Biomimetic Synthesis of the Bicyclic Guanidine Moieties of Crambines A and B

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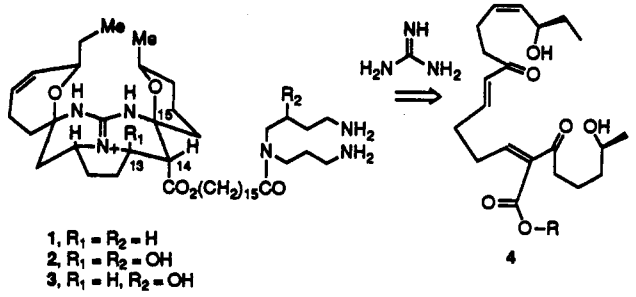
Received January 21, 1992

Summary: The acyl portions of crambine A (six steps, 29% overall yield) and crambine B (six steps, 26% overall yield) have been efficiently and stereospecifically synthesized from methyl acetoacetate.

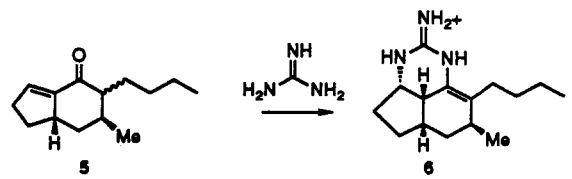
In 1989, Kashman and Kakisawa reported the isolation of the novel polycyclic guanidine alkaloid ptilomycalin A (1) from the Caribbean sponge *Ptlocaulis spiculifer* and from a red *Hemimycale sp.* of the Red Sea.[1] Ptilomycalin A shows cytotoxicity against P388 with IC_{50} = 0.1 μg/mL and antifungal and antimicrobial activity against *Candida albicans* (MIC = 0.8 μg/mL) as well as antiviral activity (HSV) at 0.2 μg/mL. The structure was determined by a combination of 1D and 2D NMR experiments. In 1991, Rinehart reported the isolation of the closely related antiviral and cytotoxic crambescidins from the red, encrusting Mediterranean sponge *Crambe crambe*.[2] The crambescidins have the same pentacyclic guanidine moiety with an additional hydroxy group on the side chain in crambescidin 800 (3) and on both the ring and side chain in crambescidin 816 (2).



1, $R_1 = R_2 = H$
2, $R_1 = R_2 = OH$
3, $R_1 = H$, $R_2 = OH$

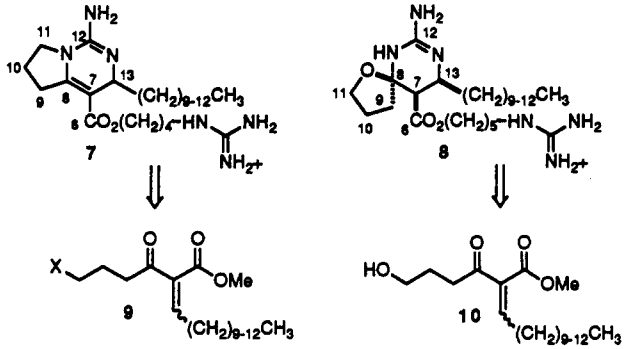
4

We were intrigued by the structural similarities between ptilomycalin A (1) and ptilocaulin (6), which was also isolated from *P. spiculifer*.[3] We reported the first synthesis of ptilocaulin in 1983, which was based on the retrosynthetic analysis that ptilocaulin could be prepared by Michael addition of guanidine to enone 5 followed by intramolecular enamine formation.[4] The facile formation of ptilocaulin (6) from 5 and guanidine suggests that ptilocaulin, and perhaps 1 as well, are produced by addition of guanidine to a polyketide in the last step. This analysis suggests that addition of guanidine to the double Michael acceptor 4 followed by imine and then aminal formation could give the pentacyclic framework of 1 in a single step.



5 6

In 1990, Berlink and co-workers reported the isolation of crambines A (7) and B (8) from *C. crambe*.[5] We chose to carry out syntheses of these alkaloids as a model study for the synthesis of ptilomycalin A (1). The spirocyclic framework of 8 is quite similar to the two right-hand rings of 1. The stereochemistry at C-7 and C-13 in 8 is identical to that at C-13 and C-14 in 1. The stereochemistry of the aminal linkage (C-8 in 8 and C-15 in 1) is different. However, the stereochemistry of this center of crambine B was tentatively assigned based only on the NOE between H-7 and H-9.



