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A highly diastereoselective oxa-Pictet-Spengler approach to (+)-astropaquinone B and (+)-astropaquinone C and the formation of astropaquinone B dimer

Rodney A. Fernandes *, Sandip V. Mulay

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, Maharashtra, India

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ABSTRACT

A concise and highly diastereoselective synthesis of (+)-astropaquinone B and (+)-astropaquinone C is reported. The synthetic strategy is based on an efficient combination of Dötz benzannulation using a chiral alkyne to construct the naphthalene unit and a highly diastereoselective oxa-Pictet-Spengler reaction to install the *trans*-configured pyran ring as the key steps.

1. Introduction

Pyranonaphthoquinone antibiotics are isolated from various strains of bacteria and fungi, most of them being of microbial origin.[1] This class of antibiotics shows activity against various gram-positive bacteria, pathogenic fungi, and yeasts, as well as having antiviral activity.[1] Several pyranonaphthoquinones have been proposed to act as effective bioreductive alkylating agents.[2] Wang et al.[3] isolated three new naphthoquinones: astropaquinone A **1** and the pyranonaphthoquinones with a unique lactol ring, astropaquinones B **2**, and C **3** (Fig. 1) from the cultures of the fresh water fungus *Astrosphaeriella papuana* YMF 1.01181, along with the known compound 6-hydroxy-2,4-dimethoxy-7-methylanthraquinone **4**. Their structures were determined by spectroscopic techniques including 1D and 2D NMR. They showed moderate antagonistic activity against fungi and bacteria.[3] Astropaquinone C **3** is a 7,9-dimethyl ether of pyranonaphthoquinone, (−)-thysanone 7,[4] which was isolated from *Thysanophora penicilloides* (MF 5636, Merck Culture Collection). (−)-Thysanone **7** shows potent activity against human rhinoviruses (HRVs) 3C-protease (IC_{50} 13 μg/mL). Related compounds ascomycones A **5** and B **6**[5] were isolated from the culture of an unknown ascomycete found on the bark of a dead twig in French Guiana. Recently, Zhang et al.[6] isolated the enantiomers of astropaquinone B **2** and C **3**, that is, *ent*-**2** and *ent*-**3** from the fungus *Torula herbarum*. Brimble et al.[7] reported the first and only total synthesis of both astropaquinones B **2** and C **3** through a Staunton-Weinreb annulation.[8] Due to the significant biological activity of thysanone **7** against HRV-3C protease several approaches for its synthesis and those of its analogs have been reported.[9]

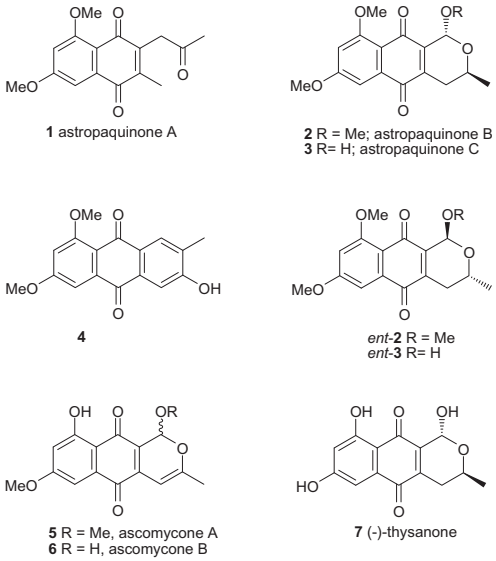

Figure 1. Structures of astropaquinones **1–3**, thysanone **7**, and related molecules.

In continuation of our research program aimed at the stereoselective synthesis of pyranonapthoquinones and related compounds[10] by employing the Dötz benzannulation[11] reaction as a key step, we became interested in the unique lactol containing pyranonaphthoquinones: (+)-astropaquinone B **2** and (+)-astropaquinone C **3**. Demethylation of any of these could give thysanone **7**. Herein we report a concise and highly diastereoselective synthesis of (+)-astropaquinone B **2** and (+)-astropaquinone C **3** along with the oxidative formation of a unique dimer of astropaquinone B **2**.

