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The first total synthesis of (±)-1-desoxyhypnophilin

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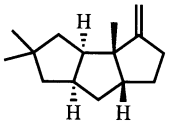
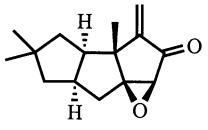
Abstract—The paper describes the first total synthesis of (±)-1-desoxyhypnophilin, a linear triquinane from the East African mushroom *Lentinus crinitus* which displays promising antimicrobial activity. A key feature is the use of a ring closing metathesis reaction with a tertiary allylic alcohol, in conjunction with a PCC induced oxidative rearrangement, to construct a cyclopentenone.

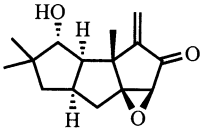
Polyquinanes have stimulated considerable interest within the synthetic chemistry community as a result of their widespread occurrence in nature and their associated biological activities.[1] Linear triquinanes form the largest subgroup of natural products in this class, encompassing the hirsutanes, capnellanes, ceratopicanes and pleurotellanes. A recent addition to this family is 1-desoxyhypnophilin **2**, a constituent of the East African mushroom *Lentinus crinitus*.[2] Closely related to hirsutene **1**, hypnophilin **3** and coriolin **4**, 1-desoxyhypnophilin exhibits useful antimicrobial activity.[2] In this paper we describe the first total synthesis of (±)-1-desoxyhypnophilin **2**.[3]



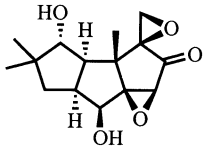
Hirsutene **1**



1-Desoxyhypnophilin **2**



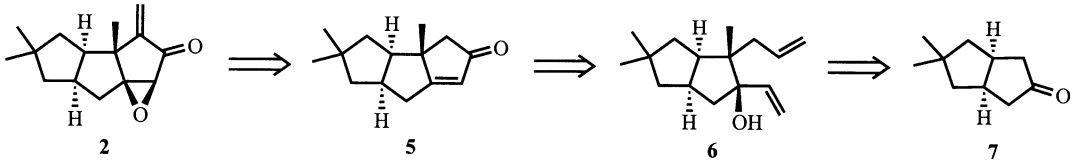
Hypnophilin **3**



Coriolin **4**

The route we envisioned made use of the known bicyclic ketone **7**,[4,5] to which we planned to elaborate the oxygenated methyenecyclopentanone ring. Our idea was to take advantage of lower steric encumbrance on the convex face of this molecule to control the diastereoselective introduction of two alkenes. With diene **6** in hand we proposed to use a ring closing metathesis reaction to generate the triquinane and an oxidative rearrangement to install the enone **5**. Methylenation and epoxidation would then complete the total synthesis (Scheme 1).

The route we adopted for the synthesis of bicyclic ketone **7** draws heavily on the work of Piers and Karunaratne.[6] Thus, monoacetalisation of the commercially available diketone **8** gave a statistical 1:2:1 product mixture comprising bis-acetal **10**, mono-acetal **11** and recovered starting material **8** that was readily separated by column chromatography. The bis-acetal **10** was then hydrolysed to **8** (99%), combined with the recovered starting material and recycled. In this way the desired mono-acetal **11** was given in ca. 75% yield after two itterations.[6] Sequential Wittig methylenation to **14**, acetal hydrolysis to **18** and reduction to **17** then facilitated cyclopropanation of the alkene giving **16**.[6] Hydrogenolysis to **15** next installed the gem-dimethyl moiety (Scheme 2) while a Dess–Martin periodinane oxi-



2 **5** **6** **7**

Scheme 1.

