Synthesis of enantiomerically pure quaternary glutamic acids via chemo- and diastereoselective alkylation of (5*S*)-3-([2–methoxycarbonyl]ethyl)-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one [i]

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Dedicated to Professor Otto Meth-Cohn, on the occasion of his 65th birthday

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Abstract

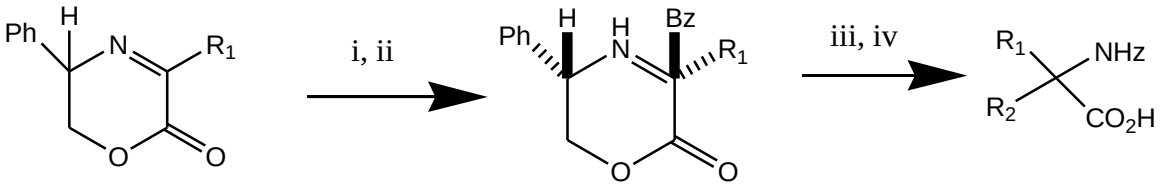
The imine moiety of (5S)-3-([2-methoxycarbonyl]ethyl)-5-phenyl-5,6-dihydro-2H-1,4-oxazin-2-one 2 undergoes highly diastereocontrolled reduction and Lewis acid–mediated chemo- and diastereoselective nucleophilic addition of Grignard reagents. Subsequent dismantling of the cyclic template permits ready access to enantiomerically pure glutamic acid analogues.

Keywords: Imines, stereocontrolled reduction, stereoselective nucleophilic addition

Introduction

We have previously reported the formation of a–substituted amino acid derivatives, *via* an approach in which enantiomerically pure 3–substituted 5–phenyl–5,6–dihydro-2*H*–1,4–oxazin–2–one 1a, prepared by cyclisation of (2*S*)–phenylglycinol with α-keto ester derivatives, underwent diastereocontrolled nucleophilic attack by Grignard reagents using Lewis acid activation to facilitate chemoselection between the imine and lactone functionalities.2 The parent 3,4–dehydrooxazinone 1b, lacking 3–substitution, cannot be prepared by the direct approach but may be obtained *via* one–pot bromination–

dehydrobromination of 5–phenyl–3,4,5,6–tetrahydro-2*H*–1,4–oxazin–2–one, 2 and has also been prepared by oxidative rearrangement of 2–methyl–4–phenyl–4,5–dihydrooxazole.2 Although 1b is readily isomerised to 5–phenyl–3,6–dihydro–*2H*–1,4–oxazin–2–one in the presence of mild base, with concomitant loss of chirality, we were again able to achieve chemo- and diastereocontrolled imine alkylation using Grignard reagents after low temperature pre–complexation with boron trifluoride etherate, and to convert these adducts subsequently to enantiomerically pure a–amino acids (Scheme 1).2 The chemoselectivity demonstrated by substrates 1 in our studies is complementary to that observed by Molinski on related substrates in the absence of Lewis acid, when phenylmagnesium bromide was shown to react *via* initial attack at the lactone of the 5,6–dihydro-2*H*–1,4–oxazin–2–one system.[3]

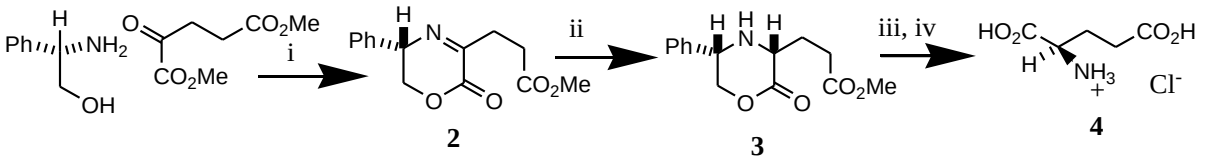


a R^1 = alkyl
b = R^1 = H

Scheme 1. *Reagents and conditions:* i, BF_3. Bt_2O (1.1 equiv.). THF, -40 ˚C, 2h; ii, R^2MgX (1.3 equiv.). -40 ˚C → 30 ˚C, 30 min.; iii, H_2 (5 bar), Pd $(OH)_2$ –C, aq. MeOH, TFA, 24h; iv, Dowex 50WZ8 – 100.

During a recent programme, we required access to a series of a–substituted D–glutamic acid derivatives for structure–activity relationship studies. Glutamic acid plays a key rôle in the neuronal biochemistry of the mammalian central nervous system, being the main excitatory transmitter. It excites virtually all central neurones by activating the kainate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and *N*-methyl-D-aspartate (NMDA) ionotropic receptor subclasses, mediating intercellular signal transmission.[i][ii] However, excessive release of glutamate leads to neuronal damage, which has been linked with a variety of neurodegenerative disorders. To allow a greater insight into the structural and physiological characterisation of these receptors and increase understanding of conditions such as Alzheimer's and Parkinson's diseases, the synthesis of unnatural glutamate analogues has received much attention. [iii] Our alkylation approach appeared to promise a convenient and direct means of access to the desired quaternary glutamic acid analogues. However, the requisite precursor, (5*S*)–3–([2–methoxycarbonyl]ethyl)–5–phenyl –5,6–dihydro–2*H*–1,4–oxazin–2–one 2, possesses a side chain ester and this caused concern as to whether the chemoselective imine alkylation previously observed with substrates 1 could be achieved.

