Oxazinanones as chiral auxiliaries: synthesis and evaluation in enolate alkylations and aldol reactions

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Homochiral β-amino esters (prepared on multigram scale by lithium amide conjugate addition) are readily transformed into oxazinanones. *N*-Acyl derivatives of oxazinanones undergo stereoselective enolate alkylation reactions, with higher stereoselectivities observed for the enolate alkylation of (*R*)-*N*-propanoyl-4-*iso*-propyl-6,6-dimethyl-oxazinan-2-one than the corresponding Evans oxazolidin-2-one. A C(4)-*iso*-propyl stereodirecting group within the oxazinanone conveys higher stereoselectivity than the analogous C(4)-phenyl substituent. *gem*-Dimethyl substitution at C(6) within the oxazinanone framework facilitates exclusive exocyclic cleavage upon hydrolysis to furnish α-substituted carboxylic acid derivatives and the parent oxazinanone in good yield. Asymmetric aldol reactions of a range of aromatic and aliphatic aldehydes with the chlorotitanium enolate of (*R*)-*N*-propanoyl-4-*iso*-propyl-6,6-dimethyl-oxazinan-2-one proceed with excellent diastereoselectivity. Hydrolysis of the aldol products affords homochiral α-methyl-β-hydroxy-carboxylic acids.

Introduction

The rapid development and widespread use of chiral auxiliaries in synthetic applications has resulted in a profusion of asymmetric templates for the preparation of enantiomerically enriched materials. The most commonly used chiral auxiliaries are derived from α-amino acids, carbohydrates, or terpenes, as the commercial availability of these naturally occurring compounds in both enantiomeric forms makes them ideal starting materials. Oxazolidin-2-ones, first introduced by Evans and derived from α-amino acids, are perhaps the most commonly used chiral auxiliaries in synthesis and have been successfully applied for an enormous variety of asymmetric transformations.[1] While versatile, alkylations of the enolates derived from *N*-acyl oxazolidinones often do not proceed to completion and with incomplete stereocontrol.[2] Furthermore, cleavage of the functionalised fragment from oxazolidinones may be problematic, with the undesired endocyclic cleavage mode predominating with bulky α-substituted derivatives.[3] Within this area we,[4] and then others,[5] have developed oxazolidinone analogues with geminal substitution at C(5) that offer two-fold advantages over traditional Evans oxazolidinones.[6] Primarily, this substitution pattern suppresses the endocyclic cleavage pathway that can compete upon cleavage of *N*-acyl oxazolidinones, facilitating isolation of the enantiomerically enriched target and recycling of the auxiliary. Furthermore, the C(5)-*gem*-dimethyl group also biases the conformation of the adjacent C(4)-stereodirecting group such that the combination of the *gem*-dimethyl- and 4-*iso*-propyl-groups within an oxazolidinone framework mimics a C(4)-*tert*-butyl group, showing enhanced stereoselectivity in a range of reactions in comparison with the corresponding Evans analogue.[7]

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As part of our ongoing programme of research concerned with the development and synthetic applications of novel chiral auxiliaries,[4,8] an evaluation of the ability of oxazinanones **2** to act as chiral auxiliaries was proposed.[9] The introduction of an additional carbon within the backbone skeleton of an oxazinanone, compared to α-amino acid-derived oxazolidinones, suggested that these oxazinanones could be derived from the corresponding β-amino acid derivatives **1**. It was envisaged that these starting materials could be readily prepared on a multigram scale and in either enantiomeric form *via* the lithium amide conjugate addition methodology that has been developed within our laboratory and widely used.[10] Variation of the C(4)-stereodirecting substituent in the oxazinanone would allow the effect upon the diastereoselectivity of subsequent asymmetric transformations of **3** to be evaluated. Furthermore, the ability of a *gem*-dimethyl substituent at C(6) within the oxazinanone structure to restrict the conformation of the C(4)-stereodirecting group through minimisation of 1,3-interactions and to promote exocyclic cleavage of the chiral fragment by suppression of any endocyclic cleavage would also be appraised (Fig. 1).

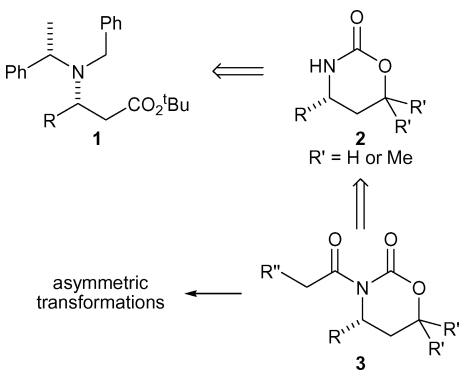


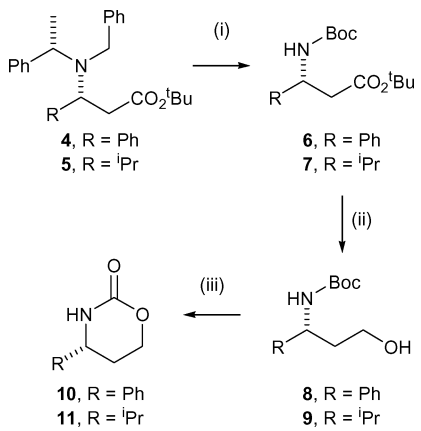
Fig. 1 β-Amino ester-derived oxazinanones as chiral auxiliaries.

We detail herein preliminary investigations directed toward the synthesis of a number of chiral oxazinanone auxiliaries and an evaluation of their stereodirecting ability in enolate alkylation and aldol reactions of their *N*-acyl derivatives.

Results and discussion

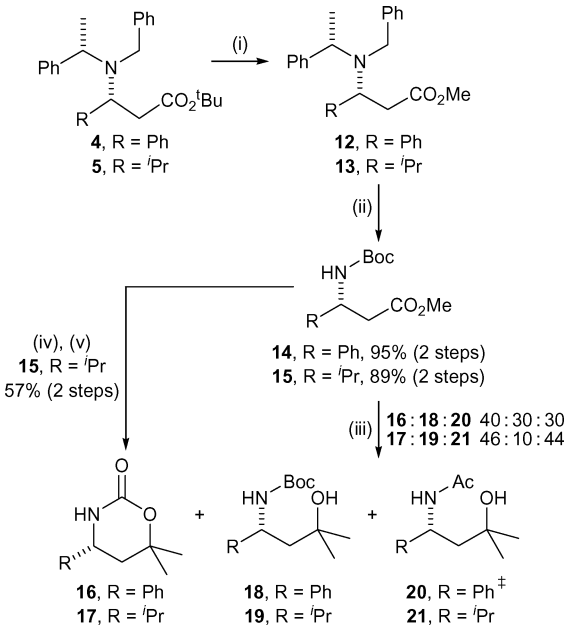
Synthesis of oxazinanones

Initial studies focused upon the development of a straightforward route to the desired oxazinanones from the known β-amino esters **4** and **5**, which were prepared following the literature protocol on a multigram scale by the highly diastereoselective conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to the corresponding α,β-unsaturated esters.[10] Elaboration of **4** and **5** to the corresponding oxazinanones was based around the established route to the SuperQuat chiral auxiliaries utilising an *N*-Boc protecting group as a sacrificial carbonyl equivalent.[11] β-Amino esters **4** and **5** were converted to *N*-Boc protected β-amino esters **6** and **7** in excellent yield by hydrogenolysis and concomitant *N*-Boc protection, and then reduced to the *N*-Boc amino alcohols **8** and **9**. Base-promoted cyclisation of *N*-Boc amino alcohols **8** and **9** generated (*R*)-4-phenyl-(1,3)-oxazinan-2-one **10** and (*R*)-4-*iso*-propyl-(1,3)-oxazinan-2-one **11** respectively (Scheme 1).



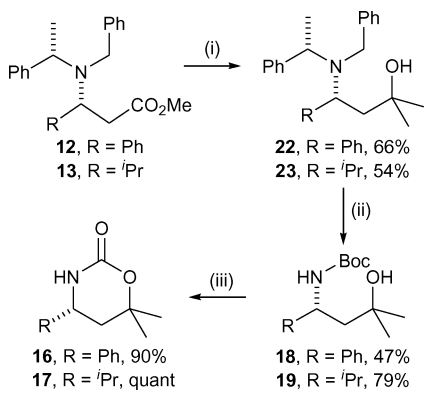
Scheme 1 *Reagents and conditions*: (i) H_2 (5 atm), Boc_2O, $Pd(OH)_2/C$, MeOH; (ii) $LiAlH_4$, THF, 0 °C to rt; (iii) ^{t}BuOK, THF, 0 °C to rt.

A similar design strategy was applied toward the synthesis of oxazinanone chiral auxiliaries with geminal dimethyl substitution at C(6). Transesterification of **4** and **5** to the corresponding methyl esters **12** and **13** was followed by hydrogenolysis and concomitant carbamate protection, giving **14** and **15** respectively. Treatment of **14** and **15** with 4.0 equivalents of MeMgBr furnished (*R*)-4-phenyl-6,6-dimethyl-(1,3)-oxazinan-2-one **16** and (*R*)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one **17** directly, although in low isolated yields (30 and 35%), along with alcohols **18** and **19** and the corresponding *N*-acetyl species **20** and **21** in the ratios 40 : 30 : 30 and 46 : 10 : 44 respectively. Reaction optimisation showed that the addition of cerium chloride[12] to **15** before the addition of the Grignard reaction suppressed *N*-acetyl formation, giving a 50 : 50 mixture of oxazinanone **17** and alcohol **19**, with the resultant crude product mixture treated with ^{t}BuOK to yield the oxazinanone **17** in a much improved 57% yield over two steps from **15** (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) HCl (g), MeOH, 2 h; (ii) H_2 (5 atm), Boc_2O, $Pd(OH)_2/C$, MeOH; (iii) MeMgBr, THF, −78 °C to rt; (iv) MeMgBr, $CeCl_3$, THF; (v) ^{t}BuOK, THF, 0 °C to rt. ‡ **20** was not isolated from this reaction protocol.

An alternative strategy for the selective synthesis of *N*-Boc alcohols **18** and **19** was also followed, with addition of MeMgBr to methyl esters **12** and **13** giving the *N*-protected tertiary alcohols **22** and **23** in reasonable yields. Hydrogenolysis and concomitant carbamate formation gave *N*-Boc alcohols **18** and **19** that, upon treatment with ^{t}BuOK, gave oxazinanones **16** and **17** respectively (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) MeMgBr, THF, −78 °C to rt; (ii) H_2 (5 atm), Boc_2O, $Pd(OH)_2/C$, MeOH; (iii) ^{t}BuOK, THF, 0 °C to rt.

X-Ray crystallographic analysis of the C(4)-phenyl oxazinanones **10** and **16** allowed the solid state conformation of these compounds to be probed. In the C(6)-unsubstituted heterocycle **10**, the phenyl group at C(4) is situated in a pseudo-axial position, whereas 1,3-interactions arising from the presence of geminal methyl groups at C(6) in **16** may influence the pseudo-equatorial orientation of the C(4)-phenyl group (Fig. 2).

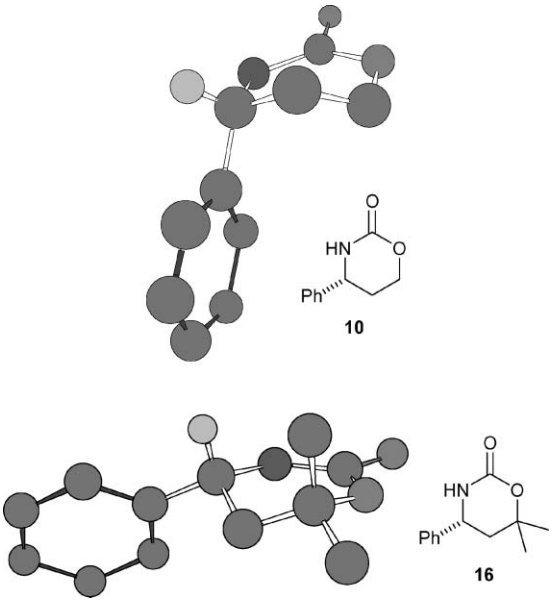


Fig. 2 Chem3D representations of the X-ray crystal structures of C(4)-phenyl oxazinanones **10** and **16** (some H atoms omitted for clarity).

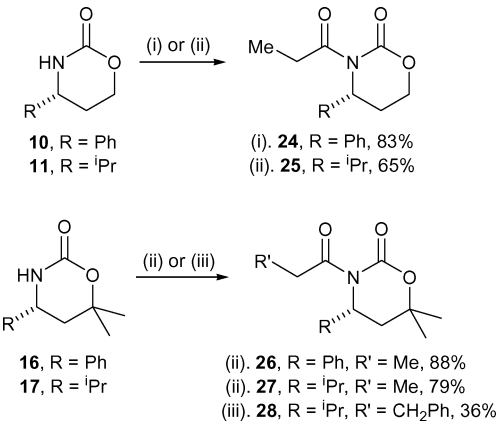
N-Acylation of oxazinanone auxiliaries

Attention next turned toward the preparation of *N*-acyl derivatives of oxazinanones **10**, **11**, **16** and **17**, in order to assess their utility in asymmetric transformations. A variety of methodologies are available for *N*-acylation of α-amino acid-derived oxazolidinones, and among the most popular is deprotonation with BuLi, followed by the addition of an acid chloride,[13] although catalytic DMAP and an organic base can be exploited for the *N*-acylation of oxazolidinone auxiliaries, eliminating the need for strong base.[14] Attempts to prepare *N*-propanoyl derivatives of oxazinanones **10**, **11**, **16** and **17** using either of these methodologies give disappointing results. Treatment with BuLi and propanoyl chloride resulted in a complex mixture of products whilst using DMAP and either Et_3N or Hünig's base led to inconsistent and incomplete (typically <50%) reaction conversion. Concurrent with this work, Hitchcock and co-workers reported difficulty in the *N*-acylation of their 1,3,4-oxadiazinan-2-one auxiliary,[15] with LiH as the base of choice for this troublesome reaction. The efficacy of LiH to affect *N*-acylation of oxazinanone auxiliaries was therefore investigated. *N*-Propanoyl oxazinanone **24** was readily prepared in 83% isolated yield *via* acylation of oxazinanone **10** following this procedure, although irreproducible reaction conversion was noted for acylation of oxazinanones **11**, **16** and **17**. Treatment of oxazinanones **11**, **16** and **17** with LiHMDS and the requisite acid chloride, however, proved the optimal synthetic strategy for the preparation of *N*-acyl oxazinanone analogues, reliably proceeding to afford *N*-acylated oxazinanones **25**–**28** in moderate to good yield after purification (Scheme 4).

With a range of *N*-acyl derivatives of oxazinanones in hand, their utility in asymmetric enolate alkylation and aldol reactions was investigated.

