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A convergent synthesis of the imidazopyridine scaffold of fluorescent alkaloid ageladine A

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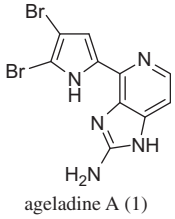
ABSTRACT

A convergent synthesis of the imidazopyridine scaffold of fluorescent alkaloid ageladine A (**1**) has been achieved, employing 3-amino-2-chloropyridine as the staring material. A carboxylic acid was introduced using *n*-butyllithium and dry ice as the key reaction.

Isolation of a fluorescent alkaloid, ageladine A (**1**), from the marine sponge *Agelas nakamurai* was reported by Fusetani and co-workers in 2003 (Fig. 1).[1] The entire structure of ageladine A was elucidated with a detailed two-dimensional (2D) NMR interpretation including COSY and HMBC. Ageladine A also reportedly shows inhibitory activity at micromolar levels against matrix metalloproteinase 2 (MMP-2). MMP-2 is known to be involved in the formation of a complex at the head of the migrating malignant tumor cells.[2] Also, MMP-2 is known to regulate angiogenesis on the surface of endothelial cells.[3] Due to these properties, MMP-2 inhibitors are promising candidates for use as antimetastatic agents as well as antiangiogenic agents, and in fact some are already being tested in clinical trials.[4] The suggested MMP-2 inhibitory mechanism caused by ageladine A can be of significant attention, not forming a zinc complex like common MMP-2 inhibitors. Furthermore, the fluorescent property of ageladine A was discovered, and its utility as a fluorescent bioprobe is suggested.[1] Indeed, with respect to fluorescence-based bioprobe research, a number of advanced studies have been reported, which is a promising indication of the utility of ageladine A.[5]



ageladine A (1)

Figure 1. Structure of ageladine A.

In 2006, Weinreb established the first total synthesis of ageladine A in a 12-step process,[6] and Karuso subsequently reported a shorter version of total synthesis.[7]

Here, the basic strategy for the synthesis of the imidazopyridine scaffold of ageladine A is elucidated in Scheme 1. As the starting material, 3-amino-2-chloropyridine (**2**) was protected by a Boc group. To the resulting Boc-protected aminopyridine **3**, carboxylate was introduced at the 4-position of the pyridine ring as the key reaction. The reaction condition included two steps, deprotonation using *n*-butyllithium and then carboxylation in succession pouring the reaction mixture onto crushed dry ice. Empirically, 3.0 equiv of *n*-butyllithium was needed while our initial attempt recovered about half of the Boc-protected aminopyridine **3** using 1.5 equiv of *n*-butyllithium. It is worth noting that carboxylation was carried out only at the 4-position of the pyridine ring, as far as can be ascertained. This step was established successfully with a good yield and excellent positional selectivity. In order to protect the entire amino moiety, compound **4** was subjected to a condensation reaction with phthalic anhydride after the removal of the Boc protection.[8] The obtained phthalimide-protected carboxylate **5** was converted to **6** with a Boc-protected amino functional group, by Curtius rearrangement with DPPA heated at 140 °C for 2 h and with *t*-BuOH heated at the same temperature overnight.[9] When water was employed instead of *t*-BuOH in the second step, the reaction was not successful, and did not form the expected amine product. Meanwhile, when compound **4** was subjected to the above conditions of Curtius rearrangement, unwanted bicycle of imidazolidinone was generated as the major product. Again, Boc protection of compound **6** was cleaved using TFA, which gave **7** in an almost quantitative yield. The phthalimide portion of **7** was then disconnected by heating at 90 °C for 2 h with 30% CH_3NH_2 in EtOH,[10] which furnished **8** containing two of the free amino groups at the 3- and 4-positions of the pyridine ring. The reaction with a volatile reagent proceeded cleanly and required no tedious work up steps. These diamino sub-

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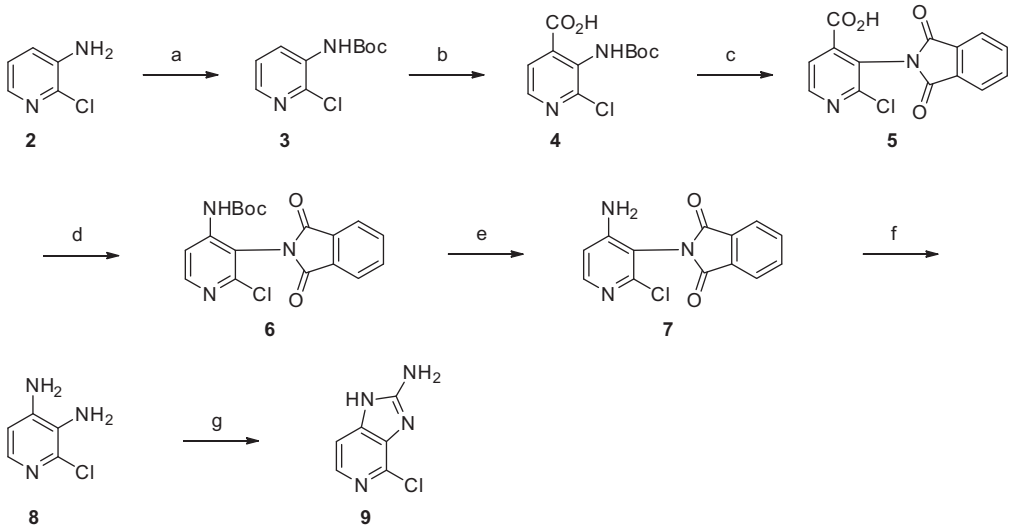

Scheme 1. Synthetic route. Reagents and conditions: (a) Boc_2O, DMAP, CH_2Cl_2, rt, 3 h, 89%; (b) (i) *n*-BuLi, THF, −78 °C, 1 h; (ii) CO_2 excess, 75% in two steps; (c) (i) TFA, CH_2Cl_2, rt, 30 min; (ii) phthalic anhydride, AcOH/TFA (10:1), 140 °C, 24 h, 68% in two steps; (d) (i) DPPA, toluene/1,3-dimethyl-2-imidazolidinone (9:1), 140 °C, 2 h; (ii) *t*-BuOH, 140 °C, overnight, 84% in two steps; (e) TFA, CH_2Cl_2, rt, 30 min, 97%; (f) 30% CH_3NH_2 in EtOH, 90 °C, 2 h, 91%; (g) CNBr, EtOH, rt, 1 h, 83%.

stituents of **8** were finally cyclised using CNBr,[11] which gave the desired product **9** in a good yield of 83%.

In summary, an efficient synthetic sequence for compound **9** was established—the composition of the imidazopyridine scaffold of fluorescent alkaloid ageladine A. Compound **9** possesses a halogen, one of the functional groups for coupling reactions, at the pyrrole ring position of ageladine A. This synthetic approach was designed with versatility in mind to enable structural modifications for an enhancement of characteristic analysis. The short and efficient synthetic route introduced here should promote the versatility of research. Studies of further applications are ongoing.

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