1 PERKIN

Tetrahydro-1,3-oxazin-6-ones as templates for the stereoselective synthesis of β-substituted L-aspartic acids[1]

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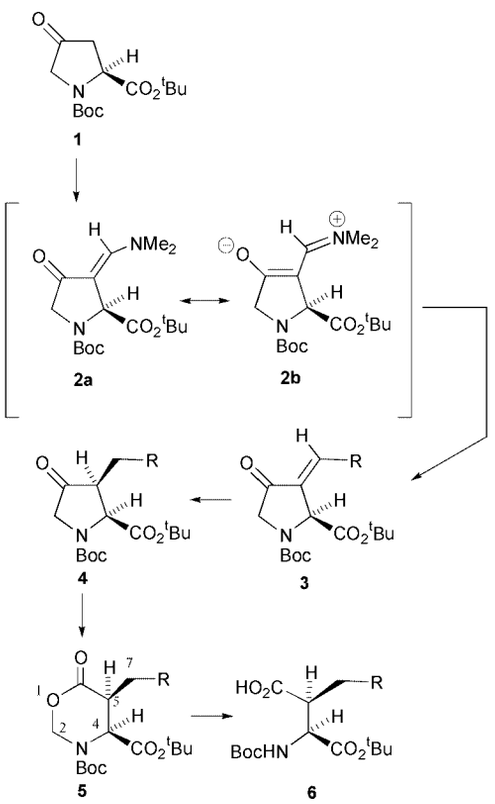
Protected (4*S*)-4-carboxytetrahydro-1,3-oxazin-6-ones have been synthesised either by Baeyer–Villiger reaction on a 4-ketoproline derivative or, more directly, from an aspartate derivative. Two strategies have been used to develop these compounds as chiral templates in the synthesis of β-substituted aspartic acids. In the first, formation of an enaminone using Bredereck's reagent, followed by reaction with a Grignard reagent gave a series of alkylidene derivatives which could be reduced from the less hindered side by heterogeneous catalytic hydrogenation to give *cis*-oxazinones in a completely stereoselective manner. Alternatively, an alkylation strategy, although *trans*-selective, gave mixtures of isomers. The oxazinones were converted to β-substituted aspartic acids and to regioselectively protected β-substituted aspartic acids without loss of stereochemistry at either centre.

The stereospecific synthesis of non-natural amino acids has assumed great interest because of the use of these compounds as synthons for a wide variety of natural products, as drug molecules and as probes for understanding the mechanism of biological reactions. Stereospecifically β-alkylated aspartic acids have been of particular interest in this respect. Direct alkylation of aspartic acid derivatives was first reported by Seebach in 1981,[2] and later by Baldwin and other workers.[3–12] Except for reports of stereospecific allylation,[10,11] these reactions gave mixtures of diastereoisomers. A recent study has indicated how the structural and experimental features in such reactions affect the diastereoselectivity.[12] Single diastereoisomeric β-alkyl-aspartates have been synthesised indirectly using chiral β-lactam esters as templates which are alkylated *trans* to the ester group.[13–16]

We have developed a stereoselective method of preparing homochiral 4-substituted glutamic acids and prolines by using pyroglutamic acid as a chiral template.[17] We have also applied the method to the use of protected 4-ketoprolines such as **1** as chiral templates to prepare the *cis*-alkyl compounds **4**.[18] Our general method involved preparation of enaminones such as **2** using Bredereck's reagent, followed by reaction with a suitable Grignard reagent to yield enones such as **3**. Catalytic hydrogenation then occurred stereospecifically from the less hindered side of **3** to give the *cis*-isomer **4** as the sole diastereoisomeric product, as shown in Scheme 1.[18] We reasoned that, if the compounds **4** could be converted to oxazinones such as **5** by an appropriately regiospecific Baeyer–Villiger process, then hydrolysis would lead to a new and stereoselective route to β-substituted aspartic acids **6**. This would provide a stereoselective method which would give access to epimers of the compounds prepared by alkylation of β-lactam esters.



Scheme 1

We had prepared the substituted prolines **4** (R = Me) and **4** (R = Ph) as single diastereoisomers by the above route[18] and, although these compounds proved to be prone to epimerisation even when subjected to chromatography on silica gel, we were in a position to study the Baeyer–Villiger reaction. Treatment of the unsubstituted ketone **1** with *m*-chloroperbenzoic acid or with trifluoroperacetic acid failed to elicit any reaction. Bolm *et al.*[19] have shown that copper(II) acetate can be used to catalyse Baeyer–Villiger oxidation of ketones with molecular oxygen and when we used this catalyst with *m*-chloroperbenzoic acid at room temperature, a 79% yield of tetrahydro-1,3-oxazin-6-one **9** was obtained. The room temperature NMR spectra of the product were broad and difficult to interpret, but at −30 °C they became clear, indicating the presence of a 7:3 mixture of rotamers. This phenomenon is expected of acylproline derivatives[16,20] and so it was not surprising that it occurred with the reduced oxazinone analogues. The regiospecificity of the Baeyer–Villiger reaction was proved by hydrolysis of compound **9** to (*S*)-aspartic acid **10** and the specific rotation of this product indicated that no racemisation had occurred at the α-centre during the reaction. The most likely explanation for

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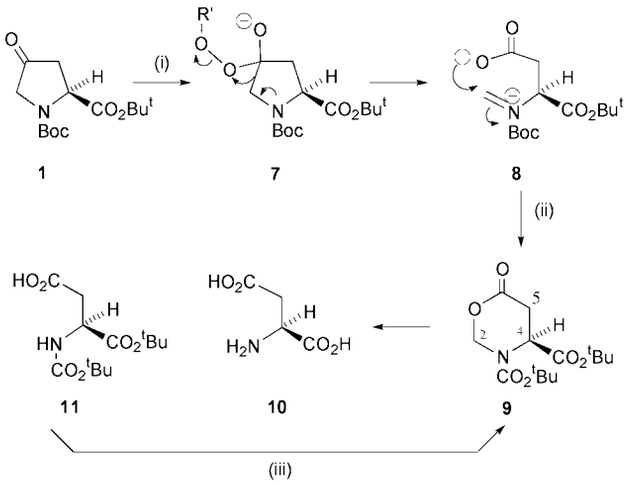
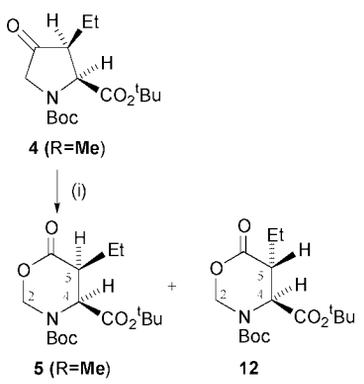
the regiospecificity of the Baeyer–Villiger reaction would be that it is controlled by involvement of the nitrogen lone pair in intermediate **7** to give the acyclic intermediate **8**, as suggested in Scheme 2.



Scheme 2 *Reagents*: (i) MCPBA–$CuOAc_2$; (ii) 6 M HCl; (iii) H_2CO–H^+.

Since the rearrangement had given us the desired oxazine, we now attempted to use the method to prepare oxazinones which were stereospecifically substituted at C-5, as shown in Scheme 3. The *cis* 3-ethyl derivative **4** (R = Me) was therefore

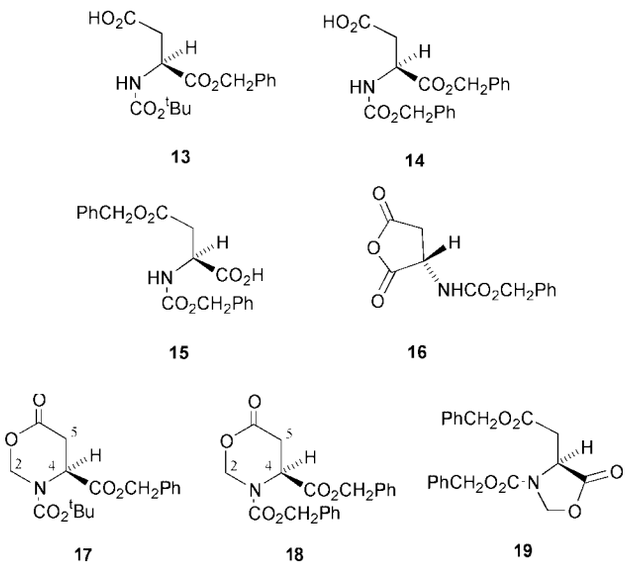


Scheme 3 *Reagents*: (i) MCPBA–$CuOAc_2$.

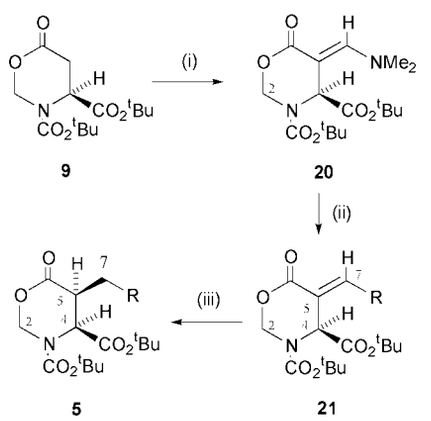
reacted with *m*-chloroperbenzoic acid and copper(II) acetate. The expected oxazinone **5** (R = Me) was obtained in only 12% yield at room temperature together with a 2% yield of the *trans* epimer **12**. The yield could be improved on heating to reflux but epimerisation at the β-centre was exacerbated.

Although there are obvious problems in our strategy of accessing stereospecifically alkylated aspartic acids from 3-ketoproline derivatives *via* the corresponding oxazinones, the possibility of using the oxazinones directly as chiral templates in the synthesis of these compounds remained attractive. We therefore examined the preparation of tetrahydro-1,3-oxazinones by an alternative and more straightforward method than our Baeyer–Villiger approach. We prepared the aspartate α-ester urethanes **11**[21] and **13**[22] by literature methods and the urethane α-ester **14** was prepared as a 3:1 mixture with the corresponding β-ester **15** by reaction of the anhydride **16** with benzyl alcohol. These compounds were reacted with an excess of paraformaldehyde in refluxing toluene in the presence of camphorsulfonic acid and 4 Å molecular sieves to yield the corresponding oxazinones **9**, **17** and **18** in good yields. The mixture of benzyl esters **14** and **15** was resolved at this stage by chromatographic separation of the oxazinone **18** from the oxazolone **19**.

