A Concise Synthesis of the Anthraquinone Portion of Dynemicin A

Philip Magnus,* Shane A. Eisenbeis and Nicholas A. Magnus

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, USA

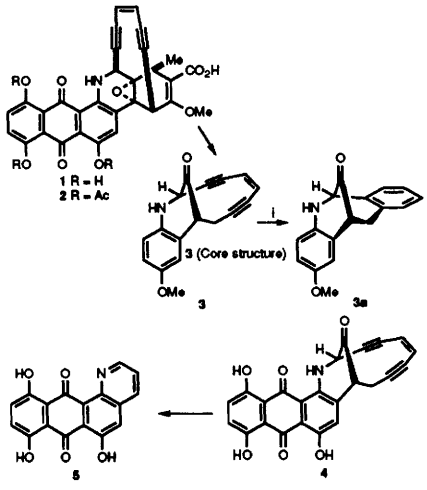
Addition of the lactone anion derived from **29** to **13** gave the adduct **30**, which was dehydrated to give **20**; subsequent conversion of **20** into the anthraquinone **26** was achieved in two steps.

The recently isolated antitumour antibiotic dynemicin A **1**, and its derived acetate **2**, have attracted considerable synthetic interest because of their unusual structures, potent antitumour activity, and speculated *in vitro* mechanism of action.[1] We have synthesized the core azabicyclo[7.3.1]enediyne core structure **3**, and have found that it shows both *in vitro* and *in vivo* antitumour activity even though it does not cycloaromatize *via* a 1,4-diyl to give **3a** until heated to >90 °C.[2] This demonstrated that the widely accepted assumption that the 1,4-diyl (diradical) formed under physiological conditions is necessary for biological activity, is not valid.[3] Both natural, and simpler synthetic anthraquinones, frequently exhibit potent antitumour activity.[4] Therefore it seemed reasonable to see if the anthraquinone portion of dynemicin A **1** displayed any antitumour activity.

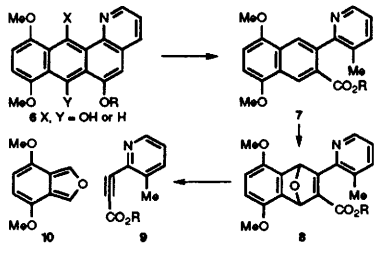
Incorporating the core structure **3** into the anthraquinone results in **4**, and the anthraquinone core portion is **5** (Scheme 1). There have been reports of the synthesis of the anthraquinone portions of dynemicin A, and the synthesis of di-*O*-methyl dynemicin.[5] The parent quinone **5** has not been described.

While numerous methods have been used for the synthesis of anthraquinones, we focused on the Snieckus strategy since it appeared to offer the most direct route.[6] We have examined this strategy at different oxidation levels in order to assess which would be the most convenient.

A general convergent retrosynthetic pathway (Scheme 2) requires the synthesis of two components; the 4,7-dimethoxyisobenzofuran **10**, and a 3-methylpyridine dienophile **9**. It was anticipated that the cycloaddition adduct **8** could be aromatized to give **7**. Treatment of **7** with an amide base would result in formation of the 3-methylpyridine anion which should cyclize to give **6**. Subsequent oxidation would provide the anthraquinone core structure of dynemicin A.



Scheme 1 *Conditions*: i, >90 °C

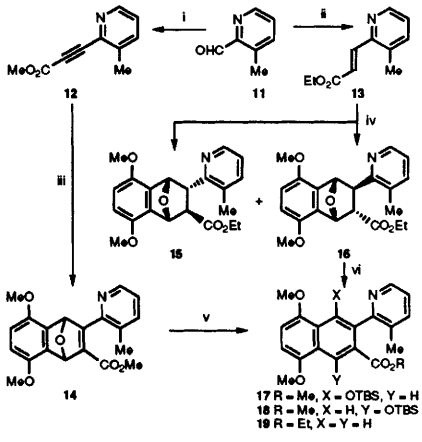


Scheme 2

4,7-Dimethoxyisobenzofuran **10** was prepared by treatment of the furan 1,4-dimethoxybenzyne adduct **i**† with 1,4-dipyridyltetrazine **ii**, and isolated as a moderately stable crystalline solid. 3-Methyl-2-pyridine carboxaldehyde **11** was converted into the acetylenic ester **12** (Scheme 3) and treated with **10** to give the adduct **14** (>95%). The adduct **14** was readily aromatized to a mixture of **17** and **18** when treated with TBSOTf–CH_2Cl_2 (>95%, 5:1). Similarly, treatment of **13** with **10** gave the two cycloaddition adducts **15** and **16** (>95%, 2:1). The major adduct **16** was separated by crystallization (structure by X-ray diffraction). It proved to be extremely resistant to aromatization using acidic conditions, but upon treatment with lithium diisopropylamide at −78 °C was converted into the naphthalene derivative **19**. Continued exposure of **19** to the above conditions, but with warming to 50 °C, resulted in cyclization to give **24** (90%, after pivaloylation). Interestingly, the minor adduct **15** was inert to these aromatization conditions.

