Tetrahedron 66 (2010) 4167–4194

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Alkylation and aldol reactions of acyl derivatives of *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine: asymmetric synthesis of α-alkoxy-, α-substituted-β-alkoxy- and α,β-dialkoxyaldehydes

Alexander N. Chernega [a], Stephen G. Davies [a,*], Ai M. Fletcher [a], Christopher J. Goodwin [b], David Hepworth [a,†], R. Shyam Prasad [a], Paul M. Roberts [a], Edward D. Savory [a], Andrew D. Smith [a], James E. Thomson [a]

[a] *Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK*
[b] *AstraZeneca R&D Charnwood, Process R&D, Bakewell Road, Loughborough, Leicestershire LE11 5RH, UK*

ARTICLE INFO

Article history:
Received 11 January 2010
Received in revised form 11 March 2010
Accepted 29 March 2010
Available online 2 April 2010

Keywords:
Weinreb amide
Glycolate enolate
Diastereoselective alkylation
Aldol reaction

ABSTRACT

Treatment of a range of *O*-protected glycolate derivatives of the chiral auxiliary *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine with KHMDS in the presence of 18-crown-6 followed by addition of an alkyl halide generates α-substituted derivatives with very high levels of diastereoselectivity. Alternatively, reaction of the potassium enolate of a propanoate or *O*-protected glycolate derivative of *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine with a range of aldehydes gives *syn*-aldol products with high levels of diastereoselectivity. These adducts may be reductively cleaved with $LiAlH_4$ to give enantiopure α-alkoxy-, α-substituted-β-alkoxy- and α,β-dialkoxyaldehydes in good yield.

1. Introduction

Chiral glycolate enolates are useful synthetic intermediates for the preparation of α-hydroxy carbonyl compounds through stereoselective alkylation reactions, and α,β-dihydroxy carbonyl compounds through stereoselective aldol reactions, as demonstrated by the application of both these approaches to the synthesis of complex natural product targets.[1] We have recently reported that *N*-acyl derivatives of *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **1** are able to act as chiral Weinreb amide equivalents.[2,3] Treatment of *N*-acyl derivatives **2** with KHMDS followed by an alkyl halide proceeds with high levels of diastereoselectivity (>95:5 dr) to give the corresponding α-substituted derivatives **3** in good yield and as single diastereoisomers (>99:1 dr) after purification. We have rationalized the stereochemical outcome of these alkylation reactions by invoking a chiral relay mechanism.[4] Treatment of **3** with $LiAlH_4$ or MeLi gives direct access to the corresponding α-stereogenic aldehyde or ketone **4** (Fig. 1).

As part of our ongoing exploitation of this auxiliary for the synthesis of enantiopure building blocks,[5] we examined the preparation of glycolate derivatives of **1** and their subsequent stereoselective alkylation and aldol reactions, followed by reductive cleavage to facilitate the preparation of α-hydroxy- and α,β-dihydroxyaldehydes. The results of these investigations are delineated herein.

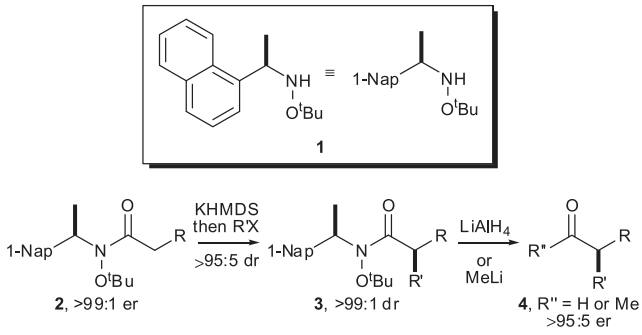


Figure 1. Alkylation of chiral Weinreb amide equivalents **2**, derived from *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **1**, and cleavage to give homochiral carbonyl compounds **4**. [1-Nap=1-naphthyl.].

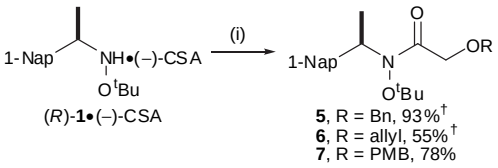
* Corresponding author. E-mail address: steve.davies@chem.ox.ac.uk (S.G. Davies).
† Present address: Pfizer Groton Laboratories, Eastern Point Road, Groton, CT 06340, USA.

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.03.105

2. Results and discussion

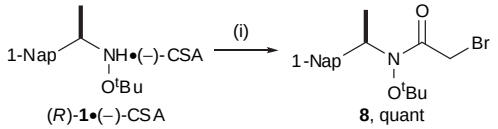
2.1. Synthesis of α-alkoxyacetyl derivatives of *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine

α-Alkoxy hydroxamates **5**–**7** were prepared upon treatment of the diastereoisomerically pure camphorsulfonic acid (CSA) salt (*R*)-**1**·(−)-CSA [or (*S*)-**1**·(+)-CSA][2] with the requisite *O*-protected glycolic acid chloride under Schotten–Baumann[6] conditions (Scheme 1).



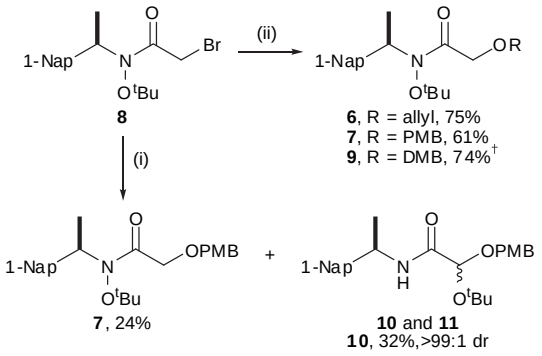
Scheme 1. Reagents and conditions: (i) $ROCH_2COCl$, NaOH (2 M aq), CH_2Cl_2, 0 °C to rt. [1-Nap=1-naphthyl. PMB=4-methoxybenzyl. †Reaction performed in both enantiomeric series].

Although this method was generally high yielding, preparation of some of the *O*-protected glycolic acid chlorides required multistep syntheses. We have previously shown that acylation of 4-alkyl-5,5-dimethyloxazolidin-2-one (SuperQuat) chiral auxiliaries[7] with bromoacetyl bromide can be followed by displacement of bromide ion with a secondary amine to give α-aminoacetyl SuperQuat derivatives for use in aldol reactions,[8] and it was anticipated that a similar approach could be employed for the preparation of the desired glycolate derivatives of **1**. Acylation of (*R*)-**1**·(−)-CSA with bromoacetyl bromide and K_2CO_3 in CH_2Cl_2 gave *N*-bromoacetyl hydroxamate **8** in quantitative yield after chromatography (Scheme 2).



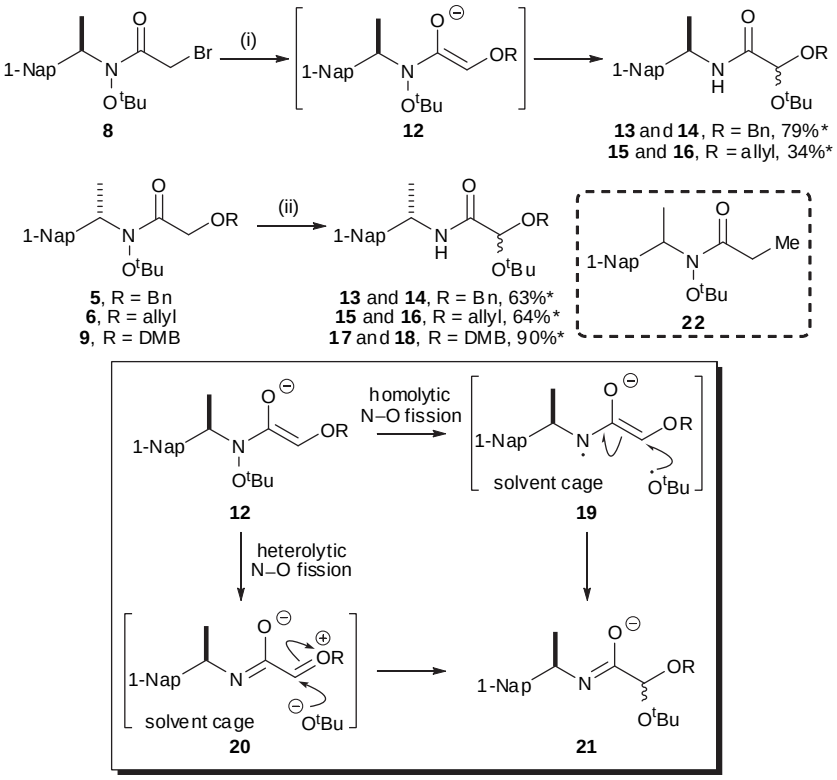
Scheme 2. Reagents and conditions: (i) $BrCH_2COBr$, K_2CO_3, CH_2Cl_2, 0 °C. [1-Nap=1-naphthyl.].

Attempted preparation of 4-methoxybenzyloxyacetyl adduct **7** from bromide **8** by displacement with sodium 4-methoxybenzyloxide (prepared by treatment of 4-methoxybenzylalcohol with NaH) gave 50% conversion to **7**. An attempt to drive the reaction to completion by increasing the number of equivalents of alkoxide resulted in >90% consumption of starting material to give a mixture of the required product and the diastereoisomeric acetals **10** and **11** [whose absolute C(2)-configurations were not assigned]. Chromatography allowed isolation of the desired product **7** and the less polar acetal **10** in 24 and 32% yield, respectively. Repeated column chromatography failed to afford a pure sample of the more polar acetal diastereoisomer **11**. Optimisation of this reaction to favour the production of **7** revealed that long reaction times and the use of excess alkoxide were deleterious, and resulted in decomposition of required product **7** to acetals **10** and **11**. However, when the displacement reaction was conducted with 1.05 equiv of sodium 4-methoxybenzyloxide in the presence of 15-crown-5 and catalytic tetrabutylammonium iodide in THF, a 90:5:5 mixture of **7**:**10**:**11** (along with trace amounts of other unknown impurities) was produced, from which **7** was isolated in 61% yield after chromatography. This procedure is readily applicable to gram-scale synthesis, and enabled the synthesis of glycolate derivatives **6** and **9** in good yield by use of allyl alcohol and 3,4-dimethoxybenzyl alcohol in an analogous reaction protocol, respectively (Scheme 3).



Scheme 3. Reagents and conditions: (i) NaH (1.5 equiv), PMBOH (2.0 equiv), THF, 0 °C to rt, 6 h; (ii) NaOR (1.05 equiv), 15-crown-5, $Bu_4N^+I^-$ (cat), THF, 0 °C to rt, 2 h. [1-Nap=1-naphthyl. PMB=4-methoxybenzyl. DMB=3,4-dimethoxybenzyl. †Reaction performed in the opposite enantiomeric series].

The production of the diastereoisomeric acetals **10** and **11** in these reactions was unexpected. The corresponding *O*-benzyl and *O*-allyl compounds **13**–**16** were also produced as the major products when (*R*)-**8** was treated with an excess of the corresponding alkoxide ion in the absence of tetrabutylammonium iodide. There appear to be two plausible mechanisms for this interesting rearrangement. Displacement of bromide by alkoxide gives the corresponding alkoxyacetyl adduct; in the presence of excess alkoxide, this species may be deprotonated to give an enolate **12**, which may rearrange by two possible pathways. Homolytic fission of the weak N−O bond leads to a radical pair **19**, contained in a solvent cage.[9] The electrophilic *tert*-butoxy radical attacks the enolate radical anion to give **21**, which gives the diastereoisomeric acetal products upon work-up. This mechanism is analogous to that of the well-known [1,2]-Wittig rearrangement of ethers[10] and the Stevens rearrangement of quaternary ammonium salts.[11] Alternatively, heterolytic fission of the N−O bond, assisted by the oxygen lone pair, results in an ion pair **20** confined within a solvent cage.[9] The *tert*-butoxide anion attacks the oxonium moiety to form **21**, leading to the acetals upon work-up. This mechanism also has a close relative in β-lactam chemistry[12] where it is possible to add nucleophiles to the α-carbon of the enolate of a β-lactam derivative bearing a good leaving group on the nitrogen atom. In order to probe these mechanistic hypotheses (i.e., that the diastereoisomeric acetals result from an enolate decomposition pathway), hydroxamate (*S*)-**9** was treated with KHMDS; the solution turned pale yellow, consistent with the presence of the enolate, and was held at −78 °C for 1 h. After aqueous work-up ^1H NMR spectroscopic analysis revealed only the presence of starting material (quantitative mass return), indicating that the potassium enolate of (*S*)-**9** is stable at −78 °C. However, when the experiment was repeated and the mixture was allowed to warm to 0 °C over 30 min, an 80:20 mixture of the diastereoisomeric acetals **17** and **18** was produced. Chromatography allowed partial separation, giving a sample enriched in the major diastereoisomer in 86:14 dr and 73% yield, and a sample enriched in the minor diastereoisomer in 58:42 dr and 17% yield. An analogous procedure applied to (*S*)-**5** gave an 80:20 mixture of acetals **13** and **14**. Chromatography allowed the isolation of the major diastereoisomer in 53% yield and >95:5 dr, and the minor diastereoisomer in 10% yield and 93:7 dr, after further purification by crystallisation. Similar treatment of (*R*)-**6** resulted in the formation of **15** and **16** (80:20 dr) as the only products; no trace of any products resulting from a [2,3]-Wittig rearrangement were

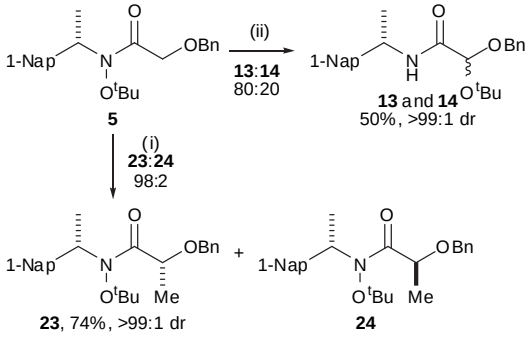


Scheme 4. Reagents and conditions: (i) NaH, ROH, THF, 0 °C to rt, 2 h; (ii) KHMDS, THF, −78 °C to 0 °C, 1 h. [1-Nap=1-naphthyl. PMB=4-methoxybenzyl. DMB=3,4-dimethoxybenzyl. *Combined yield for both diastereoisomers].

noted. In contrast to these observations, we have previously reported that the potassium enolate of (*RS*)-**22** does not fragment or rearrange upon warming,[2] which suggests that the presence of the oxygen atom within **5**–**7** and **9** is important in promoting this enolate fragmentation reaction (Scheme 4).

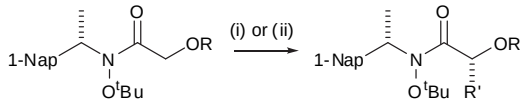
2.2. Alkylation reactions of α-alkoxyacetyl hydroxamates

With an efficient route to a range of α-alkoxyacetate derivatives **5**–**7** and **9** in hand, attention focused on their diastereoselective elaboration by enolate alkylation. Having established that the potassium enolate derived from the *O*-DMB glyoxalate derivative **9** was stable at −78 °C but rearranged upon warming to rt, it was hoped that enolate alkylation reactions of **5**–**7** and **9** could be carried out at −78 °C as our previous studies in this area have revealed enolates derived from hydroxamates such as **22** are highly reactive, even at −78 °C, and undergo efficient alkylation reactions with less reactive alkyl halides such as ethyl iodide.[2] Under our previously reported conditions,[2,4] treatment of **5** with KHMDS in THF at −78 °C followed by addition of MeI gave **23** in 98:2 dr. Chromatographic purification gave (2*R*,1′*S*)-**23** in 74% yield and >99:1 dr. The relative configuration within **23** was assigned by analogy to the alkylation reactions of the simple acyl derivatives (e.g., **22**),[2,4] with the absolute configuration being assigned from the known (*S*)-stereocentre within the chiral auxiliary. Encouraged by this initial result, alkylation with less reactive electrophiles was investigated. Unfortunately, treatment of **5** with KHMDS followed by ethyl iodide or pentyl iodide returned only staring material in both cases. When the alkylation reaction with pentyl iodide was allowed to warm slowly to rt, an 80:20 mixture of the diastereoisomeric acetals **13** and **14** was produced, indicating that enolate fragmentation, rather than alkylation, was the favoured pathway (Scheme 5).



Scheme 5. Reagents and conditions: (i) KHMDS, THF, −78 °C, 30 min, then MeI, −78 °C, 8 h; (ii) KHMDS, THF, −78 °C, 30 min, then $C_5H_{11}I$, −78 °C to rt, 24 h. [1-Nap=1-naphthyl.].

These results suggest that the enolate derived from **5** is less nucleophilic than those of the standard acyl derivatives of the chiral auxiliary **1** (e.g., the enolate derived from **22**). It was therefore reasoned that the reactivity of the enolate needed to be increased to allow efficient alkylation by a range of unactivated electrophiles. We have previously demonstrated that benzylation of the potassium enolate derived from hydroxamate **22** proceeds with high levels of diastereoselectivity at −78 °C both in the absence and presence of 18-crown-6.[4] It was hoped that employing this additive with hydroxamate **5** would generate the corresponding (more reactive) 'naked' enolate, which may undergo alkylation at −78 °C. Deprotonation of **5** in the presence of 18-crown-6 followed by addition of pentyl iodide at −78 °C gave >90% conversion to a single diastereoisomer (>95:5 dr) of alkylated product. Purification gave **28** in 63% yield and >99:1 dr. Encouraged by these results, a range of alkylation reactions of hydroxamates **5**–**7** and **9** were performed. In each case, excellent levels of diastereoselectivity were noted and



5-7 and **9** — **23** and **25-35**

	R	conditions	R′X	product	*dr*[a]	yield %[b]
5[‡]	Bn	(i)	MeI	**23**[‡]	>95:5	74
5	Bn	(ii)	MeI	**23**	>95:5	81
5	Bn	(i)	allylBr	**25**	>95:5	37
5	Bn	(ii)	allylBr	**25**	>95:5	95
5	Bn	(ii)	EtI	**26**	>95:5	79
5	Bn	(ii)	$ArCH_2Br$	**27**	>95:5	81
5	Bn	(ii)	$C_5H_{11}I$	**28**	>95:5	63
6[†]	allyl	(i)	MeI	**29**[†]	>95:5	quant
6[†]	allyl	(ii)	MeI	**29**[†]	>95:5	96
6	allyl	(ii)	allylBr	**30**	>95:5	76
6[†]	allyl	(ii)	PrI	**31**[†]	>95:5	62
6	allyl	(ii)	BnBr	**32**	>95:5	88
7[†]	PMB	(ii)	$C_5H_{11}I$	**33**[†]	>95:5	87
9	DMB	(ii)	MeI	**34**	>95:5	51
9	DMB	(ii)	PrI	**35**	>95:5	92

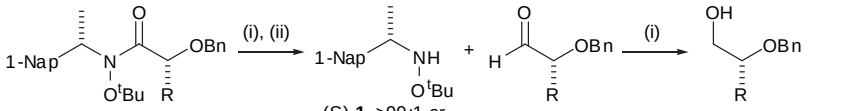
Scheme 6. Reagents and conditions: (i) KHMDS, THF, −78 °C, 30 min, then R′X, −78 °C, 8 h; (ii) KHMDS, 18-crown-6, THF, −78 °C, 30 min, then R′X, −78 °C, 8 h. [1-Nap=1-naphthyl. PMB=4-methoxybenzyl. DMB=3,4-dimethoxybenzyl. Ar=2-bromophenyl. [a]Crude. [b]Isolated yield of major diastereoisomer (>99:1 dr). [†]Reaction performed in the opposite enantiomeric series. [‡]Reaction performed in both enantiomeric series].

the alkylated products **23** and **25**–**35** were isolated as single diastereoisomers (>99:1 dr) after purification by column chromatography. In each case, the configuration of the newly formed stereocentre within the major diastereoisomeric product was assigned by analogy to the simple alkyl systems and in the case of **29** was proven unambiguously by independent synthesis from methyl (*S*)-lactate (Scheme 6).

2.3. Cleavage of α-alkoxyacetyl hydroxamates: synthesis of α-alkoxyacetyl aldehydes, ketones and iodolactones

Reduction of hydroxamate (2*S*,1′*R*)-**23** with $LiAlH_4$ gave the known aldehyde (*S*)-**36**[13] and auxiliary (*R*)-**1**. Separation was achieved by precipitation of (*R*)-**1**·(−)-CSA from pentane, which allowed isolation of (*S*)-**36** in quantitative yield and 97:3 er, and (*R*)-**1** in 87% yield and >99:1 er[14] after basification and extraction. The enantiomeric purity of **36** was determined by reduction to the known alcohol **39**[13,15] and conversion to the corresponding Mosher's ester.[16] The specific rotation of **39** {$[\alpha]_D^{21}$ +40.0 (*c* 0.1 in $CHCl_3$); lit.[13] $[\alpha]_D$ +45.9 (*c* 6.4 in $CHCl_3$); lit.[15] $[\alpha]_D^{20}$ +44.7 (*c* 3.5 in $CHCl_3$)} confirmed the absolute (*S*)-configuration, and with it the absolute (2*S*,1′*R*)-configuration within hydroxamate **23**, since the auxiliary was known to have the (*R*)-configuration. This analysis also established that the facial selectivity observed in the enolate alkylation of α-benzyloxyacetate derivative **5** was identical to that previously reported for standard acyl derivatives such as **22**.[2,4] An analogous procedure applied to hydroxamates **25** and **26** gave aldehydes **37**[17] and **38**,[18] which were assessed to be 98:2 er in both cases by reduction to alcohols **40**[17] and **41**,[18c] and subsequent conversion to the corresponding Mosher's esters[16] (Scheme 7).

Rather than isolate the aldehyde directly, it could be readily trapped by treatment of the crude reaction mixture with an ylide. Reduction of hydroxamate (2*R*,1′*S*)-**23** with $LiAlH_4$ and treatment of the crude product mixture with $Ph_3P{=}CHCO_2Me$ gave a 30:20:50 mixture of olefin isomers (*R*,*E*)-**42** (for which $^3J_{2,3}$=15.8 Hz) and (*R*,*Z*)-**43** (for which $^3J_{2,3}$=11.8 Hz), and auxiliary **1**, which were isolated in 49, 32 and 95% yield, respectively, from **23**. Despite their relatively frequent occurrence in the literature[19] there appears to be some discrepancy concerning the specific rotations of **42** and **43**. For (*R*,*E*)-**42**, we obtained $[\alpha]_D^{23}$ +67.0 (*c* 1.2 in $CHCl_3$); cf. lit. for enantiomer[19a] $[\alpha]_D^{20}$ −44 (*c* 0.2 in $CHCl_3$); lit. for enantiomer[19g] $[\alpha]_D^{23}$ −34.8 (*c* 1.2 in $CHCl_3$). For (*R*,*Z*)-**43** we obtained $[\alpha]_D^{23}$ −55.9 (*c* 0.7 in $CHCl_3$); cf. lit. for enantiomer[19a] $[\alpha]_D^{20}$ +36 (*c* 0.6 in $CHCl_3$); lit. for enantiomer[19b] $[\alpha]_D^{22}$ +25.5 (*c* 1.0 in $CHCl_3$); lit.[19j] $[\alpha]_D^{25}$ −49.2 (*c* 0.5 in $CHCl_3$). However, the previously reported preparative routes to these compounds either perform a Wittig reaction in protic solvents or a Wadsworth–Emmons-type olefination reaction using a Group I metal hydride as the base. Either of these conditions could easily cause racemisation of the stereochemically labile aldehyde **36**.[20] It is notable that the specific rotations obtained by Valverde et al.[19a] and Annunziata et al.[19b,19g] (who report values for both isomers) are smaller than the values obtained by us by factors of approximately 0.5 and 0.65, respectively, for both isomers, suggesting that that the aldehyde starting material **36** may have been racemised at some stage. In order to determine the enantiomeric purity of (*R*,*E*)-**42** and (*R*,*Z*)-**43**, the racemates were prepared by an identical route, starting from (2*RS*,1′*SR*)-**23**, and analysis of these samples by chiral HPLC showed (*R*,*E*)-**42** and (*R*,*Z*)-**43** to be of 99:1 er and 98:2 er, respectively. Thus, little or no racemisation occurs during the Wittig reaction under our conditions and, therefore, the specific rotations determined here are reliable (Scheme 8).



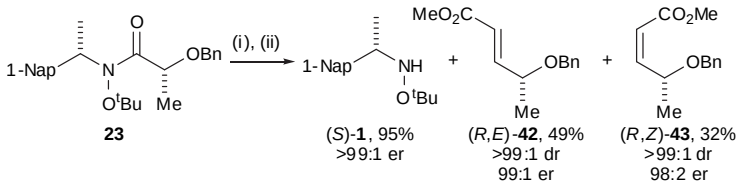
23, R = Me[†]
25, R = allyl
26, R = Et

(*S*)-**1**, >99:1 er
87% from **23**[†]
85% from **25**
85% from **26**

36, R = Me, quant[†]
37, R = allyl, 93%
38, R = Et, 98%

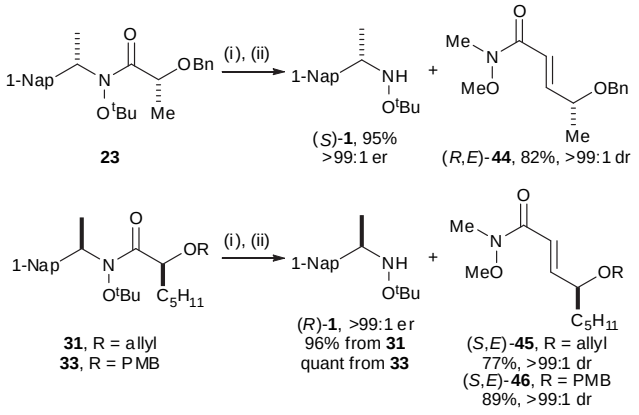
39, R = Me, 97:3 er[†]
40, R = allyl, 98:2 er
41, R = Et, 98:2 er

Scheme 7. Reagents and conditions: (i) $LiAlH_4$, THF, −10 °C; (ii) (+)-CSA, pentane. [[†]Reaction performed in the opposite enantiomeric series].



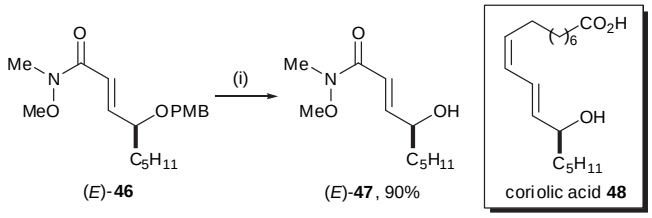
Scheme 8. Reagents and conditions: (i) $LiAlH_4$, THF, −10 °C; (ii) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, −10 °C to rt.

The reduction/Wittig olefination procedure was repeated for **23** using $Ph_3P{=}CHCON(Me)(OMe)$. This afforded α,β-unsaturated Weinreb amide **44** in a much improved (*E*)/(*Z*) ratio of 90:10. The C=C bond geometry within **44** was readily assigned from the coupling constant of 15.9 Hz between the vinylic protons in the ^1H NMR spectrum. This reaction sequence was also applied to hydroxamates **31** and **33** to produce the α,β-unsaturated Weinreb amides **45** and **46** as the major products [(*E*)/(*Z*) ≥93:7 in each case], which were isolated in good yield as single diastereoisomers after chromatographic separation from auxiliary **1**. The vinylic coupling constants in the ^1H NMR spectra of **45** and **46** (15.7 Hz for **45**, 15.4 Hz for **46**) were indicative of a *trans*-configured olefin (Scheme 9).



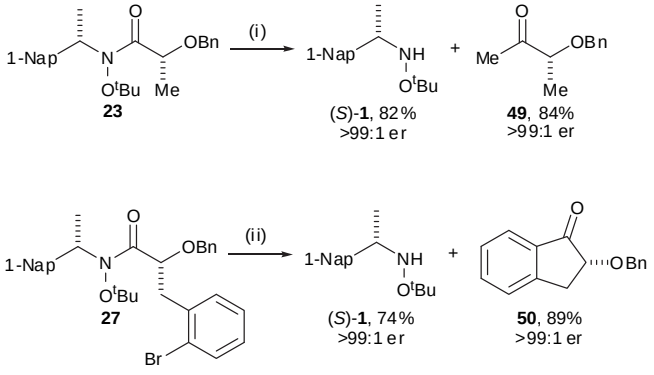
Scheme 9. Reagents and conditions: (i) $LiAlH_4$, THF, −10 °C; (ii) $Ph_3P{=}CHCON(Me)(OMe)$, CH_2Cl_2, −10 °C to rt.

Weinreb amide **46** was oxidatively debenzylated by treatment with CAN to provide **47** in 90% yield, which has been used for the synthesis of the fatty-acid metabolite Coriolic acid **48** reported by Bennani and Sharpless[21] (Scheme 10).



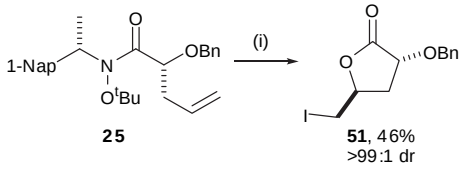
Scheme 10. Reagents and conditions: (i) CAN, MeCN, H_2O.

Treatment of (2*R*,1′*S*)-**23** with methyllithium gave a 50:50 mixture of methyl ketone **49** and auxiliary (*S*)-**1**, which were separated by flash column chromatography to give **49** in 84% yield and >99:1 er,[22] and auxiliary **1** in 82% yield and >99:1 er.[14] A halogen-metal exchange cyclisation procedure using 2-bromobenzyl substituted hydroxamate **27** gave indanone **50** and auxiliary (*S*)-**1**, which were separated by precipitation of (*S*)-**1**·(+)-CSA from pentane, followed by distillation of the residue to afford **50** in 89% yield and >99:1 er.[22] Auxiliary (*S*)-**1** was recovered in 74% yield and >99:1 er[14] upon basification of the precipitate and basic aqueous extraction (Scheme 11).



Scheme 11. Reagents and conditions: (i) MeLi, Et_2O, −15 °C; (ii) ^{t}BuLi (2 equiv), Et_2O, −78 °C.

Reaction of **25** with I_2 in THF/H_2O required eight days before the starting material was consumed; failure to let the reaction proceed to completion caused problems in the purification of the products. The reaction produced a number of by-products, and the *trans*/*cis* ratio was tentatively assigned as 85:15. Nevertheless, **51** was isolated in 46% yield and >99:1 dr after flash column chromatography. The trans relative configuration within **51** was assigned on the basis of a ^1H NMR NOE difference experiment (Scheme 12).



