

# Concise synthesis of the tricyclic core of lycoposerramine S†‡

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Received 18th March 2008, Accepted 14th April 2008

First published as an Advance Article on the web 16th May 2008

DOI: 10.1039/b804664f

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<sup>1</sup> is a structurally-fascinating group of compounds which includes fawcettimine (**1**) itself along with various other alkaloids including lycoposerramines S<sup>2</sup> (**2**) and A<sup>3</sup> (**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,<sup>4</sup> most notably by Heathcock in a landmark 1986 synthesis, and only very recently has the first enantioselective total synthesis been reported.<sup>5</sup>

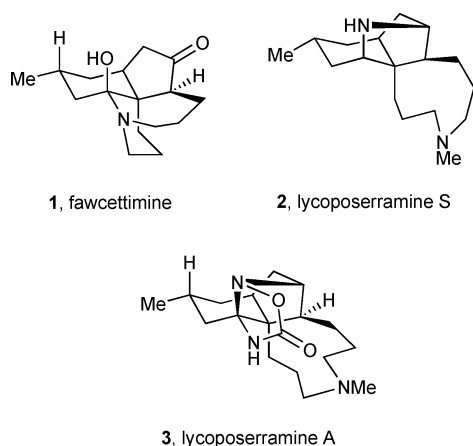


Fig. 1 Fawcettimine and lycoposerramine alkaloids.

These compounds are structurally-related to magellanine and paniculatine, which have been synthesised a number of times.<sup>6</sup> However, to date the only synthetic work on this structural group<sup>7</sup>

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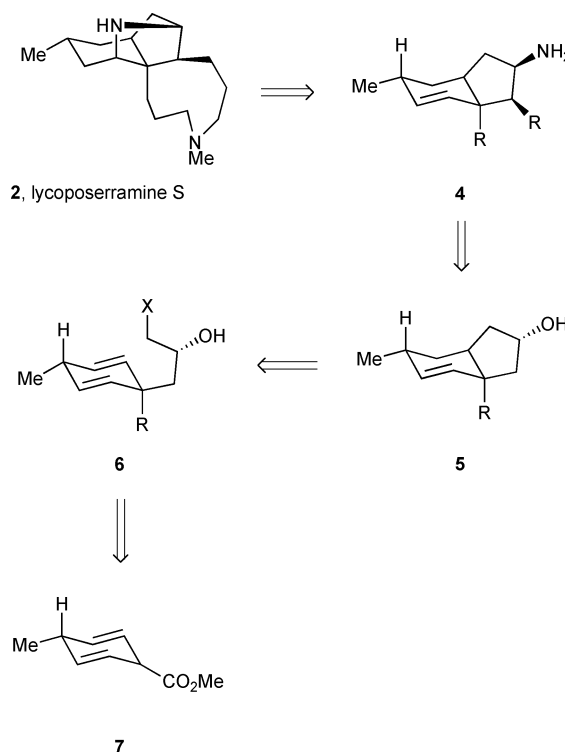
† Dedicated to Professor Andreas Pfaltz on the occasion of his 60th birthday.

‡ Electronic supplementary information (ESI) available: Copies of proton and carbon NMR spectra of new compounds. See DOI: 10.1039/b804664f

of lycoposerramine alkaloids is the conversion of serratinine into lycoposerramine B reported by Takayama and co-workers.<sup>8</sup>

## Results and discussion

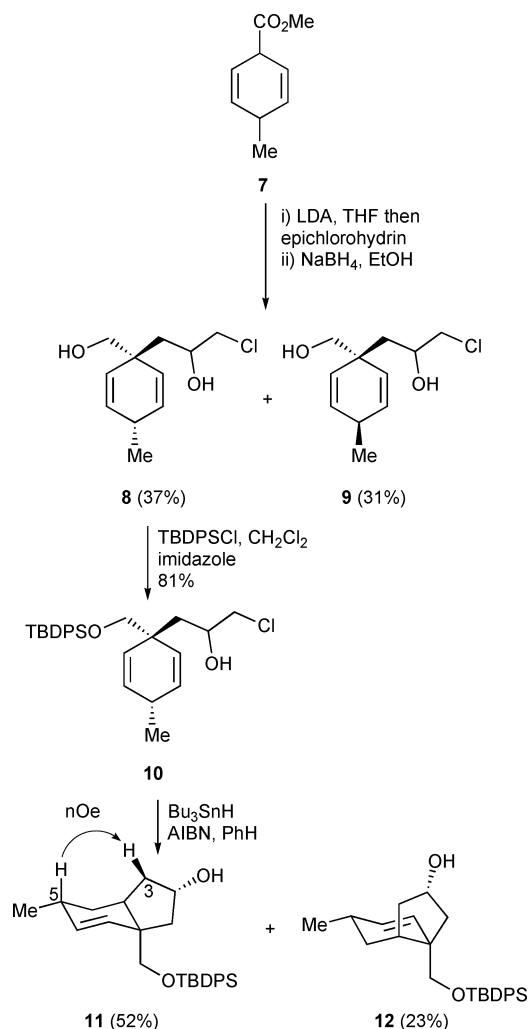
We have recently reported that desymmetrisation reactions of cyclohexa-1,4-dienes<sup>9</sup> provide convenient access to 6–5 fused ring systems containing quaternary stereogenic centres, and have demonstrated the application of free-radical<sup>10</sup> and halocyclisation methodology<sup>11</sup> in this context. Other related work includes the application of chiral sulfoxides to this process,<sup>12</sup> and also a novel Prins-pinacol sequence.<sup>13</sup> 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).<sup>14</sup> We now



Scheme 1 Retrosynthetic analysis of lycoposerramine S.

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.<sup>14</sup> 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).

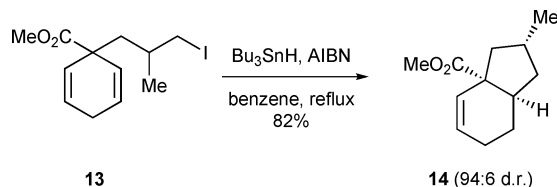


**Scheme 2** Synthesis of the carbobicyclic core.

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 H3 $\beta$  as shown on structure **11**. A similar NOE was used to assign the natural product stereochemistry.<sup>2</sup>

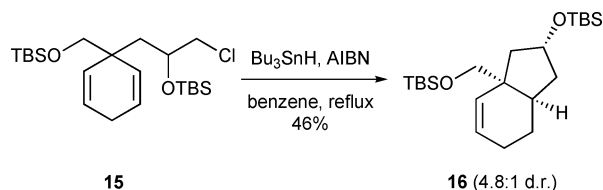
### Stereoselectivity of the free-radical cyclisation

The modest level of diastereocontrol 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).<sup>15</sup>



**Scheme 3** Related cyclisation from the work of Curran.<sup>15</sup>

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).



