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DIOXA-CAGE AND BRIDGED COMPOUNDS AS POSSIBLE PRECURSORS FOR TRICYCLO[5.5.0.0^{4,10}]DODECA-2,5,8,11-TETRAENE

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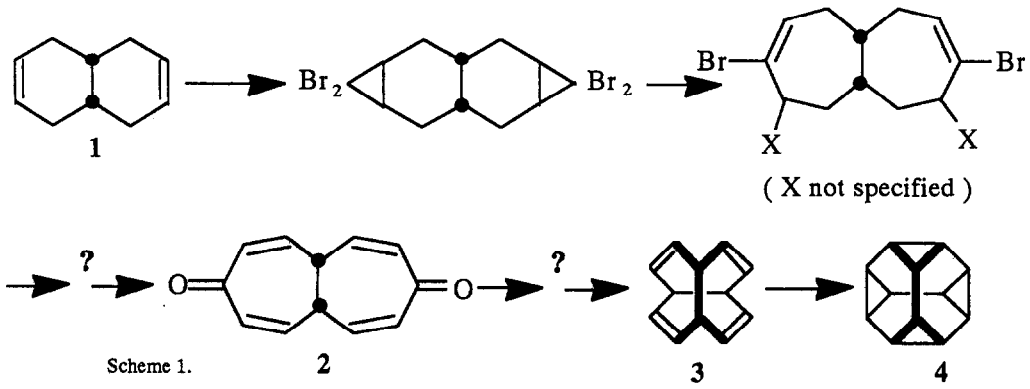
Abstract: *The bis-dibromocarbene adduct 6 of oxa-[4.4.3]propelladiene (5) was solvolyzed in the presence of silver nitrate yielding 7 and the novel cage compound 8. Attempts at conversion of the latter into a derivative of 3 were not sucessful as yet. Experiments towards ring enlargement of 9 via silylenol ethers / carbene additions gave 10-13. In another novel and unique transformation, bridged polycycles 14 and 15 are formed by dibromocarbene additions to the bis-enol ether of 12.*

Only a small minority of the 357 isomers of $(CH)_{12}$ listed by Balaban[1] are known. The challenging title compound **3** has been the goal of calculative [2-3] and synthetic [4-6] endeavour ever since Woodward and Hoffmann [7] predicted its $\pi 2_a + \pi 2_a + \pi 2_a + \pi 2_a$ photocyclization to the highly symmetrical $(CH)_{12}$ "truncated tetrahedrane" (**4**).[8] It occurred to us that a cis-1,4,5,8,9,10-hexahydronaphthalene like **1** might be a useful starting material towards hydroheptalenenediones of type **2** as shown in Scheme 1. These in turn could possibly be cyclized intramolecularly and be elaborated further by subsequent conversion into **3** or its derivatives.

