Metabolites from the Purple Heartwood of Mimosoideae. Part 3.† *Acacia crombei* C. T. White: Structure and Partial Synthesis of Crombenin, A Natural Spiropeltogynoid

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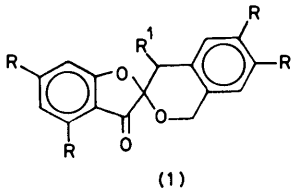
Crombenin, 4,4',6,6',7-pentahydroxyisochroman-3'-spirobenzofuran-3(2*H*)-one, the first spiropeltogynoid, is related to the concomitant crombeone (8-hydroxypeltogynone) from which it is derived *via* oxidation with alkaline hydrogen peroxide of the chalcone intermediate. The method of synthesis and i.r. spectroscopy define the stereochemistry as either 2(3')*R*,4'*R* or 2(3')*S*,4'*S*. Crombenin is accompanied by the first natural 5,6-dihydroxyphthalide.

CONTINUED phytochemical investigations of Australian *Acacia* species [1-3] include a detailed examination of *Acacia crombei* C. T. White, a relatively rare phyllodinous tree with natural distribution essentially restricted to the Hughenden district of Queensland. The heartwood exhibits a conspicuous deep purple which also characterises related peltogynoid-containing species (*cf.* *A. peuce* [2] and *A. carnei* [3]).

RESULTS AND DISCUSSION

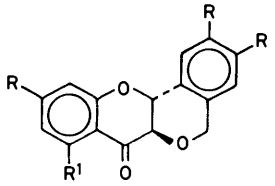
Exhaustive examination of metabolites from the heartwood of *A. crombei* reveals, as in the case of *A. carnei*,[3] the presence of both resorcinol- and phloroglucinol-type (A-ring) peltogynoids. The latter group includes a novel type of spiropeltogynoid at exceptionally low concentrations (0.03% of the total extract). Crombenin [4] is assigned a 4'-hydroxyisochroman-3'-spiro-2-benzofuran-3(2*H*)-one structure (1a) by synthesis of racemic crombenin tetramethyl ether (1b) from the concomitant crombeone [3,5] (2a) *via* the chalcone intermediate. These 8-hydroxypeltogynoids are accompanied by their flavonol analogue, β-photomethylquercetin (4a), as well as by the 8-deoxy-analogues (+)-6a,12a-*trans*-6a,7-*trans*- (3a) and (+)-6a,12a-*trans*-6a,7-*cis*-peltogynols (3b), peltogynone (2c), and peltogynin (4b). Conventional flavonoids comprise (+)-2,3-*trans*-3,4-*trans*-mollisacacidin (6a), (±)-2,3-*trans*-fustin (5a), and fisetin (7a), while the presence of 5,6-dihydroxyphthalide (8a) is apparently associated with the peltogynoid content of the heartwood. All metabolites were identified as their methyl ether derivatives by n.m.r., mass spectrometry, optical rotation, and circular dichroism, and their structures confirmed by comparison with natural or synthetic reference samples.

Tetra-*O*-methylcrombenin (1b) (M^+ 388) exhibits an upfield benzenoid *meta*-coupled AB quartet (δ 6.16, 5.99, J 2.0 Hz), indicative of phloroglucinol A-ring flavonoids. These resonances, accompanied by a pair of *para*-coupled singlets to lower field (δ 7.22, 6.56, $J \leqslant 1.0$ Hz), closely resemble those shown by crombeone tetramethyl ether (2b).[3] The broadened singlet (δ 5.22), allocated to H-4', alone undergoes a pronounced downfield shift (Δδ −1.19) on acetylation [(1c), M^+ 430],



