The Synthesis of Desertorin C, a Bicoumarin from the Fungus *Emericella desertorum*

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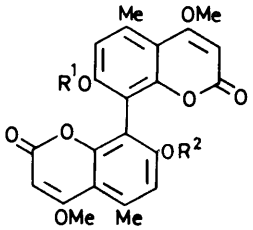
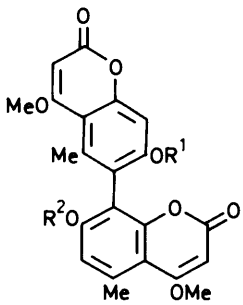
The structure of desertorin C, a metabolite of the mould *Emericella desertorum*, is confirmed as 4,4',7,7'-tetramethoxy-5,5'-dimethyl-6,8'-bicoumarin (**6**), by its synthesis in racemic form. The key step involved the construction of the unsymmetrical biphenyl, 2,2',4,6'-tetramethoxy-4',6-dimethylbiphenyl (**19**), using dihydro-oxazole chemistry.

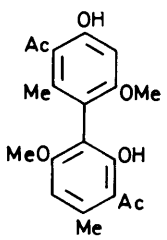
The bicoumarins are a rare group of fungal metabolites and until recently the sole examples were the symmetrical 4-methoxycoumarin dimers orlandin (**1**),[1] demethylkotanin (**2**), and kotanin (**3**)[2] which were isolated from *Aspergillus* sp. Kawai and his co-workers have reported the isolation of three related unsymmetrical 4-methoxycoumarin dimers, desertorins A (**4**), B (**5**), and C (**6**), from the mould *Emericella desertorum* Samson and Mouchacca.[3] These compounds are optically



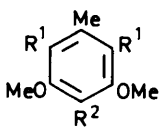
(**1**) $R^1 = R^2 = H$
(**2**) $R^1 = H$, $R^2 = Me$
(**3**) $R^1 = R^2 = Me$



(**4**) $R^1 = R^2 = H$
(**5**) $R^1 = H$, $R^2 = Me$
(**6**) $R^1 = R^2 = Me$



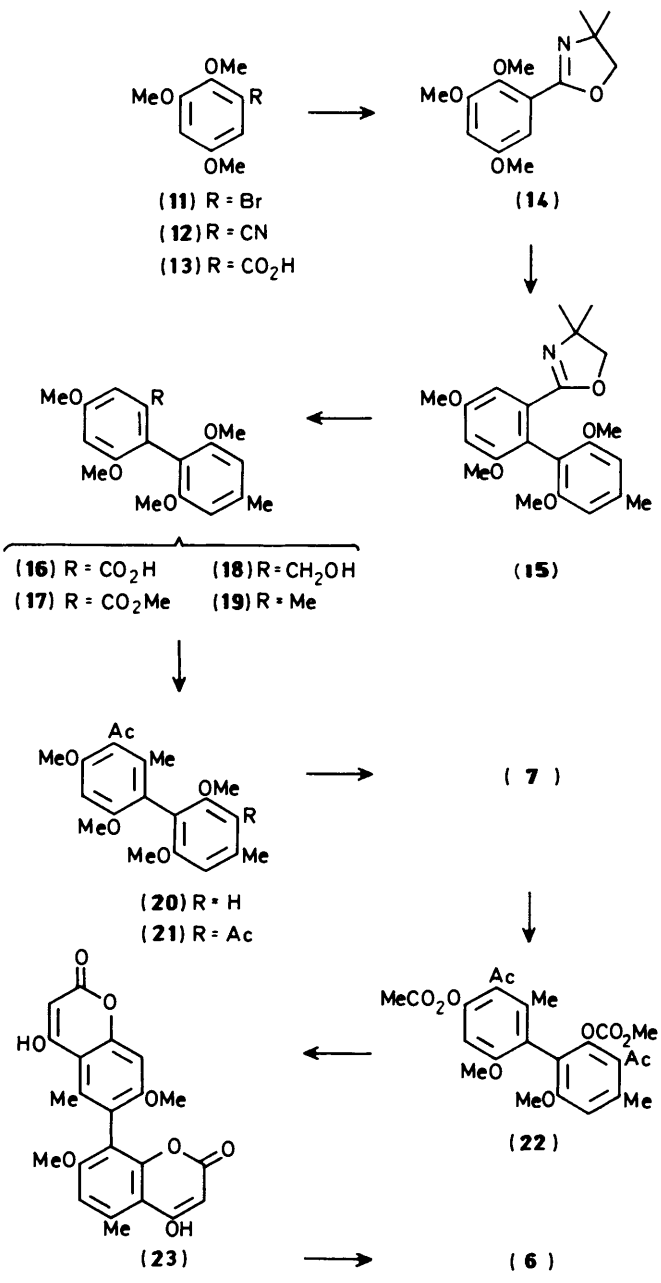
(**7**)



