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Total Synthesis of (–)-Heliespirone A and (+)-Heliespirone C

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Total syntheses of the spiro-epimeric natural products (–)-heliespirone A and (+)-heliespirone C are described. The successful strategy involved an aromatic Claisen rearrangement, a diastereoselective Sharpless asymmetric dihydroxylation (AD) reaction, and an intramolecular oxa-Michael addition.

Introduction

Competition between plant species for limited natural resources has provided evolutionary pressure for the development of allelochemicals that function as naturally occurring herbicides. One attractive branch of research looks to discover new agrochemicals by identifying the allelochemical components that are responsible for specific plant–plant (or plant–microbe) interactions. It was in this setting that heliespirones A, C, and B (**1**–**3**) were first isolated by Macías and co-workers from a sunflower cultivar, *H. annuus* L. cv. SH-222 (Figure 1).[1] Initially described as the 6,6-spiro compound,[1a,2] the structure of heliespirone A (**1**) was revised to the spiro epimer of the 6,5-spiro compound heliespirone C (**2**).[1b,3] The natural occurrence of both diastereomers **1** and **2** suggests a biosynthesis involving an oxa-Michael addition onto a quinone **4**, and this prompted Macías to propose a biosynthetic route to these compounds from the co-isolate, heliannuol C (**5**).[1b] All three of the reported total syntheses of heliespirones A and C (**1** and **2**) use this conjugate addition strategy for the spirocyclization step. The novelty of previous synthetic approaches is therefore confined to the generation of the quinone **4**.

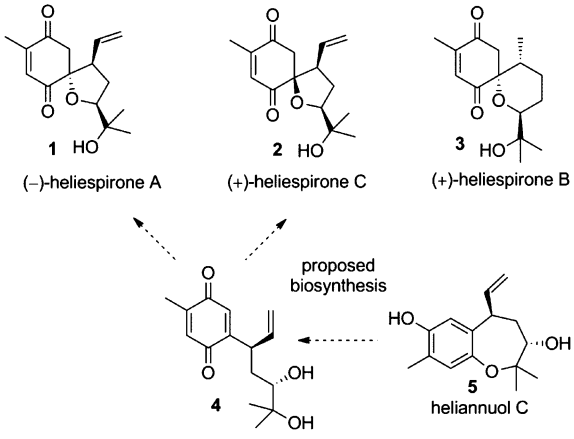
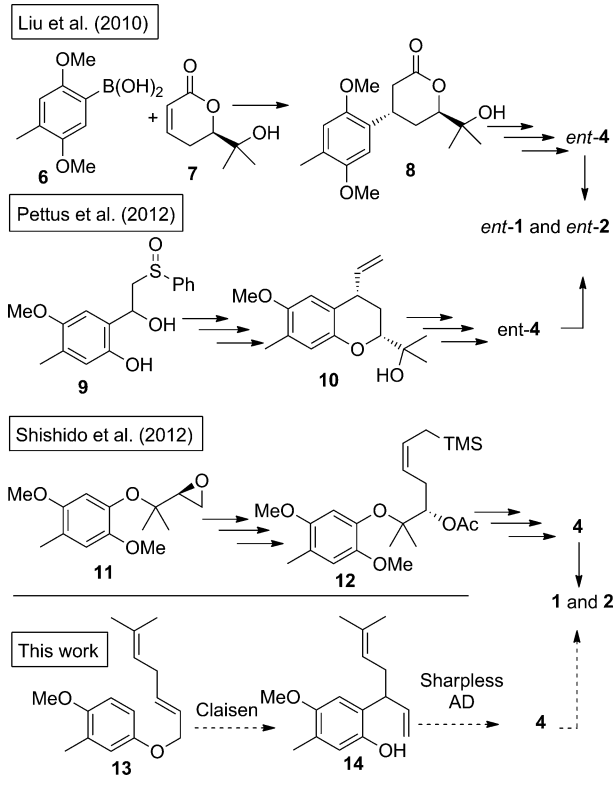


Figure 1. Heliespirone natural products.

In the first asymmetric approach (Scheme 1), Liu and coworker used a palladium-catalysed conjugate addition of arylboronic acid **6** onto unsaturated lactone **7**.[4] Synthetic manipulations then unveiled quinone *ent*-**4** en route to *ent*-



Scheme 1. Strategies for the synthesis of the heliespirones. TMS = trimethylsilyl.

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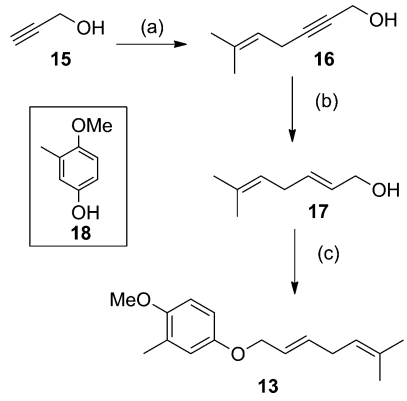
1 and *ent*-**2**. Pettus and co-workers also reported syntheses of *ent*-**1** and *ent*-**2**.[5] They accessed quinone *ent*-**4** via chroman **10**, which they generated using a [4+2] cycloaddition on an *o*-quinone methide generated in situ from **9**.[5] Finally, Shishido and co-workers used an intramolecular Hosomi–Sakurai reaction to generate the carbon–carbon bond of the spirocentre and give quinone **4**.[6] As such, Shishido and co-workers were able to complete the first total synthesis of the naturally occurring enantiomers (–)-**1** and (+)-**2**.

