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Investigative Studies on the Formation of the Imidazo [4',5':3,4]pyrido[2,3-b]indole Ring: Formal Synthesis of the Alkaloids Grossularines-1 and 2. X-Ray Crystal Structures of 5-Indol-3-yl-imidazole and Bisimidazo-carbazole Derivatives.

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Abstract

Reactions of several 2,3-disubstituted indoles, bearing a chlorine or amino function at position 2 and an 1,2-dicarbonyl group or bromoacetyl substituent at position 3, with N,N-dimethylguanidine is reported. In general, 5-indol-3-yl imidazole derivatives are found to be the reaction products, however when the 3-bromoacetyl-2-tertbutoxycarbonylaminoindole is used the 2-dimethylamino-4-hydroxy-6-methoxymethyl-3H-imidazo[4',5':3,4]pyrido[2,3-b]indole is obtained through a step-wise formation of the pyridine and the imidazole rings. The crystal molecular structure of **5**.H_2O and **7**.HBr.H_2O.3/2 EtOH have been determined by X-Ray analysis. The water molecules in **5**. H_2O act as both donor (O-H...N) and acceptor (N-H...O) and are responsible for the formation of strands along the b axis.

Keyword: *Indoles, imidazoles, imidazolines, sponges, X-Ray crystal structures*

Marine organisms are among the most promising sources of new and biologically active molecules. Certain secondary metabolites are non-traditional guanidine-based alkaloids[1] that possess a broad spectrum of powerful biological activities. The guanidine moiety is most frequently found in the guise of a 2-aminoimidazole ring that is generally substituted with alkyl groups on carbon or nitrogen.[2-8]

Marine alkaloids grossularines, possessing a cyclic guanidine moiety in the form of 2-dimethylaminoimidazole subunit, were isolated in 1984 from the marine tunicate *Dendrodoa grossularia* (Stylidae) collected in the coast of Brittany.[9-10] These compounds, which are

Dedicated to Prof. Alan R. Katritzky for his important contribution to Organic Chemistry

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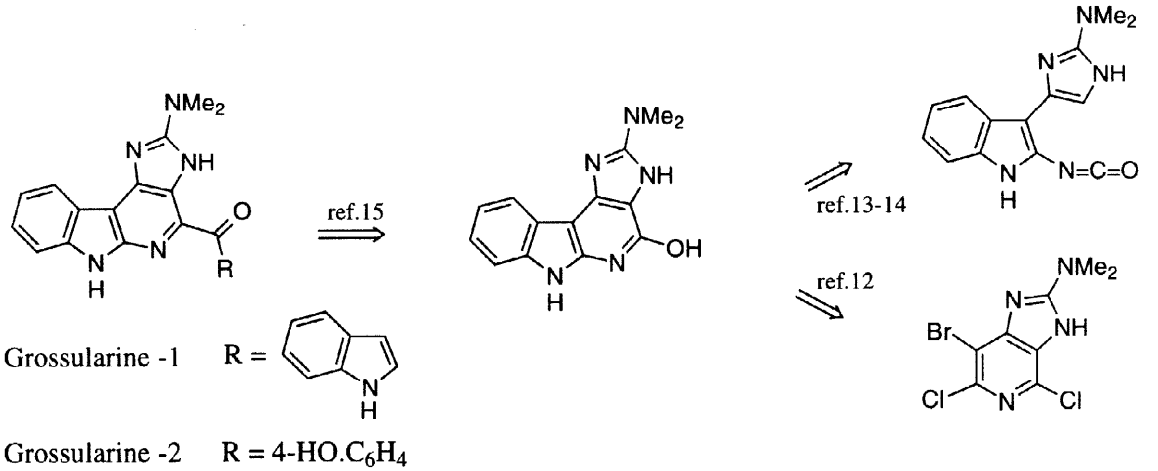
the first examples of naturally ocurring pyrido[2,3-b]indoles (α-carbolines), exhibit marked cytotoxicity toward murine and human tumor cells.[11]



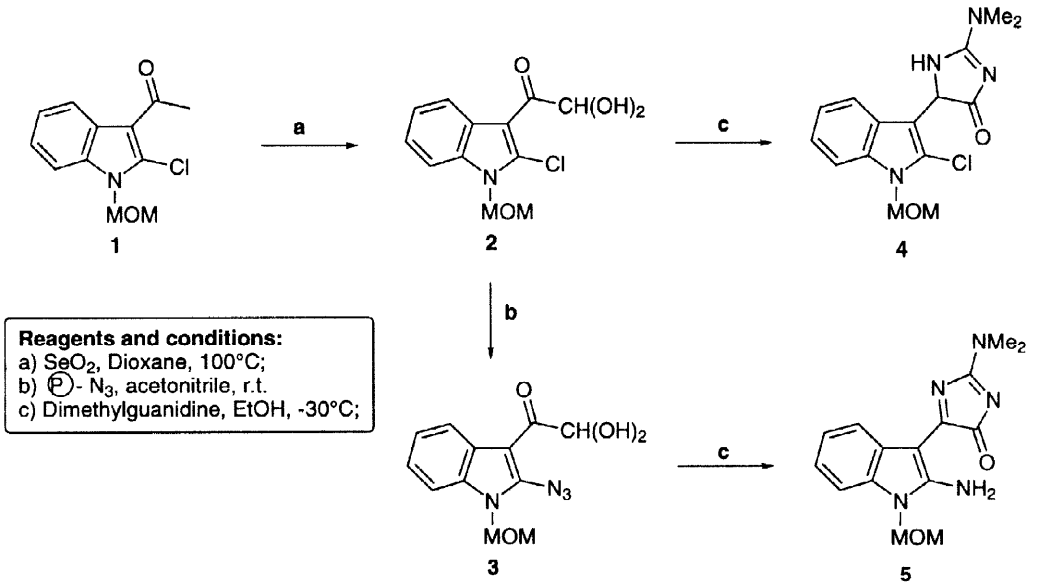
Recently, two approaches have been developed for the construction of the tetracyclic imidazo[4',5':3,4]pyrido[2,3-b]indole framework of the titled compounds. The first is based on the palladium-catalyzed cross coupling between the appropriately substituted imidazo[4,5-c]pyridine and a stannane aniline followed by base-promoted intramolecular cyclization of the resulting biaryl compound to construct the α-carboline ring system.[12]

In the second approach, the formation of the α-carboline ring is based on the thermal electrocyclic ring-closure of a 2-azahexatriene system, including the indole 2,3-bond and the imidazole 4,5-bond. The starting material 3-imidazolylindole derivative was prepared by cross-coupling reaction between 3-iodoindole-2-carboxylate and the directed metallation-derived imidazole followed by hydrolysis of the ester group and further Curtius rearrangement with diphenyl phosphorazidate (DPPA).[13-14] In the first total synthesis of grossularines, the tetracyclic ring system was elaborated into the target compounds through a sequence involving triflate formation and subsequent arylation by way of the Stille or Suzuki cross-coupling methodologies with or without carbon monoxide insertion.[15]

Following our programme directed toward the synthesis of imidazole-containing alkaloids from marine origin,[16-18] we wish to report an efficient synthesis of the 2-dimethylamino-4-hydroxy-6-methoxymethyl-3H-imidazo[4',5':3,4]pyrido[2,3-b]indole, successfully used in the above mentioned synthesis of the alkaloids grossularines-1 and 2. Our approach is based on the sequential formation of the imidazole and pyridine rings starting from a 2,3-disubstituted indole possessing suitable functionalities. In this sense, the substituent at position 3 of the starting indole must be suitable to build-up the desired 2-dimethylaminoimidazole ring, whereas the pyridine ring could be formed by cyclization of the appropriate nitrogen functionality at position 2 onto the preformed imidazole ring and thus completing the assemblage of the gross ring system of the target molecule.

