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Total syntheses of (+)-agelastatin A and (+)-agelastatin B through cationic cyclizations

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ABSTRACT

We report concise asymmetric total syntheses of tetracyclic marine alkaloids (+)-agelastatin A and (+)-agelastatin B using a cationic cyclization-based approach, which features straightforward transformations with cost-effective chemicals and reagents.

1. Introduction

Agelastatins belong to the pyrrole-imidazole family of marine alkaloids (Fig. 1).[1] This group of architecturally unusual tetracyclic compounds features a densely functionalized cyclopentane ring bearing four contiguous stereogenic centers substituted with nitrogen functionalities. Of the many fascinating secondary metabolites uncovered in recent years, agelastatins stood out not only for their intriguing chemical structures but also for their exceptional biological activities. For instance, Agelastatin A (**1**, Fig. 1), originally isolated by Pietra and co-workers in 1993,[2] exhibits nanomolar cytotoxicity against a wide range of human cancer cell lines.[3] It also displays selective inhibition of GSK-3β (glycogen synthase kinase-3β) at low concentrations, suggesting its potential role in preventing Alzheimer's disease.[4] In addition, the alkaloid might function as a novel insulin mimetic,[4a] as well as potent insecticide against larvae of beet army worm and corn rootworm.[5] The highly complex heterocyclic framework, biological and pharmacological functions, as well as limited natural supply of agelastatins have prompted substantial interest from synthetic community, leading to various innovative solutions to their total syntheses.[6]

2. Results/Discussion

Intrigued by the synthetic challenge posed by agelastatins, we initiated a program to study the total synthesis of this small group of marine alkaloids in mid-2009. To best of our knowledge, all reported synthetic strategies prior to our study had relied on elaboration of 5-membered carbocyclic intermediates to introduce the required substituents on the densely functionalized cyclopentane ring. We conceived a new strategy which harnesses the intrinsic chemical reactivity of an intermediate **9** to generate the central C ring at the late stage of the synthesis through a cationic cyclization (Scheme 1). Specifically, activation of the hemiaminal **9** with acid would produce a highly electrophilic *N*-acyl iminium ion **8**, which would be quenched by the electron-rich double bond in the imidazolone heterocycle and afford another reactive acyliminium ion **7**.[7] Subsequent substitution reaction with water would convert this cationic intermediate to agelastatin A. We speculated that the key intermediate **9** utilized in this strategy could be readily prepared from lactone **11** through an aminolysis and oxidation sequence. Taken together, our strategy breaks down the complex fused tetracyclic target molecule into a much less complicated bicyclic

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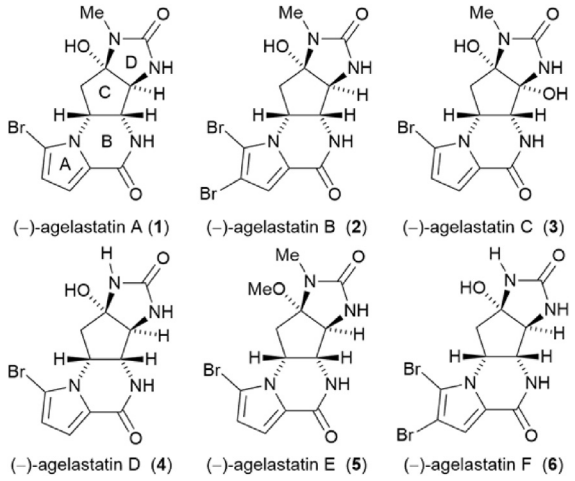
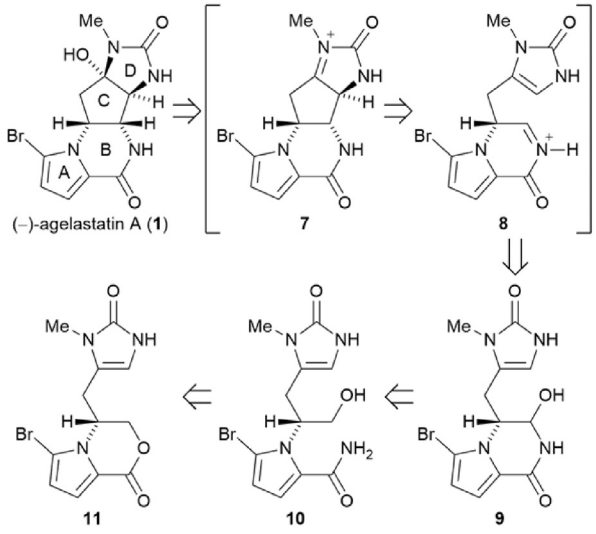


