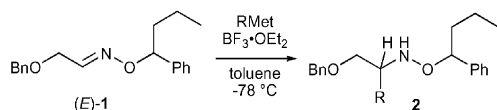
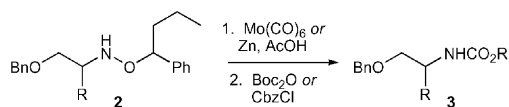


Table 1 Addition of organometallic reagents to *O*-(1-phenylbutyl)benzyloxyacetaldoxime **1**

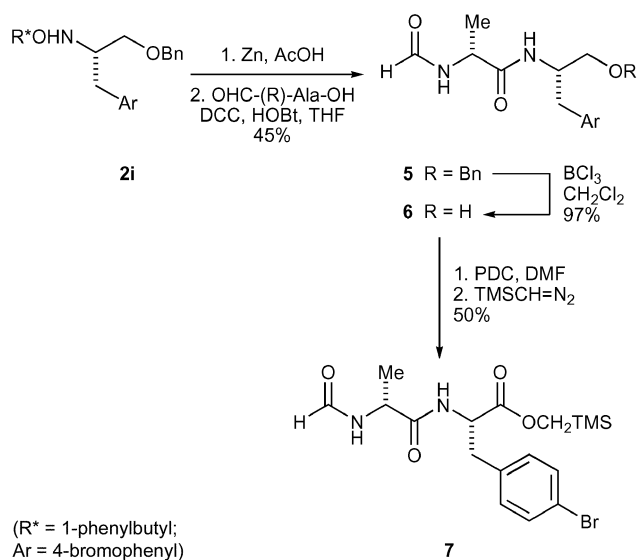
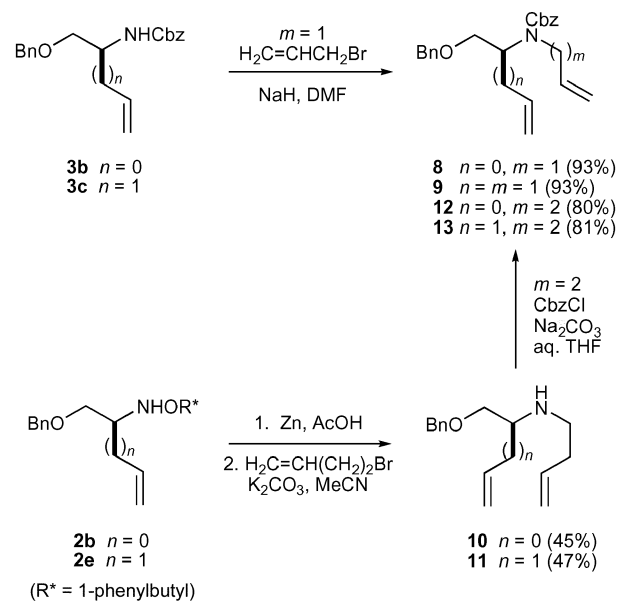
Oxime configuration	Organometallic reagent	Hydroxylamine (configuration at new centre)	Yield (%)	De ^a (%)
<i>R</i>	MeLi	2a (<i>R</i>)	75	75
<i>S</i>	H ₂ C=CHLi	2b (<i>S</i>)	61	87
<i>R</i>	H ₂ C=CHLi	2b (<i>R</i>)	69	89
<i>R</i>	<i>n</i> -PrMgCl	2c (<i>R</i>)	82	90
<i>R</i>	<i>i</i> -PrMgCl	2d (<i>R</i>)	79	90
<i>S</i>	H ₂ C=CHCH ₂ MgBr	2e (<i>S</i>)	44 ^b	42
<i>R</i>	<i>n</i> -BuLi	2f (<i>R</i>)	72	90
<i>R</i>	PhLi	2g (<i>R</i>)	56	>95
<i>S</i>	PhCH ₂ MgBr	2h (<i>S</i>)	83	90
<i>S</i>	4-BrC ₆ H ₄ CH ₂ MgBr	2i (<i>S</i>)	45	90
<i>R</i>	2-Lithiothiophene	2j (<i>S</i>)	81	80
<i>R</i>	2-Lithiothiazole	2k (<i>S</i>)	84	>95

^a Determined from the ¹H-NMR spectrum of crude hydroxylamine **2** (before chromatography) by integration of the CHNH signals. ^b Yield of the major diastereomer after separation.

Table 2 N–O bond cleavage in hydroxylamines **2** and protection of resulting amines as carbamates **3**

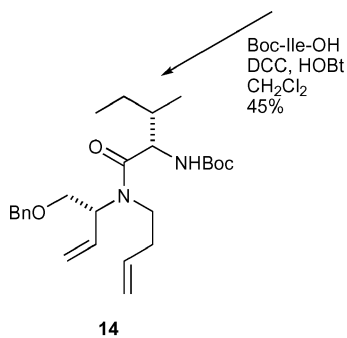
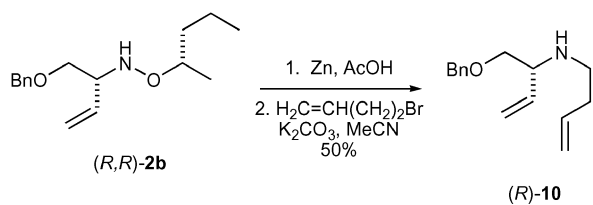
Hydroxylamine	Method ^a	R	R'	Protected 1,2-aminoalcohol 3 configuration	Yield (%)	Ee ^b (%)
2a	A	Me	<i>t</i> -Bu	3a <i>R</i>	67	97
2b	B	H ₂ C=CH	Bn	3b <i>S</i>	76	Nd ^c
2e^d	B	H ₂ C=CHCH ₂	Bn	3c <i>S</i>	70	91
2f	A	<i>n</i> -Bu	<i>t</i> -Bu	3d <i>R</i>	67	93
2h	A	Bn	<i>t</i> -Bu	3e <i>S</i>	84	83
2i	B	4-BrC ₆ H ₄ CH ₂	<i>t</i> -Bu	3f <i>S</i>	53	97
2k	A	2-Thiazolyl	<i>t</i> -Bu	3g <i>S</i>	77	98

^a Method A: Mo(CO)₆, MeCN; Method B: Zn, AcOH, ultrasound. ^b Determined by HPLC on ChiralCel OD using hexane–isopropanol (85 : 15 to 95 : 5) as eluant. ^c Nd = not determined ^d The pure major diastereomer was used in this reaction.

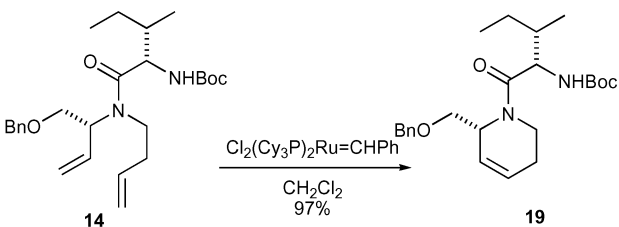
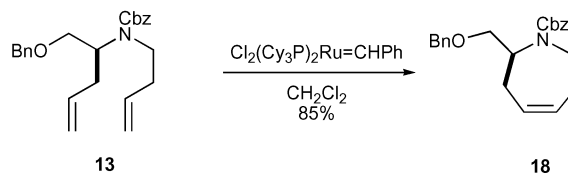
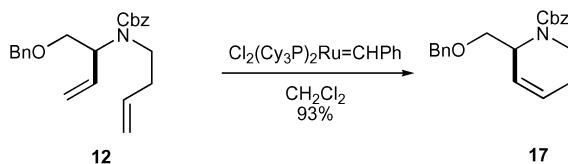
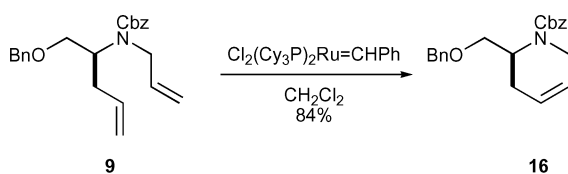
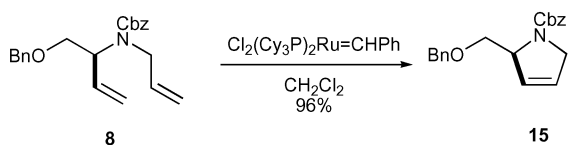
**Scheme 2****Scheme 3**

of nitrogen heterocycles (Schemes 3–6). This was conveniently achieved by the incorporation of a second unsaturated sidechain (allyl or butenyl) into the derivatives obtained by addition of vinyl and allyl nucleophiles, thereby setting up dienyl systems for ring-closure by a ring-closing metathesis (RCM) reaction.²⁵

Thus *N*-allylation of the benzyl carbamates **3b** and **3c** gave the corresponding (*S*)-*N*-allyl derivatives **8** and **9** in good yield. Attempted reaction of carbamates **3b** and **3c** with 4-bromobutene under similar conditions was unsatisfactory, and therefore the



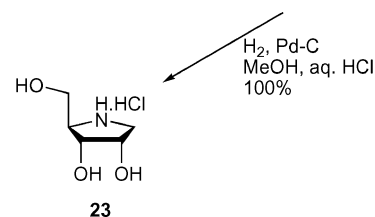
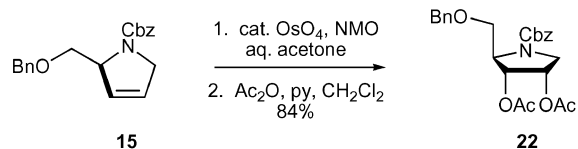
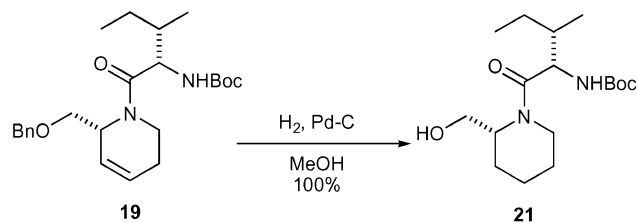
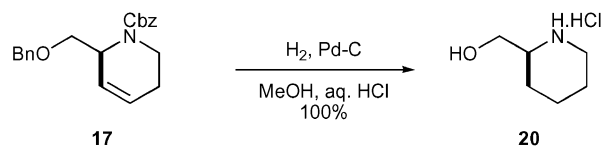
Scheme 4



Scheme 5

RCM precursors **12** and **13** were prepared differently. The N–O bond in hydroxylamines **2b** and **2e** was cleaved as before, and the resulting amines were alkylated with 4-bromobutene to give the (*S*)-secondary amines **10** and **11**, protection of which with benzyl chloroformate gave the (*S*)-dienes **12** and **13** (Scheme 3). In a related sequence, hydroxylamine (*R,R*)-**2b** was converted into (*R*)-**10**, DCC-coupling of which with *N*-Boc isoleucine gave the RCM precursor **14** (Scheme 4).

The RCM reactions of the five dienes were carried out by stirring a dichloromethane solution of the diene with benzylidene-



Scheme 6

bis-(tricyclohexylphosphine)dichlororuthenium (10 mol%) (Grubbs' catalyst) at room temperature until complete consumption of starting material was observed by TLC. The 2-benzyloxymethyl-5-, -6-, and -7-membered heterocycles **15–19** were formed in excellent yield as shown in Scheme 5. Thus the dihydropyrrole **15**, the isomeric tetrahydropyridines **16** and **17**, the tetrahydroazepine **18** and the tetrahydropyridine **19** were all prepared by this method.

Some of the 2-benzyloxymethyl heterocycles formed in the RCM reaction were elaborated further as shown in Scheme 6. Catalytic hydrogenation of tetrahydropyridine **17** over palladium-on-carbon resulted in concomitant reduction of the double bond and hydrogenolysis of the benzyl ether protecting group to give (*S*)-piperidine-2-methanol **20**. Similarly, the tetrahydropyridine **19** gave the isoleucinyl piperidine **21**, a potential precursor (by oxidation of the hydroxymethyl group) of the isoleucinyl pipecolic acid dipeptide of the apicidins, naturally occurring cyclic peptides.²⁶ Finally, the dihydropyrrole **15** was used in a synthesis of 1,4-dideoxy-1,4-imino-D-ribose **23**, a naturally occurring glycosidase inhibitor isolated from the mulberry tree *Morus alba*.^{27–31} Thus reaction of the dihydropyrrole **15** with a catalytic amount of osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide (NMO) resulted in dihydroxylation from the least hindered face to give, after acetylation, the protected iminosugar **22** (84% over two steps). Hydrogenolysis of **22** over palladium-on-carbon in methanolic hydrochloric acid gave 1,4-dideoxy-1,4-imino-D-ribitol **23** as its hydrochloride salt in quantitative yield (Scheme 6).