A survey of the literature reveals that classical methods for the preparation of 2-aminoimidazole derivatives involve condensation of α-aminocarbonyl compounds with

cyanamide,[19-22] reaction of α-dicarbonyl compounds with guanidine followed by reduction,[23-24] and reaction of α-haloketones with N-acetylguanidine.[7]



Scheme1

Thus, we initially required a N-protected 2,3-disubstituted indole and the starting material of choice was the N-methoxymethyl-3-acetyl-2-chloroindole **1**, which was prepared in 85% yields from 3-acetyl-2-chloroindole[25] and methoxymethyl chloride in the presence of sodium hydride. Oxidation of compound **1** with selenium dioxide afforded the 3-indolylglyoxal hydrate **2** in 96% yield which was converted into the corresponding azide **3** in 80% yield by treatment with polymeric quaternary ammonium azide.[26] The reaction of **2** and **3** with N,N-dimethylguanidine in ethanol at -30°C gave **4** (91%) and **5** (95%) respectively. The unexpected formation of the aminocompound **5** possessing an unusual 4H-imidazol-4-one ring could be understood by initial formation of an intermediate 3-indolyl dihydroimidazolone like **4** which under the reactions conditions underwent dehydrogenation of the dihydroimidazole ring with concomitant reduction of the azido group to give **5**. It is noteworthy that the inmuno-modulating 2-(dimethylamino)-5-(1H-indol-3-yl)-4H-imidazol-4-one has been isolated from *Dendrodoa grossularia* [27] and represents the first naturally ocurring member of the 4H-imidazol-4-one ring.

Suitable crystals of **5** allowed an X-Ray structure analysis. The monohydrate of **5**, as it exists in the solid state, is depicted in Fig.1a together with the numbering scheme. As far as we know [Cambridge Structural Database[28] (October 1997 release; CSD hereinafter)], it is noteworthy that it is the first time that the crystal structure of an imidazol-4-one ring is reported (Fig. 1, Table 1). The N4-C11 bond shows double-bond character while a certain degree of electron delocalization is observed in the other N-C bonds. The N atoms of the amino groups (N2 and N5) are sp^2 hybridized (Table 1). A strong intramolecular hydrogen bond (Table 1) is found between one N-H group and O=C one of the five-membered ring (Fig. 1a) that cause remarkable variation, mainly, in the bond distances and angles of the

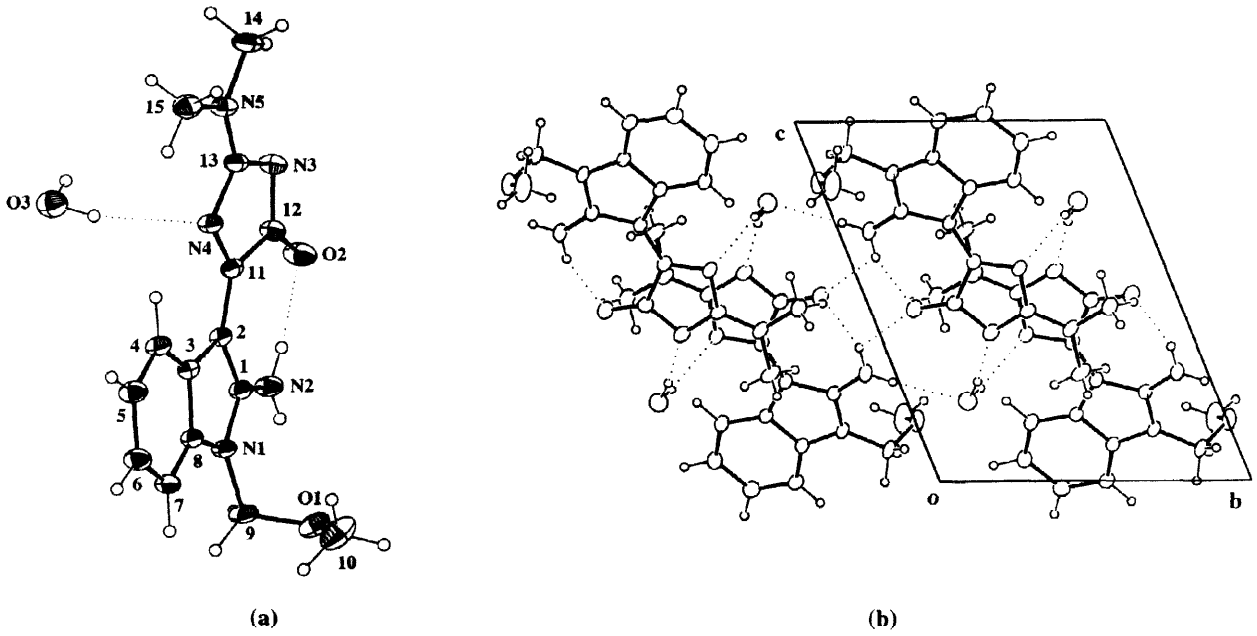


Fig. 1.- (a) Displacement ellipsoid plot (30% probability level) of **5**.H_2O showing the atom-numbering. (b) A view of one hydrogen-bonded strand of dimers along the **b** axis. Dotted lines represent hydrogen bond interactions.

Table 1. Selected geometrical parameters (Å,°) for compound **5**.H_2O.

N1-C1	1.363(3)	N1-C8	1.406(3)	N1-C9	1.461(4)
N2-C1	1.312(3)	C1-C2	1.442(3)	C2-C3	1.457(2)
C3-C8	1.408(3)	C2-C11	1.396(3)	C11-C12	1.527(2)
N3-C12	1.354(4)	N3-C13	1.353(3)	N4-C13	1.382(3)
N4-C11	1.338(3)	C12-O2	1.232(3)	C13-N15	1.324(4)
N5-C14	1.458(3)	N5-C15	1.454(3)		
C8-N1-C1	110.2(2)	C8-N1-C9	125.3(3)	C1-N1-C9	124.2(2)
N1-C1-C2	108.6(2)	N1-C1-N2	122.2(2)	C2-C1-N2	129.2(2)
C1-C2-C3	105.7(2)	C1-C2-C11	128.9(2)	C3-C2-C11	125.3(2)
C2-C3-C8	107.5(2)	C3-C8-N1	107.9(2)	N4-C11-C12	108.0(2)
C11-C12-N3	107.2(2)	C11-C12-O2	127.0(2)	N3-C12-O2	125.9(2)
C12-N3-C13	103.8(2)	N3-C13-N4	117.7(2)	C13-N4-C11	103.3(2)
N3-C13-N5	122.3(2)	N4-C13-N5	120.0(2)	C13-N5-C14	121.4(2)
C13-N5-C15	122.1(2)	C14-N5-C15	116.6(2)		
C8-N1-C9-O1	68.7(3)	C14-N5-C13-N3	2.1(4)	C1-C2-C11-C12	-3.3(4)
N1-C9-O1-C10	68.6(3)	C15-N5-C13-N4	3.8(3)		