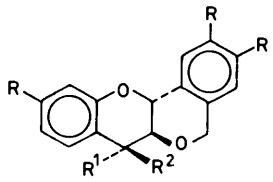
(1)

a; R = R^1 = OH
b; R = OMe; R^1 = OH
c; R = OMe; R^1 = OAc



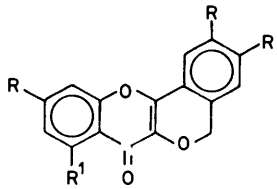
(2)

a; R = R^1 = OH
b; R = R^1 = OMe
c; R = OH; R^1 = H
d; R = OMe; R^1 = H



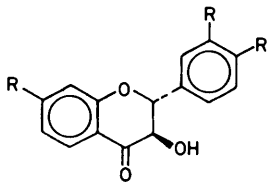
(3)

a; R = R^1 = OH; R^2 = H
b; R = R^2 = OH; R^1 = H
c; R = OMe; R^1 = OH; R^2 = H
d; R = OMe; R^2 = OH; R^1 = H



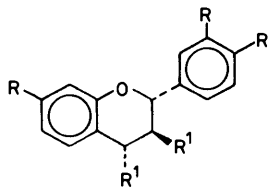
(4)

a; R = R^1 = OH
b; R = OH; R^1 = H
c; R = R^1 = OMe
d; R = OMe; R^1 = H



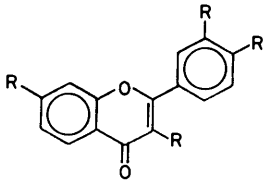
(5)

a; R = OH
b; R = OMe



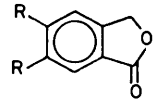
(6)

a; R = R^1 = OH
b; R = OMe; R^1 = OH
c; R = OMe; R^1 = OAc



(7)

a; R = OH
b; R = OMe



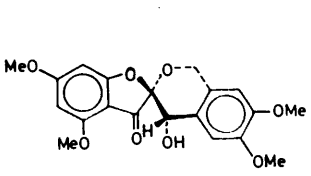
(8)

a; R = OH
b; R = OMe

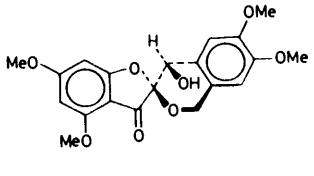
† Part 2 is ref. 3.

consistent with its position geminal to the hydroxy-function. Persistence of a degree of line-broadening after acetylation illustrates the benzylic nature of this proton. The above, supplemented by evidence of a methylene containing D-ring system (δ 5.23, 4.93, *J* 16.0 Hz; *cf.* crombeone),[3] four methoxy-groups (δ 3.93, 3.90, 3.87, 3.87), and a single acetoxy-function (δ 2.03), is alone consistent with structure (1a). This structure permits rationalization of mass-spectral fragmentations of the derivatives (1b and c).

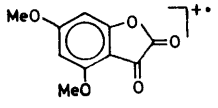
In conjunction with n.m.r. evidence, corroborative proof of the structure is provided by the retro-Diels–Alder fragmentation of the D-ring in the tetramethyl ether acetate (1c), yielding ions at *m/e* 208 (10.7) (15) and 222 (12.7) (16). Such fragmentations are obviously limited to compounds of the peltogynoid type and not applicable to 'conventional' 2-methoxy-α-hydroxy-benzofuranones [*e.g.* (11)], lacking a D-ring. Evidently



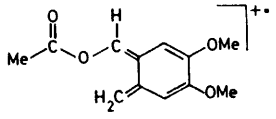
(13) (*S*,*S*)



(14) (*R*,*R*)



(15)

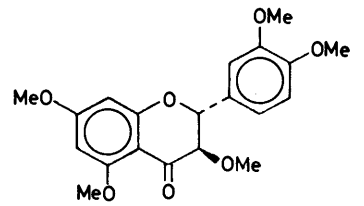


(16)

the retro-Diels–Alder fragmentation may be preceded by the loss of an acetoxy-radical (M^+ 430 (0.7) $\xrightarrow{-\cdot OAc}$ *m/e* 371 (5.4) $\xrightarrow{-H^\cdot, m^*}$ *m/e* 370 (5.1)], thus supporting its benzylic nature.

