Pergamon

Tetrahedron Letters 39 (1998) 27–30

TETRAHEDRON LETTERS

Toward the Construction of Enediyne Prodrug Systems Related to the Ring Expanded Artifact Produced Upon Isolation of Maduropeptin Chromophore

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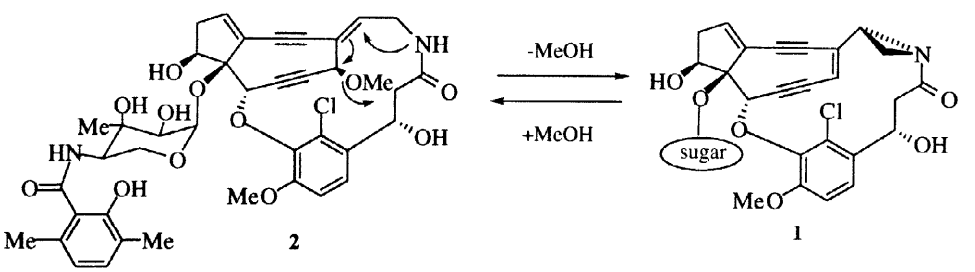
Received 15 October 1997; accepted 22 October 1997

Abstract : *As part of a modular approach to synthesize maduropeptin analogues of general formula* ***3****, the diacetylene substituted dihydro-1,2-oxazine synthon* ***13*** *was constructed via a hetero Diels-Alder reaction between diene* ***10*** *and the nitrosodienophile* ***12****. Reductive cleavage of the N-O bond in* ***13****, and acylation of the derived amine* ***16*** *gave the stable amide* ***17****.* © 1997 Published by Elsevier Science Ltd. All rights reserved.

Maduropeptin, the most recent of the growing family of enediyne antitumor antibiotics to be described, consists of a 1 : 1 complex of an acidic stabilizing protein and a labile 9-membered enediyne chromophore for which the structure **1** is proposed.[1] Most intriging is the observation that on controlled methanolysis of this chromoprotein complex the ring expanded artifact **2** was isolated, and further, that at slightly basic pH this compound undergoes the reverse reaction generating enediyne **1**. This highly strained system cycloaromatizes spontaneously to a 1,4-phenylene diradical species which efficiently cleaves double strand DNA.[1,2] Thus, in essence, artifact **2** represents a more stable prodrug form of the highly reactive maduropeptin chromophore.



Our interest in the maduropeptin system resides in efforts to construct bio active analogues of artifact **2**, which conserve different aspects of the aziridine formation-allylic displacement (S_N') mechanism whereby the central enediyne double bond is generated.[3,4] This has led us to develop methodology permitting the synthesis of compounds possessing the general formula **3** (Scheme 1).

As can be seen, the dihydro-1,2-oxazine ring in **3** contains all the functionality present in the allyl amide trigger in **2**, and is thus potentially susceptible to react with nucleophiles in a S_N2' type process leading to ring opening and double bond migration. Further, the pyrrole ring in **3** comprizes an integral part of an oligoheterocycle type DNA recognition element.[5] Note also, that the direct connection of diverse DNA ligands obtained from combinatorial synthesis to the prodrug system is a design feature to study optimization of the positioning of the ensemble on the deoxynucleic acid surface.[6]

