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O-(DIHYDROBENZOFURANYL)-DIBENZO-α-PYRONES FROM *UMTIZA LISTERANA*

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Key Word Index—*Umtiza listerana*; Leguminosae; heartwood metabolites; (2′*S*,3′*R*)-3,10-dihydroxy-9-*O*-(6′-hydroxy-2′-hydroxymethyldihydrobenzofuran-3-yl)-dibenz-[b,d]-pyran-6-one; (2′*S*,3′*R*)-3,10-dihydroxy-9-*O*-(5′,6′-dihydroxy-2′-hydroxymethyldihydrobenzofuran-3-yl)-dibenz-[b,d]-pyran-6-one; 3,9,10-trihydroxydibenz-[b,d]-pyran-6-one; flavonoids; ^{1}H NMR; synthesis.

Abstract—The novel metabolites (2′*S*,3′*R*)-3,10-dihydroxy-9-*O*-(6′-hydroxy-2′-hydroxymethyldihydrofuran-3-yl)-dibenz-[b,d]-pyran-6-one and its 5′,6′-dihydroxy analogue are accompanied in the heartwood of *Umtiza listerana* by several known flavonoids and the parent 3,9,10-trihydroxydibenz-[b,d]-pyran-6-one. The latter, used for structural elucidation of the complex dibenzo-α-pyrones, was synthesized via a Hurtley condensation.

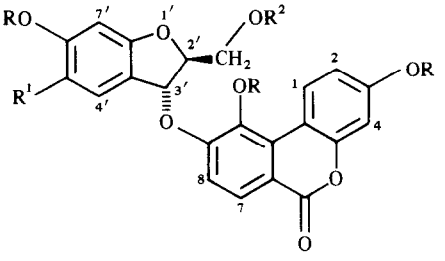
INTRODUCTION

Umtiza listerana, the only species in this genus, occurs as a small, spiny, evergreen tree in isolated parts of the Eastern Cape. Notwithstanding profuse seeding, it exhibits an extraordinary localized distribution, essentially restricted to the forested ravines near East London [1]. The trunks, covered by a dark, fissured bark, are characteristically buttressed and contain a dark rusty brown heartwood which on aging develops a distinct purple hue, indicative of the presence of peltogynoids [2] and related chromogenic flavonoids [3].

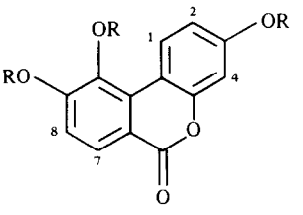
The metabolic pool present in the heartwood of *U. listerana* is shown to contain three dibenzo-α-pyrones, a limited group of natural compounds generally associated with cytotoxicity [4, 5]. Two of these, 3,10-dihydroxy-9-*O*-(6′-hydroxy-2′-hydroxymethyldihydrobenzofuran-3-yl)-dibenz-[b, d]-pyran-6-one (**1**) and its 5′,6′-dihydroxy analogue (**2**), represent hitherto unknown complex structures of hetero-dimeric nature. They are accompanied by fasciculiferol [6] (3,9,10-trihydroxydibenz-[b,d]-pyran-6-one) (**7**) and known flavonoids based mainly on the 7,3′,4′-trihydroxy substitution pattern or its equivalent: (+)-mollisacacidin and its 3,4-*cis* isomer, (−)-liquiritigenin, (−)-butin, (+)-fustin, fisetin, 7,3′,4′-trihydroxyflavone, (+)-peltogynol and (+)-2,6,3′,4′-tetrahydroxy-2-benzylbenzofuran-3(2H)-one.