(**8**) $R^1 = R^2 = H$
(**9**) $R^1 = Ac$, $R^2 = H$
(**10**) $R^1 = H$, $R^2 = Br$

active on account of restricted rotation about the biphenyl linkage. Their structural elucidation rests chiefly on their spectroscopic properties and the conversion by methylation of both desertorins A (**4**) and B (**5**) into desertorin C (**6**) and the hydrolytic degradation of the last-mentioned compound to the diacetylbiphenyl (**7**). We now report the confirmation of the structure of desertorin C (**6**) by its synthesis in racemic form.

Our initial synthetic goal was the degradation product (**7**)



Scheme.

since this would be readily converted into desertorin C (**6**). It was perceived that this compound should be easily available by acetylation of the unsymmetrical biphenyl (**19**) (see Scheme) followed by selective demethylation of the expected product (**21**) with boron trichloride. Electrophilic substitution of 3,5-dimethoxytoluene (**8**) occurs readily at the 2- and 6-positions but it is difficult by this means to introduce a substituent at the 4-position.[4] Thus we found that treatment for a prolonged period at room temperature of 3,5-dimethoxytoluene (**8**) with an excess of the mixed anhydride formed from acetic acid and trifluoroacetic anhydride yielded only the symmetrical diacetyl compound (**9**).

An efficient synthesis of the biphenyl (**19**) was therefore required. We chose to adopt the biphenyl synthesis of Meyers[5] for this purpose and the dihydro-oxazole (**14**) and the bromo compound (**10**) were therefore required. The bromo compound (**10**) is readily available from 3,5-dimethoxytoluene (**8**).[4] For the synthesis of the dihydro-oxazole (**14**), vanillin was converted into the known bromo compound (**11**)[6] which on addition of copper(I) cyanide then gave the nitrile (**12**). Hydrolysis of this intermediate gave the acid (**13**) which was converted into the dihydro-oxazole (**14**) by the usual method.[5]

On reaction with the Grignard reagent derived from the bromo compound (**10**), the dihydro-oxazole (**14**) gave a high yield of the substitution product (**15**). The masked carboxy group in this compound was deprotected and the resultant carboxylic acid (**16**) was converted into its methyl ester (**17**). On reduction with lithium aluminium hydride, the ester (**17**) yielded the hydroxymethyl compound (**18**) which on further reduction with hydrogen over palladized charcoal gave the biphenyl (**19**). Acetylation of (**19**) with 2 mol equiv. of the mixed anhydride derived from acetic acid and trifluoroacetic anhydride gave the monoacetyl compound (**20**), as revealed by its ^{1}H n.m.r. spectrum, and this was accompanied by the diacetyl compound (**21**). Further acetylation of compound (**20**) or treatment of the biphenyl (**19**) with an excess of the acetylating agent gave the diacetyl compound (**21**) in high yield. Again the structure of this compound was revealed by its ^{1}H n.m.r. spectrum.

