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Regio- and stereoselective 6-*exo-trig* radical cyclisations onto chiral perhydro-1,3-benzoxazines: synthesis of enantiopure 3-alkylpiperidines

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Abstract

Enantiopure 3-alkyl substituted piperidines are prepared by diastereoselective 6-*exo-trig* cyclisation of perhydro-1,3-benzoxazines derived from (–)-(8)-amino menthol. The diastereoselective cyclisation is promoted by tributyltin hydride, and the competitive 1,5-hydrogen migration depends on the position of the acceptor double bond and the radical site.

1. Introduction

Radical cyclisations are a very useful methodology for ring construction from simple to polycyclic structures,[1–3] and carbocyclic and heterocyclic compounds of a diverse size are usual targets in modern radical chemistry.[4,5] However, synthetic applications are somewhat constrained to the generation of five-membered rings due to the well-known behaviour of 5-hexenyl radicals in terms of regioselectivity and stereoinduction during cyclisation.[6] Formation of larger rings by radical cyclisation is a less general synthetic pathway. In fact, ring closure is slower as the ring size increases and, contrasting with 5-hexenyl radicals, secondary competitive processes, such as inter- or intramolecular hydrogen abstraction,[7] ring expansion[8] or neophyl rearrangements[9] can appear. As a result, a loss of regio- and stereoselectivity can be expected when forming six-membered or larger rings.

In spite of the above considerations a good choice of starting substrates may provide good results avoiding undesired by-products. Although very few examples are known, some highly stereoselective *6-exo* cyclisations have been reported in the syntheses of indolizidine and quinolizidine alkaloids using alkyl radicals.[10–12]

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As an extension of our previous approach[13] to chiral pyrrolidines by cyclisation of 5-hexenyl radicals, and isoquinoline or benzazepine derivatives from 6-heptenyl radicals,[14] we report here on the synthesis of enantiopure 3-alkyl piperidines by 6-*exo* radical ring closure on perhydro-1,3-benzoxazines used as chiral auxiliaries.

2. Results

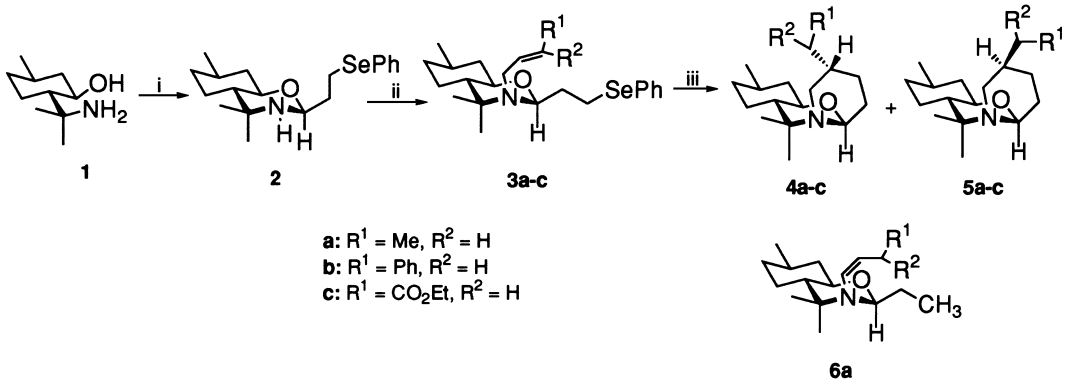
Preparations of perhydrobenzoxazines **3a–c** were accomplished in two steps from (–)-8-amino menthol **1**.[15] Condensation of **1** with 3-phenylselenopropionaldehyde afforded quantitatively **2** which was further alkylated with allylic bromides in the presence of potassium carbonate in refluxing acetonitrile.

The reaction of perhydrobenzoxazine **3a** with tributyltin hydride and AIBN in refluxing benzene was complete after 9 h. Crude ^{1}H NMR analysis showed three compounds in the ratio 32:29:39 which were assigned to **4a**, **5a** and **6a**, respectively (Table 1, entry 1). Cyclised products **4a** and **5a** were isolated by flash chromatography and characterised as 6-*exo* products (Scheme 1). Attempts to isolate **6a** led to decomposition during purification. This compound must arise from a favoured intramolecular 1,5-hydrogen abstraction in which the double bond isomerisation takes place.

Table 1
Radical cyclisations of perhydrobenzoxazines **3a–c**

R^1	R^2	Benzoxazine	Yield (%)[a]	Products (dr)[b]
Me	H	**3a**	(51)[c]	**4a** (32); **5a** (29); **6a** (39)
Ph	H	**3b**	(90)	**4b** (63); **5b** (37)
CO_2Et	H	**3c**	(90)	**4c** (63); **5c** (37)

[a] Numbers in parentheses refer to the total yields of isomers isolated after flash chromatography. [b]Determined by ^{1}H NMR in the reaction mixture. [c] Total yield of **4a** and **5a** isolated after flash chromatography.

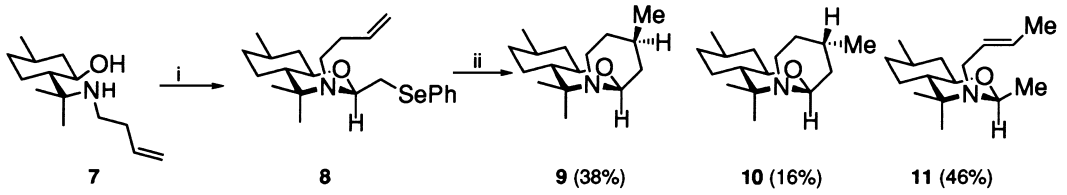


Scheme 1. *Reagents and conditions*: (i) $PhSeCH_2CH_2CHO$, CH_2Cl_2, rt, 3 h; (ii) $BrCH_2CH{=}CR^1R^2$, K_2CO_3, CH_3CN, reflux, 48 h; (iii) Bu_3SnH (1.5 equiv.), AIBN (0.1 equiv.), benzene, reflux, 7–9 h

Activation of the olefinic acceptor (R = Ph, CO_2Et) increased the chemical yield in cyclised products **4**–**5** avoiding formation of undesired non-cyclic compound **6** (Table 1, entries 2 and 3). Furthermore, an improvement in diastereoselection is encountered for cyclisation of **3b**–**c**.

In an effort to improve the stereoselectivity of the cyclisation we thought that a radical centre closer to the auxiliary would be beneficial. To this end, homoallyl perhydrobenzoxazine **8** was prepared by condensation of *N*-(3-butenyl)-8-amino menthol **7**[15] with phenylselenoacetaldehyde[16] in benzene at reflux.

