ARTICLE

OBC
www.rsc.org/obc

Michael, Michael–aldol and Michael–Michael reactions of enolate equivalents of butane-2,3-diacetal protected glycolic acid derivatives

Steven V. Ley,* Darren J. Dixon, Richard T. Guy, Félix Rodríguez and Tom D. Sheppard
Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW. E-mail: svl1000@cam.ac.uk; Fax: +44 (0)1223 336442; Tel: +44 (0)1223 336398

Received 6th September 2005, Accepted 30th September 2005
First published as an Advance Article on the web 19th October 2005

Consecutive coupling reactions of butane-2,3-diacetal protected glycolic acid derivatives with Michael acceptors and aldehydes are reported. An enantiopure sample of this building block was used to kinetically resolve a chiral Michael acceptor present as a racemic mixture of enantiomers.

Introduction

Multi-component and sequential reaction cascades are proving useful in complex molecule synthesis, especially for the rapid production of compound libraries. The one-pot nature of these processes inevitably leads to a reduction in costs, time and waste products.[1] Amongst the more powerful of these processes are domino or consecutive sequences such as the Ugi reaction[2] and related examples, MIMIC chemistry as introduced by Posner *et al.*,[3] and the whole range of tandem reaction sequences.[4] These chemistries rapidly produce functionally-dense architectures useful in many different areas of science. Nevertheless, while these methods create desirable features around a central core, more often than not they lack stereocontrol and lead to mixtures of diastereoisomers. The discovery of new sequences that give greatly improved enantio- and diastereo-selectivity in the coupling process is therefore important.

Accordingly, we have studied the use of the butane-2,3-diacetal (BDA) desymmetrized glycolic acid derivatives **1** and **2**[5] (Fig. 1) for these types of reactions: the excellent levels of stereocontrol imparted by these building blocks in lithium enolate alkylation, aldol and Michael reactions, and the abundance of biologically active and pharamaceutically-significant α-hydroxy acids[6] make them ideal candidates for such a study. It was anticipated that **1** and **2** would act as a source of chirality to influence further stereochemistry in subsequent C–C bond forming events. Here we report in full on the highly diastereoselective Michael addition[7] reactions of **1** and **2** with a range of acceptors and on new stereoselective, one-pot consecutive reactions that lead to α-hydroxy acid derivatives with up to five new stereogenic centres in high yield and high diastereoisomeric excess.

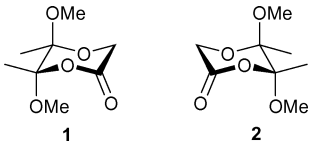


Fig. 1

Michael additions

Prior to the study of multi-component coupling reactions we embarked on a preliminary study to evaluate the diastereoselectivity in Michael addition reactions of the lithium enolates generated from **1** and **2**. In the initial experiments, **1** or **2** was treated with lithium hexamethyldisilazide (LHMDS) in THF at −78 °C and allowed to react with a small series of Michael acceptors, added *via* syringe. The crude product was purified by silica gel chromatography to give the corresponding Michael adducts **3–10** (Table 1). The reactions proceeded with generally good to excellent yields and selectivities. No axially-alkylated products were observed, and the structures of products **5**, **6**, **8**, and **10** were additionally confirmed by single crystal X-ray diffraction. The product stereochemistry is consistent with the Michael acceptor approaching the lithium enolate from the face opposite to the axial 1,3-related methoxy groups (see A in Fig. 2).[8] Also, the assigned configuration of the products is compatible with a combination of the two trigonal centres involved in the reaction according to the model shown in B (Fig. 2).[9] The Michael acceptor is always approached by the same face of the enolate, irrespective of its geometry (*Z* or *E*).

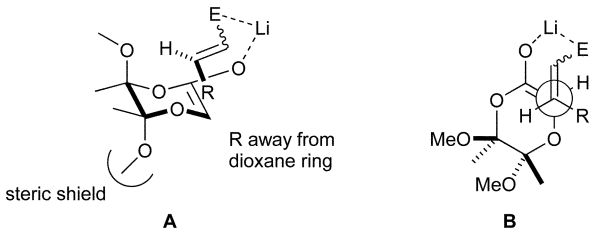
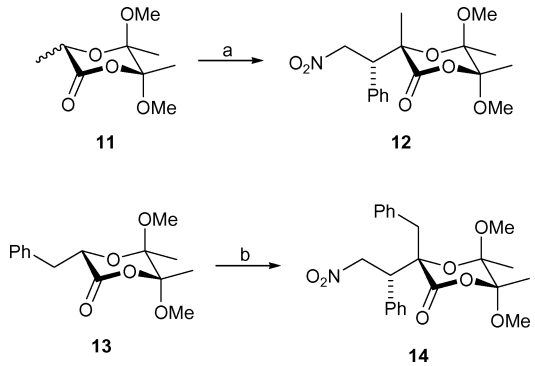


Fig. 2 Approaching models of the two trigonal centres in the reaction of lithium enolates derived from BDA desymmetrized glycolic acid **1** and Michael acceptors.

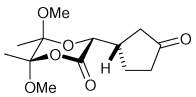
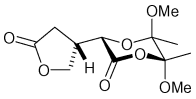
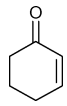
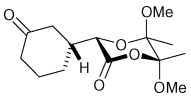
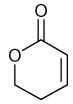
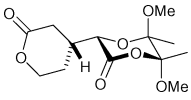
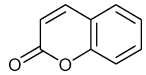
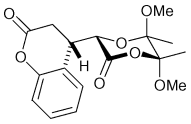
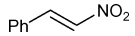
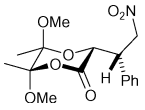
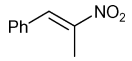
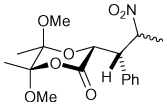
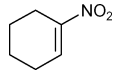
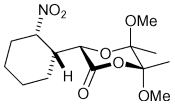
This reaction was extended to the alkylated glycolates **11** and **13**[5] which underwent highly diastereoselective reactions with *trans*-2-nitrostyrene to give the glycolate derivatives **12** and **14**, each bearing a fully-substituted carbon atom (Scheme 1).



Scheme 1 a) KHMDS, *trans*-2-nitrostyrene, 57%; b) KHMDS, *trans*-2-nitrostyrene, 25%.

DOI:10.1039/b512410g

Table 1 Asymmetric Michael addition reactions of **1** or **2**

Entry	Michael acceptor	Dr[a]	Yield	Product	
1		14 : 1	61%		**3**
2		10 : 1	35%[b]		**4**
3		13 : 1	30%		**5**
4		22 : 1	63%		**6**
5		65 : 1	90%		**7**
6		34 : 1	96%		**8**
7		1.4 : 1[c]	55%		**9**
8		16 : 1	98%		**10**

[a] Determined by ^{1}H NMR of the crude reaction product. The diastereoselectivities indicated reflect ratio at the newly formed side-chain stereogenic centres. [b] 33% of starting BDA-protected glycolic acid was recovered. [c] Mixture at the α-position to the nitro group. The dr of each diastereomer was found to be >20 : 1.

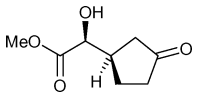
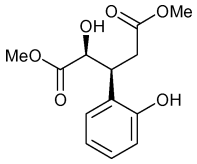
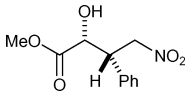
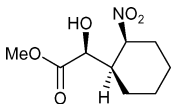
To prove that the BDA group could be readily removed, Michael adducts **3**, **7**, **8** and **10** were treated with HCl in methanol to give the corresponding methyl esters **15–18** (Table 2). As expected, when **7** was reacted under these conditions (entry 2), we obtained the ring-opened product **16** in 74% yield.

To further illustrate the utility of the Michael adducts, we transformed the nitrostyrene adduct **8** firstly to functionalised γ-lactam **19** (Scheme 2) by reduction of the nitro group, partial deprotection and cyclization, and subsequently to α-hydroxy-γ-amino ester **20** by reaction with methoxide in methanol and finally a catalytic quantity of triphenylphosphine hydrobromide. This sequence illustrates the potential for diverse changes in the products which could be of use in compound library generation at a later stage, or as building-blocks for natural product synthesis programmes.

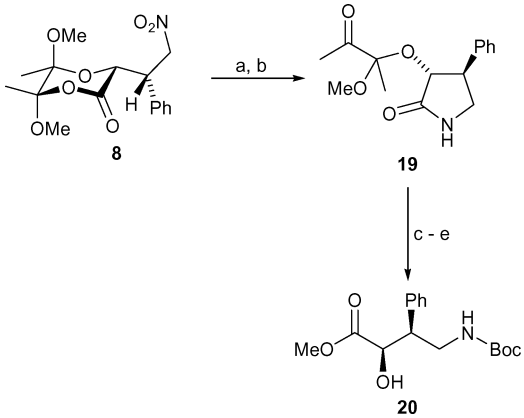
Michael–aldol reactions

Sequential Michael–aldol reactions of **1** and **2** were next explored. Once again, **2** was deprotonated with LHMDS (1 equiv.) in THF at −78 °C and treated with a Michael acceptor (5,6-dihydro-2*H*-pyran-2-one or coumarin). After 30 min a second electrophile, either benzaldehyde or anisaldehyde, was added and the corresponding three-component coupled products **21**, **22**, **23** (Scheme 3) were obtained as a mixture of only two diastereoisomers in a process leading to two new C–C bonds and three new stereogenic centres (Table 3). When trimethyl borate was added at the intermediate Michael reaction stage, improved selectivity was noted in the final product.

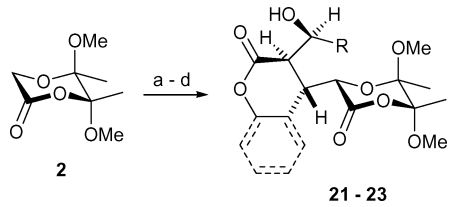
Table 2 α-Hydroxy methyl ester derivatives obtained from the Michael adducts

Entry	Adduct	Yield	Product	
1	**3**[a]	94%		**15**
2	**7**	74%		**16**
3	**8**	95%		**17**
4	**10**	91%		**18**

[a] The enantiomeric starting material was used.



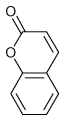
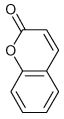
Scheme 2 a) Raney-Ni; b) SiO_2, 73% over two steps; c) $(Boc)_2O$, Et_3N, DMAP; d) NaOMe, MeOH; e) Ph_3PHBr, MeOH, 69% over three steps.



Scheme 3 a) LHMDS (1.05 eq.), THF, −78 °C, 10 min; b) 5,6-dihydro-2*H*-pyran-2-one or coumarin; c) additive; d) RCHO.

The structures of the products were determined by detailed ^{1}H and ^{13}C NMR analysis and, in the case of **21** and **22**, single crystal X-ray diffraction methods. These studies indicate that the diastereomers are epimeric at the carbon atom that bears the free hydroxyl group in the final aldol coupling product. The stereochemical outcome of the reactions suggest the first Michael acceptor approaches the lithium enolate derived from

Table 3 Michael–aldol reactions

Entry	Michael acceptor	R	Additive	Dr[a]	Yield[b]	
1		Ph	—	2.8 : 1	74%	**21**
2		Ph	$B(OMe)_3$	4.0 : 1	72%	**21**
3		4-MeO-C_6H_4	—	2.5 : 1	66%	**22**
4		4-MeO-C_6H_4	$B(OMe)_3$	5.2 : 1	63%	**22**
5		4-MeO-C_6H_4	—	3.2 : 1	73%	**23**
6		4-MeO-C_6H_4	$B(OMe)_3$	3.3 : 1	64%	**23**

[a] Determined by ^{1}H NMR of the crude reaction product. [b] Yield based on starting BDA desymmetrised glycolic acid derivative.

the glycolate **1** as discussed previously. This enolate then undergoes a *syn*-aldol addition to the aldehyde presumably through a closed twist-boat transition state (Fig 3).[10,11]

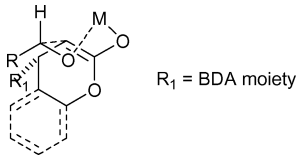
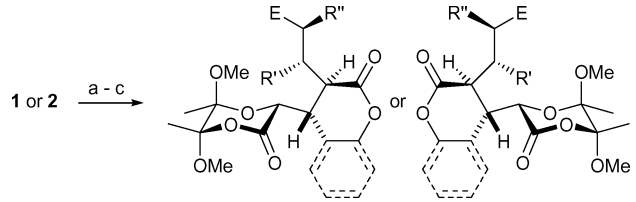


Fig. 3 Proposed transition state for Michael–aldol reactions.

Michael–Michael reactions

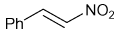
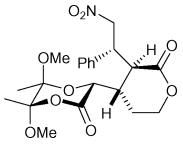
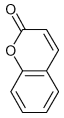
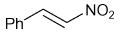
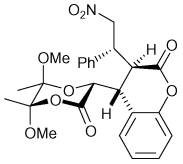
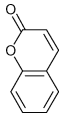
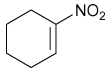
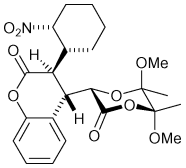
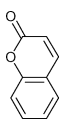
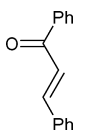
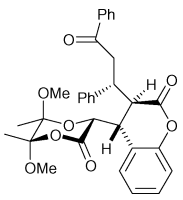
A consecutive Michael–Michael reaction was next investigated. Reaction of the enolate of **1** with either 5,6-dihydro-2*H*-pyran-2-one or coumarin, followed by either *trans*-β-nitrostyrene, 1-nitro-1-cyclohexene or *trans*-chalcone led to the corresponding addition products **24–27** (Scheme 4, Table 4) in a sequence that established two new C–C bonds and up to five stereogenic centres in a single step. X-Ray crystallography performed on crystals of **24**, **26** and **27** confirmed the stereochemical outcome.



