PERKIN 1

Highly effective and recyclable chiral auxiliaries: a study of the synthesis and use of three 4-isopropyl-5,5-diaryloxazolidin-2-ones

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A series of three 5,5-diaryl substituted oxazolidin-2-ones (diphenyl, dinaphthyl and ditolyl) have been synthesised. Studies on the benzylation of the lithium enolates of *N*-acyl derivatives reveal that the yields obtained were sensitive to the method of quenching the reaction. This was particularly acute for the 5,5-diphenyl system where effective yields (69%) and high diastereoselectivities (dr 98 : 2) are only observed when the reactions were quenched into aqueous buffer. Methylation studies on the *N*-acyl derivatives showed that the most advantageous results (58–69%, dr ⩾ 91 : 9) were only observed using the sodium enolates. The 5,5-ditolyl-4-isopropyloxazolidin-2-one proved to be more efficacious in terms of efficiency and diastereoselectivity (dr ⩾ 97 : 3). Subsequent, simple alkaline hydrolyses of the alkylation products allowed for the high recovery and recyclability of the 5,5-diaryl substituted oxazolidin-2-ones without any deleterious endocyclic cleavage. In addition, the acyl portions were recovered in high yield from the alkaline hydrolyses without any evidence of racemisation.

Introduction

Chiral auxiliary methodology continues to be an effective method in asymmetric synthesis.[1] Currently, the most useful chiral auxiliaries are those which function by controlling the diastereoselectivity of attached acyl fragments. In this context, perhaps the most widely used auxiliaries are the versatile oxazolidin-2-one chiral auxiliaries **1** and **2**, pioneered by Evans. The *N*-acyl derivatives of Evans auxiliaries **1** and **2** have been utilised in numerous highly diastereoselective reactions including alkylation, amination, azidation, bromination, hydroxylation, aldol additions, Diels–Alder cycloadditions and conjugate additions.[2] The wide ranging usefulness of the Evans auxiliaries **1** and **2** coupled with the generally high diastereoselectivities has led to the development of a broad range of oxazolidin-2-one auxiliaries. Thus, oxazolidin-2-one auxiliaries have been prepared from a number of chiral sources including terpenes (*e.g.* **3–5**),[3] carbohydrates (*e.g.* **6–8**),[4] anthracenes,[5] amino indanols[6] and abiogenetic amino acids[7] (see Fig. 1). Recently, solid phase synthesis has been applied to auxiliary chemistry with the development of a number of polymer supported oxazolidin-2-ones (*e.g.* **9** and **10**).[8] However, problems have been reported with the polymer attachment of serine based oxazolidinones in the preparation of **9**.[8e]

A crucial factor for the utility of a chiral auxiliary is that it must be efficiently introduced and it must be easily removed without disrupting the newly formed stereogenic centres. One of the drawbacks of the Evans methodology involves the removal of the auxiliary. If the *N*-acyl group is sterically demanding or α-branched then the unwanted endocyclic hydrolysis can predominate to give a ring opened amide **12** rather than the required exocyclic cleavage to afford the carboxylic acid derivative **13** and the recovered chiral auxiliary **1** (Scheme 1).[9] The endocyclic cleavage can be circumvented by hydrolysis using lithium hydroperoxide, however, the

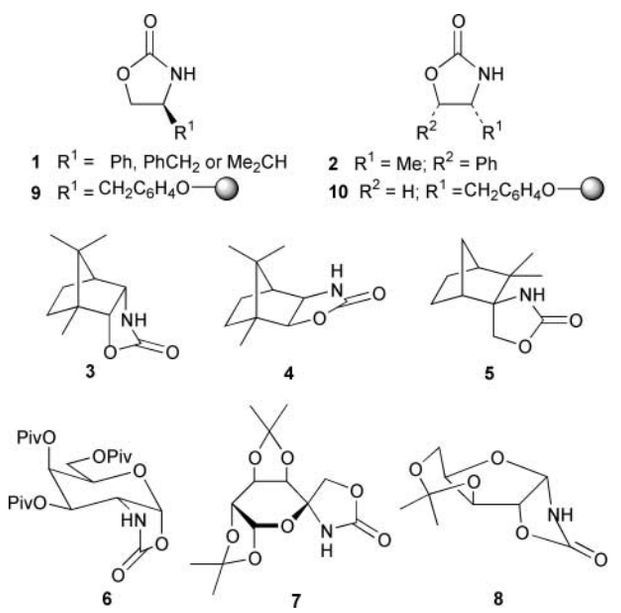
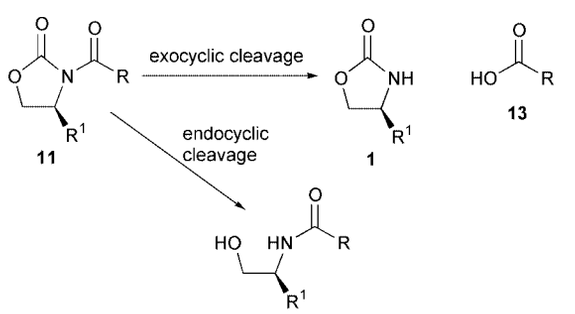


Fig. 1 Some representative examples of oxazolidin-2-one auxiliaries.



Scheme 1

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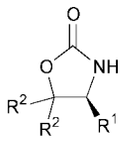


14 R^1 = Me, Ph, $PhCH_2$ or Me_2CH; R^2 = Me
15 R^1 = CH_2Ind; R^2 = Me, Pr^n, nBu^n
16a R^1 = Me_2CH; R^2 = Ph
16b R^1 = Me_2CH; R^2 = 2-naphthyl
16c R^1 = Me_2CH; R^2 = 4-MeC_6H_4
17 R^1 = Me_2CH, Me_2CHCH_2, $PhCH_2$, Ph, Me_3C; R^2 = Ph

Fig. 2

hazardous nature of this reagent detracts from its large scale applicability.

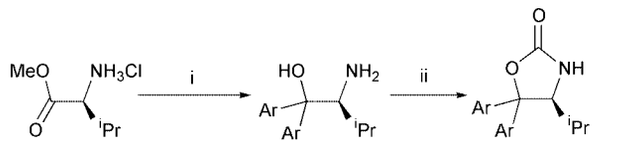
A solution to the problem of undesired endocyclic hydrolysis is the use of 5,5-disubstituted oxazolidin-2-ones **14**–**17**. Thus, Davies *et al.* introduced the 5,5-dimethyloxazolidin-2-ones **14**,[10] while Cardillo *et al.* have used the 5,5-dialkyloxazolidin-2-ones **15** in diastereoselective hydrochlorination reactions.[11] However, the 5,5-dimethyloxazolidin-2-ones **14** suffer low yields when the enolates derived from the *N*-acyl derivatives are alkylated with less reactive alkyl halides. Consequently, we[12] and others[13,14] have investigated the 5,5-diaryloxazolidin-2-ones **16** and **17** with the aim of generating highly diastereoselective and efficient auxiliaries that do not undergo subsequent undesirable endocyclic cleavage. Subsequently, Hintermann and Seebach reported an elegant and comprehensive study of the use of *N*-acyl derivatives of 5,5-diphenyloxazolidin-2-one **16a** in a number of diastereoselective reactions.[15,16] These studies included enolate alkylation reactions of *N*-acyl derivatives of 5,5-diphenyloxazolidin-2-one **16a** where decomposition of the enolate was observed. This decomposition led to acyl cleavage and formation of 5,5-diphenyloxazolidin-2-one **16a**.[15] Recently, Davies and co-workers compared the benzylation of *N*-acyl derivatives of 5,5-dialkyloxazolidin-2-ones **15** and the 5,5-diphenyloxazolidin-2-ones **17** (see Fig. 2) and observed enolate alkylation problems with the latter.[17] We now describe the preparation of 5,5-diaryl-4-isopropyloxazolidin-2-ones **16a**–**c** including a comprehensive study on the alkylation (methylation and benzylation) and azidation of *N*-acyl enolates. The judicious use of appropriate work up of the benzylation reactions leads to a maximisation of alkylation yields while efficient enolate methylations were achieved using sodium enolates. These studies also indicate that the 5,5-ditolyl-1,3-oxazolidin-2-one **16c** is the most effective in terms of diastereoselective and efficiency. Part of this work has previously been communicated.[12]

Results and discussion

Synthesis of 5,5-diaryl auxiliaries

The syntheses of the 5,5-diaryl-1,3-oxazolidin-2-ones **16a**–**c** were realised by a two step procedure involving addition of the appropriate Grignard reagents to (*S*)-valine methyl ester hydrochloride **18**. Thus, addition of 6 equivalents of phenylmagnesium bromide to ester hydrochloride **18** furnished the diphenyl alcohol **19a** in 54% yield. We also wished to probe the effect of the steric space about the C-5 position in 1,3-oxazolidin-2-ones **16**, consequently, the di(2-naphthyl)amino alcohol **19b** was similarly prepared in 60% yield. However, attempts to prepare the more sterically demanding di(1-naphthyl) or di(2-tolyl)amino alcohols by a similar approach were unsuccessful. Since the preparation of diphenyl amino alcohol **19a** generates three equivalents of benzene we wished to prepare a more environmentally friendly 1,3-oxazolidin-2-one that would be amenable to large scale use. Thus, the di(4-tolyl) amino alcohol **19c** was prepared similarly in 52% yield.

Treatment of the amino alcohols **19a**–**c** with triphosgene under biphasic conditions in toluene and aqueous potassium hydroxide provided the 5,5-diaryl-1,3-oxazolidin-2-ones **16a** (73%), **16b** (59%) and **16c** (54%). Alternatively, the di(4-tolyl)-1,3-oxazolidin-2-one **16c** could be prepared in 62% yield using triphosgene and triethylamine in THF (Scheme 2).[18]



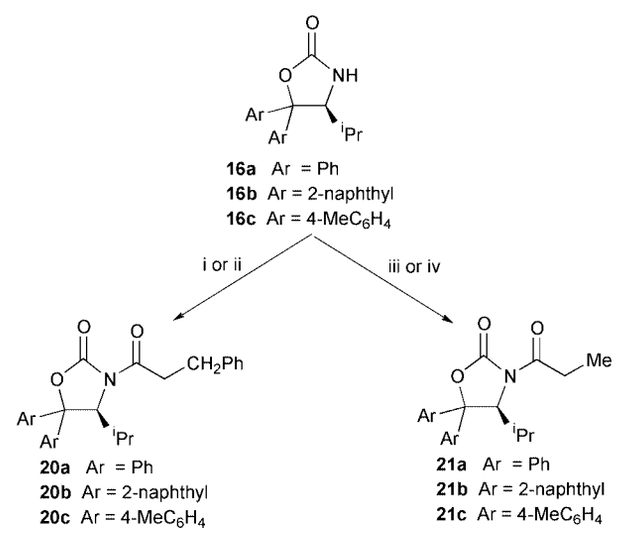
18 **19a** Ar = Ph; **19b** Ar = 2-naphthyl; **19c** Ar = 4-MeC_6H_4; **16a** Ar = Ph; **16b** Ar = 2-naphthyl; **16c** Ar = 4-MeC_6H_4

Scheme 2 *Reagents and conditions*: i, 6 equiv. ArMgBr, −10 °C; ii, $Cl_3COC(O)OCl_3$, KOH, $CH_3C_6H_5$ or Et_3N, THF.

N-Acylation of the 5,5-diaryl-1,3-oxazolidin-2-ones

The *N*-acylation of 1,3-oxazolidin-2-ones is usually carried out by *N*-deprotonation with butyllithium at −78 °C.[19] Using this methodology the *N*-acyl-5,5-diaryl-1,3-oxazolidin-2-ones **20a**–**c** and **21a**–**c** were prepared in 46–98% yield. It should be noted that the 5,5-diphenyl auxiliary **16a** gave consistently lower *N*-acylation yields using this procedure (entries 1 and 6, Table 1). This is a consequence of the fact that the 5,5-diphenyl auxiliary **16a** is poorly soluble in THF even at room temperature while the auxiliaries **16b** and **16c** are fully soluble at −78 °C.

In an attempt to use conditions that were more amenable to large scale generation of *N*-acylated 1,3-oxazolidin-2-ones we investigated alternative procedures.[4e,20] Thus, improved yields (84%) in the *N*-acylation of the 5,5-diphenyl-1,3-oxazolidin-2-one **16a** were realised using the appropriate acid chloride with triethylamine and *N*,*N*-dimethylaminopyridine (entry 2, Table 1). Similarly, **20c** was obtained in quantitative yield using this modified procedure (entry 5, Table 1) (Scheme 3).



16a Ar = Ph
16b Ar = 2-naphthyl
16c Ar = 4-MeC_6H_4

i or ii; iii or iv

20a Ar = Ph; **20b** Ar = 2-naphthyl; **20c** Ar = 4-MeC_6H_4
21a Ar = Ph; **21b** Ar = 2-naphthyl; **21c** Ar = 4-MeC_6H_4

Scheme 3 *Reagents and conditions*: i, BuLi, −78 °C, $PhCH_2CH_2COCl$; ii, Et_3N, 20 mol% DMAP, $PhCH_2CH_2COCl$, CH_2Cl_2; iii, BuLi, −78 °C, CH_3CH_2COCl; iv, Et_3N, 20 mol% DMAP, CH_3CH_2COCl; CH_2Cl_2.

