Synthesis of a Pentacyclic Model of Ptilomycalin A

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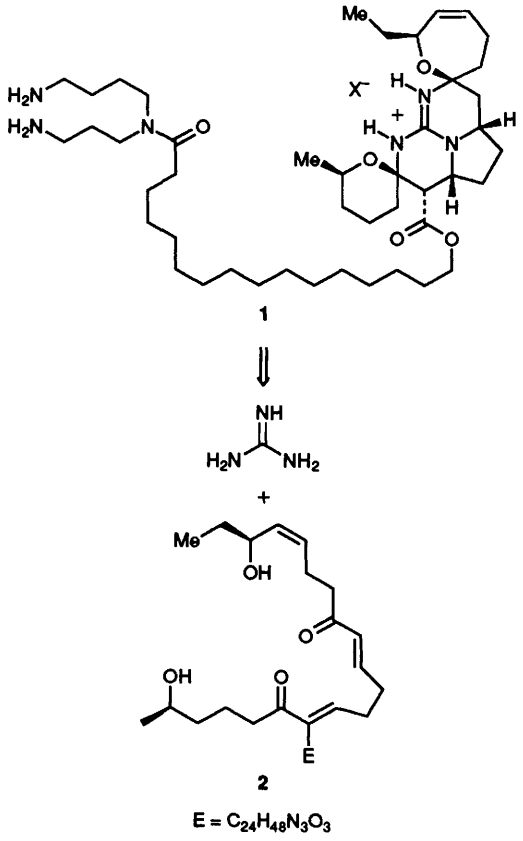
The conversion of dienes **3** and **10** into the pentacyclic guanidine compounds **6** and **11** is reported; their preparation illustrates a potentially biomimetic synthetic route to the biologically active natural product Ptilomycalin A **1**.

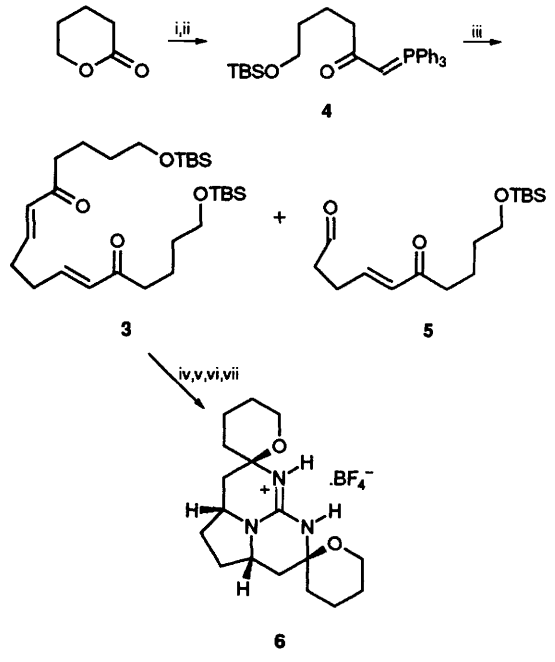
Recently Kashman and Kakisawa reported the isolation of the guanidinium containing natural product ptilomycalin A **1** from the sponge *ptilocaulis spiculifer*, which was shown to have a range of biological properties, including antifungal, antiviral and antitumour activity.[1] Subsequently a range of related structures have been isolated[2] and have stimulated synthetic interest.[3,4] As a continuation of our own preliminary work,[5] we now report the first preparation of a model system containing the pentacyclic core found in ptilomycalin A. Retrosynthetic analysis of **1** illustrates the possibility of a rapid assembly of the pentacyclic core found in ptilomycalin A *via* a double Michael addition of guanidine to a bis-α-β-unsaturated ketone **2** with subsequent double spirocyclisation (Scheme 1).

To test this hypothesis we prepared the diene **3** *via* a three-step route from δ-valerolactone. Reaction of δ-valerolactone with 2 equiv. of methylenetriphenylphosphorane followed by silyl protection of the intermediate phosphonium alkoxide gave the phosphorane **4**. Double Wittig reaction of this phosphorane with 0.4 equiv. of succinaldehyde gave the required diene **3** in 45% overall yield together with a variable yield (15–30%) of the aldehyde **5**.† On reaction of **3** with 1 equiv. of guanidine, followed by removal of solvent, deprotection and cyclisation with methanolic HCl and finally counter ion exchange, we were pleased to observe the formation of one major product **6**‡ in 25% overall yield. This product gratifyingly had the same relative stereochemistry as that found in ptilomycalin A (Scheme 2). The low yield observed for this reaction is probably due to competing base catalysed polymerization of the diene precursor, similar to that observed by Weis and Zamir in the preparation of dihydropyrimidines.[6]

