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Biomimetic Model Studies towards Ptilomycalin A

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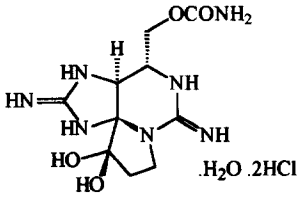
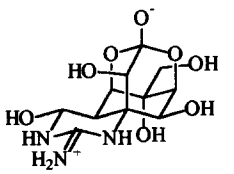
Abstract: Six model compounds, the tetracycles **14** and **15**, the tricycle **20** and the pentacycles **26**, **30** and **32** have been prepared to illustrate a biomimetic approach to the guanidine containing natural product ptilomycalin A **1**.

Introduction

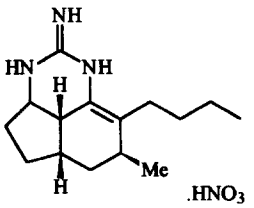
Molecules containing guanidinium sub-units are of considerable biological interest, due both to the hydrogen-bond mediated interaction of guanidinium ions with phosphate containing biomolecules[1] and because of a range of biological activities including hypotensive and adrenergic neuron blocking effects.[2] Despite the fact that compared to plant metabolites, relatively few alkaloids have been isolated from marine sources,[3] several guanidine containing natural products have been found in a variety of marine organisms.[4] Of these substances saxitoxin **1**,[5] the paralytic agent of the Alaska butter clam *Saxidomas giganteus*, is one of the most toxic of the non-protein poisons known and it has also found widespread use in the study of various nerve disorders.[6] Certain varieties of puffer fish, especially the tiger puffer (*tora fugu*) and the closely related common puffer (*ma fugu*) produce the highly toxic guanidine containing metabolite tetrodotoxin **2**, which was isolated as early as 1950,[7] the structure being partially assigned by Woodward in 1964.[8] In addition, the isolation of ptilocaulin **3** and isoptilocaulin **4** from the orange Caribbean sponge *Ptilocaulis aff. P. spiculifer* (Lamarck 1814) was reported by Rinehart and co-workers in 1981.[9] These two novel guanidine containing natural products again display anti-microbial activity against gram-positive and gram-negative bacteria, yeast's and filamentous fungi, and significant cytotoxicity towards L1210 leukemia cells.



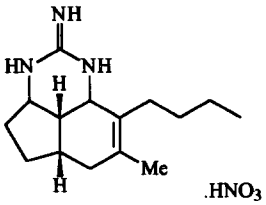
[1]



[2]



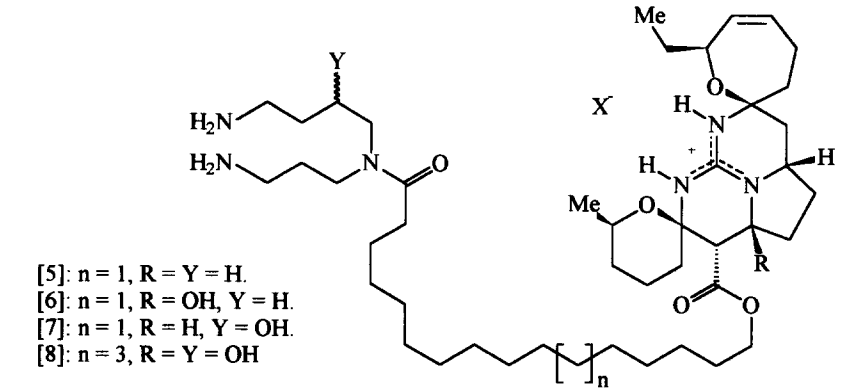
[3]

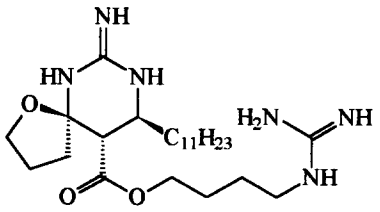


[4]

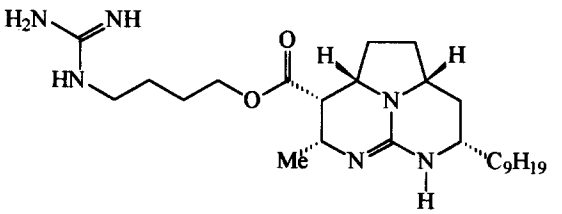
More recently, in the course of screening for novel bioactive agents from marine sponges, Kashman and Kakisawa reported[10] the isolation of an antitumor, antiviral, and antifungal compound designated ptilomycalin A **5** from the Caribbean sponge *Ptilocaulis spiculifer*. The same compound was also isolated from a Red Sea sponge of *Hemimycale sp.*[11] Ptilomycalin A possesses an intriguing structure consisting of a pentacyclic guanidine moiety linked by a long-chain ω-hydroxy acid to a spermidine unit; it also shows cytotoxicity against P388 (IC_{50} 0.1 mg/mL), L1210 (IC_{50} 0.4 mg/mL), and KB (IC_{50} 1.3 mg/mL) in addition to antifungal activity against *Candida albicans* (MIC 0.8 mg/mL) as well as very good antiviral activity (HSV) at a concentration of 0.2 mg/mL.

Ptilomycalin A can also be considered to be the parent member of a group of alkaloids which present considerable challenges both in synthetic and medicinal chemistry. Of these metabolites, the potent cytotoxic and antiviral agents, the crambescidins **6-8**, isolated from the red encrusting sponge *Crambe crambe*[12] are closest in structure to ptilomycalin A, with the simpler structures the crambines (for example crambine B **9**) also being of interest.[13] The isolation of a range of natural products typified by batzelladine D **10**[14] possessing anti-HIV activity, is also of considerable importance.



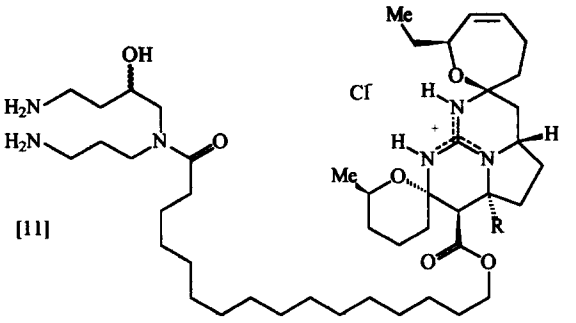


[9]



[10]

There has been some speculation[11, 15] as to the exact biological role of ptilomycalin A which has centred on its similarities to abiotic guanidine based anionic receptor molecules;[16] its involvement in an oxoanionic binding process, possibly the selective binding of nucleotides[17] or other phosphate containing biomolecules has been suggested.[15a] This premise is further supported by analysis of ptilomycalin A **5** and the crambescidins **6-8** which illustrates the presence of an enclosed ionic "pocket" at the central guanidine sub-unit of these molecules; this pocket may be acting as a recognition site and conferring much of the biological activity found in these compounds (Fig. 1). In relation to this, it is interesting to note that the subsequently isolated 13,14,15-isocrambescidine 800 **11** is substantially less cytotoxic to L1210 cells than other crambescidins and has no observed antiviral activity against HSV-1;[18] this drop in activity may be due to the lack of this structural feature (Fig. 2). Molecular recognition by abiotic synthetic receptors is an important goal in current bio-organic chemistry[19] and this observation could be of considerable importance.



[11]

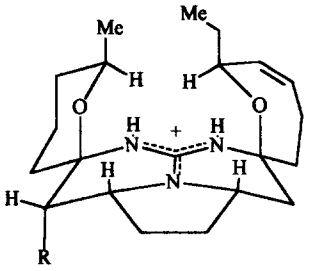


Fig. 1

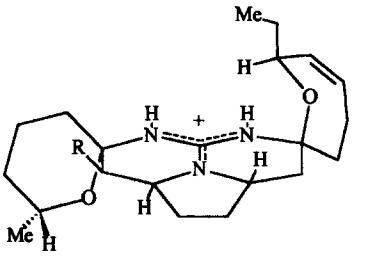
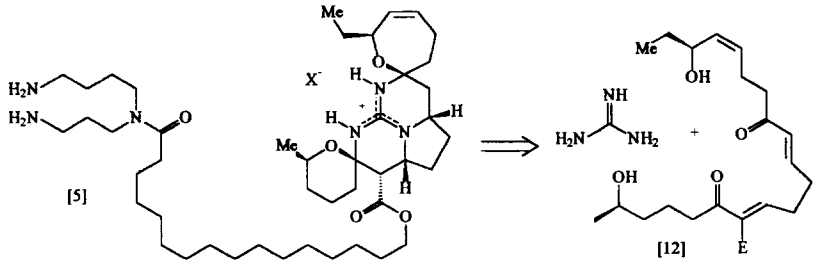


Fig. 2

With the above considerations in mind it is not surprising that there is considerable synthetic activity[20] towards ptilomycalin A and its structural relatives and we take this opportunity to report our preliminary findings in full.[21]

Synthetic Approach.

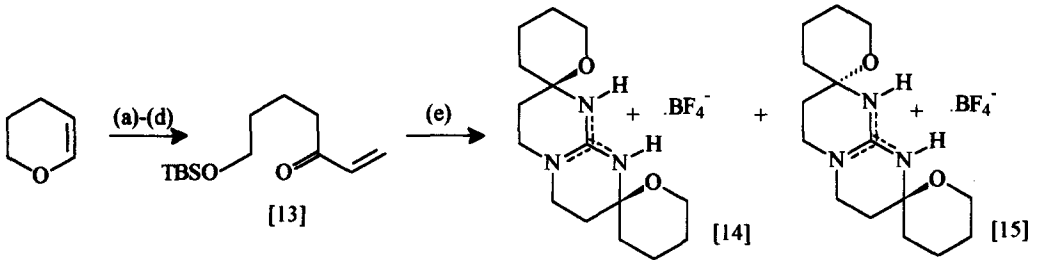
Retrosynthetic analysis of the central polycyclic unit of ptilomycalin A illustrates the possibility of a rapid and potentially, biomimetic construction of our target *via* a double Michael addition of guanidine to a *bis*-α,β-unsaturated ketone **12** (E = $C_{24}H_{48}N_3O_3$) to generate the central pyrrolidine ring; subsequent *bis*-spirocyclisation will then lead to the required pentacycle.



