Enantioselective Synthesis of (+)-Sedamine and (–)-Allosedamine

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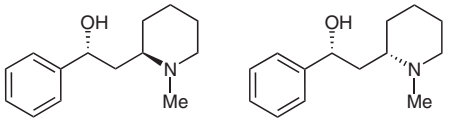
Abstract: Two different approaches to the enantioselective syntheses of (+)-sedamine and (–)-allosedamine are described, both using the Sharpless asymmetric epoxidation as the key step. Regioselective reduction of epoxides, chemoselective oxidation of alcohols, ring-closing metathesis, and nucleophilic displacements were the other key steps employed.

Key words: alkaloids, asymmetric synthesis, regioselective reduction, ring-closing metathesis

Piperidine alkaloids make up a large family of compounds. Many of them exhibit a wide range of physiological activities. Much activity has been devoted to the isolation and structure determination of such bases and to the development of general methodologies and routes for their synthesis.[1] (+)-Sedamine (**1**) (Figure 1) and its enantiomer were the first alkaloids isolated from *Sedum acre*[2] and were obtained later from a number of other *Sedum* species.[3] (–)-Allosedamine (**2**) (Figure 1) was isolated from *Lobelia inflata*,[4] which furnished a crude extract useful for the treatment of respiratory illnesses such as asthma, bronchitis, and pneumonia.[5] These alkaloids have been the subject of much synthetic activity since their isolation.[6–9]



(+)-sedamine **1** (–)-allosedamine **2**

Figure 1

Our own interest in the synthesis of enantiopure bioactives prompted us to explore the possibility of synthesising (+)-sedamine (**1**) and (–)-allosedamine (**2**). This effort has resulted in two different approaches for each target.

Our synthetic programme commenced from cinnamyl alcohol (**3**) (Scheme 1). Sharpless asymmetric epoxidation of **3** by (+)-diethyl-D-tartrate, *tert*-butyl hydroperoxide, and titanium(IV) isopropoxide at –30 °C gave epoxy alcohol **4**, which was regioselectively reduced by Red-Al to yield 1,3-diol **5**. Protection of the primary hydroxy group as a pivaloyl ester was achieved in the presence of pivaloyl chloride and pyridine at 0 °C, to give **6**, which was protected as a MOM ether **7** after reaction with chloro(methoxy)methane, *N*,*N*-diisopropylethylamine, and 4-(*N*,*N*-dimethylamino)pyridine. Deprotection of the pivaloyl ester group was achieved with potassium carbonate in methanol, resulting in primary alcohol **8**, whose oxidation under Swern conditions followed by the addition of allylmagnesium bromide to the crude aldehyde in diethyl ether produced alcohol **9** as an inseparable 1:1 diastereomeric mixture. Alcohol **9** was treated with mesyl chloride, triethylamine, and 4-(*N*,*N*-dimethylamino)pyridine to yield the corresponding mesylate, which, without purification, was subjected to nucleophilic substitution with sodium azide in *N*,*N*-dimethylformamide at 50 °C to furnish azide **10**, again as an inseparable diastereomeric mixture.

Chromatographically separable diastereomers **11** and **12** formed upon reduction of azide **10** with triphenylphosphine (TPP) in methanol followed by in situ protection of the resulting amine by the addition of Boc_2O to the mixture (Scheme 1). The stereochemistry of these diastereomers was determined by converting them into the known final targets. Diastereomer **11**, the faster-running isomer on TLC, was allylated with allyl bromide and sodium hydride in *N*,*N*-dimethylformamide at 50 °C to give Grubbs' ring-closing metathesis (RCM) precursor **13**, which, on exposure to the Grubbs-I catalyst in benzene at 50 °C, gave cyclised product **14**. Reduction of the olefinic bond with platinum(IV) oxide under a hydrogen atmosphere gave **15** which, on reduction of the Boc group with lithium aluminum hydride in refluxing tetrahydrofuran resulted in *N*-methylpiperidine derivative **16**. Deprotection of the MOM ether in **16** by use of concentrated hydrochloric acid in acetonitrile and water gave (–)-allosedamine (**2**) (in good agreement with the reported data).

The other diastereomer **12**, the slower-running isomer on TLC, was converted into (+)-sedamine **1** via allylated product **17**, RCM product **18**, and reduced products **19** and **20** under the same conditions as those described for the conversion of **11** into **2** (Scheme 1). The analytical data of compound **1** were in good agreement with the reported data.

Having succeeded in a combined approach for the synthesis of the target molecules, we explored the possibilities for the alternative and specific approaches that are also useful for the other diastereomers and structurally closely related piperidine alkaloids.

Our alternative approach is outlined in Scheme 2. We started with the chiral substrate **8**, whose synthesis was already described in Scheme 1. Oxidation of alcohol **8** un-

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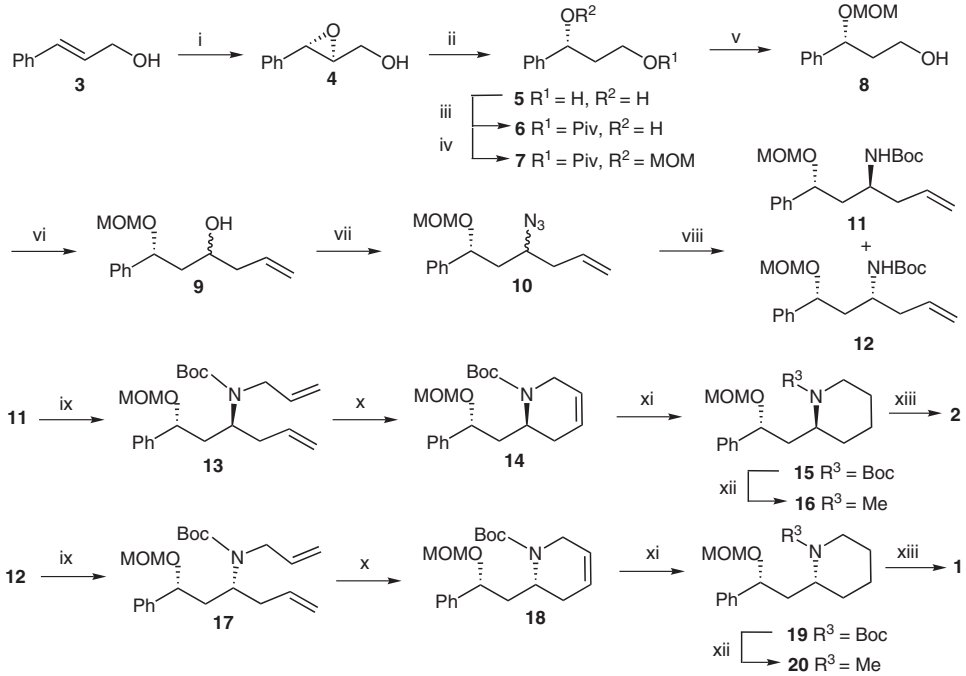


Scheme 1 *Reagents and conditions*: (i) (+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, –30 °C, 6 h, 84%; (ii) Red-Al, THF, 0 °C, 2 h, 88%; (iii) PvCl, py, CH_2Cl_2, 0 °C to r.t., 90%; (iv) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to r.t., 4 h, 98%; (v) K_2CO_3, MeOH, r.t., 2 h, 92%; (vi) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, –78 °C, then $H_2C{=}CHCH_2MgBr$, Et_2O, 0 °C, 74%; (vii) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 1 h, then NaN_3, DMF, 60 °C, 6 h, 84% (2 steps); (viii) TPP, MeOH, H_2O, then $(Boc)_2O$, r.t., 86%; (ix) NaH, $H_2C{=}CHCH_2Br$, DMF, 50 °C, 12 h, 88%; (x) Grubbs-I catalyst, benzene, 50 °C, 2 h, 90–92%; (xi) PtO_2, H_2, EtOAc, 1 atm, r.t., 2 h, 90–92%; (xii) $LiAlH_4$, THF, reflux, 6 h, 80–82%; (xiii) concd HCl, MeCN, H_2O, r.t., 3 h, 88–92%.

