

Annulation of Thioimides and Vinyl Carbodiimides to Prepare 2-Aminopyrimidines, Competent Nucleophiles for Intramolecular Alkyne Hydroamination. Synthesis of (–)-Crambidine

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Certain members of the crambescidin natural products,^{1–5} derived from the marine sponge *Crambe crambe*, have exhibited remarkable biological properties, including anticancer, anti-HIV, antifungal, and Ca²⁺ ion channel blocking activities. Many compounds within this class are characterized by a polycyclic guanidine core linked to a hydroxyspermidine moiety by a linear ω -hydroxy fatty acid. Crambidine (**1**, Figure 1) is atypical within this family of alkaloids in that it possesses a fused pyrimidine heterocyclic core, while most of its other congeners exist in more highly reduced forms. Several elegant strategies have been reported for the synthesis of crambescidin alkaloids.^{6–9} However, only a single reported synthesis of crambidone (**1**) has appeared,¹⁰ involving dihydropyrimidine construction via Biginelli condensation, followed by oxidation. We report herein a synthesis of (–)-crambidine that capitalizes on two key processes, including a [4+2] annulation of thioimides with vinyl carbodiimides and a hydroamination of alkynes with 2-aminopyrimidine nucleophiles.

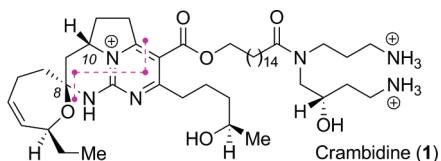
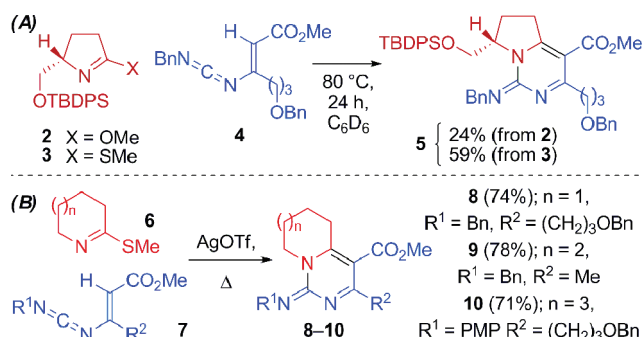


Figure 1

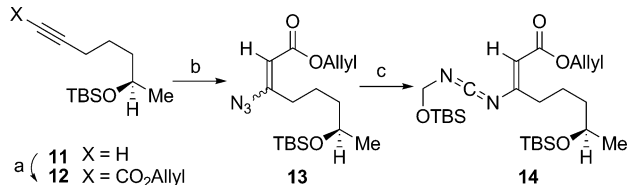
Vinylcarbodiimides derived from pyrimidine-diones have been shown to converge with *O*-methyl imidates to furnish 2-aminopyrimidines.¹¹ However, when this annulation process was applied to vinylcarbodiimides and *O*-imidates more appropriate to the synthesis of **1**, the reaction was inefficient. For example, heating a mixture of *O*-methyl imidate **2** (Scheme 1A) with benzylvinylcarbodiimide **4** at elevated temperature in C₆D₆ for 24 h provided only 24% conversion to the 2-aminopyrimidine **5**. By contrast, when the corresponding thiomethyl imidate **3** was exposed to carbodiimide **4** under otherwise identical conditions, conversion to the pyrimidine **5** was accomplished with marked improvement (59%). Addition of the thiol scavenger AgOTf further enhanced the efficiency of the thioimide annulation, allowing for the preparation of a variety of bicyclic 2-aminopyrimidines (Scheme 1B, **8–10**).

Extension of this [4+2] annulation reaction to access a complex substrate more suited to the synthesis of **1** commenced with the synthesis of a fully elaborated vinyl carbodiimide **14** (Scheme 2). Silyl ether **11**, obtained in enantiopure form according to the procedure of Campagne and co-workers,¹² was acylated with allyl chloroformate

