Synthesis of $^{13}$C-labelled, bicyclic mimetics of natural enediynes

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Using a versatile synthesis with $^{13}$CH$_3$PPh$_3$I and CH$_3^{13}$CO$_2$Et as $^{13}$C sources, the first examples of nine-membered chromophores which have been differentially labelled with $^{13}$C in their carbocyclic enediyne cores are described.

With their complex antitumour behaviours (nucleic acid/protein damage, p-diradical/p-quinone formation) and complex structures, the chemistry and biology of the enediyne-class of antitumour antibiotics has fascinated and challenged researchers for well over a decade now. Yet, despite several mechanistic studies, it can be argued that the reactive diradical intermediate which results from the cycloaromatisation of a natural enediyne has never been proven unambiguously. To address this issue, we have completely re-formulated our former approach in order to incorporate $^{13}$C into the said strategic positions of the enediyne 1 in an atom-economical fashion, the goal here was to devise a strategy that would not only be flexible to both isotopomers 2 and 3 but also be amenable to the late stage introduction of carbon-13. However, reliable synthetic routes to epoxycyclen[7,3.0]docedicycendiyne frameworks are exceedingly difficult to realise due to product instability. For the structural case at hand, we elected to pursue a new approach through the enyne 4 (Scheme 1). Apart from the practical availability of the isodicyclopentene $^5$ ($\alpha/\beta = 5$ at C9), two points should be made: (1) the ynone 4 was anticipated to be more stable than those that had been used previously $^3,6$, and (2) the coupling of 5 with acetylenic fragments like 6 or 7 was envisaged to give broad scope in carbon-13 labelling studies.

After extensive studies with non-labelled components, a streamlined synthesis of the C3, carbon-13 labelled system 2 was realised as follows. First, the $^{13}$C-labelled component 6 was prepared from 8 through an efficient, gram-scale synthesis via compounds 9 and 10 (Scheme 2). Here, it should be noted that the Wittig reaction between the ethynylirone derivative 8 (2 equiv.) and $^{13}$CH$_3$PPh$_3$I (1 equiv.)$^9$ occurred in quantitative yields and that the stereochemistry of the C4 position was superfluous to our planned synthesis of 2, since it would be oxidatively destroyed in the formation of the ynone 4 (cf. Scheme 1).

As shown in Scheme 3, using well-established Sonogashira-type conditions on 5 and $^{13}$C-labelled 6,2,5,10 the diol 11 was obtained in 72% yield as a four-component diastereomeric mixture at C4 ($\alpha/\beta = 1:1.3$) and C9 ($\alpha/\beta = 5$ at C9). Oxidative cleavage of 11 with NaIO$_4$ then cleanly furnished the desired ynone 4 ($\alpha/\beta = 5$ at C9) which proved to be stable to both silica-gel chromatography and storage. Treatment of 4 with propargyl bromide and TBS ether protection (under anionic conditions)$^{11}$ permitted the nitrile 12 to be isolated as its major diastereomer (4a, 9a) in 46% overall yield.$^+$ DIBAL reduction of the nitrile 12 afforded the cyclisation precursor 13 in excellent yield, which was immediately subjected to the typical CeCl$_3$-mediated acetylide cyclisation protocol at $-25$ °C to generate the trans-diol 14 in 45–52% isolated yield.$^{2,4,5}$ Mesylation of 14 followed by global desilylation then afforded the epoxide 15 in 76% yield over two steps. Finally, 15 was silylated selectively at the C11-allylic alcohol and then, in a one-pot reaction, mesylated at 5 °C and treated with DBU at $-40$ °C to produce the fully-fledged, $^{13}$C-labelled epoxide 16 in 34% yield.$^{5}$

As indicated in our retrosynthetic analysis (Scheme 1), the incorporation of carbon-13 into the C6-position would necessitate a simple modification of the aforementioned route. Instead of using propargyl zinc, carbon-13 incorporation was thus achieved by the anionic-addition of labelled ethyl acetate (CH$_3^{13}$CO$_2$Et) onto the enantiopure ynone 4, which was derived from the readily available synthon 7 (Scheme 3). After O-TBS silylation, 17 was subsequently obtained as a 4:1 $\alpha/\beta$ mixture at C4 in a 66% yield over two steps. Following the chemoselective reduction of the ester functionality in the presence of the nitrile group and re-oxidation, the dibromoukene 18 was generated.
and isolated in enantiopure form after silica-gel chromatography. Completion of this oxidation-homologation sequence then gave the desired C6–carbon-13 labelled alkyne 19 in 22% yield over six steps from 2. Lastly, under a parallel reaction sequence to that described for 2, the targeted epoxypenidine 3 was generated from 19 (via the C6-labelled intermediates 20–22) in a 22% overall yield over six steps.‡

In closing, we should first point out that for all isotopomers 2 and 3 the nine-membered cyclization steps to 14 or 21 have been reliably performed in yields that reflect the diastereomeric purity of the cyclization precursors 13 or 20, i.e. 45 to 72%. Second, the routes described herein are highly expedient and practical, particularly considering the high lability of the compounds involved. For example, the unlabelled enediyne 1 can now be prepared in a 10–15% overall yield from enantiopure 7† over the shortest 10-step sequence. Comprehensive EPR characterisation studies on the radical cyano-omatised states of 1–3 are currently being finalised and will be detailed elsewhere.

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Notes and references


