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Studies on the generation of enolate anions from butane-2,3-diacetal protected glycolic acid derivatives and subsequent highly diastereoselective coupling reactions with aldehydes and acid chlorides

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Received 19th August 2004, Accepted 29th September 2004
First published as an Advance Article on the web 17th November 2004

Highly diastereoselective coupling reactions of enolates derived from butane-2,3-diacetal protected glycolic acids **1** and **2** and their alkylated derivatives with aldehydes are reported together with their efficient acid-catalysed deprotection to yield enantiopure *anti*-2,3-dihydroxyesters. A procedure to provide the corresponding *syn*-2,3-dihydroxyesters is also described in two cases, proceeding *via* an acylation–reduction sequence. An usual double addition reaction of butane-2,3-diacetal protected glycolic acid to small aliphatic acid chlorides provides a synthetically useful, densely-functionalised lactone after acidic deprotection.

Introduction

The importance of the aldol reaction in organic synthesis is well recognised owing to the fact that up to two stereogenic centres are created in a single carbon–carbon bond forming event.[1] For this reason, the reaction is commonly used in natural product synthesis programmes. Similarly, the α-hydroxy acid motif occurs frequently in many biologically significant molecules and correspondingly has engendered considerable synthetic attention.[2,3]

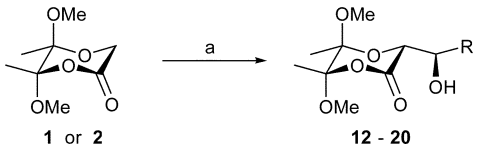
In a preceding paper[4] and in earlier communications[5–7] we described the excellent levels of stereochemical control resulting from reactions of the lithium enolate derived from the desymmetrised butane-2,3-diacetal (BDA) of glycolic acid **1** or its enantiomer **2** (Fig. 1).

Fig. 1 Structures of butane-2,3-diacetal of glycolic acid (**1**) and its enantiomer (**2**).

These chiral building blocks are crystalline and readily prepared on a multigram scale from (*S*)- or (*R*)-3-halopropane-1,2-diols[4,5] or from alternative sources of chirality such as mannitol and ascorbic acid.[8] In this work we describe in full the deprotonation of these building blocks and their subsequent highly diastereoselective reactions with aldehydes and acid chlorides. We have published previously in detail on the related reactions with ketones.[9]

Results and discussion

In the first series of experiments, compound **2** was readily deprotonated with 1.05 eq of lithium bis(trimethylsilylamide) (LHMDS) in THF at −78 °C. After 10 min an aldehyde was added *via* syringe and, after stirring for a further 5 min, the reaction was quenched by the addition of acetic acid to give the corresponding aldol products **12**–**20** (Scheme 1) in very good yields and with extremely high selectivity (Table 1).



Scheme 1 (a) LHMDS (1.05 eq), THF, −78 °C, then RCHO.

We believe that the major diastereoisomeric product arises through attack of the aldehyde to the *re*-face of the glycolate enolate, avoiding the steric clash with the 1,3-related axial methoxy group. Assuming chelation of the lithium cation of the enolate to the aldehyde oxygen and a six-membered ring chair-like transition state, placement of the R group of the aldehyde in the equatorial position (away from the dioxane ring) rationalizes the stereochemistry of the major product (Fig. 2).

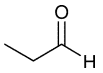
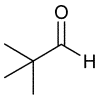
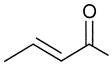
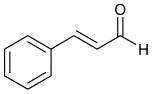
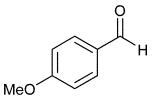
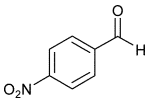
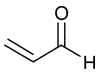
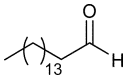
Similar, highly stereoselective adducts were also obtained by coupling of the enolates from BDA glycolate **2** with ketones.[9]

We then examined the addition of the lithium enolates of **1** and **2** to aldehydes bearing a stereogenic center at the α-position to evaluate the "matched" and "mismatched" combinations of the coupling partners (Scheme 2). Treatment of the enolate from (*S*,*S*)-**2** with the *tert*-butyldimethylsilyl-protected chiral aldehyde **21** gave an inseparable mixture of the aldol products **22** and **23** in the ratio 48 : 52 and an excellent combined yield of 82%.[10] However, reaction of the enantiomeric (*R*,*R*)-**1** derivative with **21** gave alcohol **24** as the major product, in 87% yield and >95% de. Assuming Felkin–Nguyen control,[11,12] these selectivities are consistent with the model described above and the coupling of the enolate of **1** with **21** represents the matched combination.

The reaction of glycolates (*S*,*S*)-**1** and (*R*,*R*)-**2** with chiral aldehyde **25** was investigated as a key step in the synthesis of the C_{22}-C_{28} fragment of the natural immunosuppressant rapamycin.[13,14] In this case, both (*S*,*S*)-**1** and (*R*,*R*)-**2** gave a single diastereoisomer of the aldol product (Scheme 3). The stereochemistry of compound **28** was inferred by comparison of the spectroscopic data of the two hydrolysis derivatives (*vide infra*). Aldehyde **25** exerts less influence on the stereochemical outcome of the reaction than aldehyde **21** as it lacks an electronegative atom at the chiral centre. As a consequence, the directing influence of the aldehyde can be overridden using the butanediacetal auxiliary.

DOI: 10.1039/b412790k

Table 1 Glycolate aldol reactions

Aldehyde		Yield/%	de/%	Product
3		86	92	**12**
4		86	>95	**13**
5		89	>95	**14**
6		92	95	**15**
7		90	>95	**16**
8		96	>95	**17**
9		70	94	**18**
10		86	>96	**19**
11		60	>95	**20**

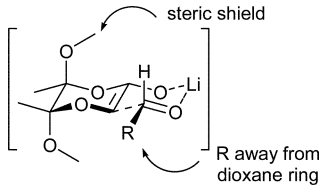
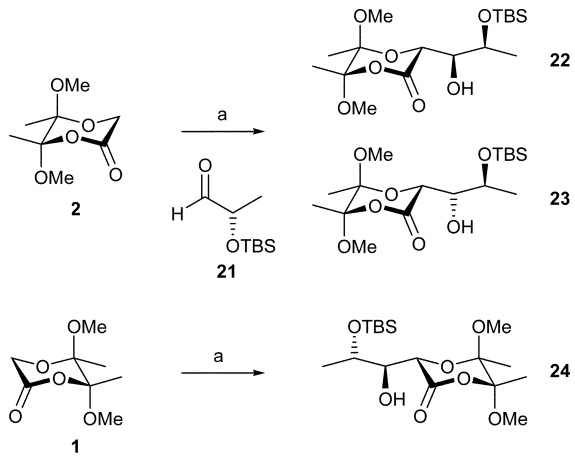
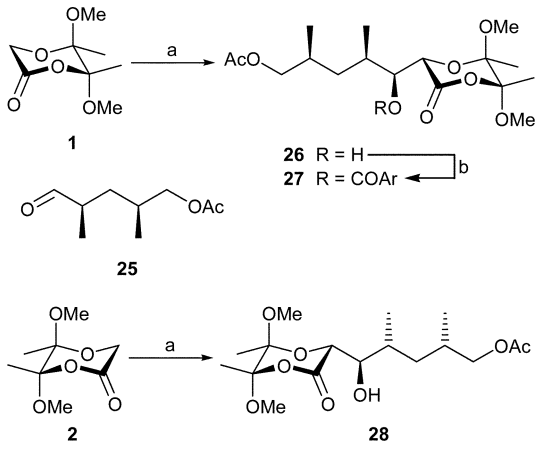


Fig. 2 Proposed transition state model leading to major diastereomer.

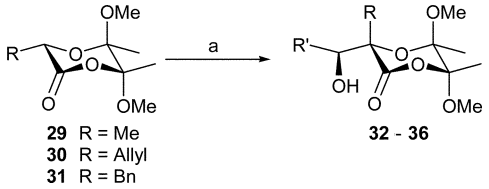


Scheme 2 (a) LHMDS (1.05 eq), THF, −78 °C, then **21**, 82% (**22** and **23**), 87% (**24**).

We have also compared the reactivity of a selected number of mono-alkylated BDA-glycolates (**29**, **30** and **31**, Scheme 4) during subsequent deprotonation and aldol reaction. These

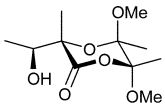
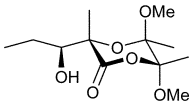
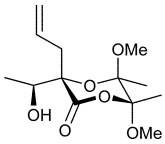
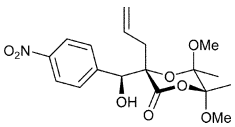
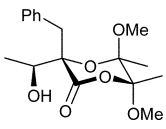


Scheme 3 (a) LHMDS (1.1 eq), THF, −78 °C, then **25**, 79% (**26**), 84% (**28**); (b) *p*-$NO_2C_6H_4COCl$, Et_3N, DMAP, rt, 98%.



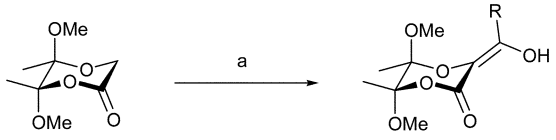
Scheme 4 (a) KHMDS (1.05 eq), THF, −78 °C, then RCHO.

Table 2 Aldol reactions of alkylated derivatives

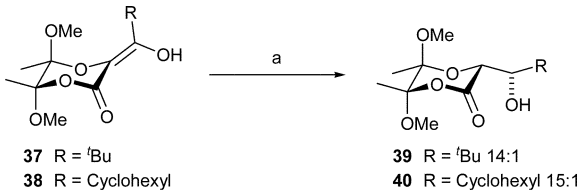
Glycolate	Aldehyde	Product		Yield/%
29	**3**		**32**	79
29	**4**		**33**	53
30	**3**		**34**	73
30	**9**		**35**	67
31	**3**		**36**	24

mono-alkylated BDA glycolates were prepared as in a preceding paper.[4] Unexpectedly, these alkylated derivatives failed to react successfully under the standard aldol conditions described above. However, when deprotonated with potassium bis(trimethylsilylamide) (KHMDS) at −78 °C, a successful reaction occurred to afford the coupled products **32–36** in a stereoselective fashion (Table 2), as anticipated from earlier results. Although an excellent yield of product **32** was obtained, the more sterically crowded products **33–36** are only produced in moderate yield, possibly due to the lower stability of the potassium enolate.

Since the stereochemical outcome of the aldol reactions with the desymmetrized BDA glycolates was, in most cases, highly stereoselective, we briefly examined a complimentary process to afford the alternative C-3 hydroxylic stereogenic centre. This was achieved in a two-step process: reaction of the enolate with an acyl chloride gave an enolised β-keto product (**37** or **38**) (Scheme 5), which was subsequently reduced with tetra-*N*-butylammonium borohydride in CH_2Cl_2 to the corresponding hydroxyl derivatives **39** and **40** with high stereoselectivity (Scheme 6). The stereochemistry obtained was shown to be complimentary to the products obtained from direct aldol reaction.

