

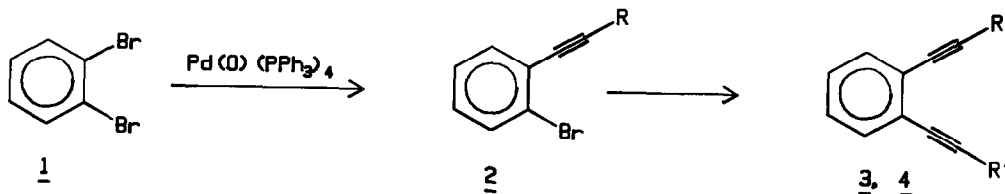
THE SYNTHESIS OF 11-13-MEMBERED DIACETYLENIC
 AND 18-MEMBERED TETRAACETYLENIC RING
 SYSTEMS

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Abstract: The synthesis of title compounds is described, starting from *o*-dibromobenzene. The palladium catalysed coupling of the latter with acetylenes occurred in a step-wise fashion, when no cocatalyst (CuI) was used.

Carzinostatin¹ and the esperamicins² and calicheamicins³ are characterized by their highly strained diacetylenic ring systems. A simple entry into the ene-diyne system of the latter would be the Pd(0) catalysed coupling of *Z*-1,2-dihalo olefins with terminal acetylenes⁴. In order to increase the stability and geometric integrity of the resulting ene diynes, we decided to use *o*-dibromobenzene as a precursor, coupling it with various terminal acetylenes.

Reaction of *o*-dibromobenzene **1** with propargyl alcohol in refluxing *n*-propylamine⁵ in the presence of 2% Pd(0)(PPh₃)₄ gave **2a**⁶ after 4-6 h in 96% yield, contaminated with 4% **3a**. In a similar manner, **2b-g** were produced.



2 **a**; R = CH₂OH, **b**; R = *n*-C₅H₁₁, **c**; R = (CH₂)₂OH, **d**; R = (CH₂)₃OH, **e**; R = Si(CH₃)₃

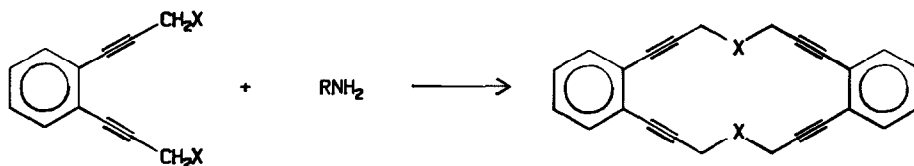
3 **a-g**; R = R'

4 **a**; R = CH₂OH, R' = *n*-C₅H₁₁, (CH₂)₂OH, (CH₂)₃OH,

b; R = *n*-C₅H₁₁, R' = (CH₂)_nOH n = 1,2,3 **c**; R = (CH₂)₂OH, R' = (CH₂)₃OH

The nature of the amine was not critical, and *n*-propylamine could be replaced with *t*-butylamine, or diethylamine. Heating **2** for a further 18 h with 1.5 eq. of the acetylene, or heating **1** with 3 eq. of acetylene gave the symmetrically disubstituted diacetylenes **3 a-g**.

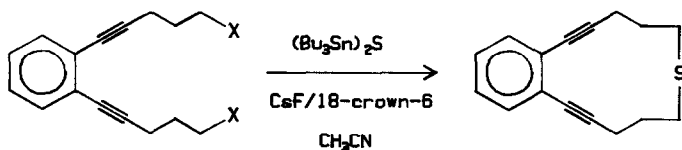
Similarly cross-coupled diynes **4 a-c** were obtained by purifying **2 a-g**, and resubmitting them to the same reaction using different terminal acetylenes. When CuI (3%) was added as a cocatalyst, the reaction time was considerably shorter (2-3 h, 25°C), and only disubstituted acetylene **3 a-g** could be isolated.



3a ;	X = OH	8 ;	X = NCH ₂ CH ₂ CH ₃
5 ;	X = OMs	9 ;	X = NCH(CH ₃) ₂
6 ;	X = SAc, 6a ;	10 ;	X = O
7 ;	X = CH(COOCH ₃) ₂	11 ;	X = S
		12 ;	X = C(COOCH ₃) ₂

