Enantioselective synthesis of α-bromo acid derivatives and bromohydrins† from tartrate derived bromoacetals

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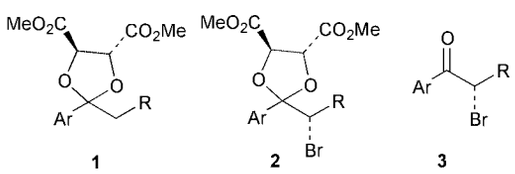
Received (in Cambridge, UK) 15th March 2000, Accepted 18th May 2000
Published on the Web 10th July 2000

Bromination of the acetals **4** derived from aryl alkyl ketones, ArCOR, and (2*R*,3*R*)-tartaric acid results in bromoacetals **5** with 78–90% de. Hydrolysis of those compounds with Ar = 4-methoxyphenyl or 3-bromo-4-methoxyphenyl results, after recrystallisation, in α-bromoketones **8** with 66–98% ee which are shown to undergo the Baeyer–Villiger oxidation to α-bromoesters **9** with minimal racemisation. α-Bromoketone **8d** is shown to undergo carbonyl reduction to *threo*-bromohydrin **15** with retention of stereochemistry.

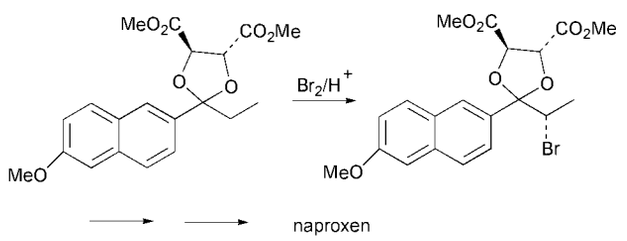
Introduction

The diastereoselective bromination of tartrate acetals of the type **1** has been developed over recent years by Giordano *et al.*,[1]



1 **2** **3**

although the mechanistic rationale for the stereoselection is still open to some speculation.[2] This chemistry now forms the basis for one of the commercial approaches to Naproxen (Scheme 1)



Scheme 1

via a 1,2-aryl shift on the derived bromoacetal. The route is particularly elegant in that both diastereoisomers of the bromoacetal can be used to produce the same enantiomer of Naproxen.[3]

Giordano and co-workers reported the bromination of a number of acetals **1**, with Ar being phenyl, 4-chlorophenyl, 4-isobutylphenyl, 4-methoxyphenyl and 6-methoxy-2-naphthyl, and in all but one case, R was methyl. It was shown that the diastereoselectivity of the bromination was slightly affected by the nature of the solvent used, but that Ar had little effect. In all cases the major product was **2**, with the stereochemistry at the carbon bearing the bromine being (*S*), when using acetals derived from esters of (2*R*,3*R*)-tartaric acid. The de ranged from 88 to 64%.

In further studies,[4] Giordano and Coppi showed that some of the bromoacetals **2** (R = Me) (mixture of diastereoisomers) could be hydrolysed under carefully controlled conditions (excess methanesulfonic acid, 2.5 equivalents of water) to give, in good yield, the corresponding α-bromoketones **3** (R = Me) with ee's essentially the same as the de's of the starting bromoacetals. Furthermore, these α-bromoketones could often be recrystallised to enantiomeric purity, but no descriptions were given of further synthetic uses of such potentially versatile, optically pure, substrates.

We describe here our recent studies in this area. Firstly we describe an extension of Giordano's studies on the bromination of tartrate-derived acetals, varying the nature of the aromatic substituent, of R and of the chiral auxiliary, with the particular aim of finding bromoacetals with high crystallinity, which could be recrystallised to stereochemical purity. Secondly we describe further examples of the hydrolysis of bromoacetals **2** to α-bromoketones **3**, and finally the results of using these α-bromoketones as substrates for Baeyer–Villiger oxidation and for reduction.

Results and discussion

Bromination of tartrate acetals 4

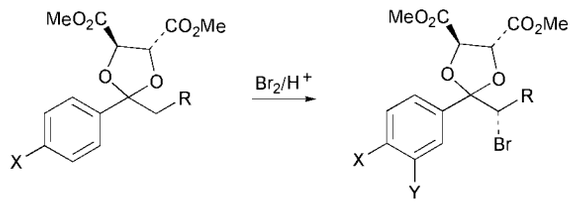
The required dimethyl tartrate acetals **4** were prepared by the standard method (dimethyl tartrate–trimethyl orthoformate–methanesulfonic acid)[1] from the appropriate aryl alkyl ketones, leading to a range of products **4** (R = alkyl; X = OMe, NHTs, NHAc; Y = H). A careful study of the bromination of acetals **4** showed that the best solvent in terms of diastereoselection was carbon tetrachloride (CCl_4), with DCM available as a slightly inferior alternative which was particularly useful for those acetals insoluble in CCl_4. The reaction was catalysed by anhydrous HCl and was conveniently carried out at −6 °C (ice–acetone). In the bromination of the 4-methoxyphenyl acetals it was difficult to avoid the production of some of the 3-bromo-4-methoxyphenyl acetals **5** (X = OMe, Y = Br), especially on a large scale, so we routinely used two equivalents of bromine in these cases making this the sole product. The results of the bromination studies are shown in Table 1, with the assumption that the configuration at the carbon bearing bromine is (*S*), as was rigorously proved by Giordano in his work.[1b]

The sulfonamide-substituted bromoacetals **5i**–**5k** were, as we had hoped, crystalline, but, disappointingly, recrystallisation from a range of solvents led to no improvement in the de for any of them. Consequently, a further attempt to furnish a crystalline acetal was made by modifying the chiral auxiliary: the liquid bromoacetal **5** (X = Y = H; R = Me) was reacted with dimethylamine in methanol to afford the diamide **6** in high yield as a viscous gum, but this could not be induced to give a homogeneous crystalline solid. Alternatively, bromination of

† The IUPAC term for bromohydrin is bromoalcohol.

DOI: 10.1039/b002106g

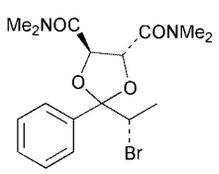
Table 1 Bromination of tartrate acetals **4**



4 **5**

Bromoacetal	X	Y	R	Solvent	Yield (%)	De (%)[a]
5a	OMe	H	CH_3	CCl_4	97	90
5b	OMe	H	CH_2CH_3	CCl_4	91	90
5c	OMe	H	Ph	CCl_4	91	84
5d	OMe	Br	CH_3	CCl_4	90	90
5e	OMe	Br	CH_2CH_3	CCl_4	91	90
5f	OMe	Br	$CH(CH_3)_2$	CCl_4	95	85
5g	OMe	Br	$(CH_2)_3CH_3$	CCl_4	90	85
5h	OMe	Br	$(CH_2)_7CH_3$	CCl_4	98	82
5i	NHTos	H	CH_3	CH_2Cl_2	80	82
5j	NHTos	H	CH_2CH_3	CH_2Cl_2	66	82
5k	NHTos	H	$CH(CH_3)_2$	CH_2Cl_2	23	78
5l	NHAc	H	CH_3	CH_2Cl_2	0[b]	—
5m	NHAc	H	$(CH_2)_3CH_3$	CH_2Cl_2	0[c]	—

[a] Measured by integration of CO_2Me signals in ^1H NMR—the highest field OMe signals in the major and minor diastereoisomers were consistently separated by approx. 0.1 ppm. [b] Decomposed on chromatography to racemic bromoketone. [c] Decomposed on aqueous work-up to racemic bromoketone.



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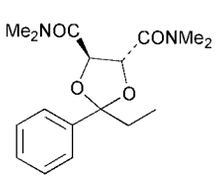

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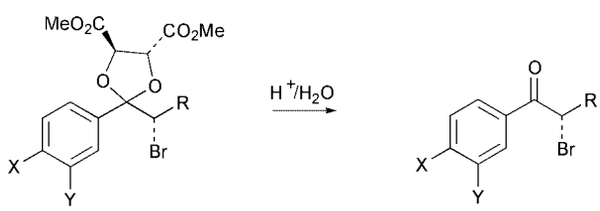
the tartramide acetal **7** gave only α-bromopropiophenone, indicating that the desired bromoacetal **6** was unstable to either the reaction or work-up conditions for the bromination. Our results confirm and extend those of Giordano, namely that the de of the bromoacetals is largely independent of the nature of the Ar and R groups in **1**. However, we have been unable so far to find an aromatic residue which allows improvement to this de by crystallisation.