**Scheme 4** Free-radical cyclisation of a double-protected substrate.

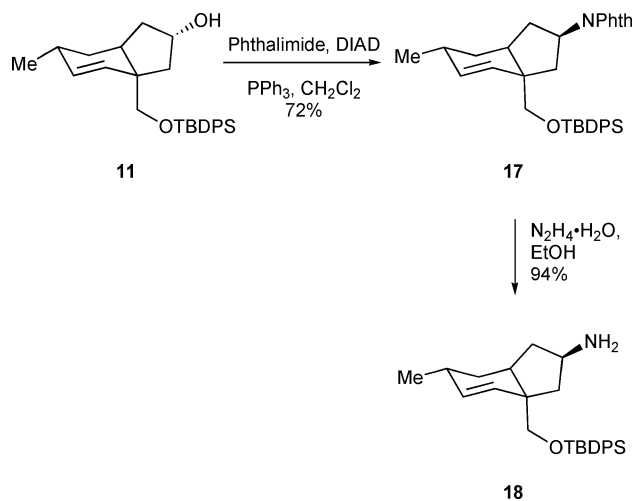
It is therefore clear that the lower stereoselectivity results from electronic as well as steric factors. We considered the various methods by which we might improve the stereochemistry of this step. A diastereoselectivity of 2 : 1 at 80 °C corresponds to an energy difference of approximately 2 kJ mol<sup>-1</sup> 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 diastereocontrol.

The stereochemical assignment of the free-radical cyclisation was initially made by analogy with cyclisation reactions reported by ourselves<sup>11</sup> and by Curran.<sup>15</sup> This was eventually confirmed by completion of the tricyclic core of the natural product (*vide infra*).

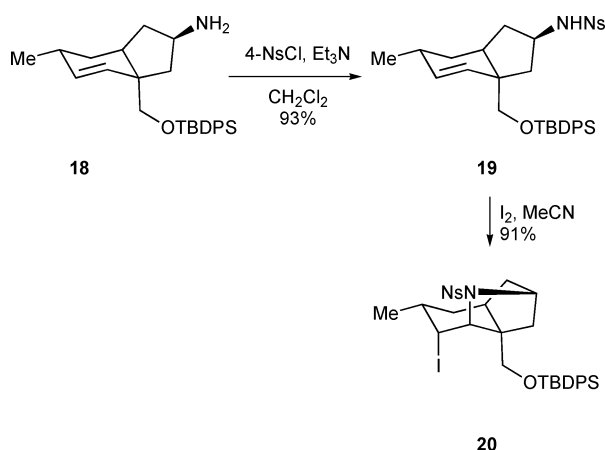
### Completion of the tricyclic core of lycoposerramine S

From this point, displacement of the secondary alcohol under Mitsunobu conditions<sup>16</sup> was followed by deprotection to give primary amine **18** (Scheme 5). It should be noted that formation of the 4-toluenesulfonate ester from compound **11** under standard conditions (TsCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub> and NaH, THF then TsCl) failed.

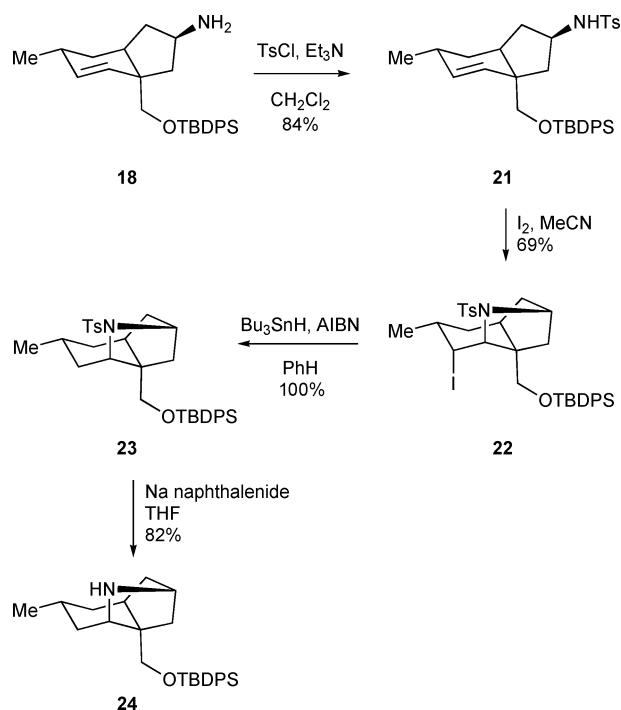


**Scheme 5** Introduction of nitrogen.

Attempts to prepare compound **24** by direct aminomercuration<sup>17</sup> of compound **18** gave only recovery of starting material. Nosyl amide **19** was therefore prepared from compound **18**. This underwent smooth iodocyclisation<sup>18</sup> to give compound **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 **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 **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



**Scheme 6** Iodocyclisation to form the pyrrolidine ring.



**Scheme 7** Completion of the tricyclic core of lycoposerramine S.

by Komeyama *et al.*<sup>19</sup> 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 **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.

**Table 1** Comparison of NMR data of compound **24** with lycoposerramine S

	2, lycoposerramine S	<b>24</b>
	Lycoposerramine S ( <b>2</b> )	Compound <b>24</b>
C4	50.5 (CH)	44.9 (CH <sub>2</sub> )
C5	60.2	56.0
C6	35.6	38.2
C7	35.0	34.1
C8	33.0	33.3
C12	49.5	49.8
C13	59.0	55.2
C14	33.7	34.6
C15	20.7	19.7
C16	22.1	21.9

## Conclusions

In summary, compound **24** has been prepared in a 12 step sequence from toluic acid. Studies towards the completion of lycoposerramine 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 on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for  $^1\text{H}$  and at 100 MHz for  $^{13}\text{C}$  at 25 °C, or on a Bruker Avance 500 spectrometer operating at 500 MHz for  $^1\text{H}$  and 125 MHz for  $^{13}\text{C}$  at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants ( $J$ ) are reported in Hz. Multiplicity in  $^1\text{H}$ -NMR is reported as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double quartet (dq), triplet (t), and multiplet (m). Multiplicity in  $^{13}\text{C}$  NMR was obtained using the DEPT pulse sequence. Flash chromatography was performed using Matrex silica 60 35–70 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, 1.1 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-carboxylate<sup>14</sup> (4.91 g, 32.3 mmol) was added dropwise. After stirring for 30 min, epichlorohydrin (3.3 mL, 42 mmol, 1.3 equiv.) was added and the reaction allowed to warm to 5 °C over 3 h. Saturated aqueous  $\text{NH}_4\text{Cl}$  (75 mL) was added and after stirring for a few minutes the organic layer was separated and the aqueous layer extracted with  $\text{Et}_2\text{O}$  (2 × 30 mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to afford the crude intermediate lactone (7.72 g) as an orange oil. This lactone was dissolved in ethanol (200 mL) and  $\text{NaBH}_4$  (2.45 g, 64.6 mmol, 2 equiv.) added in one portion. The exothermic reaction was allowed to subside and stirring continued for 1 h before quenching with glacial acetic acid (3 mL). The solvent was removed *in vacuo* and the residue partitioned between saturated aqueous  $\text{NaHCO}_3$  (200 mL) and ethyl acetate (100 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 75 mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The residue was purified by chromatography on  $\text{SiO}_2$  (50%  $\text{Et}_2\text{O}$  in petroleum ether) to give compound **8** (2.57 g, 37%) followed by the compound **9** (2.15 g, 31%), both as colourless oils.

