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Synthesis and utility of the 3,3-dimethyl-5-substituted-2-pyrrolidinone 'Quat' chiral auxiliary

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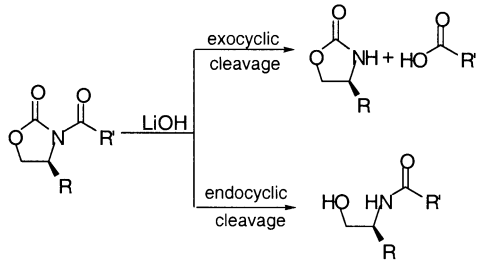
Abstract—The synthesis and utility of the 3,3-dimethyl-5-substituted-2-pyrrolidinone 'Quat' chiral auxiliary in stereoselective enolate reactions of attached *N*-acyl side chains combined with the mild and non-racemising conditions required for the ultimate removal of the chiral side chain is described.

1. Introduction

Chiral auxiliaries based upon oxazolidinone heterocycles[1] represent one of the most powerful tools available to the organic chemist. Treatment of enolates derived from *N*-acyloxazolidinones with a variety of electrophiles can lead to asymmetric alkylation,[2] acylation,[3] bromination,[4] amination,[5] hydroxylation[6] and most importantly aldol addition.[7]

However, the utility of a chiral auxiliary in any synthetic strategy is reliant upon the mild and selective removal of the auxiliary, without racemisation of the stereogenic centres present in the system. The position of nucleophilic cleavage in *N*-acyloxazolidinones is dependent upon steric and electronic requirements (Scheme 1).[8] The nucleophilic cleavage of unhindered systems is subject to electronic factors and *exocyclic* cleavage occurs to give the required products. However, when the group R′ is large, steric factors render the unwanted *endocyclic* cleavage of the oxazolidinone ring more favourable. This problem can be overcome by using lithium hydroperoxide as a nucleophile, since it is apparently less susceptible to steric hindrance. Unsurprisingly, the use of this reagent on a large scale may prove hazardous and as a result we have devised an alternative strategy to circumvent this problem.



Scheme 1.

2. Results and discussion

We believed that a substantial increase in steric bulk adjacent to the endocyclic amide bond would impede nucleophilic attack at this carbonyl and accordingly encourage an exocyclic cleavage mode of hydrolysis. As a result we synthesised the 'Quat' chiral auxiliaries **1**–**4** and investigated this hypothesis. The preliminary results of this study have previously been communicated[9,10] and herein we wish to report our full investigations into this area.

The 'Quat' auxiliaries were prepared according to Scheme 2. The synthesis began from L-pyroglutamic acid **5** which was converted into (*S*)-(+)-5-hydroxymethyl-2-pyrrolidinone **6**, via the two-step procedure of Levy and Silverman in 68% yield.[11] In order to introduce the geminal dimethyl groups adjacent to the carbonyl functionality, protection of the acidic hydroxymethyl and lactam functionality was necessary. This was effected using an excess of 2,2-dimethoxypropane and a catalytic quantity of *para*-toluene sulfonic acid, in refluxing toluene with azeotropic removal of

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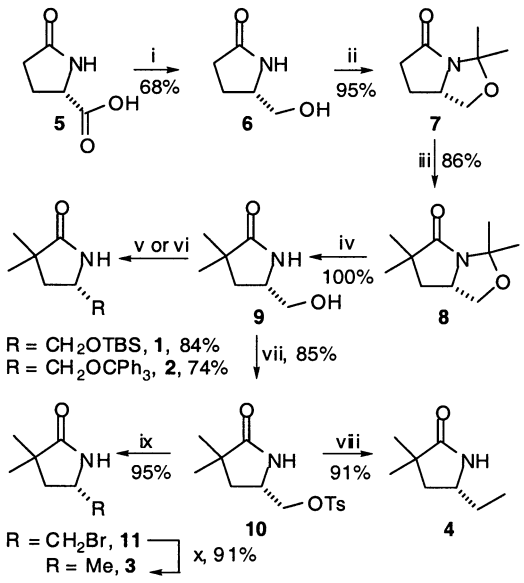


Scheme 2. *Reagents and conditions*: (i) EtOH, toluene, H_2SO_4 (cat.), Δ, then $NaBH_4$ (1 equiv.) EtOH, rt, 1.5 h; (ii) 2,2-dimethoxypropane, Tol, PTSA (cat.), Δ; (iii) LDA (1.1 equiv.), −78°C, MeI, −78°C to rt, LDA (1.1 equiv.), −78°C, MeI, −78°C to rt; (iv) MeOH, PTSA (cat.), Δ; (v) TBDMSCl, DMF, Im; (vi) Ph_3CCl, DMAP, NEt_3, CH_2Cl_2, rt; (vii) TsCl, Et_3N/CH_2Cl_2 (1:2), rt, 4 h; (ix) LiBr (3.0 equiv.), acetone, Δ, 6 h; (viii) Me_2CuLi (3 equiv.), THF, −20°C; (ix) LiBr (3.0 equiv.), acetone, Δ, 6 h; (x) H_2 (1 atm), Pd/C (20%), Et_3N, EtOH/MeOH (1:1), rt, 24 h.

methanol. The oxazolidine product **7** was then quaternized adjacent to the carbonyl group using a one-pot procedure. Thus, a −78°C THF solution of **7** was treated sequentially with LDA and methyl iodide. After warming to 0°C the reaction mixture was re-cooled to −78°C and treated once again with LDA and methyl iodide before slowly warming to room temperature overnight. Aqueous work-up and purification through a single recrystallisation afforded **8** in good yield and on multigram scale. Quantitative protecting group removal was effected under standard *trans*-acetalisation conditions. Thus, subjection of **8** to boiling methanol containing a catalytic quantity of *para*-toluene sulfonic acid gave the alcohol product **9** in quantitative yield.

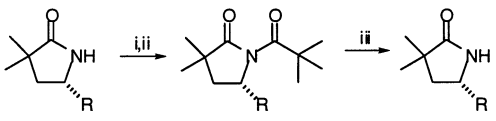
In order to convert **9** into a useful chiral auxiliary, the acidic hydroxy methyl group had to be rendered inert, either by protection or through some other transformation. Initially, standard hydroxyl protecting groups were introduced using standard procedures. Thus, treatment of **9** with TBDMSCl and imidazole in dimethylformamide gave oxazolidone **1** in good yield. Similarly, treatment of **9** with trityl chloride and triethylamine in the presence of a catalytic quantity of dimethylaminopyridine in dichloromethane gave **2** as a white solid in 71% yield. Transformation of the hydroxymethyl group to either a methyl or an ethyl group was also possible. In the former case, treatment of the alcohol with *para*-toluenesulphonyl chloride and triethylamine in dichloromethane afforded tosylate **10**, which was then converted to bromide **11** using a Finkelstein-type reaction. Reduction of the carbon–bromine bond using palladium on charcoal and triethylamine under an atmosphere of hydrogen lead to methyl 'Quat' **3** as a crystalline solid in near quantitative yield. Alternatively, addition of lithium dimethylcuprate to a THF solution of tosylate **10** at −78°C afforded ethyl 'Quat' **4** in 91% yield.

With the 'Quat' auxiliaries **1**–**4** in hand, an investigation into their propensity for exo- versus endocyclic cleavage was undertaken. We envisaged that the bulky *N*-pivaloylated auxiliaries would serve as good models in this respect. The *N*-pivaloyl derivatives **12**–**15** were readily prepared in high yield by reaction of **1**–**4** with *n*-butyllithium in tetrahydrofuran at −78°C followed by quenching with pivaloyl chloride (Scheme 3).

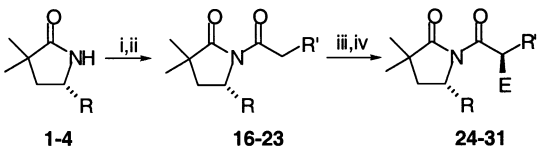
In most cases cleavage of the *N*-pivaloyl 'Quat' derivatives **12**–**15** with LiOH in a 3:1 mixture of tetrahydrofuran and water at room temperature returned the auxiliaries in near quantative yield and no endocyclic cleavage products were detected by ^1H NMR. The low yield of **1** was due to partial deprotection of the hydroxyl group under the hydrolysis conditions. The *N*-pivaloyl derivatives of the Evans oxazolidin-2-ones have previously been shown to give a mixture of exocyclic and endocyclic cleavage products in various ratios. Clearly, an increase in steric bulk adjacent to the endocyclic carbonyl does indeed favour exocyclic cleavage, however, the next step in our investigation was to ascertain the utility of these auxiliaries in asymmetric transformations, in particular the asymmetric alkylation and aldol addition.

We anticipated that lithium enolates derived from *N*-acyl derivatives **16**–**23** would react with alkyl halides in a highly stereoselective manner. On the basis of previous studies we envisaged that the diastereofacial preference would be consistent with the operation of a chelated transition state, with the alkyl halide approaching from the least sterically hindered face of the enolate. Formation of the *N*-acyl derivatives **16**–**23** according to Evans' protocol occurred smoothly. Treatment of this series with lithium diisopropylamide in tetrahydrofuran at 0°C gave the lithium enolate, which was then quenched with benzyl bromide or iodomethane to give a series of alkylated products **24**–**31** (Scheme 4, Table 1).

In all cases good to excellent diastereoselectivities were observed in the alkylation reactions. However, in some



Scheme 3. *Reagents and conditions*: (i) *n*-BuLi, pivaloyl chloride; (iii) LiOH, THF:H_2O, 3:1, rt.



Scheme 4. *Reagents and conditions*: (i) *n*-BuLi, THF, −78°C; (ii) R′CH_2COCl; (iii) LDA, THF, −78°C; (iv) EX.

cases yields were fairly moderate and methyl 'Quat' stood out as auxiliary of choice from this point of view. With the protected hydroxymethyl-based auxiliaries **16**–**19**, yields were usually low due to enolate instability and partial deprotection during the reactions, work-ups and purifications.

