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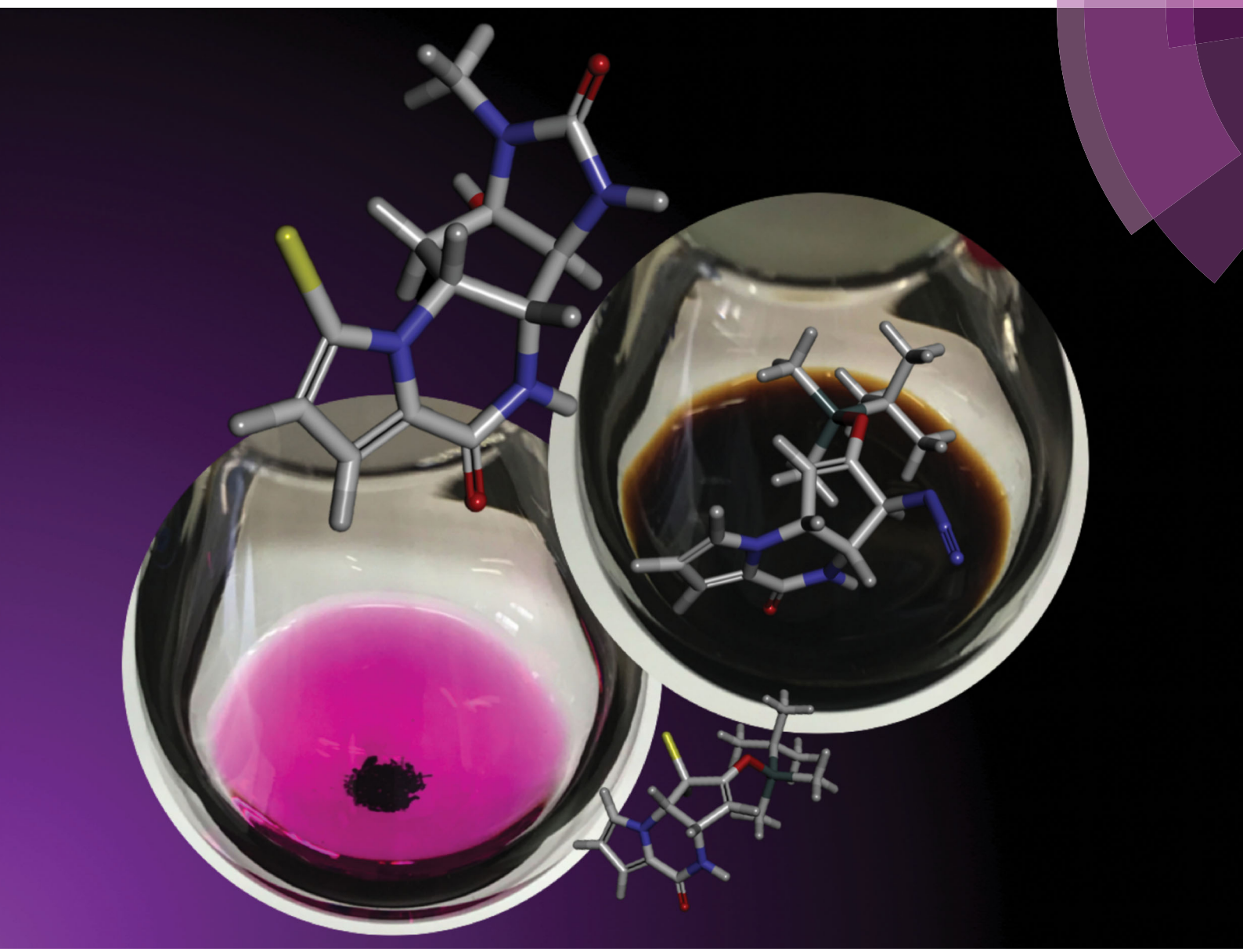

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Total synthesis of (−)-agelastatin A: an S_H2' radical azidation strategy†

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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-3β, 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**) as a promising anticancer agent.[7s] 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.

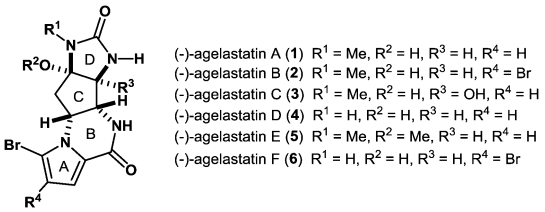

Fig. 1 Agelastatin alkaloids.

