Pergamon

Tetrahedron, Vol. 52, No. 3, pp. 849-860, 1996
Copyright © 1995 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4020/96 $15.00 + 0.00

0040-4020(95)00944-2

Nucleophilic Reaction of 1,8-Diazabicyclo[5.4.0]undec-7-ene and 1,5-Diazabicyclo[4.3.0]non-5-ene with Methyl Pheophorbide *a*. Unexpected Products

Lifu Ma and David Dolphin*

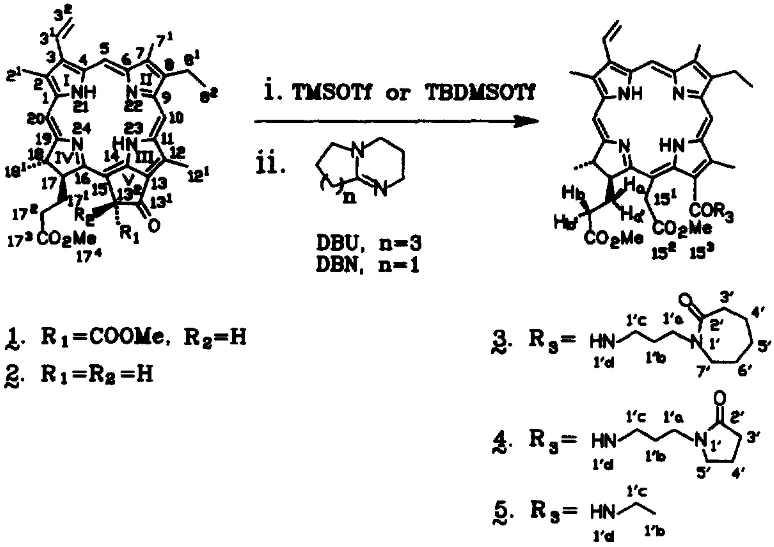
**Department of Chemistry, The University of British Columbia,
2036 Main Mall, Vancouver, B.C., Canada V6T 1Z1**

Abstract: Trialkylsilyl triflates promote the direct nucleophilic reaction of "non-nucleophilic DBU and DBN" with methyl pheophorbide *a* (**1**) to give substituted chlorin e_6 amides **3** and **4**, where the bicyclic bases have undergone ring opening. The reaction most likely results from coordination of trialkylsilyl triflates to the β-ketoester in **1**, forming an ion-pair intermediate **6**. The adduct **6** is so strongly electron-deficient that it can electrophilically attack the nonbonding nitrogen electron pairs in DBU and DBN.

Trialkylsilyl triflates[1] such as *tert*-butyldimethylsilyl triflate (TBDMSOTf) and trimethylsilyl triflate (TMSOTf) are powerful silylating agents and a wide range of active hydrogen containing compounds are silylated in the presence of amines.[2] Combination of these triflates with the hindered amidine 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[3] has also been used in the selective ring-opening reactions of oxiranes.[1] Due to the highly electron-withdrawing triflate moiety the silicon in trialkylsilyl triflates is strongly electron-deficient and can directly attack the heteroatoms in carbonyl and analogous systems,[4] and many reports have shown that they can act as catalysts to accelerate a variety of nucleophilic reactions in aprotic media.[5] We report here that a degradation product of chlorophyll *a*, methyl pheophorbide *a* (**1**) which alone does not electrophilically react with DBU or DBN, has reacted, through catalytic activation by TMSOTf and TBDMSOTf, with nucleophilic DBU and DBN.

The isocyclic ring (ring V) of methyl pheophorbide *a* (**1**) is a substituted β-ketoester and enolization occurs readily in polar solvents. However, attempts to isolate it as an enol ester or a silyl enol ether led to very unstable products.[6] In 1979, Hynninen *et al.*[7] reported that the enolate could be trapped by using tetrapropylammonium fluoride in combination with trimethylsilyl chloride (TMSCl). We repeated the reported procedure but found the yield of silyl enol ether was quite low (<10%). Due to the low stability of the trimethylsilyl enol ether we attempted to replace TMSCl with the more stable *tert*-butyldimethylsilyl chloride (TBDMSCl). Using DBU to enolize the β-ketoester function of methyl pheophorbide *a* (**1**) and subsequently treatment with TBDMSCl, to trap the enolate, surprisingly gave none of the desired silyl enol ether. Instead, a less mobile green product **3** (~5% yield) was separated from the unchanged starting material **1**. Subsequently we found that the "green product" **3** could be obtained in good yield

(>50%) by first activating **1** with TMSOTf or TBDMSOTf followed by treatment with an excess of DBU. An analogue (**4**) was also obtained from the reaction of **1** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN).



