New Routes to Chiral Evans Auxiliaries by Enzymatic Desymmetrisation and Resolution Strategies

Claudia Neri, Jonathan M. J. Williams*

Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, UK
Fax: +44-(0)1225–386231, e-mail: j.m.j.williams@bath.ac.uk

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Abstract: This paper describes how enantiomerically enriched Evans auxiliaries can be successfully prepared by either an enzymatic desymmetrisation strategy or an asymmetric synthesis using racemic auxiliaries and an enzymatic resolution. Desymmetrisation of *N*-Boc-protected serinol has been achieved in good yield and high enantiomeric excess using porcine pancreas lipase. This has been exploited in different ways to prepare enantiomerically enriched (4*R*)- and (4*S*)-substituted 2-oxazolidinones. In another approach to asymmetric synthesis, starting from a racemic Evans auxiliary, by means of a diastereoselective aldol reaction coupled with a lipase-catalysed resolution, we achieved the preparation of enantiomerically enriched β-hydroxy acids and enantiomerically enriched 2-oxazolidinones.

Keywords: acylation; aldol reaction; diastereoselectivity; enzymatic desymmetrisation; enzymatic resolution; racemic auxiliaries

Introduction

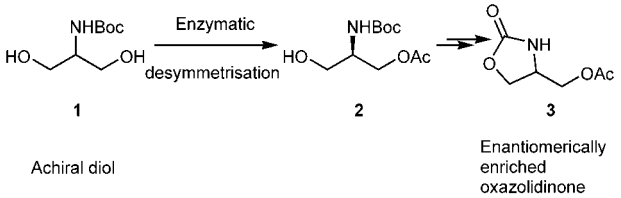
The introduction of enantiomerically pure 2-oxazolidinones (Evans chiral auxiliaries) can be considered a milestone in the history of asymmetric synthesis using covalently bound auxiliaries.[1] The ability to induce high stereocontrol in asymmetric synthesis is in practice the main reason why a specified chiral auxiliary is chosen to achieve asymmetric synthesis. Evans auxiliaries fulfil all the criteria required from a good chiral auxiliary. Nevertheless, the choice of Evans auxiliary can be limited by the availability of an appropriate enantiomerically pure amino acid or alcohol. Aside from the (*S*)-substituted 2-oxazolidinones readily available from naturally occurring α-amino acids such as L-valine and L-phenylalanine,[2] their configurational antipodes are less accessible. The sterically constrained, designed chiral 2-oxazolidinones, such as 4,5-disubstituted-2-oxazolidinones conformationally fixed by bicyclo[2.2.1] and bicyclo[2.2.2] systems,[3] are also less easily available. That explains why since 1981 much work has been published about the use of novel Evans-type chiral auxiliaries, chemically designed and from sources other than natural α-amino acids.[4–8]

We disclose herein that enantiomerically enriched Evans auxiliaries can be obtained from sources other than natural α-amino acid by two simple approaches to asymmetric synthesis, which involve the use of enzymes in desymmetrisation and resolution processes.

Desymmetrisation of *meso*-configured or otherwise prochiral substrates to yield enantiomerically enriched products is a powerful synthetic tool. The advantage of desymmetrisation over conventional kinetic resolution reactions is the potential ability to achieve high enantiomeric excess even at 100% conversion.[9] Desymmetrisation of achiral diols using enzymes is a well known process for the formation of enantiomerically enriched mono-esters.[10–13] Our overall desymmetrisation strategy involved the use of *N*-Boc-protected serinol **1** to give a mono-acetate **2**, followed by appropriate chemical transformation to afford enantiomerically enriched oxazolidinones (e.g., compound **3**) (Scheme 1).[14]

In another approach to auxiliary-based asymmetric synthesis, we decided to attempt an unusual strategy using a racemic aldol adduct from a diastereoselective aldol reaction and an enzymatic resolution. In order to achieve this goal, the auxiliary has to relay its stereochemistry to the substrate, which can then be resolved by the enzyme (Scheme 2).[15]

We envisaged that through the application of this methodology we could obtain both enantiomerically



Scheme 1. General approach to preparation of oxazolidinones by enzymatic desymmetrisation.

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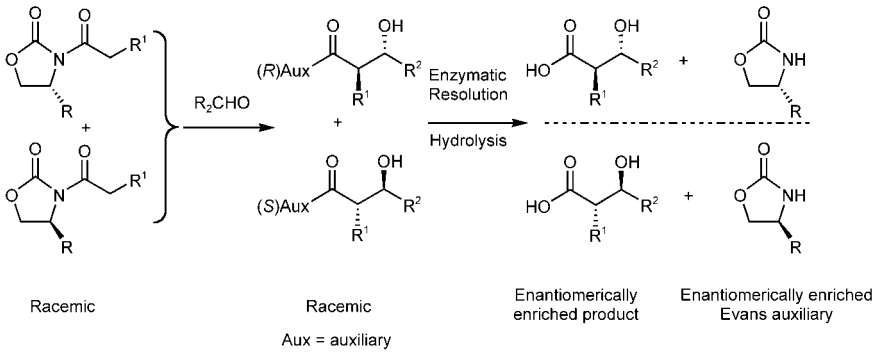


Scheme 2. General approach to asymmetric synthesis with a racemic auxiliary.

enriched auxiliary and enantiomerically enriched product.

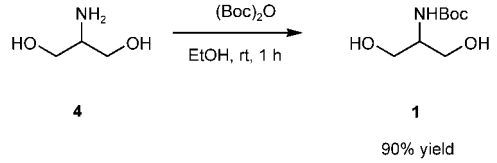
Results and Discussion

Preparation of Enantiomerically Enriched 2-Oxazolidinones by Enzymatic Desymmetrisation

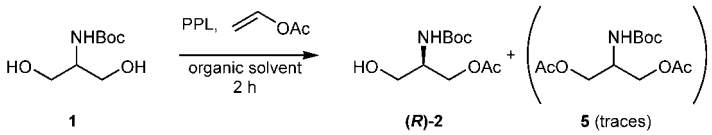
Serinol derivatives have only received limited attention in desymmetrisation reactions. A literature search reveals few examples in which serinol has been used as starting material in desymmetrisation-based syntheses.[16–18] We decided to focus our attention upon the enzymatic desymmetrisation of serinol as a potential precursor of enantiomerically enriched oxazolidinones.

Desymmetrisation of serinol (1,3-dihydroxy-2-aminopropane) required previous protection of the amino group to avoid *N*-acylation.[19] Boc-protection of achiral serinol **4** was achieved in 90% yield by treatment of serinol with Boc anhydride (Scheme 3).[20]

The desymmetrisation of *N*-Boc-serinol was achieved by the selective mono-acetylation using PPL (porcine pancreas lipase) and vinyl acetate as the acylating agent, in organic solvent (Scheme 4). A small amount of di-acetylated material was also observed, presumably formed from the unwanted enantiomer of mono-acetylated product, thereby providing a self-correcting process.[21]



Scheme 3. Boc-protection of achiral serinol **4**.



Scheme 4. Desymmetrisation of *N*-Boc-serinol by PPL.

Only one enantiomer of the mono-acetylated product was detected by chiral HPLC.

The effects of solvent and temperature variations on the conversion and selectivity of the acylation reaction were investigated. We first examined the effect of solvent on the acylation of protected serinol **1** at 30 °C (Table 1).

As can be seen (entries 1 and 3), striking differences in reactivity were found, with vinyl acetate and a mixture of THF/*n*-hexane being the best reaction solvents. The increase in conversion was particularly evident when compared with solvents such as cyclohexane, toluene and acetonitrile (entries 4, 5, 7).

The reaction in vinyl acetate was examined at different reaction temperatures. In Table 2 the relative results after 2 h are displayed.

Increasing the temperature (entries 2 and 3) had a noticeable effect upon the amount of di-acetylated product, which appears after only 2 h.

Although PPL is widely used for the resolution of prochiral diols,[23] we also examined other enzymes in our desymmetrisation strategy. Lipase from *Candida antarctica* type B (CAL B), lipase from *Candida cylindracea* (CCL), lipase from *Pseudomonas cepacia* (PCL) and from *Pseudomonas fluorescens* (PFL) immobilized on Sol-Gel-AK, lipase from *Aspergillus niger* (ANL) were tested for their activity and selectivity in the acylation reaction illustrated in Scheme 5. Again vinyl acetate was used as both the acylating agent and solvent at 30 °C (Table 3).

The conversion after 2 h was greater than 96% when PPL, CAL B, PCL and PFL (entries 1, 2, 4, 6) were used as catalysts. The best selectivity was observed with PPL.

No selectivity was observed with CAL B. The di-acetylated product only was formed in reactions in both vinyl acetate and THF/*n*-hexane media (Table 3, entry 2).

In summary, the maximum conversion (> 99%, after 2 hours) and selectivity (> 99% ee and >99% mono-/di-acetylated product) were obtained when the reaction was performed in vinyl acetate at 30 °C, using PPL as catalyst. The isolated yield of product was 69%, with some material lost on work-up.

Table 1. Influence of solvent on conversion, ee and mono-/di-acetylated product ratio.[a, b]

Entry	Solvent	Conversion [%]	ee [%]	Mono-/ di-acetylated ratio[c]
1	THF/*n*-hexane 1:1	96	>99	87
2	*i*-Pr_2O	42	>99	>99
3	Vinyl acetate	>99	>99	>99
4	Cyclohexane	28	>99	>99
5	Toluene	29	>99	>99
6	Acetone	72	>99	98
7	Acetonitrile	28	>99	>99

[a] 140 $mg_{enzyme}/mmol_{substrate}$ in 5 mL solvent using 1 mmol of *N*-Boc-serinol and 3 mmol vinyl acetate.
[b] Conversion, enantiomeric excess and mono-/di-acetylated ratio were determined by HPLC analysis.[22]
[c] (mono/mono- + di-acetylated) × 100.

Table 2. Influence of temperature on conversion, ee and mono-/di-acetylated product ratio.[a, b]

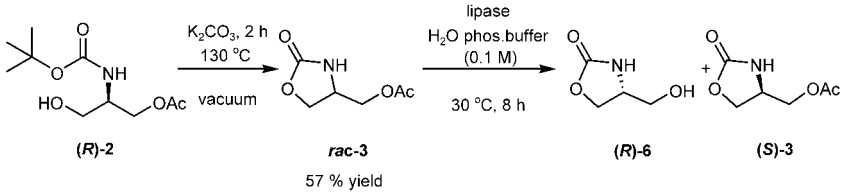
Entry	Temperature [°C]	Conversion [%]	ee [%]	Mono-/ di-acetylated ratio[c]
1	30	>99	>99	>99
2	40	>99	>99	85
3	50	>99	>99	84

[a]140 $mg_{enzyme}/mmol_{substrate}$ in 5 mL vinyl acetate using 1 mmol of *N*-Boc-serinol.
[b] Conversion, enantiomeric excess and mono-/di-acetylated ratio were determined by HPLC analysis. [22]
[c] (mono-/mono- + di-acetylated) × 100.

