Synthesis and structure of bicyclic enediynes *via* twofold carbenoid ring closure†

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Macrobicyclic enediynes were obtained in four steps from dicarboxylic diesters. The key step of the synthesis is a twofold carbenoid ring closing procedure from acyclic precursors. Crystal structure analyses showed that bicyclo[6.6.4]dienetetrayne is not strained. Thermal analysis revealed its low thermal reactivity. An attempt to obtain bicyclo[6.6.2]dienetetrayne structures using the same method failed.

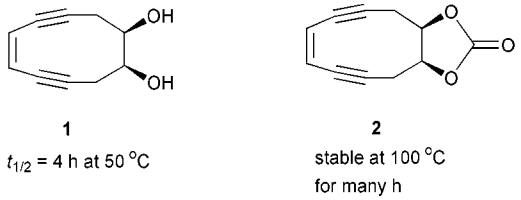
The chemistry of enediynes has received considerable attention in the last decade, since cyclic strained enediynes are the source of the antitumor activity of several natural products.[1–4] The most fascinating aspect of the compounds is the control of enediyne reactivity, which is achieved by complex trigger mechanisms. A common goal of many model studies is thus to mimic such mechanisms for the control of reactivity with simpler structures. In this context Nicolaou *et al.*[5] have reported the observation that a strained cyclic enediyne **1** is considerably stabilized if it is conformationally constrained as a cyclic carbonate, as shown in **2**. The carbonate **2** is stable in refluxing toluene for several hours, whereas the diol **1** cyclizes with a half-life of 4 h at 50 °C.[6]

In order to investigate whether a single group is able to stabilize two cyclizable enediyne moieties by the same mechanism, we selected compound **3** as our synthetic target.[7] The readily removable acetal protecting group should provide similar stabilization for **3** as the carbonate for **2**. The stereochemistry of the diol is determined by the starting material **5**, which is readily available as its *R*/*S* or *meso* isomer. Both, *cis* and *trans* acetal-protected diols are expected to stabilize **3**, but they may have different reactivity.[6] Retrosynthetic analysis shows that the bicyclic molecule might be available in four steps *via* a route that uses a twofold ring closing reaction as a key step. A protocol that allows this coupling of two propargyl (2-propynyl) bromides to a double bond has recently been reported by Jones and co-workers,[8–10] but the procedure has not widely been used so far.[11–13]

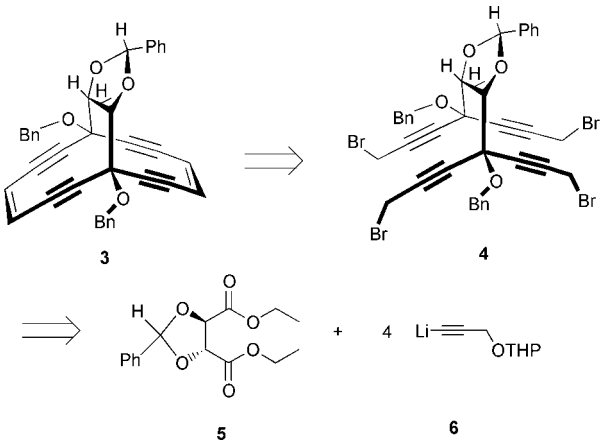
Results and discussion

The cyclization precursor **4** was synthesized starting from ketal-protected *R*,*R*-diethyl tartrate **5**. The reaction with four equivalents of the lithium acetylide **6** of tetrahydropyran (THP)-protected propargylic alcohol afforded compound **7** in good yield. The tertiary hydroxy groups were protected as benzyl ethers under standard conditions[14] and the THP-protected hydroxy groups were converted into propargyl bromides using PPh_3/Br_2.[15] Under various conditions the twofold cyclization of the stable tetrabromide **4**[16] was attempted, but without success. Rapid consumption of **4** was observed under the reaction conditions, but we were not able to isolate a stable product.[17]

To investigate whether the reaction is generally unsuitable for ring closing in such systems, or whether the target molecule is simply too strained to be made and isolated by the proposed route, we applied the carbenoid ring closing procedure to a series of similar systems **13a–c**, to give products **14a–c** that vary in ring strain. Our synthetic route to cyclization precursors **13a–c** starts from 1,*n*-dicarboxylic esters **10**, with $n = 4$, 5 or 6. Quadruple addition of the lithium alkynyl derivative of THP-protected propargyl alcohol **6** gives tetraynes **11** in moderate to good yields. As described for **8** the benzyl protection of the newly generated hydroxyl group proceeds smoothly under standard conditions and treatment of **12** with an excess of PPh_3/Br_2 yields **13** with four propargyl bromide moieties in good yield (Scheme 4). The structure of **13c** was confirmed by X-ray diffraction analysis (see Fig. 1). The molecule shows a conformation with inversion symmetry in the solid state. All distances and angles are as expected.[18]