Keywords: terpenes and terpenoids; natural products; ring closing metathesis; cyclisations; triquinanes.
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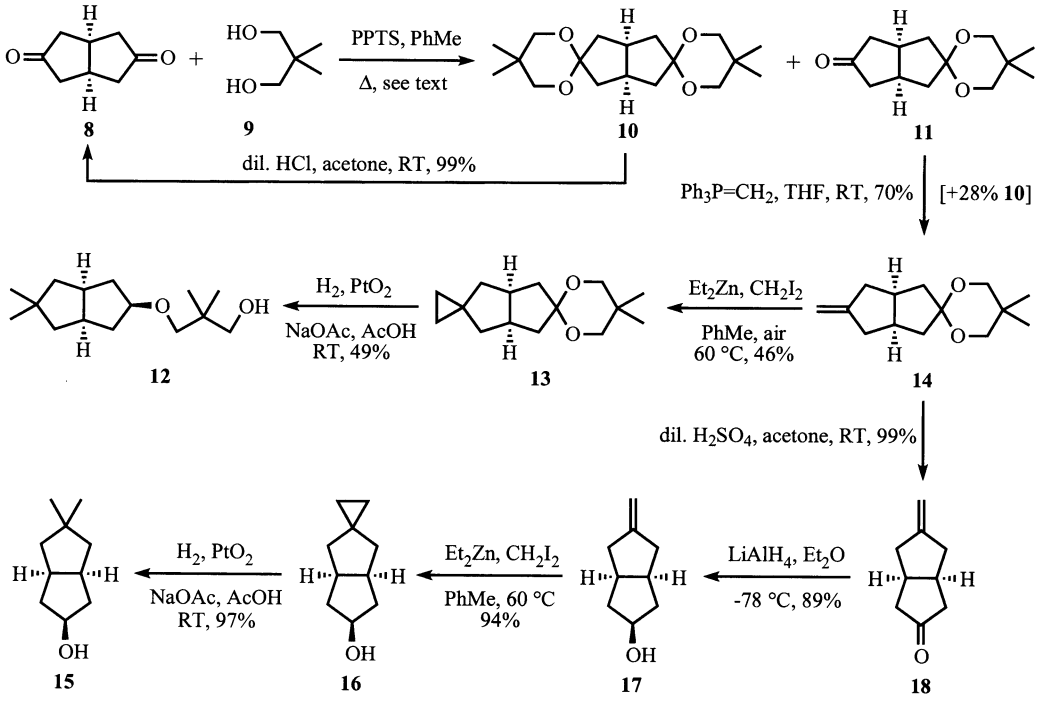
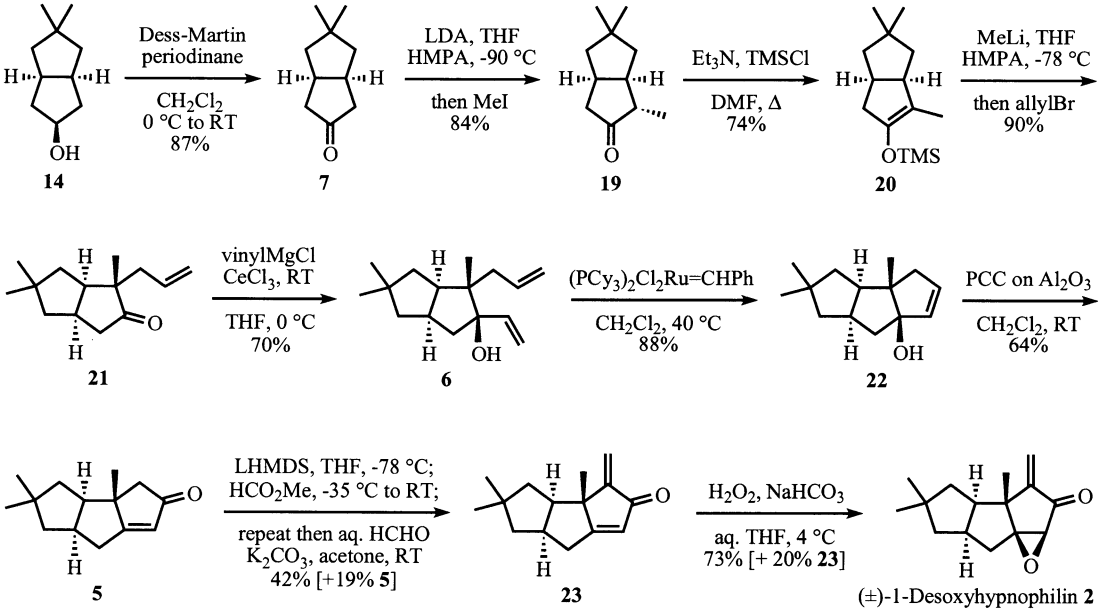


Scheme 2.

dation to **7** reinstated the ketone function, completing the first phase of the synthesis.

Though this route to ketone **7** was reasonably efficient and amenable to scale up, it was rather laborious. Unfortunately problems were encountered on each occasion we attempted to foreshorten the sequence. For example, attempts to synthesise **18** by mono-methylenation of **8** led to complex product mixtures, as indeed did exposure of ketone **11** to Reetz's reagent.[7] Similarly, while cyclopropanation of **14** could be effected in modest yield, reduction of the resulting cyclopropane **13** was accompanied by hydrogenolysis of the acetal giving ether **12** as a single diastereoisomer (presumed to be as depicted in Scheme 2).[5] Hence we decided to accept the routes shortcomings and begin construction of the triquinane.

Our next task was to introduce the second quaternary centre. To that end the lithium enolate of **7** was alkylated with methyl iodide. Initially this too proved capricious, giving both mono- and di-alkylated materials as well as diastereoisomeric mixtures of products. Through the inclusion of HMPA as a co-solvent and by ensuring that the internal temperature was maintained below −80°C during the



Scheme 3.

addition of methyl iodide, **19** could be produced routinely as a single diastereoisomer in yields exceeding 80%. Formation of the thermodynamic silyl enol ether **20**, transmetallation to the lithium enolate and quenching with allyl bromide then provided the unsaturated ketone **21**.

