Concise synthesis of the tricyclic core of lycoposerramine S†‡

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The tricyclic core of lycoposerramine S has been synthesised in 10 steps from a symmetrical cyclohexadiene precursor by way of a desymmetrising free-radical cyclisation and iodocyclisation.

Introduction

The fawcettimine class of lycopodium alkaloids is a structurally-fascinating group of compounds which includes fawcettimine (1) itself along with various other alkaloids including lycoposerramines S (2) and A (3) (Fig. 1). These compounds all feature a 6–5 carbobicyclic core with a fused azonane ring (existing preferentially as the hemiaminol in the parent compound 1). Lycoposerramine S also bridges the C5 and C13 positions with a pyrrolidine ring, while lycoposerramine A is the only natural product to date which incorporates an oxadiazolidinone ring. All of the compounds possess a quaternary stereogenic centre in the carbobicyclic core. These compounds are therefore formidable synthetic targets. Fawcettimine has been synthesised twice as the racemate, most notably by Heathcock in a landmark 1986 synthesis, and only very recently has the first enantioselective total synthesis been reported.8

Results and discussion

We have recently reported that desymmetrisation reactions of cyclohexa-1,4-dienes provide convenient access to 6–5 fused ring systems containing quaternary stereogenic centres, and have demonstrated the application of free-radical and halocyclisation methodology in this context. Other related work includes the application of chiral sulfoxides to this process, a novel Prins-pinacol sequence.13 We felt that this methodology would provide an ideal approach to the lycoposerramine alkaloids. Lycoposerramine S should be accessible by electrophile-initiated cyclisation of a compound of general structure 4, which should in turn be accessible from compound 5. This compound should be accessible with good stereocontrol by free-radical cyclisation of a precursor 6, directed by the hydroxy group. This compound could be prepared from known cyclohexadiene 7 (Scheme 1).14 We now
report the successful realisation of this strategy for a target lacking the azonane ring.

Compound 7 was prepared in two steps from toluic acid according to the previously-published procedure. Deprotonation of this compound and addition of epichlorohydrin was immediately followed by sodium borohydride reduction to give a 1 : 1 mixture of diastereoisomers from which diol 8 was isolated in 37% overall yield. Given the inexpensive nature of the starting material, this diastereoisomer separation early in the sequence is preferable to a multistep sequence to introduce the requisite methyl group stereoselectively. Regioselective protection of the primary alcohol was then followed by a diastereoselective free-radical cyclisation to give the desired stereoisomer 11 as the major component of a separable 2 : 1 mixture (Scheme 2).

Stereochemical assignment of compounds 8 and 9 was not possible. The methyl stereochemistry in compound 11 was confirmed by the NOE enhancement between H5 and one of the methylene protons adjacent to the hydroxy group. The only one of these protons in either stereoisomer which would produce such an NOE is H3β as shown on structure 11. A similar NOE was used to assign the natural product stereochemistry.

Stereoselectivity of the free-radical cyclisation

The modest level of diastereoccontrol in the free-radical cyclisation of compound 10 warrants comment. In an earlier study, Curran reported the cyclisation of compound 13 to give compound 14, with a methyl group directing the stereochemistry, with 94 : 6 diastereoselectivity at the same temperature (Scheme 3).

Clearly the difference between these two approaches is the free-radical precursor, which should not dramatically affect the stereoselectivity, and the nature of the directing group—hydroxy versus methyl. In model studies, we were able to show that increasing the size of the directing-group by introducing a bulky protecting group onto the oxygen does increase the level of stereoselectivity, but not to the levels observed by Curran, and then only at the expense of yield (Scheme 4).

It is therefore clear that the lower stereoselectivity results from electronic as well as steric factors. We considered the various methods by which we might improve the stereochemistry of this step. A diastereoselectivity of 2 : 1 at 80 °C corresponds to an energy difference of approximately 2 kJ mol⁻¹ between diastereomeric transition states. Lowering the temperature of the cyclisation to −78 °C is calculated to give 3.5 : 1 selectivity, or a maximum possible yield of 77%. This would inevitably require exchange of the chloride for a more effective radical precursor such as iodide, and so the overall efficiency of the process is unlikely to be substantially higher than the present 52%. Since the 1-iodo-2-hydroxy substrate which this would require is likely to be prone to loss of HI to form the corresponding epoxide, this strategy would require protection of the secondary alcohol, necessitating a further two synthetic manipulations. As we have already seen, introduction of a protecting group onto the secondary alcohol is detrimental to the yield of the cyclisation step.

