Preparation of 4,6,3',4'-Tetrasubstituted Aurones *via* Aluminium Oxide-Catalyzed Condensation

David Bolek and Michael Gütschow*

Pharmaceutical Institute, Poppelsdorf, University of Bonn, Kreuzbergweg 26, D-53115 Bonn, Germany

Received May 2, 2005

4,6,3',4'-Tetrasubstituted aurones were prepared by a protection-deprotection route with an alumina-catalyzed condensation of 3(2*H*)-benzofuranones with substituted aldehydes as the key step. Aureusidin (**6**) was obtained by demethylation of 4,6,3',4'-tetramethoxyaurone (**5**), a natural product from *Cyperus capitatus*. 4,6,3',4'-Tetrabenzyloxyaurone (**9**) was converted in a one hydrogenation-deprotection step to dihydroaureusidin (**10**).

J. Heterocyclic Chem., **42**, 1399 (2005).

Aurones and auronols are naturally occurring 3(2*H*)-benzofuranone derivatives, biogenetically related to chalcones. Aurones, 2-benzylidene-3(2*H*)-benzofuranones, represent a group of plant products which are structurally isomeric to flavones. Aurones have a limited occurrence in fruits and vegetables and confer bright yellow color to flowers such as *Antirrhinum, Cosmos*, and *Coreopsis*. In recent years, these compounds have received much attention, due to their promising biological activities. Noteworthy, in several cases aurones were reported to be more active than the equally substituted chalcone and flavone derivatives [1].

The affinity of aurones, particularly 4-hydroxy-6-methoxyaurones, towards the C-terminal nucleotide-binding domain of P-glycoprotein was reported [2]. Among several flavonoids tested for their ability to modulate P-glycoprotein-mediated multidrug resistance *in vitro*, 4,6-dimethoxyaurone exhibited a potent reversing activity [3]. Aurones have also been designed to mimic flavopiridol, an inhibitor of cyclin-dependent kinases, and derivatives with 4-piperidinyl moieties at position 7 were more potent and selective than flavopiridol itself [4]. Several aurones showed a strong inhibition of rat liver microsomal type I iodothyronine deiodinase [5]. Moreover, aurones could be regarded as conformationally restricted analogues of bioactive chalcones, such as α-methyl-3-hydroxy-4,3',4',5'-tetramethoxychalcone, a potent inhibitor of tubulin polymerization [6]. Sulfuretin, 6-hydroxy-2-(3,4-dihydroxybenzylidene)-3(2*H*)-benzofuranone, a naturally occurring aglycon isolated from *Cotinus* was found to be a potent antioxidant in a free-radical scavenging assay [7].