At this juncture we needed to effect the addition of vinylmagnesium chloride to the ketone. Initially our attempts to bring about this conversion returned only recovered starting material. Suspecting that the basicity of the reagent was promoting enolisation over addition of the organometallic to the sterically encumbered ketone, prompted us to add cerium trichloride to the Grignard reagent.[8] This change allowed diene **6** to be produced in 70% yield and as a single diastereoisomer. Ring closing metathesis with Grubbs' catalyst proceeded efficiently and without incident to give the triquinane **22** in 88% yield.[9,10] Oxidation of the tertiary allylic alcohol to enone **5** with pyridinium chlorochromate,[11,12] and methylenation according to the procedure of Greene then gave diene **23**.[13] Finally, selective epoxidation of the strained alkene with hydrogen peroxide provided (±)-1-desoxyhypnophilin **2** (Scheme 3):[12,14] our synthetic sample exhibiting spectral characteristics identical to those reported previously.[2]

In conclusion, we have achieved the first total synthesis of (±)-1-desoxyhypnophilin **2**, an antimicrobial linear triquinane recently identified as a constituent of the East African mushroom *Lentinus crinitus*.[2,3] The key sequence involves a ring closing metathesis to generate a cyclic 3°-allylic alcohol that is subsequently oxidised to an enone with PCC on alumina. Importantly, a homochiral synthesis of the intermediate ketone **19** has been reported,[15] affording the opportunity to use the aforementioned sequence in a homochiral synthesis of 1-desoxyhypnophilin. We are presently seeking to extend the scope of the key annulation sequence to address the synthesis of other polycycles and triquinane natural products.

1. Experimental

1.1. General

The melting point of **13** was determined using a Reichert heated stage apparatus and was uncorrected. IR spectra were recorded using either a Perkin Elmer 1600 series Fourier transform infrared spectrometer using NaCl cells or a Bio-Rad FTS 135 Fourier transform infrared spectrometer equipped with a Golden Gate Single Reflection Diamond ATR. NMR spectra were recorded on a Bruker AC300 (operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C) or a Bruker AM400 (operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C). Chemical shifts are reported as values in parts per million relative to tetramethylsilane (δ_H 0.00, δ_C 0.00) or residual $CHCl_3$ (δ_H 7.27) or $CDCl_3$ (δ_C 77.2). Mass spectra were recorded on a variety of instruments either in house or at the EPSRC mass spectrometry centre, Swansea.

All reactions were magnetically stirred under an inert atmosphere. Reactions were monitored by thin layer chromatography using Macherey–Nagel Alugram Sil G/UV$_{254}$ precoated aluminium foil plates of layer thickness 0.25 mm. Compounds were visualised firstly by UV irradiation, then by exposure to iodine vapour and finally by heating plates exposed to solutions of phosphomolybdic acid in ethanol. Column chromatography was performed on Sorbsil 60 silica (230–400 mesh), slurry packed and run under low pressure.

Sonication was performed by partial immersion of the reaction vessel into the water filled bath of a Branson 1200, Bransonic® ultrasound cleaner. Ether refers to diethyl ether and petrol refers to the fraction of petroleum ether in the boiling point range 40–60°C. Intermediates **10**, **11**, **14**, **16**, **17** and **18** were prepared following the procedures described by Piers and Karunaratne (the yields quoted in Scheme 2 are those attained in our laboratories).[8]

1.1.1. *meso*-5″,5″-Dimethyl-dispiro[cyclopropane-1,5′-perhydro-2-pentalene-2′,2″-dioxane] [13]. To a vigorously stirred solution of the alkene **14** (3.00 g, 13.5 mmol) in toluene (20 mL) at 60°C and under nitrogen was added a solution of diethylzinc (18.4 mL of a 1.1 M solution in toluene, 20.2 mmol) followed by diiodomethane (5.42 g, 1.63 mL, 20.2 mmol). Dry air was bubbled through the cloudy suspension for 1 h then the mixture was cooled to rt over 1 h and poured onto 2 M hydrochloric acid (50 mL). The phases were separated and the aqueous phase extracted with ether (3×20 mL). The combined organic phases were washed with sodium hydrogen carbonate (20 mL), water (20 mL) and brine (20 mL) then dried ($MgSO_4$), filtered and concentrated in vacuo to a yellow oil. Purification by column chromatography (silica, 5% ether in petrol) gave **13** as a colourless oil that crystallised on standing to a colourless solid. Recrystallisation from ethanol furnished colourless needles (1.48 g, 6.27 mmol, 46%); mp 53–55°C (ethanol); IR (neat, cm^{-1}) ν_{max} 2952m, 2851w, 1442w, 1395w, 1329w, 1113vs, 1096m, 1010m, 987m, 947w; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.42 (2H, s, OCH_2), 3.40 (2H, s, OCH_2), 2.56–2.48 (2H, m, 2×C*H*), 2.30–2.23 (2H, m, 2×C*H*H), 1.71 (2H, app. dd, *J*=12.8, 8.3 Hz, 2×C*H*H), 1.55 (2H, app. dd, *J*=12.8, 7.7 Hz, 2×CH*H*), 1.19 (2H, app. dd, *J*=12.8, 3.2 Hz, 2×CH*H*), 0.89 (6H, s, 2×CH_3), 0.44–0.40 (2H, m, cyclopropyl), 0.25–0.20 (2H, m, cyclopropyl); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 109.3 (O*C*O), 71.8 (O*C*H$_2$), 70.4 (O*C*H$_2$), 41.1 (2×*C*H$_2$), 39.5 (2×*C*H$_2$), 39.4 (2×*C*H), 29.1 (*C*), 22.0 (*C*, cyclopropyl), 21.7 (*C*H$_3$), 21.5 (*C*H$_3$), 11.6 (*C*H$_2$, cyclopropyl), 6.7 (*C*H$_2$, cyclopropyl); LRMS (CI) *m/z* 237 ([MH]$^+$, 100%); Anal. Found: C, 76.09; H, 10.32. $C_{15}H_{24}O_2$ requires C, 76.23; H, 10.23.

