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Structure and Biomimetic, Electrochemically-mediated Semisynthesis of the Novel Pentacyclic Indole Danuphylline

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Abstract : The structure of the novel pentacyclic indole, danuphylline, from *Kopsia dasyrachis* was established by spectral analysis. Anodic oxidation of the hexacylic alkaloid methyl 11,12-methylenedioxychanofruticosinate on platinum in TEAP/MeCN-CH_2Cl_2 (2 F mol^{-1}) yielded an iminium ion salt which on silica gel chromatography underwent a facile retro-aldol process to give danuphylline. Allowing the oxidation to proceed until consumption of 4 F mol^{-1} of charge resulted in an unprecedented electrochemically-mediated aromatic chlorination yielding 10-chloro-danuphylline.

Plants of the genus *Kopsia* have provided many novel alkaloids with intriguing carbon skeletons and interesting bioactivities.[1-7] In the course of an investigation of the alkaloidal composition of the North Borneo species, *Kopsia dasyrachis*, we obtained minor amounts of a new indole alkaloid, danuphylline, from the leaf extract, which possesses a novel pentacyclic carbon framework.[1]

Danuphylline **1** was obtained in amorphous form, $[\alpha]_D$ -30 ($CHCl_3$, *c* 0.067). The UV spectrum showed absorption maxima at 214, 225, 248, 283 and 293 nm (log ε 3.95, 4.13, 3.66, 3.03 and 2.99 respectively) typical of a dihydroindole chromophore, while the IR spectrum showed bands due to various carbonyl functions (1720 cm^{-1}, broad; 1669 cm^{-1}). The EIMS of **1** showed a molecular ion at *m/z* 470 with other significant fragment peaks at *m/z* 411 (M - CO_2Me, base) and 383 (M - CO_2Me - CH_2=CH_2). HREIMS measurements (see experimental section) gave the formula $C_{24}H_{26}N_2O_8$. The ^{13}C NMR spectrum showed a total of 24 carbon resonances, in agreement with the formula derived from the molecular ion. The ^1H and ^{13}C NMR spectral data (Table 1) showed the presence of a methylenedioxy substituent at carbon-11 and -12 (an AB doublet at δ_H 6.02, 5.97, *J* 1.5 Hz, δ_C 100.9), a CO_2Me substituent at N-1 (δ_C 153.4), a ketonic carbonyl

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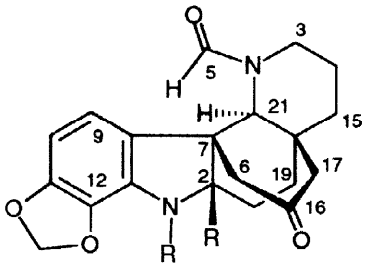
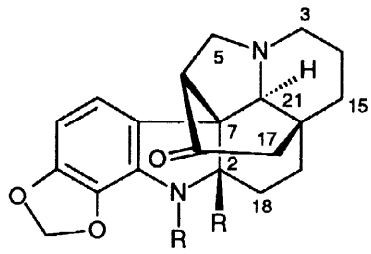
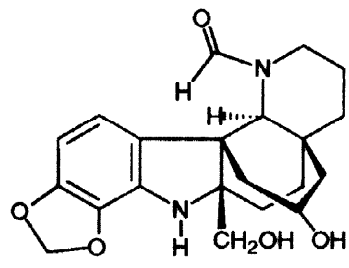
(δ_C 206.7), an ester function (δ_C 170.2) and another carbonyl function associated with a formamide group (δ_H 6.68, δ_C 165.7; IR 1669 cm^{-1}).[8] COSY and HMQC experiments revealed the presence of the following partial structures, *viz.*, 2 isolated methylene groups, a CCH_2CH_2C unit and a $CCH_2CH_2CH_2N$ fragment. The NMR data indicate that compound **1** possesses some of the features common to a basic aspidofractinine skeleton and is in some respects similar to that of the methylchanofruticosinate **2** (see Table 1) which is the major alkaloid present in the leaves, and which has been obtained previously from various *Kopsia* species.[9,10] There are however some notable differences. One major difference is the absence of signals due to the C(5)-C(6) unit and the appearance instead of an additional isolated methylene which is adjacent to a carbonyl function (δ_H 2.40, 2.74). The observation in the COSY spectrum of long range coupling (^4J, W) from one of the H-6 to one of the H-17 indicates that this methylene (C-6) is bridged by a ketonic function (C-16) to another isolated methylene (C-17). Except for this long range coupling, and the expected geminal coupling, the hydrogens of both the C-6 and C-17 methylenes show no other coupling to any adjacent proton, providing confirmation that they are linked to quaternary centres. The direct attachment of the C-6 methylene to C-7 is supported by the correlation from C-7 to H-6 in the HMBC spectrum. Likewise, a similar correlation from C-20 to H-17 confirmed the direct attachment of the C-17 methylene to the quaternary C-20. Another major difference shown by compound **1** when compared with **2** is the appearance of a formamide function (δ_H 6.68, δ_C 165.7),[8] which from the HMBC data is deduced to be at position-5 (^3J, C-5 to H-3, H-21). The location of a formamide function at position-5 is also consistent with the unusual deshielding observed for H-3β (δ_H 4.57) as a result of the anisotropy due to the proximate formamide carbonyl function, which has been observed previously in other compounds.[11] These observations and other correlations from HMBC experiments (Fig. 1) suggest structure **1** for the new compound which represents a novel skeletal arrangement in which a new 6-membered ring incorporating C-7, -6, -16, -17, -20 and -21 has been formed by cleavage of the C-5/C-6 bond of the precursor compound **2**. Compound **1** can thus be considered a "*seco*-methylchanofruticosinate" and represents the first member of this novel group obtained as a natural product.



