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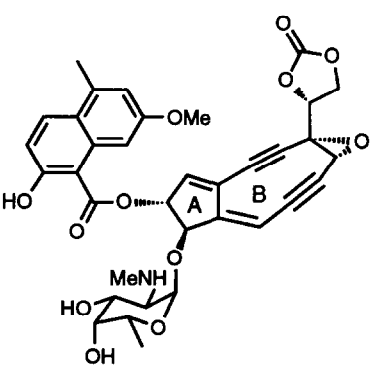
Stereoselective Synthesis of a Functionalised Bicyclic Core of Neocarzinostatin and Kedarcidin Chromophores

Stephen Caddick* and Vern M. Delisser

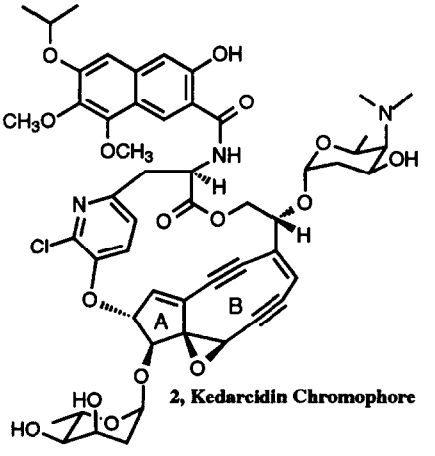
The Chemistry Laboratory, Centre for Biomolecular Design and Drug Development, University of Sussex, Falmer, Brighton, BN1 9QJ

Abstract: The stereoselective synthesis of a bicyclic ring system related to Neocarzinostatin and Kedarcidin Chromophores is described; key steps involve stereoselective conjugate addition of an enediyne to an enone and intramolecular aldol reaction of a cobalt complexed alkynyl aldehyde. © 1997 Elsevier Science Ltd.

The enediyne class of anti-cancer antibiotics have stimulated great interest in chemical synthesis, medicine and biology because of their biological activity which is dependant on activation of the unusual enediyne or dienediyne structural motif.[1] Our present research effort in this area focuses on studies toward the synthesis of enediyne analogues and the naturally occurring target molecules Neocarzinostatin Chromophore A (NCS A), **1** and Kedarcidin Chromophore **2**. These targets have both eluded total synthesis[2] although recently, a very elegant first synthesis of the aglycone of NCS Chromophore has been reported.[3]



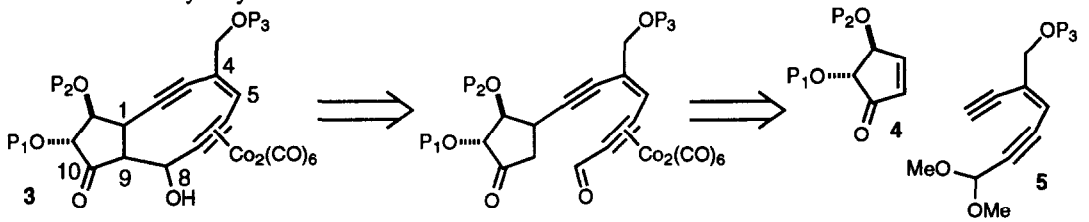
1, Neocarzinostatin Chromophore A



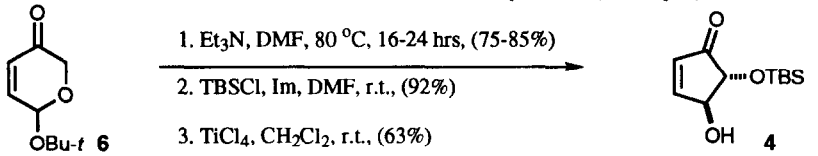
2, Kedarcidin Chromophore

As part of our long term goal we aim to develop some common elements of strategy for the synthesis of these targets and related analogue systems. As an initial priority we sought to examine several methods for the synthesis of oxygenated cyclopentenones and have recently described a practical procedure for the large-scale preparation of a fully oxygenated A-ring portion.[4] In this letter we describe a synthetic strategy which has enabled us to prepare a functionalised bicyclic ring system related to the aforementioned targets and which should have some generality for the synthesis of natural and unnatural enediynes.

