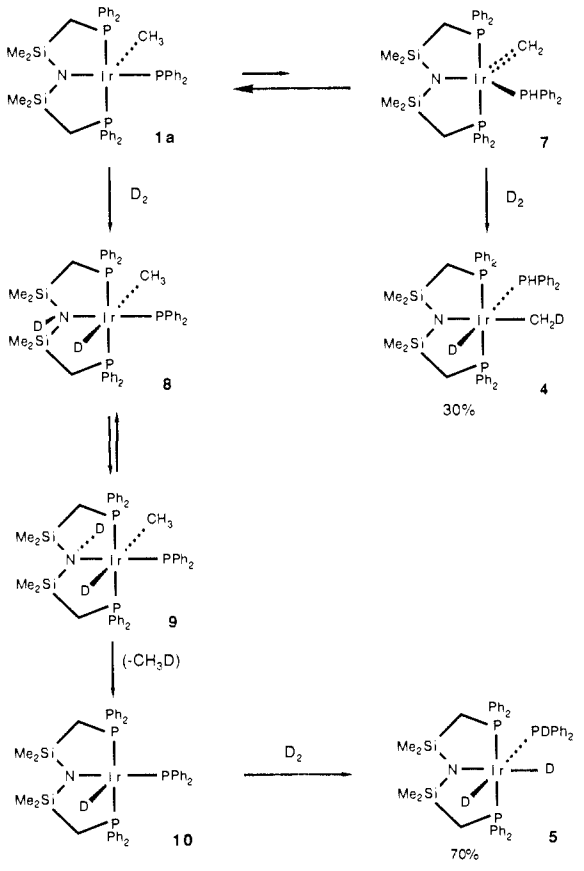
Scheme II



Although we have no evidence for **7** at the present, reaction of D_2 across the iridium–carbon double bond does generate **4**, the correct methyl hydride isotopomer. The sequence of reactions to convert **1a** to the dideuteride **5** is speculative but draws on earlier observations of ancillary ligand involvement in the activation of dihydrogen and aromatic C–H bonds.[16] In particular, addition of D_2 produces the amine deuteride **8** which can rearrange to the isomer **9** by amine dissociation, inversion at nitrogen, and reassociation; elimination of CH_3D from **9** to give the phosphido deuteride **10** followed by addition of D_2 generates the observed major product **5**.

Some preliminary mechanistic studies have been done. It can be shown that the proposed phosphido deuteride **10** does not reductively eliminate to the iridium(I) diphenylphosphine complex $Ir(PDPh_2)[N(SiMe_2CH_2PPh_2)_2]$ prior to D_2 addition since reaction of the perprotio complex $Ir(PHPh_2)[N(SiMe_2CH_2PPh_2)_2]$[17] with H_2 does not yield the *mer*-dihydride **3** but rather *fac*-$Ir(H)_2(PHPh_2)[N(SiMe_2CH_2PPh_2)_2]$ irreversibly. The attempts to prepare the proposed intermediate **7** by either the addition of 1 equiv of $PHPh_2$ to the previously reported methylidene complex, $Ir(=CH_2)[N(SiMe_2CH_2PPh_2)_2]$,[18] or by the reaction of CH_2N_2[19] with $Ir(PHPh_2)[N(SiMe_2CH_2PPh_2)_2]$ have been unsuccessful; in the former reaction, a complex mixture results, while, in the latter, the iridium(I) derivative $Ir(PMePh_2)[N(SiMe_2CH_2PPh_2)_2]$ is the only product. Clearly, neither of these procedures is kinetically feasible for accessing the proposed equilibrium in Scheme II. Further studies are underway to provide additional evidence for the reversible intramolecular proton transfer from an alkyl to a terminal phosphide ligand.

(16) Fryzuk, M. D.; MacNeil, P. A.; McManus, N. T. *Organometallics* **1987**, *6*, 882.

(17) The complex $Ir(PHPh_2)[N(SiMe_2CH_2PPh_2)_2]$ was prepared by addition of $PHPh_2$ to $Ir(\eta^2\text{-}C_8H_{14})[N(SiMe_2CH_2PPh_2)_2]$[12] ($C_8H_{14}$ = cyclooctene).

(18) Fryzuk, M. D.; MacNeil, P. A.; Rettig, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 6708.

(19) Clark, G. R.; Roper, G. R.; Wright, A. H. *J. Organomet. Chem.* **1984**, *273*, C17.

