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FUNCTIONALIZED CHLOROENAMINES IN AMINOCYCLOPROPANE SYNTHESIS - XIV.[1] AMINOANNULATED CYCLOPROPANES - RIGID BUILDING BLOCKS FOR OLIGOAMINES

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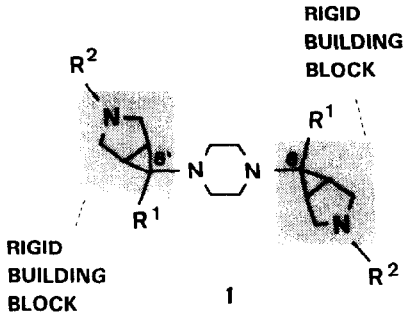
Abstract: Sterically pure meander oligoamines **5** possessing bicyclo[3.1.0]hexyl moieties as rigid building blocks were synthesized from monoketal **9** via di(chloroenamine) **14**, bicyclic diketones **16** and subsequent reductive amination of **16**. Use of the same reactions and change of the sequence of the steps led to hexamine **6a**, a diastereomer of **5a**. Hexamine **7a**, a third diastereomer of **5a**, was obtained with definite stereochemistry by a multistep approach starting from monoketal **9**, too. X-Ray analysis of hexamine **5a**, determination of basicity and studies of conformation and of molecular flexibility gave an insight in structural properties of the new type of meander oligoamines **5**.

Oligoamines **1** represent piperazine derivatives possessing two azaannulated cyclopropane units as rigid substituents. Different configurations of these 3-azabicyclo[3.1.0]hexyl building blocks lead to tetramines of various geometries: a meander type shape was found for endo,endo-derivatives **2** and a linear amine arrangement was realized for exo,exo-species **3**. The application of aminoannulated cyclopropane units as rigid building blocks for the



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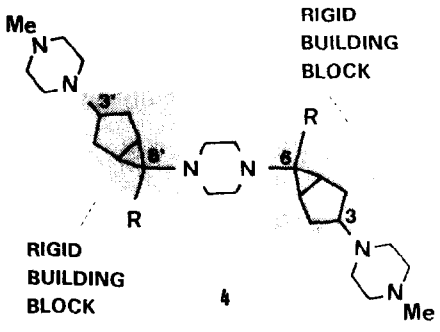


4

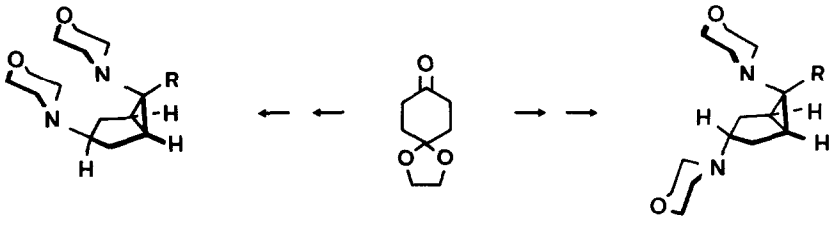
2: 6,6'-endo-piperazine
3: 6,6'-exo-piperazine
e.g. R^1, R^2 = Me

5: 3,3',6,6'-endo-piperazine
6: 3,3'-exo,6,6'-endo-piperazine
7: 3,6,6'-endo,3'-exo-piperazine

construction of oligoamines with definite N,N-distances is outlined in this paper. The use of 3-(4-methylpiperazin-1-yl)-bicyclo[3.1.0]hexyl substituents creates piperazine derivatives of the general formula **4**. Emphasis of our studies was shifted to all-endo diastereomers **5** which should be the most interesting compounds within the ensemble of various diastereomers. Additionally, a way to two further diastereomers **6** and **7** is presented for one pair of compounds.

SYNTHESIS OF DI-(PIPERAZINYLBICYCLO[3.1.0]HEXYL)-PIPERAZINES 5, 6 AND 7

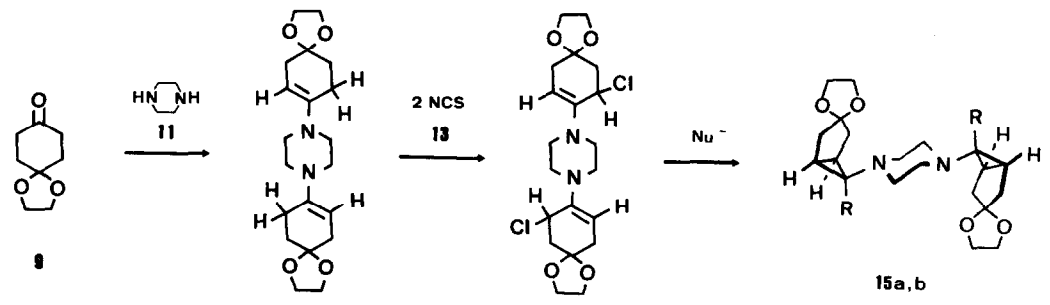
Highly stereoselective approaches[2,3] to diamines **8** and **10**, starting from cyclohexanedionemonoketal **9**, served as a basis for the synthesis of compounds **5**, **6** and **7**. Both approaches use identical synthetic steps as formation of a chloroenamine, cyclopropanation reaction and reductive amination. Variation of the sequence of the steps,[2,3] however, led either to diamines **8** or isomers **10**.



8 **9** **10**

R = H, CN R = H, CN

Preparation of all-endo piperazine derivatives **5** started with formation of di(enamine) **12** from monoketal **9** and piperazine (**11**). **12** was monochlorinated twice by N-chlorosuccinimide (**13**) to provide di(chloroenamine) **14** (86% yield, ^{13}C NMR: only two signals for the C=C-double

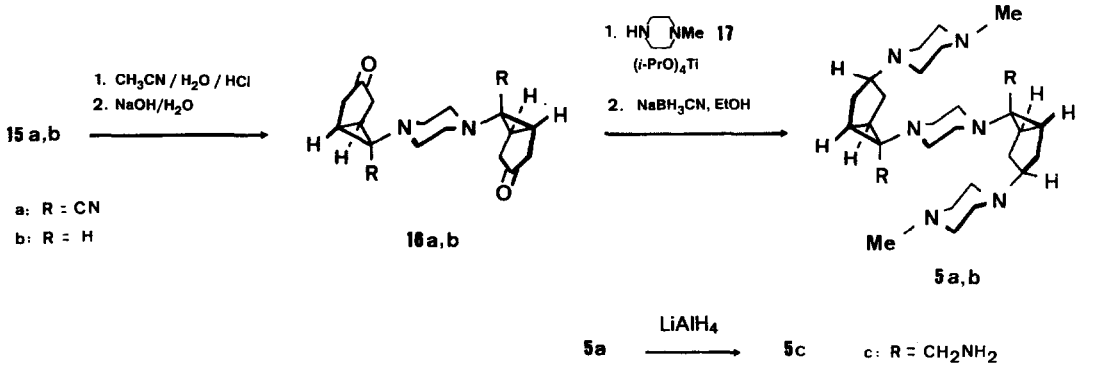


9 **12** **14** **15a,b**

a: R = CN

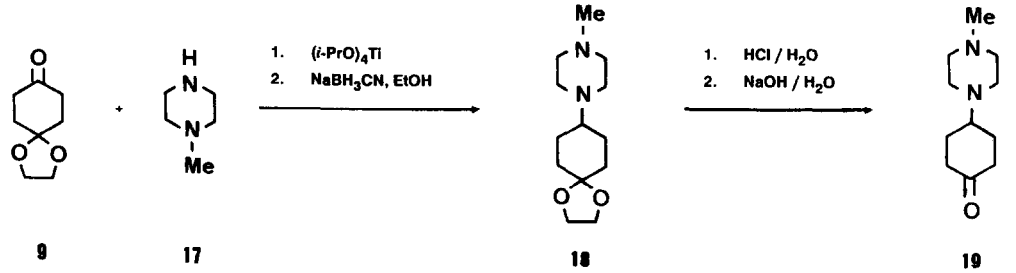
b: R = H

bonds [144.0 ppm (s); 101.7ppm (d)] and only one signal for the CHCl-moieties [53.9 ppm, (d)]. Di(bicyclohexyl)piperazines **15a** (64% yield) and **15b** (38% yield) resulted from the reaction of **14** with cyanide and sodium borohydride, respectively. Cleavage of the ketal function in **15a,b** led to diketones **16a** and **16b**. The subsequent reductive amination of **16a,b** with N-methylpiperazine (**17**) produced hexamines **5a** (44% yield) and **5b** (50% yield) with an exclusive all-endo piperazine configuration. The nitrile functions in hexamine **5a** could be reduced by lithium aluminum hydride to give the meander type octamine **5c** (67% yield).

