Synthesis of the Pyranonaphthoquinones Dehydroherbarin, (+)-Astropaquinone B and (+)-Astropaquinone C en Route to Ascomycones A and B

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Abstract: The total syntheses of the pyranonaphthoquinone natural products dehydroherbarin, (+)-astropaquinone B and (+)-astropaquinone C are described. A late stage oxidation strategy employed for the synthesis of the astropaquinones was not amenable to the conversion of dehydroherbarin into the ascomycones. The syntheses of astropaquinones B and C reported herein constitute the first total syntheses and their absolute stereochemistry was determined to be (1*R*,3*S*).

Key words: pyranonaphthoquinone, ascomycone, astropaquinone, dehydroherbarin, thysanone, 3C-protease inhibitor

Due to the ongoing studies in our laboratory on the 3C-protease inhibitory properties[1] of the pyranonaphthoquinone (–)-thysanone (**1**),[2] we were attracted to two recent reports that described the isolation of the structurally related ascomycones A and B (**2** and **3**)[3] and astropaquinones B and C (**4** and **5**)[4] from an unidentified ascomycete and the freshwater fungus *Astrosphaeriella papuana*, respectively. Due to the inherent structural similarity of **2**–**5** to the 3C-protease inhibitor (–)-thysanone (**1**), we decided to execute the syntheses of **2**–**5** in order to probe their potential as 3C-protease inhibitors thus also completing the first total syntheses of these natural products (Figure 1).

The retrosynthesis of **2**–**5** is based on our successful synthesis of the 3C-protease inhibitor (–)-thysanone (**1**). It was envisaged that ascomycone A (**2**) would be readily available from methylation of ascomycone B (**3**). Ascomycone B (**3**) would be accessed via chemoselective demethylation and benzylic oxidation of the pyranonaphthoquinone natural product dehydroherbarin[5] **6**, which in turn is available from oxidation of naphthol **8**. Staunton–Weinreb annulation[6] of aromatic coupling partner **10** with lactone **11** followed by reduction provides ready access to **8**. Similarly, astropaquinones B (**4**) and C (**5**) can be accessed via union of the same aromatic coupling partner **10** with (*S*)-lactone **12**. Oxidation of **9** and benzylic oxidation of the resulting pyranonaphthoquinone **7** affords astropaquinone C (**5**), which, upon methylation, then affords astropaquinone B (**4**; Scheme 1).

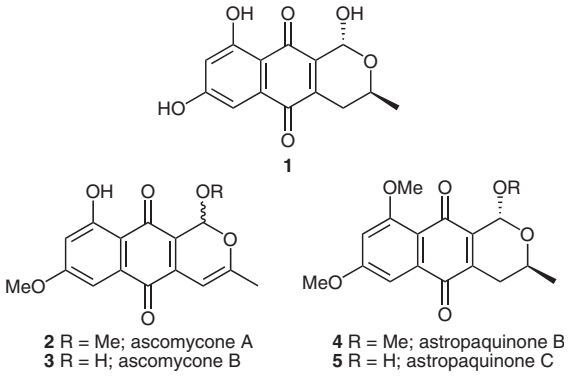
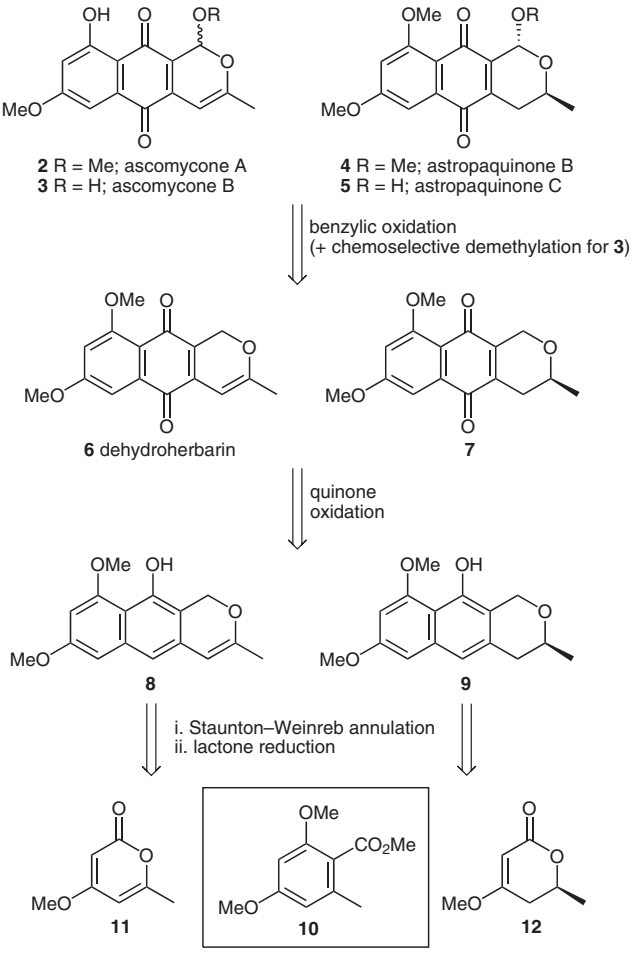


