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Synthesis of Cycloalkadiynes of Various Ring Size

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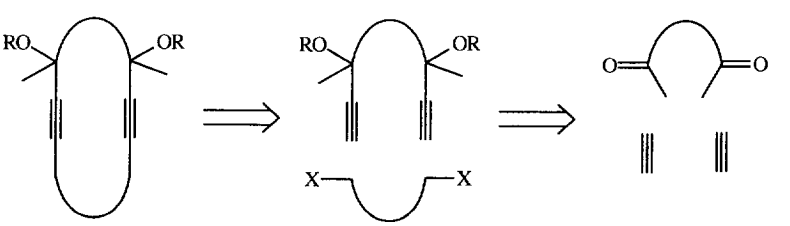
Abstract: The synthesis of the 10-, 11-, 13-, 14- and 16-membered cycloalkadiynes **3a-b**, **4a-b**, **6a-b**, **7a-b**, **10a-b** and **11a-b** containing functional groups either in two propargylic or two homopropargylic positions is described. The key step of the synthetic scheme is the DMPU assisted double alkylation of two terminal alkyne units leading to the carbocycles mentioned above in moderate to good yield via a three step pathway. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction: The interest in medium sized carbocycles is due to the fact that calicheamycine, neocarzinostatin and similar antitumor agents contain a medium sized enediyne ring as the active functionality,[1-3] that dehydroannulenes and expanded radialenes have special properties as building blocks for nanomaterials[4] and that many transition metals show novel transannular reactivity with such compounds as substrates or ligands.[5] We recently reported on the synthesis of substituted cyclododeca-1,7- and -1,5-diynes and their transformation into cyclic dienes, diallenes and alleneynes.[6,7] Here we report the synthesis of 10-, 11-, 13-, 14- and 16-membered functionalized cycloalkadiynes **3a-b**, **4a-b**, **6a-b**, **7a-b**, **10a-b** and **11a-b**.

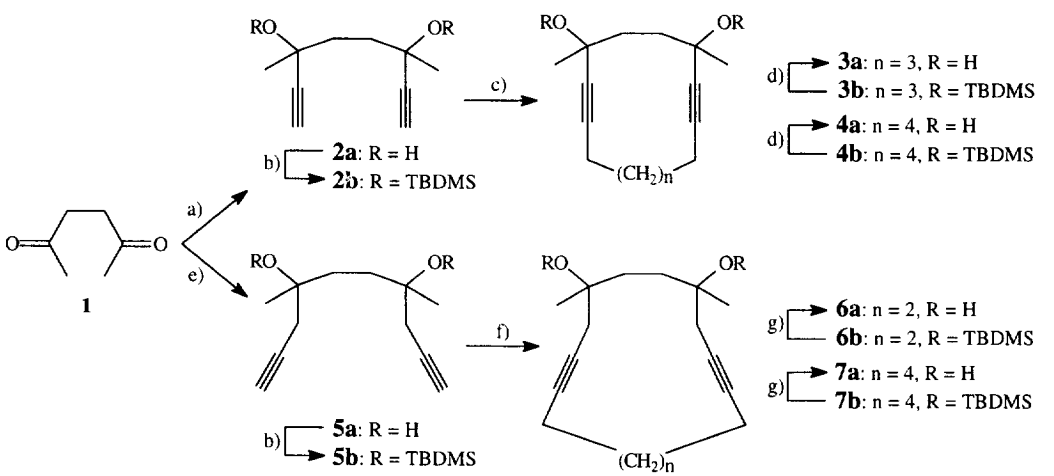
The synthetic approach for the preparation of these ring systems was shaped according to Scheme 1.[8] It involves the preparation of terminal dialkynes and their reaction with 1,ω-dihalides. The key step of this synthetic pathway is the formation of the carbocycle by a double alkylation of the terminal dialkynes, which is strongly enhanced by the presence of DMPU. This was tested in the synthesis of cyclododecadiynes: In the presence of DMPU the cyclisation step gave yields up to 55% compared to 13% without the addition of DMPU.[6]

Scheme 1



Results and Discussion: The diyne-diols **2a** and **5a** were each obtained in a ratio of *meso* : *rac.* ~ 1:1 in high yields by the reaction of acetonylacetone with HC≡CMgBr and HC≡CCH_2MgBr respectively. After silylation with TBDMSi triflate, the resulting silyloxy compounds **2b** and **5b** were deprotonated with n-BuLi in THF and treated with various 1,ω-dibromides in the presence of DMPU to give the carbocycles **3b**, **4b**, **6b** and **7b**. The reactivity of the alkyne terminii in these alkylative cyclisations was strongly dependent on the substitution pattern of the precursors. While **2b** with substituents in the propargylic positions could be cyclised at room temperature to the 13-membered ring compound **3b** in 35% yield and to the 14-membered cycloalkadiyne **4b** in 37% yield, no reaction took place under these conditions with compound **5b** with substituents in the homopropargylic positions. In this case the cyclisation required temperatures of 40-45°C. The 14-membered ring **6b** and the 16-membered ring **7b** could subsequently be obtained in 9% and in 14% yield, respectively. According to GC analyses all cycloalkadiynes were formed as ~ 1:1 diastereomeric mixtures. Deprotection of the silyloxy compounds **3b** and **4b** with TBAF gave the corresponding diols **3a** and **4a** readily at r.t., whereas reflux for 6 days and 12 eq TBAF were required for the deprotection of **6b** and **7b**.

