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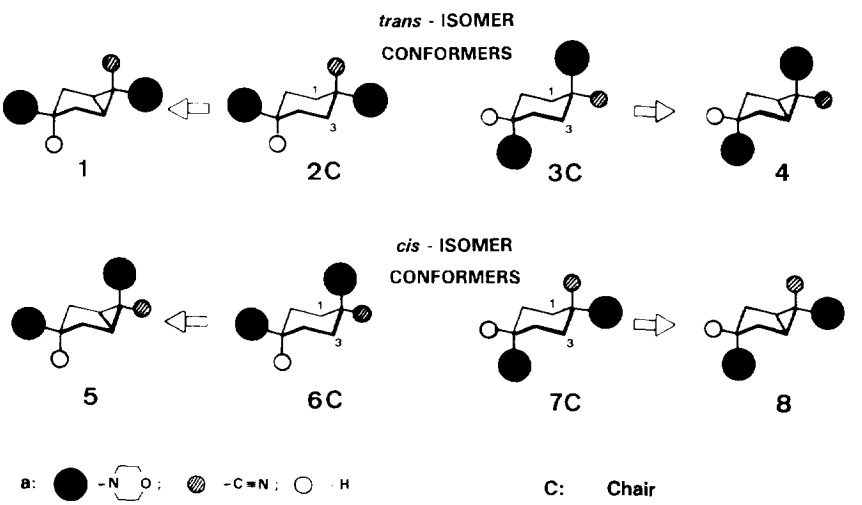
The Ensemble of 3,6-Diaminobicyclo[3.1.0]hexanecarbonitrile Diastereomers - Constrained Analogues of Conformers of Cyclohexane-1,4-diamine Species

Elmar Vilsmaier*, Matthias Dotzauer, Rolf Wagemann, Claus Tetzlaff, Joachim Fath, Wolf-Rüdiger Schlag and Uwe Bergsträßer

Fachbereich Chemie der Universität Kaiserslautern,
Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany

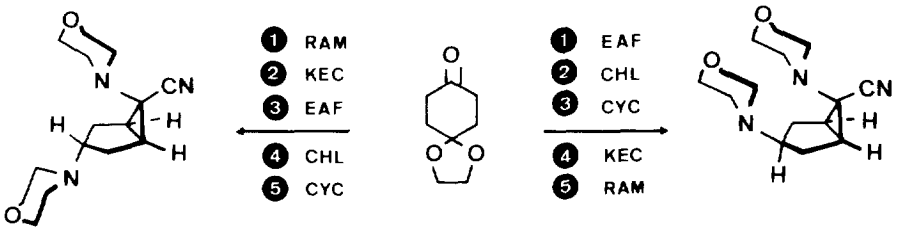
Abstract: Dimorpholinobicyclo[3.1.0]hexanecarbonitrile diastereomers **1a** and **8a** have been synthesized with high stereoselectivity starting from dichloroenamines **11** and **13**. The sequence **11** -▷ **17** -▷ **19** and reductive amination of the latter provided isomer **1a**. Ring closure of **13** by cyanide and subsequent dechlorination of **14** produced compound **8a**. The stereochemistry of the cyclopropane forming reaction was studied using cis and trans isomers of chloroenamine **12**: trans **12-t** gave almost exclusively 3α-morpholine derivatives **4a** / **8a** upon interaction of cyanide. Cis **12-c** led to 3α- and 3β-morpholine products **4a** / **8a** and **1a** / **5a** in a ratio of 3:1 indicating an aminoallylcation intermediate **30** in the former case. Cis-configuration of chloroenamine isomer **12-c** was established by X-ray structural analysis.

Cis-trans isomerism and conformational isomerism lead to four distinguished chair stereoisomers, **2C**, **3C**, **6C** and **7C**, of cyclohexane-1,4-diamine compounds. Formal 1,3-cyclization should interconvert these non separable pairs of chair conformers into stable diastereomers **1**,



4, **5** and **8**. Thus, the latter compounds can be regarded as constrained analogues of conformers **2C** / **3C** and **6C** / **7C**.

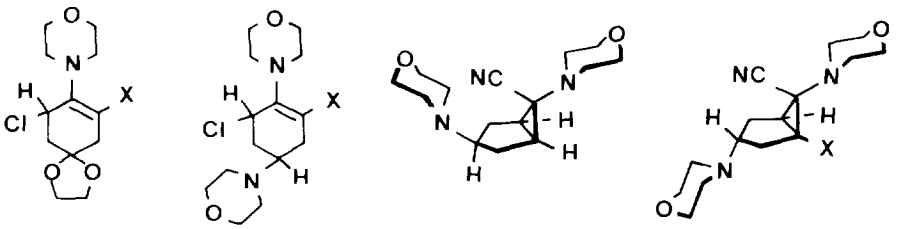
Isomers **4a** and **5a** of this ensemble of diastereomeric diamines have been synthesized with high stereoselectivity starting from ketal **9** via 5 steps.[1] Identical chemical transformations were used in both cases. Simple changing of the sequence of the 5 steps caused complementary diastereoselective approaches[1] either to **4a** or to **5a**. Meanwhile, this synthetic principle could be applied successfully to other compounds[2] **4** and **5** and also to difunctional systems.[3,4]



4a **9** **5a**

CHLORINATION - **CYC**LIZATION - **EN**A**M**INE **F**ORMATION - **KE**TAL **C**LEAVAGE - **R**EDUCTIVE **AM**INATION

Monochloroenamines **10** and **12** served as precursors for the cyclization reaction with cyanide to give bicyclic nitriles with uniform 6ß-configuration.[1] It was shown[5-7] that the reaction of cyanide with some dichloroenamines instead of monochloroenamines led to a changed stereochemical result at the C_1-bridge. We investigated therefore, if dichloroenamines **11** and **13** in the synthetic steps of Scheme 1 would provide a basis for the synthesis of the 6*a*-isomers **1a** and **8a** of the dimorpholinobicyclo[3.1.0]hexanecarbonitrile family. Additionally,

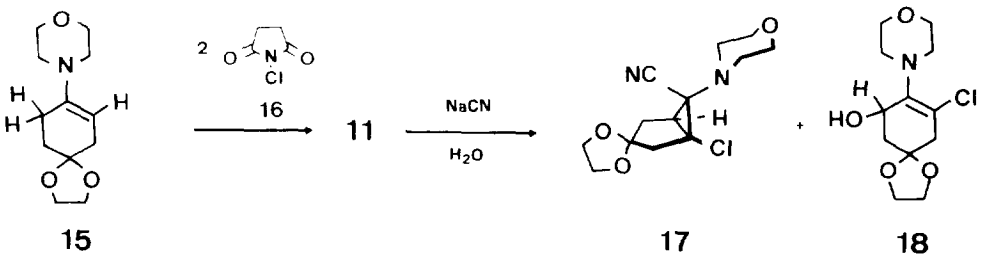


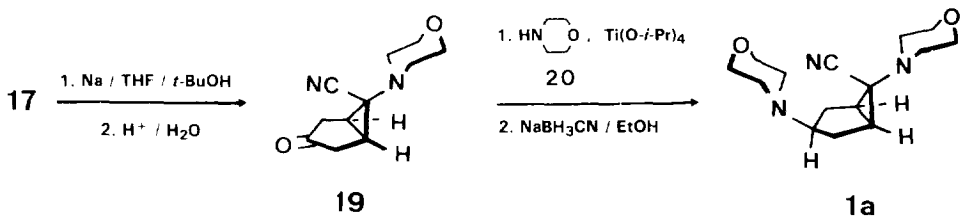
10 X = H **12** X = H **1a** **14** X = Cl
11 X = Cl **13** X = Cl **8a** X = H

isomerization at the C(6)-atom of 6β-6-aminobicyclo[3.1.0]hexanecarbonitriles as a potential approach to 6α-isomers was examined. Finally, the stereochemistry of the cyclopropane forming process was studied by analyzing the reaction of cis and trans isomers of chloroenamine **12** with cyanide. The results of these investigations are reported in this paper.

