Highly diastereoselective route to *trans*-5-substituted 2-hydroxymethylpyrrolidine derivatives by radical cyclisation

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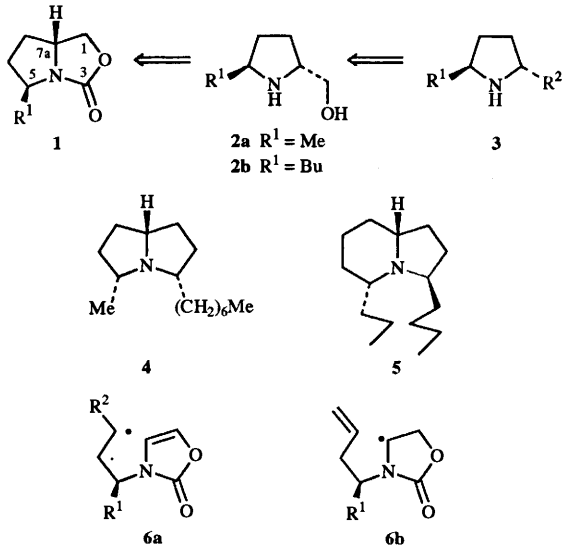
The cyclisation of radical species generated from (*S*)-*N*-(3-bromopropyl)oxazolin-2-ones 22 by treatment with tributylstannane in the presence of AIBN yielded 5-substituted pyrrolooxazolones with high diastereoselectivity. In the same reaction using (±)-*N*-(3-bromobutyl)oxazolin-2-one 25a or (±)-*N*-(4-bromopentan-2-yl)oxazolin-2-one 25b, the radical cyclisation gave predominantly the (5*S,7*S**,7a*R**)-5,7-disubstituted pyrrolooxazolines rather than the (5*S**,7*R**,7a*R**) products. The radical cyclisation of 4-phenylsulfanyloxazolidinones 29a,b also resulted in the predominant formation of the corresponding (5*S*,7*S*,7a*R*)-5,7-disubstituted pyrrolooxazolidine derivatives.**

The oxazolidinone ring can be considered as a synthon for 2-amino alcohols, since the ring can be cleaved easily under mild conditions at the two heteroatoms.[1] Thus, the pyrrolooxazolidinones **1** can be easily recognised as direct precursors for the synthesis of 5-substituted 2-hydroxymethylpyrrolidines **2**, which are useful intermediates for the synthesis of wide range of *trans*-2,5-disubstituted pyrrolidines **3** (Scheme 1). The development of diastereoselective synthetic routes to compounds of the type **3** is an area of considerable research interest. The enantiomer of **2a** is a starting material for pyrrolidine alkaloids such as **4**[2] and the enantiomer of **2b** would be a potentially useful key intermediate for the synthesis of indolizidine alkaloids such as gephyrotoxin (−)-223AB **5**.[3] Pyrrolidines **3**, which have a C_2 symmetry axis when $R^1 = R^2$, have been used as chiral auxiliaries and often give high levels of asymmetric induction. New methodologies to produce this type of pyrrolidine in optically pure form are subject to continual refinement, because only a few approaches to their asymmetric synthesis have been reported.[4] For the synthesis of pyrrolooxazolidine derivatives, the creation of the new stereogenic centre at the 2-position of the pyrrolidine derivatives *via* enantioselective cyclisation at the 4-position of the oxazolinone ring has been studied. Radical cyclisation has been widely applied as an extremely elegant method for the preparation of some carbocyclic as well as heterocyclic compounds and following our interest in free radical cyclisation,[5,6] we wish to report here the diastereoselective synthesis of 5-substituted and 5,7-disubstituted pyrroloxazolidinones by the utilization of radical species **6a** and **6b** as the asymmetric templates.

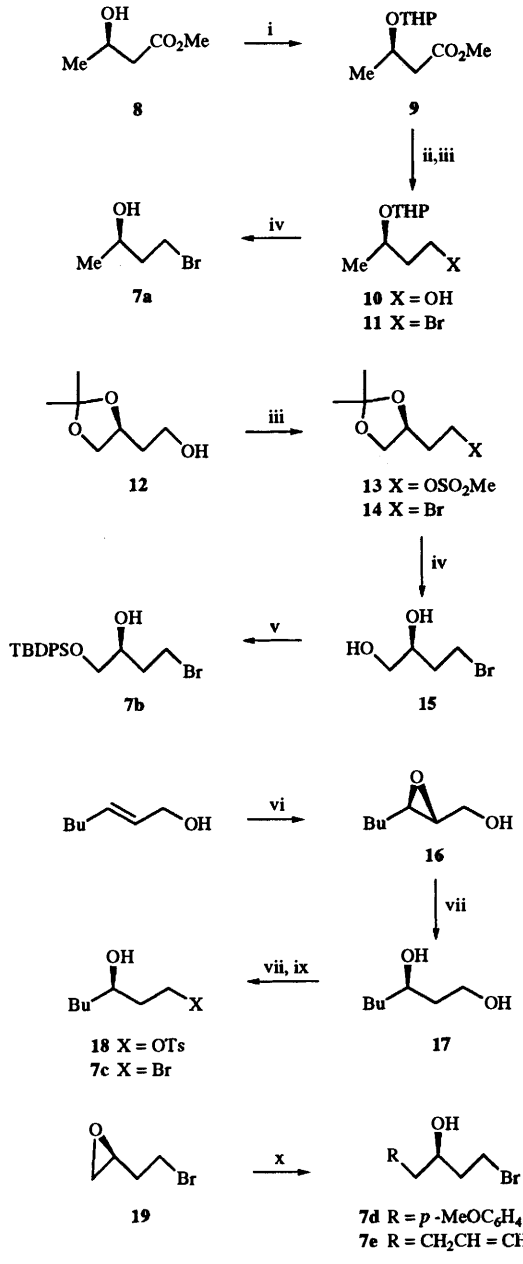


Scheme 1

Results and discussion

Synthesis of *N*-substituted oxazolidin-2-ones 22a–e, 25a,b and 29a,b

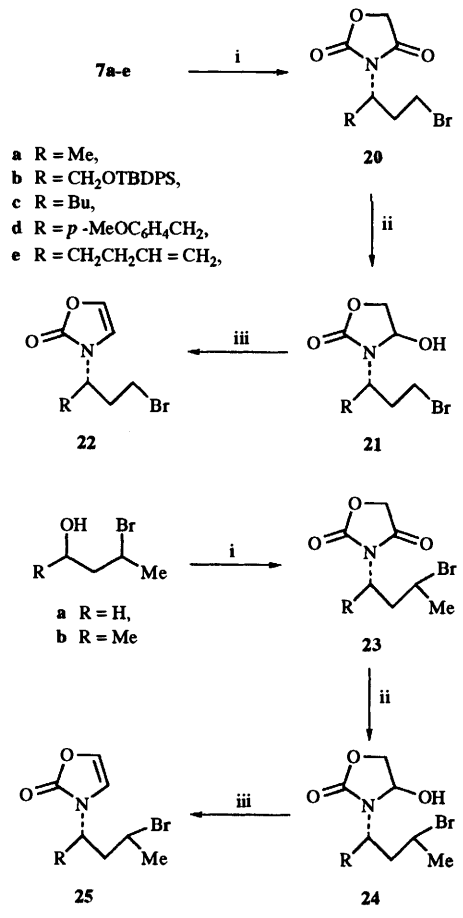
Initially, we examined the creation of the chiral centre at the 7a-position of the pyrrolooxazolidinones using the double bond of 2,3-dihydrooxazole as the radical acceptor.[7] As the first step to the *N*-(3-bromopropyl)oxazolinones which contain a latent radical centre, we synthesised the bromo alcohols **7a–e** as outlined in Scheme 2. For the synthesis of **7a–e**, the following two methods can be considered; (i) the conversion of the primary hydroxy group of selectively protected 1,3-diols or non-protected derivatives into bromide as illustrated by the synthesis of **7a–c**, (ii) ring cleavage of the oxirane ring of 3,4-epoxybutyl bromide **19**[8] as exemplified in the synthesis of **7d,e**. Thus, **7a**[9] was synthesised starting from methyl (*R*)-3-hydroxybutanoate **8**. THP protection of **8** (91.0%), followed by reduction with $LiAlH_4$ afforded (*R*)-3-pyranyloxybutyl alcohol **10** (79.9%). Methanesulfonylation of **10**, followed by treatment of the resulting methanesulfonate with LiBr in acetone gave the bromide **11** in 74.0% yield, which was then deprotected with *p*-TsOH in methanol to yield **7a** (87.7%). In a similar way, the hydroxy group of 3,4-(isopropylidenedioxy)butan-1-ol **12**,[10] derived from (*S*)-malic acid, was converted into **14**[11] (39.3%) *via* **13**. Acid-catalysed ring cleavage of **14** with *p*-TsOH in methanol yielded **15** (86.0%), followed by regioselective protection of the primary hydroxy group with *tert*-butyldiphenylsilyl chloride (TBDPSCl) furnished **7b** in 94.8% yield. The regioselective conversion of the primary hydroxy group of 1,3-diol **17**[3b,12] into bromide was illustrated by a preparation of **7c**.[3b,12] The chiral 1,3-diol **17** was easily obtained in 82% yield by reductive ring cleavage of epoxide **16**,[12] prepared from (*E*)-hept-2-en-1-ol, with sodium bis(methoxyethoxy)aluminium hydride (Red-Al). Upon toluene-*p*-sulfonylation of **17**, the reaction occurred regioselectively at the primary hydroxy group to give **18** in 92.6% yield. Treatment of **18** with LiBr in acetone yielded the desired γ-bromo alcohol **7c** in 74.0% yield. Nucleophilic ring cleavage of 3,4-epoxybutyl bromide **19**[8] with Grignard reagents was examined to get **7d,e**. Treatment of **19** with *p*-methoxyphenylmagnesium bromide in the presence of



Scheme 2 *Reagents and conditions:* i, 3,4-dihydropyran, *p*-TsOH·H_2O, Et_2O; ii, $LiAlH_4$; iii, $MeSO_2Cl$, Et_3N, then LiBr, acetone. room temp.; iv, *p*-TsOH·H_2O, MeOH; v, TBDPSCl, 4-DMAP, Et_3N, CH_2Cl_2, 0 °C; vi, *cf.* reference 12; vii, Red-Al, THF, 0 °C; viii, *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C; ix, LiBr, THF, 50 °C; x, for **7d**, *p*-$MeOC_6H_4MgBr$, CuI, THF; for **7e**, allylmagnesium bromide, CuI, THF

CuI afforded **7d** in 72% yield. Similarly, the reaction of allylmagnesium bromide with **19** gave **7e** in 86.4% yield.

