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Total Synthesis of the β-Catenin Inhibitor, (−)-Agelastatin A: A Second-Generation Approach Based on Radical Aminobromination

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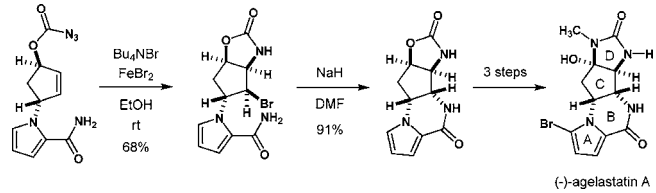
ABSTRACT



The second-generation approach to (−)-agelastatin A has been established. The present strategy features the $FeBr_2$-mediated radical cyclization of 2-cyclopentenyloxycarbonyl azide that allows for the stereoselective installation of a cis-vicinal aminobromo functionality suitable for producing the BCD-ring system of agelastatin A. The aminobromination method streamlines access to oxazolidinone, a key intermediate in the previously reported synthesis, thereby culminating in the new total synthesis of (−)-agelastatin A.

The potent antitumor activity of (−)-agelastatin A (**1**)[1] makes this unique alkaloid a highly attractive target for chemical synthesis.[2] Special interest in its mode of action has emerged because of the recent report by the laboratory of Hale and El-Tanani, which indicated that (−)-agelastatin A (**1**) inhibits osteopontin-mediated malignant transformation through its potent downregulation of β-catenin expression and its simultaneous upregulation of Tcf-4 levels within human cancer cells. As such, (−)-agelastatin A has been shown to function as a new powerful antimetastatic agent.[3]

Our laboratory has been fascinated by this natural compound and has recently accomplished a stereospecific synthesis of (−)-**1**[4] by a strategy featuring an intramolecular aziridination followed by a nucleophilic azidation that allowed for a net trans-diamination suitable for producing

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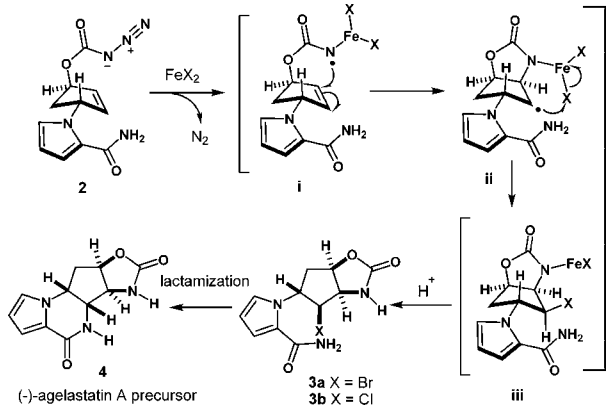
the agelastatin core. In the present study, we established a second-generation route to (−)-**1** by utilizing the $FeBr_2$-initiated radical cyclization of azidoformate **2** to streamline access to the oxazolidinone lactam **4**, which can be readily transformed into (−)-agelastatin A (**1**).

The new route occurred to us with the prospect that the β-aminohalogen motif, an aziridine equivalent, would enable stereospecific installation of the trans-diamino group present in the agelastatin core by lactamization with a 2-pyrrocarboxamide group. In this context, pioneering studies on radical amination by Bach showed that with iron(II) chloride ($FeCl_2$), 2-alkenyloxycarbonyl azides undergo radical cyclization to produce β-chlorinated cyclic carbamates.[5,6] The significance of this transformation arises from the stereochemical outcome of the halogen transfer. Bach's studies revealed that the halogen atom is introduced stepwise to a transient carbon-centered radical in the reaction. It was our belief that if the carbon−radical intermediate that was generated after N−C bond formation was conformationally fixed, the halogen might be stereoselectively transferred from the coordinated metal halogen species. Therefore, we envisioned that cyclic substrate **2** could bring about a high degree of stereocontrol because of its restricted rotation during the halogen atom transfer step (**2** → **i** → **ii** → **iii**) to afford halide **3a** or **3b**, suitable precursors for producing lactam **4** (Scheme 1). These

