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SYNTHESIS OF MELANERVIN FROM *MELALEUCA QUINQUENERVIA*, THE FIRST NATURALLY OCCURRING COMPOUND WITH A TRIPHENYLMETHANE STRUCTURE[1]

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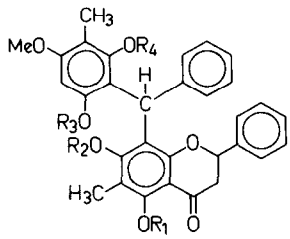
Abstract—Melanervin from *Melaleuca quinquenervia*, the first naturally occurring compound with a triphenylmethane structure, has been synthesized and its structure thereby confirmed.

In two preceding publications[2,3] we have described the isolation and structure elucidation of melanervin, a new flavonoid type from *Melaleuca quinquenervia*. The structure of melanervin could be determined as 8-(2″,6″-dihydroxy - 4″ - methoxy - 3″ - methyl) - diphenylmethyl - strobopinin (**1**) mainly by spectroscopic investigations and a GC–MS analysis of its degradation products. Since melanervin represents a hitherto unique structure type and some alternative structures with regard to the substitution pattern were also tenable, an unambiguous structure proof by synthesis was imperative.

We conceived a synthetic route which in addition to furnishing the structure proof of melanervin enabled us to synthesize the stereoisomers of melanervin also and thereby establish the absolute configurations at both chiral centers C-2 and C-9.

Therefore it seemed to be favourable to synthesize the flavanone part and the complex substituted diphenyl residue independently, followed by a coupling of the two moieties. In this case, according to the literature,[4,5] however, the coupling of the diphenyl residue with the flavanone molecule was the crucial point of the synthesis. Therefore, we studied this reaction by coupling the readily available naringenin **7** with benzhydrol in the presence of BF_3-etherate according to the conditions of Lasswell and Hufford.[6] This reaction resulted in a mixture of three main components, which could be separated by tlc. The compound with the highest R_f-value (0.65) was the 6,8-bis-diphenyl-methyl-naringenin (**8**), whereas the polar components turned out to be a mixture of mono substituted naringenin derivatives (**10**, **11**), which could be further separated in their peracetylated form. The structure proof of the substitution pattern could be derived from NMR-spectroscopic investigations and from the diphenylmethyl ion fragment observed in the MS, which is also characteristic for melanervin (**1**).[2]



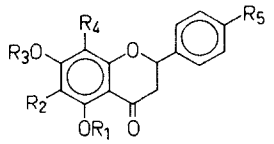
	R_1	R_2	R_3	R_4
1	H	H	H	H
2	Ac	Ac	Ac	Ac
3	Me	H	Me	Me
4	Me	Me	Me	Me
5	Me	H	$PhCH_2$	$PhCH_2$
6	H	H	$PhCH_2$	$PhCH_2$

Fig. 1.

The model reaction showed that a higher yield (75%) of the coupling product could be achieved carrying out the reaction at room temperature. Moreover it was remarkable that neither a coupling reaction took place at the C-atom adjacent to the 4′-hydroxy-group in the side phenyl ring of naringnin (**7**), nor any further rearrangement reaction of the diphenylmethyl-carbonium ion[7,8] took place. The substitution at C-6 seemed to be favoured since analysis showed a mixture of **12**/**13** in the proportion 4:1. In order to confirm the basic structure and the substitution pattern of melanervin, we tried first to synthesize racemic melanervinchalcone-pentamethylether (**16**), which we had previously obtained by permethylation of natural melanervin with dimethylsulfate.[2,3] The starting material was racemic 5-0-methyl-strobopinin (**14**), which was synthesized by a modified method of Seshadri *et al.*[10]†

Condensation of **14** with 2,4,6-trimethoxy-3-methyl-diphenylcarbinol (**23**) using the above mentioned reaction conditions gave **3** in 78% yield. **23** was obtained by $LiAlH_4$-reduction of the benzophenone **17**.[19] Subsequent methylation of the diasteriomeric mixture with dimethylsulfate in 5% NaOH resulted in the chalcone **16**, which was identical in its m.p., IR-, MS- and NMR-spectra with the permethylether obtained from natural melanervin.

†The 6-C-methyl-flavanone structure of strobopinin and its derivatives has never been established unequivocally by Whalley,[9] Seshadri[10] and others.[11–14] We have carried out this confirmation on the basis of NOE experiments.[15] A 14–16% increase in the intensity of the methoxyl-signal in 5-0-methyl-strobopinin is observed on irradiation of the C-methyl signal confirming the proposed structure.