[5] [12]

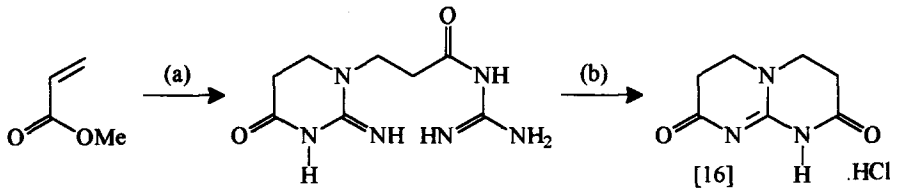
To test this hypothesis, we wished to access a simple model compound and thus prepared the vinyl ketone **13** *via* a four step route from 2,3-dihydropyran (hydrolysis, vinyl magnesium bromide, selective silylation and oxidation) in an overall yield of 40%. Reaction of **13** with half an equivalent of guanidine in DMF for four hours followed by removal of solvent, deprotection/cyclisation with methanolic HCl and counter ion exchange, led to the formation, in 80% yield, of a 1:1 mixture of the desired *syn*-spirocyclic model

compound **14** and the corresponding *anti*-isomer **15**. The *syn*-product, **14**, was separated from the mixture by crystallisation and the structure of both **14** and **15** were confirmed by X-ray crystallography.



(a) 0.1 M HCl, 5 min; 75%, (b) CH_2=CHMgBr, THF; 70%, (c) TBDMSCl, Imidazole, DMF; 98%, (d) PCC, CH_2Cl_2, Celite; 78%, (e) (i) Guanidine, DMF, (ii) MeOH, HCl, 0 °C, (iii) Saturated aq. $NaBF_4$; 80% overall, **14** : **15**, 1 : 1.

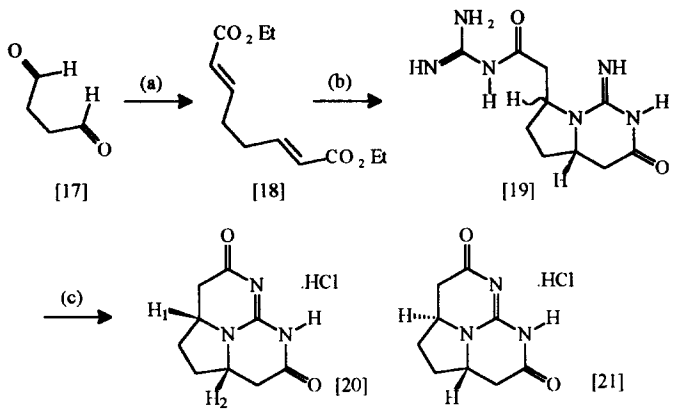
With this success we then investigated the stereochemistry of the pyrrolidine ring formation and were interested by the observation[22] that free guanidine undergoes a double Michael addition and subsequent cyclisation with methyl acrylate to give the pyrimido[1,2-a]pyrimidinedione **16** in excellent overall yield.



(a) Guanidine, DMF; 92%, (b) c.HCl; 82%.

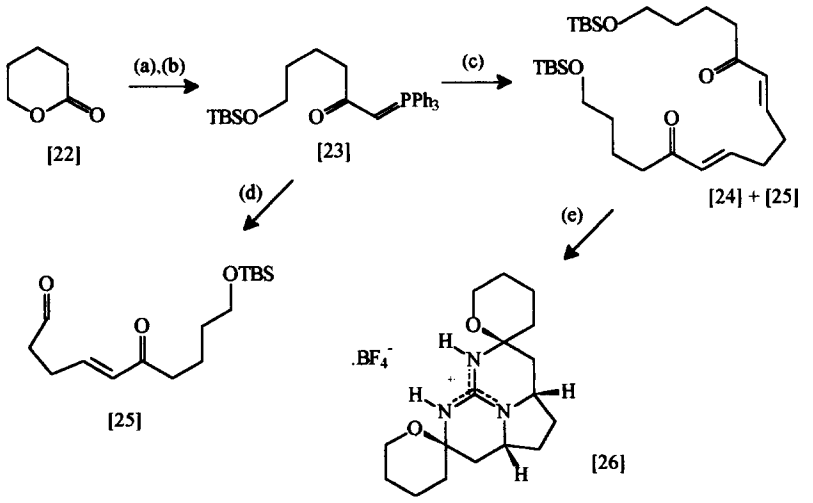
We next proposed that by joining together the two acrylate functions using a two carbon bridge we would be able to prepare a tricyclic model of ptilomycalin A using analogous methodology to that shown above. Preparation of a suitable substrate for this reaction was straightforward and involved the treatment of succinaldehyde **17**[23] with excess carboethoxymethylenetriphenylphosphorane to give the requisite unsaturated diester **18** in 76% yield. Reaction of **18** with guanidine gave the bicyclic intermediate **19** as a 2~3:1 mixture of diastereoisomers in 25% yield (this reaction proceeds with considerable decomposition which is attributed to competitive deprotonation and subsequent polymerisation of **18** under the reaction conditions;[24] such decomposition was not observed during the preparation of **14** and **15**).

These bicyclic intermediates were converted to the tricyclic model compounds **20** and **21** in an identical ratio by treatment with concentrated hydrochloric acid. The structure of the major isomer **20** was confirmed by the observation of reciprocal nOe enhancements between protons H_1 and H_2 which were not observed in **21**. Fortunately the central guanidine is not the site of protonation in these molecules, which led to the net desymmetrisation of the systems and enables us to perform such nOe experiments. By contrast, the corresponding hydrogen carbonates of **20** and **21** (formed from **19** on treatment with atmospheric CO_2) were protonated at guanidine and thus displayed symmetry in the corresponding spectra; this is almost certainly due to the nature of the carbonate counter ion. Pleasingly the stereoselection observed for the formation of the pyrrolidine ring leads to the stereochemistry found in ptilomycalin A; this almost certainly originates from kinetic control.



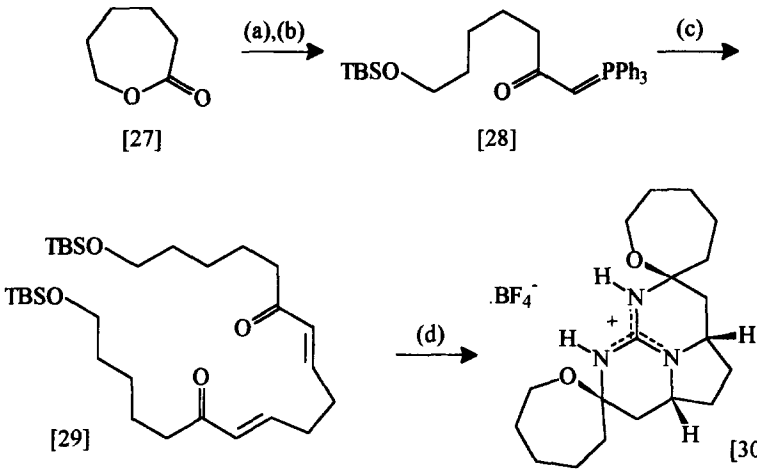
(a) 2 eqv. $EtO_2CCH{=}PPh_3$, THF; 78%, (b) Guanidine, DMF; 25%, (c) Conc. HCl, 100%, **20** : **21**, 2 : 1.

Having successfully devised synthetic routes for the formation of the tetracyclic analogue **14** and the tricyclic analogue **20**, we then converged these two methodologies in order to construct a polycyclic guanidine ring system similar to that of ptilomycalin A. Preparation of the requisite diene **24** was again straightforward; reaction of δ-valerolactone **22** with two equivalents of methylenetriphenylphosphorane followed by silyl-protection of the intermediate phosphonium alkoxide gave the phosphorane **23**. Wittig reaction of this phosphorane with 0.4 equivalents of succinaldehyde gave the required diene **24** in 54% overall yield together with aldehyde **25** as a by-product. This aldehyde is of importance to our synthetic strategy as it is an intermediate in the synthesis of unsymmetrical ptilomycalin A analogues and if required can be obtained in 43% overall yield by reaction with a ten fold excess of succinaldehyde (conditions d). Reaction of **24** with one equivalent of guanidine, followed by removal of solvent, deprotection/cyclisation with methanolic HCl and finally counter ion exchange, afforded two pentacyclic products in a ~4:1 ratio (^{1}H nmr) in 32% overall yield. The major product was isolated by trituration with diethyl ether and identified by X-ray crystallography as the 6,6,5,6,6-pentacycle **26**, which again had the same relative stereochemistry as that found in ptilomycalin A.