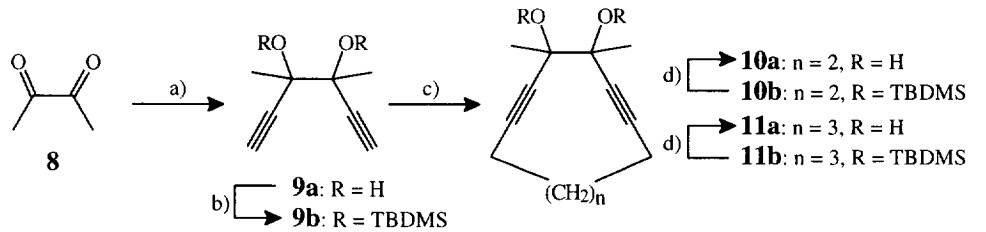
Scheme 2



a) HC≡CMgBr, THF, -20°C to r.t.; b) TBDMSi triflate, NEt_3, THF; c) **3b**: 2 n-BuLi, DMPU, 1,5-dibromopentane; **4b**: 2 n-BuLi, DMPU, 1,6-dibromohexane; d) TBAF, THF, r.t., 4d; e) HC≡CCH_2MgBr, ether, -20°C to r.t.; f) **6b**: 2 n-BuLi, DMPU, 1,4-dibromobutane; **7b**: 2 n-BuLi, DMPU, 1,6-dibromohexane; g) TBAF, THF, reflux, 6d.

The synthesis of the 10- and 11-membered cycloalkadiynes **10b** and **11b**, which are potential enediyne precursors, started with the addition of HC≡CMgBr to diacetyl **8**. The diol **9a** (*meso* : *rac.* ~ 1:1) was protected with TBDMSi triflate to give **9b** in an isolated yield of only 31%. This might be due to steric interactions between the two bulky TBDMS groups. In addition to **9b**, the monosilylated byproduct was obtained in 48% yield.[9]

Scheme 3



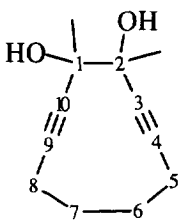
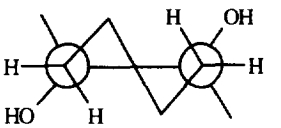
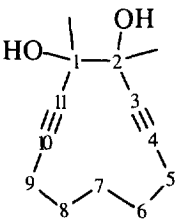
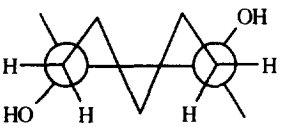
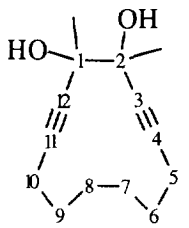
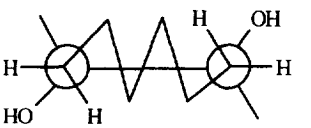
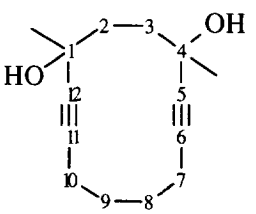
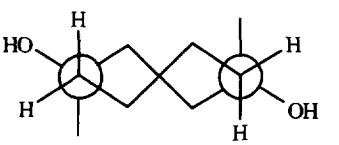
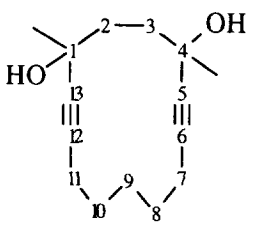
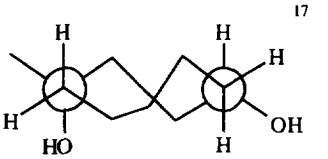
a) HC≡CMgBr, THF, -20°C to r.t.; b) TBDMSi triflate, NEt_3, THF; c) **10b**: 2n-BuLi, DMPU, 1,4-dibromobutane; **11b**: 2 n-BuLi, DMPU, 1,5-dibromopentane; d) TBAF, THF, r.t., 24h.

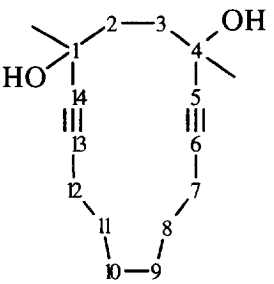
The cyclisation of **9b** with 1,4-dibromobutane in the presence of DMPU to **10b** was achieved at 45°C. Compound **10b** could be isolated in 9% yield as a single diastereomer. According to GC analyses with a chiral stationary phase after deprotection of **10b**, only the racemic isomer of the diol **10a** was detected.

Under the same conditions the alkylation of **9b** with 1,5-dibromopentane gave the 11-membered ring **11b** in 23% yield as a mixture of the diastereomers. According to GC analysis of the diol **11a** with a chiral stationary phase the ratio *meso* : *rac.* turned out to be ~ 1:5, which shows the preferential formation of the racemic isomer similar to the result described for **10a**. In the recently described cyclisation of **9b** with 1,6-dibromohexane the two diastereomers of the 12-membered ring compound were obtained as a ~ 1:1-mixture of the diastereomers.[6] These results clearly indicate that the diastereoselectivity in the cyclisation reaction of **9b** depends strongly on the ring size to be formed.

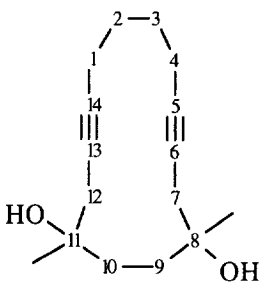
Structure: The cyclic structures of **3a-b**, **4a-b**, **6a-b**, **7a-b**, **10a-b** and **11a-b** are confirmed by their ^{13}C NMR spectra, which show two sets of signals for the ring scaffold of the 13-, 14- and 16-membered rings with a ~ 1:1 intensity. Only one set of ^{13}C NMR signals was found in the case of **10a-b** and two sets with the intensity of ~ 3:1 in the case of **11a-b**. Further evidence for the 13-membered ring system of **3a** is provided by the X-ray structure analysis of the *meso*-isomer.[10] The geometry of the triple bonds deviates slightly from the linear arrangement. The bond lengths of the triple bonds are in the expected range of 1.18-1.19Å. These structural features are well within the range determined for the 12-membered ring analogues.[11,12] At room

