Access to 2,6-Disubstituted 4-Oxopiperidines using a 6-*endo-trig* Cyclization: Stereoselective Synthesis of Spruce Alkaloid and (+)-241D

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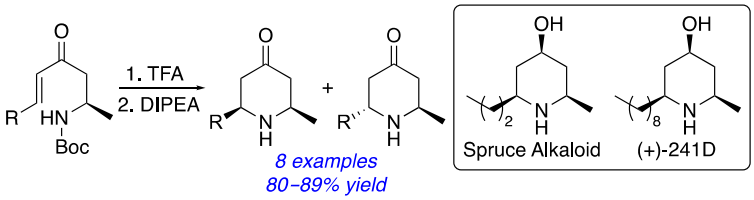


Abstract: A synthetic route to *cis*-2-methyl-4-oxo-6-alkylpiperidines has been developed using a 6-*endo*-*trig* cyclization of *E*-enones. The base-mediated intramolecular cyclization was found to be general for both alkyl and aryl substituted enones, providing the corresponding 4-oxopiperidines in high yields (80–89%). Stereoselective reduction of the 2,6-*cis*-disubstituted 4-oxopiperidines then gave the 2,4,6-*cis*,*cis*-trisubstituted 4-hydroxypiperidines in high diastereoselectivity. The general nature of this approach was demonstrated with the synthesis of the natural products, spruce alkaloid and (+)-241D.

The piperidine ring system is found as a key structural element in a vast array of natural products and pharmaceutically active compounds.[1] Among the various structural classes, 2,6-*cis*-dialkylpiperidines have been isolated from plants, insects and amphibians and have demonstrated a wide range of biological activities.[1] These include *cis*,*cis*-2-methyl-4-hydroxy-6-alkylpiperidines such as spruce alkaloid (**1**), isolated from the Colorado blue spruce, *Picea pungens* (Figure 1).[2] Interestingly, the absolute configuration of spruce alkaloid (**1**) is not known. The structure was determined from GC-MS data, a racemic synthesis and analogy to similar 2,6-disubstituted piperidines from conifers, which generally possess the same absolute configuration at the C2-methyl center.[2] Other examples of this class of alkaloid include (+)-241D (**2**), isolated from the skin of the Panamanian poison frog *Dendrobates speciosus*.[3] (+)-241D (**2**) and the corresponding 4-piperidone **3** are potent inhibitors of binding of [^{3}H]perhydrohistrionicotoxin to nicotinic acetylcholine receptor ion channels.[4]

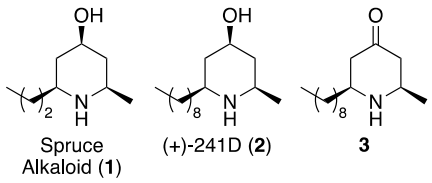


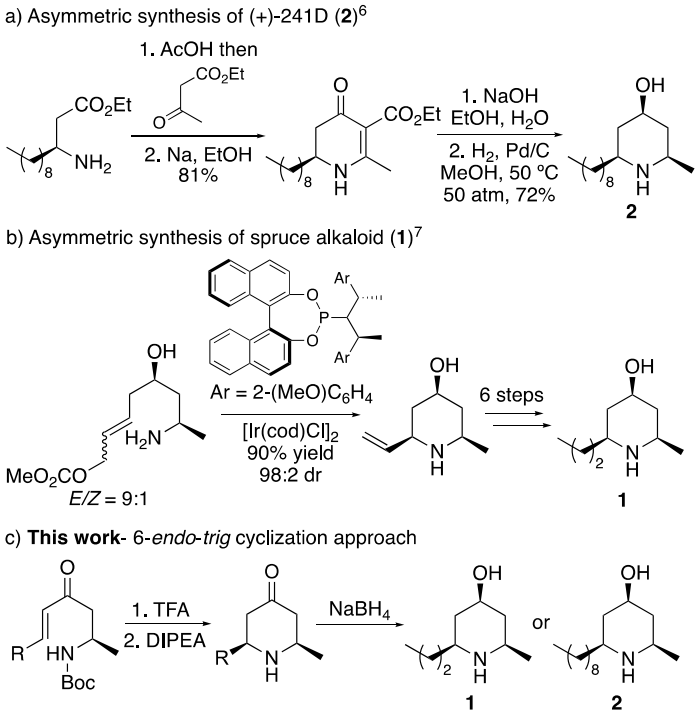
Figure 1. Structures of biologically active *cis*-2,6-disubstituted piperidines.

As a result of significant biological activity and the common *cis*,*cis*-2-methyl-4-hydroxy-6-alkylpiperidine framework, there have been significant interest in developing approaches for the synthesis of these alkaloids. In particular, many strategies have been reported for the asymmetric synthesis of (+)-241D (**2**).[5] These include a highly efficient, six-step approach reported by Ma and Sun involving the condensation of ethyl acetoacetate with a β-amino ester, followed by hydrolytic decarboxylation and high pressure hydrogenation (Scheme 1a).[6] This gave (+)-241D (**2**) in 46% overall yield. In contrast, only one asymmetric synthesis has been reported for the proposed structure of spruce alkaloid (**1**).[7] Helmchen and co-workers used an iridium-catalyzed allylic cyclization, in combination with the matched pairing of a chiral allylic carbonate and a chiral phosphoramidite ligand as the key transformation in a fourteen-step synthesis of spruce alkaloid (**1**) (Scheme 1b). This approach was also

used for the preparation of other 2,6-*cis*-dialkylpiperidine alkaloids such as (+)-prosophylline and (+)-241D.[7]

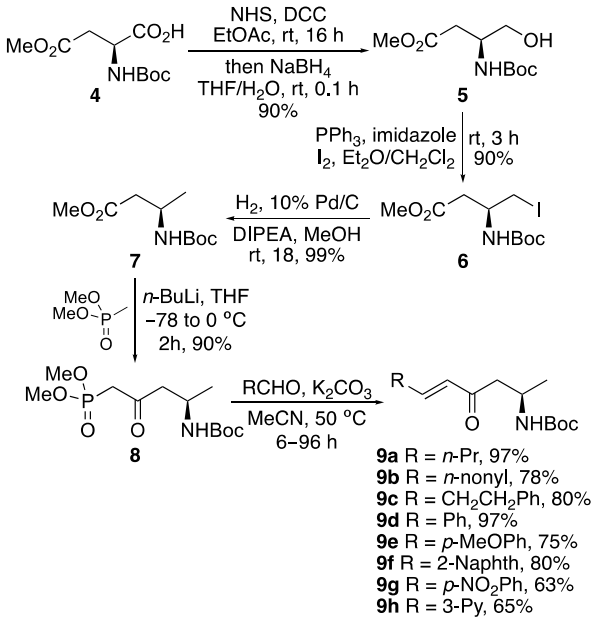
In recent years, we have reported stereoselective methods for the synthesis of highly substituted pipecolic acid analogues using a 6-*endo-trig* cyclization of enone-derived α-amino acids.[8,9] We found that formation of a particular cyclization conformer using substrate control generated either 2,6-*trans*- or 2,6-*cis*-6-substituted 4-oxopipecolic acids. We were interested in investigating a similar approach for the synthesis of *cis*-2-methyl-4-oxo-6-alkylpiperidines (Scheme 1c). Herein, we now report the use of a 6-*endo-trig* cyclization of amine-substituted enones for the preparation of a series of 2-methyl-4-hydroxy-6-alkylpiperidines and the application of this approach for the eight-step synthesis of spruce alkaloid and (+)-241D.

Scheme 1. Methods for the Synthesis of *cis*,*cis*-2-Methyl-4-hydroxy-6-alkylpiperidines



A series of amine-substituted enones were prepared in five steps from commercially available *N*-Boc-L-aspartic acid 4-methyl ester (**4**) (Scheme 2). The α-carboxylic acid of **4** was reduced in a two-stage process involving activation with *N*-hydroxysuccinimide (NHS) and DCC, followed by reduction of the resulting succinimide ester with sodium borohydride.[10] Direct conversion of alcohol **5** to iodide **6** was achieved using triphenylphosphine, imidazole and iodine under Tanner's modified conditions.[11] Basic hydrodehalogenation under mild conditions allowed the highly efficient synthesis of β-homoalanine derivative **7**. It should be noted that Hünig's base is required during the hydrodehalogenation to neutralize the hydrogen iodide formed and prevent poisoning of the Pd/C catalyst.[12] Reaction of **7** with the lithium anion of dimethyl methylphosphonate (2.5 equivalents) completed the four-step synthesis of β-ketophosphonate ester **8** in 72% overall yield.[13] It should be noted that this simple and robust four-step synthesis was easily scalable for the efficient multigram synthesis of β-ketophosphonate ester **8**. Horner-Wadsworth-Emmons (HWE) reaction of **8** with various alkyl and aryl aldehydes gave the corresponding *E*-enones **9a**–**9h** as the sole products in 63–97% yield.[14]

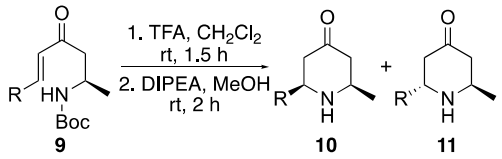
Scheme 2. Synthesis of *E*-Enones 9[a]



[a]Isolated yields are shown.

Enones **9** were then converted to 2,6-disubstituted 4-oxopiperidines **10** and **11** by acidic removal of the Boc-protecting group, followed by cyclization of the resulting amine by treatment with DIPEA (Table 1). In our previous study involving 6-*endo-trig* cyclization of α-amino acid derived enones, the use of this two-step approach gave the corresponding 2,6-*cis*-6-substituted 4-oxopipecolic acids as the major products, although with modest diastereoselectivity.[9] As expected of enones **9**, with a smaller methyl group to impart facial selectivity during the conjugate addition, the 2,6-*cis*- and 2,6-*trans*-6-substituted 4-oxopiperidines were formed in essentially a 1:1 ratio.[15,16] However, these structurally more simple substrates were found to undergo the two-stage deprotection and cyclization in a highly efficient and general manner, forming the two diastereomers in highly consistent yields (80–89%), irrespective of the enone side-chain. Furthermore, 4-oxopiperidines **10** and **11** were easily separated by column chromatography, allowing the isolation of the 2,6-*cis*-diastereomer in 41–46% yields over two steps.