On demethylation with boron trichloride, the diacetyl compound (**21**) gave the degradation product (**7**) which had spectroscopic properties identical with those reported in the literature.[3] This compound was treated with methyl chloroformate and pyridine and the resultant biscarbonate (**22**), on cyclization with potassium t-butoxide in t-butyl alcohol, gave a high yield of the dimeric 4-hydroxycoumarin (**23**). Methylation of this compound gave the racemic form of the natural product (**6**). The synthetic material proved to be identical with an authentic sample of the natural product in its spectroscopic properties and in its chromatographic behaviour. However, the racemic material had a higher melting point than the natural enantiomorph, a not unusual phenomenon. The structure of desertorin C is therefore confirmed.

Experimental

General directions have been given previously.[7] N.m.r. spectra were recorded for solutions in deuteriochloroform unless stated otherwise.

2,3,5-*Trimethoxybenzonitrile* (**12**).—A solution of 2,3,5-trimethoxybromobenzene (**11**) (9.9 g)[6] in anhydrous *N,N*-dimethylformamide (150 ml) was stirred and heated under reflux under dry nitrogen with copper(I) cyanide (7.5 g) for 16 h. The cooled solution was poured into an excess of aqueous EDTA. Isolation of the crude product with ethyl acetate gave the nitrile (7.3 g, 98%) as needles (from dichloromethane–light petroleum), m.p. 61—62.5 °C (lit.,[8] 60—63 °C); δ_H(60 MHz) 3.73, 3.81, and 3.89 (each 3 H, s, OMe), and 6.48 and 6.65 (2 H, AB, *J* 2.5 Hz, ArH).

2,3,5-*Trimethoxybenzoic Acid* (**13**).—The nitrile (**12**) (8.0 g) and sodium hydroxide (10.0 g) were heated under reflux in water (40 ml) and methanol (120 ml) for 3 days. Much of the methanol was removed by distillation and the cooled residue was diluted with water and extracted with ether. The aqueous phase was acidified and the crude acid was isolated with ethyl acetate. The title compound crystallized from dichloromethane–light petroleum as needles (7.4 g, 84%), m.p. 99—102 °C (lit.,[9] 99—101.5 °C); δ_H(60 MHz) 3.60, 3.79, and 3.89 (each 3 H, s, OMe), and 6.60 and 7.00 (2 H, AB, *J* 2.5 Hz, ArH).

4,5-*Dihydro*-4,4-*dimethyl*-2-(2,3,5-*trimethoxyphenyl*)*oxazole* (**14**).—The acid (**13**) (4.0 g) and thionyl chloride (4.0 ml) were stirred at room temperature for 20 h. The excess of thionyl chloride was removed under reduced pressure and finally azeotropically with carbon tetrachloride. A solution of the crude acid chloride in dichloromethane (40 ml) was added dropwise with stirring to a solution of 2-amino-2-methylpropan-1-ol (3.36 g) in dichloromethane (20 ml) at 0 °C. The mixture was stirred at room temperature for 2 h and the precipitated hydrochloride was separated by filtration and was washed with a little dichloromethane. The solvent was removed from the filtrate, the residue dissolved in dichloromethane (20 ml), stirred, and treated dropwise at 0 °C with thionyl chloride (4.0 ml). The solution was stirred at room temperature for 1.5 h and then treated with an excess of ice and water. The aqueous layer was washed with ethyl acetate and then basified with ammonia. The crude *dihydro-oxazole* (**14**) was isolated with ethyl acetate as an oil (4.70 g, 94%), b.p. 145—150 °C at 0.04 mmHg (Kugelrohr) (Found: C, 63.45; H, 7.25%; M^+, 265. $C_{14}H_{19}NO_4$ requires C, 63.4; H, 7.2%; *M*, 265); δ_H(80 MHz) 1.96 (6 H, s, Me_2), 3.80 (6 H, s, 2 × OMe), 3.84 (3 H, s, OMe), 4.12 (2 H, s, CH_2), and 6.58 and 6.78 (2 H, AB, *J* 2.4 Hz, ArH).