Our continuing interest in discovering efficient protocols for the generation of quinone natural products[7] led us to take on the challenge of synthesizing heliespirones A (**1**) and C (**2**). At the outset, we hoped to use an on-water-catalysed[8] aromatic Claisen rearrangement to give diene **14**,[9] and that the stereocentre generated in this process would create a matched–mismatched scenario in which a simple Sharpless asymmetric dihydroxylation (AD) would result in a kinetic resolution.[10]



Scheme 2. Synthesis of Claisen rearrangement precursor **13**. Reagents and conditions: (a) *n*BuLi, CuI, $(CH_3)_2CCHCH_2Br$, 89%; (b) $LiAlH_4$, 94%; (c) **18**, PPh_3, DIAD (diisopropyl azodicarboxylate), 80%.

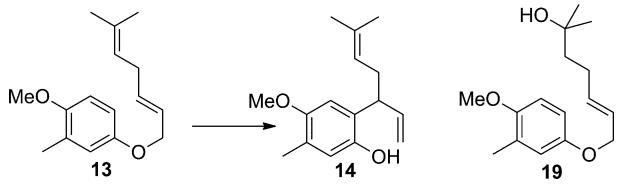
Results and Discussion

Our synthesis began with the construction of diene **13**. As shown in Scheme 2, propargyl alcohol **15** was deprotonated with excess butyllithium, and subsequent treatment with prenyl bromide gave enyne **16** in good yield. Chemo- and diastereoselective reduction was carried out with lithium aluminium hydride to give (*E*)-configured diene **17**. Mitsunobu coupling with 4-methoxy-*m*-cresol (**18**)[11]gave **13**, the substrate for the planned aromatic Claisen rearrangement.

We have previously shown that on-water catalysis results from the acidic nature of interfacial water in oil-in-water emulsions.[12] On-water catalysis has been successfully used by us[12b,13] and others[8,14] to facilitate aromatic Claisen rearrangements of a variety of substrates by protonation of the ether oxygen atom and subsequent charge-accelerated rearrangement. However, substrate **13** represents an example in which there is a competing site for protonation. The methyl ether of **13** is sterically less congested and less hydrophobic than the alternative ether, so it was not clear whether **13** would participate in an on-water-catalysed aromatic Claisen rearrangement.

As shown in Table 1, attempted on-water rearrangement of **13** at either room temperature (Table 1, Entry 1) or 80 °C (Table 1, Entry 2) led to recovery of the starting material with no observed rearrangement. Increasing the temperature to 150 °C in a sealed tube was similarly unproductive (Table 1, Entry 3). With an experimentally measured isoelectric point between pH = 3 and 4, interfacial water has an acidity comparable to that of carboxylic acids.[15] We therefore attempted a Brønsted-acid-catalysed rearrangement with benzoic acid (pK_a = 4.2; Table 1, Entry 4). Unsurprisingly, compound **13** did not undergo rearrangement under those conditions. Using a stronger carboxylic acid, trifluoroacetic acid (pK_a = 0.23; Table 1, Entry 5), did not lead to rearrangement, but it did allow the trisubstituted alkene to participate in a hydration reaction upon aqueous workup to give undesired compound **19**. It was clear from this data that the oxygen atom of the allyl phenyl ether portion of **13** could not be protonated by interfacial water or by Brønsted acids of comparable acidity. Attempted thermal rearrangement was also unproductive (Table 1, En-

Table 1. Claisen rearrangement of compound **13**.



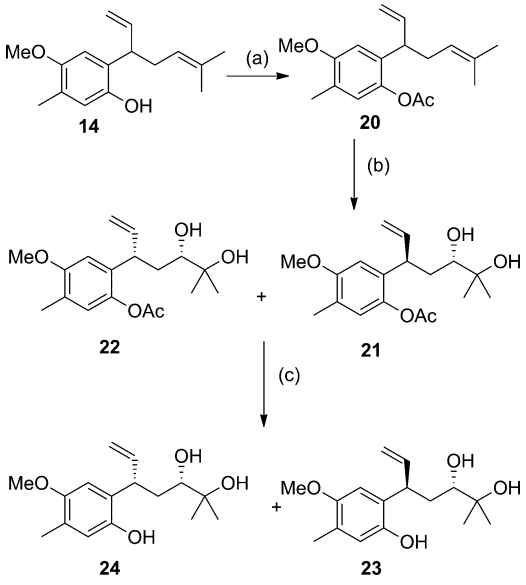
Entry	Acid	Solvent	Temperature [°C]	Yield of **14** [%][a]	Yield of **19** [%][a]
1	–	on-H_2O	25	0	0
2	–	on-H_2O	80	0	0
3[b]	–	H_2O	150	0	0
4	benzoic acid	CH_2Cl_2	25	0	0
5[c]	trifluoroacetic acid	CH_2Cl_2	25	0	12
6	–	*N*,*N*-diethylaniline	216	0	0
7	Me_2AlCl	*n*-pentane	–78 → 0	93	0

[a] Isolated after chromatography. [b] Sealed tube. [c] Containing <3% v/v H_2O.

