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A Stereodivergent Strategy to Both Product Enantiomers from the Same Enantiomer of a Stereoinducing Catalyst: Agelastatin A

Barry M. Trost* and Guangbin Dong[a]

Abstract: In this article, we report a full account of our recent development of pyrroles and *N*-alkoxyamides as new classes of nucleophiles for palladium-catalyzed AAA reactions, along with application of these methodologies in the total synthesis of agelastatin A, a marine natural product with exceptional anticancer activity and other biological properties. Our method allows for access to either regioisomer of the pyrrolopiperazinones (**6** and **19**) with high efficiency and enantioselectivity. Note that isomer **19** was obtained via a cascade reaction through a double allylic alkylation pathway. From regioisomer **6**, the total synthesis of (+)-agelastatin A was completed in a very short fashion (four steps from **6**), during the course of which we developed a new copper catalyst for aziridination and an $In(OTf)_3$/DMSO system to oxidatively open an *N*-tosyl aziridine. Starting with the other pyrrolopiperazinone **19**, a five-step sequence has been developed to furnish a formal total synthesis of (−)-agelastatin A. A unique feature of our syntheses is the use of two rather different strategies for the total syntheses of both enantiomers of agelastatin A using the same enantiomer of a chiral palladium catalyst.

Keywords: alkaloids · antitumor agents · asymmetric catalysis · pyrrole · total synthesis

Introduction

During the last several decades, asymmetric catalysis has dramatically improved the synthetic efficiency of producing biologically important molecules. Among various catalytic asymmetric methods, metal-catalyzed asymmetric allylic alkylation (AAA) constitutes an incredibly feasible reaction, largely attributed to its broad substrate scope and its capability to asymmetrically form different bonds, including carbon–carbon, carbon–oxygen, carbon–nitrogen, and carbon–sulfur bonds.[1] For those AAA reactions, however, the scope of the potential nucleophiles is still unknown. Recently, due to the increased medicinal significance of nitrogen containing bioactive molecules,[2] especially those with a bromopyrrole moiety[3] such as the agelastatins (Figure 1), we began to explore pyrroles and *N*-alkoxyamides as nucleophiles in AAA reactions. In this article, we report a full account of our recent development of Pd-catalyzed pyrrole- and *N*-alkoxyamide-based AAA reactions, along with a detailed description of our enantioselective total synthesis of both (+) and (−) agelastatin A via two rather different strategies that rely on the use of the same enantiomer of a chiral palladium catalyst.

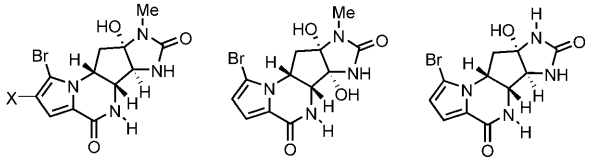

Figure 1. Agelastatin A–D.

Agelastatins A–D, which possess a highly fused tetracyclic ring structure, comprise a family of oroidin alkaloids. Agelastatin A (**1**) along with agelastatin B (**2**), were first isolated in 1993 by Pietra et al. from a deep water marine sponge *Agelas dendromorpha* collected in the Coral Sea near New Caledonia.[4] Later in 1998, agelastatin C (**3**) and D (**4**) were isolated from the West Australia sponge *Cymbastela* sp. by Molinski and co-workers.[5] The agelastatins exhibit exceptional biological activities; most notable of these is their nanomolar activity against a broad range of cancer cell lines

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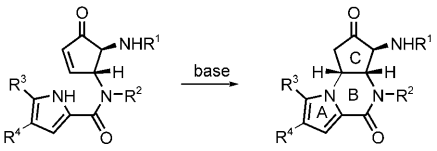
that include human KB nasopharyngeal cancer cells (IC_{50} = 0.075 μg mL^{-1}), L1210 murine tumor cell line, RT112/84 bladder carcinoma cells, SK-MEL-5 melanoma cells, HCT-116 colon carcinoma cells, and MDA-MB-435s breast cancer cells.[6] In many cases, agelastatin A was shown to be 1.5 to 16 times more potent than the frontline chemotherapeutic agent cisplatin at inhibiting cell growth.[6c] Very recently, agelastatin A has been found to inhibit osteopontin-mediated adhesion, invasion, and colony formation.[7] It also inhibits glycogen synthase kinase-3 β (GSK-3β) at low concentration, suggesting a potential approach for the treatment of Alzheimer's disease.[4] Hale et al. has also suggested that agelastatin A might also function as a novel insulin mimetic.[8] In addition, agelastin A has been reported to possess potent activity against brine shrimp (LC_{50} = 1.7 ppm), larvae of beet army worm and corn rootworm.[5]

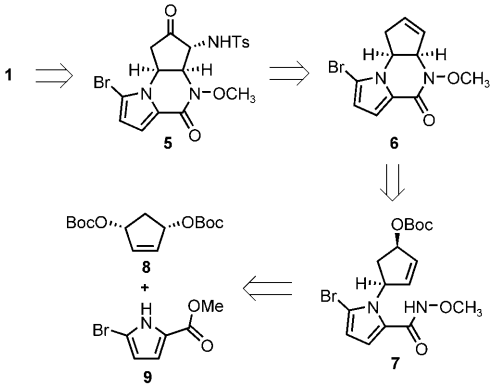
Besides these appealing biological activities, the structure of agelastain A has also been attractive to the synthetic community. First, this natural product contains an unusual 5-6-5-5 fused tetracylic system, including a bromo-pyrrole motif. Second, it contains four contiguous stereocenters, all of which are located in a five-membered ring. In addition, each of these stereogenic centers bears a nitrogen atom. All of these features constitute significant challenges for the total synthesis of agelastatin A. To date, several elegant total syntheses of this natural product have been reported.[9] In 1999, Weinreb et al. completed the first total synthesis of racemic agelastatin A, highlighted by a novel *N*-sulfinyl dienophile Diels–Alder reaction followed by a tandem N–S bond cleavage, [2,3]-sigmatropic rearrangement, and oxazolidinone formation to efficiently construct a [3.3.0] bicycle from cyclopentadiene.[10] Feldman and Saunders in 2002 reported the first enantioselective synthesis of (−)-agelastatin A and B, in which a unique approach using alkynyliodonium salts was described.[11] Starting from the Hough–Richardson aziridine, Hale and co-workers completed a formal total synthesis of (−)-agelastatin A in 2003 along with a new total synthesis in 2004.[12] The Davis group then published an asymmetric synthesis of **1** in 2005 using a chiral sulfinimine.[13] Shortly after, Wehn and Du Bois completed a total synthesis of (−)-agelastatin A by application of a Rh-catalyzed intramolecular aziridination reaction.[14] A recent synthesis by the Ichikawa group in 2007 featured the double usage of a [3,3]-sigmatropic rearrangement of allyl cyanate.[15] In 2008, Yoshimitsu–Tanaka disclosed a new asymmetric synthesis of agelastatin A using an azidoformate-mediated aziridination reaction.[16] Most recently, a racemic synthesis was reported by Dickson and Wardrop, employing a strategy based on multiple usage of the trichloroacetamide functionality.[17] While most previous total syntheses relied on an intramolecular Michael addition to provide the ABC-ring system of **1** [Eq. (1)], we devised a new strategy to construct this key tricycle by dual usage of Pd-AAA reactions. Herein, we provide a full report of our work directed towards the total synthesis of agelastatin A.[18]