* Corresponding author. Tel.: +91 (22) 25767174; fax: +91 (22) 25767152.
E-mail address: rfernand@chem.iitb.ac.in (R.A. Fernandes).

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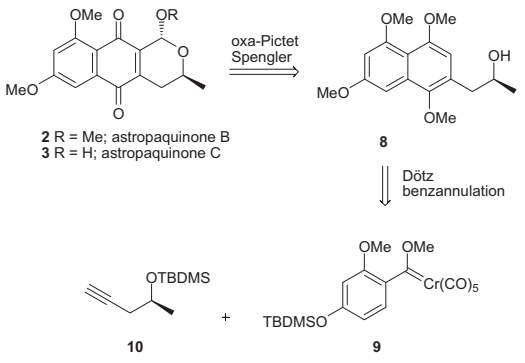
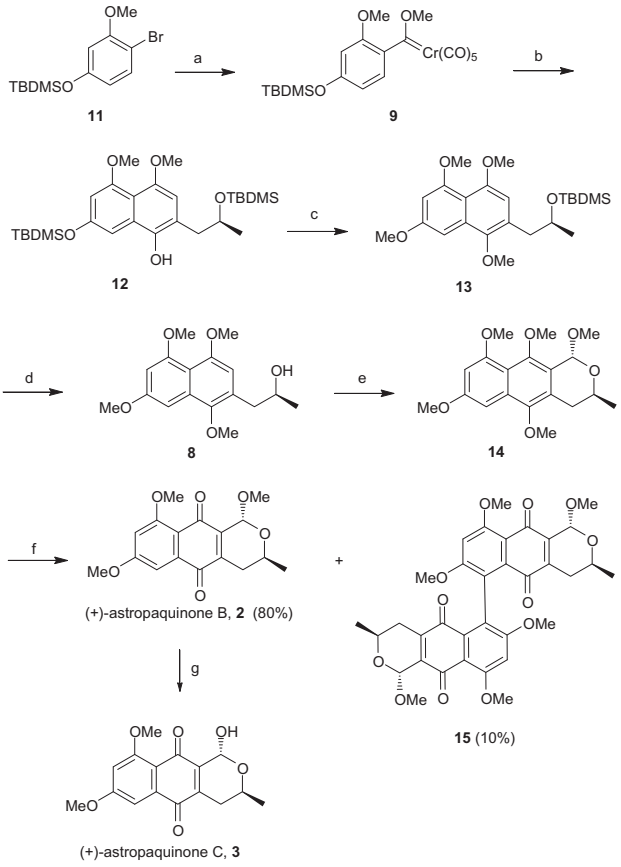
2. Results and discussion

Our retrosynthetic route to **2** and **3** is shown in Scheme 1. The synthesis of compounds **2** and **3** could be envisioned from the naphthyl alcohol **8** through an oxa-Pictet-Spengler reaction. The substituted naphthalene ring could be easily accessed by a Dötz benzannulation reaction of Fischer carbene **9** with chiral alkyne **10**. The TBDMS protection of the OH group *para* to the carbene carbon on the Fischer carbene **9** was aimed to increase the benzannulation reaction yield although its introduction adds one step to the synthesis. It is reported in the literature[12] that Fischer carbenes with an electron donating group at the *para* position of the aromatic ring (such as –OMe) give poor yields in Dötz benzannulation reactions which is one of the key steps in the synthesis.