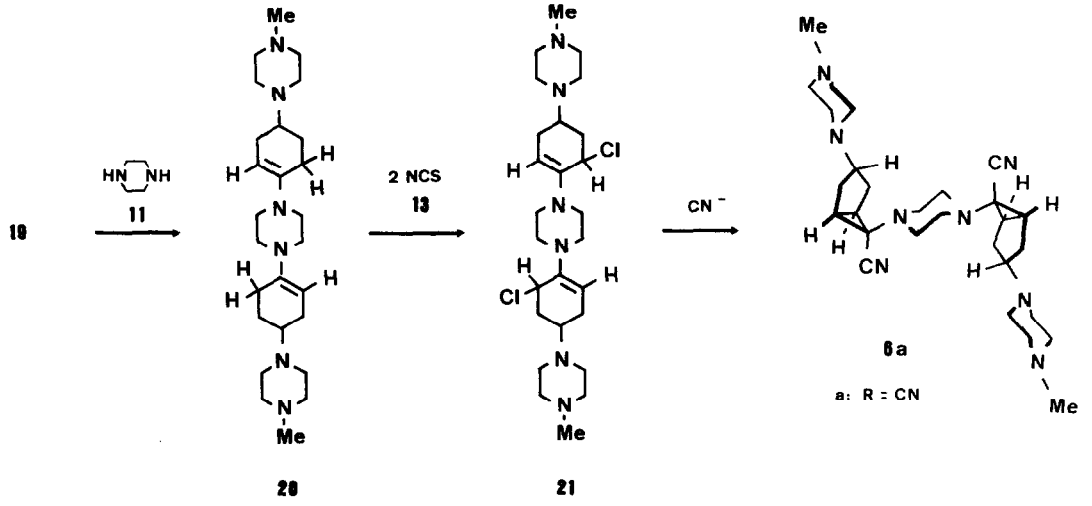


Further transferability of the stereochemical results[2,3] of the syntheses of diamines **8** and **10** on difunctional systems was explored in the case of hexaminedinitriles **4a**. Compound **6a** with two 3-exo-piperazinylbicyclohexyl building blocks and compound **7a** possessing one 3-exo- and one 3-endo-piperazinylbicyclohexyl building block were selected as target molecules.

Reductive amination of monoketal **9** by N-methylpiperazine (**17**) and sodium cyanoborohydride followed by cleavage of the ketal unit of **18** generating ketone **19** were the first steps in the synthetic approach to **6a**.

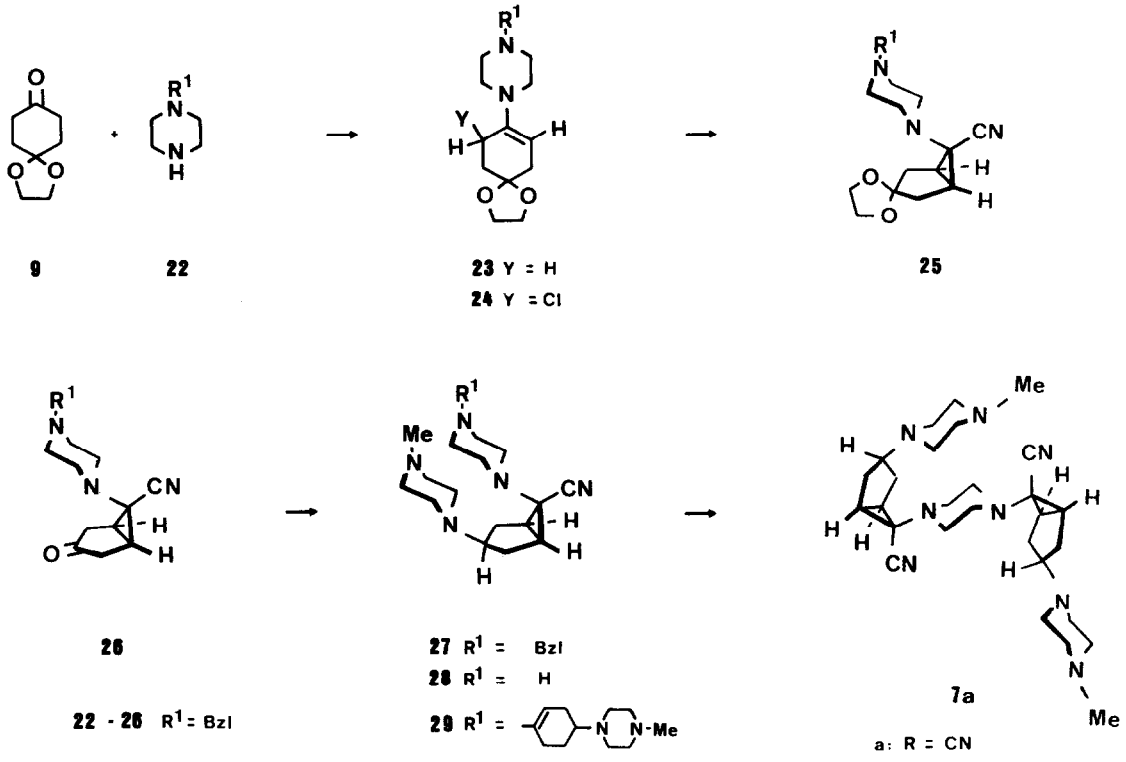


Formation of di(enamine) **20** (80% yield) from **19** and piperazine (**11**), twofold "monochlorination" of **20** by N-chlorosuccinimide (**13**) and cyclopropanation of di(chlorenamine) **21** with cyanide provided hexamine **6a** (32% yield) with an 3,3'-exo,-6,6'-endo-arrangement of the three piperazine units.



Di(chloroenamine) **21** resulted as a mixture of diastereomers which was used directly without further characterization and separation for the cyclopropanation step; yield of **6a** is based, therefore, on enamine **20**.

Synthesis of diastereomer **7a** with two bicyclo[3.1.0]hexyl building blocks with different configuration at C(3) required a multistep procedure: Enamine **23** was obtained from monoketal **9** and N-benzylpiperazine (**22**). Chlorination of **23** by N-chlorosuccinimide (**13**), cyclopropanation of chloroenamine **24** by cyanide, and cleavage of bicyclic ketal **25** to produce ketone **26** were the subsequent steps. Ketone **26** was reductively aminated by N-methylpiperazine (**17**) to give tetramine **27**. The benzyl group of **27** was removed by hydrogenolysis. Enamine **29** was obtained from tetramine **28** and 4-(N-methylpiperazinyl)cyclohexanone (**19**) by a standard procedure. Monochlorination of enamine **29** by N-chlorosuccinimide (**13**) and 1,3-ring closure by interaction of the chloroenamine with cyanide were the final steps on the way to hexamine **7a**. The latter was isolated in 40% yield (based on enamine **29**) as pure 3,6,6'-endo,3'-exo-piperazine isomer.



CONFIGURATION AND CONFORMATION OF DI-(PIPERAZINYLBICYCLO[3.1.0]HEXYL)-PIPERAZINES 5, 6 AND 7

X-Ray structure analysis of isomer **5a** showed the presence of a 3,3',6,6'-all endo-configuration; as expected (X-ray structural analysis of diamine **8**),[3] the bicyclo[3.1.0]hexane units of **5a** were found in a chair conformation with a marked ring buckle of 28.6°. Distortion of the 3,3'-piperazine moieties in **5a** is caused by lone pair - lone pair interaction of the central and the peripheric piperazine rings. Distances of the nitrogen atoms in hexamine **5a** are listed in Table 1. A clear meander-type arrangement of the nitrogen atoms in all-endo oligoamine of type **5** is clearly indicated by the plot of molecule **5a** (Fig. 1).

