Synthesis of the Alkaloids, 3',4'-Dimethoxy-2-(2-piperidyl)acetophenone, Julandine, and Cryptopleurine †

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Condensation of (3,4-dimethoxybenzoyl)acetic acid (2) with enzyme-generated 3,4,5,6-tetrahydropyridine (3) gives 3',4'-dimethoxy-2-(2-piperidyl)acetophenone (4) which, by reaction with *p*-methoxyphenylacetaldehyde followed by titanium(IV) chloride- or silicon(IV) chloride-catalysed cyclisation of the resulting enamine (6), leads to julandine (7); thallium(III) trifluoroacetate oxidation of (7) gives cryptopleurine (8) and, as a very minor product, the isomer (9).

THE ALKALOIDS represented by cryptopleurine (8) and tylophorine (1) exhibit various interesting biological properties including anti-cancer action.[1,2] Exploitation of these properties in the synthesis of analogues depends on the efficient elaboration of these ring systems. A number of syntheses have been published [3-5] and an economical synthesis [5] of tylophorine is based on the biosynthetic route to this alkaloid. Extension of this route to the synthesis of cryptoleurine (8), an alkaloid of *Boehmeria* and *Cryptocarya* species,[2,6,7] though simple in principle, proved more difficult in practice; but there were some interesting consequences.

3',4'-Dimethoxy-2-(2-piperidyl)acetophenone (4) is an alkaloid found in *Boehmeria platyphylla* and *B. cylindrica*.[2,8] It was easily synthesized and it served as a key intermediate in our synthesis of cryptopleurine. Condensation of (3,4-dimethoxybenzoyl)acetic acid (2) [5] with 3,4,5,6-tetrahydropyridine (3), generated *in situ* from cadaverine using partially purified pea seedling diamine oxidase,[9,10] gave compound (4) in high yield.

Condensation of 2-pyrrolidin-2-ylacetophenones [as compound (4)] with substituted phenylacetaldehydes in benzene at room temperature very rapidly affords the enamine [as compound (6)].[5] Ring-closure by reaction of the enamine function with the keto-group, a rarely observed reaction, occurs here readily in methanol at room temperature.[5] In the condensation of the piperidine (4) with *p*-methoxyphenylacetaldehyde in methanol, the overall reaction failed although enamine formation was again rapid and complete in hexadeuterio benzene as judged by n.m.r. analysis, which showed disappearance of the aldehyde proton at δ 9.4, this being replaced by two enamine protons, one of which was clearly visible at δ 5.5.

Cyclisation of the enamine-ketone (6) could, however, be achieved using selected Lewis acid catalysts, most notably titanium(IV) chloride and silicon(IV) chloride in benzene (Table). Dehydration also occurred and the product was reduced with sodium borohydride in propan-2-ol to give compound (7). This alkaloid, called for convenience julandine, has been isolated from *B. platyphylla*.[7] The properties of our synthetic material accorded closely with those of synthetic [4b] and natural julandine (7).

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It was found that 1 equiv. of the titanium(IV) and silicon(IV) chlorides was optimal for the synthesis of julandine (7). We noted further with the various Lewis acid catalysts tested for the enamine-ketone condensation that the yields of julandine (7) obtained (Table) showed a direct, though rough, correlation with recorded metal–oxygen bond strengths which are high for silicon, titanium, boron, and zirconium, and low for the others.[11]