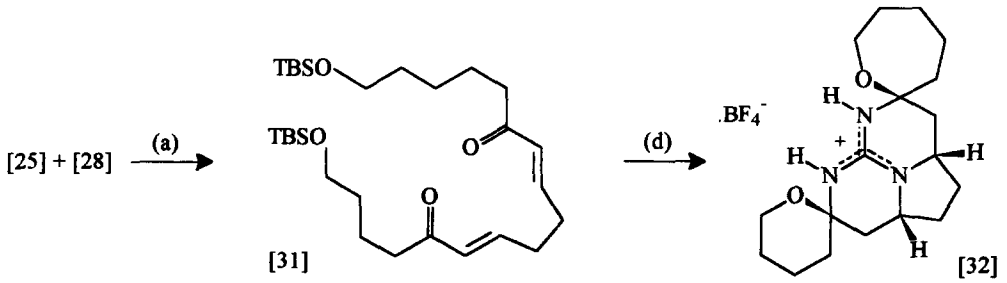
(a) 2 Eqv. $CH_2{=}PPh_3$, THF, -78 °C, (b) TBDMSCl, imidazole, DMF, (c) 0.4 eqv. succinaldehyde, THF, 48hrs; 54% overall, (d)10 eqv. succinaldehyde 43% overall, (e) (i) Guanidine, DMF, 3 hours, (ii) MeOH, HCl, 0 °C to R.T./24 hrs, (iii) Saturated aq. $NaBF_4$, (iv) Trituration and crystallisation; 25% overall.

A similar sequence of reactions enabled the preparation of a 7,6,5,6,7 model, thus the reaction of caprolactone **27** with two equivalents of methylenetriphenylphosphorane followed by silyl protection of the intermediate phosphonium alkoxide gave the phosphorane **28**. Double Wittig reaction of this phosphorane with 0.4 equivalents of succinaldehyde gave the required diene **29** in 20% overall yield. Reaction of **29** under the standard conditions again afforded two pentacyclic products in a ~5:1 ratio (^{1}H nmr) in 27% overall yield. The major product was once again isolated in 20% yield by trituration with diethyl ether and identified by X-ray crystallography as the expected 7,6,5,6,7-pentacycle **30**.



(a) 2 eqv. CH_2=PPh_3/THF/-78 °C, (b) TBDMSCl/imidazole/DMF, (c) 0.4 eqv. succinaldehyde, 20%, (d) (i) Guanidine/DMF/3 hrs, (ii) then MeOH/HCl/0°C to R.T./24 hrs, (iii) Saturated aq. $NaBF_4$, (iv) Trituration and crystallisation; 20% overall.

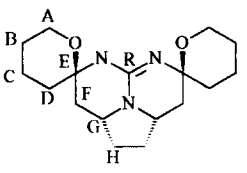
We next sought to prepare an exact 7,6,5,6,6 model of ptilomycalin A and the required unsymmetrical *bis*-α,β-unsaturated ketone **31** was prepared in 37% yield (70% based on recovered **25**) by reaction of the phosphorane **28** with aldehyde **25**. Once formed ketone **31** was reacted under the standard conditions to give two pentacyclic products in a ~4:1 ratio (^{1}H nmr) in 37% overall yield. The major product was once again isolated in 20% yield by trituration with diethyl ether and identified by ^{1}H and ^{13}C nmr as the expected 7,6,5,6,6-pentacycle **32** an exact model of the ring system found in ptilomycalin A.



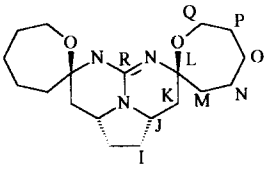
(a) THF, 48hrs; 37%, (b) (i) Guanidine/DMF/3 hrs, (ii) then MeOH/HCl/0 °C to R.T./24 hrs, (iii) Saturated aq. $NaBF_4$, (iv) Trituration and crystallisation; 20% overall.

All three pentacycles **26**, **30** and **32**, show excellent correlation with respect to their ^{13}C nmr spectra, (**Table 1**) together with some correlation to ptilomycalin A **5** where possible;[10] in addition the unsymmetrical system **32** displayed similar nOe characteristics to the naturally occurring ptilomycalin A.[10] Further support for the stereoselectivity of the guanidine addition comes from ^{13}C nmr spectral data available on the presumed isomeric minor isomers **33-35**. Although we were unable to isolate these compounds in a pure state we have obtained good correlation for all the ^{13}C resonances observed for these substances from unrecystallised mixtures of isomeric pentacycles and in addition, good correlation with the structurally similar naturally occurring 13,14,15-isocrambescidine 800 **11** has also been observed (**Table 2**).

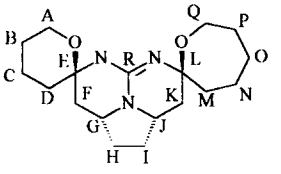
Table 1: NMR data on the major pentacyclic models 26, 30 and 32



[26]



[30]



[32]

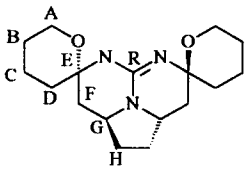
Assignment[1]	26	30	32	5[2]
C	17.61		17.74	18.01
O		22.38	22.56	------
B	24.70		24.84	32.06
N		29.03	29.17	23.74
P		29.88	29.83	------
H	29.84		30.15	26.81
I		30.77	30.83	30.65
D	34.13		34.34	31.68
M		38.77	38.89	36.22
K		39.20	39.13	36.89
F	39.34		39.41	------
G (CH)	52.05		52.17	52.13
J (CH)		52.83	52.97	54.06
A	61.81		61.87	------
Q		62.99	63.12	------
E (C)	80.03		79.86	80.82
L (C)		84.26	84.23	83.86
R (C)	147.64	147.61	147.43	149.09

1. All spectra run in $CDCl_3$, assignments (δ) refer to methylenes unless otherwise stated.
2. See reference 10.

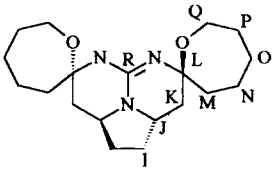
X-ray Structural Studies

As mentioned previously, X-ray structures studies were undertaken for four compounds (**14**, **15**, **26** and **30**) in order to correctly identify these products and establish their stereochemistry. These studies showed that compound **14** crystallised as a CCl_4 solvate, and both **26** and **30** as $CHCl_3$ solvates. The organic cations and BF_4^- anions in all cases are held together in the crystal by weak C-H...F interactions and strong N-H...F hydrogen bonds [H...F, N...F distances and N-H-F angles, respectively, are 2.14, 2.90Å and 146° (**14**), 2.20/2.06, 2/92/2.90Å and 174/159° (**15**), 2.04/2.21, 2.94/3.09Å and 155/153° (**26**) and 2.03/2.22, 2.88/3.07Å and 174/170° (**30**)]. The solvate molecules are not hydrogen bonded but involved in only weak van der Waals interactions.

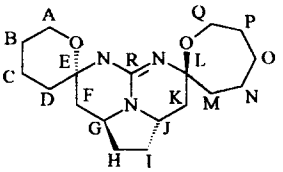
Table 2: NMR data on the minor pentacyclic models 33, 34 and 35.



[33]



[34]



[35]

Assignment[1]	33	34	35	11[2]
C	17.60		17.65	20.9
O		22.69	22.75	-----
B	24.55		25.29	32.9
H	29.44		29.66	29.6
N		29.6[3]	30.34[3]	24.9
P		30.4[3]	30.40[3]	-----
I		30.7[3]	30.80[3]	30.8
D	34.62		34.86	33.6
M		38.29	38.26	39.0
F	38.50		38.85	-----
K		39.65	39.45	39.0
G (CH)	51.41		51.55	54.2
J (CH)		52.39	52.57	54.6
A	61.46		61.58	-----
Q		62.57	62.23	-----
E (C)	81.24		81.39	84.4
L (C)		85.76	85.94	86.6
R(C)	148.31	148.37	148.37	150.1

1. All spectra run in $CDCl_3$, assignments (δ) refer to methylenes unless otherwise stated.
2. Spectrum run in CD_3OD, see reference 18.
3. Interchangeable assignments.

The structures of the cations in the four compounds are shown in Fig. 3. Cations in **14** and **15**, respectively, are clearly shown to be the *syn-* and *anti-* isomers of the same spirocyclic compound. The cation in **14** has a crystallographic mirror plane passing through the N(2) and C(8) atoms whilst the cation in **15** has an approximate 2-fold axis of symmetry. The corresponding bond lengths and angles in the two cations are comparable and very similar to those expected for this type of species. The three C(8)-N bond distances in the pyrimidine ring [1.322(10)-1.344(6)Å] are consistent with a delocalised CN_3 moiety. In both cases, the six-membered OC_5 heterocycles are found to adopt chair conformations.