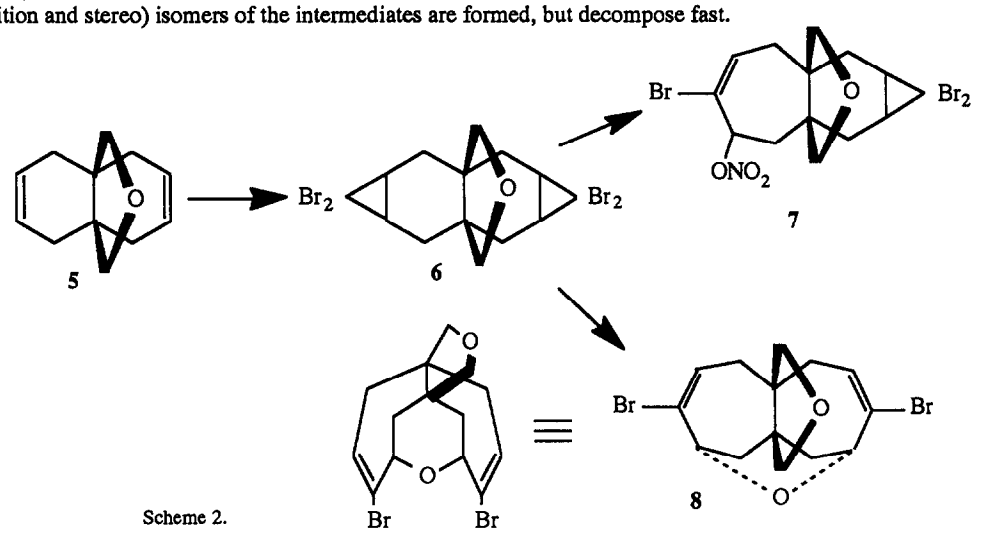


Scheme 1. **2** **3** **4**

Compound **5**, a stereochemically fixed derivative of **1**, was chosen as an easily available starting material [9] (Scheme 2). Double addition of dibromocarbene under phase transfer catalysis furnished **6** in 50 % yield as a mixture of stereoisomers which could not be separated. ^{1}H- and ^{13}C-NMR spectroscopy indicated that the major isomer (~ 5 : 1) is probably syn-anti- **6**. Solvolysis of the mixture with silver nitrate in acetone/water at

90°C did not yield the expected diol. Instead, relatively low yields of compounds **7** (6%) and **8** (11 - 24%, depending on reaction time) were obtained. Working with silver trifluoroacetate instead of $AgNO_3$ in dioxane/water, only **8** was isolated in up to 32 % yield. The structure of substance **7** follows mainly from its molecular formula in combination with the occurrence of IR signals for a nitrate group and the ^{13}C spectrum, indicating one intact cyclopropane ring plus two olefinic C-atoms, one bromine and one hydrogen carrying. The cage structure of compound **8** is derived again from the molecular composition and the relatively simple NMR. A total analysis of the ^1H spectrum is possible with the help of a COSY for compound **7** and by double resonance for substance **8.**

The formation of substances **7** and **8** can be understood by assuming ring opening of one dibromocyclopropane moiety to give an allyl cation which can be trapped either by nitrate ion (giving compound **7**) or by hydroxide. The anion of the allylic alcohol formed in the latter case can attack the second cyclopropane ring intramolecularly or alternatively trap the respective allyl cation, yielding compound **8** in both cases. Closure of the "cage" necessitates *endo* stereochemistry of the intermediate alcohol; whereas stereochemical details of the minor nitrate compound **7** remain unknown. Low yields may indicate that other (position and stereo) isomers of the intermediates are formed, but decompose fast.