Table 1 Selected bond lengths, atom distances and interplanar angles of hexamine[a] **5a**

bond lengths [Å]		atom distances [Å]	
C(1) - C(5)	1.496(4)	N(1) - N(1')	2.830(4)
C(1) - C(6)	1.520(4)	N(1) - N(2)	4.195(3)
C(4) - C(5)	1.520(4)	N(1) - N(3)	6.221(3)
C(3) - N(2)	1.439(4)	N(2) - N(2')	9.992(4)
C(6) - N(1)	1.422(3)	N(2) - N(3)	2.854(4)
		N(3) - N(3')	12.986(4)

interplanar angles [°]

C(1)C(5)C(6) - C(1)C(2)C(4)C(5)	67.7
C(1)C(2)C(4)C(5) - C(2)C(3)C(4)	28.6
N(3)N(2)C(3) - C(6)N(1)N(4)	73.5 ± 0.5

[a] The numbering of the nitrogen atoms in Fig. 1 and Table 1 in this paper was partially changed with respect to the numbering in the deposited data for better comparison with other systems.

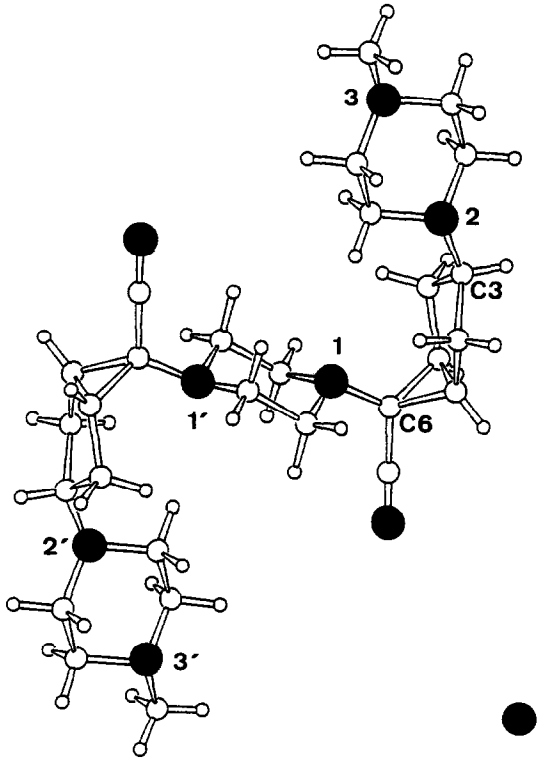


Fig. 1 Schakal[4] plot of hexamine **5a**

Bicyclo[3.1.0]hexane-**6,6'-configuration** in **5b**, **6a** and **7a** was indicated by typical ^3J coupling of the syn-substituents at the cyclopropane ring (**5b**: H_Y: $^3J_{HH}$ = 6.8 Hz; **6a**: CN: $^3J_{CH}$ = 3.8 Hz; **7a**: CN: $^3J_{CH}$ not detectable due to superposition of the two different CN signals) and by the uniform chemical shift of the cyano and the bicyclohexane-C(6) ^{13}C NMR signal in **5a**, **6a** and **7a**, respectively (CN-signal: **5a**: 117.9 ppm; **6a**: 117.6 ppm; **7a**: 117.9 ppm; **8**: 118.0 ppm;[2] **10**: 118.0 ppm;[2] C(6) signal: **5a**: 44.0 ppm; **6a**: 41.0 ppm; **7a**: 43.8, 41.1 ppm; **8**: 44.4 ppm;[2] **10**: 41.3 ppm.[2] δ-Values of 115.5 ppm and 53.9 ppm were found for the analogous signals of an 6-exo-morpholino diastereomer[5] of **8**).

Strong anisotropic influence of the cyclopropane ring on the C(3)-atom of a bicyclo[3.1.0]hexane-3,6-diamine in a boat conformation and the detection of an axial or equatorial position of the hydrogen atom H_A at C(3) allow the assignment of **3,3'-configuration** by selected ^1H and ^{13}C NMR data. The $^3J_{HH}$ couplings which were found for H_A are consistant only with an axial-bonded hydrogen atom (and an equatorial piperazinyl substituent) in all cases (Table 2 and ref.[3]). A 3,3'-exo-piperazinyl configuration and a boat conformation of the bicyclo[3.1.0]hexyl substituents thus follow from the high field shifting of C(3) - ^{13}C NMR signal of **6a**. A low field shifting of C(3) - ^{13}C NMR signal on the other hand is characteristic of a chair conformation and of the 3,3'-endo-piperazinyl configuration of the two bicyclo[3.1.0]hexane units of **5a**, **5b** and **5c**. Different conformations and 3-configurations of the two bicyclo[3.1.0]hexyl substituents followed for **7a** according to the observed values. Missing or observable $^3J_{MX}$ coupling additionally indicated the presence of a boat or a chair conformation of the bicyclo[3.1.0]hexyl substituents in **5**, **6** and **7** (Table 2 and ref.[3]).

Table 2 ^1H NMR data of the $H_MH_NC(2)$-$C(3)H_A$-$C(4)H_{M'}H_{N'}$ unit (in $C_6D_5CD_3$) and ^{13}C NMR signal of the C(3)-atom (in $CDCl_3$) of the bicyclo[3.1.0]hexane moieties in **5**, **6** and **7**; δ-values in ppm (TMS), J in Hz

	^1H NMR						^{13}C NMR
	$H_M/H_{M'}$[a]	$H_N/H_{N'}$[b]	$J_{MX}/J_{M'X'}$	H_A	$^3J_{HH}$	$^3J_{HH}$	C(3)
5a	1.27	1.55	1.4	2.98[c]	8.2	10.2	74.6
5b	1.42	1.76	1.5	3.05	8.0	10.4	75.9
5c	1.45	1.77	1.5	3.09	8.0	10.4	76.0
6a	1.57	1.62	0	2.84	7.5	7.5	66.4
7a	1.28	1.56	1.5	3.01	8.4	10.3	74.5
	1.56	1.59	0	2.83	7.4	7.4	66.5

[a] $H_M/H_{M'}$ are in the endo-position of the bicyclo[3.1.0]hexane system.- [b] $H_N/H_{N'}$ are in the exo-position of the bicyclo[3.1.0]hexane system.- [c] 110°C.-

BASICITY AND MOLECULAR FLEXIBILITY OF DI-(PIPERAZINYLBICYCLO[3.1.0]HEXYL)-PIPERAZINES 5

Meander-type arrangement of the amino moieties and intramolecular hydrogen bonding upon protonation of oligoamines **4** with rigid bicyclo[3.1.0]hexyl building blocks should best be realized in diastereomers **5**. Oligoamines of type **5**, therefore, were selected for studying basicity and molecular flexibility.

Aqueous hydrochloric acid (0.1 N) was used for the titration of oligoamines **5a**, **5b** and **5c** in water. pK_a-values were determined by the application of the Henderson - Hasselbalch equation[6] at the corresponding half neutralization points leading to the simple expression: pH = pK_a. The pH of aqueous solutions was measured with a combined glass electrode; aqueous buffer solutions of pH 4.0, 7.0 and 9.0 were used for the calibration. The used concentrations (c_0) and the pK_a-values are given in Table 3.

Titration of oligoamines **5a** and **5c** gave plots with one clear step corresponding to the uptake of 2 protons in the case of **5a** and 4 protons in the case of **5c**. Before this step the titration curve descended continously; this part of the curve showed a small buckle upon titration of **5c** indicating the uptake of the first two protons. A clear step was absent in titration of **5b**; buckles of the curve were observable upon uptake of 2 and 3 protons, respectively.

