Stereospecific conversion of (1*R**,3*S**)- and (1*R**,3*R**)-3-cyclohexyl-1-phenylpropane-1,3-diol into the corresponding 2,4-disubstituted oxetanes

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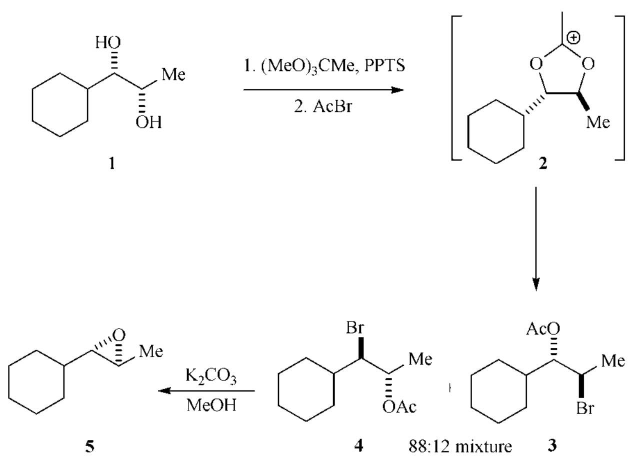
Conversion of two diastereoisomeric 1,3-diols (3-cyclohexyl-1-phenylpropane-1,3-diol) into orthoesters was followed by treatment with acetyl bromide. The 1,3-bromo acetates (acetic acid 3-bromo-1-cyclohexyl-3-phenylpropyl esters) were obtained with complete inversion of configuration at a benzylic site. Methanolysis of the bromo acetates, followed by ring-closure, resulted in a second inversion of configuration at a benzylic site to give the corresponding oxetanes with overall retention of configuration.

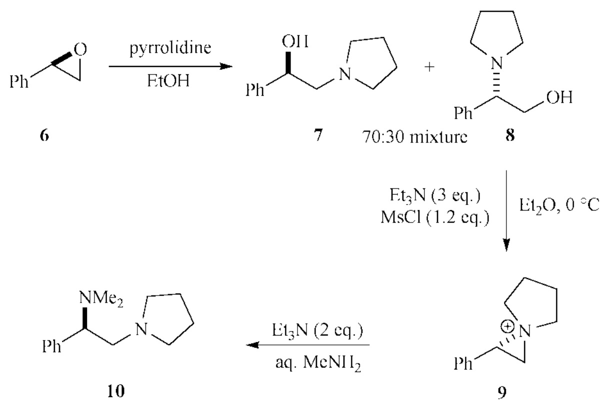
Introduction

There are a number of synthetic methods in which the stereochemistry of the product is controlled by two inversions of configuration in a reaction sequence. For example, conversion of the diol **1** into the corresponding orthoester, and reaction with acetyl bromide, gave an 88 : 12 mixture of regioisomeric acetoxy bromides **3** and **4**; the bromides **3** and **4** were converted into the epoxide **5** by methanolysis of the acetate group and ring closure (Scheme 1).[1] The success of the strategy lies in the two inversion reactions: one of the stereogenic centres of **1** is inverted twice (stereochemically equivalent to retention of configuration) and the other centre is untouched. The regioselectivity of the ring opening **2**→**3** + **4** is inconsequential because both regioisomers **3** and **4** are converted into the same stereoisomer **5** and, therefore, the enantiomeric excess of the starting material is not compromised.



Scheme 1

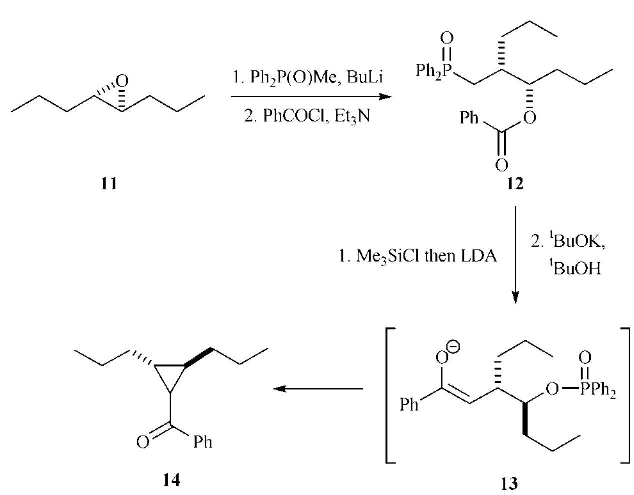
A similar strategy can be exploited in the synthesis of optically active compounds with only one stereogenic centre. Styrene oxide was opened with pyrrolidine to give a 70 : 30 mixture of the amino alcohols **7** and **8** (Scheme 2).[2] Mesylation of the alcohols **7** and **8** and participation of the nitrogen atom resulted in inversion at the other end of the original epoxide; both **7** and **8** gave the same enantiomer of the aziridinium ion **9**. Treatment



Scheme 2

of the aziridinium ion **9** with aqueous methylamine gave the diamine **10**.

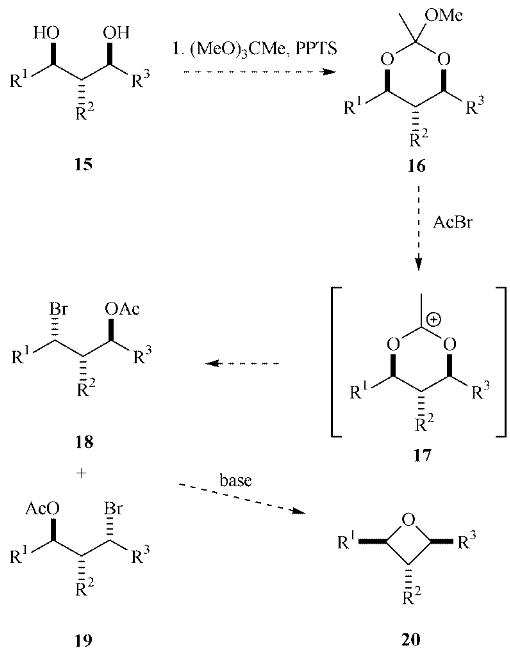
The transformation of the epoxide **11** into the cyclopropyl ketone **14** is another reaction sequence which involves inversion at both ends of an epoxide.[3] The epoxide **11** was opened with the lithium derivative of methyldiphenylphosphine oxide and the resulting alcohol was benzoylated (→**12**) (Scheme 3).



Scheme 3

Intramolecular acylation of the benzoate **12**, and treatment with potassium *tert*-butoxide in *tert*-butyl alcohol, initiated a cascade of reactions, including a second inversion **13**→**14**, leading to the formation of the cyclopropyl ketone **14**. The geometry of the epoxide **11** was therefore reflected in the product **14**.

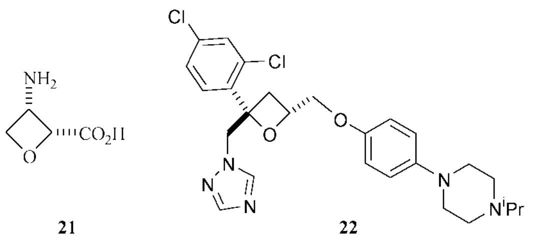
With compounds with three or more stereogenic centres, at least one of the stereogenic centres remains untouched and acts as a "reference" centre. At the start of our investigation, we planned a synthesis of oxetanes **20** from 1,3-diols **15** which would result in net retention of all of the stereogenic centres of **15**. Conversion of 1,3-diols such as **15** into the corresponding orthoesters **16**, and reaction with acetyl bromide, was expected to give the regioisomeric acetoxy bromides **18** and **19** with inversion of configuration at one of the stereogenic centres (Scheme 4). Hydrolysis of the acetates of **18** and **19**, and



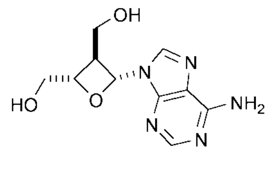
Scheme 4

ring-closure, would then invert the configuration of the *same* stereogenic centre to give a single oxetane **20**. The aim of the proposed research was to develop a general synthesis of oxetanes (*e.g.* **20**) which could be used to synthesise any diastereoisomer at will.