1.1.2. rel-(2*endo*,3a*R*,6a*S*)-3-[(5,5-Dimethylperhydro-2-pentalenyl)oxy]-2,2-dimethyl-1-propanol [12]. A solution of cyclopropane **13** (240 mg, 1.02 mmol), sodium acetate (89 mg, 1.06 mmol) and platinum oxide (23 mg, 0.102 mmol) in acetic acid (5 mL) was stirred at ambient temperature under an atmosphere of hydrogen for 18 h. Water (10 mL) and ether (10 mL) were then added, followed by sodium hydrogen carbonate, portionwise until effervescence ceased. The mixture was filtered through Celite® and the aqueous phase was extracted with ether (3×10 mL). The combined organic phases were washed with water (2×5 mL), saturated aqueous sodium hydrogen carbonate (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to furnish **12** (120 mg, 0.50 mmol, 49%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3500–3000

brm, 2949s, 2864m, 1465m, 1364m, 1278w, 1119s, 1090vs, 1047s, 906w; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.88 (1H, app. quintet, J=5.0 Hz, OC*H*), 3.46 (2H, s, OCH_2), 3.27 (2H, s, CH_2OH), 2.84–2.79 (1H, br s, O*H*), 2.63–2.54 (2H, m, 2×C*H*), 1.95–1.85 (2H, m, 2×C*H*H), 1.67 (2H, app. br. dd, J=12.3, 8.3 Hz, 2×C*H*H), 1.55 (2H, app. dt, J=13.3, 4.5 Hz, 2×CH*H*), 1.32 (2H, br. dd, J=12.0, 8.3 Hz, 2×CH*H*), 1.06 (3H, s, CH_3), 0.94 (6H, app. s, 2×CH_3), 0.92 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 84.2 (O*C*H), 78.3 (OCH_2), 71.8 (CH_2OH), 48.2 (2×CH_2), 41.6 (*C*), 40.4 (2×*C*H), 37.6 (2×CH_2), 35.1 (*C*), 28.0 (CH_3), 26.2 (CH_3), 21.2 (2×CH_3); LRMS (CI) m/z 241 ($[MH]^+$, 22%), 153 ($[M-C_5H_{11}O]^+$, 30%), 137 ($[M-C_5H_{11}O_2]^+$, 80%), 95 (68%), 81 (100%); HRMS (CI) m/z Found MH^+: 241.2170, $C_{15}H_{29}O_2$ requires 241.2168.

1.1.3. rel-(2*endo*,3a*R*,6a*S*)-5,5-Dimethylperhydro-2-pentalenol [15].[5] A solution of cyclopropane **16** (2.40 g, 15.8 mmol), sodium acetate (1.30 g, 15.8 mmol) and platinum oxide (269 mg, 1.19 mmol) in acetic acid (30 mL) was stirred at ambient temperature under an atmosphere of hydrogen for 24 h. Water (50 mL) and ether (30 mL) were then added, followed by sodium hydrogen carbonate, portionwise until effervescence ceased. The mixture was filtered through Celite® and the aqueous phase was extracted with ether (4×25 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate (2×30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to furnish **15** (2.35 g, 15.3 mmol, 97%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3350 brs, 2948s, 2931s, 2858m, 1464m, 1364m, 1268w, 1110s, 1076m, 1023w; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.26 (1H, app. tt, J=7.2, 5.7 Hz, C*H*OH), 2.60–2.49 (2H, m, 2×C*H*), 2.15–2.02 (2H, m, 2×C*H*H), 1.74–1.65 (2H, app. br dd, J=12.6, 8.2 Hz, 2×C*H*H), 1.54 (1H, s, O*H*), 1.40–1.25 (4H, m, 4×CH*H*), 1.05 (3H, s, CH_3), 0.89 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 76.8 (*C*HOH), 49.5 (2×CH_2), 43.1 (*C*), 42.7 (2×CH_2), 41.1 (2×*C*H), 29.2 (CH_3), 27.3 (CH_3); LRMS (CI) m/z 136 ($[M-H_2O]^+$, 60%), 121 ($[M-H_2O-CH_3]^+$, 40%), 95 (100%); HRMS (CI) m/z Found $[MH-H_2O]^+$: 137.1331, $C_{10}H_{17}$ requires 137.1330.