Diastereoselective alkylations

The efficacy of 1,3-oxazolidin-2-one auxiliaries are generally expressed in terms of the diastereoselectivities and yields achieved in alkylation reactions of enolates derived from *N*-acyl-1,3-oxazolidin-2-ones.[2–8,12,13,15–17] Accordingly, we initially investigated the benzylation of the enolates derived from the *N*-propionyl-1,3-oxazolidin-2-ones **21a**–**c** (Scheme 4). Thus, LDA mediated enolate formation was carried out at 0 °C

Table 1 Synthesis of *N*-acylated 5,5-diaryl-1,3-oxazolidin-2-ones **20a–c** and **21a–c**

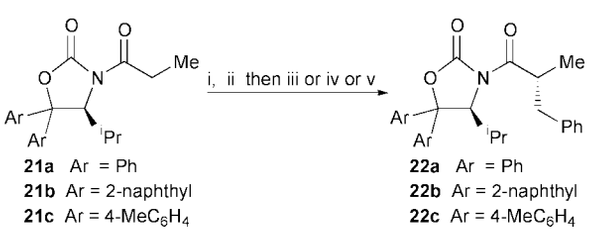
Entry	Reactant	Ar	Method[a,b]	*N*-Acylated 1,3-oxazolidin-2-one yield (%)
1	**16a**	Ph	A	**20a** (46)
2	**16a**	Ph	B	**20a** (84)
3	**16b**	2-Naphthyl	A	**20b** (97)
4	**16c**	4-Tolyl	A	**20c** (82)
5	**16c**	4-Tolyl	B	**20c** (100)
6	**16a**	Ph	A	**21a** (70)
7	**16b**	2-Naphthyl	A	**21b** (90)
8	**16c**	4-Tolyl	A	**21c** (98)
9	**16c**	4-Tolyl	B	**21c** (74)

[a] Method A BuLi, THF, −78 °C, acid chloride. [b] Method B Et_3N, DMAP, room temperature, acid chloride.

Table 2 Enolate alkylations of *N*-acylated-1,3-oxazolidin-2-ones **20a–c** and **21a–c**

Entry	1,3-Oxazolidin-2-one	Base	Electrophile	Alkylated product (%)	dr[a]
1	**21a**	LDA	BnBr	**22a** (46)[b]	98.5 : 1.5
2	**21a**	LDA	BnBr	**22a** (33)[c]	98.5 : 1.5
3	**21a**	LDA	BnBr	**22a** (69)[d]	98 : 2
4	**21b**	LDA	BnBr	**22b** (55)[b]	95.5 : 4.5
5	**21b**	LDA	BnBr	**22b** (34)[c]	96 : 2
6	**21c**	LDA	BnBr	**22c** (66)[b]	98 : 2
7	**21c**	LDA	BnBr	**22c** (31)[c]	96 : 4
8	**20a**	LDA	MeI	**23a** (48)[c]	96 : 4
9	**20a**	NaHMDS	MeI	**23a** (69)[b]	95.5 : 4.5
10	**20b**	LDA	MeI	**23b** (42)[d]	93 : 7
11	**20b**	NaHMDS	MeI	**23b** (58)[b]	91 : 9
12	**20c**	LDA	MeI	**23c** (32)[d]	97.5 : 2.5
13	**20c**	NaHMDS	MeI	**23c** (64)[b]	97 : 3

[a] Determined by ^1H NMR. [b] Reaction quenched *via* the addition of aq. NH_4Cl. [c] Reaction quenched *via* the addition of 0.01 M phosphate buffer pH 7. [d] Reaction quenched *via* the addition of 0.16 M phosphate buffer pH 7.



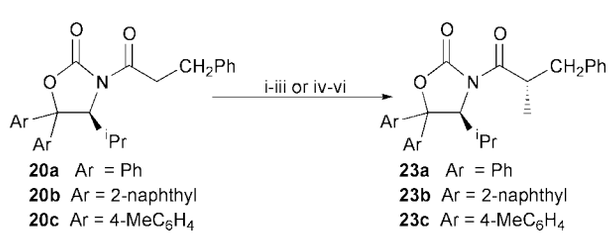
Scheme 4 *Reagents and conditions*: i, LDA, 0 °C, 2.5 h; ii, 3 equiv. BnBr, 0 °C, 23 h; iii, aq.NH_4Cl; iv, 0.01 M phosphate buffer pH 7; v, 0.16 M phosphate buffer pH 7.

followed by treatment with excess benzyl bromide. In the case of *N*-acyl derivative **21a**, although a satisfying 98.5 : 1.5 diastereomeric ratio of **22a** was achieved after quenching the reaction into aqueous ammonium chloride, the efficiency was a moderate 46% (Table 2 entry 1). Changing the conditions for quenching the reaction by the use of 0.01 M phosphate buffer led to a diminished yield of 33% (Table 2 entry 2). The use of a 0.16 M phosphate buffer at pH 7 was found to be the most efficacious method of quenching the benzylation reaction and led to a greatly improved yield of 69% (Table 2 entry 3). While the diastereomeric ratio is 98 : 2 in this case, a single recrystallisation from pentane gave diastereomerically pure **22a**.

After the completion of our studies[21] Hintermann and Seebach reported that low yields of benzylation were obtained from lithium enolates of *N*-acyl-5,5-diphenyl-1,3-oxazolidin-2-ones.[15] These workers attributed the low yields to the decomposition of the lithium enolate *via* a ketene pathway. Furthermore, Davies and co-workers attributed the low yields of **22a** (35%), generated under similar conditions, to the unreactive nature of the lithium enolate of **21a**.[17] However, using our conditions followed by the appropriate reaction quench conditions provides benzylated **22a** in 69% yield.

The work up methodology was less critical in the benzylation of the lithium enolates of 1,3-oxazolidin-2-ones **21b** and **21c**. In these cases, the alkylated products were obtained in 55% (dr 95.5 : 4.5) and 66% (dr 98 : 2) yields, respectively (Table 2, entries 4 and 6), after quenching into aqueous ammonium chloride.

As a further measure of the efficacy of our auxiliaries, the alkylation of the *N*-dihydrocinnamoyl-5,5-diaryl-1,3-oxazolidin-2-ones **20a–c** was investigated using the less reactive methyl iodide as the electrophile (Scheme 5). Accordingly, generation



Scheme 5 *Reagents and conditions*: i, LDA, 0 °C, 1 h; ii, 3 equiv. MeI, 0 °C, 20 h; iii, 0.16 M phosphate buffer pH 7; iv, NaHMDS, −78 °C, 1 h; v, 5 equiv. MeI, −78 °C, 20 h; vi, aq. NH_4Cl.

of the lithium enolate of *N*-dihydrocinnamoyl-5,5-diaryl-1,3-oxazolidin-2-ones **20a** followed by methylation at 0 °C gave a poor yield (48%) of the alkylated product **23a** (Table 2 entry 8). The use of our modified reaction quench procedure of 0.16 M phosphate buffer at pH 7 also gave a poor yield of methylated products **23b** and **23c** (Table 2 entries 10 and 12). Evans *et al.* have documented that the methylation of sodium enolates of *N*-acyl-1,3-oxazolidin-2-ones resulted in superior yields over the corresponding lithium enolates. Thus, formation of the sodium enolates of the *N*-dihydrocinnamoyl-5,5-diaryl-1,3-oxazolidin-2-ones **20a–c** and methylation at −78 °C with excess methyl iodide provided the alkylated products *N*-dihydrocinnamoyl-5,5-diaryl-1,3-oxazolidin-2-ones **23a–c** in improved yields (58–69%) (Table 2, entries 9, 11 and 13). Although the yields are significantly better in the methylations using sodium

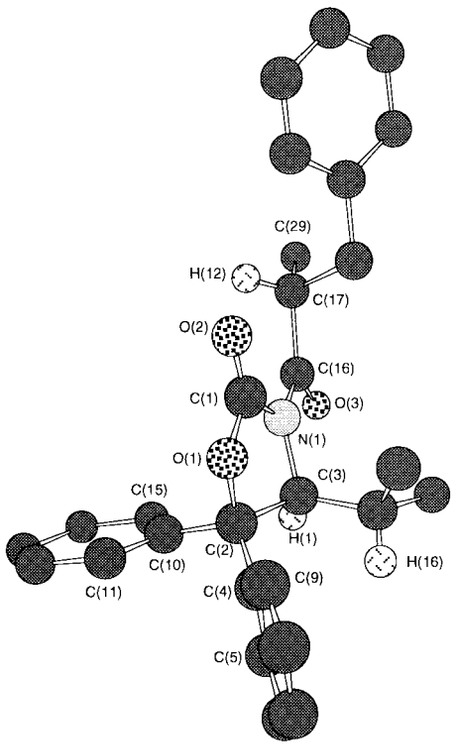


Fig. 3 Chem3D Pro representation of the X-ray structure of **22a**.

enolates relative to the lithium counterparts, there is little difference in the diastereoselectivities observed (Table 2, entries 8–13).

The 5,5-ditolyl-1,3-oxazolidin-2-one derivatives **20c** and **21c** proved to be the most efficacious in these alkylation studies giving diastereomeric ratios of ≥97 : 3 and yields ≥64%. These results compare well with other 5,5-disubstituted 1,3-oxazolidin-2-one auxiliaries.[10,13–17] Although enolate alkylations of the 5,5-diphenyl-1,3-oxazolidin-2-one derivatives **20a** and **21a** were less diastereoselective (dr ≥ 93 : 7), the advantages are the highly crystalline nature of all the 5,5-diphenyl-1,3-oxazolidin-2-one derivatives **16a**, **20a**–**23a**. This feature has already been outlined by Seebach *et al.*[15] and allows easier purification and separation of the diastereomers. However, the production of benzene as a by-product in the preparation of amino alcohol **19a** may have adverse environmental implications.

The foregoing benzylated products **22a**–**c** and methylated compounds **23a**–**c** represent complementary diastereomers which allowed the rapid establishment of the diastereomeric ratios. These ratios were determined by ^{1}H NMR by measurement and comparison of the peak areas on expanded spectra corresponding to the benzyl protons of each complementary diastereomer present. Alternatively or additionally, the peak areas of the three methyl resonances were measured and the proportions established of the major and minor diastereomers.

X-Ray crystallographic studies

In order to establish the absolute configuration at the newly formed stereocentre at C-2′ (C(17) X-ray numbering) in the alkylation reactions a single crystal X-ray analysis was carried out on the recrystallised **22a** (dr >99.5 : 0.5) (Fig. 3).‡ The diffraction data, by themselves, give no reliable information of the absolute structure, this was based on the known (*S*) configuration at C(3). This established the configuration at C(17) as (*R*) and is consistent with the *lk* delivery of the electrophile to the 2*Si* face of a carbonyl-metal-carbonyl *Z*-enolate of **21a**, in accord with the results of Evans *et al*. and Davies and Sanganee.[22,10*a*]

In line with the published crystal structure of **20a**,[15] the two methyl groups of the C(3) isopropyl group in **22a** are directed away from the C(2) phenyl groups. Their position lies over the 1,3-oxazolidin-2-one ring such that they effectively shield the *Re* face of the C(16) amide carbonyl so that the isopropyl group acts as a pseudo *tert*-butyl group.[10*e*,15]

The X-ray structure indicates that the two C(2) phenyl groups on the 1,3-oxazolidin-2-one ring in **22a** are not directed over the heterocyclic ring. Indeed, in **22a** the *pro-S* phenyl group is approximately co-linear with the C(2)–C(3) bond, with C3–C2–C10–C15 and C3–C2–C10–C11 torsional angles of −3.2(6)° and −179.6(3)°, respectively. The *pro-R* phenyl group in **22a** is approximately co-linear with the C(2)–O(1) bond with O1–C2–C4–C9 and O1–C2–C4–C5 torsional angles of −1.1(5)° and 178.9(3)°, respectively. The arrangements of these phenyl groups ensure that there is no deleterious shielding of the C(1) *Re* face. This is in contrast to the molecular modelling studies of Davies and co-workers on the enolate of a (4*S*)-*N*-acyl-4,5,5-triphenyl-1,3-oxazolidin-2-one.[17] In these modelling studies, a C-5 *pro-R* phenyl ring was orientated over the 1,3-oxazolidin-2-one ring, resulting in steric hindrance of both faces of the heterocyclic ring. The decrease in diastereoselectivity using the (4*S*)-*N*-acyl-4,5,5–triphenyl-1,3-oxazolidin-2-one over the 5,5-dimethyl analogue was attributed to the facial steric hindrance of the C-5 *pro-R* phenyl ring in the former.

