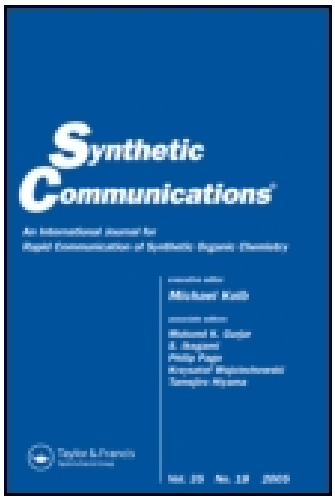

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Highly Diastereoselective Alkylation of the Dellaria Oxazinone Template with Bifunctional Electrophiles

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ABSTRACT

This study investigates the efficiency of alkylation of the Dellaria oxazinone glycinate template with sensitive bifunctional electrophiles. In addition to improved access to the template, triflate/halide bifunctional combinations provided good yields (85–93%) of highly diastereoselective alkylation products.

As part of a programme directed at natural product synthesis, we had a need to investigate the highly diastereoselective alkylation of a

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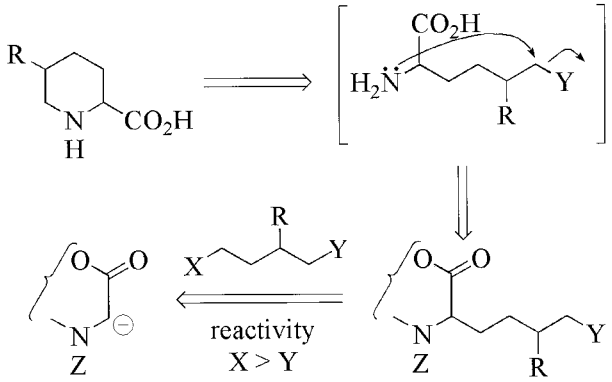
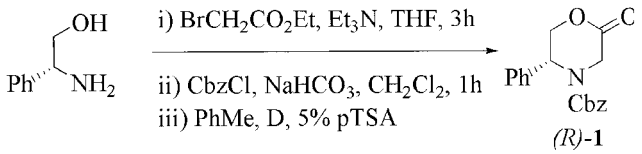
suitable chiral glycine enolate synthon. The literature abounds with many auxiliary-[1] and template-based[2] methodologies aimed at this end. Due to considerations of subsequent manipulations of the intermediate products, we specifically sought a protocol that would allow the release of the amino acid products under very mild conditions. In particular, it was hoped that the unmasking of the amino acid could be combined with subsequent cyclization (Sch. 1). After evaluation of reported alkylation methodologies, yields and cleavage procedures, the Dellaria and Santarsiero[3] oxazinone template **1** was selected for this purpose.

Initially some difficulty was experienced in reproducing the template preparation by the reported method. However, simple modification of the original route (Sch. 2) produced a highly reproducible "one-pot" protocol which was amenable to useful laboratory scales (>20 g).[4] In this way, both enantiomeric templates were available in high purity in 73–80% overall yield. The related enantiomeric templates **2**, containing *–NBoc* were also prepared.

Literature alkylations of these and the Williams' templates indicated high yields and diastereoselectivity with activated electrophiles (e.g., methyl-, allyl-, and benzylbromides). Efficiency dropped dramatically



Scheme 1. Analysis of the template-cyclization approach.



Scheme 2. Oxazinone preparation.

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with less activated systems (e.g., *n*-butyliodide). In addition, usually at least 3–10 equiv. of electrophile were required to ensure significant alkylation.

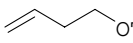
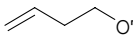
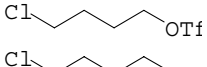
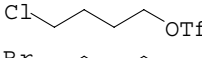
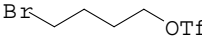
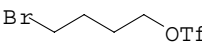
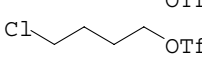
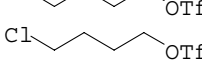
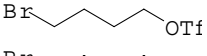
Initial studies were conducted with a range of 1,4-di-*X* substituted butane electrophiles (*X* = Br, I, OMs, OTs). These proved to be largely unsuccessful, with only the diiodide showing any reactivity.[5] Similar low reactivity was observed with both homoallyl bromide or iodide. However, a single clean product could be isolated in 40% yield from the latter system when 15-crown-5 was employed as an additive.