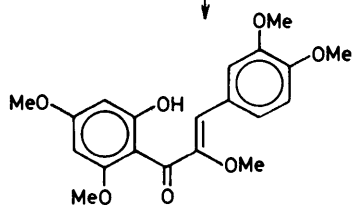
Strong Cotton effects observed with c.d. measurements for the tetramethyl ether (1b) indicate a high degree of optical activity for crombenin ($[\alpha]_D^{24}$ −7°). Accommodation of a hydrogen-bonded hydroxy (3 450 cm^{-1}) as well as carbonyl function (1 695 cm^{-1}), the latter shifting to higher frequency (1 725 cm^{-1}) on acetylation, requires their juxtaposition with the 4′-OH in an *axial* position on the D-ring. This prerequisite is only met for two possible molecular arrangements, which limit the relative configuration of crombenin to either 2(3′)*S*,4′*S* (13) or 2(3′)*R*,4′*R* (14).

Synthesis of tetra-*O*-methylcrombenin (1b) is accomplished by conversion from crombeone [(2a) from *A. carnei*] *via* its tetramethyl ether (2b). However, due to the limited availability of crombeone, the suggested sequence was first attempted on an analogous series, starting with commercial (+)-dihydroquercetin (*cf.* Scheme 1). In the parallel sequence crombeone (2a) is methylated to its tetramethyl ether (2b) and successively converted under identical conditions into the 2′-hydroxypeltogynoid chalcone (12) and into tetra-*O*-methylcrombenin (1b) (*cf.* Scheme 2). The course of the final Algar–Flynn–Oyamada reaction [6,7] (oxidation with alkaline hydrogen peroxide) is directed, as in the former synthesis, by the presence of a 6′-methoxy-group in the 2′-hydroxychalcone.[8,9] The synthetic compound (1b) and the acetate thus obtained gave n.m.r. and mass spectra identical with those of the related derivatives (1b,c) of the natural product (1a). The stereoselective nature of the intramolecular cycloaddition of the 2′-hydroxy-function of the peltogynoid chalcone to the αβ-epoxide, formed during alkaline hydrogen peroxide oxidation,



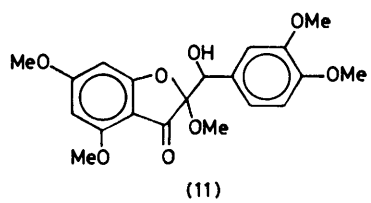
(9)

KOH | H_2O



(10)

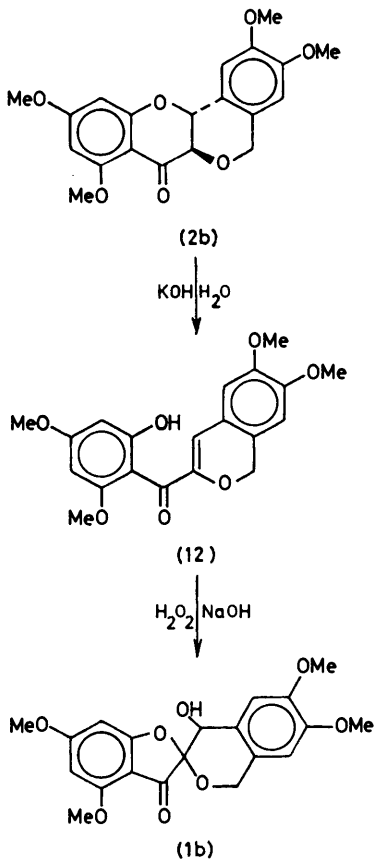
H_2O_2 | NaOH



(11)

SCHEME 1

defines the 2(3′)*R*,4′*R* and 2(3′)*S*, 4′*S* configuration of the racemate, and hence indicates that the absolute configuration of natural crombenin is restricted to these alternatives in which the benzylic 4′-*axial*-hydroxy is *trans* relative to the heterocyclic oxygen of the furanone C-ring. The fused nature of crystals of the tetramethyl ether has hitherto not been conducive to determination of its absolute configuration by *X*-ray crystallographic methods. The high mobility of the free phenolic form of crombeone (R_F 0.74) in a predominantly aqueous medium (20% acetic acid) on paper chromatograms differentiates it from the relatively low range of R_F values (0.0—0.32) of all known peltogynoids, a difference which is almost certainly attributable to its extreme non-planarity as a



SCHEME 2

spiro-structure, compared with the planarity or near-planarity of all other known peltogynoids.