(1)

Results and Discussion

Synthesis plan: From a retrosynthetic viewpoint (Scheme 1), agelastatin A (**1**) could be accessed from tricyclic amino ketone **5** that in turn could be derived from tricyclic olefin **6**. An intramolecular Pd-catalyzed allylic alkylation of amide **7** was envisioned to provide pyrrolopiperazinone **6**. Amide **7** could be ultimately synthesized from an intermolecular Pd-catalyzed desymmetrization AAA between bisallylic carbonate **8** and pyrrole **9**. The most attractive feature of this sequence was that a complex tricyclic structure such as **6** could be efficiently and enantioselectively obtained from two consecutive AAA reactions.

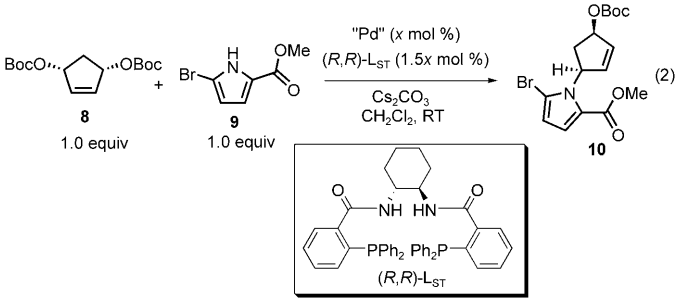


Scheme 1. Retrosynthetic analysis.

Pd-catalyzed AAA reactions with pyrroles and *N*-methoxyamides as nucleophiles leading to the formation of tricycle pyrrolopiperazinone 6: Throughout the initial studies for the Pd-catalyzed AAA between **8** and **9**, Cs_2CO_3 and CH_2Cl_2 were found to be the best base and solvent combination [Eq. (2)]. The use of other solvents, such as THF or DMF, or other bases, such as NaH, Hünig's base or DBU, gave either low conversion or decomposition of the starting materials. The yield and enantioselectivity of this desymmetrization reaction were further optimized by varying the palladium source, catalyst loading, base loading, and concentration (Table 1). Lowering the amount of base increased the enantioselectivity from 84 to 92% ee, but reduced the yield (entries 1 and 2). Entry 3 indicated that lowering the catalyst loading at the same substrate concentration afforded the same yield for this transformation, but a reduction in ee value (66%) was obtained. When the catalyst loading was decreased while keeping the catalyst concentration the same as in entry 1, almost the same enantioselectivity was ob-

tained but with lower yield (entry 4). Upon changing the palladium source from $[Pd_2(dba)_3]\cdot CHCl_3$ to $[Pd(\pi\text{-}C_3H_5)Cl]_2$, both the yield and the enantioselectivity were significantly enhanced. From these studies emerged the most practical set of conditions, as shown in entry 6, which provided the *N*-alkyl pyrrole **10** in 83% yield and 92% ee. At this point, the absolute configuration was tentatively assigned by analogy to other AAA reactions of substrate **8**.[1]

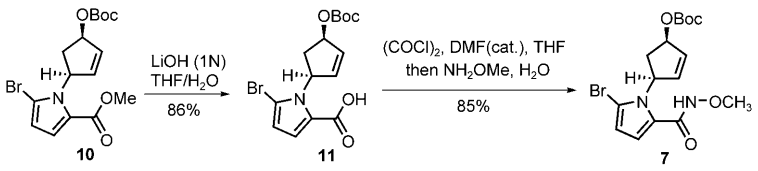
Table 1. Selected optimization studies.



Entry	Pd source (mol%)	Cs_2CO_3 (equiv)	Substrate conc. [M]	Yield [%][a]	*ee* [%][b]
1	$[Pd_2(dba)_3]\cdot CHCl_3$ (5)	1.0	0.02	90	84
2	$[Pd_2(dba)_3]\cdot CHCl_3$ (5)	0.7	0.02	75	92
3	$[Pd_2(dba)_3]\cdot CHCl_3$ (2.5)	1.0	0.02	89	66
4	$[Pd_2(dba)_3]\cdot CHCl_3$ (1.25)	1.0	0.08	75	85
5	$[\{Pd(\pi\text{-}C_3H_5)Cl\}_2]$ (2)	1.0	0.17	88-93	87
6	$[\{Pd(\pi\text{-}C_3H_5)Cl\}_2]$ (1.25)	1.0	0.08	83	92

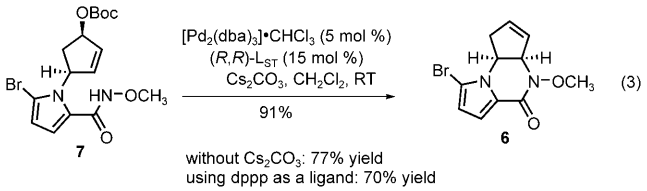
[a] Isolated yield. [b] Enantioselectivities were determined by chiral HPLC.

Direct transformation of the carboxylate ester **10** to *N*-methoxyamide **7** was next attempted, however, treatment with a variety of reagents[19] resulted in either no product or cleavage of the *tert*-butyl carbonate (Boc) group. A two-step process was then developed involving careful hydrolysis of the methyl ester with lithium hydroxide, followed by amide formation via the acyl chloride to give *N*-methoxyamide **7** in high yield (Scheme 2). Notably, the *N*-methoxyamide was chosen because of the increased nucleophilicity relative to a simple amide, which should facilitate the subsequent cyclization.

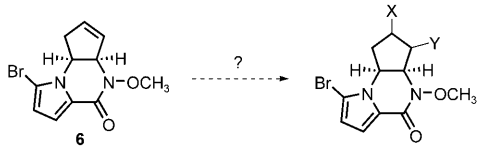


Scheme 2. Synthesis of compound **7**.

The intramolecular Pd-catalyzed AAA with *N*-methoxyamide as the nucleophile proceeded successfully [Eq. (3)]. Although a chiral ligand is not necessary for this cyclization, when (R,R)-L_{ST} (L_{ST}: standard Trost ligand) was used as ligand,[20] piperazinone **6** was obtained in 91% yield. Use of achiral dppp proved to be less efficient and gave **6** in 70% yield. Cs_2CO_3 was not required for this cyclization, but in the absence of base, tricycle **6** was obtained in only 77% yield.



