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Total Synthesis of (−)-Agelastatin A

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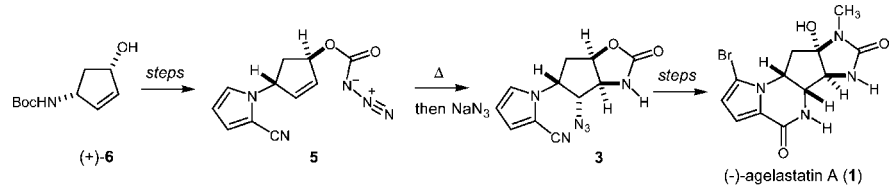
ABSTRACT



A new route to (−)-agelastatin A is reported. The requisite nitrogen functionalities of the agelastatin core have been installed by intramolecular aziridination of an azidoformate and subsequent regioselective azidation, leading to net *trans*-diamination of the double bond. The present synthesis also demonstrates two new protocols for the preparation of an imidazolidinone hemiaminal motif from an oxazolidinone intermediate which comprise sequential *N-tert*-butoxycarbonylation, urea formation, hydrolysis, and oxidative cyclization, and direct aminolysis and subsequent oxidative cyclization.

(−)-Agelastatin A (**1**) is a unique tetracyclic oroidin alkaloid isolated from the axinellid marine sponge *Agelas dendromorpha* in 1993 by Pietra and co-workers.[1] This naturally occurring compound exerts potent antiproliferative activity toward several human cancer cell lines as well as glycogen synthase kinase-3β (GSK-3β) inhibitory activity, and as such has attracted considerable biological interest.[2]

As part of our effort to develop new agents for molecularly targeted cancer therapy, we have been engaging in the chemical synthesis of several natural and synthetic leads for preclinical research.[3] In this context, the potent biological activities of (−)-agelastatin A have inspired us to pursue an enantioselective approach that would provide a basis for suitable derivatizations and allow further biological evaluations.[4] In the present paper, we report a new route for the asymmetric synthesis of (−)-agelastatin A featuring stereospecific diamination of the central cyclopentane motif to create an array of nitrogen-substituted stereogenic centers.

In our retrosynthetic analysis of agelastatin A (**1**), we dissected the 6-membered lactam (B ring) and the imidazolidinone motif (D ring) into cyclization precursors (**2** and **3**) (Scheme 1). We envisaged that oxazolidinone **3** would serve as an appropriate precursor of ketone **2** to produce a hemiaminal scaffold and that **3** having requisite nitrogen functionalities would be produced by sequential nitrogen

(1) (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305. (b) Guerriero, A.; D'Ambrosio, M.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1994**, *77*, 1895. (c) D'Ambrosio, M.; Guerriero, A.; Ripamonti, M.; Debitus, C.; Waikedre, J.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 727. (d) Hong, T. M.; Jimenez, D. R.; Molinski, T. F. *J. Nat. Prod.* **1998**, *61*, 158. (e) Pettit, G. R.; Ducki, S.; Herald, D. L.; Doubek, D. L.; Schmidt, J. M.; Chapuis, J.-C. *Oncol. Res.* **2005**, *15*, 11.

(2) Studies on the biological activity of agelastatin A: (a) Mason, C. K.; McFarlane, S.; Johnston, P. G.; Crowe, P.; Erwin, P. J.; Domostoj, M. M.; Campbell, F. C.; Manaviazar, S.; Hale, K. J.; El-Tanani, M. *Mol. Cancer Ther.* **2008**, *7*, 548. (b) Hale, K. J.; Domostoj, M. M.; El-Tanani, M.; Campbell, F. C.; Mason, C. K. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Academic Press: London, 2005; p 352.

(3) Synthetic studies on the potent anticancer natural compounds from this laboratory: (a) Yoshimitsu, T.; Sasaki, S.; Arano, Y.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 9262. (b) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 1993. (c) Yoshimitsu, T.; Nakajima, H.; Nagaoka, H. *Tetrahedron Lett.* **2002**, *43*, 8587. (d) Yoshimitsu, T.; Nagaoka, H.; Tanaka, T. *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 665.