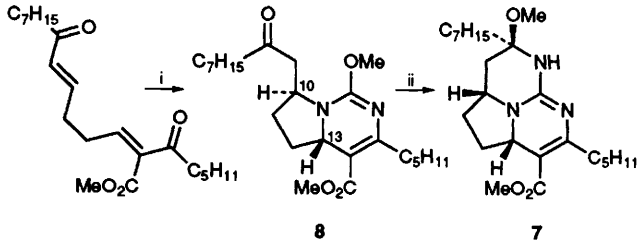
Interestingly, the overall stereoselectivity observed in this reaction contrasts with that reported by Snider and Shi[3] who utilised a two step procedure to construct a tricyclic model compound **7**. They observed the preferential formation of a *trans*-pyrrolidine intermediate **8** (3:1 with the *cis* isomer) which was then isomerised§ in an independent step to give **7** (Scheme 3). It is somewhat difficult to rationalise the difference in original stereoselectivity insomuch as the exact sequence of reactions involved in the formation of the pyrrolidine and pyrimidine rings is unknown. It is possible however that differences in geometry between the dihydropyrimidine and our supposed tetrahydropyrimidine intermediates may account for the result, or indeed that in our case the



Scheme 1



Scheme 2 *Reagents and conditions*: i, 2 equiv. CH_2=PPh_3–THF, −78 °C; ii, TBSCl–imidazole–DMF; iii, succinaldehyde–THF, 48 h, 45% overall; iv, guanidine–DMF, 3 h; v, MeOH–HCl/0 °C to room temp., 24 h; vi, saturated aq. $NaBF_4$, vii, crystallisation; 25% overall

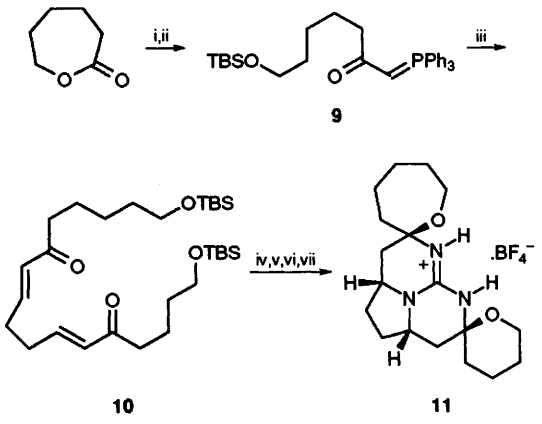


Scheme 3 *Reagents and conditions*: i, *O*-Methylisourea sulfate–$NaHCO_3$–DMF, 50 °C; ii, NH_3–NH_4OAc–MeOH, 60 °C/4 d

precursor involved in pyrrolidine ring formation may be acyclic.

With this result in hand we were interested in preparing an unsymmetrical ring system and to this end prepared the phosphorane **9** from caprolactone in an identical manner to that previously illustrated: reaction of **9** with aldehyde **5** led to the formation of the required diene **10** in 70% yield. Treatment of this under identical conditions to those previously used in the preparation of **6** led to the formation of the 7,6,5,6,6-pentacyclic model compound **11** in 20% overall isolated yield‡ (Scheme 4).

Despite the somewhat simplistic nature of our cyclisation precursors these results demonstrate the potential of this methodology for the synthesis of ptilomycalin A, or possibly of more importance, the synthesis of analogues of **1** which will enable us to investigate in detail the origins of the biological activity found in this and related systems.[2] In addition to this,



Scheme 4 *Reagents and conditions*: i, 2 equiv. CH_2=PPh_3–THF, −78 °C; ii, TBSCl–imidazole–DMF; iii, **5**–THF, 48 h; 70% overall; iv, guanidine–DMF, 3 h; v, MeOH–HCl, 0 °C to room temp., 24 h; vi, saturated aq. $NaBF_4$; vii, crystallisation; 20% overall

the observed stereoselectivity of our reactions and their facile nature may be acting as an indicator to the biosynthetic pathways which led to the formation of **1** and related molecules.[2]

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Footnotes

† It is possible to obtain higher yields of aldehyde **5** by reaction of phosphorane **4** with an excess of succinaldehyde.

‡ Compounds **6** and **11** represented >80% of the mixture of pentacyclic products obtained after chromatography (0–1% MeOH in chloroform; 30% and 37% yield respectively) and were separable by crystallisation (chloroform–diethyl ether). The structure of **6** was confirmed by X-ray crystallography.

§ Detailed information as to the nature of this isomerisation is not available in the literature but it is presumably occurring *via* a retro Michael/Michael reaction at C-10.[3] We are assuming kinetic control in the stereochemistry observed for the formation of the pyrrolidine ring in **6** and **11**.

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