Synthetic Studies Towards the Preparation of 2-Benzyl-2-hydroxybenzofuran-3(2*H*)-one, the Prototype of Naturally Occurring Hydrated Auronols

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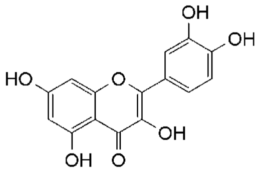
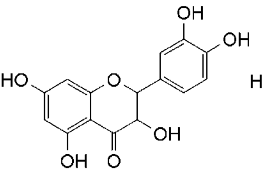
Various synthetic approaches were employed to prepare 2-benzyl-2-hydroxybenzofuran-3(2*H*)-one (**8**), the prototype of naturally occurring auronols. While the base-induced ring transformation of 3-hydroxyflavanone (**2**) as well as the hydration of 2-benzylidenebenzofuran-3(2*H*)-one (=aurone; **6**) proved to be inappropriate, the hydrogenolytic epoxide-ring opening of 2′-phenylspiro[benzofuran-2(3*H*),2′-oxiran]-3-one (**7**), obtained from **6**, represents an efficient method to afford the auronol **8**.

Introduction. – Flavonoids represent a large group of plant natural products exhibiting multiple biological activities and are very abundant in nutrients such as fruits and vegetables [1]. Joining together the shikimate and polyketide pathways, they are secondary metabolites of mixed biosynthetic origin. However, in contrast to the detailed knowledge concerning the biosynthesis, the biodegradation of these compounds is poorly investigated [2]. It has been shown that the degradation of the hydroxyflavone quercetin (**A**) to phloroglucinol and (3,4-dihydroxyphenyl)pyruvic acid by *Eubacterium ramulus*, a strictly anaerobic bacterium living in the human gut, proceeds *via* the hydroxyflavanone taxifolin (**B**) and the auronol derivative alphitonin (**C**) [3]. When compared to phenylchromanones (=2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-ones), aurones (=2-benzylidenebenzofuran-3(2*H*)-ones) are less-investigated flavonoids. To study the bioactivity of auronols, it is necessary to develop suitable preparative methods to provide sufficient amounts for biological investigations. Herein, we wish to report an efficient synthetic route to 2-benzyl-2-hydroxybenzofuran-3(2*H*)-one (**8**) as a prototype of auronols. The key step of this route is based on the regioselective reductive ring opening of the aurone-derived epoxide **7**. Auronol **8** has already been isolated in small amounts from the wood of the Australian tree *Flindersia brasii* [4].

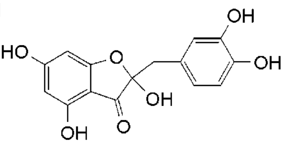
Results and Discussion. – It has been reported by *Kiehlmann* and *Li* that taxifolin (**B**) underwent a ring contraction to alphitonin (**C**) after prolonged heating. Due to dehydrogenation, quercetin (**A**) was formed as the by-product [5]. In an attempt to prepare aurone derivative **8** in a similar manner, the hydroxyflavanone **2** was required. Starting from **1**, we prepared racemic **2** in a one-pot procedure including epoxidation



A

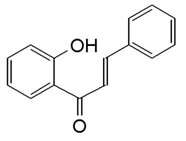


B

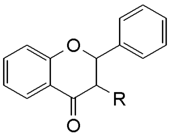


C

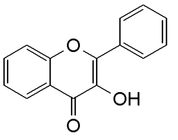
and subsequent intramolecular opening of the epoxide (*Algar–Flynn–Oyamada* reaction [6]). This conversion took place as a β-cyclization with respect to the attack of the 2′-phenolic group; products of an α-cyclization [7] were not observed. The *trans*-configuration of **2** was confirmed by the ^3J coupling constant, which indicated the *anti*-periplanar geometry of the H–C(2) and H–C(3). In the next step, **2** was subjected to different conditions of a ring transformation to produce **8**.