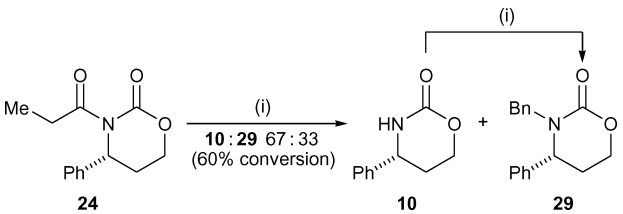
Evaluation of *N*-acyl oxazinanones in enolate alkylations

The asymmetric alkylation of lithium and sodium enolates of oxazolidinone and camphor sultam auxiliaries is a common



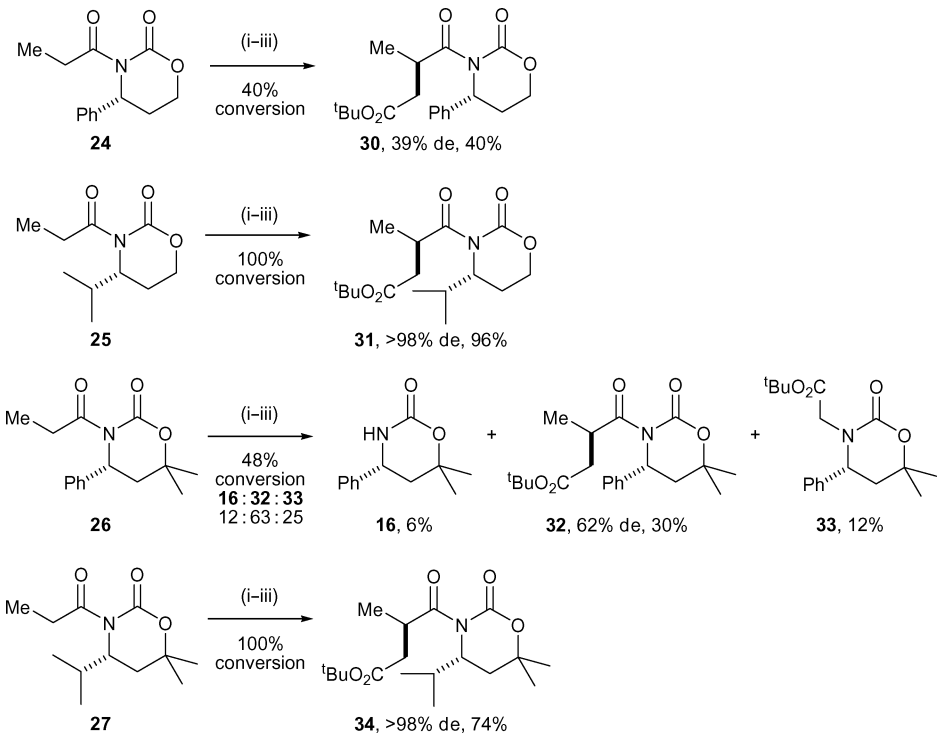
Scheme 4 *Reagents and conditions*: (i) LiH, CH_3CH_2COCl, THF, 0 °C to rt; (ii) LiHMDS, CH_3CH_2COCl, THF, −78 °C to rt; (iii) LiHMDS, $PhCH_2COCl$, THF, −78 °C to rt.

transformation for the preparation of α-functionalised carboxylate derivatives, with a number of experimental conditions having been developed for this transformation. Within this laboratory, optimised conditions for the alkylation of *N*-acyl SuperQuat derivatives involves deprotonation with LiHMDS at −78 °C, followed by treatment with an electrophile and warming to ambient temperature.[6] Initial studies applied these conditions to the benzylation of *N*-propanoyl oxazinanone **24** giving, at 60% conversion, a 67 : 33 ratio of the parent oxazinanone **10** and *N*-benzyl oxazinanone **29**, respectively. Such deacylation reactions in attempted enolate alkylations are not uncommon[6a,16] and this product distribution presumably arises from decomposition of the enolate to afford a ketene and the anion of the parent oxazinanone, which is subsequently alkylated by benzyl bromide to afford *N*-benzyl oxazinanone **29**. To confirm the nature of this product, an authentic sample of **29** was prepared directly by deprotonation of the oxazinanone **10** with LiHMDS, followed by the addition of BnBr (Scheme 5).



Scheme 5 *Reagents and conditions*: (i) LiHMDS, THF, −78 °C, then BnBr to rt.

In order to circumvent this decomposition manifold, it was proposed that alkylation with the more reactive *tert*-butyl bromoacetate would allow alkylation to occur at lower temperatures, therefore prevailing over decomposition; a range of bases was screened in order to determine the most effective reagent for this protocol. Treatment of **25** with LDA or LiTMP at −78 °C for one hour, followed by addition of *tert*-butyl bromoacetate and stirring at −78 °C for a further hour prior to aqueous work-up, returned only starting material, whilst LiHMDS and NaHMDS gave complex product mixtures at poor conversion (<20%). The more reactive potassium enolate, derived from deprotonation with KHMDS under these reaction conditions, gave the alkylated

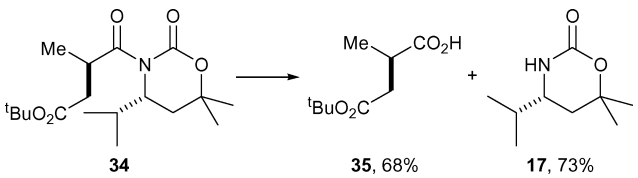


Scheme 6 *Reagents and conditions*: (i) KHMDS, THF, −78 °C, 1 h; (ii) $BrCH_2CO_2{}^tBu$, −78 °C, 2 h; (iii) NH_4Cl (sat., aq), −78 °C to rt.

product **31** in >98% de,[17] and in 96% yield and >98% de after purification by column chromatography (Scheme 6).

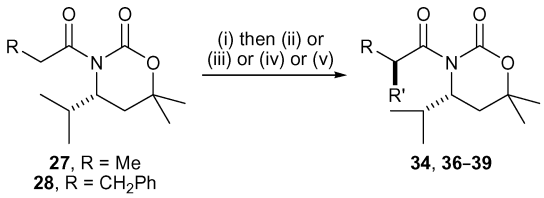
The effect of changing the C(4)-stereocontrolling group and the incorporation of the C(6)-*gem*-dimethyl functionality upon the stereoselectivity of the reaction was next evaluated, by treatment of *N*-propanoyl oxazinanones **24**, **26** and **27** under the same conditions. Reaction of the C(4)-phenyl *N*-propanoyl oxazinanones **24** and **26** both proceeded with poor conversion and low stereoselectivity under these conditions. Thus, *N*-propanoyl oxazinanone **24** gave, at 40% conversion, C(2′)-alkylated product **30** in 39% de,[17] while *N*-propanoyl oxazinanone **26** gave, at 48% conversion, a 12 : 63 : 25 mixture of oxazinanone **16**, the C(2′)-alkylated product **32** (62% de)[17] and *N*-(2′-*tert*-butoxy-2′-oxoethyl)oxazinanone **33**,[18] respectively, indicating that partial enolate decomposition is observed upon alkylation of **26**. In contrast, C(4)-*iso*-propyl *N*-propanoyl oxazinanone **27** proceeded to full conversion, giving **34** with excellent diastereoselectivity (>98% de) and in good isolated yield. These results indicate that a C(4)-*iso*-propyl substituent conveys better stereofacial selectivity than the analogous C(4)-phenyl substituent for asymmetric enolate alkylations (Scheme 6).

To determine the absolute configuration at C(2′) within **31** and **34**, cleavage of the functionalised fragment from the parent oxazinanone was undertaken by treatment of **31** and **34** with lithium hydroperoxide. While treatment of **31** gave a complex mixture of indeterminable products, treatment of **34** afforded the parent oxazinanone **17** and (*R*)-4-*tert*-butoxy-4-oxo-2-methylbutanoic acid **35** {$[\alpha]_D^{25}$ +3.9 (*c* 0.9 in DCM); lit.[19] $[\alpha]_D^{25}$ +3.9 (*c* 1.0 in DCM)} in 73 and 68% yields, respectively, after purification. These data demonstrate that *gem*-dimethyl substitution at C(6) in the oxazinanone template is necessary for effective exocyclic cleavage to furnish the desired carboxylic acid derivatives (Scheme 7).



Scheme 7 *Reagents and conditions*: LiOH, H_2O_2, THF–H_2O (3 : 1), 0 °C to rt.

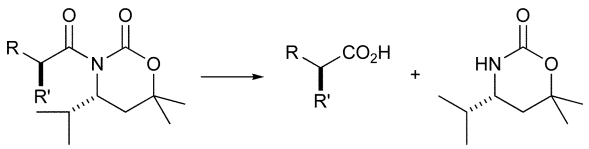
Having demonstrated that alkylation of *N*-acyl oxazinanone **27** occurs readily with a highly activated electrophile, attention next turned to exploring the generality of this protocol. Noting that these systems have a tendency to follow a decomposition pathway upon warming, the effect of temperature on the stability of the potassium enolate of *N*-propanoyl oxazinanone **27** was investigated. Analysis of the product mixtures arising from treatment of **27** with KHMDS at −78 °C followed by warming to various temperatures indicated that at −40 °C, <20% decomposition to the parent oxazinanone **17** occurred. Complete deacylation was observed upon warming to room temperature. It was therefore proposed that initial deprotonation at −78 °C, followed by addition of the electrophile and controlled warming to −40 °C would extend the range of electrophiles suitable for alkylation. Using these improved reaction conditions, alkylation of the potassium enolates of *N*-propanoyl oxazinanone **27** with benzyl bromide and allyl bromide, and of *N*-hydrocinnamoyl oxazinanone **28** with *tert*-butyl bromoacetate and methyl iodide proceeded in moderate to complete conversion,[17] and in >98% de in each case,[17] to afford α-substituted *N*-acyl oxazinanone derivatives **36**–**39** which were isolated in moderate to good yields after chromatography. The configuration at C(2′) within **36**–**39** was assigned by analogy to that proven for **34** (Scheme 8).



Product	R	R'	Conditions	Conversion (%)	Yield (%)	de (%)
34	Me	$CH_2CO_2{}^tBu$	(ii)	quant	74	>98
36	Me	CH_2Ph	(iii)	quant	78	>98
37	Me	$CH_2CH{=}CH_2$	(iv)	50	27	>98
38	CH_2Ph	$CH_2CO_2{}^tBu$	(ii)	quant	60	>98
39	CH_2Ph	Me	(v)	85	38	>98

Scheme 8 *Reagents and conditions*: (i) KHMDS, THF, −78 °C; (ii) $BrCH_2CO_2{}^tBu$, −78 °C then NH_4Cl (sat., aq); (iii) $BrCH_2Ph$, −78 to −40 °C, then NH_4Cl (sat., aq); (iv) $BrCH_2CH{=}CH_2$, −78 to −40 °C, then NH_4Cl (sat., aq); (v) MeI, −78 to −40 °C, then NH_4Cl (sat., aq).

The absolute configurations within **36**, **38** and **39** were subsequently determined by hydrolysis with lithium hydroperoxide, affording both the parent oxazinanone **17** and the α-substituted carboxylic acid derivatives **40**–**42** in quantitative yield in each case, and with comparable spectroscopic properties to the literature in each case {**40** $[\alpha]_D^{25}$ −21.6 (*c* 0.8 in $CHCl_3$); lit.[20] $[\alpha]_D^{25}$ −23.1 (*c* 1.0 in $CHCl_3$); **41** $[\alpha]_D^{25}$ +7.7 (*c* 1.0 in DCM); lit.[19] $[\alpha]_D^{25}$ +7.1 (*c* 1.0 in DCM); **42** $[\alpha]_D^{25}$ +26.8 (*c* 0.6 in $CHCl_3$); lit.[21] $[\alpha]_D^{25}$ +25.5 (*c* 1.0 in $CHCl_3$)} (Scheme 9).



Product	R	R'	Yield (%)
40	Me	CH_2Ph	quant
41	CH_2Ph	$CH_2CO_2{}^tBu$	quant
42	CH_2Ph	Me	quant

Scheme 9 *Reagents and conditions*: LiOH, H_2O_2, THF–H_2O (3 : 1), 0 °C to rt.

The product configuration for enolate alkylations of **27** and **28** is consistent with preferential alkylation of an intermediate chelated (*Z*)-enolate *anti*-to the C(4)-stereodirecting group, analogous to that universally accepted for the diastereoselective alkylation of *N*-acyl oxazolidinones (Fig. 3).

Having demonstrated the utility of *N*-acyl oxazolidinones for the asymmetric synthesis of α-substituted carboxylic acids, their ability to effect asymmetric aldol reactions was investigated.

Evaluation of *N*-acyl oxazinanones in aldol reactions

Chiral auxiliary-mediated asymmetric aldol reactions are widely applied for the synthesis of β-hydroxycarbonyls,[22] with a number of efficient metal-mediated aldol reaction protocols having been developed within this area. Initial investigations focused upon boron-mediated aldol reactions of oxazinanone derivatives; however, both 9-BBN(OTf)- and Et_2BOTf-promoted reactions gave mixtures of diastereoisomers, consistent with low stereocontrol in this reaction manifold. As an alternative, the use of titanium(IV) chloride and an amine base to promote the aldol reaction was investigated. Within this area, Evans *et al.* have reported titanium-mediated aldol reactions of *N*-acyl oxazolidinones, although these reactions proceed with slightly lower selectivity (70–98% de) than the corresponding dibutylboron enolates (>98% de).[23] Similarly, Hitchcock and co-workers have explored $TiCl_4$-mediated aldol reactions of *N*-propanoyl oxadiazinones, although only moderate levels of selectivity for a range of aldol products were observed (50–92% de).[15] The titanium enolate of *N*-propanoyl oxazinanone **26** was generated by the addition of $TiCl_4$ to a solution of **26** in DCM at 0 °C and subsequent addition of Hünig's base. The resultant enolate was cooled to −78 °C and treated with benzaldehyde, and the reaction mixtures were allowed to warm to room temperature over four hours, giving (at 75% conversion) an inseparable 76 : 24 mixture of diastereoisomeric aldol products **44** and **45** respectively, in 47% yield after purification. Under identical reaction conditions, the addition of benzaldehyde to C(4)-*iso*-propyl *N*-propanoyl oxazinanone **27** proceeded to 73% conversion to give (4*R*,2′*R*,3′*R*)-**46** as a single diastereoisomer in 64% isolated yield after purification (Scheme 10). The relative configuration within **46** was initially assigned as *syn* using 400 MHz ^{1}H NMR spectroscopic analysis ($J_{2'-3'}$ 2.9 Hz) on the assumption that the hydroxycarbonyl aldol product **46** exists in an intramolecularly hydrogen bonded form in solution.[24] X-Ray crystallographic analysis of **46** unambiguously established the relative *syn*-configuration, with the absolute (4*R*,2′*R*,3′*R*)-configuration assigned relative to the known (*R*)-stereocentre at C(4). Crystallographic analysis also showed that a hydrogen bond exists between the C(3′) hydroxy and the endocyclic carbonyl in the solid state, consistent with the suppositions required for analysis of the ^{1}H NMR coupling constants to determine the *syn*-geometry (Fig. 4).

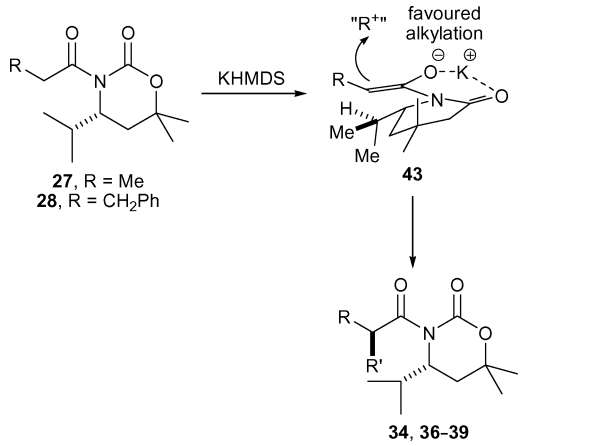
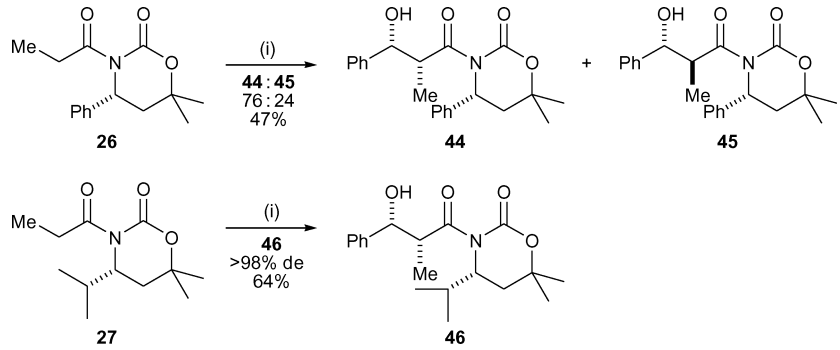


Fig. 3 Proposed transition state **43** for enolate alkylations of *N*-acyl oxazinanones **27** and **28**.