The bromopropanols **7a–e** thus obtained were subjected to a coupling reaction with oxazolidine-2,4-dione utilising an application of the Mitsunobu reaction [13] [Ph_3P, ($Pr^iOC(O)N{=}$)$_2$ in THF] to yield **20a–e** (58.6–70.8%). Reduction of **20a–e** with $NaBH_4$, followed by dehydration of the resulting 4-hydroxyoxazolidin-2-ones **21a–e** with methanesulfonyl chloride in the presence of triethylamine at room temperature gave the desired *N*-substituted 2,3-dihydrooxazol-2-ones **22a–e** (54.6–57.2%). In order to examine the diastereoselective creation of the two stereogenic centres at the 7- and 7a-positions of the 5,7-disubstituted pyrrolooxazolidinones **32**, the oxazolones **25a,b** were also prepared. Condensation of 3-bromobutanol or (±)-4-bromopentan-2-ol with oxazolidine-2,4-dione afforded the corresponding *N*-substituted oxazolidine-2,4-diones **23a** and **23b**, respectively. Since a diastereoisomeric mixture of 4-bromopentan-2-ol was used for the condensation, **23b** was



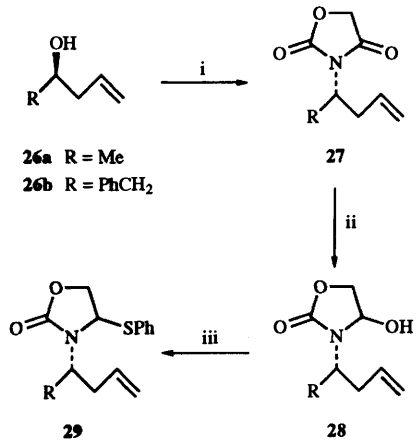
Scheme 3 *Reagents and conditions:* i, oxazolidine-2,4-dione, Ph_3P, ($Pr^iOC(O)N{=}$)$_2$, THF, 0 °C; ii, $NaBH_4$, MeOH, 0 °C; iii, $MeSO_2Cl$, Et_3N, RT

obtained as a 1:1 diastereoisomeric mixture, which was used for the following reaction without separation of the isomers. Compounds **23a,b** were converted into **25a,b** *via* **24a,b** in 58.6 and 60.4% yields, respectively. The ^1H NMR of **25b** clearly indicates this to be a 1:1 mixture of diastereoisomers, which was used for the radical cyclisation without resolution of the stereoisomers.

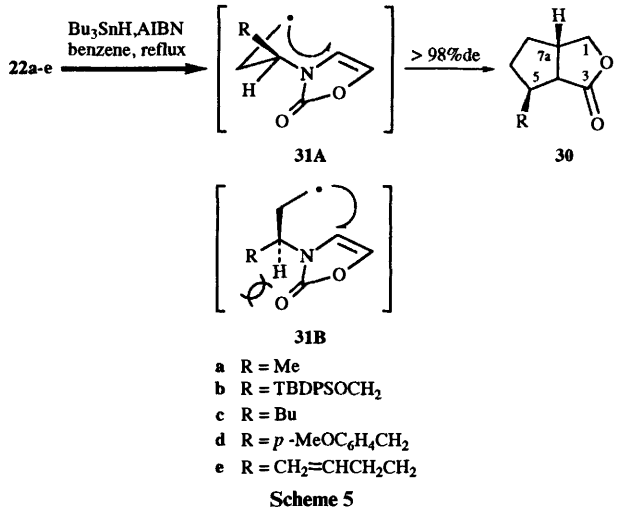
As an alternative method for synthesising the 5,7-disubstituted pyrrolooxazolidinones, we examined the cyclisation of the radicals generated from 4-phenylsulfanyloxazolidinones **29a,b**. The synthetic utility of α-acylamino radical cyclisations has been widely reported.[14] We therefore investigated radical cyclisations using the 4-phenylsulfanyloxazolidinones **29a,b** as latent radical centres, in the expectation that 5,7-disubstituted pyrrolooxazolidinones might be formed with high diastereoselectivity. Condensation of (±)-pent-4-en-2-ol, and (*S*)-1-phenylpent-4-en-2-ol with oxazolidine-2,4-dione afforded the corresponding *N*-substituted oxazolidine-2,4-diones **27a** (61.0%) and **27b** (63.0%), respectively. 4-Hydroxyoxazolidinones **28a,b**, obtained by reduction of **27a,b**, were treated with diphenyl disulfide in the presence of tributylphosphine to give the corresponding cyclisation precursors **29a** (62.5%) and **29b** (57.8%), respectively.

Radical cyclisation of 22a–e

We started investigating the radical cyclisations with **22a**. A benzene solution of **22a** was heated with Bu_3SnH in the presence of AIBN under reflux to yield the (5*S*,7a*R*)-5-methylpyrrolooxazolidinone **30a** as a single product in 72% yield without formation of the alternative stereoisomer as expected. A particularly noteworthy feature was that the radical cyclisation proceeded with complete facial selectivity with respect to the relative configurations at the 5-H and 7a-H



Scheme 4 *Reagents and conditions:* i, oxazolidine-2,4-dione, Ph_3P, $(Pr^iOC(O)N{=})_2$, THF, 0 °C; ii, $NaBH_4$, MeOH, 0 °C; iii, PhSSPh, Bu_3P, THF, RT



Scheme 5

positions. The relative configuration at these positions was easily established without unambiguity based on the signals due to 5-CH_3 (δ_H 1.17, d, J 6.6) and 5-H (δ_H 4.07, dd, J 3.5 and 8.9) in its ^1H NMR ($CDCl_3$) spectrum. The chemical shifts and coupling constants of these signals indicate that the 5-methyl group is *cis* to 7a-H according to our previous work.[6]

The same reaction conditions using **22b–e** gave the corresponding 5-substituted pyrrolooxazolidinones **30b–e**. Generally, cyclisation products were obtained in around 70–73% yield and the reaction was found to proceed with particularly high diastereoselectivity without formation of the alternative diastereoisomer. The high diastereoselectivity can be accounted for by adopting transition state **31A** in preferance to **31B** during cyclisation, in order to avoid 1,3-steric interactions between the amide carbonyl and the alkyl substituent.[6,7]

Radical cyclisation of 25a,b and 29a,b

In view of our interest in the application of radical cyclisation toward polysubstituted pyrrolidine derivatives, we examined successively the creation of the two stereogenic centres at positions 7 and 7a of the 7-substituted pyrrolooxazolidinones formed by radical cyclisation of **25a,b** and **29a,b** (Scheme 6). In the radical cyclisation of **25a**, **32a** and **33a** were obtained in a ratio of 2.1:1. Predominant formation of the (7*S**,7a*R**)-isomer can be accounted for by the stability of the 'chair-like' transition state **34A** rather than the 'boat-like' one **34B**, of the two possible transition states. Similar stereochemical behaviour was also observed in the radical cyclisation of **25b**. In these reactions, **32b** and **33b** were obtained in a ratio of *ca.* 2.4:1. In both cases, high stereoselectivity at positions 5 and 7a was obtained as in the cases of **22a–e**. However, regarding the relative configurations at 7a-H and 7-H, formation of the (7*S**, 7a*R**) isomer is more favourable than the (7*R**,7a*R**)-isomer. The relative configurations for **32b** and **33b** could be assigned by the study of 2D NMR (NOESY) as shown in Fig. 1. As the alternative approach to the formation of the two stereogenic centres at 7 and 7a, radical cyclisation of **29a,b** was also examined. In contrast to the radical cyclisation of **25b**, the reaction with **29a** resulted in the formation predominantly of **32b** in 78% yield without formation of the alternative stereoisomer. This considerable difference between **25b** and **29a** is due to the different reactivities of the alkyl and α-acylamino radicals.[15] Since the reactivity of an α-acylamino radical is diminished by an α-heteroatom, the activation energy for the cyclisation transition state may increase so that the cyclisation would proceed *via* transition state **35A**, which is thermodynamically more stable than transition state **35B**. Similarly radical cyclisation with **29b** afforded **36** as the sole product.

Conversion of pyrrolooxazolidinones into *trans*-5-substituted 2-hydroxymethylpyrrolidines

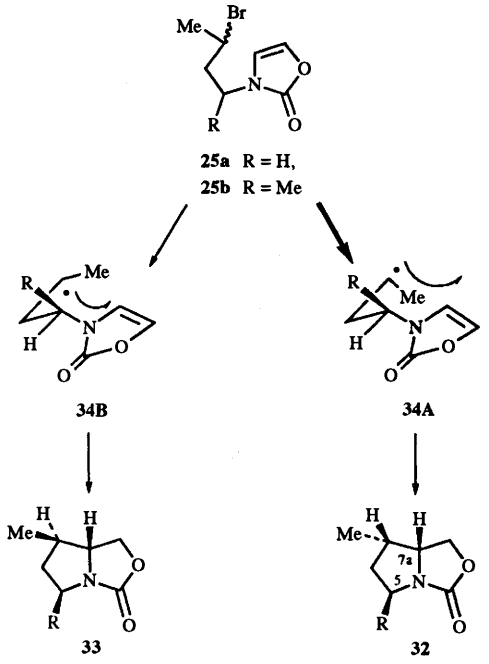
Ring cleavage of **30a** (10% NaOH–EtOH) gave **37**, which afforded **38** on benzyloxycarbonylation with benzyl chloroformate (ZCl) and K_2CO_3. The enantiomer of **38** could be converted into the pyrrolidine alkaloid **4**,[2] and therefore this work constitutes a formal synthesis of the enantiomer of **4**. The *trans* pyrrolidines **43** and **44** which have been widely used as chiral auxiliaries in asymmetric synthesis, were chosen as the appropriate benchmark for the synthetic utility of radical cyclisation product **30b**. Desilylation of **30b** with tetrabutylammonium fluoride gave 5-hydroxymethylpyrrolooxazolidinone **39** in nearly quantitative yield, which was easily convertible into a variety of 2,5-bis(alkoxymethyl)pyrrolidine derivatives. Benzylation of **39**, followed by alkaline hydrolysis of the resulting *O*-benzyl derivative **40a** yielded **41a**, conversion of which into the pyrrolidine **42** was easily achieved by reaction with benzyl bromide in the presence of NaH in DMF. The spectral data and specific rotation of **42** were identical with those in the literature.[16] Since conversion of **42** into 2*R*,5*R*-bis(benzyloxymethyl)pyrrolidine **43**[15] and *trans*-2,5-dicarboxylic acid **44**[17] is already known, this work should be widely applicable to a synthesis of a variety of pyrrolidines with a C_2 symmetry axis. Furthermore, *O*-methylation of **39** (NaH, CH_3I, DMF) afforded **40b** and *O*-methoxymethylation (Pr^i_2NEt, MOMCl) yielded **40c**. Ring cleavage of **40b,c** (10% NaOH–EtOH, reflux) gave the corresponding *trans*-2,5-disubstituted pyrrolidine derivatives **41b,c**, respectively. The compound **39** would be potentially useful for the synthesis of a variety of *trans*-2,5-disubstituted pyrrolidines including a variety of derivatives with a C_2 symmetry axis.

