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Synthesis of a Dihydroxylated Dienediyne Analogue Related to Neocarzinostatin Chromophore

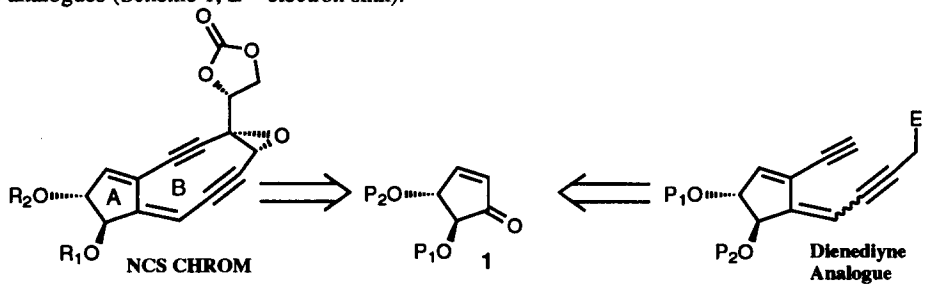
Stephen Caddick,* Safraz Khan, Nichola J. Smith, Douglas M. Barr, Vern M. Delisser

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

Abstract: A 12-step synthesis of a dihydroxylated dienediyne analogue related to Neocarzinostatin Chromophore is reported. © 1997 Elsevier Science Ltd.

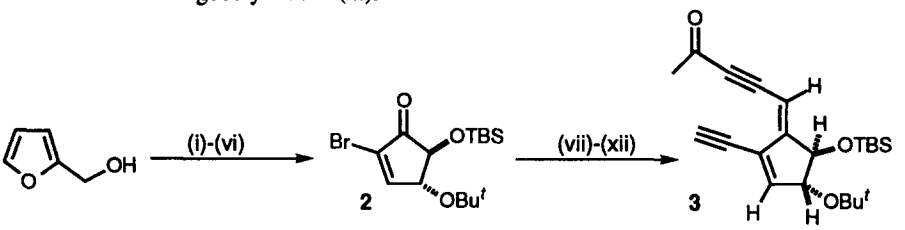
The enediyne class of natural products has provided potentially important leads for cancer chemotherapy and their unusual structure and mode of action has stimulated numerous research groups to engage in this area of scientific endeavour.[1] An important feature of many research efforts, including our own, is the design and synthesis of analogues which would improve the understanding of the interaction of this important class of compounds with DNA.[2] For our programme, compound **1** became an important synthetic intermediate on which we could base syntheses of the natural products and unnatural enediynes as biological/mechanistic probes. We have recently described the synthesis of this functionalised cyclopentenone fragment using a base-promoted isomerization reaction[3] and have used this in a concise synthesis of an elaborated functionalised bicyclic core of Neocarzinostatin (NCS) and Kedarcidin chromophores.[4] We herein present the completion of the first of our strategic objectives which was to demonstrate that **1** can additionally be useful for the synthesis of dienediyne analogues (Scheme 1, E = electron sink).[5]

Scheme 1



We have improved the synthesis of compound **2** such that it can now be prepared in 6 synthetic steps as shown in scheme 2. The use of NBS to transform furfuryl alcohol into the pyranone directly is dependant on the use of sodium bicarbonate. Routine manipulation gives the *tert*-butyl pyranone which undergoes smooth ring contraction under our standard conditions. Protection of the C-5 hydroxyl using TBSCl proceeds in high yield and bromination delivers the fully elaborated cyclopentenone **2**. Notable features of the synthesis of **3** from **2** include: the stereochemistry of the product from the addition of propargylmagnesium bromide; X-ray crystallography confirms a *syn*-relationship between the propargyl and the TBSO group; the importance of elevated temperature and high purity catalyst for the success of (ix) and the critical use of the

Dess-Martin periodinane to obtain good yields in (xi).



Scheme 2

Reagents and Conditions: (i) NBS (1 eq), $NaHCO_3$ (2 eq), H_2O, 0 °C, 92% (ii) Ac_2O (3.9 eq), Pyr (1.4 eq), 0 °C to r.t. 67%; (iii) $SnCl_4$ (0.05 eq), t-BuOH (4.9 eq), $ClCH_2CH_2Cl$, r.t. 61%; (iv) Et_3N (5 eq), DMF, 80 °C, 75-85%; (v) TBSCl (1.2 eq), Im (1.2 eq), DMF, r.t. 87-92%; (vi) Br_2 (1.3 eq), Et_3N (3 eq), CH_2Cl_2, 98%; (vii) $BrMgCH_2CCH$ (1.9 eq), Et_2O, -41 °C to r.t., 76-85%; (viii) LHMDS (2.4 eq), CH_3CHO (3 eq), THF, -30 °C, 55% (100% BORSM); (ix) $PdCl_2(PPh_3)_2$ (0.03 eq), TMSCCH (2 eq), n-$PrNH_2$ (10 eq), CuI (0.09 eq), THF, 45-60 °C, 70-78%; (x) KF, (3 eq), MeOH, r.t. 90%; (xi) Dess-Martin periodinane (3 eq), CH_2Cl_2, r.t. 76%; (xii) Martin Sulfurane (1 eq), CH_2Cl_2, -40 °C to r.t. 65-70%.

Attempted elimination under a number of standard conditions did provide the desired product but in modest yields and with varying levels of purity. However we found that by far the superior procedure made use of the Martin sulfurane reagent which enabled us to isolate the desired adduct **3** as the major isomer in yields of 65-70%. The stereochemistry of **3** was established using n.O.e difference experiments.[6]

In conclusion we have developed a synthetic route which will provide important new dienediyne analogues for biological evaluation.[7] An exciting prospect will be the attachment of the carbohydrate and naphthoate groups present in NCS CHROM; this should give important information pertaining to the drug-DNA interaction.

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6. Ratio of isomers obtained was at least 10:1 in favour of the isomer shown in scheme 2.
7. All compounds are racemic, isolated yields are quoted and all compounds exhibited spectroscopic data consistent with their structure.

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