Synthesis and Structural Properties of Bridged 1,8-Diazacyclotetradeca-4,11-diynes

Volker Wolfart[a], Rolf Gleiter*[a], Hermann Irngartinger[a], Thomas Oeser[a], and Claus Krieger[b]

Organisch-Chemisches Institut der Universität Heidelberg[a],
Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany

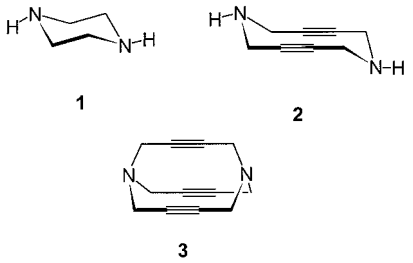
Abteilung Chemie des Max-Planck Instituts für Medizinische Forschung[b],
Jahnstraße 26, D-69120 Heidelberg, Germany

Received July 3, 1998

Keywords: Alkynes / Cyclizations / Nitrogen heterocycles

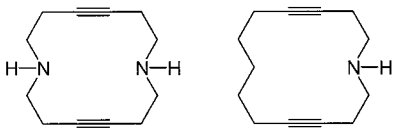
The synthesis of 1,8-diazacyclotetradeca-4,11-diyne (**4**) was accomplished by reaction of 1,6-dibromo-3-hexyne (**11**) with ammonia. Similarly, the preparation of 1-azacyclotetradeca-4,11-diyne (**5**) was achieved from 1,13-dibromotrideca-3,11-diyne (**10**) and ammonia. The reaction of α,ω-diamines of linear hydrocarbons of the chain length C_4 to C_{10} with **11** yielded the corresponding bicyclic diynes **23–29**. The reaction of **4** with **11** yielded 1,8-diazabicyclo[6.6.6]icosa-4,11,16-triyne (**14**). Similarly, the reaction of **4** with 1,4-dibromo-2-butyne yielded 1,8-diazabicyclo[6.6.4]octadeca-4,11,16-triyne (**31**). The molecular structures of 1,8-diisopropyl-1,8-diazacyclotetradeca-4,11-diyne (**13a**), as well as of **14**, **24**, **27** and **31** were studied by means of the X-ray technique. It was found that **13a** adopts a chair-like conformation (C_{2h}) with an equatorial orientation of the isopropyl groups. In **14**, **24**, **27**, and **31** the 14-membered rings adopt a twist-boat conformation. The distance between the nitrogen atoms varies between 4.662(2) and 5.189(2) Å. In the case of **14**, **24** and **27** the nitrogen atoms are pyramidalized and point inside the cage while in **31** the substituents at each nitrogen atom and the nitrogen atoms are situated in one plane.

The formal insertion of one alkyne unit each into the ethano bridges of piperazine (**1**) leads to 1,6-diazacyclodeca-3,8-diyne (**2**). This elongation of the C,C skeleton has two main consequences for **2**: The torsional strain between the CH_2 groups and the transannular interactions between the axial substituents at the nitrogen atoms are reduced to zero. These differences between **1** and **2** imply for the six-membered ring of **1** the well-known preferences for the chair conformation and for the axial conformation of the substituents at the nitrogen atoms.[1][2] In the case of **2**, an equilibrium between boat and chair conformations as well as axial and equatorial conformations of the substituents at the nitrogen atoms are preferred.[3] This was shown by spectroscopic studies on **2** and several 1,6-dialkyl- and diaryl-substituted products.[3] As a consequence of the boat-chair equilibrium of **2** at room temperature it was possible to prepare 1,6-diazabicyclo[4.4.4]tetradeca-3,8,12-triyne (**3**) by treating **2** with 1,4-dibromobut-2-yne.[4] Unfortunately, **3** is rather unstable; therefore we focused on higher homologues. To derive these we investigated the preparation of 1,8-diazacyclotetradeca-4,11-diyne (**4**) and 1-azacyclotetradeca-4,11-diyne (**5**) and explored possibilities to bridge the 1,8-positions of **4** by a 3-hexyne and a 2-butyne unit.



1 **2**

3



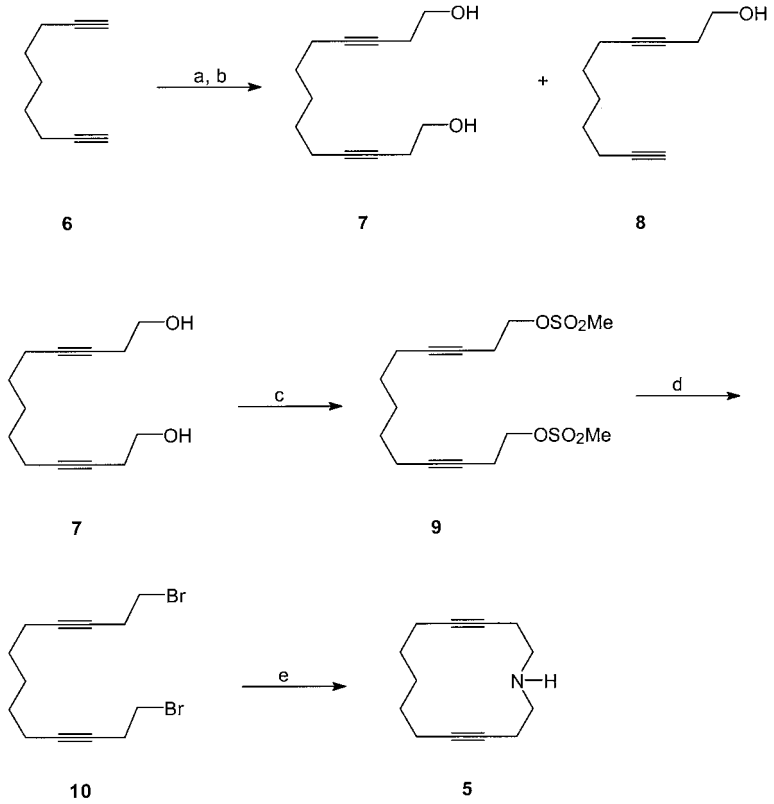
4 **5**

Synthesis of 1,8-Diazacyclotetradeca-4,11-diyne (4) and 1-Azacyclotetradeca-4,11-diyne (5)

The synthesis of **5** was achieved in a straightforward way (Scheme 1). Starting point was the lithium salt of 1,8-nonadiyne (**6**)[5] which was treated with a surplus of ethylene oxide to yield the diol **7**. As side product the monoalcohol **8** was isolated. The transformation of **7** into the dibromide **10** was achieved by reaction of the diol with methylsulfonyl chloride to yield the dimesylate which was treated with lith-

  1434–193X/98/1212–2803 $ 17.50+.50/0

Scheme 1. a) Li/NH_3, −50°C; b) C_2H_4O; c) CH_3SO_2Cl/Et_3N, 0°C; d) LiBr/$(CH_3)_2CO$; e) NH_3, −70°C



ium bromide to yield **10**. This path proved to be more efficient than the direct reaction of **7** with hydrogen bromide. The dibromide **10** was treated with ammonia in acetonitrile at −70°C to afford **5** in 9−11% yield.