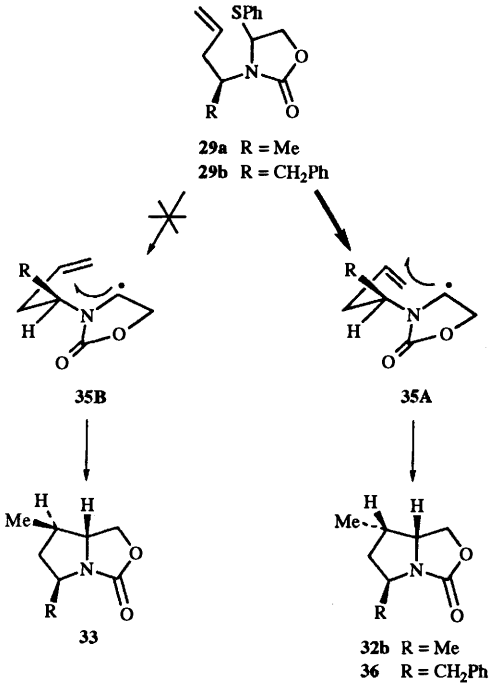
Conclusion

Radical cyclisation of **6a** (R^2 = H) [formed from *N*-(3-bromopropyl)oxazolin-2-ones] by treatment with Bu_3SnH in the presence of AIBN, was found to give the corresponding 5-substituted pyrrolooxazolidin-2-ones with high diastereoselectivity. Cyclisation of **6b** (R^2 = Me) furnished pyrrolooxazolidin-2-ones with high diastereoselectivity with regard to the 5- and 7a-positions, although diastereoselectivity for the relative configuration of the 7- and 7a-positions was not observed, being at most 2:1. However, high diastereoselectivity at both the 7 and 7a centres was observed in the radical cyclisation of the 4-phenylsulfanyloxazolidinone derivatives.

Experimental

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under nitrogen. Tetrahydrofuran (THF)





Scheme 6

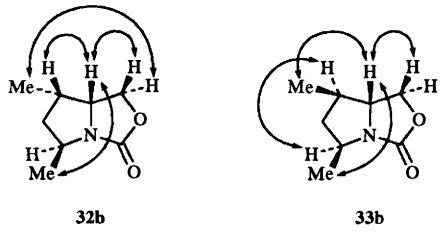
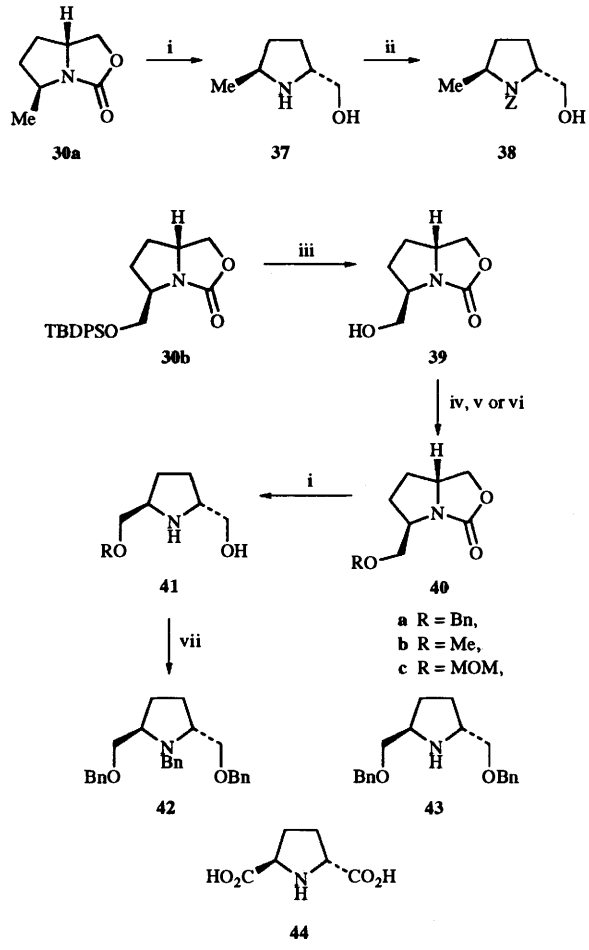


Fig. 1 NOESY correlations in **32b** and **33b**



Scheme 7 *Reagents and conditions:* i, 10% NaOH–EtOH; ii, ZCl, K_2CO_3, CH_2Cl_2; iii, HCl–THF (1:4); iv, for **a** NaH, BnBr; v, for **b** NaH, MeI; vi, for **c** diisopropylamine, MOMCl; vii, NaH, BnBr

and diethyl ether ('ether') were distilled from sodium benzophenone ketyl; methylene dichloride (CH_2Cl_2) was distilled from CaH_2. All reactions were monitored by TLC using commercially available glass-backed plates. For column chromatography, silica gel 60 (0.043–0.063 mm) was used and the columns were eluted in the flash mode.[18] ^1H NMR spectra were recorded on a Bruker AM 400 or Varian Gemini 300 operating at 400 MHz and 300 MHz, respectively, in $CDCl_3$. Chemical shift data were measured relative to tetramethylsilane (TMS). The multiplicity of the signal is indicated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad signal. Coupling constants (J) are given in Hz. ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AM-400 (100 MHz) relative to $CDCl_3$ (δ_C 77.0) unless stated otherwise. Optical rotations were determined with a JASCO DIP-4 polarimeter and $[\alpha]_D$ values are expressed in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded using a Perkin-Elmer 1710 spectrometer and only characteristic bands are given indicating representative functional groups such as OH and C=O. Mass spectra (MS) were measured on a TSQ 700 and VG Auto Spec instrument.

(*R*)-4-Bromobutan-2-ol 7a

A mixture of **8** (10.6 g, 90 mmol), 3,4-dihydropyran (9.08 g, 107.8 mmol), ether (100 cm^3) and *p*-TsOH·H_2O (toluene-*p*-sulfonic acid; 1.7 g, 9.0 mmol) was stirred at room temp. for 10 h and then the mixture was basified with 5% aq. $NaHCO_3$. The organic layer was evaporated to give **9** (17.0 g, 91.0%), 78–86 °C/2 mm Hg; this was reduced with $LiAlH_4$ (4.79 g, 126.1 mmol) in ether (50 cm^3) and worked up to give **10** (13.9 g, 79.9%), 86–95 °C/2 mmHg. To an ice-cooled, stirred mixture of **10** (13.0 g, 74.7 mmol), triethylamine (15.1 g, 149.4 mmol) and CH_2Cl_2 (60 cm^3) was slowly added methanesulfonyl chloride (12.8 g, 112.1 mmol). The ice-cooled mixture was stirred for 15 min, and then at room temp. for 12 h, after which the reaction

mixture was quenched with water and extracted with $CHCl_3$. The organic extract was evaporated and the resultant residue was chromatographed on silica gel using hexane–ethyl acetate (6:1) as eluent. The appropriate fractions were evaporated and a mixture of the resulting residue, LiBr (12.8 g, 149.4 mmol) and acetone (100 cm^3) was stirred at room temp. for 4 h. The mixture was evaporated and the resulting residue was diluted with water and extracted with $CHCl_3$. The organic extract was evaporated under reduced pressure and the remaining residue was chromatographed on silica gel, using hexane–ethyl acetate as eluent to give **11** (13.0 g, 74.0%); δ_H 1.23 (3 H, d, *J* 6.3), 1.5–1.70 (2 H, m), 1.87–1.96 (6 H, m), 3.41 (2 H, t, *J* 6.9), 3.73 (2 H, dt, *J* 2.7, 11.5), 4.09 (1 H, dd, *J* 4.9, 11.5) and 4.53 (1 H, t, *J* 4.9); *m/z* (EI) 236 (M^+) and 238 ($M^+ + 2$). The bromide **11** was stirred at room temp. with a mixture of methanol (70 cm^3) and *p*-TsOH·H_2O (0.1 g), after which the mixture was evaporated and the resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (4:1) gave **7a**[9] (7.34 g, 87.7%), $[\alpha]_D$ −31.8 (*c* 3.68, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3370 (OH); δ_H 1.25 (3 H, d, *J* 6.2), 1.97 (2 H, q, *J* 6.1), 3.53 (2 H, q, *J* 6.1) and 3.99–4.09 (1 H, m); *m/z* (EI) 154 and 152 (M^+), 137 and 135 ($M^+ - OH$).

(*S*)-4-Bromo-1,2-isopropylidenedioxybutane 14

Methanesulfonyl chloride (29.4 g, 256.8 mmol) was slowly added to an ice-cooled, stirred mixture of **12** (25 g, 171.2 mmol) and triethylamine (34.7 g, 342.5 mmol) in CH_2Cl_2 (75 cm^3). The mixture was stirred at the same temp. for 1 h, and then for an additional 12 h at room temp. The mixture was diluted with $CHCl_3$, washed successively with aq. HCl (0.5 mol dm^{-3}) and aq. $NaHCO_3$ (5%) and evaporated and the resulting residue was chromatographed on silica gel using hexane–ethyl acetate (3:1). Evaporation of the appropriate fractions gave **13** (37.1 g, 96.8%), which was used for the following reaction without further purification. A mixture of **13** (37.1 g), LiBr (36.0 g, 414.1 mmol) and acetone (100 cm^3) was stirred at room temperature for 1 h, after which the mixture was evaporated and the residue chromatographed on silica gel. Elution with hexane–ethyl acetate (5:1) yielded **14**[11] (14.1 g, 39.3% from **12**) as a colourless oil; $[\alpha]_D$ −27.9 (*c* 1.22, $CHCl_3$); δ_H 1.34 (3 H, s), 1.42 (3 H, s), 1.98–2.23 (2 H, m), 3.45–3.54 (2 H, m), 3.59 (1 H, dd, *J* 6.1 and 8.1), 4.11 (1 H, dd, *J* 6.1 and 8.1) and 4.22–4.31 (1 H, m); *m/z* (EI) 211 and 209 ($M^+ + 1$).