Alkene elaboration: Elaboration of intermediate **6** to the natural product required dual functionalization of the cyclopentene olefin (Scheme 3). Hydroxybromination and hydroxyiodination of **6** only yielded the pyrrole-brominated or iodinated products, while the alkene functionality remained intact.

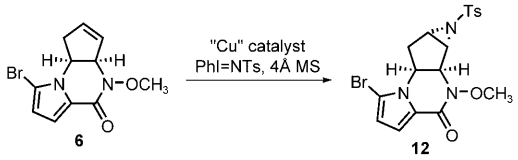


Scheme 3. Advancement of compound **6**.

Thus, an aziridination route to transform pyrrolopiperazinone **6** was eventually sought. Although no reaction occurred either using either Sharpless' method[21] with bromine as catalyst or using tosyl azide under thermal or photochemical conditions,[22] a copper-catalyzed aziridination with PhI=N-Ts as the nitrene source[23] proved to be more promising [Eq. (4), Table 2]. Due to the rather electron-deficient character of the olefin moiety in **6**, a number of different copper catalysts, solvents, and other conditions were examined. Selected optimization results are summarized in Table 2. Molecular sieves have been found to be a critical additive to secure consistent results. Among the various catalyst systems employed, copper(I) thiophene-2-carboxylate (CuTc, entry 2) in acetonitrile and copper(I) triflate (CuOTf) in benzene (entries 6 and 7) exhibited good reactivity. A more effective catalyst was found when using complex **13** or **14**, and the desired aziridine product **12** was obtained in 51 and 52% yield, respectively (entries 10

and 11). Although *N*-heterocyclic carbene (NHC) metal complexes have been known to enable carbene transfer to olefins,[24] to our knowledge, these examples represent the first NHC-copper catalyzed aziridination reactions.[25]

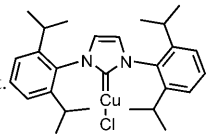
Table 2. Selected optimization of aziridination reaction.

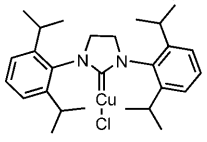


(4)

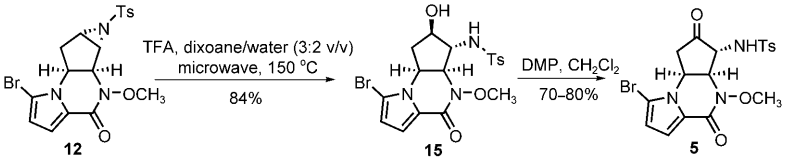
Entry	Catalyst (mol%)	PhI=NTs (equiv)	Solvent	*T* [°C]	Yield [%][a]
1	$Cu(acac)_2$ (10)	2	CH_3CN	0 to RT	28
2	CuTc (20)	2	CH_3CN	0 to RT	29–40
3	$Cu(OTf)_2$ (20)	2	CH_3CN	RT	trace
4	CuOTf (10)	2	DME	RT	0
5	CuOTf (30)	3	CH_3CN	RT	16
6	CuOTf (10)	2	benzene	0 to RT	30
7	CuOTf (50)	2	benzene	RT	41
8	CuOTf (100)	2	benzene	RT	47
9	$Cu(py)_2Cl_2$ (100)	2	CH_2Cl_2	RT	<30
10	catalyst **13** (50)	5	benzene[b]	0 to RT	52
11	catalyst **14** (50)	5	benzene	0 to RT	51

[a] Isolated yield. [b] Decomposition was observed when CH_3CN was used as solvent.





Hydrolytic ring opening of the un-activated tosyl aziridine functionality in **12** proved non-trivial. When treating aziridine **12** either with ceric ammomium nitrate (CAN; 10 mol% up to 1 equiv)[26] or $BF_3{\cdot}Et_2O$ (0.2 equiv) in aqueous acetonitrile,[27] or with a catalytic amount of TFA in aqueous acetone at room temperature, only recovered starting material was provided. Reaction of **12** with excess TFA upon conventional heating (97 °C) in aqueous dioxane ultimately delivered the desired α-amino alcohol **15** in 97% yield. However, this result is difficult to reproduce. Moreover, this reaction required a long reaction time (ca. 48 h) with continuous refilling of TFA every 8 h. To increase the rate of this transformation, the effect of microwave heating was investigated. To our delight, the microwave-assisted hydrolytic ring opening was completed in only 2.5 h at 150 °C, and amino alcohol **15** was obtained reproducibly in 84% yield (Scheme 4). The α-amino ketone **5** was then secured in 70–80% yield by treatment of **15** with Dess–Martin periodinane.[28]

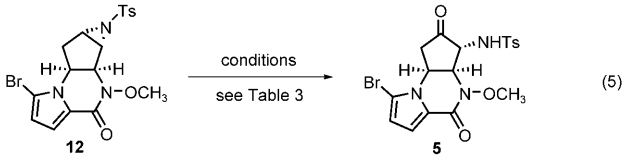


Scheme 4. Synthesis of compound **5**.

With access to **5**, a direct oxidative ring opening of aziridine **12** was then pursued [Eq. (5)], and the explored conditions are summarized in Table 3. When using *o*-iodoxybenzoic acid (IBX) as oxidant in combination with β-cyclodextrin[29] in aqueous acetone at room temperature (entry 1), only the starting material **12** was isolated. Higher reaction temperatures (50–60 °C) using aqueous dioxane as solvent led to decomposition of the substrate (entry 2). DMSO has been known to be able to oxidatively open epoxides to give α-hydroxy ketones,[30] however, few cases existed using DMSO in oxidative aziridine ring opening.[31] Heating **12** in dry DMSO at 80 °C did provide the desired α-amino ketone **5** but in only 42% yield (entry 3). A substantial amount of the direct hydrolytic ring-opening product **15** was observed as the major product. As shown in entry 4, addition of molecular sieves did not help minimize the formation of hydrolysis byproducts. On the contrary, it seemed to be detrimental for this reaction, and no desired product could be isolated. Although microwave conditions were demonstrated to be efficient in the hydrolytic ring opening of aziridine **12**, significant decomposition was detected after heating **12** in DMSO for 1 h at 150 °C in a microwave apparatus (entry 5). A broad range of additives were also surveyed to improve the reaction yield. For example, addition of a stoichiometric amount of Hünig's base or sodium chloride generated a complex mixture of products, and addition of water yielded more hydrolytic product **15**. On the other hand, addition of a Lewis acid, $In(OTf)_3$, was found to be most effective for this transformation. Treatment of **12** with 0.7 equiv $In(OTf)_3$[32] in dry DMSO at 80 °C for 6 h cleanly produced α-amino ketone **5** in 91% yield (entry 6), and the direct hydrolytic ring opening only occurred to a very limited amount (ca. 5%). This observation can be plausibly explained by the mild Lewis acidity of $In(OTf)_3$ to chemoselectively activate the aziridine functionality,[33] thus allowing facile attack by DMSO (A plausible mechanism is shown in Scheme 5). To the best of our knowledge, this reaction represents the first In^{III}-catalyzed oxidative ring opening of a tosyl aziridine with DMSO.