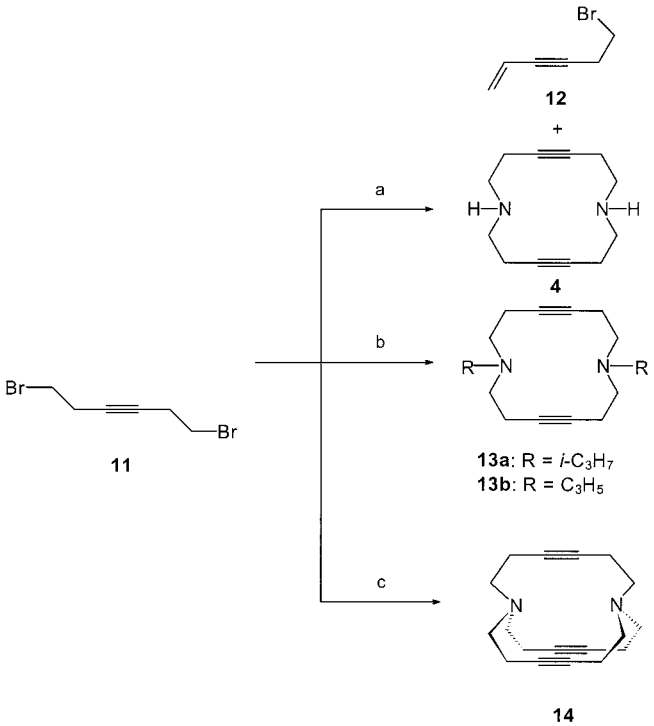
Encouraged by the fact that this simple procedure worked we tried the reaction of 1,6-dibromohex-3-yne (**11**)[6] with ammonia in acetonitrile. This protocol yielded **4**[7] and the elimination product of **11**, **12**, in 30% yield each, and in traces (1%) the triyne **14** (see below, Scheme 2).

When the reaction of **11** was carried out with isopropylamine in the presence of potassium carbonate, 1,8-diisopropyl-1,8-diazacyclotetradeca-8,11-diyne (**13a**) resulted. Similarly, 1,8-diallyl-1,8-diazacyclotetradeca-8,11-diyne (**13b**) could be obtained from allylamine and **11**. The reaction of the diamine **4** with **11** in the presence of potassium carbonate as base afforded 1,8-diazabicyclo[6.6.6]icosa-4,11,17-triyne (**14**) in 30% yield.[7]

In contrast to **3**, its homologue **14** proved to be thermally stable up to 100°C. The hydrogenation of **14** with Lindlar's catalyst[8] afforded 1,8-diazabicyclo[6.6.6]icosa-4,11,17-triene (**15**, Scheme 5) in 90% yield.

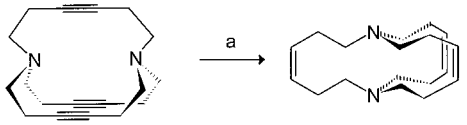
We rationalized the occurrence of **14** (1%) in the products of the reaction of **11** with NH_3 by assuming 1,6-diaminohex-3-yne as intermediate. In following this assumption we treated α,ω-diamines of linear alkanes of chain lengths C_4 to C_{10} with **11** (Scheme 4). This yielded the anticipated 1,8-bridged 1,8-diazacyclotetradeca-4,11-diynes **23**−**29**. The reaction of 1,4-diamino-2-butyne (**30**) with **11** yielded

Scheme 2. a) NH_3/CH_3CN, −70°C; b) $iPrNH_2/K_2CO_3/CH_2CN$, room temperature; c) **4**, K_2CO_3, 80°C



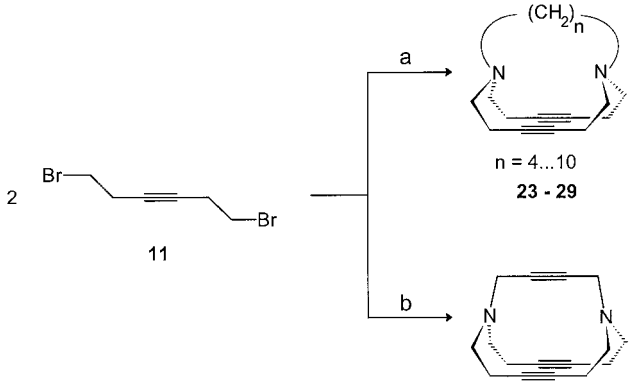
1,8-diazabicyclo[6.6.4]octadeca-4,11,16-triyne (**31**)[9] in 18% yield as a waxy solid.

Scheme 3. a) H_2/Lindlar catalyst/room temperature/16 h/90%



14 **15**

Scheme 4. a) α,ω-diaminoalkane [$H_2N(CH_2)_nNH_2$, **16**−**22**] with n = 4−10; b) 1,4-diamino-2-butyne (**30**)

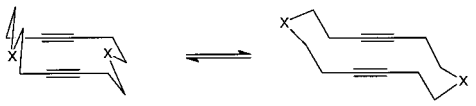


Structural Investigations

We were able to grow single crystals of **13a**, **14**,[9] **24** , **27**, and **31**[9] which allowed the study of their molecular structure in the solid state.

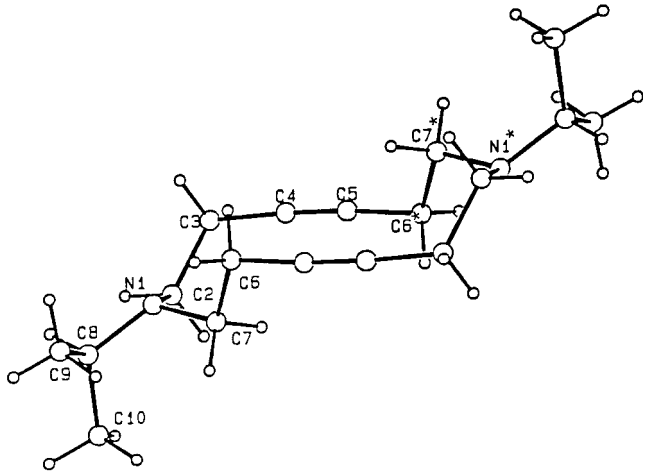
In the solid state the diyne **13a** adopts a chair-like conformation belonging to point group C_{2h}. The chains, consisting of the four sp^3-carbon atoms and the nitrogen atom, adopt not a zig-zag conformation as anticipated from 1,8-dioxacyclodeca-4,11-diyne[10] (Scheme 5) but an envelope conformation. The principle of minimization of the gauche interaction[11] does not seem to be followed in this case. Model calculations carried out on **4** suggest only small energy differences between both conformers shown in Scheme 5.