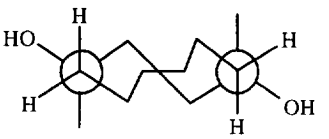
Table 1: Conformational Analysis of Cycloalkadiynes of Various Ring Size, AM1-results (* X-ray data)

Formulae	Twist angles (°)	Torsion angles (°)	Conformations
	12.9	C_{10}-C_1-C_2-C_1 -22.6 C_5-C_6-C_7-C_8 -115.7	 *rac.*-**10a**
	19.2	C_{11}-C_1-C_2-C_3 -40.7 C_5-C_6-C_7-C_8 126.1 C_6-C_7-C_8-C_9 -140.9	 *rac.*-**11a**
	25.1	C_{12}-C_1-C_2-C_3 -43.5 C_5-C_6-C_7-C_8 -92.9 C_6-C_7-C_8-C_9 147.8 C_7-C_8-C_9-C_{10} -160.7	 *rac.*-**12**
	26.9	C_1-C_2-C_3-C_4 -142.4 C_7-C_8-C_9-C_{10} 139.8 C_1-C_2-C_3-C_4* 146.8 C_7-C_8-C_9-C_{10}* 145.7	[16]  *rac.*-**13**
	27.1	C_1-C_2-C_3-C_4 159.8 C_7-C_8-C_9-C_{10} 166.5 C_8-C_9-C_{10}-C_{11} 147.7 C_1-C_2-C_3-C_4* -154.6 C_7-C_8-C_9-C_{10}* 166.9 C_8-C_9-C_{10}-C_{11}* 159.4	[17]  *meso*-**3a**

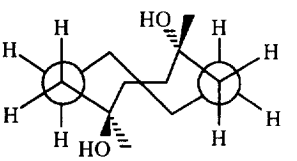


35.7	C_1-C_2-C_3-C_4 -163.6 C_7-C_8-C_9-C_{10} -175.3 C_8-C_9-C_{10}-C_{11} -81.6 C_9-C_{10}-C_{11}-C_{12} -91.8
32.6	C_1-C_2-C_3-C_4 -163.4 C_7-C_8-C_9-C_{10} -171.5 C_8-C_9-C_{10}-C_{11} -122.3 C_9-C_{10}-C_{11}-C_{12} -75.9





rac.-**4a**



rac.-**6a**

temperature the X-ray analysis of **3a** shows two conformations in a ~7:3 ratio, whereas only one conformation is detected at -80°C. The behaviour of the 13-membered ring system with its two conformations for the unsubstituted methylene chain of the molecule at room temperature, is in agreement with the general conformational behaviour of medium sized ring systems, which allows conformational changes involving only parts of the molecule.[13] Moreover AM1-calculations of the cyclic diynediols give results very similar to the X-ray structures.

In the 10-14-membered ring systems **10a**, **11a**, **12**, **13**, **3a**, **4a** and **6a** the two alkyne units show a crossed arrangement with twist angles in the range of 12.9° - 35.7°. This shows the tendency of an increasing twist angle by the introduction of one elongated methylene chain between the two triple bonds. For the 12 membered ring system of **13**, the determined value of 26.9° for the twist angle is in good agreement with that of unsubstituted cycldoedeca-1,7-diyne.[15] Whereas all cyclodeca-1,6-diynes show a coplanar arrangement of the two triple bonds,[14] a twist angle of 12.9° has been calculated for the 10-membered 1,5-diyne **10a**. This is most likely due to the substituents at the ethylene bridge, which induce a staggered conformation and hence a twist for the adjacent alkyne groups. The alkylene chains in the cyclic dialkynes **3a**, **4a**, **6a**, **10a**, **11a**, **12** and **13** have conformations with at least one dihedral angle in the range described for medium sized cycloalkanes.[13] Relative to each other, the two alkylene chains adopt a crossed arrangement in these cyclic dialkynes (cf. Table 1). Ignoring the twist of the two alkyne groups, the crossed arrangement of the alkylene

chains in **4a** and **6a** can be sketched in an idealised view as shown in Table 1. This arrangement is almost independent of whether the substituents are located in the propargylic positions of the butylene chain or in the homopropargylic positions of the hexylene chain. Due to the quasi-equatorial attachment of both alkylene chains to the alkyne group the molecules are rather "flat".

Concluding remarks: Our results show the general applicability of the described strategy for the synthesis of medium sized functionalized cycloalkadiynes. According to our experience,[6] the yields of the cyclisation reactions are strongly increased by the presence of DMPU. Substitution of the cyclisation precursors by silyloxy groups in the propargylic positions enhances the reactivity of the alkyne terminii in the alkylative cyclisation compared to substitution by silyloxy groups in the homopropargylic positions. This is also reflected in the deprotection where the homopropargylic silyloxy groups are more resistent towards the reaction with F^--ions. The short synthetic pathway leading to the functionalized cycloalkadiynes calls for an investigation of their transannular reactivity.

