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Iminophosphorane-Mediated Imidazole Ring Formation: A New and General Entry to Aplysinopsin-type Alkaloids of Marine Origin.

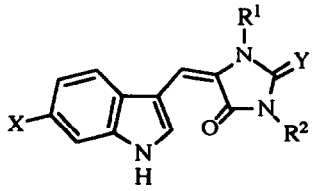
Pedro Molina*, Pedro Almendros, Pilar M. Fresneda

Departamento de Química Orgánica, Facultad de Química,
Campus de Espinardo, E-30071 Murcia, Spain.

Abstract.- Aza Wittig-type reactions of iminophosphoranes **21**, derived from ethyl α-azido-β-(3-indolyl)propenoates and triphenylphosphine, with methyl isocyanate, carbon dioxide or carbon disulfide provide the corresponding heterocumulenes **22**, **25** and **28** which undergo cyclization by the action of nitrogenous reagents completing the assemblage of the framework of aplysinopsin. Further deprotection leads to naturally occurring aplysinopsin analogues.

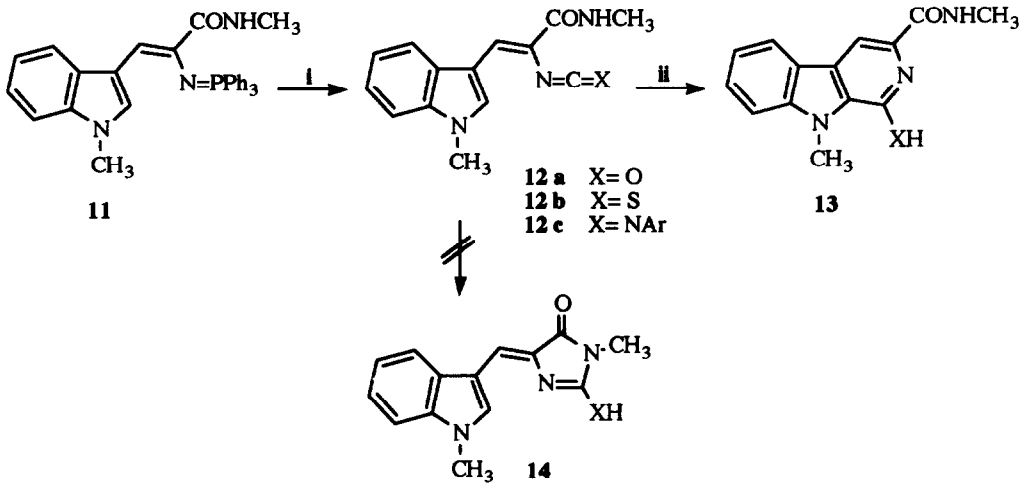
There is considerable interest in Aplysinopsin-type alkaloids which have significant biological activities[1]. Aplysinopsin itself **1** was first isolated from the sponge genus *Thorecta* of the Australian Great Barrier Reef[2] and *Verongia spengelii*[3]. A number of related alkaloids have also been isolated from both dendrophylliids and sponges. Thus, 2-demethyl aplysinopsin **2** has been isolated from the marine sponge *Dercitus* sp. (Choristida) collected in Belize waters[4], 2'-demethyl-3'methylaplysinopsin **3** and 3'-deimino-3'-oxoaplysinopsin **4** have been isolated from dendrophylliid coral *Tubastrea* sp. collected at Palawan, Philippines[5,6], and the 3'-deimino-2'-4'-bis(demethyl)-3'-oxoaplysinopsin **5** isolated from the Mediterranean dendrophylliids *Leptosammia pruvoti*[6]. In addition, the dendrophylliids *A. Calycularis*[7] and *Tubastrea coccinea*[8] of Hawai proved to contain 6-bromoaplysinopsin **6**, the bromo derivatives **7** and **8** have been isolated from the dendrophylliid coral *Dendrophyllia*[5] s.p., collected at Palawan, the 6-bromo analogue **9** isolated from the sponge *Dercitus* in Belize waters[4], and the compound **10** from the Mediterranean dendrophylliids *Leptosammia pruvoti*[6], collected near Marseille (France). These compounds display interesting biological activities, worthy of note among these are aplysinopsin which shows specific cytotoxicity for cancer cells[3], and 3-methylaplysinopsin which is effective in affecting neurotransmission[1].

1	X= H	R^1= CH_3	R^2= CH_3	Y= NH
2	X= H	R^1= H	R^2= CH_3	Y= NH
3	X= H	R^1= CH_3	R^2= CH_3	Y= NCH_3
4	X= H	R^1= CH_3	R^2= CH_3	Y= O
5	X= H	R^1= H	R^2= H	Y= O
6	X= Br	R^1= CH_3	R^2= CH_3	Y= NH
7	X= Br	R^1= H	R^2= CH_3	Y= NH
8	X= Br	R^1= H	R^2= CH_3	Y= NCH_3
9	X= Br	R^1= CH_3	R^2= CH_3	Y= O
10	X= Br	R^1= H	R^2= H	Y= O



Synthetic approaches towards aplysinopsin-type structures involve base-catalyzed condensation of the appropiate 3-formylindole with a five membered ring α-methylene carbonyl compound[4,5,6,9].

In the course of our studies directed towards the synthesis of fused heterocycles based on the heterocyclization reaction of C=C-conjugated heterocumulenes, we have developed the tandem aza Wittig/heterocumulene-mediated annelation[10]. The method is based on the aza Wittig reaction of functionalized iminophosphoranes, bearing a NH group placed at an appropriate position, with carbon dioxide, carbon disulfide or isocyanates to give functionalized heterocumulenes which undergo ring closure by nucleophilic attack of the NH group on the central carbon atom of the heterocumulene portion to give five, six and even seven-membered rings possessing the N-C-N unit. The versatility of the method is shown by the fact that the NH group can be a primary or secondary amino group and even an amido one[11].

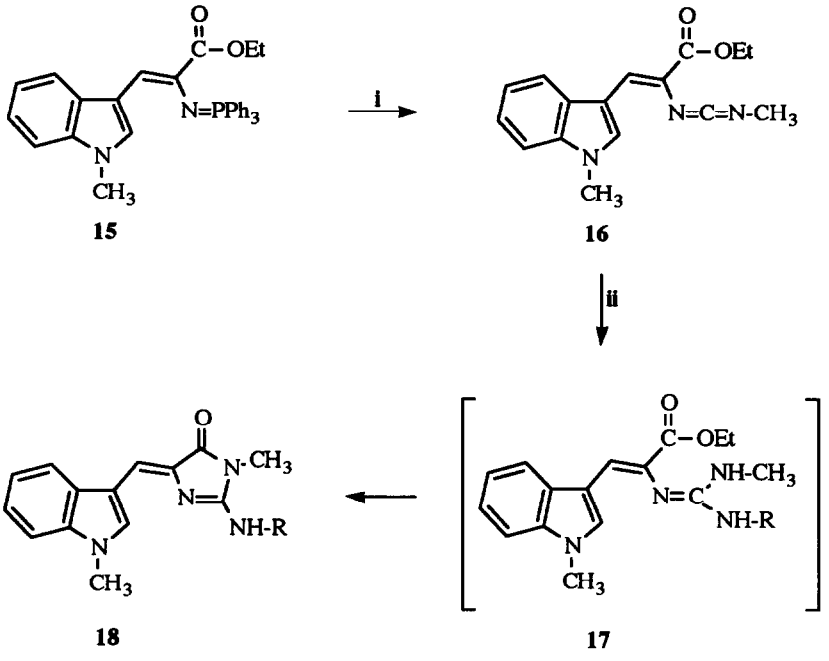


Reagents: i) For **12a** : CO_2, toluene, sealed tube 45 °C; for **12b**: CS_2, toluene, reflux temperature; for **12c**: 4-CH_3O-C_6H_4-NCO, toluene, r.t.; ii) toluene, reflux temperature.

In this context we have tried to prepare the aplysinopsin framework from the iminophosphorane **11**, available in 28% overall yield from 3-formylindole by standard chemistry: (a) condensation with ethyl azidoacetate, (b) hydrolysis, (c) coupling with methylamine and (d) Staudinger reaction with triphenylphosphine. Reaction of iminophosphorane **11** with carbon dioxide, carbon disulfide and 4-methoxyphenylisocyanate under mild reaction conditions provided the corresponding heterocumulene **12**. Compounds **12** by heating in toluene at reflux temperature underwent electrocyclic ring-closure to give β-carboline derivatives **13** and no products **14** derived from the nucleophilic attack of the amido group on the central carbon atom of the heterocumulene moiety could be detected in the crude product.