24 - 27

Scheme 4 a) LHMDS (1.05 eq.), THF, −78 °C, 10 min; b) 5,6-dihydro-2*H*-pyran-2-one or coumarin; c) *trans*-β-nitrostyrene, 1-nitro-1-cyclohexene or *trans*-chalcone.

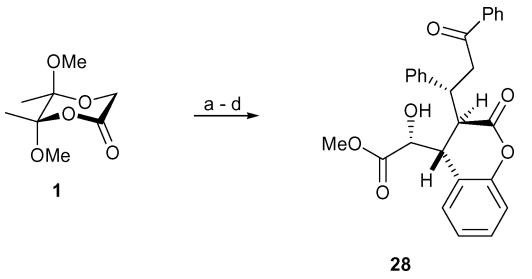
Table 4 Michael–Michael reactions

	Entry	1st component	2nd component	Dr[a]	Yield[b]	Product	
	1			3 : 1	80%		**24**
	2			>20 : 1	81%		**25**
	3			>20 : 1	90%		**26**
	4			>20 : 1	95%		**27**

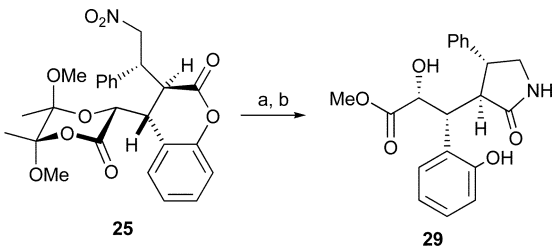
[a] Determined by ^{1}H NMR of the crude reaction product. [b] Yield based on starting BDA desymmetrised glycolic acid derivative.

Mechanistically, the second Michael addition seems to occur through a closed (chelated) transition state previously proposed for related reactions.[9]

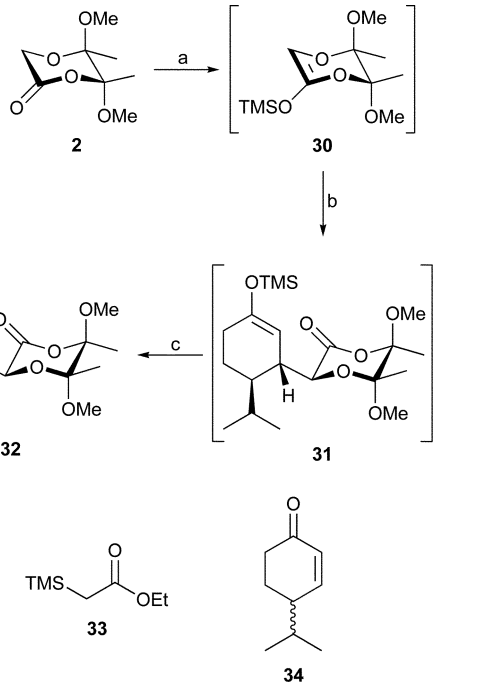
A tandem Michael–Michael-deprotection sequence was also studied. The enolate of **1** was reacted with coumarin followed by *trans*-chalcone, and finally with trimethylsilyl chloride and methanol to give **28** in 76% overall yield and a diastereomeric ratio of 20 : 1 (Scheme 5). We have also shown that **25** can be reduced with Raney-nickel to the primary amine which spontaneously ring opens the coumarin lactone to give a γ-lactam. This gives **29** after the usual methanolysis (Scheme 6). These examples illustrate the potential of this methodology to efficiently obtain highly-functionalized compounds as single enantiomers from simple starting materials.



Scheme 5 a) LHMDS (1.05 eq.), THF, −78 °C, 10 min; b) coumarin c) chalcone; d) MeOH, TMSCl; 76% over four steps; dr 20 : 1.



Scheme 6 a) Raney-Ni; b) MeOH, TMSCl; 86% over two steps.



Scheme 7 a) **33**, TBAT, THF, rt; b) **34** (3 equiv.), TBAT, THF, −78 °C, c) TBAF–AcOH, THF, rt, 85% over three steps, dr 14.1 : 1.5 : 1.0 (^{1}H NMR).

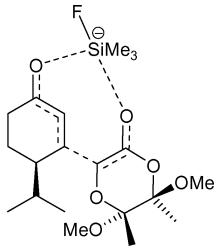


Fig. 4 Proposed transition state for Michael reaction of silyl ketene acetal **30** with (*R*)-cryptone **34**.

Kinetic resolution

The lithium enolates of **1** and **2** have been shown to react well with a range of Michael acceptors, but the scope of this reaction is limited by their propensity to undergo competitive aldol and deprotonation processes. For a synthetic project, we were interested in the Michael addition of **2** with chiral cyclohexenones such as cryptone **34**.[12] It was hoped that enantiopure **2** would react more quickly with one enantiomer of racemic cryptone than the other and thereby result in a single product bearing three stereocentres in a useful level of selectivity, without recourse to an asymmetric synthesis of the Michael acceptor—a non-trivial undertaking.[13] A softer, less basic enolate equivalent was thought necessary to favour Michael addition over aldol reaction or deprotonation and the trimethylsilyl ketene acetal **30** was investigated.[14] It was found that a one pot,[15] TBAT[16] (tetra-*N*-butylammonium triphenyldifluorosilicate)-catalyzed ketene acetal formation and Michael addition to cryptone gave the ketone **32** in excellent yield and diastereoselectivity (Scheme 7); the stereochemistry of **32** was confirmed by X-ray crystallography.

The reaction is proposed to proceed through a closed transition state in which the *R* enantiomer of cryptone is attacked by the ketene acetal from the opposite side of the cryptone ring to the isopropyl group (Fig. 4).[17]

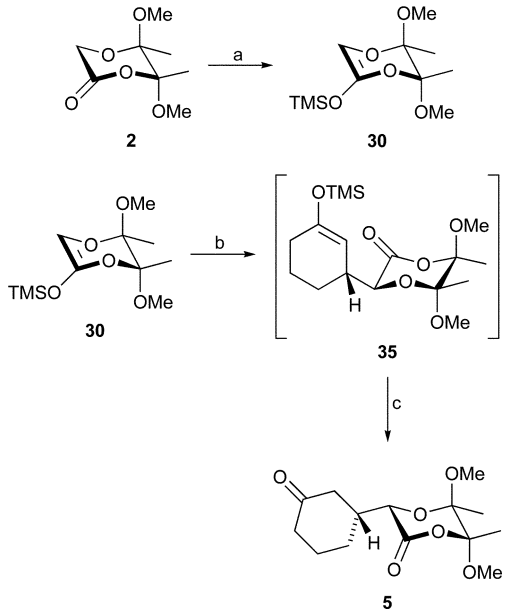
Trimethylsilyl ketene acetal **30** could also be prepared using LDA and TMSCl, and purified by distillation.[18] When one equivalent was used to kinetically resolve one equivalent of cryptone, ketone **32** was obtained in a dr of 8.1 : 1.2 : 1.0 : 0.4 (^{1}H NMR; normalized to the minor diastereomer in Scheme 7 above). The enantiomeric excess of recovered cryptone was 92% (chiral HPLC), and the combined yield of ketone diastereomers 67%. Ketene acetal **30** also underwent a successful Michael addition with cyclohexenone under TBAT catalysis to yield ketone **5** as the major diastereomeric product in 89% yield (Scheme 8). Only a 30% yield of **5** was obtained using the lithium enolate conditions described above (Table 1).

Kinetic resolution—aldol

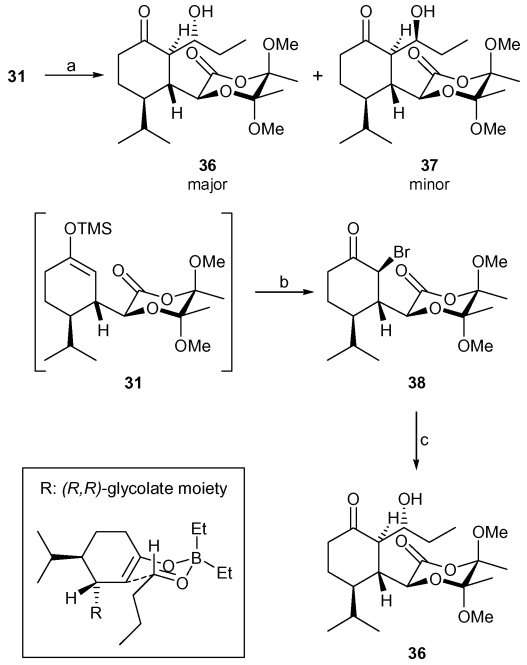
A Michael–aldol sequence based on this kinetic resolution was next investigated. Trimethylsilyl enol ether intermediate **31** was elaborated to alcohols **36** and **37** in 35% yield from **30** and a dr of 1.1 : 1 using BF_3.THF and propionaldehyde.[19] As this aldol reaction was essentially unselective, **31** was brominated using NBS and the resulting α-bromoketone **38** reacted with propionaldehyde, triphenyltin hydride and triethylborane[20] to give alcohol **36**, this time as the only discernable diastereomer. The stereochemistry of **36** was determined by X-ray analysis, and can be accounted for by the six-membered transition state shown (Scheme 9).

Conclusion

It has been shown that **1**, **2** and their alkylated derivatives undergo highly diastereoselective Michael addition reactions with a range of acceptors. The tandem reaction sequences effect



Scheme 8 a) TMSCl, LDA, THF, −78 °C, 100%; b) cyclohexenone, TBAT, THF, −78 °C to rt; c. TBAF–AcOH, 0 °C to rt, THF, 89% over 2 steps, dr 29.1 : 1.1 : 1 (^{1}H NMR).



Scheme 9 a) C_2H_5CHO, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 35% (from **30**, dr 1.1 : 1; b) NBS, THF, 0 °C, 41% (from **30**); c) Ph_3SnH, Et_3B, C_2H_5CHO, toluene, rt, 63%.

the one-pot assembly of up to five stereocentres to give multifunctional products rapidly and efficiently with a high level of stereocontrol. The simplicity of the overall processes and the high yields of relatively clean products make them ideal for the design of compound arrays.

The selective kinetic resolution of cryptone **34** marks a new paradigm in the chemistry of glycolates **1** and **2**. To the best of our knowledge it is the first report of either a TBAT-catalyzed Michael addition of a silyl ketene acetal, or the use of ethyl (trimethylsilyl)acetate as the source of silicon in this type of reaction. Its extension to a variety of other chiral and achiral Michael acceptors and application in total synthesis is ongoing and additional results will be disclosed in due course.

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 either sodium benzophenone ketyl or lithium aluminium hydride–calcium hydride; 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. The BDA-glycolates **1** and **2** were recrystallised to >99% ee (as measured by chiral GC) before use. Column chromatography was carried out using Merck Kieselgel (230–400 mesh) or pre-packed silica columns (Biotage). 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 either neat or using thin films deposited from chloroform, dichloromethane or methanol solutions. Microanalyses were determined using a CE-440 Elemental Analyser. HPLC was performed on an Agilent 1100 series HPLC using HPLC-grade solvents and UV detection at the specified wavelength. 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.

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

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **1** (38 mg, 0.20 mmol) in THF (1.5 ml) at −78 °C. The pale yellow solution was stirred for 15 min, warmed to −50 °C, and stirred for a further 15 min. Cyclopentenone (0.20 µl, 0.24 mmol) was added, and the solution stirred at −50 °C for 3 h. The reaction was quenched by addition of acetic acid (24 µl, 0.4 mmol), diluted with ether (4 ml) and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product. This was purified by column chromatography to give the ketone as a white solid (33 mg, 61%): δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, Me), 1.50 (3H, s, Me), 2.00–2.06 (2H, m, C*HH*CH$_2$C(O)), 2.10–2.20 (1H, m, CH$_2$C*H*HC(O)), 2.26–2.46 (3H, m, CHC*HH*C(O), CH$_2$C*H*HC(O)), 2.89–2.97 (1H, m, C*H*CH$_2$C(O)), 3.29 (3H, s, OMe), 3.43 (3H, s, OMe), 4.22 (1H, d, J 3.9, OCHC(O)), δ_C (100 MHz, $CDCl_3$) 16.9, 17.7, 24.0, 38.0, 38.5, 40.8, 49.2, 49.9, 72.1, 98.2, 105.2, 169.2, 218.6; ν_{max} (film/cm^{-1}) 2953, 1734, 1380, 1257, 1218, 1145, 1117, 1090, 1046, 1025; found (EI): calcd for $C_{13}H_{20}O_6Na$ $[M + Na]^+$ 295.1158, found: 295.1148; mp 129 °C; $[a]_D^{25}$ +133.4 (c 1.03, $CHCl_3$).

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

Lithium bis(trimethylsilyl)amide (0.40 ml, 1 M solution in THF, 0.40 mmol) was added drop-wise to a solution of glycolate **2** (76 mg, 0.40 mmol) in THF (1.2 ml) at −78 °C. The pale yellow solution was stirred for 15 min. A solution of 2(5*H*)-furanone (37 mg, 0.44 mmol in 1.2 ml THF) was drop-wise over 30 min. The solution was stirred for 30 min at −78 °C, quenched by addition of silica gel (100 mg), and diluted with ether (8 ml), and

allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product. This was purified by column chromatography to give the ketone as a white solid (38 mg, 35%): δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, Me), 1.50 (3H, s, Me), 2.62 (1H, dd, *J* 17.8, 8.4, C*H*HC(O)), 2.67 (1H, dd, *J* 17.8, 8.8, CH*H*C(O)), 3.18–3.26 (1H, m, C*H*CH_2C(O)), 3.31 (3H, s, OMe), 3.43 (3H, s, OMe), 4.19 (1H, d, *J* 4.8, OCHC(O)O), 4.35 (1H, dd, *J* 10.9, 7.1, C*H*HO), 4.37 (1H, dd, *J* 10.9, 7.1, CH*H*O); δ_C (100 MHz, $CDCl_3$) 16.8, 17.6, 30.5, 37.4, 49.2, 50.1, 68.7, 70.0, 98.4, 105.6, 168.1, 176.1; ν_{max} (film/cm^{-1}) 2952, 2844, 1776, 1742, 1459, 1382, 1267, 1217, 1177, 1149, 1118, 1033, 1007; found (EI): calcd for $C_{12}H_{18}O_7Na$ $[M + Na]^+$ 297.0950, found: 297.0952; mp 120–123 °C; $[\alpha]_D^{25}$ −150.2 (*c* 0.48, $CHCl_3$).

