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PAPER

Heteroatom-directed Wacker oxidations. A protection-free synthesis of (−)-heliophenanthrone†‡

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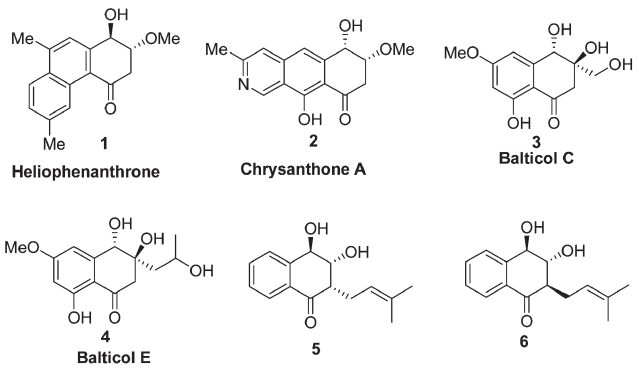
The first enantioselective six-step synthesis of (−)-heliophenanthrone has been achieved without any protection–deprotection protocol at an overall yield of 28%. Key features of this synthesis comprise a heteroatom-directed Wacker oxidation of an internal cyclic olefin in addition to asymmetric Brown allylation and ring closing metathesis (RCM).

Introduction

Heliophenanthrone (**1**) was isolated from the aerial part of the herbaceous plant *Heliotropium ovalifolium* in 2003.[1] In spite of the notorious toxicity of this plant for cattle and sheep it also produces some antifungal and antibacterial compounds from its aerial part. Although no biological activity of heliophenanthrone has been reported to date, it shares common structural features with other bioactive natural products, such as antiangiogenic chrysanthone A (**2**),[2] balticol C (**3**) and E (**4**) which show antiviral activity against influenza virus and herpes simplex virus[3] and cytotoxic 3,4-dihydro-3,4-dihydroxy-2-(3-methylbut-2-enyl)-1(2*H*)-napthalenones **5** and **6**.[4] Among these heliophenanthrone and chrysanthone A closely resemble each other because of the presence of a sensitive monomethyl ether protected keto–diol motif. Very recently, Dyker and Hildebrandt[5] have published a racemic synthesis of heliophenanthrone using a transition metal mediated domino reaction in the key step. However, no synthetic effort has yet been reported in the literature for chrysanthone A.



Since the art and science of modern day total synthesis demand several "economies"[6] as well as protection free sequences,[7] we were intrigued to develop a novel strategy which might deliver both targets in fewer steps and with high overall yield.

To explore the feasibility of our combined approach we deemed it important to perform a model study as outlined in Fig. 1. We envisaged that conversion of aldehyde **7** into *syn*-alkoxyhomoallyl alcohol **8** can easily be achieved in a single step using Brown's protocol.[8] It will then involve in a two-step sequence, namely ring closing metathesis (RCM, **8** → **9**) followed by Wacker oxidation to furnish the requisite motif (*cf.* **10**) for heliophenanthrone (**1**) rapidly. Additionally, the *syn*-diastereoisomer **8** could potentially be converted to the *anti*-diastereoisomer and sequential RCM together with olefinic oxidation (**11** → **12**) possibly complete the model study for chrysanthone A (**2**).

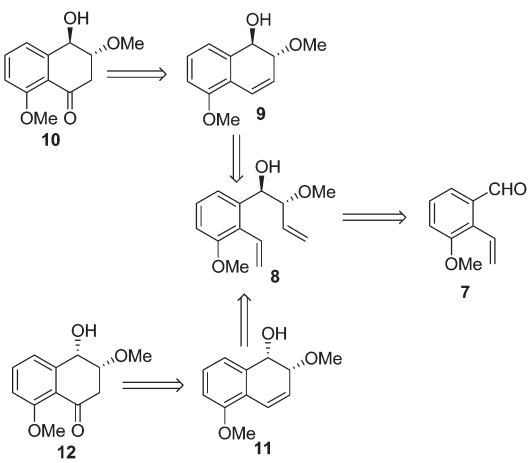


Fig. 1 Retrosynthetic analysis.

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†Dedicated to Professor R. Venkateswaran on the occasion of his 65th birthday.