Compounds **26** and **30** are both the *syn*-isomers of two very related products containing 6,6,5,6,6 and 7,6,5,6,7 pentacycles respectively. The relative stereochemistry is the same as the pentacyclic guanidine moiety in ptilomycalin A. The C(7)-N bond distances in each cation, 1.331-1.339(6)Å (**26**) and 1.327-1.335(4)Å (**30**), are consistent with delocalised CN_3 system; other geometry parameters are as expected. It is observed, however, that the nitrogen atom in the 5-membered ring [N(1)] in each cation is slightly non-planar as shown by the sum of interbond angles 357.0° (**26**) and 357.2° (**30**). These distortions are small but seem to be real since both cations indicate very similar deviations; in fact, this is not unexpected in 5-membered ring systems possessing considerable strain. The two 6-membered O-heterocycles in **26** have chair conformations and orientated very similarly with respect to the N-H bonds. The two 7-membered O-heterocycles in **30** may also be considered to possess similar "chair-like" conformations with OC(6)/C(8) atoms occupying one corner

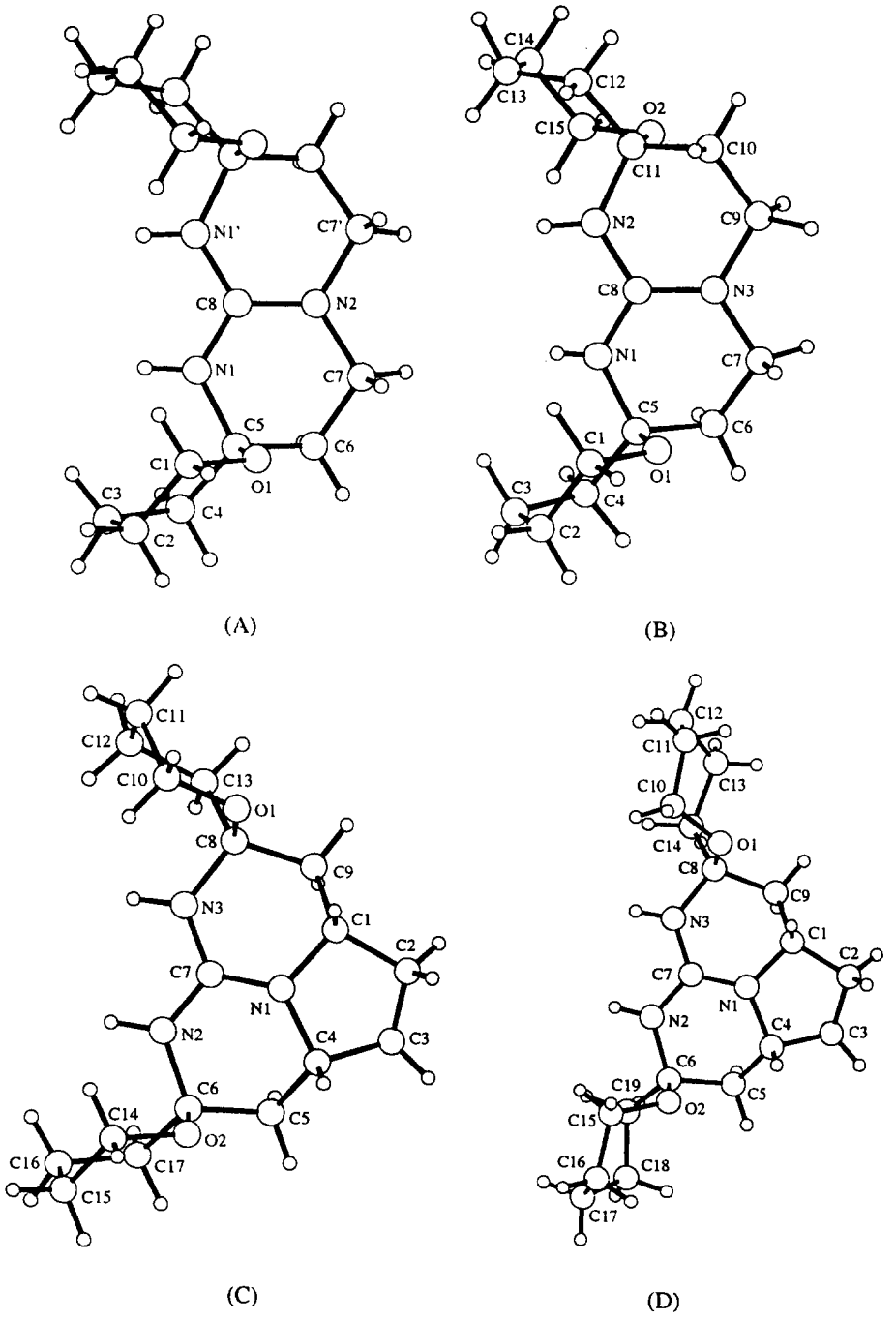


Fig. 3. Structures of the cations $[C_{15}H_{26}N_3O_2]^+$ in **14** (A) and in **15** (B), $[C_{17}H_{28}N_3O_2]^+$ in **26** (C) and $[C_{19}H_{32}N_3O_2^+]$ in **30** (D)

of the chair. It is also noticed that in **26**, the terminal heterocycles are oriented quite close to the N-H bonds but those in **30** lie further away from the N-H bonds.

Conclusion

We have demonstrated through the preparation of model compounds **20**, **21**, **26**, **30** and **32-35**, that the overall selectivity found in the double Michael addition of guanidine to *bis*-α,β-unsaturated ketones and esters gives rise to the same overall relative stereochemistry as that found in the natural products ptilomycalin A **5**[10] and the crambescidins **6-8**.[13] Interestingly, the overall stereoselectivity observed in this reaction contrasts that reported by Snider and Shi,[20a,b] who utilised similar methodology, *viz.* the double Michael addition of *O*-methylisourea to a similar *bis*-α,β-unsaturated ketone and subsequent treatment with ammonia/ammonium acetate, to construct tricyclic synthetic intermediates. The initial selectivity for the *O*-methylisourea addition was found to favour the formation of a *trans*-pyrrolidine intermediate (ca 3 : 1 with the cis isomer) which was then isomerised upon treatment with ammonia. This difference in selectivity is somewhat difficult to rationalise, 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 precursor to pyrrolidine ring formation may be acyclic. In all these processes we are assuming kinetic control in the stereochemistry observed for the formation of the pyrrolidine ring in the model compounds.

Despite the 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 **5** which will enable us to investigate in detail the origins of the biological activity found in this and related systems. In addition to this, the observed stereoselectivity of our reactions and their facile nature may be acting as an indicator to the biosynthetic pathways which lead to the formation of **5** and related molecules.

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Experimental

Column chromatography was carried out on BDH Silica Gel (particle size 40 to 63μm) and TLC were conducted on a precoated Kieselgel 60 F254 (Art. 5554; Merck) with the eluent specified in each case. All non-aqueous reactions were conducted in oven-dried apparatus under a static atmosphere of argon. Ether and tetrahydrofuran were distilled from sodium and benzophenone whilst chloroform and carbontetrachloride were distilled from P_2O_5. Methanol was dried by distillation from magnesium and iodine whereas dry DMF was purchased from Aldrich. Petrol was distilled and collected between the boiling range of 40-60°C. Dichloromethane was freshly distilled from calcium hydride. Chemical shifts are reported in δ values relative to tetramethylsilane as an internal standard. Proton and carbon NMR spectra were recorded in deuteriochloroform (unless otherwise stated) on a Bruker AC250 spectrometer unless otherwise stated. Infrared spectra were recorded as thin films (oils) or as chloroform solutions on a Perkin Elmer 1600 series instrument. Mass spectra were recorded on a VG Masslab Model 12/253 spectrometer using chemical ionisation (with ammonia as the reagent gas). Accurate mass determinations were recorded on a VG Analytical ZAB-E spectrometer using chemical ionisation (with ammonia as the reagent gas). Melting points were recorded with a Gallenkamp MF370 apparatus and are uncorrected.

1,5-Dihydroxyhept-6-ene.

An aqueous solution of HCl (0.2N, 30ml) was added to a cooled (0°C), stirred sample of 2,3-dihydropyran (9.22g, 10ml, 109.6mmol). The mixture was stirred at 0°C for 15 minutes before being warmed to room temperature for 1 hour. The mixture was then extracted with dichloromethane (6 x 50ml) and the combined organic layers were washed with sodium hydrogen carbonate (saturated, 50ml). Drying over

anhydrous magnesium sulphate followed by evaporation of the solvent afforded 2-hydroxytetrahydropyran (8.32g, 75%) as an oil: **^{1}H nmr;** δ = 4.88 (1H, br s, CH), 4.0 (1H, m, CH), 3.54 (1H, m, CH), 3.18 (1H, br s, OH), 1.8 (2H, m, CH_2), 1.5 (4H, m, 2 x CH_2).

Without further purification a solution of the 2-hydroxytetrahydropyran (8.32g, 81.6mmol) in dry THF (70ml) was slowly added to a solution of vinyl magnesium bromide (179.5ml, of a 1M solution in THF, 179.5mmol) at room temperature; this resulted in an exothermic reaction which on cooling resulted in the solidification of the reaction mixture; this was then treated with further THF (50ml) and the suspension stirred vigorously for 16 hours. The reaction was then quenched with HCl (150ml, 0.2M) and was filtered through a Celite pad, the aqueous layer was then saturated with NaCl and extracted sequentially with ethyl acetate (7 x 75ml) and dichloromethane (2 x 50ml). Drying over anhydrous magnesium sulphate and evaporation of the solvent gave an oil, which on chromatography (Gradient elution with 60-100% ethyl acetate in petrol) afforded the title compound (7.45g, 70%, Rf in 50% ethyl acetate/petrol = 0.12) as an oil.

Data: **^{1}H nmr**; δ = 5.80 (1H, ddd, J = 16.1, 9.8, 5.6 Hz, CH), 5.23 (1H, dd, J = 16.1, 3.5Hz, CH), 5.1 (1H, dd, J = 9.8, 3.5Hz, CH), 4.13 (1H, m, CH), 3.65 (2H, t, J = 5.3 Hz, CH_2), 1.5 (6H, m, 3 x CH_2), 1.85 (2H, br s, 2 x OH). **^{13}C nmr**; δ = 141.11 (CH), 114.24 (CH_2), 72.65 (CH), 62.06 (CH_2), 36.41 (CH_2), 32.15 (CH_2), 21.39 (CH_2). **IR;** ν max = 3268 (O-H), 2924 (C-H), 1644 (C=C). **MS(CI)**; 148 (100%, $[M+NH_4]^+$), 130 (20%, $[M]^+$). **HRMS;** found: 148.1338, ($[M+NH_4]^+$) $C_7H_{18}O_2N$ requires: 143.1338.

5-Hydroxy-1-(*t*-butyldimethylsilyloxy)hept-6-ene.