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

Procedure 1. Lithium bis(trimethylsilyl)amide (0.36 ml, 1 M solution in THF, 0.36 mmol) was added drop-wise to a solution of glycolate **2** (62 mg, 0.33 mmol) in THF (2.5 ml) at −78 °C. After 10 min, a solution of cyclohexenone (32 µl, 0.33 mmol in 0.6 ml THF) was added *via* cannula. The reaction was allowed to warm to rt overnight, quenched with acetic acid (39 µl, 0.65 mmol), diluted with ether (10 ml), filtered through a pad of silica, eluting with ether (50 ml) and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 3 : 1 petrol : ether with 1% triethylamine, eluting to 2 : 1 petrol : ether with 1% triethylamine) to give the ketone as a white solid (28 mg, 30%).

Procedure 2. Ketene acetal **30** (1.0 ml, 3.62 mmol) was added drop-wise to a solution of cyclohexenone (0.29 ml, 3.02 mmol) and TBAT (18 mg, 33 µmol) in THF (4 ml) at −78 °C. The reaction was allowed to warm to rt overnight and re-cooled to 0 °C. A solution of TBAF (1 ml, 1 M solution in THF, 1.0 mmol) and acetic acid (1 ml, 17.5 mmol) were added and the mixture allowed to warm to rt and stirred for 4 h. The reaction was quenched with sodium bicarbonate solution (10 ml), extracted with ether (3 × 20 ml), washed with brine (20 ml), dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified by column chromatography (Biotage, silica, 1 : 1 petrol : ether) to give the ketone as a white solid (769 mg, 89%): δ_H (400 MHz; $CDCl_3$) 1.37 (3H, s, Me), 1.47 (3H, s, Me), 1.59–1.63 (1H, m, C*H*HCH_2C(O)), 1.66–1.70 (1H, m, C*H*HCH_2CH_2C(O)), 1.79–1.86 (1H, m, CH*H*CH_2CH_2C(O)), 2.05–2.11 (1H, m, C*H*HCH_2C(O)), 2.20–2.28 (1H, td, *J* 13.1, 6.3, CH_2C*H*HC(O)), 2.33–2.46 (4H, m, C*H*CH_2C(O), 2 × CHC*HH*C(O), CH_2CH*H*C(O)), 3.27 (3H, s, OMe), 3.40 (3H, s, OMe), 4.00 (1H, d, *J* 2.2, OCHC(O)); δ_C (100 MHz; $CDCl_3$) 16.9, 17.8, 24.7, 25.4, 40.9, 41.1, 43.8, 49.1, 49.9, 73.1, 98.2, 105.1, 168.8, 210.7; ν_{max} (film)/cm^{-1} 2951, 1749, 1712, 1450, 1381, 1256, 1224, 1148, 1124, 1036; found (ESI) $[MNa]^+$ 309.1380, $C_{14}H_{22}O_6Na$ requires 309.1314; mp 79–81 °C; $[\alpha]_D^{25}$ −167.2 (*c* 0.5, $CHCl_3$); found C 58.70%, H 7.68%, $C_{14}H_{22}O_6$ requires C 58.72%, H 7.74%.

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

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **1** (38 mg, 0.20 mmol) in THF (1 ml) at −78 °C. The pale yellow solution was stirred for 15 min. 5,6-Dihydro-2*H*-pyran-2-one (17 µl, 0.20 mmol) was added, and the solution stirred for at −78 °C for 30 min. The reaction was quenched by addition of acetic acid (24 µl, 0.4 mmol), diluted with ether (4 ml) and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product. Unreacted 5,6-dihydro-2*H*-pyran-2-one was removed by heating the crude product to 100 °C under a vacuum of approximately 1 mmHg, and the residue purified by column chromatography to give the lactone as a white solid (36 mg, 63%): δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, Me), 1.30 (3H, s, Me), 2.60 (3H, s, OMe), 2.84 (1H, dd, *J* 16.2, 1.7), 2.92 (1H, dd, *J* 16.2, 7.2), 3.31 (3H, s, OMe), 3.76–3.79 (1H, m, C*H*CH_2C(O)), 4.37 (1H, d, *J* 3.2, OCHC(O)), 7.03–7.08 (2H, m, Ar), 7.18 (1H, dd, *J* 7.6, 1.7, Ar), 7.25–7.29 (1H, m, Ar); δ_C (100 MHz, $CDCl_3$) 16.2, 17.5, 32.9, 37.7, 49.4, 49.4, 74.9, 98.5, 105.4, 116.8, 120.4, 124.0, 129.1, 129.6, 153.3, 167.5, 167.7; ν_{max} (film/cm^{-1}) 1743, 1384, 1260, 1150, 1035; found (ESI) $[MNa]^+$ 311.1107, $C_{13}H_{20}O_7Na$ requires 311.1103; mp 129–131 °C; $[\alpha]_D^{25}$ −161.6 (*c* 0.80, $CHCl_3$).

(4*S*,3′*S*,5′*R*,6′*R*)-4-(5,6-Dimethoxy-5,6-dimethyl-3-oxo-[1,4]dioxan-2-yl)-chroman-2-one (7)

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **1** (38 mg, 0.20 mmol) in THF (1.5 ml) at −78 °C. The pale yellow solution was stirred for 15 min. Coumarin (32 mg, 0.20 mmol, solution in 0.5 ml THF) was added, and the solution stirred for at −78 °C for 30 min. The reaction was quenched by addition of acetic acid (24 µl, 0.4 mmol), diluted with ether (4 ml) and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product. This was purified by column chromatography to give the lactone as a white solid (60 mg, 90%): δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, Me), 1.30 (3H, s, Me), 2.60 (3H, s, OMe), 2.84 (1H, dd, *J* 16.2, 1.7), 2.92 (1H, dd, *J* 16.2, 7.2), 3.31 (3H, s, OMe), 3.76–3.79 (1H, m, C*H*CH_2C(O)), 4.37 (1H, d, *J* 3.2, OCHC(O)), 7.03–7.08 (2H, m, Ar), 7.18 (1H, dd, *J* 7.6, 1.7, Ar), 7.25–7.29 (1H, m, Ar); δ_C (100 MHz, $CDCl_3$) 16.2, 17.5, 32.9, 37.7, 49.4, 49.4, 74.9, 98.5, 105.4, 116.8, 120.4, 124.0, 129.1, 129.6, 153.3, 167.5, 167.7; ν_{max} (film/cm^{-1}) 2942, 1771, 1741, 1613, 1589, 1491, 1456, 1425, 1379, 1361, 1346, 1289, 1263, 1242, 1217, 1167, 1147, 1130, 1109, 1076, 1035, 1002; found (ESI): calcd for $C_{17}H_{20}O_7Na$ $[M + Na]^+$ 359.1107, found: 359.1109; mp 176 °C; $[\alpha]_D^{25}$ −211.6 (*c* 0.85, $CHCl_3$).

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

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **1** (38 mg, 0.20 mmol) in THF (1.5 ml) at −78 °C. The pale yellow solution was stirred for 15 min. *trans*-2-Nitrostyrene (30 mg, 0.20 mmol, solution in 0.5 ml THF) was added, and the solution stirred for at −78 °C for 15 min. The reaction was quenched by addition of acetic acid (24 µl, 0.4 mmol), diluted with ether (4 ml) and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product. This was purified by column chromatography to give the nitroalkane as a white solid (65 mg, 96%): δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, Me), 1.42 (3H, s, Me), 2.73 (3H, s, OMe), 3.32 (3H, s, OMe), 4.23 (1H, ddd, *J* 9.6, 6.3, 3.5, CHPh), 4.51 (1H, d, *J* 3.5, OCHC(O)), 4.70 (1H, dd, *J* 12.8, 6.3, C*H*HNO_2), 5.03 (1H, dd, *J* 12.8, 9.6, CH*H*NO_2), 7.27–7.36 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 16.8, 17.7, 45.0, 49.0, 49.2, 70.5, 75.8, 98.6, 105.2, 128.1, 128.2, 129.9, 134.3, 167.2; ν_{max} (film/cm^{-1}) 2968, 2366, 2068, 1721, 1551, 1497, 1457, 1427, 1379, 1353, 1328, 1292, 1255, 1217, 1155, 1116, 1080, 1048, 1034, 1012; found (EI): calcd for $C_{16}H_{21}O_7NNa$ $[M + Na]^+$ 362.1216, found: 362.1211; mp 108 °C; $[\alpha]_D^{25}$ +145.0 (*c* 1.00, $CHCl_3$).

(3*R*,5*S*,6*S*,1′*S*,2′*R*)-5,6-Dimethoxy-5,6-dimethyl-3-(2-nitro-1-phenylpropyl)-[1,4]dioxan-2-one (major diastereomer) (9) and (3*R*,5*S*,6*S*,1′*S*,2′*S*)-5,6-dimethoxy-5,6-dimethyl-3-(2-nitro-1-phenylpropyl)-[1,4]dioxan-2-one (minor diastereomer)

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **1** (38 mg, 0.20 mmol) in THF (1 ml) at −78 °C. The pale yellow solution was stirred for 15 min. 2-Nitro-1-phenylpropene (36 mg, 0.22 mmol, solution in 0.5 ml THF) was added, and the solution stirred for at −78 °C for 30 min. The reaction was quenched by addition of acetic acid (30 μl, 0.5 mmol, solution in 0.5 ml ether), diluted with ether (4 ml) and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product. This was purified by column chromatography to give the nitroalkanes as white solids (39 mg, 55% and 21 mg, 30%): (major diastereomer) δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, Me), 1.41 (3H, s, Me), 1.75 (3H, d, *J* 6.6, CHMe), 2.62 (3H, s, OMe), 3.34 (3H, s, OMe), 3.81 (1H, dd, *J* 11.2, 3.2, CHPh), 4.55 (1H, d, *J* 3.2, CHCO), 5.29 (1H, dq, *J* 11.2, 6.6, C*H*Me), 7.21–7.23 (3H, m, Ph), 7.33–7.35 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 16.8, 17.7, 18.3, 48.9, 49.3, 50.6, 70.6, 84.8, 98.7, 105.0, 127.8, 127.9, 130.5, 133.9, 167.2; ν_{max} (film/cm^{-1}) 2942, 1737, 1552, 1495, 1456, 1382, 1353, 1328, 1296, 1256, 1199, 1178, 1152, 1119, 1081, 1049, 1035; found (EI): calcd for $C_{17}H_{23}O_7NNa$ [M + Na]$^+$ 376.1372, found: 376.1356; mp 153 °C; $[\alpha]_D^{25}$ +60.0 (*c* 0.15, $CHCl_3$); (minor diastereomer) δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, Me), 1.35 (3H, d, *J* 6.8, CHMe), 1.43 (3H, s, Me), 2.68 (3H, s, OMe), 3.27 (3H, s, OMe), 3.83 (1H, dd *J* 11.4, 3.2, C*H*Ph), 4.33 (1H, d, 3.2, CHCO), 5.32 (1H, dq *J* 11.4, 6.8, C*H*Me), 7.27–7.29 (3H, m, Ph), 7.34–7.36 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 16.8, 17.7, 18.8, 48.9, 49.2, 50.9, 70.2, 83.4, 98.5, 105.1, 128.0, 128.2, 130.8, 133.8, 167.2; ν_{max} (film/cm^{-1}) 2947, 1740, 1547, 1499, 1457, 1391, 1380, 1356, 1329, 1296, 1263, 1215, 1179, 1147, 1119, 1078, 1029, found (EI): calcd for $C_{17}H_{23}O_7NNa$ [M + Na]$^+$ 376.1372, found: 376.1364; mp 117–119 °C; $[\alpha]_D^{25}$ +139.3 (*c* 0.41, $CHCl_3$).

(3*S*,5*R*,6*R*,1′*R*,2′*S*)-5,6-Dimethoxy-5,6-dimethyl-3-(2-nitrocyclohexyl)-[1,4]dioxan-2-one (10)

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **1** (38 mg, 0.20 mmol) in THF (1 ml) at −78 °C. The pale yellow solution was stirred for 15 min. 1-Nitro-1-cyclohexene (25 μl, 0.22 mmol, solution in 0.5 ml THF) was added, and the solution stirred at −78 °C for 30 min. The reaction was quenched by addition of acetic acid (30 μl, 0.5 mmol), diluted by drop-wise addition of ether (3 ml), stirred for 10 min at −78 °C and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product. This was purified by column chromatography to give the nitroalkane as a white solid (62 mg, 98%): δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, Me), 1.33–1.39 (1H, m, C*H*HCH$_2$CHNO$_2$), 1.44 (3H, s, Me), 1.50–1.61 (2H, m, C*H*HCH$_2$CH$_2$CHNO$_2$, CH*H*CHCHNO$_2$), 1.74–1.82 (1H, m, C*H*HCHNO$_2$), 1.84–1.93 (2H, m, CH*H*CH$_2$CH$_2$CHNO$_2$, CH*H*CH$_2$CHNO$_2$), 2.00–2.13 (1H, m, C*H*HCHCHNO$_2$), 2.31–2.35, 1H, m, C*H*HCHNO$_2$), 2.52–2.58 (1H, m, C*H*CHNO$_2$), 3.27 (3H, s, OMe), 3.37 (3H, s, OMe), 4.33 (1H, d, *J* 3.6, OCHC(O), 4.83 (1H, q, *J* 4.3, CHNO$_2$); δ_C (100 MHz, $CDCl_3$) 16.6, 17.6, 20.5, 22.4, 24.0, 29.5, 41.8, 49.3, 49.8, 71.9, 84.2, 98.0, 105.3, 168.7; ν_{max} (film/cm^{-1}) 2948, 1744, 1550, 1449, 1379, 1268, 1148, 1035; found (ESI): calcd for $C_{14}H_{23}O_7NNa$ [M + Na]$^+$ 340.1372, found: 340.1373; mp 131 °C; $[\alpha]_D^{25}$ −204.2 (*c* 0.24, $CHCl_3$).