Figure 1 Thysanone, ascomycones A and B and astropaquinones B and C



Scheme 1 Retrosynthesis of ascomycones A/B (**2**/**3**) and astropaquinones B/C (**4**/**5**)

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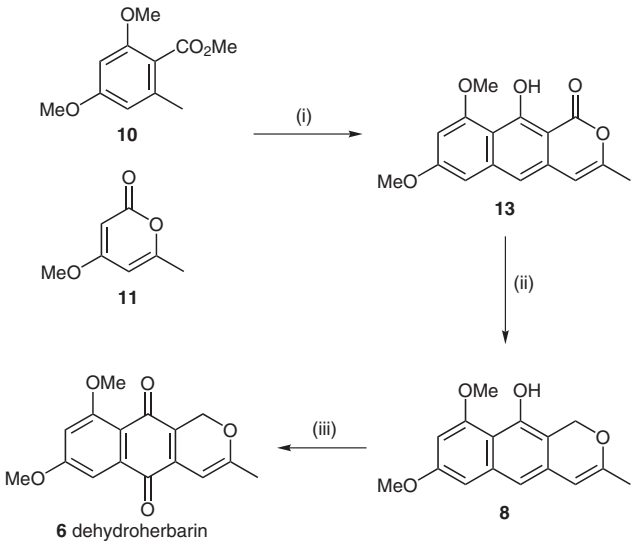
With these ideas in mind, the synthesis of ascomycones A (**2**) and B (**3**) was initiated (Scheme 2). Aromatic coupling partner **10** was available in multigram quantities by using our previously described procedure.[2] Lactone **11** was prepared in multigram quantities by straightforward methylation of commercially available triacetic acid lactone (TAL).[7] Following the literature procedure,[8] Staunton–Weinreb annulation of **10** with **11** proceeded smoothly to furnish naphthol **13**,[6a,8] with the poor yield consistent with literature results. With naphthol **13** in hand, reduction of the lactone was next undertaken. Borane-based reductions were abandoned due to ready hydroboration of the pyran double bond being observed thereby restricting yields of **8** to <15%. After attempting a plethora of metal hydride based conditions, it was found that addition of four equivalents of diisobutylaluminum hydride in toluene to a solution of lactone **13** in tetrahydrofuran delivered **8** in good yield (67%). In a result that has not been rationalized at this time, conducting the same experiment with different diisobutylaluminum hydride solutions (CH_2Cl_2, hexanes, or THF) with the substrate **13** dissolved in solvents other than tetrahydrofuran (toluene, hexanes, or CH_2Cl_2) prior to addition of the reducing agent, only led to poor yields of the desired product **8** (0–25%).



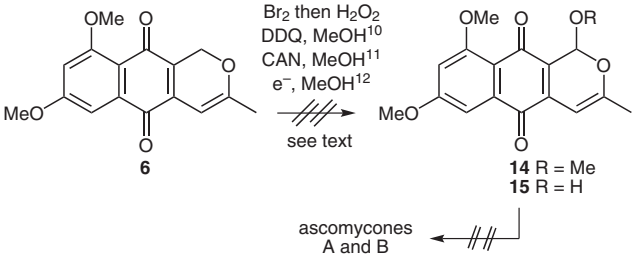
Scheme 2 *Reagents and conditions*: (i) LDA, THF, –78 °C to r.t., 16 h, 27%; (ii) DIBAL-H (1.2 M in toluene), THF, r.t., 48 h, 67%; (iii) O_2, salcomine, MeCN, r.t., 3 h, 72%.