Acknowledgment. We thank NSERC and the Alfred P. Sloan Foundation for financial support. Johnson-Matthey is gratefully acknowledged for a generous loan of $IrCl_3$.

Supplementary Material Available: Experimental details, ^1H and ^{31}P NMR data, elemental analyses, and ^2H NMR spectrum for the reaction of **1a** with D_2 are available (3 pages). Ordering information is given on any current masthead page.

Positive Evidence for Tetrahedral $R'C(OR)_3H^+$ Intermediates in the Gas Phase

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Most acyl-transfer reactions occur in solution via an addition–elimination pathway, involving a tetrahedral intermediate under both acid and base catalysis.[1,2] So far, the role of tetrahedral intermediates has not found a comparable recognition in the gas phase where parallel reactions at the carbonyl group seem to take a different course,[3-5] as shown by ion cyclotron resonance (ICR) spectrometry. The discrepancy between the mechanistic patterns prevailing in solution and in the low-pressure gaseous environment typical of ICR studies poses the question of whether a bridge between such extremes can be found in reaction media of intermediate molecular density. To this purpose, alcoholysis of esters has been examined in the gas phase at atmospheric pressure, exploiting a radiolytic technique which has proved useful in similar problems.[6] The results now reveal close analogies with the addition–elimination pathway prevailing in solution. Furthermore, a suitable choice of reactants has allowed me to quench the ester alcoholysis reaction and to actually obtain orthoesters as neutral end products, thus achieving unequivocal characterization of cationic tetrahedral species as the charged reaction intermediates.

Table I illustrates typical experiments where carboxylic esters have been methylated by the gaseous Me_2F^+ Lewis acid[7] in the presence of an alcohol and occasionally of basic additives. In general, the carbonyl oxygen of esters is the thermodynamically favored site for electrophilic attack, in particular for protonation,[8] although intermediates protonated at the ether oxygen are seen to play a kinetic role.[4,9] The present results, especially the detection of ortho esters, require that a significant fraction of electrophilic methylation occurs at the carbonyl oxygen, either

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(3) Riveros, J. M.; Jose, S. M.; Takashima, K. *Adv. Phys. Org. Chem.* **1985**, *21*, 197.

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Table I. Gas-Phase Formation of Carboxylic Esters Induced by Me_2F^+ Ion Attack on RCO_2R'

entry	system composition[a] (Torr) RCO_2R'	$R''OH$	MeF	product yields[b] (G_{+M})
1	$MeCO_2Et$ (1.3)	MeOH (0.8)	(700)	$MeCO_2Me$ 2.7
2	$MeCO_2Et$ (1.8)	MeOH (1.9)	(700)[c]	$MeCO_2Me$ 0.61
3	$MeCO_2Me$ (0.97)	EtOH (1.05)	(700)	$MeCO_2Et$ 0.21
4	$PhCO_2Me$ (0.80)	EtOH (1.7)	(700)	$PhCO_2Et$ 0.19
5	$MeCO_2Et$ (1.65)	CD_3OD (2.6)	(700)	$MeCO_2CH_3$ 0.52; $MeCO_2CD_3$ 0.68
6	$MeCO_2Et$ (1.3)	CD_3OD (5.8)	(700)	$MeCO_2CH_3$ 0.11; $MeCO_2CD_3$ 0.64
7	$MeCO_2Et$ (1.6)	CD_3OD (2.1)	(70)	$MeCO_2CH_3$ 0.31; $MeCO_2CD_3$ 1.30
8	$MeCO_2H$ (4.6)	CD_3OD (2.7)	(700)	$MeCO_2CH_3$ 1.51; $MeCO_2CD_3$ 0.17
9	$MeCO_2Ph$ (0.99)	CD_3OD (1.34)	(700)	$MeCO_2CH_3$ 0.65; $MeCO_2CD_3$ 1.01
10	$PhCO_2Et$ (0.71)	CD_3OD (1.05)	(700)	$PhCO_2CH_3$ 0.13; $PhCO_2CD_3$ 0.07
11	$C_6F_5CO_2Et$ (0.77)	CD_3OD (1.22)	(700)	$C_6F_5CO_2CH_3$ 0.67; $C_6F_5CO_2CD_3$ 0.29

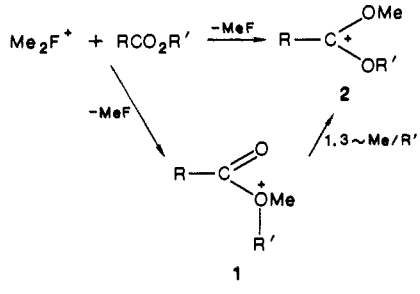
[a] All systems contained a free radical scavenger (O_2, 10 Torr). Irradiations were carried out at 37 °C, at a dose rate of 6×10^3 Gy h^{-1} to a total dose of 1.8×10^4 Gy. [b] The absolute yields of products are expressed by their G_{+M} values, i.e., the number of molecules formed per 100 eV absorbed. The analysis was carried out by GLC and GLC/MS. [c] NMe_3 (1.5).

