ALTERNATIVE ROUTES TO VINCAMINE[1]

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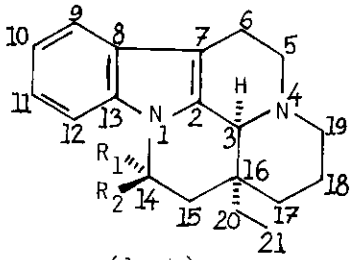
Abstract - The preparation of vincamine (**1a**) *via* indoloquinolizine propionic esters (**7**) is discussed. A new synthesis of the starting material methyl 2-acetoxyacrylate and an oxidative transformation of **7b** to **1a** are described and an alternative, more efficient route is reported.

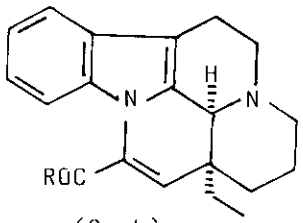
The potent cerebrovascular activity of vinca alkaloids and their semi-synthetic derivatives as (+)-vincamine (**1a**)[2a-c] ethyl apovincaminate (**2b**)[3] and (-)-eburnamenine[4] (**3**) has stimulated several syntheses of (**1a**)[5a-c,6-9] and its derivatives, however yields, number of steps and ready availibility of starting materials can still be improved. In an effort to find a practical synthesis, the strategy originally elaborated by Szántay and co-workers, i.e. alkylation of the tetracyclic enamine (**4**) by an electrophilic olefin (**5a-c**) to hexahydroindoloquinolizines (**6**)[5a-c] was followed.
Adducts (**6**) after stereoselective reduction and resolution (route A[5a]) combined with subsequent deacetylation (route B[5b]) or nitrosation (route C[5c]) led to key intermediates (**7a-c**). Compounds (**7**) - depending on the oxidation level of the propionic acid side chain - can be transformed in one or more steps to **1a**.
Our first attempt toward the rationalization of the synthesis involved application of methyl acrylate (**5a**) for route B. This involved the



(1a-b)

(1a) $R_1 = CO_2CH_3$, $R_2 = OH$

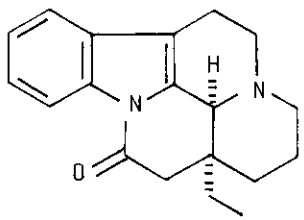
(1b) $R_1 = OH$, $R_2 = CO_2CH_3$



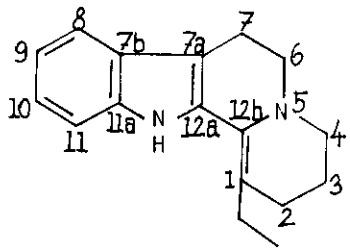
(2a-b)

(2a) $R = CH_3$

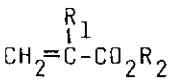
(2b) $R = C_2H_5$



(3)

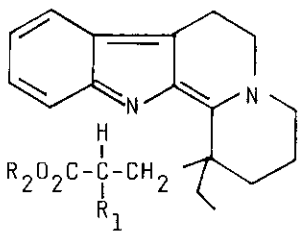


(4)

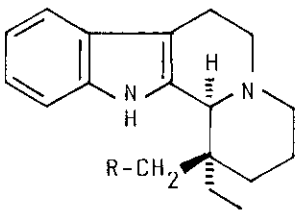


(5a-c)

	R_1	R_2
(a)	H	CH_3
(b)	$OCOCH_3$	CH_3
(c)	CO_2H_5	C_2H_5



(6a-c)



(7a-e)

(7a) $R = CH_2\text{-}CO_2CH_3$

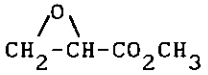
(7b) $R = CHOH\text{-}CO_2CH_3$

(7c) $R = C(=NOH)\text{-}CO_2C_2H_5$

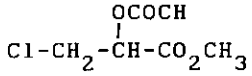
(7d) $R = C(=NOH)\text{-}CO_2CH_3$

(7e) $R = CN$

elaboration of a new method for the synthesis of methyl 2-acetoxyacrylate[10] which consisted of the conversion of methyl acrylate into methyl 2,3-epoxypropionate by aqueous sodium hypochlorite/sodium hydrogencarbonate/carbon dioxide system, followed by $ZnCl_2$ catalyzed regioselective electrophilic addition of acetyl chloride to give methyl 2-acetoxy-3-chloropropionate and finally dehydrochlorination by triethylamine in benzene.[11] Latter two steps can be carried out without previous isolation of **9**.



