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Full Paper

Synthesis of Highly Enantio-Enriched Heliespirones A and C by a Diastereoselective Aromatic Claisen Rearrangement

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Computational methods were used to investigate the stereochemical course of the extra-annular Claisen rearrangement. The stereochemical fidelity of the synthetic strategy and comparison of the optical properties support the hypothesis that the heliespirones are scalemic natural products.

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Introduction

Macías and coworkers reported the isolation of heliespirone A (**1**) and heliespirone C (**2**) from a sunflower cultivar in 1998 and 2006 respectively (Fig. 1).[1,2] The source plant has demonstrated natural herbicidal activity against the seedling growth of several common weeds, and consequently, it has been exploited as a potential source of new agrichemicals. Macías suggested that the spiro-epimeric heliespirones may ultimately derive from the co-isolate, heliannuol C (**4**), which possesses the same absolute configuration.[2,3] Another possible biosynthetic progenitor is the six-membered variant, heliannuol E (**5**), which possesses the opposite configuration at the cyclic ether.

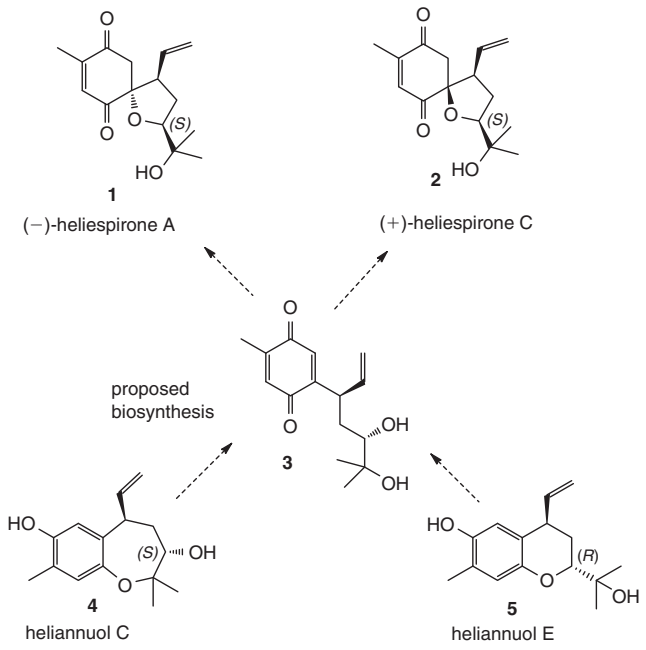
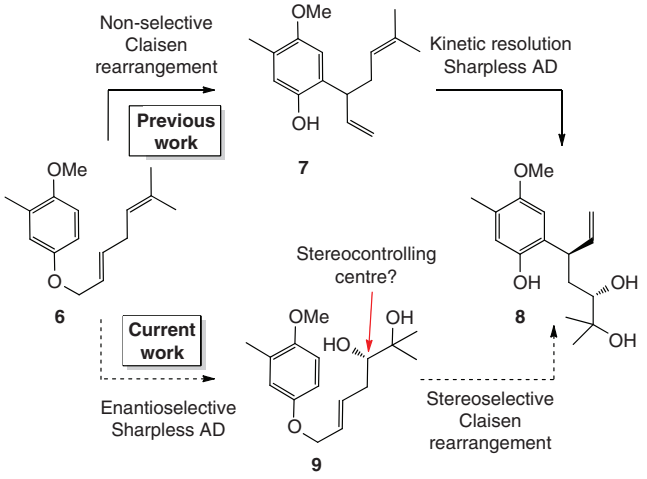


Fig. 1. Heliespirones A (**1**) and C (**2**), and some possible biosynthetic progenitors.

Asymmetric total synthesis of both **4** and **5** has confirmed that these compounds exist naturally in highly enantio-enriched forms.[4]

The heliespirones have attracted significant synthetic interest, with four total syntheses reported to date, either of the naturally occurring enantiomers[5,6] or their antipodes.[7,8] Our recently reported synthesis utilized an aromatic Claisen rearrangement, followed by a Sharpless asymmetric dihydroxylation (AD) reaction to generate the key intermediate **8** (Scheme 1).[5] However, the Sharpless AD reaction does not perform well on compounds such as **7**,[9,10] and in that instance, the level of enantiomeric excess (ee) that could be induced in the process was only 17 %. When this material was advanced through the synthetic sequence, we were very surprised to find that both our synthetic heliespirone A (**1**) and heliespirone C (**2**) had the same values of optical rotation as the isolated compounds. A range of values for the optical rotation of synthetic heliespirones have been reported in the literature (see Supplementary Material) and, in particular, Shishido reported that the



Scheme 1. Pathways to the proposed biosynthetic intermediate **8**.

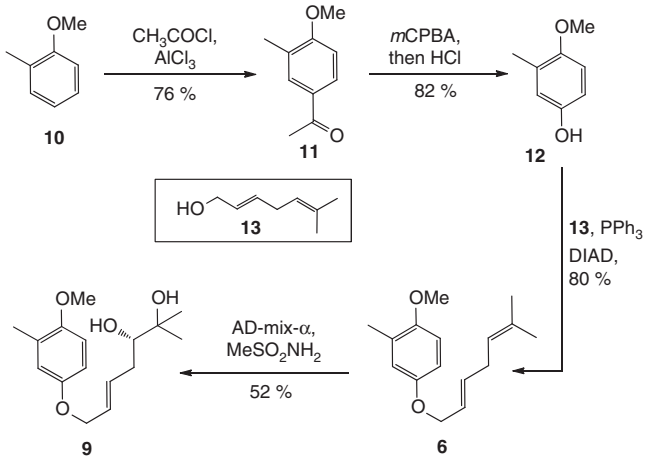
enantiomerically pure samples possessed significantly higher specific rotations.[6] Given that heliespirone A (**1**) and heliespirone C (**2**) were isolated independently, it is unlikely that co-incident measurement errors were responsible for the apparent low ee. If an inadvertent resolution had occurred during our reported synthetic sequence, it is improbable (though not impossible) that the optical rotation data would individually match both of the natural products. Does this mean that the naturally occurring heliespirones exist as scalemic mixtures?[11,12] To clarify the situation, we devised a second-generation strategy to the heliespirones, which is reported below.

