

A Short Total Synthesis of the Marine Sponge Pyrrole-2-aminoimidazole Alkaloid ($\pm$)-Agelastatin A**

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Dedicated to Professor Derrick Clive

Agelastatin A (**1**, Figure 1) is the most prevalent congener of the structurally unique subset of pyrrole-2-aminoimidazole (P2AI) alkaloids,^[1] biosynthetically derived from oroidin. It was first isolated by Pietra in 1993 from the axinellid sponge *Agelas dendromorpha*, along with a small, inseparable

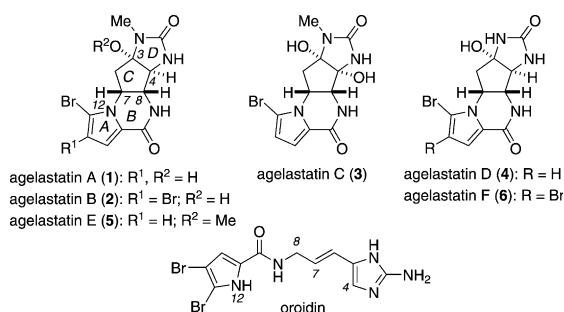


Figure 1. The agelastatins and their biosynthetic precursor oroidin.

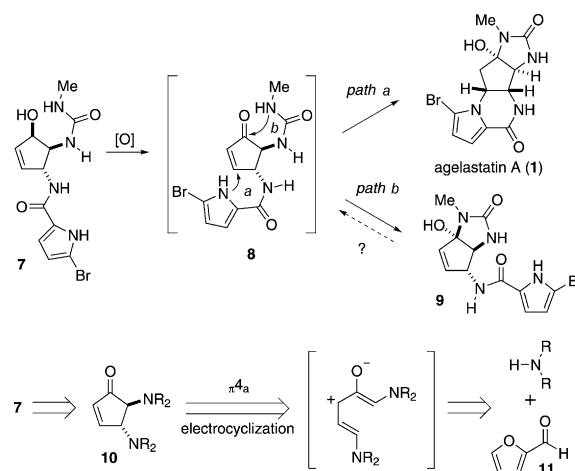
amount of agelastatin B (**2**).^[2] It has since been isolated by Molinski et al. from the sponge *Cymbastela* sp, along with minor metabolites agelastatin C (**3**) and D (**4**),^[3] and by Al-Mourabit et al., who identified two more minor metabolites from *A. dendromorpha*, agelastatin E (**5**) and F (**6**).^[4]

The biological activity of **1** sets it apart from other P2AI alkaloids, with high levels of cytotoxicity reported against a variety of human cancer cell lines,^[5] and a potency between 3–16 times that of cisplatin.^[5b] It also selectively inhibits GSK-3 β ,^[6] which has been implicated in diabetes,^[7] Alzheimer's disease,^[8] and depression.^[9] Perhaps most notably, it down-regulates osteopontin, which, at high levels, has been heavily implicated in the metastasis of cancer cells.^[10] The significant synthetic challenges posed by agelastatin A, comprising a densely functionalized tetracyclic core with four contiguous

C–N stereocenters, a cyclic urea, and a bromopyrrole amide, have resulted in it being the subject of numerous total^[11,12] and formal syntheses,^[13] and other synthetic studies.^[14]

With the exception of the biomimetically inspired approaches,^[11m,n] the reported syntheses of **1** are centered on the formation of the C-ring, correctly stereoconfigured at either the C4 and C8 or C3 and C7 positions, prior to further functionalization. Upon reaching the core however, most approaches closely follow the C-ring elaboration established by the seminal synthesis described by Weinreb and co-workers, requiring lengthy synthetic sequences.^[11a] Although some of the problems raised in this influential first total synthesis of agelastatin A have been addressed in later syntheses, further challenges remain.

Following the general concept of efficiency first codified by Hendrickson,^[15] and more recently elaborated and refined,^[16] our goal was to synthesize agelastatin A in a direct manner,^[17] using a rapid approach to the C-ring followed by a streamlined endgame, relying minimally on protecting group strategies. We envisaged a domino oxidation/aza-Michael addition/hemiaminal formation from alcohol **7**. Such an approach to **1** has not been investigated before, but necessitates that aza-Michael addition (path a) occurs from **8** in preference to hemiaminal formation (path b) (Scheme 1). Previous syntheses have relied upon protecting group strategies to achieve this selectivity.^[11] Alcohol **7** itself could be viewed as an elaborated derivative of *trans*-4,5-diaminocyclopentenone **10**, with the amino functional groups differentiated into the N3 urea and N9 amide of **1**.