Upon consideration then, we feel that the brevity of the present approach offsets any disappointment which we might feel at the modest levels of diastereoccontrol.

The stereochemical assignment of the free-radical cyclisation was initially made by analogy with cyclisation reactions reported by ourselves and by Curran. This was eventually confirmed by completion of the tricyclic core of the natural product (vide infra).
Completion of the tricyclic core of lycoposerramine S

From this point, displacement of the secondary alcohol under Mitsunobu conditions by deprotection to give primary amine \( \text{18} \) (Scheme 5). It should be noted that formation of the 4-toluenesulfonate ester from compound \( \text{11} \) under standard conditions (TsCl, Et,N, DMAP, CH\(_2\)Cl\(_2\) and NaH, THF then TsCl) failed.

![Scheme 5](image)

Attempts to prepare compound \( \text{24} \) by direct aminomercuration of compound \( \text{18} \) gave only recovery of starting material. Nosyl amide \( \text{19} \) was therefore prepared from compound \( \text{18} \). This underwent smooth iodocyclisation to give compound \( \text{20} \) (Scheme 6). We were unable to remove the iodine and nosyl groups from this compound, and therefore reverted to the more robust tosyl group. Iodocyclisation was once again effective, producing compound \( \text{22} \) in good yield. The best conditions for removal of the iodine used tri-\( n \)-butyltin hydride–AIBN in benzene. This was then followed by sodium naphthalenide-mediated removal of the tosyl group to give compound \( \text{24} \) in an encouraging 82% yield over the two steps (Scheme 7). This compound contains the fully functionalised tricyclic core of lycoposerramine S. An attempt to shorten this sequence using the direct hydroamination reported by Komeyama et al. failed, although there was some indication of product formation by TLC analysis in the early part of the reaction. It seems possible that the TBDPS protecting group is incompatible with the reaction conditions, although no products were isolated.

The structure of compound \( \text{24} \) was confirmed by a range of NMR methods (COSY, NOESY, HSQC), and also by comparison with the NMR data of lycoposerramine S. Selected data are presented in Table 1.

![Scheme 6](image)

Table 1 Comparison of NMR data of compound \( \text{24} \) with lycoposerramine S

<table>
<thead>
<tr>
<th></th>
<th>Lycoposerramine S (2)</th>
<th>Compound 24</th>
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<tbody>
<tr>
<td>C4</td>
<td>50.5 (CH)</td>
<td>44.9 (CH(_3))</td>
</tr>
<tr>
<td>C5</td>
<td>60.2</td>
<td>56.0</td>
</tr>
<tr>
<td>C6</td>
<td>35.6</td>
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<tr>
<td>C16</td>
<td>22.1</td>
<td>21.9</td>
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</table>
Conclusions

In summary, compound 24 has been prepared in a 12 step sequence from toluic acid. Studies towards the completion of lykoposerramine S are underway and will be reported in due course.

Experimental section

General experimental points

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker Avance 500 spectrometer operating at 500 MHz for 1H and 125 MHz for 13C at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (J) are reported in Hz. Multiplicity in 1H-NMR is reported as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double quartet (dq), triplet (t), and multiplet (m). Multiplicity in 13C NMR was obtained using the DEPT pulse sequence. Flash chromatography was performed using Matrex silica 60 30–70 micron.

1,4-cis-1-(3-Chloro-2-hydroxypropyl)-1-hydroxymethyl-4-methylcyclohexa-2,5-diene (8) and 1,4-trans-1-(3-chloro-2-hydroxypropyl-1-hydroxymethyl-4-methylcyclohexa-2,5-diene (9). n-BuLi (22.2 mL, 1.6 M in hexanes, 1 equiv.) was added to a cooled (−78 °C) solution of diisopropylamine (5.0 mL, 35.5 mmol, 1.1 equiv.) in THF (30 mL) and the resulting solution allowed to warm to room temperature. After re-cooling to −78 °C, methyl 4-methylcyclohexa-2,5-diene-1-carboxylate4 (4.91 g, 32.3 mmol) was added dropwise. After stirring for 30 min, chloroform (3.3 mL) was added and the reaction was quenched with saturated aqueous NH4Cl (30 mL) and the organic layer was separated and the aqueous layer extracted with ethyl acetate (200 mL) and ethyl acetate (100 mL). The organic layer was dried over Na2SO4 and the combined organic extracts were dried over Na2SO4 and concentrated in vacuo. The residue was purified by chromatography on SiO2 (50% Et2O in petroleum ether) to give compound 8 (2.57 g, 32%).