	R_1	R_2	R_3	R_4	R_5
7	H	H	H	H	OH
8	H	Ph_2CH	H	Ph_2CH	OH
9	Ac	Ph_2CH	Ac	Ph_2CH	OAc
10	H	Ph_2CH	H	H	OH
11	H	H	H	Ph_2CH	OH
12	Ac	Ph_2CH	Ac	H	OAc
13	Ac	H	Ac	Ph_2CH	OAc
14	Me	Me	H	H	H
15	H	Me	H	H	H

Fig. 2.

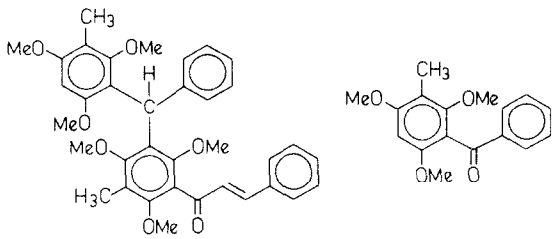


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Fig. 3.

As a side product the permethylated flavanone derivative (**4**) was also obtained. In contrast to natural melanervin the same compound could also be obtained by methylation of **3** with dimethylsulfate in acetone in the presence of potassium carbonate. For the synthesis of **1**, first the carbinol **24** was synthesized in 6 steps in a total yield of 15.9% starting from 2,4,6-trihydroxy-3-methyl-benzophenone.[16] The benzophenone was O-alkylated under mild conditions with chloro-dimethylether to **18** and subsequently benzylated to **19**. Cleavage of the methoxymethyl groups led in high yield (89%) to the dihydroxy-derivative (**20**), which gave on careful methylation **21**. Subsequent benzylation of **21** gave the ether **22**, which was reduced with $LiAlH_4$ under usual conditions to carbinol **24**.

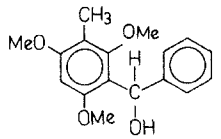

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Fig. 5.

This carbinol was condensed with 5-methyl-strobopinin (**14**) to yield **5** following the procedure described above. Compound **5** was obtained by repeated crystallization from methanol as a chromatographically pure substance with a sharp melting point of 158–160°.

The ^{1}H-NMR-spectrum confirmed the structure and showed that **5** was a diastereoisomeric mixture with predominance of one pair of enantiomers in the proportion 2:1 as calculated from the integration values of the signals of H-9 (δ = 6.33 and 6.36 ppm) and H-5″ (δ = 6.71 and 6.78 ppm).[17]

As partial demethylation of **5** according to the method of Seshadri[10] resulted in a rather poor yield (29%), we demethylated **14** to **15** (90%) and repeated the condensation of the latter with carbinol **24** to give rise to **6** in a 75% yield, proving at the same time that ring isomerization has not taken place in the demethylation process.

According to ^{1}H-NMR-spectra **6** is a diastereomeric mixture as well, which could not be separated by chromatography or by repeated crystallization.

Debenzylation of **6** resulted in racemic melanervin (**1**), from which after several crystallizations using a benzene–hexane mixture a compound with a sharp melting point of 182° could be obtained. The spectral properties (NMR, IR and MS) of this compound were in complete agreement with those of the natural product, thus supporting our success in obtaining one of the enantiomeric pairs in perfect purity.

After the successful synthesis of racemic melanervin via compounds **15**, **6** and **1** we adopted the method also for the synthesis of (−)-melanervin using (−)2S-strobopinin[18] as the starting compound, in order to establish the absolute configuration of natural melanervin at C-2 and C-9. The details of this synthesis and the corresponding CD-studies will be reported elsewhere.

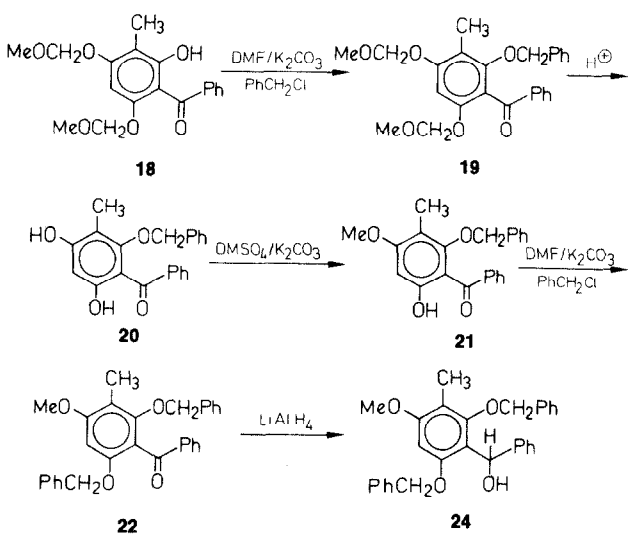

Fig. 4.