Table 3. pK_a-Values of oligoamines **5a**, **5b** and **5c** in water

	$c_0 \cdot 10^{-3}$ [a]	uptake of H^+	pK_a[b]		$c_0 \cdot 10^{-3}$ [a]	uptake of H^+	pK_a[b]
5a	0.50	2	7.68	**5c**	0.50	2	9.20
						2	7.41
5b	0.50	2	8.02				
		1	5.38				

[a] 50 mL of the solution were used for each titration.- [b] limit of error for pK_a-units: $\pm$ 0.02.-

Protonation of piperazine nitrogen atoms of **5** should take place at the piperazine units in 3,3'-position; uptake of protons by the central piperazine system in **5** is not favourable in all cases due to steric and electronic desactivation by the bicyclohexyl substituents (e.g. ref.[1]). Since

the remote cyano group in **5a** reduces basicity of 3-bonded piperazine with respect to **5b**, an effect of intramolecular hydrogen bonding on basicity of the latter can be deduced. Preferential protonation of the primary amino moieties in **5c** can be supposed by its stronger basicity. Comparation of pKa values of **5** with those which were reported for N,N'-dimethylpiperazine (pK_a = 8.4 and 4.6)[7] and cyclopropylmethanamine (pK_a = 10.64)[8], however, indicate steric problems upon protonation of meander oligoamines **5**. Further information upon the site of protonation of oligoamines **5** and the structure of the corresponding ammonium salts will be published.[9]

Temperature dependent ^1H NMR spectroscopy allowed determination of the dynamics of the piperazine units in 3,3' and 6,6'-position separately. Hindrance of the dynamics of the piperazine groups in 3- and 3'-position is almost not influenced by the substituent R in 6- and 6'-position, it is comparable to that of N,N'-dimethylpiperazine [$\Delta G^{\ddagger}$ = 55.6 kJ/mol (CD_2Cl_2)[10], 55.7 kJ/mol[1]]. Flexibility of the central piperazine system is strongly affected in **5a** and **5c**; moderate hindrance of the dynamics of the central piperazine was found for **5b**. In all cases, however, bulkiness of the bicyclohexyl substituents leads to a high population of piperazine species with diequatorial substituents.

Table 4 $\Delta G^{\ddagger}$ - Values of the dynamics of the piperazine rings of the compounds **5a**, **5b** and **5c**, determined on the basis of ^1H NMR data (400 MHz) and coalescence temperatures (T_c) in d_8-toluene

	3,3'-piperazine						6,6'-piperazine				
	T [K]	H_A/H_X [ppm]	H_B/H_Y [ppm]	$^2J_{HH}$ [Hz]	T_c [K]	$\Delta G^{\ddagger}$ [a] [kJ/mol]	T [K]	$H_A/H_{A'}$ [ppm]	$H_X/H_{X'}$ [ppm]	T_c [K]	$\Delta G^{\ddagger}$ [b] [kJ/mol]
5a	240	2.72	2.28	9.2	273	53.1	305	2.50	2.16	395	79.2
5b	240	2.67	2.13	8.4	273	52.6	240	2.60	2.43	310	61.4
		2.51	2.13	8.4	270	52.8					
5c	240	2.79	2.30	9.3	275	53.2	300	2.88	2.41	395	78.1
		2.61	2.24	9.0	275	53.8					

[a] Calculated with the approximation formula for the coupled case (ref.[11]).- [b] Calculated with the approximation formula for the uncoupled case (ref.[12]). δ-Values could be determined easily in spite of a complicated spin system due to the symmetrical shape of each signal splitting; δ-values of $H_A/H_{A'}$, $H_B/H_{B'}$, obtained by extrapolation at T_c, were used for the approximation formula.

These investigations of dynamics show that bicyclo[3.1.0]hexyl substituents at a piperazine unit indeed represent rigid building blocks for the construction of less flexible oligoamines. Thus, meander type oligoamines **5** are obtained in which either six (as in **5a**/**5b**) or eight nitrogen atoms (as in **5c**) are arranged in a definite manner.

EXPERIMENTAL

Apparatus which were used for IR, ^{1}H NMR, ^{13}C NMR and mass spectra, microanalyses and titrations are listed in ref.[1].

1,4-Bis-(1,4-dioxaspiro[4,5]dec-7-en-8-yl)-piperazine (12): A solution of piperazine (**11**) (4.30 g, 50 mmol), cyclohexane-1,4-dione-monoacetal **9** (15.62 g, 0.1 mol) and 4-toluenesulfonic acid (0.2 g, 1.05 mmol) in toluene (150 mL) was heated in a Dean-Stark apparatus for 12 h. Concentration of the solution to 75 mL and standing at room temperature gave crystalline di(enamine) **12** which was isolated by suction and washed with ice-cold ether (20 mL). Yield: 14.5 g (80%), mp 123°C; IR (KBr, cm^{-1}) 1640 (C=C); ^{1}H NMR (C_6D_6) δ 1.85 (t, 4H), 2.27 (t, 4H), 2.50-2.52 (m, 4H), 2.70 [s (broad), 4H], 3.53-3.62 (m, 8H), 4.50 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 144.5 (s), 107.8 (s), 96.9 (d), 64.3 (t), 47.7 (t), 34.7 (t), 31.2 (t), 25.9 (t). Anal. Calcd for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.3; H, 8.3; N, 7.8.

1,4-Bis-(9-chloro-1,4-dioxaspiro[4,5]dec-7-en-8-yl)-piperazine (14): A solution of N-chlorosuccinimide (**13**) (5.34 g, 40 mmol) in dichloromethane (140 mL) was dropped at -50°C during 1 h to a stirred solution of di(enamine) **12** (7.25 g, 20 mmol) in dichloromethane (60 mL). Stirring was continued at -50°C for 1 h. Then cooling was removed to warm up the mixture to room temperature. The crude solution was evaporated in vacuo; the remaining solid was triturated with saturated aqueous sodium carbonate solution (3 x 200 mL) and isolated by suction. Yield: 7.42 g (86%), mp 140°C (decomp.); IR (KBr, cm^{-1}) 1630 (C=C); ^{1}H NMR ($CDCl_3$) δ 2.18-2.22 (H_{B1}, H_{B2}, 4H), 2.36 (H_{A1}, 2H), 2.45 (H_{A2}, 2H), 4.69 (H_{X1}, 2H), 4.74 (H_{X2}, 2H) (2 ABX-systems), 2.67-2.80 (m, 4H), 2.92-3.05 (m, 4H), 3.85-3.98 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 144.0 (s), 106.7 (s), 101.7 (d), 64.5 (t), 64.4 (t), 53.9 (d), 48.1 (t), 41.7 (t), 34.9 (t). Anal. Calcd for $C_{20}H_{28}Cl_2N_2O_4$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.9; H, 6.5; N, 6.5.

6,6'-(Piperazine-1,4-diyl)-bis(1α,5α,6β-spiro{bicyclo[3.1.0]hexane-3,2'-1'3'-dioxolane}-6-carbonitrile) (15a) Di(chloroenamine) **14** (4.31 g, 10 mmol) and sodium cyanide (1.23 g, 25 mmol) were heated in a mixture of acetonitrile (80 mL) and water (8 mL) to 50-60°C for 12 h.

Precipitated bicyclic dinitrile **15a** was isolated by suction; the solvent of the filtrate was evaporated in vacuo and the residue was dissolved in dichloromethane (60 mL). Washing the solution with water (2 x 50 mL) and evaporating the dichloromethane gave further **15a** which was recrystallized from acetonitrile. Yield: 2.64 g (64%), mp 235°C (decomp.); IR (KBr, cm^{-1}) 2200 (C≡N); ^1H NMR ($CDCl_3$) δ 1.72-1.82 (m, 4H), 2.05-2.16 (m, 8H), 2.57-2.63 (m, 4H), 2.78-2.84 (m, 4H), 3.83-3.96 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 124.4 (s), 118.5 (t, $^3J_{CH}$ = 4.3 Hz), 65.4 (t), 63.8 (t), 49.8 (t), 43.6 (s), 34.0 (t), 30.4 (d, $^1J_{CH}$ = 171 Hz). Anal. Calcd for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.1; H, 6.9; N, 13.7.