Compound 8. Colourless oil (Found: MH+ = CH3OH, 184.0655. C11H13ClO requires M, 184.0655; νmax (neat)/cm−1 = 3420, 2957, 1516, 1454, 1048, 805 and 748; δH (400 MHz; CDCl3) 5.94–5.86 (2 H, m, CHCH=CH), 5.61–5.55 (1 H, m, one of CH2Cl), 3.42 (1 H, app. broad d, J 10.2, 2.1, one of CH2C=CH), 3.05 (1 H, broad t, J 10.2, 1.9, one of CH2C=CH), 2.81–2.73 (1 H, m, CH2=CH), 2.11 (1 H, t, J 5.8, CH2OH), 1.64 (1 H, dd, J 14.3, 8.1, one of CH3OH), 1.55 (1 H, dd, J 14.3, 3.4, one of CH3OH) and 1.08 (3 H, J 7.3, CH3); δC (100 MHz: CDCl3) 134.3 (CH), 134.0 (CH), 128.3 (CH), 128.1 (CH), 69.9 (CH), 69.0 (CH), 50.2 (CH2), 42.2 (C), 41.8 (C), 30.9 (CH) and 22.3 (CH3); m/z (TOF ES+) = 184 (M−CH3OH, 17%) and 167 (100).

Compound 9. Colourless oil (Found: MH+ = CH3OH, 184.0655. C11H13ClO requires M, 184.0655; νmax (neat)/cm−1 = 3412, 2957, 1516, 1454, 1048, 805 and 748; δH (400 MHz; CDCl3) 5.94–5.86 (2 H, m, CHCH=CH), 5.61–5.55 (1 H, m, one of CH2Cl), 3.42 (1 H, dd, J 10.2, 1.9, one of CH2C=CH), 3.05 (1 H, broad t, J 10.2, 1.9, one of CH2C=CH), 2.81–2.73 (1 H, m, CH2=CH), 2.11 (1 H, t, J 5.8, CH2OH), 1.64 (1 H, dd, J 14.3, 8.1, one of CH3OH), 1.55 (1 H, dd, J 14.3, 3.4, one of CH3OH) and 1.08 (3 H, J 7.3, CH3); δC (100 MHz: CDCl3) 134.3 (CH), 134.0 (CH), 128.3 (CH), 128.1 (CH), 69.9 (CH), 69.0 (CH), 50.2 (CH2), 42.2 (C), 41.6 (C), 30.8 (CH) and 21.9 (CH3); m/z (TOF ES+) = 184 (M−CH3OH, 21%) and 167 (100).