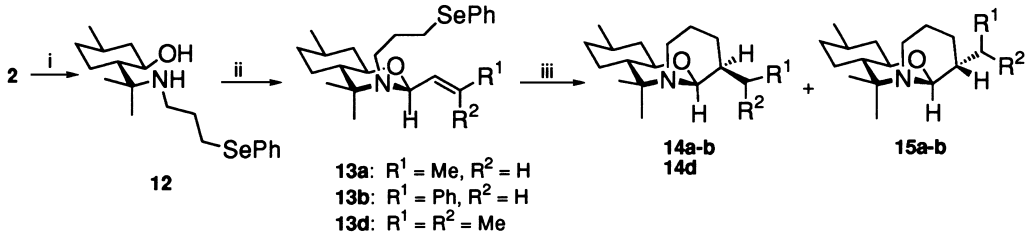
Reaction of **8** with Bu_3SnH and AIBN under dilute conditions yielded a mixture of three compounds in the 38:16:46 ratio (^1H NMR). Isolation by flash chromatography afforded 6-*exo* diastereomers **9** and **10** together with the unexpected reduced perhydrobenzoxazine **11** in 80% combined yield (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) $PhSeCH_2CHO$, benzene, reflux, 3 h (70%); (ii) Bu_3SnH (1.5 equiv.), AIBN (0.1 equiv.), benzene, reflux, 7–9 h (80%)

Unfortunately, the open perhydrobenzoxazine **11**, resulting from the competitive 1,5-hydrogen migration, was the major compound obtained and remarkable changes in stereodifferentiation of the radical cyclisation were not observed. Then we turned to promote the cyclisation on substrates **13a**–**d** by changing the radical centre to the nitrogen substituent, and placing the acceptor double bond at the acetallic carbon. The cyclisation in this type of arrangement is controlled by the A-strain[1,3] as reported for similar 5-hexenyl radical cyclisations.[17]

The starting benzoxazines **13a**–**b**,**d** were obtained by reductive cleavage of selenylated benzoxazine **2** using borane–THF and subsequent condensation of **12** with unsaturated aldehydes in refluxing benzene. Slow addition of a solution of Bu_3SnH and AIBN in benzene to a solution of **13a**–**b** in the same solvent, at reflux, led to a mixture of only two products **14a**–**b** and **15a**–**b** corresponding to the 6-*exo* diastereomers (Scheme 3, Table 2). NOESY experiments allowed the establishment of a *trans*-relationship between the acetallic proton and its adjacent proton for major diastereoisomers **14a**–**d** or a *cis*-relationship for the minor ones **15a**–**b**.



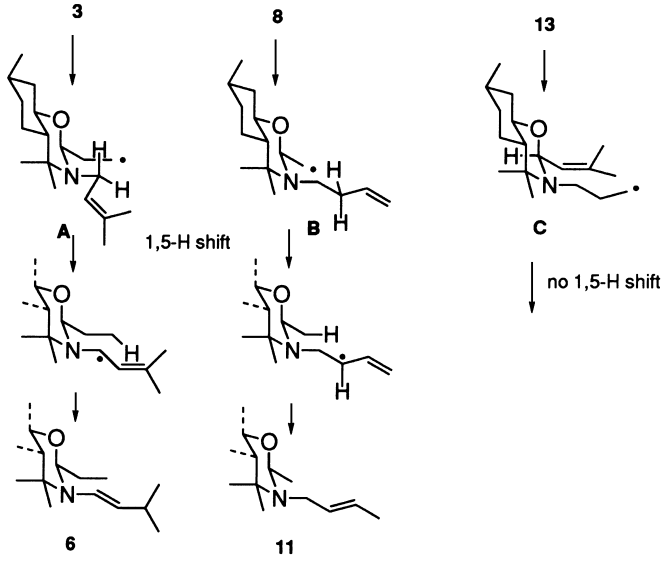
Scheme 3. *Reagents and conditions*: (i) $NaBH_4$–BF_3OEt_2, THF, 0°C to rt, 3 h (94%); (ii) $OHCCH{=}CR^1R^2$, benzene, reflux, 4 h (54–80%); (iii) Bu_3SnH (1.5 equiv.), AIBN (0.1 equiv.), benzene, reflux, 7–9 h

Table 2
Radical cyclisations of perhydrobenzoxazines **13a–b,d**

R^1	R^2	Benzoxazine	Yield (%)[a]	Products (dr)[b]
Me	H	**13a**	(78)	**14a** (62); **15a** (38)
Ph	H	**13b**	(94)	**14b** (59); **15b** (41)
Me	Me	**13d**	(40)	**14d**

[a] Numbers in parentheses refer to the total yields of isomers isolated after flash chromatography. [b] The yields of diastereoisomers were determined after separation and purification

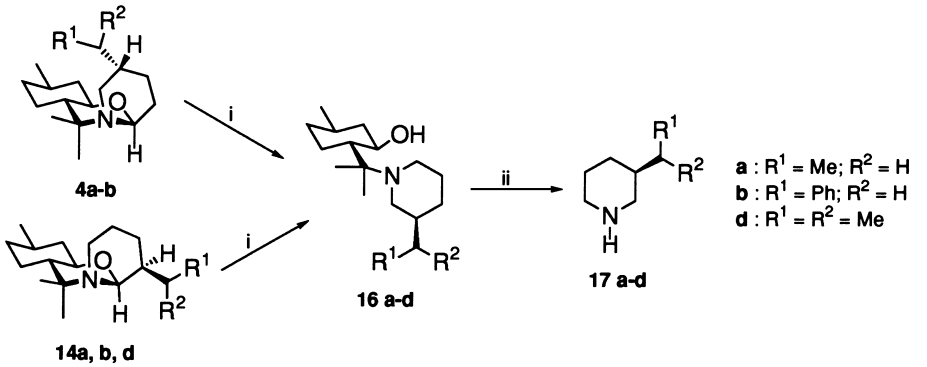
As expected, a single diastereomer **14d** was formed in the cyclisation of **13d** (Table 2, entry 3) as a result of the strong local allylic strain operating when $R^2 \neq H$, and the reduced acyclic products were not formed for **13a–d** whatever the nature of groups R^1 or R^2. The formation of the 1,5-migration products from **3** and **8**, and the absence of this by-product from **13**, is a consequence of the concerted six-membered transition state required for these transformations. In fact, *N*-axial substituted radicals formed from **3** and **8** can easily adopt the chair-like conformations **A** and **B** required for H-migration (Scheme 4), while the radical **C**, formed from **13** is unable to adopt the correct conformation for the migration of the *N*,*O*-acetallic hydrogen, in contrast with dioxolane and other acetals.[18,19]



Scheme 4.

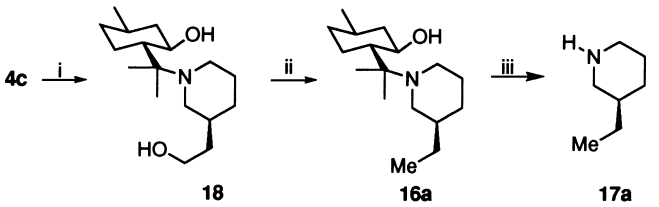
Assuming the axial preference for the substituent at the nitrogen in all of these benzoxazines, the exact stereochemistry of major cyclisation products **4a–c** and **9** can be correctly justified in terms of the proposed model for 6-heptenyl radicals,[20] whereas the formation of **14a–d** is a consequence of the allylic strain in the radical intermediate **C**.[17]

The major cyclisation stereoisomers **4a**–**b** and **14a**,**b**,**d**, after separation by flash chromatography, were transformed into enantiopure 3-alkyl piperidines in two steps (Scheme 5). Treatment of **4a**–**b** or **14a**–**b**,**d** with $LiAlH_4$ and $AlCl_3$ in THF at 0°C led to the piperidinyl menthols **16a**–**d** in nearly quantitative yield. The menthol derivatives were converted into 3-substituted piperidines by oxidation with PCC to the corresponding piperidinyl menthones, followed by reaction with KOH in MeOH–THF. In this way, (*R*)-3-ethylpiperidine **17a**[21] and (*S*)-3-benzylpiperidine **17b** were obtained. These products were also formed starting from **14a** and **14b**, respectively. In addition, diastereomer **14d** provided (*S*)-3-isopropylpiperidine **17d** following the same sequence.



