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Preparation of enantiopure butane-2,3-diacetals of glycolic acid and alkylation reactions leading to α-hydroxyacid and amide derivatives

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The preparation of butane-2,3-diacetal protected glycolic acid and related systems is described together with highly selective alkylation reactions of (*R*,*R*) and (*S*,*S*) butanediacetal protected glycolic acid. These compounds are readily deprotected to give enantiopure α-hydroxyacids, α-hydroxyesters or α-hydroxyamides by suitable choice of conditions.

Introduction

Mono- or dialkylated α-hydroxycarbonyl functional groups are present in a wide range of biologically and pharmacologically important compounds.[1] Consequently, a range of strategies have been developed for the enantioenriched synthesis of these α-hydroxycarbonyl motifs.[2] A common approach has been the use of a chiral glycolic acid equivalent which undergoes diastereoselective enolate reactions with readily available electrophiles.[3]

Some years ago we introduced the use of bis-dihydropyrans for the protection of α-hydroxyacids as the corresponding dispiroketals.[4] When chiral versions of the bis-dihydropyrans were used, we found that the 1,2-diacetal products could be deprotonated and alkylated with high diastereoselectivity; subsequent deprotection afforded enantiopure α-hydroxy acids.[5] While this methodology has served us well, the expense of the chiral protecting groups was limiting, and consequently we have sought alternative, cheaper solutions. Recently we have introduced a number of butanediacetal (BDA) protected compounds as useful building blocks for asymmetric synthesis.[6] Here we report in full on the butane-2,3-diacetal protection of glycolic acid and other related systems.[7] We also describe the preparation of these derivatives in enantiopure forms and their highly diastereoselective enolate alkylation reactions.[8]

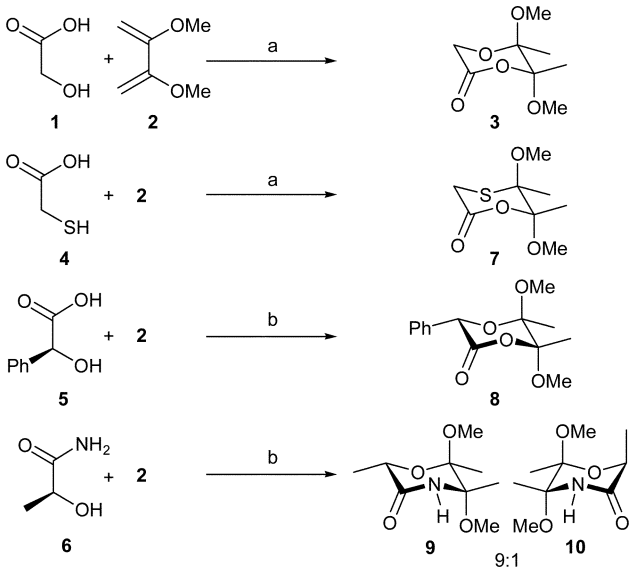
Results and discussion

Initial investigation showed that glycolic acid **1** could be BDA protected with 2,3-dimethoxybutadiene **2** in the presence of catalytic triphenylphosphine hydrobromide.[9] The resulting butane-2,3-diacetal **3** was obtained in 83% yield (Scheme 1). Related systems such as thioglycolic acid **4**, (*S*)-mandelic acid **5** and the (*S*)-lactamide **6** reacted similarly to give protected derivatives **7**, **8**, **9** and **10**. In the case of the lactamide two products **9** and **10** were produced in a ratio of 9 : 1 which on recrystallisation gave pure **9** in 51% isolated yield. (Scheme 1).

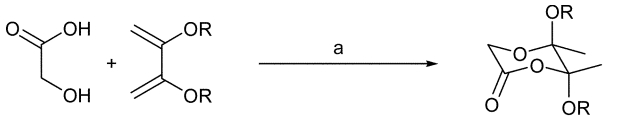
Likewise, bis-enol ethers **11** and **12** reacted with glycolic acid to give butane-2,3-diacetal products **13** and **14** respectively (Scheme 2). These derivatives were selected to allow the use of alternative deprotection conditions, should this be necessary in other synthesis programmes.

Whilst the above methods readily afforded racemic butane-2,3-diacetal protected glycolic acid, an enantiospecific route to (*R*,*R*)-**15** and (*S*,*S*)-**16** was required (Fig. 1).

Multi-gram quantities of both are accessible from mannitol or ascorbic acid using chemistry previously published by our group, but the routes are long (7–10 steps).[10] In this work, we report full procedures for three step routes from 3-halopropane-1,2-diols in which the chirality is set *via* a chiral memory protocol.[11]



Scheme 1 (a) PPh_3·HBr, CH_2Cl_2, 3 h, rt, 83% (**3**), 57% (**7**) (b) PPh_3·HBr, CH_2Cl_2, 24 h, rt, 51% (**8**), 51% (**9**).



Scheme 2 (a) PPh_3·HBr, CH_2Cl_2, 24 h, rt, 95% (**13**), 92% (**14**).

Fig. 1 Structures for compounds **15** and **16**

(*S*)-3-Bromopropane-1,2-diol **17**, prepared from epibromohydrin in consistently good enantiomeric excess (96–97%),[12] may be used as the chiral precursor. This reacts with a methanol solution of butane-2,3-dione in the presence of trimethylorthoformate and catalytic camphor sulfonic acid to give the protected adduct **18** as a single product in 85% yield. The bromomethyl side chain adopts an equatorial position due to the thermodynamic conditions used and the methoxy groups adopt an axial configuration due to the operating anomeric effects (exoanomeric

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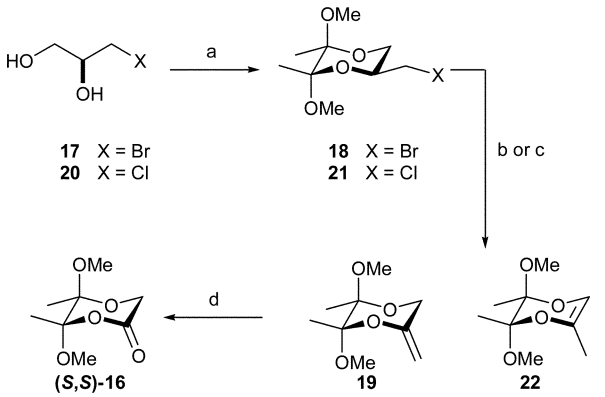
effects). This process embeds chirality into the protecting group with the two acetal centres having an (*S*,*S*) configuration. Elimination of **18** with potassium hexamethyldisilazide cleanly afforded the *exo*-methylene derivative **19** in 85% yield. Oxidative cleavage of the double bond gave the lactone **16** in 59% overall yield from diol **17** (Scheme 3).

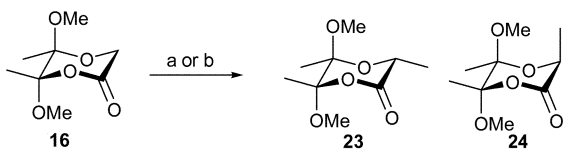


Scheme 3 (a) Butane-2,3-dione, $(MeO)_3CH$, CSA, MeOH, reflux, 85% from **17**, 90% from **20** (b) KHMDS, THF, 0 °C to rt, 85% (c) KO^{t}Bu, THF, reflux, 80% (d) O_3, CH_2Cl_2–MeCOMe, −78 °C, then Me_2S, 59% over three steps from **17**, 62% over three steps from **20**.

For larger scale preparations, reaction of (*S*)-3-chloropropane-1,2-diol **20** with butane-2,3-dione under the same conditions gave the protected adduct **21** in 90% yield. Elimination with potassium *tert*-butoxide in THF typically gave a 15 : 1 ratio of *exo*- and *endo*-alkene isomers **19** and **22** in 80% yield. Treatment of this alkene mixture with ozone in dichloromethane–acetone afforded the (*S*,*S*)-glycolic acid derivative **16**. The three steps may be carried out without the need for chromatographic purification of the intermediates to give the lactone **16** in 62% overall yield from **20** on a 30 g scale.

The enantiopurity of this product is dependent on the enantiopurity of the 3-chloropropanediol **20**, either purchased from chemical suppliers or obtained by resolution of epichlorohydrin.[12] This varied considerably over several batches and we recommend careful analysis of the final product formed. As **16** is crystalline, recrystallisation after the ozonolysis leads to essentially enantiopure **16** (as determined by chiral GC) but inevitably with some loss of material. The enantiomeric (*R*,*R*)-glycolate **15** can be similarly prepared from the corresponding (*R*)-3-halopropane-1,2-diol precursors.

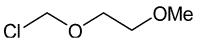
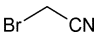
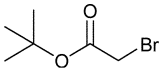
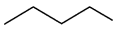
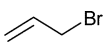
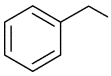
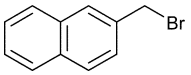
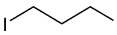
With the enantiopure (≥99% ee) glycolic acid diacetals **15** and **16** readily available, we studied their deprotonation and subsequent alkylation with alkyl halides. In the initial experiments, **15** was deprotonated with lithium bis(trimethylsilyl)amide (LHMDS) (1.05 eq) in THF at −78 °C, then treated with methyl iodide to give the alkylated products **23** and **24** in a ratio of 70 : 1 (Scheme 4).



Scheme 4 (a) LHMDS (1.05 eq), THF, −78 °C, 10 min, then MeI (3.0 eq), −78 °C to −30 °C over 2 h, then AcOH (2.0 eq), 89%, (b) LHMDS, (0.9 eq), THF, −78 °C, 10 min, then MeI (3.0 eq), −78 °C to −30 °C over 2 h, then AcOH (2.0 eq), 93%.

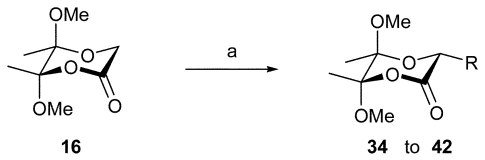
If the conditions for deprotonation were changed slightly to 0.9 eq LHMDS then the ratio of alkylated products changed significantly to only 9 : 1 in favour of **23** over **24** (93% yield). This result suggested a thermodynamic equilibrium in the formation of the preferred equatorially alkylated material **23**.

