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A Short Synthetic Route to the Tricyclic Guanidinium Core of The Batzelladine Alkaloids

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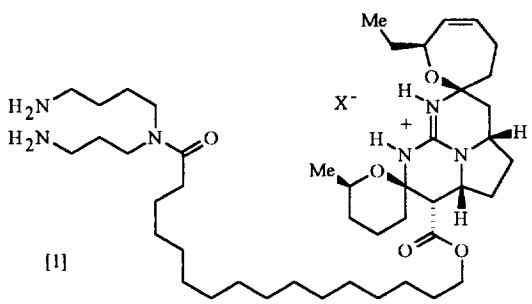
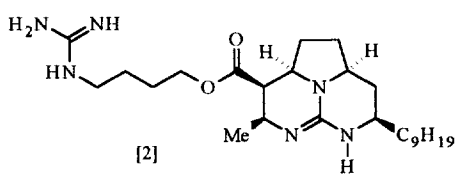
Abstract: A rapid construction of the tricyclic core **10** of the batzelladine series of natural products is reported *via* a reductive addition of guanidine to *bis*-enone **6**.

There is considerable current biological[1,2] and synthetic[3,4] interest in guanidine containing biomolecules. Much of this interest has been generated by the isolation of the novel bioactive natural product ptilomycalin A **1**, initially from the Caribbean sponge *Ptilocaulis spiculifer*[1a] but subsequently from two other sources.[1b,2] Ptilomycalin A has demonstrated high cytotoxic, antifungal and antiviral activity. Possibly of more significance is the recent isolation, from the same organism, of a series of natural products, the batzelladines, typified by batzelladine D **2**,[2] as several of these compounds have shown interesting anti-HIV activity.

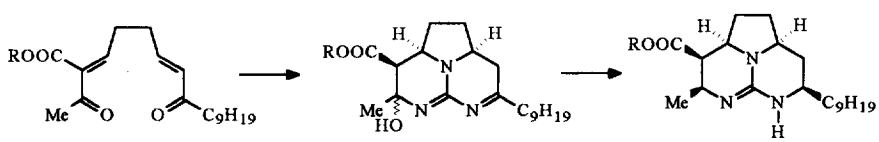


[1]



[2]

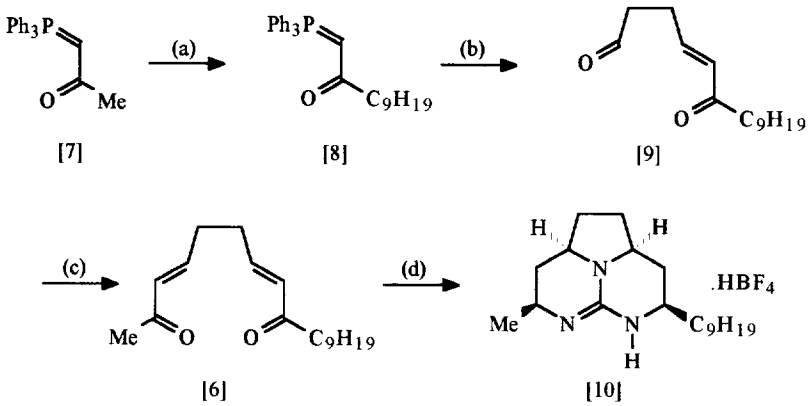
Based on our previous work,[4] we reasoned that the tricyclic core of **2** (structure **3**) could be prepared using a proposed biomimetic approach, *via* a sequential double Michael addition of guanidine to the *bis*-α,β-unsaturated ketone **4**, to give hemi-aminal **5**, which on subsequent stereoselective reduction would hopefully give **3** with a high degree of stereocontrol.



[4] [5] [3]

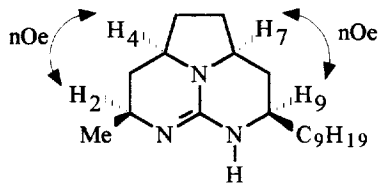
In order to test this hypothesis we prepared the ketone **6** *via* a simple, high yielding three step procedure. Deprotonation of the commercially available phosphorane **7** with *n*-butyl lithium followed by alkylation with *n*-octyl iodide[5] gave the phosphorane **8** in near quantitative yield. Without purification this was reacted further

with three equivalents of succinaldehyde[6] to give the aldehyde **9** in 71% overall yield. Reaction of **9** with a further equivalent of phosphorane **7** gave the required ketone **6** in 66% yield. Treatment of **6** with one equivalent of guanidine in DMF for 5 hours, followed by dilution with methanol/water, sodium borohydride reduction, acidification and counterion exchange gave, after purification, the required product **10** as its fluoroborate salt in 31% yield. This material was obtained as a *single diastereoisomer* with no distinct minor isomers detectable by ^{1}H or ^{13}C nmr analysis of the crude reaction products.