6α-3,6-Dimorpholinobicyclo[3.1.0]hexanecarbonitriles 1a and 8a via Dichloroenamines 11 and 13

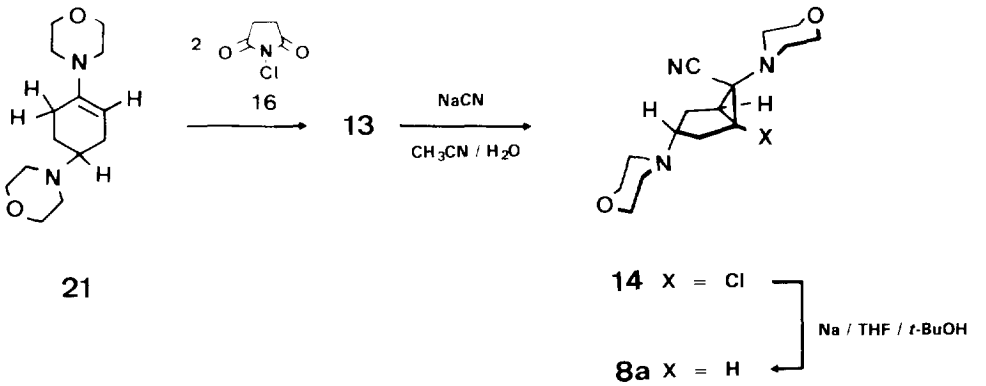
Dichloroenamine **11** was obtained in 91% yield from enamine **15** and two equivalents of N-chlorosuccinimide (**16**). Reaction of **11** with an aqueous solution of sodium cyanide (0.3 M; threefold molar excess) gave a mixture of bicyclic nitrile **17** (52% yield) and enaminoalcohol **18** (26% yield). The ratio of **17** / **18** decreased if cyanide was used in a lower concentration (0.1 M; threefold molar excess; **17**: 25%, **18**: 66%). Nitrile **17** was insoluble in water, it could be separated easily from the water soluble enaminoalcohol **18**. The chlorine atom in **17** was removed by finely powdered sodium in tertiary butylalcohol - tetrahydrofuran; subsequent cleavage of the ketal function gave oxonitrile **19** in 59% yield. Reductive amination of **19** with titanium tetraisopropoxide, morpholine (**20**) and sodium cyanoborohydride finally led to target molecule **1a** which was isolated as pure isomer in 45% yield.





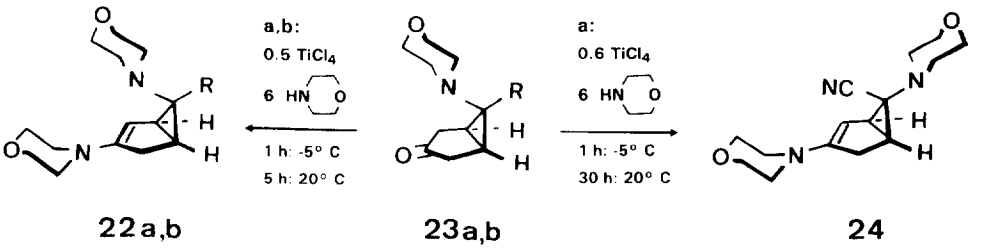
Reaction of enamine **21** with two eqivalents of N-chlorosuccinimide (**16**) and extraction of the crude product with pentane in a Soxhlet apparatus provided dichloroenamine **13** as a single diastereomer (78% yield). Cyclopropanation of the latter with cyanide in a mixture of acetonitrile and water (10:1) led to bicyclic nitrile **14** as pure isomer in 59% yield. Reductive

dechlorination, as described before, gave dimorpholinobicyclo[3.1.0]hexanecarbonitrile **8a** in the 3α,6β-configuration (58% yield). Using dichloroenamines in the cyclization step of Scheme 1 and addition of a dechlorination step indeed led to bicyclic nitriles **1a** and **8a** with 6α-configuration. The preferred endo-attack of cyanide to the annulated cyclopropaniminium intermediate could be explained by repulsive effects of the Cl-atom at the α-side and a secondary orbital effect at the β-side (interaction of cyanide HOMO with the C-Cl-σ^*-orbital; see ref. [8]).



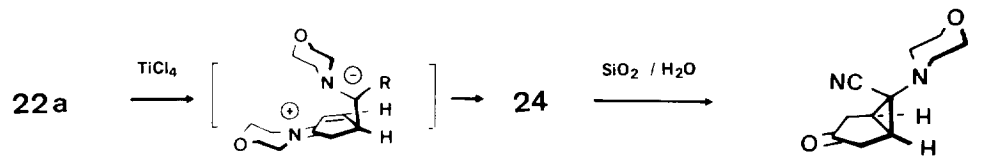
3β,6α-3,6-Dimorpholinobicyclo[3.1.0]hexanecarbonitrile 1a via an Isomerization Process

Isomerization at C(6) as potential access to a 3β,6α-aminobicyclohexanecarbonitrile **1a** was found upon preparation of enamine **22a** from ketone **23a** according to Weingarten's method.[9] The expected 6β-enamine **22a** could be isolated in 74% yield if reaction time was short (5 h at room temperature) and titanium tetrachloride was used in a demimolar ratio with respect to ketone **23a**. A small increase of the amount of $TiCl_4$ (molar ratio of ketone **23a** : $TiCl_4$ = 1:0.6) and prolonging the reaction time (30 h at room temperature) gave 6α-enamine **24** in 78% yield. Formation of 6α-enamine **24** is the consequence of an isomerization of primarily formed 6β-enamine **22a** under the influence of the titanium tetrachloride - morpholine catalyst system. This could be demonstrated with pure 6β-enamine **22a** which provided 6α-isomer **24** in 82% yield in the presence of the catalyst [molar ratio of enamine **22a** : $TiCl_4$: morpholine (**20**) = 5:1:30]. Subsequent hydrolysis of enamine **20a** by silicagel led to ketone **19** (93% yield) as the starting material for the synthesis of diamine **1a**. Partial isomerization of enamine **22a** into **24** was also observed upon heating besides decomposition reactions. The combination of an enamine and a nitrile function in **22a** is essential for the isomerization process. Neither nitrile[6] **26** nor enamine **22b**, which was obtained from ketone[2] **23b** and morpholine (**20**), could be isomerized in the presence of titanium tetrachloride - morpholine (**20**) or upon heating. Interaction of $TiCl_4$ with the nitrile function in **22a** (complexation of nitriles with $TiCl_4$ see ref.[10]) and stabilization of the negative charge in zwitterion **25a** by the cyano group should be important for the isomerization.



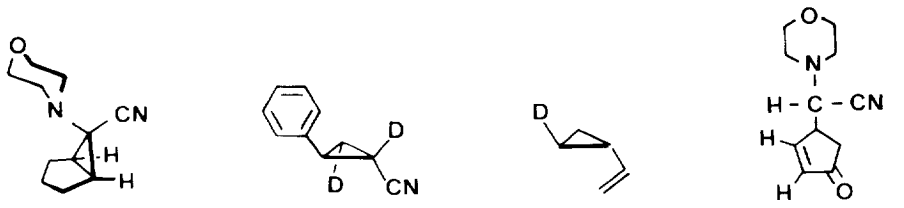
22a,b 23a,b 24

a: R = CN; b: R = H



25a 19

Thermally induced cis-trans isomerization reactions of partially deuterated phenylcyclopropanenitrile[11] **27** or vinylcyclopropane[12] **28** via diradical intermediates are known.[13] The presence of donor - acceptor substituents in **22a** should favour a zwitterionic intermediate of type **25** towards a diradical species. Attempts to isomerize ketone **23a** via its anion have not been successful so far. Compound **29** from a ring opening reaction was the only isolable product upon treating ketone **23a** with an aqueous sodium hydroxide solution. Here, protonation of the ring opened intermediate is faster in the aqueous medium than the ring closure reaction leading back to a bicyclic system.