Scheme 1

The exocyclic ring V of **1** has frequently been the focus of attention because of its special role in photosynthesis. This ring is particularly sensitive to nucleophilic attack, such as by alkoxides and by primary and secondary amines which afford chlorin e_6 and chlorin e_6 amide derivatives.[9] In this present work we have found that ring V can be cleaved by the normally non-nucleophilic bicyclic amidines DBU and DBN which can act as nucleophiles under certain conditions. These observations could help explain the previously observed and anomalous products in enolate-trapping reaction of chlorophyll *a* and related compounds.[7,10]

The nucleophilic behaviour of DBU and DBN has also recently been reported in two other cases. Reed *et al.*[11] described remarkable nucleophilicity of DBU and DBN in reactions with halogenated compounds of main group elements. Lammers *et al.*[12] have also observed nucleophility in the reaction of DBU and DBN with 4-halo-3,5-dimethyl-1-nitro-1H-pyrazoles. DBU and DBN react with phosphanes resulting in the formation of ion-pair products where the bicyclic rings of DBU and DBN remain unchanged.[11] However, Lammers *et al.* obtained lactam-type products in which one of the bicyclic rings in DBU and DBN was opened by water.[12] The products, **3** and **4** were found to be chlorin e_6 lactams, in

parallel to Lammers' results.[12] However the reaction of DBU and DBN with methyl pheophorbide (1) is induced by the Lewis acids, TMSOTf and TBDMSOTf.

RESULTS AND DISCUSSION

The reaction can run in either dry THF or dry DMF. In THF, DBU and DBN with methyl pheophorbide *a* (**1**) give yields greater than 50% along with ~20% recovered starting material **1**. In DMF the reactions proceeded faster reaching completion in ~3h, but only ~45% yields were obtained along with ~20% side (degradative) products. The reactions promoted by TMSOTf and TBDMSOTf were both efficient, and no difference was observed between them.

Unambiguous structure assignments of **3** and **4** were carried out using mass spectroscopy, ^{1}H NMR, proton decoupling, ^{13}C NMR, attached proton tests (APT), ^{1}H homonuclear correlation spectra (COSY) and ^{1}H-^{13}C heteronuclear correlation spectra (HETCOR). Furthermore, the structure of **3** was confirmed by nuclear Overhauser effect (NOE) measurements while the structure of **4** was confirmed by its direct preparation through reaction of commercially available 1-(3-aminopropyl)2-pyrrolidinone with **1**. The assignments are described as follows.

HRMS and elemental analysis showed **3** to be an adduct of DBU and methyl pheophorbide *a* (**1**) plus the elements of a molecule water (formula: $C_{45}H_{56}N_6O_6$). ^{13}C NMR showed that **3** consists of 45 carbons (36 carbons in **1**) and an attached proton test (APT) confirmed that 8 of the additional 9 carbon atoms are methylene carbons in the high field region and only one sp^2 carbon at low field. The ^{13}C signals of the 8 additional methylene carbons are matched with related chemical shifts in DBU.[13] In its ^{1}H homonuclear correlation spectrum (COSY, not shown), **3**, like the starting material **1**, has only three downfield methine peaks (1H each) suggesting that one of the compound's four bridging carbons (i.e. C-15) is still functionalized. Five sharp singlets (3H each) between 3.0 and 4.0 ppm suggest three aryl-substituted methyls as well as two methoxyl groups, which showed that these groups were unchanged after the reaction. A doublet of quartets at 4.46 ppm (1H) was coupled to one proton (ddd) at 4.39 ppm (1H), suggesting the former is H-18 and the latter is H-17. H-17 is also coupled to two other multiplet hydrogens at 2.23 and 1.83 ppm, these two protons were found to be coupled with the corresponding carbon at 29.66 ppm (see Table 2 for ^{13}C NMR data) as shown by a HETCOR spectrum (Fig. 1). This methylene is assigned to the 17^1-CH_2 and the two hydrogens are assigned as Ha-17^1 (2.23 ppm) and Ha'-17^1 (1.83 ppm). Consequently, Hb-17^2 (2.52 ppm) and Hb'-17^2 (2.12 ppm) were identified based on their coupling to Ha-17^1 and Ha'-17^1. There are two other obvious coupled pairs at low field. (i). a triplet (1H, J = 6.0 Hz) at 7.55

ppm was exchangeable with CD_3OD and coupled to the multiplets at 3.68 and 3.64 ppm (1H each) suggested a possible CO-$NHCH_2$ unit, (ii) an asymmetrically substituted methylene was suggested by a split AB quartet at 5.54 and 5.27 ppm (1H each) with coupling constant $J = 19.1$ Hz, whose corresponding carbon signal is at 38.02 ppm. Assignment of this methylene unit as C-15^1 was based on an NOE enhancement (Scheme 2) of H-17 (4.39 ppm). These assignments confirmed that the exocyclic ring V was the only part of the molecule to have reacted and also suggested that 3 has a chlorin-e_6-type structure. Since it contains a $CONHCH_2$ moiety, it was believed to be a chlorin e_6 amide derivative. This conclusion is firmly supported by its absorption spectrum, a typical chlorin-e_6-type spectrum with the Soret band at 404 nm (ε 171,900) and Q band at 666 nm (48,700).[14]

