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Synthesis of the Tetracyclic Core of Anthracycline Antibiotics by an Intramolecular Dehydro Diels–Alder Approach

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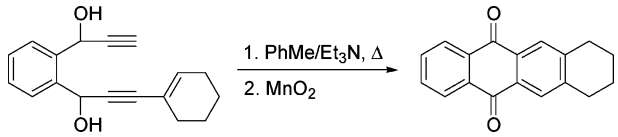
ABSTRACT



A conceptually new approach to the tetracyclic core of the anthracycline antibiotics is reported. With use of this approach, the 7,8,9,10-tetrahydronaphthacene-5,12-dione skeleton has been synthesized in three steps, from commercially available reagents, in yields of up to 85%.

Since the early 1970s, anthracycline antibiotics[1] such as the well-known doxorubicin (**1**) and daunorubicin (**2**) have been widely used as clinically effective antitumor agents against acute leukemia, Hodgkin's disease, lymphomas, breast carcinomas, and sarcomas (Figure 1).[2] During this time, the search for anthracyclines with greater potency and less cardiotoxicity, such as the 4-demethoxy derivative idarubicin (**3**),[3] has led to the development of many methods for the synthesis of natural and nonnatural anthracyclines.[4]

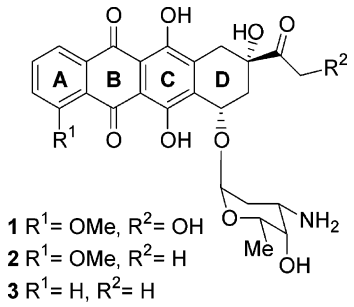


Figure 1. Anthracycline antibiotics.

In most, the tetracyclic core of the antibiotic is synthesized by addition to anthraquinones[5] (ring D formation) or by intermolecular Diels−Alder reactions forming the B or C ring.[3f,6] Although it has long been claimed that cobalt and rhodium-mediated [2+2+2] inter- and intramolecular cyclizations should be capable of simultaneous formation of

(1) (a) Priebe, W. *Anthracycline Antibiotics*: *New Analogues, Method of Delivery, and Mechanisms of Action*; ACS Symp. Ser. No. 574; American Chemical Society: Washington, DC, 1995. (b) Arcamone, F. *Doxorubicin*; Academic Press: New York, 1980. (c) El Khadem, H. S. *Anthracycline Antibiotics*; Academic Press: New York, 1982.

(2) (a) Weis, R. B.; Sarosy, G.; Clagget-Carr, K.; Russo, M.; Leyland-Jones, B. *Cancer Chemother. Pharmacol.* **1986**, *18*, 185−197. (b) Weiss, R. B. *Semin. Oncol.* **1992**, *19*, 670−686. (c) Lown, J. W. *Chem. Soc. Rev.* **1993**, 165−176.

(3) Di Marco, A.; Casazza, A. M.; Giuliani, F.; Pratesi, G.; Arcamone, F.; Bernadi, L.; Franchi, G.; Giradino, P.; Patelli, B.; Penco, S. *Cancer Treat. Rep.* **1978**, *62*, 375−380.

(4) (a) Arcamone, F.; Cassinelli, G. *Curr. Med. Chem.* **1988**, *5*, 391−419. (b) Thomson, R. H. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1992; pp 311−531. (c) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790−807. (d) Wulff, W. D.; Su, J.; Tang, P.-C.; Xu, Y.-C. *Synthesis* **1999**, 415−422. (e) Hauser, F. M.; Ganguly, D. *J. Org. Chem.* **2000**, *65*, 1842−1849. (f) Achmatowicz, O.; Szechner, B. *J. Org. Chem.* **2003**, *68*, 2398−2404.

(5) Krohn, K. *Tetrahedron* **1990**, 46, 291−318.

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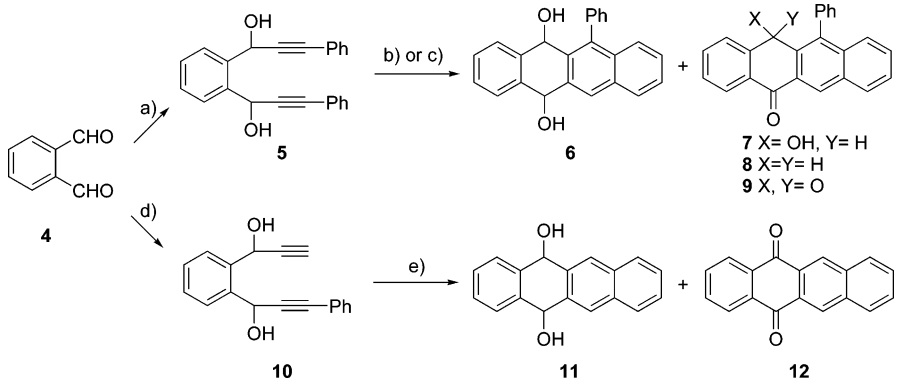
Scheme 1[a]