1,4-cis-1-(3-Chloro-2-hydroxypropyl)-1-(tert-butyldiphenylsilyloxy)methyl)-4-methylcyclohexa-2,5-diene (10). Imidazole (1.68 g, 26.2 mmol, 2.2 equiv.) and TBDPSCl (3.4 mL, 13.1 mmol, 1.1 equiv.) were added to a solution of diol 8 (2.57 g, 11.9 mmol) in CH2Cl2 (20 mL). After stirring overnight, the reaction was quenched with saturated aqueous NH4Cl (30 mL) and the organic layer separated. The aqueous layer was extracted with CH2Cl2 (2 × 15 mL) and the combined organic extracts dried over Na2SO4 and concentrated in vacuo. The residue was purified by chromatography on SiO2 (10% Et2O in petroleum ether) to give the title compound (4.35 g, 81%) as a colourless viscous oil (Found: MH+, 455.2190. C27H36ClO2Si requires M, 455.2173; νmax (neat)/cm−1 = 3420, 3072, 2931, 2858, 1590, 1516, 1470, 1428, 1390, 1111, 805 and 748; δH (400 MHz; CDCl3) 4.95–4.91 (2 H, m, CHCH=CH), 4.58–4.53 (1 H, m, one of CH2C=CH), 3.94 (1 H, app. dt, J 10.2, 2.1, one of CHCH=CH), 5.39 (1 H, app. dt, J 10.2, 2.1, one of CHCH=CH), 3.94 (1 H, m, CHOHOH), 3.53 (1 H, dd, J 11.1, 4.1, one of CH3Cl), 3.45 (1 H, dd, J 11.1, 6.5, one of CH3Cl), 3.36 (1 H, app. broad d, J 10.2, 1.9, one of CH2C=CH), 3.05 (1 H, broad t, J 10.2, 1.9, one of CH2C=CH), 2.81–2.73 (1 H, m, CH2=CH), 2.11 (1 H, t, J 5.8, CH2OH), 1.64 (1 H, dd, J 14.3, 8.1, one of CH3OH), 1.55 (1 H, dd, J 14.3, 3.4, one of CH3OH) and 1.08 (3 H, J 7.3, CH3); δC (100 MHz: CDCl3) 134.3 (CH), 134.0 (CH), 128.3 (CH), 128.1 (CH), 69.9 (CH), 69.0 (CH), 50.2 (CH2), 42.2 (C), 41.8 (C), 30.9 (CH) and 22.3 (CH3); m/z (TOF ES+) = 184 (M−CH3OH, 21%) and 167 (100).
to reflux and solutions of AIBN (88 mg, 0.54 mmol, 0.1 equiv.) and Bu₃SnH (1.7 mL, 6.42 mmol, 1.2 equiv.), each in benzene (5 mL), were added over 10 h by syringe pump. After a total of 18 h reflux, the solution was concentrated in vacuo and purified by silica gel chromatography (5% to 10% ethyl acetate in petroleum ether) to give compound 11 (1.16 g, 52%) followed by compound 12 (0.51 g, 23%) as colourless oils.

**Compound 11.** Colourless oil (Found: MH⁺, 421.2605. C₂₇H₃₇O₂Si requires M, 421.2563); νmax (neat)/cm⁻¹ 3361, 3071, 2952, 1657, 1464, 1348, 1110, 822, 743 and 703; δH (400 MHz; CDCl₃) 7.70–7.65 (4 H, m, aromatic CH), 7.47–7.36 (6 H, m, aromatic CH), 5.45 (1 H, app. broad d, J 10.1, CHCH=CH=CH) 5.26 (1 H, app. broad dd, J 10.1, 2.4, CHCH=CH=CH), 4.19 (1 H, app. tt, J 4.6, 2.2, CHOH), 3.40 (2 H, app. s, CH₂O), 2.63–2.54 (1 H, m, CH₂CH₃CH), 2.16–2.08 (1 H, m, MeCH), 1.95 (1 H, app. dt, J 14.0, 2.1, one of CH₃CHO), 1.81–1.64 (4 H, m, one of MeCH₂CH, and three of CH₂CH₂CHO), 1.18 (1 H, dd, J 13.3, 11.1, 4.6, one of MeCH₂CH₂ and three of CH₂CH₂CHO), 1.08 (9 H, s, C(CH₃)₃) and 0.93 (3 H, d, J 7.0, CH₃), δC (100 MHz; CDCl₃) 135.7 (2 × CH), 135.7 (2 × CH), 133.0 (C), 132.9 (C), 132.9 (CH₁), 129.1 (2 × CH₂), 127.7 (4 × CH), 71.4 (CH), 69.0 (CH₂O), 45.8 (C), 45.7 (CH₂O), 39.7 (CH₂O), 35.4 (CH), 31.2 (CH₂O), 26.9 (CH₂CH₃), 25.3 (CH), 21.5 (CH), and 19.2 ((CH₃)₃C); m/z (TOF ES+) 422 (18) and 421 (MH⁺, 100%).