Scheme 5



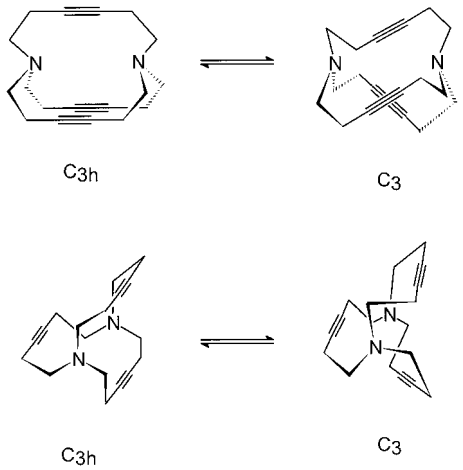
The strongest difference between the two conformers shown in Scheme 5 is encountered in the distance between the triple bonds. The transannular distance of the triple bonds in **13a** amounts to 3.853(2) Å which is considerably longer than in 1,6-diisopropyl-1,6-diazacyclodeca-3,8-diyne (**3**) [2.952(2) Å].[3] The distance between the triple bonds in **13a** is, however, sizeably shorter than in cyclotetradeca-1,8-diyne [4.641(2) Å][10] or in 1,8-dioxacyclotetradeca-4,11-diyne [4.707(3) Å].[10] The isopropyl groups in **13a** are oriented equatorially with respect of the C3/C2/N1/C7/C6 fragment (Figure 1).

Figure 1. Molecular structure of **13a**; selected bond lengths [Å] and angles [°]: N1−C2 1.457(2), N1−C8 1.474(2), C2−C3 1.529(2), C3−C4 1.468(2), N1···C4 3.160(2), N1···C5 3.977(2), C4−C5 1.187(2), C8−C9 1.515(2); C2−N1−C7 113.5(1), C2−N1−C8 112.4(1), C7−N1−C8 114.5(1), N1−C2−C3 114.5(1), C3−C4−C5 176.4(2)



The conformation of **14** can be derived by bridging the boat conformer of **4** by a 3-hexyne unit. This leads in a first step to a cage compound with C_{3h} symmetry, in which all triple bonds are oriented parallel to each other (Scheme 6). By rotation of one $N(CH_2)_3$ unit along the N···N axis as shown schematically in Scheme 6, the symmetry is reduced to C_3 and the originally parallel triple bonds are inclined towards each other. The boat conformation of each 14-membered ring in **14** is now relaxed into a boat-twist conformation. This reduces the strain energy by about 20 kJ/mol (MMX).[12]

Scheme 6



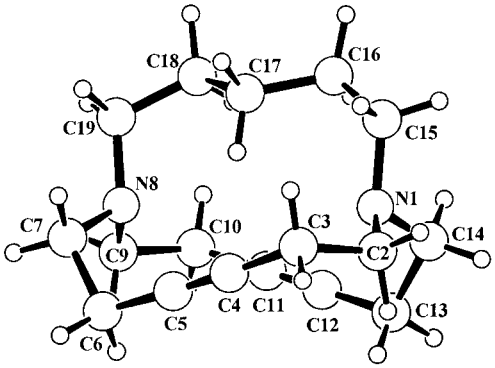
In the crystal **14** adopts C_3 symmetry, the inclination angle between two triple bonds amounts to 47.8°.[9] The nitrogen atoms at the bridgehead positions are pyramidalized (sum of the C−N−C angles is 344.4°) and point towards the inside of the cage, the distance between the two nitrogen atoms amounts to 5.049(3) Å. The bond angles at the sp

centers deviate only slightly (3.6°) from the linear arrangement. The activation energy for the transformation of **14** (C_3) into its mirror image was calculated (MMX[12]) to be 20 kJ/mol. In line with this result is the finding that in the ^{1}H-NMR spectrum of **14** there are two triplets at $\delta = 2.22$ and 2.41 which are not resolved even at 190 K. This points towards a fast interconversion of the axial and equatorial protons of the CH_2 groups.

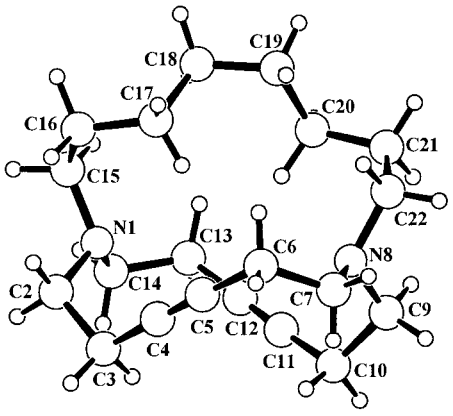
Analogous to **14** we can derive the conformation of **31** by starting with 1,8-diazacyclotetradeca-4,11-diyne in a boat conformation (C_{2v}) which is bridged by a 2-butyne unit. In the resulting triyne all three triple bonds are oriented parallel to each other (C_{2v} symmetry). The relaxation of the 14-membered ring into a twist-boat conformation reduces the symmetry to C_2. As a result the two triple bonds in the 14-membered unit are inclined by 48.6°.[9] The most important change between **14** and **31** is the increase of the C−N−C bond angles which makes the bridgeheads almost flat (sum of the C−N−C angles is 358.71 and 358.85°, respectively). The distance between the two nitrogen atoms is 4.99 Å.

The molecular structures of **24** and **27** both show a 14-membered ring in a twist-boat conformation in which the two triple bonds are inclined to each other by 30.7° (**24**) and 53.4° (**27**). The distances between the nitrogen atoms are 4.662(2) Å in the case of **24** and 5.189(2) Å in **27**. In both cases the nitrogen atoms are pyramidalized and the lone pairs point towards the inside of the cage. The sum of the C−N−C angles was found to be 341.0(1)/341.3(2)° for **24** and 338.4(1)/339.2(1)° for **27**.