der Swern conditions followed by in situ C2 Wittig olefination resulted in the formation of α,β-unsaturated ester **21**. Controlled reduction of compound **21** with diisobutylaluminum hydride in dichloromethane yielded allyl alcohol **22**, which, on Sharpless asymmetric epoxidation using (–)-diethyl-D-tartrate gave epoxy alcohol **23**. Regioselective reduction of epoxide **23** by Red-Al afforded 1,3-diol **24**. One-pot chemoselective oxidation and C2 elongation was carried out by reaction with TEMPO, (diacetoxyiodo)benzene, and then the stable ylide (ethoxycarbonylmethylene)triphenylphosphorane in dichloromethane to produce conjugated ester **25**.[10] Reduction of ester **25** with lithium aluminum hydride yielded saturated diol **26**, which, on dimesylation using mesyl chloride, triethylamine, and 4-(*N*,*N*-dimethylamino)pyridine in dichloromethane followed by treatment of the corresponding dimesylate with 40% methylamine in water and *N*,*N*-dimethylformamide resulted in *N*-methylpiperidine derivative **20** after sequential intermolecular and intramolecular nucleophilic displacements.[11] Hydrogen chloride mediated deprotection of the MOM ether furnished (+)-sedamine (**1**) (Scheme 2).

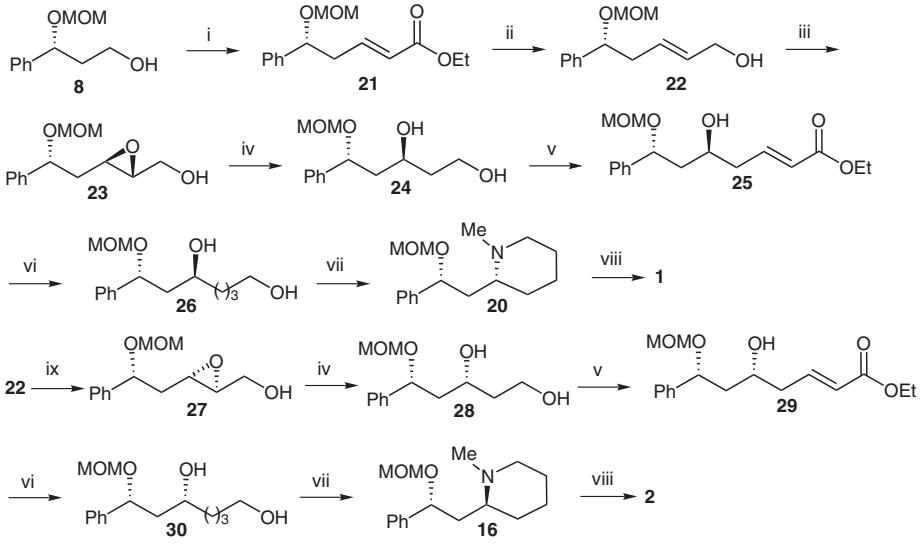
In an alternative route (Scheme 2), Sharpless asymmetric epoxidation of allyl alcohol **22** by (+)-diethyl-L-tartrate resulted in the formation of epoxy alcohol **27**, which was converted into (–)-allosedamine (**2**) via 1,3-diol **28**, Wittig product **29**, 1,5-diol **30**, and piperidine derivative **16** by use of the same reagents and conditions as those described for the conversion of **23** into **1**.

Thus, we have reported two divergent approaches for the synthesis of each of (+)-sedamine (**1**) and (–)-allosedamine (**2**) from the same starting material, cinnamyl alcohol (**3**). Both approaches generate the required stereogenic centres from Sharpless asymmetric epoxidation as the sole chiral source. The approaches are practically applicable in the synthesis of other diastereomers and structurally closely related analogues when appropriate starting materials and reagents are chosen for Sharpless asymmetric epoxidation.

Commercial reagents were used without further purification. All solvents were purified by standard techniques. Infrared (IR) spectra were recorded on a Perkin-Elmer 683 spectrometer. Optical rotations were obtained on a Jasco Dip 360 digital polarimeter. Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ as solvent on Varian Gemini 200, Bruker 300, or Varian Unity 400 NMR spectrometers. Chemical shifts (δ) are quoted in ppm and are referenced to TMS as internal standard. Coupling constants (*J*) are quoted in Hz. Column chromatographic separations were carried out on silica gel (60–120 mesh) and flash chromatographic separations were carried out using 230–400 mesh size silica gel. Mass spectra were obtained on a Finnegan MAT 1020B or a micro mass VG 70-70H spectrometer operating at 70 eV and using a direct inlet system.

[(2*R*,3*R*)-3-Phenyloxiran-2-yl]methanol (4)

A mixture of Ti(O*i*-Pr)$_4$ (2.75 g, 9.68 mmol), (+)-DET (2.30 g, 11.16 mmol), and activated powdered 4-Å MS (5 g) was stirred in anhyd CH_2Cl_2 (200 mL) at –30 °C for 30 min. Cinnamyl alcohol **3** (10.0 g, 74.62 mmol) in CH_2Cl_2 (20 mL) was added at –30 °C, and the resulting mixture was stirred at –30 °C for 30 min. The mixture



Scheme 2 *Reagents and conditions*: (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, Et_3N, then Ph_3PCHCO_2Et, 82% (2 steps); (ii) DIBAL-H, CH_2Cl_2, 0 °C to r.t., 1 h, 88%; (iii) (–)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, –30 °C, 6 h, 82%; (iv) Red-Al, THF, 0 °C to r.t., 2 h, 84–86%; (v) TEMPO, Ph[I(OAc)$_2$], CH_2Cl_2, then Ph_3PCHCO_2Et, 0 °C to r.t., 3 h, 61–65%; (vi) $LiAlH_4$, THF, 0 °C to r.t., 4 h, 90–92%; (vii) (a) Et_3N, MsCl, DMAP, CH_2Cl_2, 0 °C to r.t., 1 h, (b) 40% $MeNH_2$ in H_2O, DMF, 50 °C, 12 h, 76–78% (two steps); (viii) concd HCl, MeCN, H_2O, 3 h, 90%; (ix) (+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, –30 °C, 6 h, 84%.

was treated with 3.0 M *t*-BuOOH in toluene (62.5 mL) and stirred for 4 h at –30 °C. It was then allowed to warm to 0 °C and poured into a freshly prepared and cooled (0 °C) soln of $FeSO_4$ (12 g) and tartaric acid (3.5 g) in deionised H_2O (20 mL). The two-phase mixture was stirred for 25–30 min, and the aqueous phase was separated and extracted with Et_2O (2 × 100 mL). The combined organic phases were treated with a precooled (0 °C) 30% (w/v) soln of NaOH in sat. brine (5 mL). The two-phase mixture was then stirred for 1 h at r.t. and the aqueous layer was separated and treated with Et_2O (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (silica gel, EtOAc–hexanes, 1:4) afforded **4** as a liquid.

Yield: 9.4 g (84%); R_f = 0.5 (EtOAc–hexanes, 40:60); $[\alpha]_D^{20}$ –50.2 (*c* 1.0, EtOH).