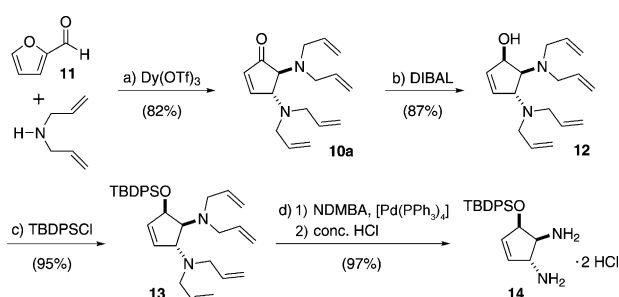
Scheme 1. Electrocyclization/aza-Michael based route to **1**.

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Previous studies have shown **10** to be readily accessed in good to excellent yields and d.r. values from the Lewis acid catalyzed reaction of 2-furaldehyde (**11**) with secondary amines.^[18] This remarkable rearrangement proceeds through a domino condensation/ring-opening/Nazarov like conrotatory π_4a electrocyclization reaction pathway (Scheme 1). Unfortunately, attempts to synthesize **10** ($\text{NR}_2 = \text{NH}_2$) with NH_3 or ammonia equivalents (such as carbamates, amides, hydrazines, and hydroxylamines) under a variety of reaction conditions were unsuccessful. After screening the reaction of **11** with several secondary aliphatic amines, incorporating known alkyl-based nitrogen protecting groups, and evaluating for the efficiency of the subsequent deprotection, it was determined that the bis(diallyl) system was the most effective. Thus, the reaction of **11** with diallylamine (2 equiv) and $\text{Dy}(\text{OTf})_3$ ^[19] (2 mol %; Tf = Trifluoromethanesulfonyl) gave enone **10a** in 82 % yield (d.r. $\geq 95:5$; Scheme 2). The electro-



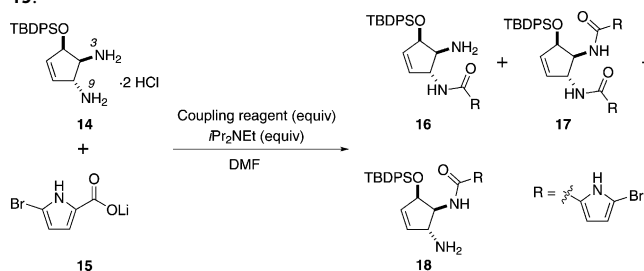
Scheme 2. Synthesis of diammonium salt **14** as an agelastatin core. a) $\text{Dy}(\text{OTf})_3$ (2 mol %), 4 Å MS, acetonitrile, 16 h, 82 %. b) DIBAL (1.4 equiv), toluene, -78°C , 1 h, 87 %. c) TBDPSCl (1.1 equiv), imidazole (2.0 equiv), CH_2Cl_2 , 5.5 h, 95 %. d) 1) NDMBA (4.0 equiv), $[\text{Pd}(\text{PPh}_3)_4]$ (8.5 mol %), CH_2Cl_2 , 45°C , 3.5 h; 2) conc. HCl (2.2 equiv), 1 h, 95 %. TBDPS = *tert*-butyldiphenylsilyl, DIBAL = diisobutylaluminum hydride, MS = Molecular sieves, NDMBA = *N,N'*-dimethylbarbituric acid.

philicity of enone **10a** was problematic for subsequent transformations, but was eliminated through stereoselective reduction to allylic alcohol **12** (d.r. = 92:8). Subsequent silylation gave **13**, which could be fully deallylated to **14** using a modification of the conditions of Guibé and co-workers.^[20] Although deallylation could be carried out directly on **12** in similar yields, the hygroscopicity of the resulting diammonium salt made its isolation, handling, and storage difficult. Conversely, **14** proved easy to handle and was stored for 11 months under argon without any notable increase in water content. This high-yielding four-step approach provided access to the agelastatin A core **14** on a multi-gram scale from readily available (< \$0.20 g) starting materials.