**Compound 8**. Colourless oil (Found:  $\text{MH}^+ - \text{CH}_3\text{OH}$ , 184.0667.  $\text{C}_{11}\text{H}_{13}\text{ClO}$  requires M, 184.0655);  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3364, 2958, 2869, 1516, 1429, 1047, 803 and 743;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.89 (1 H, ddd,  $J$  10.2, 3.1, 1.9, one of  $\text{CHCH}=\text{CH}$ ), 5.87 (1 H, ddd,  $J$  10.2, 3.1, 1.9, one of  $\text{CHCH}=\text{CH}$ ), 5.58 (1 H, app. dt,  $J$

10.2, 2.1, one of  $\text{CHCH}=\text{CH}$ ), 5.39 (1 H, app. dt,  $J$  10.2, 2.1, one of  $\text{CHCH}=\text{CH}$ ), 3.94 (1 H, m,  $\text{CHOH}$ ), 3.53 (1 H, dd,  $J$  11.1, 4.1, one of  $\text{CH}_2\text{Cl}$ ), 3.45 (1 H, dd,  $J$  11.1, 6.5, one of  $\text{CH}_2\text{Cl}$ ), 3.36 (1 H, app. broad d,  $J$  11.4, one of  $\text{CH}_2\text{OH}$ ), 3.34 (1 H, app. broad d,  $J$  11.4, one of  $\text{CH}_2\text{OH}$ ), 2.83 (1 H, d,  $J$  3.1,  $\text{CHOH}$ ), 2.81–2.73 (1 H, m,  $\text{CHCH}_3$ ), 2.11 (1 H, t,  $J$  5.8,  $\text{CH}_2\text{OH}$ ), 1.64 (1 H, dd,  $J$  14.3, 8.1, one of  $\text{CH}_2\text{CHOH}$ ), 1.55 (1 H, dd,  $J$  14.3, 3.4, one of  $\text{CH}_2\text{CHOH}$ ) and 1.08 (3 H, d,  $J$  7.3,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 134.3 (CH), 134.0 (CH), 128.3 (CH), 128.1 (CH), 69.9 ( $\text{CH}_2$ ), 69.0 (CH), 50.2 ( $\text{CH}_2$ ), 42.2 (C), 41.8 ( $\text{CH}_2$ ), 30.9 (CH) and 22.3 ( $\text{CH}_3$ );  $m/z$  (TOF ES+) 184 (M –  $\text{CH}_3\text{OH}$ , 17%) and 167 (100).

**Compound 9**. Colourless oil (Found:  $\text{MH}^+ - \text{CH}_3\text{OH}$ , 184.0655.  $\text{C}_{11}\text{H}_{13}\text{ClO}$  requires M, 184.0655);  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3412, 2957, 1516, 1454, 1048, 805 and 748;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.94–5.86 (2 H, m,  $\text{CHCH}=\text{CH}$ ), 5.61–5.55 (1 H, m, one of  $\text{CHCH}=\text{CH}$ ), 5.42–5.37 (1 H, m, one of  $\text{CHCH}=\text{CH}$ ), 3.94 (1 H, app. ddt,  $J$  8.0, 6.4, 3.8,  $\text{CHOH}$ ), 3.55 (1 H, dd,  $J$  11.1, 4.1, one of  $\text{CH}_2\text{Cl}$ ), 3.45 (1 H, dd,  $J$  11.1, 6.4, one of  $\text{CH}_2\text{Cl}$ ), 3.37 (2 H, app. s,  $\text{CH}_2\text{OH}$ ), 2.83–2.73 (1 H, m,  $\text{MeCH}$ ), 2.70 (1 H, broad s, OH), 2.01 (1 H, broad s, OH), 1.64 (1 H, dd,  $J$  14.3, 8.0, one of  $\text{CH}_2\text{CHOH}$ ), 1.54 (1 H, dd,  $J$  14.3, 3.5, one of  $\text{CH}_2\text{CHOH}$ ) and 1.09 (3 H, d,  $J$  7.3,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 134.4 (CH), 134.0 (CH), 128.2 (CH), 128.1 (CH), 70.2 ( $\text{CH}_2$ ), 69.0 (CH), 50.2 ( $\text{CH}_2$ ), 42.2 ( $\text{CH}_2$ ), 41.6 (C), 30.8 (CH) and 21.9 ( $\text{CH}_3$ );  $m/z$  (TOF ES+) 184 (M –  $\text{CH}_3\text{OH}$ , 21%) and 167 (100).

**1,4-cis-1-(3-Chloro-2-hydroxypropyl)-1-(tert-butylidiphenylsilyloxymethyl)-4-methylcyclohexa-2,5-diene (10)**. Imidazole (1.68 g, 26.2 mmol, 2.2 equiv.) and TBDPSCI (3.4 mL, 13.1 mmol, 1.1 equiv.) were added to a solution of diol **8** (2.57 g, 11.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL). After stirring overnight, the reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (30 mL) and the organic layer separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 × 15 mL) and the combined organic extracts dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The residue was purified by chromatography on  $\text{SiO}_2$  (10%  $\text{Et}_2\text{O}$  in petroleum ether) to give the *title compound* (4.35 g, 81%) as a colourless viscous oil (Found:  $\text{MH}^+$ , 455.2190.  $\text{C}_{27}\text{H}_{36}\text{ClO}_2\text{Si}$  requires M, 455.2173);  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3420, 3072, 2931, 2858, 1590, 1516, 1470, 1428, 1390, 1362, 1303, 1261 and 1111;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.66–7.63 (4 H, m, aromatic CH), 7.45–7.35 (6 H, m, aromatic CH), 5.83–5.77 (2 H, m,  $\text{CHCH}=\text{CH}$ ), 5.69 (1 H, app. dt,  $J$  10.0, 1.9, one of  $\text{CHCH}=\text{CH}$ ), 5.49 (1 H, app. dt,  $J$  10.0, 1.9, one of  $\text{CHCH}=\text{CH}$ ), 3.97–3.91 (1 H, m,  $\text{CHOH}$ ), 3.55 (1 H, dd,  $J$  11.0, 4.2, one of  $\text{CH}_2\text{Cl}$ ), 3.48 (1 H, dd,  $J$  11.0, 6.3, one of  $\text{CH}_2\text{Cl}$ ), 3.44 (1 H, d,  $J$  10.3, one of  $\text{CH}_2\text{O}$ ), 3.42 (1 H, d,  $J$  10.3, one of  $\text{CH}_2\text{O}$ ), 2.80–2.73 (1 H, m,  $\text{CHCH}_3$ ), 2.60–2.50 (1 H, broad s, OH), 1.80–1.72 (2 H, m,  $\text{CH}_2\text{CH}(\text{OH})$ ), 1.06 (9 H, s, ( $\text{CH}_3$ )<sub>3</sub>C) and 1.02 (3 H, d,  $J$  7.3,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (125 MHz;  $\text{CDCl}_3$ ) 135.7 (4 × CH), 133.3 (C), 133.3 (C) 132.7 (CH), 132.4 (CH), 129.7 (2 × CH), 129.4 (CH), 128.6 (CH), 127.6 (4 × CH), 72.5 ( $\text{CH}_2$ ), 69.6 (CH), 50.2 ( $\text{CH}_2$ ), 42.0 ( $\text{CH}_2$ ), 41.7 (C), 31.1 (CH), 26.9 ( $\text{CH}_3$ ), 22.0 ( $\text{CH}_3$ ) and 19.4 (C);  $m/z$  (TOF ES+) 457 (26%), 455 ( $\text{MH}^+$ , 100), 280 (12) and 199 (10).