Diastereoselective azidation reactions

As a further test of the utility of 5,5-diaryl-1,3-oxazolidin-2-ones **16a**–**c** as chiral auxiliaries we decided to investigate the use of these systems in diastereoselective azidation processes. Evans *et al.* have reported a comprehensive study on the use of the Evans' phenylalaninol 1,3-oxazolidin-2-one auxiliaries **1** in two complementary approaches to the synthesis of 2-azido-carboxylic acids (dr 97 : 3 and 91 : 9).[23] Accordingly, we investigated these azidation protocols using our most efficacious 5,5-ditolyl auxiliary in the form of the *N*-dihydrocinnamoyl derivative **20c**. Treatment of *N*-dihydrocinnamoyl derivative **20c** with potassium hexamethyldisilylamide at −78 °C followed by the addition of a pre-cooled (−78 °C) solution of 2,4,6-triisopropylsulfonyl azide.[24] The reaction was allowed to age for just two minutes before quenching with glacial acetic acid which afforded the azide 1,3-oxazolidin-2-one **24** in 65% yield and a diastereomeric ratio of 96 : 4. Alternatively, preparation of the boron enolate of *N*-dihydrocinnamoyl derivative **20c** followed by treatment with *N*-bromosuccinimide provided the crude bromo-1,3-oxazolidin-2-one **25**. The crude bromo-1,3-oxazolidin-2-one **25** was reacted with tetramethylguanidinium azide[25] to afford the 1,3-oxazolidin-2-one azide **26** in 55% yield and a diastereomeric ratio of 95.5 : 4.5.

With the complementary diastereomers **24** and **26**, in hand, it was possible to determine the respective diastereoselectivities by normal phase HPLC analysis (Scheme 6).

Hydrolysis and recovery of the chiral auxiliaries

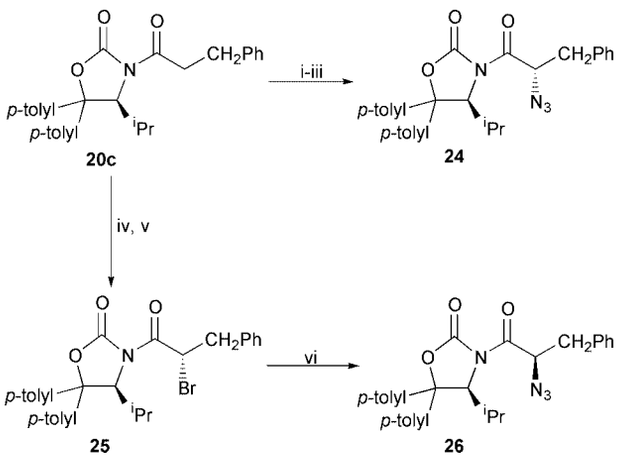
Following diastereoselective reactions, chiral auxiliaries must be efficiently cleaved from the acyl portion in order to isolate the newly formed chiral product and recover the parent 1,3-oxazolidin-2-one. In the light of the reported problems in

‡ *X-Ray crystallographic data*: $C_{28}H_{29}NO_3$, $M = 427.52$, monoclinic, $a = 10.765(4)$, $b = 9.013(4)$, $c = 12.835(5)$ Å, $\beta = 111.43(3)°$, $U = 1159.3(8)$ Å^3, $T = 123$ K, space group $P2_1$, $Z = 2$, μ(Mo-Kα) = 0.079 mm^{-1}, 5803 measured reflections, 4556 unique ($R_{int} = 0.0406$), $2\theta_{max} = 52°$. Final refinement to convergence using SHELXL97 on F^2 gave $R_1 = 0.0635$ for 2954 observed reflections with $I > 2\sigma(I)$ and w$R_2 = 0.1890$ for all reflections. All non-hydrogen atoms were treated anisotropically and all hydrogen atoms were placed in calculated positions and in a riding mode. As the diffraction data on their own give no reliable information on the absolute structure, this was based on the known stereochemistry at C3. CCDC reference number 159626. See http://www.rsc.org/suppdata/p1/b1/b102020j/ for crystallographic files in .cif or other electronic format.

Table 3 Hydrolysis of *N*-acylated 5,5-diaryl-1,3-oxazolidin-2-ones **22a–c** and **23a–c**

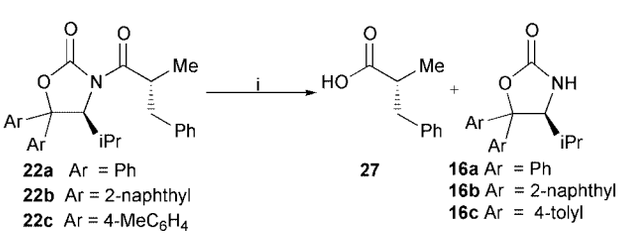
Entry	1,3-Oxazolidin-2-one (dr)	Recovered oxazolidin-2-one (%)	Acid (%)	%ee Acid[a]
1	**22a** (>99 : 1)	**16a** (94)	**27** (60)	98[b]
2	**22b** (95.5 : 4.5)	**16b** (91)	**27** (71)	92
3	**22c** (98 : 2)	**16c** (98)	**27** (55)	96
4	**23a** (96 : 4)	**16a** (95)	**28** (94)	89[b]
5	**23b** (91 : 9)	**16b** (100)	**28** (72)	81
6	**23c** (97 : 3)	**16c** (100)	**28** (62)	92[b]

[a] Determined by comparison of the $[\alpha]_D$ with the literature values.[27] [b] The $[\alpha]_D$ was measured at a significantly lower concentration than the literature value.



Scheme 6 *Reagents and conditions*: i, KHMDS, −78 °C; ii, 2,4,6-triisopropylsulfonyl azide, −78 °C; iii, AcOH −78–30 °C; iv, Bu_2BOTf, $^iPr_2NEt$, −78 °C; v, *N*-bromosuccinimide; vi, tetramethylguanidinium azide, 0 °C.

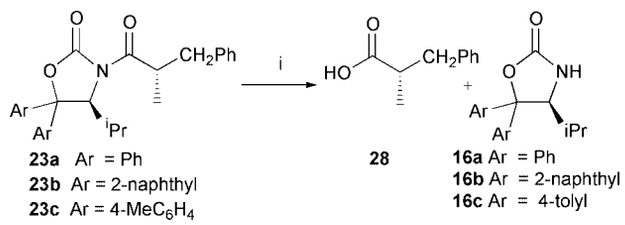
1,3-oxazolidin-2-one removal (*vide supra*)[9] it was important to confirm that the presence of aromatic groups at C-5 allowed for the mild non-destructive cleavage. By suppressing the unwanted endocyclic cleavage this should lead to efficient recovery of the auxiliary and acyl portion. The archetypal test of 1,3-oxazolidin-2-one recyclability has been the hydrolysis of alkylated acyl auxiliaries.[9,10a,15,17] Accordingly, alkaline hydrolysis of the benzylated products **22a–c** with lithium hydroxide in aqueous THF afforded the (*R*)-2-methyl-3-phenylpropionic acid **27** in 55–71% yield together with the recovered auxiliaries **16a** (94%), **16b** (91%), and **16c** (98%), respectively. No products resulting from the undesired endocyclic cleavage pathway were observed and this was further evidenced by the exceptionally high recovery of the auxiliaries **16a–c** (Scheme 7, Table 3 entries 1–3).



Scheme 7 *Reagents and conditions*: i, 2 equiv. LiOH, THF–H_2O.

Similar lithium hydroxide hydrolysis of the methylated products **23a–c** afforded (*S*)-2-methyl-3-phenylpropionic acid **28** in 62–94% yield as well as the recovered auxiliaries **16a** (95%), **16b** (100%), and **16c** (100%), respectively (Scheme 8, Table 3 entries 3–6).

Initial attempts to determine the ees of (*R*)-2-methyl-3-phenylpropionic acid **27** and the (*S*) enantiomer **28** by ^1H NMR in conjunction with the chiral solvating agent (*R,R*)-diphenyldiaminoethane[10a,26] were unsuccessful because of insufficient differences in the chemical shifts of the comple-



Scheme 8 *Reagents and conditions*: i, 2 equiv. LiOH, THF–H_2O.

mentary diastereomeric complexes. Consequently, the absolute configuration and the ees of (*R*)-2-methyl-3-phenylpropionic acid **27** and (*S*)-2-methyl-3-phenylpropionic acid **28** were established by comparison of the measured specific rotation with the published value.[27] Within the constraints of using specific rotations to determine the ees, there was no evidence of substantial loss of stereochemical integrity at C-2 in (*R*)-2-methyl-3-phenylpropionic acid **27** or (*S*)-2-methyl-3-phenylpropionic acid **28**, with respect to the original diastereomeric ratios (Table 3).

Conclusions

Studies of the benzylation of three *N*-propionyl-5,5-diaryl substituted 1,3-oxazolidin-2-ones **21a–c** revealed that expedient use of the appropriate reaction quench (pH 7 buffer for **21a**, aqueous NH_4Cl for **21b,c**) leads to maximal yields (55–68%) as well as high stereoinduction (dr 95.5 : 4.5–98 : 2). Similar investigations on the methylation of three *N*-dihydrocinnamoyl-5,5-diaryl substituted 1,3-oxazolidin-2-ones **20a–c** disclosed that the use of sodium enolates led to the most efficacious reactions (58–69%).

The presence of the 5,5-diaryl groups completely suppressed any unwanted endocyclic cleavage in subsequent simple alkaline hydrolyses. This allowed for the high recovery and recyclability of the 5,5-diaryl substituted 1,3-oxazolidin-2-ones **16a–c**. In addition, the acyl portion was recovered in high yield without any evidence of racemisation.

In general, the 5,5-ditolyl-1,3-oxazolidin-2-ones **16c** gave the best levels of stereoinduction (dr ≥ 97 : 3) in the alkylation of the appropriate *N*-acyl derivatives. While lower levels of stereoinduction (dr ≥ 93 : 7) were realised in similar studies with the 5,5-diphenyl-1,3-oxazolidin-2-ones **16a**, the highly crystalline nature of the derivatives provides a rapid method of purification and enhancement of diastereomeric purity (100%) through recrystallisation. However, the synthesis of 5,5-diphenyl-1,3-oxazolidin-2-ones **16a** is deleterious in environmental terms as a result of the production of benzene as a by-product.

Experimental

Instrumentation

Melting points were determined on a Reichert 7905 hot stage and are uncorrected. Specific rotations were measured at 20 °C in a 1 cm^3 cell with a pathlength of 10 cm using a Perkin-Elmer

341 polarimeter. The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and the concentrations are given in g 100 cm^{-3}. ^{1}H NMR spectra were recorded on Bruker WM-250, JEOL 270, or Bruker 400 spectrometers in the indicated solvents operating at 250, 270 or 400 MHz, respectively. ^{13}C NMR spectra were obtained on the same instruments operating at 62.89, 67.80, and 100 MHz, respectively. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dq, doublet of quartets; sep, septet. Coupling constants were recorded in Hz. Infrared (IR) spectra were recorded on a Nicolet Impact 400D FTIR spectrometer either as liquid films or as KBr discs. Mass spectra were recorded on a JEOL JMS AX505 spectrometer at Strathclyde or at the EPSRC National Mass Spectrometry service, Swansea. Microanalyses were performed by the microanalytical service at Strathclyde. HPLC analysis was performed using an Applied Chromatography Systems (ACS) Model 351 isocratic pump in conjunction with a Zorbax 5 μm silica column (250 × 4.6 mm) with 1% *tert*-butyl methyl ether in isooctane (1 cm^3 min^{-1}) as the eluant. The peaks were detected with an ACS Model 750/12 UV detector set at 254 nm and an ACS Chiramonitor. The data were collected on a Viglen computer fitted with a SUMMIT data card and the chromatograms were integrated using COMUS SUMMIT software.

General methods

Anhydrous reactions were carried out under an atmosphere of nitrogen in oven-dried glassware (140 °C). Anhydrous solvents were obtained using standard procedures: glacial acetic acid (Ac_2O, CrO_3), dichloroethane (NaH), diisopropylamine (CaH_2), diisopropylethylamine (CaH_2), methanol ($Mg(OMe)_2$), THF (K metal), toluene (Na metal) and triethylamine (CaH_2). Benzyl bromide (79–81 °C @ 14 mmHg), dihydrocinnamoyl chloride (111–112 °C @ 18 mmHg), methyl iodide (43–44 °C), propionyl chloride (77–79 °C) and thionyl chloride (77–79 °C) were all fractionally distilled before use. All other reagents were used as supplied. The 0.01 phosphate buffer was prepared by dissolving the appropriate buffer tablet in water (200 cm^3) (0.01 M phosphate buffer, 2.7 mM KCl, 0.137 M NaCl). The 0.16 M phosphate buffer solution (pH 7.0) was prepared using 82 cm^3 of 0.2 M Na_2HPO_4 and 37 cm^3 of 0.1 M citric acid. Flash column chromatography was performed according to the procedure of Still *et al.*[28] using silica gel (230–400 mesh).

Measurement of alkylation diastereomeric ratios

The diastereomeric ratios of **22a–c** and **23a–c** were measured using ^{1}H NMR analysis. This was achieved by comparison of the peak areas on expanded sections of the spectra for the benzyl methylene resonances for each complementary diastereomer present in the reaction mixture and/or the three methyl resonances of both diastereomers.