Table 1. 6-*Endo-Trig* Cyclization of *E*-Enones 9[a]



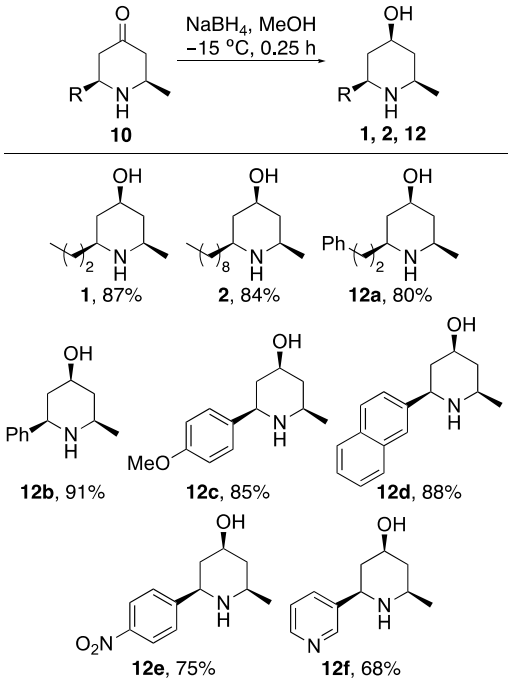
9 **10** **11**

entry	R	overall yield (%)	**10** (%)	**11** (%)
1	*n*-Pr (**9a**)	85	43	42
2	*n*-nonyl (**9b**)	89	45	44
3	CH_2CH_2Ph (**9c**)	82	42	40
4	Ph (**9d**)	82	42	40
5	*p*-MeOPh (**9e**)	83	46	37
6	2-Naphth (**9f**)	86	44	42
7	*p*-NO_2Ph (**9g**)	84	43	41
8	3-Py (**9h**)	80	41	39

[a]Isolated yields are shown.

To complete the synthesis of spruce alkaloid (**1**) and (+)-241D (**2**) required the stereoselective reduction of the 2,6-*cis*-4-oxopiperidines. We briefly surveyed various reducing agents [e.g. L-selectride, $NaBH_3CN$ and $NaBH(OAc)_3$] and found that sodium borohydride was fast, selective and high yielding (Scheme 3).[5d,17] In all cases, this gave a diastereoselective ratio of 9:1 with the major *cis*,*cis*-4-hydroxypiperidines isolated in 68–91% yields. This completed the total synthesis of spruce alkaloid (**1**) and (+)-241D (**2**) in eight steps and in 26% and 21% overall yield, respectively, as well as various novel *cis*,*cis*-2-methyl-4-hydroxy-6-arylpiperidines (**12c**–**12f**). The relative stereochemistry of all novel compounds generated from the 6-*endo*-*trig* cyclization and the stereoselective reduction was confirmed using NOE experiments.[18]

Scheme 3. Stereoselective Reduction of 4-Piperidones 10[a]



[a]Isolated yields of *cis*,*cis*-4-hydroxypiperidines are shown.

In summary, a short and efficient synthesis of a series of amino substituted *E*-enones was developed from an L-aspartic acid analogue using hydrodehalogenation and HWE reactions as the key steps. These

compounds were investigated as substrates for a base-mediated 6-*endo-trig* cyclization. The two-stage deprotection-cyclization process was highly efficient and tolerant of both aliphatic and aryl side chains. Stereoselective reduction of the resulting 2,6-*cis*-4-oxopiperidines completed a new approach for the preparation of the natural products, spruce alkaloid and (+)-241D, as well as the synthesis of a series of novel *cis*,*cis*-2-methyl-4-hydroxy-6-arylpiperidines.

EXPERIMENTAL SECTION

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a solvent purification system. All reactions were performed in oven-dried glassware under an atmosphere of argon unless otherwise stated. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was performed using silica gel 60 (40–63 μm). Aluminium-backed plates pre-coated with silica gel $60F_{254}$ were used for thin layer chromatography and were visualized with a UV lamp or by staining with potassium permanganate. ^{1}H NMR spectra were recorded on a NMR spectrometer at either 400 or 500 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane or the solvent as the internal standard ($CDCl_3$, δ 7.26 ppm or CD_3OD, δ 3.31 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances, integration). ^{13}C NMR spectra were recorded on a NMR spectrometer at either 101 or 126 MHz and data are reported as follows: chemical shift in ppm relative to tetramethylsilane or the solvent as internal standard ($CDCl_3$, δ 77.0 ppm or CD_3OD, δ 49.0 ppm), multiplicity with respect to hydrogen (deduced from DEPT experiments, C, CH, CH_2 or CH_3). IR spectra were recorded on a FTIR spectrometer; wavenumbers are indicated in cm^{-1}. Mass spectra were recorded using electrospray techniques. HRMS spectra were recorded using a dual-focusing magnetic analyzer mass spectrometer. Melting points are uncorrected. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using a polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

Methyl (3*S*)-3-(*tert*-butoxycarbonylamino)-4-hydroxybutanoate (5).[19] To a solution of *N*-Boc-L-aspartic acid 4-methyl ester (**4**) (8.27 g, 33.5 mmol) in ethyl acetate (200 mL) at 0 °C was added *N*-hydroxysuccinimide (4.24 g, 36.9 mmol). *N*,*N*'-Dicyclohexylcarbodiimide (7.05 g, 34.2 mmol) in ethyl acetate (20 mL) was then added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Once the reaction was complete, the reaction mixture was filtered through Celite. The filtrate was washed with saturated sodium carbonate solution (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was then dissolved in tetrahydrofuran (20 mL) and added dropwise to a solution of sodium borohydride (2.03 g, 53.6 mmol) in a mixture of tetrahydrofuran and water (7.5:1, 85 mL). The reaction mixture was stirred for 0.1 h before quenching with saturated aqueous ammonium chloride (5 mL). The reaction mixture was extracted with dichloromethane (3 × 50 mL). The organic fractions were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel, eluting with 30% ethyl acetate in dichloromethane gave methyl (3*S*)-3-(*tert*-butoxycarbonylamino)-4-hydroxybutanoate (**5**) as a colorless oil (7.03 g, 90%). R_f 0.22 (40% ethyl acetate in dichloromethane); $[\alpha]_D^{26}$ +5.6 (*c* 1.0, $CHCl_3$), lit.[19] $[\alpha]_D^{23}$ +6.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.62 (d, J = 6.1 Hz, 2H), 2.82 (br s, 1H), 3.65–3.73 (m, 5H), 3.92–4.04 (m, 1H), 5.25 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.4 (3 × CH_3), 35.8 (CH_2), 49.4 (CH), 51.9 (CH_3), 64.3 (CH_2), 79.8 (C), 155.9 (C), 172.3 (C); MS (ESI) *m/z* 256 (MNa^+, 100).

Methyl (3*S*)-3-(*tert*-butoxycarbonylamino)-4-iodobutanoate (6).[10] To a suspension of imidazole (4.11 g, 60.4 mmol) and triphenylphosphine (11.9 g, 45.3 mmol) in a mixture of diethyl ether and dichloromethane (2:1, 100 mL) at 0 °C was added iodine (11.5 g, 45.3 mmol) in three portions over 0.5 h. After stirring for a further 0.2 h, a solution of methyl (3*S*)-3-(*tert*-butoxycarbonylamino)-4-hydroxybutanoate (**5**) (7.03 g, 30.2 mmol) in a mixture of diethyl ether and dichloromethane (2:1, 50 mL) was added and the resulting mixture was stirred for 3 h at room temperature. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo.* Purification by flash column

chromatography on silica gel, eluting with 30% diethyl ether in petroleum ether (40–60) gave methyl (3*S*)-3-(*tert*-butoxycarbonylamino)-4-iodobutanoate (**6**) (9.33 g, 90%) as a colorless oil. Spectroscopic data were consistent with the literature.[10] R_f 0.27 (20% ethyl acetate in petroleum ether); $[\alpha]_D^{33}$ +7.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.60 (dd, J = 16.4, 6.1 Hz, 1H), 2.70 (dd, J = 16.4, 5.6 Hz, 1H), 3.28–3.45 (m, 2H), 3.66 (s, 3H), 3.81–3.95 (m, 1H), 5.11 (d, J = 7.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.1 (CH_2), 28.3 (3 × CH_3), 38.5 (CH_2), 47.7 (CH), 51.9 (CH_3), 80.0 (C) 154.7 (C), 171.1 (C); MS (ESI) *m/z* 366 (MNa^+, 100).

Methyl (3*R*)-3-(*tert*-butoxycarbonylamino)butanoate (7).[20] A solution of methyl (3*S*)-3-(*tert*-butoxycarbonylamino)-4-iodobutanoate (**6**) (9.33 g, 27.2 mmol), *N*,*N*-diisopropylethylamine (7.11 mL, 40.8 mmol) and 10% Pd/C (2.89 g, 2.72 mmol) in methanol (50 mL) were purged with hydrogen for 0.5 h. The reaction mixture was stirred under an atmosphere of hydrogen for 18 h at room temperature. The mixture was then filtered through Celite and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in dichloromethane (100 mL) and washed with a saturated solution of sodium hydrogen carbonate (50 mL), 1 M hydrochloric acid (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give methyl (3*R*)-3-(*tert*-butoxycarbonylamino)butanoate (**7**) as a colorless oil (5.87 g, 99%). Spectroscopic data were consistent with the literature.[20] R_f 0.17 (20% ethyl acetate in petroleum ether); $[\alpha]_D^{26}$ +21.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J = 6.8 Hz, 3H), 1.43 (s, 9H), 2.47 (dd, J = 15.5, 6.0 Hz, 1H), 2.52 (dd, J = 15.5, 5.4 Hz, 1H), 3.68 (s, 3H), 4.03 (br s, 1H), 4.91 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6 (CH_3), 28.5 (3 × CH_3), 40.8 (CH_2), 43.6 (CH), 51.8 (CH_3), 79.4 (C), 155.2 (C), 172.1 (C); MS (ESI) *m/z* 240 (MNa^+, 100).

