GUANIDINIUM CARBOXYLATES: PREPARATION OF 3-CARBOXYOCTAHYDRO-9a*H*-PYRIMIDIN-9a-YLIUM CHLORIDE

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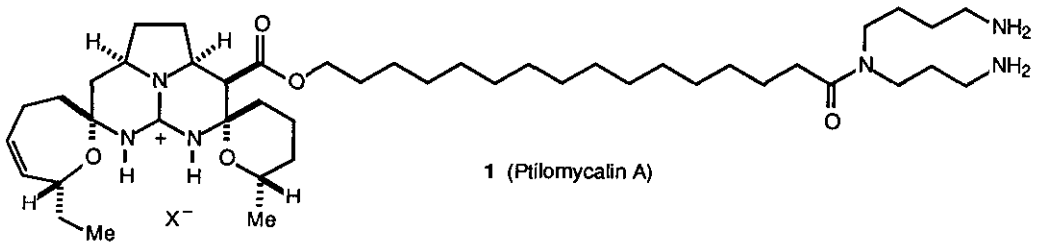
Abstract – The title guanidinium carboxylate (**2**) was prepared from *tert*-butyl 2-bromomethylacrylate (**3**) using an 11-reaction sequence in 12% overall yield. Sequential addition of two differentiated amino groups to the starting acrylate played a key role in the synthesis.

Ptilomycalin A (**1**) is one member of a small family of marine natural products that contain guanidinium carboxylate (**2**) as a substructure.[1,2] Although an elegant biomimetic approach to ptilomycalin A has been reported, a synthesis of guanidinium carboxylate (**2**) has yet to be described.[3,4] As part of a research program designed to provide analogs of **1** for biological evaluation, we undertook a synthesis of **2** and our results are described in this communication.[5]



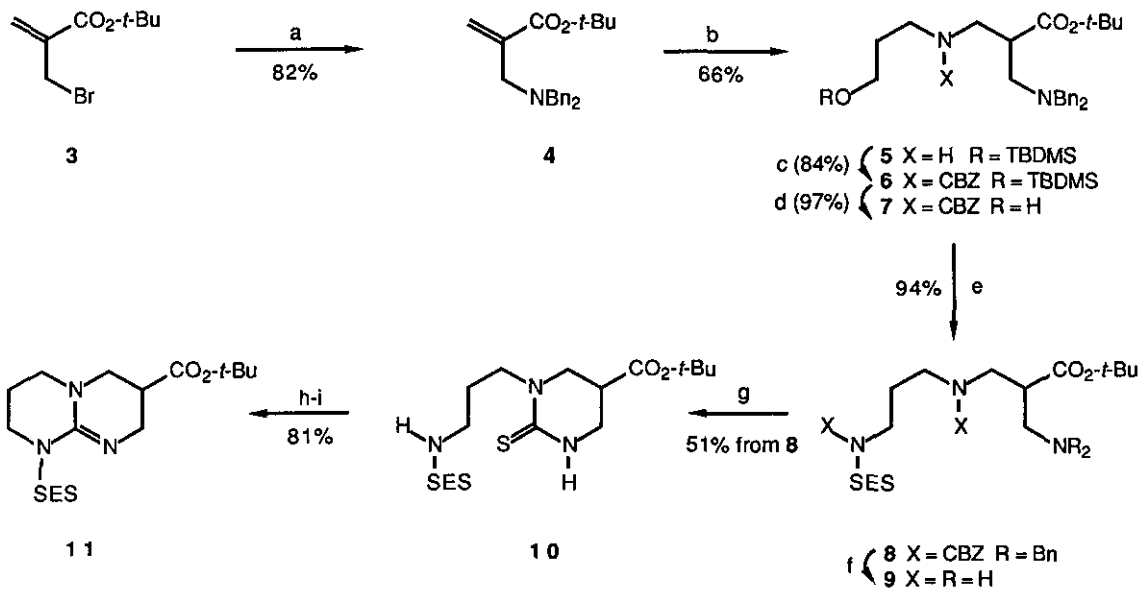
1 (Ptilomycalin A)

A number of approaches to bicyclic guanidinium salts and guanidinium carboxylates have been reported.[6] Our approach was related to strategies used by Echavarren, Schmidtchen, and Corey in their syntheses of C_2-symmetric bicyclic guanidines in that we decided to first prepare an appropriately functionalized triamine and then wrap this unit around a one carbon fragment at the carbon dioxide oxidation state.[7-9]

