Pergamon

Tetrahedron Letters, Vol. 37, No. 6, pp. 905-908, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02258-9

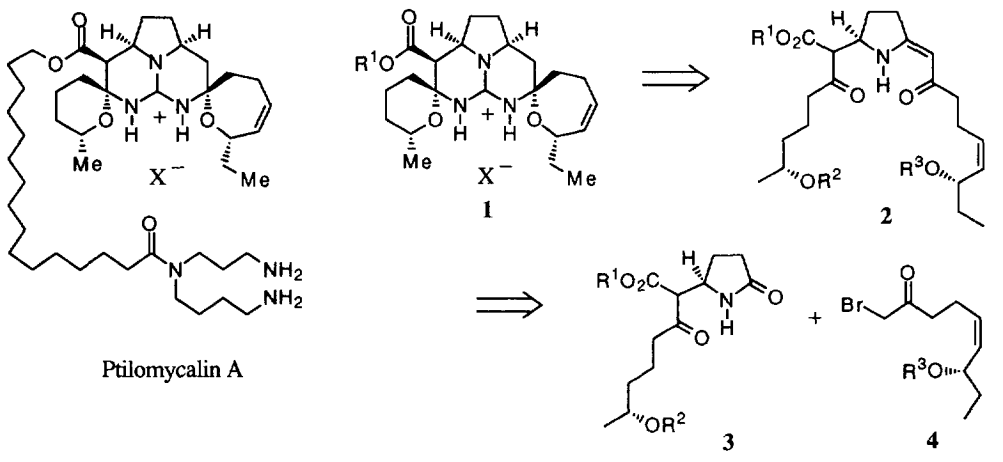
Studies towards the Synthesis of Guanidine Alkaloids; Synthesis of a Tricyclic Guanidine from Succinimide

Saskia Louwrier, Martin Ostendorf, Antonin Tuynman and Henk Hiemstra*

Amsterdam Institute of Molecular Studies, Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Abstract: The synthesis of a tricyclic guanidine as a model compound for ptilomycalin A and related guanidine alkaloids is described. The synthesis starts from succinimide and features an *N*-acyliminium ion coupling, an Eschenmoser sulfide-contraction and an *N*-guanylation as the key steps.

Recently, several novel guanidine alkaloids were isolated from different species of warm water sponges. The complex guanidine alkaloid ptilomycalin A[1] was first reported in 1989 after its isolation from the Caribbean sponge *Ptilocaulus spiculifer* and from a Rea Sea sponge of *Hemimycale* sp. With the subsequent discovery of several closely related alkaloids, viz. the crambescidins[2], celeromycalin[3] and fromiamycalin[3], ptilomycalin A has become a member of a remarkable family of pentacyclic guanidine alkaloids. In addition, several guanidine alkaloids containing bicyclic and tricyclic guanidine units, viz. the crambescins A-C[4] and the batzelladines A-E[5] have been isolated. Substantial cytotoxic, antiviral and antifungal activities have been reported for ptilomycalin A[1], and several of the other related guanidines[2-5]. A number of different approaches have been reported for the construction of the pentacyclic guanidine moiety of ptilomycalin A[6], including the first total synthesis by Overman et al[6a].

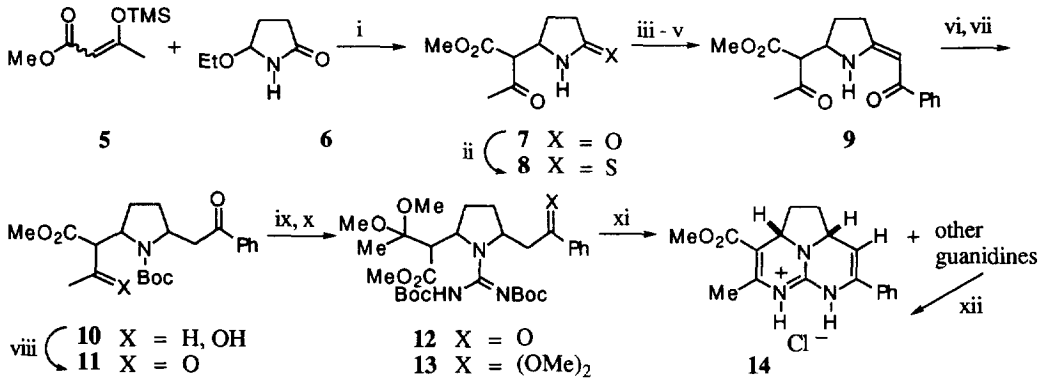


Scheme 1. Retrosynthetic Analysis.