Scheme 5. *Reagents and conditions*: (i) $LiAlH_4$–$AlCl_3$, THF, 0°C, 15 min, H_2O (93–96%); (ii) PCC, CH_2Cl_2, rt, then KOH, MeOH–THF (42–72%)

For compound **4c**, the configuration of the stereocentre at C-3 in the piperidine ring was assigned by transformation into piperidine **17a** following the sequence depicted on Scheme 6.



Scheme 6. *Reagents and conditions*: (i) DIBALH, toluene, 0°C, 1 h, H_2O (92%); (ii) CBr_4, Ph_3P, CH_2Cl_2, 0°C, 1.5 h then Bu_3SnH, AIBN, benzene, reflux (65%); (iii) PCC, CH_2Cl_2, rt, then KOH, MeOH–THF (68%)

In summary a concise, efficient protocol to access chiral 3-alkylpiperidines is described by mild radical cyclisation.

3. Experimental

All the reactions were monitored by TLC. Preparative chromatography was performed on silica gel (230–400 mesh) by the flash technique. Melting points were measured in open capillary tubes and are uncorrected. NMR spectra were registered on Bruker AC-300 and ARX-300

spectrometers at 300 MHz (^{1}H) and 75 MHz (^{13}C DEPT). Optical rotations were obtained from a Perkin–Elmer 241 polarimeter.

3.1. 3-Phenylselenopropionaldehyde

A solution containing diphenyldiselenide (2.0 g, 6.4 mmol) in absolute ethanol (60 mL) was treated with sodium borohydride (0.5 g, 13 mmol) in portions. Then 3-chloropropionaldehyde diethylacetal (2.0 mL, 11.4 mmol) was added at once and the mixture refluxed for 4 h. The mixture was poured into water, extracted with ether and concentrated in vacuo. The crude acetal was hydrolysed by stirring with 2N aqueous HCl solution (50 mL) for 18 h. Extractions with ether and concentration yielded a residue which was purified by flash chromatography yielding pure aldehyde (1.97 g, 81%). Yellow oil; ^{1}H NMR ($CDCl_3$): $\delta = 2.85$ (dt, 2H, $J = 7.0$ Hz, $J = 1.1$ Hz), 3.09 (t, 2H, $J = 7.0$ Hz), 7.20–7.50 (m, 5H), 9.71 (t, 1H, $J = 1.1$ Hz). IR (liquid film, cm^{-1}): 2810, 2710, 1710. MS (EI, m/z): 214 (M, 34), 158 (86), 78 (100).

3.2. 2-(2′-Phenylselenoethyl)-perhydro-1,3-benzoxazine **2**

A mixture of (–)-8-amino menthol **1**[15] (1.4 g, 8.4 mmol) and 3-phenylselenopropionaldehyde (1.8 g, 8.4 mmol) was stirred in dichloromethane (5 mL) at room temperature for 3 h. The solvent was removed in vacuo yielding pure benzoxazine (3.0 g, 99%). Yellow oil; ^{1}H NMR ($CDCl_3$): $\delta = 0.86$–1.09 (m, 4H), 0.91 (d, 3H, $J = 6.5$ Hz), 1.03 (s, 3H), 1.04 (s, 3H), 1.25–1.42 (m, 2H), 1.68 (m, 2H), 1.84–1.97 (m, 3H), 3.00 (t, 2H, $J = 7.5$ Hz), 3.28 (dt, 1H, $J = 4.2$ Hz, $J = 10.2$ Hz), 4.37 (dd, 1H, $J = 5.5$ Hz, $J = 6.1$ Hz), 7.20–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 19.7$, 22.2, 23.4, 25.5, 29.8, 31.3, 34.9, 36.8, 41.6, 51.2, 51.7, 74.8, 81.9, 126.6, 128.9 (2C), 130.4, 132.5 (2C). IR (liquid film, cm^{-1}): 3280, 730, 685. Anal. calcd for $C_{19}H_{29}NOSe$: C, 62.28; H, 7.98; N, 3.82. Found: C, 62.53; H, 8.14; N, 4.14.

3.3. Synthesis of perhydro-1,3-benzoxazines **3a–c**

General procedure. Compounds **3a–c** were prepared, as previouly described for related compounds,[22] by alkylation of **2** with the corresponding allylic bromide in the presence of potassium carbonate in acetonitrile at reflux for 48 h.

3.4. N-Crotyl-2-(2′-phenylselenoethyl)-perhydro-1,3-benzoxazine **3a**

Oil, 97%; ^{1}H NMR ($CDCl_3$): $\delta = 0.87$–1.05 (m, 3H), 0.91 (d, 3H, $J = 6.5$ Hz), 1.12 (s, 6H), 1.32–1.55 (m, 2H), 1.56–1.70 (m, 2H), 1.62 (dd, 3H, $J = 1.3$ Hz, $J = 3.3$ Hz), 1.85 (m, 1H), 1.87–2.02 (m, 2H), 2.99 (m, 3H), 3.28 (m, 2H), 4.65 (dd, 1H, $J = 4.7$ Hz, $J = 7.2$ Hz), 5.44 (m, 2H), 7.20–7.52 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 17.7$, 20.3, 22.2, 24.3, 25.0, 26.9, 31.3, 34.7, 35.0, 41.4, 44.5, 46.2, 56.9, 75.8, 86.6, 124.4, 126.5, 128.9 (2C), 130.6, 132.5 (2C), 133.3. IR (liquid film, cm^{-1}): 730, 690. MS (CI, m/z): 422 (M+1, 13), 264 (100), 236 (83). Anal. calcd for $C_{23}H_{35}NOSe$: C, 65.70; H, 8.39; N, 3.33. Found: C, 65.47; H, 8.52; N, 3.16.

3.5. N-Cinnamyl-2-(2′-phenylselenoethyl)-perhydro-1,3-benzoxazine **3b**

Oil, 63%; $[\alpha]_D^{20} = -31.2$ (c 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta = 0.86$–1.07 (m, 3H), 0.91 (d, 3H, $J = 6.3$ Hz), 1.15 (s, 3H), 1.16 (s, 3H), 1.32–1.34 (m, 2H), 1.56 (m, 1H), 1.68 (m, 1H), 1.83 (m,

1H), 1.87–2.05 (m, 2H), 2.99 (dt, 2H, $J=3.0$ Hz, $J=7.4$ Hz), 3.27–3.35 (m, 2H), 3.53 (dd, 1H, $J=5.8$ Hz, $J=18.1$ Hz), 4.71 (dd, 1H, $J=4.8$ Hz, $J=7.3$ Hz), 6.23 (dt, 1H, $J=5.4$ Hz, $J=15.9$ Hz), 6.43 (d, 1H, $J=15.9$ Hz), 7.17–7.56 (m, 10H); ^{13}C NMR ($CDCl_3$): $\delta=20.5$, 22.2, 24.4, 25.0, 26.9, 31.3, 34.7, 35.0, 41.4, 44.8, 46.4, 57.1, 75.9, 86.5, 126.1 (2C), 126.6, 126.9, 128.4 (2C), 128.9 (3C), 130.4, 132.7 (3C), 137.5. IR (liquid film, cm^{-1}): 730, 690. Anal. calcd for $C_{28}H_{37}NOSe$: C, 69.69; H, 7.73; N, 2.90. Found: C, 69.52; H, 7.51; N, 3.08.

