Enantioselective Total Synthesis of (−)-Ptilomycalin A

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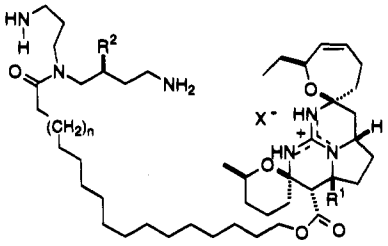
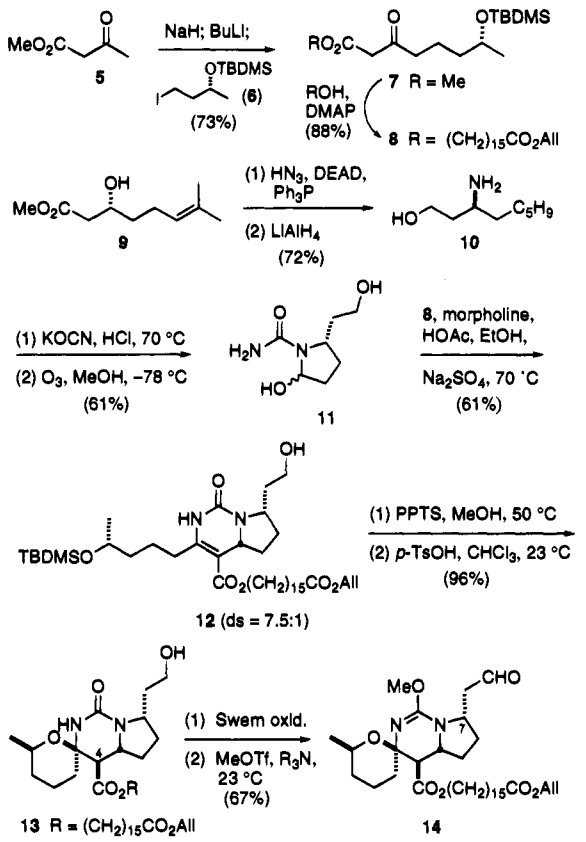
A remarkable family of complex guanidinium alkaloids is found in several species of warm water sponges.[2-4] Ptilomycalin A (**1**) was first isolated in 1989 by Kashman, Kakisawa, and co-workers from chloroform extracts of the Caribbean sponge *Ptilocaulis spiculifer* and the Red Sea sponge *Hemimycale* sp.,[2] while a related series of alkaloids, exemplified by the crambescidins 800 (**2**), 816 (**3**), and 844 (**4**), were obtained by Rinehart and co-workers from the Mediterranean sponge *Crambe crambe*.[3] This alkaloid group is characterized by a structurally unique pentacyclic guanidinium core that has a spermidine or hydroxyspermidine residue tethered by a long chain ω-hydroxycarboxylic acid spacer.



ptilomycalin A (1, $R^1 = R^2 = H$; n = 1)
crambescidin 800 (2, $R^1 = H$, $R^2 = OH$; n = 1)
crambescidin 816 (3, $R^1 = R^2 = OH$; n = 1)
crambescidin 844 (4, $R^1 = R^2 = OH$; n = 3)

Extensive NMR studies have shown that the relative stereochemistry of the pentacyclic guanidinium portions of ptilomycalin A and the crambescidins **2**–**4** is identical, while oxidative degradation of crambescidin 816 (**3**) has defined the absolute stereochemistry of the central guanidinium fragment of this alkaloid.[3b] Substantial antitumor, antiviral, and antifungal activities have been described for ptilomycalin A[2] and several of the crambescidins,[3] and crambescidin 816 has been shown to be a potent calcium channel blocker.[4] Notable progress toward assembling the guanidinium core of this alkaloid group by a biomimetic strategy has been recorded,[5] highlighted by Snider's construction of a methyl ester analog of **1**.[6] Herein we disclose the first total synthesis of a member of the ptilomycalin A–crambescidin guanidinium alkaloid family. This enantioselective total synthesis of (−)-ptilomycalin A rigorously establishes the absolute configuration of **1** and additionally defines a practical method for obtaining substantial quantities of ptilomycalin A and congeners for pharmacological and structural investigations.[7]

