.57 (H_{A1},$H_{A1'}$, 4H) (AA'XX'-system); ^{13}C NMR ($CDCl_3$) δ 67.9 (t), 55.7 (t), 51.5 (s), 49.9 (t), 41.5 (q), 31.5 (d, $^1J_{CH}$= 166 Hz), 31.0 (t), 23.8 (t), 22.7 (t), 14.1 (q). Anal. Calcd for $C_{14}H_{26}N_2O$: C, 70.58; H, 10.92; N, 11.76. Found: C, 70.7; H, 10.8; N, 11.5.

4-(1α,5α,6α-3-Methyl-6-phenyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (11c): mp 112°C; IR (KBr, cm^{-1}) 1640 (C=C); ^{1}H NMR (CD_2Cl_2) δ 1.79 (H_{X2},$H_{X2'}$, 2H), 2.43 (H_{B2},$H_{B2'}$, 2H), 2.82 (H_{A2},$H_{A2'}$, 2H) (AA'BB'XX'-system; $^2J_{AB}$ = 9.6 Hz), 1.89 (s, 3H), 2.33 (H_{X1},$H_{X1'}$, 4H), 3.51 (H_{A1},$H_{A1'}$, 4H) (AA'XX'-system), 7.00-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 130.2 (s), 129.9 (d), 129.8 (d), 127.3 (d), 67.3 (t), 55.5 (s), 55.2 (t), 49.4 (t), 41.0 (q), 31.9 (d, $^1J_{CH}$ = 169 Hz). Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.2; H, 8.5; N, 10.5.

1,3-Dimethyl-piperidin-4-one (12a): bp 68°C/2 Torr (ref[18]: 43-43.4°C/5.5 Torr); IR (Film, cm^{-1}) 1720 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.00 (d, $^3J_{HH}$= 6.7 Hz, 3H), 2.07 (m_c, 1H), 2.31-2.40 (m, 2H), 2.38 (s, 3H), 2.63 (m_c, 2H), 3.06 (m_c, 2H); ^{13}C NMR data were analogous to those which

were reported in ref.[19]. Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.02. Found C, 65.6; H, 10.1; N, 11.2.

3-Butyl-1-methyl-piperidin-4-one (12b): bp 50°C/10^{-3} Torr; IR (Film, cm^{-1}) 1725 (C=O); ^1H NMR ($CDCl_3$) δ 0.88 (m_c, 3H), 1.17-1.36 (m, 5H), 1.76-1.86 (m, 1H), 2.15 (m_c, 1H), 2.35-2.63 (m, 4H), 2.94-3.50 (m, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 210.4 (s), 61.4 (t), 56.1 (t), 49.5 (d), 45.4 (q), 40.9 (t), 29.2 (t), 26.9 (t), 22.7 (t), 13.9 (q). Anal. Calcd for $C_{10}H_{19}NO$: C, 71.01; H, 11.33; N, 8.28. Found: C, 70.3; H, 11.1; N, 8.0.

1-Methyl-3-phenyl-piperidin-4-one (12c): bp 70°C/10^{-3} Torr (ref.[20]: 98-99.5°C/0.05 Torr; ref.[21]: mp 28°C); IR (Film, cm^{-1}) 1720 (C=O); ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H), 2.45-2.70 (m, 4H), 3.05 (H_{A1}, 1H), 3.13 (H_{B1}, 1H), 3.82 (H_{X1}, 1H) (ABX-system; $^3J_{AX}$ = 10 Hz, $^3J_{BX}$ = 4.5 Hz), 7.20-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 207.5 (s), 136.5 (s), 128.8 (d), 128.3 (d), 127.1 (d), 62.2 (t), 56.2 (d), 55.9 (t), 45.2 (q), 40.6 (t). Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.4. Found: C, 75.7; H, 8.0; N, 7.5.

4-(1α,5α,6α-6-Methoxy-3-methyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (13): Chloroenamine[2] **4** (2.16 g, 10 mmol) was added to a solution of sodium methoxide in methanol [obtained from sodium (0.23 g, 10 mmol) in methanol (60 mL)]. Stirring at room temperature for 20 h, removal of the methanol by evaporation and distillation of the residue in a Kugelrohr apparatus gave pure **13**. Yield: 1.5 g (71%); bp 103-105°C/0.03 Torr (ref.[5]: bp 103-105°C/0.03 Torr); ^1H NMR ($CDCl_3$) δ 2.05 (H_X,$H_{X'}$, 2H), 2.11 (H_B,$H_{B'}$, 2H), 3.18 (H_A,$H_{A'}$, 2H) (AA'BB'XX'-system; $^2J_{AB}$ = $^2J_{A'B'}$ = 9.8Hz, $^3J_{BX}$ = $^3J_{B'X'}$ = 3Hz, $^3J_{AX}$ = $^3J_{A'X'}$ = 6.3Hz), 2.27 (s, 3H), 2.40-3.29 (m, 4H), 3.34-3.96 (m, 4H), 3.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 85.9 (s), 67.3 (t), 56.5 (q), 55.4 (t), 48.8 (t), 40.6 (q), 33.4 (d, $^1J_{CH}$ = 170 Hz). Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.24; H, 9.50; N, 13.20. Found: C, 62,0; H, 9.3; N, 13.1.