(**8**)



(**9**)

The conversion of the alcohol (**7b**) into vincamine 14-epimers (**1a**:**1b** = 3:2) (as determined by hplc) was succeeded in 54 % yield using *t*-butyl nitrite/potassium *t*-butoxide in toluene. **1b** was then transformed to **1a** by treatment with sodium methoxide.[5b]

From practical standpoint the synthesis of **7d** was especially attractive since this substance could serve as a common intermediate for **1a**, **2a** and **3**. We have found that the reaction of the propionic ester (**7a**)[5b,6] with *t*-butylnitrite/potassium *t*-butoxide in toluene/dimethylformamide/methanol led to the pyruvate oxime methyl ester (**7d**), which was isolated as the hydrochloride in 70 % yield.

Attempts were made for the direct transformation of **7d**·HCl to alkaloids (**1a**) or (**2a**). Heating **7d**·HCl in boiling toluene in the presence of *p*-toluenesulfonic acid furnished apovincamine (**2a**) in 80 % yield. As a minor product, the 1-cyanomethyl derivative (**7e**), identical with the product obtained by Le Men *et al.* *via* the Beckman rearrangement of 16-oximinoaspidospermidine[12a] or 16-oximino-E-homoeburnamonine[12b] was isolated. The side reaction apparently proceeded *via* initial acylation of **7d**, to give the intermediate *N-O*-tosyl derivative, which then underwent a Beckmann rearrangement, involving cleavage of the *C-C* bond. Indeed when the oxime ester (**7d**) was reacted under similar conditions with *p*-toluenesulfonyl chloride, the cyanomethyl compound (**7e**) was obtained in 60 % yield. On the other hand, no by-product was

detected, when **7d** as base was reacted with dry *p*-toluenesulfonic acid.

For the transformation of **7d** to vincamine (**1a**) it seemed to be convenient to carry sodium bisulfite aided deoximation[13] instead of hydrolysis.[5c] In fact treatment of **7d** in a sodium bisulfite/aqueous acetic acid system at pH 4-5 and 90 °C, furnished a mixture of vincamine and epivincamine (2:1) in 60 % combined yield, but no apovincamine.

In addition about 1 % of the nitrile (**7e**) was isolated. In contrast **7d**, when heating for 10 h in aqueous sodium acetate solution in the abscence of sodium bisulfite, gave 41 % of **7e** as the main product. In this case **7e** resulted as product of a successive hydrolysis, decarboxylation and dehydration. Exploiting these observation, **7d** was transformed directly to (-)-eburnamonine, by heating it in ethylene glycol/sodium hydroxide at 160 °C.

The known transformation of the epimeric mixture (**1a**) and (**1b**) to **1a** completed the synthesis, in 45 % overall yield starting from **7a** produced **1a**.

(+)-Apovincamine (**2a**) and (-)-eburnamonine (**3**) were prepared with the above described methods in 66 and 68 % yields, respectively.

EXPERIMENTAL

Ir spectra (υ, cm^{-1}) were recorded on a Perkin-Elmer 402 spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded in pFT mode at 299.9 and 75.4 MHz, respectively, on a Varian VXR-300 instrument. Chemical shifts are reported relative to TMS. Mps are uncorrected.

Methyl 2,3-Epoxypropionate (**8**). Sodium hypochlorite (15 % aqueous solution, 800 ml) was added to a stirred solution of sodium carbonate (160 g) in water (400 ml) and methyl acrylate (**5a**) (117g, 1.36 mol) at 10 °C. Stirring was continued for 1 h, while a stream of CO_2 (80 g) was passed through the flask at 20-25 °C (exothermic reaction). The mixture was extracted with dichloromethane (4x150 ml) and the combined organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by distillation under reduced pressure. Yield 72.0 g (50 %). bp 72 °C (40 Torr). Ir: 1752 (CO), 1213, 1299 (COC); ^1H nmr ($CDCl_3$): δ 3.78 (s, OCH_3), 3.44 (1H, dd, J = 6.6 and 2.7 Hz, CH),

2.95 (m, CH_2). Anal. Calcd for $C_9H_6O_3$: C, 47.05; H, 6.05. Found C, 27.02; H, 6.15.