**(2*RS*,3*aRS*,5*SR*,7*aRS*)-7*a*-((*tert*-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-inden-2-ol (11)** and **(2*SR*,3*aRS*,5*SR*,7*aRS*)-7*a*-((*tert*-butyldiphenylsilyloxy)methyl)-5-methyl-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-inden-2-ol (12)**. A solution of chloride **10** (2.43 g, 5.35 mmol) in benzene (40 mL) was heated

to reflux and solutions of AIBN (88 mg, 0.54 mmol, 0.1 equiv.) and  $\text{Bu}_3\text{SnH}$  (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:  $\text{MH}^+$ , 421.2605.  $\text{C}_{27}\text{H}_{37}\text{O}_2\text{Si}$  requires M, 421.2563);  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3361, 3071, 2952, 1657, 1464, 1428, 1391, 1110, 822, 743 and 703;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 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,  $\text{CHCH}=\text{CH}$ ), 5.26 (1 H, app. broad dd,  $J$  10.1, 2.4,  $\text{CHCH}=\text{CH}$ ), 4.19 (1 H, app. tt,  $J$  4.6, 2.2,  $\text{CHOH}$ ), 3.40 (2 H, app. s,  $\text{CH}_2\text{O}$ ), 2.63–2.54 (1 H, m,  $\text{CH}_2\text{CHCH}_2$ ), 2.16–2.08 (1 H, m,  $\text{MeCH}$ ), 1.95 (1 H, app. dt,  $J$  14.0, 2.1, one of  $\text{CH}_2\text{CHO}$ ), 1.81–1.64 (4 H, m, one of  $\text{MeCHCH}_2$  and three of  $\text{CH}_2\text{CHO}$ ), 1.18 (1 H, ddd,  $J$  13.3, 11.1, 4.6, one of  $\text{MeCHCH}_2$ ), 1.08 (9 H, s,  $\text{C}(\text{CH}_3)_3$ ) and 0.93 (3 H, d,  $J$  7.0,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 135.7 ( $2 \times \text{CH}$ ), 135.7 ( $2 \times \text{CH}$ ), 133.0 (C), 132.9 (C), 132.9 (CH), 131.5 (CH), 129.8 ( $2 \times \text{CH}$ ), 127.7 ( $4 \times \text{CH}$ ), 71.4 (CH), 69.0 ( $\text{CH}_2$ ), 45.8 (C), 45.7 ( $\text{CH}_2$ ), 39.7 ( $\text{CH}_2$ ), 35.4 (CH), 31.2 ( $\text{CH}_2$ ), 26.9 ( $(\text{CH}_3)_3\text{C}$ ), 25.3 (CH), 21.5 ( $\text{CH}_3$ ) and 19.2 ( $(\text{CH}_3)_3\text{C}$ );  $m/z$  (TOF ES+) 422 (18) and 421 ( $\text{MH}^+$ , 100%).

**Compound 12.** Colourless oil (Found:  $\text{MH}^+$ , 421.2570.  $\text{C}_{27}\text{H}_{37}\text{O}_2\text{Si}$  requires M, 421.2563);  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  3360, 3030, 2943, 1649, 1590, 1461, 1425, 1390, 1108, 820, 744 and 697;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 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,  $\text{CHCH}=\text{CH}$ ), 5.49 (1 H, dd,  $J$  10.1, 1.8,  $\text{CHCH}=\text{CH}$ ), 4.26–4.19 (1 H, m,  $\text{CHOH}$ ), 3.41 (1 H, d,  $J$  9.8,  $\text{CH}_2\text{O}$ ), 3.38 (1 H, d,  $J$  9.8,  $\text{CH}_2\text{O}$ ), 2.26–2.13 (4 H, m,  $\text{MeCH}$ ,  $\text{CH}_2\text{CHCH}_2$  and two of  $\text{CH}_2\text{CHO}$ ), 1.70–1.55 (2 H, m, one of  $\text{MeCHCH}_2$  and one of  $\text{CH}_2\text{CHO}$ ), 1.51 (1 H, dd,  $J$  13.4, 4.4, one of  $\text{CH}_2\text{CHO}$ ), 1.25–1.14 (1 H, m, one of  $\text{MeCHCH}_2$ ), 1.06 (9 H, s,  $\text{C}(\text{CH}_3)_3$ ) and 0.97 (3 H, d,  $J$  7.0,  $\text{CH}_3$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 135.7 ( $2 \times \text{CH}$ ), 135.6 ( $2 \times \text{CH}$ ), 133.7 (CH), 133.6 (C), 133.6 (C), 132.8 (CH), 129.6 (CH), 129.6 (CH), 127.6 ( $4 \times \text{CH}$ ), 72.4 (CH), 69.0 ( $\text{CH}_2$ ), 46.6 (C), 44.6 ( $\text{CH}_2$ ), 40.0 ( $\text{CH}_2$ ), 36.8 (CH), 31.2 ( $\text{CH}_2$ ), 26.9 ( $(\text{CH}_3)_3\text{C}$ ), 25.5 (CH), 21.3 ( $\text{CH}_3$ ) and 19.4 ( $(\text{CH}_3)_3\text{C}$ );  $m/z$  (TOF ES+) 422 (19) and 421 ( $\text{MH}^+$ , 100%).

**3-[2-(*tert*-Butyldimethylsilyloxy)-3-chloropropyl]-3-(*tert*-butyldimethylsilyloxymethyl)-cyclohexa-1,4-diene (15).** *t*-Butyldimethylsilyl trifluoromethane sulfonate (0.48 ml, 2.07 mmol, 4.4 equiv.) was added to a solution of 1-chloro-3-(1-hydroxymethylcyclohexa-2,5-dienyl)-propan-2-ol<sup>11</sup> (95 mg, 0.47 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (15 ml). 2,6-Lutidine (0.33 ml, 2.8 mmol, 6.0 equiv.) was added and the resulting mixture was stirred at room temperature and under a nitrogen atmosphere for 3 days. Aqueous 2 M HCl solution (10 ml) was added and the organic material was extracted into  $\text{CH}_2\text{Cl}_2$  ( $3 \times 15$  ml). The combined extracts were dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford brown oil. Purification by flash chromatography (eluting with ethyl acetate–hexane 0.5 : 9.5) afforded the *title compound* (185 mg, 91%) as a colourless oil;  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ )/ $\text{cm}^{-1}$  2956, 2885, 2856, 1472, 1256, 1094, 940, 837, 775;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.84–5.78 (2 H, m,  $2 \times \text{CH}=\text{CH}-\text{CH}_2$ ), 5.53 (1 H, app. dq,  $J$  10.3, 2.0,

one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 5.41 (1 H, app. dq,  $J$  10.3, 2.1 one of  $\text{CH}=\text{CH}-\text{CH}_2$ ), 3.84–3.77 (1 H, m,  $\text{CH}-\text{O}$ ), 3.59 (1 H, dd,  $J$  11.1, 3.2, one of  $\text{CH}_2-\text{Cl}$ ), 3.38 (1 H, dd,  $J$  11.1, 6.1, one of  $\text{CH}_2-\text{Cl}$ ), 3.29 (2 H, app. s,  $\text{CH}_2-\text{O}$ ), 2.66–2.61 (2 H, m, ring  $\text{CH}_2$ ), 1.79 (1 H, dd,  $J$  14.4, 3.8, one of  $\text{CH}_2-\text{C}_q$ ), 1.72 (1 H, dd,  $J$  14.4, 8.1, one of  $\text{CH}_2-\text{C}_q$ ), 0.88 (9 H, s,  $\text{Si}-\text{C}_q(\text{CH}_3)_3$ ), 0.86 (9 H, s,  $\text{Si}-\text{C}_q(\text{CH}_3)_3$ ), 0.07 (3 H, s, one of  $\text{CH}-\text{O}-\text{Si}(\text{CH}_3)_2$ ) (3 H, s, one of  $\text{CH}-\text{O}-\text{Si}(\text{CH}_3)_2$ ), 0.00 (6 H, s,  $\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_2$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 130.6 (alkene CH), 130.1 (alkene CH), 125.8 (alkene CH), 125.3 (alkene CH), 71.7 ( $\text{CH}_2-\text{Cl}$ ), 70.8 ( $\text{CH}-\text{O}$ ), 50.6 ( $\text{CH}_2-\text{O}$ ), 42.5 ( $\text{CH}_2-\text{C}_q$ ), 41.1 (ring  $\text{C}_q$ ), 26.7 (ring  $\text{CH}_2$ ), 25.9 ( $2 \times \text{Si}(\text{CH}_3)_3$ ), 18.3 ( $\text{Si}-\text{C}_q(\text{CH}_3)_3$ ), 18.1 ( $\text{Si}-\text{C}_q(\text{CH}_3)_3$ ), -4.3 ( $\text{Si}-\text{CH}_3$ ), -4.5 ( $\text{Si}-\text{CH}_3$ ), -5.4 ( $\text{Si}-\text{CH}_3$ ), -5.5 ( $\text{Si}-\text{CH}_3$ ).