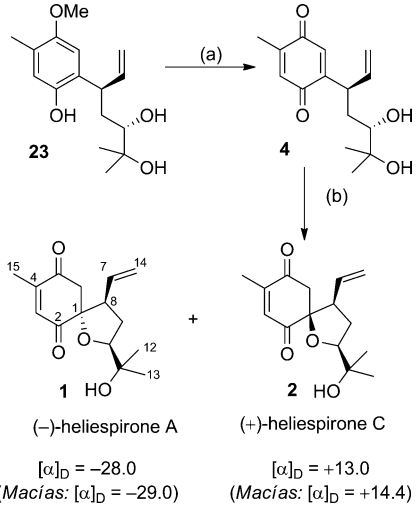
try 6), with compound **13** being consumed, but with none of the desired compound (i.e., **14**) being isolated. We therefore resorted to Lewis acid catalysis.[14a,16] Treatment of compound **13** with dimethylaluminium chloride at low temperature gave smooth conversion to the desired product (i.e., **14**; Table 1, Entry 7).[17]

With compound **14** in hand, our attention turned to the kinetic resolution using a Sharpless AD reaction (Scheme 3). We anticipated that the more electron-rich trisubstituted alkene would react in preference to the terminal alkene or the aromatic ring. In the event, reactions of **14** with commercially sourced AD-mixtures (or other osmium-based oxidants) led to intractable mixtures. Imagining that interference by the relatively electron-rich aromatic ring was the reason for this undesired outcome, we masked the phenol unit with an electron-withdrawing acetate group to give compound **20**. Sharpless AD of **20** proceeded smoothly. We were gratified to observe that the desired compound (i.e., **21**) was produced in a 5:1 ratio with the undesired diastereomer (i.e., **22**). Removal of the acetate group allowed the diastereomers (i.e., **23** and **24**) to be separated by simple silica gel chromatography.

As shown in Scheme 4, the synthesis was completed by oxidation of **23** with ceric ammonium nitrate to give proposed biosynthetic intermediate **4**. Finally, treatment of **4** with cesium carbonate in dichloromethane facilitated an intramolecular oxa-Michael addition to give the easily separable diastereomers (–)-heliespirone A (**1**) in 22% yield and (+)-heliespirone C (**2**) in 20% yield.



Scheme 3. Kinetic resolution by Sharpless asymmetric dihydroxylation. Reagents and conditions: (a) Ac_2O, Et_3N, DMAP [4-(dimethylamino)pyridine], 100%; (b) AD-mix-α, $CH_3SO_2NH_2$, 53%; (c) CH_3OH, K_2CO_3, 70% (**23**) and 14% (**24**).



Scheme 4. Synthesis of heliespirones A and C. (a) $Ce(NH_4)_2(NO_3)_6$, 35%; (b) Cs_2CO_3, 22% (**1**) and 20% (**2**).

Table 2. Comparison of natural and synthetic samples of heliespirone A and heliespirone C.

	(–)-Heliespirone A					
	Synthetic[a]		Natural[b]		Difference	
Carbon no.	δ_H	δ_C	δ_H	δ_C	$\Delta\delta_H$	$\Delta\delta_C$
1	–	87.7	–	87.6	–	0.1
2	–	201.3	–	201.5	–	–0.2
3	6.61	137.2	6.61	137.0	0.00	0.2
4	–	153.6	–	153.4	–	0.2
5	–	195.6	–	195.5[c]	–	0.1
6	3.24, 2.96	51.9	3.23, 2.95	51.8	0.01, 0.01	0.1
7	5.31	135.5	5.29	135.3	0.02	0.2
8	2.92	57.2	2.91	57.1	0.01	0.1
9	2.15, 1.97	32.0	2.14, 1.96	31.9	0.01, 0.01	0.1
10	4.04	86.8	4.03	86.7	0.01	0.1
11	–	70.3	–	70.1	–	0.2
12	1.10	28.5	1.09	28.3	0.01	0.2
13	1.33	25.4	1.32	25.3	0.01	0.1
14	5.06, 4.96	118.6	5.06, 4.96	118.4	0.00, 0.00	0.2
15	1.97	16.0	1.96	15.9	0.01	0.1
	(+)-Heliespirone C					
	Synthetic[a]		Natural[b]		Difference	
Carbon no.	δ_H	δ_C	δ_H	δ_C	$\Delta\delta_H$	$\Delta\delta_C$
1	–	87.0	–	86.9	–	0.1
2	–	196.8	–	196.5	–	0.3
3	6.68	137.1	6.63	136.9	0.05	0.2
4	–	151.9	–	151.7	–	0.2
5	–	196.3	–	196.3	–	0.0
6	2.95, 2.83	48.8	2.95, 2.83	48.5	0.00, 0.00	0.3
7	5.62	134.7	5.61	134.6	0.01	0.1
8	3.28	47.1	3.26	47.0	0.02	0.1
9	2.05, 1.93	32.5	2.04, 1.92	32.4	0.01, 0.01	0.1
10	3.95	86.8	3.95	86.7	0.00	0.1
11	–	70.4	–	70.3	–	0.1
12	1.13	27.7	1.12	27.5	0.01	0.2
13	1.24	24.6	1.23	24.5	0.01	0.1
14	5.13, 5.09	119.9	5.12, 5.09	119.6	0.01, 0.00	0.3
15	1.99	16.3	1.98	16.1	0.01	0.2

[a] ^1H NMR (300 MHz, $CDCl_3$), ^{13}C NMR (75 MHz, $CDCl_3$). [b] ^1H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$). [c] See ref.[4] for the correction of a typographical error found in the isolation paper.