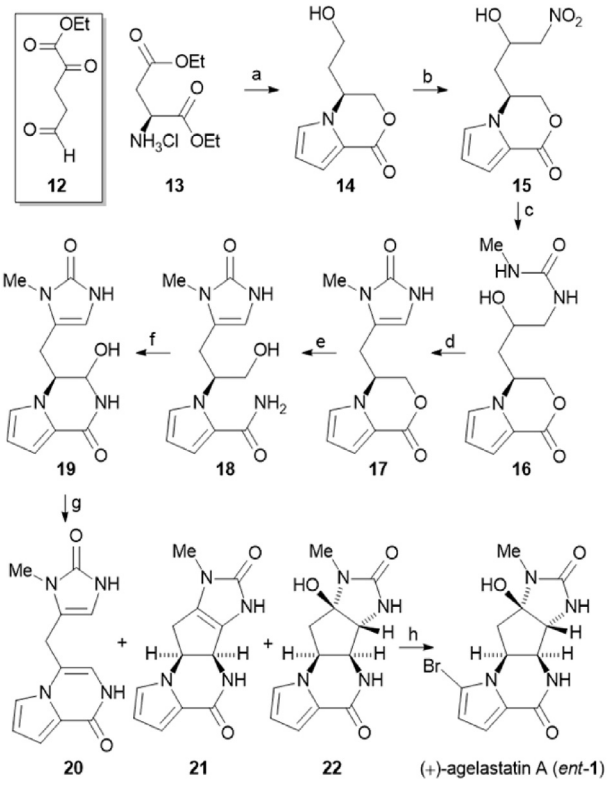
Fig. 1. Structures of agelastatin alkaloids.



Scheme 1. Retrosynthetic analysis of (−)-agelastatin A.

precursor **11** with only one stereogenic center, which could be derived from D-aspartic acid.

To examine the feasibility of our strategy, we pursued a forward synthesis (Scheme 2) starting with the cost-effective HCl salt of L-aspartic acid diethyl ester (**13**, Scheme 2). A facile one-pot reaction converted **13** to lactone **14** in 52% yield. We assume that reduction of the amino ester **13** with $LiAlH_4$ produced amino dialcohol, which underwent a Paal-Knorr pyrrole synthesis[8] upon the treatment of AcOH and **12**.[9] Subsequent addition of concentrated sulfuric acid catalyzed the transesterification to afford the lactone in reasonable yield. The Parikh-Doering oxidation[10] of the alcohol **14** to aldehyde and subsequent Henry reaction[11] in the same pot accomplished the carbon chain elongation with a nitro group in **15**. Further functionalization of the nitro group through a hydrogenation and nucleophilic addition sequence easily generated **16**. Treatment of **16** under a typical Swern oxidation[12] condition successfully drove tandem oxidation, ring closure and elimination to furnish the imidazolone heterocycle in **17**. As we anticipated, aminolysis on the lactone **17** and subsequent Swern oxidation of **18** provided the hemiaminal **19** as a pair of diastereomers. Under the optimal reflux condition in 0.1 N hydrochloric acid, the key intermediate **19** was transformed to the desired product **22** in 29% yield together with



Scheme 2. Total synthesis of (+)-agelastatin A. *Reagents and conditions*: [a] $LiAlH_4$, THF, then AcOH, **12**, H_2SO_4, 52%; [b] SO_3·Py, DMSO, NEt_3, RT, then $MeNO_2$, 85%; [c] H_2, Pd/C, MeOH, RT, then methyl isocyanate, 100%; [d] $(COCl)_2$, DMSO, −78 °C, then NEt_3, -78 °C to RT, 82%; [e] NH_3, MeOH, 40 °C, 90%; [f] $(COCl)_2$, DMSO, −78 °C, then $(i\text{-}Pr)_2NEt$, −78 °C to RT, 85%; [g] 0.1N HCl(aq), reflux, 21% (**20**), 36% (**21**), 29% (**22**); [h] NBS, MeOH, RT, 79% (**22** → *ent*-**1**).

two side products **20** and **21** in 21% and 36% yield, respectively. We speculate that the side product **20** was obtained from **23** due to elimination occurring before the C ring formation (Scheme 3). After the C ring formation, nucleophilic substitution on the cationic intermediate with water produced **22** as the desired product. Meanwhile, a competitive elimination reaction led to the undesired **21** as a side product. Notably, our attempt to convert **21** to **22** by testing a variety of acidic conditions turned out to be fruitless. Nevertheless, by following a well-established bromination procedure,[13] we achieved a total synthesis of (+)-agelastatin A in 8 steps from L-aspartic acid derivative **13**.

While encouraged by the accomplishment of an asymmetric total synthesis of (+)-agelastatin A, we were concerned about the optical purity of the product since it might be eroded by potential epimerization through equilibrium described in Scheme 3. To accurately qualify the optical purity of *ent*-1 using chiral HPLC analysis, we carried out a racemic synthesis of (±)-**22**.

Our synthesis of (±)-**18**, the precursor of (±)-**22**, was illustrated in Scheme 4. This synthetic sequence employed the classic hydrogenation strategy for unnatural amino acid preparation. The unsaturated substrate **27** for hydrogenation was synthesized from aldehyde **25**[14] and phosphonate **26**.[15] Pd/C catalyzed hydrogenation of **27** neatly produced the unnatural amino ester **28** in 95% yield. Treatment of **28** with Na in liquid NH_3 fulfilled both debenzylation and reduction of the ester group to produce the amino alcohol **29** in good yield. The Paal-Knorr pyrrole synthesis using **12** followed by aminolysis smoothly generated (±)-**18**. Applying the reaction conditions for synthesis of **22** described earlier in this study, we were able to convert (±)-**18** to the reference standard (±)-**22**.