With a successful reaction protocol in hand, the generality of aldol additions to titanium enolates of *N*-propanoyl oxazinanone **27** was examined. Although Hitchcock and co-workers have reported that aldol reactions of *N*-propanoyl oxadiazinones and aliphatic aldehydes are sluggish, with the dominant product being the chiral auxiliary resulting from *N*-deacylation,[15b] the reactivity of **27** with a variety of substituted benzaldehydes and straight chain and α-branched aliphatic aldehydes was investigated for purposes of comparison. In each case, the reaction proceeded in low to moderate conversion, but gave each aldol product as essentially a single diastereoisomer,[17] giving aldol products **47**–**51** in 12–58% isolated yield and in >98% de after chromatographic purification.



Scheme 10 *Reagents and conditions*: (i) $TiCl_4$, DIPEA, DCM, 0 °C, 30 min then PhCHO, −78 °C to rt, 4 h.

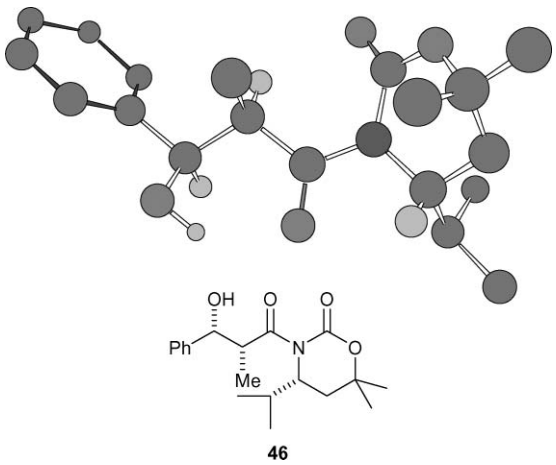


Fig. 4 Chem3D representation of the X-ray crystal structure of **46** (some H atoms omitted for clarity).

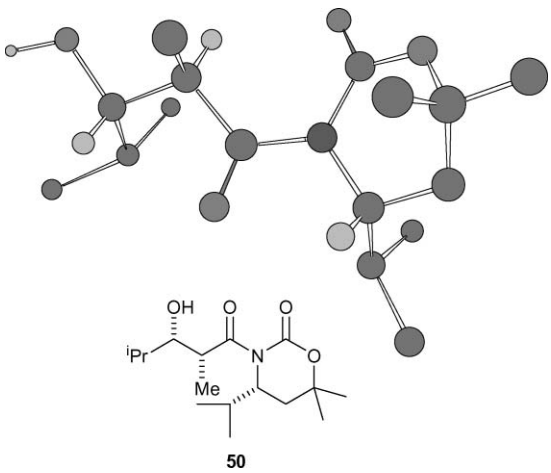
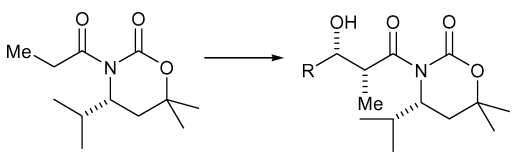


Fig. 5 Chem3D representation of the X-ray crystal structure of **50** (some H atoms omitted for clarity).

These results indicate that titanium enolates of *N*-propanoyl oxazinanone **27** accommodate both electron-withdrawing and electron-donating aromatic and both non-enolizable and enolizable aldehydes in its reactions (Scheme 11).[25] The relative configuration within each aldol product **47**–**51** was determined to be *syn* from ^{1}H NMR coupling constants ($J_{2',3'}$ 2.2–3.3 Hz). X-Ray crystallographic analysis of aldol product **50** unambiguously confirmed the relative *syn*-configuration, with the absolute (4*R*,2′*R*,3′*S*)-configuration known relative to the known (*R*)-stereocentre at C(4). An intramolecular hydrogen bond between the C(3′)-hydroxy and the endocyclic carbonyl was not present in the solid state X-ray structure of **50**; instead, intermolecular hydrogen bonds were evident within the lattice (Fig. 5).



Product	R	Conversion (%)	Yield (%)	de (%)
46	Ph	73	64	>98
47	*p*-$MeOC_6H_4$	59	54	>98
48	*p*-$NO_2C_6H_4$	43	20	>98
49	Et	63	58	>98
50	^{i}Pr	59	45	>98
51	^{t}Bu	15	12	>98

Scheme 11 *Reagents and conditions*: $TiCl_4$, DIPEA, DCM, 0 °C, 30 min then RCHO, −78 °C to rt, 4 h.

The observation of *syn*-aldol products suggests that the reactions of the chlorotitanium enolate of **27** proceed *via* a chair-like Zimmerman–Traxler transition state in which both the aldehyde and the oxazinanone are co-ordinated to titanium (Fig. 6).[26] A similar transition state has been proposed for titanium enolates

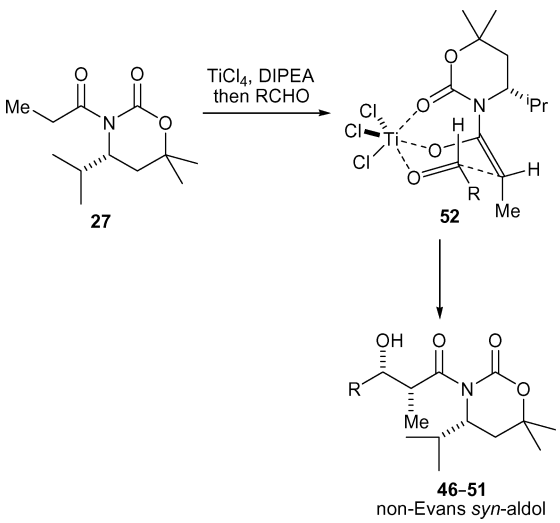
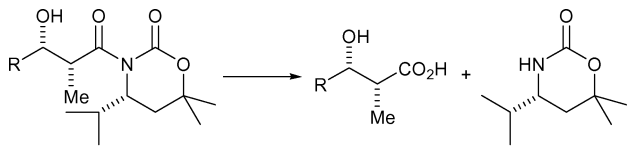


Fig. 6 Proposed transition state **52** for titanium-mediated aldol reaction of *N*-acyl oxazinanone **27**.

of *N*-acyl oxazolidinones, *N*-acyl oxazolidinethiones, and *N*-acyl thiazolidinethiones to rationalise the observed non-Evans *syn* aldol product.[27]

Cleavage of the aldol products **46**–**50** to the corresponding α-methyl-β-hydroxy-carboxylic acids was next investigated. Treatment of aldol products **46**–**50** with lithium hydroperoxide afforded the corresponding α-methyl-β-hydroxy-carboxylic acid derivatives **53**–**57** in high yield and as single diastereoisomers in each case, consistent with no epimerisation in this cleavage step. The parent oxazinanone **17** was also returned in quantitative yield in each case (Scheme 12). Carboxylic acids **53**, **56** and **57** showed comparable spectroscopic properties to the reported literature values {**53** $[\alpha]_D^{22}$ +28.5 (*c* 1.0 in $CHCl_3$), lit.[28] $[\alpha]_D^{20}$ +28.5 (*c* 1.2 in $CHCl_3$); **56** $[\alpha]_D^{22}$ −4.0 (*c* 0.8 in $CHCl_3$), lit.[29] $[\alpha]_D^{23}$ −4.1 (*c* 0.7 in $CHCl_3$); **57** $[\alpha]_D^{22}$ +11.3 (*c* 0.7 in $CHCl_3$), lit.[30] $[\alpha]_D^{20}$ +10.5 (*c* 0.1 in $CHCl_3$)}. The configurations within **54** and **55** were assigned by analogy.



46–50 **53–57** **17**, quant

Product	R	Yield (%)	de (%)
53	Ph	quant	>98
54	*p*-$MeOC_6H_4$	quant	>98
55	*p*-$NO_2C_6H_4$	quant	>98
56	Et	94	>98
57	^{i}Pr	quant	>98

Scheme 12 *Reagents and conditions*: LiOH, H_2O_2, THF–H_2O (3 : 1), 0 °C to rt.

Conclusion

In conclusion, oxazinanones are readily prepared from β-amino esters, and *N*-acylated by deprotonation with LiHMDS and addition of the desired acid chloride. Both counterion and temperature play an important role in the stability of enolates generated from *N*-acyl oxazinanones, with asymmetric alkylation readily achieved by formation of the potassium enolate, addition of the electrophile at −78 °C and controlled warming to −40 °C. A C(4)-*iso*-propyl stereodirecting group conveys higher stereoselectivity than the analogous C(4)-phenyl substituent in these alkylation reactions, with *gem*-dimethyl substitution at C(6) facilitating exclusive exocyclic cleavage upon hydrolysis to furnish the target α-substituted carboxylic acids and the parent oxazinanone nearly quantitatively. Furthermore, asymmetric aldol reactions of a range of aromatic and aliphatic aldehydes with the chlorotitanium enolate of (*R*)-*N*-propanoyl-4-*iso*-propyl-6,6-dimethyl-oxazinan-2-one **27** proceed with excellent diastereoselectivity (>98% de) for the non-Evans *syn*-configuration. Treatment of the *syn*-aldol products with lithium hydroperoxide affords homochiral α-methyl-β-hydroxy-carboxylic acids as single diastereoisomers in excellent yield and returns the parent oxazinanone in quantitative yield. Further applications of oxazinanones as chiral auxiliaries, and the preparation and evaluation of alternative chiral auxiliaries derived from β-amino acid derivatives, are currently underway in this laboratory.

Experimental

General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried by passing through a column of activated basic alumina (Brockmann 1, standard grade, *ca.* 150 mesh) according to the procedure outlined by Grubbs and co-workers.[31] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on either a Bruker Avance 500 or a Bruker Avance 400 spectrometer in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF and were internally calibrated with polyanaline in positive and negative modes, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

General procedure 1: tandem hydrogenolysis and *N*-carbamylation

$Pd(OH_2)/C$ (catalytic) was added to a vigorously stirred solution of the requisite amine (1.0 equiv.) and Boc_2O (1.1 equiv.) in degassed MeOH at rt. The reaction vessel was flushed with H_2 and the reaction mixture was left to stir under H_2 (5 atm) for 24 h. The reaction mixture was filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*.

General procedure 2: reduction of *tert*-butyl ester with $LiAlH_4$

A solution of substrate (1.0 equiv.) in THF at 0 °C was treated with $LiAlH_4$ (5.0 equiv.). The reaction mixture was allowed to warm to rt over 12 h, then cooled again to 0 °C prior to the careful addition of ice. The resulting mixture was diluted with EtOAc, stirred for several hours, then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*.

General procedure 3: cyclisation promoted by ^{t}BuOK

^{t}BuOK (1.5 equiv.) was added to a solution of *N*-Boc amino alcohol (1.0 equiv.) in THF at 0 °C. After being allowed to warm

to rt over 12 h, NH_4Cl (sat., aq) was added. The resulting mixture was extracted with EtOAc and the organic phase was washed with brine, then dried and concentrated *in vacuo*.

General procedure 4: Grignard addition

MeMgBr (3.0 equiv.) was added to a solution of β-amino methyl ester (1.0 equiv.) in THF at −78 °C. After being allowed to warm to rt over 12 h, the reaction mixture was cooled to 0 °C and NH_4Cl (sat., aq) was added. The resulting mixture was allowed to warm to rt over 30 min, then extracted with DCM. The organic phase was washed with brine, then dried and concentrated *in vacuo*.

General procedure 5: *N*-acylation of oxazinanones

LiHMDS (1.2 equiv.) was added to a solution of oxazinanone (1.0 equiv.) in THF at −78 °C. After 30 min, the requisite acid chloride (1.5 equiv.) was added. The reaction mixture was allowed to warm to rt over 12 h, followed by addition of NH_4Cl (sat., aq). The resulting mixture was extracted with either EtOAc and the organic phase was washed with $NaHCO_3$ (sat., aq), dried, and concentrated *in vacuo*.

General procedure 6: carboximide hydrolysis with lithium hydroperoxide

A solution of substrate (1.0 equiv.) in THF–H_2O (v : v, 3 : 1) at 0 °C was treated with 35% aqueous H_2O_2 (5.0 equiv.) and LiOH (2.0 equiv.). After being allowed to warm to rt over 16 h, Na_2SO_4 (10%, aq) was added and the reaction mixture was stirred for a further 30 min. The mixture was then buffered to pH 9–10 with $NaHCO_3$ (sat., aq) and extracted with DCM. The organic layer was dried and concentrated *in vacuo* to afford the requisite oxazinanone. The aqueous layer was acidified to pH 1–2 with HCl (2 M, aq), extracted with EtOAc, and the organic extracts were dried and concentrated *in vacuo* to afford the requisite carboxylic acid.

General procedure 7: alkylation of *N*-acyl oxazinanone

A solution of *N*-acyl oxazinanone (1.0 equiv.) in THF at −78 °C was treated with KHMDS (1.25 equiv.). After 1 h, the requisite electrophile (1.5–3.0 equiv.) was added and the reaction mixture was either: (*Method A*) stirred at −78 °C for 3 h; or (*Method B*) warmed to −40 °C and stirred for 3–5 h. NH_4Cl (sat., aq) was added and the reaction mixture was allowed to warm to rt, then extracted with EtOAc. The organic phase was washed with brine, then dried and concentrated *in vacuo*.

General procedure 8: aldol condensation with titanium(IV) chloride

A solution of *N*-propanoyl oxazinanone (1.0 equiv.) in DCM at 0 °C was treated with $TiCl_4$ (1.05 equiv.) and DIPEA (1.1 equiv.). The resultant dark red enolate was stirred for 30 min, then the reaction mixture was cooled to −78 °C. Freshly distilled aldehyde was added, and the reaction mixture was allowed to warm to rt over 4 h. NH_4Cl (sat., aq) was added and the organic phase was washed with brine, then dried and concentrated *in vacuo*.

***tert*-Butyl (*R*)-3-[*N*-(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate 6**

Following *General procedure 1*, Pearlman's catalyst (1.05 g), **4** (2.10 g, 5.10 mmol) and Boc_2O (1.20 g, 5.60 mmol) in MeOH (10 mL) under H_2 (5 atm) at rt gave the crude reaction mixture. Purification *via* flash column chromatography (eluent pentane–Et_2O 20 : 1) gave **6** as a white solid (1.50 g, 94%); mp 61–63 °C (Et_2O); $[\alpha]_D^{25}$ +21.0 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3406 (N–H), 1731 (C=O, ester), 1695 (C=O, carbamate); δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s, C*Me*$_3$), 1.43 (9H, s, C*Me*$_3$), 2.62–2.80 [2H, m, C(2)*H*$_2$], 5.02–5.11 [1H, m, C(3)*H*], 5.49 (1H, br s, N*H*), 7.19–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9, 28.3, 42.2, 57.0, 81.1, 126.2, 127.3, 128.3, 128.4, 128.5, 155.0, 173.1; *m*/*z* (APCI$^+$) 166 ([M − $C_9H_{16}O_2$]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{28}NO_4^+$ (M + H$^+$) requires 322.2018; found 322.2024.