In summary, we have shown that the oxime ether **1** is a versatile reagent for the asymmetric synthesis of protected 1,2-aminoalcohols and nitrogen heterocycles.

Experimental

For general experimental details, see ref. 12. With the exception of compound **2e**, which was isolated as a single diastereomer, hydroxylamines **2** were characterized as diastereomeric mixtures; the NMR data refer to the major diastereomer.

(E)-(S)-(-)-O-(1-Phenylbutyl)benzyloxyacetaldoxime (E)-(S)-1

Obtained from the cleavage of (S)-(-)-N-(1-phenylbutoxy)-phthalimide¹⁰ (10.17 mmol) and subsequent condensation of the hydroxylamine with benzyloxyacetaldehyde (10.17 mmol). The crude product was purified by column chromatography on silica gel, eluting with light petroleum–dichloromethane (1 : 2) to give the pure product as a colourless oil (49%); (Found: C, 77.0; H, 8.0; N, 4.7. C₁₉H₂₃NO₂ requires C, 76.7; H, 7.8; N, 4.7%); (Found: MH⁺, 298.1806. C₁₉H₂₃NO₂ + H requires 298.1807); [α]_D²⁴ -6.7 (c 0.90, CHCl₃); ν_{max} (film)/cm⁻¹ 3063, 3032, 2960, 2935, 2868, 1496, 1450, 1363, 1091, 1020, 922, 738, 697; δ_H (300 MHz; CDCl₃) 7.54 (1 H, t, J = 6.8 Hz, N=CH), 7.31 (10 H, m, ArH), 5.09 (1 H, t, J 7.0, OCH), 4.44 (2 H, AB, J 12.5, CH₂Ph), 4.07 (2 H, m, CH₂CHN), 1.95 (1 H, m, CHH), 1.73 (1 H, m, CHH), 1.51–1.26 (2 H, m, CH₂Me), 0.95 (3 H, t, J 7.3, Me); δ_C (75 MHz; CDCl₃) 147.5 (CH), 142.8 (C), 137.9 (C), 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.1 (CH), 85.6 (CH), 72.7 (CH₂), 67.1 (CH₂), 38.7 (CH₂), 19.3 (CH₂), 14.4 (Me); m/z (CI) 298 (MH⁺, 4%), 174 (6), 133 (100), 117 (35), 107 (35), 105 (95), 92 (88), 77 (99), 51 (81).

Also formed was (Z)-(S)-O-(1-phenylbutyl)benzyloxyacetaldoxime (Z)-(S)-1 as a colourless oil (22%); δ_H (300 MHz; CDCl₃) 7.30 (10 H, m, ArH), 6.89 (1 H, t, J = 3.6 Hz, N=CH), 5.07 (1 H, t, J 6.9, OCH), 4.57 (2 H, s, CH₂Ph), 4.43 (2 H, m, CH₂CHN), 1.92 (1 H, m, CHH), 1.71 (1 H, m, CHH), 1.49–1.24 (2 H, m, CH₂Me), 0.94 (3 H, t, J 7.4, Me); δ_C (75 MHz; CDCl₃) 150.7 (CH), 142.9 (C), 137.9 (C), 128.9 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 126.8 (CH), 85.9 (CH), 73.6 (CH₂), 65.2 (CH₂), 38.7 (CH₂), 19.3 (CH₂), 14.4 (Me).

(E)-(R)-(+)-O-(1-Phenylbutyl)benzyloxyacetaldoxime (E)-(R)-1

Obtained from the cleavage of (R)-(+)-N-(1-phenylbutoxy)-phthalimide¹⁰ (10.17 mmol) and subsequent condensation of the hydroxylamine with benzyloxyacetaldehyde (10.17 mmol). The crude product was purified by column chromatography on silica gel, eluting with light petroleum–dichloromethane (1 : 2) to give the pure product as a colourless oil (60%); [α]_D²⁶ +11.2 (c 1.07, CH₂Cl₂); spectroscopic properties are identical to the (S)-enantiomer (E)-(S)-1.

General procedure for the addition of organometallics

The oxime ether **1** (3.9 mmol, 1 equiv.) was dissolved in toluene (10 mL) under nitrogen and cooled to -78 °C or -90 °C. Boron trifluoride etherate (11.8 mmol, 3 equiv.) was added and the mixture stirred for 15 min. The organometallic reagent (11.8 mmol, 3 equiv.) was added dropwise over 30 min at this temperature, and the mixture stirred until all starting material was consumed. The reaction mixture was quenched at this temperature with aqueous saturated ammonium chloride solution (10 mL), and allowed to warm to room temperature. The mixture was extracted with diethyl ether (3 × 15 mL), combined, dried (K₂CO₃), filtered and evaporated. The residue was purified by column chromatography on silica gel.

(2R,1'R)-1-Benzyloxymethyl-N-(1-phenylbutoxy)-2-propylamine 2a. Obtained from the addition of methylolithium to oxime (E)-(R)-1 as a colourless oil (75%, 75% de); [α]_D¹⁸ +41.6 (c 1.4, CHCl₃); (Found: MH⁺, 314.2131. C₂₀H₂₇NO₂ + H requires 314.2120); ν_{max} (film)/cm⁻¹ 3238 (NH), 3011, 2965, 2873, 1449; δ_H (300 MHz; CDCl₃) 7.22 (10 H, m, ArH), 5.59 (1 H, br s, NH), 4.49 (1 H, t, J = 5.9 Hz, OCH), 4.38 (2 H, s, CH₂Ph), 3.35 (1 H, m, NCH), 3.23 (2 H, m, OCH₂), 1.46 (1 H, m, CHH), 1.34 (1 H, m, CHH), 1.23 (2 H, m, CH₂), 1.00 (3 H, t, J 6.2, Me), 0.86 (3 H, t, J 7.3, Me); δ_C (75 MHz; CDCl₃) 143.6 (C), 138.7 (C), 128.72 (CH), 128.69 (CH), 127.9 (2 × CH), 127.6 (CH), 126.9 (CH), 85.8 (CH), 73.4 (CH₂), 71.8 (CH₂), 56.1 (CH), 39.3 (CH₂), 19.6 (CH₂), 15.8 (Me), 14.5 (Me); m/z (CI) 314 (MH⁺, 12%), 210 (4), 192 (3), 181 (69), 164 (7), 150 (37), 133 (100), 91 (65).

(2S,1'S)-(-)-1-Benzyloxy-N-(1-phenylbutoxy)-2-but-3-enylamine (S,S)-2b. Obtained from the addition of vinylolithium (6.05 mmol) (prepared from tetravinyltin and methylolithium³²) to oxime (E)-(S)-1 (1.85 mmol). The crude product was purified by column chromatography on silica gel, eluting with light petroleum–dichloromethane (1 : 2) to give the pure product as a colourless oil (61%, 87% de); (Found: C, 77.9; H, 9.0; N, 4.3. C₂₁H₂₇NO₂ requires C, 77.5; H, 8.4; N, 4.3%); (Found: MH⁺, 326.2123. C₂₁H₂₇NO₂ + H requires 326.2120); [α]_D²² -42.5 (c 1.20, CHCl₃); ν_{max} (film)/cm⁻¹ 3263 (NH), 3083, 3068, 3032, 2950, 2930, 2863, 1501, 1455, 1363, 1096, 1030, 994, 917, 738, 692; δ_H (300 MHz; CDCl₃) 7.31 (10 H, m, ArH), 5.78 (2 H, m, =CH, NH), 5.24 (2 H, m, =CH₂), 4.57 (1 H, dd, J = 7.6, 5.8 Hz, OCH), 4.46 (2 H, AB, J 12.3, CH₂Ph), 3.75 (1 H, m, NCH), 3.48 (1 H, dd, J 9.6, 4.3, OCHH), 3.39 (1 H, dd, J 9.6, 8.1, OCHH), 1.79 (1 H, m, CHH), 1.59–1.16 (3 H, m, CHH, CH₂), 0.89 (3 H, t, J 7.2, Me); δ_C (75 MHz; CDCl₃) 143.7 (C), 138.5 (C), 136.6 (CH), 128.8 (CH), 128.7 (CH), 128.06 (CH), 128.03 (CH), 127.7 (CH), 127.0 (CH), 118.3 (CH₂), 85.8 (CH), 73.5 (CH₂), 70.5 (CH₂), 63.9 (CH), 39.3 (CH₂), 19.6 (CH₂), 14.5 (Me); m/z (CI) 326 (MH⁺, 10%), 194 (59), 193 (15), 162 (31), 133 (100), 119 (9), 107 (11), 91 (99).

(2R,1'R)-(+)-1-Benzyloxy-N-(1-phenylbutoxy)-2-but-3-enylamine (R,R)-2b. Obtained from the addition of vinylolithium (20.20 mmol) to oxime (E)-(R)-1 (6.73 mmol). The crude product was purified by column chromatography on silica gel, eluting with light petroleum–dichloromethane (1 : 2) to give the pure product as a colourless oil (69%, 89% de); [α]_D²³ +45.7 (c 1.05, CHCl₃); spectroscopic properties are identical to the enantiomer (S,S)-2b.

(2R,1'R)-1-Benzyloxy-N-(1-phenylbutoxy)-2-pentylamine 2c. Obtained from the addition of *n*-propylmagnesium chloride to oxime (E)-(R)-1 as a colourless oil (82%, 90% de); [α]_D¹⁷ +57.4 (c 0.6, CHCl₃); (Found: MH⁺, 342.2441. C₂₂H₃₁NO₂ + H requires 342.2433); ν_{max} (film)/cm⁻¹ 3262 (NH), 3032, 2863, 1454; δ_H (300 MHz; CDCl₃) 7.45–7.08 (10 H, m, ArH), 5.56 (1 H, br s, NH), 4.45 (1 H, t, J = 5.9 Hz, OCH), 4.39 (2 H, AB, J 14.0, CH₂Ph), 3.45 (1 H, dd, J 9.5, 3.9, OCHH), 3.28 (1 H, dd, J 9.5, 6.5, OCHH), 2.99 (1 H, m, NCH), 1.74 (1 H, m, CHH), 1.26 (7 H, m, CHH, 3 × CH₂), 0.83 (6 H, m, 2 × Me); δ_C (75 MHz; CDCl₃) 143.9 (C), 139.1 (C), 129.7 (CH), 129.0 (2 × CH), 128.2 (CH), 127.9 (CH), 127.3 (CH), 85.8 (CH), 73.7 (CH₂), 70.4 (CH₂), 60.8 (NCH), 39.4 (CH₂), 32.3 (CH₂), 19.9 (CH₂), 19.8 (CH₂), 14.9 (Me), 14.7 (Me); m/z (CI) 342 (MH⁺, 100%), 286 (22), 210 (89), 133 (9).

(2R,1'R)-1-Benzyloxy-3-methyl-N-(1-phenylbutoxy)-2-butylamine 2d. Obtained from the addition of isopropylmagnesium chloride to oxime (E)-(R)-1 as a colourless oil (79%, 90% de); [α]_D¹⁹ +38.8 (c 1.6, CHCl₃); (Found: M⁺, 341.2373. C₂₂H₃₁NO₂ requires 341.2355); ν_{max} (film)/cm⁻¹ 3252 (NH), 3032, 2955, 2868, 1490, 1454; δ_H (300 MHz; CDCl₃) 7.23 (10 H, m, ArH), 6.15 (1 H, br s, NH), 4.47 (1 H, t, J = 5.9 Hz, OCH), 4.37 (2 H, AB, J 12.0, CH₂Ph), 3.47 (1 H, dd, J 9.7, 6.3, OCHH), 3.26 (1 H, dd, J 9.7, 7.3, OCHH), 2.83 (1 H, m, NCH), 1.84 (1 H, m, CHMe₂), 1.64 (1 H, m, CHH), 1.46 (1 H, m, CHH), 1.32 (2 H, m, CH₂), 0.86 (6 H, d, J 6.8, 2 × Me), 0.79 (3 H, t, J 7.2, Me); δ_C (75 MHz; CDCl₃) 143.8 (C), 138.8 (C), 128.7 (CH), 128.6 (CH), 127.9 (2 × CH), 127.6 (CH), 127.0 (CH), 85.3 (CH), 73.4 (CH₂), 67.8 (CH₂), 65.9 (CH), 39.1 (CH₂), 27.7 (CH), 20.1 (Me), 19.6 (CH₂), 18.8 (Me), 14.5 (Me); m/z (EI) 341 (M⁺, 6%), 298 (10), 278 (8), 209 (22), 178 (87), 133 (100), 107 (29), 91 (83), 77 (26).

