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Enantioselective Synthesis of Neocarzinostatin Chromophore Aglycon

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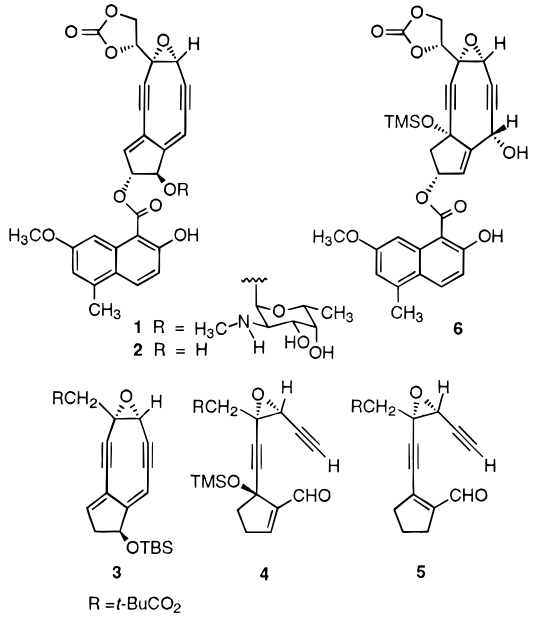
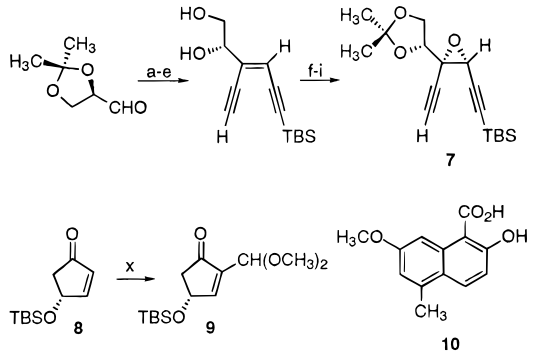
Neocarzinostatin is the first of the "enediyne" antitumor agents to be characterized and is further distinguished as the first chromoprotein antibiotic.[1] The DNA-cleaving properties of the neocarzinostatin protein−chromophore complex have been shown to reside solely within the chromophore component (**1**) which, in isolation, is exceedingly unstable.[2,3] The strain, structural complexity, and, most importantly, high reactivity of the chromophore core define an extraordinarily challenging synthetic target. In this work, we describe an enantioselective route that provides for the first time neocarzinostatin chromophore aglycon (**2**), a substance which proves to be even less stable than **1** and which, almost certainly, could not be derived from the parent antibiotic.



We have previously described the preparation of compound **3**, to date the only synthetic construct that bears the epoxy diendiyne functionality of **1**.[4,5] The route that was developed involved the intramolecular addition of an acetylide to an aldehyde within the precursor **4**, followed by 1,3-allylic transposition of the tertiary (trimethylsilyl)oxy group and 1,4-elimination of water to produce **3**. Preliminary studies had shown that seemingly more direct approaches to the core functionality of **1** involving intramolecular acetylide addition within precursors such as **5** failed, presumably due to the poor trajectory of the addition reaction. Thus, the strategy that had been successful in our earlier work brings with it a necessary 1,3-allylic transposition step—a step that ultimately proved to be the undoing of this approach within the more highly oxygenated, complex substrates necessary to produce **2**. For example, although the intermediate **6** could be prepared efficiently and in enantiomerically pure form, we were unable to bring about the necessary 1,3-transposition reaction within this substrate, even after much effort. Herein, we report that modification of our earlier strategy by epoxidation of the 5-membered ring olefin avoids the allylic transposition problem, preserves a favorable trajectory for the intramolecular acetylide addition reaction, and, unexpectedly, defers to the final step many of the instability issues which plagued the earlier approaches.