7 8

9 10

Our retrosynthetic analysis suggested that crambine B (8) could be prepared by addition of guanidine to enone ester 10 and that crambine A (7) could be prepared by addition of guanidine to 9, where X is a leaving group. Although the addition of guanidine to enones to form dihydropyrimidines has been extensively investigated,[6-8] the addition of guanidine or amidines to enone esters leads to the formation of tetrahydropyrimidinones (e.g., 17) by Michael addition and amide formation in addition to, or instead of, the desired dihydropyrimidines.[9,10]

Alkylation of the dianion of methyl acetoacetate with ethylene oxide as previously reported affords 11, which cyclizes spontaneously to methyl tetrahydrofuranylideneacetate.[11] The hydroxy group of 11 must be protected prior to workup. Reaction of 1 equiv of ethylene oxide with the dianion of methyl acetoacetate in THF (0 °C, 2h) and addition of TBDMSCl (rt, 12 h) affords 58% of 12.[12] Knoevenagel condensation[13] of 12 with tridecanal (benzene, catalytic piperidine 1 h at rt, 30 min at 80 °C and 12 h at rt) provides 88% of 13 as a 1.1:1 mixture of *E*-*Z* isomers.[14] Unfortunately, addition of guanidine (prepared from the carbonate[15]) to 13 in 2-methyl-2-propanol (5 h, rt) gives 71% of tetrahydropyrimidinone 17[16] as the only product. Similar results were obtained in several other solvents.

(1) Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtani, I.; Kusumi, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1989**, *111*, 8925.
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(3) Harbour, G. C.; Tymiak, A. A.; Rinehart, K. L., Jr.; Shaw, P. D.; Hughes, R. G., Jr.; Mizsak, S. A.; Coats, J. H.; Zurenko, G. E.; Li, L. H.; Kuentzel, S. L. *J. Am. Chem. Soc.* **1981**, *103*, 5604.
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(12) Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1417.
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(16) Guanidines 17, 18, and 21-26 were isolated as the hydrochlorides.

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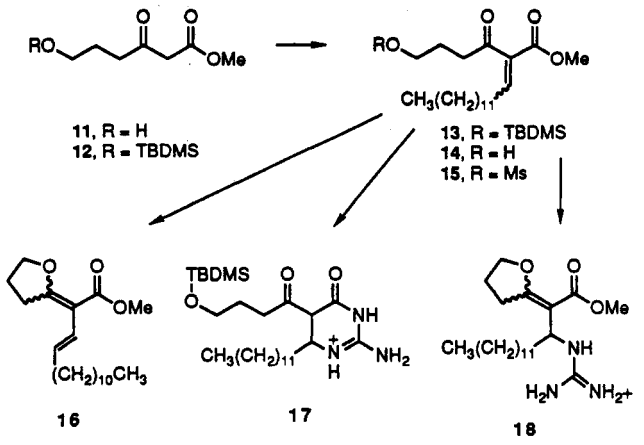

Mesylate **15** was prepared as a potential precursor to crambine A (**7**). Hydrolysis of **13** in 1:1:3 THF–H_2O–AcOH (6 h, rt) affords 90% of crude **14** that cyclizes to give 64% of **16** on chromatography. Reaction of crude **14** with MsCl (CH_2Cl_2, Et_3N, 0 °C, 2 h) affords 84% of mesylate **15**. Addition of guanidine[15] to mesylate **15** in acetone (10 h, rt) affords 14% of **16**, 40% of **18**[16] as a 1:1 mixture of *E–Z* isomers,[17] and 40% of material which appears to result from the addition of the guanidine of **18** to a second molecule of **15**.

These results demonstrate that guanidine cannot be added directly to **13** or **15** to give the desired dihydropyrimidine products. We therefore turned our attention to a two-step route involving the addition of less basic *O*-methylisourea to **13** and conversion of the methoxydihydropyrimidine **20** to aminodihydropyrimidine **21** that has been used successfully on other enone esters.[18] Reaction of **13**, *O*-methylisourea sulfate (2 equiv) and $NaHCO_3$ (7 equiv) in DMF for 12 h at 60 °C furnishes 79% of the desired dihydropyrimidine **19**. Hydrolysis of the silyl ether (TBAF, THF, 12 h, rt) yields 90% of **20** and 4% of the corresponding urea. Heating a solution of **20** and NH_4OAc (1.5 equiv) in MeOH saturated with anhydrous NH_3 at 60 °C for 2 d[18] provides 61% of aminodihydropyrimidine **21**[16] and 37% of a 10:6:1 mixture of **24** or **26**, **25**, and **26** or **24**, respectively. The ^1H and ^{13}C NMR spectra[16,19] of the major spiroaminal are identical to those reported for the acyl portion of crambine B (**8**), with the exception of slight shifts in the ^{13}C spectra due to the different ester, while the spectral data of the other two spiroaminals are quite different.