We were now in a position to examine the use of our chiral templates in the preparation of stereospecifically β-substituted



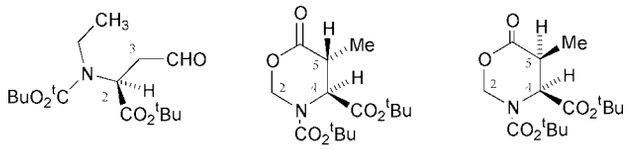
aspartic acids. When the oxazinone **9** was reacted with Bredereck's reagent, the enaminone **20** was obtained in 70% yield (Scheme 4). This was shown to be the single *E*-isomer by



Scheme 4 *Reagents and yields*: (i) $HC(NMe_2)_2O^tBu$; 70%; (ii) RMgBr; R = Me, 46%; R = Ph, 88%; (iii) H_2–Pd/C–EtOAc; >90%.

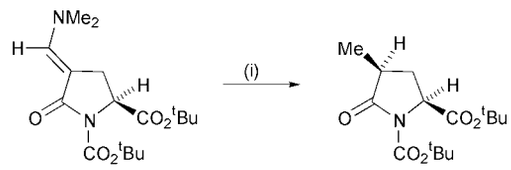
the NOE observed in the resonance due to the α-hydrogen, H-4, when the NMe_2 resonance was irradiated. Reaction of the enaminone **20** with MeMgBr in THF gave the *E*-isomer **21** (R = Me) in 46% yield accompanied by a by-product with the spectral characteristics of the aldehyde **22**. This presumably originated by reaction of the Grignard reagent with the oxazinone or its ring opened form analogous to **8**, followed by hydrolysis of the enaminone and decarboxylation of the resultant β-aldehydo acid in the work up. A similar by-product was not evident when the enaminone was reacted with PhMgBr, when an 88% yield of the *E*-isomer **21** (R = Ph) was obtained. NOE studies indicated that this was the *E*-isomer. Hydrogenation of the enones **21** in ethyl acetate using palladium on carbon as catalyst gave single isomers **5** in nearly quantitative yields. As the NMR spectra were complicated by rotational isomerism, the stereochemistry of **5** (R = Me) was proved by a single crystal X-ray structure determination[1,23] which showed the oxazine ring to be in a boat conformation and the side chain at C-5 to be *cis* to the ester at C-4. The stereochemistry of **5** (R = Ph) followed from the single crystal X-ray structure[1,23] of the *trans*-epimer **28** whose synthesis is reported below. Interestingly, when the *cis* isomer **5** (R = Me) was treated with LiI in DMF at 130 °C, epimerisation occurred giving 55% of the *trans*-epimer **12** together with 26% of the starting material **5** (R = Me).

When we reduced the enaminone **20** directly with hydrogen and palladium on charcoal in ethyl acetate, we obtained a



22 23 24

mixture of two compounds in the ratio 1.8 : 1 which were separable chromatographically. These proved to be the *trans* and *cis* isomers **23** and **24** respectively and so this reaction was not stereoselective as had been the case for the alkylated products **21**. In our work on the pyroglutamic acid series we had shown that reduction of the enaminone **25** led to a single diastereoisomer **26**[24] (Scheme 5), a reaction subsequently reproduced by

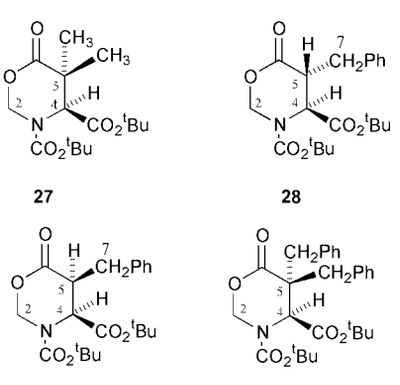


25 26

Scheme 5 (i) ref. 24.

Coudert *et al.*[25] using the corresponding methyl ester. We had confirmed the stereochemistry of our product **26** by NOE[24] and X-ray structure analysis[26] whilst Coudert *et al.*[25] used degradative methods. As we felt that the lack of diastereoselectivity might be due to the possibility of epimerisation at C-5 by the dimethylamine liberated in the reaction, we conducted the hydrogenation in the presence of acetic acid. The rate of the reaction appeared to be accelerated but there was still a 1 : 1 mixture of the diastereoisomers **23** and **24**.

As our Bredereck–Grignard–hydrogenation sequence had been so successful in obtaining single stereoisomers, it was of interest to study stereoselectivity in alkylation of the parent oxazinone **9**. Reaction with excess MeI and LHMDS at −20 °C gave a 52% yield of a mixture of the diastereoisomeric monomethyl derivatives **23** and **24** in a 1.3 : 1 ratio together with a 28% yield of the dialkylated product **27**. The overall stereoselectivity in the monoalkylation reaction proved to be *trans*. Use of KHMDS at −72 °C increased the *trans* : *cis* ratio to 3.9 : 1. Benzylation, which had been shown to be entirely *trans* selective in the pyroglutamic acid series,[27] was achieved by reacting the oxazinone **9** with excess benzyl bromide and either LHMDS or NaHMDS. In the oxazinone series, although the *trans* isomer was the predominant isomer, it was not exclusively so. The *trans* : *cis* ratio **28** : **5** (R = Ph) was 4 : 1 (LHMDS) and 4.4 : 1 (NaHMDS) and bisbenzylation to yield **29** was observed.



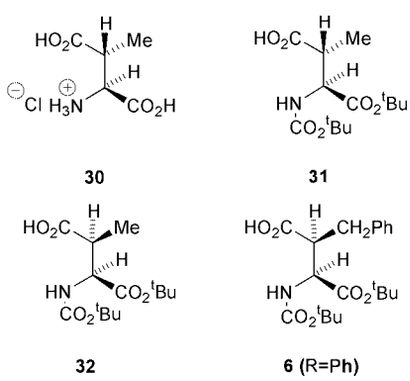
27 28

5 (R=Ph) 29

Treatment of the *trans*-methyloxazinone **23** with 6 M HCl at room temperature gave (2*S*,3*R*)-3-methylaspartic acid hydrochloride **30** as a single isomer in 80% yield and with analytical and spectral data in accord with the literature.[16] The stereochemistry of the centres C-4 and C-5 of the tetrahydro-1,3-oxazinone had therefore not been affected either during its formation, or on alkylation or deprotection.

The synthetic utility of the alkylated oxazinones would be enhanced if protection of the amine and α-ester groups could be retained in the aspartate products. Use of strong base for deprotection caused epimerisation, but when the oxazinone **23** was treated with 4 : 1 acetic acid : water at 45 °C *tert*-butyl (2*S*,3*R*)-*N*-*tert*-butoxycarbonyl-3-methylaspartate **31** was obtained pure in 56% yield. Hydrolysis of the epimer **24** gave the pure (2*S*,3*S*)-isomer **32** in 53% yield under these conditions. Reaction of **5** (R = Ph) with 4 : 1 acetic acid : water at 45 °C gave (2*S*,3*S*)-3-benzyl-*N*-*tert*-butoxycarbonylaspartic acid **6** (R = Ph) in 51% yield. Regioselective deprotection could also be effected using one equivalent of aqueous LiOOH in THF, as under these conditions, the oxazinone **23** gave *tert*-butyl (2*S*,3*R*)-*N*-*tert*-butoxycarbonyl-3-methylaspartate **32** in 40% yield as a single stereoisomer.

We have developed two new strategies for the synthesis of free β-substituted aspartic acids and their α-bis-protected derivatives, using tetrahydro-1,3-oxazin-6-ones as chiral templates. One, the enaminone–Grignard strategy, is entirely stereoselective, giving the *cis* products. The method is therefore complementary to the β-lactam strategy[13–16] which gives the *trans* aspartates. Our second strategy, involving alkylation, gives mixtures of diastereoisomers with *trans* products predominating.



30 31

32 6 (R=Ph)

Experimental

Melting points were determined on a Kofler hot stage and optical rotations (in units of 10^{-1} deg cm^2 g^{-1}) on a Perkin-Elmer PE 241 polarimeter using a 1 dm path length. IR spectra were recorded on a Perkin-Elmer 1710 Fourier transform instrument. ^{1}H NMR spectra were determined on Bruker DPX 300 (300 MHz), WM 360 (360 MHz) or AMX 500 (500 MHz) FT instruments and ^{13}C NMR spectra (^{1}H decoupled) on Bruker AC-P 250 (62.9 MHz), DPX 300 (75.5 MHz) or AMX-500 (125.8 MHz) instruments with INEPT experiments to help assign the spectra and residual solvent peaks as internal references. NOE experiments were recorded by Dr A. G. Avent on a Bruker AMX 500 FT instrument. *J* values are given in Hz. Mass spectra were recorded on Kratos MF 80RF or Fisons VG-Autospec instruments by Mr A. M. Greenway and Dr A. Abdul-Sada (Sussex) and on Kratos MS50 and Fisons VG BIO Q instruments by Drs D. Dell and D. Cooper at Wellcome Research Laboratories. 3-NBA refers to 3-nitrobenzyl alcohol. Accurate mass measurements were obtained from the EPSRC Central Mass Spectrometry Service, Swansea or from Dr S. Chotai (Wellcome) and microanalyses were performed by Medac Ltd and by Miss W. C. Man and Mrs C. Lawless (Wellcome). Column chromatography was performed using Merck Kieselgel 60 (230–400 mesh - Art 9385), Sorbsil C60 40/60 A and Fluka Silica Gel 60 (220–440 mesh). Petroleum ether refers throughout to a fraction of alkanes, bp 60–80 °C. Non aqueous

reactions were conducted in oven-dried glassware under an atmosphere of nitrogen.