Scheme 12. Reagents and conditions: (i) I_2, THF/H_2O (3:1).

2.4. Aldol reactions of α-alkyl and α-alkoxy hydroxamates

Having developed efficient methodology for the asymmetric synthesis of α-alkoxy substituted compounds, attention was turned to the production of β-alkoxy- and α,β-dialkoxy substituted derivatives. It was hoped that this goal could be achieved by employing an asymmetric aldol reaction. Enolate aldol reactions of hydroxamate **22** were first investigated. Treatment of **22** with KHMDS in THF at −78 °C gave a bright yellow solution, consistent with enolate formation. Addition of benzaldehyde followed by aqueous work-up after 5 min gave >90% conversion to **52** in >95:5 dr. Purification gave **52** in 72% yield and >99:1 dr. The relative configuration within **52** was unambiguously established by single-

crystal X-ray analysis, with the absolute (2*S*,3*S*,1′*R*)-configuration being assigned from the known (*R*)-configuration of the auxiliary (Fig. 2); furthermore the determination of a Flack parameter[23] for the structure of +0.17(1), which satisfies the criterion for a reliable assignment of absolute configuration of a material known to be homochiral,[24] allowed the absolute (2*S*,3*S*,1′*R*)-configuration to be confirmed. Further analysis of the X-ray crystal structure of **52** revealed that the relative configuration of the nitrogen atom induced by the adjacent stereogenic carbon centre is in contrast to that in the X-ray structure of the alkylated hydroxamate derivative **3** (R=Bn, R′=Me) previously reported by us,[2] and that a hydrogen-bond is present between the C(3)-hydroxyl and carbonyl group. The hydrogen-bonded chelate has a flattened chair-type conformation,

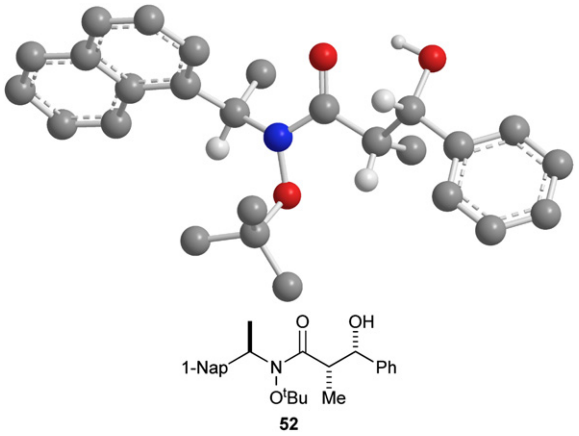
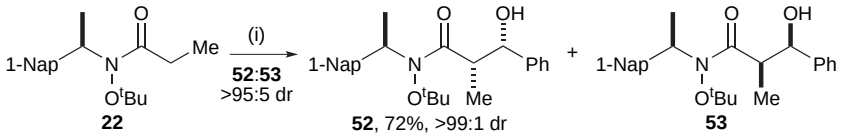


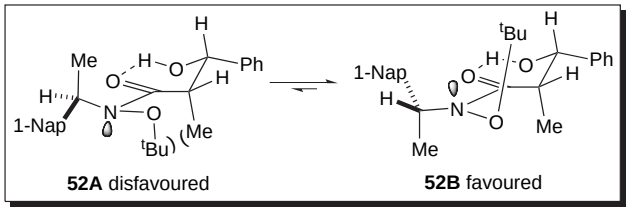
Figure 2. Chem3D representation of the single-crystal X-ray structure of **52** (some H atoms omitted for clarity).

in which the C(2)-methyl group adopts a pseudo-axial position. Adoption of the usual auxiliary conformation would result in a rather severe steric interaction between the *tert*-butyl group and the pseudo-axial C(2)-methyl group (conformation **52A**). In order to avoid this unfavourable structure, the *tert*-butyl group prefers to occupy the opposite face (conformation **52B**), with the nitrogen lone-pair *syn*-periplanar to it, i.e., a conformation about the N–O bond in accordance with the preferred conformation for hydroxylamine itself,[25] in which lone pairs and bonds are eclipsed to minimise lone pair–lone pair interactions. It is interesting to note that an intramolecular hydrogen bond is formed, rather than the putative preferred auxiliary conformation at nitrogen:[4] this suggests that more energy is gained from the former than is lost by adoption of an alternative conformation by the hydroxamate fragment, although this may be a result of crystal packing effects. In solution, it was noted that the $^3J_{2,3}$ coupling constant of 2.1 Hz was diagnostic of a *syn*-relationship.[26] Following this analysis, the minor isomer **53** observed in the crude reaction mixture was assigned a *syn*-relative configuration based upon the $^3J_{2,3}$ coupling constant of 3.2 Hz[26] (Scheme 13).

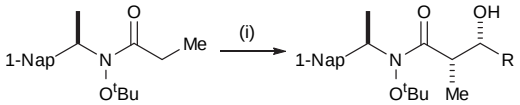
In order to test the generality of this asymmetric aldol reaction, the reaction was performed using a variety of aldehydes. Reaction of the potassium (*Z*)-enolate of **22** with pivalaldehyde gave **54** in 98:2 dr. Three diastereoisomeric products were noted in the reaction with cinnamaldehyde, with the ratio of the major diastereoisomer to the sum of the others being conservatively assigned as >95:5. Aldol reaction with isobutyraldehyde resulted in incomplete conversion to **56** as the major diastereoisomeric product and was accompanied by the formation of significant quantities of side products, thought to be aldehyde self-condensation products. Both these observations are consistent with the relatively high basicity of the potassium enolate promoting proton transfer from the enolisable aldehyde to the enolate; the resultant aldehyde enolate presumably then undergoes self-aldol reaction. When the reaction was run at −95 °C, the diastereoselectivity of the reaction remained the same although **56** was isolated in an improved 61% yield and 97:3 dr. Finally, the aldol methodology was tested using acetaldehyde, which gave **57** in 95:5 dr, which was isolated in 60% yield and 95:5 dr. In each case, the absolute configuration within the major diastereoisomeric product was assigned by analogy to that unambiguously established for the reaction with benzaldehyde to give **52**; in some cases the value of the $^3J_{2,3}$ coupling constant could be obtained (3.0–3.5 Hz) and was also supportive of these assignments (Scheme 14).

The stereochemical outcome of these enolate aldol reactions demonstrates that the facial selectivity observed is identical to that noted upon enolate alkylation. Furthermore the high level of diastereoselectivity observed here is notable, given that Group I metal enolates usually show low levels of selectivity in their enolate re-





Scheme 13. Reagents and conditions: (i) KHMDS, THF, −78 °C, 30 min, then PhCHO, THF, −78 °C, 5 min.



R	product	*dr*[a]	yield % (*dr*)[b]
^{t}Bu	**54**	98:2	60 (>99:1)
(*E*)-CH=CHPh	**55**	>95:5	78 (>99:1)
^{i}Pr	**56**	92:8	42 (97:3)
Me	**57**	95:5	60 (95:5)

Scheme 14. Reagents and conditions: (i) KHMDS, THF, −78 °C, 30 min, then RCHO, THF, −78 °C, 2 h. [[a]Crude. [b]Purified].

actions. Although the relative *syn*-configurations within **52** and **54**–**57** would be consistent with that predicted by reaction of the intermediate potassium (*Z*)-enolate through a chelated, Zimmerman–Traxler,[27] chair-like transition state, this seems unlikely due

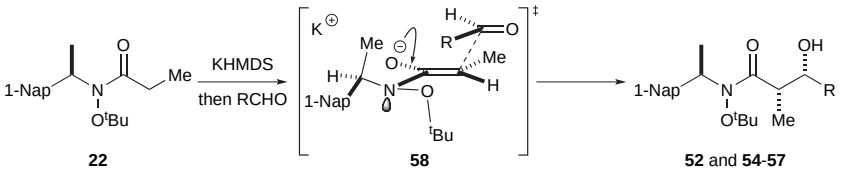


Figure 3. Postulated transition state **58** for aldol reaction of the potassium (*Z*)-enolate derived from hydroxamate **22**.

to the known, low Lewis acidity of potassium ions. In order to probe the role of the potassium counter-ion, reaction with benzaldehyde was repeated but in the presence of 18-crown-6. The diastereoselectivity of the reaction and yield of aldol products remained unaffected, which may therefore suggest that the reaction proceeds through reaction of the potassium (*Z*)-enolate [or 'naked' (*Z*)-enolate] through an open transition state[28] such as **58**, with enolate diastereofacial selectivity consistent with our proposed chiral relay model, which accounts for the high diastereofacial selectivity of alkylation[4] (Fig. 3).

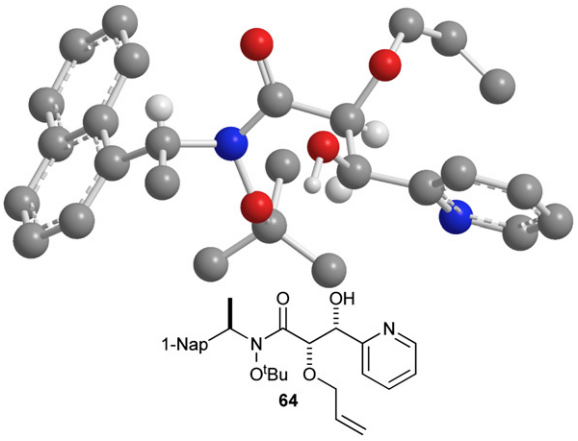
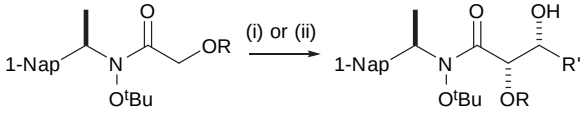


Figure 4. Chem3D representation of the single-crystal X-ray structure of **64** (some H atoms omitted for clarity).

Reaction of the potassium (*Z*)-enolate of *N*-allyloxyacetyl hydroxamate **6** with benzaldehyde was next investigated,[29] which gave aldol product **61** in 96:4 dr. Purification gave **61** in 92% yield and >99:1 dr. When the reaction was repeated in the presence of 18-crown-6, the diastereoselectivity and yield of the reaction remained high. Application to a range of aldehydes (acetaldehyde, butyraldehyde and pyridine-2-carboxaldehyde) gave similarly high levels of selectivity with the major products being isolated in modest to good yield after chromatography. The relative configuration within the pyridine-2-carboxaldehyde adduct **64** was established unambiguously by single-crystal X-ray analysis, with the absolute (2*S*,3*R*,1′*R*)-configuration being assigned from the known (*R*)-configuration within the auxiliary (Fig. 4). Therefore, the absolute configurations within the other aldol products **61**–**63** were assigned by analogy, with this analysis suggesting that the facial selectivities in the propanoate and glycolate aldol reactions are the same in this case.[30] The similar levels of selectivity observed when the reaction with benzaldehyde was performed either in the presence or absence of 18-crown-6 underscores the insignificant role of the potassium counterion in these reactions and is in accordance with an open transition state[28] analogous to **58**. In a similar manner, aldol reactions of the *O*-benzyl, *O*-PMB and *O*-DMB hydroxamates **5**, **7** and **9** with a range of aliphatic, aromatic and heteroaromatic aldehydes were performed and proceeded with modest to good levels of diastereoselectivity. On occasion, the presence of impurities in the ^{1}H NMR spectra of the crude reaction mixtures prevented the determination of the reaction diastereoselectivity. Reactions with acetaldehyde and 1-decanal proceeded to incomplete conversion, consistent with deprotonation of the aldehyde by the basic enolate; these transenolisation processes



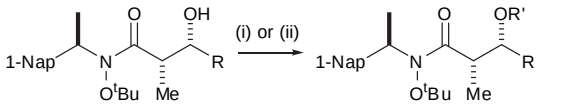
	R	conditions	R′	product	*dr*[a]	yield % (*dr*)[b]
5	Bn	(i)	Ph	**59**	86:14	75 (95:5)
5	Bn	(i)	Me	**60**	80:20	75 (80:20)
6†	allyl	(i)	Ph	**61**†	96:4	92 (>99:1)
6†	allyl	(ii)	Ph	**61**†	95:5	90 (>99:1)
6†	allyl	(i)	Me	**62**†	-	90 (>95:5)
6†	allyl	(i)	C_3H_7	**63**†	-	55 (95:5)
6	allyl	(i)	2-pyridyl	**64**	94:6	66 (>99:1)
7	PMB	(i)	Ph	**65**	83:17	87 (87:13)
7	PMB	(i)	Me	**66**	69:31	69 (87:13)
7	PMB	(i)	*p*-$C_6H_4NO_2$	**67**	-	49 (>95:5)
7	PMB	(i)	2-pyridyl	**68**	-	72 (>99:1)
7	PMB	(i)	^{t}Bu	**69**	-	95 (90:10)
7	PMB	(i)	2-thiophenyl	**70**	-	81 (90:10)
7	PMB	(i)	2-furanyl	**71**	-	71 (88:12)
7	PMB	(i)	piperonyl	**72**	81:19	66 (82:18)
8†	DMB	(i)	Ph	**73**†	83:17	77 (85:15)
8†	DMB	(i)	Me	**74**†	80:20	45 (80:20)
8†	DMB	(i)	2-pyridyl	**75**†	80:20	32 (>99:1)
8†	DMB	(i)	^{t}Bu	**76**†	85:15	72 (86:14)

Scheme 15. Reagents and conditions: (i) KHMDS, THF, −78 °C, 30 min, then R′CHO, −78 °C, 8 h; (ii) KHMDS, 18-crown-6, THF, −78 °C, 30 min, then R′CHO, −78 °C, 8 h. [1-Nap=1-naphthyl. PMB=4-methoxybenzyl. DMB=3,4-dimethoxybenzyl. †Reaction performed in the opposite enantiomeric series. [a]Crude. [b]Purified].

also resulted in the production of large amounts of impurities derived from polymerisation of the aldehyde. Chromatography gave the desired aldol products **59**, **60** and **65**–**76** in modest to good yield. In all cases, the relative configurations within the products were assigned by analogy to those proven unambiguously for **52** and **64** and, in several cases, measurement of the ^{1}H NMR $^3J_{2,3}$ coupling constants were possible; the small values recorded ($J_{2,3}$=1.0–3.0 Hz) are consistent with the assigned *syn*-configurations within these aldol adducts[26] (Scheme 15).

2.5. Cleavage of β-alkoxy hydroxamates: synthesis of α,β-dialkoxyaldehydes

Having obtained a number of aldol products with high diastereoisomeric purity, attention was turned to their transformation into enantiomerically enriched products. Reductive cleavage of the propanoate adducts with $LiAlH_4$ to produce α-alkyl-β-hydroxy-aldehydes was first examined. Prior to this, it was deemed prudent to protect the β-hydroxy group, in order to prevent problems of retro-aldol reaction during cleavage or isolation of the aldehyde products: benzyl, *tert*-butyldimethylsilyl (TBDMS) and benzyloxymethyl (BOM) were investigated for this purpose. Initially, it was hoped that a one-pot aldol reaction/O-protection sequence may be developed, making use of the high nucleophilicity of the intermediate potassium aldolate by its interception with benzyl bromide. Aldol reaction of the enolate derived from **22** with benzaldehyde was performed at −78 °C before the addition of benzyl bromide, and then the reaction mixture was allowed to warm to 0 °C. Analysis of the crude reaction product showed the production of several diastereoisomeric products **77**, consistent with a reduction in selectivity occurring through a retro-aldol/re-aldol process as the temperature was allowed to rise. This prediction was reinforced by treatment of the diastereoisomerically pure aldol product **52** with KHMDS and benzyl bromide at 0 °C, which gave the same mixture of *O*-benzylated products **77** observed previously and the *C*-benzylated product **78**,[2] which presumably arises from a retro-aldol fragmentation of the potassium aldolate followed by trapping of the so-formed potassium enolate by benzyl bromide[2] (Scheme 16).



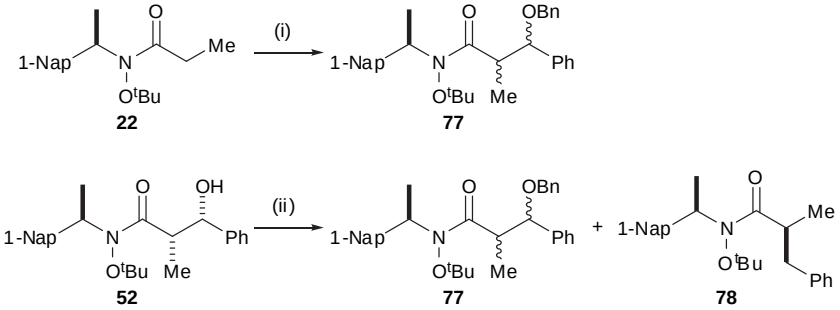
52 and **55** — **79**-**81**

	R	R'	product	yield %
52	Ph	TBDMS	**79**	80
52	Ph	BOM	**80**	94
55	(*E*)-CH=CHPh	BOM	**81**	94

Scheme 17. Reagents and conditions: (i) TBDMSCl, imidazole, DMF; (ii) BOMCl, ^{i}Pr$_2$NEt, CH_2Cl_2, Bu_4NI, 48 h.

BOM protected adducts **80** and **81** with $LiAlH_4$ under the standard conditions allowed exclusive production of the corresponding aldehydes (as single diastereoisomers, indicating that no epimerisation was occurring during the cleavage step) and auxiliary (*R*)-**1**. Attempts to isolate the aldehydes by flash column chromatography on silica gel were unsuccessful due to partial decomposition. Instead, the aldehydes were trapped by performing a Wittig reaction on the crude reduction mixture to produce unsaturated esters **82** and **83**, which were obtained as single diastereoisomers after flash column chromatography. The (*E*)-geometry of the olefins was determined from the characteristic ^{1}H NMR ^3J coupling constants of 15.9 Hz in both **82** and **83**. In both cases auxiliary (*R*)-**1** was recovered in high yield and >99:1 er[14] (Scheme 18).

Attempted application of an analogous procedure to facilitate the preparation of α,β-dihydroxyaldehydes unfortunately met with failure: treatment of **59** with BOMCl, ^{i}Pr$_2$NEt and TBAI in CH_2Cl_2 returned a complex mixture of unidentified products. However, when the aldol reaction of **5** with benzaldehyde was performed and quenched with an excess of methyl iodide at low temperature, it proved possible to trap the intermediate potassium aldolate to give an 83:17 mixture of the diastereoisomeric products **84** and **88**, respectively. The absence of acetals **13** and **14** and starting material **5** suggests rapid, complete alkylation of the potassium aldolate anion occurs at a temperature which is sufficiently low such that the enolate decomposition pathway does not compete at an appreciable rate; the observation that the diastereoselectivities are slightly lower than those of the aldol reactions themselves is consistent

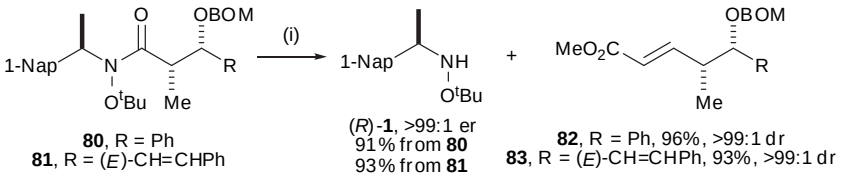


Scheme 16. Reagents and conditions: (i) KHMDS, THF, −78 °C, 30 min, then PhCHO, −78 °C, 8 h, then BnBr, −78 °C to rt; (ii) KHMDS, THF, 0 °C, 30 min, then BnBr.

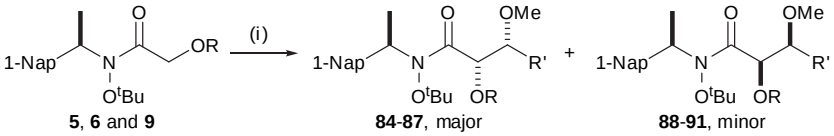
Protection of the hydroxyl group within **52** and **55** without recourse to the formation of an intermediate aldolate was investigated. Thus, O-protection upon treatment with TBDMSCl and BOMCl was achieved in high yield under mild conditions to give **79**–**81** in good yield (Scheme 17).

Attempts to cleave the auxiliary within *O*-silyl protected **79** with $LiAlH_4$ failed: at −10 °C the reaction was prohibitively slow, and allowing it to warm to rt led to a complex mixture of products, possibly due to over-reduction and/or protecting group loss. Presumably, the bulky protecting group hinders nucleophilic attack at the carbonyl group; it may also prevent chelation to the β-oxygen atom, which may otherwise assist the cleavage reaction. However, treatment of both *O*-with a degree of reversibility at the temperature of aldolate alkylation. Application to reaction of **6** and **9** with benzaldehyde, and **6** with acetaldehyde, gave mixtures of the corresponding diastereoisomeric products **85**–**87** (major products) and **89**–**91** (minor products). In each case, chromatographic purification gave samples of the major diastereoisomers **84**–**87** and in two cases it was possible to isolate and fully characterise samples of the minor diastereoisomers (**88** and **91**), for which the alternative relative *syn*-configuration was tentatively assigned (Scheme 19).

Treatment of **85** with $LiAlH_4$ resulted in the exclusive production of a 50:50 mixture of the corresponding aldehyde and auxiliary (*R*)-**1**. The crude mixture was treated with $Ph_3P{=}CHCO_2Me$ in the



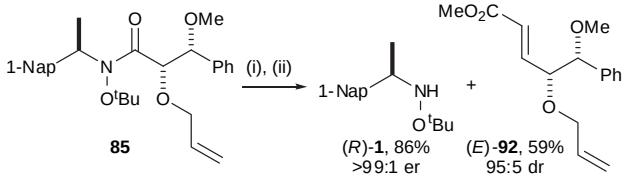
Scheme 18. Reagents and conditions: (i) $LiAlH_4$, THF, −10 °C; (ii) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, −10 °C to rt.



	R	R′	products	*dr*[a]	yield of major % (*dr*)[b]	yield of minor % (*dr*)[b]
5	Bn	Ph	**84**:**88**	83:17	72 (96:4)	10 (>99:1)
6	allyl	Ph	**85**:**89**	88:12	73 (>99:1)	-
6†	allyl	Me	**86**:**90**†	-	56 (>99:1)	-
9†	DMB	Ph	**87**:**91**†	83:17	63 (96:4)	5 (>99:1)

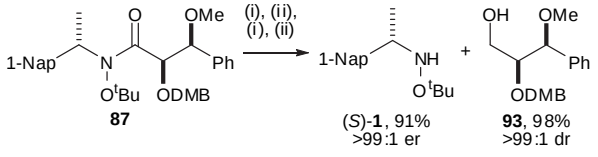
Scheme 19. Reagents and conditions: (i) KHMDS, THF, −78 °C, then RCHO, then MeI (15 equiv), −78 °C to rt. [†Reaction performed in the opposite enantiomeric series. [a]crude. [b]purified].

presence of powdered 3 Å molecular sieves to give **92** ($^3J_{2,3}$=15.7 Hz) in 95:5 dr. Purification gave auxiliary (*R*)-**1** in 86% yield and >99:1 er[14] and olefin **92** in 59% yield and 95:5 dr from **85** (Scheme 20).



Scheme 20. Reagents and conditions: (i) $LiAlH_4$, THF, −15 °C; (ii) $Ph_3P{=}CHCO_2Me$, 3 Å MS, CH_2Cl_2, 0 °C to rt.

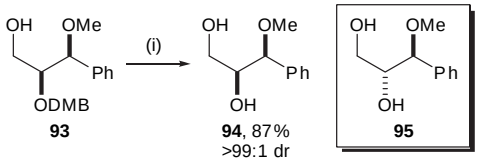
Reductive cleavage of **87** gave a 50:50 mixture of the corresponding aldehyde and auxiliary (*S*)-**1**, which was treated, without purification, with $LiAlH_4$. Chromatographic purification of the crude reaction product gave auxiliary (*S*)-**1** in 91% yield and >99:1 er[14] and alcohol **93** in 98% yield and >99:1 dr from **87** (Scheme 21).



Scheme 21. Reagents and conditions: (i) $LiAlH_4$, THF, −15 °C; (ii) pH7 phosphate buffer, pentane, 0 °C.

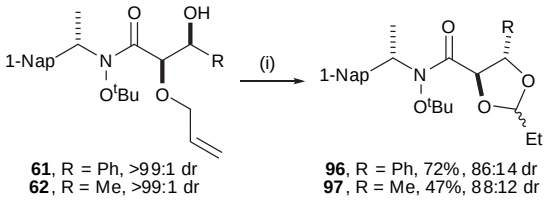
Alcohol **93** was subsequently debenzylated using DDQ to give *syn*-**94**.[31] The *anti*-alcohol **95**[32] was absent by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Column chromatography and recrystallisation from pentane afforded **94** in 87% yield and >99:1 dr. The *syn*-configuration within **94** further confirms the *syn*-diastereoselectivity of the aldol reactions (Scheme 22).

An alternative strategy for protection of the *O*-allyl glycolate aldol adducts was also devised via formation of an acetal through allyl isomerisation. Although refluxing **61** or **62** with Wilkinson's catalyst for 3 h returned starting material, and reaction for extended periods (>24 h) resulted in extensive decomposition to unknown product mixtures, refluxing **62** with *trans*-$Pd(NH_3)_2Cl_2$ (0.33 equiv) in *tert*-



Scheme 22. Reagents and conditions: (i) DDQ, CH_2Cl_2/H_2O (5:1).

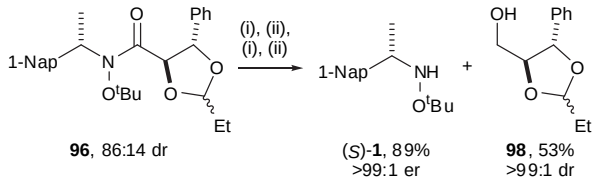
butanol for 18 h[33] gave the required product **97** as a 75:25 mixture of diastereoisomers. Chromatography gave **97** in 47% yield, as an 88:12 mixture of diastereoisomers. The reaction of **61** with 0.1 equiv of *trans*-$Pd(NH_3)_2Cl_2$ gave **96** as an 86:14 mixture of diastereoisomers, in 72% isolated yield (and 86:14 dr) after chromatography. The palladium-catalysed procedure provided high yields of *O*-protected aldol adducts in a single, experimentally simple synthetic step, and the low diastereoselectivity of cyclisation is not believed to be a drawback of this approach since the diastereoisomerism is only a feature of the protecting group (Scheme 23).



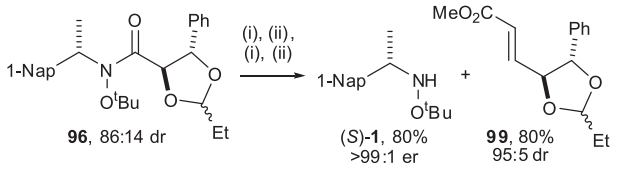
Scheme 23. Reagents and conditions: (i) *trans*-$Pd(NH_3)_2Cl_2$, ^{t}BuOH, reflux.

Reductive cleavage of **96** using $LiAlH_4$, to give a 50:50 mixture of auxiliary (*S*)-**1** and the corresponding aldehyde, which was treated with $LiAlH_4$ without further purification to give a mixture of (*S*)-**1** and alcohol **98**. Purification by column chromatography afforded auxiliary (*S*)-**1** in 89% yield and >99:1 er[14] and alcohol **98** as a single diastereoisomer (of unknown configuration at the acetal stereogenic centre) in 53% yield from **96** (Scheme 24).

Similarly, sequential treatment of **96** with $LiAlH_4$ followed by $Ph_3P{=}CHCO_2Me$ gave a mixture of auxiliary (*S*)-**1**, and (*E*)-olefin **99** in 95:5 dr. Purification by chromatography gave (*S*)-**1** in 80% yield and >99:1 er[14] and (*E*)-**99** in 80% yield and 95:5 dr (Scheme 25).



Scheme 24. Reagents and conditions: (i) $LiAlH_4$, THF, −15 °C; (ii) pH7 phosphate buffer, pentane, 0 °C.



Scheme 25. Reagents and conditions: (i) $LiAlH_4$, THF, −15 °C; (ii) $Ph_3P{=}CHCO_2Me$, 3 Å MS, CH_2Cl_2, 0 °C to rt.

3. Conclusion

The chiral auxiliary *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine has been used to promote highly diastereoselective alkylation reactions on an α-alkoxyacetate side chain. These reactions generally require the addition of 18-crown-6 to enhance the rate of alkylation and suppress the enolate rearrangement which occurs at temperatures above −78 °C. The alkylated α-alkoxyacetate derivatives are readily transformed into α-alkoxy aldehydes, ketones and iodolactones with high enantiomeric purity. A number of *O*-protected γ-hydroxy-α,β-unsaturated carbonyl compounds were also produced by a sequential reductive cleavage/Wittig reaction procedure. Alternatively, aldol reaction of the potassium enolate gave *syn*-aldol products upon reaction with an aldehyde. Good diastereocontrol over both newly generated stereogenic centres was observed. After suitable protection of the β-hydroxyl group, the aldol products may be reductively cleaved with $LiAlH_4$ to afford aldehydes with high diastereoisomeric and enantiomeric purity. Thus, the chiral auxiliary *N*-1-(1′-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine has been shown to be effective for the synthesis of a range of chiral oxygen-containing molecules in high enantiomeric purity.

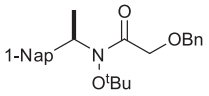
4. Experimental

4.1. 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 according to the procedure outlined by Grubbs et al.,[34] or by distillation from sodium benzophenone ketyl (THF). KHMDS was titrated according to an amalgamation of the procedures reported by Duhamel and Plaquevent,[35] and Lin and Paquette.[36] Other solvents and reagents 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 Dyson Perrins Laboratory, University of Oxford, UK, or 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 a 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 Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. The ^{13}C NMR spectra of many of hydroxamate derivatives contained peaks that were very broad (and in some cases absent). 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 Micro-TOF internally calibrated with polyalanine, 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.