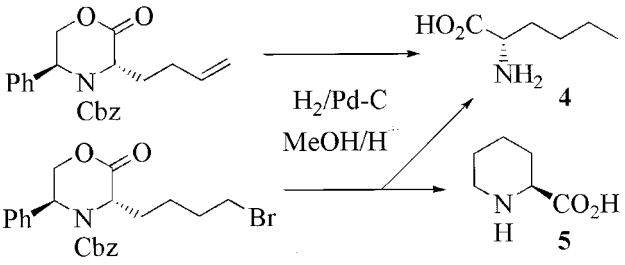
Following a report by Uenishi et al.,[6] the utility of triflate as a leaving group was explored. The required functionalized triflates were readily accessed from 3-buten-1-ol (for homoallyl triflate) and THF (for the 4-halo-1-triflates). These reactive substrates proved to be stable at low temperature (−4°C) for periods up to a week.

Alkylation of the templates **1** and **2** with the homoallyl, chloro, and bromo triflates (≤1.25 equiv.) reproduceably provided high yields of diastereomerically pure products (Table 1). The iodo triflate, on the other hand, led to multiple products. No trace of the alternative diastereomers could be detected either by HPLC or NMR.

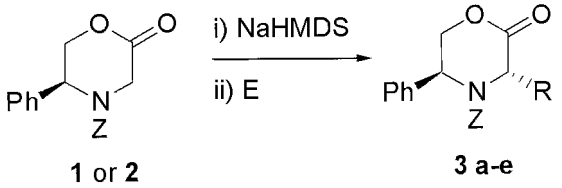
To confirm the pattern of configurational assignments (Sch. 3), (*S,S*)-**3a** (*R* = homoallyl; *Z* = Cbz) was converted in 89% (H_2/Pd-C) to (*S*)-norleucine **4** with $[\alpha]_D$ 22.9° (Lit.[7] 22.8°). In a similar reaction, (*S,S*)-**3c** (*R* = bromobutyl, *Z* = Cbz) afforded a small amount of (*S*)-

Table 1. Diastereoselective alkylation of oxazinones **1** and **2**.

Template	*E*	3%	Config/$[\alpha]_D$
(*R*)-**1**		93	(*R*,*R*) − 146°
(*S*)-**1**		92	(*S*,*S*) + 145°
(*R*)-**1**		85	(*R*,*R*) − 136°
(*S*)-**1**		83	(*S*,*S*) + 136°
(*R*)-**1**		90	(*R*,*R*) − 128°
(*S*)-**1**		90	(*S*,*S*) + 129°
(*R*)-**2**		95	(*R*,*R*) − 145°
(*S*)-**2**		93	(*S*,*S*) + 144°
(*R*)-**2**		80	(*R*,*R*) − 133°
(*S*)-**2**		81	(*S*,*S*) + 133°



Scheme 3. Hydrogenation of selected alkylation products.



norleucine **4** (12%) along with the expected (*S*)-pipecolic acid **5** (45%) with $[\alpha]_D$ −25.9° (Lit.[8] −25.8°).

EXPERIMENTAL

General

Nuclear magnetic resonance spectra were recorded on a Bruker Advance DPX-300 (^{1}H, 300 MHz; ^{13}C, 75.5 MHz). All spectra were run in deuterochloroform at ambient (25°C) temperature with tetramethylsilane as an internal standard unless stated otherwise.

