Electrochemical oxidation of aspidofractinine-type alkaloids: Formation of kopsine, kopsidine, kopsinitarine and bisindole derivatives

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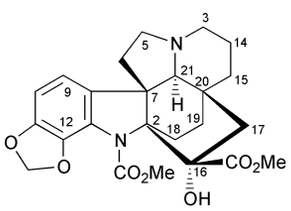
Anodic oxidation of kopsamine on platinum in acetonitrile results in cyanation or cyanomethylation, following ring closure, while oxidation on vitreous carbon in methanol yields a dimerization product with a C_2 element of symmetry. This behaviour is reproduced in the aromatic congeners of kopsamine, kopsiflorine and 11-methoxy-kopsilongine. Oxidation of kopsingine on platinum in CH_2Cl_2–MeCN leads to a stable conjugated iminium salt which can be trapped by alcohol or water nucleophiles to give kopsidines A, B, and C. Kopsidines A and B can also be obtained directly from electrooxidation in methanol or ethanol. Oxidation of dihydrokopsingine in acetonitrile gives the 17-to-5 and 17-to-3 oxo-bridged compounds directly, while oxidation in methanol yields an additional product which is a caged kopsinitarine derivative. Oxidation of an aspidofractinine derivative without unsaturation in the piperidine ring and with a C(17)-αOH function gives a C_2 symmetric dimerization product as well as a caged kopsinitarine-type product. Possible pathways leading to the various products are presented.

Although there have been extensive studies on the reactions and synthesis of the monoterpenoid indole alkaloids, there has been comparatively much less attention devoted to the electroorganic chemistry of this important group of compounds. Electrochemically mediated reactions offer mild, often higher-yielding alternatives for carbon–carbon bond formation as well as functional-group interconversions, in contrast to conventional chemical methods, and in addition can also provide useful mechanistic and biogenetic insights into the relationships between the various skeletal groups of indole alkaloids.[1–19] We have previously reported the preliminary results of our investigations on the anodic oxidation of some indole derivatives of the aspidofractinine group and herein would like to present the full results.[17,18] The availability of the aspidofractinine compounds kopsamine **1** and kopsingine **2**, which are the major alkaloidal constituents of *Kopsia dasyrachis* and *K. teoi*, respectively,[20,21] afforded the opportunity to probe the behaviour of these representative aspidofractinine compounds on anodic oxidation.



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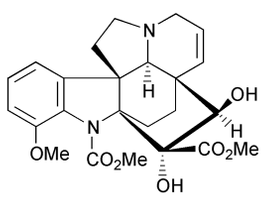

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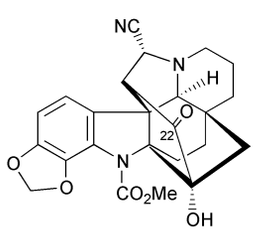

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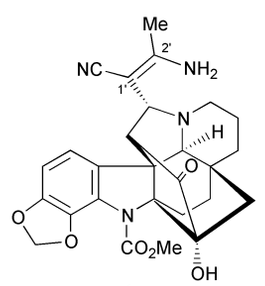

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Results and discussion

On electrochemical oxidation on a platinum anode in acetonitrile, in the presence of 0.1 M Et_4NClO_4 as supporting electrolyte, kopsamine **1** exhibits two irreversible waves at 0.86 and 1.66 V *versus* Ag/AgCl in the potential range investigated as revealed by cyclic voltammetry (CV). Controlled-potential electrolysis (CPE) (Pt gauze anode, Pt cathode) at the first potential peak (1.05 V) in the presence of 2,6-lutidine (2,6-dimethylpyridine) as proton scavenger resulted in the consumption of 2.5 faradays mol^{-1}. † Analysis of the electrolysed solution revealed the formation of two products in moderate yields (combined yield of 45%) and chromatographic separation followed by spectroscopic analysis revealed the structures **3** (23%) and **4** (22%) for the two products.

† 1 faraday = 96490 C.

Compound **3** was obtained as a light yellow oil. The IR spectrum showed bands at 3303, 2250, 1761, and 1681 cm^{-1}, suggesting the presence of hydroxylic, cyano, cyclic ketone, and carbamate functionalities, respectively. The EI-mass spectrum showed an M^+ at *m*/*z* 449, indicating the presence of a third nitrogen, and HRMS provided the molecular formula $C_{24}H_{23}N_3O_6$. The presence of a strong fragment peak due to loss of CN in the mass spectrum (*m*/*z* 423), an IR absorption band at 2250 cm^{-1}, and a quaternary carbon resonance at δ_C 118.8 in the ^{13}C NMR spectrum indicated the presence of a cyano group. Comparison of the ^1H and ^{13}C NMR spectral data of the starting compound kopsamine **1** with compound **3**, revealed some notable changes. For instance, while the signals of the carbamate function are intact, the signals due to the C(16) ester function are conspicuously absent in **3**; instead a low-field carbon resonance at δ_C 210.2 due to a ketone function

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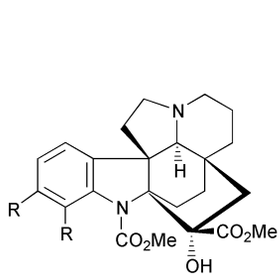
is observed. The ^{1}H NMR spectrum showed a pair of AB doublets at δ 4.12 and 2.80 with J 3.5 Hz, in addition to the two others due to the aromatic H(9), H(10), and the methylenedioxy group, which are also common in the spectrum of kopsamine. The COSY and HMQC spectra revealed the presence of the following partial structures *N*CHCH, *N*$CH_2CH_2CH_2$, and CH_2CH_2, from which it can be inferred that the AB doublets at δ 4.12 and 2.80 correspond to H(5) and H(6) respectively, indicating that both these positions are substituted in **3**. The molecular formula [15 double-bond equivalents (DBE)] requires a heptacyclic ring system, suggesting that additional ring formation has occurred, which leads to a 5-cyano-substituted kopsine structure as shown in **3**. Further confirmation of the structure was provided by the observed two-bond correlations from CN to H(5), C(22) to H(6), and three-bond correlations from CN, C(16), C(8) to H(6), and C(22) to H(17) in the HMBC spectrum. Since the stereochemistry of H(6) is fixed by formation of the carbonyl bridge, the observed H(5)–H(6) coupling constant of 3.5 Hz requires H(5) and H(6) to be *trans*, and hence the stereochemistry of the CN substituent must be α.

Compound **4** analysed for $C_{27}H_{28}N_4O_6$, indicating incorporation of an additional mole of MeCN when compared with compound **3**. The IR spectrum showed the presence of cyano (2186 cm^{-1}) and NH_2 (3262, 3246 cm^{-1}) functions, in addition to hydroxylic (3360 cm^{-1}), cyclic ketone (1746 cm^{-1}) and carbamate (1679 cm^{-1}) absorptions. Analysis of the NMR spectral data revealed a kopsine-like derivative[20] substituted at position-5 by a four-carbon side chain ($C_4H_5N_2$). This is also indicated by the observation of strong fragment peaks at *m*/*z* 422 (M − $C_4H_5N_2$ − H) and 394 (M − $C_4H_5N_2$ − CH_2=CH_2 − H) in the mass spectrum. The ^{1}H NMR spectrum also showed a pair of AB doublets due to H(5) and H(6) at δ 3.79 and 2.37 respectively, and the ^{13}C NMR spectrum showed a resonance at δ_C 216.3 due to a ketone function in place of peaks due to the ester group, indicating the presence of the same kopsinyl moiety as in compound **3**. In addition, the NMR spectral data showed the presence of a vinylic methyl (δ_H 2.06), NH_2 (δ_H 4.91), CN (δ_C 120.4) and a conjugated, tetrasubstituted double bond (δ_C 85.4, 154.6), revealing at the same time the substituents of the olefinic moiety comprising the four-carbon side chain at carbon-5. The observation of three- and two-bond correlations in the HMBC spectrum from the higher field olefinic carbon (δ_C 85.4) to H(6) and H(5), respectively, indicates placement of the CN substituent at the α-carbon (C-1′). The geometry of the double bond in the side-chain substituent was assigned as *E*, as irradiation of the amino hydrogens causes NOE enhancements of H(5) and H(6), in addition to the methyl group, indicating that the amino group is on the same side as the kopsinyl moiety. The observed J_{5-6}-value of 3.5 Hz fixes the stereochemistry of the side-chain substituent as α (*vide infra*). Other HMBC correlations observed {C(1′) to Me; CN to Me, NH_2; C(5) to NH_2} are also entirely consistent with the proposed structure of **4**.

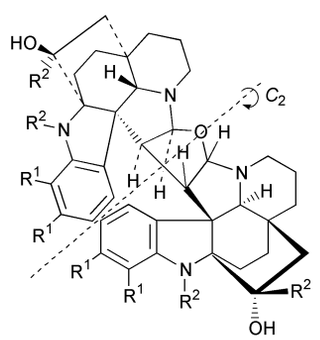
We rationalize the formation of these unusual products as shown in Scheme 1. Electrooxidation of **1** results in stepwise loss of an electron, deprotonation, followed by loss of another electron to give the iminium ion intermediate **5**. A further deprotonation of **5** gives the enamine **6**, which undergoes cyclization to the iminium ion **7** *via* an intramolecular enamine–ester reaction. Reaction of the iminium ion **7** with CN^- gives compound **3**. The source of the CN^- anion is probably from decomposition of the acetonitrile anion radical **8**, formed by a side reaction in the counter electrode chamber, which can undergo the alternative decomposition to the cyanomethyl anion.[22] Attack of this anion on the iminium intermediate **7** gives the 5-cyanomethylated derivative **9**, which on subsequent reaction with a second mole of MeCN, as shown, eventually results in compound **4**.

Since electrolysis under the above conditions gave rise to these unusual products, caused in part by decomposition of the acetonitrile solvent, we were prompted to test electrolysis under a different set of conditions. CV of **1** on a vitreous carbon anode in 0.1 M $LiClO_4$–MeOH showed two irreversible waves at 0.83 and 1.53 V (*versus* Ag/AgCl). Controlled potential electrolysis on a carbon anode in 0.1 M $LiClO_4$–MeOH (0.95 V *versus* Ag/AgCl, Pt cathode) in the presence of lutidine, proceeded with consumption of 2.5 faradays mol^{-1} and resulted in the formation of a single product **14** in moderate yield (30%). That this product is dimeric was indicated by API-LCMS, FABMS as well as HREIMS which yielded the molecular formula $C_{48}H_{52}N_4O_{15}$. The ^{1}H and ^{13}C NMR spectra, however, showed homotropic behaviour, displaying resonances for only one half of the dimeric molecule, suggesting the presence of an element of symmetry.[23,24] The NMR data showed position-5 and -6 to be methines (constituting an AB spin system) and furthermore position-5 was shown to be oxygenated (δ_H 4.97; δ_C 96.2; α to both N and O). Furthermore, the observed J_{5-6}-value of 5 Hz is consistent with H(5) and H(6) being *cis* to each other in a five-membered ring. The molecular formula of **14** indicates that the dimeric product is constituted from the union of two units of kopsamine, with four hydrogens less, but with incorporation of an additional oxygen atom. This observation, coupled with the presence of an element of symmetry indicated by the NMR spectral data, is satisfied in structure **14** for the dimeric product, which has a C_2 axis passing through the oxygen of the central tetrahydrofuran ring.[23,24]

The formation of the dimeric product is rationalized in Scheme 2. A further one-electron oxidation of the enamine **6** gives the cation radical intermediate **12** which on head-to-head coupling in the manner shown results in the formation of the C(6)–C(6′) linkage.[25] The resulting diiminium ion **13** is immediately quenched by methanol to give a biscarbinol amine ether which then undergoes a presumably facile hydrolysis/condensation to give the cyclic ether **14**.

