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Total Synthesis of (±)-Eucophylline. A Free-Radical Approach to the Synthesis of the Azabicyclo[3.3.1]nonane Skeleton

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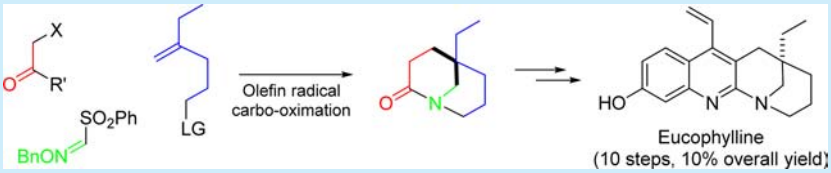
Supporting Information



ABSTRACT: The first total synthesis of eucophylline was reported in 10 steps and 10% overall yield. The naphthyridine core of eucophylline was prepared through the coupling between a strained azabicyclo[3.3.1]nonan-2-one and a trisubstituted benzonitrile, followed by a cyclization of the corresponding amidine. This coupling reaction was shown to proceed through a stable bicyclic chloroenamine intermediate. The azabicyclo[3.3.1]nonan-2-one skeleton was in turn accessible through a straightforward sequence including a free-radical three-component olefin carbo-oximation as a key step.

Leucophyllidine **1** is a cytotoxic dimeric terpene indole alkaloid recently isolated by Kam and co-workers from the EtOH extract of the stem-bark of *Leuconotis griffithii*, an apocynaceae found in the Malaysian peninsula (Figure 1).[1] This

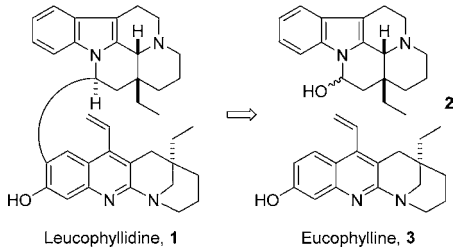
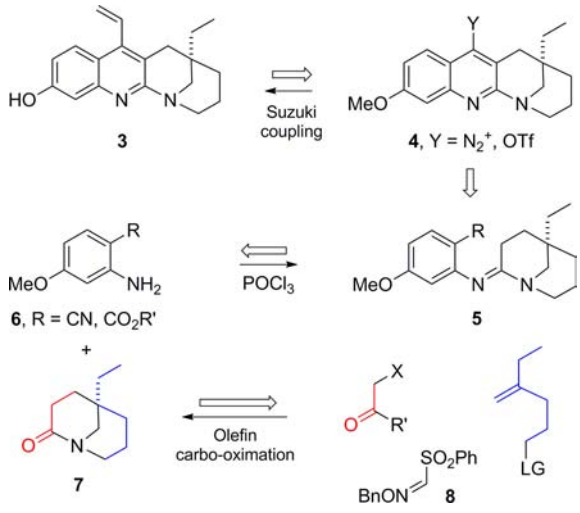


Figure 1. Leucophyllidine **1** and its biogenetic precursors.

complex alkaloid shows inhibition of NO production and exhibits a pronounced in vitro cytotoxicity toward vincristine-resistant human KB cells with an IC_{50} value of 2.92 μg/mL. Compound **1** is constituted by an eburnan unit **2** and a novel tetrahydrobenzo-[*b*][1,8]naphthyridine ring system **3**, recently isolated by Morita et al. from *Leuconotis eugenifolius* and named eucophylline.[2] With compounds **1** and **3** being both present in *L. eugenifolius*, the biogenetic pathway to **1** was proposed to involve a Mannich-type coupling between eburnan **2** and eucophylline **3**. The precedent for such couplings has been reported in other apocynaceae.[3] In the endeavor of searching for more potent antitumor agents active against drug-resistant cells[4] and structurally close to vincristine and vinblastine,[5] dimers such as **1** are of significant interest. The unusual dimeric structure of **1**, established unambiguously through X-ray diffraction studies, its potent biological activity, and low availability (7.1 mg/kg) prompted us to study its total synthesis, anticipating as a last step a biomimetic coupling between **2** and **3**. No synthesis of **1** or **3** has been reported to date.

