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First total synthesis of the only known 2-isopropyliden-2*H*-benzofuran-3-one isolated from *V. luetzelburgii*†

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The first total synthesis of 5-(1-hydroxy-1-ethyl)-2-isopropyliden-2*H*-benzofuran-3-one, is reported in its racemic and in one of its optically active [(*S*)-(−)] forms. This heterocycle, isolated from *Verbesina luetzelburgii*, is the only known 2-isopropyliden-2*H*-benzofuran-3-one produced by species of *Verbesina*. The sequence took place in eight steps and 19% overall yield (up to 33% for the chiral form), from 4′-hydroxyacetophenone. It entailed carbonyl group protection as the 1,3-dioxolane and a phenol *ortho* formylation, followed by a Williamson etherification with chloroacetone and an organocatalytic cross-aldolization, to afford a 2-acetyl-2,3-dihydrobenzofuran-3-ol intermediate. The latter underwent a methyl Grignard addition to the carbonyl moiety, followed by selective oxidation of the benzylic alcohol and deprotection, resulting in a β-hydroxy diketone derivative. A MsCl-assisted dehydration of the tertiary alcohol, established the isopropylidene motif, whereas the syntheses culminated by chemical or enzymatic (carrot, celeriac) selective reductions of the exocyclic carbonyl group.

Introduction

The benzofuran-3-one nucleus, a derivative of the privileged benzofuran core,[1] is one of the most studied heterocyclic structural units by synthetic and medicinal chemists.[2] This motif is widely found in bioactive natural and synthetic compounds, such as in the antifungal agent griseofulvin.[3]

The aurones and the 2-isopropylidene-benzofuran-3-ones are two families of 2-methylene-benzofuran-3-one derivatives. Many of them display interesting biological activities, including anti-protozoal[4] and anti-cancer.[5] The aurones (**1a–e**),[6] which are more widespread (Fig. 1), exhibit different aromatic rings and olefin configurations,[7] whereas the 2-isopropylidene-benzofuran-3-ones display a tetrasubstituted alkene motif and comprise a handful of exceptional products isolated from fungi and plants.

Fungi-derived 2-isopropylidene-benzofuran-3-ones include compound **2a**,[8] pergillin (**2b**), penicisochroman A (**2c**), the ustusoranes A (**2d**) and C (**3**), and TMC-120B (**4**). The latter is produced by terrestrial and marine-derived fungi.[9] All these heterocycles have attracted marked attention for their bioactivity, and as synthetic targets.[10,11]

Examples of plant-produced 2-isopropylidene-benzofuran-3-ones include alcohol **5a**,[12a,b] esters **5b–f**,[12b,c] as well as the 5-acetyl coumaranone **6a**, and the related heterocycle **6b**, isolated from American specimens.[13a,b] It also comprises compound **6c**, obtained from Chinese perennial herbs.[13c,d]

In addition, some 2-isopropylidene-benzofuran-3-ones have been prepared as synthetic intermediates. Compound **6d** was described in connection with antitumor agents,[14a,b] **6e** served as key intermediate toward griseofulvin analogs[14c] and furocoumarin **7** was used for the synthesis of poly-azamacrocycles.[15]

Verbesina is a large American genus within the Heliantheae, distributed from Canada to Argentina. Its members are used in folk medicine to treat digestive and respiratory conditions, and as wound healing agents;[16] however, few species of *Verbesina* have been chemically investigated.[17] *V. luetzelburgii* is a green bush, which grows chiefly in the State of Bahia (Brazil).[18] It was chemically studied only once,[19] yielding the unique 2-isopropylidene-benzofuran-3-one **8** and the ketone **9**, its logical metabolic precursor, and a handful of other unrelated compounds.

Compound **8** is the only benzofuran derivative found among species of *Verbesina*. This heterocycle seems to be the prototypic and simplest 2-isopropylidene-benzofuran-3-one representative. Notably, this class of compounds has been barely studied, due to the limited amounts of isolated material and the scarcity of synthetic protocols to provide an affordable access to them.

We have previously employed filifolinol (**10**), a heliantaceous 2,3-dihydrobenzofuran for the synthesis of inhibitors of the human complement cascade[20] and have synthesized a potential