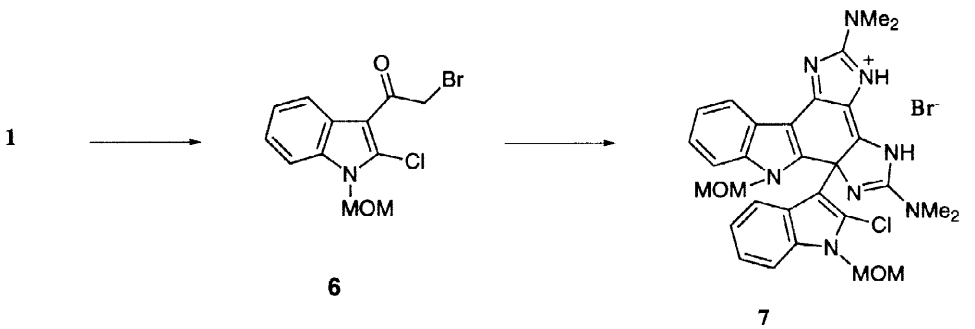
Hydrogen interactions

X-H...Y	X-H	X...Y	H...Y	X-H...Y
N2-H21...O1	0.82(4)	3.211(3)	2.83(3)	111(3)
N2-H21...O3(x,y-1,z)	0.82(4)	3.042(3)	2.23(4)	174(3)
N2-H22...O2	0.88(3)	2.712(3)	1.91(4)	151(3)
N2-H22...O2(-x,-y,1-z)	0.88(3)	3.034(2)	2.46(3)	124(3)
O3-H31...N3(-x,1-y,1-z)	0.92(3)	2.854(2)	1.94(3)	170(5)
O3-H32...N4	0.93(5)	3.141(3)	2.28(4)	153(3)
C4-H4...N4	0.99(3)	3.050(3)	2.45(2)	119(2)

pseudo-seven-membered ring formed. The C2-C11, C1-C2 and C2-C3 bonds are significanly elongated as compared to the Csp^2-Csp^2 value[29] [C=C-C(=O)-C=C: 1.478(31Å, the sample standard deviation being in parenthesis] and to the average values corresponding to 47 N-indole derivatives retrieved from CSD [1.371(39) and 1.437(11)Å for C1-C2 and C2-C3 respectively]. The external angles at C1, C2 and C11, that correspond to the internal angles in the pseudo-seven-membered ring are widened and the differences between the two external angles at each atom are highly significant (Table1). The indole and the imidazole systems are almost coplanar aided by the intramolecular interactions.

As illustrated in Fig. 1b, the water molecules link molecules of **5** to form dimers related by inversion centres that are further joined through N-H...OH_2 and N-H...O=C bonds to give strands along the **b** axis.

All attemps to reduce the dihydroimidazolone ring in compound **4** with a wide variety of reagents ($NaBH_4$ / $TiCl_4$; $NaBH_4$ / ^tBuOOH; $BH_3.SM_2$; H_2 / Pd/C; $LiAlH_4$ / Et_2O; $NaBH_4$ / CH_3SO_3K / DMSO; DIBAL-H) were unsuccessful and complex mixtures were obtained. Unfortunately, the treatment of compound **5** with the same reagents led to the unchanged starting material.



Reagents and Conditions: a) Br_2, Et_2O,$AlCl_3$, 0°C→ r.t.; b) DMG, Et_3N, DMF, 0°C→ r.t.

Scheme 2

These frustrating results led us to select a less oxidizable substituent at position 3. To this end, bromination of indole derivative **1** in the presence of $AlCl_3$ at 0°C provide the 2-bromoacetyl-3-chloroindole **6** in 75% yield. When an ethanolic solution of **6** was treated with N,N-dimethylguanidine at room temperature the bisimidazocarbazole derivative **7** was obtained in 60% yield in almost pure form, instead of the expected 5-(3-indolyl)imidazole (Scheme 2). An X-ray structure determination confirmed the proposed structure. (Fig 2, Table 2).

It was tempting to speculate about the mechanism for the conversion **6**→**7**. A tentative mechanism could involve initial formation of the enamine **8** which undergoes alkylation by action of the second equivalent of **6** to give **9** which, by loss of HBr, led to the 1-azadiene **10**. An intramolecular Michael addition takes place to give **11** which undergoes cyclization across the tautomeric form **12** to afford the bisimidazolyl **13**. Dehydrogenation followed by intramolecular nucleophilic displacement of the chlorine atom at position 2 of the indole

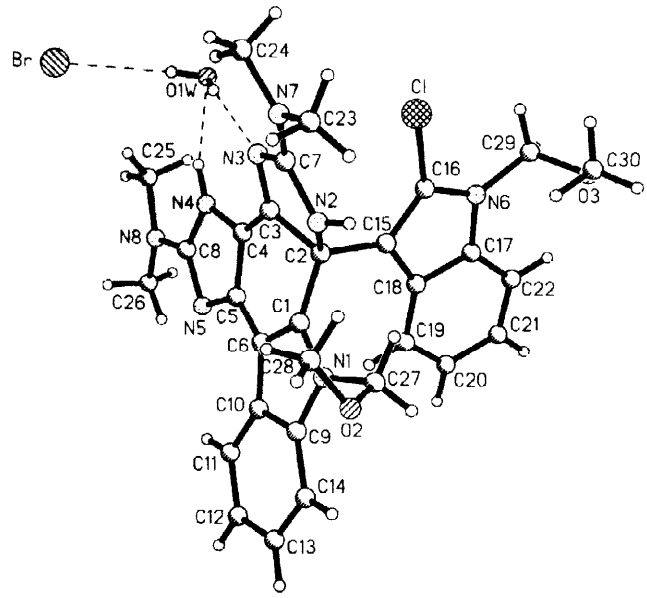


Fig. 2.- Structure of $7.H_2O$. 3/2 CH_3CH_2OH showing the atom numbering scheme. Ethanol molecules have been omitted for clarity.

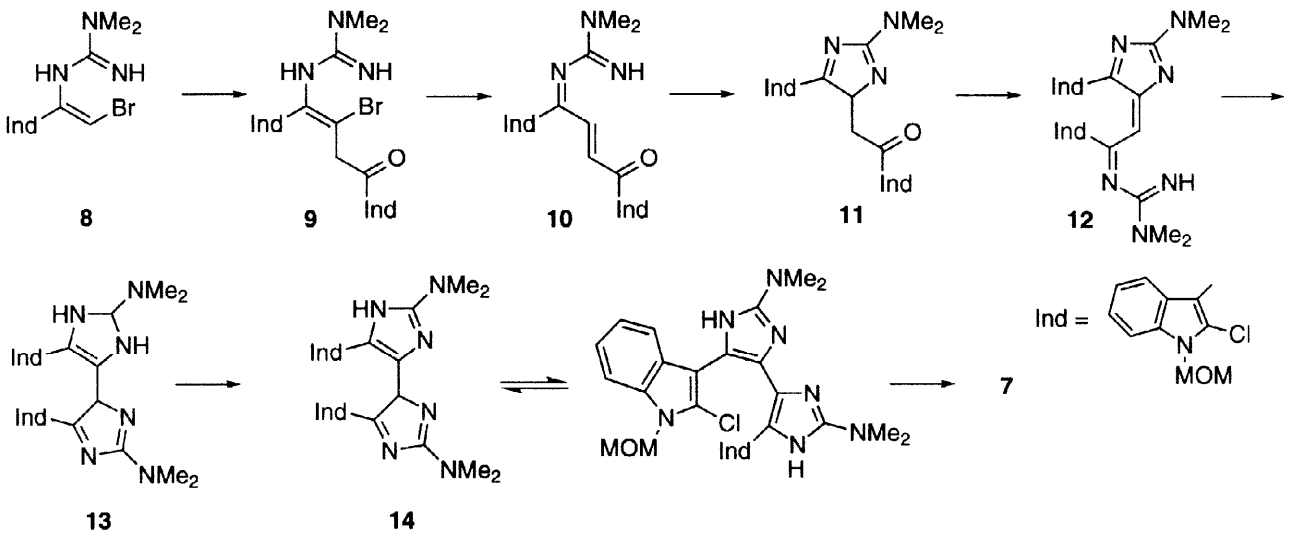
Table 2. Selected bond lengths [Å] and angles [°] for $7 \cdot H_2O \cdot 3/2CH_3CH_2OH$