EXPERIMENTAL

General. Mps were determined on a Kofler apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR-spectra were measured on VARIAN A-60A at 60 MHz and Bruker-WP 80 at 80 MHz using TMS as internal reference. Mass-spectra were measured with MS 30 or AEI, IR-spectra with Beckman IR-8 and the CD-spectra with a Dichrograph II (Jonan-Jobin-Yvon-ISa) at conc. of about $1–1.5 \cdot 10^{-4}$ (mol/l.) at room temperature.

6,8-Bis-diphenylmethyl-naringenin (**8**)

To a soln of **7** (0.870 g, 3.20 m) and benzhydrol (0.588 g, 3.20 mM) in 50 ml anhydrous dioxane were added 5 ml BF_3-etherate with stirring under exclusion of H_2O at room temp. After 1 hr the soln was diluted with 50 ml ether and washed 5 times with H_2O (5 × 20 ml). The organic layer was dried (Na_2SO_4) and then concentrated. The reaction mixture was separated by column chromatography (Kieselgel, toluene–EtOAc 8:2) to give after crystallisation from n-hexane-toluene (2:1) **8** in colourless needles (0.364 g, 25%) m.p. 212–4°, R_f 0.65 in toluene–EtOAc (8:2). ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.50–3.20 (m, 2H, CH_2-3); 5.20 (dd, J = 10 Hza. 5 Hz, 1H, CH-2); 5.80 (br s, 1H, 7-OH); 5.89, 6.14 (s, 2H,6,8-CH-PH_2); 6.70 (d, J = 9 Hz, 2H, H-3′, 5′); 6.98 (d, J = 9 Hz, 2H, H-2′6′); 7.13, 7.16, 7.24 (s, 20 H, Ph); 13.43 (s, 1H, 5-OH). MS(st 200°, pt 180°, 70 eV, R 1000, 4 KV) *m/z* (rel. int.) 604 M^+ (66), 484 (40), 455 (33), 407 (6), 377 (12), 167 (100) 91 (61). (Found: C, 81.44; H, 5.27; Calc. for $C_{41}H_{32}O_5$ (604.4): C, 81.47; H, 5.29%.)

6,8-Bis-diphenylmethyl-naringenin-triacetate (**9**)

Compound **8** (0.1 g) was acetylated with acetic anhydride in pyridine to yield **9** from EtOH (0.057 g, 42%) m.p. 111–3°. ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.90, 192 (s, 6H, 5,7-OAc); 2.32 (s, 3H, 4′-OAc); 2.47–3.10 (m, 2H, CH_2-3); 5.20 (dd, J = 10 Hz, a5 Hz, 1H, Ch-2); 5.65 (s, 2H, CH-Ph_2); 6.60–7.50 (bm, 14 H, Ph.a.H-2′3′5′6′). (Found: C, 77.25; H, 5.17; Calc. for $C_{47}H_{38}O_8$ (730.1): C, 77.30 H, 5.20%.)

8-Diphenylmethyl-naringenin-triacetate (**12**) *and 6-diphenyl-methyl-naringenin-triacetate* (**13**)

Further column chromatography of the reaction mixture **8** led to a mixture of **10** and **11** (4:1), (0.735 g, 50%) R_f = 0.52. Acetylation of this mixture with aceticanhydride and pyridine and subsequent column chromatography on Kieselgel in toluene–EtOAc (8:1) gave **12** and **13**. **12**: (0.353 g, 38%) m.p. 110–13° from 90% MeOH, R_f = 0.27. ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.83 (s, 3H, 7-OAc); 2.18 (s, 3H, 5-OAc; 2.35 (s, 3H, 4′-OAc); 2.60–3.27 (m, 2H, CH_2-3); 5.50 (dd, J = 10 Hz.a.5 Hz, 1H, CH-2); 5.78 (s, 1H, CH-Ph_2); 6.80 (s, 1H, H-8); 7.08–7.52 (bm, 14H, Ph.a.H-2′,3′,5′,6′). **13**: (0.09 g, 10%) m.p. 163–5° from n-hexane–benzene, R_f = 0.20. ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.78 (s, 3H, 7-OAc); 2.30 (s, 3H, 4′-OAc); 2.38 (s, 3H, 5-OAc); 2.55–3.17 (m, 2H, CH_2-3); 5.35 (dd, J = 10 Hz a.5 Hz, 1H, CH-2); 5.90 (s, 1H, CH-Ph_2); 6.57 (s, 1H, H-6); 6.90–7.40 (bm, 14H, Ph = a.H-2′, 3′, 5′, 6′).