Having prepared a range of bromoacetals of reasonable de, we briefly investigated their direct use in synthesis. Attempted S_N2 reaction on the bromoacetal **5a** with sodium azide under a range of conditions gave either no reaction or a complex mixture of products, whilst attempts to cleave the benzylic C–O bonds under various hydrogenolysis conditions gave either no reaction or simply reduction of the C–Br bond.

Table 2 Hydrolysis of tartrate bromoacetals **5** to bromoketones **8**



5 **8**

Bromoketone	X	Y	R	Yield (%)	Ee (%)[a]
8a	OMe	H	CH_3	58	80[b]
8b	OMe	H	CH_2CH_3	65	92
8c	OMe	H	Ph	45	[c]
8d	OMe	Br	CH_3	52	>98[b]
8e	OMe	Br	CH_2CH_3	50	>98[b]
8f	OMe	Br	$CH(CH_3)_2$	70	71[d]
8g	OMe	Br	$(CH_2)_3CH_3$	67	66[d]
8h	OMe	Br	$(CH_2)_7CH_3$	43	>98[b]
8i	NHTos	H	CH_3	[e]	—

[a] Using $Eu(hfc)_3$ the signals for aromatic proton *ortho* to OMe were resolved to baseline. [b] After recrystallisation. [c] Enantiomers not resolved by NMR. [d] Could not be recrystallised to enantiomeric purity. [e] Partial removal of sulfonamide group also occurred.

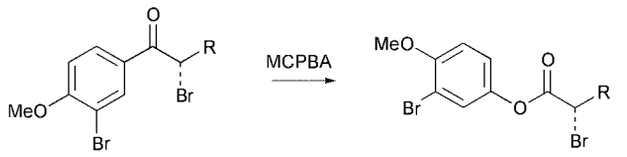
Hydrolysis of bromoacetals 5

Using the conditions developed by Giordano, the acetals **5** were hydrolysed to give the corresponding α-bromoketones **8** whose ee's were measured by ^1H NMR in the presence of europium D-3-heptafluorobutyrylcamphorate ($Eu(hfc)_3$). The results for these reactions are shown in Table 2, and demonstrate that in a number of cases it was possible to obtain **8** essentially enantiomerically pure. In the case of the sulfonamido-substituted acetal **5i**, the reaction was complicated by partial hydrolysis of the sulfonamide group in the strongly acidic conditions, and further studies on this derivative were abandoned.

Baeyer–Villiger oxidation of α-bromoketones 8d–h

It is well known that in the Baeyer–Villiger oxidation of aryl alkyl ketones the aryl will preferentially migrate,[5] and that the effect of a bromine attached to the alkyl group is to reduce its migratory aptitude,[6] so it was expected that oxidative rearrangement of **8** would lead to the esters **9**. Treatment of the α-bromoketone **8d** with trifluoroperacetic acid, generated from urea–hydrogen peroxide and TFAA,[7] gave no reaction. Use of MCPBA in refluxing 1,2-dichloroethane, in the presence of disodium hydrogen phosphate,[8] gave the desired product **9d** in 79% yield, but the best yield (98%) was obtained with these same reagents in chloroform at room temperature. Using these conditions, the α-bromoketones **8e**–**h** were also oxidised in good yield (70–87%). In all cases it was necessary to follow the reaction by ^1H NMR since the starting material and product had the same R_f on TLC. The enantiomeric purity of the esters **9** was now assessed by hydrolysis to the corresponding α-bromoacids **10** followed by esterification with diazomethane to the methyl

Table 3 Baeyer–Villiger oxidation of α-bromoketones **8d–h**



8 **9**

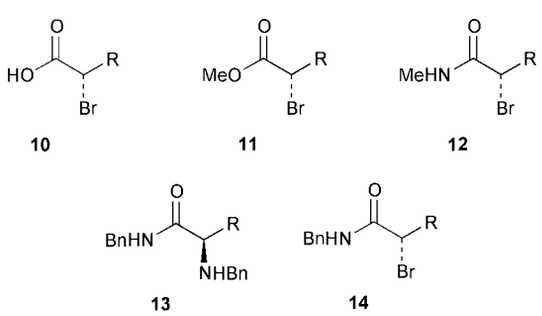
Ester	R	Yield (%)	Ee (%) of ketone **8**	Ee (%) of ester **11**	Ee (%) of amide **12**[b]
9d	CH_3	79	>98	96[a]	>95
9e	CH_2CH_3	87	>98	94[a]	>95
9f	$CH(CH_3)_2$	70	71	70[b]	—
9g	$(CH_2)_3CH_3$	85	66	65[b]	60
9h	$(CH_2)_7CH_3$	82	>98	88[b]	—

[a] By chiral GC with Supelco β-DEX 225 column. [b] By chiral NMR with $Eu(hfc)_3$, for **11** using the signals for proton *ortho* to OMe and for **12** using signals for NMe.

esters **11** and analysis by chiral GC or by ^{1}H NMR in the presence of $Eu(hfc)_3$. Alternatively the esters **9** were converted to the amides **12** which were analysed by ^{1}H NMR in the presence of $Eu(hfc)_3$.

Various methods for the hydrolysis of chiral, non-racemic esters that have an epimerisable α-carbon have been studied.[9] In some cases aqueous hydroxide is acceptable for hydrolysis with minimal racemisation, whilst in others basic hydrogen peroxide is better. The latter conditions ($LiOH–H_2O_2$) with the ester **9d** gave complete hydrolysis within five minutes, but there were a number of by-products, probably formed by peroxide oxidation of the 3-bromo-4-methoxyphenol produced during the hydrolysis. Fortunately, treatment of **9d** with aqueous LiOH caused instantaneous hydrolysis and the α-bromoacid **10d** was isolated in 72% yield. Treatment of **10d** with diazomethane gave the methyl ester **11d** whose ee was measured as 96% by chiral GC. A similar series of reactions with the esters **9e–h** gave the results shown in Table 3.

Alternatively we investigated the reaction of the α-bromoester **9d** with amines. With 2.2 equivalents of benzylamine in refluxing toluene, the α-aminoamide **13** was obtained (56%), whilst under the same conditions 1.1 equivalents of benzylamine gave (73%) the α-bromoamide **14**. However, problems

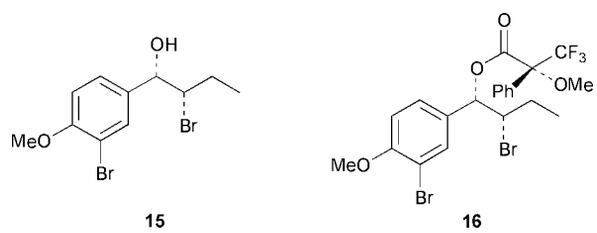


10 **11** **12** **13** **14**

with overlapping signals meant that it was not possible to use either of these compounds in chiral shift NMR studies. Fortunately the problem was solved by using methylamine instead of benzylamine, since the *N*-methylamide **12d**, formed in 52% yield by using aqueous methylamine in THF, did allow ee measurement by NMR. Again the procedure was repeated with the α-bromoesters **9e–h** and the results are shown in Table 3. The conclusion from these studies is that minimal racemisation occurs either on base catalysed hydrolysis of α-bromoesters **9** or on their reaction with amines and that overall the method allows the conversion of acetals **4** to α-bromoacids and amides with good ee.