(4*R*)-4-(*tert*-Butoxycarbonylamino)-1-(dimethyloxyphosphoryl)pentan-2-one (8). Dimethyl methylphosphonate (3.74 mL, 34.5 mmol) was dissolved in tetrahydrofuran (100 mL) and cooled to −78 °C under an argon atmosphere. *n*-Butyl lithium (2.5 M, in hexane, 13.8 mL, 34.5 mmol) was added dropwise and the mixture was stirred for 0.3 h. A solution of methyl (3*R*)-3-(*tert*-butoxycarbonylamino)butanoate (**7**) (3.00 g, 13.8 mmol) in tetrahydrofuran (20 mL) was added

dropwise. The resulting mixture was then stirred at −78 °C for 0.5 h and allowed to warm to 0 °C over a period of 1 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (4 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel, eluting with 40% ethyl acetate in dichloromethane gave (4*R*)-4-(*tert*-butoxycarbonylamino)-1-(dimethyloxyphosphoryl)pentan-2-one (**8**) (3.84 g, 90%) as a colorless oil. R_f 0.19 (100% ethyl acetate); IR (neat) 3316, 2976, 1704, 1700, 1248 cm^{-1}; $[\alpha]_D^{31}$ +38.3 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J = 6.7 Hz, 3H), 1.39 (s, 9H), 2.71 (dd, J = 16.9, 5.9 Hz, 1H), 2.80 (dd, J = 16.9, 5.9 Hz, 1H), 3.03 (dd, J = 22.6, 13.6 Hz, 1H), 3.12 (dd, J = 22.6, 13.6 Hz, 1H), 3.74 (d, J = 0.8 Hz, 3H), 3.77 (d, J = 0.8 Hz, 3H), 3.93–4.09 (m, 1H), 4.92 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6 (CH_3), 28.4 (3 × CH_3), 41.9 (d, $J_{C\text{-}P}$ = 127.5 Hz, CH_2), 43.3 (CH), 50.2 (CH_2), 53.1 (d, $J_{C\text{-}O\text{-}P}$ = 6.5 Hz, CH_3), 53.2 (d, $J_{C\text{-}O\text{-}P}$ = 6.5 Hz, CH_3), 79.3 (C), 155.2 (C), 200.6 (C); MS (ESI) *m/z* 332 (MNa^+, 100); HRMS (ESI) calcd for $C_{12}H_{24}NNaO_6P$ (MNa^+), 332.1233, found 332.1225.

(2*R*,5*E*)-2-(*tert*-Butoxycarbonylamino)-4-oxonona-5-ene (9a). (4*R*)-4-(*tert*-Butoxycarbonylamino)-1-(dimethyloxyphosphoryl)pentan-2-one (**8**) (0.421 g, 1.36 mmol) was dissolved in anhydrous acetonitrile (14 mL) and potassium carbonate (0.225 g, 1.63 mmol) was added. The mixture was stirred at room temperature for 0.5 h followed by addition of butyraldehyde (0.250 mL, 2.72 mmol). The temperature was increased to 50 °C and the mixture stirred for 72 h. The solution was then concentrated *in vacuo*, redissolved in ethyl acetate (20 mL), washed with water (2 × 15 mL) and then brine (15 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification using a plug of silica gel, eluting with 20% ethyl acetate in petroleum ether (40–60) gave (2*R*,5*E*)-2-(*tert*-butoxycarbonylamino)-4-oxonona-5-ene (**9a**) as a clear colorless oil (0.337 g, 97%). R_f 0.24 (20% ethyl acetate/petroleum ether); IR (neat) 3350, 2968, 1689, 1516, 1365 cm^{-1}; $[\alpha]_D^{26}$ +9.3 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H), 1.43 (s, 9H), 1.46–1.55 (m, 2H), 2.20 (qd, J = 6.9, 1.5 Hz, 2H), 2.64 (dd, J = 15.9, 6.5 Hz, 1H), 2.86 (dd, J = 15.9, 4.5 Hz, 1H), 3.98–4.09 (m, 1H),

5.02 (br s, 1H), 6.09 (dt, J = 15.9, 1.5 Hz, 1H), 6.86 (dt, J = 15.9, 6.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7 (CH_3), 20.5 (CH_3), 21.3 (CH_2), 28.4 (3 × CH_3), 34.5 (CH_2), 43.7 (CH), 45.7 (CH_2), 79.1 (C), 130.8 (CH), 148.2 (CH), 155.2 (C), 199.2 (C); MS (ESI) *m/z* 278 (MNa^+, 100); HRMS (ESI) calcd for $C_{14}H_{25}NNaO_3$ (MNa^+), 278.1727, found 278.1725.

(2*R*,5*E*)-2-(*tert*-Butoxycarbonylamino)-4-oxopentadec-5-ene (9b). The reaction was carried out according to the procedure for the synthesis of **9a** using (4*R*)-4-(*tert*-butoxycarbonylamino)-1-(dimethyloxyphosphoryl)pentan-2-one (**8**) (0.405 g, 1.31 mmol) and decanal (0.500 mL, 2.62 mmol) for 96 h. Purification by flash column chromatography on silica gel, eluting with 30% diethyl ether in petroleum ether (40–60) gave (2*R*,5*E*)-2-(*tert*-butoxycarbonylamino)-4-oxopentadec-5-ene (**9b**) (0.345 g, 78%) as a colorless oil. R_f 0.25 (30% diethyl ether in petroleum ether); IR (neat) 3327, 2958, 1693, 1365 cm^{-1}; $[\alpha]_D^{25}$ +4.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.3 Hz, 3H), 1.20 (d, J = 6.7 Hz, 3H), 1.23–1.34 (m, 12H), 1.39–1.50 (m, 11H), 2.20 (q, J = 7.0 Hz, 2H), 2.63 (dd, J = 15.7, 6.6 Hz, 1H), 2.85 (dd, J = 15.7, 4.5 Hz, 1H), 3.96–4.08 (m, 1H), 4.95 (br s, 1H), 6.08 (d, J = 15.6 Hz, 1H), 6.85 (dt, J = 15.6, 7.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1 (CH_3), 20.5 (CH_3), 22.7 (CH_2), 28.1 (CH_2), 28.4 (3 × CH_3), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 32.5 (CH_2), 43.7 (CH), 45.7 (CH_2), 79.2 (C), 130.6 (CH), 148.5 (CH), 155.2 (C), 199.2 (C); MS (ESI) *m/z* 362 (MNa^+, 100); HRMS (ESI) calcd for $C_{20}H_{37}NNaO_3$ (MNa^+), 362.2666, found 362.2649.

(2*R*,5*E*)-8-Phenyl-2-(*tert*-butoxycarbonylamino)-4-oxooct-5-ene (9c). The reaction was carried out according to the procedure for the synthesis of **9a** using (4*R*)-4-(*tert*-butoxycarbonylamino)-1-(dimethyloxyphosphoryl)pentan-2-one (**8**) (0.349 g, 1.13 mmol) and hydrocinnamaldehyde (0.300 mL, 2.26 mmol) for 48 h. Purification by flash column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40–60) gave (2*R*,5*E*)-8-phenyl-2-(*tert*-butoxycarbonylamino)-4-oxooct-5-ene (**9c**) (0.288 g, 80%) as a pale yellow oil. R_f 0.19 (20% ethyl acetate in petroleum ether); IR (neat) 3353, 2976, 1692, 1496, 1247, 1221, 1054 cm^{-1}; $[\alpha]_D^{23}$ +4.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J = 6.7 Hz, 3H), 1.43 (s, 9H), 2.53 (q, J = 6.8 Hz, 2H), 2.60 (dd, J = 15.7, 7.8 Hz,

1H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.84 (dd, *J* = 15.7, 4.5 Hz, 1H), 3.95–4.08 (m, 1H), 4.99 (br s, 1H), 6.09 (d, *J* = 15.9 Hz, 1H), 6.87 (dt, *J* = 15.9, 6.8 Hz, 1H), 7.14–7.23 (m, 3H), 7.25–7.32 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.5 (CH_3), 28.4 (3 × CH_3), 34.2 (CH_2), 34.3 (CH_2), 43.7 (CH), 45.8 (CH_2), 79.1 (C), 126.2 (CH), 128.3 (2 × CH), 128.5 (2 × CH), 131.0 (CH), 140.6 (C), 146.9 (CH), 155.1 (C), 198.9 (C); MS (ESI) *m/z* 340 (MNa^+, 100); HRMS (ESI) calcd for $C_{19}H_{27}NNaO_3$ (MNa^+), 340.1883, found 340.1868.

(2*R*,5*E*)-6-Phenyl-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (9d). The reaction was carried out according to the procedure for the synthesis of **9a** using (4*R*)-4-(*tert*-butoxycarbonylamino)-1-(dimethyloxyphosphoryl)pentan-2-one (**8**) (0.251 g, 0.810 mmol) and benzaldehyde (0.160 mL, 1.62 mmol) for 48 h. Purification by flash column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40–60) gave (2*R*,5*E*)-6-phenyl-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (**9d**) (0.227 g, 97%) as a white solid. Mp 59–62 °C; R_f 0.18 (20% ethyl acetate in petroleum ether); IR (neat) 3345, 2976, 1687, 1655, 1608, 1495 cm^{-1}; $[\alpha]_D^{23}$ +10.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, *J* = 6.8 Hz, 3H), 1.43 (s, 9H), 2.77 (dd, *J* = 15.8, 6.8 Hz, 1H), 3.00 (dd, *J* = 15.8, 4.6 Hz, 1H), 4.05–4.18 (m, 1H), 5.04 (br s, 1H), 6.73 (d, *J* = 16.2 Hz, 1H), 7.36–7.41 (m, 3H), 7.52–7.54 (m, 2H), 7.56 (d, *J* = 16.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6 (CH_3), 28.4 (3 × CH_3), 43.8 (CH), 46.6 (CH_2), 79.2 (C), 126.4 (CH), 128.4 (2 × CH), 129.0 (2 × CH), 130.6 (CH), 134.4 (C), 143.2 (CH), 155.2 (C), 198.9 (C); MS (ESI) *m/z* 312 (MNa^+, 100); HRMS (ESI) calcd for $C_{17}H_{23}NNaO_3$ (MNa^+), 312.1570, found 312.1558.