(4*S*)-3,4-Bis(*tert*-butoxycarbonyl)tetrahydro-1,3-oxazin-6-one, 9

Method A. From *tert*-butyl (2*S*)-*N*-*tert*-butoxycarbonyl-4-oxoproline, 1, by Baeyer–Villiger reaction. *m*-Chloroperbenzoic acid (50–60%, 25 g, 72–87 mmol) followed by copper(II) acetate monohydrate (2 g, 10 mmol) was added to a solution of *tert*-butyl (2*S*)-*N*-*tert*-butoxycarbonyl-4-oxoproline **1**[18] (19 g, 66.7 mmol) in 1,2-dichloroethane (110 ml). The reaction was stirred overnight at room temperature. A further portion of *m*-chloroperbenzoic acid (50–60%, 10 g, 29–35 mmol) was added and the mixture was stirred for a further 5 h. The white solid was filtered off and the filtrate was concentrated, extracted with ethyl acetate and washed with saturated aqueous $NaHCO_3$, water and brine and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel, eluting with petroleum ether–ethyl acetate (84:16) to give *(4S)-3,4-bis(tert-butoxycarbonyl)tetrahydro-1,3-oxazin-6-one* **9** as a white solid which was recrystallised from petroleum ether (15.9 g, 79%); mp 84–85 °C; $[\alpha]_D^{25}$ −120.14 (*c* 1, $CHCl_3$) (Found: C, 55.9; H, 7.9; N, 4.6. $C_{14}H_{23}NO_6$ requires C, 55.8; H, 7.7; N, 4.6%); *m/z* (CI-NH_3) 319 ($[M + NH_4]^+$) and 302 ($[M + H]^+$); ν_{max} (KBr)/cm^{-1} 1770 (lactone), 1743 (ester) and 1710 (urethane); δ_H (500 MHz, C^2HCl_3, 2 rotational isomers at −30 °C) (*First rotamer*, 71%) 1.44 (18H, m, $C(CH_3)_3$), 2.79 (1H, dd, $J_{5A,4}$ 11.3, $J_{5A,5B}$ 15.7, H-5A), 3.04 (1H, dd, $J_{5B,4}$ 6.9, $J_{5B,5A}$ 15.7, H-5B), 4.40 (1H, dd, $J_{4,5B}$ 6.9, $J_{4,5A}$ 11.3, H-4), 5.19 (1H, d, $J_{2A,2B}$ 10.5, H-2A) and 5.89 (1H, d, $J_{2B,2A}$ 10.5, H-2B) (*Second rotamer*, 29%) 1.44 (18H, m, $C(CH_3)_3$), 2.80 (1H, dd, $J_{5A,4}$ 10.5, $J_{5A,5B}$ 16.00, H-5A), 3.11 (1H, dd, $J_{5B,4}$ 7.6, $J_{5B,5A}$ 16.0, H-5B), 4.53 (1H, dd, $J_{4,5B}$ 7.6, $J_{4,5A}$ 10.5, H-4), 5.23 (1H, d, $J_{2A,2B}$ 10.7, H-2A) and 5.75 (1H, d, $J_{2B,2A}$ 10.7, H-2B); δ_C (125.8 MHz, C^2HCl_3, 2 rotational isomers at −30 °C) 27.63 and 27.67 ($C(CH_3)_3$), 27.84 and 27.87 ($C(CH_3)_3$), 31.94 (C-5), 51.42 and 52.21 (C-4) 72.32 and 73.22 (C-2), 82.50 and 82.73 ($OC(CH_3)_3$), 82.89 and 83.00 ($OC(CH_3)_3$), 152.11 and 152.26 (urethane), 168.92 and 169.08 (ester) and 169.14 (lactone).

Stereochemistry of 9 by hydrolysis to (2*S*)-aspartic acid, 10. Hydrochloric acid (6 M, 2 ml) was added to a solution of (4*S*)-3,4-bis(*tert*-butoxycarbonyl)tetrahydro-1,3-oxazin-6-one **9** (50 mg, 0.17 mmol) in tetrahydrofuran (2 ml). After stirring overnight at room temperature, the solvent was removed *in vacuo* to give a brown solid (33 mg, quantitative) with an identical ^1H NMR spectrum to that of commercial *L-aspartic acid hydrochloride*; $[\alpha]_D^{25}$ +13.1 (*c* 0.7, H_2O), (commercial L-aspartic acid hydrochloride. $[\alpha]_D^{25}$ +14.2 (*c* 1, H_2O)).

Method B. Reaction of 1-*tert*-butyl (2*S*)-*N*-butoxycarbonyl-aspartate, 11, with formaldehyde. 1-*tert*-Butyl (2*S*)-*N*-butoxycarbonylaspartate **11**[21] (11.3 g, 39.1 mmol) was dissolved in dry toluene (220 ml) under nitrogen. Paraformaldehyde (5.47 g, 182 mmol), camphorsulfonic acid (1.8 g, 7.82 mmol) and 4 Å activated molecular sieves (24 g) were successively added. The mixture was stirred for 3 h at 90 °C and filtered through Celite® at room temperature. The organic layer was washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (10, 15, 20%) as eluent to afford *(4S)-3,4-bis(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **9** as a white crystalline solid (7.1 g, 60%); mp 72–73 °C, $[\alpha]_D^{25}$ −111.1 (*c* 1, $CHCl_3$) with identical spectra to the sample prepared by method A.

Baeyer–Villiger reaction on compound 4 (R = Me). *m*-Chloroperbenzoic acid (50–60%, 800 mg, 2.3–2.8 mmol) was added to a solution of crude *tert*-butyl (2*S*,3*S*)-*N*-*tert*-butoxycarbonyl-3-ethyl-4-oxoproline **4** (R = Me)[18] (670 mg 2.2 mmol) in 1,2-dichloroethane (10 ml) followed by copper(II) acetate monohydrate (70 mg, 0.35 mmol). The mixture was stirred for 40 h at room temperature, further *m*-chloroperbenzoic acid (50–60%, 400 mg, 1.1–1.4 mmol) was added and the mixture was stirred for a further 20 h. The mixture was filtered, the solvent was removed *in vacuo* from the filtrate, and the residue was chromatographed on silica gel, eluting with a gradient of petroleum ether–ethyl acetate (9:1 to 8:2) to give *(4S,5S)-3,4-bis(tert-butoxycarbonyl)-5-ethyltetrahydro-1,3-oxazin-6-one* **5** (R = Me) (87 mg, 12%) together with the epimer *(4S,5R)-3,4-bis(tert-butoxycarbonyl)-5-ethyltetrahydro-1,3-oxazin-6-one* **12** (12 mg, 2%) and starting material (140 mg, 21%). The new compounds had identical spectra to those reported below for samples prepared by independent methods.

(2*S*)-1-Benzyl and (2*S*)-4-benzyl *N*-benzyloxycarbonylaspartate, 14 and 15

(2*S*)-*N*-Benzyloxycarbonylaspartic acid (24.4 g, 91.1 mmol), dimethylaminopyridine (1.1 g, 9.0 mmol) and dry benzyl alcohol (14.2 ml, 137 mmol) were dissolved in dry dichloromethane (460 ml) and cooled to 0 °C under nitrogen. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (17.5 g, 91.3 mmol) was added with stirring. Stirring was continued at 0 °C for 2 h and at room temperature for 18 h. The mixture was washed with 0.5 M aqueous hydrochloride acid and water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of dichloromethane–methanol (0, 1 and 2%) as eluent to afford a 1:3 mixture of *(2S)-4-benzyl and (2S)-1-benzyl N-benzyloxycarbonylaspartate* **14** and **15** as a white solid (25.5 g, 78%); *m/z* [+ve FAB (3-NBA)] 358 ($[M + H]^+$) and 380 ($[M + Na]^+$); δ_H (300 MHz, C^2HCl_3) 9.48 (1H, br s, CO_2H), 7.31 (5H, s, ArH), 7.29 (5H, s, ArH), 5.76 (1H, d, $J_{NH,2}$ 8.3, NH), 5.15 (30% of 4H, s, CH_2Ph), 5.09 (70% of 4H, s, CH_2Ph), 4.67–4.64 (1H, m, H-2), 3.09 (1H, dd, $J_{3A,3B}$ 17.7, $J_{3A,2}$ 4.1, H-3A) and 2.89 (1H, dd, $J_{3B,3A}$ 17.7, $J_{3B,2}$ 4.3, H-3B); δ_C (75.5 MHz, C^2HCl_3) 175.9 (acid), 170.5 (ester), 156.1 (urethane), 135.9, 135.0, 128.6, 128.5, 128.4, 128.3, 128.2 and 128.1 (Ar), 67.7 and 67.3 (CH_2Ph), 50.3 (C-2) and 36.4 (C-3).

(4*S*)-3,4-Bis(benzyloxycarbonyl)-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one, 18

The mixture 4-benzyl and 1-benzyl (2*S*)-*N*-benzyloxycarbonylaspartate **14** and **15** (1 g, 2.8 mmol) was dissolved in dry toluene (20 ml) under nitrogen. Paraformaldehyde (392 mg, 13.1 mmol), camphorsulfonic acid (130 mg, 0.56 mmol) and 4 Å activated molecular sieves (1.7 g) were successively added. The mixture was stirred for 4 h at 90 °C and filtered through Celite® at room temperature. The organic layer was washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (10, 15, 20%) as eluent to afford *(4S)-benzyl 2-(3-benzyloxycarbonyl-5-oxo-1,3-oxazolidin-4-yl)acetate* **19** as an oil (196 mg, 19%) which was discarded and *(4S)-3,4-bis(benzyloxycarbonyl)-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **18** as a colourless oil which crystallised on long standing (633 mg, 62%); $[\alpha]_D^{25}$ −77.4 (*c* 1, $CHCl_3$) (Found: C, 64.9; H, 5.2; N, 3.75. $C_{20}H_{19}NO_6$ requires C, 65.0; H, 5.2; N, 3.8%); *m/z* [+ve FAB (3-NBA)] 370 ($[M + H]^+$) and 392 ($[M + Na]^+$); ν_{max} (film)/cm^{-1} 1752 (lactone/ester) and 1719 (urethane); δ_H (500 MHz, C^2HCl_3, 2 rotamers at −15 °C) (*First rotamer* 53%) 7.48–7.22 (10H, m, ArH), 5.94 (1H, d, $J_{2A,2B}$ 10.5, H-2A), 5.28–5.08 (5H, m, H-2B and 2 × CH_2Ph), 4.68 (1H, dd, $J_{4,5A}$ 10.7, $J_{4,5B}$ 7.2, H-4), 3.07 (1H, dd, $J_{5A,5B}$ 16.1, $J_{5S,4}$ 7.2, H-5A), 2.85 (1H, dd, $J_{5B,5A}$ 16.1, $J_{5B,4}$ 10.7, H-5B) (*Second rotamer* 47%) 7.48–7.22 (10H, m, ArH), 5.83 (1H, d, $J_{2A,2B}$ 10.9, H-2A), 5.28–5.08 (5H, m, H-2B and 2 × CH_2Ph), 4.82 (1H, dd, $J_{4,5B}$ 10.8,

$J_{4,5A}$ 7.6, H-4), 3.15 (1H, dd, $J_{5A,5B}$ 16.1, $J_{5S,4}$ 7.6, H-5A) and 2.84 (1H, dd, $J_{5B,5A}$ 16.1, $J_{5B,4}$ 10.8, H-5B); δ_C (125.8 MHz, C^2HCl_3, 2 rotational isomers at −34 °C) 169.7 and 169.5 (ester/lactone), 168.0 and 167.9 (ester/lactone), 153.3 and 153.2 (urethane), 134.7, 134.5, 134.3, 134.2, 128.8, 128.7, 128.6, 128.5 and 128.0 (Ar), 72.7 and 72.6 (C-2), 68.6, 68.3 and 67.7 (CH_2Ph), 51.6 and 51.2 (C-4), and 31.6 and 31.5 (C-5).