Reduction of α-bromoketone 8d

Over the last few years, much work has gone into the preparation of enantiomerically pure epoxides which are versatile synthetic precursors to a wide variety of compounds. Since epoxides are readily available from halohydrins,[10] we investigated the reduction of enantiomerically pure α-bromoketone **8e**. Related α-haloketones have been reduced either microbiologically[10a] or with dibutyltin hydride.[11] In both cases the major, or exclusive, product was the *threo* isomer of the halohydrin. Treatment of **8e** with sodium borohydride in methanol at room temperature gave a mixture of bromohydrins in a 13:1 ratio. The major isomer showed a peak in its ^{1}H NMR spectrum for C*H*OH at δ 4.65 (*J* 7) whilst the minor isomer showed the corresponding signal at δ 5.00 (*J* 4). Comparison with literature data for related chlorohydrins[10a] suggested our major product was the *threo* isomer **15**. The simple expedient of carrying out the reaction at −78 °C afforded **15** exclusively, as shown by the total disappearance of the peak at δ 5.00. It now remained to determine whether there had been any racemisation of **8e** under the basic reaction conditions of the borohydride reduction. This was investigated by converting the bromohydrin product **15** obtained from enantiomerically pure α-bromoketone **8e**, and that from racemic **8e**, into their respective Moshers esters **16**. NMR analysis of these esters proved that no racemisation had occurred, since the product from racemic ketone showed two well resolved doublets at δ 5.90 and 6.00 for C*H*OCO, whilst that from enantiomerically pure ketone showed only the latter of these two signals. Thus enantiomerically pure α-bromoketones of the type **8** show potential as sources of enantiomerically pure bromohydrins and hence epoxides.



15 **16**

Experimental

General methods

Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. IR spectra were obtained on an ATI Mattson Genesis Series FTIR spectrophotometer. NMR spectra were obtained on a Bruker 250AC spectrometer. *J* values are quoted in Hz. In measuring ee values by NMR, a solution of $Eu(hfc)_3$ in $CDCl_3$ (25 mg cm^{-3}) was added a few drops at a time to a solution of the analyte in $CDCl_3$ (25 mg cm^{-3}) and the NMR spectrum was measured after each addition until maximum resolution was achieved. High resolution mass spectra were obtained on a VG Micromass 70/70F mass spectrometer fitted with a MSS data system. TLC was performed on Merck 555 Alufolien Kieselgel $60F_{254}$ plates, and flash chromatography was performed on Sorbsil C-60H (40–60 μm) silica gel.

Light petroleum refers to the fraction boiling between 40 and 60 °C. Solvents were dried and distilled prior to use.

General procedure for tartrate acetals 4

The aryl alkyl ketone (125 mmol), dimethyl tartrate (130 mmol) and trimethyl orthoformate (250 mmol) were heated to 50 °C prior to the addition of methanesulfonic acid (8 mmol). The reaction mixture was then heated at 95 °C for 5 days, during which time methanol and methyl formate were distilled off, and then cooled before being poured into vigorously stirred saturated aq sodium carbonate (150 cm^3) and extracted with

dichloromethane (2 × 100 cm^3). The combined organic extracts were washed with water (100 cm^3), dried ($MgSO_4$) and evaporated to afford the product which was purified by vacuum distillation or flash chromatography (ethyl acetate–light petroleum).

Dimethyl (4*R*,5*R*)-2-ethyl-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate 4a. Colourless oil (yield 82%) (Found M^+, 324.1181. $C_{16}H_{20}O_7$ requires 324.1209); ν_{max}(film)/cm^{-1} 1769, 1736; δ_H(250 MHz; $CDCl_3$) 1.10 (3H, t, *J* 7, CH_2CH_3), 2.15 (2H, q, *J* 7, CH_2CH_3), 3.75, 3.95, 4.00 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.95 (1H, d, *J* 6, OCH), 5.00 (1H, d, *J* 6, OCH), 7.00 (2H, d, *J* 9, ArH), 7.55 (2H, d, *J* 9, ArH); δ_C(62.5 MHz; $CDCl_3$) 7.9, 34.0, 52.7, 53.1, 55.5, 76.5, 77.6, 113.5, 115.5, 127.7, 133.0, 159.9 and 169.8.

Dimethyl (4*R*,5*R*)-2-(4-methoxyphenyl)-2-propyl-1,3-dioxolane-4,5-dicarboxylate 4b. Colourless oil (yield 69%) (Found M^+, 338.1342. $C_{17}H_{22}O_7$ requires 338.1366); ν_{max}(film)/cm^{-1} 1766, 1736; δ_H(250 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7, $CH_2CH_2CH_3$), 1.35 (2H, m, $CH_2CH_2CH_3$), 1.90 (2H, t, *J* 7, $CH_2CH_2CH_3$), 3.55, 3.75, 3.80 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.75 (1H, d, *J* 6, OCH), 4.80 (1H, d, *J* 6, OCH), 6.80 (2H, d, *J* 9, ArH), 7.35 (2H, d, *J* 9, ArH); δ_C(62.5 MHz; $CDCl_3$) 14.2, 16.9, 43.1, 52.5, 52.9, 55.3, 76.4, 77.6, 113.4, 115.0, 127.6, 133.2, 159.9 and 169.7.

Dimethyl (4*R*,5*R*)-2-benzyl-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate 4c. White solid (yield 81%); mp 65–66 °C (methanol) (Found M^+, 386.1370. $C_{21}H_{22}O_7$ requires 386.1366); ν_{max}(KBr)/cm^{-1} 1768, 1739; δ_H(250 MHz; $CDCl_3$) 3.30 (2H, s, CH_2), 3.55, 3.80, 3.85 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.65 (1H, d, *J* 5, OCH), 4.85 (1H, d, *J* 5, OCH), 6.80 (2H, d, *J* 9, ArH), 7.10–7.30 (7H, m, ArH); δ_C(62.5 MHz; $CDCl_3$) 47.6, 52.7, 53.0, 55.4, 76.7, 77.7, 113.3, 114.5, 126.9, 127.9, 131.3, 132.9, 135.3, 159.9 and 169.7.

Dimethyl (4*R*,5*R*)-2-(2-methylpropyl)-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate 4f. Colourless oil (yield 68%) (Found M^+, 352.1516. $C_{18}H_{24}O_7$ requires 352.1522); ν_{max}(film)/cm^{-1} 1769, 1738; δ_H(250 MHz; $CDCl_3$) 0.85 (6H, d, *J* 7, $(CH_3)_2CH$), 1.70 (1H, m, $CH(CH_3)_2$), 1.85 (2H, t, *J* 7, CH_2), 3.50, 3.75, 3.80 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.75 (1H, d, *J* 6, OCH), 4.80 (1H, d, *J* 6, OCH), 6.80 (2H, d, *J* 9, ArH), 7.35 (2H, d, *J* 9, ArH); δ_C(62.5 MHz; $CDCl_3$) 24.1, 25.4, 49.2, 52.6, 53.0, 55.5, 76.5, 77.9, 113.5, 115.5, 127.6, 133.4, 159.8, 169.8 and 169.9.

Dimethyl (4*R*,5*R*)-2-(4-methoxyphenyl)-2-pentyl-1,3-dioxolane-4,5-dicarboxylate 4g. Colourless oil (yield 69%) (Found M^+, 366.1691. $C_{19}H_{26}O_7$ requires 366.1679); ν_{max}(film)/cm^{-1} 1766, 1741; δ_H(250 MHz; $CDCl_3$) 0.80 (3H, t, *J* 7, CH_3), 1.20–1.45 (6H, m, 3 × CH_2), 1.95 (2H, m, CH_2), 3.55, 3.75, 3.80 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.75 (1H, d, *J* 6, OCH), 4.80 (1H, d, *J* 6, OCH), 6.80 (2H, d, *J* 9, ArH), 7.35 (2H, d, *J* 9, ArH); δ_C(62.5 MHz; $CDCl_3$) 14.3, 22.8, 23.3, 31.9, 41.0, 52.6, 53.0, 55.5, 76.5, 77.8, 113.5, 115.2, 159.9, 133.2, 127.6 169.8 and 169.9.

Dimethyl (4*R*,5*R*)-2-(4-methoxyphenyl)-2-nonyl-1,3-dioxolane-4,5-dicarboxylate 4h. Colourless oil (yield 84%) (Found $M^+ - OCH_3$, 391.2118. $C_{23}H_{34}O_7$ requires $M - OCH_3$ 391.2121); ν_{max}(film)/cm^{-1} 1771, 1741; δ_H(250 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7, CH_3), 1.15–1.40 (14H, m, 7 × CH_2), 1.95 (2H, m, CH_2), 3.55, 3.75, 3.85 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.75 (1H, d, *J* 6, OCH), 4.85 (1H, d, *J* 6, OCH), 6.80 (2H, d, *J* 9, ArH), 7.35 (2H, d, *J* 9, ArH); δ_C(62.5 MHz; $CDCl_3$) 14.4, 22.9, 23.6, 29.5, 29.8, 32.1, 41.1, 52.6, 52.9, 55.4, 76.4, 113.5, 115.2, 127.6, 133.2, 159.9 and 169.8.