The synthesis of **2** and **3** started from the known bromo compound **11**[12] (Scheme 2). The Fischer carbene **9** was prepared from **11** in good yield (65%). The Dötz benzannulation reaction of **9** with alkyne **10**[10e] gave naphthol **12** in a moderate yield of 48%. A similar Fischer carbene with an –OMe group instead of –OTBDMS gave only 35% yield.[10i] The protection of the phenolic OH group using NaH (1.2 equiv) in DMF solvent gave a mixture of compounds, in which **13** was formed through aryl-OTBDMS deprotection and methylation along with the expected TBDMS containing compound. Increasing the base concentration (NaH, 2.2 equiv) resulted in only **13** (70%) where the complete removal of the phenolic TBDMS group occurred followed by methylation. The aliphatic-OTBDMS group remained intact. Removal of this from **13** gave the desired alcohol **8** in 96% yield. The latter was subjected to an oxa-Pictet-Spengler[13] reaction with trimethylorthoformate in the presence of a catalytic amount of *p*-TsOH to furnish the *trans*-configured pyran **14** exclusively in excellent yields (92%).[14] No trace of the *cis*-pyran product was observed within the detectable limits of NMR. The oxidation of compound **14** using phenyliodinebis(trifluoroacetate) (PIFA) provided (+)-astropaquinone B **2** in 80% yield {$[\alpha]_D^{25} = +42.3$ (*c* 0.12, $CHCl_3$), lit.[7] $[\alpha]_D^{19} = +35.0$ (*c* 0.14, $CHCl_3$), lit.[3] $[\alpha]_D^{27.8} = +45.1$ (*c* 0.12, $CHCl_3$)} along with a small amount of dimerized product **15** (10%). The formation of **15** was ascertained by the presence of only one aryl-H in the ^{1}H NMR corresponding to 8-Ar*H* (and 8′-Ar*H*) and by mass analysis. The formation of **15** is similar to the dimerization of ventiloquinone L as observed by Brimble et al.[15] when quinone formation was carried out by using cerium ammonium nitrate. Further treatment of **2** with a catalytic amount of *p*-TsOH and water in benzene gave astropaquinone C **3** in 75% yield {$[\alpha]_D^{25} = +44.0$ (*c* 0.1, $CHCl_3$), lit.[7] $[\alpha]_D^{19} = +31.1$ (*c* 0.10, $CHCl_3$), lit.[3] $[\alpha]_D^{24.7} = +53.9$ (*c* 0.10, $CHCl_3$)}. The spectroscopic data of both **2** and **3** were in excellent agreement with that reported in the literature.[3,7]



Scheme 1. Retrosynthesis of astropaquinones B **2** and C **3**.



Scheme 2. Synthesis of (+)-astropaquinone B **2**, (+)-astropaquinone C **3** and the formation of dimer **15**. Reagents and conditions: (a) (i) *n*-BuLi, Et_2O, −50 °C, 15 min; (ii) $Cr(CO)_6$, Et_2O, 0 °C, 1 h, rt, 2 h; (iii) Me_3OBF_4, CH_2Cl_2, 0 °C, 1 h, rt, 2 h, 65%, (b) **10**, THF, 45 °C, 12 h, 48%, (c) NaH, DMF, MeI, 0 °C to rt, 6 h, 70%, (d) TBAF, THF, rt, 6 h, 96%, (e) $CH(OMe)_3$, *p*-TsOH, CH_2Cl_2, rt, 1 h, 92%, (f) PIFA, CH_3CN–H_2O, 0 °C, 5 min, **2** 80% and **15** 10%, (g) *p*-TsOH; H_2O, benzene, reflux, 4 h, 75%.

3. Conclusion

In conclusion, a concise diastereoselective synthesis of (+)-astropaquinone B and (+)-astropaquinone C has been achieved. A unique dimer of the former was isolated during quinone formation. The synthetic strategy features an efficient combination of a Dötz benzannulation reaction of a Fischer carbene with a chiral alkyne to construct the naphthalene unit and a highly diastereoselective oxa-Pictet-Spengler reaction to install the *trans*-configured pyran ring as the key steps. The synthesis was completed from the known compound **11** in six steps for **2** (15.4% overall yield) and seven steps for **3** (11.6% overall yield).

4. Experimental

4.1. General

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 at 400 and 100 MHz respectively, and chemical shifts are based on TMS peak at $\delta = 0.00$ ppm for proton NMR, and $CDCl_3$ peak at $\delta = 77.00$ ppm (t) for carbon NMR. IR samples were prepared by

evaporation from $CHCl_3$ on CsBr plates. High-resolution mass spectra were obtained using positive electrospray ionization.