(4) Total and formal syntheses of agelastatin A: (a) Anderson, G. T.; Chase, C. E.; Koh, Y.-H.; Stien, D.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1998**, *63*, 7594. (b) Stien, D.; Anderson, G. T.; Chase, C. E.; Koh, Y.-H.; Weinreb, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 9574. (c) Feldman, K. S.; Saunders, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 9060. (d) Feldman, K. S.; Saunders, J. C.; Wrobleski, M. L. *J. Org. Chem.* **2002**, *67*, 7096. (e) Hale, K. J.; Domostoj, M. M.; Tocher, D. A.; Irving, E.; Scheinmann, F. *Org. Lett.* **2003**, *5*, 2927. (f) Domostoj, M. M.; Irving, E.; Scheinmann, F.; Hale, K. J. *Org. Lett.* **2004**, *6*, 2615. (g) Davis, F. A.; Deng, J. *Org. Lett.* **2005**, *7*, 621. (h) Trost, B. M.; Dong, G. *J. Am. Chem. Soc.* **2006**, *128*, 6054. (i) Ichikawa, Y.; Yamaoka, T.; Nakano, K.; Kotsuki, H. *Org. Lett.* **2007**, *9*, 2989. (j) Baron, E.; O'Brien, P.; Towers, T. D. *Tetrahedron Lett.* **2002**, *43*, 723.

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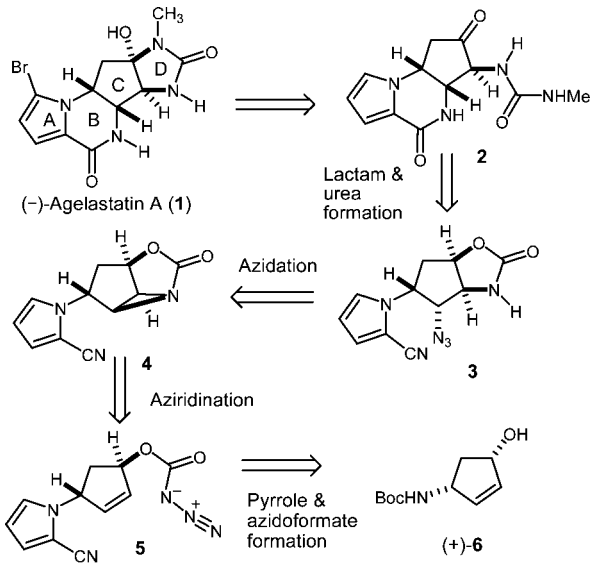
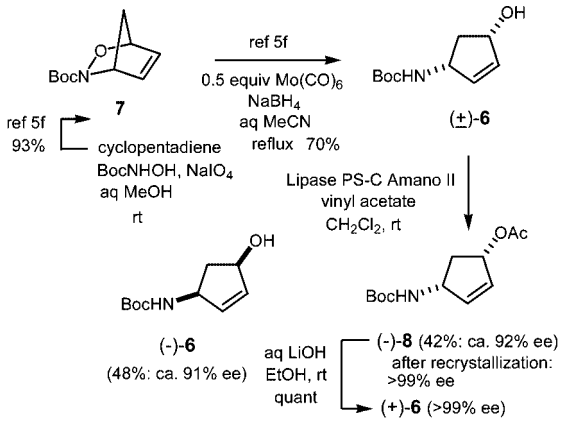
Scheme 1. Retrosynthesis of (−)-Agelastatin A (**1**)



functionalization of the central cyclopentane ring (**5** → **4** → **3**). Key azidoformate intermediate **5** suitable for such transformations would be readily accessible in a stereospecific manner from known chiral 1-hydroxy-4-aminocyclopentene derivative (+)-**6**. It should be emphasized that in the present approach, installation of a pyrrole unit at the early stage of the synthesis exempted us from having to handle labile enone intermediates or their reactive equivalents necessary for pyrrole unit incorporation at the later stage, as well as from having to use highly toxic methyl isocyanate owing to the facile direct and indirect aminolysis techniques to produce urea motif, the pivotal functionality of the agelastatin hemiaminal core.