As expected, the chemical shifts of the synthetic products were in close agreement with those of the originally isolated compounds (Table 2).

Conclusions

We have completed the synthesis of the quinone natural products (–)-heliespirone A (**1**) and (+)-heliespirone C (**2**). The key steps in this straightforward approach were an aromatic Claisen rearrangement and a diastereoselective Sharpless asymmetric dihydroxylation.

Experimental Section

General: 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 with a Bruker Alpha-E ATR spectrometer. UV/Vis absorption spectra were recorded with a Varian Cary 50 spectrophotometer, and absorption maxima are expressed in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded with 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 (δ = 7.26 ppm) or residual methanol (δ = 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 Hz. ^{13}C NMR chemical shifts are expressed as parts per million (ppm) with residual chloroform (δ = 77.1 ppm) or residual methanol (δ = 49.0 ppm) as internal reference and are reported as chemical shift (δ_C); and multiplicity (assigned from DEPT experiments). High-resolution mass spectra were recorded with 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 visualised using UV light (254 nm and 365 nm) and ethanolic anisaldehyde.

6-Methylhept-5-en-2-yn-1-ol (16): *n*-Butyllithium (2.2 M in hexanes; 7.3 mL, 16 mmol) was added dropwise to a solution of propargyl alcohol (475 μL, 8.0 mmol) in THF (20 mL) at 0 °C. After 1 h, cuprous iodide (170 mg, 0.89 mmol) was added. After a further 30 min, a solution of prenyl bromide (1.21 g, 8.1 mmol) in THF (20 mL) was added slowly, and the reaction mixture was allowed to return to room temperature overnight. Saturated ammonium chloride solution (30 mL) was added. The mixture was extracted with diethyl ether (3× 30 mL) and dried with Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica (ethyl acetate/light petroleum, 1:9) to give **16** (881 mg, 89%) as a pale yellow oil. R_f = 0.31 (ethyl acetate/light petroleum, 1:9). IR: $\tilde{\nu}$ = 3318, 2915, 1446, 1376, 1288, 1135, 1093, 1005 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.17 (tsept, J = 6.9, 1.4 Hz, 1 H), 4.24 (s, 2 H), 2.91 (br. d, J = 6.9 Hz, 2 H), 1.70 (d, J = 1.2 Hz, 3 H), 1.68 (br. s, 1 H, OH), 1.62 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.3 (C), 118.8 (CH), 85.4 (C), 78.0 (C), 51.6 (CH_2), 25.7 (CH_3), 18.1 (CH_2), 17.8 (CH_3) ppm. MS (APCI): m/z (%) = 123 (100) [M – H^+], 93 (34) [M – CH_2OH].

(*E*)-6-Methylhepta-2,5-dien-1-ol (17): A solution of 6-methylhept-5-en-2-yn-1-ol (689 mg, 5.5 mmol) in THF (2 mL) was added dropwise to a suspension of lithium aluminium hydride (335 mg, 8.8 mmol, 1.6 equiv.) in dry THF (12 mL) at 0 °C. The reaction mixture was heated to reflux for 8 h, then it was cooled again to 0 °C and quenched with hydrochloric acid (1 M; 30 mL). The mixture was extracted with diethyl ether (3× 30 mL), the combined organic extracts were washed with brine (30 mL) and dried with Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica (ethyl acetate/light petroleum, 1:9) to give **17** (659 mg, 94%) as a colourless oil. R_f = 0.17 (ethyl acetate/light petroleum, 1:9). IR: $\tilde{\nu}$ = 3311, 2916, 2857, 1438, 1376, 1090 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.67–5.62 (m, 2 H), 5.16–5.10 (m, 1 H), 4.08 (d, J = 3.9 Hz, 2 H), 2.72 (m, 2 H), 1.70 (d, J = 0.9 Hz, 3 H), 1.61 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.0 (C), 132.0 (CH), 129.0 (CH), 121.7 (CH), 63.9 (CH_2), 31.0 (CH_2), 25.8 (CH_3), 17.8 (CH_3) ppm.