Table 1 Alkylation reactions of lactone **16**

	Alkyl halide	d.r.	Yield (conv.)/%	Product
25		10 : 1	64	**34**
26		10 : 1	85 (97)	**35**[a]
27		15 : 1	61 (87)	**36**
28		18 : 1	92	**37**[b]
29		21 : 1	57	**38**
30		60 : 1	89 (96)	**39**[a]
31		>99 : 1	96	**40**
32		>99 : 1	84 (91)	**41**[b]
33		>24 : 1	62	**42**[a,c]

[a] Configuration determined by single-crystal X-ray diffraction. [b] Configuration determined by NOE experiments. [c] (*R*,*R*)-glycolate (**15**) was used as a starting material.

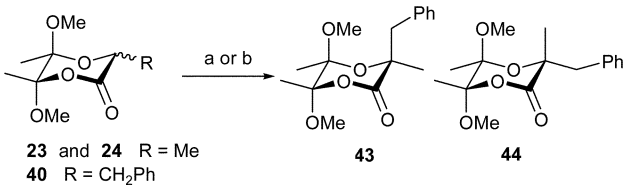
Following these initial observations we studied the selective alkylation with other electrophiles taking care to ensure that the observed selectivity in the alkylation reactions was due to the principal attack of the lithium enolate of **15** or **16** on the alkyl halide and not through some secondary isomerising enhancement effect. This was achieved by using sub-stoichiometric quantities of base. The results are summarized in Table 1. Alkylation with halides **25**–**33** using 0.95 eq of LHMDS and excess electrophile at −78 to −30 °C gave the preferentially equatorially alkylated products **34**–**42**, respectively (Scheme 5).



Scheme 5 (a) LHMDS (0.95 eq), THF, −78 °C, 10 min, then RX (3 eq).

It can be seen from these results that alkylation selectivity improves with increasing size of the electrophile. The yields are good even with quite unreactive halides such as **27**, **29** and **33**. With benzyl bromide **31** or the naphthyl methyl bromide **32**, no minor diastereoisomers were detected in the crude reaction mixtures. In three cases (**35**, **39** and **42**) the stereochemical outcome was confirmed by X-ray crystal structure analysis, showing that the preferred alkylation occurs from the face opposing the 1,3-axial methoxy group.

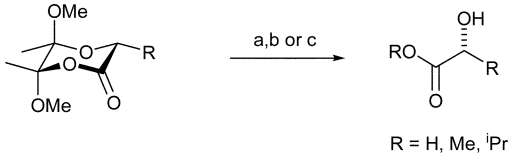
We also investigated how these monoalkylated products could be dialkylated in a selective fashion. Benzylated derivative **40** was deprotonated with LHMDS (1.1 eq) in the usual way and reacted with methyl iodide to give the two separable diastereomeric products **43** and **44** in a 3 : 1 ratio and a combined yield of 82% (Scheme 6). When the mixture of **23** and **24** was alkylated with benzyl bromide, **44** was obtained in 93% yield as essentially a single product. These dialkylation experiments suggest the diastereoselectivity depends on the relative sizes of both the pendent alkyl group and attacking electrophile.



Scheme 6 (a) LHMDS (1.1 eq), THF, −78 °C, 10 min, then MeI (3.0 eq), −78 °C to −30 °C over 2 h, then AcOH (2.0 eq), 82%; (b) LHMDS (1.1 eq), THF, −78 °C, 10 min, then $PhCH_2Br$ (3.0 eq), −78 °C to −30 °C over 2 h, then AcOH (2.0 eq), 93%.

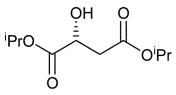
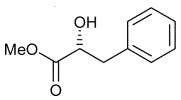
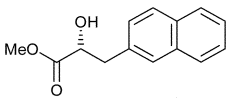
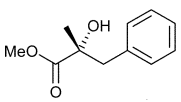
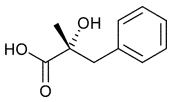
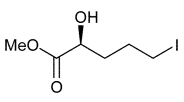
Diacetal deprotection by acid mediated hydrolysis or transesterification was carried out for selected examples (Scheme 7 and Table 2). In three cases, the absolute configuration of the products was verified as (*R*) through comparison of the specific rotations of the compounds **45**, **46** and **49** with literature data.[13–15] Derivatisation of **47** as the (*R*) and (*S*)-Mosher's esters confirmed the enantiopurity as >98% suggesting that no racemization occurs in either the alkylation or deprotection steps, and confirming the absolute stereochemistry as the (*R*)-configuration.[16]

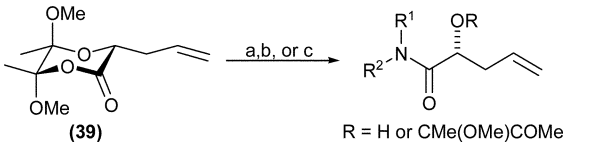
Aminolysis reactions were also investigated to establish alternative BDA deprotection conditions and enable easy synthesis of the corresponding α-hydroxyamide products (Scheme 8 and Table 3). Lactone **39** can be readily opened with primary, branched and secondary amines by stirring in neat amine, or in the case of the Weinreb amine, by activation of the amine with a Grignard reagent.[17] The readily accessible amide products **56** and **57** offer a potentially simple route to protected



Scheme 7 (a) HCl, ^{i}PrOH, reflux; (b) HCl, MeOH, rt or 50 °C; (c) TFA–H_2O, rt.

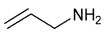
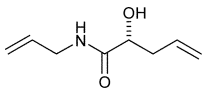
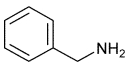
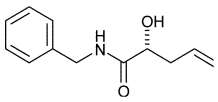
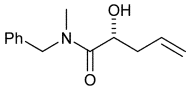
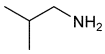
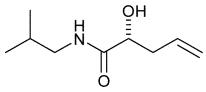
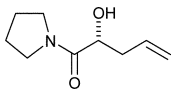
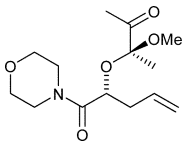
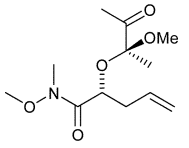
Table 2 Deprotection of the BDA group

Compound	Conditions	Product		Yield/%
37	a		**45**	77
40	b		**46**	100
41	b		**47**	95
44	b		**48**	87
44	c		**49**	85
42	b		**50**	90



Scheme 8 (a) R_1R_2NH (neat), rt, 5 d, then TFA–H_2O, rt, 15 min; (b) R_1R_2NH (neat), rt, 2 d; (c) $R_1R_2NH.HCl$, ^{i}PrMgCl, THF, 0 °C, 15 min.

Table 3 Aminolysis of lactone **39**

Amine	Conditions	Product		Yield/%
	a		**51**	77
	a		**52**	69
	a		**53**	66
	a		**54**	68
	a		**55**	75
	b		**56**	100
	c		**57**	67

α-hydroxyketones by controlled addition of organometallic reagents.[18]

Conclusions

In summary, we have described methods for the protection of glycolic acid and related derivatives as their corresponding butaneacetals. Enantiopure (*R*,*R*) and (*S*,*S*) BDA-protected glycolic acids have been synthesised on multigram scale as useful chiral building blocks for asymmetric synthesis. Following deprotonation and subsequent alkylation or dialkylation, protected chiral α-hydroxyacids are generated in good yield. The products of these alkylation reactions can be hydrolysed, transesterified or treated with amines to afford α-hydroxy acids, esters or amides, respectively. Further reactions of the key building blocks **15** and **16** are described in a following paper.[19]

Experimental

All reactions were performed under an atmosphere of argon and carried out using oven dried glassware, cooled under a continuous stream of argon prior to use, unless otherwise stated. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl; dichloromethane (CH_2Cl_2), acetonitrile (MeCN), toluene (PhMe) and benzene (PhH) from

calcium hydride; methanol (MeOH) from magnesium methoxide and triethylamine (Et_3N) from potassium hydroxide. All other reagents and solvents were purified by standard procedures or were used as supplied from commercial sources as appropriate. Ozonolysis reactions were performed using a Peak Scientific ozone generator. The BDA-glycolates **15** and **16** were recrystallised to >99% ee (as measured by chiral GC) before use. Flash column chromatography was carried out using Merck Kieselgel (230–400 mesh) or prepacked silica columns (FLASH Biotage). Unless otherwise stated, all compounds containing the butanediacetal protected lactone functionality were purified on columns that had been packed with solvent containing 1% triethylamine by volume; 1% triethylamine was also added to the eluent. Melting points were performed on a Reichert hot stage apparatus and are uncorrected. Boiling points were measured during distillation. Optical rotations were measured using a Perkin Elmer Model 343 polarimeter and $[\alpha]_D^{25}$ values are given in 10^{-1} deg cm^2 g^{-1}, concentration (c) in g per 100 ml. Infrared spectra were recorded on a Perkin Elmer "Spectrum One" spectrometer equipped with an attenuated total reflectance (ATR) sampling accessory. Spectra were recorded on thin films deposited from chloroform, dichloromethane or methanol solutions. Microanalyses were determined using a CE-440 Elemental Analyser. Mass spectra were obtained on Kratos Concept 1H, Micromass Q-TOF or Bruker BIOAPEX 4.7E T FTICR spectrometers, using electron impact (EI) or electrospray (ESI) techniques. NMR spectra were recorded on Bruker DRX-600, DRX-500 or DPX-400 spectrometers, in $CDCl_3$ at 300 K, unless otherwise stated. Chemical shifts (δ) in ppm are given relative to Me_4Si, coupling constants (J) in Hz.

