# Preparation of the *A*-Ring of Neocarzinostatin and Kedarcidin Chromophores *via* a Stereocontrolled Base Mediated Isomerisation Reaction

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A new base promoted isomerisation of 6-(1,1-dimethylethoxy)-2H-pyran-3-one to 4-(1,1-dimethylethoxy)-5-hydroxy-2-cyclopentenone is used in the preparation of 2-bromo-5-[(1,1-dimethylethyl)dimethylsilyloxy]-4-hydroxy-2-cyclopentenone, a potential intermediate for use in the synthesis of Neocarzinostatin and Kedarcidin chromophores.

The enediyne class of anti-cancer antibiotics have stimulated great interest in chemical synthesis, medicine and biology because of their biological activity which is dependent 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** both of which have, to date, eluded total synthesis.[2]

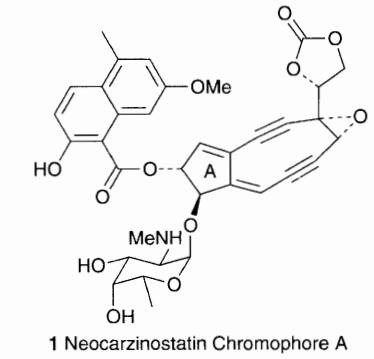
We envisage a common synthetic strategy and in particular we note the structural similarities between the central dienediyne fragments of both natural products; thus a selectively oxidised form of **3** should serve as an intermediate for total synthesis of both of these targets. Further retrosynthetic analysis allows us to identify **4** as a key intermediate for our synthesis plan.

It is interesting to note that whilst NCS A **1**, in common with many other members of the enediyne class, has been the subject of intensive synthetic endeavours, there are relatively few syntheses of the deceptively simple *A* ring portion.[3] Moreover compound **4** is a particularly good primary target since its availability would enable us to utilise it in the production of novel NCS A-related, enediyne analogue systems using modifications of known synthetic sequences.[4] In order to prepare **4** we investigated a previously described isomerisation procedure which we initially used to transform pyranone **5** to cyclopentenone **6** (approximate yields from **5a**, R = Bu$^t$, 21%; **5b**, R = $CH_2Ph$, 50%; conditions $Pd(OAc)_2$, $NaHCO_3$, $Bu_4NCl$, DMF, 80 °C).[5] However under the conditions described we encountered some difficulties with the transformation and of particular concern was our inability to prepare sufficient quantities of products **6** (*i.e.* > 2 g). Our requirement for large quantities of **6** for our synthesis effort and the recognition that such cyclopentenones have applications in the synthesis of a range of extremely valuable cyclopentanoid containing target-molecules[5,6] led us to investigate alternative reaction conditions. We found that treatment of pyranone **5a** or **5b** with 5 equiv. of triethylamine in DMF led to cyclopentenone **6a** or **6b** in good yield as shown in Scheme **1** (71–76%).

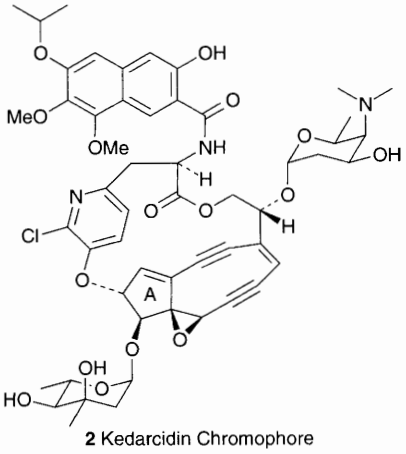
The reactions can be carried out on a preparatively useful scale and we are able to produce consistently good yields of products **6a** and **6b**.† We believe that this new procedure provides a very simple and practical method for the preparation of functionalised cyclopentenones and whilst it is tempting to speculate on both the reaction mechanism and the source of stereoselectivity, further studies are ongoing and are directed toward delineating scope, limitation and applications in synthesis.

Elaboration of **6a** to intermediate **4b**‡ was readily achieved by alcohol protection (TBSOTf, 2,6-lutidine, −78 °C to room temp., 60–67%) followed by bromination ($Br_2$, $CH_2Cl_2$, 0 °C, 1 h, $Et_3N$, $CH_2Cl_2$ 0 °C–room temp., 3 h, 74–87%). Deprotection of the *tert*-butyl protecting group in **4b** can be achieved using TFA in dichloromethane to give **4c**§ (55–61%), Scheme 2. The selective manipulation of either hydroxy functionality in these systems may offer some useful synthetic opportunities.