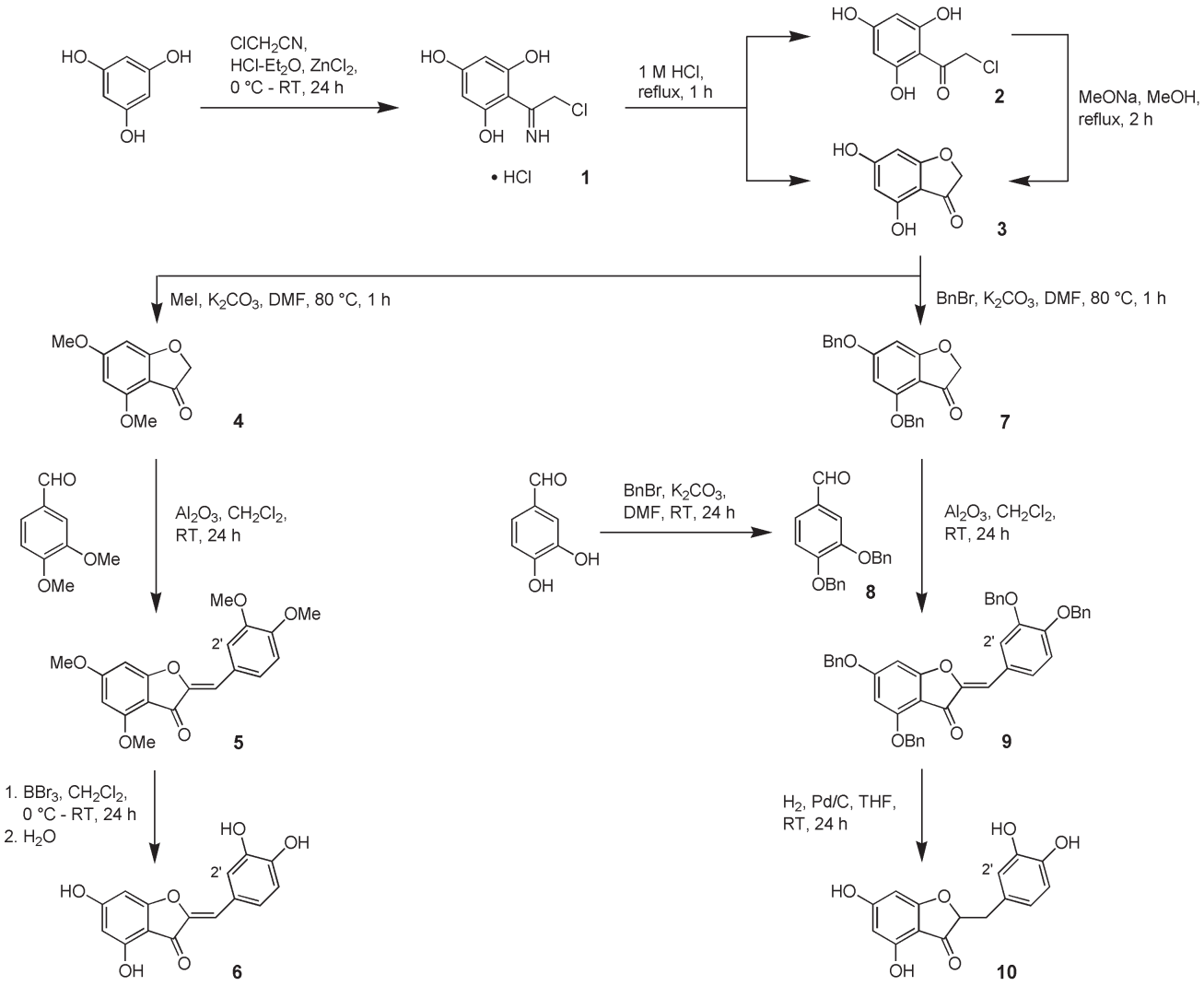
The biosynthesis of aurones includes the oxidative cyclization of corresponding chalcones, a process that is catalyzed by aureusidin synthase [8]. Aureusidin (**6**) is the best known aurone and has been isolated from several species of *Cyperus*. Aureusidin shares the hydroxy substitution pattern with the frequently cited flavonol quercetin, whose glycosides are highly abundant dietary flavonoids, the dihydroflavonol taxifolin, and the auronol alphitonin (= 2,4,6-trihydroxy-2-(3,4-dihydroxybenzyl)-3(2*H*)-benzofuranone). The latter compound has been identified as an intermediate of the quercetin degradation by the human intestinal bacterium *Eubacterium ramulus* [9]. We have recently reported on the synthesis of 2-benzyl-2-hydroxybenzofuran-3(2*H*)-one, the prototype of naturally occurring auronols [10]. Besides aureusidin (**6**), 4,6,3',4'-tetramethoxyaurone (**5**) was isolated from the rhizomes of *Cyperus capitatus* [11]. Herein, we describe a facile synthetic route to 4,6,3',4'-tetrasubstituted aurones including the closely related dihydroaureusidin (**10**), which has not been reported as a secondary plant metabolite thus far.

Main synthetic pathways to aurones are (i) *via* an oxidative ring closure of 2'-hydroxychalcones [1], *e.g*. by *Algar-Flynn-Oyamada* reaction [12], (ii) from α-halogen-β-alkoxy-dihydrochalcones (*Wheeler* reaction) [13], (iii) by silver(I) ion- or tetrakis(triphenylphosphine)palladium-catalyzed cyclization of phenylethinyl-(2-hydroxyphenyl) ketones [14], and (iv) condensation of benzofuran-3(2*H*)-ones with substituted benzaldehydes. The latter method was used for the syntheses presented in this report.