Scheme 1



Scheme 2^a



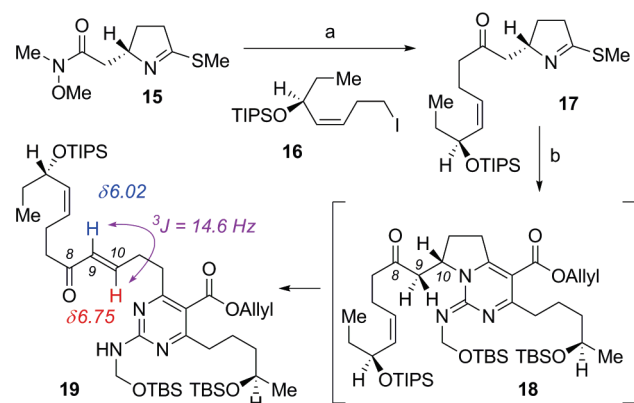
^a Reagents and conditions: (a) *n*-BuLi, THF, –78 °C; AllylOCOCl, 90%; (b) (Me₂N)₂C=NH₂N₃, CHCl₃, 23 °C, 69% (2:1, *E/Z*); (c) PPh₃, CH₂Cl₂, 23 °C; add TBSOCH₂N=C=O, PhH, 80 °C, 49% from (*E*)-**13**, 43% from (*Z*)-**13**.

to afford the propargylic ester **12**. This intermediate was subjected to conjugate addition with azide to afford a separable *E/Z* mixture (2:1) of the corresponding β -azidoacrylate **13**. Reduction of the azide in (*E*)-**13** with PPh₃, followed by condensation with TBSOCH₂N=C=O, provided the vinyl carbodiimide **14**. Importantly, advancement of (*Z*)-**13** under analogous conditions also led to the formation of the (*E*)-isomer of **14** in a similar yield, wherein stereochemical convergence occurs at the iminophosphorane stage.

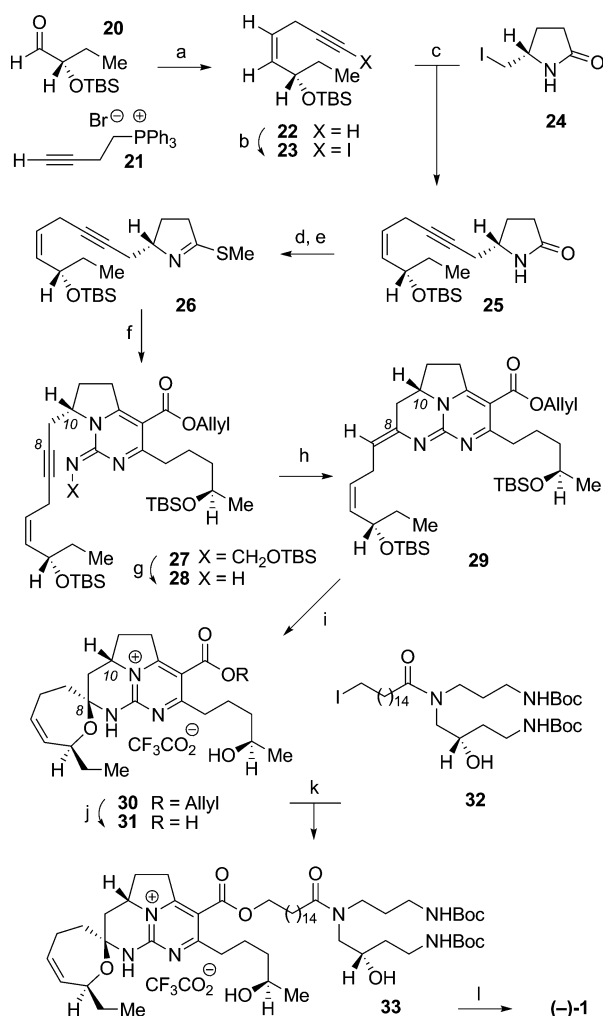
Synthesis of an initial crambidine-relevant thioimide employed methyl thioimide **15**¹³ (Scheme 3). This served as a suitable acylation agent for the alkyl lithium species derived from the homoallylic iodide **16**, prepared in the manner described by Overman.¹⁴ The resulting keto-thioimide **17** was then heated with vinyl carbodiimide **14** to effect [4+2] annulation. Unfortunately, the bicyclic pyrimidine **18** was not observed; instead, the sole isolable product was pyrimidine **19**, presumably a result of C9–C10 β -elimination of the heterocycle in **18**.⁷

Given that the fragmentation (**18**→**19**) and concomitant destruction of the C10 stereoconfiguration could not be avoided, attention turned to thioimide **26** (Scheme 4) as an alternate annulation substrate in which the internal alkyne would serve as a less acidic ketone surrogate. Thus, *Z*-selective Wittig olefination of (*S*)-2-(*tert*-butylsilyloxy)bu-

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Scheme 4^a



lowing iodination of the terminal alkyne, the alkynyl iodide **23** was subjected to a sequence involving the following: (1) Cu-mediated coupling with pyrrolidinone **24** to afford internal alkyne **25**; (2) a two-step conversion of the lactam **25** to the thioimide **26** via carbonyl thionation and *S*-alkylation; (3) [4+2] annulation with vinylcarbodiimide **14** to furnish bicyclic pyrimidine **27**; and (4) chemoselective *N*-deprotection to provide the free 2-aminopyrimidine **28**, a substrate poised for intramolecular alkyne hydroamination.