When the TBDMS protected derivatives **17** and **18** were treated with lithium diisopropylamide in THF at 25 °C, followed by Bu^{t}COCl, they were converted into the anthracene derivatives **21** and **22** respectively [(72%), only **21** formed a pivaloate derivative]. The mixture of **21** and **22** was readily oxidized to the anthraquinone **25** (72%, $Ag^{II}O$, HNO_3–dioxane, **22** was destroyed).[7] The compound **24** was preferentially oxidized in the terminal ring to give **28**, (Scheme 4). While the route to **25** is short, we also explored a regiospecific route that avoided the use of 4,7-dimethoxyisobenzofuran.

o-Lithiation of 2,5-dimethoxybenzyl alcohol using *n*-butyllithium in THF at reflux, followed by quenching the resulting dianion with carbon dioxide and acidification, gave the lactone **29** (80%).[8] Addition of the lactone **29** to a solution of lithium diisopropylamide in THF, followed by the α,β-unsaturated ester **13** gave the adduct **30** (and stereoisomer) in excellent



Scheme 3 *Reagents and conditions*: i, CBr_4–Ph_3P–NEt_3–CH_2Cl_2 (71%) then $LiN(SiMe_3)_2$ (1.2 equiv.)–Bu^{n}Li (2.1 equiv.)–THF −78 °C, inverse addition to $ClCO_2Me$ (3.0 equiv.)–THF, −78 °C (95%), ii, $(EtO)_2POCH_2CO_2Et$–NaH–THF (95%); iii, **10**–PhH, reflux 10 h (95%); iv, **10**–PhH, 25 °C (90%); v, TBSOTf (10 equiv.)–2,6-lutidine (20 equiv.) –CH_2Cl_2 (95%); vi, $LiNPr^i_2$–THF, −78 °C

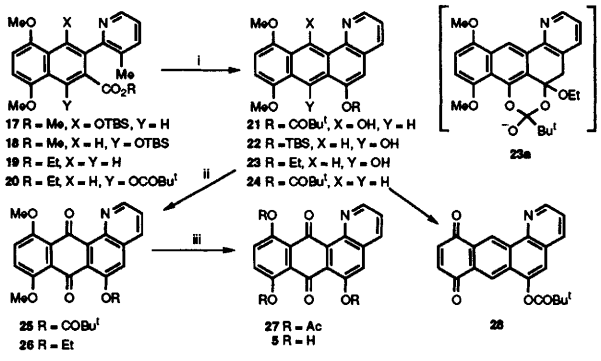
yield. Exposure of **30** to toluene-*p*-sulfonic acid in chloroform at 25 °C resulted in clean aromatization to give, after pivaloylation, the naphthalene derivative **20** (87% from **30**), (Scheme 5). When the derived pivaloyl ester derivative **20** was treated with lithium diisopropylamide in THF at 50 °C it was converted into the anthracene **23** (95%). Presumably, the origin of the ethyl ether **23** is *via* the intermediate *ortho*-ester **23a**, which prefers to eliminate pivaloate anion rather than ethoxide anion, thus providing an unexpected *in situ* protection of the newly formed anthracene **23**.

Oxidation of **23** with ceric ammonium nitrate in MeCN–H_2O gave the anthraquinone **26** as an orange crystalline solid (72%).[9] Deprotection of **26** to give **27** was accomplished using hydrogen bromide acid in acetic acid heated at reflux, (Scheme 4).

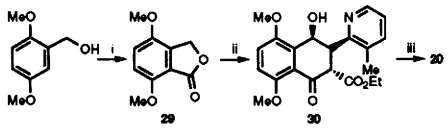
The insoluble blue–violet trihydroxyanthraquinone **5** was characterized as its derived triacetate **27** (Ac_2O–pyridine). The overall route to the triacetoxyanthraquinone **28** is very short [five steps *via* **31**, **20**, **24** and **25/26**], and currently several of these quinones are undergoing biological evaluation.

The National Institutes of Health, National Science Foundation and Bristol–Myers Squibb are thanked for their financial support.