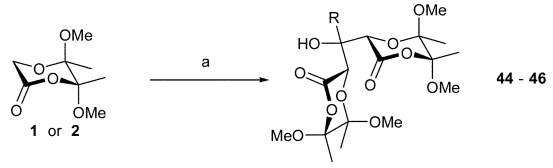


Scheme 5 (a) LHMDS (1.05 eq), THF, −78 °C, then RCOCl, 73% (**37**), 68% (**38**)



Scheme 6 (a) Bu_4NBH_4, CH_2Cl_2, 68% (**39**), 76% (**40**)

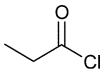
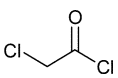
When the enolate of **1** or **2** was reacted with less hindered acyl chlorides **41–43**, dimeric adducts **44–46** were obtained in moderate to excellent yield as white crystalline solids after simple trituration of the crude reaction product (Scheme 7 and Table 3). These unusual bis-BDA derivatives result from addition of two equivalents of the glycolate enolate to the acid chloride, suggesting that under the reaction conditions the intermediate ketone is consumed faster than the acid chloride.



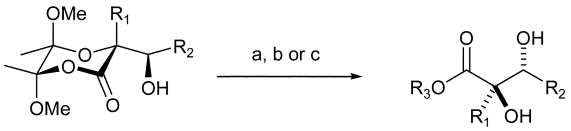
Scheme 7 (a) LHMDS (1.05 eq), THF, −78 °C, then RCOCl (**41–43**)

We investigated the removal of the BDA protecting group in selected examples by acid mediated hydrolysis or transesterification (Scheme 8 and Table 4). Accordingly, aldehyde adducts **12–19** were readily converted to the corresponding 2,3-dihydroxy methyl esters **47–54**. These reactions occur in good to excellent yields, and in some cases the structures of the products were assigned by comparison with literature data.

Table 3 Double addition to unhindered acid chlorides

Acid chloride		Product	Yield/%
41		**44**	88
42		**45**[a]	41[a]
43		**46**	10

[a] (*S*,*S*)-glycolate **2** was used.

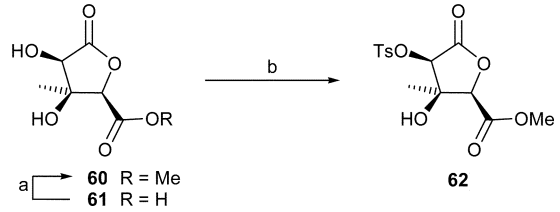


Scheme 8 (a) HCl, MeOH, rt; (b) CSA, MeOH, reflux; (c) TFA, H_2O, rt.

These results provide further evidence for the selectivity of the coupling reactions and in addition show that no isomerisation occurs on hydrolysis.

The contiguous triol feature embedded in the aldol products **22–24** could be of use in further synthesis programmes and, upon acidic hydrolysis in methanol with camphor sulfonic acid, the inseparable aldol products **22** and **23** were converted to a separable mixture of lactones **55** and **56** in 45% and 34% yields, respectively. These lactones were known from previous studies and therefore, by careful spectroscopic comparison with the literature, we confirmed the stereochemical outcome of these aldol reactions.[15–17] The product of the matched aldol reaction **24** was deprotected to a known lactone **57** in 75% yield. Similarly, the aldol products **28** and **29** were subjected to acetal deprotection conditions to yield the methyl esters **58** and **59** with concomitant removal of the primary acetate.

Alcohol **44** contains two diastereotopic butanediacetal protected lactones which can be successfully differentiated by acidic methanolysis to give the lactone **60**. This creates a chiral centre at the tertiary alcohol, favouring the *syn*-diol lactone **60** in a 13 : 1 ratio. Acidic hydrolysis gave the corresponding acid **61** as a more favourable 25 : 1 ratio of diastereoisomers. Spectroscopic data was insufficient to determine the stereochemistry of these products but conversion to the tosylate derivative **62** enabled the absolute and relative stereochemistry to be determined by X-ray diffraction techniques (Scheme 9).†



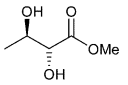
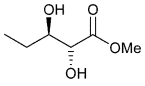
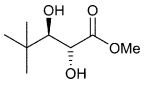
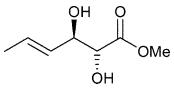
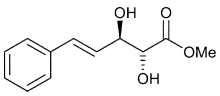
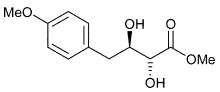
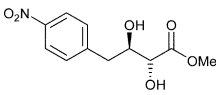
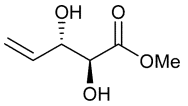
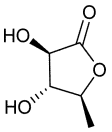
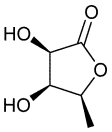
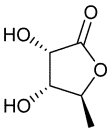
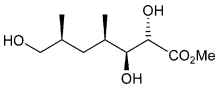
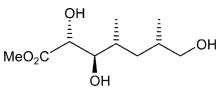
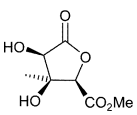
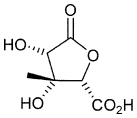
Scheme 9 (a) $Me_2NC(Cl)=CHMe$, CH_2Cl_2, then MeOH, 59%; (b) TsCl, pyridine, rt, 33%

Conclusions

In summary, the BDA-desymmetrised glycolates **1** and **2** have been shown to undergo highly *anti*-selective lithium enolate aldol reactions which provide *anti*-2,3-dihydroxyesters in good yield upon deprotection. Potassium enolate aldol reactions of substituted lactones provide protected 2,2-disubstituted-2,3-dihydroxyacids with excellent selectivity. A complimentary acylation–reduction sequence was developed to provide the protected *syn*-2,3-dihydroxyesters. The discovery of a novel double addition reaction of the lithium enolate of **1** with acid chlorides provided highly crystalline bis-BDA compounds which upon deprotection provide a usefully differentiated contiguous secondary–tertiary–secondary triol unit. Further highly diastereoselective reactions of **1** and **2** will be reported shortly.

† CCDC reference number 251197. See http://www.rsc.org/suppdata/ob/b4/b412790k/ for crystallographic data in .cif format.

Table 4 Acidic deprotection of the BDA group

Lactone	Conditions	Product		Yield/%
12	B[a]		**47**	75
13	A		**48**	86
14	A		**49**	89
15	A		**50**	93
16	A		**51**	73
17	A		**52**	85
18	A		**53**	99
19	A		**54**	57
22 and 23	B		**55**	45
	B		**56**	34
24	B		**57**	75
26	B[a]		**58**	88
28	B[a]		**59**	85
44	A		**60**	100
ent-**44**	C		**61**	99

[a] Reaction carried out at rt.

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 **1** and **2** 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 $[a]_D^{25}$ 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.

Representative procedure for lithium enolate aldol reaction: preparation of (+)-(3*R*, 5*S*, 6*S*, 1′*R*)-5,6-dimethoxy-5,6-dimethyl-3-(1′-ol-1′-*p*-methoxyphenyl-1′-yl)-[1,4]-dioxan-2-one (17)

Lithium bis(trimethylsilylamide) (1.0 M in THF, 0.86 ml, 0.86 mmol) was added to a solution of lactone **1** (155 mg, 0.82 mmol) in THF (2.5 ml) at −78 °C. After stirring for 10 min, *p*-anisaldehyde (0.1 ml, 0.90 mmol) was added in one portion and the reaction mixture was stirred for a further 5 min before quenching with acetic acid (0.1 ml, 1.6 mmol) and warming to rt. Diethyl ether (2 ml) was added and the reaction mixture filtered through a small plug of silica eluting with Et_2O (15 ml). The filtrate was concentrated under reduced pressure and purified by column chromatography to give the aldol product **17** (250 mg, 96%) as a white crystalline solid; mp 67–69 °C (from Et_2O); $[a]_D^{31}$ +107.1 (c 1.37, $CHCl_3$); ν_{max} (film)/cm^{-1} 3488, 1754, 1150; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, CH_3), 1.47 (3H, s, CH_3), 3.28 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.74 (1H, d, J 2.0, OH), 3.80 (3H, s, $ArOCH_3$), 4.31 (1H, d, J 4.0, COCH), 5.08 (1H, dd, J 2 and 4, C*H*OH), 6.87 (2H, d, J 9.0, Ar), 7.32 (2H, d, J 9.0, Ar); δ_C (100 MHz, $CDCl_3$) 16.8, 17.9, 49.3, 50.1, 55.2, 74.0, 75.4, 98.3, 105.0, 113.4, 128.1, 130.5, 159.3, 167.0; Found (ES): $[MNa]^+$, 349.1274. $C_{16}H_{22}O_7$ requires *MNa*, 349.1258.

(+)-(3*R*, 5*S*, 6*S*, 1′*R*)-5,6-Dimethoxy-5,6-dimethyl-3-(1′-ethanol-1′-yl)-[1,4]-dioxan-2-one (12)

$[a]_D^{31}$ +165.5 (c 0.89, $CHCl_3$); ν_{max} (film)/cm^{-1} 3514, 1749; δ_H(400 MHz, $CDCl_3$) 1.31 (3H, d, J 6.5, CH_3COH), 1.41 (3H, s, CH_3), 1.49 (3H, s, CH_3), 3.29 (1H, d, J 2.0, OH), 3.32 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 4.06 (1H, d, J 3.7, COCH), 4.16–4.14 (1H, m, CH_3C*H*OH); δ_c (100 MHz, $CDCl_3$) 16.8, 17.6, 17.8,

49.2, 50.2, 68.7, 75.1, 98.1, 104.9, 167.4; Found (ES): $[MNa]^+$, 257.1004. $C_{10}H_{18}O_6$ requires *MNa*, 257.0995.