(*E*)-1-Methoxy-2-methyl-4-[(6-methylhepta-2,5-dien-1-yl)oxy]benzene (13): 4-Methoxy-3-methylphenol (570 mg, 4.13 mmol, 2 equiv.), 6-methylhepta-2,5-dien-1-ol (260 mg, 2.06 mmol, 1 equiv.), and triphenylphosphine (1.08 g, 4.12 mmol, 2 equiv.) were dissolved in THF (7 mL), and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (820 μL, 4.16 mmol, 2 equiv.) was added, and the reaction mixture was allowed to return to room temperature overnight. The reaction mixture was quenched by addition of water (15 mL) and extracted with ethyl acetate (2× 20 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica (ethyl acetate/light petroleum, 1:19) to give **13** (404 mg, 80%) as a yellow oil. R_f = 0.74 (ethyl acetate/light petroleum, 1:9). IR: $\tilde{\nu}$ = 2926, 1499, 1463, 1441, 1377, 1280, 1215, 1181, 1162, 1036 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.82–6.81 (m, 1 H, ArH), 6.76–6.75 (m, 2 H, ArH), 5.91–5.71 (m, 2 H, CH=CH), 5.24 (t, J = 7.3 Hz, 1 H, CH), 4.46 (dd, J = 5.7, 0.9 Hz, 2 H, OCH_2), 3.82 (s, 3 H, OCH_3), 2.84 (dd, J = 6.3, 6.3 Hz, 2 H, CH_2), 2.27 (s, 3 H, $ArCH_3$), 1.79 (s, 3 H, CH_3), 1.69 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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) ppm. HRMS (ESI): calcd. for $C_{16}H_{23}O_2$ [M + H]$^+$ 247.1693; found 247.1694.

4-Methoxy-5-methyl-2-(6-methylhepta-1,5-dien-3-yl)phenol (14): Dimethylaluminium chloride (1 M solution in hexanes; 2.1 mL, 1 equiv.) was added to a solution of (*E*)-1-methoxy-2-methyl-4-[(6-methylhepta-2,5-dien-1-yl)oxy]benzene (500 mg, 2.0 mmol) in *n*-pentane (20 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min, then it was warmed to 0 °C over 15 min, and then quenched by addition of water (10 mL). The mixture was extracted with ethyl acetate (2× 20 mL), and the combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica (ethyl acetate/light petroleum, 1:19) to give **14** (465 mg, 93%) as a colourless oil. R_f = 0.33 (ethyl acetate/light petroleum, 1:9). IR: $\tilde{\nu}$ = 3422, 2973, 2927, 1513, 1450, 1407, 1376, 1197, 1157, 1099, 1019 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.63 (s, 1 H, ArH), 6.61 (s, 1 H, ArH), 6.05 (ddd, J = 17.0, 10.6, 6.4 Hz, 1 H), 5.17–5.10 (m, 3 H), 4.71–4.70 (m, 1 H), 3.79 (s, 3 H), 3.54 (dt, J = 7.2, 7.2 Hz, 1 H), 2.55–2.38 (m, 2 H), 2.17 (s, 3 H), 1.69 (s, 3 H), 1.60 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.2 (C), 147.2 (C), 141.1 (CH), 133.3 (C), 127.1 (C), 125.9 (C), 122.4 (CH), 119.0 (CH), 115.0

(CH_2), 111.2 (CH), 56.3 (CH_3), 44.1 (CH), 32.4 (CH_2), 25.9 (CH_3), 18.0 (CH_3), 15.9 (CH_3) ppm. HRMS (ESI): calcd. for $C_{16}H_{22}O_2Na$ $[M + Na]^+$ 269.1512; found 269.1514.

4-Methoxy-5-methyl-2-(6-methylhepta-1,5-dien-3-yl)phenyl Acetate (20): A solution of acetic anhydride (260 μL, 2.75 mmol, 2 equiv.) and triethylamine (380 μL, 2.72 mmol, 2 equiv.) in dichloromethane (12 mL) was added to a mixture of 4-methoxy-5-methyl-2-(6-methylhepta-1,5-dien-3-yl)phenol (337 mg, 1.37 mmol) and 4-(dimethylamino)pyridine (17 mg, 0.14 mmol), and the reaction mixture was stirred at room temperature overnight. The mixture was then concentrated in vacuo, and the residue was purified by flash chromatography on silica (ethyl acetate/light petroleum, 1:19) to give **20** (395 mg, 100%) as a colourless oil. R_f = 0.64 (ethyl acetate/light petroleum, 1:9). IR: $\tilde{\nu}$ = 2927, 1757, 1503, 1464, 1398, 1368, 1256, 1212, 1191, 1174, 1023 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.83 (s, 1 H, ArH), 5.96 (ddd, J = 17.1, 10.2, 6.6 Hz, 1 H), 5.13–5.02 (m, 3 H), 3.82 (s, 3 H), 3.44 (dt, J = 7.2, 7.2 Hz, 1 H), 2.47–2.35 (m, 2 H, CH_2), 2.29 (s, 3 H), 2.20 (s, 3 H), 1.69 (s, 3 H), 1.61 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9 (C), 155.6 (C), 141.5 (C), 140.6 (CH), 133.6 (C), 132.7 (C), 125.6 (C), 124.5 (CH), 122.2 (CH), 114.6 (CH_2), 109.6 (CH), 55.6 (CH_3), 43.3 (CH), 33.1 (CH_2), 25.8 (CH_3), 21.0 (CH_3), 17.9 (CH_3), 15.9 (CH_3) ppm. HRMS (ESI): calcd. for $C_{18}H_{24}O_3Na$ $[M + Na]^+$ 311.1618; found 311.1618.