(*S*)-4-Bromobutane-1,2-diol 15

A mixture of **14** (14.1 g, 67.46 mmol), *p*-TsOH·H_2O (1.28 g, 6.75 mmol) and methanol (200 cm^3) was stirred at room temp. for 0.5 h, and then basified with aq. $NaHCO_3$ (5%). The mixture was filtered and the filtrate evaporated to give an oil, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (1:2) gave **15** (9.80 g, 86%) as a colourless oil; $[\alpha]_D$ −38.4 (*c* 1.64, $CHCl_3$); δ_H 1.99–2.12 (2 H, m), 3.52–3.64 (2 H, m), 3.52 (1 H, dd, *J* 7.1 and 11.1), 3.72 (1 H, dd, *J* 3.2 and 11.1) and 3.92–4.02 (1 H, m); *m/z* (CI) 171 and 169 ($M^+ + 1$), 154 and 152 ($M^+ + 1 - OH$) [Found: ($M^+ - OH$), 150.9747. Calc. for C_4H_8BrO, ($M - OH$), 150.9759].

(*S*)-4-Bromo-1-*tert*-butyldiphenylsilyloxybutan-2-ol 7b

Triethylamine (8.80 g, 86.98 mmol) was added to an ice-cooled, stirred mixture of **15** (9.80 g, 57.96 mmol), TBDPSCl (8.73 g, 57.96 mmol), 4-*N*,*N*′-dimethylaminopyridine (0.71 g, 5.80 mmol) and CH_2Cl_2 (100 cm^3) and the mixture was stirred for 12 h at the same temperature. The mixture was poured onto water and extracted with $CHCl_3$. The organic extract was evaporated and the residue was chromatographed on silica gel with hexane–ethyl acetate (8:1) as eluent to yield **7b** (15.6 g, 94.8%) as colourless oil; $[\alpha]_D$ −17.0 (*c* 1.01, $CHCl_3$); δ_H 1.08 (6 H, s), 1.57 (3 H, s), 1.82–2.06 (2 H, m), 3.46–3.61 (3 H, m), 3.69 (1 H, dd, *J* 3.6, 10.1), 3.84–3.98 (1 H, m), 7.34–7.50 (6 H, m) and 7.61–7.75 (4 H, m); *m/z* (EI) 351 and 349 ($M^+ - tert$-Bu) [Found: ($M^+ - tert$-Bu), 349.0331. Calc. for $C_{16}H_{18}BrO_2Si$, ($M - tert$-Bu), 349.0329].

(*R*)-Heptane-1,3-diol 17

To a stirred solution of **16** (7.8 g, 60.0 mmol) in THF (150 cm^3), Red-Al was slowly added (3.4 mol dm^{-3} solution in toluene; 35.3 cm^3) at 0 °C and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was quenched with aq. HCl (5%), stirred for an additional 0.5 h, filtered and the filtrate was evaporated. The resulting residue was chromatographed on silica gel with hexane–ethyl acetate (1:3) as eluent to yield **17**[3b] (6.5 g, 82%); $[\alpha]_D$ −1.94 (*c* 1.64, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3349 (OH); δ_H 0.88–0.99 (3 H, m), 1.25–1.80 (8 H, m) and 3.78–3.96 (3 H, m); *m/z* (EI) 132 (M^+).

(*R*)-3-Hydroxyheptyl toluene-*p*-sulfonate 18

Triethylamine (4.43 g, 43.8 mmol) was slowly added to an ice-cooled, stirred mixture of **17** (3.85 g, 29.2 mmol), 4-*N*,*N*′-dimethylaminopyridine (0.36 g, 2.92 mmol), *p*-TsCl (5.85 g, 30.7 mmol) and CH_2Cl_2 (80 cm^3) and the mixture was stirred for 4 h at the same temperature. The mixture was poured onto water and extracted with $CHCl_3$. The organic extract was evaporated and the residue was chromatographed on silica gel with hexane–ethyl acetate as eluent to give **18** (7.74 g, 92.6%); $[\alpha]_D$ −5.2 (*c* 1.04, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3563 (OH); δ_H 0.86–0.95 (3 H, m), 1.23–1.46 (6 H, m), 1.59–1.72 (1 H, m), 1.81–1.92 (1 H, m), 3.68–3.78 (1 H, m, OH), 4.09–4.18 (2 H, m), 4.21–4.32 (1 H, m), 7.35 (2 H, d, *J* 8.3) and 7.81 (2 H, d, *J* 8.3); *m/z* (EI) 286 (M^+).

(*R*)-1-Bromoheptan-3-ol 7c

A mixture of **18** (7.74 g, 27.04 mmol), LiBr (5.87 g, 67.6 mmol) and THF (85 cm^3) was stirred at 50 °C for 12 h, after which the mixture was evaporated and the resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (9:1) gave **7c**[3b] (3.9 g, 74%); $[\alpha]_D$ −20.0 (*c* 1.03, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3354 (OH); δ_H 0.86–0.96 (3 H, m), 1.24–1.55 (6 H, m), 1.91–2.03 (2 H, m), 3.50–3.64 (2 H, m) and 3.73–3.86 (1 H, m); *m/z* (EI) 196 and 194 (M^+) [Found: ($M^+ - H$), 193.0235. Calc. for $C_7H_{15}OBr$, ($M - H$), 193.0228].

(*R*)-4-Bromo-1-(4-methoxyphenyl)butan-2-ol 7d

To a mixture of CuI (0.95 g) in THF (150 cm^3) 4-methoxyphenylmagnesium bromide (1 mol dm^{-3} solution in THF; 49.67 cm^3) was added at −30 °C and the mixture was stirred for 15 min after which **19** (5.0 g, 33.11 mmol) was slowly added. The mixture was stirred at 0 °C for 2 h, poured onto water and then extracted with ether. The organic extract was washed with aq. NH_4Cl, dried (Na_2SO_4) and evaporated. The resulting residue was chromatographed on silica gel using hexane–ethyl acetate (10:1) as eluent to yield **7d** (6.17 g, 72.0%) as colourless needles, mp 83–84 °C; $[\alpha]_D$ −29.1 (*c* 1.1, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3337 (OH); δ_H 1.98–2.11 (2 H, m), 2.65 (1 H, dd, *J* 8.4 and 13.7), 2.79 (1 H, dd, *J* 4.3 and 13.7), 3.57 (2 H, t, *J* 9.9), 3.80 (3 H, s), 3.92–4.05 (1 H, m), 6.87 (2 H, d, *J* 8.7) and 7.14 (2 H, d, *J* 8.7); *m/z* (EI) 259 and 257 (M^+) (Found: C, 51.1; H, 5.85. $C_{11}H_{15}BrO_2$ requires C, 51.15; H, 5.85%).

(*R*)-1-Bromohept-6-ene-3-ol 7e

This compound (5.52 g, 86.4%) was obtained as a colourless oil from **19** (5 g, 33.1 mmol) and allylmagnesium bromide (1 mol dm^{-3} solution in THF; 49.67 cm^3) according to the same conditions as above: $[\alpha]_D$ −1.0 (*c* 1.21, $CHCl_3$); ν_{max}-($CHCl_3$)/cm^{-1} 3364 (OH); δ_H 1.55–1.69 (2 H, m), 1.93–2.08 (2 H, m), 2.10–2.32 (2 H, m), 3.49–3.68 (2 H, m), 3.80–3.95 (1 H, m), 4.90–5.16 (2 H, m) and 5.73–5.93 (1 H, m); *m/z* (EI) 139 and 137 ($M^+ - CH_2{=}CHCH_2CH_2$).

General procedure for the synthesis of 20a–e, 23a,b and 27a,b

To an ice-cooled, stirred mixture of alcohol, oxazolidine-2,4-

dione (1.05 equiv. to the alcohol), Ph_3P (1.05 equiv. to the alcohol) and THF (for a *ca.* 2 mol dm^{-3} solution for the alcohol), a solution of diisopropyl azodicarboxylate (1.05 equiv. to the alcohol) in THF was slowly added. The mixture was stirred at room temperature for 12 h, after which it was evaporated and the resulting residue was chromatographed on silica gel using the solvent shown below as an eluent. Evaporation of the appropriate fractions under reduced pressure yielded the corresponding *N*-substituted oxazolidine-2,4-dione.

(*S*)-*N*-(4-Bromobutan-2-yl)oxazolidine-2,4-dione 20a. The coupling reaction of oxazolidine-2,4-dione with **7a** (6.06 g, 39.6 mmol) gave **20a** (64.0%, 5.98 g) as a colourless oil. Hexane–ethyl acetate (6:1) was used as eluent; $[\alpha]_D$ +13.4 (*c* 1.64, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1811 (C=O) and 1741 (C=O); δ_H 1.27 (3 H, d, *J* 6.2), 2.20–2.31 (1 H, m), 2.65–2.68 (1 H, m), 3.34–3.42 (2 H, m), 4.38–4.50 (1 H, m) and 4.66 (2 H, s); *m/z* (EI) 238 and 236 (M^+), 130 and 128 ($M^+ - CH_2CH_2Br$) (Found: M^+, 236.9824. Calc. for $C_7H_{10}BrNO_3$, *M*, 236.9790).

(*R*)-*N*-[4-Bromo-1-(*tert*-butyldiphenylsilyloxy)butan-2-yl]-oxazolidine-2,4-dione 20b. The coupling reaction of oxazolidine-2,4-dione with **7b** (15.5 g, 54.77 mmol) gave **20b** (58.6%, 15.7 g) as a colourless oil. Hexane–ethyl acetate (6:1) was used as eluent· $[\alpha]_D$ −11.2 (*c* 1.18, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1816 (C=O) and 1746 (C=O); δ_H 1.01 (6 H, s), 1.55 (3 H, s), 2.06–2.18 (1 H, m), 2.48–2.62 (1 H, m), 3.25–3.41 (2 H, m), 3.66 (1 H, dd, *J* 5.3 and 10.2), 4.07 (1 H, dd, *J* 9.6 and 10.2), 4.42–4.54 (1 H, m), 4.62 (2 H, s), 7.37–7.50 (6 H, m) and 7.58–7.66 (4 H, m); *m/z* (EI) 476 and 474 ($M^+ - CH_3$), 434 and 432 (M^+ – *tert*-Bu) [Found: (M^+ – *tert*-Bu), 432.0276. Calc. for $C_{19}H_{19}BrNO_4Si$, (*M* – *tert*-Bu), 432.0267].

(*S*)-*N*-(1-Bromoheptan-3-yl)oxazolidine-2,4-dione 20c. The coupling reaction of oxazolidine-2,4-dione with **7c** (5.0 g, 25.64 mmol) gave **20c** (65%, 4.62 g) as a colourless oil. Hexane–ethyl acetate (6:1) was used as eluent; $[\alpha]_D$ +6.37 (*c* 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1815 (C=O) and 1746 (C=O); δ_H 0.88 (3 H, t, *J* 7), 1.14–1.41 (4 H, m), 1.59–1.73 (1 H, m), 1.90–2.05 (1 H, m), 2.14–2.26 (1 H, m), 2.54–2.66 (1 H, m), 3.25–3.44 (2 H, m), 4.18–4.30 (1 H, m) and 4.67 (2 H, s); *m/z* (EI) 277 (M^+) (Found: M^+, 277.0330. Calc. for $C_{10}H_{16}BrNO_3$, *M*, 277.0314).