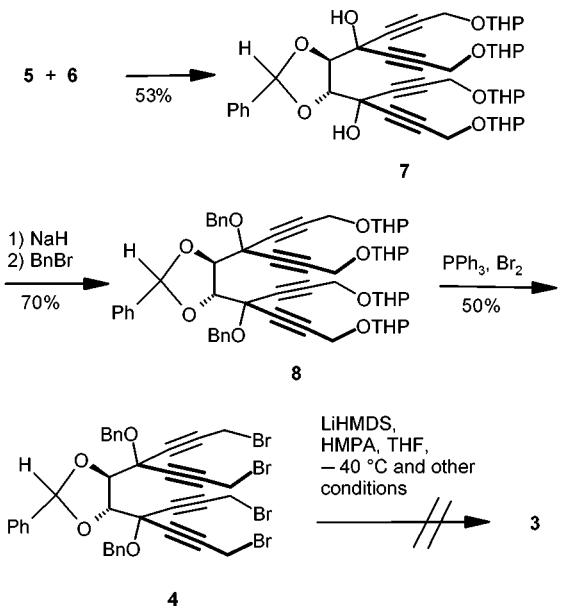
Scheme 1



Scheme 2

† Electronic supplementary information (ESI) available: NMR spectra. See http://www.rsc.org/suppdata/nj/b1/b101572a

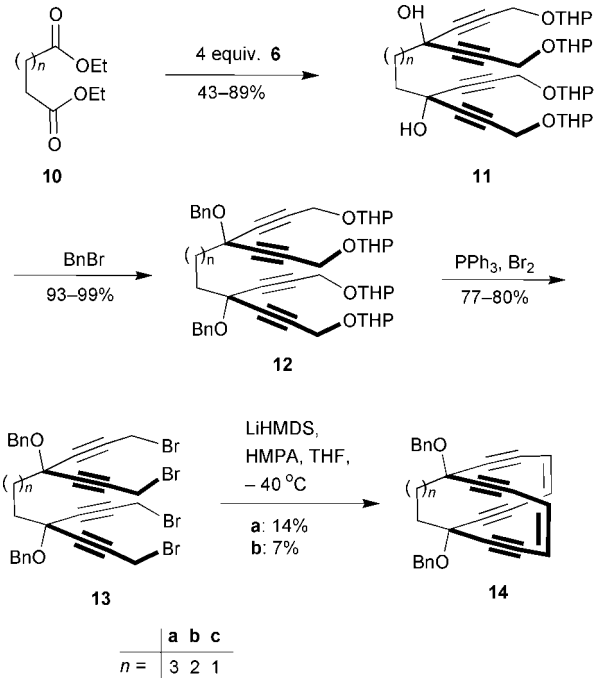
 DOI: 10.1039/b101572a



Scheme 3

With compounds **13a–c** the stage is set for a double carbenoid cyclization following the procedure of Jones *et al.*[8–10] From **13a** the bicyclic [6.6.4]dienetetrayne **14a** was obtained in 14% isolated yield as a colorless solid. As shown by differential scanning calorimetry[19] the compound is thermally stable up to 190 °C, indicating negligible ring strain of the enediyne moieties. Single crystals of **14a** (Fig. 2) were obtained from dichloromethane–light petroleum and an X-ray diffraction analysis confirmed the proposed constitution of the molecule. The reduced set of resonance signals in the ^{1}H and ^{13}C NMR spectra of the molecule reflect its symmetry, whereas the enediyne moieties are not equivalent in the solid state. The distances between the outer acetylenic carbons (C2–C7; C9–C14) in the two enediyne moieties are 389.2 and 387.1 pm. The enediyne moieties are oriented with an interplanar angle of 61.7° (plane C2, C3, C4, C5, C6, C7 to plane C9, C10, C11, C12, C13, C14).

Applying the same conditions to **13b** gave the [6.6.3]bicyclic double enediyne **14b**. The less efficient double carbenoid cyclization of **13b** and the significantly reduced stability of **14b** compared to that of **14a** account for the low yield



Scheme 4

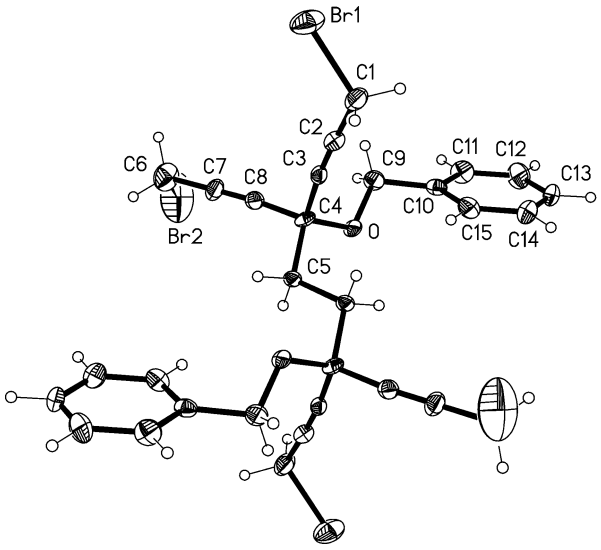


Fig. 1 Structure of **13c** in the solid state. Ellipsoids represent the 50% probability level.

of only 7%. The next smallest homologue, [6.6.2]bicyclic double enediyne **14c**, could not be isolated from the reaction mixture, although monitoring of the reaction by TLC showed rapid consumption of the starting material.[20]

Conclusion

Bicyclic double enediynes **14a** and **14b** have been obtained from acyclic precursors *via* a twofold ring closing reaction which presumably proceeds stepwise *via* carbenoid intermediates. The crystal structure and thermal analysis of **14a** indicate that its structure is not strained. The synthesis of the highly strained compounds **3** and **14c**, with bicyclo[6.6.2]dienetetrayne structures, could not be achieved using the same procedure. This leads us to the conclusion that twofold carbenoid ring closing is an applicable strategy for the synthesis of unsaturated bicycles if the products are not highly strained and reactive.