2-[(3*R*,5*S*)-5,6-Dihydroxy-6-methylhept-1-en-3-yl]-4-methoxy-5-methylphenyl Acetate (21) and 2-[(3*S*,5*S*)-5,6-Dihydroxy-6-methylhept-1-en-3-yl]-4-methoxy-5-methylphenyl Acetate (22): Water (10 mL) and *tert*-butyl alcohol (10 mL) were added to a mixture of AD-mix-α (2.74 g, Aldrich, 1.4 g per mmol of olefin) and methanesulfonamide (232 mg, 2.44 mmol). The mixture was stirred vigorously until complete dissolution had taken place, then the solution was cooled to 0 °C. A solution of 4-methoxy-5-methyl-2-(6-methylhepta-1,5-dien-3-yl)phenyl acetate (555 mg, 1.92 mmol) in water (10 mL) and *tert*-butyl alcohol (10 mL) was then added. The reaction mixture was stirred at 0 °C for 1 h, then it was allowed to return to room temperature, and stirred for a further 24 h. The mixture was diluted with water (25 mL), then sodium sulfite (1.0 g) was added, and the mixture was stirred for a further 1 h. The mixture was extracted with dichloromethane (3 × 50 mL), and the combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica (ethyl acetate/light petroleum, 1:1) to give a mixture of **23** and **24** (329 mg, 53%) as a pale pink oil. R_f = 0.35 (ethyl acetate/light petroleum, 1:1). $[\alpha]_D$ = –5.87 (c = 0.47, $CHCl_3$). IR: $\tilde{\nu}$ = 3466, 2976, 2931, 1736, 1503, 1465, 1398, 1370, 1218, 1192, 1176, 1070, 1044, 1025 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.77–6.60 (m, 2 H, ArH), 5.94–5.82 (m, 1 H, *H*C=CH_2), 5.13–4.94 (m, 2 H, HC=C*H*$_2$), 3.78–3.66 (m, 4 H, OCH_3, CH), 3.42 (d, J = 10.2 Hz, 1 H, *major isomer* CH), 3.08 (d, J = 10.2 Hz, 1 H, *minor isomer* CH), 2.83 (br. s, 1 H, OH), 2.78 (br. s, 1 H, OH), 2.28 (s, 3 H, *major isomer* CH_3), 2.26 (s, 3 H, *minor isomer* CH_3), 2.16 (s, 3 H, *minor isomer* CH_3), 2.15 (s, 3 H, *major isomer* CH_3), 1.83–1.75 (m, 1 H, CH), 1.60–1.51 (m, 1 H, CH), 1.16 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 170.5, 155.8, 155.6, 141.9, 141.5, 140.9, 139.5, 134.3, 131.9, 126.0, 125.6, 124.4, 115.8, 113.8, 109.2, 75.8, 75.3, 72.9, 72.7, 55.5, 39.8, 39.1, 36.6, 35.8, 26.1, 23.4, 23.2, 20.8, 15.7 ppm. HRMS (ESI): calcd. for $C_{18}H_{26}O_5Na$ $[M + Na]^+$ 345.1673; found 345.1673.

(3*S*,5*R*)-5-(2-Hydroxy-5-methoxy-4-methylphenyl)-2-methylhept-6-ene-2,3-diol (23) and (3*S*,5*S*)-5-(2-Hydroxy-5-methoxy-4-methylphenyl)-2-methylhept-6-ene-2,3-diol (24): Potassium carbonate (84 mg, 0.61 mmol, 3 equiv.) was added to a solution of 2-[(5*S*)-5,6-dihydroxy-6-methylhept-1-en-3-yl]-4-methoxy-5-methylphenyl acetate (mixture of diastereomers; 65 mg, 0.20 mmol) in methanol (3 mL). The reaction mixture was stirred vigorously for 1 h, then it was diluted with methanol (10 mL) and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by flash chromatography on silica (ethyl acetate/light petroleum, 2:3) to give **23** (39 mg, 70%, 17% *ee*) as a colourless solid and **24** (8 mg, 14%) as a colourless oil. **23:** R_f = 0.25 (ethyl acetate/light petroleum, 1:1). m.p. 157–159 °C. $[\alpha]_D$ = –8.0 (c = 0.40, MeOH). IR: $\tilde{\nu}$ = 3398 (br.), 2964, 2929, 1706, 1639, 1512, 1462, 1408, 1376, 1365, 1323, 1199, 1162, 1119, 1073, 1021, 1005 cm^{-1}. ^1H NMR (300 MHz, [D$_4$]methanol): δ = 6.65 (s, 1 H), 6.56 (s, 1 H), 6.03 (ddd, J = 17.4, 9.9, 8.4 Hz, 1 H), 5.14–5.02 (m, 2 H), 3.92–3.84 (m, 1 H), 3.73 (s, 3 H), 3.44 (ddd, J = 10.2, 1.2 Hz, 1 H), 2.15–2.06 (m, 4 H, CH, CH_3), 1.53 (ddd, J = 14.1, 10.8, 3.3 Hz, 1 H), 1.17 (s, 3 H), 1.14 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_4$]methanol): δ = 152.6 (C), 148.8 (C), 142.2 (CH), 130.6 (C), 125.9 (C), 119.0 (CH), 115.2 (CH_2), 111.9 (CH), 77.1 (CH), 73.8 (C), 56.6 (CH_3), 41.6 (CH), 37.5 (CH_2), 25.8 (CH_3), 25.0 (CH_3), 15.9 (CH_3) ppm. HRMS (ESI): calcd. for $C_{16}H_{24}O_4Na$ $[M + Na]^+$ 303.1567; found 303.1567. Enantiomeric excess was determined by HPLC analysis [CHIRALCEL OD-H column, 2% ethanol/hexane, 0.7 mL/min, retention times 49.3 (minor) and 53.9 (major)]. **24:** R_f = 0.32 (ethyl acetate/light petroleum, 1:1). $[\alpha]_D$ = –19.62 (c = 0.52, $CHCl_3$). IR: $\tilde{\nu}$ = 3376 (br.), 2972, 2926, 1705, 1637, 1501, 1463, 1410, 1364, 1200, 1165, 1079, 1023, 1001 cm^{-1}. ^1H NMR (300 MHz, [D$_4$]methanol): δ = 6.61 (s, 1 H), 6.59 (s, 1 H), 6.12 (ddd, J = 17.1, 10.2, 6.6 Hz, 1 H), 5.06–4.95 (m, 2 H), 3.96–3.89 (m, 1 H), 3.72 (s, 3 H), 3.06 (dd, J = 10.5, 1.2 Hz, 1 H), 2.12–2.03 (m, 4 H, CH, CH_3), 1.68 (ddd, J = 14.1, 10.8, 3.9 Hz, 1 H), 1.12 (s, 3 H), 1.08 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_4$]methanol): δ = 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) ppm. HRMS (ESI): calcd. for $C_{16}H_{24}O_4Na$ $[M + Na]^+$ 303.1567; found 303.1568.