End game: Advancement of α-amino ketone **5** to agelastatin A required installation of the D-ring urea. After an extensive study, Cs_2CO_3 was found to most efficiently catalyze the *N*-acylation of sulfonamide with methyl isocyanate (Scheme 6). Treatment of **5** with 20 mol% Cs_2CO_3 in meth-

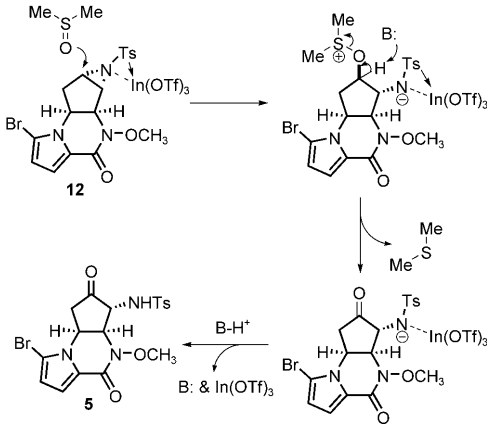
Table 3. Oxidative ring-opening of aziridine **12**.



(5)

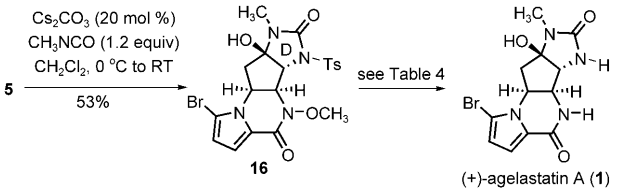
Entry	Conditions	Results
1	IBX, β-cyclodextrin, aqueous acetone, RT	recovered **12** only
2	IBX, β-cyclodextrin, aqueous dioxane, 50–60 °C	decomposition of **12**
3	DMSO, 80 °C	**5** (42 % yield[a])
4	DMSO, molecular sieves, 80 °C	decomposition of **12**
5	DMSO, microwave, 150 °C	decomposition of **12**
6	DMSO, $In(OTf)_3$ (0.7 equiv), 80 °C	**5** (91 % yield[a])

[a] Isolated yield.



Scheme 5. Plausible mechanism for the oxidative ring-opening of aziridine **12**.

ylene chloride at 0 °C followed by slow addition of a benzene solution of methyl isocyanate at room temperature successfully provided tetracycle **16** in 53 % yield. Using a weaker base such as K_2CO_3 or using CuCl as catalyst[34] proved less effective.



Scheme 6. End game.

It is not totally unexpected that removal of the *N*-Ts group of **16** needed a great extent of experimentation. A summary of attempted conditions is summarized in Table 4. Dissolving metal reduction of **16** with lithium in the presence of a catalytic amount of naphthalene only yielded the debrominated products (entry 1). Attempts to remove the *N*-Ts group either with magnesium metal in methanol[35] or with TBAF[36] also failed (entries 2, 3 and 4). Photochemical conditions have been demonstrated to cleave nitrogen–sulfone bonds,[37] however, irradiation of **16** with UV light (254 nm) in several solvents (entries 5–7) did not afford any useful amount of product. In the end, we turned to the SmI_2-mediated radical reduction method.[38] Gratifyingly, treatment of **16** with freshly prepared SmI_2/THF solution selectively removed both the *N*-Ts and *N*-OMe groups without reduction of the pyrrolyl bromide, which ultimately provided (+)-agelastatin A (**1**) in 88 % yield. Synthetic (+)-agelastatin A displayed identical spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, MS, and R_f value) to those reported for the natural product. The optical rotation of synthetic (+)-agelastatin A was $[\alpha]_D^{20} = +53.2$ ($c = 0.13$, MeOH), which compared well to the rotation of naturally isolated (−)-agelastatin A $[\alpha]_D^{20} = -59.3$ ($c = 0.13$, MeOH)[5] reported under identical conditions. This also established the absolute configuration of the Pd AAA as shown in Equation (2).

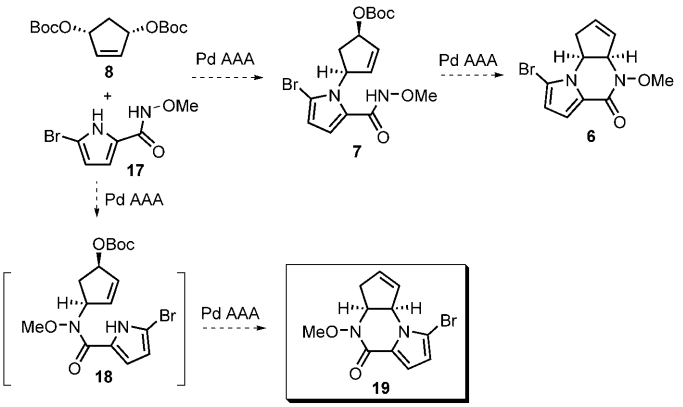
Table 4. Removal of the *N*-Ts and *N*-OMe groups.

Entry	Conditions	Results
1	Li, cat. naphthalene, −78 °C	debrominated products
2	Mg, MeOH, sonication	no reaction
3	Mg, MeOH, reflux	debrominated products
4	TBAF, THF	decomposition of **16**
5	*hv* (254 nm), CH_3CN	**1** (trace) + decomposition of **16**
6	*hv* (254 nm), dry THF	decomposition of **16**
7	*hv* (254 nm), THF/H_2O	decomposition of **16**
8	SmI_2 (8 equiv), THF, 0 °C to RT	**1** (88 % yield[a])

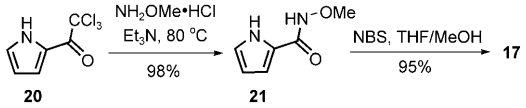
[a] Isolated yield.

Development of Pd-catalyzed one-pot cascade AAA to enable a more efficient tricyclic pyrrolopiperazinone formation: With successful application of both the pyrrole and the *N*-methoxyamide as nucleophiles respectively in the Pd-catalyzed AAA, a cascade cyclization reaction was next designed to streamline the synthesis (Scheme 7). For a nucleophile containing both pyrrole and *N*-methoxyamide (**17**), a one-pot double AAA could be envisioned, in which a tricyclic pyrrolopiperazinone (**6** or **19**) could be obtained with high efficiency. A further intriguing question arises—which nitrogen will serve as the kinetically faster nucleophile?