Reaction of (2S)–phenylglycinol with dimethyl 2–oxoglutarate in 2,2,2-trifluoroethanol at reflux in the presence of activated 3Å molecular sieves according to our previous protocol1 afforded (5S)–3–[2–(methoxycarbonyl)ethyl]–5–phenyl–5,6–dihydro–2H–1,4–oxazin–2–one 2 in 60% purified yield.[iv] To assess the degree of diastereocontrol possible with this substrate without the complication of chemoselectivity associated with alkylation studies, hydrogenation of the imine function was effected under one atmosphere of hydrogen over Adams' catalyst. In contrast to our previously observed moderate diastereoselection in the hydrogenation of 3–ethyl–5–phenyl–5,6–dihydro–2H–1,4–oxazin–2–one,[ii][v] hydrogenation furnished the 3,5–syn–disubstituted tetra-Hydrooxazinone 3 in higher than 94% d.e. according to integration of the proton NMR spectrum of the crude reaction mixture, the pure major diastereomer being isolated in 89% recrystallised yield. Subsequent degradation of the cyclic template using our standard conditions [H2/Pd(OH)2–C, aq MeOH, TFA2] furnished a two component mixture shown to consist of glutamic acid and pyroglutamic acid. However, heating this mixture in 5M HCl (conditions known not to cause racemisation [vi]) afforded pure D–glutamic acid 4 in 97% isolated yield {$[\alpha]_D^{23}$ = –22.6 (c 0.31, H2O); lit for L–enantiomer [vii] $[\alpha]_D^{22}$= +24.4 (c 6.0, H2O)} (Scheme 2). This overall conversion can be considered to constitute a biomimetic pathway, since L–glutamic acid is synthesised in vivo by reductive amination of 2–oxoglutarate in the presence of glutamate dehydrogenase.8



2 **3** **4**

Scheme 2. *Reagents and conditions:* i, CF_3CH_2OH, 3A molecular sieves, 60%; ii, (1Hatm.), Pt_2O CH_2l_2, r.t., 3h, 89%; iii, (1H5tm.), $Pd(OH_2)$-C, TFA, aq. MeOH, r.t.; iv, 4M HCl, 89%.

Having established effective diastereocontrol in hydrogenation of 2 we turned our attention to alkylation of the cyclic imine whereupon initial efforts were disappointing. A series of conditions in a range of solvents using varying equivalents of Lewis acids, including those conditions that had previously proven successful, resulted in complex mixtures or recovered starting material. Aware that complexation of up to three equivalents of Lewis acid would lead to a sterically very encumbered substrate, we turned our attention to the use of aromatic solvents in an attempt to accelerate reaction. Accordingly, precomplexation of 2 with 3 equivalents of boron trifluoride etherate in toluene at –78 ^oC, followed by the addition of 1.2 equivalents of benzylmagnesium bromide and usual work–up after 5 hours furnished a single adduct in 74% recrystallised yield (Scheme 3). Spectroscopic and X–ray crystallographic analysis8 (Figure) confirmed its structure as that of the desired adduct 5a. Close scrutiny of

the crude reaction mixture showed this to be the only diastereoisomer present, the rationale for the diastereocontrol being in accordance with our prediction based upon axial approach of the nucleophile to a conformationally locked substrate from the opposite face to the phenyl substituent.[2]

Applying this modified protocol more generally always led to excellent chemoselectivity, but it was observed that increasing steric bulk at the α–position of the Grignard reagent led to a decrease in diastereoselectivity. Thus, whereas methyl 5b and ethyl 5c (Figure) adducts were obtained diastereoisomerically pure (40% and 74% purified yields respectively), the diastereomeric *iso*butyl adducts 5d, 6d were obtained a ratio of 10.3 : 1.0, with the major isomer being isolated in recrystallised 43% yield. Likewise, the *iso*propyl adducts 5e, 6e were obtained as a 20.6 : 1.0 mixture of diastereoisomers (major isomer 37% isolated yield) and the *tert*–butyl adducts 5f, 6f were obtained in a 3.0 : 1.0 ratio (major isomer 39% isolated yield) (Table).

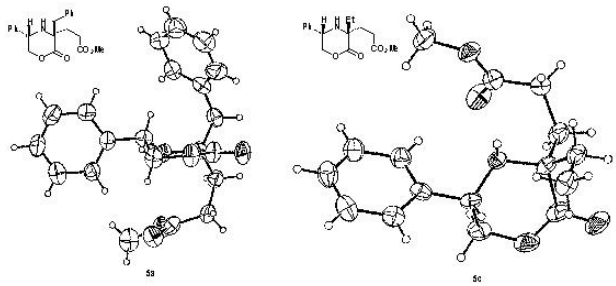


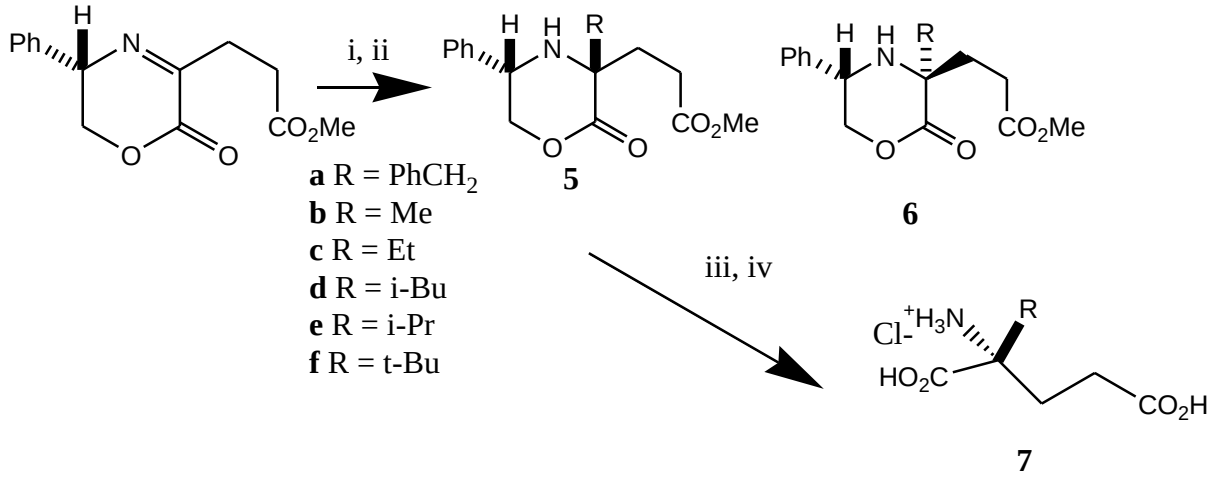
Figure 1

R	ratio 5 : 6	5, isolated yield (%)	7, isolated yield (%)	$[\alpha]_D^{24}$ c = 0.3, H_2O
$PhCH_2$	a	74	93	–10.0
Me	a	40	81	+ 1.9
Et	a	74	86	– 6.3
i–Bu	10.3 : 1.0	43	96	+18.1
i–Pr	20.6 : 1.0	36	86	– 2.6
t–Bu	3.0 : 1.0	39	b	b

