FULL PAPER

Expedient Approach to 6-Bromo-2-isopropylidenecoumaranone, a Potential Intermediate for the Synthesis of TMC-120B, Pseudodeflectusin, and Their Congeners

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A straightforward approach toward 6-bromo-2-isopropylidenecoumaranone, a potential intermediate toward alkaloid TMC 120-B, pseudodeflectusin, and other natural products, was reported. The synthetic sequence involved the reaction of 3-bromosalicylaldehyde with chloroacetone and cyclization of the resulting ether to a 2-acetylcoumaranol intermediate. This was followed by sequential methyl *Grignard* addition and *Jones*' oxidation to the corresponding coumaranone, which was dehydrated to the final product with the methanesulfonyl chloride/pyridine reagent. The protection of the coumaranol as the corresponding THP-ether resulted in improved product yields.

Keywords: 6-Bromo-2-isopropylidenecoumaranone, TMC-120B, Pseudodeflectusin, Natural product synthesis, Proline-mediated cyclization.

Introduction

The benzofuran framework, consisting of fused benzene and furan rings, has been identified as a privileged core structure [1]. Naturally occurring 2-methylene-3-benzofuranones comprise a series of compounds, widely spread in species of higher plants [2 – 4], which display interesting biological activities; among them, they are antiprotozoan [5] and anti-cancer [6] agents.

The more elaborated 2-isopropylidenecoumaranone motif is present in a smaller range of natural products isolated, to date, exclusively from the Asteraceae family of plants. In addition, some 2-isopropylidenecoumaranones were obtained from fungi, whereas compounds bearing this feature have also been used as valuable synthetic intermediates.

Thus, among the plant-derived compounds, the heterocyclic alcohols **1** and **2** were found in *Verbesina luetselhurgii* MATTF. and *Oyedaea boliviana*, respectively [4][7], whereas the related ester **3** was obtained from the leaves of both, *Enceliopsis couillei* and *E. argophylla* [3][8]. The latter plant also provided the congeneric esters **4** – **7**.

Further, the 5-acetylcoumaranone derivative **8** has been isolated from the perennial herbs *Ligularia kongkalingensis* and *L. nelumbifolia*, which grow in the Chinese provinces of Wuminhshan and Gansu, respectively [9]. The related phenolic ether **9** was obtained from the rhizomatous *Heliopsis helianthoides*, collected in Mexico [10]. However, high concentrations of some of these benzofurans were found in the leaves, probably reflecting their defensive role against herbivorous insects. Finally, the 4,6-dimethoxy derivative **10** was isolated from the little shrub *Calea peckii* grown in Costa Rica [11].

On the other hand, the related 7-chloro derivative **11** was employed as key intermediate for the synthesis of analogs of the antifungal agent, griseofulvin [12], and the 4-hydroxy compound **12** was synthesized as an intermediate toward heterocyclic derivatives containing polysubstituted alkyl ethers that have been patented as antitumor and antimetastatic agents, with activity against the urokinase-type plasminogen activator (uPA) [13].

Another member of this family is the linear furocoumarin **13**, which was obtained from the related, naturally occurring peucedanin and oreoselone [14], and was employed as an intermediate toward the synthesis of polyazamacrocycles.

In addition, the 2-isopropylidene-substituted heterocyclic motif has also been found among the fungal metabolites, pseudodeflectusin (**14**), ustusorane C (**15**), pergillin (**16**), penicisochroman A (**17**), and ustusorane A (**18**), as well as among other ustusoranes. Finally, the feature is also characteristic of the much studied furo[3,2-*h*] isoquinoline alkaloid TMC-120B (**19**) [15].

Pseudodeflectusin (**14**) was isolated from the fungus *Aspergillus pseudodeflectus* and from the sea fan-derived fungus *Penicillium* sp. PSU-F40. The natural product exhibits cytotoxicity toward several human cancer cell lines. On the other hand, tricycle **19** was isolated from

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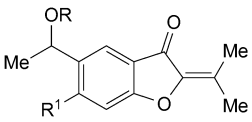
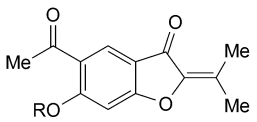
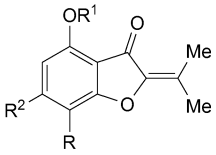


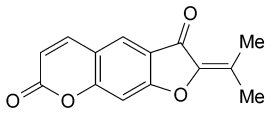
	R	R^1
1	H	H
2	H	MeO
3	Me_2C=CHCO	MeO
4	$MeCH_2CO$	MeO
5	Me_2CHCO	MeO
6	MeCH=C(Me)CO	MeO
7	CH_2=C(Me)CO	MeO