(4*S*)-4-Benzyloxycarbonyl-3-*tert*-butoxycarbonyl-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one, 17

1-Benzyl (2*S*)-*N*-*tert*-butoxycarbonylaspartate **13**[22] (6.3 g, 19.5 mmol) was dissolved in dry toluene (110 ml) under nitrogen. Paraformaldehyde (2.8 g, 93.3 mmol), camphorsulfonic acid (1 g, 4 mmol) and 4 Å activated molecular sieves (12 mg) were successively added. The mixture was stirred for 4 h at 90 °C and filtered through Celite® at room temperature. The organic layer was washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (10, 15, 20%) as eluent to afford *(4S)-4-benzyloxycarbonyl-3-tert-butoxycarbonyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **17** as a colourless oil which crystallised on long standing (3.9 g, 60%); mp 49–50 °C; $[\alpha]_D^{25}$ −93.0 (*c* 1, $CHCl_3$) (Found: C, 60.9; H, 6.3; N, 4.1. $C_{17}H_{21}NO_6$ requires C, 60.9; H, 6.3; N, 4.2%); *m/z* [+ve FAB (3-NBA)] 336 ($[M + H]^+$) and 358 ($[M + Na]^+$); ν_{max} (film)/cm^{-1} 1773 (lactone/ester) and 1719 (urethane); δ_H (500 MHz, C^2HCl_3, 2 rotational isomers at −15 °C) (*First rotamer* 55%) 7.41–7.32 (5H, m, ArH), 5.94 (1H, d, $J_{2A,2B}$ 10.5, H-2A), 5.26–5.10 (3H, m, H-2B and CH_2Ph), 4.51 (1H, dd, $J_{4,5B}$ 11.0, $J_{4,5A}$ 7.1, H-4), 3.05 (1H, dd, $J_{5A,5B}$ 16.0, $J_{5A,4}$ 7.1, H-5A), 2.81 (1H, dd, $J_{5B,5A}$ 16.0, $J_{5B,4}$ 11.0, H-5B) and 1.34 (9H, s, OC(CH_3)$_3$) (*Second rotamer* 45%) 7.41–7.32 (5H, m, ArH), 5.81 (1H, d, $J_{2A,2B}$ 10.8, H-2A), 5.26–5.10 (3H, m, H-2B and CH_2Ph), 4.61 (1H, dd, $J_{4,5B}$ 10.7, $J_{4,5A}$ 7.5, H-4), 3.12 (1H, dd, $J_{5A,5B}$ 16.2, $J_{5A,4}$ 7.5, H-5A), 2.83 (1H, dd, $J_{5B,5A}$ 16.2, $J_{5B,4}$ 10.7, H-5B) and 1.47 (9H, s, OC(CH_3)$_3$); δ_C (125.8 MHz, C^2HCl_3, 2 rotational isomers at −15 °C) 168.8, 168.4 and 168.2 (ester/lactone), 153.4 and 153.2 (urethane), 134.7, 134.6, 128.6, 128.5, 128.4, 128.3 and 128.0 (Ar), 83.3 and 83.1 (O*C*(CH$_3$)$_3$), 72.8 and 72.7 (C-2), 68.5 and 68.3 (CH_2Ph), 52.1 and 51.8 (C-4), 31.9 (C-5) and 27.7 and 27.5 (OC(*C*H$_3$)$_3$).

(4*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-(dimethylaminomethylene)tetrahydro-1,3-oxazin-6-one, 20

tert-Butoxybis(dimethylamino)methane (Bredereck's reagent) (33 ml, 160 mmol) was added to a solution of (4*S*)-3,4-bis(*tert*-butoxycarbonyl)tetrahydro-1,3-oxazin-6-one **9** (15.8 g, 52.5 mmol) in dry dimethoxyethane (350 ml). The solution was heated at reflux for 1 h and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel, eluting with petroleum ether–ethyl acetate (1:2). The product was recrystallised from petroleum ether to give a white solid (12 g). Further chromatography of the mother liquors afforded further material (1.1 g) (total yield 13.1 g, 70%); mp 101–102 °C; $[\alpha]_D^{25}$ +79.41 (*c* 1, $CHCl_3$) (Found C, 56.9; H, 7.9; N, 7.7. $C_{17}H_{28}N_2O_6$requires C, 57.3; H, 7.9; N, 7.9%) (*m/z* (EI) 356.19379. $C_{17}H_{28}N_2O_6$requires 356.1946); λ_{max} MeOH/nm 296; ν_{max} (KBr)/cm^{-1} 1730 (ester), 1710 (urethane) and 1688 (lactone); δ_H (500 MHz, C^2HCl_3, 2 rotational isomers at −34 °C) (*First rotamer*, 70%) 7.69 (1H, s, HC=), 5.69 (1H, s, H-4), 5.49 (1H, d, $J_{2A,2B}$ 10.2, H-2A), 5.21 (1H, d, $J_{2B,2A}$ 10.2, H-2B), 3.16 (6H, s, N(CH$_3$)$_2$), 1.45 (9H, s, OC(CH_3)$_3$) and 1.42 (9H, s, OC(CH_3)$_3$) (*Second rotamer*, 30%) 7.57 (1H, s, HC=), 5.42 (1H, s, H-4), 5.40 (1H, d, $J_{2A,2B}$ 9.7, H-2A), 5.28 (1H, d, $J_{2B,2A}$ 9.7, H-2B), 3.18 (6H, s, N(CH$_3$)$_2$), 1.44 (9H, s, OC(CH_3)$_3$) and 1.40 (9H, s, OC(CH_3)$_3$); the geometry of the enaminone was assigned on the basis of NOE difference spectra at 25 °C as irradiation of the N(CH$_3$)$_2$ singlet resulted in a NOE of 16.6% in the H-4 singlets and of 13.5% in the ethylenic singlets, whilst irradiation of the ethylenic singlets resulted in a NOE of 1.3% in the N(CH$_3$)$_2$ singlet; δ_C (125.8 MHz, C^2HCl_3, 2 rotational isomers at −34 °C) 27.56 and 27.89 (C(*C*H$_3$)$_3$), 52.49 and 54.01 (N(CH$_3$)$_2$), 71.30 and 72.09 (C-2), 81.77 and 82.02 (O*C*(CH$_3$)$_3$), 82.32 and 82.47 (O*C*(CH$_3$)$_3$), 84.61 and 84.93 (C-5), 151.58 and 152.27 (H*C*=), 152.68 (urethane), 168.20 and 169.42 (ester), and 169.62 and 169.85 (lactone).

(4*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-ethylidenetetrahydro-1,3-oxazin-6-one, 21 (R = Me)

A solution of methylmagnesium bromide (3 M in tetrahydrofuran, 34 ml, 102 mmol) was added dropwise to a solution of (4*S*)-3,4-bis(*tert*-butoxycarbonyl)-5-(dimethylaminomethylene)-tetrahydro-1,3-oxazin-6-one **20** (12 g, 33.7 mmol) in dry ether (400 ml) cooled to −78 °C, under nitrogen. The mixture was stirred for 15 min at this temperature and for 5 h at 0 °C. The reaction was quenched by addition of saturated aqueous NH_4Cl and the ether layer was washed with water, brine and dried (Na_2SO_4). The solvent was removed *in vacuo*. Chromatography on silica gel, eluting with petroleum ether–ethyl acetate (85:15) afforded *(4S)-3,4-bis(tert-butoxycarbonyl)-5-ethylidenetetrahydro-1,3-oxazin-6-one* **21** (R = Me) as a colourless oil (5.33 g, 48%); $[\alpha]_D^{20}$ +26.11 (*c* 1, $CHCl_3$) (*m/z* (EI) (M + H−Boc) 227.11428. $C_{11}H_{17}NO_4$ requires 227.11569); *m/z* (FAB) 328 ($[M + H]^+$); ν_{max}(film)/cm^{-1} 1741 (ester/lactone) and 1713 (urethane); δ_H (500 MHz, C^2HCl_3, 2 rotational isomers at −34 °C) (*First rotamer*, 69%) 1.42 (18H, s, C(CH_3)$_3$), 1.97 (3H, d, *J* 7.4, CH$_3$), 5.59 (1H, s, H-4), and 5.42 (1H, d, $J_{2A,2B}$ 10.5, H-2A), 5.62 (1H, d, $J_{2B,2A}$ 10.5, H-2B) and 7.39 (1H, q, *J* 7.4, HC=) (*Second rotamer*, 31%) 1.45 (18H, s, C(CH_3)$_3$), 1.97 (3H, d, *J* 7.4, CH$_3$), 5.26 (1H, s, H-4), 5.37 (1H, d, $J_{2A,2B}$ 10.1, H-2A), 5.55 (1H, d, $J_{2B,2A}$ 10.1, H-2B) and 7.23 (1H, q, *J* 7.4, HC=); the geometry of the ethylidene group was assigned on the basis of NOE difference spectra at 273 K, irradiation of the CH$_3$ doublet resulting in a NOE of 10.5% in the H-4 singlets and of 9.3% in the ethylenic multiplets, while irradiation of the ethylenic multiplets gave a NOE of 2.5% in the CH$_3$ doublet; δ_C (125.8 MHz, C^2HCl_3, 2 rotational isomers at −34 °C) 15.18 and 15.82 (*C*H$_3$), 27.62 and 27.66 (C(*C*H$_3$)$_3$), 27.88 (C(*C*H$_3$)$_3$), 53.81 and 55.81 (C-4), 71.99 and 73.08 (C-2), 82.61 and 82.77 (O*C*(CH$_3$)$_3$), 83.16 and 83.47 (O*C*(CH$_3$)$_3$), 122.05 and 122.48 (*C*=), 145.46 and 146.98 (H*C*=), 152.05 and 152.26 (urethane), 163.91 and 165.01 (ester), and 167.23 and 167.27 (lactone). A further product, *tert-butyl N-tert-butoxycarbonyl-N-ethyl-aspart-4-al* **22**, was a colourless oil (1.76 g 17%); $[\alpha]_D^{20}$ −2.20 (*c* 1, $CHCl_3$) (*m/z* (EI) 200.12783 ($[M-Boc]^+$). $C_{10}H_{18}NO_3$ requires 200.1286); *m/z* (FAB) 302 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 1703 (urethane/aldehyde) and 1725 (ester); δ_H (360 MHz, C^2HCl_3, 2 rotational isomers) (*First rotamer*, 56%) 1.15 (3H, t, *J* 7, CH$_3$), 1.45 (18H, s, C(CH_3)$_3$), 2.88 (1H, dd, $J_{3A,3B}$ 17.9, $J_{3A,2}$ 7, H-3A), 3.12 (1H, 2qd, J_{AB} 14, *J* 7, CH_A-CH$_3$), 3.37 (1H, dd, $J_{3B,2}$ 7.2, $J_{3B,3A}$ 17.9, H-3B), 3.45 (1H, 2qd, J_{AB} 14, *J* 7, CH_B-CH$_3$), 4.31–4.35 (1H, m, H-2), and 9.80 (1H, s, CHO) (*Second rotamer*, 44%) 1.15 (3H, t, *J* 7, CH$_3$), 1.45 (18H, s, C(CH_3)$_3$), 2.74 (1H, dd, $J_{3A,3B}$ 17.9, $J_{3A,2}$ 5.4, H-3A), 3.20 (1H, qd, J_{AB} 14, *J* 7, CH_A-CH$_3$), 3.53 (1H, qd, J_{BA} 14, *J* 7, CH_B-CH$_3$), 4.31–4.35 (1H, m, H-2) and 9.80 (1H, s, CHO); δ_C (125.8 MHz, C^2HCl_3, 2 rotational isomers) 13.50 and 13.85 (CH$_3$), 27.54 and 27.71 (C(*C*H$_3$)$_3$), 28.14 (C(*C*H$_3$)$_3$), 44.19 and 45.47 (*C*H$_2$-CH$_3$), 44.40 (C-3), 79.88 and 80.65 (O*C*(CH$_3$)$_3$), 81.55 and 81.9 (O*C*(CH$_3$)$_3$), 154.02 and 154.55 (urethane), 169.62 and 169.92 (ester), and 199.89 and 200.74 (CHO).