Although the NMR data strongly suggest that the major spiroaminal has the same stereochemistry as crambine B, there is still some question about the stereochemistry at the aminal center C-8. The relative stereochemistry at C-7 and C-13 is easily established by the coupling constant between H-7 and H-13 which is 4.0–4.2 Hz in the cis isomers **24** and **26** and 11.5 Hz in the trans isomer **25**. The stereochemistry of the aminal center must be determined by NOE. ROESY experiments show an NOE between H-7 and H-9 in crambine B.[5] This does not mean that H-7 is cis to C-9 since examination of models suggests that the dihedral angle between H-7 and C-9 is 60° in both **24** and **26**. As expected, the ROESY spectra shows intense cross-peaks between H-7 and H-9 and between H-7 and H-13 in both **24** and **26**.[20]

An NOE between H-9 and H-13 would conclusively establish the stereochemistry of the major spiroaminal since this distance is calculated to be 2.5–3.0 Å in **24** and 4.5–5.0 Å in **26**. The ROESY spectra shows intense cross peaks between H-9 and H-13 in the minor spiroaminal and no cross peak in the major spiroaminal. *Therefore the major isomer is **26** not **24**.* This stereochemical assignment is supported by the chemical shift of H-13 which absorbs downfield by 0.16 ppm in the major isomer **26** since it is deshielded by the axial oxygen.[21] Since the spectral data suggest that the major spiroaminal **26** has the same stereochemistry as the natural product, *it is likely that crambine B has the opposite stereochemistry at C-8 to that shown in **8*** and therefore the same stereochemistry as at C-15 of ptilomycalin A.

The 61:22:13:2 mixture of **21** and spiroaminals **26**, **25**, and **24**, respectively, appears to be an equilibrium mixture that can be established in methanol under either acidic or basic conditions. Heating either **21** or the mixture of aminals for 1 d at 60 °C in methanol containing Et_3N or for 3 d at 60 °C in methanol containing HCl affords similar mixtures of products.

The yield and selectivity for the desired spiroaminal **26** can be improved by carrying out the cyclization in $CHCl_3$. Heating **21** with Et_3N in $CHCl_3$ (12 h, 60 °C) affords 5% of **21** and 94% of a 20:2:1 mixture of **26**, **25**, and **24**. The change in solvent favors the spiroaminals **24–26** at the expense of the dihydropyrimidine **21** and favors the desired spiroaminal **26** at the expense of isomers **24** and **25**. Furthermore, the 10:6:1 mixture of **26**, **25** and **24** is stable for 3 d in $CHCl_3$ at reflux containing either HCl or Et_3N, suggesting that the cyclization of **21** in basic $CHCl_3$ to give **26** is kinetically controlled. Spiroaminal **26** should be the major product under kinetically controlled conditions since both new bonds have been formed on the less hindered face of the dihydropyrimidine. Stereoelectronic preference for axial attack, via a chairlike transition state, should also favor the formation of **26**. The selective formation of the desired stereoisomer in the cyclization of **21** strongly suggests that the biosynthesis of crambine B involves the addition of guanidine to an enone ester analogous to **14**.

In aqueous solution, dihydropyrimidine **21** is more stable than the spiroaminals. A mixture of **24–26** is quantitatively

