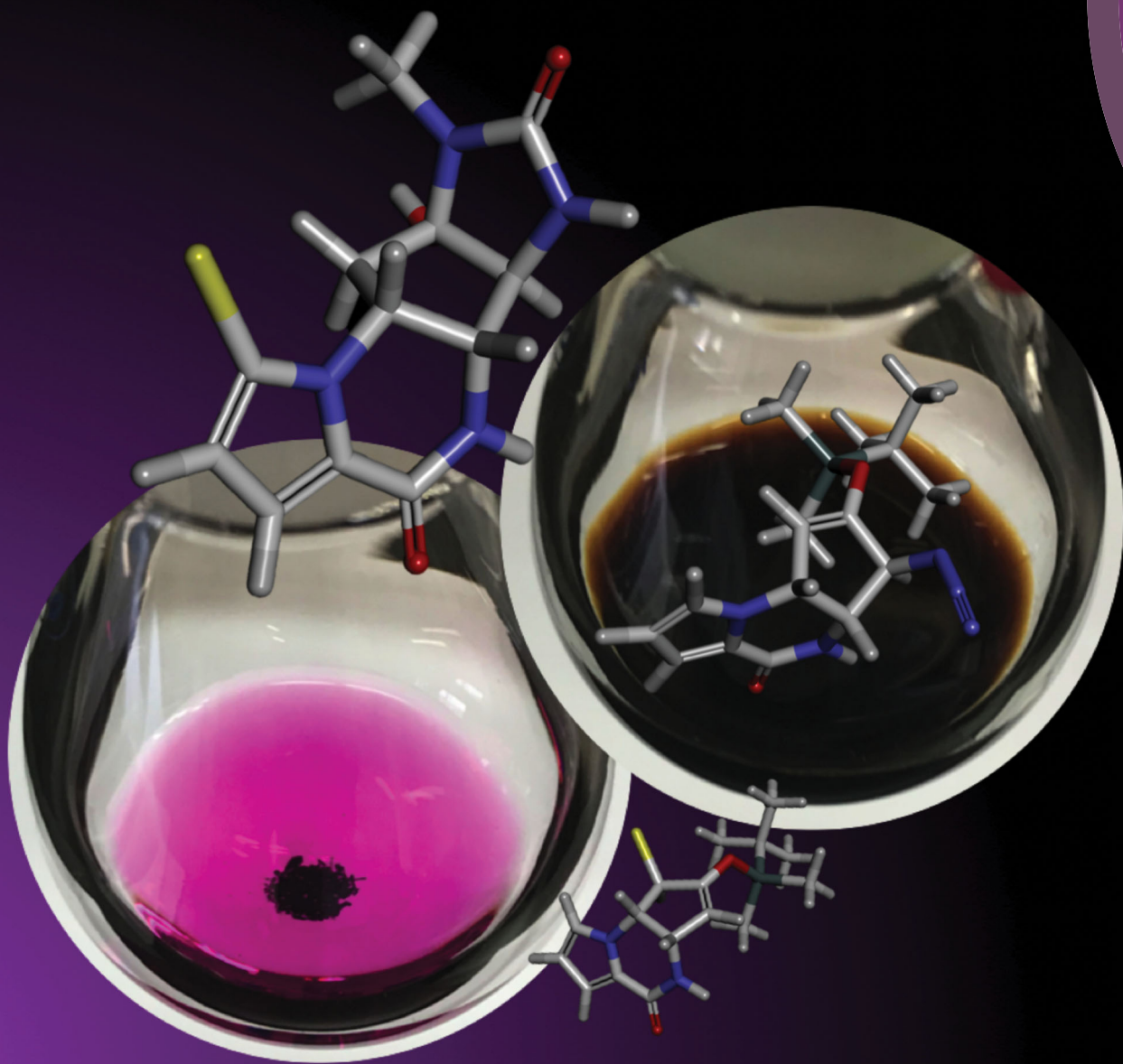


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Total synthesis of (–)-agelastatin A: an S_H2' radical azidation strategy†

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A reagent generated from $TMSN_3/KMnO_4/BnEt_3NCl$ was found to promote an S_H2' radical azidation of a bromo silyl enol ether to furnish an azido silyl enol ether via olefin transposition. With the present azidation protocol, a new synthetic approach to agelastatin A, a potent antitumor marine alkaloid, has been established.