1 R = CO_2Me



2 R = CO_2Me



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Irradiation of the H-21 resonance causes NOE enhancement of the formamide resonance and *vice-versa*, indicating that the H-21 and the *N*-4 lone pair are now in a *trans* arrangement, in contrast to the conformation

adopted in other aspidofractinine compounds such as kopsingine[12] and the methylchanofruticosinate **2**.[9] Additional confirmation of the structure is provided by reduction ($NaBH_4$/MeOH, 15 min, 29 °C) of **1** which yielded a single product **3** (FABMS, MH^+ *m/z* 387, $C_{21}H_{26}N_2O_5$). The hydroxymethyl protons of **3** are clearly seen as a pair of AB doublets (δ 3.31, 3.96; *J* 11 Hz) as is the H-16 oxymethine which is seen as a doublet of doublets at δ 4.32 (*J* 9, 7 Hz). The HMBC correlations (Fig. 2) observed from the hydroxymethyl protons to C-2 (^2J) as well as to C-7 and C-18 (^3J) provided confirmation for the attachment of the ester function at C-2 in danuphylline **1**. Furthermore, the three bond correlation from H-16 to C-7 and C-20 in the HMBC spectrum of **3** provided further confirmation for the location of the C-16 carbonyl function in danuphylline **1**.

Table 1. ^1H and ^{13}C NMR Spectral Data[a] for **1**, **2**[b] and **3**[c]

Position	δ_C(2)	δ_C(1)	δ_H (1)	δ_C(3)	δ_H (3)
2	76.0	79.1	-	72.4	-
3α	46.5	34.7	2.70 m	34.5	2.69 ddd (14, 11, 7)
3β	-	-	4.57 dd (14.5, 9.5)	-	4.18 dd (14, 9)
5	52.5	165.7	6.68 s	166.0	6.55 s
6α	55.5	39.3	2.40 br d (17)	28.0	1.69 d (16)
6β	-	-	2.74 d (17)	-	2.10 dd (16, 7)
7	58.4	54.5	-	49.5	-
8	129.1	125.0	-	129.4	-
9	116.9	117.0	6.35 d (8)	116.7	6.31 d (8)
10	103.4	103.6	6.56 d (8)	98.6	6.28 d (8)
11	149.0	150.4	-	148.2	-
12	133.9	134.9	-	132.2	-
13	124.1	124.9	-	130.2	-
14a	17.5	19.3	1.73 m	19.1	1.67-1.82 m
14b	-	-	1.95 m	-	1.67-1.82 m
15a	35.3	29.6	1.29 dt (13.5, 9)	31.0	1.17 dt (13, 10)
15b	-	-	1.65 m	-	1.52-1.61 m
16	208.1	206.7	-	62.4	4.32 dd (9, 7)
17a	43.1	46.1	2.48 d (20)	37.2	2.54 d (17)
17b	-	-	2.72 d (20)	-	2.37 dd (17, 9)
18a	23.5	23.0	2.36 ddd (16.5, 12, 8)	24.1	1.93 ddd (15, 6, 1)
18b	-	-	3.28 dt (16.5, 3.5)	-	2.53 ddd (15, 13, 7)
19a	34.9	39.4	1.65 m	39.4	1.52-1.61 m
19b	-	-	1.65 m	-	1.67-1.82 m
20	36.0	34.5	-	31.3	-
21	68.5	61.5	3.38 s	59.5	3.50 s
OCH_2O	100.7	100.9	5.97 d (1.5); 6.02 d (1.5)	100.4	5.85 d (1.5); 5.93 d (1.5)
$NCO_2\underline{Me}$	52.6	53.1	3.88 s	-	-
$N\underline{C}O_2Me$	153.0	153.4	-	-	-
$CO_2\underline{Me}$	53.0	53.0	3.63 s	-	-
$\underline{C}O_2Me$	170.9	170.2	-	-	-
CH_2OH	-	-	-	64.3	3.31 d (11); 3.96 d (11)

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC and NOE; [b] ^{13}C NMR data only; [c] with CD_3OD added

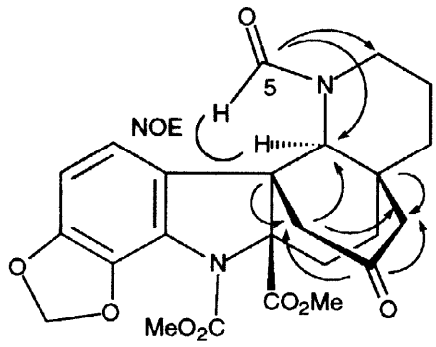


Fig. 1

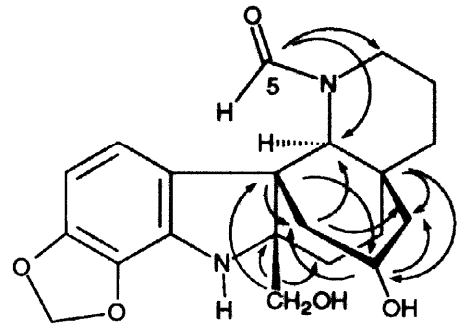
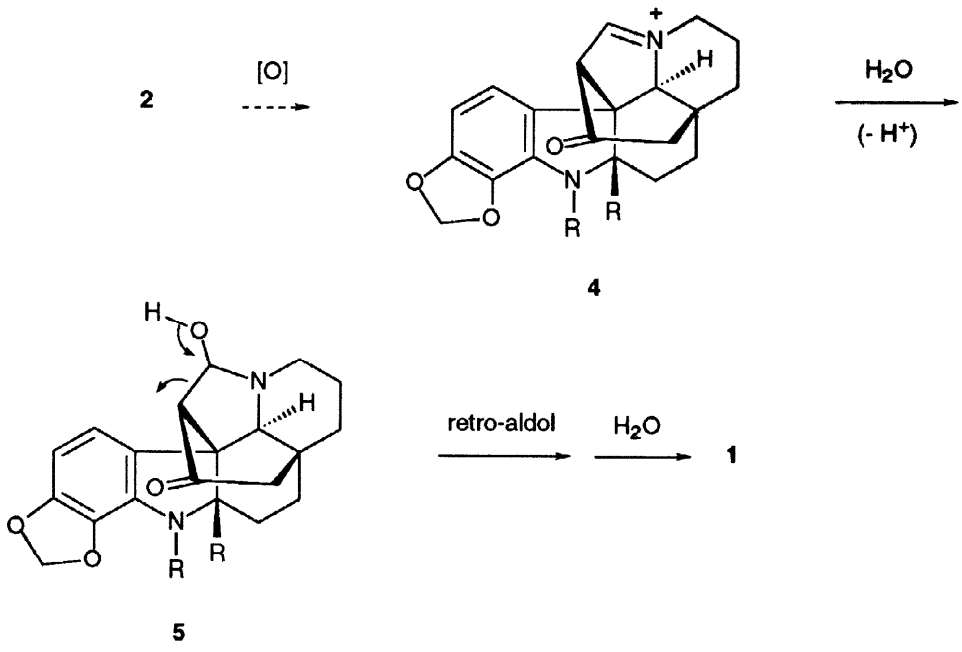