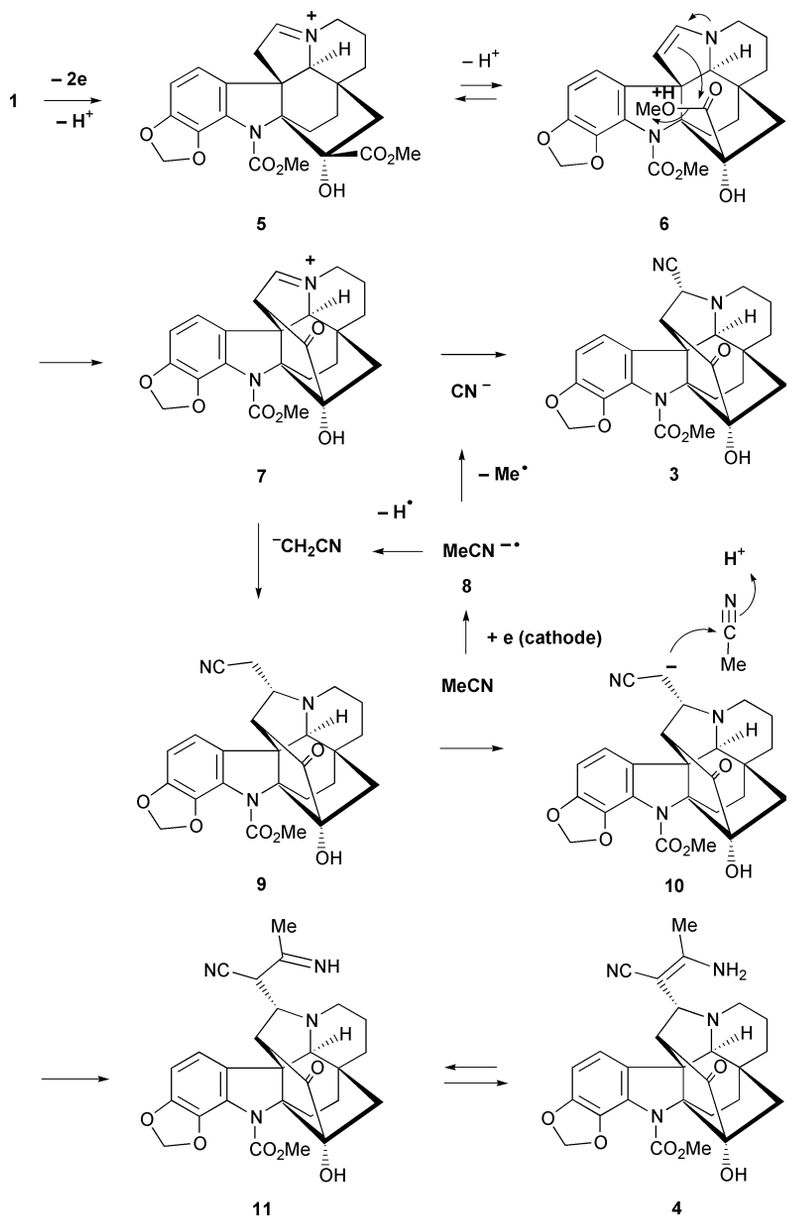


15 R = H
16 R = OMe

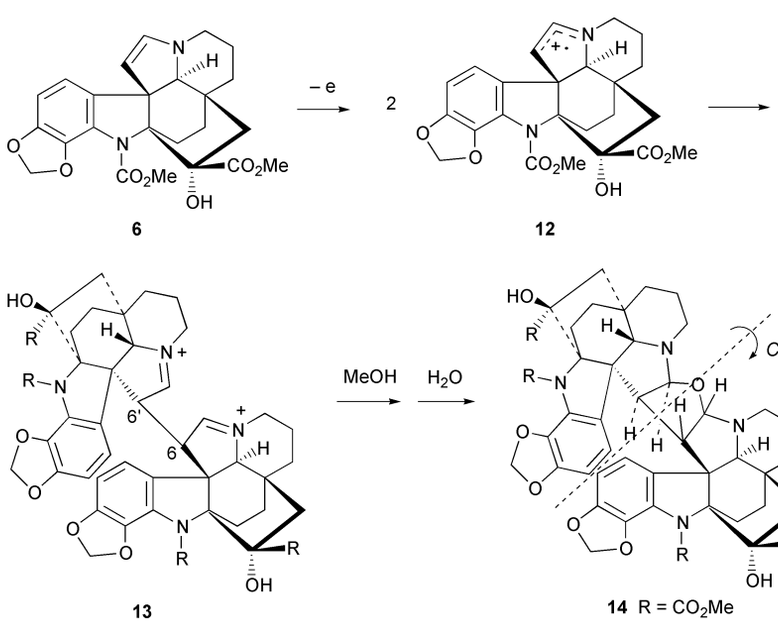


17 R^1 = H, R^2 = CO_2Me
18 R^1 = OMe, R^2 = CO_2Me

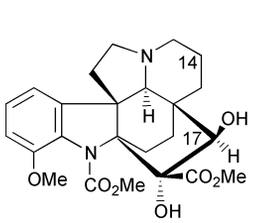
The aromatic congeners of kopsamine **1**, kopsiflorine **15** and 11-methoxykopsilongine **16**, were next examined. CV in acetonitrile showed a similar oxidation pattern as in kopsamine, displaying the presence of two irreversible waves (see Experimental section). However, due to paucity of material and the probable likelihood of decomposition as indicated by preliminary experiments, preparative electrolysis in acetonitrile was not carried out. CPE of kopsiflorine **15** and 11-methoxykopsilongine **16** on a carbon anode in $LiClO_4$–MeOH, however, led to the formation of the anticipated dimeric products (**17** and **18**, respectively) with C_2 symmetry, similar to that formed in the kopsamine reaction. In the case of the dimethoxy derivative, 11-methoxykopsilongine **16**, however, the yield was low and the dimeric product was inherently unstable and decomposed rapidly during silica gel chromatography, although it could be detected directly in the electrolysed solution by API-LCMS (MH^+ 957, $C_{50}H_{60}N_4O_{15}$ + H). It thus appears that modifications in the aromatic ring do not substantially alter the reaction course.



Scheme 1



Scheme 2



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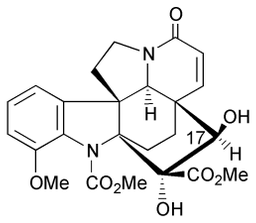

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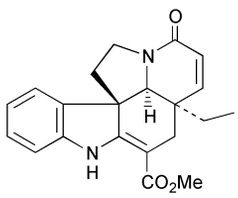

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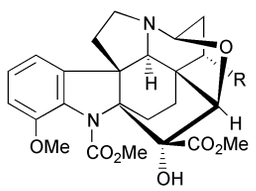
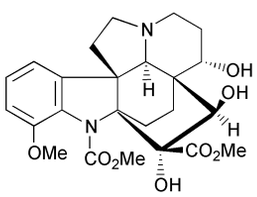


22 R = OMe
23 R = OEt
24 R = OH



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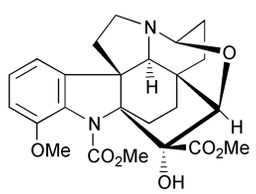

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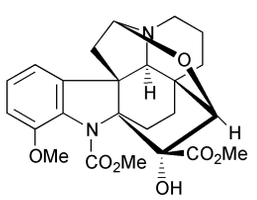

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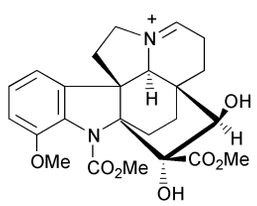

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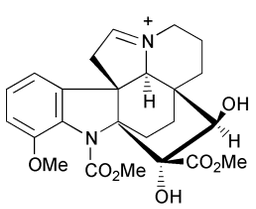

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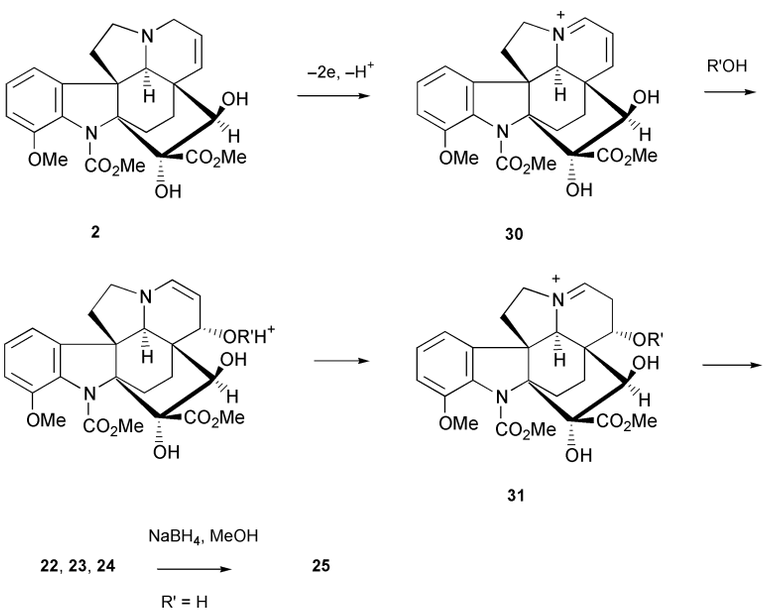
The aspidofractinine compound kopsingine **2** was next investigated. Kopsingine **2** differs from kopsamine **1** in having unsaturation in the piperidine ring as well as a β-OH function on carbon-17. CV on a platinum anode (0.1 M Et_4NClO_4, 30% CH_2Cl_2–MeCN) revealed two irreversible waves at 0.78 and 1.38 V *versus* Ag/AgCl. CPE (Pt gauze anode, Pt cathode) at the first potential peak (0.87 V) in the presence of lutidine as proton scavenger resulted in the consumption of 2.1 faradays mol^{-1} and resulted in the formation of a single product, which was the stable conjugated iminium salt, detected as a polar, baseline spot on TLC. Addition of methanol to precipitate out the bulk of the supporting electrolyte after evaporation of the solvent resulted in the formation of a new product in 72% yield, which was identified as the oxo-bridged alkaloid kopsidine A **22**, previously isolated from a *Kopsia* species.[26,27] Repetition of the same essential procedure but using ethanol in place of methanol gave kopsidine B **23** in 70% overall yield.[26,27] Hydrolysis of the oxidation product in 1 : 1 MeCN–water was slow in comparison with the alcohol reactions and resulted in only 15% yield of kopsidine C **24**[26,27] after 4 days. Hydrolysis in a two-phase medium (CH_2Cl_2–water) with phase-transfer catalysis did not substantially improve the yield (yield of kopsidine C 20%). Reduction of kopsidine C **24** with sodium borohydride gave kopsinganol **25**,[28] another new aspidofractinine alkaloid recently obtained from *Kopsia* (90% yield from kopsidine C).

The reactions described can be rationalized as shown in Scheme 3. Electrooxidation results in stepwise loss of an electron, deprotonation, followed by loss of another electron to give the conjugated iminium salt **30** as the main product of the electrochemical process.[29] Addition of methanol results in conjugate addition of the nucleophile onto carbon-15 resulting eventually in another iminium ion intermediate **31** which then undergoes intramolecular 1,2-addition of the 17β-OH function, yielding kopsidine A **22**.