Cl-C16	1.737(4)	N1-C1	1.373(5)	N1-C9	1.398(5)
N2-C7	1.380(5)	N2-C2	1.477(5)	N3-C3	1.347(5)
N3-C7	1.361(5)	N4-C8	1.355(5)	N4-C4	1.390(5)
N5-C5	1.352(5)	N5-C8	1.370(5)	N7-C7	1.300(5)
N7-C23	1.447(6)	N7-C24	1.450(6)	N8-C8	1.330(5)
N8-C25	1.452(6)	N8-C26	1.458(5)	C1-C6	1.378(5)
C1-C2	1.514(6)	C2-C3	1.539(5)	C2-C15	1.546(5)
C3-C4	1.360(5)	C4-C5	1.405(6)	C5-C6	1.443(6)
C6-C10	1.421(6)	C15-C16	1.385(6)		
C1-N1-C27	128.9(3)	C8-N8-C25	118.4(3)	N7-C7-N2	123.9(4)
C9-N1-C27	122.4(3)	C7-N2-C2	107.8(4)	N3-C7-N2	113.6(4)
C3-N3-C7	105.6(3)	C8-N4-C4	106.4(3)	N8-C8-N4	122.3(4)
C5-N5-C8	103.9(3)	C16-N6-C17	107.2(3)	N8-C8-N5	124.9(4)
C16-N6-C29	128.9(4)	C17-N6-C29	123.6(3)	N4-C8-N5	112.7(3)
C7-N7-C23	121.9(4)	C7-N7-C24	120.9(4)	C14-C9-N1	129.4(4)
C8-N8-C26	119.8(4)	C29-O3-C30	112.7(3)	N1-C9-C10	108.0(4)
N1-C1-C6	109.0(3)	N1-C1-C2	127.6(3)	C11-C10-C6	134.6(4)
C6-C1-C2	122.6(4)	N2-C2-C1	117.2(4)	C14-C13-C12	121.2(4)
N2-C2-C3	98.0(3)	C1-C2-C3	109.0(3)	N6-C17-C18	109.1(3)
N2-C2-C15	112.4(3)	C1-C2-C15	110.3(3)	C16-C15-C2	126.6(3)
C3-C2-C15	109.0(3)	N3-C3-C4	129.4(4)	C18-C15-C2	128.0(3)
N3-C3-C2	111.9(3)	C4-C3-C2	118.6(3)	C15-C16-Cl	130.5(3)
C3-C4-N4	132.1(4)	C3-C4-C5	121.5(4)	N6-C17-C22	127.8(4)
N4-C4-C5	105.1(3)	N5-C5-C4	111.7(4)	C19-C18-C15	136.5(4)
N5-C5-C6	128.2(4)	C4-C5-C6	119.8(4)	C17-C18-C15	106.3(4)
C1-C6-C5	118.9(4)	C12-C11-C10	118.0(4)	O2-C27-N1	113.2(3)
C10-C6-C5	133.0(4)	N7-C7-N3	122.4(4)		

Hydrogen bonds.

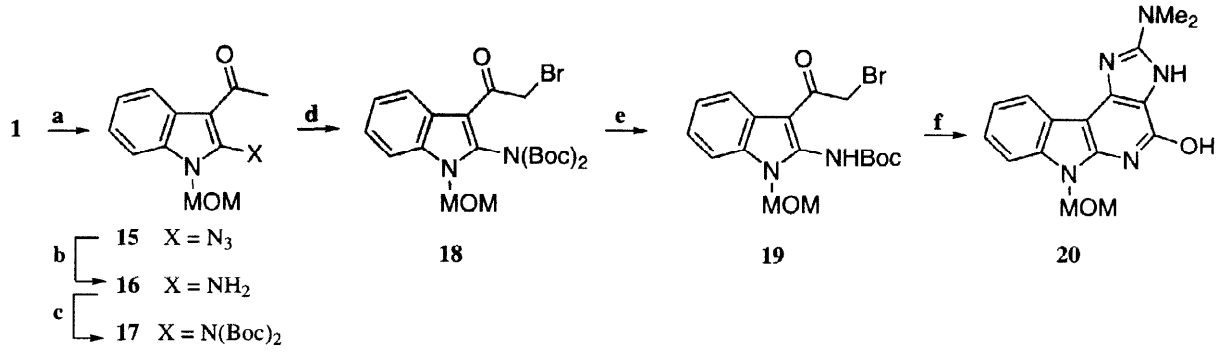
X-H...Y	X...Y	H...Y	XHY
O1W-H01...Br	3.274(3)	2.42(4)	162.2(4.9)
O1W-H02...N3	2.905(5)	2.14(5)	140.2(4.9)
N4-H4...O1W	2.805(5)	2.02(1)	147.6(0.1)
N2-H03...Br (x-1, y, z)	3.447(4)	2.66(5)	172.57(4.9)

by the enamine-vinylogous system provided the final product. Another plausible pathway would involve formation of the expected 5-(3-indolyl)imidazole which undergoes cyclodimerization through a Diels-Alder reaction, whereby the C=C double bond of the indole ring and the C=C double bond of the imidazole ring at position 3 functions as a diene, and the C=C double bond of the imidazole ring of the other molecule has taken the role of dienophile. Loss of HCl from the cycloadduct, followed by an oxidative aromatization, furnishes **7**.(Scheme 3).



Scheme 3

The behaviour of indole **6** towards N,N-dimethylguanidine led us to reexamine the reaction sequence. Conversion of **1** into the azidoindole **15** was performed in 65% yield by reaction with sodium azide in DMSO at 45°C. Staundinger reaction of **15** with triphenylphosphine in diethyl ether at room temperature, and further treatment with THF/H_2O in the presence of catalytic amounts of hydrochloric acid provided **16** in 85% yield. Treatment of **16** with $(Boc)_2O$/DMAP at room temperature afforded **17** in 70% yield. Bromination of compound **17** in methanol gave **18** in 84% yield, which by treatment with trifluoroacetic acid in dichloromethane at room temperature provided **19** in 81% yield. However, when compound **17** was treated with Br_2 in chloroform at 50°C underwent bromination with concomitant N-Boc deprotection to give directly **19** in 70% yield. The reaction of **19** with N,N-dimethylguanidine in ethanol at room temperature directly provided **20** in 80% yield.



Reagents and Conditions: a) NaN_3, DMSO, 45°C, 65 %; b) Ph_3P, Et_2O, r.t. then THF, H_2O, HCl, r.t.; c) $(Boc)_2O$, DMAP, r.t.; d) Br_2, MeOH,DMF, r.t.; e) CF_3COOH, CH_2Cl_2, 50°C→ r.t. f) DMG, EtOH, r.t.

Scheme 4

Taking into account that a) the formation of isocyanates from carbamates usually requires either strong acid conditions or high temperatures[30] and b) in the previously reported synthesis[15] the electrocyclization of the isocyanate group at position 2 onto the preformed imidazole at position 3 to give the pyridine ring is carried out at high temperature, we reasonably thought that the conversion **19→20** does not involve the formation of the intermediate isocyanate. A tentative mechanism for this conversion could involve initial formation of a dihydropyridone ring by nucleophilic attack of the enolate ion derived from the bromoacetyl substituent at position 3 on the carbamate group at position 2 and further formation of the imidazole ring accross the remaining α-bromocarbonyl moiety.

Formation of compound **20** constitutes a formal total synthesis of grossularines-1 and -2, since **20** may be easily converted into the target molecules in a straightforward manner.

EXPERIMENTAL SECTION

General Methods.

All melting points were determined on a Kofler hot-plate melting point aparatus and are uncorrected. IR spectra were obtained as Nujol emulsion or films on a Nicolet Impact 400 spectrophotometer. NMR spectra were recorded on a Bruker AC200 (200MHz) or a varian Unity 300 (300MHz). Mass spectra were recorded on a Hewlett-Packard 5993C spectrometer or a Fisson AUTOSPEC5000 VG. Microanalyses were performed on a Perkin Elmer 240C instrument.

X-ray Analysis.- A summary of data collection and refinement process is given in Table 3. The structure of **5**.H_2O was solved by direct methods (SIR92)[31] and refined by least-squares procedures. All hydrogens were obtained from difference Fourier synthesis and refined isotropically in the last cycles. Scattering factors for **5**.H_2O, were taken from the International Tables for X-Ray Crystallography[32] and the calculations were carried out with the XTAL,[33] PESOS[34] and PARST[35] set of programs running on a DEC3000-300X workstation.

Table 3. Crystal analysis parameters.