Dimethyl (4*R*,5*R*)-2-ethyl-2-[4-(toluene-*p*-sulfonamido)-phenyl]-1,3-dioxolane-4,5-dicarboxylate 4i. White solid (yield 83%); mp 136–138 °C (methanol) (Found M^+, 463.1323. $C_{22}H_{25}NO_8S$ requires 463.1301); ν_{max}(KBr)/cm^{-1} 3288, 1742, 1732; δ_H(250 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7, CH_2CH_3), 1.95 (2H, q, *J* 7, CH_2CH_3), 2.40 (3H, s, $ArCH_3$), 3.45 (3H, s, CO_2CH_3), 3.85 (3H, s, CO_2CH_3), 4.75 (1H, d, *J* 6, OCH), 4.80 (1H, d, *J* 6, OCH), 7.05 (2H, d, *J* 8, ArH), 7.15 (1H, s, NH), 7.25 (2H, d, *J* 8, ArH), 7.35 (2H, d, *J* 8, ArH), 7.65 (2H, d, *J* 8, ArH); δ_C(62.5 MHz; $CDCl_3$) 7.9, 21.9, 33.9, 52.6, 53.2, 76.5, 77.7, 115.1, 120.9, 127.6, 130.0, 136.4, 137.0, 137.8, 144.3 and 169.7.

Dimethyl (4*R*,5*R*)-2-propyl-2-[4-(toluene-*p*-sulfonamido)-phenyl]-1,3-dioxolane-4,5-dicarboxylate 4j. White solid (yield 90%); mp 115–116 °C (methanol) (Found M^+, 477.1440. $C_{23}H_{27}NO_8S$ requires 477.1458); ν_{max}(KBr)/cm^{-1} 3285, 1745, 1730; δ_H(250 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7, CH_2CH_3), 1.30 (2H, m, CH_2CH_3), 1.90 (2H, m, CH_2CH_2), 2.40 (3H, s, $ArCH_3$), 3.45 (3H, s, CO_2CH_3), 3.85 (3H, s, CO_2CH_3), 4.75 (1H, d, *J* 6, OCH), 4.80 (1H, d, *J* 6, OCH), 6.85 (1H, s, NH), 7.00 (2H, d, *J* 8, ArH), 7.25 (2H, d, *J* 8, ArH), 7.35 (2H, d, *J* 8, ArH), 7.65 (2H, d, *J* 8, ArH); δ_C(62.5 MHz; $CDCl_3$) 14.2, 16.9, 21.8, 42.9, 52.6, 53.2, 76.4, 114.3, 114.8, 120.9, 127.6, 129.9, 136.9 and 169.6.

Dimethyl (4*R*,5*R*)-2-(2-methylpropyl)-2-[4-(toluene-*p*-sulfonamido)phenyl]-1,3-dioxolane-4,5-dicarboxylate 4k. White solid (yield 88%); mp 105–107 °C (methanol) (Found M^+, 491.1618. $C_{24}H_{29}NO_8S$ requires 491.1614); ν_{max}(KBr)/cm^{-1} 3281, 1741, 1732; δ_H(250 MHz; $CDCl_3$) 0.85 (6H, d, *J* 7, $CH(CH_3)_2$), 1.65 (1H, m, $CHCH_2$), 1.85 (2H, d, *J* 6.5, CH_2CH), 2.35 (3H, s, $ArCH_3$), 3.45 (3H, s, CO_2CH_3), 3.85 (3H, s, CO_2CH_3), 4.75 (1H, d, *J* 6, OCH), 4.80 (1H, d, *J* 6, OCH), 6.85 (1H, s, NH) 7.00 (2H, d, *J* 8, ArH), 7.25 (2H, d, *J* 8, ArH), 7.35 (2H, d, *J* 8, ArH), 7.65 (2H, d, *J* 8, ArH); δ_C(62.5 MHz; $CDCl_3$) 21.8, 24.0, 49.0, 52.5, 53.1, 76.4, 77.3, 115.1, 120.7, 127.4, 127.6, 129.9, 136.4, 137.3, 137.9, 144.2 and 169.8.

Dimethyl (4*R*,5*R*)-2-(4-acetamidophenyl)-2-ethyl-1,3-dioxolane-4,5-dicarboxylate 4l. Colourless oil (yield 46%) (Found M^+, 351.1324. $C_{17}H_{21}NO_7$ requires 351.1318); ν_{max}(film)/cm^{-1} 1742, 1732, 1666; δ_H(250 MHz; $CDCl_3$) 0.90 (3H, t, *J* 8, CH_2CH_3), 2.15 (2H, q, *J* 8, CH_2CH_3), 2.10 (3H, s, $NCOCH_3$), 3.55 (3H, s, CO_2CH_3), 3.80 (3H, s, CO_2CH_3), 4.75 (1H, d, *J* 5, OCH), 4.80 (1H, d, *J* 5, OCH), 7.35 (2H, d, *J* 8, ArH), 7.45 (2H, d, *J* 8, ArH), 8.00 (1H, s, NH); δ_C(62.5 MHz; $CDCl_3$) 15.2, 24.3, 33.9, 52.8, 53.2, 76.3, 115.3, 119.3, 126.6, 136.3, 138.8 and 169.8.

Dimethyl (4*R*,5*R*)-2-(4-acetamidophenyl)-2-pentyl-1,3-dioxolane-4,5-dicarboxylate 4m. Colourless oil (yield 44%) (Found M^+, 393.1789. $C_{20}H_{27}NO_7$ requires 393.1788); ν_{max}(film)/cm^{-1} 1742, 1732, 1666; δ_H(250 MHz; $CDCl_3$) 0.80 (3H, t, *J* 7.5, CH_3), 1.20–1.40 (6H, m, 3 × CH_2), 1.90 (2H, CH_2), 2.10 (3H, s, $NCOCH_3$), 3.55 (3H, s, CO_2CH_3), 3.80 (3H, s, CO_2CH_3), 4.75 (1H, d, *J* 5, OCH), 4.80 (1H, d, *J* 5, OCH), 7.35 (2H, d, *J* 8, ArH), 7.45 (2H, d, *J* 8, ArH), 7.90 (1H, s, NH); δ_C(62.5 MHz; $CDCl_3$) 13.9, 22.5, 23.0, 24.1, 31.7, 40.6, 52.3, 52.7, 76.3, 114.8, 119.3, 126.6, 136.3, 138.8, 169.6 and 169.7.

General procedure for brominated tartrate acetals 5

The appropriate acetal **4** (17 mmol), was dissolved in CCl_4 or DCM (40 cm^3) prior to the addition of the same solvent (5 cm^3) saturated with dry HCl. The reaction mixture was maintained at −6 °C (ice–acetone) during the dropwise addition of bromine (2.85 g, 17.6 mmol) in CCl_4 or DCM (10 cm^3). When TLC analysis showed reaction was complete (negative reaction to 2,4-dinitrophenylhydrazine spray), the reaction mixture was slowly added to anhydrous potassium carbonate (10 g) in DCM (50 cm^3) and the slurry was stirred for 10 min before adding water (50 cm^3). The layers were separated and the aqueous layer was further extracted with DCM (2 × 50 cm^3). The combined organic extracts were washed with water (50 cm^3), dried

($MgSO_4$) and evaporated to afford the product as either a viscous oil or a solid.

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate 5a. Colourless oil (yield 97%, 90% de) (Found M^+, 402.0346. $C_{16}H_{19}{}^{79}BrO_7$ requires 402.0314); ν_{max}(film)/cm^{-1} 1766, 1739; δ_H(250 MHz; $CDCl_3$) 1.60 (3H, d, *J* 7, CH_3), 3.55, 3.80, 3.85 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.35 (1H, q, *J* 7, CHBr), 4.85 (1H, d, *J* 6, OCH), 4.90 (1H, d, *J* 6, OCH), 6.85 (2H, d, *J* 9, ArH), 7.45 (2H, d, *J* 9, ArH); δ_C(62.5 MHz; $CDCl_3$) 20.9, 52.8, 53.2, 55.5, 77.3, 78.2, 113.4, 113.6, 128.8, 129.3, 160.5, 169.2 and 168.9.