Table II. Gas-Phase Ortho Ester Formation Reactions

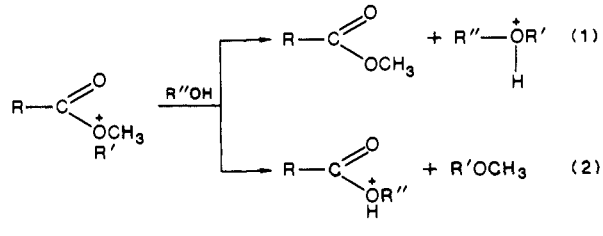
system composition[a] (Torr) RCO_2R'	$R''OH$	MeF	base	product yields[b] (G_{+M})
$PhCO_2Me$ (0.70)	MeOH (1.09)	(700)	-	n.d.[c]
$PhCO_2Me$ (0.95)	MeOH (2.8)	(700)	NMe_3 (2.0)	n.d.
$MeCO_2Me$ (2.8)	MeOH (2.8)	(700)	NMe_3 (1.5)	n.d.
$MeCO_2Me$ (4.0)	MeOH (4.8)	(700)	NMe_3 (2.0)	n.d.
$MeCO_2Me$ (6.2)	MeOH (13.3)	(700)	NMe_3 (3.0)	n.d.[d]
$C_6F_5CO_2Me$ (1.10)	MeOH (2.7)	(700)	-	n.d.
$MeCO_2Me$ (0.50)	MeOH (1.16)	(700)	NEt_3 (0.40)	$MeC(OMe)_3$ 0.10
$PhCO_2Me$ (0.97)	MeOH (2.6)	(700)	NEt_3 (0.64)	$PhC(OMe)_3$ 0.17
$C_6F_5CO_2Me$ (0.75)	MeOH (2.4)	(700)	NEt_3 (0.65)	$C_6F_5C(OMe)_3$ 0.10
$C_6F_5CO_2Et$ (0.81)	EtOH (2.6)	(700)	NEt_3 (0.84)	$C_6F_5CO_2Me$ 0.39; $C_6F_5C(OEt)_2(OMe)$ 0.20
$MeCO_2CH_2CF_3$ (0.60)	MeOH (1.55)	(700)	NEt_3 (0.50)	$MeC(OMe)_2(OCH_2CF_3)$ 0.22

[a] See Table I, footnote *a*. [b] See Table I, footnote *b*. [c] The lower detection limit is set as $G_{+M} = 0.02$. [d] The irradiation of this sample was increased to a total dose of 8×10^4 Gy in the attempt to increase the conversion into products with a higher energy deposition.

directly or via kinetic attack at the ether oxygen, followed by a 1,3-methyl shift.[10]

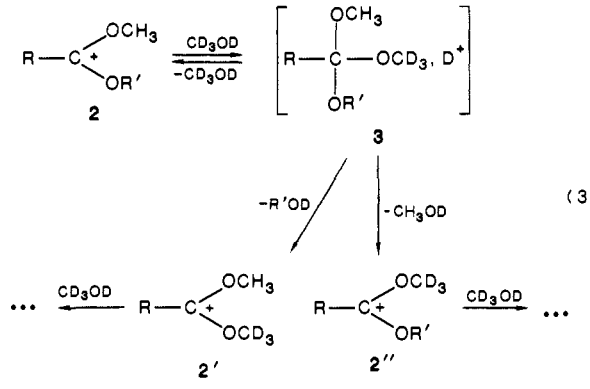


Intermediate **1** may easily evolve to ester product either by nucleophilic attack at R′ (eq 1) or by the concerted acyl group transfer (eq 2), occurring under ICR conditions.[4]



Routes 1 and 2 cannot individually account for the observed product pattern. In fact, if $R''OH = CD_3OD$, route 1 should yield exclusively $R–CO–OCH_3$ since the entering Me group from Me_2F^+ is unlabeled, and route 2 should yield $R–CO–OCD_3$. On the contrary, both isotopomers are formed (entries 5–11 of Table I), which at least requires operation of both mechanisms, if to a different extent. Furthermore, when R′ = Ph, R″ = CD_3OD (entry 9), one would expect formation of anisole together with the methyl ester, rather than phenol, the actually formed product.