EXPERIMENTAL

General: Melting points were determined on a *Büchi 510* melting point apparatus and are uncorrected. IR spectra were measured in $CHCl_3$ (recorded on a *Perkin-Elmer-782* IR spectrophotometer). NMR spectra were measured in $CDCl_3$ or d_6-acetone (recorded on a *Bruker AC 300* spectrometer [^1H, 300 MHz; ^{13}C, 75 MHz]). Chemical shifts are given in (δ) ppm relative to internal $CHCl_3$ δ(7.27) or d_6-acetone δ(2.04) for ^1H NMR and $CDCl_3$ δ(77.0) or d_6-acetone δ(29.8) for ^{13}C NMR. Multiplicities are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet m = multiplet, and st = stack. Mass spectra (MS) were determined on a *Varian MAT CH7A* (70eV, EI) and a *Fisons Autospec Q* spectrometer and are reported in units of *m/z* and in relative intensities to the base peak. GC-MS were performed on a *VG Autospec* spectrometer. Reactions were normally performed under an Ar or N_2 atmosphere. After work up by pouring the reaction mixture onto sat. NH_4Cl solution and extraction with ether, the solutions were dried over $MgSO_4$. Thin layer chromatography was performed on silicagel plates SIL G/UV_{254} (*Macherey & Nagel*); solvents used: *1*(ether), *2*(hexane/ether), *3*(hexane/ethyl acetate), *4*(pentane). GC analysis were performed on a *Hewlett Packard HP-5890* instrument (He, 43kPa) with a HP-5 Ultra capillary column (length 10m, i.d. 0.2mm) with a temperature program 40-220°C (3°/min), t_r in min.. Chiral analyses: *Hewlett Packard HP-5890* instrument (He, 100kPa) with modified cyclodextrins as chiral stationary phase and variable temperature programs; column *A*: 10m, 30% octakis-{2,3-di-O-acetoxy-6-O-[(*tert*-butyl)-dimethylsilyl]}-γ-cyclodextrin in OV 1701; column *B*: 25m, 40% heptakis-{2,3-di-O-ethyl-6-O-[(*tert*-butyl)-dimethylsilyl]}-β-cyclodextrin in OV 1701. Preparative HPLC was performed with a 715004 ET, 250/10, Nuc. 50-7 column (*Macherey & Nagel*), flow: 12 ml/min.

Chemicals were purchased from commercial suppliers and used without further purification. THF was dried by distillation from sodium, diethyl ether from sodium hydride. Acronyms used: TBME: *tert*-Butyl-methyl ether; TBDMSi: *tert*-Butyl-dimethyl-silyl; DMPU: 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone; TBAF: Tetrabutylammonium fluoride Trihydrate.

***Preparation of the acyclic diyne-diols* 2a, 5a *and* 9a**

***3,6-Dimethyl-octa-1,7-diyne-3,6-diol* (2a):** Ethyne was bubbled through 100 ml THF for 45 min at 0°C. After addition of 18.68 ml (52.5 mmol) C_2H_5MgBr, obtained from 1.90 g (80 mmol) Mg and 8.10 g (75 mmol) C_2H_5Br in THF, at T < +3°C by syringe techniques and stirring for 1 h, a solution of 2 g (17.5 mmol) acetonylacetone in 8 ml THF was added at -20°C. After stirring for 12 h at r.t. and work up, a yellow powder was obtained, which after crystallization from TBME-hexane gave **2a** as a white powder in a yield of 2.69 g (92.5%). Mp.: 83-84°C. R_f (*1*): 0.54. GC: t_R 12.28 and 12.69 (~1:1); column *A*; t_R 25.02 and 33.82 (48%, 1:1, *rac.*), 27.18 (52%, *meso*). IR: 3510*s*; 3115*vs*; 2995*s*; 2940*s*; 1380*s*; 1285*s*; 1243*s*; 1110*s*; 1070*s*; 920*s*; 661*vs*; 643*vs*. ^{1}H NMR: 1.48(s, 2x3H); 1.49(s, 2x3H); 1.77-2.05(m, 2x4H); 2.40(s, 2x2H); 2.79(s, 2x2H). ^{13}C NMR: *meso*: 30.68(q); 38.59(t); 67.89(s); 72.10(d); 87.28(s); (52%), *rac.*: 29.96(q); 38.41(t); 67.73(s); 71.90(d); 87.50(s); (48%). MS: 166(M^+, 0.5); 133(81); 105(57); 81(37); 80(96); 79(100); 77(51); 69(82); 65(30); 53(45); 43(59).

***4,7-Dimethyl-deca-1,9-diyne-4,7-diol* (5a):** A solution of 13.1 mmol propargylmagnesium bromide, obtained from 0.64 g (26 mmol) Mg and 1.56 g (13.1 mmol) propargyl bromide in 50 ml ether, was slowly added to a solution of 0.5 g (4.38 mmol) acetonylacetone in 100 ml ether at -50°C. After stirring for 12 h at r.t., work up and chromatography (silicagel; ether), 809 mg (95%) **5a** could be isolated as a colourless liquid. R_f (*2*): 0.21. GC: t_R 15.37 and 15.78 (~1:1). IR: 3570*s*; 3400*vs*; 3300*vs*; 2980*s*; 2920*s*; 2875*s*; 2120*m*; 1460*s*; 1380*s*; 1270*s*; 1110*vs*; 1070*s*; 945*m*. ^{1}H NMR: 1.30(s, 6H); 1.58-1.82(st, 4H); 2.11(t, 2H); 2.40(d, 4H); 2.52(s, 2H, OH). ^{13}C NMR: [26.33(q); 26.44(q)]; [32.44(t); 32.56(t)]; 34.77(t); 71.26(d); 71.43(s); 80.80(s). MS: 194(M^+, 1); 160(68); 131(63); 107(47); 106(91); 105(100); 103(66); 93(72); 89(35); 78(42); 67(31).