Scheme 1[a]



[a] (a) LiC≡CTMS, THF, −78 °C, 81%. (b) PDC, AcOH, 3A molecular sieves, CH_2Cl_2, 23 °C. (c) $Ph_3PCH_2C{\equiv}CTBS^+$ Br^-, KN(TMS)$_2$, THF, −78 → −40 °C, 79% (steps b and c), 3:1 *E*/*Z*. (d) K_2CO_3, CH_3OH, 0 °C. (e) 1 N HCl, THF, 23 °C, separate isomers, 64% (*E*-isomer, steps d and e). (f) TDSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C. (g) (−)-DET, Ti(O*i*-Pr)$_4$, TBHP, 4A molecular sieves, CH_2Cl_2, −20 °C, 94% (steps f and g). (h) $Et_3N{\cdot}3HF$, THF, 23 °C, 92%. (i) 2-Methoxypropene, TsOH, DMF, 23 °C, 82%. (x) i. PhSeTMS, TMSOTf, CH_2Cl_2, −78 °C; ii. $HC(OCH_3)_3$, −25 → −20 °C; iii. H_2O_2, Py, −20 °C, 80%.

The successful route to **2** involved the convergent assembly of three components. The epoxy diyne **7** (≥95% ee) was synthesized from D-glyceraldehyde acetonide, as shown in Scheme 1. The cyclopentenone **9** (≥90% ee) was prepared from the well-known prostaglandin intermediate **8**[6] in one step in 75−85% yield by a carefully optimized modification of the method of Noyori et al.[7] The third component, the naphthoic acid **10**, was prepared in six steps (31−37% yield) from 4-bromo-3-methylanisole.[8]

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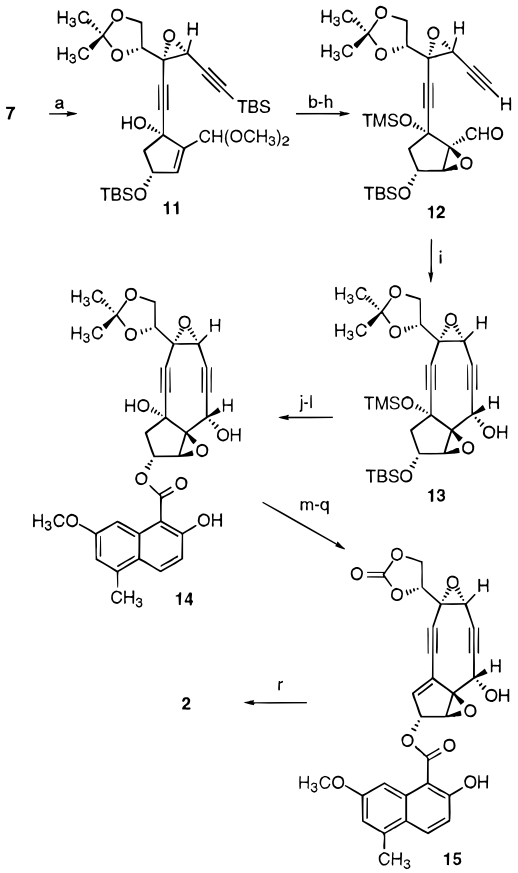
Scheme 2[a]



[a] (a) $LiN(TMS)_2$, $PhCH_3$, −78 °C; **9**, 75%. (b) Bu_4NF, THF, 0 °C. (c) TBSCl, Et_3N, DMAP, CH_2Cl_2, 0 → 23 °C, 92% (steps b and c). (d) TsOH, acetone, 23 °C, 90%. (e) TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 88%. (f) DIBAL, $PhCH_3$, −78 °C, 92%. (g) (+)-DET, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, 4A molecular sieves, CH_2Cl_2, −20 °C, 91%. (h) Dess−Martin Periodinane, Py, CH_2Cl_2, 23 °C, 97%. (i) $LiN(SiPh(CH_3)_2)_2$, LiCl, THF, −78 °C, 79%. (j) $(ClCH_2CO)_2O$, Py, CH_2Cl_2, 0 °C, 89%. (k) $Et_3N{\cdot}3HF$, CH_3CN, 23 °C, 81%. (l) **10**, DCC, THF, 0 °C; *n*-$PrNH_2$, 71%. (m) TsOH, CH_3OH, 23 °C, 67%. (n) CDI, THF, 0 → 23 °C; CSA, 2:1 CH_3CN/H_2O, 23 °C, 67%. (o) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 79%. (p) Martin Sulfurane, CH_2Cl_2, 23 °C, 79%. (q) $Et_3N{\cdot}3HF$, THF, 0 °C, 99%. (r) PPh_3, I_2, imidazole, CH_2Cl_2, −17 °C, 15−30% after purification.

