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# Iterative synthesis of nitrogen-containing polyketide *via* oxime intermediates†

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Typical polyketides consist of C, H, and O atoms, whereas several types of N-containing polyketides are known to show intriguing properties. Because conventional synthetic approaches for such compounds focus on only specific structures, a more general method is desirable. Here, we have developed an iterative synthesis of nitrogen-containing polyketide. Chain elongation of carboxylic acid *via* decarboxylative Claisen condensation with malonic acid half thioester was iteratively performed to construct carbon frameworks.  $\beta$ -Keto groups formed by the chain elongation were appropriately converted to *O*-methyl oximes for incorporation of nitrogen atoms. Cyclization of the resulting oxime intermediates followed by reductive N–O cleavage afforded structurally diverse nitrogen-containing polyketides such as 2-pyridone, 4-aminopyrone, and 4-aminosalicylate. This method was finally applied to the synthesis of (*R*)-6-aminomellein, which is a nitrogen-substituted derivative of bioactive compound, (*R*)-6-methoxymellein. The versatility of the present method would enable the synthesis of diverse polyketides with nitrogen functional groups, which can be potentially utilized for the development of novel bioactive compounds.

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## Introduction

Polyketides constitute an important class of secondary metabolites owing to their biological activities and have been utilized for potent pharmaceuticals.<sup>1</sup> We have recently developed an iterative method for polyketide synthesis inspired by the biosynthetic mechanism.<sup>2</sup> In this method, chain elongation of carboxylic acid *via* decarboxylative dehydration condensation with malonic acid half thioester (MAHT) is iteratively performed to form polyketide precursors. The advantage of the above strategy is that a variety of structures can be constructed by a tailored method, and chemical modifications such as reduction or alkylation can be easily made to the intended positions.

Similar to the typical natural polyketides, the constituent elements of the products obtained by our method are limited to carbon, hydrogen, and oxygen. Meanwhile, several types of nitrogen-containing polyketides are known in nature.<sup>3</sup> For example, 2-pyridone is one of the most notable compounds because of their intriguing and valuable biological properties,<sup>4</sup> and the studies on their chemical synthesis has attracted much attention<sup>5,6</sup> (Fig. 1a). In addition, the replacement of oxygen functional group in polyketides with nitrogen counterparts can be an effective approach for drug design. Wang and co-workers reported the development of E6201, a novel compound exhibiting anti-inflammatory effect, by replacing methoxy group of

natural polyketide with ethylamino group<sup>7</sup> (Fig. 1b). From these points of view, the versatile method for the synthesis of nitrogen-containing polyketide is of great value, and we considered that our iterative method has potential to be utilized for such strategy on account of its flexibility.

The proposed method is shown in Scheme 1. The carbon frameworks are iteratively constructed by the condensation with MAHT **1**. The  $\beta$ -keto group formed in each chain elongation is converted to *O*-methyl oxime (or protected as appropriate). Oxime intermediates thus obtained are cyclized, and the N–O bond is cleaved to afford nitrogen-containing polyketides.

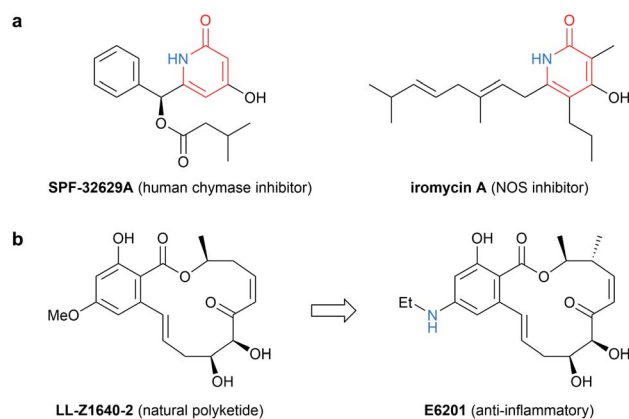
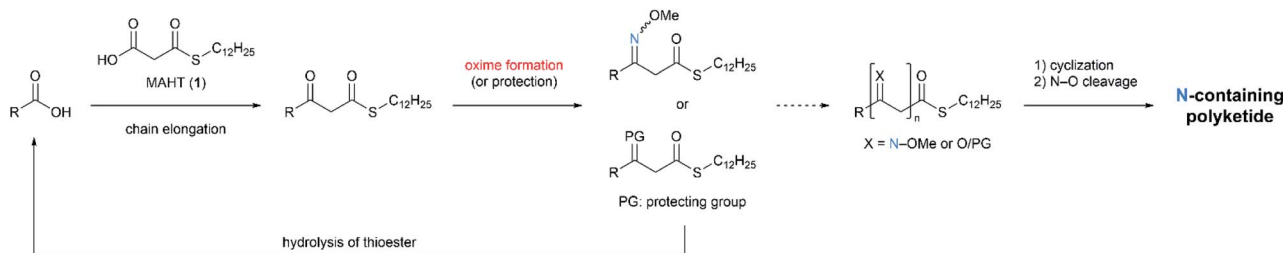