4.1.1. (4-Bromo-3-methoxyphenoxy)(*tert*-butyl)-dimethyl-silane 11[12]

To a stirred solution of 4-bromoresorcinol (3.0 g, 15.87 mmol) in dry acetone (60 mL) were added K_2CO_3 (10.97 g, 79.36 mmol, 5.0 equiv) and TsCl (3.18 g, 16.7 mmol, 1.05 equiv). The reaction mixture was refluxed for 16 h and then cooled to room temperature. To the reaction mixture was added MeI (2.47 mL, 39.67 mmol, 2.5 equiv) and further refluxed for 12 h. It was then cooled to room temperature and the precipitated solid was filtered off. The filtrate was concentrated under reduced pressure and the residue diluted with water and EtOAc (1:1, 50 mL). The separated aqueous layer was extracted with EtOAc (2 × 30 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 4-bromo-3-methoxyphenyl-4-methylbenzenesulfonate (5.05 g, 89%) as a white solid: mp 68–70 °C; IR ($CHCl_3$): ν = 3015, 2942, 2862, 1596, 1578, 1481, 1446, 1403, 1374, 1307, 1292, 1273, 1211, 1194, 1179, 1139, 1120, 1092, 1048, 1025, 949, 855, 816, 784, 720, 703, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 2.46 (s, 3H), 3.78 (s, 3H), 6.40 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 56.3, 106.9, 109.9, 115.2, 128.5, 129.8, 131.9, 133.2, 145.6, 149.5, 156.4; HRMS *m/z* calcd for $[C_{14}H_{13}BrO_4S + Na]^+$ 378.9610, found: 378.9610.

To a stirred solution of the above 4-bromo-3-methoxyphenyl-4-methylbenzenesulfonate (4.2 g, 11.76 mmol) in ethanol (30 mL) was added KOH (1.32 g, 23.52 mmol, 2.0 equiv). The reaction mixture was refluxed for 3 h and then cooled to room temperature. The solvent was evaporated at reduced pressure and the residue diluted with water and EtOAc (1:1, 50 mL). The separated aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with 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 4-bromo-3-methoxyphenol (2.1 g, 88%) as a white solid: mp 74–76 °C; IR ($CHCl_3$): *v* = 3462, 3010, 2943, 1607, 1590, 1487, 1468, 1450, 1430, 1297, 1267, 1199, 1168, 1128, 1047, 1024, 951, 830, 797, 758, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 3.84 (s, 3H), 5.68 (s, 1H, *OH*), 6.34 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.45 (d, *J* = 2.7 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1, 100.5, 102.1, 108.6, 133.3, 156.1, 156.6; HRMS *m/z* calcd for $[C_7H_7BrO_2 + Na]^+$ 224.9522, found: 224.9523.

To a solution of the above 4-bromo-3-methoxyphenol (1.80 g, 8.87 mmol) in dry THF (30 mL) was added NaH (0.277 g, 11.53 mmol, 1.3 equiv) at 0 °C and stirred for 15 min. Next, TBDMSCl (2.0 g, 13.31 mmol, 1.5 equiv) was added at 0 °C and then slowly warmed to room temperature and the reaction mixture stirred for 12 h. After completion of the reaction, it was quenched with sat. aq. $NaHCO_3$ (20 mL). The solvent was evaporated at reduced pressure and the aqueous layer extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5 to 9:1) as eluent to afford **11** (2.75 g, 98%) as a colorless oil; IR ($CHCl_3$): *v* = 2956, 2930, 2858, 1589, 1486, 1448, 1404, 1302, 1257, 1205, 1170, 1121, 1053, 1026, 979, 841, 781, 705, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 0.20 (s, 6H), 0.98 (s, 9H), 3.85 (s, 3H), 6.34 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.41 (d, *J* = 2.6 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.5, 18.2, 25.6, 56.1, 103.0, 105.0, 113.2, 133.0, 156.2, 156.4; HRMS *m/z* calcd for $[C_{13}H_{21}BrO_2Si + H]^+$ 317.0567, found: 317.0567.