26 **27** **28** **29**

Configuration and Conformation of Dimorpholinobicyclohexanecarbonitriles 1a/8a and Enamines 22/24

The **uniform 6α-configuration** of **1a** and **8a** was determined spectroscopically[1-8] by ^{1}H NMR: AA'XX'-signal systems for all morpholine moieties at room temperature and $\Delta G^{\ddagger}$-values of 48 - 49 kJ/mol for the morpholine dynamics were found for **1a** and **8a** (CD_2Cl_2: **1a**:[14,15] H_{A1}: 3.74, H_{A2}: 3.67, H_{B1}: 3.33, H_{B2}: 3.51; $^2J_{A1B1}$ = 10.8 Hz, $^2J_{A2B2}$ = 10.6 Hz; T_{c1} = 246 K; T_{c2} = 242 K; $\Delta G^{\ddagger}_1$ = 47.7 kJ/mol, $\Delta G^{\ddagger}_2$ = 48.7 kJ/mol; **8a**:[14,16] H_{A1}: 3.84, H_{A2}: 3.80, H_{B1}: 3.51,

H_{B2}: 3.44; $^2J_{AB}$ = 11.8 Hz; T_c = 248 K; $\Delta G^{\ddagger}_{max}$ = 48.8 kJ/mol, $\Delta G^{\ddagger}_{min}$ = 48.2 kJ/mol; H_X: 2.72, H_Y: 2.07; $^2J_{XY}$ = 10.7 Hz; T_c = 256 K; $\Delta G^{\ddagger}$ = 48.8 kJ/mol). This indicates the absence of sterical influences on the morpholine dynamics. Morpholine in the 6-position, therefore, is located at the exo-site of the bicyclo[3.1.0]hexane skeleton. A uniform 6α-configuration follows from this for precursors **14**, **17** and **19**, too.

C(6)-configuration of enamines **22a** and **24** was established by the ^1H NMR data of the corresponding morpholino systems. In particular, the OCH_2-signals can be used since assymmetry of molecules **22a** and **24** caused no disturbing anisochronism of these H-atoms (broad coalescing signals of a hindered morpholine in the case of **22a**; no sterical hindrance indicated in the case of **24**). Endo-morpholine configuration of enamine **22b** was assigned by the coupling of the cyclopropane H-atoms[2-4] (H_z: δ 1.59, t with $^3J_{HH}$ = 6.4 Hz).

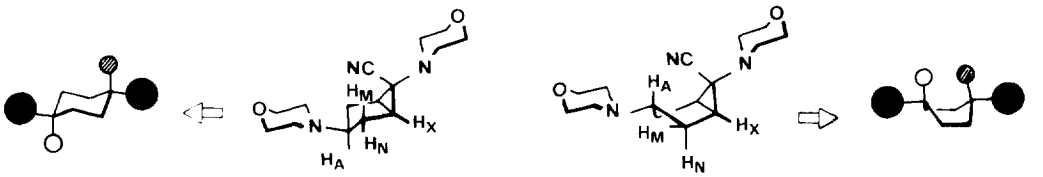
Different conformations were found for the C(3)-configurational isomers **4a** (boat) and **5a** (chair) due to the equatorial anchoring of the C(3)-morpholine moiety.[1,2] Determination of conformation of compounds of this structural type can be used for **assignment of C(3)-configuration**: High field shifting of $H(2)_N/H(4)_N$ [**5a** / **4a**: $\Delta\delta$ = 0.54 ppm ($CDCl_3$)][1,2] and low field shifting of the C(3)-H unit [**5a** / **4a**: ^{13}C NMR: $\Delta\delta$ = 8.4 ppm; ^1H NMR: $\Delta\delta$ = 0.30 ppm ($CDCl_3$)][1,2] correspond to a chair conformation and the 3β-configuration; the absence of a detectable coupling for $^3J_{1,2N}$ / $^3J_{5,4N}$ (J < 0.8 Hz) indicate a boat conformation and the 3α-configuration. According to this, **1a** is to be described as 3β-isomer in a chair conformation; a 3α-configuration and a boat conformation, on the other hand, follows for **8a** (see Table 1).

Table 1 ^1H NMR data of the bicyclo[3.1.0]hexane skeleton and C(3) ^{13}C NMR data of nitrile diastereomers[a] **1a** and **8a**; $CDCl_3$, δ-values [ppm]; $^3J_{HH}$ coupling constants [Hz].

	C(3)	$H(1)_X$ $H(5)_{X'}$	$H(2)_N$ $H(4)_{N'}$	$H(2)_M$ $H(4)_{M'}$	$H(3)_A$	$J_{1,2N}$ $J_{5,4N'}$	$J_{1,2M}$ $J_{5,4M'}$	$J_{3,2N}$ $J_{3,4N'}$	$J_{3,2M}$ $J_{3,4M'}$
1a	74.2	1.78	2.22	1.51	3.10	5.8	1.3	8.1	10.7
8a	64.9	1.89	1.99	2.16	2.87	3.8	< 0.8	7.8	7.8

[a] Numbers of atoms correspond to the usual counting in a bicyclo[3.1.0]hexane system, with $H(2)_M$ and $H(4)_{M'}$ in the endo-position and $H(2)_N$ and $H(4)_{N'}$ in the exo-position.

Conformational analysis demonstrates that compound **1a** indeed represents a constrained analogue of chair conformation **2C**. **8a**, however, must be regarded as constrained copy of boat conformation **7B** instead of chair species **7C**. This corresponds to the situation[1,2] of **4a** (= **3B**) and **5a** (= **6C**).

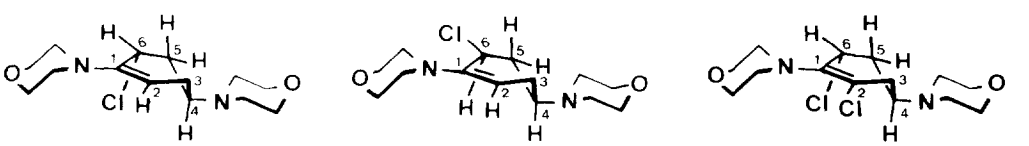


Diastereoselectivity of the Cyclopropane Formation of (Chlorocyclohexenediyl)-dimorpholine 12

Accessibility of all four diastereomers of the diaminobicyclohexanenitrile ensemble **1a**, **4a**, **5a** and **8a** allowed an investigation of the stereochemistry of the 1,3-ring closure reaction of chloroenamine **12**.

cis- and trans-Chloroenamines 12-c and 12-t

Chloroenamine **12** which was used so far in the reaction with cyanide[1] consisted of a mixture of two isomers (7:3 ratio). Separation of both isomers could be achieved by trituration with acetonitrile and subsequent recrystallization. The more soluble and major isomer was recrystallized from pentane (23% yield); the less soluble and minor isomer was recrystallized from acetonitrile / ether (1:3) (13% yield). The configuration of both isomers was determined spectroscopically by ^1H NMR via the $^3J_{HH}$ coupling constant of the axial H-atom at C(5) with the H-atom at C(6): the less soluble isomer gave a large coupling ($^3J_{HH}$ = 10.6 Hz, δ_H: 1.95 ppm) indicating a pseudoaxial positon of the H-atom at C(6) and hence cis-structure **12-c**.



A small coupling ($^3J_{HH}$ = 3.9 Hz; δ_H 1.85 ppm) was observed for the more soluble isomer; this requires a pseudoequatorial H-atom at C(6) which is present in the trans-isomer **12-t**. Additionally, two large coupling constants were found for the axial H of C(5) in both isomers

[$^2J_{HH}$; $^3J_{HH}$ (coupling with H of C(4), axial-H due to equatorial anchoring of the morpholine substituent)]. Trans-configuration **13-t** could be established analogously for the isolated dichloroenamine **13** [^{1}H NMR (C_6D_6): C(6)-H: δ_H 1.29 ppm, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 3.9 Hz)].