8 R = H
9 R = Me



	R	R^1	R^2
10	H	Me	MeO
11	Cl	Me	MeO
12	H	H	MeO



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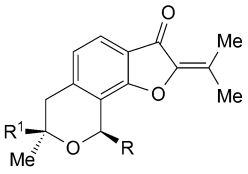
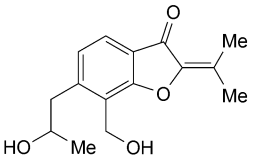


	R	R^1
14	OH	H
15	MeO	H
16	H	OH
17	H	MeO



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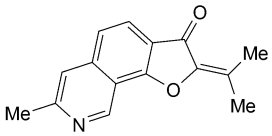

19

Aspergillus ustus TC 1118 and has shown moderate inhibitory activity against the interleukin-5 mediated prolongation of eosinophil survival [16]. Further, we have recently reported that aspergillitine, the alkaloid obtained from *Aspergillus versicolor*, isolated from the marine sponge *Xestospongia exigua*, to which an angular tricyclic chromonic skeleton was assigned, is actually TMC-120B [17]. The interesting bioactivity of the latter compounds has attracted considerable attention, and their total syntheses have been reported [18].

In view of the widespread occurrence of the 2-isopropylidenecoumaranone motif among natural products and taking into account our previous efforts related to TMC-120B [17], herein, we report an efficient approach toward 6-bromo-2-isopropylidenecoumaranone (**20**) from 3-bromophenol (**21**). The former is a potential intermediate toward pseudodeflectusin (**14**), related natural products (**15** – **18**) and alkaloid TMC-120B (**19**).

Results and Discussion

The synthesis was initiated with the transformation of commercial 3-bromophenol (**21**) into the known salicylaldehyde derivative **22** [19] (*Scheme*). The reaction, following *Casiraghi's* protocol [20] with paraformaldehyde in refluxing toluene under $SnCl_4$ catalysis, afforded the aldehyde in 27% yield; however, better results (75%) were obtained under the conditions of *Skatebol* [21] with paraformaldehyde, strictly anhyd. $MgCl_2$, and Et_3N, in refluxing THF.

Despite other alternatives are available that would require extensive protection and deprotection steps [22], it was opted to access the cyclized product **24** more directly, by way of an aldol reaction. To that end, the *Williamson* etherification of aldehyde **22** was performed with freshly prepared monochloroacetone [23] in acetone, employing K_2CO_3 as base.

To be successful, the reaction had to be conducted at temperatures below 40 °C, in order to avoid reduced yields due to the concomitant uncontrolled base-catalyzed cyclization of the resulting acetonyl ether to afford alcohol **24** and its diasteromer **24a**, and the generation of unwanted side products [24]. Under these conditions, the yield of **23** was 82%.

The next step was the 5-*enolexo-exo-trig* aldolization process toward **24**. In order to have better control of the cyclization, the *O*-acetonylsalicylaldehyde **23** was exposed to catalytic amounts of L-proline in DMF, to which 1.0 equivalent of H_2O was added. These conditions furnished 84% of aldol **24** as a single diasteromer, after 36 h at room temperature [25]. The stereochemistry of the resulting solid product was ascertained as *cis* by analysis of the coupling constants between H–C(2) and H–C(3) (J = 6.6 Hz).

It was postulated that the reaction may proceed through an intramolecular version of a *Houk–List*-type transition-state model; this may explain the *cis*-configuration observed [25].

Interestingly, carrying the cyclization reaction in the presence of catalytic amounts of K_2CO_3 enabled the formation of inseparable mixtures of cyclized products, containing variable amounts of the *anti*-isomer **24a** ($J_{H–C(2)\ –\ H–C(3)}$ = 4.5 Hz). The latter proved to be unstable, becoming dehydrated at room temperature with relative ease.

