A concise approach towards the synthesis of steganone analogues

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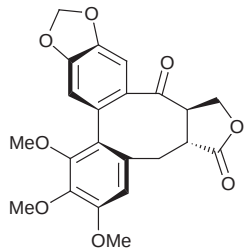
The cobalt-mediated [2+2+2] cycloaddition of a tethered deca-1,9-diyne is used as a key step in a highly convergent route to steganone analogues.

Steganone **1** is one member of the family of four bisbenzocyclooctadiene lignan lactones isolated from the Ethiopean shrub *Steganotaenia araliciae* Hochst and characterised by Kupchan[1]



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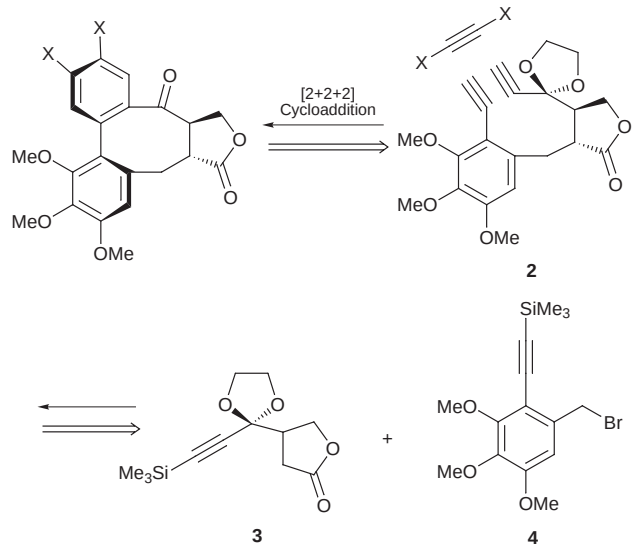
in 1973. These compounds have displayed significant activity *in vivo* against P-388 leukemia in mice and *in vitro* against cells derived from human carcinoma of the nasopharynx (KB). They act as spindle poisons and function by stabilising dimeric tubulin and thereby inhibiting formation of microtubules.[2] These intriguing structures, comprising an eight-membered ring fused to a biaryl moiety, are composed of three stereochemical elements, two deriving from the *trans*-fused γ-lactone, whilst the third is the stereogenic axis of the atropisomeric biaryl unit. Since its discovery, steganone **1** has proven to be a favoured target for sustained synthetic effort, and for more than two decades a wide variety of synthetic strategies have culminated in a number of total/formal syntheses.[3] Careful scrutiny of these approaches reveals striking parallels in retrosynthetic analysis, with no less than ten of the syntheses requiring a late stage installation of the *trans*-fused γ-lactone. Moreover, in every single instance to date some variant of a biaryl coupling reaction is used to forge the crucial carbon–carbon bond between the two aromatic rings.

Since the properties of steganone **1** itself are well known, our own objective in this area was to develop a highly convergent route which would be potentially amenable to the syntheses of a wide variety of differentially substituted aromatic analogues for use in structure–activity studies. To the best of our knowledge, only a single analogue of this type has thus far been reported.[4] As shown in Scheme 1, the key element of the present strategy involves the use of the tethered diyne **2** in a cobalt mediated [2+2+2] cycloaddition,[5] thereby enabling closure of the eight-membered carbocyclic ring with concomitant construction of a usefully functionalised northern aryl unit for further elaboration. We also envisaged that the required *trans* stereochemistry round the γ-lactone **2** would be derived by alkylation of the lactone enolate from **3** with the benzylic bromide **4** or congeners thereof which would allow yet further variation in aromatic functionality to be introduced at an antepenultimate stage.

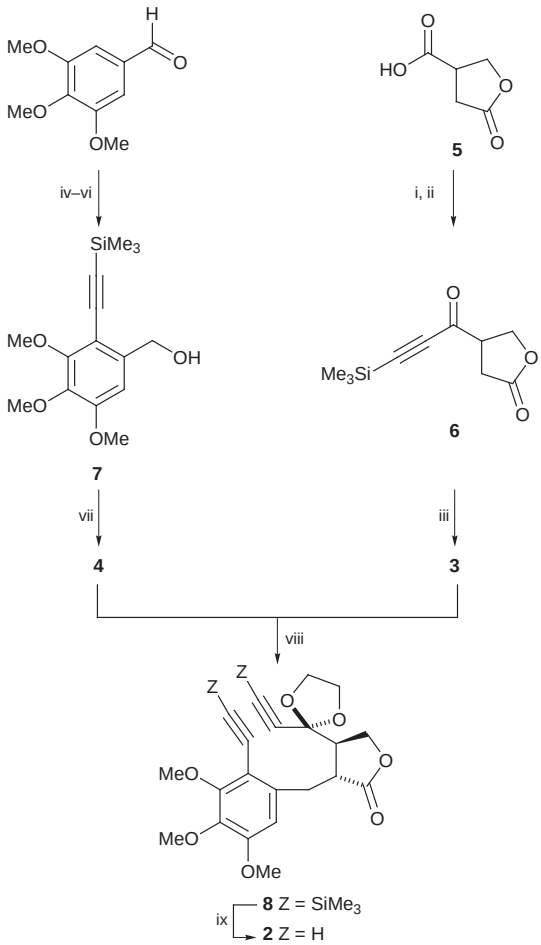
In the event, as outlined in Scheme 2, it was possible to develop a concise and highly efficient route to multigram quantities of the required diyne **2**. Thus, the protected lactone **3** was readily prepared from racemic paraconic acid **5** *via* palladium-catalysed coupling of the derived acid chloride with $Me_3SiC{\equiv}CSnMe_3$ followed by ketalisation of the resultant ynone **6**, whilst the known benzylic alcohol[7] **7** was available from 3,4,5-trimethoxybenzaldehyde *via* a straightforward sequence involving iodination, borohydride reduction, and a second palladium catalysed coupling reaction of the resultant iodoarene with $Me_3SiC{\equiv}CH$. The transformation to the corresponding bromide **4** was then acheived using the PPh_3–CBr_4 protocol. The coupling reaction of the two fragments proceeded smoothly through prior generation of the lithium enolate of lactone **3** with LDA at −78 °C followed by alkylation with the benzylic bromide **4** at −35 °C to give **8** as a single diastereoisomer. Deprotection of the acetylenic groups then furnished the parent diyne **2**.