1.1.4. rel-(3a*R*,6a*S*)-5,5-Dimethylperhydro-2-pentalenone [7].[4,5] To a stirred suspension of Dess–Martin periodinane (1.70 g, 4.00 mmol) in dichloromethane (10 mL) at ambient temperature and under nitrogen was added alcohol **14** (0.522 g, 3.39 mmol) as a solution in dichloromethane (5 mL). After 90 min, sodium hydrogen carbonate (2 g) was added. After a further 5 min the mixture was filtered through Celite® and the filtrate concentrated in vacuo to a white solid. Purification by column chromatography (silica, 10% ether in petrol) gave **7** (0.441 g, 2.90 mmol, 87%) as a colourless oil. The spectral and physical characteristics recorded were consistent with literature values.[16]

1.1.5. rel-(1*S*,3a*R*,6a*R*)-1,5,5-Trimethylperhydro-2-pentalenone [19].[5,15–17] To a stirred solution of *N*,*N*-diisopropylamine (0.82 g, 1.06 mL, 8.15 mmol) in tetrahydrofuran (15 mL) at −78°C and under argon was added *n*-butyllithium (5.66 mL of a 1.44 M solution in hexanes, 8.15 mmol). After 2 min, HMPA (2 mL) was added. The mixture was warmed to −10°C over 20 min then recooled to −88°C. A solution of ketone **7** (1.18 g, 7.76 mmol) in THF (20 mL) was added dropwise over 5 min. After 30 min, a solution of methyl iodide (1.32 g, 0.58 mL, 9.32 mmol) in THF (20 mL) was added dropwise over 6 min [ensuring that the internal temperature did not exceed −80°C]. After 6 h, the reaction was warmed to ambient temperature, stirred for 15 h then partitioned between saturated ammonium chloride (20 mL) and ether (25 mL). The aqueous phase was extracted with ether (3×25 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo to a yellow oil. Purification by column chromatography (silica, 2.5% ether in petrol) gave **19** (1.08 g, 6.51 mmol, 84%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2952m, 2931m, 2866w, 1738vs, 1456m, 1408w, 1367m, 1168m, 913w, 734w; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.83–2.68 (1H, app dtdd, J=10.7, 9.4, 7.5, 4.3 Hz, CH_2CHCH_2), 2.46 (1H, dd, J=19.1, 9.4 Hz, C*H*HC=O), 2.28 (1H, qd, J 8.4, 6.6 Hz, C*H*C=O), 2.15 (1H, ddd, J=19.1, 4.3, 1.5 Hz, CH*H*C=O), 1.98 (1H, app qd, J=7.0, 1.2 Hz, C*H*CHC=O), 1.90 (1H, ddd, J=13.1, 8.0, 1.5 Hz, C*H*HCHCHC=O), 1.81 (1H, ddd, J=12.6, 7.5, 1.3 Hz, C*H*HCHCH$_2$C=O), 1.34 (1H, dd, J=13.1, 6.3 Hz, CH*H*CHCHC=O), 1.26 (1H, dd, J=12.6, 10.7 Hz, CH*H*CHCH$_2$C=O), 1.09 (3H, s, CH_3C), 1.05 (3H, d, J=7.2 Hz, CH_3CH), 0.99 (3H, s, CH_3C); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 222.4 (*C*=O), 50.6 (*C*H), 49.0 (CH_2), 48.0 (*C*H), 47.9 (CH_2), 43.2 (CH_2), 41.4 (*C*), 36.9 (*C*H), 30.3 (CH_3), 29.2 (CH_3), 14.5 (CH_3); LRMS (CI) m/z 184 ($[M+NH_4]^+$, 100%), 166 (M^+, 98%); HRMS (ES) m/z Found $[MH]^+$: 167.1436. $C_{11}H_{19}O$ requires 167.1436.

1.1.6. rel-(3a*R*,6a*R*)-3,5,5-Trimethyl-1,3a,4,5,6,6a-hexahydro-2-pentalenyl trimethylsilyl ether [20].[18] To a stirred solution of the ketone **19** (0.350 g, 2.11 mmol) in dry DMF (4 mL) and under argon were added triethylamine (1.28 g, 1.76 mL, 12.7 mmol) and trimethylsilyl chloride (0.64 g, 0.74 mL, 5.91 mmol). The solution was stirred at reflux for 24 h then cooled and filtered. The solid residue was washed with ether (20 mL), then the combined organic phases were washed successively with saturated sodium hydrogen carbonate (10 mL), 0.5 M hydrochloric acid (4 mL), saturated sodium hydrogen carbonate (10 mL) and brine (10 mL). The organic phase was then dried ($MgSO_4$), filtered and concentrated in vacuo to brown oil. Purification by column chromatography (silica, 20% ether in petrol) gave **20** (0.374 g, 1.57 mmol, 74%) as a yellow oil; IR (neat, cm^{-1}) ν_{max} 2956m, 2926m, 2871w, 2851w, 1689m, 1253m, 1208m, 843w; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.94 (1H, app. qm, J=8.3 Hz), 2.67–2.46 (2H, m), 2.06–1.90 (2H, m), 1.71 (1H, ddd, J=12.0, 7.6, 2.0 Hz), 1.64 (1H, ddd, J=12.3, 8.3, 2.1 Hz), 1.48 (3H, br. s, =CCH_3), 1.10–0.95 (1H, obscured), 1.02 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.18 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 142.5 (*C*), 116.5 (*C*), 49.2 (CH_2), 49.0 (*C*H), 45.7 (CH_2), 39.7 (*C*), 39.5 (CH_2), 35.8 (*C*H), 28.4 (CH_3), 26.7 (CH_3), 10.0 (CH_3), 0.0 (Si(CH_3)$_3$); LRMS (CI) m/z 239 ($[MH]^+$, 100%), 181 (60%), 165 ($[M-SiMe_3]^+$, 25%), 90 (34%), 73 (80%).