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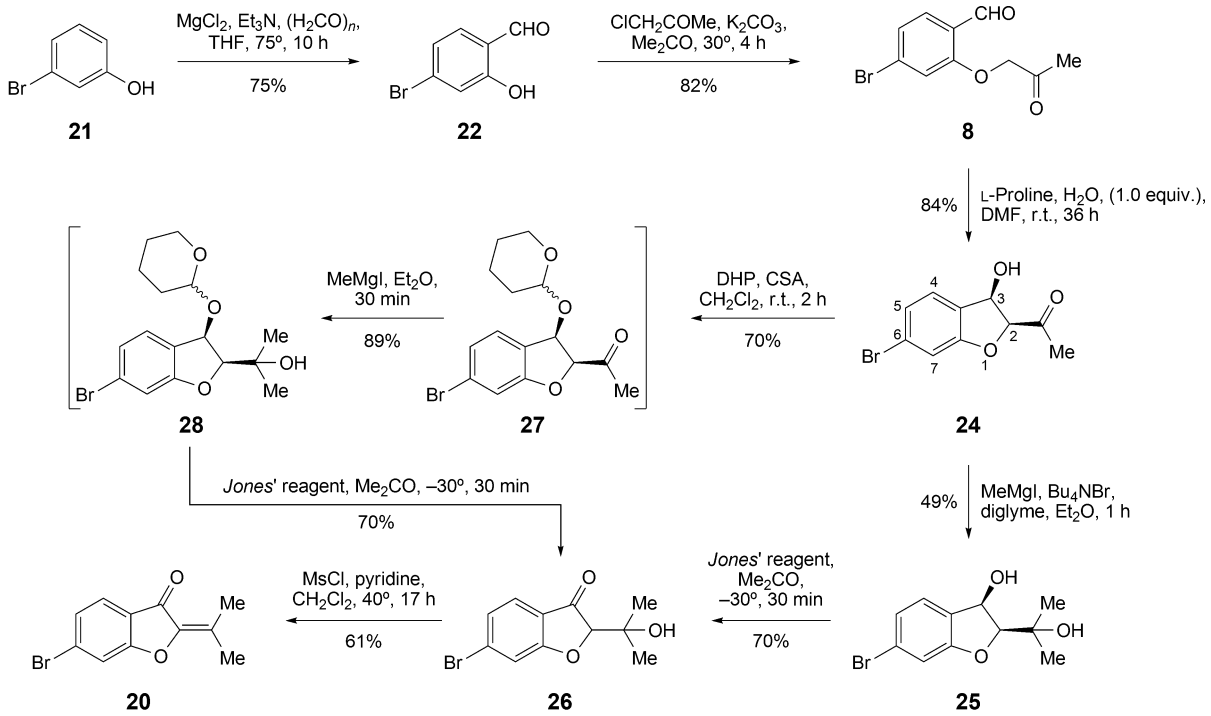
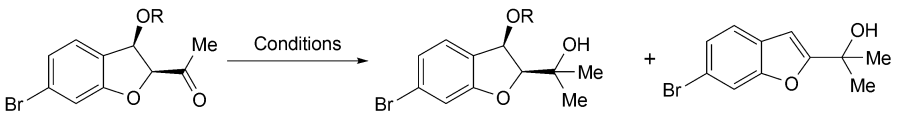
Scheme. Synthesis of 6-bromo-2-isopropylidenecoumaranone (**20**).



Next, the installation of the isopropylidene feature was undertaken, and a *Grignard* addition-alcohol elimination sequence seemed to be the most straightforward approach. However, this transformation proved challenging from the beginning, due to the instability [26] and poor solubility of the starting material in the reaction medium, in addition, to the marked proneness to enolization of the carbonyl moiety.

Thus, the reaction of **24** with MeMgI gave 26% of diol **25** when performed in Et_2O at −78 °C for 30 min. (*Table*, *Entry 1*). Increasing the temperature to −50 °C proved to be detrimental to the yield, despite 4.0 equivalents MeMgI were added (*Entry 2*). However, using diglyme as solvent afforded 31% of the expected diol after 60 min at 0 °C (*Entry 3*) and running the transformation in Et_2O/diglyme in the presence of 1.0 equivalent of Bu_4NBr as additive, the outcome to 49% yield of **25** (*Entry 4*) was improved. A further improvement to 54% was achieved when 1.1 equivalents of LiCl was added (*Entry 5*).

Table. *Grignard* addition to the carbonyl moieties of **24** and **27**



Entry	MeMgI [equiv.]	Solvent	Additive [equiv.]	Temp. [°]	Time [min]	Prod.	Yield [%]
1	2.0	Et_2O	–	−78	30	**25**	26
2	4.0	Et_2O	–	−50	30	**25**	10
3	3.0	Diglyme	–	0	60	**25**	31
4	3.0	Et_2O/Diglyme	Bu_4NBr (1.0)	0	90	**25**	49
5	2.0	Et_2O/Diglyme	Bu_4NBr (1.0), LiCl (1.1)	0	30	**25**	54
6	2.0	Et_2O	$CeCl_3$ (1.0)	0	30	**29**	90
7[a])	3.0	Et_2O	–	−20	30	**28**	89

[a]) The reaction was performed with THP ether **27**.

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This reagent mixture enabled to activate the C=O group, improve substrate solubility, and optimize *Grignard* reactivity [27]. However, the use of 1.0 equivalents of anhyd. $CeCl_3$ gave 90% of benzofuran **29** as the sole product (*Entry 6*).

However, due to the not so unexpected instability of the 1,3-diol **25** and in order to ensure access to a stable heterocycle, the latter was immediately subjected to a *Jones*' oxidation at −20 °C, which enabled to get the ketone **26** in 70% yield.