Fig. 2

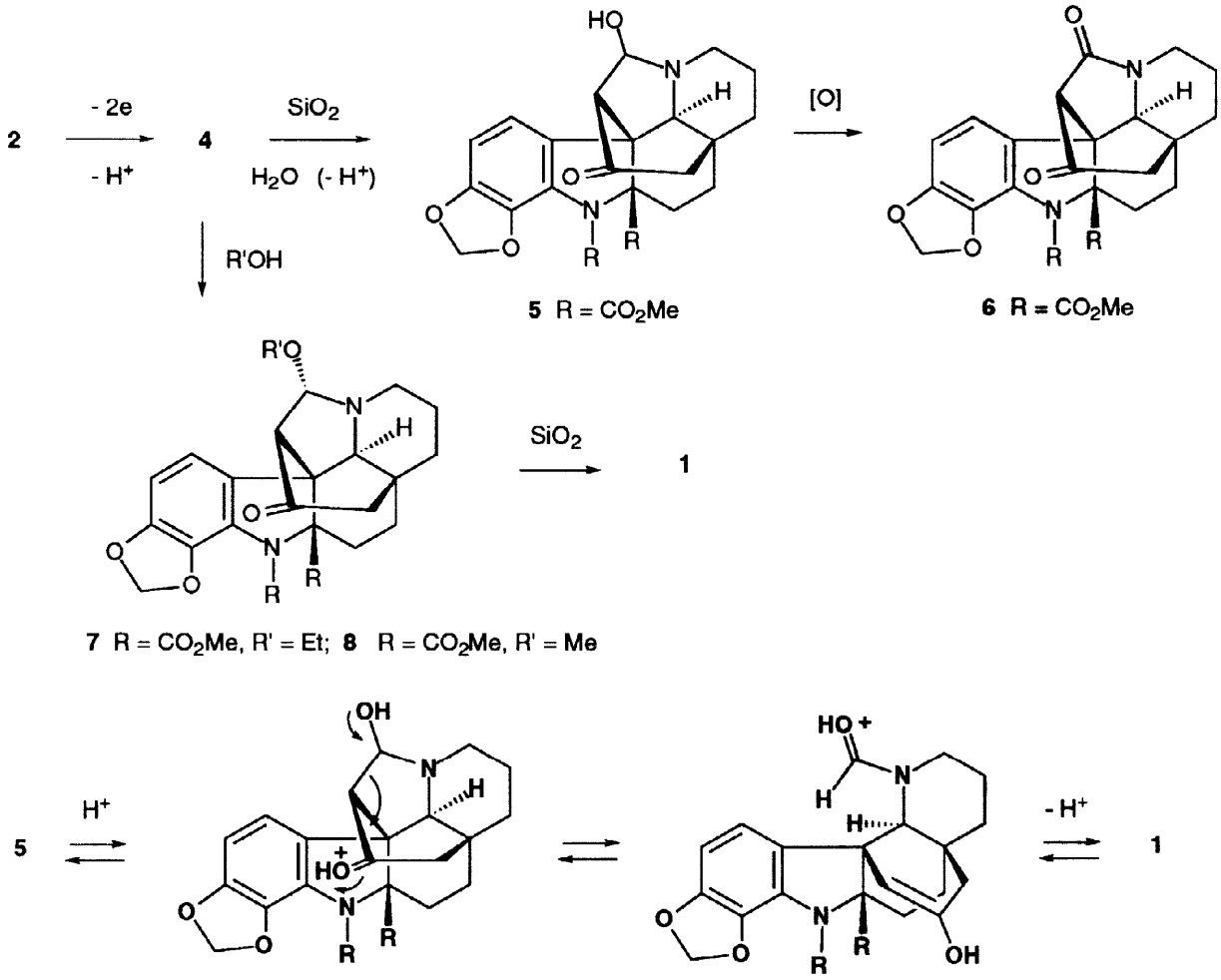
Examination of models indicates that there should be considerable hindrance to free rotation about the formamide C-N bond due to the proximity of the formamide function to the aromatic ring.[13] Rotation about the C-N bond would result in severe repulsive interactions as the π-electron density of the formamide C=O as well as that of the 2 lone-pairs of the oxygen are brought into undue proximity with the π-electron density of the aromatic system. For this same reason a preferred conformation appears to have been adopted such that the formamide carbonyl is directed away from the aromatic ring, which in turn results in the formamide-H being placed within the shielding zone of the aromatic ring current, thus accounting for the unusually high field resonance observed for the formamide-H.



Scheme 1

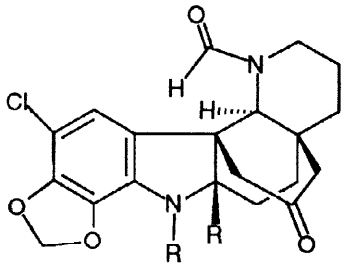
A possible origin of this ring-opened alkaloid[8,14] is from the methylchanofruticosinate **2** which on oxidation provides the iminium ion **4** (Scheme 1). Hydrolysis of this iminium ion **4** gives, the presumably unstable carbinol amine **5**, which could then undergo a retro-aldol-type reaction to provide the *seco*-compound, danuphylline **1**. Since the precursor alkaloid **2** is the abundant alkaloid in the leaf extract, we decided to attempt such a biomimetic conversion of **2** to **1** *via* the electrochemically-generated iminium ion **4**.[15]