6,6'-(Piperazine-1,4-diyl)-bis(1α,5α,6β-3-oxo-bicyclo[3.1.0]hexane-6-carbonitrile) (**16a**): A suspension of di(ketal) **15a** (0.41 g, 1.0 mmol) was stirred in a mixture of acetonitrile (40 mL) and aqueous hydrochloric acid (1 N, 10 mL) at room temperature for 2 d. The resulting precipitate was isolated by suction. Yield: 0.29 g (90%), mp 230°C (decomp.); IR (KBr, cm1) 2200 (C≡N), 1700 (C=O); ^1H NMR (CF_3COOD) δ 2.23 (s, 4H), 2.38 (d, 4H), 2.42-2.58 (m, 10H), 2.60-2.72 (m, 2H); ^{13}C NMR (CF_3COOD) δ 221.0 (s), 117.9 (s), 51.3 (t), 42.5 (s), 38.5 (t), 29.0 (d, $^1J_{CH}$ = 180 Hz). Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.5; H, 6.2; N, 17.3.

1,4-Bis-(1α,5α,6β-spiro[bicyclo[3.1.0]hexane-3,2'-1',3'-dioxolan]-6-yl)-piperazine (**15b**): A suspension of di(chloroenamine) **14** (4.31 g, 10 mmol) and sodium borohydride (3.78 g, 100 mmol) in acetonitrile (120 mL) was stirred at 70°C for 100 h. Excess borohydride was removed by filtration. The filtrate was evaporated in vacuo, the residue was triturated with water (60 mL) and stirred for 5 h. Extraction with ether (4 x 100 mL), concentration of the ethereal solution to 80 mL and cooling to -20°C gave crystalline di(ketal) **15b**. Yield: 1.37 g (38%), mp 175°C (decomp.); ^1H NMR ($CDCl_3$) δ 1.35-1.46 (m, 4H), 1.69 (t, $^3J_{HH}$ = 6.5 Hz, 2H), 1.60-1.72 (m, 4H), 1.82-1.92 (m, 4H), 2.47 (broad, unsplit, 8H), 3.83-3.96 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 126.0 (s), 64.9 (t), 63.1 (t), 52.0 (t), 48.0 (d, $^1J_{CH}$ = 163 Hz), 32.7 (t), 20.1 (d, $^1J_{CH}$ = 170 Hz). Anal. Calcd for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.4; H, 8.3; N, 7.8.

6,6'-(Piperazine-1,4-diyl)-bis(1α,5α,6β-bicyclo[3.1.0]hexan-3-one) (**16b**): Di(ketal) **15b** (0.72 g, 2.0 mmol) was dissolved in a mixture of acetonitrile (60 mL) and aqueous hydrochloric acid (1 N, 10 mL) and stirred for 15 h at room temperature. Then the solvent was evaporated in vacuo, the residue was dissolved in water (10 mL) and brought to pH 12 by addition of aqueous sodium hydroxide solution (5 N). Extraction with dichloromethane (3 x 30 mL) gave crude **16b** which was recrystallized from acetonitrile. Yield: 0.45 g (85%), mp 170°C; IR (KBr, cm^{-1}) 1710 (C=O); ^1H NMR ($CDCl_3$) δ 1.46-1.53 (H_X, $H_{X'}$, 4H), 1.84 (H_Y, $^3J_{XY}$ = $^3J_{X'Y}$ = 6.4 Hz, 2H), 2.14 (H_A, $H_{A'}$, 4H), 2.47 (H_B, $H_{B'}$, 4H) (AA'BB'XX'Y-system), 2.20-2.55 (s, broad,

8H); ^{13}C NMR ($CDCl_3$) δ 213.9 (s), 51.3 (t), 43.1 (d, $^1J_{CH}$ = 167 Hz), 36.4 (t), 16.5 (d, $^1J_{CH}$ = 172 Hz). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.8; H, 8.0; N, 10.4.

Meander-Type Hexamines 5a and 5b - General Procedure: A mixture of diketone **16** (2.5 mmol; **16a**: 0.81 g; **16b**: 0.69 g), 4-methylpiperazine (**17**) (1.50 g, 15 mmol for **16a**; 0.50 g, 5.0 mmol for **16b**) and titanium tetraisopropoxide (7.11 g, 25 mmol) was stirred at room temperature (24 h for **16a**; 1 h for **16b**). Then $NaBH_3CN$ (0.75 g, 12 mmol) and ethanol (40 mL) were added and stirring was continued (7 d for **14a**; 30 h for **14b**). Water (30 mL) was added, the solid was removed by suction, the remaining solution was concentrated to a volume of 30 mL and excess $NaBH_3CN$ was destroyed by addition of aqueous hydrochloric acid (1 N, 20 mL) and stirring for 1 h. The mixture was made alkaline with aqueous sodium hydroxide (1 N, 40 mL) and extracted with dichloromethane (3 x 30 mL). Evaporation of the dichloromethane afforded crude hexamines **5** which were crystallized from acetonitrile to give colorless plates.

6,6'-(Piperazine-1,4-diyl)-bis{1α,3β,5α,6β-3-(4-methylpiperazin-1-yl)-bicyclo[3.1.0]hexane-6-carbonitrile} (**5a**) Yield: 0.54 g (44%), mp 213°C; IR (KBr, cm^{-1}) 2210 (C≡N); ^1H NMR ($C_6D_5CD_3$) δ 1.27 (H_M, $H_{M'}$, 4H), 1.44 (H_{X1}, $H_{X'1}$, 4H), 1.55 (H_N, $H_{N'}$, 4H), 2.98 (H_{A1}, $^3J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 10.2 Hz, 2H) (AMM'NN'XX'-system), 2.13 (s, 6H), 2.16 (H_{X2}, 4H), 2.50 (H_{A2}, 4H) (AA'XX'-system), 2.42 (unsplit signal, 16H); ^{13}C NMR ($CDCl_3$) δ 117.9 (s), 74.6 (d), 54.9 (t), 50.4 (t), 49.3 (t), 45.8 (q), 44.0 (s), 30.9 (d, $^1J_{CH}$ = 173 Hz), 24.1 (t). Anal. Calcd for $C_{28}H_{44}N_8$: C, 68.26; H, 9.00; N, 22.74. Found: C, 68.4; H, 9.0; N, 22.8.

1,4-Bis-{1α,3β,5α,6β-3-(4-Methylpiperazin-1-yl)-bicyclo[3.1.0]hex-6-yl}-piperazine (**5b**): Yield: 0.54 g (50%), mp 185°C; ^1H NMR ($CDCl_3$) δ 1.15 (H_X, $H_{X'}$, 4H), 1.42 (H_M; $H_{M'}$; 4H); 1.45 (H_Y, $^3J_{XY}$ = $^3J_{X'Y}$ = 6.8 Hz, 2H), 1.76 (H_N, $H_{N'}$, 4H), 3.05 (H_A, $^3J_{HH}$ = 8.0 Hz; $^3J_{HH}$ = 10.4 Hz, 2H) (AMM'NN'XX'Y-system), 2.10 (s, 6H), 2.32 (broad, unsplit signal, 12H), 2.50 (broad, unsplit signal, 12H); ^{13}C NMR ($CDCl_3$) δ 75.9 (d), 55.2 (t), 52.1 (t), 50.4 (t), 49.1 (d, $^1J_{CH}$ = 164 Hz), 46.0 (q), 24.2 (t), 21.2 (d, $^1J_{CH}$ = 163 Hz); MS (35 eV) m/e = 443.7 [(M+1)$^+$, 66%], 359.2 [100%]. Anal. Calcd for $C_{26}H_{46}N_6$: C, 70.54; H, 10.47; N, 18.98. Found: C, 70.6; H, 10.4; N, 18.8.