Table 3. Influence of catalyst on conversion, ee and mono-/di-acetylated product ratio.[a]

Entry	Lipase	Conversion [%]	ee [%]	Mono-/ di-acetylated[c]
1	PPL	>99	>99	>99
2	CAL B[b]	>99	1	<1
3	CCL	49	>99	94
4	PCL	96	>99	91
5	ANL	16	>99	>99
6	PFL	96	>99	92

[a] For reaction conditions see Table 1.
[b] Reaction with CAL B was performed in both vinyl acetate and THF/*n*-hexane solution.
[c] {(mono-)/(mono- + di-acetylated)} × 100.



Scheme 5. Lipase-catalysed kinetic resolution of ***rac*-3**.

The next step in our study was to establish the cyclisation of acetate **2**.

The intramolecular reaction was first attempted under basic conditions. Treatment of enantiomerically enriched acetate **2** with potassium carbonate at 130 °C under vacuum[24] (Scheme 6) afforded the racemic oxazolidinone **3**. Unfortunately, this product was obtained as a racemic mixture. We assume that intramolecular acetyl transfer occurs prior to the cyclisation, thereby affording the racemic product. Nevertheless, kinetic resolution of ***rac*-3** was achieved by enzymatic hydrolysis in phosphate buffer (Scheme 5).

Table 4. Kinetic resolution of ***rac*-3** with different lipases.[a]

Entry	Lipase	Yield [%]	Optical purity [%][b]
1	CAL B	33	93
2	PCL	36	90
3	PPL	42	84

[a] 140 $mg_{enzyme}/mmol_{substrate}$ in 1.5 mL phosphate buffer solution (0.1 M, pH 7) using 0.6 mmol of racemic 4-acetoxymethyl-2-oxazolidinone **3**.

[b] Optical purity (%) = {$[\alpha]^{D}_{30}$ of obtained (*R*)-4}/{$[\alpha]_{D}^{30}$ of enantiopure (*R*)-4} × 100.

Porcine pancreas lipase, lipase from *Pseudomonas cepacia* and from *Candida antarctica* type B were examined for their activity and selectivity towards the reaction studied. The reactions were stopped after 8 hours by removal of the enzymes by filtration. The yields of the reactions catalysed by the different lipases were determined after chromatographic purification of the products. The optical purity of hydroxymethyl-oxazolidinone **(*R*)-6** was determined by comparing the specific rotation of the obtained alcohol with that reported in the literature for the corresponding enantiopure form.[25] The results are illustrated in Table 4.

The (*R*)-enantiomer of oxazolidinone **3** reacted faster than the (*S*)-enantiomer. After 8 hours, optical purities greater than 84% were detected.

We decided to try another approach to the cyclisation reaction and to avoid basic conditions. Enantiomerically enriched (*S*)-oxazolidinone **(*S*)-3** was obtained in a one-step reaction by cyclisation with thionyl chloride (Scheme 6).[26] The reaction proceeded with >98% enantiomeric excess and 72% yield. The absolute stereochemistry of oxazolidinone **(*S*)-3** was confirmed by enzymatic hydrolysis of the acetate group (Scheme 6) and comparison of the specific rotation of hydroxy-oxazolidinone **(*S*)-6** with literature data.[25]

In an alternative approach, we envisaged that protection of the oxygen would be an advantage. The enantiomerically enriched mono-acetate **2** was benzylated using benzyl trichloroacetimidate, in the presence of a catalytic amount of triflic acid,[27] to afford the *N*-benzyloxycarbonyl-*O*-benzyl acylated serinol **7** in reasonable yield. Cyclisation with potassium carbonate then provided the (*R*)-oxazolidinone **8** in >99% ee (Scheme 7).

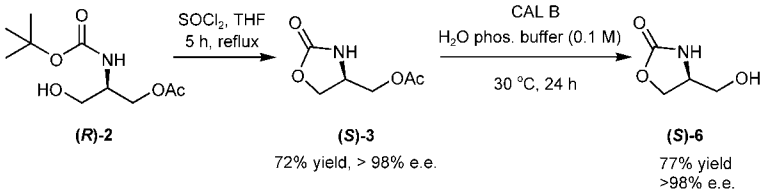
Protection of the hydroxylic group avoided any racemisation during the base-catalysed cyclisation reaction. Catalytic water was found to be essential for the activation of the acylated hydroxy group as nucleophile.

Racemic Auxiliaries: Applications to Asymmetric Synthesis

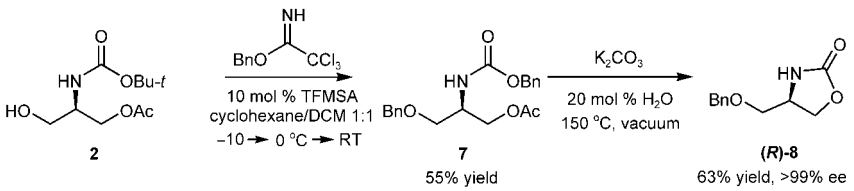
The main objective of our resolution strategy was to find a good stereoselective aldol reaction, which could afford only two enantiomers, separable by an enzyme-catalysed resolution. The actual number of isomers formed depends upon the stereoselectivity of the aldol reaction used.

Given the high diastereomeric excess obtained in aldol reactions with $TiCl_4$[28] and $ClTi(O\text{-}i\text{-}Pr)_3$,[29] we decided to investigate the use of Ti-enolates, particularly a tetrachlorotitanium-enolate generated by diisopropylethylamine. Instead of using the racemic auxiliary directly, we simplified the matter. The stereochemical outcome of the aldol reaction was determined by reacting (*R*)-3-propionyl-4-benzyl-2-oxazolidinone **(*R*)-9** and (*S*)-3-propionyl-4-benzyl-2-oxazolidinone **(*S*)-9** separately. Considering the effect of lipase specificity towards the steric bulk of the substituents,[30] acetaldehyde was selected instead of benzaldehyde.

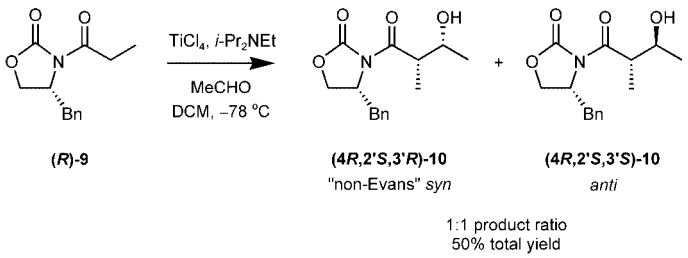
First, we examined the aldol reaction between oxazolidinone **(*R*)-9** and acetaldehyde in the presence of titanium tetrachloride and diisopropylethylamine (Scheme 8).



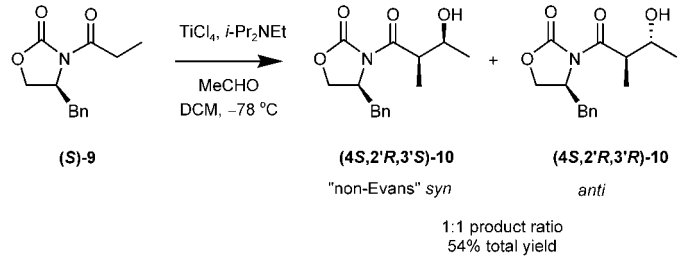
Scheme 6. Synthesis of (*S*)-4-acetoxymethyl-2-oxazolidinone **3** and its enzymatic hydrolysis.



Scheme 7. Synthesis of enantiomerically enriched 4-benzyloxymethyl-2-oxazolidinone.



Scheme 8. The synthesis of the (4*R*)-aldol adducts *via* $TiCl_4$/*i*-Pr_2NEt-enolates.



Scheme 9. The synthesis of the (4*S*)-aldol adducts *via* $TiCl_4$ / *i*-Pr_2NEt-enolates.

Of the four possible isomers that could be obtained, we got only the "non-Evans" *syn* and the *anti* aldol adducts, in a 1:1 ratio.

The "non-Evans" *syn* and the *anti* relative configurations for aldol adducts **10** were established from the observed ^{1}H NMR coupling constants for the vicinal protons at the newly created stereogenic centres,[31] by comparison with analogous compounds synthesised by us in subsequent studies and by enzymatic resolution of the diastereomeric product (see below).

Given that the reaction with the (*R*)-enantiomer proceeded diastereoselectively, we wanted then to ensure that the same diastereoselectivity could be observed when the other enantiomer was used. Oxazolidinone **(*S*)-9** was reacted in the same reaction conditions, as shown in Scheme 9.

Again, only the "non-Evans" *syn* and the *anti* aldol adducts were formed in 1:1 ratio.

In summary, each enantiomer of the acylated oxazolidinone **9** gave as the major products two of the four possible diastereomers of aldol adduct **10**, according to chiral HPLC and NMR analysis. The given yield is the total yield of the aldol mixture, calculated after chromatographic purification.

Table 5. Time course and diastereoselectivity of the enzymatic reaction in hexane.[a]

t [h]	% conv.	% de_p[b]	% de_s[c]
0	0	–	0
3	30	> 99	42
6	46	> 99	84
24	50	> 99	> 99
48	56	88	> 99

[a] 50 mg_{enzyme}/$mmol_{substrate}$ in 5 mL solvent using 1 mmol of diastereomeric aldol and 2 mmol vinyl acetate.
[b] Diastereomeric excess of the product.
[c] Diastereomeric excess of the remaining substrate.

Each pair of aldol adducts was tested in the enzymatic resolution. The enzymatic resolution of aldols **(4*R*,2′*S*,3′*R*)-10** and **(4*R*,2′*S*,3′*S*)-10** from oxazolidinone (*R*)-9 was carried out using vinyl acetate in hexane at 40 °C, catalysed by lipase from *Candida antarctica* type B (Scheme 10).

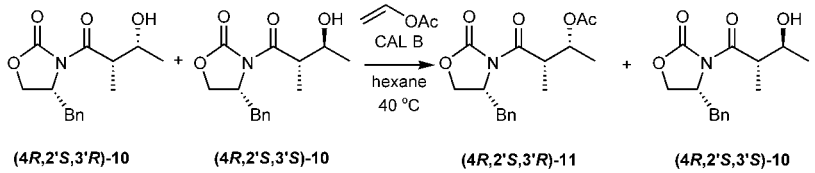
The enzymatic resolution was successful. The (3′*R*) diastereomer reacted faster than the (3′*S*) one. The progress and the diastereomeric excess of the reaction were monitored by chiral HPLC analysis after removal of the enzyme by filtration. In Table 5, the transesterification rate and diastereoselectivity of the enzymatic reaction in hexane are illustrated.