Fig. 1 (a) Natural bioactive 2-pyridone compounds. (b) Replacement of methoxy group in natural polyketide with ethylamino group for the discovery of E6201.

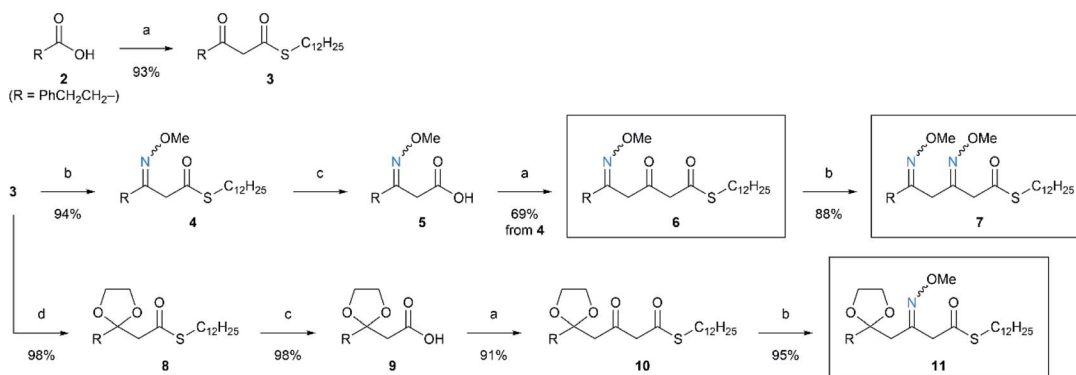
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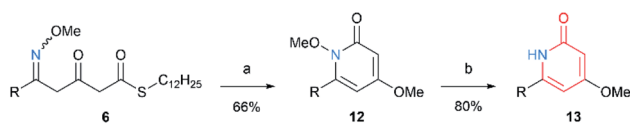




Scheme 1 Proposed method for the synthesis of nitrogen-containing polyketide. R = alkyl group.



Scheme 2 Synthesis of linear triketide compounds with *O*-methyl oxime(s): (a) COMU, DIEA, then **1**, *i*PrMgBr, DME, rt; (b) MeONH<sub>2</sub>·HCl, CH<sub>2</sub>Cl<sub>2</sub>/pyridine, rt; (c) CsOH, H<sub>2</sub>O<sub>2</sub>, 1,4-dioxane/H<sub>2</sub>O, rt; (d) TMSO(CH<sub>2</sub>)<sub>2</sub>OTMS, TMSOTf, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt.



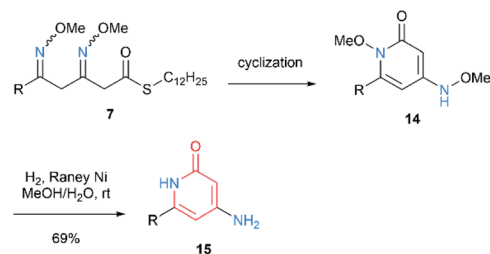
Scheme 3 Formation of 2-pyridone structure through cyclization of **6** and reductive N–O bond cleavage: (a) DBU, CH<sub>2</sub>Cl<sub>2</sub>, rt, then (MeO)<sub>2</sub>SO<sub>2</sub>, DIEA, rt; (b) Sml<sub>2</sub>, THF, rt.

## Results and discussion

We started from the synthesis of nitrogen-containing triketide compounds to confirm the viability of the proposed method (Scheme 2). Firstly, chain elongation of carboxylic acid **2** with MAHT **1** was carried out according to our previous reports.<sup>2a</sup> The keto group of the resulting  $\beta$ -ketothioester **3** was subjected to condensation with *O*-methyl hydroxylamine hydrochloride to give *O*-methyl oxime **4** in high yield. Hydrolysis of this compound followed by second chain elongation gave  $\delta$ -methoxyimino- $\beta$ -ketothioester **6**. The second oxyamation could be carried out on **6** under the same conditions as the first one to form  $\beta,\delta$ -bis(methoxyimino)thioester **7**. On the other hand, the  $\beta$ -keto group of **3** was protected as 1,3-dioxolane to afford thioester **8**, which was converted to  $\beta$ -ketothioester **10** *via* carboxylic acid **9** by hydrolysis and chain elongation as reported.<sup>2a</sup> The oxime formation on **10** gave  $\beta$ -methoxyiminiothioester **11**. Thus, the series of linear triketides **6**, **7**, and **11** containing the oxime(s) in different positions were synthesized.