RESULTS AND DISCUSSION

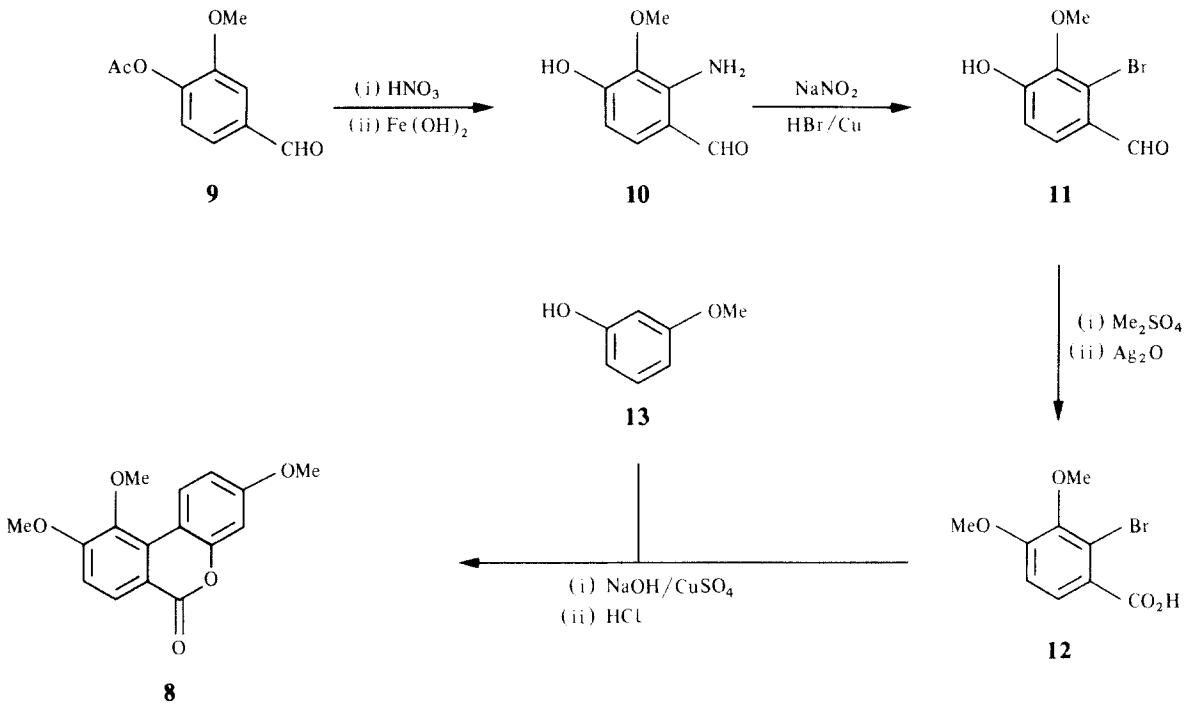
3,10-Dihydroxy-9-*O*-(6′-hydroxy-2′-hydroxymethyldihydrobenzofuran-3-yl)-dibenz-[b, d]-pyran-6-one (**1**) and the 5′,6′-dihydroxy analogue (**2**) occurred at exceptionally low concentrations (*ca* 0.0002 and 0.0003 % of the phenolic content, respectively) and were isolated as the methyl ethers (**3**, **4**), following fractionation of the heartwood extract by preparative paper chromatography (R_f 0.31 in acetic acid–water) and methylation. These were accompanied on paper (R_f 0.11 in acetic acid–water) by the dibenzpyranone analogue fasciculiferol (**7**), recently isolated by us from *Acacia fasciculifera* [6], the structure being confirmed by the present synthesis of its trimethyl ether (**8**) via final Hurtley condensation [7, 8] (cf. Scheme 1: **9** → **10** → **11** → **12** + **13** → **8**).



1 R = R^1 = R^2 = H
2 R = R^2 = H, R^1 = OH
3 R = Me, R^1 = R^2 = H
4 R = Me, R^1 = OMe, R^2 = H
5 R = Me, R^1 = H, R^2 = Ac
6 R = Me, R^1 = OMe, R^2 = Ac



7 R = H
8 R = Me



Scheme 1.

The mutual presence of the identical dibenzo-α-pyrone moiety in these compounds (**1**, **2**, **7**) was indicated by comparison of the ^{1}H NMR spectrum of 3,9,10-tri-*O*-methylfasciculiferol (**8**) with that of the methyl ethers **3** and **4**, in which all aromatic resonances of the former (**8**) were clearly reproduced. H-1 appeared in all instances (**3**, **4** and **8**) as a characteristically deshielded doublet [9] [J = 8.8 Hz: δ8.82 for **3** and δ8.79 for **4**; J = 8.7 Hz: δ8.75 for **8**], broadened by long-distance coupling [10] with the 10-methoxy group. Similar coupling between H-8 and the 9-methoxy group was, however, only evident for the methyl ether (**8**); its absence in compounds **3** and **4** indicating linkage via oxygen at C-9 to the dihydrobenzofuran moiety. Carbonyl absorption at 1720–1730 cm^{-1} confirmed the presence of a lactone ring [11] in both **3** and **4**.

