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Synthetic Studies on Maduropeptin Chromophore 1. Construction of the Aryl Ether and Attempted Synthesis of the [7.3.0] Bicyclic System

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Abstract: *The aryl ether system of the maduropeptin chromophore artifact* ***1*** *was constructed via an aldol type condensation (****7+6****, Schemes 1 and 2,* ***7+19****, Scheme 4), but attempted synthesis and ring closure of aldehyde* ***25*** *(Scheme 4) to afford the enediyne core of* ***1*** *failed.* © 1997 Elsevier Science Ltd.

In the course of screening for natural compounds that are active against murine P388 leukemia in mice, a complex of novel macromolecular antibiotics, designated as maduropeptin (MDP), was isolated in 1991 from the broth filtrate of *Actinomadura madurae*, an organism obtained from a soil sample collected in Germany.[1] Shortly thereafter, it was reported[2] that MDP consists of a 1:1 complex of an acidic, water soluble 32 kDa carrier protein and a 9-membered ring enediyne chromophore possessing impressive antibacterial and antitumor properties. The naked chromophore was proven too labile for isolation, but in the presence of methanol the artifact compound **1** (Fig. 1) was isolated and characterized. The novelty and biological activity against tumor cells of compound **1** prompted us to consider it for total synthesis.

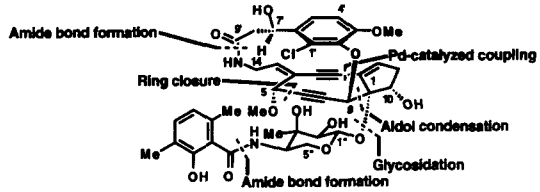
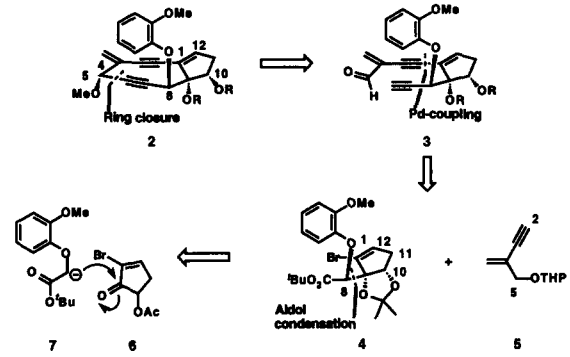


Figure 1. Structure and possible strategic bond disconnections of artifact of maduropeptin chromophore 1.

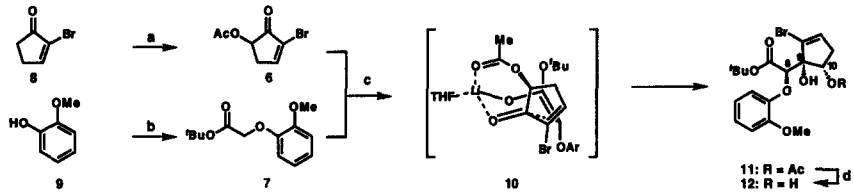
Scheme 1 outlines a possible retrosynthetic analysis of **1** which relies on an aldol condensation, a palladium-catalyzed C–C bond formation, and an acetylide-aldehyde condensation to form the challenging 9-membered ring. In order to explore the initial stages of such a plan we targeted model system **2** (Scheme 1) for synthesis. It was envisioned that acetylene-aldehyde **3** could serve as a precursor to **2** by intramolecular, base-induced addition of the acetylene to the aldehyde. Furthermore, it was expected that palladium-catalyzed coupling of **5** and **4** could facilitate construction of **3**, whereas **4** could be derived by an aldol type condensation of enolate **7** with cyclopentenone **6** (Scheme 1). A novel feature of this approach is the promise to form the aryl ether bond of the target molecule early on in the sequence and before the intermediates become too sensitive to withstand the rather strong conditions that may be required for its formation.

Scheme 2 summarizes the successful and stereoselective construction of the C8–C13 region of the molecule by the proposed enolate-ketone condensation. Thus, 2-bromocyclopentenone **8**[3] was converted by a modified literature procedure[4] to the acetoxy derivative **6** (69% yield), whereas the other requisite component, α-aryloxy-*tert*-butyl ester **7** was obtained in quantitative yield by S_N2 displacement of the bromide in *tert*-butyl bromoacetate with the potassium salt of 2-methoxyphenol **9**. The lithium enolate of **7** generated in THF at

–78 °C by the action of $LiN(SiMe_3)_2$ reacted with cyclopentenone derivative **6** to afford, in 44% yield, compound **11** as a single stereoisomer. Methanolysis of the acetate in **11** in the presence of K_2CO_3 resulted in the crystalline diol **12** (80% yield), m.p.125-126 °C (EtOAc/hexanes). X-ray crystallographic analysis of **12** confirmed the indicated stereochemistry (see ORTEP drawing, Fig. 2). The formation of the same relative stereochemistry as that of the corresponding stereocenters of MDP chromophore artifact **1** in these intermediates (**11** and **12**) by this reaction bodes well for potential application of this enolate condensation to the total synthesis of the target molecule **1** and could be rationalized by transition state **10** (Scheme 2) formed by lithium assisted complexation of the reactants in THF.