4.1.2. (*S*)-7-(*tert*-Butyldimethylsilyloxy)-2-[2-(*tert*-butyldi-methylsilyloxy)propyl]-4,5-dimethoxynaphthalen-1-ol 12

To a solution of **11** (1.0 g, 3.15 mmol) in dry Et_2O (25 mL) at −50 °C was added *n*-BuLi (2.2 mL 3.49 mmol, 1.1 equiv, 1.6 M solution in hexane) and the reaction mixture was stirred for 15 min. It was then transferred to a suspension of $Cr(CO)_6$ (0.832 g, 3.78 mmol, 1.2 equiv) in dry Et_2O (25 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then at room temperature for 2 h. Next, Et_2O was evaporated off and the residue was dissolved in dry CH_2Cl_2 (25 mL). To this solution was added Me_3OBF_4 (0.70 g, 4.73 mmol, 1.5 equiv) in portions at 0 °C and the reaction mixture was stirred for 1 h. It was warmed to room temperature and stirred for 2 h. The red colored reaction mixture was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/CH_2Cl_2 (9:1 to 4:1) as eluent to give **9** (0.968 g, 65%) as a red colored semisolid. This was used immediately in the next step.

To a solution of freshly prepared Fischer carbene **9** (0.94 g, 1.99 mmol) in dry and degassed THF (15 mL) was added a solution of alkyne **10** (0.79 g, 3.98 mmol, 2.0 equiv 99% e.e.) in dry and degassed THF (5 mL). The reaction mixture was heated at 45 °C for 12 h and then allowed to cool to room temperature, exposed to air, and further stirred for 1 h. Next, the THF was removed and the residue purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to afford **12** (0.484 g, 48%) as a light yellow semisolid; $[\alpha]_D^{25} = -10.6$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): ν = 3434, 2956, 2927, 2856, 1653, 1605, 1592, 1512, 1464, 1378, 1328, 1258, 1216, 1159, 1125, 1090, 1036, 985, 939, 838, 780, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = −0.12 (s, 3H), 0.04 (s, 3H), 0.26 (s, 6H), 0.88 (s, 9H), 1.01 (s, 9H), 1.23 (d, *J* = 6.1 Hz, 3H), 2.88 (d, *J* = 5.2 Hz, 2H), 3.88 (s, 3H), 3.93 (s, 3H), 4.21–4.28 (m, 1H), 6.39 (s, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 7.26 (d, *J* = 2.4 Hz, 1H), 8.4 (s, 1H, *OH*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.3, −4.9, −4.44, −4.39, 17.9, 18.3, 23.1, 25.7, 25.8, 41.7, 56.1, 57.4, 71.7, 102.2, 102.6, 108.8, 113.4, 118.9, 129.6, 144.1, 150.2, 153.5, 157.7; HRMS *m/z* calcd for $[C_{27}H_{46}O_5Si_2+H]^+$ 507.2962, found: 507.2955.

4.1.3. (*S*)-*tert*-Butyldimethyl[1-(1,4,5,7-tetramethoxy-naphthalen-2-yl)propan-2-yloxy]silane 13

To a solution of **12** (0.4 g, 0.789 mmol) in dry DMF (15 mL) at 0 °C was added NaH (41.6 mg, 1.74 mmol, 2.2 equiv) and stirred for 30 min. Next, MeI (0.2 mL, 3.16 mmol, 4.0 equiv) was added and the reaction mixture was stirred for 6 h at room temperature. Ice cooled water was added and the reaction mixture extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and 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 **13** (0.232 g, 70%) as a colorless oil; $[\alpha]_D^{25} = +24.6$ (*c* 0.25, $CHCl_3$); IR ($CHCl_3$): *v* = 2956, 2930, 2856, 1676, 1621, 1606, 1468, 1404, 1380, 1246, 1155, 1124, 1083, 1061, 1006, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = −0.14 (s, 3H), −0.03 (s, 3H), 0.84 (s, 9H), 1.19 (d, *J* = 6.0 Hz, 3H), 2.78 (dd, *J* = 13.1, 5.9 Hz, 1H), 2.92 (dd, *J* = 13.1, 7.0 Hz, 1H), 3.84 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 4.15–4.23 (m, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.54 (s, 1H), 6.96 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.0, −4.9, 18.1, 23.8, 25.8, 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; HRMS *m/z* calcd for $[C_{23}H_{36}O_5Si+H]^+$ 421.2410, found: 421.2398.