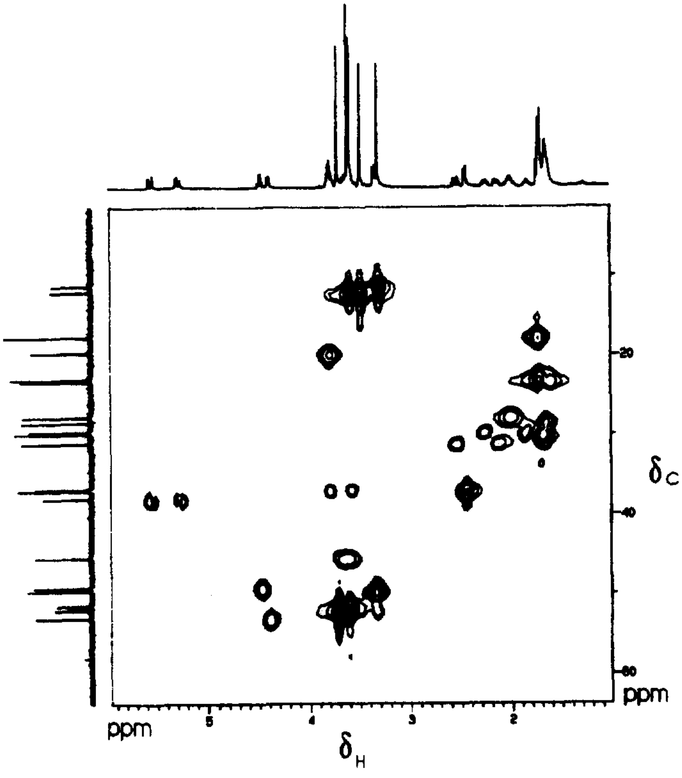
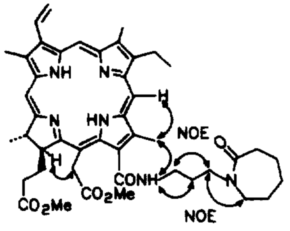


Figure 1. ^1H-^{13}C Heteronuclear correlation spectrum of chlorin e_6 amide 3 (12.0 mg in 1.0 mL $CDCl_3$) between δ_H 0.0-6.0 ppm for proton resonances, and between δ_C 0-60 ppm for the carbon resonances



Scheme 2

Reaction of ethylamine with methyl pheophorbide *a* (**1**), gave chlorin e_6 ethylamide **5**, an analog of **3**. Compound **5** exhibited a relative simple and easily-assigned NMR spectrum. Comparing the spectral data of **3** and **5**, the assignment of **3** as a chlorin e_6 amide with 13-substitution was confirmed.

Further details of the NMR assignments are given in Tables 1 and 2. In addition, NOE experiments (Scheme 2) have confirmed the above assignments. Compound **3** is thus shown to be chlorin e_6 13-[1-(3-*N*-propyl)-2-azacycloheptane]amide-15,17-dimethyl ester.

A similar analysis of spectral data has shown that **4** is chlorin e_6 13-[1-(3-*N*-propyl)-2-pyrrolidinone]amide-15,17-dimethyl ester. This was further confirmed by comparison with the product from direct nucleophilic reaction of commercially-available 1-(3-aminopropyl)2-pyrrolidinone with methyl pheophorbide *a* (**1**). The products prepared by these two methods were identical.

Table 1. ^{1}H NMR Spectral Data($CDCl_3$, 400 MHz)