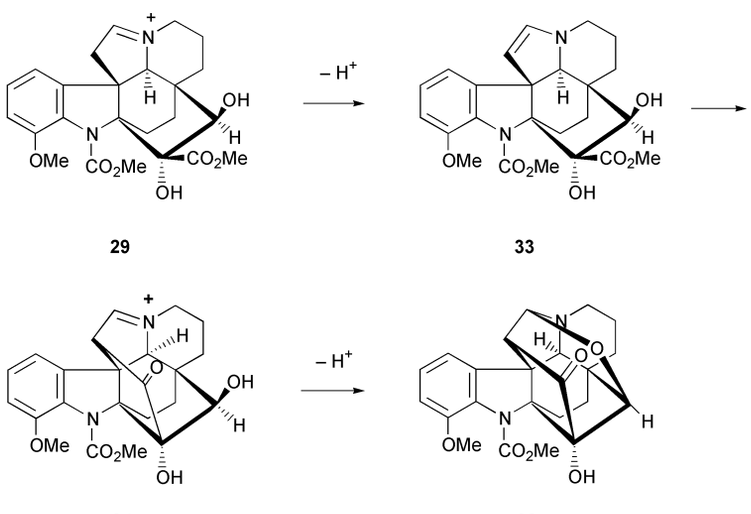
In the light of the above results it was of interest to investigate the behaviour of dihydrokopsingine **19**, to see what effect if any the 14,15-double bond of the piperidine ring has on the course of the electrooxidation. Compound **19** was readily obtained *via* catalytic hydrogenation (H_2, Pd/C) of kopsingine **2**. Preliminary CV showed a similar pattern of oxidation as that observed for kopsingine except that the oxidation peaks are observed at lower potentials compared with **2** (0.76 and 1.36 V). CPE at the first potential peak (0.81 V) under similar conditions as that used for **2** results also in the consumption of 2 faradays mol^{-1}. TLC analysis of the product mixture indicated two major products and subsequent chromatography gave the oxo-bridged compounds **26** and **27** in yields of 20 and 55%, respectively.

The structures of **26** and **27** were established based on extensive spectral analysis including 2-D NMR analysis. In the case of the 3-to-17 oxo-bridged product **26**, the NMR spectral data are similar to those of kopsidines A and B. In common with the kopsidines, the signal due to 17-OH is absent and H(3) is a methine shifted downfield to δ 4.39 (δ_C 86.4). Unlike the kopsidines, however, there is no signal due to any C(15)-alkoxy substituent, in agreement with the $NCHCH_2CH_2$ fragment (in addition to two ethylene fragments) revealed by the COSY spectrum. The observed three-bond correlation from C(17) to H(3) in the HMBC spectrum confirms the 3-to-17 oxo link in **26**. Similarly, in the case of the 5-to-17 oxo-bridged product **27**, the COSY spectrum revealed the fragments $NCHCH_2$, NCH_2-CH_2CH_2, and CH_2CH_2. The methine of the first fragment showed a low-field H signal at δ 4.74 and the corresponding carbon signal was observed at δ_C 90.2, indicating that it is adjacent to both a nitrogen and an oxygen atom. As in the case of the previous compound **26**, the observed three-bond correlation from C(17) to H(5) in the HMBC spectrum confirms the 5-to-17 oxo-bridge in compound **27**. It is apparent that in the case of the dihydro compound **19**, electrooxidation also results in formation of iminium ion intermediates such as **28** and **29**, which unlike the more stabilized conjugated iminium ion **30**, do not persist, but undergo facile intramolecular ring closure *via* 1,2-addition of the 17β-OH. The behaviour of the 3-oxokopsingine derivative **20** was also investigated but it was found to be inert to electrooxidation in the potential range investigated (up to 1.8 V *versus* Ag/AgCl), which is not unexpected as it has been previously observed that amides and carbamates are more difficult to oxidize (>1.8 V *versus* SCE),[7] and in the case of the β-anilinoacrylate alkaloid 3-oxotabersonine, **21**, it was found that oxidation occurred at the indoline N(1) rather than at N(4), *i.e.*, the enamine function is oxidized in preference to the enamide.[15]

Electrooxidation in methanol and ethanol solvents were next investigated to see whether the oxo-bridged compounds, kopsidines A and B, could be formed directly in one step. In the event the anodic oxidation of kopsingine could be carried out on a carbon anode in 0.1 M $LiClO_4$ in mixed solvents, 20% CH_2Cl_2–MeOH and 20% CH_2Cl_2–EtOH, to furnish kopsidine A **22** (36%) and kopsidine B **23** (55%) respectively, albeit in diminished yields compared with the previous two-step process.



Scheme 3

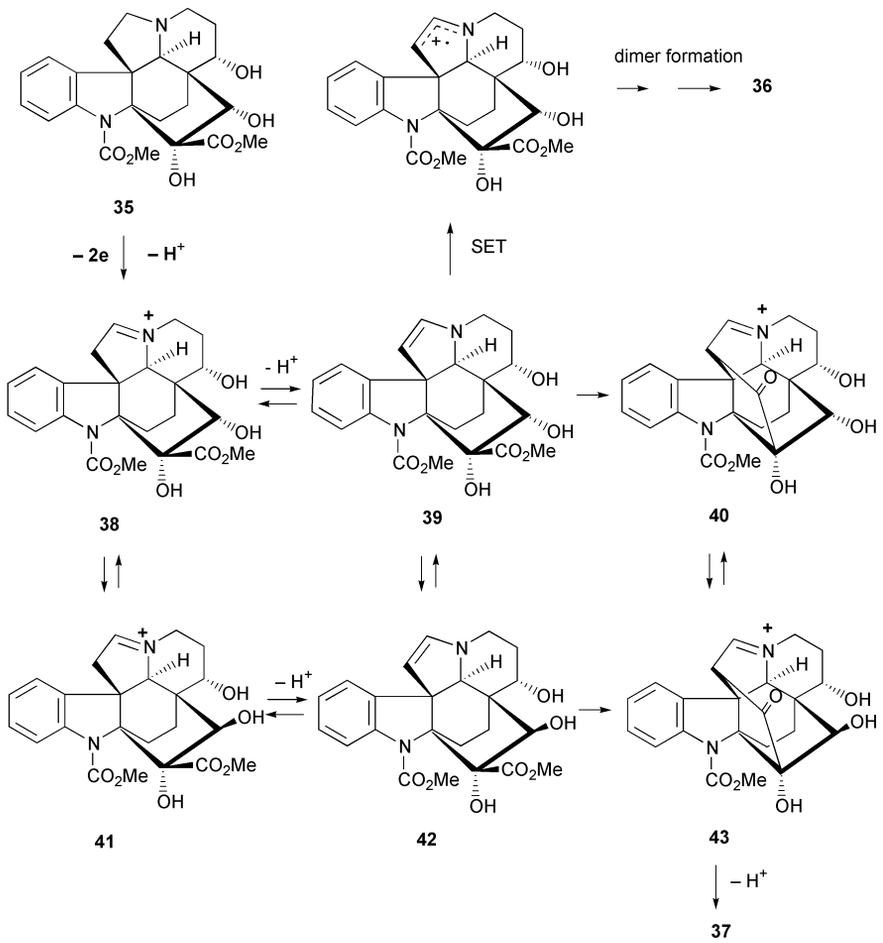


Scheme 4

Electrooxidation of dihydrokopsingine **19** under the same conditions (carbon anode, Pt cathode, 0.1 M $LiClO_4$–20% CH_2Cl_2–MeOH, 0.95 V *versus* Ag/AgCl), however, gave an unexpected result, in that while the anticipated oxo-bridged products, **26** (27%) and **27** (22%), were obtained, a third product **32** was also obtained, in 25% yield. The third product **32** was obtained as an amorphous powder. The mass spectrum showed a molecular ion at *m*/*z* 424 which analysed for $C_{23}H_{24}N_2O_6$. The IR spectrum showed bands due to OH (3330 cm^{-1}), five-membered cyclic ketone (1770 cm^{-1}), and carbamate (1674 cm^{-1}) functions, while the UV spectrum is typical of dihydroindole chromophores (217, 245, 290 nm). The NMR spectrum of **32** was different from that of the other two products **26** and **27**, and showed substantial departure from that of the starting compound **19**. The resonances due the C(16) ester and the C(17) hydroxy functions of the starting compound **19** are absent, instead a low-field carbon resonance due to a ketone function is observed at δ_C 205.9. A prominent feature of the ^1H NMR spectrum is the presence of a pair of AB doublets at δ 5.25 and 2.80 with coupling constant of 5 Hz which corresponds to the *N*CHCH fragment revealed by the COSY spectrum. Other fragments revealed from the COSY spectrum include $NCH_2CH_2CH_2$, CH_2CH_2, and two isolated methines. The HMQC spectrum indicated that the low-field methine doublet at δ 5.25 corresponds to the carbon resonance at δ_C-94.6, suggesting that this carbon is α to both a nitrogen and an oxygen atom. This low-field doublet can therefore be attributed to H(5) which is coupled to H(6), with a *cis* configuration between the two hydrogens as required for a five-membered ring, in agreement with the observed coupling J_{5-6} value of 5 Hz. It remains only to assemble the molecule by linking C(5) and C(17) with an oxo-bridge, and C(6) and C(16) with a carbonyl bridge, leading to the cage-like structure shown in **32**. This conclusion is also supported by the HMBC data which showed long-range correlations from C(5) to H(17), C(16) to H(6), C(17) to H(5), and C=O to H(5), H(17). This compound is dihydrokopsinitarine A which is related to the naturally occurring kopsinitarines A, B, C, and D, previously isolated from *Kopsia* species.[30,31]

The formation of the caged product **32** can be rationalized as shown in Scheme 4. Deprotonation of the iminium ion **29** leads to the enamine **33** which undergoes an intramolecular enamine–ester reaction to give another iminium ion intermediate **34**. Intramolecular 1,2-addition of the 17-β-OH onto the iminium function leads to the full cage structure **32**.

From the above results it can be seen that introduction of further functionalities into the basic aspidofractinine carbon skeleton modifies the course of the electrooxidation. The compounds of the kopsamine series are characterized by lack of unsaturation in the piperidine ring and absence of



Scheme 5

functionalization on carbon-17. This leads to the observed dichotomous behaviour on anodic oxidation which is determined primarily by the solvent; cyclization–cyanation, or cyclization–double cyanomethylation occurring in acetonitrile, *versus* dimer formation *via* cation radical intermediates occurring in methanol. In the kopsingine series, the presence of unsaturation in the piperidine ring results in formation of a stabilized conjugated iminium salt which can nevertheless be trapped with alcohol nucleophiles, leading eventually to the oxo-bridged kopsidine compounds. Removal of the piperidine ring unsaturation leads to iminium ions which are captured by direct intramolecular attack by the appositely oriented 17β-OH function. The same reaction of the dihydro derivative in methanol gave, in addition to the oxo-bridged products, a caged product similar to the naturally occurring kopsinitarines, which arises from a double cyclization sequence, *viz.*, an intramolecular enamine–ester reaction followed by another intramolecular hydroxy–iminium ion reaction.

Since the compounds of the kopsamine series and those of the kopsingine series show such disparate behaviour on electrooxidation, it would be of interest to investigate the behaviour of a substrate with structural features intermediate between that of the kopsamine and kopsingine compounds. A compound fitting this requirement and available in sufficient amounts from our ongoing work in alkaloid chemistry is 12-demethoxy-17-epikopsinganol **35** obtained from another *Kopsia* species.[32] This compound lacks unsaturation in the piperidine ring but has a hydroxy function on carbon-17, but of the opposite stereochemistry (17α-OH), and therefore would not be expected to react intramolecularly with any iminium intermediates generated on anodic oxidation.

