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Synthesis of Veprisine Dimers and the Formation of a Novel Cyclic Tetramer from Precocene I

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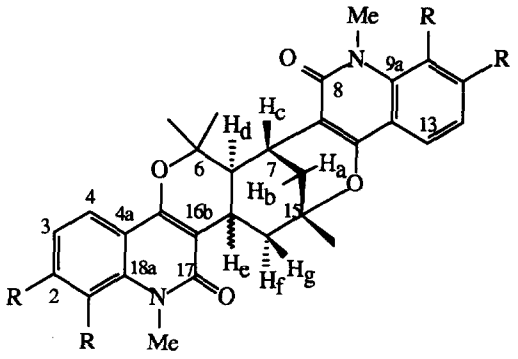
Abstract: Thermolysis of veprisine afforded vepridimerines A-D and in addition, a new dimer, vepridimerine E. The full details of the ^{1}H and ^{13}C NMR spectroscopic properties of vepridimerines A-E are presented. Acid treatment of veprisine gave another new dimer, diveprisine, analogous to the known precocene II dimer. Under the same conditions precocene I was transformed into a cyclic tetramer. High field NMR examination of the coumarin dimer, reported by Barnes et al. in 1963, confirmed the assigned structure.

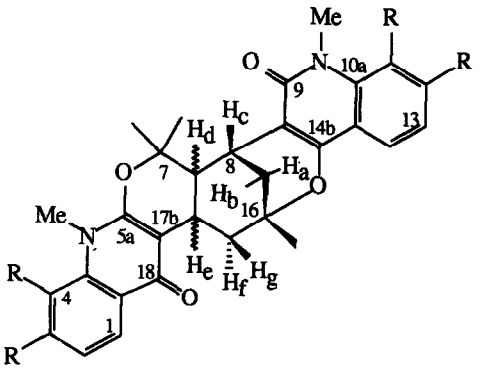
For many years we have been interested in the Rutaceae family because of the occurrence of tetranortriterpenoids, coumarins and alkaloids[1]. A few years ago we reported that the bark of the Cameroonian plant Vepris louisii contains quinolone and indolopyridoquinazoline alkaloids[2-4]. A re-investigation of the bark of the same plant and of Oricia renieri[5] from Ruwanda led to the isolation† of four new heptacyclic bis-quinolone alkaloids, vepridimerines A(1), B(2), C(3) and D(4). More recently three further bis-2-quinolone dimers, araliopdimerines A(5), B(6) and C(7) have been isolated from Araliopsis tabouensis[6]. We now report the full details of the synthesis of vepridimerines A-D (1)-(4) from veprisine (10) and their ^{1}H and ^{13}C NMR spectra[7]. The structures of two new synthetic dimers vepridimerine E(8) and diveprisine (9) are also discussed. Model experiments with the chromenes precocene II (11) and precocene I (12) afforded respectively the known dimer (13)[8] and a novel cyclic tetramer (14). The structural elucidation of the latter is described. Investigation by high field NMR of the "coumarin dimer" (15) supports the structure proposed[9] by Barnes and his colleagues in 1963.

Mass measurement of the six veprisine dimers shows that they are isomeric and have the molecular formula $C_{34}H_{38}N_2O_8$. The spectroscopic properties of vepridimerines A(1) and B(2) (Tables 1 and 3) are consistent

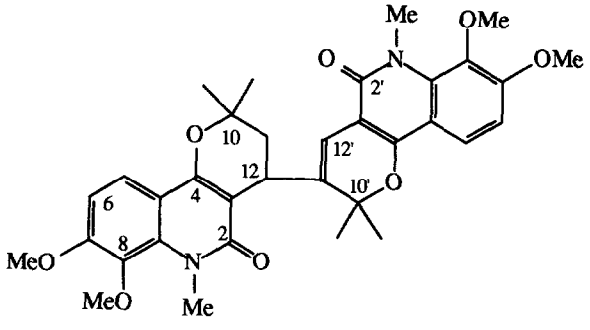
† Vepridimerines A, B and C were isolated by us from V. louisii while vepridimerines B, C and D were isolated from Oricia renieri by Professor Peter Waterman and his colleagues.



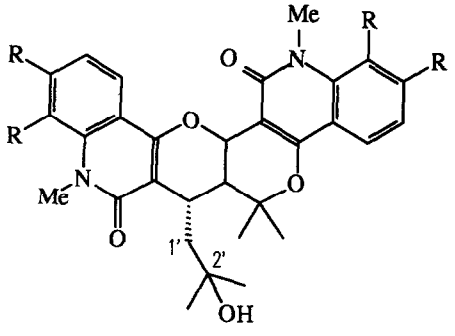
(1) α-H_e, R = OMe
(2) β-H_e, R = OMe
(7) $\Delta^{16,16a}$, R = OMe
(19) α-H_e, R = H
(20) β-H_e, R = H
(25) $\Delta^{16,16a}$, R = H



(3) α-H_d, α-H_e, R = OMe
(4) α-H_d, β-H_e, R = OMe
(8) β-H_d, α-H_e, R = OMe
(18) β-H_d, α-H_e, R = H
(21) α-H_d, α-H_e, R = H
(22) α-H_d, β-H_e, R = H