Following a report of Beney *et al*. [15], condensation of phloroglucinol with chloroacetonitrile was catalyzed by zinc chloride to give the iminium intermediate **1** in 52 % yield. We have isolated and characterized this salt, and nmr data (*e.g*. three distinct OH signals) revealed that the corresponding atoms of the trihydroxyphenyl substituent were not equivalent. This can be explained by a hydrogen bond interaction between the iminium nitrogen and the hydroxy oxygen of the phenyl group. The iminium salt **1** was hydrolyzed with aqueous hydrochloric acid to provide a 1:1 mixture of the acetophenone derivative **2** and its cyclized form, the benzofuranone **3**. The mixture was treated with sodium methoxide to quantitatively produce **3**. An analytical sample of **2** was separated from the mixture and showed equivalent nmr signals at positions 2, 6 and 3, 5 of the phenyl group, respectively. Treatment of **3** with methyl iodide yielded the protected benzofuranone **4**.

4,6,3',4'-Tetramethoxyaurone (**5**) was readily prepared in 73 % yield by condensation of **4** with 3,4-dimethoxybenzaldehyde on an alumina surface, according to a methodology of Varma and Varma [16]. The reaction was carried out in the dark in order to prevent a light-induced

Scheme 1



isomerization. As reported, the isolation of **5** from *Cyperus capitatus* led to a mixture of the (*E*)- and more stable (*Z*)-form which could not be separated [11]. The procedure described herein, exclusively yielded the pure (*Z*)-isomer, as determined by ^{1}H and ^{13}C nmr spectra. The values are consistent with those present in the literature for (*Z*)-aurones [10,11,15]. The assignment is mainly based on differences in the shift of the olefinic proton being around 6.70 ppm for the (*Z*)- and around 7.00 ppm for the (*E*)-isomer. It is also in agreement with literature data on the chemical shift of the C-2' hydrogen of **5** with a significantly lower value for the (*Z*)-isomer (δ = 7.55 ppm) than for the (*E*)-isomer (δ = 8.48 ppm) [11]. Accordingly, the nmr spectra of the tetrabenzyl derivative **9** (δ = 6.62 ppm, -CH=) revealed the occurrence of the (*Z*)-form. However, thin-layer chromatograms of **5** and **9** showed two spots indicating the aforementioned isomerization.

Demethylation of **5** to afford aureusidin (**6**) turned out to be difficult. A complete deprotection with boron tribromide (eight equivalents) was not attained and traces of a monomethylated byproduct had to be removed by recrystallization. Boumendjel *et al.* [2] reported on a selective demethylation at position 4 of 4,6-dimethoxyaurones using two equivalents boron tribromide in methylene chloride.

The benzofuranone **3** was also converted to the protected form **7**. Reaction of **3** with benzyl bromide afforded a product mixture which was fractionated by column chromatography to obtain **7**. The further synthetic route to dihydroaureusidin (**10**) involved the preparation of 3,4-dibenzyloxybenzaldehyde (**8**) and its condensation with **7** to produce the tetrabenzyloxy derivative **9** in 73 % yield. Again, this reaction was accomplished in the presence of basic aluminum oxide in a minimum amount of methylene chloride. The approach to combine hydrogenation and deprotection

into a one step to obtain the benzyl derivative **10** was successful. The reaction was performed on palladium/charcoal in tetrahydrofuran at room temperature, and only a single recrystallization was required to obtain the desired dihydroaureusidin (**10**). In the light of the biological activities of analogously substituted flavonoids, an evaluation of the potential of compound **10** appears particularly promising.

EXPERIMENTAL

Melting points were obtained on a Rapido Boetius apparatus and are uncorrected. The ir spectra were recorded on Bruker Tensor 27 FT-IR spectrometer. ^{1}H nmr spectra (500 MHz) and ^{13}C nmr spectra (125 MHz) were recorded on a Bruker Avance instrument. Mass spectra (70 eV) were obtained on a MS-50 A.E.I spectrometer. Elemental analyses were performed on a Vario EL apparatus. Thin-layer chromatography was carried out using aluminum sheets coated with silica gel 60 F_{254} (Merck). Chromatograms were detected by UV fluorescence and visualized with $FeCl_3$ (in 0.5 *M* hydrochloric acid) or I_2/KI (in ethanol/water 1:10) and 2 *N* hydrochloric acid. Column chromatography was performed with silica gel 60 G (Merck).

2-(2-Chloro-1-iminoethyl)-1,3,5-benzenetriol hydrochloride (**1**).