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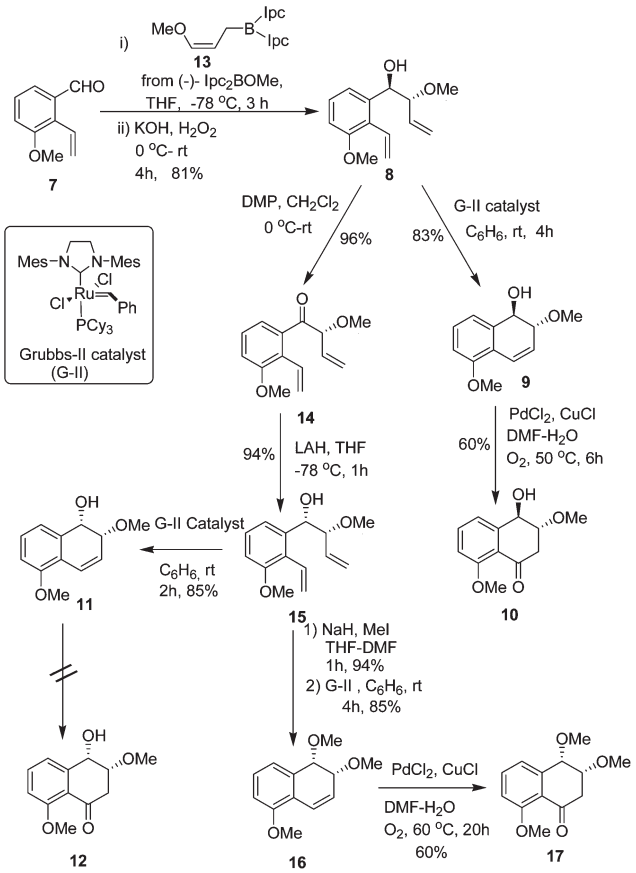


Scheme 1 Model study.

Results and discussions

Accordingly, the starting *o*-vinylbenzaldehyde **7** was subjected to the aforementioned allylborane methodology. Thus, metalation of allyl methyl ether using *sec*-butyllithium at −78 °C and sequential reaction of the resultant *Z*-lithio derivative with (−)-*B*-methoxydiisopinocampheylborane and BF_3-etherate gave the *Z*-reagent **13** (Scheme 1). Addition of *o*-vinylbenzaldehyde **7** at −78 °C afforded alcohol **8** in 81% yield (d.r. = 96 : 4, ee = 88%).[9] At this point **8** was channelled into two different routes to check the feasibility of accessing two different target molecules.

For heliophenanthrone, **8** was directly subjected to ring closing metathesis (RCM) to yield **9**.

At this stage Wacker oxidation appeared to be the automatic choice although it is well known that Wacker oxidation of internal cyclic olefins are highly inefficient.[10] This coupled with the regioselectivity problem is probably the main reason for remarkably rare appearance of this reaction in natural product synthesis. Although an improved method for internal cyclic olefins in presence of inorganic acid was developed, its utility is restricted for acid sensitive substrates.[11] Recently, Gruner and Knölker showed regioselectivity in Wacker oxidation of a cyclic internal olefin which is presumably governed by benzylic carbocation stability; however, this reaction necessitated strong acidic conditions and high temperature.[12] In some cases Wacker oxidation of cyclic internal olefins appears to be aided by an additional coordination between palladium and the heteroatom in the substrate.[13,14] Indeed, we have reported Wacker oxidation of acetonide protected *cis*-dihydroarenediols where the keto group was installed regioselectively at the benzylic position.[15] However, it was not clear whether chelation of one or both the oxygen of acetonide functionality was essential for the success of the reaction.[16] Additionally, whether the reactions were partly or wholly driven by benzylic carbocation stability was also not certain.[18] Due to these unresolved issues feasibility of this reaction in our system was of prime concern. Much to our delight, however, when **9** was subjected to regular Wacker oxidation condition it afforded only one regioisomer **10** with keto group at the benzylic position in good yield. The absolute stereochemistry of the two chiral centres as well as the position of the keto functionality is exactly same as it is in heliophenanthrone (**1**) itself.

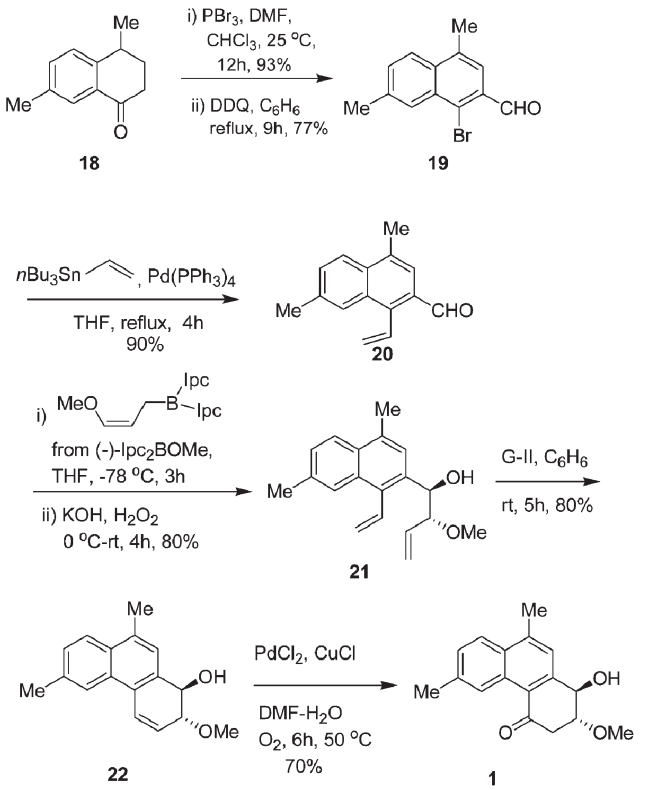
Remaining work on the model study to check the validity of our unified strategy for the synthesis of chrysanthone A was then immediately carried out. Several attempts to get the required *anti*-diastereoisomer **15** *via* one-step Mitsunobu inversion[19] of **8** turned out to be disappointing as in each case either no reaction occurred or intractable mixture formed. However, a two-step sequence involving oxidation of the alcohol with Dess–Martin periodinane followed by highly diastereoselective reduction of ketone **14** by $LiAlH_4$ at −78 °C delivered the *anti*-diastereoisomer **15** (d.r. = 94 : 6, ee = 72%) in 94% yield.[9,20] As the stereochemistry of alkoxyhomoallylalcohol **15** was fixed it was directly used for RCM to afford **11**.