Methyl 2-Acetoxy-3-chloropropionate (**9**). Acetyl chloride (78.5 g, 1.0 mol) was added dropwise to a stirred mixture of methyl 2,3-epoxypropionate (**8**) (102 g, 1.0 mol), benzene (400 ml), $ZnCl_2$ (1.0 g) and conc. hydrochloric acid (0.1 ml) at 10 °C. After the addition was completed (30 min), the mixture was stirred for 30 min, the solvent was removed in vacuo, and the residue was purified by distillation under reduced pressure. Yield: 141.0 g (78 %). bp 93 °C/9 Torr (lit.,[11] bp 92.8-93.5/9). Ir: 1750 (CO), 1220 (COC); ^{1}H nmr ($CDCl_3$): δ 3.79 (s, $COOCH_3$), 3.87 (m, Cl-CH_2), 5.38, 5.36 (d, J = 3.8 Hz, CH); 2.19 (s, $COCH_3$).

Methyl 2-Acetoxyacrylate (**5b**). Method A. Triethylamine (80 g, 0.79 mol) was added to a stirred solution of **9** (142.5 g, 0.79 mol) in benzene (500 ml) and the mixture was stirred and refluxed for 3 h. The reaction mixture was cooled (10 °C), the separated crystals of triethylamine hydrochloride was filtered off by suction and washed with benzene. The solvent was evaporated and the residue was fractionated through a Vigreux column (3x40 cm). Yield: 89.8 g (79 %); bp 63 °C/10 Torr (lit.,[11] bp 63-64/10). Ir: 1773, 1742 (CO), 1219, 1194, 1151 (COC); ^{1}H nmr ($CDCl_3$): δ 6.03, 6.47 (d, J = 1.8 Hz, CH_2=), 3.80 (s, $COOCH_3$), 2.23 (s, $COCH_3$).

Method B. Acetyl chloride (78.5 g, 1.0 mol) was added dropwise to a stirred mixture of **8** (102 g, 1.0 mol), benzene (500 ml), $ZnCl_2$ (1,0 g), and conc. hydrochloric acid (0.1 ml) at 10 °C. After the addition was completed (30 min) the mixture was stirred for an additional 30 min, then triethylamine (109 g, 1.08 mol) was added and the mixture was stirred and refluxed for 3 h. The reaction mixture was cooled to 10 °C, filtered and the crystals were washed with benzene. Concentration of the filtrate and fractionation of the residual oil yielded 112.6 g (78.5 %), bp 63 °C/10 Torr.

(-)-Methyl 1,2,3,4,6,7,12,12bα-Octahydroindolo[2,3-a]quinolizine(1β-yl) pyruvate oxime (**7d**). To a suspension of (-)-1β-methoxycarbonylethyl-1α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizine (**7a**) (34 g, 0.1

mol) in toluene (20 ml), *t*-butyl nitrite (30 ml, in 60 % toluene solution, 0.15 mol) and potassium *t*-butoxide (17 g, 0.15 mol) were added. After stirring at 25-30 °C for 10 min, methanol (150 ml) was added and stirring was continued for 3 h at 30 °C. The reaction mixture was cooled to 20 °C, acidified with conc. hydrochloric acid to pH 1, and stirred for 1 h at 10 °C. The separated crystals were filtered off, washed with water and methanol and dried at 60 °C to give **7d**·HCl (32.5 g, 80 %), mp 268-270 °C; $[\alpha]_D^{20}$: -57° (c=1, DMF). Ir (KBr): 3340 (NH), 3200-2400 (NH+OH), 1728 (CO), 1687 (C=N), 1160 (C-O-C), 1021 (N-OH), 765, 749 (Ar).