(3*S*,5*R*,6*R*)-5,6-Dimethoxy-3,5,6-trimethyl-3-((*R*)-2-nitro-1-phenylethyl)-[1,4]dioxan-2-one (12)

Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.84 ml, 0.42 mmol) was added drop-wise to a stirred solution of (*R*,*R*)-**137** (77 mg, 0.38 mmol) in THF (0.75 ml) at −78 °C. After stirring for 15 min, *trans*-2-nitrostyrene (57 mg, 0.38 mmol) in THF (0.63 mmol) was added drop-wise *via* cannula. The solution was stirred for a further 4 h at −78 °C then acetic acid (50 μl, 0.84 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 *in vacuo*. The residue was purified by column chromatography (ether–petrol 1 : 9 then 3 : 17) to give the nitroalkane as a white prisms (64 mg, 57%): δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, Me), 1.43 (3H, s, Me), 1.49 (3H, s, Me), 3.07 (3H, s, OMe), 3.24 (3H, s, OMe), 4.16 (1H, dd, *J* 10.6, 4.8, PhC*H*), 4.85 (1H, dd, *J* 13.5, 10.6, O$_2$NC*H*H), 4.97 (1H, dd, *J* 13.5, 4.8, O$_2$NCH*H*), 7.24–7.28 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) (100 MHz, $CDCl_3$) 17.5, 18.0, 24.7, 49.4, 49.5, 50.7, 75.5, 77.1, 99.0, 106.1, 127.86, 127.87, 130.4, 134.7, 170.8; ν_{max} (film/cm^{-1}) 2950, 1737, 1554, 1378; Found (ES): [MNa]$^+$ 376.1385, $C_{17}H_{23}NO_7Na$ requires 376.1372; mp 116–118 °C; $[\alpha]_D^{25}$ −99.1 (*c* 0.32, $CHCl_3$); anal. calc. for $C_{17}H_{23}NO_7$ C, 57.78; H, 6.56; N, 3.96; Found: C, 58.08; H, 6.62; N, 3.84%.

(3*S*,5*R*,6*R*)-3-Benzyl-5,6-dimethoxy-5,6-dimethyl-3-((*R*)-2-nitro-1-phenylethyl)-[1,4]dioxan-2-one (14)

Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 0.42 ml, 0.21 mmol) was added drop-wise to a stirred solution of (*R*,*R*)-**139** (53 mg, 0.19 mmol) in THF (0.4 ml) at −78 °C. After stirring for 15 min, *trans*-2-nitrostyrene (29 mg, 0.19 mmol) was added in THF (0.6 ml) drop-wise *via* cannula. The solution was stirred for a further 60 min at −78 °C then acetic acid (26 μl, 0.42 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 *in vacuo*. The residue was purified by column chromatography (ether–petrol 1 : 9 then 3 : 17) to give the nitroalkane as a white prisms (20 mg, 25%): δ_H (400 MHz, $CDCl_3$) 1.44 (3H, s, Me), 1.48 (3H, s, Me), 3.01 (3H, s, OMe), 3.12 (1H, d, *J* 14.8, C*H*HPh), 3.22 (3H, s, OMe), 3.28 (1H, d, *J* 14.8, CH*H*Ph), 4.26 (1H, dd, *J* 11.7, 3.8, CHPh), 4.89 (1H, dd, *J* 13.3, 11.7. C*H*HNO$_2$), 5.16 (1H, dd, *J* 13.3, 3.8, CH*H*NO$_2$), 7.10–7.15 (2H, m, Ph), 7.15–7.22 (3H, m, Ph), 7.22–7.29 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 17.6, 18.3, 42.0, 48.6, 49.4, 49.8, 75.9, 81.0, 99.4, 106.4, 127.1, 127.7, 127.8, 128.4, 130.6, 130.8, 134.1, 135.4, 168.9; ν_{max} (film/cm^{-1}) 2949, 1743, 1555, 1379; found (ES): [MNa]$^+$ 452.1694, $C_{23}H_{27}NO_7Na$ requires 452.1685; mp 162–163 °C; $[\alpha]_D^{25}$ −90.8 (*c* 0.25, $CHCl_3$).

General procedure for the preparation of 15–18

A solution of HCl in MeOH was prepared by adding trimethylsilyl chloride (0.35 ml) to MeOH (5 ml) at 0 °C. This solution was added to 1 mmol of adduct and the mixture allowed to stir at rt for 1 h. The solution was concentrated *in vacuo* and the residue purified by column chromatography.

Methyl (*S*,*S*)-hydroxy-(3-oxocyclopentyl)acetate (15). Clear gum: δ_H (400 MHz, $CDCl_3$) 1.77–1.95 (2H, m, C*HH*CH$_2$C(O)), 2.12–2.19 (2H, m, CHC*H*HC(O), C*H*HC(O)), 2.29–2.41 (2H, m, CHCH*H*C(O), CH*H*C(O)), 2.59–2.66 (1H, m, C*H*CH$_2$C(O)), 2.85 (1H, d, *J* 5.0, OH), 3.83 (3H, s, OMe), 4.24 (1H, t, *J* 5.0, C*H*OH); δ_C (100 MHz, $CDCl_3$) 23.2, 38.1, 40.0, 41.0, 52.8, 71.6, 174.5, 217.8; ν_{max} (film/cm^{-1}) 3442, 2958, 1728, 1439, 1403, 1211, 1158, 1105, 1076, 1015; found (ESI): [MNa]$^+$ 195.0641, $C_8H_{12}O_4Na$ requires 195.0633; $[\alpha]_D^{25}$ +59.0 (*c* 1.00, $CHCl_3$).

Dimethyl (2*S*,3*S*)-2-hydroxy-3-(2-hydroxyphenyl)pentanedioate (16). Clear gum: δ_H (400 MHz, $CDCl_3$) 2.87 (1H, dd, *J* 16.8, 7.0, C*H*HCO$_2$Me), 3.15 (1H, dd, *J* 16.8, 8.3, C*H*HCO$_2$Me), 3.65 (3H, s, OMe), 3.69 (3H, s, OMe), 3.83 (1H, ddd, *J* 8.3, 7.0, 3.3, CHAr), 4.68 (1H, d, *J* 3.3, C*H*OH), 6.80 (1H, dt, *J* 7.5, 1.1, Ar), 6.86 (1H, dd, *J* 8.1, 1.1), 7.05 (1H, dd, *J* 7.5, 1.6, Ar), 7.13 (1H, dt, *J* 7.8, 1.6), 7.60 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 34.6, 42.7, 51.9, 52.8, 73.5, 118.1, 120.5, 124.3, 129.3, 131.3, 154.9, 172.7, 173.3; ν_{max} (film/cm^{-1}) 3417, 2956, 1738, 1456, 1224, 1107; found (ESI): [MNa]$^+$ 291.0847, $C_{13}H_{16}O_6Na$ requires 291.0845; $[\alpha]_D^{25}$ +37.8 (*c* 0.55, $CHCl_3$).

Methyl (2*R*,3*S*)-2-hydroxy-4-nitro-3-phenylbutyrate (17). White solid: δ_H (400 MHz, $CDCl_3$) 2.96 (1H, d, *J* 5.6, OH), 3.68 (3H, s, OMe), 3.97–4.02 (1H, m, CHPh), 4.55–4.58 (1H, m, C*H*OH), 4.77 (1H, dd, *J* 13.4, 7.2, C*H*HNO$_2$), 5.00 (1H, dd, *J* 13.4, 8.1, CH*H*NO$_2$), 7.22–7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 46.5, 52.8, 70.8, 76.2, 128.5, 128.5, 128.8, 134.1, 172.7; ν_{max} (film/cm^{-1}) 3234, 2973, 1733, 1677, 1606, 1541, 1491, 1456, 1380, 1345, 1264, 1239, 1215, 1177, 1148, 1119, 1100, 1047, 1033; found (ES): [MNa]$^+$ 262.0686, $C_{11}H_{13}NO_5Na$ requires 262.0691; mp 74–76 °C; $[\alpha]_D^{25}$ −17.2 (*c* 0.72, $CHCl_3$).

Methyl (*S*,1′*R*,2′*S*)-hydroxy-(2-nitrocyclohexyl)-acetate (18). White solid: δ_H (400 MHz, $CDCl_3$) 1.28–1.41 (1H, m, C*H*HCH$_2$CH$_2$CHNO$_2$), 1.54–1.61 (1H, m, C*H*HCH$_2$CHNO$_2$), 1.64–1.85 (3H, m, C*H*HCHCHNO$_2$, C*H*HCH$_2$CHNO$_2$, C*H*HCHNO$_2$), 1.88–1.93 (1H, m, CH*H*CH$_2$CH$_2$CHNO$_2$), 1.96–2.06 (1H, m, CH*H*CHCHNO$_2$), 2.15–2.21 (1H, m, C*H*CHNO$_2$), 2.32–2.42 (1H, m, CH*H*CHNO$_2$), 2.75 (1H, d, *J* 5.8, OH), 3.80 (3H, s, OMe), 4.35 (1H, t, *J* 5.7, C*H*OH), 4.74–4.79 (1H, m, C*H*NO$_2$); δ_C (100 MHz, $CDCl_3$) 20.7, 22.5, 24.3, 29.9, 43.6, 52.8, 71.8, 83.2, 174.0; ν_{max} (film/cm^{-1}) 3476, 2928, 1738, 1547, 1449, 1376, 1222, 1121; found (ESI): [MNa]$^+$ 240.0843, $C_9H_{15}NO_5Na$ requires 240.0848; mp 56–57 °C; $[\alpha]_D^{25}$ +30.0 (*c* 0.14, $CHCl_3$).

(3*R*,4*S*)-3-((*S*)-1-Methoxy-1-methyl-2-oxopropoxy)-4-phenylpyrrolidin-2-one (19)

Raney-nickel (0.30 g, 50% suspension in water) was rinsed with MeOH (5 ml × 5) and EtOAc (5 ml × 2) and suspended in EtOAc (5 ml). Glycolate **8** (50 mg, 0.18 mmol) was added to this suspension and the reaction stirred under a balloon of hydrogen for 16 h.[21] The Raney-nickel was removed by filtration, the solution concentrated *in vacuo*, and re-dissolved in CH_2Cl_2 (5 ml). Silica gel (200 mg) was added and the suspension stirred at rt overnight. The suspension was filtered and concentrated *in vacuo*, and the residue purified by column chromatography (silica, EtOAc) to give the lactam as a clear oil (32 mg, 78%): δ_H (400 MHz; $CDCl_3$) 1.02 (3H, s, MeC), 2.22 (3H, s, MeC(O)), 3.22 (3H, s, OMe), 3.38 (1H, dd, *J* 9.6, 8.4, C*H*Ph), 3.52 (1H, q, *J* 8.3, C*H*HNH), 3.72 (1H, ddd, *J* 9.7, 8.3, 1.4, CH*H*NH), 4.52 (1H, d, *J* 8.4, CHO), 6.29 (1H, br s, NH), 7.27–7.30 (3H, m, Ph), 7.35–7.38 (2H, m, Ph); δ_C (125 MHz; $CDCl_3$) 21.5, 26.1, 29.7, 46.0, 49.6, 51.0, 75.3, 102.8, 127.8, 129.0, 139.3, 173.9, 205.9; ν_{max} (film/cm^{-1}) 3282, 2920, 1717, 1491, 1456, 1356, 1254, 1167, 1116, 1047; found (ESI) [MNa]$^+$ 300.1205, $C_{15}H_{19}NO_4Na$ requires 300.1212; $[\alpha]_D^{25}$ (*ent*-**19**) −24.4 (*c* 0.14, $CHCl_3$).

Methyl (2*R*,3*S*)-4-*tert*-butoxycarbonylamino-2-hydroxy-3-phenylbutyrate (20)

Triethylamine (11 µl, 0.08 mmol), *tert*-butoxycarbonylanhydride (35 mg, 0.16 mmol) and 4-dimethylaminopyridine (cat) were added to a solution of lactam **19** (22 mg, 0.08 mmol) in CH_2Cl_2 (1 ml) at rt. The solution was stirred overnight, concentrated *in vacuo* and the residue directly purified by column chromatography to give *N*-Boc **19** (29 mg, 95%). Sodium methoxide (0.39 ml, 0.33 M solution in MeOH, 0.13 mmol) was added to a solution of *N*-Boc **19** (49 mg, 0.13 mmol) in MeOH at 0 °C. After 1 h, additional sodium methoxide (0.08 ml, 0.33 M solution in MeOH, 0.03 mmol) was added and the solution stirred for 30 min. The reaction was diluted with ether (2 ml) and ammonium chloride solution (2 ml), extracted with ether (5 ml), washed with brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica, petrol : EtOAc 1 : 1) to give *O*-C(Me)(OMe)C(O)Me **20** (40 mg, 76%). Triphenylphosphine hydrobromide (0.3 ml, 0.01 M solution in MeOH, 3 µmol) was added to a solution of *O*-C(Me)(OMe)C(O)Me **20** (14 mg, 0.034 mmol) in MeOH (2 ml) at rt. The solution was stirred overnight and concentrated *in vacuo*, and the residue purified by column chromatography (silica, petrol : ether 1 : 1 to 1 : 2) to give **20** as a clear gum (10 mg, 95%; 69% over three steps): δ_H (400 MHz; $CDCl_3$) 1.44 (9H, s, C(Me)$_3$), 3.27–3.35 (2H, m, OH, C*H*Ph), 3.41–3.46 (1H, m, C*H*H), 3.62 (3H, s, OMe), 3.72–3.80 (1H, m, CH*H*), 4.55 (1H, dd, *J* 5.6, 3.1, C*H*OH), 4.74 (1H, br s, NH), 7.23–7.30 (5H, m, Ph), δ_C (100 MHz; $CDCl_3$) 28.4, 42.3, 48.9, 52.3, 71.3, 79.8, 127.6, 128.4, 128.8, 137.1, 156.5, 173.8; ν_{max} (film)/cm^{-1} 3360, 2977, 1738, 1712, 1518, 1454, 1393, 1367, 1251, 1169, 1118, 1014; found (ESI) [MNa]$^+$ 332.1462, $C_{16}H_{23}NO_5Na$ requires 332.1474; $[\alpha]_D^{25}$ −18.2 (*c* 0.70, $CHCl_3$).

