Total Syntheses of Di- and Tri-*O*-methyl Dynemicin A Methyl Esters

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Dynemicin A (**1**) is a potent cytotoxin with several notable structural features, including a complex heterocyclic skeleton and a network of sensitive functional groups (Scheme I).[1] Especially precarious with regard to a total synthesis of dynemicin A is the juxtaposition of epoxide, enediyne, and anthraquinone elements.[2,3] Under suitable conditions, the interactive chemistry of these groups leads to a cascade of intermediates, one or more of which are able to cleave the backbone of DNA in vitro.[4] We now report a reaction sequence that results in the total syntheses of (±)-di- and -tri-*O*-methyl dynemicin A methyl esters (compounds **2** and **3**, respectively).

Examination of the X-ray crystal structure of triacetyl dynemicin A led to the hypothesis that severe steric buttressing would destabilize an *N*-acylated angular anthraquinone.[5] It was therefore deemed necessary to develop a protecting group strategy in which nitrogen deprotection would directly precede completion of the anthraquinone segment. Since our earlier procedure for the elaboration of the 1,4-cyclohexadiene core of dynemicin A involved both strongly basic and acidic conditions,[2a] we found it necessary to use a latent, base-labile protecting group in which a substituted propionate that is capable of β-elimination derives from a protected 1,3-propanediol.[6]

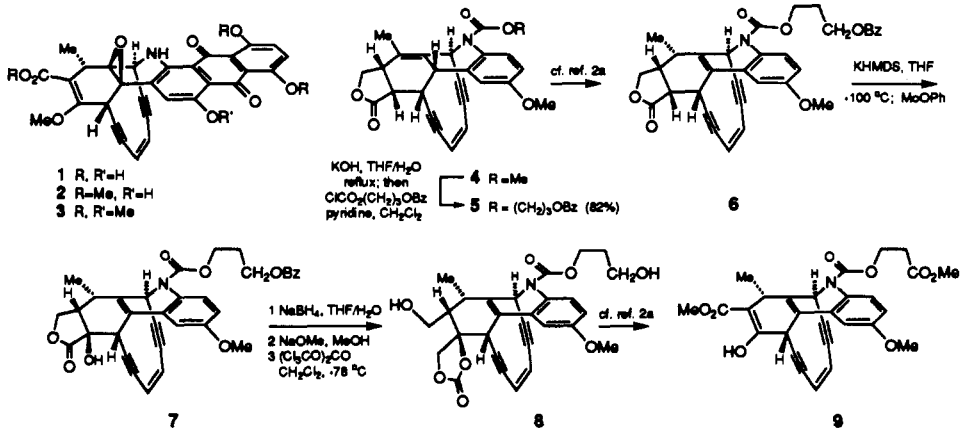
The methyl urethane of the product of a transannular Diels–Alder cyclization, **4**, was exchanged by the action of potassium hydroxide in refluxing THF/water followed by treatment of the free amine with 3-benzoyloxypropyl chloroformate (Scheme I).[7] Thus protected, compound **5** was converted into the enol diester **9** by using slight modifications of procedures we had developed previously. This synthetically economical sequence exploits an alcohol → acid oxidation to simultaneously transform a base-stable urethane (cf. **6** → **7**) into a protecting group that can now be removed under mildly basic conditions.

Because molecules that incorporated a vinylogous carbonate were relatively unstable toward Lewis acids, the subsequent annulation required considerable experimentation and optimization (Scheme II). Under scrupulously anhydrous conditions, silver triflate promoted the regioselective Friedel–Crafts-type coupling of **9** to 3-bromo-4,7-dimethoxyphthalide[2c] within 1 min at 0 °C to give a 1:1 mixture of diastereomeric lactones. Methylation (K_2CO_3, Me_2SO_4, acetone, 23 °C, 2.5 h) of the crude mixture provided compounds **10a,b** in 57% overall yield. The lactone was then reductively opened with the reagent combination $Et_3SiH/MeAlCl_2$ (CH_2Cl_2, −78 °C → 50 °C, 1 h, 82% yield). Cyclization of the resultant acid **11** was effected by conversion to the acid chloride followed by treatment with trimethylsilyl triflate. This gave an unstable anthracenol derivative ($t_{1/2} \approx 30$ min) that was immediately oxidized (DDQ, 0 °C, aqueous THF, 5 min) to give the hexacyclic ketol **12** in 51% overall yield.[8]

To complete the synthesis, we needed only to epoxidize the olefin, remove the urethane protecting group, and oxidize the secondary alcohol to a ketone. We took notice of the fact that a deprotected, epoxy ketol such as **13**, formally a two-electron reduction product of our target, would be a tautomer of the hydroanthraquinone **14**. Since **14** was expected to undergo spontaneous Bergman cyclization (cf. **15**) by analogy to the known behavior of dynemicin A under reducing conditions, we initially sought to avoid possible entry into this equilibrium.[4,9] Model studies that investigated alternative pathways failed to produce any enediyne-containing anthraquinones. Hence, we opted to proceed through intermediate **13**, hoping that a kinetic barrier to tautomerization would prevent epoxide opening and Bergman cyclization. Success was finally realized with the following sequence of reactions: (1) regioselective epoxidation of **12** with $MCPBA/CH_2Cl_2$ (23 °C, 2.5 h, 73% yield), (2) urethane deprotection with 0.11 M DBU/MeOH (23 °C, 1 h), and (3) oxidation with ceric ammonium nitrate in aqueous acetonitrile (2.6 equiv, 0 °C, 0.75 h). The cerium(IV) oxidation presumably occurs via iminoquinone **16**, which then tautomerizes to furnish the selectively demethylated anthraquinone **2** (red-violet; λ 544, MeOH). For the purpose of comparison to a natural sample, the crude product from this reaction was methylated (Cs_2CO_3, CH_3I, acetone, 23 °C, 3 h) to afford, after chromatographic purification, an intensely colored orange-red compound (**3**, λ 504, MeOH; 50% yield, three steps). This material was judged to be identical with a naturally derived sample of tri-*O*-methyl dynemicin A methyl ester kindly provided by Dr. T. Ohnuma (Bristol-Myers Research Institute) on the basis of its physical properties and spectroscopic data (^1H NMR, IR, UV, HRMS, HPLC/TLC).