1.1.7. rel-(1*S*,3a*R*,6a*R*)-1-Allyl-1,5,5-trimethylperhydro-2-pentalenone [21].[17] To a stirred solution of silyl enol ether **20** (0.350 g, 1.47 mmol) in THF (10 mL) at −10°C and under argon was added methyllithium (0.97 mL of a

1.6 M solution in THF, 1.55 mmol). After 15 min, HMPA (1 mL) was added, the mixture was cooled to −78°C, then allyl bromide (0.186 g, 0.13 mL, 1.54 mmol) was added over 30 s. After 3 h the mixture was warmed to ambient temperature over 1 h then quenched with saturated aqueous ammonium chloride (10 mL). The phases were separated and the aqueous phase extracted with ether (2×10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL) then dried ($MgSO_4$), filtered and concentrated in vacuo to yellow oil. Purification by column chromatography (silica, 2% ether in petrol) gave **21** (0.273 g, 1.33 mmol, 90%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2932s, 2865m, 1733vs, 1639w, 1459m, 1409m, 1374m, 1366w, 994m, 913s; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.70 (1H, ddt, J=17.3, 9.9, 7.4 Hz, =C*H*), 5.10–4.99 (2H, m, =CH_2), 2.80–2.55 (3H, m), 2.11 (2H, m, CH_2CH=), 1.95–1.85 (2H, m), 1.44 (1H, ddd, J=12.5, 6.8, 1.5 Hz), 1.20 (1H, dd, J=13.2, 4.6 Hz), 1.11 (1H, app. t, J=12.5 Hz), 1.06 (3H, s, CH_3), 0.97 (3H, s, CH_3), 0.95 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 222.8 (*C*=O), 133.6 (=*C*H), 118.4 (=*C*H_2), 52.7 (*C*), 50.2 (*C*H), 49.1 (*C*H_2), 44.7 (*C*H_2), 43.8 (*C*H_2), 43.7 (*C*H_2), 40.4 (*C*), 34.3 (*C*H), 30.2 (*C*H_3), 28.7 (*C*H_3), 17.5 (*C*H_3); LRMS (CI) *m/z* 207 ($[MH]^+$, 100%), 206 (M^+, 70%), 149 (50%), 123 (100%); HRMS (ES) *m/z* Found $[MH]^+$: 207.1747. $C_{14}H_{23}O$ requires 207.1749.

1.1.8. rel-(1*S*,2*R*,3a*R*,6a*R*)-1-Allyl-1,5,5-trimethyl-2-vinyl-perhydro-2-pentalenol [6]. Cerium trichloride heptahydrate (3.36 g, 9.56 mmol) was warmed to 140°C under high vacuum with stirring for 150 min. The resulting white powder was cooled under argon, suspended in THF (20 mL), and sonicated for 30 min. After cooling to 0°C a solution of ketone **21** (0.197 g, 0.956 mmol) in THF (5 mL) was added followed by vinylmagnesium chloride (5.56 mL of a 1.72 M solution in THF, 9.56 mmol). After 2 h the mixture was warmed to ambient temperature over 30 min. After 16 h the mixture was poured onto 2 M HCl (50 mL) then extracted with ether (3×15 mL). The combined organic phases were washed with brine (25 mL) then dried ($MgSO_4$), filtered and concentrated in vacuo to yellow oil. Purification by column chromatography (silica, 4% ether in petrol) gave **6** (0.157 g, 0.671 mmol, 70%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3600–3400w, 2950m, 2864w, 1637w, 1463w, 1376w, 997m, 913s; ^1H NMR (300 MHz, $CDCl_3$) δ_H 6.03 (1H, dd, J=17.4, 10.8 Hz, =C*H*C), 5.80 (1H, ddt, J=17.7, 10.3, 7.4 Hz, =C*H*CH_2), 5.25 (1H, dd, J=17.4, 1.6 Hz, C*H*H=CHC), 5.11 (1H, dd, J=10.8, 1.6 Hz, CH*H*=CHC), 5.05–4.93 (2H, m, CH_2=CHCH_2), 2.62–2.50 (2H, m, 2×C*H*), 2.11 (1H, app. dd, J=13.4, 9.3 Hz, C*H*H), 2.00–1.85 (2H, m, 2×CH_2CH=), 1.74–1.62 (2H, m, 2×CH*H*), 1.53 (1H, dd, J=13.4, 3.8 Hz, CH*H*), 1.39–1.25 (3H, m, 2×CH*H*+O*H*), 1.05 (3H, s, CH_3), 0.90 (6H, app. s, C(CH_3)$_2$); these assignments were established by ^1H–^1H COSY; ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 144.0 (=*C*H), 138.3 (=*C*H), 119.0 (=*C*H_2), 114.8 (=*C*H_2), 89.7 (*C*OH), 52.8 (*C*H), 51.7 (*C*H_2), 51.5 (*C*), 46.6 (*C*H_2), 45.8 (*C*H_2), 45.4 (*C*H_2), 44.1 (*C*), 41.1 (*C*H), 31.1 (*C*H_3), 29.0 (*C*H_3), 18.0 (*C*H_3); LRMS (CI) *m/z* 235 ($[MH]^+$, 10%), 217 ($[MH-H_2O]^+$, 76%), 177 (100%); HRMS (ES) *m/z* Found $[M+Na]^+$: 257.1879. $C_{16}H_{26}NaO$ requires 257.1881; Found $[MH-H_2O]^+$: 217.1955. $C_{16}H_{25}$ requires 217.1956.