Proton	Compound				Proton	Compound			
	3^a	**4**^{b}	**5**^{b}	**1**^{a}		**3**^{a}	**4**^{b}	**5**^{b}	**1**^{a}
H-10	9.69(s)	9.70(s)	9.70(s)	9.52(s)	NH	-1.60(br s)	-1.60(br s)	-1.87(br s)	0.53(br s)
H-5	9.62(s)	9.63(s)	9.62(s)	9.39(s)	NH	-1.82(br s)	-1.82(br s)	-1.96(br s)	-1.62(br s)
H-20	8.89(s)	8.80(s)	8.80(s)	8.57(s)	H-15^1/13^2	5.54(d)	5.51(d)	5.56(d)	6.27(s)
H-3^1	8.07(dd)	8.08(dd)	8.05(s)	8.01(s)		5.27(d)	5.23(d)	5.25(d)	
H-3^2(E)	6.32(dd)	6.34(dd)	6.38(dd)	6.30(dd)	H-17^4	3.60(s)	3.58(s)	3.59(s)	3.57(s)
H-3^2(Z)	6.10(dd)	6.12(dd)	6.15(dd)	6.19(dd)	H-15^3/13^4	3.69(s)	3.71(s)	3.80(s)	3.88(s)
H-8^1	3.78(q)	3.79(q)	3.79(q)	3.67(q)	H-D-1'd	7.55(t)	7.31(t)	6.40(t)	
H-12^1	3.57(s)	3.57(s)	3.55(s)	3.68(s)	H-D-1'c	3.68(m)	3.81(m)	3.80(q)	
H-2^1	3.47(s)	3.48(s)	3.48(s)	3.39(s)		3.64(m)	3.60(m)		
H-7^1	3.30(s)	3.30(s)	3.32(s)	3.21(s)	H-D-1'b	2.08(m)	2.08(m)	1.41(t)	
H-18^1	1.71(d)	1.68(d)	1.70(d)	1.80(d)	H-D-1'a	3.64(m)	3.51(m)		
H-8^2	1.70(t)	1.70(t)	1.70(t)	1.68(t)	H-D-3'	2.48(dd)	2.37(t)		
H-18	4.46(dq)	4.44(q)	4.46(dq)	4.47(q)	H-D-4'	1.64(m)	2.08(m)		
H-17	4.39(ddd)	4.36(dd)	4.35(dd)	4.20(dd)	H-D-5'	1.66(m)	3.50dd)		
Ha-17^1	2.23(m)	2.21(m)	2.15(m)	2.62(dt)	H-D-6'	1.70(m)			
Ha'-17^1	1.83(m)	1.80(m)	1.78(m)	2.31(dt)	H-D-7'	3.41(dd)			
Hb-17^2	2.52(ddd)	2.52(ddd)	2.50(ddd)	2.50(dt)					
Hb'-17^2	2.12(ddd)	2.13(ddd)	2.15(m)	2.24(t)					

[a]Concentration 1.5mg / 0.6mL [b]Concentration 1.0mg / 0.6mL

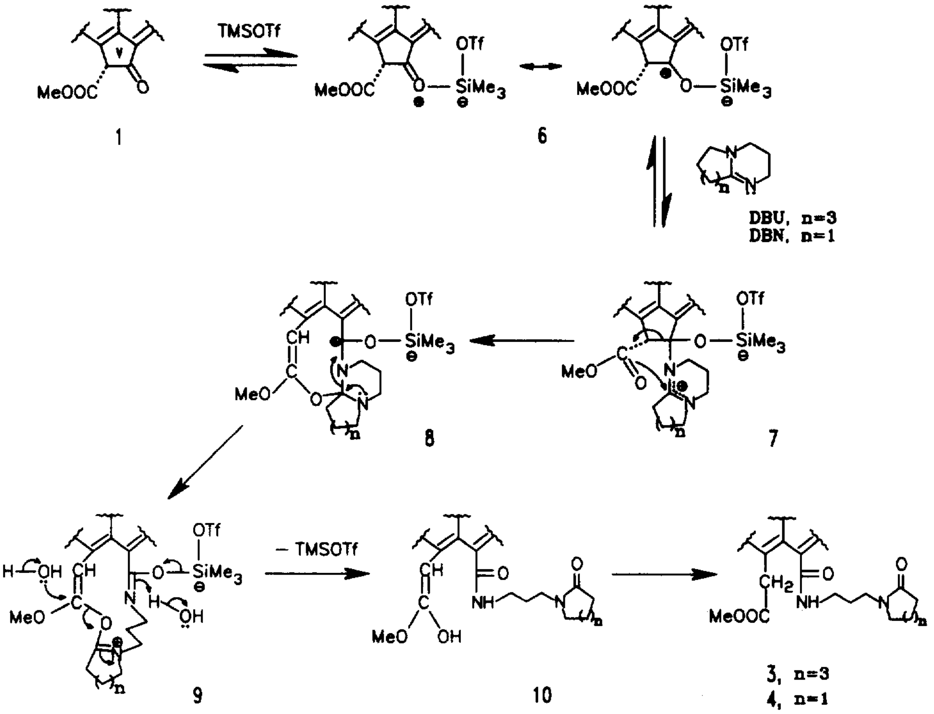
Table 2 ^{13}C NMR Spectral Data ($CDCl_3$, 125MHz)