Figure 2. Molecular structures of **24** and **27**; selected bond lengths [Å] and angles [°]: **24**: C4−C5 1.186(2), C11−C12 1.191(3), N1···N8 4.662(2), [C4−C5]···[C11−C12] 4.185; C7−N8−C9 111.9(2), C7−N8−C19 114.2(2), C9−N8−C19 115.2(2), C2−N1−C14 112.6(1), C2−N1−C15 114.7(1), C14−N1−C15 113.7(2); **27**: C4−C5 1.184(2), C11−C12 1.183(2), N1···N8 5.189(2), [C4−C5]···[C11−C12] 3.774; C7−N8−C9 112.6(1), C7−N8−C22 112.0(1), C9−N8−C22 113.8(1), C2−N1−C14 113.8(1), C2−N1−C15 113.2(1), C14−N1−C15 113.2(1)



24



27

Conclusion

The molecular structure of **13a** deviates considerably from all other 14-membered diynes investigated so far.[10] The chains between the triple bonds adopt an envelope conformation instead of a zig-zag arrangement. The bicyclic species **14**, **24**−**27** and **31** provide a series of medium-ring bicyclic systems[13] in which the 1,8-diazacyclotetradeca-4,11-diyne system adopts a twist-boat conformation. The X-ray investigations reveal for **14**, **23** and **29** that the substituents at the nitrogen atoms are pyramidalized and the lone pair points towards the inside of the cage. In the case of **31** the carbon atoms at the nitrogen atoms are situated in a plane with the nitrogen atom, providing a planar surrounding at the bridgehead positions.

We are grateful to the *Deutsche Forschungsgemeinschaft* (SFB 247), the *Fonds der Chemischen Industrie* and the *BASF Aktiengesellschaft*, Ludwigshafen, for financial support.

Experimental Section

General Methods: Moisture-sensitive reactions were conducted in oven-dried (150°C) glassware under argon. Solvents were distilled and dried under argon before use. Melting points: Dr. Tottoli apparatus (Büchi); uncorrected values. − Material used for column chromatography: Silica gel 60 (Merck, Macherey-Nagel). GLC: HP 5810 A instrument connected to a Shimadzu C-R 3A integrator. A capillary column Ultra 2 (PhMe Silicone, 25 m × 0.32 mm × 0.52 nm) was used with nitrogen as a carrier gas and a flame-ionization detector (FID). − ^{1}H NMR and ^{13}C NMR: Bruker WH 300 by using the solvent as internal standard. − IR: Perkin−Elmer 580B, Bruker, IFS 66 and Bruker IFS 88. − UV: Hewlett Packard HP 8452A. − High-resolution MS: ZAB high-resolution mass spectrometer (Fa. Vacuum Generators). − Elemental analyses were carried out by the Mikroanalytisches Laboratorium der Universität Heidelberg.

Trideca-3,10-diyne-1,13-diol (**7**) *and Undeca-1,3-diyn-1-ol* (**8**): To a suspension of 200 mg of iron(III) nitrate in 1000 ml of liquid ammonia, 6.2 g (893 mmol) of lithium wire was added at −50°C within 30 min. The resulting lithium amide suspension was stirred for another 30 min. Subsequently, 50 g of 1,8-nonadiyne (420 mmol) was added dropwise within 30 min and stirring commenced for 2 h, after which 95 g (2.16 mol) of crude ethylene oxide (precooled to −40°C) was added in portions at 5-min intervals. The mixture was stirred for another 50 h. The ammonia was removed by evaporation using a water bath and the residue dissolved in a mixture of 750 ml of water and 80 g of ammonium chloride. The

aqueous layer was extracted several times with diethyl ether. The combined organic layers were dried with pottassium carbonate, filtered and the solvent was evaporated. Purification by column chromatography (silica gel, cyclohexane/ethyl acetate 2:1) yielded 35 g (40%) of **7** (R_f = 0.12) and 13 g (19%) of **8** (R_f = 0.44). − **7**: White solid, mp 54.5°C. − ^{1}H NMR ($CDCl_3$): δ = 3.61 (q, 4 H, ^{3}J = 5.8 Hz, CH_2O), 2.63 (s, 2 H, OH), 2.36 (m, 4 H, CH_2) 2.15 (q, 2 H, ^{3}J = 2.3 Hz, $CH_2CH_2CH_2$), 1.42 (t, 8 H, ^{3}J = 9.9 Hz, $CH_2C{\equiv}CCH_2$). − ^{13}C NMR ($CDCl_3$): δ = 18.6 ($CH_2C{\equiv}C$), 23.1 ($CH_2C{\equiv}C$), 28.0 (CH_2), 28.4 (CH_2), 61.3 (CH_2O), 76.7 (C≡*C*), 82.1 (*C*≡C). − IR (KBr): $\tilde{\nu}$ = 2941 cm^{-1}, 2888, 2862, 2245, 1046. − UV/Vis ($CHCl_3$): λ_{max} (lg ε) = 242 nm (2.35). − HRMS (EI, 70 eV): $C_{13}H_{20}O_2$: calcd. 208.1463; found 208.1441. − **8**: Colourless oil. − ^{1}H NMR ($CDCl_3$): δ = 3.61 (dt, 2 H, $^3J_1$ = 1.3 Hz, $^3J_1$ = 5.0 Hz, CH_2O), 2.33−2.44 (m, 3 H, $CH_2C{\equiv}C$, OH), 2.12 (m, 4 H, CH_2-C≡C), 1.90 (s, 1 H, C≡CH), 1.45 (m, 6 H, CH_2). − ^{13}C NMR ($CDCl_3$): δ = 18.0 (CH_2), 18.4 (CH_2), 22.9 (CH_2), 27.6 (CH_2), 27.7(CH_2), 28.2 (CH_2), 61.1(CH_2O), 68.1(C≡*C*H), 76.4 (*C*≡CH), 82.0 (C≡*C*), 84.2 (*C*≡C). − UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 230 nm (1.62). − HRMS (EI, 70 eV): $C_{11}H_{16}O$: calcd. 164.1201; found 164.1243.

Trideca-3,10-diyne-1,13-diyl Bis(methanesulfonate) (**9**): To a solution of 10 g (48 mmol) of **7** in 200 ml of dry diethyl ether and 100 ml of dry tetrahydrofuran, 9.7 g (96 mmol) of triethylamine was added with cooling to 0°C by means of a salt/ice bath. 12.5 g (96 mmol) of methanesulfonyl chloride was added at such a rate that the temperature could be maintained at 0°C. After 45 min, the addition was complete and the suspension was stirred for 2 h. For workup, 100 ml of water was added and the organic layer was extracted with 5% sulfuric acid, saturated sodium hydrogen carbonate solution and water. The organic layer was dried with sodium sulfate and the solvent evaporated. Purification by column chromatography (silica gel; cyclohexane/ethyl acetate, 2:1) afforded 11.6 g (61%) of **9** as a yellow oil. − ^{1}H NMR ($CDCl_3$): δ = 1.45 (m, 6 H, CH_2), 2.20 (m, 4 H, $CH_2C{\equiv}C$), 2.59 (m, $C{\equiv}CCH_2$), 3.02 (s, 6 H, CH_3SO_2), 4.23 (t, CH_2O). − ^{13}C NMR ($CDCl_3$): δ = 18.5 ($C{\equiv}CCH_2$), 20.1 ($C{\equiv}CCH_2$), 28.0 (CH_2), 28.2 (CH_2), 37.6 (CH_3SO_2), 68.9 (CH_2O), 74.3 (*C*≡C), 82.8 (C≡*C*). − IR (KBr): $\tilde{\nu}$ = 3559 cm^{-1}, 2938, 1734, 1356, 1175, 963. − UV/Vis ($CHCl_3$): λ_{max} (lg ε) = 242 nm (1.25). − HRMS (EI, 70 eV): $C_{15}H_{24}O_6S_2$: calcd. 364.1014; found 364.1056.

