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PAPER

Stereoselective synthesis of (−)-1-*epi*-ventiloquinone L and (+)-ventiloquinone L, the monomeric unit of cardinalin 3†

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A stereoselective synthesis of (−)-1-*epi*-ventiloquinone L and (+)-ventiloquinone L, the monomeric unit of cardinalin 3 has been described. The synthesis is completed in 7 steps with 10.5% and 13% overall yields for (−)-1-*epi*-ventiloquinone L and (+)-ventiloquinone L respectively. The key steps involve Dötz benzannulation of carbene **5** with alkyne **6** to give a substituted naphthalene moiety and oxa-Pictet–Spengler reaction to install the 1,3-dimethylpyran moiety.

Introduction

The 1,3-dimethylpyranonaphthoquinone moiety is observed in a large number of pyranonaphthoquinone natural products which show a wide range of biological activities.[1] They have also been shown to act as bis-alkylating agents upon bioreduction in a mode resembling the antitumor drug mitomycin C.[2] In our efforts towards the synthesis of pyranonapthoquinone containing natural products,[3] we observed that the sequence of Dötz benzannulation[4] and oxa-Pictet–Spengler[5] reaction enables the rapid construction of the 1,3-dimethyl pyranonaphthoquinone framework. In this endeavour we have successfully completed the synthesis of (+)-eleutherin,[3a,b] (+)-allo-eleutherin,[3a,b] (−)-hongconin,[3c] (−)-1-*epi*-hongconin,[3c] regioisomeric core of cardinalin 3[3d] and (+)-demethoxy cardinalin 3.[3e]

(+)-Ventiloquinone L **2** is a *cis*-1,3-dimethylpyranonaphthoquinone natural product isolated from the acetone extract of the root bark of *Ventilago goughii*.[6] Recently Brimble and co-workers reported that ventiloquinone L **2** acts as specific topoisomerase II catalytic inhibitor.[7] It is also a monomer of dimeric pyranonaphthoquinone natural product (−)-cardinalin 3 **3** (Fig. 1). The latter is isolated from the New Zealand toadstool fungi *Dermocybe cardinalis*.[8] The crude ethanolic extract of *Dermocybe cardinalis* is a potent inhibitor of the growth of P388 murine leukemia cells (IC50 0.47 μg cm^{-3}).[8b] There is one racemic[9a] and two enantioselective[9b,c] syntheses of (+)-ventiloquinone L known in the literature. The first enantioselective synthesis is based on Diels–Alder reaction of silyloxybutadiene with a bromoquinone derived from (*S*)-mellein as the key step and is completed in 10 steps.[9b] The second enantioselective synthesis of **2** is based on Hauser–Kraus phthalide annulation with a requisite chiral enone and is completed in 7 steps.[9c] There is one racemic synthesis of 1-*epi*-ventiloquinone L **1**[9d] which was known well before the isolation of (+)-ventiloquinone L **2**. Herein we report a stereoselective synthesis of (−)-1-*epi*-ventiloquinone L **1** and (+)-ventiloquinone L **2** employing the Dötz benzannulation[4] and oxa-Pictet–Spengler[5] reactions as key steps.

The synthesis of (−)-1-*epi*-ventiloquinone L and (+)-ventiloquinone L can be retrosynthetically visualized from compound **4** by oxa-Pictet–Spengler reaction followed by oxidation and chemoselective demethylation (Scheme 1). Compound **4** can be obtained from the Fischer carbene **5** by Dötz benzannulation with alkyne **6**. From our earlier work, the oxa-Pictet–Spengler reaction can be controlled to stereoselectively produce either a *syn* or *trans*-1,3-dimethylpyran moiety.[3b,e]

The Fischer carbene **5**[10] was prepared from commercially available 1-bromo-2,4-dimethoxybenzene **7**. The Dötz benzannulation of carbene **5** with alkyne[3e] **6** in benzene at 45 °C

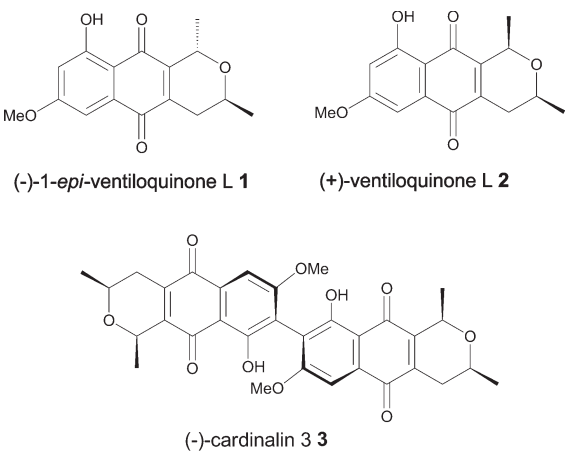

Fig. 1 (−)-1-*Epi*-ventiloquinone L **1**, (+)-ventiloquinone L **2** and (−)-cardinalin 3 **3**.