TABLE

Synthesis of julandine (7) using various Lewis acids

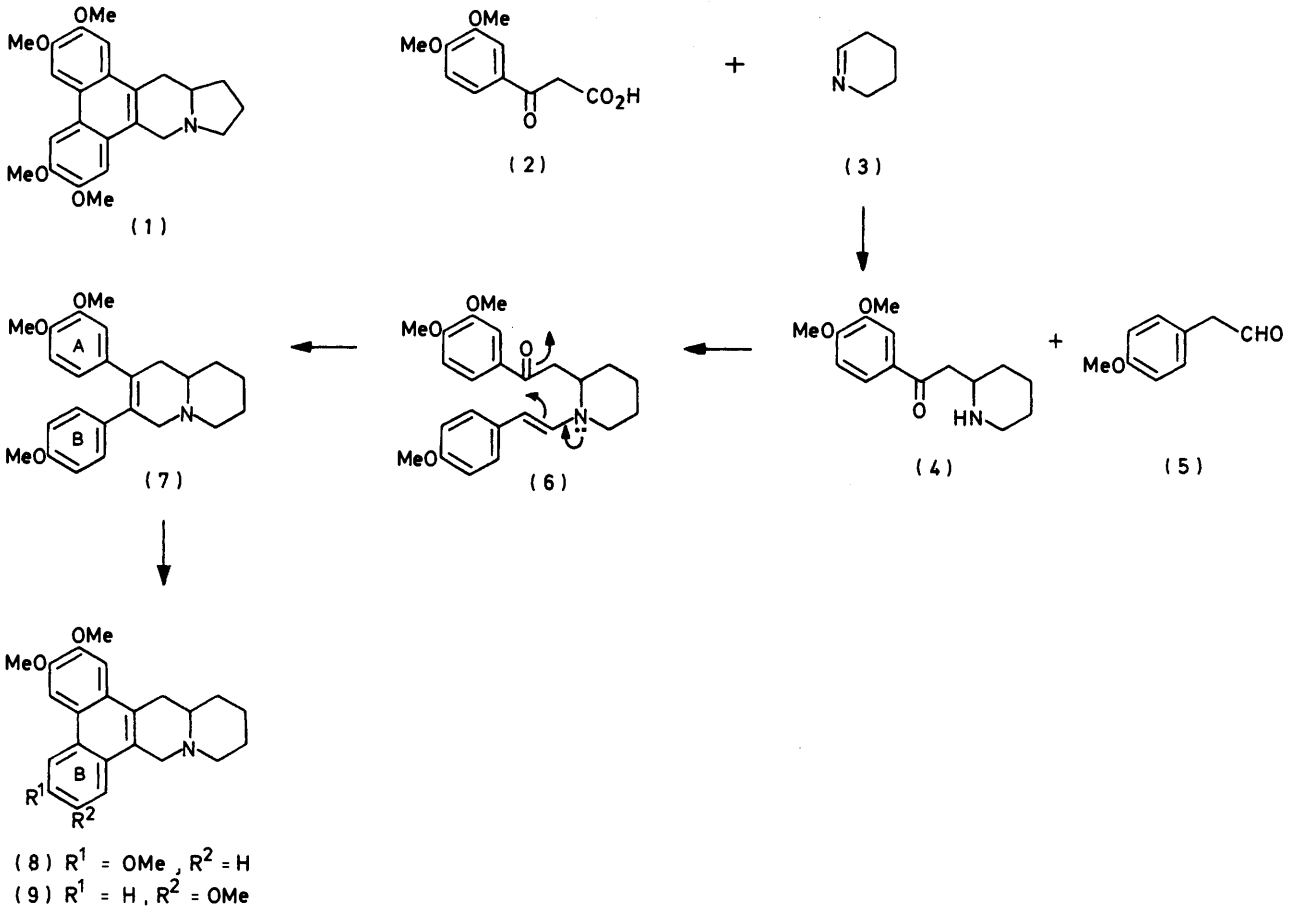
Lewis acid	Solvent	Equiv. used	Yield (%)
$TiCl_4$	C_6H_6	7	16 [a]
$TiCl_4$	C_6H_6	3	36 [b]
$TiCl_4$	C_6H_6	1	32 [a]
$TiCl_4$	C_6H_6	0.5	18 [b]
$TiCl_4$	CH_2Cl_2	1	29 [a]
$SiCl_4$	C_6H_6	3	16 [b]
$SiCl_4$	C_6H_6	2	18 [a]
$SiCl_4$	C_6H_6	1	42 [a]
$SiCl_4$	C_6H_6	0.5	17 [b]
$SnCl_4$	C_6H_6	1	18 [b]
$BF_3{\cdot}OEt_2$	C_6H_6	1	13 [b]
$ZrCl_4$	C_6H_6	1	12 [b]
$AlCl_3$	C_6H_6–Et_2O	1	11 [b]
$FeCl_3$	Et_2O	1	5 [b]

[a] Crystallized yield. [b] Yield after chromatography.

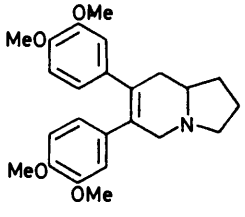
The yield of julandine (7) with zirconium(IV) chloride was low, probably for solubility reasons. Complex formation of boron trifluoride as $BF_3{\cdot}OEt_2$ clearly prevented effective complexation of the ketone in (6) and a low yield of julandine resulted.