Exposure of **11** to regular Wacker oxidation conditions for a prolonged time resulted in complete recovery of starting material. This failure may be attributed to the lack of coordination of palladium with alkoxy oxygen atom owing to its hydrogen bonding with the neighbouring hydroxyl group. Indeed, the corresponding methyl ether underwent smooth Wacker oxidation to give **17** in 60% yield, thus completing the model study for the synthesis of chrysanthone A (**2**).

We then embarked on the synthesis of heliophenanthrone (**1**) as showcased in Scheme 2. Thus, the readily available *α*-tetralone **18**[22] was subjected to Vilsmeier–Haack type reaction followed by aromatization with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give **19**. High-yielding Stille coupling was then performed to introduce the requisite vinyl group *ortho* to the aldehyde (**19** → **20**). Merely a three-step sequence therefore provides the starting *o*-vinylaldehyde **20** which will now follow the same sequence as in the model study.

The aldehyde **20** was then condensed with [(*Z*)-γ-methoxyallyl]diisopinocamphenylborane **13** to generate the corresponding β-methoxyhomoallyl alcohol **21** as a single diastereoisomer in 90% ee and 80% yield.[9] Successful RCM then followed at room temperature to furnish **22**. To our uttermost satisfaction Wacker oxidation of **22** proceeds under identical conditions to the model and afforded heliophenanthrone (**1**) in 70% yield.

The spectroscopic data of pure heliophenanthrone were in perfect agreement with those previously reported for the natural product;[1,5] the optical rotation, $[\alpha]_D^{26.2} = -19.1$ (*c* 0.28, MeOH), is slightly higher than reported for the natural product,[1] $[\alpha]_D^{25} = -10.8$ (*c* 0.6, MeOH). To the best of our knowledge this is the first example of bay-region Wacker oxidation employed in a natural product synthesis.



Scheme 2 Total synthesis of heliophenanthrone.

Conclusions

In summary, we have accomplished the first asymmetric total synthesis of (−)-heliophenanthrone in six steps and 28% overall yield where nearly every step is skeleton-building and involves strategic redox processes (the only exception being the DDQ mediated aromatization which is non-strategic). The efficiency of our synthesis is evident from its protection-free sequences coupled with a reduced number of *concession steps* which gives our synthesis a relatively high ideality number (>80%) according to Baran's definition.[23] Further studies on the expansion of this strategy and its extension to other targets of interest are currently under way.

Experimental section

General experimental

All melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature at 400 and 200 MHz and 125, 100 and 50 MHz, respectively. The data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration. Optical rotations were measured on a Jasco P1020 polarimeter using a quartz cell with 10 cm path length. Unless otherwise stated, all reactions were carried out under an inert atmosphere in flame-dried flasks. All reagents were commercially obtained and, where appropriate, purified prior to use unless specified otherwise. Solvents were dried as follows: THF, toluene, benzene and Diethyl ether (Et_2O) from sodium benzophenone ketyl; CH_2Cl_2 (DCM) and $CHCl_3$ from P_2O_5. Methanol was distilled from $Mg(OMe)_2$. After drying, organic extracts were evaporated under reduced pressure and the residue was chromatographed on silica gel (Rankem, 230–400 mesh) using EtOAc, petroleum ether (60–80 °C) mixture as eluent. TLC was recorded using precoated plate (Merck, silica gel 60 F_{254}).