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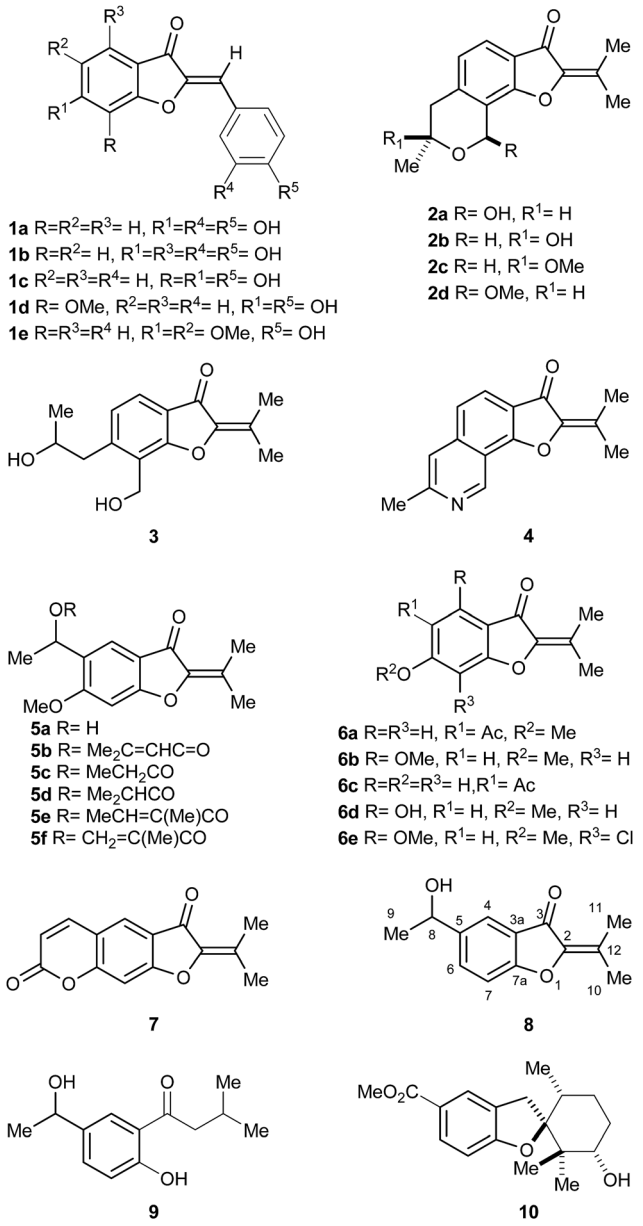
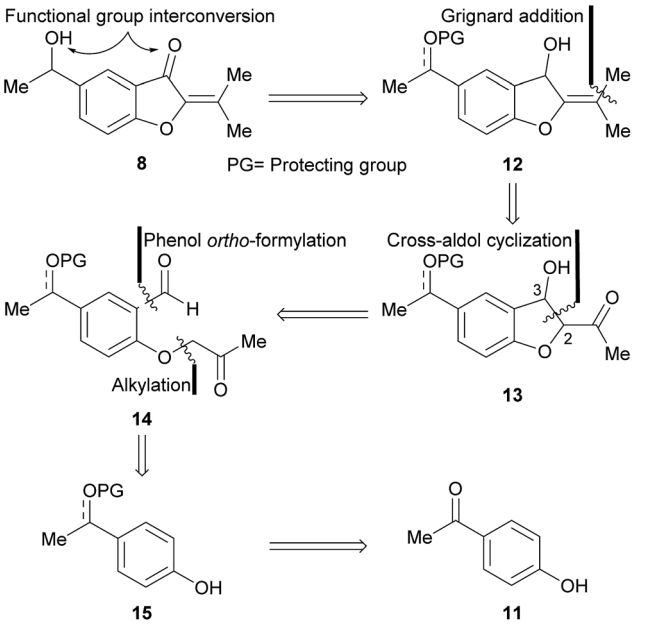


Fig. 1 Natural products carrying the 2-isopropylidene benzofuran-3-one motif, and related structures.

key intermediate toward TMC-120B (**4**).[21] In pursuit of our studies on naturally-occurring benzofuran derivatives, herein we report the first total synthesis of the 2-isopropylidene-benzofuran-3-one **8** in its racemic and in one of its optically active forms, from a common intermediate and employing 4′-hydroxyacetophenone (**11**) as starting material.

Results and discussion

The approach toward **8** was based on a retrosynthetic analysis (Scheme 1). It was conjectured that the oxygen functionalities could be adjusted to their proper oxidation states at a late stage of the synthesis. Accordingly, compound **12** carrying a protected alcohol or ketone moiety, was postulated as a valid advanced intermediate.



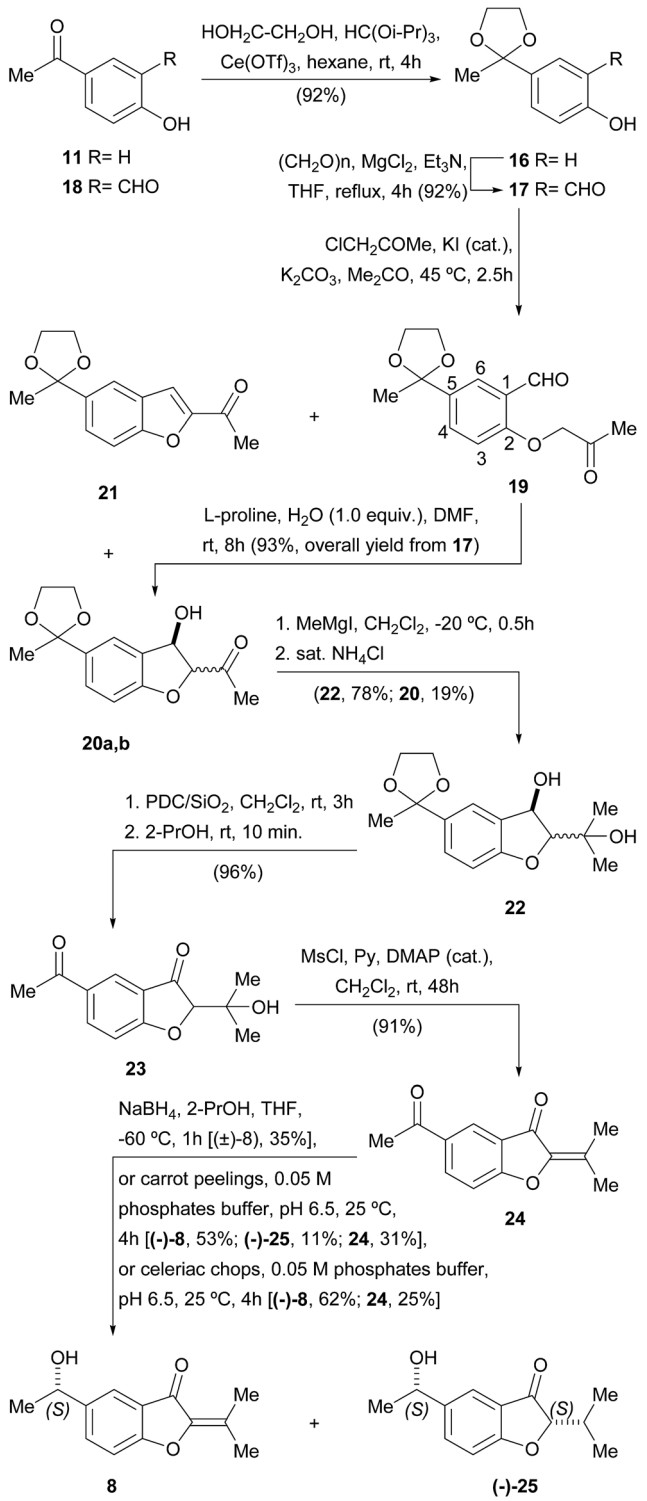
Scheme 1 Retrosynthetic analysis of the target natural product (**8**).