Results and Discussion

As shown in the lower section of Scheme 1, we planned to perform the Sharpless AD reaction on compound **6** to give compound **9**. We then hoped that the newly installed stereogenic centre would influence the stereochemical outcome of a subsequent Claisen rearrangement and give compound **8** in a stereoselective fashion. The projected stereo-directing centre is two carbons removed from the newly forming bond, and resides on a flexible carbon chain. To the best of our knowledge, there are no examples in the literature of an aromatic Claisen rearrangement being influenced by such a remote extra-annular stereocentre.[13–16]

In analogy to our previous work, the synthesis began with Friedel–Crafts acylation of 2-methylanisole (**10**) in the presence of anhydrous aluminium trichloride to give compound **11**[17] (Scheme 2). Baeyer–Villiger oxidation with *m*-chloroperoxybenzoic acid and acidic hydrolysis gave 4-methoxy-*m*-cresol (**12**) in high yield.[13] This was coupled with the known alcohol **13**[5] under Mitsunobu conditions to give the desired compound **6**, which was expected to perform well under Sharpless AD reaction conditions.[9,10] Pleasingly, treatment of **6** with commercial AD-mix-α gave compound **9** in moderate yield but, importantly, with excellent enantioselectivity, >97% ee. (Fig. 2). Compound **9** was the substrate for the planned diastereoselective aromatic Claisen rearrangement.

The aromatic Claisen rearrangement is known to proceed preferentially through a chair-like transition state.[18] We hoped that a chelating Lewis acid would sequester the diol unit, and that minimization of $A_{1,3}$-strain would result in one face of the alkene being shielded by the geminal methyl groups (Fig. 3). When subjected to the action of 2 equivalents of Me_2AlCl at low temperature in a non-polar solvent, compound **9** did undergo a moderately stereoselective aromatic Claisen rearrangement (Scheme 3). The remote stereogenic centre imposed a substrate-controlled reaction that produced a 2 : 1 mixture of diastereomers **14** and **8**.[19] In opposition to expectation, the desired isomer **8** was the minor component of the mixture. Single-crystal X-ray analysis served to unambiguously demonstrate the relative stereochemistry of compound **8** (Fig. 4). Other Lewis and protic acids were screened for this transformation, as well as simple heating, but in all instances, elimination of the stereochemically defined alcohol was observed. Enantioselective HPLC analysis of compound **8** demonstrated that the absolute stereochemical integrity of the molecule remained intact (Fig. 5).



Scheme 2. Synthesis of compound **9**.

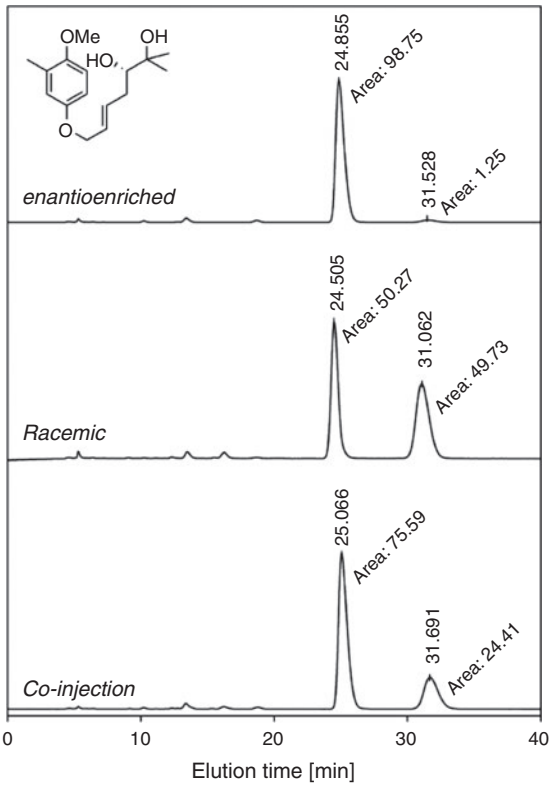


Fig. 2. Enantioselective HPLC traces of (−)-**9** and (±)-**9**.

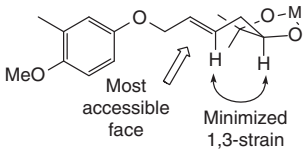
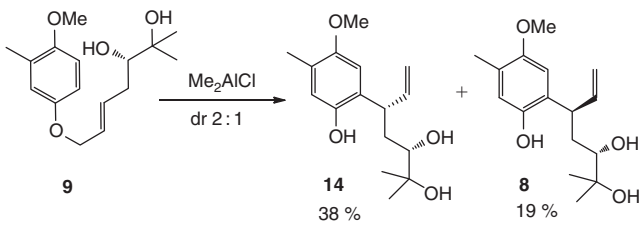


Fig. 3. Anticipated complex between Me_2AlCl and compound (−)-**9**. M = metal atom.