This outcome prompted to explore modifications in the reaction conditions toward **26**. In order to increase the solubility of the substrate, alcohol **24** was tetrahydropyranylated under mild standard conditions to afford 70% of the diasteromeric THP-ethers **27**, which without separation furnished 89% yield of the expected compound **28** upon exposure to MeMgI at −20 °C during 30 min (*Entry 7*). The spectral complexities of the latter were simplified after reaction with *Jones*' reagent, which enabled *in situ* deprotection of the THP-ether moiety and oxidation of the benzylic alcohol, providing 70% of **26**.

To end the proposed synthesis, dehydration of aldol **26** was required. The use of dimethylformamide dimethyl acetal smoothly furnished 54% yield of **20** after refluxing in Et_2O for 42 h [28]. However, the transformation exhibited poor reproducibility and was difficult to be scaled-up, probably due to its ability to form a vinylogous enaminone from the resulting vinylogous methyl ketone product. Luckily, slightly better but highly reproducible yields (61%) were achieved with the use of the MsCl/pyridine reagent system at 40 °C [29].

Interestingly, a Pd-catalyzed reaction of iodoarenes with 3-aryl-1-(2-*tert*-butyldimethylsilyloxy)phenyl-2-propyn-1-ones toward differentially substituted 2-alkylidenecoumaranones has also been reported [30]. However, the only example given on the use of 3-alkyl instead of 3-aryl substituted starting materials, afforded a 2-alkyl chromenone instead of the expected 2-alkylidenecoumaranone, being this approach unsuitable for targets like **20**.

Conclusions

A straightforward synthesis of 6-bromo-2-isopropylidene coumaranone (**20**) as a potential key intermediate toward pseudodeflectusin (**14**), its congeneric angular tricyclic naturally occurring coumaranones **15** – **18,** and alkaloid TMC-120B (**19**), was carried out. The synthesis featured an L-proline-catalyzed aldolization to form the heterocyclic ring, and a *Grignard* addition – alcohol oxidation and dehydration sequence in order to install the isopropylidene side chain. The OH group protection of the aldol intermediate enabled an improved yield of the final product. The synthesis took place in seven steps and 13.7% overall yield from the commercially available 3-bromophenol (**21**), or six steps and 10.8% yield, when omitting the protection stage.

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Experimental Part

General

All the reactions were carried out under dry N_2 or Ar atmospheres, employing oven-dried glassware. Anhyd. THF, anhyd. Et_2O, and anhyd. diglyme were obtained by reflux of the AR solvent over Na metal (benzophenone as indicator), followed by distillation. Anhys. CH_2Cl_2 were obtained from a solvent purification and dispenser system (*M. Braun*, Stratham, New Hampshire, USA). Anhyd. acetone was prepared by refluxing 4 h the AR grade product over K_2CO_3 and distilling the solvent at atmospheric pressure. Anhyd. Et_3N was prepared by a 4 h reflux of the solvent over CaH_2 followed by atmospheric pressure distillation. Abs. EtOH was prepared by refluxing the product over Mg turnings to which a crystal of iodine was added, and distilling the solvent from the so formed magnesium ethoxide. All other reagents were used as received. M.p.: *Ernst Leitz* (Wetzlar, Germany) model *350* hot-stage microscope and are reported uncorrected.

Chromatographic Methods

The flash column chromatographies were run with silica gel *60 H* (SiO_2; *Merck*, Darmstadt, Germany), eluting with hexane/AcOEt mixtures, under positive pressure and employing gradient of solvent polarity techniques. All new compounds gave single spots on TLC plates (silica gel *60 GF_{254}*) run in different hexane/AcOEt solvent systems. The chromatographic spots were detected by exposure to 254 nm UV light, followed by spraying with ethanolic *p*-anisaldehyde/H_2SO_4 reagent and final careful heating of the plates for improving selectivity. IR spectra: *Shimadzu Prestige 21* (*Shimadzu*, Kyoto, Japan) IR spectrophotometer, as thin films held between NaCl cells for oils or as solid dispersions in KBr disks, for solid samples. Absorption frequencies (ν) are in cm^{-1}. ^{1}H-NMR spectra: 300.13 MHz in $CDCl_3$ on a *Bruker Avance™ 300* (*Bruker*, Rheinstetten, Germany) NMR spectrometer. Chemical shifts are reported in ppm on the δ scale; $w_{1/2}$ and *J*-values are given in Hz. The residual solvent peak ($CHCl_3$ in $CDCl_3$, δ(H) 7.26) was used as the internal standard. ^{13}C-NMR spectra were recorded at 75.48 MHz on a *Bruker Avance* spectrometer. The solvent peak ($CDCl_3$, δ(C) 77.0) was used as the internal standard. In special cases, 2D-NMR experiments (HMBC and HSQC) were also employed to aid the interpretation and assignment of the spectra. HR-MS: *Bruker MicroTOF-Q II* instrument (*Bruker Daltonics*, Billerica, MA, USA). Detection of the ions was performed in electrospray ionization, positive ion mode.