A solution of phloroglucinol (25.2 g, 200 mmoles) in anhydrous diethyl ether (125 ml) was prepared at 0 °C. Chloroacetonitrile (15.1 g, 200 mmoles), freshly glowed zinc chloride (0.9 g, 6.6 mmoles) and subsequently a solution of hydrogen chloride in anhydrous diethyl ether (1 *M*, 375 ml) was added. The mixture was stirred at 0 °C for 3 hours and additional 21 hours at room temperature. The precipitate was removed by filtration, washed with anhydrous diethyl ether (2 × 40 ml) and dried to give 24.8 g (52%) of **1** as a yellow solid, mp 230-233 °C; ^{1}H nmr (DMSO-d_6): δ 5.44 (s, 2H, CH_2), 6.08, 6.32 (each d, J = 1.9 Hz, 2H, H-3 and -5), 7.52 (s, 2H, NH_2^+), 9.87, 10.96, 12.59 (each s, total 3H, OH); ^{13}C nmr (DMSO-d_6): δ 76.1 (CH_2), 90.9, 97.9 (Ph C-3 and -5), 100.2 (Ph C-1), 161.3, 173.8, 174.5, 176.7 (C=NH_2^+, Ph C-2, -4 and -6).

Anal. Calcd. for $C_8H_9Cl_2NO_3$: C, 40.36; H, 3.81; N, 5.88. Found: C, 39.99; H, 3.82; N, 5.92.

2-Chloro-1-(2,4,6-trihydroxyphenyl)ethanone (**2**).

A mixture of the salt **1** (23.8 g, 100 mmoles) and 1 *M* hydrochloric acid (500 ml) was refluxed for 1 hour. The red solution was kept at 0 °C overnight, and the precipitate was collected by filtration, washed with ice-cold water (20 ml) and thoroughly dried *in vacuo* over phosphorus pentoxide to give 13.4 g of a mixture of the compounds **2** and **3** (in a relation of approximately 1:1 as determined by ^{1}H nmr). This mixture can be used without purification in the next step. The material was recrystallized three times from ethanol/water to obtain 1.0 g (5%) of **2** as a colorless solid, mp 207-208 °C, conversion 184-203 °C, ref [15] 185-187 °C; ^{1}H nmr (DMSO-d_6): δ 4.96 (s, 2H, CH_2), 5.83 (s, 2H, Ph H-3 and -5), 10.49 (s, 1H, OH), 12.03 (s, 2H, OH); ^{13}C nmr (DMSO-d_6): δ 51.0 (C-2), 94.9 (Ph C-3 and -5), 102.7 (Ph C-1), 164.1 (Ph C-2 and -6), 165.6 (Ph C-4), 194.8 (CO).

4,6-Dihydroxy-3(2*H*)-benzofuranone (**3**).

A mixture of **2** and **3** (in a molar relation of approximately 1:1) was prepared as described above. This mixture (5 g, approximately 27 mmoles) was added to a solution of sodium methoxide prepared from sodium (2.1 g, 91.3 mmoles) and methanol (50 ml). The red solution was refluxed over 2 hours and became violet. After evaporation under reduced pressure, the residue was partitioned between 1 *M* hydrochloric acid (180 ml) and ethyl acetate (60 ml). Insoluble material was separated by filtration and was pure product **3**. The aqueous phase was extracted with ethyl acetate (3 × 60 ml), the organic layers were combined, washed with water (90 ml) and brine (90 ml), dried over sodium sulfate and evaporated to dryness to obtain additional pure product **3** as a light-brown solid. Yield 4.0 g (89 %), mp 253-256 °C, ref 210-212 °C [15], 250-256.6 [17]; ^{1}H nmr (DMSO-d_6): δ 4.53 (s, 2H, CH_2), 5.90, 5.92 (each d, J = 1.85 Hz, 2H, H-5 and -7), 10.53, 10.54 (each s, total 2H, OH); ^{13}C nmr (DMSO-d_6): δ 74.9 (C-2), 90.3, 96.4 (C-5, C-7), 102.8 (C-3a), 157.6, 167.7, 175.8 (C-4, C-6, C-7a), 194.1 (CO).

4,6-Dimethoxy-3(2*H*)-benzofuranone (**4**).