(9)
(26) 11',12'-dihydro



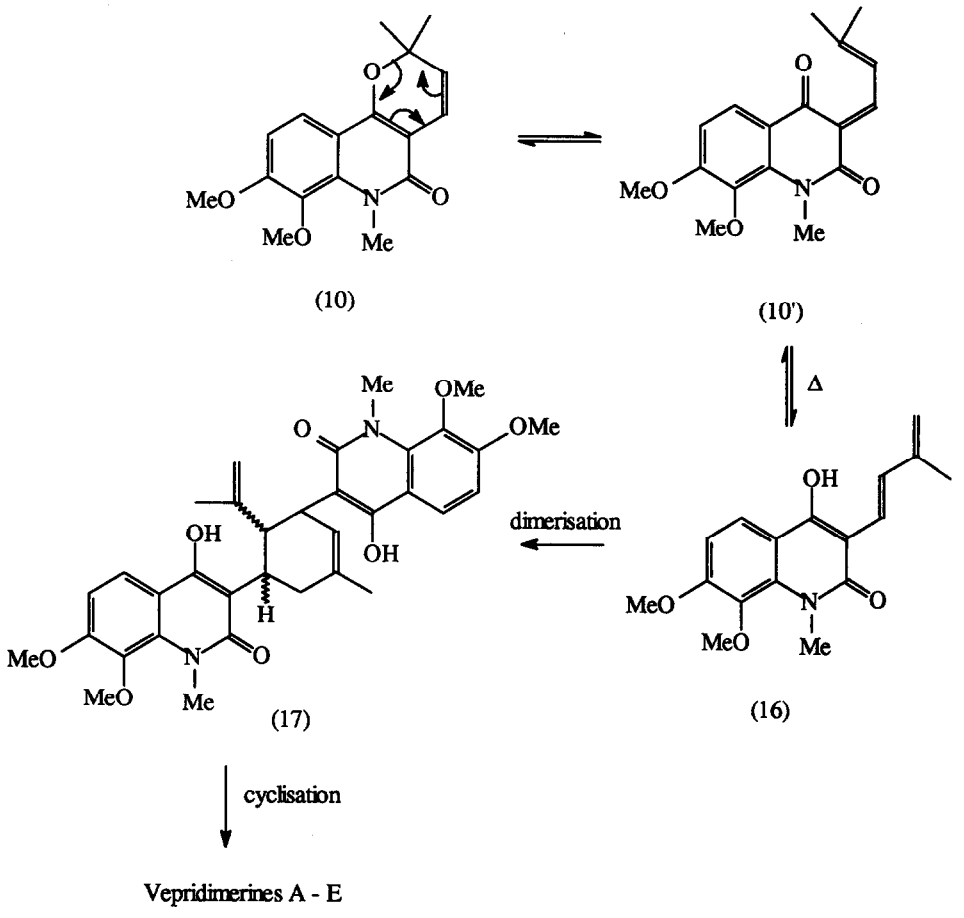
(5) R = OMe, 1',2'-anhydro
(23) R = H, 1',2'-anhydro
(6) R = OMe
(24) R = H

with the presence of two veprisine (10) units linked by a C_{10} moiety which consists of three tertiary methyls, two methylenes, three methines and two fully substituted carbons bearing oxygen. Decoupling experiments at 360 MHz readily revealed the connectivity of the protons associated with the C_{10} moiety and led to the gross structures (1) and (2). It was clear from the values of the coupling constants that vepridimerine A and B differ in stereochemistry. In vepridimerine A the protons H_d and H_e are cis (^3J 6.1 Hz). Moreover, with the cyclohexane ring in a chair conformation, there is a perfect W relationship between H_f and H_a which accounts for the observed ^4J coupling (2.2 Hz) between these protons. In vepridimerine B H_d and H_e have a trans relationship (^3J 12.5 Hz). It is clear from models that in structure (2) the cyclohexane ring must adopt a boat conformation thus excluding the possibility of a ^4J coupling between H_f and H_a. In this case none is observed. The alternative trans arrangement does permit a chair conformation of the cyclohexane and a long-range coupling between H_f and H_a would be expected and is indeed observed (see vepridimerine E below).

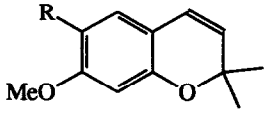
It was apparent from the spectroscopic properties of vepridimerines C(3) and D(4) (Tables 2 and 4) that they contain a 4-quinolone unit and a 2-quinolone unit joined by the same C_{10} moiety as above. The 4-quinolone unit is readily recognised by the downfield chemical shifts of H-1 (δ_H 8.05) and the carbonyl carbon (δ_C 176.29) together with the change of their UV spectra in the presence of dilute hydrochloric acid. Vepridimerine C(3) is the cis isomer ($^3J_{H_d,H_e}$ 6.8 Hz) while vepridimerine D(4) is the trans isomer ($^3J_{H_d,H_e}$ 12.6 Hz). In our preliminary communication[5] the 4-quinolone was placed on the left hand side because of small chemical shift differences of H_e and H_f between (1) and (3) and of H_e and H_g between (2) and (4). Direct confirmation of these assignments has now been obtained from 2D long-range δ_C/δ_H correlation experiments. The 2-quinolone carbonyl group showed correlation with H_c thus confirming that the 2-quinolone unit is on the right-hand side.