2-Methoxy-(3-methoxy-2-vinyl-phenyl)-but-3-en-1-ol (8)

s-BuLi (1.0 M in cyclohexane, 7.4 mL, 7.4 mmol) was added dropwise to a stirred solution of allyl methyl ether (0.86 mL, 9.2 mmol) in 4 mL of THF at −78 °C. The solution was stirred at the same temperature for 0.5 h, then a 1 M solution of (−)-$Ipc_2B(OMe)$ (2.9 g, 9.2 mmol) in THF was added dropwise. The reaction was left to stir at this temperature for 1 h. After 1 h, $BF_3{\cdot}OEt_2$ (1.26 mL, 9.9 mmol) was added dropwise, followed by the immediate addition of a solution of **7** (1.2 g, 7.4 mmol) in 5 mL of THF and the reaction was left to stir at −78 °C for 3 h. The reaction was quenched by the addition of 3.0 M NaOH (15 mL) and 30% H_2O_2 (10 mL). The reaction mixture was warmed to ambient temperature and stirred for 4 h. The solution was diluted with EtOAc and the aqueous layer was further extracted with EtOAc (3×). The organic layers were combined dried over Na_2SO_4, filtered and concentrated under vacuum. The crude residue was purified by column chromatography to afford **8** (1.4 g, 81%) (d.r. = 96 : 4). The enantiomeric purity of **8** was determined to be 88% ee by Mosher ester analysis.[9] R_f = 0.34 (Petroleum ether : ethyl acetate, 8 : 2); $[\alpha]_D^{29.2}$ = −13.69 (*c* 0.96, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.14 (d, J = 2.4 Hz, 1H), 3.36 (s, 3H), 3.74–3.81 (m, 1H), 3.82 (s, 3H), 4.98 (dd, J = 2.4, 7.6 Hz, 1H), 5.08 (d, J = 18.0 Hz, 1H), 5.12 (d, J = 11.2 Hz, 1H), 5.47–5.56 (m, 3H), 6.69 (dd, J = 11.4, 17.8 Hz, 1H), 6.82 (d, J = 4.0 Hz, 1H), 7.14 (d, J = 4.0 Hz, 1H), 7.23–7.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 55.6, 56.8, 72.4, 87.3, 109.8, 119.2, 119.7, 120.6, 127.3, 127.9, 130.9, 134.1, 138.7, 157.0; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{18}O_3Na$: 257.1154, found: 257.1154.

2,5-Dimethoxy-1,2-dihydro-napthalen-1-ol (9)

Grubbs II catalyst (10 mol %) was added to a degassed solution (N_2) of **8** (0.64 mmol) in benzene (6.4 mL). The reaction mixture was stirred at rt for 4 h. Volatiles were then removed under reduced pressure. The residue was then flash-chromatographed on a silica gel column to yield **9** (110 mg, 83%) as a white solid. R_f = 0.25 (Petroleum ether : ethyl acetate, 8 : 2); mp: 72–74 °C; $[\alpha]_D^{27.8}$ = −184.09 (*c* 0.5, DCM); IR (KBr, cm^{-1}): 3279, 2833, 2814, 1575, 1475, 1288, 1263, 1109, 1049, 756, 680; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.58 (d, J = 3.8, 1H), 3.51 (s, 3H), 3.83 (s, 3H), 4.08 (td, J = 2.2, 10.2 Hz, 1H), 4.85 (dd, J = 3.6, 10.4 Hz, 1H), 6.03 (dd, J = 2.4, 10.0 Hz, 1H), 6.78–6.89 (m, 2H), 7.18–7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 55.8, 56.9, 72.7, 82.0, 110.4, 117.6, 120.8, 122.5, 125.6, 128.0, 137.6, 155.0; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{14}O_3Na$: 229.0841, found: 229.0842.

4-Hydroxy-3,8-dimethoxy-3,4-dihydro-2*H*-napthalen-1-one (10)

9 (0.15 mmol) was added to a stirred solution of $PdCl_2$ (10 mol %) and CuCl (1.1 equiv.) in DMF and H_2O (1.2 mL, 9 : 1) under oxygen atmosphere. The resulting dark brown solution was stirred vigorously for 6 h at 50 °C and then extracted with ether. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure. The residue was then purified by flash chromatography to afford **10** (20 mg, 60%). R_f = 0.5 (Petroleum ether : ethyl acetate, 3 : 7); $[\alpha]_D^{28.3}$ = −6.10 (*c* 0.75, DCM); IR (neat, cm^{-1}): 3448, 3016, 2928, 1676, 1595, 1471, 1276, 1246, 1215, 1097, 1051, 756. ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 2.56 (dd, *J* = 10.2, 16.6 Hz, 1H), 3.21 (dd, *J* = 4.6, 16.6 Hz, 1H), 3.49 (s, 3H), 3.66 (ddd, *J* = 4.6, 7.1, 11.6 Hz, 1H), 3.95 (s, 3H), 4.79 (d, *J* = 8.2 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 7.37–7.41 (m, 1H), 7.59 (t, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) *δ*: 42.9, 56.3, 57.0, 72.2, 80.1, 111.7, 118.6, 120.5, 135.4, 144.8, 160.1, 194.1; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{12}H_{14}O_4Na$: 245.0790, found: 245.0790.