In the event, the results were not entirely what was anticipated. Preliminary CV of compound **35** at a vitreous carbon anode in 0.1 M $LiClO_4$–MeOH showed two oxidation peaks at 0.91 and 1.49 V *versus* Ag/AgCl. CPE in 0.1 M $LiClO_4$–MeOH at the first peak potential (0.95 V) resulted in the consumption of 2.5 faradays mol^{-1} and led to the formation of two products **36** and **37** in 37 and 17% yield, respectively. The major product **36** was the anticipated dimeric product with C_2 symmetry, similar to those obtained in the kopsamine series (see Experimental section). The minor product **37** was obtained as an amorphous solid, and high-resolution mass measurements gave the formula $C_{22}H_{22}N_2O_6$. The IR spectrum showed absorptions due to OH (3316 cm^{-1}), cyclic ketone (1772 cm^{-1}) and carbamate functionalities (1676 cm^{-1}). The ^1H NMR spectrum is characterized by the prominent AB doublets at δ 5.23 and 2.62 with J 5 Hz corresponding to H(5) and H(6) respectively, reminiscent of the caged compound **32** discussed earlier (*vide infra*). Other similar features include the ketone resonance at δ_C 206.4 and the downfield shift of C(5) at δ_C 95.0. Complete analysis of the NMR spectral data confirmed that **37** was the caged compound 12-demethoxykopsinitarine D, a derivative of the naturally occurring kopsinitarine D. The formation of the caged product was not anticipated and requires epimerization at carbon-17 to occur at some stage. Repetition of the oxidation showed that the results are reproducible, and control experiments showed that the starting compound was completely inert when placed in the same medium as that used in the electrolysis and could be recovered intact without any epimerization detected at carbon-17. A possible explanation for the formation of the caged product **37** is that epimerization could have occurred during the electrooxidation, possibly at the stage of the first iminium ion **38**, or the enamine **39**, or the second iminium species **40**, or involving all three intermediates (Scheme 5). In those instances intramolecular 1,2-addition of the 17β-OH to the iminium intermediate **43** will lead to the observed caged product **37**.

The above systematic investigation of the electrochemical

oxidation of the aspidofractinine derivatives has provided useful insights into the reactivity of these substrates on anodic oxidation, and has shown how subtle changes in the structure of these compounds influence the course of the electrooxidation. It has also yielded some insight into the possible origin of some of the compounds previously obtained from plants, especially *Kopsia*, such as the heptacyclic kopsine derivatives,[20,33–35] the oxo-bridged kopsidines[26,27] and singapurensines,[36] and the octacyclic caged kopsinitarines.[30,31]

Experimental

Mps were determined on a Leitz Wetzler melting-point apparatus and are uncorrected. 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 measured on a JASCO DIP-370 digital polarimeter and the $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. 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, Australia National University. API-LCMS was obtained on a Perkin-Elmer API 100 instrument. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a JEOL JMN-LA400 spectrometer at 400 and 100 MHz, respectively. Coupling constants (J) are reported in Hz. All solvents were of analytical grade and were distilled before use. Acetonitrile and dichloromethane were distilled from calcium hydride, and methanol was distilled from magnesium turnings. All electrochemical experiments (CV, coulometry, preparative electrolysis) 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 CV 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 (3 M) as the reference electrode. Preparative electrolyses 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). The progress of electrolysis was also monitored by TLC as well as by CV.

Compounds for electrochemical investigation

Kopsamine **1** (colourless crystals from Et_2O, mp 208–209 °C), kopsiflorine **15** (light yellowish crystals from hexane, mp 138–140 °C), and 11-methoxykopsilongine **16** (colourless crystals from Et_2O, mp 167–168 °C) were previously obtained from *Kopsia dasyrachis*.[20] Kopsingine **2** (colourless crystals from EtOH, mp 270–272 °C) was previously obtained from *Kopsia teoi*.[21] Compound **35**, 12-demethoxy-17-epikopsinganol, was obtained from *Kopsia singapurensis*.[32]

12-Demethoxy-17-epikopsinganol **35** was obtained as light yellowish crystals from Et_2O–MeOH, mp 172–174 °C, $[\alpha]_D$ −40 (*c* 0.28, $CHCl_3$); ν_{max} (film)/cm^{-1} 3474, 3207, 1736 and 1676; λ_{max} (EtOH)/nm 206 (log ε/L mol^{-1} cm^{-1} 3.28), 243 (2.98), 279 (2.02) and 288 (1.76); δ_H (400 MHz; $CDCl_3$) 1.42 (1 H, ddd, *J* 13, 11 and 8.5, H-18), 1.48–1.56 (2 H, m, H-6 and H-14), 1.52–1.60 (1 H, m, H-19), 1.68 (1 H, ddd, *J* 13, 11 and 8.5, H-19), 2.01 (1 H, ddd, *J* 14, 8 and 5, H-6), 2.21 (1 H, ddd, *J* 13, 11 and 2, H-18), 2.24–2.30 (1 H, m, H-14), 2.87 (1 H, ddd, *J* 13, 5 and 2, H-3), 2.99 (1 H, td, *J* 8 and 5, H-5), 3.06 (1 H, td, *J* 8 and 6, H-5), 3.37 (1 H, td, *J* 13 and 3, H-3), 3.41 (1 H, s, H-21), 3.51 (1 H, d, *J* 7.5, 17α-OH), 3.78 (3 H, s, CO_2Me), 3.98 (3 H, s, NCO_2Me), 4.20 (1 H, t, *J* 3, H-15), 4.81 (1 H, dd, *J* 7.5 and 2, H-17), 7.03 (1 H, td, *J* 7.5 and 1, H-10), 7.16 (1 H, td, *J* 7.5 and 1, H-11), 7.29 (1 H, dd, *J* 7.5 and 1, H-9), 7.49 (1 H, br d, *J* 7.5, H-12) and 8.40 (1H, s, 16α-OH); δ_C (100 MHz; $CDCl_3$) 19.0 (C-19), 23.5 (C-18), 24.9 (C-14), 37.3 (C-6), 40.9 (C-3), 41.4 (C-20), 50.3 (C-5), 52.5 (CO_2*Me*), 53.5 (NCO_2*Me*), 55.5 (C-7), 61.8 (C-21), 66.5 (C-15), 69.3 (C-17), 73.9 (C-16), 74.1 (C-2), 115.1 (C-12), 121.7 (C-9), 123.9 (C-11), 127.1 (C-10), 139.6 (C-8 and C-13), 156.9 (N*C*O_2Me) and 171.9 (*C*O_2Me); *m*/*z* (EI) 444.1889 (M$^+$, 96%. $C_{23}H_{28}N_2O_7$ requires *M*, 444.1897), 395 (98), 385 (100), 367 (18), 325 (11), 309 (9), 281 (12), 243 (19) and 156 (12).

Dihydrokopsingine 19

Kopsingine **2** (500 mg, 1 mmol) in 15 mL of CH_2Cl_2 was stirred over 10% Pd/C (150 mg) under a hydrogen atmosphere at room temperature for 2 h. The mixture was then filtered over silica gel to provide dihydrokopsingine **19** in quantitative yield. Dihydrokopsingine **19** was obtained as colourless crystals from dichloromethane–acetone, mp 252–253 °C; $[\alpha]_D$ +58 (*c* 0.24, $CHCl_3$); ν_{max} (film)/cm^{-1} 3390br, 1741, 1670 and 1058; λ_{max} (EtOH)/nm 217 (log ε/L mol^{-1} cm^{-1} 4.50), 253 (3.99), 281 (3.50) and 291 (3.40); δ_H (400 MHz; $CDCl_3$) 0.95 (1 H, ddd, *J* 13, 11 and 1.5, H-19), 1.32 (1 H, td, *J* 14 and 6, H-15), 1.39 (1 H, ddd, *J* 13, 11 and 8, H-18), 1.64 (1 H, ddd, *J* 13, 11 and 8, H-19), 1.66–1.70 (1 H, m, H-14), 1.70 (1 H, dd, *J* 13 and 4, H-6), 2.02 (1 H, dd, *J* 14 and 6, H-15), 2.06 (1 H, ddd, *J* 13, 11 and 1.5, H-18), 2.20 (1 H, qt, *J* 13 and 6, H-14), 2.57 (1 H, td, *J* 13 and 3, H-3), 2.59 (1 H, ddd, *J* 12, 8.5 and 4, H-5), 2.69 (1 H, d, *J* 2, H-21), 2.80 (1 H, dd, *J* 8.5 and 6, H-5), 3.11–3.21 (1 H, m, H-3), 3.18 (1 H, ddd, *J* 13, 12 and 6, H-6), 3.80 (6 H, s, NCO_2Me and CO_2Me), 3.84 (3 H, s, 12-OMe), 3.86 (1 H, dd, *J* 7 and 2, H-17), 5.64 (1 H, s, 16-OH), 6.80 (1 H, dd, *J* 7 and 1, H-9), 6.83 (1 H, dd, *J* 8 and 1, H-11), 7.03 (1 H, dd, *J* 8 and 7, H-10) and 8.58 (1 H, d, *J* 7, 17-OH); δ_C (100 MHz; $CDCl_3$) 24.3 (C-14), 27.3 (C-18), 28.8 (C-19), 35.3 (C-15), 35.8 (C-20), 40.9 (C-6), 49.0 (C-5), 49.1 (C-3), 51.8 (CO_2*Me*), 52.9 (NCO_2*Me*), 56.0 (12-OMe), 57.1 (C-7), 70.0 (C-21), 76.2 (C-2), 80.9 (C-16), 85.3 (C-17), 111.8 (C-11), 113.0 (C-9), 124.8 (C-10), 128.4 (C-13), 144.7 (C-8), 149.3 (C-12), 155.5 (N*C*O_2Me) and 172.2 (*C*O_2Me); *m*/*z* (EI) 458 (M$^+$, 100%), 430 (10), 399 (24), 370 (42), 355 (14), 341 (21), 315 (20) and 301 (38).

3-Oxokopsingine 20[37]

To a solution of kopsingine **2** (100 mg, 0.2 mmol) and 70% *t*-BuOOH (150 μL, 1.0 mmol) in dichloromethane (5 mL) was added CrO_3 (2 mg, 0.02 mmol) and the mixture was stirred at room temperature for 45 min (91% reacted). The mixture was then concentrated, and chromatographed over neutral alumina with 1% MeOH–$CHCl_3$ as eluent to give 3-oxokopsingine **20** (71 mg, 76% based on the consumed kopsingine) as an amorphous solid, ν_{max} (film)/cm^{-1} 3349br, 1743, 1667 and 1659; λ_{max} (EtOH) 216 (log ε/L mol^{-1} cm^{-1} 4.58), 253 (4.04), 280 (3.54) and 291 (3.45); δ_H (400 MHz; $CDCl_3$) 1.38 (1 H, ddd, *J* 12.5, 11 and 1, H-19), 1.60 (1 H, ddd, *J* 13, 11 and 8, H-18), 1.62 (1 H, dd, *J* 12 and 5, H-6), 1.84 (1 H, ddd, *J* 12.5, 10.5 and 8, H-19), 2.20 (1 H, ddd, *J* 13, 10.5 and 1, H-18), 2.93 (1 H, td, *J* 12 and 8, H-6), 3.13 (1 H, d, *J* 5, 17-OH), 3.78 (3 H, s, CO_2Me), 3.83 (3 H, s, NCO_2Me), 3.91 (1 H, br s, H-21), 4.04 (1 H, dd, *J* 12 and 8, H-5), 6.11 (1 H, d, *J* 9.8, H-15), 6.18 (1 H, d, *J* 9.8, H-14), 6.37 (1 H, s, 16-OH), 6.84 (1 H, dd, *J* 7.4 and 1, H-9), 6.88 (1 H, dd, *J* 8.3 and 1, H-11) and 7.09 (1 H, dd, *J* 8.3 and 7.4, H-10); δ_C (100 MHz; $CDCl_3$) 25.3 (C-19), 25.4 (C-18), 36.4 (C-6), 39.3 (C-20), 43.3 (C-5), 51.8 (CO_2*Me*), 52.9 (NCO_2*Me*), 55.9 (12-OMe), 58.2 (C-7), 63.3 (C-21), 75.2 (C-2), 79.2 (C-17), 79.3 (C-16), 112.1 (C-11), 113.6 (C-9), 125.3 (C-10), 127.6 (C-13), 128.1 (C-15), 141.0 (C-8), 141.5 (C-14), 148.9 (C-12), 155.6 (N*C*O_2Me), 162.9 (C-3) and 170.7 (*C*O_2Me); *m*/*z* (EI) 470 (M$^+$, 100%), 441 (7), 411 (8), 383 (7), 353 (15), 319 (7), 260 (13), 244 (15) and 232 (9).