Assignment of configuration of chloroenamine isomers of **12** was confirmed by X-ray structural analysis of cis-compound **12-c**. **12-c** crystallized in the centrosymmetric space group $P2_1/n$. The cyclohexene unit adopts a "sofa"-conformation[18] in this molecule as shown by the Ortep plot (Fig. 1, only one enantiomer is depicted) and by the typical torsion angles of the ring C-atoms (Table 2). A clear pyramidal structure of the enamine N-atom is indicated by the difference of the torsion angles of C(2)C(1)N(2) with C(7) and C(10), respectively (e.g. ref.[18,19]). Large torsion angles H(6)-C(6)-C(5)-C(5_a) and H(4)-C(4)-C(5)-C(5_a) are in accordance with the large coupling constants of the corresponding ^{1}H NMR signals.

Table 2 Selected Torsion Angles[a] of 4,4'-(cis-6-Chloro-cyclohexene-1,4-diyl)-dimorpholine **12-c**

H(6)-C(6)-C(5)-H(5_a)	- 165.3	C(6)-C(1)-C(2)-C(3)	0.5
H(6)-C(6)-C(5)-H(5_e)	- 46.0	C(1)-C(2)-C(3)-C(4)	21.7
H(4)-C(4)-C(5)-H(5_a)	- 176.4	C(2)-C(3)-C(4)-C(5)	- 51.4
H(4)-C(4)-C(5)-H(5_e)	64.3	C(3)-C(4)-C(5)-C(6)	63.7
H(2)-C(2)-C(3)-H(3_a)	81.3	C(4)-C(5)-C(6)-C(1)	- 42.5
H(2)-C(2)-C(3)-H(3_e)	- 38.2	C(5)-C(6)-C(1)-C(2)	10.0
Cl-C(6)-C(1)-C(2)	130.8	C(10)-N(2)-C(1)-C(2)	1.2
H(6)-C(6)-C(1)-C(2)	- 108.6	C(7)-N(2)-C(1)-C(2)	135.1

[a] The designation of some atoms in Fig. 1 and Table 2 in this paper was partially changed with respect to the designation in the deposited data.-

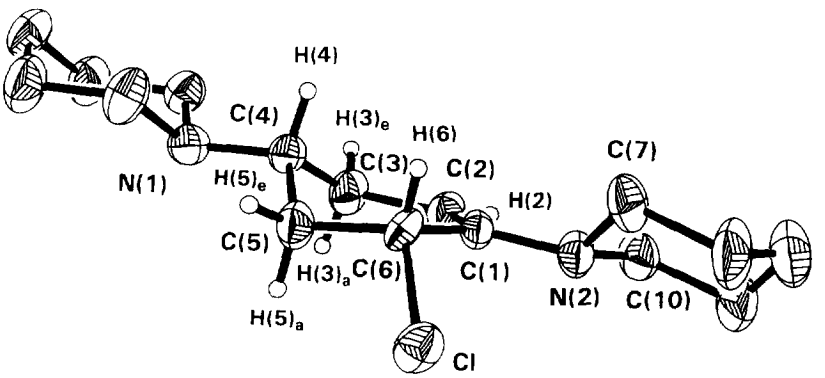
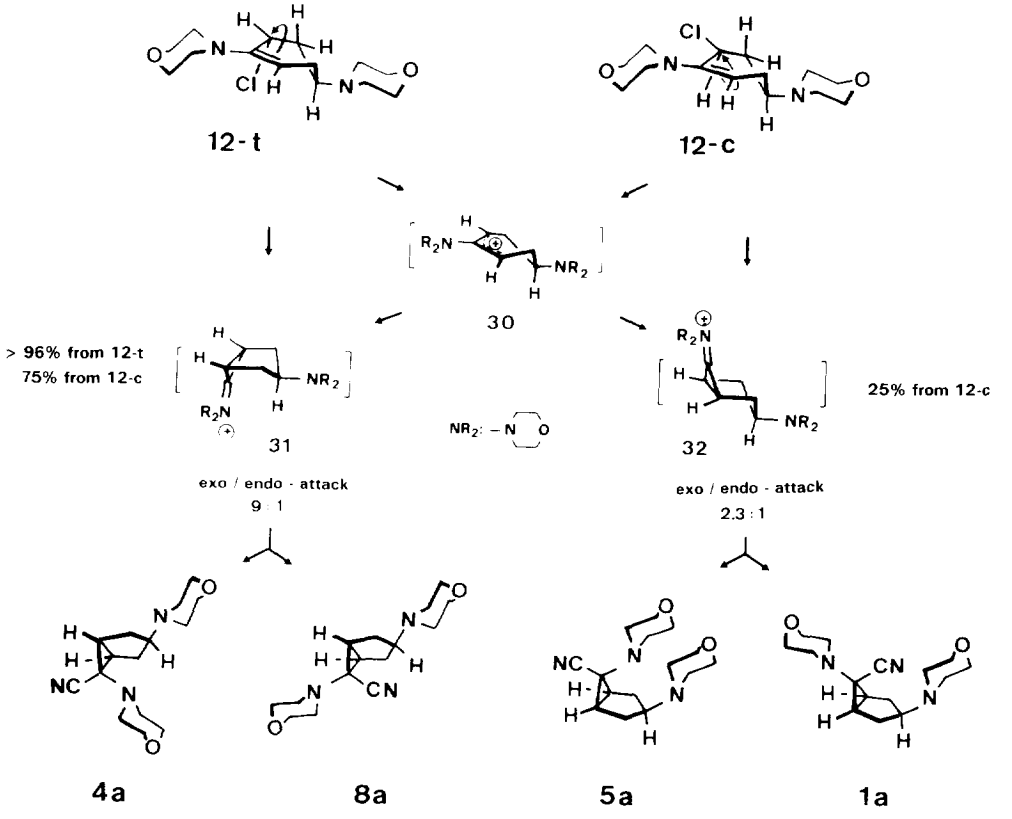


Fig. 1 Thermal ellipsoid plot of **12-c** with the atom-labelling scheme. Ellipsoids are scaled to enclose 50% of the electron density. Only one of the two enantiomers of the unit cell is depicted.

Reaction of Cyclohexenediyldimorpholine Isomers **12-c** *and* **12-t** *with Cyanide in Acetonitrile / Water (10:1)*

Deuterated solvents (acetonitrile / water 10:1) were used for analytical study of the reactions of chloroenamine isomers **12-c** and **12-t** with cyanide. The products were analyzed by ^1H NMR spectroscopy in $CDCl_3$ (evaporation of CD_3CN / D_2O in vacuo). Ratios of the isomeric bicyclic nitriles **1a**, **4a**, **5a** and **8a** were determined with the C(3)-H-signal of the bicyclo[3.1.0]hexane unit [δ-values ($CDCl_3$) **1a**: 3.10; **4a**:[1] 2.92; **5a**:[1] 3.23; **8a**: 2.87 ppm].



Only 3α-isomers **4a** / **8a** (> 96%; ratio 9:1) were detected as products from the reaction of trans-chloroenamine **12-t** with cyanide. Analogous reaction of cis chloroenamine **12-c** with cyanide gave a mixture of all nitrile isomers **1a**, **4a**, **5a** and **8a** in a ratio of 1:9:2.3:1. The different ratios for exo-/endo-attack of the cyanide on iminium ions **31** and **32** can be understood in terms of less steric repulsion at the inside of a bicyclohexyl system which prefers a chair conformation. Proton-catalyzed or chloride-induced isomerization of **12-c** into

12-t prior to the reaction with cyanide was excluded (no incorporation of deuterium from D_2O into the products and no change of the observed ratio of products upon running the reaction in the presence of sodium chloride).

Assistance of the C=C-double bond in the displacement of the chloride in **12** should specifically produce 3α-cation **31** from **12-t** and 3β-iminium ion **32** from **12-c**, respectively. The generation of 3α-products **4a** / **8a** (more than 96%) from trans-isomer **12-t** would be in accordance with this. The formation of 75% of **4a** / **8a** from cis-isomer **12-c**, however, requires the participation of allyl cation **30** and its selective ring closure to 3α-iminium ion **31**. The magnitude of this selectivity, at least 75%, is not clear as yet. From the experimental point of view, the missing information about a potential involvement of allyl cation **30** in the exclusive transformation of **12-t** into **31** is a crucial point which prohibits a more detailed discussion.