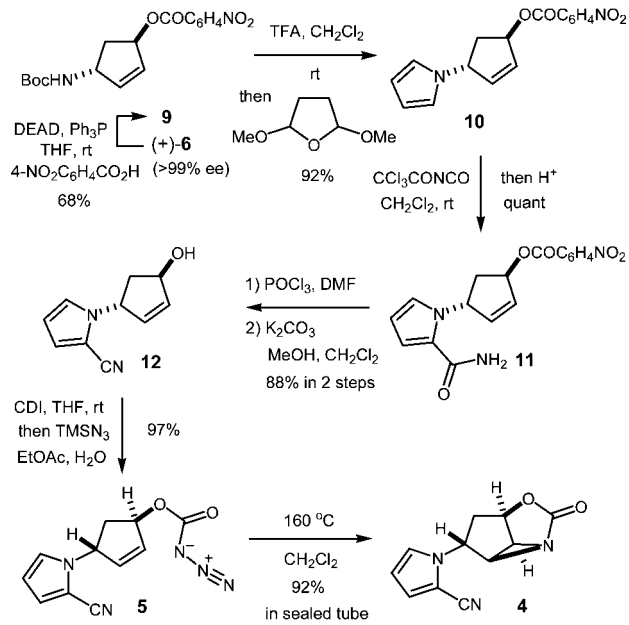
The total synthesis based on the above-mentioned plan was initiated with known Boc-protected 4-aminocyclopenten-1-ol (+)-**6** that was prepared via nitroso hetero-Diels−Alder reaction of cyclopentadiene with acylnitroso dienophile and

Scheme 2. Preparation of Chiral 1-Hydroxy-4-aminocyclopentene (+)-**6**



subsequent reductive N−O cleavage, in accordance with the Miller procedure (Scheme 2).[5] Enzymatic resolution of amino alcohol (±)-**6** with vinyl acetate using lipase PS-C Amano II, followed by fractional recrystallization of the resulting acetate (~92% ee), provided enantiomerically pure acetate (−)-**8** successfully (>99% ee). Acetate (−)-**8** was hydrolyzed with aqueous LiOH to provide alcohol (+)-**6**, which was then esterified with 4-nitrobenzoic acid under Mitsunobu conditions to give ester **9** in 68% yield (Scheme 3).

Scheme 3. Synthesis of Aziridine **4**



The pyrrole unit was efficiently elaborated by the modified Paal−Knorr condensation[6] between 2,5-dimethoxytetrahydrofuran and an amine that was derived from carbamate **9** by acidic removal of the *N*-Boc group. C1-unit installation at the 2-position of the pyrrole ring was achieved by carbamoylation with trichloroacetyl isocyanate, followed by selective removal of the trichloroacetyl group under mild acidic conditions using aqueous methanol in the presence of acetic acid, to give amide **11** in quantitative yield without any unwanted ester hydrolysis. Amide **11** was then converted by dehydration with $POCl_3$ into nitrile, and this in turn was subjected to methanolysis to give alcohol **12** in good overall yield (88%).