(+)-(3*R*, 5*S*, 6*S*, 1′*R*)-5,6-Dimethoxy-5,6-dimethyl-3-(1′-propanol-1′-yl)-[1,4]-dioxan-2-one (13)

mp 42–43 °C (from Et_2O); $[a]_D^{31}$ +155.7 (*c* 1.27, $CHCl_3$); ν_{max} (film)/cm^{-1} 3502, 1751, 1150; δ_H (400 MHz, $CDCl_3$) 1.03–0.99 (3H, t, *J* 7.4, CH_2CH_3), 1.41 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.72–1.66 (2H, m, CH_2), 3.30 (1H, d, *J* 2.0, OH), 3.32 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 3.89–3.86 (1H, m, C*H*OH), 4.12 (1H, d, *J* 3.6, COC*H*); δ_c (100 MHz, $CDCl_3$) 10.1, 16.8, 17.8, 24.7, 49.2, 50.2, 74.05, 74.1, 98.1, 104.8, 167.4; Found (ES): $[MNa]^+$, 271.1162. $C_{11}H_{20}O_6$ requires *MNa*, 271.1152

(+)-(3*R*, 5*S*, 6*S*, 1′*R*)-5,6-Dimethoxy-5,6-dimethyl-3-(2′,2′-dimethyl-1′1-propanol-1′-yl)-[1,4]-dioxan-2-one (14)

$[a]_D^{31}$ +149.5 (*c* 1.78, $CHCl_3$); ν_{max} (film)/cm^{-1} 3496, 1733, 1150; δ_H (400 MHz, $CDCl_3$) 1.02 (9H, s, $C(CH_3)_3$), 1.38 (1H, s, CH_3), 1.49 (3H, s, CH_3), 3.25 (1H, d, *J* 4.7, OH), 3.31 (3H, s, OCH_3), 3.44 (3H, s, OCH_3), 3.65 (1H, dd, *J* 5.0 and 4.7, C*H*COH), 4.23 (1H, d, *J* 5.0, COCH); δ_c (100 MHz, $CDCl_3$) 16.9, 17.9, 26.3, 35.0, 49.2, 50.2, 72.8, 79.4, 98.1, 105.1, 169.3; Found (ES): $[MNa]^+$, 299.1461. $C_{13}H_{24}O_6$ requires *MNa*, 299.1465.

(+)-(3*R*, 5*S*, 6*S*, 1′*R*)-5,6-Dimethoxy-5,6-dimethyl-3-(2′buten-1′-ol-1′-yl)-[1,4]-dioxan-2-one (15)

mp 93–95 °C (from Et_2O); $[a]_D^{31}$ +128.9 (*c* 0.81, $CHCl_3$); ν_{max} (film)/cm^{-1} 3497, 1750; δ_H (400 MHz, $CDCl_3$) 1.42 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.72 (3H, d, *J* 6.0, CHCHCH_3), 3.19 (1H, d, *J* 3.1, OH), 3.32 (3H, s, OCH_3), 3.41 (3H, s, OCH_3), 4.19 (1H, d, *J* 3.5, COC*H*), 4.45–4.41 (1H, m, C*H*OH), 5.69 (1H, dd, *J* 15.5 and 7.5, CH_3CHC*H*), 5.80 (1H, dq, *J* 15.5 and 6.5, CH_3C*H*CH); δ_c (100 MHz, $CDCl_3$) 16.8, 17.8, 17.9, 49.3, 50.1, 73.9, 75.0, 98.2, 104.8, 127.8, 129.9, 166.8; Found (ES): $[MNa]^+$, 283.1165. $C_{12}H_{20}O_6$ requires *MNa*, 283.1152.

(+)-(3*R*, 5*S*, 6*S*, 1′*R*)-5,6-Dimethoxy-5,6-dimethyl-3-(1′ol-3′phenyl-2′propen-1′-yl)-[1,4]-dioxan-2-one (16)

mp 94–95 °C (from Et_2O); $[a]_D^{31}$ +95.4 (*c* 0.76, $CHCl_3$); ν_{max} (film)/cm^{-1} 3496, 1752, 1600; δ_H (400 MHz, $CDCl_3$) 1.45 (3H, s, CH_3), 1.50 (3H, s, CH_3), 3.33 (1H, br s, OH), 3.34 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 4.30 (1H, d, *J* 3.3, COCH), 4.68 (1H, m, C*H*OH), 6.40 (1H, dd, *J* 16.0 and 7.0, ArCHC*H*), 6.69 (1H, d, *J* 16.0, ArCH), 7.43–7.21 (5H, m, Ar); δ_c (100 MHz, $CDCl_3$) 16.8, 17.8, 49.3, 50.2, 73.7, 75.0, 98.3, 104.9, 126.1, 127.7, 127.8, 128.5, 132.7, 136.6, 166.8; Found (ES): $[MNa]^+$, 345.1320. $C_{17}H_{22}O_6$ requires *MNa*, 345.1308.

(+)-(3*R*, 5*S*, 6*S*, 1′*R*)-5,6-Dimethoxy-5,6-dimethyl-3-(1′-ol-1′-*p*-nitrophenyl-1′-yl)-[1,4]-dioxan-2-one (18)

mp 120–122 °C (from Et_2O); $[a]_D^{31}$ +83.3 (*c* 0.73, $CHCl_3$); ν_{max} (film)/cm^{-1} 3486, 1755, 1524; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, s, CH_3), 1.50 (3H, s, CH_3), 3.30 (3H, s, OCH_3), 3.40 (3H, s, OCH_3), 4.04 (1H, d, *J* 1.6, OH), 4.33 (1H, d, *J* 4.4, COCH), 5.21 (1H, dd, *J* 4.4 and 1.6, *CH*OH), 7.58 (2H, d, *J* 8.7, Ar), 8.20 (2H, d, *J* 8.7, Ar); δ_c (100 MHz, $CDCl_3$) 16.8, 17.8, 49.5, 50.4, 73.6, 75.4, 98.4, 105.2, 123.2, 127.6, 145.6, 147.5, 166.3; Found (ES): $[MNa]^+$, 364.1000. $C_{15}H_{19}NO_8$ requires *MNa*, 364.1003.

(3*S*,5*R*,6*R*)-3-((*S*)-1-Hydroxy-allyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (19)

Lithium bis(trimethylsilyl)amide (1.0 M in THF, 8.3 ml, 8.3 mmol) was added to a stirred solution of the (*R*,*R*)-glycolate **1** (1.50 g, 7.89 mmol) in THF (40 ml) at −78 °C. After 10 min, freshly distilled acrolein (0.63 ml, 9.47 mmol) was added and the solution stirred at −78 °C for further 5 min. The reaction was then quenched by addition of acetic acid (0.9 ml, 15.78 mmol) at −78 °C and was allowed to warm to rt. Diethyl ether was added (20 ml) and the heterogeneous mixture was filtered through a short plug of silica eluting with Et_2O (150 ml). The filtrate was concentrated under reduced pressure. The reaction de was found to be >95% by integration of the signals in the 600 MHz proton NMR spectrum. Biotage flash chromatography eluting with Et_2O–petrol, 1 : 2 gave the desired isomer (1.66 g, 86%) as a colourless oil. $[a]_D^{31}$ −151.6 (*c* 1.24, $CHCl_3$); (Found: C, 52.07; H, 7.27. Calc. for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37); ν_{max}(film)/cm^{-1} 3487, 2951, 1741, 1032; δ_H 1.42 (3H, s, CH_3), 1.49 (3H, s, CH_3), 3.32 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 4.19 (1H, d, *J* 3.5, COC*H*), 4.49 (1H, m, C*H*OH), 5.26 (1H, d, *J* 10.5, CHCH*H*), 5.37 (1H, d, *J* 17.2, CHC*H*H), 6.04–5.96 (1H, m, C*H*CH_2); δ_c 16.8, 17.8, 49.3, 50.1, 73.7, 75.0, 98.2, 104.8, 117.3, 134.8, 166.7; Found: $[MNa]^+$, 269.1005, $C_{11}H_{18}O_6$ requires *MNa* 269.1001.

(3*R*,5*S*,6*S*)-3-((*R*)-1-Hydroxy-hexadecyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (20)

Lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.60 ml, 0.60 mmol) was added dropwise to a stirred solution of (*S*,*S*)-**2** (109 mg, 0.57 mmol) in THF (1.5 ml) at −78 °C. After stirring for 15 min, hexadecanal (151 mg, 0.63 mmol) was added dropwise *via* canula as a solution in THF (2 ml). The reaction was stirred for 2 h at −78 °C before quenching with acetic acid (68 µl, 1.2 mmol). The resulting gel was filtered through a short plug of silica, washing with Et_2O (20 ml) and then concentrated. The residue was purified by column chromatography (Et2O–petrol, 1 : 4) to give the *alcohol* as a white powder (147 mg, 60%); mp 50–51 °C; $[a]_D^{31}$ +104.0 (*c* 0.60, $CHCl_3$); (Found: C, 66.54; H, 10.71. Calc. for $C_{24}H_{46}O_6$: C, 66.94; H, 11.77); ν_{max} (film)/cm^{-1} 3506, 2919, 2850, 1754, 1464, 1378; δ_H ($CDCl_3$) 0.88 (3H, t, 6.8, *Me*CH_2), 1.2–1.4 (26H, m, CH_2), 1.38 (3H, s, Me), 1.50 (3H, s, Me), 1.55–1.72 (2H, m, *CH*$_2$CHOH), 3.26 (1H, br d, *J* 0.5, OH), 3.33 (3H, s, OMe), 3.43 (3H, s, OMe), 3.95 (1H, m, C*H*OH), 4.11 (1H, d, *J* 3.4, axial H); δ_C 14.5, 17.2, 18.3, 23.1, 26.2, 29.3, 29.56, 29.57, 29.60, 29.64, 29.65, 29.67, 29.68, 31.7, 31.9, 49.7, 50.6, 73.2, 75.0, 98.5, 105.2, 167.7; Found (ES): $[MNa]^+$ 453.3195 $C_{24}H_{46}O_6$ requires *MNa*, 453.3192.

2-(*tert*-Butyl-dimethyl-silanyloxy)-propionaldehyde (21)

The aldehyde was prepared from (*S*)-ethyl lactate, according to the published procedure, as a colourless oil (61%);[10] bp 67–68 °C at 14 mm Hg; $[a]_D^{31}$ −11.1 (*c* 2.7, $CHCl_3$).