7d·HCl (20 g, 49 mmol), methanol (80 ml), ammonium hydroxide (20 ml, 25 %) and water (30 ml) were stirred for 30 min at 70 °C, then for 1 h at 20 °C. The separated crystals was filtered off, washed with water (2x50 ml) then with methanol (30 ml) and dried at 60 °C to give **7d** (17.1 g, 95 %). mp 212-214 °C (MeOH); $[\alpha]_D^{20}$: -62° (c=1, DMF) (lit.,[5c] mp 195 °C, $[\alpha]_D^{20}$: -61.4°). Ir (KBr): 3455 (NH), 3200-2200 (OH), 1712 (CO), 1168 (C=O), 1104 (COC), 743 (Ar); ^{1}H nmr ($CDCl_3$): δ 1.13 (3H, t, J = 7.6 Hz, H_3-14), 1.54-1.68 (3H, m, He-3, H_2-2), 1.78 (1H, dq, J = 15.5 and 7.6 Hz, Hx-13), 2.14 (1H, dq, J = 15.5 and 7.6 Hz, Hy-13), 2.24 (1H, m, Ha-3), 2.40 (1H, ddd, J = 11.3, 11.1 and 2.7 Hz, Ha-4), 2.57-2.71 (2H, m, Hx-7, Hx-6), 2.73 (1H, d, J = 13.5 Hz, Hx-15), 2.85 (1H, d, J = 13.5 Hz, Hy-15), 3.02-3.18 (3H, m, He-4, Hy-6, Hy-7), 3.37 (1H, s, H-12b), 3.50 (3H, s, OMe), 7.07 (1H, td, J = 7.7 and 1.4 Hz, H-9), 7.13 (1H, td, J = 7.7 and 1.4 Hz, H-12), 7.30 (1H, d, J = 7.7 Hz, H-11), 7.46 (1H, d, J = 7.6 Hz, H-8), 7.98 (1H, s, NH), 11.46 (1H, br s, OH) (Ha, e, x, y: axial, equatorial or unidentified H, resp.); ^{13}C nmr ($CDCl_3$): δ 8.2 (C-14), 20.9 (C-7), 21.4 (C-3), 28.5 (C-15), 32.3 (C-13), 33.5 (C-2), 42.0 (C-7), 52.2 (OMe), 54.3 (C-6), 56.7 (C-4), 67.3 (C-12b), 110.7 (C-11), 112.4 (C-7a), 118.2 (C-8), 119.4 (C-11), 121.8 (C-10), 126.5 (C-7b), 131.5 (C-12a), 136.5 (C-11a), 154.0 (C=NOH), 165.4 (C=O).

(+)-Apovincamine (**2a**). To a mixture of *p*-toluenesulfonic acid monohydrate (47.5 g, 250 mmol) and toluene (1000 ml) **7d**·HCl (40.6 g, 100 mmol) was added and after distilling an azeotropic mixture of water-toluene (300 ml) the

mixture was refluxed for 2 h. To the reaction mixture water (300 ml) was added at room temperature, pH adjusted to 9 with conc. NH_4OH. The organic layer was separated, dried (Na_2SO_4), filtered, evaporated in vacuo and the residue was crystallized from MeOH (150 ml) to yield **2a** (26.0 g, 76 %). mp 160-162 °C (MeOH) (lit.,[3b] mp 160-162 °C); $[\alpha]_D^{20}$: +150.7° (c=1, $CHCl_3$). Ir (KBr): 2840 (OCH_3), 1727 (CO), 1632 (C=C), 1281, 1080 (C-O-C), 1608, 743 (Ar); ^1H nmr ($CDCl_3$): δ 0.99 (1H, td, J = 13.4 and 3.9 Hz, Ha-17), 1.00 (3H, t, J = 7.6 Hz, H_3-21), 1.38 (1H, d, J = 13.4 Hz, He-18), 1.49 (1H, d, J = 13.4 Hz, He-17), 1.69 (1H, ddddd, J = 13.4, 13.4, 12.5, 3.4 and 3.2 Hz, Ha-18), 1.80-2.00 (2H, m, H_2-20), 2.47 (1H, dm, J = 16.8 Hz, Me-6), 2.59 (2H, m, H_2-19), 3.00 (1H, m, Ha-6), 3.22 (1H, ddd, J = 13.9, 10.6 and 5.7 Hz, Ha-5), 3.33 (1H, ddd, = 13.9, 13.9 and 6.6 Hz, Me-5), 3.93 (3H, s, OMe), 4.12 (1H, t, J = 1.0 Hz, H-3), 6.13 (1H, s, H-15), 7.08-7.19 (2H, m, H-10, H-11), 7.22 (1H, d, J = 7.6 Hz, H-12), 7.45 (1H, d, J = 7.6 Hz, H-19); ^{13}C nmr ($CDCl_3$): δ 3.6 (C-21), 16.2 (C-6), 20.2 (C-18), 27.2 (C-20), 28.5 (C-17), 37.6 (C-16), 44.8 (C-19), 51.3 (C-5), 52.4 (OMe), 55.6 (C-3), 108.6 (C-7), 112.3 (C-12), 118.1 (C-9), 120.1 (C-10), 121.8 (C-11), 128.0 (C-14), 128.2 (C-15), 129.0 (C-8), 130.9 (C-2), 133.9 (C-13), 163.8 (C=O). The mother liquor was evaporated and subjected to column chromatography (Merck Kieselgel 40, benzene:methanol = 5:1). Evaporation of the Rf = 0.65 fractions, followed by recrystallization (ethanol) gave (-)-1β-cyanoethyl-1α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizine (**7e**), 0.4 g, mp 203-204 °C (lit.,[11b] mp 202-203 °C); $[\alpha]_D^{20}$: -96° (c=1, CH_2Cl_2). Ir (KBr): 3400 (NH), 2750, 2780, 2280 (C=N); ^1H nmr ($CDCl_3$): δ 1.24 (3H, t, J = 7.7 Hz, H_3-14), 1.60-1.98 (7H, m, H_2-13, Hx-15), 2.41 (1H, td, J = 11.3 and 2.9 Hz, Ha-4), 2.53-2.65 (2H, m, Ha-6, He-7), 2.79-3.03 (3H, m, Ha-7, He-6, He-4), 3.24 (1H, d, J = 17.5 Hz, Hy-15), 3.41 (1H, s, H-12b), 7.08 (1H, t, J = 7.6 Hz, H-9), 7.15 (1H, t, J = 7.5 Hz, H-10), 7.32 (1H, d, J = 7.6 Hz, H-11), 7.46 (1H, d, J = 7.6 Hz, H-8), 7.80 (1H, s, NH); ^{13}C nmr ($CDCl_3$): δ 7.9 (C-14), 21.9 (C-7), 22.8 (C-15), 31.6 (C-13), 32.3 (C-2), 39.7 (C-1), 53.4 (C-6), 56.4 (C-4), 64.6 (C-12b), 110.9 (C-11), 112.9 (C-7a), 118 (C-8),