Scheme 1. Disconnection Approach to Eucophylline 3



Our preliminary efforts were thus directed toward the synthesis of **3** and its unique azabicyclo[3.3.1]nonane skeleton. A retrosynthetic analysis was drawn in which it was envisaged that the reactive vinylic fragment of **3** could be introduced late in the synthesis through a Suzuki coupling from a substituted quinoline such as **4** (Scheme 1). The latter would in turn be formed by a base-mediated cyclization of an amidine **5** (Friedländer type cyclization),[6] bearing an aromatic ester or a nitrile (R) functional group. Coumpound **5** would then be formed via a coupling between a simple trisubstituted aniline **6** and the azabicyclo-

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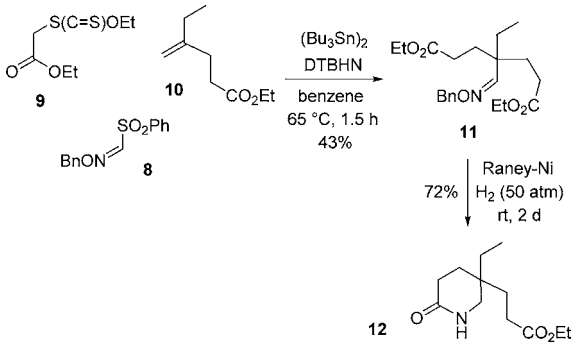
[3.3.1]nonan-2-one **7** containing the stereogenic quaternary center.

This straightforward sequence however raised two main issues. Whereas the synthesis of amidines starting from a monocyclic amide and an aniline is well precedented,[7] its extension to bicyclic amide **7** might prove more difficult. It was thus anticipated that the activation of this strained amide through an α-chloroiminium (using $POCl_3$) or an iminium triflate (using Tf_2O) might be unfavorable owing to the "anti-Bredt" nature of such intermediates.[8] Moreover, the synthesis of bridgehead amides such as **7** remains challenging, as indicated by the very few methods reported so far and the low efficiency of most of them.[9] We report here that these putative pitfalls can be efficiently overcome and that the azabicyclo[3.3.1]nonan-2-one skeleton of **7** is easily accessible through a short sequence involving as a key step a free-radical three-component carbo-oximation of a suitable olefin.[10] Interestingly, activation of bicyclic **7** upon exposure to $POCl_3$ also led to the formation of a useful α-chloroenamine intermediate which showed unusual stability. Coupling between **6** and **7** and further elaboration of amidine **5** are shown to afford natural **3** in good overall yield in only 10 steps.

Our preliminary efforts toward the synthesis of bicyclic amide **7** started with the carbo-oximation of olefin **10** with xanthate **9**, sulfonyloxime **8** in the presence of $(Bu_3Sn)_2$ and DTBHN as an initiator (Scheme 2).[10b] This led to the desired addition product

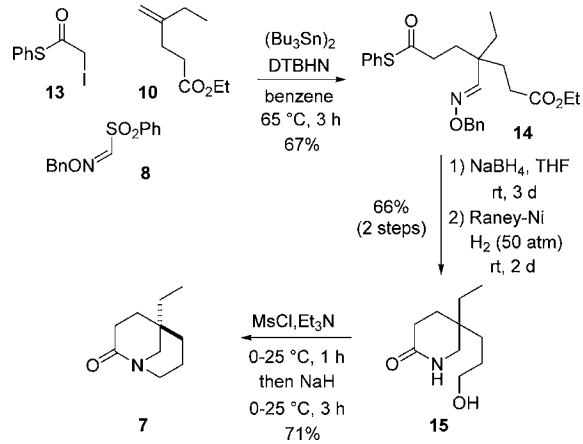
Scheme 2. Preparation of Piperidinone 12



11, albeit in modest yield. Subsequent hydrogenation of the benzyl oxime ether using Raney nickel, with concomitant lactamization, afforded the piperidinone **12** in 72% yield,[11] without a trace of the corresponding imide, in good agreement with the early studies of Buchanan,[8c] indicating that further ring closure in systems such as **12** is difficult. All our efforts to further cyclize **12** into **7** through the chemoselective reduction of the amide (Red-Al) or the ester ($NaBH_4$, MeOH), followed by a cyclization, unfortunately failed.

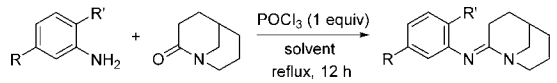
An alternative strategy was thus employed relying on the versatility of the three-component carbo-oximation process, which allowed the use of a more reactive α-iodothioester **13** as a radical precursor (Scheme 3). Carbo-oximation of olefin **10** with **13** under the same conditions as the above-mentioned afforded addition product **14** in good and reproducible yield. Chemoselective reduction of the thioester group into an alcohol[12] and hydrogenolysis of the oxime,[13] followed by lactamization, finally led to the hydroxy-lactam **15**, which was cyclized into the desired bicyclic lactam **7**, after activation of the hydroxyl group as a mesylate.[14] This short sequence thus provides a new straightforward access to these strained bicyclic amides.