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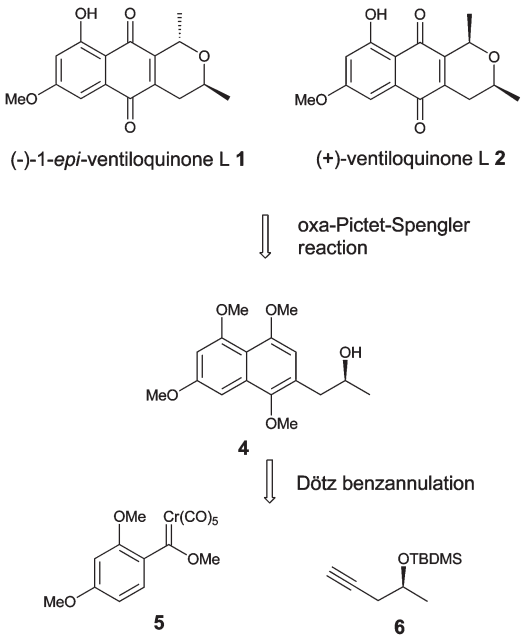
†Electronic supplementary information (ESI) available: Copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/c2ob25453k

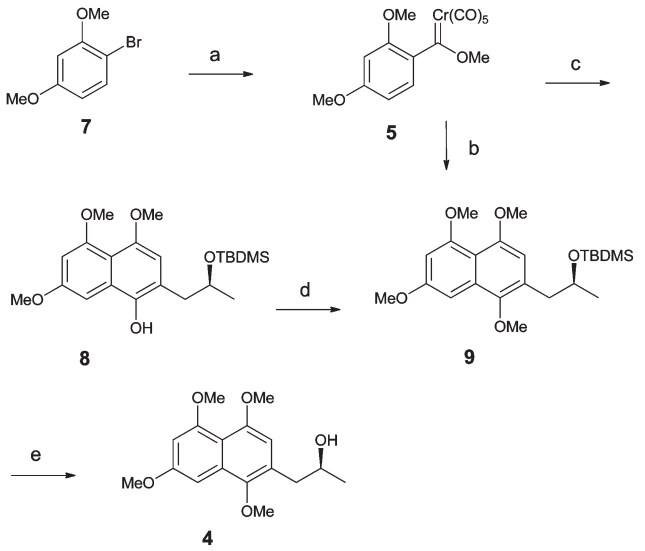


Scheme 1 Retrosynthetic analysis of (−)-1-*epi*-ventiloquinone L **1** and (+)-ventiloquinone L **2**.

and the *in situ* methylation of the resulting naphthol gave the tetramethoxy naphthalene compound **9** in poor yield (15%). We then adopted a stepwise process involving the Dötz benzannulation and isolation of the naphthol **8** in 35% yield. Further methylation gave **9** in 81% yield (28% over two steps from **5**). The lower yield in the Dötz benzannulation of carbene **5** with alkyne **6** is attributed to the presence of electron rich substituents (–OMe) at the *para* and *ortho* positions of the aryl part of the carbene carbon.[11] The compound **9**, upon TBDMS group removal, afforded the desired alcohol **4** in 95% yield (Scheme 2).

The alcohol **4**, on oxa-Pictet–Spengler reaction with acetaldehyde dimethyl acetal in the presence of Lewis acid $BF_3{\cdot}Et_2O$ in CH_2Cl_2, delivered the mixture of **10a** : **10b** in a 72 : 28 ratio. Our earlier studies showed that the oxa-Pictet–Spengler reactions under protic acid conditions (bubbling HCl gas) in ether solvent were *syn* selective.[3b,e] When the reaction was carried out by bubbling HCl gas in ether at 0 °C to room temperature for 2 h, the mixture of **10a** : **10b** was obtained in a 33 : 67 ratio. Lowering the reaction temperature to −5 °C to 0 °C for 2.5 hour, improved the **10a** : **10b** ratio to 12 : 88. Further lowering the reaction temperature did not change the diastereoselectivity. Moreover at −15 °C the reaction did not proceed. The two diastereomers **10a** : **10b** were easily separated by flash column chromatography.

The oxidation of compound **10b** using cerium ammonium nitrate (CAN) gave the dimerized products as reported earlier.[9c] However, when phenyliodine bis(trifluoroacetate) (PIFA) was used **10a** gave the naphthoquinone **11a** in 90% yield. The chemoselective demethylation of naphthoquinone **11a** afforded (−)-1-*epi*-ventiloquinone L **1** (82%). The compound **10b**, after a similar sequence of PIFA oxidation (90%) and demethylation, afforded (+)-ventiloquinone L **2** (81%, Scheme 3), {$[\alpha]_D^{25}$ = +394.1 (c = 0.03, $CHCl_3$), lit.[6] $[\alpha]_D^{30}$ +387.1 (c = 0.01, $CHCl_3$)}.



Scheme 2 Synthesis of compound **4**; Reagents and conditions: (a) *n*-BuLi (1.1 equiv), Et_2O, −78 °C, 20 min, $Cr(CO)_6$ (1.1 equiv), Et_2O, 0 °C to r.t., 3 h then $Me_3O{\cdot}BF_4$ (1.5 equiv), CH_2Cl_2, 0 °C to r.t., 3 h, 80%; (b) **6** (2.0 equiv), benzene, 45 °C, 12 h, NaH (3.0 equiv), THF, MeI (3.0 equiv), 0 °C to r.t., 6 h, 15%; (c) **6** (2.0 equiv), benzene, 45 °C, 12 h, 35%; (d) NaH (2.0 equiv), THF, MeI (2.0 equiv), 0 °C to r.t., 6 h, 81%; (e) TBAF, THF, r.t., 6 h, 95%.