**Compound 12.** Colourless oil (Found: MH⁺, 421.2570. C₂₇H₃₇O₂Si requires M, 421.2563); νmax (neat)/cm⁻¹ 3360, 3030, 2943, 1649, 1590, 1461, 1390, 1108, 820, 744 and 697; δH (400 MHz; CDCl₃) 7.67–7.62 (4 H, m, aromatic CH), 7.45–7.35 (6 H, m, aromatic CH), 5.57 (1 H, app. broad d, J 10.1, CHCH=CH=CH), 5.49 (1 H, dd, J 10.1, 1.8, CHCH=CH=CH), 4.26–4.19 (1 H, m, CH₂O), 3.40 (4 H, m, MeCH₂, CH₂CH₃CH, and two of CH₂CH₂CHO), 1.70–1.55 (2 H, m, one of MeCH₂CH, and one of CH₂CH₂CHO), 1.51 (1 H, dd, J 13.4, 4.4, one of MeCH₂CH₂CHO, and one of CH₂CH₂CHO), 1.25–1.14 (1 H, m, one of MeCH₂CH₂CHO), 1.06 (9 H, s, C(CH₃)₃) and 0.97 (3 H, d, J 7.0, CH₃); δC (100 MHz; CDCl₃) 135.7 (2 × CH), 135.6 (2 × CH), 133.7 (CH), 133.6 (C), 133.6 (C), 132.8 (CH), 129.6 (CH₂O), 129.6 (CH₂O), 127.6 (4 × CH), 72.4 (CH), 69.0 (CH₂O), 46.6 (C), 44.6 (CH₂O), 40.0 (CH₂O), 36.8 (CH), 31.2 (CH₂O), 26.9 (CH₂CH₃), 25.3 (CH), 21.3 (CH), and 19.4 ((CH₃)₃C); m/z (TOF ES+) 422 (19) and 421 (MH⁺, 100%).