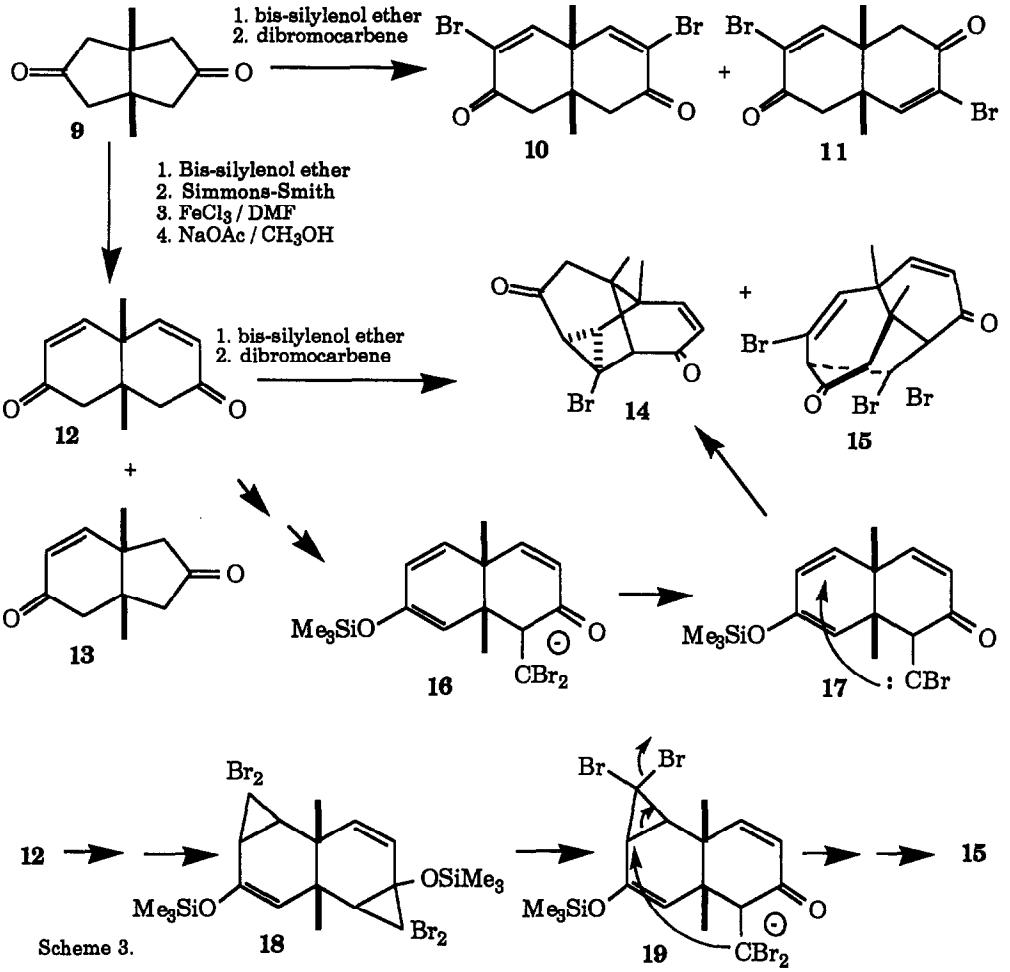


Scheme 2.

Compound **8** with its fixed geometry is rather close to the first synthetic goal of this study, a derivative of substance **2.** The ether bridge arranges the molecule in a geometry that should help in the planned C-C-bond formation. Preliminary experiments were performed to hydrolyze the vinylic bromides to ketones or to transform them by metal-halogen exchange (*tert*-butyl lithium) with subsequent trapping by various reagents. A series of such experiments was not met by success as yet.

Another approch towards **2**-like substances could be a fourfold ring enlargement of substance **9.**[10] This compound (Scheme 3) was transformed into a mixture of isomeric bis-(trimethylsilyl)enol ethers which in turn were treated with dibromocarbene from bromoform / potassium *tert* -butoxide to give a mixture of compounds **10** and **11.** Interestingly, yields (5 to 36%) were strongly dependent on the brand of commercial KOt-Bu

used.[11] It turned out that a small residual amount of *tert* -butanol in the tert-butanolate was beneficial. If the silylenol ethers were prepared by LDA / chlorotrimethylsilane / THF at -90°C (kinetic control), the ratio of compounds **10** and **11** was ca. 55 : 45 whereas a preparation *via* NEt_3 / $ClSiMe_3$ / DMF (thermodynamic control) led to a 1 : 11 ratio. The isomers could be separated by chromatography. Renewed transformation of substances **10** and **11** into enol ethers and carbene addition did not yield any traceable products. Standard methods of dehalogenation did not succeed either.



Scheme 3.

Therefore, ring enlargement of the **9**-bis-silylenol ether (prepared *via* the LDA route) was attempted by *Simmons-Smith* cyclopropanation using Zn/Cu / CH_2I_2 / ether followed by reaction with $FeCl_3$ in DMF and NaOAc in methanol.[12] Substances **12** (13% yield) and **13** (17%) were isolated from the very complex reaction mixture. A regio-isomer of **12** was not found. Next substance **12** in turn was transformed into the respective bis-silylenol ether and converted with dibromocarbene either from KOt-Bu / $HCBr_3$ or from the *Seyferth* reagent Ph-Hg-CBr_3. In both cases an 18% yield of unexpected polycyclic compound **14** was

separated as the only pure product from the reaction mixture. Its structure can be deduced again from ^{1}H- and ^{13}C-NMR spectra. In addition, a small amount of a Br_3-diketone (which could not be separated completely from re-isolated **13**) was found in the bromoform / potassium tert-butoxide conversions. MS and NMR data indicate that this must be compound **15**.

