A New Convergent Approach to the Polycyclic Framework of Dynemicin A†

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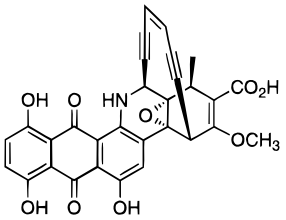
Dynemicin A (**1**), a cyclic enediyne antibiotic isolated from *Micromonospora chersina*,[1] has been the subject of intensive chemical and biological research owing to its potent antibacterial and anticancer activities and its unique molecular structure, which combines an enediyne unit with the anthraquinone chromophore of the anthracyclinones.[2]

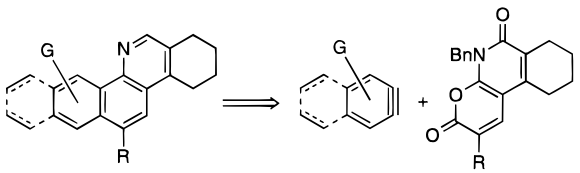


Dynemicin A, **1**

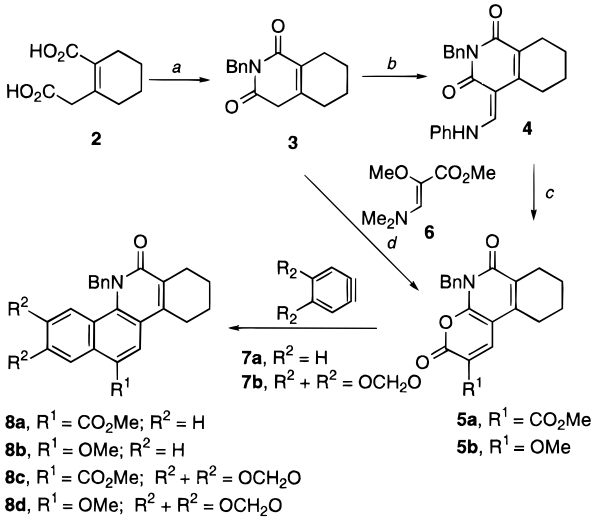
Various structural features of dynemicin A are thought to play important roles in its mechanism of action. The anthraquinone moiety is believed to act both as *delivery system*, allowing intercalation and binding of the molecule at specific sites along the minor groove of DNA, and as *triggering device*, undergoing a bioreduction that facilitates opening of the epoxide and Bergman cyclization of the enediyne, which gives a diradical capable of hydrogen abstraction and subsequent cleavage of the DNA.[3] In view of this, a general synthesis of the polycyclic skeleton[4] of dynemicin A is of great interest not only as part of an approach to this natural product and analogous enediynes but also as a route to novel anthraquinones that are potential DNA intercalators.

In relation to our work on the synthesis of planar antitumor benzophenanthridines by intermolecular Diels−Alder reaction of pyrones with benzyne,[5] we sought a similar approach to the synthesis of the polycyclic framework of dynemicin A and analogs with different planar moieties (Scheme 1). This paper reports our preliminary results.

Scheme 1



Scheme 2[a]



[a] Key: (a) $BnNH_2$, reflux; 68%; (b) $CH(OCH_3)_3$, $PhNH_2$, AcOH, DMF; 80%; (c) (for **5a**) $NCCH_2CO_2Me$, $KOBu^t$, DMF; 93%; (d) (for **5b**) **6**, 180 °C; 77%.

Pyrones **5** were easily prepared in two or three steps from acid **2** (Scheme 2).[6] Condensation of **2** with benzylamine afforded imide **3** in 68% yield. Reaction of **3** with trimethyl orthoformate and aniline in DMF yielded enamine **4**, which upon treatment with methyl cyanoacetate and $KOBu^t$ gave pyrone **5a** in 74% overall yield from **3**. Pyrone **5b** was obtained in 77% yield by reaction of **3** with methyl 3-(dimethylamino)-2-methoxyacrylate (**6**), which was prepared by a published procedure.[7] The dimethylamine eliminated in the condensation of **3** and **6** must be removed by passing a strong current of an inert gas through the reaction vessel; otherwise, nucleophilic attack on the pyrone by this amine causes decomposition.

Diels−Alder reaction of **5b** with benzyne (generated by thermal decomposition of benzenediazonium 2-carboxylate),[8] followed by CO_2 extrusion, afforded the tetrahydrobenzophenanthridine **8b** in 77% yield; but pyrone **5a**, with an ester group at position 3, proved to be less reactive, giving compound **8a** in only 42% yield, together with unreacted **5a** (76% yield on the basis of unrecovered starting material). Attempts to consume all of the starting **5a** by adding an excess of benzyne resulted in a competitive reaction involving addition of a second benzyne unit to ring C of **8a**.

It has been suggested that the presence of one nitrogen and two oxygen atoms with a particular relative geometry can determine the mode of binding of benzophenan-

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† Dedicated to Prof. Eckehardt Winterfeldt on the occasion of his 65th birthday.

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(2) For selected references on the synthesis of dynemicin A and model systems, see: (a) Danishefsky, S. J.; Shair, M. D. *J. Org. Chem.* **1996**, *61*, 16. (b) Shair, M. D., Yoon, T.-Y.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1721. (c) Takahashi, T.; Sakamoto, Y.; Yamada, H.; Usui, S.; Fukazawa, Y. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1345. (d) Nishikawa, T.; Ino, A.; Isobe, M. *Tetrahedron* **1994**, *50*, 1449. (e) Taunton, J.; Wood, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10378. (f) Nicolaou, K. C.; Dai, W.-M.; Hong, Y. P.; Tsay, S. C.; Baldridge, K. K.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 7944. (g) Wender, P. A.; Zercher, C. K.; Beckham, S.; Haubold, E.-M. *J. Org. Chem.* **1993**, *58*, 5867.