(2*R*,5*E*)-6-(4'-Methoxyphenyl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (9e). The reaction was carried out according to the procedure for the synthesis of **9a** using (4*R*)-4-(*tert*-butoxycarbonylamino)-1-(dimethyloxyphosphoryl)pentan-2-one (**8**) (0.241 g, 0.781 mmol) and anisaldehyde (0.190 mL, 1.56 mmol) for 96 h. Purification by flash column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40–60) gave (2*R*,5*E*)-6-(4'-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (**9e**) (0.186 g, 75%) as a white solid. Mp 102–105 °C; R_f 0.10 (20% ethyl acetate in

petroleum ether); IR (neat) 3375, 2980, 1682, 1600, 1511 cm^{-1}; $[\alpha]_D^{23}$ +50.1 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.8 Hz, 3H), 1.43 (s, 9H), 2.74 (dd, *J* = 15.7, 6.8 Hz, 1H), 2.97 (dd, *J* = 15.7, 4.5 Hz, 1H), 3.84 (s, 3H), 4.04–4.16 (m, 1H), 5.03 (br s, 1H), 6.62 (d, *J* = 16.1 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6 (CH_3), 28.4 (3 × CH_3), 43.9 (CH), 46.4 (CH_2), 55.4 (CH_3), 79.2 (C), 114.4 (2 × CH), 124.2 (CH), 127.0 (C), 130.1 (2 × CH), 143.1 (CH), 155.2 (C), 161.7 (C), 198.8 (C); MS (ESI) *m/z* 342 (MNa^+, 100); HRMS (ESI) calcd for $C_{18}H_{25}NNaO_4$ (MNa^+), 342.1676, found 342.1661.

(2*R*,5*E*)-6-(Naphthalen-2'-yl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (9f). The reaction was carried out according to the procedure for the synthesis of **9a** using (4*R*)-4-(*tert*-butoxycarbonylamino)-1-(dimethyloxyphosphoryl)pentan-2-one (**8**) (0.262 g, 0.849 mmol) and 2-naphthaldehyde (0.265 g, 1.70 mmol) for 48 h. Purification by flash column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40–60) gave (2*R*,5*E*)-6-(naphthalen-2'-yl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (**9f**) (0.231 g, 80%) as a white solid. Mp 103–106 °C; R_f 0.35 (30% ethyl acetate in petroleum ether); IR (neat) 3358, 2972, 1683, 1518, 1364 cm^{-1}; $[\alpha]_D^{23}$ +30.4 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, *J* = 6.7 Hz, 3H), 1.44 (s, 9H), 2.81 (dd, *J* = 15.9, 6.7 Hz, 1H), 3.04 (dd, *J* = 15.9, 4.4 Hz, 1H), 4.07–4.21 (m, 1H), 5.00 (br s, 1H), 6.85 (d, *J* = 16.1 Hz, 1H), 7.48–7.56 (m, 2H), 7.68 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.75 (d, *J* = 16.1 Hz, 1H), 7.81–7.90 (m, 3H), 7.97 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6 (CH_3), 28.4 (3 × CH_3), 43.9 (CH), 46.7 (CH_2), 79.2 (C), 123.5 (CH), 126.4 (CH), 126.8 (CH), 127.4 (CH), 127.8 (CH), 128.6 (CH), 128.7 (CH), 130.5 (CH), 131.9 (C), 133.3 (C), 134.4 (C), 143.2 (CH), 155.2 (C), 198.8 (C); MS (ESI) *m/z* 362 (MNa^+, 100); HRMS (ESI) calcd for $C_{21}H_{25}NNaO_3$ (MNa^+), 362.1727, found 362.1710.

(2*R*,5*E*)-6-(4'-Nitrophenyl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (9g). The reaction was carried out according to the procedure for the synthesis of **9a** using (4*R*)-4-(*tert*-butoxycarbonylamino)-1-(dimethyloxyphosphoryl)pentan-2-one (**8**) (0.209 g, 0.676 mmol) and 4-nitrobenzaldehyde (0.204 g, 1.35 mmol) for 6 h. Purification by flash column chromatography on silica gel, eluting with 30% ethyl

acetate in petroleum ether (40–60) gave (2*R*,5*E*)-6-(4'-nitrophenyl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (**9g**) (0.143 g, 63%) as a pale yellow solid. Mp 122–126 °C; R_f 0.19 (30% ethyl acetate in petroleum ether); IR (neat) 3365, 2980, 1683, 1612, 1514 cm^{-1}; $[\alpha]_D^{26}$ +14.7 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, *J* = 6.7 Hz, 3H), 1.43 (s, 9H), 2.80 (dd, *J* = 15.8, 6.7 Hz, 1H), 3.06 (dd, *J* = 15.8, 4.2 Hz, 1H), 4.07–4.20 (m, 1H), 4.94 (br s, 1H), 6.86 (d, *J* = 16.2 Hz, 1H), 7.63 (d, *J* = 16.2 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 8.26 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6 (CH_3), 28.4 (3 × CH_3), 43.8 (CH), 47.4 (CH_2), 79.4 (C), 124.2 (2 × CH), 128.9 (2 × CH), 129.6 (CH), 140.0 (CH), 140.7 (C), 148.6 (C), 155.2 (C), 198.2 (C); MS (ESI) *m/z* 357 (MNa^+, 100); HRMS (ESI) calcd for $C_{17}H_{22}N_2NaO_5$ (MNa^+), 357.1421, found 357.1405.

(2*R*,5*E*)-6-(Pyridin-3'-yl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (9h). The reaction was carried out according to the procedure for the synthesis of **9a** using (4*R*)-4-(*tert*-butoxycarbonylamino)-1-(dimethyloxyphosphoryl)pentan-2-one (**8**) (0.212 g, 0.687 mmol) and 3-pyridinecarboxaldehyde (0.130 mL, 1.37 mmol) for 24 h. Purification by flash column chromatography on silica gel, eluting with 40% ethyl acetate in dichloromethane gave (2*R*,5*E*)-6-(pyridin-3'-yl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (**9h**) (0.130 g, 65%) as an off-white solid. Mp 93–96 °C; R_f 0.1 (40% ethyl acetate in dichloromethane); IR (neat) 3362, 2970, 1678, 1519, 1365 cm^{-1}; $[\alpha]_D^{26}$ +6.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.8 Hz, 3H), 1.43 (s, 9H), 2.78 (dd, *J* = 15.8, 6.8 Hz, 1H), 3.03 (dd, *J* = 15.8, 4.6 Hz, 1H), 4.06–4.19 (m, 1H), 5.03 (br s, 1H), 6.81 (d, *J* = 16.3 Hz, 1H), 7.35 (dd, *J* = 7.9, 4.1 Hz, 1H), 7.59 (d, *J* = 16.3 Hz, 1H), 7.85–7.91 (m, 1H), 8.62 (d, *J* = 4.1 Hz, 1H), 8.77 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.6 (CH_3), 28.4 (3 × CH_3), 43.8 (CH), 47.1 (CH_2), 79.3 (C), 123.8 (CH), 128.0 (CH), 130.3 (C), 134.4 (CH), 139.3 (CH), 150.1 (CH), 151.2 (CH), 155.2 (C), 198.3 (C); MS (ESI) *m/z* 313 (MNa^+, 100); HRMS (ESI) calcd for $C_{16}H_{22}N_2NaO_3$ (MNa^+), 313.1523, found 313.1513.

(2*R*,6*S*)-2-Methyl-6-propylpiperidin-4-one (10a) and (2*R*,6*R*)-2-methyl-6-propylpiperidin-4-one (11a). (2*R*,5*E*)-2-(*tert*-Butoxycarbonylamino)-4-oxonona-5-ene (**9a**) (0.298 g, 1.17 mmol) was

dissolved in dichloromethane (12 mL) and trifluoroacetic acid (0.890 mL, 11.7 mmol) was added dropwise. The mixture was stirred for 1.5 h at room temperature. The mixture was then concentrated *in vacuo* and the crude residue was redissolved in methanol (12 mL) and cooled to 0 °C. *N*,*N*-Diisopropylethylamine (0.300 mL, 1.75 mmol) was added dropwise and the mixture was allowed to warm to room temperature and left to stir for 2 h. The mixture was then diluted with ethyl acetate (15 mL) and washed with a saturated aqueous solution of sodium hydrogen carbonate (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (soaked with 1% triethylamine/dichloromethane), with a gradient elution from 40% ethyl acetate/10% dichloromethane/1% triethylamine in petroleum ether (40–60) to 40% ethyl acetate/30% dichloromethane/1% triethylamine in petroleum ether (40–60) gave (2*R*,6*S*)-2-methyl-6-propylpiperidin-4-one (**10a**) (0.0780 g, 43%) as a dark orange oil. Further elution yielded (2*R*,6*R*)-2-methyl-6-propylpiperidin-4-one (**11a**) (0.0760 g, 42%) as a dark orange oil. Data for (2*R*,6*S*)-2-methyl-6-propylpiperidin-4-one (**10a**): R_f 0.47 (40% ethyl acetate/30% dichloromethane/1% triethylamine in petroleum ether); IR (neat) 3302, 2962, 1658, 1527 cm^{-1}; $[\alpha]_D^{26}$ +9.8 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H), 1.29–1.68 (m, 5H), 1.99–2.12 (m, 2H), 2.30–2.39 (m, 2H), 2.85 (tdd, J = 9.1, 6.2, 2.9 Hz, 1H), 2.96 (dqd, J = 12.4, 6.2, 2.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1 (CH_3), 18.9 (CH_2), 22.7 (CH_3), 39.2 (CH_2), 48.2 (CH_2), 50.2 (CH_2), 52.1 (CH), 56.3 (CH), 209.6 (C); MS (ESI) *m/z* 156 (MH^+, 100); HRMS (ESI) calcd for $C_9H_{18}NO$ (MH^+), 156.1383, found 156.1377. Data for (2*R*,6*R*)-2-methyl-6-propylpiperidin-4-one (**11a**): R_f 0.23 (40% ethyl acetate/30% dichloromethane/1% triethylamine in petroleum ether); IR (neat) 3271, 2954, 1720, 1535 cm^{-1}; $[\alpha]_D^{26}$ −7.9 (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J = 7.1 Hz, 3H), 1.16 (d, J = 6.5 Hz, 3H), 1.23–1.52 (m, 4H), 1.61 (br s, 1H), 2.14 (dddd, J = 13.6, 11.6, 6.0, 1.6 Hz, 2H), 2.47 (dddd, J = 15.6, 14.0, 5.2, 1.6 Hz, 2H), 3.27–3.36 (m, 1H), 3.39–3.49 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.9 (CH_3), 19.3 (CH_2), 21.6 (CH_3), 36.9 (CH_2), 47.8 (CH_2 and CH), 49.6 (CH_2), 52.3 (CH), 210.0 (C); MS (ESI) *m/z* 156 (MH^+, 100); HRMS (ESI) calcd for $C_9H_{18}NO$ (MH^+), 156.1383, found 156.1378.

