Synthesis of Dibenzodiynes: Exceptionally Easy Formation of a Chrysene Biradical

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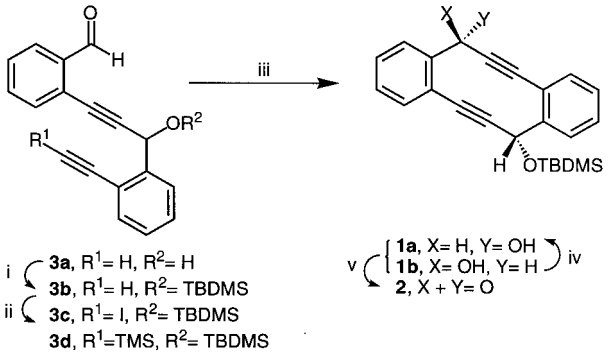
Abstract: The new dibenzodiynes **1** and **2** have been synthesized using a Nozaki-Hiyama-Kishi reaction as the key step. Treatment of dibenzodiynone **2** with base at –50°C afforded an enyne-cumulene intermediate that underwent a regioselective cycloaromatization *via* a chrysene biradical.

Current research on the thermal biradical cyclizations of enediynes, enyne-allenes and enyne-cumulenes focuses on their utility in the construction of polycyclic ring systems,[1] and on the synthesis of models of the natural enediyne antitumor antibiotics.[2] Myers[3] has developed such a model based on the fact that 1,6-didehydro[10]annulene cyclizes to the 1,5-didehydronaphthalene biradical at -51°C. In the present work, with the ultimate goal of developing simple and stable DNA-cleaving agents that can be activated under controlled conditions, we report preparation of new dibenzodiynes **1** and **2**[4,5] (Scheme 1) using a Nozaki–Hiyama–Kishi reaction as the key step and the novel regioselective cycloaromatization of dibenzodiynone **2** to a chrysene biradical upon treatment with base.

Benzaldehydes **3** were chosen as the immediate synthetic precursors of **1** (Scheme 1). Compound **3a** was prepared in 76% yield by coupling of the acetylide derivative of 2-(2-(ethynylphenyl)-1,3-dioxane with *o*-ethynylbenzaldehyde (both prepared from *o*-bromobenzaldehyde),[6] followed by deprotection of the acetal group. Silyl ether **3b** was obtained by treating **3a** with TBDMSCl.



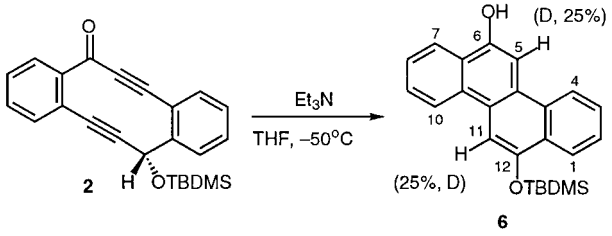
Scheme 1 *Reagents and conditions* : (i) TBDMSCl, imidazole, DMF, r.t., 12 h, 90%; (ii) DBU, I_2, benzene, r.t.,15 min, 92%; (iii) $CrCl_2$ (3 equiv), $NiCl_2$ (0.5 equiv), THF, –20˚C, 1h, 53%; (iv) a) MsCl, Et_3N, –78˚C, 12 h; b) H_2O, –30˚C, 53% (**1a**:**1b**, 3:1); (v) Dess-Martin, ^tBuOH, CH_3CN, r.t., 53%

Attempts to cyclize **3b** to dibenzodiyne **1** by intramolecular nucleophilic addition of the acetylide of **3b** to its aldehyde[7] [LiHMDS or NaHMDS (2 equiv) in THF at -78°C] afforded a complex mixture of products, among which the desired dibenzodiyne **1** was not detected. Next, we tried treating the trimethylsilylacetylene **3d**[8] with cesium fluoride [CsF (3.5 equiv), $NaHCO_3$ (2 equiv), Ac_2O (2 equiv)],[9] which led quantitatively to the desilylated acetylene **3b**. Finally, the terminal alkyne was converted into the alkynyl iodide **3c** by a standard method using DBU as a base,[10] and ring–closure was achieved by the Nozaki-Hiyama-Kishi reaction.[11] Thus, slow addition of a solution of **3c** to a suspension of $CrCl_2$ (3 equiv) and $NiCl_2$ (0.5 equiv) in THF at -20°C gave, after separation by flash column chromatography, a 53% yield of **1** as a 5:95 mixture of diastereomers (Scheme 1). Diastereomers **1a** and **1b** were both stable in $CHCl_3$ or THF solution at r.t.; however, they slowly decomposed when kept neat.