Carbon	Compound			
	3[a]	**4**[b]	**5**[c]	**1**[d]
C-17^3	173.5	173.6	173.5	173.4
C-13^1	173.6	173.6	174.2	189.6
C-$15^2/13^3$	169.3	169.4	169.4	169.6
C-19	168.5	168.6	168.7	172.1
C-16	166.7	166.7	166.6	161.2
C-6	153.9	154.0	154.2	155.5
C-9	149.1	149.1	149.1	150.9
C-14	144.6	144.7	144.7	149.6
C-8	138.7	138.8	138.8	145.1
C-1	136.0	136.8	136.1	142.0
C-11	135.3	135.2	134.9	137.9
C-3	134.7	134.8	134.9	136.4
C-4	134.6	134.7	134.8	136.1
C-7	134.3	134.4	134.0	136.0
C-2	130.1	130.0	130.1	131.8
C-12	129.9	130.0	130.1	128.9
C-3^1	129.5	129.5	129.5	128.9
C-13	128.8	128.5	128.3	128.9
C-3^2	121.4	121.5	121.6	122.7
C-15	102.4	102.3	102.1	105.1
C-10	101.3	101.4	101.4	104.3
C-5	98.8	98.8	98.8	97.4
C-20	93.5	93.6	93.7	93.1
C-$15^1/13^2$	38.0	38.0	37.8	64.7
C-17	53.1	53.1	53.1	52.9
C-18	49.2	49.2	49.2	51.7
C-17^2	31.1	31.1	31.1	31.1
C-17^1	29.7	29.7	29.7	29.9
C-18^1	23.0	23.0	23.1	23.1
C-8^1	19.7	19.7	19.7	19.3
C-8^2	17.7	17.7	17.8	17.4
C-12^1	12.1	12.2	12.2	12.1
C-2^1	12.1	12.1	11.9	12.1
C-7^1	11.3	11.3	11.4	11.1
C-17^4	51.5	51.6	51.6	50.1
C-$15^3/13^4$	52.1	52.1	52.1	51.1
C-D-1'c	36.9	37.2	35.5	
C-D-1'b	27.8	17.9	14.8	
C-D-1'a	45.5	40.0		
C-D-2'	176.6	175.7		
C-D-3'	37.1	30.8		
C-D-4'	23.4	27.2		
C-D-5'	28.5	47.3		
C-D-6'	29.9			
C-D-7'	49.6			

[a]Concentration 12.0 mg /1.0 mL [b]Concentration 9.0 mg /1.0 mL
[c]Concentration 18.0 mg /1.0 mL [d]Concentration 25.0 mg /1.0 mL

This reaction requires the β-ketoester system of methyl pheophorbide *a* (**1**). Reaction with methyl pyropheophorbide *a* (**2**), a decarboxylated product of methyl pheophorbide *a* (**1**), failed. Because of the similarity of methyl 2-oxocyclopentanecarboxylate to the ring V in methyl pheophorbide *a* (**1**), we also investigated its reaction with the amidine bases but found that ring opening did not occur. The initial reaction between methyl 2-oxocyclopentanecarboxylate and DBU (DBN) resulted in the formation of a trace amount of a 1:1 "adduct", which could be only identified by mass spectroscopic and chromatographic analysis.

Since direct mixing of TMSOTf with DBU resulted in no new products and the enolate from deprotonation of methyl pheophorbide *a* (**1**) by DBU (DBN) is relative stable in the absence of oxygen in the dark,[8] the nucleophilic behaviour of DBU and DBN must be initiated from the activation of **1** by Lewis acids (TMSOTf and TBDMSOTf). In Scheme 3 a mechanism is proposed for the formation of **3** and **4**. The first step is coordination of the 13^1-carbonyl group of **1** by TMSOTf or TBDMSOTf to generate a reactive ion-pair intermediate **6**. This kind of ion-pair intermediate is common and found to form easily in the TMSOTf (TBDMSOTf) catalyzed aldol-type reaction of silyl enol ethers and acetals.[4] The pentacoordinate silicon species[5] are so electron-deficient that they can react with the nonbonding nitrogen electrons in DBU and/or DBN to give **7**. The further cleavage of bond (C-13^1–C-13^2) of ring V, step **7** to **8**, drives the reaction towards completion. Indeed, the formation of **5** from the nucleophilic reaction of ethylamine with **1** is also through this type of bond breakage. The intramolecular rearrangement to generate **9** is facilitated thermodynamically by the formation of the amide. Similar rearrangements have been extensively studied during hydrolysis of bicyclic imidates by Deslongchamps *et al.*[15]



Scheme 3

CONCLUSION

Upon activation by trialkylsilyl triflates, trimethylsilyl triflate and *tert*-butyldimethylsilyl triflate, methyl pheophorbide *a* (**1**) behaves as a powerful electrophile and reacts with DBU and DBN giving ring opened adducts, substituted chlorin e_6 amides **3** and **4**, in good yields. The nucleophilicity is most likely due to electron-deficiency of the activated ion-pair intermediate **6** which can react with the nonbonding nitrogen electron pairs in DBU/DBN, showing again that DBU and DBN under appropriate conditions, can act as nucleophiles as well as strong bases.