In turn, it was supposed that the isopropylidene motif could result from a Grignard addition–dehydration sequence, to a conveniently placed carbonyl moiety. This reasoning unveiled the intervention of the β-hydroxy ketone **13**, which was disconnected at C-2–C-3, under the consideration that it may arise from the cross-aldol condensation of a 1,6-dicarbonyl precursor such as **14**. Further analysis unearthed the protected aromatic derivative **15**, as a suitable intermediate readily available from the acetophenone **11**.

Accordingly, the synthesis of **8** was initiated (Scheme 2) with the protection of the carbonyl moiety of **11** as the corresponding 1,3-dioxolane (**16**). This group was chosen on account of its improved stability over its acyclic congeners, and relative ease of hydrolytic removal.[22] Conventional ketalization methods (ethyleneglycol, TsOH, 4 Å molecular sieves, PhMe)[23] without previous protection of the phenol[23c,d] proved unsatisfactory; however, the reaction with ethyleneglycol in hexane–$HC(OiPr)_3$ under $Ce(OTf)_3$ catalysis afforded 92% of the protected ketone **16** [64% using $HC(OEt)_3$], a yield that remained high even on a gram scale.[24]

Next, the *ortho*-formylation was undertaken, employing the procedure of Skattebøl,[25] where a mixture of paraformaldehyde, Et_3N, anhydrous $MgCl_2$ and **16** was refluxed in THF, cleanly furnishing **17** in 92% yield. Contrastingly, however, it was observed that formylation of the unprotected ketone **11** gave only 20% of the related salicylaldehyde derivative **18**,[25a] whereas literature precedents suggested that the Friedel–Crafts acylation of salicylaldehyde was not a better option toward **18**.[26] Hence, the Skattebøl formylation of **16** proved to be the best alternative to get salicylaldehyde **17**.

The Williamson etherification of **17** with freshly distilled chloroacetone[27] and K_2CO_3 in acetone at 45 °C smoothly gave the projected acetonyl ether **19** admixed with variable amounts (25–65%) of the diastereomeric alcohols **20a,b**. The latter



Scheme 2 Synthesis of compounds **8** and (−)-**25**.

presumably resulted from the unwanted and uncontrolled intramolecular cross-aldol reaction of **19** under K_2CO_3 promotion.[28]

Since **19** and **20a,b** formed a hardly separable mixture, where purification of **19** proved to be very difficult, attempts were made to induce completion of the cyclization, by modifying the reaction time (3–6 h) and/or temperature (50–60 °C), and by changing the promoter ($NaHCO_3$, Li_2CO_3, $MgCO_3$, Et_3N). However, all those alternatives were fruitless, resulting at best in a diastereomeric mixture of **20**, along with minor amounts of the benzofuran derivative **21**, produced by dehydration of its benzylic alcohol moiety.

Thus, it became evident that a milder procedure was required for the cyclization stage; therefore, we turned our attention to the organocatalytic protocol of Enders.[29] Luckily, treatment of the crude extract of the alkylation step, containing **19** along with some amount of **20a,b**, with L-proline in DMF to which water (1 equiv.) was added, effected the desired cyclization, giving a mixture of alcohols **20a,b** in 93% overall yield from **17**.

In view of the structure of the target natural product (**8**), access to these alcohols as a diastereomeric mixture was not considered an obstacle for pursuing the synthetic sequence, which was therefore focused on the addition of the required methyl group to the ketonic carbonyl group.

Although initial experiments with MeMgI in THF at 0 °C were discouraging, even in the presence of anhydrous $CeCl_3$,[30a] it was soon discovered that the outcome of the reaction was greatly improved when it was carried out in CH_2Cl_2 at −20 °C.[30b] Under these conditions, 78% yield of diol **22** was achieved, together with 19% of **20a,b** that seemed to enolize, remaining refractory to the Grignard reagent and was recovered as unreacted starting material.

Next, sequential oxidation of the benzylic alcohol and deprotection of the 1,3-dioxolane were accomplished by exposing a cold solution of **22** to Jones' reagent. However, these conditions afforded only moderate yields of the diketone **23**. Luckily, the secondary alcohol could be successfully oxidized with PDC/SiO_2 in CH_2Cl_2, which also ensured the deprotection of the 1,3-dioxolane moiety, giving 96% of the diketone **23**. In turn, the latter was smoothly dehydrated with MsCl and pyridine in CH_2Cl_2,[31] which cleanly furnished 91% yield of the α,β-unsaturated ketone **24**.

Finally, the dicarbonylic compound **24** was submitted to a challenging and scarcely precedented selective reduction of its exocyclic ketone in the presence of the reactive α,β-unsaturated ketone system containing an endocyclic carbonyl moiety. Following the literature, this transformation was performed with $NaBH_4$ at −60 °C, in anhydrous THF to which a small amount of 2-propanol was added.[32] Fortunately, 35% of the target α-phenethyl alcohol (±)-**8** was obtained under these conditions.