(±)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (3)

Triphenylphosphine hydrobromide (165 mg, 0.48 mmol) was added to a stirred solution of glycolic acid **1** (270 mg, 3.55 mmol) and 2,3-dimethoxy-1,3-butadiene **2** (490 mg, 4.29 mmol) in CH_2Cl_2 (10 ml) at rt. After 3 h, the reaction mixture was diluted with CH_2Cl_2 (20 ml). The organic phase was washed with saturated aqueous $NaHCO_3$ (20 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc 4 : 1) to give the lactone as a white solid (559 mg, 83%); mp 64–65 °C; ν_{max} (film)/cm^{-1} 2952, 1742; δ_H (400 MHz, $CDCl_3$)1.38 (3H, s, Me), 1.49 (3H, s, Me), 3.30 (3H, s, OMe), 3.43 (3H, s, OMe), 4.14 (1H, d, J 17.6, CH_2), 4.28 (1H, d, J 17.6, CH_2); δ_C (100 MHz, $CDCl_3$)16.9, 17.8, 49.1, 50.3, 60.3, 97.8, 105.0, 167.5; Found (ES): $[MNa]^+$ 213.0734 $C_8H_{14}O_5$ requires *MNa*, 213.0739.

(±)-5,6-Dimethoxy-5,6-dimethyl-[1,4]oxathian-2-one (7)

Triphenylphosphine hydrobromide (143 mg, 0.42 mmol) was added to a stirred solution of mercaptoacetic acid **4** (270 μL, 3.88 mmol) and 2,3-dimethoxy-1,3-butadiene **2** (564 mg, 4.95 mmol) in CH_2Cl_2 (20 ml) at rt. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (20 ml). The organic phase was washed with saturated aqueous $NaHCO_3$ (20 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc 4 : 1) to give the lactone as a white solid (449 mg, 57%); mp 52–53 °C; ν_{max} (film)/cm^{-1} 1727; δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, Me), 1.47 (3H, s, Me), 3.18 (1H, d, J 15.0, CH_2), 3.27 (3H, s, OMe), 3.38 (3H, s, OMe), 3.40 (1H, d, J 15.0, CH_2); δ_C (100 MHz, $CDCl_3$) 17.6, 20.3, 27.0, 49.7, 50.2, 87.5, 108.7, 166.0; Found (ES): $[MNa]^+$ 229.0513 $C_8H_{14}NaO_4S$ requires *MNa*, 229.0511.

(3*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-phenyl-[1,4]dioxan-2-one (8)

Triphenylphosphine hydrobromide (206 mg, 0.60 mmol) was added to a stirred solution of (*S*)-mandelic acid **5** (950 mg, 6.24 mmol) and 2,3-dimethoxy-1,3-butadiene **2** (857 mg, 7.51 mmol) in CH_2Cl_2 (20 ml) at rt. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (20 ml). The organic phase was washed with saturated aqueous $NaHCO_3$ (30 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc 19 : 1 then 9 : 1) to give the lactone as a white solid (847 mg, 51%); mp 118–119 °C; $[\alpha]_D^{28}$ −72.5 (c 0.91, $CHCl_3$); ν_{max} (film)/cm^{-1} 1734; δ_H (400 MHz, $CDCl_3$) 1.50 (3H, s, Me), 1.56 (3H, s, Me), 3.42 (3H, s, OMe), 3.45 (3H, s, OMe), 5.19 (1H, s, CH), 7.30–7.40 (3H, m, Ph), 7.56–7.59 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 17.0, 17.9, 49.3, 49.9, 73.6, 98.5, 105.2, 127.7, 128.4, 128.5, 136.0, 168.3; Found (ES): $[MNa]^+$ 289.1050, $C_{14}H_{18}O_5$ requires *MNa*, 289.1052.

(2*S*,5*S*,6*R*)-5,6-Dimethoxy-2,5,6-trimethyl-morpholin-3-one (9)

Triphenylphosphine hydrobromide (325 mg, 0.94 mmol) was added to a stirred solution of (*S*)-lactamide **6** (670 mg, 7.52 mmol) and 2,3-dimethoxy-1,3-butadiene **2** (1.03 g, 9.03 mmol) in CH_2Cl_2 (30 ml) at rt. After 48 h, the reaction mixture was diluted with CH_2Cl_2 (30 ml). The organic phase was washed with saturated aqueous $NaHCO_3$ (30 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2–acetone 9 : 1 then 4 : 1) to give a white solid (1.1 g, dr 9 : 1) which was recrystallised from hexane to give the pure lactam as white needles (777 mg, 51%); mp 117–118 °C (hexane); $[\alpha]_D^{25}$ −189.4 (c 1.035, $CHCl_3$); [Found (ES): MNa^+ 226.1060, $C_9H_{17}NO_4$ requires MNa, 226.1055]; ν_{max} (film)/cm^{-1} 1674, 1639; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, s, Me), 1.40 (3H, s, Me), 1.48 (3H, d, J 7.0, Me), 3.28 (6H, s, Me), 4.10 (1H, q, J 7.0, CH), 6.76 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 16.5, 17.7, 21.6, 49.0, 49.5, 68.1, 86.2, 99.7, 172.7.

2,3-Dibenzyloxy-1,3-butadiene (11)

Potassium *tert*-butoxide (12.5 g, 102 mmol) was added to a stirred solution of (*2S*, *3S*)-2,3-dibenzyloxy-1,4-ditosyloxy-butane (22.4 g, 36.7 mmol) in THF (350 ml).[20] The reaction mixture was heated to reflux for 30 min and then diluted with Et_2O (350 ml). The organic phase was washed with brine (350 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc 39 : 1 then 19 : 1) to give the diene as a white solid (9.14 g, 93%); mp 96 °C; ν_{max} (film)/cm^{-1} 1582; δ_H (400 MHz, $CDCl_3$) 4.32 (2H, d, J 1.2, 2 × C=C*H*H), 4.90 (4H, s, OCH_2), 4.92 (2H, d, J 1.2, 2 × C=CH*H*), 7.44–7.31 (10H, m, Ph); δ_C (100 MHz, $CDCl_3$) 69.7, 84.3, 127.3, 127.7, 128.4, 137.1, 155.3; Found (ES): $[M]^+$ 266.1305, $C_8H_{14}O_5$ requires *M*, 266.1307.

2,3-Diallyloxy-1,3-butadiene (12)

A solution of diethyl L-tartrate (13.5 ml, 78.8 mmol) in THF (100 ml) was added dropwise to a stirred suspension of sodium hydride (60% in mineral oil, 6.4 g, 160 mmol) in THF (205 ml) at 0 °C. After 1 h, tetrabutylammonium iodide (6.50 g, 17.6 mmol) and 18-crown-6 (300 mg, 1.13 mmol) were added in one portion. Allyl bromide (13.5 ml, 156 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 90 min at rt, quenched with HCl (3N) and diluted with Et_2O (300 ml). The organic phase was washed with water (300 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an oil (15.39 g). The crude product was used without further purification.

A solution of the previous diester in THF (20 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (4.00 g, 105 mmol) in THF (200 ml) at 0 °C and stirred overnight. The reaction was quenched by the dropwise addition of water (4 ml) then NaOH (3.75 M, 4 ml) and water (12 ml) at 0 °C. The reaction mixture was filtered through Celite and concentrated *in vacuo*. The crude diol was used without further purification.

Tosyl chloride (21.2 g, 111 mmol) was added in one portion to a stirred solution of the previous diol in anhydrous pyridine (100 ml) at −5 °C and stirred at rt for 24 h. The solvent was removed

in vacuo and the residue dissolved in CH_2Cl_2 (200 ml). The organic phase was washed with water (100 ml), HCl (1N, 100 ml) and brine (100 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc 8 : 2 then 7 : 3) to give a colourless oil (17.2 g, 43% over 3 steps).

Potassium *tert*-butoxide (11.94 g, 106.4 mmol) was added to a stirred solution of the ditosylate (17.2 g, 33.8 mmol) in THF (300 ml). The reaction mixture was heated to reflux for 30 min and then diluted with Et_2O (300 ml). The organic phase was washed with brine (300 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc 19 : 1) to give a the diene as a colourless oil (solid at −20 °C, 3.82 g, 68%); ν_{max} (film)/cm^{-1} 1650, 1585, 1199; δ_H (400 MHz, $CDCl_3$) 4.18 (2H, d, *J* 0.9, 2 × C=C*H*H), 4.33 (4H, d, *J* 5.2, 2 × OCH_2), 4.81 (2H, d, *J* 0.9, 2 × C=CH*H*), 5.23 (2H, dd, *J* 10.5, 1.3, 2 × HC=C*H*H), 5.37 (2H, dd, *J* 17.2, 1.3, 2 × HC=CH*H*), 6.01 (2H, ddt, *J* 17.2, 10.5, 5.2, 2 × *H*C=CH$_2$), δ_C (100 MHz, $CDCl_3$) 68.3, 83.7, 116.8, 133.1, 155.0; Found (ES): [M]$^+$ 166.0999 $C_{10}H_{14}O_2$ requires *M*, 166.0994.

5,6-Bis-benzyloxy-5,6-dimethyl-[1,4]dioxan-2-one (13)

Triphenylphosphine hydrobromide (103 mg, 0.30 mmol) was added to a stirred solution of glycolic acid **1** (125 mg, 1.64 mmol) and 2,3-dibenzyloxy-1,3-butadiene **11** (525 mg, 1.97 mmol) in CH_2Cl_2 (20 ml) at rt. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (20 ml). The organic phase was washed with saturated aqueous $NaHCO_3$ (20 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc 9 : 1 then 4 : 1) to give the lactone as a white solid (533 mg, 95%); mp 68 °C; ν_{max} (film)/cm^{-1} 1739; δ_H (400 MHz, $CDCl_3$) 1.58 (3H, s, Me), 1.69 (3H, s, Me), 4.20 (1H, d, *J* 17.6, COC*H*H), 4.35 (1H, d, *J* 17.6, COCH*H*), 4.67 (2H, s, PhCH_2), 4.74 (1H, d, *J* 11.6, PhC*H*H), 4.85 (1H, d, *J* 11.6, PhCH*H*), 7.25–7.40 (10H, m, Ph); δ_C (100 MHz, $CDCl_3$) 18.2, 19.1, 60.5, 63.6, 64.8, 98.0, 105.0, 126.8, 127.2, 127.6, 127.7, 128.46, 128.49, 137.4, 137.5, 167.3; Found (ES): [MNa]$^+$ 365.1382 $C_{20}H_{22}O_5$ requires *MNa*, 365.1365.