On electrochemical oxidation (Pt anode, 30% CH_2Cl_2-MeCN, 0.1M Et_4NClO_4), compound **2** showed two irreversible waves at 1.06 and 1.55 V *vs* Ag/AgCl in the potential range studied as revealed by cyclic voltammetry. Controlled potential electrolysis (Pt gauze anode, Pt cathode) at the first potential peak (1.2 V) in the presence of 2,6-lutidine as proton scavenger, was allowed to proceed until consumption of 2 F mol^{-1}. TLC analysis of the electrolysed solution did not reveal the formation of any discernable product except for the

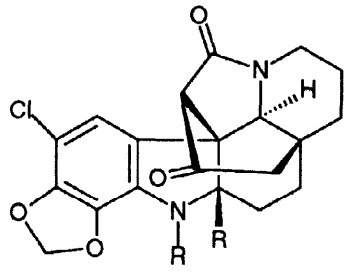


Scheme 2

presence of a strong polar component which was detectable under UV light. Development of the TLC using 2% EtOH-CH_2Cl_2 (or 2% MeOH-CH_2Cl_2) resulted in the formation of a new non-polar product at the expense of the original polar base-line product. Removal of the solvent under reduced pressure, followed by removal of the bulk of the supporting electrolyte by precipitation with CH_2Cl_2, followed by silica gel chromatography (solvent CH_2Cl_2) resulted in the isolation of danuphylline **1** (45%), accompanied by the lactam **6** (5%) as a minor product. If chloroform (without prior removal of the 0.5% of ethanol normally present as stabilizer) was used as the eluting solvent in chromatography, the major products obtained are a mixture of the carbinol amine ether **7** and danuphylline **1**, accompanied by minor amounts of the lactam **6**. The relative proportion of the ether **7** *versus* danuphylline **1** is a function of the time the product mixture is retained on the silica gel (plate or column) during chromatography, indicating that the ether **7** is readily converted to danuphylline **1** on SiO_2. This type of behaviour is typical of an iminium salt formed as the primary product from the anodic oxidation, which is readily quenched by alcohol to give the ether **7**.[15] The iminium salt **4** as well as the carbinol amine ether **7** are also readily transformed by silica gel *via* a facile retro-aldol process to the ring-opened alkaloid danuphylline **1** (Scheme 2). Electrolysis of compound **2** at a carbon anode in 0.1M $LiClO_4$/MeOH (2 F mol^{-1}) on the other hand, gave exclusively the carbinol amine methyl ether **8** which on SiO_2 chromatography furnished a mixture of the methyl ether **8** (72%) and danuphylline **1** (21%).



9 R = CO_2Me



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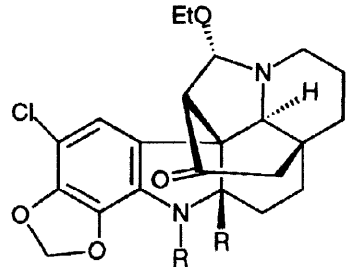

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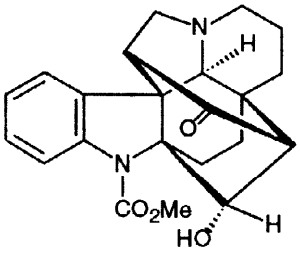

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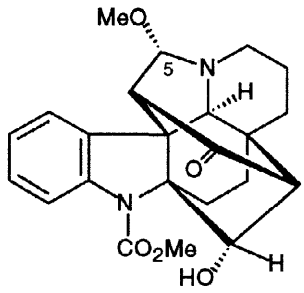
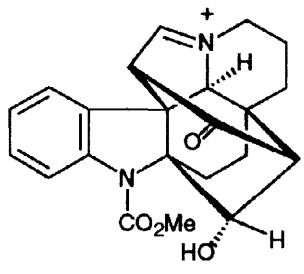


13



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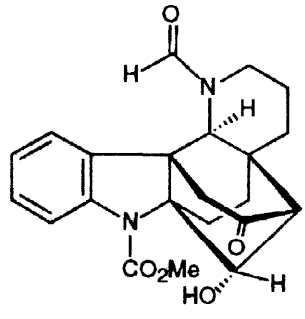

15

If the electrolysis is allowed to proceed smoothly at 1.2 V until consumption of 4 F mol^{-1} of charge, and then the product mixture worked up as before, the chlorinated derivatives **9**, **10** (and **11**) are obtained. Aromatic chlorination of the primary electrochemical product **4** is due to molecular chlorine, generated by oxidation of chloride ions at the anode. The chloride ions are in turn formed by reduction of CH_2Cl_2 at the cathode.[16]

Since these unusual transformations were effected *via* an initial electrochemical oxidation of the methylchanofruticosinate **2**, we were prompted to compare the behaviour of the related heptacyclic carbonyl-bridged indole alkaloid, fruticosamine **12** under similar conditions, since it would be of interest to see whether an iminium ion could be generated which might undergo a similarly facile ring opening to **15**. In the event, anodic oxidation of fruticosamine **12** (carbon anode, Pt cathode, 1.05 V *vs* Ag/AgCl, $LiClO_4$/MeOH, 2 F mol^{-1}) gave the carbinol amine methyl ether **13** (45%) which was presumably formed from nucleophilic solvent attack of the electrochemically-generated iminium ion **14**. Electrolysis of **12** at a platinum anode (Pt cathode, 0.1M TEAP/30% CH_2Cl_2-MeCN) on the other hand, consumes 2 F mol^{-1} of charge and gave a stable iminium salt which on treatment with MeOH gave exclusively the 5α-methyl ether **13**. In contrast to the ether **8**, the carbinol amine ether **13** was stable under the conditions of silica gel chromatography with no evidence of formation of any ring-opened product.[17]

The above concise semisynthesis has therefore confirmed the structure of danuphylline **1** and in addition vindicated the proposal that the likely origin of danuphylline **1** is *via* a facile retro-aldol reaction of the carbinol amine **5** derived from the iminium salt of the abundant methyl chanofruticosinate precursor **2**.

