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

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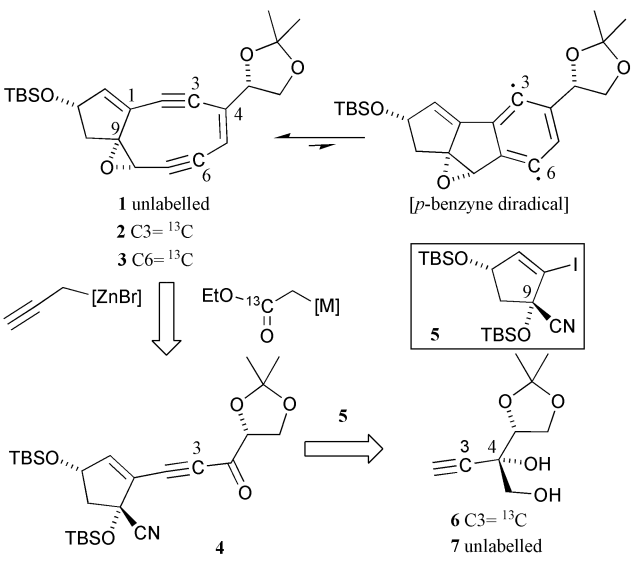
Using a versatile synthesis with $^{13}CH_3PPh_3I$ and $CH_3{}^{13}CO_2Et$ as ^{13}C sources, the first examples of nine-membered chromophores which have been differentially labelled with ^{13}C in their carbocyclic enediyne cores are described.

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.[1–3] 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.[3] To address this issue, we have completely re-formulated our former synthesis of the core structure (**1**) of the kedarcidin chromophore (like kedarcidin which exhibits paramagnetic behaviour)[3b,4] and herein provide carbobicyclic models (**2**, **3**) labelled with ^{13}C at either the 3 or 6 position for the precise characterisation of *p*-benzyne and other radical species through EPR measurements (Scheme 1).

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 epoxybicyclo[7.3.0]dodecenediyne frameworks are exceedingly difficult to realise due to product instability.[2,5] For the structural case at hand, we elected to pursue a new approach through the ynone **4** (Scheme 1). Apart from the practical availability of the iodocyclopentene **5**[5] (α/β = 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,[5,6] and (2) the coupling of **5** with acetylenic fragments like **6** or **7**[7] was envisaged to give broad scope in carbon-13 labelling studies.

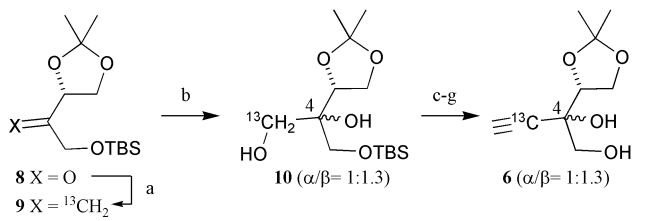


Scheme 1 Versatile retrosynthesis of **1**, **2** and **3**.

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**[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 erythrulose derivative **8** (2 equiv.) and $^{13}CH_3PPh_3I$ (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**,[2c,5,10] the diol **11** was obtained in 72% yield as a four-component diastereomeric mixture at C4 (α/β = 1:1.3) and C9 (α/β = 5 at C9. Oxidative cleavage of **11** with $NaIO_4$ then cleanly furnished the desired ynone **4** (α/β = 5 at C9) which proved to be stable to both silica-gel chromatography and storage. Treatment of **4** with propargyl zinc bromide and TBS ether protection (under anionic conditions)[11] permitted the nitrile **12** to be isolated as its major diastereomer (4α, 9α) 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.[2c,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 epoxydienediyne **2** in high purities and in yields of about 45–50%.‡

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 propargylic zinc, carbon-13 incorporation was thus achieved by the anionic-addition of labeled ethyl acetate ($CH_3{}^{13}CO_2Et$) onto the enantiopure ynone **4**, that was derived from the readily available synthon **7**[7] (Scheme 3). After *O*-TBS silylation, **17** was subsequently obtained as a 4:1 α/β 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 dibromoalkene **18** was generated



Scheme 2 *Reagents and conditions*: (a) $^{13}CH_3PPh_3I$, $NaN(TMS)_2$, THF, −78 °C to rt, 1 h, quantitative; (b) OsO_4 (0.01 eq.), NMO (2.5 eq.), acetone–H_2O (4:1), 12 h, 86%; (c) SO_3·Py (3 eq.), Et_3N (15 eq.), DMSO, 10 min, rt; (d) TBSOTf (3 eq.), 2,6-lutidine (4 eq.), CH_2Cl_2, 1 h, rt; (e) CBr_4 (3 eq.), Ph_3P (6 eq.), CH_2Cl_2, 1 h rt; (f) *n*-BuLi (2.2 eq.), THF, −78 °C, 1 h; (g) TBAF (3 eq.), THF, 1 h, rt, 63% for five steps.