Scheme 1



Our earlier model studies in this area[8] demonstrated that an intramolecular variant of the venerable Biginelli condensation[9] could be employed to construct the central pyrrolidine ring of ptilomycalin A and relate the stereochemistry of this fragment to that of the spirocyclic hydropyran unit.[10] The synthesis of the β-ketoester and ureido aldehyde components of the critical tethered Biginelli condensation is summarized in Scheme 1. Alkylation of the dianion of methyl acetoacetate (**5**)[11] with the readily available enantiopure (*R*)-siloxy iodide **6**[12] provided **7**,[13] which was transesterified[14] with the allyl ester of 16-hydroxyhexadecanoic acid to give the (*R*)-β-ketoester **8** in 64% overall yield from **5**. The (*S*)-ureido aldehyde **11**, whose enantiomer we had described earlier,[8] was similarly accessed on a large scale in four steps and 44% overall yield from the enantiopure (*R*)-β-hydroxy ester **9**.[15]

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(2) (a) Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtani, I.; Kusumi, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1989**, *111*, 8925. (b) Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh, S. *J. Am. Chem. Soc.* **1992**, *114*, 8472. (c) Ohtani, I.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1992**, *33*, 2525.

(3) (a) Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 5712. (b) Jares-Erijman, E. A.; Ingrum, A. L.; Carney, J. R.; Rinehart, K. L.; Sakai, R. *J. Org. Chem.* **1993**, *58*, 4805. (c) Taveras, R.; Daloze, D.; Braekman, J. C.; Hajdue, E. *Biochem. Syst. Ecol.* **1994**, *22*, 645.

(4) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Ferri, S.; Spampinato, S.; Speroni, E. *J. Nat. Prod.* **1993**, *56*, 1007.

(5) (a) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1992**, *57*, 2526. (b) Snider, B. B.; Shi, Z. *Tetrahedron Lett.* **1993**, *34*, 2099. (c) Murphy, P. J.; Williams; H. L. *J. Chem. Soc., Chem. Commun.* **1994**, 819. (d) Murphy, P. J.; Williams, H. L.; Hursthouse, M. B.; Malik, K. M. A. *J. Chem. Soc., Chem. Commun.* **1994**, 119.

(6) Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 549.

(7) Ptilomycalin A has been shown to be an anion receptor.[2b] It is tempting to speculate that in vivo the polymethylene tether of ptilomycalin A is embedded in a membrane in a way that enhances anion binding. Studies to explore the structure of **1** and analogs in membrane models are planned.

(8) Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1993**, *58*, 3235.

(9) (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360. (b) For a recent review, see: Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.

(10) The appealing biomimetic approach to ptilomycalin A and the crambescidins[5,6] suffers from lack of any apparent way to correlate the stereocenters of the secondary alcohols, C(3) and C(19) of **1**, to the stereogenic centers of the central pyrrolidine ring.

(11) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(12) (a) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187. (b) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans 1* **1980**, 2866.

(13) All intermediates were fully characterized by ^1H and ^{13}C NMR, IR, and MS analysis. The elemental composition of analytical samples of new compounds was confirmed by combustion analysis or high-resolution mass spectrometry. Yields refer to isolated products purified on silica gel unless noted otherwise. Abbreviations employed are defined in *J. Org. Chem.* **1994**, *59*, 7A.

(14) Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618.