(–)-Agelastatin A (**1**), along with its congener agelastatin B (**2**), was first isolated as a cytotoxic constituent from the Coral Sea sponge *Agelas dendromorpha* by Pietra and co-workers in 1993 (Fig. 1).¹ Thereafter, Molinski and co-workers identified the Indian Ocean sponge *Cymbastela* sp. as another source that produces **1** along with agelastatins C (**3**) and D (**4**), two additional agelastatin members.² In 2010, Al-Mourabit and co-workers reported the isolation of agelastatins E (**5**) and F (**6**) from the New Caledonian sponge *A. dendromorpha*.³ Early biological assessments of agelastatins conducted by the aforementioned laboratories have revealed that compound **1** exhibits remarkable properties, including antitumor activity,^{1,3} brine shrimp toxicity,² and insecticidal activity.² In addition, Meijer and Pettit have found that agelastatin A (**1**) is a potent inhibitor of GSK-3 β , a pivotal serine/threonine kinase.⁴ Hale and El-Tanani have reported that agelastatin A (**1**) dramatically decreases β -catenin levels in cancer cells and inhibits cancer cell proliferation by arresting cell cycle at G2 phase.⁵

The biological significance of agelastatin A (**1**) has made it an attractive target for medicinal studies.^{6,7} For instance, Movassaghi's comparative cytotoxicity assay of all agelastatin members, i.e., A (**1**) to F (**6**), has successfully validated the relevance of agelastatin A (**1**)

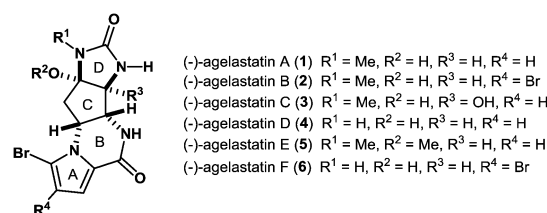


Fig. 1 Agelastatin alkaloids.

as a promising anticancer agent.^{7a} In addition, structure–activity relationship (SAR) studies on agelastatin analogues have recently been disclosed by the groups of Molinski,⁸ Romo/Liu,⁹ and Movassaghi,¹⁰ boosting the applications of agelastatin particularly to blood cancer chemotherapy.

Our group has also been engaged in synthetic and medicinal studies on **1** and has demonstrated that agelastatin analogues potentially attenuate brain cancer.¹¹ Furthermore, our SAR study has revealed that structural modifications of the N1-substituent of the D-ring of **1** could retain the *in vitro* and *in vivo* therapeutic efficacies of agelastatin analogues.^{12,13} Movassaghi's group has further clarified that D-ring modifications expand the scope of derivatization of agelastatins to access potent analogues.¹⁰

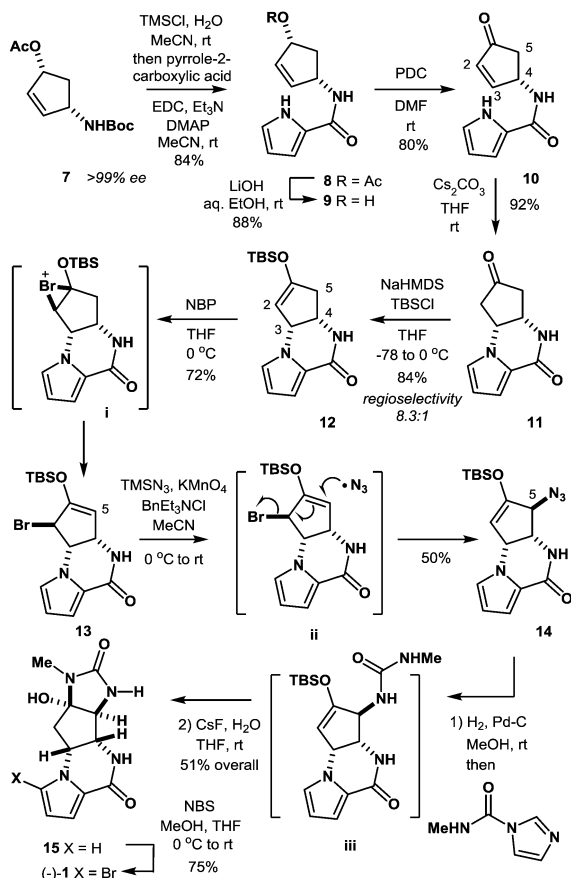
In the present study, we have established a new route to agelastatin A (**1**) through an S_H2' radical azidation protocol using $TMSN_3/KMnO_4/BnEt_3NCl$ that enables the allylic transposition of a bromo silyl enol ether into an azido silyl enol ether, which serves as a useful D-ring precursor of the target natural product (Scheme 1).

The synthesis was commenced with Boc-protected amino-alcohol derivative **7** (>99% ee).¹⁴ The Boc group of **7** was removed with hydrochloric acid (HCl) generated *in situ* from $TMSCl$ in aq. MeCN to provide an ammonium salt (structure not shown). After evaporation of the solvents under reduced pressure, the resultant crude product was coupled with pyrrole-2-carboxylic acid using EDC, Et_3N , and DMAP in MeCN to furnish compound **8** in 84% yield. Then, compound **8** was hydrolyzed with LiOH in aq. EtOH to provide alcohol **9** in 88% yield. PDC oxidation of alcohol **9** in DMF delivered enone **10** in

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Scheme 1 Total synthesis of (–)-agelastatin A (**1**).