Table a, minor isomer not detected in crude reaction mixture; b, pure7f not isolated

This reduction in diastereocontrol is presumably a reflection of the greater tendency for the bulkier nucleophiles to approach 2 *via* an equatorial trajectory. Notwithstanding this fall of in stereocontrol, the pure major adducts 5a–e could be simply isolated from the reaction mixture by chromatography and subsequent hydrogenolytic degradation of the tetrahydrooxazinone templates proceeded uneventfully, for the main part, using the two step procedure described above to furnish the D–α–substituted glutamic acids as their hydrochloride salts 7a – 7e in

excellent yields. However, it proved impossible to isolate the *t*–butyl derivative 7f free of its corresponding anhydride (Scheme 3)



Scheme 3. *Reagents and conditions:* i, BF_3Bt_2O (3 equiv.). toluene, -78 ˚C, 2h; ii, RMgX (1,5 equiv.), -78 ˚C, 4h; iii, H_2 (5 bar), $Pd(OH)_2$ /-C, TFA, aq. MeOH, r.t.; iv, 5MHCl, d.

In summary, this three step procedure permits ready access to a wide range of diastereoisomerically and enantiomerically pure α–substituted glutamic acid derivatives *via* chemo and diastereocontrolled functionalisation of the glutamic acid a–cation synthetic equivalent 2

Experimental Section

(5S)-3-[2-(Methoxycarbonyl)ethyl]-5-phenyl-5,6-dihydro-2H-1,4-oxazin-2-one (2). To a solution of 2-(*S*)-phenylglycinol (4.00 g, 29.16 mmol, 1 equiv.) in anhydrous 2,2,2-trifluoroethanol (90 mL) within a flask charged with activated 3A molecular sieves (15.00 g) under nitrogen was added dimethyl 2-oxoglutarate (4.20 mL, 5.05 g, 29.01 mmol, 1 equiv.). The reaction mixture was heated to reflux for 19 h, allowed to cool, filtered through Celite® and the solvent evaporated *in vacuo* to leave an orange oil. Purification by flash chromatography, eluting with diethyl ether-light petroleum (2:3), furnished the title compound as a colourless oil (4.57 g, 60%); ν_{max} (film) 2952 (C-H), 1736br (C=O), 1647 (C=N) and 1437 (C-H) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.43-7.24 (5 H, m, Ph), 4.92-4.80 (1 H, m, 5β-H), 4.55 (1 H, dd, *J* 11.5, *J'* 4.5 Hz, 6β-H), 4.20 (1 H, t, *J* 11.3 Hz, 6α-H), 3.68 (3 H, s, CH_3), 3.17-3.03 (2 H, m, C*H*$_2$$CH_2CO_2$) and 2.88-2.61 (2 H, m, CH_2C*H*$_2$$CO_2$); δ_C (125.8 MHz,

$CDCl_3$) 173.13 (C=O, ester), 161.08 (C=N), 155.29 (C=O, lactone), 136.88 (*i*-Ph), 128.79 (*o*-Ph or *m*-Ph), 128.21 (*p*-Ph), 127.02 (*m*-Ph or *o*-Ph), 71.34 (C-6), 59.45 (C-5), 51.67 (CH_3), 29.36 ($CH_2CH_2CO_2$) and 28.88 ($CH_2CH_2CO_2$); *m/z* (CI, NH_3) 262 (100%, MH^+), 230 (9, MH^+ -MeOH), 219 (7), 202 (8), 130 (7) and 104 (40, $PhCHCH_2^+$); HRMS found 262.1076, $C_{14}H_{16}NO_4$ requires 262.1079; $[\alpha]_D^{21}$+184.2 (*c* 1.31, $CHCl_3$).

(3R,5S)-3-[2-(Methoxycarbonyl)ethyl]-5-phenyl-3,4,5,6-tetrahydro-2H-1,4-oxazin-2-one (3). To a solution of (5*S*)-3-[2-(methoxycarbonyl)ethyl]-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one 298 (366 mg, 1.40 mmol, 1 equiv.) in anhydrous dichloromethane (40 mL) was added Adams' catalyst (40 mg, 0.1 equiv. by mass). The solution was twice consecutively degassed and purged with hydrogen and then left stirring vigorously under an atmosphere of hydrogen for 3 h. The suspension was filtered through Celite® and the solvent evaporated *in vacuo* to leave a colourless waxy solid. Purification by flash chromatography, eluting with diethyl ether-light petroleum (1:1), and recrystallisation from diethyl ether furnished the title compound as colourless needles (328 mg, 89%); mp 63-64 °C; anal. found C: 63.6, H: 6.57, N: 5.15%, $C_{14}H_{17}NO_4$ requires C: 63.9, H: 6.51, N: 5.32%; ν_{max} (KBr) 3325 (N-H), 2954 (C-H), 2923 (C-H), 1733 (C=O), 1720 (C=O), 1496 (N-H), 1456 (C-H) and 1440 (C-H) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.46-7.30 (5 H, m, Ph), 4.36-4.21 (3 H, m, 5β-H + 6α-H + 6β-H), 3.96 (1 H, t, *J* 5.1 Hz, 3β-H), 3.70 (3 H, s, CH_3), 2.73-2.47 (2 H, m, $CH_2CH_2CO_2$), 2.35-2.22 (2 H, m, $CH_2CH_2CO_2$) and 1.96 (1 H, br s, NH); δ_C (100.4 MHz, $CDCl_3$) 173.82 (C=O), 169.30 (C=O), 137.52 (*i*-Ph), 128.87 (*o*-Ph or *m*-Ph), 128.72 (*p*-Ph), 127.02 (*m*-Ph or *o*-Ph), 74.71 (C-6), 58.16 (C-3), 57.23 (C-5), 51.67 (CH_3), 30.18 ($CH_2CH_2CO_2$) and 28.10 ($CH_2CH_2CO_2$); *m/z* (CI, NH_3) 264 (81%, MH^+), 232 (16, MH^+- MeOH), 132 (20), 104 (100, $PhCHCH_2^+$) and 91 (10, $C_7H_7^+$); HRMS found 264.1228, $C_{14}H_{18}NO_4$ requires 264.1236; $[\alpha]_D^{22}$+83.0 (*c* 1.05, $CHCl_3$).