Oxetanes are most usually synthesised using the Paterno–Büchi cycloaddition[4] of aldehydes and alkenes and, although this reaction is often highly stereoselective, it is often limited to the synthesis of one of the possible diastereomeric products. The oxetane ring is found in a number of biologically active molecules such as the β-amino acid oxetin[5] ((2*R*,3*S*)-3-amino-oxetane-2-carboxylic acid) **21**, the antifungal triazole[6] **22**, the antiviral nucleoside[7] **23** and the anticancer compound, Taxol.[8] In syntheses of these, and related compounds, a number of different approaches have been adopted including the Paterno–Büchi reaction,[9] the ring contraction of a γ-lactone[10] and iodoetherification.[11]



21 **22**

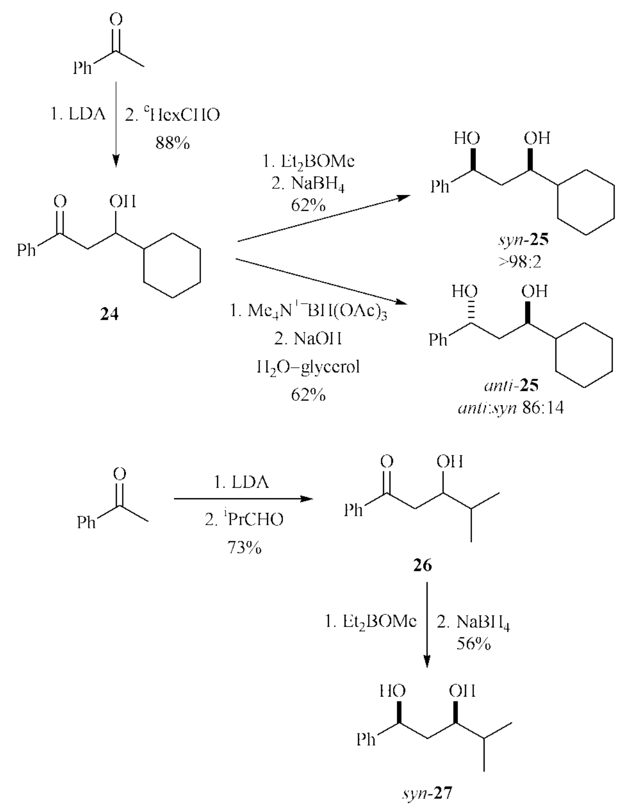


23

Results and discussion

Synthesis of starting materials

The aldols **24** and **26** were synthesised by reacting the lithium enolate of acetophenone with cyclohexanecarbaldehyde and 2-methylpropanal respectively (Scheme 5).[1,3] *syn*-Selective reduction of the aldols **24** and **26** was achieved using the method[12] of Prasad and co-workers; reduction of the chelated aldols with sodium borohydride at −78 °C in THF–methanol gave the diols



Scheme 5

syn-**25** and *syn*-**27** as single diastereoisomers. However,[1,3] *anti*-selective reduction of the aldol **24**, by delivery of the reducing agent to the ketone using tetramethylammonium triacetoxyborohydride,[13] was rather less selective, yielding the diols *anti*-**25** as a 86 : 14 mixture of diastereoisomers.

The aldols **28** were synthesised, as a 65 : 35 mixture of diastereoisomers, by treating the lithium enolate of propiophenone with cyclohexanecarbaldehyde and were separated by careful chromatography (Scheme 6). The aldols *syn*- and *anti*-**28** were treated with diethylmethoxyborane at −78 °C in THF–methanol,[12] and sodium borohydride was added to the resulting chelates (entries 1 and 3; Table 1). The aldol *syn*-**28** was reduced cleanly to give the diol **29** as a single diastereoisomer. Reduction of the aldol *anti*-**28** was, however, extremely sluggish and less diastereoselective; the diols **31** and **32** were obtained as a 78 : 22 mixture of diastereoisomers in a combined yield of 19% along with 13% recovered starting material. Reduction of the aldols *syn*- and *anti*-**28** was also investigated using sodium borohydride in ethanol (entries 2 and 4; Table 1).

The relative stereochemistry of the diols *syn*-**25** and **29** was

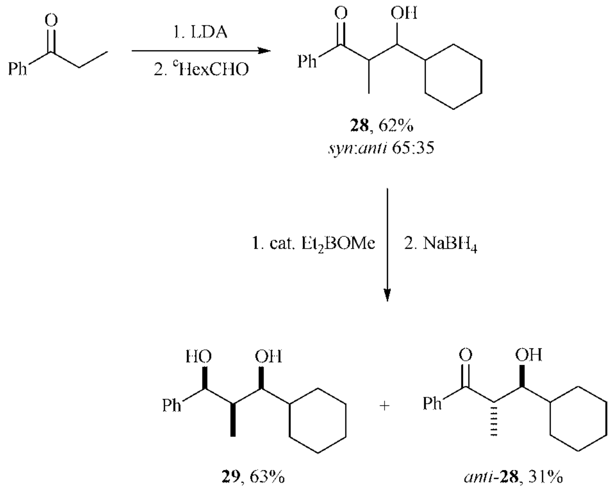
Table 1 Reductions of the aldols **28**

Entry	Starting material	Conditions	Products	Ratio	Yield (%)
1	*syn*-**28**	1. Et_2BOMe, −78 °C; 2. $NaBH_4$	**29**	>98:2	71[a]
2	*syn*-**28**	$NaBH_4$, EtOH, 0 °C	**29** + **30**	85:15	87[b]
3	*anti*-**28**	1. Et_2BOMe, −78 °C; 2. $NaBH_4$	**31** + **32**	78:22	19[a,c]
4	*anti*-**28**	$NaBH_4$, EtOH, 0 °C	**31**	>90:10	66[b]

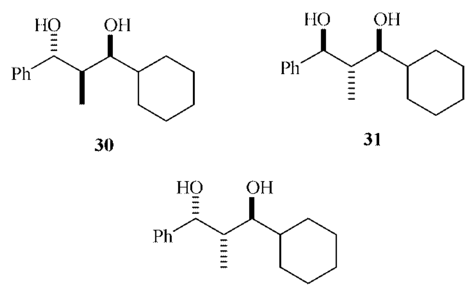
[a] Yield of major isomer. [b] Yield of mixture of isomers. [c] Starting material recovered in 13% yield.

Table 2 Diagnostic spectroscopic data for the acetonides **33** and **34**

	$^3J(H_{ax}H_{ax})$/Hz		$^3J(H_{ax}H_{eq})$/Hz		δ_C	
Acetonide	H^A	H^B	H^A	H^B	Me^C,Me^D	CMe^CMe^D
33	11.6	11.5	2.7	1.3	20.2, 28.3	99.3
34	—	—	2.4	2.0	20.0, 26.1	99.5



Scheme 6

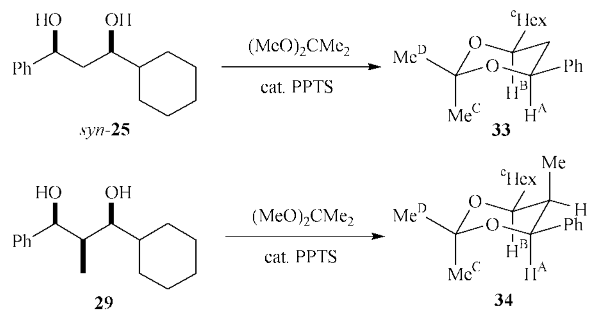


30 **31** **32**

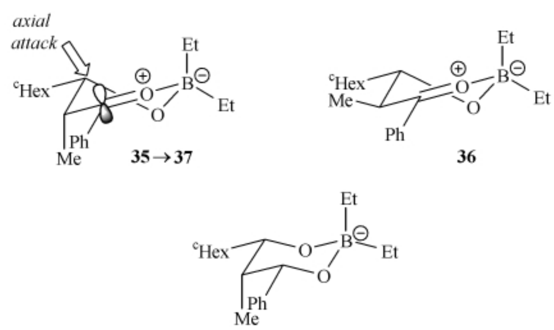
proved by conversion into the corresponding acetonides **33** and **34** (Scheme 7). The ^{13}C chemical shifts of Me^C, Me^D and the acetal carbon were characteristic[14] of acetonides formed from *syn*-1,3-diols and the coupling constants were typical[15] of six-membered rings adopting chair-like conformations (Table 2). Furthermore, a mutual NOE interaction was observed between H^A and H^B in each case.