Experimental

Melting points were taken on a hot-plate microscope apparatus and are not corrected. NMR spectra were recorded at

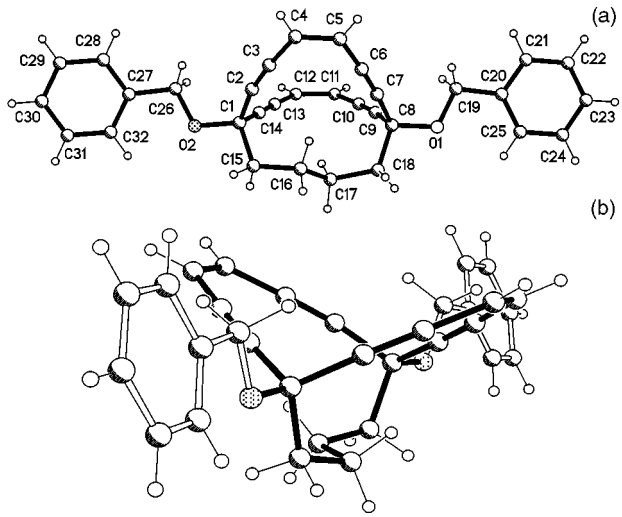


Fig. 2 Structure of **14a** in the solid state. Side view (a) and along the axis (b). Only one of two independent molecules is shown. Radii are arbitrary. The bridge C15–C18 is disordered over two positions.

400 (^{1}H) and 100 MHz (^{13}C) in $CDCl_3$ solutions unless otherwise stated. The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as: (+) for CH_3 or CH, (−) for CH_2 and (C_{quat}) for quaternary carbons. Differential scanning calorimetry: Rheometric Scientific DSC SP; heating and cooling rate 10 K min^{-1}. CC means column chromatography on silica gel unless otherwise stated. PE means light petroleum with a boiling range of 60 to 70 °C. EE means ethyl acetate. Solvents were obtained from commercial suppliers and purified by standard laboratory methods before use. Reagents were used as received.

Crystal structure determinations

Compound 13c. *Crystal data.* $C_{30}H_{26}Br_4O_2$, $M_r = 738.15$, monoclinic, space group $P2_1/n$, $a = 953.2(2)$, $b = 1585.0(2)$, $c = 1035.73(11)$ pm, $\beta = 110.16(1)°$, $V = 1.4689$ nm^3, $Z = 2$, λ(Mo-Kα) = 71.073 pm, $\mu = 5.504$ mm^{-1}, $T = -100$ °C.

A colorless prism was mounted in inert oil on a glass fiber and transferred to the cold gas stream of the diffractometer (Siemens-P4 with LT-2 low temperature attachment). 4556 Intensities (2547 unique, R_{int} 0.042) to $2\theta_{max} = 50°$ were measured with the ω-scan method. Absorption correction with Ψ scans. The structure was solved by direct methods and refined anisotropically on F^2 using the program SHELXL 93.[21] The final $wR(F^2)$ was 0.106 for all reflections and 164 parameters, conventional $R(F)$ 0.047.

Compound 14a. *Crystal data.* $C_{32}H_{26}O_2$, $M_r = 442.53$, triclinic, space group $P\bar{1}$, $a = 910.8(4)$, $b = 1119.9(3)$, $c = 2519.0(6)$ pm, $\alpha = 96.03(3)$, $\beta = 97.72(2)$, $\gamma = 109.50(3)°$, $V = 2.3689$ nm^3, $Z = 4$, λ(Mo-Kα) = 71.073 pm, $\mu = 0.076$ mm^{-1}, $T = -130$ °C.

A colorless prism was mounted as above on a Stoe STADI-4 diffractometer with LT-2 low temperature attachment. 15 813 Intensities (8350 unique, R_{int} 0.069) to $2\theta_{max} = 50°$ were measured with the ω–θ-scan method. The structure was solved and refined as above. There are two independent molecules; in both the bridge C15–C18 is disordered over two positions. The final $wR(F^2)$ was 0.145 for all reflections and 651 parameters, conventional $R(F)$ 0.061.

CCDC reference numbers 100823 and 116500. See http://www.rsc.org/suppdata/nj/b1/b101572a/ for crystallographic data in CIF or other electronic format.