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(18) (a) O'Reilly, B. C.; Atwal, K. S. *Heterocycles* **1987**, *26*, 1185 and 1189. (b) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898.
(19) Spectral data for **23–26** were recorded in CD_3OD (*J* values in Hz) and are reported in using the numbering scheme previously used for crambines A and B.[5] **23**: OMe (3.75; 52.4), C-6 (166.9), C-7 (103.4), C-8 (153.1), H_2C-9 (2.96 ddd, 9.3/9.3/18.0 Hz and 3.32 ddd, 3.0/8.4/18.0 Hz; 32.1), H_2C-10 (2.09 m and 2.23 m; 23.2), H_2C-11 (3.66 ddd, 7.3/9.1/9.3 Hz and 3.81 ddd, 2.9/9.1/9.1 Hz; 49.3), C-12 (153.3), HC-13 (4.38 dd, 5.9/5.9 Hz; 51.6), H_2C-14 (1.56 m; 37.7), H_2C-15 (1.45 m; 25.4), H_2C-16 to H_2C-22 (1.2–1.4 m; 31.07, 31.04, 31.04, 30.96, 30.87, 30.77, 30.6), H_2C-23 (1.2–1.4 m; 33.4), H_2C-24 (1.2–1.4 m; 24.0), H_3C-25 (0.89 t 6.7 Hz; 14.7). **24**: OMe (3.69; 52.5), C-6 (170.3), HC-7 (3.10 d, 4.0 Hz; 50.4), C-8 (92.7), H_2C-9 (2.0–2.2 m; 41.5), H_2C-10 (2.0–2.2 m; 25.6), H_2C-11 (3.92 and 4.06 m; 70.6), C-12 (155.0), HC-13 (3.69 m; 51.8), H_2C-14 (1.55 m; 33.3), H_2C-15 (1.2–1.4 m; 26.8), H_2C-16 to H_2C-22 (1.2–1.4 m; 31.05, 30.94, 30.89, 30.78, 30.78, 30.78, 30.69), H_2C-23 (1.2–1.4 m; 33.4), H_2C-24 (1.2–1.4 m; 24.0), H_3C-15 (0.90 t 6.7 Hz; 14.7). **25**: OMe (3.76; 51.8), C-6 (170.5), HC-7 (2.92 d, 11.5 Hz; 50.5*), C-8 (90.4), H_2C-9 (2.0-2.4 m; 36.5), H_2C-10 (1.8–2.3 m; 25.7), H_2C-11 (3.80–4.00 m; 70.0), C-12 (155.1), HC-13 (3.80–3.4 m; 53.3*), H_2C-14 (1.55 m; 34.2), H_2C-15 (1.2–1.4 m; 26.3), H_2C-16 to H_2C-22 (1.2–1.4 m; 31.1, 31.1, 30.94, 30.87, 30.78, 30.67, 30.64), H_2C-23 (1.2–1.4 m; 33.4), H_2C-24 (1.2–1.4 m; 24.0), H_3C-15 (0.89 t 6.7 Hz; 14.7). **26**: OMe (3.72; 52.8), C-6 (170.5), HC-7 (3.00 d, 4.2 Hz; 49.8), C-8 (90.2), H_2C-9 (2.1 m; 36.4), H_2C-10 (2.1–2.3 m; 26.0), H_2C-11 (3.92 and 4.02 m; 69.2), C-12 (155.4), HC-13 (3.85 ddd, 4.2/7.3/7.3 Hz; 50.4), H_2C-14 (1.55 m; 33.0), H_2C-15 (1.2–1.4 m; 26.7), H_2C-16 to H_2C-22 (1.2–1.4 m; 31.05, 31.02, 30.89, 30.76, 30.76, 30.76, 30.65), H_2C-23 (1.2–1.4 m; 33.4), H_2C-24 (1.2–1.4 m; 24.0), H_3C-15 (0.89 t 6.7 Hz; 14.7).

(20) Bothner-By, A. A.; Stephens, R. L.; Lee, J.-M.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811. Bax, A.; Davis, D. G. *J. Mag. Res.* **1985**, *63*, 207. Two-dimensional phase-sensitive ROESY spectra were obtained on a 500-MHz Bruker AMX-500 spectrometer. Data workup was performed using Hare's FELIX program operating on a Silicon Graphics Iris Workstation. Spin-locking periods of 100 and 200 ms were used with a spin-lock field of 2.5 kHz ($\pi/2$ = 100 μs).
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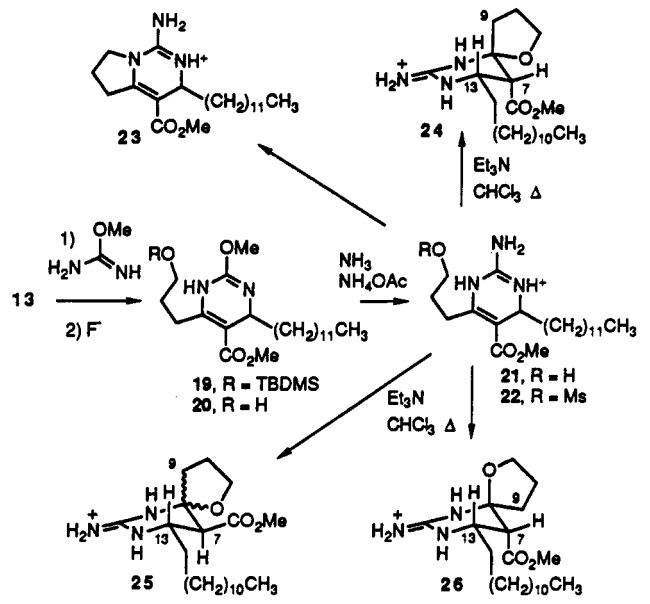

converted to **21** on treatment with K_2CO_3 in 1:1 H_2O–MeOH for 1 d at rt, permitting the recycling of **24** and **25**. The solvent effects on the equilibrium between **21** and **24–26** are similar to those in related hydroxy imines in which polar solvents that can hydrogen bond to the alcohol favor the open form.[22]