(3*R*,5*S*,6*S*)-3-[(1*R*,2*S*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-hydroxy-propyl]-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (23) and (3*R*,5*S*,6*S*)-3-[(1*S*,2*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-hydroxy-propyl]-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (22)

Lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.86 ml, 0.86 mmol) was added dropwise to a stirred solution of (*S*,*S*)-**1** (155 mg, 0.82 mmol) in THF (2.5 ml) at −78 °C. After stirring for 15 min aldehyde **21** (171 mg, 0.96 mmol) was added and the resulting solution stirred for 20 min at −78 °C. Acetic acid (90 µl, 1.5 mmol) was added and the solution warmed to rt and filtered through a short plug of silica gel eluting with ether (50 ml). The filtrate was concentrated under reduced pressure and then purified by column chromatography (Et_2O–petrol, 1 : 9) to give the alcohols (246 mg, 0.65 mmol, 79%) as prisms; $[a]_D^{31}$+115.5 (*c* 0.98, $CHCl_3$); ν_{max} (film)/cm^{-1} 3491, 2955, 2932, 2857, 1749; major isomer **23**: δ_H 0.07 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.88 (9H, s, ^{t}Bu), 1.24 (3H, d, *J* 5.9, *Me*COSiMe$_2{}^t$BuH), 1.42 (3H, s, Me), 1.50 (3H, s, Me), 3.19 (1H, d, *J* 10.61, OH), 3.34 (3H, s, OMe), 3.43 (3H, s, OMe), 3.70 (1H, m C*H*OH), 3.82 (1H, dq, *J* 8.8, 6.0, C*H*OSiMe$_2{}^t$BuMe), 4.59 (1H, br s, axial H); δ_C −4.8, −3.7, 16.8, 17.9, 18.0, 20.7, 25.8, 49.5,50.2, 68.0, 71.0, 76.1, 98.0, 104.4, 169.2; minor isomer **22**: δ_H. 0.09 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.90 (9H, s, ^{t}Bu), 1.27 (3H, d, *J* 6.3,

*Me*COSiMe$_2$^{t}BuH), 1.39 (3H, s, Me), 1.49 (3H, s, Me), 2.90 (1H, d, *J* 5.5, OH), 3.31 (3H, s, OMe), 3.42 (3H, s, OMe), 3.61 (1H, m C*H*OH), 4.12 (1H, d, *J* 5.7 axial H), 4.19 (1H, dq, *J* 4.4,6.3 C*H*OSiMe$_2$^{t}BuMe); δ_C −4.7, −4.2, 16.8, 17.9, 17.9, 18.0, 20.4, 25.8, 49.5, 50.0, 67.3, 71.6, 78.0, 98.3, 104.4, 168.0; Found (ES): [MNa]$^+$ 401.19860 $C_{17}H_{34}O_7Si$ requires *MNa*, 401.1972.

(3*S*,5*R*,6*R*)-3-[(1*R*,2*S*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-hydroxy-propyl]-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (24)

Lithium bis(trimethylsilyl)amide (1.0 M in THF, 0.86 ml, 0.86 mmol) was added dropwise to a stirred solution of (*R*,*R*)-**1** (155 mg, 0.82 mmol) in THF (2.5 ml) at −78 °C. After stirring for 15 min aldehyde **21** (171 mg, 0.96 mmol) was added and the resulting solution stirred for 20 min at −78 °C. Acetic acid (90 µl, 1.5 mmol) was added and the solution warmed to rt and filtered through a short plug of silica gel eluting with ether (50 ml). The filtrate was concentrated under reduced pressure and then purified by column chromatography (Et$_2$O–petrol, 1 : 9) to give the alcohol (260 mg, 0.69 mmol, 84%) as a colourless oil; $[\alpha]_D^{31}$ −74.7 (*c* 0.45, $CHCl_3$); (Found: C, 54.12; H, 9.03. Calc. for $C_{17}H_{34}O_7Si$: C, 53.94; H, 9.05); ν_{max} (film)/cm^{-1} 3493, 2955, 2931, 2857, 1755; δ_H 0.11 (3H, s, SiMe), 0.12 (3H, s, SiMe), 0.89 (9H, s, ^{t}Bu), 1.23 (3H, d, *J* 6.2, *Me*COSiMe$_2$^{t}BuH), 1.41 (3H, s, Me), 1.49 (3H, s, Me), 3.17 (1H, d, *J* 2.2, OH), 3.32 (3H, s, OMe), 3.43 (3H, s, OMe), 3.67 (1H, br dt, *J* 8.4, 2.2, C*H*OH), 4.12 (1H, dq, *J* 8.4, 6.2, C*H*OSiMe$_2$^{t}BuMe), 4.51 (1H, d, *J* 2.2, axial H); δ_C −5.0, −4.2, 16.8, 17.8, 17.9, 20.6, 25.8, 49.1, 50.2, 67.3, 72.5, 78.1, 98.0, 104.5, 166.6; Found (ES): [MNa]$^+$ 401.19860 $C_{17}H_{34}O_7Si$ requires *MNa*, 401.1972.

(2*R*,4*S*)-5-Acetoxy-2,4-dimethylpentanal (25)

The described (2*R*,4*S*)-5-acetoxy-2,4-dimethylpentanol[13] (190 mg, 1.1 mmol) in dry CH_2Cl_2 (15 ml) was successively treated with Hunig's base (0.76 ml, 4.4 mmol) and a solution of sulfur trioxide–pyridine complex (520 mg, 3.3 mmol) in dry DMSO (0.5 ml) at 0 ° C. The reaction was stirred at the same temperature for 2 h and then quenched with pH 7 phosphate buffer (15 ml). The crude was diluted with ether (50 ml) and washed four times with a saturated ammonium chloride solution. The organic layer was dried (Mg_2SO_4), concentrated under reduced pressure and used directly in the next step; $[\alpha]_D^{31}$ +3.6 (*c* 0.85, $CHCl_3$), δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.7, Me), 0.98 (3H, d, *J* 7.0, *Me*), 1.01–1.09 (1H, m, CH), 1.67–1.79 (2H, m, CH_2), 1.92 (3H, s, *Me*COO), 2.28–2.36 (1H, m, C*H*CHO), 3.73–3.81 (2H, m, C*H*$_2$OAc), 9.45 (1H, d, *J* 2.2, C*H*O); δ_C(100 MHz, $CDCl_3$) 14.5, 17.5, 21.2, 30.6, 34.8, 44.2, 69.1, 171.4, 204.8.

(3*R*,5*R*,6*R*)-3-[(1*S*,2*R*,4*S*)-5-Acetyloxy-5-hydroxy-2,4-dimethylpentanyl]-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (26)

Lithium bis(trimethylsilyl)amide (1.0 M in hexane, 1.10 ml, 1.10 mmol) was added dropwise to a stirred solution of (*R*,*R*)-**1** (190 mg, 1.00 mmol) in dry THF (20 ml) at −78 °C. After stirring for 15 min aldehyde **25** (172 mg, 1.00 mmol) was added and the resulting solution stirred for 30 min at −78 °C. Acetic acid (90 µL, 1.5 mmol) was added and the solution warmed to rt and filtered through a short plug of silica gel eluting with ethyl acetate (50 ml). The filtrate was concentrated under reduced pressure and then purified by column chromatography (Et$_2$O–petrol, 1 : 1) to give the *alcohol* **26** (305 mg, 0.84 mmol, 84%) as a colourless oil; $[\alpha]_D^{31}$ −88.8 (*c* 0.10, $CHCl_3$); ν_{max} (film)/cm^{-1} 1737; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.5, Me), 0.91 (3H, d, *J* 6.5, Me), 0.94–1.07 (1H, m, C*H*Me), 1.33 (3H, s, Me), 1.43 (3H, s, Me), 1.46–1.53 (1H, m, C*H*Me), 1.85–1.90 (1H, m, CH_2), 1.95–1.97 (1H, m, CH_2), 1.98 (3H, s, MeCO), 3.27 (3H, s. OMe), 3.35 (3H, s. OMe), 3.62 (1H, dd, *J* 6.3, 5.3, C*H*OH), 3.78 (1H, dd, *J* 10.8, 7.0, C*H*$_2$OAc), 3.94 (1H, dd, *J* 10.8, 5.2, C*H*$_2$OAc), 4.05 (1H, d, *J* 6.3, axial H); δ_C(100 MHz, $CDCl_3$) 14.4, 17.2, 18.1, 18.3, 21.3, 30.1, 31.1, 37.6, 49.6, 50.6, 69.4, 71.8, 74.8, 98.5, 105.4, 168.8, 171.6; Found: [MNa]$^+$, 385.1838. $C_{17}H_{30}O_8$ requires *MNa* 385.1838.

(3*R*,5*R*,6*R*)-3-[(1*S*,2*R*,4*S*)-5-Acetyloxy-2,4-dimethyl-5-*para*-nitrobenzoyloxypentanyl]-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (27)

Alcohol **26** (175 mg, 0.47 mmol) in dry CH_2Cl_2 (10 ml) was successively treated with triethylamine (129 µL, 0.93 mmol), *p*-nitrobenzoyl choride (172 mg, 0.93 mmol) and DMAP (6 mg, 0.05 mmol). After stirring for 45 min, the reaction mixture was diluted with ether (50 ml) and washed twice with a saturated ammonium chloride solution. The organic layer was dried (Mg_2SO_4), concentrated under reduced pressure and purified by column chromatography (Et$_2$O–petrol, 1 : 1) to give the *ester* **27** (242 mg, 0.46 mmol, 98%) as a colourless oil, that was crystallised from hexane–ether; mp 114 °C (from Et$_2$O–hexane); $[\alpha]_D^{31}$ −53.4 (*c* 0.95, $CHCl_3$); ν_{max} (film)/cm^{-1} 1733, 1266; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.7, Me), 1.00–1.05 (1H, m, C*H*Me), 1.02 (3H, d, *J* 6.8, Me), 1.33 (3H, s, Me), 1.35–1.39 (1H, m, C*H*Me), 1.42 (3H, s, Me), 1.89 (3H, s, MeCO), 1.91–1.92 (1H, m, CH_2), 2.40 (1H, ddd, *J* 7.5, 6.8, 3.7, CH_2), 3.24 (3H, s, OMe), 3.35 (3H, s, OMe), 3.82 (2H, d, *J* 6.1, CH_2OAc), 4.25 (1H, d, *J* 6.1, axial H), 5.46 (1H, dd, *J* 7.8, 3.3, C*H*OPNP), 8.13 (2H, d, *J* 8.8, C*H*CCO), 8.21 (2H, d, *J* 8.8, C*H*CNO$_2$); δ_C(100 MHz, $CDCl_3$) 14.4, 16.8, 16.9, 17.8, 20.7, 29.7, 30.2, 37.3, 49.1, 50.1, 69.0, 69.5, 74.7, 98.5, 105.0, 123.4, 130.9, 135.5, 150.6, 164.1, 167.1, 171.0; Found: [MNa]$^+$, 534.1938. $C_{24}H_{33}NO_{11}$ requires *MNa* 534.1951.

(3*R*,5*S*,6*S*)-3-[(1*R*,2*R*,4*S*)-5-Acetyloxy-5-hydroxy-2,4-dimethylpentanyl]-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (28)

Lithium bis(trimethylsilyl)amide (1.0 M in hexanes, 1.10 ml, 1.10 mmol) was added dropwise to a stirred solution of (*S*,*S*)-**2** (190 mg, 1.00 mmol) in dry THF (20 ml) at −78 °C. After stirring for 15 min aldehyde **25** (172 mg, 1.00 mmol) was added and the resulting solution stirred for 30 min at −78 °C. Acetic acid (90 µL, 1.5 mmol) was added and the solution warmed to rt and filtered through a short plug of silica gel eluting with ethyl acetate (50 ml). The filtrate was concentrated under reduced pressure and then purified by column chromatography (Et$_2$O–petrol, 1 : 1) to give the *alcohol* **28** (285 mg, 0.79 mmol, 79%) as a colourless oil; $[\alpha]_D^{31}$ +109.6 (*c* 0.29, $CHCl_3$); ν_{max} (film)/cm^{-1} 1734; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.7, Me), 0.97 (3H, d, *J* 6.7, Me), 0.99–1.05 (1H, m, C*H*Me), 1.37 (3H, s, Me), 1.46 (3H, s, Me), 1.61–1.68 (1H, m, C*H*Me), 1.90–1.99 (2H, m, CH_2), 2.01 (3H, s, MeCO), 3.29 (3H, s, OMe), 3.39 (3H, s, OMe), 3.57 (1H, dd, *J* 7.4, 4.4, C*H*OH), 3.73 (1H, dd, *J* 10.8, 7.4, C*H*$_2$OAc), 3.99 (1H, dd, *J* 10.8, 5.1, C*H*$_2$OAc), 4.18 (1H, d, *J* 4.4, axial H); δ_C (100 MHz, $CDCl_3$) 16.5, 16.8, 17.8, 18.7, 21.0, 30.0, 31.6, 36.7, 49.4, 50.3, 65.8, 69.3, 72.3, 77.1, 98.1, 104.8, 168.1, 171.3; Found: [MNa]$^+$, 385.1839. $C_{17}H_{30}O_8$ requires *MNa* 385.1838.