Preparations

4-(5-{Hydroxy-5,3-[3-(tetrahydropyran-2-yloxy)prop-1-ynyl]methyl}-2-phenyl-1,3-dioxolan-4-yl)-1,7-bis(tetrahydropyran-2-yloxy)hepta-2,5-diyn-4-ol 7. To a solution of 2(prop-2-ynyloxy) tetrahydropyran (5.9 g, 42 mmol) in diethyl ether (50 ml) was added at −30 °C butyllithium (4.2 ml, 42 mmol, 10 M in hexane) and the mixture stirred for 10 min at 0 °C. 2-Phenyl-1, 3-dioxolane-4,5-dicarboxylic acid diethyl ester (2 g, 6.8 mmol) was added, the reaction mixture stirred for 1 h at 0 °C and poured into 200 ml of aqueous sat. NH_4Cl solution. The mixture was extracted with diethyl ether (4 × 50 ml), the combined organic phase was washed with aqueous sat. NH_4Cl (50 ml) and brine, dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude product was purified by CC (PE : EE 1 : 1) to yield 2.74 g (53%) **7** (R_f = 0.23), as slightly yellow crystals, mp = 40 °C. IR (KBr): $\tilde{\nu}$ = 3388, 2943, 2869, 2242, 1119, 1026 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 198 (4.140), 202 (4.030), 206 (3.990), 224 nm (3.030). ^{1}H NMR: δ 1.65 (m, 24 H), 3.54 (m, 4 H), 3.83 (m, 4 H), 4.03 (s, 2 H), 4.30 (m, 8 H), 4.58 (m, 1 H), 4.69 (m, 1 H), 4.79 (m, 4 H), 6.46 (m, 1 H), 7.35 (m, 5 H), 7.47 (m, 5 H). ^{13}C NMR: δ 18.9 (−), 25.2 (−), 30.1 (−), 54.6 (−), 60.3 (C_{quat}), 62.0 (−), 65.0 (C_{quat}), 82.2 (C_{quat}), 84.0 (+), 97.2 (+), 106.7 (+), 127.3 (+), 128.2 (+), 129.5 (+), 136.6 (+). MS (EI): *m*/*z* (%) 726 (0.04) [M$^+$], 676 (0.46) [M$^+$ − THP], 593 (0.24) [M$^+$ − (THP)$_2$], 85 (100) [THP]. $C_{43}H_{54}O_{12}$: calc. C 67.69, H 7.14; found C 67.60, H 7.16%.

The dibenzyl ether of 7, *i.e.* 8. A suspension of **7** (1.0 g, 1.3 mmol) and NaH (57 mg, 1.4 mmol, 60% in mineral oil) in THF (75 ml) was stirred at room temperature for 30 min, benzyl bromide (250 mg, 1.4 mmol) and tetrabutylammonium iodide (24 mg, 0.07 mmol) were added and the mixture was stirred for 24 h. It was poured into aqueous sat. NH_4Cl (200 ml), extracted with diethyl ether (4 × 50 ml), the combined organic phases were washed with brine (50 ml), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by CC. Excess benzyl bromide was eluted with PE. Elution with diethyl ether gave **8** (860 mg, 70%), as a slightly yellow solid, mp = 42 °C. IR (neat): $\tilde{\nu}$ = 2943, 2870, 2248, 1738, 1202, 1121 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 192 (4.990), 200 (4.480), 202 (4.400), 206 (4.350), 226 (3.350), 230 nm (3.140). ^{1}H NMR: δ 1.52 (m, 24 H), 3.37 (m, 4 H), 3.72 (m, 4 H), 3.95 (m, 2 H), 4.12 (m, 4 H), 4.19 (m, 2 H), 4.70 (m, 10 H), 6.37 (s, 1 H), 7.24 (m, 13 H), 7.51 (m, 2 H). ^{13}C NMR: δ 19.0 (−), 25.3 (−), 30.2 (−), 54.1 (−), 60.3 (C_{quat}), 62.1 (−), 68.0 (−), 72.3 (C_{quat}), 81.1–82.1 (C_{quat}), 82.7 (+), 84.0 (+), 97.0 (+), 107.1 (+), 127.4–129.0 (+), 137.4 (C_{quat}), 138.0 (C_{quat}). MS (EI): *m*/*z* (%) 942 (0.05) [M$^+$], 106 (50), 91 (100), 85 (100) [THP].

4,5-Bis[benzyloxybis(3-bromoprop-1-ynyl)methyl]-2-phenyl-1,3-dioxolane 4. To a solution of triphenylphosphine (556 mg, 2.1 mmol) in 50 ml of CH_2Cl_2 was slowly added at 0 °C 0.1 ml (2.1 mmol) of bromine and the mixture stirred for 20 min. A solution of compound **8** (400 mg, 0.4 mmol) in 5 ml of CH_2Cl_2 was added, the mixture stirred for 5 h at room temperature, 2/3 of the solvent removed by distillation and reaction mixture filtered through silica gel. The silica gel was eluted with diethyl ether (50 ml), the combined organic phases were evaporated to dryness *in vacuo* and the crude product was purified by CC (PE : EE, 2 : 1) to yield 181 mg (50%) of **4** (R_f = 0.24), as a colorless oil. IR (neat): $\tilde{\nu}$ = 3452, 3064, 1211, 1101, 1061 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 192 (5.170), 202 (4.730), 204 (4.700), 226 (4.110), 236 nm (3.760). ^{1}H NMR: δ 3.48 (s, 2 H), 3.72 (d, 2 H, J = 1.5), 3.79 (d, 2 H, J = 4.3), 3.84 (d, 2 H, J = 5.0), 4.66 (d, 1 H, J = 3.0), 4.74 (d, 1 H, J = 3.0 Hz), 4.77 (m, 4 H), 6.41 (s, 1 H), 7.34 (m, 13 H), 7.59 (m, 2 H). ^{13}C NMR: δ 13.3 (−), 13.4 (−), 13.5 (−), 13.6 (−), 68.3 (−), 68.5 (−), 71.9 (C_{quat}), 72.3 (C_{quat}), 81.3 (C_{quat}), 81.6 (C_{quat}), 81.9 (C_{quat}), 82.3 (C_{quat}), 82.5 (C_{quart}), 82.6 (C_{quat}), 82.6 (+), 82.6 (C_{quat}), 83.1 (C_{quat}), 83.9 (+), 107.1 (+), 127.4 (+), 127.8 (+), 127.9 (+), 128.1 (+), 128.1 (+), 128.4 (+), 128.4 (+), 128.8 (+), 129.3 (+), 137.0 (C_{quat}), 137.5 (C_{quat}), 137.6 (C_{quat}). MS (EI): *m*/*z* (%) 862/860/858/856/854[22] (<0.1) [M$^+$], 367 (3), 105 (20), 91 (100) [Bn].