Having the linear oxime intermediates in hand, we sought the optimal conditions for cyclization and N–O scission. At first, we treated the precursor **6** with DBU to induce cyclization *via* acyl substitution of thioester with oxime nitrogen, and subsequent methylation afforded *N*-methoxy-2-pyridone **12** (Scheme 3). The N–O bond of the product **12** was successfully cleaved by

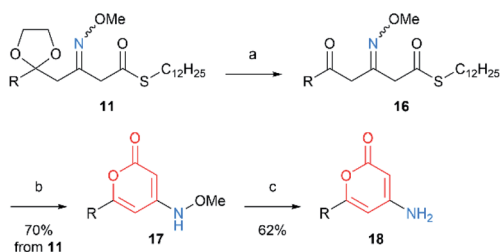
Table 1 Cyclization of **7** and reductive N–O bond cleavage for the formation of 4-amino-2-pyridone



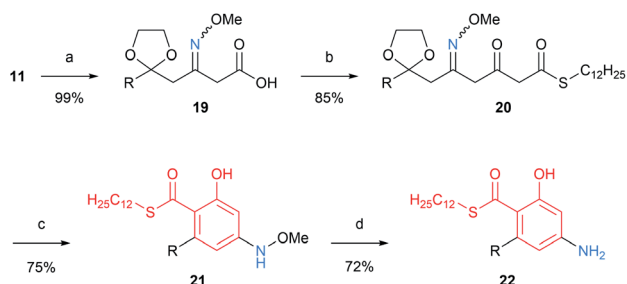
Entry	Cyclization conditions <sup>a</sup>	Yield <sup>b</sup> of <b>14</b> (%)
1	DBU, CH <sub>2</sub> Cl <sub>2</sub> , 8 h	n.r.
2	KHMDS, CH <sub>2</sub> Cl <sub>2</sub> , 8 h	n.r.
3	NBS, CH <sub>2</sub> Cl <sub>2</sub> , 1.5 h	0
4	Cu(OTf) <sub>2</sub> , THF, 2 h	n.r.
5	CF <sub>3</sub> CO <sub>2</sub> Ag, THF, 2 h	23
6	CF <sub>3</sub> CO <sub>2</sub> Ag, oxyma, THF, 24 h	74

<sup>a</sup> All of the reactions were performed at room temperature. <sup>b</sup> Isolated yield.





**Scheme 4** Formation of 4-amino-2-pyrone structure through cyclization of **11** and reductive N–O bond cleavage: (a) conc. HCl/1,4-dioxane, rt; (b) CF<sub>3</sub>CO<sub>2</sub>Ag, oxyma, THF, rt; (c) Sml<sub>2</sub>, THF, rt.



**Scheme 5** Chain elongation for the linear tetraketide compounds with *O*-methyl oxime and the formation of 4-aminosalicylate structure through cyclization of **20** and reductive N–O bond cleavage: (a) CsOH, H<sub>2</sub>O<sub>2</sub>, 1,4-dioxane/H<sub>2</sub>O, rt; (b) COMU, DIEA, then **1**, iPrMgBr, DME, rt; (c) conc. HCl/1,4-dioxane, rt, then Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt; (d) Sml<sub>2</sub>, THF, rt.