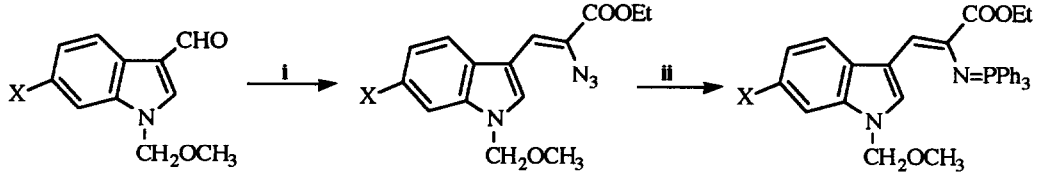
Keeping this in mind, we tested a slight modification of this strategy in order to prepare the imidazole ring of the aplysinopsin framework. Thus, iminophosphorane **15** derived from ethyl α-azido-β-(3-indolyl)propenoate, easily prepared from 3-formyl-1-methylindole[12], reacts with methyl isocyanate at room temperature to give the carbodiimide **16**, which was cyclized by treatment with several nitrogen-containing reagents such as: ammonia, aliphatic amines and hydrazines to give **18** in 70-85% yields thus completing the formation of the imidazole ring

through a guanidine-substituted intermediate **17**, which undergoes regioselective cyclization across the ester and methylamino functionality.



Reagents: i) CH_3-NCO, toluene, r.t.; ii) R-NH_2, toluene, 45 °C.

Having established that carbodiimide **16** is a suitable precursor of the imidazole ring, we turned our attention to the synthesis of the carbon skeleton of aplysinopsin-type alkaloids using this methodology. Thus, we initially required N-protected 3-formylindoles and the protecting group of choice was the methoxymethyl group. To this end N-methoxymethyl-3-formylindole[13] **19a** and N-methoxymethyl-6-bromo-3-formylindole **19b** (80%) were prepared from 3-formylindole and 6-bromo-3-formylindole[14] respectively. Conversion of **19** into azides **20** was performed by reaction with ethyl azidoacetate under standard conditions[15]. Staudinger reaction of azides **20** with



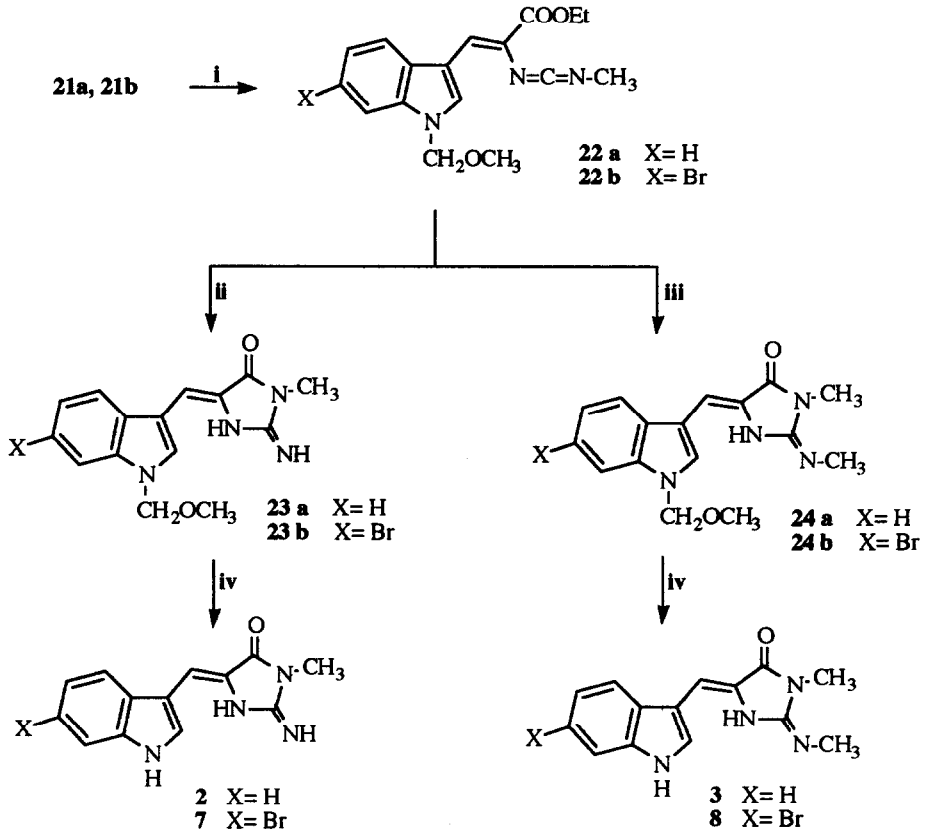
19 a X= H
19 b X= Br

20 a X= H
20 b X= Br

21 a X= H
21 b X= Br

Reagents: i) $N_3CH_2COOC_2H_5$, NaOEt, EtOH, -15 °C; ii) Ph_3P, CH_2Cl_2, r.t.

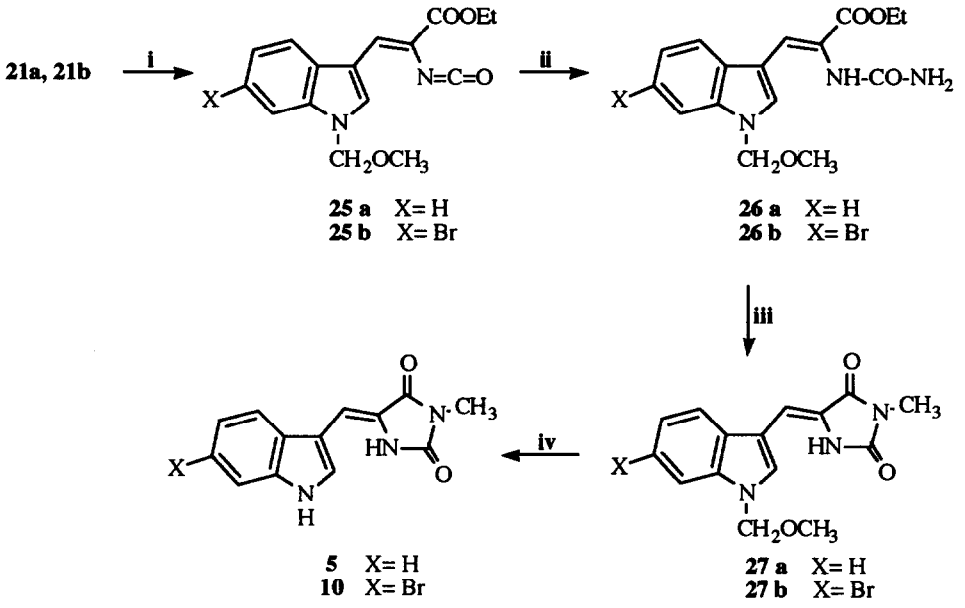
triphenylphosphine provided the iminophosphoranes **21** in excellent yields (86-91%). Aza Wittig-type reaction of iminophosphoranes **21** with methyl isocyanate in toluene at room temperature furnishes carbodiimides **22** in almost quantitative yields, which were used without further purification for the next step. When a toluene solution of the carbodiimide **22** was treated with ammonia at room temperature the corresponding cyclized product **23** was obtained in excellent yield (72-75%). When compounds **23** were treated with formic acid at reflux temperature deprotection took place and 2'-demethylaplysinopsin **2** (48%) and its 6-bromo analogue **7** (46%) were obtained. Conversion of carbodiimides **22** into 2'-demethyl-3-methylaplisinopsin **3** and its 6-bromo analogue **8** was achieved in 40% overall yield by reaction with methylamine in toluene at 45 °C and further deprotection of the resulting cyclized product **24** by treatment with formic acid.



Reagents: i) CH_3-NCO, toluene, r.t.; ii) NH_3, toluene, 45 °C; iii) CH_3-NH_2, toluene, 45 °C; iv) HCOOH, reflux temperature.

On the other hand, iminophosphoranes **21** reacted with carbon dioxide in a sealed tube at 45 °C to give the isocyanates **25** in 80% yield, which were used without purification for the next step. Isocyanates **25** reacted with ammonium acetate in acetonitrile at room temperature to give the ureas **26** in good yields (78-80%), which

underwent cyclization by the action of acetic anhydride to give **27** in 50-52% yields. Eventually deprotection with formic acid provided 3'-deimino-2',4'-bis(demethyl)-3'-oxoaplysinopsin **5** and its 6-bromo analogue **10** in moderate yields (45-46%).