7-Hydroxy-5-methoxy-6-methyl-flavanone (**14**)

To a soln of 2,4-dihydroxy-6-methoxy-5-methyl-acetophenone (0.5 g, 2.55 mM) benzaldehyde (0.5 ml) and EtOH (5 ml), KOH (4 g) in H_2O (3 ml) were added and the mixture stirred for 24 hr under N_2-atmosphere and room temp. We added further 3 ml benzaldehyde after 4 hr, diluted the soln with H_2O (20)ml and extracted once with ether to remove the excess benzaldehyde. After that the soln was acidified with 10% HCl (pH 5), extracted with ether and washed first with 2% $NaHCO_3$-soln, then with H_2O, dried (Na_2SO_4) and concentrated. The residue was crystallised from toluene to give white crystals (0.470 g, 65%) m.p. 205–7° (lit.[9] 205–6°). IR (KBr) $\tilde{\nu}$ = 1800 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.10 (s, 3H, CH_3-6); 2.7–3.02 (m, 2H, CH_2-3); 3.78 (s, 3H, O-CH_3); 5.40 (dd, J = 10 Hz a.5 Hz, 1H, CH-2); 7.4 (s, 5H, Ph); 9.71 (br, 1H, OH-7) NOE:OCH_3 = 15% (irr. at 2.1018 ppm). (Found: C, 71.81; H, 5.60; Calc. for $C_{17}H_{10}O_4$ (284.10): C, 71.81; H, 5.67%.)

5,7-Dihydroxy-6-methyl-flavanone, (±)-stropopinin (**15**)

14 (0.165 g, 0.58 mM) was dissolved in abs, acetonitrile (48 ml), $AlCl_3$ (0.33 g) added and the soln heated for 1 hr. After usual work up the crude product was crystallised from MeOH yielding colourless needles (0.142 g, 90%) m.p. 232–3° (lit.[9] 232°). ^{13}C-NMR (DMSO-d_6) δ (ppm) 45.7 (C-3), 79.1 (C-2), 99.6 (C-8), 109.4 (C-10, $J_{C10,5\text{-}OH}$ = 4.6 Hz), 112.7 (C-6, $J_{C6,5\text{-}OH}$ = 3.6 Hz), 126.2 (C-2′, 6′), 128.7 (C-3′4′5′), 139.0 (C-1′), 160.6 (C-9, J_{C9H_8} = 3.8 Hz), 161.4 (C-7), 162.3 (C-5), 189.3 (C-4). (Found: C-71.08; H, 5.14; Calc. for $C_{16}H_{14}O_4$ (270.1): C, 71.13; H, 5.18%.)

2,4,6-Trimethoxy-3-methyl-diphenylcarbinol (**23**)

2,4,6-Trimethoxy-3-methyl-benzophenone[19] (0.1 g, 0.36 mM) was reduced with $LiAlH_4$ (20 mg) in ether (40 ml) at room temp. After usual work up the carbinol crystallised from acetone in fine white needles, (0.095 g, 96%) m.p. 94°. IR (KBr) $\tilde{\nu}$ = 3585 cm^{-1} (OH). ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.10 (s, 3H, CH_3Ar); 3.48, 3.75, 3.85 (s, 9H, OCH_3); 4.07 (d, J = 11 Hz, 1H, OH); 6.20 (d, J = 11 Hz, 1H, CH); 6.36 (s, 1H, H-5); 7.18–7.49 (m, 5H, Ph). (Found: C, 70.74; H, 6.94; Calc. for $C_{17}H_{20}O_4$ (288.3): C, 70.81; H, 6.99%.)

2,4,6 - Trimethoxytolyl - 3 (5 - methoxy - 6 - methyl - 7 - hydroxy) - flavanonyl - 8 - phenylmethan (**3**)

23 (0.15 g, 0.52 mM) and **14** (0.09 g, 0.32 mM) were dissolved in dried dioxane (20 ml). After adding BF_3-etherate (0.8 ml) dropwise the soln was stirred for 3 hr at room temp. After work up according to **8**, the resulting compound **3** was purified by preparative thin layer chromatography using the solvent system n-hexane–ether–acetone (5:5:1) to give a light yellow amorphous product (0.23 g, 78%) m.p. 123–8°. IR (KBr) $\tilde{\nu}$ = 3290 cm^{-1} (OH), 2940 (Ar), 1670 (C=O), 1540, 1490, 1415 (Ar). MS (st 200°, pt 150°, 70 eV, R 3000, 4 KV) *m/z* (rel. int.) M^+ 554 (8), 373 (16), 372 (58), 371 (16), 268 (15), 267 (23), 225 (16), 183 (15), 182 (100), 91 (17). (Found: C, 73.61; H, 6.10; Calc. for $C_{34}H_{34}O_7$ (554.3): C, 73.67; H, 6.13%.