Experimental Section

General Experimental Procedures. UV spectra were recorded on a Shimadzu UV-3101PC spectrophotometer. IR spectra were recorded on a Perkin-Elmer 1600 Series FT-IR spectrophotometer. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. EI mass spectra were obtained on a VG ProSpec mass spectrometer. HREIMS and FABMS were obtained on a VG AutoSpec mass spectrometer courtesy of Dr. J. K. MacLeod, Research School of Chemistry, Australian National University. LCMS was obtained on a Perkin Elmer API 100 instrument. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a JEOL JNM-LA400 spectrometer at 400 and 100 MHz respectively. All electrochemical experiments were performed on a BAS 100B electrochemical analysis system using a 100 mL cylindrical glass cell (BAS MR-1195) fitted with a teflon cell top. The electrodes used for cyclic voltammetry were a platinum wire electrode (1.6 mm diameter), or a glassy carbon electrode (3 mm diameter), with platinum as the counter electrode, and Ag/AgCl/NaCl (3M) as the reference electrode. Preparative electrolysis were performed with a platinum gauze electrode (diameter 4 cm, height 5 cm), or a reticulated vitreous carbon electrode (5 mm thickness, diameter 4 cm, height 5 cm).

Collection, Extraction and Isolation. Plant material was collected in Sabah, Malaysia. Herbarium voucher specimens are deposited at the Herbarium of the Sabah Forest Department, Sandakan, Sabah, Malaysia. Extraction of the ground leaves was carried out in the usual manner by partitioning the concentrated EtOH extract with dilute acid to yield a basic fraction as described in detail elsewhere.[12,18] The crude alkaloidal mixture was first chromatographed over SiO_2 and eluted with $CHCl_3$ with increasing proportions of MeOH to give 13 major fractions. The middle fraction (fraction 7), which comprised a mixture of several alkaloids, was subjected to repeated fractionation (CC and Centrifugal TLC) to give danuphylline **1** (amorphous solid, yield 0.008 g Kg^{-1}). Solvent systems used were 2% MeOH-$CHCl_3$ (CC) and $CHCl_3$ (centrifugal TLC).

Danuphylline 1. $[\alpha]_D$ -30 ($CHCl_3$, *c* 0.067). IR (dry film) υ max 1720 (broad) and 1669 cm^{-1}. UV (EtOH), λ_{max} (log ε) 214 (3.95), 225 (4.13), 248 (3.66), 283 (3.03) and 293 (2.99). EIMS, *m/z* (rel. int.): 470 [M^+] (48), 411 (100), 383 (18), 354 (11), 291 (9), 124 (16), and 96 (10). HREIMS found *m/z* 470.1694 , calcd for $C_{24}H_{26}N_2O_8$, 470.1694. ^1H and ^{13}C NMR: see Table 1.

Reduction of danuphylline 1 to the diol 3. To a solution of danuphylline **1** (12 mg) in MeOH (2 mL) was added $NaBH_4$ (10 mg) and the mixture stirred at room temperature (29 °C) for 15 min. The solvent was then removed under reduced pressure and water (5 mL) was added. The mixture was then thoroughly extracted with $CHCl_3$ and the extract washed with water and then dried (Na_2SO_4). Chromatography of the residue after removal of the solvent (SiO_2, 2% MeOH-CH_2Cl_2) gave the diol **3** (5.4 mg, 45%).

Compound 3. Amorphous solid, $[\alpha]_D$ -93 (MeOH, *c* 0.028). IR (Nujol) υ max 3426, 3338, 3235, 1639, and 1056 cm^{-1}. UV (EtOH), λ_{max} (log ε) 220 (4.09), 248 (3.43) and 285 (3.60). EIMS, *m/z* (rel. int.): 368 [M - H_2O] (100), 355 (51), 350 (40), 337 (28), 242 (31), 124 (32) and 96 (27). FABMS, MH^+, *m/z* 387 ($C_{21}H_{26}N_2O_5$ + H). API-LCMS, MH^+, *m/z* 387 ($C_{21}H_{26}N_2O_5$ + H). ^1H and ^{13}C NMR: see Table 1.

Anodic oxidation of methyl 11,12-methylenedioxychanofruticosinate 2. A typical experimental procedure is as follows: Methyl 11,12-methylenedioxychanofruticosinate **2** (50 mg, 0.1 mmol) in 50 mL of a mixed solvent (30% CH_2Cl_2-MeCN) containing Et_4NClO_4 (0.1 M) and 2,6-lutidine (0.2 mmol) was placed in a divided cell under nitrogen. The anodic potential (Pt gauze) was maintained at 1.2 V *vs* Ag/AgCl and the electrolysis continued until 2 F mol^{-1} had been transferred. The progress of electrolysis was also monitored by cyclic voltammetry. The solution was then evaporated to dryness and CH_2Cl_2 (12 mL) was added. The precipitated electrolyte was then filtered off and the residue washed with CH_2Cl_2. The CH_2Cl_2 extract was then chromatographed over silca gel (CH_2Cl_2) to afford the lactam **6** (5%) and danuphylline **1** (45%). If chloroform (without prior removal of the 0.5% of ethanol normally present as stabilizer) was used as the eluting solvent in chromatography, the major products obtained were a mixture of the carbinol amine ethyl ether **7** (61%) and danuphylline **1** (4%), accompanied by minor amounts of the lactam **6** (5%). The relative

proportion of the ether **7** *versus* danuphylline **1** is a function of the time the product mixture is retained on the silica gel (plate or column) during chromatography.