119.1 (C≡N), 119.5 (C-9), 121.9 (C-10), 126.5 (C-7b), 131.2 (C-12a), 136.1 (C-11a).

7d *(37.1 g, 100 mmol) gave under the same circumstances 30 g (87 %) of* **2a**.

(+)-Vincamine (**1a**). Method A. Sodium pyrosulfite (12 g, 62 mmol) and **7d** (22 g, 60 mmol) were stirred in a mixture of water (100 ml) and acetic acid (20 ml) for 6 h at 90-92 °C. pH was adjusted to 9 with conc. NH_4OH and extracted with CH_2Cl_2 (2x60 ml). The combined extract was dried (Na_2SO_4) and evaporated to dryness. (The epimeric ratio of (**1a**) : (**1b**), established by hplc was 2:1). The residue was refluxed in MeOH (50 ml) containing potassium methoxide (0.5 g) for 4 h. After cooling the separated crystals were filtered off and washed twice with methanol to give **1a** (12.8 g, 60 %), mp 234-235 °C, (lit.,[5a] mp 234-235 °C); $[\alpha]_D^{20}$: +44.5° (c=1, pyridine) (lit.,[5a] +44°).

Ir (KBr): 3400-2400 (OH), 1748 (C=O), 1073 (C-OH), 1208 (C-O-C), 742 (Ar); ^{1}H nmr ($CDCl_3$): δ 0.90 (3H, t, J = 7.6 Hz, H_3-21), 1.32-1.82 (5H, m, H_2-17, H_2-18, Hx-20), 2.11 (1H, d, J = 14.4 Hz, H_β-15), 2.22 (1H, d, J = 14.4 Hz, H_β-15), 2.24 (1H, dq, J = 15.5 and 7.6 Hz, Hy-20), 2.44-2.64 (3H, m, H_2-19, He-6), 2.18 (1H, m, Ha-6), 3.31-3.38 (2H, m, H_2-5), 3.82 (3H, m, OMe), 3.91 (1H, t, J = 1.0 Hz, H-3), 4.66 (1H, s, OH), 7.06-7.15 (3H, m, H-10, H-11, H-12), 7.48 (1H, m, H-9); ^{13}C nmr ($CDCl_3$): δ 7.6 (C-21), 16.8 (C-6), 20.8 (C-18), 25.1 (C-17), 28.9 (C-20), 35.0 (C-16), 44.4 (C-15), 44.5 (C-19), 50.9 (C-5), 54.2 (OMe), 59.1 (C-3), 81.9 (C-14), 105.9 (C-7), 110.3 (C-12), 118.4 (C-9), 120.2 (C-10), 121.6 (C-11), 129.0 (C-8), 131.4 (C-2), 134.0 (C-13), 174.4 (C=O).