5,6-Bis-allyloxy-5,6-dimethyl-[1,4]dioxan-2-one (14)

Triphenylphosphine hydrobromide (110 mg, 0.32 mmol) was added to a stirred solution of glycolic acid **1** (120 mg, 1.57 mmol) and 2,3-diallyloxy-1,3-butadiene **12** (314 mg, 1.89 mmol) in CH_2Cl_2 (20 ml) at rt. After 3 h, the reaction mixture was diluted with CH_2Cl_2 (20 ml). The organic phase was washed with saturated aqueous $NaHCO_3$ (20 ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane–EtOAc 9 : 1) to give the lactone as a colourless oil (321 mg, 82%); ν_{max} (film)/cm^{-1} 1753, 1648; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, s, Me), 1.50 (3H, s, Me), 4.00–4.24 (6H, m, 2 × OCH_2, COCH_2), 5.04–5.10 (2H, m, 2 × CH=C*H*H), 5.17–5.24 (2H, m, 2 × CH=CH*H*), 5.75–5.87 (2H, m, 2 × C*H*=CH$_2$); δ_C (100 MHz, $CDCl_3$) 17.7, 18.6, 60.1, 62.1, 63.5, 97.5, 104.6, 115.8, 116.4, 133.6, 133.8, 167.1; Found (ES): [MNa]$^+$ 265.1033 $C_{12}H_{18}O_5$ requires *MNa*, 265.1052.

(2*S*,3*S*)-5-Bromomethyl-2,3-dimethoxy-2,3-dimethyl-[1,4]dioxane (97% ee) (18)

Butanedione (12.2 ml, 139 mmol), trimethylorthoformate (30.5 ml, 279 mmol) and (±)-camphor sulfonic acid (2.93 g, 12.6 mmol) were added to a solution of bromopropanediol **17** (19.6 g, 127 mmol) in MeOH (63 ml) and heated under reflux for 2 h. The reaction was quenched at rt with triethylamine (1.9 ml, 14 mmol) and diluted with Et_2O (250 ml). The organic solution was washed with water (2 × 250 ml), saturated aqueous $NaHCO_3$ (100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield the bromide as a pale yellow oil which was purified by flash column chromatography (petrol–Et_2O 4 : 1) give a colourless oil (28.94 g, 85%, 97% ee); $[\alpha]_D^{25}$ +182.7 (*c* 1.29, $CHCl_3$); (Found: C, 40.11; H, 6.35. Calc. for $C_9H_{17}BrO_4$: C, 40.16; H, 6.37); ν_{max} (film)/cm^{-1} 2951, 1447; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, Me), 1.31 (3H, s, Me), 3.22 (1H, dd, *J* 6.1, 10.5, CH_2Br), 3.26 (3H, s, OMe), 3.31 (3H, s, OMe), 3.31 (1 H, dd, *J* 6.7, 10.5, CH_2Br), 3.56 (1H, t, *J* 11.1, OCH$_2$), 3.63 (1H, dd, *J* 3.3, 11.1, OCH$_2$), 4.11 (1H, dddd, *J* 3.3, 6.1, 6.7, 11.0, OCH); δ_C (100 MHz, $CDCl_3$) 17.4, 17.7, 30.2, 48.1, 48.1, 62.1, 67.4, 98.0, 99.9; Found (ES): [MNa]$^+$ 291.0215 $C_9H_{17}BrO_4$ requires *MNa*, 291.0208.

(2*S*,3*S*)-2,3-Dimethoxy-2,3-dimethyl-5-methylene-[1,4]dioxane (19)

Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 56 ml, 28 mmol) was added dropwise to a solution of bromide **18** (7.1 g, 26.5 mmol) in THF (70 ml) at 0 °C. The solution was allowed to warm to rt over 30 min and stirred for a further 12 h. The reaction was diluted with Et_2O (200 ml) and H_2O (200 ml). The organic layer was washed with water (200 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield the enol ether as a pale yellow oil which was used without further purification. The enol ether could be purified by column chromatography (petrol–Et_2O 10 : 1) to give a colourless liquid (4.22 g, 85%); $[\alpha]_D^{25}$ +189.2 (*c* 2.55, $CHCl_3$); (Found: C, 57.16; H, 8.62. Calc. for $C_9H_{16}O_4$: C, 57.43; H, 8.57); ν_{max} (film)/cm^{-1} 2948, 1660, 1462; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, Me), 1.39 (3H, s, Me), 3.32 (3H, s, OMe), 3.37 (3H, s, OMe), 3.99 (1H, d, *J* 13.3, OCH$_2$), 4.29 (1H, d, *J* 13.3, OCH$_2$), 4.29 (1H, s, CH$_2$), 4.48 (1H, s, CH$_2$); δ_C (100 MHz, $CDCl_3$) 17.5, 17.6, 48.3, 48.5, 59.9, 93.2, 98.2, 101.2, 152.6; Found (ES): [MNa]$^+$ 188.10453 $C_9H_{16}O_4$ requires *MNa*, 188.10486.

(2*S*,3*S*)-5-Chloromethyl-2,3-dimethoxy-2,3-dimethyl-[1,4]dioxane (21)

Butanedione (27.4 ml, 312 mmol), trimethylorthoformate (65 ml, 592 mmol) and (±)-camphor sulfonic acid (6.5 g, 28.0 mmol) were added to a solution of chloropropanediol **20** (31.1 g, 280 mmol) in MeOH (156 ml) and heated under reflux for 90 min. The reaction was quenched at rt with triethylamine (4.3 ml, 30.8 mmol). The solution was then poured onto saturated $NaHCO_3$–H_2O (1 : 1, 400 ml) and extracted with Et_2O (3 × 400 ml). The combined organic extracts were washed with brine (500 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield the chloride as a pale yellow oil which was used without further purification. The BDA-protected chloride could be purified by flash column chromatography (petrol–Et_2O 10 : 1) to give a colourless oil; $[\alpha]_D^{25}$ −204.1 (*c* 2.03, $CHCl_3$); (Found: C, 47.93; H, 7.65. Calc. for $C_9H_{17}ClO_4$: C, 48.11; H, 7.63); ν_{max} (film)/cm^{-1} 2951, 1374; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, Me), 1.30 (3H, s, Me), 3.26 (3H, s, OMe), 3.30 (3H, s, OMe), 3.39 (1 H, dd, *J* 6.2, 11.3, CH$_2$Cl), 3.49 (1H, dd, *J* 6.2, 11.3, CH$_2$Cl), 3.63–3.58 (2H, m, OCH$_2$), 4.08 (1H, m, OCH); δ_C (100 MHz, $CDCl_3$) 17.6, 42.9, 47.9, 47.9, 61.4, 67.4, 98.0, 99.3; Found (ES): [MNa]$^+$ 247.0704 $C_9H_{17}ClO_4$ requires *MNa*, 247.0713.

(2*S*,3*S*)-2,3-Dimethoxy-2,3-dimethyl-5-methylene-[1,4]dioxane (96% ee) (19) and (2*S*,3*S*)-2,3-dimethoxy-2,3,5-trimethyl-2,3-dihydro-[1,4]dioxine (22)

Fresh potassium *tert*-butoxide (60.8 g, 542 mmol) was added to a solution of crude chloride **21** (assume 280 mmol) in THF (570 ml) and heated under reflux for 80 min. The reaction mixture was cooled and poured onto H_2O (300 ml) and extracted with Et_2O (3 × 450 ml). The combined organic extracts were washed with brine (450 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield the enol ether as a pale yellow oil which was used without further purification. The BDA-protected enol ether mixture could be purified by flash column chromatography (petrol–Et_2O 10 : 1) to give the enol ethers as a colourless oil;

22: δ_H (400 MHz, $CDCl_3$) 1.42 (3H, s, Me), 1.46 (3H, s, Me), 1.72 (3H, br d, *J* 1.5, allylic Me), 3.28 (3H, s, OMe), 3.31 (3H, s, OMe), 5.67 (1H, br q, *J* 1.5, C*H*=C).

(5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (>99% ee) (15)

A solution of the crude enol ether mixture (**19** and **22**) (assumed to be 280 mmol) in CH_2Cl_2 (240 ml) and acetone (60 ml) was degassed by passing a stream of oxygen through it for 5 min at −78 °C. Ozone was passed through the reaction to form a saturated solution (4 h, permanent blue colour). Oxygen was then passed through the solution (the blue colour disappeared) and methyl sulfide (24.75 ml, 336.4 mmol) and pyridine (10.2 ml, 126 mmol) were added. The solution was allowed to warm to rt overnight. The solution was concentrated *in vacuo* to yield the lactone as a yellow oil which was purified by flash column chromatography (petrol–Et_2O–Et_3N 80 : 20 : 1) to give the lactone as a white crystalline solid (32.4 g, 61%). The product was recrystallised [Et_2O–petrol (1 : 5, 192 ml), −20 °C] to provide material with >99% ee before further use;[21] mp 44 °C (from Et_2O); $[\alpha]_D^{25}$ +213.3 (*c* 0.83, $CHCl_3$); (Found: C, 50.54; H, 7.42. Calc. for $C_8H_{14}O_5$: C, 50.52; H, 7.42); ν_{max} (film)/cm^{-1} 2954, 1754; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, s, Me), 1.49 (3H, s, Me), 3.30 (3H, s, OMe), 3.43 (3H, s, OMe), 4.14 (1H, d, *J* 17.6, CH_2), 4.28 (1H, d, *J* 17.6, CH_2); δ_C (100 MHz, $CDCl_3$) 16.9, 17.8, 49.1, 50.3, 60.3, 97.8, 105.0, 167.5; Found (ES): $[MNa]^+$ 213.07380 $C_8H_{14}O_5$ requires *MNa*, 213.07380.

(5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (>99% ee) (16)

The *R*,*R*-glycolate **16** was prepared in the same manner as **15** starting from the (2*R*,3*R*)-halopropane 1,2-diol precursor; $[\alpha]_D^{25}$ −212.1 (*c* 1.07, $CHCl_3$).