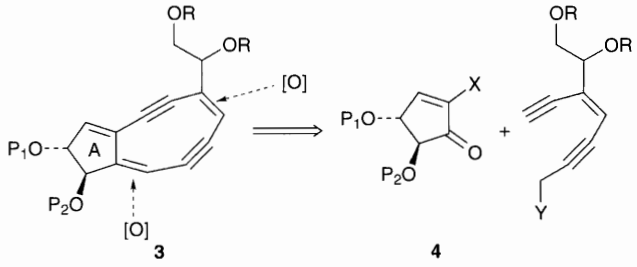
In summary we have described the synthesis of a highly functionalised 4,5-dihydroxylated cyclopentenone **4** in seven steps from commercially available furfuryl alcohol *via* pyran-



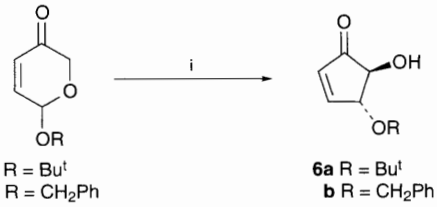

**1** Neocarzinostatin Chromophore A




**2** Kedarcidin Chromophore



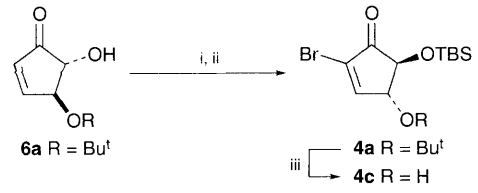

**3** **4**




**5a** R = Bu$^t$
**b** R = $CH_2Ph$

**6a** R = Bu$^t$
**b** R = $CH_2Ph$

**Scheme 1** *Reagents and conditions*: i, $Et_3N$, DMF, 80 °C, 16–24 h, 71–76%




**Scheme 2** *Reagents and conditions*: i, TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C to room temp., 60–67%; ii, $Br_2$, $CH_2Cl_2$, 0 °C, 1 h, $Et_3N$, 0 °C to room temp. 3 h, 74–87%; iii, TFA (5 equiv.), $CH_2Cl_2$, 0 °C to room temp., 24 h, 55–61%

one **5**.[7] This intermediate has the potential to be transformed into a range of natural and unnatural enediyne systems; we are vigorously pursuing this goal. The synthesis is based on a new and highly efficient base promoted isomerisation which transforms readily available pyranones into cyclopentenones with a high degree of stereocontrol in good yield. The synthetic potential of functionalised cyclopentenones of this type is particularly promising as they are available in multi-gram quantities and should undergo a range of useful synthetic manipulations which we are currently investigating; these will be reported in due course.

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## Footnotes

† *Experimental procedure*: A stirred solution of pyranone **5a** (26 g, 0.153 mol) in DMF (300 ml) and triethylamine (106 ml, 0.760 mol) was heated at 80 °C for 24 h. The black reaction mixture was allowed to cool to room temp. and concentrated *in vacuo* to give the crude product. Purification by silica gel chromatography (light petroleum : diethyl ether, 2 : 1) gave cyclopentenone **6a** (19.14 g, 73.6%) as a white solid (*mp* 52–53 °C, lit.[5] 52.5–53 °C).

‡ All compounds are racemic and exhibited satisfactory analytical data (IR, $^1H$ and $^{13}C$ NMR, HRMS).

§ *Spectroscopic data* for **4c** IR (film)/$cm^{-1}$ 3434, 2931, 2858, 1726, 1586, 1471, 1362, 1309, 1254, 1145, 1050, 883, 841 and 781; $\delta_H$ ($CDCl_3$, 360 MHz) 7.50 (dd, 1 H, $J$ = 2.2 and 1.3 Hz, $H^3$), 4.72 (br s, 1 H, $H^4$), 4.22 (dd, 1 H, $J$ = 2.4 and 1.4 Hz, $H^5$), 2.35 (brs, 1 H, OH), 0.95 (s, 9 H, $Bu^tSi$), 0.22 (s, 3 H, SiMe) and 0.19 (s, 3 H, SiMe); $\delta_C$ ($CDCl_3$, 125.6 MHz) 196.06, 156.57, 125.30, 80.84, 77.26, 25.68, 18.31, −4.58 and −5.18; HRMS found for $(M - Bu^t)^+$, 248.957837, $C_7H_{10}BrO_3Si$ requires *m/z* 248.958259.

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