The spectral and analytical data of **1**[9d] and **2**[6] is in full agreement with the literature data.

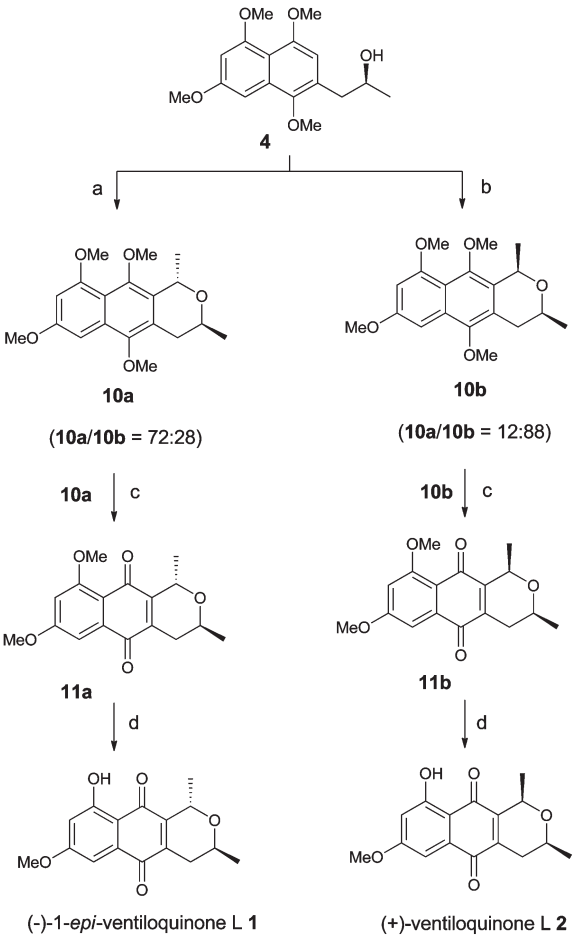
Conclusions

In conclusion, the Dötz benzannulation and oxa-Pictet–Spengler reactions were efficiently employed for the synthesis of 1,3-dimethyl pyranonaphthoquinones, (−)-1-*epi*-ventiloquinone L **1** and (+)-ventiloquinone L **2**. The synthesis was completed in 7 steps with 10.5% and 13% overall yields for (−)-1-*epi*-ventiloquinone L **1** and (+)-ventiloquinone L **2** respectively. (+)-Ventiloquinone L **2** is a monomeric unit of the dimeric pyranonaphthoquinone, cardinalin 3.

Experimental section

General remarks

Flasks were oven or flame dried and cooled in a desiccator. Dry reactions were carried out under an atmosphere of Ar or N_2. Solvents and reagents were purified by standard methods. Thin-layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by UV lamp. ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker Avance^{III} 400 spectrometer and the chemical shifts are based on TMS peak at δ = 0.00 pm for proton NMR and $CDCl_3$ peak at δ = 77.00 ppm (t) in carbon NMR. IR spectra were obtained on a Perkin Elmer Spectrum One FT-IR spectrometer. Optical rotations were measured with a Jasco P-2000 polarimeter. HRMS was recorded using a Micromass: Q-Tof micro (YA-105) spectrometer.



Scheme 3 Synthesis of (−)-1-*epi*-ventiloquinone L and (+)-ventiloquinone L; Reagents and conditions: (a) $(CH_3O)_2CHCH_3$ (2.0 equiv), $BF_3{\cdot}Et_2O$ (1.5 equiv), CH_2Cl_2, r.t., 3 h, **10a** (66%), **10b** (26%); (b) $(CH_3O)_2CHCH_3$ (10.0 equiv), HCl(g), Et_2O, −5 °C to 0 °C, 2.5 h, **10a** (11%), **10b** (81%); (c) PIFA (2.0 equiv), H_2O–CH_3CN (1 : 1), 0 °C, 5 min, 90%; (d) BCl_3 (2.0 equiv), CH_2Cl_2, −78 °C, 30 min, r.t., 2 h, **1** (82%), **2** (81%).

Methoxy (2,4-dimethoxyphenyl)methylene pentacarbonyl chromium (5)

To a solution of 1-bromo-2,4-dimethoxybenzene **7** (2.0 g, 9.21 mmol) in dry ether (40 mL) at −78 °C under an argon atmosphere was added *n*-BuLi (6.3 mL, 10.13 mmol, 1.6 M in hexane, 1.1 equiv). The reaction mixture was stirred for 20 min and then added to a suspension of chromium hexacarbonyl (2.23 g, 10.13 mmol, 1.1 equiv) in dry ether (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and brought to room temperature and stirred for 2 hours and then concentrated. The residue was dissolved in dry CH_2Cl_2 (60 mL), cooled to 0 °C and $Me_3{\cdot}OBF_4$ (2.04 g, 13.82 mmol, 1.5 equiv) was added in portions. The reaction mixture was stirred at 0 °C for 1 hour and room temperature for 2 hours and concentrated. The residue was purified by silica gel column chromatography using petroleum ether–CH_2Cl_2 (9 : 1 to 4 : 1) as eluent to give **5** (2.74 g, 80%) as a brown–red solid. M.p. 72–73 °C, lit.[10] 73–74 °C. ^{1}H-NMR (400 MHz, $CDCl_3$/TMS): δ = 3.20 (s, 3H, *OMe*), 3.32 (s, 3H, *OMe*), 3.50 (s, 3H, *OMe*), 6.16 (m, 2H, Ar-*H*), 6.60 (d, J = 8.2 Hz, 1H, Ar-*H*). Other spectroscopic data is the same as reported.[10]