Taking into account that the tiny amounts of the natural product that were isolated originally prevented from acquiring suitable optical rotation data, a biotransformation-based synthesis of **8** was also put in place. This choice was based on the facts that the bioreduction of acetophenone derivatives is known to be a highly enantioselective and eco-friendly process.[33]

Thus, the dicarbonylic intermediate **24** was exposed to a suspension of carrot (*Daucus carota* L., Apiaceae) peelings in 0.05 M phosphate buffer, pH 6.5. In this way, the natural product (−)-**8** was obtained in 53% yield, along with 11% of the

1,4-reduced compound (−)-**25**, unveiling an ene-reductase activity, and unreacted starting material. Unfortunately, longer reaction times produced increased amounts of the unwanted compound (−)-**25**, forcing termination of the biotransformation before all the starting material was consumed.

Better yields were obtained when the biotransformation was carried out with chopped pieces of celeriac (*Apium graveolens* L., var. *rapaceum*, Apiaceae) in place of the carrot peelings; in this case, the benzofuranone (−)-**8** $\{[\alpha]_D^{23} = -8.1$ ($c = 4.00$, $CHCl_3$)$\}$ was accessed in 62% yield, along with only 25% of unreacted starting material. Unfortunately, longer reaction times also lead to an increased production of (−)-**25**.

Noteworthy, despite the wide distribution of the ene reductase activity among microorganisms and plants, its presence in carrot and celeriac has not been specifically reported to date.[34] This observation may have impact on the synthesis of the related 2-isopropyl furanone-type natural products.[10a–c,12c,35]

According to literature precedents, the selective bioreduction of aromatic methyl ketones by carrots and celeriac follows "Prelog behaviour",[33e,f] to afford the corresponding *S*-enantiomers.[33a] Hence, this configuration was attributed to the α-phenethyl alcohol centers of (−)-**8** and (−)-**25**. In addition, the chiral HPLC analysis of (−)-**8** determined its enantiomeric excess (ee) as 87%. The IR and ^{1}H NMR spectral data of the thus synthesized compound **8** in both, racemic and optically active forms, were in full agreement with those informed for the natural product.[19] and its ^{13}C NMR spectral data agreed with the proposed structure.

On the other hand, the absolute configuration of the C-2 center of (−)-**25** was established as *S* employing electronic circular dichroism (ECD) measurements and comparing the results with theoretical ECD calculations.[36] These results were also in agreement with the modified octant rule, defining the relationship between the chirality of aryl ketone derivatives and the sign of their high wavelength Cotton effect.[37]

Conclusions

We have developed efficient first total syntheses of the naturally occurring 5-(1-hydroxy-1-ethyl)-2-isopropyliden-2*H*-benzofuran-3-one (**8**), isolated from the Brazilian plant *Verbesina luetzelburgii* in its racemic form and as one of its enantiomers. The syntheses were achieved in 8 steps and 19% overall yield [up to 33% for (−)-**8**] from commercially available 4′-hydroxyacetophenone.

Protecting the carbonyl moiety of the starting ketone, as the 1,3-dioxolane derivative, enabled the development of an efficient *ortho*-formylation of the phenol and a low-temperature Grignard 1,2-addition to a carbonyl group in CH_2Cl_2, as pivotal synthetic steps.

The first critical transformation was complemented with an etherification and a proline-mediated aldolization, which afforded the heterocyclic ring, whilst a secondary alcohol oxidation and a MsCl-assisted dehydration supplemented the second key reaction, and installed the conjugated isopropylidene side chain.

The stability of the cyclic ketal motif combined with its facile deprotection reduced the burden associated to the use of protecting groups during the synthetic sequence, whereas the challenging differentiation between the endocyclic and exocyclic carbonyl groups was performed by chemical ($NaBH_4$/iPrOH) and enzymatic (carrot peels, celeriac chops) means. The strategy developed toward **8** is a useful starting point to gain access to other, still non-synthesized congeners and to unveil their potentially interesting bioactivities. Work in this direction is under way and the results will be disclosed in due time.

Experimental section

General information

The reactions were executed under anhydrous argon atmospheres, employing oven-dried glassware and freshly distilled anhydrous solvents. Anhydrous THF and toluene were obtained by reflux of AR solvents over sodium metal (benzophenone as indicator), followed by distillation. Anhydrous acetone was prepared by refluxing 4 h the AR grade product over dry K_2CO_3 followed by distillation. Anhydrous CH_2Cl_2 was obtained from an M. Braun solvent purification and dispenser system. Anhydrous Et_3N was prepared by refluxing the solvent over CaH_2 for 4 h, followed by distillation. 2-Propanol was dried by reaction with sodium and distillation from the so formed sodium isopropoxide. Anhydrous DMF was prepared by heating and reduced pressure distillation from dry BaO. All the anhydrous solvents were transferred *via* cannula and stored in dry Young ampoules containing molecular sieves. Fresh carrot and celeriac were purchased in a local market. HPLC separations were performed with HPLC grade solvents. All other reagents were used as received.

The reactions were monitored by TLC developed in different hexane–EtOAc solvent mixtures. The chromatographic spots were detected by exposure to 254 nm UV light, and by spraying with ethanolic *p*-anisaldehyde/sulfuric acid reagent, followed by careful heating to improve selectivity. Flash column chromatography was performed with silica gel 60 H (particle size 63–200 μm), eluting with hexane–EtOAc mixtures, under positive pressure and employing solvent gradients.

Equipment

The melting points were measured on an Ernst Leitz Wetzlar model 350 hot-stage microscope. The FT-IR spectra were recorded on a Shimadzu Prestige 21 spectrophotometer, as solid dispersions in KBr disks or as thin films held between NaCl cells.

The nuclear magnetic resonance spectra were acquired in $CDCl_3$ unless otherwise noted, on a FT-NMR Bruker Avance 300 spectrometer, at 300.13 (^{1}H) and 75.48 (^{13}C) MHz. The chemical shifts are consigned in parts per million in the δ scale. TMS was used as the internal standard (resonances of $CHCl_3$ in $CDCl_3$: δ 7.26 and 77.0 for ^{1}H and ^{13}C NMR, respectively). An asterisk (*) designates signals which attribution can be exchanged. The coupling constants (J) and half-width ($w_{1/2}$) values are given in hertz. Some 2D-NMR experiments were also performed.

