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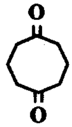
SYNTHESIS OF
CYCLODODECA-2,8-DIYNE-1,7-DIONE

Bernhard Bodenmann and Reinhart Keese*

Institut für organische Chemie, Universität Bern, Freiestrasse 3, CH-3012 Bern, Switzerland

Abstract: The 12-membered carbocyclic compound **5**, containing 2 α,β-unsaturated alkynone functionalities is prepared from 5-hexyn-1-ol in 9 steps. Ring closure is achieved by reductive C-C bond formation between the terminal iodoalkyne and aldehyde group using $CrCl_2$ in a yield of 62%.

Transannular interactions play an important role in medium-sized carbocyclic compounds like the diketone **1**, the diene **2** and diynes like **3**[1] and **4**.[2] For cyclic diynes of type **3** the results of Gleiter are particularly relevant[1]. The chemistry of compounds like **5**, where 1,4-additions to α,β-unsaturated carbonyl groups could be linked to transannular reactivity, is essentially unknown. It was therefore of interest to prepare the cyclic diyne-dione **5** as a member of this family of compounds.



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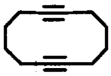

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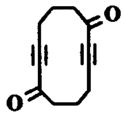

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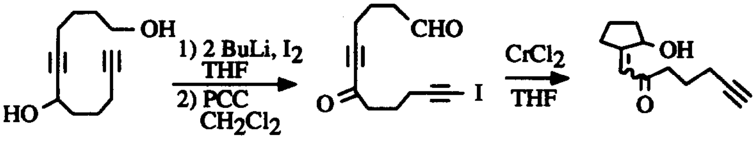
The $CrCl_2$ induced coupling of an iodoalkyne with an aldehyde according to Takai and Nozaki[3] was used successfully as key step for cyclisation[4]. In a first attempt the reductive cyclodimerisation of 6-iodohex-5-ynal **7b** was investigated. The latter compound is readily available from **6a** by treatment with 2 BuLi and I_2[5] and subsequent oxidation with PCC[6]. Since the cyclodimerisation of **7b** gave **14** only in low yield (<5%) the cyclisation was tried with **9**, which is prepared from hexynol **6a** and hexynal **7a** via **8**. However, in this case only **10** (22%) was obtained instead of the 12-membered ring compound. Reductive cyclisation to give the 12-membered ring compound **13** in over 60% was eventually achieved, when the oxidation of the secondary hydroxy group in **8** was intercepted.

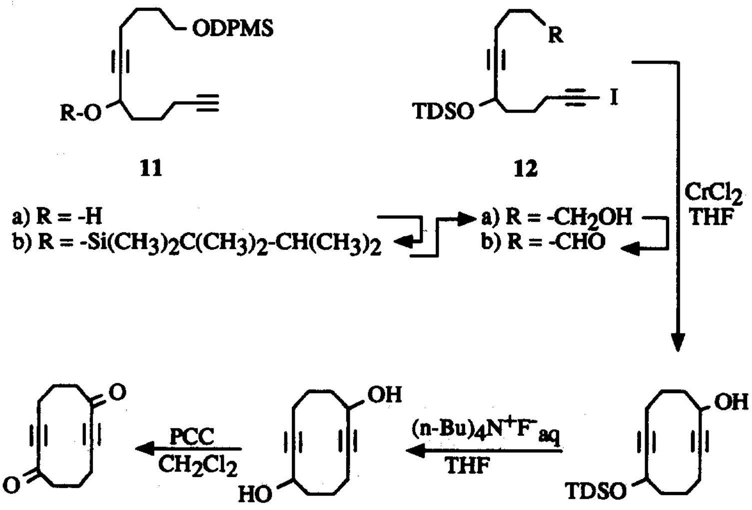
6 a) R = -H
b) R = $-Si(C_6H_5)_2CH_3$

7 a) R = -H
b) R = -I



8 **9** **10**

For this purpose the primary hydroxy group in **8** had to be protected in such a way, that it could readily be set free after blocking the secondary hydroxy group. This was achieved by using the diphenylmethyl silyl (DPMS) group, which according to Denmark[7] is stable toward Grignard reagents but labile to BuLi. Accordingly 5-hexyn-1-ol **6a** was treated with DPMSCl and imidazole in DMF to give **6b** in a yield of 91%. The Grignard reagent prepared from **6b** with EtMgBr was then added to hex-5-ynal to give 88% of **11a**. The secondary hydroxy group of **11a** was treated with



