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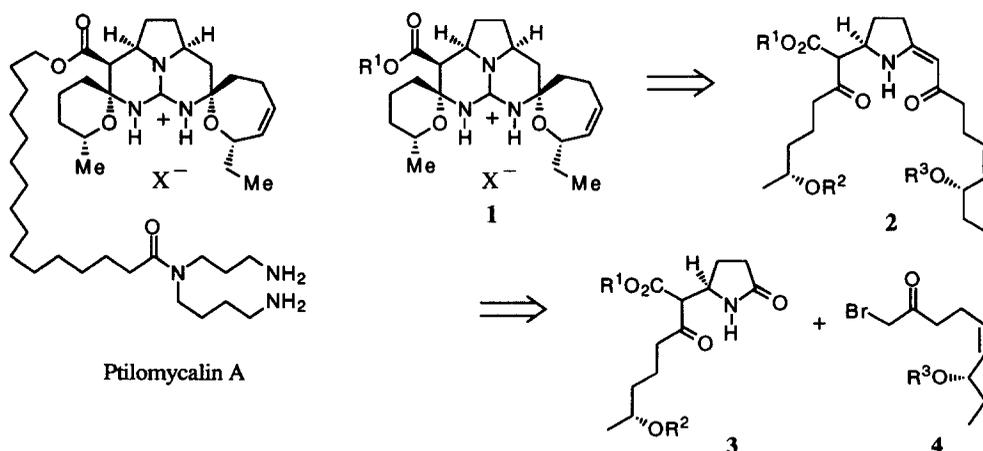
## Studies towards the Synthesis of Guanidine Alkaloids; Synthesis of a Tricyclic Guanidine from Succinimide

Saskia Louwrier, Martin Ostendorf, Antonin Tuijnman 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<sup>1</sup> was first reported in 1989 after its isolation from the Caribbean sponge *Ptilocaulus spiculifer* and from a Red Sea sponge of *Hemimycale* sp. With the subsequent discovery of several closely related alkaloids, viz. the crambescidins<sup>2</sup>, celeromycalin<sup>3</sup> and fromiamycalin<sup>3</sup>, 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<sup>4</sup> and the batzelladines A-E<sup>5</sup> have been isolated. Substantial cytotoxic, antiviral and antifungal activities have been reported for ptilomycalin A<sup>1</sup>, and several of the other related guanidines<sup>2-5</sup>. A number of different approaches have been reported for the construction of the pentacyclic guanidine moiety of ptilomycalin A<sup>6</sup>, including the first total synthesis by Overman et al<sup>6a</sup>.

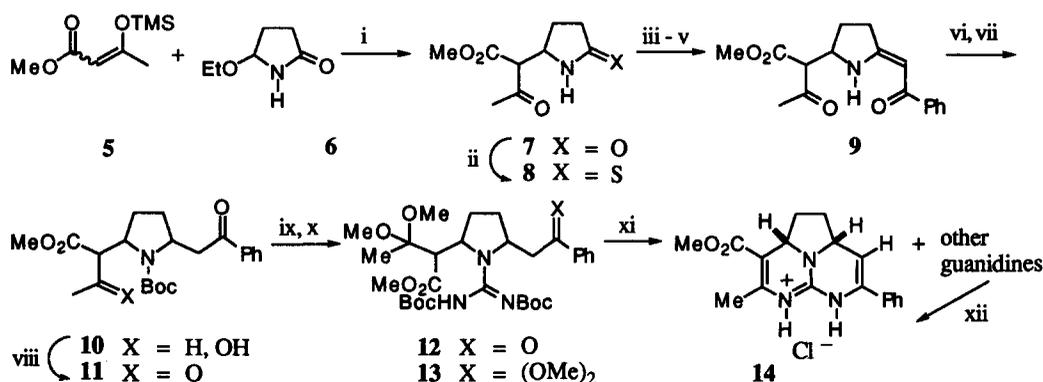


Scheme 1. Retrosynthetic Analysis.

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  $\alpha$ -bromoketone **4** via an Eschenmoser coupling reaction<sup>7</sup>. Studies on the synthesis of enantiopure **3** are described elsewhere<sup>8</sup>. A recent communication by Rama Rao et al.<sup>9</sup> 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-trimethylsilyloxy-2-butenate (**5**) with ethoxylactam **6**<sup>10a</sup> in the presence of TMSOTf (Scheme 2)<sup>10b</sup> gave **7** in 63% yield as a 1:1 mixture of two isomers,<sup>11</sup> both keto tautomers. Treatment of **7** with 0.55 equiv of Lawesson's reagent<sup>12</sup> at 85 °C for 10 min afforded the desired thiolactam **8** in high yield as the sole product, without affecting the  $\beta$ -ketoester. Reaction of thiolactam **8** with 2-bromoacetophenone in diethyl ether<sup>13</sup>, 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<sup>14</sup>, probably the *Z*-isomer<sup>7</sup>.