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4-Bromo-2-hydroxybenzaldehyde (**22**). A solution of 3-bromophenol (**21**, 1100 mg, 6.3 mmol) and anhyd. Et_3N (1.8 ml) in dry THF (13 ml) was treated with anhyd. $MgCl_2$ (1200 mg, 12.6 mmol). After stirring for 10 min., $(CHO)_n$ (572 mg, 18.69 mmol) was added and heated under reflux for 10 h. The mixture was then cooled to room temperature, 5% aq. HCl was added, and the product extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The chromatography of the residue gave **22** (950 mg, 75%), as a pale yellow solid. M.p.: 42 °C. Lit.: 50 – 51.5 °C [21]. R_f = 0.66; hexane/AcOEt 85:15. IR (KBr): 3381, 2924, 2850, 1651, 1557, 1479, 1304, 1188, 1067, 907, 862, 799. ^{1}H-NMR: 11.11 (*s*, 1 H, O*H*); 9.85 (*s*, 1 H, CO*H*); 7.41 (*d*, *J* = 8.1, 1 H, H–C(6)); 7.19 (*d*, *J* = 1.6, 1 H, H–C(3)); 7.16 (*dd*, *J* = 8.1, 1.6, 1 H, H–C(5)). ^{13}C-NMR: 195.8 (*C*OH); 161.9 (C(2)); 134.5 (C(6)); 132.0 (C(4)); 123.5 (C(5)); 121.1 (C(3)); 119.5 (C(1)).

4-Bromo-2-(2-oxopropoxy)benzaldehyde (**23**). A solution of aldehyde **22** (800 mg, 3.11 mmol) in dry acetone was treated with K_2CO_3 (644 mg, 4.67 mmol), $ClCH_2COMe$ (2.42 ml, 4.04 mmol), and a catalytic amount of KI. The reaction was stirred for 4 h at 30 °C. After cooling to room temperature, the K_2CO_3 was filtered off, the solvent was evaporated, and the residue was chromatographed, furnishing compound **23** (655 mg, 82%), as a yellow oil. R_f = 0.22; hexane/AcOEt 85:15. IR (film): 3454, 1732, 1680, 1587, 1406, 1246, 1064, 889. ^{1}H-NMR: 10.48 (*s*, 1 H, CO*H*); 7.73 (*d*, *J* = 8.4, 1 H, H–C(6)); 7.24 (*dd*, *J* = 8.4, 1.5, 1 H, H–C(5)); 6.97 (*d*, *J* = 1.5, 1 H, H–C(3)); 4,69 (*s*, 2 H, CH_2COCH$_3$); 2.33 (*s*, 3 H, CH$_2$COC*H*$_3$). ^{13}C-NMR: 202.8 (CH$_2$*C*OCH$_3$); 189.0 (*C*OH); 159.9 (C(2)); 132.5 (C(4)); 130.4 (C(6)); 125.5 (C(5)); 124.0 (C(1)); 116.6 (C(3)); 73.2 (*C*H$_2$COCH$_3$); 26.7 (CH$_2$CO*C*H$_3$). HR-ESI-TOF-MS: 278.9621 ([*M*+Na]$^+$, $C_{10}H_9BrNaO_3^+$; calc. 278.9633).

1-[(2*R,3*S**)-6-Bromo-2,3-dihydro-3-hydroxy-1-benzofuran-2-yl]ethanone** (**24**). To a solution of **23** (500 mg, 1.95 mmol) in DMF (8.3 ml) was added H_2O (0.035 ml, 1.95 mmol) and L-proline (44 mg, 0.39 mmol). The mixture was stirred for 30 h at room temperature. After addition of brine (10 ml), the product was extracted with AcOEt (4 × 25 ml). The organic extracts were combined, successively washed with H_2O (5 × 10 ml) and brine (10 ml), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the residue gave **24** (421 mg, 84%), as a white solid. M.p.: 130 – 132 °C (hexane/AcOEt). R_f = 0.39; hexane/AcOEt 70:30. IR (KBr): 3439, 1714, 1604, 1448, 1286, 1180, 897. ^{1}H-NMR: 7.28 (*d*, *J* = 7.2, 1 H, H–C(4)); 7.15 (*d*, *J* = 1.7, 1 H, H–C(7)); 7.13 (*dd*, *J* = 7.2, 1.7, 1 H, H–C(5)); 5.50 (*d*, *J* = 6.6, 1 H, H–C(3)); 4.96 (*d*, *J* = 6.6, 1 H, H–C(2)); 2.35 (*s*, 3 H, COC*H*$_3$); 1.55 (br. *s*, 1 H, O*H*). ^{13}C-NMR: 205.8 (*C*OCH$_3$); 160.4 (C(7a)); 126.9 (C(4)); 126.0 (C(3a)); 125.2 (C(5)); 124.6 (C(6)); 114.5 (C(7)); 90.7 (C(2)); 72.4 (C(3)); 28.5 (CO*C*H$_3$). HR-ESI-TOF-MS: 278.9628 ([*M*+Na]$^+$, $C_{10}H_9BrNaO_3^+$; calc. 278.9633).