With **8** in hand, smooth oxidation with salcomine delivered the purple natural product dehydroherbarin **6** in excellent yield, for which the spectroscopic data was in full agreement with the literature.[5,9] It is also noteworthy that, although not the primary aim of the work, this sequence provides a shorter route to dehydroherbarin **6** (five steps) than those reported to date.[9]

With sufficient quantities of dehydroherbarin **6** in hand, the key benzylic oxidation could be attempted. Following the successful two-step protocol employed during our total synthesis of (–)-thysanone (**1**), a solution of dehydroherbarin **6** and bromine (1.05 equiv) in carbon tetrachloride was irradiated with a tungsten filament lamp at a variety of temperatures.

Although TLC indicated consumption of the starting material, no benzylic bromide could be detected by NMR analysis, with mostly degradation products being observed; subsequent hydrolysis did not furnish ascomycone B methyl ether **15**. Confident that the double bond present in the pyran ring of dehydroherbarin **6** was adversely affecting the bromination, the literature was surveyed to find a direct oxidation protocol that would circumvent the need to proceed through an intermediate benzylic bromide.

The direct introduction of a methoxy group into the benzylic position of isochroman derivatives has been achieved using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[10] and cerium(IV) ammonium nitrate (CAN),[11] however in the present case only degradation was observed and the desired product (ascomycone A methyl ether **14**) was not detected using these reagents at a variety of temperatures. Electrochemical oxidation[12] also failed to deliver compound **14** (Scheme 3).



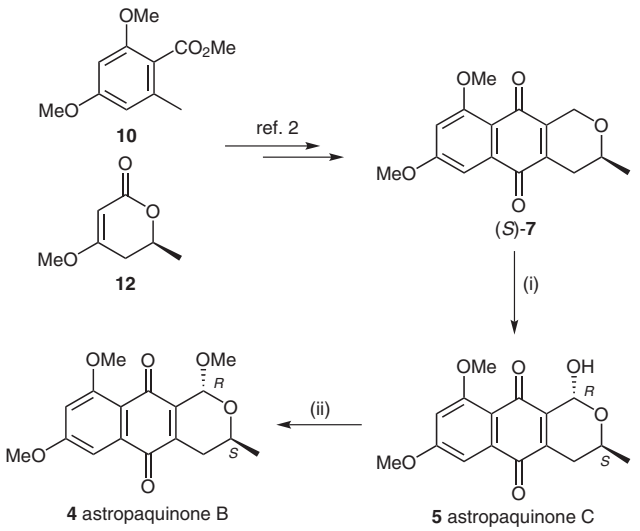
Scheme 3 Unsuccessful benzylic oxidation approach to the ascomycones

Astropaquinones

Undeterred by the disappointing results obtained for the attempted synthesis of the ascomycones, our attention next turned to the synthesis of astropaquinones B (**4**) and C (**5**). By repeating the initial stages of our chiral pool based total synthesis of (–)-thysanone (**1**),[2] we were able to obtain suitable quantities of enantiopure (*S*)-pyranonaphthoquinone (**7**) (Scheme 4).

Gratifyingly, subjecting **7** to radical bromination followed by hydrolysis delivered astropaquinone C (**5**) as a single diastereomer. Facile methylation then delivered astropaquinone B (**4**), again as a single diastereomer (Scheme 4). The spectroscopic data of both astropaquinone B (**4**) and C (**5**) were in excellent agreement with the literature values[4] (Figure 2, Table 1).