1,4-Bis-{1α,3β,5α,6β-6-Aminomethyl-3-(4-methylpiperazin-1-yl)-bicyclo[3.1.0]hex-6-yl}-piperazine (**5c**): Lithium aluminum hydride (1.14 g, 30 mmol) was added to a suspension of dinitrile **5b** (0.74 g, 1.5 mmol) in ether (100 mL). The mixture was refluxed for 3 d. Excess lithium aluminum hydride was destroyed at -20°C by aqueous potassium hydroxide (20%, 30 mL). Insoluble crude octamine **5c** was obtained by filtration at room temperature and washing

with water (5 mL) and ether (5 mL). Extraction with acetonitrile (90 mL) at 80°C, concentration of the filtrate to 60 mL and cooling at 0°C gave pure crystals of **5c**. Yield: 0.50 g, (67%), mp 163°C; ^{1}H NMR ($C_6D_5CD_3$) δ 0.50 (broad, unsplit, 4H), 1.15 (H_{X1}, $H_{X'1}$, 4H), 1.45 (H_M, $H_{M'}$, 4H); 1.77 (H_N, $H_{N'}$, 4H), 3.09 (H_{A1}, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 10.4 Hz, 2H) (AMM'NN'XX'-system), 2.14 (s, 6H), 2.37 (broad, unsplit, 8H), 2.55 (broad, unsplit, 8H), 2.41 (H_{X2}, $H_{X'2}$, 4H), 2.88 (H_{A2}, $H_{A'2}$, 4H) (AA'XX'-system); 2.53 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 76.0 (d), 55.2 (t), 54.9 (s), 50.2 (t), 50.0 (t), 45.9 (q), 44.2 (t), 28.1 (d, $^1J_{CH}$ = 165 Hz), 24.2 (t); MS (35 eV) m/e = 500.2 [M$^+$, 100%]. Anal. Calcd for $C_{28}H_{52}N_8$: C, 67.16; H, 10.47; N, 22.38. Found: C, 67.0; H, 10.4; N, 22.5.

4-(1,4-Dioxaspiro[4,5]dec-8-yl)-1-methylpiperazine (18): Compound **18** was synthesized from ketone **9** (15.62 g, 0.1 mol), N-methylpiperazine (17) (10.02 g, 0.1 mol), titanium tetraisopropoxide (35.53 g, 0.125 mol), sodium cyanoborohydride (9.4 g, 0.15 mol) and ethanol (200 mL) according to a general procedure given in ref.[2,3]. Working up by distillation in a Kugelrohr apparatus at 115°C / 0.001Torr gave 17.29 g (72%) of ketal **18**. ^{1}H NMR ($CDCl_3$) δ 1.51-1.64 (m, 4H), 1.80-1.82 (m, 4H), 2.28 (s, 3H), 2.34-2.38 (m, 1H), 2.44 (broad, unsplit, 4H), 2.60 (broad, unsplit, 4H), 3.93 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 108.3 (s), 64.0 (t), 61.7 (d), 55.4 (t), 48.8 (t), 45.9 (q), 33.5 (t), 25.3 (t). Anal. Calcd for $C_{13}H_{24}N_2O_2$: C, 64.97; H, 10.07; N, 11.66. Found: C, 65.0; H, 9.9; N, 11.5.

4-(4-Methyl-piperazin-1-yl)-cyclohexanone (19): Ketal **18** (16.18 g, 67 mmol) was cleaved by addition of water (200 mL) and aqueous hydrochloric acid (12.5 N, 25 mL) and stirring the mixture at room temperature for 4 d. The solution was made alkaline by addition of sodium hydroxide (5 N, 100 mL). Extraction with dichloromethane (5 x 100 mL) gave aminoketone **19** which was purified by distillation in a Kugelrohr apparatus. Yield: 8.72 g (66%), bp 85°C/ 0.005 Torr; IR (film, cm^{-1}) 1705 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.81-1.91 (m, 2H), 2.02-2.08 (m, 2H), 2.27-2.35 (m, 2H), 2.30 (s, 3H), 2.46-2.52 (m, 6H), 2.63-2.69 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 210.5 (s), 59.6 (d), 55.0 (t), 48.9 (t), 45.6 (q), 38.4 (t), 27.5 (t). Anal. Calcd for $C_{11}H_{20}N_2O$: C, 67.31%; H, 10.27; N, 14.27. Found: C, 67.1; H, 10.2; N, 14.3.

1,4-Bis-[4-(4-methyl-piperazin-1-yl)-cyclohexen-1-yl]-piperazine (20): A solution of piperazine (11) (1.68 g, 19.5 mmol), ketone **19** (7.7 g, 39 mmol) and 4-toluenesulfonic acid (0.2 g, 1.05 mmol) in toluene (150 mL) was heated in a Dean-Stark apparatus for 12 h. Concentration of the solution to 50 mL and standing at room temperature gave crystalline **20** which was isolated by suction and washed with ether (2 x 10 mL). Yield: 6.93 g (80%), mp 206°C (decomp.); IR (KBr, cm^{-1}) 1645 (C=C); ^{1}H NMR ($CDCl_3$) δ 1.45-1.55 (m, 2H), 2.02-2.12 (m, 4H), 2.18 (broad, unsplit, 4H), 2.25-2.35 (m, 4H), 2.28 (s, 6H), 2.47 (broad, unsplit, 8H), 2.62 (broad, unsplit, 8H), 2.70-2.91 (m, 8H), 4.61 (m_c, 2H); ^{13}C NMR ($CDCl_3$) δ 144.9 (s), 98.6 (d), 60.1

(d), 55.4 (t), 49.0 (t), 47.9 (t), 45.9 (q), 27.3 (t), 26.7 (t), 26.1 (t). Anal. Calcd for $C_{26}H_{46}N_6$: C, 70.54; H, 10.47; N, 18.98. Found: C, 70.5; H, 10.3; N, 18.6.

6,6'-(Piperazine-1,4-diyl)-bis{1*α*,3*α*,5*α*,6*β*-3-(4-methylpiperazin-1-yl)-bicyclo[3.1.0]hexane-6-carbonitrile} (6a): A solution of N-chlorosuccinimide (**13**) (2.14 g, 16 mmol) in dichloromethane (100 mL) was dropped at -50°C during 1 h to a stirred solution of di(enamine) **20** (3.54 g, 8.0 mmol) in dichloromethane (50 mL). Stirring was continued at -50°C for 1 h. Then cooling was removed to warm up the mixture to room temperature. The crude solution was extracted with saturated aqueous sodium carbonate solution (3 x 60 mL) and water (60 mL). Evaporation of dichloromethane and trituration of the residue with pentane (100 mL) gave crude di(chloroenamine) **21** which was heated together with sodium cyanide (0.98 g, 20 mmol) in a mixture of acetonitrile (100 mL) and water (10 mL) to 50-60°C for 12 h. The solvent was evaporated; aqueous sodium hydroxide (1 N, 60 mL) was added to the residue. Extraction with dichloromethane (4 x 40 mL) gave crude dinitrile **6a** which was recrystallized from acetonitrile. Yield: 1.26 g (32%), mp 299°C (decomp.); IR (KBr, cm^{-1}) 2210 (C≡N); ^1H NMR ($C_6D_5CD_3$) δ 1.49 (H_{X1}, $H_{X'1}$, 4H), 1.57 (H_M, $H_{M'}$, 4H), 1.62 (H_N, $H_{N'}$, 4H), 2.84 (H_{A1}, $^3J_{AM} = {}^3J_{AM'} = {}^3J_{AN} = {}^3J_{AN'} = 7.5$ Hz, 2H) (AMM'NN'XX'-system), 2.13 (s, 6H), 2.23 (H_{X2}, 4H), 2.47 (H_{A2}, 4H) (AA'XX'-system), 2.26 (unsplit signal, 16H); ^{13}C NMR ($CDCl_3$) δ 117.6 (t, $^3J_{CH} = 3.8$ Hz), 66.4 (d), 54.9 (t), 50.9 (t), 50.4 (t), 45.7 (q), 41.0 (s), 31.7 (d, $^1J_{CH} = 172$ Hz), 29.6 (t). Anal. Calcd for $C_{28}H_{44}N_8$: C, 68.26; H, 9.00; N, 22.74. Found: C, 67.7; H, 8.8; N, 22.5.