Kinetic separation of the diastereomeric aldols 28

The diastereomeric aldols **28** could also be separated using a remarkable kinetically controlled separation. Treatment of a 65:35 mixture of *syn*- and *anti*-**28** with 10 mol% diethylmethoxyborane and sodium borohydride at −78 °C in THF–methanol gave the diol **29** (63% yield) and the aldol *anti*-**28** (31% yield), both as single diastereoisomers (Scheme 6). We have rationalised this result in terms of competition between the two substrates for the borane catalyst. We believe that the chelate **35** is more stable than **36** because **36** suffers from two unfavourable *gauche* interactions (Ph↔Me; cHex↔Me) (the axial methyl group of **35** does not suffer from any 1,3-diaxial interactions).† Reduction of **35** occurs from an axial direction to give the borate **37**. In the previous section, we have already noted that the reduction of *anti*-**28** with sodium borohydride in the presence of one equivalent of diethylmethoxyborane was extremely sluggish. Previously, substoichiometric quantities of alkoxyboranes have been used in 1,3-*syn*-selective reductions without significant loss of stereoselectivity,[12,17] though stereoselective reductions with as little as 10 mol% alkoxyborane have not, to our knowledge, been previously reported.



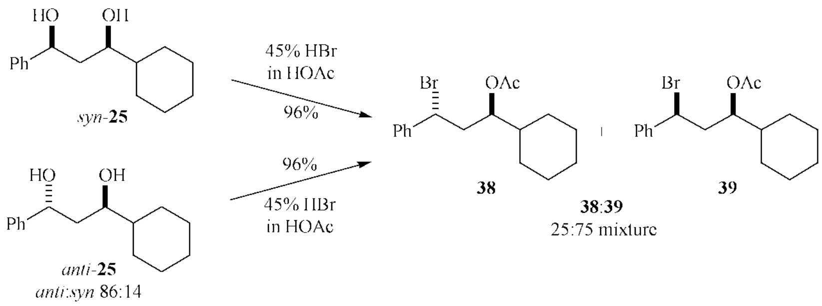
Scheme 7



Optimisation of the conversion of 1,3-diols into acyloxy halides

As a starting point for our investigation,[18] we treated the

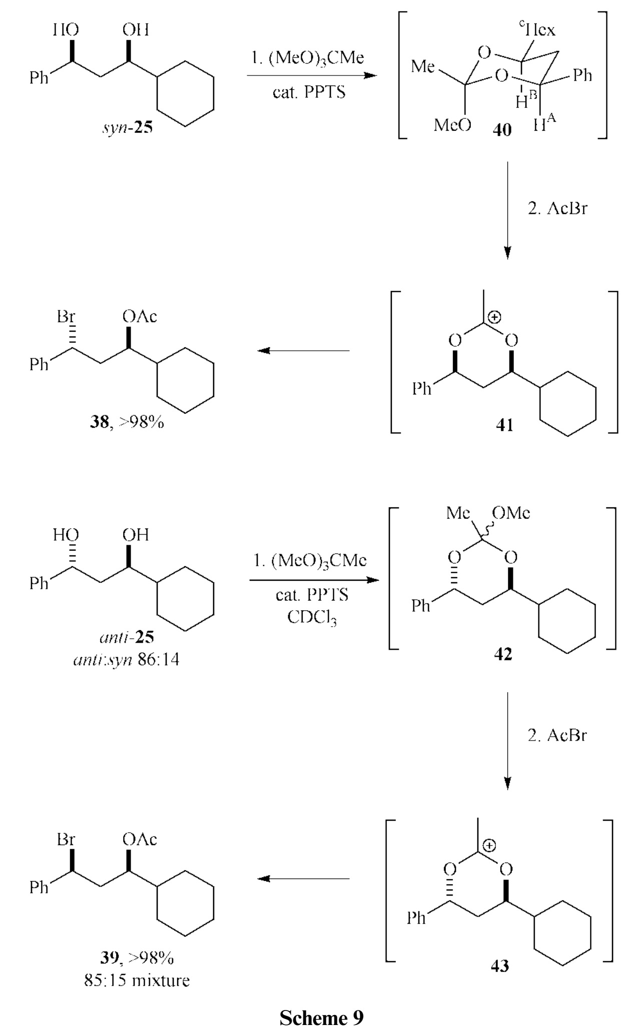
† For a remarkable conformational effect which results from a steric repulsion between equatorial substituents, see ref. 16.



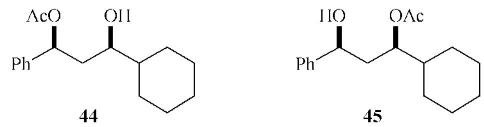
Scheme 8

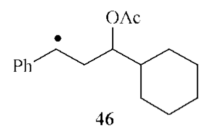
diastereomeric diols *syn*- and *anti*-**25** with 45% hydrogen bromide in acetic acid;[19] the same 25:75 mixture of compounds was obtained in each case (Scheme 8). At this stage of the investigation, it was unclear whether these compounds were stereo- or regioisomers. In fact, the products were shown to be the diastereomeric acetoxy bromides **38** and **39** since *both* compounds exhibited an HMBC crosspeak between the carbonyl carbon and the benzylic proton. Under these reaction conditions, therefore, the transformation was not stereospecific since both diols were converted into the same mixture of acetoxy bromides **38** and **39**.

An alternative strategy involved the treatment of the orthoesters, derived from the diols **25**, with acetyl bromide (Scheme 9).[1] Accordingly, the diols **25** were treated with trimethyl orthoacetate and catalytic pyridinium toluene-*p*-sulfonate in deuterochloroform and the formation of the corresponding orthoesters (**40** and **42**) was observed by 500 MHz ^{1}H NMR spectroscopy. The orthoester **40** was, however, rather unstable, and attempted aqueous work-up of this reaction gave the regioisomeric acetates **44** and **45**. In separate experiments,

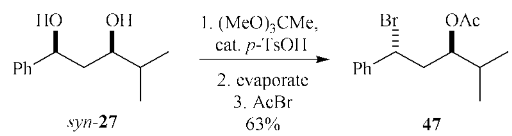


Scheme 9





treatment of the orthoesters **40** and **42**, derived from *syn*- and *anti*-**25**, with acetyl bromide at −78 °C gave the acetoxy bromides **38** and **39** respectively. The ratio of products obtained under these reaction conditions reflected the starting mixture of diols **25**, indicating that nucleophilic substitution of the dioxonium ions (**41** and **43**) was stereospecific. In a similar vein, the diol *syn*-**27** was converted into the acetoxy bromide **47** with complete inversion of configuration at the benzylic site (Scheme 10). The acetoxy bromides **38** and **39** epimerised slowly on standing in diffuse light, a process which presumably involved the intermediacy of the benzylic radical **46**.‡



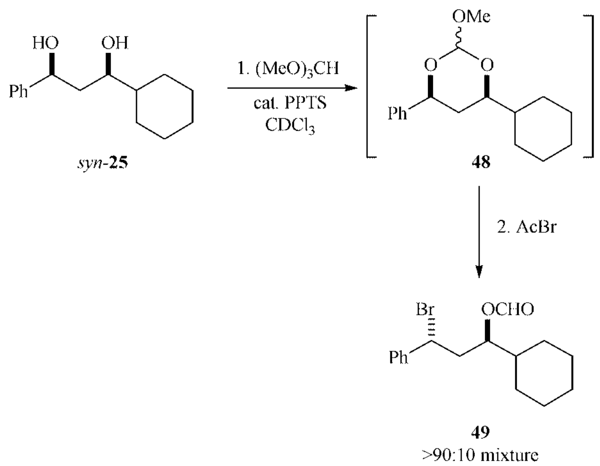
Scheme 10

Similarly, the diol *syn*-**25** was converted into the corresponding bromo formate **49** (Scheme 11). The formation of the orthoformate **48** was much slower than that of the orthoester **40** and the kinetic mixture of orthoester epimers (*ca.* 15:85 mixture after five minutes, together with unreacted starting material) slowly equilibrated over two hours to give a thermodynamic 60:40 mixture of epimeric orthoformates. Once again, treatment of the orthoformates **48** with acetyl bromide was stereospecific yielding the bromo formate **49** as a >90:10 mixture of diastereoisomers.