The formation of the vepridimerines (Scheme 1) can be rationalised in terms of Diels Alder dimerisation of the trans diene (16) to give the racemic intermediate (17). This diene (16) can be obtained from a thermal heteroelectrocyclic ring opening reaction of the "cyclo-hexadiene ⇌ hexatriene" type of veprisine (10) followed by a {1,7} sigmatropic shift[7]. Cycloaddition of 2- or 4-hydroxyl groups to the residual double bonds of the former intermediate (17), which can exist in several tautomeric forms, would then give the vepridimerines A-E.

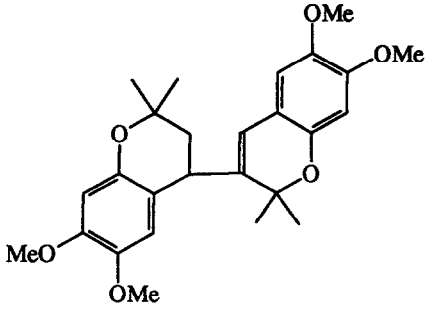
Preparation of the vepridimerines was achieved by heating veprisine (10), sealed under reduced pressure in a pyrex tube, at 200-220° for



Scheme 1



(11) R = OMe
(12) R = H



(13)

15 hours. Careful chromatography of the crude product afforded vepridimerines A(1), B(2), C(3) and D(4) identified by comparison with authentic samples[5]. The spectroscopic properties of a fifth dimer, vepridimerine E were similar to those reported[10] for di-N-methyl geigedimerine (18), apart from the presence of the methoxyl resonances. It was apparent from the high field ^{1}H NMR spectrum that the ring junction protons H_d and H_e are trans (^3J 12.0 Hz). The observation of a ^4J coupling between H_a and H_g indicated that the cyclohexane ring has a chair conformation, only possible with the relative stereochemistry of H_d and H_e as in (8). 2D Long-range shift correlation of H_c with the 2-quinolone carbonyl carbon confirmed the relative dispositions of the quinolone moieties as shown in (8). Vepridimerines A-E and araliopdimerines A-C are respectively the tetramethoxy-derivatives of paraensidimerines A(19), C(20), A'(21), C'(22), F'(18), D (23), B(24) and G(25). Paraensidimerines A-D and G were isolated from Euxylophora paraensis[11] (Rutaceae) by Jurd and his colleagues while paraensidimerines A', C' and F' were synthesized[12] by Ngadjui et al.

Attempts to dimerise veprisine by acid treatment led to a new crystalline dimer, diveprisine, which was assigned structure (9) on the following evidence. Diveprisine (9) $C_{34}H_{38}N_2O_8$, mp 280-281°, m/z 602 (M^+, 100%), 302(84), 301(39); ν_{max} (CCl_4) 1651, 1639 and 1592 cm^{-1} has resonances for four tertiary methyl groups (δ_H 1.27, 1.49, 1.56 and 1.91; δ_C 24.1, 26.6, 27.3 and 29.1), two N-methyl groups (δ_H 3.71, 3.76; δ_C 33.4, 33.5), four methoxyl groups (δ_H 3.81, 3.83, 3.92, 3.94; δ_C 56.17, 56.20, 61.55, 61.63) and two ortho-coupled aromatic AB systems {δ_H 7.69 and 7.68; 6.83 and 6.85 (all d, J 9.0 Hz)} consistent with two veprisine units joined via the chromene rings. The presence of four methyl groups clearly indicates that the carbon skeleton of diveprisine is different from that of the vepridimerines[5]. The remaining spectroscopic features of diveprisine include a trisubstituted double bond {δ_H 6.29(s); δ_C 141.2(s) and 112.4(d)} and an AMX system comprising a methylene group {δ_H 1.92 (H_A, dd, J 10.0, 13.9 Hz), 2.19 (H_M, dd, J 7.2, 13.9 Hz); δ_C 43.8(t)} and a methine {δ_H 3.49 (H_X, dd, J 7.2, 10.0 Hz); δ_C 31.7(d)}. These data can be readily accommodated in structure (9) for diveprisine. The three other possible ways of joining the two veprisine units can be excluded on the basis of the unsymmetrical nature of the hydrogenation products and on the magnitude of the geminal coupling constant (J 13.9 Hz) of the methylene group (see below).

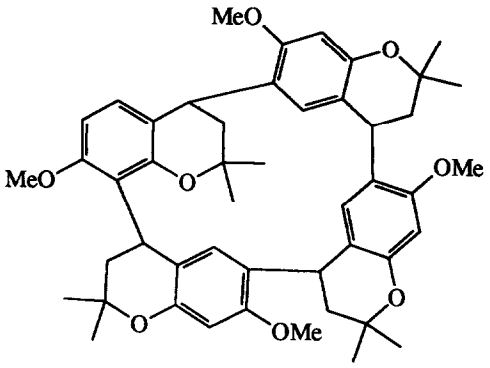
Hydrogenation of diveprisine afforded two dihydro-derivatives (26) both of which show a small parent ion at m/z 604 (1%) and a base peak at m/z 302. It is clear from the ^{13}C NMR spectra of these products that they

are non-symmetrical. The ^{1}H and ^{13}C NMR spectra of the major isomer, mp 218-220°, are, in part, broad, presumably as a result of restricted rotation. The minor isomer, mp 148-150° is unaffected by this phenomenon and has resonances for two methylene groups (δ_C 19.8 and 34.0) and two methines (δ_C 30.9 and 37.3). The associated proton shifts and coupling constants are given in the Experimental. The fact that the newly created methylene group has a geminal coupling constant of 18.2 Hz indicates that it is α to the veprisine nucleus and confirms the structure of diveprisine as (9). The relative configuration of the two dihydro-derivatives remains undetermined.