Attempts to cyclize **4** used procedures as described for the synthesis of **14a**. Compound **4** (140 mg, 0.16 mmol) was treated with LiHMDS from HMDS (0.15 ml, 0.72 mmol) and butyllithium (0.5 ml, 0.75 mmol, 1.5 M in hexane) and HMPA (1.26 ml, 7.18 mmol) in THF (50 ml). No product could be isolated.

1,12-Bis(tetrahydropyran-2-yloxy)-4,9-bis-[3-(tetrahydropyran-2-yloxy)-prop-1-ynyl]dodeca-2,10-diyne-4,9-diol 11a. To a solution of THP-protected propargyl alcohol (9.66 g, 69.0 mmol) in 60 mL of THF at −30 °C were added 46 mL of butyllithium (69 mmol, 1.5 M in hexane) and the reaction mixture was stirred for 0.5 h. 1,6-Hexanedioic acid diethyl ester **10a** (2.0 g, 11.5 mmol) was slowly added, the reaction mixture allowed to warm to 0 °C, stirred for 0.5 h at this temperature and poured into sat. aqueous NH_4Cl (80 mL). The aqueous phase was extracted with diethyl ether, the combined organic phases dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue was chromatographed on silica gel (PE : Et_2O, 1 : 1) to yield 6.8 g (89%) of **11a** (R_f = 0.22), as a colorless oil. IR (KBr): $\tilde{\nu}$ = 3387, 2946, 1202 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 192 (3.660), 198 (3.529, sh), 232 nm

(2.764, sh). ^{1}H NMR: δ 1.72 (m, 34 H), 3.56 (m, 4 H), 3.84 (m, 4 H), 4.28 (d, 4 H, ^2J = 15.7), 4.34 (d, 4 H, ^2J = 15.7), 4.84 (t, 4 H, ^3J = 2.95 Hz). ^{13}C NMR: δ 18.5 (−), 23.8 (−), 25.0 (−), 29.8 (−), 43.2 (−), 53.8 (−), 61.4 (−), 62.6 (C_{quat}), 78.7 (C_{quat}), 86.1 (C_{quat}), 96.3 (+). MS (CI, negative ion, NH_3): *m/z* (%) 669 (4) [M − 1], 568 (6) [M − OTHP], 101 (100) [OTHP].

Dibenzyl ether of 11a, *i.e.* 12a. To a suspension of NaH (390 mg, 16 mmol) in 100 mL of THF at room temperature was slowly added a solution of **11a** (5.0 g, 7.5 mmol) in 20 mL of THF. The mixture was stirred for 0.5 h, benzyl bromide (2.0 ml, 16.4 mmol) and *n*-Bu_4NI (1.4 g, 3.7 mmol) were added and stirring was continued for 5 h. The reaction mixture was poured into aqueous NH_4Cl, the aqueous phase extracted with ether (4 × 80 ml), the combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. CC of the crude product (PE : Et_2O, 9 : 1) gave 6.2 g (98%) of **12a** (R_f = 0.12), as a yellow oil. IR (KBr): $\tilde{\nu}$ = 3031, 2942, 1121, 736 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 194 (4.871), 210 (4.241), 218 (4.148), 228 nm (3.897). ^{1}H NMR: δ 1.68 (m, 28 H), 2.01 (m, 4 H), 3.53 (m, 4 H), 3.85 (m, 4 H), 4.33 (m, 8 H), 4.75 (s, 4 H), 4.81 (m, 4 H), 7.32 (m, 10 H). ^{13}C NMR: δ 19.0 (−), 25.3 (−), 26.9 (−), 30.2 (−), 42.8 (−), 54.1 (−), 62.0 (−), 67.9 (−), 69.8 (C_{quat}), 81.1 (C_{quat}), 84.0 (C_{quat}), 96.8 (+), 127.4 (+), 127.8 (+), 128.2 (+), 138.4 (C_{quat}). MS (CI, positive ion, NH_3): *m/z* (%) 868 (2) [M + NH_4^+], 85 (100).