(a) nBuLi/-78°C; then $C_8H_{17}I$/RT/16hrs. (b) 3.0 eqv. succinaldehyde/THF/24hrs.
(c) $MeCOCHPPh_3$/DCM/24hrs. (d) (i) Guanidine/DMF/0°C-RT/5hrs, (ii) 3:1:3 DMF/H_2O/MeOH, then $NaBH_4$/16hrs, (iii) HCl, (iv) Saturated aq. $NaBF_4$.

This observation was some what surprising as in previous work we[4] had demonstrated that the double Michael addition of guanidine to bis-α,β-unsaturated ketones leads to the preferential formation of *cis*-substituted pyrrolidines with *ca* 4 : 1 selectivity and were fully expecting this work to parallel these observations. Confirmation of the relative stereochemistry of the product was obtained by selective nOe experiments which confirmed that the protons H_2 and H_4 together with H_7 and H_9 are on the same face of the tricycle.



[10] .HBF_4

Confirmation of the relative stereochemistry of the pyrrolidine ring was taken from analogy with our previous work, however we were unable to prepare suitable crystals of **10** for X-ray analysis. In order to overcome this shortfall and to confirm the generality of this methodology we prepared a series of symmetrical tricycles in the hope that these one of these substances would be suitably crystalline. Thus phosphoranes **11a-d** gave the *bis*-α,β-unsaturated ketones **12a-d** when reacted with succinaldehyde and on treatment of these under the conditions previously outlined tricyclic guanidines **13a-d** were obtained in comparable overall yield (table 1)

With the exception of **11a** (R = Me), which was isolated as a 10 : 1 mixture of diasteromers (the minor isomer being unidentified), all of these molecules were isolated as a single diastereoisomer and displayed similar spectroscopic data to **10**.[7] However despite considerable effort they still proved very difficult to crystallise to the standard required for X-ray structure determination. Somewhat fortuitously, we discovered that **13b** (R = Ph) could be isolated as a 1:1 complex with triphenylphosphine oxide and were pleased when crystals of this complex (ethyl acetate/ether) were found to be suitable for X-ray analysis.[8]

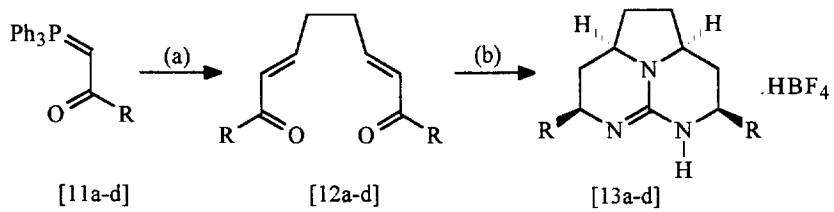


Table 1

	R =	Yield (**12a-d**)	Yield (**13a-d**)
11a	Me	74%	33%
11b	Ph	68%	32%
11c	n-pentyl	54%	27%
11d	n-nonyl	36%	22%

(a) 0.4 eqv. succinaldehyde/THF/24-48hrs. (b) (i) Guanidine/DMF/0°C-RT/5-8hrs, (ii) 3:1:3 DMF/H_2O/MeOH, then $NaBH_4$/16hrs, (iii) HCl, (iv) Saturated aq. $NaBF_4$.

Details of this structure (figure 1) illustrate a unique arrangement in which the oxygen of the phosphine oxide is linked to the guanidinium cation through two N-H....O hydrogen bonds. The dimensions of these bonds [N(1)-H(1)....O(1)/N(2)-H(2)....O(1)] are: N-H = 1.01(4)/0.91(5), H....O = 1.83(5)/1.97(5), N....O = 2.780(5)/2.817(5) Å, <N-H....O = 154(4)/154(4)°, and indicate quite strong interactions. It is to noted that in related guanidinium fluoroborates the guanidine NH groups are always hydrogen bonded to the BF_4^- anions,[4c] but in the present case the hydrogen bonding preferentially occurs through the oxygen of the triphenylphosphine oxide. In fact, triphenylphosphine oxide, initially used to modify substrate properties by complexation,[9] has been found to yield high quality crystalline complexes with a large number of organic compounds which, by themselves, form only very poor quality crystals.[10] This property of triphenylphosphine oxide as a crystallisation aid may be attributed to the ease with which it can form hydrogen bonds with suitable NH or OH donor groups. As yet we are unsure as to the generality of this interaction however we intend to investigate this observation in more detail.