4,5-*Dihydro*-4,4-*dimethyl*-2-(2,2′,4,6′-*tetramethoxy*-4′-*methylbiphenyl*-6-*yl*)*oxazole* (**15**).—The Grignard reagent, prepared under dry argon in the usual way from the bromo compound (**10**) (7.5 g),[4] magnesium (1.0 g), and THF (50 ml), was added in a thin stream at room temperature to a stirred solution of the dihydro-oxazole (**14**) (3.9 g) in THF (50 ml) under argon. The solution was stirred at room temperature for 1 h, and then heated under reflux for 18 h. The solution was cooled and poured into water and then extracted with ethyl acetate. The crude dihydro-oxazole was extracted into dilute hydrochloric acid, the extract was basified with ammonia, and the dihydro-oxazole isolated with ethyl acetate, and crystallized from methanol whereupon it was obtained as *needles* (5.2 g, 92%), m.p. 142—143 °C (Found: C, 68.25; H, 7.3; N, 3.6. $C_{22}H_{27}NO_5$ requires C, 68.55; H, 7.05; N, 3.65%); δ_H(80 MHz) 1.19 (6 H, s, Me_2), 2.38 (3 H, s, Me), 3.67 (9 H, s, 3 × OMe), 3.70 (3 H, s, OMe), 3.85 (2 H, s, CH_2), 6.40 (2 H, s, 3′- and 5′-H), and 6.61 and 6.95 (2 H, AB, *J* 2.5 Hz, 3- and 5-H).

Methyl 2′,4,6,6′-*Tetramethoxy*-4′-*methylbiphenyl*-2-*carboxylate* (**17**).—The dihydro-oxazole (**15**) (5.1 g) and iodomethane (5.0 ml) were stirred and heated at 70 °C (bath) in nitromethane (20 ml) for 23 h. The solvents were removed under reduced pressure and the residue stirred and heated under reflux for 48 h with methanol (50 ml), water (50 ml), and potassium hydroxide (10 g). Most of the methanol was removed by distillation and the solution was then diluted with water and extracted with ether. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The residue resulting on removal of the solvent was methylated with iodomethane and potassium carbonate in *N,N*-dimethyl-

formamide at room temperature. The *ester* (**17**) (4.35 g, 95%) formed prisms (from methanol), m.p. 131—132 °C (Found: C, 65.8; H, 6.7%; M^+, 346. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%; *M*, 346); δ_H(80 MHz) 2.38 (3 H, s, Me), 3.59 (3 H, s, OMe), 3.67 (6 H, s, 2 × OMe), 3.71 and 3.85 (each 3 H, s, OMe), and 6.43 (2 H, s, 3′- and 5′-H).

2′,4,6,6′-*Tetramethoxy*-4′-*methylbiphenyl*-2-*ylmethanol* (**18**).—The ester (**17**) (4.2 g) in anhydrous THF (50 ml) was added dropwise with stirring to lithium aluminium hydride (500 mg) in anhydrous THF (20 ml). The solution was stirred at room temperature for 0.5 h and next cooled in ice and treated with an excess of cold dilute hydrochloric acid. The crude product was isolated with ethyl acetate and then crystallized from dichloromethane–light petroleum whereupon it formed prisms of the *alcohol* (**18**) (3.76 g, 97%), m.p. 148—149 °C (Found: C, 67.9; H, 7.25%; M^+, 318. $C_{18}H_{22}O_5$ requires C, 67.9; H, 6.95%; *M*, 318); δ_H(80 MHz) 2.05 (1 H, br, D_2O exchangeable OH), 2.40 (3 H, s, Me), 3.68 (9 H, s, 3 × OMe), 3.85 (3 H, s, OMe), 4.25 (2 H, s, CH_2), 6.49 (2 H, s, 3′- and 5′-H), and 6.51 and 6.71 (2 H, AB, *J* 2.3 Hz, 3- and 5-H).