**Scheme 2. Reagents and conditions:** (i) **5** (1.5 equiv), TMSOTf (1.1 equiv),  $\text{CH}_2\text{Cl}_2$ , -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),  $\text{Et}_2\text{O}$ , rt, 18 h. (iv)  $\text{Et}_3\text{N}$  (2.05 equiv),  $\text{CH}_2\text{Cl}_2$ , rt, 2 h, 83% (from **8**). (v)  $\text{PPh}_3$  (4 equiv),  $\text{CHCl}_3$ , 60 °C, 18 h, 82%. (vi)  $\text{NaBH}_3\text{CN}$  (1.1 equiv), 3:1  $\text{AcOH}/\text{THF}$ , 0 °C, 40 min, 99%. (vii)  $\text{Boc}_2\text{O}$  (1.1 equiv), DIPEA (1.1 equiv), THF, rt, 18 h, 91%. (viii) PCC (2.0 equiv), molecular sieves 4 Å,  $\text{CH}_2\text{Cl}_2$ , rt, 3 h, 91%. (ix)  $\text{CH}(\text{OMe})_3$  (excess),  $\text{H}_2\text{SO}_4$  (cat), MeOH, 50 °C, 5 h. (x) bis-Boc-thiourea (1.05 equiv),  $\text{HgCl}_2$  (1.05 equiv),  $\text{Et}_3\text{N}$  (3.5 equiv), DMF, 0 °C 30 min, rt, 18 h. (xi) HCl, MeOH, rt, 3 h, 33% (from **11**). (xii)  $\text{NH}_3$ ,  $\text{NH}_4\text{OAc}$ , 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<sup>7,15,16</sup> and reduction with borohydride reagents<sup>15-17</sup>. 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<sup>17a</sup> 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  $\beta$ -ketoester<sup>18</sup>. The reduction of the ketone probably proceeds via the enol tautomer, as sodium cyanoborohydride in acetic acid has been reported to reduce enol acetates<sup>17a</sup>. Protection of amino alcohol **10** with  $\text{Boc}_2\text{O}$  in THF in the presence of diisopropylethylamine afforded the corresponding carbamate in 91% yield. Subsequent oxidation of the  $\beta$ -hydroxyester was accomplished by reaction with PCC in the presence of molecular sieves to give the desired  $\beta$ -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  $\beta$ -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<sup>19</sup> 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**<sup>20</sup> 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<sup>6b</sup> 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 <sup>13</sup>C NMR chemical shifts of several C-atoms in **14** compare well with those reported for batzelladines B and E<sup>5</sup>. This tricyclic guanidine resembles the tricyclic skeleton found in the batzelladines<sup>5</sup>, and can be considered as a model system for the synthesis of the pentacyclic core of pilomycin A.

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<sub>2</sub> allowed the construction of the tricyclic guanidine **14**.

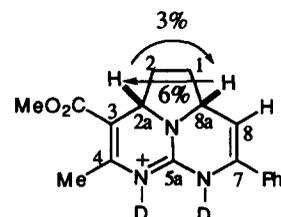


Figure 1. NOE effects for **14**

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11. Spectral data for **7**: IR (CHCl<sub>3</sub>) 3430, 2990, 2950, 1735, 1700, 1245. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 1:1 mixture of diastereomers) 1.73-1.83 (m, 1H), 2.25-2.38 (m, 6H, including CH<sub>3</sub>O), 3.57 (d, *J* = 9.5 Hz, 0.5H, CH(CO)<sub>2</sub>), 3.62 (d, *J* = 8.6 Hz, 0.5H, CH(CO)<sub>2</sub>), 3.76 (s) and 3.77 (s, 3H, CH<sub>3</sub>O), 4.40-4.27 (m, 1H, H-2), 6.43 (br s, 1H, NH). <sup>13</sup>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<sub>3</sub>), 52.49, 52.60, 52.84, 52.95, 64.13 and 65.14 (CH<sub>3</sub>O, C-2 and CH(CO)<sub>2</sub>), 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<sub>2</sub>Me) calculated for C<sub>7</sub>H<sub>11</sub>NO<sub>2</sub> 140.0712, found 140.0709.
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14. Spectral data for **9**: IR (CHCl<sub>3</sub>) 3400, 3020, 2990, 2950, 2840, 1740, 1715, 1610, 1575, 1520, 1255. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 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<sub>3</sub>), 2.69-2.75 (m, 2H, H-4), 3.58 (d, *J* = 9.1 Hz, 0.5H) and 3.61 (d, *J* = 9.2 Hz, 0.5H, CH(CO)<sub>2</sub>), 3.74 (s, 1.5H) and 3.79 (s, 1.5H, CH<sub>3</sub>O), 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). <sup>13</sup>C NMR (100 MHz, mixture of diastereomers) 25.34 and 25.74 (CH<sub>2</sub>), 29.75 and 30.59 (CH<sub>3</sub>CO), 31.60 and 31.77 (CH<sub>2</sub>), 52.78 and 52.99 (CH<sub>3</sub>O), 58.30, 58.38, 64.22 and 64.67 (C-2 and CH(CO)<sub>2</sub>), 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<sub>17</sub>H<sub>19</sub>NO<sub>4</sub> 301.1314, found 301.1303.
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19. Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677.
20. Spectral data for **14**: IR (CHCl<sub>3</sub>) 3690, 3434, 3023, 3019, 3015, 2997, 2952, 2929, 2857, 1681, 1601, 1503, 1435. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 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<sub>3</sub>), 2.27-2.37 (m, 1H, H-2-cis), 3.70 (s, 3H, CH<sub>3</sub>O), 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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, assignment with C-H correlation) 19.86 (CH<sub>3</sub>), 33.31 and 33.59 (C-1 and C-2), 50.79 (CH<sub>3</sub>O), 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).

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