A satisfactory rationalization for the experimental observations can be based on the role of **2** as the reaction intermediate. This ion is susceptible of undergoing the reversible addition–elimination process shown in eq 3 for $R''OH = CD_3OD$.



Ions **2**–**2″** can evolve to neutral products by releasing an alkyl group to a suitable nucleophile. Reaction 3 is also consistent with the behavior displayed by 1,1-dimethoxyethyl cations **2**, R = R′ = Me, m/z 89, when they are formed by protonation of $MeC(OMe)_3$ in isobutane chemical ionization. Product ions are formed, whose m/z ratios are 92, 95 when CD_3OD is added and 91, 93 in the presence of $CH_3{}^{18}OH$. This is indicative of a methoxy group exchange consistent with the addition–elimination sequence 3.[11] At the higher pressure prevailing in the radiolytic systems, the

(10) We are currently investigating this isomerization process which, in similar systems, is predicted to involve high activation barriers due to orbital symmetry restrictions. See: Bouma, W. J.; Poppinger, D.; Radom, L. *J. Am. Chem. Soc.* **1977**, *99*, 6443.

(11) No reaction was observed with several nucleophiles in a similar experiment run under ICR conditions, ref 4b. Whether a covalent structure **3** is an intermediate or a transition state cannot be said from the present experiments because the observation of m/z 125, formally $[MeC^+(OCH_3)_2 \cdot CD_3OD]$, at higher CD_3OD partial pressures, agrees with a loose ion–molecule complex as well.

postulated intermediate **3** can be deprotonated to the corresponding ortho ester, whose formation provides positive proof of its existence along the reaction pathway.[12] Conditions were chosen such as to maximize its stability toward fragmentation and to maximize its deprotonation rate by the base over the nucleophilic attack of the latter at the precursor ion **2**. Table II illustrates the mixed success encountered in the experiments directed to isolate ortho esters. Successful results have been obtained when one or more of the following conditions were fulfilled: (i) the presence of a strong base of moderate nucleophilicity, such as NEt_3, (ii) the presence of a phenyl substituent at the carbon center, which stabilizes **3** relative to **2**,[13] (iii) the presence of fluorine atoms in R or R',[2c] which inductively destabilize **2** with respect to **3**.

In conclusion, the evidence from this study supports an addition–elimination mechanism as the major pathway for the gas-phase cation-induced ester alcoholysis, showing that the latter occurs via a tetrahedral intermediate, the discrepancy with the mechanism invoked in low-pressure ICR spectrometry probably arising from the different reaction environment. Fast collisional quenching of excited intermediates and stabilization of charged species by multiple interactions with dipolar molecules make the fundamental difference between low-pressure mass spectrometric studies and the radiolytic approach, undoubtedly a better way to derive reactivity models for liquid-phase reactions.

Acknowledgment. The author is grateful to Prof. F. Cacace for his interest and helpful discussions, to Dr. A. Di Marzio for chemical ionization experiments, and to Ministero della Pubblica Istruzione for financial support.

Registry No. $MeCO_2Et$, 141-78-6; $MeCO_2Me$, 79-20-9; $PhCO_2Me$, 93-58-3; $MeCO_2H$, 64-19-7; $MeCO_2Ph$, 122-79-2; $PhCO_2Et$, 93-89-0; $C_6F_5CO_2Et$, 4522-93-4; Me_2F, 64710-12-9.

(12) For a recent review on ortho esters and dialkoxycarbenium ions see: Pindur, U.; Müller, J.; Flo, C.; Witsel, H. *Chem. Soc. Rev.* **1987**, *16*, 75.
(13) Burt, R. A.; Chambers, C. A.; Chiang, Y.; Hillock, C. S.; Kresge, A. J.; Larsen, J. W. *J. Org. Chem.* **1984**, *49*, 2622.

