Studies toward the Total Synthesis of (+)-Ptilomycalin A. Use of a Tethered Biginelli Condensation for the Preparation of an Advanced Tricyclic Intermediate

Larry E. Overman* and Michael H. Rabinowitz

Department of Chemistry, University of California, Irvine, California 92717-2025

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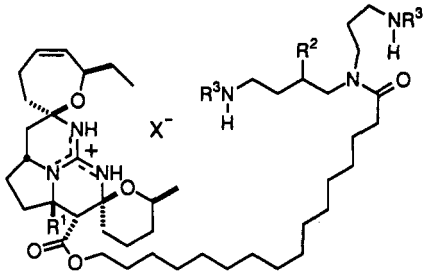
Summary: An intramolecular ureidoaldehyde condensation, **16** + (*R*)-**14** → **19**, is the key step in a seven-step preparation of the enantiopure spirotricycle **23**, a potential intermediate for the enantioselective total synthesis of ptilomycalin A.

(+)-Ptilomycalin A (**1**) is a structurally novel guanidinium alkaloid isolated from the Caribbean sponge *Ptilocaulus speculifer* and the Dead Sea sponge *Hemimycale* sp.[1] Four hydroxylated analogs, the crambescidins (*e.g.*, **2**), were recently characterized from extracts of the

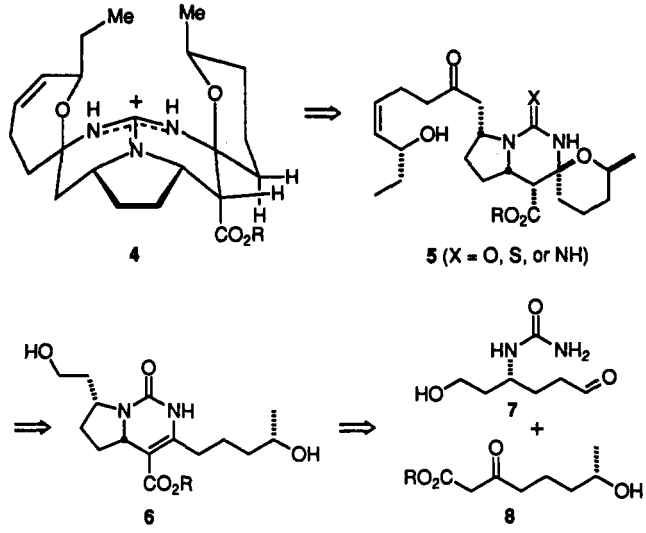


1 ptilomycalin A ($R^1 = R^2 = R^3 = H$, X = unknown)
2 crambescidin 816 ($R^1 = R^2 = OH$, $R^3 = H$, X = unknown)
3 $R^1 = R^2 = H$, $R^3 = COCF_3$, $X = CF_3CO_2$

Mediterranean sponge *C. crambe*.[2] Extensive NMR spectral investigations have defined the relative stereochemistry of the seven stereogenic centers of the pentacyclic core of ptilomycalin A to be as shown in **1**, while the absolute stereochemistry remains unknown. NMR studies of a bis-trifluoroacetate derivative of **1** suggest that the spermidine-containing side chain organizes with the guanidinium core to form an anion receptor as depicted in **3**.[1b,3] Preliminary pharmacological assessment of **1** shows it to be a potent antitumor and antiviral agent as well as a good antifungal.[1] This paper reports the enantioselective synthesis of an advanced intermediate **23**, which embodies three of the five rings and five of the seven stereogenic centers of the ptilomycalin A core.[4]

Our plan for accessing the pentacyclic core of ptilomycalin A is outlined in antithetic format in Scheme I. The axial orientation of the ether oxygens in **4** suggests that the stereochemistry of the unusual spiroaminal centers may arise naturally from stereoelectronic considerations.[5] The hexahydro-1-oxopyrrolo[1,2-c]pyrimidine **6**, a plausible precursor of the tricyclic intermediate **5**, was envisaged to arise from the chiral fragments **7** and **8** through an intramolecular variant of the classical Biginelli condensation.[6,7]