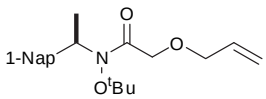
4.1.1. *(R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl 2-benzyloxyacetamide (R)-**5**.*



2-Benzyloxyacetyl chloride (4.50 g, 24.4 mmol) was added dropwise to a vigorously stirred mixture of 2 M aq NaOH (20 mL, 40 mmol) and (*R*)-**1**·(−)-CSA (5.78 g, 12.2 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After 48 h, the reaction mixture was partitioned between 1 M aq NaOH (100 mL) and CH_2Cl_2 (100 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, pentane/Et_2O, 19:1; increased to pentane/Et_2O, 4:1) gave (*R*)-**5** as a colourless oil (4.44 g, 93%); R_f 0.35 (pentane/Et_2O, 9:1); found C, 76.9; H, 7.6; N, 3.3%; $C_{25}H_{29}NO_3$ requires C, 76.7; H, 7.5; N, 3.6%; $[\alpha]_D^{23}$ +28.6 (*c* 1.1 in $CHCl_3$); ν_{max}(film) 1683 (C=O), 1600 (C=C); δ_H (500 MHz, PhMe-d_8, 70 °C) 0.64 (9H, br s, CMe_3), 1.63 (3H, d, *J* 6.8, C(1′)*Me*), 4.22 (1H, d, *J* 16.6, C(2)H_A), 4.34 (1H, d, *J* 16.6, C(2)H_B), 4.63 (1H, d, *J* 11.8, OC$H_A$$H_B$Ph), 4.68 (1H, d, *J* 11.8, OCH$_A$$H_B$Ph), 6.25 (1H, q, *J* 6.8, C(1′)*H*), 6.98–7.67 (11H, m, *Ar*, *Ph*), 8.42–8.46 (1H, br m, *Ar*); δ_C (50 MHz, $CDCl_3$) 27.7, 55.0, 69.0, 73.3, 82.6, 124.9, 125.7, 126.1, 126.6, 127.9, 128.3, 128.5, 133.6, 137.5; *m*/*z* (APCI$^+$) 392 ([M+H]$^+$, 100%).

Analogous treatment of (*S*)-**1**·(+)-CSA gave (*S*)-**5** as a colourless oil; $[\alpha]_D^{23}$ −28.9 (*c* 1.6 in $CHCl_3$).

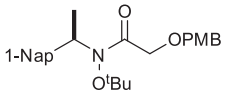
4.1.2. *(R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl 2-allyloxyacetamide **6**.*



2-Allyloxyacetyl chloride (4.39 g, 23.8 mmol) was added dropwise to a vigorously stirred mixture of 2 M aq NaOH (10 mL, 20 mmol) and (*R*)-**1**·(−)-CSA (3.03 g, 6.4 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After 48 h, the reaction mixture was partitioned between 1 M aq NaOH (100 mL) and CH_2Cl_2 (100 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **6** as a colourless oil (1.19 g, 55%); found C, 73.4; H, 7.9; N, 4.4%; $C_{21}H_{27}NO_3$ requires C, 73.9; H, 8.0; N, 4.1%; $[\alpha]_D^{23}$ +33.9 (*c* 1.2 in $CHCl_3$); ν_{max}(film) 1686 (C=O),

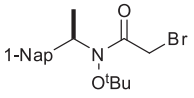
1600 (C=C); δ_H (300 MHz, $CDCl_3$) 0.66 (9H, s, CMe_3), 1.60 (3H, d, *J* 6.9, C(1′)*Me*), 4.03–4.17 (2H, m, OCH_2CH=CH_2), 4.21 (1H, d, *J* 16.0, C(2)H_A), 4.28 (1H, d, *J* 16.0, C(2)H_B), 5.01–5.05 (1H, m, CH_2CH=CH_AH$_B$), 5.10–5.14 (1H, m, CH=CH_AH$_B$), 5.89 (1H, ddt, *J* 17.3, 10.5, 5.5, C*H*=CH_2), 6.20 (1H, q, *J* 6.9, C(1′)*H*), 7.16–7.37 (3H, m, *Ar*), 7.50–7.61 (3H, m, *Ar*), 8.37 (1H, d, *J* 8.4, *Ar*); δ_C (50 MHz, $CDCl_3$) 15.0, 27.7, 55.0, 69.0, 72.4, 82.6, 118.0, 124.9, 125.7, 126.1, 126.5, 128.6, 133.6, 134.3, 135.5, 176.0; *m*/*z* (APCI$^+$) 342 ([M+H]$^+$, 100%).

4.1.3. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl 2-(4‴-methoxybenzyloxy)acetamide ***7***.



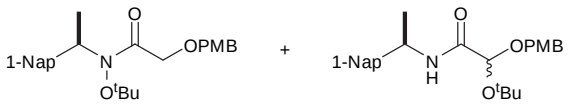
2-(4′-Methoxybenzyloxy)acetyl chloride (3.10 g, 14.5 mmol) was added dropwise to a vigorously stirred mixture of 2 M aq NaOH (11 mL, 22 mmol) and (*R*)-**1**·(−)-CSA (3.44 g, 7.24 mmol) in CH_2Cl_2 (15 mL) at 0 °C. After 48 h, the reaction mixture was partitioned between 1 M aq NaOH (100 mL) and CH_2Cl_2 (100 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **7** as a colourless oil (2.39 g, 78%); found C, 73.7; H, 7.5; N, 3.4%; $C_{26}H_{31}NO_4$ requires C, 74.1; H, 7.4; N, 3.3%; $[\alpha]_D^{21}$ +28.9 (*c* 1.2 in $CHCl_3$); ν_{max}(film) 1682 (C=O), 1613 (C=C), 1587 (C=C); δ_H (250 MHz, PhMe-d_8, 70 °C) 0.65 (9H, s, CMe_3), 1.64 (3H, d, *J* 6.9, C(1′)*Me*), 3.37 (3H, s, O*Me*), 4.26 (1H, d, *J* 16.1, C(2)H_A), 4.33 (1H, d, *J* 16.1, C(2)H_B), 4.60 (1H, d, *J* 11.4, OCH_AH$_B$Ar), 4.67 (1H, d, *J* 11.4, OCH$_A$$H_B$Ar), 6.24 (1H, q, *J* 6.9, C(1′)*H*), 6.71–6.76 (4H, m, *Ar*), 7.18–7.39 (4H, m, *Ar*), 7.54–7.62 (2H, m, *Ar*), 8.41 (1H, d, *J* 8.5, *Ar*); δ_C (50 MHz, $CDCl_3$) 16.0, 27.6, 55.1, 68.6, 72.9, 82.5, 113.8, 124.1, 124.9, 125.7, 126.1, 126.5, 128.7, 129.6, 129.9, 132.0, 133.6, 136.0, 159.4, 176.0; *m*/*z* (APCI$^+$) 444 ([M+Na]$^+$, 100%); HRMS (CI$^+$) found 422.2325; $C_{26}H_{32}NO_4^+$ ([M+H]$^+$) requires 422.2326.

4.1.4. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl 2-bromoacetamide ***8***.



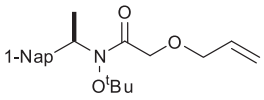
K_2CO_3 (12.0 g, 86.9 mmol) was added to a vigorously stirred solution of (*R*)-**1**·(−)-CSA (6.87 g, 14.5 mmol) in CH_2Cl_2 (300 mL). The resulting slurry was cooled to 0 °C and bromoacetyl bromide (6.30 mL, 72.3 mmol) was added dropwise. The mixture was left to stir for 2 h, before the addition of H_2O (200 mL) and the addition of K_2CO_3 until pH >11 was achieved. The resultant mixture was stirred for a further 10 min (to ensure consumption of any unreacted bromoacetyl bromide). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent pentane/Et_2O, 9:1) gave **8** as a colourless oil (5.3 g, 100%); R_f 0.30 (pentane/Et_2O, 9:1); $[\alpha]_D^{23}$ +16.7 (*c* 4.1 in $CHCl_3$); ν_{max} (film) 2977 (C–H), 1666 (C=O), 1368, 1093; δ_H (200 MHz, $CDCl_3$) 0.89 (9H, s, CMe_3), 1.82 (3H, d, *J* 7.0, C(1′)*Me*), 4.12–4.18 (2H, m, C(2)H_2), 6.10–6.30 (1H, br m, C(1′)*H*), 7.40–7.90 (6H, m, *Ar*), 8.20–8.23 (1H, br m, *Ar*); δ_C (50 MHz, $CDCl_3$) 16.3, 27.6, 28.9, 56.6, 83.5, 123.8, 123.9, 125.2, 125.9, 126.3, 126.8, 129.0, 133.8, 173.1; *m*/*z* (ESI$^+$) 366 ([M+H]$^+$, ^{81}Br, 96%), 364 ([M+H]$^+$, ^{79}Br, 100%); HRMS (ESI$^+$) found 364.0906; $C_{18}H_{23}{}^{79}BrNO_2^+$ ([M+H]$^+$) requires 364.0912.

4.1.5. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl 2-(4‴-methoxybenzyloxy)acetamide ***7*** *and (R)-N-1′-(1″-naphthyl)ethyl (ξ)-2-(4‴-methoxybenzyloxy)-2-tert-butoxyacetamide* ***10*** *from* ***8***.



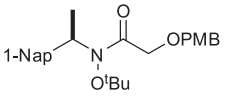
p-Methoxybenzyl alcohol (0.13 mL, 1.13 mmol) was added dropwise over 10 min to a stirred slurry of NaH (34 mg, 0.85 mmol) in THF (2 mL) at 0 °C and the resulting mixture was allowed to warm to rt over 1 h. A solution of **8** (206 mg, 0.56 mmol) in THF (5 mL) was added dropwise. After 6 h, the reaction was quenched by addition of satd aq NH_4Cl (10 mL) and extracted with Et_2O (3×10 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, pentane/Et_2O, 9:1; increased to Et_2O) gave **7** as a colourless oil (56 mg, 24%). Further elution gave **10** [of unknown configuration at C(2′)] as a colourless oil (76 mg, 32%, >99:1 dr); R_f 0.20 (pentane/Et_2O, 1:1); $[\alpha]_D^{23}$ −7.1 (*c* 0.2 in $CHCl_3$); ν_{max} (film) 3418 (N–H), 2962 (C–H), 1683 (C=O), 1515, 1260, 1099, 1024; δ_H (500 MHz, $CDCl_3$) 1.19 (9H, s, CMe_3), 1.69 (3H, d, *J* 6.8, C(1′)*Me*), 3.81 (3H, s, O*Me*), 4.51 (1H, d, *J* 10.9, OCH_AH$_B$Ar), 4.61 (1H, d, *J* 10.9, OCH$_A$$H_B$Ar), 5.09 (1H, s, C(2)*H*), 5.90–5.93 (1H, m, C(1′)*H*), 6.87 (2H, d, *J* 8.6, *Ar*), 6.93 (1H, br d, *J* 8.5, N*H*), 7.28–7.90 (8H, m, *Ar*), 8.11 (1H, d, *J* 8.3, *Ar*); δ_C (125 MHz, $CDCl_3$), 21.0, 28.4, 44.4, 55.2, 67.0, 76.1, 93.6, 113.7, 122.3, 123.3, 125.1, 125.7, 126.3, 128.2, 128.6, 129.4, 129.5, 130.8, 133.8, 138.1, 159.1, 167.8; *m*/*z* (ESI$^+$) 444 ([M+Na]$^+$, 100%), 422 ([M+H]$^+$, 11%); HRMS (ESI$^+$) found 444.2151; $C_{26}H_{31}NNaO_4^+$ ([M+Na]$^+$) requires 444.2145.

4.1.6. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl 2-allyloxyacetamide ***6*** *from* ***8***.



Allyl alcohol (0.74 mL, 10.9 mmol) was added dropwise over 10 min to a stirred slurry of NaH (414 mg, 10.4 mmol) in THF (10 mL) at 0 °C and the resulting mixture was allowed to warm to rt over 1 h. 15-Crown-5 (2.15 mL, 10.9 mmol) and tetrabutylammonium iodide (100 mg) were added, and stirring was continued at rt while a solution of **8** (3.61 g, 9.9 mmol) in THF (20 mL) was added dropwise. After 2 h, the reaction was quenched by addition of satd aq NH_4Cl (30 mL) and extracted with Et_2O (3×30 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, pentane/Et_2O, 19:1; increased to Et_2O) gave **6** as a colourless oil (2.5 g, 75%).

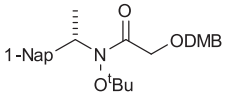
4.1.7. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl 2-(4‴-methoxybenzyloxy)acetamide ***7*** *from* ***8***.



4-Methoxybenzylalcohol (2.03 mL, 16.3 mmol) was added dropwise over 10 min to a stirred slurry of NaH (623 mg, 15.6 mmol) in THF (20 mL) at 0 °C and the resulting mixture was allowed to warm to rt over 1 h. 15-Crown-5 (3.12 mL, 15.6 mmol) and tetrabutylammonium iodide (100 mg) were added, and stirring was continued at rt while a solution of **8** (5.41 g, 14.8 mmol) in THF (20 mL) was added dropwise. After 2 h, the reaction was quenched

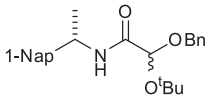
by addition of satd aq NH_4Cl (30 mL) and extracted with Et_2O (3×30 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, pentane/Et_2O, 9:1; increased to Et_2O) gave **7** as a colourless oil (3.80 g, 61%).

*4.1.8. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl 2-(3‴,4‴-dimethoxybenzyloxy)acetamide **9** from **8**.*



3,4-Dimethoxybenzyl alcohol (2.25 mL, 15.5 mmol) was added dropwise over 10 min to a stirred slurry of NaH (592 mg, 14.8 mmol) in THF (20 mL) at 0 °C and the resulting mixture was allowed to warm to rt over 1 h. 15-Crown-5 (2.96 mL, 14.8 mmol) and tetrabutylammonium iodide (100 mg) were added, and stirring was continued at rt while a solution of **8** (5.15 g, 14.1 mmol) in THF (20 mL) was added dropwise. After 2 h, the reaction was quenched by addition of satd aq NH_4Cl (20 mL) and extracted with Et_2O (3×30 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent pentane/Et_2O, 1:1) gave **9** as a colourless oil (4.73 g, 74%); R_f 0.20 (pentane/Et_2O, 1:1); $[\alpha]_D^{23}$ −21.4 (*c* 2.0 in $CHCl_3$); ν_{max} (film) 2975 (C–H), 1684 (C=O), 1594, 1516, 1464, 1419, 1368; δ_H (400 MHz, $CDCl_3$) 0.72 (9H, s, C*Me*$_3$), 1.77 (3H, d, *J* 6.5, C(1′)*Me*), 3.88 (3H, s, O*Me*), 3.90 (3H, s, O*Me*), 4.29–4.31 (2H, m, C(2)H_2), 4.60 (1H, d, *J* 11.3, OCH_AH$_B$Ar), 4.67 (1H, d, *J* 11.3, OCH$_A$$H_B$Ar), 6.35–6.37 (1H, br m, C(1′)*H*), 6.82 (1H, d, *J* 8.1, *Ar*), 6.90 (1H, dd, *J* 8.1, 1.8, *Ar*), 7.01 (1H, d, *J* 1.8, *Ar*), 7.41–7.88 (6H, m, *Ar*), 8.33–8.35 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.9, 27.6, 55.3, 55.8, 55.9, 68.6, 73.2, 82.6, 110.7, 111.4, 120.9, 124.2, 124.8, 125.6, 126.1, 126.5, 128.5, 128.6, 130.0, 133.5, 148.7, 149.0, 177.5; *m*/*z* (ESI$^+$) 474 ([M+Na]$^+$, 100%), 452 ([M+H]$^+$, 13%); HRMS (ESI$^+$) found 474.2256; $C_{27}H_{33}NNaO_5^+$ ([M+Na]$^+$) requires 474.2251.

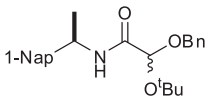
*4.1.9. (S)-N-1′-(1″-Naphthyl)ethyl (R)-2-benzyloxy-2-tert-butoxyacetamide and (S)-N-1′-(1″-naphthyl)ethyl (S)-2-benzyloxy-2-tert-butoxyacetamide **13** and **14**.*



13 and **14**

From (*S*)-***5***: KHMDS (1.38 mmol) was added to a solution of **5** (279 mg, 0.71 mmol) in THF (2 mL) at −78 °C. The resulting solution was stirred at this temperature for 10 min, then allowed to warm to 0 °C over 30 min and stirred for a further 1 h. The reaction was quenched by addition of pH 7 phosphate buffer (2 mL) and the mixture was concentrated in vacuo to give an 80:20 mixture of **13**:**14**. Purification via flash chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave the major diastereoisomer **13** as a colourless oil, which was crystallised from pentane to give a cream powder (147 mg, 50%, >99:1 dr); found C, 76.75; H, 7.55; N, 3.4%; $C_{25}H_{29}NO_3$ requires C, 76.7; H, 7.5; N, 3.6%; R_f 0.20 (pentane/Et_2O, 4:1); mp 67–68 °C; $[\alpha]_D^{23}$ +8.0 (*c* 1.1 in $CHCl_3$); ν_{max} (KBr) 3255 (N–H), 1685 (C=O), 1638 (C=O), 1599 (C=C); δ_H (400 MHz, $CDCl_3$) 1.21 (9H, s, C*Me*$_3$), 1.71 (3H, d, *J* 7.0, C(1′)*Me*), 4.60 (1H, d, *J* 11.2, OCH_AH$_B$Ph), 4.70 (1H, d, *J* 11.2, OCH$_A$$H_B$Ph), 5.15 (1H, s, C(2)*H*), 5.96 (1H, q, *J* 7.0, C(1′)*H*), 6.98 (1H, br d, *J* 8.4, N*H*), 7.30–8.15 (12H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.1, 28.5, 44.5, 67.2, 76.3, 93.8, 122.4, 123.4, 125.2, 125.8, 126.5, 127.7, 128.0, 128.3, 128.4, 128.8, 130.9, 133.9, 137.4, 138.1, 167.8; *m*/*z* (CI$^+$) 414 ([M+Na]$^+$, 100%), 392 ([M+H]$^+$, 30%); HRMS (CI$^+$) found 392.2219; $C_{25}H_{30}NO_3^+$ ([M+H]$^+$) requires 392.2220.

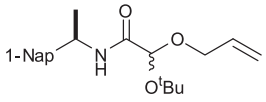
*4.1.10. (R)-N-1′-(1″-Naphthyl)ethyl (S)-2-benzyloxy-2-tert-butoxyacetamide and (R)-N-1′-(1″-naphthyl)ethyl (R)-2-benzyloxy-2-tert-butoxyacetamide **13** and **14**.*



13 and **14**

From (*R*)-***8***: Benzyl alcohol (0.79 mL, 7.60 mmol) was added dropwise over 10 min to a stirred slurry of NaH (292 mg, 7.30 mmol) in THF (5 mL) at 0 °C and the resulting mixture was allowed to warm to rt over 20 min. A solution of **8** (2.22 g, 6.08 mmol) in THF (10 mL) was added dropwise. After 2 h, the reaction was quenched by addition of satd aq NH_4Cl (20 mL) and extracted with Et_2O (3×30 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, pentane/Et_2O, 19:1; increased to Et_2O) gave **13** as a colourless oil (876 mg, 37%, 92:8 dr); $[\alpha]_D^{23}$ −7.1 (*c* 0.9 in $CHCl_3$). Further elution gave **14** as a colourless oil (989 mg, 42%, 86:14 dr); R_f 0.15 (pentane/Et_2O, 4:1); δ_H (400 MHz, $CDCl_3$), 1.31 (9H, s, C*Me*$_3$), 1.71 (3H, d, *J* 7.0, C(1′)*Me*), 4.44 (2H, ABq, OCH_2Ph), 5.18 (1H, s, C(2)*H*), 5.97 (1H, q, *J* 7.0, C(1′)*H*), 6.95 (1H, br d, *J* 8.5, N*H*), 7.20–8.20 (12H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.8, 28.6, 44.3, 66.8, 76.4, 93.9, 122.5, 123.3, 125.2, 125.9, 126.5, 127.5, 127.9, 128.1, 128.4, 128.5, 128.8, 131.0, 133.9, 137.4, 138.0, 167.7.

*4.1.11. (R)-N-1′-(1″-Naphthyl)ethyl (S)-2-allyloxy-2-tert-butoxyacetamide and (R)-N-1′-(1″-naphthyl)ethyl (R)-2-allyloxy-2-tert-butoxyacetamide **15** and **16**.*

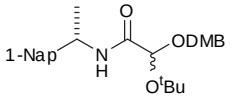


15 and **16**

Allyl alcohol (70 μL, 1.07 mmol) was added dropwise over 10 min to a stirred slurry of NaH (39 mg, 1.07 mmol) in THF (2 mL) at 0 °C and the resulting mixture was allowed to warm to rt over 1 h. A solution of **8** (300 mg, 0.82 mmol) in THF (5 mL) was added dropwise. After 2 h, the reaction was quenched by addition of satd aq NH_4Cl (10 mL) and extracted with Et_2O (3×10 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, pentane/Et_2O, 10:1; increased to Et_2O) gave a mixture of **15** and **16**. Recrystallisation from pentane gave **15** as colourless needles (105 mg, 28%, >99:1 dr); R_f 0.20 (pentane/Et_2O, 4:1); found C, 73.6; H, 8.3; N, 4.0%; $C_{21}H_{27}NO_3$ requires C, 73.9; H, 8.0; N, 4.1%; mp 56–58 °C; $[\alpha]_D^{24}$ −1.0 (*c* 0.9 in $CHCl_3$); ν_{max} (KBr) 3264 (N–H), 1688 (C=O), 1647 (C=O), 1600 (C=C); δ_H (300 MHz, $CDCl_3$) 1.18 (9H, s, C*Me*$_3$), 1.69 (3H, d, *J* 6.8, C(1′)*Me*), 4.06–4.18 (2H, m, CH_2CH=CH$_2$), 5.04 (1H, s, C(2)*H*), 5.15–5.33 (2H, m CH=CH_2), 5.90–5.94 (1H, m, C(1′)*H*), 5.95 (1H, ddt, *J* 11.2, 10.4, 5.6, CH$_2$C*H*=CH$_2$), 6.92 (1H, br d, *J* 8.4, N*H*), 7.54–7.45 (5H, m, *Ar*), 7.87 (1H, dd, *J* 8.5, 1.4, *Ar*), 8.10 (1H, d, *J* 8.4, *Ar*); δ_C (50 MHz, $CDCl_3$) 21.0, 28.4, 44.4, 66.2, 76.1, 93.6, 117.2, 122.3, 123.3, 125.1, 125.7, 126.3, 128.7, 130.9, 133.8, 134.0, 138.1, 167.8; *m*/*z* (APCI$^+$) 342 ([M+H]$^+$, 100%). Concentration of the mother liquors gave **16** as a colourless oil (17 mg, 6%, >99:1 dr); R_f 0.20 (Et_2O:pentane 1:4); ν_{max} (KBr) 3303, 3242 (N–H), 1686, 1654 (C=O), 1599 (C=C); δ_H (300 MHz, $CDCl_3$) 1.18 (9H, s, C*Me*$_3$), 1.69 (3H, d, *J* 6.8, C(1′)*Me*), 3.90–3.97 (2H, m, CH_2CH=CH$_2$), 5.08 (1H, s, C(2)*H*), 5.09 (1H, dd, *J* 10.5, 1.4, CH$_2$CH=CH_AH$_B$), 5.16 (1H, dd, *J*

17.2, 1.4, $CH_2CH{=}CH_AH_B$), 5.82 (1H, ddt, *J* 17.2, 10.5, 5.3, $CH_2CH{=}CH_2$), 5.91–5.95 (1H, m, C(1′)*H*), 6.90 (1H, br d, *J* 8.4, N*H*), 7.45–7.55 (4H, m, *Ar*), 7.81 (1H, d, *J* 8.1, *Ar*), 7.87–7.89 (1H, m, *Ar*), 8.11 (1H, d, *J* 8.3, *Ar*); δ_C (50 MHz, $CDCl_3$) 20.9, 28.5, 44.3, 65.8, 76.3, 93.7, 117.0, 122.4, 123.4, 125.2, 125.8, 126.4, 128.3, 128.8, 131.0, 133.9, 138.0, 167.8; *m*/*z* (APCI$^+$) 364 ([M+Na]$^+$), 342 ([M+H]$^+$, 40%); HRMS (CI$^+$) found 342.2071; $C_{21}H_{28}NO_3^+$ ([M+H]$^+$) requires 342.2064.

*4.1.12. (S)-N-1′-(1″-Naphthyl)ethyl (R)-2-(3‴,4‴-dimethoxybenzyl)-2-tert-butoxyacetamide and (S)-N-1′-(1″-naphthyl)ethyl (S)-2-(3‴,4‴-dimethoxybenzyl)-2-tert-butoxyacetamide **17** and **18**.*



17 and **18**

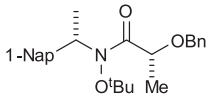
KHMDS (0.70 mmol) was added to a solution of **9** (227 mg, 0.50 mmol) in THF (6 mL) at −78 °C. The resulting solution was stirred at this temperature for 20 min, then allowed to warm to rt over 30 min and stirred for a further 30 min. The reaction was quenched by addition of pH 7 phosphate buffer (0.4 mL) and the mixture was concentrated in vacuo. The residue was redissolved in Et_2O (100 mL) and filtered through a silica gel/$MgSO_4$ plug (eluent Et_2O, 200 mL). The filtrate was concentrated in vacuo. Exhaustive flash column chromatography (gradient elution, pentane/Et_2O, 1:1; increased to Et_2O) gave **17** as a colourless oil (166 mg, 73%, 86:14 dr); R_f 0.60 (Et_2O); $[\alpha]_D^{23}$ −4.1 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3417 (N–H), 2974 (C–H), 1682 (C=O), 1516, 1264, 1159, 1138; δ_H (400 MHz, $CDCl_3$) 1.19 (9H, s, C*Me*$_3$), 1.69 (3H, d, *J* 6.8, C(1′)*Me*), 3.87 (3H, s, O*Me*), 3.88 (3H, s, O*Me*), 4.54 (1H, d, *J* 11.0, OCH_AH_BAr), 4.62 (1H, d, *J* 11.0, OCH_AH_BAr), 5.11 (1H, s, C(2)*H*), 5.91–5.94 (1H, m, C(1′)*H*), 6.81–6.96 (4H, m, N*H*, *Ar*), 7.43–7.52 (4H, m, *Ar*), 7.80 (1H, d, *J* 7.8, *Ar*), 7.87 (1H, d, *J* 7.5, *Ar*), 8.11 (1H, d, *J* 8.3, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.1, 28.5, 44.5, 55.8, 55.9, 67.2, 76.3, 93.6, 110.8, 111.4, 120.5, 122.4, 123.4, 125.2, 125.8, 126.4, 128.3, 128.8, 130.0, 130.9, 133.9, 138.1, 148.6, 148.9, 167.9; *m*/*z* (ESI$^+$) 474 ([M+Na]$^+$, 100%), 452 ([M+H]$^+$, 5%); HRMS (ESI$^+$) found 474.2263; $C_{27}H_{33}NNaO_5^+$ ([M+Na]$^+$) requires 474.2251. Further elution gave **18** (39 mg, 17%, 61:39 dr); R_f 0.50 (Et_2O); δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.30 (9H, s, C*Me*$_3$), 1.69 (3H, d, *J* 6.8, C(1′)*Me*), 3.78 (3H, s, O*Me*), 3.86 (3H, s, O*Me*), 4.38 (2H, A_2, OCH_2Ar), 5.16 (1H, s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 20.9, 28.6, 44.3, 55.7, 55.8, 66.9, 76.4, 93.8, 110.7, 111.2, 120.3, 122.5, 123.4, 125.2, 125.9, 126.4, 128.4, 128.8, 129.9, 131.0, 138.0, 148.5, 148.8, 167.8.

4.2. General procedure for enolate alkylations

Titration procedure: KHMDS in PhMe solution (ca. 0.5 M) was added dropwise to a solution of an accurately weighed sample of menthol (ca. 150 mg in 3 mL of PhMe), containing a trace of (*E*)-*N*-benzylidenebiphenyl-4-amine as an indicator, at 0 °C. A single drop of excess KHMDS caused the formation of an intense blue colouration.[37] The titration was repeated twice more by the addition of a further aliquot of menthol.

Freshly titrated KHMDS (ca. 0.5 M in PhMe) was added dropwise to a degassed solution of the substrate and 18-crown-6 in THF at −78 °C. After stirring for 30 min at this temperature, the requisite alkylating agent was added dropwise and stirring was continued at −78 °C for the time stated. The reaction was then quenched by the dropwise addition of pH 7 phosphate buffer and allowed to warm to rt. The mixture was concentrated in vacuo, the residue was dissolved in Et_2O and filtered through a short, silica/$MgSO_4$ plug (eluent Et_2O). The filtrate was concentrated in vacuo and purified as described.

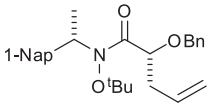
*4.2.1. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-2-benzyloxypropanamide **23**.*



Compound (*S*)-**5** (97 mg, 0.25 mmol) in THF (2 mL) was treated with KHMDS (0.28 mmol) and 18-crown-6 (280 mg, 1.06 mmol) in THF (2 mL) and MeI (0.47 mL, 0.75 mmol) according to the *general procedure*. The reaction was held at −78 °C for 1 h before being quenched. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **23** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **23** as a colourless oil, which crystallised upon prolonged standing (82 mg, 81%, >99:1 dr); found C, 77.3; H, 8.0; N, 3.3%; $C_{26}H_{31}NO_3$ requires C, 77.0; H, 7.7; N, 3.45%; mp 63–65 °C; $[\alpha]_D^{23}$ −41.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1683 (C=O), 1600 (C=C); δ_H (250 MHz, PhMe-d_8, 70 °C) 0.64 (9H, s, C*Me*$_3$), 1.39 (3H, d, *J* 6.7, C(3)H_3), 1.62 (3H, d, *J* 6.9, C(1′)*Me*), 4.45 (1H, d, *J* 12.0, OCH_AH_BPh), 4.57 (1H, q, *J* 6.7, C(2)*H*), 4.80 (1H, d, *J* 12.0, OCH_AH_BPh), 6.36 (1H, q, *J* 6.9, C(1′)*H*), 6.96–7.62 (11H, m, *Ar*, *Ph*), 8.55 (1H, br d, *J* 8.5, *Ar*); δ_C (50 MHz, $CDCl_3$) 16.0, 16.3, 27.6, 55.8, 70.9, 73.0, 82.6, 124.7, 125.1, 125.9, 126.5, 126.6, 127.9, 128.0, 128.6, 128.9, 129.0, 132.5, 133.9, 135.8, 138.4, 180.2; *m*/*z* (CI$^+$) 406 ([M+H]$^+$, 100%).