Scheme 3. Synthesis of Bicyclic Lactam 7



With amide **7** in hand, we then considered its coupling with anilines **6**. Preliminary experiments were first carried out using bicyclic amide model **16**, readily available following a literature procedure,[15] and $POCl_3$ (1 equiv) in a CH_2Cl_2/THF mixture. While previous attempts using monocyclic lactams afforded the desired amidines in good yields under such conditions,[16] such was not the case using bicyclic amide **16**. First trials with ester **6a** and nitrile **6b** were disappointing, leading to amidines **17a** and **17b** in modest 24% and 18% yield respectively (Table 1, entries 1−2).

Table 1. Preparation of Amidines 17a−c: Preliminary Studies



6a, R = OMe; R' = CO_2Me **16** **17a**, R = OMe; R' = CO_2Me
6b, R = OMe; R' = CN **17b**, R = OMe; R' = CN
6c, R = H; R' = CN **17c**, R = H; R' = CN

entry	aniline	solvent	amidine	yield, %[a]
1	**6a**	CH_2Cl_2/THF	**17a**	24
2	**6b**	CH_2Cl_2/THF	**17b**	18
3	**6b**	benzene	**17b**	16
4	**6b**	CH_3CN	**17b**	34
5	**6b**	CH_2Cl_2	**17b**	46
6	**6b**[b]	CH_2Cl_2	**17b**	70
7	**6c**[b]	CH_2Cl_2	**17c**	70

[a]Isolated yields. [b]1.5 equiv of **6b−c** was used.

Substituting CH_2Cl_2/THF for the less polar benzene also led to poor results (Table 1, entry 3), while a better yield was observed in CH_3CN (Table 1, entry 4). Finally, optimal results were obtained in pure CH_2Cl_2 (Table 1, entry 5) and when increasing the amount of aniline to 1.5 equiv (Table 1, entries 6 and 7). X-ray diffraction studies on **17c** showed that amidines possess an *E*-configuration, adopting a boat-chair conformation, similar to that of the parent 1-azabicyclo[3.3.1]nonan-2-one **16** (Scheme 4).[8c,9e]

The reaction between amides and $POCl_3$ is well-known to afford the corresponding α-choroiminiums, which react efficiently with nucleophiles, including amines. However, the formation, as an intermediate, of a highly strained bridgehead iminium species in the case of amide **16** appeared unlikely.[8] In order to obtain information regarding the mechanism of the coupling mentioned above, bicyclic lactam **16** was treated with $POCl_3$ (2.2 equiv) in CH_2Cl_2 under reflux for 3 h. This led, after basic treatment, to α-chloroenamine **18** (60% yield), the structure of which could be established unambiguously through extensive

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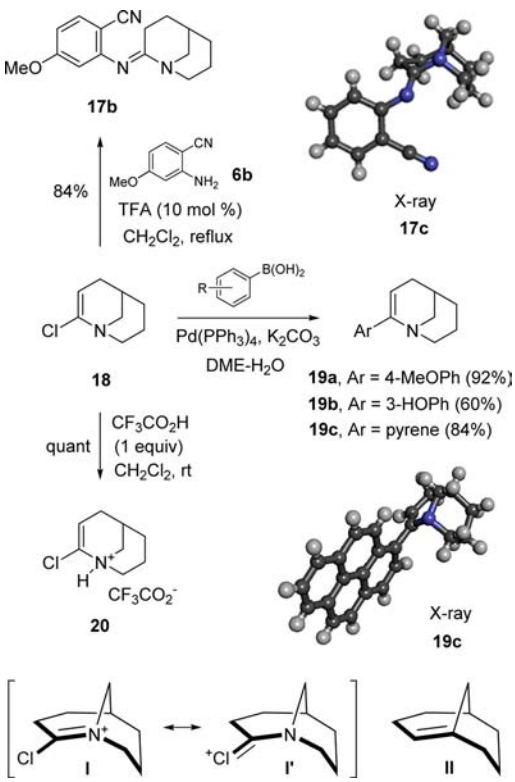
Scheme 4. α-Chloroenamine Intermediate 18 and X-ray Structures of Bicyclic Lactam 17c and Enamine 19c