2-Methoxy-1(3-methoxy-2-vinyl-phenyl)-but-3-ene-1-one (14)

Dess–Martin periodinane (1.36 g, 3.2 mmol) was added portion-wise over 30 min to a solution of **8** (500 mg, 2.13 mmol), $NaHCO_3$ (125 mg), and 38 mL of DCM at 0 °C. The reaction mixture was then warmed to rt slowly and stirred at rt for 45 min and then quenched by the slow addition of a 1 : 1 solution of sat. aq. $NaHCO_3$: 20% aq $Na_2S_2O_3$. The layers were separated and the aqueous layer was further extracted with DCM. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated up to 1/3rd of its total volume under vacuum. It was then purified by column chromatography using 1 : 2 diethyl ether: n-pentane as eluent to afford **14** (480 mg, 96%), as a clear oil. R_f = 0.5 (petroleum ether : ethyl acetate, 8.5 : 1.5); $[\alpha]_D^{28.8}$ = −76.02 (*c* 0.95, DCM); ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 3.37 (s, 3H), 3.85 (s, 3H), 4.67 (d, *J* = 6.6 Hz, 1H), 5.22–5.48 (m, 4H), 5.69 (ddd, *J* = 6.8, 10.1, 17.1 Hz, 1H), 6.86–7.00 (m, 3H), 7.26 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) *δ*: 55.7, 57.0, 87.1, 112.5, 120.0, 120.3, 121.3, 125.8, 128.4, 131.0, 132.8, 139.4, 157.1, 204.1; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{14}H_{16}O_3Na$: 255.0997, found: 255.0997.

2-Methoxy-1(3-methoxy-2-vinyl-phenyl)-but-3-ene-1-ol (15)

A solution of **14** (400 mg, 1.7 mmol) in 2 mL of THF at −78 °C was added to a suspension of lithium aluminum hydride (327 mg, 8.6 mmol) in 30 mL of dry THF over a period of 20 min. After being stirred at −78 °C for 1 h as TLC showed complete consumption of starting material it was quenched with saturated aqueous NH_4Cl solution. Then it was allowed to warm to rt and filtered. The residue was washed with DCM and the organic fractions were combined, dried and passed through a short column of silica gel using EtOAc and hexane as eluent to afford **15** (380 mg, 94%) (d.r. = 94 : 6) as a thick oil. The enantiomeric purity of **15** was determined to be 72% ee by Mosher ester analysis.[9] R_f = 0.42 (Petroleum ether : ethyl acetate, 8 : 2); $[\alpha]_D^{27.8}$ = +34.47 (*c* 0.8, DCM); ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 2.51 (bs, 1H), 3.31 (s, 3H), 3.78–3.84 (m, 1H), 3.82 (s, 3H), 5.11–5.29 (m, 3H), 5.55–5.79 (m, 3H), 6.72 (dd, *J* = 11.8, 17.5 Hz, 1H), 6.79–6.84 (m, 1H), 7.15–7.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) *δ*: 55.8, 56.7, 71.4, 85.4, 109.8, 119.4, 120.1, 120.8, 126.1, 127.9, 130.7, 133.8, 139.4, 157.0; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{14}H_{18}O_3Na$: 257.1154, found: 257.1155.

2,5-Dimethoxy-1,2-dihydro-napthalen-1-ol (11)

Grubbs II catalyst (10 mol%) was added to a degassed solution (N_2) of **15** (0.17 mmol) in benzene (1.7 mL). The reaction mixture was stirred at rt for 2 h. Volatiles were then removed under reduced pressure. The residue was then flash-chromatographed on a silica gel column to yield **11** (30 mg, 85%) as a white solid. R_f = 0.33 (Petroleum ether : ethyl acetate, 8 : 2); mp: 66–68 °C; $[\alpha]_D^{28.0}$ = −125.65 (*c* 0.6, DCM); IR (neat, cm^{-1}): 2918, 2848, 1575, 1471, 1265, 1105, 1035, 767; ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 2.66 (d, *J* = 7.6 Hz, 1H), 3.44 (s, 3H), 3.83 (s, 3H), 3.98 (t, *J* = 4.6 Hz, 1H), 4.71–4.76 (m, 1H), 6.05 (dd, *J* = 4.0, 10.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 10.0 Hz, 1H), 7.16 (t, *J* = 7.0 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) *δ*: 55.6, 56.6, 69.2, 75.7, 110.6, 119.2, 120.6, 124.1, 124.2, 129.0, 137.5, 155.1; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{12}H_{14}O_3Na$: 229.0841, found: 229.0840.