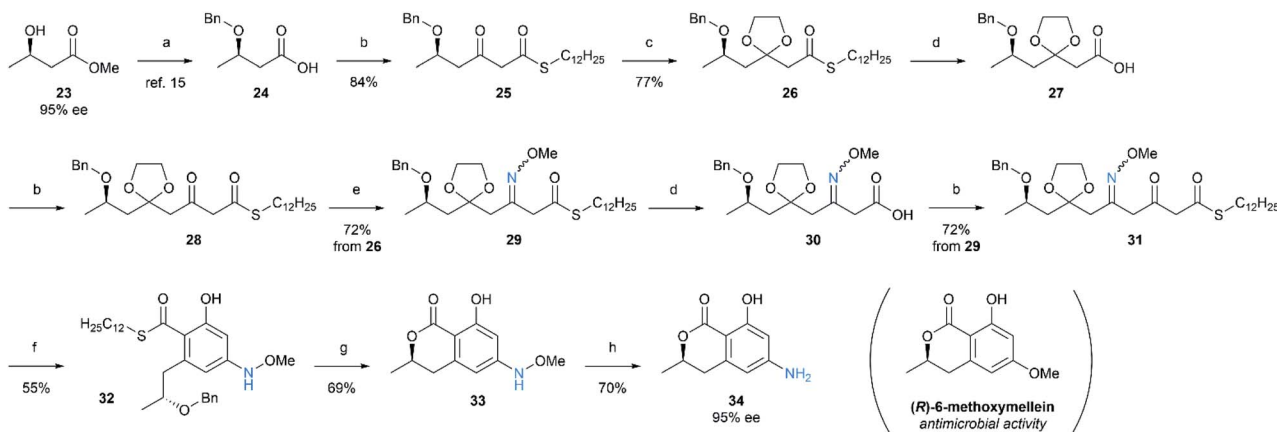
the treatment with samarium(II) iodide<sup>8</sup> under mild conditions to give the desired product, 2-pyridone **13**.

Next, we applied the above cyclization conditions to **7** but no conversion was observed (Table 1, entry 1). Use of stronger base also resulted in no reaction (entry 2). Hence, we tried the cyclization through activation of thioester using thiophilic reagents. When we used NBS,<sup>9</sup> the starting material was consumed but complex mixture was obtained without the desired product (entry 3). While Cu(II)<sup>10a</sup> did not promote the

intended reaction (entry 4), Ag(I)<sup>10</sup> quickly converted the thioester and afforded the cyclized product with low yield (entry 5). This result seemed to be due to side reactions through ketene formation.<sup>10e</sup> Fortunately, we eventually found that use of ethyl 2-cyano-2-(hydroxyimino)acetate (oxyma), a recently developed additive for peptide synthesis,<sup>11</sup> suppressed the side reactions and gave the desired product in good yield<sup>12</sup> (entry 6). Both of the two N–O bonds in **14** were reductively cleaved by RANEY® Ni to generate 4-amino-2-pyridone **15**.<sup>13</sup> Then, we conducted deprotection of 1,3-dioxolane in **11** for subsequent cyclization. Notably, the oxime moiety was stable under the moderately acidic hydrolysis conditions, and β-methoxyimino-δ-keto-thioester **16** was obtained. Subsequently, the same procedure was followed for **7**. The cyclization proceeded *via* an intramolecular transesterification to give 4-methoxyamino-2-pyrone **17** (Scheme 4). Finally, the N–O bond cleavage was done by samarium(II) iodide, furnishing **18**. The 4-amino-2-pyrone structure thus obtained has a few examples of existence in natural polyketide compounds.<sup>14</sup> These results demonstrated that the structure of products can be diversified by simply changing the position of oxime(s) in linear intermediates.

This method was further extended to nitrogen-containing tetraketide compound by performing three chain elongations (Scheme 5). Hydrolysis of thioester **11** and chain elongation of the resulting carboxylic acid **19** gave β-ketothioester **20**. Deprotection of 1,3-dioxolane followed by cyclization resulted in the formation of salicylate **21**. Remarkably, the cyclization proceeded *via* an intramolecular aldol condensation in priority to potentially competing 2-pyridone formation by employing the suitable reaction conditions. Samarium(II) iodide was also available in the cleavage of N–O bond in **21**, and 4-aminosalicylate **22** was obtained.

Finally, we applied the present method to the synthesis of amino analogue of a natural polyketide with oxyfunctionality. (*R*)-6-Methoxymellein is a dihydroisocoumarin compound isolated from carrot cells, and it is known as a phytoalexin which inhibits the growth of several fungi and bacteria.<sup>15</sup> We chose this compound as a target molecule for our purpose, and



**Scheme 6** Synthesis of (*R*)-6-aminomellein: (a) (i) benzyl 2,2,2-trichloroacetimidate, TfOH, 4 Å molecular sieves, cyclohexane/CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt; (ii) LiOH, THF/H<sub>2</sub>O, rt; (b) COMU, DIEA, then **1**, iPrMgBr, DME, rt; (c) TMSO(CH<sub>2</sub>)<sub>2</sub>OTMS, TBSOTf, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (d) CsOH, H<sub>2</sub>O<sub>2</sub>, 1,4-dioxane/H<sub>2</sub>O, rt; (e) MeONH<sub>2</sub>·HCl, CH<sub>2</sub>Cl<sub>2</sub>/pyridine, rt; (f) TsOH·H<sub>2</sub>O, acetone, rt, then Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt; (g) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C; (h) Sml<sub>2</sub>, THF, rt.