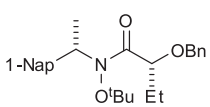
Analogous treatment of (*R*)-**5** gave (2*S*,1′*R*)-**23** as a colourless oil; $[\alpha]_D^{23}$ +42.1 (*c* 1.0 in $CHCl_3$).

*4.2.2. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-2-benzyloxypent-4-enamide **25**.*



Compound (*S*)-**5** (491 mg, 1.25 mmol) in THF (5 mL) was treated with KHMDS (1.38 mmol) and 18-crown-6 (687 mg, 2.6 mmol) in THF (5 mL) and allyl bromide (324 μL, 3.75 mmol) according to the *general procedure*. The reaction was held at −78 °C for 1.5 h before being quenched. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **25** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **25** as a colourless oil (511 mg, 95%, >99:1 dr); found C, 78.0; H, 7.95; N, 3.35%; $C_{28}H_{33}NO_3$ requires C, 77.9; H, 7.7; N, 3.25%; $[\alpha]_D^{21}$ +56.4 (*c* 1.7 in $CHCl_3$); ν_{max} (film) 1680 (C=O), 1600 (C=C); δ_H (250 MHz, PhMe-d_8, 70 °C) 0.64 (9H, s, C*Me*$_3$), 1.63 (3H, d, *J* 6.9, C(1′)*Me*), 2.39–2.64 (2H, m, C(3)H_2), 4.47 (1H, d, *J* 11.8, OCH_AH_BPh), 4.56 (1H, dd, *J* 8.0, 4.0, C(2)*H*), 4.84 (1H, d, *J* 11.8, OCH_AH_BPh), 4.95–5.08 (2H, m, C(5)H_2), 5.99 (1H, ddt, *J* 17.1, 10.2, 6.9, C(4)*H*), 6.38 (1H, q, *J* 6.9, C(1′)*H*), 6.97–7.62 (11H, m, *Ar*, *Ph*), 8.54 (1H, d, *J* 8.5, *Ar*); δ_C (50 MHz, $CDCl_3$) 16.3, 27.7, 35.0, 55.8, 71.2, 76.8, 82.8, 117.5, 124.6, 125.1, 125.9, 126.6, 127.9, 128.6, 128.9, 129.0, 132.5, 133.9, 134.5, 135.7, 138.4, 178.6; *m*/*z* (APCI$^+$) 454 ([M+Na]$^+$, 100%), 432 ([M+H]$^+$, 20%).

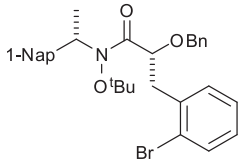
*4.2.3. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-2-benzyloxybutanamide **26**.*



Compound (*S*)-**5** (670 mg, 1.71 mmol) in THF (6 mL) was treated with KHMDS (1.38 mmol) and 18-crown-6 (700 mg, 2.65 mmol) in THF (5 mL) and EtI (410 μL, 5.13 mmol) according to the *general*

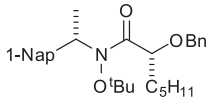
procedure. The reaction was held at −78 °C for 6 h before being quenched. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **26** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **26** as a colourless oil (567 mg, 79%, >99:1 dr); found C, 77.5; H, 8.1; N, 3.6%; $C_{27}H_{33}NO_3$ requires C, 77.3; H, 7.9; N, 3.3%; $[\alpha]_D^{21}$ +50.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1676 (C═O), 1600 (C═C); δ_H (250 MHz, PhMe-d_8, 70 °C) 0.64 (9H, s, CMe_3), 0.64 (3H, t, *J* 7.4, C(4)H_3), 1.63 (3H, d, *J* 6.9, C(1′)*Me*), 1.68–1.92 (2H, m, C(3)H_2), 4.45 (1H, dd, *J* 7.6, 3.9, C(2)*H*), 4.45 (1H, d, *J* 12.0, OCH_AH$_B$Ph), 4.85 (1H, d, *J* 12.0, OCH$_A$$H_B$Ph), 6.39 (1H, q, *J* 6.9, C(1′)*H*), 6.97–7.63 (11H, m, *Ar*, *Ph*), 8.58 (1H, d, *J* 8.5, *Ar*); δ_C (50 MHz, $CDCl_3$) 10.1, 16.3, 23.7, 27.7, 55.7, 71.2, 78.3, 82.5, 124.7, 125.0, 125.9, 126.6, 127.8, 127.9, 128.3, 128.5, 128.9, 129.0, 132.5, 133.9, 135.8, 138.6, 179.4; *m*/*z* (CI$^+$) 442 ([M+Na]$^+$, 100%), 420 ([M+H]$^+$, 50%).

*4.2.4. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-2-benzyloxy-3-(2‴-bromophenyl)propanamide **27**.*



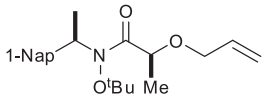
Compound (*S*)-**5** (517 mg, 1.32 mmol) in THF (10 mL) was treated with KHMDS (1.45 mmol) and 18-crown-6 (700 mg, 2.65 mmol) in THF (10 mL) and 2-bromobenzylbromide (990 mg, 3.96 mmol) according to the *general procedure*. The reaction was held at −78 °C for 6 h before being quenched. ^{1}H NMR spectroscopic analysis of the crude reaction mixture (250 MHz, PhMe-d_8, 70 °C) showed the presence of **27** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **27** as a colourless glass (595 mg, 81%, >99:1 dr); found C, 68.3; H, 6.1; N, 2.5%; $C_{32}H_{34}BrNO_3$ requires C, 68.6; H, 6.1; N, 2.5%; $[\alpha]_D^{21}$ +44.7 (*c* 1.1 in $CHCl_3$); ν_{max} (KBr) 1673 (C═O), 1599 (C═C); δ_H (250 MHz, PhMe-d_8, 70 °C) 0.76 (9H, s, CMe_3), 1.69 (3H, d, *J* 6.8, C(1′)*Me*), 3.15 (1H, dd, *J* 13.7, 7.8, C(3)H_A), 3.33 (1H, dd, *J* 13.7, 5.5, C(3)H_B), 4.49 (1H, d, *J* 11.8, OCH_AH$_B$Ph), 4.76 (1H, d, *J* 11.8, OCH$_A$$H_B$Ph), 4.95 (1H, dd, *J* 7.8, 5.5, C(2)*H*), 6.12 (1H, br q, *J* 6.8, C(1′)*H*), 6.67 (1H, dt, *J* 7.7, 1.7, *Ar*), 6.86 (1H, dt, *J* 7.5, 1.2, *Ar*), 6.97–7.61 (13H, m, *Ar*, *Ph*), 8.36 (1H, br s, *Ar*); δ_C (125 MHz, $CDCl_3$) 17.3, 27.7, 36.9, 58.0, 71.3, 75.6, 83.1, 124.5, 125.1, 125.2, 125.8, 126.6, 126.8, 127.3, 127.7, 128.4, 128.9, 132.5, 132.7, 133.9, 137.3, 138.2; *m*/*z* (CI$^+$) 562 ([M+H]$^+$, ^{81}Br, 100%), 560 ([M+H]$^+$, ^{79}Br, 100%).

*4.2.5. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-2-benzyloxyheptanamide **28**.*



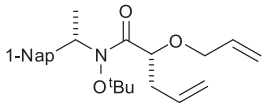
Compound (*S*)-**5** (1.42 g, 3.61 mmol) in THF (20 mL) was treated with KHMDS (10.6 mmol) and 18-crown-6 (2.80 g, 10.6 mmol) in THF (20 mL) and 1-iodopentane (1.41 mL, 10.8 mmol) according to the *general procedure*. The reaction was held at −78 °C for 5 h before being quenched. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **28** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **28** as a colourless oil (1.05 g, 63%, >99:1 dr); found C, 78.1; H, 8.6; N, 3.3%; $C_{30}H_{39}NO_3$ requires C, 78.05; H, 8.5; N, 3.0%; $[\alpha]_D^{22}$ +60.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1676 (C═O), 1600 (C═C); δ_H (250 MHz, PhMe-d_8, 70 °C) 0.74 (9H, s, CMe_3), 0.82 (3H, t, *J* 6.7, C(7)H_3), 1.11–1.51 (6H, m, C(4)H_2–C(6)H_2), 1.58–1.83 (2H, m, C(3)H_2) overlapping 1.69 (3H, d, *J* 7.0, C(1′)*Me*), 4.45 (1H, d, *J* 11.8, OCH_AH$_B$Ph), 4.51 (1H, dd, *J* 7.7, 4.1, C(2)*H*), 4.82 (1H, d, *J* 11.8, OCH$_A$$H_B$Ph), 6.29 (1H, q, *J* 7.0, C(1′)*H*), 6.97–7.63 (11H, m, *Ar*, *Ph*), 8.55 (1H, d, *J* 8.5, *Ar*); δ_C (50 MHz, $CDCl_3$) 13.9, 16.4, 22.3, 25.0, 27.7, 30.3, 31.5, 56.4, 71.2, 82.5, 124.7, 125.0, 125.8, 126.5, 126.7, 127.7, 127.8, 128.2, 128.5, 128.8, 128.9, 132.5, 133.9, 135.7, 138.6, 179.5; *m*/*z* (CI$^+$) 462 ([M+H]$^+$, 100%). Further elution gave returned starting material (*S*)-**5** (462 mg, 31%).

*4.2.6. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S)-2-allyloxypropanamide **29**.*



Compound (*R*)-**6** (200 mg, 0.59 mmol) in THF (4 mL) was treated with KHMDS (0.70 mmol) and 18-crown-6 (400 mg, 1.52 mmol) in THF (4 mL) and MeI (0.15 mL, 2.43 mmol) according to the *general procedure*. The reaction was held at −78 °C for 5 h before being quenched. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **29** in >95:5 dr. Purification via flash column chromatography (gradient elution, 30–40 °C petrol/Et_2O, 19:1; increased to 30–40 °C petrol/Et_2O, 2:1) gave **29** as a colourless oil, which crystallised upon prolonged standing to yield colourless needles (200 mg, 96%, >99:1 dr); R_f 0.30 (30–40 °C petrol/Et_2O, 2:1); $[\alpha]_D^{23}$ +29.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2978 (C–H), 1681 (C═O), 1512, 1371, 1238, 1109; δ_H (400 MHz, $CDCl_3$) 0.82 (9H, s, CMe_3), 1.23 (3H, d, *J* 6.2, C(3)H_3), 1.77 (3H, d, *J* 6.9, C(1′)*Me*), 3.93 (1H, dd, *J* 12.6, 6.0, OCH_AH$_B$CH═CH$_2$), 4.22 (1H, dd, *J* 12.6, 4.7, OCH$_A$$H_B$CH═CH$_2$), 4.49 (1H, q, *J* 6.2, C(2)*H*), 5.17–5.33 (2H, m, OCH$_2$CH═CH_2), 5.96–5.99 (1H, m, OCH$_2$C*H*═CH$_2$), 6.29–6.32 (1H, br m, C(1′)*H*), 7.41–7.87 (6H, m, *Ar*), 8.38–8.41 (1H, br m, *Ar*); δ_C (50 MHz, $CDCl_3$) 16.3, 16.4, 27.8, 56.0, 70.1, 73.3, 82.5, 117.1, 124.3, 124.8, 125.6, 126.3, 128.6, 128.7, 132.1, 133.6, 134.8, 135.5, 179.8; *m*/*z* (ESI$^+$) 378 ([M+Na]$^+$, 100%), 356 ([M+H]$^+$, 91%); HRMS (ESI$^+$) found 356.2216; $C_{22}H_{30}NO_3^+$ ([M+H]$^+$) requires 356.2220.

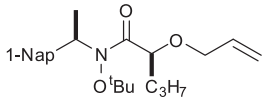
*4.2.7. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-2-allyloxypent-4-enamide **30**.*



Compound (*S*)-**6** (200 mg, 0.59 mmol) in THF (4 mL) was treated with KHMDS (0.70 mmol) and 18-crown-6 (400 mg, 1.52 mmol) in THF (4 mL) and allyl bromide (0.12 mL, 1.36 mmol) according to the *general procedure*. The reaction was held at −78 °C for 5 h before being quenched. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **30** in >95:5 dr. Purification via flash column chromatography (gradient elution, 30–40 °C petrol/Et_2O, 9:1; increased to 30–40 °C petrol/Et_2O, 3:2) gave **30** as a colourless oil, which crystallised upon prolonged standing to yield colourless needles (170 mg, 76%, >99:1 dr); R_f 0.65 (pentane/Et_2O, 3:2); mp 74–76 °C; $[\alpha]_D^{23}$ +41.7 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 2978 (C–H), 1682 (C═O), 1370, 1170, 1100, 1092; δ_H (400 MHz, $CDCl_3$) 0.83 (9H, s, CMe_3), 1.78 (3H, d, *J* 7.0, C(1′)*Me*), 2.19–2.21 (1H, br m, C(3)H_A), 2.41–2.44 (1H, br m, C(3)H_B), 3.90 (1H, dd, *J* 13.0, 6.0, OCH_AH$_B$CH═CH$_2$), 4.26 (1H, dd, *J* 13.0, 4.7, OCH$_A$$H_B$CH═CH$_2$), 4.42 (1H, dd, *J* 8.6, 3.0, C(2)*H*), 4.99–5.01 (2H, br m, C(5)H_2), 5.18 (1H, app dq, *J* 10.4, 1.4, OCH$_2$CH═CH_AH$_B$), 5.30 (1H, app dq, *J* 17.3, 1.5, OCH$_2$CH═CH$_A$$H_B$), 5.81–5.84 (1H, m, CH$_2$C*H*═CH$_2$), 5.92–5.96 (1H, m, CH$_2$C*H*═CH$_2$), 6.31–6.34 (1H, br m, C(1′)*H*), 7.41–7.88 (6H, m, *Ar*), 8.38–8.41 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.3, 27.8, 55.7, 70.4, 77.2, 82.7, 117.0, 117.1, 124.4, 124.8, 125.6, 126.3, 126.4, 128.6, 128.7, 132.2, 133.6, 134.2, 134.8, 135.5, 178.3; *m*/*z*

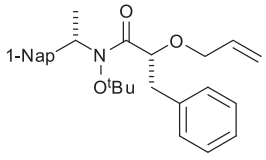
(ESI$^+$) 404 ([M+Na]$^+$, 100%), 382 ([M+H]$^+$, 80%); HRMS (ESI$^+$) found 404.2194; $C_{24}H_{31}NNaO_3^+$ ([M+Na]$^+$) requires 404.2196.

*4.2.8. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S)-2-allyloxypentanamide **31**.*



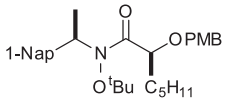
Compound (*R*)-**6** (311 mg, 0.91 mmol) in THF (8 mL) was treated with KHMDS (1.19 mmol) and 18-crown-6 (470 mg, 1.78 mmol) in THF (8 mL) and 1-iodopropane (0.18 mL, 1.82 mmol) according to the *general procedure*. The reaction was held at −78 °C for 5 h before being quenched. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **31** in >95:5 dr. Purification via flash column chromatography (gradient elution, 30–40 °C petrol/Et$_2$O, 19:1; increased to 30–40 °C petrol/Et$_2$O, 2:1) gave **31** as a colourless oil, which crystallised upon prolonged standing to yield colourless needles (215 mg, 62%, >99:1 dr); mp 64 °C; R_f 0.30 (pentane/Et$_2$O, 9:1); $[\alpha]_D^{23}$ −40.7 (*c* 2.2, CHCl$_3$); ν_{max} (film) 2963 (C–H), 1678 (C=O), 1456, 1368, 1238, 1170, 1144, 1111, 1092; δ_H (400 MHz, CDCl$_3$) 0.78 (3H, br t, *J* 6.8, C(5)*H*$_3$), 0.86 (9H, s, C*Me*$_3$), 1.28–1.35 (3H, br m, C(3)*H*$_A$, C(4)*H*$_2$), 1.55–1.58 (1H, br m, C(3)*H*$_B$), 1.79 (3H, d, *J* 7.0, C(1′)*Me*), 3.86 (1H, dd, *J* 12.7, 6.0, OC*H*$_A$H$_B$CH=CH$_2$), 4.24 (1H, dd, *J* 12.7, 4.3, OCH$_A$*H*$_B$CH=CH$_2$), 4.34–4.38 (1H, br m, C(2)*H*), 5.16–5.33 (2H, m OCH$_2$CH=C*H*$_2$), 5.95–5.99 (1H, m, OCH$_2$C*H*=CH$_2$) 6.25–6.28 (1H, br m, C(1′)*H*), 7.41–7.86 (6H, m, *Ar*), 8.40–8.43 (1H, br m, *Ar*); δ_C (100 MHz, CDCl$_3$) 13.8, 16.3, 18.7, 27.8, 32.4, 56.1, 70.4, 77.2, 82.4, 116.8, 124.5, 124.7, 125.6, 126.2, 126.4, 128.5, 128.6, 132.2, 133.6, 135.0, 135.4, 179.2; *m*/*z* (ESI$^+$) 406 ([M+Na]$^+$, 100%), 384 ([M+H]$^+$, 96%); HRMS (ESI$^+$) found 384.2556; $C_{24}H_{34}NO_3^+$ ([M+H]$^+$) requires 384.2533.

*4.2.9. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-2-allyloxy-3-phenylpropanamide **32**.*



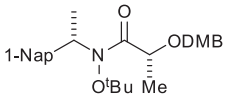
Compound (*S*)-**6** (200 mg, 0.59 mmol) in THF (4 mL) was treated with KHMDS (0.70 mmol) and 18-crown-6 (400 mg, 1.52 mmol) in THF (4 mL) and benzyl bromide (0.14 mL, 1.17 mmol) according to the *general procedure*. The reaction was held at −78 °C for 5 h before being quenched. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **32** in >95:5 dr. Purification via flash column chromatography (gradient elution, 30–40 °C petrol/Et$_2$O, 19:1; increased to 30–40 °C petrol/Et$_2$O, 4:1) gave **32** as a colourless oil, which crystallised upon prolonged standing to yield colourless needles (222 mg, 88%, >99:1 dr); mp 79–82 °C; R_f 0.40 (30–40 °C petrol/Et$_2$O, 9:1); $[\alpha]_D^{23}$ −3.2 (*c* 0.9 in CHCl$_3$); ν_{max} (film) 2973 (C–H), 1678 (C=O), 1453, 1091; δ_H (400 MHz, CDCl$_3$) 0.92 (9H, s, C*Me*$_3$), 1.85 (3H, d, *J* 7.0, C(1′)*Me*), 2.51 (1H, br m C(3)*H*$_A$), 2.77–2.80 (1H, br m, C(3)*H*$_B$), 3.75–3.78 (1H, m, OC*H*$_A$H$_B$CH=CH$_2$), 4.16 (1H, app dd, *J* 13.1, 4.6, OCH$_A$*H*$_B$CH=CH$_2$), 4.49–4.52 (1H, m, C(2)*H*), 5.02–5.06 (2H, m, OCH$_2$CH=C*H*$_2$), 5.69–5.72 (1H, m, OCH$_2$C*H*=CH$_2$), 6.23–6.27 (1H, br m, C(1′)*H*), 7.18–7.29 (5H, m, *Ar*), 7.32–7.87 (6H, m, *Ar*), 8.42–8.45 (1H, m, *Ar*); δ_C (50 MHz, CDCl$_3$) 16.7, 27.9, 56.6, 70.4, 78.3, 82.9, 116.5, 124.3, 124.9, 125.6, 126.3, 126.5, 128.0, 128.6, 128.7, 129.6, 133.6, 134.6, 138.4, 175.8; *m*/*z* (CI$^+$) 432 ([M+H]$^+$, 46%); HRMS (CI$^+$) found 432.2528; $C_{28}H_{34}NO_3^+$ ([M+H]$^+$) requires 432.2533.

*4.2.10. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S)-2-(4‴-methoxybenzyloxy)heptanamide **33**.*



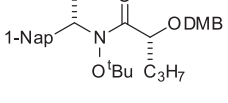
Compound (*S*)-**7** (2.20 g, 5.22 mmol) in THF (20 mL) was treated with KHMDS (11.7 mmol) and 18-crown-6 (2.50 g, 9.46 mmol) in THF (20 mL) and 1-iodopentane (2.04 mL, 10.8 mmol) according to the *general procedure*. The reaction was held at −78 °C for 4 h before being quenched. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **33** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 2:1) gave **33** as a colourless oil (2.23 g, 87%, >99:1 dr); found C, 75.5; H, 8.6; N, 2.7%; $C_{31}H_{41}NO_4$ requires C, 75.7; H, 8.4; N, 2.85%; $[\alpha]_D^{23}$ −53.1 (*c* 1.7 in CHCl$_3$); ν_{max} (film) 1675 (C=O), 1614, 1587 (C=C); δ_H (250 MHz, PhMe-d_8, 70 °C) 0.72 (9H, s, C*Me*$_3$), 0.84 (3H, t, *J* 7.4, C(7)*H*$_3$), 1.10–1.59 (6H, m, C(4)*H*$_2$–C(6)*H*$_2$), 1.61–1.86 (2H, m, C(3)*H*$_2$) overlapping 1.68 (3H, d, *J* 7.0, C(1′)*Me*), 3.36 (3H, s, O*Me*), 4.42 (1H, dd, *J* 11.8, OC*H*$_A$H$_B$Ar), 4.52 (1H, dd, *J* 7.8, 3.8, C(2)*H*), 4.82 (1H, d, *J* 11.8, OCH$_A$*H*$_B$Ar), 6.35 (1H, q, *J* 7.0, C(1′)*H*), 6.74 (2H, app d, *J* 8.6, *Ar*), 7.64–7.18 (8H, m, *Ar*), 8.61 (1H, d, *J* 8.5, *Ar*); δ_C (50 MHz, CDCl$_3$) 14.1, 16.4, 22.4, 25.1, 27.8, 30.3, 31.5, 55.1, 55.3, 70.8, 76.8, 82.4, 113.7, 124.5, 124.8, 125.6, 126.2, 126.5, 128.7, 129.2, 130.4, 132.3, 133.7, 135.4, 159.2, 179.2; *m*/*z* (APCI$^+$) 514 ([M+Na]$^+$, 100%), 492 ([M+H]$^+$, 50%). Further elution gave returned starting material (*R*)-**7** (181 mg, 8%).

*4.2.11. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-2-(3‴,4‴-dimethoxybenzyloxy)propanamide **34**.*



Compound (*S*)-**9** (161 mg, 0.36 mmol) in THF (4 mL) was treated with KHMDS (0.50 mmol) and 18-crown-6 (200 mg, 0.76 mmol) in THF (4 mL) and MeI (0.13 mL, 2.09 mmol) according to the *general procedure*. The reaction was held at −78 °C for 4 h before being quenched. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **34** in >95:5 dr. Purification via flash column chromatography (gradient elution, 30–40 °C petrol/Et$_2$O, 4:1; increased to 30–40 °C petrol/Et$_2$O, 1:1) gave **34** as a white foam (84 mg, 51%, >99:1 dr); $[\alpha]_D^{23}$ +28.6 (*c* 3.3 in CHCl$_3$); ν_{max} (film) 2977 (C–H), 1678 (C=O), 1594 (C=C); δ_H (400 MHz, CDCl$_3$) 0.67 (9H, br s, C*Me*$_3$), 1.26 (3H, d, *J* 6.5, C(3)*H*$_3$), 1.75 (3H, d, *J* 6.9, C(1′)*Me*), 3.83 (3H, s, O*Me*), 3.86 (3H, s, O*Me*), 4.42 (1H, d, *J* 11.6, OC*H*$_A$H$_B$Ar), 4.49 (1H, q, *J* 6.5, C(2)*H*), 4.69 (1H, d, *J* 11.6, OCH$_A$*H*$_B$Ar), 6.30–6.34 (1H, br m, C(1′)*H*), 6.79 (1H, d, *J* 8.2, *Ar*), 6.90 (1H, dd, *J* 8.1, 1.6, *Ar*), 6.99 (1H, s, *Ar*), 7.30–7.89 (6H, m, *Ar*), 8.39–8.41 (1H, br m, *Ar*); δ_C (100 MHz, CDCl$_3$) 16.0, 16.3, 27.6, 55.8, 55.9, 70.7, 72.7, 82.5, 110.8, 111.1, 120.3, 124.4, 124.8, 125.6, 126.3, 128.6, 128.7, 130.6, 132.2, 133.6, 135.5, 148.6, 149.0, 179.8; *m*/*z* (ESI$^+$) 488 ([M+Na]$^+$, 100%), 466 ([M+H]$^+$, 16%); HRMS (ESI$^+$) found 488.2419; $C_{28}H_{35}NNaO_5^+$ ([M+Na]$^+$) requires 488.2402.

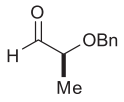
*4.2.12. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (R)-2-(3‴,4‴-dimethoxybenzyloxy)pentanamide **35**.*



Compound (*S*)-**9** (272 mg, 0.60 mmol) in THF (8 mL) was treated with KHMDS (0.78 mmol) and 18-crown-6 (300 mg, 1.14 mmol) in

THF (8 mL) and 1-iodopropane (0.12 mL, 1.21 mmol) according to the *general procedure*. The reaction was held at −78 °C for 4 h before being quenched. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **35** in >95:5 dr. Purification via flash column chromatography (gradient elution, 30–40 °C petrol/Et_2O, 9:1; increased to 30–40 °C petrol/Et_2O, 2:1) gave **35** as a colourless oil, which solidified upon prolonged standing to yield an amorphous solid (274 mg, 92%, >99:1 dr); R_f 0.15 (30–40 °C petrol/Et_2O, 5:1); $[\alpha]_D^{23}$ +50.9 (*c* 1.4 in $CHCl_3$); ν_{max} (film) 2961 (C–H), 1675 (C=O); δ_H (400 MHz, $CDCl_3$) 0.74 (9H, s, CMe_3), 0.78 (3H, t, *J* 7.0, C(5)H_3), 1.35–1.43 (3H, br m, C(3)H_A, C(4)H_2), 1.58–1.65 (1H, br m, C(3)H_B) 1.78 (3H, d, *J* 6.9, C(1′)*Me*), 3.85 (3H, s, O*Me*), 3.87 (3H, s, O*Me*), 4.34 (1H, d, *J* 11.9, OCH_AH_BAr), 4.35–4.40 (1H, br m, C(2)*H*), 4.74 (1H, d, *J* 11.9, OCH$_A$$H_B$Ar), 6.29–6.34 (1H, br m, C(1′)*H*), 6.79 (1H, d, *J* 8.2, *Ar*), 6.88 (1H, dd, *J* 8.2, 1.7, *Ar*), 6.99 (1H, s, *Ar*), 7.41–7.87 (6H, m, *Ar*), 8.42–8.46 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.8, 16.2, 18.9, 27.8, 32.4, 55.7, 55.9, 56.0, 71.0, 77.2, 82.4, 110.7, 110.9, 120.1, 124.5, 124.7, 125.6, 126.2, 126.4, 128.6, 128.7, 130.9, 132.3, 133.6, 135.4, 148.4, 149.9, 179.4; *m*/*z* (ESI$^+$) 516 ([M+Na]$^+$, 100%), 494 ([M+H]$^+$, 45%); HRMS (ESI$^+$) found 494.2907; $C_{30}H_{40}NO_5^+$ ([M+H]$^+$) requires 494.2896.

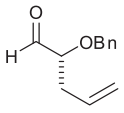
*4.2.13. (S)-2-Benzyloxypropanal **36**.*



Compound (2*S*,1′*R*)-**23** (130 mg, 0.32 mmol) was dissolved in THF (2 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 1 mL, 1 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give an approximate 50:50 mixture of auxiliary (*R*)-**1** and aldehyde (*S*)-**36**.

The crude mixture of auxiliary (*R*)-**1** and aldehyde (*S*)-**36** was dissolved in pentane (2.5 mL), the solution was stirred and (−)-CSA (149 mg, 0.64 mmol) was added. After 1 h a white precipitate had formed, which was collected by filtration. The filtrate was passed through a short plug of silica gel (eluent Et_2O) and concentrated in vacuo to give (*S*)-**36** as a colourless oil (53 mg, quant);[13] $[\alpha]_D^{23}$ −50.2 (*c* 1.0 in $CHCl_3$); {lit.[13] $[\alpha]_D$ −52.2 (*c* 6.5 in $CHCl_3$);}; δ_H (200 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.9, C(3)H_3), 3.91 (1H, dq, *J* 6.9, 1.7, C(2)*H*), 4.60 (1H, d, *J* 11.7, OCH_AH_BPh), 4.68 (1H, d, *J* 11.7, CH$_A$$H_B$Ph), 7.63–7.35 (5H, m, *Ph*), 9.68 (1H, d, *J* 1.7, C(1)*H*). The precipitate was basified by the addition of satd aq $NaHCO_3$ (20 mL) and the mixture was extracted with 30–40 °C petrol (3×20 mL). The combined organic extracts were dried and concentrated in vacuo to give (*R*)-**1** as a colourless oil (68 mg, 87%, >99:1 er).

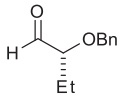
*4.2.14. (R)-2-Benzyloxypent-4-enal **37**.*



Compound (2*R*,1′*S*)-**25** (297 mg, 0.69 mmol) was dissolved in THF (4 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 2 mL, 2 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give an approximate 50:50 mixture of auxiliary (*S*)-**1** and aldehyde (*R*)-**37**.

The crude mixture of auxiliary (*S*)-**1** and aldehyde (*R*)-**37** was dissolved in pentane (2.5 mL), the solution was stirred and (+)-CSA (321 mg, 1.38 mmol) was added. After 1 h a white precipitate had formed, which was collected by filtration. The filtrate was passed through a short plug of silica gel (eluent Et_2O) and concentrated in vacuo to give (*R*)-**37** as a colourless oil (130 mg, 93%);[17] $[\alpha]_D^{23}$ +68.6 (*c* 2.0 in $CHCl_3$); {lit. for enantiomer ca. 82% ee[17] $[\alpha]_D^{25}$ −46.4 (*c* 2.5 in $CHCl_3$)}; δ_H (300 MHz, $CDCl_3$) 2.54–2.48 (2H, m, C(3)H_2), 3.85 (1H, dt, *J* 6.4, 1.9, C(2)*H*), 4.61 (1H, d, *J* 11.8, OCH_AH_BPh), 4.70 (1H, d, *J* 11.8, OCH$_A$$H_B$Ph), 5.12–5.21 (2H, m, C(5)H_2), 5.83 (1H, ddt, *J* 17.1, 10.1, 6.9, C(4)*H*), 7.27–7.38 (5H, m, *Ph*), 9.67 (1H, d, *J* 1.9, C(1)*H*). The precipitate was basified by the addition of satd aq $NaHCO_3$ (20 mL) and the mixture was extracted with 30–40 °C petrol (3×20 mL). The combined organic extracts were dried and concentrated in vacuo to give (*S*)-**1** as a colourless oil (142 mg, 85%, >99:1 er).