(3*S*,5*R*,6*R*)-3-[(3*R*,4*R*)-3-((*R*)-Hydroxyphenylmethyl)-2-oxotetrahydropyran-4-yl]-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (major diastereomer) (21) and (3*S*,5*R*,6*R*)-3-[(3*R*,4*R*)-3-((*S*)-hydroxyphenylmethyl)-2-oxotetrahydropyran-4-yl]-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (minor diastereomer)

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **2** (38 mg, 0.20 mmol) in THF (1.5 ml) at −78 °C. The pale yellow solution was stirred for 15 min. 5,6-Dihydro-2*H*-pyran-2-one (20 mg, 0.20 mmol) was added, and the solution stirred for 1 h at −78 °C. Benzaldehyde (25 mg, 0.24 mmol) was added, and the solution stirred for 30 min at −78 °C. The reaction was quenched by addition of acetic acid (24 µl, 0.4 mmol), diluted with ether (4 ml) and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product. Unreacted 5,6-dihydro-2*H*-pyran-2-one and benzaldehyde was removed by heating the crude product to 100 °C under a vacuum of approximately 1 mmHg, and the residue purified by column chromatography (silica, ether) to give the alcohol as a white solid (58 mg, 74%): (major diastereomer) δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, Me), 1.38 (3H, s, Me), 1.58–1.65 (1H, m, C*H*HCHHO), 1.95–2.04 (1H, m, CH*H*CHHO), 2.91 (3H, s, OMe), 2.97 (1H, d, *J* 4.4, OH), 3.00–3.06 (1H, m, C*H*CHC(O)O), 3.09 (1H, d, *J* 2.7, OCHC(O)O), 3.13–3.18 (1H, m, CHC*H*C(O)OCHH), 3.34 (3H, s, OMe), 4.20 (1H, dt, *J* 10.5, 2.4, C*H*HOC(O)), 4.36–4.41 (1H, m, CH*H*OC(O)), 5.52 (1H, s, C*H*OH), 7.29 (1H, d, *J* 7.3, Ph), 7.36 (2H, t, *J* 7.3, Ph), 7.47 (2H, d, *J* 7.5, Ph); δ_C (100 MHz, $CDCl_3$) 16.8, 17.5, 24.1, 33.5, 48.3, 49.0, 49.8, 67.6, 71.3, 73.7, 98.1, 105.1, 125.8, 128.0, 128.8, 141.0, 168.3, 173.4; ν_{max} (film/cm^{-1}) 3423, 2951, 1726, 1453, 1384, 1276, 1215, 1151, 1133, 1086, 1053, 1035; found (ESI): calcd for $C_{20}H_{26}O_8Na$ [M + Na]$^+$ 417.1525, found: 417.1531; mp 189–191 °C; $[\alpha]_D^{25}$ −89.3 (*c* 0.8, $CHCl_3$); (minor diastereomer) δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, Me), 1.44 (3H, s, Me), 1.68 (1H, dqn, *J* 7.3, 3.3, C*H*HCHHO), 1.94 (1H, dqn, *J* 7.3, 3.2, CH*H*CHHO), 2.74 (1H, dq, *J* 7.1, 2.8, C*H*CHC(O)O), 3.21 (3H, s, OMe), 3.22–3.25 (1H, m, CHC*H*C(O)OCHH), 3.36 (3H, s, OMe), 3.75 (1H, d, *J* 3.7, OH), 3.77 (1H, d, *J* 2.8, OCHC(O)O), 3.89 (1H, ddd, *J* 10.9, 7.8, 3.3, C*H*HOC(O)), 4.35 (1H, ddd, *J* 10.9, 7.4, 3.2, CH*H*OC(O)), 5.18 (1H, dd, *J* 6.2, 3.7, C*H*OH), 7.29–7.39 (3H, m, Ph), 7.43–7.46 (2H, m, Ph); δ_C (100 MHz, $CDCl_3$) 16.9, 17.6, 24.5, 34.9, 47.5, 49.3, 49.9, 67.3, 71.7, 74.5, 98.3, 105.3, 126.6, 128.4, 128.7, 140.5, 168.5, 173.3; ν_{max} (film/cm^{-1}) 3526, 2950, 2837, 1734, 1459, 1405, 1382, 1328, 1268, 1223, 1172, 1152, 1125, 1100, 1085, 1067, 1050, 1038,

1009; found (ESI): calcd for $C_{20}H_{26}O_8Na$ [M + Na]$^+$ 417.1525, found: 417.1505; mp 172–173 °C; $[\alpha]_D^{25}$ −125.2 (*c* 0.5, $CHCl_3$).

When $B(OMe)_3$ was used as an additive, 1.3 equiv. was added *via* syringe immediately before the aldehyde.

(3*S*,5*R*,6*R*)-3-(3*R*,4*R*)-3-[(*R*)-Hydroxy-(4-methoxyphenyl)-methyl]-2-oxotetrahydropyran-4-yl}-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (major diastereomer) (22) and (3*S*,5*R*,6*R*)-3-(3*R*,4*R*)-3-[(*S*)-hydroxy-(4-methoxyphenyl)-methyl]-2-oxotetrahydropyran-4-yl}-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (minor diastereomer)

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **2** (38 mg, 0.20 mmol) in THF (0.6 ml) at −78 °C. The pale yellow solution was stirred for 20 min. 5,6-Dihydro-2*H*-pyran-2-one (20 µl, 0.20 mmol, solution in 0.5 ml THF) was added, and the solution stirred for 30 min at −78 °C. *p*-Anisaldehyde (26 µl, 0.22 mmol, solution in 0.5 ml THF) was added, and the solution stirred for 30 min at −78 °C. The reaction was quenched by addition of acetic acid (24 µl, 0.4 mmol), diluted with ether (4 ml) and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product which was twice purified by column chromatography (silica, petrol : EtOAc 2 : 1 eluting to 1 : 1; then silica, ether : CH_2Cl_2 1 : 2) to give the alcohol as a white solid (56 mg, 66%): (major diastereomer) δ_H (500 MHz, $CDCl_3$) 1.29 (3H, s, Me), 1.39 (3H, s, Me), 1.56–1.66 (1H, m, C*H*HCH$_2$O), 1.94–2.05 (1H, m, CH*H*CH$_2$O), 2.93 (1H, d, *J* 5.1, OH), 2.94–3.01 (1H, m, C*H*CHC(O)O), 2.97 (3H, s, OMe), 3.12 (1H, dd, *J* 8.1, 3.3, CHC*H*C(O)O), 3.21 (1H, d, *J* 2.6, OCHC(O)O), 3.34 (3H, s, OMe), 3.78 (3H, s, OMe), 4.17 (1H, td, *J* 10.6, 2.6, CH$_2$C*H*HO), 4.36 (1H, ddd, *J* 10.6, 4.8, 3.7, CH$_2$CH*H*O), 5.42 (1H, br t, *J* 3.7, C*H*OH), 6.87 (2H, d, *J* 8.8, Ar), 7.36 (2H, d, *J* 8.8, Ar); δ_C (125 MHz, $CDCl_3$) 16.8, 17.6, 24.0, 33.8, 48.3, 49.0, 49.8, 55.3, 67.6, 71.3, 73.5, 98.1, 105.1, 114.1, 127.0, 133.0, 159.3, 168.4, 173.5; ν_{max} (film/cm^{-1}) 3458, 2958, 1725, 1612, 1513, 1458, 1384, 1251, 1215, 1151, 1076, 1035; found (ESI): calcd for $C_{21}H_{28}O_9Na$ [M + Na]$^+$ 447.1631, found: 447.1613; mp 65–67 °C; $[\alpha]_D^{25}$ −106.4 (*c* 0.1, $CHCl_3$); (minor diastereomer) δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, Me), 1.45 (3H, s, Me), 1.63–1.71 (1H, m, C*H*HCH$_2$O), 1.91–1.99 (1H, m, CH*H*CH$_2$O), 2.94–3.01 (1H, dq, *J* 7.3, 2.7, C*H*CHC(O)O), 3.19–3.22 (1H, m, CHC*H*C(O)O), 3.22 (3H, s, OMe), 3.36 (3H, s, OMe), 3.80 (3H, s, OMe), 3.80–3.81 (1H, m, OCHC(O)O), 3.87–92 (1H, m, CH$_2$CH*H*O), 4.36 (1H, ddd, *J* 10.6, 7.2, 3.1, CH$_2$C*H*HO), 5.15 (1H, d, *J* 6.4, C*H*OH), 6.90 (2H, d, *J* 8.6, Ar), 7.36 (2H, d, *J* 8.6, Ar); δ_C (100 MHz, $CDCl_3$) 16.9, 17.6, 24.5, 35.0, 47.6, 49.3, 49.9, 55.3, 67.3, 71.9, 74.3, 98.3, 105.3, 114.1, 127.9, 132.4, 159.6, 168.6, 173.4; ν_{max} (film/cm^{-1}) 2958, 1726, 1513, 1383, 1253, 1150, 1036, found (ESI): calcd for $C_{21}H_{28}O_9Na$ [M + Na]$^+$ 447.1631, found: 447.1614; mp 45–48 °C; $[\alpha]_D^{25}$ −146.7 (*c* 0.03, $CHCl_3$).

When $B(OMe)_3$ was used as an additive, 1.3 equiv. was added *via* syringe immediately before the aldehyde.

(3*R*,4*S*)-4-((2*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-oxo-[1,4]dioxan-2-yl)-3-[(*R*)-hydroxy-(4-methoxyphenyl)methyl]chroman-2-one (23)

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **2** (38 mg, 0.20 mmol) in THF (0.8 ml) at −78 °C. The pale yellow solution was stirred for 20 min. Coumarin (30 mg, 0.20 mmol, solution in 0.5 ml THF) was added, and the solution stirred for 30 min at −78 °C. *p*-Anisaldehyde (26 µl, 0.22 mmol, solution in 0.5 ml THF) was added, and the solution stirred for 30 min at −78 °C. The reaction was quenched by addition of acetic acid (24 µl, 0.4 mmol), diluted with ether (4 ml) and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product which was purified by column chromatography (silica, petrol : EtOAc 1 : 1) to give the alcohol as a white solid (69 mg, 73%): (major diastereomer) δ_H (400 MHz, $CDCl_3$) 1.25 (6H, s, 2 × Me), 2.45 (1H, br s, OH), 2.55 (3H, s, OMe), 3.08 (1H, dd, *J* 9.6, 1.0, CHC*H*C(O)O), 3.21 (1H, d, *J* 3.1, C*H*CHC(O)O), 3.26 (3H, s, OMe), 3.80 (3H, s, OMe), 4.15 (1H, d, *J* 3.1, OCHC(O)O), 4.50 (1H, d, *J* 9.6, C*H*OH), 6.84 (2H, d, *J* 8.7, Ar), 6.99–7.07 (3H, m, Ar), 7.10 (2H, d, *J* 8.7, Ar), 7.26–7.29 (1H, m, Ar); δ_C (100 MHz, $CDCl_3$) 16.1, 17.5, 40.5, 49.3, 49.4, 51.8, 55.3, 72.6, 74.8, 98.5, 105.4, 114.4, 116.5, 118.8, 124.1, 127.6, 129.2, 130.0, 132.0, 152.8, 160.0, 167.4, 167.8; ν_{max} (film/cm^{-1}) 3461, 2946, 2840, 1740, 1612, 1588, 1514, 1490, 1457, 1379, 1360, 1300, 1248, 1221, 1151, 1110, 1078, 1032; found (ESI): calcd for $C_{25}H_{28}O_9Na$ [M + Na]$^+$ 495.1631, found: 495.1609; mp 78–81 °C; $[\alpha]_D^{25}$ −131.9 (*c* 0.36, $CHCl_3$).

When $B(OMe)_3$ was used as an additive, 1.3 equiv. was added *via* syringe immediately before the aldehyde.