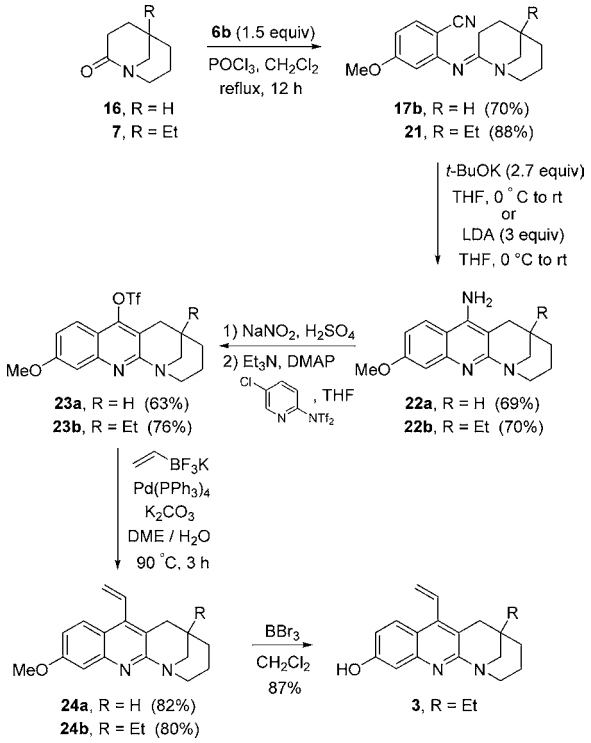


^{1}H and ^{13}C NMR studies. In contrast with reported α-chloroenamines,[17] **18** was found to be remarkably stable.[18] The treatment of **18** with trifluoroacetic acid (1 equiv) did not generate the α-choroiminium, but led to the kinetic protonation at the nitrogen center with the formation of the α-chloro-enaminium salt **20** in quantitative yield. In turn, reaction of **18** with benzonitrile **6b**, in the presence of 10 mol % of TFA led to amidine **17b** in 84% yield. Although an α-chloroiminium such as **I** (Scheme 4) could not be isolated or detected, it is assumed that an *in situ* prototropy in **20** could provide **I**–**I**′, able to react further with anilines **6a**–**c**.[19] Bicyclo[3.3.1]non-1-ene **II**, the bridgehead alkene analogue of **I**, has been isolated and is reasonably stable,[20] which provides support to the hypothesis that **I** could be a competent intermediate in the reaction with anilines **6a**–**c**.

Surprisingly, reaction of **18** with **6b** in the absence of TFA or with 10 mol % of 2,6-di-*tert*-butylpyridine also led to amidine **17b** in good yields. α-Chloroenamines are known to react with nucleophiles,[17] including amines via a ketene-iminium intermediate, which is unlikely with bicyclic **18**.[21] Although further studies will be required to firmly establish the mechanism of this coupling, strong coloration observed upon mixing **18** and **6b** might be indicative of a single electron-transfer initiation process occurring under neutral or basic conditions. In parallel, **18** was also reacted with a series of aryl boronic acids under Pd-catalysis,[22] leading to stable aryl-enamines **19a**–**c** in excellent yields. Inspection of the X-ray crystallographic data of the pyrene-enamine **19c** indicates that the bicyclic system enforces the nitrogen lone pair to be quasi orthogonal to the enamine π-system, explaining the unusual stability of such enamines and chloro-enamines.[23]

The procedure for the synthesis of amidine **17b**–**c** was then applied to the strained amide **7**, which upon coupling with aniline **6b** afforded the desired amidine **21** in excellent yield (Scheme 5).

Scheme 5. Synthesis of Eucophylline 3



The formation of the quinoline skeleton was then carried out through cyclization of amidines **17b** and **21** under basic conditions. Using *t*-BuOK (2.6 equiv) as a base, the cyclization of **17b** was shown to be slow, however affording the amino-naphthyridine skeleton **22a** in 69%.