4.1.4. (*S*)-1-(1,4,5,7-Tetramethoxynaphthalen-2-yl)-propan-2-ol 8

To a solution of compound **13** (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) and THF was removed under reduced pressure. The solution was extracted with EtOAc (3 × 20 mL) and 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 **8** (0.140 g, 96%) as a colorless 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}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.29 (d, *J* = 6.2 Hz, 3H), 2.90 (d, *J* = 6.1 Hz, 2H), 3.86 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 4.16–4.21 (m, 1H), 6.51 (s, 2H), 6.96 (d, *J* = 2.3 Hz, 1H); ^{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; HRMS *m/z* calcd for $[C_{17}H_{22}O_5+H]^+$ 307.1545, found: 307.1550.

4.1.5. (1*R*,3*S*)-1,5,7,9,10-Pentamethoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]isochromene 14

To a solution of alcohol **8** (100 mg, 0.326 mmol) in CH_2Cl_2 (8 mL) were added trimethylorthoformate (0.36 mL, 3.26 mmol, 10.0 equiv) and *p*-TsOH.H_2O (5.6 mg, 0.0294 mmol). The reaction mixture was stirred at room temperature for 1 h and then quenched with satd aq $NaHCO_3$ (8 mL) and the solution extracted with CH_2Cl_2 (3 × 15 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 **14** (104 mg, 92%) as a colorless oil; $[\alpha]_D^{25} = -89.7$ (*c* 0.64, $CHCl_3$); IR ($CHCl_3$): ν = 2972, 2935, 2842, 1622, 1603, 1585, 1504, 1469, 1452, 1414, 1387, 1343, 1261, 1231, 1205, 1161, 1134, 1116, 1083, 1068, 1047, 1008, 974, 941, 849, 833, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.43 (d, *J* = 6.2 Hz, 3H), 2.56 (dd, *J* = 17.0, 11.6 Hz, 1H), 3.03 (dd, *J* = 17.0, 3.3 Hz, 1H), 3.59 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 4.33–4.41 (m, 1H), 5.83 (s, 1H), 6.50 (d, *J* = 2.3 Hz, 1H), 6.94 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 30.2, 54.8, 55.2, 55.9, 60.1, 61.8, 63.0, 92.4, 96.0, 98.5, 115.2, 122.7, 124.8, 131.6, 147.6, 150.8, 157.6, 158.5; HRMS *m/z* calcd for $[C_{19}H_{24}O_6+H]^+$ 349.1651, found: 349.1657.

4.1.6. (+)-Astropaquinone B 2 and (1*R*,1′*R*,3*S*,3′*S*)-1,1′,7,7′,9,9′-hexamethoxy-3,3′-dimethyl-3,3′,4,4′-tetrahydro-1*H*,1′*H*-6,6′-dibenzo[*g*]isochromene-5,5′,10,10′-tetraone 15

