Total synthesis of (±)-aglaiastatin, a novel bioactive alkaloid

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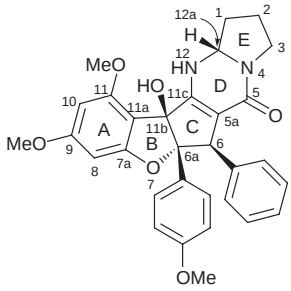
The first total synthesis of aglaiastatin has been accomplished using pyrrolopyrimidinone construction by simultaneous nucleophilic attack of a nitrogen unit at the carbonyl group and the acyl iminium ion.

We recently isolated aglaiastatin **1**, a novel alkaloid, from the leaves of the tropical plant *Aglaia odorata*; it acts as an agent that induces normal morphology in K-*ras*-transformed fibroblasts.[1] It was shown to be a specific inhibitor of protein synthesis, and the alkaloid displayed potent growth inhibition against various tumor cell lines (*e.g.* IC_{50} value for K-*ras*-NRK cells: 1.67 ng ml^{-1}).

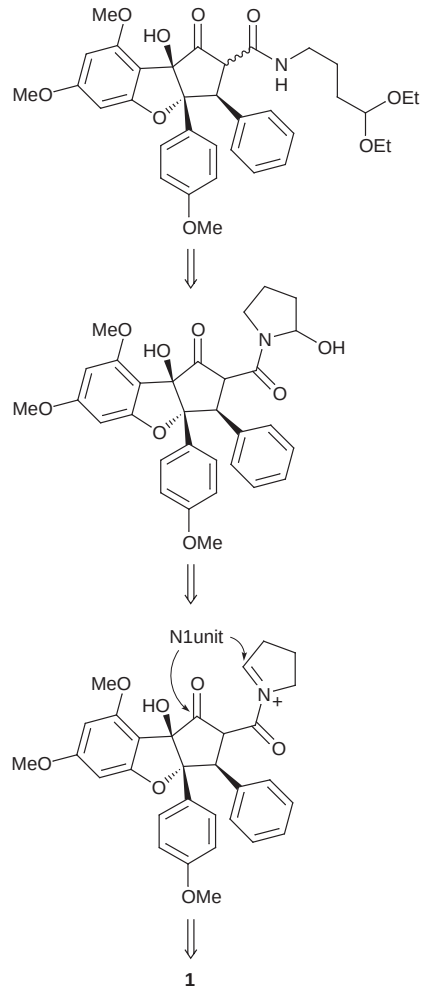


aglaiastatin **1**

Aglaiastatin consists of five fused rings (indicated as A, B, C, D, and E rings for convenience). Related benzofurocyclopentane systems (rings ABC) can be seen in the structures of other natural products such as rocaglamide,[2] and rocaglaol,[3] however, the five-ring system in **1** is rare and has not been reported, except in the case of an unnamed alkaloid.[4] Rocaglamide has been synthesized,[5] but aglaiastatin and the unnamed compound containing the pyrrolopyrimidinone system have never been synthesized.

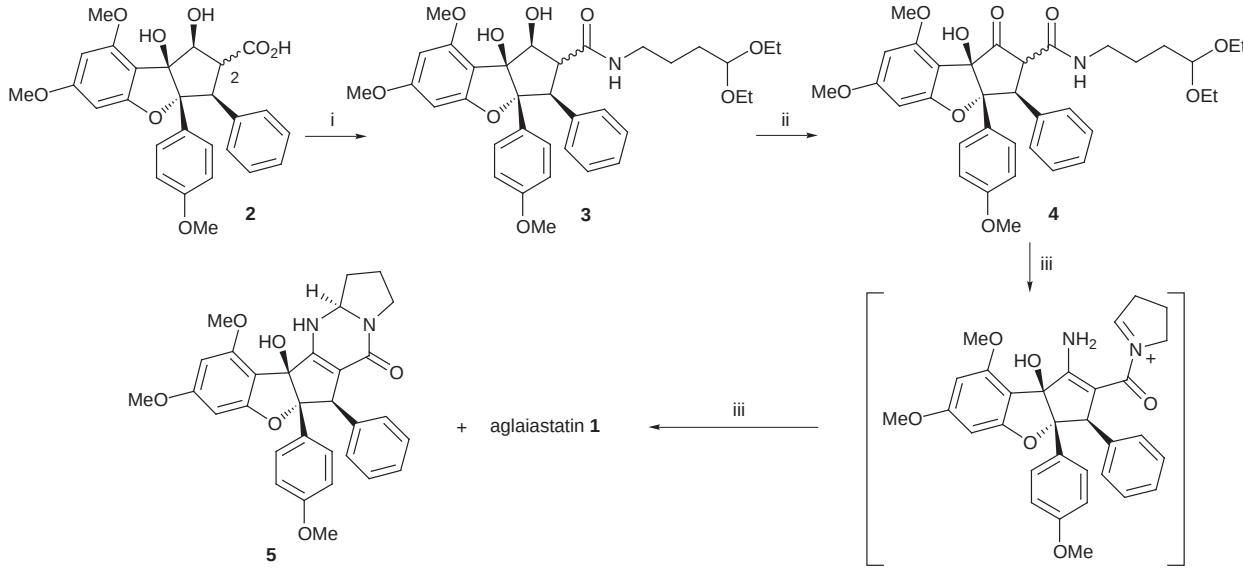
Since construction of the ABC ring system had already been reported by several groups, development of methodology to construct the CDE ring system was the most challenging task. For the synthesis of aglaiastatin, an ABC ring system with a side chain at the C-5a position as a DE ring precursor was expected to be a promising intermediate for this synthesis. Starting from this substance, E ring formation and subsequent closure of the D ring could afford aglaiastatin. We anticipated that these reaction steps to form the DE ring system could be performed in one synthetic operation. Scheme 1 shows our strategy for the synthesis. At first, we planned to introduce a protected aminobutyraldehyde into the ABC ring prepared according to the reported procedure.[5b] Hydrolysis of the acetal should cause nucleophilic addition of the amide nitrogen to the aldehyde to afford the desired five-membered ring corresponding to the E ring. We anticipated that an acyl iminium ion should be generated by dehydration under acidic conditions. With this compound thus accessible, simultaneous nucleophilic addition of one nitrogen unit to two electrophilic groups, the ketone on the C ring and the acyl iminium moiety on the E ring, would form the D ring. Use of an ammonium salt as the one nitrogen unit for double nucleophilic reaction has been reported in some synthetic studies.[6]