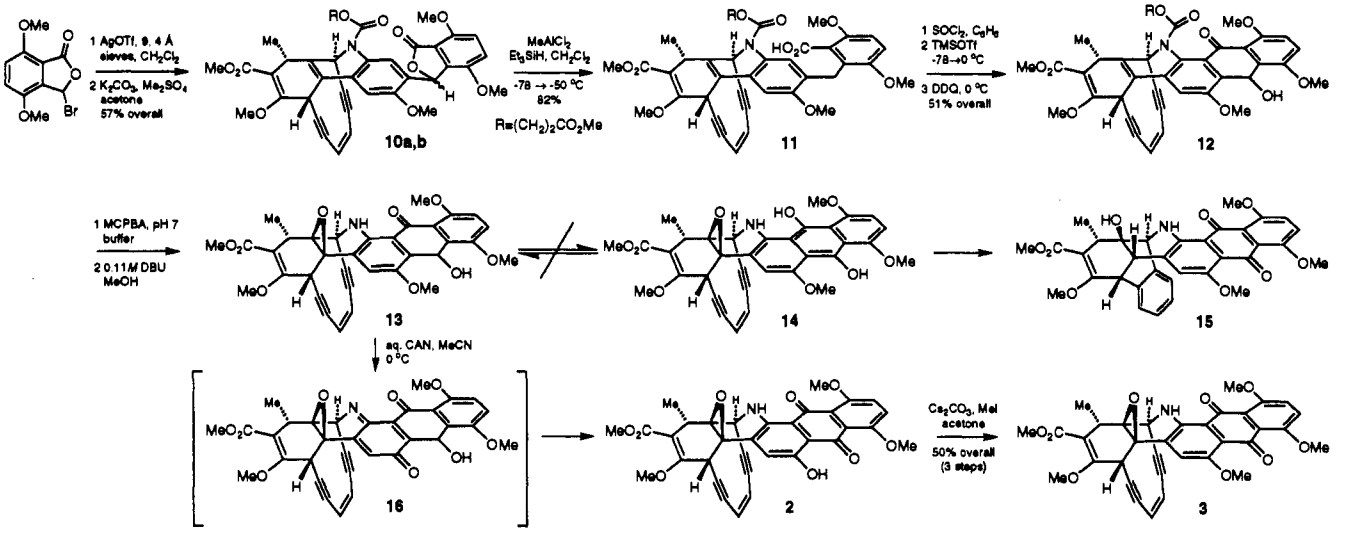
Although considerable progress has been made in understanding dynemicin A's chemical properties, there is still much to be learned about its effects on cultured cells. The synthetic studies detailed herein and elsewhere[2] feature a transannular Diels–Alder polycyclization that rapidly assembles the molecule's core as well as a novel anthraquinone annulation sequence that culminates in the preparation of a selectively methylated derivative of dynemicin A. Because the annulation sequence begins at a relatively late point in the synthesis, our route should be amenable to the preparation of compounds with a variety of end-ring phenolic

Scheme I



0002-7863/93/1515-10378$04.00/0

Scheme II



substituents (including R = H, cf. **1**). The route thus provides an opportunity to explore the cellular properties of dynemicin A and dynemicin A-like molecules.

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Supplementary Material Available: Spectral data for **8–12** and the di- and tri-*O*-methyl dynemicin methyl esters (2 pages). Ordering information is given on any current masthead page.

(1) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449.

(2) (a) Wood, J. L.; Porco, J. A., Jr.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898. (b) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410. (c) Chikashita, H.; Porco, J. A., Jr.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Org. Chem.* **1991**, *56*, 1692.

(3) For a review of synthetic work, see: Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387 and references therein.

(4) Sugiura, Y.; Arakawa, T.; Uesugi, M.; Shirake, T.; Ohkuma, H.; Konishi, M. *Biochemistry* **1991**, *30*, 2989.

(5) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715.

(6) Fukuyama, T.; Linton, S. D.; Tun, M. M. *Tetrahedron Lett.* **1990**, *31*, 5989.

(7) The chloroformate was prepared by syringe pump addition (over 2 h) of 3-benzoyloxypropanol (2.9 equiv) and pyridine (3.0 equiv) to a 0 °C methylene chloride solution of triphosgene (1.0 equiv).

(8) Only one diastereomeric ketol, of unknown relative configuration, was produced in this reaction.

(9) Miyoshi, M.; Morisaki, N.; Tokiwa, Y.; Kobayashi, H.; Iwasaki, S.; Konishi, M.; Oki, T. *Tetrahedron Lett.* **1991**, *32*, 6007.