Formal synthesis of (−)-calicheamicinone and of (+)-calicheamicinone

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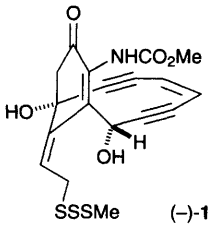
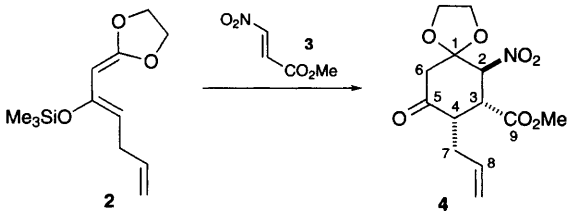
An asymmetric Diels–Alder reaction between ketene acetal 2 and the 3-nitropropenoate 10, derived from (−)-8-phenylmenthol, affords the optically pure adduct 15, which can be converted into either enantiomer of calicheamicinone 1.

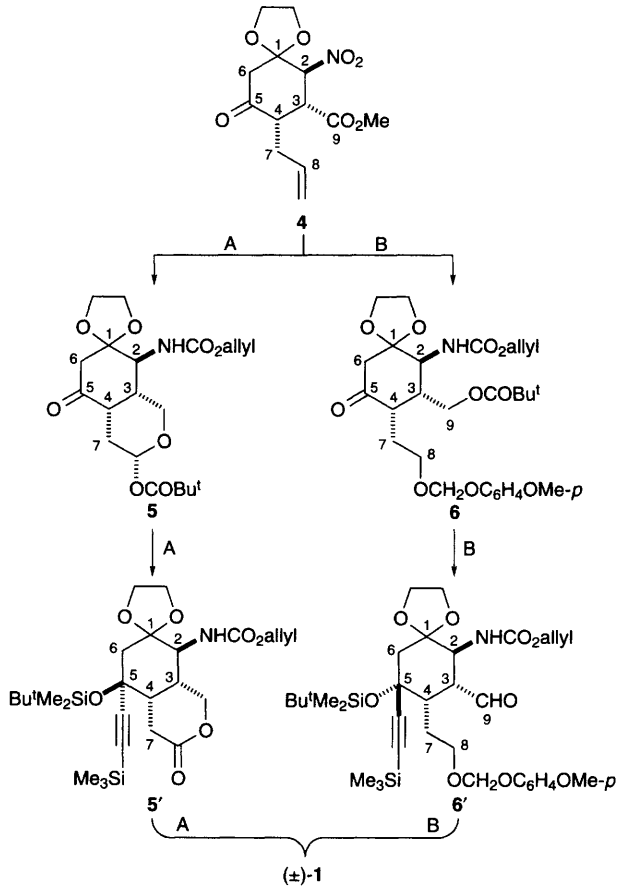
(−)-Calicheamicinone [(−)-**1**] is the aglycone of the antitumour agent calicheamicin γ_1^I.[1] We describe separate formal routes to (−)-**1** and its enantiomer, based on a synthesis of racemic calicheamicinone[2] reported from this laboratory. That earlier work involved a Diels–Alder reaction between ketene acetal **2** and methyl 3-nitropropenoate **3**, to give ketone **4** (Scheme 1). This highly functionalized ketone was then converted (Scheme 2) by two related methods, *via* **5** and **5′** (in one route) and **6** and **6′** (in the other) into racemic calicheamicinone. The transformations **4**→**5**→**5′**→(±)-**1** and **4**→**6**→**6′**→(±)-**1** were done using racemic compounds, but only one enantiomer is shown in the Scheme for each, and the diagrams are drawn in such a way as to indicate the critical fact that in one route the acetylene at C-5 is introduced *syn* to the nitrogen, while in the other the relationship is *anti*. Further elaboration of **5′** and **6′** involves converting C-2, C-3, and C-4 to sp^2 hybridization, so that the only stereogenic centre in **5′** and **6′** that is retained is C-5. A consequence of this situation is that either enantiomer of **4** can serve equally well for the preparation of (−)-**1**: the enantiomer of **4** with 2*S* absolute configuration would be processed by route A, while the 2*R* isomer would also give (−)-**1**, but by route B. Against this background, it was necessary only to find an efficient procedure for carrying out the initial Diels–Alder reaction (*cf.* Scheme 1) in an asymmetric manner, the absolute configuration of the product being immaterial. To this end, we sought to prepare a nitroalkene **7** in which the group X is a chiral auxiliary. Our initial choice fell on oxazolidinones,[3] but we were unable to prepare compound **8**—at least within the short time we devoted to the problem—and so we turned to (−)-8-phenylmenthol **9**, which is readily available from *R*-pulegone,[4] and also has a fine reputation as a chiral auxiliary in asymmetric Diels–Alder reactions.[5] While the performance of this compound was eventually very satisfactory, development of a route to the derived 3-nitropropenoate **10** was unexpectedly difficult, and appreciable effort was required before we found a satisfactory procedure for converting **9** into **10**.