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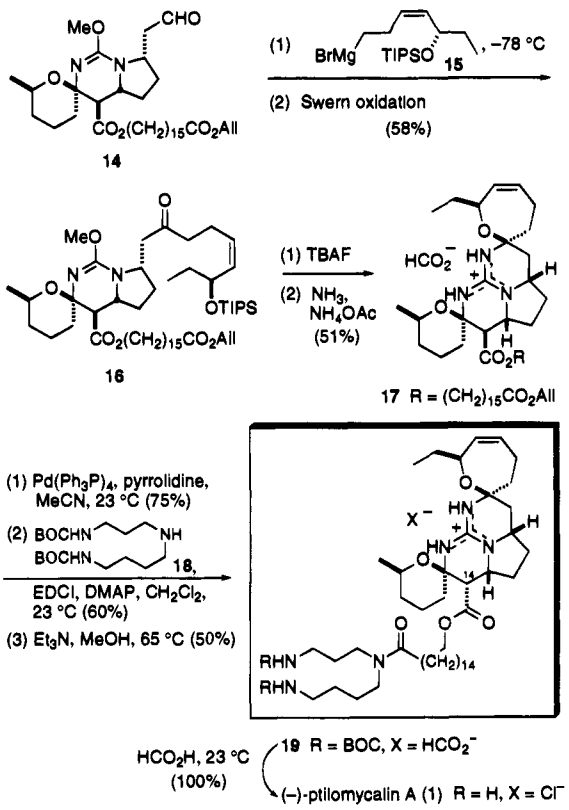
Scheme 2



Condensation of **11** and **8** took place with good diastereoselection (ds = 7.5:1) at 70 °C in EtOH in the presence of 1 equiv of morpholinium acetate, a catalytic amount of acetic acid, and excess Na_2SO_4. After chromatographic separation of 8% of the minor epimer, the hexahydro-1-oxopyrrolo[1,2-*c*]-pyrimidine **12** was obtained in 61% yield on a 10 g scale. While **12** could be converted in one step to the spirotricyclic intermediate **13** by exposure to a slight excess of *p*-TsOH for several hours, the reaction was more reproducible on a large scale if the TBDMS group was first cleaved with PPTS–MeOH and the resulting alcohol cyclized with a catalytic amount of *p*-TsOH at 23 °C. This sequence provided a single tricyclic product **13** in essentially quantitative yield. That this compound was the β-carboalkoxy stereoisomer, and thus epimeric with ptilomycalin A at this site, was signaled by the 11.5 Hz coupling constant of the C(4) methine hydrogen.[8] Although epimerization to the α-ester epimer should, in principle, be possible at this point,[8] we chose in this first generation effort to defer this adjustment to the final stage of the synthesis. To prepare for the addition of the remaining carbons of the oxepene ring, **13** was oxidized with the Swern reagent,[16] and the urea moiety was protected and activated for subsequent guanidine formation by *O*-methylation to provide the pseudourea aldehyde **14** in 67% overall yield.[17]

The construction of ptilomycalin A was completed as follows (Scheme 2). Condensation of **14** with 2 equiv of Grignard reagent **15**[18] at −78 °C in THF, followed by quenching at −78 °C with morpholinium acetate, filtration of the crude secondary alcohol through Celite, and finally Swern oxidation,[16] provided ketone **16** in 58% overall yield.[21] The pentacyclic guanidinium core was then fashioned by cleavage of the TIPS protecting group and treatment of the resulting keto alcohol with a solution of NH_3 and NH_4OAc in *t*-BuOH at 60 °C in a sealed tube.[6] This sequence provided a single pentacyclic guanidinium product **17**, which was isolated after purification on silica gel (95:5:0.1 EtOAc–MeOH–HCO_2H) in 51% yield. The allyl ester of **17** was then cleaved[22] and the resulting acid coupled with the bis-BOC-protected spermidine **18**[23] to afford the corresponding amide. At this point the ester was epimerized by heating in MeOH in the presence of 10 equiv of Et_3N. Although this step is yet to be optimized, chromatographic separation of the product epimer provided, after three recycles, the α-ester **19** in 50% yield (diagnostic d, J = 4.8 Hz, at δ 2.93 for H-14).[24] Cleavage of the BOC protecting groups with HCO_2H, followed by concentration and washing with aqueous NaOH–NaCl, provided (−)-ptilomycalin A (**1**) in quantitative yield. Synthetic **1** showed ^1H and ^{13}C NMR spectra consistent with those reported for (−)-ptilomycalin A[2ab] and was indistinguishable from an authentic sample by TLC comparisons on three adsorbents. To further verify identity, synthetic **1** was converted[2b] to bis(trifluoroacetyl)ptilomycalin A trifluoroacetate, which exhibited ^1H and ^{13}C NMR spectra indistinguishable from those reported for this well-characterized derivative of (−)-ptilomycalin A.[2b] Synthetic bis(trifluoroacetyl)ptilomycalin A trifluoroacetate showed $[\alpha]^{23}_D$ −15.9° and $[\alpha]^{23}_{577}$ −20.2° (*c* 0.79, $CHCl_3$), while $[\alpha]^{25}_D$ −15.8° (*c* 0.68, $CHCl_3$) is reported for this derivative of the natural product.[2b,25]