Transition metal catalyzed hydroamination of alkynes^{15,16} is a powerful reaction in synthesis;^{17–19} however, the paucity of guanidine or 2-aminopyrimidine nucleophiles engaging in this reaction is notable. After extensive experimentation, this transformation was validated by treatment of alkyne **28** (Scheme 4) with 10 mol % AuCl₃²⁰ at 40 °C, leading to efficient production of the tricyclic pyrimidine **29** as a single isomer (78%).

Subsequent spiroaminal formation at C8 in enamine **29** was conducted under carefully controlled acidic conditions, being mindful of the possibility of undesired C10–N bond rupture via potential C8–iminium reactivity. This liability was precluded by treatment with TsOH, effecting TBS removal and spirocyclization to provide the tetracyclic pyrimidinium **30** (77%).²¹ The final stages of the synthesis involved conversion of the allyl ester **30** to its Cs-carboxylate. This nucleophile, obtained from carboxylic acid **31**, was amenable to selective alkylation with iodide **32**.¹³ The resulting ester **33** was then subjected to *tert*-butylcarbamate removal to afford (–)-crambidine (**1**).

A convergent synthesis of crambidine has been described, showcasing a [4+2] thioimide-vinyl carbodiimide annulation and an intramolecular alkyne-guanidine hydroamination. This strategy should not only prove useful for preparing other members of the crambescidins, but also provide an attractive means with which to access complex *N*-heterocycles in general.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Heys, L.; Moore, C. G.; Murphy, P. J. *J. Chem. Soc. Rev.* **2000**, 29, 57–67.
- (2) Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L. *J. Org. Chem.* **1991**, 56, 5712–5715.
- (3) Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh, S. *J. Am. Chem. Soc.* **1992**, 114, 8472–8479.
- (4) Berlinck, R. G. S.; Braekman, J. C.; Daloz, D.; Bruno, I.; Riccio, R.; Ferré, S.; Spampinato, S.; Speroni, E. *J. Nat. Prod.* **1993**, 56, 1007–1015.
- (5) Jares-Erijman, E. A.; Ingram, A. L.; Carney, J. R.; Rinehart, K. L.; Sakai, R. *J. Org. Chem.* **1993**, 58, 4805–4808.
- (6) Snider, B. B.; Shi, Z. P. *J. Am. Chem. Soc.* **1994**, 116, 549–557.
- (7) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **2000**, 122, 4893–4903.
- (8) Nagasawa, K.; Georgieva, A.; Koshino, H.; Nakata, T.; Kita, T.; Hashimoto, Y. *Org. Lett.* **2002**, 4, 177–180.
- (9) Moore, C. G.; Murphy, P. J.; Williams, H. L.; McGown, A. T.; Smith, N. K. *Tetrahedron Lett.* **2003**, 44, 251–254.
- (10) Overman, L. E.; Rhee, Y. H. *J. Am. Chem. Soc.* **2005**, 127, 15652–15658.
- (11) Wamhoff, H.; Schmidt, A. *Heterocycles* **1993**, 35, 1055–1066.
- (12) Pétry, N.; Parenty, A.; Campagne, J.-M. *Tetrahedron: Asymmetry* **2004**, 15, 1199–1201.
- (13) See Supporting Information.
- (14) Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Stappenbeck, F. J. *Am. Chem. Soc.* **1999**, 121, 6944–6945.
- (15) Pohli, F.; Doye, S. *Chem. Soc. Rev.* **2003**, 32, 104–114.
- (16) Müller, T. E.; Hultsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, 108, 3795–3892.
- (17) McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, 115, 11485–11489.
- (18) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2006**, 8, 3995–3998.
- (19) Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661–662.
- (20) Fukuda, Y.; Utimoto, K. *Synthesis* **1991**, 975–978.
- (21) This and subsequent aminopyrimidine intermediates were purified by RP-HPLC (water/MeCN/TFA).