1



2 R = OH
3 R = H



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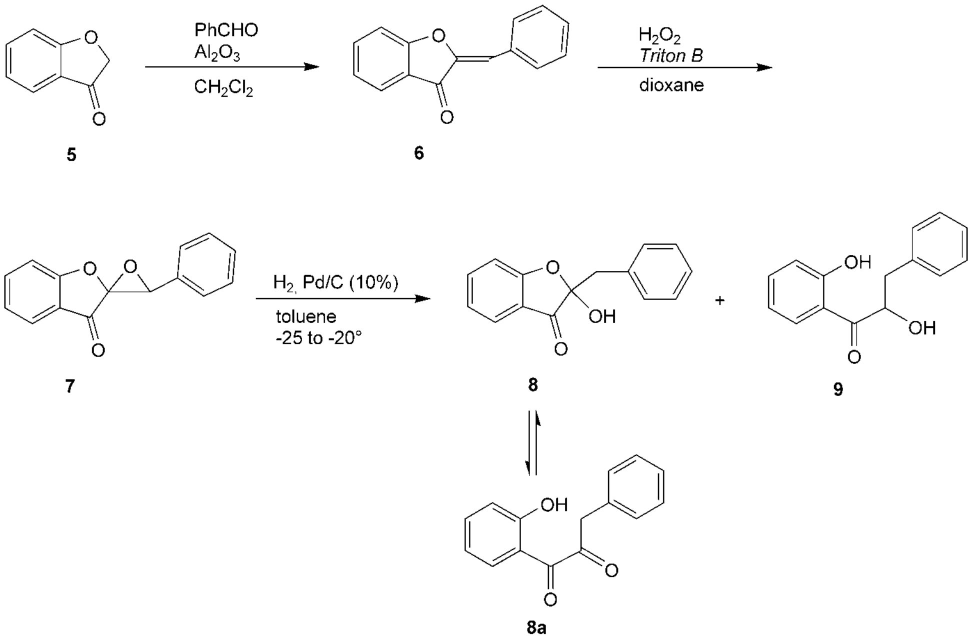
The conversion of taxifolin (**B**) to alphitonin (**C**) was achieved upon heating **B** in H_2O in a sealed tube at 115° for 93 h [5]. Since hydroxyflavanone **2** is less soluble in H_2O than **B**, a mixture of ^iPrOH and H_2O was used in an attempt to prepare **8** from **2**. However, the reaction proceeded very slowly and was, therefore, performed under base catalysis. Thus, **2** was treated with a 1:2 mixture of ^iPrOH and 0.15N NaOH under an inert atmosphere in a sealed tube at 120° for a prolonged time. The formation of the hydroxyflavone **4** [8] was detected by TLC, besides other unidentified products. To avoid dehydrogenation of **2**, the reaction was conducted in the presence of HCl and Zn dust, again resulting in a mixture of products, from which the undesired flavanone **3** was isolated in small amounts.

Next, aurone (**6**) was prepared by condensation of benzofuran-3(2*H*)-one (**5**) with benzaldehyde on an alumina surface (*Scheme*), according to a methodology of *Varma* and *Varma* [9]. Aurone (**6**) was subjected to conditions of a direct, acid-catalyzed hydration, as described for other electron-deficient enol ethers [10]. This approach was unsuccessful, too.

Therefore, it was envisaged to prepare **8** by reductive opening of aurone-derived epoxide **7** under Pd-catalyzed hydrogenolysis. This transformation seemed to be reliable and should proceed regioselectively because the hydrogenolysis of the 'benzylic' PhCH–O bond is favored over the 'nonbenzylic' PhCHC–O bond [11]. To prepare the required epoxide **7**, aurone (**6**) was treated with H_2O_2 and *Triton® B* [12]. NMR Data of the product indicated the presence of a single diastereoisomer. Epoxide **7** in EtOH was then exposed to H_2 in the presence of 10% Pd/C as catalyst, but the desired product could not be obtained, probably due to decomposition of the starting material. By changing the solvent from EtOH to toluene, a defined reaction course took place, and the products were isolated by prep. chromatography. When the reaction was carried out at room temperature, a product mixture of auronol **8** and α-hydroxy ketone **9** was obtained, whereby **9** was the main product (30%). This over-reduction to **9** is assumed to be caused by hydrogenolysis of the 'oxabenzylic' C–O bond in the furanone ring subsequent to epoxide opening rather than by hydrogenation of the carbonyl group in the open-chain 1,2-diketone **8a** that might be formed from intermediate **8**.

