

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

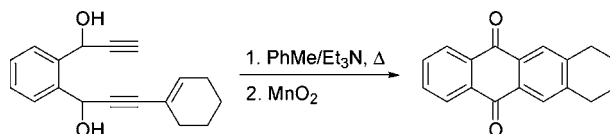
David Rodríguez, Luis Castedo, Domingo Domínguez, and Carlos Saá*

Departamento de Química Orgánica e Unidade Asociada ó CSIC,
Facultade de Química, Universidade de Santiago de Compostela,
15782 Santiago de Compostela, Spain

qocsaa@usc.es

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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 antibiotics¹ 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

(**3**),³ has led to the development of many methods for the synthesis of natural and nonnatural anthracyclines.⁴

In most, the tetracyclic core of the antibiotic is synthesized by addition to anthraquinones⁵ (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

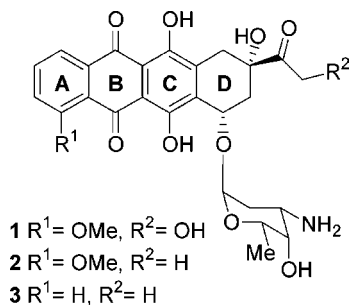


Figure 1. Anthracycline antibiotics.

search for anthracyclines with greater potency and less cardiotoxicity, such as the 4-demethoxy derivative idarubicin

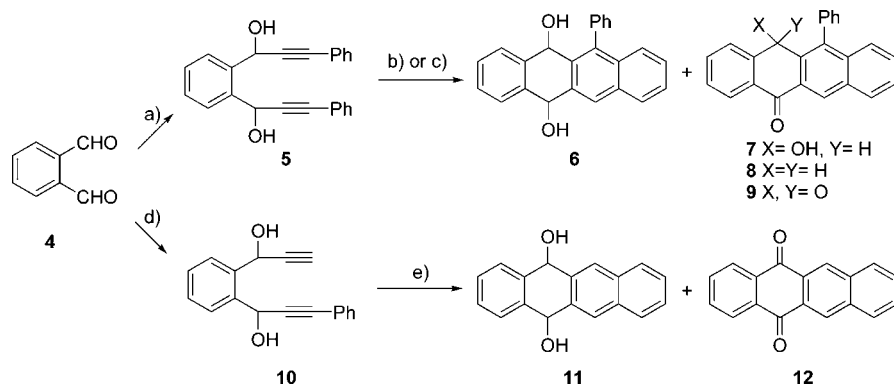
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Scheme 1^a

^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**).

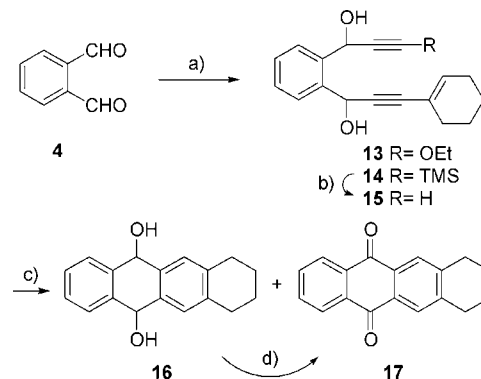
rings B and C,⁷ it is only quite recently that a Co-mediated route of this kind has been patented.⁸

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 phthalaldehyde **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 $\text{CF}_3\text{CO}_2\text{H}$ 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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(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.

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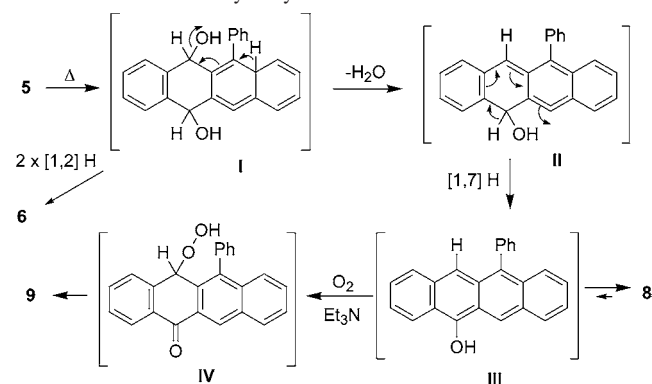
(12) The side products may have arisen, in part, from reaction with oxygen present in the solvent. When the toluene was degassed prior to use, the yields of **7** and **8** decreased to 6% and 2%, respectively. Assignment of the structures was supported by the observation of an HMBC correlation between 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 MnO₂ (not shown in Scheme 1). However, all attempts to cyclize the diketone under thermal or catalyzed conditions (CH₃CO₂H, Et₃N, ZnCl₂, AlCl₃) 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 phthalaldehyde 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/Et₃N solution of **10** in a

(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**



(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.

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 to be thermally unstable, decomposing under the cyclization 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 phthalaldehyde.

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

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(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.