3-[2-(tert-Butyldimethylsilanyloxy)-3-chloropropyl]-3-(tert-butyldimethylsilanoloxymethyl)-cyclohexa-1,4-diene (15). t-Butyl dimethysilyl trifluoromethane sulfonate (0.48 ml, 2.07 mmol, 4.4 equiv.) was added to a solution of 1-chloro-3-(1-hydroxymethyl-dimethylsilyl trifluoromethane sulfonate (0.48 ml, 2.07 mmol, 4.4 equiv.) in dry benzene (15 ml). After heating the mixture to reflux, tributyltin hydride (0.14 ml, 0.52 mmol, 1.5 equiv.) was added and the resulting mixture was refluxed for 30 hours. The solvent was removed under reduced pressure to afford the crude product as a yellow oil (mixture of two isomers major : minor ratio 4.8 : 1.0). Purification by flash column chromatography over silica gel containing KF 10% w/w (eluting with ethyl acetate–hexane 0.6 : 9.4) afforded the title compound as a mixture of the two diastereoisomers (63 mg, 46%) as a pale yellow oil; νmax (neat)/cm⁻¹ 2928, 2856, 1464, 1255, 1094, 836, 774; δH (400 MHz; CDCl₃) 5.69–5.60 (2 H, m, CH=CH–CH₂, of both major and minor isomers), 5.44–5.36 (2 H, m, CH=CH–CH₂ of each isomer), 4.18 (1 H, app. quintet, J 5.6, CH–O of major isomer), 4.16–4.08 (1 H, m, CH–O of minor isomer), 3.43 and 3.40 (2 H, AB quartet, J 9.5, CH₃–O of major isomer), 3.26–3.23 (2 H, AB quartet, J 9.8, CH₂–O of minor isomer), 2.24 (1 H, app. tt, J 8.4, 4.1, ring junction CH of major isomer), 2.13–2.04 (1 H, m, ring junction CH of minor isomer), 2.01–1.78 (4 H, m, CH₂ one of each isomer), 1.73–1.38 (12 H, m, 3 × CH₃ of each isomer), 0.90 (9 H, s, 3 × CH₃ of minor isomer), 0.87 (9 H, s, 3 × CH₃ of major isomer), 0.85 (9 H, s, 3 × CH₃ of major isomer), 0.05 (3 H, s, one of CH₃–Si of minor isomer), 0.00 (18 H, s, 4 × CH₃–Si of major isomer and 2 × CH₃–Si of minor isomer), −0.05 (3 H, s, one of CH₃–Si of minor isomer); δC (100 MHz; CDCl₃) 133.7 (alkene CH of major isomer), 133.3 (alkene CH of minor isomer), 126.5 (alkene CH of major isomer), 125.5 (alkene CH of minor isomer), 72.3 (CH–O of major isomer), 72.0 (CH–O of minor isomer), 68.7 (CH₂–O of minor isomer), 46.2 (ring junction Cq of major isomer), 45.4 (ring junction Cq of minor isomer), 45.1 (CH₂ of major isomer), 44.3 (CH₃ of minor isomer), 39.7 (CH₃ of minor isomer), 39.5 (CH₃ of major isomer), 36.3 (ring junction CH of major isomer), 35.5 (ring junction CH of minor isomer), 25.9 (Si–Cq(CH₃)₃ of both isomers), 25.8 (Si–Cq(CH₃)₃ of major isomer), 23.7 (CH₃ of major isomer), 22.8 (CH₃ of minor isomer), 21.2 (CH₁ of minor isomer), 20.8 (CH₁ of major isomer), 18.4 (Si–Cq(CH₃)₃ of major isomer), 18.3 (Si–Cq(CH₃)₃ of minor isomer), 18.2 (Si–Cq(CH₃)₃ of both isomers), 13.7 (Si–Cq(CH₃)₃ of minor isomer), −4.7 (CH₃–Si), −4.7 (2 × CH₃–Si), −5.4 (CH₃–Si), −5.4 (CH₃–Si), −5.5 (CH₃–Si), −5.5 (CH₃–Si).
Triethylphosphine (660 mg, 2.52 mmol, 1.5 equiv.) and phthalimide (370 mg, 2.52 mmol, 1.5 equiv.) were added to a solution of alcohol 11 (705 mg, 1.68 mmol) in CH₂Cl₂ (15 mL). After the phosphine had dissolved, disopropyl azodicarboxylate (0.49 mL, 2.52 mmol, 1.5 equiv.) was added dropwise. The resulting yellow-orange solution was stirred for 20 min, concentrated in vacuo and chromatographed on silica (10% Et₂O in petroleum ether) to give the title compound (665 mg, 72%) as a colourless oil (Found: MH⁺, 550.2775. C₃₆H₄₀NO₃Si requires M, 550.2777; νmax (neat)/cm⁻¹: 3071, 2954, 2855, 1770, 1713, 1468, 1372 and 1105; δν (400 MHz; CDCl₃) 7.68–7.63 (4 H, m, aromatic CH), 7.45–7.35 (6 H, m, aromatic CH), 4.92 (1 H, d, J 9.7, one of CH₂O), 3.39 (1 H, d, J 9.9, one of CH₂O), 3.31–3.22 (1 H, m, one of CH₂O) and 0.74 (1 H, app. broad, d, J 10.0, one of CH₂O); m/z (TOF ES+) 551 (20%), 550 (MH⁺, 100) and 294 (14).