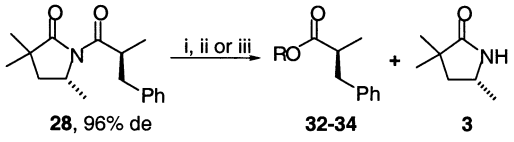
Having established that enolates derived from *N*-acyl derivatives **16**–**23** react with electrophiles in a highly stereoselective manner, the cleavage of the alkylated products with LiOH, MeOMgBr, and $PhCH_2OLi$ (Scheme 5, Table 2) was then investigated. Cleavage of **28** gave rise to respectively (*S*)-2-benzylpropionic acid **32**, methyl ester **33**, and the benzyl ester **34** and again a total absence of endocyclic cleavage products. The absolute configurations were determined by measurement of the specific rotation and comparison with the literature values, which confirmed that a chelation control model could account for the sense of stereochemical induction. The use of chiral shift reagents confirmed that no racemisation had occurred during the cleavage reactions.

Having demonstrated the effectiveness of the 'Quat' auxiliaries in asymmetric alkylation, attention was turned to asymmetric aldol methodology. The *N*-propionyl derivative **20** was subjected to the dibutylboron aldol methodology developed by Evans (Scheme 6).

A methylene chloride solution of the *N*-propionyl methyl 'Quat' **20**, at 0°C under an argon atmosphere, was treated successively with a 1.0 M solution of dibutylboron triflate in methylene chloride (1.1 equiv.) and then diisopropylethylamine (1.2 equiv.). To the resulting solution cooled to −78°C was added benzaldehyde (1.2 equiv.) and this mixture was stirred for 1 h at −78°C and 1.5 h at 0°C. The reaction was then quenched by the addition of a pH 7 phosphate buffer solution and methanol, and treated with methanolic hydrogen peroxide at 0°C for 1 h. Analysis of the crude product mixture by 300 MHz ^{1}H NMR spectroscopy indicated the presence of only one diastereoisomeric product **35** (de >97%). The non-crystalline adduct **35** was purified by flash column chromatography on silica gel. The *syn* relative stereochemistry of the aldol product was assigned on the basis of ^{1}H NMR coupling constants.[12] The coupling constant H_2–H_3 measured for the product **35** was 3.0 Hz, consistent with the expected *syn* relative stereochemistry. The absolute configurations of the new stereogenic centres in **35** were assigned after removal of the chiral auxiliary. Hydrolysis of **35** using LiOH in a 3:1 mixture of tetrahydrofuran and water at 0°C generated 3-hydroxy-2-methyl-3-phenylpropionic acid **36** as a single diastereoisomer in 94% yield. Comparison of the specific rotation {$[\alpha]_D^{21}$ +26.8 (*c* 0.5, CH_2Cl_2)} of the crystalline 3-hydroxy-2-methyl-3-phenylpropionic acid **36** thus obtained, with the literature value[13] for (2*S*,3*S*)-**36** {$[\alpha]_D^{22}=-26.4$ (*c* 1.04, CH_2Cl_2)} established its absolute configuration as (2*R*,3*R*) (Scheme 7). The 'Quat' chiral auxiliary **3** was recovered nearly quantitatively in this hydrolysis reaction with no products from endocyclic cleavage being observed.

3. Conclusions

A series of chiral auxiliaries bearing a quaternised carbon adjacent to the carbonyl group have been synthesised and their effectiveness as chiral auxiliaries tested. The geminal dimethyl groups were introduced to act as a steric shield, protecting the auxiliary carbonyl from nucleophilic attack by lithium hydroxide during the sidechain hydrolysis step. This was indeed found to be the case and furthermore the diastereoselectivities in the alkylation and aldol reactions of attached *N*-acyl sidechains were good to excellent making the auxiliaries attractive from a synthetic point of view. Further chemistry of the 'Quat' auxiliaries will be reported in the near future.



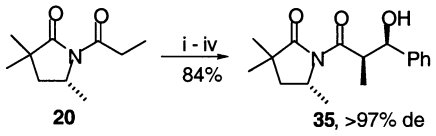
Scheme 5. *Reagents and conditions*: (i) LiOH, THF:H_2O, 3:1, rt; (ii) MeOMgBr, MeOH, 0°C; (iii) BnOLi, THF, 0°C.

Table 1. *N*-Acylations and *C*-alkylations of 'Quat' chiral auxiliaries

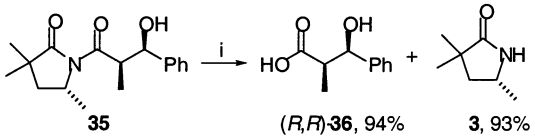
Entry	R	R′	Acylation yield (%)	Product	EX	Alkylation yield (%)	Product	de (%)
1	$CH_2OSiMe_2{}^tBu$	Me	84	**16**	$PhCH_2Br$	33	**24**	95
2	$CH_2OSiMe_2{}^tBu$	CH_2Ph	66	**17**	MeI	64	**25**	94
3	CH_2OCPh_3	Me	84	**18**	$PhCH_2Br$	51	**26**	96
4	CH_2OCPh_3	CH_2Ph	80	**19**	MeI	44	**27**	91
5	Me	Me	90	**20**	$PhCH_2Br$	80	**28**	96
6	Me	CH_2Ph	91	**21**	MeI	62	**29**	89
7	Et	Me	87	**22**	$PhCH_2Br$	78	**30**	95
8	Et	CH_2Ph	85	**23**	MeI	42	**31**	95

Table 2. Cleavage reactions of *N*-acyl 'Quats' **28**

Entry	Product	R	Yield (%)	ee (%)	Yield of **3** (%)
1	**32**	H	83	96	95
2	**33**	Me	82	96	92
3	**34**	$PhCH_2$	94	96	97



Scheme 6. *Reagents and conditions*: (i) Bu_2BOTf; (ii) $^iPr_2NEt$; (iii) PhCHO; (iv) H_2O_2.



Scheme 7. *Reagents and conditions*: (i) LiOH, THF:H_2O, 3:1, rt.

4. Experimental

Optical rotations were recorded using a Perkin–Elmer 241 which has a thermally jacketed 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were obtained by the Dyson Perrins analytical department using a Carla Erba 1106 analyser. Melting points were recorded using a Gallenkamp hot stage apparatus and are uncorrected. Infrared spectra were obtained using a Perkin–Elmer 1750 spectrophotometer; solid samples as KBr discs and liquid samples as a thin film between sodium chloride plates. NMR spectra were recorded using either a Bruker AM500 (^1H; 500.13 MHz and ^{13}C; 125.8 MHz), WH 300 (^1H; 300.13 MHz), AM200 (^1H; 200 MHz and ^{13}C; 50.3 MHz) or Varian Gemini 200 (^1H; 200 MHz and ^{13}C; 50.32 MHz). All spectra were recorded using deuteriochloroform as solvent and internally referenced to residual protiochloroform (δ_H 7.27 and δ_C 77.0) unless otherwise stated. ^1H NMR spectra were run on a Bruker WH 300 unless otherwise stated. ^{13}C NMR were obtained with DEPT editing or assigned by analogy with spectra so recorded. All chemical shifts are given in parts per million relative to tetramethylsilane (δ_H 0.00) and coupling constants (J) are given in hertz. Mass spectra were obtained in the Dyson Perrins analytical department using chemical ionisation (CI) or electronic ionisation (EI) on a VG MASSLAB VG 20-250 or on a Open Linx Micromass Platform 1 using $APCI^+$ or $APCI^-$. High resolution mass spectra were recorded using chemical ionisation (CI) on a VG-AutoSpec Instrument. Flash chromatography was carried out using silica gel (Kieselgel 60). Tetrahydrofuran was distilled from sodium benzophenone ketyl. Acetonitrile and dichloromethane were heated at reflux for 1 h over calcium hydride prior to distillation. Methanol was distilled from glass. Pet. ether refers to that fraction of petroleum ether boiling between 40 and 60°C and was redistilled before use. All other solvents were used as received. Reactions were performed under an atmosphere of dry nitrogen unless otherwise stated.

4.1. (5*S*)-5-Hydroxymethyl-pyrrolidin-2-one 6

To a stirred suspension of pyroglutamic acid **5** (52.0 g, 403 mmol) in dry toluene (260 mL) was added ethanol (50 g) in one portion and concentrated sulphuric acid (1 mL) via pipette. The reaction vessel was fitted with a Dean–Stark apparatus and the mixture refluxed with azeotropic removal of water for 6 h. On cooling, the reaction mixture was diluted with chloroform (250 mL) and then treated with anhydrous potassium carbonate (20 g, 145 mmol). After effervescence ceased, the reaction mixture was filtered through Celite® and concentrated in vacuo to afford pyroglutamic acid ethyl ester as a colourless solid which was used directly in the next step without further purification or characterisation.

This material was dissolved in ethanol, cooled to 0°C with stirring and treated with sodium borohydride (15.13 g, 400.0 mmol) portionwise over 10 min. The reaction mixture was slowly warmed to room temperature (20 min) and stirred for a further 90 min at this temperature. After cooling to 0°C, concentrated hydrochloric acid (~20 mL) was cautiously added to quench the reaction. Filtration of the precipitated salts through Celite® and concentration of the resultant liquor in vacuo afforded a colourless oil. Purification of this material by silica gel chromatography [ethyl acetate/methanol (4:1)] afforded the title compound **6** as colourless crystals (31.2 g, 68%); mp 84–86°C; (lit.[11] mp 66–68°C); $[\alpha]_D^{22}$ +31.8 (*c* 5.0, EtOH); lit.[11] $[\alpha]_D^{20}$ +29.5 (*c* 5, EtOH); δ_H (lit.[11]) 7.40 (1H br s, NH), 4.35 (1H, br s, OH), 3.84–3.76 (1H, m, CHN), 3.69–3.65 (1H, m, CH_2OH), 3.48–3.42 (1H, m, CH_2OH), 2.44–2.26 (2H, m, CH_2CO), 2.22–2.10 (1H, m, CH_2CH_2CO), 1.84–1.73 (1H, m, CH_2CH_2CO).

