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# Synthesis of a Cyclic Dienediyne Related to the Maduropeptin Chromophore

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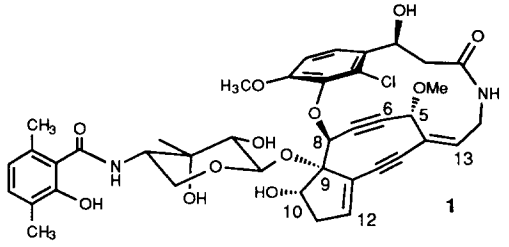
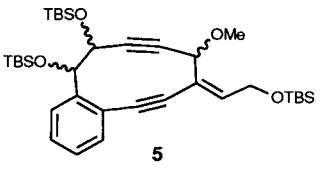
**Abstract**: We herein report the synthesis of aromatic analogues of the maduropeptin chromophore. Compounds **16a**, **16b** and **17** were conveniently prepared starting from 2-ethynylbenzaldehyde through a modified Nozaki-Hiyama reaction © 1997 Elsevier Science Ltd.

The recent discovery of the naturally occuring enediynes has aroused great interest in the scientific community.[1] The total synthesis of these new molecules as well as the search of new methodologies for the construction of structural analogues are actively pursued in many groups. We are interested in preparing of new structural analogues of maduropeptin, a new antibiotic recently described in the literature,[2] possessing very strong antibacterial and antitumor properties. Maduropeptin **2** is a 9 membered ring enediyne chromophore which exists in association with an acidic water soluble carrier protein (32 Kd) that shows no sequence homology to the related chromoproteins neocarzinostatin, C-1027 and kedarcidin.

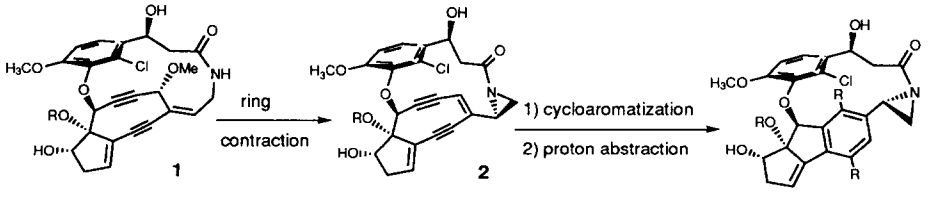



**1**




**5**

The maduropeptin apoprotein represents a new protein class. Compound **1** was separated from its protein by a new methanolysis protocol wich resulted in formation of the methanol adduct **1**.




**Scheme 1**

From the structure of this interesting molecule and its cycloaromatization product **4** coming from **3** both the structure of maduropeptin and its mechanism of action were deduced. Indeed, aromatization of **1**

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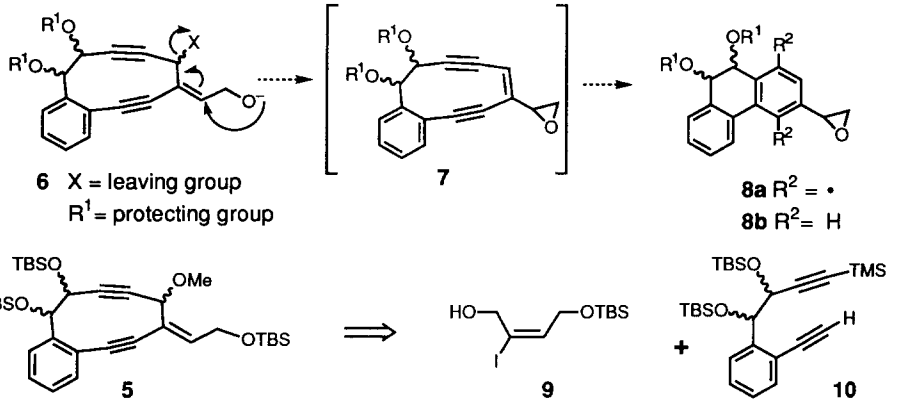
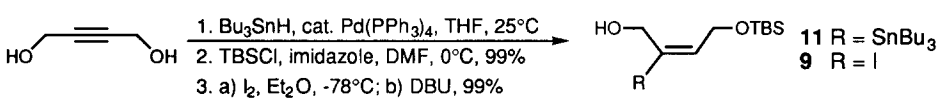
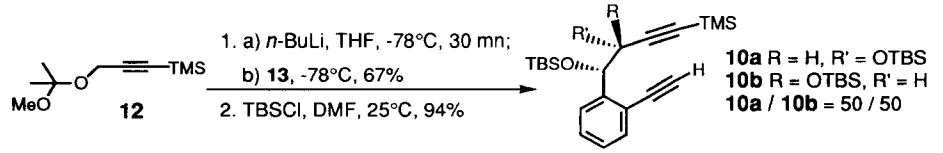
follows through the aziridine **2**, by intramolecular attack of the amide nitrogen to C-13 causing double migration and antielimination of the group that initially combined at C-5. In order to obtain evidence for the mechanism of cycloaromatization of the parent natural chromophore and to stabilize the enediyne system we propose to prepare compound **5** bearing an aromatic ring. One can imagine the rearrangement of this 10 membered bicyclic ring system by intramolecular nucleophilic addition of the activated allylic alcoholate **6**, giving the strained enediyne **7** which cycloaromatises into the diradical species **8a** which abstracts hydrogen to give **8b**. The synthesis of **5** is seen to involve condensation of the iodoalkene **9** and the terminal alkyne **10** *via* a palladium catalyzed cross-coupling reaction.