EXPERIMENTAL

M.P.s were measured on a Thomas/Bristoline microscopic hot stage apparatus and are uncorrected. ^1H NMR, proton decoupling and two dimensional ^1H-^1H correlation specta (COSY) were recorded on a Bruker WH-400 Spectrometer, and attached proton test (APT) were run on a Varian XL-300 spectrometer. ^{13}C and two dimensional ^1H-^{13}C correlation spectra (HETCOR) were performed on a Bruker AMX-500 spectrometer. All spectra were measured at 25°C in $CDCl_3$ in a 5 mm wide tube (the residual $CHCl_3$ used as the standard, δ_H 7.24 and δ_C 77.0 ppm). ^1H NMR chemical shifts of overlapping signals were obtained by repeated decoupling of relevant signals (see also footnotes of Tables 1 and 2) and COSY spectra. Silica gel 60 [(70-230 Mesh, Merck), usually silica III (i.e. deactivated with 6% water), and Brockmann Grade III (neutral alumina deactivated with 6% water), Brockmann Grade V (neutral alumina deactivated with 15% water) were used for column chromatography. Preparative thin layer chromatography was carried on 20×20 cm glass plates coated with Merck G_{254} silica gel (0.5 mm thickness). Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} silica gel (precoated sheets, 0.2 mm thickness). Fast Atom bombardment (FAB) mass spectra were measured on a Varian Mat CH 4-B spectrometer with 1-thioglycerol as a matrix. Electron impact mass spectra (EIMS) were recorded on a Kratos/AEI MS-902 spectrometer. Elemental analyses were carried out in the microanalytical laboratory at UBC using a Carlo Erba Elemental Analyzer 1106. Electronic absorption spectra were measured in chloroform or dichloromethane using a HP8452A Diode Array spectrophotometer. Reactions were monitored by TLC and spectrophotometry and were carried out under nitrogen and in the dark. Tetrahedrofuran (THF) was dried overnight with calcium hydride and distilled from sodium wire and benzophenone. Dimethylformamide (DMF) was dried over $MgSO_4$ and distilled under reduced pressure. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 98%), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN, 95%), trimethylsilyl triflate (TMSOTf, 99%), *tert*-butyldimethylsilyl triflate (TBDMSOTf, 98%) were purchased from Aldrich. The other solvents used were of reagent grade.

*Methyl pheophorbide a (**1**) from Spirulina maxima*[16]

Approximately 1 kg of dried *Spirulina maxima* alga was slurried in acetone (3 L) in a 5 L three-neck round-bottom flask and liquid nitrogen was added to rupture the cells. The frozen slush was left for 1h and then refluxed under nitrogen with continuous stirring for 2 h. The supernatant was then filtered through a Buchner funnel and washed with acetone (~2 L). Even though the filter cake remained dark blue, the yield of pigment obtained by further washing was low. The green filtrate was evaporated and the viscous oil so obtained was dissolved in petroleum ether (1.5 L, 35-60°C) before washing with water (3 times) to remove the residual supernatant and water solubles. The pet. ether layer was further washed with 30% aqueous methanol until the aqueous phase was colorless. Petroleum ether was then evaporated and the dark green residue was redissolved in diethyl ether (800 mL) before treating with conc. HCl (~80 mL) for 1 min (color changed from green to black), followed by immediate washing with water (2×800 mL) and 20% aqueous methanol (3×800 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and the filtrate evaporated. The extract was purified by flash chromatography on Brockmann Grade III neutral alumina, eluting first with methanol to remove most of a yellow-red band, then with dichloromethane to remove the major black pheophytin *a* band. Flash chromatography was repeated, eluting first with hexane (or petroleum ether) to remove the residual yellow band, and then with 30% dichloromethane in tetrachloromethane to remove the pheophytin *a*. The eluate was taken to dryness and recrystallized from dichloromethane/methanol to give 6.5 g pheophytin *a* as a black solid. This solid was treated with 5% sulfuric acid in methanol (900 mL, v/v) (degassed by bubbling with nitrogen) for 13 h at room temperature in the dark, followed by dilution with dichloromethane. The organic layer was washed with water (×2) saturated sodium bicarbonate once and then water (×3). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated. Recrystallization of the product from dichloromethane/methanol gave the title compound as 4.2 g of blue prisms. m.p. 241°C [lit.[16] 228°C, lit.[17] 206°C. UV-Vis λ_{max} ($CHCl_3$) 668 nm (ε 45 300), 610 (13 100), 536 (14 000), 506 (15 800), 412 (104 800). [lit.[16] λ_{max} (CH_2Cl_2) 668 (44 600), 610 (8 620), 538 (9 710), 506 (10 800), 412 (106 000)]; ^1H NMR data see Table 1 and ^{13}C data see Table 2.