(*S*)-*N*-[4-Bromo-1-(4-methoxyphenyl)butan-2-yl]oxazolidine-2,4-dione 20d. The coupling reaction of oxazolidine-2,4-dione with **7d** (5.9 g, 23.01 mmol) gave **20d** (4.9 g, 62.5%) as a colourless oil. Hexane–ethyl acetate (10:1) was used as eluent; $[\alpha]_D$ −34.3 (*c* 0.8, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1811 (C=O) and 1736 (C=O); δ_H 2.25–2.38 (1 H, m), 2.63–2.77 (1 H, m), 3.00 (1 H, dd, *J* 5.8 and 14.0), (1 H, dd, *J* 10.1 and 14.0), 3.32–3.47 (2 H, m), 3.78 (3 H, s), 4.42 (1 H, d, *J* 16.2), 4.52 (1 H, d, *J* 16.2), 6.82 (2 H, d, *J* 8.6) and 7.09 (2 H, d, *J* 8.6); *m/z* (EI) 343 and 341 (M^+) (Found: M^+, 341.0281. Calc. for $C_{14}H_{16}BrNO_4$, *M*, 341.0263).

(*S*)-*N*-(1-Bromohept-6-en-3-yl)oxazolidine-2,4-dione 20e. The coupling reaction of oxazolidine-2,4-dione with **7e** (5.53 g, 28.6 mmol) gave **20e** (5.57 g, 70.8%) as a colourless oil. Hexane–ethyl acetate (8:1) was used as eluent; $[\alpha]_D$ +12.7 (*c* 0.49, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1814 (C=O) and 1736 (C=O); δ_H 1.72–1.84 (1 H, m), 1.96–2.29 (4 H, m), 2.55–2.62 (1 H, m), 3.27–3.43 (2 H, m), 4.24–4.35 (1 H, m), 4.65 (2 H, s), 4.95–5.12 (2 H, m) and 5.67–5.83 (1 H, m); *m/z* (CI) 278 and 276 (M^+ + 1) [Found: ($M^+ - CH_2CH_2CH{=}CH_2$), 219.9582. Calc. for $C_6H_7BrNO_3$, ($M - CH_2CH_2CH{=}CH_2$), 219.9609].

(±)-*N*-(3-Bromobutyl)oxazolidine-2,4-dione 23a. The coupling reaction of 3-bromobutanol (5.0 g, 32.68 mmol) with oxazolidine-2,4-dione gave **23a** (5.17 g, 62.3%) as an oil; ν_{max}(neat)/cm^{-1} 1818 (C=O) and 1734 (C=O); δ_H 1.76 (3 H, d, *J* 6.7), 2.13–2.22 (2 H, m), 3.65–3.87 (2 H, m), 4.03–4.17 (1 H, m) and 4.71 (2 H, s); *m/z* (EI) 237 and 235 (M^+) (Found: M^+, 234.9837. Calc. for $C_7H_{10}BrNO_3$, *M*, 234.9844).

(±)-*N*-(4-Bromopentan-2-yl)oxazolidine-2,4-dione 23b. The coupling reaction of 4-bromopentan-2-ol (5.0 g, 29.94 mmol) with oxazolidine-2,4-dione gave **23b** (4.96 g, 66.5%) as a colourless oil; ν_{max}(neat)/cm^{-1} 1817 (C=O) and 1729 (C=O); δ_H 1.43 (1.5 H, d, *J* 7.0), 1.44 (1.5 H, d, *J* 7.0), 1.74 (1.5 H, d, *J* 6.7), 1.75 (1.5 H, d, *J* 6.7), 1.92–2.05 (0.5 H, m), 2.21–2.31 (0.5 H, m), 2.35–2.46 (0.5 H, m), 2.67–2.78 (0.5 H, m), 3.86–4.16 (1 H, m), 4.36–4.50 (0.5 H, m), 4.50–4.60 (0.5 H, m), 4.65 (1 H, s) and 4.67 (1 H, s); *m/z* (EI) 251 and 249 (M^+) (Found: M^+, 249.0007. Calc. for $C_8H_{12}BrNO_3$, *M*, 249.0001).

(±)-*N*-(Pent-4-en-2-yl)oxazolidine-2,4-dione 27a. The coupling reaction of pent-4-en-2-ol (2.0 g, 23.26 mmol) with oxazolidine-2,4-dione gave **27a** (2.40 g, 61.0%) as a colourless oil. Hexane–ethyl acetate (7:1) was used as eluent; ν_{max}(neat)/cm^{-1} 1820 (C=O) and 1732 (C=O); δ_H 1.45 (3 H, d, *J* 6.2), 2.38–2.49 (1 H, m), 2.65–2.80 (1 H, m), 4.16–4.29 (1 H, m), 4.60 (2 H, s), 5.02–5.14 (2 H, m) and 5.62–5.78 (1 H, m); *m/z* (EI) 169 (M^+) (Found: M^+, 169.0728. Calc. for $C_8H_{11}NO_3$, *M*, 169.0739).

(*R*)-*N*-(1-Phenylpent-4-en-2-yl)oxazolidine-2,4-dione 27b. The coupling reaction of (*S*)-1-phenylpent-4-en-2-ol (2.0 g, 12.35 mmol) with oxazolidine-2,4-dione gave **27b** (1.91 g, 63.0%) as a colourless oil; $[\alpha]_D$ +79.3 (*c* 0.89, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1815 (C=O) and 1741 (C=O); δ_H 2.54 (1 H, dt, *J* 5.2 and 14.2), 2.82 (1 H, dt, *J* 9.3 and 14.0), 3.08 (1 H, dd, *J* 6.0 and 14.0), 3.26 (1 H, d, *J* 10.2 and 14.0), 4.32–4.45 (1 H, m), 4.41 (1 H, m), 4.44 (1 H, m), 5.07–5.18 (2 H, m), 5.66–5.80 (1 H, m) and 7.15–7.34 (5 H, m); *m/z* (CI) 246 (M^+ + 1), *m/z* (EI) 245 (M^+) (Found: M^+, 245.1072. Calc. for $C_{14}H_{15}NO_3$, *M*, 245.1052).

General procedure for the synthesis of 2,3-dihydrooxazol-2-ones 22 and 25

To an ice-cooled stirred solution of **20a–e** (or **23a,b**) in methanol (0.2 mol dm^{-3}), $NaBH_4$ (2 equiv.) was slowly added and the mixture was stirred at the same temperature for 0.5 h and then for a further 2 h at room temperature. The reaction mixture was quenched with acetone and evaporated and the resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (4:1) gave the corresponding 4-hydroxy derivatives **21** (or **24**). To an ice-cooled, stirred mixture of compounds **21** or **24** and triethylamine (2 equiv.) in CH_2Cl_2 (0.15 mol dm^{-3} for **21** or **24**) methanesulfonyl chloride (1.5 equiv.) was slowly added. The mixture was stirred for 0.5 h at the same temperature and then for a further 12 h at room temperature after which the mixture was extracted with $CHCl_3$. The extract was washed successively with aq. HCl (0.5 mol dm^{-3}) and brine, and evaporated and the remaining residue was chromatographed on silica gel using hexane–ethyl acetate (8:1) as eluent.

(*S*)-*N*-(4-Bromobutan-2-yl)-2,3-dihydrooxazol-2-one 22a. Compound **22a** (2.31 g, 55.3%) was obtained as a colourless oil from **20a** (4.50 g, 19.05 mmol); $[\alpha]_D$ +13.87 (*c* 2.64, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1741 (C=O); δ_H 1.38 (3 H, d, *J* 6.9), 2.06–2.18 (1 H, m), 2.26–2.38 (1 H, m), 3.26–3.40 (2 H, m), 4.20–4.28 (1 H, m), 6.52 (1 H, d, *J* 2.1) and 6.81 (1 H, d, *J* 2.1); *m/z* (EI) 221 and 219 (M^+) (Found: M^+, 218.9856. Calc. for $C_7H_{10}NO_2Br$, *M*, 218.9895).

(*R*)-*N*-[4-Bromo-1-(*tert*-butyldiphenylsilyloxy)butan-2-yl]-2,3-dihydrooxazol-2-one 22b. Compound **22b** (8.08 g, 54.6%) was obtained as a colourless oil from **20b** (15.3 g, 31.29 mmol); $[\alpha]_D$ +19.2 (*c* 1.03, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1747 (C=O); δ_H 1.07 (6 H, s), 1.60 (3 H, s), 2.12–2.26 (1 H, m), 2.34–2.48 (1 H, m), 3.20–3.39 (2 H, m), 3.82 (2 H, d, *J* 4.8), 4.15–4.28 (1 H, m), 6.68 (1 H, d, *J* 2.0), 6.82 (1 H, d, *J* 2.0), 7.35–7.49 (6 H, m) and 7.55–7.68 (4 H, m); *m/z* (EI) 418 and 416 (M^+ – *tert*-Bu) [Found: (M^+ – *tert*-Bu), 416.0320. Calc. for $C_{19}H_{19}BrNO_3Si$, (*M* – *tert*-Bu), 416.0318].

(*S*)-*N*-(1-Bromoheptan-3-yl)-2,3-dihydrooxazol-2-one 22c. Compound **22c** (1.90 g, 55.6%) was obtained as a colourless oil from **20c** (3.62 g, 13.1 mmol); $[\alpha]_D$ +15.5 (*c* 1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1747 (C=O); δ_H 0.87 (3 H, t, *J* 7.0), 1.15–1.44 (4 H, m), 1.56–1.84 (2 H, m), 2.07–2.36 (2 H, m), 3.21–3.41 (2 H,

m), 3.99–4.13 (1 H, m), 6.49 (1 H, d, *J* 2.0) and 6.83 (1 H, d, *J* 2.0); *m/z* (EI) 263 and 261 (M^+) (Found: M^+, 261.0350. Calc. for $C_{10}H_{16}BrNO_2$, *M*, 261.0364).