1.1.9. rel-(3a*R*,3b*S*,6a*R*,7a*R*)-2,2,3b-Trimethyl-2,3,3a,3b,4,6a,7,7a-octahydro-1*H*-cyclopenta[*a*]pentalen-6a-ol [22]. A solution of diene **6** (0.160 g, 0.684 mmol) and Grubbs' catalyst (31.6 mg, 0.038 mmol) in dichloromethane (10 mL) was heated at 40°C with under argon for 5 h. The mixture was then concentrated in vacuo and purified by column chromatography (silica, 5–20% ether in petrol) to give **22** (0.116 g, 0.604 mmol, 88%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 3500–3300 brm, 2933m, 2863w, 1463w, 1363m, 1277w, 1077s, 1009vs, 770m, 732s; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.79 (1H, app. dt, J=5.6, 2.4 Hz, CH=C*H*CH$_2$), 5.58 (1H, app. dt, J=5.6, 2.1 Hz, C*H*=CHCH$_2$), 2.29 (2H, app. t, J=2.2 Hz, CH_2CH=), 2.32–2.12 (3H, m), 1.65–1.50 (2H, m), 1.50–1.32 (3H, m), 1.19 (1H, dd, J=12.8, 4.6 Hz), 1.08 (3H, s, CH_3), 0.99 (3H, s, CH_3), 0.90 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 136.6 (=*C*H), 132.8 (=*C*H), 95.1 (*C*OH), 56.6 (*C*H), 50.2 (*C*H_2), 50.1 (*C*), 47.3 (*C*H_2), 45.6 (*C*H_2), 42.9 (*C*H_2), 41.4 (*C*), 40.2 (*C*H), 30.8 (*C*H_3), 29.1 (*C*H_3), 19.5 (*C*H_3); LRMS (CI) *m/z* 206 (M^+ and/or $[M+NH_4-H_2O]^+$, 22%), 189 ($[MH-H_2O]^+$, 12%), 96 (100%); HRMS (CI) *m/z* Found $[M+NH_4-H_2O]^+$: 206.1914. $C_{14}H_{22}N$ requires 206.1909.

1.1.10. rel-(3a*R*,3b*S*,7a*R*)-2,2,3b-Trimethyl-2,3,3a,4,5,7,7a-octahydro-1*H*-cyclopenta[*a*]pentalen-5-one [5]. To a solution of the allyl alcohol **22** (49 mg, 0.238 mmol) in dichloromethane (5 mL) was added PCC on alumina (0.55 g of ca. 20% wt on alumina, 0.510 mmol) at ambient temperature under argon. After 24 h the reaction mixture was poured onto a pre-loaded silica chromatography column and eluted (20–50% ether in petrol) to give **5** (31 mg, 0.152 mmol, 64%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2951w, 2866w, 1708vs, 1633m, 1465w, 1366w, 1223w, 1151w, 909w, 843w; ^1H NMR (300 MHz, $CDCl_3$) δ_H 5.68 (1H, d, J=1.9 Hz, =C*H*), 2.85–2.74 (2H, m), 2.44–2.20 (4H, m), 1.79 (1H, ddd, J=12.2, 7.2, 1.6 Hz, C*H*), 1.53 (1H, ddd, J=12.9, 8.7, 1.6 Hz), 1.45 (1H, dd, J=12.9, 8.5 Hz), 1.25–1.15 (1H, m), 1.10 (3H, s, CH_3), 1.08 (3H, s, CH_3), 0.95 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 211.1 (*C*=O), 196.0 (=*C*), 122.2 (=*C*H), 52.9 (*C*H_2C=O), 50.7 (*C*H), 49.7 (*C*H_2), 49.5 (*C*), 44.6 (*C*H), 44.0 (*C*), 40.5 (*C*H_2), 33.1 (*C*H_2), 29.2 (*C*H_3), 27.6 (*C*H_3), 24.8 (*C*H_3); LRMS (CI) *m/z* 205 ($[MH]^+$, 100%); HRMS (CI) *m/z* Found $[MH]^+$: 205.1590. $C_{14}H_{21}O$ requires 205.1592.