(3*R*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-3-[(3*R*,4*S*)-3-((*R*)-2-nitro-1-phenylethyl)-2-oxotetrahydropyran-4-yl]-[1,4]dioxan-2-one (major diastereomer) (24) and (3*R*,5*S*,6*S*)-5,6-dimethoxy-5,6-dimethyl-3-[(3′*R*,4′*S*)-3-((*S*)-2-nitro-1-phenylethyl)-2-oxotetrahydropyran-4-yl]-[1,4]dioxan-2-one (minor diastereomer)

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **2** (38 mg, 0.20 mmol) in THF (0.8 ml) at −78 °C. The pale yellow solution was stirred for 20 min. 5,6-Dihydro-2*H*-pyran-2-one (22 mg, 0.22 mmol, solution in 0.5 ml THF) was added, and the solution stirred for 1 h at −78 °C. *trans*-2-Nitrostyrene (33 mg, 0.22 mmol, solution in 0.5 ml THF) was added, and the solution stirred for 1.5 h at −78 °C. The reaction was quenched by addition of acetic acid (24 µl, 0.4 mmol), diluted with ether (4 ml) and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product which was purified by column chromatography (silica, petrol : ether 1 : 2) to give the nitroalkanes as white solids (56 mg, 64% and 14 mg, 16%): (major diastereomer) δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, Me), 1.44 (3H, s, Me), 1.72–1.80 (1H, m, C*H*HCH$_2$O), 1.97–2.09 (1H, m, CH*H*CH$_2$O), 2.64–2.70 (1H, m, C*H*CH$_2$CH$_2$), 3.11 (1H, dd, *J* 6.5, 5.6, CHC(O)O), 3.18 (3H, s, OMe), 3.35 (3H, s, OMe), 3.84–3.89 (2H, m, OCHC(O), PhCH), 4.12 (1H, ddd, *J* 11.3, 8.5, 3.7, CH$_2$C*H*HO), 4.42 (1H, ddd, *J* 11.3, 6.5, 4.1, CH$_2$CH*H*O), 4.89 (1H, dd, *J* 13.7, 8.5, C*H*HNO$_2$), 4.93 (1H, dd, *J* 13.7, 6.7, CH*H*NO$_2$), 7.29–7.39 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 16.8, 17.6, 22.7, 37.7, 45.4, 45.4, 49.2, 49.9, 67.1, 71.6, 77.5, 98.5, 105.5, 128.1, 128.6, 129.4, 137.1, 168.0, 171.4; ν_{max} (film/cm^{-1}) 2950, 1730, 1553, 1456, 1380, 1326, 1266, 1212, 1151, 1115, 1080, 1050, 1035; found (ESI): calcd for $C_{21}H_{27}O_9NNa$ [M + Na]$^+$ 460.1584, found: 460.1584; mp 157 °C; $[\alpha]_D^{25}$ +133.1 (*c* 0.48, $CHCl_3$); (minor diastereomer) δ_H (500 MHz, $CDCl_3$) 1.41 (3H, s, Me), 1.42–1.46 (1H, m, C*H*HCH$_2$O), 1.51 (3H, s, Me), 1.99–2.07 (1H, m, CH*H*CH$_2$O), 2.60–2.64 (1H, m, C*H*CH$_2$CH$_2$), 3.21 (1H, dd, *J* 9.3, 3.1, CHC(O)O), 3.30–3.34 (1H, m, CH$_2$CH*H*O), 3.38 (3H, s, OMe), 3.41 (3H, s, OMe), 3.77–3.81 (1H, ddd, *J* 9.0, 5.6, 3.2, PhCH), 4.13 (1H, dt, *J* 11.0, 3.5, CH$_2$CH*H*O), 4.40 (1H, d, *J* 2.5, OCHC(O)O), 4.81 (1H, dd, *J* 14.3, 5.6, C*H*HNO$_2$), 5.54 (1H, dd, *J* 14.3, 9.0, CH*H*NO$_2$), 7.28–7.29 (2H, m, Ph), 7.35–7.40 (3H, m, Ph); δ_C (125 MHz, $CDCl_3$) 16.7, 17.5, 23.0, 38.3, 43.5, 44.2, 49.3, 49.8, 67.4, 69.5, 77.4, 98.3, 105.3, 128.6, 128.8, 129.2, 135.1, 168.6, 170.9; ν_{max} (film/cm^{-1}) 2954, 1728, 1553, 1381, 1276, 1151, 1082, 1036; found (ESI): calcd for $C_{21}H_{27}O_9NNa$ [M + Na]$^+$ 460.1584, found: 460.1566; mp 206 °C; $[\alpha]_D^{25}$ +34.0 (*c* 0.3, $CHCl_3$).

(3*R*,4*R*)-4-((2*R*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-3-oxo-[1,4]dioxan-2-yl)-3-((*R*)-2-nitro-1-phenylethyl)chroman-2-one (25)

Lithium bis(trimethylsilyl)amide (0.60 ml, 1 M solution in THF, 0.60 mmol) was added drop-wise to a solution of glycolate **2** (114 mg, 0.60 mmol) in THF (2.5 ml) at −78 °C. The pale yellow solution was stirred for 15 min. Coumarin (88 mg, 0.60 mmol, solution in 1 ml THF) was added, and the solution stirred for 1 h at −78 °C. *trans*-2-Nitrostyrene (89 mg, 0.60 mmol, solution in 1 ml THF) was added, and the solution stirred for 2 h at −78 °C. The reaction was quenched by addition of acetic acid (72 µl, 1.2 mmol), diluted with ether (12 ml) and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product which was purified by column chromatography (silica, petrol : ether : CH_2Cl_2 2 : 1 : 2) to give the nitroalkane as a white solid (236 mg, 81%): δ_H (400 MHz, $CDCl_3$) 1.26 (6H, s, 2 × Me), 2.55 (3H, s, OMe), 3.04 (1H, d, *J* 11.9, CHC*H*C(O)O), 3.15 (1H, d, *J* 3.2, C*H*CHC(O)O), 3.28 (3H, s, OMe), 3.31–3.39 (1H, m, CHPh), 4.14 (1H, d, *J* 3.4, OCHC(O)O), 4.79–4.81 (2H, m, 2 × CH*H*NO_2), 6.95 (1H, dd, *J* 7.6, 1.3, Ar), 6.99–7.02 (2H, m, Ar), 7.10–7.15 (2H, m, Ar), 7.13–7.39 (4H, m, Ar); δ_C (100 MHz, $CDCl_3$) 16.1, 17.4, 41.1, 42.7, 46.8, 49.3, 49.5, 74.7, 77.2, 78.3, 98.6, 105.3, 116.6, 117.8, 124.8, 127.6, 129.1, 129.6, 130.5, 135.2, 152.4, 166.9, 167.9; ν_{max} (film/cm^{-1}) 2950, 1745, 1589, 1557, 1490, 1458, 1379, 1295, 1222, 1167, 1122, 1111, 1085, 1036; found (ESI): calcd for $C_{25}H_{27}NO_9Na$ [M + Na]$^+$ 508.1884, found: 508.1590; mp 82 °C; $[a]_D^{25}$ +85.3 (*c* 0.8, $CHCl_3$).

(3*S*,4*S*)-4-((2*S*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-3-oxo-[1,4]dioxan-2-yl)-3-((1*R*,2*R*)-2-nitrocyclohexyl)-chroman-2-one (26)

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **2** (38 mg, 0.20 mmol) in THF (0.8 ml) at −78 °C. The pale yellow solution was stirred for 20 min. Coumarin (33 mg, 0.22 mmol, solution in 0.5 ml THF), and the solution stirred for 20 min at −78 °C. 1-Nitro-1-cyclohexene (25 µl, 0.22 mmol, solution in 0.5 ml THF) was added, and the solution stirred for 3 h at −78 °C. The reaction was quenched by addition of acetic acid (30 µl, 0.5 mmol), stirred for 10 min at −78 °C, diluted with ether (4 ml) and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product which was purified by column chromatography (silica, petrol : CH_2Cl_2 1 : 2 to CH_2Cl_2 to petrol : CH_2Cl_2 : ether 2 : 1) to give the nitroalkane as a white solid (83 mg, 90%): δ_H (400 MHz, $CDCl_3$) 1.24 (3H, s, Me), 1.28 (3H, s, Me), 1.35 (1H, tt, *J* 13.3, 3.2, C*H*HCH_2CHNO_2), 1.49–1.61 (3H, m, CH*H*CH_2CHNO_2, CHNO_2C*H*CH, C*H*H-CHNO_2), 1.62–1.68 (1H, m, C*H*HCHCHNO_2), 1.74–1.79 (1H, m, C*H*HCH_2CHCHNO_2), 1.81–1.88 (1H, m, CH*H*CH_2CHCHNO_2), 2.06 (1H, dq, *J* 12.8, 4.2, CH*H*CHCHNO_2), 2.40–2.45 (1H, m, CH*H*CHNO_2), 2.58 (3H, s, OMe), 3.09 (1H, dd, *J* 11.1, 1.1, CHC*H*C(O)O), 3.29 (3H, s, OMe), 3.79 (1H, d, *J* 2.5, C*H*CHC(O)O), 4.35 (1H, d, *J* 3.0, OCHC(O)O), 4.67–4.69 (1H, m, CHNO_2), 7.02 (1H, dd, *J* 8.2, 1.0, Ar), 7.09 (td, *J* 7.5, 1.2, Ar), 7.18 (dd, *J* 7.6, 1.7), 7.28–7.32 (1H, m, Ph); δ_C (100 MHz, $CDCl_3$) 16.1, 17.5, 19.9, 23.7, 24.9, 31.6, 38.1, 40.2, 45.5, 49.4, 49.6, 75.2, 82.9, 98.6, 105.5, 116.4, 118.2, 124.4, 129.3, 130.3, 152.7, 167.6, 167.7; ν_{max} (film/cm^{-1}) 2942, 2866, 1766, 1745, 1548, 1490, 1459, 1380, 1303, 1223, 1194, 1156, 1122, 1111, 1095, 1079, 1036; found (ESI): calcd for $C_{23}H_{29}NO_9Na$ [M + Na]$^+$ 486.1740, found: 486.1728; mp 168–171 °C; $[a]_D^{25}$ −175.1 (*c* 0.4, $CHCl_3$).

(3*R*,4*R*)-4-((2*R*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-3-oxo-[1,4]dioxan-2-yl)-3-((*R*)-3-oxo-1,3-diphenylpropyl)chroman-2-one (27)

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **2** (38 mg, 0.20 mmol) in THF (0.8 ml) at −78 °C. The pale yellow solution was stirred for 20 min. Coumarin (33 mg, 0.22 mmol, solution in 0.5 ml THF), and the solution stirred for 20 min at −78 °C. Chalcone (45 mg, 0.22 mmol, solution in 0.5 ml THF) was added, and the solution stirred for 30 min at −78 °C. The reaction was quenched by addition of acetic acid (30 µl, 0.5 mmol), stirred for 10 min at −78 °C, diluted with ether (4 ml) and allowed to warm to rt. After 30 min, the resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product which was purified by column chromatography (silica, petrol : ether : CH_2Cl_2 5 : 1 : 10) to give the ketone as a white solid (103 mg, 95%): δ_H (400 MHz, $CDCl_3$) 1.26 (6H, s, 2 × Me), 2.56 (3H, s, OMe), 3.07 (1H, d, *J* 11.5, CHC*H*C(O)O), 3.19 (1H, d, *J* 3.3, C*H*CHC(O)O), 3.28 (3H, s, OMe), 3.34–3.40 (1H, m, PhCH), 3.50 (1H, dd, *J* 17.6, 8.3, PhC(O)C*H*H), 3.59 (1H, dd, *J* 17.6, 4.9, PhC(O)CH*H*), 4.13 (1H, d, *J* 3.3, OCHC(O)), 6.98 (1H, dd, *J* 7.5, 1.0, Ph), 7.05–7.13 (4H, m, Ph), 7.21–7.39 (6H, m, Ph), 7.49 (1H, t, *J* 7.4, Ph), 7.82 (2H, d, *J* 7.3, Ph); δ_C (100 MHz, $CDCl_3$) 16.2, 17.5, 39.7, 41.4, 43.0, 49.3, 49.3, 49.4, 74.8, 98.5, 105.2, 116.5, 118.7, 124.3, 127.7, 127.8, 127.9, 128.5, 129.1, 129.3, 130.5, 133.0, 136.8, 140.5, 152.8, 167.2, 169.3, 197.1; ν_{max} (film/cm^{-1}) 2948, 1764, 1729, 1689, 1591, 1495, 1448, 1429, 1377, 1294, 1267, 1224, 1165, 1148, 1110, 1074, 1046, 1032, 1013, 1001; found (ESI): calcd for $C_{32}H_{32}O_8Na$ [M + Na]$^+$ 567.1995, found: 567.1969; mp 75–77 °C; $[a]_D^{25}$ +146.2 (*c* 0.69, $CHCl_3$).

Methyl (*R*)-hydroxy[(3*R*,4*R*)-2-oxo-3-((*R*)-3-oxo-1,3-diphenylpropyl)-chroman-4-yl]acetate (28)

Lithium bis(trimethylsilyl)amide (0.20 ml, 1 M solution in THF, 0.20 mmol) was added drop-wise to a solution of glycolate **2** (38 mg, 0.20 mmol) in THF (0.8 ml) at −78 °C. The pale yellow solution was stirred for 20 min. Coumarin (33 mg, 0.22 mmol, solution in 0.5 ml THF), and the solution stirred for 20 min at −78 °C. Chalcone (45 mg, 0.22 mmol, solution in 0.5 ml THF) was added, and the solution stirred for 30 min at −78 °C. A solution of trimethylsilyl chloride (0.35 ml) in MeOH (5 ml) was added at −78 °C and the reaction allowed to warm to rt overnight. The resulting suspension was filtered through a short plug (1–2 cm) of silica gel, eluting with ether, and the mixture concentrated *in vacuo* to give the crude product which was purified by column chromatography (silica, petrol : EtOAc 1 : 1) to give the alcohol as a white solid (65 mg, 74%): δ_H (400 MHz, $CDCl_3$) 2.84 (1H, d, *J* 5.8, OH), 2.95 (1H, d, *J* 2.5, C*H*CHOH), 3.21 (1H, d, *J* 11.6, C*H*C(O)O), 3.31–3.40 (1H, m, C*H*Ph), 3.56 (2H, d, *J* 6.6, C*HH*C(O)), 3.69 (3H, s, OMe), 4.22 (1H, dd, *J* 5.6, 3.1), 6.78 (1H, d, *J* 6.7, Ar), 7.06–7.15 (4H, m, Ar), 7.22–7.40 (6H, m, Ar), 7.50 (1H, t, *J* 7.4), 7.81 (2H, d, *J* 7.3, Ar); δ_C (100 MHz, $CDCl_3$) 39.8, 42.9, 43.6, 49.1, 52.6, 74.7, 117.1, 117.7, 124.6, 127.5, 127.9, 127.9, 128.0, 128.4, 128.9, 129.0, 129.8, 133.0, 136.7, 140.7, 152.2, 172.2, 197.2; ν_{max} (film/cm^{-1}) 3508, 2953, 1754, 1732, 1678, 1590, 1492, 1461, 1438, 1414, 1362, 1222, 1175, 1109, 1024; found (ESI): calcd for $C_{27}H_{24}O_6Na$ [M + Na]$^+$ 467.1471, found: 467.1469; mp 83 °C; $[a]_D^{25}$ +30.5 (*c* 1.4, $CHCl_3$).