	5.H_2O	**7.H_2O.3/2CH_3CH_2OH**
Crystal data		
Formula	$C_{15}H_{17}N_5O_2 . H_2O$	$C_{30}H_{32}BrClN_8O_2 . H_2O . 3/2CH_3CH_2OH$
Crystal habit	Orange, prism	Red Block
Crystal size (mm)	0.43 x 0.30 x 0.17	0.62 x 0.20 x 0.13
Symmetry	Triclinic, P-1	Triclinic, P-1
Unit cell determination:	Least-squares fit from 58 reflections ($2.0<\theta<45.0°$)	Least-squares fit from 74 reflections ($11.2<\theta<25.1°$)
Unit cell dimensions (Å,°)	a=8.2372(7)	a=10.7719(14)
	b=8.9473(7)	b=14.178(2)
	c=11.5910(11)	c=14.386(2)
	α=109.079(7)	α=106.680(10)
	β=103.591(10)	β=100.440(10)
	γ=96.509(13)	γ=106.530(8)
Packing: V(Å³), Z	767.7(1), 2	1933.2(5), 2
Dc(g/cm³), M, F(000)	1.373, 317.34, 336	1.270, 739.11, 770
μ(cm^{-1})	8.175	11.78
Experimental data		
Technique	Four circle diffractometer: Seifert XRD3000-S Bisecting geometry. Graphite oriented monochromator. ω/2θ scans. Detector apertures 1 x 1°. 1 min./reflex.	Siemens P4 four circle diffractometer Graphite monochromator. ω scans
Radiation	CuKα	MoKα
Scan width:	1.7°	1.3°
θ_{max}	65°	25°
Temperature (K)	295	173
Number of reflexions:		
Collected	2648	7787
Independent (Rint.)	2446(0.033)	6578 (0.023)
Observed ($2\sigma(I)$ criterion)	1986	6571
Standard reflexions:	2 reflexions every 100 reflect. No variation	3 every 250 reflect. 2% decay
Solution and refinement		
Solution	Direct methods	Direct methods
Refinement:	Fo, full matrix	F^2, full matrix
Secondary extinction ($x10^4$)	0.206(6)	–
Parameters:		
Number of variables	285	396
Number of restraints	–	412
Final <shift/error>	0.005	0.003
H atoms	From difference synthesis	N-H and water difference synthesis, rigid methyls, others riding
Weighting-scheme	Empirical as to give no trends in $<\omega\Delta^2F>$ vs. $<\|Fobs\|>$ and $<\sin\theta/\lambda>$	$w^{-1} = \sigma^2(F^2) + (aP)^2 + bP$, $3P = (2Fc^2 + Fo^2)$ a and b are constants
Max. thermal value (Å²)	U33[C(10)]=0.128(3)	U33(C24)=0.087(5)
Final ΔF peaks and holes(e$Å^{-3}$)	0.20, –0.27	0.646, -0.614
Final R and Rw	0.039, 0.040	0.054, 0.145

The structure of 7.H2O.3/2CH_3CH_2OH was solved by direct methods and refined anisotropically on F^2 (SHELXTL).[36] Hydrogen atoms for the water molecule and the NH group were located in a difference Fourier synthesis and refined with restrained O-H and N-H bond lengths. Other hydrogen atoms were included as rigid methyl groups or using a riding model. The ethanol molecules were not well resolved, one of them being disordered over two sites and ethanol hydrogen atoms were not considered. The final R(F) was 0.0541, for 439 parameters, 4181 observed reflections and 412 restraints (Table 3) to local symmetry and U components of neighbouring light atoms. The scattering factors were taken from International Tables for Crystallography.[37]

N-Methoxymethyl-3-acetyl-2-chloroindole ***1***. To a suspension of sodium hydride (1.06 g, 2.65 mmol) in dry dimethylformamide (30 mL), was added dropwise a solution of 3-acetyl-2-chloroindole (4.32 g, 2.23 mmol) in the same solvent (60 mL). The mixture was stirred at room temperature for 1 h. After this time, the solution was cooled to 0°C and chloromethylmethyl ether (2.13 g, 2.65 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 **1** (85%) m.p. 88-90°C (colourless prisms). ^{1}H n.m.r. (200 MHz $CDCl_3$) δ 2.69 (s, 3H, CH_3O), 3.32 (s, 3H, CH_3O), 5.57 (s, 2H, CH_2O), 7.25-7.35 (m, 2H, H-5 + H-6), 7.35-7.5 (m, 1H, H-7), 8.30-8.4 (m, 1H, H-4). ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 30.9 (CH_3), 56.4 (CH_3O), 74.15 (CH_2O), 109.73 (C-7), 114.3 (C-3), 122.1 and 124.0 (C-5 or C-6), 123.4 (C-4). IR (nujol) ν 1642 (C=O) cm^{-1}. MS: m/z (%) (EI positive) 239 (M+2, 31), 237 (M, 100). Anal. Calcd. for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.09; N, 5.89. Found; C, 60.43; H, 4.95; N, 5.97.

[3-(N-Methoxymethyl)-2-chloroindolyl]glyoxal hydrate ***2***. To a solution of SeO_2 (1.90 g, 16.7 mmol) in H_2O (5 mL) a solution of **1** (2.0 g, 8.4 mmol) in dioxane (40 mL) was added. The resultant solution was heated at 100°C for 24 h and then filtered. The solvent was removed from the filtrate and the crude product was recrystallized from diethyl ether/n-hexane to give **2** (96%) m.p. 96-97°C (oranges prisms) ^{1}H n.m.r. (300 MHz, DMSO-d_6) δ 3.28 (s, 3H, CH_3O), 5.70 (s, 2H, CH_2O), 5.86 (t, 1H, J=8.1 Hz, $CH(OH)_2$), 6.53 (d, 2H, J=8.1 Hz, OH), 7.2-7.4 (m, 2H, H-5 + H-6), 7.72 (d, 1H, 1H, J=8.1 Hz, H-7), 8.24 (dd, 1H, J=7.2, 1.2 Hz, H-4). ^{13}C n.m.r. (75 MHz, DMSO-d_6) δ 56.0 (CH_3O), 74.0 (CH_2O), 87.8 ($CH(OH)_2$), 110.4 (C-3), 110.9 (C-7), 121.4 (C-4), 123.0 and 123.9 (C-5 or C-6), 125.3 (C-3a), 132.0 (C-2), 135.5 (C-7a), 189.2 (C=O). IR (nujol) ν : 3346 (m), 1641(s) cm^{-1}. MS: m/z (%) (FAB positive, NBA) 252 (M-H_2O+H, 67), 222 (100). Anal. Calcd. for $C_{12}H_{12}ClNO_4$: C, 53.44; H, 4.49; N, 5.19. Found: C, 53.57; H, 4.29; N, 5.31.

[3-(N-Methoxymethyl)-2-azidoindolyl]glyoxal hydrate ***3***. A mixture of compound **2** (0.53 g, 1.96 mmol), polymeric azide (9.22 g) and dry acetonitrile (50 mL) was stirred at room temperature for 48 h. The mixture was filtered and the solvent was removed under reduced pressure from the filtrate. The crude product was chromatographed on a silica gel column, with diethyl ether as eluent and then recrystallized from diethyl ether/n-hexane to give **3**

(80%) m.p. 84°C (orange prisms) ^{1}H n.m.r. (200 MHz, DMSO-d_6) δ 3.25 (s, 3H, CH_3O), 5.57 (s, 2H, CH_2O), 5.71 (t, 1H, J= 8Hz, $CH(OH)_2$), 6.62 (d, 2H, J=8 Hz, OH), 7.25-7.31 (m, 2H, H-5, H-6), 7.58-7.65 (m, 1H, H-7), 7.9-8.1 (m, 1H, H-4). ^{13}C n.m.r. (50 MHz, DMSO-d_6) δ 56.1 (CH_3O), 73.0 (CH_2O), 88.9 ($CH(OH)_2$), 104.0 (C-3), 110.8 (C-7), 121.5 (C-4), 122.7 and 123.1 (C-5 or C-6), 123.8 (C-3a), 133.5 (C-7a), 142.1 (C-2), 191.7 (C=O). IR (nujol) ν 3334 (m), 2164 (s), 1640 (s) cm^{-1}. MS: m/z (%) (EI positive) 258 (M-H_2O, 20), 230 (26), 143 (100). Anal. Calcd. for $C_{12}H_{12}N_4O_4$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.29; H, 4.63; N, 20.13.