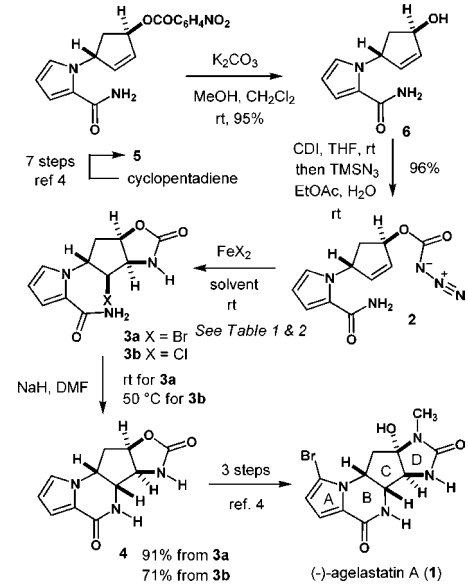
Scheme 1. Key Transformations of Second-Generation Approach to (−)-Agelastatin A (**1**)



prospects thus inspired us to devise a new radical-based route to (−)-**1** via the two-step transformation of azidoformate **2** into lactam **4**, a key intermediate employed in our previous agelastatin synthesis.

The present route commenced from 4-nitrobenzoate **5**, a known material in our first-generation synthesis.[4] Methanolysis of compound **5** with K_2CO_3 smoothly took place in MeOH−CH_2Cl_2 at room temperature to give alcohol **6** in 95% yield (Scheme 2). Installation of an azidocarbonyl group

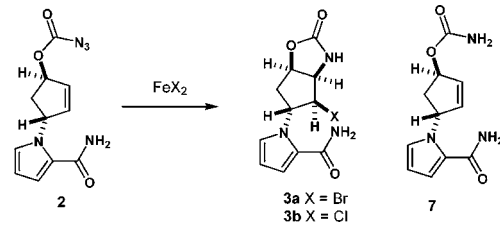
Scheme 2. Second-Generation Total Synthesis of Agelastatin A (**1**)



into this alcohol was carried out via a one-pot protocol; alcohol **6** was initially treated with *N*,*N*-carbonyldiimidazole (CDI) in THF at room temperature. Then, the resulting imidazolide intermediate was subjected to azidation with $TMSN_3$ in a two-phase mixture of EtOAc and H_2O at room temperature, providing azidoformate **2** in 96% yield.

With compound **2**, we evaluated iron(II) halide-promoted radical aminohalogenation reactions (Table 1).[7] As expected,

Table 1. Iron(II) Halide-Promoted Radical Aminohalogenation of Azidoformate **2**



entry	reagents (equiv)	solvent	time (h)	yield (%)[a]
1	$FeBr_2$ (1)	MeCN	5	**3a** (65), **7** (13)
2	$FeBr_2$ (1)	EtOH	48	**3a** (65), **7** (8)[b]
3	$FeBr_2$ (0.1), TMSBr (3)	MeCN	3	**3a** (66)
4	$FeCl_2$ (1)	MeCN	22	**3b** (15), **7** (3)[c]
5	$FeCl_2$ (1)	EtOH	23	**3b** (24), **7** (9)[d]
6	$FeCl_2$ (0.1), TMSCl (1.5)	MeCN	20	**3b** (37)
7	$FeCl_2$ (0.1), TMSCl (1.5)	EtOH	28	**3b** (31)[e]

[a] For the details of other minor byproducts, see the Supporting Information. [b] 15% of azide **2** was recovered. [c] 65% of azide **2** was recovered. [d] 33% of azide **2** was recovered. [e] 18% of azide **2** was recovered.

