Towards Enediyne Libraries: Cyclic Enediynes *via* an Intramolecular Carbenoid Coupling Protocol

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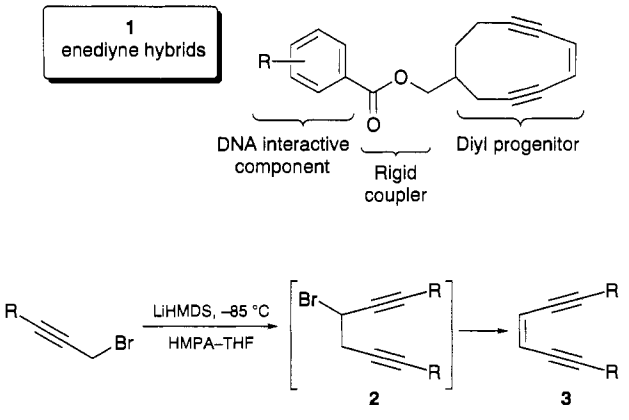
Functionalised bioactive enediynes can be produced *via* an intramolecular carbenoid coupling of bis-prop-2-ynylic halides, and elaborated into useful synthons *via* their dicobalt hexacarbonyl complexes.

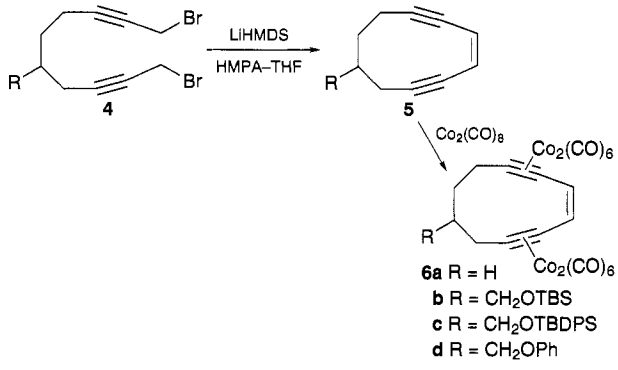
The enediyne antitumor agents, of which dynemicin A is a representative example, have sparked numerous synthetic investigations, aimed both at total synthesis and the preparation of therapeutic agents.[1] The pharmacophore of the enediynes is represented by a nine or ten membered cyclic enediyne function, thus numerous synthetic routes to this subgroup have been investigated.[2] We,[3] and others,[4] have become actively involved in the development of hybrid enediyne libraries *e.g.* **1**, which are composed of a cyclic ten membered enediyne unit tethered to a DNA interactive component *via* a rigid coupling group. We recently reported a new route to the versatile 1,6-[Bis(trimethylsilyl)]hex-3-ene-1,5-diyne **3** (R = TMS) based upon a novel tandem carbenoid coupling–elimination of trimethylsilylprop-2-ynyl bromide (R = TMS), which proceeds *via* E2 elimination from bromide **2** (Scheme 1).[5]

Extension of this coupling to encompass other propynylic species proved possible and the yields of product **3** range from good to excellent.[3] Preoccupied with the task of synthesising cyclic endediynes, we became interested in the development of an intramolecular variant of the process, specifically one which would give access to functionalized ten membered cyclic enediynes (Scheme 2). Thus, a series of bis-prop-2-ynylic bromides **4** were assembled and subjected to conditions designed to induce cyclisation to the corresponding enediynes **5**.

Initial results were disappointing, in that employing typical conditions for intermolecular coupling, only regenerated starting material could be isolated from the workup mixtures (Table 1, entries 1 and 2). By increasing the reaction temperatures from −85 to −45 °C however, low yields of the desired cyclic species could be obtained, along with varying amounts of starting material together with intermolecular coupling products (entry 3). As in the case of the intermolecular variant of this reaction, the hindered LiHMDS proved to be the base of choice—substitution with LDA or LTMP lowered the overall yields of the desired products (entries 4 and 5). A key feature for increasing efficiency of the cyclisation proved to be the concentration of the HMPA additive, and when the ratio of HMPA : base was increased from 1 : 1 to 10 : 1 substantial quantities of the desired enediynes could be recovered (entry 6).