General method for preparation of tetrahydro-oxazinones 5a–f

To a solution of (5*S*)-3-[2-(methoxycarbonyl)ethyl]-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one 2 (150 mg, 0.57 mmol, 1 equiv.) in anhydrous toluene (5 mL) at -78 °C (cardice-acetone bath) under nitrogen was added boron trifluoride etherate (0.22 mL, 246 mg, 1.74 mmol, 3 equiv.) in a single portion and the reaction mixture stirred for 2 h. The requisite Grignard reagent (0.85 mmol, 1.5 equiv.) was added dropwise *via* syringe over 15 min. The solution was stirred for a further 5 h and the reaction quenched at -78 °C by the addition of saturated aqueous ammonium chloride (10 mL). The organic phase was removed, brine (10 mL) added and the aqueous phase further extracted with diethyl ether (2 x 20 mL). The combined organic fractions were washed with brine (50 mL), dried over magnesium sulfate and the solvent evaporated *in vacuo* to leave the crude tetrahydro-oxazinone.

***(3S,5S)*-3-Benzyl-3-[2-(methoxycarbonyl)ethyl]-5-phenyl-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (5a).** Purification by flash chromatography, eluting with diethyl ether-light petroleum (3:7), followed by recrystallisation from diethyl ether-light petroleum furnished the

title compound as colourless needles (150 mg, 74%); mp 88-89 °C; anal. found C: 71.2, H: 6.54, N: 3.97%, $C_{21}H_{23}NO_4$ requires C: 71.4, H: 6.56, N: 3.96%; ν_{max} (KBr) 3335 (N-H), 3027 (C-H), 2949 (C-H), 1734 (C=O), 1717 (C=O), 1494 (N-H), 1455 (C-H) and 1441 (C-H) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.45-7.23 (8 H, m, Ph), 7.22-7.11 (2 H, m, Ph), 4.25 (1 H, t, *J* 10.4 Hz, 6α-H), 4.17 (1 H, dd, *J* 10.4, *J'* 3.6 Hz, 6β-H), 3.99 (1 H, dd, *J* 10.3, *J'* 3.5 Hz, 5β-H), 3.68 (3 H, s, CH_3), 3.56 (1 H, d, *J* 13.6 Hz, C*H*HPh), 2.88 (1 H, d, *J* 13.6 Hz, CH*H*Ph), 2.79-2.62 (1 H, m, CH_2CHHCO_2), 2.53-2.30 (2 H, m, C*H*HCH*H*CO_2), 1.95-1.77 (1 H, m, CH*H*CH_2CO_2) and 1.61 (1 H, br s, NH); δ_C (75.5 MHz, $CDCl_3$) 173.87 (C=O), 172.36 (C=O), 137.20 (*i*-Ph), 135.07 (*i*-Ph), 130.28 (*o*-Ph or *m*-Ph), 128.83 (*m*-Ph or *o*-Ph), 128.82 (*o*-Ph or *m*-Ph), 128.77 (*p*-Ph), 127.39 (*p*-Ph), 127.23 (*m*-Ph or *o*-Ph), 74.99 (C-6), 64.62 (C-3), 52.94 (C-5), 51.63 (CH_3), 44.61 (CH_2Ph), 35.35 ($CH_2CH_2CO_2$) and 29.93 ($CH_2CH_2CO_2$); $^m/z$ (CI, NH_3) 354 (25%, MH^+), 262 (58), 190 (16), 130 (12), 104 (100, $PhCHCH_2^+$), 91 (38, $C_7H_7^+$) and 77 (14, $C_6H_5^+$); HRMS found 354.1706, $C_{21}H_{24}NO_4$ requires 354.1705; $[\alpha]_D^{21}$-48.7 (*c* 0.53, $CHCl_3$).

(3*R*,5*S*)-3-[2-(Methoxycarbonyl)ethyl]-3-methyl-5-phenyl-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (5b). Purification by flash chromatography, eluting with diethyl ether-light petroleum (1:3), followed by recrystallisation from diethyl ether-light petroleum furnished the title compound as colourless needles (64 mg, 40%); mp 140-142 °C; anal. found C: 64.8, H: 6.86, N: 4.95%, $C_{15}H_{19}NO_4$ requires C: 65.0, H: 6.91, N: 5.05%; ν_{max} (KBr) 3316 (N-H), 2957 (C-H), 1737 (C=O), 1722 (C=O), 1497 (N-H) and 1457 (C-H) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.45-7.30 (5 H, m, Ph), 4.40 (1H, dd, *J*10. 3, *J'*3.6Hz, 5β-H),4.28 (1 H, dd, *J* 10.4, *J'* 3.7 Hz, 6β-H), 4.22 (1 H, t, *J* 10.4 Hz, 6α-H), 3.71 (3 H, s, OCH_3), 2.69-2.61 (1 H, m, CH_2CHHCO_2), 2.51-2.34 (2 H, m, C*H*HCH*H*CO_2), 2.04-1.88 (1 H, m, CH*H*CH_2CO_2), 1.59 (3 H, s, $NCCH_3$) and 1.43 (1 H, br s, NH); δ_C (100.4 MHz, $CDCl_3$) 174.09 (C=O), 172.46 (C=O), 137.63 (*i*-Ph), 128.85 (*o*-Ph or *m*-Ph), 128.74 (*p*-Ph), 127.18 (*m*-Ph or *o*-Ph), 75.28 (C-6), 60.98 (C-3), 53.02 (C-5), 51.64 (OCH_3), 36.99 ($CH_2CH_2CO_2$), 30.07 ($CH_2CH_2CO_2$) and 27.28 ($NCCH_3$); $^m/z$ (CI, NH_3) 278 (75%, MH^+), 233 (25), 219 (10), 190 (8), 146 (16), 142 (15), 104 (100, $PhCHCH_2^+$) and 91 (13, $C_7H_7^+$); HRMS found 278.1391, $C_{15}H_{20}NO_4$ requires 278.1392; $[\alpha]_D^{22}$+21.5 (*c* 0.85, $CHCl_3$).