1-[(2*S,3*S**)-6-Bromo-2,3-dihydro-3-hydroxy-1-benzofuran-2-yl]ethanone** (**24a**). K_2CO_3 (7 mg, 0.05 mmol) was added to a solution of **23** (50 mg, 0.20 mmol) in AcOEt (25 ml), and the solvent was slowly evaporated in a rotary evaporator at 40 °C. AcOEt (10 ml) was added to the residue, the solid was filtered off, and the solvent was evaporated under reduced pressure. The residue was chromatographed, furnishing an inseparable mixture of cyclized compounds containing **24** and **24a** (35 mg, 70%), as an oil. Compound **24a**: R_f = 0.39; hexane/AcOEt 70:30. ^{1}H-NMR: 7.24 (*d*, *J* = 8.0, 1 H, H–C(4)); 7.14 (*d*, *J* = 1.5, 1 H, H–C(7)); 7.14 (*dd*, *J* = 8.0, 1.5, 1 H, H–C(5)); 5.50 (br. *d*, *J* = 4.5, 1 H, H–C(3)); 4.89 (*d*, *J* = 4.5, 1 H, H–C(2)); 2.25 (*s*, 3 H, COC*H*$_3$); 1.55 (br. *s*, 1 H, O*H*). ^{13}C-NMR: 206.4 (*C*OCH$_3$); 160.1 (C(7a)); 125.2 (C(4)); 126.0 (C(3a)); 125.2 (C(5)); 124.5 (C(6)); 114.4 (C(7)); 94.6 (C(2)); 74.6 (C(3)); 26.6 (CO*C*H$_3$). HR-ESI-TOF-MS: 278.9628 ([*M* + Na]$^+$, $C_{10}H_9BrNaO_3^+$; calc. 278.9633).

6-Bromo-2,3-dihydro-2-(1-hydroxypropan-2-yl)-1-benzofuran-3-ol (**25**). A mixture of MeMgI (1.5 ml, 1.38 mmol), Bu_4NBr (27 mg, 0.092 mmol), and LiCl (21 mg, 0.51 mmol) in a mixture of anhyd. Et_2O (1.4 ml) and anhyd. diglyme (0.17 ml, 1.14 mmol) was stirred for 30 min at 0 °C. Then, a solution of methyl ketone **24** (125 mg, 0.46 mmol) in ether (0.5 ml) was added and the mixture was allowed to warm to room temperature. After 1 h, the reaction was quenched with saturated solution of NH_4Cl (5 ml) and extracted with CH_2Cl_2 (4 × 20 ml). The combined organic extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed, affording diol **25** (68 mg, 54%) as a brownish oil. R_f = 0.21; hexane/AcOEt 70:30. IR (film): 3377, 2924, 1603, 1472, 1225, 1005, 893. ^{1}H-NMR: 7.26 (*d*, *J* = 7.5, 1 H, H–C(4)); 7.08 (*dd*, *J* = 7.5, 1.7, 1 H, H–C(5)); 7.06 (*d*, *J* = 1.7, 1 H, H–C(7)); 5.27 (*d*, *J* = 6.2, 1 H, H–C(3)); 4.24 (*d*, *J* = 6.2, 1 H, H–C(2)); 4.03 (br. *s*, 1 H, O*H*–C(3)); 2.71 (br. *s*, 1 H, C(CH$_3$)$_2$O*H*); 1.56 (*s*, 3 H, COHC*H*$_3$); 1.50 (*s*, 3 H, COHC*H*$_3$). ^{13}C-NMR: 160.2 (C(7a)); 129.2 (C(3a)); 126.5 (C(4)); 124.6 (C(5)); 123.7 (C(6)); 114.1 (C(7)); 89.7 (C(2)); 72.8 (*C*OHCH$_3$); 72.4 (C(3)); 28.4 (COH*C*H$_3$); 25.3 (COHCH$_3$). HR-ESI-TOF-MS: 294.9945 ([*M*+Na]$^+$, $C_{11}H_{13}BrNaO_3^+$; calc. 294.9946).