The synthesis of compound **9** started from 1,4-butyndiol, reacting with tributyltin hydride in the presence of a catalytic amount of *tetrakis*(triphenylphosphine) palladium (0) in THF,[3] followed by protection of the less hindered hydroxy group and gives 11 in 99% overall yield. It has be noted that the protection of the bisallylic alcohol is totally regioselective. No trace of the TBS protected hydroxy β to the tin was observed. Iododestanylation and treatment with DBU, finally gave **9** in excellent yield.[4,5]

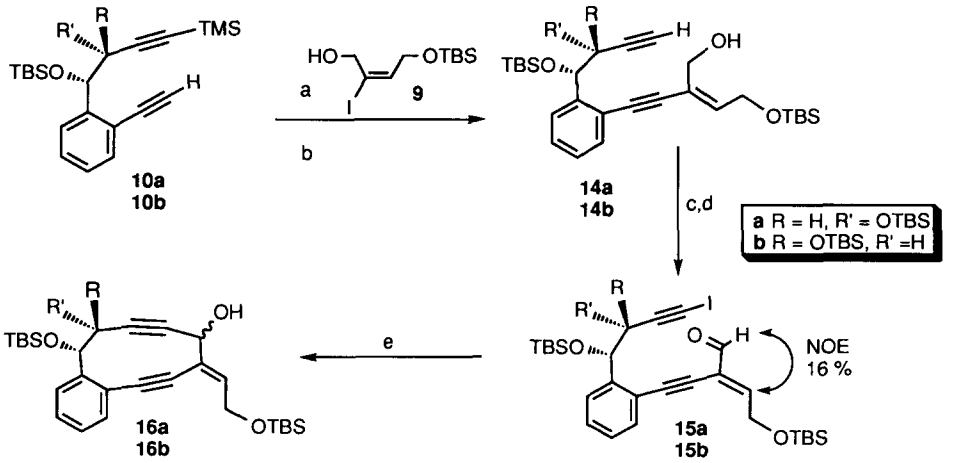



The preparation of terminal alkyne **10** started with the protection of propargylalcohol (with 2-methoxypropene in the presence of a catalytic amount of PPTS in dichloromethane at 0°C, followed by treatment with *n*-BuLi and TMSCl at -78°C) leading to **12**.



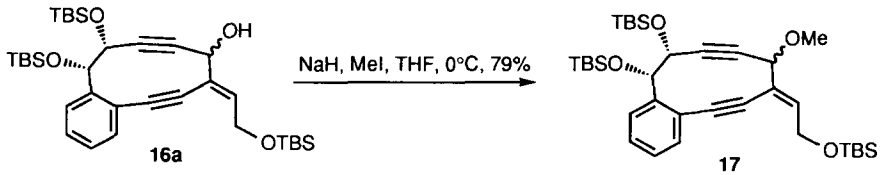

The protected propargylic alcohol **12** was deprotonated at the propargylic position by *n*-butyllithium at –78°C in THF and trapped by 2-ethynylbenzaldehyde **13**. The two diastereomers *syn*-**10a** and *anti*-**10b** could be separated by flash chromatography after protection of the two hydroxy groups under standard

conditions.[6] Palladium catalysed cross-coupling between **10a** or **10b** and **9**, followed by deprotection of the trimethylsilyl groups gave the acyclic enediynes **14a** and **14b** in 73% an 76% yield respectively. Iodination[7] of the terminal alkyne followed by Dess-Martin oxydation[8] of both products gave the corresponding aldehydes **15a** and **15b** in 89 and 77% (2 steps).