EXPERIMENTAL

Authenticated samples of the cross-section of the stem of *A. crombei* were collected at Rockwood Station, Hughenden, Queensland (February 1970) and Spring Valley Station, 56 km north-west of Hughenden (March 1970 and November 1971). These were kindly supplied by Dr. Mary D. Tindale, Royal Botanic Gardens and National Herbarium, Sydney, Australia.

Experimental details are as defined for *A. peuce*.[2]

Extraction and Fractionation of Compounds from A. crombei.—Heartwood drillings (688 g) from *A. crombei* were de-waxed with n-hexane–benzene (7 : 2 v/v) (4 × 3.5 l, 12 h) at *ca.* 28 °C. The dry wax-free drillings (687.6 g) were extracted at ambient temperatures (*ca.* 27 °C) with ethyl acetate (5 × 3 l, 24 h) and subsequently with MeOH (5 × 3 l, 24 h) to give light brown (15.0 g) and red-brown solids (44.5 g), respectively, on removal of the solvents.

Application of preparative paper chromatography (p.p.c.) to the ethyl acetate extract (15.0 g) yielded three fractions A—C [R_F 0.32 (1.1 g), 0.26 (4.2 g), and 0.18 (2.8 g), respectively], when developed in 20% acetic acid. The latter, due to the complexity of the mixture (from qualitative two-dimensional paper chromatography), was re-fractionated by p.p.c. (downward migration; water-saturated butan-2-ol) into sub-fractions C_1 (R_F 0.74, 468 mg) and C_2 (R_F 0.27, 768 mg). The MeOH extract was simplified to a single fraction D (R_F 0.71, 3.4 g), by p.p.c. in 20% acetic acid.

Isolation and Identification of Compounds from A. crombei. (−)-*4′-Hydroxy-4,6,6′,7′-tetramethoxyisochroman-3′-spiro-2-benzofuran-3(2H)-one* (1b).—A portion of fraction D (1.5 g) was methylated with dimethyl sulphate. The product (1.53 g) was separated by t.l.c. (benzene–acetone, 7 : 3 v/v) and yielded the compound (R_F 0.44) which crystallized from acetone as *platelets* (17.7 mg), m.p. 228 °C (Found: C, 61.6; H, 5.1. $C_{20}H_{20}O_8$ requires C, 61.8; H, 5.2%); *m/e* 388 (5.5%, M^+), 370 (13), 209 (10), 207 (4.8), 194 (21), 181 (29), 180 (100), 179 (29), and 165 (18); $[\alpha]_D^{24}$ −7° (*c* 0.44 in C_5H_5N); c.d. (*c* 0.012 in MeOH) $[\theta]_{310}$ 0, $[\theta]_{296}$ 1.2 × 10^5, $[\theta]_{290}$ 0, $[\theta]_{279}$ −5.7 × 10^5, $[\theta]_{254}$ 2.4 × 10^5, $[\theta]_{235}$ −8 × 10^5, $[\theta]_{226}$ −1.7 × 10^5, $[\theta]_{210}$ 0, $[\theta]_{205}$ 3.5 × 10^5; δ($CDCl_3$) 7.22 (s, H-5′), 6.56 (s, H-8′), 6.16 (d, *J* 2.0 Hz, H-5), 5.99 (d, *J* 2.0 Hz, H-7), 5.22 (br s, H-4′), 5.17 (d, *J* 15.6 Hz, H-1′), 4.89 (d, *J* 15.6 Hz, H-1′), 3.89 (s, 2 × OMe), 3.82 (2 × OMe), and 3.26 (br s, 4′-OH); $\nu_{max.}$ 1 695 (CO) and 3 450 cm^{-1} (OH).