The high resolution mass spectra were obtained from UMYMFOR (Buenos Aires, Argentina) with a Bruker MicroTOF-Q II instrument. Detection of the ions was performed in electrospray ionization, positive ion mode.

The specific optical rotations were measured with a Jasco DIP-1000 polarimeter using a 1 cm microcell. The circular dichroism measurements were carried out in a Jasco J-710 circular dichroism spectrometer, with a 1 cm cell and the sample dissolved in acetonitrile, at a concentration of 0.25 mg mL^{-1}.

The chiral HPLC determinations were carried out on a Varian Prostar 210 instrument consisting of two pumps, a manual injector fitted with a 20 μL loop and a Prostar 325 variable dual-wavelength UV-vis detector. The determinations were performed on a Chiralcel OD analytical column (250 mm × 4.6 mm I.D., 5 μm particle size) thermostated at 30 °C. The mobile phase was a hexanes : 2-propanol mixture (91/9, v/v), pumped at 1.0 mL min^{-1}. The detection wavelengths were 254 and 360 nm. All samples were filtered through 0.45 μm nylon filters before injection.

4-(2-Methyl-1,3-dioxolan-2-yl)phenol (16). A stirred mixture of 4-hydroxyacetophenone (**11**, 2.00 g, 14.4 mmol), ethane-1,2-diol (1.36 g, 22 mmol), and $Ce(OTf)_3$ (80 mg, 0.07 mmol) in hexane (30 mL) was treated dropwise with $HC(Oi\text{-}Pr)_3$ (4.9 mL, 3.0 mmol). The mixture was stirred for 4 h at room temperature, when it was quenched with Et_3N (101 mg, 1.0 mmol) and saturated aqueous solution of $NaHCO_3$ (10 mL). The organic products were extracted with EtOAc (4 × 20 mL) and combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Column chromatography of the residue afforded **16** (1.80 g, 92%), as a colorless solid, mp 78.5–79.5 °C (Lit. 80–82 °C).[24c] IR (KBr, ν): 3358, 2986, 2891, 1599, 1514, 1371, 1169, 1038 and 837 cm^{-1}. ^1H NMR: δ 7.35 (d, 2H, J = 8.8, H-3, H-5), 6.79 (d, 2H, J = 8.8, H-2, H-6), 4.94 (s, 1H, O*H*), 4.02 (m, 2H, OCH_2CH_2O), 3.78 (m, 2H, OCH$_2$CH_2O) and 1.64 (s, 3H, H-2′). ^{13}C NMR: δ 155.2 (C-4), 135.7 (C-1), 126.8 (2C, C-3 and C-5), 114.9 (2C, C-2 and C-6), 108.8 (C-1′), 64.4 (OCH$_2$-CH_2O) and 27.6 (C-2′).

2-Hydroxy-5-(2-methyl-1,3-dioxolan-2-yl)benzaldehyde (17). Anhydrous $MgCl_2$ (1375 mg, 14.4 mmol) was added at once to a stirred solution of phenol **16** (1.3 g, 7.2 mmol) and anhydrous Et_3N (3.6 mL) in dry THF (30 mL). After stirring for 10 min, anhydrous paraformaldehyde (650 mg, 21.6 mmol) was added and the mixture was heated under reflux for 4 h. The reaction was then cooled to room temperature, treated with a saturated solution of NH_4Cl (10 mL) and the organic products were extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed once with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography of the residue (silica gel, EtOAc–hexane containing 0.1% Et_3N) gave **17** (1382 mg, 92%), as a white solid; mp 78–80 °C. IR (KBr, ν): 3094, 1686, 1655, 1605, 1582, 1385, 1364, 1312, 1275, 1219, 1132, 1072, 956, 904 and 773 cm^{-1}. ^1H NMR: δ 11.0 (s, 1H, O*H*), 9.89 (s, 1H, C*H*O), 7.68 (d, 1H, J = 2.3, H-6), 7.63 (dd, 1H, J = 2.3 and 8.6, H-4), 6.96 (d, 1H, J = 8.6, H-3), 4.05 (m, 2H, OCH_2CH_2O), 3.78 (m, 2H, OCH$_2$CH_2O) and 1.64 (s, 3H, Me). ^{13}C NMR: δ 196.6 (*C*HO), 161.3 (C-2), 135.4 (C-5), 134.3 (C-4), 130.4 (C-6), 120.0 (C-1), 117.6 (C-3), 108.2 (C-2′), 64.6 (2C, OCH_2CH_2O) and 27.5 (Me). HRMS: calcd for $C_{11}H_{13}O_4$ $[M + H]^+$ 209.0808; found 209.0807.