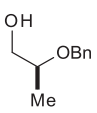
*4.2.15. (R)-2-Benzyloxybutanal **38**.*



Compound (2*R*,1′*S*)-**26** (275 mg, 0.66 mmol) was dissolved in THF (4 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 2 mL, 2 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give an approximate 50:50 mixture of auxiliary (*S*)-**1** and aldehyde (*R*)-**38**.

The crude mixture of auxiliary (*S*)-**1** and aldehyde (*R*)-**38** was dissolved in pentane (2.5 mL), the solution was stirred and (+)-CSA (307 mg, 1.32 mmol) was added. After 1 h a white precipitate had formed, which was collected by filtration. The filtrate was passed through a short plug of silica gel (eluent Et_2O) and concentrated in vacuo to give (*R*)-**38** as a colourless oil (115 mg, 98%);[18] $[\alpha]_D^{23}$ +93.6 (*c* 1.0 in $CHCl_3$); {lit. for enantiomer[18a] $[\alpha]_D^{20}$ −95 (*c* 1.0 in $CHCl_3$); lit. for enantiomer[18b] $[\alpha]_D^{23}$ −98.3 (*c* 0.95 in $CHCl_3$)}; δ_H (200 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.2, C(4)H_3), 1.77 (2H, q, *J* 7.2, C(3)H_2), 3.73 (1H, dt, *J* 7.2, 2.1, C(2)*H*), 4.58 (1H, d, *J* 11.7, OCH_AH_BPh), 4.71 (1H, d, *J* 11.7, OCH$_A$$H_B$Ph), 7.22–7.39 (5H, m, *Ph*), 9.69 (1H, d, *J* 2.1, C(1)*H*). The precipitate was basified by the addition of satd aq $NaHCO_3$ (20 mL) and the mixture was extracted with 30–40 °C petrol (3×20 mL). The combined organic extracts were dried and concentrated in vacuo to give (*S*)-**1** as a colourless oil (65 mg, 85%, >99:1 er).

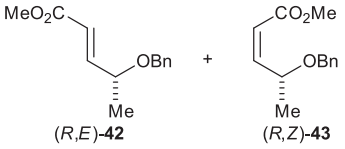
*4.2.16. (S)-2-Benzyloxypropan-1-ol **39**.*



Compound (*S*)-**36** (10 mg, 0.06 mmol) was dissolved in THF (1 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 2 mL, 2 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 10 min. The reaction mixture was quenched with solid $Na_2SO_4{\cdot}10H_2O$. The mixture was diluted with Et_2O (50 mL) and filtered through a short plug of $MgSO_4$ (eluent Et_2O). The filtrate was concentrated in vacuo to give (*S*)-**39** as a colourless oil (8 mg, 80%, 97:3 er);[13,15] $[\alpha]_D^{21}$ +40.0

(c 0.1 in $CHCl_3$); {lit.[13] $[\alpha]_D$ +45.9 (c 6.4 in $CHCl_3$); lit.[15] $[\alpha]_D^{20}$ +44.7 (c 3.5 in $CHCl_3$)}; δ_H (200 MHz, $CDCl_3$) 1.19 (3H, d, J 6.2, C(3)H_3), 2.13 (1H, br s, OH), 3.50–3.74 (3H, m, C(1)H_2, C(2)H), 4.50 (1H, d, J 11.6, CH_AH$_B$Ph), 4.67 (1H, d, J 11.6, CH$_A$$H_B$Ph), 7.27–7.36 (5H, m, *Ph*).

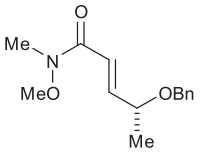
4.2.17. Methyl (R,E)-4-benzyloxypent-2-enoate 42 and methyl (R,Z)-4-benzyloxypent-2-enoate ***43***.



Compound (2*R*,1′*S*)-**23** (302 mg, 0.75 mmol) was dissolved in THF (4 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 2.2 mL, 2.2 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give an approximate 50:50 mixture of auxiliary (*S*)-**1** and aldehyde (*R*)-**36**.

The crude mixture of auxiliary (*S*)-**1** and aldehyde (*R*)-**36** was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C. $Ph_3P{=}CHCO_2Me$ (513 mg, 1.49 mmol) was added. The reaction mixture was allowed to warm to rt over 16 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave auxiliary (*S*)-**1** (173 mg, 95%, >99:1 er). Further elution gave (*R*,*Z*)-**43** as a colourless oil (53 mg, 32%, >99:1 dr, 98:2 er);[19] $[\alpha]_D^{23}$ −55.9 (c 0.7 in $CHCl_3$); {lit. for enantiomer[19a] $[\alpha]_D^{20}$ +36 (c 0.6 in $CHCl_3$); lit. for enantiomer[19b] $[\alpha]_D^{25}$ +25.5 (c 1.0 in $CHCl_3$); lit.[19j] $[\alpha]_D^{25}$ −49.2 (c 0.5 in $CHCl_3$)}; δ_H (300 MHz, $CDCl_3$) 1.33 (3H, d, J 6.5, C(5)H_3), 3.72 (3H, s, O*Me*), 4.44 (1H, d, J 11.6, CH_AH$_B$Ph), 4.52 (1H, d, J 11.6, CH$_A$$H_B$Ph), 5.15–5.19 (1H, m, C(4)H), 5.87 (1H, app dd, J 11.8, C(2)H), 6.25 (1H, dd, J 11.8, 8.4, C(3)H), 7.24–7.36 (5H, m, *Ph*). Further elution gave (*R*,*E*)-**42** as a colourless oil (81 mg, 49%);[19] $[\alpha]_D^{23}$ +67.0 (c 1.2 in $CHCl_3$); {lit. for enantiomer[19a] $[\alpha]_D^{20}$ −44 (c 0.2 in $CHCl_3$); lit. for enantiomer[19g] $[\alpha]_D^{23}$ −34.8 (c 1.2 in $CHCl_3$)}; δ_H (300 MHz, $CDCl_3$) 1.33 (3H, d, J 6.5, C(5)H_3), 3.77 (3H, s, O*Me*), 4.10–4.14 (1H, m, C(4)H), 4.43 (1H, d, J 11.9, CH_AH$_B$Ph), 4.58 (1H, d, J 11.9, CH$_A$$H_B$Ph), 6.04 (1H, dd, J 15.8, 1.5, C(2)H), 6.91 (1H, dd, J 15.8, 6.1, C(3)H), 7.26–7.36 (5H, m, *Ph*).

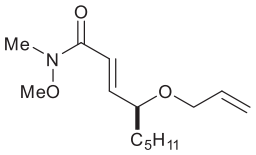
4.2.18. N-Methoxy-N-methyl (R,E)-4-benzyloxypent-2-enamide ***44***.



Compound (2*R*,1′*S*)-**23** (250 mg, 0.62 mmol) was dissolved in THF (4 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 2 mL, 2 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give an approximate 50:50 mixture of auxiliary (*S*)-**1** and aldehyde (*R*)-**36**.

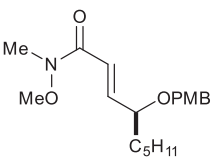
The crude mixture of auxiliary (*S*)-**1** and aldehyde (*R*)-**36** was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C, then $Ph_3P{=}CHCON(Me)(OMe)$ (447 mg, 1.23 mmol) was added. The reaction mixture was allowed to warm to rt over 16 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave auxiliary (*S*)-**1** (143 mg, 95%, >99:1 er). Further elution gave (*R*,*E*)-**44** as a colourless oil (125 mg, 82%); $[\alpha]_D^{21}$ +39.8 (c 1.0 in $CHCl_3$); ν_{max} (film) 1666 (C=O), 1638 (C=C); δ_H (300 MHz, $CDCl_3$) 1.32 (3H, d, J 6.6, C(5)H_3), 3.23 (3H, s, N*Me*), 3.66 (3H, s, O*Me*), 4.15 (1H, app quintet d, J 6.2, 1.0, C(4)H), 4.42 (1H, d, J 11.9, CH_AH$_B$Ph), 4.57 (1H, d, J 11.9, CH$_A$$H_B$Ph), 6.60 (1H, d, J 15.9, C(2)H), 6.91 (1H, dd, J 15.9, 6.2, C(3)H), 7.23–7.32 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 20.8, 32.3, 61.7, 70.7, 74.3, 118.7, 127.8, 128.6, 138.5, 148.0, 166.7; m/z (Cl^+) 250 ($[M+H]^+$, 100%); HRMS (Cl^+) found 250.1445; $C_{14}H_{20}NO_3^+$ ($[M+H]^+$) requires 250.1438.

4.2.19. N-Methoxy-N-methyl (S,E)-4-allyloxynona-2-enamide ***45***.



Compound (2*S*,1′*R*)-**31** (271 mg, 0.66 mmol) was dissolved in THF (20 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 2 mL, 2 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C, then $Ph_3P{=}CHCON(Me)(OMe)$ (478 mg, 5.26 mmol) was added. The reaction mixture was allowed to warm to rt over 16 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1) gave auxiliary (*R*)-**1** (154 mg, 96%, >99:1 er). Further elution gave (*S*,*E*)-**45** as a colourless oil (130 mg, 77%, >99:1 dr); $[\alpha]_D^{21}$ −22.7 (c 1.1 in $CHCl_3$); ν_{max} (film) 1667 (C=O), 1639 (C=C); δ_H (300 MHz, $CDCl_3$) 0.82 (3H, t, J 6.8, C(9)H_3), 1.14–1.59 (8H, m, C(5)H_2–C(8)H_2), 3.20 (3H, s, N*Me*), 3.65 (3H, s, O*Me*), 3.81 (1H, app ddt, J 12.7, 5.7, 1.4, CH_AH$_B$CH=CH$_2$), 3.89 (1H, app q, J 6.3, C(4)H), 3.89 (1H, app ddt, J 12.7, 5.7, 1.4, CH$_A$$H_B$CH=CH$_2$), 5.11 (1H, dq, J 10.5, 1.4, CH$_2$CH=CH_AH$_B$), 5.21 (1H, dq, J 17.2, 1.4, CH$_2$CH=CH$_A$$H_B$), 5.84 (1H, ddt, J 17.2, 10.5, 5.7, CH$_2$CH=CH$_2$), 6.50 (1H, d, J 15.7, C(2)H), 6.78 (1H, dd, J 15.7, 6.3, C(3)H); δ_C (50 MHz, $CDCl_3$) 13.8, 22.4, 24.7, 31.6, 32.2, 34.9, 61.7, 69.9, 78.5, 117.0, 119.2, 135.0, 147.3, 166.6; m/z (Cl^+) 256 ($[M+H]^+$, 100%); HRMS (Cl^+) found 256.1913; $C_{14}H_{26}NO_3^+$ ($[M+H]^+$) requires 256.1907. Further elution gave an impure sample of the (*S*,*Z*)-isomer (9 mg, ~5%); δ_H (300 MHz, $CDCl_3$) 0.87 (3H, t, J 6.8, C(9)H_3), 1.19–1.68 (8H, m, C(5)H_2–C(8)H_2), 3.23 (3H, s, N*Me*), 3.70 (3H, s, O*Me*), 3.91 (1H, app ddt, J 12.8, 5.6, 1.2, CH_AH$_B$CH=CH$_2$), 4.02 (1H, app ddt, J 12.8, 5.6, 1.2, CH$_A$$H_B$CH=CH$_2$), 4.92–4.96 (1H, m, C(4)H), 5.15 (1H, app dt, J 10.4, 1.2, CH$_2$CH=CH_AH$_B$), 5.26 (1H, dq, J 17.2, 1.2, CH$_2$CH=CH$_A$$H_B$), 5.92 (1H, app ddt, J 17.2, 10.4, 5.6, CH$_2$CH=CH$_2$), 6.03 (1H, dd, J 11.8, 8.7, C(3)H), 6.38 (1H, d, J 11.8, C(2)H).

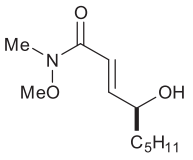
4.2.20. N-Methoxy-N-methyl (S,E)-4-(4′-methoxybenzyloxy)nona-2-enamide ***46***.



Compound (2*S*,1′*R*)-**33** (1.3 g, 2.63 mmol) was dissolved in THF (20 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 7.9 mL, 7.9 mmol) was added dropwise via

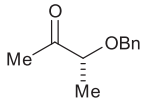
syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C, then Ph_3P=CHCON(Me)(OMe) (1.90 g, 5.26 mmol) was added. The reaction mixture was allowed to warm to rt over 16 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 10:1) gave auxiliary (*R*)-**1** (649 mg, quant, >99:1 er). Further elution gave (*S*,*E*)-**46** as a colourless oil (783 mg, 89%, >99:1 dr); $[\alpha]_D^{21}$ −50.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1666 (C=O), 1637, 1614, 1587 (C=C); δ_H (300 MHz, $CDCl_3$) 0.83–0.90 (3H, m, C(9)H_3), 1.22–1.68 (8H, m, C(5)H_2–C(8)H_2), 3.27 (3H, s, N*Me*), 3.71 (3H, s, O*Me*), 3.81 (3H, s, O*Me*), 3.98 (1H, app q, *J* 6.2, C(4)*H*), 4.32 (1H, d, *J* 11.4, CH_AH$_B$Ar), 4.54 (1H, d, *J* 11.4, CH$_A$$H_B$Ar), 6.60 (1H, d *J* 15.4, C(2)*H*), 6.87–6.94 (1H, dd, *J* 15.4, 6.2, C(3)*H*) overlapping 6.88 (2H, d, *J* 8.6, *Ar*), 7.27 (2H, d, *J* 8.6, *Ar*); δ_C (50 MHz, $CDCl_3$) 14.0, 22.5, 24.9, 31.6, 32.3, 35.1, 55.2, 61.7, 70.5, 78.0, 113.7, 119.2, 129.3, 130.4, 147.2, 159.1, 166.4; *m*/*z* (APCI$^+$) 336 ([M+H]$^+$, 100%); HRMS (CI$^+$) found 336.2170; $C_{19}H_{30}NO_4^+$ ([M+H]$^+$) requires 336.2169. Further elution gave an impure sample of the (*S*,*Z*)-isomer (53 mg, ~6%); δ_H (300 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.8, C(9)H_3), 1.20–1.69 (8H, m, C(5)H_2–C(8)H_2), 3.22 (3H, s, N*Me*), 3.69 (3H, s, O*Me*), 3.78 (3H, s, O*Me*), 4.36 (1H, d, *J* 11.2, CH_AH$_B$Ar), 4.46 (1H, d, *J* 11.2, CH$_A$$H_B$Ar), 4.99–5.02 (1H, m, C(4)*H*), 6.07 (1H, dd, *J* 11.9, 8.6, C(3)*H*), 6.38 (1H, d, *J* 11.9, C(2)*H*), 6.85 (2H, d, *J* 8.6, *Ar*), 7.25 (2H, d, *J* 8.6, *Ar*).

4.2.21. *N-Methoxy-N-methyl (S,E)-4-hydroxynona-2-enamide* ***47***.



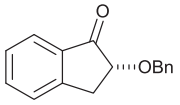
Compound **46** (203 mg, 0.61 mmol) was dissolved in MeCN (4 mL) and the resultant solution was cooled to 0 °C. A solution of CAN (995 mg, 1.82 mmol) in H_2O (2 mL) was added dropwise and stirring was maintained at 0 °C for 2 h. The solution was allowed to warm to rt over a further 1 h. The reaction mixture was then diluted with brine (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:2) gave **47** as a colourless oil (118 mg, 90%);[21] $[\alpha]_D^{21}$ +26.1 (*c* 0.4 in $CHCl_3$); ν_{max} (film) 3414 (O–H), 1661, 1621 (C=C); δ_H (300 MHz, $CDCl_3$) 0.87–0.90 (3H, m, C(9)H_3), 1.20–1.63 (8H, m, C(5)H_2–C(8)H_2), 3.25 (3H, s, N*Me*), 3.71 (3H, s, O*Me*), 4.34 (1H, app dq, *J* 5.9, 1.3, C(4)*H*), 6.61 (1H, d, *J* 15.3, C(2)*H*), 6.97 (1H, dd, *J* 15.3, 4.9, C(3)*H*); δ_C (125 MHz, $CDCl_3$) 13.9, 22.4, 24.8, 31.6, 32.3, 36.7, 61.7, 71.3, 117.2, 149.3, 166.7; *m*/*z* (APCI$^+$) 216 ([M+H]$^+$, 100%); HRMS (CI$^+$) found 216.1600; $C_{11}H_{22}NO_3^+$ ([M+H]$^+$) requires 216.1594.

4.2.22. *(R)-3-Benzyloxybutanone* ***49***.



Compound (2*R*,1′*S*)-**23** (248 mg, 0.61 mmol) was dissolved in Et_2O (2 mL) and the resultant solution was cooled to −10 °C in a salt/ice bath. MeLi (1.6 M in Et_2O, 1.15 mL, 1.84 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −10 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (12 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give an approximate 50:50 mixture of auxiliary (*S*)-**1** and ketone **49**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave (*S*)-**1** as a colourless oil (122 mg, 82%, >99:1 er). Further elution gave (*R*)-**49** as a colourless oil (92 mg, 84%); found C, 74.2; H, 8.0%; $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%; $[\alpha]_D^{23}$ +47.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1719 (C=O); δ_H (200 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.9, C(4)H_3), 2.21 (3H, s, C(1)H_3), 3.93 (1H, q, *J* 6.9, C(3)*H*), 4.50 (1H, d, *J* 11.7, CH_AH$_B$Ph), 4.59 (1H, d, *J* 11.7, CH$_A$$H_B$Ph), 7.28–7.39 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 17.1, 24.9, 71.9, 80.9, 128.0, 128.1, 128.7, 137.8, 211.8; *m*/*z* (CI$^+$) 196 ([M+NH$_4$]$^+$, 100%), 179 ([M+H]$^+$, 45%).

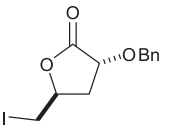
4.2.23. *(R)-2-Benzyloxyindan-1-one* ***50***.



Compound (2*R*,1′*S*)-**27** (221 mg, 0.39 mmol) was dissolved in Et_2O (3 mL) and the resultant solution was cooled to −78 °C in a dry-ice/acetone bath. ^{t}BuLi (1.5 M in pentane, 0.53 mL, 0.79 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was transferred dropwise via cannula to a stirred solution pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give an approximate 50:50 mixture of auxiliary (*S*)-**1** and indanone (*R*)-**50**.

The crude mixture of auxiliary (*S*)-**1** and indanone (*R*)-**50** was dissolved in pentane (2.5 mL), the solution was stirred and (+)-CSA (181 mg, 0.78 mmol) was added. After 1 h a white precipitate had formed, which was collected by filtration. The filtrate was passed through a short plug of silica gel (eluent Et_2O) and concentrated in vacuo to give an oil, which was further purified by vacuum distillation (bp ca. 200 °C, 0.1 mmHg) to give (*R*)-**50** as a colourless oil (84 mg, 89%); found C, 80.55; H, 6.0%; $C_{16}H_{14}O_2$ requires C, 80.65; H, 5.9%; $[\alpha]_D^{24}$ +46.1 (*c* 1.05 in $CHCl_3$); ν_{max} (film) 1722 (C=O); δ_H (200 MHz, $CDCl_3$) 3.01 (1H, dd, *J* 17.0, 4.5, C(3)H_A), 3.46 (1H, dd, *J* 17.0, 7.6, C(3)H_B), 4.34 (1H, dd, *J* 7.6, 4.5, C(2)*H*), 4.86 (1H, d, *J* 11.8, CH_AH$_B$Ph), 5.64 (1H, d, *J* 11.8, CH$_A$$H_B$Ph), 7.45–7.32 (7H, m, *Ar*), 7.61 (1H, dt, *J* 6.6, 1.2, *Ar*), 7.78 (1H, d, *J* 7.4, *Ar*); δ_C (50 MHz, $CDCl_3$) 33.8, 72.4, 79.0, 124.4, 126.9, 128.1, 128.3, 128.7, 135.1, 135.8, 137.9, 151.1, 204.3; *m*/*z* (CI$^+$) 256 ([M+NH$_4$]$^+$, 100%), 239 ([M+H]$^+$, 60%). The precipitate was basified by the addition of satd aq $NaHCO_3$ (20 mL) and the mixture was extracted with 30–40 °C petrol (3×20 mL). The combined organic extracts were dried and concentrated in vacuo to give (*S*)-**1** as a colourless oil (71 mg, 74%, >99:1 er).

4.2.24. *(3R,5S)-3-Benzyloxy-5-iodomethyltetrahydrofuran-2-one* ***51***.



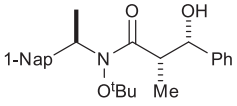
Compound (2*R*,1′*S*)-**25** (215 mg, 0.5 mmol) was dissolved in THF/H_2O (v/v 3:1, 2.5 mL) and iodine (379 mg, 1.5 mmol) was added. The reaction mixture was stirred at rt for eight days. The reaction was quenched by the addition of 1 M aq $Na_2S_2O_3$ (15 mL). Satd aq $NaHCO_3$ (15 mL) was added and the mixture was extracted with 30–40 °C petrol (3×30 mL). The combined organic extracts were dried and concentrated in vacuo to give **51** in 85:15 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave a white powder, which was further purified by

recrystallisation from pentane to give **51** as a colourless solid (76 mg, 46%, >99:1 dr); found C, 43.5; H, 3.8%; $C_{12}H_{13}IO_3$ requires C, 43.4; H, 3.95%; $[\alpha]_D^{24}$ +53.1 (*c* 0.5 in $CHCl_3$); ν_{max} (KBr) 1773 (C=O); δ_H (300 MHz, $CDCl_3$) 2.19 (1H, app dt, *J* 14.0, 7.3, C(4)H_A), 2.48 (1H, ddd, *J* 14.0, 6.8, 4.0, C(4)H_B), 3.30 (1H, dd, *J* 10.6, 7.1, CH_AH_BI), 3.40 (1H, dd, *J* 10.6, 4.3, CH_AH_BI), 4.26 (1H, dd, *J* 7.3, 4.0, C(3)*H*), 4.69 (1H, d, *J* 11.6, CH_AH_BPh), 4.67–4.74 (1H, m, C(5)*H*), 4.91 (1H, d, *J* 11.6, CH$_A$H$_B$Ph), 7.32–7.38 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 7.4, 36.2, 72.2, 73.5, 77.0, 128.3, 128.6, 136.8, 173.7; *m*/*z* (CI^+) 350 ($[M+NH_4]^+$, 100%).

4.3. General procedure for enolate aldol reactions

Freshly titrated KHMDS (ca. 0.5 M in PhMe) was added dropwise to a degassed solution of the substrate and in THF at −78 °C. After stirring for 30 min at this temperature, the requisite aldehyde (freshly distilled or dried) was added dropwise (neat or as a solution in THF) and stirring was continued at −78 °C for 2 h. The reaction was then quenched by the dropwise addition of pH 7 phosphate buffer and allowed to warm to rt. The mixture was concentrated in vacuo, the residue was dissolved in Et_2O and filtered through a short, silica/$MgSO_4$ plug (eluent Et_2O). The filtrate was concentrated in vacuo and purified as described.

*4.3.1. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S,S)-2-methyl-3-hydroxy-3-phenylpropanamide **52**.*



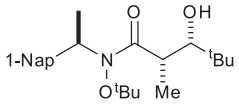
Compound (*R*)-**22** (501 mg, 2.31 mmol) in THF (6 mL) was treated with KHMDS (1.84 mmol) in THF (6 mL) and benzaldehyde (508 μL, 6.93 mmol) according to the *general procedure*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **52** in 98:2 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave a white solid, which was recrystallised from pentane to give **52** as colourless crystals (485 mg, 72%, >99:1 dr); found C, 77.0; H, 7.7; N, 3.4%; $C_{26}H_{31}NO_3$ requires C, 77.0; H, 7.7; N, 3.45%; mp 137–138 °C; $[\alpha]_D^{21}$ +22.8 (*c*. 1.1 in $CHCl_3$); ν_{max} (KBr) 3448 (O–H), 1639 (C=O), 1597 (C=C); δ_H (250 MHz, PhMe-d_8, 70 °C) 0.81 (9H, s, CMe_3), 1.31 (3H, d, *J* 6.9, C(2)*Me*), 1.61 (3H, d, *J* 6.9, C(1′)*Me*), 3.37 (1H, dq, *J* 6.9, 2.7, C(2)*H*), 3.81 (1H, br s, O*H*), 4.97 (1H, br d, *J* 2.7, C(3)*H*), 6.08 (1H, q, *J* 6.9, C(1′)*H*), 6.96–7.64 (11H, m, *Ar*, *Ph*), 8.17 (1H, d, *J* 8.4, *Ar*); δ_C (125 MHz, $CDCl_3$) 9.0, 27.7, 42.8, 75.2, 83.2, 124.0, 125.4, 125.8, 126.1, 126.7, 127.3, 128.3, 128.7, 129.1, 133.9, 141.8, 183.1; *m*/*z* (CI^+) 406 ($[M+H]^+$, 100%).

*4.3.2. X-ray crystal structure determination for **52**.* Data were collected using an Enraf-Nonius MACH3 diffractometer with graphite monochromated Cu 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.[38]

X-ray crystal structure data for **52** [$C_{26}H_{31}NO_3$]: *M*=405.54, orthorhombic, space group $P\,2_1\,2_1\,2_1$, *a*=9.0403(5) Å, *b*=11.4794(4) Å, *c*=22.682(2) Å, *V*=2353.8(2) Å^3, *Z*=4, μ=0.553 mm^{-1}, colourless plate, crystal dimensions=0.13×0.32×0.58 mm^3. A total of 2494 unique reflections were measured for $5<\theta<27$ and 2160 reflections were used in the refinement. The final parameters were wR_2=0.046 and R_1=0.041 [$I>3.0\sigma(I)$], Flack enantiopole=0.17(1).

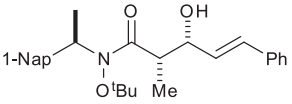
Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 745789. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

*4.3.3. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S,S)-2,4,4-trimethyl-3-hydroxypentanamide **54**.*



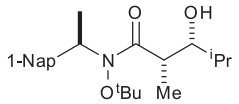
Compound (*R*)-**22** (194 mg, 0.65 mmol) in THF (2 mL) was treated with KHMDS (0.71 mmol) in THF (2 mL) and pivalaldehyde (211 μL, 1.95 mmol) according to the *general procedure*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **52** in 98:2 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **54** as a colourless oil (151 mg, 60%, >99:1 dr); $[\alpha]_D^{21}$ −22.5 (*c*. 0.9 in $CHCl_3$); ν_{max} (KBr) 3468 (O–H), 1646 (C=O); δ_H (250 MHz, toluene-d_8, 90 °C) 0.85 (9H, s, CMe_3), 0.92 (9H, s, CMe_3), 1.22 (3H, d, *J* 6.9, C(2)*Me*), 1.69 (3H, d, *J* 7.0, C(1′)*Me*), 3.22–3.26 (2H, br m, C(3)*H*, O*H*), 3.36 (1H, dq, *J* 6.9, 1.1, C(2)*H*), 6.02 (1H, q, *J* 7.0, C(1′)*H*), 7.19–7.37 (3H, m, *Ar*), 7.53–7.63 (3H, m, *Ar*), 8.23 (1H, d, *J* 8.3, *Ar*); δ_C (125 MHz, $CDCl_3$) 10.4, 17.0, 27.0, 27.6, 35.2, 37.0, 57.0, 76.0, 82.9, 124.0, 125.2, 125.8, 126.4, 126.5, 128.7, 129.0, 133.9, 184.0; *m*/*z* (CI^+) 386 ($[M+H]^+$, 100%); HRMS (CI^+) found 386.2683; $C_{24}H_{36}NO_3^+$ ($[M+H]^+$) requires 386.2690.

*4.3.4. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R,E)-2-methyl-3-hydroxy-5-phenylpent-4-enamide **55**.*



Compound (*R*)-**22** (504 mg, 1.68 mmol) in THF (6 mL) was treated with KHMDS (1.85 mmol) in THF (6 mL) and cinnamaldehyde (636 μL, 5.04 mmol) according to the *general procedure*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **55** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **55** as a colourless glass (565 mg, 78%, >99:1 dr); found C, 78.0; H, 7.7; N, 3.0%; $C_{28}H_{33}NO_3$ requires C, 77.9; H, 7.7; N, 3.25%; $[\alpha]_D^{21}$ +27.8 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 3436 (O–H), 1651 (C=O), 1600 (C=C); δ_H (250 MHz, PhMe-d_8, 90 °C) 0.79 (9H, s, CMe_3), 1.30 (3H, d, *J* 6.9, C(2)*Me*), 1.67 (3H, d, *J* 7.0, C(1′)*Me*), 3.24–3.34 (1H, br s, O*H*), 3.29 (1H, dq, *J* 6.9, 3.8, C(2)*H*), 4.50–4.53 (1H, m, C(3)*H*), 6.12–6.21 (1H, m, C(1′)*H*) overlapping 6.16 (1H, dd, *J* 15.9, 5.5, C(4)*H*), 6.70 (1H, d, *J* 15.9, C(5)*H*), 6.97–7.62 (11H, m, *Ar*, *Ph*), 8.21 (1H, d, *J* 8.3, *Ar*); δ_C (125 MHz, $CDCl_3$) 10.0, 27.8, 41.8, 72.3, 83.1, 125.2, 125.7, 126.6, 127.6, 128.6, 129.0, 131.0, 133.7, 136.9, 182.2; *m*/*z* (ESI^+) 449 ($[M+NH_4]^+$, 20%), 432 ($[M+H]^+$, 100%).