(*S*)-2-(2-(*tert*-Butyldimethylsilyloxy)propyl)-4,5,7-trimethoxynaphthalen-1-ol (8)

To a freshly prepared chromium carbene complex **5** (2.74 g, 7.36 mmol) in dry and degassed benzene (50 mL) was added (*S*)-*tert*-butyldimethyl(pent-4-yn-2-yloxy)silane **6**[3e] (2.92 g, 14.72 mmol, 2.0 equiv). The reaction mixture was stirred at 45 °C for 12 h. It was then cooled to room temperature and exposed to air and stirred for a further 30 min. The reaction mixture was concentrated and the residue purified by silica gel column chromatography using petroleum ether–EtOAc (9 : 1 to 4 : 1) as eluent to give **8** (1.05 g, 35%) as a pale yellow liquid. $[\alpha]_D^{25}$ = −31.9 (c = 0.28, $CHCl_3$). IR ($CHCl_3$): ν = 3414, 3019, 2932, 2858, 1699, 1624, 1610, 1465, 1381, 1324, 1258, 1155, 1122, 1075, 1057, 1001, 837 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$/TMS): δ = −0.04 (s, 3H, CH_3-Si), 0.07 (s, 3H, CH_3-Si), 0.91 (s, 9H, 3 × CH_3-C-Si), 1.20 (d, J = 6.1 Hz, 3H, 3′-CH_3), 2.78 (dd, J = 14.5, 7.1 Hz, 1H, 1′-H_a), 2.92 (dd, J = 14.5, 2.3 Hz, 1H, 1′-H_b), 3.88 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.26–4.32 (m, 1H, 2′-*H*), 6.40 (s, 1H, 3-Ar-*H*), 6.50 (d, J = 2.3 Hz, 1H, 6-Ar-*H*), 7.20 (d, J = 2.4 Hz, 1H, 8-Ar-*H*), 8.23 (s, 1H, *OH*) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = −5.2, −4.8, 18.0, 22.8, 25.8 (3C), 41.8, 55.3, 56.1, 57.5, 71.4, 93.4, 98.6, 109.2, 119.0, 129.5, 137.3, 144.3, 150.2, 157.7 (2C) ppm. HRMS (ESI+) calcd for $[C_{22}H_{34}O_5Si + H]^+$: 407.2254, found: 407.2250.

(*S*)-*tert*-Butyldimethyl[1-(1,4,5,7-tetramethoxynaphthalen-2-yl)-propan-2-yloxy]silane (9)

To a solution of **8** (0.4 g, 0.984 mmol) in THF (15 mL) was added oil free NaH (47.2 mg, 1.97 mmol, 2.0 equiv) at 0 °C and the mixture stirred for 10 min. Then MeI (0.123 mL, 1.97 mmol, 2.0 equiv) was added and stirred for 6 hours. The reaction was quenched with water (10 mL) and the solution extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether–EtOAc (9 : 1 to 4 : 1) as eluent to afford **9** (0.335 g, 81%) as pale yellow liquid. $[\alpha]_D^{25}$ = 24.1 (c = 0.3, $CHCl_3$). IR ($CHCl_3$): ν = 2956, 2930, 2856, 1676, 1621, 1606, 1468, 1404, 1380, 1246, 1155, 1124, 1083, 1061, 1006, 833 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$/TMS): δ = −0.14 (s, 3H, CH_3-Si), −0.03 (s, 3H, CH_3-Si), 0.84 (s, 9H, 3 × CH_3-C-Si), 1.19 (d, J = 6.0 Hz, 3H, 3-CH_3), 2.78 (dd, J = 13.1, 5.9 Hz, 1H, 1-H_a), 2.92 (dd, J = 13.1, 7.0 Hz, 1H, 1-H_b), 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.11–4.17 (m, 1H, 2-*H*), 6.49, (d, J = 2.4 Hz, 1H, 6′-Ar-*H*), 6.55 (s, 1H, 3′-Ar-*H*), 6.96 (d, J = 2.3 Hz, 1H, 8′-Ar-*H*) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = −5.00, −4.9, 18.1, 23.8, 25.8 (3C), 40.8, 55.2, 56.2, 56.6, 61.0, 69.2, 92.9, 98.3, 107.5, 113.0, 128.8, 132.0, 146.9, 153.0, 158.4, 158.6 ppm. HRMS (ESI+) calcd for $[C_{23}H_{36}O_5Si + H]^+$: 421.2410, found: 421.2392.