Scheme



However, performance of the reaction at temperatures ranging from – 25 to – 20° and thorough TLC control led to a more-convenient product distribution. Thus, the desired 2-benzyl-2-hydroxybenzofuran-3(2*H*)-one (**8**) was obtained in 65% yield. NMR Analysis of **8** in $CDCl_3$ at 30° revealed the occurrence of a ring-chain tautomeric equilibrium [13] between **8** and the 1,2-diketone **8a** (ratio 1:0.15). This tautomerism, however, was not observed in a DMSO solution of **8**.

Conclusions. – The hydrogenolysis of aurone-derived epoxides promises to be an efficient new method to prepare auronols, as demonstrated in the preparation of the parent compound, 2-benzyl-2-hydroxybenzofuran-3(2*H*)-one (**8**). The applicability of this method to the synthesis of polyhydroxylated auronols is under current investigation in our laboratories and will be reported in the future.

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Experimental Part

General. The 2′-hydroxychalcone (=1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one; **1**) was purchased from *Merck*, Darmstadt, Germany, 3-hydroxyflavone (=3-hydroxy-2-phenyl-4*H*-1-benzopyran-4-one; **4**) and aluminum oxide from *Aldrich*, Steinheim, Germany, and benzofuran-3(2*H*)-one (**5**) from *Fluka*, Buchs, Switzerland. TLC: *Merck* aluminum sheets, silica gel *60 F254*. Melting points: not corrected. ^{1}H- and ^{13}C-NMR Spectra: at 500 and 125 MHz, resp.; $CDCl_3$ solns., unless otherwise stated; δ in ppm, J in Hz. MS: electron-impact ionization (EI) at 70 eV; in m/z (rel. %).

*(±)-*trans*-2,3-Dihydro-3-hydroxy-2-phenyl-4*H*-1-benzopyran-4-one* (**2**). A mixture of **1** (2 g, 8.9 mmol), Et_2NH (3.25 g, 44.5 mmol), and dioxane (135 ml) was stirred at 0–5°. Then, a 30% aq. H_2O_2 soln. (112 ml) was added within 40 min. The mixture was kept at 5° for 40 h, and the precipitate was filtered off: **2** (690 mg, 32%). M.p. 178–180° ([14]: 178°). ^{1}H-NMR: 3.65 (*d*, $J=1.9$, OH); 4.63 (*dd*, $J=12.3$, 1.9, H−C(3)); 5.13 (*d*, $J=12.3$, H−C(2)); 7.02–7.06 (*m*, H−C(8)); 7.08–7.12 (*m*, H−C(6)); 7.40–7.49 (*m*, H−C(3′), H−C(4′), H−C(5′)); 7.52–7.60 (*m*, H−C(7), H−C(2′), H−C(6′)); 7.92 (*dd*, $J=7.9$, 1.6, H−C(5)). ^{13}C-NMR: 73.62 (C(3)); 83.87 (C(2)); 118.13 (C(8)); 118.50 (C(4a)); 122.11 (C(6)); 127.33 (C(5)); 127.53 (C(2′), C(6′)); 128.71 (C(3′), C(5′)); 129.33 (C(4′)); 136.28 (C(1′)); 136.94 (C(7)); 161.72 (C(8a)); 194.22 (C(4)). EI-MS: 240 (40, $M^{+\cdot}$), 211 (100), 121 (72).

*(±)-2,3-Dihydro-2-phenyl-4*H*-1-benzopyran-4-one* (**3**). A mixture of H_2O (200 ml) and ^{i}PrOH (100 ml) was degassed in an ultrasonic bath and treated with N_2 (each 15 min). Compound **2** (1.50 g, 6.2 mmol), Zn dust (500 mg, 7.6 mmol), and 6N HCl (5 ml) were added. The mixture was refluxed for 95 h under Ar, extracted with CH_2Cl_2, and subjected to column chromatography (silica gel): **3** (35 mg, 2%). M.p. 60–61° ([15]: 75–76°). ^{1}H-NMR: 2.88 (*dd*, $J=17.0$, 3.0, 1 H, CH_2); 3.07 (*dd*, $J=17.0$, 13.5, 1 H, CH_2); 5.47 (*dd*, $J=13.5$, 3.0, H−C(2)); 7.02–7.06 (*m*, H−C(6), H−C(8)); 7.35–7.51 (*m*, 6 arom. H); 7.92 (*dd*, $J=8.1$, 1.6, H−C(5)). ^{13}C-NMR: 44.68 (C(3)); 79.60 (C(2)); 118.13 (C(8)); 120.93 (C(4a)); 121.62 (C(6)); 126.14 (C(2′), C(6′)); 127.05 (C(5)); 128.78 (C(4′)); 128.85 (C(3′), C(5′)); 136.20 (C(7)); 138.73 (C(1′)); 161.56 (C(8a)); 191.98 (C(4)). EI-MS: 224 (100, $M^{+\cdot}$), 223 (65), 147 (43), 120 (72), 104 (20).