Scheme 3. Diastereoselective aromatic Claisen rearrangement. d.r. = diastereomeric ratio.

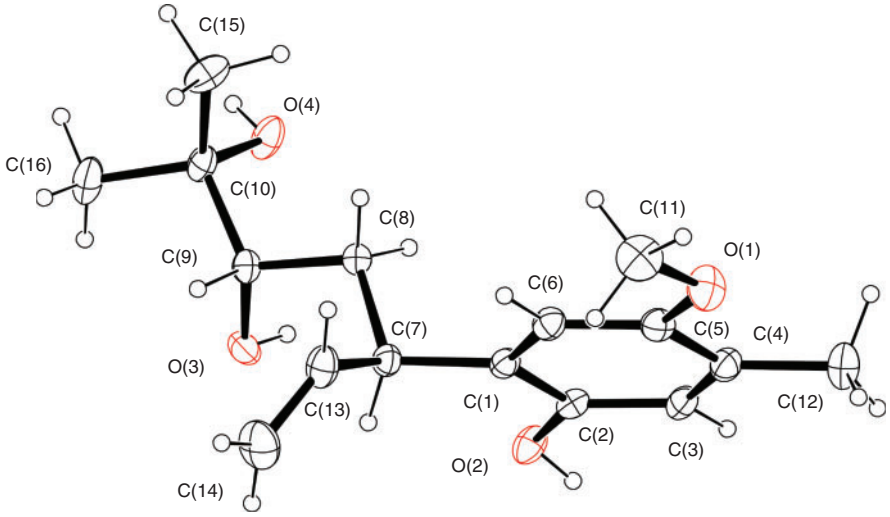


Fig. 4. *ORTEP* representation of diastereomer **8**.

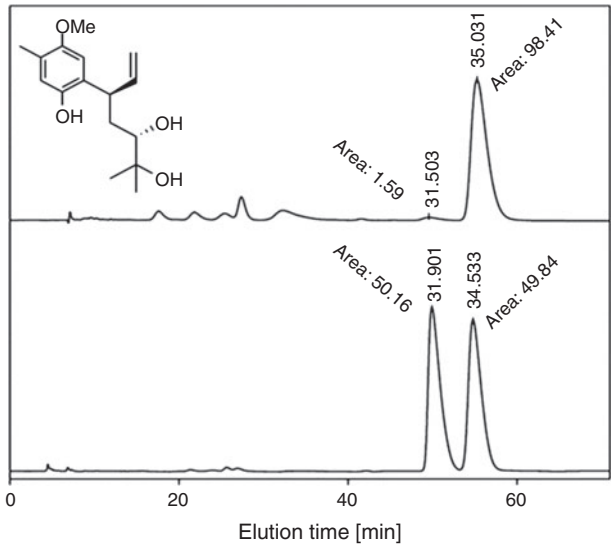
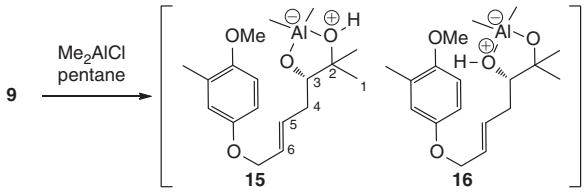


Fig. 5. Enantioselective HPLC traces of (−)-**8** and (±)-**8**.



Scheme 4. Relative energies of possible precursors for the aromatic Claisen rearrangement.

Because there was no literature precedent for this type of diastereoselective extra-annular aromatic Claisen rearrangement, we investigated the transformation using computational methods. Based on the relative pK_a values of secondary and tertiary alcohols, we anticipated that reaction between diol **9** and Me_2AlCl would yield intermediate **15** in preference to intermediate **16** (Scheme 4).

The transitions state structures (**TS15a–d**) for the aromatic Claisen rearrangement of intermediate **15** were calculated at the

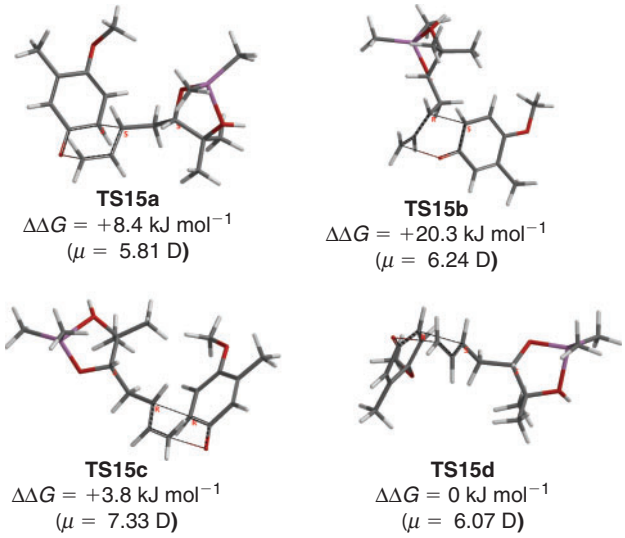
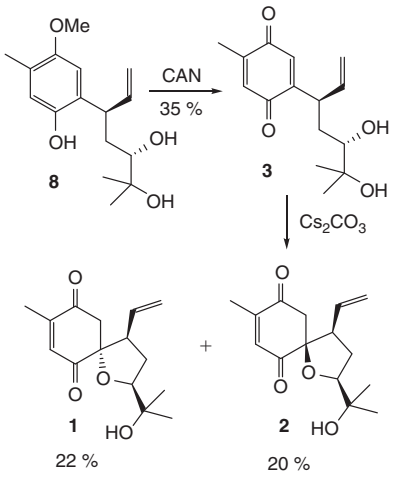


Fig. 6. Transition-state structures for the aromatic Claisen rearrangement of intermediate **15**. Purple = Al; red = O; grey = C; white = H. Dipole moment (μ) in debyes (D).