1,13-Dibromotrideca-3,11-diyne (**10**): 40 g (465 mmol) of anhydrous lithium bromide was slowly added to 250 ml of dry acetone and stirred until a clear solution was obtained. A solution of 9 g (22.7 mmol) of **9** in 200 ml of dry acetone was added dropwise over a few minutes. The mixture was heated at reflux for 2−3 h and then 100 ml of water was added. The acetone was removed by evaporation and the residual aqueous layer was extracted intensively with ethyl acetate and the combined organic layers were concentrated. The oily residue was purified by column chromatography (silica gel; cyclohexane/ethyl acetate, 2:1 to yield 7.5 (97%) of **10** as a colourless oil. − ^{1}H NMR ($CDCl_3$): δ = 1.45 (m, 6 H, CH_2), 2.12 (m, 4 H, $CH_2C{\equiv}C$), 2.67 (m, 4 H, $C{\equiv}CCH_2$), 3.38 (t, 4 H, CH_2Br). − ^{13}C NMR ($CDCl_3$): δ = 18.4 ($C{\equiv}CCH_2$), 231 ($C{\equiv}CCH_2$), 27.8 (CH_2), 28.1 (CH_2), 30.1 (CH_2Br), 76.8 (*C*≡C), 82.2 (C≡*C*). − IR (KBr): $\tilde{\nu}$ = 2937 cm^{-1}, 2859, 2022, 1432, 1212, 641. − UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 232 nm (3.6). − HRMS (EI, 70 eV): $C_{13}H_{18}Br_2$: calcd. 333.9775; found 333.9787.

1-Azacyclotetradeca-4,11-diyne (**5**): 150 mL of liquid ammonia at −70°C was mixed with 150 ml of distilled acetonitrile. As soon as the first crystals of solidified acetonitrile appeared, 3 g (9.0 mmol) of **10** in 50 ml of acetonitrile was added quickly. The reaction vessel was put into a dry ice/methanol bath and kept at −70°C for 1 h. Without adding new dry ice the stirring was continued for 2 d. The mixture was neutralized with concd. hydrochloric acid and extracted several times with 1 N hydrochloric acid/saturated sodium chloride solution. The acidic layers were combined and added to 220 ml of dichloromethane. To the stirred mixture of both solutions a 5 N KOH solution was added at 0°C until pH = 12 was achieved. The extraction of the aqueous layer with dichloromethane and the evaporation of the solvents yielded a yellow-brown oil that was purified by column chromatography (aluminium oxide; ethyl acetate): R_f = 0.57. Yield: 180 mg (11%) of **5** as colourless plates, mp. 106°C. − ^{1}H NMR ($CDCl_3$): δ = 1.37 (m, 4 H, CH_2), 1.61 (m, 2 H, CH_2), 1.91 (s, 1 H, NH), 2.13 (t, 4 H, $C{\equiv}CCH_2$), 2.31 (t, 4 H, $C{\equiv}CCH_2$), 2.62 (t, 4 H, CH_2N). − ^{13}C NMR ($CDCl_3$): δ = 18.2 ($CH_2C{\equiv}C$), 19.9 ($CH_2C{\equiv}C$), 26.3 (CH_2), 27.1 (CH_2), 47.9 (CH_2N), 78.7 (*C*≡C), 81.5 (C≡*C*). − IR (KBr): $\tilde{\nu}$ = 3446 cm^{-1}, 2928, 2815, 2737, 1635, 1455, 1330, 1138, 1116, 770. − UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 232 nm (2.41). − HRMS (EI, 70 eV): $C_{13}H_{19}N$: calcd. 189.1596; found 189.1466.

1,8-Diazacyclotetradeca-4,11-diyne (**4**) *and 1,8-Diazabicyclo-[6.6.6]icosa-4,11,17-triyne* (**14**): A mixture of **1** and **14** was obtained when 2 g (8.33 mmol) of 1,6-dibromohexyne (**11**) in 50 ml of freshly distilled acetonitrile was mixed with 150 ml of liquid ammonia according to the procedure given for the preparation of **5**. Application of the described workup and subsequent chromatography [**4**: aluminium oxide; ethyl acetate; R_f(**4**) = 0.3; **1**: aluminium oxide; chloroform/methanol, 10:1; R_f(**1**) = 0.2] yielded **4** and **14** in a ratio of 17:1. − **4**: (250 mg, 32%), yellow crystals, mp. 117°C. − ^{1}H NMR ($CDCl_3$): δ = 2.30 (t, 8 H, $CH_2C{\equiv}C$), 2.57 (t, 8 H, CH_2N), 3.24 (s, 2 H, NH). − ^{13}C NMR ($CDCl_3$): δ = 19.1 ($CH_2C{\equiv}C$), 46.8 (CH_2N), 79.5 (*C*≡*C*). − UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 232 nm (3.08). − IR (KBr): $\tilde{\nu}$ = 3418 cm^{-1}, 3281, 2933, 2818, 1685, 1636, 1457, 1111, 771. − HRMS (EI, 70 eV): $C_{12}H_{18}N_2$ calcd. 190.1469; found 190.1434. − **14**: 21.5 mg (2%), yellow crystals, mp. 216°C. − ^{1}H NMR ($CDCl_3$): δ = 2.22 (t, 12 H, $CH_2C{\equiv}C$), 2.41 (t, 12 H, CH_2N). − ^{13}C NMR ($CDCl_3$): δ = 19.7 ($CH_2C{\equiv}C$), 53.4 (CH_2N), 79.7 (*C*≡*C*). − HRMS (EI, 70 eV): $C_{18}H_{24}N_2$: calcd. 268.1940; found 268.1942. − $C_{18}H_{24}N_2$ (268.19): calcd. C 80.55, H 9.01, N 10.44; found C 80.36, H. 9.10, N 10.40.