In summary, the first total synthesis of (−)-ptilomycalin A (**1**) was accomplished in a convergent fashion from three readily available enantioenriched secondary alcohols: **9**[15] and the alcohol precursors of **6**[12] and **15**.[15] The synthesis in its present form is capable of preparing **1** and congeners on gram scales for pharmacological and structural studies.[7]

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Supplementary Material Available: Listings of spectroscopic, analytical, and optical data for new compounds reported in Schemes 1 and 2, and copies of ^1H and ^{13}C NMR spectra for synthetic (−)-**1** and synthetic bis(trifluoroacetyl)ptilomycalin A trifluoroacetate (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(16) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(17) It was critical that the methylation be performed under mild conditions (MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 23 °C) and that **14** be purified rapidly on Et_3N-treated silica gel or else significant epimerization at C(7) resulted.

(18) The bromide precursor of **15** (86% ee) was prepared from 7-(*tert*-butyldimethylsiloxy)-4-heptyn-3-one[19] by the following conventional sequence: (a) $LiAlH_4$, *ent*-Darvon alcohol;[20] (b) H_2, $Pd/CaCO_3$–quinoline; (c) TIPSOTf, 2,6-lutidine; (d) PPTS, MeOH; (e) CBr_4, $(Ph_2PCH_2)_2$.

(19) 7-(*tert*-Butyldimethylsiloxy)-4-heptyn-3-one was prepared in three steps from commercially available 3-butyn-1-ol by the following sequence: (a) TBDMSCl, imidazole; (b) *n*-BuLi, propanal; (c) $(COCl)_2$, DMSO, Et_3N.

(20) Cohen, N.; Lopresti, R. J.; Neukon, C.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 582.

(21) Approximately 5% of a diastereomer, resulting from the minor enantiomer of **15**, was removed at this point.

(22) Deziel, R. *Tetrahedron Lett.* **1987**, *28*, 4371.

(23) Cohen, G. M.; Cullis, P. M.; Hartley, J. A.; Mather, A.; Symons, M. C. R.; Wheelhouse, R. T. *J. Chem Soc., Chem. Commun.* **1992**, 298.

(24) After 4 days at 60 °C, the ratio of ester epimers was ~3:1 (β:α). This mixture was readily separated on silica gel (95:5:0.1 EtOAc–MeOH–HCO_2H), and the β-epimer was recycled.

(25) A small rotation is reported[2b] for (−)-ptilomycalin A (anion unspecified): $[\alpha]^{25}_D$ −2.5° (*c* 0.7, $CHCl_3$); synthetic **1** (chloride counterion) showed $[\alpha]^{23}_D$ −11.3°, $[\alpha]^{23}_{577}$ −12.0° (*c* 0.60, $CHCl_3$).