2,4,6-Trimethoxytolyl-3-(2′, 4′, 6′-trimethoxy-3′methyl)-chalconyl-5′-phenylmethane (**16**) *and 2,4,6-trimethoxy-tolyl-3-(5,7-dimethoxy-6-methyl)-flavanonyl-8-phenylmethane* (**4**)

3 (0.2 g, 0.36 mM) was heated for 7 hr under reflux in EtOH (2 ml) with 5% NaOH (4 ml) and dimethylsulfate (2 ml). To the reaction mixture H_2O was added and the soln extracted with ether. The ether phase was washed with H_2O, dried, concentrated and then separated on Kieselgel plates using the solvent system n-hexane–ether–acetone (5:5:1) to yield **16** (19 mg, 9%) m.p. 70–5° (lit.[3] 70–5°), R_f = 0.60. IR (KBr) $\tilde{\nu}$ = 2930, 2820 cm^{-1} (CH), 1640 (CO), 1580 (Ar), 1100 (CO), 690 (Ar). ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.10 (s, 3H), 2.19 (s, 3H, CH_3Ar); 3.16, 3.22, 3.50, 3.71, 3.81 (s, 18H, OCH_3); 6.82, 6.31 (s, 2H, CH-9, Ar–H); 6.95 (d, J = 16 Hz, 1H, CH-α); 7.0–7.5 (m, 11H, Ph); 7.41 (d, J = 16 Hz, 1H, CH-β), MS (st 200°, pt 150°, 70 eV, R 1000, 4 KV) *m/z* (rel. int.) M^+ 582 (100), 568 (22), 567 (59), 552 (16), 551 (37), 536 (37), 535 (75), 519 (10), 459 (7), 431 (6), 401 (3), 271 (11), 270 (33), 255 (9), 239 (30), 227 (7), 195 (35), 193 (35), 179 (12), 165 (24), 131 (45), 117 (22), 105 (15), 103 (43), 91 (76), 77 (22), 44 (76). (Found: C, 73.51; H, 6.61; Calc. for $C_{36}H_{38}O_7$ (582.66): C, 74.20; H, 6.57%.) **4** (0.06 g, 30%); m.p. 142–54°, from MeOH, R_f = 0.45. ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.06, 2.16 (s, 6H, Ch_3–Ar); 2.70–2.82 (m, 2H, CH_2-3); 3.08, 3.19, 3.24, 3.39, 3.80, 3.83 (s, 15H, OCH_3); 5.13 (dd, J = 5 Hz a.10 Hz, 1H, H-2); 6.09 (s, 1H, CH-9); 6.30 (s, 1H, H-3″); 6.78–7.35 (m, 10 H, Ph). (Found: C, 73.91; H, 612; Calc. for $C_{35}H_{36}O_7$ 586.4): C, 73.96; H, 6.33%.)

2-Hydroxy-3-methyl-4,6-dimethoxymethyl-benzophenone (**18**)

2,4,6-Trihydroxy-3-methyl-benzophenone[16] (1.952 g, 8.00 mM) was dissolved in anhydrous acetone, and after adding K_2CO_3 (32 g), a soln of chlorodimethylether (1.6 ml) in dried acetone (64 ml) was added dropwise stirring 1 hr. The soln was diluted with H_2O (500 ml), neutralised with 5% HCl and then extracted with $CHCl_3$. The $CHCl_3$-phase was washed with H_2O, dried ($MgSO_4$), evaporated and the residue purified on a silicagel column, eluent toluene–EtOAc (9:1) to yield **18** (1.45 g, 55%) as yellow oil, R_f = 0.54. ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.11 (s, 3H, CH_3); 3.11, 3.49 (s, 6H, 2 OCH_3); 4.74 (s, 2H, OCH_2-6); 5.24 (s, 2H, OCH_2-4); 6.40 (s, 1H, H-5); 7.25–7.70 (m, 5H, Ph); 12.48 (s, 1H, OH-2); MS (st 200°, pt 180°, 70 eV, R 1000, 4 KV) *m/z* (rel.

int.) M^+ 332 (100), 301 (17), 300 (30), 271 (11), 269 (11), 257 (14), 256 (18), 255 (45), 241 (12), 227 (18), 197 (12), 196 (50), 195 (11), 166 (12), 165 (12), 164 (11), 137 (12), 129 (15), 115 (18), 106 (50), 105 (71), 91 (42), 83 (15), 77 (26), 69 (18), 65 (14), 62 (11), 55 (14), 54 (12), 53 (15), 52 (42), 50 (27), 46 (50), 45 (61), 44 (50), 43 (20), 41 (14), 40 (18), 39 (27).