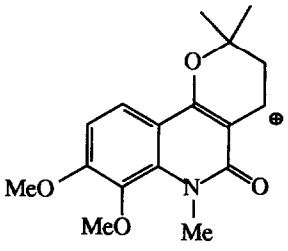
The formation of diveprisine can be rationalized in terms of protonation of the chromene double bond of veprisine (10) to give a resonance-stabilized electrophilic species (27) which then reacts with a second veprisine molecule followed by proton loss. Presumably the presence of the methoxyl group on C-7 favours protonation at the expense of formation of the diene (16).

Treatment of the chromene, precocene II (11)[13], under the same conditions gave the previously reported[8] dimer (13) whose spectroscopic properties are in accord with its structure. The mode of coupling is readily revealed by the size of the geminal coupling constant (J 12.4 Hz) of the methylene group. The structure of dimer (13) has recently been confirmed by X-ray analysis[8].

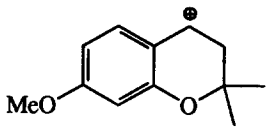
Unexpectedly, the corresponding monomethoxychromene, precocene I (12), did not yield the analogous dimer on exposure to acid but instead afforded a cyclic tetramer (14), $C_{48}H_{56}O_8$, mp 242-243°, m/z 760 (M^+, 35%) which has eight tertiary methyl groups (δ_H 0.77, 1.11, 1.12, 1.21, 1.28, 1.40, 1.45, 1.46), four methoxy groups (δ_H 3.84(2), 3.45, 3.29), six aromatic proton singlets (δ_H 6.86, 6.43, 6.34, 6.18, 6.16, 5.95) and one ortho-coupled AB system {δ_H 6.76, 6.27 (both d, J 8.3 Hz)}. It is immediately apparent that the formation of the tetramer must have involved aromatic substitution. The tetramer also has resonances for four methylene groups (δ_C 41.30, 41.29, 38.6, 37.7) and four methines (δ_C 38.0, 35.6, 32.3, 28.0) which constitute four separate AMX systems. These must arise from the chromene double bonds of the four monomer units and clearly indicate that the tetramer is cyclic. A possible mode of formation of the tetramer involves attack by electrophilic species (28) on C-6 of a second molecule. The resulting dimer is protonated and reacts with a third monomer molecule. The process is repeated once more to give a linear tetramer which cyclises by electrophilic substitution at the more hindered C-8 position of the starting unit. The relative configuration and the conformation of (14) must await X-ray analysis.


MeO
O
MeO
O
OMe
O
O
OMe

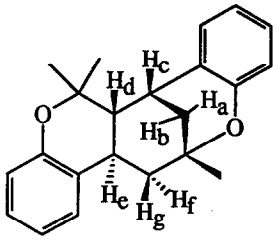
(14)


O
⊕
MeO
N
O
MeO
Me

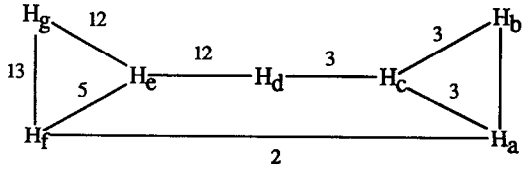
(27)


⊕
MeO
O

(28)


Hc
Hd
Ha
O
Hb
O
He
Hg
Hf

(15)


Hg
12
Hb
3
12
3
13
He
Hd
Hc
5
3
Hf
Ha
2

(29)

Recently Cordell and his colleagues have reported[14] that acid treatment of the antitumour alkaloid, acronycine, afforded dimers and trimers whose formation also involved electrophilic substitution of an aromatic ring by a protonated chromene species.

After the publication of our vepridimerine paper we became aware of the work by Barnes and his colleagues[9] on the structure of the "coumarin dimer" (15). Since this represents the alternative trans ring junction to vepridimerine B and D, we decided to investigate the structure by high field NMR. The labelling of the spin system is shown in (29). At 360 MHz the ^1H NMR spectrum of (15) still shows some second order character but decoupling of H_d [δ 1.95 (dd, J 12, 3 Hz)] along with H_a and H_b [which have apparently coincident chemical shifts δ 1.93 (dd, J 3, 1 Hz)] enables the patterns for H_e [δ 2.81 (td, J 12, 5 Hz)], H_f [δ 2.75 (ddt, J 13, 5, 1 Hz)] and H_g [δ 1.51 (dd, J 13, 12 Hz after decoupling H_d, H_a, and H_b)] to be deciphered. H_f appears to couple equally to H_a and H_b but only the sum of the two couplings is ascertainable, and we prefer the interpretation that there is a 2 Hz W coupling between H_a and H_f. The remaining proton H_c is at δ 3.33 (q, J 3 Hz). The coupling arrangement illustrated in (29) is entirely consistent with the proposed structure. In particular, since models show that with this trans arrangement the cyclohexane ring can exist in a chair conformation, the expected ^4J coupling between H_f and H_a is observed as in the case of vepridimerine E. In the alternative trans arrangement found in vepridimerines B and D the cyclohexane must adopt a boat conformation and no ^4J coupling is possible.