The 250 MHz ^{1}H NMR spectra of the methyl ether acetates **5** and **6** respectively displayed an 'additional' aromatic ABC-system for compound **5** and an AB-system for compound **6** which were allocated to the aromatic protons of dihydrobenzofuran units present in the respective compounds. Both exhibited an additional heterocyclic ABMX-system in which the methylene protons appeared as two doublet-of-doublets (δ4.52, J = 3.0 and 12.0 Hz; δ4.14, J = 5.8 and 12.0 Hz for both **5** and **6** after pronounced deshielding ($\Delta\delta$ *ca* 0.6) on acetylation. This clearly indicated the presence of a hydroxymethyl group in the parent compound, the allocation being supported by mass spectrometry of the acetate ($[M]^+$ m/z 492 − 42 → m/z 450 and $[M]^+$ m/z 522 − 42 → m/z 480 respectively, as well as McLafferty rearrangements $[M-60]^+$ in each instance). The non-equivalence of these methylene protons is in line with their proximity to their respective C-2′ chiral centres. The latter was reflected by the coupling constants (J = 3.0 and 5.8 Hz) of the H-2′ multiplet (J = 3.0, 5.8 and 8.0 Hz; δ4.42 for **5** and δ4.41 for **6**). Successive decouplings of H-4′ and H-3′ confirmed, respectively, the benzylic positions of the 3′-protons [J = 8.0 Hz: δ5.04 for both **5** and **6**] and also their vicinal relationships with H-2′—thus defining C-3′ as the site of coupling with the dibenzo-α-pyrone moiety. The proposed structures were supported by mass spectrometry of the methyl ethers **3** and **4** yielding prominent $[M]^+$ m/z 450 (56%) and m/z 480 (60%) ions, respectively. Fragmentation resulted essentially from fission of the ether linkage, the oxygen being retained by either the dihydrobenzofuran ($[M]^+$ m/z 450 − 256 → m/z 194 for **3** and $[M]^+$ m/z 480 − 256 → m/z 224 for **4**) or the dibenzo-α-pyrone fragment ($[M]^+$ m/z 450 − 180 → m/z 270 − H$^\cdot$ → m/z 269 for **3** and $[M]^+$ m/z 480 − 210 → m/z 270 − H$^\cdot$ → m/z 269 for **4**). CD measurements of both compounds **3** and **4** exhibited strong negative Cotton effects ($[\theta]_{202}$ − 68 727 and $[\theta]_{206}$ − 201 230, respectively) in the low wavelength (200–220 nm) region. In conjunction with the 2′,3′-*trans*-configuration inferred by the large H-2′,3′ coupling constant (J = 8.0 Hz) in the 5-membered ring [12], these data suggest a 2′*S*,3′*R*-configuration for both compounds **3** and **4** on the basis of the aromatic quadrant rule [13].

The origin of the purple colour developed in the heartwood is not immediately evident, considering the low concentration of (+)-peltogynol, known for its chromogenic properties [14]. However, 2-benzyl-2-hydroxybenzofuran-3(2H)-ones under acid conditions develop deep colours attributed to the abstraction of the elements of water [3]. This property is shared by the complex dibenzo-α-pyrones, presumably due to the presence of the 2-hydroxymethyldihydrobenzofuran moiety. Accordingly, compounds **1** and **2**, together with the associated (+)-peltogynol and (+)-2,6,3′,4′-tetra-

hydroxy-2-benzylbenzofuran-3(2H)-one may be jointly responsible for this phenomenon in the heartwood of *U. listerana*.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 80 and 250 MHz for solns in $CDCl_3$ (unless otherwise stated) with TMS as int. ref. CD and UV spectra were determined in MeOH. Media used for separation of components were Whatman No. 3 for prep. PC, DC-Plastikfolin Kieselgel 60 F_{254}—0.25 mm for TLC and Kieselgel PF_{254} (1 mm, 20 × 20 cm) for prep. TLC. TLC bands were located under UV and/or with H_2SO_4–HCHO (40:1) spray reagent. Methylations were performed with excess CH_2N_2 and acetylations in Ac_2O–pyridine. Although comprehensive ^{1}H NMR and MS data are cited only for the novel compounds, these techniques were used extensively for the structural elucidation of all compounds.