4-(1α,5α,6β-3-Benzyl-6-methyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (15): 15 was prepared from chloroenamine[2] **14** (2.92 g, 10 mmol) and methylmagnesium bromide [**5a**: 25 mL (50 mmol) of a 2 M ethereal solution] according to Method A; running the reaction and working up were done analogously to the preparation of **10a**. Yield of **15**: 1.44 g (53%), mp 41.3°C; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H), 1.57 (H_{X1},$H_{X1'}$,2H), 2.21 (H_{B1},$H_{B1'}$,2H), 3.10 (H_{A1},$H_{A1'}$,2H) (AA'BB'XX'-system; $^2J_{AB}$ = 8.5 Hz), 2.35 (H_{Y2},$H_{Y2'}$,2H), 2.69 (H_{X2},$H_{X2'}$,2H), 3.64 (H_{B2},$H_{B2'}$,2H), 3.78 (H_{A2},$H_{A2'}$,2H) (broad, unsplit signals), 3.65 (s, 2H), 7.21-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 139.5 (s), 128.6 (d), 128.0 (d), 126.6 (d), 67.3 (t), 58.7 (t), 52.3 (t), 49.2 (s), 48.5 (t), 33.9 (d, $^1J_{CH}$ = 166 Hz), 14.6 (q). Anal. Calcd for $C_{17}H_{24}N_2O$: C, 75.00; H, 8.82; N, 10.29. Found: C, 75.0; H, 8.8; N, 10.2.

4-(1α,5α,6β-6-Methyl-3-azabicyclo[3.1.0]hex-6-yl)-morpholine (16): Palladium on C (10% Pd; 0.60 g) was saturated with hydrogen; then a solution of bicyclic amine **15** (1.20 g, 4.4 mmol) in methanol (70 mL) was added and stirred for 16 h in a hydrogen atmosphere. Filtration and

evaporation of the solvent gave crude amine **16** which was purified by distillation in a Kugelrohr apparatus at 60°C/0.0001 Torr. Yield 0.35 g (44%); mp 51°C; ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 3H), 1.30 (H_{X1},$H_{X1'}$,2H), 2.89 (H_{B1},$H_{B1'}$,2H), 2.92 (H_{A1},$H_{A1'}$,2H) (AA'BB'XX'-system; $^2J_{AB}$ = 12.0 Hz), 2.38 (H_{Y2},$H_{Y2'}$,2H), 2.69 (H_{X2},$H_{X2'}$,2H), 3.41 (H_{B2},$H_{B2'}$,2H), 3.76 (H_{A2},$H_{A2'}$,2H) (ABXY-system, $^2J_{AB}$ = $^2J_{XY}$ = 12.0 Hz); ^{13}C NMR ($CDCl_3$) δ 67.5 (t), 49.6 (t), 48.5 (t), 46.1 (s), 32.7 (d, $^1J_{CH}$ = 166 Hz), 14.3 (q). Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.93; H, 9.89; N, 15.38. Found: C, 65.9; H, 10.0; N, 15.1.

4-(1α,5α,6β-6-Methyl-bicyclo[3.1.0]hex-6-yl)-morpholine (23) from the reaction of chloroenamine 22 with Grignard compound 5a: An ethereal solution of Grignard compound **5a** (30 mmol, 10 mL of 3M MeMgBr/ether solution) was added to a solution[22] of **22** (2.01 g, 10 mmol) in ether (50 mL). The mixture was stirred at room temperature for 15 h; then water (50 mL) and 90% H_2SO_4 (2 mL) were added for hydrolysis. Basification by 20% aqueous NaOH (15 mL) and extraction with ether (6 x 50 mL) gave crude **23** which was purified by distillation in a Kugelrohr apparatus. Yield: 0.97 g (54%); bp 30°C/10^{-3} Torr; ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.18 (m, 2H), 1.60-1.92 (m, 6H), 2.43 (H_Y, 2H), 2.68 (H_X, 2H), 3.51 (H_B, 2H), 3.77 (H_A, 2H) (broad, unsplit signals); ^{13}C NMR ($CDCl_3$) δ 67.6 (t), 49.6 (t), 46.9 (s), 33.8 (d, $^1J_{CH}$ = 169 Hz), 28.1 (t), 26.1 (t), 15.1 (q). Anal. Calcd for $C_{11}H_{19}NO$: C, 72.92; H, 10.49; N, 7.73. Found: C, 72.8; H, 10.4; N, 7.7.

4-(1α,5α,6β-6-Methyl-bicyclo[3.1.0]hex-6-yl)-morpholine (23) from the reaction of N,O-acetal 25 with Grignard compound 5a: An ethereal solution of Grignard compound **5a** (6 mmol, 2 mL of 3M MeMgBr/ether solution) was added to a solution[23] of **25** (0.40 g, 2.0 mmol) in ether (30 mL). The mixture was stirred at room temperature for 3 d; then water (20 mL) and 90% H_2SO_4 (1 mL) were added for hydrolysis. Basification by 20% aqueous NaOH (5 mL) and extraction with pentane (3 x 30 mL) gave crude **23** which was purified by distillation in a Kugelrohr apparatus. Yield: 0.24 g (66%). Bp, ^{1}H and ^{13}C NMR data were identical with those of **23** which was obtained from **5a** and **22**.

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