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A four-step route to synthetic equivalents of ortho-xylylenes: Dötz benzannulation, desilylation, bromo-dehydroxylation, and sultine formation. A concise approach to oxygenated linearly fused polycyclic aromatics

Sambasivarao Kotha *, Vikas R. Aswar †, Amarender Manchoju †

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai, 400 076, Maharashtra, India

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ABSTRACT

A new route has been reported for the synthesis of densely oxygenated polycyclic aromatic compounds via cycloaddition approach. This strategy involves the Dötz benzannulation and Diels-Alder reaction as key steps. Naphthalene synthons required here were generated by Dötz benzannulation between aryl chromium carbene complexes and symmetrical internal alkyne.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) such as anthracyclines which are valuable anticancer drugs and they are mostly used in combination therapy. Clinical work showed that daunorubicin **1** and doxorubicin **2** are exhibit a broad range of anticancer activities. Many PAHs (**1**–**5**)[1] were synthesized and tested in the laboratory. However, there is a need to design new and useful analogues which possess better activity and less toxicity. In this context, we are interested in synthesizing PAHs by Dötz benzannulation[2] and Diels-Alder (DA)[3] reaction as key steps. Several intricate targets (Fig. 1) are synthesized by Dötz benzannulation reaction. The examples include: doxorubicin **2** daunomycinone **4a**, 11-deoxydaunomycinone **4b**, which are useful for synthesis of hexaoxonaphthyl system of γ-rubromycin **6**.[4] Regioselectivity[5] in Dötz benzannulation depends on the type of Fischer carbene and steric nature of alkyne. In the literature[6] Dötz benzannulation is reported with symmetrical internal alkynes. Generally, in benzannulation terminal alkyne gives aromatic products bearing the substituent *ortho* to the phenolic −OH. However, unsymmetrical alkynes deliver regioisomeric mixture of products of varied ratio depending on the steric bulk of the substituents present in the unsymmetrical terminal alkyne.

Generally, highly substituted aromatic compounds are assembled by benzannulation[7] methods and various approaches include: 1, 6 electrocyclization,[8] Yamamoto benzannulation,[9] Fe(III) catalyzed benzannulation,[10] transition metal-catalyzed [2+2+2] cyclotrimerization,[11] and double Claisen rearrangement followed by ring-closing metathesis.[12] In this context, [3+2+1] strategy involving Fisher carbene complexes and alkyne seems to be an alternate route for the construction of densely functionalized naphthalene derivatives.

2. Results and discussion

Our strategy towards highly oxygenated PAHs involve Dötz benzannulation and DA reaction as key steps (Fig. 2). The PAHs **11**, **12** and **13** could be assembled from Sultine[13] **10** via DA reaction with suitable dienophile followed by aromatization. The sultine **10** could be synthesized from diol **9** through bromination and rongalite reaction. Diol **9** could be synthesized from Fischer carbene **7** through Dötz benzannulation, O-methylation and subsequent silyl ether deprotection.

* Corresponding author. Fax: +91(22) 2572 7152; e-mail address: srk@chem.iitb.ac.in (S. Kotha).
† Both authors contributed equally.

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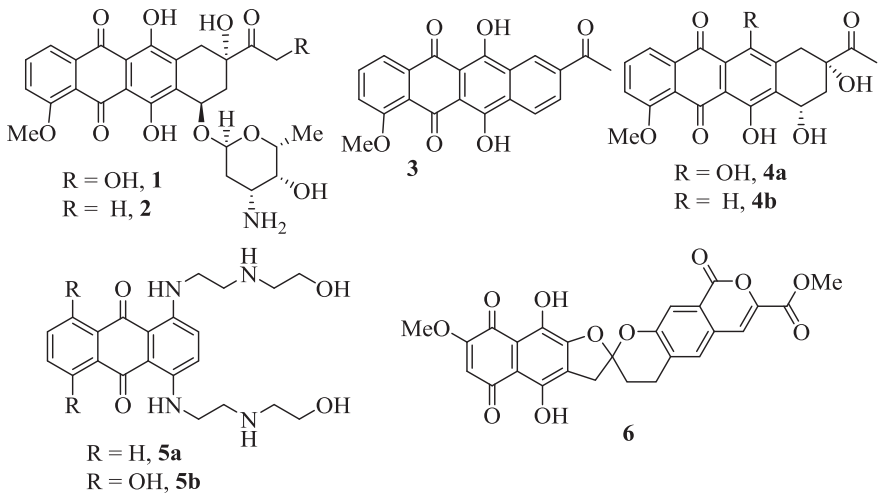

Fig. 1. Doxorubicin (**1**), daunomycin (**2**), bisanhydrodaunomycinone (**3**), daunomycinone (**4a**), 11-dehydroxydinomycinone (**4b**), ametantrone (**5a**), mitoxantrone (**5b**), γ-rubromycin (**6**).