1-((2*S,3*R**)-3-Hydroxy-5-(2-methyl-1,3-dioxolan-2-yl)-2,3-dihydrobenzofuran-2-yl)ethan-1-one (20a) and 1-((2*S**,3*S**)-3-hydroxy-5-(2-methyl-1,3-dioxolan-2-yl)-2,3-dihydrobenzo furan-2-yl)ethan-1-one (20b).** A solution of salicylaldehyde **17** (1 g, 4.8 mmol) in dry acetone was treated with K_2CO_3 (995 mg, 7.2 mmol), $ClCH_2COMe$ (0.5 mL, 6.3 mmol) and a catalytic amount of KI. The reaction was stirred for 2.5 h at 45 °C. After cooling to room temperature, the K_2CO_3 was filtered off and the solvent was evaporated. The organic residue was dissolved with EtOAc (30 mL) and washed with brine (10 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuum, furnishing **19** along with the (3-hydroxy-5-(2-methyl-1,3-dioxolan-2-yl)-2,3-dihydro benzo furan-2-yl)ethan-1-ones **20a,b**, as an inseparable mixture (1.28 g, 98% combined yield). Careful column chromatography enabled the isolation of a small sample of compound **19.** IR (film, ν): 3435, 2986, 2889, 1718, 1684, 1609, 1491, 1175 and 1038 cm^{-1}. ^1H NMR: δ 10.52 (s, 1H, C*H*O), 7.96 (d, 1H, J = 2.4, H-6), 7.63 (dd, 1H, J = 2.4 and 8.7, H-4), 6.76 (d, 1H, J = 8.7, H-3), 4.67 (s, 2H, OCH_2COMe), 3.99–4.01 (m, 2H, OCH$_2$CH_2O), 3.71–3.74 (m, 2H, OCH$_2$CH_2O), 2.30 (s, 3H, OCH$_2$CO*Me*) and 1.60 (s, 3H, Me). ^{13}C NMR: δ 204.0 (OCH$_2$-*C*OMe), 189.1 (*C*HO), 159.4 (C-2), 137.3 (C-5), 133.0 (C-3), 126.2 (C-6), 124.7 (C-1), 112.3 (C-4), 108.2 (C-2′), 73.2 (OCH_2COMe), 64.6 (2C, OCH_2CH_2O), 27.4 (Me-2′) and 26.7 (OCH$_2$CO*Me*). HRMS: calcd for $C_{14}H_{17}O_5$ $[M + H]^+$ 265.1071; found 265.1070.

A portion of the dried extract containing the keto-aldehyde **19** along with **20a,b** (500 mg, 1.88 mmol) was dissolved in DMF (7.5 mL), and successively treated with distilled water (0.035 mL, 1.88 mmol) and L-proline (88 mg, 0.75 mmol). The reaction was stirred for 8 h at 25 °C, when brine (10 mL) was added and the organic products were extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Filtration of the residue through a short pad of silica afforded a barely separable mixture of **20a** and **20b** (475 mg, 95%), as a pale yellow oil (**20a** : **20b** = 1 : 1.6). Compound **20a:** oil; IR (film, ν): 3418, 2986, 2891, 1715, 1614, 1487 and 1038 cm^{-1}. ^1H NMR: δ 7.52 (d, 1H, J = 2.0, H-4), 7.43 (dd, 1H, J = 2.0 and 8.2, H-6), 6.91 (d, 1H, J = 8.2, H-7), 5.51 (d, 1H, J = 6.7, H-3), 4.94 (d, 1H, J = 6.7, H-2), 3.98–4.02 (m, 2H, OCH$_2$CH_2O), 3.73–3.77 (m, 2H, OCH$_2$CH_2O), 2.35 (s, 3H, H-10) and 1.61 (s, 3H, H-9). ^{13}C NMR: δ 206.4 (C-12), 159.2 (C-7a), 137.4 (C-5), 128.5 (C-6), 126.8 (C-3a), 123.0 (C-4), 110.4 (C-7), 108.7 (C-8), 90.6 (C-2), 72.9 (C-3), 64.4 (2C, OCH_2CH_2O), 28.4 (C-10) and 27.7 (C-9). HRMS: calcd for $C_{14}H_{17}O_5$ $[M + H]^+$ 265.1071; found 265.1073. Compound **20b:** oil; IR (film, ν): 3418, 2986, 2891, 1715, 1614, 1487 and 1038 cm^{-1}. ^1H NMR: δ 7.50 (d, 1H, J = 2.0, H-4), 7.40 (dd, 1H, J = 2.0 and 8.2, H-6), 6.91 (d, 1H, J = 8.2, H-7), 5.38 (d, 1H, J = 3.4, H-3), 4.88 (d, 1H, J = 3.4, H-2), 3.98–4.02 (m, 2H, OCH$_2$CH_2O), 3.73–3.77 (m, 2H, OCH$_2$CH_2O), 2.24 (s, 3H, H-10) and 1.60 (s, 3H, H-9). ^{13}C NMR: δ 207.2 (C-12), 159.0 (C-7a), 137.4 (C-5), 128.3 (C-6), 126.7 (C-3a), 122.8 (C-4), 110.2 (C-7), 108.7 (C-8), 94.3 (C-2), 75.1 (C-3), 64.4 (2C, OCH_2CH_2O), 27.7 (C-9) and 26.6 (C-10). HRMS: calcd for $C_{14}H_{17}O_5$ $[M + H]^+$ 265.1071; found 265.1073.