(*S*)-1-(1,4,5,7-Tetramethoxynaphthalen-2-yl)propan-2-ol (4)

To a solution of compound **9** (0.2 g, 0.475 mmol) in dry THF (20 mL) was added TBAF (0.95 mL, 0.95 mmol, 1 M solution in THF, 2.0 equiv). The reaction mixture was stirred at room temperature for 6 h. It was then quenched with water (10 mL), THF was removed under reduced pressure and the solution extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether–EtOAc (9 : 1 to 3 : 2) as eluent to give **4** (0.138 g, 95%) as a thick oil. $[\alpha]_D^{25}$ = 26.7 (*c* = 0.4, $CHCl_3$). IR ($CHCl_3$): *ν* = 3481, 3018, 2965, 2939, 2843, 1619,1606, 1511, 1467, 1450, 1404, 1381, 1355, 1263, 1173, 1154, 1121, 1082, 1060, 1004, 941, 930, 834 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$/TMS): *δ* = 1.29 (d, *J* = 6.2 Hz, 3H, 3-CH_3), 2.90 (d, *J* = 6.1 Hz, 2H, 1-*H*), 3.86 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.16–4.21 (m, 1H, 2-*H*), 6.49, (d, *J* = 2.4 Hz, 1H, 6′-Ar-*H*), 6.51 (s, 1H, 3′-Ar-*H*), 6.96 (d, *J* = 2.3 Hz, 1H, 8′-Ar-*H*) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 23.2, 40.4, 55.2, 56.3, 56.7, 61.0, 68.6, 92.9, 98.6, 106.5, 113.2, 127.9, 132.0, 146.8, 153.7, 158.7 (2C) ppm. HRMS (ESI+) calcd for $[C_{17}H_{22}O_5 + H]^+$: 307.1545, found: 307.1550.

(1*S*,3*S*)-5,7,9,10-Tetramethoxy-1,3-dimethyl-3,4-dihydro-1*H*-benzo[*g*]isochromene (10a) and (1*R*,3*S*)-5,7,9,10-tetramethoxy-1,3-dimethyl-3,4-dihydro-1*H*-benzo[*g*]isochromene (10b) [Reaction conditions (a) in Scheme 3]

To a stirred solution of **4** (20 mg, 0.065 mmol) in dry CH_2Cl_2 (10 mL) was added $(CH_3O)_2CHCH_3$ (11.72 mg, 0.13 mmol, 2.0 equiv) and $BF_3{\cdot}OEt_2$ (13.9 mg, 0.098 mmol, 1.5 equiv) at room temperature. The reaction mixture was stirred for 3 hours at room temperature. Water (10 mL) was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether–EtOAc (9 : 1 to 4 : 1) as eluent to give a mixture of **10a** and **10b** (20.4 mg, 94%) as a colorless oil (^{1}H NMR analysis of the mixture indicated, **10a** : **10b** = 72 : 28). The mixture was separated by flash silica gel column chromatography using petroleum ether–EtOAc (19 : 1 to 9 : 1) to give **10b** (5.6 mg, 26%) and further elution gave **10a** (14.3 mg, 66%). Data for **10a**: colorless solid; m.p. 65–67 °C. $[\alpha]_D^{25}$ = 31.5 (*c* = 0.2, $CHCl_3$). IR ($CHCl_3$): *ν* = 2967, 2931, 2839, 1623, 1600, 1580, 1465, 1451, 1411, 1383, 1358, 1342, 1259, 1229, 1204, 1160, 1104, 1070, 1056, 1012, 975, 944, 832 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$/TMS): *δ* = 1.39 (d, *J* = 6.1 Hz, 3H, 3-CH_3), 1.62 (d, *J* = 6.6 Hz, 3H, 1-CH_3), 2.57 (dd, *J* = 16.9, 11.0 Hz, 1H, 4-H_a), 3.04 (dd, *J* = 17.0, 3.3 Hz, 1H, 4-H_b), 3.78 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.09–4.17 (m, 1H, 3-*H*), 5.29 (q, *J* = 6.6 Hz, 1H, 1-*H*), 6.50 (d, *J* = 2.3 Hz, 1H, 8-Ar-*H*), 6.95 (d, *J* = 2.3 Hz, 1H, 6-Ar-*H*) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 20.8, 22.1, 30.7, 55.3, 56.0, 60.1, 61.9, 62.2, 68.8, 92.3, 98.6, 115.1, 124.9, 127.5, 130.3, 148.0, 148.3, 157.3, 157.9 ppm. HRMS (ESI+) calcd for $[C_{19}H_{24}O_5 + H]^+$: 333.1702, found: 333.1706. Data for **10b**: colorless solid; m.p. 74–76 °C, lit.[9c] 75–76 °C. $[\alpha]_D^{25}$ = 62.4 (*c* = 0.35, CH_2Cl_2) lit.[9c] $[\alpha]_D^{25}$ = 65.6 (*c* 0.44, CH_2Cl_2). IR ($CHCl_3$): *ν* = 3005, 2971, 2935, 2839, 1622, 1599, 1583, 1499, 1468, 1450, 1411, 1382, 1338, 1259, 1226, 1205, 1183, 1157, 1133, 1076, 1057, 1018, 973, 942, 832 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$/TMS): *δ* = 1.41 (d, *J* = 6.1 Hz, 3H, 3-CH_3), 1.67 (d, *J* = 6.2 Hz, 3H, 1-CH_3), 2.57 (dd, *J* = 16.0, 10.9 Hz, 1H, 4-H_a), 3.03 (dd, *J* = 16.0, 1.5 Hz, 1H, 4-H_b), 3.64–3.69 (m, 1H, 3-*H*), 3.74 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 5.20 (q, *J* = 6.2 Hz, 1H, 1-*H*), 6.51 (d, *J* = 2.2 Hz, 1H, 8-Ar-*H*), 6.97 (d, *J* = 2.3 Hz, 1H, 6-Ar-*H*) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 21.8, 23.2, 32.0, 55.3, 56.1, 60.6, 61.5, 69.3, 71.2, 92.3, 98.7, 115.3, 126.6, 127.8, 130.3, 147.7, 149.4, 157.4, 158.0 ppm. HRMS (ESI+) calcd for $[C_{19}H_{24}O_5 + H]^+$: 333.1702, found: 333.1700.