Scheme 2 shows the protocol for the synthesis, which was begun by a coupling between commercially available 4-aminobutyraldehyde diethyl acetal and carboxylic acid **2** by use of the BOP [benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate] reagent[7] to give amide **3** in excellent yield. Starting material **2** (racemic form) is an intermediate formed in Taylor's procedure for the total synthesis of rocaglamide[5b] and was prepared as an epimeric mixture at the C-2 carboxy group ($\alpha:\beta$ = 55:45). The subsequent oxidation step was unexpectedly problematic. Swern oxidation and Dess–Martin oxidation of **3** could not afford the desired ketone **4** reproducibly. Then, we turned our attention to SO_3·pyridine oxidation.[8] However, the reaction rate under the standard procedure was very sluggish. After optimization of the reaction



1

Scheme 1



Scheme 2 *Reagents and conditions*: i, $H_2N(CH_2)_3CH(OEt)_2$, BOP reagent, Et_3N, room temp., CH_2Cl_2, 95%; ii, SO_3·pyridine, Et_3N, room temp., DMSO, 97%; iii, 1 M HCl, THF, then HCO_2H, HCO_2NH_4, room temp., MeOH, 70% for two steps (**1** : **5** = 2 : 1). The yield of **1** and **5** after chromatographic separation was 40 and 19%, respectively.

conditions, the use of a large excess of reagent finally gave satisfactory results. When the reaction was conducted for 1 h using 30 equiv. of SO_3·pyridine, the required ketone **4** was obtained in 97% yield. Prolonged reaction time or heating resulted in contaminating by-products. Although the α : β distribution about the amide group at C-2 varied in every trial, the β isomer was obtained predominantly. For the final pyrrolopyrimidinone formation, hydrolysis of the acetal with HCl and concomitant cyclization would have given the *N*-acyl hydroxypyrrolidine intermediate (not isolated) depicted in Scheme 1. After the usual workup, the crude material was treated with 99% formic acid in the presence of a large excess of ammonium formate (*ca.* 100 equiv.) in MeOH for 4 days. As a consequence, the desired (±)-aglaiastatin was obtained as a mixture of diastereomers at C-12a in high combined yield (70%). Fortunately, aglaiastatin was the predominant product [aglaiastatin (**1**) : diastereomer (**5**) = 2 : 1 determined by ^{1}H NMR]. Selectivity in the formation of **1** *versus* **5** would be explained by nucleophilic attack of the NH_2 group in the convex structure of ABC ring at the downward facing surface of the E ring. The iminium ion would probably be facing upwards due to steric hindrance. These stereoisomers could be easily separated by silica gel column chromatography to give pure **1** and **5** in 40 and 19% yield, respectively. Thus, we accomplished the first total synthesis of (±)-aglaiastatin.

The spectral properties (^{1}H and ^{13}C NMR, FABMS, IR) of the synthetic aglaiastatin, were indistinguishable from those of the natural aglaiastatin, except for optical rotation. Further, optically active aglaiastatin was obtained by separation with semi-preparative scale chiral HPLC (Daicel Chiralpak AD). One of the separated samples of synthetic aglaiastatin showed nearly the same value {$[\alpha]_D^{23}$ + 148.1 (*c* 0.1, MeOH)} as natural aglaiastatin [+151.2 (*c* 0.1, MeOH)]. It also displayed identical growth-inhibitory activity toward K-*ras*-NRK cells (IC_{50} value: 1.49 ng ml^{-1}) to that of the authentic sample (IC_{50} value: 1.67 ng ml^{-1}).

In conclusion, we have accomplished the first total synthesis of the novel protein synthesis inhibitor aglaiastatin. In the process, we developed a new methodology for pyrrolopyrimidinone construction using one nitrogen unit for the ring closure. Attempts to utilize this synthetic scheme for the synthesis of structurally related analogs and enantiomeric synthesis of aglaiastatin are under way.

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Notes and References

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