2-Benzyloxy-3-methyl-4,6-dimethoxymethyl-benzophenone (**19**)

To a soln of **18** (1.269 g, 3.82 mM) in DMF (16 ml) benzylchloride (0.51 ml, 4.50 mM) and K_2CO_3 (1.65 g) were added and the mixture refluxed under stirring for 25 min. After addition of H_2O (400 ml) the soln was extracted with $CHCl_3$, the $CHCl_3$ phase dried and evaporated, to yield an orange, chromatographically pure oil (1.58 g, 97%). $R_f = 0.61$ in toluene–EtOAc (85:15). ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.16 (s, 3H, CH_3); 3.25 (s, 3H, OCH_3-6); 3.52 (s, 3H, OCH_3-4); 4.79, 5.01, 5.23 (s, 6H, 3 OCH_2); 6.79 (s, 1H, H-5); 7.21 (s, 5H, Ph); 7.34–7.59 (m, 3H, H-3′, 4′, 5′); 7.77–8.0 (m, 2H, H-2′, 6′). (Found: C, 70.60; H, 6.24; Calc. for $C_{25}H_{26}O_6$ (422.2): C, 71.07; H, 6.20%.)

2-Benzyloxy-3-methyl-4,6-dihydroxy-benzophenone (**20**)

19 (1.62 g, 3.83 mM) was dissolved in MeOH (16 ml) and after adding 10% HCl (16.2 ml) the soln was heated for 40 min under reflux. The mixture was diluted with H_2O, extracted with $CHCl_3$ and the organic soln washed with H_2O, dried ($MgSO_4$) and evaporated. The residue was crystallised from a mixture of n-hexane–benzene (2:1) to yield colourless needles (1.14 g, 89%) m.p. 155°. ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.0 (s, 3H, CH_3); 4.40 (s, 2H, OCH_2); 6.41 (s, 1H, H-5); 6.58–7.28 (m, 5H, Ph); 7.31–7.55 (m, 3H, H-3′, 4′5′); 7.58–7.83 (m, 2H, H-2′, 6′); 11.42 (s, br, 6 Hz, 1H, OH-6). MS (st 200°, pt150°, 70 eV, R1000, 4 KV) *m/z* (rel. int.) M^+ 334 (50), 33 (10), 316 (11), 244 (12), 243 (38), 229 (45), 194 (23), 167 (13), 166 (11), 106 (12), 105 (100), 92 (50), 91 (95), 77 (53), 69 (16), 65 (14), 51 (16), 41 (10). (Found: C, 74,51; H, 5.42; Calc. for $C_{20}H_{18}O_4$ (322.2): C, 74.56; H, 5.58%.)

2-Benzyloxy-3-methyl-4-methoxy-6-hydroxy-benzophenone (**21**)

A soln of **20** (1.146 g, 3.43 mM) in acetone (100 ml), K_2CO_3 (1 g) and dimethyl-sulfate (0.34 ml, 3.50 mM) was heated for 10 min under stirring. The soln was filtered, evaporated and the residue purified on a silicagel column, eluant toluene–EtOAc (95:15) to yield a colourless oil (1.19 g, 96%), $R_f = 0.69$ in toluene–acetone (9:1). ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.98 (s, 3H, CH_3); 3.88 (s, 3H, OCH_3); 4.38 (s, 2H, OCH_2); 6.38 (s, 1H, H-5); 6.50–7.28 (m, 5H, Ph); 7.31–7.55 (m, 3H, H-3′, 4′, 5′); 7.59–7.83 (m, 2H, H-2′, 6′); 11.49 (s, br, 1H, OH). (Found: C, 74.69; H, 5.87; Calc. for $C_{21}H_{20}O_4$ (336.2): C, 75.02; H, 5.94%.)

2,6-Dibenzyloxy-3-methyl-4-methoxy-benzophenone (**22**)

21 (1.2 g, 3.44 mM) was dissolved in 40 ml DMF and heated with K_2CO_3 (1 g) and benzylchloride (0.45 ml, 3.90 mM) under reflux and stirring for 20 min. After usual work up the resulting product was crystallised from 80 ml MeOH. Colourless prisms, (0.773 g, 51%), m.p. 146–7°. ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.11 (s, 3H, CH_3); 3.81 (s, 3H, OCH_3) 4.83 (s, 4H, $2OCH_2$); 6.38 (s, 1H, H-5); 6.92–7.32 (m, 10 H, 2 Ph); 7.32–7.58 (m, 3H, H-3′, 4′, 5′); 7.74–7.99 (m, 2H, H-2′, 6′). (Found: C, 79.13; H, 6.12; Calc. for $C_{29}H_{26}O_4$ (438.50): C, 79.43; H, 5.98%.)