(*S*)-*N*-[4-Bromo-1-(4-methoxyphenyl)butan-2-yl]-2,3-dihydrooxazol-2-one 22d. Compound **22d** (2.43 g, 57.2%) was obtained as colourless needles from **20d** (4.46 g, 13.07 mmol), mp 77–78 °C; $[\alpha]_D$ −15.5 (*c* 0.62, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1746 (C=O); δ_H 2.13–2.27 (3 H, m), 2.40–2.54 (1 H, m), 2.91 (1 H, dd, *J* 6.1 and 14.0), 3.07 (1 H, dd, *J* 8.8 and 14.0), 3.27 (1 H, ddd, *J* 6.0, 9.1 and 10.4), 3.41 (1 H, ddd, *J* 4.9, 6.7 and 10.4), 3.79 (3 H, s), 4.16–4.27 (1 H, m), 6.29 (1 H, d, *J* 2.0), 6.70 (1 H, d, *J* 2.0), 6.82 (2 H, d, *J* 8.7) and 7.05 (2 H, d, *J* 8.7); *m/z* (EI) 327 and 325 (M^+) (Found: C, 51.75; H, 4.95; N, 4.35. $C_{14}H_{16}BrNO_3$ requires C, 51.7; H, 4.95; N, 4.3%).

(*S*)-*N*-(1-Bromohept-6-en-3-yl)-2,3-dihydrooxazol-2-one 22e. Compound **22e** (2.87 g, 55.2%) was obtained as a colourless oil from **20e** (5.53 g, 20.01 mmol); $[\alpha]_D$ +36.2 (*c* 0.72, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1746 (C=O); δ_H 1.64–1.78 (1 H, m), 1.78–1.91 (1 H, m), 1.97–2.19 (3 H, m), 2.23–2.37 (1 H, m), 3.25 (1 H, ddd, *J* 6.4, 8.6 and 10.4), 3.35 (1 H, ddd, *J* 5.2, 7.0 and 10.4), 4.00–4.13 (1 H, m), 4.90–5.07 (2 H, m), 5.64–5.70 (1 H, m), 6.51 (1 H, d, *J* 2.1), 6.81 (1 H, d, *J* 2.1), 6.82 (2 H, d, *J* 8.7) and 7.05 (2 H, d, *J* 8.7); *m/z* (EI) 261 and 259 (M^+), 206 and 204 ($M^+ - CH_2CH_2CH{=}CH_2$) (Found: M^+, 259.0217. Calc. for $C_{10}H_{14}BrNO_2$, *M*, 259.0208).

(±)-*N*-(3-Bromobutyl)-2,3-hydrooxazol-2-one 25a. Compound **25a** (1.98 g, 58.6%) was obtained as a colourless oil from **23a** (3.62 g, 15.40 mmol); ν_{max}(neat)/cm^{-1} 1752 (C=O); δ_H 1.76 (3 H, d, *J* 6.7), 1.97–2.10 (1 H, m), 2.22–2.32 (1 H, m), 3.65–3.77 (1 H, m), 3.79–3.90 (1 H, m), 4.01–4.12 (1 H, m), 6.61 (1 H, d, *J* 2.0) and 6.80 (1 H, d, *J* 2.0); *m/z* (EI) 221 and 219 (M^+), 140 (M^+ − Br) (Found: M^+, 218.9856. Calc. for $C_7H_{10}BrNO_2$, *M*, 218.9895).

(±)-*N*-(4-Bromopentan-2-yl)-2,3-dihydrooxazol-2-one 25b. Compound **25b** (2.39 g, 60.4%) was obtained as a colourless oil from **23b** (4.23 g, 17.0 mmol); ν_{max}(neat)/cm^{-1} 1747 (C=O); δ_H 1.35 (1.5 H, d, *J* 6.7), 1.41 (1.5 H, d, *J* 6.7), 1.72 (1.5 H, d, *J* 7.5), 1.75 (1.5 H, d, *J* 7.5), 1.90–2.14 (1 H, m), 2.21–2.43 (1 H, m), 3.85–4.02 (0.5 H, m), 4.19–4.32 (0.5 H, m), 6.51 (0.5 H, d, *J* 2.1), 6.52 (0.5 H, d, *J* 2.1), 6.80 (0.5 H, d, *J* 2.1) and 6.82 (0.5 H, d, *J* 2.1); *m/z* (EI) 235 and 233 (M^+) (Found: M^+, 233.0057. Calc. for $C_8H_{12}BrNO_2$, *M*, 233.0051).

(±)-*N*-(Pent-4-en-2-yl)-4-phenylsulfanyloxazolidin-2-one 29a

To an ice-cooled, stirred solution of **27a** (2.08 g, 12.34 mmol) in methanol (30 cm^3), $NaBH_4$ (0.810 g, 24.56 mmol) was added in small portions and the mixture was stirred at the same temperature for 0.5 h and then at room temperature for a further 2 h. The reaction mixture was quenched with acetone and evaporated under reduced pressure after which the residue was diluted with water and extracted with $CHCl_3$. The extract was evaporated and remaining residue was chromatographed on silica gel with hexane–ethyl acetate (4:1) as eluent to give **28a**. To a stirred mixture of **28a** and diphenyl disulfide (2.67 g, 12.28 mmol) and THF (20 cm^3), tributylphosphine (2.6 g, 12.9 mmol) was slowly added and the mixture was stirred at the same temperature for 0.5 h and then for a further 12 h at room temperature. The mixture was evaporated and the remaining residue was chromatographed on silica gel using hexane–ethyl acetate (8:1) as eluent. Evaporation of the appropriate fractions gave **29a** (2.02 g, 62.5%); ν_{max}(neat)/cm^{-1} 1757 (C=O); δ_H 1.47 (3 H, d, *J* 6.9), 2.36–2.47 (0.5 H, m), 2.52 (1 H, dd, *J* 7.2 and 7.6), 2.71–2.82 (0.5 H, m), 3.69–3.82 (0.5 H, m), 3.95–4.08 (0.5 H, m), 4.29–4.36 (1 H, m), 4.94–4.55 (1 H, m), 5.02–5.20 (3 H, m), 5.70–5.86 (1 H, m) and 7.31–7.53 (5 H, m); *m/z* (CI) 264 (M^+ + 1) and 155 (M^+ − SPh) (Found: M^+, 263.0994. Calc. for $C_{14}H_{17}NO_2S$, *M*, 263.0980).

(*R*)-*N*-(1-Phenylpent-4-en-2-yl)-4-phenylsulfanyloxazolidin-2-one 29b

Compound **29b** (1.31 g, 57.8%) was obtained as a colourless oil from **28b** (1.67 g, 6.82 mmol) with the same conditions as for the preparation of **29a**; $[\alpha]_D$ +49.6 (*c* 0.48, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1752 (C=O); δ_H 2.37–2.46 (1 H, m), 2.74–2.86 (1 H, m), 3.16–3.23 (2 H, m), 4.15–4.25 (2 H, m), 4.26–4.37 (2 H, m), 5.07–5.17 (2 H, m), 5.70–5.90 (1 H, m) and 7.10–7.47 (5 H, m); *m/z* (CI) 340 (M^+ + 1) and 234 (M^+ − SPh) (Found: M^+, 339.1260. Calc. for $C_{20}H_{21}NO_2S$, *M*, 339.1293).

General procedure for radical cyclisation of 22a–e, 25a,b and 29a,b

To a stirred solution of **22** (or **25**, **29**) (0.01 mol dm^{-3}) in benzene was added a solution of tributylstannane (1.5 equiv. to **22**; 0.045 mol dm^{-3}) in benzene with heating during 3 h. During the addition of tributylstannane, AIBN (0.1 equiv. to **22**) was added at 0.5 h intervals. After the mixture had been heated for 5 h under reflux, it was evaporated and the residue was chromatographed on silica gel using the solvent shown below as eluent.

(5*S*,7a*R*)-5-Methyltetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one 30a. Compound **30a** (492 mg, 72.0%) was obtained as a colourless oil from **22a** (1.06 g, 4.85 mmol). Hexane–ethyl acetate (4:1) was used as eluent; $[\alpha]_D$ +70.7 (*c* 0.89, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1747 (C=O); δ_H 1.17 (3 H, d, *J* 6.6), 1.40–1.55 (2 H, m), 1.94–2.03 (1 H, m), 2.18–2.28 (1 H, m), 3.84 (1 H, dd, *J* 6.6 and 13.2), 3.88–4.04 (1 H, m), 4.07 (1 H, dd, *J* 3.5 and 8.9) and 4.40 (1 H, dd, *J* 8.3 and 8.9); δ_C 21.7, 31.5, 34.6, 54.3, 58.4, 67.7 and 161.4; *m/z* (EI) 141 (M^+), 126 ($M^+ - CH_3$) (Found: M^+, 141.0774. Calc. for $C_7H_{11}NO_2$, *M*, 141.0790).

(5*R*,7a*R*)-5-*tert*-Butyldiphenylsilyloxymethyltetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one 30b. Compound **30b** (1.5 g, 78%) was obtained from **22b** (2.3 g, 4.85 mmol) as colourless needles. Hexane–ethyl acetate (6:1) was used as eluent; mp 91–93 °C (from ethyl acetate–hexane); $[\alpha]_D$ +30.0 (*c* 1.03, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1757 (C=O); δ_H 1.07 (6 H, s), 1.59 (3 H, s), 1.29–1.44 (1 H, m), 1.45–1.61 (1 H, m), 1.92–2.21 (2 H, m), 3.67 (1 H, dd, *J* 4.1 and 10.7), 3.84–3.94 (1 H, m), 3.97–4.05 (1 H, m), 4.14 (1 H, dd, *J* 3.3 and 8.7), 4.43 (1 H, dd, *J* 8.1 and 8.7), 7.34–7.49 (6 H, m) and 7.61–7.70 (4 H, m); δ_C 19.3, 26.9, 28.2, 33.6, 59.5, 59.8, 66.0, 67.6, 127.7, 133.4, 135.6 and 162.2; *m/z* (CI) 396 (M^+ + 1) (Found: C, 70.0; H, 7.35; N, 3.6. $C_{23}H_{29}NO_3Si$ requires C, 69.85; H, 7.4; N, 3.55%).

(5*S*,7a*R*)-5-Butyltetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one 30c. Compound **30c** (611 mg, 68.5%) was obtained from **22c** (1.26 g, 4.85 mmol) as a colourless oil. Hexane–ethyl acetate (5:1) was used as eluent; $[\alpha]_D$ +52.8 (*c* 1.02, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1752 (C=O); δ_H 0.82–0.94 (3 H, m), 1.25–1.69 (8 H, m), 1.96–2.06 (1 H, m), 2.19–2.30 (1 H, m), 3.72–4.98 (2 H, m), 4.14 (1 H, dd, *J* 8.0 and 8.9) and 4.46 (1 H, dd, *J* 3.2 and 8.9); δ_C 13.9, 22.4, 28.5, 32.7, 33.3, 36.3, 58.7, 59.0, 67.3 and 161.7; *m/z* (EI) 183 (M^+) (Found: M^+, 183.1256. Calc. for $C_{10}H_{17}NO_2$, *M*, 183.1259).