4.2. (5*S*)-1-Aza-2,2-dimethyl-3-oxa-8-oxo-bicyclo[3,3,0]-octane 7

To a stirred suspension of alcohol **6** (23.12 g, 200.8 mmol) and PTSA (0.180 g, 0.95 mmol) in toluene (500 mL) at room temperature was added 2,2-dimethoxypropane (70 mL, 569.0 mmol) in one portion. The reaction mixture was heated under reflux for 2 h before the boiling fraction between 65 and 92°C was removed by distillation. A further portion of 2,2-dimethoxypropane (70 mL, 569.0 mmol) was added and the reaction mixture was heated under reflux for an

additional 2 h. On cooling, the reaction mixture was concentrated in vacuo to afford a pale yellow solid. Dissolution of this crude product in diethyl ether (300 mL) and subsequent decantation of the upper layer effectively removed the residual PTSA impurity. The ethereal portion was concentrated in vacuo to afford the title compound **7** as fine colourless needles (29.60 g, 95%); mp 38°C; ν_{max} (CH_2Cl_2)/cm^{-1} 1690; $[\alpha]_D^{25}$ +114.7 (*c* 1.0 in $CHCl_3$); (found: C, 61.55; H, 8.75; N, 8.77. $C_8H_{13}NO_2$ requires C, 61.91; H, 8.33; N, 9.03%); δ_H 4.30–4.20 (1H, m, CHN), 4.07 (1H, dd, *J* 8.1 and 5.6, CH_2O), 3.44 (1H, t, *J* 8.9, CH_2O), 2.80 (1H, ddd, 16.6, 12.2 and 8.5, CH_2CO), 2.52 (1H, ddd, *J* 16.5, 9.1 and 0.9, CH_2CO), 2.21–2.17 (1H, m, CH_2CHN), 1.82–1.68 (1H, m, CH_2CHN), 1.66 (3H, s, CH_3), 1.46 (3H, s, CH_3); δ_C ($CDCl_3$; 50 MHz) 23.51 (CH_3), 24.06 (CH_2), 26.57 (CH_3), 36.96 (CH_2), 61.45 (CH), 69.76 (CH_2), 91.12 (C), and 171.59 (CO); *m*/*z* (CI^+, NH_3) 156 (M^++1).

4.3. (5*S*)-1-Aza-2,2-dimethyl-7,7-dimethyl-3-oxa-8-oxo-bicyclo[3,3,0]octane 8

To a stirred solution of acetonide **6** (8.60 g, 55.5 mmol) in THF (200 mL) at −78°C was added a chilled (~0°C) solution of LDA (66.5 mmol) in THF (100 mL) via cannula. Stirring was maintained at this temperature for a further 45 min before neat methyl iodide (4.15 mL, 66.6 mmol) was added slowly via syringe. On warming to room temperature (30 min) and rapid cooling to −78°C, a second chilled (~0°C) portion of LDA (66.5 mmol) in THF (100 mL) was added via cannula to the reaction mixture, which was maintained at this temperature for a further 60 min. A second quantity of methyl iodide (4.15 mL, 66.6 mmol) was then added and the reaction mixture was slowly warmed to room temperature overnight. Removal of volatiles in vacuo afforded a crude yellow oil which was partitioned between dichloromethane (200 mL) and water (150 mL) and further extracted with dichloromethane (2×150 mL). The combined organic portions were washed with brine (80 mL), dried (magnesium sulphate), filtered and concentrated in vacuo to afford a crude yellow solid. Recrystallisation of this material from diethyl ether/pentane afforded the title compound **8** as colourless flaky plates (8.74 g, 86%); mp 82–83°C; ν_{max} (CH_2Cl_2)/cm^{-1} 1686; $[\alpha]_D^{25}$ +75.3 (*c* 1.00, $CHCl_3$); (found: C, 65.47; H, 9.44; N, 7.32. $C_{10}H_{17}NO_2$ requires C, 65.54; H, 9.35; N, 7.64%); δ_H 4.20–4.06 (2H, m, CHN and CH_2O), 3.37 (1H, t, *J* 8.3, CH_2O), 2.00 (1H, dd, *J* 12.1 and 5.8, CH_2CH), 1.63 (3H, s, CH_3), 1.56 (1H, dd, *J* 12.0 and 8.5, CH_2CH), 1.44 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.16 (3H, s, CH_3); δ_C ($CDCl_3$; 50 MHz) 23.64 (CH_3), 24.18 (CH_3), 25.00 (CH_3), 26.54 (CH_3), 39.62 (CH_2), 47.59 (C), 57.30 (CH), 70.15 (CH_2), 91.15 (C), and 176.43 (CO); *m*/*z* (CI^+, NH_3) 184 (M^++1).

4.4. (5*S*)-3,3-Dimethyl-5-hydroxymethyl-pyrrolidin-2-one 9

To a stirred solution of **8** (12.86 g, 70.2 mmol) in methanol (200 mL) at room temperature was added PTSA (0.133 g, 0.70 mmol) in one portion and the reaction mixture was heated at reflux for 4 h. On cooling, the volatiles were removed in vacuo to afford essentially pure title compound **9** as colourless crystals. A small quantity of this material was recrystallised from diethyl ether/pentane for analysis (10.11 g, ~100%); mp 48–49°C; ν_{max} (CH_2Cl_2)/cm^{-1} 1685 and 3333; $[\alpha]_D^{23}$ +82.6 (*c* 1.00, $CHCl_3$); (found: C, 58.89; H, 8.91; N, 9.71. $C_7H_{13}NO_2$ requires C, 58.72; H, 9.15; N, 9.70%); δ_H 7.46 (1H, br s, NH), 4.14 (1H, br s, OH), 3.80–3.71 (1H, m, CHN), 3.66 (1H, dd, *J* 11.5 and 2.9, CH_2O), 3.42 (1H, dd, *J* 11.5 and 2.9, CH_2O), 1.95 (1H, dd, *J* 11.5 and 2.9, CH_2CH), 1.54 (1H, dd, *J* 11.5 and 2.9, CH_2CH), 1.16 (3H, s, CH_3), 1.15 (3H, s, CH_3); δ_C ($CDCl_3$, 50 MHz) 24.89 (CH_3), 25.01 (CH_3), 38.20 (CH_2), 40.49 (C), 53.46 (CH), 65.11 (CH_2), and 183.89 (CO); *m*/*z* (CI^+, NH_3) 144 (M^++1).

4.5. (5*S*)-*O*-*p*-Toluenesulfynylmethyl-3,3-dimethyl-5-pyrrolidin-2-one 10

To a stirred solution of alcohol **8** (10.06 g, 70.3 mmol) and *p*-toluenesulfonyl chloride (21.46 g, 112.6 mmol) in dichloromethane (120 mL) at room temperature, was added freshly distilled triethylamine (60 mL) in one portion. The reaction mixture was stirred at room temperature for 4 h before the volatiles were removed in vacuo to afford a brown solid which was subsequently dissolved in dichloromethane (200 mL). This solution was washed with aqueous hydrochloric acid (1 M, 2×100 mL) and then brine (100 mL), dried (magnesium sulphate), filtered and concentrated in vacuo to afford a pale brown solid. A single recrystallisation of this material from dichloromethane/pet. ether afforded the title compound **10** as off-white crystals (17.72 g, 85%); mp 116–117°C; ν_{max} (CH_2Cl_2): 1713 cm^{-1}; $[\alpha]_D^{23}$ +21.6 (*c* 0.50, $CHCl_3$); (found: C, 56.39; H, 6.66; N, 4.56. $C_{14}H_{19}SNO_4$ requires C, 56.55; H, 6.44; N, 4.71%); δ_H 7.79 (2H, d, *J* 8.2, Ar), 7.37 (2H, d, *J* 8.1, Ar), 5.90 (1H, br s, NH), 4.08 (1H, dd, *J* 9.1 and 2.6, CH_2O), 3.92–3.79 (2H, m, CH_2O and CHN), 2.46 (3H, s, $ArCH_3$), 2.04 (1H, dd, *J* 12.8 and 6.7, CH_2CH), 1.54 (1H, dd, *J* 12.9 and 7.4, CH_2CH), 1.15 (3H, s, CH_3), 1.15 (3H, s, CH_3); δ_C ($CDCl_3$, 50 MHz): 21.00 (aryl-CH_3), 25.05 ($C(CH_3)_2$), 38.16 (CH_2), 39.90 ($C(CH_3)_2$), 49.44 (CH), 72.30 (CH_2), 128.12 (CH), 130.24 (CH), 132.55 (C), 143.56 (C), and 182.83 (CO); *m*/*z* (CI^+, NH_3): 298 (M^++1).

4.6. (5*S*)-5-Bromomethyl-3,3-dimethyl-pyrrolidin-2-one 11

A solution of tosylate **10** (17.72 g, 59.6 mmol) and lithium bromide (15.54 g, 178.9 mmol) in acetone (120 mL) was heated at reflux for 6 h during which time the formation of a fine precipitate was observed. On cooling, the volatiles were removed in vacuo and the residual material was partitioned between dichloromethane (80 mL) and distilled water (80 mL) and further extracted with dichloromethane (2×80

mL). The combined organic portions were washed with brine (50 mL), dried (magnesium sulphate), filtered and concentrated in vacuo to yield a crude yellow solid. A single recrystallisation of this material from ethyl acetate and pet. ether afforded the title compound **11** as colourless crystals (11.62 g, 95%); mp 123–124°C; $[\alpha]_D^{23}$ +25.4 (*c* 1.00, $CHCl_3$); (found: C, 41.02; H, 5.60; N, 6.75. $C_7H_{12}NOBr$ requires C, 40.80; H, 5.87; N, 6.80%); ν_{max} (KBr disk)/cm^{-1} 1700s (C=O), 1662s; δ_H 6.27 (1H, br s, NH), 3.94–3.85 (1H, m, CHN), 3.43 (1H, dd, *J* 10.1 and 4.9, CH_2Br), 3.31 (1H, dd, *J* 10.0 and 7.6, CH_2Br), 2.16 (1H, dd, *J* 12.9 and 7.1, CH_2CH), 1.66 (1H, dd, *J* 13.0 and 7.7, CH_2CH), 1.21 (3H, s, CH_3), 1.18 (3H, s, CH_3); δ_C 183.1 (CO), 51.9 (CHN), 41.6 (CH_2Br), 40.8 [$(CH_3)_2C$], 36.5 (CH_2CH), 25.3 [$(CH_3)_2C$], 25.2 [$(CH_3)_2C$]; *m*/*z* 208 (89%, MH^+), 206 (92%, MH^+), 167 (100%), 158 (13%), 144 (42%), 126 (74%, MH^+-Br).

4.7. (5*R*)-3,3,5-Trimethyl-pyrrolidin-2-one 3

To a stirred solution of bromide **11** (11.626 g, 56.445 mmol) and palladium on charcoal (2.32 g, 20%) in a degassed mixture of ethanol (50 mL) and methanol (50 mL) under a nitrogen atmosphere was added triethylamine (6.84 g, 67.72 mmol) in one portion. The reaction vessel was fitted with a balloon of hydrogen and the solution stirred vigorously for 24 h. Filtration of the reaction mixture through Celite® and subsequent removal of volatiles in vacuo afforded a white crystalline residue. Exhaustive trituration of this material with pet. ether/diethyl ether (9:1) afforded, after concentration in vacuo, a crude white solid. Further purification of this material by sublimation (70°C, 0.1 mmHg) afforded the title compound **3** (6.523 g, 91%) as white needles.