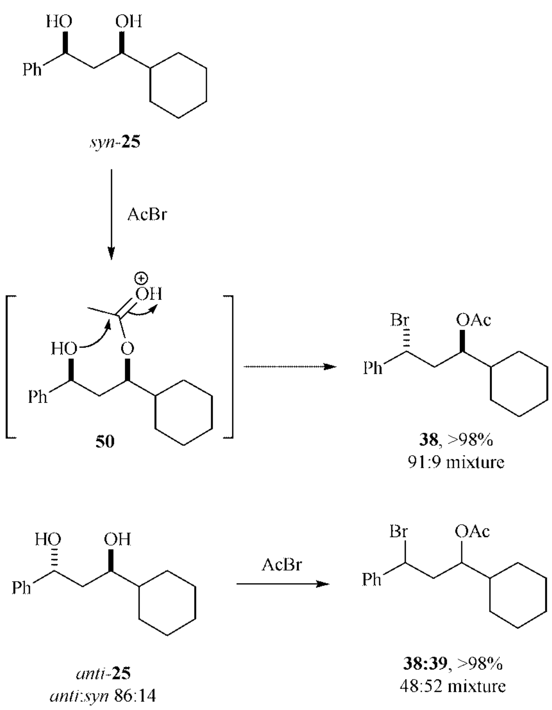
Intriguingly, the diols **25** could be converted into acetoxy bromides simply by treatment with acetyl bromide in dichloromethane at −78 °C (Scheme 12). Presumably, participation (*e.g.* **50** arrows) is faster than acetylation of the intermediate hydroxy acetate.§ The process was, however, incompletely stereospecific; *syn*-**25** was converted into a 91:9 mixture of **38** and **39**, and the diol *anti*-**25** gave a 48:52 mixture of products.

‡ For a rearrangement which proceeds *via* a similar intermediate, see ref. 20.

§ Treatment of a 37:63 mixture of the hydroxy acetates **44** and **45** gave only the acetoxy bromide **38**.



Scheme 11



Scheme 12

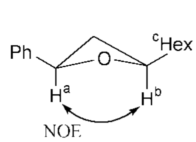


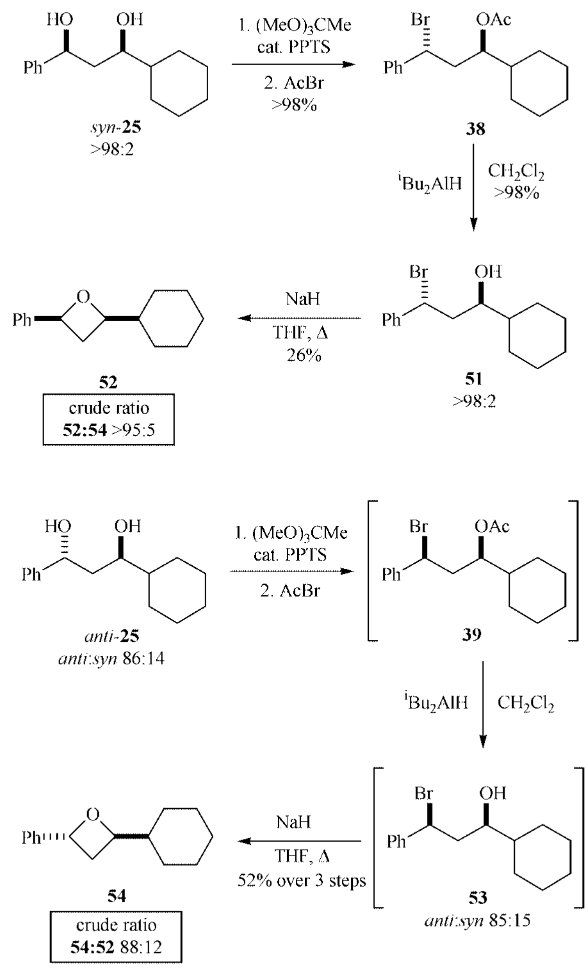
Fig. 1 Diagnostic NOEs in the oxetane **52**.

Synthesis of 2,4-disubstituted oxetanes

The acetoxy bromides **38** and **39** were converted into the hydroxy bromides **51** and **53** by reduction with diisobutylaluminium hydride (Scheme 13). A range of reaction conditions (K_2CO_3, methanol; ^{t}BuOK, DMSO;[21] ^{t}BuOK, hexane;[22] BuLi, THF[23]) were screened for the conversion of the hydroxy bromides **51** and **53** into the oxetanes **52** and **54**; although the phase-transfer catalysed[24] (Bu_4NHSO_4, NaOH) ring closure of **51** was reasonably high yielding, a mixture of the diastereomeric oxetanes was obtained, perhaps as a result of competing Walden[25] inversion. The best method involved the treatment of the hydroxy bromides **51** and **53** with sodium hydride in refluxing THF. The relative stereochemistry of the oxetanes **52** and **54** was determined by measurement of their coupling constants (Table 3);[15] **52** exhibited a mutual NOE enhancement between the protons H^A and H^B (Fig. 1). The yield of the *trans* disubstituted oxetane **54** was higher than that of **52**, presumably because the cyclisation with substituents on opposite sides of the forming ring (Fig. 2) was better able to compete with fragmentation (**55** arrows) than the cyclisation leading to **52** (Fig. 2).¶

Table 3 Diagnostic coupling constants for oxetane products

Oxetane	$^3J_{HH}$ (*cis*)/Hz	$^3J_{HH}$ (*trans*)/Hz
52	8.1, 8.1	6.9, 6.9
54	8.5, 8.5	6.2, 6.2
57	8.0	6.0



Scheme 13

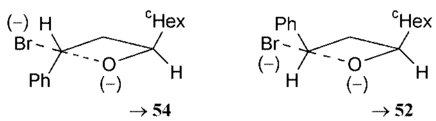
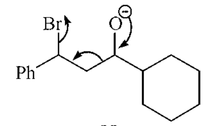


Fig. 2 Transition states leading to the oxetanes **52** and **54**.



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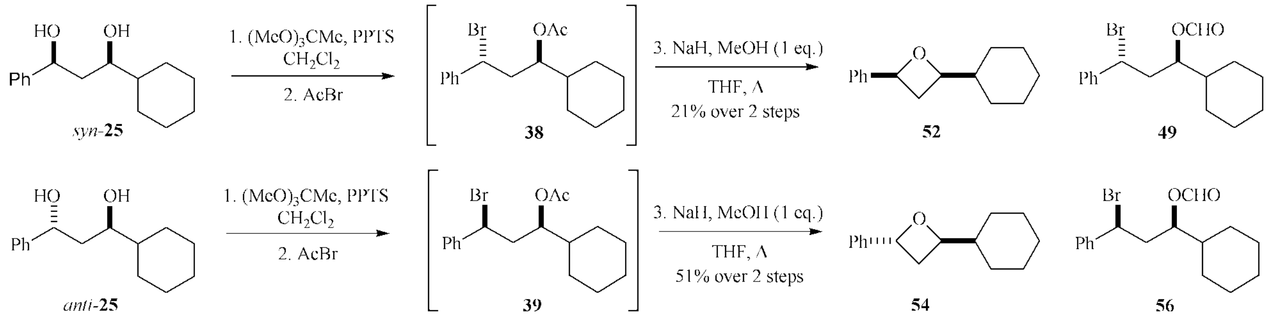
The stereospecificity of the transformations **51**→**52** and **53**→**54** was assessed by analysis of the crude reaction mixtures by 300 MHz ^{1}H NMR (Scheme 13). The hydroxy bromide **51**

¶ The products of the fragmentation of **55** were observed in ^{1}H NMR spectra of crude reaction mixtures.



Scheme 14

Table 4 Two-pot conversion of 1,3-diols **25** into oxetanes **52** and **54**

Entry	Starting material	Reagent	Bromoester	Oxetane	Yield[a] (%)
1	*syn*-**25**	$(MeO)_3CMe$	**38**	**52**	21
2	*syn*-**25**	$(MeO)_3CH$	**49**	**54**	15
3	*anti*-**25**	$(MeO)_3CMe$	**39**	**52**	51
4	*anti*-**25**	$(MeO)_3CH$	**56**	**54**	47

[a] Yield over two steps.

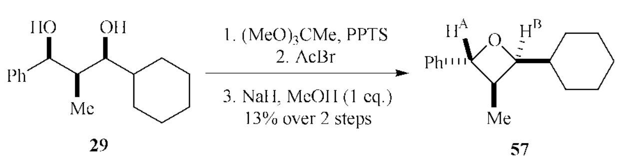
gave the oxetane **52** as a >95 : 5 mixture of diastereoisomers and an 86 : 14 mixture of **53** and **51** gave the oxetanes **54** and **52** as an 88 : 12 mixture of isomers; the cyclisation of the hydroxy bromides **51** and **53** proceeded with a high level of stereospecificity. Under the optimised reaction conditions, therefore, both formation of the acetoxy bromide (→**38** or **39**) and cyclisation (→**52** or **54**) proceeded with inversion of configuration as was required by the strategy outlined in the introduction.