(5*S*,7a*R*)-5-(*p*-Methoxybenzyl)tetrahydro-1*H*,3*H*-pyrrolo-[1,2-*c*]oxazol-3-one 30d. Compound **30d** (820 mg, 68.7%) was obtained from **22d** (1.58 g, 4.85 mmol) as a colourless oil. Hexane–ethyl acetate (5:1) was used as eluent; $[\alpha]_D$ +51.9 (*c* 0.53, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1752 (C=O); δ_H 1.35–1.53 (1 H, m), 1.58–1.75 (1 H, m), 1.91–2.02 (1 H, m), 2.02–2.17 (1 H, m), 2.75 (1 H, dd, *J* 7.6 and 13.8), 2.91 (1 H, dd, *J* 5.2 and 13.8), 3.79 (3 H, s), 3.68–3.80 (1 H, m), 4.06–4.17 (1 H, m), 4.11 (1 H, dd, *J* 3.5 and 8.9), 4.45 (1 H, dd, *J* 7.9 and 8.9), 6.84 (2 H, d, *J* 8.6) and 7.15 (2 H, d, *J* 8.6); δ_C 31.3, 31.5, 40.5, 55.1, 58.8, 59.4, 67.5, 113.6 (2 lines), 129.5, 130.4 (2 lines), 158.1 and 161.3; *m/z* (EI) 247 (M^+), 126 ($M^+ - CH_2C_6H_4OCH_3$) (Found: M^+, 247.1200. Calc. for $C_{14}H_{17}NO_3$, *M*, 247.1208).

(5*S*,7a*R*)-5-But-3′-enyltetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]-oxazol-3-one 30e. Compound **30e** (665 mg, 75.8%) was obtained from **22e** (1.26 g, 4.85 mmol) as a colourless oil. Hexane–ethyl acetate (5:1) was used as eluent; $[\alpha]_D$ +47.7 (*c* 0.65, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1747 (C=O); δ_H 1.25–1.43 (1 H, m), 1.43–1.71 (4 H, m), 1.99–2.10 (1 H, m), 2.12–2.35 (2 H, m),

3.79–3.97 (2 H, m), 4.17 (1 H, dd, *J* 3.2 and 9.0), 4.48 (1 H, dd, *J* 8.0 and 9.0), 4.93–5.12 (2 H, m) and 5.79–5.94 (1 H, m); δ_C 30.5, 31.1, 32.5, 35.5, 58.4, 58.5, 67.2, 114.5, 137.6 and 161.6; *m/z* (EI) 181 (M^+), 126 ($M^+ - CH_2CH_2$ CH=CH_2) (Found: M^+, 181.1113. Calc. for $C_{10}H_{15}NO_2$, *M*, 181.1103).

Radical cyclisation of 25a; Synthesis of (7*S,7a*R**)-7-methyltetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one 32a and (7*R**,7a*R**)-7-methyltetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one 33a.** Compound **25a** (1.06 g, 4.85 mmol) was treated with tributylstannane in the presence of AIBN and worked up according to the same conditions as above. Elution with hexane–ethyl acetate (2:1) gave **32a** (288 mg, 42.1%); ν_{max}(neat)/cm^{-1} 1752 (C=O); δ_H 0.89 (3 H, d, *J* 7.1), 1.70–1.81 (1 H, m), 2.03–2.29 (2 H, m), 3.19 (1 H, dt, *J* 3.2 and 9.4), 3.58 (1 H, dt, *J* 8.2 and 11.2), 3.98 (1 H, ddd, *J* 3.3, 5.2 and 8.5), 4.27 (1 H, dd, *J* 3.3 and 9.3) and 4.37 (1 H, dd, *J* 8.5 and 9.3); δ_C 12.8, 33.4, 33.5, 43.5, 62.1, 63.8 and 161.5; *m/z* (EI) 141 (M^+) (Found: M^+, 141.0784. Calc. for $C_7H_{11}NO_2$, *M*, 141.0790). Successive elution with hexane–ethyl acetate (1:1) yielded **33a** (139 mg, 20.3%); ν_{max}(neat)/cm^{-1} 1752 (C=O); δ_H 1.06 (3 H, d, *J* 6.5), 1.70–1.89 (2 H, m), 2.18–2.30 (1 H, m), 3.25–3.36 (1 H, m), 3.36–3.46 (1 H, m), 3.59 (1 H, dt, *J* 8.4 and 11.5), 4.17 (1 H, dd, *J* 3.1 and 8.9) and 4.47 (1 H, dd, *J* 7.8 and 8.9); δ_C 15.0, 34.2, 38.5, 45.6, 65.5, 66.4 and 161.6; *m/z* (EI) 141 (M^+) (Found: M^+, 141.0792. Calc. for $C_7H_{11}NO_2$, *M*, 141.0790).

Radical cyclisation of 25b; Synthesis of (5*S,7*S**,7a*R**)-5,7-dimethyltetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one 32b and (5*S**,7*R**,7a*R**)-5,7-dimethyltetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]-oxazol-3-one 33b.** Compound **25b** (1.13 g, 4.85 mmol) was treated with tributylstannane in the presence of AIBN and worked up as above. Elution with hexane–ethyl acetate (2:1) yielded **32b** (338 mg, 45.0%); ν_{max}(neat)/cm^{-1} 1746 (C=O); δ_H 0.89 (3 H, d, *J* 7.2), 1.27 (3 H, d, *J* 6.5), 1.72 (1 H, ddd, *J* 6.0, 8.5 and 13.0), 2.00 (1 H, ddd, *J* 1.3, 7.0 and 13.0), 2.16–2.29 (1 H, m), 3.87–4.00 (1 H, m), 4.05 (1 H, ddd, *J* 3.3, 5.0 and 8.5), 4.25 (1 H, dd, *J* 3.4 and 9.3) and 4.41 (1 H, dd, *J* 8.5 and 9.3); δ_C 13.0, 21.7, 34.8, 42.7, 52.2, 61.5, 63.8 and 161.5; *m/z* (EI) 155 (M^+) (Found: M^+, 155.0967. Calc. for $C_8H_{13}NO_2$, *M*, 155.0946). Successive elution with hexane–ethyl acetate (1:1) yielded **33b** (138 mg, 18.4%), ν_{max}(neat)/cm^{-1} 1752 (C=O); δ_H 1.03 (3 H, d, *J* 6.5), 1.28 (3 H, d, *J* 6.4), 1.17–1.28 (1 H, m), 1.74–1.92 (1 H, m), 2.42 (1 H, dt, *J* 7.1 and 13.0), 3.48 (1 H, ddd, *J* 3.3, 8.0 and 8.7), 3.86–3.99 (1 H, m), 4.14 (1 H, dd, *J* 3.2 and 9.0) and 4.44 (1 H, dd, *J* 8.0 and 9.0); δ_C 14.8, 22.4, 39.9, 43.7, 54.8, 64.6, 66.3 and 161.5; *m/z* (EI) 155 (M^+) (Found: M^+, 155.0937. Calc. for $C_8H_{13}NO_2$, *M*, 155.0946).

Radical cyclisation of 29a. Compound **29a** (1.06 g, 4.02 mmol) was treated with tributylstannane (1.75 g, 8.04 mmol) in the presence of AIBN and worked up as above. Elution with hexane–ethyl acetate (2:1) gave **32b** (486 mg, 78%), the spectral data of which were identical with those of **32b**, obtained from **25b**.

(5*S*,7*S*,7a*R*)-5-Benzyl-7-methyltetrahydro-1*H*,3*H*-pyrrolo-[1,2-*c*]oxazol-3-one 36. Compound **36** (446 mg, 65.5%) was obtained from **29b** (1.00 g, 2.95 mmol), $[\alpha]_D$ −48.46 (*c* 0.97, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1751 (C=O); δ_H 0.85 (3 H, d, *J* 7.2), 1.73–1.92 (2 H, m), 2.08–2.28 (1 H, m), 2.79 (1 H, dd, *J* 8.0 and 13.4), 3.03 (1 H, dd, *J* 4.9 and 13.4), 3.85 (1 H, ddd, *J* 3.3, 5.0 and 8.3), 4.08–4.18 (1 H, m), 4.23 (1 H, dd, *J* 3.3 and 9.3), 4.39 (1 H, dd, *J* 8.3 and 9.3) and 7.19–7.33 (5 H, m); δ_C 13.3, 34.7, 39.8, 41.5, 57.3, 61.9, 63.9, 126.5, 128.3 (2 lines), 129.6 (2 lines), 137.5 and 161.5; *m/z* (EI) 231 (M^+), 140, ($M^+ - CH_2C_6H_5$) (Found: M^+, 231.1259. Calc. for $C_{14}H_{17}NO_3$, *M*, 231.1259).

(2*R*,5*S*)-1-Benzyloxycarbonyl-2-hydroxymethyl-5-methyl-pyrrolidine 38

A mixture of **30a** (463 mg, 3.29 mmol) and NaOH in EtOH (10%; 10 cm^3) was heated for 12 h under reflux, after which it was extracted with $CHCl_3$ (50 cm^3). The organic extract was evaporated and the residue (310 mg, 82%) was used for the following reaction without purification. To a stirred solution of the oily residue in CH_2Cl_2 (5 cm^3) was added K_2CO_3 (350 mg) and then a solution of benzylchloroformate in toluene (30%; 1.6 cm^3) toluene solution (1.6 cm^3) at room temperature.

The mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with aq. citric acid and then evaporated. The resulting residue was chromatographed on silica gel using hexane–ethyl acetate (3:1) as eluent and evaporation of the fractions yielded **38** (428 mg, 52.3% from **30a**); $[\alpha]_D$ −43.8 (*c* 0.10, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3431 (OH) and 1696 (C=O); δ_H 1.14 (3 H, d, *J* 6.3), 1.48–1.56 (1 H, m), 1.63–1.72 (1 H, m), 2.00–2.15 (2 H, m), 3.56 (1 H, dd, *J* 4.0 and 11.0), 3.71 (1 H, dd, *J* 6.9 and 11.0), 4.01–4.10 (2 H, m), 5.13 (2 H, q, *J* 12.3) and 7.26–7.40 (5 H, m); δ_C 20.2, 26.1, 31.0, 54.2, 60.1, 66.3, 67.1, 127.9 (3 lines), 128.4 (2 lines), 136.4 and 156.5; *m/z* (EI) 250 (M^+), 142 ($M^+ - CH_2C_6H_5$) (Found: M^+, 249.1351. Calc. for $C_{14}H_{19}NO_3$, *M*, 249.1365).