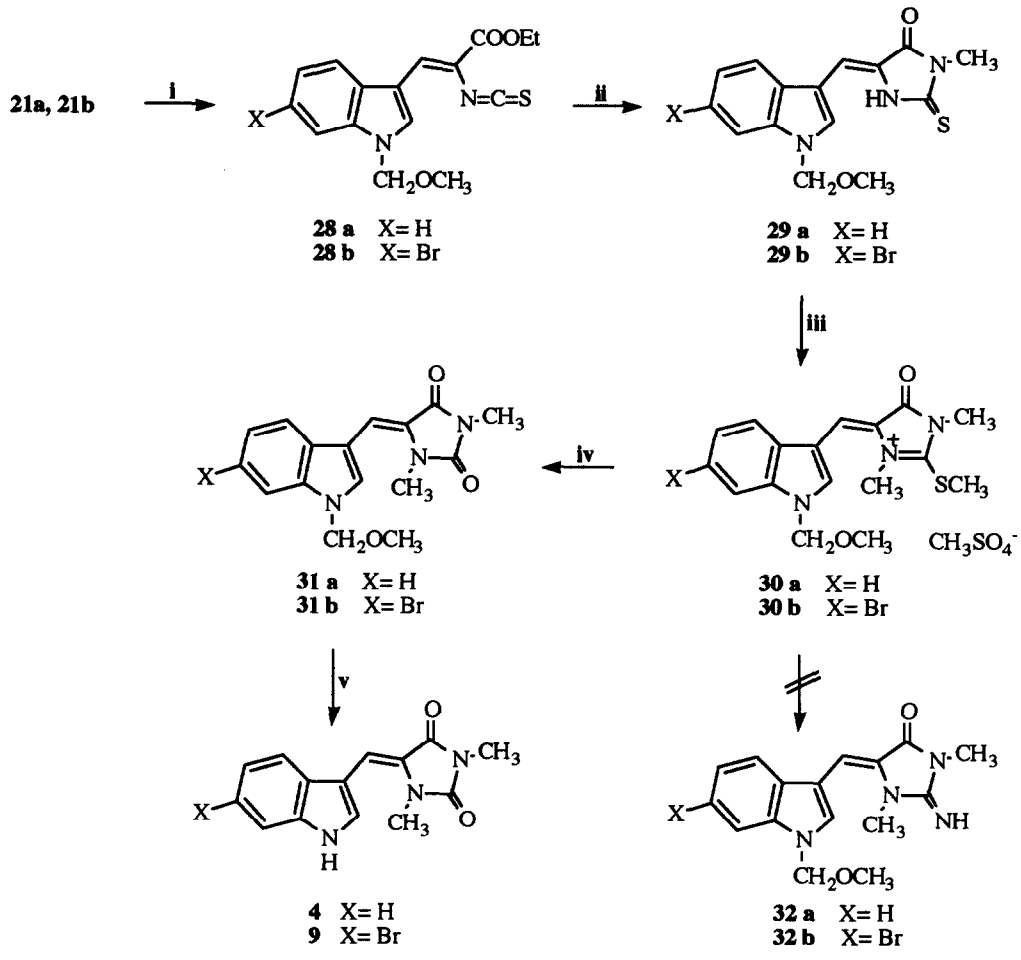


Reagents: i) CO_2, toluene, sealed tube, 45 °C; ii) NH_4CH_3COO, r.t.; iii) Ac_2O, 85 °C; iv) HCOOH, reflux temperature.

Finally, isothiocyanates **28**, readily available in 90% yield from iminophosphoranes **21** and carbon disulfide, reacted with methylamine in toluene at 45 °C directly giving the cyclized products **29** in excellent yields (82-85%), which were converted into the imidazolium salts **30** (70-72%) by the action of an excess of alkylating reagent. Alkaline hydrolysis afforded the oxoanalogue **31** (61-63%), which were converted into 3'-deimino-3'-oxoaplysinopsin **4** and its 6-bromo analogue **9** in moderate yields (50-52%) by treatment with formic acid. Unfortunatly, all attempts to perform the conversion of imidazolinium salts **30** into N-methoxymethyl aplysinopsin **32** by reaction with reagents which usually promote this kind of reaction such as: ammonium acetate, ammonia, and the system ammonia/silver nitrate under a variaty of reaction conditions were unsucessful.

A final word about the E/Z configuration of compounds prepared is relevant. It has been reported[6] that the E/Z configuration of aplysinopsin-type alkaloids can be assigned on the basis of a larger H-C(8), C(5') ^1H-^{13}C heteronuclear coupling constant in the E (J= 9.8-11.0 Hz) than in the Z (J= 4.2-5.2 Hz) stereoisomer. Configuration-Z for all compounds prepared in this work is assigned on the basis of small value of the H-C(8), C(5') ^1H-^{13}C coupling constant (J= 4.4-5.2 Hz) observed.

In conclusion, the results reported here show that the tandem aza-Wittig/heterocumulene-mediated strategy, affords a new and versatile entry to a variety of aplysinopsin derivatives bearing a nitrogen, oxygen or sulfur atom at 3' position, in the imidazole ring. Taking into account that the main structural difference between the natural



Reagents: i) CS_2, toluene, reflux temperature; ii) CH_3NH_2, toluene, 45 °C; iii) $(CH_3)_2SO_4$, ethanol, r.t.; iv) KOH, H_2O, ethanol, reflux temperature; v) HCOOH, reflux temperature.

ocurring aplysinopsin-type alkaloids is found to be the type of functionalization at the imidazole ring, the method described here shows to be an useful alternative to those previously reported which need as precursors appropriate functionalized imidazole derivatives to construct the aplysinosin framework.

EXPERIMENTAL

All melting points were determined on a Kofler hot-plate melting points apparatus and are uncorrected. IR spectra were obtained as Nujol emulsions on a Nicolet FT-5DX spectrophotometer. NMR spectra were recorded

on a Bruker AC-200 (200 MHz) or a Varian Unity 300 (300 MHz). Electron-impact mass spectra were carried out on a Hewlett-Packard 5993C spectrometer at an ionization potential of 70 eV. Microanalyseswere performed on a Perkin-Elmer 240 C instrument.

α-Azido-β-(1-methyl-3-indolyl)propenoic Acid.

To a solution of ethyl α-azido-β-(1-methyl-3-indolyl)propenoate**13** (1.03 g, 4 mmol) in tetrahydrofuran (50 ml) was added a solution of lithium hydroxide (0.50 g, 12 mmol) in water (10 ml). The mixture was stirred at room temperature for 5 h. Then 6N HCl was added until pH= 2 and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with water (2 x 20 ml) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol to give α-azido-β-(1-methyl-3-indolyl)propenoic acid (85%), m.p. 118-120°C (brown prisms from ethanol). (Found: C, 59.82; H, 4.06; N, 22.85. $C_{12}H_{10}N_4O_2$ requires: C, 59.50; H, 4.16; N, 23.13); i.r. (Nujol) 3346, 2317 and 1665 cm^{-1}; ^1H n.m.r. δ (DMSO-d6): 3.87 (s, 3H, CH_3), 7.17 (t, 1H, J= 7.2 Hz, H-5), 7.24 (s, 1H, H-β), 7.25 (t, 1H, J= 7.2 Hz, H-6), 7.50 (d, 1H, J=7.8 Hz, H-7), 7.77 (d, 1H, J= 7.8 Hz, H-4), 8.26 (s, 1H, H-2), 11.81 (s, 1H, COOH); ^{13}C n.m.r. δ (DMSO-d_6): 32.9 (CH_3), 108.1 (C-α), 110.3 (C-7), 117.2 (C-6), 118.1 (C-4), 120.0 (C-3), 120.6 (C-5), 122.3 (C-b), 127.3 (C-3a), 133.0 (C-2), 136.3 (C-7a), 164.9 (CO); m/e (%): 242 (M^+, 5), 214 (100).

α-Azido-β-(1-methyl-3-indolyl)propenamide.

To a mixture of α-azido-β-(1-methyl-3-indolyl)propenoic acid (0.46 g, 2 mmol), 4-dimethylaminopyridine (0.27 g, 2.2 mmol), methylamine (0.12 g, 4 mmol) and dry tetrahydrofuran (40 ml) a solution of N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide chlorhydrate (0.42 g, 2.2 mmol) in dry dichloromethane (10 ml) was added at 0 °C. The resultant mixture was stirred at room temperature under nitrogen for 12 h, and then concentrated to dryness. 1N HCl (8ml) was added and the mixture extracted with ethyl acetate (2 x 15 ml). The combined organic layers were washed with 5% aqueous solution of $NaHCO_3$ (2 x 10 ml), water (2 x 10 ml) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residual material was chromatographed on a silica gel column using ethyl acetate/n-hexane as eluent (3:2) to give α-azido-β-(1-methyl-3-indolyl)propenamide (60%), m.p. 65-67 °C (colourless prisms from ethyl acetate/petroleum ether). (Found: C, 61.03; H, 5.22; N, 27.52. $C_{13}H_{13}N_5O$ requires: C, 61.17; H, 5.13; N, 27.43); i.r. (Nujol) 3238, 2120 and 1626 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 2.77 (d, 3H, J= 4.2 Hz, NH-*CH_3*), 3.85 (s, 3H, N-CH_3), 6.96 (s, 1H, H-β), 7.16 (t, 1H, J= 7.2 Hz, H-5), 7.23 (t, 1H, J= 7.2 Hz, H-6), 7.47 (d, 1H, J= 7.8 Hz, H-7), 7.82 (d, 1H, J= 7.8 Hz, H-4), 8.12 (s, 1H, H-2), 8.44 (q, 1H, J= 4.2 Hz, *NH*-CH_3); m/z (%): 255 (M+, 4), 227 (100).