(1*S*,3*S*)-5,7,9,10-Tetramethoxy-1,3-dimethyl-3,4-dihydro-1*H*-benzo[*g*]isochromene (10a) and (1*R*,3*S*)-5,7,9,10-tetramethoxy-1,3-dimethyl-3,4-dihydro-1*H*-benzo[*g*]isochromene (10b) [Reaction conditions (b) in Scheme 3]

Dry HCl gas was bubbled through a stirred solution of **4** (0.13 g, 0.424 mmol) and $(CH_3O)_2CHCH_3$ (0.45 mL, 4.24 mmol, 10.0 equiv) in dry ether (10 mL) at −5 °C for 1 hour. It was then stirred at 0 °C for 1.5 h. The solvent was evaporated and the residue was purified by silica gel column chromatography using petroleum ether–EtOAc (9 : 1 to 4 : 1) as eluent to give a mixture of **10a** and **10b** (131 mg, 93%) as a colorless oil (^{1}H NMR analysis of the mixture indicated, **10a** : **10b** = 12 : 88). The mixture was separated by flash silica gel column chromatography using petroleum ether–EtOAc (19 : 1 to 9 : 1) to give **10b** (112.5 mg, 81%) and further elution gave **10a** (15 mg, 11%). Data for **10a** and **10b** were the same as above.

(1*S*,3*S*)-7,9-Dimethoxy-1,3-dimethyl-3,4-dihydro-1*H*-benzo[*g*]-isochromene-5,10-dione (11a)

To a stirred solution of **10a** (20 mg, 0.06 mmol) in CH_3CN (5 mL) and water (5 mL) was added phenyliodine bis(trifluoroacetate) (PIFA) (51.6 mg, 0.12 mmol, 2.0 equiv). The reaction mixture was stirred 0 °C for 5 min. It was then diluted with EtOAc (10 mL) and the organic layer separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether–EtOAc (4 : 1 to 7 : 3) as eluent to afford **11a** (16.4 mg, 90%) as a yellow solid. M.p. 146–148 °C, lit.[9d] 147–149 °C (for racemic). $[\alpha]_D^{25}$ = −3.9 (*c* = 0.4, $CHCl_3$). IR ($CHCl_3$): *ν* = 3020, 2978, 2934, 1652, 1596, 1566, 1456, 1429, 1320, 1275, 1160, 1067, 921 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$/TMS): *δ* = 1.34 (d, *J* = 6.2 Hz, 3H, 3-CH_3), 1.54 (d, *J* = 6.8 Hz, 3H, 1-CH_3), 2.22 (ddd, *J* = 18.9, 10.2, 2.0 Hz, 1H, 4-H_a), 2.68 (dd, *J* = 18.9, 3.4 Hz, 1H, 4-H_b), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.36–4.01 (m, 1H, 3-*H*), 5.00 (dq, *J* = 6.8, 1.4 Hz, 1H, 1-*H*), 6.72 (d, *J* = 2.4 Hz, 1H, 8-Ar-*H*), 7.26 (d, *J* = 2.4 Hz, 1H, 6-Ar-*H*) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): *δ* = 19.9, 21.5, 29.5, 55.9, 56.4, 62.4, 67.5, 103.1, 104.1, 114.2, 135.7, 138.7, 148.2, 161.9, 164.5, 181.7, 184.3 ppm. HRMS (ESI+) calcd for $[C_{17}H_{18}O_5 + H]^+$: 303.1232, found: 303.1236.