Anodic oxidation of kopsamine 1 (Pt anode, acetonitrile)

Kopsamine **1** (50 mg, 0.1 mmol) in 50 mL of 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 1.05 V *versus* Ag/AgCl and electrolysis was

allowed to proceed until 2.5 faradays mol^{-1} had been transferred (initial current reached a steady low value at this stage). The electrolysis was accompanied by changes in the counter-electrode compartment as indicated by the development of a brownish colour as the reaction progresses. The solution was then evaporated to dryness under reduced pressure and CH_2Cl_2 (10 mL) was added. The precipitated electrolyte was then filtered off and the residue was washed with CH_2Cl_2. The CH_2Cl_2 extract was chromatographed over silica gel (1% MeOH–$CHCl_3$) before further purification by centrifugal TLC (SiO_2; Et_2O) to give two products, **3** and **4**.

Compound **3** (11 mg, 23%) was obtained as a light yellow oil, $[\alpha]_D$ +10.5 (*c* 0.02, $CHCl_3$); ν_{max} (film)/cm^{-1} 3303, 2250, 1761 and 1681; λ_{max} (EtOH)/nm 227 (log ε/L mol^{-1} cm^{-1} 4.18), 255 (3.95), 285 (2.90) and 290 (2.83); δ_H (400 MHz; $CDCl_3$) 1.30–1.40 (2 H, m, H-15 and H-19), 1.36–1.44 (1 H, m, H-14), 1.54–1.72 (4 H, m, H-14, H-15, H-18 and H-19), 1.65 (1 H, dd, *J* 15 and 2, H-17), 2.16 (1 H, dd, *J* 15 and 4, H-17), 2.53 (1 H, ddd, *J* 14, 11 and 5, H-18), 2.80 (1 H, d, *J* 3.5, H-6), 3.03 (1 H, td, *J* 14 and 3.5, H-3), 3.18 (1 H, dd, *J* 14 and 4.5, H-3), 3.28 (1 H, d, *J* 2, H-21), 3.81 (3 H, s, NCO_2Me), 4.12 (1 H, d, *J* 3.5, H-5), 5.93 (1 H, d, *J* 1.5, OCH_2O), 5.95 (1 H, d, *J* 1.5, OCH_2O), 6.67 (1 H, d, *J* 8, H-10), 6.98 (1 H, d, *J* 8, H-9), 7.15 (1 H, s, 16-OH); δ_C (100 MHz; $CDCl_3$) 16.6 (C-14), 19.5 (C-18), 32.4 (C-19), 32.8 (C-20), 33.6 (C-15), 43.2 (C-17), 45.4 (C-3), 53.8 (C-5), 54.5 (NCO_2*Me*), 58.0 (C-7), 58.6 (C-6), 69.1 (C-21), 75.3 (C-2), 82.3 (C-16), 100.8 (OCH_2O), 105.6 (C-10), 115.8 (C-9), 118.8 (CN), 123.4 (C-13), 129.7 (C-8), 136.0 (C-12), 149.6 (C-11), 155.5 (N*C*O_2Me) and 210.2 (C-22); *m*/*z* (EI) 449.1587 (M^+, 100%. $C_{24}H_{23}N_3O_6$ requires *M*, 449.1587), 423 (92), 406 (21), 395 (26) and 379 (20).

Compound **4** (12 mg, 22%) was obtained as an amorphous solid, $[\alpha]_D$ +50.0 (*c* 0.09, $CHCl_3$); ν_{max} (film)/cm^{-1} 3360, 3262, 3246, 2186, 1746 and 1679; λ_{max} (EtOH)/nm 226 (log ε/L mol^{-1} cm^{-1} 4.30), 256 (4.07), 283 (2.95) and 293 (2.90); δ_H (400 MHz; $CDCl_3$) 1.25–1.31 (1 H, m, H-14), 1.32–1.40 (2 H, m, H-15 and H-19), 1.50–1.80 (4 H, m, H-14, H-15, H-18 and H-19), 1.65 (1 H, dd, *J* 15 and 2, H-17), 2.06 (3 H, s, C=CCH_3), 2.27 (1 H, dd, *J* 15 and 4, H-17), 2.37 (1 H, d, *J* 3.5, H-6), 2.52 (1 H, ddd, *J* 14, 12 and 4, H-18), 3.00–3.10 (2 H, m, 2 × H-3), 3.42 (1 H, d, *J* 2, H-21), 3.79 (1 H, d, *J* 3.5, H-5), 3.80 (3 H, s, NCO_2Me), 4.91 (2 H, br s, NH_2), 5.89 (1 H, d, *J* 2, OCH_2O), 5.91 (1 H, d, *J* 2, OCH_2O), 6.69 (1 H, d, *J* 8, H-10), 7.14 (1 H, d, *J* 8, H-9), 7.21 (1 H, s, 16-OH); δ_C (100 MHz; $CDCl_3$) 15.6 (C-14), 19.4 (C-18), 21.3 (C=C*C*H_3), 32.3 (C-19), 33.1 (C-15), 34.4 (C-20), 44.1 (C-17), 45.0 (C-3), 53.6 (NCO_2*Me*), 58.3 (C-7), 62.6 (C-5), 63.1 (C-6), 69.7 (C-21), 75.7 (C-2), 82.6 (C-16), 85.4 (C-1′), 100.5 (OCH_2O), 105.9 (C-10), 116.2 (C-9), 120.4 (CN), 123.5 (C-13), 131.3 (C-8), 135.6 (C-12), 149.1 (C-11), 154.6 (C-2′), 155.7 (N*C*O_2Me) and 216.3 (C-22); *m*/*z* (EI) 504.2010 (M^+, 31%. $C_{27}H_{28}N_4O_6$ requires *M*, 504.2009), 503 (100), 422 (57), 394 (84), 325 (42), 205 (44), 82 (76) and 67 (62).

Anodic oxidation of kopsamine 1 (carbon anode, methanol)

Anodic oxidation of kopsamine **1** (50 mg, 0.1 mmol) was carried out at a vitreous carbon anode (0.95 V *versus* Ag/AgCl) in 0.1 M $LiClO_4$–MeOH and 2,6-lutidine (0.2 mmol) under nitrogen in a divided cell. The reaction proceeded smoothly with the consumption of 2.5 faradays mol^{-1}. The electrolysed solution was concentrated by evaporation under reduced pressure after which water (15 mL) was added and the mixture was extracted with CH_2Cl_2. The extract was then washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed over silica gel with diethyl ether as eluent to give *compound* **14** (15 mg, 30%) as an amorphous solid, $[\alpha]_D$ +36.6 (*c* 0.09, $CHCl_3$); ν_{max} (film)/cm^{-1} 3313, 1751 and 1679; λ_{max} (EtOH)/nm 227 (log ε/L mol^{-1} cm^{-1} 4.35), 250 (4.05), 255 (3.90), 286 (2.95) and 292 (2.86); δ_H (400 MHz; $CDCl_3$) 0.92 (2 H, br t, *J* 12, H-19, H-19′), 1.14 (2 H, td, *J* 13.5 and 3, H-15, H-15′), 1.20–1.30 (2 H, m, H-14, H-14′), 1.24 (2 H, dd, *J* 14.5 and 1.5, H-17, H-17′), 1.27 (2 H, ddd, *J* 12, 11 and 8, H-18, H-18′), 1.45–1.55 (2 H, m, H-14, H-14′), 1.55 (2 H, br d, *J* 13.5, H-15, H-15′), 1.73 (2 H, ddd, *J* 12, 11 and 8, H-19, H-19′), 1.99 (2 H, d, *J* 14.5, H-17, H-17′), 2.04 (2 H, br t, *J* 12, H-18, H-18′), 2.45 (2 H, d, *J* 5, H-6, H-6′), 2.77 (2 H, td, *J* 12.5 and 2, H-3, H-3′), 2.96 (2 H, d, *J* 1.5, H-21, H-21′), 3.19 (2 H, dd, *J* 12.5 and 3, H-3, H-3′), 3.70 (6 H, s, CO_2Me, CO_2Me′), 3.78 (6 H, s, NCO_2Me, NCO_2Me′), 4.97 (2 H, d, *J* 5, H-5, H-5′), 5.76 (2 H, d, *J* 1.3, OC*H*HO and OC*H*′HO), 5.94 (2 H, d, *J* 1.3, OCH*H*O, OCH*H*′O), 6.20 (2 H, s, 16-OH, 16-OH′), 6.52 (2 H, d, *J* 7.9, H-10, H-10′) and 6.83 (2 H, d, *J* 7.9, H-9, H-9′); δ_C (100 MHz; $CDCl_3$) 19.4 (C-14, C-14′), 27.9 (C-18, C-18′), 30.8 (C-19, C-19′), 32.8 (C-20, C-20′), 36.4 (C-15, C-15′), 39.0 (C-17, C-17′), 45.7 (C-3, C-3′), 51.5 (CO_2*Me*, CO_2*Me*′), 52.6 (NCO_2*Me*, NCO_2*Me*′), 53.3 (C-6, C-6′), 60.4 (C-7, C-7′), 70.4 (C-21, C-21′), 73.6 (C-16, C-16′), 77.4 (C-2, C-2′), 96.2 (C-5, C-5′), 100.3 (OCH_2O and OCH_2O′), 103.1 (C-10, C-10′), 117.1 (C-9, C-9′), 127.2 (C-13, C-13′), 132.5 (C-8, C-8′), 135.6 (C-12, C-12′), 147.7 (C-11, C-11′), 155.3 (N*C*O_2Me, N*C*O_2Me′) and 170.5 (*C*O_2Me, *C*O_2Me′); *m*/*z* (EI) 924.3397 (M^+, 18%. $C_{48}H_{52}N_4O_{15}$ requires *M*, 924.3429), 923 (20), 906 (5), 895 (5), 865 (3), 441 (100), 397 (30) and 205 (52); *m*/*z* (API-LCMS, MeOH) 925 [MH^+]; *m*/*z* (FABMS, NBA) 925 [MH^+].

Anodic oxidation of kopsiflorine 15 and 11-methoxykopsilongine 16 (Pt anode, acetonitrile)

Preliminary electrochemical oxidation (Pt anode, 0.1 M Et_4NClO_4–MeCN) of kopsiflorine **15** indicated that it has a similar electrochemical behaviour to that of kopsamine **1** as revealed by two irreversible waves at 0.86 and 1.66 V *versus* Ag/AgCl in the cyclic voltammogram. The preparative-scale electrolysis for compounds **15** and **16** was not carried out in acetonitrile due to paucity of material and the probable likelihood of decomposition as indicated in the preliminary experiments.