(2*R*,6*S*)-2-Methyl-6-nonylpiperidin-4-one (10b)[5d] and (2*R*,6*R*)-2-methyl-6-nonylpiperidin-4-one (11b). The reaction was carried out according to the procedure for the synthesis of **10a** and **11a** using (2*R*,5*E*)-2-(*tert*-butoxycarbonylamino)-4-oxopentadec-5-ene (**9b**) (0.30 g, 0.89 mmol). Purification by flash column chromatography on silica gel, (soaked with 1% triethylamine/petroleum ether) eluting with 20% ethyl acetate/1% triethylamine in petroleum ether (40–60) gave (2*R*,6*S*)-2-methyl-6-nonylpiperidin-4-one (**10b**) (0.095 g, 45%) as an orange oil. Further elution yielded (2*R*,6*R*)-2-methyl-6-nonylpiperidin-4-one (**11b**) (0.093 g, 44%) as an orange oil. Data for (2*R*,6*S*)-2-methyl-6-nonylpiperidin-4-one (**10b**): R_f 0.22 (20% ethyl acetate/1% triethylamine in petroleum ether); $[\alpha]_D^{26}$ −2.4 (*c* 1.0, $CHCl_3$), lit.[5d] $[\alpha]_D^{22}$ −1.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 5.8 Hz, 3H), 1.23–1.61 (m, 17H), 1.99–2.12 (m, 2H), 2.24–2.45 (m, 2H), 2.77–2.89 (m, 1H), 2.90–3.04 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_3 and CH_2), 25.7 (CH_2), 29.3 (CH_2), 29.5 (2 × CH_2), 29.6 (CH_2), 31.9 (CH_2), 37.1 (CH_2), 48.2 (CH_2), 50.2 (CH_2), 52.1 (CH), 56.6 (CH), 209.6 (C); MS (ESI) *m/z* 240 (MH^+, 100). Data for (2*R*,6*R*)-2-methyl-6-nonylpiperidin-4-one (**11b**): R_f 0.07 (20% ethyl acetate/1% triethylamine in petroleum ether); IR (neat) 3300, 2958, 1710, 1458 cm^{-1}; $[\alpha]_D^{26}$ −3.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.3 Hz, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.20–1.54 (m, 17H), 2.09–2.20 (m, 2H), 2.42–2.54 (m, 2H), 3.24–3.34 (m, 1H), 3.39–3.49 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.1 (CH_3), 21.7 (CH_3), 22.7 (CH_2), 26.1 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 34.8 (CH_2), 47.8 (CH), 47.8 (CH_2), 49.6 (CH_2), 52.7 (CH), 210.0 (C); MS (ESI) *m/z* 240 (MH^+, 100); HRMS (ESI) calcd for $C_{15}H_{30}NO$ (MH^+), 240.2322, found 240.2316.

(2*R*,6*S*)-2-Methyl-6-(2'-phenylethyl)piperidin-4-one (10c) and (2*R*,6*R*)-2-methyl-6-(2'-phenylethyl)piperidin-4-one (11c). The reaction was carried out according to the procedure for the synthesis of **10a** and **11a** using (2*R*,5*E*)-8-phenyl-2-(*tert*-butoxycarbonylamino)-4-oxooct-5-ene (**9c**) (0.133 g, 0.420 mmol). Purification by flash column chromatography on silica gel (soaked with 1% triethylamine/petroleum ether), with a gradient elution from 60% ethyl acetate/1% triethylamine in

petroleum ether (40–60) to 90% ethyl acetate/1% triethylamine in petroleum ether (40–60) gave (2*R*,6*S*)-2-methyl-6-(2'-phenylethyl)piperidin-4-one (**10c**) (0.0380 g, 42%) as a brown oil. Further elution yielded (2*R*,6*R*)-2-methyl-6-(2'-phenylethyl)piperidin-4-one (**11c**) (0.0360 g, 40%) as a brown oil. Data for (2*R*,6*S*)-2-methyl-6-(2'-phenylethyl)piperidin-4-one (**10c**): R_f 0.32 (60% ethyl acetate/1% triethylamine in petroleum ether); IR (neat) 3300, 2960, 1714, 1454 cm^{-1}; $[\alpha]_D^{26}$ +2.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, J = 6.2 Hz, 3H), 1.67 (br s, 1H), 1.75–1.91 (m, 2H), 2.04–2.14 (m, 2H), 2.34 (dt, J = 15.0, 5.0 Hz, 1H), 2.41 (dt, J = 15.0, 5.0 Hz, 1H), 2.70 (t, J = 8.0 Hz, 2H), 2.84–2.98 (m, 2H), 7.15–7.32 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.6 (CH_3), 32.2 (CH_2), 38.6 (CH_2), 48.1 (CH_2), 50.2 (CH_2), 52.0 (CH), 56.1 (CH), 126.1 (CH), 128.3 (2 × CH), 128.5 (2 × CH), 141.4 (C), 209.2 (C); MS (ESI) *m/z* 218 (MH^+, 100); HRMS (ESI) calcd for $C_{14}H_{20}NO$ (MH^+), 218.1539, found 218.1540. Data for (2*R*,6*R*)-2-methyl-6-(2'-phenylethyl)piperidin-4-one (**11c**): R_f 0.11 (60% ethyl acetate/1% triethylamine in petroleum ether); IR (neat) 3300, 2926, 1708, 1454 cm^{-1}; $[\alpha]_D^{26}$ +6.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, J = 6.5 Hz, 3H), 1.68–1.86 (m, 3H), 2.13 (ddd, J = 13.8, 7.3, 1.4 Hz, 1H), 2.21 (ddd, J = 13.8, 6.0, 1.4 Hz, 1H), 2.47 (ddd, J = 13.8, 4.6, 1.4 Hz, 1H), 2.52 (ddd, J = 13.8, 5.1, 1.4 Hz, 1H), 2.61–2.73 (m, 2H), 3.31–3.38 (m, 1H), 3.40–3.48 (m, 1H), 7.15–7.31 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6 (CH_3), 32.5 (CH_2), 36.2 (CH_2), 47.8 (CH_2), 47.8 (CH), 49.7 (CH_2), 52.3 (CH), 126.0 (CH), 128.3 (2 × CH), 128.5 (2 × CH), 141.4 (C), 209.6 (C); MS (ESI) *m/z* 218 (MH^+, 100); HRMS (ESI) calcd for $C_{14}H_{20}NO$ (MH^+), 218.1539, found 218.1537.

(2*R*,6*R*)-2-Methyl-6-phenylpiperidin-4-one (10d)[16b] and (2*R*,6*S*)-2-methyl-6-phenylpiperidin-4-one (11d). The reaction was carried out according to the procedure for the synthesis of **10a** and **11a** using (2*R*,5*E*)-6-phenyl-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (**9d**) (0.105 g, 0.365 mmol), dichloromethane (4 mL) and trifluoroacetic acid (0.279 mL, 3.65 mmol). Purification by flash column chromatography on silica gel (soaked with 1% triethylamine/petroleum ether), with a gradient elution from 30% ethyl acetate/1% triethylamine in petroleum ether (40–60) to 60% ethyl acetate/1% triethylamine in petroleum ether (40–60) gave (2*R*,6*R*)-2-methyl-6-phenylpiperidin-4-one (**10d**) (0.0290

g, 42%) as an orange solid. Further elution yielded (2*R*,6*S*)-2-methyl-6-phenylpiperidin-4-one (**11d**) (0.0280 g, 40%) as an orange solid. Data for (2*R*,6*R*)-2-methyl-6-phenylpiperidin-4-one (**10d**): Mp 58–61 °C; R_f 0.30 (30% ethyl acetate/1% triethylamine in petroleum ether); $[\alpha]_D^{26}$ +69.4 (*c* 0.9, $CHCl_3$), lit.[16b] $[\alpha]_D^{20}$ +72.2 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.1 Hz, 3H), 1.80 (br s, 1H), 2.23 (dd, *J* = 14.0, 11.9 Hz, 1H), 2.41 (dd, *J* = 14.0, 2.7 Hz, 1H), 2.47–2.53 (m, 2H), 3.12 (dqd, *J* = 11.9, 6.1, 2.7 Hz, 1H), 3.96 (dt, *J* = 11.9, 8.0 Hz, 1H), 7.27–7.43 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.7 (CH_3), 49.8 (CH_2), 50.0 (CH_2), 52.4 (CH), 61.1 (CH), 126.5 (2 × CH), 127.9 (CH), 128.8 (2 × CH), 142.7 (C), 208.9 (C); MS (ESI) *m/z* 190 (MH^+, 100). Data for (2*R*,6*S*)-2-methyl-6-phenylpiperidin-4-one (**11d**): Mp 65–69 °C; R_f 0.06 (30% ethyl acetate/1% triethylamine in petroleum ether); IR (neat) 3309, 2962, 1712, 1450 cm^{-1}; $[\alpha]_D^{26}$ +8.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.4 Hz, 3H), 1.82 (br s, 1H), 2.23 (ddd, *J* = 14.2, 6.4, 1.1 Hz, 1H), 2.59–2.73 (m, 3H), 3.41–3.51 (m, 1H), 4.48 (t, *J* = 8.0 Hz, 1H), 7.25–7.41 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.2 (CH_3), 47.8 (CH), 47.8 (CH_2), 48.9 (CH_2), 55.6 (CH), 126.9 (2 × CH), 127.6 (CH), 128.7 (2 × CH), 142.7 (C), 209.5 (C); MS (ESI) *m/z* 190 (MH^+, 100); HRMS (ESI) calcd for $C_{12}H_{16}NO$ (MH^+), 190.1226, found 190.1226.