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromopropyl]-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate 5b. Colourless oil (yield 91%, 90% de) (Found M^+, 416.0486. $C_{17}H_{21}{}^{79}BrO_7$ requires 416.0471); ν_{max}(film)/cm^{-1} 1772, 1746; δ_H(250 MHz; $CDCl_3$) 1.00 (3H, t, *J* 7, CH_3), 1.60 (1H, m, C*H*HCH_3), 1.95 (1H, m, CH*H*CH_3), 3.55, 3.80, 3.85 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.15 (1H, dd, *J* 11, 2, CHBr), 4.85 (1H, d, *J* 6, OCH), 4.90 (1H, d, *J* 6, OCH), 6.85 (2H, d, *J* 9, ArH), 7.45 (2H, d, *J* 9, ArH); δ_C(62.5 MHz; $CDCl_3$) 12.9, 26.4, 52.8, 53.2, 55.5, 62.7, 77.3, 113.5, 113.6, 128.8, 129.7, 160.4, 168.9 and 169.2.

Dimethyl (4*R*,5*R*)-2-[(*S*)-bromo(phenyl)methyl]-2-(4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate 5c. Colourless oil (yield 91%, 85% de) (Found M^+, 464.0458. $C_{21}H_{21}{}^{79}BrO_7$ requires 464.0471); ν_{max}(film)/cm^{-1} 1767, 1735; δ_H(250 MHz; $CDCl_3$) 3.70, 3.80, 3.85 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.65 (1H, d, *J* 6, OCH), 4.85 (1H, d, *J* 6, OCH), 6.70 (1H, s, CHBr), 6.80 (2H, d, *J* 9, ArH), 7.10–7.30 (7H, m, ArH); δ_C(62.5 MHz; $CDCl_3$) 52.8, 53.2, 55.5, 77.3, 78.2, 113.6, 116.8, 126.6, 127.0, 127.4, 127.5, 134.1, 139.5, 157.2, 168.9 and 169.2.

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-(3-bromo-4-methoxyphenyl)-1,3-dioxolane-4,5-dicarboxylate 5d. 2 Equivalents of bromine used. White solid (yield 88%, 90% de); mp 80–82 °C (methanol) (Found M^+, 479.9432. $C_{16}H_{18}{}^{79}Br_2O_7$ requires 479.9419); ν_{max}(KBr)/cm^{-1} 1769, 1740; δ_H(250 MHz; $CDCl_3$) 1.75 (3H, d, *J* 7, CH_3), 3.75, 4.00, 4.05 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.45 (1H, q, *J* 7, CHBr), 4.95 (1H, d, *J* 6, OCH), 5.05 (1H, d, *J* 6, OCH), 7.00 (1H, d, *J* 9, ArH), 7.60 (1H, dd, *J* 9,2, ArH), 7.85 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 20.8, 52.7, 53.0, 53.3, 56.6, 77.2, 78.4, 111.2, 112.9, 128.2, 130.8, 132.5, 132.6, 156.7, 168.7 and 169.1.

Dimethyl (4*R*,5*R*)-2-(3-bromo-4-methoxyphenyl)-2-[(*S*)-1-bromopropyl]-1,3-dioxolane-4,5-dicarboxylate 5e. 2 Equivalents of bromine used. Colourless oil (yield 91%, 90% de) (Found M^+, 493.9598. $C_{17}H_{20}{}^{79}Br_2O_7$ requires 493.9576); ν_{max}(film)/cm^{-1} 1765, 1742; δ_H(250 MHz; $CDCl_3$) 1.05 (3H, t, *J* 7, CH_3), 1.60 (1H, m, C*H*HCH_3), 2.00 (1H, m, CH*H*CH_3), 3.65, 3.85, 3.95 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.10 (1H, dd, *J* 11, 2, CHBr), 4.80 (1H, d, *J* 6, OCH), 4.90 (1H, d, *J* 6, OCH), 6.85 (1H, d, *J* 8, ArH), 7.45 (1H, dd, *J* 8, 2, ArH), 7.70 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 12.9, 26.3, 52.9, 53.3, 56.5, 62.2, 77.3, 111.2, 112.9, 128.1, 131.2, 132.4, 156.6, 168.7 and 169.0.

Dimethyl (4*R*,5*R*)-2-(3-bromo-4-methoxyphenyl)-2-[(*S*)-1-bromo-2-methyl-1-propyl]-1,3-dioxolane-4,5-dicarboxylate 5f. 2 Equivalents of bromine used. Colourless oil (yield 95%, 85% de) (Found M^+, 507.9750. $C_{18}H_{22}{}^{79}Br_2O_7$ requires 507.9732); ν_{max}(film)/cm^{-1} 1766, 1737; δ_H(250 MHz; $CDCl_3$) 0.95 (6H, d, *J* 7, $(CH_3)_2CH$), 1.80 (1H, m, C*H*$(CH_3)_2$), 3.60, 3.80, 3.90 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.25 (1H, d, *J* 2, CHBr), 4.85 (1H, d, *J* 6, OCH), 4.95 (1H, d, *J* 6, OCH), 6.85 (1H, d, *J* 9, ArH), 7.45 (1H, dd, *J* 9, 2, ArH), 7.70 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 17.9, 23.5, 29.2, 53.3, 56.6, 68.2, 79.1, 111.6, 113.3, 127.4, 130.4, 131.9, 134.7, 156.7 and 168.9.

Dimethyl (4*R*,5*R*)-2-(3-bromo-4-methoxyphenyl)-2-[(*S*)-1-bromopentyl]-1,3-dioxolane-4,5-dicarboxylate 5g. 2 Equivalents of bromine used. Colourless oil (yield 91%, 85% de) (Found M^+, 521.9862. $C_{19}H_{24}{}^{79}Br_2O_7$ requires 521.9889); ν_{max}(film)/cm^{-1} 1762, 1731; δ_H(250 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7, CH_3), 1.30 (2H, m, CH_2CH_3), 1.60 (3H, m, CHBrC*H*HCH_2 and C$H_2CH_2CH_3$), 1.90 (1H, m, CHBrCH*H*CH_2), 3.65, 3.85, 3.95 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.20 (1H, dd, *J* 11, 2, CHBr), 4.85 (1H, d, *J* 6, OCH), 4.95 (1H, d, *J* 6, OCH), 6.85 (1H, d, *J* 8, ArH), 7.50 (1H, dd, *J* 8, 2, ArH), 7.70 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 14.2, 22.2, 30.1, 32.6, 53.3, 56.6, 60.1, 79.1, 111.2, 113.0, 128.3, 131.2, 132.6, 156.6 and 168.8.

Dimethyl (4*R*,5*R*)-2-(3-bromo-4-methoxyphenyl)-2-[(*S*)-1-bromononyl]-1,3-dioxolane-4,5-dicarboxylate 5h. 2 Equivalents of bromine used. Colourless oil (yield 98%, 82% de) (Found M^+, 578.0511. $C_{23}H_{32}{}^{79}Br_2O_7$ requires 578.0515); ν_{max}(film)/cm^{-1} 1764, 1736; δ_H(250 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7, CH_3), 1.25 (10H, m, 5 × CH_2), 1.65 (2H, m, CH_2CH_2CHBr), 1.85 (2H, m, CH_2CH_2CHBr), 3.65, 3.85, 3.90 (3 × 3H, 3 × s, $ArOCH_3$ and 2 × CO_2CH_3), 4.20 (1H, dd, *J* 11, 2, CHBr), 4.85 (1H, d, *J* 6, OCH), 4.90 (1H, d, *J* 6, OCH), 6.85 (1H, d, *J* 8, ArH), 7.45 (1H, dd, *J* 8, 2, ArH), 7.70 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 14.1, 22.7, 24.6, 26.3, 29.4, 29.7, 31.8, 35.3, 53.3, 56.6, 60.1, 79.1, 111.2, 113.0, 128.3, 131.2, 132.6, 156.6 and 168.8.