Extractions and preliminary separations. Heartwood drillings (4.5 kg) of *U. listerana* Sim. were successively extracted with H_2O (10 × 3 l., 24 hr each) and MeOH (15 × 3 l., 24 hr each) at ambient temp. Exhaustive re-extraction of the H_2O extract with EtOAc yielded H_2O-soluble components (24 g) on evapn, while a crude solid (163 g) was obtained from the MeOH extract. H_2O-soluble components (20 g) were fractionated by prep. PC (2% HOAc; ascending) into two high R_f fractions (A, R_f 0.63, 7.7 g and B, R_f 0.55, 4.2 g). Similar treatment of a portion of the MeOH extractives (38 g), but with increased solvent polarity (prep. PC; 20% HOAc; ascending) produced 5 fractions (C, R_f 0.43, 3.2 g; D, R_f 0.31, 3.7 g; E, R_f 0.20, 2.0 g; F, R_f 0.11, 3.9 g; E, R_f 0.00, 9.2 g). Fractions A, B, D–G were subsequently methylated to yield the corresponding *O*-methyl ether derivatives A′, B′, D′, E′, F′ and G′, respectively.

(2′S,3′R)-3,10-*Dimethoxy*-9-O-(6′-*methoxy*-2′-*hydroxymethyldihydrobenzofuran*-3-*yl*)-*dibenz*-[*b,d*]-*pyran*-6-*one* (**3**). Following purification of the methyl ethers (D′, 4.2 g) by prep. TLC (C_6H_6–Me_2CO, 4:1), the mixture of compounds (**3** and **4**) thus obtained (R_f 0.58, 36 mg) was separated by prep. TLC (1,2-dichloroethane–Me_2CO, 19:1, ×2) to yield the complex dibenzo-α-pyrone (**3**) (R_f 0.34, 8 mg). Crystallization from EtOH gave white needles, mp 234–235° (Found: C, 66.5; H, 5.1. $C_{25}H_{22}O_8$ requires: C, 66.7; H, 4.9%). MS *m/z* (rel. int.): 450 (56) $[M]^+$, 270 (5.9), 269 (22), 228 (12), 194 (25), 193 (4.3), 179 (2.5), 177 (4.5), 165 (14), 164 (11), 161 (3.5), 151 (66); CD: $[\theta]_{320}$ +4909, $[\theta]_{312}$ 0, $[\theta]_{300}$ −7363, $[\theta]_{362}$ 0, $[\theta]_{255}$ +20454, $[\theta]_{235}$ +11454, $[\theta]_{227}$ +15545, $[\theta]_{207}$ 0, $[\theta]_{202}$ −68727; ^{1}H NMR: δ8.82 (*d*, *J* = 8.8 Hz, H-1), 8.05 (*d*, *J* = 8.8 Hz, H-7), 7.09 (*d*, *J* = 8.8 Hz, H-8), 7.09–6.82 (*m*, H-2, 4,4′,5′,7′), 5.23 (*d*, *J* = 8.0 Hz, H-3′), 4.35–3.54 (*m*, H-2′, CH_2), 3.95, 3.90 (*s*, 3 × OMe); IR ν_{CO} cm^{-1}: 1720.