Development of a convenient preparation of oxetanes

Although we had developed a conversion of 1,3-diols into oxetanes which proceeded with overall retention of configuration (Scheme 13), the method was rather cumbersome because it involved three separate reactions including a reduction with diisobutylaluminium hydride (→**51** or **53**) which was difficult to work up. We therefore developed a reaction sequence which was more convenient.

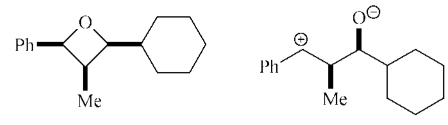
Reaction conditions were screened for the direct conversion of the bromo acetates **38** and **39** and the bromo formates **49** and **56** into the oxetanes **52** and **54**. The optimum method involved treatment of the crude bromo esters with one equivalent of methanol and three equivalents of sodium hydride in refluxing THF; deacylation by sodium methoxide was followed by cyclisation to the oxetanes **52** and **54** (Scheme 14). Yields for this transformation are summarised in Table 4; the bromo acetates **38** and **39** (entries 1 and 3) gave a higher yield of the oxetanes **52** and **54** than did the bromo formates **49** and **56** (entries 2 and 4). Other reaction conditions investigated (*e.g.* K_2CO_3, MeOH; NaOMe, MeOH) resulted in greater fragmentation of the intermediate alkoxide **55**.

In a similar way, it was expected that the diol **29** would be transformed into the oxetane **58**. This transformation is a particularly stern test of stereospecificity because all three substituents would be on the same face of the forming ring. In fact, the product of the reaction was not the expected oxetane **58** but the oxetane **57** (Scheme 15). The relative stereochemistry of



Scheme 15

57 was determined by analysis[15] of $^3J_{HH}$ coupling constants (Table 3) and the absence of an NOE enhancement between H^A and H^B. Cyclisation *via* the benzylic cation **59** is presumably



competitive with the usual S_N2 reaction pathway; other cyclisation reactions suffer loss of stereospecificity in particularly unfavourable cases.[3,10a]

Conclusion

We have developed a convenient two-pot procedure for the formal dehydration of the 1,3-diols *syn*- and *anti*-**25** to give the oxetanes **52** and **54**. The method proceeds with overall retention at both of the stereogenic centres and should be applicable to the synthesis of optically active, as well as racemic, oxetanes.

Experimental

All solvents were distilled before use. THF and Et_2O were freshly distilled from lithium aluminium hydride whilst CH_2Cl_2 and toluene were freshly distilled from calcium hydride. Ether refers to diethyl ether and petrol refers to petroleum spirit (bp 40–60 °C) unless otherwise stated. Diisopropylamine was purified prior to use by distillation from calcium hydride. Solvents were removed under reduced pressure using a Büchi rotary evaporator at water aspirator pressure. Triphenylmethane was used as indicator for THF. *n*-Butyllithium was titrated against diphenylacetic acid before use. All non-aqueous reactions were carried out under argon using oven-dried glassware.

Flash column chromatography was carried out using silica (35–70 µm particles) according to the method of Still *et al.*[26] Thin-layer chromatography was carried out on commercially available pre-coated plates (Merck silica Kieselgel $60F_{254}$). Unless otherwise stated, R_f values were measured with ethyl acetate as eluant. Proton and carbon NMR spectra were recorded on a Bruker WM 250, DPX 300 or DRX 500 Fourier transform spectrometer using an internal deuterium lock. Chemical shifts are quoted in parts per million downfield of tetramethylsilane and values of coupling constants (*J*) are given in Hz. The symbol * after the proton NMR chemical shift indicates that the signal disappears after a D_2O "shake". Carbon NMR spectra were recorded with broad band proton decoupling and Attached Proton Test. The symbols + and − after the carbon NMR chemical shift indicate odd and even numbers of attached protons respectively.

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR ESP infrared spectrophotometer and signals were referenced to the polystyrene 1601 cm^{-1}

absorption. Mass spectra were recorded on a VG autospec mass spectrometer, operating at 70 eV, using both the electron impact and fast atom bombardment methods of ionisation. Accurate molecular weights were obtained by peak matching using perfluorokerosene as a standard. Electron Impact was used unless Fast Atom Bombardment (+FAB) is indicated. Microanalyses were carried out by the staff of the School of Chemistry using a Carlo Erba 1106 automatic analysers. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter (using the sodium D line; 589 nm) and $[\alpha]_D^{20}$ are given in units of 10^{-1} deg cm^2 g^{-1}.

3-Cyclohexyl-3-hydroxy-1-phenylpropan-1-one 24

Butyllithium (1.6 M in hexanes, 57.5 ml, 92 mmol) was added to a stirred solution of diisopropylamine (13.45 ml, 96 mmol) in dry THF (200 ml) and the reaction mixture was stirred for 15 minutes at 0 °C. The reaction mixture was then cooled to −78 °C, acetophenone (9.73 ml, 83 mmol) in dry THF (40 ml) was added dropwise and the reaction mixture was stirred for a further 30 minutes. Cyclohexanecarbaldehyde (12.1 ml, 100 mmol) in dry THF (40 ml) was added dropwise and the reaction mixture was stirred for 30 minutes at −78 °C. The reaction mixture was quenched with saturated aqueous ammonium chloride (100 ml) and was slowly warmed to room temperature. The reaction mixture was diluted with water (100 ml) and extracted with ethyl acetate (3 × 100 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield a crude product which was purified by flash chromatography, eluting with 1 : 9 ethyl acetate–petrol to give the *aldol* **24** (16.91 g, 88%) as yellow needles, mp 42.8–44.4 °C; R_f 0.30 (20% EtOAc in petrol) (Found: C, 77.9; H, 8.95; $C_{15}H_{20}O_2$ requires C, 77.5; H, 8.70%); ν_{max}/cm^{-1} (Nujol) 3470 (OH), 1683 (C=O), 1317 and 1099; δ_H (300 MHz, $CDCl_3$) 7.9 (2 H, d, *J* 7.1, *ortho*-Ph), 7.6 (1 H, t, *J* 7.4, *para*-Ph), 7.5 (2 H, app t, *J* 7.7, *meta*-Ph), 4.0–3.96 (1 H, m, C*H*OH), 3.2–3.1 (2 H, m, CH_AH_B and OH), 3.05 (1 H, dd, *J* 9.3 and 8.2, CH_AH_B) and 2.2–1.0 (11 H, m); δ_C (300 MHz, $CDCl_3$) 201.7, 137.3, 134.8, 129.1, 128.6, 72.2 (CHOH), 43.5, 42.6, 29.4, 28.7, 26.9, 26.6 and 26.5; *m/z* (EI) 232 (4%, M^+), 214 ($M - H_2O$), 163 (53, $M - C_5H_9$), 149 (37, $M - C_6H_{10}$), 134 (17, $C_7H_{12}O$), 105 (100, PhCO), 77 (47, C_6H_5) and 41 (19).

3-Hydroxy-4-methyl-1-phenylpentan-1-one 26

By the same general method, acetophenone (1.94 cm^3, 16.7 mmol) and isobutyraldehyde (1.44 cm^3, 15.8 mmol) gave a crude product which was purified by column chromatography, eluting with 4 : 1 petrol–ether, to give the *aldol* **26** (2.33 g, 73%) as white needles, R_f 0.30 (4 : 1 petrol–ether 4 : 1) (Found: MH^+, 193.1216; $C_{12}H_{17}O_2$ requires *M*, 193.1228); $\nu_{max}(CHCl_3)/cm^{-1}$ 3422 (OH), 1725 (C=O) and 1599 (C=C); δ_H (400 MHz; $CDCl_3$) 7.95 (2 H, d, *J* 7.1, Ph *ortho*-H), 7.58 (1 H, t, *J* 7.4, Ph *para*-H), 7.48 (2 H, t, *J* 7.8, Ph *meta*-H), 3.98 (1 H, ddd, *J* 11.8, 5.7 and 2.3, C*H*OH), 3.15 (1 H, dd, *J* 17.5 and 2.4, CH_2), 3.02 (1 H, ddd, *J* 17.5, 9.5 and 2.0, CH_2), 1.78 (1 H, dq, *J* 13.4 and 6.7, $CHMe_2$), 1.10 (3 H, d, *J* 6.8, Me) and 0.80 (3 H, d, *J* 6.8, Me); δ_C (101 MHz; $CDCl_3$) 201.4^- (CO), 137.0^- (Ph *ipso*-C), 133.5^+, 128.7^+, 128.1^+, 72.4^+ (COH), 41.9^- (CH_2), 33.1^+ ($CHMe_2$), 18.6^+ (Me) and 17.9^+ (Me); *m/z* (+CI) 193.0 (89%, M + 1), 175.0 (37, M − OH), 149.0 (10, $MH - {}^iPr$), 105.0 (100, M − PhCO) and 77.0 (15, Ph).