In order to explore the ease of ring formation, propargyl alcohol derivative **3a** was converted to its dimesylate, and the dimesylated **5** (0.43 mmol/5 mL THF) was added slowly⁷ to n-propylamine (1 eq./4 eq. NEt₃/10 mL THF) or isopropylamine (1 eq./4 eq. NEt₃/10 mL THF) at 25°C. The 18-membered tetraacetylenic amines **8**, m.p. 128-130°C, and **9**, m.p. 145-148°C were obtained in nearly quantitative yield⁶. Similarly, ether **10**, m.p. 181-183°C, was obtained in 91% yield by a slow addition of dimesylate **5**, (0.43 mmol/5 mL THF) to the dianion of **3a** (1 eq./2eq. n-BuLi/-78°/10 mL THF). Reaction of dimesylate **5** (1 eq.) with potassium thioacetate (2 eq./THF) gave dithioacetate **6** which upon reaction with sodium methoxide in methanol, followed by the addition of dimesylate **5** in THF, gave bis thio ether **11**, m.p. 138-140°C, in 91% yield. Reaction of **5** (1eq.) with dimethyl malonate (5 eq./8eq. K₂CO₃/DMF-THF (1:1)) gave bis malonate **7**, and slow addition of **5** (0.43 mmol/5 mL THF) to dimethyl malonate anion of **7** (1 eq./2eq. NaH/10 mL THF/0°C) provided carbocycle **12**, m.p. 165-168°C, in 88% yield. Whereas the absence of formation of a 9-membered ring was not unexpected; the high yields obtained for the formation of 18-membered ring systems **8** - **12** is remarkable.

In order to explore which size ring system is available by a relatively simple reaction, diol **3d** was converted to its diiodo

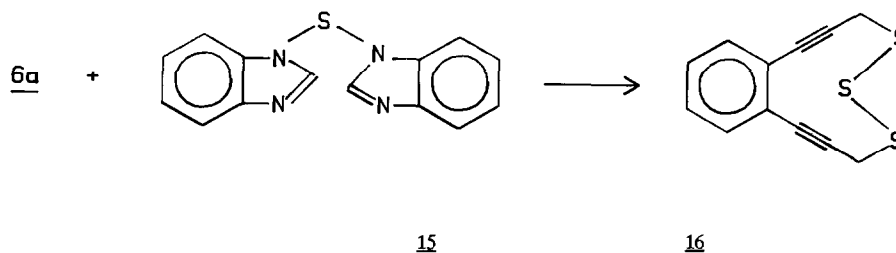


3d; X = OH **13**; X = I

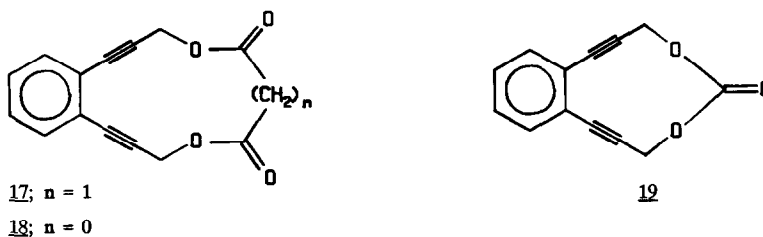
14

derivative **13**. Coupling with NaSH or Na₂S did not provide a useful product. However, reaction with the recently developed (Bu₃Sn)₂S⁸ at 70° gave the 13-membered ring sulfide **14**, m.p. 123-126°C, in 86% yield.

When thiol 6a (0.43 mmol/10 mL PhH), derived from thioacetate 6 by reaction with NaOMe/MeOH, was treated with sulfur transfer reagent 15⁹ (0.43 mmol/15 mL PhH), the 11-membered trisulfide 16, m.p. 78-81°C, was obtained in a 30% yield.



Finally, reaction of diol 3a (0.43 mmol) with malonyl dichloride (1 eq./1 eq. Py/cat. DMAP/20 mL CH₂Cl₂, 0°C), oxalyl chloride (1 eq./1 eq. Py/cat. DMAP/20 mL CH₂Cl₂, 0°C) and carbonyldiimidazole (1 eq./20 mL PhH/20°C) gave the 13,12, and 11-membered ester 17, m.p. 125-128°C, 18, m.p. 101-108°C, and 19, m.p. 96-99°C, in 62%, 55% and 30% yield respectively.