The synthesis of the B-ring of NCS A and related natural products has been the subject of considerable synthetic endeavours and a number of exciting and imaginative synthetic methodologies have been developed.[5] However only a small proportion of these have been extended to incorporate the requisite functionality in the five membered ring. The synthesis of an intermediate such as **3** is attractive because it incorporates oxygen functionality at C_8 which could be useful for the synthesis of NCS A and Kedarcidin Chromophores. The required 4,5-epoxy moiety required for NCS A might be introduced either prior or subsequent to nine-membered ring formation. We were attracted to the prospect of using an intramolecular aldol reaction, as a method for forming the C_8-C_9 bond. The pioneering work of Magnus and co-workers had demonstrated the advantages associated with using cobalt complexed alkynyl aldehydes in intramolecular aldol reactions for enediyne synthesis.[6]

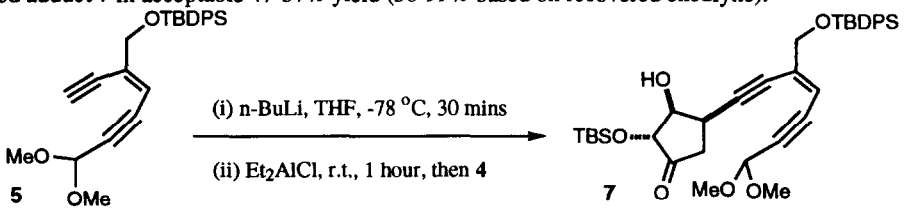


Our synthesis required the availability of **4** and **5**. The desired enone **4** (P_1 = TBS, P_2 = H) was prepared by stereocontrolled isomerisation of pyranone **6** to a five membered cyclopentenone[4] which can be selectively manipulated to generate the 4-hydroxy-5-*tert*-butyldimethylsilyloxy-cyclopenten-2-one **4**; the presence of the free hydroxyl allows the stereocontrolled introduction of the enediyne unit (*vide infra*).



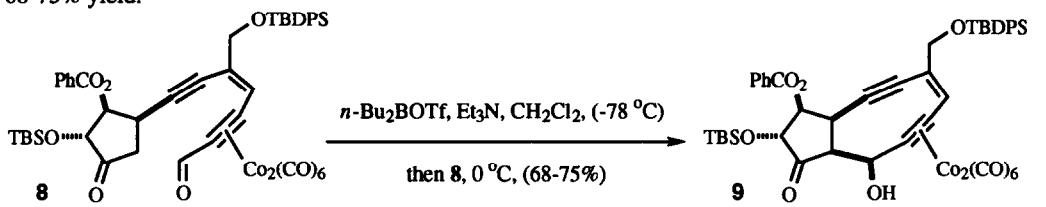
Enediyne **5** (P_3 = TBDPS) is readily prepared from ethyl propiolate making extensive use of palladium catalysed cross coupling technology. The use of freshly prepared $Pd(PPh_3)_4$ is critical for optimal yields; however using standard organic procedures we are able to prepare multi-gram quantities of the desired material.[7]

In order to effect the union of enediyne **5** with enone **4** we were able to use a conjugate addition reaction[8] of an intermediate alkynyl aluminium reagent generated from **5**. Our initial results were very disappointing and, in stark contrast to the literature reports, we found that the use of ligroin as solvent suppressed rather than enhanced the reaction. We were pleased to find however that the use of THF as solvent enabled us to isolate the desired adduct **7** in acceptable 47-57% yield (50-99% based on recovered enediyne).[9]



Protection of the hydroxyl group of **7** (PhCOCl, Pyr, DMAP, CH_2Cl_2, 79%) followed by regioselective alkyne complexation ($Co_2(CO)_8$, CH_2Cl_2, 0 °C, 92%) and acetal cleavage (TFA (30%, aqueous), CH_2Cl_2,

98%) gave the aldol precursor **8** in good yield. Treatment of **8** with freshly distilled di-*n*-butylboron triflate and Et_3N (-78 °C to 0 °C) promoted a stereocontrolled intramolecular aldol reaction to give **9** as the major product in 68-75% yield.[10]



In summary we have described the synthesis of a highly functionalised bicyclic ring system which we believe can be used for the synthesis of Neocarzinostatin and Kedarcidin Chromophores. The brevity of the approach also has the potential to make some functionalised analogue systems available for biological evaluation. Overall the synthetic scheme is highly regio- and stereo-controlled and notable features include the use of a chelation controlled stereoselective conjugate addition reaction and a stereoselective intramolecular aldol reaction. We are now vigorously engaged in applying the strategy to the total synthesis of NCS Chromophore and analogue systems.[11]

