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EFFICIENT AND CONVENIENT PYRIDINE RING-E FORMATION OF THE CYTOTOXIC MARINE ALKALOID ASCIDIDEMIN AND RELATED ANALOGUES.

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Abstract Conversion of tetracyclic quinone **1** to the cytotoxic pentacyclic alkaloid ascididemin (**2**) in 80% yield is achieved by reaction with paraformaldehyde and ammonium chloride in refluxing acetic acid. High yielding annelations are also observed for the related analogues N-8 deaza ascididemin (**3**) and kuanoniamine A (**4**).

Pyridoacridine and pyridoacridone-based marine alkaloids are of interest to both chemists and pharmacologists - the selectively functionalised polycyclic structures are a challenge to the synthetic chemist, and their widely varied biological activities against such clinically useful targets as pathogenic fungi, virii and human tumours makes them of intense interest to pharmacologists.[1] A major hindrance to the exploitation of such marine natural products however is usually their limited supply from natural sources, and so efficient syntheses are required.

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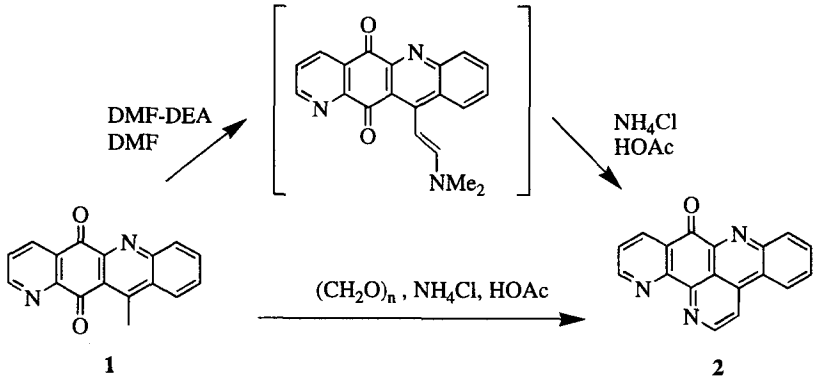
We have recently begun a study of the pharmacological uses of ascididemin (**2**), one of the first pyridoacridone alkaloids, originally isolated from a *Didemnum* species ascidian.[2] Whilst other groups have paid attention to the potential antileukaemic activity of the compound,[3] we have been interested in the ability of the compound to act as a molecular probe to study the mechanism of function of human topoisomerase IIα enzyme, and to exhibit cytotoxicity to human solid tumours.[4] Our initial *in vitro* evaluation of **2** has indicated promising tumour cell type selectivity, but in order to supply the requisite multigram quantities for *in vivo* testing, an optimised synthesis was required.

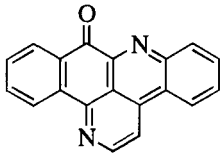


1 **2**

The most generally applicable procedure reported to-date for the synthesis of ascididemin and related ring-A modified alkaloids is Bracher's methodology which achieves a final ring-E annelation (i.e. **1** to **2**) using dimethylformamide-diethylacetal in DMF under nitrogen to form an enamine, which is then cyclised to the pentacyclic product with ammonium chloride in acetic acid.[5] This two-step,

one-pot procedure is the lowest yielding step (59%) in the synthesis of ascididemin.

We now report that this final ring-E annelation can also be achieved conveniently and cost-effectively in a one-step procedure by reaction of quinone **1** with paraformaldehyde and ammonium chloride in refluxing acetic acid. Workup and chromatography affords ascididemin (**2**) in 80% yield from **1**.



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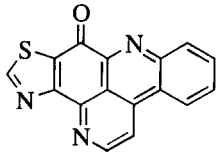

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We have also used this method to synthesise the structurally related alkaloids N-8 deaza ascididemin (benzo[4,5]sampangine) (**3**) and kuanoniamine A (**4**) from their corresponding tetracyclic quinone precursors in yields of 99% (vs. 56%) [6] and 80% (vs. 47%) [7, 8] respectively.

Alkaloids **2**, **3** and **4** were found to exhibit *in vitro* cytotoxicity towards the human colon tumour cell line HCT116, with IC_{50} values of 0.3, 74[9] and 0.03 μM, and the murine leukaemia cell line P388 with IC_{50} values of 0.4, 1.6 and 0.4 μM respectively. The structurally related pyridoacridine alkaloid dercitin has been reported to possess both cytotoxic and antiviral properties.[10] We now report that of **2**, **3** and **4**, only **3** was found to inhibit virii (Herpes simplex type 1 (ATCC VR 733) (no detectable toxicity to viral host (BSC-1 African Green Monkey kidney)

cells, complete viral inhibition at 80 μg/well), Polio virus type 1 (Pfiser vaccine strain) (no detectable toxicity, partial viral inhibition at 80 μg/well) and HIV-1 (maximum protection of 46% at 0.7 μM, IC_{50} 10 μM)).

We are currently employing the synthetic methodology presented here to incorporate ^{14}C-label into **2** to facilitate biological tracer studies.