Acylation of **9** with acryloyl chloride (Et_3N, DMAP, 93%) gave ester **11** (Scheme 3), and the double bond was then cleaved[6] with $NaIO_4$–OsO_4 to afford (*ca.* 100%) a mixture of

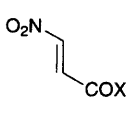


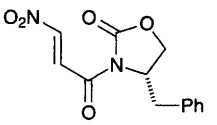


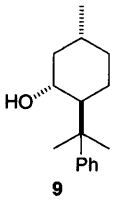
Scheme 1

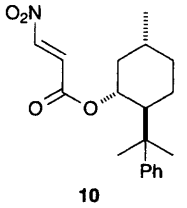


Scheme 2



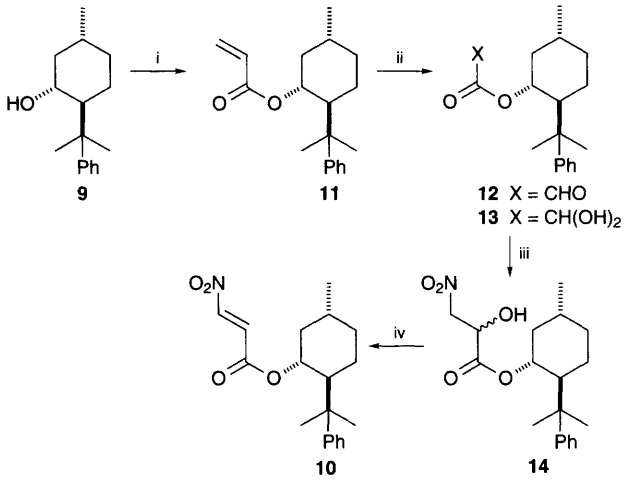




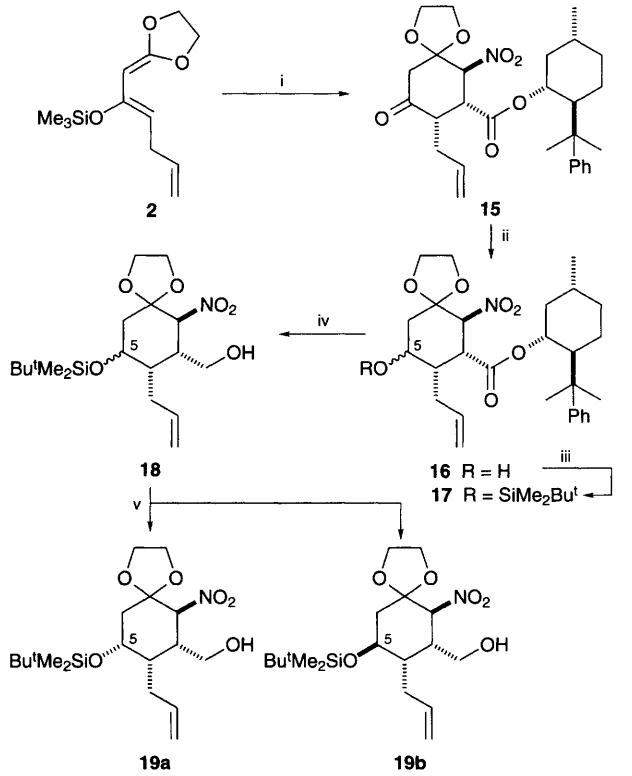


glyoxylate **12** and the corresponding hydrate **13**. This material underwent efficient Henry reaction (91%) with nitromethane in the presence of neutral alumina[7] to give a mixture of alcohols, and these were easily dehydrated (90%) by mesylation and *in situ* elimination to the required 3-nitropropenoate **10**.†