2-Dimethylamino-5-[3-(N-methoxymethyl)-2-chloroindolyl]-1,5-dihydro-4H-imidazol-4-one ***4***. To a cooled -30°C solution of N,N-dimethylguanidine (0.138 g, 1.58 mmol) in anhydrous ethanol (10 mL) were added glacial acetic acid (1 mL) and a solution of compound **2** (0.40 g, 1.58 mmol) in anhydrous ethanol (10 mL). The resultant mixture was stirred at that temperature for 12 h. Then, it was poured in ice-water and extracted with chloroform (5x15 mL). The combined organic layers were concentrated to dryness and the crude product was chromatographed on a silica gel column using first ethyl acetate/n-hexane (3:2) and then methanol. Concentration to dryness of the methanolic fractions provided **4**. (91%) m.p. 183°C (yellow prisms) ^{1}H n.m.r. (300 MHz, DMSO-d_6) δ 2.96 (s, 3H, CH_3N), 3.15 (s, 3H, CH_3N), 3.23 (d, 3H, J=0.9 Hz, CH_3O), 5.11 (d, 1H, J=0.9 Hz, H-5), 5.55 (d, 1H, J=11.5 Hz, CH_2O) , 5.58 (d, 1H, J=11.5 Hz, CH_2O), 7.09 (dt, 1H, J=7.2, 0.9 Hz, H-6'), 7.20 (d, 1H, J=7.5 Hz, H-7'), 7.24 (dt, 1H, J=7.2, 1,2 Hz, H-5'), 7.63 (d, 1H, J= 8.1 Hz, H-4'). ^{13}C n.m.r. (75 MHz, DMSO-d_6) δ 36.0 (CH_3N), 38.0 (CH_3N), 55.7 (CH_3O), 57.5 (C-5), 73.4 (CH_2O), 108.6 (C-3'), 110.4 (C-7'), 118.1 (C-4'), 120.9 and 122.9 (C-5' or C-6'), 124.75 and 124. 78 (C-3a' or C-2'), 135.8 (C-7a'), 171.25 (C-2), 185.6 (C-4). IR (nujol) ν : 3177(m), 1688 (s), 1602 (s) cm^{-1}. MS: m/z (%) (FAB positive, NBA) 323 (M+2+H, 10), 322 (M+2, 22), 321 (M+H, 54), 286 (M-Cl+H, 4), 285 (M-Cl, 4), 320 (M, 13), 67 (100); (EI positive) 322 (M+2, 1), 320 (M, 3). Anal. Calcd. for $C_{15}H_{17}ClN_4O_2$: C, 56.17; H, 5.34; N, 17.47. Found: C, 56.08; H, 5.43; N, 12.61.

2-Dimethylamino-5-[3-(N-methoxymethyl)-2-aminoindolyl]-4H-imidazol-4-one ***5***. To a cooled -30°C solution of N,N-dimethylguanidine (0.268 g, 3.08 mmol) in anhydrous ethanol (20 mL) was added dropwise a solution of compound **3** (0.85 g, 3.08 mmol) in anhydrous ethanol/dry tetrahydrofuran (1:1) (20 mL). The mixture was stirred at that temperature for 4 h. The solvent was removed under reduced pressure and the residue was recrystallized from tetrahydrofuran/n-hexane (1:1) to give **5** (95%) m.p. 256°C (red prisms) ^{1}H n.m.r. (300 MHz, DMSO-d_6) δ 3.29 (s, 3H,CH_3O), 3.31 (s, 3H, CH_3N), 3.44 (s, 3H, CH_3N), 5.47 (s, 2H, CH_2O), 7.10-7.22 (m, 2H, H-5' + H-6'), 7.28-7.38 (m, 1H, H-7'), 8.28-8.38 (m, 1H, H-4'). ^{13}C n.m.r. (75 MHz, DMSO-d_6) δ 37.0 (CH_3N), 38.1 (CH_3N), 55.7 (CH_3O), 72.1 (CH_2O), 95.6 (C-3'), 109.1 (C-7'), 122.7 (C-5'), 123.1 (C-4'), 123.8 (C-6'), 126.1 (C-3a'), 138.2 (C-7a'), 157.6 (C-2'), 166.1 (C-2), 181.4 (C-4), 183.3 (C-5). IR (nujol) ν 3180 (m), 1663 (m), 1605 (m), 1555 (s) cm^{-1}. MS: m/z (%) (EI positive) 300 (M+1, 6), 299 (M, 34), 99 (100).Anal. Calcd. for $C_{15}H_{17}N_5O_2$: C, 60.19; H, 5.72; N, 23.40. Found: C, 59.93; H, 5.87; N, 23.22.

N-Methoxymethyl-3-bromoacetyl-2-chloroindole **6**. To a mixture of compound **1** (0.35 g, 1.47 mmol), $AlCl_3$ (0.004 g) and dry diethyl ether (20 mL), Br_2 (0.235 g, 1.47 mmol) was slowly added at 0°C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 1 h, and concentrated to *ca.* 10 mL. After cooling, the precipitated solid was collected by filtration and chromatographed on a silica gel column with ethyl acetate/n-hexane (3:2) as eluent to give **6** (75%) m.p. 109-110°C (colourless prisms from ethyl ether/n-hexane). ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 3.34 (s, 3H, CH_3O), 4.55 (s, 2H, CH_2Br), 5.59 (s, 2H, CH_2O), 7.29-7.38 (m, 2H, H-5 + H-6), 7.50-7.41 (m, 1H, H-7), 8.38-8.26 (m, 1H, H-4). ^{13}C n.m.r. (75 MHz, $CDCl_3$) δ 56.5 (CH_2Br), 56.5 (CH_3O), 74.4 (CH_2O), 110.0 (C-7), 111.7 (C-3), 122.2 and 124.5 (C-5 or C-6), 123.8 (C-4), 126.0 (C-3a), 131.1 (C-2), 135.6 (C-7a), 185.7 (C=O). IR (nujol) ν 1641 (C=O) cm^{-1}. MS: m/z (%) (EI positive) 319 (M+4, 19), 318 (M+3, 10), 317 (M+2, 56), 316 (M+1, 9), 315 (M, 48). Anal. Calcd. for $C_{12}H_{11}BrClNO_2$: C, 45.53; H, 3.50; N, 4.42. Found: C, 45.42; H, 3.39; N, 4.61.