The formation of these bridged compounds is rather unique and remarkable. We propose the following reaction paths that lead to compounds **14** and **15**, respectively: (1) Addition of :CBr_2 to one enol ether group of **12**-bis trimethylsilylenol ether. (2) Nucleophilic attack at silicon and ring opening yields anion **16**. (3) Elimination of Br$^-$ gives the new carbene **17**. (4) This in turn adds to the far double bond as indicated. (5) Hydrolysis of the remaining enol silyl ether function furnishes substance **14**. For the formation of compound **15**, the bis-dibromocarbene adduct **18** can be opened similarly to give **19**. Attack of the stabilized anion on the other dibromocyclopropane moiety and hydrolysis of the remaining trimethylsilyl enol ether finishes this reaction path.

To sum up then, novel unexpected intramolecular reactions have been discovered. The experiments indicate that compound **8** is the more likely candidate for preparing compound **2** or derivatives thereof.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ with the Bruker AM 300 instrument.

4,4,10,10-Tetrabromo-1,7-methanoxymethano-tetracyclo[5.5.0.0^{3,5}.0^{9,10}]dodecane (**6**; mixture of isomers): 10.0 g (51.5 mmol) of **5** and 310 mg of benzyltriethylammonium chloride are dissolved in 42 ml bromoform (0.47 mol) and 10 ml dichloromethane. This solution is dropped into a mixture of 46 g 50 % NaOH (0.575 mol) and 1.5 ml ethanol at 0°C under nitrogen. The reaction is stirred for 24 h at room temperature. The brownish sludge is diluted by ice-water, acidified by conc. HCl, and extracted repeatedly with CH_2Cl_2. The combined extracts are washed with dil. $NaHCO_3$, dried with Na_2SO_4, and evaporated to dryness. The residue is crystallized from ethyl acetate or chromatographed on silica gel with petroleum ether (b.p. 30-60°C) / ethyl acetate 2:1. -Yield: 11.2 g (38%), m.p.196-198°C, $C_{14}H_{16}Br_4O$ (519.9) req.: C 32.34 H 3.10 ; found: C 32.47 H 3.30. - ^{1}H-NMR : ∂ 1.05-1.14 (m; 4H), 1.62-1.67 (m; 2H), 1.77-1.84 (m; 2H), 1.87-2.02 (m; 4H), 3.56 (s; 4H); signals of lower intensity for the minor isomer (17 %) for second isomer: 0.79-0.87 (m), 3.76 (s). ^{13}C-NMR of major isomer: ∂ 26.8, 26.9 (C-tert), 29.7, 33.3, (C-sec), 41.5, 40.0, 43.8 (C-quart), 79.7 (C-sec).

Silver salt assisted solvolysis of **6** :
a) *with $AgNO_3$* : 7.5 g (14.4 mmol) of **6** are suspended in 200 ml acetone, a solution of 8.3 g (48.9 mmol) $AgNO_3$ in 60 ml water is added, and the mixture is refluxed for 78 h. Thereafter, the mixture is poured into saturated aqueous NaCl. After filtration, phases are separated, the aqueous layer is extracted by CH_2Cl_2, and the combined organic extracts are dried over Na_2SO_4 and then evaporated. The residue is chromatographed over silica gel with petroleum ether (b.p.30-60°C) / ethyl acetate 2:1. One after the other **6**, **7** (6%), and **8** (24%) are eluted.
5-Nitrato-4,4,10-tribromo-1,7-methanoxymethano-tricyclo[5.5.0.0^{3,5}]dodec-10-ene (**7**):
m.p. 205-207 °C (dec.); IR: 1270, 1625 cm^{-1}; $C_{14}H_{16}Br_3NO_4$ (502.0) req.: C 33.50 H3.21 N 2.79, found C 33.80 H 3.16 N 2.95.- ^{1}H-NMR: ∂ 6.44 (dd, J = 5.2 + 10.2; 1H), 5.66 (ddd, J = 1.9 + 6.1 + 11.9; 1H), 3.84 (d, J= 9.5; 1H), 3.75 (d, J=9.4; 1H), 3.55 ("t", J=8.6; 2H), 2.71 (ddd, J=2.0 + 5.2 + 15.2; 1H), 2.51 (dd, J=14.1 + 11.9; 1H), 1.83-2.14 (m; 6H), 1.21-1.28 (m; 1H), 1.01-1.14 (m; 1H). ^{13}C-NMR: ∂ 26.4, 26.5 (C-tert), 29.7, 31.3, 35.3, 38.0 (C-sec), 40.9, 43.9, 47.8 (C-quart), 81.5, 82.2 (C-sec), 84.2 (C-tert), 118.1 (C-quart), 137.0 (C-tert).