2,6-Dibenzyloxy-3-methyl-4-methoxy-diphenylcarbinol (**24**)

22 (0.75 g, 1.70 mM) in ether (220 ml) was reduced with $LiAlH_4$ (0.2 g, 5.40 mM) at room temp. for 1 hr. The usual work up gave the carbinol (**24**) from MeOH as white needles. (0.701 g, 93%) m.p. 119°. ^{1}H-NMR ($CDCl_3$) δ (ppm) 2.13 (s, 3H, CH_3); 3.79 (s, 3H, OCH_3); 4.64 (dd, J = 11 a. 14 Hz, 2H, CH_2–O); 4.97 (dd, J = 11 a. 14 Hz, 2H, CH_2–O); 6.26 (s, 1H, CH–O); 6.39 (s, 1H, H-5); 6.98–7.47 (m, 15H, 3Ph). MS (st 210°, pt 150°, 70 eV R1000, 4 KV) *m/z* (rel. int.) M^+ 440 (45), 349 (14), 335 (14), 334 (34), 333 (91), 331 (100), 315 (11), 258 (16), 257 (36), 243 (27), 242 (30), 241 (95), 240 (30), 213 (14), 181 (30), 180 (14), 178 (16), 152 (11), 106 (14), 105 (91), 92 (91), 91 (91), 90 (11), 89 (16), 79 (14). (Found: C, 78.98; H, 6.50; Calc. for $C_{29}H_{28}O_4$ (440.51): C, 79.07; H, 6.41%.)

(2,4-Dibenzyloxy-6-methoxy)-tolyl-3-(7-hydroxy-6-methyl-5-methoxy)-flavanonyl-8-phenylmethane (**5**)

To a soln of **24** (0.155 g, 0.352 mM) and **14** (0.2 g, 0.704 mM) in anhydrous dioxane, BF_3-etherate (0.352 ml) in dioxan (5 ml) was added dropwise with stirring at room temp. and the mixture stirred another 0.5 hr. After usual work up the reaction product was separated on silicagel plates in the system toluene–EtOAc (9:1) to yield from MeOH the condensation product **5** (0.207 g, 83%) m.p. 158–60° besides 0.108 g of the non-condensed flavanone **14**. IR (KBr) $\tilde{\nu} = 3300\ cm^{-1}$ (OH), 2860 (CH arom.), 1665 (C=O), 1585, 1490, 1450 (Ar). ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.93, 2.01, 2.10 (s, 6H, CH_3-6, 1″); 2.50–2.84 (m, 2H, CH_2-3); 3.72, 3.79, 3.82 (s, 6H, OCH_3-5, 6″); 4.21–4.42 (m, 2H, CH_2-O); 4.72–4.98 (m, 2H, CH_2); 5.27 (dd, J_{aa} = 6 Hz, J_{aa} = 10 Hz, 1H, H-2); 6.33, 6.36 (s, 1H, H-9); 6.71, 6.78 (s, 1H, H-5″); 6.83–7.39 (m, 20 H, 4 Ph). (Found: C, 78.43; H, 6.04; Calc. for $C_{46}H_{12}O_7$ (706.8): C, 78.17; 5.99%.)

(2,4-Dibenzyloxy-6-methoxy)-tolyl-3-(5,7-dihydroxy-6-methyl)-flavanonyl-8-phenyl-methane (**6**)

(a) **5** (0.14, 0.198 mM) and $AlCl_3$ (0.3 g) were dissolved in dried acetonitrile (80 ml) and heated under reflux for 15 min. The usual work up yielded a crude product (0.18 g), which was purified by preparative tlc using the solvent system toluene–EtOAc (79:3) to yield from n-hexane–benzene **6** (0.04 g, 29%) m.p. 169.75°.

(b) **15** (see above) (0.08 g, 0.29 mM) and **24** (0.15 g, 0.29 mM) were dissolved in dioxane (10 ml) and BF_3-etherate (0.3 ml) in dioxane (5 ml) added dropwise with stirring for 1 hr at room temp. Usual work up yielded a reaction product (0.22 g), which was purified by silicagel plate chromatography to yield **6** (0.150 g, 75%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.94, 1.95, 2.03, 2.12 (s, 6H, CH_3-6, 1″); 2.50–2.89 (m, 2H, CH_2-3); 3.73, 3.76 (s, 3H, OCH_3); 4.23–4.45 (m, 2H, CH_2-O); 4.67–4.91 (m, 2H, CH_2-O); 5.29 (dd, J = 6 a. 10 Hz, 1H, H-2); 6.33, 6.37 (s, 1H, H-9); 6.67, 6.72 (s, 1H, H-5″); 6.88–7.41 (m, 20 H, 4 Ph); 12.15, 12.18 (s, 1H, OH-5). (Found: C, 76.13; H, 5.78; Calc. for $C_{45}H_{40}O_7$ (692.82): C, 78.02; H, 5.82%.)