(3*R*,5*S*)-3-Ethyl-3-[2-(methoxycarbonyl)ethyl]-5-phenyl-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (5c). Purification by flash chromatography, eluting with diethyl ether-light petroleum (3:7), followed by recrystallisation from diethyl ether-light petroleum furnished the title compound as colourless filaments (122 mg, 74%); mp 59-61 °C; anal. found C: 66.0, H: 7.28, N: 4.72%, $C_{16}H_{21}NO_4$ requires C: 66.0, H: 7.27, N: 4.81%; ν_{max} (KBr) 3331 (N-H), 2983 (C-H), 2960 (C-H), 2944 (C-H), 1733 (C=O), 1717 (C=O), 1498 (N-H), 1456 (C-H) and 1436 (C-H) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.52-7.30 (5 H, m, Ph), 4.37 (1 H, dd, *J* 9.8, *J'* 4.1 Hz, 5β-H), 4.33-4.23 (1 H, m, 6β-H), 4.22 (1 H, t, *J* 10.3 Hz, 6α-H), 3.72 (3 H, s, OCH_3), 2.78-2.61 (1 H, m, CH_2CHHCO_2), 2.52-2.37 (1 H, m, CH_2CHHCO_2), 2.33-2.19 (1 H, m, C*H*HCH_2CO_2), 2.19-2.04 (1 H, m, C*H*HCH_3), 2.04-1.94 (1 H, m, CH*H*CH_2CO_2), 1.94-1.79 (1

H, m, CH*H*CH_3), 1.76 (1 H, br s, NH) and 0.99 (3 H, t, *J* 7.5 Hz, CH_2CH_3); δ_C (75.5 MHz, $CDCl_3$) 174.23 (C=O), 172.39 (C=O), 137.79 (*i*-Ph), 128.84 (*o*-Ph or *m*-Ph), 128.76 (*p*-Ph), 127.20 (*m*-Ph or *o*-Ph), 75.02 (C-6), 63.68 (C-3), 52.88 (C-5), 51.60 (OCH_3), 33.66 ($CH_2CH_2CO_2$), 31.23 (CH_2CH_3), 30.07 ($CH_2CH_2CO_2$) and 7.63 (CH_2CH_3); *m/z* (CI, NH_3) 292 (100%, MH^+), 262 (31), 247 (24), 160 (14), 156 (21), 104 (76, $PhCHCH_2^+$) and 91 (15, $C_7H_7^+$); HRMS found 292.1536, $C_{16}H_{22}NO_4$ requires 292.1549; $[\alpha]_D^{21}$+4.0 (*c* 0.95, $CHCl_3$).

(3*S*,5S)-3-Isobutyl-3-[2-(methoxycarbonyl)ethyl]-5-phenyl-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (5d). Purification by flash chromatography, eluting with diethyl ether-light petroleum (1:4), followed by recrystallisation from diethyl ether-light petroleum furnished the title compound as colourless needles (79 mg, 43%); mp 85-88 °C; anal. found C: 67.4, H: 7.86, N: 4.19%, $C_{18}H_{25}NO_2$ requires C: 67.7, H: 7.89, N: 4.39%; ν_{max} (KBr) 3326 (N-H), 2974 (C-H), 2956 (C-H), 1733 (C=O), 1716 (C=O), 1495 (N-H), 1461 (C-H) and 1439 (C-H) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.52-7.46 (5 H, m, Ph), 4.40 (1 H, dd, *J* 9.8, *J'* 4.2 Hz, 5β-H), 4.28 (1 H, m, 6β-H), 4.24 (1 H, t, *J* 10.3 Hz, 6α-H), 3.71 (3 H, s, OCH_3), 2.77-2.61 (1 H, m, CH_2CHCO_2), 2.51-2.22 (2 H, m, $CHCHCO_2$), 2.13-1.96 (2 H, m, $CHCH_2CO_2$+ $CHCH(CH_3)_2$), 1.96-1.75 (1 H, m, $CH(CH_3)_2$), 1.69 (1 H, dd, *J* 14.2, *J'* 4.6 Hz, $CHCH(CH_3)_2$), 1.63 (1 H, br s, NH) and 1.00 (6 H, d, *J* 6.6 Hz, $CH(CH_3)_2$); δ_C (75.5 MHz, $CDCl_3$) 174.22 (C=O), 172.55 (C=O), 137.67 (*i*-Ph), 128.86 (*o*-Ph or *m*-Ph), 128.77 (*p*-Ph), 127.24 (*m*-Ph or *o*-Ph), 75.00 (C-6), 63.85 (C-3), 53.17 (C-5), 51.66 (OCH_3), 47.53 ($CH(CH_3)_2$), 35.48 ($CH_2CH_2CO_2$), 30.20 ($CH_2CH_2CO_2$), 25.12 ($CH_2CH(CH_3)_2$), 24.32 ($CH(CH_3)CH_3$) and 23.89 ($CH(CH_3)CH_3$); *m/z* (CI, NH_3) 320 (51%, MH^+), 262 (35), 232 (15), 190 (23), 130 (15), 104 (100, $PhCHCH_2^+$), 91 (14, $C_7H_7^+$) and 77 (12, $C_6H_5^+$); HRMS found 320.1859, $C_{18}H_{26}NO_4$ requires 320.1862; $[\alpha]_D^{21}$+11.2 (*c* 0.69, $CHCl_3$).