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-[4-(toluene-*p*-sulfonamido)phenyl]-1,3-dioxolane-4,5-dicarboxylate 5i. Off-white solid (yield 80%, 82% de); mp 121–123 °C (methanol) (Found M^+, 541.0422. $C_{22}H_{24}{}^{79}BrNO_8$ requires 541.0406); ν_{max}(KBr)/cm^{-1} 3292, 1740; δ_H(250 MHz; $CDCl_3$) 1.55 (3H, t, *J* 7, CHBrCH_3), 2.35 (3H, s, $ArCH_3$), 3.45 (3H, s, CO_2CH_3), 3.85 (3H, s, CO_2CH_3), 4.30 (1H, q, *J* 7, CHBr), 4.80 (1H, d, *J* 6, OCH), 4.90 (1H, d, *J* 6, OCH), 6.70 (1H, s, NH), 7.05 (2H, d, *J* 8, ArH), 7.25 (2H, d, *J* 8, ArH), 7.40 (2H, d, *J* 8, ArH), 7.70 (2H, d, *J* 8, ArH); δ_C(62.5 MHz; $CDCl_3$) 20.8, 21.8, 52.7, 53.3, 78.2, 113.3, 120.2, 127.6, 128.6, 130.0, 133.8, 136.4, 137.9, 144.4, 168.9 and 169.1.

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromopropyl]-2-[4-(toluene-*p*-sulfonamido)phenyl]-1,3-dioxolane-4,5-dicarboxylate 5j. Off-white solid (yield 66%, 82% de); mp 136–138 °C (methanol) (Found M^+, 555.0575. $C_{23}H_{26}{}^{79}BrNO_8$ requires 555.0563); ν_{max}(KBr)/cm^{-1} 3299, 1735; δ_H(250 MHz; $CDCl_3$) 0.95 (3H, t, *J* 7, CH_2CH_3), 1.55 (1H, m, C*H*HCHBr), 1.90 (1H, m, CH*H*CHBr), 2.35 (3H, s, $ArCH_3$), 3.45 (3H, s, CO_2CH_3), 3.85 (3H, s, CO_2CH_3), 4.10 (1H, dd, *J* 11, 2, CHBr), 4.80 (1H, d, *J* 6, OCH), 4.90 (1H, d, *J* 6, OCH), 7.05 (2H, d, *J* 8, ArH), 7.25 (2H, d, *J* 8, ArH), 7.40 (2H, d, *J* 8, ArH), 7.55 (1H, s, NH), 7.70 (2H, d, *J* 8, ArH); δ_C(62.5 MHz; $CDCl_3$) 12.9, 21.8, 26.3, 52.7, 53.3, 62.2, 78.2, 113.3, 119.1, 120.2, 127.6, 128.6, 130.0, 130.9, 134.2, 136.4, 137.9, 144.3, 168.9 and 169.1.

Dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromo-2-methylpropyl]-2-[4-(toluene-*p*-sulfonamido)phenyl]-1,3-dioxolane-4,5-dicarboxylate 5k. Off-white solid (yield 23%, 78% de); mp 122–124 °C (methanol) (Found M^+, 569.0724. $C_{24}H_{28}{}^{79}BrNO_8$ requires 569.0719); ν_{max}(KBr)/cm^{-1} 3290, 1735; δ_H(250 MHz; $CDCl_3$) 0.90 (6H, m, $(CH_3)_2CH$), 1.60 (1H, m, C*H*$(CH_3)_2$), 2.35 (3H, s, $ArCH_3$), 3.45 (3H, s, CO_2CH_3), 3.85 (3H, s, CO_2CH_3), 4.25 (1H, d, *J* 2, CHBr), 4.80 (1H, d, *J* 6, OCH), 4.90 (1H, d, *J* 6, OCH), 7.05 (2H, d, *J* 8, ArH), 7.25 (2H, d, *J* 8, ArH), 7.35 (2H, d, *J* 8, ArH), 7.70 (2H, d, *J* 8, ArH), 7.80 (1H, s, NH); δ_C(62.5 MHz; $CDCl_3$) 17.8, 21.8, 23.4, 29.1, 52.7, 53.2, 68.2, 78.2, 113.6, 120.6, 127.6, 127.9, 130.0, 135.2, 136.4, 137.9, 144.4, 168.6 and 169.3.

(4*R*,5*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxamide 6

Dimethylamine was distilled from a 40% aqueous solution (20 cm^3), collected at −78 °C and dried over potassium hydroxide. This was added to dimethyl (4*R*,5*R*)-2-[(*S*)-1-bromoethyl]-2-phenyl-1,3-dioxolane-4,5-dicarboxylate (1.03 g, 2.76 mmol) in dry methanol (7 cm^3) cooled to −78 °C. The reaction mixture was allowed to warm to −5 °C and maintained at this temperature for 3 days. Removal of the solvent gave the product as a white gum (1.05 g, 95%) (Found M^+, 398.0418. $C_{17}H_{23}{}^{79}BrN_2O_4$ requires 398.0412); ν_{max}(film)/cm^{-1} 1672–1643; δ_H(250 MHz; $CDCl_3$) 1.60 (3H, d, *J* 7, CH_3), 2.85, 3.00, 3.20, 3.25 (4 × 3H, 4 × s, 4 × NCH_3), 4.35 (1H, q, *J* 7, CHBr), 5.20 (1H, d, *J* 6, OCH), 5.30 (1H, d, *J* 6, OCH), 7.30–7.45 (5H, m, ArH); δ_C(62.5 MHz; $CDCl_3$) 20.9, 35.7, 35.9, 37.3, 53.2, 77.3, 78.7, 113.9, 125.7, 128.2, 128.4, 142.3, 169.6 and 171.2.

General procedure for α-bromoketones 8

The appropriate bromoacetal **5** (8.06 mmol) was dissolved in methanesulfonic acid (40 cm^3) and stirred for 5 min prior to the addition of water (0.38 g, 21.1 mmol) over 5 min. After 1 h the reaction mixture was slowly poured on to crushed ice (60 g) and ether (30 cm^3), the layers were separated and the aqueous layer was extracted with ether (2 × 20 cm^3). The combined ether layers were washed with water (20 cm^3), dried ($MgSO_4$) and evaporated. The residue was purified by recrystallisation (methanol) or flash chromatography (ethyl acetate–light petroleum).

(*S*)-2-Bromo-1-(4-methoxyphenyl)propan-1-one 8a. White solid (yield 58%, 80% ee); mp 63–64 °C (methanol) (Found M^+, 241.9921. $C_{10}H_{11}{}^{79}BrO_2$ requires 241.9942); ν_{max}(KBr)/cm^{-1} 1666; δ_H(250 MHz; $CDCl_3$) 1.85 (3H, d, *J* 7, CH_3), 3.85 (3H, s, $ArOCH_3$), 5.25 (1H, q, *J* 7, CHBr), 6.95 (2H, d, *J* 8, ArH), 8.00 (2H, d, *J* 8, ArH); δ_C(62.5 MHz; $CDCl_3$) 20.6, 41.9, 55.8, 114.3, 127.1, 131.6, 164.3 and 192.3.

(*S*)-2-Bromo-1-(4-methoxyphenyl)butan-1-one 8b. White solid (yield 65%, 92% ee); mp 51–53 °C (methanol) (Found M^+, 256.0115. $C_{11}H_{13}{}^{79}BrO_2$ requires 256.0099); ν_{max}(KBr)/cm^{-1} 1676; δ_H(250 MHz; $CDCl_3$) 1.10 (3H, t, *J* 7, CH_3), 2.20 (2H, m, CH_2), 3.90 (3H, s, $ArOCH_3$), 5.05 (1H, t, *J* 7, CHBr), 7.00 (2H, d, *J* 8, ArH), 8.05 (2H, d, *J* 8, ArH); δ_C(62.5 MHz; $CDCl_3$) 12.4, 28.6, 49.1, 55.8, 113.3, 129.1, 131.6, 164.3 and 192.3.

(*S*)-2-Bromo-1-(4-methoxyphenyl)-2-phenylethan-1-one 8c. White solid (yield 45%); mp 136–138 °C (methanol) (Found M^+, 292.0082. $C_{14}H_{13}{}^{79}BrO_2$ requires 292.0099); ν_{max}(KBr)/cm^{-1} 1669; δ_H(250 MHz; $CDCl_3$) 3.80 (3H, s, $ArOCH_3$), 5.80 (1H, s, CHBr), 7.10 (2H, d, *J* 8, ArH), 7.40 (5H, m, ArH), 8.20 (2H, d, *J* 8, ArH); δ_C(62.5 MHz; $CDCl_3$) 55.1, 113.9, 127.5, 129.0, 130.2, 130.5, 132.0, 163.9 and 187.6.