(−)-*4′-Acetoxy-4,6,6′,7′-tetramethoxyisochroman-3′-spiro-2-benzofuran-3(2H)-one* (1c).—Acetylation of crombenin tetramethyl ether (1d) (15.9 mg) gave the *monoacetate* as an *amorphous solid* (16.0 mg), m.p. 67 °C (Found: M^+, 430.126. $C_{22}H_{22}O_9$ requires *M*, 430.126); *m/e* 430 (2.0%, M^+), 371 (5.0), 370 (5.1), 342 (41), 341 (100), 208 (10), 194 (10), 181 (42), 180 (70), and 179 (28); $[\alpha]_D^{25}$ −2.4° (*c* 0.47 in C_5H_5N); δ($CDCl_3$) 6.70 (s, H-5′), 6.61 (s, H-8′), 6.41 (s, H-4′), 6.20 (d, *J* 2.0 Hz, H-5), 6.09 (d, *J* 2.0 Hz, H-7), 5.23 (d, *J* 16.0 Hz, H-1′), 4.93 (d, *J* 16.0 Hz, H-1′), 3.93, 3.90 (s, 2 × OMe), 3.87 (s, 2 × OMe), and 2.03 (s, 4′-OAc); $\nu_{max.}$ 1 725 cm^{-1} (CO).

(+)-2,3-trans-3,4-trans-3,4-*Dihydroxy-3′,4′,7-trimethoxyflavan* (6b).—Compound (6b) was isolated by t.l.c. from the methylated portion of fraction D (1.53 g) as indicated for crombenin tetramethyl ether (1b). The compound (R_F 0.33) was obtained as a yellow amorphous solid (38.6 mg, M^+ 332) which was purified as the diacetate. Following acetylation of compound (6b) (38.6 mg) the diacetate (6c) (R_F 0.62) was purified by t.l.c. [benzene–acetone (8 : 2 v/v)] and crystallized from EtOH as needles (21.0 mg), m.p. 130 °C (lit.,[10] 102 °C); M^+ 416; $[\alpha]_D^{29}$ −11° (*c* 0.41 in $CHCl_3$) {lit.,[10] $[\alpha]_D$ −17° (*c* 1.52 in $Cl_2CHCHCl_2$)}; n.m.r. identical to that in the literature.[11]

(±)-2,3-trans-3-*Hydroxy-3′,4′,7-trimethoxyflavan* (5b).—Compounds (1b) and (6b) were accompanied in the methylated portion of fraction D (1.53 g) by compound (5b) which was isolated by t.l.c. as indicated for compound (1b). The compound (R_F 0.54) crystallized as needles (21.0 mg) from EtOH, m.p. 143 °C (lit.,[12] 138—140 °C); M^+ 330; racemic; n.m.r. identical to that of an authentic sample.

5,6-*Dimethoxyisobenzofuran-3(1H)-one* (8b).—A portion of fraction B (1.0 g) was methylated with dimethyl sulphate. The product (1.2 g) was separated by t.l.c. [benzene–acetone (7 : 3 v/v)] and yielded compound (8b) (R_F 0.62) which crystallized from EtOH (40% v/v) as *needles* (29.9 mg), m.p. 156 °C (lit.,[13] 157 °C; synthetic), mixed m.p. 157 °C (with the synthetic product); δ($CDCl_3$) 7.14 (s, H-4), 7.01 (s, H-7), 5.27 (s, 1-CH_2), 4.02, 3.97 (s, 2 × OMe), identical to the synthetic product (see below).

6a,12a-trans-6a,7-trans-7-*Hydroxy-2,3,10-trimethoxy-5,6a,7,12a-tetrahydro*[1]*benzopyrano*[3,2-c][2]*benzopyran* (3c).—Compound (8b) is accompanied in the methylated portion of fraction B (1.2 g) by compound (3c) (R_F 0.54) which was separated by t.l.c. (see above) and yielded needles (604.2 mg) from EtOH, m.p. 199 °C (lit.,[14] 200 °C).

The compound was identical to that isolated from *A. peuce* (ref. 2).