EXPERIMENTAL

Mps were measured on a Kofler hot stage and are uncorrected. IR spectra were recorded on a Perkin Elmer 727B spectrometer and UV spectra on a Beckmann 25 grating spectrometer. NMR spectra were run in $CDCl_3$ solution at 360.13 MHz or 200.13 MHz for ^1H (shifts relative to $CHCl_3$ at δ_H 7.25) and at 90.32 MHz or 50.32 MHz for ^{13}C (shifts relative to $CDCl_3$ at δ_C 77.0). EIMS were obtained at 70 eV. Optical rotations were measured on an AA-100 digital polarimeter.

Extraction and Isolation

The stem bark of Vepris louisii used in this study was collected in the East Province of Cameroon. The sun-dried stem bark was extracted and chromatographed as previously reported.[2-5] The chloroform extract, after column chromatography and extensive TLC ($CHCl_3$:MeOH - 98:2) afforded, in

addition to pyranoquinolone and acridone alkaloids, the following new heptacyclic bisquinolone alkaloids.

Vepridimerine A (1) mp 343-345°C (ex $CHCl_3$); $[\alpha]_D^{25}$ ± 0 (c, 1.02 in $CHCl_3$); UV λ_{max}(EtOH) (log ε): 243(4.83), 260(4.50), 288(4.20), 297(4.23), 317(4.22), 329(4.16) nm; λ_{max}(EtOH + HCl) no change. IR ν_{max}(KBr) 1630, 1600, 1580, 1560, 1510, 1500, 1495, 1460, 1300, 1260, 1220, 1050, 980, 940, 800 cm^{-1}. MS m\z(%) 602 (M^+ 100), 587(36), 559(21), 386(84), 367(40), 366(30), 355(50), 354(35), 341(46), 302(45), 301(37), 300(29), 287(27), 286(69), 236(29). ^1H and ^{13}C NMR see Tables 1 and 3.

Vepridimerine B (2) mp 278-279°C (ex $CHCl_3$-MeOH); $[\alpha]_D^{25}$ ± 0 (c, 1.02 in $CHCl_3$); λ_{max}(EtOH) (log ε) 233(4.82), 260(4.46), 288sh(4.17), 296(4.21), 317(4.17), 330(4.12) nm; no change on addition of HCl. IR ν_{max}($CHCl_3$) 1635, 1590, 1490, 1460, 1440, 1420, 1390, 1320, 1275, 1255, 1205, 1100, 1050, 980, 870 cm^{-1}. MS m/z (%) 602 (M^+ 100), 587(25), 559(10), 368(30), 355(13), 302(27), 301(23). ^1H and ^{13}C NMR see Tables 1 and 3.

Vepridimerine C (3) mp 272°C (ex EtOAc); $[\alpha]_D^{25}$ ± 0 (c, 1.01 in $CHCl_3$); λ_{max}(EtOH) (log ε) 237(4.64), 250(4.61), 314(4.08), 326(4.03) nm; λ_{max}(EtOH + HCl) 236(4.62), 254(4.61), 314(4.08), 326 nm. IR ν_{max}(KBr) 1640, 1590, 1525, 1460, 1390, 1340, 1300, 1260, 1120, 1060 cm^{-1}. MS m/z(%) 602 (M^+ 100), 588(10), 587(20), 301(40), 300(10), 286(23). ^1H and ^{13}C NMR see Tables 2 and 4.

Thermolysis of Veprisine (10)

Veprisine (10) (2.0 g) was placed in a pyrex tube which was sealed under reduced pressure. After heating in an oil bath at 200-220°C for 15 h the tube was broken and the contents dissolved in $CHCl_3$. Extensive column chromatographic separation of the crude product afforded five pure dimers in 40% overall yield. Four of the compounds were identified as vepridimerines A (1) (30%), B (2) (35%), C (3) (10%), and D (4) (9%) by direct comparison. Vepridimerine D (4) was originally isolated from Oricia renieri[5]. The fifth dimer was named vepridimerine E (8).

Vepridimerine D (4) mp 269-270°C (ex $CHCl_3$-MeOH); $[\alpha]_D$ ± 0 (c, 1.04 in $CHCl_3$); λ_{max}(EtOH) (log ε) 236(4.63), 251(4.60). 295sh(4.00), 314(4.05), 326(4.06) nm; λ_{max}(EtOH + HCl) 236, 255, 315, 326 nm. IR ν_{max}(KBr) 1635, 1595, 1520, 1455, 1400, 1385, 1350, 1300, 1245, 1200, 1125, 1050, 1000 cm^{-1}. MS m/z(%) 602 (M^+ 100), 587(25), 359(15), 301(8). ^1H and ^{13}C NMR see Tables 2 and 4.

Vepridimerine E (8) mp 287-288°C (ex MeOH); $[\alpha]_D$ ± 0 (c, 1.01 in MeOH); UV λ_{max}(EtOH) (log ε) 237(4.64), 250(4.60), 314(4.08), 326(4.03) nm; λ_{max}(EtOH + HCl) 237(4.61), 254 (4.61), 314(4.07), 326 nm. IR ν_{max}(KBr) 1625, 1590, 950, 900, 880, 860, 825, 810, 780 cm^{-1}. MS m/z(%) 602

(M^+ 100), 587(28), 368(30), 355(42), 316(40), 302(40), 301(71). ^1H and ^{13}C NMR see Tables 2 and 4.