(3*S*,5*R*,6*R*)-5,6-Dimethoxy-3,5,6-trimethyl-[1,4]dioxan-2-one (23) and (3*R*,5*R*,6*R*)-5,6-dimethoxy-3,5,6-trimethyl-[1,4]dioxan-2-one (24)

Lithium bis(trimethylsilyl)amide (1 M in THF; 0.95 ml) was added to a stirred solution of glycolate **15** (194 mg, 1.02 mmol) in THF (2 ml) at −78 °C. After 15 min, methyl iodide (0.187 ml, 3.00 mmol) was added, the resulting solution stirred at −78 °C for 90 min and then warmed to −30 °C. The reaction was quenched at −30 °C with acetic acid (0.115 ml, 2.01 mmol), Et_2O was added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified by flash column chromatography (Et_2O–petrol 1 : 6 eluting to 1 : 2) to give the lactone as a colourless oil (190 mg, 93%, 8 : 1 dr); $[\alpha]_D^{25}$ −182.4 (*c* 1.955, $CHCl_3$); ν_{max} (film)/cm^{-1} 2997, 2950, 2841, 1750; **23**: δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, Me), 1.49 (3H, s, Me), 1.51 (3H, d, *J* 7.0, *Me*CH), 3.32 (3H, s, OMe), 3.44 (3H, s, OMe), 4.27 (1H, q, *J* 7.0, MeC*H*); δ_C (100 MHz, $CDCl_3$) 16.9, 17.6, 18.3, 48.8, 49.9, 66.8, 97.9, 104.8, 170.5; **24**: δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, Me), 1.47 (3H, d, *J* 7.0, *Me*CH), 1.52 (3H, s, Me), 3.32 (3H, s, OMe), 3.45 (3H, s, OMe), 4.45 (1H, q, *J* 7.0, MeC*H*); Found (ES): $[MNa]^+$ 227.0890 $C_9H_{16}O_5$ requires *MNa*, 227.0895.

(3*S*,5*R*,6*R*)-5,6-Dimethoxy-3-(2-methoxy-ethoxymethyl)-5,6-dimethyl-[1,4]dioxan-2-one (34)

Lithium bis(trimethylsilyl)amide (1 M in THF, 0.50 ml, 0.50 mmol) was added to a stirred solution of glycolate **16** (100 mg, 0.53 mmol) in THF (1 ml) at −78 °C. After 15 min, 2-methoxyethoxymethyl chloride **25** (0.178 ml, 1.56 mmol) was added, the resulting solution stirred at −78 °C for 1 h and then warmed to −30 °C. The reaction was quenched at −30 °C with acetic acid (0.060 ml, 1.1 mmol), Et_2O was added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified by flash column chromatography (Et_2O–petrol 1 : 1) to give the lactone as a colourless oil (93.1 mg, 64%, 10 : 1 dr); $[\alpha]_D^{25}$ −97.6 (*c* 1.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2886, 2840, 1747, 1456; δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, Me), 1.46 (3H, s, Me), 3.30 (3H, s, OMe), 3.34 (3H, s, CH_2OMe), 3.39 (3H, s, OMe), 3.51–3.54 (2H, m, $MeOCH_2CH_2$), 3.63–3.75 (2H, m, $MeOCH_2$), 3.87 (1H, dd, *J* 11.0, 3.0, CHC*H*HOR), 3.92 (1H, dd, *J* 11.0, 5.5, CHCH*H*OR), 4.31 (1H, dd, *J* 5.5, 3.0, axial H); δ_C (100 MHz, $CDCl_3$) 17.0, 17.9, 49.1, 50.0, 58.9, 71.1, 71.5, 71.8, 98.3, 105.0, 167.8; Found (ES): $[MNa]^+$ 301.1256 $C_{12}H_{22}O_7$ requires *MNa*, 301.1263.

(3*R*,5*S*,6*S*)-3-Cyanomethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (35)

Lithium bis(trimethylsilyl)amide (1 M in THF, 0.55 ml, 0.55 mmol) was added to a stirred solution of glycolate **16** (109 mg, 0.57 mmol) in THF (1.1 ml) at −78 °C. After 15 min, bromoacetonitrile **26** (0.119 ml, 1.71 mmol) was added, the resulting solution stirred at 78 °C for 1 h and then warmed to −30 °C. The reaction was quenched at −30 °C with acetic acid (0.065 ml, 1.14 mmol), Et_2O was added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified by flash column chromatography (Et_2O–petrol 1 : 3 eluting to 1 : 2) to give the lactone as a white solid (110.9 mg, 85%, 10 : 1 dr). A small sample was recrystallised (Et_2O–petrol) to give a diastereomerically pure sample for analysis; mp 86–87 °C (from Et_2O–petrol); $[\alpha]_D^{25}$ +174.7 (*c* 0.27, $CHCl_3$); ν_{max} (film)/cm^{-1} 2953, 2842, 1747, 1458; δ_H (400 MHz, $CDCl_3$) 1.42 (3H, s, Me), 1.49 (3H, s, Me), 2.90–2.91 (2H, m, CH_2CN), 3.33 (3H, s, OMe), 3.43 (3H, s, OMe), 4.36 (1H, dd, *J* 6.5, 5.1, CH); δ_C (100 MHz, $CDCl_3$) 17.0, 17.5, 21.8, 49.3, 50.2, 66.7, 98.8, 105.9, 116.0, 167.2; Found (ES): $[MNa]^+$ 252.0847 $C_{10}H_{15}O_5N$ requires *MNa*, 252.0848.

(3*R*,5*S*,6*S*)-3-Ethyl-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (36)

Lithium bis(trimethylsilyl)amide (1 M in THF, 0.95 ml, 0.95 mmol) was added to a stirred solution of glycolate **16** (190 mg, 1.00 mmol) in THF (2 ml) at −78 °C. After 15 min, ethyl iodide **27** (0.240 ml, 3.00 mmol) was added, the resulting solution stirred at −78 °C for 1 h and then warmed to −30 °C. The reaction was quenched at −30 °C with acetic acid (0.114 ml, 1.99 mmol), Et_2O was added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified by flash column chromatography (Et_2O–petrol 1 : 8 eluting to 1 : 6) to give the lactone as a colourless oil (132.3 mg, 61%, 14 : 1 mixture of diastereoisomers); $[\alpha]_D^{25}$ +196.8 (*c* 1.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2953, 2880, 2840, 1747, 1460; δ_H (400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.4, CH_2CH_3), 1.36 (3H, s, Me), 1.44 (3H, s, Me), 1.89–1.91 (2H, m, CH_2CH_3), 3.27 (3H, s, OMe), 3.37 (3H, s, OMe), 4.08 (1H, t, *J* 5.6, CH); δ_C (100 MHz, $CDCl_3$) 9.4, 17.0, 17.8, 25.9, 48.9, 49.8, 71.5, 97.7, 104.8, 170.0; Found (ES): $[MNa]^+$ 241.1044 $C_{10}H_{18}O_5$ requires *MNa*, 241.1052.

tert-Butyl-[(2*R*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-3-oxo-[1,4]dioxan-2-yl]-acetate (37)

Lithium bis(trimethylsilyl)amide (1 M in THF, 1.0 ml, 1.0 mmol) was added to a stirred solution of glycolate **16** (200 mg, 1.05 mmol) in THF (2.1 ml) at −78 °C. After 15 min, *tert*-butyl bromoacetate **28** (0.509 ml, 3.45 mmol) was added, the resulting solution stirred at −78 °C for 1 h and then warmed to −30 °C. The reaction was quenched at −30 °C with acetic acid (0.120 ml, 2.10 mmol), Et_2O was added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified by flash column chromatography (Et_2O–petrol 1 : 6 eluting to 1 : 4) to give the lactone as a white solid (293.9 mg; 92%); mp 72–73 °C (from Et_2O); $[\alpha]_D^{25}$ +152.4 (*c* 1.09, $CHCl_3$); ν_{max} (film)/cm^{-1} 2978, 2840, 1732 (br), 1457, 1432; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, Me), 1.45 (9H, s, tBu), 1.47 (3H, s, Me), 2.68

(1H, dd, *J* 16.1, 9.2, CHH), 2.88 (1H, dd, *J* 16.1, 3.5, CHH), 3.34 (3H, s, OMe), 3.42 (3H, s, OMe), 4.59 (1H, dd, *J* 9.2, 3.5, CH); δ_C (100 MHz, $CDCl_3$) 16.9, 17.7, 28.0, 38.6, 49.0, 50.0, 67.3, 81.1, 98.2, 105.4, 169.0, 169.2; Found (ES): [MNa]+ 327.1403 $C1_4H_{24}O_7$ requires *MNa*, 327.1420.

(3*R*,5*S*,6*S*)-3-Butyl-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (38)

Lithium bis(trimethylsilyl)amide (1 M in THF, 0.52 ml, 0.52 mmol) was added to a stirred solution of glycolate **16** (104 mg, 0.55 mmol) in THF (1.1 ml) at −78 °C. After 15 min, *n*-butyl iodide **29** (0.186 ml, 1.63 mmol) was added and the solution stirred at −78 °C for 1 h and then warmed to −20 °C for 2.5 h. The reaction was quenched at −20 °C with acetic acid (0.063 ml, 1.10 mmol), Et_2O was added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified by flash column chromatography (Et_2O–petrol 1 : 8) to give the lactone as a colourless oil (76.6 mg, 57%, 28 : 1 mixture of diastereoisomers); $[\alpha]_D^{25}$ +177.6 (*c* 1.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 2955, 2874, 1749, 1461; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.2, CH_2CH_3), 1.29–1.50 (4H, m, $CH_2CH_2CH_3$), 1.37 (3H, s, Me), 1.46 (3H, s, Me), 1.82–1.88 (2H, m, $CHCH_2$), 3.28 (3H, s, OMe), 3.39 (3H, s, OMe), 4.12 (1H, t, *J* 5.9, CH); δ_C (100 MHz, $CDCl_3$) 13.9, 17.0, 17.8, 22.3, 27.2, 32.4, 48.9, 49.8, 70.5, 97.9, 104.8, 170.3; Found (ES): $[MNa]^+$ 269.1373 $C_{12}H_{22}O_5$ requires *MNa*, 269.1365.