Acknowledgements

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- 5) General procedure: To *o*-dibromobenzene (5.0 mmol, 0.60 mL) in *n*-propylamine (15 mL), under nitrogen, at room temperature was added propargyl alcohol (7.5 mmol, 0.44 mL) and tetrakis(triphenylphosphine)palladium (0) (116 mg, 2%). The reaction mixture was heated and stirred for 5h. The reaction mixture was then quenched with aqueous ammonium chloride and the products were isolated by flash chromatography.
- 6) All compounds were characterized by ^1H NMR (CDCl_3 , 200 MHz) LRMS with specific ion monitoring to ascertain purity and HRMS. Compounds **2a-g** had a multiplet characteristic of the aromatic ring at δ 7.14-7.57 and all other compounds had two multiplets centered at δ 7.29-7.33 and δ 7.47-7.51. Significant characterization data includes: **2a**: δ 4.54 (s, 2H); m/e 211.9707 (calcd 211.9661). **3a**: δ 4.54 (s, 4H); m/e 186.0673 (calcd 186.0681). **5**: δ 3.15 (s, 6H, 2 CH_3), 5.11 (s, 4H, 2 CH_2); m/e 342.0114 (calcd 342.0231). **6**: 2.39 (s, 6H, 2 CH_3), 3.96 (s, 4H, 2 CH_2); m/e (CI with NH_3) 303 ($\text{M} + \text{H}^+ - \text{NH}_3$), 320.0777 (calcd 320.0778). **6a**: δ 2.13 (t, 2H, $J=7.3\text{Hz}$, 2SH), 3.55 (d, 4H, $J=7.3\text{Hz}$, 2 CH_2); m/e (CI with NH_3) 236 ($\text{M} + \text{H}^+ + \text{NH}_3$), 185 ($\text{M} + \text{H}^+ - \text{H}_2\text{S}$), 219.0300 (calcd 219.0302). **7**: δ 3.03 (d, 4H, $J=7.8\text{Hz}$, 2 CH_2), 3.69 (t, 2H, $J=7.8\text{Hz}$, 2CH); m/e (CI with NH_3) 432 ($\text{M} + \text{H}^+ + \text{NH}_3$), 415 ($\text{M} + \text{H}^+$), 415.1394 (calcd 415.1392). **8**: δ 0.93 (t, 6H, $J=7.23$, 2 CH_3), 1.58 (m, 4H, $J=7.23$, 2 CH_2), 2.69 (t, 4H, $J=7.23$, 2 CH_2N), 3.85 (s, 8H, 4 CH_2); m/e (CI with NH_3) 419 ($\text{M} + \text{H}^+$), 419.2477 (calcd 419.2487). **9**: δ 1.20 (d, 12H, $J=6.35$, 4 CH_3), 2.96 (q, 2H, $J=6.35$, 2CH), 3.95 (s, 8H, 4 CH_2); m/e (CI with NH_3) 419 ($\text{M} + \text{H}^+$), 419.2485 (calcd 419.2487). **10**: δ 4.66 (s, 8H, 4 CH_2); m/e (CI with NH_3) 354 ($\text{M} + \text{H}^+ + \text{NH}_3$), 337 ($\text{M} + \text{H}^+$), 354.1494 (calcd 354.1494). **11**: δ 3.82 (s, 8H, 4 CH_2); m/e (CI with NH_3) 386 ($\text{M} + \text{H}^+ + \text{NH}_3$), 369 ($\text{M} + \text{H}^+$), 369.0768 (calcd 369.0771). **12**: δ 3.40 (s, 8H, 4 CH_2), 3.80 (s, 12H, 4 CH_3O^-); m/e (CI with NH_3) 582 ($\text{M} + \text{H}^+ + \text{NH}_3$), 565 ($\text{M} + \text{H}^+$), 565.1861 (calcd 565.1862). **13**: δ 2.09 (q, 4H, $J=6.3\text{Hz}$, 2 CH_2), 2.60 (t, 4H, $J=6.3\text{Hz}$, 2 $\text{CH}_2 - \text{C}=\text{C}^-$), 3.39 (t, 4H, $J=6.5\text{Hz}$, 2 CH_2J); m/e 461.9699 (calcd 461.8093). **14**: δ 2.09 (q, 4H, $J=6.3\text{Hz}$, 2 CH_2), 2.60 (t, 4H, $J=6.3\text{Hz}$, 2 $\text{CH}_2 - \text{C}=\text{C}^-$), 3.90 (t, 4H, $J=6.3\text{Hz}$, 2 CH_2); m/e (CI with NH_3) 241 ($\text{M} + \text{H}^+$), 241.1052 (calcd 241.1050). **16**: δ 3.91 (s, 4H, 2 CH_2); m/e 247.9764 (calcd 247.9787). **17**: 5.05 (s, 4H, 2 CH_2); m/e 254.0591 (calcd 254.0578). **18**: 5.16 (s, 4H, 2 CH_2); m/e 240.0431 (calcd 240.0422). **19**: 5.02 (s, 4H, 2 CH_2); m/e 212.0468 (calcd 212.0473).
- 7) In cyclization reactions all additions were made using a syringe pump and were performed at a period of 20-30 h.
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