1-(1,2-Dimethoxy-but-3-enyl)-3-methoxy-2-vinyl-benzene

NaH (10 mg, 0.25 mmol, 60% in mineral oil) and MeI (0.34 mmol) were added To a stirred solution of **15** (50 mg, 0.21 mmol) in anhydrous THF (2 mL) and DMF (2 mL) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 1 h. As the TLC showed complete consumption of starting material it was then quenched with H_2O. The aqueous layer was extracted with diethyl ether. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography to afford 1-(1,2-dimethoxy-but-3-enyl)-3-methoxy-2-vinyl-benzene (50 mg, 94%) as a colorless oil. R_f = 0.41 (Petroleum ether : ethyl acetate, 9.5 : 0.5); $[\alpha]_D^{27.8}$ = +112.73 (*c* 1.4, DCM); ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 3.20 (s, 3H), 3.23 (s, 3H), 3.63–3.69 (m, 1H), 3.83 (s, 3H), 4.79 (d, *J* = 4.6 Hz, 1H), 5.10 (td, *J* = 1.0, 17.2 Hz, 1H), 5.26 (dd, *J* = 2.0, 10.4 Hz, 1H), 5.53–5.63 (m, 2H), 5.61–5.62 (m, 1H), 5.83 (ddd, *J* = 7.8, 10.1, 17.4 Hz, 1H), 6.69–6.84 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) *δ*: 55.7, 57.0, 57.2, 81.6, 86.0, 109.7, 119.4, 119.9, 121.0, 127.5, 127.8, 130.7, 134.5, 138.3, 157.1; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{20}O_3Na$: 271.1310, found: 271.1313.

1,2,5-Trimethoxy-1,2-dihydro-napthalene (16)

Grubbs II catalyst (10 mol%) was added to a degassed solution (N_2) of **26** (0.16 mmol) in benzene (1.6 mL). The reaction mixture was stirred at rt for 4 h. Volatiles were then removed under reduced pressure. The residue was then flash-chromatographed on a silica gel column to yield **16** (30 mg, 85%). R_f = 0.2 (Petroleum ether : ethyl acetate, 9.5 : 0.5); $[\alpha]_D^{28.6}$ = −101.24 (*c* 1.24, DCM); ^1H NMR ($CDCl_3$, 200 MHz) *δ*: 3.39 (s, 3H), 3.48 (s, 3H), 3.83 (s, 3H), 4.16–4.20 (m, 1H), 4.24 (d, *J* = 4.4 Hz, 1H), 6.05 (dd, *J* = 2.4, 9.9 Hz, 1H), 6.83–7.00 (m, 3H), 7.19

(t, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 55.6, 56.7, 57.0, 76.2, 78.1, 111.1, 120.6, 121.6, 122.3, 126.6, 128.0, 134.4, 155.3; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{16}O_3Na$: 243.0997, found: 243.0997.

3,4,8-Trimethoxy-3,4-dihydro-2*H*-napthalen-1-one (17)

17 (24 mg, 0.11 mmol) was added to a stirred solution of $PdCl_2$ (10 mol%) and CuCl (1.1 equiv.) in DMF and H_2O (1 mL, 9 : 1) under oxygen atmosphere. The resulting dark brown solution was stirred for 20 h at 60 °C and then extracted with ether. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure. The residue was then purified by flash chromatography to yield **17** (15 mg, 60%). R_f = 0.16 (Petroleum ether : ethyl acetate, 7 : 3); $[\alpha]_D^{27.6}$ = +47.97 (c 0.75, DCM); IR (neat, cm^{-1}): 2926, 1678, 1593, 1469, 1278, 1238, 1103, 1076, 752; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.84 (dd, J = 5.6, 17.2 Hz, 1H), 3.01 (dd, J = 9.4, 17.6 Hz, 1H), 3.36 (s, 3H), 3.45 (s, 3H), 3.84–3.94 (m, 1H), 3.91 (s, 3H), 4.48 (d, J = 2.2 Hz, 1H) 6.99–7.06 (m, 2H), 7.50 (t, J = 8.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.5, 56.3, 56.9, 57.1, 76.6, 78.7, 113.0, 121.5, 134.4, 142.1, 160.3, 195.4; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_{17}O_4$: 237.1127, found: 237.1122.