9-Methyl-1-(p-methoxyphenylamino)-pirido [4,3-b]indolyl-3-N-methyl carboxamide 13c.

To a solution of α-azido-β-(1-methyl-3-indolyl)propenamide (0.24 g, 1 mmol) in dry toluene (30 ml), a solution of triphenylphosphine (0.26 g, 1 mmol) in the same solvent (10 ml) was added. The solution was stirred at room temperature for 10 h. To the resulting iminophosphorane **11** a solution of 4-methoxyphenylisocyanate (0.16 g, 1 mmol) in dry toluene (10 ml) was added. The resultant solution was heated at reflux temperature for 10 h, and then concentrated to dryness. The residual material was recrystallized from toluene/n-hexane (1:1) to give 13c (80%), m.p. 274-275 °C (brown prisms). (Found: C, 69.90; H, 5.70; N, 15.50. $C_{21}H_{20}N_4O_2$ requires: C, 69.98; H, 5.59; N, 15.54); i.r. (Nujol) 3379 and 1647 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 2.86 (d, 1H, J= 4.6 Hz, NH-*CH_3*), 3.75 (s, 3H, N-CH_3), 4.16 (s, 3H, OCH_3), 6.93 (d, 2H, J= 8.6 Hz, H_m), 7.31 (t, 1H, J= 7.8 Hz, H-6), 7.33 (d, 2H, J= 8.6 Hz, H_o), 7.61 (t, 1H, J= 7.8 Hz, H-7), 7.73 (d, 1H, J= 7.8 Hz, H-8), 7.84 (q, 1H, J= 4.6 Hz, *NH*-CH_3), 8.32 (d, 1H,

J= 7.8 Hz, H-5), 8.41 (s, 2H, H-4 + NH-Ar); ^{13}C n.m.r. δ (DMSO-d_6): 26.1 (NH-CH_3), 32.2 (N-CH_3), 55.4 (OCH_3), 108.1 (C-8), 110.8 (C-4), 114.3 (C_m), 120.3 (C-6), 120.6 (C_o), 121.4 (C-4a), 121.6 (C-5), 128.1 (C-7), 128.4 (C-4b), 129.4 (C-9a), 135.9 (C-8a), 137.8 (C-3), 141.7 (C_i), 142.3 (C_p), 154.2 (C-1), 165.4 (CO); m/z (%): 360 (M^+, 100), 169 (77).

General Procedure for the Preparation of 1-Methyl-2-demethyl-3'-N-alkyl Aplysinopsins 18.

To a solution of iminophosphorane13 15 (0.5 g, 1 mmol) in dry toluene (50 ml), a solution of methylisocyanate (0.057 g, 1 mmol) in the same solvent (10 ml) was added under nitrogen. The mixture was stirred at room temperature for 35 h. To the resulting carbodiimide **16** a solution of the appropriate amine (1 mmol) in dry toluene (10 ml) was added. The resultant solution was stirred at 45 °C for 10 h. The precipitated solid was collected by filtration and recrystallized from toluene to give **18**.

18a: (R= H) (75%), m.p. 169-171 °C (yellow prisms); (Found: C, 66.02; H, 5.60; N, 22.10. $C_{14}H_{14}N_4O$ requires: C, 66.14; H, 5.51; N, 22.05); i.r. (Nujol) 3305 and 1702 cm^{-1}; ^{1}H n.m.r. δ (DMSO-d_6): 3.06 (s, 3H, N_4-CH_3), 3.81 (s, 3H, N_1-CH_3), 6.76 (s, 1H, H-8), 7.11 (td, 1H, J= 7.9, 1.1 Hz, H-5), 7.20 (td, 1H, J= 8.2, 1.1 Hz, H-6), 7.43 (d, 1H, J= 8.2 Hz, H-7), 7.91 (d, 1H, J= 7.9 Hz, H-4), 8.13 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 25.5 (N_4-CH_3), 32.8 (N_1-CH_3), 106.5 (C-8), 109.9 (C-7), 111.0 (C-3), 118.9 (C-4), 119.8 (C-5), 121. 9 (C-6), 127. 3 (C-3a), 132.5 (C-2), 136.4 (C-1'), 136.6 (C-7a), 157.5 (C-3'), 169.1 (C-5'); m/z (%): 254 (M^+, 90), 170 (100).

18b: (R= CH_3) (80%), m.p. 251-253 °C; (yellow prisms). (Found: C, 67.03; H, 6.19; N, 20.80. $C_{15}H_{16}N_4O$ requires: C, 67.15; H, 6.01; N, 20.88); i.r. (Nujol) 3310 and 1704 cm^{-1}; ^{1}H n.m.r. δ (DMSO-d_6): 3.01 (d, 3H, J= 4.3 Hz), 3.04 (s, 3H, N_4-CH_3), 3.84 (s, 3H, N_1-CH_3), 6.78 (s, 1H, H-8), 7.12 (t, 1H, J= 7.5 Hz, H-5), 7.20 (t, 1H, J= 7.9 Hz, H-6), 7.40 (d, 1H, J= 4.3 Hz, NH), 7.45 (d, 1H, 7.9 Hz, H-7), 7.96 (d, 1H, J= 7.5 Hz, H-4), 8.26 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 25.4 (NH-CH_3), 27.8 (N_4-CH_3), 32.9 (N_1-CH_3), 106.7 (C-8), 110.0 (C-7), 110.8 (C-3), 118.9 (C-4), 119.8 (C-5), 121.9 (C-6), 127.2 (C-3a), 132.8 (C-2), 136.1 (C-1'), 136.4 (C-7a), 156.9 (C-3'), 169.0 (C-5'); m/z (%): 268 (M^+, 13), 55 (100).

18c: (R= $(CH_3)_2$-CH) (85%), m.p. 285-287 °C; (yellow prisms). (Found: C, 68.80; H, 6.90; N, 18.85. $C_{17}H_{20}N_4O$ requires: C, 68.92; H, 6.76; N, 18.92); i.r. (Nujol) 3337 and 1699 cm^{-1}; ^{1}H n.m.r. δ (DMSO-d_6): 1.31 (d, 6H, J= 6.6 Hz, (CH_3)$_2$-CH), 3.05 (s, 3H, N_4-CH_3), 3.83 (s, 3H, N_1-CH_3), 4.28 (m, 1H, J= 6.6 Hz, $(CH_3)_2$-*CH*), 6.76 (s, 1H, H-8), 6.97 (d, 1H, J= 7.7 Hz, NH), 7.11 (dt, 1H, J= 7.7, 1.1 Hz, H-5), 7.20 (dt, 1H, J= 8.0, 1.1 Hz, H-6), 7.43 (d, 1H, J= 7.5 Hz, H-7), 7.99 (d, 1H, J= 7.5 Hz, H-4), 8.16 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 22.1 ((CH_3)$_2$-CH), 25.2 (N_4-CH_3), 32.6 (N_1-CH_3), 43.1 ((CH_3)$_2$-*CH*), 106.3 (C-8), 109.7 (C-7), 110.9 (C-3), 118.9 (C-4), 119.5 (C-5), 121.6 (C-6), 127.0 (C-3a), 132.4 (C-2), 135.9 (C-1'), 136.38 (C-7a), 155.4 (C-3'), 168.8 (C-5'); m/z (%): 296 (M^+, 100), 169 (41).

18d: (R= $(CH_3)_2$-N) (75%), m.p. 227-228 °C (brown prisms from toluene/n-hexane). (Found: C, 64.50; H, 6.57; N, 23.65. $C_{16}H_{19}N_5O$ requires: C, 64.64; H, 6.40; N, 23.57); i.r. (Nujol) 3268 and 1704 cm^{-1}; ^{1}H n.m.r. δ (CDCl3): 3.04 (s, 6H),, 3.19 (s, 3H, N_4-CH_3), 3.76 (s, 3H, N_1-CH_3), 7.15 (dt, 1H, J= 6.8, 1.6 Hz, H-5), 7.16 (s, 1H, H-8), 7.20 (dt, 1H, J= 6.6, 1.3 Hz, H-6), 7.24 (s, 1H, NH), 7.25 (dd, J= 7.1, 1.6 Hz, H-7), 7.86 (dd, 1H, J= 7.1, 1.6 Hz, H-4), 8.18 (s, 1H, H-2); ^{13}C n.m.r. δ ($CDCl_3$): 29.6 (N^4-CH_3), 33.3 (N_1-CH_3), 39.6 ((CH_3)$_2$-N), 109.5 (C-8), 112.0 (C-7), 11.5 (C-3), 119.2 (C-4), 120.5 (C-5), 122.4 (C-6), 128.1 (C-3a), 133.4 (C-2), 134.5 (C-1'), 136.8 (C-7a), 159.9 (C-3'), 171.2 (C-5'); m/z (%): 297 (M^+, 16), 282 (77), 149 (33), 91 (66), 69 (100).