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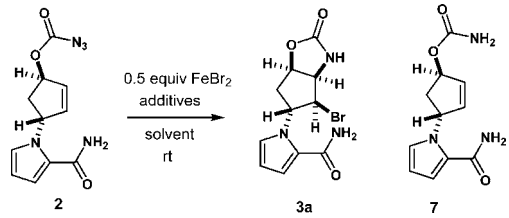
(7) One can reasonably assume that heating compound **2** would lead to aziridine which, by ring-opening with the carbamoyl group at the 2-position of the pyrrole ring, would provide desired lactam **4**. However, such attempts only gave a complex mixture without any detectable lactam **4**.

both $FeBr_2$ and $FeCl_2$ were effective for transferring the aminohalogen functionality, giving rise to desired halogenated oxazolidinones **3a** and **3b**, respectively. Stoichiometric use of $FeBr_2$ gave bromide **3a** in 65% yield along with a small amount of uncyclized carbamate **7** (entry 1). EtOH also served as a useful medium and aminobromination product **3a** was produced in 65% yield (entry 2). According to Bach's reports, we envisioned that a trimethylsilyl halide would allow this radical aminobromination process to become catalytic (entry 3). Indeed, catalytic use of $FeBr_2$ (0.1 equiv) in combination with TMSBr (3 equiv) led to bromide **3a** in satisfactory yield. $FeCl_2$ was also examined under various conditions (entries 4−7). Although stoichiometric $FeCl_2$ was found to afford **3b** in a rather poor yield (~24%), use of Bach's catalytic conditions in the presence of 1.5 equiv of TMSCl slightly increased the yields (entries 6 and 7). Switching from MeCN to EtOH under these catalytic reaction conditions led to a slight decrease in product yield as well as a prolonged reaction time.

The relative configurations of products **3a** and **3b** were unambiguously determined by NOE experiments that showed proximity between methine protons at the newly introduced stereocenters. This stereochemical outcome agreed well with a mechanistic rationale that hypothesized the coordination of iron(II) complex **ii** with the carbamoyl nitrogen atom, as shown in Scheme 1. Thus, aminohalogenation of **2** yielded cis-arranged vicinal aminohalogenated products **3a** and **3b** stereoselectively with the halogen atom coming from the concave face of the newly formed bicyclic oxazolidinone scaffold.

We further investigated the effects of several bromide salts as additives that would allow us to reduce the required quantity of $FeBr_2$ (Table 2). On the basis of the hypothetical

Table 2. Iron(II) Bromide-Promoted Radical Aminobromination of Azidoformate **2**



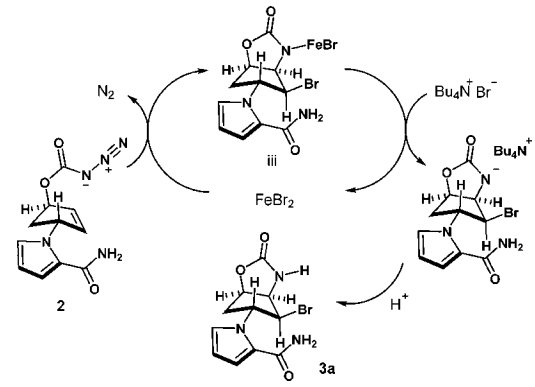
2 3a 7

entry	additive (equiv)	solvent	time (h)	yield (%)[a]
1	LiBr (1.5), 15-crown-5 (1.5)	MeCN	23	**3a** (62)
2	LiBr (1.5)	EtOH	50	**3a** (64), **7** (5)
3	Bu_4NBr (1.5)	MeCN	25	**3a** (62), **7** (trace)
4	Bu_4NBr (1.5)	EtOH	19	**3a** (68), **7** (11)
5	none	EtOH	111	**3a** (28), **7** (5)

[a] For the details of other minor byproducts, see the Supporting Information.

cycle where a bromide ion may regenerate $FeBr_2$, as shown in Scheme 3,[8] we evaluated representative bromides, LiBr and Bu_4NBr, as the bromine atom source. Table 2 clearly demonstrates that the addition of these salts promoted bromination to moderately increase the yield of compound

Scheme 3. Hypothetical Bromide Exchange in Iron(II) Bromide-Promoted Radical Aminobromination of Azidoformate **2**



3a: only 28% of **3a** was obtained in the absence of these salts (entry 5), whereas the addition of the salts increased the yield of **3a** to twice that of the former (entries 1−4).[9] There was essentially no difference in the yields of **3a** when the solvent was switched, i.e., MeCN vs. EtOH. However, the reaction was slightly accelerated when EtOH was used as the solvent in the presence of Bu_4NBr (entries 3 and 4).