Methyl iodide (12.8 g, 5.6 ml, 90 mmoles) was added to a mixture of **3** (5.0 g, 30 mmoles), potassium carbonate (8.3 g, 60 mmoles) and dimethylformamide (75 ml). The mixture was stirred at 80 °C for 1 hour. It was evaporated under reduced pressure, and the residue was partitioned between water (150 ml) and ethyl acetate (150 ml). Insoluble material was separated by filtration and was crude product **4**. The aqueous phase was extracted with ethyl acetate (1 × 150 ml, 2 × 60 ml), the organic layers were combined, washed with water (100 ml) and brine (100 ml), dried over sodium sulfate and evaporated to dryness to obtain additional crude product **4**. The combined crude material was recrystallized from ethyl acetate to obtain 2.6 g (45 %) of **4** as yellow crystals, mp 132-136 °C, ref [15] 132-133 °C; ^{1}H nmr (DMSO-d_6): δ 3.81, 3.84 (each s, total 6H, CH_3), 4.64 (s, 2H, CH_2), 5.88, 6.02 (each d, J = 1.7 Hz, 2H, H-5 and –7); ^{13}C nmr (DMSO-d_6): δ 55.9, 56.3 (CH_3), 75.4 (C-2), 89.5, 93.0 (C-5, C-7), 104.2 (C-3a), 158.4, 169.4, 176.4 (C-4, C-6, C-7a), 194.0 (CO).

(*Z*)-2-[(3,4-Dimethoxyphenyl)methylene]-4,6-dimethoxy-3(2*H*)-benzofuranone (**5**).

Aluminum oxide (65 g; activated, basic, type *5016A Brockmann* I) was added to a solution of **4** (3.88 g, 20 mmoles) and 3,4-dimethoxybenzaldehyde (3.99 g, 24 mmoles) in methylene chloride (40 ml). The mixture was thoroughly stirred for 16 hours at room temperature under exclusion of light. The suspension was filtered off, the residue was washed with methylene chloride (4 × 130 ml) and the washes were combined with the filtrate. The solvent was evaporated and the residue recrystallized from methylene chloride/methanol 1:1 to give 5.0 g (73 %) of **5** as a yellow solid, mp 163-167 °C, ref [18] 169-170 °C; ^{1}H nmr (deuteriochloroform): δ 3.89, 3.91, 3.93, 3.94 (each s, total 12H, CH_3), 6.11, 6.33 (each d, J = 1.9 Hz, 2H, H-5 and -7), 6.71 (s, 1H, CH), 6.89 (d, J = 8.5 Hz, 1H, H-5'), 7.42 (dd, J = 8.5, 1.9 Hz, 1H, H-6'), 7.44 (d, J = 1.9 Hz, 1H, H-2'); ^{13}C nmr (deuteriochloroform): δ 55.92, 55.94, 56.1, 56.2 (CH_3), 89.1, 93.9 (C-5, C-7), 105.4 (C-3a), 111.16, 111.23, 113.6 (CH, C-2', C-5'), 125.3 (C-6'), 125.5 (C-1'), 146.8, 149.0, 150.3 (C-2, C-3', C-4'), 159.4, 168.70, 168.73 (C-4, C-6, C-7a), 180.5 (CO).

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.48; H, 5.36.

(*Z*)-2-[(3,4-Dihydroxyphenyl)methylene)-4,6-dihydroxy-3(2*H*)-benzofuranone (**6**).