1,8-Diisopropyl-1,8-diazacyclotetradeca-4,11-diyne (**13a**): To a suspension of 10 g of potassium carbonate in 1000 ml of acetonitrile was added dropwise at room temperature within 16 h simultaneously 1.12 g (0.02 mmol) of isopropylamine and 5 g (20.8) mmol) of 1,6-dibromo-3-hexyne in 250 ml of anhydrous THF. After the addition was completed, the mixture was heated at 50°C for 20 h followed by refluxing for 24 h. To workup, a mixture of 400 ml of water, 20 ml of concd. H_3PO_4, and 20 ml of acetic acid was added quickly. After filtering, NaCl was added until two phases had formed. The organic phase was separated and extracted twice with a solution of 100 ml of H_2O/15 ml of H_3PO_4. Addition of 5 N KOH solution until pH = 12, repeated extraction with chloroform and removal of the solvent yielded a brown oil which was purified by column chromatography on aluminium oxide (neutral, 6% water) and petroleum ether/diethyl ether, 5:1. Yield: 70 mg (2.6%) of **13a** as colourless crystals, mp. 52°C. − ^{1}H NMR ($CDCl_3$): δ = 2.75 (m, 2 H, CH), 2.71 (t, 8 H, ^3J = 7.5 Hz, CH_2N), 2.42 (t, 8 H, ^3J = 7.4 Hz, $CH_2C{\equiv}C$), 0.96 (d, 12 H, ^3J = 7.5 Hz, CH_3). − ^{13}C NMR ($CDCl_3$): δ = 80.9 (*C*≡C), 52.3 (CHN), 49.5 (CH_2N), 20.8 ($CH_2C{\equiv}C$), 18.6 (CH_3). − UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 232 nm (3.37). − IR (KBr) $\tilde{\nu}$ = 2962 cm^{-1}, 2902, 2809, 1173. − HRMS (EI, 70 eV): $C_{18}H_{30}N_2$: calcd. 274.2409; found 274.2388. − $C_{18}H_{30}N_2$ (274.24): calcd. C 78.83, H 10.95, N 10.22; found C 78.61, H 11.02, N 10.11.

1,8-Diallyl-1,8-diazacyclotetradeca-4,11-diyne (**13b**): The compound was prepared according to **13a** by using 5 g (20 mmol) of 1,6-dibromo-3-hexyne and 1.2 g (21 mmol) of allylamine. The workup was done in the same manner. Chromatography on aluminium oxide with ethyl acetate yielded 725 mg (27%) of **13b** as a colourless oil which solidified in the refrigerator at about 4°C. – ^{1}H NMR ($CDCl_3$): δ = 5.82 (tt, 2 H, CH_2=C*H*CH_2N, $^3J_{cis}$ = 10.1 Hz, $^3J_{trans}$ = 16.1 Hz), 5.18 (t, 2 H, $^2J_{gem}$ = 2.5 Hz, C=CH_2), 5.10 (tt, 2 H, C=CH_2, $^2J_{gem}$ = 2.5 Hz, $^3J_{cis}$ = 10.1 Hz), 3.07 (d, 4 H, ^3J = 6.4 Hz, CH_2N), 2.75 (t, 8 H, ^3J = 6.0 Hz, CH_2N), 2.30 (t, 8 H, ^3J = 6.0 Hz, CH_2C≡C). – ^{13}C NMR ($CDCl_3$): δ = 136.7 (C=C), 117.4 (C=CH_2), 79.8 (*C*≡C), 57.2 (CHN), 51.8 (CH_2N), 17.5 (*C*H_2C≡C). – UV/Vis (CH_2Cl_2) : λ_{max} (lg ε) = 322 nm (1.76). – IR (KBr): $\tilde{\nu}$ = 3075 cm^{-1}, 3003, 2975, 2810, 1641, 1454, 1420, 1380, 1357, 1333, 1282, 1145, 1112, 1031, 1011, 995, 915. – HRMS (EI, 70 eV): $C_{18}H_{26}N_2$: calcd. 270.2096; found 270.2043.

1,8-Diazabicyclo[6.6.6]icosa-4,11,16-triyne (**14**) *from 1,8-Diazacyclotetradeca-4,11-diyne* (**4**): Solutions of 400 mg (2.1 mmol) of **4** and 500 mg (2.1 mmol) of 1,6-dibromo-3-hexyne (**11**) each in 250 ml of dry acetonitrile were added dropwise to the stirred slurry of 1 g (7.1 mmol) of potassium carbonate in 1 l of acetonitrile at a rate of approx. 2 drops/s at reflux temperature. After 24 h, one half of the solvent was removed within 5 h by distillation. The total reaction time was 120 h. Application of the above workup (see **5**) and subsequent chromatography led to 200 mg (35%) of **14** as yellow crystals. – Analytical data of **14** see above.

1,8-Diazabicyclo[6.6.6]icosa-4,11,17-triene (**15**): 45 mg (0.17 mmol) of 1,8-diazabicyclo[6.6.6]icosa-4,11,17-triyne (**14**) in 70 ml of distilled methanol and 5 mg of Lindlar's catalyst[8] were stirred under hydrogen (0.05 bar) for 16 h at room temperature. The mixture was filtered through aluminium oxide (neutral, 6% H_2O) in a glovebox and the solvent removed in vacuo. It resulted in 45 mg (95%) of **15** as a colourless, very labile oil that rapidly absorbed carbon dioxide and water and decomposed fast on air exposure. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.42–5.62 (m, 8 H, HC=CH), 2.71 (s, 12 H, CH_2N), 2.26–2.30 (m, 12 H, CH_2C=C). – ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.4 (CH_2C=C), 58.9 (CH_2N), 129.2 (C=C). – HRMS (EI, 70 eV): $C_{18}H_{30}N_2$: calcd. 274.2409; found 274.2484; [M – 1]: calcd. 273.2331; found 273.2335.

General Procedure for the Cyclization of α,ω-Diamines with 1,6-Dibromo-3-hexyne 12 to the Bicyclic Diynes **23**–**29**: 4 g (16.7 mmol) of dibromo-3-hexyne (**11**) and 5 mmol of the diamine **16**–**22** were added at once to a suspension of 10 g (72.5 mmol) of finely powdered potassium carbonate in 300 ml of dry acetonitrile at room temperature. The mixture was stirred intensively and refluxed for 16–72 h until all starting material was consumed. Subsequently, the mixture was cooled, filtered and extracted with 1 N HCl in brine. The combined aqueous layers were stirred with 200 ml of $CHCl_3$ and alkalized with 5 N KOH solution. The phases were separated and the aqueous phase was extracted twice with $CHCl_3$. The solvent was removed in vacuo and the residue was purified by chromatography on aluminium oxide.