(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)propan-1-one 8d. White solid (yield 52%, 98% ee); mp 108–110 °C (methanol) (Found M^+, 319.9068. $C_{10}H_{10}{}^{79}Br_2O_2$ requires 319.9048); ν_{max}(KBr)/cm^{-1} 1669; δ_H(250 MHz; $CDCl_3$) 1.85 (3H, d, *J* 7, CH_3), 3.95 (3H, s, $ArOCH_3$), 5.20 (1H, q, *J* 7, CHBr), 6.95 (1H, d, *J* 8, ArH), 7.95 (1H, dd, *J* 8, 2, ArH), 8.20 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 20.4, 41.5, 56.9, 111.5, 112.5, 128.2, 130.5, 134.7, 160.4 and 191.3.

(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)butan-1-one 8e. White solid (yield 50%, 98% ee); mp 82–84 °C (methanol) (Found M^+, 333.9231. $C_{11}H_{12}{}^{79}Br_2O_2$ requires 333.9204); ν_{max}(KBr)/cm^{-1} 1666; δ_H(250 MHz; $CDCl_3$) 1.10 (3H, t, *J* 7, CH_3), 2.20 (2H, m, CH_2), 4.00 (3H, s, $ArOCH_3$), 5.00 (1H, t, *J* 8, CHBr), 6.95 (1H, d, *J* 8, ArH), 7.95 (1H, dd, *J* 8, 2, ArH), 8.20 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 12.5, 27.2, 49.1, 56.9, 111.6, 112.5, 128.7, 130.5, 134.6, 160.4 and 191.2.

(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)-3-methylbutan-1-one 8f. Pale brown oil (yield 70%, 71% ee) (Found M^+, 347.9392. $C_{12}H_{14}{}^{79}Br_2O_2$ requires 347.9361); ν_{max}(film)/cm^{-1} 1669; δ_H(250 MHz; $CDCl_3$) 1.00 (6H, d, *J* 7, CH_3), 2.45 (1H, m, CH), 4.00 (3H, s, $ArOCH_3$), 4.85 (1H, d, *J* 7, CHBr), 6.95 (1H, d, *J* 8, ArH), 7.90 (1H, dd, *J* 8, 2, ArH), 8.20 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 21.0, 32.8, 56.9, 59.1, 112.6, 114.9, 130.3, 130.5, 134.6, 161.4 and 191.2.

(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)hexan-1-one 8g. White solid (yield 67%, 66% ee); mp 58–60 °C (methanol) (Found M^+, 361.9501. $C_{13}H_{16}{}^{79}Br_2O_2$ requires 361.9517); ν_{max}(KBr)/cm^{-1} 1665; δ_H(250 MHz; $CDCl_3$) 0.95 (3H, t, *J* 7, CH_3), 1.40 (4H, m, 2 × CH_2), 2.15 (2H, m, $CHBrCH_2$), 4.00 (3H, s, $ArOCH_3$), 5.05 (1H, t, *J* 7, CHBr), 6.95 (1H, d, *J* 8, ArH), 7.95 (1H, dd, *J* 8, 2, ArH), 8.20 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 14.2, 22.6, 30.0, 33.5, 47.3, 56.9, 111.6, 112.5, 128.7, 130.5, 134.7, 160.4 and 191.3.

(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)decan-1-one 8h. White solid (yield 43%, >98% ee); mp 58–59 °C (methanol) (Found M^+, 418.0129. $C_{17}H_{24}{}^{79}Br_2O_2$ requires 418.0143); ν_{max}(KBr)/cm^{-1} 1669; δ_H(250 MHz; $CDCl_3$) 0.90 (3H, t, *J* 7, CH_3), 1.20–1.55 (12H, m, 6 × CH_2), 2.15 (2H, m, $CHBrCH_2$), 4.00 (3H, s, $ArOCH_3$), 5.05 (1H, t, *J* 7, CHBr), 6.95 (1H, d, *J* 8, ArH), 8.00 (1H, dd, *J* 8, 2, ArH), 8.20 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 14.4, 22.9, 28.0, 29.0, 29.5, 29.6, 32.1, 32.8, 47.6, 56.5, 111.3, 112.5, 128.8, 130.5, 134.6, 160.4 and 191.5.

General procedure for α-bromoesters 9

The appropriate α-bromoketone **8** (12.4 mmol) was dissolved in chloroform (125 cm^3). Disodium hydrogen phosphate (4.0 g, 28.2 mmol) and MCPBA (57–86% w/w, 9.4 g) were added and the reaction mixture was stirred at room temperature until complete consumption of **8** had occurred (approx. 2 days, NMR analysis). The mixture was poured into water (75 cm^3) and saturated aq. sodium hydrogen carbonate (75 cm^3), the layers were separated and the aqueous phase was extracted with DCM (2 × 100 cm^3). The combined organic layers were washed with water (50 cm^3), dried ($MgSO_4$) and evaporated to give the crude product which was purified by flash chromatography with ethyl acetate–light petroleum (1 : 19).

3-Bromo-4-methoxyphenyl (*S*)-2-bromopropanoate 9d. Pale brown oil (yield 98%) (Found M^+, 335.9018. $C_{10}H_{10}{}^{79}Br_2O_3$ requires 335.8997); ν_{max}(film)/cm^{-1} 1765; δ_H(250 MHz; $CDCl_3$) 1.95 (3H, d, *J* 7, CH_3), 3.90 (3H, s, $ArOCH_3$), 4.10 (1H, q, *J* 7, CHBr), 6.90 (1H, d, *J* 8, ArH), 7.10 (1H, dd, *J* 8, 2, ArH), 7.40 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 24.1, 45.4, 56.6, 112.2, 121.2, 126.4, 128.6, 148.2, 153.5 and 169.4.

3-Bromo-4-methoxyphenyl (*S*)-2-bromobutanoate 9e. Pale brown oil (yield 87%) (Found M^+, 349.9139. $C_{11}H_{12}{}^{79}Br_2O_3$ requires 349.9153); ν_{max}(film)/cm^{-1} 1769; δ_H(250 MHz; $CDCl_3$) 1.15 (3H, t, *J* 7, CH_3), 2.20 (2H, m, CH_2), 3.90 (3H, s, $ArOCH_3$), 4.10 (1H, t, *J* 7, CHBr), 6.90 (1H, d, *J* 8, ArH), 7.10 (1H, dd, *J* 8, 2, ArH), 7.35 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 12.0, 24.4, 54.0, 56.6, 112.2, 121.2, 126.6, 144.2, 153.5 and 168.7.

3-Bromo-4-methoxyphenyl (*S*)-2-bromo-3-methylbutanoate 9f. Pale brown oil (yield 70%) (Found M^+, 363.9302. $C_{12}H_{14}{}^{79}Br_2O_3$ requires 363.9310); ν_{max}(film)/cm^{-1} 1761; δ_H(250 MHz; $CDCl_3$) 1.15 (6H, d, *J* 7, 2 × CH_3), 2.35 (1H, m, CH), 3.90 (3H, s, $ArOCH_3$), 4.20 (1H, d, *J* 8, CHBr), 6.90 (1H, d, *J* 8, ArH), 7.10 (1H, dd, *J* 8, 2, ArH), 7.40 (1H, d, *J* 2, ArH); δ_C(62.5

MHz; $CDCl_3$) 20.4, 32.6, 54.0, 56.9, 112.2, 121.2, 126.4, 128.6, 144.2, 154.5 and 168.3.

3-Bromo-4-methoxyphenyl (*S*)-2-bromohexanoate 9g. Pale brown oil (yield 85%) (Found M^+, 377.9459. $C_{13}H_{16}{}^{79}Br_2O_3$ requires 377.9466); ν_{max}(film)/cm^{-1} 1771; δ_H(250 MHz; $CDCl_3$) 0.95 (3H, t, *J* 7, CH_3), 1.40 (4H, m, CH_2CH_2), 2.15 (2H, m, CHBrCH_2), 3.85 (3H, s, $ArOCH_3$), 4.40 (1H, t, *J* 8, CHBr), 6.90 (1H, d, *J* 8, ArH), 7.05 (1H, dd, *J* 8, 2, ArH), 7.35 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 14.1, 21.3, 27.9, 34.7, 45.6, 56.8, 111.9, 112.2, 121.2, 126.4, 144.2, 154.5 and 168.7.