***3,4-Dimethyl-hexa-1,5-diyne-3,4-diol* (9a):** Ethyne was bubbled into 60 ml THF for 45 min at -5°C. After addition of 40 ml (43.5 mmol) C_4H_9MgBr, obtained form 1.11 g (45.7 mmol) Mg and 4.03 g (43.5 mmol) C_4H_9Br in THF, at T < +3°C by syringe techniques and stirring for an additional hour, a solution of 1 g (11.6 mmol) diacetyl and 547 mg (2.3 mmol) anhydrous $MgBr_2$ in 10 ml THF was added at -25°C. After stirring for 12 h at r.t., work up gave 1.5 g (97%) **9a**, which could be used without further purification. R_f (*1*): 0.58. GC: t_R 4.05 and 4.98 (~1:1). IR: 3540*vs*; 3430*vs*; 3300*vs*; 2980*s*; 2960*s*; 2930*s*; 2120*m*; 1370*vs*; 1335*vs*; 1170*s*; 1150*vs*; 1110*vs*; 1060*vs*; 940*vs*; 830*s*; 640*vs*; 610*s*; 550*s*. ^{1}H NMR: *major isomer*: 1.50(s, 6H); 2.50(s, 2H); 3.19(s, 2H, OH); *minor isomer*: 1.58(s, 6H); 2.52(s, 2H); 3.32(s, 2H, OH). ^{13}C NMR: *major isomer*: 22.97(q); 73.42(s); 73.53(d); 84.26(s); *minor isomer*: 24.76(q); 73.42(s); 73.78(d); 85.06(s).

***Preparation of the acyclic silyloxy compounds* 2b, 5b *and* 9b**

General procedure: Silylation was performed in THF (2 ml/mmol) with 2 eq NEt_3 and 1.5 eq TBDMSi triflate at 0°C for 2-3 h followed by work up and chromatography.

***3,6-Dimethyl-3,6-bis-(tert-butyldimethylsilyloxy)-octa-1,7-diyne* (2b):** According to the general procedure 1 g (6.02 mmol) **2a** gave 2.28 g (96%) **2b** as white crystals. Mp.: 32-34°C. R_f (*2*, 2:1): 0.72. GC: t_R 36.06. IR: 3302*s*; 2960*vs*; 2930*vs*; 2890*s*; 2860*vs*; 1471*s*; 1462*s*; 1250*vs*; 1170*s*; 1085*vs*; 1000*s*; 838*vs*. ^{1}H NMR: 0.05(s, 12H); 0.70(s, 18H); 1.30(s, 6H); 1.60-1.72(m, 4H); 2.25(s, 2H). ^{13}C NMR: *major isomer*: -2.77(q); 18.18(s); 25.83(q); 31.26(q); 40.19(t); 68.80(s); 72.02(d); 88.24(s). *minor isomer*: -3.01(q); 18.26(s); 25.83(q); 31.19(q); 40.19(t); 68.85(s); 71.97(d); 88.24(s). MS: 391([M-3]$^+$, 1); 379(1.5); 365(2); 338(8); 337(28); 319(8); 279(2); 263(8); 257(10); 247(10); 237(14); 205(20); 183(46); 147(71); 133(20); 131(26); 116(25); 115(27); 91(30); 83(26); 75(79); 73(100); 57(11); 43(11). Anal. calc. for $C_{22}H_{42}O_2Si_2$: C 66.93, H 10.72, found: C 66.84, H 10.51.

***4,7-Dimethyl-4,7-bis-(tert-butyldimethylsilyloxy)-deca-1,9-diyne* (5b):** According to the general procedure 850 mg (4.38 mmol) **5a** gave 1.85 g (100%) **5b** as a white solid. Mp.: 37-39°C. R_f (*1*): 0.40. GC: t_R 44.12. IR: 3330*s*; 2925*vs*; 2910*s*; 2880*vs*; 2140*w*; 1475*m*; 1385*m*; 1370*m*; 1265*vs*; 1100*vs*; 1030*s*; 845*m*. ^{1}H NMR: 0.11(s, 12H); 0.89(s, 18H); 1.33(s, 6H); 1.58-1.77(st, 4H); 1.99(t, 2H); 2.36(d, 4H). ^{13}C NMR: [-2.07(q); -2.05(q)]; 18.22(s); 25.86(q); [27.19(q); 27.24(q)]; [32.84(t); 32.88(t)]; [36.06(t); 36.10(t)]; 70.13(s); [74.85(d); 74.87(d)]; 81.78(s).

***3,4-Dimethyl-3,4-bis-(tert-butyldimethylsilyloxy)-hexa-1,5-diyne* (9b):** According to the general procedure 2 g (14.51 mmol) **9a** gave 1.65 g (31%) of **9b** and 1.75 g (48%) of monosilylated byproduct as colourless liquids. R_f (2, 1:1): 0.71. GC: t_R 32.21 and 32.44 (~1:1). IR: 3295*m*; 2890*s*; 2880*m*; 2850*m*; 2120*vw*; 1250*s*; 1150*s*; 1140*s*; 1115*s*; 835*s*. ^{1}H NMR: *major isomer*: 0.20(s, 12H); 0.88(s, 18H); 1.55(s, 6H); 2.38(s, 2H); *minor isomer*: 0.23(s, 12H); 0.89(s, 18H); 1.62(s, 6H); 2.45(s, 2H). ^{13}C NMR: *major isomer*: -3.44(q); -3.00(q); 18.11(s); 25.24(q); 25.55(q); 72.93(d); 74.87(s); 85.86(s); *minor isomer*: -3.06(q); -2.97(q); 18.11(s); 25.62(q); 26.19(q); 73.21(d); 74.94(s); 86.88(s). MS: 366(M$^+$, 2); 310(20); 309(72); 189(32); 183(20); 149(22); 148(38); 147(100); 133(20); 73(42).

***Preparation of the cycloalkadiynes* 3b, 4b, 6b, 7b, 10b *and* 11b**

General cyclisation procedure: Under an argon atmosphere 2.2 eq of n-BuLi (solution in hexane) were added to a 0.02M solution of the cyclisation precursors **2b**, **5b** or **9b** at -20°C. The reaction mixture was warmed to r.t. and stirring continued for 1h. Then 2.0 eq DMPU and 2.0 eq of the appropriate 1,ω-dibromide were added via syringe techniques in one portion. For **2b** the reaction mixture was stirred for 3 days at r.t.. For **5b** with substituents in homopropargylic positions and the 1,5-diyne **9b** the reaction mixture was stirred for 3 - 4 days at 40-45°C. After cooling to 0°C and work up by sat. NH_4Cl solution followed by extraction with

hexane/ether = 1:1 and chromatography over silica gel with hexane/ethyl acetate = 100:1 the cycloalkadiynes could be isolated in yields of 35% (**3b**), 37% (**4b**), 9% (**6b**), 14% (**7b**), 9% (**10b**) and 23% (**11b**).