Method B. To a mixture of **7b**[5a] (14.4 g, 37 mmol), toluene (100 ml), and methyl formate (5g, 84 mmol) after potassium *t*-butoxide (10 g, 90 mmol), *t*-butyl nitrite (18 ml, 60 % soln. in toluene, 90 mmol) was added at 15-20 °C. The reaction mixture was stirred for 90 min at 40 °C. After usual workup **1a** (7.6 g, 52 %) was obtained, mp 234-235 °C; $[\alpha]_D^{20}$: +42.4° (c=1, pyridine).

(-)-1β-Cyanomethyl-1α-ethyl-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a] quinolizine (**7e**). Method A. The mixture of *oxime ester* (**7d**) *(7.6 g, 20 mmol)* toluene (150 ml) and *p*-toluenesulfonyl chloride (7.6 g, 45 mmol) was

refluxed for 2 h. After cooling, water (100 ml) was added and the solution was made alkaline with conc. ammonium hydroxide (20 ml). The organic layer was separated and the aqueous solution was extracted with toluene (50 ml). The toluene solution was dried (Na_2SO_4) and evaporated to dryness. The residue was recrystallized from ethanol to yield **7e**, 3.5 *g* (60 %), *mp* 202-203 °C; $[\alpha]_D^{20}$: -85° (c=1, $CHCl_3$).

Method B. A mixture of **7d** (10 g, 27 mmol), water (50 ml) and acetic acid (30 ml) was adjusted to pH 5 with 40 % sodium hydroxide and refluxed for 16 h. After cooling, the separated crystals were filtered off and recrystallized from ethanol to afford **7e**, 3.25 g (41 %), *mp* 201-202 °C; $[\alpha]_D^{20}$: -81° (c=1, $CHCl_3$).

(-)-Eburnamonine (**3**). The mixture of **7d** (18.5 g, 50 mmol), ethylene glycol (100 ml), water (5 ml) and sodium hydroxide (6 g, 150 mmol) was heated at 160 °C for 3 h. Water (200 ml) was added to the reaction mixture at 40 °C, the separated crystals were filtered off, washed with water and dried at 60 °C. Crude **3** (14 g) was dissolved in dichloromethane (50 ml), the solution was stirred with charcoal (1 g), filtered and evaporated. The residue was recrystallized from methanol (50 ml) to give **3**, (13.0 g, 90%), mp 176-177 °C, (lit.,[12b] mp 177-178 °C); $[\alpha]_D^{20}$: -96° (c=1, $CHCl_3$), (lit.,[5c] -97.6°).

Ir (KBr): 1696 (*C=O*), 1626 (*C=C*), 752 (Ar); ^1H *nmr* ($CDCl_3$): δ 0.92 (3H, t, J = 7.6 Hz, H_3-21), 1.00 (1H, td, J = 13.4 and 3.9 Hz, Ha-17), 1.37 (1H, d, J = 13.4 Hz, He-18), 1.47 (1H, d, J = 13.4 Hz, He-17), 1.63 (1H, dq, J = 14.2 and 7.6 Hz, Hx-20), 1.75 (1H, ddddd, J = 13.4, 13.4, 12.5, 3.4 and 3.2 Hz, Ha-18), 2.03 (1H, dq, J = 14.2 and 7.6 Hz, Hy-20), 2.39 (1H, ddd, J = 12.5, 10.7 and 2.9 Hz, Ha-19), 2.45 (1H, d, J = 16.8 Hz, He-6), 2.56 (1H, d, J = 16.6 Hz, Ha-15), 2.58 (1H, d, J = 10.7 Hz, He-9), 2.64 (1H, d, J = 16.6 Hz, He-15), 2.88 (1H, m, Ha-6), 3.19 (1H, ddd, J = 13.9, 10.6 and 5.7 Hz, Ha-5), 3.31 (1H, dd, J = 13.9 and 6.6 Hz, He-5), 3.91 (1H, t, J = 1.0 Hz, H-3), 7.24-7.34 (2H, m, H-10, H-11), 7.41 (1H, d, J = 7.6 Hz, H-9), 8.36 (1H, d, J = 7.6 Hz, H-12); ^{13}C *nmr* ($CDCl_3$): δ 7.6 (C-21), 16.5 (C-6), 20.6 (C-18), 26.9 (C-17), 28.3 (C-20), 38.3 (C-16), 44.2 (C-15), 44.3 (C-19),

50.5 (C-5), 57.5 (C-3), 112.5 (C-7), 116.2 (C-12), 118.0 (C-9), 124.8 (C-10), 124.2 (C-11), 130.3 (C-8), 131.9 (C-2), 134.1 (C-13), 167.6 (C=O).

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