B3LYP/6–31G* level of theory, with inclusion of solvent effects using the C-PCM (conductor-like polarizable continuum model) method. As displayed in Fig. 6, all four transition-state structures possessed common features: (1) $A_{1,3}$-strain was minimized between the hydrogen atoms attached to C-4 and C-6 during the rearrangement; (2) the C-3 stereocentre was oriented with the smallest substituent (the H atom) projecting over the C-5–C-6 alkene; and (3) the methoxy substituent on the aromatic ring rotated to minimize steric interactions.

Transition-state structures **TS15a** and **TS15c** possess chair-like conformations and, as predicted at the outset of the synthesis, the lower-energy structure **TS15c** leads to the naturally occurring (*R*)-configuration at the newly formed stereocentre of compound **8**. In contrast, transition-state structures **TS15b** and **TS15d** possess boat-like conformations, but surprisingly, **TS15d** proved to be on the lowest-energy pathway for the aromatic Claisen rearrangement, giving compound **14**. The preference for **TS15d** results from not only a minimization of steric interactions (**TS15a** versus **TS15d**), but also from a



Scheme 5. Synthesis of the heliespirones **1** and **2**.

minimization of the structure's overall dipole moment (**TS15c** versus **TS15d**). As such, the nature of the solvent is likely to play a crucial role in the stereochemical outcome of this and related reactions. Although the calculated difference in activation energies between **TS15c** and **TS15d** does not exactly predict the observed 2 : 1 ratio of product diastereomers, it does predict the predominant isomer. The calculated energies starting from compound **16** also showed favoured production of the observed stereoisomer (Supplementary Material). It is important to note that charge acceleration and the nature of the counter-ion were not included in these calculations.

To complete the total synthesis, compound **8** was converted into the quinone **3** (Scheme 5), and subsequently treated with Cs_2CO_3 gave the desired products (−)-heliespirone A (**1**) and (+)-heliespirone C (**2**). Again, analysis by enantioselective HPLC demonstrated that the reaction sequence had not affected the absolute stereochemistry of the compounds (see Supplementary Material). As outlined in Table 1, the heliespirone natural products were produced in a highly enantio-enriched fashion, and the observed specific rotations were in good agreement with Shishido's values.[6] This demonstrated that an inadvertent resolution had not taken place during our first generation synthesis, and that naturally occurring heliespirone A (**1**) and heliespirone C (**2**) possess enantiomeric excesses lower than 20 %.

Conclusion

This article describes a second-generation synthesis of the plant-derived natural products (−)-heliespirone A (**1**) and (+)-heliespirone C (**2**). The improved route is not only shorter than our previous approach (eight steps for the longest linear synthesis) but features a diastereoselective aromatic Claisen rearrangement in which the stereocontroling unit is distal to the rearranging bonds. Both natural products were obtained with excellent enantiopurity, and the outcomes of this work suggest that the heliespirones occur naturally as scalemic mixtures.[20–23]

Experimental

General Experimental

Reagent-grade dichloromethane and triethylamine were freshly distilled from calcium hydride. Tetrahydrofuran and methanol were collected using an Innovative Technology Inc. PureSolv™ solvent purification system. All other solvents and reagents were used as received from commercial sources. Melting points were determined using a Stanford Research Systems Optimelt automated melting point system and are uncorrected. Infrared spectra were acquired neat on a Bruker Alpha-E attenuated total reflectance (ATR) spectrometer (cm^{-1}). UV-vis absorption spectra were recorded on a Varian Cary 50 spectrophotometer and absorption maxima are expressed in wavenumbers. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX300 (^1H frequency 300 MHz; ^{13}C frequency 75 MHz). ^1H chemical shifts are expressed as parts per million (ppm) with residual chloroform (7.26 ppm) or residual methanol (3.31 ppm) as reference and are reported as chemical shift (δ_H); relative integral; multiplicity (s = singlet, br = broad, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, q = quartet, m = multiplet), and coupling constants (*J*) reported in hertz. ^{13}C NMR chemical shifts are expressed as parts per million (ppm) with residual chloroform (77.1 ppm) or residual methanol (49.0 ppm) as internal reference and are reported as chemical shift (δ_C); multiplicity (assigned from DEPT experiments). High-resolution mass spectra (HRMS) were recorded on a Bruker ApexII Fourier-transform ion cyclotron resonance mass spectrometer with a 7.0-T magnet, fitted with an off-axis analytical electrospray source. Column chromatography was performed using Grace Davidson 40–63-μm (230–400 mesh) silica gel using distilled solvents. Analytical thin layer chromatography was performed using preconditioned plates (Merck TLC silica gel 60 F254 on aluminium) and visualized using UV light (254 and 365 nm) and ethanolic anisaldehyde.

Density functional theory (DFT) calculations were carried out with the *Spartan '16* program.[24] Geometries and energies of transition states and intermediates were obtained using the B3LYP functional with the 6–31G* basis set. The vibrational frequencies of stationary points were inspected to ensure that they corresponded to minima on the potential energy surface. All relative energies are reported uncorrected at 298 K in kilojoules per mole.