Anodic oxidation of kopsiflorine 15 (carbon anode, methanol)

Preliminary CV of kopsiflorine **15** (vitreous carbon anode, 0.1 M $LiClO_4$–MeOH) showed two irreversible oxidative waves at 0.88 and 1.72 V *versus* Ag/AgCl. Bulk electrolysis of kopsiflorine **15** (17 mg, 0.04 mmol) at the first potential peak (vitreous carbon anode, 1.0 V *versus* Ag/AgCl) was carried out as described above and resulted in the consumption of 2.5 faradays mol^{-1}. The electrolysed solution was concentrated by evaporation under reduced pressure after which water (15 mL) was added and the mixture was extracted with CH_2Cl_2. The extract was then washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed over silica gel with diethyl ether as eluent to give compound **17** (5 mg, 30%) as a light yellow oil, ν_{max} (film)/cm^{-1} 3310br, 1752, 1676 and 1099; δ_H (400 MHz; $CDCl_3$) 0.83 (2 H, br t, *J* 11, H-19, H-19′), 1.14 (2 H, td, *J* 14 and 4, H-15, H-15′), 1.17–1.26 (2 H, m, H-14, H-14′), 1.24 (2 H, dd, *J* 15 and 1.5, H-17, H-17′), 1.34–1.40 (2 H, m, H-18, H-18′), 1.56 (2 H, br d, *J* 15, H-17, H-17′), 1.64–1.72 (2 H, m, H-15, H-15′), 1.76–1.88 (4 H, m, H-14, H-14′, and H-19, H-19′), 1.90 (2 H, ddd, *J* 13, 11 and 1.5, H-18, H-18′), 2.08 (2 H, d, *J* 5, H-6, H-6′), 2.83 (2 H, td, *J* 13 and 2.5, H-3, H-3′), 3.07 (2 H, d, *J* 1.5, H-21, H-21′), 3.19 (2 H, dd, *J* 13 and 3, H-3, H-3′), 3.77 (6 H, s, CO_2Me, CO_2Me′), 3.87 (6 H, s, NCO_2Me, NCO_2Me′), 4.92 (2 H, d, *J* 5, H-5, H-5′), 6.34 (2 H, s, 16-OH, 16-OH′), 6.99 (2 H, td, *J* 8 and 1.5, H-10, H-10′), 7.14 (2 H, td, *J* 8 and 1.5, H-11, H-11′), 7.42 (2 H, dd, *J* 8 and 1.5, H-9, H-9′) and 7.56 (2 H, br d, *J* 8, H-12, H-12′); δ_C (100 MHz; $CDCl_3$) 19.5 (C-14, C-14′), 27.9 (C-18, C-18′), 31.2 (C-20, C-20′), 32.5 (C-19, C-19′), 36.2 (C-15, C-15′), 38.7 (C-17, C-17′), 45.8 (C-3, C-3′), 52.3 (C-6, C-6′), 52.8 (CO_2*Me*, CO_2*Me*′), 53.6 (NCO_2*Me*, NCO_2*Me*′), 60.1 (C-7, C-7′), 69.8 (C-21, C-21′), 73.6 (C-2, C-2′), 77.3 (C-16, C-16′),

96.6 (C-5, C-5′), 116.9 (C-12, C-12′), 122.4 (C-9, C-9′), 124.9 (C-10, C-10′), 126.9 (C-11, C-11′), 135.4 (C-8, C-8′), 143.3 (C-13, C-13′), 156.0 (N*C*O$_2$Me, N*C*O$_2$Me′) and 170.0 (*C*O$_2$Me, *C*O$_2$Me′); *m*/*z* (API-LCMS, MeOH) 837 (MH$^+$, $C_{46}H_{52}N_4O_{11}$ + H).

Anodic oxidation of 11-methoxykopsilongine 16 (carbon anode, methanol)

Preliminary CV of 11-methoxykopsilongine **16** (carbon anode, 0.1 M LiClO$_4$–MeOH) showed two irreversible oxidative waves at 0.92 and 1.53 V *versus* Ag/AgCl. Preparative scale electrolysis of 11-methoxykopsilongine **16** (20 mg, 0.045 mmol) at the first potential peak (carbon anode, 1.0 V *versus* Ag/AgCl) was carried out as described above and the reaction proceeded smoothly with consumption of 2.5 faradays mol^{-1}. The electrolysed solution was concentrated by evaporation under reduced pressure after which water (15 mL) was added and the mixture was extracted with CH_2Cl_2. At this stage analysis of the crude extract by API-LCMS showed only a single product (*m*/*z* 957, MH$^+$, $C_{50}H_{60}N_4O_{15}$ + H). However, attempted purification of this dimeric product by SiO_2 chromatography was unsuccessful presumably due to SiO_2-induced decomposition.

Anodic oxidation of kopsingine 2 (Pt anode, dichloromethane–acetonitrile)

Anodic oxidation (Pt gauze, 0.87 V *versus* Ag/AgCl) of kopsingine **2** (100 mg, 0.2 mmol) in 30% CH_2Cl_2–MeCN containing Et_4NClO_4 (0.1 M) and 2,6-lutidine (0.4 mmol) proceeded smoothly until 2.1 faradays mol^{-1} had been transferred. The solution was then evaporated to dryness and methanol (12 mL) was added. The precipitated electrolyte was then filtered off and the residue was washed with methanol. The methanol solution was then stirred for 25 h and the solvent was removed under reduced pressure. The resulting product was then chromatographed over silica gel (1% MeOH–$CHCl_3$) to afford pure kopsidine A **22** (77 mg, 72% from kopsingine **2**) as a light yellow oil, $[a]_D$ +17 (*c* 0.76, $CHCl_3$); ν_{max} (film)/cm^{-1} 3357br, 1743, 1670, 1243 and 1092; λ_{max} (EtOH)/nm 217 (log ε/L mol^{-1} cm^{-1} 4.50), 254 (4.10), 281 (3.40) and 291 (3.25); δ_H (400 MHz; $CDCl_3$) 1.44–1.50 (2 H, m, H-6 and H-19), 1.53 (1 H, ddd, *J* 14, 10 and 8, H-18), 1.73 (1 H, br t, *J* 14, H-19), 2.02 (1 H, ddd, *J* 14, 2.5 and 1, H-14), 2.06–2.14 (1 H, m, H-18), 2.15 (1 H, ddd, *J* 14, 8 and 2.5, H-14), 2.92–3.04 (1 H, m, H-5), 3.08–3.20 (2 H, m, H-5 and H-6), 3.32 (1 H, br d, *J* 8, H-15), 3.37 (3 H, s, 15-OMe), 3.71 (1 H, d, *J* 2.5, H-21), 3.72 (1 H, d, *J* 2.5, H-17), 3.80 (3 H, s, CO_2Me), 3.84 (6 H, s, 12-OMe and NCO_2Me), 4.47 (1 H, t, *J* 2.5, H-3), 6.13 (1 H, s, 16-OH), 6.82 (1 H, dd, *J* 8 and 1, H-11), 6.83 (1 H, dd, *J* 7.5 and 1, H-9) and 7.01 (1 H, dd, *J* 8 and 7.5, H-10); δ_C (100 MHz; $CDCl_3$) 21.0 (C-19), 25.6 (C-18), 35.8 (C-14), 37.1 (C-20), 40.7 (C-6), 52.2 (CO$_2$*Me*), 53.0 (NCO$_2$*Me*), 53.4 (C-5), 56.2 (12-OMe), 56.9 (15-OMe), 58.8 (C-7), 59.4 (C-21), 76.4 (C-15), 76.7 (C-2), 77.4 (C-16), 79.8 (C-17), 86.4 (C-3), 112.2 (C-11), 113.1 (C-9), 124.9 (C-10), 128.2 (C-13), 143.9 (C-8), 148.8 (C-12), 156.1 (N*C*O$_2$Me) and 171.3 (*C*O$_2$Me); *m*/*z* (EI) 486 (M$^+$, 4%), 458 (3), 455 (3), 441 (1), 427 (15), 425 (12), 369 (5), 337 (9), 130 (7) and 107 (16).

Conversion of kopsingine 2 to kopsidine B 23

Repetition of the above procedure for the oxidation of kopsingine **2** but adding EtOH (10 mL) to the residue in place of MeOH, followed by stirring for 25 h and subsequent chromatography of the resultant mixture (SiO_2; 1% MeOH–$CHCl_3$), afforded kopsidine B **23** (77 mg, 70% from kopsingine **2**) as a light yellow oil, $[a]_D$ + 15 (*c* 0.27, $CHCl_3$); ν_{max} (film)/cm^{-1} 3360, 1740 and 1669; λ_{max} (EtOH)/nm 217 (log ε/L mol^{-1} cm^{-1} 4.59), 253 (4.14), 281 (3.49) and 291 (3.30); δ_H (400 MHz; $CDCl_3$) 1.19 (3 H, t, *J* 7, OCH$_2$C*H*$_3$), 1.42–1.52 (2 H, m, H-6 and H-19), 1.53 (1 H, ddd, *J* 13, 10 and 8, H-18), 1.73 (1 H, br t, *J* 12, H-19), 2.00 (1 H, dd, *J* 14 and 2.5, H-14), 2.06–2.14 (1 H, m, H-18), 2.19 (1 H, ddd, *J* 14, 8.5 and 2.5, H-14), 2.93–3.03 (1 H, m, H-5), 3.09–3.19 (2 H, m, H-5 and H-6), 3.37 (1 H, dq, *J* 10 and 7, OC*H*$_2$CH$_3$), 3.41 (1 H, d, *J* 8.5, H-15), 3.71 (1 H, d, *J* 2, H-21), 3.71 (1 H, dq, *J* 10 and 7, OC*H*$_2$CH$_3$), 3.74 (1 H, d, *J* 2, H-17), 3.80 (3 H, s, CO_2Me), 3.83 (3 H, s, 12-OMe), 3.84 (3 H, s, NCO_2Me), 4.46 (1 H, t, *J* 2.5, H-3), 6.13 (1 H, s, 16-OH), 6.83 (1 H, d, *J* 8, H-11), 6.84 (1 H, d, *J* 7, H-9) and 7.02 (1 H, dd, *J* 8 and 7, H-10); δ_C (100 MHz; $CDCl_3$) 15.2 (OCH$_2$*C*H$_3$), 20.9 (C-19), 25.5 (C-18), 36.9 (C-14), 37.0 (C-20), 40.6 (C-6), 52.2 (CO$_2$*Me*), 53.0 (NCO$_2$*Me*), 53.4 (C-5), 56.2 (12-OMe), 58.8 (C-7), 59.5 (C-21), 64.9 (O*C*H$_2$CH$_3$), 74.5 (C-15), 76.4 (C-2), 77.4 (C-16), 80.0 (C-17), 86.5 (C-3), 112.2 (C-11), 113.2 (C-9), 124.9 (C-10), 128.2 (C-13), 143.9 (C-8), 148.7 (C-12), 156.1 (N*C*O$_2$Me) and 171.3 (*C*O$_2$Me); *m*/*z* (EI) 500 (M$^+$, 6%), 472 (3), 455 (2), 441 (4), 427 (12), 425 (11), 383 (7), 337 (5), 130 (4) and 107 (3).

