Synthetic Studies Related to the Esperamicin/Calicheamicin Aglycone: Efficient Construction of a Homochiral Oxabicyclo [7:3:1] Analogue from D-Xylose

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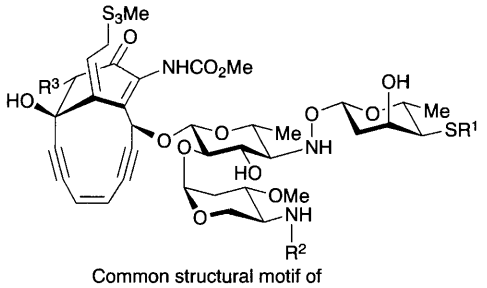
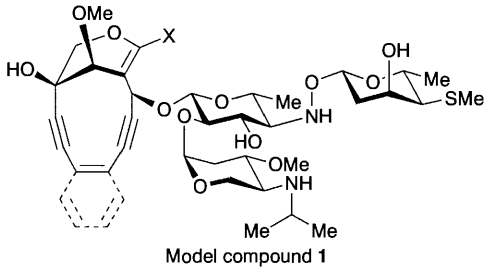
The synthesis of a bicyclic model of the calicheamicin/esperamicin aglycone is described using a highly efficient and stereospecific Nozaki–Kishi reaction for the ring closure.

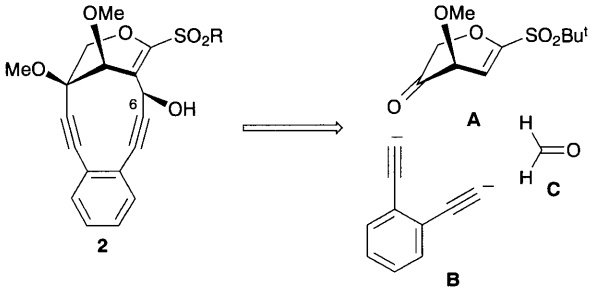
A great deal of work has been in progress on the recently discovered enediyne antibiotics calicheamicin γ_1^I and esperamicin A_1.[1] These antibiotics not only have remarkable DNA cleaving abilities involving an aryl diradical intermediate, but also enormous potential as selective antitumour agents. Investigating the DNA binding properties of the common trisaccharide motif of these substances is a current goal in our group. Several seminal studies have already been reported in this area[2–8] and have revealed that in addition to the oligosaccharide component, the enediyne moiety may also contribute to the overall binding energy to specific four base-pair sequences of DNA duplexes.[4] To obtain a better understanding of the factors involved in the contribution of the aglycone–DNA binding, it is important that model compounds be available for comparative studies. Compound **1** could represent a potential model for such investigations. We recently reported the total synthesis of the required trisaccharide fragment found in esperamicin A_1[9] and now disclose the synthesis of the novel [7.3.1] bicyclic model **2** of the calicheamicin/esperamicin aglycone in enantiomerically pure form, which includes a highly efficient Ni^{II}–Cr^{II}-mediated cyclization as a key step.



Common structural motif of calicheamicin γ_1^I and esperamicin A_1



Model compound **1**



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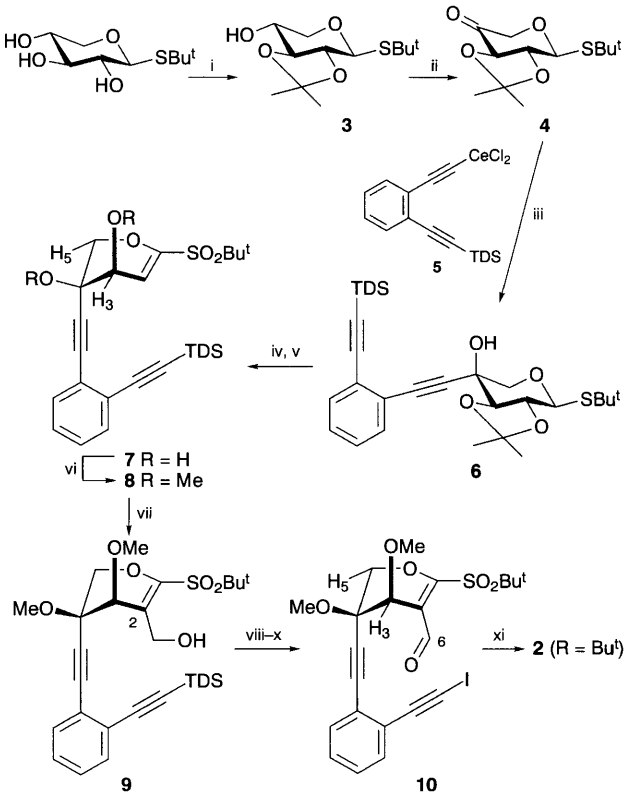
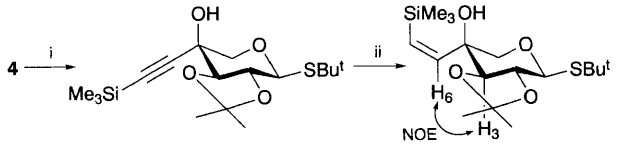
The preparation of aglycone **2** was conceived using a three-component strategy starting from fragments **A**, **B** and **C**, with **A** being derived from D-xylose.