(4*S*,5*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-ethyltetrahydro-1,3-oxazin-6-one, 5 (R = Me)

(4*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-ethylidenetetrahydro-1,3-oxazin-6-one **21** (R = Me) (5.33 g, 16.7 mmol) was hydrogenated in ethyl acetate (100 ml) for 2 h in the presence of 10%

palladium on activated carbon (1.4 g). After a filtration on Celite®, the solvent was removed from the filtrate *in vacuo* and the residue was chromatographed on silica gel, eluting with petroleum ether–ethyl acetate (8:2) to give *(4S,5S)-3,4-bis(tert-butoxycarbonyl)-5-ethyltetrahydro-1,3-oxazin-6-one* **5** (R = Me) as a white solid (5.06 g, 95%); mp 67–68 °C; $[\alpha]_D^{20}$ +107.77 (*c* 1, $CHCl_3$) (Found: C, 57.9; H, 8.2; N, 4.2. $C_{16}H_{27}NO_6$ requires C, 58.3; H, 8.3; N, 4.3%) (*m/z* (EI) 229.13051 ($[M-Boc]^+$). $C_{11}H_{19}NO_4$ requires 229.1313); ν_{max} (KBr)/cm^{-1} 1772 (lactone), 1741 (ester) and 1713 (urethane); δ_H (360 MHz, C^2HCl_3, 2 rotational isomers) (*First rotamer*, 56%) 1.07 (3H, t, *J* 7.5, CH_3), 1.43 (18H, m, $C(CH_3)_3$), 1.6–1.9 (2H, m, CH_2-CH_3), 2.78 (1H, m, H-5), 4.36 (1H, d, $J_{4,5}$ 7.0, H-4), 5.13 and 5.88 (2H, 2 × d, $J_{2A,2B}$ 10.1, H-2) (*Second rotamer*) 1.07 (3H, t, *J* 7.5, CH_3), 1.43 (18H, m, $C(CH_3)_3$), 4.39 (1H, d, $J_{4,5}$ 7.15, H-4), 5.17 and 5.73 (2H, 2 × d, $J_{2A,2B}$ 10.1, H-2); δ_C (62.9 MHz, C^2HCl_3, 2 rotational isomers) 11.80 (CH_3-CH_2), 19.47 (CH_2-CH_3), 27.6, 27.78 and 28.08 ($C(CH_3)_3$), 42.39 (C-5), 57.92 and 58.22 (C-4), 71.52 and 72.03 (C-2), 82.53 and 82.94 ($C(CH_3)_3$), 152.42 (urethane), 167.53 (ester) and 170.55 (lactone). The X-ray crystal structure data for this compound have been lodged at the CCDC,[23] with reference code KAGJUX.

(4*S*,5*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-benzylidene-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one, 21 (R = Ph)

(4*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-(dimethylaminomethylene)-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one **20** (1.0 g, 2.81 mmol) was dissolved in diethyl ether (30 ml) and cooled to −30 °C under nitrogen. Phenylmagnesium bromide (3.0 M in diethyl ether, 2.81 ml, 8.43 mmol) was added dropwise with stirring. The mixture was allowed to warm to room temperature over a period of 1.5 h. After stirring at 22 °C for 45 min, the mixture was quenched with excess saturated aqueous ammonium chloride at room temperature and extracted with ethyl acetate. The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (5, 10%) as eluent to afford *(4S,5S)-3,4-bis(tert-butoxycarbonyl)-5-benzylidene-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **21** (R = Ph) as an oil (0.96 g, 88%); $[\alpha]_D^{25}$ +77.7 (*c* 1, $CHCl_3$) (*m/z* (FAB) (3-NBA) Found: 390.1882. $C_{21}H_{28}NO_6$ ($[M + H]^+$) requires 390.1917); *m/z* [+ve FAB (3-NBA)] 390 ($[M + H]^+$) and 412 ($[M + Na]^+$); ν_{max} (film)/cm^{-1} 1739 (br, ester/lactone) and 1719 (urethane); δ_H (500 MHz, C^2HCl_3, 2 rotamers at −20 °C) (*First rotamer*, 59%) 7.87 (1H, s, HC=), 7.65–7.63 (2H, m, ArH), 7.46–7.45 (1H, m, ArH), 7.41–7.40 (2H, m, ArH), 5.70 (1H, s, H-4), 5.55 (1H, d, $J_{2A,2B}$ 10.3, H-2A), 5.28 (1H, d, $J_{2B,2A}$ 10.3, H-2B), 1.46 (9H, s, $OC(CH_3)_3$) and 1.36 (9H, s, $OC(CH_3)_3$) (*Second rotamer*, 41%) 7.78 (1H, s, HC=), 7.65–7.63 (2H, m, ArH), 7.46–7.45 (1H, m, ArH), 7.41–7.40 (2H, m, ArH), 5.67 (1H, d, $J_{2A,2B}$ 10.1, H-2A), 5.51 (1H, s, H-4), 5.18 (1H, d, $J_{2B,2A}$ 10.1, H-2B), 1.42 (9H, s, $OC(CH_3)_3$) and 1.40 (9H, s, $OC(CH_3)_3$); δ_C (125.8 MHz, C^2HCl_3, 2 rotamers at −15 °C) 167.2 (ester), 152.0 (urethane), 144.8 and 143.8 (HC=), 132.7, 132.6, 130.4, 130.3, 130.2, 129.9, 128.8 and 128.7 (Ar), 122.1 and 121.3 (C-5), 83.7, 83.5, 82.9 and 82.7 ($OC(CH_3)_3$), 72.7 and 71.9 (C-2), 56.8 and 55.7 (C-4) and 27.9, 27.8, 27.6 and 27.4 ($OC(CH_3)_3$).

(4*S*,5*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-benzyl-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one, 5 (R = Ph)

Method A. By catalytic hydrogenation of 21 (R = Ph). (4*S*,5*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-benzylidene-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one **21** (R = Ph) (880 mg, 2.26 mmol) was dissolved in ethyl acetate (25 ml) and 10% palladium on carbon (220 mg, 25% w/w) was added. The reaction was stirred under an atmosphere of hydrogen for 3 days at room temperature and filtered through Celite®. The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (5, 10, 15%) as eluent to afford *(4S,5S)-3,4-bis(tert-butoxycarbonyl)-5-benzyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **5** (R = Ph) (797 mg, 90%) as a white crystalline solid; mp 100–101 °C; $[\alpha]_D^{25}$ −15.8 (*c* 1, $CHCl_3$) (Found: C, 64.6; H, 7.5; N, 3.5. $C_{21}H_{29}NO_6$ requires C, 64.4; H, 7.4; N, 3.6%); *m/z* [+ve FAB (3-NBA)] 392 ($[M + H]^+$) and 414 ($[M + Na]^+$); ν_{max} (film)/cm^{-1} 1772 (lactone), 1740 (ester) and 1713 (urethane); δ_H (500 MHz, C^2HCl_3, 2 rotamers at −25 °C) (*First rotamer*, 53%) 7.34–7.25 (5H, m, ArH), 5.95 (1H, d, $J_{2A,2B}$ 10.3, H-2A), 5.13 (1H, d, $J_{2B,2A}$ 10.3, H-2B), 4.27 (1H, d, $J_{4,5}$ 6.7, H-4), 3.26 (1H, dd, $J_{7A,7B}$ 14.4, $J_{7A,5}$ 5.0, H-7A), 3.18–3.14 (1H, m, H-5), 2.64 (1H, dd, $J_{7B,7A}$ 14.4, $J_{7B,5}$ 8.7, H-7B), 1.52 (9H, s, $OC(CH_3)_3$) and 1.43 (9H, s, $OC(CH_3)_3$) (*Second rotamer*, 47%) 7.34–7.25 (5H, m, ArH), 5.79 (1H, d, $J_{2A,2B}$ 10.3, H-2A), 5.07 (1H, d, $J_{2B,2A}$ 10.3, H-2B), 4.32 (1H, d, $J_{4,5}$ 6.8, H-4), 3.26 (1H, dd, $J_{7A,7B}$ 14.4, $J_{7A,5}$ 5.0, H-7A), 3.18–3.14 (1H, m, H-5), 2.68 (1H, dd, $J_{7B,7A}$ 14.4, $J_{7B,5}$ 8.9, H-7B), 1.50 (9H, s, $OC(CH_3)_3$) and 1.45 (9H, s, $OC(CH_3)_3$); δ_C (125.8 MHz, C^2HCl_3, 2 rotamers at −25 °C) 170.8 and 170.7 (lactone), 167.9 and 167.5 (ester), 152.2 and 152.1 (urethane), 137.3, 129.3, 129.2, 128.6, 128.5 and 126.8 (Ar), 83.3, 83.0, 82.7 and 82.5 ($OC(CH_3)_3$), 72.0, 71.4 (C-2), 57.6 and 57.2 (C-4), 43.2 (C-5), 31.1 and 31.0 (CH_2Ph), and 27.9, 27.8, 27.6 and 27.5 ($OC(CH_3)_3$).