Crystallographic data for compound **8** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) and can be obtained free of charge on quoting the depository number CCDC 1825691 (http://www.ccdc.cam.ac.uk).

Table 1. Comparison of enantiomeric excess from second-generation synthesis

Compound	Measured ee [%]	Specific optical rotation
Compound **8**	98[A]	−16.4 (*c* 0.29, $CHCl_3$)
Compound **3**	97[B]	−107 (*c* 0.55, $CHCl_3$)
Natural heliespirone A (**1**)	–	−29 (*c* 0.1, $CHCl_3$)
Synthetic heliespirone A	95[C]	−47 (*c* 0.12, $CHCl_3$)
Shishido's heliespirone A[6]	–	−55.2 (*c* 0.13, $CHCl_3$)
Natural heliespirone C (**2**)	–	+14.4 (*c* 0.1, $CHCl_3$)
Synthetic heliespirone C	97[D]	+48 (*c* 0.09, $CHCl_3$)
Shishido's heliespirone C[6]	–	+50.4 (*c* 0.4, $CHCl_3$)

[A]Measured on a Chiralcel OD-H column, 8 % isopropanol in hexane.
[B]Measured on a Chiralcel OD-H column, 4 % ethanol in hexane.
[C]Measured on a Chiralcel OD-H column, 8 % isopropanol in hexane.
[D]Measured on a Chiralcel OD-H column, 4 % isopropanol in hexane.

4′-Methoxy-3′-methylacetophenone **11**[17]

To a mixture of anhydrous aluminium chloride (2.4 g, 18 mmol) in CH_2Cl_2 (4 mL) was added slowly a solution of 2-methylanisole (3.4 g, 28 mmol) in CH_2Cl_2 (4 mL), then acetyl chloride (2.3 mL, 32 mmol) in CH_2Cl_2 (2 mL). The mixture was heated to reflux for

2 h, then cooled, quenched with aqueous HCl (3 M, 3 mL) and extracted with diethyl ether (2 × 20 mL), washed with brine (10 mL), dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography on silica gel, eluting with 20 % ethyl acetate in light petroleum, gave **11** (3.5 g, 76 %) as a colourless oil; R_f 0.32 (20 % ethyl acetate in light petroleum). ν_{max} (oil)/cm^{-1} 2958, 2840, 1671, 1599, 1581, 1502, 1414, 1356, 1295, 1254, 1174, 1129, 1082, 1025. δ_H (300 MHz, $CDCl_3$) 7.77–7.73 (2 H, m, ArH), 6.77 (1 H, d, *J* 8.4, ArH), 3.82 (3 H, d, *J* 2.1, OCH_3), 2.49 (3 H, d, *J* 2.4, CH_3CO), 2.21 (3 H, s, CH_3). δ_C (75 MHz, $CDCl_3$) 196.4 (C), 161.4 (C), 130.4 (CH), 129.5 (C), 128.2 (CH), 126.3 (C), 108.8 (CH), 55.1 (CH_3), 25.8 (CH_3), 15.8 (CH_3).

4-Methoxy-3-methylphenol ***12***[17]

To a solution of **11** (3.5 g, 21 mmol) in CH_2Cl_2 (15 mL) at 0°C was added meta-chloroperbenzoic acid (*m*-CPBA) (85 % with chlorobenzoic acid; 7.8 g, 38 mmol) and the reaction mixture was heated to reflux overnight. The mixture was cooled, then quenched with saturated $Na_2S_2O_3$ solution (10 mL), extracted with ether (2 × 20 mL), and washed successively with further saturated $Na_2S_2O_3$ solution (10 mL), saturated $NaHCO_3$ solution (10 mL), water (10 mL), and brine (10 mL), then dried over Na_2SO_4, and concentrated under vacuum. Purification by flash chromatography on silica gel, eluting with 5 % ethyl acetate in light petroleum, gave 4-methoxy-3-methylphenylacetate (3.2 g, 83 %) as a light yellow oil; R_f 0.69 (20 % ethyl acetate in light petroleum). ν_{max} (oil)/cm^{-1} 2952, 2837, 1754, 1497, 1368, 1223, 1196, 1176, 1150, 1118, 1031, 1014. δ_H (300 MHz, $CDCl_3$) 6.92–6.87 (2 H, m, ArH), 6.81–6.78 (1 H, m, ArH), 3.80 (3 H, s, OCH_3), 2.27 (3 H, s, CH_3), 2.24 (3 H, s, CH_3). δ_C (75 MHz, $CDCl_3$) 169.7 (C), 155.3 (C), 143.7 (C), 127.6 (C), 123.5 (CH), 119.0 (CH), 110.1 (CH), 55.4 (CH_3), 20.8 (CH_3), 16.1 (CH_3). A mixture of 4-methoxy-3-methylphenylacetate (2.0 g, 11 mmol) in THF (10 mL) and aqueous HCl (3 M, 3 mL) was heated to reflux overnight. The reaction mixture was allowed to cool, then diluted with water (30 mL), extracted with diethyl ether (2 × 30 mL), washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography on silica gel, eluting with 10 % ethyl acetate in light petroleum, gave **12** (1.5 g, 99 %) as a light yellow oil; R_f 0.45 (20 % ethyl acetate in light petroleum). ν_{max} (oil)/cm^{-1} 3325, 2951, 2833, 1500, 1464, 1430, 1286, 1212, 1178, 1154, 1119, 1033. δ_H (300 MHz, $CDCl_3$) 6.81 (1 H, br s, OH), 6.68–6.67 (3 H, m, ArH), 3.75 (3 H, s, OCH_3), 2.17 (3 H, s). δ_C (75 MHz, $CDCl_3$) 151.8 (C), 149.2 (C), 128.1 (C), 118.1 (CH), 112.8 (CH), 111.8 (CH), 56.1 (CH_3), 16.2 (CH_3).