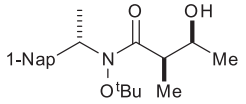
*4.3.5. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R)-2,4-dimethyl-3-hydroxypentanamide **56**.*



Compound (*R*)-**22** (287 mg, 0.96 mmol) in THF (4 mL) was treated with KHMDS (1.05 mmol) in THF (4 mL) and isobutyraldehyde (261 μL, 3.0 mmol) according to the *general procedure*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **56** in 92:8 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave

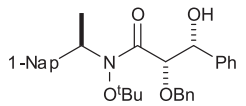
a colourless oil, which was crystallised from pentane at −30 °C to give **56** as colourless blocks (151 mg, 42%, 97:3 dr); found C, 74.1; H, 9.2; N, 3.7%; $C_{23}H_{33}NO_3$ requires C, 74.4; H, 8.95; N, 3.8%; mp 63–64 °C; $[\alpha]_D^{21}$ −6.4 (*c* 0.8 in $CHCl_3$); ν_{max} (KBr) 3488 (O–H), 1641 (C=O), 1600 (C=C); δ_H (250 MHz, PhMe-d_8, 90 °C) 0.71 (3H, d, *J* 6.8, *Me*), 0.81 (9H, s, C*Me*$_3$), 1.04 (3H, d, *J* 6.8, *Me*), 1.17 (3H, d, *J* 6.8, *Me*), 1.67 (3H, d, *J* 7.0, C(1′)*Me*), 1.61–1.73 (1H, m, C(4)*H*), 3.22–3.29 (2H, m, C(2)*H*, C(3)*H*), 3.32 (1H, br s, O*H*), 6.07 (1H, q, *J* 7.0, C(1′)*H*), 7.19–7.37 (3H, m, *Ar*), 7.53–7.62 (3H, m, *Ar*), 8.21 (1H, d, *J* 8.3, *Ar*); δ_C (125 MHz, $CDCl_3$) 9.1, 17.5, 18.8, 19.4, 27.7, 30.4, 37.3, 56.5, 76.0, 82.8, 123.7, 125.0, 125.5, 125.5, 126.3, 128.8, 133.6, 136.1, 183.4; *m*/*z* (APCI$^+$) 394 ([M+Na]$^+$, 30%), 372 ([M+H]$^+$, 100%).

*4.3.6. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2R,3S)-2-methyl-3-hydroxybutanamide **57**.*



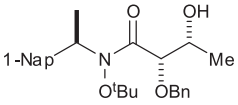
Compound (*S*)-**22** (288 mg, 0.96 mmol) in THF (4 mL) was treated with KHMDS (1.06 mmol) in THF (4 mL) and propanal (161 μL, 2.89 mmol) according to the *general procedure*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **57** in 95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave a colourless oil, which was crystallised from pentane at −30 °C to give **57** as colourless blocks (197 mg, 60%, 95:5 dr); found C, 73.6; H, 8.65; N, 4.0%; $C_{21}H_{29}NO_3$ requires C, 73.4; H, 8.5; N, 4.1%; mp 105–107 °C; $[\alpha]_D^{21}$ +5.5 (*c* 1.45 in $CHCl_3$); ν_{max} (KBr) 3420 (O–H), 1636 (C=O); δ_H (250 MHz, PhMe-d_8, 90 °C) 0.77 (9H, s, C*Me*$_3$), 1.08 (3H, d, *J* 6.4, C(4)*H*$_3$), 1.20 (3H, d, *J* 7.0, C(2)*Me*), 1.67 (3H, d, *J* 7.0, C(1′)*Me*), 2.98–3.08 (1H, br s, O*H*) overlapping 3.03 (1H, dq, *J* 7.0, 3.5, C(2)*H*), 3.99 (1H, dq, *J* 6.4, 3.5, C(3)*H*), 6.14 (1H, q, *J* 7.0, C(1′)*H*), 7.22 (1H, app t, *J* 7.9, *Ar*), 7.29–7.36 (2H, m, *Ar*), 7.55 (1H, app d, *J* 8.2, *Ar*), 7.61 (2H, app d, *J* 7.3, *Ar*), 8.21 (1H, d, *J* 8.4, *Ar*); δ_C (125 MHz, $CDCl_3$) 9.6, 18.0, 19.9, 27.7, 41.6, 55.5, 67.1, 82.9, 123.5, 125.0, 126.1, 126.4, 128.5, 128.8, 136.2, 133.6, 182.8; *m*/*z* (APCI$^+$) 366 ([M+Na]$^+$, 100%), 344 ([M+H]$^+$, 50%).

*4.3.7. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R)-2-benzyloxy-3-hydroxy-3-phenylpropanamide **59**.*



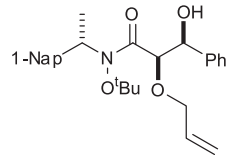
Compound (*R*)-**5** (175 mg, 0.45 mmol) in THF (8 mL) was treated with KHMDS (0.63 mmol) in THF (8 mL) and benzaldehyde (0.14 mL, 1.34 mmol) according to the *general procedure*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **59** in 86:14 dr. Purification via flash column chromatography (gradient elution, 30–40 °C petrol/Et_2O, 3:1; increased to Et_2O) gave **59** as a colourless oil (167 mg, 75%, 95:5 dr); R_f 0.35 (30–40 °C petrol/Et_2O, 1:1); $[\alpha]_D^{23}$ −25.7 (*c* 1.3 in $CHCl_3$); ν_{max} (film) 3459 (O–H), 2977 (C–H), 1674 (C=O), 1600 (C=C), 1512, 1495, 1454, 1393, 1368; δ_H (400 MHz, $CDCl_3$) 0.73 (9H, s, C*Me*$_3$), 1.87 (3H, d, *J* 7.0, C(1′)*Me*), 2.94 (1H, br s, O*H*), 4.39 (1H, d, *J* 12.4, C*H*$_A$H$_B$Ph), 4.68 (1H, d, *J* 1.7, C(2)*H*), 4.77 (1H, d, *J* 12.4, CH$_A$*H*$_B$Ph), 5.01–5.05 (1H, br m, C(3)*H*), 6.34–6.37 (1H, br m, C(1′)*H*), 6.96–7.69 (16H, m, *Ar*, *Ph*), 8.46–8.49 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.2, 27.8, 57.2, 71.5, 71.7, 79.3, 83.1, 124.1, 124.9, 125.7, 126.4, 127.5, 127.6, 128.1, 128.2, 128.7, 132.1, 133.6, 135.4, 137.3, 141.1, 176.7; *m*/*z* (ESI$^+$) 520 ([M+Na]$^+$, 100%), 498 ([M+H]$^+$, 18%); HRMS (ESI$^+$) found 520.2456; $C_{32}H_{35}NNaO_4^+$ ([M+Na]$^+$) requires 520.2458.

*4.3.8. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R)-2-benzyloxy-3-hydroxybutanamide **60**.*



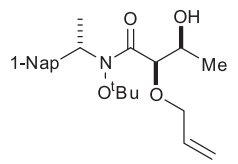
Compound (*R*)-**5** (217 mg, 0.56 mmol) in THF (8 mL) was treated with KHMDS (0.78 mmol) in THF (8 mL) and acetaldehyde (244 mg, 5.55 mmol) according to the *general procedure*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **60** in 80:20 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **60** as a colourless oil (180 mg, 75%, 80:20 dr); R_f 0.25 (30–40 °C petrol/Et_2O, 1:1); $[\alpha]_D^{23}$ −38.3 (*c* 1.6 in $CHCl_3$); ν_{max} (film) 3467 (O–H), 2976 (C–H), 1674 (C=O), 1600 (C=C); δ_H (400 MHz, $CDCl_3$) 0.67 (9H, s, C*Me*$_3$), 1.27 (3H, d, *J* 6.5, C(4)*H*$_3$), 1.82 (3H, d, *J* 6.9, C(1′)*Me*), 2.44–2.48 (1H, br m, O*H*), 4.18–4.22 (1H, br m, C(3)*H*), 4.42 (1H, d, *J* 2.1, C(2)*H*), 4.51 (1H, d, *J* 12.0, C*H*$_A$H$_B$Ph), 4.94 (1H, d, *J* 12.0, CH$_A$*H*$_B$Ph), 6.41–6.46 (1H, br m, C(1′)*H*), 7.26–7.90 (11H, m, *Ar*, *Ph*), 8.41–8.45 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.9, 20.2, 27.8, 55.9, 66.6, 71.6, 79.6, 82.8, 124.2, 124.8, 125.2, 125.5, 125.7, 126.3, 127.7, 127.9, 128.3, 128.4, 128.7, 128.8, 132.2, 133.6, 135.5, 137.7, 177.0; *m*/*z* (ESI$^+$) 458 ([M+Na]$^+$, 100%), 436 ([M+H]$^+$, 33%); HRMS (ESI$^+$) found 458.2316; $C_{27}H_{33}NNaO_4^+$ ([M+Na]$^+$) requires 458.2302.

*4.3.9. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2R,3S)-2-allyloxy-3-hydroxy-3-phenylpropanamide **61**.*



Compound (*S*)-**6** (593 mg, 1.74 mmol) in THF (15 mL) was treated with KHMDS (2.61 mmol) in THF (15 mL) and benzaldehyde (0.53 mL, 5.22 mmol) according to the *general procedure*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **61** in 96:4 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **61** as a colourless oil (720 mg, 92%, >99:1 dr); R_f 0.20 (30–40 °C petrol/Et_2O, 5:1); $[\alpha]_D^{23}$ +8.5 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3400 (O–H), 2976 (C–H), 1666 (C=O); δ_H (400 MHz, $CDCl_3$) 0.85 (9H, s, C*Me*$_3$), 1.84 (3H, d, *J* 6.9, C(1′)*Me*), 2.92 (1H, br s, O*H*) 3.84 (1H, app dd, *J* 12.9, 4.8, C*H*$_A$H$_B$CH=CH$_2$), 4.22 (1H, app dd, *J* 12.9, 4.4, CH$_A$*H*$_B$CH=CH$_2$), 4.65–4.68 (1H, br m, C(2)*H*), 5.01–5.06 (3H, br m, OCH$_2$CH=C*H*$_2$, C(3)*H*), 5.69–5.73 (1H, m, CH$_2$C*H*=CH$_2$), 6.32–6.36 (1H, br m, C(1′)*H*), 7.25–7.88 (11H, m, *Ar*, *Ph*), 8.41–8.46 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.2, 27.9, 56.8, 70.8, 71.8, 79.4, 83.2, 117.1, 124.1, 124.4, 124.9, 125.2, 125.6, 125.7, 126.4, 126.6, 127.5, 128.0, 128.7, 128.8, 133.6, 134.1, 135.4, 136.6, 141.0, 176.8; *m*/*z* (ESI$^+$) 470 ([M+Na]$^+$, 100%), 448 ([M+H]$^+$, 57%); HRMS (ESI$^+$) found 448.2497; $C_{28}H_{34}NO_4^+$ ([M+H]$^+$) requires 448.2482.

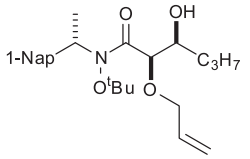
*4.3.10. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2R,3S)-2-allyloxy-3-hydroxybutanamide **62**.*



Compound (*S*)-**6** (540 mg, 1.58 mmol) in THF (20 mL) was treated with KHMDS (1.85 mmol) in THF (20 mL) and acetaldehyde (0.44 mL, 7.92 mmol) according to the *general procedure*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave

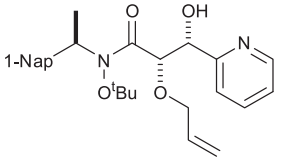
a white solid, which was further purified by recrystallisation from pentane to give **62** as colourless blocks (548 mg, 90%, >95:5 dr); R_f 0.15 (30–40 °C petrol/Et_2O, 2:1); mp 92–93 °C; $[\alpha]_D^{23}$ +25.1 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3460 (O–H), 2978 (C–H), 1672 (C=O), 1371, 1093; δ_H (400 MHz, $CDCl_3$) 0.78 (9H, s, CMe_3), 1.23, (3H, d, *J* 6.3, C(4)H_3), 1.81 (3H, d, *J* 6.9, C(1′)*Me*), 2.38 (1H, br s, O*H*) 3.95 (1H, app dd, *J* 12.7, 6.2, CH_AH_BCH=CH_2), 4.11–4.15 (1H, br m, C(3)*H*), 4.32–4.36 (2H, br m, C(2)*H*, CH_AH_BCH=CH_2), 5.22 (1H, dd, *J* 10.5, 1.1, CH_2CH=CH_AH_B), 5.31 (1H, dd, *J* 17.3, 1.1, CH_2CH=CH_AH_B), 5.95–5.99 (1H, m, CH_2C*H*=CH_2) 6.38–6.41 (1H, br m, C(1′)*H*), 7.42–7.88 (6H, m, *Ar*), 8.37–8.41 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.9, 20.1, 27.8, 56.1, 66.6, 70.8, 79.7, 82.8, 117.4, 124.2, 124.8, 125.7, 126.4, 128.7, 128.8, 132.1, 133.6, 134.5, 135.4, 177.0; *m*/*z* (ESI$^+$) 408 ([M+Na]$^+$, 100%), 386 ([M+H]$^+$, 40%); HRMS (ESI$^+$) found 386.2341; $C_{23}H_{32}NO_4^+$ ([M+H]$^+$) requires 386.2326.

*4.3.11. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2R,3S)-2-allyloxy-3-hydroxyhexanamide **63**.*



Compound (*S*)-**6** (250 mg, 0.73 mmol) in THF (9 mL) was treated with KHMDS (0.95 mmol) in THF (9 mL) and butyraldehyde (158 mg, 2.20 mmol) according to the *general procedure*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **63** as a colourless oil (166 mg, 55%, 95:5 dr); R_f 0.20 (30–40 °C petrol/Et_2O, 4:1); $[\alpha]_D^{23}$ +22.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3472 (O–H), 2993 (C–H), 1682 (C=O), 1600 (C=C); δ_H (400 MHz, $CDCl_3$) 0.82 (9H, s, CMe_3), 0.87 (3H, t, *J* 7.1, C(6)H_3), 1.25–1.65 (4H, m, C(4)H_2, C(5)H_2), 1.83 (3H, d, *J* 7.0, C(1′)*Me*), 2.07–2.10 (1H, br m, O*H*), 3.89–3.92 (2H, br m, C(3)*H*, CH_AH_BCH=CH_2), 4.35 (1H, app dd, *J* 12.8, 4.5, CH_AH_BCH=CH_2), 4.42 (1H, app s, C(2)*H*), 5.21 (1H, dd, *J* 10.8, 1.2, CH_2CH=CH_AH_B), 5.30 (1H, dd, *J* 17.3, 1.2, CH_2CH=CH_AH_B), 5.93–5.96 (1H, m, CH_2C*H*=CH_2), 6.32–6.35 (1H, br m, C(1′)*H*), 7.42–7.88 (6H, m, *Ar*), 8.40–8.43 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.9, 16.0, 18.9, 27.9, 36.4, 56.4, 69.8, 70.8, 78.9, 82.7, 117.4, 125.2, 125.5, 125.6, 125.8, 126.4, 128.3, 128.6, 128.8, 133.6, 135.4, 134.6, 177.4; *m*/*z* (ESI$^+$) 436 ([M+Na]$^+$, 100%), 414 ([M+H]$^+$, 18%); HRMS (ESI$^+$) found 436.2451; $C_{25}H_{35}NNaO_4^+$ ([M+Na]$^+$) requires 436.2458.

*4.3.12. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R)-2-allyloxy-3-hydroxy-3-(2‴-pyridyl)propanamide **64**.*



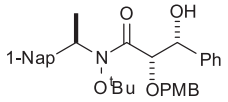
Compound (*R*)-**6** (461 mg, 1.35 mmol) in THF (10 mL) was treated with KHMDS (1.89 mmol) in THF (10 mL) and pyridine-2-carboxaldehyde (0.26 mL, 2.70 mmol) according to the *general procedure*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **64** in 94:6 dr. Purification via flash column chromatography (gradient elution, 30–40 °C petrol/Et_2O, 2:1; increased to 30–40 °C petrol/Et_2O, 1:1) gave a colourless oil, which was crystallised from pentane at −30 °C to give **64** as colourless blocks (402 mg, 66%, >99:1 dr); R_f 0.40 (30–40 °C petrol/Et_2O, 1:1); mp 98–100 °C; $[\alpha]_D^{23}$ −3.5 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3460 (O–H), 2977 (C–H), 1674, (C=O), 1591, 1369, 1112, 1070; δ_H (400 MHz, $CDCl_3$) 0.87 (9H, s, CMe_3), 1.87 (3H, d, *J* 6.9, C(1′)*Me*), 3.51 (1H, br s, O*H*) 3.80 (1H, app dd, *J* 13.3, 6.0, CH_AH_BCH=CH_2), 4.16 (1H, dd, *J* 13.3, 4.7, CH_AH_BCH=CH_2), 4.94 (1H, app d, *J* 17.5, CH_2CH=CH_AH_B), 4.99 (1H, d, *J* 10.5, CH_2CH=CH_AH_B), 5.17–5.20 (1H, br m, C(2)*H*), 5.24–5.27 (1H, br m, C(3)*H*), 5.56–5.60 (1H, m, OCH_2C*H*=CH_2) 6.42–6.48 (1H, br m, C(1′)*H*), 7.13–7.88 (9H, m, *Ar*), 8.46–8.50 (1H, br m, *Ar*), 8.52 (1H, d, *J* 4.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.9, 27.9, 56.5, 70.9, 72.0, 79.2, 83.1, 116.9, 120.7, 121.5, 122.0, 124.3, 124.9, 125.7, 125.9, 126.5, 128.8, 132.3, 133.6, 134.4, 135.7, 136.2, 136.7, 148.4, 160.1, 176.8; *m*/*z* (ESI$^+$) 471 ([M+Na]$^+$, 100%), 449 ([M+H]$^+$, 32%); HRMS (ESI$^+$) found 449.2440; $C_{27}H_{33}N_2O_4^+$ ([M+H]$^+$) requires 449.2435.

*4.3.13. X-ray crystal structure determination for **64**.* 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.[38]

X-ray crystal structure data for **64** [$C_{27}H_{27}N_2O_4$]: M=443.52, monoclinic, space group *C* 2, a=25.6677(9) Å, b=8.0723(3) Å, c=12.5059(4) Å, β=108.6000(17)°, V=2455.85(15) Å^3, Z=4, μ=0.081 mm^{-1}, colourless block, crystal dimensions=0.20×0.20×0.20 mm^3. A total of 2970 unique reflections were measured for $5<\theta<27$ and 2670 reflections were used in the refinement. The final parameters were wR_2=0.059 and R_1=0.054 [$I>1.0\sigma(I)$].

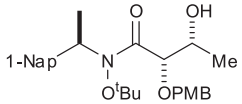
Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 745790. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

*4.3.14. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R)-2-(4‴-methoxybenzyloxy)-3-hydroxy-3-phenylpropanamide **65**.*



Compound (*R*)-**7** (103 mg, 0.25 mmol) in THF (4 mL) was treated with KHMDS (0.37 mmol) in THF (4 mL) and benzaldehyde (0.08 mL, 0.74 mmol) according to the *general procedure*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **65** in 87:13 dr. Purification via flash column chromatography (gradient elution, pentane; increased to Et_2O) gave **65** as a colourless oil (112 mg, 87%, 87:13 dr); R_f 0.20 (pentane/Et_2O 4:1); $[\alpha]_D^{23}$ −14.3 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 3420 (O–H), 2974 (C–H), 1674 (C=O), 1613 (C=C); δ_H (400 MHz, $CDCl_3$) 0.74 (9H, s, CMe_3), 1.86 (3H, d, *J* 6.9, C(1′)*Me*) 3.76 (3H, s, O*Me*), 4.32 (1H, d, *J* 11.9, OCH_AH_BAr), 4.65–4.67 (2H, br m, C(2)*H*, OCH_AH_BAr), 5.04 (1H, br d, *J* 3.2, C(3)*H*), 6.34–6.36 (1H, br m, C(1′)*H*), 6.72 (2H, d, *J* 8.4, *Ar*), 7.34 (2H, d, *J* 8.0, *Ar*), 7.28–7.89 (11H, m, *Ar*), 8.45–8.48 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.2, 27.8, 55.3, 56.9, 71.3, 71.7, 79.1, 83.1, 113.6, 122.4, 123.4, 124.9, 125.3, 125.7, 126.4, 126.5, 127.4, 128.2, 128.3, 128.8, 129.1, 129.3, 130.9, 132.1, 133.5, 133.6, 135.4, 138.4, 159.2, 176.9; *m*/*z* (ESI$^+$) 550 ([M+Na]$^+$, 100%), 528 ([M+H]$^+$, 5%); HRMS (ESI$^+$) found 550.2579; $C_{33}H_{37}NNaO_5^+$ ([M+Na]$^+$) requires 550.2564.

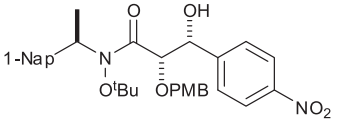
*4.3.15. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R)-2-(4‴-methoxybenzyloxy)-3-hydroxybutanamide **66**.*



Compound (*R*)-**7** (111 mg, 0.26 mmol) in THF (4 mL) was treated with KHMDS (0.40 mmol) in THF (4 mL) and acetaldehyde (0.15 mL,

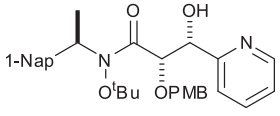
2.63 mmol) according to the *general procedure*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **66** in 69:31 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 4:1) gave **66** as a colourless oil (84 mg, 69%, 87:13 dr); R_f 0.15 (pentane/Et_2O, 4:1); $[\alpha]_D^{23}$ −30.5 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 3462 (O–H), 2975 (C–H), 1674 (C=O), 1613 (C=C); δ_H (500 MHz, $CDCl_3$) 0.69 (9H, s, C*Me*$_3$), 1.24 (3H, d, *J* 6.3, C(4)*H*$_3$), 1.82 (3H, d, *J* 6.9, C(1′)*Me*), 2.49–2.51 (1H, br m, O*H*), 3.80 (3H, s, O*Me*), 4.17–4.20 (1H, br m, C(3)*H*), 4.37–4.41 (1H, br m, C(2)*H*), 4.43 (1H, d, *J* 11.5, C*H*$_A$H$_B$Ar), 4.85 (1H, d, *J* 11.5, CH$_A$*H*$_B$Ar), 6.42–6.45 (1H, br m, C(1′)*H*), 6.88 (2H, d, *J* 8.5, *Ar*), 7.34 (2H, d, *J* 8.5, *Ar*), 7.43–7.88 (6H, m, *Ar*), 8.41–8.44 (1H, br m, *Ar*); δ_C (125 MHz, $CDCl_3$) 15.8, 20.1, 27.8, 55.2, 55.9, 66.5, 71.3, 79.4, 82.7, 113.6, 124.2, 124.7, 125.4, 125.6, 126.3, 128.6, 128.7, 129.2, 129.3, 129.4, 129.6, 133.5, 133.6, 135.4, 159.3, 177.0; *m*/*z* (ESI$^+$) 488 ([M+Na]$^+$, 100%), 466 ([M+H]$^+$, 4%); HRMS (ESI$^+$) found 488.2424; $C_{28}H_{35}NNaO_5^+$ ([M+Na]$^+$) requires 488.2407.

*4.3.16. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R)-2-(4‴-methoxybenzyloxy)-3-hydroxy-3-(4⁗-nitrophenyl)propanamide **67**.*



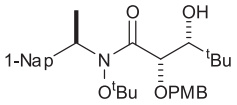
Compound (*R*)-**7** (100 mg, 0.24 mmol) in THF (5 mL) was treated with KHMDS (0.36 mmol) in THF (5 mL) and 4-nitrobenzaldehyde (112 mg, 0.74 mmol) in THF (1 mL) according to the *general procedure*. Purification via exhaustive flash column chromatography (eluent pentane/Et_2O, 1:1) gave **67** as a colourless oil (66 mg, 49%, >95:5 dr); R_f 0.20 (pentane/Et_2O, 1:1); $[\alpha]_D^{23}$ −11.9 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 3440 (O–H), 2976 (C–H), 1668 (C=O), 1610 (C=C) 1515, 1346 (NO_2), 1249, 1109, 1092, 1069; δ_H (400 MHz, $CDCl_3$) 0.87 (9H, s, C*Me*$_3$), 1.92 (3H, d, *J* 6.9, C(1′)*Me*) 3.75 (3H, s, O*Me*), 4.24 (1H, d, *J* 12.0, C*H*$_A$H$_B$Ar), 4.61 (1H, d, *J* 1.5, C(2)*H*), 4.68 (1H, d, *J* 12.0, CH$_A$*H*$_B$Ar), 4.97–5.01 (1H, br m, C(3)*H*), 6.23–6.25 (1H, br m, C(1′)*H*), 6.70 (2H, d, *J* 8.5, *Ar*), 6.91 (2H, d, *J* 8.5, *Ar*), 7.33–8.41 (10H, m, *Ar*), 8.39–8.41 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.6, 27.9, 55.2, 57.6, 71.3, 72.5, 78.3, 83.6, 113.6, 122.9, 123.2, 123.3, 123.7, 123.9, 124.9, 125.5, 125.6, 125.8, 126.4, 126.9, 127.3, 128.5, 128.7, 129.2, 130.9, 133.7, 134.9, 135.7, 147.3, 159.3, 175.7; *m*/*z* (ESI$^+$) 595 ([M+Na]$^+$, 100%), 573 ([M+H]$^+$, 7%); HRMS (ESI$^+$) found 595.2441; $C_{33}H_{36}N_2NaO_7^+$ ([M+Na]$^+$) requires 595.2415.

*4.3.17. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R)-2-(4‴-methoxybenzyloxy)-3-hydroxy-3-(pyridin-2⁗-yl)propanamide **68**.*



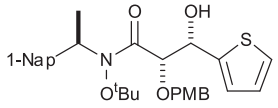
Compound (*R*)-**7** (120 mg, 0.29 mmol) in THF (6 mL) was treated with KHMDS (0.43 mmol) in THF (6 mL) and pyridine-2-carboxaldehyde (91 mg, 0.86 mmol) according to the *general procedure*. Purification via flash column chromatography (eluent pentane/Et_2O, 4:1) gave **68** as a colourless oil (109 mg, 72%, >99:1 dr); R_f 0.15 (pentane/Et_2O, 1:1); $[\alpha]_D^{23}$ −26.8 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3460 (O–H), 2975 (C–H), 1682 (C=O), 1613 (C=C); δ_H (400 MHz, $CDCl_3$) 0.76 (9H, s, C*Me*$_3$), 1.88 (3H, d, *J* 6.9, C(1′)*Me*), 3.49–3.51 (1H, br m, O*H*), 3.75 (3H, s, O*Me*), 4.27 (1H, d, *J* 11.9, C*H*$_A$H$_B$Ar), 4.64 (1H, d, *J* 11.9, CH$_A$*H*$_B$Ar), 5.13 (1H, d, *J* 2.0, C(2)*H*), 5.26 (1H, d, *J* 2.0, C(3)*H*), 6.45–6.47 (1H, br m, C(1′)*H*) 6.68 (2H, d, *J* 8.6, *Ar*), 6.83 (2H, d, *J* 8.4, *Ar*), 7.18–7.89 (9H, m, *Ar*), 8.49–8.51 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.9, 27.8, 55.2, 56.6, 71.3, 72.0, 78.9, 83.0, 113.4, 120.8, 122.0, 122.4, 124.3, 124.9, 125.7, 126.5, 127.9, 128.7, 129.0, 129.6, 133.6, 135.7, 136.2, 148.4, 159.0, 160.2, 177.6; *m*/*z* (ESI$^+$) 551 ([M+Na]$^+$, 8%), 529 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 529.2712; $C_{32}H_{37}N_2O_5^+$ ([M+H]$^+$) requires 529.2697.

*4.3.18. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R)-2-(4‴-methoxybenzyloxy)-3-hydroxy-4,4-dimethylpentanamide **69**.*



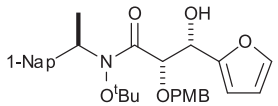
Compound (*R*)-**7** (90 mg, 0.21 mmol) in THF (5 mL) was treated with KHMDS (0.32 mmol) in THF (5 mL) and pivalaldehyde (74 mL, 0.86 mmol) according to the *general procedure*. Purification via flash column chromatography (eluent pentane/Et_2O, 4:1) gave **68** as a colourless oil (103 mg, 95%, 90:10 dr); R_f 0.25 (pentane/Et_2O, 4:1); $[\alpha]_D^{23}$ −34.1 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 3566 (O–H), 2958 (C–H), 1682 (C=O), 1614 (C=C), 1515, 1249, 1110, 1037; δ_H (400 MHz, $CDCl_3$) 0.86 (9H, s, C*Me*$_3$), 0.93 (9H, s, C*Me*$_3$), 1.93 (3H, d, *J* 7.0, C(1′)*Me*), 2.05–2.07 (1H, br m, O*H*), 3.09 (1H, br d, *J* 8.2, C(3)*H*), 3.81 (3H, s, O*Me*), 4.28 (1H, d, *J* 10.7, C*H*$_A$H$_B$Ar), 4.66 (1H, d, *J* 10.7, CH$_A$*H*$_B$Ar), 4.74 (1H, app s, C(2)*H*), 6.19 (1H, q, *J* 7.0, C(1′)*H*) 6.87 (2H, d, *J* 8.6, *Ar*), 7.33 (2H, d, *J* 8.5, *Ar*), 7.45–7.88 (6H, m, *Ar*), 8.54 (1H, d, *J* 8.3, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.4, 26.8, 27.9, 35.6, 55.2, 58.3, 68.0, 71.2, 75.3, 82.9, 113.6, 124.4, 124.8, 125.5, 126.2, 126.5, 128.7, 128.8, 129.6, 129.8, 132.2, 133.7, 135.2, 159.2, 178.4; *m*/*z* (ESI$^+$) 530 ([M+Na]$^+$, 100%), 508 ([M+H]$^+$, 16%); HRMS (ESI$^+$) found 508.3069; $C_{31}H_{42}NO_5^+$ ([M+H]$^+$) requires 508.3057.