3,8-Dibromo-5a,10a-methanoxymethano-4,7-epoxy-1,4,5,5a,6,7,10,10a-octahydroheptalene (**8**):
m.p. 167-170°C; $C_{14}H_{16}Br_2O_2$ (376.1) req.: C 44.71 H 4.29; found: C 44.67 H 4.28. ^{1}H-NMR: ∂ 6.26 (dd, J=3.1 + 9.8; 1H), 4.62 (dd, J=1.0 + 6.3; 1H), 3.48 (s; 2H), 3.69 (s; 2H), 2.72 (dd, J=3.1 + 16.4; 1H), 2.61 (dd, J=1.0 + 14.1; 1H), 1.98 (dd, J=6.3 + 14.1; 1H), 1.92 (dd, J=9.8 + 16.4; 1H).- ^{13}C-NMR: ∂ 36.8, 39.0 (C-sec), 42.2, 56.3 (C-quart),78.2 (C-tert), 84.9, 85.7 (C-sec),125.2 (C-quart),133.8 (C-tert).
b) *With Ag trifluoroacetate* : 6.0 g (11.5 mmol) **6** in 100 ml dioxane are mixed with 7.5 g (34 mmol) AgO_2CCF_3 in 25 ml water and refluxed for 12 h. Workup is performed as above; yield: 1.39 g (32%) **8**.
Isomer mixture of the bis-trimethylsilylenol ethers of (**9**):
a) A solution of 15.0 g (90.2 mmol) **9** [11] and 30 ml $ClSiCl_3$ (0.24 mol) in 200 ml absol.THF are cooled to -80°C and 0.21 mol LDA in hexane/THF (precooled to -60°C) are slowly dropped in under nitrogen. The mixture is stirred for 30 min., then slowly warmed to room temperature within 2 hours under continued stirring. Solvents are removed *in vacuo* , the residue is taken up in petroleum ether, washed twice with aq. $NaHCO_3$, dried over Na_2SO_4. It is used as such (see below), but can be distilled in a Kugelrohr apparatus (b.p. 130-140°C / 0.3 mbar).
b) 20 ml absol. NEt_3 are dropped into 10.0 (60.2 mmol) **9** and 18 ml $ClSiCl_3$ (0.14 mol) in 60 ml absol. DMF under nitrogen, and the mixture is stirred for 2 h at 70-80°C and 15 h at room temperature. The brownish suspension is treated with 300 ml petroleum ether (b.p. 30-60°C), and the precipitate is filtered off and washed with petroleum ether. The combined organic phases are washed with aq.$NaHCO_3$ and worked up as above.
Dibromocarbene addition to the bis-enol ethers :
60.0 g (0.54 mol) of commercial potassium tert-butylate containing some tert-butanol[11] (alternatively,"dry" material is treated with about 1/2 molar eqivalent of tert-butanol) are suspended in 150 ml petroleum ether (b.p. 30-60°C), the solution of bis-enol ethers from 15 g **9** (see a), above) is added, and the mixture is cooled to -40°C. Under nitrogen, 22 ml (0.25 mol) of bromoform are dropped in slowly. The mixture becomes brownish and hard to stir. If necessary, more petroleum ether is added. Stirring is continued after the addition for 3h at room temperature. The mixture is worked up by pouring into ice-water, acidifying with dil.HCl, phase separation, extraction of the aqueous phase with dichloromethane, drying of the organic extracts with Na_2SO_4, and removal of the solvents *in vacuo*. The dark tarry product is taken up in 250 ml of methanol. 