Methyl (2*R*,3*R*)-2-hydroxy-3-(2-hydroxyphenyl)-3-((3*R*,4*R*)-4-phenylpyrrolidin-3-yl)propionate (29)

Raney-nickel (0.60 g, 50% suspension in water) was rinsed with MeOH (5 ml × 5) and EtOAc (5 ml × 2) and suspended in a 1 : 1 mixture of EtOAc : MeOH (6 ml). Glycolate **25** (100 mg, 0.20 mmol) was added to this

suspension and the reaction stirred under a balloon of hydrogen overnight. The Raney-nickel was removed by filtration, the solution concentrated *in vacuo*, and the residue purified by column chromatography (silica, EtOAc : MeOH 10 : 1) to give a white solid (84 mg, 93%). A sample of this (38 mg) was dissolved in 1 ml of a pre-mixed solution of trimethylsilyl chloride (0.35 ml) in MeOH (5 ml). The solution was stirred at rt for 1 h, concentrated *in vacuo* and the residue purified by column chromatography (EtOAc : MeOH 10 : 1) to give the alcohol as a clear gum (27 mg, 92%; 86% over 2 steps): δ_H (400 MHz, $CDCl_3$) 3.18 (1H, dd, *J* 10.1, 4.4, CHC(O)N), 3.23–3.32 (1H, m, CHPh), 3.41 (1H, t, *J* 8.9, C*H*HNH), 3.51 (1H, t, *J* 8.9, CH*H*NH), 3.60 (3H, s, OMe), 3.72 (1H, t, *J* 4.4, C*H*CHOH), 4.88 (1H, d, *J* 2.7, C*H*OH), 6.20 (1H, br s, OH/NH), 6.38 (1H, br s, NH/OH), 6.89 (1H, t, *J* 7.6, Ar), 6.93 (1H, d, *J* 8.0, Ar), 7.16–7.38 (7H, m, Ar); δ_C (100 MHz, $CDCl_3$) 44.9, 48.7, 52.6, 54.2, 74.7, 77.2, 118.3, 121.1, 122.8, 127.7, 128.9, 129.0, 129.1, 131.8, 139.9, 154.9, 173.4, 179.0; ν_{max} (film/cm^{-1}) 3275, 1743, 1670, 1456, 1231, 1127; found (ESI): calcd for $C_{20}H_{21}NO_5Na$ [M + Na]$^+$ 378.1317, found: 378.1302; $[\alpha]_D^{25}$ −35.0 (*c* 0.46, $CHCl_3$).

(5*R*,6*R*)-(5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxin-2-yloxy)trimethylsilane (30)

Procedure 1. *n*-Butyllithium (15.1 ml, 2.5 M solution in hexanes, 0.038 mol) was added drop-wise to a solution of diisopropylamine (5.3 ml, 0.038 mol) in THF (20 ml) at 0 °C. The solution was stirred for 30 min, cooled to −78 °C, and then a solution of glycolate **2** (7.19 g, 0.038 mol) in THF (20 ml) was added drop-wise, *via* cannula. The solution was stirred for 3 h at −78 °C, then trimethylsilyl chloride (4.8 ml, 0.038 mol) was added drop-wise and the solution allowed to warm to rt overnight. The mixture was concentrated *in vacuo* to give an orange residue which was distilled directly to afford the ketene acetal as a colourless oil (7.53 g, 76%), bp 62 °C/0.05 mmHg.

Procedure 2[18]**.** Lithium diisopropylamide (8.9 ml, 1.3 M solution in THF–heptane–ethylbenzene, 0.012 mol) was added to a solution of glycolate **2** (2.01 g, 0.011 mol) in THF (21 ml) at −78 °C. After 30 min, trimethylsilyl chloride (1.5 ml, 0.011 mol) was added and the mixture was allowed to warm to rt overnight. The mixture was concentrated *in vacuo* to afford a orange residue which was rapidly filtered through a small pad of Celite (8 mm deep; 21 mm diameter), eluting with dry hexane (15 ml). The hexane was removed by evaporation to afford the ketene acetal as a brown oil (2.91 g, 100%): δ_H (400 MHz; C_6D_6) 0.32 (9H, s, $SiMe_3$), 1.48 (3H, s, Me), 1.51 (3H, s, Me), 3.24 (3H, s, OMe), 3.30 (3H, s, OMe), 5.82 (1H, s, C=CH); δ_C (100 MHz; C_6D_6) −0.01, 17.1, 17.7, 48.4, 48.9, 96.9, 100.4, 105.3, 144.0; δ_H (400 MHz; $CDCl_3$) 0.19 (9H, s, $SiMe_3$), 1.35 (3H, s, Me), 1.48 (3H, s, Me), 3.20 (3H, s, OMe), 3.34 (3H, s, OMe), 5.48 (1H, s, C=CH); δ_C (100 MHz; $CDCl_3$) −0.3, 16.8, 17.3, 48.3, 49.2, 96.3, 100.2, 104.3, 143.5; $[\alpha]_D^{25}$ −193.5 (*c* 7.3, PhMe).

Cryptone; 4-isopropylcyclohexen-2-one (34)[12]

Methyl vinyl ketone (10.9 g, 13.0 ml, 0.16 mol) was added to 1-(3-methylbut-1-enyl)-piperidine (23.8 g, 0.16 mol) and the solution stirred at rt. After 24 h, hydrochloric acid (106 ml, 32% solution in 120 ml water) was added and the mixture stirred at rt for a further 36 h, after which it was refluxed at 105 °C for 30 min, allowed to cool to rt, and extracted into ether (250 ml). The organic layer was washed with 1.5 M hydrochloric acid (120 ml), water (250 ml) and brine (250 ml); dried (magnesium sulfate), and distilled to afford a 2.5 : 1 mixture by ^{1}H NMR of cryptone and 4-isopropylcyclohexen-3-one as a yellow oil (10.9 g, 50%). This was purified by column chromatography: a large column (9.5 cm diameter) was packed with a pad of silica (12.0 cm deep) and loaded with the cryptone–4-isopropylcyclohexen-3-one mixture (15 g), prepared above. Four litres of eluant (10 : 1 petrol : ether) were passed through the column before the collecting of fractions commenced. After a further 3.5 litres of this eluant, the polarity was increased (8 : 1 petrol : ether). All mixed fractions were discarded. After evaporation and distillation of the appropriate unmixed fractions, cryptone was obtained as a colourless oil (5 g, ∼50% product recovery): bp 97 °C/11 mmHg (lit. 103–104 °C/15 mmHg); δ_H (400 MHz; $CDCl_3$) 0.96 (3H, d, *J* 6.3, CHMe), 0.97 (3H, d, *J* 6.3, CHMe), 1.72–1.88 (2H, m, C*H*HCHCHMe$_2$, C*H*Me$_2$), 1.97–2.04 (1H, m, CH*H*CHCHMe$_2$), 2.26–2.38 (2H, m, C*H*CHMe$_2$, C*H*HC(O)), 2.51 (1H, dt, *J* 16.6, 4.2, CH*H*C(O)), 6.00 (1H, dd, *J* 10.3, 2.5, C(O)CHC*H*), 6.89 (1H, d, *J* 10.3, C(O)C*H*); δ_C (100 MHz; $CDCl_3$) 19.5, 19.6, 25.3, 31.5, 37.4, 42.5, 129.7, 154.2, 200.0; found (ESI) [MH]$^+$ 139.1116, $C_9H_{15}O$ requires 139.1117.

HPLC conditions: Chirapak AD column, 95.5 : 0.5 hexane : isopropanol, 1 ml min^{-1}; 215 nm.

(1′*R*,2′*R*,3*S*,5*R*,6*R*)-3-(2-Isopropyl-5-oxocyclohexyl)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-one (32)[22]

Procedure 1. Ethyl (trimethylsilyl)acetate (0.59 ml, 3.23 mmol) was added to a solution of TBAT (9 mg, 17 μmol) and glycolate **2** (308 mg, 1.61 mmol) in THF (0.9 ml) at rt. After 3 h, ^{1}H NMR analysis of the reaction mixture showed trimethylsilyl ketene acetal **30** to have been formed in approximately 50% conversion. The solution was cooled to −78 °C and a second solution of cryptone (0.71 ml, 4.84 mmol) and TBAT (14 mg, 26 μmol) in THF (0.6 ml) was added *via* cannula. The reaction was allowed to warm to rt overnight, concentrated *in vacuo* and the residue purified by column chromatography (silica, petrol : ether 20 : 1, with 1% triethylamine) to give the ketone as a white solid (449 mg, 1.37 mmol, 85%) which was recrystallized (ether–petrol) to aid characterization.

Procedure 2. Ketene acetal **30** (0.28 ml, 1.00 mmol) was added drop-wise to a solution of cryptone (0.15 ml, 1.00 mmol) and TBAT (6 mg, 11 μmol) in THF (1 ml) at −78 °C. The reaction was allowed to warm to rt overnight. A solution of TBAF (1 ml, 1 M solution in THF, 1.0 mmol) and acetic acid (57 μl, 1.0 mmol) were added and the mixture stirred at rt for 4 h. The reaction was quenched with sodium bicarbonate solution (5 ml), extracted with ether (3 × 10 ml), washed with brine (10 ml), dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 9 : 1 to 2 : 1 petrol : ether) to give the ketone as a white solid (208.9 mg, 64%): δ_H (400 MHz; $CDCl_3$) 0.84 (3H, d, *J* 6.6, CHMe), 0.99 (3H, d, *J* 6.5, CHMe), 1.35 (3H, s, Me), 1.44–1.51 (1H, m, C*H*HCH$_2$C(O)), 1.47 (3H, s, Me), 1.96–2.04 (3H, m, CH*H*CH$_2$C(O), C*H*CHMe$_2$, CHMe$_2$), 2.21 (1H, dd, *J* 14.7, 8.6, CHC*H*HC(O)), 2.30 (1H, dt, *J* 16.0, 5.4, CH$_2$C*H*HC(O)), 2.34–2.38 (1H, m, CH$_2$CH*H*C(O)), 2.46–2.48 (1H, m, C*H*CH$_2$C(O)), 2.63 (1H, dd, *J* 14.7, 5.3, CHCH*H*C(O)), 3.27 (3H, s, OMe), 3.40 (3H, s, OMe), 4.18 (1H, d, *J* 2.6, OCHC(O)); δ_C (100 MHz; $CDCl_3$) 16.1, 16.7, 17.7, 21.4, 22.6, 28.4, 39.6, 40.6, 41.4, 42.5, 49.1, 49.7, 72.2, 98.3, 105.3, 168.3, 211.6; ν_{max} (film)/cm^{-1} 2956, 1746, 1715, 1460, 1380, 1247, 1204, 1146, 1118, 1092, 1034; mp 95 °C; found (ESI) [MNa]$^+$ 351.17780, $C_{17}H_{28}O_6Na$ requires 351.1784; $[\alpha]_D^{25}$ −48.9 (*c* 0.4, $CHCl_3$).

(1′*S*,1″*R*,2′*R*,3*S*,5*R*,6*R*,6′*R*)-3-[2-(1-Hydroxypropyl)-6-isopropyl-3-oxocyclohexyl]-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-3-one (36)

Procedure 1. Ketene acetal **30** (0.28 ml, 1.00 mmol) was added drop-wise to a solution of cryptone (0.36 ml, 2.50 mmol) and TBAT (6 mg, 11 μmol) in THF (1 ml) at −78 °C. The reaction was allowed to warm to rt overnight and the solution divided into two equal portions, one of which was used for the preparation of **36**: the solvents were removed *in vacuo* and the residue re-dissolved in CH_2Cl_2 (0.5 ml). The solution was cooled to −78 °C and propionaldehyde (54 μl, 0.75 mmol) followed by

$BF_3{\cdot}Et_2O$ complex (58 μl, 0.5 mmol) added drop-wise. The reaction was stirred for 2 h and quenched by the drop-wise addition of $NaHCO_3$ (1 ml), extracted with CH_2Cl_2 (3 × 10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 1 : 1 petrol : ether) to give the alcohol as a white solid (67.7 mg, 35%) which was recrystallized (CH_2Cl_2–petrol) for the purposes of characterization.

Procedure 2. A solution of α-bromoketone **38** (121.6 mg, 0.299 mmol) and propionaldehyde (22 μl, 0.23 mmol) in toluene (0.5 ml) was added *via* cannula to a solution of triphenyltin hydride (104.8 mg, 0.299 mmol) and triethylborane (0.33 ml, 1 M solution in hexanes, 0.33 mmol) in toluene (0.5 ml) at rt. The reaction was stirred for 2 h, diluted with ether (100 ml), washed with a solution of potassium fluoride[23,24] (1.6 g in 9.4 ml water) and filtered through Celite (eluting with ether), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (Biotage, 1 : 1 petrol : ether) to give the alcohol as a white solid (72.5 mg, 63%): δ_H (500 MHz; C_6D_6) 0.88 (3H, d, *J* 6.7, CHMe), 1.06 (3H, t, *J* 7.4, CH_2Me), 1.09 (3H, d, *J* 6.7, CHMe), 1.21 (3H, s, Me), 1.29 (3H, s, Me), 1.56–1.63 (1H, m, C*H*HCH$_2$C(O)), 1.71–1.86 (3H, m, 2 × C*HH*Me, $CHMe_2$), 1.92–1.95 (1H, m, C*H*$CHMe_2$), 2.00–2.03 (1H, m, CH*H*CH$_2$C(O)), 2.11–2.18 (1H, m, C*H*HC(O)), 2.31–2.38 (1H, m, CH*H*C(O)), 2.71–2.73 (1H, m, OH), 2.79 (1H, dd, *J* 7.4, 3.6, CHC(O)), 2.93 (3H, s, OMe), 3.08–3.10 (1H, m, C*H*CHC(O)), 3.15 (3H, s, OMe), 3.82 (1H, br s, C*H*OH), 4.53 (1H, d, *J* 2.6, OCHC(O)); δ_C (125 MHz; C_6D_6) 11.0, 16.8, 17.8, 18.5, 21.8, 21.9, 29.0, 29.1, 38.4, 41.3, 42.8, 48.6, 49.4, 53.7, 73.2, 73.4, 98.5, 104.8, 167.9, 214.1; ν_{max} (neat)/cm^{-1} 3485, 2958, 1748, 1703, 1463, 1380, 1251, 1214, 1150, 1122, 1036, mp 111 °C; found (ESI) [MNa]$^+$ 409.2211, $C_{20}H_{34}O_7Na$ requires 409.2197; $[\alpha]_D^{25}$ −76.7 (*c* 0.1, $CHCl_3$).