80% yield, which, upon treatment with Cs_2CO_3 in THF, gave tricyclic ketone **11** *via* a conjugate addition of the pyrrole nitrogen to the enone double bond. No racemization at C4 position took place in this transformation (**9** \rightarrow **10** \rightarrow **11**), retaining the optical purity of **11** (>99% ee).¹⁵ Then, ketone **11** was subjected to enolization with NaHMDS followed by *O*-silylation with *tert*-butyldimethylsilyl chloride to produce silyl enol ether **12** along with its minor regioisomer **16** (**12**:**16** = 8.3:1) (Fig. 2). Obviously, major product **12** was not ideal for further functionalization as it lacked a reactive alkene functionality at C5 position. However, we found that **12** and **16** underwent olefin isomerization with a trace acid probably due to their strained nature.¹⁶ Therefore, we envisioned that the brominative olefin transposition of **12** would take place *via* a bromonium formation followed by deprotonation to allow net olefin transposition that affords an enol ether suitable for C5 functionalization. To our delight, the treatment of silyl enol ether **12** with

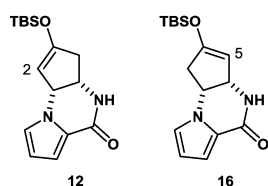


Fig. 2 TBS enol ethers **12** and **16** generated from **11**.

N-bromophthalimide (NBP) was found to deliver allylic bromide **13** in stereoselective and regiospecific manners as we had expected.

With compound **13** in possession, the nitrogen functionalization at C5 position was examined to access key intermediate **14** (Table 1). An attempted ionic $\text{S}_{\text{N}}2'$ azidation of **13** with NaN_3 in DMF was unsuccessful (entry 5), giving rise to a desilylated product. To this end, we expected that the electrophilic nitrogen radical species would preferentially undergo an addition reaction with the electron-rich enol double bond to facilitate $\text{S}_{\text{H}}2'$ radical azidation to deliver compound **14**.

An azide radical is known to be generated from an anionic azide by oxidation processes. The Magnus protocol represents such an example, which utilizes trimethylsilylazide (TMSN_3) in combination with iodosylbenzene (PhIO) in CH_2Cl_2 at low temperature (-78°C). The Magnus method was proved to afford desired product **14** albeit in moderate yield (entry 8).¹⁷ Therefore, we sought a new reagent system to deliver an azido radical and found that the treatment of **13** with TMSN_3 (10 equiv.)/ KMnO_4 (0.3 equiv.)/ BnEt_3NCl (0.3 equiv.) successfully produced azide **14** in 50% yield along with regioisomeric azide **17** (21%) and bromide **18** (3%)¹⁸ (entry 1). In the absence of KMnO_4 , no reaction took place and unreacted **13** was recovered (entries 6 and 7). When catalytic KMnO_4 (0.1 equiv.) was used in combination with TMSN_3 (10 equiv.) and BnEt_3NCl (0.1 equiv.) in either the presence or absence of molecular oxygen (O_2), the chemical yield was low, suggesting that catalysis by O_2 in the present radical azidation was not operative (entries 2 and 3). Increasing the amount of $\text{Mn}(\text{VI})$ reagent was found to have no impact on the improvement of the chemical yields (entry 4).

It should be mentioned that the addition of TMSN_3 to the mixture of KMnO_4 and BnEt_3NCl at 0°C caused the evolution of molecular nitrogen (N_2) accompanied by a color change of the solution from purple to dark brown, suggesting the production of low-valent manganese species from the Mn(VII) reagent. Although the reactive species responsible for the present radical azidation remains unclear, we assume that permanganate(VII) (MnO_4^-) reacts with TMSN_3 to generate a low-valent mangan azide complex that serves as a metastable azide radical source. To clarify this hypothesis, we measured the amount of nitrogen gas (N_2) that was generated from the reagent system. When KMnO_4 (0.33 mmol) was treated with BnEt_3NCl (0.33 mmol) and a large excess of TMSN_3 (11.1 mmol), 20–24 mL (*ca.* 0.9–1.1 mmol) of molecular nitrogen, which corresponds to *ca.* 3.0 equiv. relative to 1.0 equiv. of permanganate ion (MnO_4^-), was generated. Assuming that 1.0 equiv. of permanganate reacts with 5.0 equiv. of TMSN_3 to produce 3.0 equiv. of molecular nitrogen, we propose that a pentavalent Mn(V) species is produced from the Mn(VII) species (Scheme 2).