(*S*)-Valine methyl ester hydrochloride 18

To a suspension of L-valine (30 g, 256 mmol) in dry MeOH (250 cm^3) at −10 °C under N_2 was added thionyl chloride (23.25 cm^3, 320 mmol) portionwise over 10 min. The heterogeneous mixture was warmed to room temperature and heated at reflux for 2 h. The reaction mixture was allowed to cool to room temperature to afford a white crystalline solid (33.763 g, 202 mmol, 79%) (MeOH–diethyl ether), mp 168–169 °C (lit.[29] 165–170 °C) (Found: C, 42.68; H, 8.86; N, 8.36. Calculated for $C_6H_{14}NO_2Cl$: C, 42.99; H, 8.42; N, 8.36%); $[\alpha]_D$ +24.1 (c = 1.98, MeOH) (lit.,[29] = +23 ± 1 (c = 2, MeOH)); ν_{max} (KBr) 1740 (s, C=O *str*) cm^{-1}; δ_H ($CDCl_3$) 8.76 (s, 3H, –NH_3), 3.96 (d, 1H, J 3.1, –NCH), 3.77 (s, 3H, –OCH_3), 2.43 (m, 1H, CH(CH_3)$_2$), 1.15 (d, 3H, J 3.0, –CH_3), 1.12 (d, 3H, J 3.0, –CH_3); δ_C ($CDCl_3$) 169.02 (CO_2H), 58.78 (–OCH_3), 52.96 (–NCH), 29.96 (–CH(CH_3)$_2$), 18.57, 18.34 (–CH_3).

General procedure for the synthesis of the diaryl amino alcohols

(*S*)-Valine methyl ester hydrochloride **18** (*ca.* 60 mmol) was added portionwise over 20 min to a 2 M solution of the appropriate Grignard reagent [prepared from aryl bromide (8 equiv.) in THF (240 cm^3) and magnesium turnings (8.8 equiv.)] cooled in an ice–salt bath under a N_2 atmosphere. The reaction mixture was stirred for 4 h at room temperature before being quenched into a mixture of 2 M aqueous HCl and crushed ice. The mixture was basified by the addition of aqueous ammonia. The organic layer was separated and the aqueous layer was washed with EtOAc (×3). The organic extracts were combined, dried over $MgSO_4$ and the solvent removed *in vacuo* to yield the crude amino alcohol which was recrystallised.

(*S*)-2-Amino-1,1-diphenyl-3-methylbutan-1-ol 19a. The required amino alcohol was obtained from (*S*)-valine methyl ester hydrochloride **18** (10.079 g, 59.99 mmol) as a white solid, (8.241 g, 32.23 mmol, 54%) (EtOH), mp 93–96 °C (lit.[30] 94–95 °C) (Found: C, 79.77; H, 8.15; N, 5.70: MH^+ 256.1704. Calculated for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49%: 256.1701); $[\alpha]_D$ −130.2 (c = 1.10, $CHCl_3$) (lit.[30] −127.7 (c = 0.639, $CHCl_3$)); ν_{max} (KBr) 3380 (br, O–H), 3338 (m, N–H), 3278 (m, N–H), 3082, 3057, 3019 (m, aromatic C–H), 1658, 1592 (m, C=C) cm^{-1}; δ_H ($CDCl_3$) 7.63–7.11 (m, 10H, aryl-H), 3.83 (d, 1H, J 2.2, –CHNH_2), 1.76 (m, 1H, –CH(CH_3)$_2$), 0.91 (d, 3H, J 7.0, –CH_3), 0.86 (d, 3H, J 7.0, –CH_3); δ_C ($CDCl_3$) 148.16, 145.05, 128.57, 128.20, 127.00, 126.43, 126.07, 125.85 (aryl-C), 79.85 (C-β), 60.33 (C-α), 28.00 (–CH(CH_3)), 23.15 (–CH_3), 16.28 (–CH_3).

(*S*)-2-Amino-1,1-di(2′-naphthyl)-3-methylbutan-1-ol 19b. The amino alcohol was obtained from (*S*)-valine methyl ester hydrochloride **18** (7.022 g, 41.80 mmol) as a white solid (8.653 g, 24.37 mmol, 60%) (Pr^{i}OH), mp 196–198 °C (Found: C, 84.56; H, 6.99; N, 3.89: MH^+ 356.2060. $C_{25}H_{25}NO$ requires: C, 84.47; H, 7.09; N, 3.94%: 356.2014); $[\alpha]_D$ −372.2 (c = 0.70, $CHCl_3$); ν_{max} (KBr) 3443 (br, O–H), 3411 (m, N–H), 3334 (m, N–H), 3064, 3040 (m, aromatic C–H), 1626, 1597 (m, C=C) cm^{-1}; δ_H (CD_2Cl_2) 8.21–7.43 (m, 14H, aryl-H), 4.19 (d, 1H, J 2.2, –CHNH_2), 1.81 (m, 1H, –CH(CH_3)$_2$), 1.00 (d, 3H, J 7.0, –CH_3), 0.96 (d, 3H, J 7.0, –CH_3); δ_C (CD_2Cl_2) 146.09, 142.98, 133.90, 132.85, 132.71, 128.75, 128.68, 128.07, 127.93, 126.65, 126.51, 126.44, 126.22, 125.97, 124.82, 124.49, 124.22 (aryl-C), 80.48 (C-β), 60.03 (C-α), 28.75 (–CH(CH_3)$_2$), 23.17, 16.37 (–CH_3).

(*S*)-2-Amino-1,1-di(4′-tolyl)-3-methylbutanol 19c. The desired amino alcohol was obtained from (*S*)-valine methyl ester hydrochloride **18** (6.995 g, 41.64 mmol) as colourless needles (6.132 g, 21.67 mmol, 52%) (EtOH–H_2O), mp 96–98 °C (Found: C, 80.40; H, 8.87; N, 5.00: MH^+ 284.2041. $C_{19}H_{25}NO$ requires: C, 80.52; H, 8.89; N, 4.94%: 284.2014); $[\alpha]_D$ −108.4 (c = 0.66, $CHCl_3$); ν_{max} (KBr) 3513 (br, O–H), 3390 (m, N–H), 3323 (m, N–H), 3092, 3057, 3022 (m, aromatic C–H), 1603, 1508 (m, C=C) cm^{-1}; δ_H ($CDCl_3$) 7.49–7.06 (m, 8H, aryl-H), 3.78 (d, 1H, J 2.4, –NCH), 2.27 (s, 6H, –PhCH_3), 1.76 (m, 1H, –CH(CH_3)$_2$), 0.92 (d, 3H, J 7.0, –CH_3), 0.88 (d, 3H, J 7.0, –CH_3); δ_C ($CDCl_3$) 145.32, 142.35, 136.27, 135.87, 129.30, 128.93, 125.92, 125.46 (aryl-C), 79.75 (C-β), 60.38 (C-α), 28.01 (–CH(CH_3)$_2$), 23.19 (–CH_3), 21.18 (PhCH_3), 16.31 (–CH_3).

General procedures for the preparation of the 1,3-oxazolidin-2-ones

Method A. Using aqueous potassium hydroxide. To a vigorously stirred suspension of the amino alcohol (1 equiv.) in 12.5% aqueous potassium hydroxide (6.2–6.4 equiv.) and toluene (1.4 M) at room temperature under N_2 was added a 1.7 M solution of triphosgene in toluene (3.6 equiv.) dropwise over 20 min. The resultant slurry was aged for 2 h and the white solid

formed was filtered off and washed several times with water and toluene. Recrystallisation gave the appropriate 1,3-oxazolidin-2-ones **16a**–**c**.

Method B. Using triethylamine. To a suspension of the amino alcohol (1 equiv.) in THF (0.2 M) cooled in an ice bath under N_2 was added triethylamine (2.2 equiv.) in one portion. A 0.35 M solution of triphosgene in THF (1.16 equiv.) was added rapidly. The ice bath was removed and the slurry was aged for 45 min at room temperature. The resultant white solid was filtered and washed with THF and EtOAc. The filtrate was dried over $MgSO_4$ and the solvent removed *in vacuo* to give a white solid. Column chromatography (EtOAc–hexane, 1 : 1) and recrystallisation gave the desired compound.

(S)-5,5-Diphenyl-4-isopropyl-1,3-oxazolidin-2-one ***16a***. Using method A with (*S*)-2-amino-1,1-diphenyl-3-methylbutan-1-ol **19a** (3.945 g, 15.47 mmol) afforded the title compound as white needle-like crystals (3.176 g, 11.3 mmol, 73%) (EtOH–H_2O), mp 247–250 °C (lit.[13] 253.2–253.9 °C) (Found: C, 76.73; H, 6.85; N, 4.87: MH^+ 282.1400. Calculated for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98%: 282.1494); $[\alpha]_D$ −263.4 (c = 0.51, $CHCl_3$) (lit.[13] $[\alpha]_D$ −253.1 (c = 0.1, $CHCl_3$)); ν_{max} (KBr) 3292 (m, N–H), 1764, 1745 (s, C=O) cm^{-1}; δ_H (d_6-DMSO) 8.13 (s, 1H, −N*H*), 7.68–7.21 (m, 6H, aryl-*H*), 4.38 (s, 1H, HN–*H*), 1.83 (m, 1H, –C*H*$(CH_3)_2$), 0.90 (d, 3H, *J* 6.8, –C*H*$_3$), 0.52 (d, 3H, *J* 6.8, –C*H*$_3$); δ_C (d_6-DMSO) 157.33 (*C*=O), 145.36, 139.80, 128.37, 128.06, 127.68, 127.19, 125.51, 125.09 (aryl-*C*), 87.65 (*C*-β), 64.19 (*C*-α), 29.06 (*C*H$(CH_3)_2$), 16.60, 14.50 (–*C*H$_3$).

(S)-5,5-Di(2′-naphthyl)-4-isopropyl-1,3-oxazolidin-2-one ***16b***. Using method A with (*S*)-2-amino-1,1-di(2′-naphthyl)-3-methylbutan-1-ol **19b** (2.483 g, 6.99 mmol) gave the title compound as white needles (1.581 g, 4.15 mmol, 59%) (toluene), mp 240–242 °C (Found: C, 81.65; H, 5.78; N, 3.37: MH^+ 382.1818. $C_{26}H_{23}NO_2$ requires: C, 81.86; H, 6.08; N, 3.67%: 382.1807); $[\alpha]_D$ −373.6 (c = 0.06, $CHCl_3$); ν_{max} (KBr) 3285 (br, N–H), 1754, 1706 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 8.09–7.16 (m, 14H, aryl-*H*), 6.62 (s, 1H, –CHN*H*), 4.63 (d, 1H, *J* 2.9, HNC*H*), 1.93 (m, 1H, –C*H*$(CH_3)_2$), 0.97 (d, 3H, *J* 6.8, –C*H*$_3$), 0.75 (d, 3H, *J* 6.8, –C*H*$_3$); δ_C ($CDCl_3$) 158.97 (*C*=O), 136.59, 133.17, 132.98, 132.97, 132.75, 128.80, 128.69, 128.63, 128.02, 127.75, 127.71, 126.86, 126.77, 126.77, 126.73, 126.69, 125.52, 124.80, 124.59, 124.52, 124.40 (aryl-*C*), 89.99 (*C*-β), 65.43 (*C*-α), 29.96 (–*C*H$(CH_3)_2$), 21.25, 15.90 (–*C*H$_3$).

(S)-5,5-Di(4′-tolyl)-4-isopropyl-1,3-oxazolidin-2-one ***16c***. Using method A with (*S*)-2-amino-1,1-di(4′-tolyl)-3-methylbutanol **19c** (2.000 g, 7.07 mmol) gave the title compound as colourless needles (1.182 g, 3.83 mmol, 54%) (EtOH), mp 186–188 °C (Found: C, 77.45; H, 7.53; N, 4.55: MH^+ 310.1829. $C_{20}H_{23}NO_2$ requires: C, 77.64; H, 7.48; N, 4.53%: 310.1807); $[\alpha]_D$ −235.7 (c = 1.03, $CHCl_3$); ν_{max} (KBr) 3264 (br, N–H), 1749, 1717 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 7.44–7.09 (m, 8H, aryl-*H*), 6.52 (s, 1H, –CHN*H*), 4.32 (d, 1H, *J* 3.2, –C*H*NH), 2.32 (s, 6H, PhC*H*$_3$), 1.83 (m, 1H, –C*H*$(CH_3)_2$), 0.89 (d, 3H, *J* 6.8, –C*H*$_3$), 0.71 (d, 3H, *J* 6.8, –C*H*$_3$); δ_C ($CDCl_3$) 159.00 (*C*=O), 141.40, 138.09, 137.50, 136.67, 129.33, 128.89, 126.47, 125.83 (aryl-*C*), 89.64 (*C*-β), 66.06 (*C*-α), 29.81 (–*C*H$(CH_3)_2$), 21.23, 21.06 (Ph*C*H$_3$), 15.97 (–*C*H$_3$).