IR (neat): 3580, 3450, 2980, 1600, 1450, 1380 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.20 (br s, 1 H), 3.25–3.33 (m, 1 H), 3.81 (dd, *J* = 5.1 Hz, 1 H), 3.95 (d, *J* = 3.0 Hz, 1 H), 4.18 (dd, *J* = 3.1 Hz, 1 H), 7.20–7.50 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.5, 128.3, 128.1, 125.5, 62.5, 61.4, 55.7.

HRMS (EI): *m*/*z* calcd for $C_9H_{10}O_2$ [M$^+$]: 150.0681; found: 150.0687.

(1*R*)-1-Phenylpropane-1,3-diol (5)

A 70 wt% mixture of Red-Al in toluene (24.7 mL, 122.2 mmol) was added dropwise to a cold (0 °C) soln of epoxide **4** (9.2 g, 61.3 mmol) in THF (200 mL). After 4 h at 0 °C, the mixture was quenched carefully by dropwise addition of sat. aq sodium potassium tartrate (Rochelle's salt). EtOAc (200 mL) was added and the mixture was allowed to warm to r.t. The organic layer was washed with brine (2 × 50 mL) and the combined aqueous layers were extracted several times with EtOAc (2 × 100 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, EtOAc–hexanes, 1:2).

Yield: 8.2 g (88%); colourless oil; R_f = 0.4 (EtOAc–hexanes, 60:40); $[\alpha]_D^{20}$ +34.8 (*c* 1.5, MeOH).

IR (neat): 3356, 2943, 1050, 700 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38–7.09 (m, 5 H), 4.86 (dd, *J* = 7.8, 4.3 Hz, 1 H), 3.77 (t, *J* = 6.0 Hz, 2 H), 3.44–3.31 (br s, 1 H), 3.11–2.88 (br s, 1 H), 1.99–1.74 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.2, 128.2, 126.5, 125.5, 73.1, 59.7, 40.1.

LSIMS: *m*/*z* = 175.1 [M$^+$ + Na].

(3*R*)-3-Hydroxy-3-phenylpropyl Pivalate (6)

PvCl (4.4 mL, 35.9 mmol) was added very slowly at 0 °C to diol **5** (5.2 g, 34.2 mmol) and Et_3N (14.2 mL, 101.9 mmol) in CH_2Cl_2 (70 mL). The mixture was allowed to warm to r.t. and stirred for 4 h. After completion of the reaction, H_2O (100 mL) was added to the mixture, and the organic layer was separated and washed with H_2O (2 × 50 mL) and brine (2 × 50 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography (silica gel, EtOAc–hexanes, 1:9).

Yield: 7.2 g (90%); colourless oil; R_f = 0.6 (EtOAc–hexanes, 20:80); $[\alpha]_D^{20}$ +6.62 (*c* 1. 0, $CHCl_3$).

IR (neat): 3446, 2969, 1726, 1161, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.27 (m, 5 H), 4.72 (dd, *J* = 7.5, 5.2 Hz, 1 H), 4.37–4.28 (m, 1 H), 4.12–4.04 (m, 1 H), 2.28–2.11 (br s, 1 H) 2.07–1.94 (m, 2 H), 1.20 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.6, 143.8, 128.4, 127.5, 125.6, 71.2, 61.4, 38.6, 38.0, 27.0.

LSIMS: *m*/*z* = 259.1 [M$^+$ + Na].

ESI-HRMS: *m*/*z* calcd for $C_{14}H_{20}O_3Na$ [M$^+$ + Na]: 259.1310; found: 259.1313.

(3*R*)-3-(Methoxymethoxy)-3-phenylpropyl Pivalate (7)

To alcohol **6** (5.6 g, 23.7 mmol) in anhyd CH_2Cl_2 (50 mL) at 0 °C, DMAP, DIPEA (12.4 mL, 71.1 mmol), and MOMCl (3.5 mL, 47.3 mmol) were added successively, and the mixture was stirred for 4 h at r.t. After completion of the reaction, the mixture was quenched by addition of H_2O and extracted with CH_2Cl_2 (2 × 100 mL). The organic extracts were washed with brine (2 × 50 mL), dried (Na_2SO_4), and concentrated under vacuum to remove the solvent,

and the crude product was purified by column chromatography (silica gel, EtOAc–hexanes, 1:19) to afford pure product **7**.

Yield: 6.52 g (98%); colourless oil; R_f = 0.7 (silica gel, EtOAc–hexanes, 20:80); $[\alpha]_D^{20}$ +95.4 (*c* 1.75, $CHCl_3$).

IR (neat): 2963, 1730, 1156, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 5 H), 4.72 (dd, *J* = 7.5, 5.2 Hz, 1 H), 4.46 (d, *J* = 6.7, 1 H), 4.45 (d, *J* = 6.7 Hz, 1 H), 4.36–4.28 (m, 1 H), 4.13–4.04 (m, 1 H), 3.32 (s, 3 H), 2.05–1.97 (m, 2 H), 1.20 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.3, 141.3, 128.5, 127.8, 126.7, 94.1, 74.6, 61.0, 55.5, 38.6, 37.0, 27.1.

LSIMS: *m*/*z* = 303.1 [M^+ + Na].

ESI-HRMS: *m*/*z* calcd for $C_{16}H_{24}O_4Na$ [M^+ + Na]: 303.1572; found: 303.1572.

(3*R*)-3-(Methoxymethoxy)-3-phenylpropan-1-ol (8)

Pivalate **7** (7.2 g, 25.7 mmol) was dissolved in MeOH (60 ml), K_2CO_3 (3.5 g, 25.7 mmol) was added at r.t., and the mixture was stirred for 2 h. Then the MeOH was removed under reduced pressure and H_2O (100 mL) was added. The mixture was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude was purified by column chromatography (silica gel, EtOAc–hexanes, 1:4).

Yield: 4.63 g (92%); colourless liquid; R_f = 0.4 (silica gel, EtOAc–hexanes, 40:60); $[\alpha]_D^{20}$ +179.5 (*c* 1.0, $CHCl_3$).

IR (neat): 3426, 2926, 1029, 701 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 5 H), 4.80 (dd, *J* = 9.5, 4.3 Hz, 1 H), 4.49 (s, 2 H), 3.81–3.68 (m, 2 H), 3.38 (s, 3 H), 2.21–1.8 (br s, 1 H), 2.07–1.99 (m, 1 H), 1.93–1.83 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.5, 128.5, 127.7, 126.7, 94.2, 76.4, 59.9, 55.6, 40.4.

LSIMS: *m*/*z* = 219.1 [M^+ + Na].

ESI-HRMS: *m*/*z* calcd for $C_{11}H_{16}O_3Na$ [M^+ + Na]: 219.0997; found: 219.0990.

(1*R*)-1-(Methoxymethoxy)-1-phenylhex-5-en-3-ol (9)

DMSO (1.79 g, 19.1 mmol) in CH_2Cl_2 (4 mL) was added by cannula to oxalyl chloride (1.92 g, 15.3 mmol) in CH_2Cl_2 (30 mL) cooled to –78 °C. The mixture was stirred at –78 °C for 1 h before a soln of the alcohol **8** (1.5 g, 7.65 mmol) in CH_2Cl_2 (4 mL) was added dropwise by cannula. The mixture was stirred for 30 min and then DIPEA (9.33 mL, 53.5 mmol) was added dropwise over 10 min. The mixture was stirred at –78 °C for 15 min and then warmed to 0 °C. It was stirred for 5 min at 0 °C and then quenched by the addition of 0.5 M $NaHSO_4$. The organic extracts were washed with H_2O (25 mL) and brine (2 × 30 mL), dried (Na_2SO_4), and concentrated; this gave the crude aldehyde that was used in the next reaction without purification.