To a stirred solution of **14** (50 mg, 0.144 mmol) in CH_3CN (5 mL) and water (5 mL) was added phenyliodine bis(trifluoroacetate) (PIFA, 124 mg, 0.288 mmol, 2.0 equiv). The reaction mixture was stirred at 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 and 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 **2** (36.5 mg, 80%) as a yellow solid. Further elution with petroleum ether/EtOAc (2:3) as eluent gave **15** (9.1 mg, 10%) as a yellow solid. Data for **2**: mp = 162–164 °C, lit.[7] mp = 164–167 °C; $[\alpha]_D^{25}$ = + 42.3 (*c* 0.12, $CHCl_3$), lit.[7] $[\alpha]_D^{19} = +35.0$ (*c* 0.14, $CHCl_3$), lit.[3] $[\alpha]_D^{27.8} = +45.1$ (*c* 0.12, $CHCl_3$); IR ($CHCl_3$): ν = 3015, 2963, 2930, 2852, 1659, 1594, 1563, 1467, 1457, 1385, 1339, 1322, 1196, 1160, 1089, 1071, 1055, 1038, 961, 940, 860, 840, 821, 720, 686, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.38 (d, *J* = 6.3 Hz, 3H), 2.23 (dd, *J* = 19.1, 11.0 Hz, 1H), 2.66 (dd, *J* = 19.1, 3.5 Hz, 1H), 3.56 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.19–4.25 (m, 1H), 5.54 (s, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 29.0, 55.9, 56.2, 56.4, 62.0, 93.7, 103.2, 104.3, 114.2, 135.7, 140.5, 140.9, 162.0, 164.5, 180.8, 184.9; HRMS *m/z* calcd for $[C_{17}H_{18}O_6+H]^+$ 319.1182, found: 319.1181. Data for **15**: mp = 155–165 °C (decomp); $[\alpha]_D^{25} = +19.6$ (*c* 0.2, $CHCl_3$); IR ($CHCl_3$): ν = 3017, 2973, 2934, 1666, 1579, 1550, 1470, 1433, 1344, 1304, 1264, 1220, 1167, 1126, 1094, 1049, 978, 924, 831, 707, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.38 (d, *J* = 6.2 Hz, 6H), 2.28 (dd, *J* = 18.9, 11.2 Hz, 2H), 2.63 (dd, *J* = 18.9, 3.4 Hz, 2H), 3.56 (s, 6H), 4.02 (s, 6H), 4.03 (s, 6H), 4.14–4.23 (m, 2H), 5.53 (s, 2H), 6.76 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 29.3, 56.1, 56.6, 56.7, 62.1, 93.4, 100.3, 114.7, 115.8, 130.9, 139.4, 142.2, 160.5, 160.7, 180.2, 184.2; HRMS *m/z* calcd for $[C_{34}H_{34}O_{12}+H]^+$635.2128, found: 635.2132.

4.1.7. (+)-Astropaquinone C 3

To a stirred solution of **2** (20 mg, 0.063 mmol) in benzene (5 mL) and water (1 drop) was added *p*-TsOH·H_2O (cat). The reaction mixture was refluxed for 4 h. It was then quenched with satd aq $NaHCO_3$ (2 mL) and the aqueous layer extracted with EtOAc (3 × 10 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 (4:1 to 2:1) as eluent to afford **3** (14.4 mg, 75%) as a yellow solid: mp = 181–183 °C, lit.[7] mp = 178–181 °C; $[\alpha]_D^{25} = +44.0$ (*c* 0.1, $CHCl_3$), lit.[7] $[\alpha]_D^{19} = +31.1$ (*c* 0.10, $CHCl_3$), lit.[3] $[\alpha]_D^{24.7} = +53.9$ (*c* 0.10, $CHCl_3$); IR ($CHCl_3$): ν = 3434, 3011, 2925, 2854, 1658, 1595, 1563, 1463, 1380, 1347, 1321, 1277, 1217, 1160, 1122, 1081, 1031, 968, 941, 922, 863, 829, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.40 (d, *J* = 6.2 Hz, 3H), 2.23 (dd, *J* = 19.1, 11.1 Hz, 1H), 2.71 (dd, *J* = 19.1, 3.2 Hz, 1H), 3.96 (s, 3H), 3.97 (s, 3H), 4.28–4.36 (m, 1H), 6.02 (s, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 7.26(d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 29.0, 56.0, 56.4, 62.9, 87.2, 103.6, 104.3, 113.9, 135.7, 140.4, 142.1, 162.1, 164.9, 182.1, 184.6; HRMS *m/z* calcd for $[C_{16}H_{16}O_6+K]^+$ 343.0584, found: 343.0586.

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