As part of our research towards the total synthesis of ptilomycalin A, the synthesis of a tricyclic guanidine as a model compound was investigated. The retrosynthetic analysis of the pentacyclic core of ptilomycalin A (**1**)

is outlined in Scheme 1. The vinylogous amide **2** was deemed to be a plausible precursor of the pentacyclic guanidine **1**. It was envisaged to arise from the lactam **3** and the α-bromoketone **4** via an Eschenmoser coupling reaction[7]. Studies on the synthesis of enantiopure **3** are described elsewhere[8]. A recent communication by Rama Rao et al.[9] prompts us to report herein our synthesis of a tricyclic guanidine from succinimide, with an *N*-acyliminium ion coupling reaction and an Eschenmoser coupling as the key steps.

The *N*-acyliminium ion reaction of commercially available methyl 3-trimethylsiloxy-2-butenoate (**5**) with ethoxylactam **6**[10a] in the presence of TMSOTf (Scheme 2)[10b] gave **7** in 63% yield as a 1:1 mixture of two isomers,[11] both keto tautomers. Treatment of **7** with 0.55 equiv of Lawesson's reagent[12] at 85 °C for 10 min afforded the desired thiolactam **8** in high yield as the sole product, without affecting the β-ketoester. Reaction of thiolactam **8** with 2-bromoacetophenone in diethyl ether[13], followed by treatment with triethylamine in dichloromethane and triphenylphosphine in chloroform at 60 °C produced the desired vinylogous amide **9** in 68% yield as a single geometric isomer about the double bond[14], probably the *Z*-isomer[7].



Scheme 2. *Reagents and conditions*: (i) **5** (1.5 equiv), TMSOTf (1.1 equiv), CH_2Cl_2, -78 °C 1 h, rt, 18 h, 63%. (ii) Lawesson's reagent (0.55 equiv), toluene, 80 °C, 10 min, 91%. (iii) 2-bromoacetophenone (1.2 equiv), Et_2O, rt, 18 h. (iv) Et_3N (2.05 equiv), CH_2Cl_2, rt, 2 h, 83% (from **8**). (v) PPh_3 (4 equiv), $CHCl_3$, 60 °C, 18 h, 82%. (vi) $NaBH_3CN$ (1.1 equiv), 3:1 AcOH/THF, 0 °C, 40 min, 99%. (vii) Boc_2O (1.1 equiv), DIPEA (1.1 equiv), THF, rt, 18 h, 91%. (viii) PCC (2.0 equiv), molecular sieves 4 Å, CH_2Cl_2, rt, 3 h, 91%. (ix) $CH(OMe)_3$ (excess), H_2SO_4 (cat), MeOH, 50 °C, 5 h. (x) bis-Boc-thiourea (1.05 equiv), $HgCl_2$(1.05 equiv), Et_3N (3.5 equiv), DMF, 0 °C 30 min, rt, 18 h. (xi) HCl, MeOH, rt, 3 h, 33% (from **11**). (xii) NH_3, NH_4OAc, MeOH, 60 °C, 3 days, 20% (from **11**).

Several methods have been reported for the reduction of the CC double bond of a vinylogous amide, viz. catalytic hydrogenation with various metal catalysts[7,15,16] and reduction with borohydride reagents[15-17]. In the projected synthesis of ptilomycalin A, the CC double bond of a vinylogous amide has to be chemoselectively reduced (Scheme 1) without affecting the isolated *Z*-alkene. Therefore, the reduction of **9** with sodium cyanoborohydride was investigated. As attempted reduction in methanolic HCl at pH 4 produced only starting material, the reaction was performed in a 3:1 mixture of acetic acid[17a] and THF to give the amino alcohol **10** as a mixture of isomers in 99% yield. Apparently, under these conditions not only the CC double bond was reduced, but also the ketone of the β-ketoester[18]. The reduction of the ketone probably proceeds via the enol tautomer, as sodium cyanoborohydride in acetic acid has been reported to reduce enol acetates[17a]. Protection of amino alcohol **10** with Boc_2O in THF in the presence of diisopropylethylamine afforded the corresponding carbamate in 91% yield. Subsequent oxidation of the β-hydroxyester was accomplished by reaction with PCC in the presence of molecular sieves to give the desired β-ketoester **11** in 91% yield as a mixture of four diastereomers.

In order to successfully convert **11** into a guanidine derivative it appeared necessary to protect the ketone of the β-ketoester. Thus, treatment of the *N*-Boc-protected pyrrolidine **11** with trimethyl orthoformate in methanol in the presence of a catalytic amount of sulfuric acid at 50 °C afforded a mixture of mono- and diacetals. This mixture was immediately subjected to guanylation by using bis-Boc-thiourea and mercury(II) chloride[19] to

produce the protected guanidines **12** and **13** in ca. 75% overall yield from **11**. Treatment of this mixture with HCl in methanol effected double cyclisation and dehydration to a mixture of free guanidine HCl salts. The tricyclic guanidine **14**[20] was easily separated from other guanidines by flash chromatography and was obtained in 33% overall yield from pyrrolidine **11**. A more polar fraction, presumably containing 2,5-trans-disubstituted pyrrolidine derivatives, was also transformed into the tricyclic guanidine upon reaction with ammonia and ammonium acetate in methanol at 60 °C[6b] to give an additional 20% yield of **14** (from **11**).