(4*S*,5*R*)-3,4-Bis(*tert*-butoxycarbonyl)-5-ethyltetrahydro-1,3-oxazin-6-one, 12

Lithium iodide (320 mg, 2.1 mmol) was added to a solution of (4*S*,5*S*)-3,4-bis(*tert*-butoxycarbonyl)-5-ethyltetrahydro-1,3-oxazin-6-one **5** (R = Me) (80 mg, 0.24 mmol) in dimethylformamide (8 ml) and the mixture was stirred at 130 °C until no further reaction was observed by TLC (6 h). The solution was concentrated and extracted with ethyl acetate. The extracts were washed with water and dried (Na_2SO_4). The solvents were removed *in vacuo* and the residue was chromatographed on silica gel. Elution with petroleum ether–ethyl acetate (85:15) afforded *(4S,5R)-3,4-bis(tert-butoxycarbonyl)-5-ethyltetrahydro-1,3-oxazin-6-one* **12** as a colourless oil (44 mg, 55%); $[\alpha]_D^{20}$ −113.40 (*c* 0.5, $CHCl_3$); *m/z* (FAB-MS) 330 ($[M + H]^+$); ν_{max} (film)/cm^{-1} 1770 (lactone), 1745 (ester) and 1720 (urethane); δ_H (500 MHz, C^2HCl_3, 2 rotational isomers) (*First rotamer*, 75%) 1.05 (3H, t, *J* 7.3, CH_3), 1.44 (9H, s, $C(CH_3)_3$), 1.48 (9H, 2s, $C(CH_3)_3$), 1.68–1.85 (2H, m, CH_2-CH_3), 2.77–2.85 (1H, m, H-5), 4.01 (1H, d, $J_{4,5}$ 11.6, H-4), 5.18 (1H, d, $J_{2A,2B}$ 10.4, H-2A) and 5.91 (1H, d, $J_{2B,2A}$ 10.4, H-2B) (*Second rotamer*, 25%) 1.05 (3H, t, *J* 7.3, CH_3), 1.44 (9H, s, $C(CH_3)_3$), 1.47 (9H, 2s, $C(CH_3)_3$), 1.68–1.85 (2H, m, CH_2CH_3), 2.77–2.85 (1H, m, H-5), 4.17 (1H, d, $J_{4,5}$ 11.6, H-4), 5.24 (1H, d, $J_{2A,2B}$ 10.6, H-2A) and 5.75 (1H, d, $J_{2B,2A}$ 10.6, H-2B); δ_C (125.8 MHz, C^2HCl_3, 2 rotational isomers) 10.96 and 11.38 (CH_3), 19.95 and 20.13 (CH_2-CH_3), 27.66 and 27.71 ($C(CH_3)_3$), 27.85 and 27.91 ($C(CH_3)_3$), 42.72 and 42.85 (C-5), 55.73 and 56.80 (C-4), 71.52 and 72.49 (C-2), 82.49 and 82.56 ($OC(CH_3)_3$), 82.82 and 82.95 ($OC(CH_3)_3$), 151.96 and 152.10 (urethane), 170.09 and 170.23 (ester) and 171.05 and 171.22 (lactone). Subsequent elution with petroleum ether–ethyl acetate (8:2) afforded starting material (21 mg 26%).

(4*S*,5*R*)- and (4*S*,5*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one, 23 and 24

Method A. By catalytic hydrogenation of the enaminone 20 in EtOAc. (4*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-(dimethylaminomethylene)-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one **20** (322 mg, 0.9 mmol) was dissolved in ethyl acetate (8 ml) and 10% palladium on carbon (160 mg, 50% w/w) was added. The reaction was stirred under an atmosphere of hydrogen for 3 days at room temperature and filtered through Celite®. The solvent was

removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (15, 20%) as eluent to afford *(4S,5R)-3,4-bis(tert-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **23** (161 mg, 57%) as a white crystalline solid; mp 47–48 °C; $[\alpha]_D^{25}$ −121.4 (*c* 1, $CHCl_3$) (Found: C, 57.1; H, 8.1; N, 4.4. $C_{15}H_{25}NO_6$ requires C, 57.1; H, 8.0; N, 4.4%); *m/z* [+ve FAB (3-NBA)] 316 ($[M + H]^+$) and 338 ($[M + Na]^+$); ν_{max} (film)/cm^{-1} 1763 (lactone), 1735 (ester) and 1719 (urethane); δ_H [500 MHz, $(C^2H_3)_2SO$, 42 °C] 5.67 (1H, d, $J_{2A,2B}$ 9, H-2A), 5.25 (1H, d, $J_{2B,2A}$ 9, H-2B), 3.95 (1H, d, $J_{4,5}$ 11.3, H-4), 3.24–2.99 (1H, m, H-5), 1.45 (9H, s, $OC(CH_3)_3$), 1.41 (9H, s, $OC(CH_3)_3$) and 1.19 (1H, d, *J* 6.6, Me); δ_C [125.8 MHz, $(C^2H_3)_2SO$, 5 °C] 171.5 (lactone), 169.7 (ester), 151.9 (urethane), 81.7 and 81.2 ($OC(CH_3)_3$), 71.2 (C-2), 58.5 (C-4), 36.1 (C-5), 27.7 and 27.5 ($OC(CH_3)_3$) and 12.5 (CH_3) and *(4S,5S)-3,4-bis(tert-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **24** (87 mg, 31%) as a white crystalline solid; mp 114–115 °C; $[\alpha]_D^{25}$ +84.2 (*c* 1, $CHCl_3$) (Found: C, 57.2; H, 8.0; N, 4.4. $C_{15}H_{25}NO_6$ requires C, 57.1; H, 8.0; N, 4.4%); *m/z* [+ve FAB (3-NBA)] 316 ($[M + H]^+$) and 338 ($[M + Na]^+$); ν_{max} (KBr)/cm^{-1} 1763 (lactone), 1735 (ester) and 1719 (urethane); δ_H [500 MHz, $(C^2H_3)_2SO$, 2 rotamers at 25 °C] (*First rotamer*, 57%) 5.67 (1H, d, $J_{2A,2B}$ 9.9, H-2A), 5.22 (1H, d, $J_{2B,2A}$ 9.9, H-2B), 4.27 (1H, d, $J_{4,5}$ 7.0, H-4), 3.51–3.46 (1H, m, H-5), 1.38 (18H, s, $OC(CH_3)_3$) and 1.02 (3H, d, *J* 6.4, CH_3) (*Second rotamer* 43%) 5.60 (1H, d, $J_{2A,2B}$ 10.2, H-2A), 5.28 (1H, d, $J_{2B,2A}$ 10.2, H-2B), 4.18 (1H, d, $J_{4,5}$ 7.3, H-4), 3.51–3.46 (1H, m, H-5), 1.41 (9H, s, $OC(CH_3)_3$), 1.33 (9H, s, $OC(CH_3)_3$) and 1.02 (3H, d, *J* 6.4, CH_3); δ_C [125.8 MHz, $(C^2H_3)_2SO$, 2 rotamers at 25 °C] (*First rotamer*, 57%) 171.8 and 171.7 (lactone), 168.4 and 167.9 (ester), 151.9 (urethane), 81.9, 81.3, 81.2 and 81.1 ($OC(CH_3)_3$), 71.7 and 71.2 (C-2), 59.1 and 59.0 (C-4), 34.7 and 34.4 (C-5), 27.8, 27.7, 27.5 and 27.4 ($OC(CH_3)_3$), 10.9 and 10.8 (CH_3).

Method B. By hydrogenation of enaminone 20 in presence of acetic acid. (4*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-(dimethylaminomethylene)-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one **20** (1.5 g, 4.19 mmol) was dissolved in a mixture of ethyl acetate (30 ml) and acetic acid (2 ml) and 10% palladium on carbon (780 mg, 50% w/w) was added. The reaction was stirred under an atmosphere of hydrogen for 2 days at room temperature and filtered through Celite®. The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (15, 20%) as eluent to afford *(4S,5R)-3,4-bis(tert-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **23** (640 mg, 48%) and *(4S,5S)-3,4-bis(tert-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **24** (660 mg, 50%) as white crystalline solids with identical spectra to those of the samples prepared above.

Method C. By alkylation of 9 using methyl iodide and LHMDS. (4*S*)-3,4-Bis(*tert*-butoxycarbonyl)-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one **9** (100 mg, 0.33 mmol) was dissolved in dry tetrahydrofuran (1 ml) and cooled to −75 °C under nitrogen. Lithium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 0.73 ml, 0.73 mmol) was added with stirring. Stirring was continued at −75 °C for 1 h and methyl iodide (0.1 ml, 1.6 mmol) was added. The resulting solution was stirred for 1 h at −75 °C and allowed to warm to −20 °C over a period of 4 h. The mixture was quenched with excess saturated aqueous ammonium chloride at −20 °C and extracted with ethyl acetate. The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (10, 15 and 20%) as eluent to afford *(4S,5R)-3,4-bis(tert-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **23** (30 mg, 29%) as a colourless oil; $[\alpha]_D^{25}$ −112.8 (*c* 1, $CHCl_3$) with identical spectra to those of the sample prepared above; and *(4S,5S)-3,4-bis(tert-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **24** (24 mg, 23%) as a white crystalline solid, mp 98–99 °C; $[\alpha]_D^{25}$ +67.8 (*c* 1, $CHCl_3$) with identical spectra to those of the sample prepared above. The column also yielded starting material (5 mg, 5%) and the dialkylated product *(4S)-3,4-bis(tert-butoxycarbonyl)-5,5-dimethyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **27** (30 mg, 28%); mp 91–92 °C; $[\alpha]_D^{25}$ −65.8 (*c* 1, $CHCl_3$) (Found: C, 58.3; H, 8.2; N, 4.2. $C_{16}H_{27}NO_6$ requires C, 58.3; H, 8.3; N, 4.3%); *m/z* [+ve FAB (3-NBA)] 330 ($[M + H]^+$) and 352 ($[M + Na]^+$); δ_H (300 MHz, C^2HCl_3, 2 rotamers at 27 °C) (*First rotamer*, 57%) 5.88 (1H, d, $J_{2A,2B}$ 10.1, H-2A), 5.40 (1H, d, $J_{2B,2A}$ 10.2, H-2B), 4.19 (1H, s, H-4), 1.47 (9H, s, $OC(CH_3)_3$), 1.46 (9H, s, $OC(CH_3)_3$), 1.43 (3H, s, CH_3) and 1.29 (3H, s, CH_3) (*Second rotamer* 43%) 5.73 (1H, d, $J_{2A,2B}$ 10.1, H-2A), 5.31 (1H, d, $J_{2B,2A}$ 10.0, H-2B), 4.20 (1H, s, H-4), 1.45 (9H, s, $OC(CH_3)_3$), 1.44 (9H, s, $OC(CH_3)_3$), 1.43 (3H, s, CH_3) and 1.29 (3H, s, CH_3); δ_C (75.5 MHz, C^2HCl_3, 2 rotamers at 27 °C) 173.4 and 173.3 (lactone), 168.1 (ester), 152.2 (urethane), 83.1, 82.5 and 82.4 ($OC(CH_3)_3$), 73.2 and 72.3 (C-2), 62.4 and 61.4 (C-4), 40.6 and 40.1 (C-5), 28.1 and 28.0 ($OC(CH_3)_3$) and 26.6, 26.5 and 22.2 (CH_3).