To address the challenge of converting **14** into alcohol **7**, the *trans*-diamine functional groups must be differentially functionalized. Although perhaps the simplest strategy would involve a *syn* 1,2-protection of the amino alcohol, we opted to avoid further protecting group chemistry and instead chose to rely on the steric encumbrance of the *tert*-butyldiphenylsilyl (TBDPS) group to accomplish direct acylation at N9 over N3. This would ideally be achieved by coupling either the

corresponding acid or acid chloride of 5-bromopyrrole to **14**. Unfortunately, these compounds are very unstable,^[21,22] and consequently many approaches to **1** require the coupling of an unsubstituted pyrrole and a subsequent bromination of debromoagelastatin A.^[11a-d,f-i,k,l] Lithium carboxylate salt **15**^[11a] is, however, known to be a stable bromopyrrole derivative. Although there are no general methods for direct amide coupling of alkali carboxylate salts without relying on acid addition^[23] or the in situ formation of an acid chloride,^[24] we envisaged the direct use of **15** for the amide bond formation. Such a direct carboxylate salt coupling would not only avoid a late stage bromination, but the presence of the electron-withdrawing bromine substituent would assist in the aza-Michael addition by lowering the $\text{p}K_a$ of N-H.^[25] Preliminary studies revealed a small number of coupling reagents^[26] that showed adequate reactivity for the coupling of **15** with **14** by limiting unproductive symmetrical anhydride formation, which proved quite problematic in a number of cases (Table 1).^[27] Among these, 2-(2-pyridon-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) gave the best selectivity for the formation of N9-acylated **16** over either diacylated **17** or N3-acylated **18** (entry 9). Further optimization of the base, temperature, time, and stoichiometry allowed for the isolation of bromopyrrole amide **16** in 54 % yield,

Table 1: Selective acylation of **14** with lithium bromopyrrole carboxylate **15**.

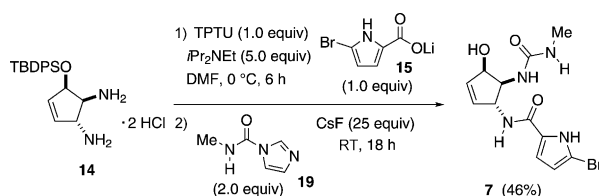


Entry	15 and reagent (equiv)	<i>i</i> Pr ₂ NEt [equiv]	<i>T</i> [°C]	<i>t</i> [h]	14:16:17:18 ^[a]
1	PyBOP (1.0)	10.0	RT	14	23:47:11:19
2 ^[b]	MNBA (1.2)	10.0	RT	14	26:37:16:21
3 ^[c]	Yamaguchi (1.0)	5.0	RT	18	50:32:0:18
4	BOP-Cl (1.0)	5.0	RT	6	100:0:0:0
5	PyBrOP (1.0)	5.0	RT	21	100:0:0:0
6	CDI (1.0)	—	RT	5	decomposition
7	HBTU (1.0)	5.0	RT	15.5	13:57:17:13
8	TDBTU (1.0)	5.0	RT	15.5	13:54:20:13
9	TPTU (1.0)	5.0	RT	15.5	19:57:11:12
10 ^[d]	TPTU (1.0)	5.0	0	7.5	16:60(54):16(12):8

[a] Ratios determined by ¹H NMR analysis of the crude reaction mixtures. [b] DMAP (10 mol %) added to the reaction. [c] DMAP (60 mol %) added to the reaction. [d] Yields of isolated products are given in parentheses. BOP-Cl = *N,N'*-bis(2-oxo-3-oxazolidinyl)phosphonic chloride, CDI = 1,1'-carbonyldiimidazole, HBTU = *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, MNBA = 2-methyl-6-nitrobenzoic anhydride, PyBOP = benzotriazol-1-yloxytri(pyrrolidino)phosphonium hexafluorophosphate, PyBrOP = bromotri(pyrrolidino)phosphonium hexafluorophosphate, TDBTU = 2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

along with a 12% yield of diacylated **17** (entry 10).^[28] Efforts to further limit diacylation through the slow addition of carboxylate **15** or the corresponding preformed activated ester proved ineffective.