*4.3.19. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S,S)-2-(4‴-methoxybenzyloxy)-3-hydroxy-3-(thiophen-2⁗-yl)propanamide **70**.*



Compound (*R*)-**7** (112 mg, 0.27 mmol) in THF (5 mL) was treated with KHMDS (0.40 mmol) in THF (5 mL) and thiophene 2-carboxaldehyde (0.74 mL, 0.80 mmol) according to the *general procedure*. Purification via flash column chromatography (eluent pentane/Et_2O, 5:1) gave **70** as a colourless oil (115 mg, 81%, 90:10 dr); R_f 0.50 (Et_2O:pentane 1:1); $[\alpha]_D^{23}$ −19.1 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 3422 (O–H), 2973 (C–H), 1679 (C=O), 1613 (C=C), 1514, 1463, 1393, 1368, 1250, 1174, 1110; δ_H (400 MHz, $CDCl_3$) 0.69 (9H, s, C*Me*$_3$), 1.85 (3H, d, *J* 6.9, C(1′)*Me*), 3.02–3.06 (1H, br m, O*H*), 3.79 (3H, s, O*Me*), 4.46 (1H, d, *J* 11.3, C*H*$_A$H$_B$Ar), 4.70 (1H, d, *J* 2.3, C(2)*H*), 4.76 (1H, d, *J* 11.3, CH$_A$*H*$_B$Ar), 5.37 (1H, br d, *J* 2.3, C(3)*H*), 6.39–6.42 (1H, br m, C(1′)*H*), 6.82 (2H, d, *J* 8.5, *Ar*), 6.95–6.98 (2H, m, *Ar*), 7.20 (2H, d, *J* 8.5, *Ar*), 7.25–7.89 (7H, m, *Ar*), 8.41–8.45 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.1, 27.8, 55.2, 56.6, 68.4, 71.7, 79.4, 83.1, 113.7, 122.4, 123.4, 124.1, 124.6, 124.9, 125.2, 125.7, 126.3, 128.3, 128.7, 128.8, 129.3, 129.6, 133.6, 135.4, 159.3, 176.2; *m*/*z* (ESI$^+$) 556 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 556.2123; $C_{31}H_{35}NNaO_5S^+$ ([M+Na]$^+$) requires 556.2128.

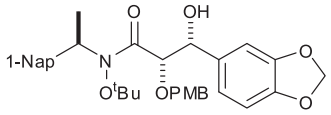
*4.3.20. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S,S)-2-(4‴-methoxybenzyloxy)-3-hydroxy-3-(furan-2⁗-yl)propanamide **71**.*



Compound (*R*)-**7** (99 mg, 0.24 mmol) in THF (4 mL) was treated with KHMDS (0.35 mmol) in THF (4 mL) and 2-furan 2-carboxaldehyde (0.58 mL, 0.71 mmol) according to the *general procedure*. Purification via flash column chromatography (eluent pentane/

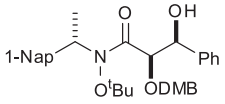
Et_2O, 9:1) gave **71** as a colourless oil (87 mg, 71%, 88:12 dr); $[\alpha]_D^{23}$ −24.8 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 3455 (O–H), 2976 (C–H), 1682 (C=O), 1613 (C=C), 1514, 1369, 1248, 1112, 1081; δ_H (400 MHz, $CDCl_3$) 0.66 (9H, s, C*Me*$_3$), 1.83 (3H, d, *J* 6.9, C(1′)*Me*), 2.98 (1H, br s, O*H*), 3.77 (3H, s, O*Me*), 4.43 (1H, d, *J* 11.9, CH_AH_BAr), 4.72 (1H, d, *J* 11.9, CH$_A$*H*$_B$Ar), 4.86 (1H, d, *J* 2.9, C(2)*H*), 5.19 (1H, d, *J* 2.9, C(3)*H*), 6.35–6.38 (2H, m, *Ar*), 6.41–6.45 (1H, br m, C(1′)*H*) 6.79 (2H, d, *J* 8.6, *Ar*), 7.08 (2H, d, *J* 8.6, *Ar*), 7.35–7.89 (7H, m, *Ar*), 8.40–8.44 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.9, 27.7, 55.2, 56.2, 67.0, 71.4, 77.2, 83.1, 106.8, 110.4, 113.7, 124.2, 124.8, 125.5, 125.7, 126.3, 126.4, 128.7, 128.8, 129.3, 129.4, 132.2, 133.6, 135.5, 141.5, 154.3, 159.2, 176.4; *m*/*z* (ESI^+) 540 ($[M+Na]^+$, 100%), 518 ($[M+H]^+$, 9%); HRMS (ESI^+) found 518.2531; $C_{31}H_{36}NO_6^+$ ($[M+H]^+$) requires 518.2537.

4.3.21. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R)-2-(4‴-methoxybenzyloxy)-3-hydroxy-3-(3‴,4‴-methylenedioxyphenyl)propanamide ***72***.



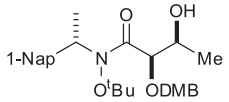
Compound (*R*)-**7** (100 mg, 0.24 mmol) in THF (5 mL) was treated with KHMDS (0.36 mmol) in THF (5 mL) and piperonal (112 mg, 0.74 mmol) according to the *general procedure*. ^1H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **72** in 81:19 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 4:1) gave **72** as a colourless oil (89 mg, 66%, 82:18 dr); R_f 0.30 (pentane/Et_2O, 1:1); $[\alpha]_D^{23}$ −6.8 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 3466 (O–H), 2975 (C–H), 1669 (C=O), 1613 (C=C), 1513, 1247, 1093, 1038; δ_H (400 MHz, $CDCl_3$) 0.75 (9H, s, C*Me*$_3$), 1.85 (3H, d, *J* 6.9, C(1′)*Me*), 2.86–2.90 (1H, br m, O*H*), 3.75 (3H, s, O*Me*), 4.35 (1H, d, *J* 11.7, CH_AH_BAr), 4.61 (1H, d, *J* 2.0, C(2)*H*), 4.70 (1H, d, *J* 11.7, CH$_A$*H*$_B$Ar), 4.90–4.93 (1H, br m, C(3)*H*), 5.92–5.98 (2H, m, OCH_2O), 6.30–6.35 (1H, br m, C(1′)*H*), 6.73–7.89 (13H, m, *Ar*), 8.42–8.45 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.3, 27.8, 55.2, 57.0, 71.4, 71.6, 79.2, 83.2, 100.9, 107.4, 107.8, 107.9, 113.6, 119.9, 123.4, 124.1, 124.9, 125.2, 125.5, 126.1, 128.3, 129.3, 132.1, 133.6, 135.4, 146.8, 147.4, 159.2, 176.6; *m*/*z* (ESI^+) 594 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 594.2460; $C_{34}H_{37}NNaO_7^+$ ($[M+Na]^+$) requires 594.2462.

4.3.22. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2R,3S)-2-(3‴,4‴-dimethoxybenzloxy)-3-hydroxy-3-phenylpropanamide ***73***.



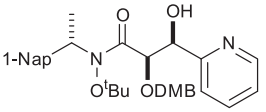
Compound (*S*)-**8** (589 mg, 1.31 mmol) in THF (15 mL) was treated with KHMDS (1.96 mmol) in THF (15 mL) and benzaldehyde (0.40 mL, 3.92 mmol) according to the *general procedure*. ^1H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **73** in 83:17 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 1:1) gave **73** as a white foam (556 mg, 77%, 85:15 dr); R_f 0.60 (Et_2O); $[\alpha]_D^{23}$ +21.9 (*c* 1.7 in $CHCl_3$); ν_{max} (film) 3454 (O–H), 2975 (C–H), 1674 (C=O), 1594 (C=C), 1515, 1435, 1368, 1264, 1239, 1158, 1112, 1029; δ_H (400 MHz, $CDCl_3$) 0.72 (9H, s, C*Me*$_3$), 1.86 (3H, d, *J* 6.9, C(1′)*Me*), 2.95–2.98 (1H, br m, O*H*), 3.66 (3H, s, O*Me*), 3.81 (3H, s, O*Me*), 4.38 (1H, d, *J* 12.1, CH_AH_BAr), 4.69 (1H, d, *J* 12.0, CH$_A$*H*$_B$Ar), 4.69 (1H, d, *J* 1.6, C(2)*H*), 5.02–5.06 (1H, br m, C(3)*H*), 6.34–6.38 (1H, br m, C(1′)*H*), 6.55–7.90 (14H, m, *Ar*, *Ph*), 8.46–8.50 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.2, 27.8, 55.7, 55.8, 57.1, 71.4, 71.6, 79.0, 83.1, 110.5, 110.6, 120.0, 120.2, 122.4, 123.4, 124.1, 124.9, 125.5, 125.8, 126.4, 127.4, 128.2, 128.7, 129.3, 129.9, 130.9, 133.9, 135.4, 141.4, 148.5, 148.9, 176.8; *m*/*z* (ESI^+) 580 ($[M+Na]^+$, 100%), 558 ($[M+H]^+$, 5%); HRMS (ESI^+) found 580.2693; $C_{34}H_{39}NNaO_6^+$ ($[M+Na]^+$) requires 580.2670.

4.3.23. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2R,3S)-2-(3‴,4‴-dimethoxybenzloxy)-3-hydroxybutanamide ***74***.



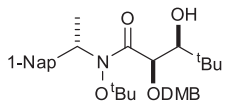
Compound (*S*)-**8** (510 mg, 1.13 mmol) in THF (10 mL) was treated with KHMDS (1.58 mmol) in THF (10 mL) and acetaldehyde (0.45 mL, 7.96 mmol) according to the *general procedure*. ^1H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **74** in 80:20 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 1:1) gave **74** as a white foam (252 mg, 45%, 80:20 dr); R_f 0.50 (Et_2O); $[\alpha]_D^{23}$ +41.4 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3482 (O–H), 2973 (C–H), 1674 (C=O), 1515, 1464, 1369, 1263, 1158, 1091, 1029; δ_H (400 MHz, $CDCl_3$) 0.65 (9H, s, C*Me*$_3$), 1.24 (3H, d, *J* 6.6, C(4)H_3), 1.80 (3H, d, *J* 6.9, C(1′)*Me*), 2.44 (1H, br s, O*H*), 3.85 (3H, s, O*Me*), 3.88 (3H, s, O*Me*), 4.16–4.20 (1H, br m, C(3)*H*), 4.37 (1H, d, *J* 2.1, C(2)*H*), 4.44 (1H, d, *J* 11.8, CH_AH_BAr), 4.85 (1H, d, *J* 11.8, CH$_A$*H*$_B$Ar), 6.41–6.44 (1H, br m, C(1′)*H*), 6.77–7.89 (9H, m, *Ar*), 8.40–8.43 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.8, 20.2, 27.8, 55.8, 55.9, 66.5, 71.6, 79.3, 82.7, 110.7, 111.1, 120.4, 124.2, 124.8, 125.5, 125.7, 126.4, 128.7, 128.8, 130.2, 132.2, 133.6, 135.4, 148.7, 149.0, 177.1; *m*/*z* (ESI^+) 518 ($[M+Na]^+$, 100%), 496 ($[M+H]^+$, 6%); HRMS (ESI^+) found 518.2518; $C_{29}H_{37}NNaO_6^+$ ($[M+Na]^+$) requires 518.2513.

4.3.24. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2R,3S)-2-(3‴,4‴-dimethoxybenzloxy)-3-hydroxy-3-(pyridin-2‴-yl)propanamide ***75***.



Compound (*S*)-**8** (247 mg, 0.55 mmol) in THF (6 mL) was treated with KHMDS (0.77 mmol) in THF (6 mL) and pyridine-2-carboxaldehyde (0.10 mL, 1.09 mmol) according to the *general procedure*. ^1H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **75** in 80:20 dr. Purification via flash column chromatography (gradient elution, pentane/Et_2O, 1:1; increased to Et_2O) gave **75** as a colourless foam (97 mg, 32%, >99:1 dr); R_f 0.2 (Et_2O); $[\alpha]_D^{23}$ +25.0 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 3501 (O–H), 2973 (C–H), 1683 (C=O), 1591 (C=C), 1516, 1464, 1263, 1158, 1138, 1029; δ_H (400 MHz, $CDCl_3$) 0.76 (9H, s, C*Me*$_3$), 1.88 (3H, d, *J* 6.9, C(1′)*Me*), 3.48–3.53 (1H, br m, O*H*), 3.70 (3H, s, O*Me*), 3.82 (3H, s, O*Me*), 4.30 (1H, d, *J* 11.9, CH_AH_BAr), 4.62 (1H, d, *J* 11.9, CH$_A$*H*$_B$Ar), 5.19 (1H, app s, C(2)*H*), 5.24–5.27 (1H, br m, C(3)*H*), 6.44–6.46 (1H, br m, C(1′)*H*), 6.50–6.53 (1H, m, *Ar*), 6.65 (1H, d, *J* 8.7, *Ar*), 7.15–7.89 (10H, m, *Ar*), 8.48–8.51 (2H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.9, 27.8, 55.7, 55.8, 56.5, 71.7, 72.0, 79.0, 83.1, 110.4, 110.9, 120.1, 120.7, 121.9, 124.3, 124.9, 125.5, 125.7, 126.3, 128.2, 128.6, 130.1, 132.3, 133.6, 135.7, 136.2, 148.5, 148.7, 160.3, 177.5; *m*/*z* (ESI^+) 581 ($[M+Na]^+$, 26%), 559 ($[M+H]^+$, 100%); HRMS (ESI^+) found 559.2805; $C_{33}H_{39}N_2O_6^+$ requires ($[M+H]^+$) 559.2803.

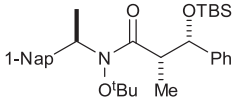
4.3.25. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2R,3S)-2-(3‴,4‴-dimethoxybenzloxy)-3-hydroxy-4,4-dimethylpentanamide ***76***.



Compound (*S*)-**8** (180 mg, 0.40 mmol) in THF (15 mL) was treated with KHMDS (0.60 mmol) in THF (15 mL) and pivalaldehyde (0.95 mL, 0.86 mmol) according to the *general procedure*. ^1H NMR

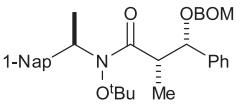
spectroscopic analysis of the crude reaction mixture showed the presence of **76** in 85:15 dr. Purification via flash column chromatography (eluent pentane/Et_2O, 3:1) gave **76** as a colourless oil (155 mg, 72%, 86:14 dr); R_f 0.30 (pentane/Et_2O, 3:1); $[\alpha]_D^{23}$ +38.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3566 (O–H), 2956 (C–H), 1674 (C=O), 1516, 1465, 1393, 1369, 1263, 1240, 1160, 1111, 1029; δ_H (400 MHz, $CDCl_3$) 0.87 (9H, s, C*Me*$_3$), 0.95 (9H, s, C*Me*$_3$), 1.93 (3H, d, *J* 7.0, C(1′)*Me*), 2.00–2.05 (1H, br m, O*H*), 3.08–3.10 (1H, br m, C(3)*H*), 3.87 (3H, s, O*Me*), 3.88 (3H, s, O*Me*), 4.30 (1H, d, *J* 11.1, CH_AH_BAr), 4.70 (1H, d, *J* 11.1, CH$_A$*H*$_B$Ar), 4.71–4.74 (1H, br m, C(2)*H*), 6.18 (1H, d, *J* 7.0, C(1′)*H*), 6.79–7.88 (9H, m, *Ar*), 8.53 (1H, br d, *J* 8.4, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.6, 26.8, 27.9, 35.5, 55.7, 55.9, 58.4, 71.4, 75.3, 77.3, 82.9, 110.6, 111.4, 120.4, 124.4, 124.8, 125.5, 126.2, 126.5, 128.7, 128.8, 130.2, 132.2, 133.7, 135.1, 148.6, 148.8, 178.3; *m*/*z* (ESI$^+$) 560 ([M+Na]$^+$, 100%), 538 ([M+H]$^+$, 4%); HRMS (ESI$^+$) found 538.3176; $C_{32}H_{44}NO_6^+$ ([M+H]$^+$) requires 538.3163.

*4.3.26. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S,S)-2-methyl-3-tert-butyldimethylsilyloxy-3-phenylpropanamide **79**.*



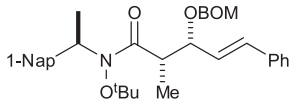
TBDMSCl (40 mg, 0.27 mmol) and imidazole (37 mg, 0.54 mmol) were added sequentially to a stirred solution of **52** (88 mg, 0.22 mmol) in DMF (1 mL). After stirring for two days, H_2O (10 mL) was added and the mixture was extracted with 30–40 °C petrol (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **79** as a colourless oil (90 mg, 80%); $[\alpha]_D^{21}$ −19.4 (*c* 1.9 in $CHCl_3$); ν_{max} (KBr) 1654 (C=O); δ_H (250 MHz, PhMe-d_8, 90 °C) −0.16 (3H, s, Si*Me*), 0.09 (3H, s, Si*Me*), 0.63 (9H, s, SiC*Me*$_3$), 0.93 (9H, s, OC*Me*$_3$), 1.26 (3H, br d, *J* 6.7, C(2)*Me*), 1.52 (3H, d, *J* 6.8, C(1′)*Me*), 3.57 (1H, dq, *J* 8.5, 6.7, C(2)*H*), 5.04 (1H, d, *J* 8.5, C(3)*H*), 6.10 (1H, q, *J* 6.8, C(1′)*H*), 6.97–7.60 (11H, m, *Ar*, *Ph*), 8.23 (1H, d, *J* 8.3, *Ar*); δ_C (50 MHz, $CDCl_3$) −5.1, −4.7, 15.9, 18.1, 25.7, 27.7, 82.2, 125.0, 125.6, 126.4, 126.4, 127.6, 127.9, 128.0, 128.8, 133.7, 137.0, 143.0; *m*/*z* (APCI$^+$) 542 ([M+Na]$^+$, 40%), 520 ([M+H]$^+$, 100%); HRMS (CI$^+$) found 520.3247; $C_{32}H_{46}NO_3Si^+$ ([M+H]$^+$) requires 520.3241.

*4.3.27. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (S,S)-2-methyl-3-benzyloxymethoxy-3-phenylpropanamide **80**.*



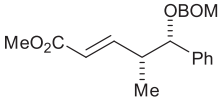
Compound **52** (415 mg, 1.02 mmol) was dissolved in CH_2Cl_2 (1 mL) and Bu_4NI (100 mg, 0.3 mmol) was added. Di-*iso*-propylethylamine (1.07 mL, 6.1 mmol) and BOMCl (ca. 90% pure, 810 μL, 4.1 mmol) were then added sequentially. The reaction mixture was stirred at rt for 2 days. H_2O (10 mL) was added and the mixture was stirred for a further 6 h. The mixture was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried, filtered through a short plug of alumina (grade V, eluent CH_2Cl_2), then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **80** as a colourless oil (503 mg, 94%); found C, 77.6; H, 7.6; N, 2.7%; $C_{34}H_{39}NO_4$ requires C, 77.7; H, 7.5; N, 2.7%; $[\alpha]_D^{21}$ −63.0 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1653 (C=O), 1600 (C=C); δ_H (250 MHz, PhMe-d_8, 90 °C) 0.66 (9H, s, C*Me*$_3$), 1.24 (3H, d, *J* 6.8, C(2)*Me*), 1.55 (3H, d, *J* 6.8, C(1′)*Me*), 3.68 (1H, dq, *J* 8.5, 6.8, C(2)*H*), 4.40 (1H, d, *J* 12.0, OCH_AH_BO), 4.58 (2H, A$_2$, CH_2Ph), 4.60 (1H, d, *J* 12.0, OCH$_A$*H*$_B$O), 5.01 (1H, d, *J* 8.5, C(3)*H*), 6.14 (1H, q, *J* 6.8, C(1′)*H*), 6.97–7.61 (16H, m, *Ar*), 8.30 (1H, d, *J* 8.3, *Ar*); δ_C (125 MHz, $CDCl_3$) 15.1, 27.9, 42.0, 54.0, 69.8, 80.9, 82.5, 92.6, 124.5, 125.1, 125.8, 126.5, 126.6, 127.9, 128.2, 128.6, 128.9, 133.8, 136.8, 138.0, 140.0, 180.0; *m*/*z* (APCI$^+$) 526 ([M+H]$^+$, 100%).

*4.3.28. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R,E)-2-methyl-3-benzyloxymethoxy-5-phenylpent-4-enoate **81**.*



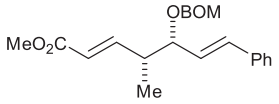
Compound **55** (552 mg, 1.02 mmol) was dissolved in CH_2Cl_2 (1 mL) and Bu_4NI (100 mg, 0.3 mmol) was added. Di-*iso*-propylethylamine (1.12 mL, 6.4 mmol) and BOMCl (ca. 80% pure, 1.1 mL, 4.1 mmol) were then added sequentially. The reaction mixture was stirred at rt for two days. H_2O (10 mL) was added and the mixture was stirred for a further 6 h. The mixture was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried, filtered through a short plug of alumina (grade V, eluent CH_2Cl_2), then concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **81** as a colourless oil (677 mg, 94%); found C, 78.2; H, 7.75; N, 2.9%; $C_{36}H_{41}NO_4$ requires C, 78.4; H, 7.5; N, 2.5%; $[\alpha]_D^{21}$ −75.4 (*c* 0.9 in $CHCl_3$); ν_{max} (KBr) 1654 (C=O), 1599 (C=C); δ_H (250 MHz, PhMe-d_8, 90 °C) 0.75 (9H, s, C*Me*$_3$), 1.46 (3H, d, *J* 6.9, C(2)*Me*), 1.61 (3H, d, *J* 6.9, C(1′)*Me*), 3.57 (1H, app quintet, *J* 6.9, C(2)*H*), 4.45–4.82 (5H, m, C(3)*H*, OCH_2OCH_2Ph), 6.28–6.37 (1H, m, C(1′)*H*) overlapping 6.33 (1H, dd, *J* 16.0, 7.9, C(4)*H*), 6.62 (1H, d, *J* 16.0, C(5)*H*), 6.97–7.53 (15H, m, *Ar*, *Ph*), 7.59 (1H, *J* 8.1, *Ar*), 8.37 (1H, d, *J* 8.3, *Ar*); δ_C (125 MHz, $CDCl_3$) 14.1, 16.0, 27.9, 41.0, 54.0, 69.6, 79.5, 82.4, 91.6, 124.4, 124.8, 125.5, 126.6, 127.6, 127.7, 127.9, 128.3, 128.5, 133.5, 134.2, 136.4, 137.8, 180.0; *m*/*z* (CI$^+$) 552 ([M+H]$^+$, 100%).

*4.3.29. Methyl (4R,5S,E)-4-methyl-5-benzyloxymethoxy-5-phenylpent-2-enoate **82**.*



Compound **80** (160 mg, 0.3 mmol) was dissolved in THF (2 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 0.9 mL, 0.9 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C, then Ph_3P=$CHCO_2Me$ (203 mg, 0.61 mmol) was added. The reaction mixture was allowed to warm to rt over 16 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 6:1) gave auxiliary (*R*)-**1** (67 mg, 91%, >99:1 er). Further elution gave a colourless oil, which was crystallised from pentane to give **82** as yellow needles (99 mg, 96%, >99:1 dr); found C, 74.1; H, 7.3%; $C_{21}H_{24}O_4$ requires C, 74.1; H, 7.1%; mp 53–54 °C; $[\alpha]_D^{23}$ −105.8 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1724 (C=O), 1657 (C=C); δ_H (300 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.9, C(4)*Me*), 2.76 (1H, app d sextet, *J* 6.6, 1.1, C(4)*H*), 3.69 (3H, s, O*Me*), 4.51 (1H, d, *J* 11.6, CH_AH_BPh), 4.66 (1H, d, *J* 7.1, OCH_AH_BO), 4.73 (1H, d, *J* 11.6, CH$_A$*H*$_B$Ph), 4.75 (1H, d, *J* 7.1, OCH$_A$*H*$_B$O), 5.76 (1H, dd, *J* 15.8, 1.1, C(2)*H*), 6.99 (1H, dd, *J* 15.8, 7.7, C(3)*H*), 7.26–7.38 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 14.6, 43.0, 51.4, 69.9, 80.9, 92.5, 121.3, 127.7, 127.9, 128.1, 128.5, 128.6, 138.0, 139.6, 150.9, 167.2; *m*/*z* (ESI$^+$) 358 ([M+NH$_4$]$^+$, 100%).

*4.3.30. Methyl (4R,5S,E,E)-4-methyl-5-benzyloxymethoxy-7-phenyl-hept-2,6-dienoate **83**.*

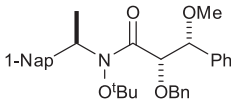


Compound **81** (252 mg, 0.46 mmol) was dissolved in THF (4 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 1.0 mL, 1.0 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (50 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×50 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C, then $Ph_3P{=}CHCO_2Me$ (306 mg, 0.61 mmol) was added. The reaction mixture was allowed to warm to rt over 16 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave auxiliary (*R*)-**1** (103 mg, 93%, >99:1 er). Further elution gave **83** as a colourless oil (131 mg, 93%, >99:1 dr); found C, 75.2; H, 7.1%; $C_{23}H_{26}O_4$ requires C, 75.4; H, 7.15%; $[\alpha]_D^{21}$ −122.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1723 (C=O), 1657 (C=C), 1600 (C=C); δ_H (300 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.8, C(4)*Me*), 2.72 (1H, app d sextet, *J* 6.8, 1.0, C(4)*H*), 3.75 (3H, s, O*Me*), 4.29 (1H, dd, *J* 8.3, 5.5, C(5)*H*), 4.66 (1H, d, *J* 11.8, OCH_AH_BO), 4.77 (1H, d, *J* 11.8, OCH_AH_BO), 4.79 (1H, d, *J* 7.0, CH_AH_BPh), 4.90 (1H, d, *J* 7.0, CH_AH_BPh), 5.95 (1H, dd, *J* 15.9, 1.1, C*H*, olefin), 6.08 (1H, dd, *J* 15.9, 8.3, C*H*, olefin), 6.62 (1H, d, *J* 15.9, C*H*, olefin), 7.16 (1H, dd, *J* 15.9, 7.3, C*H*, olefin), 7.26–7.43 (10H, m, *Ar*); δ_C (50 MHz, $CDCl_3$) 14.9, 41.4, 51.5, 69.8, 79.8, 91.8, 121.3, 126.4, 126.7, 127.8, 127.8, 128.0, 128.5, 128.6, 136.2, 137.9, 150.6, 167.0; *m*/*z* (ES^+) 384 ($[M+NH_4]^+$, 100%), 367 ($[M+H]^+$, 5%).

4.4. General procedure for enolate aldol reactions and tandem O-methylation

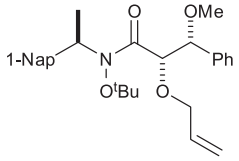
Freshly titrated KHMDS (ca. 0.5 M in PhMe) was added dropwise to a degassed solution of the substrate and in THF at −78 °C. After stirring for 30 min at this temperature, the requisite aldehyde (freshly distilled or dried) was added dropwise (neat or as a solution in THF) and stirring was continued at −78 °C for 2 h. MeI was then added dropwise and the mixture was stirred at −78 °C for a further 10 min before being allowed to warm to rt over 12 h. The reaction was then quenched by the dropwise addition of pH 7 phosphate buffer. The mixture was concentrated in vacuo, the residue was dissolved in Et_2O and filtered through a short, silica/$MgSO_4$ plug (eluent Et_2O). The filtrate was concentrated in vacuo and purified as described.

*4.4.1. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R)-2-benzyloxy-3-methoxy-3-phenylpropanamide **84**.*



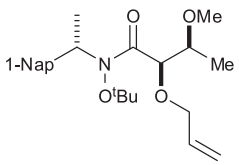
Compound (*R*)-**5** (187 mg, 0.48 mmol) in THF (6 mL) was treated with KHMDS (0.67 mmol) in THF (6 mL), benzaldehyde (0.15 mL, 1.43 mmol) and then MeI (0.45 mL, 7.17 mmol) according to the *general procedure*. ^1H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **84**:**88** in 83:17 dr. Purification via flash column chromatography (gradient elution, pentane; increased to Et_2O) gave **84** as a colourless oil (176 mg, 72%, 96:4 dr); R_f 0.50 (pentane/Et_2O, 1:1); $[\alpha]_D^{23}$ −74.5 (*c* 2.2 in $CHCl_3$); ν_{max} (film) 2978 (C–H), 1682 (C=O), 1600 (C=C), 1512, 1495, 1454, 1393, 1369, 1239, 1173, 1092; δ_H (400 MHz, $CDCl_3$) 0.79 (9H, s, C*Me*$_3$), 1.80 (3H, d, *J* 7.0, C(1′)*Me*), 2.81 (1H, br s, O*Me*), 4.42 (1H, br d, *J* 12.8, OCH_AH_BPh), 4.47 (1H, br d, *J* 2.6, C(2)*H*), 4.64–4.69 (1H, br m, C(3)*H*), 4.81 (1H, d, *J* 12.9, OCH_AH_BPh), 6.19–6.22 (1H, br m, C(1′)*H*), 6.80–7.89 (16H, m, *Ar*, *Ph*), 8.47–8.50 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.5, 27.8, 56.5, 57.2, 71.4, 79.4, 81.0, 83.1, 124.4, 125.0, 125.5, 126.3, 126.8, 127.2, 127.3, 127.7, 128.0, 128.1, 128.5, 128.6, 133.7, 135.4, 137.8, 138.1, 175.2; *m*/*z* (ESI^+) 534 ($[M+Na]^+$, 100%), 512 ($[M+H]^+$, 25%); HRMS (ESI^+) found 512.2787; $C_{33}H_{38}NO_4^+$ ($[M+H]^+$) requires 512.2801. Further elution gave **88** as a colourless oil (24 mg, 10%, >99:1 dr); R_f 0.65 (pentane/Et_2O, 1:1); $[\alpha]_D^{23}$ −27.5 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 2976 (C–H), 1668 (C=O), 1513, 1454, 1368, 1247, 1092; δ_H (400 MHz, $CDCl_3$) 0.88 (9H, s, C*Me*$_3$), 1.78 (3H, br d, *J* 6.5, C(1′)*Me*), 3.27 (1H, br s, O*Me*), 4.55–4.59 (2H, br m, C(2)*H*, OCH_AH_BPh), 4.84 (1H, br d, *J* 12.1, OCH_AH_BPh), 4.93–4.96 (1H, br m, C(3)*H*), 5.55–6.05 (1H, br m, C(1′)*H*), 6.85–7.90 (16H, m, *Ar*, *Ph*), 7.98 (1H, br d, *J* 7.9, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.5, 27.3, 57.3, 72.1, 79.8, 82.3, 82.9, 123.0, 125.3, 125.6, 126.3, 127.2, 127.5, 127.8, 128.0, 128.1, 128.9, 133.5, 138.2, 174.2; *m*/*z* (ESI^+) 534 ($[M+Na]^+$, 100%), 512 ($[M+H]^+$, 53%); HRMS (ESI^+) found 534.2621; $C_{33}H_{37}NNaO_4^+$ ($[M+Na]^+$) requires 534.2620.