Conversion of kopsingine 2 to kopsidine C 24

Anodic oxidation of kopsingine **2** was carried out as described above. After removal of the solvent, CH_2Cl_2 was added and the precipitated electrolyte was filtered off. The residue was washed with CH_2Cl_2 and the extract was evaporated under reduced pressure, after which 10 mL of a mixed solvent (MeCN–water, 1 : 1) was added to the residue, followed by stirring for 4 days. The solution was then concentrated under reduced pressure and extracted with $CHCl_3$. The extract was washed, dried (Na_2SO_4), and the solvent was then removed under reduced pressure. The resulting product was chromatographed over SiO_2 (1% MeOH–$CHCl_3$) to afford pure kopsidine C **24** (15 mg, 15% from kopsingine **2**) as a light yellow oil, $[a]_D$ +48 (*c* 0.20, $CHCl_3$); ν_{max} (film)/cm^{-1} 3378, 1741 and 1670; λ_{max} (EtOH)/nm 217 (log ε/L mol^{-1} cm^{-1} 4.27), 253 (3.95), 284 (3.15) and 290 (3.11); δ_H (400 MHz; $CDCl_3$) 1.42–1.52 (1 H, m, H-19), 1.49 (1 H, dd, *J* 13 and 5, H-6), 1.54 (1 H, ddd, *J* 14, 10.5 and 8, H-18), 1.68–1.78 (1 H, m, H-19), 1.91 (1 H, ddd, *J* 14.5, 2.5 and 1, H-14), 2.12 (1 H, ddd, *J* 14, 10 and 2, H-18), 2.39 (1 H, ddd, *J* 14.5, 8 and 2.5, H-14), 2.94–3.04 (1 H, m, H-5), 3.11 (1 H, td, *J* 13 and 5, H-5), 3.18 (1 H, td, *J* 13 and 7, H-6), 3.32 (1 H, br d, *J* 8, H-15), 3.71 (1 H, d, *J* 2.5, H-21), 3.73 (1 H, d, *J* 2.5, H-17), 3.80 (3 H, s, CO_2Me), 3.84 (6 H, s, 12-OMe and NCO_2Me), 4.45 (1 H, t, *J* 2.5, H-3), 6.11 (1 H, s, 16-OH), 6.83 (1 H, dd, *J* 7 and 1, H-9), 6.84 (1 H, dd, *J* 8 and 1, H-11) and 7.02 (1 H, dd, *J* 8, 7, H-10); δ_C (100 MHz; $CDCl_3$) 21.0 (C-19), 25.6 (C-18), 37.7 (C-20), 40.0 (C-14), 40.7 (C-6), 52.3 (CO$_2$*Me*), 53.1 (NCO$_2$*Me*), 53.4 (C-5), 56.2 (12-OMe), 58.8 (C-7), 59.2 (C-21), 67.5 (C-15), 76.4 (C-2), 77.3 (C-16), 79.5 (C-17), 86.4 (C-3), 112.2 (C-11), 113.0 (C-9), 125.0 (C-10), 128.2 (C-13), 143.8 (C-8), 148.9 (C-12), 156.1 (N*C*O$_2$Me) and 171.2 (*C*O$_2$Me); *m*/*z* (EI) 472 (M$^+$, 43%), 444 (35), 427 (20), 425 (50), 413 (12), 355 (11), 337 (100) and 107 (18).

Alternatively, the residue obtained after removal of the solvent and the bulk of the supporting electrolyte was stirred in 10 mL of a mixed solvent (CH_2Cl_2–water, 1 : 1) containing $C_6H_5CH_2NMe_3^+Cl^-$ (0.02 mmol) as phase-transfer catalyst, at room temperature, for 4 days. Subsequent extraction ($CHCl_3$) and chromatography as described above gave kopsidine C **24** (21 mg, 20% from kopsingine **2**).

Reduction of kopsidine C 24 to kopsinganol 25

To a solution of kopsidine C **24** (20 mg, 0.04 mmol) in MeOH (2 mL) was added $NaBH_4$ (13 mg, 0.3 mmol) and the mixture was stirred at room temperature for 30 min. The solvent was then removed under reduced pressure and water (5 mL) was added. The mixture was then extracted with $CHCl_3$ and the extract was washed with water and then dried (Na_2SO_4). Chromatography of the residue after removal of the solvent (SiO_2; 1% MeOH–$CHCl_3$) gave kopsinganol **25** (18 mg, 90%) as a light yellow oil, $[a]_D$ +46 (*c* 0.12, $CHCl_3$); ν_{max} (film)/cm^{-1} 3378, 1745 and 1670; λ_{max} (EtOH)/nm 217 (log ε/L mol^{-1} cm^{-1} 4.42), 254

(4.05), 282 (3.35) and 294 (3.28); δ_H (400 MHz; $CDCl_3$) 1.33–1.45 (2 H, m, H-18 and H-19), 1.66–1.76 (1 H, m, H-19), 1.71 (1 H, dd, *J* 12 and 4, H-6), 1.84 (1 H, br d, *J* 14, H-14), 2.09 (1 H, ddd, *J* 14, 12 and 2, H-18), 2.54 (1 H, dddd, *J* 14, 11, 6 and 4, H-14), 2.61 (1 H, ddd, *J* 12, 8.5 and 4, H-5), 2.79 (1 H, dd, *J* 8.5 and 6, H-5), 2.89 (1 H, td, *J* 11 and 3, H-3), 2.98 (1 H, ddd, *J* 11, 6 and 1.5, H-3), 3.16 (1 H, d, *J* 2, H-21), 3.21 (1H, td, *J* 12 and 6, H-6), 3.80 (6 H, s, CO_2Me and NCO_2Me), ≈ 3.80 (1 H, H-17), 3.84 (3 H, s, 12-OMe), 3.95 (1 H, dd, *J* 6 and 4, H-15), 5.69 (1 H, s, 16-OH), 6.82 (1 H, d, *J* 7, H-9), 6.83 (1 H, d, *J* 8, H-11), 7.03 (1 H, dd, *J* 8 and 7, H-10) and 8.72 (1 H, d, *J* 7, 17-OH); δ_C (100 MHz; $CDCl_3$) 21.4 (C-19), 27.0 (C-18), 33.9 (C-14), 40.9 (C-20), 41.0 (C-6), 44.3 (C-3), 48.9 (C-5), 51.9 (CO_2*Me*), 53.0 (NCO_2*Me*), 56.1 (12-OMe), 57.0 (C-7), 64.3 (C-21), 69.9 (C-15), 76.3 (C-2), 81.3 (C-16), 83.1 (C-17), 111.9 (C-11), 113.1 (C-9), 124.9 (C-10), 128.2 (C-13), 144.6 (C-8), 149.3 (C-12), 155.5 (N*C*O_2Me) and 172.1 (*C*O_2Me); *m*/*z* (EI) 474 (M^+, 100%), 430 (10), 399 (24), 370 (42), 355 (14), 341 (21), 315 (20) and 301 (38).

Anodic oxidation of dihydrokopsingine 19 (Pt anode, dichloromethane–acetonitrile)

Anodic oxidation (Pt gauze, 0.81 V *versus* Ag/AgCl) of dihydrokopsingine **19** (400 mg, 0.4 mmol) in 30% CH_2Cl_2–MeCN containing Et_4NClO_4 (0.1 M) and 2,6-lutidine (0.8 mmol) proceeded smoothly until the consumption of 2 faradays mol^{-1}. Removal of the solvent and the supporting electrolyte following the procedure described above gave a residue, which on chromatography (SiO_2; 1% MeOH–$CHCl_3$) gave two products, **26** and **27**. Compound **26** (80 mg, 20%) was obtained as a colourless oil, $[\alpha]_D$ −4.5 (*c* 0.34, $CHCl_3$); ν_{max} (film)/cm^{-1} 3361br, 1740 and 1670; λ_{max} (EtOH)/nm 217 (log ε/L mol^{-1} cm^{-1} 4.56), 254 (4.07), 284 (3.33) and 290 (3.20); δ_H (400 MHz; $CDCl_3$) 1.18 (1 H, ddd, *J* 13, 11 and 2, H-19), 1.45–1.51 (1 H, m, H-6), 1.48 (1 H, ddd, *J* 13, 11 and 8, H-18), 1.57–1.69 (2 H, m, H-14 and H-15), 1.66 (1 H, ddd, *J* 13, 11 and 8, H-19), 1.95–2.01 (2 H, m, H-14 and H-15), 2.10 (1 H, ddd, *J* 13, 11 and 2, H-18), 2.98–3.12 (2 H, m, 2 × H-5), 3.15 (1 H, td, *J* 12.5 and 7, H-6), 3.41 (1 H, d, *J* 2, H-21), 3.80 (3 H, s, CO_2Me), 3.84 (6 H, s, 12-OMe and NCO_2-Me), 3.89 (1 H, d, *J* 2, H-17), 4.39 (1 H, t, *J* 2, H-3), 6.07 (1 H, s, 16-OH), 6.81 (1 H, dd, *J* 7 and 1, H-9), 6.83 (1 H, dd, *J* 8 and 1, H-11), 7.02 (1 H, dd, *J* 8 and 7, H-10); δ_C (100 MHz; $CDCl_3$) 25.0 (C-19), 25.9 (C-18), 26.8 (C-15), 28.2 (C-14), 32.8 (C-20), 40.8 (C-6), 52.2 (CO_2*Me*), 53.0 (NCO_2*Me*), 53.2 (C-5), 56.2 (12-OMe), 59.2 (C-7), 65.8 (C-21), 76.4 (C-2), 77.5 (C-16), 82.0 (C-17), 86.4 (C-3), 112.2 (C-11), 112.9 (C-9), 124.9 (C-10), 128.3 (C-13), 144.0 (C-8), 148.8 (C-12), 156.0 (N*C*O_2Me) and 171.4 (*C*O_2Me); *m*/*z* (EI) 456.1896 (M^+, 44%. $C_{24}H_{28}N_2O_7$ requires *M*, 456.1897), 428 (65), 427 (100), 397 (13), 369 (18) and 339 (47).

Compound **27** (219 mg, 55%) was obtained as a colourless oil, $[\alpha]_D$ −26.6 (*c* 0.90, $CHCl_3$); ν_{max} (film)/cm^{-1} 3373br, 1739 and 1671; λ_{max} (EtOH)/nm 217 (log ε/L mol^{-1} cm^{-1} 4.55), 253 (4.05), 284 (3.30) and 291 (3.25); δ_H (400 MHz; $CDCl_3$) 1.03 (1 H, dd, *J* 13 and 10.5, H-19), 1.37–1.48 (2 H, m, H-14 and H-15), 1.57 (1 H, ddd, *J* 13, 10.5 and 9, H-18), 1.73 (1 H, dd, *J* 14 and 2.5, H-6), 1.81 (1 H, ddd, *J* 13, 10.5 and 9, H-19), 1.87–1.97 (1 H, m, H-15), 2.02 (1 H, dd, *J* 13 and 10.5, H-18), 2.34 (1 H, qt, *J* 14 and 5, H-14), 3.05 (1 H, td, *J* 14 and 4.5, H-3), 3.27 (1 H, d, *J* 2, H-21), 3.40 (1 H, dd, *J* 14 and 5, H-3), 3.41 (1 H, d, *J* 14, H-6), 3.79 (3 H, s, CO_2Me), 3.84 (6 H, s, 12-OMe and NCO_2Me), 3.96 (1 H, d, *J* 2, H-17), 4.74 (1 H, d, *J* 2.5, H-5), 5.80 (1 H, s, 16-OH), 6.81 (1 H, dd, *J* 8 and 1, H-11), 6.89 (1 H, dd, *J* 7 and 1, H-9), 7.03 (1 H, dd, *J* 8 and 7, H-10); δ_C (100 MHz; $CDCl_3$) 21.5 (C-14), 24.6 (C-18), 28.0 (C-19), 30.4 (C-20), 36.2 (C-15), 45.3 (C-6), 47.1 (C-3), 52.2 (CO_2*Me*), 52.9 (NCO_2*Me*), 56.2 (C-7 and 12-OMe), 63.0 (C-21), 74.1 (C-2), 79.7 (C-16), 83.9 (C-17), 90.2 (C-5), 112.5 (C-11), 114.4 (C-9), 125.1 (C-10), 128.8 (C-13), 140.3 (C-8), 148.1 (C-12), 156.0 (N*C*O_2Me) and 172.4 (*C*O_2Me); *m*/*z* (EI) 456.1897 (M^+, 59%. $C_{24}H_{28}N_2O_7$ requires *M*, 456.1897), 428 (74), 427 (100), 399 (51) and 314 (68).

Anodic oxidation of 3-oxokopsingine 20 (Pt anode, dichloromethane–acetonitrile)

CV of 3-oxokopsingine **20** (Pt anode and cathode, 30% CH_2Cl_2–MeCN containing 0.1 M Et_4NClO_4) showed no oxidation peaks up to 1.8 V *versus* Ag/AgCl.