Using method B with (*S*)-2-amino-1,1-di(4′-tolyl)-3-methylbutanol **19c** (0.255 g, 0.90 mmol) the title compound was obtained as fine, white needle-like crystals (0.171 g, 0.56 mmol, 62%) (EtOH–H_2O) with identical spectroscopic data to those reported above.

General procedures for the acylation of the 1,3-oxazolidin-2-ones

Method C. Using *n*-butyllithium. To a solution or suspension of the 1,3-oxazolidin-2-one (1 equiv.) in THF (0.07–0.1 M) at −78 °C under N_2 was added *n*-butyllithium (1.6 M in hexane, 1.04 equiv.) portionwise over 10 min and the mixture was stirred for 2 h at this temperature. Freshly distilled acid chloride (1.1 equiv.) was added dropwise at −78 °C and the mixture was stirred for 30 min and at room temperature for a further 24 h. The reaction mixture was poured into phosphate buffer (0.01 M) and the organic phase was separated. The aqueous layer was washed with DCM (×2) and the organic extracts were combined and washed with aqueous saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. Flash column chromatography afforded the appropriate acylated 1,3-oxazolidin-2-ones.

Method D. Using triethylamine. To a solution or suspension of the 1,3-oxazolidin-2-one (1 equiv.) in DCM (0.1–0.16 M) at room temperature under N_2 was added DMAP (0.2 equiv.) and triethylamine (1.2 equiv.). Freshly distilled acid chloride (1.3 equiv.) was added dropwise over 5 min and the mixture was stirred for 5 h at room temperature. The reaction mixture was quenched into saturated aqueous NH_4Cl and the organic phase was separated. The aqueous layer was washed with DCM (×3) and the organic extracts were combined, washed with aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification *via* flash column chromatography afforded the requisite acylated 1,3-oxazolidin-2-ones.

(S)-5,5-Diphenyl-4-isopropyl-3-(1′-oxopropyl)-1,3-oxazolidin-2-one ***21a***. Using method C with (*S*)-5,5-diphenyl-4-isopropyl-1,3-oxazolidin-2-one **16a** (0.563 g, 2.00 mmol) and propionyl chloride (0.2 cm^3, 2.3 mmol) followed by flash column chromatography eluting with DCM–hexane (6 : 4) furnished the title compound **21a** as a white solid (0.471 g, 1.4 mmol, 70%), mp 110–113 °C (lit.[15] 111–112 °C) (Found: C, 74.83; H, 7.06; N, 4.04; MH^+ 338.1749. Calculated for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15%: 338.1756.); $[\alpha]_D$ −258.3 (c = 1.04, $CHCl_3$) (lit.[15] $[\alpha]_D$ −239.7 (c = 0.74, $CHCl_3$)); ν_{max} (KBr) 1772 (s, C=O), 1708 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 7.49–7.25 (m, 10H, aryl-*H*), 5.38 (d, 1H, *J* 3.5, –NC*H*), 2.93 (dq, 1H, *J* 17.3 and 7.3, –C*H*$_A$HCH$_3$), 2.73 (dq, 1H, *J* 17.3 and 7.3, –CH*H*$_B$CH$_3$), 1.98 (m, 1H, –C*H*$(CH_3)_2$), 1.09 (t, 3H, *J* 7.3, –CH$_A$H$_B$C*H*$_3$), 0.88 (d, 3H, *J* 7.0, –C*H*$_3$), 0.76 (d, 3H, *J* 6.5, –C*H*$_3$); δ_C ($CDCl_3$) 174.19 (*C*(=O)CH$_2$CH$_3$), 153.28 (*C*=O), 142.57, 138.43, 129.09, 128.77, 128.57, 128.13, 126.14, 125.83 (aryl-*C*), 89.56 (*C*-β), 64.60 (*C*-α), 30.11 (–*C*H$_2$CH$_3$), 29.10 (–*C*H$(CH_3)_2$), 22.00, 16.57 (–*C*H$_3$), 8.85 (–CH$_2$*C*H$_3$).

(S)-5,5-Di(2′-naphthyl)-4-isopropyl-3-(1″-oxopropyl)-1,3-oxazolidin-2-one ***21b***. Using method C with (*S*)-5,5-di(2′-naphthyl)-4-isopropyl-1,3-oxazolidin-2-one **16b** (0.258 g, 0.69 mmol) and propionyl chloride (0.07 cm^3, 0.81 mmol) followed by flash column chromatography using DCM–hexane (9 : 1) as the eluant furnished the desired product as a white crystalline solid (0.265 g, 0.62 mmol, 90%), mp 145–147 °C (EtOH) (Found: C, 79.90; H, 6.13; N, 3.19: MH^+ 438.2109. $C_{29}H_{27}NO_3$ requires: C, 79.61; H, 6.22; N, 3.21%: 438.2069); $[\alpha]_D$ −385.2 (c = 1.02, $CHCl_3$); ν_{max} (KBr) 1770 (s, C=O), 1713 (s, C=O) cm^{-1}; δ_H (CD_2Cl_2) 7.80–6.94 (m, 14H, aryl-*H*), 5.31 (d, 1H, *J* 3.0, –NC*H*), 2.55 (dq, 1H, *J* 17.4 and 7.3, –C*H*$_A$HCH$_3$), 2.32 (dq, 1H, *J* 17.4 and 7.3, –CH*H*$_B$CH$_3$), 1.66 (m, 1H, –C*H*$(CH_3)_2$), 0.68 (t, 3H, *J* 7.3 –CH$_2$C*H*$_3$), 0.56 (d, 3H, *J* 6.8, –C*H*$_3$), 0.42 (d, 3H, *J* 6.8, –C*H*$_3$); δ_C (CD_2Cl_2) 174.33 (–(*C*=O)CH$_2$CH$_3$), 153.51 (*C*=O), 139.92, 136.05, 133.59, 133.41, 133.18, 129.54, 129.11, 128.89, 128.78, 128.13, 127.99, 127.52, 127.31, 127.25, 125.22, 125.01, 124.55, 124.32 (aryl-*C*), 90.11 (*C*-β), 64.37 (*C*-α), 30.82 (–*C*H$_2$CH$_3$), 29.16 (*C*H$(CH_3)_2$), 22.31, 16.62 (–*C*H$_3$), 8.97 (–CH$_2$*C*H$_3$).

(S)-5,5-Di(4′-tolyl)-4-isopropyl-3-(1″-oxopropyl)-1,3-oxazolidin-2-one ***21c***. Using method C with (*S*)-5,5-di(4′-tolyl)-4-isopropyl-1,3-oxazolidin-2-one **16c** (0.250 g, 0.81 mmol) and propionyl chloride (0.08 cm^3 0.92 mmol) followed by flash column chromatography using hexane–EtOAc (3 : 1) as the eluant furnished the title compound as a colourless solid (0.288 g, 0.79 mmol, 98%), mp 58.5–60.5 °C (Found: C, 75.54; H, 7.63; N, 3.74: MH^+ 366.2042. $C_{27}H_{27}NO_3$ requires: C, 75.59; H, 7.45;

N, 3.83%: 366.2069); $[\alpha]_D$ −218.9 (c = 1.00, $CHCl_3$); ν_{max} (KBr) 1773 (s, C=O), 1702 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 7.36–7.10 (m, 8H, aryl-*H*), 5.33 (d, 1H, *J* 3.5, –NC*H*), 2.94 (dq, 1H, *J* 17.3 and 7.3, –CH_AHCH$_3$), 2.73 (dq, 1H, *J* 17.3 and 7.3, –CHH_BCH$_3$), 2.31 (s, 3H, –PhCH_3), 2.29 (s, 3H, –PhCH_3), 1.09 (t, 3H, *J* 7.3 –CH$_2$CH_3), 0.87 (d, 3H, *J* 6.9, –CH_3), 0.75 (d, 3H, *J* 6.9, –CH_3); δ_C ($CDCl_3$) 174.22 (–(*C*=O)CH$_2$CH$_3$), 153.40 (*C*=O), 139.87, 137.81, 135.71, 129.70, 129.19, 126.00, 125.70 (aryl-*C*), 89.66 (*C*-β), 64.60 (*C*-α), 30.08 (*C*H$_2$CH$_3$), 29.10 (C*H*(CH$_3$)$_2$), 22.02 (–*C*H$_3$), 21.26, 21.18 (–PhCH$_3$), 16.60 (–*C*H$_3$), 8.83 (–CH$_2$*C*H$_3$).

Using method D with (*S*)-5,5-di(4′-tolyl)-4-isopropyl-1,3-oxazolidin-2-one **16c** (0.650 g, 2.10 mmol) and propionyl chloride (0.24 cm^3, 2.76 mmol) followed by flash column chromatography using EtOAc–hexane (1 : 1) as the eluant gave the title compound as a colourless oil (0.568 g, 1.56 mmol, 74%) with identical spectroscopic data to those reported above.

(S)-5,5-Diphenyl-4-isopropyl-3-(1′-oxo-3′-phenylpropyl)-1,3-oxazolidin-2-one ***20a****.* Using method C with (*S*)-5,5-diphenyl-4-isopropyl-1,3-oxazolidin-2-one **16a** (0.562 g, 2.00 mmol) and dihydrocinnamoyl chloride (0.3 cm^3, 2.1 mmol) followed by flash column chromatography using DCM–hexane (17 : 3) furnished the title compound as a white solid (0.379 g, 0.92 mmol, 46%) (EtOAc–hexane), mp 89.0–92.5 °C (lit.[15] 97–98 °C) (Found: C, 78.51; H, 6.59; N, 3.31: MH^+ 414.2072. Calculated for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39%: 414.2069); $[\alpha]_D$ −168.3 (c = 0.66, $CHCl_3$) (lit.[15] $[\alpha]_D$ −179.0 (c = 1.14, $CHCl_3$)); ν_{max} (KBr) 1776 (s, C=O), 1695 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 7.47–7.17 (m, 15H, aryl-*H*), 5.39 (d, 1H, *J* 3.3, –NC*H*), 3.33–2.81 (m, 4H, –CH_2CH_2–), 1.96 (m, 1H, –C*H*(CH$_3$)$_2$), 0.85 (d, 3H, *J* 6.8, –CH_3), 0.74 (d, 3H, *J* 6.8, –CH_3); δ_C ($CDCl_3$) 172.44 (–(*C*=O)CH$_2$–), 153.23 (*C*=O), 142.51, 140.50, 138.35, 133.02, 129.14, 128.81, 128.60, 128.17, 126.36, 126.13, 125.81 (aryl-*C*), 89.64 (*C*-β), 64.74 (*C*-α), 33.09 (CH$_2$*C*H$_2$Ph), 30.66 (*C*H$_2$CH$_2$Ph), 30.08 (–*C*H(CH$_3$)$_2$), 21.93, 16.56 (–*C*H$_3$).

Using method D with (*S*)-5,5-diphenyl-4-isopropyl-1,3-oxazolidin-2-one **16a** (0.450 g, 1.60 mmol) and dihydrocinnamoyl chloride (0.31 cm^3, 2.08 mmol) followed by flash column chromatography using EtOAc–hexane (1 : 1) as the eluant gave the title compound as a white solid (0.556 g, 1.34 mmol, 84%) with identical spectroscopic data to those reported above.

(S)-5,5-Di(2′-naphthyl)-4-isopropyl-3-(1′-oxo-3′-phenylpropyl)-1,3-oxazolidin-2-one ***20b****.* Using method C with (*S*)-5,5-di(2′-naphthyl)-4-isopropyl-1,3-oxazolidin-2-one **16b** (0.226 g, 0.59 mmol) and dihydrocinnamoyl chloride (0.10 cm^3 0.65 mmol) followed by flash column chromatography using EtOAc–hexane (1 : 1) as the eluant furnished the title compound as a viscous, colourless oil (0.294 g, 0.57 mmol, 97%) (Found: MH^+ 514.2390. $C_{35}H_{32}NO_3$ requires MH^+: 514.2382); $[\alpha]_D$ −233.5 (c = 1.02, $CHCl_3$); ν_{max} (liq. film) 1779 (s, C=O), 1712 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 8.15–7.09 (m, 19H, aryl-*H*), 5.66 (d, 1H, *J* 3.2, –NC*H*), 3.34–2.87 (m, 4H, –CH_2CH_2–), 2.02 (m, 1H, –C*H*(CH$_3$)$_2$), 0.92 (d, 3H, *J* 7.0, –CH_3), 0.78 (d, 3H, *J* 7.0, –CH_3); δ_C ($CDCl_3$) 172.53 (–(*C*=O)CH$_2$–), 153.23 (*C*=O), 140.44, 139.23, 135.43, 133.25, 132.99, 132.79, 129.38, 128.91, 128.55, 127.84, 127.74, 127.22, 127.00, 126.32, 124.89, 124.74, 124.15, 123.89 (aryl-*C*), 90.01 (*C*-β), 64.18 (*C*-α), 36.94 (CH$_2$*C*H$_2$Ph), 30.60 (*C*H$_2$CH$_2$Ph), 30.33 (–*C*H(CH$_3$)$_2$), 22.16, 16.58 (–*C*H$_3$).

