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THE TOTAL SYNTHESIS OF (±) - PTILOCAULIN

Barry B. Snider*[1] and William C. Faith

Department of Chemistry

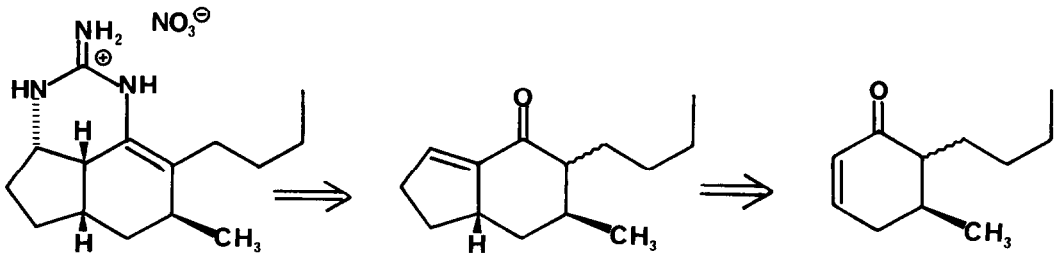
Brandeis University

Waltham, Massachusetts 02254

Abstract: A seven step synthesis of ptilocaulin via the addition of guanidine to enone 2 is described.

Rinehart et al. have recently reported the isolation of the antimicrobial and cytotoxic cyclic guanidine ptilocaulin (1) from the Caribbean sponge Ptilocaulis aff. P. spiculifer.[2] They suggested that this novel toxin was "derived from addition of guanidine to a polyketonide chain."

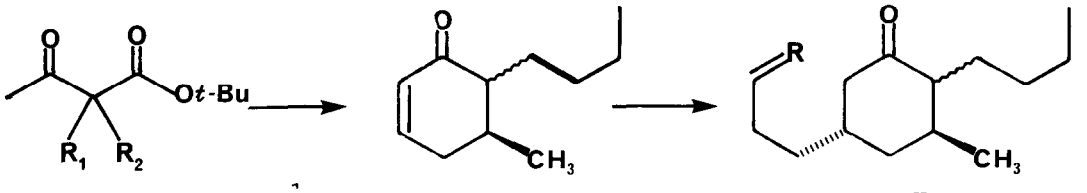
We report here a short synthesis of (±) - ptilocaulin (1) based on a similar retrosynthetic analysis. Addition of guanidine to enone 2 should give ptilocaulin. Related additions of guanidine to enones are well known, although dihydropyrimidinimines with an endocyclic double bond are the normal product.[3] Enone 2 should be readily available by conjugate addition of a 3-carbon synthon to 6-butyl-5-methyl-2-cychohexenone (3) followed by aldol condensation[4] since conjugate addition to 5-substituted cyclohexenones leads selectively to trans-3, 5-disubstituted cyclohexanones.[5]



1 2 3

t-Butyl acetoacetate (4) is converted to 5 in 55% yield (Na, dioxane, n-BuI).[6] Acetoacetate 5 is converted to 3 by a modification of the procedure of Carney and Johnson for the synthesis of 6-(3-butyn-1-yl)-2-cyclohexenone.[7] Crotonaldehyde is added over 16 hr to a solution of the sodium salt of 5 in methanol at -40°C to give a 39% yield of 6 as a mixture of diastereomers. The moderate yield of 6 is typical for Michael additions to crotonaldehyde.[8] Cyclization of 6 and decarboxylation (acetic acid, water, conc. HCl 10:10:1, 17 hr, 25°C) gives a 58% yield of 3 as a 1.7:1 trans-cis mixture.

Addition of the cuprate[9] prepared from 3-butenylmagnesium bromide and $CuBr \cdot S(CH_3)_2$ to 3 gives a 45% yield of 7 as a 1.7:1 mixtures of isomers.[10] Ozonolysis of 7 (O_3, MeOH, -78°C, then $(CH_3)_2S$) gives a quantitative yield of 8 which is cyclized (HCl, THF) to an easily separable 1:1 mixture of cis-2[10] (β-butyl) and trans-2[10] in 70% yield.



4 $R_1 = R_2 = H$

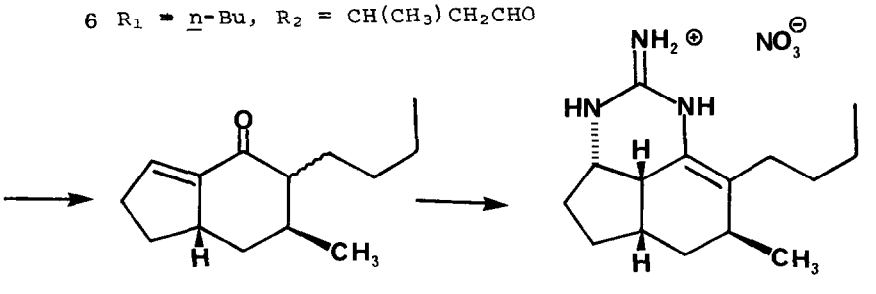
5 R_1 = n-Bu, $R_2 = H$

6 R_1 = n-Bu, $R_2 = CH(CH_3)CH_2CHO$

3

7 R = CH_2

8 R = O



2

1

Guanidine and cis-2 are heated at reflux in benzene under nitrogen for 24 hr with azeotropic removal of water.[3] The reaction is quenched with a slight excess of 1% nitric acid. The organic layer is washed with water, dried and evaporated to give crude ptilocaulin nitrate (1). Chromatography on silica gel (83:17 $CHCl_3$-MeOH) gives pure ptilocaulin (35% yield) which is identical to natural material by IR, ^1H NMR and MS comparison.[12] Reaction of trans-2 with guanidine gives similar results.

This synthesis leads efficiently to ptilocaulin in only 7 steps. The key step, addition of guanidine to 2, which selectively introduces two of the four stereocenters of ptilocaulin, is probably related to its biosynthesis. Optimization of these reactions and extension of this route to isoptilocaulin will be reported in due course.

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10. Careful chromatographic and spectroscopic analysis indicate that only two of the four possible disastereomers are present. Literature precedent,[5] spectroscopic data[11] and further conversion of both isomers to ptilocaulin suggest that 7 and 2 are isomeric at the carbon bearing the butyl group.

11. NMR ($CDCl_3$) δ cis-7, 0.75 (d, 3, J = 7Hz); trans-7, 0.98 (d, 3, J = 7Hz); cis-2, 6.42 (m, 1), 3.08 (m, 1), 0.88 (d, 3, J = 7Hz); trans-2, 6.54 (m, 1), 3.05 (m, 1), 1.04 (d, 3, J = 7Hz).

12. We thank Professor Rinehart for providing us with a comparison sample of and spectral data for ptilocaulin nitrate.

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