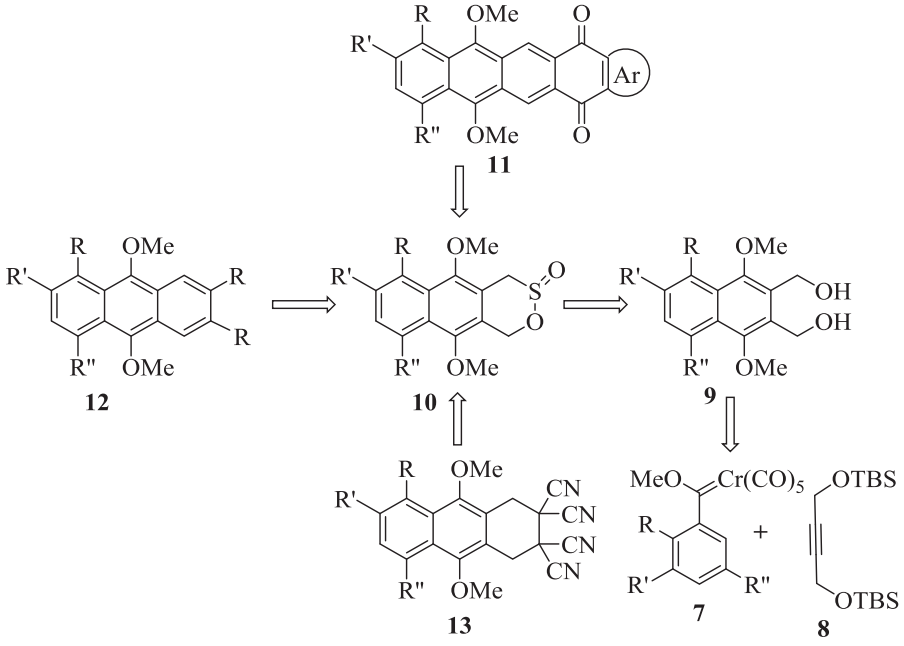

Fig. 2. Retrosynthetic route to polycyclic aromatic compounds.

Synthesis of sultine derivatives **26**, **27a** and **27b** begins with the preparation of Fischer carbene complexes **16** and **17**. They are derived from bromobenzene such as **14** and **15**.[14] The Dötz benzannulation reaction between freshly prepared Fischer carbene **16** and protected alkyne **8**[15] in THF in the presence of an additive[16] such as Ac_2O (1.0 equiv) gave naphthalene derivative **18** (52%). Later, methylation of the naphthol **18** has been attempted with NaH, MeI. However, the desired product was not obtained, then we switched to K_2CO_3/MeI in DMF conditions and this protocol delivered the desired methyl ether **20** (88%).[17] Later, the silyl ether deprotection was carried out with TBAF in THF to deliver the diol **22** (87%).[18] Bromination of naphthalene derivative **22** with PBr_3 gave the corresponding dibromo compound **24** (93%). Along similar lines, the dibromo compound **25** was synthesized from Fischer carbene complex **17**. Further, the dibromo naphthalene derivative **24** was treated with rongalite under phase-transfer catalyst TBAB conditions to afford the sultine derivative **26** (78%). However, in the case of dibromo compound **25** an inseparable mixture of regioisomers **27a** and **27b** (1:1) were obtained in 94% yield under similar reaction conditions (Scheme 1).

Similarly the sultine derivative **35a** (or **35b**) has been assembled from Fisher carbene complex **29** which in turn was prepared from the bromo compound **28**.[19] The naphthol derivative **30** (32%) has been synthesized by Dötz benzannulation of carbene complex **29** and protected alkyne **8** in THF in the presence of Ac_2O as an additive. The methylation was carried out in the presence of K_2CO_3/MeI in acetone to afford a highly oxygenated naphthol derivative **31** (64%) and similar yield was obtained in DMF solvent under low temperature conditions. Then, the naphthalene derivative **31** was subjected to deprotection using TBAF in THF to afford the diol **32** in 84% yield. Further, bromination of the diol **32** has been attempted under different reaction conditions.[20] However, the corresponding dibromo compound was not obtained because of the presence of several methoxy groups which make the aromatic ring highly electron rich and benzylic bromination step difficult. Therefore, one of the aromatic rings is oxidized by employing CAN/CH_3CN/H_2O conditions[21] to **32** affording the quinone **33** in 88% yield. Then, bromination sequence was attempted with PBr_3 in CH_2Cl_2 conditions to deliver the corresponding dibromo compound which was