Conclusion

Extension of the synthetic principle of Scheme 1 by a dichlorination - reductive dechlorination sequence allows the selective preparation of all members of the ensemble of 3,6-diaminobicyclo[3.1.0]hexanecarbonitrile diastereomers **1a**, **4a**, **5a** and **8a**. Chloroenamines **12-t** and **13-t** with a trans-configuration are best suitable for the access to 3α-diastereomers **4a** and **8a**, respectively. Whilst **13** was obtained exclusively as pure isomer **13-t** upon chlorination, a mixture of cis-trans isomers (**12-c** : **12-t** = 3:7) was available in the case of chloroenamine[1] **12**. This mixture, however, can be used directly for the reaction with cyanide in acetonitrile - water (10:1) for the synthesis of **5a**. The observed diastereoselectivity of 83% for nitrile **5a** is sufficient from a preparative point of view.

EXPERIMENTAL

^1H NMR spectra were obtained with a Bruker AMX 400 or, if noted, with a Bruker AC 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 using a Perkin-Elmer 2400 Elemental Analyzer. Reductive dehalogenation with sodium powder and reactions with titanium tetrachloride or N-chlorosuccinimide were run in a nitrogen atmosphere. The solvents for the reductive dechlorination must be absolutely free of water (tetrahydrofuran freshly distilled from lithium aluminum hydride, sodium was added to *tert*-butyl alcohol prior to distillation).

4-(7,9-Dichloro-1,4-dioxaspiro[4.5]dec-7-en-8-yl)-morpholine (11): A solution of N-chlorosuccinimide (**16**) (13.35 g, 0.1 mol) in dichloromethane (700 mL) was dropped at 0°C within 1 h to a solution of enamine[20] **15** (11.26 g, 50 mmol) in dichloromethane (200 mL). Stirring was continued at 0°C for 1 h and then at 20°C for 2 h. Removal of the solvent in vacuo and extraction of the residue in a Soxhlet apparatus with pentane (350 mL, 48 h) gave pure dichloroenamine **11**. Yield: 13.34 g (91%); mp 100°C; ^1H NMR ($CDCl_3$) δ 2.27-2.40 (m, 2H), 2.68-2.80 (m, 2H), 2.90-2.98 (m, 2H), 3.20-3.28 (m, 2H), 3.74 (m_c, 4H) 3.90-3.99 (m,

2H), 4.02-4.10 (m, 2H), 4.89 (m_C, 1H); ^{13}C NMR ($CDCl_3$) δ 139.4 (s), 121.4 (s), 105.7 (s), 67.2 (t), 64.6 (t), 64.1 (t), 54.3 (d), 49.3 (t), 43.7 (t), 40.2 (t). Anal. Calcd for $C_{12}H_{17}Cl_2NO_3$: C, 49.00; H, 5.82; N, 4.76. Found: C, 49.0; H, 5.8; N, 4.8.

Reaction of dichloroenamine 11 with cyanide: A mixture of dichloroenamine **11** (1.47 g, 5.0 mmol) and sodium cyanide (0.74 g, 15 mmol) in water (50 mL) was stirred vigorously for 3 d at 20°C. The resulting solid was isolated by suction and recrystallized from ether to give pure bicyclic nitrile **17**. The filtrate was extracted with ether (4 x 25 mL). Concentration of the ether extract to 50 mL and storing at -18°C gave chlorohydroxyenamine **18**.

1α,5α,6α-1-Chloro-6-morpholinospiro{bicyclo[3.1.0]hexane-3,2'-[1',3']-dioxolane}-6-carbonitrile (**17**): Yield: 0.74 g (52%), mp 102°C; IR (KBr, cm^{-1}) 2215 (C≡N); ^1H NMR ($C_6D_5CD_3$) δ 1.51 (H_X, 1H), 1.88 (H_M, 1H), 2.19 (H_N, 1H) (MNX-system, $^3J_{MX}$ = 2.4 Hz, $^3J_{NX}$ = 7.3 Hz), 2.22-2.35 (m, 2H), 2.45-2.60 (m, 4H), 3.35 (m_C, 4H), 3.45 (m_C, 4H); ^{13}C NMR ($CDCl_3$) δ 119.9 (s), 112.4 (s), 66.4 (t), 65.2 (t), 63.9 (t), 55.3 (s), 54.3 (s), 50.5 (t), 47.8 (t), 38.1 (t), 37.7 (d, $^1J_{CH}$ = 181 Hz). Anal. Calcd for $C_{13}H_{17}ClN_2O_3$: C, 54.84; H, 6.02; N, 9.84. Found: C, 54.9; H, 6.0; N, 9.8.

9-Chloro-8-morpholino-1,4-dioxaspiro[4.5]dec-8-en-7-ol (**18**): Yield: 0.35 g (26%), mp 75°C; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.08 (d, H_{X1}, H_{Y1}, 2H), 4.47 (t, H_A, 1H), 2.57 (H_{X2}, 1H), 2.76 (H_{Y2}, 1H) (AB-system), 2.83-2.98 (m, 2H), 3.13-3.27 (m, 2H), 3.33 (t, d, 1H, OH), 3.76 (m_C, 4H), 3.88-4.13 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 142.8 (s), 118.1 (s), 107.3 (s), 67.2 (t), 65.5 (d), 64.5 (t), 64.4 (t), 50.0 (t), 43.6 (t), 38.8 (t). Anal. Calcd for $C_{12}H_{18}ClNO_4$: C, 52.27; H, 6.58; N, 5.08. Found: C, 52.0; H, 6.6; N, 5.2.

Using 150 mL instead of 50 mL of water in this reaction led mainly to chlorohydroxyenamine **18**. Analogous working up gave 25% (0.35 g) of bicyclic nitrile **17** and 66% (0.91 g) of chlorohydroxyenamine **18**.

1α,5α,6α-6-Morpholino-3-oxobicyclo[3.1.0]hexane-6-carbonitrile (19): Chlorobicyclohexanecarbonitrile **17** (0.94 g, 3.30 mmol) was added to a suspension of finely powdered sodium (0.45 g, 19.57 mmol) in tetrahydrofuran (20 mL) at 0°C under stirring. Stirring was continued for 20 min at room temperature. Then a solution of *tert*-butyl alcohol (0.078 g, 10.52 mmol) in tetrahydrofuran (15 mL) was dropped into the suspension over 20 min. Stirring was continued for 3 h at 20°C. The mixture was filtered by suction; the residue was washed with tetrahydrofuran (3 x 5 mL). Aqueous hydrochloric acid (5 N, 2 mL) was added to the filtrate and stirred for 2 h. The solvent was removed in vacuo, the residue was dissolved in water (10 mL) and the solution was extracted with dichloromethane (3 x 10 mL) to give crude carbonitrile **19** which was purified by sublimation (130°C/10^{-3} Torr). Yield: 0.40 g (59%), mp (decomp.) 179°C; IR (KBr, cm^{-1}) 2215 (C≡N), 1745 (C=O); ^1H NMR ($CDCl_3$) δ 2.10 (H_{X1}, $H_{X'1}$, 2H), 2.43 (H_M, $H_{M'}$, 2H), 2.70 (H_N, $H_{N'}$, 2H), (MM'NN'XX'-system), 2.73 (H_{X2}, $H_{X'2}$, 4H), 3.69 (H_A, $H_{A'}$, 4H) (AA'XX'-system); ^{13}C NMR ($CDCl_3$) δ 213.5 (s), 113.6 (s), 66.4 (t), 50.6 (t), 48.7 (s), 37.8 (d, d), 28.0 (d, $^1J_{CH}$ = 177 Hz). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.2; H, 6.9; N, 13.5.