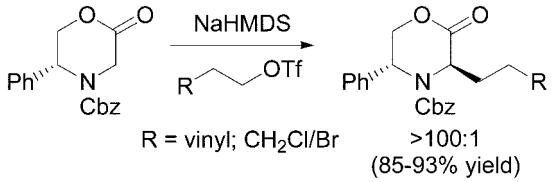
High-resolution mass spectra were measured on a VG Autospec Mass Spectrometer. High-pressure liquid chromatography was carried out on a GBC LC 1150 system using a 25 cm Chiracell OD or an Alltech Econosil C18 column. The detector was a Knauer variable wavelength monitor set at 254 nm. Infrared spectra were recorded on a Perkin Elmer 1720-X Fourier Transform Spectrometer as KBr discs (solids) or as thin films (liquids and oils). Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were obtained on an Optical Activity PolAAr 2001 polarimeter. Thin layer chromatography was carried out on aluminium

plates coated with Kieselgel 60 F_{254}. Radial chromatography was performed on a Harrison Research Ltd. "Chromatotron" with coatings of Merck silica gel 60 PF_{254}.

Hexanes refers to the fraction of petroleum distillate that boils in the range 65°C–70°C, ether refers to diethyl ether. Sodium bicarbonate and brine solutions were used as saturated solutions at ambient temperature. Magnesium and sodium sulphate drying agents were oven-dried at 200°C for 3 h (and cooled in a vacuum desiccator) prior to use. All solvents were distilled prior to use. All quoted yields refer to isolated compounds obtained after chromatography, distillation or recrystallization.

(*R*)-2,3,5,6-Tetrahydro-5-phenyl-*N*-(benzyloxycarbonyl)-4H-1,4-oxazine-2-one (*R*)-1

(*R*)-Phenylglycinol (1.37 g, 0.01 mol) was suspended in dry THF



(20 mL) with dry triethylamine (1.21 g, 1.65 mL, 0.012 mol) and cooled to 0°C under a stream of N_2. Ethyl bromoacetate (2.00 g, 1.33 mL, 0.012 mol) was added and the reaction stirred for 3 h (0°C → rt). The reaction was cooled in ice, filtered, and the filter cake washed with cold THF (10 mL). The combined organics were concentrated (45°C) and the residue taken up in CH_2Cl_2 (20 mL) and $NaHCO_3$ (40 mL). Benzyl chloroformate (1.88 g, 1.65 mL, 0.011 mol) was added dropwise and the reaction vigorously stirred for 1 h. The phases were separated, the aqueous phase washed with CH_2Cl_2 (3 × 20mL) and the combined organics washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was diluted with toluene (100 mL), pTSA (0.19 g, 0.001 mol) added and the solvent slowly distilled (down to ~5 mL) at atmospheric pressure. The remaining toluene was evaporated (rotorvap.) and the residue taken up in ether (100 mL). The ether was washed with water (25 mL), dried ($MgSO_4$), and concentrated to ~5 mL. The product (2.47 g, 80%) crystallized on cooling, sometimes by trituration with hexanes (1–2 mL): m.p. 123–123.5°C (CH_2Cl_2/ether); Lit.[3] m.p. 97–98°C (acetone/ether). IR (KBr) 1773, 1695 cm^{-1}. $[\alpha]_D^{21}$ −56.6°

($c = 1.0$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 60°C) δ 7.36–7.15 (m, 10H, Ph), 5.22 (t, 1H, $J = 4.5$ Hz, H5), 5.14 (d, 1H, $J = 12.3$ Hz, PhC*H*HO-), 5.08 (d, 1H, $J = 12.3$ Hz, PhCH*H*O-), 4.64 (d, 1H, $J = 18$ Hz, H3), 4.59 (dd, 1H, $J = 4.3$ and 12 Hz, H6), 4.50 (dd, 1H, $J = 5.3$ and 12 Hz, H6), 4.20 (d, 1H, $J = 18$ Hz, H3). ^{13}C NMR δ 167, 155, 137, 136, 129, 129, 128, 126, 70, 68.2, 54.1, 44.8.

(*S*)-2,3,5,6-Tetrahydro-5-phenyl-*N*-(benzyloxycarbonyl)-4H-1,4-oxazine-2-one (*S*)-1

The (*S*)-enantiomer was derived in a similar manner from (*S*)-phenylglycinol: $[\alpha]_D^{21}$ 56.4 ($c = 1.0$, $CHCl_3$). All spectroscopic and physical data were identical to the above.