3.6. N-*(3-Ethoxycarbonyl-2-propenyl)-2-(2′-phenylselenoethyl)-perhydro-1,3-benzoxazine* ***3c***

Oil, 84%; $[\alpha]_D^{20}=-27.8$ (*c* 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta=0.85$–1.07 (m, 3H), 0.90 (d, 3H, $J=6.5$ Hz), 1.05 (s, 3H), 1.16 (s, 3H), 1.23–1.33 (m, 1H), 1.30 (t, 3H, $J=7.1$ Hz), 1.42 (m, 1H), 1.57 (m, 1H), 1.69 (m, 1H), 1.71–1.93 (m, 3H), 2.90–3.00 (m, 2H), 3.27 (dt, 1H, $J=3.9$ Hz, $J=10.6$ Hz), 3.33 (dd, 1H, $J=1.9$ Hz, $J=4.3$ Hz), 3.50 (ddd, 1H, $J=1.8$ Hz, $J=4.7$ Hz, $J=19.8$ Hz), 4.18 (q, 2H, $J=7.1$ Hz), 4.71 (dd, 1H, $J=4.2$ Hz, $J=7.7$ Hz), 6.04 (dt, 1H, $J=1.5$ Hz, $J=15.5$ Hz), 6.98 (dt, 1H, $J=4.5$ Hz, $J=15.5$ Hz), 7.20–7.56 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=14.2$, 20.9, 22.2, 24.3, 24.9, 26.7, 31.3, 34.5, 34.9, 41.3, 43.6, 45.9, 57.0, 60.1, 76.0, 86.1, 120.8, 126.7, 128.9 (2C), 130.2, 132.8 (2C), 151.1, 166.8. IR (liquid film, cm^{-1}): 1670, 730, 690. Anal. calcd for $C_{25}H_{37}NO_3Se$: C, 62.75; H, 7.79; N, 2.93. Found: C, 62.98; H, 7.92; N, 3.14.

3.7. *Radical cyclisation of perhydrobenzoxazines* ***3a–c***

General method: To a solution of the corresponding benzoxazine **3a–c** (1.5 mmol) in refluxing benzene (70 mL) was injected (5–7 h, syringe pump) a solution of tributyltin hydride (0.66 mL, 2.2 mmol) and AIBN (24 mg) in benzene (25 mL). The reflux was maintained until disappearance of starting compound (TLC). Then, the solvent was removed and the residue was purified by flash chromatography on silica gel.

3.8. *Compound* ***4a***

Colourless oil, 16%; ^{1}H NMR ($CDCl_3$): $\delta=0.84$–0.99 (m, 3H), 0.87 (t, 3H, $J=7.6$ Hz), 0.89 (d, 3H, $J=6.3$ Hz), 1.11 (s, 3H), 1.17 (s, 3H), 1.03–1.87 (m, 12H), 2.52 (t, 1H, $J=10.2$ Hz), 2.70 (d, 1H, $J=9.1$ Hz), 3.44 (dt, 1H, $J=4.0$ Hz, $J=10.4$ Hz), 4.72 (t, 1H, $J=3.3$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=11.4$, 20.9, 22.2, 24.9, 25.1, 26.9, 27.2, 30.8, 31.3, 35.0, 37.9, 41.3, 43.7, 45.9, 56.0, 75.9, 81.7. IR (liquid film, cm^{-1}): 1450, 735, 690. Anal. calcd for $C_{17}H_{31}NO$: C, 76.92; H, 11.77; N, 5.28. Found: C, 77.11; H, 11.94; N, 5.43.

3.9. *Compound* ***4b***

Colourless oil, 57%; ^{1}H NMR ($CDCl_3$): $\delta=0.90$–1.04 (m, 2H), 0.92 (d, 3H, $J=6.6$ Hz), 1.05–1.16 (m, 1H), 1.06 (s, 3H), 1.14 (s, 3H), 1.35–1.61 (m, 6H), 1.70 (m, 1H), 1.76–1.93 (m, 3H), 2.50 (dd, 1H, $J=7.9$ Hz, $J=13.4$ Hz), 2.61 (dd, 1H, $J=6.7$ Hz, $J=13.6$ Hz), 2.63 (t, 1H, $J=3.3$ Hz), 2.69 (dd, 1H, $J=4.1$ Hz, $J=10.6$ Hz), 3.45 (dt, 1H, $J=4.1$ Hz, $J=10.6$ Hz), 4.70 (t, 1H, $J=3.3$ Hz), 7.13–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=20.6$, 22.3, 25.1 (2C), 26.9, 30.7, 31.3, 35.0, 38.2, 40.9, 41.4, 44.0, 46.1, 55.8, 75.8, 81.7, 125.6, 128.1 (2C), 129.0 (2C), 140.7. IR (liquid film, cm^{-1}): 1445, 740, 695. Anal. calcd for $C_{22}H_{33}NO$: C, 80.68; H, 10.16; N, 4.28. Found: C, 80.53; H, 10.29; N, 4.41.

3.10. Compound **4c**

Colourless oil, 57%; ^{1}H NMR ($CDCl_3$): $\delta = 0.88$–1.04 (m, 2H), 0.91 (d, 3H, $J = 6.4$ Hz), 1.06–1.13 (m, 1H), 1.09 (s, 3H), 1.13 (s, 3H), 1.24 (t, 3H, $J = 7.0$ Hz), 1.26–1.63 (m, 7H), 1.76 (m, 1H), 1.83 (m, 1H), 1.90–2.10 (m, 1H), 2.20–2.30 (m, 2H), 2.62–2.70 (m, 2H), 3.44 (dt, 1H, $J = 4.0$ Hz, $J = 10.1$ Hz), 4.11 (q, 2H, $J = 7.0$ Hz), 4.66 (t, 1H, $J = 3.5$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 14.2$, 19.8, 22.2, 25.0, 25.5, 26.8, 30.3, 31.3, 33.1, 34.9, 39.0, 41.2, 44.4, 45.7, 55.8, 60.2, 75.7, 81.7, 172.8. IR (liquid film, cm^{-1}): 1730, 1070, 1030. Anal. calcd for $C_{19}H_{33}NO_3$: C, 70.55; H, 10.28; N, 4.33. Found: C, 70.42; H, 10.41; N, 4.24.