(2′S,3′R)-3,10-*Dimethoxy*-9-O-(6′-*methoxy*-2′-*acetoxymethyldihydrobenzofuran*-3-*yl*)-*dibenz*-[*b,d*]-*pyran*-6-*one* (**5**). Acetylation of **3** (4 mg) gave the methyl ether acetate **5** as a non-crystalline white solid (5 mg). MS *m/z* (rel. int.): 492 (70) $[M]^+$, 450 (1.7), 432 (8.5), 236 (100), 228 (14), 194 (28), 193 (40), 177 (44), 165 (21), 164 (18), 151 (14); ^{1}H NMR: δ 8.84 (*d*, *J* = 8.0 Hz, H-1), 8.02 (*d*, *J* = 8.0 Hz, H-7), 7.09 (*d*, *J* = 8.0 Hz, H-8), 7.00 (*dd*, *J* = 8.0, 2.0 Hz, H-5′), 6.94 (*d*, *J* = 8.0 Hz, H-4′), 6.93 (*d*, *J* = 2.0 Hz, H-7′), 6.87 (*d*, *J* = 2.0 Hz, H-4), 6.85 (*dd*, *J* = 8.0, 2.0 Hz, H-2), 5.04 (*d*, *J* = 8.0 Hz, H-3′), 4.52 (*dd*, *J* = 12, 0, 3.0 Hz, CH_2), 4.42 (*m*, *J* = 3.0, 5.8, 8.0 Hz, H-2′), 4.14 (*dd*, *J* = 12.0, 5.8 Hz, CH_2), 3.91, 3.88 (*s*, 3 × OMe), 2.14 (*s*, OAc).

(2′S,3′R)-3,10-*Dimethoxy*-9-O-(5′,6′-*dimethoxy*-2′-*hydroxymethyldihydrobenzofuran*-3-*yl*)-*dibenz*-[*b,d*]-*pyran*-6-*one* (**4**). Compound **4** was separated from its analogue **3** by prep. TLC as indicated above and obtained (R_f 0.30) as a white non-crystalline solid (13 mg) (Found: C, 65.3; H, 5.4. $C_{26}H_{24}O_9$ requires: C, 65.0; H, 5.0%). MS *m/z* (rel. int.): 480 (60) $[M]^+$, 270 (2.5), 269 (30), 228 (12), 224 (100), 223 (2.9), 209 (9.2), 207 (2.7), 195 (24), 194 (9.6), 191 (5.5), 185 (7.1), 181 (29); CD: $[\theta]_{320}$ 0, $[\theta]_{290}$ −2769, $[\theta]_{280}$ 0, $[\theta]_{266}$ −17588, $[\theta]_{257}$ −31384, $[\theta]_{247}$ −10153, $[\theta]_{232}$ −31384, $[\theta]_{220}$ −14769, $[\theta]_{206}$ −201230; ^{1}H NMR: δ8.79 (*d*, *J* = 8.8 Hz, H-1), 8.00 (*d*, *J* = 8.8 Hz, H-7), 7.08 (*d*, *J* = 8.8 Hz, H-8), 6.85 (*dd*, *J* = 8.8, 2.5 Hz, H-2), 6.78 (*s*, H-4, 4′, 7′), 5.23 (*d*, *J* = 8.0 Hz, H-3′), 4.35–3.53 (*m*, H-2′, CH_2), 3.93, 3.92, 3.89 (*s*, 4 × OMe); IR ν_{CO} cm^{-1}: 1730.

(2′S,3′R)-3,10-*Dimethoxy*-9-*O*-(5′,6′-*dimethoxy*-2′-*acetoxymethyldihydrobenzofuran*-3-*yl*)-*dibenz*-[*b,d*]-*pyran*-6-*one* (**6**). Following acetylation of the methyl ether **4** (5 mg), the corresponding monoacetate **6** was obtained as a white non-crystalline solid (6 mg). MS *m/z* (rel. int.): 522 (69) $[M]^+$, 480 (1.9), 462 (1.8), 266 (100), 228 (10), 224 (12), 223 (17), 207 (14), 195 (10), 194 (7.8), 181 (10); ^{1}H NMR: δ8.80 (*d*, *J* = 8.0 Hz, H-1), 8.05 (*d*, *J* = 8.0 Hz, H-7), 7.13 (*d*, *J* = 8.0 Hz, H-8), 6.89 (*d*, *J* = 2.0 Hz, H-4), 6.86 (*dd*, *J* = 8.0, 2.0 Hz, H-2), 6.63 (*s*, H-4′, 7′), 5.04 (*d*, *J* = 8.0 Hz, H-3′), 4.52 (*dd*, *J* = 12.0, 3.0 Hz, CH_2), 4.41 (*m*, *J* = 3.0, 5.8, 8.0 Hz, H-2′), 4.14 (*dd*, *J* = 12.0, 5.8 Hz, CH_2), 3.86, 3.85 (*s*, 4 × OMe), 2.14 (*s*, OAc).