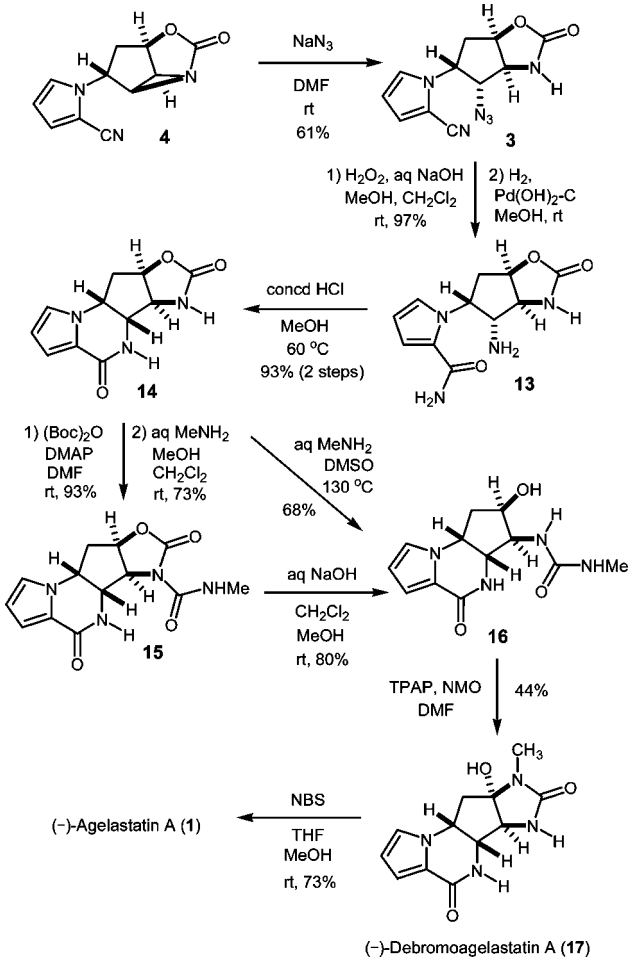
The next task required the preparation of key azidoformate intermediate **5** necessary for the aziridination reaction that

(5) (a) Li, F.; Brogan, J. B.; Gage, J. L.; Zhang, D.; Miller, M. J. *J. Org. Chem.* **2004**, *69*, 4538. (b) Li, F.; Warshakoon, N. C.; Miller, M. J. *J. Org. Chem.* **2004**, *69*, 8836. (c) Mineo, T.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 6591. (d) Davis, F. A.; Wu, Y. *Org. Lett.* **2004**, *6*, 1269. (e) Jiang, M. X.-W.; Warshakoon, N. C.; Miller, M. J. *J. Org. Chem.* **2005**, *70*, 2824. (f) Mulvihill, M. J.; Gage, J. L.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 3357. Also see: (g) Nakagawa, H.; Sugahara, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3181.

(6) This is also known as the Clauson−Kaas pyrrole synthesis: (a) Gourlay, B. S.; Molesworth, P. P.; Ryan, J. H.; Smith, J. A. *Tetrahedron Lett.* **2006**, *47*, 799. (b) Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342. (c) Dinsmore, A.; Mandy, K.; Michael, J. P. *Org. Biomol. Chem.* **2006**, *4*, 1032.

effects stereospecific dinitrogenation.[7] Initial attempts to prepare the labile azidoformate group, which involved carbamoylation with 1,1′-carbonyldiimidazole and subsequent azidation with NaN_3, were not fruitful owing to an inefficient azide-imidazole exchange as well as more pronounced S_N2 substitution at the allylic position. Nevertheless, we eventually found that azidoformate **5** could be efficiently produced by treating the imidazolide intermediate with $TMSN_3$ in the presence of water. The addition of water in this case was indispensable for successful transformation; it presumably *in situ* produced hydrazic acid (HN_3) that efficiently effects the azidation reaction with carbonyl imidazolide and also prevented resultant azidoformate **5** from undergoing reversible imidazolation since highly protic water could reduce the nucleophilicity of imidazole that is responsible for the undesired side reaction.[8]

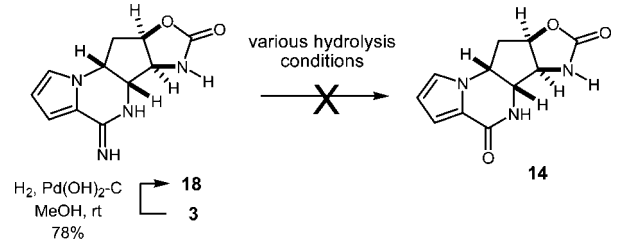
Scheme 4. Total Synthesis of (−)-Agelastatin A (**1**)