(2*R*,6*R*)-2-Methyl-6-(4'-methoxyphenyl)piperidin-4-one (10e) and (2*R*,6*S*)-2-methyl-6-(4'-methoxyphenyl)piperidin-4-one (11e). The reaction was carried out according to the procedure for the synthesis of **10a** and **11a** using (2*R*,5*E*)-6-(4'-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (**9e**) (0.18 g, 0.56 mmol). Purification by flash column chromatography on silica gel (soaked with 1% triethylamine/petroleum ether), with a gradient elution from 40% ethyl acetate/1% triethylamine in petroleum ether (40–60) to 80% ethyl acetate/1% triethylamine in petroleum ether (40–60) gave (2*R*,6*R*)-2-methyl-6-(4'-methoxyphenyl)piperidin-4-one (**10e**) (0.056 g, 46%) as an orange solid. Further elution yielded (2*R*,6*S*)-2-methyl-6-(4'-methoxyphenyl)piperidin-4-one (**11e**) (0.045 g, 37%) as a red solid. Data for (2*R*,6*R*)-2-methyl-6-(4'-methoxyphenyl)piperidin-4-one (**10e**): Mp 83–85 °C; R_f 0.22 (40% ethyl acetate/1% triethylamine in petroleum ether); IR (neat) 3300, 2966, 1708, 1510 cm^{-1};

$[\alpha]_D^{26}$ +65.3 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (d, *J* = 6.2 Hz, 3H), 1.79 (br s, 1H), 2.21 (dd, *J* = 14.0, 11.9 Hz, 1H), 2.39 (dd, *J* = 14.0, 2.6 Hz, 1H), 2.44–2.51 (m, 2H), 3.10 (dqd, *J* = 11.9, 6.2, 2.6 Hz, 1H), 3.80 (s, 3H), 3.90 (dd, *J* = 8.6, 6.2 Hz, 1H), 6.87–6.91 (m, 2H), 7.30–7.34 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.6 (CH_3), 49.8 (CH_2), 50.1 (CH_2), 52.3 (CH), 55.3 (CH_3), 60.5 (CH), 114.1 (2 × CH), 127.7 (2 × CH), 134.9 (C), 159.2 (C), 209.0 (C); MS (ESI) *m/z* 220 (MH^+, 100); HRMS (ESI) calcd for $C_{13}H_{18}NO_2$ (MH^+), 220.1332, found 220.1327. Data for (2*R*,6*S*)-2-methyl-6-(4'-methoxyphenyl)piperidin-4-one (**11e**): Mp 78–80 °C; R_f 0.070 (40% ethyl acetate/1% triethylamine in petroleum ether); IR (neat) 3300, 2823, 1705, 1512 cm^{-1}; $[\alpha]_D^{26}$ +34.7 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.5 Hz, 3H), 1.76 (br s, 1H), 2.22 (ddd, *J* = 14.2, 6.5, 1.1 Hz, 1H), 2.58–2.70 (m, 3H), 3.39–3.48 (m, 1H), 3.80 (s, 3H), 4.44 (t, *J* = 6.5 Hz, 1H), 6.85–6.90 (m, 2H), 7.23–7.29 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.2 (CH_3), 47.7 (CH), 48.0 (CH_2), 48.9 (CH_2), 55.1 (CH_3), 55.3 (CH), 114.0 (2 × CH), 128.0 (2 × CH), 134.8 (C), 158.9 (C), 209.7 (C); MS (ESI) *m/z* 220 (MH^+, 100); HRMS (ESI) calcd for $C_{13}H_{18}NO_2$ (MH^+), 220.1332, found 220.1331.

(2*R*,6*R*)-2-Methyl-6-(naphthalen-2'-yl)piperidin-4-one (10f) and (2*R*,6*S*)-2-methyl-6-(naphthalen-2'-yl)piperidin-4-one (11f). The reaction was carried out according to the procedure for the synthesis of **10a** and **11a** using (2*R*,5*E*)-6-(naphthalen-2'-yl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (**9f**) (0.13 g, 0.39 mmol). Purification by flash column chromatography on silica gel (soaked with 1% triethylamine/petroleum ether), with a gradient elution from 40% ethyl acetate/1% triethylamine in petroleum ether (40–60) to 1% triethylamine in ethyl acetate gave (2*R*,6*R*)-2-methyl-6-(naphthalen-2'-yl)piperidin-4-one (**10f**) (0.041 g, 44%) as an orange oil. Further elution yielded (2*R*,6*S*)-2-methyl-6-(naphthalen-2'-yl)piperidin-4-one (**11f**) (0.039 g, 42%) as an orange oil. Data for (2*R*,6*R*)-2-methyl-6-(naphthalen-2'-yl)piperidin-4-one (**10f**): R_f 0.39 (40% ethyl acetate/1% triethylamine in petroleum ether); IR (neat) 3311, 2970, 1714, 1373 cm^{-1}; $[\alpha]_D^{26}$ +65.9 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.2 Hz, 3H), 1.91 (br s, 1H), 2.27 (dd, *J* = 14.0, 11.9 Hz, 1H), 2.44 (dd, *J* = 14.0, 2.7 Hz, 1H), 2.57 (d, *J* = 8.0 Hz, 2H), 3.17 (dqd, *J* = 11.9, 6.2, 2.7 Hz, 1H), 4.08–4.15 (m, 1H), 7.45–7.51 (m,

2H), 7.52 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.80–7.86 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.7 (CH_3), 49.8 (CH_2), 49.9 (CH_2), 52.4 (CH), 61.1 (CH), 124.7 (CH), 125.1 (CH), 126.0 (CH), 126.3 (CH), 127.7 (CH), 127.9 (CH), 128.5 (CH), 133.1 (C), 133.4 (C), 140.0 (C), 208.7 (C); MS (ESI) *m/z* 240 (MH^+, 100); HRMS (ESI) calcd for $C_{16}H_{18}NO$ (MH^+), 240.1383, found 240.1379. Data for (2*R*,6*S*)-2-methyl-6-(naphthalen-2'-yl)piperidin-4-one (**11f**): R_f 0.10 (40% ethyl acetate/1% triethylamine in petroleum ether); IR (neat) 3315, 2964, 1708, 1506, 1305 cm^{-1}; $[\alpha]_D^{26}$ −58.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.6 Hz, 3H), 1.86 (br s, 1H), 2.26 (ddd, *J* = 14.2, 6.6, 1.4 Hz, 1H), 2.65 (ddd, *J* = 14.2, 4.9, 1.4 Hz, 1H), 2.74 (ddd, *J* = 14.4, 5.3, 1.4 Hz, 1H), 2.81 (ddd, *J* = 14.4, 6.9, 1.4 Hz, 1H), 3.41–3.49 (m, 1H), 4.65 (dd, *J* = 6.9, 5.3 Hz, 1H), 7.45–7.51 (m, 3H), 7.75 (br s, 1H), 7.79–7.86 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.1 (CH_3), 47.4 (CH_2), 47.8 (CH), 48.8 (CH_2), 55.7 (CH), 125.1 (CH), 125.6 (CH), 126.1 (CH), 126.4 (CH), 127.6 (CH), 128.0 (CH), 128.6 (CH), 132.8 (C), 133.2 (C), 139.5 (C), 208.6 (C); MS (ESI) *m/z* 240 (MH^+, 100); HRMS (ESI) calcd for $C_{16}H_{18}NO$ (MH^+), 240.1383, found 240.1386.

(2*R*,6*R*)-2-Methyl-6-(4'-nitrophenyl)piperidin-4-one (10g) and (2*R*,6*S*)-2-methyl-6-(4'-nitrophenyl)piperidin-4-one (11g). The reaction was carried out according to the procedure for the synthesis of **10a** and **11a** using (2*R*,5*E*)-6-(4'-nitrophenyl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (**9g**) (0.103 g, 0.309 mmol). Purification by flash column chromatography on silica gel (soaked with 1% triethylamine/petroleum ether), eluting with 40% ethyl acetate/1% triethylamine in petroleum ether (40–60) gave (2*R*,6*R*)-2-methyl-6-(4'-nitrophenyl)piperidin-4-one (**10g**) (0.0310 g, 43%) as a red solid. Further elution yielded (2*R*,6*S*)-2-methyl-6-(4'-nitrophenyl)piperidin-4-one (**11g**) (0.0300 g, 41%) as a brown solid. Data for (2*R*,6*R*)-2-methyl-6-(4'-nitrophenyl)piperidin-4-one (**10g**): Mp 117–120 °C; R_f 0.21 (40% ethyl acetate/1% triethylamine in petroleum ether); IR (neat) 3321, 2968, 1705, 1510, 1346 cm^{-1}; $[\alpha]_D^{26}$ +62.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.1 Hz, 3H), 1.86 (br s, 1H), 2.25 (ddd, *J* = 14.0, 12.0, 0.8 Hz, 1H), 2.37–2.54 (m, 3H), 3.15 (dqd, *J* = 12.0, 6.1, 2.9 Hz, 1H), 4.09 (dd, *J* = 11.8, 3.2 Hz, 1H), 7.58–7.64 (m, 2H), 8.19–8.26 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

22.6 (CH_3), 49.6 (CH_2), 49.7 (CH_2), 52.2 (CH), 60.3 (CH), 124.1 (2 × CH), 127.4 (2 × CH), 147.5 (C), 149.9 (C), 207.4 (C); MS (ESI) *m/z* 235 (MH^+, 100); HRMS (ESI) calcd for $C_{12}H_{15}N_2O_3$ (MH^+), 235.1077, found 235.1073. Data for (2*R*,6*S*)-2-methyl-6-(4'-nitrophenyl)piperidin-4-one (**11g**): Mp 88–91 °C; R_f 0.07 (40% ethyl acetate/1% triethylamine in petroleum ether); IR (neat) 3300, 2962, 1707, 1508, 1344 cm^{-1}; $[\alpha]_D^{26}$ +11.1 (*c* 0.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (d, *J* = 6.6 Hz, 3H), 1.82 (br s, 1H), 2.26 (ddd, *J* = 14.0, 6.1, 1.0 Hz, 1H), 2.61–2.72 (m, 3H), 3.42–3.50 (m, 1H), 4.59 (t, *J* = 5.0 Hz, 1H), 7.55–7.60 (m, 2H), 8.18–8.23 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.1 (CH_3), 47.7 (CH_2), 48.2 (CH), 48.9 (CH_2), 55.2 (CH), 123.9 (2 × CH), 127.8 (2 × CH), 147.3 (C), 150.0 (C), 208.3 (C); MS (ESI) *m/z* 235 (MH^+, 100); HRMS (ESI) calcd for $C_{12}H_{15}N_2O_3$ (MH^+), 235.1077, found 235.1075.