Scheme I



The tethered Biginelli reaction was initially examined in a racemic model series in order to verify our expectation that this condensation would provide a hydropyrimidinone product having the required cis relationship of the two methine hydrogens that flank the angular nitrogen.[8] Reduction of aminoester *rac*-**9**[9] with $LiAlH_4$ followed by selective reaction of the hydrochloride salt of the derived amino alcohol with aqueous potassium cyanate at 80 °C provided the urea *rac*-**12** in 80% overall yield.[11] Ozonolysis of this intermediate at −78 °C in MeOH gave *rac*-**14** as a mixture of hemiaminal stereoisomers along with a minor amount of the open-chain aldehyde. Attempted condensation of this crude product with methyl acetoacetate (**15**) in refluxing methanol in the presence of catalytic acid (typical Biginelli conditions),[6,7] or in methanol in the presence of piperidine and acetic acid (typical Knoevenagel

(1) (a) Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtani, I.; Takenori, K.; Kakisawa, H. *J. Am. Chem. Soc.* **1989**, *111*, 8925–8926. (b) Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh, S. *J. Am. Chem. Soc.* **1992**, *114*, 8472–8479.

(2) Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 5712–5715.

(3) Ohtani, I.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1992**, *33*, 2525.

(4) While our investigations were underway, syntheses of the heterocyclic portions of crambines A and B, which contain bicyclic guandidine moieties related to those found in **1**, were described; see: Snider, B. B.; Shi, Z. *J. Org. Chem.* **1992**, *57*, 2526.

(5) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: London, 1983; Chapter 1.

(6) (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360. (b) Folkers, K.; Harwood, H. J.; Johnson, T. B. *J. Am. Chem. Soc.* **1932**, *54*, 3751–3758. (c) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898–5907.

(7) For brief reviews, see: Brown, D. J. In *The Pyrimidines*; Brown, D. J., Ed., Wiley: New York, 1962; pp 440–441. Brown, D. J. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1982; Vol. 3, pp 117–118.

(8) Molecular mechanics calculations (MM2) using the Monte Carlo molecular dynamics package in Macromodel indicates that an intermediate 2,5-cis dialkyl *N*-amidoylpyrrolidine is ~2 kcal/mol lower in energy than the corresponding trans isomer.

(9) Prepared from the addition of NH_3 (sealed tube, 23 °C) to methyl (*E,E*)-2,6-octadienoate.[10]

(10) Crandall, J. K.; Mayer, C. F. *J. Org. Chem.* **1970**, *35*, 3049.

(11) 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, purified products unless noted otherwise. Chiral compounds are enantioenriched unless indicated otherwise.