*(*E*)-1-Methoxy-2-methyl-4-((6-methylhepta-2,5-dien-1-yl) oxy)benzene* ***6***[5]

To a solution of **12** (570 mg, 4.13 mmol), 6-methylhepta-2,5-dien-1-ol (**13**) (260 mg, 2.06 mmol) and triphenylphosphine (1.08 g, 4.12 mmol) in THF (7 mL) at 0°C was added di-isopropyl azodicarboxylate (820 µL, 4.16 mmol) and the reaction mixture was allowed to return to room temperature overnight. The reaction was quenched by addition of water (15 mL), and the mixture was extracted with ethyl acetate (2 × 20 mL), dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography on silica gel, eluting with 5 % ethyl acetate in light petroleum, gave **6** (404 mg, 80 %) as a yellow oil; R_f 0.74 (10 % ethyl acetate in light petroleum). ν_{max} (oil)/cm^{-1} 2926, 1499, 1463, 1441, 1377, 1280, 1215, 1181, 1162, 1036. δ_H (300 MHz, $CDCl_3$) 6.82–6.81 (1 H, m, ArH), 6.76–6.75 (2 H, m, ArH), 5.91–5.71 (2 H, m, CH=CH), 5.24 (1 H, t, *J* 7.3, CH), 4.46 (2 H, dd, *J* 5.7, 0.9, OCH_2), 3.82 (3 H, s, OCH_3), 2.84 (2 H, dd, *J* 6.3, 6.3, CH_2), 2.27 (3 H, s, $ArCH_3$), 1.79 (3 H, s, CH_3), 1.69 (3 H, s, CH_3). δ_C (75 MHz, $CDCl_3$) 152.6 (C), 152.1 (C), 133.5 (CH), 132.9 (C), 127.7 (C), 125.3 (CH), 121.5 (CH), 118.1 (CH), 111.9 (CH), 110.8 (CH), 69.3 (CH_2), 55.7 (CH_3), 31.0 (CH_2), 25.7 (CH_3), 17.7 (CH_3), 16.4 (CH_3). *m*/*z* (electrospray ionization (ESI) HRMS) 247.1694 [MH^+]. $C_{16}H_{23}O_2^+$ requires 247.1693.

*(3*S*, 5*E*)-7-(4-Methoxy-3-methylphenoxy)-2-methylhept-5-ene-2,3-diol (−)-****9***

To a mixture of AD-mix-α (1.4 g) and methanesulfonamide (114 mg, 1.20 mmol) was added water (5 mL) and *tert*-butanol (5 mL). The mixture was stirred vigorously until complete dissolution, then cooled to 0°C. Compound **6** (250 mg, 1.0 mmol) was added and the reaction mixture was stirred at 0°C for 1 h, then at room temperature overnight. Sodium sulfite (500 mg) was added and the mixture was stirred for a further 20 min, then diluted with water (10 mL), extracted with ethyl acetate (3 × 20 mL), dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography on silica gel, eluting with 40 % ethyl acetate in light petroleum, gave **(−)-9** (148 mg, 52 %, 98 % ee) as a colourless oil; R_f 0.26 (50 % ethyl acetate in light petroleum). $[\alpha]_D^{20}$ −16.4 (*c* 0.29, $CHCl_3$). ν_{max} (oil)/cm^{-1} 3409 (br), 2971, 1667, 1500, 1217, 1064. δ_H (300 MHz, $CDCl_3$) 6.73–6.65 (3 H, m), 5.93–5.75 (2 H, m), 4.42 (2 H, d, *J* 4.9), 3.77 (3 H, s), 3.43 (1 H, dd, *J* 10.0, 1.6), 2.62 (1 H, br s, OH), 2.46 (1 H, br s, OH), 2.36–2.09 (2 H, m), 2.19 (3 H, s), 1.21 (3 H, s), 1.16 (3 H, s). δ_C (75 MHz, $CDCl_3$) 152.3 (C), 152.2 (C), 131.8 (CH), 128.2 (CH), 127.8 (C), 118.1 (CH), 112.0 (CH), 110.9 (CH), 77.4 (CH), 72.8 (C), 69.1 (CH_2), 55.9 (CH_3), 35.0 (CH_2), 26.4 (CH_3), 23.6 (CH_3), 16.4 (CH_3). *m*/*z* (ESI HRMS) 303.1567 [MNa^+]. $C_{16}H_{24}O_4Na^+$ requires 303.1567. Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, 8 % *iso*-propanol/hexane, 0.7 mL min^{-1}, retention times 24.9 min (major) and 31.5 min (minor)).

*(±)-(*E*)-7-(4-Methoxy-3-methylphenoxy)-2-methylhept-5-ene-2,3-diol (±)-****9***

To a solution of **6** (250 mg, 1.0 mmol) in *tert*-butanol (5 mL) and water (5 mL) was added potassium osmate(VI) dihydrate (2 mg, 5 µmol, 0.5 mol-%) and *N*-methylmorpholine-*N*-oxide (129 mg, 1.1 mmol). The reaction mixture was stirred at room temperature for 24 h, then diluted with water (10 mL), extracted with ethyl acetate (3 × 10 mL), dried over Na_2SO_4, and concentrated under vacuum to give (±)-**9**.