6a,12a-trans-6a,7-cis-7-*Hydroxy*-2,3,10-*trimethoxy*-5,6a,7,12a-*tetrahydro*[1]*benzopyrano*[3,2-c][2]*benzopyran* (3d).—Following methylation of fraction A (1.1 g) with dimethyl sulphate, purification by t.l.c. [benzene–acetone (8 : 2 v/v)] gave compound (3d) (peltogynol B trimethyl ether) (R_F 0.41) which crystallized from EtOH (90% v/v) as needles (53.1 mg), m.p. 141 °C (lit.,[15] 140 °C), identical to the compound from *A. peuce* (ref. 2).

(+)-6a,12a-trans-2,3,8,10-*Tetramethoxy*-6a,12a-*dihydro*-[1]*benzopyrano*[3,2-c][2]*benzopyran*-7(5H)-*one* (2b).—Methylation (dimethyl sulphate) and purification by t.l.c. [1,2-dichloroethane–acetone (9 : 1 v/v)] of a portion (363 mg) of fraction C_2 yielded compound (2b) (R_F 0.64) as needles (142.9 mg), m.p. 192 °C (lit.,[3] 192 °C) from EtOH. This compound is identical to that derived from *A. carnei* (ref. 3).

(+)-6a,12a-trans-2,3,8-*Trimethoxy*-6a,12a-*dihydro*[1]-*benzopyrano*[3,2-c][2]*benzopyran*-7(5H)-*one* (2d) *and* 3,3′,-4′,7-*Tetramethoxyflavone* (7b).—A portion (324 mg) of fraction C_1 was methylated with diazomethane and separated by t.l.c. [1,2-dichloroethane–acetone (9 : 1 v/v)]. Compounds (2d) (R_F 0.53) and (7b) (R_F 0.39) thus obtained both crystallized as needles, m.p. 214 and 178 °C (lit.,[15,16] 213 and 180 °C) (21.3 and 36.7 mg, respectively) from ethanol and ethyl acetate, respectively, and were indistinguishable from their counterparts isolated from *A. carnei* (ref. 3).

2,3,8-*Trimethoxy*[1]*benzopyrano*[3,2-c][2]*benzopyran*-7(5H)-*one* (4d) *and* 2,3,8,10-*Tetramethoxy*[1]*benzopyrano*-[3,2-c][2]*benzopyran*-7(5H)-*one* (4c).—Compounds isolated from the methylated fraction C_1 [(2d) and (7b)] were accompanied by extremely low concentrations of (4d) and (4c). This was established by t.l.c. [1,2-dichloroethane–acetone (9 : 1 v/v)] with authentic samples (ref. 3) as reference (R_F 0.23 and 0.06, respectively; yellow with H_2SO_4–HCHO and turquoise fluorescence under u.v. light).

Synthesis of (±)-2-(α-*Hydroxy*-3′,4′-*dimethoxybenzyl*)-2,4,-6-*trimethoxybenzofuran*-3(2H)-*one* (11).—2′-*Hydroxy*-α,3,4,-4′,6′-*pentamethoxy*-trans-*chalcone* (10). (+)-3,3′,4′,5,7-Pentamethoxy-2,3-*trans*-flavanone (9) (200 mg), prepared by the methylation of commercial (+)-dihydroquercetin with dimethyl sulphate under rigidly anhydrous conditions, was stirred with aqueous KOH (10% w/v) (48 ml) for 2 h at *ca.* 95 °C.[15] The orange solution was filtered and the filtrate acidified with 2N HCl to pH *ca.* 2. The resultant chalcone precipitate crystallized from EtOH as yellow needles (158 mg), m.p. 116 °C (lit.,[17] 115—116 °C) (Found: M^+, 374.136. Calc. for $C_{20}H_{22}O_7$: M, 374.136); δ($CDCl_3$) 7.45 (d, J 2.0 Hz, H-2), 7.26 (dd, J 2.0 and 9.0 Hz, H-6), 6.85 (d, J 9.0 Hz, H-5), 6.65 (d, J 2.4 Hz, H-5′), 6.10 (s, H-β), 6.03 (d, J 2.4 Hz, H-3′), 3.90 (s, 2 × OMe), 3.84, 3.75, 3.71 (s, 3 × OMe).