Our hypothetical scheme for the regeneration of $FeBr_2$ through bromide exchange was supported by the following comparison experiments: compound **2** was initially subjected to aminochlorination by using 0.5 equiv of $FeCl_2$. After 23 h at which time no more free $FeCl_2$ seemed to remain in the reaction mixture, 1.5 equiv of Bu_4NBr was added and the mixture was stirred for an additional 47 h. ^1H NMR analysis of the products suggested that both chloride **3b** and bromide **3a** were produced in a ratio of 5:4 in 40% combined yield (bromide **3a** 18% and chloride **3b** 22%). In contrast, chloride **3b** was obtained in 24% yield in the absence of Bu_4NBr after 23 h, indicating that the 18% yield of bromide **3a** was produced by iron(II) bromide species, such as FeClBr and $FeBr_2$, both of which could be regenerated by the exchange of the iron(II)−substrate complex with a bromide ion. In another control experiment, we were able to confirm that no reactive $FeCl_2$ existed in the reaction mixture after 23 h. Thus, the reaction mixture was stirred for a long time, ca. 70 h, giving **3b** in 20% yield. This result indicated that the aminobromination took place not via rapid exchange of the remaining $FeCl_2$ with Bu_4NBr, but via exchange of the coordinated iron(II) species with Bu_4NBr.[10]

Then, halides **3a** and **3b** were subjected to base-mediated lactamization, respectively (Scheme 2). Treatment of bromide **3a** with NaH in DMF at room temperature promoted facile

(8) It is likely that iron(II) complexes are solvated in the reaction mixture. For instance, $FeBr_2$ has been shown to form a stable terahydrate complex with water (*Inorg. Chim. Acta*, **1992**, *192*, 173). Because of its clarity, however, the mechanism shown in Schemes 1 and 3 omitted the solvating molecules.

(9) Further reduction of the amount of $FeBr_2$ led to a significant decrease in product yield; for instance, the use of $FeBr_2$ (0.2 equiv) in the presence of Bu_4NBr (1.5 equiv) gave only 35% of **3a**. The origin of the retardation under these conditions is currently unclear.

lactamization, furnishing lactam **4** in 91% yield. Chloride **3b** was, however, slightly less reactive than bromide **3a** and required gentle heating at 50 °C to ensure the production of lactam **4**. The previously reported three-step manipulation of lactam **4** delivered (−)-agelastatin A (**1**). The present approach has allowed us to considerably reduce the number of steps necessary for delivering key intermediate **4**, facilitating more rapid access (14 steps including one-pot operations from cyclopentadiene) to the target compound than our first-generation synthesis.

In conclusion, we have established a second-generation route to (−)-agelastatin A (**1**). The present approach uses an Fe(II) halide-mediated radical aminobromination of 2-cyclopentenyloxy azidoformate **2** followed by facile lactamization under very mild conditions. The new route has allowed us to streamline the chemical processes necessary for producing key lactam intermediate **4**; the lactam was obtainable from readily available precursor **5** in four steps (including one-pot operation), in contrast to the previous approach that required eight manipulations. Further application of radical aminohalogenation that would provide latent aziridine functionality is currently being undertaken with a view to synthesizing structurally elaborated nitrogen-containing natural products of biological significance.

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Supporting Information Available: Experimental procedures, characterization data, and $^{1}H/^{13}C$ NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) One of the reviewers has pointed out that a stable $[FeBr_4][Et_4N]_2$ complex is generated by reacting 1 equiv of $FeBr_2$ with 2 equiv of Et_4NBr (*Inorg. Synth.* **1967**, *9*, 139). The present conditions may also produce such bis(tetraalkylammonium) tetrabromoferrate(II) complex in the reaction mixture. Nevertheless, our successful aminobromination reactions indicate that the iron(II) complex serves as an efficient radical mediator to deliver aminobromides.