(2S,1'S)-(-)-1-Benzyloxy-N-(1-phenylbutoxy)-2-pent-4-enylamine 2e. Obtained from the addition of allylmagnesium bromide (3.03 mmol) to oxime (E)-(S)-1 (1.01 mmol). The crude product was purified by column chromatography on silica gel, eluting with light petroleum–dichloromethane (1 : 2) to give the pure product as a colourless oil (44% of major

diastereoisomer, 42% de); (Found: C, 78.0; H, 8.8; N, 3.9. $C_{22}H_{29}NO_2$ requires C, 77.8; H, 8.6; N, 4.1%); (Found: M^+ , 339.2209. $C_{22}H_{29}NO_2$ requires 339.2198); $[a]_D^{24} -44.7$ (c 0.76, $CHCl_3$); ν_{max} (film)/ cm^{-1} 3478 (NH), 3063, 3027, 2960, 2925, 2863, 1496, 1450, 1358, 1102, 1025, 917, 733, 692; δ_H (300 MHz; $CDCl_3$) 7.30 (10 H, m, ArH), 5.79 (1 H, m, =CH), 5.67 (1 H, br s, NH), 5.05 (2 H, m, =CH₂), 4.55 (1 H, t, $J = 6.8$ Hz, OCH), 4.46 (2 H, AB, J 12.1, CH_2Ph), 3.50 (1 H, dd, J 9.6, 4.1, $OCHH$), 3.38 (1 H, dd, J 9.6, 7.0, $OCHH$), 3.17 (1 H, m, NCH), 2.34 (1 H, m, $CHHCH=$), 2.19 (1 H, m, $CHHCH=$), 1.80 (1 H, m, CHH), 1.55 (1 H, m, CHH), 1.48–1.20 (2 H, m, CH_2), 0.91 (3 H, t, J 7.4, Me); δ_C (75 MHz; $CDCl_3$) 143.5 (C), 138.7 (C), 135.6 (CH), 128.73 (CH), 128.69 (CH), 127.98 (CH), 127.96 (CH), 127.7 (CH), 127.0 (CH), 117.5 (CH_2), 85.7 (CH), 73.5 (CH_2), 69.8 (CH_2), 60.3 (CH), 39.1 (CH_2), 34.4 (CH_2), 19.6 (CH_2), 14.5 (Me); m/z (EI) 339 (M^+ , 3%), 298 (3), 207 (24), 176 (23), 166 (96), 133 (88), 107 (48), 91 (100), 77 (39).

(2R,1'R)-1-Benzylxy-N-(1-phenylbutoxy)-2-hexylamine 2f. Obtained from the addition of *n*-butyllithium to oxime (*E*)-(*R*)-**1** as a colourless oil (72%, 90% de); $[a]_D^{24} +38.6$ (c 1.1, $CHCl_3$); (Found: M^+ , 355.2518. $C_{23}H_{33}NO_2$ requires 355.2511); ν_{max} (film)/ cm^{-1} 3032, 2965, 2863, 1495, 1449; δ_H (300 MHz; $CDCl_3$) 7.21 (10 H, m, ArH), 5.22 (1 H, br s, NH), 4.67 (1 H, t, $J = 5.7$ Hz, OCH), 4.38 (2 H, AB, J 12.0, CH_2Ph), 3.42 (1 H, m, $OCHH$), 3.28 (1 H, m, $OCHH$), 2.98 (1 H, m, NCH), 1.70 (1 H, m, CHH), 1.47 (1 H, m, CHH), 1.26 (2 H, m, CH_2), 1.19 (6 H, m, $3 \times CH_2$), 0.84 (3 H, t, J 7.3, Me), 0.79 (3 H, t, J 4.0, Me); δ_C (75 MHz; $CDCl_3$) 143.6 (C), 138.8 (C), 128.7 (CH), 128.6 (CH), 127.94 (CH), 127.91 (CH), 127.6 (CH), 126.9 (CH), 85.5 (CH), 73.5 (CH_2), 70.1 (CH_2), 60.8 (CH), 39.2 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 23.3 (CH_2), 19.6 (CH_2), 14.6 (Me), 14.4 (Me); m/z (EI) 355 (M^+ , 4%), 223 (24), 192 (99), 174 (7), 150 (4), 133 (83), 107 (40), 91 (100), 77 (32).

(1R,1'R)-1-Benzylxy-1-phenyl-N-(1-phenylbutoxy)ethylamine 2g. Obtained from the addition of phenyllithium to oxime (*E*)-(*R*)-**1** as a colourless oil (56%, >95% de); $[a]_D^{21} +45.8$ (c 0.5, $CHCl_3$); (Found: MH^+ , 376.2286. $C_{25}H_{29}NO_2 + H$ requires 376.2277); ν_{max} (film)/ cm^{-1} 3243 (NH), 3023, 2955, 2866, 1497, 1448; δ_H (300 MHz; $CDCl_3$) 7.21 (15 H, m, ArH), 5.89 (1 H, br s, NH), 4.37 (2 H, s, CH_2Ph), 4.30 (3 H, m, OCH, OCH_2), 3.39 (1 H, m, NCH), 1.47 (1 H, m, CHH), 1.24 (1 H, m, CHH), 0.85 (2 H, m, CH_2), 0.56 (3 H, t, $J = 7.3$ Hz, Me); δ_C (75 MHz; $CDCl_3$) 144.0 (C), 140.2 (C), 138.3 (C), 128.8–126.4 ($9 \times CH$), 85.7 (CH), 73.5 (CH_2), 72.2 (CH_2), 65.5 (CH), 39.3 (CH_2), 19.4 (CH_2), 14.4 (Me); m/z (CI) 376 (MH^+ , 14) 254 (19), 244 (41), 212 (57), 182 (7), 150 (8), 133 (100), 122 (23), 107 (68), 91 (99).

(2S,1'S)-1-Benzylxy-3-phenyl-N-(1-phenylbutoxy)-2-propylamine 2h. Obtained from the addition of benzylmagnesium bromide to oxime (*E*)-(*S*)-**1** as a colourless oil (83%, 90% de); $[a]_D^{21} -37.4$ (c 0.8, $CHCl_3$); (Found: MH^+ , 390.2454. $C_{26}H_{31}NO_2 + H$ requires 390.2433); ν_{max} (film)/ cm^{-1} 3233 (NH), 3032, 2954, 2868, 1496, 1448; δ_H (300 MHz; $CDCl_3$) 7.21 (15 H, m, ArH), 5.56 (1 H, br s, NH), 4.47 (1 H, t, $J = 6.0$ Hz, OCH), 4.35 (2 H, AB, J 11.9, OCH_2Ph), 3.40 (1 H, m, NCH), 3.31 (2 H, m, OCH_2), 2.86 (1 H, dd, J 11.9, 7.5, $CHHPh$), 2.59 (1 H, dd, J 11.9, 7.5, $CHHPh$), 1.69 (1 H, m, CHH), 1.49 (1 H, m, CHH), 1.18 (2 H, m, CH_2), 0.82 (3 H, t, J 6.2, Me); δ_C (75 MHz; $CDCl_3$) 143.5 (C), 139.3 (C), 138.7 (C), 130.2–126.6 ($9 \times CH$), 85.8 (CH), 73.6 (CH_2), 69.5 (CH_2), 62.4 (CH), 39.1 (CH_2), 36.1 (CH_2), 19.7 (CH_2), 14.5 (Me); m/z (CI) 390 (MH^+ , 84%), 365 (3), 298 (37), 278 (33), 258 (100), 242 (42), 210 (32), 165 (31).

(2S,1'S)-1-Benzylxy-3-(4-bromophenyl)-N-(1-phenylbutoxy)-2-propylamine 2i. Obtained from the addition of 4-bromo-benzylmagnesium bromide to oxime (*E*)-(*S*)-**1** as a yellow oil (45%, 90% de); (Found: MH^+ , 468.1534. $C_{26}H_{30}^{79}BrNO_2 + H$ requires 468.1538); $[a]_D^{26} -28.9$ (c 1.38, $CHCl_3$); ν_{max} (film)/ cm^{-1} 3062, 3021, 2934, 2868, 1490, 1449, 1357, 1203, 1014, 901, 691; δ_H (300 MHz; $CDCl_3$) 7.40 (2 H, d, $J = 8.2$ Hz, ArH), 7.39 –

7.28 (10 H, m, ArH), 7.07 (2 H, d, J 8.2, ArH), 5.62 (1 H, br s, NH), 4.54 (1 H, dd, J 6.1, 7.7, OCH), 4.49 (2 H, dd, J 11.8, 22.5 CH_2Ar), 3.48 (1 H, dd, J 5.2, 9.4, $CHHOCH_2Ph$), 3.36 (1 H, dd, J 5.2, 9.4, $CHHOCH_2Ph$), 3.26 (1 H, m, $HCNH$), 2.87 (1 H, dd, J 7.0, 12.7, $CH_2OCHHPh$), 2.64 (1 H, dd, J 7.0, 12.7, $CH_2OCHHPh$), 1.80 (1 H, m, CHH), 1.57 (1 H, m, CHH), 1.43 (1 H, m, CHH), 1.30 (1 H, m, CHH), 0.93 (3 H, t, J 7.3, Me); δ_C (75 MHz; $CDCl_3$) 142.9 (C), 138.1 (C), 137.9 (C), 131.4 (CH), 131.1 (CH), 130.9 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 126.6 (CH), 120.0 (C), 85.3 (CH), 73.1 (CH_2), 68.9 (CH_2), 61.7 (CH), 38.6 (CH_2), 35.0 (CH_2), 19.2 (CH_2), 14.1 (Me); m/z (CI) 468/466 (MH^+ , 46%), 320 (15), 166 (13), 150 (100), 133 (21), 108 (40), 91 (64), 78 (5).

(2S,1'R)-1-Benzylxy-N-(1-phenylbutoxy)-1-(2-thienyl)ethylamine 2j. Obtained from the addition of 2-lithiothiophene to oxime (*E*)-(*R*)-**1** as a yellow oil (81%, 80% de); $[a]_D^{24} +86.9$ (c 1.0, $CHCl_3$); (Found: MH^+ , 382.1835. $C_{23}H_{27}NO_2S + H$ requires 382.1841); ν_{max} (film)/ cm^{-1} 3267 (NH), 3027, 2955, 2929, 1454, 1106; δ_H (300 MHz; $CDCl_3$) 7.31 (11 H, m, ArH), 7.01 (2 H, m, ArH), 5.98 (1 H, br, NH), 4.63 (1 H, m, OCH), 4.53 (1 H, m, NCH), 4.50 (2 H, s, CH_2Ph), 3.61 (2 H, m, OCH_2), 1.66 (1 H, m, CHH), 1.44 (1 H, m, CHH), 1.31 (2 H, m, CH_2), 0.78 (3 H, t, $J = 7.3$ Hz, Me); δ_C (75 MHz; $CDCl_3$) 143.7 (C), 143.5 (C), 138.2 (C), 128.8–124.9 ($9 \times CH$), 85.9 (CH), 73.6 (CH_2), 72.0 (CH_2), 61.2 (CH), 39.1 (CH_2), 19.3 (CH_2), 14.3 (Me); m/z (CI) 382 (MH^+ , 23%), 309 (4), 281 (10), 260 (17), 237 (36), 217 (58), 199 (7), 133 (32), 107 (13), 91 (100).