*4.4.2. (R)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2S,3R)-2-allyloxy-3-methoxy-3-phenylpropanamide **85**.*



Compound (*R*)-**6** (200 mg, 0.59 mmol) in THF (5 mL) was treated with KHMDS (0.75 mmol) in THF (5 mL), benzaldehyde (0.15 mL, 1.47 mmol) and then MeI (0.36 mL, 5.87 mmol) according to the *general procedure*. ^1H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **85**:**89** in 88:12 dr. Purification via flash column chromatography (gradient elution, pentane/Et_2O, 9:1; increased to pentane/Et_2O, 1:1) gave **85** as a colourless oil, which solidified upon prolonged standing to give a pale yellow amorphous solid (195 mg, 73%, >99:1 dr), R_f 0.30 (pentane/Et_2O, 2:1); $[\alpha]_D^{23}$ +52.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2978 (C–H), 1683 (C=O), 1369, 1091; δ_H (400 MHz, $CDCl_3$) 0.93 (9H, s, C*Me*$_3$), 1.75 (3H, d, *J* 7.0, C(1′)*Me*), 2.81 (3H, br s, O*Me*) 3.82–3.85 (1H, br m, $OCH_AH_BCH{=}CH_2$), 4.23 (1H, dd, *J* 13.3, 4.5, $OCH_AH_BCH{=}CH_2$), 4.51 (1H, d, *J* 3.1, C(2)*H*), 4.61 (1H, d, *J* 3.0, C(3)*H*), 4.92–4.97 (2H, m, $CH_2CH{=}CH_2$), 5.60–5.63 (1H, br m, $OCH_2CH{=}CH_2$) 6.17–6.21 (1H, br m, C(1′)*H*), 7.25–7.85 (11H, m, *Ar*, *Ph*), 8.45–8.48 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.4, 27.9, 56.5, 57.1, 71.0, 79.8, 81.2, 83.1, 116.4, 124.4 125.0, 125.5, 126.3, 126.8, 127.8, 128.2, 128.5, 128.6, 128.9, 129.4, 132.2, 133.5, 134.7, 135.4, 138.0, 175.4; *m*/*z* (ESI^+) 462 ($[M+H]^+$, 10%); HRMS (ESI^+) found 462.2650; $C_{29}H_{36}NO_4^+$ ($[M+H]^+$) requires 462.2644.

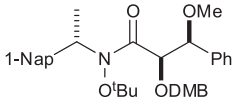
*4.4.3. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2R,3S)-2-allyloxy-3-methoxybutanamide **86**.*



Compound (*S*)-**6** (380 mg, 1.11 mmol) in THF (9 mL) was treated with KHMDS (1.50 mmol) in THF (9 mL), acetaldehyde (0.15 mL, 2.61 mmol) and then MeI (1.00 mL, 16.2 mmol) according to the *general procedure*. Purification via flash column chromatography (gradient elution, pentane/Et_2O, 19:1; increased to Et_2O) gave **86** as a colourless oil (248 mg, 56%, >99:1 dr), R_f 0.20 (pentane/Et_2O, 3:1); $[\alpha]_D^{23}$ +40.8 (*c* 2.0 in $CHCl_3$); ν_{max} (film) 2976 (C–H), 1678 (C=O), 1370,

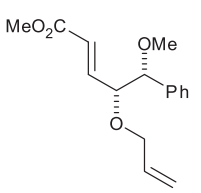
1093; δ_H (400 MHz, $CDCl_3$) 0.85 (9H, s, CMe_3), 1.15, (3H, d, J 6.3, C(4)H_3), 1.81 (3H, d, J 7.0, NapCHMe), 3.10 (3H, br s, OMe), 3.85 (1H, dq, J 6.3, 3.5, C(3)H), 3.91–3.94 (1H, br m, OCH_AH$_B$CH=CH$_2$), 4.32 (1H, d, J 3.3, C(2)H), 4.36 (1H, dd, J 13.1, 4.3, OCH$_A$$H_B$CH=CH$_2$), 5.17 (1H, dd, J 10.4, 0.8, OCH$_2$CH=CH_AH$_B$), 5.28 (1H, dd, J 17.3, 1.5, OCH$_2$CH=CH$_A$$H_B$), 5.92–5.96 (1H, br m, OCH$_2$CH=CH$_2$) 6.30–6.33 (1H, br m, C(1′)H), 7.41–7.85 (6H, m, Ar), 8.45–8.48 (1H, br m, Ar); δ_C (100 MHz, $CDCl_3$) 15.3, 16.3, 27.9, 56.0, 56.4, 71.1, 74.9, 80.1, 82.7, 117.0, 124.5, 124.8, 125.6, 126.3, 126.6, 128.5, 128.6, 132.3, 133.6, 135.1, 135.5, 175.0; m/z (ESI$^+$) 422 ([M+Na]$^+$, 100%), 400 ([M+H]$^+$, 40%); HRMS (ESI$^+$) found 400.2487; $C_{24}H_{34}NO_4^+$ ([M+H]$^+$) requires 400.2488.

*4.4.4. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2R,3S)-2-(3‴,4‴-dimethoxybenzyloxy)-3-methoxy-3-phenylpropanamide **87**.*



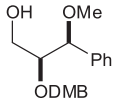
Compound (*S*)-**9** (540 mg, 1.20 mmol) in THF (8 mL) was treated with KHMDS (1.55 mmol) in THF (8 mL), benzaldehyde (0.24 mL, 2.39 mmol) and then MeI (0.99 mL, 16.0 mmol) according to the *general procedure*. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed the presence of **87**:**91** in 88:12 dr. Purification via flash column chromatography (gradient elution, pentane/Et_2O, 3:2; increased to pentane/Et_2O, 2:3) gave **87** as a colourless oil (433 mg, 63%, 96:4 dr); R_f 0.25 (pentane/Et_2O); $[\alpha]_D^{23}$ +52.8 (*c* 2.8 in $CHCl_3$); ν_{max} (film) 2976, 2936 (C–H), 1680 (C=O), 1594 (C=C), 1515, 1465, 1370, 1264, 1237, 1092, 1029; δ_H (400 MHz, $CDCl_3$) 0.79 (9H, s, CMe_3), 1.80 (3H, d, J 7.0, C(1′)Me), 2.77 (3H, br s, OMe), 3.60 (3H, s, OMe), 3.79 (3H, s, OMe), 4.42 (1H, br d, J 12.6, OCH_AH$_B$Ar), 4.49 (1H, d, J 2.7, C(2)H), 4.64 (1H, app br s, C(3)H), 4.71 (1H, d, J 12.6, OCH$_A$$H_B$Ar), 6.19–6.22 (1H, br m, C(1′)H), 6.52–6.55 (3H, br m, Ar), 7.26–7.85 (11H, m, Ar, Ph), 8.46–8.49 (1H, br m, Ar); δ_C (100 MHz, $CDCl_3$) 16.5, 27.8, 55.6, 55.8, 56.5, 57.1, 71.4, 79.1, 80.9, 83.1, 110.4, 110.4, 119.8, 124.4, 125.0, 125.5, 126.2, 126.5, 126.8, 127.7, 128.0, 128.3, 128.5, 128.6, 130.4, 132.2, 133.7, 135.3, 138.2, 148.2, 148.7, 175.2; m/z (ESI$^+$) 594 ([M+Na]$^+$, 100%), 572 ([M+H]$^+$, 3%); HRMS (ESI$^+$) found 572.3013; $C_{35}H_{42}NO_6^+$ ([M+H]$^+$) requires 572.3012. Further elution gave **91** as a colourless oil (36 mg, 5%, >99:1 dr); R_f 0.35 (pentane/Et_2O, 1:1); $[\alpha]_D^{23}$ +17.0 (*c* 1.3 in $CHCl_3$); ν_{max} (film) 2927 (C–H), 1668 (C=O), 1594, 1515 (C=C), 1368, 1264, 1238, 1158, 1138, 1090, 1029; δ_H (400 MHz, $CDCl_3$) 0.88 (9H, br s, CMe_3), 1.79 (3H, br d, J 6.4, C(1′)Me), 3.25 (3H, br s, OMe), 3.72 (3H, br s, OMe), 3.84 (3H, br s, OMe), 4.52–4.57 (2H, br m, C(2)H, OCH_AH$_B$Ar), 4.74 (1H, d, J 11.9, OCH$_A$$H_B$Ar), 4.95 (1H, app br s, C(3)H), 5.78–5.81 (1H, br m, C(1′)H), 6.62–6.66 (3H, br m, Ar), 7.28–7.90 (12H, m, Ar, Ph); δ_C (100 MHz, $CDCl_3$) 18.5, 27.3, 55.7, 55.8, 57.2, 72.2, 79.6, 81.9, 82.9, 110.4, 110.8, 120.0, 123.0, 125.3, 125.6, 126.3, 126.9, 127.8, 127.9, 128.1, 128.2, 128.6, 128.9, 130.6, 133.5, 138.3, 148.2, 148.7, 174.1; m/z (ESI$^+$) 594 ([M+Na]$^+$, 100%), 572 ([M+H]$^+$, 39%); HRMS (ESI$^+$) found 572.3010; $C_{35}H_{42}NO_6^+$ ([M+H]$^+$) requires 572.3012.

*4.4.5. Methyl (R,R,E)-4-allyloxy-5-methoxy-5-phenylpenten-2-enoate **92**.*



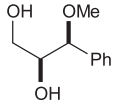
Compound **85** (261 mg, 0.57 mmol) was dissolved in THF (3 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 1.7 mL, 1.7 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (15 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×15 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and 3 Å powdered molecular sieves (~50 mg) were added. The resultant slurry was cooled to 0 °C. Ph_3P=$CHCO_2Me$ (189 mg, 0.57 mmol) was added. The reaction mixture was allowed to warm to rt over 16 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 9:1) gave auxiliary (*R*)-**1** (118 mg, 86%, >99:1 er). Further elution gave **92** as a colourless oil (93 mg, 59%, 95:5 dr); R_f 0.30 (Et_2O:pentane 1:9); $[\alpha]_D^{23}$ +38.9 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 2970 (C–H), 1724 (C=O), 1436, 1273, 1168, 1102; δ_H (400 MHz, $CDCl_3$) 3.27 (3H, s, OMe), 3.70 (3H, s, OMe), 3.95 (1H, ddt, J 13.0, 5.9, 1.3, OCH_AH$_B$CH=CH$_2$), 4.06 (1H, ddt, J 13.1, 5.3, 1.4, OCH$_A$$H_B$CH=CH$_2$), 4.15 (1H, td, J 5.8, 1.4, C(4)H), 4.24 (1H, d, J 5.8, C(5)H), 5.14 (1H, ddd, J 10.5, 2.9, 1.4, OCH$_2$CH=CH_AH$_B$), 5.21 (1H, ddd, J 17.3, 3.2, 1.5, OCH$_2$CH=CH$_A$$H_B$), 5.78–5.83 (1H, m, OCH$_2CH$=CH$_2$), 5.92 (1H, dd, J 15.7, 1.4, C(2)H), 6.68 (1H, dd, J 15.7, 5.8, C(3)H), 7.26–7.37 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 51.5, 57.2, 71.1, 81.0, 85.6, 117.2, 122.6, 127.6, 128.1, 128.2, 134.3, 137.6, 145.1, 166.4; m/z (ESI$^+$) 299 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 299.1253; $C_{16}H_{20}NaO_4^+$ ([M+Na]$^+$) requires 299.1259.

*4.4.6. (2R,3S)-2-(3′,4′-Dimethoxybenzloxy)-3-methoxy-3-phenylpropan-1-ol **93**.*



Compound **87** (383 mg, 0.67 mmol) was dissolved in THF (5 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 2.01 mL, 2.01 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in THF (1 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 1.34 mL, 1.34 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 6:1) gave auxiliary (*S*)-**1** (149 mg, 91%, >99:1 er). Further elution gave **93** as a colourless oil (233 mg, 98%); R_f 0.10 (pentane/Et_2O, 1:1); $[\alpha]_D^{23}$ +32.2 (*c* 2.4 in $CHCl_3$); ν_{max} (film) 3458 (O–H), 2935 (C–H), 1593 (C=C), 1516, 1454, 1264, 1237, 1028; δ_H (400 MHz, $CDCl_3$) 2.16 (1H, t, J 5.9, OH), 3.28 (3H, s, OMe), 3.35–3.38 (1H, m, C(1)H_A), 3.48–3.52 (1H, m, C(1)H$_B$), 3.64–3.67 (1H, m, C(2)H), 3.86 (3H, s, OMe), 3.87 (3H, s, OMe), 4.36 (1H, d, J 6.2, C(3)H), 4.54 (1H, d, J 11.4, OCH_AH$_B$Ar), 4.71 (1H, d, J 11.4, OCH$_A$$H_B$Ar), 6.82–6.92 (3H, m, Ar), 7.19–7.43 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 55.8, 55.9, 57.1, 62.0, 73.5, 82.2, 85.2, 110.8, 111.2, 120.5, 127.4, 128.1, 128.4, 130.9, 138.3, 148.6, 148.9; m/z (ESI$^+$) 355 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 355.1515; $C_{19}H_{24}NaO_5^+$ ([M+Na]$^+$) requires 355.1521.

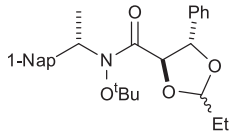
*4.4.7. (2R,3S)-3-Methoxy-3-phenyl-propane-1,2-diol **94**.*



DDQ (110 mg, 0.49 mmol) was added to a solution of **93** (164 mg, 0.49 mmol) in CH_2Cl_2:H_2O (v/v 5:1, 5 mL) and the mixture was stirred

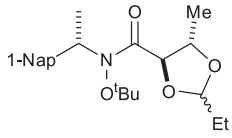
at rt for 18 h and then concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 9:1) and recrystallisation from pentane gave **94** as fine colourless needles (78 mg, 87%);[31] mp 71 °C; $[\alpha]_D^{23}$ +102.9 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3370 (O–H), 2881 (C–H), 1461, 1310, 1264, 1119, 1038; δ_H (400 MHz, $CDCl_3$) 2.36–2.39 (1H, br m, O*H*), 3.27 (3H, s, O*Me*), 3.35 (1H, dd, *J* 11.8, 4.7, C(1)H_A), 3.55 (1H, dd, *J* 11.8, 3.1, C(1)H_A), 3.75 (1H, ddd, *J* 8.1, 4.7, 3.1, C(2)*H*), 4.21 (1H, d, *J* 8.1, C(3)*H*), 7.30–7.42 (5H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 56.8, 62.4, 75.7, 84.6, 127.7, 128.6, 128.8, 137.9; HRMS (CI^+) found 200.1289; $C_{10}H_{18}NO_3^+$ ($[M+NH_4]^+$) requires 200.1287.

4.4.8. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2ξ,4R,5S)-2-ethyl-5-phenyl-1,3-dioxolane-4-carboxamide ***96****.*



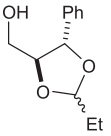
trans-Pd$(NH_3)_2Cl_2$ (16 mg, 0.08 mmol) was added to a solution of **61** (340 mg, 0.76 mmol) in degassed ^{t}BuOH (9 mL). The resultant solution was heated at reflux for 18 h, cooled to rt and diluted with MeOH (10 mL). The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (gradient elution, pentane/Et_2O, 19:1; increased to pentane/Et_2O, 4:1) gave **96** as a colourless oil (246 mg, 72%); R_f 0.25 (pentane/Et_2O, 19:1); $[\alpha]_D^{23}$ +10.4 (*c* 1.8 in $CHCl_3$); ν_{max} (film) 2976 (C–H), 1682 (C=O), 1600 (C=C), 1455, 1369, 1265, 1169; δ_H (400 MHz, $CDCl_3$) 0.75 (9H, s, CMe_3), 1.06 (3H, t, *J* 7.0, C(2)CH_2CH_3), 1.86 (3H, d, *J* 7.0, C(1′)*Me*), 1.90–1.93 (2H, m, C(2)CH_2CH_3), 4.87–4.90 (1H, br m, C(4)*H*), 5.01–5.04 (1H, br m, C(5)*H*), 5.36 (1H, t, *J* 5.0, C(2)*H*), 6.21 (1H, br q, *J* 6.8, C(1′)*H*), 7.10–7.90 (11H, m, *Ar*, *Ph*), 8.35–8.37 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 8.4, 16.9, 27.5, 27.7, 56.9, 79.5, 81.0, 83.4, 108.0, 124.3, 124.8, 125.4, 125.6, 126.4, 127.2, 128.1, 128.4, 128.6, 128.8, 129.1, 132.0, 133.6, 135.1, 138.8, 175.6; *m*/*z* (ESI^+) 470 ($[M+Na]^+$, 100%), 448 ($[M+H]^+$, 82%); HRMS (ESI^+) found 470.2316; $C_{28}H_{33}NNaO_4^+$ ($[M+Na]^+$) requires 470.2307.

4.4.9. (S)-N-tert-Butoxy-N-1′-(1″-naphthyl)ethyl (2ξ,4R,5S)-2-ethyl-5-methyl-1,3-dioxolane-4-carboxamide ***97****.*



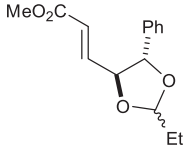
trans-Pd$(NH_3)_2Cl_2$ (37 mg, 0.17 mmol) was added to a solution of **62** (200 mg, 0.52 mmol) in degassed ^{t}BuOH (8 mL). The resultant solution was heated at reflux for 18 h, cooled to rt and diluted with MeOH (10 mL). The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (gradient elution, pentane; increased to pentane/Et_2O, 9:1) gave **97** as a colourless oil (94 mg, 47%); R_f 0.35 (pentane/Et_2O, 4:1); $[\alpha]_D^{23}$ −37.6 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 2976 (C–H), 1683 (C=O), 1456, 1371, 1239, 1166; δ_H (400 MHz, $CDCl_3$) 0.83 (9H, s, CMe_3), 1.04 (3H, t, *J* 7.6, C(2)CH_2CH_3), 1.29 (3H, d, *J* 6.4, C(5)*Me*), 1.79 (3H, d, *J* 6.9, C(1′)*Me*), 1.85–1.89 (2H, m, C(2)CH_2CH_3), 4.10–4.13 (1H, br m, C(5)*H*), 4.71–4.75 (1H, br m, C(4)*H*), 5.18 (1H, t, *J* 5.0, C(2)*H*), 6.34 (1H, br q, *J* 6.9, C(1′)*H*), 7.41–7.88 (6H, m, *Ar*), 8.38–8.42 (1H, br m, *Ar*); δ_C (100 MHz, $CDCl_3$) 8.4, 16.4, 18.3, 27.4, 27.9, 56.3, 75.7, 79.4, 83.4, 106.3, 124.3, 124.7, 125.7, 126.2, 126.5, 128.5, 128.9, 132.1, 133.6, 135.2, 176.7; *m*/*z* (ESI^+) 408 ($[M+Na]^+$, 100%), 386 ($[M+H]^+$, 67%); HRMS (ESI^+) found 408.2149; $C_{23}H_{31}NNaO_4^+$ ($[M+Na]^+$) requires 408.2151.

4.4.10. (2ξ,4S,5S)-2-(Ethyl-5-phenyl-1,3-dioxolan-4-yl)methanol ***98****.*



Compound **96** (200 mg, 0.45 mmol) was dissolved in THF (3 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 1.34 mL, 1.34 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in THF (1 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 1.34 mL, 1.34 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (25 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave auxiliary (*S*)-**1** (96 mg, 89%, >99:1 er). Further elution gave **98** as a colourless oil (49 mg, 53%); R_f 0.55 (pentane/Et_2O, 1:1); $[\alpha]_D^{23}$ +3.2 (*c* 1.7 in $CHCl_3$); ν_{max} (film) 3437 (O–H), 2931, 2889 (C–H), 1455, 1119, 1045; δ_H (400 MHz, $CDCl_3$) 1.04 (3H, t, *J* 7.6, C(3)CH_2CH_3), 1.80 (2H, app. dq, *J* 7.6, 4.6, C(3)CH_2CH_3), 2.25–2.28 (1H, br m, O*H*), 3.72–3.75 (1H, br m, CH_AH_BOH), 3.93 (1H, br app d, *J* 12.5, CH_AH_BOH), 3.98–4.01 (1H, m, C(4)*H*), 4.86 (1H, d, *J* 7.6, C(5)*H*), 5.33 (1H, t, *J* 4.6, C(2)*H*), 7.30–7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 7.9, 27.5, 61.3, 78.4, 84.7, 106.2, 126.1, 128.1, 128.7, 139.4; *m*/*z* (CI^+) 208 ($[M]^+$, 39%), 191 (100%); HRMS (CI^+) found 226.1440; $C_{12}H_{20}NO_3^+$ ($[M+NH_4]^+$) requires 226.1443.

4.4.11. Methyl (2′ξ,4′S,5′S,E)-3-(2′-ethyl-5′-phenyl-1′,3′-dioxolan-4′-yl)-propenoate ***99****.*



Compound **96** (220 mg, 0.49 mmol) was dissolved in THF (3 mL) and the resultant solution was cooled to −15 °C in a salt/ice bath. $LiAlH_4$ (1 M in THF, 1.48 mL, 1.48 mmol) was added dropwise via syringe, and the reaction mixture was stirred at −15 °C for 1 h. The reaction mixture was transferred dropwise via cannula to stirred pH 7 phosphate buffer solution (15 mL) at 0 °C. The mixture was extracted with 30–40 °C petrol (3×15 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and 3 Å powdered molecular sieves (~50 mg) were added. The resultant slurry was cooled to 0 °C. $Ph_3P{=}CHCO_2Me$ (164 mg, 0.49 mmol) was added. The reaction mixture was allowed to warm to rt over 16 h before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave auxiliary (*S*)-**1** (96 mg, 80%, >99:1 er). Further elution gave **99** as a colourless oil (104 mg, 80%, 95:5 dr); R_f 0.25 (pentane/Et_2O, 9:1); $[\alpha]_D^{23}$ +2.9 (*c* 1.7 in $CHCl_3$); ν_{max} (film) 2973, 2881 (C–H), 1728 (C=O), 1456, 1199, 1031; δ_H (400 MHz, $CDCl_3$) 1.05 (3H, t, *J* 7.5, C(2′)CH_2CH_3), 1.79–1.82 (2H, m, C(2′)CH_2CH_3), 3.76 (3H, s, O*Me*), 4.40 (1H, ddd, *J* 7.9, 5.6, 1.4, C(5′)H_A), 4.66 (1H, d, *J* 7.9, C(4′)*H*), 5.40 (1H, t, *J* 4.6, C(2′)*H*), 6.12 (1H, dd, *J* 15.7,

1.4, C(2)*H*), 6.97 (1H, dd, *J* 15.7, 5.6, C(3)*H*), 7.30–7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 7.7, 27.7, 51.8, 82.4, 83.4, 106.8, 122.8, 126.1, 128.0, 128.7, 137.9, 142.3, 166.2; *m*/*z* (CI^+) 263 ($[M+H]^+$, 47%), 205 (100%); HRMS (CI^+) found 263.1283; $C_{15}H_{19}O_4^+$ ($[M+H]^+$) requires 263.1283.

References and notes

1. For instance, see: (a) Andrus, M. B.; Soma Sekhar, B. B. V.; Turner, T. M.; Meredith, E. L. *Tetrahedron Lett.* **2001**, *42*, 7197; (b) Dixon, D. J.; Guarna, A.; Ley, S. V.; Polara, A.; Rodriguez, F. *Synthesis* **2002**, 1973; (c) Andrus, M. B.; Meredith, E. L.; Simmons, B. L.; Soma Sekhar, B. B. V.; Hicken, E. J. *Org. Lett.* **2002**, *4*, 3549; (d) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162.
2. Chernega, A. N.; Davies, S. G.; Goodwin, C. J.; Hepworth, D.; Kurosawa, W.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 3254.
3. Masamune has also reported a benzopyranoisoxazolidine auxiliary which is capable of acting as a chiral Weinreb amide equivalent; see: Abiko, A.; Moriya, O.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 793; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1081.
4. Davies, S. G.; Goodwin, C. J.; Hepworth, D.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2010**, *75*, 1214.
5. Brown, J. M.; Davies, S. G. *Nature* **1989**, 631.
6. Smith, M. B.; March, J. *March's Advanced Organic Chemistry—Reactions, Mechanisms, and Structure*, 5th ed.; John Wiley & Sons: New York, NY, 2001.
7. For selected recent applications of enantiomerically pure 4-alkyl-5,5-dimethyloxazolidin-2-one (SuperQuat) chiral auxiliaries in synthesis from this laboratory, see: Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Synlett* **2002**, 1637; Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2886; Davies, S. G.; Key, M.-S.; Rodriguez-Solla, H.; Sanganee, H. J.; Savory, E. D.; Smith, A. D. *Synlett* **2003**, 1659; Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 348; Aciro, C.; Davies, S. G.; Garner, A. C.; Ishii, Y.; Key, M.-S.; Ling, K. B.; Prasad, R. S.; Roberts, P. M.; Rodriguez-Solla, H.; O'Leary-Steele, C.; Russell, A. J.; Sanganee, H. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron* **2008**, *64*, 9320.
8. Davies, S. G.; Hunter, I. A.; Nicholson, R. L.; Roberts, P. M.; Savory, E. D.; Smith, A. D. *Tetrahedron* **2004**, *60*, 7553.
9. The absence of significant amounts of products resulting from the reaction of radical anion **19** or oxonium species **20** with excess alkoxide points to a fast intramolecular reaction occurring within the solvent cage.
10. For a review, see: Schollkopf, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 763.
11. Heard, G. L.; Yates, B. F. *Aust. J. Chem.* **1994**, *47*, 1685.
12. Gasparski, C. M.; Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 548; Guzzo, P. R.; Teng, M.; Miller, M. J. *Tetrahedron* **1994**, *40*, 8275.
13. Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247.
14. The enantiomeric excess of **1** was determined by ^1H NMR spectroscopic analysis in the presence of (*S*)-*O*-acetylmandelic acid as a chiral shift reagent, and comparison with an authentic racemic sample.
15. Kobayashi, Y.; Takase, M.; Ito, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3038.
16. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
17. Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843.
18. (a) Bernardi, R.; Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1981**, *22*, 4021; (b) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *101*, 1256; (c) Aoyagi, S.; Hirashima, S.; Saito, K.; Kibayashi, C. *J. Org. Chem.* **2002**, *67*, 5517.
19. (a) Valverde, S.; Martin-Lomas, M.; Herradon, B.; Garcia-Ochoa, S. *Tetrahedron* **1987**, *43*, 1895; (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Dondio, G.; Raimondi, L. *Tetrahedron* **1987**, *43*, 2369; (c) Bernardi, A.; Cardani, S.; Scolastico, C.; Villa, R. *Tetrahedron* **1988**, *44*, 491; (d) Mortlock, S. V.; Thomas, E. J. *Tetrahedron Lett.* **1988**, *29*, 2479; (e) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *J. Org. Chem.* **1990**, *55*, 1901; (f) Gung, B. W.; Peat, A. J. *Synth. Commun.* **1991**, *21*, 1797; (g) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Pilati, T. *Tetrahedron: Asymmetry* **1991**, *2*, 1329; (h) Désert, S.; Metzner, P. *Tetrahedron* **1992**, *48*, 10327; (i) Enders, D.; Finkam, M. *Synlett* **1993**, 401; (j) Kan, T.; Oikawa, M.; Hosokawa, S.; Yanagiya, M.; Matsuda, F.; Shirahama, H. *Synlett* **1994**, 801; (k) Kan, T.; Oikawa, M.; Hosokawa, S.; Yanagiya, M.; Matsuda, F.; Shirahama, H. *Synlett* **1994**, 805; (l) Enders, D.; Jandeleit, B. *Acros Organics Acta* **1995**, *1*, 59; (m) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Eur. J. Org. Chem.* **1998**, 1823; (n) Enders, D.; Jandeleit, B.; von Berg, S.; Raabe, G.; Runsink, J. *Organometallics* **2001**, *20*, 4312; (o) Kireev, A. S.; Manpadi, M.; Kornienko, A. *J. Org. Chem.* **2006**, *71*, 2630.
20. We have recently reported a variant of the Wadsworth–Emmons olefination using MeMgBr as the base, which is amenable to the olefination of stereochemically labile aldehydes; see: Claridge, T. D. W.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437.
21. Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2083.
22. The enantiomeric excesses of **49** and **50** were determined by Chiral GC analysis.
23. Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876.
24. Flack, H. D.; Bernardelli, G. *Acta Crystallogr.* **1999**, *A55*, 908.
25. Ali, S. A.; Hassan, A.; Wazeer, M. I. M. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1479.
26. Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.
27. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920; See also: Kleschnick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247; Heathcock, C. H.; Buse, C. T.; Kleschnick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.
28. Danda, H.; Hansen, M. N.; Heathcock, C. H. *J. Org. Chem.* **1990**, *66*, 173; Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747.
29. Efforts to achieve an aldol reaction upon treatment of **6** with dibutylboron triflate, triethylamine and benzaldehyde were unsuccessful.
30. Reversal of diastereoselectivity in aldol reactions of glycolates relative to propionates has been observed; see, for example, Ref. 1a within.
31. Handa, S.; Hawes, J. E.; Pryce, R. J. *Synth. Commun.* **1995**, *25*, 2837.
32. Takano, S.; Yanase, M.; Ogasawara, K. *Synthesis* **1989**, 39; Niibo, Y.; Nakata, T.; Otera, J.; Nozaki, H. *Synlett* **1991**, 97.
33. Bieg, T.; Szeja, W. *J. Carbohydr. Chem.* **1985**, *4*, 441.
34. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
35. Duhamel, L.; Plaquevent, J.-C. *J. Organomet. Chem.* **1993**, *448*, 1.
36. Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.
37. Use of PhMe as the solvent provided a sharper end-point than THF.
38. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *CRYSTALS*; Chemical Crystallography Laboratory, University of Oxford: UK, 2001.