Method D. By alkylation using methyl iodide and KHMDS. (4*S*)-3,4-Bis(*tert*-butoxycarbonyl)-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one **9** (100 mg, 0.33 mmol) was dissolved in dry tetrahydrofuran (1 ml) and cooled to −75 °C under nitrogen. Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 1.2 ml, 0.6 mmol) was added with stirring. Stirring was continued at −75 °C for 1 h and methyl iodide (0.062 ml, 0.99 mmol) was added. The solution was stirred 7.5 h at −75 °C, quenched with excess saturated aqueous ammonium chloride at −20 °C and extracted with ethyl acetate. The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (10, 15 and 20%) as eluent to afford *(4S,5R)-3,4-bis(tert-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **23** (31 mg, 30%), *(4S,5S)-3,4-bis(tert-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **24** (8 mg, 8%), *(4S)-3,4-bis(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **9** (24 mg, 24%) and *(4S)-3,4-bis(tert-butoxycarbonyl)-5,5-dimethyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **27** (18 mg, 17%), all with spectra in keeping with those of authentic samples.

(4*S*,5*R*)- and (4*S*,5*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-benzyl-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one 28 and 5 (R = Ph)

Method A. By alkylation using benzyl bromide LHMDS and HMPA. (4*S*)-3,4-Bis(*tert*-butoxycarbonyl)-2,3,4,5-tetrahydro-6*H*-1,3,oxazin-6-one **9** (100 mg, 0.33 mmol) was dissolved in dry tetrahydrofuran (1 ml) with hexamethylphosphoramide (0.2 ml) and cooled to −75 °C under nitrogen. Lithium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 0.73 ml, 0.73 mmol) was added with stirring. Stirring was continued at −75 °C for 1 h and benzyl bromide (0.2 ml, 1.65 mmol) was added. The resulting solution was stirred for 7 h at −75 °C and allowed to warm to −40 °C over a period of 1 h. The mixture was quenched by adding oxalic acid (89 mg) in diethyl ether (1 ml) at −75 °C and extracted with ethyl acetate. The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (10, 15 and 20%) as eluent to afford *(4S,5R)-3,4-bis(tert-butoxycarbonyl)-5-benzyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **28** (35 mg, 27%) as a white crystalline solid; mp 134–135 °C; $[\alpha]_D^{25}$ −144.0 (*c* 1, $CHCl_3$) (Found: C, 64.45; H, 7.5; N, 3.6. $C_{21}H_{29}NO_6$ requires C, 64.4; H,

7.5; N, 3.6%); *m/z* [+ve FAB (3-NBA)] 392 ([M + H]$^+$) and 414 ([M + Na]$^+$); ν_{max} (KBr)/cm^{-1} 1772 (lactone), 1740 (ester) and 1713 (urethane); δ_H [500 MHz, (C^{2}H$_3$)$_2$SO, 42 °C] 7.31–7.12 (5H, m, ArH), 5.64 (1H, d, $J_{2A,2B}$ 10, H-2A), 5.34 (1H, d, $J_{2B,2A}$ 10, H-2B), 4.18 (1H, d, $J_{4,5}$ 10.8, H-4), 3.52 (1H, ddd, $J_{5,4}$ 10.8, $J_{5,7A}$ 7.9, $J_{5,7B}$ 3.2, H-5), 3.12 (1H, dd, $J_{7A,7B}$ 14.8, $J_{7A,5}$ 7.9, H-7A), 2.99 (1H, dd, $J_{7B,7A}$ 14.8, $J_{7B,5}$ 3.2, H-7B), 1.41 (9H, s, OC(C*H*$_3$)$_3$) and 1.39 (9H, s, OC(C*H*$_3$)$_3$); δ_C (125.8 MHz, C^{2}HCl$_3$, 2 rotamers at −25 °C; ratio 53:47) 170.8 and 170.7 (lactone), 170.0 and 169.9 (ester), 152.0 and 151.9 (urethane), 138.0, 137.9, 129.5, 129.4, 128.5, 128.3 and 126.8 (Ar), 83.3, 83.2, 82.7 and 82.6 (O*C*(CH$_3$)$_3$), 72.6 and 71.6 (C-2), 57.5 and 56.4 (C-4), 44.4 and 44.3 (C-5), 32.8 and 31.2 (*C*H$_2$Ph), 28.0, 27.9 and 27.8 (OC(*C*H$_3$)$_3$). The X-ray crystal structure data for this compound have been lodged with the CCDC,[23] reference code KAGNOV. *(4S,5S)-3,4-Bis(tert-butoxycarbonyl)-5-benzyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **5** (R = Ph) (8 mg, 6%) was also obtained from the column as a colourless oil with spectra identical to those from the sample from hydrogenation of the benzylidene compound **21** (R = Ph). The column also gave *(4S)-3,4-bis(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **9** (37 mg, 37%) and the dialkylated product *(4S)-3,4-bis(tert-butoxycarbonyl)-5,5-dibenzyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **29** (17 mg, 11%); $[\alpha]_D^{25}$ −11.5 (*c* 1, CHCl$_3$) (Found 482.2576. $C_{28}H_{36}NO_6$ ([M + H]$^+$) requires 482.2543); *m/z* [+ve FAB (3-NBA)] 482 ([M + H]$^+$) and 504 ([M + Na]$^+$); ν_{max} (film)/cm^{-1} 1749 (lactone/ester) and 1719 (urethane); δ_H (500 MHz, C^{2}HCl$_3$, 2 rotamers at −25 °C) (*First rotamer*, 73%) 7.42–7.19 (10H, m, ArH), 5.94 (1H, d, $J_{2A,2B}$ 10.3, H-2A), 5.34 (1H, d, $J_{2B,2A}$ 10.3, H-2B), 4.82 (1H, s, H-4), 3.69 (1H, d, J_{AB} 13.6, C*H*$_2$Ph), 3.33 (1H, d, J_{BA} 13.6, C*H*$_2$Ph), 2.86 (1H, d, J_{AB} 13.7, C*H*$_2$Ph), 2.80 (1H, d, J_{BA} 13.7, C*H*$_2$Ph), 1.66 (9H, s, OC(CH$_3$)$_3$) and 1.25 (9H, s, OC(CH$_3$)$_3$) (*Second rotamer*, 26%) 7.42–7.19 (10H, m, ArH), 5.76 (1H, d, $J_{2A,2B}$ 10.3, H-2A), 5.51 (1H, d, $J_{2B,2A}$ 10.3, H-2B), 4.85 (1H, s, H-4), 3.59 (1H, d, J_{AB} 13.8, C*H*$_2$Ph), 3.37 (1H, d, $J_{A,B}$ 13.9, C*H*$_2$Ph), 2.85 (1H, d, $J_{B,A}$ 13.9, C*H*$_2$Ph), 2.80 (1H, d, $J_{B,A}$ 13.8, CH$_2$Ph), 1.62 (9H, s, OC(C*H*$_3$)$_3$) and 1.41 (9H, s, OC(C*H*$_3$)$_3$); δ_C (125.8 MHz, C^{2}HCl$_3$, 2 rotamers at −25 °C) 169.0 and 168.9 (lactone), 168.6 and 168.4 (ester), 151.6 and 151.3 (urethane), 136.2, 135.7, 133.8, 133.6, 131.5, 131.3, 130.4, 130.2, 128.3, 128.2, 127.7 and 127.0 (Ar), 83.4, 83.3, 82.4 and 81.9 (O*C*(CH$_3$)$_3$), 72.0 and 70.8 (C-2), 55.7 and 55.4 (C-4), 50.9 and 50.4 (C-5), 41.1, 40.8, 40.1 and 39.7 (*C*H$_2$Ph), 28.1, 28.0, 27.9 and 27.6 (OC(*C*H$_3$)$_3$).

Method B. Alkylation using sodium bis(trimethylsilyl)amide. (4*S*)-3,4-Bis(*tert*-butoxycarbonyl)-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one **9** (100 mg, 0.33 mmol) was dissolved in dry tetrahydrofuran (1 ml) and cooled to −75 °C under nitrogen. Sodium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 0.73 ml, 0.73 mmol) was added with stirring. Stirring was continued at −75 °C for 1 h and benzyl bromide (0.2 ml, 1.65 mmol) was added. The resulting solution was stirred 6.5 h at −75 °C. The mixture was quenched by adding oxalic acid (89 mg) in diethyl ether (1 ml) at −75 °C and extracted with ethyl acetate. The combined organic layers were washed with water and dried (MgSO$_4$). The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (10, 15 and 20%) as eluent to afford *(4S,5R)-3,4-bis(tert-butoxycarbonyl)-5-benzyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **28** (28 mg, 22%), *(4S,5S)-3,4-bis(tert-butoxycarbonyl)-5-benzyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **5** (R = Ph) (7 mg, 5%), *(4S)-3,4-bis(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **9** (43 mg, 43%) and *(4S)-3,4-bis(tert-butoxycarbonyl)-5,5-dibenzyl-2,3,4,5-tetrahydro-6H-1,3-oxazin-6-one* **29** (16 mg, 10%) with spectra identical to those of authentic samples.