The synthesis of the acyl portion of crambine A is completed by reaction of **21** with MsCl and Et_3N in CH_2Cl_2 (30 min, 0 °C; 6 h, rt) to give mesylate **22**. Reaction of **22** with Et_3N in $CHCl_3$ (reflux, 12 h) provides 90% of **23** whose ^1H and ^{13}C NMR spectra[16,19] are virtually identical to those reported for the acyl portion of crambine A (**7**).

The acyl portions of crambine A (six steps, 29% overall yield) and crambine B (six steps, 26% overall yield) have been efficiently and stereospecifically synthesized from methyl acetoacetate. Aminodihydropyrimidine **21** is formed efficiently from enone ester **13** by a two-step procedure involving addition of *O*-methylisourea to give **19** and displacement of the methoxy group of **20** with ammonia to give **21**. Aminal formation from **21** in $CHCl_3$ proceeds in high yield with good selectivity for **26**, the acyl portion of crambine B (**8**). Reaction of alcohol **21** with MsCl and base affords **23**, the acyl portion of crambine A (**7**). The methods developed here should be applicable to the synthesis of the more complex targets ptilomycalin A and the crambescidins.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support. We thank Prof. Thomas Pochapsky and Mr. Anping Wang for carrying out the ROESY experiment.

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A Palladium-Mediated Approach to Construction of Nitrogen Heterocycles

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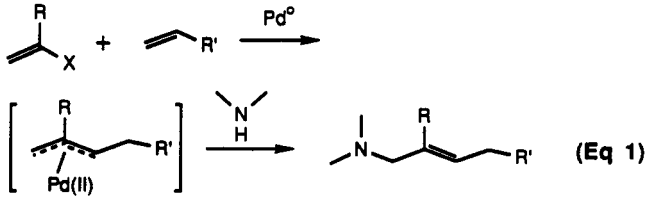
Received February 27, 1992

Summary: Sequential regiospecific C–C and C–N bond-forming reactions via a novel variation of the Heck reaction can be used to synthesize nitrogen-containing heterocyclic systems.

The Heck reaction of vinyl or aryl halides with alkenes catalyzed by palladium is a powerful tool for carbon–carbon bond formation.[1] Recently, elegant variations of this methodology have been used for synthesis of complex polycyclic systems.[2] When vinyl halides are used in Heck reactions, a problem which often arises is formation of stable π-allylpalladium intermediates (eq 1) which serve



(Eq 1)

to remove the metal catalyst and thus terminate the catalytic cycle.[1] Heck found that if a secondary amine is included, coupling of a vinyl bromide or iodide and an alkene can be effected catalytically, leading ultimately to an allylic amine (eq 1).[3] In this paper we reveal that this three-component condensation can be effected intramolecularly in a novel, efficient approach to bicyclic nitrogen heterocycles from acyclic precursors.

Initial feasibility studies were conducted with cyclization substrates **1** and **2** (eq 2).[4] Exposure of secondary amine **1** to various Pd^0 precursors under a variety of conditions gave bicyclic allylic amine **3**, but only in poor yields (~10%).[5] However, sulfonamide **2** cyclized under the reaction conditions shown[6] to afford bicyclic sulfonamide **4** in good yield. Varying amounts of isomeric bridged compound **5** were also produced (<1–20% of the product mixture). In order to explore some mechanistic issues relevant to these cyclizations (vide infra), isomeric vinyl bromide **6** was prepared[4] and upon subjection to the Heck

(1) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. Heck, R. F. *Org. React.* **1982**, *27*, 345.

(2) See for example: Larock, R. C.; Yong-de, L.; Bain, A. C. *J. Org. Chem.* **1991**, *56*, 4589. Zhang, Y.; Wu, G.-Z.; Angel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590. Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846. Grigg, R.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1991**, *32*, 3855. Meyer, F. E.; de Meijere, A. *Synlett* **1991**, 777. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701.

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(4) Cyclization substrates were prepared by short, straightforward routes which will be described in a subsequent full paper. For example, substrates like **6** and **20** can be prepared via alkylation of the dianion of 1-hepten-6-yne followed by conversion of the acetylene to the desired vinyl halide.

(5) A reported attempt by Heck to effect a related cyclization process met with failure.[3b]

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