(1S,1'R)-1-Benzylxy-N-(1-phenylbutoxy)-1-(2-thiazolyl)ethylamine 2k. Obtained from the addition of 2-lithiothiazole to oxime (*E*)-(*R*)-**1** as a yellow oil (84%, >95% de); $[a]_D^{18} +31.7$ (c 2.3, $CHCl_3$); (Found: M^+ , 382.1720. $C_{22}H_{26}N_2O_2S$ requires 382.1715); ν_{max} (film)/ cm^{-1} 3262 (NH), 3037, 2960, 2960, 2868, 1501, 1460; δ_H (300 MHz; $CDCl_3$) 7.61 (1 H, d, $J = 3.3$ Hz, thiazole H-4), 7.16 (11 H, m, ArH, thiazole H-5), 5.96 (1 H, br s, NH), 4.60 (1 H, dd, J 8.9, 4.1, NCH), 4.51 (1 H, t, J 5.8, OCH), 4.35 (2 H, AB, J 12.0, CH_2Ph), 3.65 (1 H, dd, J 9.9, 4.1, $OCHH$), 3.46 (1 H, dd, J 9.9, 4.0, $OCHH$), 1.53 (1 H, m, CHH), 1.36 (1 H, m, CHH), 1.21 (2 H, m, CH_2), 0.65 (3 H, t, J 7.3, Me); δ_C (75 MHz; $CDCl_3$) 170.9 (C), 143.1 (C), 142.7 (CH), 137.9 (C), 128.8 ($2 \times CH$), 128.2 (CH), 128.0 (CH), 127.8 (CH), 126.9 (CH), 119.5 (CH), 86.1 (CH), 73.6 (CH_2), 70.6 (CH_2), 63.5 (CH), 39.0 (CH_2), 19.3 (CH_2), 14.3 (Me); m/z (EI) 382 (M^+ , 5%), 295 (3), 219 (15), 250 (25), 199 (11), 150 (7), 133 (38), 107 (58), 91 (100), 85 (25), 77 (32).

General procedure for the preparation of *N*-Boc-protected amines **3** ($R = Bu$)

Hydroxylamine **2** (0.5 mmol) was dissolved in acetonitrile (8 mL) and water (2 mL). Molybdenum hexacarbonyl (0.5 mmol) was added and the mixture heated under reflux overnight. The reaction mixture was allowed to cool to room temperature, di-*tert*-butyl dicarbonate (2 mmol) and 4-(*N,N*-dimethylamino)pyridine (catalyst) were added and the mixture was allowed to stir overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with ethyl acetate–light petroleum. The enantiomeric purity of the product was assessed by HPLC on a ChiralCel OD column using hexane–2-propanol (95 : 5) as eluant.

General procedure for the preparation of *N*-Cbz-protected amines **3** ($R = Bn$)

Zinc dust (15 mmol) was added to a solution of the hydroxylamine **2** (0.38 mmol) in acetic acid–water (1 : 1; 6 mL). The mixture was placed in a sonic bath at 40 °C until all the starting material was consumed (TLC, typically 1.5–4 h). The zinc was filtered off and rigorously washed with water and diethyl ether. The filtrate was extracted with diethyl ether (5 \times), the aqueous layer was basified to pH 12 with aqueous sodium

hydroxide solution (2 M) and a little saturated ammonium chloride solution was added to disperse the emulsion. The solution was further extracted with dichloromethane (3×). The dichloromethane organic layers were combined and evaporated. The residue was dissolved in THF–water (1 : 1; 20 mL) and sodium carbonate (1.52 mmol) was added. The solution was cooled to 0 °C and benzyl chloroformate (0.50 mmol) added dropwise. The mixture was allowed to warm to room temperature and was stirred overnight. The THF was evaporated under reduce pressure. Diethyl ether (10 mL) was added, the layers were separated, and the aqueous layer was extracted with further portions of diethyl ether (3×). The organic layers were combined, dried (MgSO₄), filtered and evaporated. The enantiomeric purity of the product was assessed by HPLC on a ChiralCel OD column using hexane–2-propanol (85 : 15 to 95 : 5) as eluant, flow rate 1 mL min⁻¹.

(R)-1-Benzyloxy-*N*-tert-butoxycarbonyl-2-propylamine 3a. Obtained as a colourless oil (67%, 97% ee) (lit.,²⁰ no data); [α]_D¹⁹ +24.5 (c 0.5, CHCl₃); δ_H (300 MHz; CDCl₃) 7.24 (5 H, m, ArH), 4.65 (1 H, br s, NH), 4.46 (2 H, AB, *J* = 12.0 Hz, CH₂Ph), 3.81 (1 H, br, NCH), 3.38 (2 H, m, OCH₂), 1.36 (9 H, s, CMe₃), 1.11 (3 H, d, *J* 6.7, Me); HPLC: hexane–2-propanol (95 : 5), *t*_R = 8.8 (major) and 11.9 min.

(S)-(–)-1-Benzyloxy-*N*-benzyloxycarbonyl-2-but-3-enylamine 3b. Obtained as a colourless oil (76%) that slowly solidifies; mp 39–40 °C; (Found: MH⁺, 312.1606. C₁₉H₂₁NO₃ + H requires 312.1600); [α]_D²² –27.2 (c 0.92, CHCl₃); ν_{max} (film)/cm⁻¹ 3416 (NH), 3324, 3088, 3063, 3027, 2940, 2894, 2853, 1716 (C=O), 1496, 1450, 1404, 1342, 1219, 1096, 912, 733, 687; δ_H (300 MHz; CDCl₃) 7.34 (10 H, m, ArH), 5.89 (1 H, ddd, *J* = 17.2, 10.4, 5.5 Hz, =CH), 5.33–5.07 (5 H, m, CH₂Ph, =CH₂, NH), 4.54 (2 H, AB, *J* 12.2, CH₂Ph), 4.41 (1 H, br, NCH), 3.56 (2 H, m, NCHCH₂); δ_C (75 MHz; CDCl₃) 156.3 (C), 138.2 (C), 136.9 (C), 136.4 (CH), 128.94 (CH), 128.86 (CH), 128.5 (2 × CH), 128.2 (CH), 128.1 (CH), 116.5 (CH₂), 73.7 (CH₂), 72.3 (CH₂), 67.2 (CH₂), 53.5 (CH); *m/z* (CI) 312 (MH⁺, 23%), 268 (92), 204 (29), 181 (32), 91 (100).

(S)-(–)-1-Benzyloxy-*N*-benzyloxycarbonyl-2-pent-4-enylamine 3c. Obtained as a colourless oil (70%, 91% ee); (Found: MH⁺, 326.1758. C₂₀H₂₃NO₃ + H requires 326.1756); [α]_D²⁶ –10.8 (c 0.83, CHCl₃); ν_{max} (film)/cm⁻¹ 3416 (NH), 3329, 3068, 3027, 2940, 2863, 1716 (C=O), 1501, 1235, 1112, 1055, 912, 738, 697; δ_H (300 MHz; CDCl₃) 7.32 (10 H, m, ArH), 5.76 (1 H, m, =CH), 5.05 (5 H, m, CH₂Ph, =CH₂, NH), 4.51 (2 H, AB, *J* = 12.0 Hz, CH₂Ph), 3.89 (1 H, br, NCH), 3.50 (2 H, m, NCHCH₂), 2.37 (2 H, m, CH₂CH=); δ_C (75 MHz; CDCl₃) 156.3 (C), 138.4 (C), 137.0 (C), 134.7 (CH), 128.9 (CH), 128.8 (CH), 128.48 (CH), 128.46 (CH), 128.1 (CH), 128.0 (CH), 118.3 (CH₂), 73.6 (CH₂), 71.3 (CH₂), 67.0 (CH₂), 50.8 (CH), 36.8 (CH₂); *m/z* (CI) 326 (MH⁺, 25%), 282 (100), 240 (25), 181 (39), 91 (75); HPLC: hexane–2-propanol (85 : 15), *t*_R = 8.1 and 10.4 (major) min.

(R)-1-Benzyloxy-*N*-tert-butoxycarbonyl-2-hexylamine 3d. Obtained as a colourless oil (63%, 93% ee); [α]_D²³ +17.6 (c 0.9, CHCl₃); δ_H (300 MHz; CDCl₃) 7.23 (5 H, m, ArH), 4.61 (1 H, br s, NH), 4.43 (2 H, AB, *J* = 12.1 Hz, CH₂Ph), 3.64 (1 H, br, NCH), 3.39 (2 H, m, OCH₂), 1.37 (9 H, s, 3 × Me), 1.22 (6 H, m, 3 × CH₂), 0.81 (3 H, t, *J* 6.7, Me); δ_C (75 MHz; CDCl₃) 156.0 (C), 137.8 (C), 128.8 (CH), 128.0 (CH), 127.9 (CH), 79.4 (C), 73.4 (OCH₂), 72.4 (OCH₂), 50.8 (CH), 32.3 (CH₂), 28.8 (Me), 28.6 (CH₂), 23.0 (CH₂), 14.4 (Me).

(S)-1-Benzyloxy-*N*-tert-butoxycarbonyl-3-phenyl-2-propylamine 3e. Obtained as a colourless oil (84%, 88% ee); [α]_D¹⁹ –22.0 (c 0.5, CHCl₃) {lit.,³³ [α]_D²⁸ –4.9 (c 0.45, CHCl₃)}; ν_{max} (film)/cm⁻¹ 3375 (NH), 2929, 2852, 1685 (C=O), 1527; δ_H (300 MHz; CDCl₃) 7.28 (10 H, m, ArH), 4.90 (1 H, br d, *J* = 8.3 Hz, NH), 4.50 (2 H, AB, *J* 12.0, OCH₂Ph), 3.96 (1 H,

br, NCH), 3.39 (2 H, m, OCH₂), 2.88 (2 H, m, CH₂Ph), 1.43 (9 H, s, CMe₃); δ_C (75 MHz; CDCl₃) 155.8 (C), 138.6 (C), 138.5 (C), 129.9 (CH), 128.8 (CH), 128.7 (CH), 128.2 (2 × CH), 127.6 (CH), 79.7 (C), 73.6 (CH₂), 70.5 (CH₂), 52.1 (CH), 38.3 (CH₂), 28.8 (Me); HPLC: hexane–2-propanol (90 : 10), *t*_R = 8.1 and 8.7 (major) min.

(S)-1-Benzyloxy-3-(4-bromophenyl)-*N*-tert-butoxycarbonyl-2-propylamine 3f. Obtained as a colourless solid (53%, 97% ee), mp 72–73 °C; (Found: MH⁺, 420.1171. C₂₁H₂₆⁷⁹BrNO₃ + H requires 420.1174); [α]_D²⁶ –4.0 (c 1.04, CH₃Cl); ν_{max} (KBr)/cm⁻¹ 3359, 2919, 2847, 1685, 1526, 1490, 1362, 1168; δ_H (300 MHz; CDCl₃) 7.40–7.30 (5 H, m, ArH), 7.35 (2 H, d, *J* = 8.2 Hz, ArH), 7.03 (2 H, d, *J* 8.2, ArH), 4.93 (1 H, d, *J* 8.2, NH), 4.48 (2 H, dd, *J* 11.8, 24.4, CH₂OCH₂Ph), 3.90 (1 H, m, HCNH), 3.39 (1 H, dd, *J* 3.9, 9.3, CH₂OCHHPh), 3.35 (1 H, dd, *J* 3.9, 9.3, CH₂OCHHPh), 2.83 (2 H, m, CH₂Ar), 1.45 (9 H, s, 3 × Me); δ_C (75 MHz; CDCl₃) 155.3 (C), 137.9 (C), 137.2 (C), 131.4 (CH), 131.2 (CH), 127.86 (CH), 127.83 (CH), 126.4 (CH), 120.2 (C), 73.3 (CH₂), 69.9 (CH₂), 51.5 (CH), 37.3 (C), 27.9 (Me), 27.8 (CH₂); *m/z* (CI) 420/418 (MH⁺, 3%), 386 (10), 339 (8), 322 (19), 193 (13), 161 (25), 129 (100), 97 (64), 90 (33).