A *Schlenk* tube containing compound **5** (1.03 g, 3 mmoles) was evacuated and flushed with argon. Anhydrous methylene chloride (25 ml) was injected *via* septum. A solution of boron tribromide (6.0 g, 2.3 ml, 24 mmoles) in anhydrous methylene chloride (10 ml) was injected at 0 °C. The mixture was stirred for 3 hours at this temperature and for additional 21 hours at room temperature. Ice-water (30 ml) was carefully added, it was stirred for 5 minutes and the precipitate was separated by suction filtration. The crude product was recrystallized from methanol/water 1:1 to obtain 0.31 g (36%) of compound **6** as an orange solid. This material contains a monomethoxy compound (δ = 3.83 ppm) as an impurity. An analytic sample was obtained by repeated recrystallization from ethyl acetate, mp 285-290 °C, conversion 235-240 °C, ref [19] 265-270 °C; ^{1}H nmr (DMSO-d_6): δ 6.05, 6.16 (each d, J = 1.6 Hz, 2H, H-5 and -7), 6.43 (s, 1H, CH), 6.80 (d, J = 8.2 Hz, 1H, H-5'), 7.16 (dd, J = 8.2, 2.0 Hz, 1H, H-6'), 7.37 (d, J = 2.0 Hz, 1H, H-2'), 9.15, 9.49, 10.76, 10.78 (each s, total 4H, OH); ^{13}C nmr (DMSO-d_6): δ 90.4, 97.8 (C-5, C-7), 103.0 (C-3a), 109.7, 116.1, 117.7 (CH, C-2', C-5'), 123.8 (C-1'), 124.0 (C-6'), 145.6, 146.0, 147.6 (C-2, C-3', C-4'), 158.3, 167.1, 167.7 (C-4, C-6, C-7a), 179.2 (CO).

4,6-Dibenzyloxy-3(2*H*)-benzofuranone (**7**).

Benzyl bromide (11.29 g, 7.85 ml, 66 mmoles) was added to a mixture of compound **3** (4.98 g, 30 mmoles), potassium carbonate (9.12 g, 66 mmoles) and dimethylformamide (100 ml). The mixture was stirred at 80 °C for 1 hour, and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (150 ml) and water (100 ml). The aqueous layer was extracted with ethyl acetate (1 × 150 ml, 2 × 60 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried over sodium sulfate and evaporated to dryness. The crude material was purified by column chromatography (petroleum ether/ethyl acetate 1:1) to yield 2.8 g (27 %) of **7** as colorless crystals, mp 102-103 °C, ref [20] 105-106 °C; ^{1}H nmr (deuteriochloroform): δ 4.85 (s, 2H, CH_2), 5.03, 5.19 (each s, total 4H, OC*H*$_2$Ph), 6.09, 6.20 (each d, J = 2.9 Hz, 2H, H-5 and -7), 7.27-7.44 (m, 10H, Ph); ^{13}C nmr (deuteriochloroform): δ 70.4, 70.7 (*C*H$_2$Ph), 75.6 (C-2), 90.3, 95.2 (C-5, C-7), 105.4 (C-3a), 126.7, 127.6, 127.9, 128.5, 128.6, 128.7 (Ph), 135.5, 136.0 (C-1', C-1''), 157.8, 168.5, 177.0 (C-4, C-6, C-7a), 194.7 (CO).

3,4-Dibenzyloxybenzaldehyde (**8**).

Benzyl bromide (11.29 g, 7.85 ml, 66 mmoles) was added to a mixture of 3,4-dihydroxybenzaldehyde (4.14 g, 30 mmoles), potassium carbonate (9.12 g, 66 mmoles) and dimethylformamide (100 ml). The mixture was stirred overnight at room temperature. It was evaporated under reduced pressure, and the residue was partitioned between water (50 ml) and ethyl acetate (50 ml). The aqueous layer was extracted with ethyl acetate (1 × 50 ml, 2 × 25 ml), the organic layers were combined, washed with water (50 ml) and brine (50 ml) and dried over sodium sulfate. The volume was reduced *in vacuo* to 30 ml and poured into petroleum ether (150 ml). The precipitate was collected by filtration and recrystallized from ethanol/water 9:1 to give 3.8 g (40 %) of **8** as colorless crystals, mp 85-87 °C, ref [21] 85-86 °C; ^{1}H nmr (DMSO-d_6): δ 5.21, 5.27 (each s, total 4H, OC*H*$_2$Ph), 7.27-7.54 (m, 13H, Ph), 9.81 (s, 1H, CHO); ^{13}C nmr (DMSO-d_6): δ 70.1 (CH_2), 112.3, 113.5 (C-2, C-5), 126.3 (C-6), 127.6, 127.7, 128.5, 128.6 (C-2', C-2'', C-3', C-3''), 128.0, 128.1 (C-4', C-4''), 130.0 (C-1), 136.7, 137.0 (C-1', C-1''), 148.6 (C-3), 153.8 (C-4), 191.4 (CO).

(*Z*)-2-[(3,4-Dibenzyloxyphenyl)methylene]-4,6-dibenzyloxy-3(2*H*)-benzofuranone (**9**).