1,11-Dimethyl-1,11-bis-(tert-butyldimethylsilyloxy)-cyclotrideca-2,9-diyne **(3b):** R_f (*3*, 100:1): 0.48. GC: t_R 52.38 and 52.53 (~1:1). IR: 2960*s*; 2935*vs*; 2860*s*; 1250*s*; 1095*vs*; 840*vs*. ^{1}H NMR: 0.19(s, 12H); 0.88(s, 18H); 1.25-1.31(m, 2H); 1.47(s, 6H); 1.66-1.99(st, 8H); 2.17-2.28(st, 4H). ^{13}C NMR: [-2.95(q); -2.93(q)]; 18.03(s); [18.05(t); 18.07(t)]; [25.12(t); 25.20(t)]; [25.73(q); 25.76(q)]; [26.58(t); 26.63(t)]; [30.87(q); 30.99(q)]; 41.94(t); [69.93(s); 69.95(s)]; 82.80(s); 85.98(s). GC-MS: 462(M^+, 4); 447(5); 434(6); 419(5); 405(10); 331(20); 273(14); 229(9); 199(42); 185(19); 158(14); 147(28); 115(14); 91(9); 75(100); 73(90); 59(20); 57(10).

1,12-Dimethyl-1,12-bis-(tert-butyldimethylsilyloxy)-cyclotetradeca-2,10-diyne **(4b):** R_f (*3*, 100:1): 0.53. GC: t_R 54.17 and 54.23 (~1:1). IR: 2985*s*; 2970*vs*; 2940*s*; 2875*s*; 2860*s*; 1262*s*; 1100*vs*; 910*vs*. ^{1}H NMR: [0.16(s, 6H); 0.18(s, 6H)]; 0.88(s, 18H); [1.45(s, 3H); 1.48(s, 3H)]; 1.50-1.62(st, 8H); 1.80-1.95(st, 4H); 2.27(m, 4H). ^{13}C NMR: [-2.94(q); -2.92(q)]; [17.83(t); 17.86(t)]; 18.05(s); [25.77(q); 25.83(q)]; [27.19(t); 27.28(t)]; [27.33(t); 27.35(t)]; [31.15(q); 31.23(q)]; [41.73(t); 41.80(t)]; [69.84(s); 69.90(s)]; 83.38(s); 85.15(s). GC-MS: 476(M^+, 0.5); 461([M-15]$^+$, 2); 448(4); 433(1); 419(10); 347(4); 345(6); 329(6); 319(2); 287(21); 243(6); 213(30); 185(21); 147(30); 115(16); 75(100); 73(80); 59(19); 41(16).

1,12-Dimethyl-1,12-bis-(tert-butyldimethylsilyloxy)-cyclotetradeca-3,9-diyne **(6b):** R_f (*3*, 100:1): 0.51. GC: t_R 59.70 and 60.05 (~1:1). IR: 2959*s*; 2930*vs*; 2900*m*; 2880*m*; 2860*s*; 1470*m*; 1460*m*; 1360*w*; 1240*m*; 1125*m*; 1095*s*; 1020*m*; 1000*m*; 905*w*; 835*vs*. ^{1}H NMR: [0.08(s); 0.09(s); 0.10(s); 0.11(s); 12H]; [0.85(s); 0.87(s); 18H]; 1.32(s, 6H); 1.55-1.91(st, 8H); 2.12-2.27(m, 4H); 2.31-2.47(m, 4H). ^{13}C NMR: [-2.04(q); -2.02(q)]; 18.18(s); [18.48(t); 18.53(t)]; [25.84(q); 25.87(q)]; [27.37(t); 27.50(t)]; [28.57(q); 28.74(q)]; [32.03(t); 32.14(t)]; [35.31(t); 35.79(t)]; [75.48(s); 75.55(s)]; [77.80(s); 77.95(s)]; 81.68(s). GC-MS: 419([M-57]$^+$, 10); 377(8); 345(9); 330(8); 329(21); 303(10); 291(15); 287(36); 269(12); 247(15); 229(24); 213(100); 212(52); 211(58); 197(45); 185(82); 171(43); 155(83); 146(41); 143(42); 129(45); 115(92); 91(42); 77(62); 76(75); 75(98); 73(96); 59(69); 41(95).

1,14-Dimethyl-1,14-bis-(tert-butyldimethylsilyloxy)-cyclohexadeca-3,11-diyne **(7b):** R_f (*3*, 100:1): 0.54. GC: t_R 64.08 and 64.25 (~1:1). IR: 2985*s*; 2865*s*; 2250*vw*; 1450*m*; 1370*m*; 1250*m*; 1140*m*; 1110*s*; 1090*s*; 1000*m*; 900*w*. ^{1}H NMR: [0.08(s); 0.09(s); 0.10(s); 0.11(s); 12H)]; [0.88(s, 9H); 0.89(s, 9H)]; 1.32(s, 6H); 1.38-1.75(st, 14H); 2.10-2.44(st, 6H). ^{13}C NMR: [-2.1(q); -2.06(q)]; 17.70(s); [22.63(t); 22.65(t)]; [25.80(q); 25.83(q)]; [26.82(t); 26.89(t)]; [27.51(q); 27.57(q)]; [28.08(t); 28.11(t)]; 33.22(t); [35.39(t); 35.58(t)]; [75.44(s); 75.54(s)]; [77.87(s); 78.07(s)]; [81.04(s); 81.21(s)]. GC-MS: 504(M^+, 3); 449(5); 448(7); 447(9); 372(10); 357(11); 319(15); 315(19); 282(7); 263(14); 241(20); 240(20); 224(15); 207(30); 185(38); 171(14); 169(24); 155(40); 143(30); 131(21); 115(55); 105(54); 91(65); 75(100); 73(93); 56(45); 41(79).