The stereochemistry of the tricyclic guanidine **14** was established by NOE experiments. The observed NOE-effects are shown in Figure 1, with clear NOE-effects for H-2a and H-8a indicating a cis orientation. The ^{13}C NMR chemical shifts of several C-atoms in **14** compare well with those reported for batzelladines B and E[5]. This tricyclic guanidine resembles the tricyclic skeleton found in the batzelladines[5], and can be considered as a model system for the synthesis of the pentacyclic core of ptilomycalin A.

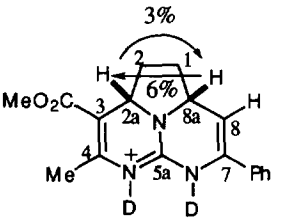


Figure 1. NOE effects for **14**

In conclusion, a successful synthesis of a tricyclic guanidine has been achieved starting from succinimide. In this approach, the requisite C-5 substituted lactam was prepared via an *N*-acyliminium ion coupling reaction with a silyl enol ether. An Eschenmoser coupling reaction with 2-bromoacetophenone was applied to prepare a 2,5-disubstituted pyrrolidine from a C-5 substituted lactam. An efficient direct guanylation with *N*,*N*'-bis-(*tert*-butoxycarbonyl)thiourea in the presence of $HgCl_2$ allowed the construction of the tricyclic guanidine **14**.

Acknowledgement

We wish to thank Professor W. N. Speckamp for stimulating discussions.

References and Notes

1. (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.
2. (a) Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 5712. (b) Berlinck, R. G. S.; Breakman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Ferri, S.; Spampinato, S.; Speroni, E. *J. Nat. Prod.* **1993**, *56*, 1007. (c) Jares-Erijman, E. A.; Ingrum, A. L.; Carney, J. R.; Rinehart, K. L.; Sakai, R. *J. Org. Chem.* **1993**, *58*, 4805.
3. Palagiano, E.; De Marino, S.; Minale, L.; Riccio, R.; Zollo, F.; Iorizzi, M.; Carré, J. B.; Debitus, C.; Lucarain, L.; Provost, J. *Tetrahedron* **1995**, *51*, 3675.
4. (a) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Hallenga, K.; Ottinger, R.; Bruno, I.; Riccio, R. *Tetrahedron Lett.* **1990**, *31*, 6531. (b) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Rogeau, D.; Amade, P. *J. Nat. Prod.* **1993**, *56*, 528. (c) Jares-Erijman, E. A.; Ingrum, A. A.; Sun, F.; Rinehart, K. L. *J. Nat. Prod.* **1993**, *56*, 2186.
5. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182.
6. (a) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2657. (b) Snider, B. B.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 549. (c) Murphy, P. J.; Williams, H. L.; Hursthouse, M. B.; Malik, K. M. A. *J. Chem. Soc. Chem. Commun.* **1994**, 119. (d) Murphy, P. J.; Williams, H. L. *J. Chem. Soc., Chem. Commun.* **1994**, 819. (e) Grillot, A. L.; Hart, D. J. *Heterocycles* **1994**, *39*, 435.
7. (a) Shiosaki, K.; in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 2, Chapter 3.7 (pp 865). (b) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.