(*R*)-2,3,5,6-Tetrahydro-5-phenyl-*N*-(*tert*-butyloxycarbonyl)-4H-1,4-oxazine-2-one (*R*)-2

A similar method to that of the Lit.[3] was followed (0.01 mol scale of (*R*)-phenylglycinol) with the alkylation reaction time being shortened to 3 h. The product (1.35 g, 49%, unoptimized) was recrystallized from ether/hexanes as needles: m.p. 87–89°C; Lit.[3] m.p. 87–88°C (EtOAc/hexanes). IR (KBr) 1761, 1671 cm^{-1}. $[\alpha]_D^{21}$ −67.5° ($c = 1.0$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 60°C) δ 7.39–7.21 (m, 5H, Ph), 5.17 (m, 1H, H5), 4.58 (dd, 1H, $J = 5.9$ and 12 Hz, H6), 4.15(d, 1H, $J = 18$ Hz, H3), 1.33 (s, 9H, *tert*-butyl). ^{13}C NMR δ 167, 154, 138, 129, 128, 126, 81.7, 70.0, 54.2, 44.6, 28.2.

(*S*)-2,3,5,6-Tetrahydro-5-phenyl-*N*-(*tert*-butyloxycarbonyl)-4H-1,4-oxazine-2-one (*S*)-2

The (*S*)-enantiomer was derived in a similar manner from (*S*)-phenylglycinol: $[\alpha]_D^{21}$ +67.5° ($c = 1.0$, $CHCl_3$). All spectroscopic and physical data were identical to the above.

General Procedure for the Preparation of Triflates

K_2CO_3 (1.10 g, 8 mmol) was added to a three necked flask fitted with a nitrogen inlet/outlet, a rubber septum and a glass stopper. The flask was

flame dried then cooled to −50°C, under a gentle flow of N_2. Dry CH_2Cl_2 (10 mL), triflic anhydride (2.1 mL, 12.5 mmol), and DMAP (0.122 g, 1 mmol) were added sequentially to the stirred mixture. After 10 min, the alcohol[9] (10 mmol, neat) was added and the reaction stirred for 1 h. CH_2Cl_2 (10 mL) and H_2O (5 mL) were added, the layers separated and the aqueous phase extracted with further CH_2Cl_2 (5 mL). The combined CH_2Cl_2 fractions were dried ($MgSO_4$) and concentrated (rotorvap. at 40°C). The residue was distilled in a Kugelrohr apparatus to produce the triflate as a colorless oil. All triflates were stored under nitrogen in the fridge and were stable for up to a week (although some discoloration did occur). All proved too unstable for successful microanalysis.

3-Butenyl-1-trifluoromethanesulphonate

Seventy two percent distilled. This product had physical and spectroscopic details that were identical to that reported in the Lit.[10]

4-Bromobutanol-1-trifluoromethanesulphonate

Seventy percent distilled: b.p. 75°C at 0.03 mm Hg. ^{1}H NMR ($CDCl_3$) δ 4.59 (m, 2H, H1), 3.46 (m, 2H, H4), 2.02 (m, 4H, H2 and H3). ^{13}C NMR δ 119, 76.6, 43.7, 28.2, 27.9.

4-Chlorobutanol-1-trifluoromethanesulphonate

Seventy nine percent distilled: b.p. 65°C at 0.04 mm Hg. ^{1}H NMR ($CDCl_3$) δ 4.60 (m, 2H, H1), 3.62 (m, 2H, H4), 2.00 (m, 4H, H2 and H3). ^{13}C NMR δ 119, 76.7, 43.8, 28.2, 26.7.