(2*S,3*R**)-2-(2-Hydroxypropan-2-yl)-5-(2-methyl-1,3-dioxolan-2-yl)-2,3-dihydrobenzofuran-3-ol (22a) and (2*S**,3*S**)-2-(2-hydroxypropan-2-yl)-5-(2-methyl-1,3-dioxolan-2-yl)-2,3-dihydrobenzofuran-3-ol (22b).** A stirred solution of **20a,b** (390 mg, 1.5 mmol) in CH_2Cl_2 (7 mL) was cooled to −20 °C and treated dropwise with a 6.4 M solution of MeMgI (0.7 mL, 4.5 mmol). The mixture was stirred for 0.5 h, when a saturated solution of NH_4Cl (10 mL) was added. The reaction was warmed to room temperature and the organic products were extracted with EtOAc (4 × 20 mL). The combined extracts were washed with brine (10 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Chromatography of the residue enabled the recovery of unreacted **20** (75 mg, 19%); increasing solvent polarity furnished a 1 : 3 mixture of **22a** and **22b** (323 mg, 78%), as a thick yellow oil. Compound **22a**: IR (film, ν): 3418, 2984, 2930, 1715, 1690, 1614, 1487, 1373, 1258, 1038 and 824 cm^{-1}. ^1H NMR: δ 7.49 (d, 1H, J = 1.9, H-4), 7.37 (dd, 1H, J = 1.9 and 8.5, H-6), 6.80 (d, 1H, J = 8.5, H-7), 5.37 (d, 1H, J = 4.9, H-3), 4.29 (d, 1H, J = 4.9, H-2), 3.99–4.04 (m, 2H, OCH_2CH$_2$O), 3.77–3.81 (m, 3H, OCH$_2$CH_2O, O*H*), 2.88 (br s, 1H, O*H*), 1.64 (s, 3H, H-9), 1.36 (s, 3H, H-10)* and 1.29 (s, 3H, H-11).* ^{13}C NMR: δ 159.5 (C-7a), 136.6 (C-5), 128.5 (C-3a), 127.8 (C-6), 122.3 (C-4), 109.7 (C-7), 108.8 (C-8), 97.1 (C-2), 73.6 (C-3), 71.5 (C-12), 64.5 (2C, OCH_2-CH_2O), 27.7 (C-9), 25.9 (C-10)* and 24.4 (C11).* HRMS: calcd for $C_{15}H_{20}NaO_5$ $[M + Na]^+$ 303.1203; found 303.1171. Compound **22b**: IR (film, ν): 3418, 2984, 2930, 1715, 1690, 1614, 1487, 1373, 1258, 1038 and 824 cm^{-1}. ^1H NMR: δ 7.52 (d, 1H, J = 1.9, H-4), 7.39 (dd, 1H, J = 1.9 and 8.5, H-6), 6.85 (d, 1H, J = 8.5, H-7), 5.29 (d, 1H, J = 6.0, H-3), 4.21 (d, 1H, J = 6.0, H-2), 3.99–4.04 (m, 2H, OCH_2CH$_2$O), 3.77–3.81 (m, 3H, OCH$_2$CH_2O, O*H*), 2.88 (br s, 1H, O*H*), 1.64 (s, 3H, H-9), 1.57 (s, 3H, H-11)* and 1.51 (s, 3H, H-10).* ^{13}C NMR: δ 159.1 (C-7a), 136.8 (C-5), 129.7 (C-3a), 127.8 (C-6), 122.5 (C-4), 110.0 (C-7), 108.8 (C-8), 89.4 (C-2), 72.9 (C-3),* 72.7 (C-12),* 64.5 (2C, OCH_2CH_2O), 28.4 (C-9), 27.7 (C-10)* and 25.5 (C-11).* HRMS: calcd for $C_{15}H_{20}NaO_5$ $[M + Na]^+$ 303.1203; found 303.1170.

5-Acetyl-2-(2-hydroxypropan-2-yl)benzofuran-3(2*H*)-one (23). PDC/SiO_2 (50% w/w, 1260 mg; 2.2 mmol) was added to a stirred solution of the dihydrobenzofuran-3-ol **21** (300 mg, 1.1 mmol) in anhydrous CH_2Cl_2 (25 mL) and the reaction was further stirred for 3 h at room temperature. 2-Propanol (2 mL) was added and 10 min later the suspension was filtered under reduced pressure through a Celite pad. The flask and the Celite pad were washed with EtOAc (4 × 10 mL) and the filtrate was washed with brine (10 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Chromatography (silica gel, EtOAc–hexane) of the residue gave **22** (240 mg, 96%), as a colorless oil. IR (film, ν): 3439, 2926, 1715, 1614, 1487, 1360, 1256, 1119 and 831 cm^{-1}. ^1H NMR: δ 8.32 (dd, 1H, J = 1.8 and 8.8, H-6), 8.24 (d, 1H, J = 1.8, H-7), 7.23 (d, 1H, J = 8.8, H-4), 4.50 (s, 1H, H-2), 2.87 (bs, 1H, O*H*), 2.60 (s, 3H, H-9), 1.38 (s, 3H, H-10)* and 1.28 (s, 3H, H-11).* ^{13}C NMR: δ 200.0 (C-3), 195.8 (C-8), 175.4 (C-7a), 138.2 (C-6), 131.9 (C-5), 125.6 (C-4), 121.7 (C-3a), 113.8 (C-7), 90.6 (C-2), 72.5 (C-12), 26.4 (C-9), 25.4 (C-11)* and 24.5 (C-10). HRMS: calcd for $C_{13}H_{15}O_4$ $[M + H]^+$ 235.0965; found 235.0957.

5-(1-Hydroxy-1-ethyl)-2-isopropyliden-2*H*-benzofuran-3-one (24). A solution of MsCl (0.33 mL, 4.2 mmol) was added dropwise to a stirred mixture of alcohol **23** (240 mg, 1.0 mmol), pyridine (0.080 mL, 10 mmol) and DMAP (10 mg, 0.09 mmol) in anhydrous CH_2Cl_2 (15 mL) cooled to 0 °C. After 30 min, the solution was left to attain room temperature, and further stirred for 48 h, when it was quenched by addition of brine (10 mL). The organic products were extracted with EtOAc (4 × 15 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue furnished **24** (200 mg, 91%), as a yellow solid, mp 112 °C (dec.). IR (film, ν): 2924, 2853, 1699, 1676, 1609, 1593, 1362, 1261 and 827 cm^{-1}. ^1H NMR: δ 8.30 (d, 1H, J = 1.8, H-4), 8.26 (dd, 1H, J = 1.8 and 8.7, H-6), 7.25 (d, 1H, J = 8.7, H-7), 2.61 (s, 3H, H-9), 2.38 (s, 3H, H-11) and 2.13 (s, 3H, H-10). ^{13}C NMR: δ 196.2 (C-8), 183.0 (C-3), 166.9 (C-7a), 145.4 (C-2), 136.1 (C-6), 134.1 (C-12), 131.9 (C-5), 125.6 (C-4), 123.3 (C-3a), 113.0 (C-7), 26.5 (C-9), 20.3 (C-10) and 17.6 (C-11). HRMS: calcd for $C_{13}H_{13}O_3$ $[M + H]^+$ 217.0859; found 217.0850.