1,5-Dihydroxyhept-6-ene (6.56g, 50.4mmol) was dissolved in dry DMF (80ml) and was treated with imidazole (4.13g, 60.65mmol) followed by *t*-butyldimethylsilylchloride (7.60g, 50.4mmol) at -5°C. After 20 minutes, diethyl ether (150ml) and water (150ml) were added, the organic layer separated and the aqueous layer further extracted with diethyl ether (4 x 50ml). After drying over anhydrous magnesium sulphate and evaporation of solvent, chromatography (12% ether/petrol, Rf = 0.27) gave the title alcohol as a pale yellow oil (11.3g, 93%)

Data: **^{1}H nmr;** δ = 5.89 (1H, ddd, J = 16.9, 10.4, 6.2Hz, CH), 5.23 (1H, dd, J = 16.9, 1.3Hz, CH), 5.1 (1H, d, J = 9.2Hz CH), 4.12 (1H, m, CH), 3.63 (2H, t, J = 6.2Hz, CH_2), 1.5 (6H, m, 3 x CH_2), 0.8 (9H, s, 3 x CH_3), 0.05 (6H, s, 2 x CH_3). **^{13}C nmr;** δ = 141.04 (CH), 114.31 (CH_2), 72.91 (CH), 62.86 (CH_2), 36.49 (CH), 32.40 (CH), 25.75 (3 x CH_3), 21.41 (CH), 18.12 (C), 5.30 (2 x CH_3). **IR;** ν max 3352 (O-H), 2930 (C-H), 2858 (C-H), 1102 (C-O). **MS(CI);** 227 (68% $[M-OH]^+$), 244 (85% $[M]^+$), 245 (100% $[M+H]^+$). **HRMS**; found: 245.1937, $C_{13}H_{29}O_2Si$ ($[M+H]^+$) requires: 243.1937.

1-(*t*-Butyldimethylsilyloxy)-5-oxohept-6-ene 13.

5-Hydroxy-1-(-*t*-butyldimethylsilyloxy)hept-6-ene (0.878g, 3.6mmol) was dissolved in dichloromethane (70ml) and cooled (0°C); with stirring, pyridinium dichromate (2.5g, 7.2mmol) and Celite (17g) were added and the reaction stirred for 15 minutes before being allowed to warm to room temperature. After 24 hours the chocolate coloured mixture was filtered through a short pad of Celite and the filtrate evaporated to furnish an oil. Purification by column chromatography (8% ether/petrol) afforded vinyl ketone **13** as an oil (0.537g, 62%).

Data for **13**: **^{1}H nmr**; δ = 6.32 (1H, dd, J = 17.6, 10.1Hz CH) 6.18 (1H, dd, 17.6, 1.6Hz CH), 5.75 (1H, dd, J = 10.1, 1.6Hz CH), 3.60 (2H, t, J = 6.4Hz, CH_2), 2.60 (2H, t, J = 6.7Hz, CH_2), 1.6 (4H, m, 2 x CH_2), 0.84 (9H, s, 3 x CH_3), 0.05 (6H, s, 2 x CH_3). **^{13}C nmr;** δ = 200.77 (C=O), 136.57 (CH), 127.84 (CH_2), 62.82 (CH_2), 39.36 (CH_2), 32.25 (CH_2), 26.20 (3 x CH_3), 20.49 (CH_2), 18.32 (CH_2), -4.86 (3 x CH_3). **IR**; ν max 1684.7 (C=O), 1616.4 (C=C). **MS(CI);** 243 (100% $[M+H]^+$). **HRMS**; found 243.1780, $C_{13}H_{27}O_2Si$ ($[M+H]^+$) requires 243.1780.

Preparation of guanidine

Sodium (2.4g, 104.7mmol) was washed with dry petrol and added in small portions to dry methanol (200ml) which gave, after evolution of hydrogen was complete, a solution of sodium methoxide. Guanidine hydrochloride (10g, 104.7 mmol) was added to the solution and on stirring for 16hrs a white precipitate of NaCl was obtained, which was filtered from the solution under an argon atmosphere. After evaporation to

dryness the resulting oil was redissolved in dry methanol (20ml) and was again filtered to remove any residual NaCl. Evaporation of the solvent gave guanidine (5.5g, 90%) as a low melting solid.

Tetracyclic (6,6,6,6) model compounds 14 and 15

Guanidine (90mg, 1.55mmol) was dissolved in dry DMF (10ml) and cooled (0°C), whereupon a solution of **13** (0.75g, 3.1mmol) in DMF (1 ml) was added dropwise over 15 min. The resulting solution was warmed to room temperature and was allowed to stir for 4 hours until tlc indicated the complete consumption of **13**. At this point the solvent was removed to afford an oil, which was dissolved in methanol (10ml) and cooled (0°C) before being treated with anhydrous HCl (g) to furnish a brown solution which was allowed to stir for 15 minutes. This solution was evaporated to dryness to yield an oil which was dissolved in dichloromethane (25ml) and washed with saturated LiBr solution (25ml) which was back extracted with further dichloromethane (4 x 25ml); these extracts were dried over anhydrous magnesium sulphate and evaporated to yield the hydrochloride salt of the spirocycle as an oil. This oil was then treated with a sodium tetrafluoroborate solution (saturated, 25ml) and stirred vigorously for 30 minutes. The resultant solution was extracted with dichloromethane (4 x 25ml), dried over anhydrous magnesium sulphate and evaporated to yield **14** and **15** as a 1:1 mixture (598.5mg, 80%). The anti- isomer **15** was isolated by crystallisation of the mixture from ether, whereas the syn isomer **14** was separated by fractional crystallisation from chloroform/carbon tetrachloride (1:1).

Data for **14**: **^{1}H nmr;** δ = 7.70 (2H, s, 2 x NH), 3.75 (6H, m, 2 x CH_2, 2 x CH), 3.15 (2H, ddd, J = 12.1, 5.83, 1.25Hz, 2 x CH), 1.80 (16H, m, 8 x CH_2). **^{13}C nmr;** δ = 149.54 (C), 77.24 (2 x C), 61.73 (2 x CH_2), 44.05 (2 x CH_2), 34.24 (2 x CH_2), 30.93 (2 x CH_2), 24.67 (2 x CH_2), 17.47 (2 x CH_2). **IR;** ν max = 3268 (N-H), 2943 (C-H), 1601 (C=N), 1045 (C-O). **MS(CI);** 280 (1% $[M+H]^+$). **Microanalysis;** found C = 36.90, H = 5.05, N = 7.87; $C_{15}H_{26}N_3O_2BF_4.CCl_4$ requires: C = 36.88, H = 5.03, N = 8.07. **M.pt.;** 128°C.

Data for **15**: **^{1}H nmr;** δ = 7.67 (2H, s, 2 x NH), 3.7 (6H, m, 2 x CH_2 and 2 x CH), 3.23 (2H, ddd, J = 12.1, 6.0, 1.4Hz, 2 x CH), 1.80 (16H, m, 8 x CH_2). **^{13}C nmr;** δ = 148.64 (C), 78.56 (2 x C), 61.95 (2 x CH_2), 42.92 (2 x CH_2), 34.12 (2 x CH_2), 32.46 (2 x CH_2), 24.73 (2 x CH_2), 17.47 (2 x CH_2).**IR;** ν max = 3268 (N-H), 2943 (C-H), 1601 (C=N), 1044 (C-O). **MS(CI);** 280 (1% $[M+H]^+$). **Microanalysis;** found C = 48.95, H = 7.21, N = 11.10; $C_{15}H_{26}N_3O_2BF_4$ requires C = 49.07, H = 7.14, N = 11.44. **M.pt.;** 125°C.

***EE*-Diethyl octa-2,6-dienedioate 18.**

A solution of succinaldehyde[23] (0.1g, 1.16mmol) in dry THF (50ml) was treated with carboethoxymethylenetriphenylphosphorane (0.89g, 2.56mmol) and 3A molecular sieves (1g) and the resulting solution stirred at room temperature for 48 hours. The reaction mixture was filtered through a pad of Celite, evaporated and subjected to chromatography (gradient elution with 0-50% ethyl acetate/petrol) to give **18** (199mg, 76%, Rf value in 20% ethyl acetate/petrol = 0.43) as an oil .

Data for **18**: **^{1}H nmr;** δ = 6.93 (2H, dm, J = 15.8Hz, 2 x CH), 5.85 (2H, d, J = 15.8Hz, 2 x CH), 4.15 (4H, q, J = 7.1Hz, 2 x CH_2), 2.4 (4H, m, 2 x CH_2), 1.28 (6H, t, J = 7.1Hz, 2 x CH_3). **^{13}C nmr;** δ = 166.29 (2 x C), 146.87 (2 x CH), 122.32 (2 x CH), 60.23 (2 x CH_2), 30.40 (2 x CH_2), 14.21 (2 x CH_3). **IR;** ν max = 1724 (C=O), 1655 (C=C). **MS(CI);** 227 (15%, $[M+H]^+$), 244 (100%, $[M+NH_4]^+$). **HRMS;** found 227.1283, $C_{12}H_{19}O_4$ ($[M+H]^+$) requires 227.1283.

Tricyclic (6,5,6) model compounds 20 and 21.

