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Synthesis of 1,2,3,4-Tetrahydroascididemin

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Abstract. 1,2,3,4-Tetrahydroascididemin was synthesized in six steps from 2-nitro-3,6-dimethoxyacetophenone. The core linear tetracyclic pyrido[2,3-*b*]acridine system (**6**) was prepared through combination of a Friedländer reaction and an hetero Diels-Alder cycloaddition as the key steps, and the fifth ring was created using a tandem Mannich reaction-intramolecular imine formation. 1,2,3,4-Tetrahydroascididemin showed excellent *in vitro* antitumour activity, which was particularly selective for the human non-small cell lung cancer cell line (A-549).

There is currently a growing interest in marine organisms as a source of new bioactive compounds. One of the most interesting and novel groups of compounds of marine origin is the family of polycyclic aromatic alkaloids derived from the pyrido[*kl*]acridine skeleton, which have been isolated from sponges or tunicates.[1] These marine alkaloids exhibit very interesting biological properties, including excellent antitumour activities,[2] but they are normally isolated in minute amounts and are not readily available. These factors have precluded their systematic study. Ascididemin[3] is one of the most interesting pyridoacridine alkaloids from the point of view of its cytotoxicity. It exhibits an excellent *in vitro* antitumour activity,[4] and has been shown to inhibit topoisomerase II at a 30 μM concentration.[2a] In an effort to contribute to the study of structure-activity relationships in this area, we describe the synthesis and *in vitro* antitumour activity of 1,2,3,4-tetrahydroascididemin **1** and its synthetic intermediates.

Our route to **1** is based on the combination of the Friedländer and hetero Diels-Alder reactions for the construction of the pyridine rings (Scheme 1). 2-Nitro-3,6-dimethoxyacetophenone **2**[5] was reduced to the corresponding aminoketone in 99 % yield by treatment with iron in acetic acid and a catalytic amount of hydrochloric acid. Treatment of this amine with a slight deficiency of bromine resulted in a selective bromination at C-5, affording compound **3** in 62 % yield. A Friedländer reaction of **3** with cyclohexanone under Fehnel conditions[6] gave a quantitative yield of the acridine **4**, which was transformed into bromoquinone **5** by oxidative demethylation with cerium ammonium nitrate. A hetero Diels-Alder reaction between **5** and acrolein dimethylhydrazone[7] yielded the tetracyclic pyrido[2,3-*b*]acridine derivative **6** in 78 % yield. Creation of the fifth ring was achieved in 14 % yield through a Mannich reaction of the activated methyl group of compound **6**, followed by intramolecular cyclization.[4] The low yield was partially due to a competing Mannich reaction at the methylene group adjacent to the acridine nitrogen in compound **6**, followed by elimination.

The antitumour activity of compounds **1** and **6** was studied on murine limphoma (P-388), human non-small cell lung carcinoma (A-549), human colon carcinoma (HT-29) and human melanoma (MEL-28) cell lines (Table 1). The pentacyclic compound **1** exhibited excellent activity and selectivity towards the A-549 cell line. Comparison between the antitumour activities of **1** and ascididemin was hampered by the fact that literature data

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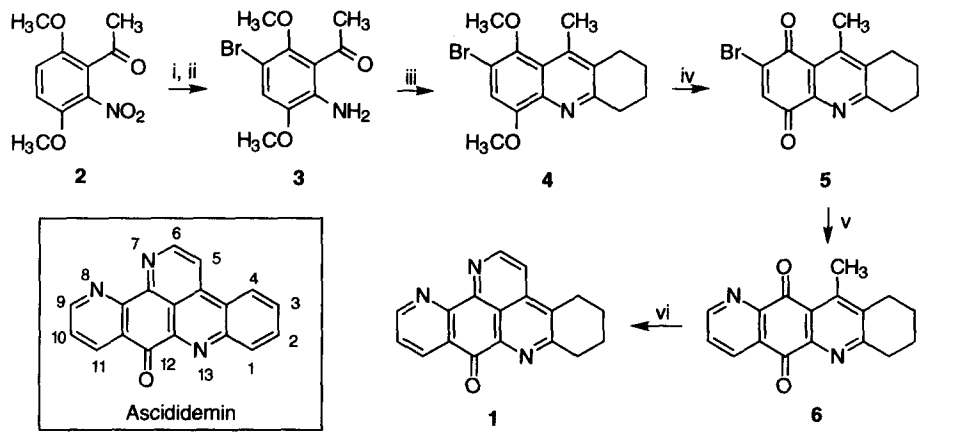
for the natural product have been obtained on different cell lines, but our data suggest that both compounds have similar activities.



Reagents and conditions. i. Fe, HCl, AcOH, reflux, 30 min (99%). ii. Br_2 (0.9 eq.), Et_2O-$CHCl_3$, r.t., 15 min (62%). iii. Cyclohexanone, AcOH, cat. H_2SO_4, reflux, 2 h (100%). iv. $Ce(NH_4)_2(NO)_6$, CH_3CN-H_2O, r.t., 1 h (98%). v. Acrolein dimethylhydrazone, CH_3CN, r.t., 18 h (79%). vi. $(CH_2O)_n$, NH_4Cl, AcOH, 110 °C, 90 min (14%).

Scheme 1

Table 1.- Antitumour activities (IC_{50}, μM) of compounds **1** and **6**

Compound	P-388	A-549	HT-29	MEL-28
1	1.74	0.04	0.3	0.17
6	> 35.9	4.5	18.0	18.0
Ascididemin	0.4[4,8]		0.3*	

* Obtained on the related HCT-116 cell line (reference 4)

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