Application of these conditions in the natural product series surprisingly gave **22b** with a poor conversion (~20%) along with unreacted **21** (59%). Treatment of the latter using LDA (3 equiv) at 25 °C led to the formation of **22b** in a more reproducible 70% isolated yield. Incorporation of the vinylic fragment was first planned relying on a Suzuki coupling with diazonium salts derived from **22a**–**b**.[24] The modest yields obtained with model compounds led us to envision an alternative strategy using instead triflates **23a**–**b**,[25] which were prepared through diazotation, then hydrolysis of naphthyridines **22a**–**b**, followed by the conversion of the alcohols into the corresponding triflates using Comins' reagent.[26] The Suzuki coupling was then carried out with commercial vinyl trifluoroborate,[23,27] affording the desired vinyl naphthyridines **24a** and **24b** in 82% and 80% yield, respectively. Demethylation of **24b** with BBr_3 finally afforded (±)-eucophylline **3** in 87% yield and 10% overall yield over 10 steps from iodothioester **13**. Analytical data were found to match those of the natural product isolated by Morita et al.[2a]

In summary, we reported the first total synthesis of (±)-eucophylline **3**, the south fragment of the leucophyllidine alkaloid recently isolated from *Leuconotis griffithii and L. eugenifolius*. The 10-step synthesis encompasses a new straightforward method to access to the azabicyclo[3.3.1]nonane skeleton through a three-component olefinic carbo-oximation process and its further elaboration into the naphthyridine skeleton using a $POCl_3$-mediated coupling between a strained bridgehead amide **7** and an aniline. During these studies, we also isolated enamines exhibiting unusual stabilities resulting from their strained bicyclic conformation. Further work on the total synthesis of leucophyllidine **1** with the preparation of eburnan **2** and its

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biomimetic coupling with **3** is currently in progress and will be reported in due course. An enantioselective synthesis of **3**, relying on recent work from the laboratory, is also under study.[28]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02218.

Crystallographic data for **17c** (CIF)
Crystallographic data for **19c** (CIF)
Experimental details and characterization data for the starting material and products (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Gan, C.-Y.; Robinson, W. T.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T.-S. *Org. Lett.* **2009**, *11*, 3962.

(2) (a) Deguchi, J.; Shoji, T.; Nugroho, A. E.; Hirasawa, Y.; Hosoya, T.; Shirota, O.; Awang, K.; Hadi, A. H. A.; Morita, H. *J. Nat. Prod.* **2010**, *73*, 1727. (b) Nugroho, A. E.; Morita, H. *J. Nat. Med.* **2014**, *68*, 1.

(3) (a) Nugroho, A. E.; Hirasawa, Y.; Kawahara, N.; Goda, Y.; Awang, K.; Hadi, A. H. A.; Morita, H. *J. Nat. Prod.* **2009**, *72*, 1502. (b) Büchi, G.; Manning, R. E.; Monti, S. A. *J. Am. Chem. Soc.* **1964**, *86*, 4631. (c) Honty, K.; Szanty, C., Jr.; Kolonits, P.; Demeter, A.; Szantay, C. *Tetrahedron* **1993**, *49*, 10421. (d) Langlois, N.; Guéritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017. (e) van Beek, T. A.; Verpoorte, R.; Svendsen, A. B. *Tetrahedron Lett.* **1984**, *25*, 2057. (f) Danieli, B.; Lesma, G.; Palmisano, G.; Passarella, D. *J. Org. Chem.* **1994**, *59*, 5810.

(4) Schmeller, T.; Wink, M. In *Alkaloids. Biochemistry, ecology, and medicinal applications*; Roberts, M. F., Wink, M., Eds.; Plenum Press: New York, ; p 435.

(5) (a) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *Tetrahedron* **1980**, *36*, 3053. (b) Fahy, J.; Duflos, A.; Ribet, J.-P.; Jacquesy, J.-C.; Berrier, C.; Jouannetaud, M.-P.; Zunino, F. *J. Am. Chem. Soc.* **1997**, *119*, 8576.

(6) Marco-Contelles, J.; Perez-Mayoral, E.; Samadi, A.; do Carmo Carreiras, M.; Soriano, E. *Chem. Rev.* **2009**, *109*, 2652.

(7) Lee, B. D.; Li, Z.; French, K. J.; Zhuang, Y.; Xia, Z.; Smith, C. D. *J. Med. Chem.* **2004**, *47*, 1413.

(8) For reviews on strained bridgedhead systems, see: (a) Szostak, M.; Aubé, J. *Org. Biomol. Chem.* **2011**, *9*, 27. (b) Mak, J. Y. W.; Pouwer, R. H.; Williams, C. N. *Angew. Chem., Int. Ed.* **2014**, *53*, 13664. For specific examples on lactams incorporating a nitrogen at the bridgedhead position in bicyclo[3.3.1.] systems, see: (c) Buchanan, G. L.; Kitson, D. H.; Mallinson, P. R.; Sim, G. A.; White, D. N. J.; Cox, P. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1709. (d) Greenberg, A.; Wu, G. L.; Tsai, J. C.; Chiu, Y. Y. *Struct. Chem.* **1993**, *4*, 127. (e) Greenberg, A.; Venanzi, C. A. *J. Am. Chem. Soc.* **1993**, *115*, 6951. (f) Sliter, B.; Morgan, J.; Greenberg, A. *J. Org. Chem.* **2011**, *76*, 2770.