2,2′,4,6′-*Tetramethoxy*-4′,6-*dimethylbiphenyl* (**19**).—A solution of the alcohol (**18**) (2.9 g) in ethyl acetate (150 ml) containing concentrated hydrochloric acid (2 drops) was stirred with palladized charcoal (10%, 500 mg) under an atmosphere of hydrogen until absorption ceased. Work-up gave the *biphenyl* (**19**) (2.6 g, 94%) which formed prisms (from dichloromethane–light petroleum), m.p. 130—131 °C (Found: C, 71.6; H, 7.6%; M^+, 302. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%; *M*, 302); δ_H(80 MHz) 2.00 and 2.39 (each 3 H, s, Me), 3.67 (3 H, s, OMe), 3.68 (6 H, s, 2 × OMe), 3.80 (3 H, s, OMe), 6.35 and 6.43 (2 H, AB, *J* 2.4 Hz, 3- and 5-H), and 6.46 (2 H, s, 3′- and 5′-H).

Acetylation of 3,5-*Dimethoxytoluene* (**8**).—Trifluoroacetic anhydride (4.5 ml) was added at 0 °C to a stirred solution of 3,5-dimethoxytoluene (**8**) (2.0 g) in acetic acid (2.0 ml). The solution was then stirred at room temperature for 16 h and next diluted with water and extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and with saturated brine. The crude product crystallized from dichloromethane–light petroleum as plates, m.p. 104—105 °C, of 1′,1-(4,6-*dimethoxy*-2-*methyl*-1,3-*phenylene*)*bisethanone* (**9**) (2.9 g, 94%) (Found: C, 65.9; H, 7.1%; M^+, 236. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.85%; *M*, 236); δ_H(80 MHz) 2.10 (3 H, s, Me), 2.45 (6 H, s, 2 × COMe), 3.85 (6 H, s, 2 × OMe), and 6.33 (1 H, s, ArH).

Acetylation of 2,2′,4,6′-*Tetramethoxy*-4′,6-*dimethylbiphenyl* (**19**).—(a) *With 2 equiv. of acetic acid.* Trifluoroacetic anhydride (1.15 ml) was added dropwise at 0 °C to a stirred solution of the biphenyl (**19**) (1.175 g) in dichloromethane (5.0 ml) and acetic acid (470 mg). The solution was stirred at room temperature for 2 h and next worked up. The crude product was separated by radial chromatography with 15—20% ethyl acetate–light petroleum as eluant. The first band eluted gave 1-(2′,4,6,6′-*tetramethoxy*-2,4′-*dimethylbiphenyl*-3-*yl*)*ethanone* (**20**) (214 mg, 16%) which crystallized from ethyl acetate as needles, m.p. 224—225 °C (Found: C, 69.4; H, 7.3%; M^+, 344. $C_{20}H_{24}O_5$ requires C, 69.75; H, 7.0%; *M*, 344); δ_H(300 MHz) 1.87 and 2.40 (each 3 H, s, Me), 2.51 (3 H, s, COMe), 3.69 (6 H, s, 2 × OMe), 3.72 and 3.85 (each 3 H, s, OMe), 6.41 (1 H, s, 5-H), and 6.46 (2 H, s, 3′- and 5′-H). Further elution yielded 1,1′-(2′,4,6,6′-*tetramethoxy*-2,4′-*dimethyl*-1,1′-*biphenyl*-3,3′-*diyl*)-*bisethanone* (**21**) (1.13 g, 78%) which crystallized from dichloromethane–light petroleum as rosettes of needles, m.p. 143—144 °C (Found: C, 68.0; H, 6.95%; M^+, 386. $C_{22}H_{26}O_6$ requires C, 68.4; H, 6.8%; *M*, 386); δ_H(300 MHz) 1.92 and 2.32 (each 3 H, s, Me), 2.509 and 2.512 (each 3 H, s, COMe), 3.33, 3.69, 3.72, 3.76, and 3.88 (each, 3 H, s, OMe), and 6.42 and 6.52 (each 1 H, s, ArH).