To the above aldehyde in anhyd Et_2O (15 mL) was added freshly prepared 2 M $H_2C{=}CHCH_2MgBr$ in Et_2O (7.6 mL, 15.3 mmol) [prepared from $H_2C{=}CHCH_2Br$ (1.85 g, 15.30 mmol) and Mg (0.36 g, 15.30 mmol) in Et_2O (7.5 mL)] dropwise at 0 °C over 10 min. After stirring at r.t. for 0.5 h, the mixture was quenched with sat. NH_4Cl soln. The organic layer was separated and washed with brine (2 × 20 mL). After removal of the solvent, the resulting crude product was purified by flash column chromatography (silica gel, EtOAc–hexanes, 1:9).

Yield: 1.33 g (74%); colourless liquid; R_f = 0.4 (silica gel, EtOAc–hexane, 20:80).

IR (neat): 3446, 2925, 1639, 760 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.17 (m, 5 H), 5.88–5.70 (m, 1 H), 5.11–5.00 (m, 2 H), 4.87 (dd, *J* = 9.8, 3.7 Hz, 0.5 H), 4.80 (dd, *J* = 9.8, 5.2 Hz, 0.5 H), 4.51 (d, *J* = 6.7 Hz, 0.5 H), 4.48 (d, *J* = 6.7 Hz, 0.5 H), 4.46 (s, 1 H), 4.30–4.28 (m, 0.5 H), 3.99–3.87 (m, 1 H), 3.84–3.73 (m, 0.5 H), 3.38 (s, 3 H), 3.14–3.11 (br s, 0.5 H), 2.30–2.29 (br s, 0.5 H), 2.26–2.16 (m, 2 H), 1.96–1.85 (m, 1 H), 1.80–1.65 (m, 1 H).

LSIMS: *m*/*z* = 259.1 [M^+ + Na].

[(1*S*)-3-Azido-1-(methoxymethoxy)hex-5-en-1-yl]benzene (10)

MsCl (870 mg, 7.63 mmol) was added dropwise to a soln of compound **9** (1.20 g, 5.08 mmol), DMAP (90 mg, 0.73 mmol), and Et_3N (2.12 mL, 15.24 mmol) in CH_2Cl_2 (12 mL) at 0 °C. After 0.5 h at 0 °C and 0.5 h at r.t., the mixture was diluted with CH_2Cl_2 (20 mL) and washed with H_2O (2 × 10 mL) and brine (2 × 10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The mesylate was used in the next step without purification.

A mixture of the above mesylate and NaN_3 (1.65 g, 25.38 mmol) in DMF (15 mL) was heated at 50 °C for 16 h. The mixture was cooled to r.t. and diluted with Et_2O (30 mL) and washed with H_2O (2 × 10 mL) and brine (2 × 10 mL). The organic phase was concentrated under reduced pressure and the crude was purified by column chromatography (silica gel, EtOAc–hexanes, 1:19).

Yield: 1.10 g (84%); colourless oil; R_f = 0.5 (silica gel, EtOAc–hexanes, 10:90).

IR (neat): 2946, 2102, 1027, 701 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.13 (m, 5 H), 5.95–5.62 (m, 1 H), 5.25–5.05 (m, 2 H), 4.82–4.64 (m, 1 H), 4.48 (s, 1 H), 4.45 (s, 1 H), 3.82–3.63 (m, 1 H), 3.36 (s, 1.5 H), 3.34 (s, 1.5 H), 3.26–3.11 (m, 1 H), 2.42–2.25 (m, 2 H), 2.14–1.74 (m, 1.5 H), 1.66–1.50 (m, 0.5 H).

LSIMS: *m*/*z* = 262.1 [M^+ + H].

***tert*-Butyl Carbamates 11 and 12**

To a soln of **10** (800 mg, 3.06 mmol) in MeOH–H_2O (8:2, 10 mL) was added TPP (1.12 g, 4.27 mmol), and the mixture was stirred at r.t. for 4 h. Then Boc_2O (800 mg, 3.66 mmol) was added to the mixture, which was stirred for another 4 h. The MeOH was removed under reduced pressure, and the mixture was diluted with H_2O (10 mL) and extracted with Et_2O (2 × 20 mL). The combined extracts were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, EtOAc–hexanes, 1:10); this afforded **11** and **12** as white solids.

***tert*-Butyl {(1*S*)-1-[(2*R*)-2-(Methoxymethoxy)-2-phenylethyl]but-3-enyl}carbamate (11)**

Yield: 430 mg (43%); R_f = 0.6 (EtOAc–hexanes, 20:80); mp 51–53 °C; $[\alpha]_D^{20}$ +98.9 (*c* = 1.0, $CHCl_3$).

IR (neat): 3351, 1697, 1641, 1518, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.19 (m, 5 H), 5.84–5.70 (m, 1 H), 5.09–5.04 (m, 2 H), 4.69 (dd, *J* = 10.5, 3.0 Hz, 1 H), 4.63–4.53 (m, 1 H), 4.47 (d, *J* = 6.7 Hz, 1 H), 4.44 (d, *J* = 6.7 Hz, 1 H), 3.99–3.86 (m, 1 H), 3.32 (s, 3 H), 2.29 (t, *J* = 6.7 Hz, 2 H), 2.02–1.92 (m, 1 H), 1.61–1.52 (m, 1 H), 1.44 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 142.0, 134.5, 128.6, 127.8, 126.7, 117.8, 94.5, 79.1, 74.9, 56.0, 47.6, 42.7, 40.1, 28.5.

MS–FAB: *m*/*z* = 336 [M^+ + H].

ESI-HRMS: *m*/*z* calcd for $C_{19}H_{29}NO_4Na$ [M^+ + Na]: 358.1994; found: 358.2010.

***tert*-Butyl {(1*R*)-1-[(2*R*)-2-(Methoxymethoxy)-2-phenylethyl]but-3-enyl}carbamate (12)**

Yield: 430 mg (43%); R_f = 0.52 (EtOAc–hexanes, 20:80); mp 62–64 °C; $[\alpha]_D^{20}$ +120.5 (*c* = 1.0, $CHCl_3$).

IR (neat): 3366, 1683, 1515, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 5 H), 5.80–5.64 (m, 1 H), 5.07–5.03 (m, 2 H), 4.68–4.55 (m, 2 H), 4.44 (s, 2 H), 3.71–3.66 (m, 1 H), 3.34 (s, 3 H), 2.38–2.26 (m, 2 H), 2.02–1.89 (m, 1 H), 1.78–1.70 (m, 1 H), 1.43 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2, 141.3, 134.0, 128.4, 127.7, 126.8, 117.8, 93.9, 78.9, 75.7, 55.7, 47.8, 42.2, 39.1, 28.3.

ESI-HRMS: *m*/*z* calcd for $C_{19}H_{29}NO_4Na$ [M^+ + Na]: 358.1994; found: 358.2003.

***tert*-Butyl Allyl{(1*S*)-1-[(2*R*)-2-(methoxymethoxy)-2-phenylethyl]but-3-enyl}carbamate (13)**

Compound **11** (400 mg, 1.19 mmol) in DMF (1 mL), followed by $H_2C{=}CHCH_2Br$ (215 mg, 1.77 mmol) were added dropwise at 0 °C to a suspension of 60% NaH (85 mg, 3.54 mmol) in DMF (7 mL). The mixture was slowly warmed to 50 °C and stirred for 12 h at the same temperature. It was then quenched with NH_4Cl soln at 0 °C and extracted with Et_2O (2 × 10 mL). The combined extracts were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, EtOAc–hexanes, 1:19).