***tert*-Butyl (*R*)-3-[*N*-(*tert*-butoxycarbonyl)amino]-4-methylpentanoate 7**

Following *General procedure 1*, Pearlman's catalyst (3.15 g), **5** (6.30 g, 16.0 mmol) and Boc_2O (3.90 g, 18.0 mmol) in MeOH (10 mL) under H_2 (5 atm) at rt gave the crude reaction mixture. Purification *via* flash column chromatography (eluent pentane : Et_2O 20 : 1) gave **7** as a white solid (4.20 g, 89%); mp 79–80 °C (Et_2O); $[\alpha]_D^{23}$ −24.7 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3329 (N–H), 1728 (C=O, ester), 1680 (C=O, carbamate); δ_H (400 MHz, $CDCl_3$) 0.91 [3H, d, *J* 6.8, C(5)*H*$_3$], 0.92 [3H, d, *J* 6.8, C(4)*Me*], 1.43 (9H, s, C*Me*$_3$), 1.45 (9H, s, C*Me*$_3$), 1.74–1.82 [1H, m, C(4)*H*], 2.33 [1H, dd, *J* 14.9, 7.6 Hz, C(2)*H*$_A$], 2.44 [1H, dd, *J* 14.9, 4.8 Hz, C(2)*H*$_B$], 3.72–3.79 [1H, m, C(3)*H*], 4.88 (1H, d, *J* 9.3 Hz, N*H*); δ_C (125 MHz, $CDCl_3$) 18.3, 19.1, 28.0, 28.3, 32.0, 38.5, 53.0, 78.8, 80.7, 155.4, 171.1; *m*/*z* (ESI$^+$) 310 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{29}NO_4Na^+$ ([M + Na]$^+$) requires 310.1994; found 310.1990.

(*R*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-3-phenylpropan-1-ol 8

Following *General procedure 2*, $LiAlH_4$ (1.0 M in THF, 4.0 mL, 4.0 mmol) and **6** (254 mg, 0.79 mmol) in THF (20 mL) at 0 °C gave the crude reaction mixture. Purification *via* flash column chromatography (eluent pentane : Et_2O 10 : 1, increased to MeOH) gave **8** as a colourless oil (169 mg, 85%); $[\alpha]_D^{25}$ +55.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3350 (O–H, br), 1689 (C=O); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.86–1.96 [2H, m, C(2)*H*$_2$], 3.49–3.62 [2H, m, C(1)*H*$_2$], 4.68–4.72 [1H, m, C(3)*H*], 7.21–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.8, 39.6, 52.1, 58.8, 79.1, 126.4, 126.5, 126.7, 127.0, 128.4, 128.5, 143.9, 156.9; *m*/*z* (APCI$^+$) 152 ([M − $C_5H_8O_2$]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{22}NO_3$ ([M + H]$^+$) requires 252.1600; found 252.1600.

(*R*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-4-methylpentan-1-ol 9

Following *General procedure 2*, $LiAlH_4$ powder (2.80 g, 73.0 mmol) and **7** (4.20 g, 14.6 mmol) in THF (200 mL) at 0 °C gave the crude reaction mixture. Purification *via* flash column chromatography (eluent pentane : Et_2O 10 : 1, increased to MeOH) gave **9** as a colourless oil (2.70 g, 84%); $[\alpha]_D^{25}$ −0.93 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3341 (O–H, br), 1688 (C=O), 1530 (amide II); δ_H (400 MHz, CD_3OD) 0.92 [6H, app t, *J* 7.3 Hz, C(4)*Me*$_2$], 1.46 (9H, s, C*Me*$_3$), 1.49–1.55 [1H, m, C(2)*H*$_A$], 1.67–1.79 [2H, m, C(2)*H*$_B$ and C(4)*H*], 3.42–3.46 [1H, m, C(3)*H*], 3.54–3.64 [2H, m, C(1)*H*$_2$]; δ_C (100 MHz, CD_3OD) 18.9, 20.0, 29.2, 34.2, 36.4, 54.4, 60.8, 80.2, 159.2; *m*/*z* (ESI$^+$) 240 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{24}NO_3^+$ requires ([M + H]$^+$) 218.1756; found 218.1753.

(*R*)-4-Phenyl-(1,3)-oxazinan-2-one 10

Following *General procedure 3*, ^{t}BuOK (60 mg, 0.54 mmol) and **8** (90 mg, 0.36 mmol) in THF at 0 °C gave the crude reaction mixture. Recrystallisation from EtOAc gave **10** as white crystals (40 mg, 63%); $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.3; N, 7.9%; found C, 67.6; H, 6.3; N, 7.8%; mp 148–154 °C (EtOAc); $[a]_D^{25}$ +58.5 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1674 (C=O); δ_H (400 MHz, $CDCl_3$) 1.97–2.03 [1H, m, C(5)H_A], 2.24–2.29 [1H, m, C(5)H_B], 4.29–4.32 [2H, m, C(6)H_2], 4.65–4.69 [1H, m, C(4)*H*], 5.76 (1H, br s, N*H*), 7.31–7.42 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 30.8, 54.9, 64.9, 126.0, 128.3, 129.0, 141.1, 154.0; *m*/*z* (APCI$^+$) 178 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{12}NO_2^+$ ([M + H]$^+$) requires 178.0868; found 178.0865.

X-Ray crystal structure determination for 10. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[32]

X-Ray crystal structure data for **10** [$C_{10}H_{11}NO_2$]: $M = 177.20$, orthorhombic, space group $P2_12_12_1$, $a = 5.9454(2)$, $b = 8.1078(3)$, $c = 18.0676(6)$ Å, $V = 870.93(5)$ Å^3, $Z = 4$, $\mu = 0.095$ mm^{-1}, colourless plate, crystal dimensions = 0.05 × 0.1 × 0.1 mm. A total of 1167 unique reflections were measured for $5 < \theta < 27$ and 1056 reflections were used in the refinement. The final parameters were $wR_2 = 0.033$ and $R_1 = 0.028$ [$I > 3\sigma(I)$].

CCDC reference number 280051. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604073j.

(*R*)-4-*iso*-Propyl-(1,3)-oxazinan-2-one 11

Following *General procedure 3*, ^{t}BuOK (300 mg, 2.66 mmol) and **9** (385 mg, 1.77 mmol) in THF (20 mL) at 0 °C gave the crude reaction mixture. Purification *via* flash column chromatography (eluent EtOAc) gave **11** as a white solid (80 mg, 32%); mp 62–64 °C (EtOAc); $[a]_D^{25}$ +23.8 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1696 (C=O); δ_H (400 MHz, $CDCl_3$) 0.92 [3H, d, *J* 6.8 Hz, C(4)C*Me*$_A$], 0.96 [3H, d, *J* 6.7 Hz, C(4)C*Me*$_B$], 1.67–1.79 [2H, m, C(5)H_A and C(4)C*H*Me$_2$], 1.84–1.90 [1H, m, C(5)H_B], 3.22–3.27 [1H, m, C(4)*H*], 4.17 [1H, app td, *J* 11.0, 2.7 Hz, C(6)H_A], 4.32 [1H, app dt, *J* 11.0, 3.9 Hz, C(6)H_B], 6.29 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 17.5, 18.1, 23.9, 32.4, 56.5, 65.7, 154.9; *m*/*z* (APCI$^+$) 144 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_7H_{14}NO_2^+$ ([M + H]$^+$) requires 144.1025; found 144.1020.

Attempted preparation of (*R*)-4-phenyl-6,6-dimethyl-(1,3)-oxazinan-2-one 16 by Grignard addition to 14, and concomitant cyclisation

Following *General procedure 4*, MeMgBr (3.0 M in Et_2O, 0.97 mL, 2.90 mmol) and **14** (200 mg, 0.72 mmol) in THF at −78 °C gave a 40 : 30 : 30 ratio of **16** : **18** : **20** respectively. Purification *via* flash column chromatography (eluent pentane : EtOAc 1 : 1, then EtOAc) gave **16** as a white solid (first to elute, 44 mg, 30%), and **18** as a colourless oil.

Data for **16**: $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%; found C, 70.2; H, 7.35; N, 6.8%; mp 82–84 °C (EtOAc); $[a]_D^{25}$ +31.8 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1698 (C=O); δ_H (400 MHz, $CDCl_3$) 1.44 [3H, s, C(6)*Me*$_A$], 1.52 [3H, s, C(6)*Me*$_B$], 1.83 [1H, dd, *J* 13.8, 11.8 Hz, C(5)H_A], 2.02 [1H, ddd, *J* 13.8, 4.7, 1.5 Hz, C(5)H_B], 4.62 [1H, dd, *J* 11.8, 4.7 Hz, C(4)*H*], 5.76 (1H, br s, N*H*), 7.31–7.47 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.6, 29.4, 42.0, 53.0, 78.5, 126.1, 128.5, 129.1, 140.9, 154.0; *m*/*z* (APCI$^+$) 206 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{16}NO_2^+$ ([M + H]$^+$) requires 206.1181; found 206.1179.

Data for **18**: mp 137–138 °C (EtOAc); $[a]_D^{25}$ +41.3 (*c* 1.1 in $CHCl_3$); ν_{max} (KBr) 3383 (O–H), 1682 (C=O), 1528 (amide II); δ_H (400 MHz, $CDCl_3$) 1.26 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 1.34 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 1.41 (9H, s, C*Me*$_3$), 1.84–1.98 [2H, m, C(3)H_2], 2.34 (1H, br s, O*H*), 4.84 [1H, app br s, C(4)*H*], 5.49 (1H, br s, N*H*), 7.23–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.3, 31.1, 49.6, 52.5, 70.6, 79.7, 126.1, 127.1, 128.7, 144.0, 155.7; *m*/*z* (ESI$^+$) 302 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{26}NO_3^+$ ([M + H]$^+$) requires 280.1913; found 280.1912.

X-Ray crystal structure determination for 16. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[32]

X-Ray crystal structure data for **16** [$C_{12}H_{15}NO_2$]: $M = 205.25$, orthorhombic, space group $P2_12_12_1$, $a = 9.2401(1)$, $b = 10.5810(1)$, $c = 46.9695(5)$ Å, $V = 4592.18(8)$ Å^3, $Z = 16$, $\mu = 0.081$ mm^{-1}, colourless block, crystal dimensions = 0.1 × 0.1 × 0.1 mm. A total of 5748 unique reflections were measured for $5 < \theta < 27$ and 4682 reflections were used in the refinement. The final parameters were $wR_2 = 0.048$ and $R_1 = 0.067$ [$I > 0.5\sigma(I)$].

CCDC reference number 280052. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604073j.

Attempted preparation of (*R*)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 17 by Grignard addition to 15, and concomitant cyclisation

Following *General procedure 4*, MeMgBr (3.0 M in Et_2O, 1.50 mL, 4.60 mmol) and **15** (285 mg, 1.2 mmol) in THF at −78 °C gave a 46 : 10 : 44 ratio of **17** : **19** : **21** respectively. Purification *via* flash column chromatography (eluent pentane : EtOAc 1 :1, then EtOAc, then MeOH) gave **17** as a colourless oil (first to elute, 70 mg, 35%), **19** as a white solid (second to elute, 15 mg), and **21** as a colourless oil (third to elute, 66 mg).

Data for **17**: $[a]_D^{25}$ +3.3 (*c* 1.0 in $CHCl_3$): ν_{max} (film) 1703 (C=O); δ_H (400 MHz, $CDCl_3$) 0.93 [3H, d, *J* 6.8 Hz, CH(CH_3)$_A$(CH$_3$)$_B$], 0.96 [3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(CH_3)$_B$], 1.38 [3H, s, C(6)*Me*$_A$], 1.42 [3H, s, C(6)*Me*$_B$], 1.50–1.56 [1H, m, C(5)H_A], 1.67–1.75 [2H, m, C(5)H_B and C*H*Me$_2$], 3.29 [1H, app dt, *J* 12.0, 5.3 Hz, C(4)*H*], 6.10 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 17.5, 18.0, 25.2, 29.7, 32.4, 35.0, 53.5, 78.0, 154.7; *m*/*z* (APCI$^+$) 172 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{18}NO_2^+$ ([M + H]$^+$) requires 172.1338; found 172.1337.

Data for **19**: mp 58–60 °C (EtOAc); $[a]_D^{25}$ −7.27 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3384 (O–H), 1685 (C=O), 1527 (amide II); δ_H (500 MHz, $CDCl_3$) 0.93 [3H, d, *J* 6.6 Hz, CH(CH_3)$_A$(CH$_3$)$_B$], 0.97 [3H, d, *J* 7.1 Hz, CH(CH$_3$)$_A$(CH_3)$_B$], 1.30 [3H, s, C(CH_3)$_A$(CH$_3$)$_B$], 1.32 [3H, s, C(CH$_3$)$_A$(CH_3)$_B$], 1.49 [9H, s, OC(CH_3)$_3$], 1.51–1.56

[1H, m, C(3)H_A], 1.63–1.68 [1H, m, C(3)H_B], 1.78–1.82 [1H, m, C(5)*H*], 3.73 [1H, app br s, C(4)*H*], 4.60 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 17.4, 18.6, 28.3, 29.2, 30.3, 33.3, 45.4, 52.1, 69.9, 79.5, 157.0; *m/z* (ESI$^+$) 268 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{27}NNaO_3^+$ ([M + Na]$^+$) requires 268.1889; found 268.1878.

Data for **21**: $[\alpha]_D^{23}$ −22.1 (*c* 2.4 in $CHCl_3$); ν_{max} (film) 3290 (O–H), 1652 (C=O), 1557 (amide II); δ_H (400 MHz, CD_3OD) 0.86–0.92 [6H, m, C(5)Me_2], 1.19 [6H, s, C(2)Me_2], 1.54 (1H, dd, *J* 14.4, 9.6 z, C(3)H_A], 1.65 [1H, dd, *J* 14.4, 1.9 Hz, C(3)H_B], 1.69–1.79 [1H, m, C(5)*H*], 1.93 [1H, s, CH_3C(O)N], 3.88–3.92, [1H, m, C(4)*H*]; δ_C (100 MHz, CD_3OD) 17.1, 18.1, 21.8, 27.8, 29.1, 33.9, 44.8, 51.1, 70.1, 171.6; *m/z* (ESI$^+$) 210 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{21}NO_2Na^+$ ([M + Na]$^+$) requires 210.1470; found 210.1463.

Alternative preparation of (*R*)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 17 by modified Grignard addition to 15, and cyclisation

Anhydrous cerium(III) chloride beads (442 mg, 1.80 mmol) were added to a solution of **15** (100 mg, 0.41 mmol) in THF at room temperature. After 4 h, MeMgBr (3.0 M in Et_2O, 0.90 mL, 2.70 mmol) was added dropwise. After 10 h, the reaction mixture was treated with a 10% aqueous AcOH solution and stirred for a further 3 h. The mixture was then diluted with Et_2O and washed with $NaHCO_3$ (sat., aq) and brine. The combined organic extracts were dried and concentrated *in vacuo* to give a mixture of **17** and **19**. This mixture was then treated with ^{t}BuOK (69 mg, 0.62 mmol) in accordance with *General procedure 3* to furnish **17** (40 mg, 57% over two steps) as a colourless oil.

(4*R*,α*S*)-2-Methyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-phenylbutan-2-ol 22

Following *General procedure 4*, MeMgBr (3.0 M in Et_2O, 1.33 mL, 4.00 mmol) and **12** (500 mg, 1.34 mmol) in THF (25 mL) at −78 °C gave the crude reaction mixture. Purification *via* flash column chromatography gave **22** (330 mg, 66%) as a colourless oil; $[\alpha]_D^{25}$ +54.9 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 3400 (O–H, br); δ_H (400 MHz, $CDCl_3$) 0.63 [3H, s, C(CH_3)$_A$(CH_3)$_B$], 1.03 [3H, d, *J* 7.0 Hz, C(α)*Me*], 1.13 [3H, s, C(CH_3)$_A$(CH_3)$_B$], 1.41 [1H, dd, *J* 14.5, 3.1 Hz, C(3)H_A], 2.45 [1H, dd, *J* 14.5, 11.1 Hz, C(3)H_B], 3.60 [1H, d, *J* 13.2 Hz, NC$H_A$$H_B$Ph], 4.12 [1H, q, *J* 7.0 Hz, C(α)*H*], 4.26 (1H, *J* 13.2 Hz, NCH$_A$$H_B$Ph), 4.32 [1H, dd, *J* 11.1, 3.1 Hz, C(4)*H*], 5.83 (1H, s, O*H*), 7.23–7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.6, 27.4, 31.9, 43.6, 50.4, 56.4, 57.6, 70.4, 127.2, 127.3, 128.3, 128.5, 128.7, 128.9, 129.5, 139.0, 141.3, 142.8; *m/z* (APCI$^+$) 374 ([M + H]$^+$, 50%); HRMS (ESI$^+$) $C_{26}H_{32}NO^+$ ([M + H]$^+$) requires 374.2484; found 374.2484.