(b) *With an excess of acetic acid.* Trifluoroacetic anhydride (3.6 ml) was added dropwise at 0 °C to a stirred solution of the biphenyl (**19**) (926 mg) in dichloromethane (5 ml) and acetic acid (1.04 g). The solution was stirred at room temperature for 3 h and next worked up. The diketone (**21**) (995 mg, 85%) crystallized as rosettes of needles (from dichloromethane–light petroleum), m.p. 143—144 °C. Acetylation of the ketone (**20**) in a similar way also yielded the diketone (**21**).

1,1′-(2′,4-*Dihydroxy*-6,6′-*dimethoxy*-2,4′-*dimethylbiphenyl*-3,3′-*diyl*)*bisethanone* (**7**).—Boron trichloride (2.35 g) in dichloromethane (10 ml) was added at 0 °C to a stirred solution of the diketone (**21**) (1.935 g) in dichloromethane (20 ml). The solution was stirred at 0 °C for 40 min and then treated with an excess of water. The crude product was isolated with ethyl acetate and was crystallized from methanol whereupon it formed plates (1.728 g, 96%) of the *diketone* (**7**), m.p. 168—169 °C (lit.,[3] 149—150 °C) (Found: C, 67.15; H, 6.25. $C_{20}H_{22}O_6$ requires C, 67.05; H, 6.2%); δ_H(300 MHz) 2.25 and 2.63 (each 3 H, s, Me), 2.678 and 2.688 (each 3 H, s, COMe), 3.72 and 3.79 (each 3 H, s, OMe), 6.410 and 6.418 (each 1 H, s, ArH), and 13.23 and 13.30 (each 1 H, s, OH); δ_C[75.5 MHz, $(CD_3)_2SO$] 16.65 (q), 22.58 (q), 32.36 (q), 32.65 (q), 55.18 (q), 55.51 (q), 55.51 (q), 96.91 (d), 106.19 (d), 110.91 (s), 113.46 (s), 118.82 (s), 121.65 (s), 136.33 (s), 139.26 (s), 156.16 (s), 158.34 (s), 158.97 (s), 159.97 (s), 204.18 (s), and 204.61 (s); $\lambda_{max.}$(MeOH) 217sh, 239, and 284 nm (ε 22 600, 22 300, and 16 100, respectively); $\nu_{max.}$(KBr) 1 610 and 1 570 cm^{-1}; *m/z* 359 (12%), 358 (57, M^+), 344 (20), 343 (100), 311 (11), and 301 (20).

Biscarbonate (**22**).—A solution of the diketone (**27**) (600 mg) in pyridine (10 ml) was stirred at 0 °C and treated dropwise with methyl chloroformate (3.2 g). The solution was then stirred and heated at 70 °C (bath) for 2 h and next cooled and diluted with ethyl acetate. The solution was washed with dilute hydrochloric acid and with saturated brine. The *carbonate* (**22**) (740 mg, 94%) crystallized from methanol as plates, m.p. 168—169 °C (Found: C, 60.5; H, 5.85%; M^+, 474. $C_{24}H_{26}O_{10}$ requires C, 60.75; H, 5.5%; *M*, 474); δ_H(80 MHz) 1.98 and 2.40 (each 3 H, s, Me), 2.46 and 2.47 (each 3 H, s, COMe), 3.57, 3.71, 3.77, and 3.90 (each 3 H, s, OMe), and 6.68 and 6.72 (each 1 H, s, ArH).

4,4′-*Dihydroxy*-7,7′-*dimethoxy*-5,5′-*dimethyl*-6,8′-*bicoumarin* (**23**).—Potassium (300 mg) was dissolved in boiling anhydrous t-butyl alcohol (15 ml) under an atmosphere of argon. The carbonate (**22**) (365 mg) was added and the solution was stirred and heated under argon for 2 h. The cooled solution was diluted with water and extracted with ether. The aqueous layer was acidified with dilute hydrochloric acid and the product (311 mg, 98%) was isolated with ethyl acetate and crystallized from methanol as plates of the *bicoumarin* (**23**), m.p. 260—265 °C (Found: C, 62.85 H, 4.55%; M^+, 410. $C_{22}H_{18}O_8 \cdot 0.5H_2O$ requires C, 63.0; H, 4.55%; *M*, 410); δ_H[80 MHz, $(CD_3)_2SO$] 2.27 and 2.76 (each 3 H, s, Me), 3.69 and 3.77 (each 3 H, s, OMe), 5.38 and 5.47 (each 1 H, s, 3- and 3′-H), and 6.93 and 6.95 (each 1 H, s, ArH).