Toward this end, the bifunctional nucleophile **17** was synthesized in two steps from commercially available 2-(trichloroacetyl)pyrrole **20** (Scheme 8). To effect the Pd-catalyzed cascade AAA transformation, one challenge was to chemoselectively differentiate the two nitrogen nucleophiles in substrate **17**, enabling one to react at a much faster rate than the other. Attempts to promote initial attack by the pyrrole nitrogen were unsuccessful.[39] Given that the nitrogen of the *N*-methoxyamide should be more nucleophilic relative to the pyrrole, extensive effort was then conducted



Scheme 7. A cascade Pd-catalyzed AAA.



Scheme 8. Synthesis of compound **17**.

to allow a tandem cyclization to access pyrrolopiperazinone **19** (Table 5). Surprisingly, almost no reaction occurred in the presence of a base (entries 1, 2 and 4). We hypothesized that after deprotonation, **17** could act as a bidentate ligand for palladium (Figure 2), thereby preventing the first ionization. On the basis of this hypothesis, 10 mol% of acetic acid was added to the reaction. To our delight, piperazinone **19** was obtained in 51% yield when (*R*,*R*)-L_{ST} and $[Pd_2(dba)_3]$·$CHCl_3$ were used as catalyst (entry 6). As shown in entry 7, one equivalent of *N*,*O*-bis(trimethylsilyl) acetamide (BSA) also proved to be effective (50% yield), but given the higher cost and moisture sensitivity of BSA, further optimization was pursued on employing a catalytic amount of acetic acid. Higher yield (88%) was obtained when using racemic standard Trost lignad (L_{ST}), presumably because the rate of the second allylic alkylation (from **18** to **19**) could likely be accelerated by using the other enantiomer of the Pd catalyst as in a matched case. Based on this hypothesis, the identified optimum conditions involved addition of a portion of racemic catalyst after the completion of the first AAA, and piperazinone **19** could be obtained in up to 82% yield and 97.5% *ee* (entry 11). Thus, using the same ligand [(*R*,*R*) standard Trost ligand] as in Equation (2) and (3), but with a different pyrrole nucleophile (**17**), the other pyrrolopiperazinone regioisomer (**19**) could be efficiently accessed.

Another way to look at the tricycle **19** is that it can be considered as a pseudoenantiomer of tricycle **6**, for example, they would be enantiomers if the location of the double bond was the same.

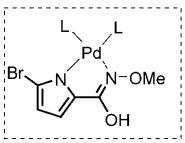
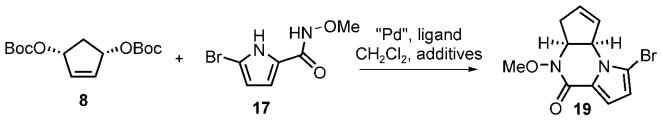


Figure 2. Plausible structure of Pd-**17** complex.

Table 5. Cascade AAA for the synthesis of piperazinone **19**.[a]



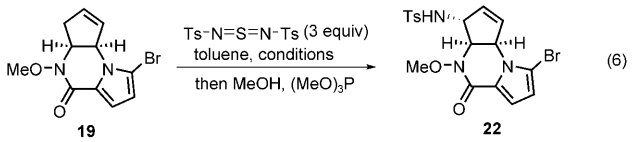
Entry	Pd source (mol%)	Ligand (mol%)	Additive (mol%)	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	$[\{Pd(\pi\text{-}C_3H_5)Cl\}_2]$ (2)	(*R*,*R*)-L_{ST} (6)	LiHMDS (100)	RT	0	NA
2	$[\{Pd(\pi\text{-}C_3H_5)Cl\}_2]$ (2)	(*R*,*R*)-L_{ST} (6)	LiHMDS (200)	RT	0	NA
3	$[\{Pd(\pi\text{-}C_3H_5)Cl\}_2]$ (2)	(*R*,*R*)-L_{ST} (6)	none	RT	trace	NA
4	$[\{Pd(\pi\text{-}C_3H_5)Cl\}_2]$ (2)	(*R*,*R*)-L_{ST} (6)	Cs_2CO_3 (100)	RT	0	NA
5	$[\{Pd(\pi\text{-}C_3H_5)Cl\}_2]$ (5)	(*R*,*R*)-L_{ST} (15)	HOAc (10)	RT	trace[d]	NA
6	$[Pd_2(dba)_3]$·$CHCl_3$ (5)	(*R*,*R*)-L_{ST} (15)	HOAc (10)	RT	51	NA
7	$[Pd_2(dba)_3]$·$CHCl_3$ (5)	(*R*,*R*)-L_{ST} (15)	BSA (100)	RT	50	NA
8	$[Pd_2(dba)_3]$·$CHCl_3$ (5)	(*R*,*R*)-L_{ST} (15)	HOAc (10)	0 to RT	65[e]	89
9	$[Pd_2(dba)_3]$·$CHCl_3$ (5)	*rac*-L_{ST} (15)	HOAc (10)	RT	88[e]	NA
10	$[Pd_2(dba)_3]$·$CHCl_3$ (5)	(*R*,*R*)-L_{ST} (15)	HOAc (10)	0 to RT	80[e,f]	96
11	$[Pd_2(dba)_3]$·$CHCl_3$ (5)	(*R*,*R*)-L_{ST} (15)	HOAc (10)	0 to RT	82[e,g]	97.5

[a] Unless otherwise indicated, all reactions were performed with 1.0 equiv of **8** and 1.0 equiv of **17** at 0.2 M in CH_2Cl_2. [b] Isolated yield. [c] Enantioselectivities were determined by chiral HPLC. [d] Single alkylation product was the main product. [e] The reaction was performed with 1.5 equiv of **8** and 1.0 equiv of **17**. [f] Another portion of $[Pd_2(dba)_3]$·$CHCl_3$ (5 mol%), (*R*,*R*)-L_{ST} (15 mol%) was added after 1 h. [g] Another portion of $[Pd_2(dba)_3]$·$CHCl_3$ (5 mol%), *rac*- L_{ST} (15 mol%) was added after 3.5 h.

Formal total synthesis of (−)-agelastatin A: With tricycle **19** in hand, we turned to examine the feasibility of transforming this advanced intermediate to the natural (−)-enantiomer of agelastatin A. Inspired by the work of Weinreb,[10,40] pyrrolopiperazinone **19** was subjected to allylic amination conditions.[41] As shown in Equation (6) (Table 6), several modifications were attempted in order to improve the yield for this Kresze reaction,[41b] but the original thermal conditions gave the best results (43–47% yield). Microwave conditions or Lewis acid additives [20 mol% $In(OTf)_3$] caused increased decomposition, and addition of NHC-copper complex **13** neither harmed nor benefited this transformation. Although the yield of this allylic amination is moderate, we were pleased to find that a single regio- and diastereomer was obtained given the complexity of substrate **19**, which was assigned as tricycle **22** by analogy.