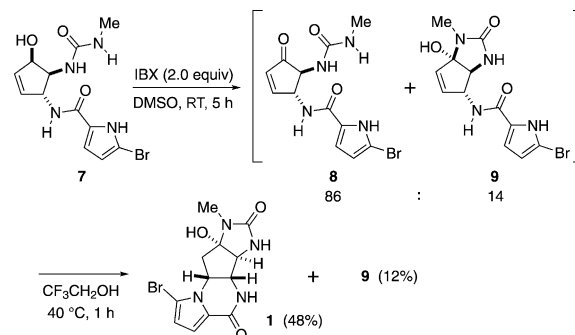
The *N*-methyl urea moiety of **7** could be accessed using methyl isocyanate (MIC), however its toxicity, coupled with the large excess generally required in similar systems,^[11a,d,f] led us to explore alternatives. An *N*-protected derivative could be used in the form of a carbamoyl chloride or similar reagent, however this approach would require an additional deprotection step, which only gives moderate yields in many related systems.^[11c,i,j] Existing MIC substitutes^[29] exhibit various drawbacks related to their syntheses and use. To overcome these issues, a new carbamoylimidazole-based equivalent **19** was developed, which has proven to be effective for the synthesis of *N*-methyl ureas and is available as a conveniently handled water-stable crystalline solid.^[30] Treatment of amide **16** with **19** gave the corresponding *N*-methyl urea with complete conversion by ¹H NMR analysis. In a more efficient approach however, **19** could be added in a one-pot fashion after amide coupling of diammonium salt **14** with the salt **15**. Furthermore, as **19** displays excellent chemoselectivity for the reaction with amines in the presence of alcohols,^[30] desilylation could in principle be carried out concurrently. This effectively eliminates a concession step^[16e] and decreases the impact of the TBDPS group on the synthesis. Thus, one-pot conversion of **14** into **7** was achieved through sequential TPTU-mediated coupling of **15** followed by the addition of **19** and CsF^[31] in 46% yield (Scheme 3).^[32] This not only allowed for the direct formation of pre-Agelastatin A **7** in only five steps from commercially available precursors, but also introduced the key bromopyrrole moiety directly, without relying on a late-stage bromination.^[11]



Scheme 3. One-pot synthesis of alcohol **7** from diammonium hydrochloride salt **14**.

The oxidative cyclization of **7** into agelastatin A requires that either cyclization of the intermediate enone **8** to the hemiaminal **9** occurs more slowly than aza-Michael cyclization^[33] to **1**, or that equilibration of **8** and **9** occurs under the reaction conditions (Scheme 1). Attempts to achieve equilibration under basic oxidizing conditions, such as those of the Swern reaction, were hampered by the poor solubility of **7**, whereas related reactions that allow for the use of dimethylsulfoxide (DMSO) as a solvent at higher temperatures proved unsuccessful. A screen of various oxidation reagents and conditions revealed *o*-iodoxybenzoic acid (IBX) to be the most effective. On monitoring the IBX oxidation of **7** by ¹H NMR spectroscopy in [D₆]DMSO however, it was observed that cyclization of **8** to **9** was slow, with the enone

favoured by a ratio of 86:14 upon consumption of **7** (Scheme 4). Concentration of the reaction mixture followed by dissolution in MeOH resulted in hemiaminal formation, confirming **9** as the thermodynamic product.^[34] The addition



Scheme 4. Synthesis of agelastatin A (**1**) through a one-pot oxidation/aza-Michael addition/hemiaminal formation reaction.

of *i*Pr₂NEt after oxidation in a one-pot fashion resulted in conversion of **8** into **1**, although decomposition resulted in a low yield of isolated product (22%). The ratio of **9** to a combination of **8**, **1**, and other intermediates remained constant at approximately 14%, suggesting that **9** and **8** do not equilibrate under the reaction conditions. However, the addition of trifluoroethanol after oxidation, with mild heating, resulted in the conversion of **8** into **1** in 48% yield (Scheme 4). Treatment of hemiaminal **9** under the reaction conditions did not lead to formation of **1**.

In summary, (±)-agelastatin A (**1**) has been synthesized in only six manipulations in 15% overall yield from inexpensive and readily available precursors. This was accomplished through the use of a condensation/ring-opening/electrocyclization domino reaction, the development of an alkali metal carboxylate amide coupling method, a crystalline water-stable MIC substitute, and a one-pot oxidation/aza-Michael addition/hemiaminal cyclization reaction. A TBDPS group serves the dual role of reducing the hygroscopicity of a key intermediate and acting as a directing group. Using these key reactions, while limiting protecting group chemistry, has resulted in the shortest route to **1** reported to date.

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- [32] The desilylated derivative of **17**, bis(dibromopyrrole amide) alcohol **20**, was also isolated from this reaction in 10% yield. See the Supporting Information.
- [33] A related aza-Michael addition of a reactive intermediate was attempted by Reyes and Romo in their agelastatin A synthesis before ultimately isolating **9** and converting it into the natural product by heating with silica gel. See reference [11n].
- [34] Although enone **8** could not be isolated, its identity was supported by comparing ¹H NMR data of the oxidation reaction mixture to that of related isolated compounds. See the Supporting Information.
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