4.8. (5*S*)-(+)-5-*tert*-Butyldimethylsiloxymethyl-3,3-dimethyl-pyrrolidin-2-one 1

To a solution of the alcohol **9** (3.12 g, 21.78 mmol) in DMF (22 mL) were added imidazole (1.56 g, 22.9 mmol) and *tert*-butyldimethylsilylchloride (3.43 g, 22.9 mmol). The reaction mixture was stirred at room temperature overnight, and was then added to water and extracted with diethyl ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue dried in vacuo. Purification by column chromatography using 50% ethyl acetate/pet. ether as eluent gave **1** as a white solid (4.7 g, 84%), recrystallised in acetonitrile; mp 94°C; ν_{max} (CH_2Cl_2)/cm^{-1} 1701; $[\alpha]_D^{22}$ +46.8 (*c* 1.0 in $CHCl_3$); (found: C, 60.57; H, 10.90; N, 5.18. $C_{13}H_{27}NO_2Si$ requires C, 60.65; H, 10.57; N, 5.44%); δ_H ($CDCl_3$; 300 MHz) 0.06 [6H, s, $Si(CH_3)_2$], 0.90 [9H, s, $SiC(CH_3)_3$], 1.20 [6H, s, $C(CH_3)_2$], 1.52 [1H, dd, *J* 7.8 and 12.5 Hz, $(CH_3)_2CCH_2$], 1.98 [1H, dd, *J* 6.9 and 12.5 Hz, $(CH_3)_2CCH_2$], 3.38 (1H, dd, *J* 8.6 and 9.8 Hz, OCH_2), 3.63–3.75 (2H, m, OCH_2 and NCH), and 5.82 (1H, s, NH); δ_C ($CDCl_3$; 50 MHz) −5.64 (CH_3), 18.06 (C) 25.13 (CH_3), 25.31 (CH_3), 25.70 (CH_3), 38.34 (CH_2), 52.44 (CH), 67.24 (CH_2), and 182.68 (CO); *m*/*z* (CI^+, NH_3) 258 (M^++1).

4.9. (5*S*)-(+)-3,3-Dimethyl-5-trityloxymethyl-pyrrolidin-2-one 2

The alcohol **9** (0.818 g, 5.72 mmol) was dissolved in dichloromethane (15 mL). To this solution were added 4-dimethylamino pyridine (DMAP) (5 mg), triethylamine (1.5 mL, 11.44 mmol), and trityl chloride (1.76 g, 6.29 mmol). The mixture was stirred at room temperature overnight before being added to a saturated aqueous sodium bicarbonate solution. The mixture was repeatedly extracted with dichloromethane and the combined organic extracts were washed with brine and dried over $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography using 50% ethyl acetate/40–60 pet. ether as eluent giving **2** as a white solid (1.63 g, 74%), recrystallised in ethyl acetate; mp 187°C; ν_{max} (CH_2Cl_2)/cm^{-1} 1702; $[\alpha]_D^{24}$ +10.6 (*c* 0.5 in $CHCl_3$); (found: C, 81.32; H, 7.00; N, 3.59. $C_{26}H_{22}NO_2$ requires C, 81.01; H, 7.06; N, 3.63%); δ_H ($CDCl_3$; 300 MHz) 1.12 (3H, s, *gem* CH_3), 1.18 (3H, s, *gem* CH_3), 1.45 [1H, dd, *J* 8.3 and 12.7 Hz, $(CH_3)_2CCH_2$], 1.94 [1H, dd, *J* 7.0 and 12.7 Hz, $(CH_3)_2CCH_2$], 2.9 (1H, t, *J* 9.0 Hz, OCH_2), 3.23 (1H, dd, *J* 3.4 and 9.2 Hz, OCH_2), 3.79–3.85 (1H, m, NCH), 5.86 (1H, br-s, NH), and 7.12–7.49 (15H, m, aryl); δ_C ($CDCl_3$, 50 MHz) 24.98 (CH_3), 25.20 (CH_3), 38.91 (CH_2), 39.98 (C), 50.69 (CH), 67.60 (CH_2), 86.85 (C), 127.38 (CH), 128.12 (CH), 128.82 (CH), 143.88 (C), and 182.79 (CO); *m*/*z* (CI^+, NH_3) 386 (M^++1).

4.10. (5*R*)-(−)-5-Ethyl-3,3-dimethyl-pyrrolidin-2-one 4

A solution of Me_2CuLi in THF was prepared at −20°C by slow addition of a methyl lithium solution (1.4 M in hexane, 25.4 mL, 35.4 mmol) to copper iodide (3.36 g, 17.7 mmol) in THF (20 mL). To this solution was then added a solution of **10** (1.75 g, 5.9 mmol) in THF (20 mL). After 45 min at this temperature, the mixture was stirred at 0°C overnight, and quenched by addition of a saturated aqueous ammonium chloride solution (50 mL). The product was extracted with diethyl ether (3×40 mL) and the combined extracts were washed with brine and dried ($MgSO_4$). Concentration in vacuo left a brown solid which was filtered on a small column of silica. Elution with EtOAc furnished **4** as a white solid (0.756 g, 91%); $\nu_{max.}$ (CH_2Cl_2): 1698 cm^{-1}; $[\alpha]_D^{22}$ −28 (*c* 2.0, $CHCl_3$); (found: C, 67.97; H, 11.28; N, 9.46. $C_8H_{15}NO$ requires C, 68.04; H, 10.71; N, 9.92%); δ_H ($CDCl_3$, 300 MHz): 0.92 (3H, t, *J* 7.4, CH_2CH_3), 1.16 (3H, s, $(CH_3)_2$), 1.18 (3H, s, $(CH_3)_2$) 1.53 (3H, m, CH_2CH_3+1H, CH_2CH), 2.06 (1H, dd, *J* 6.7 and 12.6, CH_2CH), 3.50 (1H, m, $CHCH_2CH_3$), 6.01 (1H, br-s, NH); *m*/*z* (CI^+, NH_3): 142 (M^++1).

4.11. General procedure for formation of *N*-acylated pyrrolidinone. 5-(*tert*-Butyl-dimethyl-siloxymethyl)-1-(2,2-dimethyl-propionyl)-3,3-dimethyl-pyrrolidin-2-one 12

The auxiliary **1** (0.050 g, 0.195 mmol) was dissolved in THF (3 cm^3) and this solution was cooled to −78°C. *n*-BuLi (1.4 M, 0.14 cm^3, 0.195 mmol) was then added dropwise and the mixture left to stir at −78°C for 1 h.

Pivaloyl chloride (0.036 cm^3, 0.234 mmol) was added and the solution was allowed to reach room temperature. The reaction mixture was then poured onto water and the product was extracted with diethyl ether. The combined extracts were washed with brine and dried over $MgSO_4$. After concentration in vacuo the residue was purified by column chromatography on silica gel. Elution with EtOAc/pet. ether furnished the desired compound **12** (0.046 g, 70%) as a colourless oil; $[\alpha]_D^{27}$ −41.0 (*c* 0.8 in $CHCl_3$); ν_{max} (thin film)/cm^{-1}: 1687 (CCO) and 1739 (OCO); δ_H (200 MHz, $CDCl_3$) 0.00 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$), 0.86 [9H, s, $Si(CH_3)_3$], 1.16 [3H, s, $C(CH_3)_3$], 1.24 [3H, s, $C(CH_3)_3$], 1.31 [9H, s, $COC(CH_3)_3$], 1.88 and 1.98 (2H, AB of ABX, *J* 7.0, 8.3, and 12.8, CCH_2), 3.52 and 3.87 (2H, AB of ABX, *J* 2.3, 4.2, and 10.4, OCH_2), 4.18–4.28 (1H, m, CH); δ_C (50 MHz, $CDCl_3$) −5.74 (CH_3), 18.13 (C), 25.50 (CH_3), 25.72 (CH_3), 26.36 (CH_3), 26.65 (CH_3), 34.75 (CH_2), 41.50 (C), 42.16 (C), 55.95 (CH), 62.08 (CH_2), 180.28 (CO), 182.76 (CO); *m*/*z* (CI^+, NH_3) 342 (MH^+).

4.12. (5*S*)-1-(2,2-Dimethylpropionyl)-3,3-dimethyl-5-trityloxymethyl-pyrrolidin-2-one 13

Reaction of the auxiliary **2** (0.25 g, 0.65 mmol) as a solution in THF (3 mL) with *n*-BuLi (0.46 mL, 0.65 mmol) and pivaloyl chloride (0.12 mL, 0.98 mmol) furnished the title compound **13** (0.263 g, 86%); (found: C, 79.09; H, 7.69; 2.78. $C_{31}H_{35}NO_3$ requires C, 79.29; H, 7.51; N, 2.98%); $[\alpha]_D^{27}$ −44.0 (*c* 0.5 in $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.20 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.35 (9H, s, $C(CH_3)_3$), 2.02 and 1.96 (2H, AB of ABX, *J* 6.6, 8.7 and 13.0, CCH_2), 3.23 and 3.44 (2H, AB of ABX, *J* 3.2, 5.1 and 9.4, OCH_2), 4.34–4.44 (1H, m, CH), 7.22–7.47 (15H, m, arylH); δ_C (50 MHz, $CDCl_3$) 25.6, 25.9, 26.4, 26.7, 35.3, 41.7, 42.1, 54.7, 62.8, 86.7, 127.3, 128.0, 128.9, 144.0, 180.2, 182.2.

4.13. (5*R*)-(+)-1-(2′,2′-Dimethyl-1′-oxopropyl)-5-methyl-3,3-dimethyl-pyrrolidin-2-one 14

Reaction of the auxiliary **3** (0.20 g, 1.57 mmol) in solution in THF (20 mL) with *n*-BuLi (1.6 M, 1.08 mL, 1.73 mmol) and pivaloyl chloride (0.24 mL, 1.90 mmol) furnished the *N*-acyl derivative **14** as a colourless oil (0.293 g, 88%); $\nu_{max.}$ (CH_2Cl_2): 1687 and 1731 cm^{-1}; $[\alpha]_D^{23}$ +9.0 (*c* 0.5, $CHCl_3$); (found: C, 68.40; H, 10.61; N, 6.42. $C_{12}H_{21}NO_2$ requires C, 68.21; H, 10.61; N, 6.63%); δ_H ($CDCl_3$, 300 MHz): 1.12 (3H, s, $(CH_3)_2$), 1.22 (3H, s, $(CH_3)_2$), 1.29 (9H, s, ^{t}Bu), 1.53 (1H, dd, *J* 8.1 and 13.0, CH_2CH), 2.08 (1H, dd, *J* 8.0 and 13.0, CH_2CH), 4.22 (1H, m, NCH); *m*/*z* (CI^+, NH_3): 212 (M^++1), 156, 128.