a) $PdCl_2(PPh_3)_2$, CuI, THF / $iPr_2NH$, 25 °C, **12a**, 73%, **12b** 76% b) $K_2CO_3$, MeOH, 25 °C c) morpholine, $I_2$, THF, 50 °C d) Dess-Martin periodinane $CH_2Cl_2$, – 20 °C, **15a** 89%, **15b**, 77% e) $CrCl_2$/$NiCl_2$, 3equiv./1 equiv., THF, 25°C, 9h, **16a**, 58%, **16b**, 11%, 1/1 mixture of diastereomers

Unfortunately at this stage, an unexpected isomerisation of the double bond occured during the oxidation step (as determined by NOE experiments). This isomerisation is probably due to an addition-elimination process of residual iodine on the conjugated aldehyde, thus forming the thermodynamically more stable products **15a** and **15b**. In spite of this isomerisation, one can postulate that compound **16a, 16b** or **17** as well as the expected compound **5** will give after activation through the oxirane, the cycloaromatization reaction. Than, cyclisation was performed using a modified Nozaki-Hiyama procedure[9] involving three equivalents of cobalt (II) chloride and a stoechiometric amount of nickel (II) chloride as already described by us.[10] The reactions proceeded smoothly at room temperature within 10 h giving **16a** and **16b** as 1/1 mixtures of diastereomers, in 58 and 11% yield.[11] Methylation under standard conditions of **16a** finally gave **17** in good yield as a 1/1 mixture of diastereomers which were separated by flash chromatography.[12]




In conclusion, the synthesis of analogues of maduropeptine has been accomplished in 7 steps from 2-ethynylbenzaldehyde. Although the unexpected isomerisation of the exocyclic double bond, **16a, b** and **17** should be good candidates for activation and cycloaromatization studies leading eventually to the formation of diradical intermediates. Further experiments in this sense are actually pursuing in our laboratory.