Received, 15th March 1994; Com. 4/01561D



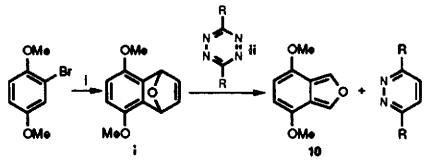
Scheme 4 *Reagents and conditions*: i, $LiNPr^i_2$ (5.0 equiv.)–THF, 0–25 °C then Bu^tCOCl (20 equiv.)–pyridine (40 equiv.)–CH_2Cl_2 (72%); ii, $Ag^{II}O$ (4.0 equiv.)–dioxane–6 mol dm^{-3} HNO_3 (cat) (72%) or $Ce(NH_4)_2(NO_2)_6$–MeCN; iii, HBr–AcOH, Ac_2O, pyridine (75%)



Scheme 5 *Reagents and conditions*: i, Bu^nLi (2.5 equiv.)–THF, −70 to 70 °C, 3 h, CO_2, 2 mol dm^{-3} HCl (80%); ii, $LiNPr^i_2$ (2.0 equiv.)–THF, −78 °C, **13** (>95%); iii, *p*-TsOH–$CHCl_3$ then Bu^tCOCl–CH_2Cl_2–Et_3N (87%)

Footnote

† 4,7-Dimethoxyisobenzofuran **10** was made by treatment of **i** with the tetrazine **ii** (R = 2-pyridyl). While **10** has been reported as an intermediate in various [2+4] cycloaddition reactions, it has not been previously isolated presumably because of its assumed instability. For the synthesis of **i** see: G. M. L. Cragg, R. G. F. Giles and G. P. H. Roos, *J. Chem. Soc. Perkin Trans. 1*, 1975, 339; **ii**, J. F. Geldard and F. Lions, *J. Org. Chem.*, 1965, **30**, 318.



i, THF, $NaNH_2$, furan, 3 h

References

1 M. Konishi, H. Ohkuma, K. Matsumoto, T. Tsuno, H. Kamei, T. Miyaki, T. Oki, H. Kawaguchi, G. D. Van Duyne and J. Clardy, *J. Antibiot.*, 1989, **42**, 1449; M. Konishi, H. Ohkuma, T. Tsuno, T. Oki, G. D. Van Duyne and J. Clardy, *J. Am. Chem. Soc.*, 1990, **112**, 3715; molecular modelling of the dynemicin–DNA complex predicts the absolute configuration to be 2*S*, 3*S*, 4*S*, 7*R*, 8*R*, D. R. Langley, T. W. Doyle and D. L. Beveridge, *J. Am. Chem. Soc.*, 1991, **113**, 4395.

2 P. Magnus and S. A. Eisenbeis, *J. Am. Chem. Soc.*, 1993, **115**, 12627; P. Magnus and S. M. Fortt, *J. Chem. Soc., Chem. Commun.*, 1991, 544.

3 K. C. Nicolaou and W.-M. Dai, *Angew. Chem., Int. Ed. Engl.*, 1991, 1387; K. C. Nicolaou, A. L. Smith, C.-K. Hwang and S. V. Wendeborn, *J. Am. Chem. Soc.*, 1991, **113**, 3114; K. C. Nicolaou, A. L. Z. Zeng and S. McComb, *J. Am. Chem. Soc.*, 1992, **114**, 9279.

4 H. D. H. Showalter, J. L. Johnson and J. M. Hoftiezer, *J. Heterocycl. Chem.*, 1986, **23**, 1491; H. D. H. Showalter, J. L. Johnson, J. M. Hoftiezer, W. R. Turner, L. M. Werbel, W. R. Leopold, J. L. Shillis, R. C. Jackson and E. F. Elslager, *J. Med. Chem.*, 1987, **30**, 121.

5 H. Chikashita, J. A. Porco, Jr., T. J. Stout, J. Clardy and S. L. Schreiber, *J. Org. Chem.*, 1991, **56**, 1692; J. Taunton, J. L. Wood and S. L. Schreiber, *J. Am. Chem. Soc.*, 1993, **115**, 10378.

6 M. A. F. Brandão, A. B. de Oliveira and V. Snieckus, *Tetrahedron Lett.*, 1993, **34**, 2437.

7 C. D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, 1972, **94**, 227.

8 D. J. Dodsworth, M. Calcagno, E. U. Ehrmann, B. Devadas and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2120.

9 T.-L. Ho, T.-W. Hall and C. M. Wong, *Synthesis*, 1973, 206.