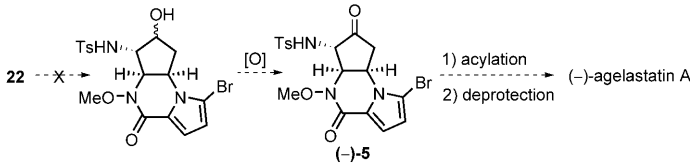
Based on the precedent from Weinreb's synthesis, it seemed to be straightforward to advance **22** to the natural product **1**. However, any attempts to functionalize the cyclopentene olefin in **22** remained unfruitful (Scheme 9). For example, under several hydroboration conditions (BH_3, 9-BBN-H, Rh-catalyzed hydroboration, etc.) and epoxidation

Table 6. Allylic amination conditions for piperazinone **19**.[a]



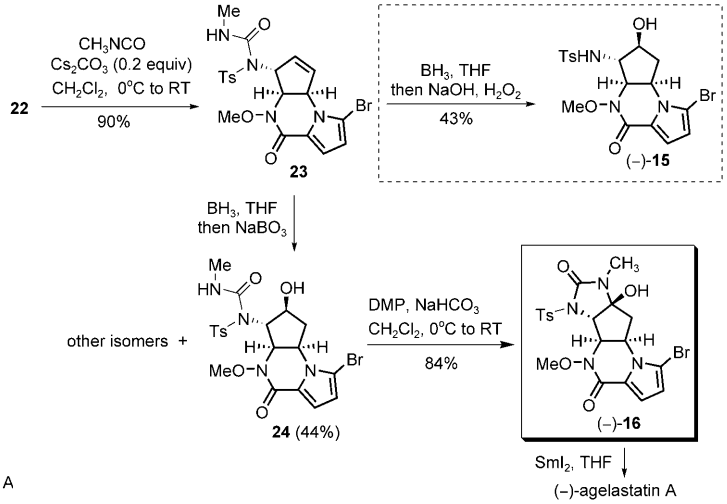
Conditions	Yield [%]
MW 150 °C, 1 h	36
100 °C, 30 h	43–47
100 °C, $In(OTf)_3$ (20 mol %)	19
100 °C, **13** (20 mol %)	47

conditions (*m*CPBA with or without a buffer, MTO-UHP, $[Mo(CO)_6]$-catalyzed epoxidation, DMDO, etc.), either a complicated reaction mixture was obtained, or no reaction occurred.



Scheme 9. Unsuccessful advancement of compound **22**.

After extensive experimentation, we eventually found that the presence of the acidic sulfonamide N-H hydrogen seemed to be detrimental for the subsequent functionalization of the adjacent olefin. The problem was solved by altering the reaction sequence between hydroboration of the olefin and acylation of the sulfonamide (Scheme 10). Reaction of **22** with methyl isocyanate and 0.2 equiv Cs_2CO_3 in CH_2Cl_2 provided urea **23** in 90 % yield. When treating **23** with BH_3 in THF followed by oxidative treatment with hydrogen peroxide and sodium hydroxide, secondary alcohol (−)-**15** was isolated as the major product, however, surprisingly, the urea group was cleaved, presumably by the basic oxidative workup. Alcohol (−)-**15** is spectroscopically identical to compound (+)-**15**, an intermediate in our synthesis of (+)-agelastatin A. The optical rotation of (−)-**15** was $[\alpha]_D^{20} = -35.6$ ($c = 0.34$, CH_2Cl_2), which compared well to the rotation of (+)-**15** $[\alpha]_D^{20} = +36.2$ ($c = 0.90$, CH_2Cl_2). This hydrolysis problem could be overcome by changing to a less-basic workup. Indeed, upon working up the hydroboration reaction with aqueous sodium perborate, alcohol **24** was obtained as the major regio- and diastereomer, and the relative stereochemistry of **24** was tentatively assigned by analogy to (−)-**15**. Subsequent Dess–Martin oxidation of **24** provided tetracycle (−)-**16** in 84 % yield, which displayed identical spectroscopic data (^1H NMR, ^{13}C NMR, IR and R_f value) to those of (+)-**16**. The optical rotation of (−)-**16** was $[\alpha]_D^{20} = -11.1$ ($c = 0.17$, $CHCl_3$), which compared well to the rotation of (+)-**16** $[\alpha]_D^{20} = +9.7$ ($c = 0.73$, $CHCl_3$). Given that the final *N*-Ts and *N*-OMe cleavage of (−)-**16** has been demonstrated on its enantiomer (Scheme 6), therefore, we completed the formal total synthesis of (−)-agelastatin A starting from pyrrolopiperazinone **19** in five steps.

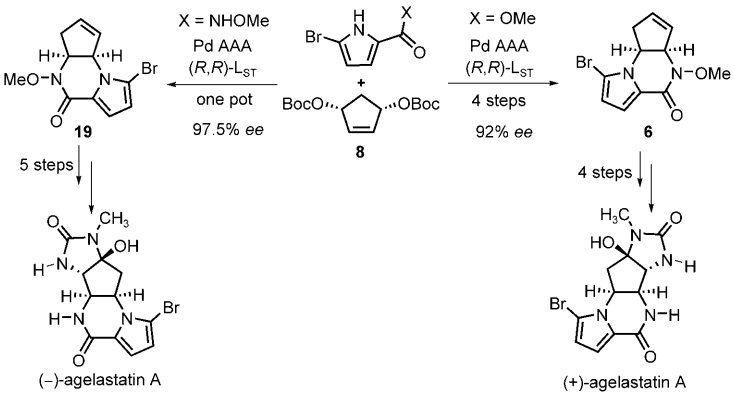


Scheme 10. Formal total synthesis of (−)-agelastatin A.