Yield: 390 mg (88%); colourless oil; R_f = 0.4 (EtOAc–hexanes, 10:90); $[\alpha]_D^{20}$ +61.7 (*c* 1.0, $CHCl_3$).

IR (neat): 2976, 2929, 1692, 702 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.16 (m, 5 H), 5.97–5.62 (m, 2 H), 5.10–4.94 (m, 4 H), 4.57–4.37 (m, 3 H), 3.95–3.78 (m, 1 H), 3.72–3.42 (m, 2 H), 3.25 (s, 3 H), 2.38–2.13 (m, 2 H), 1.96–1.66 (m, 2 H), 1.45 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$) (rotamers): δ = 155.7, 142.4, 142.2, 136.1, 135.6, 135.4, 135.1, 128.3, 128.2, 127.6, 127.5, 126.5, 126.4, 117.0, 116.8, 116.2, 115.9, 94.9, 94.6, 76.0, 75.4, 55.8, 52.5, 45.8, 41.8, 41.0, 38.5, 28.4, 28.2.

MS–FAB: *m*/*z* = 376 [M^+ + H].

***tert*-Butyl (2*S*)-2-[(2*R*)-2-(Methoxymethoxy)-2-phenylethyl]-1,2,3,6-tetrahydropyridine-1-carboxylate (14)**

To a soln of **13** (380 mg, 1.01 mmol) in anhyd benzene (50 mL) was added over 10 min a soln of the Grubbs-I catalyst [benzylidenedichlorobis(tricyclohexylphosphine)ruthenium] (35 mg, 0.2 mmol) in benzene (2 mL). The mixture was stirred for 2 h at 50 °C and was then concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, EtOAc–hexanes, 1:10).

Yield: 313 mg (90%); colourless oil; R_f = 0.6 (EtOAc–hexanes, 20:80); $[\alpha]_D^{20}$ +49.8 (*c* 0.5, $CHCl_3$).

IR (neat): 2933, 2780, 1383, 702 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.18 (m, 5 H), 5.75–5.45 (m, 2 H), 4.78–4.12 (m, 5 H), 3.44–3.29 (m, 1 H), 3.25 (s, 3 H), 2.55–2.27 (m, 1 H), 2.07–1.73 (m, 3 H), 1.43 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8, 142.2, 128.4, 127.6, 126.9, 126.6, 123.5, 95.1, 79.5, 76.7, 55.7, 55.5, 40.0, 39.4, 28.4, 28.0.

LSIMS: *m*/*z* = 370.2 [M^+ + Na].

***tert*-Butyl (2*S*)-2-[(2*R*)-2-(Methoxymethoxy)-2-phenylethyl]piperidine-1-carboxylate (15)**

To a soln of **14** (300 mg, 0.86 mmol) in EtOAc (10 mL) was added PtO_2 (10 mg, 0.04 mmol). After stirring for 1 h under a H_2 atmosphere (1 atm), the mixture was filtered through Celite and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, EtOAc–hexanes, 1:9).

Yield: 270 mg (90%); colourless oil; R_f = 0.55 (silica gel, EtOAc–hexanes, 20:80); $[\alpha]_D^{20}$ +72.9 (*c* 0.5, $CHCl_3$).

IR (neat): 2930, 1690, 1160, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.19 (m, 5 H), 4.56–4.37 (m, 4 H), 3.99–3.84 (m, 1 H), 3.25 (s, 3 H), 2.74–2.62 (m, 1 H), 1.93–1.87 (m, 2 H), 1.61–1.44 (m, 6 H), 1.43 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.0, 142.4, 128.3, 127.5, 126.6, 95.1, 79.1, 75.6, 55.6, 48.1, 39.0, 38.4, 28.8, 28.3, 25.5, 19.0.

LSIMS: *m*/*z* = 272.2 [M^+ + Na].

ESI-HRMS: *m*/*z* calcd for $C_{20}H_{31}NO_4Na$ [M^+ + Na] 372.2150; found: 372.2165.

(2*S*)-2-[(2*R*)-2-(Methoxymethoxy)-2-phenylethyl]-1-methylpiperidine (16)

To a suspension of $LiAlH_4$ (136 mg, 3.57 mmol) in anhyd THF (10 mL) was added dropwise a soln of **15** (250 mg, 0.71 mmol) in THF (2 mL). After 6 h under reflux, the mixture was quenched by addition of H_2O (0.2 mL), followed by the addition of a 15% aq NaOH soln (0.2 mL) and H_2O (0.4 mL). The mixture was filtered through Celite and the filtrate was dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, MeOH–CH_2Cl_2, 1:20).

Yield: 150 mg (80%); colourless oil; R_f = 0.44 (silica gel, MeOH–CH_2Cl_2, 10:90); $[\alpha]_D^{20}$ +99.6 (*c* 1.0, MeOH).

IR (neat): 2933, 1630, 1383, 1033, 702 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 4.66 (t, *J* = 6.7 Hz, 1 H), 4.46 (d, *J* = 6.7 Hz, 1 H), 4.43 (d, *J* = 6.7 Hz, 1 H), 3.30 (s, 3 H), 3.20–3.15 (m, 1 H), 2.66–2.58 (m, 5 H), 2.27–2.24 (m, 1 H), 2.11–1.56 (m, 6 H), 1.44–1.31 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.1, 128.4, 127.3, 125.5, 68.7, 62.0, 55.7, 40.7, 38.7, 27.6, 22.4, 21.3.

LSIMS: *m*/*z* = 264.1 [M^+ + H].

ESI-HRMS: *m*/*z* calcd for $C_{16}H_{26}NO_2$ [M^+ + H] 264.1963; found: 264.1957.

(1*R*)-2-[(2*S*)-1-Methyl-2-piperidyl]-1-phenylethanol [(–)-Allosedamine] (2)

A soln of piperidine **16** (100 mg, 0.38 mmol) in MeCN (5 mL) was treated with concd HCl (0.04 mL). After being stirred at r.t. for 4 h, the soln was diluted with an EtOAc–*i*-PrOH mixture (1:1, 10 mL) and made basic with aq $NaHCO_3$ soln until pH 9–10. The aqueous layer was extracted with EtOAc (2 × 8 mL). The organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography (silica gel, MeOH–CH_2Cl_2, 1:9).

Yield: 73 mg (88%); white solid; R_f = 0.5 (silica gel, MeOH–CH_2Cl_2, 20:80); mp 78–80 °C; $[\alpha]_D^{20}$ –29.1 (*c* 0.9, MeOH) {Lit.[9b] $[\alpha]_D^{20}$ –29.8 (*c* 0.2, MeOH)}.

IR (neat): 3358, 2936, 2864, 1448, 1052 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.11 (m, 5 H), 5.07 (dd, *J* = 10.4, 3.4 Hz, 1 H), 3.27–3.17 (m, 1 H), 2.64 (s, 3 H), 2.56–2.42 (m, 1 H), 2.18–2.05 (m, 1 H), 1.88–1.57 (m, 6 H), 1.33–1.20 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 128.5, 127.5, 125.4, 69.5, 62.5, 55.9, 39.9, 39.5, 27.9, 22.2, 21.7.

ESI-HRMS: *m*/*z* calcd for $C_{14}H_{22}NO$ $[M+H]^+$: 220.1701; found: 220.1691.

***tert*-Butyl Allyl{(1*R*)-1-[(2*R*)-2-(methoxymethoxy)-2-phenylethyl]but-3-enyl}carbamate (17)**
Compound **17** was prepared from **12** (400 mg, 1.19 mmol) following the same procedure as that described for the synthesis of **13**.