(4*R*, α*S*)-2,5-Dimethyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hexan-2-ol 23

Following *General procedure 4*, MeMgBr (3.0 M, 1.18 mL, 3.54 mmol) and **13** (400 mg, 1.18 mmol) in THF (25 mL) at −78 °C gave the crude reaction mixture. Purification *via* flash column chromatography gave **23** (215 mg, 54%) as a colourless oil; $[\alpha]_D^{21}$ +10.9 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 3305 (O–H, br); δ_H (400 MHz, $CDCl_3$) 0.35 [3H, s, C(CH_3)$_A$(CH_3)$_B$], 0.97 [6H, app t, *J* 5.6 Hz, CH(CH_3)$_2$) 1.05 [1H, dd, *J* 14.5, 2.0 Hz, C(3)H_A], 1.12 [3H, s, C(CH_3)$_A$(CH_3)$_B$], 1.45 [3H, d, *J* 7.1 Hz, C(α)*Me*], 1.79 [1H, dd, *J* 14.5, 11.9 Hz, C(3)H_B], 2.24–2.31 [1H, m, C*H*(CH_3)$_2$], 3.10 [1H, dd, *J* 11.9, 2.0 Hz, C(4)*H*], 3.64 (1H, d, *J* 12.8 Hz, NC$H_A$$H_B$Ph), 4.00–4.04 [1H, m, C(α)*H*], 4.19 (1H, d, *J* 12.8 Hz, NCH$_A$$H_B$Ph), 6.32 (1H, br s, O*H*), 7.19–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1, 18.5, 22.7, 26.6, 32.4, 36.3, 50.4, 57.4, 69.9, 127.2, 128.2, 128.5, 128.9, 129.5, 139.2; *m/z* (APCI$^+$) 340 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{33}NO^+$ ([M + H]$^+$) requires 340.2640; found 340.2642.

(*R*)-2-Methyl-4-[*N*-(*tert*-butoxycarbonyl)amino]-4-phenylbutan-2-ol 18

Following *General procedure 1*, Pearlman's catalyst (185 mg), **22** (330 mg, 0.88 mmol) and Boc_2O (212 mg, 0.97 mmol) in MeOH (5mL) under H_2 (5 atm) at rt gave the crude reaction mixture. Purification *via* flash column chromatography (eluent pentane : EtOAc 5 : 1) gave **18** as a white solid (115 mg, 47%).

(*R*)-2,5-Dimethyl-4-[*N*-(*tert*-butoxycarbonyl)amino]hexan-2-ol 19

Following *General procedure 1*, Pearlman's catalyst (140 mg), **23** (280 mg, 0.82 mmol) and Boc_2O (200 mg, 0.91 mmol) in MeOH (5 mL) under H_2 (5 atm) at rt gave the crude reaction mixture. Purification *via* flash column chromatography (eluent pentane : EtOAc 5 : 1) gave **19** as a white solid (160 mg, 79%).

(*R*)-4-Phenyl-6,6-dimethyl-(1,3)-oxazinan-2-one 16

Following *General procedure 3*, ^{t}BuOK (66 mg, 0.59 mmol) and **18** (110 mg, 0.39 mmol) in THF at 0 °C gave the crude reaction mixture. Purification *via* flash column chromatography (eluent pentane : EtOAc 4 : 1, increased to EtOAc) gave **16** as a white solid (72 mg, 90%).

(*R*)-4-*iso*-Propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 17

Following *General procedure 3*, ^{t}BuOK (69 mg, 0.61 mmol) and **19** (100 mg, 0.41 mmol) in THF at 0 °C gave the crude reaction mixture. Purification *via* flash column chromatography (eluent pentane : EtOAc 1 : 1, increased to EtOAc) gave **17** as a colourless oil (70 mg, quantitative).

(*R*)-3-Propanoyl-4-phenyl-(1,3)-oxazinan-2-one 24

LiH (9 mg, 1.12 mmol) was added to a solution of **10** (100 mg, 0.56 mmol) in THF (15.0 mL) at 0 °C. After stirring for 30 min, propanoyl chloride (58 mg, 0.63 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 16 h. H_2O was then added and the solvent was evaporated *in vacuo*. The residue was partitioned between EtOAc and H_2O, and the organic layer was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane : EtOAc 10 : 1) furnished **24** as a colourless oil (109 mg, 83%); $[\alpha]_D^{25}$ +36.9 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, t, *J* 7.3 z, CH_3CH_2CO), 2.13 [1H, app dq, *J* 14.1, 4.0 Hz, C(5)H_A], 2.42–2.51 [1H, m, C(5)H_B], 2.98–3.13 (2H, m, CH_3CH_2CO], 4.17–4.30 [2H, m, C(6)H_2], 5.71 [1H, app t, *J* 5.1 Hz, C(4)*H*], 7.17–7.39 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 9.0, 29.7, 32.2, 54.9, 64.3, 125.1, 127.6, 128.4, 128.8, 140.2, 151.6, 176.6; *m/z* (GCToF MS CI$^+$)

234 ([M + H]$^+$, 100%); HRMS (GCToF MS CI$^+$) $C_{13}H_{16}NO_3^+$ ([M + H]$^+$) requires 234.1130; found 234.1121.

(*R*)-3-Propanoyl-4-*iso*-propyl-(1,3)-oxazinan-2-one 25

Following *General procedure 5*, LiHMDS (1.0 M in THF, 2.35 mL, 2.35 mmol), **11** (280 mg, 1.96 mmol) in THF at −78 °C, and propanoyl chloride (271 mg, 2.93 mmol) gave the crude reaction mixture. Purification *via* flash column chromatography (eluent pentane : EtOAc 4 : 1) gave **25** as a colourless oil (250 mg, 65%); $[a]_D^{23}$ +140.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1744 (C=O_{endo}), 1701 (C=O_{exo}); δ_H (400 MHz, $CDCl_3$) 0.73–0.75 [6H, m, CH(CH_3)$_2$], 1.16 (3H, t, *J* 7.3 Hz, CH_3CH$_2$CO), 2.02–2.15 [3H, m, C(5)H_2 and CH(CH$_3$)$_2$], 2.75 (1H, dq, *J* 17.5, 7.3 Hz, CH$_3$CH_AH$_B$CO), 3.03 (1H, dq, *J* 17.5, 7.3 Hz, CH$_3$CH$_A$$H_B$CO), 4.18 [1H, ddd, *J* 11.3, 6.9, 5.8 Hz, C(6)H_A], 4.35 [1H, app dt, *J* 11.3, 5.8 Hz, C(6)H_B], 4.65 [1H, app q, *J* 7.1 Hz, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 9.3, 17.0, 19.0, 23.6, 30.5, 30.9, 55.2, 65.3, 153.3, 176.1; *m/z* (CI$^+$) 200 ([M + H]$^+$, 100%); HRMS (CI$^+$) $C_{10}H_{18}NO_3^+$ ([M + H]$^+$) requires 200.1287; found 200.1278.

(*R*)-3-Propanoyl-4-phenyl-6,6-dimethyl-(1,3)-oxazinan-2-one 26

Following *General procedure 5*, LiHMDS (1.0 M in THF, 1.40 mL, 1.40 mmol), **16** (240 mg, 1.17 mmol) in THF at −78 °C, and propanoyl chloride (162 mg, 1.75 mmol) gave the crude reaction mixture. Purification *via* flash column chromatography (eluent pentane : EtOAc 10 : 1) gave **26** as a colourless oil (268 mg, 88%); $[a]_D^{25}$ +63.9 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1734 (C=O_{endo}), 1701 (C=O_{exo}); δ_H (400 MHz, $CDCl_3$) 1.07 (3H, t, *J* 7.2 Hz, CH_3CH$_2$CO), 1.40 [3H, s, C(6)(CH_3)$_A$], 1.48 [3H, s, C(6)(CH_3)$_B$], 2.07 [1H, dd, *J* 14.4, 10.8 Hz, C(5)H_A], 2.33 [1H, dd, *J* 14.4, 7.4 Hz, C(5)H_B], 2.87 (1H, dq, *J* 18.4, 7.2 Hz, CH$_3$CH_AH$_B$CO), 3.02 (1H, dq, *J* 18.4, 7.2 Hz, CH$_3$CH$_A$$H_B$CO), 5.31 [1H, dd, *J* 10.8, 7.4 Hz, C(4)*H*], 7.19–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.0, 24.6, 29.0, 31.6, 43.1, 55.6, 79.5, 125.1, 127.4, 128.9, 142.3, 152.0, 176.0; *m/z* (ESI$^+$) 284 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{20}NO_3^+$ ([M + H]$^+$) requires 262.1443; found 262.1449.

(*R*)-3-Propanoyl-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 27

Following *General procedure 5*, LiHMDS (1.0 M in THF, 0.35 mL, 0.35 mmol), **17** (50 mg, 0.29 mmol) in THF at −78 °C, and propanoyl chloride (41 mg, 0.44 mmol) gave the crude reaction mixture. Purification *via* flash column chromatography (eluent pentane : EtOAc 10 : 1) gave **27** as a colourless oil (52 mg, 79%); $[a]_D^{24}$ +182.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1737 (C=O_{endo}), 1696 (C=O_{exo}); δ_H (400 MHz, $CDCl_3$) 0.82 [3H, d, *J* 6.8 Hz, CH(CH_3)$_A$(CH$_3$)$_B$], 0.87 [3H, d, *J* 6.8 Hz, CH(CH$_3$)$_A$(CH_3)$_B$], 1.14 (3H, t, *J* 7.3 Hz, CH_3CH$_2$CO), 1.34 [3H, s, C(6)(CH_3)$_A$], 1.46 [3H, s, C(6)(CH_3)$_B$], 1.88–1.98 [2H, m, C(5)H_2], 2.25–2.37 [1H, m, CH(CH$_3$)$_2$], 2.71 (1H, dq, *J* 17.4, 7.3 Hz, CH$_3$CH_AH$_B$CO), 3.01 (1H, dq, *J* 17.4, 7.3 Hz, CH$_3$CH$_A$$H_B$CO), 4.42 [1H, app dt, *J* 8.7, 5.6 Hz, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 9.3, 15.7, 18.7, 25.5, 29.8, 30.1, 30.6, 33.7, 54.7, 79.5, 152.9, 175.6; *m/z* (ESI$^+$) 250 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}NO_3^+$ ([M + H]$^+$) requires 228.1600, found 228.1596.

(*R*)-3-(3′-Phenylpropanoyl)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 28

Following *General procedure 5*, LiHMDS (1.0 M in THF, 0.74 mL, 0.74 mmol), **17** (84 mg, 0.49 mmol) in THF at −78 °C, and hydrocinnamoyl chloride (166 mg, 0.98 mmol) gave the crude reaction mixture. Purification *via* flash column chromatography (eluent pentane : EtOAc 4 : 1) gave **28** as a colourless oil (54 mg, 36%); $[a]_D^{22}$ +162.8 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 1736 (C=O_{endo}), 1693 (C=O_{exo}); δ_H (400 MHz, $CDCl_3$) 0.83 [3H, d, *J* 6.8 Hz, CH(CH_3)$_A$(CH$_3$)$_B$], 0.88 [3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(CH_3)$_B$], 1.23 [3H, s, C(6)(CH_3)$_A$], 1.45 [3H, s, C(6)(CH_3)$_B$], 1.91 [2H, app d, *J* 8.6 Hz, C(5)H_2], 2.27–2.36 [1H, m, CH(CH$_3$)$_2$], 2.92–3.10 [3H, m, C(2′)H_A and C(3′)H_2], 3.24–3.32 [2H, m, C(2′)H_B], 4.40 [1H, app td, *J* 8.6, 5.6 Hz, C(4)*H*], 7.16–7.30 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.7, 18.7, 25.4, 29.8, 30.1, 31.1, 33.7, 38.7, 54.8, 79.7, 126.1, 128.2, 128.4, 128.5, 140.9, 153.3, 173.0; *m/z* (ESI$^+$) 362 ([M + MeCN + NH$_4$]$^+$, 50%); HRMS (ESI$^+$) $C_{18}H_{26}NO_3^+$ ([M + H]$^+$) requires 304.1913; found 304.1908.

(*R*)-3-Benzyl-4-phenyl-(1,3)-oxazinan-2-one 29

LiHMDS (1.0 M in THF, 0.20 mL, 0.20 mmol) was added to a solution of **10** (30 mg, 0.17 mmol) in THF at −78 °C. After 30 min, BnBr (43 mg, 0.25 mmol) was added. The reaction mixture was allowed to warm to rt over 12 h, followed by addition of NH_4Cl (sat., aq). The resulting mixture was extracted with EtOAc and the organic phase was washed with brine, then dried and concentrated *in vacuo* to give a 40 : 60 mixture of **10** : **29** respectively. Purification *via* flash column chromatography (eluent pentane : EtOAc 5 : 1) gave **29** as a colourless wax (24 mg, 53%); $[a]_D^{23}$ +25.3 (*c* 1.6 in $CHCl_3$); ν_{max} (film) 1689 (C=O); δ_H (400 MHz, $CDCl_3$) 1.94 [1H, app dq, *J* 14.0, 3.9 Hz, C(5)H_A], 2.31–2.40 [1H, m, C(5)H_B], 3.61 (1H, d, *J* 15.2 Hz, NCH_AH$_B$Ph), 4.17–4.28 [2H, m, C(6)H_2], 4.47–4.50 [1H, m, C(4)*H*], 5.37 (1H, d, *J* 15.2 Hz, NCH$_A$$H_B$Ph), 7.21–7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 30.6, 50.2, 56.8, 62.9, 126.5, 127.7, 128.1, 128.2 128.7, 129.1, 136.7, 139.8, 154.5; *m/z* (ESI$^+$) 268 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{18}NO_2^+$ ([M + H]$^+$) requires 268.1338; found 268.1333.

(4*R*,2′*R*)-3-(4′-*tert*-Butoxy-4′-oxo-2′-methylbutanoyl)-4-*iso*-propyl-(1,3)-oxazinan-2-one 31

Following *General procedure 7*, **25** (15 mg, 0.08 mmol) in THF at −78 °C was treated with KHMDS (0.5 M in PhMe, 0.20 mL, 0.09 mmol). After 1 h, *tert*-butyl bromoacetate (0.04 mL, 0.23 mmol) was added. Purification *via* flash column chromatography (eluent pentane : Et$_2$O 10 : 1) gave **31** as a colourless oil (22 mg, 96%); $[a]_D^{25}$ +163.7 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 0.89 [3H, d, *J* 2.4 Hz, CH(CH_3)$_A$(CH$_3$)$_B$], 0.91 [3H, d, *J* 2.3 Hz, CH(CH$_3$)$_A$(CH_3)$_B$], 1.13 [3H, d, *J* 7.0 Hz, C(2′)CH_3], 1.43 [9H, s, OC(CH_3)$_3$], 2.03–2.13 [3H, m, C(5)H_2 and CH(CH$_3$)$_2$], 2.28 [1H, dd, *J* 16.1, 6.3 Hz, C(3′)H_A], 2.78 [1H, dd, *J* 16.1, 8.1 Hz, C(3′)H_B], 4.08–4.20 [2H, m, C(6)H_A and C(2′)*H*], 4.32–4.38 [1H, m, C(6)H_B], 4.51 [1H, app q, *J* 7.1 Hz, C(4)*H*]; δ_C (100 MHz, $CDCl_3$) 17.0, 17.5, 19.0, 23.8, 28.0, 30.7, 36.0, 39.3, 55.6, 65.3, 80.4, 153.1, 171.0, 177.7; *m/z* (ESI$^+$) 336 ([M + Na]$^+$, 100%), 314 (70); HRMS (ESI$^+$) $C_{16}H_{27}NNaO_5^+$ ([M + Na]$^+$) requires 336.1787; found 336.1784.