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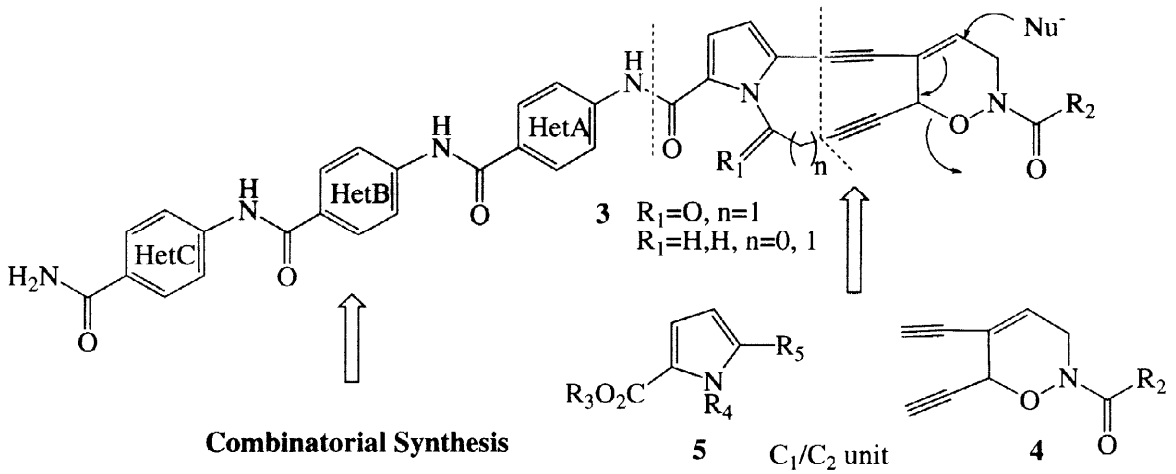
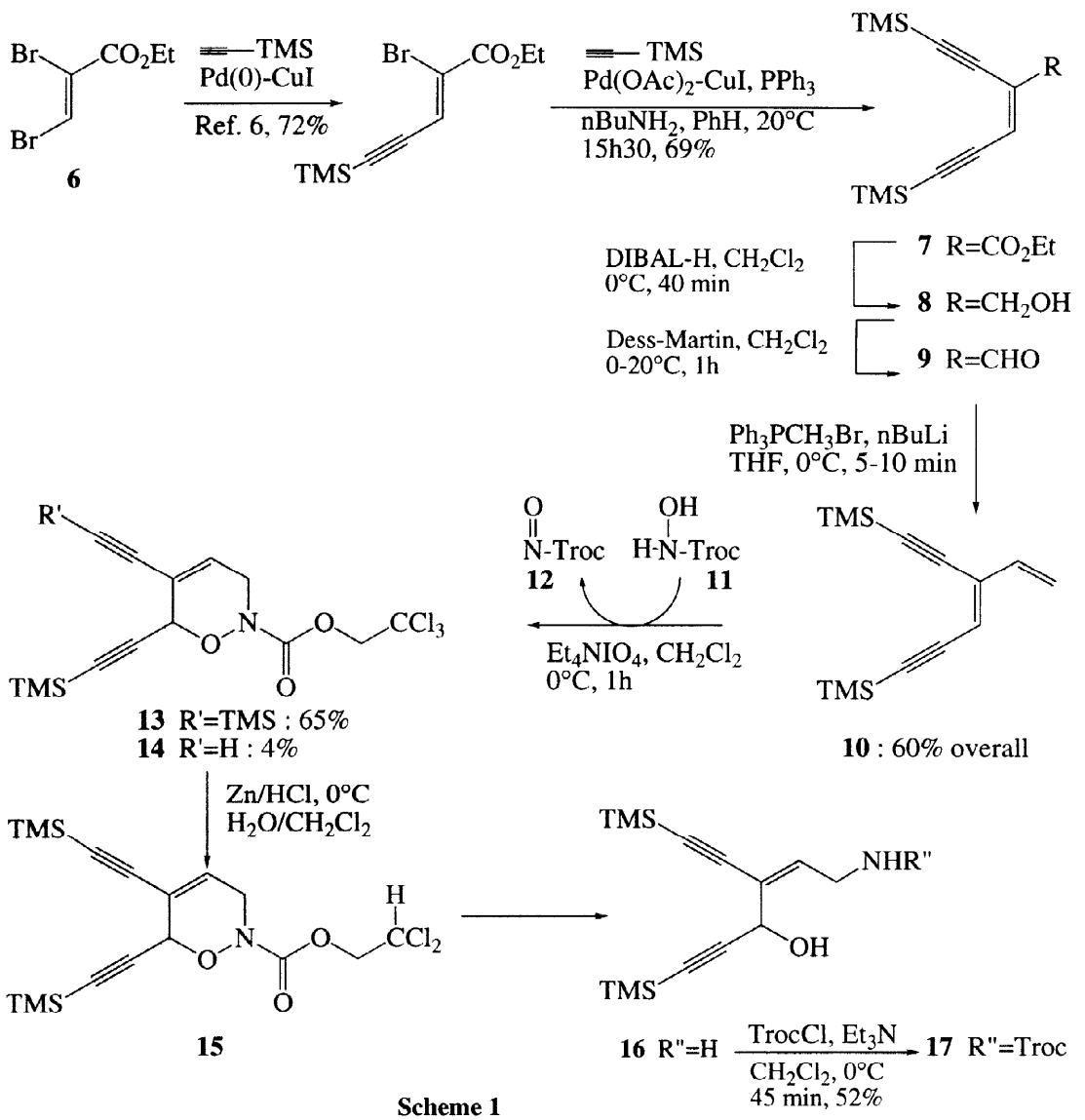
PII: S0040-4039(97)10459-2



Combinatorial Synthesis



Scheme 1

As illustrated in Scheme 1, the synthesis of compounds **3** will proceed by a modular approach whereby the bis-acetylene substituted synthon **4** and a series of polyheterocycles are assembled independently, and joined through connection to a central pyrrole intermediate (cf. **5**). In this communication we describe the preparation of the dihydro-1,2-oxazine derivative **13** related to **4** via an efficient nitroso dienophile Diels-Alder reaction, and its conversion to the ring opened form under reductive (N-O bond cleavage) conditions.