Yield: 390 mg (88%); colourless oil; R_f = 0.35 (silica gel, EtOAc–hexanes, 10:90); $[\alpha]_D^{20}$ +74.88 (*c* 1.0, $CHCl_3$).

IR (neat): 2975, 1692,1172, 1027,702 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.17 (m, 5 H), 6.03–5.48 (m, 2 H), 5.23–4.89 (m, 4 H), 4.61–4.36 (m, 3 H), 4.13–3.48 (m, 3 H), 3.32 (s, 3 H), 2.41–1.98 (m, 3 H), 1.96–1.71 (m, 1 H), 1.42 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$) (rotamers): δ = 155.4, 141.2, 136.0, 135.2, 135.1, 128.3, 127.8, 127.2, 126.6, 116.8, 115.8, 94.0, 75.7, 75.4, 55.5, 53.0, 46.8, 41.0, 40.7, 38.1, 37.5, 28.3, 28.2.

ESI-HRMS: *m*/*z* calcd for $C_{22}H_{33}NO_4Na$ [M^+ + Na]: 398.2307; found: 398.2320.

***tert*-Butyl (2*R*)-2-[(2*R*)-2-(Methoxymethoxy)-2-phenylethyl]-1,2,3,6-tetrahydropyridine-1-carboxylate (18)**
Compound **18** was prepared from **17** (380 mg, 1.01 mmol) following the same procedure as that described for the synthesis of **14**.

Yield: 320 mg (92%); colourless oil; R_f = 0.55 (silica gel, EtOAc–hexane, 20:80); $[\alpha]_D^{20}$ +102.8 (*c* 0.5, $CHCl_3$).

IR (neat): 2930, 1696, 1031, 702 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 5 H), 5.73–5.54 (m, 2 H), 4.51–4.40 (m, 3 H), 4.38–4.06 (m, 2 H), 3.59–3.38 (m, 1 H), 3.33 (s, 3 H), 2.44–2.28 (m, 1 H), 2.10–1.90 (m, 2 H), 1.87–1.62 (m, 1 H), 1.45 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.7, 141.8, 128.3, 127.7, 127.0, 126.6, 122.7, 94.1, 79.5, 75.6, 55.7, 55.5, 39.4, 38.2, 28.4, 28.0.

ESI-HRMS: *m*/*z* calcd for $C_{20}H_{29}NO_4Na$ [M^+ + Na]: 370.1994; found: 370.2003.

***tert*-Butyl (2*R*)-2-[(2*R*)-2-(Methoxymethoxy)-2-phenylethyl]piperidine-1-carboxylate (19)**
Compound **19** was prepared from **18** (300 mg, 0.86 mmol) following the same procedure as that described for the synthesis of **15**.

Yield: 280 mg (92%); colourless oil; R_f = 0.5 (silica gel, EtOAc–hexanes, 20:80); $[\alpha]_D^{20}$ +129.9 (*c* 1.0, $CHCl_3$).

IR (neat): 2932, 1690, 1161, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.20 (m, 5 H), 4.49 (dd, *J* = 7.5, 6.0 Hz, 1 H), 4.43 (s, 2 H), 4.38–4.33 (m, 1 H), 3.96–3.92 (m, 1 H), 3.32 (s, 3 H), 2.82–2.74 (m, 1 H), 2.14–2.01 (m, 1 H), 1.94–1.80 (m, 1 H), 1.67–1.49 (m, 4 H), 1.44–1.33 (m, 11 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.9, 141.8, 128.3, 127.7, 127.1, 94.0, 79.1, 75.6, 55.5, 47.6, 39.2, 38.0, 28.4, 27.4, 25.5, 18.9.

LSIMS: *m*/*z* = 372.2 [M^+ + Na].

(2*R*)-2-[(2*R*)-2-(Methoxymethoxy)-2-phenylethyl-1-methylpiperidine (20)
Compound **20** was prepared from **19** (250 mg, 0.71 mmol) following the same procedure as that described for the synthesis of **16**.

Yield: 154 mg (82%); colourless oil; R_f = 0.44 (silica gel, MeOH–CH_2Cl_2, 10:90); $[\alpha]_D^{20}$ +87.7 (*c* 1.0, MeOH).

IR (neat): 2923, 1449, 1361, 1028, 702 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 5 H), 4.64 (dd, *J* = 10.5, 3.0 Hz, 1 H), 4.43 (s, 2 H), 3.34 (s, 3 H), 3.13–3.06 (m, 1 H), 2.74–2.67 (m, 1 H), 2.51 (s, 3 H), 2.29–2.19 (m, 1 H), 2.07–1.98 (m, 1 H), 1.84–1.37 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.6, 128.7, 128.2, 126.5, 94.1, 74.3, 62.4, 56.0, 40.9, 38.5, 29.8, 27.7, 23.1, 21.8.

ESI-MS: *m*/*z* = 264 [M^+ + H].

ESI-HRMS: *m*/*z* calcd for $C_{16}H_{26}NO_2$ [M^+ + H]: 264.1963; found: 264.1952.

(1*R*)-2-[(2*R*)-1-Methyl-2-piperidyl]-1-phenylethanol [(+)-Sedamine] (1)
Compound **1** was prepared from **20** (100 mg, 0.38 mmol) following the same procedure as that described for the synthesis of **2**.

Yield: 76 mg (92%); white solid; R_f = 0.5 (silica gel, MeOH–CH_2Cl_2, 20:80); mp 57–58 °C; $[\alpha]_D^{20}$ –86.8 (*c* 1.0, EtOH).

IR (neat): 3357, 2932, 2855, 1451,1363, 1061, 756, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.42 (m, 5 H), 4.89 (dd, *J* = 10.6, 2.6 Hz, 1 H), 4.70 (br s, 1 H), 3.1 (m, 1 H), 2.9 (m, 1 H), 2.57 (m, 1 H), 2.51 (s, 3 H), 2.12 (m, 1 H), 1.20–1.81 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.7, 128.3, 127.2, 125.4, 73.4, 61.2, 52.4, 39.8, 39.3, 25.9, 22.2, 20.7.

ESI-MS: *m*/*z* = 220 [M^+ + 1].

ESI-HRMS: *m*/*z* calcd for $C_{14}H_{22}NO$ [M^+ + H]: 220.1701; found: 220.1738.

Ethyl (2*E*,5*R*)-5-(Methoxymethoxy)-5-phenylpent-2-enoate (21)
Oxalyl chloride (5.4 g, 42.8 mmol) in CH_2Cl_2 (60 mL) was cooled to –78 °C, and DMSO (5.03 g, 53.5 mmol) in CH_2Cl_2 (10 mL) was added by cannula. The mixture was stirred at –78 °C for 1 h before a soln of alcohol **8** (4.2 g, 21.42 mmol) in CH_2Cl_2 (10 mL) was added dropwise by cannula. The mixture was stirred for 30 min, and then Et_3N (20.8 mL, 150.0 mmol) was added dropwise over 10 min. The mixture was stirred at –78 °C for 15 min and then warmed to 0 °C. It was stirred for 5 min at 0 °C and then quenched by the addition of H_2O (100 mL). The organic extracts were washed with H_2O (2 × 50 mL) and brine (2 × 50 mL), dried, and concentrated. This gave the crude aldehyde, which was dissolved in dry benzene (100 mL). (Ethoxycarbonylmethylene)triphenylphosphorane (8.17 g, 23.50 mmol) was added to the soln, and the mixture was stirred for 4 h at r.t. After removal of the solvent, the resulting crude product was purified by flash column chromatography (silica gel, EtOAc–hexanes, 1:10).

Yield: 4.6 g (82%); colourless liquid; R_f = 0.6 (silica gel, EtOAc–hexane, 20:80); $[\alpha]_D^{20}$ +94.2 (*c* 1.0, $CHCl_3$).