To determine the relative stereochemistry of the diastereomers, the major one was silylated to yield the *bis*-silyloxy derivative **4** (Fig. 1). The ^1H NMR spectrum of **4** in the presence of chiral Eu^{+3} salts showed no splitting of signals, indicating **4** to be the *meso*-compound. Therefore, we have tentatively assigned *anti* relative stereochemistry to the major diastereomer, **1b**.[12]

Next, cycloaromatization of **1b** was attempted using methyl thioglycolate as nucleophile in the presence of 1,4-cyclohexadiene and triethylamine.[3,4] Several sets of reaction conditions were tried,[13] but no cycloaromatized products were detected. Activation of the system by *in situ* generation of the mesylate derivative of **1b**, followed by quenching with H_2O as nucleophile,[4b] furnished the initial diastereomeric alcohols **1a** and **1b** in 53% yield and 3:1 ratio (Scheme 1). Regardless of the mechanism of this reaction (S_N1 or S_N2), it is noteworthy that the latter diastereomeric ratio is the opposite of that obtained in the original intramolecular coupling.

To increase the reactivity of the dibenzodiynols **1**, they were oxidized to the alkynyl ketone **2** using Dess-Martin periodinane[14] (Scheme 1).[15] Alkynyl ketone **2** is rather unstable and so was immediately subjected to the cycloaromatization reaction. Gratifyingly, treatment of **2** with methylthioglycolate (2 equiv) in the presence of triethylamine (2 equiv) and 1,4-cyclohexadiene (40 equiv) in THF at 0°C for 5 min gave chrysenol **6** in 29% yield as the only cycloaromatized product.[16] Careful control of the reaction conditions showed that a similar result was obtained at –50°C with triethylamine alone (Scheme 2).



Scheme 2

Formation of **6** in the absence of the nucleophile could be explained by an enolization of **2** to give [10]annulene **7** (Fig. 1), which regioselectively cycloaromatizes to chrysenol **6** (route a). Interestingly, alternative cycloaromatization of annulene **7** to naphthacenol **8** (route b) has not been observed. In this regard, it is interesting to note that distances “a” and “b” within structure **7** are determined to be 2.934 and 2.998 Å, respectively, by AM1 calculations, suggesting that a predisposition exists for cyclization along pathway “a” within ground-state structure.[17]

To confirm that **6** (chrysenol) and not **8** (naphthacenol) had been obtained, HMQC and HMBC NMR experiments were performed on the symmetric *bis*-silyloxy derivative **9**.[18] For the sake of comparison we also detailed the most significant couplings expected for the putative isomeric naphthacenol **10** (Table 1).

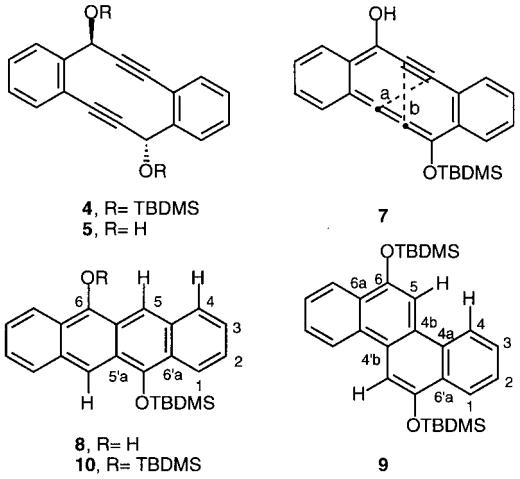


Figure 1

From the Table 1, it may be concluded that the observed coupling between H-4 and quaternary carbon C–4b and the absence of reciprocal couplings between H–5 and tertiary carbon C–4 and H–4 and tertiary carbon C–5 confirms a chrysenol–type structure for the *bis*-silylated product **9**,[19] and consequently, structure **6** for the cycloaromatization product.

Table 1. Significant couplings (HMBC) for **9** and **10**

^3J (^{1}H-^{13}C)	Chrysenol **9**	Naphthacenol **10**
H–5	Quaternary: C-4a, C–4'b, C–6a	Quaternary: C–5'a, C–6, C–6'a
	Tertiary: ——	Tertiary: C–4
H–4	Quaternary: C–4b, C–6'a	Quaternary: C-6'a
	Tertiary: C–2	Tertiary: C–2, C–5

^{1}H NMR experiments carried out in deoxygenated THF-d_8 at -50°C provided evidence for the formation of a chrysene biradical upon treatment of ketone **2** with triethylamine. Specifically, successive spectra showed slow disappearance of the starting material with concomitant formation of **6** incorporating 25% deuterium at C–5 and C–11 (Scheme 2).[20]

In summary, we synthesized new dibenzodiynes **1** and **2** and found evidence for the intermediacy of a chrysenic biradical in the novel regioselective cycloaromatization of dibenzodiynone **2** into chrysenol **6** upon treatment with base. Further work towards the development of stable DNA–cleaving agents is in progress.