Anodic oxidation of kopsingine 2 (carbon anode, dichloromethane–methanol)

Anodic oxidation of kopsingine **2** (50 mg, 0.1 mmol) was carried out at a vitreous carbon anode (1.0 V *versus* Ag/AgCl) in 50 mL of 20% CH_2Cl_2–MeOH containing $LiClO_4$ (0.1 M) and 2,6-lutidine (0.2 mmol) under nitrogen until consumption of 2 faradays mol^{-1} of charge as described above. Removal of the solvent and the supporting electrolyte in the manner described above gave a residue, which on chromatography (SiO_2; 1% MeOH–$CHCl_3$) afforded kopsidine A **22** (19 mg, 36%).

Anodic oxidation of kopsingine 2 (carbon anode, dichloromethane–ethanol)

Anodic oxidation of kopsingine **2** (50 mg, 0.1 mmol) was carried out at a vitreous carbon anode (0.95 V *versus* Ag/AgCl) in 50 mL of 20% CH_2Cl_2–EtOH containing $LiClO_4$ (0.1 M) and 2,6-lutidine (0.2 mmol) under nitrogen until consumption of 2 faradays mol^{-1} of charge as described above. Subsequent removal of the solvent and electrolyte followed by chromatography of the residue (SiO_2; 1% MeOH–$CHCl_3$) gave kopsidine B **23** (30 mg, 55%).

Anodic oxidation of dihydrokopsingine 19 (carbon anode, dichloromethane–methanol)

Anodic oxidation (vitreous carbon anode, 0.95 V *versus* Ag/AgCl) of dihydrokopsingine **19** (40 mg, 0.09 mmol) in 50 mL of mixed solvent (5% CH_2Cl_2–MeOH) containing $LiClO_4$ (0.1 M) and 2,6-lutidine (0.18 mmol) as described above proceeded smoothly until the consumption of 2 faradays mol^{-1}. The residue obtained after the removal of solvent and electrolyte as described above, followed by chromatography (SiO_2; 1% MeOH–$CHCl_3$), gave compounds **26** (11 mg, 27%), **27** (9 mg, 22%) and **32** (9 mg, 25%). *Compound* **32** (*dihydrokopsinitarine A*) was obtained as an amorphous solid, $[\alpha]_D$ −43.3 (*c* 0.21, $CHCl_3$); ν_{max} (film)/cm^{-1} 3330br, 1770 and 1674; λ_{max} (EtOH)/nm 217 (log ε/L mol^{-1} cm^{-1} 4.50), 2.45 (4.14) and 290 (3.20); δ_H (400 MHz; $CDCl_3$) 1.27 (1 H, ddd, *J* 14, 11.5 and 2, H-19), 1.44 (1 H, ddd, *J* 14, 11.5 and 8, H-19), 1.46 (1 H, dt, *J* 14 and 6, H-14), 1.56 (1 H, td, *J* 14 and 6, H-15), 1.63 (1 H, ddd, *J* 14, 11.5 and 8, H-18), 1.93 (1 H, dd, *J* 14 and 6, H-15), 2.15 (1 H, ddd, *J* 14, 11.5 and 2, H-18), 2.43 (1 H, qt, *J* 14 and 6, H-14), 2.80 (1 H, d, *J* 5, H-6), 3.19 (1 H, td, *J* 14 and 6, H-3), 3.43 (1 H, dd, *J* 14 and 6, H-3), 3.43 (1 H, d, *J* 2.5, H-21), 3.78 (3 H, s, NCO_2Me), 3.83 (3 H, s, 12-OMe), 4.05 (1 H, d, *J* 2.5, H-17), 5.25 (1 H, d, *J* 5, H-5), 6.63 (1 H, s, 16-OH), 6.86 (1 H, dd, *J* 8 and 1, H-11), 6.92 (1 H, dd, *J* 7.5 and 1, H-9), 7.12 (1 H, dd, *J* 8 and 7.5, H-10); δ_C (100 MHz; $CDCl_3$) 18.6 (C-18), 22.6 (C-14), 27.6 (C-19), 29.8 (C-20), 34.2 (C-15), 46.6 (C-3), 53.5 (NCO_2*Me*), 56.0 (12-OMe), 57.8 (C-6), 59.6 (C-7), 65.8 (C-21), 72.0 (C-2), 88.0 (C-16), 91.4 (C-17), 94.6 (C-5), 112.9 (C-11), 114.9 (C-9), 126.7 (C-10), 130.6 (C-13), 136.7 (C-8), 149.4 (C-12), 156.0 (N*C*O_2Me) and 205.9 (C-22); *m*/*z* (EI) 424.1642 (M^+, 77%. $C_{23}H_{24}N_2O_6$ *M*, requires 424.1634), 396 (38), 395 (100), 365 (13) and 337 (19).

Anodic oxidation of 12-demethoxy-17-epikopsinganol 35 (carbon anode, methanol)

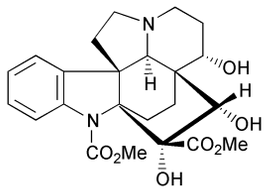
Anodic oxidation of compound **35** (20 mg, 0.045 mmol) at a vitreous carbon anode (0.95 V *versus* Ag/AgCl) in 50 mL of 0.1 M $LiClO_4$–MeOH containing 2,6-lutidine (0.09 mmol) was

carried out as described above. The reaction proceeded smoothly until consumption of 2.5 faradays mol^{-1}. The residue obtained after the removal of solvent and electrolyte as described above, followed by chromatography (SiO_2; Et_2O), gave two products, **36** and **37**.

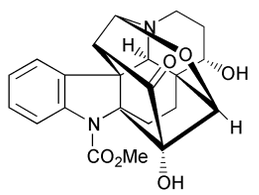
Compound **36** (8 mg, 37%) was obtained as a light yellow oil, $[\alpha]_D$ +21.4 (*c* 0.07, $CHCl_3$); ν_{max} (film)/cm^{-1} 3441br, 1754, 1667, 1235 and 1101; δ_H (400 MHz; $CDCl_3$) 1.22 (2 H, ddd, *J* 13, 10.5 and 8, H-19, H-19′), 1.41 (2 H, ddd, *J* 13, 10.5 and 1.5, H-19, H-19′), 1.44 (2 H, br d, *J* 13, H-14, H-14′), 1.60 (2 H, ddd, *J* 13, 10.5 and 8, H-18, H-18′), 1.82 (2 H, tdd, *J* 13, 5 and 3, H-14, H-14′), 1.86 (2 H, dd, *J* 13 and 10.5, H-18, H-18′), 2.26 (2 H, d, *J* 5, H-6, H-6′), 3.00 (2 H, ddd, *J* 13, 5 and 2, H-3, H-3′), 3.32 (2 H, d, *J* 7, 17-OH, 17-OH′), 3.33 (2 H, td, *J* 13 and 3, H-3, H-3′), 3.47 (2 H, s, H-21, H-21′), 3.57 (2 H, dd, *J* 7 and 1.5, H-17, H-17′), 3.77 (6 H, s, CO_2Me, CO_2Me′), 3.86 (6 H, s, NCO_2Me, NCO_2Me′), 4.02 (2 H, dd, *J* 3 and 2, H-15, H-15′), 4.87 (2 H, d, *J* 5, H-5, H-5′), 6.66 (2 H, s, 16-OH, 16-OH′), 6.97 (2 H, td, *J* 7.5 and 1, H-11, H-11′), 7.13 (2 H, td, *J* 7.5 and 1.5, H-10, H-10′), 7.39 (2 H, dd, *J* 7.5 and 1, H-9, H-9′) and 7.52 (2 H, br d, *J* 7.5, H-12, H-12′); δ_C (100 MHz; $CDCl_3$) 19.6 (C-14, C-14′), 26.8 (C-18, C-18′), 28.3 (C-19, C-19′), 39.5 (C-20, C-20′), 41.4 (C-3, C-3′), 52.5 (CO_2Me, CO_2Me′), 52.9 (NCO_2Me, NCO_2Me′), 54.0 (C-6, C-6′), 58.5 (C-7, C-7′), 63.9 (C-21, C-21′), 67.0 (C-15, C-15′), 68.9 (C-17, C-17′), 74.5 (C-2, C-2′), 76.5 (C-16, C-16′), 96.7 (C-5, C-5′), 116.8 (C-12, C-12′), 122.8 (C-11, C-11′), 124.9 (C-9, C-9′), 127.3 (C-10, C-10′), 135.1 (C-13, C-13′), 143.0 (C-8, C-8′), 152.5 (NCO_2Me, NCO_2Me′) and 169.1 (CO_2Me, CO_2Me′); *m*/*z* (API-LCMS, MeOH) 901 (MH^+, $C_{46}H_{52}N_4O_{15}$ + H).

Compound **37** (3 mg, 17%) was obtained as an amorphous solid, $[\alpha]_D$ −47.5 (*c* 0.04, $CHCl_3$); ν_{max} (film)/cm^{-1} 3316br, 1772, 1676 and 1128; δ_H (400 MHz; $CDCl_3$) 1.22 (1 H, ddd, *J* 14, 11 and 9, H-19), 1.57 (1 H, ddd, *J* 13, 11 and 9, H-18), 1.59 (1 H, ddd, *J* 14, 5 and 2, H-14), 2.12 (1 H, ddd, *J* 14, 11 and 1.5, H-19), 2.21 (1 H, ddd, *J* 13, 11 and 1.5, H-18), 2.62 (1 H, d, *J* 5, H-6), 2.74 (1 H, dddd, *J* 14, 13.5, 6.5 and 3.5, H-14), 3.27 (1 H, dd, *J* 14.5 and 6.5, H-3), 3.53 (1 H, ddd, *J* 14.5, 13.5 and 5, H-3), 3.92 (3 H, s, NCO_2Me), 3.95 (1 H, dd, *J* 3.5 and 2, H-15), 3.97 (1 H, d, *J* 2.5, H-17), 4.07 (1 H, d, *J* 2.5, H-21), 5.23 (1 H, d, *J* 5, H-5), 6.95 (1 H, br s, 16-OH), 7.09 (1 H, td, *J* 7.5 and 1, H-10), 7.23 (1 H, ddd, *J* 8, 7.5 and 1.5, H-11), 7.31 (1 H, ddd, *J* 7.5, 1.5 and 0.5, H-9) and 7.51 (1 H, br d, *J* 8, H-12); δ_C (100 MHz; $CDCl_3$) 17.4 (C-18), 22.2 (C-19), 32.5 (C-14), 34.8 (C-20), 42.1 (C-3), 54.0 (NCO_2Me), 57.7 (C-7), 58.8 (C-6), 60.2 (C-21), 70.3 (C-15), 70.8 (C-2), 87.8 (C-16), 88.4 (C-17), 95.0 (C-5), 116.6 (C-12), 122.9 (C-9), 124.7 (C-10), 128.8 (C-11), 132.9 (C-8), 141.2 (C-13), 156.3 (NCO_2Me) and 206.4 (C-22); *m*/*z* (EI) 410.1480 (M^+, 74%. $C_{22}H_{22}N_2O_6$ requires *M*, 410.1478), 382 (100), 365 (12) and 322 (20).

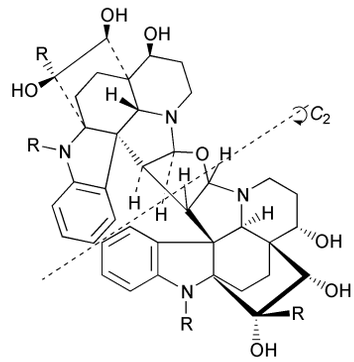
Repetition of the above oxidation gave essentially the same results, providing compounds **36** and **37** in yields of 30% and 13%, respectively. In a control experiment, a solution containing the substrate **35** (5 mg, 0.01 mmol) in 0.1 M $LiClO_4$–MeOH containing 2,6-lutidine (0.02 mmol) was stored under nitrogen for 19 h after which compound **35** was recovered intact without any epimerization detected at carbon-17.



35



37



36 R = CO_2Me

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37 Compound **20** is also obtained in minute amounts from *K. singapurensis*: T. S. Kam and G. Subramaniam, unpublished results.