4.14. (5*R*)-(−)-1-(2′,2′-Dimethyl-1′-oxopropyl)-5-ethyl-3,3-dimethyl-pyrrolidin-2-one 15

Reaction of the auxiliary **4** (0.230 g, 1.63 mmol) in solution in THF (15 mL) with *n*-BuLi (1.6 M, 1.12 mL, 1.79 mmol) and pivaloyl chloride (0.24 mL, 1.95 mmol) furnished the *N*-acyl derivative **15** as a colourless oil (0.290 g, 79%); $\nu_{max.}$ (CH_2Cl_2): 1729, and 1688 cm^{-1}; $[\alpha]_D^{21}$ −3.0 (*c* 0.4, $CHCl_3$); (found: C, 69.29; H, 10.50; N, 6.59. $C_{13}H_{23}NO_2$ requires C, 69.29; H, 10.28; N, 6.21%); δ_H ($CDCl_3$, 300 MHz): 0.85 (3H, t, *J* 7.4), 1.15 (3H, s), 1.24 (3H, s), 1.32 (9H, s), 1.38 (1H, m), 1.60 (1H, dd, *J* 7.8 and 12.9), 1.83 (1H, m), 2.02 (2H, d, *J* 7.6 and 12.9), 4.10 (1H, m); *m*/*z* (CI^+, NH_3): 228, 226 (M^++1), 142.

4.15. General experimental procedure for cleavage using LiOH

The appropriate *N*-acyl substrate was treated at 0°C with 2.3 equiv. of lithium hydroxide in a 3:1 mixture of tetrahydrofuran and water. The reaction was monitored by thin layer chromatography until all the starting material was consumed. A saturated aqueous sodium bicarbonate solution was then added and the crystalline homochiral auxiliary was recovered by extraction with diethyl ether. Acidification of the aqueous layer to pH 1, and extraction with ethyl acetate furnished the desired crude acid which was purified by column chromatography on silica gel (oil) or by recrystallisation (solid).

4.16. (5*S*)-(−)-5-*tert*-Butyldimethylsiloxymethyl-3,3-dimethyl-1-(propionyl)-pyrrolidin-2-one 16

Reaction of the auxiliary **1** (3.00 g, 11.67 mmol) in solution in THF (50 mL) at 0°C with *n*-BuLi (1.49 M, 7.83 mL, 12.84 mmol) and propionyl chloride (1.01 mL, 12.84 mmol) with work-up, by addition of water, and extraction with diethyl ether and column chromatography on silica furnished the *N*-acyl derivative **16** as a colourless oil (3.07 g, 84%); ν_{max} (CH_2Cl_2)/cm^{-1} 1694 and 1734; $[\alpha]_D^{24}$ −78.6 (*c* 0.5 in $CHCl_3$); (found: C, 61.48; H, 10.26; N, 4.55. $C_{16}H_{31}NO_2$ requires C, 61.30; H, 9.97; N, 4.47%); δ_H ($CDCl_3$; 200 MHz) −0.03 (3H, s, $SiCH_3$), −0.08 (3H, s, $SiCH_3$), 0.83 [9H, s, $SiC(CH_3)_3$], 1.10 (3H, t, *J* 7.3 Hz, CH_3), 1.16 (3H, s, CCH_3), 1.24 (3H, s, CCH_3), 1.84–2.04 [2H, m, $(CH_3)_2CCH_2$], 2.81–2.92 (2H, m, $COCH_2$), 3.63 (1H, dd, *J* 2.4 and 10.1 Hz, OCH_2), 3.95 (1H, dd, *J* 4.8 and 10.1 Hz, OCH_2), 4.16–4.27 (1H, m, NCH); δ_C ($CDCl_3$; 50 MHz) −5.67 (CH_3), 8.16 (CH_3), 18.06 (C), 25.45 (CH_3), 25.64 (CH_3), 27.31 (CH_3), 30.92 (CH_2), 34.58 (CH_2), 41.54 (C), 54.63 (CH), 62.40 (CH_2), 176.14 (CO), 181.80 (CO); *m*/*z* (CI^+, NH_3) 314 (M^++1).

4.17. (5*S*)-(−)-5-(*tert*-Butyl-dimethylsiloxymethyl)-3,3-dimethyl-1-(3-phenyl-propionyl)-pyrrolidin-2-one 17

Reaction of the auxiliary **1** (0.30 g, 1.17 mmol) in solution in THF (16 mL) at 0°C with *n*-BuLi (1.49 M, 0.78 mL, 1.17 mmol) and hydrocinnamoyl chloride (0.17 mL, 1.17 mmol) with work-up, by addition of water, and extraction with diethyl ether and column chromatography on silica furnished the *N*-acyl derivative **17** as a colourless oil (0.276 g, 66%); ν_{max} (CH_2Cl_2)/cm^{-1} 1693 and 1733; $[\alpha]_D^{25}$ −68.5 (*c* 0.2 in $CHCl_3$); δ_H ($CDCl_3$; 200 MHz) 0.01 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.87 [9H, s, $SiC(CH_3)_3$], 1.19 (3H, s, *gem* CH_3), 1.28 (3H, s, *gem* CH_3), 1.92–2.00 [2H, m, $(CH_3)_2CCH_2$], 2.96 (2H, t, *J* 7.81 Hz, $COCH_2$), 3.20–3.29 (2H, m,

CH_2Ph), 3.66 (1H, dd, J 1.2 and 10.1 Hz, OCH_2), 3.97 (1H, dd, J 4.8 and 10.1 Hz, OCH_2), 4.21–4.30 (1H, m, NCH), 7.15–7.33 (5H, m, aryl); δ_C ($CDCl_3$; 50 MHz) −5.69 (CH_3), 18.13 (C), 25.52 (CH_3), 25.74 (CH_3), 27.39 (CH_3), 30.36 (CH_2), 34.59 (CH_2), 38.95 (CH_2), 41.61 (C), 54.71 (CH), 62.46 (CH_2), 126.24 (CH), 128.58 (CH), 128.73 (CH), 141.15 (C), 174.49 (CO), 181.88 (CO); m/z (CI^+, NH_3) 390 (M^++1).

4.18. (5*S*)-(−)-3,3-Dimethyl-5-triphenylmethoxymethyl-1-propionyl-pyrrolidin-2-one 18

Reaction of the auxiliary **2** (0.30 g, 0.78 mmol) as a solution in THF (9 mL) at −78°C with *n*-BuLi (1.6 M, 0.54 mL, 0.86 mmol) and propionyl chloride (0.101 mL, 1.17 mmol) after work-up, with addition of pH 7 phosphate buffer solution, and extraction with dichloromethane and column chromatography on alumina furnished the derivative **18** as a crystalline solid (0.289 g, 84%); mp 110°C; ν_{max} ($CDCl_3$)/cm^{-1} 1697 and 1732; $[\alpha]_D^{25}$ −77.7 (c 0.09 in $CHCl_3$) (found: C, 79.10; H, 7.34; N, 3.18. $C_{28}H_{23}NO_3$ requires C, 78.88; H, 7.08; N, 3.17%); δ_H ($CDCl_3$; 200 MHz) 1.12 (3H, t, J 7.3 Hz, CH_2CH_3), 1.14 (3H, s, *gem* CH_3), 1.17 (3H, s, *gem* CH_3), 1.95–1.99 [2H, m, $(CH_3)_2CCH_2$], 2.84–2.97 (2H, m, $COCH_2$), 3.29 (1H, J 6.5 and 9.1 Hz, OCH_2), 3.43 (1H, J 3.4 and 9.1 Hz, OCH_2), 4.29–4.37 (1H, m, NCH), and 7.08–7.50 (15H, m, arylH); δ_C ($CDCl_3$; 50 MHz) 8.36 (CH_3), 25.75 (CH_3), 27.28 (CH_3), 30.80 (CH_2), 35.24 (CH_2), 41.70 (C), 53.27 (CH), 63.26 (CH_2), 86.76 (C), 127.10 (CH), 127.83 (CH), 128.68 (CH), 143.89 (C), 175.60 (CO), and 181.30 (CO); m/z (CI^+, NH_3) 442 (M^++1).

4.19. (5*S*)-(−)-3,3-Dimethyl-5-triphenylmethoxymethyl-1-(1′-phenylpropionyl)pyrrolidin-2-one 19

Reaction of the auxiliary **2** (0.100 g, 0.26 mmol) as a solution in THF (3 mL) at −78°C with *n*-BuLi (1.6 M, 0.18 mL, 0.29 mmol) and hydrocinnamoyl chloride (0.058 mL, 0.39 mmol), after work-up with addition of a pH 7 phosphate buffer solution and extraction with dichloromethane and column chromatography on alumina furnished the derivative **19** as a white solid (0.108 g, 80%); mp 40°C; ν_{max} (CH_2Cl_2)/cm^{-1} 1695 and 1733; $[\alpha]_D^{22.5}$ −43.3 (c 0.15 in $CHCl_3$); (found: C, 81.31; H, 6.50; N, 2.35. $C_{35}H_{35}NO_3$ requires C, 81.21; H, 6.81; N, 2.71%); δ_H ($CDCl_3$; 200 MHz) 1.21 (3H, s, *gem* CH_3), 1.22 (3H, s, *gem* CH_3), 2.01–2.05 [2H, m, $(CH_3)_2CCH_2$], 3.01 (2H, t, J 7.7 Hz, CH_2CH_2Ph), 3.28–3.55 (4H, m, OCH_2+CH_2CH_2Ph), 4.37–4.47 (1H, m, NCH), and 7.21–7.52 (20H, m, arylH); δ_C ($CDCl_3$; 50 MHz) 25.66 (CH_3), 27.16 (CH_3), 30.36 (CH_2), 34.98 (CH_2), 38.84 (CH_2), 41.63 (C), 53.22 (CH), 63.05 (CH_2), 86.76 (C), 126.25 (CH), 127.31 (CH), 128.05 (CH), 128.59 (CH), 128.82 (CH), 141.08 (C) 144.00 (C), 174.26 (CO), and 181.70 (CO); m/z (CI^+, NH_3) 519 (M^++1).