(3*S*,5*R*,6*R*)-3-((*S*)-1-Hydroxy-ethyl)-5,6-dimethoxy-3,5,6-trimethyl-[1,4]dioxan-2-one (32)

Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.99 ml, 0.50 mmol) was added dropwise to a stirred solution of (*R*,*R*)-**29** (92 mg, 0.45 mmol) in THF (0.9 ml) at −78 °C. After stirring for 15 min, acetaldehyde (103 µl, 1.8 mmol) was added in one portion. The solution was stirred for a further 60 min then acetic acid (54 µl, 0.9 mmol) was added and the solution warmed to rt. The reaction mixture was filtered through a small plug of silica gel, eluting with ether (20 ml) and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (Et$_2$O–petrol, 1 : 4 then 3 : 7) to give the *alcohol*

as white prisms (88 mg, 0.18 mmol, 79%); mp 50–51 °C (from Et_2O); $[\alpha]_D^{31}$ −134.8 (*c* 0.56, $CHCl_3$); (Found: C, 53.53; H, 8.18. Calc. for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12); ν_{max} (film)/cm^{-1} 3504, 3000, 1750, 1454, 1377; δ_H 1.22 (3H, d, *J* 6.4, *Me*CHOH), 1.39 (6H, s, 2 × Me), 1.48 (3H, s, Me), 3.31 (3H, s, OMe), 3.39 (3H, s, OMe), 3.81 (1H, q, *J* 6.4, C*H*OH), 3.85 (1H, br s, OH); δ_C 16.3, 17.4, 18.0, 22.7, 49.8, 50.0, 73.7, 80.7, 98.6, 105.5, 169.6; Found (ES): $[MNa]^+$ 271.1163 $C_{11}H_{20}O_6$ requires *MNa*, 271.1158.

(3*S*,5*R*,6*R*)-3-((*S*)-1-Hydroxy-propyl)-5,6-dimethoxy-3,5,6-trimethyl-[1,4]dioxan-2-one (33)

Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.7 ml, 0.35 mmol) was added dropwise to a stirred solution of (*R*,*R*)-**29** (68 mg, 0.33 mmol) in THF (0.7 ml) at −78 °C. After stirring for 15 min, propionaldehyde (50 µl, 0.67 mmol) was added in one portion. The solution was stirred for a further 60 min then acetic acid (42 µl, 0.7 mmol) was added and the solution warmed to rt. The reaction mixture was filtered through a small plug of silica gel, eluting with ether (20 ml) and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (Et_2O–petrol, 1 : 4) to give the *alcohol* as a colourless oil (46 mg, 0.18 mmol, 53%); $[\alpha]_D^{31}$ −133 (*c* 0.30, $CHCl_3$); ν_{max} (film)/cm^{-1} 3491, 2955, 1750, 1455; δ_H 1.00 (3H, t, *J* 7.3, *Me*CH_2), 1.40 (3H, s, Me), 1.42 (3H, s, Me), 1.50 (3H, s, Me), 1.50–1.65 (2H, m, CH_2), 3.32 (3H, s, OMe), 3.41 (3H, s, OMe), 3.51 (1H, br d, *J* 10.2, CH), 3.73 (1H, br s, OH); δ_C 11.2, 17.5, 18.1, 22.8, 23.6, 48.8, 50.0, 79.1, 80.5, 98.7, 105.5, 170.1; Found (ES): $[MNa]^+$ 297.1320 $C_{13}H_{22}O_6$ requires *MNa*, 297.1314.

(3*S*,5*R*,6*R*)-3-Allyl-3-((*S*)-1-hydroxy-ethyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (34)

Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 1.02 ml, 0.51 mmol) was added dropwise to a stirred solution of (*R*,*R*)-**30** (110 mg, 0.48 mmol) in THF (1.0 ml) at −78 °C. After stirring for 15 min, acetaldehyde (82 µl, 1.43 mmol) was added in one portion. The solution was stirred for a further 60 min then acetic acid (61 µl, 1.02 mmol) was added and the solution warmed to rt. The reaction mixture was filtered through a small plug of silica gel, eluting with ether (20 ml) and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (Et_2O–petrol, 1 : 9 then 1 : 4) to give the *alcohol* as white prisms (96 mg, 0.35 mmol, 73%); mp 57–58 °C (from Et_2O); $[\alpha]_D^{31}$ −57.4 (*c* 0.91, $CHCl_3$); (Found: C, 57.21; H, 8.01. Calc. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08); ν_{max} (film)/cm^{-1} 3494, 2953, 1749, 1640, 1456, 1381; δ_H 1.21 (3H, d, *J* 6.6, *Me*CHOH), 1.43 (3H, s, Me), 1.50 (3H, s, Me), 2.59 (1H, ddt, *J* 15.7, 5.1, 1.8, C*H*HCH=CH_2), 2.70 (1H, dd, *J* 15.7, 9.1, CH*H*CH=CH_2), 3.32 (3H, s, OMe), 3.41 (3H, s, OMe), 3.91 (1H, q, *J* 6.6, C*H*OH), 3.90 (1H, br s, OH), 5.13 (1H, br dd, *J* 1.8, 1.3), 5.15–5.18 (1H, m), 5.85–5.96 (1H, m, C*H*=CH_2); δ_C 15.5, 17.4, 18.2, 39.6, 50.10, 50.13, 71.6, 82.8, 98.9, 105.2, 118.9, 131.4, 168.4; Found (ES): $[MNa]^+$ 297.1304 $C_{13}H_{22}O_6$ requires *MNa*, 297.1314.

(3*S*,5*R*,6*R*)-3-Allyl-3-[(*S*)-hydroxy-(4-nitro-phenyl)-methyl]-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (35)

Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.72 ml, 0.36 mmol) was added dropwise to a stirred solution of (*R*,*R*)-**30** (79 mg, 0.34 mmol) in THF (0.72 ml) at −78 °C. After stirring for 30 min, 4-nitrobenzaldehyde (58 µg, 0.38 mmol) was added in one portion. The solution was stirred for a further 60 min then acetic acid (43 µl, 0.72 mmol) was added and the solution warmed to rt. The reaction mixture was filtered through a small plug of silica gel, eluting with ether (20 ml) and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (Et_2O–petrol, 1 : 4 then 1 : 1) to give the *alcohol* as a yellow oil (87 mg, 0.23 mmol, 67%); $[\alpha]_D^{31}$ −37.7 (*c* 1.16, $CHCl_3$); ν_{max} (film)/cm^{-1} 3459, 2953, 1749, 1639, 1606, 1523, 1457, 1434, 1381, 1346; δ_H 1.51 (3H, s, Me), 1.56 (3H, s, Me), 2.43 (1H, dd, *J* 16.5, 8.4, C*H*HCH=CH_2), 2.63 (1H, ddt, *J* 16.5, 4.8, 2.2, CH*H*CH=CH_2), *3*.33 (3H, s, OMe), 3.50 (3H, s, OMe), 4.58 (1H, s, OH), 5.06 (1H, s, C*H*OH), 5.20 (1H, br d, *J* 17.6, CH=C*H*H), 5.31 (1H, br d, *J* 10.2, CH=CH*H*), 6.09 (1H, dddd, *J* 17.2, 10.6, 8.4, 4.4), 7.57 (2H, br d, *J* 8.4, *meta* to NO_2), 8.14 (2H, br d, *J* 9.1, *ortho* to NO_2); δ_C 17.3, 18.2, 36.0, 50.3, 50.4, 76.2, 82.1, 99.4, 105.7, 119.7, 122.5, 129.3, 131.7, 145.0, 147.7, 167.9; Found (ES): $[MNa]^+$ 404.1321 $C_{18}H_{23}NO_8$ requires *MNa*, 404.1321.

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

Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.54 ml, 0.27 mmol) was added dropwise to a stirred solution of (*R*,*R*)-**31** (49 mg, 0.26 mmol) in THF (1.0 ml) at −78 °C. After stirring for 15 min, acetaldehyde (44 µl, 0.78 mmol) was added in one portion. The solution was stirred for a further 150 min then acetic acid (16 µl, 0.26 mmol) was added and the solution warmed to rt. The reaction mixture was filtered through a small plug of silica gel, eluting with ether (20 ml) and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (Et_2O–petrol, 1 : 9 then 3 : 7) to give the *alcohol* as white prisms (20 mg, 0.06 mmol, 24%); mp 158–159 °C (from Et_2O); $[\alpha]_D^{31}$ −36.5 (*c* 0.17, $CHCl_3$); ν_{max} (film)/cm^{-1} 3490, 2950, 1749, 1497, 1455; δ_H 1.16 (3H, d, *J* 6.6, *Me*CHOH), 1.57 (3H, s, Me), 1.58 (3H, s, Me), 3.26 (1H, d, *J* 15.8, C*H*HPh), 3.31 (1H, d, *J* 16.1, CH*H*Ph), 3.45 (3H, s, OMe), 3.46 (3H, s, OMe), 3.79 (1H, q, *J* 6.6), 3.91 (1H, br s, OH), 7.26 (1H, br t, *J* 7.3, *para*-H), 7.30 (2H, br t, *J* 7.3, *meta*-H), 7.48 (2H, d, *J* 7.3, *ortho*-H); δ_C 15.9, 17.6, 18.4, 40.6, 50.2, 50.8, 70.9, 84.4, 99.4, 105.5, 126.8, 128.4, 130.1, 136.0, 168.5; Found (ES): $[MNa]^+$ 347.1478 $C_{17}H_{24}O_6$ requires *MNa*, 347.1471.