***1,10-Dimethyl-1,10-bis-(tert-butyldimethylsilyloxy)-cyclodeca-2,8-diyne* (10b):** R_f (*4*): 0.58. GC: t_R 45.70. IR: 2975*vs*; 2960*vs*; 2920*vs*; 2875*vs*; 2240*w*; 1480*s*; 1470*s*; 1370*s*; 1260*vs*; 1175*vs*; 1130*vs*; 1030*s*; 1110*s*; 1000*s*; 990*m*; 840*vs*. ^{1}H NMR: 0.18(s, 12H); 0.87(s, 18H); 1.44(s, 6H); 2.02-2.28(st, 8H). ^{13}C NMR: -3.15(q); 18.11(s); 20.56(t); 25.24(q); 25.63(q); 27.36(t); 73.23(s); 77.13(s); 86.62(s). MS: 420(M^+, 19); 405(5); 378(5); 363(12); 309(12); 289(4); 248(7); 231(8); 183(10); 147(40); 135(10); 115(5); 75(27); 73(100); 59(8); 57(8).

***1,11-Dimethyl-1,11-bis-(tert-butyldimethylsilyloxy)-cycloundeca-2,9-diyne* (11b):** R_f (*4*): 0.57. GC: t_R 49.68 and 49.80 (~4:1). IR: 2940*s*; 2910*s*; 2875*s*; 1480*m*; 1470*m*; 1400*m*; 1370*m*; 1250*m*; 1115*s*; 1000*m*. ^{1}H NMR: [0.18(s, 6H); 0.19(s, 6H)]; [0.89(s, 9H); 0.91(s, 9H)]; [1.44(s, 3H); 1.51(s, 3H)]; 1.50-1.58(m, 4H); 1.70-1.95(st, 2H); 2.10-2.36(st, 4H). ^{13}C NMR: [-3.31(q); -2.98(q)]; 17.94(t); 17.96(s); [24.52(t); 24.53(t)]; [24.99(q); 25.21(q)]; [25.73(q); 25.94(q)]; [27.28(t); 27.53(t)]; [76.32(s); 76.48(s)]; [84.96(s); 85.04(s); [86.65(s); 87.00(s)]. MS: 435([M+1]$^+$, 11); 434(M^+, 33); 419(4); 378(10); 377(28); 303(5); 261(4); 245(10); 147(51); 133(10); 75(26); 73(100); 59(8); 57(7).

***Preparation of the cycloalkadiyne-diols* 3a, 4a, 6a, 7a, 10a *and* 11a**

General procedure: Deprotection was carried out by stirring the cycloalkadiynes in THF with 6 - 12 eq TBAF either at r.t. for 4 - 6 days (**3b**, **4b**, **10b**, **11b**) or at 66°C (**6b**, **7b**) for 6 days. After chromatographic purification the cyclic diynediols could be isolated in yields of 66% (**3a**), 68% (**4a**), 61% (**6a**), 69% (**7a**), 67% (**10a**) and 66% (**11a**).

***1,11-Dimethyl-cyclotrideca-2,9-diyne-1,11-diol* (3a):** Mp.: 99-101°C. R_f (*3*, 1:2): 0.40. GC: t_R 37.65 and 37.68 (~1:1). IR: 3600*s*; 2980*m*; 2940*vs*; 2860*m*; 2230*w*;1450*m*; 1435*m*; 1375*m*; 1330*m*; 1110*m*; 1080*s*; 930*s*. ^{1}H NMR: 1.43(s, 6H); 1.51(m, 4H); 1.83(m, 4H); 2.08(t, 2H); 2.26(t, 4H); 4.09(s, 2H, OH). ^{13}C NMR: *meso*: 18.35(t); 25.77(t); 27.42(t); 30.25(q); 41.36(t); 68.41(s); 81.67(s); 87.17(s); *rac.*: 17.81(t); 24.93(t); 26.34(t); 30.24(q); 39.95(t); 68.74(s); 82.59(s); 85.22(s). MS: 234(M^+, 1); 219(3); 216(7); 215(8); 202(9); 201(55); 188(14); 187(23); 174(10); 173(42); 159(30); 145(33); 131(37); 117(24); 105(37); 93(25); 91(45); 81(20); 79(53); 77(31); 67(20); 55(30); 43(100); 41(34) Anal. calc. for ($C_{15}H_{22}O_2$): C 76.87, H 9.47; found: C 76.64, H 9.47.

***1,12-Dimethyl-cyclotetradeca-2,10-diyne-1,12-diol* (4a):** Mp.: 94-95°C. R_f (*3*, 1:2): 0.55. GC: t_R 40.37 and 40.41 (~1:1). IR: 3600*vs*; 3420*m*; 2980*vs*; 2860*vs*; 2240*m*; 1450*s*; 1375*s*; 1328*s*; 1270*s*; 1085*vs*; 930*s*. ^{1}H NMR: 1.44(s, 6H); 1.49-1.66(st, 8H); 1.85(m, 2H); 2.01(m, 2H); 2.29(m, 4H); 2.94(s, 2H, OH). ^{13}C NMR: *major isomer*: 18.13(t); 27.50(t); 28.23(t); 30.61(q); 41.41(t); 68.31(s); 82.12(s); 86.58(s); *minor isomer*: 18.03(t); 27.61(t); 28.12(t); 30.69(q); 41.18(t); 68.20(s); 82.08(s); 86.42(s). MS: 231([M-17]$^+$, 2); 228(3); 227(4); 213(39); 200(12); 199(10); 185(24); 171(13); 157(16); 143(21); 129(27); 117(14); 115(14); 105(15); 103(26); 93(36); 92(27); 89(34); 77(62); 66(16); 54(14); 42(100); 40(24). Anal. calc. for ($C_{16}H_{24}O_2$): C 77.36, H 9.75; found: C 77.07, H 9.78.