2-[(3*R*,5*S*)-5,6-Dihydroxy-6-methylhept-1-en-3-yl]-5-methylcyclohexa-2,5-diene-1,4-dione (4): A solution of cerium ammonium nitrate (153 mg, 0.28 mmol, 2 equiv.) in water (1 mL) was added dropwise to a stirred mixture of (3*S*,5*R*)-5-(2-hydroxy-5-methoxy-4-methylphenyl)-2-methylhept-6-ene-2,3-diol (39 mg, 0.14 mmol) in acetonitrile (1 mL) at 0 °C. The mixture was stirred at 0 °C for 5 min, then it was diluted with water (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica (ethyl acetate/light petroleum, 1:1) to give **4** (13 mg, 35%) as a yellow oil. R_f = 0.39 (ethyl acetate/light petroleum, 1:1). $[\alpha]_D$ = –15.0 (c = 0.29 $CHCl_3$) [ref.[6] $[\alpha]_D$ = –63.2 (c = 0.38 $CHCl_3$)]. IR: $\tilde{\nu}$ = 3431 (br.), 2975, 2926, 1651, 1609, 1442, 1301, 1351, 1257, 1239, 1135, 1070, 1005 cm^{-1}. UV: λ (ε) = 329 (sh, 420), 414 (sh, 60 $L\,mol^{-1}\,cm^{-1}$) nm. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.59 (q, J = 1.6 Hz, 1 H), 6.53 (d, J = 0.9 Hz, 1 H), 5.77 (ddd, J = 17.9, 9.8, 8.6 Hz, 1 H), 5.24–5.18 (m, 2 H), 3.72 (td, J = 9.2, 3.7 Hz, 1 H), 3.45 (d, J = 10.5 Hz, 1 H), 2.33 (br. s, 1 H, OH), 2.03 (d, J = 1.2 Hz, 3 H), 1.77–1.69 (m, 1 H), 1.53 (ddd, J = 14.2, 10.6, 3.9 Hz, 1 H), 1.20 (s, 3 H), 1.14 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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) ppm. HRMS (ESI): calcd. for $C_{15}H_{20}O_4Na$ $[M + Na]^+$ 287.1254; found 287.1255.

(–)-Heliespirone A (1) and (+)-Heliespirone C (2): Cesium carbonate (295 mg, 0.91 mmol, 5 equiv.) was added to a solution of 2-[(3*R*,5*S*)-5,6-dihydroxy-6-methylhept-1-en-3-yl]-5-methylcyclo-