(5*R*,7a*R*)-5-Hydroxymethyltetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]-oxazol-3-one 39

A mixture of **30b** (650 mg, 1.65 mmol), conc. HCl (3 cm^3) and THF (9 cm^3) was heated for 1.5 h under reflux after which it was extracted with $CHCl_3$. The extract was washed with $NaHCO_3$ (5%), dried (Na_2SO_4) and evaporated and the resulting residue was chromatographed on silica gel. After removal of non-polar material by elution with hexane–ethyl acetate (6:1), successive elution with $CHCl_3$–methanol (9:1) yielded **39** (232 mg, 90%) as a colourless oil; $[\alpha]_D$ +45.8 (*c* 1.09, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3430 (OH) and 1741 (C=O); δ_H 1.46–1.62 (1 H, m), 1.70–1.84 (1 H, m), 2.05–2.18 (1 H, m), 2.19–2.29 (1 H, m), 3.50 (1 H, dd, *J* 6.9 and 11.3), 3.75 (1 H, dd, *J* 3.6 and 11.3), 3.90–4.06 (2 H, m), 4.20 (1 H, dd, *J* 4.1 and 8.9) and 4.55 (1 H, dd, *J* 8.3 and 8.9); δ_C 28.8, 31.5, 59.3, 60.8, 65.2, 68.4 and 162.2; *m/z* (EI) 157 (M^+) (Found: M^+, 157.0743. Calc. for $C_7H_{11}NO_3$, *M*, 157.0739).

(5*R*,7a*R*)-5-(Benzyloxymethyl)tetrahydro-1*H*,3*H*-pyrrolo-[1,2-*c*]oxazol-3-one 40a

To an ice-cooled, stirred mixture of **39** (300 mg, 1.91 mmol) and NaH (115 mg, 4.78 mmol; used after removal of oil by washing with light petroleum) and DMF (5 cm^3), benzyl bromide (490 mg, 2.87 mmol) was added. After the mixture was allowed to stand for 1 h at the same temp. and then stirred for an additional 2 h at room temp., it was poured onto ice–water and extracted with ether. The extract was evaporated and the residue was chromatographed on silica gel using hexane–ethyl acetate (5:1) as eluent to give **40a** (346 mg, 73.3%) as a colourless oil; $[\alpha]_D$ +58.7 (*c* 1.23, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1752 (C=O); δ_H 1.42–1.57 (1 H, m), 1.83–1.96 (1 H, m), 2.04–2.26 (2 H, m), 3.53 (1 H, dd, *J* 5.0 and 10.0), 3.57 (1 H, dd, *J* 5.0 and 10.0), 3.89–3.99 (1 H, m), 4.04–4.12 (1 H, m), 4.17 (1 H, dd, *J* 3.1 and 8.9), 4.49 (1 H, dd, *J* 7.8 and 8.9), 4.55 (1 H, d, *J* 12.0), 4.62 (1 H, d, *J* 12.0) and 7.24–7.38 (5 H, m); δ_C 28.9, 31.4, 58.1, 59.3, 67.5, 72.4, 73.2, 127.5, 127.6 (2 lines), 128.3 (2 lines), 138.1 and 161.5; *m/z* (EI) 247 (M^+) (Found: M^+, 247.1198. Calc. for $C_{14}H_{17}NO_3$; *M*, 247.1208).

(5*R*,7a*R*)-5-(Methoxymethyl)tetrahydro-1*H*,3*H*-pyrrolo-[1,2-*c*]oxazol-3-one 40b

To an ice-cooled, stirred mixture of **39** (300 mg, 1.91 mmol) and NaH (115 mg, 4.78 mmol; used after removal of oil by washing with light petroleum) and DMF (5 cm^3), methyl iodide (364 mg, 2.87 mmol) was added. After the mixture was allowed to stand for 1 h at the same temp. and then stirred for an additional 12 h at room temp., it was poured onto ice–water and extracted with ether. The extract was evaporated and the residue was chromatographed on silica gel using hexane–ethyl acetate (5:1) as eluent to give **40b** (250.6 mg, 76.7%) as a colourless oil; $[\alpha]_D$ +64.7 (*c* 1.58, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1751 (C=O); δ_H 1.41–1.56 (1 H, m), 1.76–1.85 (1 H, m), 2.02–2.25 (2 H, m), 3.39 (3 H,

s), 3.41 (1 H, dd, *J* 5.0 and 9.8), 3.88–3.98 (1 H, m), 4.00–4.09 (1 H, m), 4.17 (1 H, dd, *J* 3.0 and 8.8) and 4.49 (1 H, dd, *J* 7.8 and 8.8); δ_C 28.7, 31.4, 58.0, 59.1, 59.4, 67.5, 74.8 and 161.7; *m/z* (EI) 171 (M^+) (Found: M^+, 171.0902. Calc. for $C_8H_{13}NO_3$, *M*, 171.0895).

(5*R*,7a*R*)-5-(Methoxymethoxymethyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one 40c

To an ice-cooled, stirred mixture of **39** (300 mg, 1.91 mmol), diisopropylethylamine (549 mg, 1.87 mmol) and CH_2Cl_2 (5 cm^3), methoxymethyl chloride (MOMCl; 185 mg, 2.29 mmol) was added. The mixture was stirred at the same temp. for 0.5 h and an additional 12 h at room temperature, after which it was poured onto water and extracted with $CHCl_3$. The extract was washed with aq. HCl (5%) and aq. $NaHCO_3$ (5%) and evaporated to give a residue which was chromatographed on silica gel. Elution with hexane–ethyl acetate (3:1) yielded **40c** (312 mg, 81%) as colourless oil; $[\alpha]_D$ +59.2 (*c* 1.18, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1752 (C=O); δ_H 1.44–1.59 (1 H, m), 1.77–1.90 (1 H, m), 2.04–2.15 (2 H, m), 2.16–2.29 (1 H, m), 3.37 (3 H, s), 3.56 (1 H, dd, *J* 3.0 and 8.8), 4.49 (1 H, dd, *J* 3.0 and 8.8) and 4.65 (2 H, s); δ_C 28.8, 31.2, 55.2, 58.0, 59.2, 67.4, 69.8, 96.4 and 161.5; *m/z* (CI) 202 ($M^+ + 1$) (Found: M^+, 201.1012. Calc. for $C_9H_{15}NO_4$, *M*, 201.1001).

(2*R*,5*R*)-2-Benzyloxymethyl-5-hydroxymethylpyrrolidine 41a

A mixture of **40a** (321 mg, 1.30 mmol) and NaOH in ethanol (1 mol dm^{-3}; 9 cm^3) was heated for 2 h under reflux, after which the mixture was evaporated and extracted with $CHCl_3$. The extract was evaporated and the residue chromatographed on silica gel using $CHCl_3$–methanol (9:1) as eluent to give **41a** (218 mg, 76%) as a colourless oil; $[\alpha]_D$ −12.5 (*c* 0.10, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3325 (OH); δ_H 1.44–1.60 (2 H, m), 1.81–1.95 (2 H, m), 2.38 (1 H, br s), 3.31–3.59 (6 H, m), 4.55 (2 H, s) and 7.25–7.40 (5 H, m); δ_C 27.2, 28.2, 57.4, 58.9, 64.4, 72.3, 73.2, 127.7 (3 lines), 128.4 (2 lines) and 138.1; *m/z* (CI) 222 ($M^+ + 1$), 100 ($M^+ - CH_2OBn$) [Found: ($M^+ - CH_2OH$), 190.1239. Calc. for $C_{12}H_{16}NO$, ($M - CH_2OH$), 190.1232].

(2*R*,5*R*)-2-Hydroxymethyl-5-methoxymethylpyrrolidine 41b

A mixture of **40b** (225 mg, 1.31 mmol) and NaOH in ethanol (1 mol dm^{-3}; 9 cm^3) was heated and worked up as in the synthesis of **41a** to yield **41b** (167 mg, 88%) as a colourless oil; $[\alpha]_D$ −14.3 (*c* 0.36, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3446 (OH); δ_H 1.42–1.59 (2 H, m), 1.80–1.96 (2 H, m), 2.99 (1 H, br s), 3.28–3.44 (4 H, m), 3.36 (3 H, m) and 3.51–3.57 (2 H, m); δ_C 27.2, 28.1, 57.6, 59.0, 59.5, 63.9 and 74.3; *m/z* (CI) 146 ($M^+ + 1$), 114 ($M^+ - OCH_3$) and 100 ($M^+ - CH_2OCH_3$) [Found: ($M^+ + H$), 146.1162. Calc. for $C_7H_{16}NO_2$, ($M + H$), 146.1181].

(2*R*,5*R*)-2-Hydroxymethyl-5-methoxymethoxymethylhydroxypyrrolidine 41c

A mixture of **40c** (301.2 mg, 1.50 mmol) and NaOH in ethanol (1 mol dm^{-3}; 9 cm^3) was heated and worked up as in the synthesis of **41a** to yield **41c** (220.5 mg, 84%) as a colourless oil; $[\alpha]_D$ −11.9 (*c* 2.49, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3328 (OH); δ_H 1.48–1.62 (2 H, m), 1.86–2.00 (2 H, m), 2.83 (1 H, br s), 3.32–3.52 (4 H, m), 3.38 (3 H, m), 4.64 (1 H, d, *J* 6.4) and 4.66 (1 H, d, *J* 6.9); δ_C 27.2, 28.1, 55.2, 57.4, 59.2, 64.3, 69.6 and 96.6; *m/z* (CI) 176 ($M^+ + 1$) and 100 ($M^+ - CH_2OCH_2OCH_3$) (Found: M^+, 175.1190. Calc. for $C_8H_{17}NO_3$, *M*, 175.1208).

(2*R*,5*R*)-1-Benzyl-2,5-bis(benzyloxymethyl)pyrrolidine 42

To an ice-cooled, stirred mixture of **41a** (196.3 mg, 0.89 mmol) and NaH (106 mg, 4.44 mmol, used after removal of oil by washing with light petroleum) and DMF (5 cm^3), benzyl bromide (456 mg, 2.66 mmol) was added. The mixture was allowed to stand for 1 h at the same temp. and then stirred for an additional 2 h at room temp. after which it was poured onto ice–water and extracted with ether. The organic extract was evaporated and the remaining residue was chromatographed on silica gel using $CHCl_3$–methanol (9:1) as eluent to give **42** (143 mg, 40.0%) as a colourless oil; $[\alpha]_D$ +69.6 (*c* 1.82, $CHCl_3$); δ_H 1.63–1.80 (2 H, m), 1.94–2.12 (2 H, m), 3.18–3.29 (2 H, m), 3.30–3.48 (4 H, m), 3.85 (1 H, d, *J* 14.0), 4.08 (1 H, d, *J* 14.6), 4.47 (4 H, s) and 7.14–7.43 (15 H, m); δ_C 27.4, 52.7, 60.7, 71.9, 73.1, 126.5, 127.4, 128.2 and 138.4; *m/z* (EI) 401 (M^+), 200 ($M^+ - CH_2OBn$) (Found: M^+, 401.2345. Calc. for $C_{27}H_{31}NO_2$, *M*, 401.2355).

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