Our attention then focused on the crucial $CpCo(CO)_2$-mediated [2+2+2] cycloaddition step using diyne **2**, $Me_3SiC{\equiv}CSiMe_3$ as the third acetylenic component, and the standard irradiation conditions developed by Vollhardt.[5] To our consternation, initial experiments failed to yield any significant amounts of the desired biaryl **9**, and the beautifully crystalline orange material which could be isolated as a single diastereoisomer in up to 57% yield was shown by X-ray crystallography to be the cobaltacyclobutadiene complex **10** (Scheme 3). Although the formation of similar complexes has been previously observed[9] and is generally considered to arise when either co-ordination or insertion of the third alkyne component is problematic, it was nevertheless encouraging to note that the structure **10** confirmed both the viability of the eight-membered ring closure and also the *trans* stereochemistry around the γ-lactone. Gratifyingly however, whether *via* the intermediacy of the putative metallocyclopentadiene precursor to **10** or one of the other two possible candidates from reaction with Me_3-



2 **3** **4**

Scheme 1



Scheme 2 *Reagents and conditions*: i, $(COCl)_2$, CH_2Cl_2, DMF (cat), room temp., 1 h; ii, $Me_3SiC{\equiv}CSnMe_3$, $Pd(PPh_3)_2Cl_2$, $ClCH_2CH_2Cl$, 50 °C, 16 h, 67% over 2 steps; iii, $HOCH_2CH_2OH$, PhH, PPTS (cat), reflux, 12 h, 87%; iv, I_2, AgO_2CCF_3, CH_2Cl_2, 20 °C, 12 h, quant.; v, $NaBH_4$, MeOH, −5 °C, 30 min, quant.; vi, $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_2Cl_2$, CuI, Et_2NH, 50 °C, 2 h, 92%; vii, CBr_4, PPh_3, Et_2O, 24 h, 92%; viii, **4**, LDA, THF, −78 °C, 1 h, then add **3**, −35 °C, 1 h, 80%; ix, K_2CO_3, MeOH, 20 °C, 15 h, 95%.

$SiC{\equiv}CSiMe_3$, further variation in experimental conditions gave the desired biaryl **9** possessing the carbocyclic steganone core in 20% yield.

The structure of the indicated atropisomer of the biaryl **9**, which corresponds to the natural series, was established both by NOE experiments and also by deprotection of the ketal using wet formic acid which furnished the parent ketone **11** (ν_{max} 1674 cm^{-1}) in 54% yield (Scheme 3). Deprotection accompanied by selective mono- or di-protodesilylation could also be achieved in a single step by treatment of **9** with TFA either at room temperature or at reflux to afford the further steganone analogues **12** and **13** in 73 and 51% yield, respectively.

In summary, these preliminary results demonstrate the viability of using a tethered deca-1,9-diyne in a cobalt-mediated [2+2+2] cyclobenzannulation strategy for the construction of steganone analogues in a highly convergent manner. Within this framework, current studies are directed towards the use of further 2π addends and additional metal-based cyclotrimerisation reactions both for aromatic and heteroaromatic rings in order to further enhance the flexibility of this approach.

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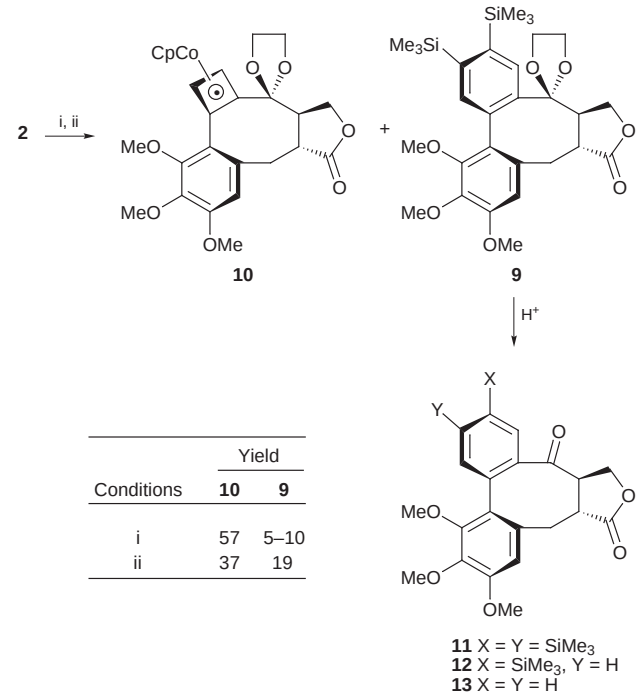

	Yield	
Conditions	**10**	**9**
i	57	5–10
ii	37	19

Scheme 3 *Reagents and conditions*: i, $Me_3SiC{\equiv}CSiMe_3$, $CpCo(CO)_2$, 50–65 °C, reflux, *hν*, addition of **2** in THF over 9 h; ii, $Me_3SiC{\equiv}CSiMe_3$, MeCN, reflux, *hν*, addition of **2** in THF over 9 h.

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