(2*R**,3*S**)-3-Cyclohexyl-3-hydroxy-2-methyl-1-phenylpropan-1-one 28

By the same general method, propiophenone (5.5 ml, 45.4 mmol) and cyclohexanecarbaldehyde (6.05 ml, 45.6 mmol) gave a crude product which was purified by column chromatography, eluting with 10% EtOAc in petrol, to give the *aldols* **28** (6.82 g, 62%, *syn* : *anti* 65 : 35). Careful column chromatography, eluting with 20% EtOAc in petrol, gave the *aldol syn*-**28** (1.83 g, 16%, *syn* : *anti* >95 : 5) as yellow needles, mp 44–46 °C; R_f 0.30 (20% EtOAc in petrol) (Found: C, 78.2; H, 9.25; $C_{16}H_{22}O_2$ requires C, 78.0; H, 9.00%); ν_{max}/cm^{-1} (Nujol) 3402 (br, OH), 2852, 1673 (C=O), 1278 and 1112; δ_H (300 MHz, $CDCl_3$) 7.92 (2 H, d, *J* 7.1, *ortho*-Ph), 7.59 (1 H, t, *J* 7.5, *para*-Ph), 7.47 (2 H, app t, *J* 7.2, *meta*-Ph), 3.68 (2 H, m, C*H*OH and C*H*Me), 3.07 (1 H, d, *J* 2.5, OH), 2.10 (1 H, br d, *J* 12.8) and 2.0–0.9 (14 H, m); δ_C (300 MHz, $CDCl_3$) 206.3, 136.3, 133.7, 129.2, 128.8, 75.7, 41.7, 40.6, 29.9, 29.6, 26.8, 26.5, 26.2 and 10.9; *m/z* (EI) 247 (11%, MH^+), 163 (31), 134 (65), 105 (100, PhCO), 77 (61, Ph), 55 (52) and 41 (41).

Also obtained were the *aldols* **28** (4.58 g, *syn* : *anti* 52 : 48, 41%).

Kinetic separation of the aldols 28. Diethylmethoxyborane (1.0 M in THF, 626 µl) was added to the aldols **28** (1.46 g, 5.93 mmol, *syn* : *anti* 65 : 35) in THF (60 ml) and methanol (15 ml) at −78 °C. The reaction was stirred for 30 minutes, sodium borohydride (262 mg, 6.89 mmol) added, and the mixture stirred for a further 16 h at −78 °C. Acetic acid (15 ml) and aqueous sodium hydroxide solution (2 M, to pH 10) were added, and the mixture was extracted with EtOAc (3 × 400 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a crude product which was purified by flash chromatography, eluting with 10% EtOAc in petrol to give the *diol* **29** (0.91 g, 63%) as pale yellow needles, mp 96–98 °C; R_f 0.26 (20% EtOAc in petrol) (Found: $M^+ - H_2O$, 230.11659; $C_{16}H_{24}O_2$ requires $M - H_2O$ 230.1670); ν_{max}/cm^{-1} (Nujol) 3330 (OH), 1460 and 1376; δ_H (300 MHz, $CDCl_3$) 7.36–7.21 (5 H, m, Ph), 4.98 (1 H, d, *J*, 2.7, PhC*H*OH), 3.57 (1 H, dd, *J* 9.2 and 1.7, C*H*OH), 3.50 (1 H, br s, OH), 2.73 (1 H, br s, OH), 1.95 (1 H, m, C*H*Me), 1.82–0.80 (11 H, m) and 0.78 (3 H, d, *J* 7.1, Me); δ_C (300 MHz, $CDCl_3$) 143.9, 128.5, 127.3, 126.1, 81.7, 79.2, 41.4, 41.0, 30.1, 29.2, 26.7, 26.3, 26.2 and 4.6; *m/z* (EI) 247 (0.5%, M^+), 231 (3), 213 (1), 124 (83), 118 (77), 107 (86), 82 (83), 82 (76), 79 (91), 77 (88), 67 (62) and 55 (100).

Also obtained was the *aldol anti*-**28** (0.46 g, 31%) as white needles, mp 32–35 °C; R_f 0.30 (20% EtOAc in petrol) (Found: C, 77.8; H, 9.30; $C_{16}H_{22}O_2$ requires C, 78.0; H, 9.00%); ν_{max}/cm^{-1} (Nujol) 3402 (br, OH), 2852, 1673 (C=O), 1278 and 1112; δ_H (300 MHz, $CDCl_3$) 7.97 (2 H, d, *J* 7.1, *ortho*-Ph), 7.59 (1 H, t, *J* 7.4, *para*-Ph), 7.48 (2 H, app t, *J* 7.7, *meta*-Ph), 3.71 (1 H, qd, *J* 5.5 and 7.2, C*H*Me), 3.57 (1 H, app q, *J* 8.0, C*H*OH), 3.00 (1 H, *J* 8.0, OH), 2.0–1.0 (11 H, m) and 1.29 (3 H, d, *J* 7.2, Me); δ_C (300 MHz, $CDCl_3$) 206.8, 136.9, 133.8, 129.2, 128.7, 79.2, 42.1, 41.7, 32.3, 30.6, 30.1, 29.7 and 16.5; *m/z* (EI) 247 (11%, MH^+), 163 (31), 134 (65), 105 (100, PhCO), 77 (61, Ph), 55 (52) and 41 (41).

(1*R**,3*S**)-3-Cyclohexyl-1-phenylpropane-1,3-diol *syn*-25

Diethylmethoxyborane (1.0 M in THF, 950 µl, 0.95 mmol) was added to a stirred solution of the 3-cyclohexyl-3-hydroxy-1-phenylpropan-1-one **24** (200 mg, 0.86 mmol) in dry THF (40 ml) and methanol (10 ml). The reaction was stirred for 15 minutes at −78 °C and sodium borohydride (36 mg, 0.95 mmol) was added. The reaction mixture was stirred for 2 hours at −78 °C. The reaction mixture was quenched with acetic acid (5 ml) and slowly warmed to room temperature. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with saturated aqueous sodium bicarbonate solution (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product, which was purified by flash chromatography, eluting with 1 : 9 ethyl acetate–petrol, and repeated dissolution in methanol (15 × 30 ml) and removal of volatile components under reduced pressure, to give the *diol syn*-**25** (124 mg, 62%) as colourless plates, mp 118.5–220.8 °C; R_f 0.20 (20% EtOAc in petrol) (Found: C, 76.8; H, 9.50; $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.45%);

ν_{max}/cm^{-1} (Nujol) 3328 (OH), 1462 and 1376; δ_H (300 MHz, $CDCl_3$) 7.39–7.26 (5 H, m, Ph), 4.93 (1 H, br dd, *J* 7.7 and 4.5, PhC*H*OH), 3.75 (1 H, m, C*H*OH), 3.39 (1 H, br s, OH), 2.7 (1 H, d, *J* 3.1, OH) and 1.84–1.00 (13 H, m); δ_C (300 MHz, $CDCl_3$) 145.1, 128.4, 127.4, 126.2, 81.8, 79.3, 40.8, 40.5, 30.2, 29.2, 26.7, 26.3 and 26.2; *m*/*z* (EI) 234 (6%, M$^+$), 216 (26, M − H_2O), 133 (89), 107 (100, PhCHOH), 79 (63) and 41 (32).