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

A solution of ketene acetal **30** (2.01 g, 7.68 mmol) in THF (3 ml) was added drop-wise to a solution of cryptone (2.7 ml, 19.19 mmol) and TBAT (34 mg, 63 μmol) in THF (9 ml) at −78 °C. The reaction was allowed to warm to rt overnight, and re-cooled to 0 °C. NBS (1.09 g, 6.14 mmol) was added and the reaction allowed to warm to rt and stirred for 4 h. The reaction was diluted with ether (40 ml), washed with sodium bicarbonate solution (3 × 20 ml), water (20 ml), and brine (20 ml); dried ($MgSO_4$), and concentrated *in vacuo*. By using 1,2,3-trimethoxybenzene (328 mg, 1.92 mmol, 0.25 equiv) as an internal standard, a yield of 41% for **38** was calculated using ^{1}H NMR. The residue was purified by column chromatography and recrystallization (ether–petrol); the typical recovery of **38** was 15%: δ_H (400 MHz; $CDCl_3$) 0.83 (3H, d, *J* 6.8, CHMe), 0.98 (3H, d, *J* 6.7, CHMe), 1.39 (3H, s, Me), 1.50 (3H, s, Me), 1.72–1.84 (2H, m, $CHMe_2$, C*H*HCH$_2$C(O)), 1.97–2.06 (2H, m, C*H*$CHMe_2$, CH*H*CH$_2$C(O)), 2.34–2.43 (1H, m, C*H*HC(O)), 2.70 (1H, dt, *J* 16.0, 8.8, CH*H*C(O)), 2.91 (1H, dt, *J* 8.0, 1.8, C*H*CHBr), 3.33 (3H, s, OMe), 3.43 (3H, s, OMe), 4.66 (1H, d, *J* 1.9, OCHC(O)), 4.69 (1H, d, *J* 8.2, CHBr); δ_C (100 MHz; $CDCl_3$) 16.6, 16.8, 17.8, 21.8, 22.0, 28.8, 37.9, 41.4, 49.2, 49.7, 49.8, 56.8, 72.1, 98.5, 105.7, 167.9, 201.9; ν_{max} (neat)/cm^{-1} 2961, 1740, 1717, 1463, 1386, 1269, 1203, 1148, 1115, 1091, 1033; mp 153 °C; found (ESI) [MNa]$^+$ 429.0890, $C_{17}H_{27}O_6BrNa$ requires 429.0889; found C 49.95%, H 6.59%, $C_{17}H_{27}O_6Br$ requires C 50.13%, H 6.68%; $[\alpha]_D^{25}$ −121.7 (*c* 0.2, $CHCl_3$).

X-Ray structures

CCDC reference numbers 171362 (**21**), 171363 [*epi*-**24** (minor diastereomer; epimeric at CHPh carbon)], 171364 (**24**), 171365 (**27**), 171366 (**22**), 171367 (**26**), 171368 [*epi*-**22** (minor diastereomer; epimeric at CHOH carbon)], 283219 (**36**), 283220 (**8**), 283221 (**10**), 283222 (**32**), 283223 (**5**), 283224 (**38**), 283225 (**6**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b512410g.

Acknowledgements

RTG thanks Dr Richard M. Turner for assistance with the HPLC. The EPSRC, Novartis, Pfizer Global Research and Development and the EU (Marie Curie fellowship to FR) are thanked for financial support, and Drs John Davies and Andrew Bond for the X-ray structures.

References and notes

1 L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; L. F. Tietze and U. Beifuss, *Angew. Chem.*, 1993, **105**, 137; L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131; G. H. Posner, *Chem. Rev.*, 1986, **86**, 831.
2 A. Dömling and I. Ugi, *Angew. Chem.*, 2000, **112**, 3300; A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3169.
3 G. H. Posner, K. S. Webb, E. Asirvatham, S. Jew and A. Del'Innocenti, *J. Am. Chem. Soc.*, 1988, **110**, 4754.
4 For examples, see T.-L. Ho, *Tandem Organic Reactions*, Wiley, New York, 1992.
5 S. V. Ley, E. Diez, D. J. Dixon, R. T. Guy, P. Michel, G. L. Natrass and T. D. Sheppard, *Org. Biomol. Chem.*, 2004, **2**, 3608; S. V. Ley, D. J. Dixon, R. T. Guy, M. A. Palomero, A. Polara, F. Rodríguez and T. D. Sheppard, *Org. Biomol. Chem.*, 2004, **2**, 3618; E. Diez, D. J. Dixon and S. V. Ley, *Angew. Chem., Int. Ed.*, 2001, **40**, 2906; D. J. Dixon, S. V. Ley, A. Polara and T. Sheppard, *Org. Lett.*, 2001, **3**, 3749; D. J. Dixon, S. V. Ley and F. Rodriguez, *Org. Lett.*, 2001, **3**, 3753; D. J. Dixon, S. V. Ley and F. Rodriguez, *Angew. Chem., Int. Ed.*, 2001, **40**, 4763; P. Michel and S. V. Ley, *Synthesis*, 2003, 1598.
6 G. M. Coppola and H. F. Schuster, in α-*Hydroxy Acids in Enantioselective Synthesis*, VCH, Weinheim, 1997; Y. Murakami, Y. Oshima and Y. Yasumoto, *Bull. Jpn. Soc. Sci. Fish.*, 1982, **48**, 69; C. N. Battershill, P. T. Northcote and L. M. West, *J. Org. Chem.*, 2000, **65**, 445.
7 D.-P. Jang, J.-W. Chang and B.-J. Uang, *Org. Lett.*, 2001, **3**, 983; R. A. Aitken and A. W. Thomas, *Synlett*, 1998, 102; K. Hattori and H. Yamamoto, *J. Org. Chem.*, 1993, **58**, 5301; G. Calderari and D. Seebach, *Helv. Chim. Acta*, 1985, **68**, 1592.
8 G.-J. Boons, R. Downham, K. S. Kim, S. V. Ley and M. Woods, *Tetrahedron*, 1994, **50**, 7157.
9 K. Suzuki and D. Seebach, *Liebigs Ann. Chem.*, 1992, 51; D. A. Oare, M. A. Henderson, M. A. Sanner and C. H. Heathcock, *J. Org. Chem.*, 1990, **55**, 132; D. A. Oare and C. H. Heathcock, *J. Org. Chem.*, 1990, **55**, 157.
10 This kind of transition state has been proposed previously for the aldol reaction between *E* enolates and aldehydes: Y. Li, M. N. Paddon-Row and K. N. Houk, *J. Org. Chem.*, 1990, **55**, 481; C. Gennari, R. Todeschini, M. G. Beretta, G. Favini and C. Scolastico, *J. Org. Chem.*, 1986, **51**, 612; R. W. Hoffmann, K. Ditrich and S. Froesch, *Tetrahedron*, 1985, **41**, 5517.
11 S. E. Denmark and B. R. Henke, *J. Am. Chem. Soc.*, 1991, **113**, 2177; R. Noyori, I. Nishida and J. Sakata, *J. Am. Chem. Soc.*, 1981, **103**, 2106; D. Dougherty, *Tetrahedron Lett.*, 1982, 4891.
12 G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.*, 1963, **85**, 207.
13 M. J. Bassindale, J. J. Crawford, K. W. Henderson and W. J. Kerr, *Tetrahedron Lett.*, 2004, **45**, 4175; E. L. Carswell, D. Hayes, K. W. Henderson, W. J. Kerr and C. J. Russell, *Synlett*, 2003, 1017; K. W. Henderson, W. J. Kerr and J. H. Moir, *Tetrahedron*, 2002, **58**, 4573; J. D. Anderson, P. G. Garcia, D. Hayes, K. W. Henderson, W. J. Kerr, J. H. Moir and K. P. Fondekar, *Tetrahedron Lett.*, 2001, **42**, 7111; K. W. Henderson, W. J. Kerr and J. H. Moir, *Chem. Commun.*, 2000, 479; K. Aoki, H. Noguchi, K. Tomioka and K. Koga, *Tetrahedron Lett.*, 1993, **34**, 5105; M. Toriyama, K. Sugasawa, S. Motohashi, N. Tokutake and K. Koga, *Chem. Pharm. Bull.*, 2001, **49**, 468; C. D. Graf, C. Malan, K. Harms and P. Knochel, *J. Org. Chem.*, 1999, **64**, 5581; C. D. Graf, C. Malan and P. Knochel, *Angew. Chem., Int. Ed.*, 1998, **37**, 3014; T. Yamashita, D. Sato, T. Kiyoto, A. Kumar and K. Koga, *Tetrahedron*, 1997, **53**, 16987; K. Aoki, K. Tomioka, H. Noguchi and K. Koga, *Tetrahedron*, 1997, **53**, 13641; R. Shirai, D. Sato, K. Aoki, M. Tanaka, H. Kawasaki and K. Koga, *Tetrahedron*, 1997, **53**, 5963; T. Yamashita, D. Sato, T. Kiyoto, A. Kumar and K. Koga, *Tetrahedron Lett.*, 1996, **37**, 8195; R. Shirai, M. Tanaka and K. Koga, *J. Am. Chem. Soc.*, 1986, **108**, 543; R. Shirai, K. Aoki, D. Sato, H. D. Kim, M. Murakata, T. Yasukata and K. Koga, *Chem. Pharm.*

Bull., 1994, **42**, 690; K. Aoki and K. Koga, *Tetrahedron Lett.*, 1997, **38**, 2505; D. E. Ward and W.-L. Lu, *J. Am. Chem. Soc.*, 1998, **120**, 1098; M. F. Hentemann and P. L. Fuchs, *Tetrahedron Lett.*, 1997, **38**, 5615; J. Evarts, E. Torres and P. L. Fuchs, *J. Am. Chem. Soc.*, 2002, **124**, 11093; M. Kato, M. Watanabe, Y. Tooyama, B. Vogler and A. Yoshikoshi, *Synthesis*, 1992, 1055; R. C. Hawley and S. L. Schreiber, *Synth. Commun.*, 1990, **20**, 1159; M. D. Soffer and G. E. Günay, *Tetrahedron Lett.*, 1965, **19**, 1355.

14 T. V. Rajanbabu, *J. Org. Chem.*, 1984, **49**, 2083.

15 E. Nakamura, T. Murofushi, M. Shimizu and I. Kuwajima, *J. Am. Chem. Soc.*, 1976, **98**, 2346.

16 A. S. Pilcher and P. DeShong, *J. Org. Chem.*, 1996, **61**, 6901; A. S. Pilcher, H. L. Ammon and P. Deshong, *J. Am. Chem. Soc.*, 1995, **117**, 5166; C. J. Handy, Y. F. Lam and P. DeShong, *J. Org. Chem.*, 2000, **65**, 3542.

17 R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura and M. Shimizu, *J. Am. Chem. Soc.*, 1977, **99**, 1265; C. Chuit, R. J. P. Corriu and C. Reye, *J. Organomet. Chem.*, 1988, **358**, 57.

18 During the course of this work, another group independently published their own synthesis of racemic **30** and used it in some palladium-catalyzed arylation methodology: X. Liu and J. F. Hartwig, *J. Am. Chem. Soc.*, 2004, **126**, 5182.

19 S. J. Danishefsky and B. Simoneau, *J. Am. Chem. Soc.*, 1989, **111**, 2599.

20 K. Nozaki, K. Oshima and K. Utimoto, *Tetrahedron Lett.*, 1988, **29**, 1041; K. Nozaki, K. Oshima and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 403.

21 The amount of time required by the reaction was found to vary with the batch of Ra-Ni, and for a particularly active batch, reduction of the ketone functionality of **19** to give the corresponding secondary alcohol was observed: δ_H (400 MHz; $CDCl_3$) 1.14 (3H, s, Me), 1.17 (3H, d, *J* 6.5, CHMe), 2.65 (3H, s, OMe), 3.38 (1H, q, *J* 9.5, NHC*H*H), 3.45 (1H, q, *J* 8.6, CHPh), 3.68 (1H, dt, *J* 9.5, 1.1, NHCH*H*), 3.82 (1H, qn, *J* 6.5, C*H*Me), 4.81 (1H, d, *J* 5.4, OH), 4.92 (1H, d, *J* 8.6, NC(O)CHO), 6.61 (1H, br s, NH), 7.27–7.37 (5H, m, Ph); δ_C (100 MHz; $CDCl_3$) 17.7, 20.3, 46.3, 49.3, 50.6, 71.9, 74.9, 103.8, 127.7, 128.1, 128.9, 139.8, 177.2. The reduction proceeded with high diastereoselectivity, but the stereochemistry at the newly-formed alcohol stereocentre was not determined.

22 Some difficulties were encountered in the reproduction of these reactions. For best results, it is essential that the TBAT is freshly recrystallized (from EtOAc) before use.

23 D. Milstein and J. K. Stille, *J. Org. Chem.*, 1979, **44**, 1613.

24 J. E. Leibner and J. Jacobus, *J. Org. Chem.*, 1979, **44**, 449.