(2RS,3RS,5SR,7RS)-7a-((tert-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3a,4,5,7a-hexahydro-1H-inden-2-amine (18). Hydrazine hydrate (0.42 mL, 8.60 mmol, 4.5 equiv.) was added to a solution of phthalimide 17 (1.05 g, 1.91 mmol) in EtOH (15 mL) and the mixture heated to reflux. After 20 min, the resulting suspension was cooled and diluted with Et₂O (30 mL) with efficient stirring. The precipitate was removed by filtration and the filter cake washed with Et₂O. The filtrate was concentrated in vacuo to give the title compound (0.75 g, 94%) as an essentially-pure colourless oil (Found: MH⁺, 420.2733. C₂₇H₃₅NO₅Si requires M, 420.2723; νmax (CDCl₃)/cm⁻¹: 3364, 3070, 3002, 2930, 2856, 1459, 1428, 1110 and 703; δν (400 MHz; CDCl₃) 7.68–7.63 (4 H, m, aromatic CH), 7.45–7.35 (6 H, m, aromatic CH), 5.47 (1 H, app. broad d, J 10.1, CH₃CH=CH), 5.41 (1 H, dd, J 10.1, 1.5, CH(CH₃)₂CH=CH), 3.39 (1 H, d, J 9.7, one of CH₂O), 3.37 (1 H, d, J 9.7, one of CH₂O), 3.31–3.22 (1 H, m, CHN), 2.26 (1 H, dd, J 13.0, 8.1, one of CH₂CH₂N), 2.22–2.09 (2 H, m, MeCH and CH₂CH(CH₃)CH₂), 1.94 (1 H, app. d, J 12.5, 6.5, one of CH(CH₃)₂CH=CH), 1.71 (2 H, broad s, NH₂), 1.64–1.57 (1 H, m, one of MeCHCH=CH), 1.37 (1 H, app. td, J 11.9, 9.5, one of CH₂CH(CH₃)₂CH=CH), 1.21–1.13 (1 H, m, one of MeCH=CH), 1.15 (1 H, dd, J 13.0, 7.9, one of CH₂CH=CH), 1.05 (9 H, s, C(CH₃)₃) and 0.95 (3 H, d, J 7.0, CH₃) δν (100 MHz; CDCl₃) 135.7 (2 × CH), 135.7 (2 × CH), 133.7 (C), 133.7 (2 × CH), 132.8 (2 × CH), 129.5 (2 × CH), 127.6 (4 × CH), 69.5 (CH), 51.0 (CH), 46.2 (C), 45.8 (CH₂), 40.9 (CH₃), 37.9 (CH₃), 31.4 (CH₃), 26.9 (CH₃), 25.6 (CH₃), 21.5 (CH₃) and 19.4 (C); m/z (TOF ES+) 461 (MH⁺-CH₂CH₂, 36%) and 420 (MH⁺+, 100).

N-(2RS,3RS,5SR,7RS)-7a-((tert-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3a,4,5,7a-hexahydro-1H-inden-2-yl)isoindoline-1,3-dione (17). Triethylamine (0.37 mL, 2.69 mmol, 1.5 equiv.) was added to a solution of amine 18 (0.75 g, 1.79 mmol) in CH₂Cl₂ (10 mL). 4-Nitrobenzenesulfonyl chloride (0.52 g, 2.33 mmol, 1.3 equiv.) was added and the resulting solution stirred overnight. The solution was then concentrated in vacuo and purified by chromatography on silica (10% to 20% ethyl acetate in petroleum ether) to give the title compound (437 mg, 91%) as a colourless solid, m.p. 173–175 °C (Found: MH⁺, 713.1436. C₃₆H₃₄NO₅Si requires M, 713.1472; νmax (CH₂Cl₂)/cm⁻¹: 3071, 2954, 2857, 1533, 1351, 1155 and 1109; δν (400 MHz; CDCl₃) 8.18 (2 H, d, J 8.8, aromatic CH), 7.96 (2 H, d, J 8.8, aromatic CH), 7.52–7.47 (4 H, m, aromatic CH), 7.45–7.27 (6 H, m, aromatic CH), 4.92 (1 H, app. broad s, CH₂), 4.19 (1 H, d, J 10.7, one of CH₂O), 3.99 (1 H, app. d, J 2.2, CH₂CH=CH), 3.92 (1 H, app. broad s, CH₁, 3.71 (1 H, d, J 10.7, one of CH₂O), 1.91–1.85 (2 H, m, CH₂CH=CH), and one of CH₂O), 1.80–1.71 (1 H, m, one of CH₂CH=CH), 1.61–1.50 (1 H, m, CHMe), 1.29–1.10 (2 H, m, MeCHCH=CH), 0.99–0.94 (13 H, m, CH₂), 0.95 (CH₃), (C), and one of CH₂CH=CH) and 0.74 (1 H, app. broad d, J 10.3, one of CH₂CH=CH), δν (100 MHz; CDCl₃) 150.0 (C), 143.2 (C), 135.8 (2 × CH), 135.6 (2 × CH), 133.3 (C), 132.9 (C), 129.8 (CH), 129.8 (CH), 128.8 (2 × CH), 127.6 (2 × CH), 127.5 (2 × CH), 124.5 (2 × CH), 65.4 (CH₂), 64.2 (CH₂), 59.6 (CH), 52.5 (C), 43.1 (CH), 40.7 (CH), 37.0 (CH), 34.1 (CH), 29.3 (CH₂), 26.9 (CH₃), 24.1 (CH and CH₂) and 19.3 (C); m/z (TOF ES+), 731.1472, 704, 614, 589, 550, 526, 503, 481, 459, 437, and 425 (M+). The IR and NMR spectra are consistent with those expected for the product.
...were added to a solution of amine (21). After stirring overnight, the solution was concentrated in vacuo and purified by chromatography on silica. The title compound was obtained in 84% yield as a colourless solid. 