5-(1-Hydroxyethyl)-2-(propan-2-ilidene)benzofuran-3(2*H*)-one [(±)-8]. $NaBH_4$ (10 mg, 0.3 mmol) was added to a stirred solution of **24** (20 mg, 0.09 mmol) in a mixture of THF (1 mL) and i-PrOH (0.060 mL, 0.72 mmol), cooled at −60 °C. The mixture was stirred for 7 h, when it was diluted with toluene (2 mL), acidified with 0.1 M HCl (0.5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with 10% $NaHCO_3$ (3 mL) and brine (5 mL) and dried over $MgSO_4$. The organic solvent was evaporated and the residue was chromatographed (silica gel, CH_2Cl_2–EtOAc), furnishing (±)-**8** (6.9 mg, 35%), as a yellow oil. IR (film, ν): 3620, 3456, 2922, 1730, 1685, 1614, 1492, 1359, 1261 and 1078 cm^{-1}. ^1H NMR: δ 7.71 (d, 1H, J = 2.0, H-4), 7.65 (dd, 1H, J = 2.0 and 8.6, H-6), 7.17 (d, 1H, J = 8.6, H-7), 4.94 (q, 1H, J = 6.7, H-8), 2.36 (s, 3H, H-11), 2.11 (s, 3H, H-10), 1.51 (d, 3H, J = 6.7, H-9) and 1.50 (br s, O*H*). ^{13}C NMR: δ 183.9 (C-3), 164.0 (C-7a), 145.3 (C-2), 140.2 (C-5), 134.0 (C-6), 132.3 (C-12), 123.4 (C-3a), 120.9 (C-4), 112.6 (C-7), 69.6 (C-8), 25.3 (C-9), 20.2 (C-10) and 17.5 (C-11). HRMS: calcd for $C_{13}H_{15}O_3$ $[M + H]^+$ 219.1016; found 219.1020.

(*S*)-5-(1-Hydroxyethyl)-2-(propan-2-ilidene)benzofuran-3(2*H*)-one [(−)-8] and (−)-5-(1-hydroxy-ethyl)-2-isopropyl-benzofuran-3(2*H*)-one [(−)-25]. A solution of **24** (32.6 mg, 0.15 mmol) in THF (0.5 mL) was added to a suspension of carrot peelings (20 g) in a mixture of distilled H_2O (50 mL) and 0.1 M phosphate buffer, pH 6.5 (50 mL) and the mixture was shaken at 70 rpm in an orbital shaker at 25 °C for 4 h. The process was monitored by TLC. The solids were filtered off and washed with distilled H_2O (15 mL); the filtrate was extracted with EtOAc (3 × 15 mL) and the combined organic extracts were washed with brine (10 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue afforded recovered starting material (10 mg), compound (−)-**8** (12.0 mg, 53%), as a colorless oil. $[\alpha]_D^{23} = -8.3$ (c = 2.00, $CHCl_3$), along with **(−)-25** (4 mg, 11%), as a colorless oil. The IR and NMR spectral data of (−)-**8** fully agreed with those recorded for the product obtained by $NaBH_4$-mediated reduction and with the literature.[19] Compound **(−)-25**:

$[\alpha]_D^{23} = -21.1$ ($c = 8.33$, $CHCl_3$); dr = 0.90 by ^1H NMR. IR (film, ν): 3358, 2964, 2340, 1614, 1492, 1244, 1143 and 989 cm^{-1}. ^1H NMR: δ 7.64–7.71 (m, 1H, H-6), 7.60–7.64 (m, 1H, H-7), 7.11 (d, 1H, $J = 8.4$, H-4), 4.91 (q, 1H, $J = 6.4$, H-8), 4.43 (d, 1H, $J = 3.8$, H-2), 2.31–2.38 (m, 1H, H-12), 1.50 (d, 3H, $J = 6.4$, H-9), 1.16 (d, 3H, $J = 6.8$, H-10)* and 0.86 (d, 3H, $J = 6.8$, H-11).* ^{13}C NMR: δ 201.9 (C-3), 172.8 (C-7a), 139.4 (C-5), 135.8 (C-6), 121.7 (C-3a), 120.6 (C-4), 113.4 (C-7), 90.1 (C-2), 69.6 (C-8), 31.0 (C-12), 25.2 (C-9), 18.9 (C-10)* and 15.6 (C-11).* HRMS: calcd for $C_{13}H_{17}O_3$ $[M + H]^+$ 221.1172; found 221.1167.

(*S*)-5-(1-Hydroxyethyl)-2-(propan-2-ilidene)benzofuran-3(2*H*)-one [(−)-8]. To a suspension of finely hand-chopped celeriac (50 g) in a mixture of distilled H_2O (50 mL) and 0.1 M phosphate buffer, pH 6.5 (50 mL) was added a solution of **24** (8 mg, 0.037 mmol) in THF (0.5 mL) and the mixture was shaken at 70 rpm in an orbital shaker at 25 °C for 4 h. The course of the process was monitored by TLC. The solids were filtered off and washed with distilled H_2O (15 mL), the filtrate was extracted with EtOAc (3 × 15 mL) and the combined organic extracts were washed with brine (10 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue gave recovered starting material (2.0 mg, 25%); increasing solvent polarity furnished (−)-**8** [5.0 mg, 62%, (83% based on recovered starting material)], as a colorless oil. $[\alpha]_D^{23} = -8.1$ ($c = 4.00$, $CHCl_3$); ee = 87%, by chiral HPLC (retention times = 11.9 and 13.3 min for the least and most abundant enantiomers, respectively). The IR and NMR spectral data of the product (−)-**8** were in full agreement with those recorded for the product obtained by $NaBH_4$-mediated reduction and with the literature.[19]

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