(3*R*,5*S*,6*S*)-3-Allyl-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (39)

Lithium bis(trimethylsilyl)amide (1 M in THF, 5.6 ml, 5.6 mmol) was added to a stirred solution of glycolate **16** (1.13 g, 5.9 mmol) in THF (15 ml) at −78 °C. After 15 min, allyl bromide **30** (1.6 ml, 17.8 mmol) was added, the resulting solution stirred at −78 °C for 1 h and then transferred to a large dry ice–MeCN bath at −50 °C, which was allowed to warm up slowly to rt overnight. The reaction was quenched with acetic acid (0.428 ml, 7.13 mmol), Et_2O was added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified by flash column chromatography (Et_2O–petrol 1 : 4) to give the lactone as a white solid (1.06 g, 4.61 mmol, 82%); mp 57–58 °C (from Et_2O); $[\alpha]_D^{25}$ +177.5 (*c* 0.65, $CHCl_3$); ν_{max} (film)/cm^{-1} 2965, 2884, 2840, 1740, 1640, 1452, 1439; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, s, Me), 1.45 (3H, s, Me), 2.58–2.70 (2H, m, CH_2), 3.30 (3H, s, OMe), 3.39 (3H, s, OMe), 4.21 (1H, dd, *J* 6.1, 5.0, $CHCH_2$), 5.09 (1H, d, *J* 9.5, CH=C*H*H), 5.15 (1H, d, *J* 17.2, CH=CH*H*), 5.91 (1H, m, C*H*=CHH); δ_C (100 MHz, $CDCl_3$) 17.0, 17.9, 36.8, 49.0, 49.9, 70.6, 98.2, 105.0, 117.7, 133.2, 169.5; Found (ES): $[MNa]^+$ 253.1060 $C_{11}H_{18}O_5$ requires *MNa*, 253.1052.

(3*R*,5*S*,6*S*)-3-Benzyl-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (40)

Lithium bis(trimethylsilyl)amide (1 M in THF, 0.95 ml, 0.95 mmol) was added to a stirred solution of glycolate **16** (192 mg, 1.01 mmol) in THF (2 ml) at −78 °C. After 15 min, benzyl bromide **31** (0.357 ml, 3.00 mmol) was added, the resulting solution stirred at −78 °C for 1 h and then warmed to −40 °C. The reaction was quenched at −40 °C with acetic acid (0.115 ml, 2.00 mmol), Et_2O was added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified by flash column chromatography (Et_2O–petrol 1 : 8 eluting to 1 : 7) to give the lactone as a colourless oil which crystallised to give white needles (269 mg, 96%) on prolonged storage in the freezer; mp 71 °C (from Et_2O); $[\alpha]_D^{25}$ +180.9 (*c* 0.69, $CHCl_3$); ν_{max} (film)/cm^{-1} 2952, 2880, 2839, 1748, 1458, 1433; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, s, Me), 1.42 (3H, s, Me), 3.11 (3H, s, OMe), 3.16 (1H, dd, *J* 14.3, 6.5, C*H*HPh), 3.19 (1H, dd, *J* 14.3, 4.4, CH*H*Ph), 3.24 (3H, s, OMe), 4.39 (1H, dd, *J* 6.5, 4.4, CH), 7.22–7.23 (1H, m, Ph), 7.26–7.30 (4H, m, Ph); δ_C (400 MHz, $CDCl_3$) 16.9, 17.8, 38.4, 49.0, 49.6, 71.5, 98.2, 105.0, 126.5, 128.0, 130.0, 137.0, 169.5; Found (ES): $[MNa]^+$ 303.1195 $C_{15}H_{20}O_5$ requires *MNa*, 303.1208.

(3*R*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-3-naphthalen-1-ylmethyl-[1,4]dioxan-2-one (41)

Lithium bis(trimethylsilyl)amide (1 M in THF, 0.95 ml, 0.95 mmol) was added to a stirred solution of glycolate **16** (190 mg, 1.00 mmol) in THF (2 ml) at −78 °C. After 15 min, 2-(bromomethyl)naphthalene **32** (668 mg, 3.02 mmol) was added, the resulting solution stirred at −78 °C for 1 h and then warmed to −30 °C for 1 h. The reaction was quenched at −30 °C with acetic acid (0.115 ml, 2.00 mmol), Et_2O was added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified by flash column chromatography (Et_2O–petrol 1 : 8 eluting to 1 : 6) to give the lactone as a white solid (279 mg, 84%, >99 : 1 dr); mp 77 °C (from Et_2O); $[\alpha]_D^{25}$ +157.0 (*c* 0.88, $CHCl_3$); ν_{max} (film)/cm^{-1} 3056, 2999, 2950, 2838, 1745, 1634, 1602, 1508, 1460, 1432; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, s, Me), 1.41 (3H, s, Me), 2.97 (3H, s, OMe), 3.23 (3H, s, OMe), 3.35 (1H, dd, *J* 13.9, 6.9, C*H*HAr), 3.36 (1H, dd, *J* 13.9, 4.1, CH*H*Ar), 4.49 (1H, dd, *J* 6.9, 4.1, CH), 7.41–7.46 (3H, m, Ar), 7.75 (1H, s, Ar), 7.75–7.82 (3H, m, Ar); δ_C (100 MHz, $CDCl_3$) 16.9, 17.8, 38.6, 49.0, 49.5, 71.6, 98.3, 105.0, 125.4, 125.4, 127.5, 127.5, 127.7, 128.5, 128.5, 132.4, 133.4, 134.6, 169.6; Found (ES): $[MNa]^+$ 353.1349 $C_{19}H_{22}O_5$ requires *MNa*, 353.1365.

(3*S*,4*R*,5*R*)-3-(3-Iodo-propyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxin-2-one (42)

Lithium bis(trimethylsilyl)amide (1 M in THF, 1.1 ml, 1.1 mmol) was added to a stirred solution of glycolate **15** (217 mg, 1.14 mmol) in THF (3.7 ml) at −78 °C. After 15 min, 1,3-diiodopropane **33** (0.40 ml, 3.4 mmol) was added, the resulting solution stirred at −60 °C for 23 h. The reaction was quenched at −60 °C with acetic acid (0.115 ml, 2.00 mmol), Et_2O added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified by flash column chromatography (Et_2O–petrol 1 : 9) to give the *lactone* as a white solid (254 mg, 62%, 24 : 1 mixture of diastereoisomers); mp 60 °C (from Et_2O); $[\alpha]_D^{25}$ −82.1 (*c* 1.01, $CHCl_3$); ν_{max} (film)/cm^{-1} 2946, 1748, 1454; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, Me), 1.47 (3H, s, Me), 1.95–1.99 (3H, m, CH_2 and CH*H*), 2.06 (1H, t, *J* 7.1, C*H*H), 3.19–3.22 (2H, m, CH_2I), 3.29 (3H, s, OMe), 3.42 (3H, s, OMe), 4.18 (1H, t, *J* 5.4, C*H*); δ_C (100 MHz, $CDCl_3$) 5.5, 17.0, 17.8, 29.4, 33.5, 49.1, 50.0, 69.8, 98.1, 105.0, 169.7; Found (ESI): $[MNa]^+$ 381.0182 $C_{11}H_{19}IO_5$ requires *MNa*, 381.0175.

(3*R*,5*S*,6*S*)-3-Benzyl-5,6-dimethoxy-3,5,6-trimethyl-[1,4]dioxan-2-one (43)

Lithium bis(trimethylsilyl)amide (1 M in THF, 0.15 ml, 0.15 mmol) was added to a stirred solution of benzyl glycolate **40** (32.2 mg, 0.115 mmol) in THF (0.23 ml) at −78 °C. After 30 min, methyl iodide (0.039 ml, 0.63 mmol) was added, the resulting solution stirred at −78 °C for 1 h and then warmed to rt overnight. The reaction was quenched with acetic acid (0.024 ml, 0.42 mmol), Et_2O was added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified by flash column chromatography (EtOAc–petrol 1 : 8) to give the mixture of lactones as a white solid (27.6 mg, 82%). A pure sample of the major isomer was obtained for characterization by further chromatographic purification; mp 94–96 °C (from Et_2O); $[\alpha]_D^{25}$ +51.5 (*c* 0.36, $CHCl_3$); ν_{max} (film)/cm^{-1} 2945, 1744, 1497, 1455; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, Me), 1.45 (3H, s, Me), 1.54 (3H, s, Me), 3.15 (1H, d, *J* 14.5, C*H*HPh), 3.27 (1H, d, *J* 14.5, CH*H*Ph), 3.44 (6H, s, 2 × OMe), 7.28 (3H, m, Ph), 7.37 (2H, d, *J* 7.3, Ph); δ_C (100 MHz, $CDCl_3$)

17.7, 18.2, 25.1, 44.2, 49.7, 50.1, 76.3, 97.9, 105.3, 126.6, 128.1, 130.8, 136.3, 173.2; Found (ES): $[MNa]^+$ 317.1371 $C_{16}H_{22}O_5$ requires *MNa*, 317.1365.

(3*S*,5*S*,6*S*)-3-Benzyl-5,6-dimethoxy-3,5,6-trimethyl-[1,4] dioxan-2-one (44)

Lithium bis(trimethylsilyl)amide (1 M in THF, 0.60 ml, 0.60 mmol) was added to a stirred solution of methyl glycolates **23** and **24** (117 mg, 0.57 mmol, 7.7 : 1 **23** : **24**) in THF (1.15 ml) at −78 °C. After 30 min, benzyl bromide (0.203 ml, 1.71 mmol) was added, the resulting solution stirred at −78 °C for 1 h and then warmed to −40 °C over 2.5 h and to between −30 °C and −20 °C for a further 1 h. The reaction was quenched with acetic acid (0.065 ml, 1.14 mmol), Et_2O was added and the precipitated salts removed by filtration through a plug of silica. The crude product was purified by flash column chromatography (Et_2O–petrol 1 : 8) to give the lactone as a white crystalline solid (156.7 mg, 93%); mp 47–49 °C (from Et_2O); $[\alpha]_D^{25}$ +169.0 (*c* 1.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 2998, 2838, 1743, 1496, 1455; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, Me), 1.41 (3H, s, Me), 1.49 (3H, s, Me), 2.86 (1H, d, *J* 13.2, C*H*HPh), 3.24 (3H, s, OMe), 3.25 (1H, d, *J* 13.2, CH*H*Ph), 3.25 (3H, s, OMe) 7.23–7.27 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 17.5, 18.0, 25.4, 46.1, 49.2, 49.4, 76.2, 98.5, 105.5, 126.6, 127.6, 131.4, 135.9, 173.0; Found (ES): $[MNa]^+$ 317.1341 $C_{16}H_{22}O_5$ requires *MNa*, 317.1365.