3.11. Compound **5a**

Colourless oil, 15%; ^{1}H NMR ($CDCl_3$): $\delta = 0.86$–0.99 (m, 2H), 0.89 (t, 3H, $J = 7.3$ Hz), 0.91 (d, 3H, $J = 6.5$ Hz), 0.92 (s, 3H), 1.02–1.17 (m, 1H), 1.16 (s, 3H), 1.17–1.64 (m, 8H), 1.66–1.94 (m, 5H), 2.98 (dt, 1H, $J = 2.6$ Hz, $J = 11.3$ Hz), 3.35 (dt, 1H, $J = 4.3$ Hz, $J = 10.6$ Hz), 3.90 (dd, 1H, $J = 3.4$ Hz, $J = 9.6$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 11.3$, 11.5, 22.1, 25.0, 25.7, 27.1, 29.1, 31.1, 32.7, 34.6, 37.8, 41.4, 49.1, 49.9, 55.7, 74.1, 85.4. IR (liquid film, cm^{-1}): 1590, 730, 690. Anal. calcd for $C_{17}H_{31}NO$: C, 76.92; H, 11.77; N, 5.28. Found: C, 76.79; H, 11.96; N, 5.09.

3.12. Compound **5b**

Colourless oil, 34%; ^{1}H NMR ($CDCl_3$): $\delta = 0.88$–1.09 (m, 3H), 0.92 (d, 3H, $J = 6.5$ Hz), 0.93 (s, 3H), 1.10 (s, 3H), 1.28–1.56 (m, 4H), 1.64–1.74 (m, 3H), 1.83–1.96 (m, 4H), 2.43 (dd, 1H, $J = 7.2$ Hz, $J = 13.5$ Hz), 2.58 (dd, 1H, $J = 6$ Hz, $J = 13.5$ Hz), 3.00 (dd, 1H, $J = 2.0$ Hz, $J = 8.0$ Hz), 3.36 (dt, 1H, $J = 4.3$ Hz, $J = 10.5$), 3.96 (dd, 1H, $J = 3.5$ Hz, $J = 9.4$ Hz), 7.14–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 11.5$, 22.1, 25.0, 25.7, 29.0, 31.1, 32.6, 34.7, 37.9, 40.8, 41.4, 49.0, 49.8, 55.7, 74.2, 85.2, 125.8, 128.1 (2C), 128.9 (2C), 140.3. IR (liquid film, cm^{-1}): 1600, 730, 697. MS (CI, m/z): 356 (M^++1, 13), 328 (100). Anal. calcd for $C_{22}H_{33}NO$: C, 80.68; H, 10.16; N, 4.28. Found: C, 80.51; H, 10.32; N, 4.46.

3.13. Compound **5c**

Colourless oil, 34%; ^{1}H NMR ($CDCl_3$): $\delta = 0.88$–1.10 (m, 4H), 0.91 (d, 3H, $J = 6.5$ Hz), 0.92 (s, 3H), 1.14 (s, 3H), 1.25 (t, 3H, $J = 7.1$ Hz), 1.30–1.93 (m, 10H), 2.18 (m, 1H), 2.20 (m, 1H), 3.04 (dt, 1H, $J = 2.6$ Hz, $J = 11.2$ Hz), 3.35 (dt, 1H, $J = 4.2$ Hz, $J = 10.5$ Hz), 3.94 (dd, 1H, $J = 3.4$ Hz, $J = 9.2$ Hz), 4.1 (q, 2H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 11.9$, 14.2, 22.0, 25.0, 25.5, 29.1, 31.0, 32.0, 33.1, 34.5, 39.0, 41.2, 48.5, 49.4, 56.0, 60.2, 74.2, 84.9, 172.3. IR (liquid film, cm^{-1}): 1630, 1170. Anal. calcd for $C_{19}H_{33}NO_3$: C, 70.55; H, 10.28; N, 4.33. Found: C, 70.70; H, 10.12; N, 4.45.

3.14. N-*(3-Butenyl)-2-(phenylselenomethyl)-perhydro-1,3-benzoxazine* **8**

Condensation of *N*-(3-butenyl)-8-amino menthol **7**[15] (5 g, 22 mmol) with phenylselenoacetaldehyde[16] (6.5 g, 33 mmol) was carried out in benzene at reflux for 24 h. Filtration on Kieselguhr and removal of the solvent afforded 6.3 g (70%) of product. Yellow oil, $[\alpha]_D^{20} = -43.7$ (c 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): $\delta = 0.85$–1.06 (m, 3H), 0.88 (d, 3H, $J = 6.4$ Hz), 1.09 (s, 3H), 1.13 (s, 3H), 1.28–1.47 (m, 2H), 1.58 (m, 1H), 1.65 (m, 1H), 1.84 (m, 1H), 2.19 (q, 2H, $J = 7.8$ Hz), 2.53

(m, 1H), 2.76 (m, 1H), 3.08 (m, 2H), 3.41 (dt, 1H, $J=4.0$ Hz, $J=10.5$ Hz), 4.77 (dd, 1H, $J=5.4$ Hz, $J=6.9$ Hz), 4.98 (m, 2H), 5.73 (ddt, 1H, $J=6.8$ Hz, $J=10.3$ Hz, $J=17.1$ Hz), 7.18–07.50 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=20.3$, 22.1, 25.0, 26.6, 31.2, 31.4, 34.9, 38.6, 41.1, 42.6, 45.8, 57.1, 76.2, 87.0, 115.4, 126.5, 128.9 (2C), 131.1, 132.1 (2C), 136.4. IR (liquid film, cm^{-1}): 1650, 740, 700. Anal. calcd for $C_{22}H_{33}NOSe$: C, 65.01; H, 8.18; N, 3.45. Found: C, 65.19; H, 8.32; N, 3.29.

3.15. *Compound* **9**

Colourless oil, 30%; ^{1}H NMR ($CDCl_3$): $\delta=0.85$–0.99 (m, 2H), 0.86 (d, 3H, $J=6.4$ Hz), 0.92 (d, 3H, $J=6.6$ Hz), 1.01–1.15 (m, 1H), 1.12 (s, 3H), 1.20 (s, 3H), 1.20–1.32 (m, 2H), 1.34–1.59 (m, 3H), 1.70 (m, 2H), 1.80 (m, 2H), 1.90 (m, 1H), 2.79 (dt, 1H, $J=3.9$ Hz, $J=11.5$ Hz), 2.92 (dt, 1H, $J=2.9$ Hz, $J=11.5$ Hz), 3.46 (dt, 1H, $J=4.0$ Hz, $J=10.5$ Hz), 4.82 (t, 1H, $J=3.0$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=21.3$, 21.6, 22.2, 24.6, 25.1, 27.1, 31.3, 34.3, 35.0, 39.5, 39.8, 41.3, 43.5, 55.0, 76.0, 81.8. IR (liquid film, cm^{-1}): 1460, 975. MS (CI, m/z): 252 (M^++1, 100), 177 (40), 131 (22). Anal calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.71; H, 11.74; N, 5.49.