N-Methoxymethyl-6-bromo-3-formylindole 19b.

To a suspension of sodium hydride (0.13 g, 5.3 mmol) in dry dimethylformamide (10 ml), was added dropwise

a solution of 6-bromo-3-formylindole (1.34 g, 5 mmol) in the same solvent (15 ml). The mixture was stirred at room temperature for 1 h. After this time the solution was cooled at 0 °C and chloromethyl methyl ether (0.43 g, 5.3 mmol) was slowly added. The solution was allowed to warm at room temperature and stirred for 1 h. Then it was poured into ice-water and the precipitated solid was collected by filtration, air-dried and recrystallized from ethyl acetate/n-hexane to give **19b** (80%), m.p. 120-121 °C (colorless prisms from ethyl acetate/petroleum ether). (Found: C, 49.40; H, 3.88; N, 5.03. $C_{11}H_{10}NBrO_2$ requires: C, 49.28; H, 3.76; N, 5.22); i.r. (Nujol) 1660 (CHO) cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 3.30 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 7.43 (dd, 1H, J= 8.4, 1.5 Hz, H-5), 7.67 (d, 1H, J= 1.5 Hz, H-7), 7.76 (s, 1H, H-2), 8.15 (d, 1H, J= 8.4 Hz, H-4), 9.99 (s, 1H, CHO); ^{13}C n.m.r. δ (DMSO-d_6): 56.4 (CH_3), 78.4 (CH_2), 113.8 (C-7), 118.0 (C-3), 118.8 (C-6), 123.3 (C-4), 124.3 (C-3a), 126.6 (C-5), 137.7 (C-7a), 138.4 (C-2), 184.6 (CO); m/z (%): 269 (M^++ 2, 5, 267 (M^+, 5), 129 (7), 115 (6), 102 (5), 45 (100).

Ethyl α-Azido-β-(6-bromo-N-methoxymethyl-3-indolyl) Propenoate 20b.

Ethyl azidoacetate (0.96 g, 7.4 mmol) and a solution of the aldehyde **19b** (0.5 g, 1.86 mmol) in anhydrous ethanol (15 ml) were added dropwise under nitrogen at -15 °C to a well-stirred solution containing sodium (0.18 g) in anhydrous ethanol (30 ml). The reaction mixture was stirred at this temperature for 7 h, poured into cold water (40 ml) and then extracted with dichloromethane (3 x 10 ml). The combined organic layers were washed with water (3 x 10 ml), dried over anhydrous sodium sulfate, and filtered. Concentration to dryness yielded a crude material which was chromatographed on a silica gel column with dichloromethane as eluent to give **20b** (65%), m.p. 105-107 °C (yellow prisms from diethyl ether/petroleum ether). Found: C, 47.32; H, 4.14 ; N, 14.95 . $C_{15}H_{15}N_4O_3Br$ requires: C, 47.51; H, 3.99; N, 14.77); i.r. (Nujol) 2110 (azide) and 1702 (COOEt) cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.41 (t, 3H, J= 7.2 Hz, CH_2CH_3), 3.21 (s, 3H, CH_2OCH_3), 4.37 (q, 2H, J= 7.2 Hz, CH_2CH_3), 5.44 (s, 2H, CH_2OCH_3), 7.17 (s, 1H, H-α), 7.34 (dd, 1H, J= 8.4, 1.8 Hz, H-5), 7.61 (d, 1H, J= 8.4 Hz, H-4), 7.66 (d, 1H, J= 1.8 Hz, H-7), 8.10 (s, 1H, H-2); ^{13}C n.m.r. δ ($CDCl_3$): 14.4 (CH_2CH_3), 56.3 (CH_2OCH_3), 62.0 (CH_2CH_3), 78.1 (CH_2OCH_3), 110.5 (C-3), 113.7 (C-7), 116.4 (C-α), 116.9 (C-6), 119.9 (C-4), 122.3 (C-3a), 124.7 (C-5), 127.3 (C-β), 131.9 (C-2), 136.7 (C-7a), 163.5 (CO); m/e (%): 381 (M^++ 2, 1), 379 (M^+, 4), 351 (70), 306 (100).

General Procedure for the Preparation of Iminophosphoranes 21.

To a solution of triphenylphosphine (1.05 g, 4 mmol) in dry dichloromethane (20 ml) was added dropwise under nitrogen a solution of the appropriate ethyl α-azido-β-(3-indolyl) propenoate **20** (4 mmol) in the same solvent (20 ml). The reaction mixture was stirred at room temperature for 12 h, and the solvent was removed under reduced pressure, the residual material was recrystallized from benzene/n-hexane (1:1).

21a: (91%), m.p. 169-170 °C (yellow prisms). (Found: C, 74.28; H, 5.98; N, 5.07 . $C_{33}H_{31}N_2O_3P$ requires: C, 74.14; H, 5.84; N, 5.24); i.r. (Nujol) 1687, 1105, 1046 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$): 0.98 (t, 3H, J= 7.1 Hz, CH_2CH_3), 3.08 (s, 3H, CH_2OCH_3), 3.90 (q, 2H, J= 7.1 Hz, CH_2CH_3), 5.20 (s, 2H, CH_2OCH_3), 7.18 (td, 1H, J= 6.9, 1.5 Hz, H-5), 7.19 (td, 1H, J= 7.0, 1.4 Hz, H-6), 7.27 (d, 1H, J_{H-P}= 6.8 Hz, H-β), 7.36-7.51 (m, 9H, $6H_m$ + $3H_p$), 7.66-7.77 (m, 7H, J_{H-P}= 12.0 Hz, $6H_o$ + H-7), 7.83 (dd, 1H, J= 7.0, 2.0 Hz, H-4), 8.32 (s, 1H, H-2); ^{13}C n.m.r. δ ($CDCl_3$): 14.1 (CH_2CH_3), 55.7 (CH_2OCH_3), 60.3 (CH_2CH_3), 77.6 (CH_2OCH_3), 109.7 (C-7), 110.3 (d, $^3J_{P-C}$= 20.7 Hz, C-β), 114.1 (C-3), 119.0 (C-4), 120.0 (C-5), 122.2 (C-6), 128.1 (d, $^3J_{P-C}$= 12.2 Hz, C_m), 129.0 (C-3a), 130.3 (C-2), 130.9 (d, $^4J_{P-C}$= 2.6 Hz, C_p), 132.0 (C-7a), 132.3 (d, $^2J_{P-C}$= 9.8 Hz, C_o), 132.9 (d, $^2J_{P-C}$= 6.9 Hz, C-α), 134.9 (d, $^1J_{P-C}$= 87.1 Hz, C_i), 167.4 (d, $^3J_{P-C}$= 6.0 Hz, CO); m/z (%): 535 (M^++ 1, 11), 534 (M^+, 29), 284 (12), 263 (21), 262 (27), 250 (82), 183 (100).

21b: (86%), m.p. 179-181 °C (yellow prism). (Found: C, 64.76; H, 5.13; N, 4.38. $C_{33}H_{30}N_2O_3BrP$ requires:

C, 64.61; H, 4.93; N, 4.57). i.r. (Nujol) 1690, 1580, 1104, 1048 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 0.99 (t, 3H, J= 7.1 Hz, CH_2CH_3), 3.10 (s, 3H, CH_2OCH_3), 3.90 (q, 2H, J= 7.1 Hz, CH_2CH_3), 5.16 (s, 2H, CH_2OCH_3), 7.18 (d, 1H, J_{H-P}= 6.7 Hz, H-β), 7.27(dd, 1H, J= 8.2, 1.6 Hz, H-5), 7.42-7.50 (m, 9H, $6H_m + 3H_p$), 7.66-7.77 (m, 8H, J_{H-P}= 12.1 Hz, $6H_o$ + H-4 + H-7), 8.29 (s, 1H, H-2); ^{13}C n.m.r. δ ($CDCl_3$): 14.1 (CH_2CH_3), 55.8 (CH_2OCH_3), 60.5 (CH_2CH_3), 77.8 (CH_2OCH_3), 112.9 (C-3 + C-7), 114.0 (d, $^3J_{P-C}$= 19.0 Hz, C-β), 115.8 (C-6), 120.3 (C-4), 123.2 (C-5), 127.9 (C-3a), 128.2 (d, $^3J_{P-C}$= 12.2 Hz, C_m), 130.6 (C-2), 131.1 (d, $^4J_{P-C}$= 2.5 Hz, C_p), 132.1 (C-7a), 132.4 (d, $^2J_{P-C}$= 9.7 Hz, C_o), 133.1 (d, $^2J_{P-C}$= 7.0 Hz, C-α), 135.7 (d, $^1J_{P-C}$= 87.0 Hz, C_i), 167.2 (d, $^3J_{P-C}$= 6.0 Hz, CO); m/z (%): 615 (M^++ 2, 2), 613 (M^+, 4), 330 (15), 328 (16), 185 (16), 183 (100).