1-Benzyl-4-(1,4-dioxaspiro[4,5]dec-7-en-8-yl)-piperazine (23): A solution of N-benzylpiperazine (**22**) (17.63 g, 0.1 mol), cyclohexanedionemonoketal **9** (15.62 g, 0.1 mol) and 4-toluenesulfonic acid (0.2 g, 1.05 mmol) in toluene (150 mL) was heated in a Dean-Stark apparatus for 12 h. Removal of the solvent and distillation of the residue in a Kugelrohr apparatus at 180°C / 0.001 Torr gave pure enamine **23**. Yield: 29.5 g (94%); IR (film, cm^{-1}) 1630 (C=C); ^1H NMR ($CDCl_3$) δ 1.82 (H_{A1},$H_{A'1}$, 2H), 2.30 (H_{X1}, $H_{X'1}$, 2H) (AA'XX'-system), 2.34 (H_{A2}, H_B, 2H), 4.52 (H_{X2}, 1H) (ABX-system), 2.48 (H_{A3}, $H_{A'3}$, 4H), 2.85 (H_{X3}, $H_{X'3}$, 4H) (AA'XX'-system), 3.51 (s, 2H), 3.99 (m_c, 4H), 7.23-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 144.4 (s), 137.9 (s), 128.8 (d), 127.9 (d), 126.7 (d), 107.7 (s), 96.5 (d), 64.1 (t), 62.8 (t), 52.9 (t), 47.6 (t), 34.6 (t), 31.2 (t), 25.9 (t). Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.6; H, 8.3; N, 8.8.

1-Benzyl-4-(9-chloro-1,4-dioxaspiro[4,5]dec-7-en-8-yl)-piperazine (24): A solution of N-chlorosuccinimide (**13**) (5.34 g, 40 mmol) in dichloromethane (140 mL) was dropped at -50°C during 1 h to a stirred solution of enamine **23** (12.58 g, 40 mmol) in dichloromethane (60 mL). Stirring was continued at -50°C for 1 h. Then cooling was removed to warm up the mixture to room temperature. The crude solution was evaporated in vacuo; the remaining solid was

extracted with pentane (2 x 350 mL); concentration of the solution to 350 mL and cooling at -20°C gave crystalline chloroenamine **24**. Yield: 10.50 g (72%), mp 83°C; IR (KBr, cm^{-1}) 1620 (C=C); ^1H NMR ($CDCl_3$) δ 2.26-2.32 (m, 2H), 2.42 (m_c, 1H), 2.49-2.57 (m, 5H), 2.71-2.76 (m, 2H), 2.99-3.04 (m, 2H), 3.52 (s, 2H), 3.92-4.03 (m, 4H), 4.71 (m_c, 1H), 4.80 (m_c, 1H), 7.23-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 144.0 (s), 138.0 (s), 129.0 (d), 128.1 (d), 126.8 (d), 106.6 (s), 101.1 (d), 64.3 (t), 64.2 (t), 62.9 (t), 53.8 (d), 52.7 (t), 48.2 (t), 41.6 (t), 43.8 (t). Anal. Calcd for $C_{19}H_{25}ClN_2O_2$: C, 65.41; H, 7.22; N, 8.03. Found: C, 65.2; H, 7.2; N, 8.0.

1α,5α,6β-6-(4-Benzyl-piperazin-1-yl)-spiro{bicyclo[3.1.0]hexane-3,2'-1'3'-dioxolane}-6-carbonitrile (25): Chloroenamine **24** (6.98 g, 20 mmol) and sodium cyanide (1.47 g, 30 mmol) were heated in a mixture of acetonitrile (150 mL) and water (15 mL) to 50-60°C for 12 h. Precipitated bicyclic nitrile **25** was isolated by suction; the solvent of the filtrate was evaporated in vacuo. Addition of aqueous sodium hydroxide solution (2.5 N, 20 mL) and extraction with dichloromethane (3 x 30 mL) gave crude **25** which was recrystallized from acetonitrile. Yield: 5.83 g (86%), mp 194°C; IR (KBr, cm^{-1}) 2205 (C≡N); ^1H NMR ($CDCl_3$) δ 1.71 (H_{B1}, $H_{B'1}$, 2H), 2.02 (H_{A1}, $H_{A'1}$, 2H), 2.00 (H_{X1}, $H_{X'1}$, 2H) (AA'BB'XX'-system), 2.17 (H_{A2}, 2H), 2.78 (H_{B2}, 2H), 2.51 (H_{X2}, 2H), 2.67 (H_Y, 2H) (ABXY-system), 3.51 (s, 2H), 3.82 (H_{A3}, $H_{A'3}$, 2H), 3.87 (H_{X3}, $H_{X'3}$, 2H) (AA'XX'-system), 7.23-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 138.1 (s), 128.9 (d), 128.1 (d), 126.8 (d), 124.3 (s), 118.3 (s), 65.0 (t), 63.4 (t), 62.7 (t), 52.5 (t), 49.6 (t), 43.3 (s), 33.4 (t), 29.7 (d, $^1J_{CH}$ = 174 Hz). Anal. Calcd for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.42; N, 12.38. Found: C, 70.6; H, 7.4; N, 12.4.

1α,5α,6β-6-(4-Benzyl-piperazin-1-yl)-3-oxo-bicyclo[3.1.0]hexane-6-carbonitrile (26): Aqueous hydrochloric acid (6 N, 2 mL) was added to a solution of ketal **25** (1.70 g, 5.0 mmol) in chloroform (20 mL); the mixture was stirred at room temperature for 2 h. Addition of aqueous sodium hydroxide (2.5 N, 20 mL) and extraction with chloroform (3 x 25 mL) gave crude ketone **26** which was recrystallized from ether. Yield: 1.03 g (70%), mp 183°C; IR (KBr, cm^{-1}) 2210 (C≡N), 1730 (C=O); ^1H NMR ($CDCl_3$) δ 2.23 (H_{A1}, $H_{A'1}$, 2H), 2.56 (H_{B1}, $H_{B'1}$, 2H), 2.18 (H_{X1}, $H_{X'1}$, 2H) (AA'BB'XX'-system), 2.05 (H_{A2}, 2H), 2.77 (H_{B2}, 2H), 2.56 (H_{X2}, 2H), 2.73 (H_Y, 2H) (ABXY-system), 3.46 (s, 2H), 7.23-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 209.4 (s), 137.9 (s), 128.8 (d), 128.1 (d), 126.9 (d), 117.2 (t, $^3J_{CH}$ = 4.2 Hz), 62.5 (t), 51.8 (t), 49.6 (t), 40.0 (s), 35.7 (d,d), 25.9 (d, $^1J_{CH}$ = 176 Hz). Anal. Calcd for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 72.9; H, 7.3; N, 14.3.

1α,3β,5α,6β-6-(4-Benzylpiperazin-1-yl)-3-(4-methylpiperazin-1-yl)-bicyclo[3.1.0]hexane-6-carbonitrile (27): A mixture of ketone **26** (1.51 g, 5.1 mmol), 4-methylpiperazine (**17**) (1.50 g, 15 mmol) and titanium tetraisopropoxide (7.11 g, 25 mmol) was stirred for 6 h at room temperature. Then $NaBH_3CN$ (0.50 g, 8.0 mmol) and ethanol (50 mL) were added and stirring

was continued for 65 h. Water (50 mL) was added, the solid was removed by suction, the remaining solution was concentrated to a volume of 50 mL and excess $NaBH_3CN$ was destroyed by addition of aqueous hydrochloric acid (1 N, 40 mL) and stirring for 1 h. The mixture was made alkaline with aqueous sodium hydroxide (2.5 N, 40 mL) and extracted with dichloromethane (4 x 80 mL). Evaporation of the dichloromethane afforded crude tetramine **27** which was crystallized from ether to give colorless crystals. Yield: 0.87 g (45%), mp 117°C; IR (KBr, cm^{-1}) 2200 (C≡N); ^1H NMR ($CDCl_3$) δ 1.48 (m_c, 2H), 1.92 (m_c, 4H), 2.17 (H_A, 2H), 2.53 (H_B, 2H), 2.76 (H_X, 2H), 2.81 (H_Y, 2H) (ABXY-system), 2.30 (s, 3H), 2.32-2.54 (broad, unsplit, 8H), 3.38 (m_c, 1H), 3.52 (s, 2H), 7.24-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 137.5 (s), 128.8 (d), 127.9 (d), 126.8 (d), 118.2 (s), 74.3 (d), 62.6 (t), 54.9 (t), 52.3 (t), 50.0 (t), 49.4 (t), 45.8 (q), 43.6 (s), 30.5 (d, $^1J_{CH}$ = 172 Hz), 23.7 (t). Anal. Calcd for $C_{23}H_{33}N_5$: C, 72.78; H, 8.71; N, 18.45. Found: C, 72.7; H, 8.8; N, 18.4.