50 ml conc. HCl are added, and the mixture is hydrolyzed overnight at room temperature. The brownish precipitate is filtered off (11.4 g = 36 % calc. rel. to **9**). It is separated by chromatography on silica gel with petroleum ether / ethyl acetate 2:1 to give
3,6-Dibromo-1,4a,8,8a-tetrahydro-4a,8a-dimethyl-2,7-naphthalenedione (**10**):
m.p. 202-205° C; $C_{12}H_{12}Br_2O_2$ (348.1) req.: C 41.41 H 3.48; found C 41.29 H 3.56. ^{1}H-NMR: ∂ 1.13 (s; 3H), 1.42 (s; 3H), 2.40-2.85 (m; 4H), 6.99 (s; 2H) .- ^{13}C-NMR: ∂ 21.3, 22.6 (C-prim), 40.9 (C-quart), 47.0 (C-sec), 47.8 (C-quart), 123.6 (C-?), 149.3 (C-?), 189.0 (C-quart)
and
3,7-Dibromo-1,4a,5,8-tetrahydro-4a,8a-dimethyl-2,6-naphthalenedione (**11**):
m.p. 192-194°C, $C_{12}H_{12}Br_2O_2$ (348.1) req.: C 41.41 H3.48; found C 41.69 H 3.81. ^{1}H-NMR: ∂ 1.29 (s; 6H), 2.65-2.85 (m; 4H), 6.97 (s; 2H).- ^{13}C-NMR: ∂ 21.8 (C-prim), 44.7 (C-quart), 46.5 (C-sec), 123.4 (C-?), 154.5 C-?), 188.0 (C-quart).
The isomer ratio is 55 :45 if the silylenol ethers are prepared *via* method a) and 1 : 11 if method b) is used.
Ring enlargement of **9** *to yield* **12** *and* **13**:
33 g Zn / Cu pair [13] are refluxed in 200 ml absol. ether while a solution of the 26.5 g (85.3 mmol) distilled bis-enol ether formed according to a) (above) and 25 ml (0.31 mol) diiodomethane in 50 ml absol. ether are slowly dropped in under nitrogen. The mixture is heated for 20 h, cooled, and carefully (exothermic reaction !) hydrolyzed with cold saturated ammonium chloride in water. The precipitate is filtered off, and the filtrate is washed with aq. NH_4Cl and $NaHCO_3$, dried over Na_2SO_4, and concentrated by rotatory evaporation. The residual turbid oil is taken up in 50 ml absol. DMF and dropped to a suspension of 35.0 dry $FeCl_3$ in 200 ml of absol. DMF under nitrogen at 0-5°C. After 3h of stirring at room temperature, the mixture is poured into an ice-cold solution of 100 ml conc. H_2SO_4 in 900 ml water. The new mixture is kept for 30 min., then it is extracted 4 times with dichloromethane. The extracts are washed with aq. $NaHCO_3$, dried with Na_2SO_4, and