IR (neat): 2938, 1719, 1033, 701 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.18 (m, 5 H), 7.03–6.85 (m, 1 H), 5.83 (d, *J* = 15.6 Hz, 1 H), 4.68 (dd, *J* = 7.8, 4.6 Hz, 1 H), 4.47 (s, 2 H), 4.14 (q, *J* = 7.0 Hz, 2 H), 3.33 (s, 3 H), 2.79–2.44 (m, 2 H), 1.28 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 144.8, 140.9, 128.5, 127.9, 126.7, 123.6, 94.1, 76.6, 60.1, 55.6, 40.6, 14.2.

LSIMS: *m*/*z* = 287.1 [M^+ + Na].

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{20}O_4Na$ [M^+ + Na]: 287.1259; found: 287.1258.

(2*E*,5*R*)-5-(Methoxymethoxy)-5-phenylpent-2-en-1-ol (22)
To a soln of **21** (3.5 g, 13.2 mmol) in CH_2Cl_2 (40 mL) at 0 °C, a 1.4 M soln of DIBAL-H in toluene (18.8 mL, 26.4 mmol) was added dropwise and the mixture was stirred for 1 h at this temperature. The reaction was quenched by the addition of MeOH (5 mL) followed by sat. aq sodium potassium tartrate soln (30 mL). It was warmed to r.t. and stirred for 1 h. The aqueous layer was extracted with EtOAc (2 × 50 mL) and washed with brine (2 × 30 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude by column chromatography (silica gel, EtOAc–hexanes, 1:4) afforded **22** as an oil.

Yield: 2.6 g (88%); R_f = 0.2 (silica gel, EtOAc–hexanes, 30:70); $[\alpha]_D^{20}$ +114.3 (*c* 1.0, $CHCl_3$).

IR (neat): 3418, 2933, 1030, 701 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.17 (m, 5 H), 5.66–5.62 (m, 2 H), 4.57 (dd, *J* = 7.8, 6.2 Hz, 1 H), 4.47 (s, 2 H), 4.11–4.03 (m, 2 H), 3.31 (s, 3 H), 2.72–2.31 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.3, 131.9, 128.3, 127.7, 126.8, 94.1, 77.7, 63.3, 55.5, 40.6.

LSIMS: *m*/*z* = 245.1 [M^+ + Na].

ESI-HRMS: *m*/*z* calcd for $C_{13}H_{18}O_3Na$ [M^+ + Na]: 245.1153; found: 245.1160.

{(2*R*,3*R*)-3-[(2*R*)-2-(Methoxymethoxy)-2-phenylethyl]oxiran-2-yl}methanol (23)

Compound **23** was prepared from **22** (2.3 g, 10.36 mmol) and (–)-DET (0.32 g, 1.55 mmol) following the same procedure as that described for the synthesis of **4**.

Yield: 2.02 g (82%); colourless oil; R_f = 0.5 (silica gel, EtOAc–hexanes, 60:40); $[\alpha]_D^{20}$ +131.3 (*c* 1.5, $CHCl_3$).

IR (neat): 3446, 2944, 1028, 702 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 5 H), 4.81 (dd, *J* = 9.5, 4.3 Hz, 1 H), 4.5 (s, 2 H), 3.86–3.80 (m, 1 H), 3.63–3.53 (m, 1 H), 3.36 (s, 3 H), 3.20–3.14 (m, 1 H), 2.93–2.76 (m, 1 H), 2.10–1.94 (m, 1 H), 1.88–1.73 (m, 1 H), 1.68–1.52 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 128.4, 127.8, 126.5, 94.0, 75.0, 61.6, 59.1, 55.5, 53.2, 40.3.

ESI-HRMS: *m*/*z* calcd for $C_{13}H_{18}O_4Na$ [M^+ + Na]: 261.1102; found: 261.1108.

(3*S*,5*R*)-5-(Methoxymethoxy)-5-phenylpentane-1,3-diol (24)

Compound **24** was prepared from **23** (1.6 g, 6.72 mmol) following the same procedure as that described for the synthesis of **5**.

Yield: 1.35 g (84%); colourless oil; R_f = 0.2 (silica gel, EtOAc–hexanes, 60:40); $[\alpha]_D^{20}$ +109.9 (*c* 1.5, MeOH).

IR (neat): 3410, 2944, 1033, 702 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 5 H), 4.90 (dd, *J* = 7.8, 5.2 Hz, 1 H), 4.55 (d, *J* = 6.0 Hz, 1 H), 4.50 (d, *J* = 6.0 Hz, 1 H), 4.25–4.05 (m, 1 H), 3.83 (t, *J* = 5.2 Hz, 2 H), 3.41 (s, 3 H), 2.73–2.54 (br s, 1 H), 1.89–1.61 (m, 4 H), 1.48–1.40 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.7, 128.5, 127.6, 126.5, 94.8, 75.6, 68.1, 61.2, 55.8, 45.4, 38.6.

ESI-HRMS: *m*/*z* calcd for $C_{13}H_{20}O_4Na$ [M^+ + Na]: 263.1259; found: 263.1249.

Ethyl (2*E*,5*S*,7*R*)-5-Hydroxy-7-(methoxymethoxy)-7-phenylhept-2-enoate (25)

To a stirred soln of diol **24** (1.1 g, 4.58 mmol) in CH_2Cl_2 (12 mL) were added Ph[I(OAc)$_2$] (1.77 g, 5.5 mmol) and TEMPO (0.07 g, 0.45 mmol). The yellow soln was stirred for 1.5 h, cooled to 0 °C, and (ethoxycarbonylmethylene)triphenylphosphorane (2.38 g, 6.85 mmol) was added. The mixture was allowed to warm to r.t., stirred for 1 h, and then filtered through a Celite pad. The residue was washed with Et_2O and the filtrate was concentrated and purified by column chromatography (silica gel, EtOAc–hexanes, 1:6).

Yield: 861 mg (61%); colourless liquid; R_f = 0.2 (silica gel, EtOAc–hexane, 20:80); $[\alpha]_D^{20}$ +30.28 (*c* 0.5, $CHCl_3$).

IR (neat): 3474, 2942, 1716, 1652, 1034 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.18 (m, 5 H), 7.06–6.84 (m, 1 H), 5.84 (d, *J* = 15.6 Hz, 1 H), 4.86 (dd, *J* = 9.3, 3.9 Hz, 1 H), 4.51 (s, 2 H), 4.15 (q, *J* = 7.0 Hz, 2 H), 4.11–3.91 (m, 1 H), 3.39 (m, 3 H), 2.63 (br s, 1 H), 2.37 (t, *J* = 6.2 Hz, 2 H), 2.00–1.67 (m, 2 H), 1.29 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 145.1, 141.4, 128.5, 127.7, 126.4, 123.7, 94.7, 75.4, 66.9, 60.2, 55.9, 44.8, 40.1, 14.2.

LSIMS: *m*/*z* = 331.1 [M^+ + Na].

ESI-HRMS: *m*/*z* calcd for $C_{17}H_{24}O_5Na$ [M^+ + Na]: 331.1521; found: 331.1515.

(5*S*,7*R*)-7-(Methoxymethoxy)-7-phenylheptane-1,5-diol (26)

To a suspension of $LiAlH_4$ (296 mg, 7.78 mmol) in dry THF (10 mL) at 0 °C was added dropwise a soln of ester **25** (800 mg, 2.59 mmol) in dry THF (3 mL). The mixture was allowed to warm to r.t. and was stirred for 2 h. It was then cooled to 0 °C and quenched by dropwise addition of sat. aq NH_4Cl (2 mL). The precipitate was collected by filtration and washed with EtOAc. The combined organic extracts were dried (Na_2SO_4) and the solvent was removed in vacuo. Column chromatography (silica gel, EtOAc–hexanes, 1:1) afforded **26** as a viscous liquid.