4.20. (5*R*)-(−)-1-(1′-Oxopropyl)-5-methyl-3,3-dimethyl-pyrrolidin-2-one 20

The auxiliary **3** (0.710 g, 5.6 mmol) was dissolved in THF (25 mL) and this solution was cooled to −78°C. *n*-BuLi as a 1.6 M solution in hexane (3.84 mL, 6.15 mmol) was then added dropwise and the mixture left to stir at −78°C for 1 h. Freshly distilled propionyl chloride (0.58 mL, 6.7 mmol) was added and the solution was allowed to reach room temperature. The reaction mixture was then poured onto water and the product was extracted with diethyl ether. The combined extracts were washed with brine and dried over $MgSO_4$. After concentration in vacuo the residue was purified by column chromatography on silica gel. Elution with EtOAc/pet. ether furnished the desired compound **20** as a colourless oil (0.92 g, 90%); $\nu_{max.}$ (CH_2Cl_2): 1696 and 1731 cm^{-1}; $[\alpha]_D^{23}$ −101 (c 0.5, $CHCl_3$); (found: C, 65.75; H, 9.04; N, 7.95. $C_{10}H_{17}NO_2$ requires C, 65.54; H, 9.35; N, 7.64%); δ_H ($CDCl_3$, 300 MHz): 1.08 (3H, t, J 7.3, CH_2CH_3), 1.30 (3H, s, $(CH_3)_2$), 1.24 (3H, s, $(CH_3)_2$) 1.34 (3H, d, J 6.3, $CHCH_3$), 1.52 (1H, dd, J 5.4 and 13.0, CH_2CH), 2.08 (1H, dd, J 9.6 and 13.0, CH_2CH), 2.86 (2H, m, CH_2CH_3), 4.20 (1H, m, $CHCH_3$); m/z (CI^+, NH_3): 184 (M^++1).

4.21. (5*R*)-(−)-1-(1′-Oxopropyl-3′-phenyl)-5-methyl-3,3-dimethyl-pyrrolidin-2-one 21

Reaction of the auxiliary **3** (0.40 g, 3.15 mmol) in solution in THF (30 mL) with *n*-BuLi (1.6 M, 2.17 mL, 3.46 mmol) and hydrocinnamoyl chloride (0.56 mL, 3.78 mmol) furnished the *N*-acyl derivative **21** as a colourless oil (0.743 g, 91%); $\nu_{max.}$ (CH_2Cl_2): 1693 and 1731 cm^{-1}; $[\alpha]_D^{23}$ −64 (c 0.5, $CHCl_3$); (found: C, 74.41; H, 8.25; N, 4.95. $C_{16}H_{21}NO_2$ requires C, 74.09; H, 8.16; N, 5.40%); δ_H ($CDCl_3$, 300 MHz): 1.18 (3H, s), 1.20 (3H, s), 1.35 (3H, d, J 6.8, CH_3CH), 1.54 (1H, dd, J 5.3 and 13.1, CH_2CH), 2.08 (1H, dd, J 7.9 and 13.1), 2.95 (2H, t, J 8.0), 3.24 (2H, t, J 8.0, CH_2CH_2), 4.24 (1H, m, NCH), 7.25 (5H, m, arylH); m/z (CI^+, NH_3): 260 (M^++1), 128.

4.22. (5*R*)-(−)-1-(1′-Oxopropyl)-5-ethyl-3,3-dimethyl-pyrrolidin-2-one 22

Reaction of the auxiliary **4** (0.756 g, 5.36 mmol) in solution in THF (15 mL) with *n*-BuLi (1.6 M, 3.69 mL, 5.90 mmol) and propionyl chloride (0.56 mL, 6.43 mmol) furnished the *N*-acyl derivative **22** as a colourless oil (0.924 g, 87%); $\nu_{max.}$ (CH_2Cl_2): 1732, and 1696 cm^{-1}; $[\alpha]_D^{21}$ −121.2 (c 0.8, $CHCl_3$); (found: C, 67.25; H, 9.91; N, 6.67. $C_{11}H_{19}NO_2$ requires C, 66.97; H, 9.71; N, 7.10%); δ_H ($CDCl_3$, 300 MHz): 0.87 (3H, t, J 7.5), 1.13 (3H, t, J 7.4), 1.17 (3H, s), 1.26 (3H, s), 1.42 (1H, m), 1.65 (1H, dd, J 5.4 and 13.2), 2.01 (2H, d, J 8.7 and 13.2), 2.06 (1H, m), 2.90 (2H, m), 4.05 (1H, m); m/z (CI^+, NH_3): 198 (M^++1).

4.23. (5*R*)-(−)-1-(1′-Oxopropyl-3′-phenyl)-5-ethyl-3,3-dimethyl-pyrrolidin-2-one 23

Reaction of the auxiliary **4** (0.40 g, 2.83 mmol) in solution in THF (15 mL) with *n*-BuLi (1.5 M, 2.08 mL, 3.12 mmol) and hydrocinnamyl chloride (0.51 mL, 3.40

mmol) furnished the *N*-acyl derivative **23** as a colourless oil (0.659 g, 85%); $\nu_{max.}$ (CH_2Cl_2): 1732, and 1694 cm^{-1}; $[\alpha]_D^{21}$ −71.2 (*c* 0.53, $CHCl_3$); (found: C, 74.58; H, 8.41. $C_{17}H_{23}NO_2$ requires C, 74.69; H, 8.48%); δ_H ($CDCl_3$, 300 MHz): 0.87 (3H, t, *J* 7.5), 1.17 (3H, s), 1.26 (3H, s), 1.41 (1H, m), 1.65 (1H, dd, *J* 5.4 and 13.2), 2.00 (2H, d, *J* 8.6 and 13.1), 2.96 (2H, t, *J* 7.8), 3.23 (2H, t, *J* 7.9), 4.06 (1H, m), 7.22 (5H, m); *m*/*z* (CI^+, NH_3): 274 (M^++1), 142.

4.24. General procedure for alkylation of the *N*-acyl derivatives

To a solution of the *N*-acyl derivatives in THF cooled to −78 or 0°C, was added a solution of the base. The mixture was stirred at this temperature for 1 h and then quenched by addition of the electrophile (3 equiv.). The mixture was stirred at this temperature (reaction followed by thin layer chromatography until complete). The reaction mixture was poured into a saturated aqueous ammonium chloride solution and extracted repeatedly with diethyl ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. After concentration in vacuo, the residue was purified by column chromatography giving the alkylated *N*-acyl derivatives. The diastereomeric excesses were measured by integration of the signal at δ_H 2.52–3.36 (PhCH_2CH) from the complementary diastereoisomers by 500 MHz ^{1}H NMR.

4.25. (5*S*,2′*S*)-5-*tert*-Butyldimethylsiloxymethyl-3,3-dimethyl-1-[(2′-methyl-1′-phenyl)propionyl]pyrrolidin-2-one 24

To a solution of **16** (0.30 g, 0.96 mmol) in THF (6 mL) at 0°C was added a solution of LDA (0.5 M as a solution in THF, 2.4 mL, 1.2 mmol). The resultant enolate was stirred at 0°C for 1 h before quenching by addition of benzyl bromide (0.340 mL, 2.88 mmol). The mixture was then stirred at 0°C for a further 4–5 h. The reaction mixture was poured into a saturated aqueous ammonium chloride solution and extracted repeatedly with diethyl ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. Concentration in vacuo and purification by column chromatography using 10% ethyl acetate/40–60 pet. ether as eluent furnished the *N*-acyl derivative **24** as a clear oil (0.127 g, 33%) with a diastereomeric excess of 95%; ν_{max} (CH_2Cl_2)/cm^{-1} 1692 and 1732; (found: C, 68.44; H, 9.42; N, 3.23. $C_{23}H_{37}NO_3Si$ requires C, 68.44; H, 9.24; N, 3.47%); δ_H ($CDCl_3$; 200 MHz) 0.02 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$), 0.87 [9H, s, $C(CH_3)_3$], 1.07 (3H, d, *J* 6.7 Hz, $CHCH_3$), 1.22 (3H, s, *gem* CH_3), 1.27 (3H, s, *gem* CH_3), 1.94–2.01 [2H, m, $(CH_3)_2CCH_2$], 2.52 (1H, dd, *J* 9.3 and 13.1 Hz, $PhCH_2CH$), 3.12 (1H, dd, *J* 5.4 and 13.1 Hz, $PhCH_2CH$), 3.64–3.67 (2H, m, OCH_2), 4.01–4.11 (1H, m, COCH), 4.23–4.28 (1H, m, NCH), 7.19–7.29 (5H, m, arylH); δ_C ($CDCl_3$; 50 MHz) −5.61 (CH_3), 15.38 (CH_3), 18.13 (C), 25.67 (CH_3), 25.77 (CH_3), 27.33 (CH_3), 34.40 (CH_2), 40.16 (CH_2), 40.83 (CH), 41.86 (C), 54.76 (CH), 62.69 (CH_2), 126.37 (CH), 128.42 (CH), 129.48 (CH), 139.77 (C), 178.64 (CO), and 181.52 (CO); *m*/*z* (CI^+, NH_3) 404 (M^++1).