2-(6-Bromo-1-benzofuran-2-yl)propan-2-ol (**29**). To a solution of **24** (100 mg, 0.39 mmol) in ether (3 ml) was slowly added at 0 °C MeMgI (0.95 ml, 0.78 mmol) and $CeCl_3$ (96 mg, 0.39 mmol). After stirring the reaction at 0 °C for 30 min it was quenched with NH_4Cl (5 ml) and extracted with CH_2Cl_2 (4 × 20 ml). The combined organic extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed, affording **29** (89.5 mg, 90%) as a brownish oil. R_f = 0.52; hexane/AcOEt 70:30. IR (film): 3381.2, 2982.0, 1606.7, 1452.0, 1273.0, 1168.9, 898.8. ^{1}H-NMR: 7.61 (*d*, *J* = 1.6 Hz, 1 H, H–C(7)); 7.38 (*d*, *J* = 8.3, 1 H, H–C(4)); 7.32 (*dd*, *J* = 8.3, 1.6, 1 H, H–C(5)); 6.54 (*s*, 1 H, H–C(3)); 2.19 (br. *s*, $w_{1/2}$ = 25 Hz, 1 H, O*H*); 1.66 (*s*, 6

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H, COH(CH_3)$_2$). ^{13}C-NMR: 163.7 (C(2)); 155.0 (C(7a)); 127.4 (C(3a)); 126.1 (C(5)); 121.9 (C(4)); 117.1 (C(6)); 114.7 (C(7)); 100.3 (C(3)); 69.3 (*C*OHCH$_3$); 28.7 (COH*C*H$_3$); 28.7 (COH*C*H$_3$). HR-ESI-TOF-MS: 292.9786 ([*M*+Na]$^+$, $C_{11}H_{11}BrNaO_2^+$; calc. 276.9840).

6-Bromo-2-(1-hydroxypropan-2-yl)-1-benzofuran-3(2*H*)-one (**26**). *Method A*: A solution of chromium trioxide and sulfuric acid in acetone (*Jones*' reagent, 0.083 ml, 0.66 mmol) was slowly added to a stirred solution of diol **25** (60 mg, 0.22 mmol) in acetone (6 ml), cooled at −20 °C. The reaction was allowed to warm to 0 °C and the excess of *Jones* reagent was quenched with isopropyl alcohol. Then, the pH of the solution was adjusted to 4.0 with a saturated solution of NaOAc, the solvent was evaporated under reduced pressure and the product extracted with Et_2O (4 × 20 ml). The combined organic extracts were washed with brine (5 ml), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the residue provided the ketone **26** (42 mg, 70%) as a brownish oil. R_f = 0.47; hexane/AcOEt 70:30. IR (film): 3418, 2926, 1713, 1601, 1427, 1315, 1198, 1016, 883. ^{1}H-NMR: 7.51 (*d*, *J* = 8.4, 1 H, H–C(4)); 7.37 (*d*, *J* = 1.4, 1 H, H–C(7)); 7.24 (*dd*, *J* = 8.4, 1.4, 1 H, H–C(5)); 4.39 (*s*, 1 H, H–C(2)); 2.96 (br. *s*, 1 H, O*H*); 1.35 (*s*, 3 H, COHC*H*$_3$); 1.24 (*s*, 3 H, COHC*H*$_3$). ^{13}C-NMR: 199.8 (C(3)); 172.9 (C(7a)); 133.2 (C(6)); 126.2 (C(5)); 125.1 (C(4)); 120.1 (C(3a)); 117.0 (C(7)); 89.8 (C(2)); 72.4 (*C*OHCH$_3$); 25.6 (COH*C*H$_3$); 24.3 (COH*C*H$_3$). HR-ESI-TOF-MS: 292.9781 ([*M*+Na]$^+$, $C_{11}H_{11}BrNaO_3^+$; calc. 292.9789).

6-Bromo-2-(1-hydroxypropan-2-yl)-1-benzofuran-3(2*H*)-one (**26**). *Method B*: Dihydropyran (0.08 ml, 0.88 mmol), camphorsulfonic acid (6.8 mg, 0.030 mmol), and powdered 4 Å molecular sieves (100 mg) were successively added to a solution of **24** (150 mg, 0.59 mmol) in CH_2Cl_2 (6 ml). The reaction was stirred at room temperature for 2 h, when brine (7 ml) was added, and the product was extracted with AcOEt (4 × 20 ml). The combined organic extracts were washed with brine (5 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed, giving **27** (140 mg, 70%) as a brownish oil. R_f = 0.68; hexane/AcOEt 70:30. IR (film) 2941, 1725, 1600, 1473, 1356, 1219, 1118, 1020, 891. ^{1}H-NMR: 7.28 (*d*, *J* = 8.4, 1 H, H–C(4)); 7.22 (*d*, *J* = 7.9, 1 H, H–C(4)); 7.15 (*m*, 1 H, H–C(7)); 7.12 (*m*, 1 H, H–C(5)); 5.42 (*d*, *J* = 7.4, 1 H, H–C(3)); 5.41 (*d*, *J* = 6.4, 1 H, H–C(3)); 4.95 (*d*, *J* = 6.4, 1 H, H–C(2)); 4.91 (*d*, *J* = 7.4, 1 H, H–C(2)); 3.67 (*m*, 2 H, H–C(6′)); 2.36 (*s*, 3 H, COC*H*$_3$); 2.28 (*s*, 3 H, COC*H*$_3$); 1.55 (m, 2 H, H–C(5′); 1.53 (*m*, 2 H, H–C(4′); 1.51 (*m*, 2 H, H–C(3′). ^{13}C-NMR: 206.2 (*C*OCH$_3$); 204.3 (*C*OCH3); 161.2 (C(7a)); 160.7 (C(7a)); 128.1 (C(4)); 127.9 (C(3a)); 127.3 (C(3a)); 127.2 (C(4)); 125.3 (C(6)); 124.9 (C(5)); 124.7 (C(6)); 124.4 (C(5)); 114.7 (C(7)); 114.2 (C(7)); 100.5 (C(2′)); 93.3 (C(2′)); 90.1 (C(2)); 89.7 (C(2)); 78.9 (C(3)); 73.1 (C(3)); 62.6 (C(3′)); 61.7 (C(3′)); 30.3 (C(6′)); 29.8 (C(6′)); 28.2 (CO*C*H$_3$); 28.1 (CO*C*H$_3$); 25.2 (C(5′)); 19.0 (C(4′)); 18.4 (C(4′)). HR-ESI-TOF-MS: 363.0202 ([*M*+Na]$^+$, $C_{15}H_{17}BrNaO_4^+$; calc. 363.0208).