Preparation of the Salt 7. To a mixture of N,N, dimethylguanidine (0.063 g, 0.727 mmol), triethylamine (0.073 g, 0.727 mmol) and dry dimethylformamide (15 mL), a solution of compound **6** (0.23 g, 0.727 mmol) in the same solvent (15 mL) was added at 0°C under nitrogen. The resultant mixture was allowed to warm to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the solid residue was washed with water (3x15 mL) and extracted with chloroform (3x20 mL). The combined organic layers were dried over anhydrous $MgSO_4$. Filtration and elimination of the solvent gave a crude product which was chromatographed on a silica gel column using methanol/dichloro methane (1:4) as eluent to give **7** (60%) m.p. 235-240°C (d) (red prisms from acetone) ^{1}H n.m.r. (300 MHz, DMSO-d_6) δ 3.17 (s, 6H, $(CH_3)_2N$), 3.22 (s, 3H, CH_3O), 3.25 (s, 3H, CH_3O), 3.38 (s, 3H, CH_3N), 3.52 (s, 3H, CH_3N), 5.56 (d, 1H, J=12 Hz, CH_2O), 5.60 (d, 1H, J=12 Hz, CH_2O), 5.75 (s, 3H, CH_2O + H-4'), 6.76 (dd, 1H, J=8.2, 7.6 Hz, H-5'), 7.15 (dd, 1H, J=8.2, 7.4 Hz, H-6'), 7.39 (dd, 1H, J=6.7, 6.7 Hz, H-10), 7.43 (dd, 1H, J=7.6, 7.0 Hz, H-9), 7.66 (d, 1H, J=8.4 Hz, H-7'), 7.78 (d, 1H, J=7.5 Hz, H-8), 8.17 (dd, 1H, J=7.3, 1.5, H-11), 9.57 (s, 1H, NH), 11.9 (s, 1H, NH). ^{13}C n.m.r. (75 MHz, DMSO-d_6), 38.0 ($N(CH_3)_2$), 38.6 (1C, $N(CH_3)_2$), 39.3 (1C, $N(CH_2)_3$), 55.5 (CH_3O), 55.9 (CH_3O), 71.9 (C-6a), 73.3 (CH_2O), 74.3 (CH_2O), 105.9 (C-11b), 107.9 (C-3'), 110.9 (C-7'), 112.3 (C-8), 115.4 (q), 117.9 (C-4'), 117.9 (C-4'), 120.9 (C-11), 121.5 (C-5'), 122.7 (C-6'), 122.9 (C-9 + 1C(q)) , 123.3 (q), 124.4 (C-10), 125.4 (q), 135.4 (q), 137.3 (s), 143.4 (q), 158.7 (q), 161.6 (q), 171.0 (q), 174.4 (q). IR (nujol) ν 3478 (m), 3395 (m) 1591 (m), 1463 (s) cm^{-1}.MS: m/z (%) (FAB positive, NBA) 573 (M+2+H,16), 572 (M+1+H,40), 571 (M+H, 100), 570 (M-1+H, 20); HREIMS $C_{30}H_{31}ClN_8O_2$ calcd. 570.2258, found 570.2203. Anal. Calcd. for $C_{30}H_{31}ClN_8O_2$:C, 63.10; H, 5.47; N, 19.62. Found: C, 62.95; H, 5.33; N, 19.51. Suitable crystals for X-ray analysis were obtained by recrystallization from tetrahydrofuran/ ethanol/n-hexane.

N-Methoxymethyl-3-acetyl-2-azidoindole ***15***. To a solution of **1** (1.50 g, 6.3 mmol) in dimethylsulfoxide (30 mL), NaN_3 (1.0 g, 16.6 mmol) was added. The mixture was stirred

at 45°C for 24 h then poured into ice-water and extracted with diethyl ether (4 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$. Filtration and concentration to dryness afforded the crude product, which was chromatographed on a silica gel column using diethyl ether/n-hexane as eluent to give **15** as oil (65%) ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 2.79 (s, 3H, CH_3CO), 3.18 (s, 3H, CH_3O), 5.50 (s, 2H, CH_2O), 7.37-7.25 (m, 2H, H-5 + H-6), 7.5-7.4 (m, 1H, H-7), 7.9-7.8 (m, 1H, H-4). ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 31.1 (CH_3CO), 56.3 (CH_3O), 73.0 (CH_2O), 107.0 (C-2), 110.4 (C-7), 119.9 (C-4), 122.8 and 122.9 (C-5 or C-6), 125.0 (C-3a), 133.4 (C-7a), 140.6 (C-2), 193.3 (C=O). IR ($CHCl_3$) ν : 2140 (s), 1722 (s) 1649 (s) cm^{-1}. MS: m/z (%) (FAB positive, NBA) 245 (M+H, 65). Anal. Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94. Found: C, 58.77; H, 4.72; N, 23.20.

N-Methoxymethyl-3-acetyl-2-aminoindole ***16***. To a cooled 0°C solution of triphenyl phosphine (0.53 g, 2.04 mmol) in dry diethyl ether (10 mL), a solution of compound **15** (0.5 g, 2.04 mmol) in the same solvent (10 mL) was added dropwise under nitrogen. The mixture was allowed to warm to room temperature and stirred for 12 h. After cooling, the precipitated solid was collected by filtration and recrystallized from benzene/n-hexane to give the N-methoxymethyl-2-acetyl-3-(triphenylphosphoranylidene) aminoindole : 0.88 g (90%) m.p. 153-152°C (colourless prisms) ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 2.15 (s, 3H, CH_3CO), 3.24 (s, 3H, CH_3O), 5.62 (s, 2H, CH_2O), 7.0-7.15 (m, 2H, H-5 + H-6) 7.20-7.33 (m, 1H, H-7), 7.34-7.48 (m, 9H, $H_m + H_p$), 7.49-7.57 (m, H-4),7.58-7.72 (m, 6H, H_o). ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 30.0 (CH_3CO), 55.8 (CH_3O), 71.7 (CH_2O), 100.9 (C-3), 108.7 (C-7), 118.4 (C-4), 120.0 (C-6), 121.2 (C-5), 127.2 (C-3a), 128.1 ($^3J_{C-P}$ = 12.8 Hz, C_m), 131.0 ($^4J_{C-P}$= 2.9 Hz, C_p), 132 ($^2J_{C-P}$= 9.9 Hz, C_o), 133.3 ($^1J_{C-P}$= 108.4 Hz, C_i), 133.9 (J_{C-P} = 1.24 Hz, C-7a), 154.0 (J_{C-P} = 10.9 Hz, C-2), 189.3 (C=O). ^{31}P n.m.r. ($CDCl_3$) δ 11.74. IR (nujol) ν :1619 (C=O)cm^{-1}. MS: m/z (%) (EI positive) 480 (M+ 2, 6), 479 (M+1, 32), 478 (M,100).Anal. Calcd. for $C_{30}H_{27}N_2O_2P$: C, 75.30; H, 5.69; N, 5.85. Found: C, 75.18; H, 5.78; N, 5.69.

To a solution of the above mentioned iminophosphorane (1.0 g, 2.1 mmol) in tetrahydrofuran (20 mL), 5% HCl (20 mL) was added. The resultant mixture was stirred at room temperature for 24 h and then concentrated to dryness. A mixture of the remaining solid and 5% HCl (20 mL) was stirred at room temperature for 30 min and then extracted with diethyl ether (2x20 mL). To the aqueous phase, was added 5% NaOH (25 mL) and then extracted with ethyl acetate (3x25 mL). The combined organic layers were dried over anhydrous $MgSO_4$. Filtration, concentration to dryness, and recrystallization from ethyl acetate gave **16** (98%) m. p. 186-188°C (colourless prisms) ^{1}H n.m.r. (200 MHz, DMSO-d_6) δ 2.44 (s, 3H, CH_3CO), 3.23 (s, 3H, CH_3O), 5.47 (s, 2H, CH_2O), 7.01 (ddd, 1H, J=7.8, 7.5, 1.5 Hz, H-6), 7.09 (ddd, 1H, J=7.5, 7.5, 0.9 Hz, H-5), 7.32 (d, 1H, J= 7.5 Hz, H-7), 8.04 (s, 2H, NH_2).^{13}C n.m.r. (50 MHz, DMSO-d_6) δ 29.7 (CH_3CO), 55.3 (CH_3O), 71.5 (CH_2O), 95.7 (C-3), 109.1 (C-7), 117.7 (C-4), 119.9 (C-6), 121.7 (C-5), 125.9 (C-3a), 133.8 (C-7a), 154.1 (C-2), 190.4 (C=O). IR (nujol) ν : 3304 (m), 3277 (m), 1636 (s) cm^{-1}.

MS: m/z (%) (EI positive) 219 (M+1, 6), 218 (M, 51), 143 (100). Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.89; H, 6.35; N, 12.71.