**(2*RS*,3*aRS*,7*aRS*)-2-(*tert*-Butyldimethylsilyloxy)-7*a*-(*tert*-butyldimethylsilyloxymethyl)-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-indene (16).** AIBN (85 mg, 0.52 mmol, 1.5 equiv.) was added to a solution of compound **15** (148 mg, 0.34 mmol, 1.0 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;  $\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$  2928, 2856, 1464, 1255, 1094, 836, 774;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.69–5.60 (2 H, m,  $\text{CH}=\text{CH}-\text{CH}_2$ , of both major and minor isomers), 5.44–5.36 (2 H, m,  $\text{CH}=\text{CH}-\text{CH}_2$  of each isomer), 4.18 (1 H, app. quintet,  $J$  5.6,  $\text{CH}-\text{O}$  of major isomer), 4.16–4.08 (1 H, m,  $\text{CH}-\text{O}$  of minor isomer), 3.43 and 3.40 (2 H, AB quartet,  $J$  9.5,  $\text{CH}_2-\text{O}$  of major isomer), 3.26–3.23 (2 H, AB quartet,  $J$  9.8,  $\text{CH}_2-\text{O}$  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,  $\text{CH}_2$  one of each isomer), 1.73–1.38 (12 H, m,  $3 \times \text{CH}_2$  of each isomer), 0.90 (9 H, s,  $3 \times \text{CH}_3$  of minor isomer), 0.87 (9 H, s,  $3 \times \text{CH}_3$  of minor isomer), 0.87 (9 H, s,  $3 \times \text{CH}_3$  of major isomer), 0.85 (9 H, s,  $3 \times \text{CH}_3$  of major isomer), 0.05 (3 H, s, one of  $\text{CH}_3-\text{Si}$  of minor isomer), 0.00 (18 H, s,  $4 \times \text{CH}_3-\text{Si}$  of major isomer and  $2 \times \text{CH}_3-\text{Si}$  of minor isomer), -0.05 (3 H, s, one of  $\text{CH}_3-\text{Si}$  of minor isomer);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 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 ( $\text{CH}-\text{O}$  of major isomer), 72.0 ( $\text{CH}-\text{O}$  of minor isomer), 70.2 ( $\text{CH}_2-\text{O}$  of major isomer), 68.7 ( $\text{CH}_2-\text{O}$  of minor isomer), 46.2 (ring junction  $\text{C}_q$  of major isomer), 45.4 (ring junction  $\text{C}_q$  of minor isomer), 45.1 ( $\text{CH}_2$  of major isomer), 44.3 ( $\text{CH}_2$  of minor isomer), 39.7 ( $\text{CH}_2$  of minor isomer), 39.5 ( $\text{CH}_2$  of major isomer), 36.3 (ring junction CH of major isomer), 35.5 (ring junction CH of minor isomer), 25.9 ( $\text{Si}-\text{C}_q(\text{CH}_3)_3$  of both isomers), 25.8 ( $\text{Si}-\text{C}_q(\text{CH}_3)_3$  of major isomer), 23.7 ( $\text{CH}_2$  of major isomer), 22.8 ( $\text{CH}_2$  of minor isomer), 21.2 ( $\text{CH}_2$  of minor isomer), 20.8 ( $\text{CH}_2$  of major isomer), 18.4 ( $\text{Si}-\text{C}_q(\text{CH}_3)_3$  of major isomer), 18.3 ( $\text{Si}-\text{C}_q(\text{CH}_3)_3$  of minor isomer), 18.2 ( $\text{Si}-\text{C}_q(\text{CH}_3)_3$  of both isomers), 13.7 ( $\text{Si}-\text{C}_q(\text{CH}_3)_3$  of minor isomer), -4.7 ( $\text{CH}_3-\text{Si}$ ), -4.7 ( $2 \times \text{CH}_3-\text{Si}$ ), -5.4 ( $\text{CH}_3-\text{Si}$ ), -5.4 ( $\text{CH}_3-\text{Si}$ ), -5.4 ( $\text{CH}_3-\text{Si}$ ), -5.5 ( $\text{CH}_3-\text{Si}$ ), -5.5 ( $\text{CH}_3-\text{Si}$ ).

**2-((2SR,3aRS,5SR,7aRS)-7a-((tert-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1H-inden-2-yl)isoindoline-1,3-dione (17)**

Triphenylphosphine (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 CH<sub>2</sub>Cl<sub>2</sub> (15 mL). After the phosphine had dissolved, diisopropyl 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% Et<sub>2</sub>O in petroleum ether) to give the *title compound* (665 mg, 72%) as a colourless oil (Found: MH<sup>+</sup>, 550.2775. C<sub>35</sub>H<sub>40</sub>NO<sub>3</sub>Si requires M, 550.2777);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3071, 3011, 2954, 2855, 1770, 1713, 1468, 1372 and 1105;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.80 (2 H, app. dd, *J* 5.5, 3.0, aromatic CH), 7.71–7.66 (6 H, m, aromatic CH), 7.46–7.37 (6 H, m, aromatic CH), 5.60 (1 H, app. broad d, *J* 10.1, CHCH=CH), 5.48 (1 H, dd, *J* 10.1, 1.8, CHCH=CH), 4.65 (1 H, app. dtd, *J* 11.5, 9.7, 6.7, CHN), 3.45 (2 H, app. s, CH<sub>2</sub>O), 2.53 (1 H, app. q, *J* 11.7, one of CHCH<sub>2</sub>CHN), 2.32–2.19 (3 H, m, MeCH, CH<sub>2</sub>CHCH<sub>2</sub> and one of CH<sub>2</sub>CHN), 2.10 (1 H, dd, *J* 12.6, 10.3, one of CH<sub>2</sub>CHN), 1.79 (1 H, app. dt, *J* 12.0, 6.2, one of CHCH<sub>2</sub>CHN), 1.71 (1 H, app. dt, *J* 13.4, 3.5, one of MeCHCH<sub>2</sub>), 1.27–1.22 (1 H, m, one of MeCHCH<sub>2</sub>), 1.10 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>) and 0.98 (3 H, d, *J* 7.0, CH<sub>3</sub>);  $\delta_{\text{C}}$  (125 MHz; CDCl<sub>3</sub>) 168.4 (2 × C=O), 135.7 (4 × CH), 133.7 (2 × CH), 133.6 (2 × C), 132.1 (2 × C), 132.0 (CH), 132.0 (CH), 129.6 (2 × CH), 127.6 (4 × CH), 122.9 (2 × CH), 69.5 (CH<sub>2</sub>), 48.9 (CH), 45.7 (C), 37.5 (CH<sub>2</sub>), 37.4 (CH), 33.1 (CH<sub>2</sub>), 31.4 (CH<sub>2</sub>), 26.9 (CH<sub>3</sub>), 25.8 (CH), 21.4 (CH<sub>3</sub>) and 19.4 (C); *m/z* (TOF ES+) 551 (20%), 550 (MH<sup>+</sup>, 100) and 294 (14).