Deprotonation of the epoxy diyne component **7** (1.05 equiv) with lithium hexamethyldisilazide at −78 °C followed by addition of the cyclopentenone **9** (1 equiv) afforded the 1,2-adduct **11** (75%) with ≥20:1 diastereoselectivity (Scheme 2). This product was transformed into the epoxy aldehyde **12** by standard methods. In a key transformation, we found that the epoxy aldehyde **12** underwent efficient ring closure upon treatment with the Masamune lithium diphenyltetramethyldisilazide base[9] at −78 °C, providing the adduct **13** as a single diastereomer in 79% yield.[10] The use of lithium chloride as an additive proved critical in this reaction. A highly noteworthy feature of the product **13** was its stability toward chromatography, concentration, and routine manipulations. This stands in marked contrast to the "olefinic" series of cyclization products (see **6**), which were found to be exceedingly difficult to handle as synthetic intermediates. Protective group manipulations within **13** and introduction of the naphthoic acid **10** then afforded the diol **14**. The selection of coupling reagent and reaction solvent in the latter step proved to be critical, with the use of DCC in THF found to be uniquely successful. The diol **14** was transformed into the epoxy alcohol **15** by the following sequence: incorporation of the carbonate group, silylation of the secondary hydroxyl and naphthol groups, elimination of the tertiary alcohol, and removal of the silyl protecting groups. Treatment of the epoxy alcohol **15** with a mixture of triphenylphosphine, iodine, and imidazole[11] led directly to the highly unstable aglycon **2**.[12] The yield of carefully purified (flash column chromatography) aglycon **2** in the latter transformation was typically 15−30% (UV determination), which is believed to reflect more the instability of **2** than the inherent efficiency of the transformation.

The carbohydrate residue of **1** clearly provides a stabilizing influence on the chromophore core, for the aglycon **2** degrades much more rapidly than **1** both in solution and in neat form. Although synthetic **2** provided good quality ^1H NMR and CD spectra, its half-life in solution was found to be insufficient to acquire a ^{13}C NMR spectrum.[13] The instability of **2** also thwarted all efforts to obtain a mass spectrum of **2** in isolation using a variety of soft-ionization techniques. Success was achieved in the latter effort by adopting Nature's solution to the stabilization of **1** in solution. Precomplexation of the synthetic aglycon **2** with purified neocarzinostatin apoprotein in water (pH 7) followed by electrospray mass spectral analysis provided peaks consistent with the protein-complexed aglycon. This finding not only establishes the molecular weight of our synthetic material but also provides the first evidence that neocarzinostatin chromophore aglycon (**2**) is capable of binding to the apoprotein. The availability of the aglycon **2** now enables important comparative studies that should help to elucidate the role of the carbohydrate residue of **1** in DNA binding and cleavage. In addition, neocarzinostatin chromophore aglycon (**2**) is anticipated to serve as a platform for the preparation of **1** and analogs with modified carbohydrate residues.

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Supporting Information Available: Reproductions of ^1H and ^{13}C NMR spectra and tabulated spectroscopic data for all new synthetic intermediates, and reproductions of ^1H NMR, IR, and CD spectra of **2** (77 pages). See any current masthead page for ordering and Internet access instructions.

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(13) As further confirmation of structure, the treatment of the aglycon with methyl thioglycolate (0.5 M), triethylamine (0.5 M), and 1,4-cyclohexadiene (1.0 M) in THF at 23 °C afforded a thiol adduct in complete analogy to **1**. This adduct has been fully characterized and was obtained in 13% yield (>90% purity, isolated by reverse-phase HPLC). Full details of this reactivity, as well as DNA cleavage by **2**, are the subject of a future manuscript.