(5*S*,6*S*)-3-[1-Hydroxy-2,2-dimethyl-prop-(*E*)-ylidene]-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (37)

Lithium bis(trimethylsilyl)amide (1.0 M in THF, 2.1 ml, 2.1 mmol) was added dropwise to a stirred solution of (*S*,*S*)-**2** (200 mg, 10.5 mmol) in THF (5 ml) at −78 °C. After stirring for 15 min, trimethylacetyl chloride (141 µl, 1.16 mmol) was added in one portion. The solution was stirred for a further 15 min then acetic acid (121 µl, 2.1 mmol) was added and the solution warmed to rt. The reaction mixture was filtered through a small plug of silica gel, eluting with ether (50 ml) and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (Biotage, ether–petrol, 1 : 9) to give the *enol* as prisms (205 mg, 0.77 mmol, 73%); mp 68–69 °C (from Et_2O); $[\alpha]_D^{31}$ +116.0 (*c* 2.0, $CHCl_3$); (Found: C, 56.82; H, 8.08. Calc. for $C_{13}H_{22}O_6$: C, 56.82; H, 8.08); ν_{max} (film)/cm^{-1} 2961, 1654, 1599, 1456, 1401, 1386, 1275, 1195, 1148, 1112, 1076, 1037, 983, 864, 813; δ_H 1.24 (9H, s, ^{t}Bu), 1.40 (3H, s, Me), 1.45 (3H, s, Me), 3.23 (3H, s, OMe), 3.35 (3H, s, OMe), 12.29 (1H, s, OH); δ_C 16.7, 17.5, 27.5, 37.4, 49.2, 49.7, 97.8, 103.6, 117.8, 166.7, 171.8; Found (ES): $[MNa]^+$ 297.1324 $C_{13}H_{22}O_6$ requires *MNa*, 297.1314.

(5*R*,6*R*)-3-[1-Cyclohexyl-1-hydroxy-meth-(*E*)-ylidene]-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (38)

Lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.1 ml, 1.1 mmol) was added dropwise to a stirred solution of (*S*,*S*)-**2** (200 mg, 10.5 mmol) in THF (5 ml) at −78 °C. After stirring for 15 min, cyclohexylcarbonyl chloride (159 µl, 1.16 mmol) was added in one portion. The solution was stirred for a further 15 min then acetic acid (121 µl, 2.1 mmol) was added and the solution warmed to rt. The reaction mixture was filtered through a small plug of silica gel, eluting with ether (50 ml) and the filtrate concentrated under reduced pressure. The solvent was evaporated under reduced pressure and the residue was purified

by column chromatography (Biotage Flash 12Mi, ether–petrol, 1 : 9) to give the *enol* as plates (201 mg, 0.71 mmol, 68%); mp 130–131 °C (from Et_2O); $[a]_D^{31}$ −100 (*c* 1.0, $CHCl_3$); (Found: C, 60.12; H, 7.94. Calc. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05); ν_{max} (film)/cm^{-1} 2937, 2855, 1770, 1664, 1617, 1452, 1395, 1348, 1295, 1263, 1227, 1151, 1117, 1037, 984, 915, 866, 811, 743; δ_H 1.32–1.21 (4H, m, cyclohexyl), 1.48 (s, Me), 1.52 (3H, s, Me), 1.54–1.82 (6H, m, cyclohexyl), 2.80 (1H, br tt, *J* 3.5, 11.6, C*H*(HO)C=C), 3.23 (3H, s, OMe), 3.43 (3H, s, OMe), 11.56 (1H, s, OH); δ_C 16.8, 17.6, 25.7, 25.8, 26.0, 28.8, 29.2, 37.2, 48.8, 50.2, 98.1, 104.2, 117.1, 166.1, 169.6; Found (ES): $[MNa]^+$ 323.1466 $C_{15}H_{24}O_6$ requires *MNa*, 323.1471.

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

Enol **37** (50 mg, 0.18 mmol) was dissolved in CH_2Cl_2 (2 ml) and cooled to 0 °C. Tetra-*N*-butylammonium borohydride (111 mg, 0.4 mmol) was added in one portion and the reaction stirred for 15 min at 0 °C. The solution was then allowed to warm to rt and then stirred for a further 5 h before diluting with ether (5 ml). The organic solution was washed with water (5 ml) and brine (5 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (ether–petrol, 1 : 9) to give the *alcohol* as needles (35 mg, 68%); mp 72–74 °C (from Et_2O); $[a]_D^{31}$ +94.4 (*c* 0.54, $CHCl_3$); (Found: C, 56.80; H, 8.68. Calc. for $C_{13}H_{24}O_6$: C, 56.51; H, 8.75); ν_{max} (film)/cm^{-1} 3530, 2345, 1752, 1460, 1382, 1275, 1165, 1123, 1034, 964, 919, 863; δ_H 0.93 (9H, s, ^{t}Bu), 1.34 (3H, s, Me), 1.42 (3H, s, Me), 3.08 (1H, d, *J* 10.1, OH), 3.26 (3H, s, OMe), 3.38 (3H, s, OMe), 3.63 (1H, dd, J 1.2, 10.1, C*H*OH), 4.34 (1H, d, *J* 1.2, axial H); δ_C 17.2, 18.1, 26.9, 35.9, 49.7, 50.5, 68.2, 80.0, 98.2, 104.7, 169.8; Found (ES): $[MNa]^+$ 299.1479 $C_{13}H_{24}O_6$ requires *MNa*, 299.1471.

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

Enol **38** (50 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (2 ml) and cooled to 0 °C. Tetrabutylammonium borohydride (111 mg, 0.4 mmol) was added in one portion and the reaction stirred for 15 min at 0 °C. The solution was then allowed to warm to rt and then stirred for a further 5 h before diluting with ether (5 ml). The organic solution was washed with water (5 ml) and brine (5 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (ether–petrol, 1 : 9) to give the *alcohol* as needles (38 mg, 76%); $[a]_D^{31}$ −267.4 (*c* 0.1, $CHCl_3$); ν_{max} (film)/cm^{-1}; δ_H 0.83–1.29 (4H, m, cyclohexyl), 1.43 (3H, s, Me), 1.50 (3H, s, Me), 1.52–1.77 (6H, m, cyclohexyl), 2.09 (1H, br d, *J* 10.5, C*H*CHOH), 2.74 (1H, d, *J* 10.5, OH), 3.28 (3H, s, OMe), 3.43 (3H, s, OMe), 3.65 (1H, t, *J* 10.5, C*H*OH), 4.33 (1H, s, axial H); δ_C 16.8, 17.8, 25.8, 25.9, 26.2, 40.5, 49.3, 50.1, 67.9, 77.3, 98.0, 104.4, 169.3; Found (ES): $[MNa]^+$ NN $C_{15}H_{26}O_6$ requires *MNa*, 302.1729.

1,1-Bis[(1*S*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one]-ethanol (44)

Lithium bis(trimethylsilyl)amide (1.0 M in THF, 2.76 ml, 2.76 mmol) was added dropwise to a stirred solution of (*R*,*R*)-**1** (500 mg, 2.63 mmol) in THF (10 ml) at −78 °C. After stirring for 15 min, acetyl chloride (95 µl, 1.31 mmol) was added at a rate of 5 µl min^{-1} using a syringe pump. The solution was stirred for a further 30 min then acetic acid (420 µl, 7 mmol) was added and the solution warmed to rt. The gel was filtered through a small plug of silica gel, eluting with ether (30 ml), CH_2Cl_2 (40 ml) and ethyl acetate (30 ml). The filtrate was concentrated under reduced pressure and the residue triturated with Et_2O–petrol (2 : 8, 10 ml) to give the *alcohol* as needles (488 mg, 88%); mp 199–200 °C (from Et_2O); $[a]_D^{31}$ −206 (*c* 1.0, $CHCl_3$); (Found: C, 51.27; H, 7.11. Calc. for $C_{18}H_{30}O_{11}$: C, 51.18; H, 7.16); ν_{max} (film)/cm^{-1} 3486, 2952, 2839, 1753, 1463, 1381, 1264, 1148, 1130, 1035, 978, 915, 865, 734; δ_H 1.38 (3H, s, Me), 1.43 (3H, s, Me), 1.49 (3H, s, Me), 1.50 (3H, s, Me), 1.55 (3H, s, *Me*R_2COH), 3.35 (3H, s, OMe), 3.36 (3H, s, OMe), 3.42 (3H, s, OMe), 3.46 (3H, s, OMe), 3.94 (1H, s, OH), 4.55 (1H, s, CH), 4.63 (1H, s, CH); δ_C 17.2, 17.3, 18.2, 18.5, 19.2, 49.3, 49.5, 50.2, 50.6, 73.2, 74.5, 76.3, 98.5, 98.6, 105.0, 105.6, 166.6, 166.9; Found (ES): $[MNa]^+$ 445.1699 $C_{18}H_{30}O_{11}$ requires *MNa*, 445.1686.

1,1-Bis[(1*R*,5*S*,6*S*)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one]-propanol (45)

Lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.65 ml, 1.65 mmol) was added dropwise to a stirred solution of (*S*,*S*)-**2** (300 mg, 2.63 mmol) in THF (6 ml) at −78 °C. After stirring for 15 min, propionoyl chloride (71 µl, 0.79 mmol) was added at a rate of 5 µl min^{-1} using a syringe pump. The solution was stirred for a further 10 min then acetic acid (180 µl, 3 mmol) was added and the solution warmed to rt. The gel was filtered through a small plug of silica gel, eluting with ether (20 ml), CH_2Cl_2 (20 ml) and ethyl acetate (20 ml). The filtrate was concentrated under reduced pressure and the residue triturated with Et_2O–petrol (3 : 7, 5 ml) to give the *alcohol* as prisms (140 mg, 41%); mp 137–138 °C (from Et_2O); $[a]_D^{31}$ +216 (*c* 1.0, $CHCl_3$); (Found: C, 52.22; H, 7.30. Calc. for $C_{19}H_{32}O_{11}$: C, 52.29; H, 7.39); ν_{max} (film)/cm^{-1} 3475, 2951, 2840, 1748, 1458, 1379, 1328, 1261, 1219, 1146, 1106, 1033, 1007, 985, 972, 956, 912, 864, 828, 768, 730; δ_H 0.99 (3H, t, *J* 7.5, *Me*CH_2), 1.35 (3H, s, Me), 1.39 (3H, s, Me), 1.46 (6H, s, 2 × Me), 2.02 (1H, quintet, *J* 7.4, CH*H*Me), 2.06 (1H, quintet, *J* 7.4, C*H*HMe), 3.32 (3H, s, OMe), 3.34 (3H, s, OMe), 3.41 (3H, s, OMe), 3.42 (3H, s, OMe), 4.01 (1H, br s, OH), 4.64 (1H, s, axial H), 4.69 (1H, s, axial H); δ_C 8.4, 17.2, 17.3, 18.2, 18.5, 26.6, 49.4, 49.5, 50.4, 50.6, 72.4, 73.4, 78.2, 98.7, 98.8, 105.1, 105.8, 166.6, 169.3; Found (ES): $[MNa]^+$ 459.1848 $C_{19}H_{32}O_{11}$ requires *MNa*, 459.1842.