Scheme 1. Retrosynthetic analysis and strategy of model enediyne compound 2.



Scheme 2. Synthesis of diol 12. *Reagents and conditions*: (a) 1.1 equiv of $Pb(OAc)_4$, benzene, Δ, 12 h, 69%; (b) 1.0 equiv of KO^{t}Bu, 1.0 equiv of $BrCH_2CO_2{}^t$Bu, THF, 1.5 h, 99%; (c) 1.05 equiv of $LiN(SiMe_3)_2$, 7, THF, -78 °C, 45 min; then 1.0 equiv of 6, -78 °C, 1 h, 44%; (d) K_2CO_3, MeOH, 25 °C, 1.5 h, 80%.

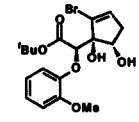
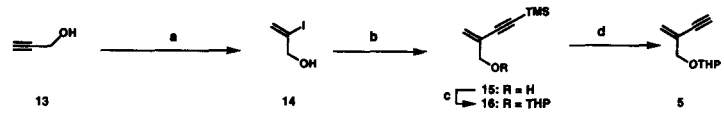


Figure 2. ORTEP drawing of compound 12.

The other required building block **5** was synthesized as shown in Scheme 3. Thus, regioselective addition of HI to propargyl alcohol **13** under Ishii's conditions[5] gave alcohol **14** in quantitative yield.

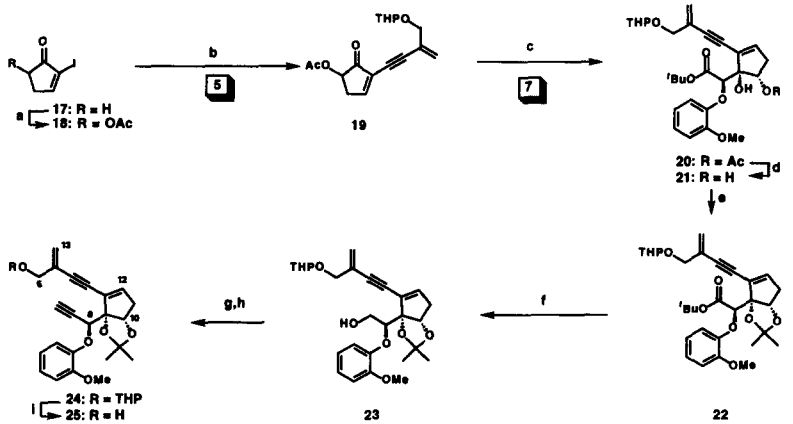
Palladium(0)-catalyzed coupling of vinyl iodide **14** and (trimethylsilyl)acetylene furnished compound **15** in 96% yield. Finally, protection of the hydroxy group in **15** as a tetrahydropyranyl (THP) ether (87% yield), followed by desilylation (K_2CO_3, MeOH), led to enyne **5** (95% yield).



Scheme 3. Synthesis of the C2-C5 fragment 5. Reagents and conditions: (a) 1.5 equiv of Me_3SiCl, 1.5 equiv of NaI, 25 °C, 100%; (b) 1.3 equiv of (trimethylsilyl)acetylene, 3 mol% of $Pd(PPh_3)_4$, 7 mol% of CuI, 1.3 equiv of Et_3N, THF, 96%; (c) 8.0 equiv of 3,4-dihydro-2H-pyran, 0.1 equiv of pyridinium *p*-toluenesulfonate (PPTS), 25 °C, 3 h, 87%; (d) K_2CO_3, MeOH, 25 °C, 40 min, 95%.

Attempted Sonogashira coupling of **11** or **12** with **5** under a variety of conditions failed; presumably due to a combination of low reactivity of the bromide and steric hindrance. We, therefore, turned our attention to the more reactive vinyl iodide **18** (Scheme 4) which was prepared by $Pb(OAc)_4$ oxidation (47%) of iodocyclopentenone **17**.[6] Gratifyingly, reaction of vinyl iodide **18** with acetylenic compound **5** under Sonogashira conditions led to coupling product **19** in 39% yield. Aldol condensation of the lithium enolate derived from **7** with ketone **19** resulted in the formation of a single adduct **20** in 40% yield, which after exposure to K_2CO_3 in methanol furnished diol **21** in 80% yield. The stereochemistry of the aldol product **20** was tentatively assigned as shown by analogy to **11**. The 1,2-diol system in compound **21** was converted to an acetonide group leading to compound **22** (70% yield), and DIBAL reduction of the *tert*-butyl ester group in **22** furnished the primary alcohol **23** (96% yield). The aldehyde derived from **23** by Swern oxidation reacted with (1-diazo-2-oxopropyl)phosphonate to afford acetylene **24** in 61% overall yield.[7,8] Allylic alcohol **25** was then generated in 81% yield from **24** by selective removal of the THP groups (PPTS, MeOH). Attempts to isolate or cyclize the crude aldehyde derived by oxidation of **25** were, however, thwarted by its apparent instability. At this stage, model compound **2** was abandoned in favor of a modified system, to be reported in due course.