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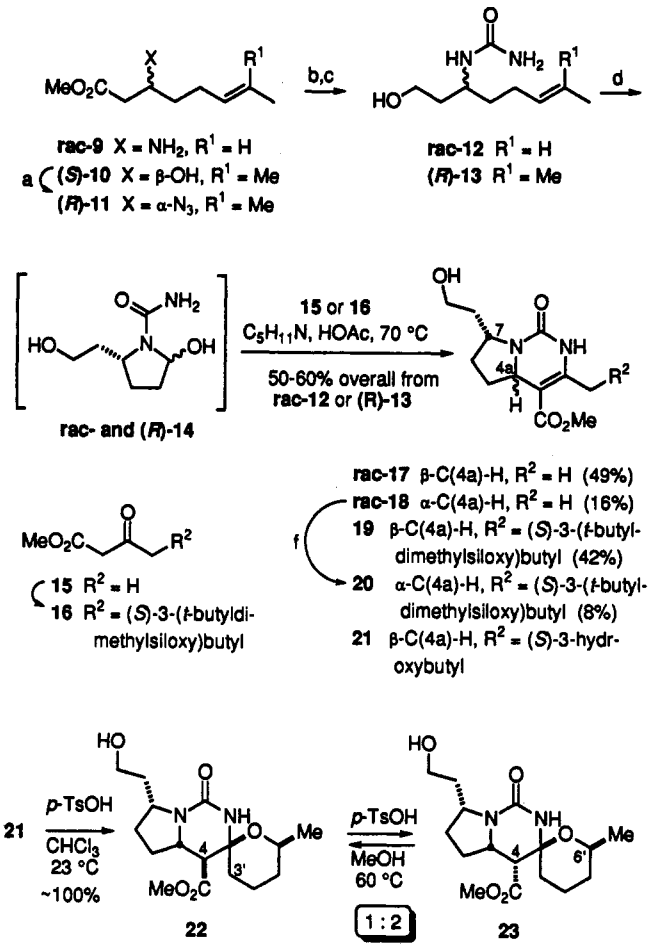
condensation conditions),[4,12] led only to recovery of the starting components. However, when the latter reaction was performed neat the crystalline *hydropyrrolopyrimidones rac*-17 and *rac*-18 *were isolated in a 3:1 ratio and in 65% overall yield from the urea rac*-12. These isomers exhibit characteristic ^{1}H NMR signals for their methine hydrogens: *rac*-17, 4.26 (H_{4a}) and 4.15 (H_7) ppm; *rac*-18, 4.32 (H_{4a}) and 4.45 (H_7) ppm. Single-crystal X-ray analysis of the minor isomer[13] established that the major product *rac*-17 had the required cis orientation of the methine hydrogens at C(4a) and C(7).

Prompted by the success of the tethered Biginelli condensation, the enantiopure urea and β-keto ester fragments (*R*)-14 and 16 were prepared to pursue the extension of this chemistry to ptilomycalin A itself.[14,15] Treatment of the readily available β-hydroxy ester (*S*)-10[16] with HN_3 under Mitsunobu conditions provided an inseparable 5:1 mixture of (*R*)-11 and methyl 7-methyl-2,6-octadienoate. Lithium aluminum hydride reduction of this mixture provided, after SiO_2 chromatography, (*R*)-3-amino-7-methyl-6-octen-1-ol in 75% yield for the two steps.[17] Treatment of this material with acidic KNCO furnished urea (*R*)-13 (82% yield), which provided the crude mixture of hemianimals (*R*)-14 upon ozonolysis.

Condensation of (*R*)-14 with the (*S*)-β-keto ester 16, directly available[18] from 15 and (*S*)-1-iodo-3-(*tert*-butyldimethylsiloxy)butane,[19-21] was best accomplished in CH_2Cl_2 at 70 °C in a sealed tube and furnished the readily separable Biginelli products 19 and 20 in a 5:1 ratio and an unoptimized combined overall yield of 50% from (*R*)-13. Stereochemical assignments followed directly from diagnostic ^{1}H NMR signals: 19, 4.25 (H_{4a}) and 4.13 (H_7) ppm; 20, 4.33 (H_{4a}) and 4.43 (H_7) ppm. Treatment of the major isomer 19 with TBAF provided the bicyclic alcohol 21 (95%). Although these basic conditions did not promote spirocyclization, treatment of 21 with catalytic acid (HCl, *p*-TsOH, or CF_3CO_2H) in $CHCl_3$ produced a single tricyclic spiroanimal 22 in quantitative yield. That this compound was the undesired β-carbomethoxy epimer was signaled by the 11.5-Hz coupling constant of the C(4) methine hydrogen, which indicates a trans diaxial arrangement of H_c and H_d (Figure 1). The stereochemistry at the spiro center was not as readily determined. However, complete assignment of the ^{1}H NMR spectrum of 22 using ^{1}H–^{1}H and ^{1}H–^{13}C two-dimensional correlation

Scheme II[a]



[a] Conditions: (a) HN_3, DEAD, Ph_3P, 0 °C → 25 °C, 15 h; (b) $LiAlH_4$, THF, 0 °C → 25 °C, 1.5 h (95% from *rac*-9; 75% from (*S*)-10); (c) HCl, KONC, H_2O, 80 °C (80–90%); (d) O_3, MeOH, −78 °C; Me_2S (~100% crude); (e) NaH, THF; *n*-BuLi; (*S*)-1-iodo-3-(*tert*-butyldimethylsiloxy)butane (60%); (f) TBAF, 23 °C, 20 h (95%).