Aluminium oxide (19.5 g; activated, basic, type *5016A Brockmann* I) was added to a solution of **7** (2.08 g, 6 mmoles) and 3,4-dibenzyloxybenzaldehyde **8** (2.87 g, 9 mmoles) in methylene chloride (12 ml). The mixture was thoroughly stirred for 12 hours at room temperature under exclusion of light. The suspension was filtered off, the residue was washed with methylene chloride (4 × 60 ml) and the washes were combined with the filtrate. The solvent was evaporated and the residue recrystallized from methylene chloride/methanol 1:1 to give 2.30 g (73 %) of **9** as a yellow solid, mp 157-160 °C; ir (potassium bromide) ν 1684 (C=O), 1616, 1595, 1512 (C=C), 1246, 1091 (C-O) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 5.21, 5.22, 5.27, 5.28 (each s, total 8H, OC*H*$_2$Ph), 6.54, 6.78 (each d, J = 1.9 Hz, 2H, H-5 and -7), 6.62 (s, 1H, CH), 7.16 (d, J = 8.5 Hz, 1H, H-5'), 7.28-7.50 (m, 21H, Ph), 7.64 (d, J = 2.2 Hz, 1H, H-2'); ^{13}C nmr (DMSO-d_6): δ 70.1, 70.2, 70.3, 70.7 (CH_2), 91.01, 96.50 (C-5, C-7), 104.8 (C-3a), 110.1 114.4, 116.7 (CH, C-2', C-5'), 125.2 (C-6'), 125.4 (C-1'), 127.6, 127.73, 127.74, 128.2, 128.5, 128.56, 128.62, 128.7 (C-2'', C-3'', C-2''', C-3''', C-2'''', C-3'''', C-2''''', C-3'''''), 127.95, 128.01, 128.1, 128.4 (C-4'', C-4''', C-4'''', C-4'''''), 136.1, 136.4, 137.0, 137.2 (C-1'', C-1''', C-1'''', C-1'''''), 146.4, 148.2, 150.0 (C-2, C-3', C-4'), 158.0, 167.7, 168.0 (C-4, C-6, C-7a), 179.0 (CO); ms: (70 ev) m/z 646 (38%, M$^+$), 91 (100%).

Anal. Calcd. for $C_{43}H_{34}O_6$: C, 79.86; H, 5.30. Found: C, 79.90; H, 5.30.

2-[(3,4-Dihydroxyphenyl)methyl]-4,6-dihydroxy-3(2*H*)-benzofuranone (**10**).

A *Schlenk* flask containing 10% Pd/C (260 mg, 0.24 mmoles) was evacuated and flushed with argon. The flask was provided with hydrogen, a solution of **9** (970 mg, 1.5 mmoles) in anhydrous tetrahydrofuran (70 ml) was injected *via* septum, and the mixture was stirred at room temperature. After 24 hours, the reaction was stopped by filtration of the catalyst. The filtrate was evaporated, and the brown oil was recrystallized from methanol/water 1:4 to give 190 mg (44 %) of **10** as a colorless solid, mp 244-247 °C; ir (potassium bromide) ν 3473, 3292 (O-H), 1669 (C=O), 1610, 1596 (C=C), 1339, 1222 (C-O) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.65 (dd, J = 14.8, 8.2 Hz, 1H, CH_2), 2.97 (dd, J = 14.8, 3.8 Hz, 1H, CH_2), 4.68 (dd, J = 8.2, 3.8 Hz, 1H, H-2), 5.84, 5.86 (each d, J = 1.6 Hz, 2H, H-5, H-7), 6.47 (dd, J = 7.9, 2.2 Hz, 1H, H-6'), 6.58 (d, J = 7.9 Hz, 1H, H-5'), 6.62 (d, J = 2.2 Hz, 1H, H-2'), 8.62, 8.69, 10.48, 10.50 (each s, total 4H, OH); ^{13}C nmr (DMSO-d_6): δ 36.4 (CH_2), 85.9, 90.1, 96.2 (C-2, C-5, C-7), 102.6 (C-3a), 115.5, 116.9 (C-2', C-5'), 120.1 (C-6'), 127.4 (C-1'), 144.0, 145.0 (C-3', C-4'), 157.7, 167.8, 174.3 (C-4, C-6, C-7a), 194.8 (CO); ms: (70 ev) m/z 288 (56%, M$^+$), 166 (100%).