Conclusions

Two new classes of nucleophiles, pyrroles and *N*-alkoxyamides (hydroxamic esters), have been employed in palladium-catalyzed AAA reactions. By varying the functional groups at the 2-position of pyrroles, we were able to efficiently and enantioselectively access either regioisomer of the pyrrolopiperazinones **6** and **19** (Scheme 11), among which **19** was obtained via a cascade reaction through a double allylic alkylation pathway. Using regioisomer **6**, we completed the total synthesis of (+)-agelastatin A in eight steps from pyrrole **9**, during the course of which, we developed a new copper catalyst for aziridination, and an $In(OTf)_3$/DMSO system to oxidatively open an *N*-tosylaziridine. Starting from the other pyrrolopiperazinone (**19**), a five-step sequence has been developed to furnish a formal total synthesis of (−)-agelastatin A, requiring just the reductive cleavage of the *N*-Ts and *N*-OMe bonds as performed on the enantiomer. In either of the two syntheses, although we use reagents that require substituents for the appropriate reactivity, which need to be removed, it is worth noting that no protecting groups have been employed in the sense of putting on such a group to impart chemoselectivity that then must be removed. For example, the *O*-Boc and *N*-OMe groups were used as activating groups, and the *N*-Ts groups were inherent from the C–N bond-forming reactions.

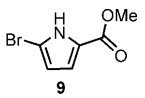
Therefore, we have developed two distinctive strategies for the enantioselective total synthesis of marine alkaloid agelastatin A. As a rather unique feature of our syntheses, two complementary routes differing only in the choice of nucleophile in the Pd-AAA reactions provide either enantiomer of this natural product.



Scheme 11. Total synthesis of (+) and (−)-agelastatin A with two different routes.

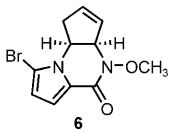
Experimental Section

Selected experimental procedures for the preparation of **9**, **6**, **12**, **5**, **19**, and **1** (agelastatin A) appear below. Full experimental details for all new compounds are given in the Supporting Information.



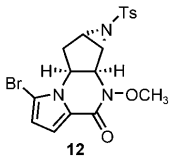
9

Compound 9: To a solution of pyrrole-2-carboxylate methyl ester (2.0 g, 16 mmol) in THF (160 mL) and MeOH (80 mL) was added NBS (recrystallized, 0.49 g, 2.8 mmol) at 0 °C. The reaction was stirred at 0 °C for 30 min, before another portion of NBS (recrystallized, 0.63 g, 3.5 mmol) was added. After 40 min, more NBS (recrystallized, 0.51 g, 2.9 mmol) was added to the reaction mixture. After another 30 min, another portion of NBS (recrystallized, 1.27 g, 7.1 mmol) was added. The resulting solution was then stirred for another 2 h, before the solvent was removed under vacuum. Compound **9** was purified via silica gel flash column chromatography (petroleum ether/diethyl ether 20:1, then 8:1) to give a white floppy solid (1.63 g, 50 %). M.p. 101–103 °C; R_f = 0.35 (petroleum ether/ether 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.1 (br s, 1H), 6.82 (dd, J = 3.0, 3.5 Hz, 1H), 6.21 (dd, J = 3.0, 3.5 Hz, 1H), 3.86 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.8, 123.7, 116.8, 112.7, 105.2, 51.8 ppm; IR (film): $\tilde{\nu}$ = 3250, 2924, 2853, 1702, 1552, 1449, 1415, 1389, 1327, 1207 cm^{-1}; HRMS ($C_6H_6NO_2Br$): m/z: calcd for: 202.958190 [M^+]; found 202.958096.



6

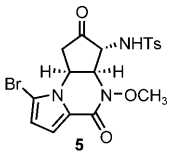
Compound 6: A solution of [Pd_2(dba)$_3$]·$CHCl_3$ (2.29 mg, 0.00025 mmol) and (*R*,*R*)-L_{ST} (5.18 mg, 0.00075 mmol) in CH_2Cl_2 (1 mL), which had been stirred at RT for 10 min, was added to a mixture of compound **7** (20 mg, 0.05 mmol) and Cs_2CO_3 (16.3 mg, 0.05 mmol) under Ar. The mixture was stirred at RT for 12 h, and then filtered through a celite cake. The solvent was removed under vacuum, and compound **6** was purified via silica gel flash column chromatography (petroleum ether/ether 8:1, then CH_2Cl_2/MeOH 40:1) to give a white solid (12.9 mg, 91.5 %). M.p. 107–109 °C; R_f = 0.6 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20}$ = +164.7 (c = 0.34, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.94 (dd, J = 1, 4 Hz, 1H), 6.30 (dd, J = 1, 4 Hz, 1H), 6.22–6.20 (m, 1H), 6.13–6.12 (m, 1H), 4.84–4.79 (m, 2H), 3.85 (s, 3H), 3.13–3.07 (m, 1H), 2.63–2.58 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 156.3, 135.5, 128.6, 123.7, 116.1, 106.8, 101.6, 64.1, 64.0, 57.2, 38.2 ppm; IR (film): $\tilde{\nu}$ = 2927, 2853, 1668, 1545, 1418, 1358, 1334, 1310, 1027 cm^{-1}; HRMS ($C_{11}H_{11}N_2O_2Br$): m/z: calcd for: 282.000389 [M^+]; found 281.999714.



12

Compound 12: Benzene (1 mL) was added to a mixture of 4 Å molecular sieve (75 mg), compound **6** (20 mg, 0.071 mmol), PhI=NTs (132 mg, 0.355 mmol) and catalyst **13** (17.3 mg, 0.0355 mmol) under N_2. The resulting mixture was stirred at RT for 4 h, before it was filtered through a silica gel cake and rinsed with ethyl acetate. The solvent was removed under vacuum, and compound **12** was purified via alumina (neutral, activity 3) flash column chromatography (petroleum ether/ethyl acetate 8:1, 4:1, then 3:1) to give a colorless foam (16.6 mg, 52 %). R_f = 0.5 (petroleum ether/ethyl acetate 3:2); $[\alpha]_D^{20}$ = +21.8 (c 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.86 (dd, J = 1.5, 6.5 Hz, 2H), 7.40 (dd, J = 0.5, 8.5 Hz, 2H), 6.94 (d, J = 4.0 Hz, 1H), 6.26 (d, J = 4.5 Hz, 1H), 4.50–4.44 (m, 2H), 3.97 (s, 3H), 3.88 (d, J = 5 Hz, 1H), 3.61 (dd, J = 2.5, 5.0 Hz, 1H), 2.77 (dd, J = 7.0, 14 Hz, 1H), 2.48 (s, 3H), 1.93 ppm (ddd, J = 14.5, 9.0, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 158.2, 145.5, 134.8, 130.3, 128.2, 122.8, 116.2, 114.1, 106.2, 64.5, 61.3, 53.3, 44.7, 44.1, 32.9, 22.0 ppm; IR (film): $\tilde{\nu}$ = 2925, 2855, 1682, 1543, 1433, 1416, 1325, 1163 cm^{-1}; HRMS ($C_{18}H_{18}N_3O_4SBr$): m/z: calcd for: 451.020139 [M^+]; found 451.020921.