Compound 6. Colourless oil, $[\alpha]_D$ 164 ($CHCl_3$, *c* 0.081). IR (dry film) υ max 1726 (broad), 1631 cm^{-1}. ^1H NMR ($CDCl_3$), δ 1.46-1.55 (2H, m, H-15, H-19), 1.57-1.63 (2H, m, H-15, H-19), 1.65-1.70 (1H, m, H-14), 1.94-2.05 (1H, m, H-14), 2.12 (1H, ddd, *J* = 16.5, 13.5, 5 Hz, H-18), 2.23 (1H, d, *J* = 19 Hz, H-17), 2.73 (1H, d, *J* = 19 Hz, H-17), 2.85 (1H, td, *J* = 13, 4.5 Hz, H-3), 3.00 (1H, s, H-21), 3.36 (1H, dt, *J* = 16.5, 4 Hz, H-18), 3.37 (1H, s, H-6), 3.63 (3H, s, CO_2Me), 3.88 (3H, s, NCO_2Me), 4.12 (1H, dd, *J* = 13, 6 Hz, H-3), 5.97 (1H, d, *J* = 1.5 Hz, OCH_2O), 5.99 (1H, d, *J* = 1.5 Hz, OCH_2O), 6.49 (1H, d, *J* = 8 Hz, H-10) and 6.52 (1H, d, *J* = 8 Hz, H-9). ^{13}C NMR ($CDCl_3$), δ 19.5 (C-14), 23.0 (C-18), 33.1 (C-19), 33.7 (C-15), 36.8 (C-20), 40.4 (C-3), 42.9 (C-17), 52.9 (CO_2Me), 53.1 (NCO_2Me), 54.0 (C-7), 64.1 (C-6), 68.4 (C-21), 75.7 (C-2), 101.0 (OCH_2O), 103.7 (C-10), 116.2 (C-9), 123.9 (C-13), 126.6 (C-8), 134.6 (C-12), 150.0 (C-11), 153.0 (NCO_2Me), 168.2 (C-5), 170.1 (CO_2Me) and 199.1 (C-16). EIMS, *m/z* (rel. int.): 468 [M^+] (76), 409 (100), 365 (59) and 349 (44). HREIMS found *m/z* 468.1530, calcd for $C_{24}H_{24}N_2O_8$, 468.1533.

Compound 7. Pale yellow oil, $[\alpha]_D$ 139 ($CHCl_3$, *c* 0.10). IR (dry film) υ max 1718 (broad), 1243 cm^{-1}. ^1H NMR ($CDCl_3$), δ 1.27 (3H, t, *J* = 7 Hz, OCH_2CH_3), 1.34-1.46 (4H, m, H-14, H-15, 2 x H-19), 1.53-1.59 (1H, m, H-15), 1.85-2.00 (1H, m, H-14), 2.05 (1H, ddd, *J* = 16, 12, 5 Hz, H-18), 2.13 (1H, d, *J* = 19 Hz, H-17), 2.63 (1H, d, *J* = 19 Hz, H-17), 2.70 (1H, s, H-21), 2.94 (1H, td, *J* = 14.5, 4 Hz, H-3), 3.10 (1H, s, H-6), 3.21 (1H, dd, *J* = 14.5, 5 Hz, H-3), 3.25 (1H, dt, *J* = 16, 3.5 Hz, H-18), 3.56 (2H, q, *J* = 7 Hz, OCH_2CH_3), 3.61 (3H, s, CO_2Me), 3.85 (3H, s, NCO_2Me), 4.31 (1H, s, H-5), 5.93 (1H, d, *J* = 1.5 Hz, OCH_2O), 5.94 (1H, d, *J* = 1.5 Hz, OCH_2O), 6.51 (1H, d, *J* = 8 Hz, H-10) and 7.72 (1H, d, *J* = 8 Hz, H-9). ^{13}C NMR ($CDCl_3$), δ 15.3 (OCH_2CH_3), 17.6 (C-14), 23.0 (C-18), 34.1 (C-19), 34.2 (C-15), 36.0 (C-20), 44.4 (C-17), 44.6 (C-3), 52.6 (CO_2Me), 52.9 (NCO_2Me), 57.5 (C-7), 62.1 (C-6), 63.8 (OCH_2CH_3), 70.7 (C-21), 76.2 (C-2), 94.1 (C-5), 100.6 (OCH_2O), 103.2 (C-10), 120.3 (C-9), 124.2 (C-13), 128.6 (C-8), 133.7 (C-12), 148.7 (C-11), 153.0 (NCO_2Me), 170.9 (CO_2Me) and 207.0 (C-16). EIMS, *m/z* (rel. int.): 498 [M^+] (36), 453 (47), 439 (100), 425 (31) and 365 (74). HREIMS found *m/z* 498.1997, calcd for $C_{26}H_{30}N_2O_8$, 498.2002.

Anodic oxidation of compound 2 at a carbon anode in methanol. Anodic oxidation of compound **2** (50 mg, 0.1 mmol) was carried out at a vitreous carbon anode (1.1 V *vs* Ag/AgCl) in 0.1 M $LiClO_4$/MeOH and 2,6-lutidine (0.2 mmol) under nitrogen until consumption of 2 F mol^{-1} of charge as described above. Water (15 mL) was then added to the anolyte and the mixture was then extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and then dried over anhydrous Na_2SO_4. The NMR spectrum of the crude

product at this stage showed that the sole product was the carbinol amine methyl ether **8**. Further purification by chromatography over SiO_2 (1% MeOH-CH_2Cl_2) gave a mixture of **8** (72%) and danuphylline **1** (21%).

Compound 8. Pale yellow oil, $[\alpha]_D$ 116 ($CHCl_3$, *c* 0.05). IR (dry film) υ max 1715 (broad), 1631, 1250 cm^{-1}. ^1H NMR ($CDCl_3$), δ 1.34-1.44 (4H, m, H-14, H-15, 2 x H-19), 1.53-1.59 (1H, m, H-15), 1.89-1.96 (1H, m, H-14), 2.06 (1H, ddd, *J* = 16, 12.5, 6 Hz, H-18), 2.13 (1H, d, *J* = 19 Hz, H-17), 2.63 (1H, d, *J* = 19 Hz, H-17), 2.70 (1H, s, H-21), 2.95 (1H, td, *J* = 14, 4 Hz, H-3), 3.12 (1H, s, H-6), 3.22 (1H, dd, *J* = 14, 5.5 Hz, H-3), 3.25 (1H, dt, *J* = 16, 4 Hz, H-18), 3.39 (3H, s, OMe), 3.61 (3H, s, CO_2Me), 3.85 (3H, s, NCO_2Me), 4.23 (1H, s, H-5), 5.93 (1H, d, *J* = 1.5 Hz, OCH_2O), 5.94 (1H, d, *J* = 1.5 Hz, OCH_2O), 6.51 (1H, d, *J* = 8 Hz, H-10) and 7.64 (1H, d, *J* = 8 Hz, H-9). ^{13}C NMR ($CDCl_3$), δ 17.6 (C-14), 23.0 (C-18), 34.1 (C-15), 34.2 (C-19), 36.1 (C-20), 44.4 (C-17), 44.8 (C-3), 52.6 (CO_2Me), 52.9 (NCO_2Me), 55.6 (OMe), 57.5 (C-7), 61.3 (C-6), 70.8 (C-21), 76.2 (C-2), 95.8 (C-5), 100.6 (OCH_2O), 103.2 (C-10), 120.3 (C-9), 124.2 (C-13), 128.6 (C-8), 133.8 (C-12), 148.8 (C-11), 153.0 (NCO_2Me), 170.9 (CO_2Me) and 207.0 (C-16). EIMS, *m/z* (rel. int.): 484 [M^+] (15), 452 (41), 424 (50), 395 (69), 365 (100) and 305 (19). HREIMS found *m/z* 484.1834, calcd for $C_{25}H_{28}N_2O_8$, 484.1846.