hexa-2,5-diene-1,4-dione (50 mg, 0.19 mmol) in dichloromethane (6.5 mL) at 0 °C. The reaction mixture was allowed to return to room temperature and then stirred for 1 h. The mixture was then diluted with water (10 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica (ethyl acetate/light petroleum, 1:3) to give **1** (11 mg, 22%) as a colourless solid and **2** (10 mg, 20%) as a colourless solid. **1:** R_f = 0.61 (ethyl acetate/light petroleum, 1:1). M.p. 106–107 °C (ref.[6] m.p. 105–106 °C). $[\alpha]_D$ = –28.0 (c = 0.1 $CHCl_3$) [ref.[6] $[\alpha]_D$ = –55.2 (c = 0.13, $CHCl_3$)]. IR: $\tilde{\nu}$ = 3458 (br.), 2972, 2925, 2854, 1681, 1780, 1348, 1242, 1128, 1062, 1005 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.61 (q, J = 1.4 Hz, 1 H), 5.31 (dt, J = 16.8, 9.6 Hz, 1 H), 5.06 (ddd, J = 16.8, 1.3, 0.7 Hz, 1 H), 4.96 (dd, J = 10.0, 1.3 Hz, 1 H), 4.80 (br. s, 1 H), 4.04 (dd, J = 10.8, 5.3 Hz, 1 H), 3.24 (d, J = 15.6 Hz, 1 H), 2.96 (d, J = 15.6 Hz, 1 H), 2.92 (ddd, J = 12.6, 9.1, 6.6 Hz, 1 H), 2.15 (td, J = 12.7, 10.8 Hz, 1 H), 2.01–1.93 (m, 1 H), 1.97 (d, J = 1.5 Hz, 3 H), 1.33 (s, 3 H), 1.10 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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) ppm. HRMS (ESI): calcd. for $C_{15}H_{20}O_4Na$ $[M + Na]^+$ 287.1254; found 287.1255. **2:** R_f = 0.48 (ethyl acetate/light petroleum, 1:1). M.p. 68–71 °C (ref.[6] m.p. 74–75 °C). $[\alpha]_D$ = +13.0 (c = 0.1 $CHCl_3$) [ref.[6] $[\alpha]_D$ = +50.4 (c = 0.4 $CHCl_3$)]. IR: $\tilde{\nu}$ = 3459 (br.), 2975, 2928, 1685, 1622, 1378, 1351, 1248, 1181, 1115, 1068, 1031, 1006 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.68 (q, J = 1.5 Hz, 1 H), 5.62 (m, 1 H), 5.13 (m, 1 H), 5.09 (d, J = 5.8 Hz, 1 H), 3.95 (dd, J = 10.7, 5.3 Hz, 1 H), 3.28 (m, 1 H), 2.95 (d, J = 16.3 Hz, 1 H), 2.83 (d, J = 16.3 Hz, 1 H), 2.05 (m, 1 H), 1.99 (d, J = 1.5 Hz, 3 H), 1.93 (m, 1 H), 1.84 (br. s, 1 H, OH), 1.24 (s, 3 H), 1.13 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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) ppm. HRMS (ESI): calcd. for $C_{15}H_{20}O_4Na$ $[M + Na]^+$ 287.1254; found 287.1254.

***rac*-2-(5,6-Dihydroxy-6-methylhept-1-en-3-yl)-4-methoxy-5-methylphenyl Acetate (*rac*-21 and *rac*-22):** Potassium osmate(VI) dihydrate (0.7 mg, 0.002 mmol, 0.5 mol-%) and *N*-methylmorpholine *N*-oxide (50 mg, 0.43 mmol, 1.1 equiv.) were added to a solution of 4-methoxy-5-methyl-2-(6-methylhepta-1,5-dien-3-yl)phenyl acetate (112 mg, 0.39 mmol) in *t*BuOH/H_2O (1:1; 0.76 mL). The reaction mixture was stirred at room temperature for 24 h, then it was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica (ethyl acetate/light petroleum, 2:3) to give a mixture of *rac*-**21** and *rac*-**22** (60 mg, 48%) as a colourless oil. R_f = 0.35 (ethyl acetate/light petroleum, 1:1). Other spectroscopic data were consistent with those obtained from enantioenriched **21** and **22**.

***anti*-5-(2-Hydroxy-5-methoxy-4-methylphenyl)-2-methylhept-6-ene-2,3-diol (*rac*-23) and *syn*-5-(2-Hydroxy-5-methoxy-4-methylphenyl)-2-methylhept-6-ene-2,3-diol (*rac*-24):** Potassium carbonate (122 mg, 0.88 mmol, 3 equiv.) was added to a solution of 2-(5,6-dihydroxy-6-methylhept-1-en-3-yl)-4-methoxy-5-methylphenyl acetate (mixture of diastereomers; 94 mg, 0.29 mmol) in methanol (4.5 mL). The reaction mixture was stirred vigorously for 1 h, then it was diluted with methanol (20 mL) and filtered. The filtrate was concentrated in vacuo, and the resulting residue was purified by flash chromatography on silica (ethyl acetate/light petroleum, 2:3) to give *rac*-**23** (31 mg, 38%) as a colourless solid and *rac*-**24** (25 mg, 31%) as a colourless oil. *rac*-**23:** R_f = 0.25 (ethyl acetate/light petroleum, 1:1). *rac*-**24:** R_f = 0.32 (ethyl acetate/light petroleum, 1:1). Other spectroscopic data were consistent with those obtained from enantioenriched **23** and **24**.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra.

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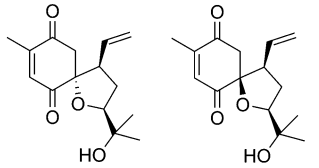
Total syntheses of the epimeric natural products (–)-heliespirone A and (+)-heliespirone C are described. The successful strategy involved an aromatic Claisen rearrangement, a diastereoselective Sharpless asymmetric dihydroxylation (AD) reaction, and an intramolecular oxa-Michael addition.



Total Synthesis

Keywords: Total synthesis / Natural products / Asymmetric synthesis / Sigmatropic rearrangement / Michael addition / Spiro compounds