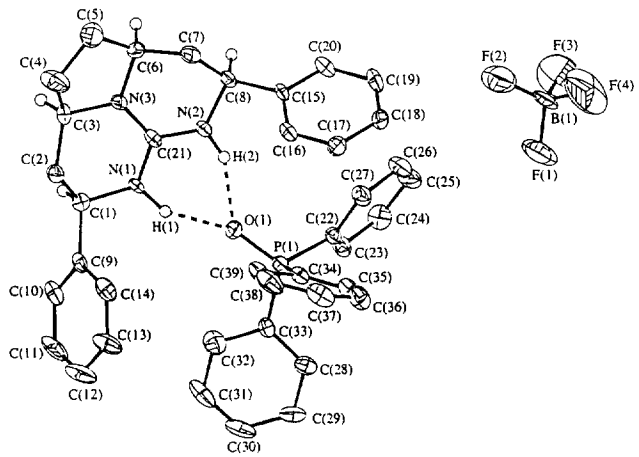


Figure 1. Structure of $[C_{21}H_{24}N_3]$. $[C_{18}H_{15}OP]$. $[BF_4]$, **13b**. Ph_3PO. HBF_4 showing the hydrogen bonds (dashed lines) between the two NH groups and the Ph_3PO oxygen. the phenyl and methylene hydrogens are omitted for clarity. The thermal ellipsoids are drawn at 50% probability level.

Of more direct relevance, we were pleased to observe that the relative stereochemistry of this compound was identical to that found in the batzelladine metabolites.

In conclusion, this methodology, which may mimic the biological pathway to these metabolites, presents a rapid entry into structurally complex molecules which are analogous to the batzelladine alkaloids, and is hopefully amenable to the total synthesis of the naturally occurring metabolites. This work and a related study of the structural requirements for their bioactivity is currently in progress.

Acknowledgements

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7 Data for **10**.HBF_4: **^{1}H nmr** (500MHz, CD_3OD): δ = 0.89 (3H, t, J = 6.6 Hz, CH_3) 1.25 (2H, m, $H_{3\alpha}$ and $H_{8\alpha}$), 1.26 (3H, d, J = 6.4 Hz, CH_3) 1.28-1.45 (14H, m, $H_{12\text{-}18}$), 1.55 (2H, m, H_{11}), 1.68 (2H, m, $H_{5\beta}$ and $H_{6\beta}$), 2.20-2.30 (4H, m, $H_{3\beta}$, $H_{5\alpha}$, $H_{6\alpha}$ and $H_{8\beta}$), 3.42 (1H, ddt, J = 3.2, 11.3, 6.6 Hz, H_9), 3.54 (1H, ddq, J = 3.2, 11.1, 6.4 Hz, H_2), 3.74 (2H, m, H_4 and H_7). **^{13}C nmr** (64MHz, $CDCl_3$) δ = 14.14, 20.26 (2 x CH_3), 22.65, 25.03, 29.23, 29.29 (4 x CH_2), 29.39, 29.48, 29.63, 30.22, 31.85, 34.45, 35.80 (12 x CH_2), 46.10, 50.47, 56.00, 56.06 (4 x CH) 149.31 (C) **IR**; ν max 3385 (N-H), 2924 (C-H), 1627 (C=N). **MS(CI)**; 306, (100%, $[M+H]^+$). **HRMS**; found 306.2909; $C_{19}H_{36}N_3$ ($[M+H]^+$) requires 306.2909.
8 *Crystal data* for $[C_{21}H_{24}N_3]$. $[C_{18}H_{15}OP]$. $[BF_4]$, **13b**.$Ph_3PO.HBF_4$. Mr = 683.51, Monoclinic, a = 22.913(5), b = 9.3242(9), c = 33.679(7) Å. β = 103.56(2)°, V = 6995(2) Å^3, space group $C2/c$, Z = 8, D_c = 1.298 g cm^{-3}, $F(000)$ = 2864, μ(Mo-K_α) = 1.36 cm^{-1}, crystal size 0.32 x 0.25 x 0.12 mm, T = 298(2) K, θ = 1.83-24.91°, $-25 \le h \le 21$, $-7 \le k \le 10$, $-36 \le l \le 36$, total data collected 10770, unique 4914 (used in refining 450 parameters). Atomic co-ordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.
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