Diisopropyl (*R*)-2-hydroxy-succinate (45)

tert-Butoxycarbonyl glycolate **37** (56.6 mg, 0.19 mmol) was dissolved in a 0.5 M solution of TMSCl in ^{i}PrOH (1.0 ml, 0.5 mmol) and heated to reflux at 80 °C for 45 h. The reaction was diluted with saturated aqueous $NaHCO_3$ (5 ml), the aqueous layer extracted with CH_2Cl_2 (5 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the ester as a colourless oil (31.2 mg, 77%); $[\alpha]_D^{32}$ +10.0 (*c* 3.12, $CHCl_3$) [(lit. $[\alpha]_D^{20}$ +11.0 (*c* 3.21, $CHCl_3$))][13]; δ_H (400 MHz, $CDCl_3$) 1.23 (6H, d, *J* 6.3, 2 × Me), 1.26 (3H, d, *J* 6.3, Me), 1.27 (3H, d, *J* 4.0, Me), 2.74 (1H, dd, *J* 16.2, 5.9, C*H*H), 2.76 (1H, dd, *J* 16.2, 4.6, CH*H*), 3.22 (1H, d, *J* 5.4, OH), 4.39–4.43 (1H, m, C*H*OH), 5.03 (1H, septet, *J* 6.3, ^{i}Pr-*CH*), 5.11 (1H, septet, *J* 6.3, ^{i}Pr-*CH*), δ_C (100 MHz, $CDCl_3$) 21.6, 21.7, 21.7, 21.7, 39.0, 67.4, 68.5, 69.8, 169.9, 173.0.

Methyl (*R*)-2-hydroxy-3-phenyl-propionate (46)

Benzyl glycolate **40** (63.0 mg, 0.225 mmol) was dissolved in a 0.5 M solution of TMSCl in MeOH (1.0 ml, 0.5 mmol) and stirred at rt for 10 min. The reaction was concentrated *in vacuo* and the residue purified by flash column chromatography (petrol–Et_2O 2 : 1) to give the ester as a white solid (40.7 mg, 100%); mp 44 °C (from Et_2O); $[\alpha]_D^{32}$ +6.4 (*c* 1.82, $CHCl_3$) [lit. $[\alpha]_D^{20}$ −7.6 (*c* 2.0, $CHCl_3$), *S* isomer][14]; ν_{max} (film)/cm^{-1} 3442, 3028, 2918, 2850, 1737, 1497, 1439; δ_H (400 MHz, $CDCl_3$) 2.71 (1H, d, *J* 6.1, OH), 2.97 (1H, dd, *J* 13.9, 6.8, C*H*H), 3.13 (1H, dd, *J* 13.9, 4.4, CH*H*), 3.77 (3H, s, OMe), 4.44–4.48 (1H, m, CH), 7.21–7.32 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 40.6, 52.4, 71.3, 126.9, 128.4, 129.4, 136.3, 174.5; Found (ES): $[M]^+$ 180.0796 $C_{10}H_{12}O_3$ requires *M*, 180.0786.

Methyl (*R*)-2-hydroxy-3-naphthalen-2-yl-propionate (47)

Napthyl methyl glycolate **41** (86.7 mg, 0.262 mmol) was dissolved in a 0.5 M solution of TMSCl in MeOH (1.0 ml, 0.5 mmol) and stirred at rt for 10 min. The reaction was concentrated *in vacuo* and the residue purified by flash column chromatography (petrol–Et_2O 2 : 1) to give the ester as a white solid (57.2 mg, 95%); mp 32 °C (from Et_2O); $[\alpha]_D^{25}$ +17.2 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3458, 3052, 2953, 1737, 1601, 1508, 1439; δ_H (400 MHz, $CDCl_3$) 2.87 (1H, d, *J* 5.9, OH), 3.14 (1H, dd, *J* 13.9, 6.9, C*H*H), 3.30 (1H, dd, *J* 13.9, 4.3, CH*H*), 3.78 (3H, s, OMe), 4.55 (1H, m, CH), 7.36 (1H, dd, *J* 8.4, 1.3, Ar), 7.44–7.49 (2H, m, Ar), 7.69 (1H, s, Ar), 7.79–7.83 (3H, m, Ph); δ_C (100 MHz, $CDCl_3$) 40.7, 52.4, 71.3, 125.5, 126.0, 127.6, 127.6, 127.6, 128.0, 128.1, 132.4, 133.4, 133.9, 174.5; Found (ES): $[MNa]^+$ 253.0837 $C_{14}H_{14}O_3$ requires *MNa*, 253.0841.

Methyl (*R*)-2-hydroxy-2-methyl-3-phenyl-propionate (48)

Dialkylated glycolate **44** (49.3 mg, 0.167 mmol) was dissolved in a 0.5 M solution of TMSCl in MeOH (1.5 ml, 0.75 mmol) and stirred at 50 °C for 8 h. The reaction was concentrated *in vacuo* and the residue purified by flash column chromatography (petrol–Et_2O 8 : 1) to give the ester as a white solid (28.4 mg, 87%); ν_{max} (film)/cm^{-1} 3511, 3030, 2953, 1732, 1603, 1496, 1452; δ_H (400 MHz, $CDCl_3$) 1.50 (3H, s, Me), 2.92 (1H, d, *J* 13.5, C*H*H), 3.03 (1H, br s, OH), 3.08 (1H, d, *J* 13.5, CH*H*), 3.73 (3H, s, OMe), 7.17 (2H, m, Ph), 7.26 (3H, m, Ph); δ_C (100 MHz, $CDCl_3$) 25.7, 46.5, 52.5, 74.7, 126.9, 128.2, 130.0, 135.9, 176.5; Found (ES): MNa^+ 217.0834 $C_{11}H_{14}O_3$ requires *MNa*, 217.0841.

(*R*)-2-Hydroxy-2-methyl-3-phenyl-propionic acid (49)

Dialkylated glycolate **44** (*R*,*R*-isomer) (40.0 mg, 0.136 mmol) was dissolved in a solution of TFA–H_2O (9 : 1, 2 ml) and stirred at rt for 45 min. NaOH (2.5 M, 2 ml) was added, the mixture stirred for 15 min, and then extracted with CH_2Cl_2 (10 ml). The aqueous layer was acidified with 3N HCl, extracted with EtOAc (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the acid as a white solid (20.8 mg, 85%); mp 120 °C (from EtOAc); $[\alpha]_D^{32}$ +12.8 (*c* 1.66, dioxane) [lit. $[\alpha]_D^{20}$ +13.2 (*c* 1.5, $CHCl_3$)];[15] ν_{max} (film)/cm^{-1} 3438, 3028, 2978, 2922, 2611, 1726, 1495, 1465, 1450; δ_H (400 MHz, $CDCl_3$) 1.54 (3H, s, Me), 2.95 (1H, d, *J* 13.6, C*H*H), 3.15 (1H, d, *J* 13.6, CH*H*), 7.23 (2H, m, Ph), 7.29 (3H, m, Ph); δ_C (100 MHz, $CDCl_3$) 25.7, 46.0, 75.1, 127.2, 128.4, 130.1, 135.3, 180.6; Found (ES): $[MNa]^+$ 203.0682 $C_{10}H_{12}O_3$ requires *MNa*, 203.0684.

(*S*)-2-Hydroxy-5-iodopentanoic acid methyl ester (50)

Iodopropane glycolate **42** (277 mg, 0.77 mmol) was dissolved in a 0.3 M solution of TMSCl in MeOH (15 ml, 4.5 mmol) and stirred at rt for 25 min. The reaction was concentrated *in vacuo* and the residue purified by flash column chromatography (petrol : Et_2O 9 : 1 then 1 : 9) to give the *ester* as a pale yellow oil (180 mg, 90%); $[\alpha]_D^{25}$ +5.2 (*c* 1.21, $CHCl_3$); ν_{max} (film)/cm^{-1} 3448, 2951, 1730, 1438; δ_H (400 MHz, $CDCl_3$) 1.73 (1H, q, *J* 8.5, C*H*H), 1.92–1.99 (3H, m, CH_2 and CH*H*), 2.60 (1H, br s, OH), 3.21 (2H, br s, CH_2I), 3.80 (3H, s, OMe), 4.20 (1H, d, *J* 5.2, CH); δ_C (100 MHz, $CDCl_3$)5.9, 28.9, 35.0, 52.7, 69.5, 175.2; Found (ESI): $[MNa]^+$ 280.9654, $C_6H_{11}O_3I$ requires *MNa*, 280.9651.

(*R*)-2-Hydroxy-pent-4-enoic acid allyl-methyl-amide (51)

Allyl glycolate **39** (68.4 mg, 0.30 mmol) was dissolved in allylamine (0.09 ml, 1.2 mmol) and stirred at rt for 120 h. A solution of TFA–H_2O (9 : 1, 3 ml) was added and the mixture stirred at rt for 15 min. The reaction was concentrated *in vacuo* and purified by column chromatography to give the *amide* as a pale brown oil (45.4 mg, 77%); $[\alpha]_D^{25}$ +54.8 (*c* 0.80, $CHCl_3$); ν_{max} (film)/cm^{-1} 3311, 3081, 2914, 1639, 1530, 1421; δ_H (400 MHz, $CDCl_3$) 2.36–2.44 (1H, m, C*H*H), 2.60–2.66 (1H, m, CH*H*), 3.64 (1H, br s, OH), 3.86–3.88 (2H, m, NCH_2), 4.15 (1H, dd, *J* 7.3, 3.9, CH), 5.10–5.19 (4H, m, 2 × CH_2), 5.74–5.85 (2H, m, 2 × CH), 6.90 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 39.1, 41.4, 70.9, 116.5, 119.1, 133.2, 133.7, 173.2; Found (ES): $[M]^+$ 155.0948, $C_8H_{13}NO_2$ requires *M*, 155.0946.