Experimental

General procedure: Tetracyclic quinone (0.4 mmol) and ammonium chloride (12 mmol) in acetic acid (30 mL) are stirred at 70°C while paraformaldehyde (2 mmol) in acetic acid (10 mL) is added dropwise over 1 minute. The suspension is then gently refluxed under nitrogen for 30 - 45 min., during which time the reaction colour changes from brown to green (for **3**) or purple (for **2** and **4**). After cooling, the reaction mixture is poured into water, made basic with NH_3 (aq) and extracted with CH_2Cl_2. The organic extracts are washed with water, dried with anhydrous $MgSO_4$ and solvent removed under reduced pressure. Final purification is achieved by column chromatography on silica gel using CH_2Cl_2-CH_3OH solvent mixtures. The products obtained (**2**, **3** and **4**[11]) were identical in all respects (TLC, ^1H and ^{13}C NMR, MS) to samples synthesised using Bracher's method.

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(University of Canterbury) and the NCI (USA) for cytotoxicity and antiviral determinations and Professor P. J. Scheuer for helpful discussions.

References and Notes

1. Molinski, T.F. *Chem. Rev.* **1993**, *93*, 1825.

2. Kobayashi, J., Cheng, J.-F., Nakamura, H., Ohizumi, Y., Hirata, Y., Sasaki, T., Ohta, T., Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 1177.

3. Bonnard, I., Bontemps, N., Lahmy, S., Banaigs, B., Combaut, G., Francisco, C., Colson, P., Houssier, C., Waring, M.J., Bailly, C. *Anti-cancer Drug Design* **1995**, *10*, 333.

4. Lindsay, B.S., Barrows, L.R., Copp, B.R. *Bio. Med. Chem. Lett.* **1995**, *5*, 739.

5. Bracher, F. *Heterocycles* **1989**, *29*, 2093.

6. Peterson, J.R., Zjawiony, J.K., Liu, S., Hufford, C.D., Clark, A.M., Rogers, R.D. *J. Med. Chem.* **1992**, *35*, 4069.

7. Carroll, A.R., Scheuer, P.J. *J. Org. Chem.* **1990**, *55*, 4426.

8. Kitahara, Y., Nakahara, S., Yonezawa, T., Nagatsu, M., Kubo, A. *Heterocycles* **1993**, *36*, 943.

9. We have previously reported **3** to have an HCT116 IC_{50} value of >350 μM.[4] Repeated testing on freshly prepared material has shown the correct value to be 74 μM.

10. Gunawardana, G.P., Kohmoto, S., Gunasekera, S.P., McConnell, O.J., Koehn, F.E. *J. Am. Chem. Soc.* **1988**, *110*, 4856.

11. The ^{1}H NMR data observed for our synthetically derived sample of kuanoniamine A (**4**) agreed well with the data previously reported by Kitahara *et al.* for synthesised **4**.[8] However, these data were consistently 0.4 ppm upfield from the ^{1}H NMR data reported by Carroll and Scheuer for the naturally occurring alkaloid, despite being recorded in the same (d_6-DMSO + TMS) solvent system.[7] Interestingly, we found complete agreement between ^{13}C NMR data acquired for our synthetic sample of **4** versus the data reported for the natural product, perhaps suggesting incorrect referencing of the natural product ^{1}H NMR data. mp 258 - 260°C (decomp.) (lit.[7] 255 - 258°C (decomp.)). MS: *m/z* (%) 289 ($M^{+\bullet}$, 92). High resolution EIMS calcd. for $C_{16}H_7N_3OS$ *m/z* 289.0310, found 289.0311. ^{1}H-NMR: (DMSO-d_6 with TMS, 400 MHz), δ 8.06 (1H, td, *J* = 7.9, 1.4, H-5), 8.11 (1H, td, *J* = 8.5, 1.4, H-6), 8.47 (1H, d, *J* = 8.5, H-7), 8.92 (1H, d, *J* = 5.8, H-3), 9.04 (1H, d, *J* = 7.9, H-4), 9.15 (1H, d, *J* = 5.7, H-2), 9.72 (1H, s, H-11). ^{13}C-NMR: (^{1}H-coupled, DMSO-d_6 with TMS, 100 MHz), δ 116.54 (obscured, C-12c), 117.23 (dd, *J* = 167, 9, C-3), 123.01 (m, C-3b), 124.03 (ddd, *J* = 163, 7, 2, C-4), 130.97 (dd, *J* = 163, 8, C-5), 131.93 (dd, *J* = 163, 6, C-6), 131.98 (dd, *J* = 163, 8, C-7), 136.03 (d, *J* = 2.4, C-9a), 137.16 (m, C-3a), 144.83 (ddd, *J* = 8, 8, 2, C-7a), 147.06 (d, *J* = 11.2, C-12b), 147.20 (s, C-8a), 148.98 (dd, *J* = 181, 4, C-2), 157.79 (d, *J* = 14.4, C-12a), 162.69 (d, *J* = 217, C-11), 176.12 (s, C-9).

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