(2,4-Dihydroxy-6-methoxy)-tolyl-3-(5,7-dihydroxy-6-methyl)-flavanonyl-8-phenylmethane (**1**), (±) *melanervin*

6 (0.09 g, 0.13 mM) was dissolved in MeOH (10 ml) and hydrogenated in the presence of 0.15 g 10% Pd–C at room temp. After filtration and concentration of the solvent 0.051 g (76%) of the reaction product was obtained. The substance showed chromatographic identity with natural (−)-melanervin on silicagel in 3 solvent systems (toluene–EtOAc 9:1, $R_f = 0.27$; benzene–ether–acetone 5:5:1, $R_f = 0.35$, and dichlorethane–EtOAc-aceticanhydride, 8:1:1, $R_f = 0.79$. Crystallisation from benzene-n-hexane yielded colourless crystals, m.p. 182°. IR (KBr) $\tilde{\nu} = 3410\ cm^{-1}$ (OH), 1620 (C=O), 1440, 1120 (CO), 798, 763, 727, 693 (Ar). ^{1}H-NMR (DMSO-d_6, 120°) δ (ppm) 1.92 (s, 3H): 1.97 (s, 3H, CH_3-3″, 6); 2.80–3.23 (m, 2H, CH_2-3); 3.73 a. 3.74 (s, 3H, OCH_3); 5.52 (dd, J = 10 a. 5 Hz, CH-2); 6.18 (s, 1H, CH-9); 6.63 (s,1H, H-3″); 7.15 (s, br, 5H, Ph‴); 7.35 (s, 5H, Ph′); 9.88 (br, 3H, OH-2″, 6″, 7); 12.60 (s, 1H, OH-5). MS (st 130°, pt100°, 70 eV, R1000, 4 KV) *m/z* (rel. int.) M^+ 512 (6), 494 (1), 417 (7), 360 (18), 359 (17), 358 (18), 357 (16), 330 (24), 329 (23), 270 (100), 269 (56), 253 (24), 243 (21), 242 (58), 241 (59), 227 (18), 193 (91), 167 (36), 154 (50), 153 (29), 139 (25), 138 (81), 123 (23),110 (21), 104 (26), 103 (26), 91 (47), 77 (29), 69 (33), 55 (25), 51 (25), 51 (26), 39 (27). (Found: C, 72.67; H, 5.41; Calc. for $C_{31}H_{28}O_7$ (515.58; C, 72.64; H, 5.50%.)

(2,4-Diacetoxy-6-methoxy)-tolyl-3-(5,7-diacetoxy-6-methyl)-flavanonyl-8-phenylmethane (**2**), (±) *melanervin-tetraacetate*

1 (0.03 g, 0.058 mM) was acetylated with acetic anhydrice (1.5 ml) and pyridine (1.5 ml) at room temp. The raw product was crystallised twice from n-hexane and then from 90% EtOH to yield needles (4 mg), m.p. 185–7°. ^{1}H-NMR ($CDCl_3$) δ (ppm) 1.55, 1.66, 1.84, 1.85 a. 1.87 (s, 15H, OAc, $ArCH_3$); 2.43 (s, 3H, 5-OAc); 2.70–3.25 (m, 2H, CH_2-3); 3.75, 3.79 (s, 3H, OMe); 5.25 (dd, J = 5 a. 12 Hz, CH-2); 5.92 (s, 1H, CH-9); 6.16, 6.34 (s, 1H, ArH); 6.92–7.40 (m, 10 H, Ph). MS (st 260°, pt 100°, 70 eV, R1000, 4 KV) *m/z* (rel. int.) M^+ 680 (6), 638 (24), 596 (42), 595 (100), 576 (35), 553 (30), 535 (42), 389 (21), 241 (30), 131 (20). (Found: C, 68.62; H, 5.28; Calc. for $C_{36}H_{36}O_{11}$ (680.3): C, 68.81; H, 5.33%.)

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[17]An isomerisation due to hindered rotation along the C-8, 9 axis is not likely since no such effect could be observed in the ^{1}H-NMR-spectrum of **16** at room temp. Furthermore in a Dreiding model no great hindrance of rotation could be seen for **1–6** compared with **16** and in the ^{1}H-NMR-spectrum of **1–3** and **6** no splitting of a methoxy-signal could be observed even at higher temperature (60–120°).
[18]10 mg(−)-strobopinin isolated from *Pinus strobus*, showed the following data: $[\alpha]_D^{24} = -44°$ (c = 0.9, MeOH). CD (Dioxan)λ_{max} ($\Delta\epsilon_{max}$) 329 (+0.82), 288 (−2.41), 240 (+0.65), 220 (+2.10). (−) **6**, m.p. 167.5–9.5° (benzene-n-hexane) CD (MeOH)λ_{max} ($\Delta\epsilon_{max}$) 343 (+1.4), 314 (+1.81), 294 (−12.51), 239 (−3.83). (−) **1**, CD (MeOH) 350 (+0.67), 315 (+1.52), 291 (−8.10), 245 (−8.54), 230 (−1.75).
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