Our next step was to find out if the same diastereoselectivity could be observed when the aldol adducts from oxazolidinone **(*S*)-9** were reacted with vinyl acetate in the presence of CAL B.

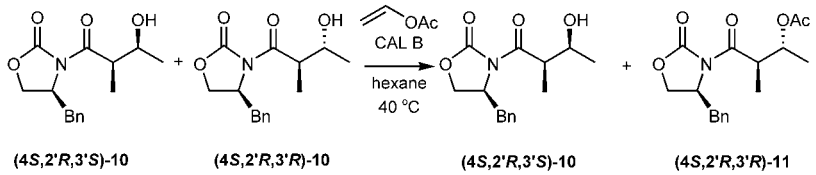
The enzymatic resolution of aldols **(4*S*,2′*R*,3′*S*)-10** and **(4*S*,2′*R*,3′*R*)-10** from oxazolidinone **(*S*)-9** was carried out as described above for aldols from **(*R*)-9** (Scheme 11).

As we expected, the (3′*R*) diastereomer reacted faster than the (3′*S*) diastereomer. Conversion and enantiomeric excess were similar to those obtained when the aldol adducts from **(*R*)-9** were enzymatically resolved. In Table 6 the time course and diastereoselectivity of the enzymatic reaction in hexane are reported.

We had found a diastereoselective aldol reaction, which employed $TiCl_4$/*i*-Pr_2NEt-enolate. Only two of the four possible diastereomers were formed from each enantiomer of the acylated oxazolidinone **9** in a 1:1 mixture. The use of CAL B as catalyst was found to be a valid method for the resolution of diastereomers of aldol



Scheme 10. The enzymatic resolution of aldol adducts.



Scheme 11. The enzymatic resolution of the adducts from $TiCl_4$ /*i*-Pr_2NEt aldol reaction.

Table 6. Time course and diastereoselectivity of the enzymatic reaction in hexane.[a]

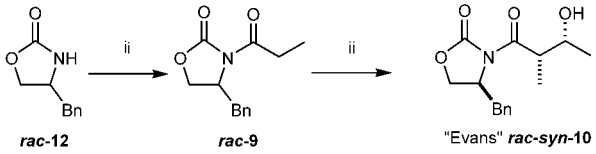
t [h]	% conv.	% de_p[b]	% de_s[c]
0	0	–	0
1	3	> 99	3
4	18	> 99	22
8	39	> 99	63
24	51	89	> 99
48	60	80	> 99

[a] 50 $mg_{enzyme}/mmol_{substrate}$ in 5 mL hexane using 1 mmol of diastereomeric aldol and 2 mmol vinyl acetate.
[b] Diastereomeric excess of the product.
[c] Diastereomeric excess of the remaining substrate.

adducts from acetaldehyde. Moreover, the (3′*R*) diastereomers were preferentially acylated by the enzyme.

We would expect that by means of an aldol reaction with better stereoselectivity, we might be able to obtain only one diastereomer from each enantiomer of *N*-propionyloxazolidinone **9**, i.e., two enantiomers, separable upon the chiral preference of the lipase towards (3*R*) stereocentres.

The desired stereoselectivity for the aldol reaction was obtained when we used the same reaction conditions reported by Crimmins and co-workers for an analogous asymmetric aldol reaction.[32]



Scheme 12. Acylation and aldol reaction of *rac*-4-benzyl-2-oxazolidinone **12**. *Reaction conditions:* (i) *n*-BuLi, EtCOCl/THF, −78 °C (88%); (ii) $TiCl_4$, (−)-sparteine, *N*-methyl-2-pyrrolidinone, CH_3CHO/DCM, 0 → −78 °C (54%).

Racemic 4-benzyl-2-oxazolidinone **12** was prepared from the corresponding racemic amino acid phenylalanine, following the procedure reported by Wu and Shen.[24] The racemic oxazolidinone was then acylated to obtain the racemic 3-propionyl-4-benzyl-2-oxazolidinone **9**.[33] The subsequent diastereoselective aldol reaction with acetaldehyde in the presence of $TiCl_4$, (−)-sparteine and *N*-methyl-2-pyrrolidinone[32] provided racemic ***syn*-10** in 99% diastereomeric excess (Scheme 12).

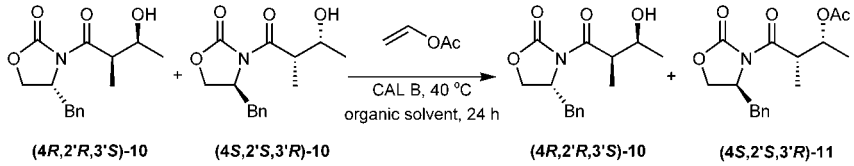
Sparteine was used as a convenient base and did not, as expected, exert any observable stereocontrol upon the aldol reaction.

Enzymatic resolution of the enantiomers of aldol adduct ***rac-syn*-10** *via* transesterification catalysed by *Candida antarctica* lipase type B, afforded the (3′*R*)-acylated aldol adduct **11** and the (3′*S*)-non-acylated aldol adduct **10** (Scheme 13). The choice of solvent was crucial to this process, and the solvent effects are illustrated in Table 7.

The reaction rate of the lipase-catalysed transesterification was faster in non-polar solvents such as *n*-hexane and toluene (Entries 1 and 3), whilst it was slower in polar solvents such as dichloromethane (Entry 5).[34–36] The selectivity of *Candida antarctica* lipase type B towards the aldol adduct enantiomers was in accordance with the reported stereoselectivity of this enzyme towards racemic secondary alcohols.[37]

Finally, hydrolysis[33] of the enzymatically resolved aldol **10** and ester **11** afforded the enantiomerically enriched 3-hydroxy-2-methylbutanoic acids **(2*R*,3*S*)-13** and **(2*S*,3*R*)-13** and the enantiomerically enriched 2-oxazolidinones **(*R*)-12** and **(*S*)-12** (Scheme 14).

For comparison, the enantiomer of the lipase-acylated oxazolidinone **11** was synthesised by chemical esterification of **(4*R*,2′*R*,3′*S*)-10** with acetic acid in the presence of DCC and dimethylaminopyridine.[38] Ester **(4*R*,2′*R*,3′*S*)-11** was prepared in 65% isolated yield.

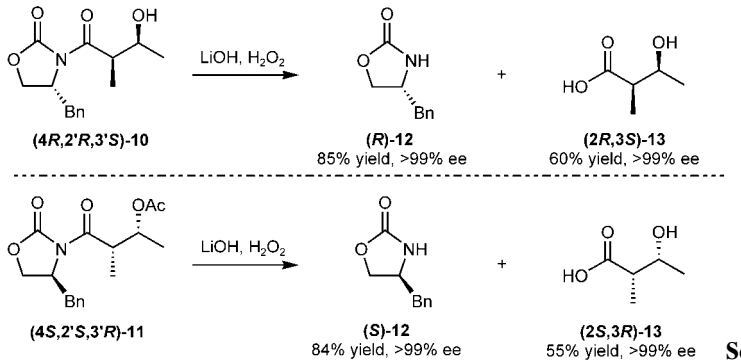


Scheme 13. Lipase-catalysed aldol adduct resolution.

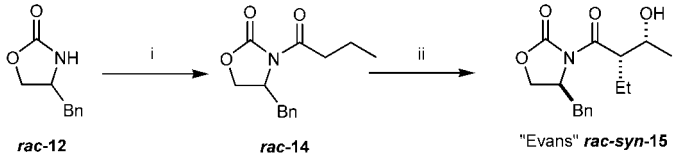
Table 7. Influence of solvent on conversion and enantiomeric excess.[a]

Entry	Solvent	Conversion [%]	(4*R*,2′*R*,3′*S*)-**10** ee %	(4*S*,2′*S*,3′*R*)-**11** ee %
1	*n*-hexane	50	>99	>99
2	*i*-Pr_2O	45	81	>99
3	toluene	42	72	>99
4	Vinyl acetate	34	51	>99
5	DCM	6	6	>99

[a] 30 $mg_{enzyme}/mmol_{substrate}$ in 5 mL solvent using 1 mmol of racemic aldol and 2 mmol vinyl acetate.



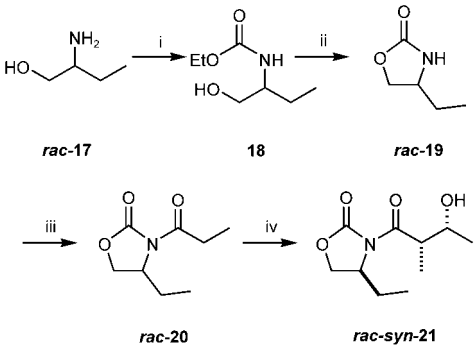
Scheme 14. Hydrolysis of enzymatic resolution products.



Scheme 15. Acylation of (±)-4-benzyl-2-oxazolidinone **12** with *n*-PrCOCl and subsequent aldol reaction. *Reaction conditions:* (i) *n*-BuLi, *n*-PrCOCl/THF, −78 °C (88%); (ii) $TiCl_4$, (−)-sparteine, *N*-methyl-2-pyrrolidinone, CH_3CHO/DCM, 0 → −78 °C (59%).

The chemical esterification gave, as expected, the ester with opposite specific rotation with respect to the ester obtained by the enzymatic reaction.

To prove the general application of our methodology to obtain enantiomerically enriched auxiliary and enantiomerically enriched product, we decided to change the acyl moiety of our oxazolidinone. We intended to see if this structural change could affect the aldol reaction diastereoselectivity or/and the enzymatic resolution. This time, the racemic oxazolidinone



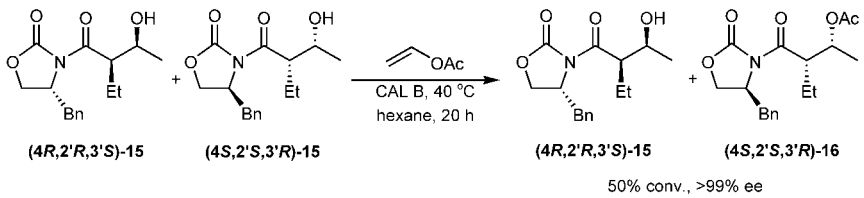
Scheme 17. The synthesis of the racemic ***rac-syn*-21** 4-ethyl-oxazolidinone. *Reaction conditions:* (i) Na_2CO_3/EtO_2CCl, H_2O; (ii) K_2CO_3, 125–130 °C, vacuum (90%); (iii) *n*-BuLi, EtCOCl/THF, −78 °C (64%); (iv) $TiCl_4$, (−)-sparteine, *N*-methyl-2-pyrrolidinone, CH_3CHO/DCM, 0 → −78 °C (54%).