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7. From ethyl propiolate: (i) Br_2, CCl_4, 70 °C, 90%; (ii) NaI, Acetone, 60 °C, 86%; (iii) $Pd(PPh_3)_4$, CuI, *i*-Pr_2NEt, TMSA, DMF, 0 °C, 85%; (iv) DIBALH, Et_2O, -78 °C to 0 °C, 76%; (v) $tBuPh_2SiCl$, DMAP, Im, DMF, 98%; (vi) K_2CO_3, MeOH, 75%; (vii) $(MeO)_3CH$, $ZnCl_2$, 160 °C, 72%; (viii) $PdCl_2(PPh_3)_2$, CuI, n-propylamine, TMSA, THF, 60 °C, 82%; (ix) K_2CO_3, MeOH, 88%
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9. *Representative Procedure:* To a stirred solution of enediyne **5** (1.22g, 2.91mmoles) in THF (14ml) at -78°C was added dropwise *n*-BuLi (2.0ml, 1.6M in hexanes, 3.2mmoles). The resulting red solution was stirred for 40 minutes at -78 °C. A solution of Et_2AlCl (3.8ml, 1.0 M in hexanes, 3.8mmoles) was added dropwise and the reaction mixture allowed to warm to room temperature with stirring. After 1 hour at room temperature the resulting alkynyl aluminium species was added *via* canula to a solution of enone **4** (0.31g, 1.36mmoles) in THF (14ml). The reaction mixture was stirred for 6 hours and then quenched with saturated ammonium chloride. Conventional work-up and silica-gel chromatography (3:1, petrol : ether) gave the product **7** (0.446g, 51%, 99% based on recovered enediyne (0.9285g)). Selected data for **7** δ_H (300MHz, $CDCl_3$) 7.63, m, 4H; 7.41, m, 6H; 6.26, s, 1H; 5.32, s, 1H; 4.21, d, 2H, (J = 1.5); 4.0, dd, 1H, (J = 8.2, 4.1); 3.9, d, 1H, (J = 4.0); 3.48, m, 1H; 3.4, s, 6H; 2.72, d, 1H, (J = 4.4); 2.5, m, 2H (AB); 1.05, s, 9H; 0.86, s, 9H; 0.11, s, 3H; 0.09, s, 3H; δ_C (75MHz, $CDCl_3$) 211.6, 136.1, 135.6, 132.9, 130.2, 128.1, 112.3, 96.0, 93.6, 90.1, 83.9, 81.4, 78.1, 75.4, 65.2, 52.8, 52.7, 39.3, 32.5, 26.9, 25.8, 19.4, 18.4, -4.6, -5.0; HRMS (CI, NH_3) $C_{37}H_{54}O_6Si_2N$ $[M+NH_4]^+$ requires 664.34897 found 664.34900
10. *Representative Procedure:* To a stirred solution of freshly distilled *n*-Bu_2BOTf (0.07ml, 0.34mmoles) in CH_2Cl_2 (5ml) at -78 °C was added Et_3N (0.09ml, 0.67mmoles) and the mixture stirred for 45 minutes and then allowed to warm to 0 °C. Keto aldehyde **8** (66.3mg, 0.067mmoles) in CH_2Cl_2 (5ml) was added dropwise *via* syringe pump over 1 hour. The resulting red solution was stirred at 0 °C for 4 hours and then diluted with CH_2Cl_2 and quenched with saturated ammonium chloride. Conventional work up and silica-gel chromatography (gradient 7:1 to 3:1, petrol : ether) gave the product **9** (49.8mg, 75%) as a 10:1 mixture of diastereomers. Selected data for *major diastereomer* **9** δ_H (300MHz, $CDCl_3$) 7.9, d, 2H, (J = 7.3), 7.6-7.2, m, 13H; 6.99, s, 1H; 5.5, dd, 1H, (J = 8.4, 5.6); 5.3, t, 1H, (J = 5.4); 4.4, d, 1H, (J = 5.2); 4.2, dd, 1H (J = 8.8, 5.8); 4.1, s, 2H; 3.6, d, 1H, (J = 5.6); 3.2, t, 1H, (J = 8.7); 1.0, s, 9H; 0.87, s, 9H; 0.15, s, 3H; 0.12, s, 3H; δ_C (75MHz, $CDCl_3$) 211.3, 196.4, 163.6, 136.8, 135.5, 133.6, 133.1, 133.0, 129.9, 129.8, 129.1, 128.7, 127.3, 100.8, 98.3, 89.6, 85.0, 77.3, 75.9, 72.0, 63.6, 55.0, 32.7, 29.7, 29.2, 26.8, 25.7, 22.7, 19.3, 18.3, 11.6, -4.6, -4.7. n.O.e difference and 2D experiments are consistent with the stereochemistry of **9**. The *major isomer* showed the following key enhancements (NCS numbering) (H-8/O-H, 2.7%; H-8/H-9, 2.4%; $H\text{-}1/H\text{-}12$, 6.4%; H-1/H-9, 6.0%).
11. All compounds are racemic and yields are quoted for chromatographically homogeneous compounds which exhibited analytical data consistent with their structures.

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