(1*S**,3*R**)-4-Methyl-1-phenylpentane-1,3-diol *syn*-27

By the same general method, the aldol **26** (0.6 g, 3.125 mmol) gave a crude product which was purified by flash chromatography, eluting with 1 : 1 petrol–ether to give the *diol syn*-**27** (340 mg, 56%) as a colourless oil, R_f 0.31 (petrol–EtOAc, 1 : 1) (Found: M$^+$, 194.1306; $C_{12}H_{18}O_2$ requires *M*, 194.1306); ν_{max}($CHCl_3$)/cm^{-1} 3608 (OH), 3488 (OH) and 1605 (C=C); δ_H (400 MHz, $CDCl_3$) 7.42–7.25 (5 H, m, Ph), 4.92 (1 H, dd, *J* 9.0 and 3.7, C*H*OHPh), 3.75 (1 H, ddd, *J* 7.6, 5.2 and 2.4, C*H*OH), 3.38 (1 H, s, OH), 2.81 (1 H, s, OH), 1.85–1.55 (3 H, m, CH_2 and C*H*Me_2), 0.92 (3 H, d, *J* 6.8, Me) and 0.91 (3 H, d, *J* 6.8, Me); δ_C (101 MHz, $CDCl_3$) 144.7$^-$ (Ph *ipso*-C), 128.5$^+$, 127.6$^+$, 125.7$^+$, 77.7$^+$ (CHOH), 75.7$^+$ (CHOH), 42.1$^-$ (CH_2), 34.3$^+$ ($CHMe_2$), 18.2$^+$ (Me) and 17.4$^+$ (Me); *m*/*z* (+EI) 194.0 (28%, M$^+$), 176.0 (52, M − H_2O), 133.0 (53, M − Pr) and 107.0 (100, PhCHOH).

(1*R**,2*R**,3*R**)-1-Cyclohexyl-2-methyl-3-phenylpropane-1,3-diol 31

By the same general method, diethylmethoxyborane (6 ml, 1 M in THF), *anti*-**28** and sodium borohydride (191 mg, 5.01 mmol) gave a crude product to which was added THF (50 ml), glycerol (50 ml) and aqueous sodium hydroxide solution (2 M, 50 ml). The mixture was stirred vigorously for 2 h, quenched with water and extracted with dichloromethane (3 × 200 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a crude product which was purified by flash chromatography, eluting with 5→15% EtOAc in petrol to give starting material (144 mg, 13%) and a crude product. The crude product was further purified by flash chromatography, eluting with 15% EtOAc in petrol to give the *diol* **31** (211 mg, 19%, **31** : **32** 78 : 22) as a colourless oil; R_f 0.19 (15% EtOAc in petrol) (Found: M$^+$ − H_2O, 230.11659; $C_{16}H_{24}O_2$ requires *M* − H_2O 230.1670); ν_{max}/cm^{-1} ($CDCl_3$ solution) 3420 (O–H), 2925, 2856, 1451 and 1108; δ_H (300 MHz, $CDCl_3$) 7.37–7.21 (5 H, m, Ph), 4.95 (1 H, d, *J* 2.7, PhCH), 3.55 (1 H, dd, *J* 9.2, 1.7, CHChex), 2.06–1.87 (1 H, m, CHMe), 1.78–0.63 (11 H, m, Chex) and 0.77 (3 H, d, *J* 7.1, Me); δ_C (300 MHz, $CDCl_3$) 143.9, 128.5, 127.3, 126.2, 87.1 (CHChex), 79.2 (PhCH), 41.0, 30.2, 29.2, 26.7, 26.3, 26.2, 10.7 and 4.6 (Me^{syn}); *m*/*z* (EI) 230 (0.75%, M − H_2O), 124 (53), 118 (96), 117 (100), 91 (50), 82 (51), 55 (83) and 41 (51).

Also obtained was recovered starting material (144 mg, 13%).

(1*R**,2*S**,3*R**)-3-Cyclohexyl-2-methyl-1-phenylpropane-1,3-diol 29

By the same general method, the aldol *syn*-**28** (503 mg, 2.53 mmol) gave a crude product. The crude product was dissolved in THF (10 ml), glycerol (10 ml) and aqueous sodium hydroxide solution (2 M, 10 ml), and the mixture was stirred vigorously for 2 h, quenched with water and extracted with dichloromethane (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a crude product which was purified by flash chromatography, eluting with 20% EtOAc in petrol, to give the *diol* **29** (360 mg, 71%), spectroscopically identical to that obtained previously.

(1*R**,2*S**,3*R**)-1-Cyclohexyl-2-methyl-3-phenylpropane-1,3-diol 29

Sodium borohydride (32 mg, 0.85 mmol) was added to a stirred solution of the aldol *syn*-**28** (190 mg, 0.77 mmol) in ethanol (5 ml) at 0 °C. The mixture was stirred for 16 h and the ethanol evaporated off under reduced pressure. The residue was dissolved in dichloromethane (5 ml), poured into water and extracted with dichloromethane (3 × 5 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a crude product. The crude product was dissolved in THF (5 ml), glycerol (5 ml) and aqueous sodium hydroxide solution (2 M, 5 ml) and the mixture stirred vigorously for 2 h. The reaction was quenched with water and extracted with dichloromethane (3 × 10 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the *diol* **29** (166 mg, 87%, **29** : **30** 85 : 15 mixture), spectroscopically identical to that obtained previously.

(1*R**,2*R**,3*R**)-1-Cyclohexyl-2-methyl-3-phenylpropane-1,3-diol 31

By the same general method, the aldol *anti*-**28** (190 mg, 0.77 mmol) gave the *diol* **31** (127 mg, 0.52 mmol, **31** : **32** >90 : 10 mixture), spectroscopically identical to that obtained previously.

(1*R**,3*R**)-3-Cyclohexyl-1-phenylpropane-1,3-diol *anti*-25

Acetic acid (20 ml) was added to a stirred solution of tetramethylammonium triacetoxyborohydride (11.6 g, 44 mmol) in dry acetonitrile (20 ml) and the reaction was stirred for 30 min. The reaction was cooled to −40 °C and a solution of the aldol **24** (1.22 g, 5.54 mmol) in acetonitrile (10 ml) was added. The reaction was stirred for 4 h, left for three days at −18 °C, quenched with aqueous sodium potassium tartrate solution (0.5 M, 40 ml) and stirred for 30 min. Dichloromethane (100 ml) and saturated aqueous sodium bicarbonate solution (100 ml) were added, the layers separated, the aqueous fraction extracted with dichloromethane (3 × 50 ml) and the combined organic fractions were washed with saturated aqueous sodium bicarbonate solution (3 × 50 ml), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. The crude product was dissolved in a mixture of THF (30 ml), glycerol (20 ml) and aqueous sodium hydroxide solution (2 M, 20 ml), stirred for 2 h, quenched with water, extracted with dichloromethane (2 × 50 ml), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product which was purified by flash chromatography, eluting with 1 : 4 ethyl acetate–petrol, to give the *diol anti*-**25** (760 mg, 62%; *anti* : *syn* 86 : 14) as colourless plates, mp 89–91 °C; R_f 0.20 (20% EtOAc in petrol) (Found: C, 76.65; H, 9.60; $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.45%); ν_{max}/cm^{-1} (Nujol) 3330 (OH), 1462 and 1376; δ_H (300 MHz, $CDCl_3$) 7.39–7.26 (5 H, m, Ph), 5.06 (1 H, t, *J* 5.8, PhC*H*OH), 3.75 (1 H, q, *J* 6.2, C*H*OH), 3.35 (1 H, br s, OH), 2.73 (1 H, br s, OH) and 1.84–1.00 (13 H, m); δ_C (300 MHz, $CDCl_3$) 145.1, 128.8, 127.6, 125.9, 73.8, 72.2, 44.0, 42.0, 29.3, 28.6, 26.8, 26.5 and 26.4; *m*/*z* (EI) 234 (M$^+$, 3%), 216 (M − H_2O, 30), 133 (85), 107 (100), 79 (85), 55 (70) and 41 (65).

(4*R**,6*S**)-6-Cyclohexyl-2,2-dimethyl-4-phenyl-1,3-dioxane 33

(1*R**,3*S**)-3-Cyclohexyl-1-phenylpropane-1,3-diol *syn*-**25** (40 mg, 0.17 mmol) was dissolved in dichloromethane (2 ml) and 2,2-dimethoxypropane (40 μl, 0.34 mmol) and pyridinium toluene-*p*-sulfonate (PPTS, 4 mg) were added. The reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was quenched with ammonium chloride and extracted with dichloromethane (3 × 5 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a crude product which was purified by flash chromatography eluting with 90 : 9 : 1 petrol–ethyl acetate–triethylamine to yield the *acetonide* **33** (45 mg, 97%) as an oil; R_f 0.35 (10% EtOAc in petrol) (Found: C, 78.4, H, 9.8; $C_{18}H_{26}O_2$ requires C, 78.6, H, 9.6%); ν_{max}/cm^{-1} (Nujol) 2918, 1450 and 1384; δ_H (500 MHz, $CDCl_3$) 7.40–7.23 (5 H, m, Ph), 4.86 (1 H, dd, *J* 11.6 and 2.7, PhC*H*), 3.7 (1 H, ddd, *J* 11.5, 7.0 and 1.3), 2.17 (3 H, m, Me), 1.97 (1 H, m) and 1.7–0.9 (15 H, m); δ_C (500 MHz, $CDCl_3$) 143.2, 128.8, 127.9, 126.5, 99.3, 73.9, 72.3, 43.2, 37.0, 31.4, 30.1, 29.7, 29.4, 29.3, 28.3 and 20.2; *m*/*z* (EI) 273 ($M^+ - H$, 11%), 105 (60) and 95 (100). The stereochemistry of the molecule was confirmed by the observation of a mutual NOE between 4-H and 6-H.