concentrated *in vacuo*. The residue is taken up in 200 ml of methanol, 20g of sodium acetate are added, and the mixture is refluxed for 2 h. Thereafter 300 ml water are added, and the solution is extracted repeatedly with dichloromethane. Drying and evaporation leave a reddish viscous oil which can be crystallized from a little ethanol. Chromatography on silica gel with petroleum ether (b.p. 30-60°C) / ethyl acetate 2 : 1 yields first 17 % of **13**, then 13 % **12**.

3,3a,7,7a-Tetrahydro-3a,7a-dimethyl-(1H)-2,6-indenedione (**13**):

m.p. 172-175°C, $C_{11}H_{14}O_2$ (178.2) req.: C 74.13 H 7.92; found C 74.30 H 7.90.- ^{1}H-NMR: ∂ 1.13 (s; 3H), 1.25 (s; 3H), 2.15 (d, J=18.5; 1H), 2.33 (d, J=18.5; 1H), 2.43-2.45 (m; 4H), 5.97 (d, J=10.1; 1H), 6.56 (d, J=10.1; 1H).- ^{13}C-NMR: ∂ 20.8, 23.6 (C-prim), 42.4, 43.3 (C-quart), 45.4, 50.5, 50.8 (C-sec), 127.7, 155.6 (C-tert), 197.9, 214.2 (C-quart).

1,4a,8,8a-Tetrahydro-4a,8a-dimethyl-2,7-naphthalenedione (**12**):

m.p. 122-125°C, $C_{12}H_{14}O_2$ (190.2) req.: C 75.76 H 7.42; found C 75.46 H 7.41.- ^{1}H-NMR: ∂ 1.10 (s; 3H), 1.34 (s; 3H), 2.10-2.75 (broad s; 4H), 6.07 (d, J=10.1; 2H), 6.54 (d, J=10.1; 2H).- ^{13}C-NMR: ∂ 21.4, 22.9 (C-prim), 40.2, 41.6 (C-quart), 47.4 (C-sec), 127,8, 150.8 (C-tert), 197.7 (C-quart).

Formation of **14** and **15**:

700 mg (3.7 mmol) **12** are transformed into the bis-trimethylsilyl enol ether by the LDA method as descibed above for **9**. This is reacted with bromoform / potassium tert-butylate and worked up as described for the **10/11** preparation. The raw product is chromatographed twice on silica gel with petroleum ether / ethyl acetate 2:1 and 3:1, respectively, to separate the tarry, multicomponent system. A mixture of **12** and **15** (calculated yield 6%) is eluted first, then **14** (18%) is washed from the column.- A reaction of the bis-enol ether with $PhHgCBr_3$ (5h of refluxing under nitrogen in benzene) gives a similar reaction mixture, which yields only 18 % **14** on chromatography.

5-Bromo-1,7-dimethyltetracyclo[5.4.0^{1,7}.0^{4,6}.0^{5,11}]undec-8-ene-3,10-dione (**14**):

m.p. 199-202°C, $C_{13}H_{13}BrO_2$ (281.1) req.: C 55.54 H 4.66; found C 55.51 H 4.76.-^{1}H-NMR: ∂ 1.28 (s; 3H), 1.37 (s; 3H), 2.20 (dd, J=7.1 + 1.1; 1H), 2.24 (d, J=7.1; 1H), 2.43 (dd, J=19.6 + 3.2; 1H), 2.47-2.50 (m; 1H), 2.76 (dd, J=19.6 + 2.5; 1H), 6.18 (d, J=9.5; 1H), 7.24 (d, J=9.5; 1H). - ^{13}C-NMR : ∂ 15.4, 17.1 (C-prim), 37.9 (C-sec), 41.0, 46.8 (C-tert), 47.4, 49.0 (C-quart), 52.5 (C-tert), 75.0 (C-quart), 126.7, 160.7 (C-tert), 191.2, 203.8 (C-quart).

5,12,12-Tribromo-1,7-dimethyltricyclo[5.4.1^{4,11}]dodeca-5,8-diene-3,10-dione (**15**):

^{1}H-NMR: ∂ 1.40 (s; 3H), 1.55 (s; 3H), 2.81-2.91 (m ; 2H), 3.39 (dd, J=16.2 + 4.1; 1H), 4.87 (s;1H), 6.23 (d J=9.6; 1H), 7.03 (d, J=9.6; 1H), 7.04 (s; 1H).- ^{13}C-NMR : ∂ 19.6, 23.5 (C-prim), 43.1(C-sec), 52.2 (C-quart), 55.0 (C-quart), 57.7, 78.3 (C-tert), 81.7, 125.9 (C-quart), 126.7, 152.8, 159.7 (C-tert), 188.6, 193.0 (C-quart).

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