12 was acylated using butyryl chloride to obtain the *N*-butanoyloxazolidinone **14**. This underwent the diastereoselective aldol reaction with acetaldehyde in the presence of $TiCl_4$/(−)-sparteine/NMP to afford the ***rac-syn*-15** in 59% yield and 95% de, according to ^1H NMR[39] and chiral HPLC analysis (Scheme 15).

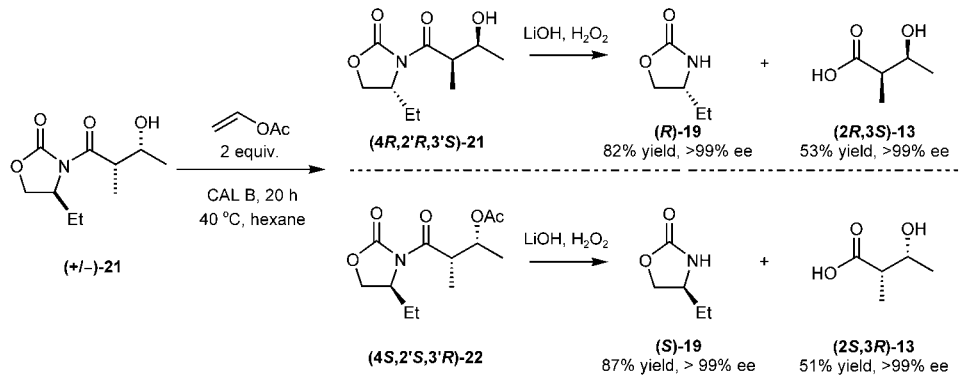
Enzymatic resolution of the enantiomers of aldol adduct **15** *via* transesterification catalysed by *Candida antarctica* lipase type B in *n*-hexane, afforded the acylated aldol adduct **16** and the non-acylated aldol adduct **15** with 50% conversion and >99% enantiomeric excess of the product after 20 hours (Scheme 16).

We were pleased to discover that the aldol reaction was still highly selective even when the acyl moiety was changed. The enzymatic resolution was effective even when the 2′-methyl substituent was exchanged with an ethyl group.

Our aim was now to prove that our approach could be generally exploited to obtain the indirect resolution of



Scheme 16. Lipase-catalysed aldol adduct resolution.



Scheme 18. Enzymatic resolution of aldols **21** and subsequent hydrolysis.

chemically designed racemic auxiliaries. For example, racemic 2-amino-1-butanol is readily available at low cost. We envisaged that using this inexpensive starting material we could obtain enantiomerically enriched 4-ethyl-2-oxazolidinones.

Racemic 2-amino-1-butanol **17** was used to synthesise racemic **(2′,3′)-*syn*-21**, following the procedure above described for the synthesis of ***rac-syn*-10** and **15** (Scheme 17).

The application of our methodology produced resolved alcohol **(4*R*,2′*R*,3′*S*)-21** and acetate **(4*S*,2′*S*,3′*R*)-22** (Scheme 18). Hydrolysis of the resolved alcohol and acetate afforded enantiomerically enriched **(2*R*,3*S*)-13** and **(2*S*,3*R*)-13** and the enantiomerically enriched 4-ethyl-2-oxazolidinones **(*R*)-19** and **(*S*)-19**. Again the strategy proved to be successful affording products with >99% ee.

Conclusion

We have developed different strategies to obtain enantiomerically enriched Evans auxiliaries, by enzymatic desymmetrisation of *N*-Boc-serinol and by enzymatic resolution of diastereomeric and enantiomeric aldol adducts.

Different lipases have been shown to catalyse selectively the mono-acetylation of *N*-Boc-serinol with vinyl acetate in organic solvent. Aspects of the reaction such as effect of solvent, temperature and lipase origin were discussed and we can conclude that the desymmetrisation of *N*-Boc-protected serinol can be successfully achieved in good yield and high ee in 2 hours, by using the inexpensive crude commercial PPL in vinyl acetate at 30 °C. The desymmetrisation of *N*-Boc-serinol has been exploited in different ways to prepare enantiomerically enriched (4*S*)- and (4*R*)-substituted 2-oxazolidinones.

Starting from a racemic Evans auxiliary, by means of a diastereoselective aldol reaction coupled with a lipase-catalysed resolution, we proved that we could achieve the preparation of enantiomerically enriched β-hydroxy acids and the indirect resolution of different 4-substituted racemic Evans auxiliaries.

Experimental Section

General Remarks

^{1}H NMR spectra were run in $CDCl_3$, unless otherwise stated, using either a Bruker AM-300 (300 MHz) or a Jeol GX400 (400 MHz) instrument. Chemical shifts are reported relative to Me_4Si ($\delta = 0.00$ ppm) as internal standard. Coupling constants (J) are given in Hertz and multiplicities denoted as singlet (s), doublet (d), triplet (t), doublet of doublets (dd), doublet of quartets (dq) or multiplet (m). ^{13}C NMR spectra were run in $CDCl_3$, unless otherwise stated, using either a Bruker AM-300 (75.5 MHz) or a Jeol GX400 (100 MHz) instrument. Mass spectra, including high-resolution spectra, were recorded on a Fisons NG-Micromass Autospec Spectrometer using electron impact (EI+) ionisation, chemical impact (CI+) ionisation and/or fast atom bombardment (FAB+) ionisation. Elemental analyses were performed using a Carlo Erba 1106 Elemental Analyser at the University of Bath. HPLC was performed using a *tsp* liquid chromatograph (Spectra Series P200 Pump, Spectra Series UV100 Lamp, ChromJet SP4400 Integrator). All HPLC separations were carried out using Chiralcel OD® and AD® columns obtained from Fisher Scientific Supplies. Flash chromatography was carried out using Merck Kiesegel 60H and Fisher Matrex Silica 60 silica. TLC using commercially available Merck Kiesegel G/UV_{254} neutral silica coated aluminium and glass plates monitored all reactions. TLC plates were visualised by 254 nm light or with $KMnO_4$ dip followed by heating. Melting points were measured on a Büchii 535 Series instrument and are uncorrected. Optical rotations were measured with a Optical Activity LTD AA-10 automatic polarimeter. IR spectra were recorded as thin films, solutions (CH_2Cl_2, $CHCl_3$ or $CDCl_3$) or KBr discs, using a Perkin-Elmer 1600 Series FT-IR spectrophotometer in the range of 4000 – 600 cm^{-1}, with internal background scan.

Candida antarctica lipase type B (CAL B, Chirazyme® L-2, carrier-fixed C3, lyophilisate) was a gift from Boeringer Mannheim. Porcine pancreas lipase (PPL, EC 3.1.1.3. type II) was from Sigma. *Pseudomonas cepacia* lipase (PCL) and *Pseudomonas fluorescens* lipase (PFL) immobilised in Sol-Gel-AK, *Candida cylindracea* lipase (CCL), and *Aspergillus*

niger lipase (ANL) were from Fluka. All enzymes were used as supplied.

Preparation of *N*-(*tert*-Butoxycarbonyl)-1,3-propanediol (*N*-Boc-Serinol) 1[20]

Di-*tert*-butyl dicarbonate (1.3 g, 6 mmol) was gently added to a stirred solution of serinol (2-amino-1,3-propanediol) **4** (455 mg, 5 mmol) in EtOH (15 mL). After 1 hour at room temperature, the solvent was removed under reduced pressure. The residue was extracted with EtOAc (2 × 15 mL), and the organic phase was dried (Na_2SO_4) and concentrated under vacuum. The obtained white solid was recrystallised from hexane/EtOAc to give **1** as white needles; yield: 1.1 g (95%); mp 84–85 °C (Lit.[20] 87–88 °C); HPLC (Chiralcel® OD column, *n*-hexane/2-propanol, 95:5, 1 mL min^{-1}, λ = 210 nm): t_R = 8.6 min; IR (CH_2Cl_2): ν = 3425, 2965, 2885, 1700, 1500, 1165, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.25 (1H, br d, *J* = 5.4 Hz, N*H*), 3.82–3.63 (5H, m, 2 × CH_2OH and C*H*N), 2.68 (4H, t, *J* = 5.5 Hz, 2 × CH_2O*H*), 1.45 (9H, s, 3 × CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 156.8 (*C*O), 80.3 (*C*(CH_3)$_3$), 63.2 (2 × *C*H_2OH), 53.5 (*C*HN), 28.7 (3 × *C*H_3); anal. calcd. for $C_8H_{17}NO_4$: C 50.25%, H 8.96%, N 7.32%; found: C 50.2%, H 8.9%, N 7.2%.

General Procedure for the Enzymatic Desymmetrisation of *N*-Boc-Serinol 1

In a typical experiment a solution of *N*-Boc-serinol **1** (0.7 g, 3.6 mmol) and vinyl acetate (2.6 mL, 28.8 mmol), in organic solvent (20 mL) was stirred with the lipase (500 mg, 140 mg_{enzyme}/$mmol_{sub}$) at different temperatures for 2 hours. Aliquots were taken from the different solutions and analysed by chiral HPLC. The reaction performed in vinyl acetate at 30 °C, using PPL as catalyst was followed until completion was reached (2 hours). The reaction was then stopped by filtering the solution. The solution was concentrated under vacuum and the residue purified by flash chromatography (SiO_2, *n*-hexane/EtOAc, 50:50) to give **(*R*)-2** as a colourless oil (587.6 mg, 69% isolated yield) and traces of **5** (30.2 mg, 3%) as a yellow oil.

(*R*)-(+)-3-*O*-Acetyl-2-*N*-(*tert*-butoxycarbonyl)serinol (*R*)-2

Desymmetrised serinol **(*R*)-2** was obtained as a colourless oil (587.6 mg, 69% isolated yield); R_f (*n*-hexane/EtOAc 50:50): 0.29; $[\alpha]_D^{30}$: +3.5 (*c* 0.56, $CHCl_3$); HPLC (Chiralcel® OD column, *n*-hexane/2-propanol, 95:5, 1 mL min^{-1}, λ = 210 nm): t_R = 10.8 min; IR (film): ν = 3370 (br), 2975, 1710, 1690, 1525, 1370, 1240, 1170, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.10 (1H, br d, *J* = 8.4 Hz, N*H*), 4.19 (2H, d, *J* = 5.7 Hz, CH_2OCO), 3.98–3.88 (1H, m, C*H*N), 3.65 (2H, dq, *J* = 4.7 and 11.4 Hz, CH_2OH), 3.02 (1H, s br, O*H*), 2.09 (3H, s, COCH_3) 1.45 (9H, s, 3 × CCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.8 (O*C*O), 155.2 (N*C*O), 80.3 (*C*(CH_3)$_3$), 63.4 (*C*H_2OCO), 62.2 (*C*H_2OH), 51.4 (*C*HN), 28.7 (3 × C*C*H_3), 21.2 (CO*C*H_3); MS (CI+, 70 eV): *m/z* = 234 (M^+ + 1, 45%), 178 (100), 160 (53), 134 (62), 118 (60), 102 (72); anal. calcd. for $C_{10}H_{19}NO_5$: C 51.49%, H 8.21%, N 6.00%; found: C 51.1%, H 8.2%, N 5.9%.