(4*R*,2′*R*)-3-(4′-*tert*-Butoxy-4′-oxo-2′-methylbutanoyl)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 34

Following *General procedure 7*, **27** (43 mg, 0.19 mmol) in THF at −78 °C was treated with KHMDS (0.5 M in PhMe, 0.50 mL, 0.24 mmol). After 1 h, *tert*-butyl bromoacetate (0.08 mL, 0.57 mmol) was added. Purification *via* flash column chromatography (eluent pentane : Et_2O 10 : 1) gave **34** as a colourless oil (48 mg, 74%); $[\alpha]_D^{25}$ +120.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1733 (C=O); δ_H (400 MHz, $CDCl_3$) 0.84 [3H, d, *J* 6.9 Hz, $CH(CH_3)_A(CH_3)_B$], 0.86 [3H, d, *J* 7.1 Hz, $CH(CH_3)_A(CH_3)_B$], 1.10 [3H, d, *J* 7.0 Hz, C(2′)CH_3], 1.34 [3H, s, C(6)$(CH_3)_A$], 1.42 [9H, s, OC$(CH_3)_3$], 1.45 [3H, s, C(6)$(CH_3)_B$], 1.93 [2H, app d, *J* 8.7 Hz, C(5)H_2], 2.24–2.33 [2H, m, C(3′)H_A and C$H(CH_3)_2$], 2.77 [1H, dd, *J* 16.1 Hz, 8.3, C(3′)H_B], 4.12–4.20 [1H, m, C(2′)*H*], 4.37–4.43 [1H, m, C(4)*H*]; δ_C (100 MHz, $CDCl_3$) 15.7, 17.3, 18.7, 25.5, 28.0, 29.8, 30.1, 33.7, 35.7, 39.3, 55.0, 79.6, 80.3, 152.6, 171.0, 177.2; *m*/*z* (ESI^+) 364 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{31}NNaO_5^+$ ($[M + Na]^+$) requires 364.2100; found 364.2097.

(*R*)-4-(*tert*-Butoxy)-4-oxo-2-methylbutanoic acid 35

Following *General procedure 6*, **34** (45 mg, 0.13 mmol) in THF–H_2O (v : v, 3 : 1, 4 mL) at 0 °C, H_2O_2 (0.06 mL, 0.67 mmol), and LiOH (6 mg, 0.26 mmol) gave **17** as a colourless oil (16 mg, 73%), and **35** as a colourless oil (17 mg, 68%); $[\alpha]_D^{25}$ +3.9 (*c* 0.9 in DCM); lit.[19] $[\alpha]_D^{25}$ +3.9 (*c* 1.0 in DCM); δ_H (400 MHz, $CDCl_3$) 1.25 [1H, d, *J* 7.2 Hz, C(2)CH_3], 1.45 [9H, s, OC$(CH_3)_3$], 2.37 [1H, dd, *J* 16.4, 5.9 Hz, C(3)H_A], 2.65 [1H, dd, *J* 16.4, 8.2 Hz, C(3)H_B], 2.86–2.95 [1H, m, C(2)*H*].

(4*R*,2′*R*)-3-(2′-Methyl-3′-phenylpropanoyl)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 36

Following *General procedure 7*, **27** (22 mg, 0.10 mmol) in THF at −78 °C was treated with KHMDS (0.5 M in PhMe, 0.24 mL, 0.12 mmol). After 1 h, BnBr (0.02 mL, 0.15 mmol) was added and the reaction mixture was stirred at −40 °C for 5 h before work-up. Purification *via* flash column chromatography (eluent pentane : Et_2O 5 : 1) gave **36** as a colourless oil (24 mg, 78%); $[\alpha]_D^{21}$ +122.3 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 1736 (C=O_{endo}], 1692 (C=O_{exo}); δ_H (400 MHz, $CDCl_3$) 0.77 [3H, d, *J* 6.8 Hz, $CH(CH_3)_A(CH_3)_B$], 0.84 [3H, d, *J* 6.9 Hz, $CH(CH_3)_A(CH_3)_B$], 1.05 [3H, d, *J* 6.7 Hz, C(2′)CH_3], 1.36 [3H, s, C(6)$(CH_3)_A$], 1.47 [3H, s, C(6)$(CH_3)_B$], 1.89–1.94 [2H, m, C(5)H_2], 2.18–2.25 [1H, m, C$H(CH_3)_2$], 2.56 [1H, dd, *J* 13.2, 9.0 Hz, C(3′)H_A], 3.30 [1H, dd, *J* 13.2, 5.5 Hz, C(3′)H_B], 3.87–3.94 [1H, m, C(2′)*H*], 4.45 [1H, app td, *J* 8.7, 5.6 Hz, C(4)*H*], 7.17–7.30 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.6, 16.6, 18.5, 25.4, 29.7, 30.1, 33.7, 39.8, 40.4, 54.7, 79.5, 126.0, 128.1, 129.2, 139.5, 152.6, 177.9; *m*/*z* (ESI^+) 340 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{28}NO_3^+$ ($[M + H]^+$) requires 318.2069; found 318.2070.

(4*R*,2′*R*)-3-(2′-Methyl-4′-pentenoyl)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 37

Following *General procedure 7*, **27** (22 mg, 0.10 mmol) in THF at −78 °C was treated with KHMDS (0.5 M in PhMe, 0.24 mL, 0.12 mmol). After 1 h, allyl bromide (0.02 mL, 0.15 mmol) was added and the reaction mixture was stirred at −40 °C for 5 h before work-up to afford a 50 : 50 mixture of **27** : **37**. Purification *via* flash column chromatography (eluent pentane : Et_2O 5 : 1) gave **37** as a colourless oil (19 mg, 27%); $[\alpha]_D^{21}$ +163.6 (*c* 1.0 in $CHCl_3$); mp 40–41 °C (pentane–Et_2O); ν_{max} (film) 1736 (C=O_{endo}), 1691 (C=O_{exo}); δ_H (400 MHz, $CDCl_3$) 0.82 [3H, d, *J* 6.8 Hz, $CH(CH_3)_A(CH_3)_B$], 0.87 [3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$], 1.09 [3H, d, *J* 6.8 Hz, C(2′)CH_3], 1.35 [3H, s, C(6)$(CH_3)_A$], 1.47 [3H, s, C(6)$(CH_3)_B$], 1.88–1.98 [2H, m, C(5)H_2], 2.13–2.20 [1H, m, C(3′)H_A], 2.23–2.31 [1H, m, C$H(CH_3)_2$], 2.56–2.63 [1H, m, C(3′)H_B], 3.66–3.74 [1H, m, C(2′)*H*], 4.44 [1H, app td, *J* 8.7, 5.5 Hz, C(4)*H*], 5.01–5.10 [2H, m, C(5′)H_2], 5.77–5.88 [1H, m, C(4′)*H*]; δ_C (100 MHz, $CDCl_3$) 15.7, 17.0, 18.7, 25.4, 29.8, 30.2, 33.7, 38.1, 38.2, 54.8, 79.6, 116.7, 135.8, 152.7, 177.9; *m*/*z* (ESI^+) 326 ($[M + MeCN + NH_4]^+$, 100%), 290 (50); HRMS (ESI^+) $C_{15}H_{26}NO_3^+$ ($[M + H]^+$) requires 268.1913; found 268.1904.

(4*R*,2′*R*)-3-(4′-*tert*-Butoxy-4′-oxo-2′-benzylbutanoyl)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 38

Following *General procedure 7*, **28** (60 mg, 0.20 mmol) in THF at −78 °C was treated with KHMDS (0.5 M in PhMe, 0.50 mL, 0.25 mmol). After 1 h, *tert*-butyl bromoacetate (0.09 mL, 0.60 mmol) was added. Purification *via* flash column chromatography (eluent pentane : Et_2O 10 : 1) gave **38** as a colourless oil (49 mg, 60%); $[\alpha]_D^{20}$ +108.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1733 (C=O_{endo}), 1692 (C=O_{exo}); δ_H (400 MHz, $CDCl_3$) 0.82–0.86 [6H, m, $CH(CH_3)_2$], 1.36 [3H, s, C(6)$(CH_3)_A$], 1.45 [12H, s, C(6)$(CH_3)_B$ and OC$(CH_3)_3$], 1.70–1.76 [1H, m, C(5)H_A], 1.81–1.91 [1H, m, C(5)H_B], 2.27–2.32 [1H, m, C$H(CH_3)_2$], 2.36 (1H, dd, *J* 15.9, 7.3 Hz, $CH_AH_BCO_2$), 2.70 (1H, dd, *J* 12.9, 6.3 Hz, CH_AH_BPh), 2.78 (1H, dd, *J* 15.9, 6.8 Hz, $CH_AH_BCO_2$), 2.97 (1H, dd, *J* 12.9, 8.6 Hz, CH_AH_BPh), 4.18–4.29 [2H, m, C(4)*H* and C(2′)*H*], 7.12–7.29 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.8, 18.7, 28.1, 28.8, 30.0, 30.1, 33.7, 37.9, 38.0, 44.1, 54.9, 79.9, 80.6, 126.1, 128.4, 129.2, 139.2, 152.6, 170.7, 175.8; *m*/*z* (ESI^+) 476 ($[M + MeCN + NH_4]^+$, 100%), 418 (55); HRMS (ESI^+) $C_{24}H_{36}NO_5^+$ ($[M + H]^+$) requires 418.2593; found 418.2600.

(4*R*,2′*S*)-3-(2′-Methyl-3′-phenylpropanoyl)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 39

Following *General procedure 7*, **28** (50 mg, 0.16 mmol) in THF at −78 °C was treated with KHMDS (0.5 M in PhMe, 0.40 mL, 0.21 mmol). After 1 h, MeI (0.02 mL, 0.33 mmol) was added and the reaction mixture was stirred at −40 °C for 5 h before work-up to give a 15 : 85 mixture of **28** : **39** respectively. Purification *via* flash column chromatography (eluent pentane : Et_2O 10 : 1) gave **39** as a pale yellow oil (20 mg, 38%); $[\alpha]_D^{20}$ +207.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1736 (C=O_{endo}), 1690 (C=O_{exo}); δ_H (400 MHz, $CDCl_3$) 0.80 [3H, d, *J* 6.8 Hz, $CH(CH_3)_A(CH_3)_B$], 0.85 [3H, d, *J* 6.9 Hz, $CH(CH_3)_A(CH_3)_B$], 1.34 [3H, s, C(6)$(CH_3)_A$], 1.36 [3H, d, *J* 6.8 Hz, C(2′)CH_3], 1.57 [3H, s, C(6)$(CH_3)_B$], 1.67 [1H, dd, *J* 13.9, 8.8 Hz, C(5)H_A], 1.79 [1H, dd, *J* 13.9, 8.3 Hz, C(5)H_B], 2.23–2.32 [1H, m, C$H(CH_3)_2$], 2.65 [1H, dd, *J* 13.1, 4.8 Hz, C(3′)H_A], 3.02 [1H, dd, *J* 13.1, 10.1 Hz, C(3′)H_B], 3.66–3.74 [1H, m, C(2′)*H*], 4.21 [1H, app td, *J* 8.4, 6.1 Hz, C(4)*H*], 7.10–7.23 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0, 16.4, 19.0, 25.4, 29.8, 30.3, 33.8, 40.3, 42.6, 54.6, 79.8, 126.2, 128.3, 129.1, 139.6, 155.4, 175.3; *m*/*z* (ESI^+) 376 ([M +

MeCN + NH_4]$^+$, 100%), 340 (95); HRMS (ESI$^+$) $C_{19}H_{28}NO_3^+$ ([M + H]$^+$) requires 318.2069; found 318.2063.

(*R*)-2-Methyl-3-phenylpropanoic acid 40

Following *General procedure 6*, **36** (23 mg, 0.07 mmol) in THF–H_2O (v : v, 3 : 1, 4 mL) at 0 °C, H_2O_2 (0.04 mL, 0.36 mmol), and LiOH (4 mg, 0.15 mmol) gave **17** as a colourless oil (12 mg, quantitative), and **40** as a colourless oil (12 mg, quantitative); $[\alpha]_D^{20}$ −21.6 (*c* 0.8 in $CHCl_3$); lit.[20] $[\alpha]_D^{20}$ −23.1 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.19 [3H, d, *J* 6.9 Hz, C(2)CH_3], 2.65–2.71 [1H, m, C(3)H_A], 2.73–2.82 [1H, m, C(2)*H*], 3.07–3.12 [1H, m, C(3)H_B], 7.19–7.37 (5H, m, *Ph*).

(*R*)-4-(*tert*-Butoxy)-4-oxo-2-benzylbutanoic acid 41

Following *General procedure 6*, **38** (45 mg, 0.11 mmol) in THF–H_2O (v : v, 3 : 1, 4 mL) at 0 °C, H_2O_2 (0.05 mL, 0.54 mmol), and LiOH (5 mg, 0.22 mmol) gave **17** as a colourless oil (18 mg, quantitative), and **41** as a colourless oil (28 mg, quantitative); $[\alpha]_D^{20}$ +7.7 (*c* 1.0 in DCM); lit.[19] $[\alpha]_D^{25}$ +7.1 (*c* 1.0 in DCM); δ_H (400 MHz, $CDCl_3$) 1.42 [9H, s, OC(CH_3)$_3$], 2.35 [1H, dd, *J* 16.8, 4.2 Hz, C(3)H_A], 2.56 [1H, dd, *J* 16.8, 8.7 Hz, C(3)H_B], 2.77 (1H, dd, *J* 15.4, 10.6 Hz, CH_AH$_B$Ph), 3.09–3.14 [2H, m, C(2)*H* and CH$_A$$H_B$Ph], 7.18–7.33 (5H, m, *Ph*).

(*S*)-2-Methyl-3-phenylpropanoic acid 42

Following *General procedure 6*, **39** (20 mg, 0.06 mmol) in THF–H_2O (v : v, 3 : 1, 4 mL) at 0 °C, H_2O_2 (0.03 mL, 0.32 mmol), and LiOH (3 mg, 0.12 mmol) gave **17** as a colourless oil (11 mg, quantitative), and **42** as a colourless oil (10 mg, quantitative); $[\alpha]_D^{25}$ +26.8 (*c* 0.6 in $CHCl_3$); lit.[21] $[\alpha]_D^{25}$ +25.5 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.19 [3H, d, *J* 6.9 Hz, C(2)CH_3], 2.66–2.71 [1H, m, C(3)H_A], 2.74–2.83 [1H, m, C(2)*H*], 3.07–3.12 [1H, m, C(3)H_B], 7.19–7.32 (5H, m, *Ph*).