The first stages of the synthesis are shown in Scheme 1. Thus, treatment of *tert*-butyl 2-bromomethylacrylate (**3**)[10] with dibenzylamine gave the substitution product (**4**) (mp 52-54°C) in 82% yield.[11] Treatment of *O*-(*tert*-butyldimethylsilyl)-3-aminopropanol with *n*-butyllithium followed by **4** provided diamine (**5**) in 66% yield.[12,13] Diamine (**5**) was then converted to carbamate (**6**) (84%) and cleavage of the silyl ether using tetra-*n*-butylammonium fluoride provided alcohol (**7**) in 97% yield.[14,15] The third amine was introduced next using a Mitsunobu reaction.[16,17] Thus, reaction of **7** with benzyl [[2-(trimethylsilyl)ethyl]sulfonyl]carbamate afforded protected triamine (**8**) in 94% yield.[18,19] Hydrogenolysis of **8** in the

presence of a catalytic amount of palladium hydroxide on carbon gave diamine (**9**) which was reacted, without purification, with thiocarbonyldiimidazole to afford cyclic thiourea (**10**) (mp 116-117°C) in 51% overall yield.[7] The thiocarbonyl group was then activated with iodomethane and cyclization was accomplished using Hunig's base to give bicyclic *N*-sulfonylguanidine (**11**) in 81% yield after purification by chromatography over basic alumina.[8,9,20]

Scheme 1

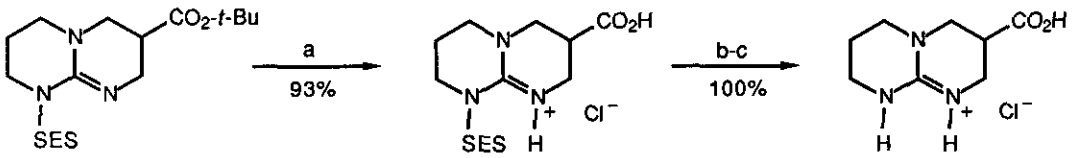


3 4 10 11

(*a*) $(PhCH_2)_2NH$, K_2CO_3, *MeCN* (*b*) $Me_2(t\text{-}Bu)SiOCH_2CH_2CH_2NHLi$, THF, -78°C (*c*) $PhCH_2OCOCl$, Et_3N, THF (d) *n*-Bu_4NF, THF (e) $Me_3SiCH_2CH_2SO_2NHCBZ$, Ph_3P, $EtO_2CN{=}NCO_2Et$, THF (f) $Pd(OH)_2/C$, EtOH, H_2 (60 psi) (g) thiocarbonyldiimidazole, CH_2Cl_2 (h) MeI, MeOH (i) $EtN(i\text{-}Pr)_2$, CH_2Cl_2

The synthesis of guanidinium carboxylate (**2**) was completed as described in Scheme 2. Conversion of *tert*-butyl ester (**11**) to carboxylic acid (**12**) was accomplished using hydrochloric acid in dichloromethane.[21] Finally, the guanidine protecting group was removed using tetra-*n*-butylammonium fluoride in DMF[19] followed by isolation of **2** (mp 209-212.5°C) as the hydrochloride salt.[22] It is notable that the FAB-MS of **2** gave not only a base peak at *m/z* 184 ($(M^+-HCl)+1$), but substantial peaks at 367 ($(M^+-HCl)_2+1$, 75% of base), 550 ($(M^+-HCl)_3+1$, 20% of base), 733 ($(M^+-HCl)_4+1$, 7% of base) and 916 ($(M^+-HCl)_5+1$, 4% of base), suggesting that this guanidinium carboxylate self-associates in the gas phase. Esterification of **2** with the ptilomycalin A sidechain and biological evaluation of the derived ptilomycalin A analog will be reported in due course.[23]

Scheme 2



11 **12** **2**

(a) HCl, CH_2Cl_2, 24 h, 5°C (b) *n*-Bu_4NF, DMF (c) HCl, H_2O

REFERENCES AND NOTES

1. This paper is dedicated to Dr. Arnold Brossi on the occasion of his 70th birthday.
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5. Taken in part from the Ph. D. Thesis of Anne-Laure Grillot, The Ohio State University (1993).
6. For a review see E. Kuehle in "Houben-Weyl: Methoden der Organischen Chemie", ed. H. Hegeman, Thieme Verlag, Stuttgart, 1983, Vol. E4, pp. 608-624.
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11. For a related reaction see I. T. Barnish, M. Corless, P. J. Dunn, D. Ellis, P. W. Finn, J. D. Hardstone, and K. James, *Tetrahedron Lett.*, 1993, **34**, 1323.
12. The *O*-(*tert*-butyldimethylsilyl)-3-aminopropanol (bp 64-66°C at 3.5 torr) was prepared in 92% yield by treating 3-aminopropanol with 2.1 equivalents of *tert*-butyldimethylsilyl chloride and DBU in benzene at reflux (1.5 h), followed by hydrolysis of the resulting crude *N,O*-bis(*tert*-butyldimethylsilyl)-3-aminopropanol at 0°C using acidic Dowex-50 in methanol.
13. Treatment of the ethyl ester corresponding to **4** with the same lithium amide gave a mixture of 1,4-addition and 1,2-addition products. 1,2-Addition was not a problem with the more hindered *tert*-butyl ester.
14. Y. Nagao, K. Kawabata, K. Seno, and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2470.
15. E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1970, **92**, 336.
16. O. Mitsunobu, *Synthesis*, 1981, 1.
17. J. A. Campbell and D. J. Hart, *J. Org. Chem.*, 1993, **58**, 2900.