(3*S*,5*S*)-3-Isopropyl-3-[2-(methoxycarbonyl)ethyl]-5-phenyl-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (5e). Purification by flash chromatography, eluting with diethyl ether-light petroleum (1:3), followed by recrystallisation from diethyl ether-light petroleum furnished the title compound as colourless filaments (64 mg, 37%); mp 60-63 °C; anal. found C: 66.6, H: 7.47, N: 4.54%, $C_{17}H_{23}NO_4$ requires C: 66.9, H: 7.59, N: 4.59%; ν_{max} (KBr) 3329 (N-H), 2970 (C-H), 2948 (C-H), 1734 (C=O), 1712 (C=O), 1495 (N-H) and 1448 (C-H) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.50-7.30 (5 H, m, Ph), 4.47 (1 H, dd, *J* 10.2, *J'* 4.0 Hz, 5β-H), 4.35-4.26 (1 H, m, 6β-H), 4.22 (1 H, t, *J* 10.3 Hz, 6α-H), 3.71 (3 H, s, OCH_3), 2.78-2.62 (1 H, m, CH_2CHCO_2), 2.46 (1 H, sept, *J* 6.9 Hz, $CH(CH_3)_2$), 2.44-2.32 (1 H, m, CH_2CHCO_2), 2.18 (1 H, ddd, *J* 13.9, *J'* 8.3, *J''* 5.7 Hz, $CHCH_2CO_2$), 2.04-1.87 (1 H, m, $CHCH_2CO_2$), 1.82 (1 H, br s, NH), 1.07 (3 H, d, *J* 6.9 Hz, $CH(CH_3)CH_3$) and 1.02 (3 H, d, *J* 6.9 Hz, $CH(CH_3)CH_3$); δ_C (75.5 MHz, $CDCl_3$) 174.23 (C=O), 172.16 (C=O), 138.01 (*i*-Ph), 128.81 (*o*-Ph or *m*-Ph), 128.72 (*p*-Ph), 127.14 (*m*-Ph or *o*-Ph), 74.79 (C-6), 65.97 (C-3), 53.40 (C-5), 51.66 (OCH_3), 35.45 ($CH_2CH_2CO_2$), 32.31 ($CH(CH_3)_2$), 30.15 ($CH_2CH_2CO_2$), 18.60 ($CH(CH_3)CH_3$) and 16.23 ($CH(CH_3)CH_3$); *m/z* (CI, NH_3) 306 (100%, MH^+), 262 (90), 230 (18), 202 (19), 104 (15,

$PhCHCH_2^+$) and 91 (10, $C_7H_7^+$); HRMS found 306.1716, $C_{17}H_{24}NO_4$ requires 306.1705; $[\alpha]_D^{22}$-21.4 (*c* 0.35, $CHCl_3$).

(3*S*,5*S*)-3-tert-Butyl-3-[2-(methoxycarbonyl)ethyl]-5-phenyl-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (5f). Purification by flash chromatography, eluting with diethyl ether-light petroleum (1:4), followed by recrystallisation from diethyl ether-light petroleum furnished the title compound as colourless filaments (72 mg, 39%); mp 116-118 °C; anal. found C: 67.5, H: 7.85, N: 4.34%, $C_{18}H_{25}NO_4$ requires C: 67.7, H: 7.89, N: 4.39%; ν_{max} (KBr) 3353 (N-H), 2973 (C-H), 2954 (C-H), 1727br (C=O), 1495 (N-H), 1449 (C-H) and 1436 (C-H) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.45-7.31 (5 H, m, Ph), 4.70 (1 H, dd, *J* 10.4, *J'* 3.8 Hz, 5β-H), 4.31 (1 H, dd, *J* 10.5, *J'* 3.8 Hz, 6β-H), 4.23 (1 H, t, *J* 10.5 Hz, 6α-H), 3.70 (3 H, s, OCH_3), 2.81-2.62 (1 H, m, CH_2CHCO_2), 2.47-2.29 (2 H, m, $CHCHCHCO_2$), 2.02-1.85 (1 H, m, $CHCH_2CO_2$), 1.58 (1 H, br s, NH) and 1.20 (9 H, s, *t*-Bu); δ_C (75.5 MHz, $CDCl_3$) 174.42 (C=O), 171.32 (C=O), 138.41 (*i*-Ph), 128.86 (*o*-Ph or *m*-Ph), 128.77 (*p*-Ph) 127.17 (*m*-Ph or *o*-Ph), 74.52 (C-6), 68.26 (C-3), 53.62 (C-5), 51.62 (OCH_3), 41.26 ($CH_2CH_2CO_2$), 32.04 ($C(CH_3)_3$), 31.07 ($CH_2CH_2CO_2$) and 27.76 ($C(CH_3)_3$); *m/z* (CI, NH_3) 320 (74%, MH^+), 262 (100), 230 (18), 202 (16), 131 (12), 104 (100, $PhCHCH_2^+$), 91 (16, $C_7H_7^+$), 77 (14, $C_6H_5^+$) and 57 (10, $C_4H_9^+$); HRMS found 320.1856, $C_{18}H_{26}NO_4$ requires 320.1862; $[\alpha]_D^{21}$-27.3 (*c* 0.74, $CHCl_3$).