(9) (a) Yakhontov, L. N.; Rubstov, M. V. *J. Gen. Chem. USSR (Engl Transl.)* **1957**, *27*, 83. (b) Pracejus, H. *Chem. Ber.* **1959**, *92*, 988. (c) Pracejus, H. *Chem. Ber.* **1965**, *98*, 2897. (d) Pracejus, H.; Kehlen, M.; Matschiner, M. *Tetrahedron* **1965**, *21*, 2257. (e) Hall, H. K.; Shaw, R. G.; Deutschmann, A. *J. Org. Chem.* **1980**, *45*, 3722. (f) Buchanan, G. L. *J. Chem. Soc., Chem. Commun.* **1981**, 814. (g) Buchanan, G. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2669.

(10) (a) Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662. (b) Landais, Y.; Robert, F.; Godineau, E.; Huet, L.; Likhite, N. *Tetrahedron* **2013**, *69*, 10073. (c) Liautard, V.; Landais, Y. In *Multicomponent Reactions*, 2nd ed.; Zhu, J., Wang, Q., Wang, M. X., Eds.; Wiley: 2014; p 401.

(11) For recent approaches to a similar skeleton, see: (a) Gualtierotti, J.-B.; Pasche, D.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9926. (b) Grover, H. K.; Kerr, M. A. *Synlett* **2015**, *26*, 815.

(12) Nagao, Y.; Ikeda, T.; Inoue, T.; Yagi, M.; Shiro, M.; Fujita, E. *J. Org. Chem.* **1985**, *50*, 4072.

(13) Zhang, F.-G.; Yang, Q.-Q.; Xuan, J.; Lu, H.-H.; Duan, S.-W.; Chen, J.-R.; Xiao, W.-J. *Org. Lett.* **2010**, *12*, 5636.

(14) Jing, P.; Yang, Z.; Zhao, C.; Zheng, H.; Fang, B.; Xie, X.; She, X. *Chem. - Eur. J.* **2012**, *18*, 6729.

(15) Steliou, K.; Poupart, M. A. *J. Am. Chem. Soc.* **1983**, *105*, 7130.

(16) Jean, M. A.; Mohammed, S.; Robert, F.; Landais Y., unpublished results.

(17) (a) Ghosez, L.; George-Koch, I.; Patiny, L.; Houtekie, M.; Bovy, P.; Nshimyumukiza, P.; Phan, T. *Tetrahedron* **1998**, *54*, 9207 and references cited therein. (b) Ghosez, L.; Notté, P.; Bernard-Henriet, C.; Maurin, R. *Heterocycles* **1981**, *15*, 1179. (c) Martin, M. L.; Ricolleau, G.; Poignant, S.; Martin, G. J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 182.

(18) **18** can be chromatographed on silica gel without degradation and exhibits the same ^{1}H NMR spectrum after heating in water at 60 °C for 3 h.

(19) Reaction between **20** and **6b** effectively produced amidine **17b** in 59% yield.

(20) (a) Marshall, J. A.; Faubl, H. *J. Am. Chem. Soc.* **1967**, *89*, 5965. (b) Wiseman, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 5966.

(21) For a discussion on the formation of ketene-iminium cations in cyclic amides, see: Staelens-Vanhorenbeeck, M., PhD Thesis, University of Louvain-La-Neuve, 1978.

(22) Beng, T. K.; Wilkerson-Hill, S. M.; Sarpong, R. *Org. Lett.* **2014**, *16*, 916.

(23) (a) *Enamines: Synthesis, Structure and Reactions*; Cook, A. G., Ed.; Marcel Dekker: New-York and London, 1969. (b) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193.

(24) Darses, S.; Michaud, G.; Genet, J. P. *Eur. J. Org. Chem.* **1999**, *1999*, 1875.

(25) Molander, G. A.; Rodriguez Rivero, M. *Org. Lett.* **2002**, *4*, 107.

(26) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

(27) Darses, S.; Michaud, G.; Genêt, J. P. *Tetrahedron Lett.* **1998**, *39*, 5045.

(28) Ovadia, B.; Robert, F.; Landais, Y. *Org. Lett.* **2015**, *17*, 1958.

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Org. Lett. 2015, 17, 4518−4521