4.26. (5*S*,2′*R*)-5-*tert*-Butyldimethylsiloxymethyl-3,3-dimethyl-1-[(2′-methyl-1′-phenyl)propionyl]pyrrolidin-2-one 25

To a solution of **17** (0.261 g, 0.67 mmol) in THF (4.7 mL) at 0°C was added a solution of LDA (0.5 M as a solution in THF, 1.67 mL, 0.84 mmol). The resultant enolate was stirred at 0°C for 1 h before quenching by addition of methyl iodide (0.125 mL, 2.01 mmol). The mixture was then stirred at 0°C for a further 45 min. The reaction mixture was worked up by addition of a pH 7 phosphate buffer solution and products extracted repeatedly with diethyl ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. Concentration in vacuo and purification by column chromatography using 10% ethyl acetate/40–60 pet. ether as eluent furnished the *N*-acyl derivative **25** as a clear oil (0.173 g, 64%) with a diastereomeric excess of 94%; ν_{max} (CH_2Cl_2)/cm^{-1} 1688 and 1732; (found: C, 68.15; H, 9.12; N, 3.16. $C_{23}H_{37}NO_3Si$ requires C, 68.44; H, 9.24; N, 3.47%); δ_H ($CDCl_3$; 300 MHz) 0.02 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$), 0.87 [9H, s, $SiC(CH_3)_3$], 1.07 (3H, s, *gem* CH_3), 1.16 (3H, d, *J* 6.8 Hz, $CHCH_3$), 1.27 (3H, s, *gem* CH_3), 1.84 [1H, dd, *J* 9.2 and 13.1 Hz, $(CH_3)_2CCH_2$], 1.96 [1H, dd, *J* 5.4 and 13.2 Hz, $(CH_3)_2CCH_2$], 2.59 (1H, dd, *J* 7.8 and 13.3 Hz, $PhCH_2CH$), 3.04 (1H, dd, *J* 7.0 and 13.3 Hz, $PhCH_2CH$), 3.63 (1H, dd, *J* 2.3 and 10.1 Hz, OCH_2), 3.98 (1H, dd, *J* 4.6 and 10.1 Hz, OCH_2), 4.09–4.20 (2H, m, NCH and COCH), and 7.15–7.29 (5H, m, arylH); δ_C ($CDCl_3$; 50 MHz) −5.67 (CH_3), 17.08 (CH_3), 18.13 (CH_3), 25.37 (CH_3), 25.74 (CH_3), 27.42 (CH_3), 34.25 (CH_2), 39.43 (CH), 40.63 (CH), 41.77 (C), 54.81 (CH), 62.62 (CH_2), 126.26 (CH), 128.42 (CH), 129.33 (CH), 139.99 (C), 178.64 (CO), and 181.56 (CO); *m*/*z* (CI^+, NH_3) 404 (M^++1).

4.27. (5*S*,2′*S*)-3,3-Dimethyl-5-triphenylmethoxymethyl-1-[(2′-methyl-1′-phenyl) propionyl]pyrrolidin-2-one 26

To a solution of **18** (0.200 g, 0.45 mmol) in THF (4.0 mL) at 0°C was added a solution of LDA (0.5 M as a solution in THF, 1.13 mL, 0.57 mmol). The resultant enolate was stirred at 0°C for 1 h before quenching by addition of benzyl bromide (0.162 mL, 1.36 mmol). The mixture was then stirred at 0°C for a further 90 min. The reaction mixture was worked up by addition of a pH 7 phosphate buffer solution and products extracted repeatedly with dichloromethane. The combined organic extracts were washed with brine and dried over $MgSO_4$. Concentration in vacuo and purification by column chromatography using 10% ethyl acetate/40–60 pet. ether as eluent furnished the *N*-acyl derivative **26** as a white solid (0.122 g, 51%) with a diastereomeric excess of 96%; mp 122°C; ν_{max} (CH_2Cl_2)/cm^{-1} 1694 and 1733; (found: C, 81.04; H, 6.76; N, 2.41. $C_{36}H_{37}NO_3$ requires C, 81.32; H, 7.01; N, 2.63%); δ_H ($CDCl_3$; 500 MHz) 1.02 (3H, s, *gem* CH_3), 1.08 (3H, d, *J* 6.7 Hz, CH_3CH), 1.16 (3H, s, *gem* CH_3), 1.83 [1H, dd, *J* 4.7 and 13.3 Hz, $(CH_3)_2CCH_2$], 1.95 [1H, dd, *J* 8.9 and 13.3 Hz, $(CH_3)_2CCH_2$], 2.51 (1H, dd, *J* 8.6 and 13.2 Hz, OCH_2), 2.97 (1H, dd, *J* 7.6 and 8.8 Hz, $PhCH_2CH$), 3.05 (1H, dd, *J* 6.3 and 13.2 Hz, OCH_2), 3.42 (1H, dd,

J 3.5 and 8.8 Hz, PhC$\underline{H}_2$CH), 4.02–4.07 (1H, m, COC$\underline{H}$), 4.32–4.37 (1H, m, NC$\underline{H}$) and 7.11–7.42 (20H, m, aryl$\underline{H}$); δ_C ($CDCl_3$; 125 MHz) 15.89 (CH_3), 25.84 (CH_3), 27.04 (CH_3), 35.29 (CH_2), 40.32 (CH_2), 40.77 (CH), 41.86 (C), 53.32 (CH), 63.43 (CH_2), 86.79 (C), 126.06 (CH), 127.08 (CH), 127.81 (CH), 128.13 (CH), 128.71 (CH), 129.18 (CH), 139.45 (C), 143.84 (C), 178.11 (CO), and 180.95 (CO); *m*/*z* (FAB^+) 532 (M^++1).

4.28. (5*S*,2′*R*)-3,3-Dimethyl-5-triphenylmethoxymethyl-1-[(2′-methyl-1′-phenyl)propionyl]pyrrolidin-2-one 27

To a solution of **19** (0.232 g, 0.45 mmol) in THF (5 mL) at 0°C was added a solution of LDA (0.5 M as a solution in THF, 1.12 mL, 0.56 mmol). The resultant enolate was stirred at 0°C for 1 h before quenching by addition of methyl iodide (0.084 mL, 1.35 mmol). The mixture was then stirred at 0°C for a further 3.5 h. The reaction mixture was worked up by addition of a pH 7 phosphate buffer solution and products extracted repeatedly with dichloromethane. The combined organic extracts were washed with brine and dried over $MgSO_4$. Concentration in vacuo and purification by column chromatography using 10% ethyl acetate/40–60 pet. ether as eluent furnished the *N*-acyl derivative **27** as a viscous oil (0.105 g, 44%) with a diastereomeric excess of 91%; ν_{max} (CH_2Cl_2)/cm^{-1} 1692 and 1734; δ_H ($CDCl_3$; 500 MHz) 1.02 (3H, s, *gem* C$\underline{H}_3$), 1.12 (3H, s, *gem* C$\underline{H}_3$), 1.16 (3H, d, *J* 6.8 Hz, C$\underline{H}_3$CH), 1.81 [1H, dd, *J* 9.0 and 13.2 Hz, $(CH_3)_2CC\underline{H}_2$], 1.88 [1H, dd, *J* 5.1 and 13.2 Hz, $(CH_3)_2CC\underline{H}_2$], 2.59 (1H, dd, *J* 7.8 and 13.4 Hz, OC$\underline{H}_2$), 3.02 (1H, dd, *J* 7.1 and 13.4 Hz, OC$\underline{H}_2$), 3.36 (2H, d, *J* 4.8 Hz, PhC$\underline{H}_2$CH), 4.10–4.16 (1H, m, COCH), 4.20–4.25 (1H, m, NC$\underline{H}$) and 7.16–7.42 (20H, m, aryl$\underline{H}$); δ_C ($CDCl_3$; 125 MHz) 17.19 (CH_3), 25.61 (CH_3), 27.29 (CH_3), 35.01 (CH_2), 39.70 (CH_2), 40.63 (CH), 41.12 (C), 53.47 (CH), 63.34 (CH_2), 86.77 (C), 126.10 (CH), 126.26 (CH), 127.09 (CH), 127.25 (CH), 127.82 (CH), 127.93 (CH), 127.96 (CH), 128.23 (CH), 128.70 (CH), 129.16 (CH), 139.77 (C), 143.85 (C), 178.07 (CO), and 181.09 (CO); *m*/*z* (CI^+, NH_3) 532 (M^++1); *m*/*z* found (MH^+) 532.2842. $C_{36}H_{38}NO_3$ requires 532.2852.

4.29. (2′*S*,5*R*)-(−)-1-(1′-Oxopropyl-2′-phenylmethyl)-3,3-dimethyl-5-methyl-pyrrolidin-2-one 28

To a solution of the *N*-acylated pyrrolidinone **20** (0.193 g, 1.05 mmol) in THF (11 mL) cooled to 0°C, was added a solution of LDA (0.5 M, 1.26 mmol) in THF. The solution was stirred at 0°C for 1 h and quenched by addition of benzyl bromide (0.38 mL, 3.15 mmol). The mixture was left to stir at 0°C for 2 h and allowed to reach room temperature overnight. The reaction mixture was then poured onto a saturated aqueous ammonium chloride solution (20 mL) and extracted repeatedly with diethyl ether (4×30 mL). The combined extracts were washed with brine and dried over $MgSO_4$. After concentration in vacuo, purification of the residue by flash column chromatography on silica furnished the desired alkylated product **28** as a colourless oil (0.231 g, 80%), with a diastereomeric excess of 96%. $\nu_{max.}$ (CH_2Cl_2): 1729 and 1693 cm^{-1}; $[\alpha]_D^{23}$ −20 (*c* 0.6, $CHCl_3$); (found: C, 74.95; H, 8.26; N, 5.07; $C_{17}H_{23}NO_2$ requires C, 74.69; H, 8.48; N, 5.12%); δ_H ($CDCl_3$, 300 MHz): 1.11 (3H, d, *J* 6.7, CH_3), 1.17 (3H, d, *J* 6.2, CH_3), 1.21 (3H, s, CH_3), 1.47 (1H, dd, *J* 7.8 and 13, C$\underline{H}_2$CH), 2.05 (1H, dd, *J* 8.5 and 13.0, C$\underline{H}_2$CH), 2.60 (1H, dd, *J* 8.0 and 13.2, C$\underline{H}_2$Ph), 3.05 (1H, dd, *J* 6.9 and 13.2, C$\underline{H}_2$Ph), 4.1 (1H, m), 4.22 (1H, m), 7.24 (5H, m); *m*/*z* (CI^+, NH_3): 274 (M^++1), 273, 258, 182, 128.

4.30. (2′*R*,5*R*)-(−)-1-(1′-Oxopropyl-2′-phenylmethyl)-3,3-dimethyl-5-methyl-pyrrolidin-2-one 29

Reaction of the *N*-acylated pyrrolidinone **21** (0.317 g, 1.22 mmol) in THF (13 mL), with LDA (0.5 M, 1.46 mmol) and methyl iodide (0.225 mL, 3.67 mmol) furnished the alkylated product **29** as a colourless oil (0.203 g, 62%) with a diastereomeric excess of 89%. $\nu_{max.}$ (CH_2Cl_2): 1729 and 1692 cm^{-1}; $[\alpha]_D^{23}$ −76 (*c* 0.6, $CHCl_3$); (found: C, 74.54; H, 9.08, $C_{17}H_{23}NO_2$ requires C, 74.69; H, 8.48%); δ_H ($CDCl_3$, 300 MHz): 1.08 (1H, s, gem C$\underline{H}_3$), 1.15 (3H, d, *J* 6.9, C$\underline{H}_3$), 1.26 (3H, s, gem C$\underline{H}_3$), 1.36 (3H, d, *J* 6.3, C$\underline{H}_3$), 1.42 (1H, dd, *J* 5.2 and 13.0, C$\underline{H}_2$CH), 2.01 (1H, dd, *J* 8.5 and 13.0, C$\underline{H}_2$CH), 2.60 (1H, dd, *J* 8.0 and 13.4, C$\underline{H}_2$Ph), 3.06 (1H, dd, *J* 6.8 and 13.4, C$\underline{H}_2$Ph), 4.17 (2H, m, CHN+COCH), 7.26 (5H, m); *m*/*z* (CI^+, NH_3): 274 (M^++1), 273, 146, 128.