[a] Reagents and conditions: (a) Phenylacetylene, *n*-BuLi, THF, −78 °C to rt, 100%. (b) Toluene, sealed tube, 160 °C, 12 h, 61% (**6**), 18% (**7**), 8% (**8**). (c) Toluene/Et_3N, sealed tube, 150 °C, 80% (**6**), 16% (**9**). (d) (i) Phenylacetylene, *n*-BuLi, THF, −78 °C, 15 min; (ii) trimethylsilylacetylene, *n*-BuLi, THF, −78 °C to rt, 1 h; (iii) KOH, MeOH, rt, 95% (3 steps). (e) *o*-Xylene/Et_3N, sealed tube, 205 °C, 12 h, 29% (**11**), 23% (**12**).

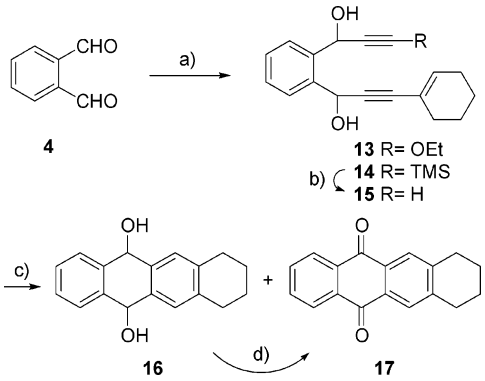
rings B and C,[7] it is only quite recently that a Co-mediated route of this kind has been patented.[8]

Having recently studied the intramolecular dehydro Diels−Alder (IDDA) reactions of diarylacetylene systems in which a three-carbon spacer linking the reacting 2π and 4π moieties allowed the synthesis of the tetracyclic core of the benzo[*b*]fluorene antibiotics,[9] we envisaged that the addition of one more atom to the linker would give access to the benzo[*b*]anthracene nucleus, the basic skeleton of anthracyclines. Here we report the first synthesis of the benzo[*b*]anthracene skeleton by simultaneous formation of rings B and C by means of an IDDA reaction.[10]

We first prepared diol **5**[11] by reacting commercially available phthaldehyde **4** with 2.1 equiv of lithium phenylacetylide (Scheme 1). This provided a quantitative yield of a diastereomeric mixture of diols that coeluted in column chromatography.

Gratifyingly, when a toluene solution of **5** was heated at 160 °C in a sealed tube, the easily oxidizable naphthacenediol **6** was isolated as a mixture of diastereoisomers in 61% yield, along with minor amounts of ketones **7** (18%) and **8** (8%).[12] We then investigated the effect of the acidity or basicity of the medium on the reaction course.[13] When the reaction was performed in the presence of triethylamine as cosolvent, it proceeded almost quantitatively, affording an 80% yield of diol **6** and a 16% yield of the previously undetected naphthacenedione **9**.[14] By contrast, heating a toluene solution of **5** in the presence of catalytic amounts of CF_3CO_2H led to the formation of a complex mixture of unidentified compounds.[15]

Scheme 2[a]



[a] Reagents and conditions: (a) (i) Ethynylcyclohexene, *n*-BuLi, THF, −78 °C, 15 min; (ii) ethylethynyl ether, *n*-BuLi, −78 °C to rt, 62% (for **13**); trimethylsilylacetylene, *n*-BuLi, −78 °C to rt, 94% (for **14**). (b) KOH (aq), THF, MeOH, rt, 100%. (c) Toluene/Et_3N, sealed tube, 150 °C, 12 h, 52% (**16**), 36% (**17**). (d) MnO_2, CH_2Cl_2, rt, 100%.

Since it is well-established that alkynyl ketones undergo IDDA reactions under milder conditions and afford higher yields than alcohols,[9b,13a] we also oxidized diol **5** to the

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(7) (a) For Co, see: Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539−556. (b) For Rh, see: Müller, E.; Beissner, C.; Jäckle, H.; Langer, E.; Muhm, G. O.; Sauerbier, M.; Segnitz, A.; Streichfuss, D.; Thomas, R. *Liebig, Ann. Chem.* **1971**, *754*, 64−89.

(8) Kreye, P.; Groth, U.; Eckenberg, P. Ger. Offen. 19708496, 1998.

(9) (a) Rodríguez, D.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **1999**, *40*, 7701−7704. (b) Rodríguez, D.; Navarro, A.; Castedo, L.; Domínguez, D.; Saá, C. *Org. Lett.* **2000**, *2*, 1497−1500. (c) Rodríguez, D.; Navarro, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Org. Chem.* **2003**, *68*, 1938−1946.

(10) Synthesis of the related benzo[*a*]anthracene nucleus and its application to the synthesis of angucyclinone antibiotics has been recently reported, being the key step in the simultaneous formation of three rings via a cobalt-mediated [2+2+2] cycloaddition of a triyne: Kalogerakis, A.; Groth, U. *Org. Lett.* **2003**, *5*, 843−844.