Scheme 1



Scheme 2

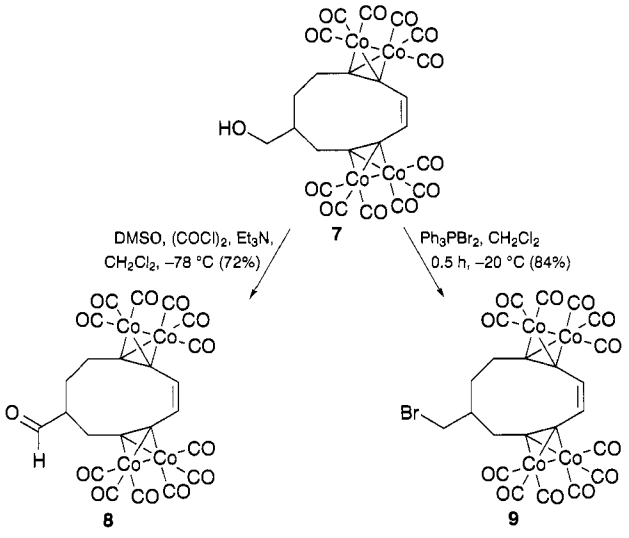
Table 1 Preparation of cyclic enediynes **5** and their complexes **6** *via* carbenoid-coupling of dibromides **4**

Entry	R	Conditions[a]	Base	C(i)[b]	*T*/°C	Solvent	Yield **5**	Yield **6**
1	H	A	LiHMDS	5.00	−78	THF	<1	—
2	H	B	LiHMDS	5.00	−85	THF/HMPA	0	—
3	H	B	LiHMDS	1.24	−40	THF/HMPA	20	—
4	H	B	LDA	1.13	−78	THF/HMPA	10	—
5	H	B	LTMP	1.12	−78	THF/HMPA	15	—
6	H	C	LiHMDS	2.50	−45	THF/HMPA	95	—
7	H	D	LiHMDS	2.50	−45	THF/HMPA	—	92[c]
8	CH_2OPh	D	LiHMDS	1.84	−45	THF/HMPA	—	25
9	CH_2-OTBDPS	C	LiHMDS	0.87	−45	THF/HMPA	93	—
10	CH_2-OTBDPS	D	LiHMDS	0.87	−45	THF/HMPA	—	86
11	CH_2-OTBDPS	D	LiHMDS	1.04	−45	THF/HMPA	—	79
12	CH_2-OTBS	D	LiHMDS	2.13	−45	THF/HMPA	—	69

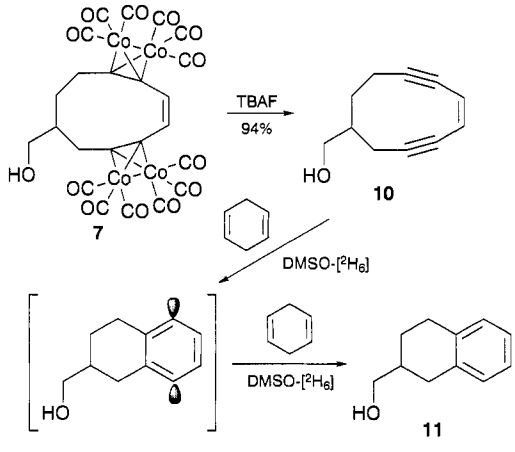
[a] Conditions: A: Solution of base (2.2 equiv.) added (2–3 h) to solution of substrate; B: Solution of base (2.2 equiv.) and HMPA (1 : 1) added (2–3 h) to solution of substrate: C: Solution of base (2.2 equiv.) added (3 h) to solution of substrate and HMPA (22 equiv.); D: As method C but modified to include immediate complexation during workup. [b] Concentration of substrate solution (10^{-2} mol dm^{-3}) prior to base addition. [c] Structure confirmed by X-ray crystallography. Data will be included in a full account of this work.