(4*R*,2′*R*,3′*R*)- and (4*R*,2′*S*,3′*R*)-3-(2′-Methyl-3′-hydroxy-3′-phenylpropanoyl)-4-phenyl-6,6-dimethyl-(1,3)-oxazinan-2-one 44 and 45

Following *General procedure 8*, **26** (75 mg, 0.29 mmol) in DCM (0.2 M) at 0 °C, $TiCl_4$ (0.03 mL, 0.30 mmol), DIPEA (0.05 mL, 0.32 mmol) and benzaldehyde (distilled from CaH_2, 0.03 mL, 0.32 mmol) at −78 °C gave a 25 : 56 : 19 mixture of **26** : **44** : **45** respectively. Purification *via* flash column chromatography (eluent pentane : Et_2O 6 : 1) gave a 76 : 24 mixture of **44** : **45** as a colourless oil (first to elute, 49 mg, 47%) and **44** as a colourless oil (second to elute, 25 mg, 24%).

Data for **44**: $[\alpha]_D^{21}$ +82.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3508 (O–H, br), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.00 [3H, d, *J* 7.0, C(2′)CH_3], 1.44 [3H, s, C(6)(CH_3)$_A$], 1.51 [3H, s, C(6)(CH_3)$_B$], 2.12 [1H, dd, *J* 14.5, 11.0 Hz, C(5)H_A], 2.39 [1H, dd, *J* 14.5, 7.5 Hz, C(5)H_B], 2.98 (1H, br s, O*H*), 4.16 [1H, qd, *J* 7.0, 2.4 Hz, C(2′)*H*], 5.19 [1H, d, *J* 2.4 Hz, C(3′)*H*], 5.32 [1H, dd, *J* 11.0, 7.5 Hz, C(4)*H*], 7.22–7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.2, 24.3, 29.1, 43.1, 45.8, 56.0, 72.7, 80.0, 125.1, 126.1, 127.1, 127.6, 128.0, 129.0, 141.1, 142.0, 151.9, 178.7; *m*/*z* (ESI$^+$) 426 ([M + MeCN + NH_4]$^+$, 100%), 390 (40); HRMS (ESI$^+$) $C_{22}H_{26}NO_4^+$ ([M + H]$^+$) requires 368.1862; found 368.1875.

(4*R*,2′*R*,3′*R*)-3-(2′-Methyl-3′-hydroxy-3′-phenylpropanoyl)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 46

Following *General procedure 8*, **27** (72 mg, 0.32 mmol) in DCM (0.3 M) at 0 °C, $TiCl_4$ (0.04 mL, 0.33 mmol), DIPEA (0.06 mL, 0.35 mmol) and benzaldehyde (distilled from CaH_2, 0.04 mL, 0.35 mmol) at −78 °C gave a 27 : 73 mixture of **27** : **46** respectively. Purification *via* flash column chromatography (eluent pentane : Et_2O 6 : 1) gave **46** as a white solid (67 mg, 64%); mp 93–94 °C; $[\alpha]_D^{21}$ +148.3 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3492 (O–H), 1735 (C=O), 1693 (C=O); δ_H (400 MHz, $CDCl_3$) 0.83 [3H, d, *J* 6.8 Hz, CH(CH_3)$_A$(CH$_3$)$_B$], 0.88 [3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(CH_3)$_B$], 1.01 [3H, d, *J* 7.0 Hz, C(2′)CH_3], 1.36 [3H, s, C(6)(CH_3)$_A$], 1.48 [3H, s, C(6)(CH_3)$_B$], 1.90–2.00 [2H, m, C(5)H_2], 2.26–2.34 [1H, m, C*H*(CH$_3$)$_2$], 3.44 (1H, br s, O*H*), 4.04 [1H, qd, *J* 7.0 Hz, 2.9, C(2′)*H*], 4.43 [1H, app td, *J* 8.7, 5.5 Hz, C(4)*H*], 5.28 [1H, d, *J* 2.9 Hz, C(3′)*H*], 7.22–7.45 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.7, 15.6, 18.6, 25.4, 29.8, 30.4, 33.6, 44.8, 55.1, 73.2, 80.1, 126.2, 127.2, 128.0, 141.3, 152.8, 178.3; *m*/*z* (ESI$^+$) 356 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{28}NO_4^+$ ([M + H]$^+$) requires 334.2018; found 334.2026.

X-Ray crystal structure determination for 46. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[32]

X-Ray crystal structure data for **46** [$C_{19}H_{27}NO_4$]: $M = 333.42$, monoclinic, space group *C*121, $a = 17.9151(5)$, $b = 9.5994(3)$, $c = 12.1722(4)$ Å, $\beta = 119.6642(13)°$, $V = 1819.0(1)$ Å^3, $Z = 4$, $\mu = 0.085$ mm^{-1}, colourless block, crystal dimensions = 0.1 × 0.1 × 0.1 mm. A total of 2192 unique reflections were measured for $5 < \theta < 27$ and 1765 reflections were used in the refinement. The final parameters were $wR_2 = 0.037$ and $R_1 = 0.032$ [$I > 2.0\sigma(I)$].

CCDC reference number 280053. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604073j.

(4*R*,2′*R*,3′*R*)-3-[2′-Methyl-3′-hydroxy-3′-(*p*-methoxyphenyl)-propanoyl]-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 47

Following *General procedure 8*, **27** (75 mg, 0.33 mmol) in DCM (0.3 M) at 0 °C, $TiCl_4$ (0.04 mL, 0.35 mmol), DIPEA (0.06 mL, 0.36 mmol) and *p*-methoxybenzaldehyde (distilled from CaH_2, 0.04 mL, 0.36 mmol) at −78 °C gave a 41 : 59 mixture of **27** : **47** respectively. Purification *via* flash column chromatography (eluent pentane : Et_2O 3 : 1) gave **47** as an orange oil (65 mg, 54%); $[\alpha]_D^{20}$ +110.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3446 (O–H, br), 1733 (C=O), 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 0.83 [3H, d, *J* 6.8 Hz, CH(CH_3)$_A$(CH$_3$)$_B$], 0.88 [3H, d, *J* 7.0 Hz, CH(CH$_3$)$_A$(CH_3)$_B$], 1.02 [3H, d, *J* 7.0 Hz, C(2′)CH_3], 1.37 [3H, s, C(6)(CH_3)$_A$], 1.49 [3H, s, C(6)(CH_3)$_B$], 1.96 [2H, app dd, *J* 8.8, 3.3 Hz, C(5)H_2], 2.26–2.34 [1H, m, C*H*(CH$_3$)$_2$], 3.36 (1H, br s, O*H*), 3.81 (3H, s, OCH_3), 4.01 [1H, qd, *J* 7.0, 3.1 Hz, C(2′)*H*], 4.44 [1H, app td, *J* 8.8, 5.4 Hz, C(4)*H*], 5.22 [1H, d, *J* 3.1 Hz, C(3′)*H*], 6.88 (2H, app d, *J* 8.8 Hz, *Ar*), 7.37 (2H, app d, *J* 8.4 Hz, *Ar*); δ_C (100 MHz, $CDCl_3$) 10.8, 15.5, 18.5, 25.3, 29.7, 30.3, 33.6, 44.8, 54.9, 55.1, 72.9, 79.9, 113.3, 127.3, 133.4, 152.7, 158.7, 178.2; *m*/*z* (ESI$^+$) 422 ([M + MeCN +

$NH_4]^+$, 100%), 386 (70); HRMS (ESI^+) $C_{20}H_{29}NNaO_5^+$ ([M + Na]$^+$) requires 386.1943; found 386.1946.

(4*R*,2′*R*,3′*R*)-3-(2′-Methyl-3′-hydroxy-3′-(*p*-nitrophenyl)-propanoyl)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 48

Following *General procedure 8*, **27** (70 mg, 0.31 mmol) in DCM (0.3 M) at 0 °C, $TiCl_4$ (0.04 mL, 0.32 mmol), DIPEA (0.06 mL, 0.34 mmol) and *p*-nitrobenzaldehyde (distilled from CaH_2, 51 mg, 0.34 mmol) at −78 °C gave a 57 : 43 mixture of **27** : **48** respectively. Purification *via* flash column chromatography (eluent pentane : Et_2O 3 : 1) gave **48** as a yellow oil (23 mg, 20%); $[\alpha]_D^{20}$ +123.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3453 (O–H), 1732 (C=O), 1696 (C=O); δ_H (400 MHz, $CDCl_3$) 0.87 [3H, d, *J* 6.8 Hz, $CH(CH_3)_A(CH_3)_B$], 0.92 [3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$], 0.96 [3H, d, *J* 7.1 Hz, C(2′)CH_3], 1.38 [3H, s, C(6)$(CH_3)_A$], 1.50 [3H, s, C(6)$(CH_3)_B$], 1.94–2.04 [2H, m, C(5)H_2], 2.32–2.39 [1H, m, $CH(CH_3)_2$], 3.73 (1H, br s, O*H*), 4.03 [1H, qd, *J* 7.0, 2.5 Hz, C(2′)*H*], 4.43 [1H, app td, *J* 8.7, 5.5 Hz, C(4)*H*], 5.38 [1H, d, *J* 2.5 Hz, C(3′)*H*], 7.64 (2H, d, *J* 8.8 Hz, *Ar*), 8.21 (2H, d, *J* 8.8 Hz, *Ar*); δ_C (100 MHz, $CDCl_3$) 10.4, 15.6, 18.7, 25.4, 29.8, 30.4, 33.6, 44.4, 55.4, 72.5, 80.5, 123.3, 127.1, 147.2, 148.7, 153.0, 177.7; *m*/*z* (ESI^+) 401 ([M + Na]$^+$, 60%); HRMS (ESI^+) $C_{19}H_{27}N_2O_6^+$ ([M + H]$^+$) requires 379.1869; found 379.1873.

(4*R*,2′*R*,3′*S*)-3-(2′-Methyl-3′-hydroxypentanoyl)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 49

Following *General procedure 8*, **27** (52 mg, 0.23 mmol) in DCM (0.2 M) at 0 °C, $TiCl_4$ (0.03 mL, 0.24 mmol), DIPEA (0.04 mL, 0.25 mmol) and propanal (distilled from CaH_2, 0.02 mL, 0.25 mmol) at −78 °C gave a 37 : 63 mixture of **27** : **49** respectively. Purification *via* flash column chromatography (eluent pentane : Et_2O 3 : 1) gave **49** as a colourless solid (38 mg, 58%); mp 65–67 °C; $[\alpha]_D^{24}$ +156.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3467 (O–H), 1736 (C=O), 1686 (C=O); δ_H (400 MHz, $CDCl_3$) 0.84 [3H, d, *J* 6.8 Hz, $CH(CH_3)_A(CH_3)_B$], 0.89 [3H, d, *J* 7.0 Hz, $CH(CH_3)_A(CH_3)_B$], 0.99 [3H, t, *J* 7.4 Hz, C(5′)H_3], 1.10 [3H, d, *J* 7.1 Hz, C(2′)CH_3], 1.37 [3H, s, C(6)$(CH_3)_A$], 1.40–1.46 [1H, m, C(4′)H_A], 1.48 [3H, s, C(6)$(CH_3)_B$], 1.49–1.60 [1H, m, C(4′)H_B], 1.90–2.00 [2H, m, C(5)H_2], 2.26–2.37 [1H, m, $CH(CH_3)_2$], 3.78 [1H, qd, *J* 7.1, 2.6 Hz, C(2′)*H*], 3.91–3.95 [1H, m, C(3′)*H*], 4.41 [1H, app td, *J* 8.7, 5.5 Hz, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 10.5, 10.8, 15.7, 18.7, 25.4, 26.5, 29.8, 30.4, 33.7, 42.2, 55.0, 73.2, 80.1, 153.0, 178.8; *m*/*z* (ESI^+) 344 ([M + MeCN + NH_4]$^+$, 100%); HRMS (ESI^+) $C_{15}H_{28}NO_4^+$ ([M + H]$^+$) requires 286.2018; found 286.2013.

(4*R*,2′*R*,3′*S*)-3-(2′,4′-Dimethyl-3′-hydroxypentanoyl)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 50

Following *General procedure 8*, **27** (50 mg, 0.22 mmol) in DCM (0.2 M) at 0 °C, $TiCl_4$ (0.03 mL, 0.23 mmol), DIPEA (0.04 mL, 0.24 mmol) and *iso*-butyraldehyde (distilled from CaH_2, 0.02 mL, 0.24 mmol) at −78 °C gave a 41 : 59 mixture of **27** : **50** respectively. Purification *via* flash column chromatography (eluent pentane : Et_2O 3 : 1) gave **50** as a colourless solid (30 mg, 45%); mp 85–86 °C; $[\alpha]_D^{24}$ +136.4 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3458 (O–H), 1738 (C=O), 1681 (C=O); δ_H (400 MHz, $CDCl_3$) 0.85 [3H, d, *J* 6.8 Hz, C(4)$CH(CH_3)_A(CH_3)_B$], 0.89 [3H, d, *J* 7.0 Hz, C(4)$CH(CH_3)_A(CH_3)_B$], 0.91 [3H, d, *J* 6.8 Hz, C(4′)$(CH_3)_A(CH_3)_B$], 1.06 [3H, d, *J* 6.5 Hz, C(4′)$(CH_3)_A(CH_3)_B$], 1.10 [3H, d, *J* 7.1 Hz, C(2′)CH_3], 1.38 [3H, s, C(6)$(CH_3)_A$], 1.48 [3H, s, C(6)$(CH_3)_B$], 1.67–1.75 [1H, m, C(4′)*H*], 1.91–2.01 [2H, m, C(5)H_2], 2.27–2.36 [1H, m, C(4)$CH(CH_3)_2$], 3.65 [1H, dd, *J* 8.8, 2.2 Hz, C(3′)*H*], 3.97 [1H, qd, *J* 7.1, 2.2 Hz, C(2′)*H*], 4.42 [1H, app td, *J* 8.7, 5.5 Hz, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 10.2, 15.6, 18.6, 18.7, 19.4, 25.4, 29.7, 30.3, 30.7, 33.6, 39.9, 55.0, 76.5, 79.9, 152.6, 179.4; *m*/*z* (ESI^+) 322 ([M + Na]$^+$, 100%); HRMS (ESI^+) $C_{16}H_{30}NO_4^+$ ([M + H]$^+$) requires 300.2175; found 300.2170.

X-Ray crystal structure determination for 50. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[32]

X-Ray crystal structure data for **50** [$C_{16}H_{29}NO_4$]: $M = 299.41$, triclinic, space group *P*1, $a = 8.8735(2)$, $b = 9.7635(3)$, $c = 11.2480(3)$ Å, $\alpha = 89.749(2)$, $\beta = 79.982(2)$, $\gamma = 64.9723(11)°$, $V = 866.90(4)$ Å^3, $Z = 2$, $\mu = 0.081$ mm^{-1}, colourless plate, crystal dimensions = 0.05 × 0.05 × 0.1 mm. A total of 3878 unique reflections were measured for $5 < \theta < 27$ and 3145 reflections were used in the refinement. The final parameters were $wR_2 = 0.038$ and $R_1 = 0.037$ [$I > 2.0\sigma(I)$].

CCDC reference number 280054. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604073j.