(S)-5,5-Di(4′-tolyl)-4-isopropyl-3-(1′-oxo-3′-phenylpropyl)-1,3-oxazolidin-2-one ***20c****.* Using method C with (*S*)-5,5-di(4′-tolyl)-4-isopropyl-1,3-oxazolidin-2-one **16c** (0.342 g, 1.11 mmol) and dihydrocinnamoyl chloride (0.18 cm^3, 1.21 mmol) followed by flash column chromatography using EtOAc–hexane (1 : 1) as the eluant furnished the title compound as a colourless oil (0.402 g, 0.91 mmol, 82%) (Found: MH^+ 442.2371. $C_{29}H_{31}NO_3$ requires MH^+: 442.2382); $[\alpha]_D$ −153.4 (c = 1.05, $CHCl_3$); ν_{max} 1784 (s, C=O), 1705 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 7.33–7.09 (m, 13H, aryl-*H*), 5.31 (d, 1H, *J* 3.8, –NC*H*), 3.31–2.81 (m, 4H, –CH_2CH_2–), 2.31 (s, 3H, –PhCH_3), 2.29 (s, 3H, –PhCH_3), 1.95 (m, 1H, –C*H*(CH$_3$)$_2$), 0.83 (d, 3H, *J* 6.9, –CH_3), 0.72 (d, 3H, *J* 6.9, –CH_3); δ_C ($CDCl_3$) 172.46 (–(*C*=O)CH$_2$–), 153.36 (*C*=O), 140.56, 139.80, 138.55, 137.84, 135.61, 129.74, 129.21, 128.59, 126.31, 126.00, 125.67 (aryl-*C*), 89.74 (*C*-β), 64.75 (*C*-α), 36.95 (CH$_2$*C*H$_2$Ph), 30.65 (*C*H$_2$-CH$_2$Ph), 30.03 (–*C*H(CH$_3$)$_2$), 21.94, 21.26, 21.19, 16.60 (–*C*H$_3$).

Using method D with (*S*)-5,5-di(4′-tolyl)-4-isopropyl-1,3-oxazolidin-2-one **16c** (0.302 g, 0.98 mmol) and dihydrocinnamoyl chloride (0.19 cm^3, 1.28 mmol) followed by flash column chromatography using EtOAc–hexane (1 : 1) as the eluant gave the desired product as a pale yellow oil (0.426 g, 0.98 mmol, 100%) with identical spectroscopic data to those reported above.

General procedures for the alkylation of the *N*-acyl-1,3-oxazolidin-2-ones

Method E. Using LDA with 0.01 M phosphate buffer. To a solution of the appropriate *N*-acyl-1,3-oxazolidin-2-one THF (0.15 M) at 0 °C was added a solution of lithium diisopropylamide [prepared from diisopropylamine (1.01 equiv.) in THF (0.46 M) at −78 °C and *n*-butyllithium (1.6 M in hexane, 1.19 equiv.)] and the resulting enolate was stirred at 0 °C for 1 h. The appropriate alkyl halide (2.96 equiv.) was added dropwise over 10 min and the mixture stirred for 24 h at 0 °C. The reaction was quenched into 0.01 M phosphate buffer and the organic phase separated. The aqueous phase was washed with DCM (×3) and the organic extracts combined, washed with brine, dried over $MgSO_4$ and the solvent remove *in vacuo* to give the crude alkylated products. Purification *via* flash column chromatography afforded the desired products.

Method F. Using LDA with 0.16 M phosphate buffer. As per method E, except the reaction mixture was quenched into enough 0.16 M phosphate buffer so that pH 7 was maintained.

Method G. Using LDA with aqueous ammonium chloride. As per method E, except the reaction mixture was quenched into saturated aqueous NH_4Cl.

Method H. Using NaHMDS. To a solution of the appropriate *N*-acyl-1,3-oxazolidin-2-one in THF (0.24 M) at −78 °C was added a solution of sodium hexamethyldisilylamide in THF (2 M, 1.11 equiv.) and the resulting enolate was stirred at −78 °C for 1 h. Methyl iodide (5 equiv.) was added and the mixture stirred for 24 h at −78 °C. The reaction was quenched into saturated aqueous NH_4Cl and the product was extracted using DCM (×2) and EtOAc. The organic extracts were combined and washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to give the crude methylated *N*-acyl-1,3-oxazolidin-2-one. The pure methylated material was obtained *via* flash column chromatography.

(2′R,4S)-5,5-Diphenyl-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one ***22a****.* Using method E with (*S*)-5,5-diphenyl-4-isopropyl-3-(1′-oxopropyl)-1,3-oxazolidin-2-one **21a** (0.150 g, 0.455 mmol) and benzyl bromide (0.16 cm^3, 1.35 mmol) gave the crude product as a yellow semi-solid. Purification *via* flash column chromatography using DCM–hexane (3 : 1) as the eluant furnished the title compound (0.065 g, 0.15 mmol, 33%); δ_H ($CDCl_3$) 7.47–7.16 (m, 15H, aryl-*H*), 5.36 (d, 1H, *J* 3.3, –NC*H*), 4.10–3.97 (m, 1H, –C*H*CH$_3$), 3.16 (dd, 1H, *J* 13.4 and 7.3, –CH_AHPh), 2.60 (dd, 1H, *J* 13.4 and 7.9, –CH*HB*Ph), 1.87 (m, 1H, –C*H*(CH$_3$)$_2$), 0.84 (d, 3H, *J* 6.9, –CH_3), 0.70 (d, 3H, *J* 6.9, –CH_3), 0.59 (d, 3H, *J* 6.7, –CH_3). The diastereomeric ratio of 98.5 : 1.5 was obtained by measurement and comparison of peak areas in the ^1H NMR for the benzyl methylene resonances for the major (δ 3.16 and 2.60) and minor (δ 2.81 and 2.45) isomers.

Using method F with (*S*)-5,5-diphenyl-4-isopropyl-3-(1′-oxopropyl)-1,3-oxazolidin-2-one **21a** (0.154 g, 0.458 mmol) and benzyl bromide (0.17 cm^3, 1.43 mmol) followed by flash column chromatography using DCM–hexane (4 : 1) as the eluant furnished the desired compound **22a** as a white crystalline solid (0.134 g, 0.315 mmol, 69%); δ_H ($CDCl_3$) 7.48–7.10 (m, 15H, aryl-*H*), 5.35 (d, 1H, *J* 3.5, –NC*H*), 4.03 (m, 1H, –C*H*CH_3), 3.16 (dd, 1H, *J* 13.6 and 7.3, –CH_AHPh), 2.60 (dd, 1H, *J* 13.6 and 7.7, –CHH_BPh), 1.80 (m, 1H, –C*H*$(CH_3)_2$), 0.84 (d, 3H, *J* 6.5, –CH_3), 0.70 (d, 3H, *J* 7.0, –CH_3), 0.59 (d, 3H, *J* 7.0, –CH_3); δ_C ($CDCl_3$) 176.41 (–(*C*=O)CH_2–), 153.04 (*C*=O), 142.52, 140.50, 139.46, 138.32, 129.43, 129.03, 128.77, 128.57, 128.50, 128.15, 126.46, 126.11, 125.87 (aryl-*C*), 89.47 (*C*-β), 64.67 (*C*-α), 39.97 (–*C*H_2–), 39.37 (*C*HCH_3), 30.11 (–*C*H$(CH_3)_2$), 21.70, 16.53, 16.30 (–*C*H_3). The diastereomeric ratio of 98 : 2 was obtained by measurement and comparison of peak areas in the ^{1}H NMR for the benzyl methylene resonances for the major (δ 3.19 and 2.63) and minor (δ 2.85 and 2.48) isomers.

Using method G with (*S*)-5,5-diphenyl-4-isopropyl-3-(1′-oxopropyl)-1,3-oxazolidin-2-one **21a** (0.337 g, 1.00 mmol) and benzyl bromide (0.36 cm^3, 3.03 mmol) followed by flash column chromatography using DCM–hexane (4 : 1) as the eluant furnished the desired compound as a white solid (0.196 g, 0.46 mmol, 46%). The diastereomeric ratio of 98.5 : 1.5 was obtained by measurement and comparison of peak areas in the ^{1}H NMR for the benzyl methylene resonances for the major (δ 3.16 and 2.60) and minor (δ 2.81 and 2.45) isomers.

A portion of **22a** was recrystallised from pentane to give colourless needle-like crystals, mp 134–136 °C (Found: C, 78.40; H, 6.72; N, 3.03: MH^+428.2191. $C_{28}H_{29}NO_3$ requires: C, 78.65; H, 6.85; N, 3.28%: MH^+428.2226); $[\alpha]_D$ −200.6 (*c* = 0.53, $CHCl_3$); ν_{max} (KBr) 1774 (s, C=O), 1692 (s, C=O). The remaining spectroscopic data were identical to those reported above for method F. The diastereomeric ratio was found to be >99 : 1.

(2″R,4S)-5,5-Di(2′-naphthyl)-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one ***22b***. Using method G with (*S*)-5,5-di(2′-naphthyl)-4-isopropyl-3-(1″-oxopropyl)-1,3-oxazolidin-2-one **21b** (0.350 g, 0.80 mmol) and benzyl bromide (0.29 cm^3, 2.43 mmol) followed by flash column chromatography using DCM–hexane (7 : 3) as the eluant furnished the desired compound as a white semi solid (0.234 g, 0.44 mmol, 55%) (Found: MH^+ 528.2515. $C_{36}H_{33}NO_3$ requires: 528.2539); ν_{max} (KBr) 1782 (s, C=O), 1702 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 8.15–7.14 (m, 19H, aryl-*H*), 5.65 (d, 1H, *J* 2.7, –NC*H*), 4.06 (m, 1H, –C*H*CH_3), 3.20 (dd, 1H, *J* 13.3 and 7.3, –CH_AHPh), 2.62 (dd, 1H, *J* 13.3 and 7.8, –CHH_BPh), 1.92 (m, 1H, –C*H*$(CH_3)_2$), 0.84 (d, 3H, *J* 6.4, –CH_3), 0.76 (d, 3H, *J* 6.8, –CH_3), 0.64 (d, 3H, *J* 6.8, –CH_3); δ_C ($CDCl_3$) 176.58 (–(*C*=O)CH_2–), 152.99 (*C*=O), 139.43, 135.43, 132.98, 132.79, 129.45, 129.25, 129.01, 128.77, 128.60, 128.52, 127.84, 127.73, 127.20, 126.98, 126.90, 126.49, 124.92, 124.18, 123.99 (aryl-*C*), 89.85 (*C*-β), 64.19 (*C*-α), 40.09 (–*C*H_2–), 39.47 (–*C*HCH_3), 30.15 (–*C*H$(CH_3)_2$), 21.96, 16.57, 16.28 (–*C*H_3). The diastereomeric ratio of 95.5 : 4.5 was obtained by measurement and comparison of peak areas in the ^{1}H NMR for the benzyl methylene resonances for the major (δ 3.20 and 2.62) and minor (δ 2.85 and 2.47) isomers.

Using method E with (*S*)-5,5-di(2′-naphthyl)-4-isopropyl-3-(1″-oxopropyl)-1,3-oxazolidin-2-one **21b** (0.123 g, 0.281 mmol) and benzyl bromide (0.1 cm^3, 0.84 mmol) followed by flash column chromatography using DCM–hexane (7 : 3) as the eluant furnished the desired compound as a white semi-solid (0.056 g, 0.1 mmol, 34%). The spectroscopic data were identical to those reported above. The diastereomeric ratio of 96 : 4 was obtained by measurement and comparison of peak areas in the ^{1}H NMR for the benzyl methylene resonances for the major (δ 3.19 and 2.62) and minor (δ 2.85 and 2.49) isomers.