3,9,10-*Trimethoxydibenz*-[*b,d*]-*pyran*-6-*one* (3,9,10-*tri*-O-*methylfasciculiferol*) (**8**). The dibenzo-α-pyrone **8** was isolated from the methylated fraction (F′, 1.2 g) by prep. TLC in C_6H_6–Me_2CO (4:1) (R_f 0.75) and crystallized from EtOH as colourless needles (13 mg), mp 193–194°. Lit. [6] 196°. ^{1}H NMR: δ8.75 (*d*, *J* = 8.7 Hz, H-1), 8.25 (*d*, *J* = 8.7 Hz, H-7), 7.13 (*d*, *J* = 8.7 Hz, H-8), 6.93 (*dd*, *J* = 8.7, 2.5 Hz, H-2), 6.87 (*d*, *J* = 2.5 Hz, H-4), 3.94, 3.84, 3.81 (*s*, 3 × OMe); IR ν_{CO} cm^{-1}: 1730; MS (*m/z* 286 (98%) $[M]^+$) and UV identical to that in lit. [6].

3,7,3′,4′-*Tetramethoxyflavone* (3,7,3′,4′-*tetra*-O-*methylfisetin*) was isolated from fraction G′ (400 mg) by prep. TLC (C_6H_6–Me_2CO, 4:1, R_f 0.59) and crystallized from EtOAc as colourless needles (25 mg), mp 180°. Lit. [15] 180°.

7,3′,4′-*Trimethoxyflavone*. Tri-*O*-methylfisetin was accompanied in fraction G′ by 7,3′,4′-trimethoxyflavone, which was isolated (R_f 0.41) as above as colourless needles (21 mg) from EtOH, mp 176–178°. Lit. [16] 176°.

(+)-7,4′,5′-*Tri*-O-*methyl*-2,3-trans-3,4-trans-*peltogynol*. Purification of fraction E′ (1.6 g) by prep. TLC (C_6H_6–Me_2CO, 4:1) yielded tri-*O*-methylpeltogynol (R_f 0.12) which crystallized from EtOH as colourless needles (8 mg), mp 199°. Lit. [14] 200°; CD: $[\theta]_{300}$ +4018, $[\theta]_{275}$ +20093, $[\theta]_{240}$ +40186, $[\theta]_{213}$ +164766, $[\theta]_{205}$ −52242 (identical to authentic sample).

(−)-7,3′,4′-*Trimethoxyflavanone* [(−)-7,3′,4′-*tri*-O-*methylbutin*]. (−)-Butin was isolated from the phenolic fraction C (1.0 g) by prep. TLC (C_6H_6–Me_2CO, 9:1, R_f 0.36) and purified as its methyl ether, following methylation, by prep. TLC (C_6H_6–Me_2CO, 4:1, R_f 0.63). Crystallization from EtOH gave colourless needles (19 mg), mp 119°. Lit. [17] 120–121°; CD: $[\theta]_{353}$ 0, $[\theta]_{327}$ +9727, $[\theta]_{317}$ 0, $[\theta]_{300}$ −21272, $[\theta]_{256}$ 0, $[\theta]_{225}$ +16181, $[\theta]_{211}$ 0.

(−)-7,4′-*Dihydroxyflavanone* [(−)-*liquiritigenin*]. (−)-Liquiritigenin was separated from (−)-butin in the phenolic fraction C (1.0 g) by prep. TLC (C_6H_6–Me_2CO, 9:1, R_f 0.29) and crystallized from EtOH as yellow needles (24 mg), mp 206°. Lit. [18] 207°; CD: $[\theta]_{350}$ 0, $[\theta]_{325}$ +32897, $[\theta]_{315}$ 0, $[\theta]_{300}$ −56822, $[\theta]_{258}$ 0, $[\theta]_{234}$ +44859, $[\theta]_{223}$ +8971, $[\theta]_{213}$ +89719, $[\theta]_{200}$ 0.