Acid Treatment of Veprisine (10)

Veprisine (**10**) (1.55 g) was dissolved in a mixture of CH_3OH and HCl (8 M) (40 ml) and the solution refluxed for 10 h. The reaction mixture was diluted with water (100 ml) and extracted with $CHCl_3$. Column chromatography of the crude product followed by preparative TLC ($CHCl_3$:MeOH - 92:2) afforded the major product diveprisine (**9**) mp 280-281°C (ex $CHCl_3$). IR $\nu_{max}(CCl_4)$ 1651, 1639, 1592, 1545, 1495, 1420, 1365, 1210, 1055, 1000 cm^{-1}. MS m/z(%) 602 (M^+ 100) 587(28), 559(14), 368(70), 355(61), 354(65), 302(84), 301(39), 300(29), 286(28). ^1H NMR (200 MHz, $CDCl_3$) 1.27 (Me), 1.49 (Me), 1.56 (Me), 1.91 (Me), 3.71 (N-Me), 3.76 (N-Me), 3.81, 3.83, 3.92, 3.94 (all OMe), 6.29 (s, H-12'), 6.83 and 6.85 (each d, J 9.0 Hz, H-6,6'), 7.68 and 7.69 (each d, J 9.0 Hz, H-5,5'), 3.49 (dd, J 10.0, 7.2 Hz, H-12), 2.19 (dd, J 13.9, 7.2 Hz, H-11), 1.92 (dd, J 13.9, 10.0 Hz, H-11). ^{13}C NMR (50 MHz, $CDCl_3$) 163.5, 162.5 (C-2,2'), 155.6, 155.0 (C-7,7'), 154.9, 153.5 (C-4,4'), 141.2 (C-11'), 136.7, 136.6 (C-8,8'), 134.3, 134.0 (C-1a,1'a), 118.9, 118.7 (C-5,5'), 112.9, 112.3 (C-4a,4'a), 112.4 (C-12'), 107.0, 106.8 (C-6,6'), 106.2, 105.7 (C-3,3'), 81.8, 76.7 (C-10,10'), 61.63, 61.55, 56.20, 56.17 (OMe), 43.8 (C-11), 33.5, 33.4 (N-Me), 31.7 (C-12), 29.1, 27.3, 26.6, 24.1 (C-Me).

Hydrogenation of Diveprisine (9)

Diveprisine (**9**) (50 mg) was dissolved in EtOAc (8 ml), 10% Pd/C (30 mg) added and the mixture stirred at r.t. in an atmosphere of hydrogen for 24 h. Preparative TLC ($CHCl_3$) of the crude product yielded two dihydro-derivatives. Both gave the same mass spectra, m/z 604 (M^+, 1%), 303(40), 302(100). The ^1H and ^{13}C NMR spectra of the major product (22 mg) mp 218-220°C (ex $CHCl_3$) were broad presumably as a result of restricted rotation. The minor product (13 mg) (**26**) had mp 148-150°C (ex $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) 1.18, 1.36, 1.53 (6H) (Me), 1.71 (dd, J 13.9, 11.5 Hz, H-11), 1.86 (dd, J 13.9, 7.5 Hz, H-11), 2.21 (dd, J 18.2, 6.5 Hz, H-12'), 2.38 (dd, J 18.2, 7.2 Hz, H-12'), 3.40 (ddd, J 11.5, 7.5, 2.7 Hz, H-12), 3.60 (ddd, J 7.2, 6.5, 2.7 Hz, H-11'), 3.75, 3.79 (N-Me), 3.85, 3.87, 3.94 (6H) (OMe), 6.83, 6.85 (both d, J 8.9 Hz, H-6,6'), 7.61, 7.67 (both d, J 8.9 Hz, H-5,5'). ^{13}C NMR (50 MHz, $CDCl_3$) 164.8, 164.2 (C-2,2'), 157.6, 155.3 (C-7,7'), 155.1, 154.8 (C-4,4'), 136.89, 136.84 (C-8,8'), 134.2, 133.8 (C-1a,1'a), 118.8, 118.5 (C-5,5'), 113.4, 112.9 (C-4a,4'a), 107.2, 107.0 (C-6,6'), 105.8, 105.1 (C-3,3'), 80.0, 76.2

(C-10,10'), 61.71, 61.67, 56.4, 56.3 (OMe), 37.3 (C-11'), 30.8 (C-12), 34.0 (C-11), 33.4 (6H)(NMe), 29.9, 27.5, 24.5, 22.8 (C-Me), 19.8 (C-12').

