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Total synthesis of (–)-agelastatin A: an  $S_{\text{H}}2'$  radical azidation strategy



## Total synthesis of (–)-agelastatin A: an S<sub>H</sub>2' radical azidation strategy†

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A reagent generated from TMSN<sub>3</sub>/KMnO<sub>4</sub>/BnEt<sub>3</sub>NCl was found to promote an S<sub>H</sub>2' 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).<sup>1</sup> 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.<sup>2</sup> In 2010, Al-Mourabit and co-workers reported the isolation of agelastatins E (**5**) and F (**6**) from the New Caledonian sponge *A. dendromorpha*.<sup>3</sup> Early biological assessments of agelastatins conducted by the aforementioned laboratories have revealed that compound **1** exhibits remarkable properties, including antitumor activity,<sup>1,3</sup> brine shrimp toxicity,<sup>2</sup> and insecticidal activity.<sup>2</sup> In addition, Meijer and Pettit have found that agelastatin A (**1**) is a potent inhibitor of GSK-3β, a pivotal serine/threonine kinase.<sup>4</sup> 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.<sup>5</sup>

The biological significance of agelastatin A (**1**) has made it an attractive target for medicinal studies.<sup>6,7</sup> 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.<sup>7a</sup> In addition, structure–activity relationship (SAR) studies on agelastatin analogues have recently been disclosed by the groups of Molinski,<sup>8</sup> Romo/Liu,<sup>9</sup> and Movassaghi,<sup>10</sup> 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.<sup>11</sup> 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.<sup>12,13</sup> Movassaghi's group has further clarified that D-ring modifications expand the scope of derivatization of agelastatins to access potent analogues.<sup>10</sup>

In the present study, we have established a new route to agelastatin A (**1**) through an S<sub>H</sub>2' radical azidation protocol using TMSN<sub>3</sub>/KMnO<sub>4</sub>/BnEt<sub>3</sub>NCl 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).

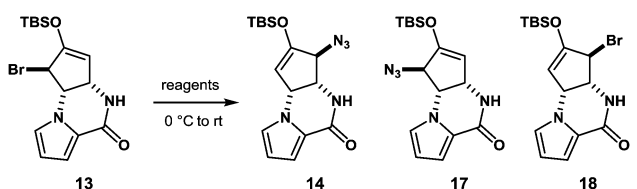
The synthesis was commenced with Boc-protected amino-alcohol derivative **7** (>99% ee).<sup>14</sup> The Boc group of **7** was removed with hydrochloric acid (HCl) generated *in situ* from TMSCl in aq. MeCN to provide an ammonium salt (structure not shown). After evaporation of the solvents under reduced pressure, the resultant crude product was coupled with pyrrole-2-carboxylic acid using EDC, Et<sub>3</sub>N, 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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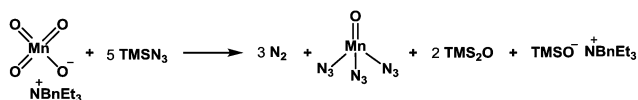


Table 1 Azidation of bromide **13** with various reagents


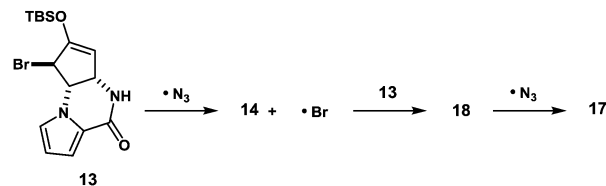
Entry	Reagents (equiv.)	Time	Yield <sup>a</sup> (%)			
			14	17	18	13 <sup>b</sup>
1	KMnO <sub>4</sub> (0.3), BnEt <sub>3</sub> NCl (0.3), TMSN <sub>3</sub> (10), MeCN	40 min	50	21	3	Trace
2	KMnO <sub>4</sub> (0.1), BnEt <sub>3</sub> NCl (0.1), TMSN <sub>3</sub> (10), MeCN	40 min	30	4	12	30
3	KMnO <sub>4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

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

<sup>d</sup> Bromoketone (60%) was produced. <sup>e</sup> The reaction was conducted at  $-78^{\circ}\text{C}$ .



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<sub>3</sub> 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<sub>3</sub> 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<sub>H</sub>2' 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<sup>20</sup>

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<sub>H</sub>2' 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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