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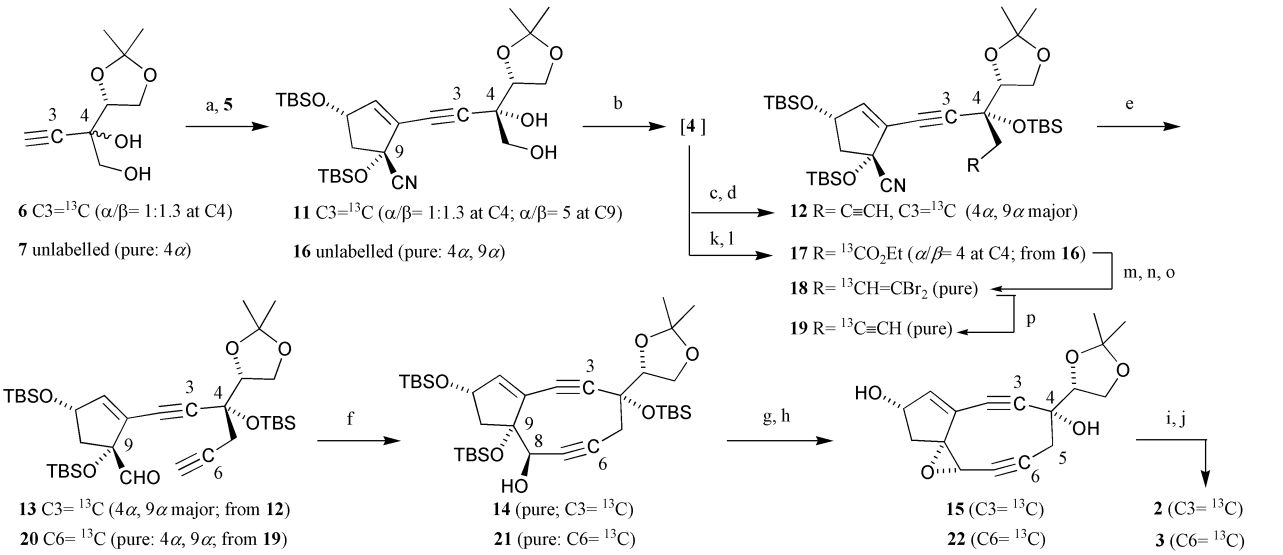

Scheme 3 *Reagents and conditions*: (a) **5** (1 eq.), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.05 eq.), CuI (0.1 eq.), DMF–*i*-Pr_2NEt (2:1), rt, 1 h, 72% for **11**, 40% for **16** (after crystallisation); (b) $NaIO_4$ (5 eq.), CH_3OH–H_2O (4:1), rt, 1 h, 84%; (c) Zn (3 eq.), propargyl bromide (3 eq.), THF, −15 °C, 1 h; (d) TBSCl (1.2 eq.), KH (3 eq.), 18-crown-6 (0.05 eq.), THF, 0 °C, 5 min, 46% for two steps; (e) DIBAL (1.5 eq.), CH_2Cl_2, −78 °C, 1 h; (f) $CeCl_3$ (25 eq.), $LiN(TMS)_2$ (26 eq.), THF, −25 °C to rt, 1 h, 45–52% for **14**, or 68–72% for **21**, for two steps; (g) MsCl (3 eq.), Et_3N (6 eq.), CH_2Cl_2, rt, 1 h; (h) TBAF (5 eq.), THF, rt, 10 min, 70–76% for **15** or **22**, for two steps; (i) TBSOTf (3 eq.), 2,6-lutidine (6 eq.), CH_2Cl_2, −78 °C, 10 min; (j) MsCl (5 eq.), Et_3N (10 eq.), CH_2Cl_2, 5 °C, 30 min, then DBU (2 eq.), CD_2Cl_2, −40 °C, then rt, 30 min, 45–50% for **2** or **3**, for two steps; (k) $CH_3{}^{13}CO_2Et$, $LiN(SiMe_3)_2$ (1.1 eq.), THF, −78 °C, 1 h, 78%; (l) TBSOTf (3 eq.), 2,6-lutidine (6 eq.), CH_2Cl_2, rt, 10 h, 85%; (m) DIBAL (4 eq.), THF, −78 to −25 °C, 2 h, 70%; (n) Dess–Martin periodinane (1.5 eq.), CH_2Cl_2, 1 h, 80%; (o) CBr_4 (3 eq.), Ph_3P (6 eq.), CH_2Cl_2, 0 °C, 30 min, then SiO_2 separation; (p) *n*-BuLi (2 eq.), THF, −78 °C, 58% for two steps.