With this pivotal compound in hand, we sought to construct vicinal dinitrogen functionalities of the agelastatin nucleus by aziridination of the π-bond. The aziridination of **5** was carried out at 160 °C in CH_2Cl_2 in a high-pressure stainless steel tube to furnish aziridine **4** in 92% yield.[9,10] Aziridine **4** was then subjected to ring-opening reaction at room temperature with NaN_3 in DMF, giving azide **3** as the sole product (Scheme 4).[11] As expected, cleavage of the weak outer bond of the tricyclic system with an azide anion took place selectively, leading to the regioselective azidation at the 3-position of the cyclopentane ring. It should be noted that basic nitrogen nucleophiles, such as aqueous ammonia and benzylamine, exclusively underwent addition to the oxazolidinone moiety to produce urea derivatives rather than aziridine-cleaving products.

Lactamization with **3** was, however, difficult despite extensive trials: the initial attempt to transform intermediate **3** into lactam **14** via amidine **18**, which was readily obtained by hydrogenolysis of **3** under Pearlman conditions, was unsuccessful due to the significant tolerance of the amidine group to hydrolysis (Scheme 5). Therefore, we first converted azide **3** into amide **13** by hydrolysis of the nitrile group with alkaline−hydrogen peroxide, followed by reduction of azide,

Scheme 5. Attempted Hydrolysis of Amidine **18**



(7) For recent reviews on catalytic aziridination chemistry using azides, see: (a) Katsuki, T. *Chem. Lett.* **2005**, *34*, 1304. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

(8) It is also likely that water hydrolyzes TMS-imidazole that is possibly generated by the reaction of carbonyl imidazolide with $TMSN_3$ and readily undergoes addition to azidoformate **5**.

(9) Thermolysis and related reactions of azidoformates leading to aziridination: (a) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852. (b) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449. (c) Bergmeier, S. C.; Stanchina, D. M. *Tetrahedron Lett.* **1995**, *36*, 4533. (d) Bach, T.; Schlummer, B.; Harms, K. *Chem. Commun.* **2000**, 287. (e) Minakata, S.; Kano, D.; Oderaotoshi, Y.; Komatsu, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 79. (f) Zhou, Y.; Murphy, P. V. *Org. Lett.* **2008**, *10*, 3777. (g) Ruppel, J. V.; Jones, J. E.; Huff, C. A.; Kamble, R. M.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2008**, *10*, 1995.

(10) This aziridination under photolytic conditions, however, furnished only a low yield (ca. 10%) of aziridine **4**. For the photolysis of azidoformates, see: (a) Mendlik, M. T.; Tao, P.; Hadad, C. M.; Coleman, R. S.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 8059. (b) Kan, C.; Long, C. M.; Paul, M.; Ring, C. M.; Tully, S. E.; Rojas, C. M. *Org. Lett.* **2001**, *3*, 381.

(11) For recent examples of aziridine opening with azides, see: (a) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084. (b) Das, B.; Reddy, V. S.; Krishnaiah, M.; Rao, Y. K. *J. Mol. Catal. A* **2007**, *270*, 89. (c) Savoia, D.; Alvaro, G.; Di Fabio, R.; Gualandi, A. *J. Org. Chem.* **2007**, *72*, 3859. (d) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312. (e) Wu, J.; Sun, X.; Ye, S.; Sun, W. *Tetrahedron Lett.* **2006**, *47*, 4813. (f) Wu, J.; Sun, X.; Xia, H.-G. *Eur. J. Org. Chem.* **2005**, 4769. (g) D'hooghe, M.; Rottiers, M.; Kerkaert, I.; De Kimpe, N. *Tetrahedron* **2005**, *61*, 8746. (h) Minakata, S.; Okada, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2005**, *7*, 3509. (i) Kim, Y.; Ha, H.-J.; Han, K.; Ko, S. W.; Yun, H.; Yoon, H. J.; Kim, M. S.; Lee, W. K. *Tetrahedron Lett.* **2005**, *46*, 4407. (j) Kumar, G. D. K.; Maskaran, S. *Synlett* **2004**, *10*, 1719. (k) Yadav, J. S.; Reddy, B. V. S.; Premalatha, K. *Adv. Synth. Catal.* **2003**, *345*, 948. (l) Bisai, A.; Pandey, G.; Pandey, M. K.; Singh, V. K. *Tetrahedron Lett.* **2003**, *44*, 5839. (m) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Yadav, J. S. *Org. Lett.* **2002**, *4*, 343. (n) Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2000**, *65*, 1344. (o) Li, Z.; Fernández, M.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1611. For a review, see: (p) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.