Methyl pyropheophorbide a (2) from methyl pheophorbide a (1)

Methyl pyropheophorbide *a* (**2**) was prepared by following the literature procedure.[16] Tiny blue needles (CH_2Cl_2/CH_3OH). m.p. 233°C [lit.[16] 217-219°C]; UV-Vis λ_{max} ($CHCl_3$) 668 nm (ε 53 500), 608 (11 200), 538 (9 800), 510 (13 500), 418 (147 700). [lit.[16] λ_{max} (CH_2Cl_2), 668 nm (ε 47 100), 610 (8 500), 538 (9 800), 508 (11 500), 410 (113 000)]. ^1H NMR (1.5 mg in 0.6 mL $CDCl_3$, 400 MHz) δ_H 9.50 (s, 1H, H-10), 9.39 (s, 1H, H-5), 8.59 (s, 1H, H-20), 8.00 (dd, 1H, J = 17.4, 11.4, 1.1 Hz, H-3^1), 6.30 [d, 1H, J = 17.4, 1.1 Hz, H-3^2(E)], 6.18 [d, 1H, J = 11.4, 1.1 Hz, H-3^2(Z)], 5.29, 5.10 (ABq, 2H, H-13^2), 4.49 (dq, 1H, J = 7.3, 2.2 Hz, H-18), 4.27 (dt, 1H, J = 7.9, 3.0, 2.2 Hz, H-17), 3.68 (q, 2H, J = 7.6 Hz, H-8^1), 3.66 (s, 3H, H-12^1), 3.60 (s, 3H, H-17^4), 3.39 (s, 3H, H-2^1), 3.22 (s, 3H, H-7^1), 1.79 (d, 3H, J = 7.3 Hz, H-18^1), 1.68 (t, 3H, J = 7.6 Hz, H-8^2), 2.68 (m, 1H, J = 7.9 Hz, H_a-17^1), 2.30 (m, 1H, J = 3.0 Hz, $H_{a'}$-17^1), 2.28 (m, 1H, H_b-17^2), 2.55 (m, $H_{b'}$-17^2).

***Typical procedure for reaction of DBU or DBN with methyl pheophorbide a* (1)**

To a solution of **1** (60.7 mg, 0.1 mmol) and imidazole (10 mg) in THF (15 mL) under nitrogen was injected TMSOTf or TBDMSOTf (0.3 mmol). After 15 min at room temperature, DBU (~1.0 mL, 6.7 mmol) or DBN (~0.83 mL) was added slowly to this blue-gray solution. The brown-red mixture was then stirred in the dark for 5 h before being poured onto ice-saturated NH_4Cl/dichloromethane. The organic layer was washed with water (2×30 mL), saturated aqueous sodium bicarbonate (30 mL) and water (2×30 mL), dried over anhydrous sodium sulfate, filtered and evaporated. The product was purified by flash column chromatography on silica III, first eluting with dichloromethane to give unreacted starting material **1** (20-25%) and eluting further with 1.5% methanol in dichloromethane to give the product. The product was recrystallized from dichloromethane/hexane.

Chlorin e_6 13-[1-(3-N-propyl)2-azacycloheptanone]amide-15,17-dimethyl ester (**3**)

The product **3** (45.3 mg, 58%) was obtained as a green powder, m.p. 124°C (Found: C, 69.77; H, 7.60; N, 10.52 $C_{45}H_{56}N_6O_6$ requires: C, 69.55; H, 7.27; N, 10.82); UV-Vis λ_{max} ($CHCl_3$) 666 nm (ε 48 700), 610 (5 700), 528 (5 000), 502 (15 100), 404 (171 900); FABMS m/z: 777 ([MH]$^+$, 100%), 579 (76); EIMS m/z: 776 (M$^+$, 73%), 744 (20), 717 (37), 606 (51); HRFABMS: $C_{45}H_{57}N_6O_6$ ([MH]$^+$): calcd 777.4339; obsd 777.4365; HREIMS: $C_{45}H_{56}N_6O_6$ (M$^+$): calcd 776.4261; obsd 776.4267. ^{1}H NMR data see Table 1 and ^{13}C data see Table 2.

Chlorin e_6 13-[1-(3-N-propyl) 2-pyrrolidinone] amide-15,17-dimethyl ester (**4**)

The product **4** (38.7 mg, 52%) was obtained as a green powder, m.p. 127°C (Found: C, 68.80; H, 7.11; N, 11.04 $C_{43}H_{52}N_6O_6$ requires: C, 68.95; H, 7.00; N, 11.23); UV-Vis λ_{max} ($CHCl_3$) 666 nm (ε 45 000), 610 (3 600), 528 (2 800), 502 (12 500), 404 (162 000); FABMS m/z: 749 ([MH]$^+$, 100%), 579 (43); HRFABMS: $C_{43}H_{53}N_6O_6$ ([MH]$^+$): cacld 749.4026; obsd 749. 4017. ^{1}H NMR data see Table 1 and ^{13}C data see Table 2.