General method for preparation of glutamic acids

To a solution of the requisite tetrahydro-oxazinone (0.50 mmol, 1 equiv.) in methanol (5 mL) within a Fischer-Porter bottle was added Pearlman's catalyst (1 equiv. by mass), trifluoroacetic acid (0.1 mL) and water (0.5 mL). The solution was degassed, the bottle was pressurised with hydrogen to 5 bar and the reaction mixture stirred rapidly for 24 h at room temperature. After depressurisation, the suspension was filtered through Celite® and the solvent evaporated *in vacuo* to afford the crude amino acid. This was dissolved in aqueous hydrochloric acid (5 *M*, 3 mL) and the solution heated at reflux for 2 h. The reaction mixture was allowed to cool and the solvent evaporated *in vacuo* to afford the amino acid hydrochloride salt.

(R)-Glutamic acid hydrochloride (4). Purification by trituration with diethyl ether (3 x 10 mL) furnished the title compound as a colourless powder (89 mg, 97%); mp 195-200 °C (dec.), lit.[9] (*ent*.) mp 214 °C (dec.); ν_{max} (KBr) 3150-2850br (O-H + N-H), 2502 (N-H), 1981 (C-H), 1729 (C=O), 1683 (C=O), 1611 (N-H), 1509 (N-H) and 1426 (C-H) cm^{-1}; δ_H (250 MHz, D_2O) 4.03 (1 H, t, *J* 6.6 Hz, NCH), 2.56 (2 H, t, *J* 7.2 Hz, $CH_2CH_2CO_2$) and 2.37-2.13 (2 H, m, $CH_2CH_2CO_2$); δ_C (100.4 MHz, D_2O) 177.24 (C=O), 172.67 (C=O), 53.17 (NCH), 30.39 ($CH_2CH_2CO_2$) and 25.81 ($CH_2CH_2CO_2$); *m/z* (CI, NH_3) 148 (12%, $[M\text{-}Cl]^+$), 130 (78, $[M\text{-}Cl]^+ - H_2O$), 102 (11, $[M\text{-}Cl]^+ - H_2O\text{-}CO$) and 84 (100, $[M\text{-}Cl]^+ - 2H_2O\text{-}CO$); HRMS found 148.0610, $C_5H_{10}NO_4$ requires 148.0160; $[\alpha]_D^{23}$-22.6 (*c* 0.31, H_2O), lit.[iv[viii]] (*ent*.) $[\alpha]_D^{22}$+24.4 (*c* 6.00, H_2O).

2-(*S*)-Benzylglutamic acid hydrochloride (7a). Purification by trituration with diethyl ether (3 x 10 mL) furnished the title compound as a colourless powder (136 mg, 86%); mp 193-198 °C (dec.); ν_{max} (KBr) 3190-2900br (O-H + N-H), 2533 (N-H), 2000 (N-H), 1733 (C=O), 1717 (C=O), 1601 (N-H), 1507 (N-H) and 1404 (C-H) cm^{-1}; δ_H (250 MHz, D_2O) 7.41-7.16 (5 H, m, Ph), 3.36 (1 H, d, *J* 14.4 Hz, C*H*HPh), 3.04 (1 H, d, *J* 14.4 Hz, CH*H*Ph), 2.67-2.39 (2 H, m, $CH_2CH_2CO_2$) and 2.39-2.05 (2 H, m, $CH_2CH_2CO_2$); δ_C (100.4 MHz, D_2O) 177.15 (C=O), 173.73 (C=O), 133.79 (*i*-Ph), 131.06 (*o*-Ph or *m*-Ph), 130.07 (*m*-Ph or *o*-Ph), 129.14 (*p*-Ph), 64.86 ($NCCO_2$), 42.07 (CH_2Ph), 31.37 ($CH_2CH_2CO_2$) and 29.29 ($CH_2CH_2CO_2$); *m/z* (CI, NH_3) 238 (4%, $[M-Cl]^+$), 220 (48, $[M-Cl]^+ -H_2O$), 192 (6, $[M-Cl]^+ -H_2O-CO$), 174 (100, $[M-Cl]^+ -2H_2O-CO$), 144 (16), 128 (33), 91 (47, $C_7H_7^+$) and 84 (53); HRMS found 238.1071, $C_{12}H_{16}NO_4$ requires 238.1079; $[\alpha]_D^{24}$-6.3 (*c* 0.30, H_2O).

2-(*R*)-Methylglutamic acid hydrochloride (7b). Purification by trituration with diethyl ether (3 x 10 mL) furnished the title compound as a colourless powder (99 mg, 93%); mp 143-148 °C (dec.); ν_{max} (KBr) 3230-2750br (O-H + N-H), 2512 (N-H), 1950 (N-H), 1721 (C=O), 1696 (C=O), 1593 (N-H), 1506 (N-H) and 1416 (C-H) cm^{-1}; δ_H (250 MHz, D_2O) 2.59-2.36 (2 H, m, $CH_2CH_2CO_2$), 2.14 (2 H, t, *J* 7.5 Hz, $CH_2CH_2CO_2$) and 1.51 (3 H, s, CH_3); δ_C (100.4 MHz, D_2O) 177.24 (C=O), 174.82 (C=O), 60.52 ($NCCO_2$), 32.34 ($CH_2CH_2CO_2$), 29.33 ($CH_2CH_2CO_2$) and 22.36 (CH_3); *m/z* (CI, NH_3) 162 (41%, $[M-Cl]^+$), 144 (100, $[M-Cl]^+ -H_2O$), 116 (24, $[M-Cl]^+ -H_2O-CO$), 98 (100, $[M-Cl]^+ -2H_2O-CO$) and 84 (19); HRMS found 162.0768, $C_5H_{10}NO_4$ requires 162.0766; $[\alpha]_D^{23}$-10.0 (*c* 0.36, H_2O).