Papuamine, an Antifungal Pentacyclic Alkaloid from a Marine Sponge, *Haliclona sp.*[1]

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Haliclona sp., a thin red encrusting sponge from Papua New Guinea, which overgrows and kills coral, contains as its major metabolite (1.3% of dry weight) a pentacyclic alkaloid, papuamine (**1**), which is formally derivable from a C_{22} unbranched hydrocarbon and 1,3-diaminopropane. Pure papuamine inhibits the growth of the fungus *Trichophyton mentagrophytes*.[2]

Haliclona sp. (120 g wet) was collected in November, 1985, at South Lion island, Papua New Guinea; the frozen sponge was thawed and extracted three times with MeOH and then chloroform. The aqueous methanolic concentrate was subjected to successive partition with hexane, carbon tetrachloride, and chloroform.[3] The antifungal activity resided in the two chloroform extracts and remained at the origin in normal (silica, EtOAc) and reversed phase TLC (RP-18, MeOH). It moved in either mode when triethylamine (5%) was added. Final purification was achieved either by flash chromatography[4] (BioSil A, EtOAc/MeOH, Et_3N, 55:40:5) which produced the natural ammonium salt (**2**)[5] or by HPLC (Waters Porasil, EtOAc/Et_3N, 95:5), which freed the amine **1** (180 mg).[6]

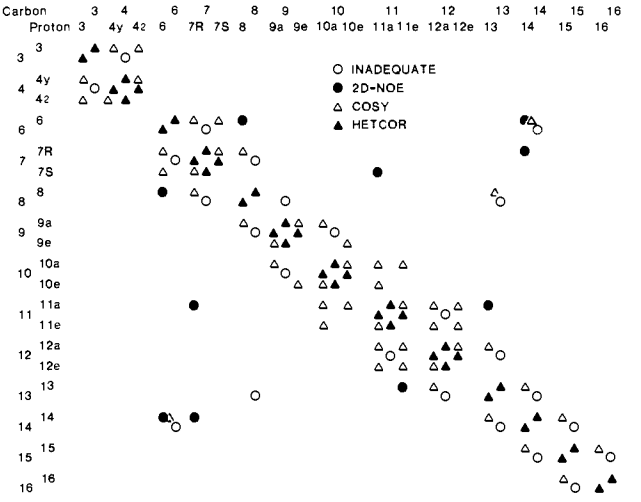

Figure 1. Selected correlations of papuamine (**1**) from INADEQUATE, 2D-NOE, COSY, and HETCOR experiments.

Papuamine (**1**) is an optically active solid of composition $C_{25}H_{40}N_2$. A diacetamide **3**,[7] $C_{29}H_{44}N_2O_2$, produced an EIMS fragment at m/z 294 ($C_{22}H_{30}$). This corresponds to the molecular ion $C_{29}H_{44}N_2O_2$ (m/z 452) minus two acetyls ($C_4H_6O_2$) minus $C_3H_8N_2$. The structure of this fragment $\rangle N^A CH_2{}^B CH_2{}^{A'} CH_2 N\langle$ rests on ^{1}HNMR data of the salt **2**. Two proton multiplets at δ 3.19 and 2.98 are assigned to pseudoaxial and pseudoequatorial protons A and A', while an apparent one-proton multiplet at δ 2.0 represents the B protons based on heteronuclear correlation data (Table V, Supplementary Material). Additionally, two complex olefinic ^{1}H NMR signals at δ 6.50 and 5.89 representing four protons are assigned to an s-trans-diene (λ_{max} 241 nm), after comparison with computer-generated spectra of conjugated dienes of different geometry. Mutually coupled signals at δ 3.55 and 2.63 arise from methines vicinal to nitrogen and olefin, respectively.