and isolated in enantiopure form after silica-gel chromotography. Completion of this oxidation-homologation sequence then gave the desired C6–carbon-13 labelled alkyne **19** in 22% yield over six steps from **4**. Lastly, under a parallel reaction sequence to that described for **2**, the targeted epoxyenediyne **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 expeditious and practical, particulary considering the high lability of the compounds involved. For example, the unlabelled enediyne **1**[4] can now be prepared in a 10–15% overall yield from enantiopure **7**[11] over the shortest 10-step sequence. Comprehensive EPR characterisation studies on the radical cycloaromatised states of **1**–**3** are currently being finalised and will be detailed elsewhere.

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Notes and references

† **12** and **13** were isolated and used as (4α, 9α):(4β, 9β) ⩾ 10:1 mixtures.

‡ *NMR data* for **2** and **3** (500 MHz, CD_2Cl_2, ref. 5.32 ppm for ^1H and 53.10 ppm for ^{13}C).

2: ^1H NMR: δ 0.11 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H), 1.37 (s, 3H), 1.46 (s, 3H), 1.86 (dd, 1H, *J* 15.0, 2.5 Hz), 2.71 (dd, 1H, *J* 15.0, 7.3 Hz), 3.75 (d, 1H, *J* 1.5 Hz), 3.80 (dd, 1H, *J* 8.3, 6.7 Hz), 4.17 (dd, 1H, *J* 8.3, 6.7 Hz), 4.63 (ddt, *J* 6.7, 1.5 Hz, $^3J_{C-H}$ 5.0 Hz), 5.00 (ddd, *J* 7.3, 2.5 Hz, $^5J_{C-H}$ 1.5 Hz), 5.99 (dt, *J* 1.5 Hz, $^3J_{C-H}$ 12.5 Hz), 6.40 (br d, *J* 2.0 Hz).

^{13}C NMR: δ −5.41, −5.34, 17.65, 25.10, 25.17, 25.74, 38.60, 49.81, 68.82 (d, J_{C-C} 1.4 Hz), 69.77 (d, J_{C-C} 2.8 Hz), 72.07, 75.07 (d, J_{C-C} 3.9 Hz), 88.38 (d, J_{C-C} 2.9 Hz), 97.18 (^{13}C label), 102.42 (d, J_{C-C} 182.6 Hz), 104.52, 110.02, 119.70 (d, J_{C-C} 1.9 Hz), 124.63 (d, J_{C-C} 11.4 Hz), 143.00 (d, J_{C-C} 89.6 Hz), 145.47 (d, J_{C-C} 4.3 Hz).

3: ^1H NMR: δ 0.11 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H), 1.37 (s, 3H), 1.46 (s, 3H), 1,86 (dd, 1H, *J* 15.0, 2.5 Hz), 2.72 (dd, 1H, *J* 15.0, 7,3 Hz), 3.75 (dd, 1H, *J* 1.5 Hz, $^2J_{C-H}$ 3.7 Hz), 3.80 (dd, 1H, *J* 8.5, 6.7 Hz), 4.17 (dd, 1H, *J* 8.5, 6.5 Hz), 4.63 (bt, 1H, *J* 6.5 Hz), 5.00 (dt, *J* 7.3, 2.5 Hz), 5.99 (br d, *J* 1.5 Hz), 6.40 (d, *J* 2.5 Hz).

^{13}C NMR: δ −5.41, −5.34, 17.65, 25.09, 25.17, 25.74, 38.60, 49.80 (d, J_{C-C} 14.4 Hz), 68.82, 69.76 (d, J_{C-C} 2.8 Hz), 72.07, 75.07 (d, J_{C-C} 6.1 Hz), 88.38 (^{13}C label), 97.17 (d, J_{C-C} 6.3 Hz), 102.36, 104.55 (d, J_{C-C} 193.9 Hz), 110.02, 118.95 (d, J_{C-C} 95.8 Hz), 124.62, 143.01 (d, J_{C-C} 3.4 Hz), 145.46.

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