(2*R*,6*R*)-2-Methyl-6-(pyridin-3'-yl)piperidin-4-one (10h) and (2*R*,6*S*)-2-methyl-6-(pyridin-3'-yl)piperidin-4-one (11h). The reaction was carried out according to the procedure for the synthesis of **10a** and **11a** using (2*R*,5*E*)-6-(pyridin-3'-yl)-2-(*tert*-butoxycarbonylamino)-4-oxohex-5-ene (**9h**) (0.096 g, 0.33 mmol). Purification by flash column chromatography on silica gel (soaked with 1% triethylamine/dichloromethane), eluting with 2% methanol/50% dichloromethane/1% triethylamine in petroleum ether (40–60) gave (2*R*,6*R*)-2-methyl-6-(pyridin-3'-yl)piperidin-4-one (**10h**) (0.026 g, 41%) as an orange oil. Further elution yielded (2*R*,6*S*)-2-methyl-6-(pyridin-3'-yl)piperidin-4-one (**11h**) (0.025 g, 39%) as an orange oil. Data for (2*R*,6*R*)-2-methyl-6-(pyridin-3'-yl)piperidin-4-one (**10h**): R_f 0.22 (2% methanol/50% dichloromethane/1% triethylamine in petroleum ether); IR (neat) 3285, 2965, 1709, 1426 cm^{-1}; $[\alpha]_D^{26}$ +70.5 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (d, *J* = 6.1 Hz, 3H), 1.85 (br s, 1H), 2.23 (dd, *J* 14.0, 10.6 Hz, 1H), 2.40–2.54 (m, 3H), 3.14 (dqd, *J* = 12.2, 6.1, 2.9 Hz, 1H), 4.01 (dd, *J* = 10.6, 4.4 Hz, 1H), 7.31 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.77 (dt, *J* = 7.9, 1.9 Hz, 1H), 8.56 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.64 (br d, *J* = 1.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.6 (CH_3), 49.6 (CH_2), 49.6 (CH_2), 52.4 (CH), 58.6 (CH), 123.7 (CH), 134.2 (CH), 138.0 (C), 148.5 (CH), 149.5 (CH), 207.9 (C); MS (ESI) *m/z* 191 (MH^+, 100); HRMS (ESI) calcd for $C_{11}H_{15}N_2O$ (MH^+), 191.1179, found 191.1181.

Data for (2*R*,6*S*)-2-methyl-6-(pyridin-3'-yl)piperidin-4-one (**11h**): R_f 0.11 (2% methanol/50% dichloromethane/1% triethylamine in petroleum ether); IR (neat) 3263, 2962, 1705, 1419 cm^{-1}; $[\alpha]_D^{26}$ +38.9 (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, *J* = 6.4 Hz, 3H), 1.69 (br s, 1H), 2.26 (dd, *J* = 14.1, 6.4 Hz, 1H), 2.62–2.70 (m, 3H), 3.42–3.52 (m, 1H), 4.54 (t, *J* = 6.2 Hz, 1H), 7.28 (dd, *J* 7.9, 4.8 Hz, 1H), 7.70 (dt, *J* = 7.9, 1.8 Hz, 1H), 8.54 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.64 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.0 (CH_3), 47.5 (CH_2), 48.1 (CH), 48.8 (CH_2), 53.6 (CH), 123.5 (CH), 134.4 (CH), 137.8 (C), 148.9 (CH), 149.1 (CH), 208.4 (C); MS (ESI) *m/z* 191 (MH^+, 100); HRMS (ESI) calcd for $C_{11}H_{15}N_2O$ (MH^+), 191.1179, found 191.1178.

(2*R*,4*S*,6*S*)-2-Methyl-6-propylpiperidin-4-ol (1).[7a] (2*R*,6*S*)-2-Methyl-6-propylpiperidin-4-one (**10a**) (0.094 g, 0.061 mmol) was dissolved in anhydrous methanol (2 mL) and cooled to −15 °C. Sodium borohydride (0.0046 g, 0.12 mmol) was added and the solution was stirred rapidly for 0.25 h. Brine (1 mL) was added to quench the reaction and the mixture was diluted with ethyl acetate (10 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography on silica gel, eluting with 30% methanol/1% triethylamine in ethyl acetate gave (2*R*,4*S*,6*S*)-2-methyl-6-propylpiperidin-4-ol (**1**) (0.080 g, 87%) as an off-white solid. Mp 74–76 °C; R_f 0.25 (30% methanol/1% triethylamine in ethyl acetate); $[\alpha]_D^{26}$ +9.0 (*c* 0.7, MeOH), lit.[7a] $[\alpha]_D^{20}$ +8.8 (*c* 0.4, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.1 Hz, 3H), 0.98 (q, *J* = 11.8 Hz, 1H), 1.03 (q, *J* = 11.8 Hz, 1H), 1.12 (d, *J* = 6.3 Hz, 3H), 1.29–1.46 (m, 4H), 1.86 (br s, 2H), 1.91–2.01 (m, 2H), 2.52–2.61 (m, 1H), 2.69 (dqd, *J* = 11.8, 6.3, 2.4 Hz, 1H), 3.65 (tt, *J* = 11.8, 4.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.2 (CH_3), 19.2 (CH_2), 22.4 (CH_3), 38.9 (CH_2), 41.6 (CH_2), 43.9 (CH_2), 50.2 (CH), 54.6 (CH), 69.3 (CH); MS (ESI) *m/z* 158 (MH^+, 100).

(2*R*,4*S*,6*S*)-2-Methyl-6-nonylpiperidin-4-ol (2).[5a] The reaction was carried out according to the procedure for the synthesis of **1** using (2*R*,6*S*)-2-methyl-6-nonylpiperidin-4-one (**10b**) (0.028 g, 0.12 mmol). Purification by flash column chromatography on silica gel, eluting with 10% methanol/1% triethylamine in ethyl acetate gave (2*R*,4*S*,6*S*)-2-methyl-6-nonylpiperidin-4-ol (**2**) (0.023 g, 84%) as an

off-white solid. Mp 86–88 °C; R_f 0.16 (10% methanol/1% triethylamine in ethyl acetate); $[\alpha]_D^{26}$ +7.9 (*c* 1.0, MeOH), lit.[5a] $[\alpha]_D^{25}$ +7.0 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 0.93–1.06 (m, 2H), 1.12 (d, *J* = 6.3 Hz, 3H), 1.20–1.48 (m, 16H), 1.63 (br s, 2H), 0.97 (q, *J* = 11.8 Hz, 1H), 1.02 (q, *J* = 11.8 Hz, 1H), 2.50–2.58 (m, 1H), 2.68 (dqd, *J* = 11.8, 6.3, 2.4 Hz, 1H), 3.65 (tt, *J* = 11.8, 4.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.5 (CH_3), 22.7 (CH_2), 26.1 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 31.9 (CH_2), 36.8 (CH_2), 41.8 (CH_2), 43.9 (CH_2), 50.2 (CH), 54.9 (CH), 69.4 (CH); MS (ESI) *m/z* 242 (MH^+, 100).

(2*R*,4*S*,6*S*)-2-Methyl-6-(2'-phenylethyl)piperidin-4-ol (12a).[21] The reaction was carried out according to the procedure for the synthesis of **1** using (2*R*,6*S*)-2-methyl-6-(2'-phenylethyl)piperidin-4-one (**10c**) (0.014 g, 0.063 mmol). Purification by flash column chromatography on silica gel, eluting with 1% methanol/1% triethylamine in dichloromethane gave (2*R*,4*S*,6*S*)-2-methyl-6-(2'-phenylethyl)piperidin-4-ol (**12a**) (0.011 g, 80%) as an off-white solid. Spectroscopic data was consistent with the literature.[21] Mp 98–102 °C; R_f 0.19 (1% methanol/1% triethylamine in dichloromethane); $[\alpha]_D^{26}$ +7.0 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (q, *J* = 11.7 Hz, 1H), 1.04 (q, *J* = 11.7 Hz, 1H), 1.12 (d, *J* = 6.3 Hz, 3H), 1.47 (br s, 2H), 1.67–1.83 (m, 2H), 1.95 (ddt, *J* = 11.7, 4.5, 2.2 Hz, 1H), 2.03 (ddt, *J* = 11.7, 4.5, 2.2 Hz, 1H), 2.56–2.72 (m, 4H), 3.66 (tt, *J* = 11.7, 4.5 Hz, 1H), 7.16–7.21 (m, 3H), 7.25–7.31 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.5 (CH_3), 32.4 (CH_2), 38.5 (CH_2), 41.7 (CH_2), 43.9 (CH_2), 50.1 (CH), 54.4 (CH), 69.3 (CH), 125.9 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 142.0 (C); MS (ESI) *m/z* 220 (MH^+, 100).