(2″R,4S)-5,5-Di(4′-tolyl)-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one ***22c***. Using method G with (*S*)-5,5-di(4′-tolyl)-4-isopropyl-3-(1″-oxopropyl)-1,3-oxazolidin-2-one **21c** (0.259 g, 0.71 mmol) and benzyl bromide (0.26 cm^3, 2.19 mmol) followed by flash column chromatography using DCM–hexane (4 : 1) as the eluant furnished the desired compound as a pale yellow oil (0.213 g, 0.47 mmol, 66%) (Found: MH^+ 456.2559. $C_{30}H_{33}NO_3$ requires: 456.2539); ν_{max} (KBr) 1779 (s, C=O), 1770 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 7.32–7.09 (m, 13H, aryl-*H*), 5.30 (d, 1H, *J* 3.5, –NC*H*), 4.04 (m, 1H, –C*H*CH_3), 3.17 (dd, 1H, *J* 13.2 and 7.0, –CH_AHPh), 2.59 (dd, 1H, *J* 13.3 and 8.3, –CHH_BPh), 2.31 (s, 3H, –PhCH_3), 2.28 (s, 3H, –PhCH_3), 1.87 (m, 1H, –C*H*$(CH_3)_2$), 0.86 (d, 3H, *J* 6.8, –CH_3), 0.70 (d, 3H, *J* 6.8, –CH_3), 0.58 (d, 3H, *J* 6.5, –CH_3); δ_C ($CDCl_3$) 176.48 (–(*C*=O)CH_2–), 153.16 (*C*=O), 139.82, 139.51, 138.55, 137.83, 135.65, 129.63, 129.45, 129.45, 129.19, 128.49, 126.46, 126.02, 125.78 (aryl-*C*), 89.58 (*C*-β), 64.65 (*C*-α), 40.04 (–CH_2–), 39.38 (–C*H*CH_3), 29.86 (–*C*H$(CH_3)_2$), 21.77 (–*C*H_3), 21.28, 21.20 (Ph*C*H_3–), 16.52, 16.33 (–*C*H_3). The diastereomeric ratio of 98 : 2 was obtained by measurement and comparison of peak areas in the ^{1}H NMR for the methyl resonances for the major (δ 0.86 and 0.58) and minor (δ 1.23 and 0.76) isomers.

Using method E with (*S*)-5,5-di(4′-tolyl)-4-isopropyl-3-(1″-oxopropyl)-1,3-oxazolidin-2-one **21c** (0.119 g, 0.324 mmol) and benzyl bromide (0.12 cm^3, 0.95 mmol) followed by flash column chromatography using DCM–hexane (4 : 1) as the eluant furnished the desired compound as a pale yellow oil (0.0461 g, 0.1 mmol, 31%) The diastereomeric ratio of 98 : 2 was obtained by measurement and comparison of peak areas in the ^{1}H NMR for the methyl resonances for the major (δ0.70 and 0.58) and minor (δ 1.23 and 0.76) isomers.

(2′S,4S)-5,5-Diphenyl-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one ***23a***. Using method E with (*S*)-5,5-diphenyl-4-isopropyl-3-(1′-oxo-3′-phenylpropyl)-1,3-oxazolidin-2-one **20a** (0.110 g, 0.27 mmol) and methyl iodide (0.05 cm^3, 0.80 mmol) followed by flash column chromatography using DCM–hexane (4 : 1) as the eluant furnished the desired product as a colourless oil (0.056 g, 0.13 mmol, 37%) (Found: MH^+ 428.2231. $C_{28}H_{30}NO_3$ requires: MH^+ 428.2226); ν_{max} (KBr) 1780 (s, C=O), 1708 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 7.38–6.97 (m, 15H, aryl-*H*), 5.37 (d, 1H, *J* 3.3, –NC*H*), 4.03–3.92 (m, 1H, –C*H*CH_3), 2.82 (dd, 1H, *J* 13.8 and 7.1, –CH_AHPh), 2.45 (dd, 1H, *J* 13.8 and 7.4, –CHH_BPh), 1.97 (m, 1H, –C*H*$(CH_3)_2$), 1.23 (d, 3H, *J* 6.9, –CH_3), 0.88 (d, 3H, *J* 6.8, –CH_3), 0.77 (d, 3H, *J* 6.8, –CH_3); δ_C ($CDCl_3$) 176.36 (–(*C*=O)CH–), 152.89 (*C*=O), 142.32, 139.29, 138.38, 129.06, 129.01, 128.77, 128.57, 128.40, 128.13, 126.26, 126.14, 125.78 (aryl-*C*), 89.47 (*C*-β), 64.56 (*C*-α), 39.42 (–CH_2–), 38.81 (*C*HCH_3), 30.13 (–*C*H$(CH_3)_2$), 22.01, 17.77, 16.53 (–*C*H_3). The diastereomeric ratio of 96 : 4 was obtained by measurement and comparison of peak areas in the ^{1}H NMR for the methyl resonances for the major (δ 0.88 and 0.77) and minor (δ 0.70 and 0.59) isomers.

Using method H with (*S*)-5,5-diphenyl-4-isopropyl-3-(1′-oxo-3′-phenylpropyl)-1,3-oxazolidin-2-one **20a** (0.150 g, 0.36 mmol) and methyl iodide (0.12 cm^3, 1.8 mmol) followed by flash column chromatography using DCM–hexane (4 : 1) as the eluant furnished the title compound as a colourless oil (0.106 g, 0.25 mmol, 69%). Spectroscopic analysis indicated that this material was identical to that given above. The diastereomeric ratio of 95.5 : 4.5 was obtained by measurement and comparison of peak areas in the ^{1}H NMR for the benzyl methylene resonances for the major (δ 2.81 and 2.45) and minor (δ 3.16 and 2.60) isomers.

(2″S,4S)-5,5-Di(2′-naphthyl)-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one ***23b***. Using method F with (*S*)-5,5-di(2′-naphthyl)-4-isopropyl-3-(1′-oxo-3′-phenylpropyl)-1,3-oxazolidin-2-one **20b** (0.137 g, 0.27 mmol) and methyl iodide (0.05 cm^3, 0.80 mmol) followed by flash column chromatography using DCM–hexane (4 : 1) as the eluant furnished the desired product as a viscous colourless oil (0.060 g, 0.11 mmol, 42%) (Found: MH^+ 528.2380. $C_{36}H_{34}NO_3$ requires 528.2539); ν_{max} ($CHCl_3$) 1778 (s, C=O), 1702 (s, C=O) cm^{-1};

δ_H ($CDCl_3$) 8.15–7.09 (m, 19H, aryl-*H*), 5.65 (d, 1H, *J* 3.0, –NC*H*), 4.01 (m, 1H, –C*H*CH_3), 2.85 (dd, 1H, *J* 13.9 and 7.9, –CH_AHPh), 2.49 (dd, 1H, *J* 13.9 and 6.9, –CHH_BPh), 2.02 (m, 1H, –C*H*$(CH_3)_2$), 1.27 (d, 3H, *J* 6.8, –CH_3), 0.90 (d, 3H, *J* 6.8, –CH_3), 0.82 (d, 3H, *J* 6.8, –CH_3); δ_C ($CDCl_3$) 176.52 (–(*C*=O)CH–), 152.86 (*C*=O), 139.07, 139.04, 135.48, 133.23, 132.99, 132.76, 129.26, 129.03, 128.71, 128.60, 128.50, 128.15, 127.84, 127.68, 127.14, 126.98, 126.78, 126.05, 124.82, 124.48, 124.15, 123.91 (aryl-*C*), 89.79 (*C*-β), 63.97 (*C*-α), 39.40 (–CH_2–), 38.79 (–*C*HCH_3), 30.42 (–*C*H$(CH_3)_2$), 22.26, 18.17, 16.53 (–CH_3). The diastereomeric ratio of 93 : 7 was obtained by measurement and comparison of peak areas in the ^{1}H NMR for the methyl resonances for the major (δ 0.82) and minor (δ 0.64) isomers.

Using method H with (*S*)-5,5-di(2′-naphthyl)-4-isopropyl-3-(1′-oxo-3′-phenylpropyl)-1,3-oxazolidin-2-one **20b** (0.694 g, 1.35 mmol) and methyl iodide (0.42 cm^3, 6.74 mmol) followed by flash column chromatography using DCM–hexane (7 : 3) as the eluant furnished the title compound as a colourless viscous oil (0.413 g, 0.78 mmol, 58%). Spectroscopic analysis indicated that this material was identical to that given above. The diastereomeric ratio of 91 : 9 was obtained by measurement and comparison of peak areas in the ^{1}H NMR for the methyl resonances for the major (δ 0.94 and 0.82) and minor (δ 0.77 and 0.64) isomers.

(2″S,4S)-5,5-Di(4′-tolyl)-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one ***23c***. Using method F with (*S*)-5,5-di(4′-tolyl)-4-isopropyl-3-(1′-oxo-3′-phenylpropyl)-1,3-oxazolidin-2-one **20c** (0.176 g, 0.40 mmol) and methyl iodide (0.08 cm^3, 1.28 mmol) followed by flash column chromatography using DCM–hexane (4 : 1) as the eluant furnished the desired product as a colourless oil (0.058 g, 0.13 mmol, 32%) (Found: MH^+ 456.2511. $C_{30}H_{34}NO_3$ requires: 456.2539); ν_{max} (KBr) 1782 (s, C=O), 1702 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 7.33–6.97 (m, 13H, aryl-*H*), 5.30 (d, 1H, *J* 3.2, –NC*H*), 3.97 (m, 1H, –C*H*CH_3), 2.84 (dd, 1H, *J* 13.9 and 7.3, –CH_AHPh), 2.47 (dd, 1H, *J* 13.9 and 7.3, –CHH_BPh), 2.31 (s, 3H, –PhCH_3), 2.29 (s, 3H, PhCH_3), 1.95 (m, 1H, –C*H*$(CH_3)_2$), 1.23 (d, 3H, *J* 7.0, –CH_3), 0.86 (d, 3H, *J* 6.8, –CH_3), 0.77 (d, 3H, *J* 6.8, –CH_3); δ_H ($CDCl_3$) 176.38 (–(*C*=O)CH–), 153.04 (*C*=O), 139.62, 139.51, 138.55, 137.83, 135.65, 129.63, 129.45, 129.45, 129.19, 128.49, 126.46, 126.02, 125.78 (aryl-*C*), 89.61 (*C*-β), 64.58 (*C*-α), 39.37 (–CH_2–), 38.83 (–C*H*CH_3), 30.08 (–*C*H$(CH_3)_2$), 22.02 (–CH_3), 21.26, 21.19 (PhCH_3–), 17.83, 16.58 (–CH_3). The diastereomeric ratio of 97.5 : 2.5 was obtained by measurement and comparison of peak areas in the ^{1}H NMR for the methyl resonances for the major (δ 0.77) and minor (δ 0.58) isomers.

Using method H with (*S*)-5,5-di(4′-tolyl)-4-isopropyl-3-(1′-oxo-3′-phenylpropyl)-1,3-oxazolidin-2-one **20c** (0.629 g, 1.43 mmol) and methyl iodide (0.44 cm^3, 7.13 mmol) followed by flash column chromatography using DCM–hexane (4 : 1) furnished the title compound as a colourless oil (0.416 g, 0.91 mmol, 64%). Spectroscopic analysis indicated that this material was identical to that given above. The diastereomeric ratio of 97 : 3 was obtained by measurement and comparison of peak areas in the ^{1}H NMR for the methyl resonances for the major (δ 0.85 and δ 0.76) and minor (δ 0.69 and 0.58) isomers.

X-Ray crystallographic study of (2′*R*,4*S*)-5,5-diphenyl-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one 22a

Colourless crystals of **22a** were grown from pentane solution. A sample with approximate dimensions 0.45 × 0.25 × 0.15 mm was mounted directly into the cold-stream of a Rigaku AFC7S diffractometer using an oil drop method.

(2′*S*,4*S*)-3-(2′-Azido-3′-phenyl-1′-oxopropyl)-5,5-di(4″-tolyl)-4-isopropyl-1,3-oxazolidin-2-one 24

To a solution of potassium hexamethyldisilylazide (0.5 M in THF, 2.54 cm^3, 1.27 mmol) in THF (4 cm^3) at −78 °C under a nitrogen atmosphere was added a pre-cooled solution of (*S*)-5,5-di(4′-tolyl)-4-isopropyl-3-(1′-oxo-3′-phenylpropyl)-1,3-oxazolidin-2-one **20c** (0.503 g, 1.11 mmol) in THF (4 cm^3) *via* cannula transfer. The resulting pale yellow potassium enolate was aged for 30 min at −78 °C. A pre-cooled (−78 °C) solution of trisyl§ azide[24] (0.410 g, 1.33 mmol) in THF (4 cm^3) was added *via* cannula. After the addition was complete, the bright yellow reaction mixture was stirred for 2 min and then quenched with glacial acetic acid (0.30 cm^3, 5.08 mmol). The reaction mixture was allowed to warm to ~30 °C in a water bath over 45 min. The solution was partitioned between DCM (25 cm^3) and brine (35 cm^3). The aqueous phase was washed with DCM (3 × 10 cm^3). The combined organic extracts were washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated. Purification of the crude residue twice by column chromatography using 5 : 1 hexane–EtOAc afforded the desired product as a colourless oil (0.354 g, 0.73 mmol, 65%) (Found: MH^+ 483.2396. $C_{29}H_{35}N_5O_3$ requires: 483.2396); ν_{max} (liq. film) 2114 (s, –N_3), 1782 (s, C=O), 1710 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 7.32–6.95 (m, 13H, aryl-*H*), 5.23 (d, 1H, *J* 3.5, –NC*H*), 5.14 (dd, 1H, *J* 8.4 and 5.4, –C*H*N_3), 2.66 (dd, 1H, *J* 14.3 and 5.4, –CH_AHCHN_3), 2.60 (dd, 1H, *J* 14.3 and 8.4, –CHH_BCHN_3), 2.24 (s, 3H, –PhCH_3), 2.21 (s, 3H, –PhCH_3), 1.94 (m, 1H, –C*H*$(CH_3)_2$), 0.84 (d, 3H, *J* 7.2 CH(CH_3)$_2$), 0.74 (d, 3H, *J* 7.2, CH(CH_3)$_2$); δ_C ($CDCl_3$) 170.22 (–(*C*=O)CH–), 152.86 (*C*=O), 139.41, 138.84, 138.13, 135.95, 135.00, 129.84, 129.47, 129.30, 128.87, 128.24, 125.87, 125.46 (aryl-*C*), 90.49 (*C*-β), 65.54 (*C*-α), 61.76 (–*C*HN_3), 37.02 (–CH_2–), 29.93 (–*C*HCH_3), 21.90 (–CH_3), 21.26, 21.18 (–PhCH_3), 16.60 (–CH_3). The diastereomeric ratio of 96 : 4 was measured by HPLC analysis (Zorbax column) using *tert*-butyl methyl ether–isooctane (99 : 1) as the eluant at 1 cm^3 min^{-1} (minor peak 27.46 min, major peak 30.56 min).