(S)-2-Benzyloxy-*N*-tert-butoxycarbonyl-1-(2-thiazolyl)ethylamine 3g. Obtained as a yellow oil (0.129 g, 77%, 98% ee); [α]_D²³ –41.7 (c 1.2, CHCl₃); (Found: C, 69.6; H, 7.3; N, 7.3. C₁₇H₂₂N₂O₃S requires C, 69.1, H, 7.0; N, 7.3%); (Found: M⁺, 334.1354. C₁₇H₂₂N₂O₃S requires 334.1351); ν_{max} (film)/cm⁻¹ 3324 (NH), 2975, 2919, 2863, 1936, 1716 (C=O); δ_H (300 MHz; CDCl₃) 7.65 (1 H, d, *J* = 3.4 Hz, thiazole H-4), 7.19 (6 H, m, ArH, thiazole H-5), 5.61 (1 H, br, NH), 5.15 (1 H, br t, *J* 3.4, NCH), 4.39 (2 H, AB, *J* 12.0, CH₂Ph), 3.88 (1 H, br, OCHH), 3.75 (1 H, dd, 9.5, 4.6, OCHH), 1.38 (9 H, s, CMe₃); δ_C (75 MHz; CDCl₃) 171.5 (C), 155.5 (C), 143.0 (CH), 138.0 (C), 128.9 (CH), 128.2 (CH), 128.0 (CH), 119.5 (CH), 80.6 (C), 73.7 (CH₂), 72.2 (CH₂), 53.2 (CH), 28.7 (Me); *m/z* (EI) 334 (M⁺, 4%), 278 (86), 230 (43), 157 (87), 139 (77), 108 (14), 91 (98), 85 (21); HPLC: hexane–2-propanol (90 : 10), *t*_R = 3.8 and 8.7 (major) min.

General procedure for the preparation of *N*-Boc-protected aminoalcohols 4

The *O*-benzyl *N*-Boc-amine **3** (0.2 mmol) and 10% Pd/C (cat.) were stirred vigorously in methanol (2 mL) under an atmosphere of hydrogen until all starting material had been consumed (as evidenced by TLC analysis). The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with dichloromethane–methanol.

(R)-*N*-tert-Butoxycarbonyl-1-hydroxy-2-propylamine (*N*-Boc-alaninol) 4a. Obtained by hydrogenolysis of **3a** as a colourless solid (0.0265 g, 70%, 96% ee), mp 49–50 °C (lit.,¹⁷ mp 52–53 °C); [α]_D¹⁹ +8.6 (c 0.8, CHCl₃) {lit.,¹⁷ [α]_D²⁶ +10.0 (c 1.0, MeOH)}; δ_H (300 MHz; MeOD) 4.65 (1 H, br s, NH), 3.76 (1 H, br, CH), 3.55 (1 H, A'AB, *J* = 10.8, 3.7 Hz, OCHH), 3.44 (1 H, AA'B, *J* 10.8, 4.6, OCHH), 2.68 (1 H, br s, OH), 1.44 (9 H, s, 3 × Me), 1.13 (3 H, d, *J* 6.8, Me).

(S)-*N*-tert-Butoxycarbonyl-1-hydroxy-3-phenyl-2-propylamine (*N*-Boc-phenylalaninol) 4b. Obtained by hydrogenolysis of **3e** as a colourless solid (0.0427 g, 83%, 88% ee), mp 89–91 °C (lit.,¹⁸ mp 91–92 °C); [α]_D¹⁷ –32.4 (c 1.0, CHCl₃) {lit.,¹⁸ [α]_D²⁵ –25.0 (c 1.0, MeOH)}; δ_H (300 MHz; CDCl₃) 7.26–7.13 (5 H, m, ArH), 4.74 (1 H, d, *J* = 6.9 Hz, NH), 3.81 (1 H, br, CH), 3.60 (1 H, A'AB, *J* 10.1, 3.7, OCHH), 3.50 (1 H, AA'B, *J* 10.1, 5.3, OCHH), 2.78 (2 H, d, *J* 7.2, PhCH₂), 2.23 (1 H, br s, OH), 1.34 (9 H, s, CMe₃).

(+)-*N*-Formyl-(*R*)-alaninyl-(*S*)-(4-bromo)phenylalaninol benzyl ether 5

N-Formyl-(*R*)-alanine²⁴ (0.20 g, 1.86 mmol) and (*S*)-1-benzyloxy-3-(4-bromophenyl)-2-propylamine (0.60 g, 1.86 mmol) [obtained from the Zn-acetic acid cleavage of (2*S*,1'*S*)-1-benzyloxy-3-(4-bromophenyl)-*N*-(1-phenylbutoxy)-2-propylamine **2i**] were dissolved in THF (10 mL) and stirred at 0 °C together with HOBT (*N*-hydroxybenzotriazole; 0.25 g, 1.86 mmol) and DCC (0.38 g, 1.86 mmol). The mixture was then allowed to warm to room temperature and was stirred for 20 h. The product was subjected to an acid-base extraction, dried, evaporated and recrystallized from acetone and hexane to give the *title compound* as a colourless solid (0.35 g, 45%); mp 150–151 °C; (Found: MH⁺, 419.0967. C₂₀H₂₃⁷⁹BrN₂O₃ + H requires 419.0970); [α]_D²¹ + 7.8 (*c* 0.65, MeOH); ν_{max} (KBr)/cm⁻¹ 3279, 1694, 1564, 1528, 1451, 1385, 1215, 1125; δ_H (300 MHz; CDCl₃) 8.10 (1 H, s, HCO), 7.37 – 7.24 (5 H, m, ArH), 7.30 (2 H, d, *J* 8.3, ArH), 7.02 (2 H, d, *J* 8.3, ArH), 6.32 (1 H, m, NH), 6.25 (1 H, m, NH), 4.46 (2 H, m, CH₂Ph), 4.46 (1 H, m, CHMe), 4.24 (1 H, m, CHCH₂Ar), 3.40 (2 H, d, *J* 3.6, CH₂OCH₂Ph), 2.85 (1 H, dd, *J* 7.0, 13.0, CHHAr), 2.80 (1 H, dd, *J* 7.0, 13.0, CHHAr), 1.26 (3 H, d, *J* 7.0, Me); δ_C (75 MHz; CDCl₃) 171.1 (C), 160.5 (C), 137.6 (C), 136.7 (C), 131.4 (CH), 131.0 (CH), 128.5 (CH), 127.9 (CH), 127.9 (CH), 120.4 (C), 73.3 (CH₂), 69.6 (CH₂), 50.2 (CH), 47.5 (CH), 36.9 (CH₂), 18.8 (Me); *m/z* (ES), 421/419 (MH⁺, 14%), 337 (10), 325 (4), 271 (6), 259 (11), 221 (9), 130 (28), 100 (39), 98 (100), 84 (98), 68 (58), 66 (39), 52 (15), 35 (83).

(+)-*N*-Formyl-(*RS*)-(4-bromo)phenylalaninol 6

(+)-*N*-Formyl-(*R*)-alaninyl-(*S*)-4-bromophenylalaninol benzyl ether **5** (12.5 mg, 0.03 mmol) in dry dichloromethane (3 mL) was treated with a solution of boron trichloride in dichloromethane (1 M; 0.6 mL, 0.6 mmol) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 2 h. The reaction was cautiously quenched with water (2 mL) and the product extracted with ethyl acetate (3 × 10 mL), dried (MgSO₄) and purified by trituration with ether to give the *title compound* as a colourless solid (9.5 mg, 97%); (Found: MH⁺, 329.0501. C₁₃H₁₇⁷⁹BrN₂O₃ + H requires 329.5000); mp 210–211 °C; [α]_D²⁴ + 3.0 (*c* 0.5, MeOH); ν_{max} (KBr)/cm⁻¹ 3412, 1632, 1398, 1112, 618; δ_H (300 MHz; CD₃OD) 8.08 (1 H, s, CHO), 7.41 (2 H, d, *J* 8.2, ArH), 7.09 (2 H, d, *J* 8.2, ArH), 4.37 (1 H, q, 6.8, CHMe), 4.07 (1 H, m, HCCH₂Ar), 3.67 (1 H, dd, *J* 4.1, 11.4, CHHOH), 3.65 (1 H, dd, *J* 4.1, 11.4, CHHOH), 2.85 (1 H, dd, *J* 7.5, 13.9, CHHAr), 2.77 (1 H, dd, *J* 7.5, 13.9, CHHAr), 1.20 (3 H, d, *J* 7.1, Me); 2 × NH and OH not observed; δ_C (75 MHz; CD₃OD) 174.7 (C), 163.8 (C), 139.7 (C), 133.6 (CH), 132.9 (CH), 121.6 (C), 64.9 (CH₂), 54.5 (CH), 49.9 (CH), 37.9 (CH₂), 19.2 (Me); *m/z* (CI), 329/327 (MH⁺, 7%), 313 (18), 311 (34), 299 (78), 297 (100), 295 (28), 260 (33), 258 (41), 219 (40), 197 (27), 168 (43), 139 (17), 116 (26), 115 (8).

(+)-*N*-Formyl-(*R*)-alaninyl-(*S*)-4-bromophenylalanine trimethylsilylmethyl ester 7

To a solution of (+)-*N*-formyl-(*R*)-alanine-(*S*)-4-bromophenylalaninol **6** (100 mg, 0.3 mmol) in anhydrous DMF (10 mL), pyridinium dichromate (323 mg, 1.5 mmol) was added and stirred at room temperature for 5 h. The mixture was diluted with water (10 mL), the aqueous layer acidified with citric acid and the product extracted with ethyl acetate, dried (MgSO₄) and concentrated. The residue was dissolved in anhydrous DMF and treated with excess TMS diazomethane and stirred overnight. The product was concentrated and purified by flash chromatography to give the *title compound* as a colourless oil (62 mg, 50%); (Found: MH⁺, 429.0843. C₁₇H₂₅⁷⁹BrN₂O₄Si + H requires 429.0845); [α]_D²⁴ + 13.9 (*c* 1.15, MeOH); ν_{max} (film)/cm⁻¹ 3405, 3298, 3052, 2955, 1731, 1654, 1521, 1383, 1250, 1203, 1009,

850; δ_H (300 MHz; CDCl₃) 8.05 (1 H, s, HCO), 7.37 (2 H, d, *J* = 8.3 Hz, ArH), 7.06 (1 H, d, *J* 7.9, NH), 6.98 (2 H, d, *J* 8.3, ArH), 6.80 (1 H, d, *J* 7.2, NH), 4.78 (1 H, m, CH), 4.53 (1 H, m, CH), 3.78 (1 H, d, *J* 14.0, CHHTMS), 3.76 (1 H, d, *J* 14.0, CHHTMS), 3.10 (1 H, dd, *J* 6.6, 14.0, CHHAr), 2.94 (1 H, dd, *J* 6.6, 14.0, CHHAr), 1.24 (3 H, d, *J* 6.9, CHMe), 0.00 (9 H, s, 3 × Me); δ_C (75 MHz; CDCl₃) 172.2 (C), 171.7 (C), 161.4 (C), 134.9 (C), 131.6 (CH), 130.9 (CH), 121.1 (C), 59.2 (CH₂), 53.2 (CH), 47.6 (CH), 37.4 (CH₂), 18.6 (Me), 0.0 (TMS); *m/z* (ES) 431/429 (MH⁺, 36%), 416 (13), 415 (60), 413 (72), 395 (25), 316 (40), 198 (4), 170 (5), 91 (7), 73 (100), 72 (38), 45 (23), 44 (73).

Preparation of ring-closing metathesis precursors

***N*-Allylation of Cbz-amines **3b** and **3c**.** Sodium hydride (0.42 mmol) was suspended in dry DMF (1 mL) and cooled to 0 °C under nitrogen. A solution of the Cbz-amine **3b/3c** (0.21 mmol) in dry DMF (1 mL) was added and the reaction mixture was allowed to warm to room temperature. After 30 min, the reaction mixture was re-cooled to 0 °C. Allyl bromide (0.04 mL, 0.42 mmol) was added and the reaction mixture was allowed to warm to room temperature. After TLC analysis showed that all starting material had been consumed, aqueous saturated ammonium chloride solution (0.5 mL) was added and the mixture was extracted with diethyl ether (3×), dried (Na₂SO₄), filtered and evaporated under reduced pressure.