8. Louwrier, S.; Ostendorf, M.; Boom, A.; Hiemstra, H.; Speckamp, W. N.; manuscript submitted for publication.
9. Rama Rao, A. V.; Gurjar, M. K.; Vasudevan, J. *J. Chem. Soc., Chem. Commun.* **1995**, 1369.
10. (a) Readily prepared from succinimide, see Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437. (b) For a review see: Hiemstra, H.; Speckamp, W. N. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds; Pergamon Press: Oxford, 1991; vol. 2, pp. 1047-1082 and references cited therein.
11. Spectral data for **7**: IR ($CHCl_3$) 3430, 2990, 2950, 1735, 1700, 1245. ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereomers) 1.73-1.83 (m, 1H), 2.25-2.38 (m, 6H, including CH_3O), 3.57 (d, J = 9.5 Hz, 0.5H, $CH(CO)_2$), 3.62 (d, J = 8.6 Hz, 0.5H, $CH(CO)_2$), 3.76 (s) and 3.77 (s, 3H, CH_3O), 4.40-4.27 (m, 1H, H-2), 6.43 (br s, 1H, NH). ^{13}C NMR (100 MHz, mixture of diastereomers) 24.58, 24.85, 29.07 and 29.22 (C-3 and C-4), 29.54 and 30.69 (CH_3), 52.49, 52.60, 52.84, 52.95, 64.13 and 65.14 (CH_3O, C-2 and $CH(CO)_2$), 167.44, 168.07, 178.10 and 178.24 (2× C=O), 201.04 and 201.65 (C=O ketone). MS (EI) 140 (100), 124 (12), 98 (27), 84 (100). HRMS (M-CO_2Me) calculated for $C_7H_{11}NO_2$ 140.0712, found 140.0709.
12. Yde, B.; Yousif, N. M.; Pedersen, U.; Thomsen, I.; Lawesson, S. O. *Tetrahedron* **1984**, *40*, 2047.
13. Ghirlando, R.; Howard, A. S.; Katz, R. B.; Michael, J. P. *Tetrahedron* **1984**, *40*, 2879.
14. Spectral data for **9**: IR ($CHCl_3$) 3400, 3020, 2990, 2950, 2840, 1740, 1715, 1610, 1575, 1520, 1255. ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereomers) 1.60-1.69 (m, 0.5H, H-3), 1.69-1.78 (m, 0.5H, H-3), 2.15-2.23 (m, 1H, H-3), 2.25 (s, 1.5H) and 2.27 (s, 1.5H, CH_3), 2.69-2.75 (m, 2H, H-4), 3.58 (d, J = 9.1Hz, 0.5H) and 3.61 (d, J = 9.2 Hz, 0.5H, $CH(CO)_2$), 3.74 (s, 1.5H) and 3.79 (s, 1.5H, CH_3O), 4.45-4.51 (m, 1H, H-2), 5.76 (s, 1H, C=CH), 7.34-7.41 (m, 3H, Ar-H), 7.83-7.85 (m, 2H, Ar-H), 10.23 (br s, 0.5H) and 10.31 (br s, 0.5H, NH). ^{13}C NMR (100 MHz, mixture of diastereomers) 25.34 and 25.74 (CH_2), 29.75 and 30.59 (CH_3CO), 31.60 and 31.77 (CH_2), 52.78 and 52.99 (CH_3O), 58.30, 58.38, 64.22 and 64.67 (C-2 and $CH(CO)_2$), 87.06 and 87.12 (C=CH), 127.04, 128.13 and 130.64 (Ar-CH), 139.92 and 140.01 (Ar-C), 167.43, 167.49, 167.64 and 167.91 (C-5 and C=O ester), 188.29 and 188.36 (C=CC=O), 200.80 and 200.89 (C=O ketone). HRMS calculated for $C_{17}H_{19}NO_4$ 301.1314, found 301.1303.
15. Fujimoto, R.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 4197.
16. Hart, D. J.; Tsai, Y. M. *J. Org. Chem.* **1982**, *47*, 4403.
17. (a) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proc. Int.* **1985**, *17*, 317. (b) Hart, D. J.; Leroy, V. *Tetrahedron* **1995**, *51*, 5757. (c) Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328.
18. The reduction of a β-ketoester during the reduction of a related vinylogous amide has been reported previously: Bachi, M. D.; Breiman, R.; Meshulam, H. *J. Org. Chem.* **1983**, *48*, 1439.
19. Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677.
20. Spectral data for **14**: IR ($CHCl_3$) 3690, 3434, 3023, 3019, 3015, 2997, 2952, 2929, 2857, 1681, 1601, 1503, 1435. ^1H NMR (400 MHz, $CDCl_3$, assignment with C-H correlation and NOE) 1.49-1.60 (m, 1H) and 1.63-1.72 (m, 1H, H-1- and H-2 -trans), 2.07-2.15 (m, 1H, H-1-cis), 2.18 (s, 3H, CH_3), 2.27-2.37 (m, 1H, H-2-cis), 3.70 (s, 3H, CH_3O), 4.04 (ddd, J = 4.1, 7.3, 9.1 Hz, 1H, H-8a), 4.12 (dd, J = 7.0, 9.2 Hz, 1H, H-2a), 5.33 (d, J = 4.1 Hz, 1H, H-8), 7.29-7.37 (m, 3H, Ar-H), 7.53-7.55 (m, 2H, Ar-H). (NH not observed). ^{13}C NMR (100 MHz, $CDCl_3$, assignment with C-H correlation) 19.86 (CH_3), 33.31 and 33.59 (C-1 and C-2), 50.79 (CH_3O), 56.93 (C-2a), 57.12 (C-8a), 99.51 (C-3), 99.67 (C-8), 125.20, 128.38 and 128.44 (Ar-CH), 136.50 (Ar-C), 138.53 (C-7), 147.74 (C-4), 150.38 (C-5a), 166.96 (C=O).

(*Received in UK* 13 *November* 1995; *accepted* 24 *November* 1995)