Chlorin e_6 13-(2-N-ethyl)amide-15,17-dimethyl ester (**5**)

To a solution of **1** (30 mg, 0.05 mmol) in THF (10 mL) under nitrogen at room temperature was added ethylamine (20 mL) and the mixture was allowed to react in the dark for 25 h before the solvent was evaporated. The product was purified by preparative TLC on silica gel (developed by 2% methanol in dichloromethane). After chromatography the product was crystallized from dichlomethane/hexane, giving 20.5 mg (63%) of a green solid, m.p. 134°C (Found: C, 69.55; H, 6.85; N, 10.76 $C_{38}H_{45}N_5O_5$ requires: C, 69.90; H, 7.11; N, 10.73); UV-Vis λ_{max} (CH_2Cl_2) 664 nm (ε 52 000), 608 (5 600), 528 (5 000), 500 (16

900), 402 (194 000); **FABMS** m/z: 652 ([MH]$^+$,100%), 580 (19); **HRFABMS**: $C_{38}H_{46}N_5O_5$ ([MH]$^+$) : cacld 652.3499, obsd 652.3475. ^{1}**H NMR data see Table** 1 **and** ^{13}**C data see Table** 2.

Chlorin e_6 13-[1-(3-N-propyl)2-pyrrolidinone]amide-15,17-dimethyl ester (**4**)

To a solution of **1** (15 mg, 0.025 mmol) in THF (5 mL) under nitrogen at room temperature was added 2 g 1-(3-aminopropyl)2-pyrrolidinone (tech., Aldrich) in THF (10 mL). The mixture was allowed to reacted in the dark for 30 h before being poured into aqueous sodium chloride/dichloromethane. The organic layer was washed with water (3×30 mL), dried over anhydrous sodium sulphate and evaporated. The product was purified first by flash chromatography on alumina (Brockman V) to remove unreacted starting material **1** (2 mg, 13%) and excess 1-(3-aminopropyl)2-pyrrolidinone and further by preparative TLC on silica gel (developed by 5% acetone,1% methanol in dichloromethane). After chromatography, the product was crystallized from dichloromethane/hexane, giving 8.5 mg (45%).as a green powder, which was found to be identical to the material prepared from the reaction of **1** with DBN.

ACKNOWLEDGEMENTS

This work was supported by the Natural Sciences and Engineering research Council of Canada.

REFERENCES

1. For excellent reviews of trialkylsilyl triflates, see: (a). Emde, H.; *et al. Synthesis* **1982**, 1-26. (b). Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, 3899-3910.
2. (a). Brownbridge, P. *Synthesis* **1983**, 1-28; 85-104; (b). Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1985**, *26(4)*, 475-476; (c). Kim, S.; Chang, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3669-3670.
3. For a review of DBU and DBN, see: Oediger, H.; Moller, F.; Eiter , K. *Synthesis* **1972**, 591-598.
4. Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44(13)*, 4259-4275.
5. Sheldon, J. C.; Hayes, R. N.; Bowie, J. H. *J. Am. Chem. Soc.* **1984**, *106*, 7711-7715.
6. Wasielewski, M. R.; Thompson, J. F. *Tetrahedron Lett.* **1978**, 1043-1046.
7. Hynninen, P. H.; Wasielewski , M. P.; Katz, J. J. *Acta Chem. Scand. B* **1979**, *33*, 637-648.
8. Ma, L.; Dolphin, D. *Tetrahedron : Asymmetry*, **1995**, *6(2)*, 313-316.
9. Pennington, P. C.; Boyd, S. D.; Horton, H.; Taylor, S. W.; Wulf, D. G.; Katz, J. J.; Strain, H. H. *J. Am. Chem. Soc.* **1967**, *89(15)*, 3871-3875.
10. Hynninen, P. H. *J. Chromatogr.* **1979**, *175*, 89-95.

11. Reed, R.; Reau, R.; Dahan, F.; Bertrand, G. *Angew. chem. Int. Ed. Engl.* **1993**, *32*, 399-401.

12. Lammers, H.; Cohen-Fernandes, P.; Habraken, C. L. *Tetrahedron* **1994**, *50(3)*, 865-870.

13. For a comparison, the spectral data of DBU are: ^{1}H NMR ($CDCl_3$, 200 MHz) δ_H 2.55 ppm (m, 6H); 1.70 ppm (m, 2H); 1.14 ppm (m, 2H); 0.96 ppm (m, 6H). ^{13}C NMR ($CDCl_3$, 50M Hz) δ_C 21.75; 25.23; 27.74; 28.93; 36.53; 43.45; 47.51; 51.94; 160.33 ppm.

14. Fuhrhop, J. H.; Smith, K. M. *Laboratory Methods in Porphyrin and Metalloporphyrin Research*, Elsevier Scientific Publishing Company: Amsterdam. 1975; pp. 132-133.

15. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press: Oxford. 1983; pp. 101-162.

16. Smith, K. M.; Goff, D. A.; Simpson, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 4946-4954.

17. Fischer, H.; Orth, H. *Die Chemie Des Pyrrols*, Johnson Reprint Corporation: New York. 1968; Vol. II, Part 2, pp. 64-66.

(*Received in USA* 20 *September* 1995; *revised* 23 *October* 1995; *accepted* 24 *October* 1995)