3.16. *Compound* **10**

White solid, 13%, mp 68–70°C (hexane); ^{1}H NMR ($CDCl_3$): $\delta=0.87$–0.99 (m, 2H), 0.90 (d, 3H, $J=2.1$ Hz), 0.91 (s, 3H), 0.92 (d, 3H, $J=1.6$ Hz), 0.99–1.12 (m, 1H), 1.15 (s, 3H), 1.13–1.50 (m, 5H), 1.55–1.72 (m, 3H), 1.81–1.93 (m, 2H), 2.11 (dt, 1H, $J=2.4$ Hz, $J=11.9$ Hz), 3.00 (dt, 1H, $J=3.3$ Hz, $J=11.5$ Hz), 3.35 (dt, 1H, $J=4.3$ Hz, $J=10.5$ Hz), 3.90 (dd, 1H, $J=3.5$ Hz, $J=9.5$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=11.3$, 21.7, 22.1, 25.0, 25.8, 29.8, 31.1, 34.1, 34.7, 41.4, 41.5, 42.6, 50.1, 55.6, 74.1, 84.7. IR (liquid film, cm^{-1}): 1445. MS (CI, m/z): 252 (M^++1, 80), 177 (45), 103 (100). Anal calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.59; H, 11.74; N, 5.48.

3.17. N-*(3′-Phenylselenopropyl)-8-amino menthol* **12**

To a mixture of sodium borohydride (1.65 g, 43.5 mmol) and BF_3–OEt_2 (8.9 mL, 72.5 mmol) in dry THF (100 mL), at 0°C under an Ar atmosphere, was slowly added a solution of benzoxazine **2** (10.6 g, 29.0 mmol) in THF, and the system was stirred at room temperature for 3 h. After this time, excess of methanol was added, and the solvents were eliminated under vacuum. The residue was treated with a 24% sodium hydroxide solution at reflux. Extractions with chloroform and removal of the solvent yielded 10.0 g (94%) of the titled amino menthol. Pale yellow oil, $[\alpha]_D^{20}=-14.6$ (c 2.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta=0.85$–1.04 (m, 3H), 0.90 (d, 3H, $J=6.6$ Hz), 1.06 (s, 3H), 1.08 (s, 3H), 1.19–1.29 (m, 2H), 1.43 (m, 1H), 1.59–1.71 (m, 2H), 1.76–1.94 (m, 3H), 2.60–2.70 (m, 2H), 2.92 (t, 2H, $J=6.2$ Hz), 3.58 (dt, 1H, $J=4.0$ Hz, $J=10.5$ Hz), 7.20–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=21.4$, 22.1, 25.4, 25.6, 26.0, 30.7, 31.0, 34.9, 40.6, 44.4, 49.5, 56.8, 72.5, 126.8, 129.0 (2C), 129.9, 132.7 (2C). IR (liquid film, cm^{-1}): 3320, 1600, 760, 710. Anal. calcd for $C_{19}H_{31}NOSe$: C, 61.94; H, 8.48; N, 3.80. Found: C, 62.12; H, 8.67; N, 3.96.

3.18. N-*Phenylselenopropyl-2-(1′-propenyl)-perhydro-1,3-benzoxazine* **13a**

Pale yelow oil, 60%; ^{1}H NMR ($CDCl_3$): $\delta=0.84$–1.18 (m, 3H), 0.90 (d, 3H, $J=6.5$ Hz), 1.05 (s, 3H), 1.11 (s, 3H), 1.22–1.44 (m, 2H), 1.57–1.94 (m, 5H), 1.67 (dd, 3H, $J=1.5$ Hz, $J=6.5$ Hz), 2.41

(ddd, 1H, $J=5.8$ Hz, $J=9.5$ Hz, $J=14.9$ Hz), 2.73 (ddd, 1H, $J=7.5$ Hz, $J=9.1$ Hz, $J=16.4$ Hz), 2.82 (dt, 2H, $J=2.6$ Hz, $J=7.2$ Hz), 3.42 (dt, 1H, $J=4.0$ Hz, $J=10.5$ Hz), 4.76 (d, 1H, $J=6.5$ Hz), 5.46 (ddd, 1H, $J=1.7$ Hz, $J=6.4$ Hz, $J=15.4$ Hz), 5.79 (dq, 1H, $J=6.5$ Hz, $J=15.4$ Hz), 7.20–7.52 (m, 5H). IR (liquid film, cm^{-1}): 730, 690. Anal. calcd for $C_{23}H_{35}NOSe$: C, 65.70; H, 8.39; N, 3.33. Found: C, 65.88; H, 8.21; N, 3.51.

3.19. N-*Phenylselenopropyl-2-styrylperhydro-1,3-benzoxazine* **13b**

Pale yellow oil, 80%; $[\alpha]_D^{20}=-37.0$ (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): $\delta=0.86$–1.01 (m, 2H), 0.94 (d, 3H, $J=6.6$ Hz), 1.04–1.21 (m, 1H), 1.15 (s, 3H), 1.16 (s, 3H), 1.36–1.52 (m, 2H), 1.61–1.76 (m, 2H), 1.77–1.87 (m, 2H), 1.94 (m, 1H), 2.53 (ddd, 1H, $J=6.1$ Hz, $J=8.8$ Hz, $J=14.8$ Hz), 2.70–2.90 (m, 3H), 3.52 (dt, 1H, $J=4.0$ Hz, $J=10.5$ Hz), 5.05 (d, 1H, $J=5.5$ Hz), 6.17 (dd, 1H, $J=5.5$ Hz, $J=16.1$ Hz), 6.65 (d, 1H, $J=16.1$ Hz), 7.10–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$): $\delta=18.3$, 22.2, 25.1, 25.4, 26.7, 31.3, 33.7, 34.9, 41.3, 44.1, 46.9, 56.8, 75.4, 87.6, 126.4, 126.6, 127.6, 128.5, 128.8, 129.0, 130.6, 132.1, 132.4, 136.6. IR (liquid film, cm^{-1}): 735, 690. Anal. calcd for $C_{28}H_{37}NOSe$: C, 69.69; H, 7.73; N, 2.90. Found: C, 69.82; H, 7.58; N, 3.17.

3.20. N-*Phenylselenopropyl-2-(2′methylpropenyl)-perhydro-1,3-benzoxazine* **13d**

Pale yellow oil, 54%; $[\alpha]_D^{20}=-14.9$ (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): $\delta=0.85$–1.03 (m, 2H), 0.92 (d, 3H, $J=6.5$ Hz), 1.07–1.14 (m, 1H), 1.12 (s, 3H), 1.13 (s, 3H), 1.27–1.38 (m, 1H), 1.46 (m, 1H), 1.62–1.93 (m, 5H), 1.69 (d, 3H, $J=1.1$ Hz), 1.70 (d, 3H, $J=1.1$ Hz), 2.45 (ddd, 1H, $J=5.7$ Hz, $J=9.2$ Hz, $J=14.8$ Hz), 2.70–2.90 (m, 3H), 3.47 (dt, 1H, $J=4.2$ Hz, $J=9.4$ Hz), 5.10 (d, 1H, $J=7.1$ Hz), 5.22 (dt, 1H, $J=1.4$ Hz, $J=7.1$ Hz), 7.20–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=17.3$, 18.4, 21.8, 24.7, 25.0, 25.4, 26.4, 30.9, 33.5, 34.5, 41.0, 43.6, 46.7, 56.3, 75.0, 84.0, 123.9, 126.0, 128.5, 130.4, 131.6, 136.0. IR (liquid film, cm^{-1}): 1640, 730, 690. Anal. calcd for $C_{24}H_{37}NOSe$: C, 66.34; H, 8.58; N, 3.22. Found: C, 66.51; H, 8.67; N, 3.09.