*(3*S*,5*S*)-5-(2-Hydroxy-5-methoxy-4-methylphenyl)-2-methylhept-6-ene-2,3-diol (−)-****14*** *and (3*S*, 5*R*)-5-(2-Hydroxy-5-methoxy-4-methylphenyl)-2-methylhept-6-ene-2,3-diol (−)-****8***

To a solution of compound **9** (88 mg, 0.31 mmol) in CH_2Cl_2 (7 mL) at −78°C was added dimethylaluminium chloride (1 M in hexanes; 0.7 mL, 0.7 mmol). The reaction mixture was allowed to return to room temperature, stirred for a further 6 h, and was then quenched by the addition of water (5 mL). The solvent was removed under vacuum and the residue purified by flash chromatography on silica gel, eluting with 40 % ethyl acetate/0.5 % acetic acid in light petroleum, to give **14** (33 mg, 38 %) as a colourless oil; R_f 0.32 (50 % ethyl acetate in light petroleum). $[\alpha]_D^{20}$ −52.3 (*c* 0.49, MeOH), ν_{max} (oil)/cm^{-1} 3376 (br), 2972, 2926, 1705, 1637, 1501, 1463, 1410, 1364, 1200,

1165, 1079, 1023, 1001. δ_H (300 MHz, $CDCl_3$) 6.61 (1 H, s), 6.59 (1 H, s), 6.12 (1 H, ddd, *J* 17.1, 10.2, 6.6), 5.06–4.95 (2 H, m), 3.96–3.89 (1 H, m), 3.72 (3 H, s), 3.06 (1 H, dd, *J* 10.5, 1.2), 2.12–2.03 (4 H, m, CH + CH_3), 1.68 (1 H, ddd, *J* 14.1, 10.8, 3.9), 1.12 (3 H, s), 1.08 (3 H, s). δ_C (75 MHz, $CDCl_3$) 152.8 (C), 149.6 (C), 143.9 (CH), 128.0 (C), 126.3 (C), 119.1 (CH), 113.3 (CH_2), 112.3 (CH), 77.1 (CH), 73.7 (C), 56.5 (CH_3), 40.9 (CH), 37.3 (CH_2), 25.4 (CH_3), 25.2 (CH_3), 15.9 (CH_3). *m/z* (ESI HRMS) 303.1568 [MNa^+]. $C_{16}H_{24}O_4Na^+$ requires 303.1567; and

Compound **8** (17 mg, 19 %, 97 % ee) as a colourless solid; R_f 0.25 (50 % ethyl acetate in light petroleum); mp 157–159°C.$[\alpha]_D^{20}$ −107.3 (*c* 0.55, $CHCl_3$). ν_{max} (film)/cm^{-1} 3398 (br), 2964, 2929, 1706, 1639, 1512, 1462, 1408, 1376, 1365, 1323, 1199, 1162, 1119, 1073, 1021, 1005. δ_H (300 MHz, $CDCl_3$) 6.65 (1 H, s), 6.56 (1 H, s), 6.03 (1 H, ddd, *J* 17.4, 9.9, 8.4), 5.14–5.02 (2 H, m), 3.92–3.84 (1 H, m), 3.73 (3 H, s), 3.44 (1 H, ddd, *J* 10.2, 1.2), 2.15–2.06 (4 H, m, CH + CH_3), 1.53 (1 H, ddd, *J* 14.1, 10.8, 3.3), 1.17 (3 H, s), 1.14 (3 H, s). δ_C (75 MHz, $CDCl_3$) 152.6 (C), 148.8 (C), 142.2 (CH), 130.6 (C), 125.9 (C), 119.1 (CH), 115.2 (CH_2), 111.9 (CH), 77.1 (CH), 73.8 (C), 56.6 (CH_3), 41.7 (CH), 37.5 (CH_2), 25.8 (CH_3), 25.0 (CH_3), 15.9 (CH_3). *m/z* (ESI HRMS) 303.1567 [MNa^+]. $C_{16}H_{24}O_4Na^+$ requires 303.1567. Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, 4 % ethanol/hexane, 0.7 mL min^{-1}, retention times 31.5 min (minor) and 35.0 min (major)).

2-((3R,5S)-5,6-Dihydroxy-6-methylhept-1-en-3-yl)-5-methylcyclohexa-2,5-diene-1,4-dione ***3***

To a stirred mixture of **8** (39 mg, 0.14 mmol) in acetonitrile (1 mL) at 0°C was added dropwise a solution of cerium ammonium nitrate (153 mg, 0.28 mmol) in water (1 mL). After stirring at 0°C for 5 min, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL), dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography on silica gel, eluting with 50 % ethyl acetate in light petroleum, gave **3** (13 mg, 35 %) as a yellow oil; R_f 0.39 (50 % ethyl acetate in light petroleum). $[\alpha]_D^{20}$ −61.2 (*c* 0.34, $CHCl_3$). ν_{max} (oil)/cm^{-1} 3431 (br), 2975, 2926, 1651, 1609, 1442, 1301, 1351, 1257, 1239, 1135, 1070, 1005. δ_H (300 MHz, $CDCl_3$) 6.59 (1 H, m), 6.53 (1 H, s), 5.77 (1 H, ddd, *J* 17.9, 9.8, 8.6), 5.23–5.17 (2 H, m), 3.72 (1 H, td, *J* 9.2, 3.7), 3.45 (1 H, d, *J* 10.5), 2.35 (1 H, br s, OH), 2.05–1.95 (4 H, m, CH_3 + OH), 1.77–1.69 (1 H, m), 1.53 (1 H, ddd, *J* 14.2, 10.6, 3.9), 1.20 (3 H, s), 1.14 (3 H, s). $\underline{\delta}_C$ (75 MHz, $CDCl_3$) 188.4 (C), 187.3 (C), 151.5 (C), 145.5 (C), 137.5 (CH), 133.9 (CH), 132.0 (CH), 118.2 (CH_2), 76.1 (CH), 73.0 (C), 39.6 (CH), 35.9 (CH_2), 26.5 (CH_3), 23.7 (CH_3), 15.5 (CH_3). *m/z* (ESI HRMS) 287.1255 [MNa^+]. $C_{15}H_{20}O_4Na^+$ requires 287.1254.