1α,3β,5α,6β-3-(4-Methylpiperazin-1-yl)-6-(piperazin-1-yl)-bicyclo[3.1.0]hexane-6-carbonitrile (28): A solution of N-benzyl compound **27** (2.12 g, 5.6 mmol) in methanol (60 mL) was added to Pd/C (10%, 1.12 g) and saturated with hydrogen. The mixture was stirred for 48 h at room temperature. Removal of the catalyst by filtration, evaporation of methanol and recrystallization of the residue from ether gave colorless crystals. Yield: 1.10 g (68%), mp 91°C; IR (KBr, cm^{-1}) 3300 (N-H), 2210 (C≡N); ^1H NMR ($CDCl_3$) δ 1.32 (broad, unsplit, 1H), 1.48 (m_c, 2H), 1.92-1.98 (m, 4H), 2.27 (s, 3H), 2.32-2.53 (broad, unsplit) and 2.56 (m_c) (12H), 2.82 (m_c, 2H), 2.98 (m_c, 2H), 3.35 (m_c, 1H); ^{13}C NMR ($CDCl_3$) δ 118.4 (s), 74.6 (d), 55.0 (t), 51.1 (t), 50.2 (t), 45.9 (q), 45.6 (t), 44.5 (s), 30.6 (d, $^1J_{CH}$ = 173 Hz), 24.1 (t). Anal. Calcd for $C_{16}H_{27}N_5$: C, 66.40; H, 9.40; N, 24.20. Found: C, 66.3; H, 9.5; N, 23.9.

1α,3β,5α,6β-3-(4-Methylpiperazin-1-yl)-6-{4-[4-(4-methylpiperazin-1-yl)-cyclohex-1-en-1-yl]-piperazin-1-yl}-bicyclo[3.1.0]hexane-6-carbonitrile (29): A solution of amine **28** (0.65 g, 2.25 mmol), piperazinylcyclohexanone **19** (0.44 g, 2.25 mmol) and 4-toluenesulfonic acid (0.1 g, 0.53 mmol) in toluene (75 mL) was heated in a Dean-Stark apparatus for 12 h. Filtration, removal of the solvent and crystallization of the residue from ether gave pure enamine **29** as colorless crystals. Yield: 0.55 g (52%), mp 140°C; IR (KBr, cm^{-1}) 2200 (C≡N), 1635 (C=C); ^1H NMR ($CD_3C_6D_5$) δ 1.23 (m_c, 2H), 1.40-1.60 (m, 7H), 1.87-1.91 (m, 1H), 1.96-1.98 (m, 1H), 2.04 (s, 3H), 2.14 (s, 3H), 2.16-2.40 (broad, unsplit, 18H), 2.51 (m_c, 4H), 2.65 (m_c, 2H), 2.79-2.89 (m, 2H), 2.95-2.97 (m, 1H), 4.44 (m_c, 1H); ^1H NMR ($CD_3C_6D_5$, 80°C) δ 2.90 (H_A, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 144.6 (s), 117.9 (s), 98.4 (d), 74.5 (d), 59.9 (d), 55.2 (t), 54.8 (t), 50.2 (t), 49.5 (t), 49.2 (t), 48.9 (t), 47.38 (t), 47.28 (t), 45.78 (q), 45.75 (q), 43.8 (s), 30.5 (d, $^1J_{CH}$ = 173 Hz), 27.2 (t), 26.6 (t), 25.9 (t), 24.1 (t). Anal. Calcd for $C_{27}H_{45}N_7$: C, 69.34; H, 9.70; N, 20.96. Found: C, 69.0; H, 9.6; N, 20.7.

6-(1α,3α,5α,6β)-6'-(1α,3β,5α,6β)-(Piperazine-1,4-diyl)-bis{3-(4-methylpiperazin-1-yl)-bicyclo[3.1.0]hexane-6-carbonitrile} (**7a**): A solution of *N*-chlorosuccinimide (**13**) (0.057 g, 0.43 mmol) in dichloromethane (30 mL) was dropped at -50°C during 30 min to a stirred solution of enamine **29** (0.200 g, 0.43 mmol) in dichloromethane (20 mL). Stirring was continued at -50°C for 1 h. Then cooling was removed to warm up the mixture to room temperature. The solvent was removed in vacuo, sodium cyanide (0.037 g, 0.75 mmol), acetonitrile (30 mL) and water (3 mL) were added to the residue and the mixture was stirred at 60°C for 2 h. Then the solvent was evaporated and the residue was triturated with aqueous sodium hydroxide (5 N, 15 mL). Extraction with dichloromethane (4 x 15 mL) gave crude dinitrile **7a** which was recrystallized from acetonitrile. Yield: 0.085 g (40%), mp 206°C (decomp.); IR (KBr, cm^{-1}) 2210 (C≡N); ^1H NMR ($C_6D_5CD_3$) δ 1.28 (H_{M1}, $H_{M'1}$, 2H), 1.56 (H_{N1}, $H_{N'1}$, 2H), 1.45 (H_{X1}, $H_{X'1}$, 2H), 3.01 (H_{A1}, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 10.3 Hz, 1H) (AMM'NN'XX'-system), 1.56 (H_{M2}, $H_{M'2}$, 2H), 1.59 (H_{N2}, $H_{N'2}$, 2H), 1.48 (H_{X2}, $H_{X'2}$, 2H), 2.83 (H_{A2}, $^3J_{HH}$ = $^3J_{HH}$ = 7.4 Hz, 1H) (AMM'NN'XX'-system), 2.13 (s, 3H), 2.15 (s, 3H), 2.16-2.30 (m, 12H), 2.35-2.50 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 117.92 (s), 117.89 (s), 74.5 (d), 66.5 (d), 54.92 (t), 54.86 (t), 51.1 (t), 50.3 (t), 50.1 (t), 49.6 (t), 45.8 (q), 43.8 (s), 41.1 (s), 31.7 (d, $^1J_{CH}$ = 175 Hz), 30.9 (d, $^1J_{CH}$ = 178 Hz), 29.8 (t), 23.9 (t); MS (35 eV) m/e = 492.2 [M^+, 34%], 366.1 [12%], 126.1 [100%]. Anal. Calcd for $C_{28}H_{44}N_8$: C, 68.26; H, 9.00; N, 22.74. Found: C, 68.3; H, 9.0; N, 22.9.

X-Ray Crystal Structure Analysis of **5a**.[13,14] Single crystals of **5a** were obtained by crystallization from acetonitrile.

Crystal data: $C_{28}H_{44}N_8$, F.W. = 492.7; triclinic, space group $P\bar{1}$; a = 8.379(7), b = 8.367(5), c = 10.996(6) Å; α = 73.61(6)°, β = 71.46(4)°, γ = 82.72(5)°, ; V = 700.6(6) $Å^3$; 1 molecule per unit cell; D_x = 1.17 g · cm^{-3}; crystal size 0.50 x 0.18 x 0.65 mm.

Data collection: Diffractometer Enraf-Nonius CAD 4, temperature: 295 K; monochromatized Mo-K_α radiation; 2209 independent reflections with 2.00 < 2Θ < 24.00° [ω/2Θ scan, scan width (1.00 + 0.35 tan Θ)°, scan speed 1.6 - 3.2 ° · min^{-1}], no absorption correction.

Structure solution and refinement: Full matrix least-squares method; H atoms were localized in a ΔF map and refined isotropically, hydrogen atom at C(12) was calculated and not refined, 1418 reflections with $I > 2\sigma(I)$; 247 variables, unit weights, maximum shift/error ratio 0.09, R = 0.049, $R_w = (\Sigma\Delta^2F / \Sigma F_o^2)^{1/2}$ = 0.047.

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REFERENCES AND NOTES

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