Next, we set out to determine the absolute configuration of **4** and **5**. In our hands, the optical rotation of synthetic astropaquinone B (**4**) and astropaquinone C (**5**) were of the same sign and of similar magnitude to those reported in the literature[4] (Table 2). The difference in values is not surprising as the structurally similar pyranonaphthoquinone (–)-thysanone (**1**) has been reported to display vast fluctuations in its optical rotation value.[14] Thus, we con-



Scheme 4 *Reagents and conditions*: (i) Br_2, Bz_2O_2, CCl_4, 60-W lamp, reflux, 1.5 h then THF–H_2O, r.t., 1.5 h, 91%; (ii) *p*-TsOH, MeOH, r.t., 16 h, 80%.

clude that the absolute stereochemistry of both astropaquinones B (**4**) and C (**5**) is in fact (1*R*,3*S*).

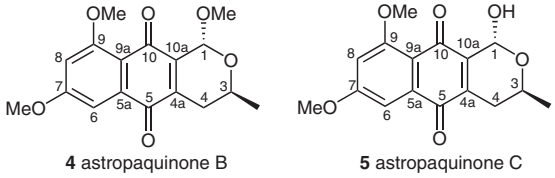


Figure 2 Carbon numbering in astropaquinones B and C

In conclusion, the total syntheses of astropaquinones B (**4**) and C (**5**) has been achieved, thus confirming the absolute stereochemistry of both natural products to be (1*R*,3*S*). An investigation into the 3C-protease-inhibitory properties of **4**, **5** and **6** is in progress. Extension of the direct oxidation strategy used for the synthesis of unsaturated ascomycones A (**2**) and B (**3**) has remained elusive to date.

Table 1 ^1H and ^{13}C NMR Data for Natural[4] and Synthetic Astropaquinones B (**4**) and C (**5**)[a]

	Astropaquinone B (**4**)				Astropaquinone C (**5**)			
	Natural[4]		Synthetic		Natural[4]		Synthetic	
Position[b]	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	5.45 (s)	93.7	5.54 (s)	93.7	6.03 (s)	87.1	5.99 (s)	87.1
1-OMe	3.49 (s)	55.9	3.57 (s)	55.9				
3	4.14 (m)	62.0	4.21 (m)	62.0	4.35 (m)	62.8	4.26 (m)	62.8
4	2.60 (dd, *J* = 19.1, 3.4 Hz, H-eq), 2.18 (dd, *J* = 19.0, 11.1 Hz, H-ax)	28.9	2.66 (dd, *J* = 19.1, 3.6 Hz, H-eq), 2.23 (dd, *J* = 19.1, 11.2 Hz, H-ax)	29.0	2.73 (dd, *J* = 19.1, 3.2 Hz, H-eq), 2.27 (dd, *J* = 19.0, 11.0 Hz, H-ax)	29.0	2.69 (dd, *J* = 19.2, 3.3 Hz, H-eq), 2.18 (dd, *J* = 19.2, 10.8 Hz, H-ax)	29.1
4a		140.6		140.6		140.3		140.4
5		184.9		184.9		184.6		184.7
5a		135.6		135.6		135.7		135.8
6	7.16 (d, *J* = 2.3 Hz)	103.4	7.24 (d, *J* = 2.4 Hz)	103.2	7.25 (d, *J* = 2.3 Hz)	103.5	7.25 (d, *J* = 2.4 Hz)	103.6
7		164.6		164.5		164.8		164.8
7-OMe	3.86 (s)	56.1	3.92 (s)	56.1	3.97 (s)	56.4	3.94 (s)	56.5
8	6.66 (d, *J* = 2.3 Hz)	104.2	6.72 (d, *J* = 2.4 Hz)	104.3	6.73 (d, *J* = 2.3 Hz)	104.2	6.71 (d, *J* = 2.4 Hz)	104.3
9		162.0		162.0		162.0		162.1
9-OMe	3.87 (s)	56.2	3.94 (s)	56.2	3.96 (s)	56.0	3.93 (s)	56.0
9a		114.7		114.2		113.9		114.1
10		180.9		180.8		182.0		182.0
10a		140.8		141.0		142.1		142.2
11	1.31 (d, *J* = 6.3 Hz)	20.8	1.38 (d, *J* = 6.2 Hz)	21.0	1.51 (d, *J* = 6.7 Hz)	21.0	1.36 (d, *J* = 6.3 Hz)	21.1

[a] Solvent: $CDCl_3$, shifts given in ppm units.
[b] See Figure 2 for the atom-numbering of **4** and **5**.