carried out the synthesis of 6-demethoxy-6-amino analogue of the compound (Scheme 6). The synthesis was launched from carboxylic acid **24** prepared from commercially available chiral alcohol **23**.<sup>16</sup> After chain elongation, the  $\beta$ -keto group of **25** was protected as 1,3-dioxolane. The thioester **26** was hydrolyzed to generate carboxylic acid **27**, which was followed by second chain elongation to give **28**. Here, the resulting  $\beta$ -keto group was converted to oxime for the O to N replacement giving **29**. Carboxylic acid **30** was obtained by hydrolysis of the thioester **29**, and subsequent third chain elongation gave a linear precursor **31**. Removal of 1,3-dioxolane followed by cyclization yielded salicylate **32**. Deprotection of benzyl ether and lactonization proceeded simultaneously by the action of  $\text{BBr}_3$  to afford lactone **33**. Finally, N–O bond cleavage by samarium(II) iodide was carried out to give (*R*)-6-aminomellein (**34**). Remarkably, no stereochemical erosion occurred along the synthesis, and the product was obtained with high optical purity.

## Conclusions

We have developed the iterative strategy for the synthesis of nitrogen-containing polyketides. Because the chain elongation was performed in the iterative manner inspired by polyketide biosynthesis, the length of carbon chain and the position of *O*-methyl oxime could be easily changed. Therefore, the products with a variety of structures were obtained by the uniformed protocol. The synthesis of nitrogen-substituted natural compound demonstrated the feasibility of present method for the development of novel bioactive compounds. We believe that this method can be further extended to more complicated compounds derived from longer intermediates by combining with the synthetic method such as convergent strategy.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## Notes and references