**(2SR,3aRS,5SR,7aRS)-7a-((tert-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3,3a,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 Et<sub>2</sub>O (30 mL) with efficient stirring. The precipitate was removed by filtration and the filter cake washed with Et<sub>2</sub>O. The filtrate was concentrated *in vacuo* to give the *title compound* (0.75 g, 94%) as an essentially-pure colourless oil (Found: MH<sup>+</sup>, 420.2733. C<sub>27</sub>H<sub>38</sub>NOSi requires M, 420.2723);  $\nu_{\max}$  (CDCl<sub>3</sub>)/cm<sup>-1</sup> 3364, 3070, 3002, 2930, 2856, 1459, 1428, 1110 and 703;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 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, CHCH=CH), 5.41 (1 H, dd, *J* 10.1, 1.5, CHCH=CH), 3.39 (1 H, d, *J* 9.7, one of CH<sub>2</sub>O), 3.37 (1 H, d, *J* 9.7, one of CH<sub>2</sub>O), 3.31–3.22 (1 H, m, CHN), 2.26 (1 H, dd, *J* 13.0, 8.1, one of CH<sub>2</sub>CHN), 2.22–2.09 (2 H, m, MeCH and CH<sub>2</sub>CHCH<sub>2</sub>), 1.94 (1 H, app. dt, *J* 12.5, 6.5, one of CHCH<sub>2</sub>CHN), 1.71 (2 H, broad s, NH<sub>2</sub>), 1.64–1.57 (1 H, m, one of MeCHCH<sub>2</sub>), 1.37 (1 H, app. td, *J* 11.9, 9.5, one of CHCH<sub>2</sub>CHN), 1.21–1.13 (1 H, m, one of MeCHCH<sub>2</sub>), 1.15 (1 H, dd, *J* 13.0, 7.9, one of CH<sub>2</sub>CHN), 1.05 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>) and 0.95 (3 H, d, *J* 7.0, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 135.7 (2 × CH), 135.7 (2 × CH), 133.7 (C), 133.7 (C), 132.8 (CH), 132.0 (CH), 129.5 (2 × CH), 127.6 (4 × CH), 69.5 (CH<sub>2</sub>), 51.0 (CH), 46.2 (C), 45.8 (CH<sub>2</sub>), 40.9 (CH<sub>2</sub>), 37.9 (CH), 31.4 (CH<sub>2</sub>), 26.9 (CH<sub>3</sub>), 25.6 (CH), 21.5 (CH<sub>3</sub>) and 19.4 (C); *m/z* (TOF ES+) 461 (MH<sup>+</sup>·CH<sub>3</sub>CN, 36%) and 420 (MH<sup>+</sup>, 100).

**N-((2SR,3aRS,5SR,7aRS)-7a-((tert-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1H-inden-2-yl)-4-nitrobenzenesulfonamide (19)**. 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 CH<sub>2</sub>Cl<sub>2</sub> (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* (1.01 g, 93%) as a pale yellow oil (Found: MH<sup>+</sup>, 605.2538. C<sub>33</sub>H<sub>41</sub>N<sub>2</sub>O<sub>5</sub>SSi requires M, 605.2505);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3282, 2956, 2857, 1531, 1349, 1165, 1093, 738, 704 and 614;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 8.32 (2 H, d, *J* 8.8, aromatic CH), 8.02 (2 H, d, *J* 8.8, aromatic CH), 7.61–7.55 (4 H, m, aromatic CH), 7.47–7.33 (6 H, m, aromatic CH), 5.51 (1 H, app. broad d, *J* 10.0, CHCH=CH), 5.29 (1 H, dd, *J* 10.0, 1.6, CHCH=CH), 4.81 (1 H, d, *J* 8.9, NH), 3.80–3.69 (1 H, m, CHN), 3.32 (1 H, d, *J* 9.9, one of CH<sub>2</sub>O), 3.31 (1 H, d, *J* 9.9, one of CH<sub>2</sub>O), 2.15 (2 H, m, CH<sub>2</sub>CHCH<sub>2</sub> and one of CH<sub>2</sub>CHN), 2.10–1.98 (2 H, m, MeCH and one of CHCH<sub>2</sub>CHN), 1.56 (1 H, app. dt, *J* 13.6, 3.6, one of MeCHCH<sub>2</sub>), 1.40 (1 H, app. dt, *J* 11.8, 8.4, one of CHCH<sub>2</sub>CHN), 1.19 (1 H, dd, *J* 13.3, 6.2, one of CH<sub>2</sub>CHN), 1.13–1.05 (1 H, m, one of MeCHCH<sub>2</sub>), 1.02 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>) and 0.93 (3 H, d, *J* 7.1, CH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 149.9 (C), 146.9 (C), 135.6 (2 × CH), 135.5 (2 × CH), 133.8 (CH), 133.3 (C), 133.2 (C), 131.6 (CH), 129.7 (2 × CH), 128.2 (2 × CH), 127.7 (4 × CH), 124.3 (2 × CH), 68.4 (CH<sub>2</sub>), 52.9 (CH), 46.1 (C), 42.5 (CH<sub>2</sub>), 37.8 (CH<sub>2</sub>), 36.7 (CH), 30.4 (CH<sub>2</sub>), 26.8 (CH<sub>3</sub>), 25.4 (CH), 21.2 (CH<sub>3</sub>) and 19.3 (C); *m/z* (TOF ES+) 606 (33%), 605 (MH<sup>+</sup>, 100), 418 (29) and 280 (63).

**(2RS,3aSR,4RS,6RS,7RS,7aRS)-3a-(tert-Butyldimethylsilyloxymethyl)-7-iodo-6-methyl-1-(4-nitrobenzenesulfonyl)-2,4-methanooctahydroindole (20)**. Sodium hydrogencarbonate (167 mg, 1.98 mmol, 3 equiv.) and iodine (505 mg, 1.98 mmol, 3 equiv.) were added to a solution of sulfonamide **19** (400 mg, 0.66 mmol) in acetonitrile (10 mL). The reaction was stirred overnight before quenching with saturated aqueous Na<sub>2</sub>SO<sub>3</sub> solution (10 mL). The organic layer was separated and the aqueous phase extracted with Et<sub>2</sub>O (2 × 10 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by chromatography on silica (10% ethyl acetate in petroleum ether) to give the *title compound* (437 mg, 91%) as a colourless solid, m.p. 173–175 °C (Found: MH<sup>+</sup>, 731.1436. C<sub>33</sub>H<sub>40</sub>IN<sub>2</sub>O<sub>5</sub>SSi requires M, 731.1472);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3071, 2959, 2857, 1533, 1351, 1155 and 1109;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 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, CHI), 4.19 (1 H, d, *J* 10.7, one of CH<sub>2</sub>O), 3.99 (1 H, app. broad d, *J* 2.2, CHICHN), 3.92 (1 H, app. broad s, CHN), 3.71 (1 H, d, *J* 10.7, one of CH<sub>2</sub>O), 1.91–1.85 (2 H, m, CH<sub>2</sub>CHCH<sub>2</sub> and one of CH<sub>2</sub>CHN), 1.80–1.71 (1 H, m, one of CH<sub>2</sub>CHN), 1.61–1.50 (1 H, m, CHMe), 1.29–1.10 (2 H, m, MeCHCH<sub>2</sub>), 0.99–0.94 (13 H, m, CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>3</sub> and one of CH<sub>2</sub>CHN) and 0.74 (1 H, app. broad d, *J* 10.3, one of CH<sub>2</sub>CHN);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 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), 64.5 (CH<sub>2</sub>), 64.2 (CH), 59.6 (CH), 52.5 (C), 43.1 (CH<sub>2</sub>), 40.7 (CH), 37.0 (CH<sub>2</sub>), 34.1 (CH), 29.3 (CH<sub>2</sub>), 26.9 (CH<sub>3</sub>), 24.1 (CH and CH<sub>3</sub>) and 19.3 (C); *m/z*

(TOF ES+) 732 (9%), 731 (MH<sup>+</sup>, 34), 603 (54), 475 (100) and 347 (19).