(±)-2-(α-*Hydroxy*-3′,4′-*dimethoxybenzyl*)-2,4,6-*trimethoxy*-*benzofuran*-3(2H)-*one* (11). The 2′-hydroxypentamethoxychalcone (10) (83 mg) was dissolved in aqueous 1N NaOH (2.5 ml) and treated with H_2O_2 (6% w/v, 0.5 ml) at *ca.* 18 °C.[6,7] When the solution was allowed to stand at ambient temperatures (*ca.* 21 °C) for 72 h, the benzofuranone (11) precipitated and was removed by centrifugation. The product (R_F 0.73) was purified by t.l.c. [benzene–acetone (7 : 3 v/v)] and crystallized from EtOH as needles (42.1 mg), m.p. 178 °C (lit.,[7] 178—181 °C) (Found: M^+, 390.132. Calc. for $C_{20}H_{22}O_8$: M, 390.131); δ($CDCl_3$) 7.09 (dd, J 2.0 and 8.5 Hz, H-6′), 7.05 (d, J 2.0 Hz, H-2′), 6.85 (d, J 8.5 Hz, H-5′), 6.17 (d, J 2.0 Hz, H-5), 5.98 (d, J 2.0 Hz, H-7), 5.04 (s, H-α), 3.88 (s, α-OH and 4 × OMe), and 3.29 (s, 2-OMe).

Synthesis of (±)-4′-*Hydroxy*-4,6,6′,7′-*tetramethoxyiso*-*chroman*-3′-*spiro*-2-*benzofuran*-3(2H)-*one* (1b).—3-(2′-*Hydroxy*-4′,6′-*dimethoxybenzoyl*)-6,7-*dimethoxyisochromen* (12). The chalcone analogue (12) was obtained by treatment of compound (2b) (100 mg) from natural sources (see above and ref. 3) with aqueous KOH (10% w/v, 24 ml) as indicated for the chalcone (10). Crystallization from ethanol yielded *yellow needles* (86.1 mg), m.p. 93 °C (Found: M^+, 372.120. $C_{20}H_{20}O_7$ requires M^+, 372.120); δ($CDCl_3$) 10.45 (br s, 2′-OH), 6.74 (s, H-5), 6.65 (s, H-8), 6.57 (s, H-4), 6.17 (d, J 2.2 Hz, H-5′), 6.04 (d, J 2.2 Hz, H-3′), 5.18 (br s, 1-CH_2), 3.71 (s, 2 × OMe), and 3.65, 3.62 (s, 2 × OMe).

Compound (1b). Reaction of the chalcone analogue (12) (80 mg) with H_2O_2 (6% w/v, 0.5 ml) in aqueous 1N NaOH (2.5 ml), according to the procedure outlined for the preparation of the benzofuranone (11), yielded tetra-*O*-methylcrombenin (1b). The product (R_F 0.45) was purified by t.l.c. [benzene–acetone (7 : 3 v/v)] and crystallized from acetone as *platelets* (24.7 mg), m.p. 216 °C (Found: M^+, 388.115. $C_{20}H_{20}O_8$ requires M, 388.116); racemic; n.m.r. ($CDCl_3$) identical to that of the natural derivative.

Synthetic 5,6-*Dihydroxyisobenzofuran*-3(1H)-*one* (8b).—According to the method by Edwards *et al.*,[13] a mixture of commercial 3,4-dimethoxybenzoic acid (3.2 g), aqueous HCHO (40% v/v, 4.0 ml), and HCl (12.5 ml) was refluxed for 12 h. The product was cooled rapidly, diluted with an equal volume of H_2O and shaken to deposit a gummy precipitate. The product, which separated from the clear filtrate as brown platelets over 12 h, was filtered, washed with aqueous Na_2CO_3 (5% w/v, 5 × 20 ml) and recrystallized from EtOH (40% v/v) as needles (0.6 g), m.p. 157 °C (lit.,[13] 155—157 °C); n.m.r. ($CDCl_3$) identical to that of the natural product.

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