CHCl₃ (10 mL) was added to a solution of acetophenone (0.06 mmol) in benzene (10 mL). The solution was treated with a spatula. After stirring for 30 min, a 1 mL aliquot of the reaction mixture was added dropwise to a solution of sulfonamide (33 mg, 0.06 mmol) in benzene (10 mL). The solution was concentrated in vacuo and purified by chromatography on silica. The title compound was obtained in 84% yield as a colourless solid. 

**N-((2SR,3aRS,5SR,7aRS)-7a-((tert-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3,4,5,6-pentahydro-1H-inden-2-yl)-toluenesulfonylamide (21).** Triethylamine (0.11 mL, 0.83 mmol, 1.5 equiv.) and 4-toluenesulfonyl chloride (126 mg, 0.66 mmol, 1.2 equiv.) were added to a solution of amine (21) (230 mg, 0.55 mmol) in CH₂Cl₂ (10 mL). After stirring overnight, the solution was concentrated in vacuo and purified by chromatography on silica to give the title compound (265 mg, 84%) as a colourless oil. 

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**N-((2RS,3aRS,6RS,7RS,7aRS)-7a-((tert-Butyldiphenylsilyloxy)methyl)-6-methyl-1-(4-toluenesulfonyl)-2,4-methanooctahydroindole (23).** Bu₂SnH (0.15 mL, 0.57 mmol, 10 equiv.) and AIBN (25 mg, 0.15 mmol, 2.7 equiv.) were added to a solution of iodide (22) (40 mg, 0.06 mmol) in benzene (10 mL). The solution was heated to reflux overnight, concentrated in vacuo and purified by chromatography on silica containing approx. 10% NaF (10% ethyl acetate in petroleum ether) to give the title compound (33 mg, 100%) as a pale oil. 

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**N-((2RS,3aRS,6RS,7RS,7aRS)-3a-((tert-Butyldiphenylsilyloxy)methyl)-6-methyl-1-(4-toluenesulfonyl)-2,4-methanooctahydroindole (24).** Sodium hydride (110 mg, 1.31 mmol, 3 equiv.) and iodine (332 mg, 1.31 mmol, 3 equiv.) were added to a solution of sulfonamide (21) (250 mg, 0.44 mmol) in acetonitrile (5 mL). After stirring overnight, the solution was quenched by the addition of saturated aqueous Na₂SO₄ solution (10 mL). The organic layer separated and the aqueous phase extracted with Et₂O (2 × 10 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by chromatography on silica (10% ethyl acetate in petroleum ether) to give the title compound (210 mg, 69%) as a colourless solid.
CCH(CH)_3, 1.85 (1 H, app. td, J 12.2, 2.8, one of CHCH(N), 1.86–1.75 (1 H, m, CHCH(N)), 1.71 (1 H, app. dt, J 9.3, 2.2, one of CCH(CH)), 1.62 (1 H, app. broad d, J 14.3, one of CCHCH), 1.55 (1 H, d, J 9.3, one of CCHCH)), 1.45 (1 H, br. d, J 13.7, one of CHCH), 1.35 (1 H, dt, J 12.5, 3.4, one of CHCH(N)), 1.05 (9 H, s, C(CH_3)_3), 0.98–0.88 (2 H, m, one of CHCH and one of CCHCH), 0.85 (3 H, d, J 6.5, CH_3); δ_c (125 MHz; CDCl_3) 135.7 (4 × CH), 133.8 (2 × C), 129.6 (2 × CH), 127.6 (4 × CH), 123.8 (CH_2), 120.5 (CH_2), 56.0 (CH), 55.2 (CH), 49.8 (C), 44.9 (CH_2), 38.2 (CH_3), 34.6 (CH_2), 34.1 (CH), 33.3 (CH_2), 26.9 (CH_2), 21.9 (CH), 19.7 (CH), 19.4 (C); m/z (TOF ES+) 422 (10%), 421 (35) and 420 (MH^+, 100).

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Notes and references

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