(*S*)-(+)-*N*-Allyl-1-benzyloxy-*N*-benzyloxycarbonyl-2-but-3-enylamine **8.** Obtained from the *N*-allylation of Cbz-amine **3b** (0.52 mmol) and purification by column chromatography on silica gel eluting with diethyl ether–light petroleum (5 : 9) as a colourless oil (93%); (Found: MH⁺, 352.1908. C₂₂H₂₅NO₃ + H requires 352.1912); [α]_D²² + 8.9 (*c* 1.23, CHCl₃); ν_{max} (film)/cm⁻¹ 3083, 3063, 3032, 2976, 2935, 2858, 1696 (C=O), 1496, 1455, 1409, 1352, 1322, 1245, 1204, 1107, 1030, 989, 917, 769, 737, 692; δ_H (400 MHz; C₆D₆, 80 °C) 7.31 (2 H, t, *J* 6.3, ArH), 7.19 (8 H, m, ArH), 5.93 (2 H, m, 2 × =CH), 5.21 (2 H, s, CH₂Ph), 5.20–4.99 (4 H, m, 2 × =CH₂), 4.83 (1 H, br q, *J* 6.0, NCH), 4.39 (2 H, AB, *J* 12.1, CH₂Ph), 4.01 (1 H, dd, *J* 16.0, 5.3, NCHH), 3.90 (1 H, dd, *J* 16.0, 5.8, NCHH), 3.75 (1 H, t, *J* 9.6, OCHH), 3.61 (1 H, dd, *J* 9.8, 5.8, OCHH); δ_C (100 MHz; C₆D₆, 80 °C) 155.8 (C), 138.7 (C), 137.4 (C), 135.9 (CH), 135.1 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 116.7 (CH₂), 115.5 (CH₂), 72.9 (CH₂), 70.8 (CH₂), 66.9 (CH₂), 59.1 (CH), 48.1 (CH₂); *m/z* (ES) 720 (2 M + NH₄, 62%), 647 (12), 369 (M + NH₄, 95), 352 (MH⁺, 100).

(*S*)-(+)-*N*-Allyl-1-benzyloxy-*N*-benzyloxycarbonyl-2-pent-4-enylamine **9.** Obtained from the *N*-allylation of Cbz-amine **3c** (0.28 mmol) and purification by column chromatography on silica gel eluting with ether–light petroleum (1:2) as a colourless oil (93%); (Found: MH⁺, 366.2061. C₂₃H₂₇NO₃ + H requires 366.2069); [α]_D²³ + 8.2 (*c* 0.97, CHCl₃); ν_{max} (film)/cm⁻¹ 3068, 3032, 2976, 2935, 2858, 1696 (C=O), 1455, 1404, 1358, 1245; δ_H (300 MHz; CDCl₃) *two rotamers* 7.32 (10 H, m, ArH), 5.77 (2 H, m, 2 × =CH), 5.21–4.96 (6 H, m, 2 × =CH₂, CH₂Ph), 4.42 (2 H, m, CH₂), 4.22 (1 H, m, NCH), 3.89 (2 H, m, CH₂), 3.55 (2 H, m, CH₂), 2.35 (2 H, m, CH₂CH=); δ_C (75 MHz; CDCl₃) *two rotamers* 156.8 (C), 156.7 (C), 138.6 (C), 138.5 (C), 137.3 (C), 137.2 (C), 136.1 (CH), 135.8 (CH), 135.3 (CH), 135.1 (CH), 128.8–128.0 (several overlapping CH), 117.8 (CH₂), 117.7 (CH), 116.6 (CH₂), 116.3 (CH₂), 73.3 (CH₂), 71.4 (CH₂), 71.1 (CH₂), 67.5 (CH₂), 67.3 (CH₂), 56.7 (CH), 56.6 (CH), 48.1 (CH₂), 47.8 (CH₂), 35.1 (CH₂), 34.5 (CH₂); *m/z* (CI) 366 (MH⁺, 35%), 322 (78), 280 (30), 258 (43), 200 (25), 181 (20), 168 (18), 119 (14), 91 (100).

General procedure for the *N*-alkylation of primary amines

Zinc dust (18.88 mmol) was added to a solution of the hydroxylamine **2** (0.47 mmol) in acetic acid–water (8 mL, 1:1). The mixture was placed in a sonic bath at 40 °C until all the

starting material was consumed (TLC; typically 1.5–4 h). The zinc was filtered and rigorously washed with water and ether. The filtrate was extracted with ether (5x), the aqueous layer was basified to pH 12 with aqueous sodium hydroxide solution (4 M) and a little saturated ammonium chloride solution was added to disperse the emulsion. The solution was further extracted with dichloromethane (3x). The dichloromethane organic layers were combined and evaporated. The crude amine (0.47 mmol) was dissolved in acetonitrile (5 mL) and potassium carbonate (0.50 mmol) and 4-bromobut-1-ene (0.80 mmol) were added to the mixture. The reaction mixture was heated under reflux for 24 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure. Water (5 mL) and ether (5 mL) were added to the mixture and the layers separated. The aqueous layer was further extracted with ether (3 × 5 mL). The organic extracts were combined, dried (Na₂SO₄), and evaporated. The residue was purified by column chromatography on silica gel to give the bis-alkene.

(S)-(+)-1-Benzylxy-*N*-but-3-enyl-2-but-3-enylamine (S)-10. Obtained from N–O bond cleavage and subsequent *N*-alkylation of hydroxylamine (*S,S*)-**2b** (0.47 mmol) and purification by column chromatography on silica gel eluting with light petroleum-ether (1:4) as a colourless oil (45%); (Found: MH⁺, 232.1706. C₁₅H₂₁NO + H requires 232.1701); [α]_D²⁵ + 20.5 (*c* 0.88, CHCl₃); ν_{max} (film)/cm⁻¹ 3329 (NH), 3073, 3027, 2976, 2909, 2853, 1639, 1450, 1352, 1091, 994, 907, 738, 697; δ_H (300 MHz; CDCl₃) 7.31 (5 H, m, ArH), 5.86 – 5.57 (2 H, m, 2 × =CH), 5.29–4.94 (4 H, m, 2 × =CH₂), 4.52 (2 H, s, CH₂Ph), 3.51 – 3.29 (3 H, m, OCH₂, NCH), 2.72 (1 H, dt, *J* 11.3, 7.2, NCHH), 2.54 (1 H, dt, *J* 11.3, 7.0, NCHH), 2.26 (2 H, m, CH₂CH=), 1.86 (1 H, br s, NH); δ_C (75 MHz; CDCl₃) 138.6 (C), 138.3 (CH), 136.9 (CH), 128.8 (CH), 128.09 (CH), 128.07 (CH), 118.0 (CH₂), 116.7 (CH₂), 73.8 (CH₂), 73.6 (CH₂), 61.9 (CH), 46.8 (CH₂), 34.8 (CH₂); *m/z* (CI) 232 (MH⁺, 41%), 164 (49), 152 (100), 149 (42).

(R)-(–)-1-Benzylxy-*N*-but-3-enyl-2-but-3-enylamine (R)-10. Obtained from N–O bond cleavage and subsequent *N*-alkylation of hydroxylamine (*R,R*)-**2b** (4.62 mmol) and purification by column chromatography on silica gel eluting with light petroleum-ether (1:3) as a colourless oil (50%); [α]_D²⁵ – 21.1 (*c* 0.95, CHCl₃); *Spectroscopic properties identical to the (S)-enantiomer (S)-10.*

(S)-(+)-1-Benzylxy-*N*-but-3-enyl-2-pent-4-enylamine 11. Obtained from N–O bond cleavage and subsequent *N*-alkylation of hydroxylamine **2e** (0.47 mmol) and purification by column chromatography on silica gel eluting with light petroleum-ether (1:2) as a colourless oil (47%); (Found: M⁺, 245.1770. C₁₆H₂₃NO requires 245.1780); [α]_D²² + 3.2 (*c* 1.24, CHCl₃); ν_{max} (film)/cm⁻¹ 3329 (NH), 3073, 3027, 2914, 2848, 1634, 1475, 1358, 1204, 1096, 994, 907, 738, 702; δ_H (300 MHz; CDCl₃) 7.32 (5 H, m, ArH), 5.78 (2 H, m, 2 × =CH), 5.07 (4 H, m, 2 × =CH₂), 4.52 (2 H, s, CH₂Ph), 3.43 (2 H, m, OCH₂), 2.82 (1 H, m, NCH), 2.69 (2 H, m, NCH₂), 2.23 (4 H, m, 2 × CH₂CH=), NH signal not observed; δ_C (75 MHz; CDCl₃) 138.8 (C), 136.8 (CH), 135.7 (CH), 128.8 (CH), 128.04 (CH), 127.99 (CH), 117.7 (CH₂), 116.8 (CH₂), 73.6 (CH₂), 72.7 (CH₂), 57.3 (CH), 46.8 (CH₂), 36.6 (CH₂), 34.9 (CH₂); *m/z* (EI) 245 (M⁺, 4%), 219 (5), 204 (79), 124 (100), 98 (5), 91 (44), 82 (12), 65 (13), 55 (26).

General procedure for the preparation of Cbz-protected secondary amines 12/13

The pure secondary amine **10/11** was dissolved in THF-water (20 mL, 1:1) and sodium carbonate (1.52 mmol) was added. The solution was cooled to 0 °C and benzyl chloroformate (0.50 mmol) added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The THF was evaporated under reduce pressure. Ether (10 mL) was added, the layers were separated, and the aqueous layer was extracted with further portions of ether (3x). The organic layers were combined, dried (MgSO₄), filtered and evaporated.

(S)-(+)-1-Benzylxy-*N*-benzyloxycarbonyl-*N*-but-3-enyl-2-but-3-enylamine 12. Obtained from the Cbz-protection of amine (*S*)-**10** (0.16 mmol) and purification by column chromatography on silica gel eluting with ether-light petroleum (1:2) as a yellow oil (80%); (Found: MH⁺, 366.2068. C₂₃H₂₇NO₃ + H requires 366.2069); [α]_D²⁵ + 8.9 (*c* 1.02, CHCl₃); ν_{max} (film)/cm⁻¹ 3063, 3027, 2976, 2935, 2858, 1696 (C=O), 1634, 1501, 1455, 1409, 1286, 1255, 1102, 989, 912, 738, 687; δ_H (400 MHz; C₆D₆, 80 °C) 7.36 – 7.11 (10 H, m, ArH), 5.96 (1 H, m, =CH), 5.78 (1 H, m, =CH), 5.21 (2 H, s, CH₂Ph), 5.19 – 4.98 (4 H, m, 2 × =CH₂), 4.71 (1 H, q, *J* 6.0, NCH), 4.39 (2 H, AB, *J* 12.1, CH₂Ph), 3.75 (1 H, t, *J* 8.1, OCHH), 3.61 (1 H, dd, *J* 9.8, 5.7, OCHH), 3.40 (2 H, m, NCH₂), 2.45 (2 H, m, NCH₂CH₂); δ_C (100 MHz; C₆D₆, 80 °C) 155.8 (C), 138.6 (C), 137.5 (C), 135.7 (CH), 135.3 (CH), 128.3 – 127.4 (6 × CH), 116.6 (CH₂), 115.8 (CH₂), 73.0 (CH₂), 70.9 (CH₂), 66.8 (CH₂), 59.6 (CH), 46.0 (CH₂), 34.1 (CH₂); *m/z* (ES) 748 (2 M + NH₄, 30%), 383 (M + NH₄, 66), 366 (MH⁺, 100).

(S)-(+)-1-Benzylxy-*N*-benzyloxycarbonyl-*N*-but-3-enyl-2-pent-4-enylamine 13. Obtained from the Cbz-protection of amine **11** (0.22 mmol) and purification by column chromatography on silica gel eluting with ether-light petroleum (1:4) as a yellow oil (81%); (Found: MH⁺, 380.2236. C₂₄H₂₉NO₃ + H requires 380.2226); [α]_D²² + 5.9 (*c* 1.02, CHCl₃); ν_{max} (film)/cm⁻¹ 3068, 3032, 2971, 2935, 2858, 1696 (C=O), 1450, 1419, 1286, 1219, 1107, 994, 912, 738; δ_H (400 MHz; C₆D₆, 80 °C) 7.26 (10 H, m, ArH), 5.76 (2 H, m, 2 × =CH), 5.17 (2 H, s, CH₂Ph), 5.07 (2 H, d, *J* = 17.2 Hz, 2 × =CHH), 5.01 (2 H, d, *J* 10.2, 2 × =CHH), 4.37 (2 H, AB, *J* 12.0, CH₂Ph), 4.16 (1 H, m, NCH), 3.65 (1 H, br, OCHH), 3.49 (1 H, br, OCHH), 3.37 (2 H, t, *J* 7.6, NCH₂), 2.41 (4 H, m, 2 × CH₂CH=); δ_C (100 MHz; C₆D₆, 80 °C) 155.8 (C), 138.7 (C), 137.6 (C), 135.9 (CH), 135.3 (CH), 128.22 (CH), 128.20 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 116.6 (CH₂), 115.7 (CH₂), 73.0 (CH₂), 71.3 (CH₂), 66.7 (CH₂), 57.8 (CH), 46.0 (CH₂), 34.6 (CH₂), 34.1 (CH₂); *m/z* (CI) 380 (MH⁺, 19%), 336 (35), 294 (35), 272 (31), 258 (21), 214 (17), 202 (15), 181 (34), 91 (100).