Diels–Alder reaction of **10** with ketene acetal **2**[2] at −78 °C proceeded smoothly to give, after mild hydrolysis (aqueous NH_4Cl, room temperature, 2 h), the adduct **15** (Scheme 4), which was isolated in 64% yield, by flash chromatography and crystallization.‡ X-Ray analysis showed that the absolute stereochemistry is as shown. The corresponding reaction with



Scheme 3 *Reagents and conditions*: i, acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C, 5 min, 93%; ii, $NaIO_4$, OsO_4, 1:3 water–dioxane, 2 h, *ca.* 100%; iii, $MeNO_2$, neutral alumina, 0 °C, 0.5 h, room temp., *ca.* 3 h, 91%; iv, MsCl, Et_3N, 0 °C, 7 min, 90%



Scheme 4 *Reagents and conditions*: i, **10**, THF, −78 °C, 35 min; aqueous NH_4Cl, room temp., 2 h, 64%; ii, $NaBH_4$, MeOH, 0 °C, 15 min, *ca.* 100%; iii, Bu^tMe_2SiOTf, 2,6-lutidine, *ca.* 100%; iv, 2 equiv. DIBAL-H, −78 °C, 4 h, −30 °C, 20 h; 2 equiv. DIBAL-H, −30 °C, 24 h, 80%; v, separate by silica flash chromatography, 9:1 hexane–EtOAc and then 4:1 hexane–EtOAc; 53% yield of **19a** and 27% yield of **19b** (from **15**)

the methyl ester **3** proceeds in 53% yield, so that the efficiency of the Diels–Alder reaction is somewhat sensitive to the nature of the *O*-alkyl group of the ester. From the absolute stereochemistry of the adduct, it was clear that further elaboration to (−)-calicheamicinone should be according to path A of Scheme 2.

Reduction of ketone **15** with $NaBH_4$ gave a mixture of alcohols epimeric at C-5, and these were then silylated (**16**→**17**; Bu^tMe_2SiOTf, 2,6-lutidine, *ca.* 100% over two steps). Next, the chiral auxiliary was disengaged by treatment with DIBAL-H, to afford **18** and **9**. This experiment had to be done under carefully defined conditions. At −78 °C, reaction with DIBAL-H is very slow and, at room temperature, the Bu^tMe_2Si group at C-5 is removed.[8] After considerable experimentation, the following procedure was developed: DIBAL-H (2 equiv.) is added at −78 °C and, after 4 h, the reaction flask is transferred to a bath at −30 °C. Another portion of DIBAL-H (2 equiv.) is added 24 h after the first batch, and stirring at −30 °C is continued for 24 h. At this point, the C-5 epimeric silyl ethers **18** can be isolated in 80% yield, and the auxiliary can be recovered in 92% yield. Epimers **18** are easily separated by flash chromatography over silica gel to afford **19a** (53% from **15**) and **19b** (27% from **15**).

Each of these alcohols, and the corresponding racemic compounds,[2] were converted into their Mosher esters,[9] which were examined by ^{19}F NMR spectroscopy. Both **19a** and **19b** were optically pure, the CF_3-signals (two in each case) for the corresponding racemic materials being well separated (22 and 57 Hz, respectively). In the racemic series,[2] material corresponding to **19a** and to **19b** had been converted into (±)-calicheamicinone by route A (Scheme 2). Consequently, the preparation of optically pure **19a** and **19b** constitutes a formal synthesis of (−)-calicheamicinone. Application of route B would lead to (+)-calicheamicinone (of unnatural stereochemistry). We note that there is evidence to suggest that the unnatural isomer, when linked to the natural carbohydrate unit, might be more efficient in causing double strand cleavage of DNA than the natural material.[1c]

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Footnotes

† The vinyl hydrogens had *J* 13.5 Hz.

‡ We did not detect other diastereoisomers but, as the mass balance is not quantitative, we cannot be certain that none were formed.

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