The synthesis of **2** (Scheme 1) began with the selective protection of the C-2 and C-3 hydroxy groups of *tert*-butyl 1-thio-D-xylopyranoside with 2-methoxypropene providing a separable 8 : 1 mixture of ketal **3**‡ and its C-3, C-4 regioisomer. Dess–Martin oxidation[10] gave the labile ketone **4** which, without chromatographic purification, was immediately condensed with the cerium(III) reagent of the TDS-protected (TDS = thexyldimethylsilyl) benzodiynyl anion **5** at −78 °C.§ This provided alcohol **6**¶ as a single stereoisomer at C-4 in a 62% yield for the two steps. The configuration at C-4 was assessed by comparing the ^{1}H NMR spectra of **11**, prepared by reacting the trimethylsilyl-acetylide anion and ketone **4** (Scheme 2) with that of **6**. Both compounds showed long-range coupling constants between the OH-4 hydrogen and H-5_{ax} (1.8 Hz in **6** and 1.5 Hz in **11**) in a $^4C_1$ conformation, diagnostic of the axial orientation of OH-4. This assignment was further confirmed by



Scheme 1 *Reagents and conditions*: i, 2-methoxypropene, catalytic camphorsulfonic acid, DMF, 60 °C, workup with MeOH, 80% plus 10% of the 2,3-regioisomer; ii, Dess–Martin periodinane (1.8 equiv.), room temp., 2 h; iii, **5** (1.3 equiv.), THF, −78 °C, 10 min, 62% from **3**; iv, MCPBA (3 equiv.), $NaHCO_3$ (5 equiv.), CH_2Cl_2, room temp., 30 min, 83%; v, BuLi (3.5 equiv.), THF, −78 to −40 °C, 1 h, 77%; vi, MeI, NaH, THF, room temp., 2 h, 89%; vii, LDA (1.4 equiv.), THF, −78 °C, 15 min then HCHO, 80%; viii, Bu_4NF, THF, room temp., 15 min, 96%; ix, I_2–morpholine, PhH, 45 °C, 2 h, 85%; x, PCC (2 equiv.), AcONa (3 equiv.), 3 Å molecular sieves, CH_2Cl_2, 45 min, 82%; xi, $CrCl_2$ (10 equiv.), $NiCl_2$ (0.1 equiv.), THF, room temp., 95%



Scheme 2 *Reagents and conditions*: i, cerium dichloride trimethylsilylacetylide (1.4 equiv.), THF, −78 °C, 15 min, 67% from **3**; ii, H_2, Lindlar catalyst, hexane : THF 1 : 2, room temp., 1.5 h, 47%

the NOE contact observed between H-3 and the vinylic H-6 in vinyl silane **12**, obtained by reduction of **11**.

Oxidation of sulfide **6** to the corresponding sulfone followed by an elimination reaction upon exposure to 3 equiv. BuLi at −78 °C provided the vinyl sulfone **7**¶ in 77% yield. The long-range coupling constant (J 1.3 Hz) between the H-3 and H-5_{eq} protons (W-effect) suggests a conformation in which the benzodiyne moiety in **7** is axially orientated, a favourable situation for the subsequent cyclization reaction. Methylation of diol **7** afforded **8** in a high yield which was lithiated at C-2 with lithium diisopropylamide at −78 °C and treated with gaseous formaldehyde to give alcohol **9** in 80% yield. Use of BuLi led to less reproducible yields. At this point, the choice of the *tert*-butyl sulfone group was justified since the above sequence using the corresponding phenyl sulfone led to a significantly competitive hydroxymethylation at the *ortho* position of the aromatic ring.