In the cyclisation of compound (6), reaction will be favoured by metal co-ordination to the ketonic oxygen and hindered by co-ordination to the enamine system. The former is clearly most favourably achieved with silicon and titanium. Titanium(IV) chloride has found useful application in synthesis as a reagent which favours co-ordination to oxygen and is an effective dehydrating agent.[12] Successful application of silicon(IV) chloride in the synthesis of julandine, which exploits properties otherwise associated with titanium(IV) chloride, suggests the possible application of silicon(IV) chloride elsewhere as an alternative reagent to titanium(IV) chloride.

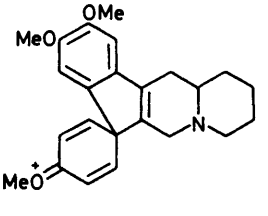
Thallium(III) trifluoroacetate has found useful application in effecting the linkage of two aromatic rings; [13,14] it transforms septicine (10) into tylophorine (1) in high yield.[5] The transformation of julandine (7) into crypto-



pleurine (8) was achieved similarly even though the linkage to ring B is *meta* to the methoxy-substituent (*cf.* refs. 13 and 14). A very minor product was identified as the cryptopleurine isomer (9). It is believed [13,14] that, in the coupling of two aromatic rings by thallium(III) trifluoroacetate, oxidation occurs by transfer of a single



(10)



(11)

electron to thallium from the aromatic ring with the lower oxidation potential, followed by electrophilic substitution of the radical-cation formed into the other aromatic ring, and further one-electron oxidation. From this it might be expected that oxidation of julandine (7) would give the cation (11) (*cf.* ref. 14) as an intermediate arising from a ring A radical-cation substituting *para* to the methoxy-group in ring B. Rearrangement of the intermediate (11) could give alternatively cryptopleurine (8), or the isomer (9). Whilst the isomer (9) and some cryptopleurine (8) may in fact be formed by way of the intermediate (11), the hundred-fold difference in the yields obtained for the two products indicates that cryptopleurine (8) is formed largely by direct coupling.

Synthetic cryptopleurine (8) and natural alkaloid were shown to be identical by comparison of mass, i.r., and u.v. spectra, t.l.c., and, crucially for the manner in which the aromatic rings are linked, n.m.r. spectra.

EXPERIMENTAL

Chromatography unless otherwise stated was carried out using short columns of Kieselgel.[15] M.p.s were obtained on a hot stage apparatus; n.m.r. spectra were recorded at 90 MHz; mass spectra were obtained by direct insertion of the sample into the source of an MS 902 spectrometer. Throughout, ether refers to diethyl ether.

Diamine Oxidase.—The enzyme was isolated from pea-seedlings following a published procedure; [10] it was purified to the stage prior to hydroxyapatite chromatography, resuspended in water, and kept frozen in 1-ml portions until required.

3′,4′-Dimethoxy-2-(2-piperidyl)acetophenone (4).—A solution of ethyl (3,4-dimethoxybenzoyl)acetate (2.02 g) in aqueous potassium hydroxide (2.5%; 140 ml) was stirred for 48 h at room temperature. The solution was extracted with ether, then acidified at 10 °C with sulphuric acid (2M).

Extraction with ether (five times), drying of the extracts, and evaporation at room temperature gave crystalline (3,4-dimethoxybenzoyl)acetic acid (1.46 g, 81.5%).[5]