3-Bromo-4-methoxyphenyl (*S*)-2-bromodecanoate 9h. Pale brown oil (yield 82%) (Found M^+, 4343.0071. $C_{17}H_{24}{}^{79}Br_2O_3$ requires 434.0092); ν_{max}(film)/cm^{-1} 1752; δ_H(250 MHz; $CDCl_3$) 0.90 (3H, t, *J* 7, CH_3), 1.20–1.65 (12H, m, 6 × CH_2), 2.15 (2H, m, CHBrCH_2), 3.90 (3H, s, $ArOCH_3$), 4.40 (1H, d, *J* 8, CHBr), 6.90 (1H, d, *J* 8, ArH), 7.10 (1H, dd, *J* 8, 2, ArH), 7.35 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 14.4, 22.9, 27.6, 29.1, 29.4, 29.6, 32.1, 35.0, 45.6, 56.9, 112.2, 121.2, 126.4, 128.6, 144.2, 154.5 and 168.8.

General procedure for hydrolysis of α-bromoesters 9

The appropriate α-bromoester **9** (0.89 mmol) was dissolved in THF (3 cm^3) and water (3 cm^3). Lithium hydroxide monohydrate (0.040 g, 0.95 mmol) was added and the reaction mixture was stirred at room temperature for 5 min, poured into 10% w/w aq. sodium hydrogen carbonate (20 cm^3) and extracted with DCM (2 × 10 cm^3). The aqueous layer was acidified with conc. HCl and extracted with DCM (2 × 20 cm^3). These organic extracts were combined, washed with water (20 cm^3), dried ($MgSO_4$) and evaporated to give the crude product (identical with an authentic sample prepared by bromination of the appropriate acid). A small portion was treated with diazomethane for chiral GC or NMR analysis.

General procedure for α-bromoamides 12

The appropriate α-bromoester (0.74 mmol) was dissolved in THF (5 cm^3) and water (3 cm^3) and 40% w/w aq. methylamine (0.81 mmol) was added. The reaction mixture was stirred at room temperature for 16 h, ethyl acetate (20 cm^3) was added and the mixture was washed with 2 M HCl (2 × 10 cm^3), 2 M NaOH (2 × 10 cm^3) and water (10 cm^3), dried ($MgSO_4$) and evaporated to give the crude product which was purified by flash chromatography with ethyl acetate–light petroleum (1:2).

(*S*)-*N*-Methyl-2-bromopropanamide 12d. White solid (yield 58%, >95% ee); mp 49–52 °C (Found M^+, 164.9785. $C_4H_8{}^{79}BrNO$ requires 164.9789); ν_{max}(KBr)/cm^{-1} 1657; δ_H(250 MHz; $CDCl_3$) 1.80 (3H, d, *J* 7, CH_3), 2.00 (2H, m, CH2), 2.80 (3H, d, *J* 5, NCH_3), 4.40 (1H, q, *J* 8, CHBr), 7.10 (1H, br s, NH); δ_C(62.5 MHz; $CDCl_3$) 22.7, 27.0, 44.0 and 171.1.

(*S*)-*N*-Methyl-2-bromobutanamide 12e. White solid (yield 66%, >95% ee); mp 31–33 °C (Found M^+, 178.9951. $C_5H_{10}{}^{79}BrNO$ requires 178.9946); ν_{max}(KBr)/cm^{-1} 1650; δ_H(250 MHz; $CDCl_3$) 0.95 (3H, t, *J* 7, CH_3), 2.00 (2H, m, CH_2), 2.80 (3H, d, *J* 5, NCH_3), 4.25 (1H, t, *J* 7, CHBr), 7.10 (1H, br s, NH); δ_C(62.5 MHz; $CDCl_3$) 12.0, 27.2, 29.6, 54.0 and 169.5.

(*S*)-*N*-Methyl-2-bromohexanamide 12g. Colourless oil (yield 66%, 60% ee) (Found M^+, 207.0252. $C_7H_{14}{}^{79}BrNO$ requires 207.0259); ν_{max}(KBr)/cm^{-1} 1659; δ_H(250 MHz; $CDCl_3$) 0.90 (3H, t, *J* 7, CH_3), 1.40 (4H, m, CH_2CH_2), 2.05 (2H, m, CHBrCH_2), 2.75 (3H, d, *J* 5, NCH_3), 4.35 (1H, dd, *J* 7, 2, CHBr), 6.50 (1H, br s, NH); δ_C(62.5 MHz; $CDCl_3$) 14.3, 21.2, 25.6, 28.8, 35.1, 50.2 and 169.4.

(1*S*,2*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)butan-1-ol 15

(*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)butan-1-one **8e** (0.25 g, 0.74 mmol) was dissolved in methanol (20 cm^3) and cooled to −78 °C. Sodium borohydride (0.028 g, 0.74 mmol) was added and the mixture was stirred for 5 min, acidified with 2 M HCl (20 cm^3) and extracted with ether (3 × 20 cm^3).The combined organic extracts were washed with water (20 cm^3), dried ($MgSO_4$) and evaporated to give the crude product which was purified by flash chromatography with ethyl acetate–light petroleum (1:4) to give a colourless oil (0.17 g, 66%) (Found M^+, 335.9353. $C_{11}H_{14}{}^{79}Br_2O_2$ requires 335.9361); ν_{max}(film)/cm^{-1} 3620; δ_H(250 MHz; $CDCl_3$) 1.05 (3H, t, *J* 8, CH_3), 1.75 (2H, m, CH_2), 2.65 (1H, br s, OH), 3.90 (3H, s, OCH_3), 4.15 (1H, m, CHBr), 4.65 (1H, d, *J* 7, *CH*OH), 6.90 (1H, d, *J* 8, ArH), 7.25 (1H, dd, *J* 8, 2, ArH), 7.55 (1H, d, *J* 2, ArH); δ_C(62.5 MHz; $CDCl_3$) 12.7, 28.6, 56.6, 67.8, 76.5, 112.1, 127.2, 131.8, 134.1 and 156.1.

The racemic bromohydrin showed identical spectral properties.

(1*S*,2*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)butyl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 16

(1*S*,2*S*)-2-Bromo-1-(3-bromo-4-methoxyphenyl)butan-1-ol **15** (0.164 g, 0.485 mmol) was dissolved in DCM (20 cm^3) and (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (0.142 g, 0.61 mmol), DCC (0.131 g, 0.61 mmol) and DMAP (0.005 g) were added. The mixture was stirred at room temperature until the consumption of **15** was complete, and was then washed with 2 M HCl (20 cm^3), 2 M NaOH (20 cm^3), and water (20 cm^3), dried ($MgSO_4$) and evaporated to give the crude product which was purified by flash chromatography with ethyl acetate–light petroleum (1:4) to give a colourless oil (0.193 g, 72%) (Found M^+, 551.9772. $C_{21}H_{21}{}^{79}Br_2F_3O_4$ requires 551.9759); ν_{max}(film)/cm^{-1} 1745; δ_H(250 MHz; $CDCl_3$) 1.00 (3H, t, *J* 7, CH_3), 1.65 (2H, m, CH_2), 3.45 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.15 (1H, m, CHBr), 6.00 (1H, d, *J* 8, *C*HOCO), 6.85 (1H, d, *J* 8, ArH), 7.25–7.65 (8H, m, ArH); δ_C(62.5 MHz; $CDCl_3$) 12.1, 27.9, 55.9, 56.6, 58.0, 79.8, 84.9, 112.0, 112.2, 125.9, 127.9, 128.5, 128.7, 129.8, 130.0, 132.1, 132.5, 156.8 and 162.5.

The ester derived from racemic bromohydrin showed extra peaks at δ_H 3.65 (3H, s, OCH_3), 5.90 (1H, d, *J* 8, *C*HOCO) and 6.80 (1H, d, *J* 8, ArH); δ_C 14.4, 21.2 and 171.4.

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