1,12-Dibromo-4,9-bis(benzyloxy)-4,9-bis(3-bromoprop-1-ynyl)dodeca-2,10-diyne 13a. To a solution of PPh_3 (14.2 g, 54.2 mmol) and Br_2 (2.8 mL, 8.7 g, 54.2 mmol) in 150 ml of CH_2Cl_2 were added at 0 °C 6.6 g (7.7 mmol) of **12a** and the reaction mixture was stirred for 15 h at room temperature. 100 ml of the solvent were distilled off, the suspension was treated with 100 ml PE, the precipitate collected by filtration and washed with PE (2 × 30 ml). The combined filtrate was evaporated *in vacuo* and the residue chromatographed on silica gel (PE : Et_2O, 1 : 1) to yield 4.5 g (77%) of **13a** (R_f = 0.54), as colorless crystals, mp = 74 °C. IR (KBr): $\tilde{\nu}$ = 3062, 2846 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 194 (4.906), 202 (4.576, sh), 212 (4.509, sh), 228 nm (3.950, sh). ^{1}H NMR: δ 1.66 (m, 4 H), 2.01 (m, 4 H), 3.94 (s, 8 H), 4.72 (s, 4 H), 7.33 (m, 10 H). ^{13}C NMR: δ 13.7 (−), 23.9 (−), 42.5 (−), 68.2 (−), 69.7 (C_{quat}), 80.5 (C_{quat}), 84.5 (C_{quat}), 127.6 (+), 127.9 (+), 128.3 (+), 138.0 (C_{quat}). MS (CI, positive ion, NH_3): *m/z* (%) 784 (100) [M + NH_4^+], 108 (42) [OBn + 1]. $C_{32}H_{30}Br_4O_2$: calc. C 50.16, H 3.95; found C 50.17, H 3.96%.

1,8-Di(benzyloxy)bicyclo[6.6.4]octadeca-4,11-diene-2,6,9,13-tetrayne 14a. To a solution of HMDS (2.88 ml, 13.8 mmol) in 10 ml of THF was added butyllithium (9.3 ml, 13.8 mmol) at 0 °C. The mixture was stirred at room temperature for 10 min, HMPA (24.0 ml, 138.0 mmol) added and this solution was added *via* syringe pump over 5 h to a solution of **13a** (1.7 g, 2.22 mmol) in 80 ml of THF at −45 °C. The reaction mixture was poured into 200 ml of ice cold aqueous sat. NH_4Cl, the aqueous phase extracted with ether (4 × 40 ml), the combined organic phases were washed subsequently with ice cold aqueous 1% HCl (20 ml), water (20 ml), aqueous sat. $NaHCO_3$ solution (20 ml) and brine (20 ml). The organic phase was dried over Na_2SO_4, the solvent removed *in vacuo* at room temperature and the residue filtered over a short silica gel column with ether. The ether solution was again concentrated *in vacuo* and the crude product purified by CC (PE : Et_2O, 9 : 1). Yield: 130 mg (14%) of **14a** (R_f = 0.21), as colorless crystals, mp = 190 °C (decomp.). IR (KBr): $\tilde{\nu}$ = 3426, 3046, 2924, 1454 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 194 (4.816), 214 (4.269, sh), 260 (4.324), 272 nm (3.979, sh). ^{1}H NMR: δ 2.10 (m, 4 H), 2.65 (m, 4 H), 4.76 (s, 4 H), 5.88 (s, 4 H), 7.34 (m, 10 H). ^{13}C NMR: δ 24.6 (−), 39.7 (−), 68.3 (−), 72.6 (C_{quat}), 86.2 (C_{quat}), 97.1(C_{quat}), 120.2 (+), 127.6(+), 127.9 (+), 128.3(+), 138.0 (C_{quat}). MS (CI, positive ion, NH_3): *m/z* (%) 460 (100) [M + NH_4^+]. $C_{32}H_{26}O_2$ (442.56): calc. C 86.85, H 5.92; found C 86.86, H 6.02%.

1,11-Bis(tetrahydropyran-2-yloxy)-4,8-bis[3-(tetrahydropyran-2-yloxy)prop-1-ynyl]undeca-2,9-diyne-4,8-diol 11b. To a solution of THP-protected propargyl alcohol (8.94 g, 63.8 mmol) in 60 ml of THF at −30 °C was added 42.5 ml of butyllithium (64 mmol, 1.5 M in hexane). The solution was stirred for 0.5 h, 1,5-pentanedioic acid diethyl ester **10b** (2.0 g, 10.6 mmol) added, the reaction mixture allowed to warm to 0 °C and stirred 0.5 h at this temperature. Work up following the procedure described for **11a** and CC (PE : Et_2O, 1 : 1) gave 5.5 g (79%) of **11b** (R_f = 0.46, Et_2O), as a colorless oil. IR (film): $\tilde{\nu}$ = 3385, 2925, 1156 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 192 (3.689), 196 (3.577, sh), 212 (2.894, sh), 258 nm (2.163). ^{1}H NMR: δ 1.72 (m, 32 H), 1.95 (s, 4 H), 3.53 (m, 4 H), 3.83 (m, 4 H), 4.28 (d, 4 H, ^2J = 15.7), 4.34 (d, 4H, ^2J = 15.7 Hz), 4.84 (m, 4 H). ^{13}C NMR: δ 18.5 (−), 19.3 (−), 25.0 (−), 29.8 (−), 43.0 (−), 53.9 (−), 61.4 (−), 62.7 (C_{quat}), 78.9 (C_{quat}), 86.1 (C_{quat}), 96.3 (+). MS (CI, negative ion, NH_3): *m/z* (%) 656 (5) [M], 655 (10) [M − 1], 554 (5) [M − OTHP], 101 (60) [OTHP]. $C_{37}H_{52}O_{10}$: calc. C 67.66, H 7.98; found C 67.56, H 8.48%.