Acknowledgements

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References and Notes:

(1) (a) Schmittel, M.; Steffen, J.-P.; Auer, D.; Maywald, M. *Tetrahedron Lett.* **1997**, *38*, 6177. (b) Wang, K. K.; Wang, Z.; Tarli, A.; Gannett, P. *J. Am. Chem. Soc.* **1996**, *118*, 10783. For reviews, see: (c) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (d) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453.

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(5) Dibenzodiynes are structural analogues of both dienediyn-1-ol[3] and golfomycin A– a known DNA-cleaving agent with antitumour activity. Nicolaou, K. C.; Skokotas, G.; Furuya, S.; Suemune, H.; Nicolaou, D. C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1064.

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(8) **3d** was prepared as described for **3b** but using *o*-iodobenzaldehyde instead of *o*-ethynylbenzaldehyde, and then coupling the resulting aryliodide with trimethylsilylacetylene using palladium catalyst (62% overall yield).

(9) Wender, P.A.; Beckham, S.; Mohler, D. L. *Tetrahedron Lett.* **1995**, *36*, 209.

(10) Nicolaou, K. C.; Liu, A; Zeng, Z.; McComb, S. *J. Am. Chem. Soc.* **1992**, *114*, 9279.

(11) Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5585.

(12) Diol **5** was highly unstable and difficult to handle, and all attempts at performing ^{1}H-NMR experiments with this compound in the presence of chiral Eu^{+3} salts failed.

(13) (a) Various solvents (THF, benzene) and conditions (0°C, 20°C, 60°C) were tried using $HSCH_2CO_2Me$ (2, 9 or 12 equiv) as nucleophile and Et_3N as base (see ref. 4b). In all cases starting material was recovered as the main product.

(14) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(15) Dibenzodiynone **2**: ^{1}H-NMR ($CDCl_3$, 250 MHz): δ= 0.25 (s, 3H), 0.27 (s, 3H), 0.99 (s, 9H), 5.89 (s, 1H), 7.29-7.67 (m, 7H), 8.21 (d, *J*= 7.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 62.8 MHz): δ= -4,6 (CH_3), -4.1 (CH_3), 18.3 (C), 25.8 (3 x CH_3), 64.3 (CH), 87.2 (C), 94.5 (C), 94.8 (C), 96.5 (C), 117.8 (C), 123.6 (C), 127.9 (CH), 128.3 (CH), 128.7 (CH), 129.3 (CH), 131.2 (CH), 132.1 (CH), 132.9 (CH), 134.6 (CH), 137.6 (C), 141.7 (C), 175.9 (C=O).

(16) Chrysenol **6**: ^{1}H-NMR (CD_2Cl_2, 250 MHz): δ= 0.32 (s, 6H), 1.14 (s, 9H), 7.61-7.70 (m, 4H), 7.94 (s, 1H), 7.98 (s, 1H), 8.33 (d, *J*= 7.6 Hz, 2H), 8.57 (d, *J*= 8.0 Hz, 2H); ^{13}C-NMR (CD_2Cl_2, 62.8 MHz): δ= -3.8 (2 x CH_3), 19.0 (C), 26.3 (3 x CH_3), 102.9 (CH), 107.4 (CH), 122.8 (CH), 123.6 (CH), 123.7 (2 x CH), 124.8 (C), 125.0 (C), 125.7 (C), 126.6 (2 x CH), 127.2 (CH), 127.5 (CH), 128.9 (C), 131.4 (C), 131.5 (C), 149.3 (C), 149.5 (C).

(17) Computer modelling was performed using the AM1 semiempirical method as implemented in MacSpartan Plus 1.1.6, Wavefunction, 1996. This modelling study is intended to be

suggestive only since the analysis does not examine the relevant transition–state energies of the two biradical–forming pathways.

(18) Chrysenic ether **9**: ^{1}H-NMR (CD_2Cl_2, 500 MHz): δ= 0.38 (s, 6H, $Si(CH_3)_2$), 1.15 (s, 9H, $C(CH_3)_3$), 7.62-7.68 (m, 2H, H-2 and H-3), 7.99 (s, 1H, H-5), 8.34 (d, *J*= 8.1 Hz, 1H, H-1), 8.56 (d, *J*= 8.1 Hz, 1H, H-4); ^{13}C-NMR (CD_2Cl_2, 62.8 MHz): δ= -3.8 (2 x CH_3), 19.0 (C), 26.3 (3 x CH_3), 107.3 (CH, C–5), 123.6 (CH, C–4), 123.7 (CH, C–1), 125.1 (C, C–4b), 126.6 (CH, C–2), 127.2 (CH, C–3), 128.9 (C, C–6a), 131.6 (C, C–4a), 149.6 (C, C–6).

(19) A two–bond ^{1}H–^{13}C coupling between H–5 and quaternary carbon C–6 is also observed.

(20) $t_{1/2}$ of **2** at –50°C ≈10 min.