1.1.11. rel-(3a*R*,3b*S*,7a*R*)-2,2,3b-Trimethyl-4-methylene-2,3,3a,3b,4,5,7,7a-octahydro-1*H*-cyclopenta[*a*]penta-len-5-one [23]. Prepared using the procedure of Greene et al.[13] Thus, enone **5** (29 mg, 0.142 mmol) in THF (2 mL) at −78°C and under argon was treated with LiHMDS (0.28 mL of a 1 M solution in THF, 0.28 mmol). The reaction was warmed to −35°C over 1 h, then methyl formate (34 mg, 0.035 mL, 0.568 mmol) was added. The mixture was warmed to ambient temperature over 45 min then cooled to −78°C and treated with a second portion of LiHMDS (0.66 mL of a 1 M solution in THF, 0.66 mmol). After warming to −35°C over 1 h, methyl formate (0.345 g, 0.354 mL, 5.76 mmol) was added and the mixture warmed to ambient temperature. 1 M HCl (5 mL) was added and the mixture extracted into dichloromethane (3×10 mL). The combined organic phases were dried ($MgSO_4$), filtered and

concentrated in vacuo to yellow oil. This crude oil was then subjected to the aforementioned procedure for a second time. The resultant oil was dissolved in acetone (5 mL) and potassium carbonate (0.119 g, 0.86 mmol) and aqueous formaldehyde (0.30 mL of a 37% wt solution in water, 3.21 mmol) were added. After 14 h, 2 M HCl (5 mL) was added and the mixture extracted with dichloromethane (3×10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to yellow oil. Purification by column chromatography (silica, 10–20% ether in petrol) gave firstly dienone **23** (13 mg, 0.060 mmol, 42%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2951m, 1702vs, 1623s, 1464w, 1368w, 1255w, 1153w, 932w, 859m, 782w; ^1H NMR (400 MHz, $CDCl_3$) δ_H 5.82 (1H, br d, J=1.8 Hz, =C*H*), 5.80 (1H, s, =C*H*H), 5.07 (1H, s, =CH*H*), 2.77–2.65 (2H, m), 2.34 (1H, dt, J=10.8, 8.8 Hz, C*H*), 2.28–2.17 (1H, m), 1.74 (1H, ddd, J=12.3, 7.5, 1.3 Hz), 1.55–1.45 (2H, m), 1.18 (1H, app. t, J=11.8 Hz), 1.09 (3H, s, CH_3), 1.06 (3H, s, CH_3), 0.88 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 198.3 (*C*=O), 190.3 (=*C*), 154.6 (=*C*), 123.6 (=*C*H), 113.3 (=*C*H_2), 52.2 (*C*), 50.1 (CH_2), 48.6 (*C*H), 45.3 (*C*H), 44.5 (*C*), 40.6 (CH_2), 33.1 (CH_2), 29.4 (CH_3), 27.8 (CH_3), 23.9 (CH_3); LRMS (CI) m/z 217 ($[MH]^+$, 26%), 95 (100%); HRMS (CI) m/z Found $[MH]^+$: 217.1591. $C_{15}H_{21}O$ requires 217.1592; then recovered **5** (5.6 mg, 19%).

1.1.12. rel-(1a*S*,3a*R*,3b*R*,6a*R*,7a*S*)-3a,5,5-Trimethyl-3-ethyleneperhydrocyclopenta[4,5]pentaleno[1,6a-*b*]oxiren-2-one [(±)-1-desoxyhypnophilin] [2].[2] A solution of **23** (8.0 mg, 0.037 mmol) in THF (1 mL) and water (1 mL) containing sodium hydrogen carbonate (50 mg) and 30% H_2O_2 (0.1 mL) was stirred at 4°C for 15 h. Ether (20 mL) was added and the organic phase was separated, dried ($MgSO_4$), filtered and concentrated to a colourless oil. Purification by column chromatography (silica, 10% ether in petrol) gave firstly (±)-1-desoxyhypnophilin **2** (6.2 mg, 0.027 mmol, 73%) as a colourless oil; IR (neat, cm^{-1}) ν_{max} 2951m, 2866w, 1728vs, 1642w, 1465w, 1417w, 1258w, 941w, 906m, 862w, 730s; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.06 (1H, s, =C*H*H), 5.27 (1H, s, =CH*H*), 3.44 (1H, s, C*H*C=O), 2.74 (1H, app. tq, J=11.1, 8.5 Hz), 2.40 (1H, dt, J=11.3, 9.2 Hz, C*H*), 2.00 (2H, app. d, J=8.5 Hz), 1.81 (1H, ddd, J=12.3, 7.5, 1.5 Hz), 1.55 (1H, dd, J=12.8, 8.6 Hz), 1.49 (1H, ddd, J=12.8, 8.8, 1.5 Hz), 1.26–1.16 (1H, obscured), 1.17 (3H, s, CH_3), 1.13 (3H, s, CH_3), 0.93 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 198.3 (*C*=O), 153.4 (=*C*), 120.1 (=*C*H_2), 76.7 (*C*, obscured by $CDCl_3$ signal), 61.2 (*C*HC=O), 50.2 (*C*H), 49.9 (CH_2), 46.6 (*C*), 42.6 (*C*), 40.5 (CH_2), 39.5 (*C*H), 30.5 (CH_2), 29.3 (CH_3), 27.6 (CH_3), 17.9 (CH_3); LRMS (CI) m/z 233 ($[MH]^+$, 1%), 217 (32%), 95 (100%); HRMS (CI) m/z Found $[M+NH_4]^+$: 250.1810. $C_{15}H_{24}NO_2$ requires 250.1807; then recovered **23** (1.6 mg, 20%).

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