(+)-7,3′,4′-*Trimethoxydihydroflavonol* [(+)-7,3′,4′-*tri*-O-*methylfustin*]. Fustin trimethyl ether was obtained from fraction B′ (1.1 g) by prep. TLC (C_6H_6–Me_2CO, 19:1, R_f 0.39) and crystallized from EtOH as colourless needles (20 mg), mp 143°. Lit. [19] 140°; CD: $[\theta]_{356}$ 0, $[\theta]_{328}$ +8364, $[\theta]_{310}$ 0, $[\theta]_{298}$ −22525, $[\theta]_{273}$ 0, $[\theta]_{265}$ +4515, $[\theta]_{244}$ +5152, $[\theta]_{226}$

+20272, $[\theta]_{207}$ 0.

2,6,3′,4′-Tetramethoxy-2-benzylbenzo-[b]-furan-3(2H)-one. The methylated fraction A′ (2.0 g) consisted of 3 major components which were separated by prep. TLC (C_6H_6–Me_2CO, 4:1) to yield 2,6,3′,4′-tetramethoxy-2-benzylbenzo-[b]-furan-3(2H)-one (R_f 0.58) which crystallized from EtOH as yellow needles (23 mg), mp 124–126°. Lit. [20] yellow oil; CD: $[\theta]_{350}$ +15636, $[\theta]_{328}$ +91863, $[\theta]_{317}$ 0, $[\theta]_{298}$ +218909, $[\theta]_{262}$ 0, $[\theta]_{222}$ +128999, $[\theta]_{205}$ 0; $[M]^+$ *m/z* 344 and ^{1}H NMR identical to that in lit. [6].

(+)-2,3-Trans-3,4-cis-7,3′,4′-trimethoxyflavan-3,4-diol. The 3,4-*cis* diol was isolated (R_f 0.27) from fraction A′ (2.0 g) as indicated for the previous compound above, and crystallized from EtOH as white needles (15 mg), mp 183°. Lit. [21] 179°. Acetylation gave the corresponding (+)-2,3-*trans*-3,4-*cis*-3,4-diacetoxy-7,3′,4′-trimethoxyflavan, which crystallized from MeOH as colourless needles, mp 80°. Lit. [21] 80°; CD: $[\theta]_{280}$ 0, $[\theta]_{265}$ +3565, $[\theta]_{250}$ +1523, $[\theta]_{230}$ +17750, $[\theta]_{220}$ +19750, $[\theta]_{212}$ +2950.

(+)-2,3-Trans-3,4-trans-7,3′,4′-trimethoxyflavan-3,4-diol [(+)-7,3′,4′-*tri*-O-*methylmollisacacidin*]. (+)-7,3′,4′-Tri-*O*-methylmollisacacidin was obtained from fraction A′ as described above (R_f 0.19) and crystallized from EtOH as white needles (20 mg), mp 128°. Lit. [22] 129°. Acetylation yielded (+)-2,3-*trans*-3,4-*trans*-3,4-diacetoxy-7,3′,4′-trimethoxyflavan (white needles from EtOH), mp 102°. Lit. [23] 104°; CD: $[\theta]_{392}$ 0, $[\theta]_{380}$ −4135, $[\theta]_{255}$ 0, $[\theta]_{230}$ −30000, $[\theta]_{220}$ −23750, $[\theta]_{212}$ −44000 (identical to authentic sample).

Synthesis of 3,9,10-*trimethoxydibenz-[b,d]-pyran-6-one* (**8**)—*4-Acetoxy-3-methoxy-2-nitrobenzaldehyde.* Conc. HNO_3 (18 ml) was added in small quantities to 4-acetoxy-3-methoxybenzaldehyde (**9**) (6 g) obtained by acetylation of vanillin at temps. < 5°. The resultant soln was stirred with ice-H_2O (400 ml) for 45 min and the precipitated product collected by filtration [24]. Crystallization from EtOH gave yellow needles (1.61 g; 27%), mp 80°. Lit. [25] 85°.