***N*-(2*SR*,3*aRS*,5*SR*,7*aRS*)-7*a*-((*tert*-Butyldiphenylsilyloxy)methyl)-5-methyl-2,3,3*a*,4,5,7*a*-hexahydro-1*H*-inden-2-yl)-toluenesulfonamide (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 **18** (230 mg, 0.55 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). After stirring overnight, the solution was concentrated *in vacuo* and purified by chromatography on silica (20% ethyl acetate in petroleum ether) to give the *title compound* (265 mg, 84%) as a colourless oil (Found: MNH<sub>4</sub><sup>+</sup>, 591.3063. C<sub>34</sub>H<sub>47</sub>N<sub>2</sub>O<sub>3</sub>SSi requires M, 591.3077);  $\nu_{\max}$  (CDCl<sub>3</sub>)/cm<sup>-1</sup> 3271, 3071, 2955, 2857, 1428, 1325, 1160, 1094, 910 and 815;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.66 (2 H, d, *J* 8.3, aromatic CH), 7.53–7.49 (4 H, m, aromatic CH), 7.38–7.27 (6 H, m, aromatic CH), 7.19 (2 H, d, *J* 8.3, aromatic CH), 5.40 (1 H, app. broad d, *J* 10.1, CHCH=CH), 5.22 (1 H, dd, *J* 10.1, 1.7, CHCH=CH), 4.62 (1 H, d, *J* 8.7, NH), 3.57 (1 H, m, CHN), 3.23 (1 H, d, *J* 9.8, one of CH<sub>2</sub>O), 3.20 (1 H, d, *J* 9.8, one of CH<sub>2</sub>O), 2.33 (3 H, s, CH<sub>3</sub>), 2.05–1.94 (2 H, m, CH<sub>2</sub>CHCH<sub>2</sub> and MeCH), 2.03 (1 H, dd, *J* 13.3, 8.2, one of CH<sub>2</sub>CHN), 1.92 (1 H, app. dt, *J* 12.3, 7.3, one of CHCH<sub>2</sub>CHN), 1.46 (1 H, app. dt, *J* 13.5, 3.7, one of MeCHCH<sub>2</sub>), 1.37–1.27 (1 H, ddd, *J* 12.3, 11.5, 8.3, one of CHCH<sub>2</sub>CHN), 1.11 (1 H, dd, *J* 13.3, 6.3, one of CH<sub>2</sub>CHN), 1.00 (1 H, ddd, *J* 13.5, 10.8, 4.1, one of MeCHCH<sub>2</sub>), 0.93 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>) and 0.84 (3 H, d, *J* 7.0, CHCH<sub>3</sub>);  $\delta_{\text{C}}$  (125 MHz; CDCl<sub>3</sub>) 143.1 (C), 138.0 (C), 135.6 (2 × CH), 135.6 (2 × CH), 133.5 (C), 133.4 (C), 133.3 (CH), 131.9 (CH), 129.6 (2 × CH), 127.6 (4 × CH), 127.1 (2 × CH), 68.8 (CH<sub>2</sub>), 52.6 (CH), 46.0 (C), 42.5 (CH<sub>2</sub>), 37.8 (CH<sub>2</sub>), 36.8 (CH), 30.7 (CH<sub>2</sub>), 26.9 (CH<sub>3</sub>), 25.4 (CH), 21.5 (CH<sub>3</sub>), 21.2 (CH<sub>3</sub>) and 19.3 (C); *m/z* (TOF ES+) 593 (19%), 592 (53) and 591 (MNH<sub>4</sub><sup>+</sup>, 100).

**(2*RS*,3*aSR*,4*RS*,6*RS*,7*RS*,7*aRS*)-3*a*-((*tert*-Butyldimethylsilyloxy)methyl)-7-iodo-6-methyl-1-(4-toluenesulfonyl)-2,4-methanooctahydroindole (22).** Sodium hydrogencarbonate (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 reaction was quenched by the addition of saturated aqueous Na<sub>2</sub>SO<sub>3</sub> solution (10 mL), the organic layer separated and the aqueous phase extracted with Et<sub>2</sub>O (2 × 10 mL). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> 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, m.p. 150–152 °C (Found: MH<sup>+</sup>, 700.1765. C<sub>34</sub>H<sub>43</sub>INO<sub>3</sub>SSi requires M, 700.1778);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3070, 2958, 2857, 1469, 1428, 1346, 1153 and 1110;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.68 (2 H, d, *J* 8.3, aromatic CH), 7.54–7.50 (4 H, m, aromatic CH), 7.46–7.28 (6 H, m, aromatic CH), 7.14 (2 H, d, *J* 8.3, aromatic CH), 4.94 (1 H, app. broad t, *J* 3.1, CHI), 4.15 (1 H, d, *J* 10.6, one of CH<sub>2</sub>O), 4.01 (1 H, broad d, *J* 2.3, CHN), 3.88 (1 H, app. broad s, CHN), 3.69 (1 H, d, *J* 10.6, one of CH<sub>2</sub>O), 2.36 (3 H, s, CH<sub>3</sub>), 1.87–1.80 (2 H, m, CH<sub>2</sub>CHCH<sub>2</sub> and one of CH<sub>2</sub>CHN), 1.76–1.70 (1 H, m, one of CH<sub>2</sub>CHN), 1.64–1.55 (1 H, m, CHMe), 1.26–1.10 (2 H, m, MeCHCH<sub>2</sub>), 0.99 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 0.95 (3 H, d, *J* 6.4, CH<sub>3</sub>), 0.95–0.91 (1 H, m, one of CH<sub>2</sub>CHN) and 0.85 (1 H, dt, *J* 10.1, 2.2, one of CH<sub>2</sub>CHN);  $\delta_{\text{C}}$  (125 MHz; CDCl<sub>3</sub>) 143.5 (C), 135.9 (2 × CH), 135.7 (2 × CH), 133.7 (C), 133.3 (C), 129.9 (2 ×

CH), 129.7 (CH), 129.6 (CH), 127.7 (2 × CH), 127.5 (2 × CH), 127.4 (2 × CH), 64.7 (CH<sub>2</sub>), 64.0 (CH), 59.3 (CH), 52.3 (C), 42.9 (CH<sub>2</sub>), 42.1 (CH), 37.1 (CH<sub>2</sub>), 34.2 (CH), 29.5 (CH<sub>2</sub>), 27.0 (CH<sub>3</sub>), 24.2 (CH<sub>3</sub>), 24.1 (CH), 21.5 (CH<sub>3</sub>) and 19.3 (C); *m/z* (TOF ES+) 701 (25%), 700 (MH<sup>+</sup>, 100) and 572 (14).