- Comprehensive Natural Products III*, ed. H.-W. Liu and T. P. Begley, Elsevier, Amsterdam, 2020, vol. 1.
- (a) K. Akagawa and K. Kudo, *Chem. Commun.*, 2017, **53**, 8645; (b) K. Akagawa and K. Kudo, *J. Org. Chem.*, 2018, **83**, 4279; (c) Y. Takeuchi, K. Akagawa and K. Kudo, *J. Org. Chem.*, 2021, **86**, 17307.
- (a) M. A. Fischbach and C. T. Walsh, *Chem. Rev.*, 2006, **106**, 3468; (b) D. Boettger and C. Hertweck, *ChemBioChem*, 2013, **14**, 28; (c) F. Hemmerling and F. Hahn, *Beilstein J. Org. Chem.*, 2016, **12**, 1512; (d) A. Miyayama, F. Kudo and T. Eguchi, *Nat. Prod. Rep.*, 2018, **35**, 1185.
- (a) T. Shimatani, N. Hosotani, M. Ohnishi, K. Kumagai and I. Saji, *J. Antibiot.*, 2006, **59**, 29; (b) F. Surup, O. Wagner, J. Von Frieling, M. Schleicher, S. Oess, P. Müller and S. Grond, *J. Org. Chem.*, 2007, **72**, 5085; (c) M. N. Thaker, M. García, K. Koteva, N. Waglechner, D. Sorensen, R. Medina and G. D. Wright, *MedChemComm*, 2012, **3**, 1020; (d) A. Haga, H. Tamoto, M. Ishino, E. Kimura, T. Sugita, K. Kinoshita, K. Takahashi, M. Shiro and K. Koyama, *J. Nat. Prod.*, 2013, **76**, 750; (e) J. Han, C. Liu, L. Li, H. Zhou, L. Liu, L. Bao, Q. Chen, F. Song, L. Zhang, E. Li, L. Liu, Y. Pei, C. Jin, Y. Xue, W. Yin, Y. Ma and H. Liu, *J. Org. Chem.*, 2017, **82**, 11474; (f) A. Chicca, R. Berg, H. J. Jessen, N. Marck, F. Schmid, P. Burch, J. Gertsch and K. Gademann, *Bioorg. Med. Chem.*, 2017, **25**, 6102; (g) W. Y. Zhang, Y. Zhong, Y. Yu, D. F. Shi, H. Y. Huang, X. L. Tang, Y. H. Wang, G. D. Chen, H. P. Zhang, C. L. Liu, D. Hu, H. Gao and X. S. Yao, *J. Nat. Prod.*, 2020, **83**, 3338.
- For the examples shown in Fig. 1, see: (a) S. R. Vegi, S. K. Boovanahalli, A. P. Sharma and K. Mukkanti, *Tetrahedron Lett.*, 2008, **49**, 6297; (b) H. Shojaei, Z. Li-Böhmer and P. Von Zezschwitz, *J. Org. Chem.*, 2007, **72**, 5091; (c) S. R. Vegi, S. K. Boovanahalli, B. Patro and K. Mukkanti, *Eur. J. Med. Chem.*, 2011, **46**, 1803.
- Synthetic methods for 2-pyridone structure were reported. For review, see: (a) H. J. Jessen and K. Gademann, *Nat. Prod. Rep.*, 2010, **27**, 1168; (b) W. S. Hamama, M. Waly, I. El-Hawary and H. H. Zoorob, *Synth. Commun.*, 2014, **44**, 1730; (c) M. M. K. Amer, M. A. Aziz, W. S. Shehab, M. H. Abdellattif and S. M. Mouneir, *J. Saudi Chem. Soc.*, 2021, **25**, 101259. For selected papers, see: (d) S. C. Yu, Y. R. Ka, O. K. Young, Y. H. Joo, J. Hong, H. Shin and S. G. Lee, *J. Org. Chem.*, 2009, **74**, 7556; (e) B. H. Patel, A. M. Mason and A. G. M. Barrett, *Org. Lett.*, 2011, **13**, 5156; (f) H. S. P. Rao, N. Muthanna and A. H. Padder, *Synlett*, 2018, **29**, 1649.
- Y. Shen, R. Boivin, N. Yoneda, H. Du, S. Schiller, T. Matsushima, M. Goto, H. Shirota, F. Gusovsky, C. Lemelin, Y. Jiang, Z. Zhang, R. Pelletier, M. Ikemori-Kawada, Y. Kawakami, A. Inoue, M. Schnaderbeck and Y. Wang, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3155.
- Samarium(II) iodide-mediated reductive cleavage of N–O bonds in *O*-alkylhydroxylamine and its *N*-acylated derivatives were reported: (a) G. E. Keck, S. F. McHardy and T. T. Wager, *Tetrahedron Lett.*, 1995, **36**, 7419; (b) J. L. Chiara, C. Destabel, P. Gallego and J. Marco-Contelles, *J. Org. Chem.*, 1996, **61**, 359; (c) G. E. Keck, T. T. Wager and S. F. McHardy, *Tetrahedron*, 1999, **55**, 11755.
- (a) T. Kumamoto and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 2111; (b) H. Minato, H. Kodama, T. Miura and M. Kobayashi, *Chem. Lett.*, 1977, **6**, 413.
- (a) S. Masamune, Y. Hayase, W. Schilling, W. K. Chan and G. S. Bates, *J. Am. Chem. Soc.*, 1977, **99**, 6756; (b) P. M. Booth, C. M. J. Fox and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1987, 121; (c) S. V. Ley, S. C. Smith and P. R. Woodward, *Tetrahedron*, 1992, **48**, 1145; (d) G. Zhou, D. Lim and D. M. Coltart, *Org. Lett.*, 2008, **10**, 3809; (e) A. E. May and T. R. Hoye, *J. Org. Chem.*, 2010, **75**, 6054.



- 11 R. Subirós-Funosas, R. Prohens, R. Barbas, A. El-Faham and F. Albericio, *Chem.–Eur. J.*, 2009, **15**, 9394.
- 12 We speculate that nucleophilic oxyma effectively traps the ketene species generated from **7** by the action of Ag(i), and the resulting ester is reactive enough to be attacked by the oxime nitrogen, affording the cyclized product **14**.
- 13 When samarium(II) iodide was used for this reaction, only one N–O bond was cleaved to give 4-methoxyamino-2-pyridone, and the desired product **15** was not obtained.
- 14 K. M. Jenkins, S. G. Toske, P. R. Jensen and W. Fenical, *Phytochemistry*, 1998, **49**, 2299.
- 15 F. Kurosaki and A. Nishi, *Phytochemistry*, 1983, **22**, 669.
- 16 H. Liu, Y. Zhang, R. Wei, G. Andolina and X. Li, *J. Am. Chem. Soc.*, 2017, **139**, 13420.