Precocene II Dimer (13)

Precocene II (11) (150 mg) was refluxed in MeOH-HCl (8 M) for 10 h. Preparative TLC of the crude product afforded one major product, the dimer (7) mp 157-158°C (ex EtOAc-light petroleum) (lit.[8] mp 160-161°C). ^{1}H NMR (200 MHz, $CDCl_3$) 1.25, 1.49 (6H), 1.56 (Me), 1.79 (dd, J 12.4, 11.8 Hz, H-3), 2.02 (dd, J 12.4, 6.1 Hz, H-3), 3.53 (dd, J 11.8, 6.1 Hz, H-4), 3.70, 3.75, 3.81, 3.82 (OMe), 5.96 (H-4'), 6.37, 6.40, 6.42, 6.58 (H-5, 5',8,8'). ^{13}C NMR (50 MHz, $CDCl_3$) 149.5, 149.0 (C-7,7'), 148.7, 146.1 (C-1a,1'a), 143.4, 142.9 (C-6,6'), 142.5 (C-3'), 121.3 (C-4'), 114.4(2) (C-4a,4'a), 112.7, 109.5 (C-5,5'), 101.3, 100.9 (C-8,8'), 79.1, 74.4 (C-2, 2'), 56.6, 56.5, 56.0, 55.8 (OMe), 43.5 (C-3), 35.4 (C-4), 29.9, 26.6, 26.1, 23.8 (C-Me).

Precocene I Tetramer (14)

Precocene I (12) (200 mg) was refluxed for 10 h in MeOH-HCl (8M) as above. Preparative TLC of the crude major product afforded the tetramer (14) mp 242-243°C (ex EtOAc-light petroleum). MS m/z(%) 761 (M^++1, 21), 760 (M^+, 35), 759(68), 690(47), 689(100). ^{1}H NMR (200 MHz, $CDCl_3$) 0.77, 1.11, 1.12, 1.21, 1.28, 1.40, 1.45, 1.46 (Me), 1.62 (dd, J 12.7, 3.8 Hz, H_A), 2.47 (t, J 12.7 Hz, H_M), 4.92 (dd, J 12.7, 3.8 Hz, H_X), 1.74 (dd, J 13.7, 6.8 Hz, $H_{A'}$), 2.15 (dd, J 13.2, 6.8 Hz, $H_{M'}$), 4.31 (t, J 6.8 Hz, $H_{X'}$), 1.82 (dd, J 13.3, 5.3 Hz, $H_{A''}$), 2.37 (dd, J 13.3, 2.6 Hz, $H_{M''}$), 4.22 (dd, J 5.3, 2.6 Hz, $H_{X''}$), 1.63 (dd, J 12.8, 6.2 Hz, $H_{A'''}$), 2.42 (t, J 12.8 Hz, $H_{M'''}$), 3.68 (dd, J 12.8, 6.2 Hz, $H_{X'''}$), 3.29, 3.45, 3.84 (6H)(OMe), 6.27 (d, J 8.3 Hz, H-6), 6.76 (d, J 8.3 Hz, H-5), 5.95, 6.16, 6.18, 6.34, 6.43, 6.86 (each s, aromatic protons). ^{13}C NMR (50 MHz, $CDCl_3$) 158.0, 157.3, 156.2, 155.6 (C-7,7',7'',7'''), 154.4, 154.3, 152.5, 151.9 (C-1a,1'a, 1''a,1'''a), 132.6 (C-5), 128.4, 126.1(2) (C-5',5'',5'''), 124.6, 124.3, 122.2, 122.1 (C-4a,4'a,4''a,4'''a), 118.1, 117.3, 117.2 (C-6',6'',6'''), 113.6 (C-8), 103.7 (C-6), 102.6, 99.1, 98.8 (C-8',8'',8'''), 77.4, 75.9, 74.6, 74.5 (C-2,2',2'',2'''), 55.7, 55.4, 55.1, 54.9 (OMe), 41.3, 41.29, 38.6, 37.7 (C-3,3',3'',3'''), 38.0, 35.6, 32.3, 28.0 (C-4,4',4'',4'''), 31.1, 30.4, 30.0, 29.6, 28.4, 26.7, 26.2, 23.3 (C-Me).

Table 1. ^{1}H NMR Data of Vepridimerines A (**1**) and B (**2**) (360 MHz, $CDCl_3$)

Protons	(1)	(2)
H-3, H-12	6.83(d, 9.0) 6.87(d, 9.0)	6.79(d, 9.0) 6.82(d, 9.0)
H-4, H-13	7.69(d, 9.0) 7.78(d,9.0)	7.63(d, 9.0) 7.66 (d, 9.0)
H_a	1.70(ddd, 13.7, 2.8, 2.2)	1.45(dd, 13.5, 2.4)
H_b	2.14(dd, 13.7, 2.7)	2.12(dd, 13.5, 3.4)
H_c	3.61(ddd, 2.8, 2.7, 1.0)	3.20(ddd, 3.4, 3.2, 2.4)
H_d	2.16(dd, 6.1, 1.0)	1.55(dd, 12.5, 3.2)
H_e	2.96(ddd, 13.4, 6.1, 5.4)	2.59(ddd, 12.9, 12.5, 4.1)
H_f	3.10(ddd, 14.2, 5.4, 2.2)	1.39(dd, 14.6, 12.9)
H_g	1.56(dd, 14.2, 13.4)	3.80(dd, 14.6, 4.1)
N-Me	3.73(s)	3.72(s)
	3.73(s)	3.74(s)
OMe	3.84(s)	3.84(s)
	3.89(s)	3.89(s)
	3.93(s)	3.91(s)
	3.95(s)	3.92(s)
CMe	1.49(s)	1.30(s)
	1.50(s)	1.68(s)
	1.81(s)	1.87(s)

Multiplicities and values of coupling constants (Hz) are given in parentheses.