2-Chloro-1,1-bis[(1*S*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one]-ethanol (46)

Lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.1 ml, 1.1 mmol) was added dropwise to a stirred solution of (*S*,*S*)-**1** (200 mg, 1.05 mmol) in THF (2.5 ml) at −78 °C. After stirring for 15 min, chloroacetyl chloride (44 µl, 0.55 mmol) was added at a rate of 5 µl min^{-1} using a syringe pump. The solution was stirred for a further 10 min then acetic acid (132 µl, 2.2 mmol) was added and the solution warmed to rt. The gel was filtered through a small plug of silica gel, eluting with ether (20 ml), CH_2Cl_2 (20 ml) and ethyl acetate (20 ml). The filtrate was concentrated under reduced pressure and the residue triturated with Et_2O–petrol (3 : 7, 5 ml)) to give the *alcohol* as prisms (94 mg, 40%); mp 124–126 °C (from Et_2O); $[a]_D^{25}$ −106 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3348, 1746; δ_H 1.33 (3H, s, Me), 1.35 (3H, s, Me), 1.42 (3H, s, Me), 1.44 (3H, s, Me), 3.26 (3H, s, OMe), 3.29 (3H, s, OMe), 3.38 (3H, s, OMe), 3.40 (3H, s, OMe), 4.04 (1H, s, *J* 11.3, CH*H*Cl), 4.23 (1H, s, *J* 11.3, C*H*HCl), 4.36 (1H, s, axial H), 4.39 (1H, s, axial H), 4.79 (1H, s, OH); δ_C 16.8, 16.9, 17.8, 18.1, 44.8, 49.1, 49.2, 50.3, 50.6, 69.5, 71.6, 77.6, 98.4, 98.6, 105.0, 105.2, 166.2, 168.4; Found (ES): $[MNa]^+$ 479.1320 $C_{18}H_{29}ClO_{11}$ requires *MNa*, 479.1296.

Representative procedure for the (±)-CSA promoted methanolysis of the aldol adducts–preparation of (−)-(2*R*,3*R*)-methyl-2,3-dihydroxy-butanoate (47)

To a stirred solution of **12** (41 mg, 0.18 mmol) in dry methanol (3 ml) at rt was added (±)-camphor sulfonic acid (44 mg, 1.1 eq). After stirring at the same temperature for 12 h the solution was evaporated *in vacuo* to leave a pale yellow oil. Purification by flash chromatography, eluting with ether gave **47** (17 mg, 75%) as a colourless oil; $[a]_D^{31}$ −17.3 (*c* 0.585, $CHCl_3$); ν_{max} (film)/cm^{-1} 3383, 1737; δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.5, COHCH_3), 2.23 (1H, d, *J* 7.0, OH), 2.99 (1H, d, *J* 5.3, OH), 3.80 (3H, s,

CH_3OCO), 4.08–4.04 (1H, m, C*H*OHCH$_3$), 4.21 (1H, dd, *J* 5.3 and 4.0, COC*H*OH); δ_C (100 MHz, $CDCl_3$) 17.4, 52.6, 69.1, 74.3, 173.1; Found: [MNa]$^+$, 157.0477. $C_5H_{10}O_4$ requires *MNa* 157.0471.

Representative procedure for the HCl promoted methanolysis of the aldol adducts–preparation of (−)-(2*R*, 3*R*)-methyl-2,3-dihydroxy-pentanoate (48)

To a stirred solution of **13** (27.5 mg, 0.1 mmol) in methanol (1 ml) at rt was added a solution of trimethylsilyl chloride in methanol (0.3M, 2.5 ml). After stirring at the same temperature for 10 min the solution was evaporated *in vacuo* to leave a pale yellow oil. Purification by flash chromatography, eluting with ether gave **48** (14 mg, 86%) as a white solid; mp 50–51 °C (from Et_2O); $[a]_D^{31}$ −18.9 (*c* 0.65, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3356, 1738, 1132; δ_H (400 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.5, CH_2CH_3), 1.61–1.48 (2H, m, CH_2CH_3), 2.22 (1H, d, *J* 6.5, OH), 3.05 (1H, d, *J* 5.5, OH), 3.77 (1H, m, COHC*H*$_2$), 3.81 (3H, s, CH_3OCO), 4.23 (1H, m, COC*H*OH); δ_C (100 MHz, $CDCl_3$) 10.2, 24.9, 52.6, 73.7, 74.7, 173.2; Found: [MNa]$^+$, 171.0630. $C_6H_{12}O_4$ requires *MNa* 171.0628.

(−)-(2*R*, 3*R*)-Methyl-2,3-dihydroxy-4,4-dimethyl-pentanoate (49)

$[a]_D^{31}$ −45.3 (*c* 0.84, $CHCl_3$); ν_{max} (film)/cm^{-1} 3438 (OH), 1735 (C=O); δ_H (400 MHz, $CDCl_3$) 0.98 (9H, s, C(CH$_3$)$_3$), 2.30 (1H, d, *J* 8, OH), 2.89 (1H, d, *J* 8.0, OH), 3.48 (1H, m, C*H*OHC(CH$_3$)$_3$), 3.79 (3H, s, CH_3OCO), 4.27 (1H, dd, *J* 8.0 and 4.5, COC*H*OH); δ_C (100 MHz, $CDCl_3$) 26.1, 34.8, 52.3, 72.1, 81.4; Found: [MNa]$^+$, 199.0944. $C_8H_{16}O_4$ requires *MNa* 199.0940.

(−)-(2*R*, 3*R*)-Methyl-2,3-dihydroxy-hex-4-enoate (50)

$[a]_D^{31}$ −19.2 (*c* 0.77, $CHCl_3$); ν_{max} (film)/cm^{-1} 3385, 1741; δ_H (400 MHz, $CDCl_3$) 1.71 (3H, d, *J* 6.5, CHC*H*$_3$), 2.33 (1H, br s, OH), 2.93 (1H, br s, OH), 3.80 (3H, s, CH_3OCO), 4.29 (1H, d, *J* 3.5, C*H*OH), 4.34 (1H, d, *J* 7.0, C*H*OH), 5.50 (1H, dd, *J* 15 and 7.0, C*H*CHCH$_3$), 5.79 (1H, dq, *J* 15.0 and 6.5, CHC*H*CH$_3$); δ_C (100 MHz, $CDCl_3$) 17.8, 52.6, 73.9, 74.1, 127.5, 130.1, 172.6; Found: [MNa]$^+$, 183.0624. $C_7H_{12}O_4$ requires *MNa* 183.0628.

(−)-(2*R*, 3*R*)-Methyl-2,3-dihydroxy-6-phenyl-pent-4-enoate (51)

mp 153–154 °C (from Et_2O); $[a]_D^{31}$ −27.6 (*c* 0.94, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3356, 1753, 1125; δ_H (400 MHz, $CDCl_3$) 2.52 (1H, d, *J* 7.0, OH), 3.06 (1H, d, *J* 6.0, OH), 3.40 (1H, dd, *J* 6.0 and 4.0, C*H*OH), 3.81 (3H, s, CH_3OCO), 4.59 (1H, m, C*H*OH), 6.20 (1H, dd, *J* 16.0 and 6.5, ArCHC*H*), 6.68 (1H, d, *J* 16.0, ArCH), 7.38–7.24 (5H, m, Ar); δ_C (100 MHz, $CDCl_3$) 52.7, 73.9, 74.1, 125.7, 126.6, 128.1, 128.6, 133.1, 136.2, 172.1; Found: [MNa]$^+$, 245.0789. $C_{12}H_{14}O_4$ requires *MNa* 245.0784.

(−)-(2*R*, 3*R*)-Methyl-2,3-dihydroxy-3-*p*-methoxyphenyl-propanoate (52)

mp 120–121 °C (from Et_2O); $[a]_D^{31}$ −41.8 (*c* 0.54, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3488, 1754, 1150; δ_H (400 MHz, $CDCl_3$) 2.77 (1H, d, *J* 6.0, OH), 2.82 (1H, d, *J* 6.5, OH), 3.71 (3H, s, CH_3OCO), 3.80 (3H, s, ArOCH_3), 4.48 (1H, dd, *J* 6.5 and 4.5, C*H*OH), 4.95 (1H, dd, *J* 5.0 and 5.0, C*H*OH), 6.87 (2H, d, *J* 9.0, Ph), 7.24 (2H, d, *J* 9.0, Ph); δ_C (100 MHz, $CDCl_3$) 172.4, 159.5, 127.6, 113.7, 74.5, 65.8, 55.2, 52.3, 15.2; Found: [MNa]$^+$, 249.0745. $C_{11}H_{14}O_5$ requires *MNa* 249.0733.

(−)-(2*R*, 3*R*)-Methyl-2,3-dihydroxy-3-*p*-nitrophenyl-propanoate (53)

mp 108–109 °C (from Et_2O); $[a]_D^{31}$ −45 (*c* 0.66, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3404, 1736, 1518, 1104; δ_H (400 MHz, $CDCl_3$) 3.18 (1H, d, *J* 5.5, OH), 3.23 (1H, d, *J* 5.5, OH), 3.69 (3H, s, CH_3OCO), 4.50 (1H, dd, *J* 5.5 and 4.5, C*H*OH), 5.12 (1H, dd, *J* 5.5 and 4.5, C*H*OH), 7.52 (2H, d, *J* 9.0, Ar), 8.20 (2H, d, *J* 9.0, Ar); δ_C (100 MHz, $CDCl_3$) 52.0, 74.0, 74.2, 123.4, 127.3, 145.9, 147.7, 171.9; Found: [MNa]$^+$, 264.0479. $C_{10}H_{11}O_6$ requires *MNa* 264.0479.

(2*S*,3*S*)-2,3-Dihydroxy-pent-4-enoic acid methyl ester (54)

Acetyl chloride (0.5 M in methanol, 1.48 ml) was added in one portion to a stirred solution of 19 (1.67 g, 6.7 mmol) in methanol (5 ml). The solution was stirred for 30 min and then all volatiles were removed *in vacuo*. This process was repeated then purification by Biotage flash chromatography eluting with Et_2O afforded the desired ester (560.4 mg, 57%) as colourless oil; $[a]_D^{31}$ +10.5 (*c* 1.1, $CHCl_3$); ν_{max} (film)/cm−1 3426, 1732; δ_H 3.03 (1H, br s, OH), 3.43 (1H, br s, OH), 3.71 (3H, s, OMe), 4.04 (1H, d, *J* 6.5, C*H*CO), 4.28 (1H, t, *J* 6.5, C*H*CHCH$_2$), 5.17 (1H, d, *J* 10.6, CHC*H*H), 5.24 (1H, d, *J* 17.3, CHCH*H*), 5.87–5.79 (1H, m, C*H*CH$_2$); δ_C 52.9, 74.2, 74.4, 118.3, 135.1, 172.9; Found: [MNa]+, 169.0473, $C_6H_{10}O_4Na$ requires, 169.0471.