(4*R*,2′*R*,3′*R*)-3-(2′,4′,4′-Trimethyl-3′-hydroxypentanoyl)-4-*iso*-propyl-6,6-dimethyl-(1,3)-oxazinan-2-one 51

Following *General procedure 8*, **27** (60 mg, 0.26 mmol) in DCM (0.3 M) at 0 °C, $TiCl_4$ (0.03 mL, 0.28 mmol), DIPEA (0.05 mL, 0.29 mmol), and pivalaldehyde (distilled from CaH_2, 0.03 mL, 0.29 mmol) at −78 °C gave an 85 : 15 mixture of **27** : **51** respectively. Purification *via* flash column chromatography (eluent pentane: Et_2O 4:1) gave **51** as a colourless oil (10 mg, 12%); $[\alpha]_D^{18}$ +131.6 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 3521 (O–H), 1735 (C=O), 1689 (C=O); δ_H (400 MHz, $CDCl_3$) 0.84 [3H, d, *J* 6.8 Hz, $CH(CH_3)_A(CH_3)_B$], 0.88 [3H, d, *J* 7.1 Hz, $CH(CH_3)_A(CH_3)_B$], 0.99 [9H, s, C$(CH_3)_3$], 1.15 [3H, d, *J* 7.1 Hz, C(2′)CH_3], 1.38 [3H, s, C(6)$(CH_3)_A$], 1.48 [3H, s, C(6)$(CH_3)_B$], 1.93–1.96 [2H, m, C(5)H_2], 2.28–2.36 [1H, m, $CH(CH_3)_2$], 3.75 [1H, d, *J* 3.3 Hz, C(3′)*H*], 4.11 [1H, qd, *J* 7.1, 3.3 Hz, C(2′)*H*], 4.39 [1H, app td, *J* 8.8, 5.4 Hz, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 13.3, 15.6, 18.7, 25.4, 26.8, 29.8, 30.2, 33.6, 39.1, 55.1, 77.9, 79.9, 80.0, 153.1, 173.5; *m*/*z* (ESI^+) 372 ([M + MeCN + NH_4]$^+$, 100%), 336 (60); HRMS (ESI^+) $C_{17}H_{32}NO_4^+$ ([M + H]$^+$) requires 314.2331; found 314.2331.

(2*R*,3*R*)-2-Methyl-3-hydroxy-3-phenylpropanoic acid 53

Following *General procedure 6*, **46** (60 mg, 0.18 mmol) in THF–H_2O (v : v, 3 : 1, 4 mL) at 0 °C, H_2O_2 (0.09 mL, 0.90 mmol), and LiOH (9 mg, 0.36 mmol) gave **17** as a colourless oil (31 mg, quantitative), and **53** as a colourless oil (32 mg, quantitative); $[\alpha]_D^{22}$ +28.5 (*c* 1.0 in $CHCl_3$); lit.[28] $[\alpha]_D^{20}$ +28.5 (*c* 1.2 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.16 [3H, d, *J* 7.2 Hz, C(2)CH_3], 2.84–2.90 [1H, m, C(2)*H*], 5.19 [1H, d, *J* 3.9 Hz, C(3)*H*], 7.29–7.38 (5H, m, *Ph*).

(2*R*,3*R*)-2-Methyl-3-hydroxy-3-(*p*-methoxyphenyl)propanoic acid 54

Following *General procedure 6*, **47** (60 mg, 0.17 mmol) in THF–H_2O (v : v, 3 : 1, 4 mL) at 0 °C, H_2O_2 (0.08 mL, 0.83 mmol), and LiOH (8 mg, 0.33 mmol) gave **17** as a colourless oil (28 mg, quantitative), and **54** as a colourless oil (35 mg, quantitative);[33] $[a]_D^{22}$ +19.2 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.16 [3H, d, *J* 7.2 Hz, C(2)CH_3], 2.78–2.84 [1H, m, C(2)*H*], 3.81 (3H, s, OCH_3), 5.10 [1H, d, *J* 4.2 Hz, C(3)*H*], 6.89 (2H, d, *J* 8.6 Hz, *Ar*), 7.28 (2H, d, *J* 8.5 Hz, *Ar*).

(2*R*,3*R*)-2-Methyl-3-hydroxy-3-(*p*-nitrophenyl)propanoic acid 55

Following *General procedure 6*, **48** (20 mg, 0.05 mmol) in THF–H_2O (v : v, 3 : 1, 4 mL) at 0 °C, H_2O_2 (0.03 mL, 0.26 mmol), and LiOH (3 mg, 0.10 mmol) gave **17** as a colourless oil (9 mg, quantitative), and **55** as a colourless oil (12 mg, quantitative);[34] $[a]_D^{22}$ +18.3 (*c* 0.6 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.13 [3H, d, *J* 7.2 Hz, C(2)CH_3], 2.84–2.90 [1H, m, C(2)*H*], 5.33 [1H, d, *J* 2.9 Hz, C(3)*H*], 7.56 (2H, d, *J* 8.6 Hz, *Ar*), 8.24 (2H, d, *J* 8.5 Hz, *Ar*).

(2*R*,3*S*)-2-Methyl-3-hydroxypentanoic acid 56

Following *General procedure 6*, **49** (35 mg, 0.11 mmol) in THF–H_2O (v : v, 3 : 1, 4 mL) at 0 °C, H_2O_2 (0.06 mL, 0.61 mmol), and LiOH (6 mg, 0.25 mmol) gave **17** as a colourless oil (21 mg, quantitative), and **56** as a colourless oil (15 mg, 94%); $[a]_D^{22}$ −4.0 (*c* 0.8 in $CHCl_3$); lit.[29] $[a]_D^{23}$ −4.1 (*c* 1.7 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.99 [3H, t, *J* 7.4 Hz, C(5)H_3], 1.21 [3H, d, *J* 7.2 Hz, C(2)CH_3], 1.44–1.60 [2H, m, C(4)H_2], 2.61–2.65 [1H, m, C(2)*H*], 3.87–3.91 [1H, m, C(3)*H*].

(2*R*,3*S*)-2,4-Dimethyl-3-hydroxypentanoic acid 57

Following *General procedure 6*, **50** (30 mg, 0.10 mmol) in THF–H_2O (v : v, 3 : 1, 4 mL) at 0 °C, H_2O_2 (0.05 mL, 0.50 mmol), and LiOH (5 mg, 0.20 mmol) gave **17** as a colourless oil (17 mg, quantitative), and **57** as a colourless oil (14 mg, quantitative); $[a]_D^{22}$ +11.3 (*c* 0.7 in $CHCl_3$); lit.[30] $[a]_D^{20}$ +10.5 (*c* 0.1 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 [3H, d, *J* 6.7 Hz, C(4)(CH_3)$_A$], 1.03 [3H, d, *J* 6.5 Hz, C(4)(CH_3)$_B$], 1.22 [3H, d, *J* 7.1 Hz, C(2)CH_3], 1.69–1.77 [1H, m, C(4)*H*], 2.70–2.76 [1H, m, C(2)*H*], 3.64 [1H, dd, *J* 8.3, 3.3, C(3)*H*].

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References and notes

1 For reviews, see: D. A. Evans, *Aldrichimica Acta*, 1982, **15**, 2; D. J. Ager, I. Prakash and D. R. Schaad, *Aldrichimica Acta*, 1997, **30**, 3; D. J. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835; M. P. Sibi, *Aldrichimica Acta*, 1999, **32**, 93.
2 D. A. Evans and J. Bartroli, *Tetrahedron Lett.*, 1982, **23**, 807.
3 D. A. Evans, T. C. Britton and J. A. Ellman, *Tetrahedron Lett.*, 1987, **28**, 6141; S. G. Davies, D. J. Dixon, G. J.-M. Doisneau, J. C. Prodger and H. J. Sanganee, *Tetrahedron: Asymmetry*, 2002, **13**, 647.
4 S. G. Davies and H. J. Sanganee, *Tetrahedron: Asymmetry*, 1995, **6**, 671.
5 K. Alexander, S. Cook, C. L. Gibson and A. R. Kennedy, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1538; C. L. Gibson, K. Gillon and S. Cook, *Tetrahedron Lett.*, 1998, **39**, 6733.
6 (*a*) S. D. Bull, S. G. Davies, S. Jones and H. J. Sanganee, *J. Chem. Soc., Perkin Trans. 1*, 1999, 387; (*b*) S. D. Bull, S. G. Davies, R. L. Nicholson, H. J. Sanganee and A. D. Smith, *Org. Biomol. Chem.*, 2003, **1**, 2886 and refs. cited therein.
7 S. D. Bull, S. G. Davies, M.-S. Key, R. L. Nicholson and E. D. Savory, *Chem. Commun.*, 2000, 1721.
8 G. J. Baird and S. G. Davies, *J. Organomet. Chem.*, 1983, **248**, Cl–C3; S. G. Davies, *Aldrichimica Acta*, 1990, **23**, 31; S. G. Davies and A. A. Mortlock, *Tetrahedron Lett.*, 1991, **32**, 4787; S. G. Davies, G. J.-M. Doisneau, J. C. Prodger and H. J. Sanganee, *Tetrahedron Lett.*, 1994, **35**, 2369.
9 For another oxazinanone chiral auxiliary, see: K. H. Ahn, S. Lee and A. Lim, *J. Org. Chem.*, 1992, **57**, 5065.
10 For a review, see: S. G. Davies, A. D. Smith and P. D. Price, *Tetrahedron: Asymmetry*, 2005, **16**, 2833. For selected representative examples, see: S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1991, **2**, 183; S. G. Davies, O. Ichihara and I. A. S. Walters, *Synlett*, 1993, 461; S. G. Davies and D. Dixon, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2629; S. D. Bull, S. G. Davies and A. D. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2931; S. D. Bull, S. G. Davies and A. D. Smith, *Tetrahedron: Asymmetry*, 2001, **12**, 2191; S. D. Bull, S. G. Davies, P. M. Roberts, E. D. Savory and A. D. Smith, *Tetrahedron*, 2002, **58**, 4629; A. Chippindale, S. G. Davies, K. Iwamoto, R. M. Parkin, C. A. P. Smethurst, A. D. Smith and H. Rodriguez-Solla, *Tetrahedron*, 2003, **59**, 3253; M. E. Bunnage, A. J. Burke, S. G. Davies, N. L. Millican, R. L. Nicholson, P. M. Roberts and A. D. Smith, *Org. Biomol. Chem.*, 2003, **1**, 3708; S. G. Davies, R. L. Nicholson, P. D. Price, P. M. Roberts and A. D. Smith, *Synlett*, 2004, 901; A. J. Burke, S. G. Davies, A. C. Garner, T. D. McCarthy, P. M. Roberts, A. D. Smith, H. Rodriguez-Solla and R. J. Vickers, *Org. Biomol. Chem.*, 2004, **2**, 1387; S. G. Davies, G. Hermann, A. D. Smith and M. J. Sweet, *Chem. Commun.*, 2004, 1128; S. G. Davies, A. C. Garner, M. J. C. Long, A. D. Smith, M. J. Sweet and J. M. Withey, *Org. Biomol. Chem.*, 2004, **2**, 3355; S. G. Davies, A. C. Garner, M. J. C. Long, R. M. Morrison, P. M. Roberts, E. D. Savory, A. D. Smith, M. J. Sweet and J. M. Withey, *Org. Biomol. Chem.*, 2005, **3**, 2762.
11 S. D. Bull, S. G. Davies, S. Jones, M. E. C. Polywka, R. S. Prasad and H. J. Sanganee, *Synlett*, 1998, 519.
12 T. Imamoto, T. Kusumoto, Y. Tawarayama, T. Mita, Y. Hatanaka and M. Yokoyama, *J. Org. Chem.*, 1984, **49**, 3904; T. Imamoto, N. Takiyama and K. Nakamura, *Tetrahedron Lett.*, 1985, **26**, 4763; T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392; T. Imamoto, *Pure Appl. Chem.*, 1990, **62**, 747.
13 J. R. Gage and D. A. Evans, *Org. Synth.*, 1990, **68**, 83; S. S. Canan Koch and A. R. Chamberlin, *J. Org. Chem.*, 1993, **58**, 2725.
14 D. A. Evans and J. R. Gage, *J. Org. Chem.*, 1992, **57**, 1958; D. A. Evans, J. R. Gage and J. L. Leighton, *J. Am. Chem. Soc.*, 1992, **114**, 9434; G.-J. Ho and D. J. Mathre, *J. Org. Chem.*, 1995, **60**, 2271; D. J. Ager, D. R. Allen, D. E. Froen and D. R. Schaad, *Synthesis*, 1996, 1283.
15 (*a*) D. M. Casper, D. Kieser, J. R. Blackburn and S. R. Hitchcock, *Synth. Commun.*, 2004, **34**, 835; (*b*) D. M. Casper, J. R. Burgeson, J. M. Esken, G. M. Ferrence and S. R. Hitchcock, *Org. Lett.*, 2002, **4**, 3739; (*c*) D. M. Casper and S. R. Hitchcock, *Tetrahedron: Asymmetry*, 2003, **14**, 517.
16 For initial observations of the ketene decomposition pathway in oxazolidinone systems, see: (*a*) D. A. Evans, M. C. Ennis and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737 and refs. cited therein. For other selected examples, see: (*b*) A. Struder, T. Hintermann and D. Seebach, *Helv. Chim. Acta*, 1995, **78**, 1185; (*c*) D. M. Casper, J. R. Blackburn, C. D. Maroules, T. Brady, J. M. Esken, G. M. Ferrence, J. M. Standard and S. M. Hitchcock, *J. Org. Chem.*, 2002, **67**, 8871.
17 As indicated by peak integration of the 400 MHz ^{1}H NMR spectrum of the crude reaction product.
18 To determine unambiguously the identity of **33**, an authentic sample was prepared by lithiation of the parent auxiliary **16** by treatment with LiHMDS and alkylation with *tert*-butyl bromoacetate, giving **33** in quantitative yield.
19 D. A. Evans, L. D. Wu, J. J. M. Wiener, J. S. Johnson, D. H. B. Ripin and J. S. Tedrow, *J. Org. Chem.*, 1999, **64**, 6411.
20 E. Tyrell, M. W. H. Tsang, G. A. Skinner and J. Fawcett, *Tetrahedron*, 1996, **52**, 9841.
21 W. Oppolzer, R. Moretti and S. Thomi, *Tetrahedron Lett.*, 1989, **30**, 5603.

22 E. Juaristi, A. K. Beck, J. Hansen, T. Matt, T. Mukhopadhyay, M. Simson and D. Seebach, *Synthesis*, 1993, 1271 and refs. cited therein.
23 D. A. Evans, J. S. Clark, R. Metternich, V. J. Novack and G. S. Sheppard, *J. Am. Chem. Soc.*, 1990, **112**, 866; D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark and M. T. Bilodeau, *J. Am. Chem. Soc.*, 1990, **112**, 8215.
24 Using this assumption, $J_{\alpha,\beta}$ is usually in the range of 2–6 Hz for *syn*-aldol products, and 7–10 Hz for *anti*-aldol products. For leading references, see: M. Stiles, R. W. Winkler, Y.-L. Chang and L. Traynor, *J. Am. Chem. Soc.*, 1964, **86**, 3337; H. O. House, D. S. Crumrine, A. Y. Teranishi and H. D. Olmstead, *J. Am. Chem. Soc.*, 1973, **95**, 3310; C. H. Heathcock, M. C. Pirrung and J. E. Sohn, *J. Org. Chem.*, 1980, **45**, 1066; C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn and J. Lampe, *J. Org. Chem.*, 1979, **44**, 4294.
25 C. R. Harrison, *Tetrahedron Lett.*, 1987, **28**, 4135.
26 M. T. Crimmins, B. W. King, E. A. Tabet and K. Chaundhary, *J. Org. Chem.*, 2001, **66**, 894.
27 B. M. Kim, S. F. Williams and S. Masamune, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 2, pp. 239–275.
28 N. A. Van Draanen, S. Arseniyadis, M. T. Crimmins and C. H. Heathcock, *J. Org. Chem.*, 1991, **56**, 2506.
29 T. Katsuki and M. Yamaguchi, *Tetrahedron Lett.*, 1985, **26**, 5807.
30 D. A. Evans and T. R. Taber, *Tetrahedron Lett.*, 1980, **21**, 4675.
31 A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, 1996, **15**, 1518.
32 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, *CRYSTALS*, Chemical Crystallography Laboratory, Oxford, UK, 2003, Issue 12.
33 Compound **54** has been reported previously by P. Galatsis, J. J. Manwell and J. M. Blackwell, *Can. J. Chem.*, 1994, **72**, 1656, although no optical rotation data are available for comparison.
34 Compound **55** has been reported previously by M. Tanaka, O. Oota, H. Hiramatsu and K. Fujiwara, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2473, although no optical rotation data are available for comparison.