23: 221 mg (15%), R_f = 0.05; cyclohexane/ethyl acetate, 5:1: mp. 58°C. –^{1}H NMR ($CDCl_3$): δ = 2.44–2.66 (m, 8 H, CH_2N), 2.45 (t, 4 H, CH_2N), 2.13–2.35 (m, 8 H, CH_2C≡C), 1.65 (tt, 4 H, CH_2). – ^{13}C NMR ($CDCl_3$): δ = 20.0 (*C*H_2C≡C), 28.1 (CH_2), 54.8 (CH_2N), 55.3 (CH_2N), 81.5 (*C*≡*C*). – UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 226 nm (3.99). – IR (KBr): $\tilde{\nu}$ = 2946 cm^{-1}, 2900, 2804, 2230, 1456, 1354, 1283, 1131, 1014, 725. – HRMS (EI, 70 eV): $C_{16}H_{24}N_2$: calcd. 244.1940; found 244.1942.

24: 220 mg (16%), R_f = 0.36; cyclohexane/ethyl acetate, 5:1; mp. 85°C. – ^{1}H NMR ($CDCl_3$): δ = 1.32–1.41 (m, 4 H, CH_2), 2.07 (q, 2 H, CH_2), 2.17–2.31 (m, 8 H, CH_2C≡C), 2.32–2.40 (m, 4 H, CH_2N), 2.41–2.56 (m, 8 H, CH_2N). – ^{13}C NMR ($CDCl_3$): δ = 19.2 (*C*H_2C≡C), 22.9 (CH_2), 29.4 (CH_2), 53.8 (CH_2N), 54.3 (CH_2N), 80.0 (*C*≡*C*). – UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 226 nm (3.94). – IR (KBr): $\tilde{\nu}$ = 3441 cm^{-1}, 2899, 2792, 2228, 1631, 1457, 1373, 1335, 1134, 1039, 717. – HRMS (EI, 70 eV): $C_{17}H_{26}N_2$: calcd. 258.2096; found 258.2117.

25: 143 mg (18%), R_f = 0.45; cyclohexane/ethyl acetate, 5:1; mp. 120°C. – ^{1}H NMR ($CDCl_3$): δ = 1.38 (t, 8 H, CH_2C≡C), 1.63 (m, 8 H, CH_2), 2.25 (m, 12 H, CH_2N). – ^{13}C NMR ($CDCl_3$): δ = 18.0 (*C*H_2C≡C), 27.3 (CH_2), 27.4 (CH_2), 52.1 (CH_2N), 52.5 (CH_2N), 79.5 (*C*≡*C*). – UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 232 nm (3.54). – IR (KBr): $\tilde{\nu}$ = 2905 cm^{-1}, 2785, 1632, 1456, 1379, 1274, 1134, 1032, 718. – HRMS (EI, 70 eV): $C_{18}H_{28}N_2$: calcd. 272.2253; found 272.2234.

26: 199 mg (17%), R_f = 0.72; cyclohexane/ethyl acetate, 1:2; mp. 102°C. – ^{1}H NMR ($CDCl_3$): δ = 1.36–1.57 (m, 10 H, CH_2), 2.14–2.25 (m, 12 H, CH_2C≡C, CH_2N), 2.27–2.41 (m, 8 H, CH_2N). – ^{13}C NMR ($CDCl_3$): δ = 18.7 (*C*H_2C≡C), 26.5 (CH_2), 27.0 (CH_2), 28.0 (CH_2), 53.6 (CH_2N), 53.9 (CH_2N), 79.3 (*C*≡*C*). – UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 232 (3.98). – IR (KBr): $\tilde{\nu}$ = 3436 cm^{-1}, 2903, 2798, 2235, 1631, 1459, 1331, 1281, 1152,1129, 1020, 746. – HRMS (EI, 70 eV): $C_{19}H_{30}N_2$: calcd. 285.2331; found 285.2332.

27: 370 mg (23%), R_f = 0.71; cyclohexane/ethyl acetate, 1:2; mp. 73°C. – ^{1}H NMR ($CDCl_3$): δ = 1.24–1.30 (m, 4 H, CH_2), 1.33–1.41 (m, 4 H, CH_2), 1.62 (tt, 4 H, CH_2), 2.15–2.45 (m, 20 H, CH_2C≡C, CH_2N). – ^{13}C NMR ($CDCl_3$): δ = 19.0 (*C*H_2C≡C), 24.2 (CH_2), 27.1 (CH_2), 27.1 (CH_2), 53.4 (CH_2N), 53.7 (CH_2N), 79.4 (*C*≡*C*). – UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 224 nm (3.92). – IR (KBr): $\tilde{\nu}$ = 3439 cm^{-1}, 2898, 2801, 2229, 1632, 1458, 1373, 1330, 1273, 1127, 1031, 709. – HRMS (EI, 70 eV): $C_{20}H_{32}N_2$: calcd. 300.2566; found 300.25.68.

28: 300 mg (23%), R_f = 0.78; cyclohexane/ethyl acetate, 1:1; mp. 80°C. – ^{1}H NMR ($CDCl_3$): δ = 1.34–1.48 (m, 10 H, CH_2), 1.5–1.63 (m, 4 H, CH_2), 2.15–2.40 (m, 16 H, CH_2C≡C, CH_2N), 2.41–2.52 (m, 4 H, CH_2N). – ^{13}C NMR ($CDCl_3$): δ = 19.4 (*C*H_2C≡C), 25.0 (CH_2), 27.1 (CH_2), 28.3 (CH_2), 29.5 (CH_2), 54.0 (CH_2N), 54.4 (CH_2N), 79.5 (*C*≡*C*). – UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 224 nm (3.98). – IR (KBr): $\tilde{\nu}$ = 3444 cm^{-1}, 2930, 2804, 2229, 1632, 1457, 1371, 1331, 1282, 1123, 1021, 728, 547. – HRMS (EI, 70 eV): $C_{21}H_{34}N_2$: calcd. 314.2722; found 314.2684.

29: 239 mg (13%), R_f = 0.43; cyclohexane/ethyl acetate, 10:1; mp. 93°C. – ^{1}H NMR ($CDCl_3$): δ = 1.31 (m, 8 H, CH_2), 1.40 (m, 8 H, CH_2), 2.18–2.28 (m, 16 H, CH_2C≡C, CH_2N), 2.44 (t, 4 H, CH_2N). – ^{13}C NMR ($CDCl_3$): δ = 19.2 (*C*H_2C≡C), 25.7 (CH_2), 26.9 (CH_2), 27.5 (CH_2), 27.7 (CH_2), 53.9 (CH_2N), 54.9 (CH_2N), 79.7 (*C*≡*C*). – UV/Vis (CH_2Cl_2): λ_{max} (lg ε) = 234 nm (3.69). – IR (KBr): $\tilde{\nu}$ = 3441 cm^{-1}, 2922, 2801, 1632, 1459, 1371, 1336, 1123, 1031, 718. – HRMS (EI, 70 eV): $C_{21}H_{34}N_2$: calcd. 328.2879; found 328.2828.