Preparation of (*R*/*S*)-(+/−)-4-Acetoxymethyl-2-oxazolidinone *rac*-3[24]

Powdered K_2CO_3 (10 mg, 0.06 mmol) was added to desymmetrised serinol **(*R*)-2** (685.8 mg, 2.94 mmol**)** and the mixture was heated to 130 °C with magnetic stirring under vacuum, until the gas evolution stopped (approximately 2 hours). After cooling down to room temperature, the mixture was purified by flash chromatography (SiO_2, *n*-hexane/EtOAc 10:90), to give ***rac*-3** as a colourless oil. Recrystallisation from *n*-hexane/isopropanol afforded ***rac*-3** as a white solid (266.7 mg, 57%); mp 77–79 °C; R_f (*n*-hexane/EtOAc, 10:90) = 0.41; HPLC (Chiralcel® AD column, *n*-hexane/2-propanol, 90:10, 1 mL min^{-1}, λ = 210 nm): t_R = 16.3 and 18.8 min; IR (film): ν = 3435, 2950, 1720, 1660, 1450, 1370, 995 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.71 (1H, br s, N*H*), 4.51 (1H, dd app. t, *J* = 8.5 Hz, C*H*HO), 4.24–4.01 (4H, m, CH_2OCOCH$_3$, CH*H*O, C*H*N), 2.11 (3H, s, COCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.8 (O*C*O), 159.8 (N*C*O), 66.9 (*C*H_2OCOCH$_3$), 64.9 (*C*H_2OCON), 51.1 (*C*HN), 20.7 (CO*C*H_3); MS (CI+, 70 eV): *m/z* 160 (M^+ + 1, 100%), 118 (23), 99 (20), 86 (30); anal. calcd. for $C_6H_9NO_4$: C 45.28%, H 5.70%, N 8.80%; found: C 45.3%, H 5.7%, N 8.6%.

General Procedure for the Enzymatic Hydrolysis of (*R*/*S*)-(+/−)-4-Acetoxymethyl-2-oxazolidinone *rac*-3

In a typical experiment a solution of ***rac*-3** (94.5 mg, 0.6 mmol) in aqueous phosphate buffer (1.5 mL, 0.1 M, pH 7) was stirred at 30 °C with the lipase (84 mg, 140 mg_{enzyme}/$mmol_{substrate}$). After 8 hours, the reaction was stopped by filtering off the enzyme. The aqueous phase was extracted with ethyl acetate (3 × 2 mL) and the combined organic extracts were concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/MeOH, 90:10) to give **(*R*)-6** as a white solid. Enantiomeric excesses were calculated comparing the obtained specific rotations with that of the pure compound reported in literature {Lit.[27] $[\alpha]_D^{30}$: +32.2 (*c* 1.04, MeOH)}.

(*R*)-(+)-4-Hydroxymethyl-2-oxazolidinone (*R*)-6[25]

Hydroxymethyloxazolidinone **(*R*)-6** was obtained as a white solid; mp 95–97 °C (Lit.[25] 96–99 °C); R_f (EtOAc/MeOH, 90:10) = 0.38; ^{1}H NMR (300 MHz, D_2O): δ = 4.50 (1H, dd app. t, *J* = 9.0 Hz, CH*H*OCON), 4.23 (1H, dd, *J* = 9.0, 5.2 Hz, C*H*HOCON), 4.04–3.97 (1H, m, C*H*N), 3.61 (1H, dd, *J* = 12.0 and 3.7 Hz, CH*H*OH), 3.52 (1H, dd, *J* = 12.0 and 4.1 Hz, C*H*HOH).

Preparation of (*S*)-(-)-4-Acetoxymethyl-2-oxazolidinone (*S*)-3[26]

To a stirred solution of **(*R*)-2** (700 mg, 3 mmol) in THF (90 mL) was added thionyl chloride (1.9 mL, 24 mmol) at room temperature under a nitrogen atmosphere. After the solution was heated at reflux for 5 hours, the reaction mixture was concentrated under vacuum and the residue was purified by flash chromatography (EtOAc/hexane, 90:10). Recrystallisation from *n*-hexane/isopropanol afforded **(*S*)-3** as a white solid (343 mg, 2.16 mmol, 72%); mp 77–79 °C; R_f (*n*-hexane/EtOAc,

10:90) = 0.41; HPLC (Chiralcel® AD column, *n*-hexane/isopropanol, 90:10, 1 mL min^{-1}, λ = 210 nm): t_R = 18.8 min; $[\alpha]_D^{30}$: −40.7 (*c* 1.35, $CHCl_3$); IR (CH_2Cl_2): ν = 3435, 2950, 1720, 1660, 1450, 1370, 995 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.71 (1H, br s, N*H*), 4.51 (1H, dd app. t, *J* = 8.5 Hz, C*H*HOCON), 4.24 – 4.01 (4H, m, CH_2OCOCH_3, CH*H*OCON, C*H*N), 2.11 (3H, s, $COCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.8 (O*C*O), 159.8 (N*C*O), 66.9 (CH_2OCOCH_3), 64.9 (CH_2OCON), 51.1 (*C*HN), 20.7 ($COCH_3$); MS (CI +, 70 eV): *m/z* = 160 (M^+ + 1, 100%), 118 (23), 99 (20), 86 (30); HRMS (FAB +): calcd. for $C_6H_9NO_4$: 159.0532; found: 159.0535; anal. calcd. for $C_6H_9NO_4$: C 45.28%, H 5.70%, N 8.80%; found: C 45.3%, H 5.7%, N 8.6%.

Preparation of (*S*)-(−)-4-Hydroxymethyl-2-oxazolidinone (*S*)-6

A solution of **(*S*)-3** (33 mg, 0.2 mmol) in aqueous phosphate buffer (0.5 mL, 0.1 M, pH 7) was stirred at 30 °C with CAL B (28 mg, 140 $mg_{enzyme}/mmol_{sub}$) for 24 hours. The aqueous layer was extracted with EtOAc (3 × 1 mL) and the combined organic extracts were concentrated under vacuum. Flash chromatography purification (SiO_2, EtOAc/MeOH, 90:10) afforded **(*S*)-6** as a white solid (18 mg, 77%); $[\alpha]_D^{30}$: −30.0 (*c* 0.6, MeOH); spectroscopic data were in accordance with those above described for **(*R*)-6**.

Preparation of (*R*)-(−)-1-*O*-Benzyl-3-*O*-acetyl-2-*N*-(benzyloxycarbonyl)serinol (*R*)-7[27]

To a stirred solution of **(*R*)-2** (1.4 g, 6 mmol) in cyclohexane/DCM (60 mL, 50:50) under nitrogen, benzyl 2,2,2,-trichloroacetimidate (3 mL, 18 mmol) was added. The reaction mixture was stirred with trifluoromethanesulphonic acid (54 μL, 0.6 mmol, 10%) at −10 °C for 2 hours, warmed to 0 °C and then left warming to room temperature overnight. The reaction mixture was filtered, quenched with saturated $NaHCO_3$ solution (20 mL), and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, *n*-hexane/EtOAc/$CHCl_3$, 70:20:10) to give **(*R*)-7** (1.2 g, 3.3 mmol, 55%) as a colourless solid, mp 119 – 121 °C; R_f (SiO_2, hexane/EtOAc/$CHCl_3$, 70:20:10) = 0.31; HPLC (Chiralcel OD® column, *n*-hexane/isopropanol, 90:10, 1 mL min^{-1}, λ = 254 nm): t_R = 8.7 min; $[\alpha]^{30}$: −5.2 (*c* 3.25, $CHCl_3$); IR (CH_2Cl_2): ν = 3365 (br), 1711 (br), 1525, 1235 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.26 (10H, m, 2 × C_6H_5), 5.19 (1H, d, *J* = 8.2 Hz, N*H*), 5.10 (2H, s, CO_2CH_2Ph), 4.50 (2H, s app. d, *J* = 3.1 Hz, CH_2OCH_2Ph), 4.24 – 4.03 (3H, m, CH_2OCOCH_3, C*H*N), 3.58 (1H, dd, *J* = 3.3 and 9.3 Hz, C*H*HOCH_2Ph), 3.50 (1H, dd, *J* = 4.7 and 9.3 Hz, CH*H*OCH_2Ph), 1.99 (3H, s, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8 (O*C*O), 155.5 (N*C*O), 137.2, 135.9, 128.2 (2C), 128.1 (2C), 127.9, 127.8, 127.5 (2C), 127.4 (2C) (aromatic C), 73.1 (CH_2OCH_2Ph), 68.4 (CH_2OCH_2Ph), 66.7 (CO_2CH_2Ph), 63.2 (CH_2OCOCH_3), 49.5 (*C*HN), 21.0 ($COCH_3$); MS (CI +, 70 eV): *m/z* = 358 (M^+ + 1, 25%), 314 (31), 181 (42), 161 (73), 91 (100).

Preparation of (*R*)-(+)-4-Benzyloxymethyl-2-oxazolidinone 8

Powdered K_2CO_3 (10 mg, 0.06 mmol) and water (8 μL, 0.4 mmol, 20%) were added to **7** (725 mg, 2.02 mmol). The mixture was heated to 150 °C with magnetic stirring under vacuum, until the gas evolution stopped. After cooling down to room temperature, the mixture was purified by flash chromatography (SiO_2, EtOAc/*n*-hexane, 65:35), to afford **8** (264.2 mg, 1.27 mmol, 63%) as a cream solid; mp 49 – 51 °C; R_f (SiO_2, EtOAc/*n*-hexane, 65:35) = 0.34; HPLC (Chiralcel OD® column, *n*-hexane/isopropanol, 75:25, 1 mL min^{-1}, λ = 254 nm): t_R = 22.0 min; $[\alpha]_D^{30}$: +25.0 (*c* 0.08, $CHCl_3$); IR (CH_2Cl_2): ν = 3450, 2865, 1760, 1400, 1225, 1098 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ?=5.28 (1H, br s, N*H*), 4.54 (2H, s, CH_2OCH_2Ph) 4.47 (1H, dd app. t, *J* = 8.4 Hz, C*H*HOCO), 4.13 – 4.02 (2H, m, CH*H*OCO, C*H*N), 3.50 – 3.46 (2H, m, CH_2OCH_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0 (N*C*O), 137.3, 128.8 (2C), 128.3, 128.0 (2C) (aromatic C), 73.9 (CH_2OCH_2Ph), 72.1 (CH_2OCH_2Ph), 67.3 (CH_2OCO), 52.2 (*C*HN); MS (CI +, 70 eV): *m/z* = 208 (M^+ + 1, 100%), 174 (21), 91 (36); HRMS (FAB +): calcd. for $C_{11}H_{13}NO_3$: 207.0895; found: 207.0904; anal. calcd. for $C_{11}H_{13}NO_3$: C 63.76%, H 6.32%, N 6.76%; found: C 64.1%, H 6.3%, N 6.4%.