(2*R*,2'*S*)-(–)-1-Benzylxy-*N*-(but-3-enyl)-*N*-(2-*tert*-butyloxy-carbonylamino-3-methylpentanoyl)-2-but-3-enylamine 14. (*S*)-*N*-Boc-isoleucine (109 mg, 0.47 mmol) and (*R*)-(–)-1-benzylxy-*N*-but-3-enyl-2-but-3-enylamine (*R*)-**10** (100 mg, 0.43 mmol) were added successively to dichloromethane (8 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature for 15 min and then re-cooled to 0 °C. *N,N'*-Dicyclohexylcarbodiimide (97 mg, 0.47 mmol) was added at this temperature and the solution was allowed to warm to room temperature and stirred overnight. The solution was filtered and evaporated. The crude product was directly purified by column chromatography on silica gel eluting with diethyl ether-light petroleum (1 : 3) to give the *title compound* (86 mg, 45%) as a colourless oil; (Found: MH⁺, 445.3076. C₂₆H₄₀N₂O₄ + H requires 445.3066); [α]_D²³ – 20.0 (*c* 0.60, CHCl₃); ν_{max} (film)/cm⁻¹ 3426, 3310 (NH), 3079, 2968, 2933, 2876, 1712 (C=O), 1636 (C=O), 1497, 1456, 1420, 1366, 1248, 1172, 1114, 1017, 919, 735; δ_H (400 MHz; d₆-DMSO, 120 °C) 7.31 (5 H, m, ArH), 6.11–5.72 (3 H, m, 2 × =CH, NH), 5.20 (2 H, m, =CH₂), 5.03 (2 H, m, =CH₂), 4.75 (1 H, br m, NCH), 4.53 (2 H, AB, *J* = 12.0 Hz, CH₂Ph), 4.29 (1 H, t, *J* 8.0, NCHCH), 3.73 (2 H, m, OCH₂), 3.37 (2 H, m, NCH₂), 2.43–2.19 (2 H, br m, CH₂), 1.81 (1 H, br, NCHCH), 1.50 (1 H, br m, CHH), 1.40 (9 H, s, CM₃), 1.11 (1 H, m, CHH), 0.82 (6 H, m, 2 × Me); δ_C (75 MHz; CDCl₃) *two rotamers* 173.0 (C), 172.7 (C), 155.6 (C), 138.0 (C), 137.5 (C), 135.7 (CH), 134.5 (CH), 134.3 (CH), 133.7 (CH), 128.42 (CH), 128.35 (CH), 127.84 (CH), 127.79 (CH), 127.6 (CH), 118.2 (CH₂), 117.5 (CH₂), 116.1 (CH₂), 79.29 (C), 79.25 (C), 73.3 (CH₂), 73.1 (CH₂), 70.3 (CH₂), 69.6 (CH₂), 59.3 (CH), 58.5 (CH), 55.1 (CH), 54.6 (CH), 47.0 (CH₂), 42.6 (CH₂), 38.9 (CH), 37.8 (CH), 34.5 (CH₂), 32.9 (CH₂), 28.3 (Me), 24.1 (CH₂),

23.8 (CH₂), 15.9 (Me), 15.7 (Me), 11.34 (Me), 11.25 (Me), the spectrum shows two signals for every C, with the exception of one C=O, ArCH, =CH₂ and Me for which only one peak is observed; *m/z* (CI) 445 (MH⁺, 27%), 389 (89), 371 (24), 345 (100), 303 (17), 259 (13), 232 (42), 190 (13), 130 (12).

General procedure for ring-closing metathesis

The diene (0.470 mmol) was dissolved in dry dichloromethane (4 mL) under nitrogen. To the solution was added benzylidenebis-(tricyclohexylphosphine)dichlororuthenium (38.7 mg, 0.047 mmol, 10 mol%) (Grubbs' catalyst) and the mixture stirred until complete consumption of starting material was observed by TLC. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with diethyl ether–light petroleum to give the corresponding heterocycle.

(S)(–)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-2,5-dihydro-pyrrole 15. Obtained from the ring-closing metathesis of bis-alkene **8** (0.38 mmol) after purification by column chromatography on silica gel eluting diethyl ether–light petroleum (1 : 2) as a colourless oil (96%); (Found: MH⁺, 324.1598. C₂₀H₂₁NO₃ + H requires 324.1599); [α]_D²⁵ –158.3 (*c* 0.84, CHCl₃); ν_{max} (film)/cm⁻¹ 3088, 3058, 3027, 2945, 2899, 2858, 1706 (C=O), 1624, 1496, 1455, 1414, 1358, 1317, 1199, 1102, 1004, 733, 697; δ_H (400 MHz; C₆D₆, 80 °C) 7.42–7.13 (10 H, m, ArH), 5.72 (1 H, m, =CH), 5.45 (1 H, m, =CH), 5.21 (2 H, AB, *J* = 12.5 Hz, CH₂Ph), 4.77 (1 H, br, NCH), 4.41 (2 H, s, CH₂Ph), 4.17 (1 H, br, CHH), 4.06 (1 H, br, CHH), 3.84 (1 H, br, CHH), 3.67 (1 H, br, CHH); δ_C (100 MHz; C₆D₆, 80 °C) 154.2 (C), 139.0 (C), 137.5 (C), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.4 (CH), 127.3 (CH), 125.6 (CH), 73.3 (CH₂), 71.4 (CH₂), 66.6 (CH₂), 64.5 (CH), 53.9 (CH₂); *m/z* (CI) 324 (MH⁺, 100%), 202 (10), 190 (85), 158 (16), 143 (10), 126 (10), 108 (48), 91 (72), 82 (52), 68 (44).

(S)(+)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-1,2,3,6-tetrahydropyridine 16. Obtained from the ring-closing metathesis of bis-alkene **9** (0.21 mmol) after purification by column chromatography on silica gel eluting diethyl ether–light petroleum (1 : 2) as a colourless oil (84%); (Found: MH⁺, 338.1756. C₂₁H₂₃NO₃ + H requires 338.1756); [α]_D²³ +7.5 (*c* 0.53, CHCl₃); ν_{max} (film)/cm⁻¹ 3068, 3037, 2899, 2853, 1696 (C=O), 1450, 1414, 1347, 1219, 1102, 1015, 743; δ_H (400 MHz; C₆D₆, 80 °C) 7.25 (10 H, m, ArH), 5.50 (1 H, m, =CH), 5.38 (1 H, m, =CH), 5.25 (2 H, s, CH₂Ph), 4.86 (1 H, br, NCH), 4.39 (3 H, m, CH₂Ph, OCHH), 3.53 (2 H, m, OCHH, NCHH), 3.33 (1 H, dd, *J* = 7.3 Hz, NCHH), 2.23 (1 H, m, NCHCHH), 1.92 (1 H, m, NCHCHH); δ_C (100 MHz; C₆D₆, 80 °C) 155.6 (C), 138.9 (C), 137.6 (C), 128.25 (CH), 128.17 (CH), 127.9 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 123.4 (CH), 122.6 (CH), 72.8 (CH₂), 69.2 (CH₂), 66.9 (CH₂), 48.0 (CH), 40.7 (CH₂), 25.4 (CH₂); *m/z* (CI) 355 (M + NH₄⁺, 3%), 338 (MH⁺, 50), 294 (5), 216 (10), 204 (100), 157 (15), 140 (12), 108 (40), 91 (56), 82 (57).

(S)(–)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-1,2,5,6-tetrahydropyridine 17. Obtained from the ring-closing metathesis of bis-alkene **12** (0.12 mmol) after purification by column chromatography on silica gel eluting diethyl ether–light petroleum (1 : 2) as a colourless oil (93%); (Found: MH⁺, 338.1755. C₂₁H₂₃NO₃ + H requires 338.1756); [α]_D²³ –173.2 (*c* 0.71, CHCl₃); ν_{max} (film)/cm⁻¹ 3088, 3058, 3027, 2925, 2894, 2848, 1701 (C=O), 1496, 1450, 1424, 1363, 1327, 1276, 1250, 1194, 1107, 1025, 738, 697; δ_H (400 MHz; C₆D₆, 80 °C) 7.36–7.10 (10 H, m, ArH), 5.69 (2 H, m, HC=CH), 5.23 (2 H, AB, *J* = 12.4 Hz, CH₂Ph), 4.83 (1 H, br, NCH), 4.41 (2 H, AB, *J* = 12.1 Hz, CH₂Ph), 4.29 (1 H, br, NCHH), 3.54 (2 H, d, *J* = 5.3 Hz, OCH₂), 2.99 (1 H, m, NCHH), 2.07 (1 H, m, NCH₂CHH), 1.63 (1 H, m, NCH₂CHH); δ_C (100 MHz; C₆D₆, 80 °C) 155.0 (C), 138.8 (C), 137.6 (C), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.42 (CH), 127.37 (CH), 127.3 (CH), 126.3 (CH), 126.2 (CH),

73.1 (CH₂), 71.6 (CH₂), 66.9 (CH₂), 52.2 (CH), 38.2 (CH₂), 24.8 (CH₂); *m/z* (CI) 355 (M + NH₄⁺, 3%), 338 (MH⁺, 85), 294 (6), 246 (5), 216 (15), 204 (100), 172 (20), 157 (13), 140 (12), 108 (38), 91 (69), 82 (79).

(S)(–)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-2,3,6,7-tetrahydro-1*H*-azepine 18. Obtained from the ring-closing metathesis of bis-alkene **13** (0.17 mmol) after purification by column chromatography on silica gel eluting diethyl ether–light petroleum (1 : 1) as a colourless oil (85%); (Found: MH⁺, 352.1910. C₂₂H₂₅NO₃ + H requires 352.1912); [α]_D²⁵ –93.1 (*c* 1.02, CHCl₃); ν_{max} (film)/cm⁻¹ 3083, 3058, 3022, 2935, 2889, 2853, 1696 (C=O), 1450, 1419, 1363, 1327, 1260, 1199, 1020, 733, 692; δ_H (400 MHz; C₆D₆, 80 °C) 7.37–7.12 (10 H, m, ArH), 5.55 (1 H, m, =CH), 5.46 (1 H, m, =CH), 5.21 (2 H, AB, *J* = 12.5 Hz, CH₂Ph), 4.58 (1 H, br, NCH), 4.40 (2 H, s, CH₂Ph), 3.85 (1 H, br, CHH), 3.53 (2 H, br, CH₂), 3.42 (1 H, m, CHH), 2.67–2.43 (2 H, br, CHH, CHH), 2.16 (1 H, m, CHH), 2.01 (1 H, m, CHH); δ_C (100 MHz; C₆D₆, 80 °C) 155.9 (C), 138.9 (C), 137.7 (C), 129.6 (CH), 128.3–127.1 (6 × CH), 124.9 (CH), 73.1 (CH₂), 72.0 (CH₂), 66.8 (CH₂), 55.5 (CH), 40.7 (CH₂), 31.0 (CH₂), 28.1 (CH₂); *m/z* (CI) 352 (MH⁺, 45%), 330 (8), 218 (100), 186 (13), 171 (20), 154 (19), 106 (60), 96 (83), 91 (66), 52 (19).