A solution of MeMgI (0.65 ml, 0.56 mmol), in Et_2O (0.6 ml) was slowly added at −20 °C to a solution of the methyl ketone **27** (125 mg, 0.37 mmol) in anhyd. Et_2O (0.4 ml) and the mixture was allowed to warm to room temperature. After 1 h, the reaction was quenched with NH_4Cl (5 ml) and extracted with CH_2Cl_2 (4 × 20 ml). The pooled organic extracts were washed with brine (5 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed to yield alcohol **28** (118 mg, 89%) as a brownish oil. R_f = 0.37; hexane/AcOEt 80:20. HR-ESI-TOF-MS: 379.0511 ([*M*+Na]$^+$, $C_{16}H_{21}BrNaO_4^+$; calc. 379.0515).

A solution of *Jones*' reagent (0.124 ml, 0.93 mmol) was slowly added to a stirred solution of protected alcohol **28** (110 mg, 0.31 mmol) in acetone (9 ml), cooled at −20 °C. The reaction was allowed to warm to 0 °C and the excess of *Jones*' reagent was quenched with ^{i}PrOH. Then, the pH of the solution was adjusted to 4.0 with a saturated solution of AcONa, the solvent was evaporated under reduced pressure, and the product extracted with Et_2O (4 × 20 ml). The combined organic extracts were washed with brine (5 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The chromatography of the residue provided the ketone **26** (59 mg, 70%) as a brownish oil. The NMR and IR data of the product were in agreement with those recorded for **26**, when obtained from **25**.

6-Bromo-2-(propan-2-ylidene)-1-benzofuran-3(2*H*)-one (**20**). A solution of MsCl in CH_2Cl_2 (2M, 0.9 ml, 1.8 mmol) was dropwise added to a stirred solution of ketone **26** (50 mg, 0.18 mmol) and DMAP (4.5 mg, 0.04 mmol) in anhyd. pyridine (0.3 ml). The reaction was further stirred for 17 h at 40 °C, when it was cooled to room temperature and the pH was adjusted to 4 – 5 with a solution of HCl (10% w/v). Then, the product was extracted with CH_2Cl_2 (4 × 20 ml), the combined organic extracts were washed with water (5 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The chromatography of the residue gave the coumaranone derivative **20** (25 mg, 61%) as a yellowish solid. M.p.: 43 – 45 °C. R_f = 0.79; hexane/AcOEt 70:30. IR (KBr): 2924, 2359, 1745, 1703, 1651, 1599, 1427, 1313, 1117, 899. ^{1}H-NMR: 7.60 (*d*, *J* = 8.3, 1 H, H–C(4)); 7.40 (*d*, *J* = 1.6, 1 H, H–C(7)); 7.27 (*dd*, *J* = 8.3, 1.6, 1 H, H–C(5)); 2.35 (*s*, 3 H, CH$_3$); 2.09 (*s*, 3 H, CH$_3$). ^{13}C-NMR: 182.7 (C(3)); 164.5 (C(7a)); 145.0 (C(2)); 130.5 (C(6)); 126.0 (C(5)); 125.2 (C(4)); 122.5 (C(3a)); 116.1 (C(7)); 133.1 (*C*(CH$_3$)$_2$); 20.2 (CH$_3$); 17.5 (CH$_3$). HR-ESI-TOF-MS: 274.9667 ([*M*+Na]$^+$, $C_{11}H_9BrNaO_2^+$; calc. 274.9684).

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