2-Amino-4-hydroxy-3-methoxybenzaldehyde (**10**). 4-Acetoxy-3-methoxy-2-nitrobenzaldehyde (1.61 g) was slowly mixed with an Fe $(OH)_2$ soln [treatment of $FeSO_4$ (13.71 g) in H_2O (50 ml) with a conc. NH_4OH soln (18 ml)] and refluxed for 20 min. Following addition of warm H_2O (30 ml), the mixture was filtered, the ppt. washed with warm H_2O (50 ml) and the combined filtrates acidified with 3 N H_2SO_4. Extraction of the resultant soln with Et_2O (3 × 50 ml) and evapn of the solvent yielded product **10** [24], which was purified by prep. TLC (C_6H_6–Me_2CO, 4:1, R_f 0.58) and crystallized from C_6H_6 as white needles (1.20 g; 88%), mp 138–139°. Lit [26] 138–139°.

2-Bromo-4-hydroxy-3-methoxybenzaldehyde (**11**). To a cooled (*ca* 4°) soln of compound **10** (1.11 g) in 40% HBr (3 ml) was gradually added a soln of $NaNO_2$ (0.50 g) in H_2O (20 ml), keeping the temp. below 5°. On completion of the diazotization the mixture was treated with Cu powder (27 mg) and refluxed for 1 hr [27]. The reaction mixture was cooled, extracted with Et_2O (3 × 20 ml) and the solvent evapd. 2-Bromo-4-hydroxy-3-methoxybenzaldehyde (**11**), thus obtained, crystallized from EtOH as colourless needles (0.92 g; 60%), mp 154–155°. Lit. [28] 154–155°.

2-Bromo-3,4-dimethoxybenzaldehyde. Compound **11** (0.85 g) in dry Me_2CO (80 ml) was stirred with K_2CO_3 (15 g) under reflux and treated with Me_2SO_4 [0.5 ml in dry Me_2CO (10 ml)] over a period of 2 hr. The methylation was subsequently allowed to proceed under reflux (60–70°) for *ca* 16 hr, after which the mixture was filtered, the solvent evapd and excess Me_2SO_4 destroyed with 1 N NH_4OH (50 ml). The product which precipitated was filtered, purified by prep. TLC (C_6H_6–Me_2CO, 4:1, R_f 0.71) and crystallized from 50% aq. EtOH as colourless needles (0.22 g; 23%), mp 84.5°. Lit. [29] 80°.

2-Bromo-3,4-dimethoxybenzoic acid (**12**). Ag_2O was freshly prepared by reacting a soln of $AgNO_3$ (0.16 g) in H_2O (7 ml) with aq. NaOH [0.04 g in H_2O (7 ml)]. Precipitated Ag_2O was filtered, washed free of nitrates with H_2O and mixed with aq. NaOH [200 mg in H_2O (10 ml)]. The reaction mixture was heated (55°), 2-bromo-3,4-dimethoxybenzaldehyde (0.22 g) added and the reaction allowed to proceed for 30 min with agitation. Following filtration the precipitated Ag was washed with H_2O (50 ml) and the combined filtrates were acidified with aq. HCl (1:1) [30]. Successive extraction with EtOAc (3 × 20 ml) and Et_2O (3 × 20 ml) followed by evapn of the solvents gave compound **12** which crystallized from EtOH as colourless needles (29 mg; 12%), mp 200°. Lit. [29] 206–208°.

3,9,10-Trimethoxybenz-[b,d]-pyran-6-one (**8**). 2-Bromo-3,4-dimethoxybenzoic acid (**12**) (27 mg), 4-methoxyphenol (**13**) (25 mg), NaOH (0.2 g) and H_2O (5 ml) were heated to boiling. $CuSO_4$ (0.5 mg) was added and the mixture refluxed for 3 hr. This was continued for a further 30 min following the addition of 2 M HCl (2.5 ml), after which the cooled mixture was extracted with Et_2O (3 × 10 ml) [7, 8, 31]. Evapn of the combined extracts yielded a mixture of compounds from which 3,9,10-trimethoxydibenz-[b,d]-pyran-6-one was isolated by prep. TLC (C_6H_6–EtOAc, 3:2, R_f 0.54). The product **8** crystallized from EtOH as colourless needles (3 mg; 8%), mp 193–194°. Lit. [6] 193–194°; MS $[M]^+$ *m/z* 286 and ^{1}H NMR identical to the natural compound and to that in lit [6].

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