(2*R*,4*S*,6*R*)-2-Methyl-6-phenylpiperidin-4-ol (12b).[22] The reaction was carried out according to the procedure for the synthesis of **1** using (2*R*,6*R*)-2-methyl-6-phenylpiperidin-4-one (**10d**) (0.015 g, 0.077 mmol). Purification by flash column chromatography on silica gel, eluting with 1% methanol/1% triethylamine in dichloromethane gave (2*R*,4*S*,6*R*)-2-methyl-6-phenylpiperidin-4-ol (**12b**) (0.013 g, 91%) as an off white solid. Mp 92–94 °C; R_f 0.19 (1% methanol/1% triethylamine in dichloromethane); $[\alpha]_D^{26}$ +27.6 (*c* 1.0, $CHCl_3$), lit.[22] $[\alpha]_D^{20}$ +29.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.21

(m, 4H), 1.45 (q, J = 11.8 Hz, 1H), 1.58 (br s, 2H), 2.00 (ddt, J = 11.8, 4.6, 2.4 Hz, 1H), 2.10 (ddt, J = 11.8, 4.6, 2.4 Hz, 1H), 2.86 (dqd, J = 11.8, 6.3, 2.4 Hz, 1H), 3.69 (dd, J = 11.8, 2.4 Hz, 1H), 3.81 (tt, J = 11.8, 4.6 Hz, 1H), 7.23–7.41 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.5 (CH_3), 43.4 (CH_2), 43.4 (CH_2), 50.7 (CH), 59.8 (CH), 69.8 (CH), 126.8 (2 × CH), 127.3 (CH), 128.5 (2 × CH), 144.0 (C); MS (ESI) *m/z* 192 (MH^+, 100).

(2*R*,4*S*,6*R*)-2-Methyl-6-(4'-methoxyphenyl)piperidin-4-ol (12c). The reaction was carried out according to the procedure for the synthesis of **1** using (2*R*,6*R*)-2-methyl-6-(4'-methoxyphenyl)piperidin-4-one (**10e**) (0.0170 g, 0.0780 mmol). Purification by flash column chromatography on silica gel, eluting with 70% ethyl acetate/1% triethylamine in dichloromethane gave (2*R*,4*S*,6*R*)-2-methyl-6-(4'-methoxyphenyl)piperidin-4-ol (**12c**) (0.015 g, 85%) as a white solid. Mp 85–90 °C; R_f 0.11 (70% ethyl acetate/1% triethylamine in dichloromethane); IR (neat) 3340, 2933, 1514, 1303 cm^{-1}; $[\alpha]_D^{26}$ +21.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09–1.19 (m, 4H), 1.43 (q, J = 12.0 Hz, 1H), 1.61 (br s, 2H), 1.99 (ddt, J = 12.0, 4.4, 2.3 Hz, 1H), 2.07 (ddt, J = 12.0, 4.4, 2.3 Hz, 1H), 2.84 (dqd, J = 12.0, 6.2, 2.3 Hz, 1H), 3.64 (dd, J = 12.0, 2.3 Hz, 1H), 3.75–3.83 (m, 4H), 6.83–6.89 (m, 2H), 7.27–7.32 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.5 (CH_3), 43.4 (2 × CH_2), 50.7 (CH), 55.3 (CH_3), 59.1 (CH), 69.8 (CH), 113.8 (2 × CH), 127.8 (2 × CH), 136.3 (C), 158.8 (C); MS (ESI) *m/z* 222 (MH^+, 95); HRMS (ESI) calcd for $C_{13}H_{20}NO_2$ (MH^+), 222.1489, found 222.1487.

(2*R*,4*S*,6*R*)-2-Methyl-6-(naphthalen-2'-yl)piperidin-4-ol (12d). The reaction was carried out according to the procedure for the synthesis of **1** using (2*R*,6*R*)-2-methyl-6-(naphthalen-2'-yl)piperidin-4-one (**10f**) (0.036 g, 0.15 mmol). Purification by flash column chromatography on silica gel, eluting with 80% ethyl acetate/1% triethylamine in dichloromethane gave (2*R*,4*S*,6*R*)-2-methyl-6-(naphthalen-2'-yl)piperidin-4-ol (**12d**) (0.032 g, 88%) as a white solid. Mp 157–160 °C; R_f 0.21 (80% ethyl acetate/1% triethylamine in dichloromethane); IR (neat) 3284, 2926, 1599, 1371 cm^{-1}; $[\alpha]_D^{26}$ +6.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.26 (m, 4H), 1.53 (q, J = 12.2 Hz, 1H), 1.68 (br s, 2H), 2.03 (ddt, J = 12.2, 4.5, 2.3 Hz, 1H), 2.18 (ddt, J = 12.2, 4.5, 2.3 Hz, 1H), 2.90 (dqd, J = 12.2, 6.3,

2.3 Hz, 1H), 3.80–3.90 (m, 2H), 7.41–7.53 (m, 3H), 7.77–7.86 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.5 (CH_3), 43.5 (CH_2), 43.5 (CH_2), 50.8 (CH), 59.8 (CH), 69.8 (CH), 125.0 (CH), 125.3 (CH), 125.6 (CH), 126.0 (CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 132.9 (C), 133.5 (C), 141.5 (C); MS (ESI) *m/z* 242 (MH^+, 100); HRMS (ESI) calcd for $C_{16}H_{20}NO$ (MH^+), 242.1539, found 242.1538.

(2*R*,4*S*,6*R*)-2-Methyl-6-(4'-nitrophenyl)piperidin-4-ol (12e). The reaction was carried out according to the procedure for the synthesis of **1** using (2*R*,6*R*)-2-methyl-6-(4'-nitrophenyl)piperidin-4-one (**10g**) (0.019 g, 0.082 mmol). Purification by flash column chromatography on silica gel, eluting with 70% ethyl acetate/1% triethylamine in petroleum ether (40–60) gave (2*R*,4*S*,6*R*)-2-methyl-6-(4'-nitrophenyl)piperidin-4-ol (**12e**) (0.015 g, 75%) as a yellow oil. R_f 0.12 (70% ethyl acetate/1% triethylamine in petroleum ether); IR (neat) 3298, 2935, 1516, 1344 cm^{-1}; $[\alpha]_D^{26}$ +20.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12–1.22 (m, 4H), 1.37 (q, *J* = 12.3 Hz, 1H), 1.58 (br s, 2H), 2.03 (ddt, *J* = 12.3, 4.5, 2.4 Hz, 1H), 2.10 (ddt, *J* = 12.3, 4.5, 2.4 Hz, 1H), 2.89 (dqd, *J* = 12.3, 6.2, 2.4 Hz, 1H), 3.79–3.88 (m, 2H), 7.54–7.58 (m, 2H), 8.16–8.21 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.5 (CH_3), 43.1 (CH_2), 43.5 (CH_2), 50.5 (CH), 59.2 (CH), 69.4 (CH), 123.8 (2 × CH), 127.6 (2 × CH), 147.2 (C), 151.6 (C); MS (ESI) *m/z* 237 (MH^+, 100); HRMS (ESI) calcd for $C_{12}H_{17}N_2O_3$ (MH^+), 237.1234, found 237.1239.

(2*R*,4*S*,6*R*)-2-Methyl-6-(pyridin-3'-yl)piperidin-4-ol (12f). The reaction was carried out according to the procedure for the synthesis of **1** using (2*R*,6*R*)-2-methyl-6-(pyridin-3'-yl)piperidin-4-one (**10h**) (0.018 g, 0.092 mmol). Purification by flash column chromatography on silica gel, eluting with 5% methanol/1% triethylamine in dichloromethane gave (2*R*,4*S*,6*R*)-2-methyl-6-(pyridin-3'-yl)piperidin-4-ol (**12f**) (0.012 g, 68%) as a pale yellow oil. R_f 0.23 (5% methanol/1% triethylamine in dichloromethane); IR (neat) 3254, 2933, 1425, 1305 cm^{-1}; $[\alpha]_D^{26}$ +17.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.23 (m, 4H), 1.44 (q, *J* = 12.2 Hz, 1H), 1.87 (br s, 2H), 2.02 (ddt, *J* = 12.2, 4.5, 2.3 Hz, 1H), 2.09 (ddt, *J* = 12.2, 4.5, 2.3 Hz, 1H), 2.88 (dqd, *J* = 12.2, 6.2, 2.3 Hz, 1H), 3.74 (dd, *J* = 12.2, 2.3 Hz, 1H), 3.82 (tt, *J* = 12.2, 4.5 Hz, 1H), 7.26 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.74 (dt, *J* = 7.9, 1.8

Hz, 1H), 8.50 (dd, J = 4.8, 1.8 Hz, 1H), 8.58 (d, J = 1.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 22.5 (CH_3), 43.2 (2 × CH_2), 50.7 (CH), 57.3 (CH), 69.4 (CH), 123.6 (CH), 134.4 (CH), 139.4 (C), 148.7 (CH), 148.8 (CH); MS (ESI) *m/z* 193 (MH^+, 100); HRMS (ESI) calcd for $C_{11}H_{17}N_2O$ (MH^+), 193.1335, found 193.1339.

SUPPORTING INFORMATION. NOE data of all novel cyclic compounds and, ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGEMENT. Financial support from the EPSRC (studentship to A.H.H., EP/K503058/1) and the University of Glasgow is gratefully acknowledged.

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(15) To investigate whether the basic conditions of the 6-*endo*-*trig* cyclization were causing conversion of the 2,6-*cis*-isomers to the more stable 2,6-*trans*-isomers during these reactions, isolated **10a** was re-subjected to the same basic conditions for 24 h. However, **10a** was found to be configurationally stable during this experiment, thus showing that the two diastereomers are formed during the cyclization and not via equilibration of the *cis*-2,6-product.

(16) The preparation of 2,6-*cis*-oxopiperidine **10b** was recently reported using a similar 6-*endo*-*trig* cyclisation. In this case, the use of triethylamine gave 2,6-*cis*-oxopiperidine **10b** in 84% yield. See: Reddy, A. A.; Reddy, P. O.; Prasad, K. R. *J. Org. Chem*. **2016**, *81*, 11363.

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