Anodic oxidation of compound 2 (4 F mol^{-1}). Anodic oxidation (Pt gauze, 1.2 V *vs* Ag/AgCl) of compound **2** (50 mg) in 30% CH_2Cl_2-MeCN containing 0.1 M Et_4NClO_4 and 2,6-lutidine (0.2 mmol) in the manner described above, but allowing the electrolysis to proceed until consumption of 4 F mol^{-1}, gave a product mixture which on work-up as described above, followed by SiO_2 chromatography (Et_2O) yielded a mixture of 10-chlorodanuphylline **9** (47%) and the chlorinated lactam **10** (5%). If chloroform was used in the work-up and subsequent chromatography, a mixture of **9** (34%), **10** (17%) and the chlorinated carbinol amine ethyl ether **11** (5%) was obtained.

10-Chlorodanuphylline 9. Colourless oil, $[\alpha]_D$ -21 ($CHCl_3$, *c* 0.38). IR (dry film) υ max 1715, 1673 cm^{-1}. ^1H NMR ($CDCl_3$), δ 1.29 (1H, dt, *J* = 13, 9 Hz, H-15), 1.57-1.73 (3H, m, H-15, 2 x H-19), 1.70-1.80 (1H, m, H-14), 1.87-2.03 (1H, m, H-14), 2.35 (1H, ddd, *J* = 17, 12.5, 7 Hz, H-18), 2.38 (1H, d, *J* = 17 Hz, H-6), 2.48 (1H, d, *J* = 20 Hz, H-17), 2.62-2.75 (1H, m, H-3), 2.71 (1H, d, *J* = 17 Hz, H-6), 2.73 (1H, d, *J* = 20 Hz, H-17), 3.27 (1H, dt, *J* = 17, 3.5 Hz, H-18), 3.39 (1H, brs, H-21), 3.64 (3H, s, CO_2Me), 3.87 (3H, s, NCO_2Me), 4.58 (1H, dd, *J* = 14.5, 9 Hz, H-3), 6.06 (1H, d, *J* = 1.5 Hz, OCH_2O), 6.11 (1H, d, *J* = 1.5 Hz, OCH_2O), 6.39 (1H, s, H-9) and 6.82 (1H, s, H-5). ^{13}C NMR ($CDCl_3$), δ 19.2 (C-14), 22.9 (C-18), 29.6 (C-15), 34.6 (C-20), 34.8 (C-3), 39.1 (C-6), 39.3 (C-19), 46.1 (C-17), 53.1 (CO_2Me), 53.2 (NCO_2Me), 54.7 (C-7), 61.3 (C-21), 79.3 (C-2), 101.7 (OCH_2O), 109.0 (C-10), 117.8 (C-9), 123.8 (C-13), 126.3 (C-8), 135.6 (C-12), 146.6 (C-11), 153.2 (NCO_2Me), 165.5 (C-5), 169.9 (CO_2Me) and 206.1 (C-16). EIMS, *m/z* (rel. int.): 506 [M + 2] (16), 504 [M^+] (50), 445 (100), 417 (20) and 388 (16). HREIMS found *m/z* 504.1296, calcd for $C_{24}H_{25}N_2{}^{35}ClO_8$, 504.1299.

Compound 10. Colourless oil, $[\alpha]_D$ 157 ($CHCl_3$, *c* 0.03). IR (dry film) υ max 1741, 1716 (broad) cm^{-1}. ^1H NMR ($CDCl_3$), δ 1.48 (1H, td, *J* = 13.5, 4 Hz, H-19), 1.54-1.72 (4H, m, H-14, 2 x H-15, H-19), 1.94-2.06 (1H, m, H-14), 2.11 (1H, ddd, *J* = 16.5, 13.5, 4.5 Hz, H-18), 2.23 (1H, d, *J* = 19 Hz, H-17), 2.74 (1H, d, *J* = 19 Hz, H-17), 2.87 (1H, td, *J* = 14, 4.5 Hz, H-3), 2.98 (1H, s, H-21), 3.35 (1H, s, H-6), 3.35 (1H, dt, *J* = 16.5, 3.5 Hz, H-18), 3.65 (3H, s, CO_2Me), 3.87 (3H, s, NCO_2Me), 4.14 (1H, dd, *J* = 14, 6 Hz, H-3), 6.06 (1H, d, *J* = 1.5 Hz, OCH_2O), 6.07 (1H, d, *J* = 1.5 Hz, OCH_2O) and 6.53 (1H, s, H-9). ^{13}C NMR ($CDCl_3$), δ 19.5 (C-14), 22.9 (C-18), 32.9 (C-19), 33.6 (C-15), 36.8 (C-20), 40.5 (C-3), 42.8 (C-17), 53.0 (CO_2Me), 53.2 (NCO_2Me), 54.1 (C-7), 63.8 (C-6), 68.3 (C-21), 75.7 (C-2), 101.8 (OCH_2O), 109.1 (C-10), 117.0 (C-9), 122.9 (C-13), 127.6 (C-8), 135.3 (C-12), 146.3 (C-11), 153.8 (NCO_2Me), 167.9 (C-5), 169.9 (CO_2Me) and 198.6 (C-16). EIMS, *m/z* (rel. int.): 504 [M^+ + 2] (7), 502 [M^+] (20), 443 (100), 399 (18) and 140 (17). HREIMS found *m/z* 502.1146, calcd for $C_{24}H_{23}N_2{}^{35}ClO_8$, 502.1143.