A solution of (3,4-dimethoxybenzoyl)acetic acid (1.46 g, 6.54 mmol), cadaverine (0.1M aqueous solution; 66 ml), and potassium phosphate buffer (0.2M aqueous solution; 21 ml; pH 6) was prepared and adjusted to pH 7. Catalase (0.5 mg) and diamine oxidase (2 ml; aqueous solution of activity 19.4 units ml^{-1}) were then added and the solution was incubated in a rotary shaker at 27 °C for 24 h; as the reaction proceeded, the solution was occasionally readjusted to pH 7. The solution was acidified and extracted with ether. It was then basified with concentrated aqueous ammonia and extracted with chloroform. Drying of the chloroform extracts and evaporation of the solvent left an oily residue of *3′,4′-dimethoxy-2-(2-piperidyl)acetophenone* (1.35 g, 79%) which was essentially pure by t.l.c. (20% MeOH–$CHCl_3$ with a few drops of ammonia). This material was used for further reactions without purification. However, it could be crystallized from acetone, m.p. 79—80.5 °C (lit.,[8] 81.5—82.5 °C); *m/z* 263.152 54 (M^+) ($C_{15}H_{21}NO_3$ requires *M*, 263.152 13), 180, 165, and 84.081 441 ($C_5H_{10}N$ requires *m/z* 84.081 32); δ ($CDCl_3$) 1.0—2.1 (6 H, unresolved), 2.21 (1 H, s, NH), 2.3—3.8 (3 H, unresolved), 3.02 (2 H, s), 3.95 (6 H, s), 6.90 (1 H, d, *J* 9 Hz), 7.55 (1 H, s), and 7.60 (1 H, d, *J* 9 Hz, further splitting into two lines seen on downfield part of doublet); $\lambda_{max.}$ (EtOH) (log ε) 231 (4.18), 276 (4.13), and 303 nm (3.97); $\nu_{max.}$ (film) 3 320, 1 665, 1 590, and 1 510 cm^{-1} (Found: C, 68.55; H, 8.1; N, 5.5. Calc. for $C_{15}H_{21}NO_3$: C, 68.44; H, 8.0; N, 5.3%).

The product also gave an *N*-acetyl derivative; *m/z* 305.162 66 (M^+) ($C_{17}H_{23}NO_4$ requires *M*, 305.162 70), 262.144 07 ($M^+ - CH_3CO$, $C_{15}H_{20}NO_3$ requires *m/z* 262.144 31), 165 ($ArCO^+$), 126, and 84.081 28 ($C_5H_{10}N$ requires *m/z* 84.081 32).

1-(3,4-Dimethoxyphenyl)-2-(2-piperidyl)ethanol.—To a stirred solution of 3′,4′-dimethoxy-2-(2-piperidyl)acetophenone (0.15 g) in dry propan-2-ol (10 ml) was added sodium borohydride (0.04 g). Stirring was continued overnight. The solvent was removed under reduced pressure and the residue was then acidified with dilute sulphuric acid. The solution obtained was extracted with ether. It was then basified with concentrated aqueous ammonia and extracted three times with chloroform. After the combined chloroform extracts had been dried, the solvent was removed under reduced pressure to give a white solid (0.19 g) which was a single spot on t.l.c. (20% MeOH in $CHCl_3$ plus a few drops of concentrated ammonia). Recrystallization [benzene–light petroleum (boiling range 60–80 °C)] gave *1-(3,4-dimethoxyphenyl)-2-(2-piperidyl)ethanol* (0.117 g, 77%), m.p. 117—120 °C (*cf.* ref. 9); *m/z* 265.167 72 (M^+) ($C_{15}H_{23}NO_3$ requires *M*, 265.167 78), 180, 165, 98, and 84; $\nu_{max.}$ (Nujol) 3 500—3 100, 1 610, 1 597, and 1 515 cm^{-1}; $\lambda_{max.}$ (EtOH) (log ε) 231 (3.89), and 279 nm (3.45); δ ($CDCl_3$) 1.0—2.0, 2.4—3.2 (11 H, unresolved), 3.55 (2 H, broad s exchangeable with D_2O), 3.84 (3 H, s), 3.87 (3 H, s), 4.77—5.03 (1 H, m), 6.83 (2 H, broad s), and 6.95 (1 H, broad s) (Found: C, 68.0; H, 8.8; N, 5.35. Calc. for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28%).

Methyl 2,3-Epoxy-3-(4-methoxyphenyl)propionate.—To a stirred solution of sodium methoxide in methanol (2.8 g of sodium, 45 ml of anhydrous methanol) at −10 °C was added methyl chloroacetate (12.0 g) and 4-methoxybenzaldehyde (13.6 g) during 1.5 h. After 1 h at −5 °C and 3 h at room temperature the reaction mixture was added to ice (200 ml) and glacial acetic acid (2 ml). The solid was collected, dried, and recrystallized from aqueous ethanol (14.5 g, 70%). A further recrystallization gave methyl 2,3-epoxy-3-(4-methoxyphenyl)propionate, m.p. 67—68 °C (lit.,[16] 60—62 °C); $\nu_{max.}$ (Nujol), 1 730, 1 616, and 1 588 cm^{-1}; *m/z* 208.073 07 (M^+) ($C_{11}H_{12}O_4$ requires *M*, 208.073 55), 151, ($ArCH{=}O^+Me$), 149 ($M^+ - CO_2Me$), 135 ($ArCO^+$), and 121 (methoxytropylium cation); δ ($CDCl_3$) 3.5 (1 H, d, *J* 2 Hz), 3.75 (3 H, s), 3.79 (3 H, s), 4.02 (1 H, d, *J* 2 Hz), 6.88 (2 H, d, *J* 9 Hz), and 7.20 (2 H, d, *J* 9 Hz) (Found: C, 63.5; H, 5.85; Calc. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.75%).