4,4′,7,7′-*Tetramethoxy*-5,5′-*dimethyl*-6,8′-*bicoumarin* (*Desertorin C*) (**6**).—The dihydroxybicoumarin (**23**) (70.0 mg), dimethyl sulphate (200 mg), and potassium carbonate (450 mg) were stirred together and heated under reflux under dry argon in acetone (10 ml) and 1,2-dimethoxyethane (5 ml) for 18 h. The salts were separated by filtration and washed with boiling acetone. The residue left on removal of the solvent was subjected to radial chromatography with dichloromethane–ethyl acetate–light petroleum (2:1:1) as eluant. Racemic *desertorin C* (**6**) (16.2

mg, 22%) crystallized from methanol as plates, m.p. >320 °C (lit.,[3] for enantiomorph, 235—237 °C) identical with the natural product (^{1}H n.m.r., mass, and i.r. spectra, and R_F values on t.l.c. in three different solvent systems) (Found: C, 65.4; H, 5.25. $C_{24}H_{22}O_8$ requires C, 65.75; H, 5.05%); δ_H(300 MHz) 2.29 and 2.75 (each 3 H, s, Me), 3.71, 3.80, 3.92, and 3.95 (each 3 H, s, OMe), 5.54 and 5.87 (each 1 H, s, 3- and 3′-H), and 6.73 and 6.77 (each 1 H, s, 6′- and 8-H); δ_C[75.5 MHz, $(CD_3)_2SO$] 18.75, 23.41, 55.98, 56.08, 56.61, 87.33, 87.64, 97.53, 107.23, 107.56, 109.30, 111.37, 119.23, 136.58, 137.96, 152.52, 155.77, 158.76, 159.93, 161.41, 161.53, and 169.26 (4- and 4′-C); δ_C(75.5 MHz, $CDCl_3$) *inter alia*, 170.18 and 169.73 (4- and 4′-C); $\lambda_{max.}$(MeOH) 208, 293sh, 308, and 320sh nm (ε 51 700, 20 000, 23 900, and 21 000, respectively); *m/z* 439 (23%), 438 (100, M^+), 423 (6), 408 (11), 407 (42), 406 (14), 364 (11), 363 (12), 362 (8), and 361 (16).

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References

1 H. G. Cutler, F. G. Crumley, R. H. Cox, O. Hernandez, R. J. Cole, and J. W. Dorner, *J. Agric. Food Chem.*, 1979, **27**, 592.
2 G. Büchi, D. H. Klaubert, R. C. Shank, S. M. Weinreb, and G. N. Wogan, *J. Org. Chem.*, 1971, **36**, 1143.
3 K. Nozawa, H. Seyea, S. Nakajima, S. Udagawa, and K. Kawai, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1735.
4 J. R. Cannon, T. M. Cresp, B. W. Metcalf, M. V. Sargent, G. Vinciguerra, and J. A. Elix, *J. Chem. Soc. C*, 1971, 3495.
5 A. I. Meyers, R. Gabel, and E. D. Mihelich, *J. Org. Chem.*, 1978, **43**, 1372.
6 I. H. Sánchez, M. I. Larraza, F. Basurto, R. Yañez, S. Avila, R. Tovar, and P. Joseph-Nathan, *Tetrahedron*, 1985, **41**, 2355.
7 M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2553.
8 D. D. Clarke and F. F. Nord, *J. Am. Chem. Soc.*, 1955, **77**, 6618.
9 A. Kreuchunas, *J. Org. Chem.*, 1956, **21**, 910.

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