Dibenzyl ether of 11b, *i.e.* 12b. NaH (320 mg, 13 mmol), **11b** (4.0 g, 6.1 mmol), *n*-Bu_4NI (1.1 g, 3.0 mmol) and benzyl bromide (1.6 ml, 13 mmol) were allowed to react in 20 ml THF according to the procedure given for compound **12a**. Work up and CC (Et_2O) yielded 4.7 g (93%) of **12b** (R_f = 0.66), as a yellowish oil. IR (KBr): $\tilde{\nu}$ = 3031, 2941, 1120, 736 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 194 (4.873), 210 (4.307), 224 nm (3.563). ^{1}H NMR: δ 1.65 (m, 26 H), 2.02 (m, 4 H), 3.50 (m, 4 H), 3.83 (m, 4 H), 4.30 (d, 4 H, ^2J = 15.7), 4.35 (d, 4 H, ^2J = 15.7 Hz), 4.76 (s, 4 H), 4.81 (m, 4 H), 7,32 (m, 10 H). ^{13}C NMR: δ 19.0 (−), 19.5 (−), 25.3 (−), 30.2 (−), 42.5 (−), 54.1 (−), 61.9 (−), 67.9 (−), 69.8 (C_{quat}), 81.2 (C_{quat}), 83.9 (C_{quat}), 96.8 (+), 127.3 (+), 127.7 (+), 128.2 (+), 138.4 (C_{quat}).

1,11-Dibromo-4,8-bis(benzyloxy)-4,8-bis(3-bromoprop-1-ynyl)undeca-2,9-diyne 13b. Triphenylphosphine 22.0 g (84.0 mmol), Br_2 4.3 ml (13.4 g, 84.0 mmol) and **12b** 10.0 g (12.0 mmol) were allowed to react in 200 ml of CH_2Cl_2 at 0 °C according to the procedure described for compound **13a**. Work up and CC (PE : Et_2O, 1 : 1) yielded 9.6 g (80%) of **13b** (R_f = 0.7), as a yellow oil. IR (film): $\tilde{\nu}$ = 3004, 2926, 1606, 737 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 192 (4.868), 210 (4.492, sh), 248 (3.760, sh), 412 nm (2.952). ^{1}H NMR: δ 2.03 (m, 6 H), 3.95 (s, 8 H), 4.74 (s, 4 H), 7.32 (m, 10 H). ^{13}C NMR: δ 13.8 (−), 19.4 (−), 42.1 (−), 68.2 (−), 69.7 (C_{quat}), 80.7 (C_{quat}), 84.3 (C_{quat}), 127.6 (+), 127.9 (+), 128.3 (+), 138.0 (C_{quat}). MS (CI, positive ion, NH_3): *m/z* (%) 770 (74) [M + NH_4^+], 664 (78) [M + 1 − OBn], 108 (63) [OBn + 1].

1,8-Di(benzyloxy)bicyclo[6.6.3]heptadeca-4,11-diene-2,6,9,13-tetrayne 14b. A solution of HMDS (1.3 ml, 6.0 mmol), butyllithium (4.0 ml, 6.0 mmol) and HMPA (10.4 ml, 60.0 mmol) in 6 ml of THF was added dropwise over 5 h to a solution of **13b** (752 mg, 1.0 mmol) in 80 ml of THF at −45 °C. The reaction mixture was worked up as described for compound **14a** and CC (PE : Et_2O, 9 : 1) gave 30 mg (7%) of **14b** (R_f = 0.32), as colorless crystals. ^{1}H NMR: δ 1.14 (m, 6 H), 4.64 (s, 4 H), 5.84 (s, 4 H), 7.29 (m, 10 H). ^{13}C NMR: δ 29.7 (−), 31.9 (−), 68.6 (−), 72.3 (C_{quat}), 86.2 (C_{quat}), 97.1 (C_{quat}), 121.4 (+), 127.6 (+), 128.0 (+), 128.3 (+), 138.0 (C_{quat}). MS (EI): *m/z* (%) 428 (1) [M^+], 91 (100) [CH_2Ph].