A solution of **18** (0.5g, 2.21mmol) in dry DMF (20ml) was added dropwise to a cooled (-20°C) solution of guanidine (0.26g, 4.42mmol) in dry DMF (20ml) and the resulting mixture warmed to room temperature over 12 hours. This led to the formation of a light brown precipitate from a red solution, which was isolated by filtration and washed sequentially with small portions of DMF, ether and dichloromethane to give the intermediate bicycle **19** as a 2:1 mixture of diastereoisomers (133mg, 24%). Data for **19**: **^{1}H nmr** (D_2O); δ = 1.6-2.75 (16H, m, 8 x CH_2, mixture of diastereoisomers), 3.65 (1H, m, CH, major diastereoisomer), 3.95 (1H, m, CH, minor diastereoisomer), 4.25 (1H, m, CH, major diastereoisomer), 4.30 (1H, m, CH, minor diastereoisomer). **IR;** ν max = 3360 (N-H), 1674 (C=O), 1614 (C=N). A suspension of **19** (127.6mg, 0.51mmol) in water (1ml) was treated with concentrated HCl (0.5ml) to give a clear solution. This

was allowed to stir overnight at room temperature before being evaporated and the crude product dried over phosphorous pentoxide. This mixture was purified by crystallisation from hot aqueous ethanol to afford an inseparable 2:1 diastereoisomeric mixture of **20** and **21** as an amorphous solid (117mg).

Data for **20**: **^{1}H nmr** (D_2O); δ = 4.4 (1H, m, CH), 4.0 (1H, m, CH), 2.85 (2H, m, 2 x CH), 2.6 (1H, m, CH), 2.55 (1H, m, CH), 2.25 (2H, m, 2 x CH), 2.1 (1H, m, CH), 1.85 (1H, m, CH). **^{13}C nmr** (D_2O); δ = 176.92 (C=O), 173.64 (C=O), 153.05 (C), 59.56 (CH), 57.50 (CH), 39.04 (CH_2), 38.23 (CH_2), 32.27 (CH_2), 31.49 (CH_2). Data for **21**: **^{1}H nmr** (D_2O); δ = 4.4 (1H, m, CH), 4.25 (1H, m, CH), 2.8 (1H, m, CH), 2.75 (1H, m, CH), 2.7 (2H, m, 2 x CH), 2.3 (2H, m, 2 x CH), 1.9 (1H, m, CH), 1.85 (1H, m, CH). **^{13}C nmr** (D_2O); δ = 177.76 (C=O), 173.19 (C=O), 153.38 (C), 59.37 (CH), 57.21 (CH), 39.22 (CH_2), 37.97 (CH_2), 32.34 (CH_2), 30.60 (CH_2). **MS(CI);** 193 (100% $[M]^+$), 194 (50% $[M + H]^+$), 387 (15% $[2M + H]^+$). **HRMS;** found 194.0930, $C_9H_{12}N_3O_2$ ($[M+H]^+$) requires 194.0930. **IR;** ν max = 3366 (N-H), 1719 (C=O), 1670 (C=N).

In addition to the above preparation we were also able to prepare the corresponding hydrogen carbonate salts of **20** and **21** by the following method: A stream of air was passed through a solution of **19** (105mg, 0.42mmol) in water (10ml) for a period of 10 hours, following which the reaction was refluxed for a further 10 hours. The resulting solution was evaporated and dried over phosphorus pentoxide to give the required hydrogen carbonates as a ~2:1 mixture of diastereoisomers; analysis was performed on the crude product.

Data for **20.HCO_3** and **21.HCO_3**; **^{1}H nmr** (D_2O); δ = 4.2 (2H, m, 2 x CH), 2.75 (2H, dd, J = 14.7, 6.3Hz, 2 x CH), 2.35 (2H, dd, J = 14.7, 7.35Hz, 2 x CH), 2.2 (2H, m, 2 x CH), 1.85 (2H, m, 2 x CH). **^{13}C nmr** (D_2O); signals for **20.HCO_3**; δ = 33.01 (CH_2), 45.64 (CH_2), 60.66 (CH), 158.00 (C), 182.15 (C=O). Signals for **21.HCO_3**; δ = 30.87 (CH_2), 42.58 (CH_2), 59.45 (CH), 160.69 (C), 182.04 (C=O). **IR;** ν max = 3368 (N-H), 1663 (C=O), 1570 (C=N). **MS;** 194 (100% $[M + H]^+$), 387 (15% $[2M + H]^+$).

1,16-*bis*(*t*-Butyldimethylsilyloxy)-5,12-dioxohexadeca-6,10-diene 24.

n-BuLi (21.8mmol, 8.7ml, 2.5M) was added dropwise to a cooled (0°C) and stirred suspension of methyltriphenylphosphonium bromide (7.79g, 21.82mmol) in THF (100ml); the resulting solution was stirred at 0°C for five minutes and then at room temperature for four hours to give a deep red coloured solution. This was cooled (-78°C) and δ-valerolactone (1.092g, 10.91mmol, 1.01ml) was added to afford a yellow precipitate, which was warmed to room temperature before stirring for one hour. Evaporation of the solvent gave a yellow solid which was re-dissolved in dry DMF (100ml) and cooled (-5°C) before being treated sequentially with imidazole (0.9g, 13.2mmol) and *t*-BDMSCl (1.809g, 12.0mmol). After 30 minutes, the mixture was warmed to room temperature and was left to stir overnight. The reaction mixture was then treated with ether (100ml) and water (100ml), following which the organic layer was separated and washed thoroughly with water (3 x 50ml). The combined aqueous fractions were then extracted with ethyl acetate (2 x 50ml) before the organic layers were combined, dried (magnesium sulphate) and evaporated to dryness to yield **23** as an oil. After redissolution in THF (50ml), succinaldehyde (0.375g, 4.35mmol) was added and the resulting solution was stirred for 72 hours, before being evaporated and purified by chromatography (15% ether/petrol) to give **24** (943mg, 45%, Rf = 0.65 (in 40% ether in petrol)) and the aldehyde **25** (187.6mg, 14%, Rf = 0.40 (in 40% ether in petrol)), both as oils.

Data for **24**: **^{1}H nmr;** δ = 0.00 (12H, s, 4 x CH_3), 0.84 (18H, s, 6 x CH_3), 1.46-1.68 (8H, m, 4 x CH_2), 2.33 (4H, m, 2 x CH_2), 2.52 (4H, t, J = 6.9Hz, 2 x CH_2), 3.58 (4H, t, 6.3Hz, 2 x CH_2), 6.07 (2H, d, 15.9Hz, 2 x CH), 6.75 (2H, dm, 15.9Hz 2 x CH). **^{13}C nmr**; δ = -5.3 (6 x CH_3), 19.99 (2 x C), 21.08 (2 x CH_2), 25.96 (2 x CH_3), 30.76 (2 x CH_2), 32.28 (2 x CH_2), 39.92 (2 x CH_2), 62.84 (2 x CH_2), 130.91 (2 x CH), 144.63 (2 x CH), 200.26 (2 x C). **IR;** ν max = 1738 (C=O). **MS(CI);** 511 (1% $[M+H]^+$). **HRMS;** found 511.3640, $C_{28}H_{55}O_4Si_2$ ($[M+H]^+$) requires 511.3640.

10-(*t*-Butyldimethylsilyloxy)-6-oxodec-4-enal 25.

n-BuLi (80.4mmol, 38.3ml, 2.5M) was added dropwise to a cooled (0°C) and stirred suspension of methyltriphenylphosphonium bromide (28.5g, 80.4mmol) in THF (500ml); the resulting solution was stirred at 0°C for five minutes and then at room temperature for four hours to give a deep red coloured solution. This

was cooled (-78°C) and δ-valerolactone (4.0g, 40.2mmol, 3.7ml) was added to afford a yellow precipitate, which was warmed to room temperature before stirring for a further hour. Evaporation of the solvent gave a yellow solid which was re-dissolved in dry DMF (300ml) and cooled (-5°C) before being treated sequentially with imidazole (3.27g, 48.24mmol) and *t*-BDMSCl (6.6g, 44.22mmol). After 30 minutes, the mixture was warmed to room temperature and was left to stir overnight. The reaction mixture was treated with ether (300ml) and water (300ml), the organic layer separated and the aqueous layer further extracted with ethyl acetate (3 x 50ml). The combined organic fractions were then washed with water (2 x 100ml), dried (magnesium sulphate) and evaporated to yield crude phosphorane **23** as an oil. This oil was then redissolved in THF (200ml) before being treated with succinaldehyde (34.2g, 402mmol, 5 equivalents). The resulting solution was allowed to stir for 72 hours before being filtered, evaporated and purified by chromatography on silica gel (15% ether/petrol) to give the unsaturated ketone **24** (927mg, 10%, Rf = 0.65 (in 40% ether in petrol)) and the aldehyde **25** (5.2g, 43%, (Rf = 0.40 (in 40% ether in petrol)) as oils.

Data for **25**: **^{1}H nmr;** δ = 9.76 (1H, s, CH), 6.76 (1H, dt, J = 15.9, 6.6Hz, CH), 6.10 (1H, d, J = 15.9Hz), 3.59 (2H, t, J = 6.25Hz, CH_2), 2.60 (2H, m, CH_2), 2.52 (4H, m, 2 x CH_2), 1.60, (4H, m, 2 x CH_2), 0.84 (9H, s, 3 x CH_3), 0.00 (6H, s, 2 x CH_3). **^{13}C nmr**; δ = -5.47 (2 x CH_3), 18.14 (C), 20.44 (CH_2), 24.45 (CH_2), 25.79 (3 x CH_3), 32.09 (CH_2), 39.85 (CH_2), 41.74 (CH_2), 62.64 (CH_2), 130.78 (CH), 143.96 (CH), 199.92 (C), 200.26 (CH). **IR;** ν max = 1725 (C=O), 1672 (HC=O), 1630 (C=C). **MS(CI);** 299 (100%, $[M+H]^+$). **HRMS;** found: 299.2042, ($[M+H]^+$), $C_{16}H_{31}O_3Si$ requires: 299.2042.

Pentacyclic (6,6,5,6,6) model compound 26.