Preparation of N-Methoxymethyl 2'-demethylaplysinopsins 23.

To a solution of the appropriate iminophosphorane **21** (0.98 mmol) in dry toluene (40 ml), a solution of methylisocyanate (0.056 g, 0.98 mmol) in the same solvent (10 ml) was added. The resultant solution was stirred under nitrogen at room temperature for 32 h. A mixture of the toluene solution of carbodiimide **22** and an excess of liquid ammonia (5 ml) was heated in a sealed tube at 45 °C for 10 h. The precipitated solid was collected by filtration and recrystallized from toluene.

23a: (72%), m.p. 185-187 °C (yellow prisms). (Found C, 63.25 ; H, 5.79; N, 19.60. $C_{15}H_{16}N_4O_2$ requires: C, 63.37; H, 5.67; N, 19.71); i.r. (Nujol): 3380 (NH) and 1705 (CO) cm^{-1}; ^1H n.m.r. d (DMSO-d_6): 3.08 (s, 3H, N-CH_3), 3.21 (s, 3H, CH_2OCH_3), 5.57 (s, 2H, CH_2OCH3), 6.76 (s, 1H, H-8), 7.17 (t, 1H, J= 7.5 Hz, H-5), 7.24 (t, 1H, J= 8.1 Hz, H-6), 7.35 (br, 2H, NH_2), 7.60 (d, 1H, J= 8.1 Hz, H-7), 7.94 (d, 1H, J= 7.5 Hz, H-4), 8.29 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 25.6 (N_4-CH_3), 55.5 (OCH_3), 76.7 (CH_2), 105.3 (C-8), 110.5 (C-7), 112.1 (C-3), 119.0 (C-4), 120.6 (C-5), 122.4 (C-6), 127.7 (C-3a), 131.4 (C-2), 136.1 (C-1'), 137.5 (C-7a), 157.9 (C-3'), 168.9 (C-5'); m/z (%): 284 (M^+, 100), 155 (43).

23b: (75%), m.p. 246-248 °C; (yellow prisms). (Found: C, 49.39; H, 4.34; N, 15.27. $C_{15}H_{15}N_4O_2Br$ requires: C, 49.60; H, 4.16; N, 15.43). i.r. (Nujol) 3401 (NH) and 1704 (CO) cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 3.07 (s, 3H, N-CH_3), 3.19 (s, 3H, CH_2OCH_3), 5.57 (s, 2H, CH_2OCH_3), 6.71 (s, 1H, H-8), 7.29 (d, J= 8.4 Hz, H-5), 7.39 (br, 2H, NH_2), 7.86 (s, 1H, H-7), 7.96 (d, 1H, J= 8.4 Hz, H-4), 8.26 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 25.7 (N-CH_3), 55.6 (OCH_3), 77.0 (CH_2), 104.7 (C-8), 112.5 (C-3), 113.5 (C-7), 115.5 (C-6), 121.2 (C-4), 123.5 (C-5), 126.7 (C-3a), 132.0 (C-2), 137.0 (C-1'), 138.2 (C-7a), 158.4 (C-3'), 169.1 (C-5'); m/z (%): 364 (M^++ 2, 30), 362 (M^+, 40), 57 (100).

Preparation of N-Methoxymethyl 2'-demethyl-3'-methylaplysinopsins 24.

To a solution of the appropriate iminophosphorane **21** (0.98 mmol) in dry toluene (40 ml), a solution of methylisocyanate (0.056 g, 0.98 mmol) in the same solvent (10 ml) was added. The mixture was stirred under nitrogen at room temperature for 32 h. A solution of methylamine (0.12 g, 4 mmol) in dry toluene (10 ml) was added, The resultant solution was stirred at 45 °C for 10 h. The yellow precipitated solid was collected by filtration and recrystallized from toluene.

24a: (76%), m.p. 241-242° C; (yellow prisms). (Found: C, 64.29; H, 6.22; N, 18.65. $C_{16}H_{18}N_4O_2$ requires: C, 64.41; H, 6.08; N, 18.78); i.r. (Nújol): 3298 (NH) and 1706 (CO) cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 3.05 (d, 3H, J= 4.3 Hz, NH-CH_3), 3.07 (s, 3H, N_4-CH_3), 3.20 (s, 3H, CH_2OCH_3), 5.60 (s, 2H, CH_2OCH_3), 6.79 (s, 1H, H-8), 7.17 (t, 1H, J= 7.8 Hz, H-5), 7.21 (t, 1H, J= 8.1 Hz, H-6), 7.47 (d, 1H, J= 4.3 Hz, NH), 7.60 (d, 1H, J= 8.1 Hz, H-7), 7.99 (d, 1H, J= 7.8 Hz, H-4), 8.38 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 25.4 (N_4-CH_3), 27.8 (NH-CH_3), 55.5 (OCH_3), 76.8 (CH_2), 105.8 (C-8), 110.5 (C-7), 112.1 (C-3), 119.1 (C-4), 120.5 (C-5), 122.4 (C-6), 127.7 (C-3a),

131.9 (C-2), 136.1 (C-1'), 137.1 (C-7a), 157.3 (C-3'), 169.0 (C-5'); m/z (%): 298 (M^+, 39), 183 (55), 71 (100).

24b: (80%), m.p. 249-250 °C (yellow prisms). (Found: C, 50.82; H, 4.67; N, 14.74. $C_{16}H_{17}N_4O_2Br$ requires: C, 50.94; H, 4.54; N, 14.85); i.r. (Nujol): 3374 (NH) and 1702 (CO) cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 3.02 (s, 3H, N_4-CH_3), 3.06 (d, 3H, J= 4.3 Hz, NH-CH_3), 3.20 (s, 3H, CH_2OCH_3), 5.60 (s, 2H, CH_2OCH_3), 6.72 (s, 1H, H-8), 7.28 (d, 1H, J= 8.4 Hz, H-5), 7.50 (d, 1H, J= 4.3 Hz, NH), 7.85 (s, 1H, H-7), 8.03 (d, 1H, J= 8.4 Hz, H-4), 8.34 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 25.5 (N_4-CH_3), 27.9 (NH-CH_3), 55.6 (OCH_3), 77.0 (CH_2), 105.2 (C-8), 112.5 (C-3), 113.5 (C-7), 115.4 (C-6), 121.4 (C-4), 123.4 (C-5), 126.7 (C-3a), 132.6 (C-2), 137.0 (C-1'), 137.7 (C-7a), 157.6 (C-3'), 169.1 (C-5'); m/z (%); 378 (M^++ 2, 30), 376 (M^+, 27), 71 (100).

Preparation of Ureas 26.

A mixture of the appropriate iminophosphorane **21** (0.98 mmol) an excess of solid carbon dioxide (0.43 g, 0.98 mmol) and dry toluene (30 ml) was heated in a sealed tube at 45 °C for 1 h. The solvent was removed under reduced pressure to give the corresponding isocyanate **25** as a solids which were used without further purification in the next step. To a solution of isocyanate **22** (0.7 mmol) in dry acetonitrile (30 ml), ammonium acetate (0.1 g, 1.4 mmol) was added. The resultant solution was stirred at room temperature for 12 h. The precipitate solid was filtered, washed with water, air-dried and recrystallized from acetonitrile.

26a: (80%); m.p. 217-218 °C; (colorless prisms). (Found: C, 60.43; H, 6.16; N, 13.12. $C_{16}H_{19}O_4N_3$ requires: C, 60.56; H, 6.03; N, 13.24); i.r. (Nujol) 3348, 3216, 1706 and 1662 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 1.26 (t, 3H, J= 7.0Hz, CH_2CH_3), 3.22 (s, 3H, CH_2OCH_3), 4.19 (q, 2H, = 7.0 Hz, CH_2CH_3), 5.59 (s, 2H, CH_2OCH_3), 5.98 (s, 2H, NH_2), 7.21 (d, 1H, J= 7.8 Hz, H-5), 7.28 (t, 1H, J= 7.8 Hz, H-6), 7.4 (s, 1H, H-β), 7.63 (s, 1H, NH), 7.64 (d, 1H, J=7.8 Hz, H-7), 7.78 (d, 1H, 7.8 Hz, H-4), 7.9 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 14.2 (CH_2CH_3), 55.6 (CH_2OCH_3), 60.2 (CH_2CH_3), 76.9 (CH_2OCH_3), 109.8 (C-3), 110.7 (C-β), 118.5 (C-7), 118.6 (C-4), 120.9 (C-5), 122.7 (C-6), 123.6 (C-3a), 127.7 (C-a), 130.6 (C-2), 135.8 (C-7a), 156.4 ($CONH_2$), 165.8 (COOEt); m/z (%): 318 (M^++ 1, 9), 317 (M^+, 55), 155 (100).