(11) Straub, H.; Hambrecht, J. *Synthesis* **1975**, 425−426.

(12) The side products may have arisen, in part, from reaction with oxygen present in the solvent. When the toluene was degassed prior to use, the yields of **7** and **8** decreased to 6% and 2%, respectively. Assignment of the structures was supported by the observation of an HMBC correlation between the ketone of the carbonyl group and the singlet corresponding to the hydrogen placed in the *peri* position.

corresponding diketone by treatment with excess activated MnO_2 (not shown in Scheme 1). However, all attempts to cyclize the diketone under thermal or catalyzed conditions (CH_3CO_2H, Et_3N, $ZnCl_2$, $AlCl_3$) led to its decomposition.

To obtain a product without the phenyl substituent, we first synthesized the asymmetric diol **10** in 95% yield by sequential treatment of phthaldehyde with lithium phenylacetylide and lithium trimethylsilylacetylide followed by KOH treatment and desilylation. However, as feared, the lack of a terminal substituent on one of the alkynes hampered its cyclization:[9a] heating an *o*-xylene/Et_3N solution of **10** in a sealed tube at 205 °C afforded only a 29% yield of diol **11** and a 23% yield of quinone **12**.

Finally, cyclohexene derivatives **13** and **14** were prepared from **4** by sequential addition of the corresponding acetylides, and cyclohexene **15** by desilylation of **14**. Alkynyl ether **13**, which would allow direct introduction of an oxygen substituent, unfortunately proved do be thermally unstable, decomposing under the cylization reaction conditions. In the case of **14**, cyclization was prevented by its bulky trimethylsilyl group, no evolution being observed after heating **14** at 180 °C for 24 h. To our delight, however, desilylated diol **15** reacted smoothly at 150 °C,[16] affording a clean mixture of diol **16** (52%) and quinone **17**[17] (36%) (due to the complexity of the spectrum of **16**, its identity was confirmed by quantitative oxidation to **17**). Once again, diketone derivatives of **14** and **15** (not shown) were easily prepared but decomposed when subjected to cyclization conditions.

In conclusion, we have demonstrated the utility of IDDA reactions for the synthesis of the 7,8,9,10-tetrahydronaphthacene-5,12-dione skeleton of the anthracycline antibiotics, which was obtained in high yields and just three steps from commercially available phthaldehyde.

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Supporting Information Available: Experimental procedures and spectral data for **5**−**9** and **13**−**17**; ^1H and ^{13}C/DEPT spectra for **13**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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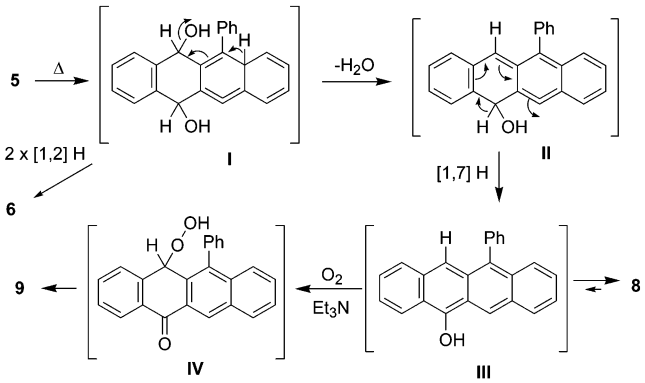
(13) (a) Danheiser, R. L.; Gould, A. E.; Fernández de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514−5515. (b) Rodríguez, D.; Navarro, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Am. Chem. Soc.* **2001**, *123*, 9178−9179. (c) Rodríguez, D.; Navarro, A.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **2002**, *43*, 2717−2720.

(14) Naphthacenedione **9** was formed during the course of the reaction and not by oxidation of diol **6**: when **6** was heated under the same reaction conditions, no evolution was observed. A plausible mechanism for the obtention of the minor products is depicted below: The first step is the formation of the intermediate allene **I**, being the most favorable process the isomerization (aromatization) via two consecutive [1, 2]-hydrogen shifts to give diol **6** (see ref 9c). The loss of water in allene **I** followed by rearomatization would lead to phenol **III**, which can tautomerize to ketone **8** or react with any adventitious oxygen present in the mixture to form the intermediate **IV**, which would easily evolve to the quinone **9**. Several pathways involving molecular oxygen could be suggested for the transformation of **I** or **II** to the hydroxy ketone **7**



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(15) Reaction of **5** in HBr or HCl/*t*-BuOH has previously been reported to afford 12-bromo- or 12-chloro-5-phenylnaphthacene; see ref 11.

(16) Due to the fact that no loss of aromaticity is required during the cycloaddition process, cyclohexene derivatives react under milder conditions than the corresponding aryl derivatives (**15**, 150 °C vs **10**, 205 °C).

(17) Compound **17** has been previously reported, but not its spectroscopic data: Semmelhack, M. F.; Neu, T.; Foubelo, F. *J. Org. Chem.* **1994**, *59*, 5038−5047.