General Procedure for the Preparation of Diastereomeric Aldol Adducts[40]

A solution of $TiCl_4$ in dichloromethane (1 M, 5.4 mL, 5.4 mmol) was added to a stirred solution of 4-benzyl-*N*-propionyl-2-oxazolidinone **(*R*)-** or **(*S*)-9** (606.5 mg, 2.6 mmol) in dichloromethane (20 mL) at −78 °C under an atmosphere of nitrogen. After 10 minutes, diisopropylethylamine (0.9 mL, 5.4 mmol) was added, followed 1 hour later by freshly distilled acetaldehyde (0.3 mL, 5.2 mmol). The reaction mixture was maintained at −78 °C for 5 hours and allowed to warm to room temperature overnight. Saturated NH_4Cl solution (10 mL) was added and the mixture was extracted with DCM (3 × 50 mL). The dichloromethane extracts were washed with water (30 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (SiO_2, *n*-hexane/EtOAc, 50:50) gave a mixture of the two diastereomers.

General Procedure for the Enzymatic Resolution of Aldol Adducts 10

In a typical experiment the two diastereomers (55.5 mg, 0.20 mmol) and *Candida antarctica* lipase type B (10 mg, 50 $mg_{enzyme}/mmol_{substrate}$) in hexane were stirred with vinyl acetate (40 μL, 0.40 mmol) at 40 °C. Periodically aliquots were removed, filtered, diluted in a *n*-hexane/isopropanol 80:20 solution, and analysed by chiral HPLC. After 24 – 48 hours, the reaction was stopped by filtering off the enzyme and the ester was separated from unreacted alcohol by flash chromatography (SiO_2, *n*-hexane/EtOAc, 60:40).

(4*R*,2′*S*,3′*R*)-*N*-(3-Acetoxy-2-methylbutanoyl)-4-benzyl-2-oxazolidinone (4*R*,2′*S*,3′*R*)-11

Ester **(4*R*,2′*S*,3′*R*)-11** was obtained as a yellow oil (25.5 mg, 40% in *n*-hexane); R_f (*n*-hexane/EtOAc, 60:40) = 0.64; HPLC (Chiralcel® OD column, *n*-hexane/2-propanol, 80:20, 1 mL min^{-1}, λ = 254 nm): t_R = 8.7 min; $[\alpha]_D^{30}$: −9.4 (*c* 1.0, $CHCl_3$); IR (film): ν = 1780, 1735, 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.22 (5H, m, C_6H_5), 5.40 (1H, dq, *J* = 4.2 and 6.4 Hz, C*H*OCOCH$_3$), 4.71–4.63 (1H, m, NC*H*), 4.20–4.08 (2H, m, CHCH_2O), 3.91 (1H, dq, *J* = 4.2 and 6.9 Hz, COC*H*CH$_3$), 3.34 (1H, dd, *J* = 3.3 and 13.4 Hz, CH*H*Ph), 2.67 (1H, dd, *J* = 10.3 and 13.4 Hz, C*H*HPh), 2.04 (3H, s, OCOCH_3), 1.33 (3H, d, *J* = 6.4 Hz, COCHCH_3), 1.22 (3H, d, *J* = 6.9 Hz, AcOCHCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 174.3 (C*C*O), 170.7 (O*C*OCH$_3$), 153.7 (O*C*ON), 135.9, 129.8 (2C), 129.3 (2C), 127.6 (aromatic *C*), 70.7 (*C*HOCOCH$_3$), 66.6 (*C*H$_2$O), 55.8 (*C*HN), 42.7 (CO*C*HCH$_3$), *C*H$_2$Ph), 21.5 (OCO*C*H$_3$), 18.4 (AcOCH*C*H$_3$), 11.2 (COCH*C*H$_3$); MS (EI+, 70 eV): *m/z* = 320 (M^+ + 1, 77%), 260 (100), 178 (15), 143 (14), 117.1 (10), 83 (69); anal. calcd. for $C_{17}H_{21}NO_5$: C 63.93%, H 6.62%, N 4.38%; found: C 63.8%, H 6.6%, N 4.3%.

(4*R*,2′*S*,3′*S*)-*N*-(3-Hydroxy-2-methylbutanoyl)-4-benzyl-2-oxazolidinone (4*R*,2′*S*,3′*S*)-10

Unreacted alcohol **(4*R*,2′*S*,3′*S*)-10** was obtained as a white solid (19.4 mg, 35% in *n*-hexane); mp 74–76 °C; R_f (*n*-hexane/EtOAc, 50:50) = 0.63; HPLC (Chiralcel® OD column, *n*-hexane/2-propanol, 80:20, 1 mL min^{-1}, λ = 254 nm): t_R 12.2 min; $[\alpha]_D^{30}$: −19.8 (*c* 0.5, $CHCl_3$); IR (CH_2Cl_2): ν = 3570 (br), 1780, 1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 7.37–7.22 (5H, m, C_6H_5), 4.73–4.65 (1H, m, NC*H*), 4.24–4.16 (2H, m, CHCH_2O), 3.96 (1H, dq app. t, *J* = 6.4 Hz, C*H*OH), 3.83 (1H, dq, *J* = 7.0 and 7.0 Hz, COC*H*CH$_3$), 3.33 (1H, dd, *J* = 3.3 and 13.4 Hz, CH*H*Ph), 2.79 (1H, dd, *J* = 9.6 and 13.4 Hz, C*H*HPh), 2.55 (1H, s br, O*H*), 1.31 (3H, d, *J* = 6.3 Hz, COCHCH_3),1.20 (3H, d, *J* = 6.9 Hz, CHOHCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 176.6 (C*C*O), 153.2 (O*C*ON), 135.2, 129.4 (2C), 128.9 (2C), 127.3 (aromatic *C*), 70.7 (*C*HOH), 66.1 (*C*H$_2$O), 55.6 (*C*HN), 45.0 (CO*C*HCH$_3$), 37.8 (*C*H$_2$Ph), 21.2 (CHOH*C*H$_3$),14.6 (COCH*C*H$_3$).

(4*S*,2′*R*,3′*R*)-*N*-(3-Acetoxy-2-methylbutanoyl)-4-benzyl-2-oxazolidinone (4*S*,2′*R*,3′*R*)-11

Acylated oxazolidinone **(4*S*,2′*R*,3′*R*)-11** was obtained as a white solid (24.3 mg, 38% in vinyl acetate); mp 89–91 °C; R_f (*n*-hexane/EtOAc, 60:40) = 0.58; HPLC (Chiralcel® OD column, *n*-hexane/2-propanol, 80:20, 1 mL min^{-1}, λ = 254 nm): t_R 14.1 min; $[\alpha]_D^{30}$: +40.0 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2): ν = 1790, 1740, 1690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.21 (5H, m, C_6H_5), 5.22 (1H, dq, *J* = 6.3 and 8.8 Hz, C*H*OCOCH$_3$), 4.74–4.66 (1H, m, NC*H*), 4.23–4.13 (2H, m, CH_2O), 4.07 (1H, dq, *J* = 7.0 and 8.8 Hz, COC*H*CH$_3$), 3.24 (1H, dd, *J* = 3.2 and 13.2 Hz, CH*H*Ph), 2.74 (1H, dd, *J* = 9.5 and 13.2 Hz, C*H*HPh), 2.00 (3H, s, OCOCH_3), 1.31 (3H, d, *J* = 6.3 Hz, COCHCH_3), 1.20 (3H, d, *J* = 7.0 Hz, AcOCHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5 (C*C*O), 170.0 (O*C*OCH$_3$), 153.0 (O*C*ON),135.0, 129.4 (2C), 129.0 (2C), 127.4 (aromatic *C*), 72.1 (*C*HOCOCH$_3$), 65.8 (*C*H$_2$O), 55.2 (*C*HN), 42.7 (CO*C*HCH$_3$), 37.7 (*C*H$_2$Ph), 21.1 (OCO*C*H$_3$), 17.2 (AcOCH*C*H$_3$), 13.7 (COCH*C*H$_3$); MS (EI+, 70 eV): *m/z* = 319 (M^+, 70%), 303 (40), 286 (26); 259 (34), 143 (32), 117 (25), 83 (100), 55 (30), 43 (60); anal. calcd. for $C_{17}H_{21}NO_5$: C 63.93%, H 6.62%, N 4.38%; found: C 63.8%, H 6.6%, N 4.4%.

(4*S*,2″*R*,3′*S*)-*N*-(3-Hydroxy-2-methylbutanoyl)-4-benzyl-2-oxazolidinone (4*S*,2′*R*,3′*S*)-10

Unreacted alcohol **(4*S*,2′*R*,3′*S*)-10** was obtained as a white solid (16.6 mg, 30% in vinyl acetate); mp 112–114 °C; R_f (*n*-hexane/EtOAc, 50:50) = 0.59; HPLC (Chiralcel® OD column, *n*-hexane/2-propanol, 80:20, 1 mL min^{-1}, λ = 254 nm): t_R = 12.8 min; $[\alpha]_D^{30}$: +42.0 (*c* 0.50, $CHCl_3$); IR (CH_2Cl_2): ν = 3575 (br), 1775, 1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.21 (5H, m, C_6H_5), 4.73–4.65 (1H, m, NC*H*), 4.24–4.15 (3H, m, CHCH_2O, C*H*OH), 3.84 (1H, dq, *J* = 3.0 and 7.0 Hz, COC*H*CH$_3$), 3.31 (1H, dd, *J* = 3.4 and 13.4 Hz, CH*H*Ph), 2.86 (1H, d, *J* = 2.5 Hz, O*H*), 2.77 (1H, dd, *J* = 9.6 and 13.4 Hz, C*H*HPh), 1.23 (3H, d, *J* = 6.4 Hz, COCHCH_3), 1.21 (3H, d, *J* = 7.0 Hz, CHOHCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 176.7 (C*C*O), 153.4 (O*C*ON), 135.1, 129.4 (2C), 128.9 (2C), 127.4 (aromatic *C*), 68.1 (*C*HOH), 66.1 (*C*H$_2$O), 55.4 (*C*HN), 43.0 (CO*C*HCH$_3$), 38.0 (*C*H$_2$Ph), 19.5 (CHOH*C*H$_3$), 10.6 (COCH*C*H$_3$).