26b: (78%), m.p. 230-231 °C (colorless prisms). (Found: C, 48.34; H, 4.70; N, 10.42. $C_{16}H_{18}N_3O_4Br$ requires: C, 48.50; H, 4.58; N, 10.60); i.r. (Nujol): 3348, 3239, 1705 and 1660 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 1.26 (t, 3H, J= 7.0 Hz, CH_2CH_3), 3.20 (s, 3H, CH_2OCH_3), 4.17 (q, 2H, J= 7.0 Hz, CH_2CH_3), 5.58 (s, 2H, CH_2OCH_3), 5.96 (s, 2H, NH_2), 7.30 (s, 1H, H-β), 7.32 (d, 1H, J= 8.4 Hz, H-5), 7.65 (s, 1H, NH), 7.74 (d, 1H, J= 8.4 Hz, H-4), 7.88 (s, 1H, H-7), 7.90 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 14.3 (CH_2CH_3), 55.7 (CH_2OCH_3), 60.4 (CH_2CH_3), 77.0 (CH_2OCH_3), 110.1 (C-3), 113.7 (C-β), 115.7 (C-6), 120.7 (C-7 + C-4), 123.8 (C-5), 124.4 (C-3a), 126.8 (C-α), 131.2 (C-2), 136.7 (C-7a), 156.3 ($CONH_2$), 165.8 (COOEt); m/z (%): 397 (M^++ 2, 7), 395 (M^+, 7), 45 (100).

Preparation of N-Methoxymethyl-3'-deimino-2',4'-bis(demethyl)-3'-oxoaplysinopsins 27.

A solution of the corresponding urea **26** (1.1 mmol) in acetic anhydride (30 ml) was heated at 85 °C for 14 h. After cooling the solvent was removed under reduced pressure and the residual oil was slurried with a cold 5% aqueous sodium hydroxide solution (20 ml). The formed solid was filtered, air-dried and recrystallized from methanol.

27a: (52%), m.p. 286-287 °C (yellow prisms). (Found: C, 62.17; H, 4.69; N, 15.62. $C_{14}H_{13}N_3O_3$ requires: C, 61.99; H, 4.83; N, 15.49); i.r. (Nújol): 3172, 3141, 1710 and 1654 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 3.21 (s, 3H, CH_3), 5.61 (s, 2H, CH_2), 6.74 (s, 1H, H-8), 7.21 (t, 1H, J= 7.7 Hz, H-5), 7.28 (t, 1H, J= 7.7 Hz, H-6), 7.63 (d, 1H, J= 7.7 Hz, H-7), 7.77 (d, 1H, J= 7.7 Hz, H-4), 7.94 (s, 1H, H-2), 9.39 (br, 2H, 2NH); ^{13}C n.m.r. δ (DMSO-d_6): 55.7 (CH_3), 77.0 (CH_2), 109.3 (C-3), 111.0 (C-8), 118.6 (C-7), 121.2 (C-4), 122.6 (C-3a), 122.9 (C-5), 124.4 (C-6), 127.8 (C-

1'), 131.4 (C-2), 135.8 (C-7a), 165.1 (C-3'), 169.1 (C-5'); m/z (%): 272 (M^++ 1, 9), 271 (M^+, 58), 155 (100).

27b: (50%), m.p. 185-287 °C (yellow prisms); (Found: C, 48.20; H, 3.26; N, 12.18. $C_{14}H_{12}N_5O_3Br$ requires: C, 48.02; H, 3.45; N, 12.00); i.r. (Nujol) 3185, 3150, 1708 and 1650 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 3.22 (s, 3H, CH_3), 5.55 (CH_2), 6.67 (s, 1H, H-8), 7.32 (d, 1H, J= 8.0 Hz, H-5), 7.79 (d, 1H, J= 8.0 Hz, H-4), 7.87 (s, 1H, H-7), 8.28 (s, 1H, H-2), 9.40 (br, 2H, 2NH); ^{13}C n.m.r. δ (DMSO-d_6): 55.83 (CH_3), 77.2 (CH_2), 99.6 (C-8), 113.7 (C-3), 109.0 (C-7), 115.8 (C-6), 120.5 (C-4), 123.8 (C-5), 125.5 (C-3a), 130.6 (C-2), 126.8 (C-1'), 136.6 (C-7a), 155.7 (C-3'), 165.6 (C-5'); m/z (%): 352 (M^++ 2, 24), 350 (M^+, 32), 154 (100).

Preparation of Thioxoaplysinopsin Derivatives 29.

To a solution of the appropriate iminophosphorane **21** (0.98 mmol) in dry toluene (30 ml), carbon disulfide (20 ml) was added. The resultant solution was heated at reflux temperature for 12 h. After cooling, the solvent was removed under reduced pressure to give the corresponding isothiocyanate **28** as yellow solid. To a solution of isothiocyanate **28** (0.98 mmol) in dry toluene (30 ml) a solution of methylamine (0.098 g, 2.9 mmol) in the same solvent (15 ml) was added. The solution was heated at 45 °C for 10 h, after cooling the precipitated solid was filtered and recrystallized from toluene.

29a: (82%), m.p. 203-204 °C (yellow prisms); (Found: C, 59.61; H, 5.20; N, 13.82. $C_{15}H_{15}O_2SN_3$ requires: C, 59.78; H, 5.02; N, 13.94); i.r. (Nujol): 3217, 1721 and 1083 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 3.17 (s, 3H, N-CH_3), 3.21 (s, 3H, CH_2OCH_3), 5.58 (s, 2H, CH_2OCH_3), 6.89 (s, 1H, H-8), 7.23 (td, 1H, J= 7.8, 1.2 Hz, H-5), 7.30 (td, 1H, J= 8.1, 1.2 Hz, H-6), 7.64 (d, 1H, J= 8.1 Hz, H-7), 7.88 (d, 1H, J= 7.8 Hz, H-4), 8.62 (s, 1H, H-2), 10.99 (br, 1H, N-H); ^{13}C n.m.r. δ (DMSO-d_6): 27.2 (N-CH_3), 55.8 (OCH_3), 77.3 (CH_2), 105.0 (C-8), 108.9 (C-3), 110.9 (C-7), 118.5 (C-4), 121.4 (C-5), 123.1 (C-6), 124.2 (C-3a), 127.9 (C-1'), 132.0 (C-2), 135.9 (C-7a), 164.2 (C-5'), 177.3 (C-3'); m/z (%): 302 (M^++ 1, 14), 301 (M^+, 74), 155 (100).

29b: (85%), m.p. 229-230 °C (yellow prisms). (Found: C, 47.22; H, 3.87; N, 10.85. $C_{15}H_{14}O_2SN_3Br$ requires: C, 47.38; H, 3.71; N, 11.05). i.r. (Nujol) 3320, 1730 and 1104cm^{-1}; ^1H n.m.r δ (DMSO-d_6): 3.14 (s, 3H, N-CH_3), 3.20 (s, 3H, CH_2OCH_3), 5.55 (s, 2H, CH_2OCH_3), 6.70 (s, 1H, H-8), 7.30 (d, 1H, J= 8.4 Hz, H-5), 7.84 (d, 1H, J= 8.4 Hz, H-4), 7.85 (s, 1H, H-7), 8.51 (s, 1H, H-2), 11.70 (br, NH); ^{13}C n.m.r. δ (DMSO-d_6): 27.2 (N-CH_3), 55.8 (OCH_3), 77.2 (CH_2), 103.4 (C-8), 110.1 (C-3), 113.7 (C-7), 115.8 (C-6), 123.9 (C-4), 126.9 (C-5 + C-3a), 128.6 (C-1'), 136.8 (C-2 + C-7a), 165.5 (C-5'), 178.0 (C-3'); m/z (%): 381 (M^++ 2, 96), 379 (M^+, 100).

Preparation of Imidazolium Salts 30.

A mixture of **29** (0.88 mmol), potassium hydroxide (0.050 g, 0.88 mmol) and anhydrous methanol (50 ml) was refluxed for 1 h. After cooling, an excess of dimethyl sulfate (3 ml) was added and the resultant solution was stirred at room temperature for 1 h. The red precipitated solid was filtered and recrystallized from ethanol/water (1:1).

30a: (70%), m.p. 198-200 °C (orange prisms from ethanol/water). (Found: C, 48.83; H, 5.40; N, 9.40. $C_{18}H_{23}N_3O_6S_2$ requires: C, 48.97; H, 5.25; N, 9.52); i.r. (Nujol) 1718 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 2.75 (s, 3H, SCH_3), 3.16 (s, 3H, N_4-CH_3), 3.17 (s, 3H, CH_2OCH_3), 3.22 (s, 3H, N_2-CH_3), 5.68 (s, 2H, CH_2OCH_3), 7.29 (t, 1H, J= 7.5 Hz, H-5), 7.33 (t, 1H, J= 7.8 Hz, H-6), 7.68 (d, 1H, J= 7.8 Hz, H-7), 7.77 (s, 1H, H-8), 7.95 (d, 1H, J= 7.5 Hz, H-4), 8.27 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 12.9 (SCH_3), 26.9 (N_4-CH_3), 53.0 (N_2-CH_3), 55.8 (CH_2OCH_3), 77.5 (CH_2OCH_3), 110.0 (C-3), 111.5 (C-8), 118.5 (C-7), 122.2 (C-4), 123.0 (C-5), 123.6 (C-6), 128.6 (C-3a), 129.8 (C-1'), 135.4 (C-2), 136.2 (C-7a), 159.2 (C-3'), 163.6 (C-5'); m/z (%): 330 (M^+, 2), 315 (100).