4-Methoxyphenylacetaldehyde.—To an ice-cold stirred solution of methyl 2,3-epoxy-3-(4-methoxyphenyl)propionate (6.0 g) in benzene (60 ml) was added methanolic sodium methoxide (0.69 g of sodium in 15 ml of methanol), followed by a mixture of ether (50 ml) and water (0.7 ml). The mixture was kept at 5 °C for 3 h. The precipitate of *sodium 2,3-epoxy-3-(4-methoxyphenyl)propionate* was collected, washed with ether, and dried (8 58 g, 94%). A mixture of the sodium salt (5.4 g), glacial acetic acid (2.7 ml), and benzene (94 ml) was refluxed for 3 h. The mixture was shaken with water and the benzene layer was dried and evaporated to give *4-methoxyphenylacetaldehyde* as a yellow oil (2.9 g), mainly a single component by t.l.c. ($CHCl_3$); $\nu_{max.}$ (film) 2 835, 2 722, 1 725, 1 613, and 1 584 cm^{-1}; *m/z* 150.067 98 (M^+) ($C_9H_{10}O_2$ requires *M*, 150.068 07); δ (C_6D_6) 3.21 (2 H, d, *J* 2 Hz), 3.40 (3 H, s), 6.76 (2 H, d, *J* 9 Hz), 6.98 (2 H, d, *J* 9 Hz), and 9.40 (1 H, t, *J* 2 Hz). The aldehyde was stored at −40 °C and was purified by chromatography ($CHCl_3$) before use.

(±)-Julandine (7).—(*a*) 3′,4′-Dimethoxy-2-(2-piperidyl)-acetophenone (92.4 mg) and 4-methoxyphenylacetaldehyde (57.1 mg) were mixed in deuteriobenzene (1 ml). The n.m.r. spectrum which was run immediately showed the absence of an aldehyde resonance at δ 9.4 and the appearance of an enamine proton at δ 5.5 (d, *J* 14 Hz); there was no further change (2 h). The material corresponded to the enamine (6); *m/z* 395.210 09 (M^+) ($C_{24}H_{29}NO_4$ requires *M*, 395.209 65) and 377.198 12 ($M^+ - H_2O$ $C_{24}H_{27}NO_3$ requires *m/z* 377.199 08).

(*b*) A solution of 3′,4′-dimethoxy-2-(2-piperidyl)acetophenone (177 mg) and 4-methoxyphenylacetaldehyde (130 mg) in dry benzene (3 ml) was stirred under nitrogen for 50 min. The solution was cooled in ice and titanium(IV) chloride (128 mg in 0.53 ml of benzene) was added dropwise; a dark brown precipitate formed. The mixture was stirred for 2 h at room temperature and the benzene was then evaporated. Dry propan-2-ol (3 ml) was added to the residue, followed by sodium borohydride (40 mg), and the reaction mixture was stirred overnight. The solvent was evaporated and water followed by hydrochloric acid were cautiously added to the residue. The solution was extracted with ether and then basified with concentrated aqueous ammonia. Extraction with chloroform, followed by drying and evaporation of the extract, gave an oil (188 mg) which contained *julandine* as the only major component by t.l.c. (5% MeOH in $CHCl_3$). Crystallization of this material from acetone and purification of the mother liquors by preparative t.l.c. (5% MeOH in $CHCl_3$), gave julandine 82 mg, 32%, m.p. 135—137 °C (undepressed on mixing with synthetic material [4b]); *m/z* 379.214 67 (M^+) ($C_{24}H_{29}NO_3$ requires *M*, 379.214 73), 364 ($M^+ - CH_3$), 296.141 06 (reverse Diels–Alder fragment, $C_{19}H_{20}O_3$ requires *m/z* 296.141 24), 281