With the C-2 carbon branch introduced, the stage was set for the ring closure step. Although a base-promoted cyclization also appeared to be a viable method,[1] the possibility of employing a Cr^{II}–Ni^{II}-mediated[11] ring closure reaction to the [7.3.1] bicyclic strained structure attracted our attention. This choice was based on our previously reported reaction for the preparation of strained monocyclic 10-membered enediyne rings,[12] which has been successfully employed since in other enediyne systems.[13]

Thus, benzodiyne **9** was desilylated, transformed into the corresponding iodoalkyne and oxidized under standard conditions to afford **10**¶ in 67% overall yield. Upon slow addition (25 min) of **10** to a suspension of $CrCl_2$ (10 equiv.) containing 1% $NiCl_2$ in THF at 20 °C, complete consumption was observed with the appearance of a single isomer characterized as **2**‖ (R = Bu^t) in 95% yield after column chromatography. The *R*-configuration at C-6, identical to that of esperamicin and calicheamicin, was established by X-ray crystallographic analysis. This facile and stereospecific ring closure may be attributed to: (i) the axial orientation of the benzodiyne subunit in **10** observed (as for **7**) through a H-3, H-5_{eq} coupling constant in the ^{1}H NMR spectrum; and (ii) a highly-biased *S-trans* conformation for the unsaturated aldehyde maintained by the bulky *tert*-butyl sulfone group, thus leading to the appropriate stereochemistry at C-6. Further work in the preparation of an enediyne analogue to **2** and subsequent coupling with the trisaccharide will be reported.[14]

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Footnotes

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‡ All new compounds gave satisfactory spectral and analytical data.

§ The cerium(III) reagent **5** of the benzodiyne unit was prepared by iterative palladium(0) catalysed coupling reactions from *o*-dibromobenzene as follows: i, thexyldimethylsilylacetylene (1.2 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), CuI (0.07 equiv.), *n*-$PrNH_2$ (1.8 equiv.), PhMe, 90 °C, 5 h, 63%; ii, excess trimethylsilylacetylene, $Pd(PPh_3)_4$ (0.1 equiv.), CuI (0.05 equiv.), *n*-$PrNH_2$ (5 equiv.), PhMe, 110 °C in a sealed system, 1.5 h, 87%; iii, K_2CO_3 (1.2 equiv.), MeOH : CH_2Cl_2 (10 : 1, *v*/*v*), room temp., 45 min, 88%; iv, BuLi (1 equiv.), THF, −78 °C, 30 min then transfer to $CeCl_3$ (1 equiv.) in suspension in THF, −78 °C, 45 min.

¶ *Selected ^{1}H NMR data* ($CDCl_3$, 300 MHz; numbering of protons is that of carbohydrate numbering). For **6** δ 0.27 (s, 6 H, $SiMe_2$), 0.95 (d, 6 H, *J* 7 Hz, thexyl), 0.97 (s, 6 H, thexyl), 1.43 (s, 9 H, SBu^t), 1.50 and 1.52 (2 s, 6 H, 2 Me), 2.58 (d, 1 H, $J_{OH,5ax}$ 1.8 Hz, OH), 3.73 (dd, 1 H, $J_{5ax,5eq}$ 12.5 Hz, H-5_{ax}), 3.75 (d, 1 H, $J_{2,3}$ 9.2 Hz, H-3), 3.82 (t, 1 H, $J_{1,2}$ 9.2 Hz, H-2), 4.14 (d, 1 H, H-5_{eq}), 4.86 (d, 1 H, H-1). For **7**: δ 3.08 (bs, 2 H, OH), 4.19 (dd, 1 H, $J_{3,5eq}$ 1.3, $J_{5ax,5eq}$ 11.5 Hz, H-5_{eq}), 4.33 (d, 1 H, H-5_{ax}), 4.60 (dd, $J_{2,3}$ 3.5 Hz, H-3), 5.98 (d, 1 H, H-2). For **10**: δ 1.39 (s, 9 H, Bu^t), 3.56 and 3.63 (2 s, 6 H, 2 OMe), 4.37 (d, 1 H, $J_{5ax,5eq}$ 10 Hz, H-5_{ax}), 4.45 (dd, 1 H, $J_{3,5eq}$ 1.8 Hz, H-5_{eq}), 4.81 (d, 1 H, H-3), 8.47 (s, 1 H, *CHO*).

‖ Prepared on a 0.3 mmol scale; mp 105 °C, $[\alpha]_D^{20}$ −301 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz; numbering of protons is that of carbohydrate numbering): δ 1.37 (s, 9 H, Bu^t), 3.53 and 3.62 (2 s, 6 H, 2 OMe), 4.31 (dd, 1 H, $J_{3,5eq}$ 1.2, $J_{5ax,5eq}$ 10.2 Hz, H-5_{eq}), 4.36 (d, 1 H, H-5_{ax}), 4.70 (d, 1 H, H-3), 6.82 (s, 1 H, H-6).

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14 Part of this work was presented at the *XVIIth International Carbohydrate Symposium*, Ottawa, July, 1994, Abst. B2.106.