Table 2 Optical Rotation Values of Natural and Synthetic Astropaquinone B (**4**) and C (**5**)

	Optical rotation (Natural)[4]	Optical rotation (Synthetic)
Astropaquinone B	$[\alpha]_D^{27.8}$ +45.1 (*c* 0.12, $CHCl_3$)	$[\alpha]_D^{19}$ +35.0 (*c* 0.14, $CHCl_3$)
Astropaquinone C	$[\alpha]_D^{24.7}$ +53.9 (*c* 0.10, $CHCl_3$)	$[\alpha]_D^{19}$ +31.1 (*c* 0.10, $CHCl_3$)

All reactions were carried out in flame-dried or oven-dried glassware under an anhydrous nitrogen atmosphere unless otherwise stated. THF and Et_2O were dried over sodium wire. CH_2Cl_2, pyridine and Et_3N were dried over CaH_2. EtOH and MeOH were dried over magnesium ethoxide and methoxide, respectively. All solvents were distilled prior to use. Flash chromatography was carried out using 0.063–0.1 mm silica gel with the desired solvent. Thin layer chromatography (TLC) was performed using UV fluorescence and/or staining with: vanillin in methanolic sulfuric acid, a solution of ammonium heptamolybdate and cerium sulfate in aqueous sulfuric acid, iodine, or a solution of potassium permanganate and potassium carbonate in aqueous sodium hydroxide. High-resolution mass spectra were recorded at a nominal resolution of 5000 to 10000. Infrared spectra were obtained using a Perkin–Elmer Spectrum One Fourier Transform IR spectrometer with a universal attenuated total refractance (ATR) attachment installed. Absorption maxima are expressed as wavenumbers (cm^{-1}). NMR spectra were recorded with either a Bruker DRX300 spectrometer operating at 300 MHz for ^1H nuclei and 75 MHz for ^{13}C nuclei, or with a Bruker DRX400 spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei. All chemical shifts are reported in parts per million (ppm) relative to TMS (^1H) and $CDCl_3$ (^{13}C). ^1H NMR data is reported as chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; dd, doublet of doublets; dt, doublet of triplets), coupling constant (*J*, Hz), relative integral and assignment. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Methyl 2,4-Dimethoxy-6-methylbenzoate (10)[2]

To a soln of methyl 2,4-dihydroxy-6-methylbenzoate[13] (0.8 g, 5.25 mmol) in acetone (20 mL) and DMF (2 mL) was added K_2CO_3 (4.35 g, 31.5 mmol) and TBAI (50 mg) followed by dimethylsulfate (1.99 mL, 21 mmol), and the resulting mixture was heated under reflux for 16 h. A soln of aq. HCl (1 M, 50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel; hexanes–EtOAc, 4:1) gave the title compound **10**.

Yield: 0.78 g, 3.7 mmol (71%); colourless oil that crystallised upon standing; mp 39–40 °C (Lit.[2] 41.6 °C).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3 H, Me), 3.78 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 6.30 (s, 2 H, Ar-H).

The ^1H NMR data obtained were in agreement with those reported in the literature.[2]

4-Methoxy-6-methyl-2*H*-pyran-2-one (11)[7,15]

To a soln of 4-hydroxy-6-methyl-2*H*-pyran-2-one (triacetic acid lactone, 2.25 g, 17.8 mmol) in anhydrous acetone (55 mL) was added K_2CO_3 (5.0 g, 36.3 mmol) and dimethyl sulfate (2.0 mL, 21.1 mmol). The reaction mixture was heated to reflux (~85 °C) and stirred for 3 h, then the contents of the reaction vessel were poured into sat. aq NH_4Cl (130 mL) and extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The remaining orange solid was purified by flash chromatography (silica gel; hexanes–EtOAc, 3:1) to afford the title compound **11**.

Yield: 2.24 g, 16.0 mmol (90%); tan solid; mp 84–84 °C (Lit.[7,15] mp not stated).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 3 H, Me), 3.72 (s, 3 H, OMe), 5.43 (s, 1 H, H-4), 5.78 (s, 1 H, H-6).