In summary, a synthetic strategy for the stereoselective construction of the C8-C10 backbone of MDP chromophore artifact **1** was developed. It is expected that, upon appropriate adjustments, this aldol-based strategy may facilitate the total synthesis of **1** and analogs for biological studies.[9]



Scheme 4. Synthesis of allylic alcohol 26. *Reagents and conditions*: (a) 1.1 equiv of $Pb(OAc)_4$, benzene, Δ, 13 h, 47%; (b) 1.5 equiv of 5, 4 mol% of $(Ph_3P)_2PdCl_2$, 8 mol% of CuI, 1.3 equiv of Et_3N, benzene, 25 °C, 0.5 h, 39%; (c) 7, 0.95 equiv of $LiN(SiMe_3)_2$, THF, -78 °C, 1 h; then 19, -78 °C, 1 h, 40%; (d) 0.2 equiv of K_2CO_3, MeOH, 25 °C, 2 h, 80 %; (e) 3.0 equiv of 2-methoxypropene, 1 mol% of CSA, CH_2Cl_2, 0 °C, 45 min, 70%; (f) 3.0 equiv of DIBAL, CH_2Cl_2, -78 °C, 40 min, 96%; (g) 3.0 equiv of $(COCl)_2$, 4.5 equiv of DMSO, -78 °C, 5 min; then 23, -78 °C; 9.0 equiv of Et_3N; (h) 1.1 equiv of (1-diazo-2-oxopropyl)phosphonate, 1.1 equiv of K_2CO_3, MeOH, 25 °C, 3 h, 60% (2 steps); (i) 0.3 equiv of pyridinium *p*-toluenesulfonate (PPTS), MeOH, 25 °C, 17 h, 81%.

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9. Selected physical data for compounds **12** and **25**. **12**: R_f = 0.30 (30% EtOAc in petroleum ether); IR (thin film): ν_{max} = 3417 (broad, O-H), 1742 (C=O), 1506, 1254, 1135, 1070, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.03 (ddd, *J* = 8.6, 8.6, 1.4 Hz, 1 H, Ar), 6.97 (dd, *J* = 8.0, 1.4 Hz, 1 H, Ar), 6.92-6.87 (m, 2 H, Ar), 6.11 (dd, *J* = 2.6, 2.6 Hz, 1 H, C12-H), 4.92 (dd, *J* = 7.1, 4.2 Hz, 1 H, C10-H), 4.71 (s, 1 H, C8-H), 4.48 (s, 1 H, OH), 3.89 (s, 3 H, OCH_3), 3.60 (s, 1 H, OH), 2.65 (ddd, *J* = 17.0, 7.1, 2.6 Hz, 1 H, C11-H), 2.33 (ddd, *J* = 17.0, 4.2, 2.6 Hz, 1 H, C11-H'), 1.45 (s, 9 H, ^{t}Bu); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.5, 149.8, 147.1, 134.4, 123.6, 121.8, 121.2, 117.2, 111.9, 83.8, 83.2, 83.1, 69.5, 55.8, 38.6, 27.8; FAB HRMS: calcd for $C_{18}H_{23}BrO_6Cs$ ($M+Cs^+$): 546.9732, found: 546.9752.
25: R_f = 0.25 (30% EtOAc in petroleum ether); IR (thin film): ν_{max} = 3413 (broad, O-H), 3282, 2932, 1502 1253, 1219, 1081, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.14 (ddd, *J* = 8.0, 1.6, 1.6 Hz, 1 H, Ar), 6.98 (ddd, *J* = 7.8, 7.8, 1.6 Hz, 1 H, Ar), 6.92-6.89 (m, 2 H, Ar), 6.25 (m, 1 H, C12-H), 5.55 (dd, *J* = 3.0, 1.5 Hz, 1 H, C13-H), 5.52 (m, 1 H, C13-H'), 5.13 (d, *J* = 2.2 Hz, 1 H, C8-H), 5.04 (d, *J* = 5.1 Hz, 1 H, C10-H), 4.18 (bs, 2 H, C5-H2), 3.82 (s, 3 H, OCH_3), 2.80 (ddd, *J* = 18.9, 5.1, 2.3 Hz, 1 H, C11-H), 2.62 (dd, *J* = 18.9, 3.1 Hz, 1 H, C11-H'), 2.43 (d, *J* = 2.2 Hz, 1 H, C6-H), 1.52 (s, 3 H, acetonide), 1.45 (s, 3 H, acetonide); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.3, 146.8, 139.8, 131.2, 125.6, 122.7, 120.7, 116.7, 112.3, 112.0, 96.5, 90.1, 85.4, 80.0, 78.5, 76.0, 69.3, 65.2, 55.8, 39.0, 29.7, 28.0, 26.4; FAB HRMS: calcd for $C_{23}H_{24}O_5Na$ ($M+Na^+$): 403.1521, found: 403.1532.

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