N-Methoxymethyl-3-acetyl-2-di(tertbutoxycarbonyl)aminoindole ***17***. To a cooled at 0°C solution of Boc_2O (2.2 g, 9.2 mmol) in dry tetrahydrofuran (25 mL) a solution of compound **16** (1.0 g, 4.6 mmol) and 4-dimethylaminopyridine (1.12 g, 9.2 mmol) in the same solvent (100 mL) was added dropwise. The resultant solution was stirred at room temperature for 18 h . The solvent was removed under reduced pressure. The solid residue was taken up in diethyl ether (50 mL), washed with 0.1N HCl (20 mL), H_2O (20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under reduced pressure to give a solid, which recrystallized from ethyl acetate/n-hexane gave **17** (85%) m.p. 122-125 (colourless prisms) ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.42 (s, 18H, $((CH_3)_3C)$, 2.54 (s, 3H, CH_3CO), 3.30 (s, 3H, CH_3O), 5.38 (s, 2H, CH_2O), 7.26-7.38 (m, 2H, H-5 + H-6), 7.48-7.56 (m, 1H, H-7), 8.28-8.34 (m, 1H, H-4). ^{13}C n.m.r . (75 MHz, $CDCl_3$) δ 27.8 $((CH_3)_3C)$, 24.6 (CH_3CO), 56.4 (CH_3O), 73.9 (CH_2O), 84.3 $((CH_3)_3C$), 110.1 (C-7), 112.4 (C-3), 122.6 (C-4), 122.9 and 124.0 (C-5 or C-6), 125.0 (C-3a), 134.3 (C-7a), 136.8 (C-2), 149.9 (COO^{t}Bu), 192.8 (C=O). IR (nujol) ν : 1805 (s), 1728 (s), 1640 (s) cm^{-1}. MS : m/z (%) (EI positive) 420 (M+2, 3), 419 (M+1, 21), 418 (M, 100), 218 (91). Anal. Calcd. for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.98; H, 7.38; N, 6.55.

N-Methoxymethyl-3-bromoacetyl-2-di(tertbutoxycarbonyl)aminoindole ***18***. To a heated at 50°C solution of compound **17** (0.1 g, 0.24 mmol) in dry dimethylformamide (10 mL) a solution of Br_2 (0.077 g, 0.48 mmol) in anhydrous methanol (10 mL) was added dropwise. The mixture was stirred at that temperature for 1h and then at room temperature for 12h. After addition of dichloromethane (20 mL), the solution was washed with saturated aqueous $NaHCO_3$ (2x10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. Concentration to dryness yielded a crude material which was chromatographed on a silica gel column with diethyl ether/n-hexane as eluent to give **18** (84%) m.p. 118-120°C (colourless prisms from diethyl ether/n-hexane). ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.40 (s, 18H, $(CH_3)_3C$), 3.27 (s, 3H, CH_3O), 4.41 (s, 2H, CH_2Br), 5.38 (s, 2H, CH_2O), 7.28-7.40 (m, 2H, H-5 + H-6), 7.52-7.60 (m, 1H, H-7), 8.09-7.17 (m, 1H, H-4). ^{13}C n.m.r. (75 MHz, $CDCl_3$) δ 27.7 $((CH_3)_3C)$, 34.2 (CH_2Br), 56.4 (CH_3O), 74.0 (CH_2O), 84.5 $((CH_3)_3C$) , 109.5 (C-3), 110.7 (C-7), 122.0 (C-4), 123.3 and 124.2 (C-5 or C-6), 124.3 (C-3a), 134.2 (C-7a), 138.0 (C-2), 149.6 (COO^{t}Bu), 185.5 (C=O). IR (nujol) ν: 3452 (m), 1798 (s), 1766 (m), 1722 (m), 1675 (s) cm^{-1}. MS : m/z (%) (IE positive) 498 (M+2, 2), 496 (M, 2), 398 (18), 396 (19), 296 (55), 143 (57), 57 (100). Anal. Calcd. for $C_{22}H_{29}BrN_2O_6$: C, 53.13; H, 5.88; N, 5.63. Found: C, 53.18; H, 5.91; N, 5.70.

N-Methoxymethyl-3-bromoacetyl-2-tertbutoxycarbonylaminoindole ***19***.

Method A. To a heated at 50°C solution of compound **17** (0.1 g, 0.24 mmol) in dry chloroform (15 mL) was added a solution of Br_2 (0.038 g, 0.24 mmol) in the same solvent (5 mL). After addition, the solution was stirred at room temperature for 12 h, then washed with saturated aqueous $NaHCO_3$ (10 mL) and water (10 mL). The organic layer was dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the

resulting solid was chromatographed on a silica gel column using diethyl ether/n-hexane (7:3) as eluent to give **19** in 70% yield.

Method B. To a cooled at 0°C solution of compound **18** (0.4 g, 0.80 mmol) in dry dichloromethane (10 mL), trifluoroacetic acid (0.27 g, 2.4 mmol) was added dropwise under nitrogen. After addition, the solution was allowed to warm to room temperature and stirring continued for 2 h. Then, dichloromethane (10 mL) was added and the resultant solution was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the crude product was chromatographed on a silica gel column using diethyl ether/n-hexane (7:3) as eluent to give **19** as oil in 81% yield: ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.44 (s, 9H, $(CH_3)_3C$), 3.03 (s, 3H, CH_3O, 4.39 (s, 2H, CH_2Br), 5.49 (s, 1H, CH_2O), 7.1-7.3 (m, 2H, H-5 + H-6), 7.37-7.46 (m, 1H, H-7), 7.51-7.65 (m, 1H, H-4). ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 27.9 ($(CH_3)_3C$), 35.0 (CH_2Br), 56.2 (CH_3O), 76.5 (CH_2O), 82.6 ($(CH_3)_3C$) , 102.1 (C-3), 118 (C-7), 120.0 (C-4), 122.9 and 123.2 (C-5 or C-6), 123.7 (C-3a), 133.8 (C-7a), 143.9 (C-2), 152.6 (COO^tBu), 187.4 (C=O). IR (nujol) ν : 3268 (m), 1733 (s), 1620 (s) cm^{-1}. MS : m/z (%) (EI positive) 398 (M+2, 33), 396 (M, 34) 296 (75). Anal. Calcd. for $C_{17}H_{21}BrN_2O_4$: C, 51.40; H, 5.33; N, 7.05. Found: C, 51.27; H, 5.21; N, 7.22.

2-Dimethylamino-6-methoxymethylimidazo[4',5':3,4]pyrido[2,3-b]indol-4-one ***20***. To a solution of the indole derivative **19** (0.397 g. 1mmol) in anhydrous ethanol (50 mL) was added dropwise a solution of N,N-dimethylguanidine (0.174 g, 2 mmol) in the same solvent (100 mL) at 0°C under nitrogen. The reaction mixture was allowed to warm at room temperature and stirred for 3 h. The solvent was removed under reduced pressure and the residual material was chromatographed on a silica gel column eluting with dichloromethane /ethanol (9:1) to give **12** (0.25 g, 80%). ^{1}H n.m.r.(300 MHz, DMSO-d_6) δ 3.10 (s, 6H, $(CH_3)_2N$) 3.24 (s, 3H, CH_3O), 5.75 (s, 2H, CH_2O), 7.19 (dt, J=7.5, 7.5, 0.9 Hz, H-9), 7.30 (dt, J=7.5, 7.5, 0.9 Hz, H-8), 7.54 (d, J=8.1 Hz, H-7), 8.12 (d, J=7.5 Hz, H-10). ^{13}C n.m.r. (75 MHz, DMSO-d_6) δ 38.0 $(CH_3)_2N$, 55.6 (CH_3O), 72.0 (CH_2O), 99.4 (q), 109.9 (C-7), 116.0 (q), 119.8 (C-9), 120.7 (C-10), 121.0 (q), 121.9 (q), 122.9 (C-8), 136.9 (q), 148.2 (q), 151.5 (q), 154.6 (q). IR (nujol) ν : 3344(m), 1684(m), 1597(s) cm^{-1}. MS: m/z(%) (FAB positive, NBA) 312 (M+H, 100); (EI positive) 312 (M+1, 23), 311 (M, 100), 280 (49), 266 (22). Anal. Calcd. for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.50; N, 22.49. Found: C, 61.58; H, 5.63; N, 22.60.

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