1-Bromo-4,7-dimethyl-3,4-dihydro-napthalene-2 carbaldehyde

A mechanically stirred solution of DMF (0.8 mL, 10.3 mmol) in anhydrous $CHCl_3$ (3 mL) was cooled in an ice bath while phosphorus tribromide (0.9 mL, 9.3 mmol) was added dropwise over a period of 15 min. The resulting yellow suspension was warmed to rt and stirred for an additional 20 min. A solution of **18** (600 mg, 3.5 mmol) in $CHCl_3$ was added dropwise over 10 min at 0 °C. Stirring was continued for 12 h at rt after which the solution was poured into ice water. Solid $NaHCO_3$ was carefully added to neutralize the acids, and the mixture was extracted with several portions of ether. The combined ethereal extracts were washed with saturated sodium chloride solution, dried over Na_2SO_4 and solvent was evaporated. Purification of the residue was done by flash chromatography to afford (846 mg, 93%) of β-bromovinylaldehyde as a light yellow liquid. R_f = 0.4 (Petroleum ether : ethyl acetate, 9.5 : 0.5); IR (neat, cm^{-1}): 2958, 2854, 1666, 1579, 1560, 1255, 1228, 821; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.20 (d, J = 6.8 Hz, 3H), 2.39 (s, 3H), 2.46–2.54 (m, 1H), 2.60–2.72 (m, 1H), 2.89–2.30 (m, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.72 (s, 1H), 10.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 19.8, 21.3, 30.7, 31.2, 126.4, 129.7, 132.1, 132.7, 133.4, 136.8, 138.8, 141.4, 193.7; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_{14}BrO$: 267.0208, found: 267.0204.

1-Bromo-4,7-dimethyl-napthalene-2 carbaldehyde (19)

To the β-bromovinylaldehyde (800 mg, 3 mmol) in dry benzene (15 mL) was added DDQ (2 g, 9 mmol). It was then refluxed for 9 h. As the TLC showed complete consumption of starting material benzene was removed and the crude product was subjected to flash chromatography to afford **19** (611 mg, 77%) as an off-white solid. R_f = 0.69 (Petroleum ether : ethyl acetate, 9.5 : 0.5); mp: 120–122 °C; IR (KBr, cm^{-1}): 2862, 1683, 1600, 1375, 1330, 977, 815, 800; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.59 (s, 3H), 2.63 (s, 3H), 7.51 (d, J = 8.4 Hz, 1H), 7.66 (s, 1H), 7.86 (d, J = 8.6 Hz, 1H), 8.25 (s, 1H), 10.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 19.4, 22.0, 123.8, 124.9, 127.8, 128.9, 131.0, 131.9, 132.2, 134.8, 135.1, 138.0, 193.4; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_{12}BrO$: 263.0072, found: 263.0066.

4,7-Dimethyl-1-vinyl-napthalene-2-carbaldehyde (20)

An argon flushed round bottom flask was charged with a mixture of aldehyde **19** (350 mg, 1.3 mmol), $Pd(PPh_3)_4$ (49 mg, 3 mol%), toluene (18 mL) and vinyl tributyltin (0.53 mL, 1.8 mmol). This was refluxed for 4 h. It was then poured into a saturated aqueous solution of KF and extracted with ether. The combined organic layer was then washed with brine, dried over anhydrous Na_2SO_4 and solvent was removed at atmospheric pressure. Column chromatography was then performed to give **20** as a low melting solid (252 mg, 90%).

R_f = 0.28 (Petroleum ether : ethyl acetate, 9.7 : 0.3); mp: 56–58 °C; IR (KBr, cm^{-1}): 2956, 2870, 1670, 1599, 1429, 1338, 943, 821; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.57 (s, 3H), 2.69 (s, 3H), 5.45 (dd, J = 1.6, 17.4 Hz, 1H), 5.98 (dd, J = 1.6, 11.2 Hz, 1H), 7.34 (dd, J = 11.4, 17.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.77 (s, 1H), 7.91–7.95 (m, 2H), 10.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 19.6, 22.0, 122.5, 124.7, 125.6, 125.9, 131.1 (2 × C), 131.3, 132.1, 133.5, 134.6, 136.5, 141.5, 193.3; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{15}H_{14}ONa$: 233.0942, found: 243.0944.

1-(4,7-Dimethyl-1-vinyl-napthalen-2-yl)-2-methoxy-but-3-en-1-ol (21)

s-BuLi (1.0 M in cyclohexane, 1.9 mL, 1.9 mmol) was added dropwise To a stirred solution of allyl methyl ether (0.2 mL, 2.3 mmol) in 2 mL of THF at −78 °C. The solution was stirred at the same temperature for 0.5 h then a 1 M solution of (−)-$Ipc_2B(OMe)$ (726 mg, 2.3 mmol) in THF was added dropwise. The reaction mixture was left to stir at this temperature for 1 h. After 1 h, $BF_3{\cdot}OEt_2$ (0.3 mL, 2.4 mmol) was added dropwise, followed immediately by a solution of **20** (400 mg, 1.9 mmol) in 2 mL of THF and the reaction mixture was left to stir at −78 °C for 3 h. The reaction was quenched by the addition of 3.0 M NaOH (4 mL) and 30% H_2O_2 (3 mL). The reaction was warmed to ambient temperature and stirred for 4 h. The solution was diluted with EtOAc and the aqueous layer was further extracted with EtOAc (3×). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude residue was purified by column chromatography to afford **21** (430 mg, 80%) as a single diastereoisomer. The enantiomeric purity of **21** was determined to be 90% ee by Mosher ester analysis.[9] R_f = 0.45 (Petroleum ether : ethyl acetate, 8.5 : 1.5); $[\alpha]_D^{28.7}$ = −58.91 (c 1.6, DCM); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.49 (s, 3H), 2.66 (s, 3H), 3.23 (d, J = 1.8 Hz, 1H), 3.39 (s, 3H), 3.82 (t, J = 7.8 Hz, 1H), 4.97–5.13 (m, 3H), 5.35 (dd, J = 2.2, 17.8 Hz, 1H), 5.44–5.58 (m, 1H) 5.73 (dd, J = 2.2, 11.4 Hz, 1H), 6.96 (dd, J = 11.4, 17.8 Hz, 1H), 7.33 (dd, J =