The ketone **24** (1g, 1.96mmol) dissolved in DMF (5ml) was slowly added over 30 min to a cooled (0°C), stirred solution of guanidine (0.1156g, 1.96mmol) in DMF (15ml). After warming to room temperature the reaction was stirred for a further three and a half hours until tlc indicated the complete consumption of **24**. After evaporation of the DMF the oil obtained was dissolved in anhydrous methanol (5ml) which was saturated with anhydrous HCl gas. After 16 hours the resulting solution was evaporated under reduced pressure to give a black oil which was dissolved in water (50ml) and extracted with dichloromethane (3 x 50ml). The organic layers were combined, washed with brine (50ml) and saturated LiBr solution (50ml) followed by drying (magnesium sulphate) and evaporation to give the crude hydrochloride salt. This was redissolved in dichloromethane (10ml) and was stirred vigorously with a saturated solution of sodium tetrafluoroborate (30ml) for fifteen minutes. The resulting emulsion was extracted with dichloromethane (3 x 50ml), the combined extracts dried over magnesium sulphate and evaporated to afford an oil which was purified by column chromatography (gradient elution 0-5% methanol/chloroform) to yield **26** and **33** (230mg, 32%) as a ~4:1 mixture of diastereoisomers. Trituration of this mixture with ether (3 x 10ml) gave **26** as a white solid (25%) which was recrystallised from chloroform/ether.

Data for **26**: **^{1}H nmr**; δ = 1.41 (2H, dd, J = 12.5, 12.5 Hz, $CH_{6\alpha}$), 1.46-1.88 (10H, m), 1.98 (2H, m, $CH_{3\alpha}$), 2.20, (2H, dd, J = 12.5, 4.4 Hz, $2CH_{6\beta}$) 2.25 (2H, m, $2CH_{8\beta}$), 3.64 (2H, ddd, J = 11.3, 2.5, 2.5 Hz, $CH_{1\beta}$) 3.74 (2H, ddd, J = 11.3, 11.3, 3.3 Hz, $CH_{1\alpha}$), 3.93 (2H, m, CH_7), 7.56 (2H, s, NH). **^{13}C nmr**; (all resonances refer to 2 carbons and to methylenes unless otherwise stated) δ = 17.61, 24.70, 29.84, 34.13, 39.34, 52.05 (CH), 61.81, 80.03 (C), 147.64 (single C, guanidine quaternary). **IR;** ν max = 3235 (N-H), 2945 (C-H), 1653, 1603 (N-H). **MS(CI)**; 306 (100%, $[M+H]^+$), **HRMS**; found: 305.2103, $C_{17}H_{27}O_2N_3^+$ ($[M^+]$), requires: 305.2103. **M. pt.**; 187°C.

1,18-*bis*(*t*-Butyldimethylsilyloxy)-6,13-dioxooctadeca-7,11-diene 29.

n-BuLi (57.8mmol, 31.2ml, 1.85M) was added dropwise to a cooled (0°C) and stirred suspension of methyltriphenylphosphonium bromide (20g, 57.8mmol) in THF (100ml); the resulting mixture was then stirred at 0°C for five minutes and then at room temperature for four hours to give a deep red coloured solution. This was cooled (-78°C) and caprolactone (3.3g, 28.9mmol) was added to afford a yellow precipitate, which was warmed to room temperature before stirring for a further hour. Evaporation of the solvent gave a yellow solid which was re-dissolved in dry DMF (100ml) and cooled (-5°C) before being treated sequentially with imidazole (2.40g, 34.7mmol) and *t*-BDMSCl (4.80g, 31.8mmol). After 30 minutes, the mixture was warmed to room temperature and was left to stir overnight. The reaction mixture was treated with water (200ml) and extracted with ethyl acetate (4 x 100ml). The combined organic fractions were then washed with water (4 x

100ml), dried (magnesium sulphate) and evaporated to yield crude phosphorane **28** as an oil. This oil was then redissolved in THF (20ml) before being treated with succinaldehyde (0.99g, 11.6mmol, 5 equivalents). The resulting solution was stirred for 5 days before being filtered, evaporated and purified by chromatography on silica gel (15% ether/petrol) to give the unsaturated ketone **29** (1.28g, 20%, Rf = 0.69 (in 50% ether in petrol)) as an oil.

Data for **29**: **^{1}H nmr;** δ = 0.06 (12H, s, 4 x CH_3), 0.9 (18H, s, 6 x CH_3), 1.50 (12H, m, 6 x CH_2), 2.40 (4H, m, 2 x CH_2), 2.55 (4H, t, J = 7.2 Hz, 2 x CH_2), 3.61 (4H, t, 6.3 Hz, 2 x CH_2), 6.14 (2H, d, 15.8Hz, 2 x CH), 6.80 (2H, dm, 15.8Hz, 2 x CH). **^{13}C nmr**; δ = -4.85 (4 x CH_3), 18.33 (2 x C), 23.93 (2 x CH_2), 25.53 (6 x CH_3), 25.95 (2 x CH_2), 30.72 (2 x CH_2), 32.60 (2 x CH_2), 40.36 (2 x CH_2), 62.97 (2 x CH_2), 130.92 (2 x CH), 144.55 (2 x CH), 200.29 (2 x C). **IR;** ν max = 2929, 2859 (C-H), 1674 (C=O), 1629 (C=C). **MS(CI);** 539 (100%, $[M+H]^+$), 556 (80%, $[M+NH_4]^+$). **HRMS;** found: 539.3950 ($[M+H]^+$), $C_{30}H_{59}O_4Si_2$ requires: 539.3952.

Pentacyclic (7,6,5,6,7) model compound 30.

The ketone **29** (1.64g, 3.06mmol) dissolved in DMF (5ml) was slowly added over 30 min to a cooled (0°C), stirred solution of guanidine (0.180g, 3.06mmol) in DMF (30ml). After warming to room temperature the reaction mixture was stirred for a further sixteen hours until tlc indicated the complete consumption of **29**. The resulting solution was evaporated to afford an oil which was dissolved in dry methanol (20ml) and was treated with anhydrous HCl (g) at 0°C; after half an hour, the reaction mixture was warmed to room temperature and was left to stir for sixteen hours. The resulting solution was evaporated under reduced pressure to give a black oil which was dissolved in water (50ml) and extracted with dichloromethane (4 x 25ml). The organic layers were combined and washed with brine (50ml) and saturated LiBr solution (50ml) followed by drying (magnesium sulphates) and evaporation to give the crude hydrochloride salt. This oil was redissolved in dichloromethane (10ml) and was stirred vigorously with a saturated solution of sodium tetrafluoroborate (50ml) for two hours. The resulting emulsion was extracted with dichloromethane (3 x 50ml), the extracts dried over magnesium sulphate and evaporated to afford an oil. This was purified by column chromatography (gradient elution 0-0.5% methanol/chloroform) to yield **30** and **34** (350mg, 27%) as a ~5:1 mixture of diastereoisomers. Trituration of this mixture with ether (3 x 10ml) gave pure **30** as a white solid which was crystallised from chloroform/ether.

Data for **30**: **^{1}H nmr**; δ = 1.28 (2H, app. t, J = 12.4 Hz, $CH_{7\alpha}$), 1.41-2.12 (18H, m), 2.31 (2H, m, $CH_{9\beta}$), 2.43 (2H, dd, J = 4.2, 12.4 Hz, $CH_{7\beta}$), 3.63 (2H, br d , J = 11.8 Hz, $CH_{1\beta}$), 3.78 (2H, app br t, J = 11.8 Hz $CH_{1\alpha}$), 3.99 (2H, m, CH_8), 7.40 (2H, s, NH). **^{13}C nmr**; (all resonances refer to 2 carbons and to methylenes unless otherwise stated) δ = 22.40, 27.04, 29.93, 30.66, 38.88, 39.21, 52.83 (CH), 63.04, 84.26 (C), 147.57 (single C, guanidine quaternary). **IR;** ν max = 3361 (broad, N-H), 2932 (C-H), 1652, 1605 (C=N). **Microanalysis**; found: C = 54.28, N = 9.78, H = 7.54; $C_{19}H_{32}N_3O_2BF_4$ requires; C = 54.17, N = 9.97, H = 7.66. **MS(CI)**; 334 (100%, $[M+H]^+$). **HRMS**; found 334.2499, $C_{19}H_{32}O_2N_3^+$ ($[M+H]^+$) requires 334.2495. **M. pt.**; 187°C.

1,17-*bis*(*t*-Butyldimethylsilyloxy)-5,12-dioxoheptadeca-6,10-diene 31.

n-BuLi (3.52ml, 8.8mmol, 2.5M) was added dropwise to a cooled (0°C) and stirred suspension of methyltriphenylphosphonium bromide (3.14g, 8.8mmol) in THF (50ml); the resulting solution was stirred at 0°C for five minutes and then at room temperature for four hours to give a deep red coloured solution. This was cooled (-78°C) and caprolactone (0.5016g, 4.4mmol, 0.488ml) was added to afford a yellow precipitate, which was warmed to room temperature before stirring for a further 90 minutes.. Evaporation of the solvent gave a yellow solid which was re-dissolved in dry DMF (50ml) and cooled (-5°C) before being treated sequentially with imidazole (0.364g, 5.28mmol) and *t*-BDMSCl (0.73g, 4.84mmol). After 30 minutes, the mixture was warmed to room temperature and was left to stir for 16 hours. The resulting reaction mixture was treated with ether (50ml) and water (50ml) and the organic layer was separated and washed thoroughly with water (3 x 25ml). The aqueous fractions were combined and further extracted with ethyl acetate (2 x 25ml), and the resulting organic layers combined, dried (anhydrous magnesium sulphate) and evaporated to yield the phosphorane **28** as an oil. This was dissolved in dry THF (40ml) and the aldehyde **25** (662mg, 2.2mmol) added as a solution in THF (10ml). After stirring for 68 hours the reaction was evaporated and the residue

purified by column chromatography (15% ether/petrol) to give **31** (421mg, 37% (70% based on recovered **25**), Rf = 0.68 (in 40% ether in petrol)) as an oil.