(4) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(5) Papuamine dihydrochloride (**2**): white solid, mp 230 °C dec; $[\alpha]_D$ −140° (c 1.3, MeOH); UV λ_{max}^{MeOH} 241 (3000) nm; IR ($CHCl_3$) ν_{max} 3700 br, 2930, 2850, 1560, 1450, 1230, 1050, 1010, 730 cm^{-1}; HREIMS m/z 368.3173 ($C_{25}H_{40}N_2$ requires 368.3192); FABMS (positive ion) m/z 369 (100%); HRFABMS m/z 369.3258 ($C_{25}H_{41}N_2$ requires 369.3270); ^{1}H NMR (300 MHz, CD_3OD) δ 6.50 (2 H, H-16, 17, complex dd, J = 10.5, 15.8 Hz), 5.89 (2 H, H-15, 18, complex dd, J = 8.3, 15.8), 3.55 (2 H, H-6, 27, br ddd, J = 8.2, 8.2, 8.8 Hz), 3.19 (2 H, H-2y, 4y, br ddd, $J_{2y\text{-}3}$ = 13.5), 2.98 (2 H, H-2z, 4z, br dt, J = 3, 10.6 Hz), 2.63 (2 H, H-14, 19, br ddd, J = 9.3, 9.3, 10.6 Hz), 2.41 (2 H, H-7R, 26S, ddd, $J_{7R\text{-}8}$ = 4.8 Hz, $J_{7R\text{-}6}$ = 8.8 Hz, $J_{7R\text{-}7S}$ = 12.0 Hz), 2.0 (2 H, H_2-3, multiplet), 1.9–1.6 (8 H, multiplet of equatorial protons), 1.4 (2 H, H-13, H-20, dddd J = 10.6), 1.3–1.1 (10 H, multiplet of axial protons), 1.0 (2 H, H-10a, 23a, ddd, J = 3, 10.2, 12.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 136.02 (d), 130.46 (d), 62.09 (d), 50.49 (d), 49.28 (d), 46.97 (t), 44.65 (d), 39.14 (t), 32.07 (t), 30.79 (t), 27.04 (t), 24.60 (t).
(6) Papuamine (**1**): white solid, mp 167.5–169 °C; $[\alpha]_D$ −150° (c 1.5, MeOH); IR (film): ν_{max} 3000, 2920, 2850, 1400, 1100 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 6.22 (2 H, H-16, 17, dd, J = 10.5, 15.8 Hz), 5.71 (2 H, H-15, 18, dd, J = 8.3, 15.8 Hz), 3.05 (2 H, H-6, 27, br dd, J = 8.2, 8.2, 8.8 Hz), 2.64 (2 H, H-2y, 4y, m), 2.22 (2 H, H-2z, 4z, m), 2.21 (2 H, H-14, 19, m), 2.17 (2 H, H-7R, 26S, m), 1.82 (2 H, H-9e, 24e, m), 1.78 (2 H, H-12e, 21e, m), 1.70 (2 H, H-10e, 23e, m), 1.68 (2 H, H-11e, 22e, m), 1.6 (2 H, H_2-3, m), 1.23 (2 H, H-8, 25, m), 1.2 (4 H, H-7S, 26R, 11a, 22a, m), 1.19 (4 H, H-13, 20, 10a, 23a, m), 0.9 (4 H, H-9a, 24a, 12a, 21a, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.85 (d), 129.37 (d), 60.91 (d), 50.02 (d), 48.88 (d), 45.99 (t), 43.58 (d), 40.40 (t), 31.26 (t), 30.09 (t), 26.08 (t), 26.03 (t).
(7) Papuamine diacetamide (**3**): prepared from 6.6 mg of **1**, 0.5 mL of Ac_2O, 2 mL of pyridine, <5 min; purified by Bond Elut (EtOAc/Et_3N, 95:5), HPLC (Waters Micro BondaPak, EtOAc/petroleum ether, 70:30); white semisolid; EIMS (70 eV) m/z (%) 452 (9.5), 409 (17.5), 294 (47.0); HREIMS 452.34071, $C_{29}H_{44}N_2O_2$ requires 452.340287; 409.32259, $C_{27}H_{41}N_2O$ requires 409.321896; 294.23466, $C_{22}H_{30}$ requires 294.234756; 158.10605, $C_7H_{14}N_2O_2$ requires 158.105531; 115.08792, $C_5H_{11}N_2O$ requires 115.087140; 43.018124, C_2H_3O requires 43.018391; FABMS (positive ion) m/z 453 (100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.1 (2 H, H-16, 17, br s), 5.6 (2 H, H-15, 18, br s), 4.5 (2 H, br s) 4.3 (2 H, br s), 3.7 (2 H, br s), 3.5 (2 H, br s), 3.2 (2 H, br s), 2.8 (2 H, br s), 2.6 (2 H, br s), 2.1 (3 H, OAc), 2.1 (3 H, OAc), 1.8 (10 H, br m), 1.2 (12 H, br m).

[†] University of Hawaii at Manoa.
[‡] Varian.
(1) From the Ph.D. Dissertation of B.J.B., University of Hawaii, 1986.
(2) A 6-mm disk containing 10 μg of papuamine produced a 12-mm zone of growth inhibition.
(3) Kupchan, S. M.; Britton, R. W.; Zeigler, M. F.; Sigel, C. W. *J. Org. Chem.* **1973**, *38*, 178–179.

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