4-Iodobutanol-1-trifluoromethanesulphonate

Fifty six percent distilled (x2): b.p. 90°C at 0.025 mm Hg. IR (Thin film) 1246, 1208, 1144 cm^{-1}. HRMS calcd. for $C_5H_8IF_3O_3S$: 331.9191. Found: 331.9188. ^{1}H NMR ($CDCl_3$) δ 4.53 (m, 2H, H1), 3.22 (m, 2H, H4), 2.00 (m, 4H, H2 and H3). ^{13}C NMR δ 119, 76.1, 33.8, 30.1, 28.8.

General Procedure for Alkylation of Oxazinones

To a flame dried three-necked flask, under a gentle stream of nitrogen, was added the template **1** or **2** and dry DME (4 mL). After complete dissolution, the flask was cooled to −78°C and a solution of NaHMDS (1.0 mL of a 1 M solution in THF) added via syringe. The mixture was stirred for 0.5 h, treated dropwise with freshly distilled triflate (1.25 mmol, neat) and stirring continued for 2 h. The reaction was quenched by the addition of EtOAc (20 mL) and brine (5 mL). The layers were separated and the aqueous phase re-extracted with EtOAc (5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was applied to a 2 mm Chromatatron plate and eluted with EtOAc in hexanes (20 → 50%).

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-(1-butenyl)-5-phenyl-*N*-(benzyloxycarbonyl)-4H-1,4-oxazine-2-one (*R*,*R*)-3a

Ninety three percent, recrystallized from ether/hexanes: m.p. 165–165.5°C. IR (KBr) 1757, 1707 cm^{-1}. $[\alpha]_D^{21}$ −146° ($c = 1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$, 60°C) δ 7.32–6.99 (m, 10H, Ph), 5.81 (m, 1H, H5′), 5.13–4.99 (m, 5H, H5′ and H6 and $PhCH_2O$-), 4.85 (dd, 1H, $J = 4.4$ and 9.5 Hz, H3), 4.77 (dd, 1H, $J = 3$ and 11.9 Hz, H6), 4.41 (dd, 1H, $J = 1.5$ and 11.9 Hz, H6), 2.26–1.86 (m, 4H, H3′ and H4′). ^{13}C NMR δ 168, 154, 139, 136, 136, 129, 128, 126, 116, 69.8, 67.9, 56.9, 55.0, 33.8, 29.8. Anal. calcd. for $C_{22}H_{23}NO_4$: C 72.58; H 6.34; N 3.83. Found: C 72.08; H 6.24; N 3.82%.

(3*S*,5*S*)-2,3,5,6-Tetrahydro-3-(1-butenyl)-5-phenyl-*N*-(benzyloxycarbonyl)-4H-1,4-oxazine-2-one (*S*,*S*)-3a

The (3*S*,5*S*)-enantiomer was purified in analogous fashion (92%) $[\alpha]_D^{22}$ +145° ($c = 1$, $CHCl_3$). All other spectroscopic and physical data were identical to the above.

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-(4-chlorobutyl)-5-phenyl-*N*-(benzyloxy-carbonyl)-4H-1,4-oxazin-2-one (*R*,*R*)-3b

Eighty five percent, recrystallized from ether: m.p. 95–96°C. IR (KBr) 1760, 1703 cm^{-1}. $[\alpha]_D^{22}$ −136° ($c = 1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$, 60°C) δ 7.28 (m, 6H, Ph), 7.08 (m, 4H, Ph), 5.13 (br s, 1H, H5), 5.09 (d, 1H,

$J = 12$ Hz, PhC*H*HO), 4.99 (d, 1H, $J = 12$ Hz, PhCH*H*O), 4.80 (m, 1H, H3), 4.74 (dd, 1H, $J = 3.0$ and 12 Hz, H6), 4.39 (d, 1H, $J = 12$ Hz, H6), 3.49 (t, 2H, $J = 6.5$ Hz, H6′), 2.06 (m, 1H, H3′), 1.93–1.72 (m, 3H, H3′ and H5′), 1.62 (m, 2H, H4′). ^{13}C NMR δ 168, 154, 139, 136, 129, 128, 125, 69.8, 67.6, 56.8, 54.6, 44.4, 33.9, 33.2, 22.9. Anal. calcd. for $C_{22}H_{24}ClO_4$: C 65.75, H 6.02, N 3.49, Found: C 65.55, H 6.05, N 3.45%.