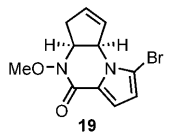
Compound 5



5

From Compound **15**: To a solution of compound **15** (10 mg, 0.0213 mmol) and $NaHCO_3$ (5.4 mg, 0.0639 mmol) in CH_2Cl_2 (0.25 mL) was added Dess–Martin periodinane (13.5 mg, 0.032 mmol). The resulting mixture was stirred at RT for 30 min before quenched with sat. aq. $Na_2S_2O_3$. Compound **5** was purified via silica gel flash column chromatography (petroleum ether/ethyl acetate 3:1, then 3:2) as a white solid (ca. 7 mg 70–80 %).

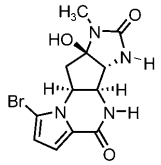
From Compound **12**: DMSO (1 mL) was added to a mixture of compound **12** (30 mg, 0.0665 mmol) and In(OTf)$_3$ (26 mg, 0.0462 mmol) at RT under N_2. The resulting solution was heated at 80 °C for 6 h, before diluted with ethyl acetate (30 mL). The solution was washed with brine. The aqueous phases were combined, and extracted with ethyl acetate three times. The combined the organic phase was dried over $MgSO_4$, and compound **5** was purified via silica gel flash column chromatography (petroleum ether/ethyl acetate 3:1, then 3:2) to give a white solid (28.3 mg, 91 %). M.p. 100–102 °C; R_f = 0.3 (petroleum ether/ethyl acetate 1:1); $[\alpha]_D^{20}$ = +57.8 (c = 0.97, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.82 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 4.0 Hz, 1H), 6.35 (d, J = 4.0 Hz, 1H), 5.63 (d, J = 7.5 Hz, 1H), 5.23–5.18 (m, 1H), 5.00 (d, J = 2.5 Hz, 1H), 4.98 (d, J = 5.5 Hz, 1H), 4.00 (br, 1H), 3.84 (s, 3H), 3.02 (dd, J = 7.5, 18 Hz, 1H), 2.68 (dd, J = 11, 18 Hz, 1H), 2.46 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 206.3, 157.9, 144.7, 134.7, 130.0, 127.7, 122.6, 116.7, 114.3, 106.4, 64.1, 61.1, 51.9, 41.2, 29.7, 21.6 ppm; IR (film): $\tilde{\nu}$ = 3252, 2924, 2854, 1768, 1652, 1548, 1416, 1338, 1162, 1093, 1025 cm^{-1}; HRMS ($C_{18}H_{18}N_3O_5SBr$): m/z: calcd for: 469.013008 [M^+]; found 469.013016.



19

Compound 19 (e.g., Table 5, entry 11): A solution of [Pd_2(dba)$_3$]·$CHCl_3$ (5.2 mg, 0.005 mmol) and (*R*,*R*)-L_{ST} (10.4 mg, 0.015 mmol) in degassed CH_2Cl_2 (0.5 mL), which had been stirred for 10 min at 0 °C, was added to a mixture of compound **17** (21.9 mg, 0.1 mmol), compound **8** (45 mg, 0.15 mmol) and HOAc (10 μL, 1 M solution in CH_2Cl_2) under Ar. The mixture was stirred at RT for 3.5 h, and then was added a solution of [Pd_2(dba)$_3$]·$CHCl_3$ (5.2 mg, 0.005 mmol) and *rac*-L_{ST} (10.4 mg, 0.015 mmol) in degassed CH_2Cl_2 (0.5 mL), which had been stirred for 10 min at RT. The resulting solution was stirred at RT for 3 h. Compound **19** was purified

via silica gel flash column chromatography (petroleum ether/ethyl acetate 4:1, then 3:1) as a colorless solid (23.0 mg, 82%, 97.5% *ee* by HPLC OD column, 90:10 heptane/isopropanol, 0.8 mL min^{-1}): m.p. 111–113 °C; R_f = 0.2 (petroleum ether/ethyl acetate 4:1); $[\alpha]_D^{20}$ = −120.2 (*c* = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.91 (d, *J* = 5.0 Hz, 1H), 6.28 (d, *J* = 5.0 Hz, 1H), 6.02 (m, 1H), 5.95 (m, 1H), 5.29 (d, *J* = 8.0 Hz, 1H), 4.65 (ddd, *J* = 8.0, 6.5, 2.5 Hz, 1H), 3.85 (s, 3H), 2.92 (d, *J* = 21.5 Hz, 1H), 2.71 ppm (ddd, *J* = 21.5, 6.5, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 157.3, 132.0, 129.0, 123.8, 114.7, 113.6, 104.8, 63.0, 61.6, 60.7, 36.4 ppm; IR (film): $\tilde{\nu}$ = 2925, 2854, 1667, 1545, 1417, 1320, 1028 cm^{-1}; HRMS ($C_{11}H_{11}N_2O_2Br$): *m*/*z*: calcd for 282.000389 [*M*$^+$]; found 281.999491.


(+)-agelastatin A (**1**)

(+)-Agelastatin A (1): Freshly made SmI_2 (1.6 mL, 0.1 M in THF) was added to compound **16** (10.0 mg, 0.019 mmol) under argon at 0 °C. The resulting blue solution was allowed to gradually warm to RT and stirred for 2 h before another 0.5 mL SmI_2 (0.1 M in THF) was added. After the solution was stirred at RT for 15 min, THF was removed under vacuum. The residue was first purified by silica gel chromatography (10% to 15% MeOH in CH_2Cl_2). A yellow solid was obtained, which was then dissolved in 15% MeOH in CH_2Cl_2 and filtered through charcoal. The (+)-agelastatin A was further purified by another silica gel chromatography (10% to 15% MeOH in CH_2Cl_2) to give an off-white solid (6.0 mg, 88%). M.p. 195 °C (decomposed); R_f = 0.25 (10% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$ = +53.2 (*c* = 0.13, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): δ = 6.91 (d, *J* = 4.0 Hz, 1H), 6.33 (d, *J* = 4.0 Hz, 1H), 4.60 (m, 1H), 4.09 (d, *J* = 5.5 Hz, 1H), 3.89 (s, 1H), 2.81 (s, 3H), 2.65 (dd, *J* = 6.5, 13 Hz, 1H), 2.10 ppm (dd, *J* = 13, 13 Hz, 1H); ^{13}C NMR (CD_3OD, 150 MHz): δ = 161.4, 161.1, 124.1, 116.0, 113.8, 107.2, 95.7, 67.4, 62.2, 54.4, 40.0, 24.2 ppm; IR (film): $\tilde{\nu}$ = 3346 (br), 2923, 1685, 1644, 1555, 1424, 1380 cm^{-1}; ESI ($C_{12}H_{13}N_4O_3Br$): *m*/*z*: 341.0 [*M*+H]$^+$, 363.0 [*M*+Na]$^+$.

Acknowledgements

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