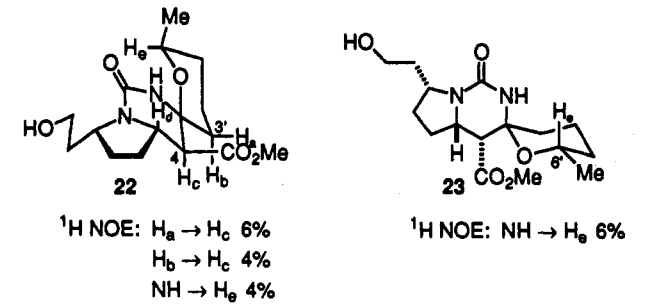


Figure 1.

experiments allowed the measurement of diagnostic NOEs between the methine hydrogen at C(4) and the C(3′) methylene group of the hydropyran ring (Figure 1).

Epimerization of the β-carbomethoxy epimer 22 with *p*-TsOH in MeOH (Scheme II) provided a separable 1:2 mixture of recovered 22 and the desired α-carbomethoxy epimer 23 in essentially quantitative yield. That this epimerization proceeded with retention of stereochemistry at the C(3) spirocenter was secured by measurement of a 6% NOE between the NH and the C(6′) methine hydrogen of the tetrahydropyran ring of 23 (Figure 1).[22]

The spirotricyclic 23, an attractive potential intermediate for the enantioselective total synthesis of ptilomycalin A, was prepared in seven steps from the known β-hydroxy

(12) Jones, G. *Org. React.* **1967**, *15*, 204.
(13) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
(14) The choice of this absolute stereochemistry is based on the faint analogy of 1 with the related alkaloid (+)-ptilocaulin, whose absolute configuration is known.[15]
(15) Snider, B. B.; Faith, W. C. *J. Am. Chem. Soc.* **1984**, *106*, 1443. Harbour, G. C.; Tymiak, A. A.; Rinehart, K. L., Jr.; Shaw, P. D.; Huges, R. G., Jr.; Mizak, S. A.; Coats, J. H.; Zurenko, G. E.; Li, L. H.; Kuentzel, S. L. *J. Am. Chem. Soc.* **1981**, *103*, 5606.
(16) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227–4230. Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.
(17) Conversion to the tetrahydro-1,3-oxazin-2-one derivative (1,1′-carbonyldiimidazole) and HPLC analysis using a Chiracel OD column established that the ee of this intermediate was >94%.
(18) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082–1087.
(19) Prepared from the (*S*)-BINAP/Ru mediated reduction[20] of methyl acetoacetate followed by conversion to the iodide as described for the preparation of the (*R*) enantiomer.[21]
(20) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1992**, *71*, 1.
(21) Maemoto, S.; Mori, K. *Chem. Lett.* **1987**, 109–112.

ester (*S*)-10 and nine overall steps from commercial methyl acetoacetate. The convergent route developed features the first example of an intramolecular ureidoaldehyde condensation (a tethered Biginelli condensation) for preparing a bicyclic fused dihydropyrimidinone. Our ongoing efforts to define the scope of this new approach to heterocycles containing the dihydropyrimidinone unit as well as to convert **23** to ptilomycalin will be reported in due course.

(22) An NOE between NH and the C-6′ methine hydrogen is observed in **1**. Models suggest that this NOE would not be seen in the alternate spiro epimer, in either of the two possible chair conformations. **Note Added in Proof**: The structure of **22** was confirmed by single-crystal X-ray analysis.

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Supplementary Material Available: Characterization data for new compounds, NMR assignments of **22** and **23**, along with 2D NMR spectra, and an ORTEP diagram of *rac*-**18** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.