11 **12**

a) R = -H
b) R = $-Si(CH_3)_2C(CH_3)_2-CH(CH_3)_2$

a) R = $-CH_2OH$
b) R = -CHO

5 **14** **13**

thexyldimethyl silyl (TDS)-triflate in THF at -10°C for 5-10 min[8]. According to Wetter and Oertle[9] TDS ethers are similar to t.-butyldimethyl silyl ethers[10,11] and stable towards BuLi. Subsequent treatment of **11b** with 2 BuLi and I_2[5] gave directly the iodoalkynol **12a** (70%)[12], which was oxidized by PCC to the aldehyde **12b**. Reductive cyclisation of **12b** with $CrCl_2$ in THF gave **13** in a yield of 62%.[14,15] After removal of the TDS group with $Bu_4N^+F^-_{aq}$ in THF the diol **14** (6:1 mixture of diastereomers)[16] was oxidized to **5** (86%).[17] The overall yield **11a** → **5** was 25%.

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12. **12a** can also be obtained from **8** by selective acetylation of the primary hydroxyl group following [ref. 13], protecting the secondary hydroxyl group with TDSCl and treatment with 2 equiv. of BuLi and I_2.

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14. Addition of $NiCl_2$ [ref. 3c,d] did not encrease the yield.

15. **1-Hydroxy-7-thexyldimethylsiloxy-cyclododeca-2,8-diyne 13**: A solution of **12b** (7.0 g, 15.2 mmol) in 50 ml THF was added at room temperature to a stirred suspension of $CrCl_2$ (9.34 g, 76.01 mmol, anhydrous Cr(II)Cl_2, Fluka AG, Buchs) in 450 ml degased, anhydrous THF by syringe techniques over a period of 55 h. After 5 more hours of stirring the reaction mixture was diluted with ether and extracted with H_2O. The ether was removed from the emulsion obtained and the residue was extracted several times with hexane and centrifuged. The combined hexane extracts were dried over $MgSO_4$ and the crude product obtained after concentration was purified by silica gel chromatography with hexane-ethyl acetate (4:1) to give 3.19 g (62%) of **13** as a clear oil.

16. **1,7-Dihydroxy-cyclododeca-2,8-diyne 14**: The TDS-protecting group was removed by stirring 0.15 g (0.45 mmol) of **13** in THF with 0.424 g (1.34 mmol) $Bu_4N^+F^-_{aq}$ for 6 h at r.t.. After silica gel column chromatography with hexane-ethyl acetate (1:3) 0.083 g (96%) of **14** was obtained as a 6:1 diastereomeric mixture (mp. = 122°C).

17. **Cyclododeca-2,8-diyne-1,7-dione 5**: A sample of 0.121 g (0.63 mmol) of **14** was stirred at r.t. with 0.543 g (2.51 mmol) PCC in CH_2Cl_2 for 3.5 h. The reaction mixture was filtered through celite/silica gel and washed with CH_2Cl_2 and ether. After silica gel chromatography with hexane-ethyl acetate (2:1) 0.102 g (86%) of **5** was obtained. mp. = 45-47 °C; ^{1}H-NMR [300 MHz, $CDCl_3$, TMS, δ(ppm)]: 2.10(tt,4H,$^3J_1$=6.12, $^3J_2$=6.39), 2.56(t,4H,^3J=6.12), 2.73(t,4H,^3J=6.39); ^{13}C-NMR [300 MHz, $CDCl_3$, TMS, δ(ppm)] 19.25(t), 23.20(t), 44.02(t), 83.12(s), 95.95(s), 187.79(s); IR ($CHCl_3$): ν[cm^{-1}] = 2215, 1670; UV (CH_3CN): λ_{max}[nm](ε)= 316 (109), 220 (11660) MS[*m/z*]; 188(M^+,21), 161(53), 132(80), 104(100), 103(52), 79(89), high resolution MS: *m/z* (M^+-H): calc. for $C_{12}H_{11}O_2$: 187.075905, found: 187.075840.

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