1,10-Bis(tetrahydropyran-2-yloxy)-4,7-bis[3-(tetrahydropyran-2-yloxy)prop-1-ynyl]deca-2,8-diyne-4,7-diol 11c. A solution of THP-protected propargyl alcohol (8.93 g, 63.8 mmol) in 60 ml of THF was treated at −30 °C with 42.5 ml of butyllithium (63.8 mmol, 1.5 M in hexane) and stirred for 0.5 h. 1,4-Butanedioic acid diethyl ester **10c** (2 ml, 2 g, 11.7 mmol) was added, the reaction mixture allowed to warm to 0 °C and worked up as described for **11a**. CC (PE : Et_2O, 1 : 1) gave 3.2 g (43%) of **11c** ($R_f = 0.25$), as a colorless oil. IR (KBr): $\tilde{\nu}$ = 3358, 2943, 2854, 2218 (C≡C), 1202 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 192 (3.784), 218 (3.885), 412 nm (2.046). ^1H NMR: δ 1.69 (m, 24 H), 2.23 (s, 4 H), 3.54 (m, 4 H), 3.84 (m, 4 H), 4.26 (d, 4 H, $^2J = 15.7$), 4.32 (d, 4 H, $^2J = 15.7$ Hz), 4.80 (m, 4 H). ^{13}C NMR: δ 18.9 (−), 25.3 (−), 30.2 (−), 38.8 (−), 54.2 (−), 61.9 (−), 62.7 (C_{quat}), 79.8 (C_{quat}), 85.7 (C_{quat}), 96.9 (+). MS (CI, negative ion, NH_3): m/z (%) 660 (98) [M + NH_4^+], 102 (100) [OTHP + 1]. $C_{36}H_{50}O_{10}$: calc. C 67.27, H 7.84; found C 67.93, H 8.31%.

Dibenzyl ether of 11c, *i.e.* 12c. NaH (242 mg, 10.1 mmol), benzyl bromide (1.2 ml, 10.1 mmol), *n*-Bu_4NI (850 mg, 2.3 mmol) and **11c** (3.0 g, 4.7 mmol) were allowed to react in 80 ml of THF as described for **12a** above. Work up and CC yielded 3.8 g (99%) of **12c** ($R_f = 0.68$), as a yellow oil. IR (KBr): $\tilde{\nu}$ = 3031, 2942, 1607, 736 cm^{-1}. UV (CH_3CN): λ_{max} (log ε) = 192 (4.907), 206 (4.264), 218 (4.062), 258 nm (3.476). ^1H NMR: δ 1.60 (m, 24 H), 2.36 (s, 4 H), 3.52 (m, 4 H), 3.81 (m, 4 H), 4.34 (m, 8 H), 4.76 (s, 4 H), 4.80 (m, 4 H), 7.32 (m, 10 H). ^{13}C NMR: δ 19.1 (−), 25.3 (−), 30.2 (−), 38.0 (−), 54.1 (−), 62.1 (−), 67.9 (−), 69.3 (C_{quat}), 81.5 (C_{quat}), 83.6 (C_{quat}), 96.9 (+), 127.3 (+), 127.8 (+), 128.2 (+), 138.2 (C_{quat}). MS (CI, positive ion, NH_3): m/z (%) 840 (0.5) [M + NH_4^+], 85 (49) [Bn^+].

1,10-Dibromo-4,7-bis(benzyloxy)-4,7-bis(3-bromoprop-1-ynyl)deca-2,8-diyne 13c. PPh_3 6.6 g (25 mmol), Br_2 1.3 ml (4.0 g, 25 mmol) and **12c** 3.0 g (3.6 mmol) were allowed to react in 100 ml CH_2Cl_2 at 0 °C as described above. Work up and CC (PE : Et_2O, 1 : 1) gave 2.1 g (78%) of **13c** ($R_f = 0.76$, Et_2O), as colorless crystals, mp = 107 °C. IR (KBr): $\tilde{\nu}$ = 3425, 3000, 2943, 1453, 749 cm^{-1} (CH_2). UV (CH_3CN): λ_{max} (log ε) = 194 (4.759), 210 (4.462, sh), 226 nm (4.011, sh). ^1H NMR: δ 2.31 (s, 4 H), 3.96 (s, 8 H), 4.74 (s, 4 H), 7.34 (m, 10 H). ^{13}C NMR: δ 13.6 (−), 37.6 (−), 68.3 (−), 69.1 (C_{quat}), 80.9 (C_{quat}), 83.9 (C_{quat}), 127.6 (+), 128.0 (+), 128.3 (+), 137.8 (C_{quat}). MS (CI, positive ion, NH_3): m/z (%) 756 (2) [M + NH_4^+], 328 (100) [M − OBn − 4 Br]. $C_{30}H_{26}Br_4O_2$: calc. C 48.82, H 3.55; found C 48.86, H 3.50%.

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17 To exclude product decomposition by thermal diradical cyclization we added $Co_2(CO)_8$ to the crude reaction mixture in order to coordinate the triple bonds of the product and reduce thereby the ring strain. The method has successfully been applied with other strained, unstable enediynes. However, in our case no products could be identified from the reaction mixture.
18 The structure of compound **13b** was also confirmed by X-ray diffraction analysis (triclinic, space group $P\bar{1}$, a = 830.6(3), b = 975.5(4), c = 1028.6(5) pm, α = 80.09(4), β = 81.98(3), γ = 88.98(3)°, $Z = 1$), but was rendered imprecise by high U values even at −45 °C; below this temperature the crystals are not stable, presumably because of a phase transition.
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