Compound 11. Pale yellow oil, $[\alpha]_D$ 110 ($CHCl_3$, *c* 0.05). IR (dry film) υ max 1720 (broad), 1241 cm^{-1}. ^1H NMR ($CDCl_3$), δ 1.31 (3H, t, *J* = 7 Hz, OCH_2CH_3), 1.32-1.48 (4H, m, H-14, H-15, 2 x H-19), 1.52-1.60 (1H, m, H-15), 1.83-1.99 (1H, m, H-14), 2.05 (1H, ddd, *J* = 16, 11, 6 Hz, H-18), 2.12 (1H, d, *J* = 19 Hz, H-17), 2.62 (1H, d, *J* = 19 Hz, H-17), 2.68 (1H, s, H-21), 2.95 (1H, td, *J* = 14.5, 5 Hz, H-3), 3.05 (1H, s, H-6), 3.21 (1H, dd, *J* = 14.5, 5 Hz, H-3), 3.22 (1H, dt, *J* = 16, 3.5 Hz, H-18), 3.50 (1H, dq, *J* = 18, 7 Hz, OCH_2CH_3), 3.57 (1H, dq, *J* = 18, 7 Hz, OCH_2CH_3), 3.62 (3H, s, CO_2Me), 3.84 (3H, s, NCO_2Me), 4.31 (1H, s, H-5), 6.02 (2H, brs, OCH_2O) and 7.94 (1H, s, H-9). ^{13}C NMR ($CDCl_3$), δ 15.2 (OCH_2CH_3), 17.8 (C-14), 23.0 (C-18), 34.2 (C-19), 36.1 (C-15), 36.1 (C-20), 44.3 (C-17), 45.0 (C-3), 52.7 (CO_2Me), 53.0 (NCO_2Me), 57.6 (C-7), 62.2 (C-6), 63.7 (OCH_2CH_3), 70.8 (C-21), 76.3 (C-2), 93.7 (C-5), 101.4 (OCH_2O), 108.2 (C-10), 121.9 (C-9), 123.4 (C-13), 129.6 (C-8), 134.4 (C-12), 145.1 (C-11), 152.9 (NCO_2Me), 170.7 (CO_2Me) and 206.7 (C-16). EIMS, *m/z* (rel. int.): 534 [M^+ + 2] (13), 532 [M^+] (40), 487 (42), 473 (100) and 428 (26). HREIMS found *m/z* 532.1611, calcd for $C_{26}H_{29}N_2ClO_8$, 532.1612.

Anodic oxidation of fruticosamine 12. Anodic oxidation (vitreous carbon anode, Pt cathode, 1.05 V *vs* Ag/AgCl) of fruticosamine **12** (50 mg) in 0.1M $LiClO_4$/MeOH and 2,6-lutidine (0.2 mmol) until consumption of 2 F mol^{-1}, gave a product mixture which on work-up as described above, followed by SiO_2 chromatography (1% MeOH-CH_2Cl_2), yielded the carbinol amine ether **13** (45%). Anodic oxidation (Pt gauze anode, Pt cathode, 1.2 V *vs* Ag/AgCl) of **12** (50 mg) in 30% CH_2Cl_2-MeCN containing Et_4NClO_4 (0.1 M) and 2,6-lutidine (0.2 mmol) until consumption of 2 F mol^{-1} gave a stable iminium salt as the primary product of the electrolysis. Addition of MeOH to the residue after removal of the solvent, followed by SiO_2 chromatography (2% MeOH-CH_2Cl_2) gave **13** (71%) as the sole product.

Compound 13. Amorphous solid, $[\alpha]_D$ 68 ($CHCl_3$, *c* 0.22). IR (dry film) υ max 3416, 1721, 1680 cm^{-1}. ^1H NMR ($CDCl_3$), δ 1.22-1.30 (1H, m, H-14), 1.22-1.30 (2H, m, 2 x H-18), 1.38 (1H, td, *J* = 13, 5 Hz, H-19), 1.60-1.70 (1H, m, H-15), 1.83 (1H, brd, *J* = 13 Hz, H-19), 2.20 (1H, dd, *J* = 12, 10 Hz, H-15), 2.27-2.36 (1H, m, H-14), 2.34 (1H, s, H-17), 2.82 (1H, s, H-6), 2.95-3.02 (1H, m, H-3), 3.05-3.12 (1H, m, H-3), 3.19 (3H, s, OMe), 3.40 (1H, s, H-21), 3.91 (3H, s, NCO_2Me), 4.09 (1H, s, H-16), 4.18 (1H, s, H-5), 5.68 (1H, s, 16-OH), 7.01 (1H, td, *J* = 8, 1 Hz, H-10), 7.20 (1H, td, *J* = 8, 1 Hz, H-11), 7.47 (1H, brd, *J* = 8 Hz, H-12) and 7.74 (1H, dd, *J* = 8, 1 Hz, H-9). ^{13}C NMR ($CDCl_3$), δ 19.5 (C-14), 21.8 (C-18), 31.4 (C-19), 34.7 (C-20), 35.1 (C-15), 47.8 (C-3), 53.2 (NCO_2Me), 53.6 (OMe), 59.0 (C-7), 59.8 (C-6), 65.8 (C-17), 65.9 (C-21), 71.2 (C-2), 71.9 (C-16), 99.4 (C-5), 115.4 (C-9), 123.1 (C-10), 128.1 (C-12), 128.5 (C-11), 130.6 (C-8), 140.2 (C-13), 155.0 (NCO_2Me) and 209.5 (CO). EIMS, *m/z* (rel. int.): 410 [M^+, $C_{23}H_{26}N_2O_5$] (35), 379 (100), 309 (20), 283 (67) and 264 (32). API-LCMS, MH^+, *m/z* 411 ($C_{23}H_{26}N_2O_5$ + H).

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References and Notes

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