**(2*RS*,3*aSR*,4*RS*,6*RS*,7*RS*,7*aRS*)-3*a*-((*tert*-Butyldimethylsilyloxy)methyl)-6-methyl-1-(4-toluenesulfonyl)-2,4-methanoctahydroindole (23).** Bu<sub>3</sub>SnH (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 (Found: MH<sup>+</sup>, 574.2834. C<sub>34</sub>H<sub>44</sub>NO<sub>3</sub>SSi requires M, 574.2811);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>)/cm<sup>-1</sup> 3071, 2956, 2855, 1457, 1341, 1156 and 1111;  $\delta_{\text{H}}$  (500 MHz; CDCl<sub>3</sub>) 7.71 (2 H, d, *J* 8.3, aromatic CH), 7.56–7.50 (4 H, m, aromatic CH), 7.45–7.33 (6 H, m, aromatic CH), 7.24 (2 H, d, *J* 8.3, aromatic CH), 4.04 (1 H, app. broad s, CHN), 3.62–3.58 (2 H, m, CHN and one of CH<sub>2</sub>O), 3.49 (1 H, d, *J* 10.7, one of CH<sub>2</sub>O), 2.39 (3 H, s, CH<sub>3</sub>), 2.12 (1 H, app. broad d, *J* 13.9, one of MeCHCH<sub>2</sub>CHN), 2.07–1.95 (1 H, m, MeCH), 1.88–1.78 (2 H, m, MeCHCH<sub>2</sub>CH and one of CHCH<sub>2</sub>CHN), 1.72–1.62 (1 H, m, one of CHCH<sub>2</sub>CHN), 1.49–1.42 (1 H, m, one of MeCHCH<sub>2</sub>CH), 1.02 (1 H, app. d, *J* 9.8, one of CCH<sub>2</sub>CHN), 0.98–0.89 (2 H, m, one of CCH<sub>2</sub>CHN and one of MeCHCH<sub>2</sub>CHN), 0.94 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 0.88–0.83 (1 H, m, one of MeCHCH<sub>2</sub>CH) and 0.86 (3 H, d, *J* 6.5, CH<sub>3</sub>);  $\delta_{\text{C}}$  (125 MHz; CDCl<sub>3</sub>) 142.9 (C), 135.6 (2 × CH), 135.5 (2 × CH<sub>2</sub>), 133.1 (C), 133.1 (C), 129.8 (CH), 129.8 (CH), 129.7 (2 × CH), 127.7 (2 × CH), 127.7 (2 × CH), 127.6 (2 × CH), 62.8 (CH<sub>2</sub>), 59.8 (CH), 59.7 (CH), 51.3 (C), 41.2 (CH<sub>2</sub>), 37.2 (CH<sub>2</sub>), 34.9 (CH), 33.7 (CH<sub>2</sub>), 33.5 (CH<sub>2</sub>), 26.8 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>), 20.2 (CH) and 19.2 (C); *m/z* (TOF ES+) 575 (22%) and 574 (MH<sup>+</sup>, 100).

**(2*RS*,3*aSR*,4*RS*,6*RS*,7*RS*,7*aRS*)-3*a*-((*tert*-Butyldimethylsilyloxy)methyl)-6-methyl-2,4-methanoctahydroindole (24).** Sodium (22 mg, 0.96 mmol) was added to a solution of naphthalene (125 mg, 0.98 mmol) in THF (2 mL) and the metal crushed with a spatula. After stirring for 30 min, a 1 mL aliquot of the resulting green solution was added dropwise to a –78 °C solution of sulfonamide **23** (25 mg, 0.04 mmol) in THF (3 mL), giving a permanent green colour. After stirring for 15 min, the reaction was quenched by addition of 2 M NaOH (10 mL) and allowed to warm to room temperature. The organic layer was separated and the aqueous phase extracted with Et<sub>2</sub>O (2 × 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by chromatography on silica (10% ethyl acetate in petroleum ether followed by 1% Et<sub>3</sub>N in MeOH) to give a yellow oily residue. This oil was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and washed with 2 M aqueous NaOH solution (10 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and the combined organic phases dried over NaOH and concentrated *in vacuo* to give the *title compound* (15 mg, 82%) as a yellow oil (Found: MH<sup>+</sup>, 420.2731. C<sub>27</sub>H<sub>38</sub>NOSi requires M, 420.2723);  $\nu_{\max}$  (neat)/cm<sup>-1</sup> 3398, 3072, 2929, 2861, 1587, 1428, 1111, 1097, 823, 737, 703;  $\delta_{\text{H}}$  (500 MHz; CDCl<sub>3</sub>) 7.66 (4 H, d, *J* 7.1, aromatic CH), 7.45–7.36 (6 H, m, aromatic CH), 3.70 (1 H, d, *J* 10.5, one of CH<sub>2</sub>O), 3.69 (1 H, d, *J* 10.5, one of CH<sub>2</sub>O), 3.29 (1 H, app. broad s, CCH<sub>2</sub>CHN), 3.22 (1 H, app. broad s, CCHN), 2.11–2.05 (1 H, m,

CCHCH<sub>2</sub>), 1.85 (1 H, app. td, *J* 12.2, 2.8, one of CHCH<sub>2</sub>CHN), 1.86–1.75 (1 H, m, CHCH<sub>3</sub>), 1.71 (1 H, app. dt, *J* 9.3, 2.2, one of CCH<sub>2</sub>CHN), 1.62 (1 H, app. broad d, *J* 14.3, one of CCHNCH<sub>2</sub>), 1.55 (1 H, d, *J* 9.3, one of CCH<sub>2</sub>CHN), 1.45 (1 H, br. d, *J* 13.7, one of CHCH<sub>2</sub>CH), 1.35 (1 H, dt, *J* 12.5, 3.4, one of CHCH<sub>2</sub>CHN), 1.05 (9 H, s, C(CH<sub>3</sub>)<sub>3</sub>), 0.98–0.88 (2 H, m, one of CHCH<sub>2</sub>CH and one of CCHNCH<sub>2</sub>), 0.85 (3 H, d, *J* 6.5, CH<sub>3</sub>);  $\delta_c$  (125 MHz; CDCl<sub>3</sub>) 135.7 (4 × CH), 133.8 (2 × C), 129.6 (2 × CH), 127.6 (4 × CH), 63.8 (CH<sub>2</sub>), 56.0 (CH), 55.2 (CH), 49.8 (C), 44.9 (CH<sub>2</sub>), 38.2 (CH<sub>2</sub>), 34.6 (CH<sub>2</sub>), 34.1 (CH), 33.3 (CH<sub>2</sub>), 26.9 (CH<sub>3</sub>), 21.9 (CH<sub>3</sub>), 19.7 (CH), 19.4 (C); *m/z* (TOF ES+) 422 (10%), 421 (35) and 420 (MH<sup>+</sup>, 100).

## Acknowledgements

We are extremely grateful to Cardiff University and EPSRC (EP/C53090X/1; GR/S25456/01) for financial support, and to Dr Robert Jenkins and Mr Robin Hicks (Cardiff University) for technical assistance. We would like to thank Dr Mike Butters and Mr Stephen Baldwin (AstraZeneca Process R & D, Bristol, UK) for helpful discussions and further technical assistance and Professor H. Takayama (Chiba University, Japan) for providing copies of NMR spectra of lycoposerramine S.

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