Preparation of the required diene **10** was achieved in 5 steps, starting with two successive Pd(0)-CuI catalyzed additions of TMS acetylene to the cis-2,3-dibromoacrylic ester **6**.[7] The derived product **7**, obtained as a stable light brown coloured oil in 50% overall yield, was then treated with DIBAL-H in CH_2Cl_2 at 0°C. This led to formation of a mixture of aldehyde **9** (50-80%) and alcohol **8**, which were readily separated by flash column chromatography (silica gel ; Pentane-EtOAc ; 98-2 then 9-1). Oxidation of alcohol **8** with the Dess-Martin periodinane was quantitative, providing additional quantities of **9** (98% combined yield). Subsequent reaction of aldehyde **9** under Wittig conditions ($Ph_3P{=}CH_2$, THF, 60%) completed formation of diene **10**. Note however, that due to the sensitivity of both aldehyde **9** and diene **10**, efforts were made to minimize storage of these materials between steps.

For the key cycloaddition step, the protocol producing the best results involved addition of 3 equivalents of the Troc ($-CO_2CH_2CCl_3$) substituted hydroxamic acid derivative **11** to a solution of diene **10** and tetraethylammonium periodate (1 equiv.) in CH_2Cl_2 at 0°C over 5 minutes.[8] After stirring for 30 minutes additional oxidant (1 equiv.) and hydroxamic acid (3 equivs.) were added in portions simultaneously, and stirring was continued for a further 30 minutes. In this way, reaction of diene **10** with the *in situ* derived nitroso dienophile **12** was driven to effective completion.[9]

Pleasing was the observation that this Diels-Alder reaction was regioselective, producing the desired dihydro-1,2-oxazine **13** as essentially the unique reaction product. Compound **13** was isolated in 65% yield (78% conversion) as a cream coloured solid after silica gel flash column chromatography (Pentane-EtOAc ; 95-5) to remove small quantities of the monodesilylated product **14** (4%) and starting diene (10-17%). Characteristic in the NMR spectra for **13** was the presence of signals for the C_3-allylic CH_2 group [δ 4.18 ddd J = 18, 3.5, 2.6 Hz and 4.39 ddd J = 18, 3.5, 2 Hz (^{1}H) ; δ 44.9, (^{13}C)] and the propargyl alcohol methine (C_6H) center [δ 5.16 m J = 2, 2.6 Hz (^{1}H) ; δ 71.0 (^{13}C)].

Having achieved the preparation of synthon **13** via this efficient and simple Diels-Alder strategy, our attention turned to a study of N-O bond cleavage, in order to compare the stability of the derived exocyclic unconjugated enediyne derivatives **16** and **17** relative to the maduropeptin artifact **2**. Ring opening was achieved by reaction of **13** with Zn/HCl in a two phase (H_2O-CH_2Cl_2) system at 0°C for a total of 2 h.[10] Under these conditions amine **16** was formed in up to quantitative yield. However, in general, the yield varied due to partial decomposition of amine **16** to unidentified olefin containing products. Small quantities of the monodechlorinated product **15** were also often detected in these experiments. Subsequent reaction of amine **16** with Troc-Cl gave the corresponding amide **17**. In the ^{1}H NMR of this product the H-6 absorption occured as a doublet (δ 5.16, J = 7.4 Hz) due to coupling with the hydroxyl group hydrogen, and the amide N-H appeared as a broad triplet (δ 6.01).

Unlike artifact **2**, the acyclic amide **17** is stable with respect to formation of the corresponding more highly conjugated enediyne. This suggests that ring strain is most probably also be a key factor contributing to the propensity of artifact **2** to rearrange to maduropeptin **1**.

Acknowledgements. This work has been financed by A.R.C. (Association pour la Recherche sur le Cancer) and La Ligue Nationale Contre le Cancer (Scholarship for C.R.).

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