Data for **31**: **^{1}H nmr**; d = 0.00 (12H, s, 4 x CH_3), 0.85 (18H, s, 6 x CH_3), 1.6 (10H, m, 5 x CH_2), 2.35 (4H, dd, 2 x CH_2), 2.45 (2H, t, J = 7.1 Hz, CH_2), 2.5 (2H, t, J = 7.1 Hz, CH_2), 3.55 (2H, t, J = 5.7 Hz, CH_2), 3.6 (2H, t, J = 5.7 Hz, CH_2), 6.1 (2H, d, J = 17.1 Hz, 2 x CH), 6.75 (2H, dm, J = 17.1 Hz, 2 x CH). **^{13}C nmr**; (all resonances refer to methylenes unless otherwise stated) d = -5.33 (4 x CH_3), 18.29 (2 x C), 25.93 (6 x CH_3) 20.60, 23.91, 25.52, 30.72, 30.59, 32.24, 32.59, 40.08, 40.34, 62.80, 62.96, 130.87 (CH), 130.90 (CH), 144.58 (CH), 144.60 (CH), 200.19 (2C). **IR**; ν max = 1738 (C=O). **MS(CI)**; 525 (100% $[M+H]^+$). **HRMS**; found 525.3800 ($[M+H]^+$) $C_{29}H_{57}O_4Si_2$ requires 525.3795.

Pentacyclic (7,6,5,6,6) model compound 32.

The ketone **31** (421mg, 0.803mmol) dissolved in DMF (5ml) was slowly added over 30 min to a cooled (0°C), stirred solution of guanidine (0.047g, 0.803mmol) in DMF (20ml). After warming to room temperature the reaction was stirred for a further six hours until tlc indicated the complete consumption of **31**. The resulting solution was evaporated to afford an oil which was dissolved in dry methanol (20ml) and was treated with anhydrous HCl (g) at 0°C; after half an hour, the reaction mixture was warmed to room temperature and was left to stir for sixteen hours. The resulting solution was evaporated under reduced pressure to give a black oil which was dissolved in water (50ml) and extracted with dichloromethane (4 x 25ml). The organic layers were combined and washed with brine (50ml) and saturated LiBr solution (50ml) followed by drying (magnesium sulphate) and evaporation to give the crude hydrochloride salt. This oil was redissolved in dichloromethane (5ml) and was stirred vigorously with a saturated solution of sodium tetrafluoroborate (50ml) for fifteen minutes. The resulting emulsion was extracted with dichloromethane (3 x 50ml), the extracts dried over magnesium sulphate and evaporated to afford an oil which was purified by column chromatography (gradient elution 0-1% methanol/chloroform) to yield **32** and **35** (120mg, 37%) as a ~4:1 mixture of diastereoisomers. Trituration of this mixture with ether (3 x 10ml) gave pure **32** as a white solid which was crystallised from chloroform/ether.

Data for **32**: **^{1}H nmr**; δ = 1.27 (1H, app. t, J = 12.5 Hz, $CH_{6\alpha}$), 1.43 (1H, app. t, J = 12.2 Hz, $CH_{11\alpha}$), 1.35-2.30 (19H, m), 2.41 (1H, dd, J = 4.4, 13.0 Hz, CH), 3.63 (2H, m, $CH_{1\beta}$ and $CH_{17\beta}$), 3.79 (2H, m, $CH_{1\alpha}$ and $CH_{17\alpha}$), 3.96 (2H, m, CH_7 and CH_{10}), 7.42 (1H, s, NH), 7.47 (1H, s, NH). **^{13}C nmr**; (all resonances refer methylenes unless otherwise stated) δ = 17.74, 22.56, 24.84, 29.17, 27.83, 30.15, 30.83, 34.34, 38.89, 39.13, 39.41, 52.17 (CH), 52.97 (CH), 61.87, 63.12, 79.86 (C), 84.23 (C), 147.43 (C). **IR**; ν max = 3351 (N-H), 2936 (C-H), 1654, 1601 (C=N), 1059.4 (C-O). **Microanalysis**; found: C = 52.97, N = 10.00, H = 7.37; $C_{18}H_{30}N_3O_2BF_4$ requires; C = 53.04, N = 10.03, H = 7.42. **MS(CI)**; 320 (100%, $[M+H]^+$), **HRMS**; found: 320.2338, $C_{18}H_{30}O_2N_3^+$ ($[M+H]^+$) requires: 320.2338. **M. Pt.**; 183°C.

X-ray Crystallography

Crystallographic measurements for all compounds (**14**, **15**, **26** and **30**) were made at 150 K using a FAST area detector diffractometer and Mo-Kα radiation (l = 0.71069Å), following previously described procedures.[25] The structures were solved by direct methods and refined on Fo^2 by full-matrix least-squares to final wR_2/R values of 0.1951/0.1079 (**14**), 0.2200/0.1177 (**15**), 0.2055/0.1091 (**26**) and 0.1083/0.0886 (**30**) for all unique data above background; the corresponding WR_2/R values for the observed data [I>2s(I)] were 0.1623/0.0665 (**14**), 0.1419/0.062 (**15**), 0.15590/0.0685 (**26**) and 0.0997/0.0467 (**30**). In all cases, the non-hydrogen atoms were anisotropic. In (**15**), the hydrogen atoms were all located from difference map and refined isotropically; in other cases they were included in idealised positions with U_{iso}s being refined (**14** and **26**) or tied to the U_{eq}s of the parents (**30**). The hydrogen on $CHCl_3$ in (**26** and **30**) was ignored. Some atoms in both the BF_4 anions and $CHCl_3$ molecules (**26** and **30**) and CCl_4 molecule (**14**) were disordered; these were assigned partial site occupancies and refined successfully. All calculations were done on a 486DX2/66 personal computer using the programs SHELX-S[26] (solution), SHELXL-93[27] (refinement) and SNOOPI[28] (diagrams). The atom scattering factors were as in SHELXL-93.[27]

The crystal data and details of data collection and structure refinement are summarised in Table 3. Atomic co-ordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, *Tetrahedron* **40**(2), ii, (1984).

Table 3

Crystal data and details of data collection and structure refinement for (**14**), (**15**), (**26**) and (**30**).

	Compound (14)	Compound (15)	Compound (26)	Compound (30)
empirical formula	$C_{15}H_{26}N_3O_2.BF_4.CCl_4$	$C_{15}H_{26}N_3O_2.BF_4$	$C_{17}H_{28}N_3O_2.BF_4.CHCl_3$	$C_{19}H_{32}N_3O_2.BF_4.CHCl_3$
formula weight	521.01	367.20	512.60	540.65
T/K	150(2)K	150(2)	150(2)	150(2)
crystal system	Orthorhombic	Monoclinic	Triclinic	Triclinic
space group	Pnma (No. 62)	$P2_1/c$ (No. 14)	P-1 (No. 2)	P-1 (No. 2)
a/Ä	19.752(6)	11.755(2)	10.3616(11)	10.043(5)
b/Ä	11.713(4)	8.729(2)	10.6317(9)	10.800(5)
c/Ä	9.551(4)	16.952(4)	11.5276(12)	13.461(8)
α/degrees	90	90	76.64(3)	75.06(3)
β/degrees	90	94.66(2)	81.84(5)	73.12(3)
γ/degrees	90	90	69.927(13)	67.26(3)
V/Ä$^{-3}$	2209.7(14)	1733.7(6)	1157.7(2)	1270.9(11)
Z	4	4	2	2
D_C/g cm^{-3}	1.566	1.407	1.470	1.413
μ(MoKα)/cm^{-1}	5.88	1.21	4.48	4.12
F(000)/*e*	1072	776	532	564
crystal size /mm	0.25 x 0.15 x 0.08	0.40 x 0.20 x 0.10	0.35 x 0.25 x 0.15	0.30 x 0.15 x 0.12
θ range for data collection/degrees	2.06 to 25.08	2.63 to 30.05	1.82 to 24.76	2.82 to 25.07
$h$min, $h$max	-23, 9	-16, 6	-8, 11	-11, 10
$k$min, $k$max	-10, 12	-11, 11	-6, 12	-11, 12
$l$min, $l$max	-10, 10	-23, 18	-12, 12	-13, 15
reflections collected	6426	8253	3611	5188
unique reflections	1808	4302	3135	3420
R_{int}	0.0535	0.0475	0.0711	0.0652
data/ parameters in the refinement	1808/168	4302/330	3135/341	3420/358
final R[a] indices	R_1 = 0.1079 (0.0665)[b] wR_2 = 0.1951 (0.1079)[b]	R_1 = 0.1177 (0.0620) wR_2 = 0.2200 (0.1419)	R_1 = 0.1091 (0.0685) wR_2 = 0.2054 (0.1559)	R_1 = 0.0886 (0.0467) wR_2 = 0.1083 (0.0997)
largest diff. peak and hole/e Ä$^{-3}$	0.841 and -0.849	0.289 and -0.359	0.569 and -0.399	0.277 and -0.256

[a] $R_1 = \Sigma(F_O-F_C)/\Sigma(F_O)$; $wR_2 = [\Sigma\{w(F_O^2-F_C^2)^2\}/\Sigma\{w(F_O^2)^2\}]^{1/2}$; $w = 1/\sigma^2(F_O^2)$.

[b] R_1 and wR_2 values for all unique data above background; those calculated for data with $I > 2\sigma(I)$ are given in parentheses.

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