(2*R*,2'*S*)-(+)-2-Benzyloxymethyl-1-(2-*tert*-butyloxycarbonyl-amino-3-methylpentanoyl)-1,2,5,6-tetrahydropyridine 19. Obtained from the ring-closing metathesis of bis-alkene **14** (0.59 mmol) after purification by column chromatography on silica gel eluting diethyl ether–light petroleum (1 : 2 to 1 : 1) as a yellow oil (97%); (Found: MH⁺, 416.2680. C₂₄H₃₃N₂O₄ + H requires 416.2675); [α]_D²³ +160.0 (*c* 0.70, CHCl₃); ν_{max} (film)/cm⁻¹ 3416, 3291 (NH), 3032, 2967, 2931, 2863, 1701 (C=O), 1635 (C=O), 1497, 1455, 1391, 1365, 1304, 1244, 1171, 1116, 1043, 737, 699; δ_H (400 MHz; DMSO, 120 °C) 7.31 (5 H, m, ArH), 6.08 (1 H, br d, *J* = 7.3 Hz, NH), 5.91 (1 H, m, =CH), 5.75 (1 H, m, =CH), 4.85 (1 H, br, NCHCH=), 4.53 (2 H, AB, *J* = 12.4 Hz, CH₂Ph), 4.31 (1 H, t, *J* = 8.6 Hz, NCH), 4.19 (1 H, br, NCHH), 3.60 (2 H, m, OCH₂), 2.87 (1 H, br, NCHH), 2.22–2.00 (1 H, m, NCH₂CH=), 1.82 (1 H, br, CHMe), 1.52 (1 H, m, CHH), 1.40 (9 H, s, CMe₃), 1.12 (1 H, m, CHH), 0.84 (6 H, m, 2 × Me); δ_C (75 MHz; CDCl₃) two rotamers 172.1 (C), 170.8 (C), 155.9 (C), 155.5 (C), 138.2 (C), 137.8 (C), 128.39 (CH), 128.35 (CH), 127.8 (CH), 127.7 (CH), 127.52 (CH), 127.49 (CH), 126.4 (CH), 125.7 (CH), 124.9 (CH), 79.4 (C), 79.3 (C), 73.2 (CH₂), 73.1 (CH₂), 70.8 (CH₂), 70.4 (CH₂), 54.8 (CH), 58.7 (CH), 53.7 (CH), 50.7 (CH), 40.8 (CH₂), 38.1 (CH), 37.3 (CH), 35.5 (CH₂), 28.34 (Me), 28.27 (Me), 25.7 (CH₂), 24.7 (CH₂), 24.1 (CH₂), 23.6 (CH₂), 16.1 (Me), 15.7 (Me), 11.6 (Me), 11.0 (Me); only three peaks for the two =CH of both rotamers; *m/z* (EI) 416 (M⁺, 3%), 360 (4), 343 (7), 295 (8), 221 (84), 195 (15), 130 (26), 91 (90), 82 (100).

Reduction and deprotection of tetrahydropyridines

(S)(+)-Piperidine-2-methanol hydrochloride 20. Tetrahydropyridine **17** (32 mg, 0.095 mmol) was dissolved in methanol (1 mL) and hydrochloric acid (1 M; 1 mL) and hydrogenated over palladium on charcoal (10% w/w; 20 mg) overnight. The catalyst was filtered through Celite and the solvent was removed *in vacuo* to give the piperidine **20** as a yellow solid (15 mg, quantitative yield); mp 126–128 °C (lit.³⁴ for the racemate, mp 130–132 °C); (Found: MH⁺, 116.1069. C₆H₁₃NO + H requires 116.1075); [α]_D²⁴ +5.8 (*c* 1.2, MeOH); ν_{max} (KBr)/cm⁻¹ 3380, 3191, 2997, 2948, 2879, 2781, 2752, 2558, 2530, 2448, 2413, 1598, 1452, 1428, 1401, 1324, 1051, 1023, 912; δ_H (300 MHz; MeOD) 3.78 (1 H, dd, *J* = 11.8, 3.8 Hz, OCHH), 3.59 (1 H, dd, *J* = 11.8, 7.0 Hz, OCHH), 3.37 (1 H, br m, NCHH), 3.20 (1 H, br, NCH), 3.02 (1 H, br m, NCHH), 2.00–1.48 (6 H, m, 3 × CH₂); OH and NH not observed; δ_C (75 MHz; MeOD) 64.0 (CH₂),

60.5 (CH), 46.5 (CH₂), 27.0 (CH₂), 24.3 (CH₂), 23.7 (CH₂); *m/z* (CI) 116 (MH⁺, 100%), 114 (17), 98 (28), 84 (11).

(2*R*,2'*S*)-(+)-1-(2-*tert*-Butyloxycarbonylamino-3-methylpentanoyl)piperidine-2-methanol 21. Tetrahydropyridine **19** (220 mg, 0.53 mmol) was dissolved in methanol (8 mL) and hydrogenated over palladium on charcoal (10% w/w; 70 mg) overnight. The catalyst was filtered through Celite and the solvent was removed *in vacuo* to give the piperidine **21** after purification by column chromatography on silica gel eluting with diethyl ether as a colourless sticky oil (quantitative yield); (Found: MH⁺, 329.2446. C₁₇H₃₂N₂O₄ + H requires 329.2440); [*a*]_D²⁶ +43.9 (*c* 0.41, CHCl₃); *v*_{max} (film)/cm⁻¹ 3416, 3327, 2965, 2936, 2875, 1701 (C=O), 1625 (C=O), 1521, 1446, 1391, 1366, 1248, 1172, 1046, 1020; *δ*_H (400 MHz; DMSO, 120 °C) 6.04 (1 H, br, NH), 4.45–4.18 (2 H, m, 2 × NCH), 4.00 (1 H, br, NCHH), 3.58 (2 H, m, OCH₂), 1.78 (2 H, m, NCHCH, CHH), 1.70–1.23 (15 H, m, CHH, 2 × CH₂, CHH, CMe₃), 1.10 (1 H, m, CHH), 0.84 (6 H, m, 2 × Me); OH and NCHH not observed; *δ*_C (100 MHz; DMSO, 120 °C) 171.2 (C), 155.7 (C), 78.7 (C), 60.0 (CH₂), 55.0 (CH), 37.0 (CH), 28.7 (Me), 25.6 (2 × CH₂), 24.5 (CH₂), 19.4 (CH₂), 16.2 (Me), 11.3 (Me); NCH and NCH₂ signals not observed, probably due to extreme broadening by *J*-coupling to N; *m/z* (CI) 329 (MH⁺, 8%), 311 (5), 273 (52), 255 (19), 229 (100), 116 (14).

4-Bromobenzoate derivative: (2*R*,2'*S*)-(-)-2-(4-bromobenzyloxymethyl)-1-(2-*tert*-butoxycarbonylamino-3-methylpentanoyl)piperidine. To a solution of alcohol **21** (45 mg, 0.14 mmol), triethylamine (0.02 mL, 0.14 mmol) and DMAP (cat.) in dichloromethane (2 mL), 4-bromobenzoyl chloride (31 mg, 0.14 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated and after purification by column chromatography on silica gel eluting with diethyl ether–light petroleum (1 : 1) the title compound was obtained (59 mg, 84%) as a colourless sticky oil; (Found: MH⁺, 511.1806. C₂₄H₃₅⁷⁹BrN₂O₅ + H requires 511.1808); [*a*]_D²⁴ +4.0 (*c* 0.99, CHCl₃); *v*_{max} (film)/cm⁻¹ 3432, 3314, 2966, 2930, 2868, 1718 (C=O), 1636 (C=O), 1588 1496, 1437, 1368, 1267, 1173, 1107, 1012; *δ*_H (400 MHz; DMSO, 120 °C) 7.83 (2 H, m, ArH), 7.67 (2 H, m, ArH), 6.07 (1 H, br, NH), 4.86 (1 H, br, NCH), 4.56 (1 H, br, OCHH), 4.40 (1 H, dd, *J* = 11.2, 6.1 Hz, OCHH), 4.28 (1 H, t, *J* 8.2, NCH), 4.02 (1 H, br, NCHH), 1.85–1.27 (17 H, m, NCHCH, CHH, 3 × CH₂, CMe₃), 1.10 (1 H, m, CHH), 0.80 (6 H, m, 2 × Me); the NCHH signal is missing and is probably under the solvent signal; *δ*_C (100 MHz; DMSO, 120 °C) 171.4 (C), 165.4 (C), 155.6 (C), 132.2 (CH), 131.5 (CH), 129.6 (C), 127.6 (C), 78.7 (C), 63.2 (CH₂), 55.0 (CH), 37.1 (CH), 28.6 (Me), 26.0 (CH₂), 25.6 (CH₂), 24.4 (CH₂), 19.5 (CH₂), 16.2 (Me), 11.2 (Me); the NCH and NCH₂ signals are not observed, probably due to extreme broadening by *J*-coupling to N; *m/z* (CI) 513/511 (MH⁺, 30%), 457/455 (22), 413/411 (100), 311 (14), 300/298 (14), 211 (24), 203/201 (24).

(2*S*,3*R*,4*S*)-(-)-1-Benzyloxycarbonyl-2-benzyloxymethyl-3,4-diacetoxypyrrolidine 22. Dihydropyrrole **15** (100 mg, 0.31 mmol) was dissolved in acetone–water (2 : 1; 6 mL) and 4-methylmorpholine *N*-oxide (72 mg, 0.62 mmol) was added followed by one crystal of osmium tetroxide. After stirring for 2 d the solution was cooled to 0 °C and a saturated aqueous solution of NaHSO₃ (6 mL) was added and warmed to room temperature. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was dissolved in dichloromethane (5 mL) at room temperature and pyridine (0.10 mL, 1.24 mmol) and acetic anhydride (0.12 mL, 1.24 mmol) were added. The mixture was stirred overnight and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel eluting ethyl acetate–light petroleum (1 : 4) to give the title compound (115 mg, 84%) as a colourless oil; (Found: MH⁺, 442.1878.

C₂₄H₂₇NO₇ + H requires 442.1866); [*a*]_D²⁵ –24.1 (*c* 0.83, CHCl₃); *v*_{max} (film)/cm⁻¹ 3063, 3032, 2950, 2894, 2858, 1750 (C=O), 1707 (C=O), 1455, 1418, 1356, 1244, 1093, 1027, 740, 699; *δ*_H (400 MHz; DMSO, 120 °C) 7.32 (10 H, m, ArH), 5.42 (2 H, m, 2 × OCH), 5.12 (2 H, AB, *J* = 13.2 Hz, CH₂Ph), 4.50 (2 H, AB, *J* 12.3, CH₂Ph), 3.96 (1 H, m, NCH), 3.75 (2 H, m, OCHH, NCHH), 3.66 (1 H, dd, *J* 10.0, 2.3, OCHH), 3.50 (1 H, m, NCHH), 2.03 (3 H, s, Me), 2.01 (3 H, s, Me); *δ*_C (100 MHz; DMSO, 120 °C) 169.8 (C), 169.7 (C), 154.4 (C), 138.6 (C), 137.2 (C), 128.8 (CH), 128.6 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 73.8 (CH), 73.2 (CH₂), 70.2 (CH), 68.7 (CH₂), 66.9 (CH₂), 61.8 (CH), 49.2 (CH₂), 20.7 (Me), 20.6 (Me); *m/z* (CI) 442 (MH⁺, 100%), 398 (69), 244 (21), 181 (38), 91 (62).

1,4-Dideoxy-1,4-imino-D-ribitol hydrochloride 23. Pyrrolidine **22** (101 mg, 0.23 mmol) was dissolved in methanol (3 mL) and hydrochloric acid (1 M; 2 mL) and hydrogenated over palladium on charcoal (10% w/w; 20 mg) overnight. The catalyst was filtered through Celite and the solvent was removed *in vacuo* to give the title compound **23** as a yellow solid (36 mg, quantitative yield); mp 124–125 °C (lit.,²⁸ mp 128–132 °C); (Found: MH⁺, 134.0817. C₃H₁₁NO₃ + H requires 134.0817); [*a*]_D²⁵ +53.3 (*c* 0.75, H₂O) {lit.,²⁸ [*a*]_D²⁰ +57.6 (*c* 0.59, H₂O)} {lit.,³⁰ [*a*]_D²⁰ +53.9 (*c* 1, H₂O)}; *δ*_H (400 MHz; D₂O) 4.36 (1 H, m, NCH₂CHOH), 4.19 (1 H, dd, *J* = 8.5, 4.0 Hz, NCHCHOH), 3.94 (1 H, dd, *J* 12.6, 2.6, CHHOH), 3.80 (1 H, dd, *J* 12.6, 6.0, CHHOH), 3.59 (1 H, m, NCH), 3.48 (1 H, dd, *J* 13.0, 4.0, NCHH), 3.34 (1 H, m, NCHH); *δ*_C (75 MHz; D₂O) 72.2 (CH), 70.4 (CH), 62.8 (CH), 59.0 (CH₂), 50.7 (CH₂); *m/z* (CI) 134 (MH⁺, 100%), 116 (20), 98 (18).

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