The ^1H NMR data obtained were in agreement with those reported in the literature.[15]

10-Hydroxy-7,9-dimethoxy-3-methyl-1*H*-benzo[*g*]isochromen-1-one-9-*O*-methyl-lactone (13)[8]

To a freshly prepared soln of LDA (9.52 mmol) in THF (16.0 mL) at –78 °C [prepared from *n*-BuLi (1.6 M soln in hexanes, 9.52 mmol, 5.95 mL) and diisopropylamine (1.38 mL, 9.52 mmol) in THF (16.0 mL) at 0 °C], was added, dropwise, a soln of methyl 2,4-dimethoxy-6-methylbenzoate (**10**; 1.00 g, 4.76 mmol) in THF (4.8 mL) and the resulting dark-red soln was stirred for 20 min at –78 °C. A soln of 4-methoxy-6-methyl-2*H*-pyran-2-one (**11**; 0.67 g, 4.76 mmol) in anhydrous THF (7.9 mL) was added over 15 min. The mixture was stirred for 3 h at –78 °C then left to warm to r.t. overnight. The resulting mixture was poured into ice-cold aq HCl (1 M, 50 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel; hexanes–EtOAc, 2:1) gave the title compound **13**.

Yield: 0.36 g, 1.33 mmol (27%); thin yellow needles; mp 201–203 °C (Lit.[8] 207–208 °C).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H, Me), 3.92 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 6.20 (s, 1 H, H-4), 6.44 (d, *J* = 2.4 Hz, 1 H, H-8), 6.61 (d, *J* = 2.4 Hz, 1 H, H-6), 6.92 (s, 1 H, H-5), 13.05 (s, 1 H, OH).

The ^1H and ^{13}C NMR data obtained were in agreement with those reported in the literature.[8]

7,9-Dimethoxy-3-methyl-1*H*-benzo[*g*]isochromen-10-ol (8)

To a soln of 10-hydroxy-7,9-dimethoxy-3-methyl-1*H*-benzo[*g*]isochromen-1-one (**13**; 70 mg, 0.245 mmol) in THF (6.0 mL) under nitrogen was added DIBAL-H (1.2 M in toluene, 1.0 mL, 1.2 mmol) at r.t. The reaction mixture was stirred for 48 h at this temperature then quenched with HCl (1 M, 5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (silica gel; hexanes–EtOAc, 2:1) gave the title compound **8**.

Yield: 44 mg, 0.016 mmol (67%); orange-yellow oil.

IR (neat): 3390, 2925, 2854, 1618, 1585, 1451, 1364, 1322, 1249, 1204, 1163, 1111, 1044, 936, 887 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.05 (s, 3 H, Me), 3.87 (s, 3 H, OMe), 4.00 (s, 3 H, OMe), 5.28 (s, 2 H, CH_2), 6.35 (d, *J* = 2.1 Hz, 1 H, H-8), 6.60 (d, *J* = 2.1 Hz, 1 H, H-6), 6.69 (s, 1 H, H-5), 9.18 (s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4 (Me), 55.7 (OMe), 56.5 (OMe), 64.2 (CH_2, C-1), 97.1 (CH, C-4), 99.7 (CH, C-8), 101.1 (CH, C-6), 108.3 (q, C-9a), 109.9 (q, C-10a), 110.8 (CH, C-5), 132.6 (q, C-3a), 137.6 (q, C-5a), 148.9 (q, C-10), 156.4 (q, C-3), 157.7 (C-O, C-7), 158.1 (C-O, C-9).

MS (EI, 70 eV): *m*/*z* (%) = 273 (24) $[M + H]^+$, 247 (29), 225 (21), 189 (7), 163 (3).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{17}O_4$: 273.1121; found: 273.1110.

Dehydroherbarin (6)

To a soln of 7,9-dimethoxy-3-methyl-1*H*-benzo[*g*]isochromen-10-ol (**8**; 20 mg, 0.07 mmol) in MeCN (3.0 mL), was added salcomine (14 mg, 0.044 mmol) and the reaction mixture was stirred at r.t. under a balloon of O_2 for 3 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography (silica gel; hexanes–EtOAc, 2:1) to give the title compound **6**.