3.21. *Compound* **14a**

48%; ^1H NMR ($CDCl_3$): $\delta=0.84$–1.13 (m, 3H), 0.87 (t, 3H, $J=7.4$ Hz), 0.91 (d, 3H, $J=6.5$ Hz), 0.94 (s, 3H), 1.15 (s, 3H), 1.25–1.95 (m, 12H), 2.18 (dt, 1H, $J=3.0$ Hz, $J=11.1$ Hz), 2.90–3.10 (m, 1H), 3.31 (dt, 1H, $J=4.3$ Hz, $J=10.6$ Hz), 3.70 (d, 1H, $J=7.5$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=11.3$, 12.7, 22.1, 24.5 (2C), 25.1 (2C), 26.1, 27.6, 31.1, 34.7, 41.3, 42.8, 49.0, 56.0, 74.5, 89.0. Anal. calcd for $C_{17}H_{31}NO$: C, 76.92; H, 11.77; N, 5.28. Found: C, 76.78; H, 11.62; N, 5.42.

3.22. *Compound* **14b**

55%; ^1H NMR ($CDCl_3$): $\delta=0.87$–1.05 (m, 2H), 0.91 (d, 3H, $J=6.5$ Hz), 0.92 (s, 3H), 1.07–1.20 (m, 1H), 1.15 (s, 3H), 1.25–1.72 (m, 8H), 1.84 (m, 1H), 1.91–2.01 (m, 1H), 2.20 (dt, 1H, $J=2.5$ Hz, $J=10.7$ Hz), 2.34 (dd, 1H, $J=9.5$ Hz, $J=13.2$ Hz), 2.93–3.05 (m, 1H), 3.17 (dd, 1H, $J=4.0$ Hz, $J=13.2$ Hz), 3.34 (dt, 1H, $J=4.1$ Hz, $J=10.5$ Hz), 3.77 (d, 1H, $J=7.4$ Hz), 7.13– 7.28 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta=13.0$, 22.2, 24.5, 25.1, 26.1, 27.6, 31.2, 34.8, 38.1, 41.3, 42.8, 43.2, 49.0, 56.1, 74.5, 88.3, 125.5, 127.9 (2C), 129.4 (2C), 140.9. Anal. calcd for $C_{22}H_{33}NO$: C, 80.68; H, 10.16; N, 4.28. Found: C, 80.49; H, 10.29; N, 4.07.

3.23. Compound **14d**

Colourless oil, 40%; ^{1}H NMR ($CDCl_3$): $\delta = 0.78$ (d, 3H, $J = 6.9$ Hz), 0.80–1.20 (m, 2H), 0.87 (d, 3H, $J = 8.5$ Hz), 0.90 (s, 6H), 0.94 (d, 3H, $J = 9.2$ Hz), 1.22–1.72 (m, 10H), 1.86–1.93 (m, 1H), 2.09–2.19 (m, 2H), 2.99–3.02 (m, 1H), 3.30 (dt, 1H, $J = 4.2$ Hz, $J = 10.5$ Hz), 3.87 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 12.8$, 13.7, 17.2, 21.1, 22.1, 25.1, 25.8, 26.8, 27.8, 31.1, 34.6, 41.2, 42.9, 46.5, 48.9, 55.0, 74.6, 86.8. Anal. calcd for $C_{18}H_{33}NO$: C, 77.36; H, 11.90; N, 5.01. Found: C, 77.23; H, 12.02; N, 4.89.

3.24. Compound **15a**

30%; ^{1}H NMR ($CDCl_3$): $\delta = 0.87$ (t, 3H, $J = 7.4$ Hz), 0.91 (d, 3H, $J = 6.5$ Hz), 1.11 (s, 3H), 1.18 (s, 3H), 2.73 (dt, 1H, $J = 4.1$ Hz, $J = 10.6$ Hz), 2.84 (dt, 1H, $J = 3.2$ Hz, $J = 12.2$ Hz), 3.35 (dt, 1H, $J = 4.0$ Hz, $J = 10.4$ Hz), 4.62 (d, 1H, $J = 1.5$ Hz). Anal. calcd for $C_{17}H_{31}NO$: C, 76.92; H, 11.77; N, 5.28. Found: C, 76.83; H, 11.54; N, 5.37.

3.25. Compound **15b**

Colourless oil, 39%; ^{1}H NMR ($CDCl_3$): $\delta = 0.86$–1.00 (m, 2H), 0.91 (d, 3H, $J = 6.3$ Hz), 1.03 (s, 3H), 1.05 (s, 3H), 1.05–1.15 (m, 1H), 1.34–1.61 (m, 6H), 1.70 (m, 2H), 1.75–1.85 (m, 1H), 1.92 (m, 1H), 2.51 (dd, 1H, $J = 7.5$ Hz, $J = 13.2$ Hz), 2.66 (dd, 1H, $J = 8.0$ Hz, $J = 13.2$ Hz), 2.70–2.75 (m, 1H), 2.85 (dt, 1H, $J = 3.0$ Hz, $J = 11.0$ Hz), 3.25 (dt, 1H, $J = 4.0$ Hz, $J = 10.4$ Hz), 4.41 (d, 1H, $J = 2.7$ Hz), 7.13–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 21.9$, 22.5, 25.0, 25.1, 25.8, 27.5, 31.7, 35.2, 39.0, 40.0, 41.5, 43.0, 43.8, 56.2, 76.3, 83.2, 125.7, 128.0 (2C), 129.1 (2C), 141.0. IR (liquid film, cm^{-1}): 1600, 745, 695. Anal. calcd for $C_{22}H_{33}NO$: C, 80.68; H, 10.16; N, 4.28. Found: C, 80.57; H, 10.02; N, 4.17.

3.26. Reduction of **4a–b** and **14a–d** to **16a–d**

General procedure. To a mixture of $LiAlH_4$ (0.60 g, 15.8 mmol) and $AlCl_3$ (0.70 g, 5.25 mmol) in anhydrous THF (40 mL) was slowly added a solution of the corresponding adduct **4a–b** or **14a–d** (3.10 mmol) in THF (20 mL), at 0°C under argon. The solution was stirred for 15 min at this temperature, and quenched by addition of H_2O. The solids were separated by filtration, and the residue was washed with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, the solvents were eliminated in vacuo, and the residue was purified by recrystallisation or chromatography.

3.27. Compound **16a**

Colourless solid, 94%, mp 55–57°C (hexane); $[\alpha]_D^{20} = -19.4$ (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta = 0.72$–1.04 (m, 3H), 0.83 (t, 3H, $J = 7.5$ Hz), 0.88 (s, 3H), 0.90 (d, 3H, $J = 6.4$ Hz), 1.05–1.23 (m, 3H), 1.14 (s, 3H), 1.24–1.53 (m, 5H), 1.37 (m, 1H), 1.62 (m, 3H), 1.88 (m, 2H), 3.10 (d, 1H, $J = 10.7$ Hz), 3.22 (d, 1H, $J = 10.7$ Hz), 3.59 (dt, 1H, $J = 4.0$ Hz, $J = 10.1$ Hz), 8.70 (br. s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 11.3$, 18.2, 20.9, 22.0, 25.6, 25.7, 27.6, 30.8, 30.9, 35.1, 39.1, 44.6, 46.5, 46.6, 51.3, 60.3, 72.2. IR (Nujol dispersion, cm^{-1}): 3120, 1180, 740.