18. The benzyl [[2-(trimethylsilyl)ethyl]sulfonyl]carbamate was prepared from [2-(trimethylsilyl)ethyl]sulfonamide[19] and benzyl chloroformate by a procedure used to prepare related reagents.[17]

19. S. M. Weinreb, D. M. Demko, T. A. Lessen, and J. P. Demers, *Tetrahedron Lett.* 1986, **27**, 2099.

20. Data for compound(**11**): ^{1}H Nmr ($CDCl_3$, 500 MHz) δ 0.01 (s, 9H, $Si(CH_3)_3$), 0.89-0.96 (m, 2H, CH_2Si), 1.42 (s, 9H, $C(CH_3)_3$), 1.94-2.04 (m, 2H, CH_2), 2.70-2.75 (m, 1H, CHCO), 3.11-3.25 (m, 3H, CH_2SO_2 and CH_2N), 3.33 (dd, J = 11.5, 8.7 Hz, 1H, CH_2N), 3.45 (dd, J = 14.7, 8.6 Hz, 1H, CH_2N), 3.53-3.68 (m, 4H, CH_2N), 3.72-3.77 (m, 1H, CH_2N); ^{13}C nmr ($CDCl_3$, 62.9 MHz) δ -2.0 (q), 10.2 (t), 23.9 (t), 28.0 (q), 38.7 (d), 43.4 (t), 46.1 (t), 48.5 (t), 49.0 (t), 51.7 (t), 80.9 (s), 145.5 (s), 171.4 (s); mass spectrum (FAB) *m/z* (relative intensity) molecular formula $C_{17}H_{33}N_3O_4S_2Si$: 404.25 (M^++1, 100).

21. Data for compound(**12**): ^{1}H Nmr (D_2O, 300 MHz) δ 0.00 (s, 9H, $Si(CH_3)_3$), 0.92-0.98 (m, 2H, CH_2Si), 2.08 (m, 2H, CH_2), 3.20 (m, 1H, CHCO), 3.44-3.59 (m, 4H, CH_2N and CH_2SO_2), 3.62 (dd, J = 8.1, 5.1 Hz, 2H, CH_2N), 3.70 (d, J = 5.0 Hz), 2H, CH_2N); ^{13}C nmr (D_2O, 62.9 MHz) δ -1.6 (q), 10.7 (t), 22.4 (t), 37.1 (d), 42.2 (t), 46.4 (t), 50.3 (t), 50.7 (t), 52.1 (t), 151.2 (s), 175.5 (s); mass spectrum (FAB) *m/z* (relative intensity) molecular formula $C_{13}H_{26}N_3O_4ClSSi$: 348.2 (M^+-HCl, 100). Anal. Calcd for $C_{13}H_{26}N_3O_4ClSSi$: C, 40.66; H, 6.83. Found C, 40.75; H, 6.78.

22. Data for compound(**2**): ^{1}H Nmr (D_2O, 300 MHz) δ 1.89 (quintet, J = 5.9 Hz, 2H, CH_2), 3.12 (quintet, J = 5.1 Hz, 1H, CHCO), 3.17 (dt, J = 5.8, 1.4 Hz, 2H, CH_2N), 3.24-2.32 (m, 2H, CH_2N), 3.43 (d, J = 4.0 Hz, 2H, CH_2N), 3.49 (m, 2H, CH_2N); ^{13}C nmr (D_2O, 75.5 MHz) δ 20.2 (t), 36.4 (d), 38.0 (t), 39.4 (t), 46.9 (t), 47.4 (t), 150.8 (s), 174.6 (s); mass spectrum (FAB) *m/z* (relative intensity) molecular formula $C_8H_{14}N_3O_2Cl$: 916 ($(M^+\text{-HCl})_5$+1, 4), 734 ($(M^+\text{-HCl})_4$+1, 7), 550 ($(M^+\text{-HCl})_3$+1, 20), 367 ($(M^+\text{-HCl})_2$+1, 75), 184 ($(M^+\text{-HCl})$+1, 100).

23. We thank the National Institutes of Health for financial support.

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