Yield: 15 mg, 0.05 mmol (72%); purple solid; mp 184–186 °C (Lit.[9] 187.2–187.5 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00 (d, *J* = 3.2 Hz, 3 H, Me), 3.93 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 5.11 (s, 2 H, CH_2), 5.83 (m, 1 H, H-4), 6.71 (d, *J* = 2.4 Hz, 1 H, H-8), 7.26 (d, *J* = 2.4 Hz, 1 H, H-6).

The spectroscopic data were consistent with those reported in the literature.[9]

(+)-Astropaquinone C (5)

To a soln of (*S*)-7,9-dimethoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]isochromene-5,10-dione (**7**;[2] 10 mg, 0.035 mmol) in CCl_4 (8.2 mL), was added a portion of Bz_2O_2 (1 crystal). Bromine (105 μL, 1 M in CCl_4, 0.105 mmol) was added every 30 min for 1.5 h, while the reaction vessel was irradiated with a 60 W desk lamp and heated to gentle reflux. The reaction mixture was concentrated to dryness in vacuo and the crude bromides were taken up in THF (2.4 mL). H_2O (1.2 mL) was added and the reaction mixture was stirred for 0.5 h before further H_2O (2.0 mL) was added and the reaction was left for 1 h. The reaction mixture was diluted with CH_2Cl_2 (8 mL) and H_2O (5 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The remaining solid was taken up in THF and loaded onto a preparative TLC plate for purification (silica gel; hexanes–EtOAc, 2:1, 1% Et_3N) to give the title compound **5**.

Yield: 9.6 mg, 0.03 mmol (91%); bright-yellow solid; mp 178–181 °C (Lit.[4] mp not stated); $[\alpha]_D^{19}$ +31.1 (*c* 0.10; $CHCl_3$) {Lit.[4] $[\alpha]_D^{19}$ +53.9 (*c* 0.10, $CHCl_3$)}.

IR (neat): 3420, 2972, 2924, 2845, 1652, 1638, 1593, 1561, 1458, 1432, 1383, 1354, 1340, 1318, 1270, 1213, 1198, 1155, 1123, 1082, 1067, 1019, 967, 941, 922, 859, 843, 830, 819, 747, 713, 685, 641 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.3 Hz, 3 H, Me), 2.18 (dd, *J* = 19.2, 10.8 Hz, 1 H, H_{ax}-4), 2.69 (dd, *J* = 19.2, 3.3 Hz, 1 H, H_{eq}-4), 3.93 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 4.26 (m, 1 H, H-3), 5.99 (s, 1 H, H-1), 6.71 (d, *J* = 2.4 Hz, 1 H, H-8), 7.25 (d, *J* = 2.4 Hz, 1 H, H-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (Me), 29.1 (CH_2, C-4), 56.0 (OMe), 56.5 (OMe), 62.8 (CH, C-3), 87.1 (CH, C-1), 103.6 (CH, C-6), 104.3 (CH, C-8), 114.1 (q, C-9a), 135.8 (q, C-5a), 140.4 (q, C-4a), 142.2 (q, C-10a), 162.1 (C-O, C-9), 164.8 (C-O, C-7), 182.0 (C=O, C-10), 184.7 (C=O, C-5).

MS (EI, 70 eV): *m*/*z* (%) = 327 (100) $[M + Na]^+$, 287 (10), 167 (5), 118 (8).

HRMS-FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{16}O_6Na$: 327.0844; found: 327.0848.

All collected data were in agreement with values reported in the literature.[4]

(+)-Astropaquinone B (4)

To a soln of astropaquinone C (**5**; 3 mg, 9.86×10^{-3} mmol) in MeOH (2 mL) was added PTSA (1 mg, 0.05 mmol) and the reaction mixture was stirred at r.t. for 16 h. The reaction mixture was concentrated in vacuo and the remaining solid was taken up in THF and loaded onto a preparative TLC plate (silica gel; hexanes–EtOAc, 2:1, 1% Et_3N) to give the title compound **4**.

