

## A Concise Synthesis of the Anthraquinone Portion of Dynemicin A

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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.<sup>1</sup> We have synthesized the core azabicyclo[7.3.1]enediynes 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.<sup>2</sup> 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.<sup>3</sup> Both natural, and simpler synthetic anthraquinones, frequently exhibit potent antitumour activity.<sup>4</sup> 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.<sup>5</sup> 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.<sup>6</sup> We have examined this strategy at different oxidation levels in order to assess which would be the most convenient.

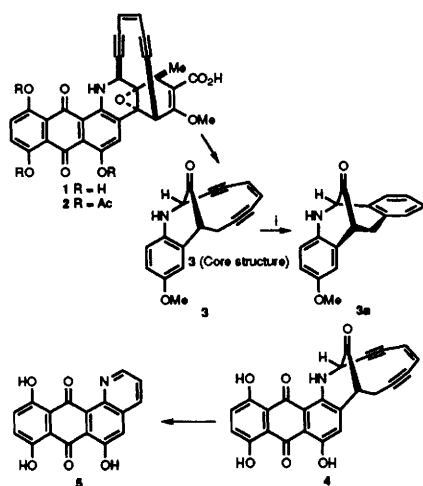
A general convergent retrosynthetic pathway (Scheme 2) requires the synthesis of two components; the 4,7-dimethoxyisobenzofuran **10**, and a 3-methylpyridine dienophile **9**. It was

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.

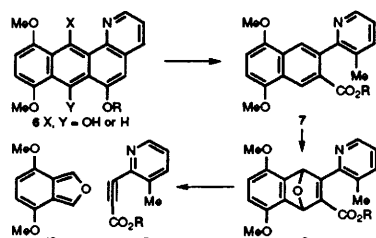
4,7-Dimethoxyisobenzofuran **10** was prepared by treatment of the furan 1,4-dimethoxybenzyl adduct **11** with 1,4-dipyridyltetrazine **ii**, and isolated as a moderately stable crystalline solid. 3-Methyl-2-pyridine carboxaldehyde **11** was converted into the acetylenic ester **12** (Scheme 3) and 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<sub>2</sub>Cl<sub>2</sub> (>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<sup>t</sup>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<sup>II</sup>O, HNO<sub>3</sub>-dioxane, **22** was destroyed).<sup>7</sup> 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 regioselective route that avoided the use of 4,7-dimethoxyisobenzofuran.

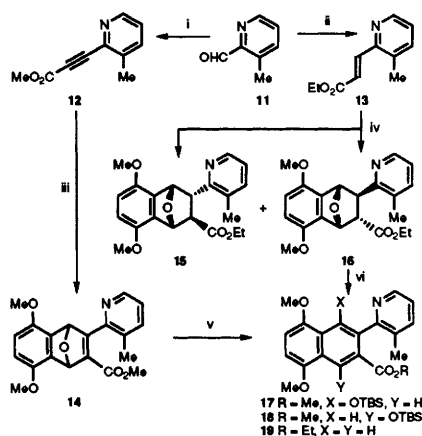
*o*-Lithiation of 2,5-dimethoxybenzyl alcohol using *n*-butyllithium in THF at reflux, followed by quenching the resulting dianion with carbon dioxide and acidification, gave the lactone **29** (80%).<sup>8</sup> Addition of the lactone **29** to a solution of lithium diisopropylamide in THF, followed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



Scheme 1 Conditions: i, >90 °C



Scheme 2



Scheme 3 Reagents and conditions: i, CBr<sub>4</sub>-Ph<sub>3</sub>P-NEt<sub>3</sub>-CH<sub>2</sub>Cl<sub>2</sub> (71%) then LiN(SiMe<sub>3</sub>)<sub>2</sub> (1.2 equiv.)-Bu<sup>n</sup>Li (2.1 equiv.)-THF -78 °C, inverse addition to ClCO<sub>2</sub>Me (3.0 equiv.)-THF, -78 °C (95%); ii, (EtO)<sub>2</sub>POCH<sub>2</sub>CO<sub>2</sub>Et-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<sub>2</sub>Cl<sub>2</sub> (95%); vi, LiNPr<sub>2</sub>-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<sub>2</sub>O gave the anthraquinone **26** as an orange crystalline solid (72%).<sup>9</sup> 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<sub>2</sub>O-pyridine). The overall route to the triacetoxanthraquinone **28** is very short [five steps *via* **31**, **20**, **24** and **25/26**], and currently several of these quinones are undergoing biological evaluation.

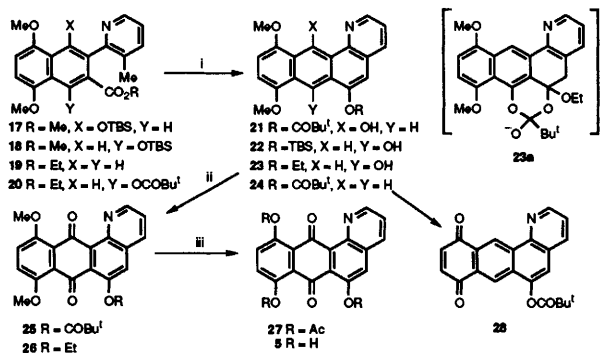
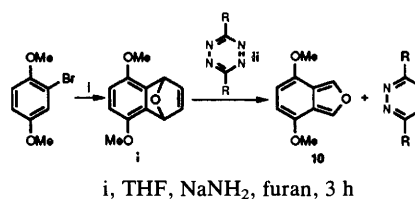
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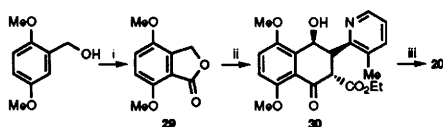
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### Footnote

† 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.



**Scheme 4 Reagents and conditions:** i, LiNPr<sub>2</sub> (5.0 equiv.)-THF, 0–25 °C then Bu<sup>t</sup>COCl (20 equiv.)-pyridine (40 equiv.)-CH<sub>2</sub>Cl<sub>2</sub> (72%); ii, Ag<sup>II</sup>O (4.0 equiv.)-dioxane-6 mol dm<sup>-3</sup> HNO<sub>3</sub> (cat) (72%) or Ce(NH<sub>4</sub>)<sub>2</sub>(NO<sub>2</sub>)<sub>6</sub>-MeCN; iii, HBr-AcOH, Ac<sub>2</sub>O, pyridine (75%)



**Scheme 5 Reagents and conditions:** i, Bu<sup>n</sup>Li (2.5 equiv.)-THF, -70 to 70 °C, 3 h, CO<sub>2</sub>, 2 mol dm<sup>-3</sup> HCl (80%); ii, LiNPr<sub>2</sub> (2.0 equiv.)-THF, -78 °C, **13** (>95%); iii, *p*-TsOH-CHCl<sub>3</sub> then Bu<sup>t</sup>COCl-CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>3</sub>N (87%)

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