1α,3β,5α,6α-3,6-Dimorpholino-bicyclo[3.1.0]hexane-6-carbonitrile (1a): A mixture of oxobicyclohexanecarbonitrile **19** (0.21 g, 1.0 mmol), titanium tetraisopropoxide (0.57 g, 2.0 mmol) and morpholine (**20**) (0.09 g, 1.0 mmol) was stirred at 20°C for 1 h. Then sodium cyanoborohydride (0.06 g, 1.0 mmol) and anhydrous ethanol (20 mL) were added and stirring

was continued for 24 h at 20°C. Amination product **1a** was obtained by addition of water (20 mL), filtration by suction, washing the residue with dichloromethane and extraction of the filtrate (concentrated to 20 mL) with dichloromethane (4 x 10 mL). Recrystallization from pentane at -18°C led to pure **1a**. Yield: 0.12 g (45%), mp 145°C; IR (KBr, cm^{-1}) 2215 (C≡N); ^1H NMR ($CDCl_3$) δ 1.51 (H_M, $H_{M'}$, 2H), 1.78 (H_{X1}, $H_{X'1}$, 2H), 2.22 (H_N, $H_{N'}$, 2H), 3.10 (H_{A1}, 1H) (AMM'NN'XX'-system, $^3J_{AM} = {}^3J_{AM'} = 10.7$ Hz, $^3J_{AN} = {}^3J_{AN'} = 8.1$ Hz, $^3J_{NX} = {}^3J_{N'X'} = 5.8$ Hz, $^3J_{MX} = {}^3J_{M'X'} = 1.3$ Hz, $^2J_{MN} = {}^2J_{M'N'} = 12.2$ Hz), 2.43 (H_{X2}, $H_{X'2}$, 4H), 3.65 (H_{A2}, $H_{A'2}$, 4H) (AA'XX'-system), 2.69 (H_{X3}, $H_{X'3}$, 4H), 3.67 (H_{A3}, $H_{A'3}$, 4H) (AA'XX'-system); ^{13}C NMR ($CDCl_3$) δ 115.5 (s), 74.2 (d, $^1J_{CH} = 131$ Hz), 66.9 (t), 53.9 (s), 52.0 (t), 50.9 (t), 32.5 (d, $^1J_{CH} = 173$ Hz), 29.3 (t). Anal. Calcd for $C_{15}H_{23}N_3O_2$: C, 64.96; H, 8.36; N, 15.15. Found: C, 64.6; H, 8.2; N, 14.9.

trans-4,4'-(2,6-Dichloro-1-cyclohexene-1,4-diyl)-dimorpholine (13-t): A solution of N-chlorosuccinimide (**16**) (1.34 g, 10 mmol) in dichloromethane (60 mL) was dropped at 0°C within 1 h to a solution of enamine[1] **21** (1.26 g, 5.0 mmol) in dichloromethane (40 mL). Stirring was continued for 1 h at 0°C and then 1 h at 20°C. Removal of the solvent and extraction of the residue in a Soxhlet apparatus with pentane (150 mL, 48 h) gave pure dichloroenamine **13-t**. Yield: 1.25 g (78%); mp 115°C (decomp.); ^1H NMR (C_6D_6) δ 1.29 (H_Z, 1H), 1.93 (H_{Y1}, 1H), 2.22 (H_{X1}, 1H), 2.37 (H_W, 1H), 2.92 (H_M, 1H), 4.37 (H_{A1}, 1H) (AMWXYZ-system, $^2J_{WX} = 17.0$ Hz, $^2J_{YZ} = 13.7$ Hz, $^3J_{AY} = 2.4$ Hz, $^3J_{AZ} = 3.9$ Hz, $^3J_{MW} = 5.6$ Hz, $^3J_{MX} = 11.0$ Hz, $^3J_{MY} = 2.4$ Hz, $^3J_{MZ} = 12.4$ Hz, $^4J_{WY} = 1.5$ Hz), 2.04 (H_{Y2}, 2H), 2.12 (H_{X2}, 2H), 3.53 (H_{A2}, H_{B2}, 4H) (ABXY-system), 2.87 (H_{Y3}, 2H), 3.19 (H_{X3}, 2H), 3.61 (H_{B3}, 2H), 3.68 (H_{A3}, 2H) (ABXY-system); ^{13}C NMR ($CDCl_3$) δ 140.5 (s), 123.0 (s), 67.2 (t), 67.0 (t), 55.7 (d), 55.4 (d), 50.7 (t), 49.4 (t), 35.8 (t), 34.7 (t). Anal. Calcd for $C_{14}H_{22}Cl_2N_2O_2$: C, 52.34; H, 6.90; N, 8.72. Found: C, 52.2; H, 6.8; N, 8.8.

1*α*,3*α*,5*α*,6*α*-1-Chloro-3,6-dimorpholinobicyclo[3.1.0]hexane-6-carbonitrile (14): A mixture of dichloroenamine **13** (1.61 g, 5.0 mmol) and sodium cyanide (0.49 g, 10 mmol) in water (10 mL) - acetonitrile (100 mL) was stirred at 20°C for 24 h. Then the solvent was removed by evaporation and aqueous sodium carbonate (1 M, 30 mL) was added to the residue. Extraction with dichloromethane (4 x 25 mL) gave crude bicyclic nitrile **14** which was recrystallized from acetone (40 mL). Yield: 0.92 g (59%); mp 135°C; IR (KBr, cm^{-1}) 2220 (C≡N); ^1H NMR ($C_6D_5CD_3$) δ 1.40 (H_X, 1H), 1.61 (H_M, 1H), 1.68 (H_N, 1H), 2.16 (H_K, 1H), 2.29 (H_L, 1H), 2.79 (H_A, 1H) (AKLMNX-system, $^3J_{AM} = 7.9$ Hz, $^3J_{AK} = 7.8$ Hz, $^3J_{AN} = 7.8$ Hz, $^3J_{AL} = 7.7$ Hz, $^3J_{NX} = 5.4$ Hz, $^3J_{MX} = 0.9$ Hz, $^2J_{MN} = 13.7$ Hz, $^2J_{KL} = 14.0$ Hz), 1.92 (m_c, 4H), 2.23-2.33 (m, 2H), 2.55 (m_c, 2H), 3.38-3.50 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 114.0 (s), 66.7 (t), 66.5 (t), 64.2 (d), 57.9 (s), 51.7 (t), 50.3 (t), 48.3 (s), 40.9 (t), 39.9 (d, $^1J_{CH} = 183$ Hz), 30.8 (t). Anal. Calcd for $C_{15}H_{22}ClN_3O_2$: C, 57.78; H, 7.11; N, 13.48. Found: C, 57.8; H, 7.1; N, 13.2.

1*α*,3*α*,5*α*,6*α*-3,6-Dimorpholino-bicyclo[3.1.0]hexane-6-carbonitrile (8a): Chlorobicyclohexane-carbonitrile **14** (0.32 g, 1.03 mmol) was added to a suspension of finely powdered sodium (0.12 g, 5.22 mmol) in tetrahydrofuran (6 mL) at 0°C with stirring. Stirring was continued for 20 min at room temperature. Then a solution of *tert*-butyl alcohol (0.234 g, 3.16 mmol) in tetrahydrofuran (5 mL) was dropped to the suspension over 10 min. Stirring was continued for 5.5 h at 20°C. The mixture was filtered by suction and the residue washed with tetrahydrofuran (3 x 5 mL). The solvent was evaporated and the residue was recrystallized from acetone (25 mL) and then from ether (15 mL) to give colorless crystals of **8a**. Yield: 0.164 g (58%), mp 182°C; IR (KBr, cm^{-1}) 2215 (C≡N); ^1H NMR ($CDCl_3$) δ 1.89 (H_{X1}, $H_{X'1}$, 2H), 1.99 (H_N, $H_{N'}$, 2H), 2.16 (H_M, $H_{M'}$, 2H), 2.87 (H_{A1}, 1H) (AMM'NN'XX'-system, $^3J_{AM} =$

$^3J_{AM'} = {}^3J_{AN} = {}^3J_{AN'} = 7.8$ Hz, $^3J_{NX} = {}^3J_{N'X'} = 3.8$ Hz, $^3J_{MX} = {}^3J_{M'X'} = < 0.8$ Hz, $^2J_{M'N'} = 13.9$ Hz), 2.42 (H_{X2}, $H_{X'2}$, 4H), 3.64 (H_{A2}, $H_{A'2}$, 4H) (AA'XX'-system), 2.64 (H_{X3}, $H_{X'3}$, 4H), 3.69 (H_{A3}, $H_{A'3}$, 4H) (AA'XX'-system); ^{13}C NMR ($CDCl_3$) δ 116.0 (s), 66.8 (t), 66.6 (t), 64.9 (d), 52.1 (t), 50.4 (t), 46.0 (s), 34.0 (d, $^1J_{CH} = 173$ Hz), 30.9 (t). Anal. Calcd for $C_{15}H_{23}N_3O_2$: C, 64.96; H, 8.36; N, 15.15. Found: C, 65.0; H, 8.4; N, 14.9.