***1,12-Dimethyl-cyclotetradeca-3,9-diyne-1,12-diol* (6a):** Mp.: 89-91°C. R_f (*3*, 1:2): 0.29. GC: t_R 42.42 and 42.63 (~1:1). IR: 3580*m*; 3420*m*; 2940*vs*; 2920*vs*; 2910*vs*; 2840*s*; 2820*s*; 1450*s*; 1425*s*; 1380*s*; 1370*s*; 1360*s*; 1270*s*; 1100*s*; 1060*s*; 920*m*; 895*m*. ^{1}H NMR: [1.25(s, 3H); 1.26(s, 3H)]; 1.63-1.86(st, 8H); 2.01(s, 2H, OH); 2.15-2.43(st, 8H). ^{13}C NMR: *major isomer*: 18.91(t); 28.22(q); 31.96(t); 34.89(t); 66.07(t); 72.24(s); 78.42(s); 82.27(s); *minor isomer*: 18.94(t); 28.32(q); 32.23(t); 35.65(t); 66.07(t); 72.25(s); 78.47(s); 82.48(s). Anal. calc. for ($C_{16}H_{24}O_2$): C 77.36, H 9.75; found: C 77.10, H 9.74.

***1,14-Dimethyl-cyclohexadeca-3,11-diyne-1,14-diol* (7a):** Mp.: 119-120°C. R_f (*3*, 1:2): 0.36. GC: t_R 47.74 and 47.93 (~1:1). IR: 3350*m*; 3425*s*; 2920*vs*; 2860*vs*; 1460*s*; 1435*s*; 1395*s*; 1375*s*; 1280*s*; 1100*s*; 1070*s*; 980*m*; 930*m*; 910*s*. ^{1}H NMR: [1.22(s, 3H); 1.24(s, 3H)]; 1.60-1.77(m, 8H); 2.23(s, 2H, OH); 2.25(m, 2H); 2.30(t, 4H); 2.35(m, 4H); 2.42(m, 2H). ^{13}C NMR: *major isomer*: 17.61(t); 26.61(q); 26.73(t); 27.83(t); 32.28(t); 34.55(t); 71.98(s); 76.78(s); 82.43(s); *minor isomer*: 17.66(t); 26.82(q); 26.85(t); 27.88(t); 32.73(t); 34.59(t); 72.10(s); 76.89(s); 82.51(s); Anal. calc. for ($C_{18}H_{28}O_2$): C 78.20, H 10.22; found: C 76.62, H 10.25.

***rac.-1,10-Dimethyl-cyclodeca-2,8-diyne-1,10-diol* (10a):** Mp.: 76-78°C. R_f (*3*, 1:1): 0.43. GC: t_R 26.69; column *B*; t_R 78.83 and 82.41 (1:1; *rac.*). IR: 3540*m*; 2960*s*; 2880*m*; 2220*w*; 1450*m*; 1380*m*; 1340*s*; 1150*m*; 1110*s*; 1070*s*; 940*m*. ^{1}H NMR: 1.63(s, 6H); 2.05(m, 4H); 2.18(st, 4H); 4.03(s, 2H). ^{13}C NMR: 23.77(t); 25.73(t); 28.07(q); 73.50(s); 73.70(s); 75.81(s). MS: 192(M^+, 7); 191([M-1]$^+$, 15); 177(20); 164(18); 159(21); 149(78); 131(40); 121(38); 107(23); 91(36); 79(25); 70(72); 69(82); 43(100).

***1,11-Dimethyl-cycloundeca-2,9-diyne-1,11-diol* (11a):** Mp.: 85-86°C. R_f (*3*, 1:1): 0.52. GC: t_R 29.41 and 30.30 (~4:1); column *B*; t_R 98.39 (22%; *meso*), 122.75 and 124.54 (78%; 1:1; *rac.*). IR: 3560*s*; 3450*m*; 2940*s*; 2880*s*; 2225*w*; 1340*s*; 1220*m*; 1145*m*; 1115*s*; 1085*s*; 1070*s*; 925*s*. ^{1}H NMR: 1.88(s, 6H); 2.06(t, 4H); 2.34(quint., 2H); 2.72(m, 4H); 4.50(s, 1H); 4.55(s, 1H). ^{13}C NMR: *major isomer*: 18.22(t); 23.71(q); 25.11(t); 25.66(t); 74.50(s); 84.94(s); 87.12(s); *minor isomer*: 18,24(t); 24.87(q); 25.23(t); 25.77(t); 74.80(s); 84.94(s); 87.60(s). MS: 206(M^+, 8); 205([M-1]$^+$, 8); 191(26); 173(12); 172(9); 163(41); 145(23); 121(26); 95(18); 91(28); 84(100); 69(56); 43(80).

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16. X-ray analysis of the cyclododeca-2,8-diyne-1,10-diol with secondary propargylic centers and the TBDMS-protected derivative of *rac*-**13** show the same conformation as depicted for *rac*-**13**, which clearly indicates that the conformations of these 12-membered rings are independent of the type of substituent.
17. For **3a** the data of the *meso*-compound are given in order to be able to compare these directly with the data of the X-ray analysis. The calculated data for *rac* and *meso* compounds are very similar in all molecules described in Table 1.

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