4.31. (2′*S*,5*R*)-(−)-1-(1′-Oxopropyl-2′-phenylmethyl)-5-ethyl-3,3-dimethyl-pyrrolidin-2-one 30

Reaction of the *N*-acylated pyrrolidinone **22** (0.194 g, 0.98 mmol) in THF (10 mL), with LDA (0.5 M, 1.17 mmol) and benzyl bromide (0.35 mL, 2.94 mmol) furnished the alkylated product **30** as a colourless oil (0.220 g, 78%) with a diastereomeric excess of 95%. $\nu_{max.}$ (CH_2Cl_2): 1730 and 1692 cm^{-1}; $[\alpha]_D^{21}$ −42.3 (*c* 0.6, $CHCl_3$); (found: C, 75.16; H, 8.65; $C_{18}H_{25}NO_2$ requires C, 75.22; H, 8.77%); δ_H ($CDCl_3$, 300 MHz): 0.80 (1H, t, *J* 7.2), 1.20 (3H, d, *J* 7), 1.19 (3H, s), 1.25 (1H, m), 1.59 (1H, dd, *J* 5.8 and 13.4), 1.87 (1H, m), 1.99 (1H, dd, *J* 8.4 and 13.5), 2.57 (1H, dd, *J* 8.6 and 13.5), 3.09 (1H, dd, *J* 6.0 and 13.4), 4.07 (2H, m), 7.23 (5H, m); *m*/*z* (EI^+): 287 (M^+), 272, 142, 118, 91.

4.32. (2′*R*,5*R*)-(−)-1-(1′-Oxopropyl-2′-phenylmethyl)-5-ethyl-3,3-dimethyl-pyrrolidin-2-one 31

Reaction of the *N*-acylated pyrrolidinone **23** (0.380 g, 1.39 mmol) in THF (14 mL), with LDA (0.5 M, 1.67 mmol) and methyl iodide (0.26 mL, 4.17 mmol) furnished the alkylated product **31** as a colourless oil (0.110 g, 42%) with a diastereomeric excess of 95%. $\nu_{max.}$ (CH_2Cl_2): 1729 and 1692 cm^{-1}; $[\alpha]_D^{22}$ −86.4 (*c* 0.9, $CHCl_3$); (found: C, 75.13; H, 9.02; N, 5.12. $C_{18}H_{25}NO_2$ requires C, 75.22; H, 8.77; N, 4.87%); δ_H ($CDCl_3$, 300 MHz): 0.88 (3H, t, *J* 7.2), 1.08 (3H, s), 1.15 (3H, d, *J* 7.3), 1.26 (3H, s), 1.46 (1H, m), 1.62 (1H, dd, *J* 6.0 and 13.3), 1.93 (1H, dd, *J* 8.7 and 13.3), 2.02 (1H, m), 2.59 (1H, dd, *J* 7.7 and 13.0), 3.06 (1H, dd, *J* 6.7 and 13.0), 4.01 (1H, m), 4.12 (1H, m), 7.23 (5H, m); *m*/*z* (CI^+, NH_3): 290, 288 (M^++1), 287, 273, 142.

4.33. (*S*)-(+)-2-Benzylpropanoic acid 32

Obtained with 83% yield from compounds **28**, using the experimental procedure described above (colourless oil); $[\alpha]_D^{21}$ +28.6 (*c* 1.0, $CHCl_3$), (lit. $[\alpha]_D^{22}$ +30.1 (*c* 3.28, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 1.20 (3H, d, *J* 6.7), 2.66 (1H, dd, *J* 8.0 and 13.1), 2.77 (1H, m), 3.10 (1H, dd, *J* 6.1 and 13.1), 7.26 (5H, m).

4.34. Methyl (*R*)-(+)-2-benzylpropionate 33

The methylester **33** was prepared in 82% yield as a clear colourless oil, from pyrrolidinone **28** (0.143 g, 0.52 mmol) in MeOH, and MeOMgBr (0.52 mL, 1.57 mmol) as a 3.0 M solution in methanol. After addition of the MeOMgBr solution the mixture was stirred for 1 h at 0°C and 5 h at rt. Usual work-up and extraction with CH_2Cl_2 furnished the crude reaction mixture which was purified by flash chromatography to yield the methylester **33** (76 mg, 82%) and the crystalline chiral auxiliary **3** (61 mg, 92%). Methyl ester: $\nu_{max.}$ (CH_2Cl_2): 3054 and 1730 cm^{-1}; $[\alpha]_D^{22}$ +34.5 (*c* 0.8, $CHCl_3$), (lit. $[\alpha]_D^{25}$ = +35.9 (*c* 1.0, $CHCl_3$)); δ_H ($CDCl_3$, 300 MHz): 1.16 (3H, d, *J* 6.7), 2.67 (1H, dd, *J* 7.8 and 12.7), 2.74 (1H, m), 3.03 (1H, dd, *J* 6.2 and 12.7), 3.65 (3H, s), 7.22 (5H, m); *m*/*z* (CI^+, NH_3): 196 (M^++18) and 91.

4.35. Benzyl (*S*)-(+)-2-benzylpropionate 34

Pyrrolidinone **28** (0.109 g, 0.4 mmol) in THF (2 mL) was added at −78°C to a solution of $PhCH_2OLi$, prepared at 0°C by addition of a *n*-BuLi 1.6 M solution (0.37 mL, 0.6 mmol) to a solution of benzyl alcohol (0.083 mL, 0.8 mmol) in THF (0.5 mL). After 1 h of stirring at 0°C, the reaction was quenched by addition of 10 mL of pH 7 buffer solution and the products were extracted with ethyl acetate. Flash chromatography on silica gel furnished the desired ester **34** (95 mg, 94%) as a clear colourless oil, and the recovered crystalline auxiliary **3** (49 mg, 97%). Benzyl ester: $\nu_{max.}$ (CH_2Cl_2): 1731 cm^{-1}; $[\alpha]_D^{21}$ +25.7 (*c* 1.15, CH_2Cl_2), (lit. $[\alpha]_D^{21}$ −26.9 (*c* 6.12, CH_2Cl_2) for the other enantiomer); δ_H ($CDCl_3$, 300 MHz): 1.19 (3H, t, *J* 6.8), 2.70 (1H, dd, *J* 7.5 and 13.0), 2.79 (1H, m), 3.06 (1H, dd, *J* 6.2 and 13.0), 5.08 (2H, s), 7.28 (10H, m); *m*/*z* (CI^+, NH_3): 273 (M^++18), 255 (M^+), 237, 108, 91.

The ee of 96% has been verified with ^1H NMR analysis using hfc$(Eu)^{III}$ as shift reagent.

4.36. (2′*R*,3′*R*,5*R*)-(−)-1-(3′-Hydroxy-2′-methyl-3′-phenyl-1′-oxopropyl)-3,3-dimethyl-5-methyl-2-pyrrolidinone 35

To a solution of the acylated pyrrolidinone **20** (0.143 g, 0.78 mmol) in methylene chloride (5 mL) cooled to 0°C were added $^iPr_2NEt$ (0.16 mL, 0.94 mmol) and a 1 M solution of Bu_2BOTf (0.86 mL, 0.86 mmol) in methylene chloride. After 0.5 h at 0°C the solution was cooled to −78°C and the freshly distilled benzaldehyde (0.095 mL, 0.94 mmol) was added. After 0.5 h at −78°C and 1 h at 0°C, buffer 7 solution (3 mL) and methanol (4 mL) were added. To this mixture, was slowly added a solution of methanol/aqueous hydrogen peroxide (2:1) (3 mL). After 1 h of stirring, the solvents were removed in vacuo and the product extracted with diethyl ether (4×40 mL). The combined organic extracts were washed with 5% aqueous bicarbonate solution and brine, and were dried over $MgSO_4$. The residue left after removal of the solvent was purified by flash column chromatography. Elution with EtOAc/pet. ether (1:4) furnished the desired compound **35** as an oil (0.189 g, 84%) which crystallised on cooling. $\nu_{max.}$ (CH_2Cl_2): 3518, 3054, 2986, 1733, 1674, 1422, 1272 and 1259 cm^{-1}; $[\alpha]_D^{22}$ −26.9 (*c* 0.7, $CHCl_3$); (found: C, 70.26; H, 7.92; N, 5.12; $C_{17}H_{23}NO_3$ requires C, 70.56; H, 8.01; N, 4.84%); δ_H ($CDCl_3$, 300 MHz): 1.09 (3H, d, *J* 7.1), 1.17 (3H, s), 1.27 (3H, s), 1.36 (3H, d, *J* 6.3 CH_3), 1.56 (1H, dd, *J* 5.6 and 13.1), 2.09 (1H, dd, *J* 8.4 and 13.1), 4.11 (1H, m), 4.26 (1H, m), 5.16 (dd, *J* 3.05, 1H), 7.36 (5H, m); *m*/*z* (CI^+, NH_3): 272 (M^+−18), 184, 128.

4.37. (2*R*,3*R*)-(+)-3-Hydroxy-2-methyl-3-phenylpropionic acid 36

Obtained with 94% yield from compounds **35** using the experimental procedure described above (white solid recrystallised in CCl_4). $\nu_{max.}$ (CH_2Cl_2): 3410, 3025, 1711, 1456 and 1233 cm^{-1}; $[\alpha]_D^{21}$ +26.8 (*c* 0.5, $CHCl_3$), (lit. $[\alpha]_D^{21}$ −26.4 (*c* 1.04, $CHCl_3$) for the other enantiomer; δ_H ($CDCl_3$, 300 MHz): 1.16 (3H, d, *J* 7.2), 2.85 (1H, m), 5.19 (1H, d, *J* 3.9), 7.29 (5H, m).

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