Enamines 22 of Bicyclic Ketones 23 - General Procedure: A solution of titanium tetrachloride (0.55 mL, 5.0 mmol) in toluene (10 mL) was dropped at -5°C with stirring within 30 min to a mixture of bicyclic ketone **23** (**23a**:[1] 2.06 g, **23b**:[2] 1.81 g; 10 mmol), morpholine (**20**) (5.2 mL, 60 mmol) and toluene (130 mL). Stirring was continued for 1 h at -5°C and 5 h at room temperature. Then the reaction mixture was filtered by suction and the solvent was removed in vacuo. Trituration of the residue with ether (25 mL) and storing at -20°C for 12 h gave pure enamine **22a**; **22b** was obtained by direct distillation of the residue in a Kugelrohr apparatus (140°C/0.015 Torr).

1α,5α,6β-3,6-Dimorpholino-bicyclo[3.1.0]hex-2-ene-6-carbonitrile (**22a**): Yield: 2.04 g (74%), mp 83°C; IR (KBr, cm^{-1}) 2110 (C≡N), 1610 (C=C); ^{1}H NMR ($CDCl_3$) δ 2.07 (H_{X1}, 1H), 2.22 ($H_{M'}$, 1H), 2.60 (H_{Y1}, 1H), 2.65 (H_N, 1H), 4.19 (H_{A1}, 1H) (AMNXY-system), 2.85 (H_{Y2}, 2H), 2.89 (H_{X2}, 2H), 3.70 (H_{A2}, H_{B1}, 4H) (ABXY-system), 2.50-2.65, 2.80-2.95 and 3.25-3.80 (8H, broad buckles, signals in coalescence); ^{13}C NMR ($CDCl_3$) δ 156.1 (s), 119.3 (s), 88.4 (d), 66.8 (t), 66.7 (t), 49.5 (t), 41.4 (s), 48.5 (t), 37.7 (d, $^1J_{CH} = 172$ Hz), 31.2 (t), 26.4 (d, $^1J_{CH} = 172$ Hz). Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.4; H, 7.7; N, 15.3.

4,4'-(1α,5α,6β-Bicyclo[3.1.0]hex-2-ene-3,6-diyl)-dimorpholine (**22b**): Yield: 1.93 g (77%), mp 69°C; ^{1}H NMR ($CDCl_3$) δ 1.44 (H_{X1}, 1H), 1.59 (H_Z, 1H), 1.86 (H_{Y1}, 1H), 2.19 (H_M, 1H), 2.50 (H_N, 1H), 4.27 (H_{A1}, 1H) (AMNXYZ-system, $^3J_{XZ} = {}^3J_{YZ} = 6.4$ Hz), 2.39 (H_{Y2}, 2H), 2.46 (H_{X2}, 2H), 3.56 (H_{B1}, 2H), 3.59 (H_{A2}, 2H) (ABXY-system), 2.80 (H_{Y3}, 2H), 2.84 (H_{X3}, 2H), 3.71 (H_{A3}, H_{B2}, 4H) (ABXY-system); ^{13}C NMR ($CDCl_3$) δ 153.7 (s), 93.0 (d), 67.0 (t), 66.2 (t), 52.1 (t), 49.0 (t), 46.4 (d, $^1J_{CH} = 165$ Hz), 30.4 (t), 26.9 (d, $^1J_{CH} = 166$ Hz), 17.5 (d, $^1J_{CH} = 169$ Hz). Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.1; H, 8.8; N, 11.0.

1α,5α,6α-3,6-Dimorpholino-bicyclo[3.1.0]hex-2-ene-6-carbonitrile (24) from Ketone 23a, Morpholine (20) and Titanium Tetrachloride: Enamine **24** was obtained when the procedure given for the preparation of **22a** was slightly changed [titanium tetrachloride (0.66 mL, 6 mmol) in toluene (10 mL); ketone **23a** (2.06 g, 10 mmol), morpholine (**20**) (5.2 mL, 60 mmol) in toluene (130 mL); addition at -5°C; stirring 1 h at -5°C, followed by 30 h at room temperature]. Working up as described above gave isomerically pure enamine **24**. Yield: 2.15 g (78%), mp 151°C; IR (KBr, cm^{-1}) 2100 (C≡N), 1610 (C=C); ^{1}H NMR ($CDCl_3$) δ 1.90 (H_{X1}, 1H), 2.39 (H_{Y1}, 1H), 2.54 ($H_{M'}$, 1H), 2.81 (H_N, 1H), 4.42 (H_{A1}, 1H) (AMNXY-system), 2.67 (H_{Y2}, 2H), 2.72 (H_{X2}, 2H), 3.65 (H_{A2}, H_{B1}, 4H) (ABXY-system), 2.90 (H_{Y3}, 2H), 2.92 (H_{X3}, 2H), 3.70 (H_{A3}, H_{B2}, 4H) (ABXY-system); ^{13}C NMR ($CDCl_3$) δ 155.1 (s), 115.3 (s), 93.4 (d), 66.9 (t), 65.9 (t), 50.4 (t), 50.2 (s), 48.6 (t), 38.2 (d, $^1J_{CH} = 172$ Hz), 32.8 (t), 27.8 (d, $^1J_{CH} = 176$ Hz). Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.2; H, 7.7; N, 15.2.

1α,5α,6α-3,6-Dimorpholino-bicyclo[3.1.0]hex-2-ene-6-carbonitrile (24) from Enamine 22a by Isomerization: A solution of titanium tetrachloride (0.11 mL, 1.0 mmol) in toluene (3 mL) was

dropped at 0°C into a mixture of enamine **22a** (1.38 g, 5.0 mmol), morpholine (**20**) (2.6 mL, 30 mmol) and toluene (75 mL). The mixture was stirred for 1 h at 0°C and for 30 h at room temperature. Removal of the solid by filtration and evaporation of the filtrate gave crude enamine **24** which was crystallized by addition of ether (10 mL) and storing at -20°C. Yield: 1.12 g (82%), mp 151°C. IR and ^{1}H NMR data were identical with the spectra described above.

Distillation of enamine **22a** at 190°C/0.001Torr in a Kugelrohr apparatus was accompanied predominantly by decompostion; the obtained brown distillate (30%) was established as a mixture of **22a** and **24** (ratio: 6:4) by the ^{1}H NMR spectrum.

Treatment of Enamine 22b with Morpholine (20) - Titanium Tetrachloride: Enamine **22b** (1.35 g, 5.34 mmol) was treated with morpholine (**20**) and titanium tetrachloride analogous to production of **22a**. Working up gave crude, not isomerized, starting material **22b** (1.27 g, 94%) which was distilled in vacuo at 140°C/0.015 Torr (1.0 g, 74%). **22b** could be distilled without decomposition and isomerization at 180°C/0.75 Torr.