Yield: 2.5 mg, 7.9×10^{-3} mmol (80%); bright-yellow amorphous solid; mp 164–167 °C (Lit.[4] mp not reported); $[\alpha]_D^{19}$ +35.0 (*c* 0.14, $CHCl_3$); {Lit.[4] $[\alpha]_D^{27.4}$ +45.1 (*c* 0.12, $CHCl_3$)}.

IR (neat): 2962, 2928, 2854, 1658, 1640, 1592, 1454, 1336, 1321, 1278, 1087, 961, 819, 741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.2 Hz, 3 H, Me), 2.23 (dd, *J* = 19.1, 11.2 Hz, 1 H, H_{ax}-4), 2.66 (dd, *J* = 19.1, 3.6 Hz, 1 H, H_{eq}-4), 3.57 (s, 3 H, OMe), 3.92 (s, 3 H, OMe), 3.94 (s, 3 H, OMe), 4.21 (m, 1 H, H-3), 5.54 (s, 1 H, H-1), 6.72 (d, *J* = 2.4 Hz, 1 H, H-8), 7.24 (d, *J* = 2.4 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0 (Me), 29.0 (CH_2), 55.9 (1-OMe), 56.1 (7-OMe), 56.2 (9-OMe), 62.0 (CH, C-3), 93.7 (CH, C-1), 103.2 (CH, C-6), 104.3 (CH, C-8), 114.2 (q, C-9a), 135.6 (q, C-5a), 140.6 (q, C-4a), 141.0 (q, C-10a), 162.0 (q, C-9), 164.5 (q, C-7), 180.8 (C=O), 184.9 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 341 (73) $[M + Na]^+$, 319 (8), 309 (4), 303 (4), 287 (100).

HRMS-FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{18}O_6Na$: 341.1364; found: 341.0987.

All collected data were in agreement with values reported in the literature.[4]

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References

(1) Singh, S. B.; Cordingley, M. G.; Ball, R. G.; Smith, J. L.; Dombrowski, A. W.; Goetz, M. A. *Tetrahedron Lett.* **1991**, *32*, 5279.
(2) Sperry, J.; Yuen, T. Y.; Brimble, M. A. *Synthesis* **2009**, 2561.
(3) Opatz, T.; Kolshorn, H.; Thines, E.; Anke, H. *J. Nat. Prod.* **2008**, *71*, 1973; Ascomycones A and B were reported to show no detectable optical rotation and were thus assigned as racemic at C1.
(4) Wang, L.; Dong, J. Y.; Song, H. C.; Shen, K. Z.; Wang, L. M.; Sun, R.; Wang, C. R.; Gao, Y. X.; Li, G. H.; Li, L.; Zhang, K. Q. *Planta Med.* **2009**, *75*, 1339.
(5) (a) Kadkol, M. V.; Gopalkrishnan, K. S.; Narasimhachari, N. *J. Antibiot.* **1971**, *24*, 245. (b) Nagarajan, R.; Narasimhachari, N.; Kadkol, M. V.; Gopalkrishnan, K. S. *J. Antibiot.* **1971**, *24*, 249.
(6) (a) Evans, G. E.; Leeper, F. J.; Murphy, J. A.; Staunton, J. *J. Chem. Soc., Chem. Commun.* **1979**, 205. (b) Dodd, J. H.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, *38*, 3593.
(7) Nakata, H. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 1693.
(8) Zhang, Z.; Yu, B. *J. Org. Chem.* **2003**, *68*, 6309.
(9) Kesteleyn, B.; De Kimpe, N. *J. Org. Chem.* **2000**, *65*, 640.
(10) Xu, Y. C.; Lebeau, E.; Gillard, J. W.; Attardo, G. *Tetrahedron Lett.* **1993**, *34*, 3841.
(11) Isobe, K.; Takeda, N.; Mohri, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1989**, *12*, 3390.
(12) Harling, J. D.; Orlek, B. S. *Tetrahedron* **1998**, *54*, 14905.
(13) Chiarello, J.; Jouillé, M. *Tetrahedron* **1988**, *44*, 41.
(14) (a) Gill, M.; Donner, C. D. *Tetrahedron Lett.* **1999**, *40*, 3921. (b) Donner, C. D.; Gill, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 938.
(15) Hansen, C. A.; Frost, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 5926.