(3*S*,5*S*)-2,3,5,6-Tetrahydro-3-(4-chlorobutyl)-5-phenyl-*N*-(benzyloxycarbonyl)-4H-1,4-oxazin-2-one (*S*,*S*)-3b

The (3*S*,5*S*)-enantiomer was purified in analogous fashion (83%). $[\alpha]_D^{22}$ +136° ($c = 1.0$, $CHCl_3$). All other spectroscopic and physical data were identical to the above.

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-(4-bromobutyl)-5-phenyl-*N*-(benzyloxycarbonyl)-4H-1,4-oxazin-2-one (*R*,*R*)-3c

Ninety percent, recrystallized from ether/hexanes: m.p. 90–92°C. IR (KBr) 1759, 1701 cm^{-1}; $[\alpha]_D^{22}$ −128° ($c = 1.0$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 60°C) δ 7.28 (m, 6H, Ph), 7.08 (m, 4H, Ph), 5.13 (br.s, 1H, H5), 5.08 (d, 1H, $J = 12$ Hz, PhC*H*H), 4.98 (d, 1H, $J = 12$ Hz, PhCH*H*), 4.80 (m, 1H, H3), 4.72 (dd, 1H, $J = 3.0$ and 12 Hz, H6), 4.37 (d, 1H, $J = 12$ Hz, H6), 3.34 (t, 2H, $J = 6.6$ Hz, H6′), 2.06 (m, 1H, H3′), 1.94–1.73 (m, 3H, H3′ and H5′), 1.63 (m, 2H, H4′). ^{13}C NMR δ 167, 153, 138, 135, 128, 127.5, 127, 125, 68.8, 66.8, 56.0, 53.8, 32.5, 31.7, 30.9, 23.4. Anal. calcd. for $C_{22}H_{24}BrNO_4$: C 59.20, H 5.42, N 3.14. Found: C 59.10, H 5.40, N 3.07%.

(3*S*,5*S*)-2,3,5,6-Tetrahydro-3-(4-bromobutyl)-5-phenyl-*N*-(benzyloxycarbonyl)-4H-1,4-oxazin-2-one (*S*,*S*)-3c

The (3*S*,5*S*)-enantiomer was purified in analogous fashion (90%). $[\alpha]_D^{22}$ +129° ($c = 1.0$, $CHCl_3$). All other spectroscopic and physical data were identical to the above.

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-(4-chlorobutyl)-5-phenyl-*N*-(*tert*-butoxycarbonyl)-4H-1,4-oxazin-2-one (*R*,*R*)-3d

Ninety five percent, recrystallized from ether: m.p. 169–172°C (dec). IR (KBr) 1754, 1698 cm^{-1}. $[\alpha]_D^{22}$ −145° ($c = 1.0$, $CHCl_3$). ^{1}H NMR

($CDCl_3$, 60°C) δ 7.29 (m, 3H, Ph), 7.08 (m, 2H, Ph), 5.05 (br.s, 1H, H5), 4.81 (m, 1H, H3), 4.76 (dd, 1H, $J = 3.0$ and 11.8 Hz, H6), 4.39 (d, 1H, $J = 11.8$ Hz, H6), 3.55 (t, 2H, H6′), 2.05 (m, 1H, H3′), 1.88 (m, 3H, H3′ and H5′), 1.68 (m, 2H, H4′), 1.28 (s, 9H, *tert*-butyl). ^{13}C NMR δ 169, 154, 140, 129, 128, 126, 81.5, 69.9, 56.8, 54.9, 44.4, 34.0, 32.0, 28.2, 23.3. Anal. calcd. for $C_{19}H_{26}ClNO_4$: C 62.03, H 7.12, N 3.81. Found: C 62.15, H 7.13, N 3.73%.