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 *N*1-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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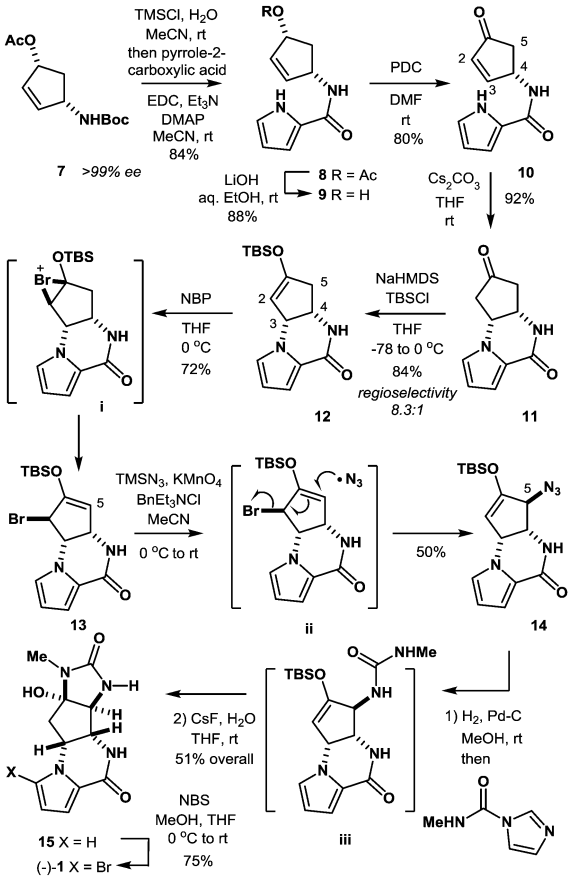
† Electronic supplementary information (ESI) available: Experimental procedures, characterization of new compounds including NMR spectra. CCDC 1852628. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc05697h



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** → **10** → **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

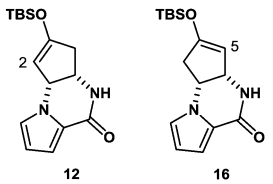


Fig. 2 TBS enol ethers **12** and **16** generated from **11**.

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

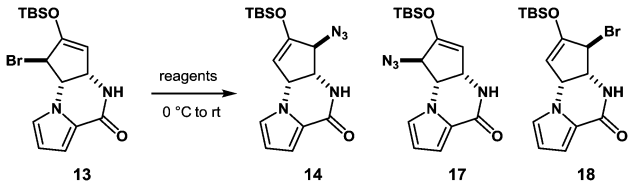
With compound **13** in possession, the nitrogen functionalization at C5 position was examined to access key intermediate **14** (Table 1). An attempted ionic S_N2' azidation of **13** with NaN_3 in DMF was unsuccessful (entry 5), giving rise to a desilylated product. To this end, we expected that the electrophilic nitrogen radical species would preferentially undergo an addition reaction with the electron-rich enol double bond to facilitate S_H2' 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 Mn(VII) 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).

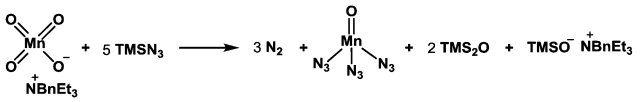
Jiao and co-workers have reported that Mn(III) generated from $MnBr_2$ in the presence of molecular oxygen serves as an effective catalyst to generate an azide radical from $TMSN_3$.[19a] We have examined $Mn(OAc)_3{\cdot}2H_2O$ in combination with $TMSN_3$ (6 equiv.) as a possible source of azido radical 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

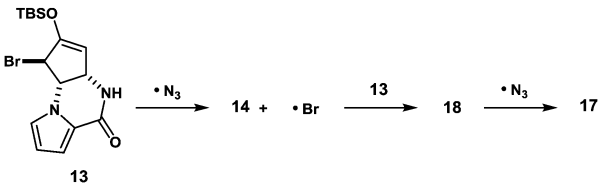


Entry	Reagents (equiv.)	Time	Yield[a] (%) 14	17	18	13[b]
1	$KMnO_4$ (0.3), $BnEt_3NCl$ (0.3), $TMSN_3$ (10), MeCN	40 min	50	21	3	Trace
2	$KMnO_4$ (0.1), $BnEt_3NCl$ (0.1), $TMSN_3$ (10), MeCN	40 min	30	4	12	30
3	$KMnO_4$ (0.1), $BnEt_3NCl$ (0.1), $TMSN_3$ (10), MeCN, O_2	40 min	31	5	11	21
4	$KMnO_4$ (0.6), $BnEt_3NCl$ (0.6), $TMSN_3$ (10), MeCN	40 min	43	11	4	9
5	NaN_3 (1.1), DMF[c]	15 min	—	—	—	—[d]
6	$BnEt_3NCl$ (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_2Cl_2[e]	40 min	24	17	14	6
9	$Mn(OAc)_3{\cdot}2H_2O$ (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.



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

species is generated from Mn(vii) with excess $TMSN_3$ 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 $TMSN_3$ 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 reagent[20] 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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