General Procedure for the Preparation of *rac-syn*-Aldol Adducts[32]

Synthesis of *rac-syn*-aldol adducts was carried out following the procedure described in the literature.[32] *N*-Acyl-2-oxazolidinone *rac*-**9**, *rac*-**14** or *rac*-**20** (2.46 mmol) was reacted with acetaldehyde (0.240 mL, 6.9 mmol) in the presence of $TiCl_4$ (1 M solution in DCM, 2.58 mg, 2.58 mmol), (−)-sparteine (0.56 mL, 2.46 mmol) and *N*-methyl-2-pyrrolidinone (0.24 mL, 2.46 mmol). Purification *via* flash chromatography (SiO_2, hexane/EtOAc) afforded *rac-syn*-aldol adducts.

General Procedure for the Enzymatic Resolution of *rac-syn*-Aldol Adducts 10, 15 or 21

In a typical experiment racemic alcohol (0.18 mmol) and *Candida antarctica* lipase type B (6 mg, 30 $mg_{enzyme}/mmol_{substrate}$) in organic solvent (vinyl acetate, *n*-hexane, toluene, dichloromethane or diisopropyl ether, 0.8 mL) were stirred with vinyl acetate (34 μL, 0.36 mmol) at 40 °C. After 24 hours, the reaction was stopped by filtering off the enzyme. The ester was separated from unreacted alcohol by flash chromatography (SiO_2, *n*-hexane/EtOAc).

(4*S*,2′*S*,3′*R*)-*N*-(3-Acetoxy-2-methylbutanoyl)-4-benzyl-2-oxazolidinone (4*S*,2′*S*,3′*R*)-11

Yellow needles (43% in hexane); mp 79–80 °C; R_f (*n*-hexane/EtOAc, 60:40) = 0.66; HPLC (Chiralcel® OD column, *n*-hexane/2-propanol, 80:20, 1 mL min^{-1}, λ = 254 nm): t_R = 8.2 min; $[\alpha]_D^{30}$: +77.7 (*c* 0.99, $CHCl_3$); IR (CH_2Cl_2): ν = 2975,

1780, 1735, 1695, 1450, 1370, 1225, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.36-7.19$ (5H, m, C_6H_5), 5.30 (1H, dq, $J = 4.3$ and 6.4 Hz, $CHOCOCH_3$), 4.64–4.56 (1H, m, NC*H*), 4.28–4.08 (2H, m, CH_2O), 3.95 (1H, dq, $J = 4.3$ and 6.9 Hz, $COCHCH_3$), 3.27 (1H, dd, $J = 3.1$ and 13.2 Hz, CH*H*Ph), 2.76 (1H, dd, $J = 9.7$ and 13.3 Hz, C*H*HPh), 2.05 (3H, s, $OCOCH_3$), 1.28 (3H, d, $J = 6.5$ Hz, $COCHCH_3$),1.22 (3H, d, $J = 6.9$ Hz, $AcOCHCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta_C = 172.2$ (C*C*O), 151.7 (O*C*ON), 168.8 (O*C*OCH$_3$), (2C), 127.1 (2C), 125.5 (aromatic C), 68.4 (*C*HOCOCH$_3$), 64.5 (*C*H$_2$O), 54.0 (N*C*H), 40.5 (CO*C*HCH$_3$), 36.1 (*C*H$_2$Ph), 19.3 (OCO*C*H$_3$), 16.2 (AcOCH*C*H$_3$), 8.9 (COCH*C*H$_3$); MS (EI+, 70 eV): $m/z = 319$ (M^+, 10%), 259 (57), 244 (46), 178 (30), 83 (95), 43 (100); HRMS (EI+): calcd. for $C_{17}H_{21}NO_5$: 319.1420; found: 319.1417; anal. calcd. for $C_{17}H_{21}NO_5$: C 63.93%, H 6.62%, N 4.38%; found: C 63.5%, H 6.6%, N 4.2%.

(4*R*,2′*R*,3′*S*)-*N*-(3-Hydroxy-2-methylbutanoyl)-4-benzyl-2-oxazolidinone (4*R*,2′*R*,3′*S*)-10

Colourless crystals (39% in hexane); mp 114–115 °C; R_f (*n*-hexane/EtOAc, 50:50) = 0.37; HPLC (Chiralcel® OD column, *n*-hexane/2-propanol, 80:20, 1 mL min^{-1}, $\lambda = 254$ nm): $t_R = 10.0$ min; $[\alpha]_D^{30}$: −54.5 (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.36-7.20$ (5H, m, C_6H_5), 4.74–4.67 (1H, m, NC*H*), 4.26–4.10 (3H, m, $CHCH_2O$, C*H*OH), 3.74 (1H, dq, $J = 2.7$ and 7.0 Hz, $COCHCH_3$), 3.25 (1H, dd, $J = 3.5$ and 13.2 Hz, CH*H*Ph), 2.91 (1H, d, $J = 2.7$ Hz, O*H*), 2.79 (1H, dd, $J = 9.7$ and 13.4 Hz, C*H*HPh), 1.27 (3H, d, $J = 7.0$ Hz, $COCHCH_3$), 1.21 (3H, d, $J = 6.2$ Hz, $CHOHCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 178.0$ (C*C*O), 153.7 (O*C*ON), 135.6, 130.0 (2C), 129.6 (2C), 128.0 (aromatic *C*), 68.2 (*C*HOH), 66.8 (*C*H$_2$O), 55.7 (*C*HN), 43.7 (CO*C*HCH$_3$), 38.4 (*C*H$_2$Ph), 20.1 (CHOH*C*H$_3$), 11.1 (COCH*C*H$_3$); MS (FAB+, 70 eV): $m/z = 278$ ($M^+ + 1$, 100%), 261 (9), 178 (25), 117 (10), 101 (7); HRMS (FAB+): calcd. for $C_{15}H_{19}NO_4$: 277.1314; found: 277.1314; anal. calcd. for $C_{15}H_{19}NO_4$: C 64.97%, H 6.91%, N 5.05%; found: C 64.3%, H 6.9%, N 5.1%.

(4*S*,2′*S*,3′*R*)-*N*-(3-Acetoxy-2-ethylbutanoyl)-4-benzyl-2-oxazolidinone (4*S*,2′*S*,3′*R*)-16

Ester **(4*S*,2′*S*,3′*R*)-16** was isolated as a cream solid (35%); recrystallised from *n*-hexane/EtOAc; mp 61–63 °C; R_f (*n*-hexane/EtOAc, 50:50) = 0.85; HPLC (Chiralcel® OD column, *n*-hexane/2-propanol, 90:10, 1 mL min^{-1}, $\lambda = 254$ nm): $t_R = 11.5$ min; $[\alpha]_D^{30}$: +57.1 (*c* 1.05, $CHCl_3$); IR (CH_2Cl_2): $\nu = 2965$, 1780, 1730, 1695, 1380, 1235, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.36-7.21$ (5H, m, C_6H_5), 5.30–5.22 (1H, m, $CHCH_3$), 4.72–4.64 (1H, m, NC*H*), 4.24–4.10 (2H, m, CH_2O), 4.04–3.98 (1H, m, $CHCH_2CH_3$), 3.32 (1H, dd, $J = 3.2$ and 13.2 Hz, CH*H*Ph), 2.73 (1H, dd, $J = 9.9$ and 13.2 Hz, C*H*HPh), 2.01 (3H, s, $OCOCH_3$), 1.91–1.83 (1H, m, $CHHCH_3$), 1.74–1.66 (1H, m, C*H*HCH$_3$), 1.27 (3H, d, $J = 6.7$ Hz, $CHCH_3$), 0.95 (3H, t, $J = 7.4$ Hz, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 173.3$ (C*C*O), 170.4 O*C*OCH$_3$), 153.4 (O*C*ON), 135.3, 129.4 (2C), 128.9 (2C), 127.3 (aromatic C), 70.1 (*C*HCH$_3$), 66.1 (*C*H$_2$O), 55.7 (*C*HN), 48.6 (*C*HCH$_2$CH$_3$), 38.1 (*C*H$_2$Ph), 21.1 (OCO*C*H3), 20.0 (*C*H$_2$CH$_3$), 17.7 (CH*C*H$_3$), 11.7 (CH$_2$*C*H$_3$); MS (EI+, 70 eV): $m/z = 333$ (M^+, 30%), 258 (20), 157 (32), 97 (100), 69 (29), 43 (50); anal. calcd. for $C_{18}H_{23}NO_5$: C 64.85%, H 6.95%, N 4.20%; found: C 64.7%, H 7.0%, N 4.0%.

(4*R*,2′*R*,3′*S*)-*N*-(3-Hydroxy-2-ethylbutanoyl)-4-benzyl-2-oxazolidinone (4*R*,2′*R*,3′*S*)-15

Alcohol **(4*R*,2′*R*,3′*S*)-15** was isolated as a cream solid (30%); mp 73–74 °C (Lit.[40] 74–76 °C); R_f (*n*-hexane/EtOAc, 50:50) = 0.55; HPLC (Chiralcel® OD column, *n*-hexane/2-propanol, 90:10, 1 mL min^{-1}, $\lambda = 254$ nm): $t_R = 14.6$ min; $[\alpha]_D^{30}$: −15.8 (*c* 1.2, $CHCl_3$); IR (CH_2Cl_2): $\nu = 3590$, 2980, 1780, 1690, 1385, 1350, 1215, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.37-7.22$ (5H, m, C_6H_5), 4.78–4.70 (1H, m, NC*H*), 4.22–4.07 (3H, m, CH_2O, C*H*OH), 4.03–3.97 (1H, m, $CHCH_2CH_3$), 3.36 (1H, dd, $J = 3.2$ and 13.2 Hz, CH*H*Ph), 2.70 (1H, dd, $J = 10.0$ and 13.2 Hz, C*H*HPh), 2.54 (1H, s, O*H*), 1.91–1.83 (1H, m, $CHHCH_3$), 1.74–1.66 (1H, m, C*H*HCH$_3$), 1.24 (3H, d, $J = 7.0$ Hz, $CHCH_3$), 0.98 (3H, t, $J = 7.4$ Hz, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 175.5$ (C*C*O), 153.9 (O*C*ON), 135.2, 129.4 (2C), 129.0 (2C), 127.4 (aromatic C), 68.6 (*C*HOH), 66.0 (*C*H$_2$O), 55.6 (*C*HN), 50.1 (*C*HCH$_2$CH$_3$), 38.1 (*C*H$_2$Ph), 20.7 (*C*H$_2$CH$_3$), 19.5 (CH*C*H$_3$), 11.9 (CH$_2$*C*H$_3$); MS (EI+, 70 eV): $m/z = 291$ ($M^{+\cdot}$, 11%), 158 (26), 128 (27), 99 (100), 86 (67), 71 (77), 53 (33), 43 (90); anal. calcd. for $C_{16}H_{21}NO_4$: C 65.96%, H 7.27%, N 4.81%; found: C 65.6%, H 7.2%, N 4.6%.