(2″*S*,4*S*)-5,5-Di(4′-tolyl)-3-(2″-bromo-3″-phenyl-1″-oxopropyl)-4-isopropyl-1,3-oxazolidin-2-one 25

To a solution of (*S*)-5,5-di(4′-tolyl)-4-isopropyl-3-(1′-oxo-3′-phenylpropyl)-1,3-oxazolidin-2-one **20c** (0.216 g, 0.49 mmol) in DCM (5 cm^3) at −78 °C under N_2 was added diisopropylethylamine (0.11 cm^3, 0.63 mmol) followed by the dropwise addition of dibutylboryl triflate¶ (1 M in DCM, 0.52 cm^3 0.52 mmol). The pale yellow boron enolate was aged for 15 min at −78 °C and then for 1 h at 0 °C. The boron enolate was then added rapidly to a pre-cooled slurry of *N*-bromosuccinimide (0.117 g, 0.66 mmol) in DCM (1 cm^3) *via* cannula transfer. The mixture was aged for 1.5 h at −78 °C before a red slurry was formed which was stirred at −78 °C for a further 1 h. The reaction mixture was quenched by pouring into 0.5 M sodium bisulfate–brine (1 : 1, 10 cm^3). The solution was extracted with EtOAc (3 × 5 cm^3) and the combined organic layers were washed with 0.5 M aqueous sodium thiosulfate–brine (10 cm^3) and brine (10 cm^3), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude α-bromocarboximide as a yellow oil (0.306 g); ν_{max} (liq. film) 1785 (s, C=O), 1708 (s, C=O), 700 (s, C–Br) cm^{-1}; δ_H ($CDCl_3$) 7.45–6.96 (m, 13H, aryl-*H*), 5.84 (dd, 1H, *J* 8.8 and 6.5, –C*H*Br), 5.34 (d, 1H, *J* 3.1, –NC*H*), 3.48 (dd, 1H, *J* 14.1 and 8.8, –CH_AHCHN_3), 3.21 (dd, 1H, *J* 14.1 and 6.5, –CHH_BCHN_3), 2.32 (s, 3H, –PhCH_3), 2.30 (s, 3H, –PhCH_3), 2.01 (m, 1H, –C*H*$(CH_3)_2$), 0.96 (d, 3H, *J* 7.0, –CH(CH_3)$_2$), 0.84 (d, 3H, *J* 7.0, –CH(CH_3)$_2$).

(2′*R*,4*S*)-3-(2′-Azido-3′-phenyl-1′-oxopropyl)-5,5-di(4″-tolyl)-4-isopropyl-1,3-oxazolidin-2-one 26

To a solution of the unpurified α-bromocarboximide **25** (0.281 g, 1.47 mmol) in DCM (4 cm^3) at 0 °C was added tetramethylguanidinium azide[25] (0.233 g, 1.47 mmol) in one portion. The

§ The IUPAC name for trisyl is 2,4,6-triisopropylsulfonyl.
¶ The IUPAC name for triflate is trifluoromethanesulfonate.

resulting solution was stirred for 4 h at 0 °C and then quenched by the addition of saturated aqueous $NaHCO_3$ (15 cm^3) and the product was extracted using DCM (3 × 15 cm^3). The organic extracts were combined and washed with brine (15 cm^3), dried over Na_2SO_4 and the solvent removed *in vacuo* to give a yellow semi-solid. The α-azidocarboximide was purified by column chromatography using hexane–EtOAc (5 : 1) then hexane–EtOAc (7 : 1) as the eluant which furnished the title compound as a colourless oil (0.189 g), contaminated by the starting oxazolidin-2-one **20c** (68 : 32), corresponding to an overall yield of 58% (Found: MH^+ 500.2662. $C_{29}H_{35}N_5O_3$ requires: 500.2662); ν_{max} (liq. film) 2114 (s, $-N_3$), 1782 (s, C=O), 1710 (s, C=O) cm^{-1}; δ_H ($CDCl_3$) 7.42–7.13 (m, 13H, aromatic-*H*), 5.42 (d, 1H, *J* 3.3, –NC*H*), 5.09 (dd, 1H, *J* 10.1 and 4.3, –C*H*N_3), 3.44 (dd, 1H, *J* 13.6 and 4.3, –CH_AHCHN_3), 3.00 (dd, 1H, *J* 13.6 and 10.3, –CHH_BCHN_3), 2.35 (s, 3H, –PhCH_3), 2.33 (s, 3H, –PhCH_3), 2.00 (m, 1H, –C*H*$(CH_3)_2$), 0.88 (d, 3H, *J* 6.8, –CH(CH_3)$_2$), 0.73 (d, 3H, *J* 6.8, CH(CH_3)$_2$); δ_C ($CDCl_3$) 170.48 (–(*C*=O)CH–), 152.85 (*C*=O), 139.17, 138.98, 138.10, 136.23, 135.24, 129.91, 128.77, 128.60, 128.58, 127.46, 125.69, 125.62 (aryl-*C*), 90.68 (*C*-β), 64.79 (*C*-α), 62.07 (–*C*HN_3), 38.09 (–*C*H_2–), 30.04 (–*C*HCH_3), 21.95 (–*C*H_3), 21.27, 21.18 (–Ph*C*H_3), 16.47 (–*C*H_3). The diastereomeric ratio of 95.5 : 4.5 was measured by HPLC analysis (Zorbax normal phase column) using *tert*-butyl methyl ether and isooctane (99 : 1) as the eluant at 1 cm^3 min^{-1} (major peak 32.26 min, minor peak 39.13 min).

General procedure I. Hydrolysis of the alkylated oxazolidin-2-ones

A portion of the alkylated 1,3-oxazolidin-2-one was dissolved in THF–H_2O (3 : 1 mixture, 0.06 M) and cooled in an ice bath. Lithium hydroxide (2 equiv.) was added in one portion and the mixture stirred at 0 °C for 1 h and at room temperature for 24 h. A saturated solution of $NaHCO_3$ was added and the organic and aqueous layers were separated. The aqueous layer was washed with DCM (×3). The organic extracts were combined, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to give the auxiliary as a white solid which was either subjected to flash column chromatography using ethyl acetate–hexane (1 : 1) as the eluant or recrystallised from the appropriate solvent. The spectroscopic data of the recovered auxiliaries were identical to those recorded above.

To the original aqueous extract was added 1 M HCl until pH 2–3 was reached. The mixture was washed with EtOAc (×3) and the organic extracts were combined, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* followed by flash column chromatography using ethyl acetate–hexane (1 : 1) as the eluant to give the carboxylic acid, 2-methyl-3-phenylpropionic acid **27** or **28** as a colourless liquid (Found: MH^+ 165.0942. $C_{10}H_{14}O_2$ requires: 165.0916); δ_H ($CDCl_3$) 7.34–7.19 (m, 5H, aryl-*H*), 3.09 (dd, 1H, *J* 12.8 and 7.8, –CH_AHPh), 2.85–2.64 (m, 2H, –CHH_BPh, –C*H*CH_3), 1.20 (d, 3H, *J* 6.8, –CH_3). The absolute configuration and enantiomeric purity were assigned by comparison of the measured optical rotation with literature values (**27** 98% ee $[\alpha]_D$ −26.2 (*c* = 1.0, $CHCl_3$), **28** 95% ee $[\alpha]_D$ +25.6 (*c* = 1.0, $CHCl_3$)).[27]

Hydrolysis of (2′R,4S)-5,5-diphenyl-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one ***22a****.* Using method I with the title compound (0.061 g, 0.141 mmol, dr >99 : 1) gave (*S*)-5,5-diphenyl-4-isopropyl-1,3-oxazolidin-2-one **16a** as a white solid (0.0371 g, 0.132 mmol, 94%), mp 247–250 °C (EtOH–H_2O) (lit.[13] 253.2–253.9 °C) (Found: C, 76.80; H, 6.99; N, 4.82. Calculated for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98%); $[\alpha]_D$ −260.4 (*c* = 0.255, $CHCl_3$) (lit.[13] $[\alpha]_D$ −253.1 (*c* = 0.1, $CHCl_3$). Also isolated as a colourless oil was (*R*)-2-methyl-3-phenylpropionic acid **27** (0.0139 g, 0.086 mmol, 60%); $[\alpha]_D$ −26.1 (*c* = 0.12, $CHCl_3$), 98% ee.

Hydrolysis of (2″R,4S)-5,5-di(2′-naphthyl)-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one ***22b****.* Using method I with the title compound (0.138 g, 0.262 mmol, dr 95.5 : 4.5) gave (*S*)-5,5-di(2′-naphthyl)-4-isopropyl-1,3-oxazolidin-2-one **16b** as a white solid (0.0912 g, 0.239 mmol, 91%). Also isolated as a colourless oil was (*R*)-2-methyl-3-phenylpropionic acid **27** (0.0304 g, 0.185 mmol, 71%); $[\alpha]_D$ −24.6 (*c* = 1.14, $CHCl_3$), 92% ee.

Hydrolysis of (2″R,4S)-5,5-di(4′-tolyl)-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one ***22c****.* Using method I with the title compound (0.143 g, 0.314 mmol, dr 98 : 2) gave (*S*)-5,5-di(4′-tolyl)-4-isopropyl-1,3-oxazolidin-2-one **16c** as a white solid (0.095 g, 0.307 mmol, 98%), mp 181–188 °C (EtOH) (Found: C, 77.60; H, 7.48; N, 4.28. Calculated for $C_{18}H_{19}NO_2$: C, 77.644; H, 7.48; N, 4.53%). Also isolated as a colourless oil was (*R*)-2-methyl-3-phenylpropionic acid **27** (0.0281 g, 0.171 mmol, 55%); $[\alpha]_D$ −25.7 (*c* = 0.92, $CHCl_3$), 96% ee.

Hydrolysis of (2′S,4S)-5,5-diphenyl-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one ***23a****.* Using method I with the title compound (0.192 g, 0.45 mmol, dr 96.5 : 3.5) gave (*S*)-5,5-diphenyl-4-isopropyl-1,3-oxazolidin-2-one **16a** as a white solid (0.0371 g, 0.132 mmol, 95%), mp 247–250 °C (EtOH–H_2O) (lit.[13] 253.2–253.9 °C) (Found: C, 76.44; H, 6.90; N, 4.83. Calculated for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98%). Also isolated as a colourless oil was (*S*)-2-methyl-3-phenylpropionic acid **28** (0.069 g, 0.423 mmol, 94%); $[\alpha]_D$ +24.1 (*c* = 0.55, $CHCl_3$), 89% ee.

Hydrolysis of (2″S,4S)-5,5-di(2′-naphthyl)-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one ***23b****.* Using method I with the title compound (0.200 g, 0.379 mmol, dr 91 : 9) gave (*S*)-5,5-di(2′-naphthyl)-4-isopropyl-1,3-oxazolidin-2-one **16b** as a white solid (0.1463 g, 0.379 mmol, 100%), mp 240–242 °C (Found: C, 81.41; H, 6.26; N, 3.54. Calculated for $C_{18}H_{19}NO_2$: C, 81.86; H, 6.08; N, 3.67%). Also isolated as a colourless oil was (*S*)-2-methyl-3-propionic acid **28** (0.0449 g, 0.273 mmol, 72%); $[\alpha]_D$ +21.7 (*c* = 0.74, $CHCl_3$), 81% ee.

Hydrolysis of (2″S,4S)-5,5-di(4′-tolyl)-4-isopropyl-3-(1′-oxo-2′-benzylpropyl)-1,3-oxazolidin-2-one ***23c****.* Using method I with the title compound (0.1916 g, 0.421 mmol, dr 97 : 3) gave (*S*)-5,5-di(4′-tolyl)-4-isopropyl-1,3-oxazolidin-2-one **16c** as a white solid (0.130 g, 0.42 mmol, 100%), mp 181–188 °C. Also isolated as a colourless oil was (*S*)-2-methyl-3-propionic acid **28** (0.0434 g, 0.265 mmol, 63%); $[\alpha]_D$ +24.9 (*c* = 0.51, $CHCl_3$), 92% ee.

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