(3) (a) Semmelhack, M. F.; Gallagher, J.; Cohen, D. *Tetrahedron Lett.* **1990**, *31*, 1521. (b) Langley, D. R.; Doyle, T. W.; Beveridge, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 4395.

(4) For references on the synthesis of the anthraquinone subunit, see: (a) Chikashita, H.; Porco, J. A., Jr.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Org. Chem.* **1991**, *56*, 1692. (b) Nicolaou, K. C.; Gross, J. L.; Kerr, M. A.; Lemus, R. H.; Ikeda, K.; Ohe, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 781. (c) Okita, T.; Isobe, M. *Tetrahedron* **1994**, *38*, 11143.

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(7) Schmidt, R. R.; Betz, R. *Synthesis* **1982**, 748.

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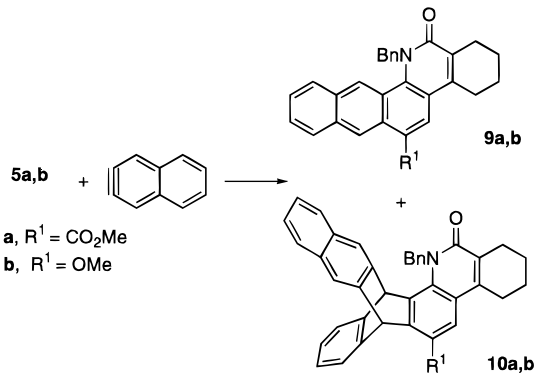
Scheme 3



thridines and other intercalating antitumor alkaloids to DNA.[9] With this in mind, we reacted 3,4-(methylenedioxy)benzyne (**7b**) with **5a** and **5b**, obtaining the corresponding tetrahydrobenzophenanthridines **8c** and **8d** in 68 and 69% yield, respectively.

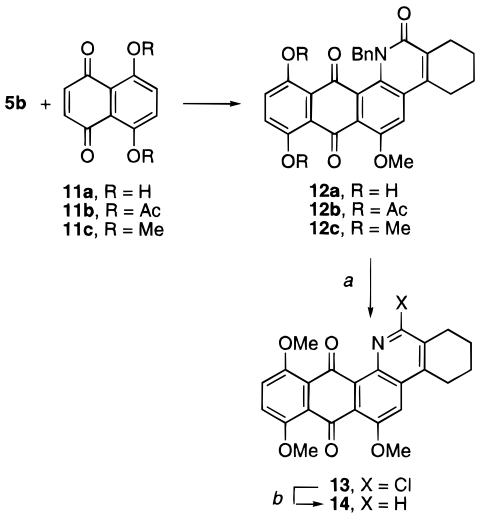
Reaction of **5a** and **5b** with 2,3-naphthalyne afforded complex reaction mixtures, which is attributable to the increased reactivity toward dienophiles of the anthracene system in the monoadduct **9** (Scheme 3). In keeping with this, we detected mono- and diadducts **9** and **10** in around 15% yields.

Encouraged by the above results, we attempted the synthesis of our main synthetic target, the anthraquinone framework of dynemicin A, using a similar methodology. It was envisaged that reaction of dienophiles, quinones **11**, with pyrones **5**, followed by extrusion of CO_2 and air oxidation, would give the desired polycyclic system (Scheme 4). Quinones **11b**[10] and **11c**[11] were prepared from commercially available 5,8-dihydroxynaphthoquinone (**11a**) by published procedures. Heating diacetate **11b** with **5b** in nitrobenzene at 180 °C for 24 h afforded compound **12b** in 11% yield. A major byproduct was **12a** (resulting from acetate cleavage of **12b**), and partial decomposition of **11b** was also observed. Compound **11a** did not react with **5b** to afford **12a**.

Reaction of **5b** with 5,8-dimethoxynaphthoquinone (**11c**) afforded **12c** in a remarkable 57% yield. Refluxing **12c** with $POCl_3$ gave chloroimine **13** in 58% yield, and hydrogenolysis of **13** over Pd/C in the presence of NaOAc

(9) Cheng, C. C.; Zee-Cheng, R. K. Y. *Heterocycles* **1981**, *15*, 1275.

Scheme 4[a]



[a] Key: (a) $POCl_3$, 60 °C; 58%; (b) H_2, 10% Pd/C, NaOAc; 100%.

afforded compound **14** in quantitative yield. Methylated anthraquinones **13** and **14** could be advanced intermediates in the total synthesis of **1**, and we obtained them in only four and five steps, respectively, from acid **2** and in significantly better overall yields than previously published procedures.

In conclusion, this paper describes a new convergent approach to the pentacyclic nucleus of dynemicin A that is based on Diels−Alder reaction between an α-pyrone and a quinone. The use of arynes instead of quinones as dienophiles allowed the synthesis of polycyclic compounds that could serve as precursors to dynemicin analogs with different intercalating moieties. Work aimed at the construction of the enediyne system on these molecules is in progress.

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Supporting Information Available: Spectroscopic data and experimental procedures for the synthesis of compounds **3**, **4**, **5a**,**b**, **8a**−**d**, **12a**−**c**, **13**, and **14** (5 pages).

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