(1*R*,3*S*)-7,9-Dimethoxy-1,3-dimethyl-3,4-dihydro-1*H*-benzo[*g*]-isochromene-5,10-dione (11b)

The title compound was prepared from **10b** (20 mg, 0.06 mmol) by a similar procedure as described for **11a** to give **11b** (16.4 mg, 90%) as a yellow solid. M.p. 150–152 °C, lit.[12] 153–154 °C. $[\alpha]_D^{25}$ = 338.9 (*c* = 0.22, CH_2Cl_2) lit.[9c] $[\alpha]_D^{20}$ 344.4 (*c* = 0.5, CH_2Cl_2). IR ($CHCl_3$): ν = 3011, 2974, 2936, 2852, 1652, 1596, 1568, 1456, 1429, 1347, 1323, 1274, 1200, 1160, 1069, 1005, 942, 845, 828 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$/TMS): δ = 1.36 (d, *J* = 6.2 Hz, 3H, 3-*CH*$_3$), 1.54 (d, *J* = 6.6 Hz, 3H, 1-*CH*$_3$), 2.19 (ddd, *J* = 18.2, 10.2, 3.8 Hz, 1H, 4-*H*$_a$), 2.72 (dt, *J* = 18.2, 2.6 Hz, 1H, 4-*H*$_b$), 3.54–3.59 (m, 1H, 3-*H*), 3.94 (s, 3H, *OCH*$_3$), 3.96 (s, 3H, *OCH*$_3$), 4.81–4.87 (m, 1H, 1-*H*), 6.71(d, *J* = 2.4 Hz, 1H, 8-Ar-*H*), 7.24 (d, *J* = 2.4 Hz, 1H, 6-Ar-*H*) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.0, 21.2, 30.0, 55.9, 56.4, 68.7, 70.4, 102.9, 104.2, 114.7, 135.7, 139.4, 148.8, 161.6, 164.4, 182.6, 184.1 ppm. HRMS (ESI+) calcd for $[C_{17}H_{18}O_5 + H]^+$: 303.1232, found: 303.1236.

(1*S*,3*S*)-9-Hydroxy-7-methoxy-1,3-dimethyl-3,4-dihydro-1*H*-benzo[*g*]isochromene-5,10-dione, (−)-1-*epi*-ventiloquinone L (1)

To a solution of **11a** (10 mg, 0.033 mmol) in CH_2Cl_2 (10 mL) was added BCl_3 (0.07 mL, 0.07 mmol, 1M solution in CH_2Cl_2, 2.0 equiv) at −78 °C. The resulting dark red solution was stirred at −78 °C for 30 min and then warmed to room temperature and stirred for 2 h. The reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether–EtOAc (19 : 1 to 9 : 1) as eluent to afford **1** (7.82 mg, 82%) as a yellow solid. M.p. 175–177 °C, lit.[9d] 176–177.5 °C for racemic compound. $[\alpha]_D^{25}$ = −59.6 (*c* = 0.1, $CHCl_3$). IR ($CHCl_3$): ν = 3434, 3019, 2978, 2930, 2852, 1633, 1642, 1614, 1490, 1446, 1390, 1369, 1311, 1272, 1164, 1147, 1055, 992, 861 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$/TMS): δ = 1.34 (d, *J* = 6.2 Hz, 3H, 3-*CH*$_3$), 1.56 (d, *J* = 6.8 Hz, 3H, 1-*CH*$_3$), 2.22 (ddd, *J* = 19.2, 10.2, 2.1 Hz, 1H, 4-*H*$_a$), 2.72 (dd, *J* = 19.3, 3.2 Hz, 1H, 4-*H*$_b$), 3.90 (s, 3H, *OCH*$_3$), 3.95–4.01 (m, 1H, 3-*H*), 4.99 (dq, *J* = 6.8, 2.0 Hz, 1H, 1-*H*), 6.62 (d, *J* = 2.5 Hz, 1H, 8-Ar-*H*), 7.17 (d, *J* = 2.5 Hz, 1H, 6-Ar-*H*), 12.28 (s, 1H, Ar-*OH*) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 19.8, 21.5, 29.9, 56.0, 62.4, 67.0, 106.1, 107.8, 109.3, 133.3, 142.0, 146.7, 164.3, 165.8, 183.2, 186.8. ppm. HRMS (ESI+) calcd for $[C_{16}H_{16}O_5 + H]^+$: 289.1076, found: 289.1062.

(1*R*,3*S*)-9-Hydroxy-7-methoxy-1,3-dimethyl-3,4-dihydro-1*H*-benzo[*g*]isochromene-5,10-dione, (+)-ventiloquinone L (2)

The title compound was prepared from **11b** (40 mg, 0.132 mmol) by a similar procedure as described for **1** to give **2** (31 mg, 81%) as a yellow solid. M.p. 122–124 °C, lit.[6] 126 °C. $[\alpha]_D^{25}$ = 394.1 (*c* = 0.03, $CHCl_3$), lit.[6] $[\alpha]_D^{30}$ = 387.1 (*c* = 0.01, $CHCl_3$). IR ($CHCl_3$): ν = 3478, 3016, 2978, 2931, 2852, 1637, 1611, 1449, 1389, 1320, 1303, 1270, 1208, 1155, 1100, 1029, 911 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$/TMS): δ = 1.37 (d, *J* = 6.2 Hz, 3H, 3-*CH*$_3$), 1.58 (d, *J* = 6.6 Hz, 3H, 1-*CH*$_3$), 2.21 (ddd, *J* = 18.6, 10.2, 4.0 Hz, 1H, 4-*H*$_a$), 2.74 (dt, *J* = 18.6, 2.6 Hz, 1H, 4-*H*$_b$), 3.54–3.62 (m, 1H, 3-*H*), 3.90 (s, 3H, *OCH*$_3$), 4.79–44.87 (m, 1H, 1-*H*), 6.63 (d, *J* = 2.5 Hz, 1H, 8-Ar-*H*), 7.17 (d, *J* = 2.4 Hz, 1H, 6-Ar-*H*), 12.26 (s, 1H, Ar-*OH*) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.18, 21.21, 30.6, 56.0, 68.6, 69.8, 106.2, 107.6, 109.6, 133.3, 143.2, 146.8, 164.3, 165.8, 183.1, 187.5 ppm. HRMS (ESI+) calcd for $[C_{16}H_{16}O_5 + H]^+$: 289.1076, found: 289.1062.