(2*S*,3*R*)-3-Methylaspartic acid hydrochloride 30

(4*S*,5*R*)-3,4-Bis(*tert*-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one **23** (55 mg, 0.17 mmol) was dissolved in a minimum of diethyl ether and 6 M aqueous hydrochloric acid (1.5 ml) was added. The mixture was stirred for 15 h at room temperature and washed with diethyl ether. The aqueous layer was lyophilised using a freeze dryer. The residual yellow foam was recrystallised in a mixture of absolute ethanol and diethyl ether to yield *(2S,3R)-3-methylaspartic acid hydrochloride* **30** (25 g, 80%); mp 165–166 °C; $[\alpha]_D^{25}$ +29.7 (*c* 1, 5 M HCl) [lit.[16] $[\alpha]_D^{25}$ +32.9 (*c* 0.8, 5 M HCl)] (Found: C, 32.7; H, 5.5; N, 7.4, $C_5H_{10}NO_4Cl$ requires C, 32.7; H, 5.5; N, 7.6%); *m/z* [+ve FAB (glycerol)] 148 ([free amino acid + H]$^+$); δ_H (300 MHz, ^2H_2O) 4.08 (1H, d, $J_{2,3}$ 4.0, H-2), 3.15 (1H, dq, $J_{3,2}$ 4.0, $J_{3,Me}$ 7.4. H-3) and 1.12 (3H, d, $J_{Me,3}$ 7.4, CH$_3$); δ_C (75.5 MHz, ^2H_2O) 176.1 (acid), 170.9 (acid), 55.0 (C-2), 39.5 (C-3) and 12.3 (CH$_3$).

1-*tert*-Butyl (2*S*,3*R*)-3-methyl-*N*-*tert*-butoxycarbonylaspartate, 31

Method A. Using HOAc–H$_2$O. (4*S*,5*R*)-3,4-Bis(*tert*-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one **(23)** (429 mg, 1.36 mmol) was dissolved in a 4:1 mixture of acetic acid and water (16 ml). The mixture was stirred for 3 days at 50 °C and the solvent was removed *in vacuo*. The residue was partitioned between diethyl ether and 1 M aqueous sodium hydroxide. The organic layer was washed with 1 M aqueous sodium hydroxide, and the combined aqueous layers were acidified to pH 2 with 10% aqueous citric acid. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and dried (MgSO$_4$). The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (10, 15 and 20%) as eluent to afford *1-tert-butyl (2S,3R)-3-methyl-N-tert-butoxycarbonylaspartate* **31** as a colourless oil which crystallised on standing (231 mg, 56%); mp 89–90 °C; $[\alpha]_D^{25}$ −12.8 (*c* 1, MeOH) (Found: C, 55.6; H, 8.2; N, 4.55. $C_{14}H_{25}NO_6$ requires C, 55.4; H, 8.3; N, 4.6%); *m/z* [+ve FAB (3 NBA)] 304 ([M + H]$^+$); ν_{max} (film)/cm^{-1} 3439 (br, acid) and 1719 (br ester/urethane); δ_H (300 MHz, C^{2}HCl$_3$, 25 °C) 10.16 (1H, br s, CO$_2$H), 5.39 (1H, d, $J_{NH,2}$ 9.0, NH), 4.42 (1H, dd, $J_{2,NH}$ 9.0, $J_{2,3}$ 3.6, H-2), 3.18 (1H, dq, $J_{2,3}$ 3.6, $J_{3,Me}$ 7.2, H-3), 1.40 (9H, s, O*C*(CH$_3$)$_3$), 1.39 (9H, s, OC(C*H*$_3$)$_3$) and 1.18 (1H, d, $J_{Me,3}$ 7.2, CH$_3$) (*peaks due to second rotamer*) 6.09 (1H, d, $J_{NH,2}$ 7.9, NH), 4.22–4.33 (1H, m, H-2) and 2.97–3.09 (1H, m, H-3); δ_C (75.5 MHz, C^{2}HCl$_3$, 25 °C) 179.3 (C-4), 169.7 (C-1), 156.0 (urethane), 82.5 (O*C*(CH$_3$)$_3$), 79.9 (O*C*(CH$_3$)$_3$), 55.5 (C-2), 41.4 (C-3), 28.2 and 27.7 (OC(*C*H$_3$)$_3$) and 12.8 (CH$_3$). Further elution gave starting material **23** (21 mg, 5%).

Method B. Using LiOOH. (4*S*,5*R*)-3,4-Bis(*tert*-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one **23** (71 mg, 0.23 mmol) was dissolved in tetrahydrofuran (3.5 ml) and water (1 ml) and cooled to 0 °C. Aqueous hydrogen peroxide (30%, 0.02 ml) and 1 M aqueous lithium hydroxide (0.27 ml, 0.27 mmol) were successively added with stirring. Stirring was continued at 0 °C for 6 h. 1.5 M Aqueous sodium sulfite (0.6 ml) was added at 0 °C and the mixture was diluted with water, washed with diethyl ether and carefully acidified to pH 2 with 2 M aqueous hydrochloric acid. The solution was extracted with ethyl acetate. The combined organic layers were washed with water and dried (MgSO$_4$). The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (10 and 20%) as eluent to yield *1-tert-butyl (2S,3R)-3-methyl-N-tert-butoxycarbonylaspartate* **31** (28 mg, 40%) identical to the sample prepared by method A.

1-*tert*-Butyl (2*S*,3*S*)-3-methyl-*N*-*tert*-butoxycarbonylaspartate, 32

(4*S*,5*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-methyl-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one **24** (362 mg, 1.15 mmol) was dissolved in a 4:1 mixture of acetic acid and water (14 ml). The mixture was stirred for 3 days at 50 °C and the solvent was removed *in vacuo*. The residue was partitioned between diethyl ether and 1 M aqueous sodium hydroxide. The organic layer was washed with 1 M aqueous sodium hydroxide and the combined aqueous layers were acidified carefully to pH 2 with 10% aqueous citric acid. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (10, 15 and 20%) as eluent to afford *1-tert-butyl (2S,3S)-3-methyl-N-tert-butoxycarbonylaspartate* **32** as an oil (184 mg, 53%) (Found: 304.1760 ($[M + H]^+$). $C_{14}H_{26}NO_6$ requires 304.1766); *m/z* [+ve FAB (3-NBA)] 304 ($[M + H]^+$) and 326 ($[M + Na]^+$); ν_{max} (film)/cm^{-1} 3341 (br, acid) and 1720 (br, ester/urethane); δ_H (300 MHz, C^2HCl_3, 25 °C) 9.76 (1H, br s, CO_2H), 5.33 (1H, d, $J_{NH,2}$ 8.7, NH), 4.45 (1H, dd $J_{2,NH}$ 8.7, $J_{2,3}$ 4.5, H-2), 2.92 (1H, dq, $J_{3,2}$ 4.5, $J_{3,Me}$ 7.2, H-3), 1.42 (9H, s, $OC(CH_3)_3$), 1.40 (9H, s, $OC(CH_3)_3$) and 1.20 (1H, d, $J_{Me,3}$ 7.2, CH_3) (*peaks due to second rotamer*) 6.12–5.97 (1H, m, NH), 4.41–4.29 (1H, m, H-2) and 2.97–3.09 (1H, m, H-3); δ_C (75.5 MHz, C^2HCl_3, 25 °C) 178.6 (C-4), 169.6 (C-1), 155.4 (urethane), 82.6 ($OC(CH_3)_3$), 80.0 ($OC(CH_3)_3$), 55.7 (C-2), 42.4 (C-3), 28.2 and 27.8 ($OC(CH_3)_3$) and 13.0 (CH_3). *Starting material* **24** (33 mg, 8%) was obtained on further elution.

1-*tert*-Butyl (2*S*,3*S*)-3-benzyl-*N*-*tert*-butoxycarbonylaspartate, 6 (R = Ph)

(4*S*,5*S*)-3,4-Bis(*tert*-butoxycarbonyl)-5-benzyl-2,3,4,5-tetrahydro-6*H*-1,3-oxazin-6-one **5** (R = Ph) (300 mg, 0.77 mmol) was dissolved in a 4:1 mixture of acetic acid and water (10 ml). The mixture was stirred for 2 days at 50 °C and the solvent was removed *in vacuo*. The residue was partitioned between diethyl ether and 1 M aqueous sodium hydroxide. The organic layer was washed with 1 M aqueous sodium hydroxide and the combined aqueous layers were acidified carefully to pH 2 with 10% aqueous citric acid. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give an oil, which was purified by column chromatography on silica gel using a gradient of petroleum ether–ethyl acetate (10, 15 and 20%) as eluent to afford *1-tert-butyl (2S,3S)-3-benzyl-N-tert-butoxycarbonylaspartate* **6**, (R = Ph) as a white crystalline solid (148 mg, 51%); mp 96–97 °C (lit.[6] mp 132–135 °C); $[\alpha]_D^{25}$ +3.8 (*c* 1, MeOH), −1.3 (*c* 1, $CHCl_3$) (Found: C, 63.3; H, 7.6; N, 3.7. $C_{20}H_{29}NO_6$ requires C, 63.3; H, 7.7; N, 3.7%); *m/z* [+ve FAB (3-NBA)] 380 ($[M + H]^+$) and 402 ($[M + Na]^+$); ν_{max} (KBr)/cm^{-1} 3267 (br, acid/NH), 1727 and 1664 (br ester/urethane); δ_H (300 MHz, C^2HCl_3, 25 °C) 9.69 (1H, br s, CO_2H), 7.22–7.10 (5H, m, ArH), 5.34 (1H, d, $J_{NH,2}$ 8.5, NH), 4.44 (1H, dd, $J_{2,NH}$ 8.5, $J_{2,3}$ 3.4, H-2), 3.05–2.95 (2H, m, H-3 and CH_2Ph), 2.85–2.78 (1H, m, CH_2Ph), 1.39 (9H, s, $OC(CH_3)_3$) and 1.35 (9H, s, $OC(CH_3)_3$) (*peaks due to second rotamer*) 6.18–6.04 (1H, m, NH) and 4.29–4.18 (1H, m, H-2); δ_C (75.5 MHz, C^2HCl_3, 25 °C) 177.7 (C-4), 169.6 (C-1), 155.3 (urethane), 138.4, 129.0, 128.6 and 126.7 (Ar), 83.1 and 80.2 ($OC(CH_3)_3$), 54.8 (C-2), 50.3 (C-3), 34.1 (CH_2Ph), 28.3 and 28.0 ($OC(CH_3)_3$).

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