Yield: 626 mg (90%); R_f = 0.2 (silica gel, EtOAc–hexane, 60:40); $[\alpha]_D^{20}$ +103.3 (*c* 1.0, MeOH).

IR (neat): 3411, 2938, 1452, 1032 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5 H), 4.88 (dd, *J* = 9.0, 3.0 Hz, 1 H), 4.52 (s, 2 H), 3.89–3.79 (m, 1 H), 3.61 (t, *J* = 6.0 Hz, 2 H), 3.39 (s, 3 H), 2.79–2.41 (br s, 2 H), 1.92–1.79 (m, 1 H), 1.78–1.36 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.8, 128.3, 127.5, 126.4, 94.7, 75.8, 68.0, 62.4, 55.7, 45.1, 36.9, 32.4, 21.7.

LSIMS: *m*/*z* = 291.1 [M^+ + Na].

(2*R*)-2-[(2*R*)-2-(Methoxymethoxy)-2-phenylethyl]-1-methylpiperidine (20)

To a soln of diol **26** (500 mg, 1.86 mmol) and Et_3N (1.03 mL, 7.42 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added MsCl (530.0 mg, 4.64 mmol). After 15 min, the mixture was poured into ice water (15 mL). The layers were separated and the organic phase was washed with 1 M aq HCl (10 mL), a sat. $NaHCO_3$ soln (10 mL), and H_2O (10 mL). The organic layer was dried (Na_2SO_4) and evaporated and the crude dimesylate was used in the next step without further purification.

A mixture of the above dimesylate and a 40% soln of $MeNH_2$ in H_2O (2.87 mL, 37.0 mmol) in DMF (10 mL) were maintained at 60 °C for 12 h. After dilution with EtOAc (20 mL), the mixture was washed with brine (5 mL) and H_2O (5 mL), dried, and evaporated. The product was purified by column chromatography (silica gel, MeOH–CH_2Cl_2, 1:19). The compound **20** prepared from **26** was identical in all respects with the one prepared from **19**.

Yield: 372 mg (76%); colourless oil; R_f = 0.44 (silica gel, MeOH–CH_2Cl_2, 10:90).

{(2*S*,3*S*)-3-[(2*R*)-2-(Methoxymethoxy)-2-phenylethyl]oxiran-2-yl}methanol (27)

Compound **27** was prepared from **22** (2.3 g, 10.36 mmol) following the same procedure as that described for the synthesis of **4**.

Yield: 2.07 g (84%); colourless oil; R_f = 0.5 (silica gel, EtOAc–hexanes, 60:40); $[\alpha]_D^{20}$ +94.10 (*c* 1.5, $CHCl_3$).

IR (neat): 3446, 2942, 1745, 1027, 702 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.43–7.24 (m, 5 H), 4.72 (dd, *J* = 7.8, 6.2 Hz, 1 H), 4.49 (s, 2 H), 3.83–3.67 (m, 1 H), 3.57–3.44 (m, 1 H), 3.36 (s, 3 H), 2.93–2.85 (m, 1 H), 2.81–2.72 (m, 1 H), 2.30–2.15 (m, 1 H), 1.90–1.74 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.9, 128.5, 128.0, 126.8, 94.1, 75.8, 61.6, 58.0, 55.5, 53.2, 39.9.

LSIMS: *m*/*z* = 261.0 [M^+ + Na].

(3*R*,5*R*)-5-(Methoxymethoxy)-5-phenylpentane-1,3-diol (28)
Compound **28** was prepared from **27** (1.6 g, 6.72 mmol) following the same procedure as that described for the synthesis of **5**.

Yield: 1.38 g (86%); colourless oil; R_f = 0.2 (silica gel, EtOAc–hexanes, 60:40); $[\alpha]_D^{20}$ +98.8 (*c* 1.5, MeOH).

IR (neat): 3413, 2944, 1449,1035, 702.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.18 (m, 5 H), 4.85 (dd, *J* = 10.5, 3.7 Hz, 1 H), 4.50 (s, 2 H), 4.20–4.09 (m, 1 H), 3.86–3.75 (m, 2 H), 3.42 (s, 3 H), 2.82–2.62 (br s, 1 H), 2.17–2.03 (m, 1 H), 1.82–1.66 (m, 3 H), 1.58–1.47 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.9, 128.5, 127.9, 126.8, 93.9, 78.0, 70.7, 60.9, 55.8, 45.1, 38.8.

LSIMS: *m*/*z* = 263.1 [M^+ + Na].

Ethyl (2*E*,5*R*,7*R*)-5-Hydroxy-7-(methoxymethoxy)-7-phenylhept-2-enoate (29)
Compound **29** was prepared from **28** (1.1 g, 4.58 mmol) following the same procedure as that described for the synthesis of **25**.

Yield: 917 mg (65%); colourless oil; R_f = 0.2 (silica gel, EtOAc–hexanes, 20:80); $[\alpha]_D^{20}$ +107.3 (*c* 1.0, $CHCl_3$).

IR (neat): 3491, 2942, 1717, 1037, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5 H), 7.01–6.88 (m, 1 H), 5.84 (d, *J* = 15.8 Hz, 1 H), 4.84 (dd, *J* = 10.5, 4.5 Hz, 1 H), 4.49 (s, 2 H), 4.18 (q, *J* = 7.5 Hz, 2 H), 4.05–3.94 (m, 1 H), 3.41 (s, 3 H), 2.46–2.31 (m, 2 H), 2.05–1.92 (m, 1 H), 1.83–1.72 (m, 1 H), 1.31 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 145.4, 141.1, 129.9, 128.6, 127.4, 124.3, 94.2, 78.5, 70.5, 60.8, 56.5, 44.9, 40.7, 14.8.

LSIMS: *m*/*z* = 331.1 [M^+ + Na].

(5*R*,7*R*)-7-(Methoxymethoxy)-7-phenylheptane-1,5-diol (30)
Compound **30** was prepared from **29** (800 mg, 2.59 mmol) following the same procedure as that described for the synthesis of **26**.

Yield: 640 mg (92%); colourless oil; R_f = 0.2 (silica gel, EtOAc–hexanes, 60:40); $[\alpha]_D^{20}$ +80.3 (*c* 1.0, MeOH).

IR (neat): 3391, 2938, 1453, 1034, 702 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34–7.18 (m, 5 H), 4.81 (dd, *J* = 9.8, 3.7 Hz, 1 H), 4.47 (s, 2 H), 3.83–3.78 (m, 1 H), 3.6 (t, *J* = 6.0 Hz, 2 H), 3.39 (s, 3 H), 2.03–1.83 (m, 1 H), 1.76–1.65 (m, 1 H), 1.57–1.38 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.0, 128.5, 127.9, 126.8, 93.8, 78.2, 70.9, 62.4, 55.8, 44.9, 32.5, 21.5.

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{24}O_4Na$ [M^+ + Na]: 291.1572; found: 291.1576.

(2*R*)-2-[(2*S*)-2-(Methoxymethoxy)-2-phenylethyl]-1-methylpiperidine (16)
Compound **16** was prepared from **30** (500 mg, 1.86 mmol) following the same procedure as that described for the synthesis of **20** from **26**. The compound **16** prepared here from **30** was identical in all respects with the one prepared from **15**.

Yield: 381 mg (78%); colourless oil; R_f = 0.44 (silica gel, MeOH–CH_2Cl_2, 10:90).

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