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Notes and references

1 M. A. Brimble, L. J. Duncalf and M. R. Nairn, *Nat. Prod. Rep.*, 1999, **16**, 267.
2 H. W. Moore and R. Czerniak, *Med. Res. Rev.*, 1981, **1**, 249.
3 (*a*) R. A. Fernandes, V. P. Chavan and A. B. Ingle, *Tetrahedron Lett.*, 2008, **49**, 6341; (*b*) R. A. Fernandes, V. P. Chavan and S. V. Mulay, *Tetrahedron: Asymmetry*, 2011, **22**, 487; (*c*) R. A. Fernandes and V. P. Chavan, *Eur. J. Org. Chem.*, 2010, 4306; (*d*) R. A. Fernandes and S. V. Mulay, *Synlett*, 2010, 2667; (*e*) R. A. Fernandes and S. V. Mulay, *J. Org. Chem.*, 2010, **75**, 7029.
4 (*a*) K. H. Dötz, *Angew. Chem.*, 1975, **87**, 672; K. H. Dötz, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 644; Reviews: (*b*) K. H. Dötz, *Angew. Chem.*, 1984, **96**, 573; K. H. Dötz, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 587; (*c*) K. H. Dötz and J. Stendel Jr., in *Modern Arene Chemistry*, ed. D. Astruc, Wiley-VCH, Weinheim, Germany, 2002, pp. 250–296; (*d*) T. Ito and M. Minato, in *Compounds of Groups 7–3, (Mn..., Cr..., V..., Ti..., Sc..., La..., Ac...) Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, ed. T. Imamoto, Thieme, Stuttgart, Germany, 2002, vol. 2, pp. 333–380; (*e*) K. H. Dötz, B. Wenzel Jr. and H. C. Jahr, *Top. Curr. Chem.*, 2005, **248**, 63; (*f*) M. L. Waters and W. D. Wulff, *Org. React.*, 2008, **70**, 121; (*g*) E. A. Couladouros and T. A. Stromgilos, in *Quinones and Heteroatom Analogues Science of Synthesis Houben-Weyl Methods of Molecular Transformations*, ed. A. G. Griesbeck, Thieme, Stuttgart, Germany, 2006, vol. 28, pp. 217–322; (*h*) M. F. Semmelhack, J. J. Bozell, T. Sato, W. Wulff, E. Spiess and A. Zask, *J. Am. Chem. Soc.*, 1982, **104**, 5850; (*i*) M. F. Semmelhack, J. J. Bozell, L. Keller, T. Sato, E. J. Spiess, W. Wulff and A. Zask, *Tetrahedron*, 1985, **41**, 5803.
5 E. L. Larghi and T. S. Kaufman, *Eur. J. Org. Chem.*, 2011, 5195, and references cited therein.
6 S. R. Jammula, S. B. Pepalla, H. Telikepalli, K. V. J. Rao and R. H. Thomson, *Phytochemistry*, 1991, **30**, 3741.
7 J. Sperry, I. Lorenzo-Castrillejo, M. A. Brimble and F. Machín, *Bioorg. Med. Chem.*, 2009, **17**, 7131.
8 (*a*) M. S. Buchanan, M. Gill and J. Yu, *Aust. J. Chem.*, 1997, **50**, 1081; (*b*) M. S. Buchanan, M. Gill and J. Yu, *J. Chem. Soc., Perkin Trans. 1*, 1997, 919.
9 (*a*) E. M. Mmutlane, J. P. Michael, I. R. Green and C. B. de Koning, *Org. Biomol. Chem.*, 2004, **2**, 2461; (*b*) L. M. Tewierik, C. Dimitriadis, C. D. Donner, M. Gill and B. Willems, *Org. Biomol. Chem.*, 2006, **4**, 3311; (*c*) J. Sperry, J. J. P. Sejberg, F. M. Stiemke and M. A. Brimble, *Org. Biomol. Chem.*, 2009, **7**, 2599; (*d*) D. W. Cameron, G. I. Feutrill and G. A. Pietersz, *Aust. J. Chem.*, 1982, **35**, 1481.
10 K. H. Dötz, W. Sturm, M. Popall and J. Riede, *J. Organomet. Chem.*, 1984, **277**, 267.
11 (*a*) M. E. Bos, W. D. Wulff, R. A. Miller, S. Chamberlin and T. A. Brandvold, *J. Am. Chem. Soc.*, 1991, **113**, 9293; (*b*) V. P. Liptak and W. D. Wulff, *Tetrahedron*, 2000, **56**, 10229.
12 L. A. Mitscher, S. R. Gollapudi, D. S. Oburn and S. Drake, *Phytochemistry*, 1985, **24**, 1681.