*(Z)-2-Benzylidenebenzofuran-3(2*H*)-one* (**6**). Aluminium oxide (16.25 g; activated, basic, type *5016A Brockmann* I) was added to a soln. of **5** (0.67 g, 5 mmol) and benzaldehyde (1.00 g, 9.33 mmol) in CH_2Cl_2 (0.67 g, 5 mmol). The mixture was thoroughly stirred for 6 h at r.t. under exclusion of light. The suspension was filtered off, the residue washed with CH_2Cl_2 (4 × 75 ml), and the washes were combined with the filtrate. The solvent was evaporated and the residue recrystallized from CH_2Cl_2/MeOH: **6** (0.74 g, 68%). M.p. 106–108° ([16]: 110–111°). ^{1}H-NMR: 6.90 (*s*, PhC*H*); 7.19–7.23 (*m*, H−C(5)); 7.31–7.33 (*m*, H−C(7)); 7.37–7.41 (*m*, H−C(4′)); 7.43–7.47 (*m*, H−C(3′), H−C(5′)); 7.62–7.66 (*m*, H−C(6)); 7.80 (*dd*, $J=7.6$, 1.3, H−C(4)); 7.90–7.93 (*m*, H−C(2′), H−C(6′)). ^{13}C-NMR: 112.94 (C(7)); 113.05 (Ph*C*H); 121.64 (C(3a)); 123.47 (C(5)); 124.68 (C(4)); 128.89 (C(3′), C(5′)); 129.89 (C(4′)); 131.54 (C(2′), C(6′)); 132.30 (C(1′)); 136.89 (C(6)); 146.88 (C(2)); 166.16 (C(7a)); 184.81 (C(3)). EI-MS: 222 (60, $M^{+\cdot}$), 221 (100).

*(±)-*trans*-3′-Phenylspiro[benzofuran-2(3*H*),2′-oxiran]-3-one* (**7**). To a soln. of **6** (1 g, 4.5 mmol) in dioxane (60 ml), simultaneously, 30% aq. H_2O_2 soln. (3 ml) and 40% benzyltrimethylammonium hydroxide in MeOH (*Triton® B*; 1 ml) were added dropwise. The mixture was stirred at r.t. for 40 min and poured onto ice-water (200 ml). The precipitate was filtered off, washed with cold H_2O, and dried. The crude product was dissolved in $CHCl_3$, and the soln. was poured onto ligroin. The precipitate formed was filtered off: **7** (0.37 g, 35%). M.p. 128–133° ([12]: 133–134°). ^{1}H-NMR: 4.55 (*s*, H−C(3′)); 7.09–7.12 (*m*, H−C(7)); 7.14–7.18 (*m*, H−C(5)); 7.39–7.44 (*m*, H−C(3″), H−C(4″), H−C(5″)); 7.48–7.51 (*m*, H−C(2″), H−C(6″)); 7.61–7.65 (*m*, H−C(6)); 7.72 (*ddd*, $^{3}J=7.7$, $^{4}J=1.4$, $^{5}J=0.7$, H−C(4)). ^{13}C-NMR: 62.94 (C(3′)); 89.46 (C(2)); 113.84 (C(7)); 120.08 (C(3a)); 123.27 (C(5)); 124.41 (C(4)); 127.55 (C(2″), C(6″)); 128.38 (C(3″), C(5″)); 129.18 (C(4″)); 131.70 (C(1″)); 138.67 (C(6)); 170.33 (C(7a)); 192.26 (C(3)). EI-MS: 238 (100, $M^{+\cdot}$), 210 (30), 121 (25), 118 (40), 90 (58).