Treatment of Nitrile 26 with Morpholine (20) - Titanium Tetrachloride: Nitrile[6] **26** (0.5 g, 2.60 mmol) was treated with morpholine (**20**) (1.4 mL, 16 mmol) and titanium tetrachloride (0.14 mL, 1.3 mmol) analogous to the preparation of enamine **24** from ketone **23a**. Working up gave crude, not isomerized starting material **26** (0.49 g, 98%).

1α,5α,6α-6-Morpholino-3-oxobicyclo[3.1.0]hexane-6-carbonitrile (19): Enamine **24** (0.80 g, 2.9 mmol), dissolved in ether (10 mL), was hydrolyzed by silica gel (chromatography; 15 cm column, ϕ 2.5 cm, ether as solvent). The first light yellow fraction was removed; the subsequent fractions provided pure ketone **19**. Yield: 0.56 g (93%), mp 176°C (decomp.). The ^{1}H NMR data were identical with those of ketone **19** which was obtained from nitrile **17** by dechlorination and cleavage of the ketal function.

2-Morpholino-2-(4-oxocyclopent-2-enyl)-acetonitrile (29): Bicyclic ketone **23a** (0.225 g, 1.09 mmol) was stirred vigorously in a mixture of toluene (15 mL) and aqueous sodium hydroxide (20%, 2.5 mL) at 20°C for 1 h. Separation of the organic layer and extraction of the aqueous layer with toluene (3 x 15 mL) gave crude nitrile **29** which was purified by chromatography (20 cm column, ϕ 2.5 cm; SiO_2, elution with ether). Crystallization from ether (4 mL) at -20°C gave **29** as a colorless precipitate. Yield: 0.07 g (31%); mp 98°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.27 (H_{Y1}, 1H), 2.66 (H_{X1}, 1H), 3.33 (H_N, 1H), 3.41 (H_M, 1H), 6.31 (H_{B1}, 1H), 7.73 (H_{A1}, 1H) (ABMNXY-system;[21] $^2J_{AB}$ = 5.8 Hz, $^3J_{AM}$ = 2.3 Hz, $^4J_{BM}$ = 2.0 Hz, $^3J_{MN}$ = 10.0 Hz, $^3J_{MX}$ = 6.7 Hz, $^3J_{MY}$ = 2.3 Hz, $^2J_{XY}$ = 18.9 Hz), 2.56 (H_{Y2}, 2H), 2.77 (H_{X2}, 2H), 3.74, 3.78 (H_{A2}, H_{B2}, 4H) (ABXY-system); ^{13}C NMR ($CDCl_3$) δ 205.8 (s), 162.0 (d), 135.7 (d), 114.8 (s), 66.2 (t), 62.0 (d), 50.3 (t), 41.0 (d), 38.0 (t). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.9; H, 6.9; N, 13.6.

4,4'-(6-Chloro-cyclohexene-1,4-diyl)-dimorpholine Isomers 12-c and 12-t: Crude chloroenamine[1] **12** (1.43 g, 5.0 mmol) was triturated with acetonitrile (5 mL). The residue was isolated by suction, washed with ice-cold acetonitrile and dried in vacuo. Evaporation of the filtrate in vacuo and addition of acetonitrile (5 mL) gave a further portion of cis-isomer **12-c** which was washed with ether (3 x 1 mL). The collected solids were recrystallized from ether - acetonitrile (3:1). The combined filtrates were evaporated. The residue was extracted with pentane (8 x 30 mL) to give trans-isomer **12-t** which was recrystallized from pentane.

4,4'-(cis-6-Chloro-cyclohexene-1,4-diyl)-dimorpholine (**12-c**): Yield: 0.18 g (13%); mp 125°C; IR (KBr, cm^{-1}) 1640 (C=C); ^1H NMR ($CDCl_3$) δ 1.95 (d, d, d, $^2J_{HH}$ = $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 10.6 Hz, 1H), 2.15-2.26 (m, 2H), 2.42-2.65 (m, 8H), 2.97 (m_c, 2H), 3.71-3.82 (m, 8H), 4.70 (m_c, 1H), 4.81 (m_c, 1H); ^{13}C NMR ($CDCl_3$) δ 144.9 (s), 103.5 (d), 67.2 (t), 66.7 (t), 59.8 (d, $^1J_{CH}$ = 128 Hz), 55.5 (d, $^1J_{CH}$ = 150 Hz), 49.6 (t), 49.0 (t), 38.0 (t), 26.8 (t). Anal. Calcd for $C_{14}H_{23}ClN_2O_2$: C, 58.63; H, 8.08; N, 9.77. Found: C, 58.4; H, 8.0; N, 9.9.

4,4'-(trans-6-Chloro-cyclohexene-1,4-diyl)-dimorpholine (**12-t**): Yield: 0.33 g (23%); mp 103°C; IR (KBr, cm^{-1}) 1640 (C=C); ^1H NMR ($CDCl_3$) δ 1.85 (H_Z, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 3.9 Hz, 1H), 2.07 (H_{X1}, 1H), 2.31 (H_W, 1H), 2.36 (H_{Y1}, 1H), 2.90 (H_M, 1H), 4.74 (H_{A1}, H_{B1}, 2H) (ABMWXYZ-system), 2.38 (H_{Y2}, 2H), 2.55 (H_{X2}, 2H), 2.76 (H_{Y3}, 2H), 2.88 (H_{X3}, 2H), 3.67, 3.69 (H_{A2}, H_{A3}, H_{B2}, H_{B3}, 8H) (2 ABXY-systems); ^{13}C NMR ($CDCl_3$) δ 144.2 (s), 103.2 (d), 67.0 (t), 66.6 (t), 54.9 (d, $^1J_{CH}$ = 135 Hz), 54.5 (d, $^1J_{CH}$ = 154 Hz), 49.7 (t), 48.1 (t), 34.8 (t), 27.0 (t). Anal. Calcd for $C_{14}H_{23}ClN_2O_2$: C, 58.63; H, 8.08; N, 9.77. Found: C, 58.3; H, 8.0; N, 9.8.

Reactions of Chloroenamine Isomers 12-t and 12-c with Cyanide - ^1H NMR Experiments: Sodium cyanide (5 mg, 0.105 mmol), dissolved in D_2O (0.5 mL) was added to a solution of pure isomer of chloroenamine **12** (**12-t**, **12-c** : 20 mg, 0.07 mmol) in CD_3CN (5 mL). The solution was stirred at 60°C for 1 h. For running the ^1H NMR spectra in $CDCl_3$, the solvent was evaporated in vacuo at room temperature. $CDCl_3$ was added to the residue.

X-Ray Crystal Structure Analysis of 4,4'-(cis-6-Chloro-cyclohexene-1,4-diyl)-dimorpholine 12-c:[22,23] Single crystals of **12-c** were obtained by crystallization from acetonitrile.

Crystal data: $C_{14}H_{23}ClN_2O_2$, F.W. = 286.6; monoclinic, space group $P2_1/n$; a = 6.552(5), b = 8.659(9), c = 25.938(12) Å; $\alpha = \gamma = 90$, β = 95.01(9)°; V = 1466(2) $Å^3$; 4 molecules per unit cell; D_x = 1.299 g · cm^{-3}; crystal size 0.25 x 0.23 x 0.30 mm; colourless rhombs.

Data collection: Diffractometer Siemens P4, temperature: 296 K; monochromatized Mo-K_α radiation; 2443 independent reflexions with 2.0 < 2Θ < 49.0° [ω scan, scan speed 5.00 - 40.00° · min^{-1}], no absorption correction.

Structure solution and refinement: Full matrix least-squares method; H atoms refined as riding on their bond neighbours with grouped isotropic thermal displacement factors, 1433 reflections with $F > 4.0\ \sigma(F)$; 172 variables, weighting scheme $w^{-1} = \sigma^2 2(F) + 0.0002\ F^2$, goodness of fit 2.32, maximum shift/error ratio 0.001, final R indices (obs. data) R = 0.0847, wR = 0.0945.

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REFERENCES AND NOTES

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