(−)-Heliespirone A ***1*** *and (+)-Heliespirone C* ***2***

To a solution of **3** (50 mg, 0.19 mmol) in dichloromethane (6.5 mL) at 0°C was added caesium carbonate (295 mg, 0.91 mmol) and the reaction was allowed to return to room temperature and stirred for 1 h. The mixture was diluted with water (10 mL) and extracted with dichloromethane (2 × 10 mL), dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography on silica gel, eluting with 25 % ethyl acetate in light petroleum, gave (−)-heliespirone A (**1**) (11 mg, 22 %, 95 % ee) as a colourless solid; R_f 0.61 (50 % ethyl acetate in light petroleum); mp 106–107°C (lit. mp 105–106°C[6]). $[\alpha]_D^{20}$ −46.7 (*c* 0.12, $CHCl_3$) (lit. $[\alpha]_D^{20}$ −55.2 (*c* 0.13, $CHCl_3$)[6]). ν_{max} (film)/cm^{-1} 3458, 2972, 2925, 2854, 1681, 1780, 1348, 1242, 1128, 1062, 1005. δ_H (300 MHz, $CDCl_3$) 6.61 (1 H, q, *J* 1.4), 5.31 (1 H, dt, *J* 16.8, 9.6), 5.06 (1 H, ddd, *J* 16.8, 1.3, 0.7), 4.96 (1 H, dd, *J* 10.0, 1.3), 4.80 (1 H, br s), 4.04 (1 H, dd, *J* 10.8, 5.3), 3.24 (1 H, d, *J* 15.6), 2.96 (1 H, d, *J* 15.6), 2.92 (1 H, ddd, *J* 12.6, 9.1, 6.6), 2.15 (1 H, td, *J* 12.7, 10.8), 2.01–1.93 (1 H, m), 1.97 (3 H, d, *J* 1.5), 1.33 (3 H, s), 1.10 (3 H, s). δ_C (75 MHz, $CDCl_3$) 201.3 (C), 195.6 (C), 153.6 (C), 137.2 (CH), 135.5 (CH), 118.6 (CH_2), 87.7 (C), 86.8 (CH), 70.3 (C), 57.2 (CH), 51.9 (CH_2), 32.0 (CH_2), 28.5 (CH_3), 25.4 (CH_3), 16.0 (CH_3). *m/z* (ESI HRMS) 287.1255 [MNa^+]. $C_{15}H_{20}O_4Na^+$ requires 287.1254. Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, 8 % *iso*-propanol/hexane, 0.7 mL min^{-1}, retention times 20.0 min (major) and 27.6 min (minor)); and

(+)-Heliespirone C (**2**) (10 mg, 20 %, 97 % ee) as a colourless solid; R_f 0.48 (50 % ethyl acetate in light petroleum); mp 68–71°C (lit. mp 74–75°C[6]); $[\alpha]_D^{20}$ +48.0 (*c* 0.09, $CHCl_3$) (lit. $[\alpha]_D^{20}$ +50.4 (*c* 0.4, $CHCl_3$)[6]). ν_{max} (film)/cm^{-1} 3459 (br), 2975, 2928, 1685, 1622, 1378, 1351, 1248, 1181, 1115, 1068, 1031, 1006. δ_H (300 MHz, $CDCl_3$) 6.68 (1 H, q, *J* 1.5), 5.62 (1 H, m), 5.13 (1 H, m), 5.09 (1 H, d, *J* 5.8), 3.95 (1 H, dd, *J* 10.7, 5.3), 3.28 (1 H, m), 2.95 (1 H, d, *J* 16.3), 2.83 (1 H, d, *J* 16.3), 2.05 (1 H, m), 1.99 (3 H, d, *J* 1.5), 1.93 (1 H, m), 1.84 (1 H, br s, OH), 1.24 (3 H, s), 1.13 (3 H, s). δ_C (75 MHz, $CDCl_3$) 196.8 (C), 196.3 (C), 151.9 (C), 137.1 (CH), 134.7 (CH), 119.9 (CH_2), 87.0 (C), 86.8 (CH), 70.4 (C), 48.8 (CH), 47.1 (CH_2), 32.5 (CH_2), 27.7 (CH_3), 24.6 (CH_3), 16.3 (CH_3). *m/z* (ESI HRMS) 287.1254 [MNa^+]. $C_{15}H_{20}O_4Na^+$ requires 287.1254. Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, 4 % *iso*-propanol/hexane, 0.7 mL min^{-1}, retention times 21.5 min (minor) and 22.9 min (major)).

Supplementary Material

^1H and ^{13}C NMR spectra for all synthesized compounds, Cartesian coordinates and absolute energies of calculated structures, and enantioselective HPLC traces of compounds **1** and **2** are available on the Journal's website.

Conflicts of Interest

The authors declare no conflicts of interest.

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