2-(*R*)-Ethylglutamic acid hydrochloride (7c). Purification by trituration with diethyl ether (3 x 10 mL) furnished the title compound as a colourless powder (106 mg, 81%); mp 169-174 °C (dec.); ν_{max} (KBr) 3140-2910br (O-H + N-H), 2546 (N-H), 1981 (N-H), 1747 (C=O), 1721 (C=O), 1614 (N-H), 1522 (N-H) and 1408 (C-H) cm^{-1}; δ_H (250 MHz, D_2O) 2.59-2.34 (2 H, m, $CH_2CH_2CO_2$), 2.20-2.10 (2 H, m, $CH_2CH_2CO_2$), 1.97 (1 H, dq, *J* 15.0, *J'* 7.5 Hz, C*H*HCH$_3$), 1.83 (1 H, dq, *J* 14.8, *J'* 7.4 Hz, CH*H*CH$_3$) and 0.91 (3 H, t, *J* 7.5 Hz, CH_3); δ_C (100.4 MHz, D_2O) 177.26 (C=O), 174.17 (C=O), 64.57 ($NCCO_2$), 30.95 ($CH_2CH_2CO_2$), 29.45 (CH_2CH_3), 29.18 ($CH_2CH_2CO_2$) and 7.91 (CH_3); *m/z* (CI, NH_3) 176 (9%, $[M-Cl]^+$), 158 (74, $[M-Cl]^+ -H_2O$), 130 (15, $[M-Cl]^+ -H_2O-CO$), 112 (100, $[M-Cl]^+ -2H_2O-CO$) and 84 (12); HRMS found 176.0919, $C_7H_{14}NO_4$ requires 176.0923; $[\alpha]_D^{23}$+1.9 (*c* 0.42, H_2O).

2-(*S*)-Isobutylglutamic acid hydrochloride (7d). Purification by trituration with diethyl ether (3 x 10 mL) furnished the title compound as a colourless powder (115 mg, 96%); mp 146-151 °C (dec.); ν_{max} (KBr) 3270-2800br (O-H + N-H), 2582 (N-H), 1697 (N-H), 1747 (C=O), 1715 (C=O), 1613 (N-H), 1517 (N-H) and 1417 (C-H) cm^{-1}; δ_H (250 MHz, D_2O) 2.62-2.30 (2 H, m, $CH_2CH_2CO_2$), 2.22-2.02 (2 H, m, $CH_2CH_2CO_2$), 1.95-1.56 (3 H, m, $CH_2CH(CH_3)_2$), 0.90 (3 H, d, *J* 6.4 Hz, CH(CH_3)CH$_3$) and 0.84 (3 H, d, *J* 6.4 Hz, CH(CH$_3$)CH_3); δ_C (100.4 MHz, D_2O) 178.26 (C=O), 175.72 (C=O), 64.53 ($NCCO_2$), 45.78 ($CH_2CH(CH_3)_2$), 33.66 ($CH_2CH_2CO_2$), 30.11 ($CH_2CH_2CO_2$), 25.19 ($CH_2CH(CH_3)_2$), 18.41

(CH(*C*H$_3$)CH$_3$) and 16.96 (CH(CH$_3$)*C*H$_3$); *m/z* (CI, NH$_3$) 204 (5%, [M-Cl]$^+$), 186 (43, [M-Cl]$^+$ -H$_2$O), 158 (6, [M-Cl]$^+$ -H$_2$O-CO), 140 (100, [M-Cl]$^+$ -2H$_2$O-CO), 124 (20), 97 (21) and 84 (19); HRMS found 204.1244, $C_9H_{18}NO_4$ requires 204.1236; $[\alpha]_D^{23}$+18.1 (*c* 0.37, H$_2$O).

2-(*S*)-Isopropylglutamic acid hydrochloride (7e). Purification by trituration with diethyl ether (3 x 10 mL) furnished the title compound as a colourless powder (97 mg, 86%); mp 139-144 °C (dec.); ν_{max} (KBr) 3360-2930br (O-H + N-H), 2603 (N-H), 1993 (N-H), 1739 (C=O), 1718 (C=O), 1617 (N-H), 1521 (N-H) and 1404 (C-H) cm^{-1}; δ_H (250 MHz, D$_2$O) 2.59-2.04 (5 H, m, C*H*(CH$_3$)$_2$+ C*H*$_2$C*H*$_2$CO$_2$) and 0.95 (6 H, t, *J* 7.2 Hz, CH(C*H*$_3$)$_2$); δ_C (100.4 MHz, D$_2$O) 176.77 (C=O), 173.73 (C=O), 67.32 (N*C*CO$_2$), 33.27 (CH$_2$*C*H$_2$CO$_2$), 28.96 (*C*H(CH$_3$)$_2$), 28.87 (*C*H$_2$CH$_2$CO$_2$), 16.91 (CH(*C*H$_3$)CH$_3$) and 15.43 (CH(CH$_3$)*C*H$_3$); *m/z* (CI, NH$_3$) 190 (63%, [M-Cl]$^+$), 172 (100, [M-Cl]$^+$ -H$_2$O), 144 (30, [M-Cl]$^+$ -H$_2$O-CO), 126 (76, [M-Cl]$^+$ -2H$_2$O-CO), 110 (15) and 84 (48); HRMS found 190.1088, $C_8H_{16}NO_4$ requires 190.1079; $[\alpha]_D^{24}$-2.6 (*c* 0.23, H$_2$O).

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X–ray crystallographic data for 5c: $C_{16}H_{21}NO_4$, M = 291.34, orthorhombic, space group $P2_12_12_1$, a = 6.060(8), b = 19.19(2), c = 13.368(15) Å, U = 1555(3) Å^3, Z = 4, δ_C = 1.245 g cm^{-3}, $F(000)$ = 624, 1477 independent reflections were obtained from 95 x 2° frames, each collected for 2 minutes on the Marresearch Image Plate system using MoK_a radiation.
Data analysis for both structures was carried out with the XDS program.[15] The structures were determined by direct methods using SHELX86[16] and refined (non-heavy atoms anisotropic, hydrogen atoms in calculated positions, isotropic) by full-matrix least squares[17] on F2 using SHELXL to R 0.0742 for 5a and R 0.0545 for 5c. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Instructions to Authors, Issue No. 1, 1999.
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