**References and Notes**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11. Compound **16a**: chromatography solvent: $Et_2O$ / hexane, 15 / 85, $R_f$ : 0.25; yellowish oil. $^1H$ NMR (200 MHz, $CDCl_3$) : δ - 0.14 (s, 3H); 0,00 (s, 3H); 0.07 (s, 3H); 0.11 (s, 3H); 0.12 (s, 3H); 0.13 (s, 3H); 0.83; 0.87; 0.93 (s, 9H); 2.13 (d, 1H, $^3J$ = 8.9 Hz, OH); 4.49 (m, 2H); 4.75 (dd, 1H, $^5J$ = 2.6 Hz, $^3J$ = 1.1 Hz); 4.82 (dd, 1H, $^3J$ = 8.9 Hz, $^4J$ = 2.6 Hz); 5.25 (d, 1H, $^4J$ = 1.1 Hz); 6.04 (t, 1H, $^3J$ = 5.9 Hz); 7.19 - 7.43 (m, 3H); 7.62 - 7.66 (m, 1H). $^{13}C$ NMR (50 MHz, $CDCl_3$) : δ -5.22; - 5.02; - 4.71; 18.12; 18.26; 18.34 (C2, C21 et C24); 25.75; 25.94; 63.04; 68.51; 69.30; 77.81; 86.37; 91.33; 91.77; 100.30; 120.51; 126.87; 127.60; 127.83; 130.10; 130.29; 130.52; 142.93. MS (CI, 70 eV) m/e (relative intensity%) : 511 [(M - *t*Bu - $CH_3$)$^+$, 62], 315 (100)
    Compound **16b**: chromatography solvent: $Et_2O$ / hexane, 10 / 90, $R_f$ : 0.20; yellowish solid. mp = 63°C. $^1H$ NMR (200 MHz, $CDCl_3$) : δ mixture of 2 diastereomers (dia. I / dia. II = 1 / 2) - 0.19 (s, 3H); - 0.12 (s, 3H,); 0.09 (s, 3H); 0.13 (s, 3H); 0.20 (s, 6H); 0.79; 0.94; 0.96 (s, 9H); 1.89 (d, 1H, $^3J$ = 9.4 Hz, OH dia. I); 2.05 (d, 1H, $^3J$ = 8.0 Hz, OH dia. II); 4.15 (d, 1H, $^3J$ = 8.6 Hz); 4.40 - 4.49 (m, 2H); 4.50 - 4.57 (m, 2H); 4.75 - 4.80 (m, 1H); 4.95 - 4.99 (m, 1H); 5.00 - 5.05 (m, 2H); 6.04 (t, 1H, $^3J$ = 6.2 Hz); 6.14 (dt, 1H, $^3J$ =5.8 Hz, $^3J$ = 1.8 Hz); 7.15 - 7.52 (m, 3H); 7.69 - 7.74 (m, 1H). $^{13}C$ NMR (50 MHz, $CDCl_3$) : δ - 5.23; - 5.04; - 4.41; - 4.86; 17.93; 18.37; 18.85; 25.66; 25.95; 26.10; 63.11; 63.32; 66.95; 68.14; 69.00; 72.81; 79.67; 87.14; 91.29; 94.04; 100.75; 120.10; 124.55; 127.20; 127.38; 128.08; 129.04; 130.47; 132.47; 132.75; 136.42; 143.12; 145.54. MS (EI, 70 eV) m/e (relative intensity %) : 612 [(M - H)$^+$, 56]
12. Compound **17**: **dia I:** chromatography solvent: $Et_2O$ / hexane, 3 / 97, $R_f$ : 0.30; yellowish oil. $^1H$ NMR (200 MHz, $CDCl_3$) : δ - 0.14 (s, 3H); 0.01 (s, 3H); 0.06 (s, 3H); 0.10 (s, 3H); 0.14 (s, 6H); 0.83; 0.88; 0.94 (s, 9H); 3.46 (s, 3H); 4.52 (dd, 2H, $^3J$ = 6.5 Hz, $^5J$ = 1.5 Hz); 4.83 (broad s, 2H,); 5.37 (broad s, 1H); 6.15 (dt, 1H, $^3J$ = 6.5 Hz, $^4J$ = 1.8 Hz); 7.16 - 7.37 (m, 3H); 7.61 - 7.65 (m, 1H). $^{13}C$ NMR (50 MHz, $CDCl_3$) : δ - 5.21; - 5.01; - 4.78; 18.12; 18.27; 25.75; 25.95; 56.16; 63.22; 69.61; 73.72; 77.74; 84.79; 91.52; 94.56; 101.12; 120.70; 123.56; 126.79; 127.65; 130.11; 130.51; 133.71; 143.01. **dia II:** chromatographiy solvent: $Et_2O$ / hexane, 3 / 97, $R_f$ : 0.19; yellowish oil. $^1H$ NMR (200 MHz, $CDCl_3$) : δ - 0.13 (s, 3H); 0.02 (s, 3H); 0.05 (s, 3H); 0.10 (s, 3H); 0.13 (s, 6H); 0.82; 0.88; 0.93 (s, 9H); 3.30 (s, 3H); 4.52 (m, 2H); 4.70 (d, 1H, $^5J$ = 2.6 Hz); 4.75 (dd,1H, $^3J$ = 2.6 Hz, $^5J$ = 1.0 Hz); 5.26 (broad s, 1H); 6.05 (t, 1H, $^3J$ = 5.7 Hz); 7.16 - 7.40 (m, 3H); 7.60 - 7.65 (m, 1H). $^{13}C$ NMR (50 MHz, $CDCl_3$) : δ - 5.21; - 5.04; - 4.85; 18.12; 18.20; 18.34; 25.66; 25.76; 25.94; 55.24; 63.11; 69.39; 75.67; 77.98; 84.20; 92.07; 92,.3; 100.74; 120.63; 124.82; 126.69; 127.61; 130.26; 130.36; 138.13; 142.90. MS (CI, 70 eV) m/e (relative intensity %) : 645 [(M + $NH_4$)$^+$, 100]


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