1.4, 8.7 Hz, 1H), 7.41 (s, 1H), 7.84–7.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 19.6, 21.8, 56.9, 73.0, 87.5, 119.1, 121.9, 124.0, 124.2, 125.9, 127.8, 130.5, 131.9, 133.5, 133.7, 134.0, 134.1, 135.1; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{22}O_2Na$: 305.1517, found: 305.1518.

2-Methoxy-6,9-dimethyl-1,2-dihydrophenanthren-1-ol (22)

Grubbs II catalyst (10 mol%) was added to a degassed solution (N_2) of **21** (0.25 mmol) in benzene (2.5 mL). The reaction mixture was stirred at rt for 5 h. Volatiles were then removed under reduced pressure. The residue was then flash-chromatographed on a silica gel column to yield **22** (51 mg, 80%) as a white solid. R_f = 0.25 (Petroleum ether : ethyl acetate, 8.5 : 1.5); mp: 142–144 °C; $[\alpha]_D^{28.6} = -281.08$ (*c* 0.65, DCM); IR (KBr, cm^{-1}) 3281, 2812, 1626, 1514, 1485, 1435, 1286, 1114, 1097, 1049, 977, 900, 806, 725, 640; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.54 (s, 3H), 2.69 (s, 3H), 3.54 (s, 3H), 4.14–4.19 (m, 1H), 5.01 (d, J = 10.8 Hz, 1H), 6.22 (dd, J = 2.0, 10.2 Hz, 1H), 7.23–7.37 (m, 2H), 7.58 (s, 1H), 7.87–7.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 19.7, 21.9, 56.7, 73.1, 82.0, 122.4, 123.1, 123.9, 124.5, 126.3, 127.6, 129.7, 130.5, 133.3, 134.6, 135.6; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}O_2Na$: 277.1204, found: 277.1206.

1-Hydroxy-2-methoxy-6,9-dimethyl-2,3-dihydro-1*H*-phenanthren-4-one (1)

22 (0.1 mmol) was added to a stirred solution of $PdCl_2$ (10 mol %) and CuCl (1.1 equiv.) in DMF and H_2O (1.2 mL, 9 : 1) under oxygen atmosphere. The resulting dark brown solution was stirred vigorously for 6 h at 50 °C and then extracted with ether. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure. The residue was then purified by flash chromatography to afford **1** (19 mg, 70%).

R_f = 0.22 (Petroleum ether : ethyl acetate, 1 : 2); mp: 170–172 °C; $[\alpha]_D^{26.2} = -19.1$ (*c* 0.28, MeOH); lit.[1] $[\alpha]_D^{25} = -10.8$ (*c* 0.6, MeOH) IR (neat, cm^{-1}) 3308, 2966, 1660, 1593, 1240, 1126, 1099, 1084, 1051, 979, 904, 815; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H), 2.65 (dd, J = 10.8, 16.2 Hz, 1H), 2.75 (s, 3H), 3.08 (s, 1H), 3.30 (dd, J = 4.4, 16.0 Hz, 1H), 3.51 (s, 3H), 3.71 (ddd, J = 4.8, 7.6, 11.6, 1H), 4.91 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.70 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 9.27 (s, 1H); ^{1}H NMR (400 MHz, acetone-d_6) δ 2.52 (s, 3H), 2.67–2.79 (m, 1H), 2.73 (s, 3H), 3.21 (dd, J = 4.0, 16.0 Hz, 1H), 3.45 (s, 3H), 3.78–3.82 (m, 1H), 4.90 (t, J = 6.0 Hz, 1H), 4.98 (d, J = 5.2 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 9.32 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 20.3, 22.2, 43.4, 57.2, 72.1, 81.4, 124.9, 125.0, 126.8, 127.2, 128.9, 131.6, 131.9, 138.8, 142.4, 146.2, 197.8; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{18}O_3Na$: 293.1154, found: 293.1154.

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