(3*R*,4*R*,5*S*)-3,4-Dihydroxy-5-methyl-dihydro-furan-2-one (55) and (3*R*,4*S*,5*S*)-3,4-dihydroxy-5-methyl-dihydro-furan-2-one (56)

The mixture of alcohols **22** and **23** (35 mg, 0.092 mmol) was dissolved in methanol (2 ml) and camphor sulfonic acid (23 mg) was added. The solution was stirred overnight at rt, toluene (2 ml) was added, and the methanol distilled out of the reaction mixture. The remaining solvent was removed under vacuum and the residue purified by column chromatography (EtOAc–petrol, 1 : 1 then 7 : 3) to give the lactones **55** (5.4 mg, 0.041 mmol, 45%) and **56** (4.1 mg, 0.031 mmol, 34%); **55**: $[a]_D^{31}$ −29.4 (*c* 0.68, EtOH) [lit. $[a]_D^{31}$ −37.0 (*c* 1.1, EtOH)][15]; δ_H (400 MHz, MeOD) 1.46 (3H, d, *J* 6.3, Me), 3.81 (1H, t, *J* 8.4, C*H*CHCO$_2$R), 4.19 (1H, qd *J* 6.3, 8.3, C*H*Me), 4.33 (1H, d, *J* 8.8, C*H*CO$_2$R); δC (100 MHz, MeOD) 18.2, 75.7, 78.7, 80.8, 176.5. **56**: $[a]_D^{31}$ −32.3 (*c* 0.34, MeOH) [lit. $[a]_D^{31}$ −34 (*c* 0.99, MeOH)][16]; δ_H (400 MHz, MeOD) 1.41 (3H, d, *J* 6.5, Me), 4.25 (1H, dd, *J* 2.8, 4.7, C*H*CHCO$_2$R), 4.55 (1H, d, *J* 4.8, C*H*CO$_2$R), 4.57 (1H, qd, *J* 6.6, 2.6, C*H*Me). δC (100 MHz, MeOD) 14.2, 72.3, 72.6, 78.5, 178.6.

(3*S*,4*R*,5*S*)-3,4-Dihydroxy-5-methyl-dihydro-furan-2-one (57)

Alcohol **24** (40 mg, 0.105 mmol) was dissolved in methanol (4 ml) and camphor sulfonic acid (5 mg) was added. The solution was refluxed for 1 h and then toluene (4 ml) was added and the methanol distilled out of the reaction mixture. The remaining solvent was removed under vacuum and the residue purified by column chromatography (EtOAc–petrol, 7 : 3) to give the lactone **57** (10.6 mg, 0.079 mmol, 75%); $[a]_D^{31}$ −19.6 (*c* 1.02,MeOH) [lit. enantiomer $[a]_D^{31}$ +17.0 (*c* 1.0, MeOH)][17]; δ_H (400 MHz, D_2O) 1.36 (3H, d, *J* 7.0, Me), 4.25 (1H, d, *J* 5.1, C*H*CHCO$_2$R), 4.64 (1H, q, *J* 7.0, C*H*Me), 4.76 (1H, d, *J* 5.1, C*H*CO$_2$R); δ_C (100 MHz, D_2O) 17.4, 69.0, 72.8, 83.7, 178.7.

(2*R*,3*R*,4*R*,6*S*)-Methyl-2,3,7-trihydroxy-4,6-dimethylheptanoate (58)

$[a]_D^{31}$ +7.0 (*c* 0.20, $CHCl_3$); ν_{max} (film)/cm^{-1} 3381, 1732; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 5.6, Me), 0.92 (3H, d, *J* 5.6, Me), 1.63–1.70 (3H, m, CH_2 and C*H*Me), 1.72–1.82 (1H, m, C*H*Me), 2.95–2.99 (1H, m, C*H*OH), 3.38 (1H, dd, *J* 10.7, 4.5, CH_2OH), 3.51 (1H, dd, *J* 7.2, 4.5, CH_2OH), 3.75 (3H, s, OMe), 4.23 (1H, d, *J* 4.7, C*H*OH); δ_C (100 MHz, $CDCl_3$) 17.5, 19.1, 33.1, 33.4, 36.2, 52.9, 67.1, 72.9, 78.6, 174.1; Found: [MNa]$^+$, 243.1209. $C_{10}H_{20}O_5$ requires *MNa* 243.1208.

(2*S*,3*S*,4*R*,6*S*)-Methyl-2,3,7-trihydroxy-4,6-dimethylheptanoate (59)

$[\alpha]_D^{31}$ +10.3 (*c* 0.38, $CHCl_3$); ν_{max} (film)/cm^{-1} 3383, 1736; δ_H(400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.7, Me), 0.86 (3H, d, *J* 6.7, Me), 1.49–1.55 (1H, m, C*H*Me), 1.62–1.67 (1H, m, C*H*Me), 1.79–1.86 (2H, m, CH_2), 3.35 (1H, dd, *J* 10.6, 5.8, CH_2OH), 3.41 (1H, dd, *J* 10.6, 5.4, CH_2OH), 3.59 (1H, dd, *J* 6.3, 4.8, C*H*OH), 3.73 (3H, s, OMe), 4.17 (1H, d, *J* 6.3, C*H*OH); δ_C (100 MHz, $CDCl_3$) 17.5, 19.1, 33.1, 33.4, 36.2, 52.9, 67.1, 72.9, 78.6, 174.1; *m*/*z* (+ESI) 385 (MNa^+); Found: MNa^+, 243.1213. $C_{10}H_{20}O_5Na$ requires 243.1208.

Methyl (2*S*,3*R*,4*S*)-3,4-dihydroxy-3-methyl-5-oxo-tetrahydro-furan-2-carboxylate (60)

Alcohol **44** (81 mg, 0.19 mmol) was dissolved in a solution of acetyl chloride in methanol (0.5 M, 3 ml, 1.5 mmol) and stirred for 10 min at rt. The solvent was removed under reduced pressure and then the residue was redissolved in methanolic HCl (3 ml) and stirred for a further 10 min. The solvent was evaporated and the residue azeotroped with methanol (20 ml) and the residue dried under high vacuum to give the mixture of *lactones* as a white powder (36 mg, 100%); A pure sample of the major lactone isomer was obtained by chromatography (EtOAc–petrol, 7 : 3).‡ as white needles; mp 113–115 °C (from MeOH); $[\alpha]_D^{31}$ +33.0 (*c* 1.25, MeOH); (Found: C, 44.46; H, 5.40. Calc. for $C_7H_{10}O_6$: C, 44.21; H, 5.30); ν_{max} (film)/cm^{-1} 3600–2900, 1738; δ_H (400 MHz, MeOD) 1.53 (3H, s, Me), 3.79 (3H, s, OMe), 4.27 (1H, s, C*H*OH), 4,85 (1H, s, C*H*CO_2Me); δ_C (100 MHz, MeOD) 22.0, 53.2, 75.4, 78.1, 83.0, 168.9, 176.8; Found (ES): $[MNa]^+$ 213.0376 $C_7H_{10}O_6$ requires *MNa*, 213.0375.

(2*R*,3*S*,4*R*)-3,4-Dihydroxy-3-methyl-5-oxo-tetrahydro-furan-2-carboxylate (61)

Alcohol **44** (436.0 mg, 1.03 mmol) was dissolved in a 2 : 1 mixture of trifluoroacetic acid–water (3 ml) and left to stand for 10 min, with occasional swirling. The solvents were removed *in vacuo* to furnish a clear oil, which was four times redissolved in water (3 ml), evaporated, and then dried on a lyopholiser overnight. to give the *acid* as a white gum (199.1 mg, 99% yield by ^{1}H NMR using 1,2,3-trimethoxybenzene as an internal standard); mp 129 °C; $[\alpha]_D^{31}$ −23.0 (*c* 1.59, acetone); ν_{max} (film)/cm^{-1} 3523, 3154 (br), 1794, 1743, 1725; δ_H (100 MHz, acetone) 1.64 (3H, s, Me), 4.41 (1H, s, C*H*OH), 4.89 (1H, s, C*H*CO_2H); δ_C (100 MHz, acetone) 21.9, 74.7, 77.2, 81.2, 168.4, 174.6; Found (ES): $[MNa]^+$ 199.0219 $C_6H_8O_6$ requires *MNa*, 199.02030.

Conversion into methyl ester *ent*-60

Acid **61** (41.5 mg, 0.236 mmol) was suspended in dichloromethane and 1-chloro-*N*,*N*-2-trimethylpropenylamine (0.13 ml, 0.943 mmol) was added. The mixture was stirred until all the acid had dissolved (1 h) then dry methanol (1 ml) was added dropwise and the solution stirred for 15 min. The solvents were removed *in vacuo* to give the ester *ent*-**60** (59% by ^{1}H NMR using 1,2,3-trimethoxybenzene as an internal standard).

Methyl (1*S*,2*S*,3*S*)-2-hydroxy-2-methyl-4-oxo-3-(toluene-4-sulfonyloxy)-cyclopentanecarboxylate (62)

Lactone **44** (43 mg, 0.23 mmol) was dissolved in pyridine (0.2 ml) and tosyl chloride (55 mg) was added in one portion. The reaction was stirred overnight at rt before quenching with water (2 ml). The aqueous solution was extracted with Et_2O (2 × 5 ml). The combined organic layers were washed with saturated copper sulfate solution (2 × 5 ml), and brine (5 ml), dried ($MgSO_4$), and concentrated to give the *tosylate* as white prisms (26 mg, 0.076 mmol, 33%); mp 154–155 °C (from Et_2O); $[\alpha]_D^{31}$ +115.5 (*c*, 0.98, MeOH), (Found: C, 49.13; H, 4.60. Calc. for $C_{14}H_{16}O_8S$: C, 48.83; H, 4.68); ν_{max} (film)/cm^{-1} 3497, 2926, 1810, 1764. 1597; δ_H (400 MHz, $CDCl_3$) 1.70 (3H, s, Me), 2.46 (3 H, s, *Me*Ar), 3.85 (3H, s, OMe), 4.73 (1 H, s, CH), 5.06 (1H, s, CH), 7.37 (2H, d, *J* 8.1, *m*-H), 7.88 (2H, d, *J* 8.4, *o*-H); δ_C (100 MHz, $CDCl_3$)21.7, 21.9, 52.9, 76.0, 78.1, 80.5, 128.3, 130.0, 132.2, 146.1, 165.1, 167.2; Found (ES): $[MNa]^+$ 367.0464 $C_{14}H_{16}O_8S$ requires *MNa*, 367.0464.

‡ The lactone **60** appears to partially decompose on silica gel.

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