(296 − Me), 265.122 56 (296 − CH_3O, $C_{18}H_{17}O_2$ requires *m/z* 265.122 85); δ ($CDCl_3$) 1—3.5 (13H, unresolved), 3.52, 3.70, and 3.80 (3 × 3 H, s), 6.47 (1 H, s), 6.66 (2 H, s), 6.67 (2 H, d, *J* 9 Hz), 6.98 (2 H, d, *J* 9 Hz); $\lambda_{max.}$ (EtOH) (log ε) 235 (4.20) and 280 nm (4.02) (Found: C, 75.75; H, 7.85; N, 3.75. Calc. for $C_{24}H_{29}NO_3$: C, 75.99; H, 7.65; N, 3.69%). Direct comparison of our sample with synthetic material [4b] [i.r. (KCl disc), u.v.] and comparison of the spectra (u.v., n.m.r., mass spec.) of our sample with those of the natural alkaloid [7] established identity between the three samples.

(±)-*Cryptopleurine*.—To a stirred solution of julandine (45 mg) in trifluoroacetic acid (10 ml) was added thallium-(III) trifluoroacetate (64.5 mg). After 20 min the mixture was added to water, basified with sodium carbonate, and extracted with chloroform. The chloroform extracts were dried and evaporated to leave a residue of (±)-*cryptopleurine* which was a single component by t.l.c. (10% MeOH in $CHCl_3$). It was crystallized from acetone (31 mg, 69%), m.p. 198—200 °C (lit.,[7] 197—198 °C); *m/z* 377.198 49 (M^+) ($C_{24}H_{27}NO_3$ requires *M*, 377.199 08), 294.125 93 (reverse Diels–Alder fragment, $C_{19}H_{18}O_3$ requires *m/z*, 294.125 59), and 279; $\lambda_{max.}$ (EtOH), 260, 287, 311, 344, and 362 nm; δ ($CDCl_3$) 1.0—3.4 (11 H, unresolved), 3.57 (1 H, d, *J* 17 Hz), 3.99, 4.04, 4.07 (3 × 3 H, s,) 4.43 (1 H, d, *J* 17 Hz), 7.18 (1 H, dd, J 2 and 9 Hz), 7.22 (1 H, s), 7.76 (1 H, d, *J* 9 Hz), 7.87 (1 H, d, *J* 2 Hz), and 7.88 (1 H, s) (Found: C, 76.4; H, 7.35; N, 3.65. Calc. for $C_{24}H_{27}NO_3$: C, 76.39; H, 7.16; N, 3.71%). The synthetic alkaloid was found to be identical with the natural material by direct comparison (t.l.c., i.r., u.v.) and by comparison of n.m.r. and mass spectra.

Cryptopleurine trifluoroacetate could also be isolated from the above reaction if the aqueous solution was extracted with chloroform without basification; m.p. 216—217 °C from acetone (Found: C, 63.3; H, 5.85; N, 2.7. Calc. for $C_{26}H_{28}F_3NO_5$: C, 63.5; H, 5.9; N, 2.85%).

The residues from several preparations of cryptopleurine from julandine were combined and purified by column chromatography (from $CHCl_3$ to 4% MeOH in $CHCl_3$) and on Merck pre-coated t.l.c. plates (Kieselgel 60 F_{254}, 0.2 mm; thrice eluted with 5% MeOH in $CHCl_3$). Separation was thus achieved between cryptopleurine and a slightly less polar, isomeric compound (0.75% yield) identified as 11,12,13,14,14a,15-*hexahydro*-2,3,7-*trimethoxy*-9H-*phenanthro*[9,10-b]*quinolizine* (9): *m/z*, 377.198 85 (M^+, $C_{24}H_{27}NO_3$), 294, and 279; δ ($CDCl_3$) 0.9—3.8 (11 H, unresolved), 3.63 (1 H, d, *J* 15 Hz), 3.97, 4.05, 4.10 (3 × 3 H, s), 4.42 (1 H, d, *J* 15 Hz), 7.21 (1 H, d, *J* 9 Hz), 7.26 (2 H, s), 7.92 (1 H, s), and 8.45 (1 H, d, *J* 9 Hz).

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