Hydrogenolysis of **7**. A *Schlenk* tube containing 10% Pd/C (315 mg, 0.29 mmol) was evacuated and flushed with Ar. The tube was provided with H_2 (balloon) and cooled to −25°. A soln. of **7** (200 mg, 0.84 mmol) in degassed and dried toluene (20 ml) was injected *via* septum. The temp. was kept at −25 to −20°, and the reaction was followed by TLC (toluene/MeCN 4:1). After 2.5 h, the reaction was stopped by filtration of the catalyst, the filtrate evaporated, and the yellow oil (191 mg) subjected to column chromatography (silica gel (16 g), CH_2Cl_2/AcOEt 99:1): **8** (132 mg, 65%) and **9** (40 mg, 20%).

*Data of (±)-2-Benzyl-2-hydroxybenzofuran-3(2*H*)-one* (**8**): Yellow solid. M.p. 93–95° ([8]: 102–103°; [4]: 105°). ^{1}H-NMR ((D_6)DMSO): 3.08 (*d*, $J=13.9$, 1 H, CH_2); 3.16 (*d*, $J=13.9$, 1 H, CH_2); 6.95–7.00 (*m*, H−C(5)); 7.04 (*d*, $J=8.6$, H−C(7)); 7.07–7.16 (*m*, 5 arom. H); 7.46 (*dd*, $J=7.7$, 0.8, H−C(4)); 7.58–7.62

(*m*, H–C(6)); 7.82 (*s*, OH). ^{13}C-NMR ((D$_6$)DMSO): 41.35 (CH$_2$); 105.22 (C(2)); 113.04, 121.74 (C(5), C(7)); 119.59 (C(3a)); 124.22 (C(4)); 126.76 (C(4′)); 127.87 (C(3′), C(5′)); 130.52 (C(2′), C(6′)); 133.83 (C(1′)); 139.03 (C(6)); 169.98 (C(7a)); 199.16 (C(3)). EI-MS: 240 (10, $M^{+\bullet}$), 121 (100), 91 (30).

Data of (±)-2-Hydroxy-1-(2-hydroxyphenyl)-3-phenylpropan-1-one (**9**): Yellow oil [4][17]. ^{1}H-NMR: 2.96 (*dd*, J = 14.2, 7.0, 1 H, CH$_2$); 3.22 (*dd*, J = 14.2, 4.1, 1 H, CH$_2$); 3.48 (*d*, J = 7.9, CHO*H*); 5.32–5.37 (*m*, C*H*OH); 6.92–6.96 (*m*, H–C(5′)); 7.05 (*dd*, J = 8.7, 1.1, H–C(3′)); 7.11–7.14 (*m*, H–C(2), H–C(6)); 7.20–7.28 (*m*, H–C(3), H–C(4), H–C(5)); 7.51–7.55 (*m*, H–C(4′)); 6.69 (*dd*, J = 8.2, 1.6, H–C(6′)); 11.57 (*s*, OH–C(2′)). ^{13}C-NMR: 42.80 (CH$_2$); 72.85 (CHOH); 116.60 (C(1′)); 119.02, 119.33 (C(3′), C(5′)); 127.03 (C(4)); 128.46 (C(3), C(5)); 129.39 (C(6′)); 129.40 (C(2), C(6)); 135.95 (C(1)); 137.25 (C(4′)); 162.77 (C(2′)); 205.26 (CO). EI-MS: 242 (6, $M^{+\bullet}$), 224 (23), 213 (10), 121 (100), 91 (21).

Selected NMR Data of **8** *and 1-(2-Hydroxyphenyl)-3-phenylpropane-1,2-dione* (**8a**) *in CDCl$_3$:* ^{1}H-NMR (400 MHz): 3.09 (*d*, J = 13.9, 1 H, CH$_2$, **8**); 3.18 (*d*, J = 13.9, 1 H, CH$_2$, **8**); 3.53 (*s*, 1 H, OH, **8**); 4.10 (*s*, 2 H, CH$_2$, **8a**); 6.70–7.60 (*m*, arom. H, **8** and **8a**); 11.21 (*s*, 1 H, OH, **8a**). ^{13}C-NMR (100 MHz): 41.62 (CH$_2$, **8**); 45.65 (CH$_2$, **8a**); 103.60 (C(2), **8**); 163.85 (C–OH, **8a**); 170.44 (C(7a), **8**); 196.54 (C(2), **8a**); 197.91 (C(1), **8a**); 198.45 (C(3), **8**).

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