Table 2. ^{1}H NMR Data of Vepridimerines C(**3**), D(**4**) and E(**8**) (360 MHz, $CDCl_3$)

Protons	(3)	(4)	(8)
H-1	8.06(d ,9.0)	8.05(d, 9.0)	8.02(d, 9.0)
H-2	6.92(d, 9.0)	6.93(d, 9.0)	6.93(d, 9.0)
H-13	6.87(d, 9.0)	6.82(d, 9.0)	6.88(d, 9.0)
H-14	7.79(d, 9.0)	7.67(d, 9.0)	7.82(d, 9.0)
H_a	1.71(ddd, 13.6, 2.2, 2.0)	1.44(dd, 13.0, 2.5)	1.77(ddd, 13.0, 3.0, 2.5)
H_b	2.10(dd, 13.6, 2.7)	2.13(dd, 13.0, 3.3)	1.97(dd, 13.0, 2.9)
H_c	3.58(ddd, 2.7, 2.0, 1.0)	3.16(ddd, 3.5, 3.3, 2.5)	3.65(q, 2.7)
H_d	2.15(dd, 6.8, 1.0)	1.57(dd, 12.6, 3.5)	1.93(dd, 12.0, 2.1)
H_e	3.13(ddd, 12.9, 6.8, 5.4)	2.71(ddd, 12.6, 12.6, 4.2)	2.84(dt, 12.0, 4.3)
H_f	3.26(ddd, 14.4, 5.4, 2.2)	1.34(dd, 14.4, 12.6)	3.80(ddd, 13.8, 4.3, 2.5)
H_g	1.54(dd, 14.4, 12.9)	3.93(dd, 14.4, 4.2)	1.17(dd, 13.8, 11.8)
N-Me	3.73(s)	3.72(s)	3.75(s)
	3.75(s)	3.73(s)	3.75(s)
OMe	3.79(s)	3.73(s)	3.72(s)
	3.89(s)	3.89(s)	3.88(s)
	3.93(s)	3.92(s)	3.92(s)
	3.94(s)	3.93(s)	3.95(s)
CMe	1.49(s)	1.37(s)	1.01(s)
	1.59(s)	1.69(s)	1.48(s)
	1.82(s)	1.88(s)	1.91(s)

Multiplicities and values of coupling constants (Hz) are given in parentheses.

Table 3. ^{13}C NMR Data of Vepridimerines A(1) and B(2) (90 MHz, $CDCl_3$)

Carbons	Multiplicities	(1)	(2)
1, 10	s	136.44, 136.67	136.71, 136.80
2, 11	s	154.96, 154.84	154.94, 154.53
3, 12	d	106.85, 107.00	107.10, 107.24
4, 13	d	119.00, 119.20	118.61, 118.88
4a, 13a	s	111.84, 112.47	112.82, 112.86
4b, 13b	s	154.80, 157.61	154.99, 155.68
6	s	79.85	81.62
6a	d	43.55	52.35
7, 16a	d	26.20, 27.60	25.56, 26.27
7a, 16b	s	107.45, 105.88	105.61, 112.3
8, 17	s	163.42, 164.33	163.27, 164.24
9a, 18a	s	133.81, 133.97	134.24, 134.23
15	s	76.83	78.33
16	t	39.48	39.78
19	t	32.23	31.08
N-Me	q	33.25, 32.94	33.08, 33.63
OMe	q	61.48, 61.41	61.43, 61.36
OMe	q	56.10, 56.18	56.22, 56.22
CMe	q	28.60, 29.05	29.18, 28.49
CMe	q	24.77	20.66

Table 4. ^{13}C NMR Data of Vepridimerines C(3), D(4) and E(8) (90 MHz, $CDCl_3$)

Carbons	Multiplicities	(3)	(4)	(8)
1, 14	d	122.06, 119.34	118.90, 121.90	119.65, 121.91
2, 13	d	108.36, 107.20	106.91, 108.22	107.11, 108.22
3, 12	s	155.04, 155.50	154.89, 155.31	155.15, 155.31
4, 11	s	136.78, 137.59	136.52, 137.53	136.51, 137.61
4a, 10a	s	134.04, 134.85	134.06, 134.81	134.00, 134.90
5a, 14b	s	156.81, 157.88	154.70, 157.53	157.21, 159.18
7	s	83.06	84.60	83.66
7a	d	43.37	52.24	53.30
8, 17a	d	25.45, 27.54	25.31, 25.72	27.70, 27.91
8a, 17b	s	100.56, 107.35	100.05, 112.67	100.40, 104.30
9	s	163.52	163.34	164.75
14a	s	112.00	112.03	111.90
16	s	78.91	78.40	78.05
17	t	39.75	39.32	42.66
18	s	176.29	176.40	176.20
18a	s	120.54	121.41	121.44
19	t	32.24	31.04	39.26
N-Me	q	33.28	33.82	33.87
N-Me	q	35.15	36.60	35.60
OMe	q	61.20, 61.52	61.60, 61.29	61.60, 61.25
OMe	q	56.24, 56.14	56.20, 56.23	56.26, 56.20
CMe	q	28.56, 29.01	28.60, 29.21	28.05, 26.92
CMe	q	25.24	21.04	19.50

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