X-ray Diffraction Analyses: The reflections were collected with a Nonius CAD4 diffractometer (Mo-K_α radiation, graphite monochromator, ω-2Θ scan). Intensities were corrected for Lorentz and polarization effects. All structures were solved by direct methods (**24**: SHELXS-97;[14] **13a** and **27**: SIR-92[15]). The structural parameters of the non-hydrogen atoms were refined anisotropically according to a full-matrix least-squares technique (F^2). The parameters of the hydrogen atoms were refined isotropically. Refinement was carried out with SHELXL[16] (**24** and **27**) and LSFM MOLEN[17] (**13a**). Table 1 contains the crystallographic data and

Table 1. Crystallographic data of **13a**, **24** and **27**

Compound	**13a**	**24**	**27**
Empirical formula	$C_{18}H_{30}N_2$	$C_{17}H_{26}N_2$	$C_{20}H_{32}N_2$
Molecular mass [g/mol]	274.45	258.4	300.5
Crystal size [mm]	0.3 × 0.3 × 0.15	0.4 × 0.4 × 0.25	0.44 × 0.44 × 0.44
Crystal colour	colourless	colourless	yellow
Crystal shape	plates	plates	prism
Space group	*Pbca*	$P2_1/c$	*P*1
a [Å]	12.092(3)	11.482(2)	7.748(1)
b [Å]	8.158(3)	14.735(2)	9.834(1)
c [Å]	17.139(6)	9.066(1)	12.588(2)
α [°]	90	90	91.53(1)
β [°]	90	90.67(1)	91.58(1)
γ [°]	90	90	105.29(1)
V [Å^3]	1691(1)	1533.7(4)	924.3(2)
$D_{calcd.}$ [Mg/m^3]	1.08	1.12	1.08
Z	4	4	2
F(000)	608	568	332
T [K]	294	223	293
h_{min}/h_{max}	0/14	0/15	0/10
k_{min}/k_{max}	0/9	0/19	−12/12
l_{min}/l_{max}	0/20	−11/11	−16/16
$(\sin\Theta/\lambda)_{max}$ [Å^{-1}]	0.62	0.66	0.66
μ [mm^{-1}]	0.06	0.07	0.06
Refl. collected	1563	3852	4765
Refl. unique	1563	3682	4439
Refl. observed [$I > 2\sigma(I)$]	1216	2390	2864
Variables	151	276	327
$(\Delta/\sigma)_{max}$	< 0.01	< 0.01	< 0.01
R	0.039	0.054	0.050
R_w	0.042	0.136	0.130
S (Gof)	1.90	1.07	1.18
$(\Delta\rho)_{max}$ [e Å^{-3}]	0.12	0.46	0.15
$(\Delta\rho)_{min}$ [e Å^{-3}]	−0.14	−0.18	−0.21

details of the refinement procedure. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101209. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-1223/336-033, E-mail: deposit@ccdc.cam.ac.uk].

[1] [1a] R. K. Harris, R. A. Spragg, *J. Chem. Soc. B* **1968**, *684*. – [1b] R. O. Hutchins, D. L. Kopp, E. L. Eliel, *J. Am. Chem. Soc.* **1968**, *90*, 7174. – [1c] P. J. Crowley, M. J. T. Robinson, M. G. Ward, *Chem. Soc., Chem. Commun.* **1974**, *825*. – [1d] E. L. Eliel, F. W. Vierhapper, *J. Am. Chem. Soc.* **1975**, *97*, 2424. – [1e] D. C. Appleton, J. McKenna, J. M. McKenna, L. B. Sims, A. R. Walley, *J. Am. Chem. Soc.* **1976**, *98*, 292. – [1f] F. A. Anet, I. Yavari, *Tetrahedron Lett.* **1976**, *17*, 2093. – [1g] F. A. Anet, I. Yavari, *J. Am. Chem. Soc.* **1977**, *99*, 2794.

[2] Reviews: [2a] J. B. Lambert, S. I. Featherman, *Chem. Rev.* **1975**, *75*, 611. – [2b] I. D. Blackburne, A. R. Katritzky, Y. Takeuchi, *Acc. Chem. Res.* **1975**, *8*, 300. – [2c] M. Rubiralta, E. Giralt, A. Diez, *Piperidine*, Elsevier, Amsterdam, **1991**. – [2d] J.-J. Delpuech in *Cyclic Organonitrogen Stereodynamics* (Eds.: J. B. Lambert, Y. Takeuchi, Eds), Verlag Chemie, Weinheim, **1992**, chapter 7. – [2e] T. A. Crabb, A. R. Katritzky, *Adv. Heterocycl. Chem.* **1984**, *36*, 3.

[3] J. Ritter, R. Gleiter, H. Irngartinger, T. Oeser, *J. Am. Chem. Soc.* **1997**, *119*, 10599.

[4] R. Gleiter, K. Hövermann, J. Ritter, B. Nuber, *Angew. Chem.* **1995**, *107*, 867; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 789.

[5] W. N. Smith, O. F. Beumel, *Synthesis* **1974**, 441.

[6] H. Musso, M. Brudermüller, *Chem. Ber.* **1988**, *121*, 2239.

[7] R. Gleiter, V. Wolfart, *Tetrahedron Lett.* **1996**, *37*, 479.

[8] H. Lindlar, *Helv. Chim. Acta* **1952**, *35*, 446; N. A. Dobson, G. Eglinton, M. Krishnamurti, R. A. Raphael, R. G. W. Illis, *Tetrahedron* **1961**, *16*, 16.

[9] V. Wolfart, R. Gleiter, C. Krieger, H. Pritzkow, *Tetrahedron Lett.* **1998**, *39*, 513.

[10] R. Gleiter, M. Ramming, H. Weigl, V. Wolfart, H. Irngartinger, T. Oeser, *Liebigs Ann.* **1997**, 1545.

[11] J. Dale, *Angew. Chem.* **1966**, *78*, 1070; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 1000.

[12] *SPARTAN*, IBM Release 3.1.7.

[13] R. W. Alder, S. P. East, *Chem. Rev.* **1996**, *96*, 2097; R. W. Alder, *Tetrahedron* **1990**, *46*, 683; *Acc. Chem. Res.* **1983**, *16*, 3d.

[14] G. M. Sheldrick, *SHELXS-97*, Universität Göttingen, Germany, **1997**.

[15] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *SIR-92*, Ist. di Ric. per lo Sviluppo di Metodologie Cristallografiche, CNR, Univ. of Bari, Italy, **1992**.

[16] G. M. Sheldrick, *SHELXL-93* and *SHELXL-97*, Universität Göttingen, Germany, **1993** and **1997**.

[17] C. K. Fair, MOLEN, Enraf−Nonius, Delft, The Netherlands, **1990**.

[O98302]