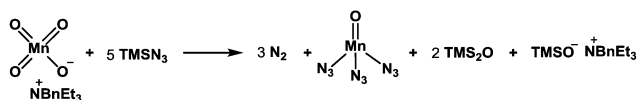
Jiao and co-workers have reported that Mn(III) generated from MnBr₂ in the presence of molecular oxygen serves as an effective catalyst to generate an azide radical from TMSN₃.^{19a} We have examined Mn(OAc)₃·2H₂O in combination with TMSN₃ (6 equiv.) as a possible source of azido radical and found that desired material **14** could be similarly produced in 42% yield along with **17** (8%) (entry 9).^{19b} This result suggests that Mn(III) azide complex is likely responsible for the present radical azidation. Based on these observations, we currently assume that metastable Mn(V)

Table 1 Azidation of bromide **13** with various reagents

Entry	Reagents (equiv.)	Time	Yield ^a (%)			
			14	17	18	13 ^b
1	KMnO ₄ (0.3), BnEt ₃ NCl (0.3), TMSN ₃ (10), MeCN	40 min	50	21	3	Trace
2	KMnO ₄ (0.1), BnEt ₃ NCl (0.1), TMSN ₃ (10), MeCN	40 min	30	4	12	30
3	KMnO ₄ (0.1), BnEt ₃ NCl (0.1), TMSN ₃ (10), MeCN, O ₂	40 min	31	5	11	21
4	KMnO ₄ (0.6), BnEt ₃ NCl (0.6), TMSN ₃ (10), MeCN	40 min	43	11	4	9
5	NaN ₃ (1.1), DMF ^c	15 min	—	—	—	— ^d
6	BnEt ₃ NCl (0.3), TMSN ₃ (10), MeCN	75 min	—	—	—	90
7	TMSN ₃ (10), MeCN	70 min	—	—	—	89
8	PhIO (1.2), TMSN ₃ (2.4), CH ₂ Cl ₂ ^e	40 min	24	17	14	6
9	Mn(OAc) ₃ ·2H ₂ O (3), TMSN ₃ (6), MeCN ^c	11 h	42	8	—	—

^a Isolated yields after purification by column chromatography. ^b Recovered unreacted starting material. ^c The reaction was conducted at r.t.

^d Bromoketone (60%) was produced. ^e The reaction was conducted at −78 °C.



Scheme 2 Plausible generation of Mn(v) azide species.

species is generated from Mn(vii) with excess TMSN₃ and that Mn(v) provides 3 equiv. of azido radical to finally become Mn(ii), which no longer serves as a radical source. To elucidate the formation of the meta-stable Mn species, we carried out a comparison experiment: after stirring the reagents for 60 min, excess remaining TMSN₃ was completely removed under reduced pressure. Then, the residual solid that likely contains the Mn species was diluted with MeCN and mixed with substrate **13**. As a result, almost identical yields of products **14** (48%), **17** (22%), and **18** (6%) were obtained as in the case of entry 1, indicating that the Mn(v) azide complex is generated as a reactive meta-stable reagent.

The formation of compounds **17** and **18**, which provides an insight into the mechanism of the present azidation, also requires elaboration (Scheme 3). When azide **14** and isomeric azide **17** were separately subjected to the same reaction conditions for 1 h, only a trace amount of corresponding azide **17** and **14** was produced along with the unreacted starting azides, respectively. This indicates that both azides **14** and **17**, once produced, were hardly susceptible to the S_H2' azidation. In contrast, when isomeric bromide **18** was treated with the reagent, compounds **14** (34%), **17** (27%), and **18** (12%) were obtained similar to the case of **13**. Based on these results, we propose that the addition of an azide radical to bromide **13** generates a Br radical that undergoes rapid addition to substrate **13** to generate regioisomeric bromide **18**. Then, **18** is further converted into compound **17** via a radical azidation.

With azide **14** in possession, we further endeavored to accomplish the total synthesis. Thus, azide **14** was subjected to catalytic hydrogenation followed by one-pot urea formation with Batey's reagent²⁰

Scheme 3 Plausible mechanisms of the production of regioisomeric byproducts **17** and **18**.

and subsequent desilylative cyclization with CsF to afford tetracyclic compound **15** in 51% yield over three steps. It should be mentioned that no purification was required in the three-step sequence, allowing ease of experimental operations. Finally, the known bromination protocol was applied to compound **15** to furnish (−)-agelastatin A (**1**).

In conclusion, we have established a new approach to (−)-agelastatin A (**1**) by the strategic implementation of brominative olefin transposition and subsequent S_H2' radical azidation. The present approach features a late-stage construction of D-ring that would allow facile production of D-ring analogues. We believe that the present synthesis would facilitate further development of new agelastatin analogues.

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Conflicts of interest

The authors declare no conflicts of interest.

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