(3*S*,5*S*)-2,3,5,6-Tetrahydro-3-(4-chlorobutyl)-5-phenyl-*N*-(*tert*-butoxycarbonyl)-4H-1,4-oxazin-2-one (*S,S*)-3d

The (3*S*,5*S*)-enantiomer (*S*,*S*)-**3d** was generated in analogous fashion (93%). $[\alpha]_D^{23}$ +144° ($c = 1.0$, $CHCl_3$). All other spectroscopic and physical data were identical to the above.

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-(4-bromobutyl)-5-phenyl-*N*-(*tert*-butoxycarbonyl)-4H-1,4-oxazin-2-one (*R*,*R*)-3e

Eighty percent, recrystallized from ether: m.p. 152–156°C (dec). IR (KBr) 1754, 1699 cm^{-1}. $[\alpha]_D^{22}$ −133° ($c = 1.0$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 60°C) δ 7.28 (m, 3H, Ph), 7.09 (m, 2H, Ph), 5.06 (br s, 1H, H5), 4.80 (m, 1H, H3), 4.76 (dd, 1H, $J = 3.0$ and 11.9 Hz, H6), 4.40 (d, 1H, $J = 11.9$ Hz, H6), 3.42 (t, 2H, $J = 11$ Hz, H6′), 2.05–1.90 (m, 4H, H3′ and H5′), 1.68 (m, 2H, H4′), 1.28 (s, 9H, *tert*-butyl). ^{13}C NMR δ 169, 153, 140, 129, 128, 125, 81.4, 69.7, 56.1, 54.9, 33.4, 33.1, 31.9, 28, 24.4. Anal. calcd. for $C_{19}H_{26}BrNO_4$: C 55.35, H 6.36, N 3.40. Found: C 55.37, H 6.34, N 3.40%.

(3*S*,5*S*)-2,3,5,6-Tetrahydro-3-(4-bromobutyl)-5-phenyl-*N*-(*tert*-butoxycarbonyl)-4H-1,4-oxazin-2-one (*S*,*S*)-3e

The (3*S*, 5*S*)-enantiomer (*S*,*S*)-**3e** was generated in analogous fashion. $[\alpha]_D^{22}$ +133° ($c = 1.0$, $CHCl_3$). All spectroscopic and physical data were identical to the above.

L-(+)-Norleucine (*S*)-4

Alkene (*S*,*S*)-**3a** (0.182 g, 0.5 mmol) was dissolved in methanol (10 mL) containing TFA (1 drop) and exhaustively (24 h) hydrogenated

at 55 psi pressure over 10% Pd-C (0.182 g). The catalyst was removed by filtration and the filtrate concentrated. The concentrate was dissolved in water (2 mL) and applied to an ion exchange column (Dowex 50X2). The column was eluted with ammonium hydroxide (1 N, 200 mL) and the eluant concentrated to give (*S*)-**4** as a colorless powder (0.058 g, 89%): $[\alpha]_D^{22}$ +22.9° (*c* = 0.5, 6 N HCl). Lit.[7] $[\alpha]_D^{22}$ +22.8° (*c* = 0.46, 6 N HCl).

L-(−)-Pipecolic Acid (*S*)-5 and L-(+)-Norleucine (*S*)-4

Bromo derivative (*S*)-**3c** (0.223 g, 0.5 mmol) was dissolved in methanol (10 mL) containing TFA (1 drop) and exhaustively (24 h) hydrogenated at 55 psi pressure over 10% Pd-C (0.182 g). The palladium catalyst was removed by filtration and the filtrate concentrated. The concentrate was dissolved in water (2 mL) and applied to an ion exchange column (Dowex 50X2). The column was eluted with ammonium hydroxide (1 N, 200 mL) and 5 mL aliquots collected and concentrated to dryness to afford firstly (*S*)-**4** (0.008 g, 12%), followed by (*S*)-**5** (0.029 g, 45%): $[\alpha]_D^{22}$ −25.9° (*c* = 1.0, H_2O). Lit.[8] $[\alpha]_D^{22}$ −25.8° (*c* = 1.0, H_2O).

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