30b: (72%), m.p. 187-189 °C (orange prisms from ethanol/water). (Found: C, 41.38; H, 4.39; N, 7.94. $C_{18}H_{22}N_3O_6S_2Br$ requires: C, 41.54; H, 4.26; N, 8.07); i.r. (Nujol) 1714 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 2.75 (s, 3H,

SCH_3), 3.08 (s, 3H, N_4-CH_3), 3.18 (s, 3H, CH_2OCH_3), 3.25 (N_2-CH_3, s, 3H), 5.60 (s, 2H, CH_2OCH_3), 7.13 (s, 1H, H-8), 7.33 (d, 1H, J= 8.4 Hz, H-5), 7.83 (s, 1H, H-7), 8.24 (d, 1H, J= 8.4 Hz, H-4), 8.39 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 12.6 (SCH_3), 26.3 (N_4-CH_3), 55.6 (N_2-CH_3), 55.7 (CH_2OCH_3), 77.1 (CH_2OCH_3), 111.6 (C-3), 113.8 (C-8), 115.4 (C-7), 115.9 (C-6), 122.2 (C-4), 124.2 (C-5), 126.5 (C-3a), 135.2 (C-1'), 135.7 (C-2), 137.2 (C-7a), 162.1 (C-3'), 168.3 (C-5'); m/z (%): 411 (M^++ 2, 3), 409 (M^+, 2), 395 (100).

Preparation of N-Methoxymethyl 3'-deimino-3'-oxoaplysinopsins 31.

A mixture of the appropriate imidazolium salt **30** (0.5 mmol), potassium hydroxide (0.11 g, 2 mmol), ethanol (25 ml) and water (25 ml) was refluxed for 12 h. After cooling, the solvent was removed and the residue was recrystallized from methanol.

31a: (63%); m.p. 273-274 °C (yellow prisms). (Found: C, 64.04; H, 5.88; N, 13.87. $C_{16}H_{17}N_3O_3$ requires: C, 64.20; H, 5.72; N, 14.04); i.r. (Nujol) 1748 and 1714 cm^{-1}; ^1H n.m.r. δ (DMSO-d_6): 2.98 (s, 3H, N_4-CH_3), 3.22 (s, 3H, CH_2OCH_3), 3.60 (s, 3H, N_2-CH_3), 5.55 (s, 2H, CH_2OCH_3), 6.83 (s, 1H, H-8), 7.21 (t, 1H, J= 7.5 Hz, H-5), 7.29 (t, 1H, J= 7.8 Hz, H-6), 7.62 (d, 1H, J= 7.8 Hz, H-7), 7.84 (d, 1H, J= 7.5 Hz, H-4), 8.31 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 24.2 (N_4-CH_3), 29.4 (N_2-CH_3), 55.9 (OCH_3), 77.3 (CH_2), 101.6 (C-8), 108.7 (C-3), 110.8 (C-7), 118.6 (C-4), 121.1 (C-5), 123.0 (C-6), 123.5 (C-3a), 127.8 (C-1'), 130.3 (C-2), 135.9 (C-7a), 155.0 (C-3'), 164.0 (C-5'); m/z (%): 300 (M^++ 1, 6), 299 (M^+, 39), 45 (100).

31b: (65%), m.p. 293-295 °C (yellow prisms). (Found: C, 50.68; H, 4.37; N, 10.97. $C_{16}H_{16}N_3O_3Br$ requires: C, 50.81; H, 4.20; N, 11.11); i.r. (Nujol) 1757, 1715 cm^{-1}; ^1H n.m.r δ (DMSO-d_6): 2.85 (s, 3H, N_4-CH_3), 3.19 (s, 3H, CH_2OCH_3), 3.56 (s, 3H, N_2-CH_3), 5.54 (s, 2H, CH_2OCH_3), 6.24 (s, 1H, H-8), 7.24 (d, 1H, J= 8.5 Hz, H-5), 7.76 (d, 1H, J= 8.5 Hz, H-4), 7.77 (s, 1H, H-7), 8.25 (s, 1H, H-2); ^{13}C n.m.r. δ (DMSO-d_6): 24.2 (N_4-CH_3), 29.4 (N_2-CH_3), 55.5 (OCH_3), 76.9 (CH_2), 94.6 (C-8), 113.0 (C-3), 113.1 (C-7), 114.8 (C-6), 120.6 (C-4), 122.7 (C-5), 127.9 (C-3a), 130.2 (C-2), 136.6 (C-1'), 140.0 (C-7a), 161.9 (C-3'), 169.2 (C-5'); m/z (%): 380 (M^++ 2, 44), 378 (M^+, 46), 45 (100).

General Procedure for Deprotection of Compounds 23, 24, 27 and 31.

A solution of the appropriate N-methoxymethyl indole **23**, **24**, **27** or **31** (2 mmol) in 85% formic acid (15 ml) was heated at reflux temperature for 48 h. After cooling the formic acid was removed under reduced pressure. The residual material was treated with a solution of triethylamine (5 ml) in tetrahydrofuran (20 ml). The formed solid was filtered and chromatographed on a silica gel column using dichloromethane/ethanol (4:1) as eluent.

2'-Demethyl aplysinopsin **2** (48%), m.p. 236-237 °C (lit.[4] m.p. 235 °C).

2'-Demethyl-3'-methylaplysinopsin **3** (50%), m.p. 251-253 °C (lit.[5] m.p. 250° C).

3'-Deimino-3'-oxoaplysinopsin **4** (52%), m.p. 280-282 °C (lit.[6] m.p. 281-282 °C).

3'-Deimino-2',4'-bis(demethyl)-oxoaplysinopsin **5** (46%), m.p. 301-303 °C (lit.[6] m.p. 300 °C).

6-Bromo-2'-demethyl aplysinopsin **7** (46%), m.p. 187-190 °C (lit.[4] m.p. 186-188 °C).

6-Bromo-2'-demethyl aplysinopsin **8** (50%), m.p. 282-284 °C (lit.[5] m.p. 280 °C)

6-Bromo-3'-deimino-3'oxoaplysinopsin **9** (50%), m.p. 301-303 °C (lit.[6] m.p. 300 °C).

6-Bromo-3'-deimino-2',4'-bis(demethyl)-3'-oxoaplysinopsin **10**, m.p. 299-300 °C (lit.[6] m.p. 300 °C).

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References.

1. Baker, J.T.; Wells, R.J. in "Natural Products as Medicinal Agents" Eds. J.L. Beal and Reinhardt, Hippokrates Verlag, Stuttgart, **1981**, pp 299-303.
2. Kazlauskas, R.; Murphy, P.T.; Quinn, R.J.; Wells, R.J. *Tetrahedron Lett.*, **1977**, 61.
3. Lollenbeak, K.H.; Schmitz, F.J. *Lloydia*, **1977**, *10*, 480.
4. Djura, P.; Faulkner, O.J. *J. Org. Chem.*, **1980**, *45*, 735.
5. Guella, G.; Mancini, I.; Zibrowius, H.; Pietra, F. *Helv. Chim. Acta*, **1989**, *72*, 1444.
6. Guella, G.; Mancini, I.; Zibrowius, H.; Pietra, F. *Helv. Chim. Acta*, **1988**, *71*, 773.
7. Fattorusso, E.; Lauzotti, V.; Magno, S.; Novellino, E. *J. Nat. Prod.*, **1985**, *48*, 924.
8. Scheuer, P.J. *Pure Appl. Chem.*, **1982**, *54*, 1907.
9. Dalkafouki, A.; Ardisson, J.; Kunesch, N.; Lacombe, L.; Poisson, J.E. *Tetrahedron Lett.*, **1991**, 5325.
10. Molina, P.; Vilaplana, M.J.; Pérez, J. *Tetrahedron*, **1991**, *47*, 4175 and references cited therein.
11. Molina, P.; Alajarín, M.; Vidal, A.; Foces-Foces, M.C.; Hernández-Cano, F. *Tetrahedron*, **1989**, *45*, 4263.
12. Molina, P.; Fresneda, P.M. *J. Chem. Soc. Perkin Trans 1*, **1988**, 1819.
13. Moody, C.J.; Ward, J.G. *J. Chem. Soc. Perkin Trans 1*, **1984**, 2903.
14. Dellar, G.; Djura, P.; Sargent, M.V. *J. Chem. Soc. Perkin Trans 1*, **1981**, 1679.
15. Fresneda, P.M.; Jones, R. A.; Voro, T.N. *Synth. Commun.*, **1990**, *20*, 2011.

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