Anal. Calcd. for $C_{15}H_{12}O_6$: C, 62.50; H, 4.20. Found: C, 62.31; H, 4.54.

Acknowledgement.

D. B. thanks the *Erasmus Program* for financial support.

REFERENCES AND NOTES

[1] A. Boumendjel, *Curr. Med. Chem.,* **10**, 2621 (2003).

[2] A. Boumendjel, C. Beney, N. Deka, A.-M. Mariotte, M. A. Lawson, D. Trompier, H. Baubichon-Cortay and A. Di Pietro, *Chem.*

Pharm. Bull., **50**, 854 (2002).

[3] M. Hadjeri, M. Barbier, X. Ronot, A.-M. Mariotte, A. Boumendjel and J. Boutonnat, *J. Med. Chem.*, **46**, 2125 (2003).

[4] J. Schoepfer, H. Fretz, B. Chaudhuri, L. Muller, E. Seeber, L. Meijer, O. Lozach, E. Vangrevelinghe and P. Furet, *J. Med. Chem.*, **45**, 1741 (2002).

[5] M. Auf'mkolk, J. Koehrle, R.-D. Hesch and V. Cody*, J. Biol. Chem.* **261**, 11623 (1986).

[6a] S. Ducki, R. Forrest, J. A. Hadfield, A. Kendall, N. J. Lawrence, A. T. McGown and D. Rennison, *Bioorg. Med. Chem. Lett.*, **8**, 1051 (1998); [b] N. J. Lawrence, D. Rennison, A. T. McGown and J. A. Hadfield, *Bioorg. Med. Chem. Lett.*, **13**, 3759 (2003).

[7] H. E. Westenburg, K.-J. Lee, S. K. Lee, H. H. S. Fong, R. B. van Breemen, J. M. Pezzuto and A. D. Kinghorn, *J. Nat. Prod.,* **63**, 1696 (2000).

[8a] T. Nakayama, K. Yonekura-Sakakibara, T. Sato, S. Kikuchi, Y. Fukui, M. Fukuchi-Mizutani, T. Ueda, M. Nakao, Y. Tanaka, T. Kusumi and T. Nishino, *Science*, **290**, 1163 (2000); [b] D. Strack and W. Schliemann, *Angew. Chem*., **113**, 3907 (2001).

[9] A. Braune, M. Gütschow, W. Engst and M. Blaut, *Appl. Environ. Microbiol.,* **67**, 5558 (2001).

[10] R. Löser, M. Chlupacova, A. Marecek, V. Opletalova and M. Gütschow, *Helv. Chim. Acta,* **87**, 2597 (2004).

[11] R. M. Seabra, P. B. Andrade, F. Ferreres and M. M. Moreira, *Phytochemistry*, **45**, 839 (1997).

[12] M. Bennett, A. J. Burke and W. I. O'Sullivan, *Tetrahedron*, **52**, 7163 (1996).

[13] J. A. Donnelly and C. L. Higginbotham, *Tetrahedron,* **46**, 7219 (1990).

[14a] Z.-W. An, M. Catellani and G. P. Chiusoli, *J. Organomet. Chem.,* **397**, 371, (1990); [b] T.-T. Jong and S.-J. Leu, *J. Chem. Soc., Perkin Trans I*, 423 (1990).

[15] C. Beney, A.-M. Mariotte and A. Boumendjel, *Heterocycles*, **55**, 967 (2001).

[16] R. S. Varma and M. Varma, *Tetrahedron Lett*., **33**, 5937 (1992).

[17] T. A. Geissman and E. Hinreiner, *J. Am. Chem. Soc.,* **73**, 782 (1951).

[18] A. Sharma and S. S. Chibber, *J. Heterocyclic Chem*., **18**, 275 (1981).

[19] L. Farkas, L. Pallos and G. Hidasi, *Chem. Ber.,* **94**, 2221 (1961).

[20] G. Büchi and S. M. Weinreb, *J. Am. Chem. Soc.,* **93**, 746 (1971).

[21] F. W. Muellner, A. N. Abdel-Sayed and L. Bauer *J. Heterocylic Chem.,* **22**, 1055 (1985).