3.28. Compound **16b**

Colourless liquid, 96%; $[\alpha]_D^{20} = -19.6$ (*c* 2.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): $\delta = 0.81$–1.14 (m, 4H), 0.87 (s, 3H), 0.89 (d, 3H, $J = 6.6$ Hz), 1.06 (s, 3H), 1.38–1.84 (m, 9H), 1.90–2.02 (m, 2H), 2.44 (dd, 1H, $J = 6.6$ Hz, $J = 13.3$ Hz), 2.49 (dd, 1H, $J = 4.9$ Hz, $J = 13.3$ Hz), 3.09 (m, 1H), 3.23 (m, 1H), 3.56 (dt, 1H, $J = 4.3$ Hz, $J = 10.3$ Hz), 7.00–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$): $\delta = 18.2$, 20.9, 22.1, 25.6, 25.8, 30.9, 31.1, 35.1, 39.2, 41.5, 44.6, 46.5 (2C), 51.4, 60.4, 72.2, 125.8, 128.1 (2C), 129.0 (2C), 140.0. IR (liquid film, cm^{-1}): 3125, 1180, 740.

3.29. Compound **16d**

Pale yellow liquid, 93%; $[\alpha]_D^{20} = -21.0$ (*c* 4.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): $\delta = 0.73$–0.99 (m, 4H), 0.74 (d, 3H, $J = 6.6$ Hz), 0.76 (d, 3H, $J = 6.0$ Hz), 0.77 (s, 3H), 0.78 (d, 3H, $J = 6.0$ Hz), 1.00 (s, 3H), 1.12–1.73 (m, 10H), 1.81 (m, 2H), 3.00 (d, 1H, $J = 9.3$ Hz), 3.10 (d, 1H, $J = 10.7$ Hz), 3.47 (dt, 1H, $J = 3.9$ Hz, $J = 10.1$ Hz), 8.70 (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 13.5$, 18.1, 20.1, 20.8, 21.9, 25.7, 26.9, 27.7, 30.8, 31.4, 35.0, 43.4, 44.5, 46.5 (2C), 49.2, 60.3, 72.1. IR (liquid film, cm^{-1}): 3120, 1185, 740.

3.30. Synthesis of enantiopure 3-alkyl-substituted piperidines **17a–d**

The final 3-akylpiperidines were isolated by oxidation and elimination of the menthol template by succesive treatment with PCC and KOH solution in MeOH–THF, as previously described.[15]

3.31. (R)-3-Ethylpiperidine **17a** hydrochloride[21]

Colourless solid, 70% from **16a**, mp 163–165°C (benzene); $[\alpha]_D^{20} = +3.0$ (*c* 0.8, MeOH) [lit.[21] $[\alpha]_D = +3.2$ (*c* 1.0, EtOH)]. ^1H NMR ($CDCl_3$): $\delta = 0.85$ (t, 3H, $J = 6.7$ Hz), 0.90–1.00 (m, 1H), 1.10–1.30 (m, 2H), 1.70–2.00 (m, 4H), 2.40 (q, 1H, $J = 11.8$ Hz), 2.68 (q, 1H, $J = 11.0$ Hz), 3.35 (t, 2H, $J = 13.2$ Hz), 9.20 (br. s, 1H), 9.60 (br. s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 10.5$, 22.0, 26.5, 28.4, 34.6, 44.2, 48.8.

3.32. (S)-3-Benzylpiperidine **17b**

This piperidine was characterised as *N*-tosylamide. White solid, 42% from **16b**, mp 121–122°C (Et_2O); $[\alpha]_D^{20} = +71.9$ (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$): $\delta = 0.80$–1.00 (m, 1H), 1.50–1.75 (m, 3H), 1.80–2.00 (m, 1H), 2.14 (dd, 1H, $J = 10.3$ Hz, $J = 10.9$ Hz), 2.30–2.50 (m, 2H), 2.44 (s, 3H), 2.62 (dd, 1H, $J = 6.6$ Hz, $J = 13.5$ Hz), 3.50–3.60 (m, 2H), 7.14 (d, 2H, $J = 8.1$ Hz), 7.20–7.40 (m, 5H), 7.63 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 21.5$, 24.2, 29.5, 37.3, 40.0, 46.7, 51.5, 126.1, 127.6 (2C), 128.3 (2C), 129.0 (2C), 129.6 (2C), 133.1, 139.3, 143.3. Anal. calcd for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04; N, 4.25. Found: C, 69.41; H, 7.18; N, 4.09.

3.33. (S)-3-Isopropylpiperidine **17d** hydrochloride

White solid, 72% from **16d**, mp 118–119°C (acetone); $[\alpha]_D^{20} = +8.4$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 0.91$ (d, 3H, $J = 4.0$ Hz), 0.92 (d, 3H, $J = 4.0$ Hz), 1.10–1.30 (m, 1H), 1.54 (m, 1H), 1.70–2.00 (m, 4H), 2.56 (t, 1H, $J = 12.3$ Hz), 2.73 (dt, 1H, $J = 4.0$ Hz, $J = 12.5$ Hz), 3.43 (t, 2H, $J = 9.0$ Hz), 9.40 (br. s, 1H), 9.70 (br. s, 1H); ^{13} C NMR ($CDCl_3$): $\delta = 18.9$, 19.4, 22.2, 25.6, 30.6,

39.0, 44.1, 47.3. Anal. calcd for $C_8H_{18}NCl$: C, 58.86; H, 11.12; N, 8.59. Found: C, 58.64; H, 11.31; N, 8.42.

3.34. Reduction and deoxygenation of compound **4c**

To a solution of diastereomer **4c** (32 mg, 0.1 mmol) in dry toluene, cooled to 0°C under an argon atmosphere, was added a solution of DIBALH (0.8 mL, 1 M in toluene) and the mixture was stirred for 1 h. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo, yielding 26 mg (92%) of **18** as a colourless oil: ^{1}H NMR ($CDCl_3$): $\delta = 0.85$–1.02 (m, 4H), 0.88 (s, 3H), 0.89 (d, 3H, $J = 6.0$ Hz), 1.14 (s, 3H), 1.27 (m, 3H), 1.33–1.82 (m, 9H), 1.83–2.02 (m, 2H), 3.18 (dd, 2H, $J = 10.8$ Hz, $J = 25.6$ Hz), 3.50–3.70 (m, 3H), 9.0 (br. s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 18.4$, 20.9, 22.0, 25.6, 29.6, 30.9, 31.4, 34.5, 35.0, 37.7, 44.5, 46.5 (2C), 51.5, 60.2, 60.8, 72.2. This product was treated with triphenylphosphine (0.14 mmol, 36 mg) and carbon tetrabromide (0.11 mmol, 38 mg) in dichloromethane at 0°C for 1.5 h. Filtration of the mixture and solvent removal afforded an oil which was subsequently reduced with tributyltin hydride (38 mL, 0.138 mmol) and AIBN (cat.) in benzene at reflux (4 h). Acid–base workup yield pure piperidinylmenthol **16a** (65%).

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