Optimum conditions involve slow addition of base to a premixed solution of substrate and HMPA in THF. In some instances intermolecular reactions served to lower the yields of the thermally stable cyclic species (*e.g.* entries 8 and 11). Where this was found to be the case, the yields of the desired products could generally be improved by increasing the dilution of the reaction medium (*viz.* entry 10 *vs.* 11). Formation of the thermally stable bis cobalt carbonyl derivatives **6** was accomplished using 3.0 equiv. of dicobalt octacarbonyl in the (dried) workup solvent mixtures (Et_2O containing THF from the cyclisation), thus allowing silica gel chromatographic purification of the masked enediynes where necessary. Using this optimised process, multigram quantities of protected enediynes **6a–d** can thus be assembled easily.

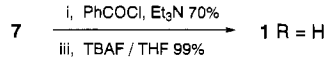
Deprotection of the *tert*-butyldimethylsilyl ether **6b** (TsOH/MeOH–THF, 2.5 h, 25 °C) afforded the corresponding alcohol **7** in quantitative yield. As expected, this alcohol proved versatile, allowing for functional group interconversions such as Swern oxidation to the aldehyde **8** (72%) or S_N2 displacement to the bromide **9** (84%) (Scheme 3).These species would appear to offer a variety of potential regimens for attachment to DNA



Scheme 3



Scheme 4



Scheme 5

binding agents to be pursued, allowing the development of libraries of hybrid enediyne–DNA binding agents.

Having secured routes to cobalt complexes **6–9**, and demonstrated both their chemical reactivity and thermal stability, we sought to confirm the ease with which the corresponding enediynes may be unmasked and undergo Bergman cyclisation. A sample of **6b**, which had been stored under a nitrogen atmosphere for over one month was examined by ^{13}C NMR and confirmed to be intact. The sample was desilylated (TsOH/MeOH, 94%) to yield alcohol **7** which was then subjected to decomplexation (TBAF, 94%), filtered (SiO_2), and concentrated *in vacuo*. The resulting oil was immediately dissolved in DMSO-[$^2H_6$] and analysed by ^1H NMR. As anticipated, the spectrum was identical to that of an independently prepared sample of **5** (R = CH_2OH) that had not undergone complexation prior to NMR analysis. The sample was doped with a hydrogen radical source (1,4-cyclohexadiene) and incubated at 37 °C, NMR analysis being undertaken at regular intervals (Scheme 4). Cyclisation was evident after only 3 h, and pronounced after 8 h, with direct conversion to the tetrahydronaphthalene **11** occurring. From this data we conclude the half-life of **10** to be 18 h at 37 °C. This value is close to that predicted from the intra-acetylenic c-d distance of 3.25 Å, calculated using MMX modelling, although in practice the half-life should be determined strictly on the basis of torsional strain.[6] The DNA cutting ability of the diyl species was independently assessed, and as expected, found to cause significant single and random double stranded cuts in φX174DNA at elevated concentration.[7]

With the biological utility of the diyl radical derived from **10** established, we sought to initially confirm the ease with which the enediyne template could be incorporated into hybrid molecules, including **1**. Accordingly, alcohol **7** was subjected to esterification with benzoyl chloride, giving a 70% yield of the derived ester, and on decomplexation, the bifunctional template **1** (R = H, 99%) (Scheme 5). As expected, hybrid structure **1** (R = H) underwent smooth Bergman cycloaromatisation at 37 °C and displayed similar DNA cleaving profile to the diyl derived from **10**.

Received, 30th May 1995; Com. 5/03434E

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7 Full details, including lesion sequence specificity and *in vitro* antitumour evaluation will be reported elsewhere.