and subsequently conducted acidic cyclization of resultant amine **13** under heating conditions to furnish lactam **14** in 91% yield.

The imidazolidinone hemiaminal constitutes the unique structural motif of agelastatin. The construction of this structural unit was achieved with both a four-step protocol comprising Boc activation, urea formation, hydrolytic removal of the carbamate group, and oxidative cyclization, and a two-step process involving direct aminolysis of oxazolidinone with $MeNH_2$, followed by oxidative cyclization. Thus, compound **14** was initially treated with $(Boc)_2O$ in the presence of DMAP to yield Boc-protected lactam. Subsequent nucleophilic aminolysis of the *N*-Boc group with aq $MeNH_2$ gave urea **15**, which smoothly underwent hydrolysis under aq NaOH conditions to deliver urea **16** with the ureido group intact.[12] We also explored the direct transformation of oxazolidinone **14** into urea **16** by treatment with aq $MeNH_2$. The desired reaction did not take place at 90 °C, due to the significant rigidity of the oxazolidinone moiety that retarded nucleophilic attack of the amine, leading to complete recovery of the starting material. However, we eventually found that harsher conditions (heating at 130 °C in DMSO for 8.5 h) effected the aminolysis to furnish urea **16** in 68% yield. Then, careful TPAP oxidation[13] afforded debromoagelastatin A (**17**) whose spectral and analytical data were identical with those reported in the literature.[4c,f,g,i] Final transformation of this compound was carried out in accordance with the established bromination procedure[4i] to furnish (−)-agelastatin A (**1**) in 73% yield. The spectroscopic properties of the synthetic compound were in good agreement with the reported data.[4c,f,g,i]

In conclusion, we have established a new route to highly potent antineoplastic (−)-agelastatin A (**1**) in 14 or 16 steps from known 1-hydroxy-4-aminocyclopentene derivative (+)-**6**, featuring stereo- and regiospecific nitrogen functionalizations of the central cyclopentane motif. Eight manipulations including **9** → **10** (one pot), **10** → **11** (one pot), **11** → **12**, **12** → **5** (one pot), **3** → **14**, and **14** → **15** in the present route essentially required no purifications, allowing expeditious access to the target compound. The derivatization and biological evaluation of synthetic compounds are in progress, and the results will be disclosed in due course.

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

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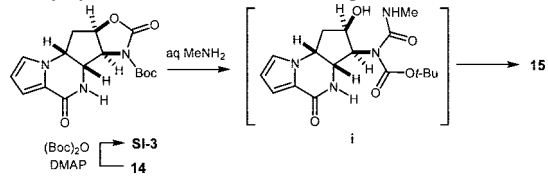
(12) The formation of carbamate **15** may also be rationalized by an alternative pathway which involves initial attack of $MeNH_2$ to the oxazolidinone carbonyl group of the Boc-protected intermediate **SI-3**, followed by cyclization of the resultant Boc-protected urea **i**.



(13) The compound **17** is somewhat unstable under the present oxidation conditions, probably due to the susceptibility to facile elimination of the pyrrole group from the ketone intermediate.