(*R*)-2-Hydroxy-pent-4-enoic acid benzylamide (52)

Allyl glycolate **39** (70.9 mg, 0.31 mmol) was dissolved in benzylamine (0.131 ml, 1.20 mmol) and stirred at rt for 120 h. A solution of TFA–H_2O (9 : 1, 3 ml) was added and the mixture stirred at rt for 15 min. The reaction was concentrated *in vacuo* to give the *amide* as a white solid (55.4 mg, 69%); mp 47–48 °C (from Et_2O); $[\alpha]_D^{25}$ +50.0 (*c* 0.29, $CHCl_3$); ν_{max} (film)/cm^{-1}

3385, 3299, 3063, 2918, 1628, 1529, 1495, 1454, 1432, 1419; δ_H (400 MHz, $CDCl_3$) 2.39–2.46 (1H, m, C*H*H), 2.63–2.70 (1H, m, CH*H*), 3.16 (1H, br s, OH), 4.16–4.18 (1H, m, C*H*OH), 4.38–4.48 (2H, m, PhCH_2), 5.17 (1H, d, *J* 15.7, CH=C*H*H), 5.17 (1H, d, *J* 11.5, CH=*CH*H), 5.75–5.85, (1H, m, *CH*=CH_2), 7.01 (1H, br s, NH), 7.24–7.34 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 39.2, 43.1, 70.9, 119.4, 127.5, 127.7, 128.7, 133.2, 137.9, 172.9; Found (ES): $[M]^+$ 205.1095, $C_{12}H_{15}NO_2$ requires *M*, 205.1103.

(*R*)-2-Hydroxy-pent-4-enoic acid benzyl-methyl-amide (53)

Allyl glycolate **39** (72.0 mg, 0.31 mmol) was dissolved in *N*-methylbenzylamine (0.155 ml, 1.20 mmol) and stirred at rt for 120 h. A solution of TFA–H_2O (9 : 1, 3 ml) was added and the mixture stirred at rt for 15 min. The reaction was concentrated *in vacuo* and purified by column chromatography to give the *amide* as a pale brown oil (58.0 mg, 66%); $[a]_D^{25}$ +21.8 (*c* 0.71, $CHCl_3$); ν_{max} (film)/cm^{-1} 3406, 2930, 1635, 1496, 1453; δ_H (500 MHz, DMSO, 120 °C) 2.30–2.36 (1H, m, C*H*H), 2.43–2.50 (1H, m, CH*H*), 2.93 (3H, s, NMe), 4.44 (1H, dd, *J* 6.8, 5.4, CH), 4.57 (1H, d, *J* 15.3, PhC*H*H), 4.60 (1H, d, *J* 15.3, PhCH*H*), 5.03 (1H, d, *J* 10.3, CH=C*H*H), 5.08 (1H, d, *J* 17.2, CH=CH*H*), 5.80–5.89 (1H, m, *CH*=CHH), 7.24–7.29 (3H, m, Ph), 7.33–7.36 (2H, m, Ph); δ_C (125 MHz, DMSO, 120 °C) 34.4, 39.1, 51.8, 68.6, 117.2, 127.5, 127.9, 128.8, 135.0, 138.0, 173.4; Found (ES): $[M]^+$ 219.1252, $C_{13}H_{17}NO_2$ requires *M*, 219.1259.

(*R*)-2-Hydroxy-pent-4-enoic acid isobutyl-amide (54)

Allyl glycolate **39** (72.7 mg, 0.32 mmol) was dissolved in isopropylamine (0.12 ml, 1.4 mmol) and stirred at rt for 120 h. A solution of TFA–H_2O (9 : 1, 3 ml) was added and the mixture stirred at rt for 15 min. The reaction was concentrated *in vacuo* and purified by column chromatography to give the *amide* as a pale brown oil (47.2 mg, 68%); $[a]_D^{25}$ +59.8 (*c* 0.44, $CHCl_3$); ν_{max} (film)/cm^{-1} 3311, 2960, 2873, 1643, 1537, 1468, 1436; δ_H (400 MHz, $CDCl_3$) 0.91 (6H, d, *J* 6.7, 2 × Me), 1.71–1.84 (1H, m, Me_2CH), 2.38–2.45 (1H, m, C*H*H), 2.62–2.68 (1H, m, CH*H*), 3.01–3.16 (2H, m, CH_2), 3.23 (1H, br s, OH), 4.13–4.15 (1H, m, CH), 5.18 (1H, d, *J* 11.6, CH=C*H*H), 5.19 (1H, d *J* 15.6, CH=CH*H*), 5.75–5.86 (1H, m, *CH*=CHH), 6.72 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 20.0, 28.5, 39.3, 46.4, 70.8, 119.4, 133.3; Found (ES): $[M]^+$ 171.1256, $C_9H_{17}NO_2$ requires *M*, 171.1259.

(*R*)-2-Hydroxy-1-pyrrolidin-1-yl-pent-4-en-1-one (55)

Allyl glycolate **39** (72.0 mg, 0.31 mmol) was dissolved in pyrrolidine (0.100 ml, 1.20 mmol) and stirred at rt for 120 h. A solution of TFA–H_2O (9 : 1, 3 ml) was added and the mixture stirred at rt for 15 min. The reaction was concentrated *in vacuo* and purified by column chromatography to give the *amide* as a pale brown oil (50.3 mg, 75%); $[a]_D^{25}$ +46.0 (*c* 0.25, $CHCl_3$); ν_{max} (film)/cm^{-1} 3392, 2974, 2879, 1623, 1455; δ_H (400 MHz, $CDCl_3$) 1.79–1.88 (2H, m, CH_2), 1.90–1.99 (2H, m, CH_2), 2.27–2.34 (1H, m, C*H*H), 2.35–2.43 (1H, m, CH*H*), 3.31–3.67 (1H, m, C*H*H), 3.40–3.49 (2H, m, CH_2), 3.51–3.57 (1H, m, CH*H*), 3.80 (1H, br s, OH), 4.26–4.28 (1H, m, C*H*OH), 5.08 (1H, d, *J* 9.5, CH=*CH*H), 5.09 (1H, d, *J* 19.0, CH=CH*H*), 5.78–5.89 (1H, m, CH); δ_C (100 MHz, $CDCl_3$) 23.8, 25.9, 38.8, 46.0, 46.2, 69.1, 117.8, 113.2, 172.2; Found (ES): $[M]^+$ 169.1097, $C_9H_{15}NO_2$ requires *M*, 169.1103.

(*R*)-2-((*S*)-1-Methoxy-1-methyl-2-oxo-propoxy)-1-morpholin-4-yl-pent-4-en-1-one (56)

Allyl glycolate **39** (27 mg, 0.12 mmol) was dissolved in morpholine (50 µl, 0.56 mmol) and stirred at rt for 48 h. The reaction was concentrated *in vacuo* to yield the *amide* as a colourless oil (35 mg, 100%); $[a]_D^{25}$ +46.7 (*c* 0.76, $CHCl_3$); ν_{max} (film)/cm^{-1} 2968, 1729, 1640; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, s, Me), 2.22 (3H, s, OCCH_3), 2.48 (2H, t, *J* 7.3, CH_2), 3.27 (3H, s, OMe), 3.55–3.71 (8H, m, 4 × CH_2), 4.44 (1H, t, *J* 7.3, CH), 5.07–5.16 (2H, m CH=CH_2), 5.74 (1H, dddd, *J* 7.3, 9.9, 10.2, 14.3, C*H*=CH_2); δ_C (100 MHz, $CDCl_3$) 20.1, 26.1, 38.5, 42.4, 46.0, 50.5, 66.43, 66.9, 71.6, 102.8, 118.6, 132.8, 169.7, 206.0; Found (ES): $[MNa]^+$ 308.1495, $C_{14}H_{23}NO_5$ requires *MNa*, 308.1474.

(*R*)-2-((*S*)-1-Methoxy-1-methyl-2-oxo-propoxy)-pent-4-enoic acid methoxy-methyl-amide (57)

Allyl glycolate **39** (148 mg, 0.64 mmol) was dissolved in THF (1 ml) and cooled to 0 °C. *N*,*O*-Dimethylhydroxylamine hydrochloride (643 mg, 6.43 mmol) was added in one portion followed by dropwise addition of ^{i}PrMgCl (2.0M solution in THF, 6.23 ml, 12.5 mmol) over 1 h using a syringe pump. The resulting suspension was stirred for 5 h and warmed to rt. Phosphate buffer (pH 7, 1 ml) and EtOAc (2 ml) were added and the suspension stirred overnight at rt. The suspension was added to H_2O (10 ml) and then extracted with EtOAc (3 × 15 ml). The combined organic layers were washed with brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (Et_2O : petrol 1 : 1 then 1 : 2) to give the *amide* as a colourless oil (111 mg, 67%); $[a]_D^{25}$ +29.0 (*c* 1.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2944, 1729, 1673; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, Me), 2.23 (3H, s, CO*Me*), 2.40–2.47 (2H, m, CH_2), 3.15 (3H, br s, NMe), 3.21 (3H, s, OMe), 3.69 (3H, s, NOMe), 4.65 (1H, m, CH), 5.02–5.13 (2H, m CH=CH_2), 5.77 (1H, dddd, *J* 7.0, 9.9, 10.2, 14.3, *CH*=CH_2); δ_C (125 MHz with CryoProbe, $CDCl_3$) 20.2, 26.0, 37.8, 50.9, 61.2, 67.9, 102.8, 118.1, 133.4, 172.6, 206.3; Found (ES): $[MNa]^+$ 282.1303, $C_{12}H_{21}NO_5$ requires *MNa*, 282.1317.

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