(4*S*,2′*S*,3′*R*)-*N*-(3-Acetoxy-2-methylbutanoyl)-4-ethyl-2-oxazolidinone (4*S*,2′*S*,3′*R*)-22

Ester **(4*S*,2′*S*,3′*R*)-22** was isolated as a yellow oil (33%); HPLC (Chiralcel® OD column, *n*-hexane/2-propanol 80:20, 1 mL min^{-1}, $\lambda = 254$): $t_R = 6.0$; $[\alpha]_D^{30}$: −86.6 (*c* 0.30, $CHCl_3$); IR (film): $\nu = 2985$, 2940, 1780, 1735, 1385, 1370, 1700, 1240, 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta_H = 5.27$ (1H, dq, $J = 3.2$ and 6.4 Hz, $CHOCOCH_3$), 4.44–4.35 (2H, m, C*H*N, OCH*H*), 4.13 (1H, dd, $J = 1.8$ and 8.0 Hz, OC*H*H), 3.96 (1H, dq, $J = 3.4$ and 6.9 Hz, $COCHCH_3$), 2.02 (3H, s, $OCOCH_3$), 1.82–1.72 (2H, m, CH_2CH_3), 1.26 (3H, d, $J = 6.4$ Hz, $COCHCH_3$), 1.19 (3H, d, $J = 6.9$ Hz, $AcOCHCH_3$), 0.92 (3H, t, $J = 7.5$ Hz, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta =$ 174.0 (C*C*O), 170.6 (O*C*OCH$_3$), 153.8 (O*C*ON), 70.3 (*C*HOC-OCH$_3$), 66.8 (*C*H$_2$O), 55.6 (*C*HN), 42.1 (CO*C*HCH$_3$), 25.1 (*C*H$_2$CH$_3$), 21.1 (OCO*C*H$_3$), 18.1 (AcOCH*C*H$_3$), 11.0 (COCH*C*H$_3$), 8.2 (CH$_2$*C*H$_3$); MS (CI+, 70 eV): $m/z = 258$ ($M^+ + 1$, 55%), 198 (100), 171 (12), 143 (21), 83 (40); anal. calcd. for $C_{12}H_{19}NO_5$: C 56.02%, H 7.44%, N 5.44%; found C 55.6%, H 7.5%, N 5.4%.

(4*R*,2′*R*,3′*S*)-*N*-(3-Hydroxy-2-methylbutanoyl)-4-ethyl-2-oxazolidinone (4*R*,2′*R*,3′*S*)-21

Unreacted alcohol **(4*R*,2′*R*,3′*S*)-21** was obtained as a colourless oil (36%); R_f (*n*-hexane/EtOAc, 40:60) = 0.53; HPLC (Chiralcel® OD column, *n*-hexane/2-propanol 80:20, 1 mL min^{-1}, $\lambda = 254$): $t_R = 7.3$ min; $[\alpha]_D^{30}$: −40.0 (*c* 0.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta_H = 4.50-4.45$ (1H, m, C*H*N), 4.40 (1H, app. t, $J = 8.5$ Hz, OCH*H*), 4.17–4.10 (2H, m, OC*H*H, C*H*OH), 3.71 (1H, dq, $J = 3.5$ and 7.1 Hz,

COC*H*CH_3), 2.98 (1H, s, O*H*), 1.82 – 1.72 (2H, m, C$H_2$$CH_3$), 1.24 (3H, d, $J = 7.0$ Hz, COCHCH_3), 1.19 (3H, d, $J = 6.4$ Hz, CHOHCH_3), 0.93 (3H, t, $J = 7.5$ Hz, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 177.9$ (C*C*O), 153.8 (O*C*ON), 67.8 (*C*HOH), 67.1 (*C*H_2O), 55.3 (*C*HN), 43.4 (CO*C*HCH$_3$), 25.3 (*C*$H_2$$CH_3$), 19.9 (CHOH*C*$H_3$), 11.0 (COCH*C*$H_3$), 8.4 ($CH_2$*C*$H_3$); MS (CI +, 70 eV): $m/z = 216$ ($M^+ + 1$, 100%), 198 (81), 171 (16), 142 (11), 116 (23), 83 (11); anal. calcd. for $C_{10}H_{17}NO_4$: C 55.80%, H 7.96%, N 6.51% ; found C 55.6%, H 7.9%, N 6.6%.

General Procedure for the Hydrolysis of Unreacted Alcohols (4*R*,2′*R*,3′*S*)-10 and 21 and Esters(4*S*,2′*S*,3′*R*)-11 and 22[33]

Hydrolyses of the enzymatically resolved esters and alcohol was carried out following the procedure reported in the literature.[34] To a solution of alcohol or ester (0.37 mmol) in THF/H_2O (2 mL, 80:20) at 0 °C, 30% aqueous hydrogen peroxide (15 μL) was added slowly, followed by LiOH (11.7 mg, 0.5 mmol) in water (1 mL).

(2*R*,3*S*)-3-Hydroxy-2-methylbutanoic Acid (2*R*,3*S*)-13

Yellow oil; $[\alpha]_D^{30}$: +6.9 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.8$ (2H, br s, 2 × O*H*), 4.15 – 3.94 (1H, dq app. m, C*H*OH), 2.59 (1H, dq, $J = 3.7$ and 7.2 Hz, COC*H*CH_3), 1.23 (3H, d, $J = 3.9$ Hz, COCHCH_3), 1.22 (3H, d, $J = 3.1$ Hz, CHOHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 180.5$ (*C*OOH), 67.9 (CO*C*HCH$_3$), 45.2 (*C*HOH), 19.7 (CHOH*C*H_3), 10.9 (COCH*C*H_3). ^{1}H and ^{13}C NMR data were in accordance with those reported in the literature.[39]

(2*S*,3*R*)-3-Hydroxy-2-methylbutanoic Acid (2*S*,3*R*)-13

Yellow oil; $[\alpha]_D^{30}$: −6.8 (*c* 1.02, $CHCl_3$); ^{1}H and ^{13}C NMR data were in accordance with those reported in the literature.[39]

(*R*)-(+)-4-Ethyl-2-oxazolidinone (*R*)-19

Yellow oil (82%); $[\alpha]_D^{30}$: +5.5 (*c* 0.63, $CHCl_3$), (Lit.[41] +5.8 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.52$ (1H, s br, N*H*), 4.48 (1H, app. t, $J = 8.5$ Hz, CH*H*O), 4.03 (1H, dd, $J = 6.0$ and 8.5 Hz, C*H*HO), 3.86 – 3.77 (1H, m, C*H*N), 1.66 – 1.55 (2H, m, C$H_2$$CH_3$),0.92 (3H, t, $J = 7.5$ Hz, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 160.3$ (N*C*O), 70.0 (*C*H_2O), 53.8 (*C*HN), 28.2 (*C*$H_2$$CH_3$), 9.3 (*C*$H_3$).

(*S*)-(−)-4-Ethyl-2-oxazolidinone (*S*)-19

Yellow oil (87%); $[\alpha]_D^{30}$: −5.3 (*c* 0.60, $CHCl_3$). ^{1}H and ^{13}C NMR data were in accordance with those above reported for 4-ethyl-2-oxazolidinone **(*R*)-19**.

Preparation of (4*R*,2′*R*,3′*S*)-*N*-(3-Acetoxy-2-methylbutanoyl)-4-benzyl-2-oxazolidinone (4*R*,2′*R*,3′*S*)-10[38]

Ester **(4*R*,2′*R*,3′*S*)-10** was prepared following the procedure reported in the literature.[40]

Acetic acid (20.2 μL, 0.35 mmol), DMAP (4-dimethylaminopyridine) (34.5 mg, 0.28 mmol) and DCC (dicyclohexylcarbodiimide) (80.4 mg, 0.39 mmol) were reacted with alcohol **(4*R*,2′*R*,3′*S*)-10** (296 mg, 1.06 mmol) in anhydrous dichloromethane (5 mL). Purification *via* flash chromatography (*n*-hexane/EtOAc, 60:40) afforded acylated aldol adduct **(4*R*,2′*R*,3′*S*)-11** as yellow needles (220 mg, 65%); mp 81 – 82 °C; R_f (*n*-hexane/EtOAc, 60:40) = 0.65; HPLC (Chiralcel® OD column, *n*-hexane/2-propanol 80:20, 1 mL min^{-1}, $\lambda =$ 254 nm): $t_R = 7.6$ min; $[\alpha]_D^{30}$: −75.5 (*c* 0.96, $CHCl_3$); IR ($CHCl_3$): $\nu = 3520$, 2980, 1780, 1735, 1700, 1450, 1380, 1235, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.36 – 7.19$ (5H, m, C_6H_5), 5.30 (1H, dq, $J = 4.3$ and 6.4 Hz, C*H*OCOCH$_3$), 4.64 – 4.56 (1H, m, NC*H*), 4.28 – 4.08 (2H, m, CH_2O), 3.95 (1H, dq, $J = 4.3$ and 6.8 Hz, COC*H*CH_3), 3.27 (1H, dd, $J = 3.2$ and 13.3 Hz, CH*H*Ph), 2.76 (1H, dd, $J = 9.7$ and 13.3 Hz, C*H*HPh), 2.05 (3H, s, OCOCH_3), 1.28 (3H, d, $J = 6.4$ Hz, COCHCH_3), 1.23 (3H, d, $J = 6.9$ Hz, AcOCHCH_3); ^{13}C NMR (75.5 MHz, CDCl3): $\delta = 172.2$ (C*C*O), 168.8 (O*C*OCH$_3$), 151.7 (O*C*ON), 135.8, 129.9 (2C), 129.4 (2C), 127.8 (aromatic C), 70.8 (*C*HOCOCH$_3$), 66.8 (*C*H_2O), 56.2 (N*C*H), 42.8 (CO*C*HCH$_3$), *C*H_2Ph), 21.6 (OCO*C*H_3), 18.5 (AcOCH*C*H_3), 11.3 (COCH*C*H_3); MS (FAB, 70 eV): $m/z = 320$ ($M^+ + 1$, 88%), 260 (100), 178 (14), 143 (12), 117 (9), 83 (65); anal. calcd. for $C_{17}H_{21}NO_5$: C 63.93%, H 6.62%, N 4.38%; found: C 64.4%, H 6.8%, N 4.0%.

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