(4*R**,5*S**,6*R**)-6-Cyclohexyl-2,2,5-trimethyl-4-phenyl-1,3-dioxane 34

By the same general method, (1*R**,2*S**,3*R**)-3-cyclohexyl-2-methyl-1-phenylpropane-1,3-diol **29** (150 mg, 0.60 mmol) gave a crude product which was purified by flash chromatography, eluting with 90:9:1 petrol–ethyl acetate–triethylamine, to yield the *acetonide* **34** (127 mg, 72%) as an oil; R_f 0.35 (10% EtOAc in petrol) (Found: C, 79.0, H, 9.7; $C_{19}H_{28}O_2$ requires C, 79.1, H, 9.8%); ν_{max}/cm^{-1} (Nujol) 2920, 1495, 1450 and 1384; δ_H (500 MHz, $CDCl_3$) 7.35–7.20 (5 H, m, Ph), 5.03 (1 H, d, *J* 2.4, PhC*H*), 3.66 (1 H, dd, *J* 9.6 and 2.0), 2.10 (1 H, br d, *J* 14.1), 1.8–0.8 (11 H, m), 1.52 (3 H, s, Me), 1.48 (3 H, s, Me) and 0.61 (3 H, d, *J* 6.9, Me); δ_C (500 MHz, $CDCl_3$) 141.8, 128.3, 127.1, 126.0, 99.5, 78.2, 75.5, 39.1, 35.4, 30.6, 30.4, 27.9, 27.1, 26.3, 26.1, 20.0 and 5.4; *m*/*z* (EI) 287 ($M^+ - H$, 15%), 105 (60) and 95 (100). The stereochemistry of the molecule was confirmed by the observation of a mutual NOE between 4-H and 6-H.

(2*R**,4*R**,6*S**)- and (2*R**,4*S**,6*R**)-2-Methoxy-4-cyclohexyl-6-phenyl-1,3-dioxane 48

By the same general method trimethyl orthoformate (14 µl, 0.13 mmol) and pyridinium toluene-*p*-sulfonate (1 mg) were added to a solution of the diol *syn*-**25** (20 mg, 0.09 mmol) in deuterochloroform. The progress of this reaction was monitored by NMR; after 5 minutes the reaction mixture consisted of a 60:40 mixture of starting material–orthoesters (<10:90 mixture of epimers) and after 12 minutes the reaction mixture consisted of a 20:80 mixture of starting material–orthoesters (38:62 mixture of epimers). After 2 h, the reaction mixture consisted of the *orthoesters* **48** (60:40 mixture of epimers), δ_H (250 MHz, $CDCl_3$) 7.39–7.27 (5 H, m, Ph), 5.59 (1 H^{maj}, s, C*H*OMe), 5.34 (1 H^{min}, s, C*H*OMe), 5.12 (1 H^{maj}, dd, *J* 16.7 and 6.3, PhCH), 4.75 (1 H^{min}, dd, *J* 16.7 and 6.3, PhCH), 3.98 (1 H^{maj}, ddd, *J* 16.7, 8.3 and 6.3, ChexCH), 3.72 (3 H^{min}, s, Me), 3.62 (1 H^{min}, ddd, *J* 16.7, 8.3 and 6.3, ChexCH), 3.54 (3 H^{maj}, s, Me) and 2.05–0.90 (13 H, m).

(1*R**,4*S**,6*R**)-6-Cyclohexyl-2-methoxy-2-methyl-4-phenyl-1,3-dioxane 40, (1*R**,3*S**)-acetic acid 3-cyclohexyl-3-hydroxy-1-phenylpropyl ester 44 and (1*R**,3*S**)-acetic acid 1-cyclohexyl-3-hydroxy-3-phenylpropyl ester 45

Trimethyl orthoacetate (10 µl, 0.10 mmol) and pyridinium toluene-*p*-sulfonate (1 mg) were added to a solution of the diol *syn*-**25** (40 mg, 0.17 mmol) in deuterochloroform (1.5 ml) in an NMR tube. After 2 min, the *orthoacetate* **40** was observed by ^{1}H NMR, δ_H (500 MHz, $CDCl_3$) 7.40–7.25 (5 H, m, Ph), 5.03 (1 H, dd, *J* 11.7 and 2.7, PhC*H*), 3.7 (1 H, ddd, *J* 11.5, 7.4 and 1.4), 3.26 (3 H, s, OMe), 1.95 (1 H, m), 1.7–1.55 (5 H, m), 1.54 (3 H, s, Me) and 1.4–0.9 (6 H, m); δ_C (500 MHz, $CDCl_3$) 141.9, 128.4, 127.6, 126.1, 113.0, 73.0, 71.1, 49.7, 42.4, 28.8, 28.0, 26.6, 26.1, 26.0 and 22.8. The stereochemistry of the molecule was proved by the observation of a mutual NOE between 4-H and 6-H.

The reaction mixture was poured into water, extracted with dichloromethane (3 × 3 ml), dried ($MgSO_4$), filtered and evaporated to give the *hydroxy acetates* **45** and **44** (63:37 mixture of regioisomers, 43 mg, 99%); R_f 0.60 (20% EtOAc in petrol) (Found: $M^+ - HOAc$, 216.1515; $C_{17}H_{24}O_3$ requires *M* − HOAc, 216.1514); ν_{max}/cm^{-1} (Nujol) 3403 (OH), 2931 and 1732 (C=O); δ_H (300 MHz, $CDCl_3$) 7.36–7.26 (5 H, m, Ph), 5.94 (1 H, dd, *J* 7.9 and 6.7, PhC*H*OH^{min}), 4.75 (2 H, m, C*H*OAc and PhC*H*OH^{maj}), 3.23 (1 H, ddd, 5.4, 4.3 and 2.6, C*H*OH^{maj}), 2.07 (3 H, s, Me^{min}), 2.00 (3 H, s, Me^{maj}) and 2.1–0.9 (16 H, m); δ_C (300 MHz, $CDCl_3$) 171.4^{maj}, 170.2^{min}, 144.2^{maj}, 140.2^{min}, 75.9^{maj}, 75.2^{min}, 73.3^{min}, 72.6^{maj}, 44.0^{min}, 41.8^{maj}, 40.8^{maj}, 40.6^{min}, 30.9$^{maj+min}$, 28.8^{min}, 28.6^{maj}, 27.9^{maj}, 27.6^{min}, 26.4^{min}, 26.3^{maj}, 26.2^{min}, 26.0^{maj}, 21.4^{min} and 21.2^{maj}; *m*/*z* (EI) 216 (40%, $M^+ - H_2O$), 133 (100) and 105 (70).

(4*S**,6*R**)-6-Cyclohexyl-2-methoxy-2-methyl-4-phenyl-1,3-dioxane 42 and (1*R**,3*S**)-acetic acid 3-bromo-1-cyclohexyl-3-phenylpropyl ester 39

Trimethyl orthoacetate (16 µl, 0.16 mmol) and pyridinium toluene-*p*-sulfonate (1 mg) were added to a solution of the diol *anti*-**25** (22 mg, 0.10 mmol) in deuterochloroform (1.5 ml) in an NMR tube. After 2 min, the *orthoacetates* (64:36 mixture of epimers) were observed by ^{1}H NMR, δ_H (250 MHz, $CDCl_3$) 7.40–7.2 (5 H, m, Ph), 5.03 (1 H, dd, *J* 9.0 and 6.2, PhC*H*^{maj}), 4.78 (1 H, dd, *J* 9.9 and 3.7, PhC*H*^{min}), 3.82 (1 H, q, 7.2, C*H*OH^{maj}), 3.59 (1 H, m, C*H*OH^{min}), 3.28 (3 H, s, OMe), 1.62 (3 H, s, Me^{min}), 1.48 (3 H, s, Me^{maj}) and 2.3–0.9 (13 H, m).

The reaction mixture was cooled to −78 °C and acetyl bromide (22 µl, 0.16 mmol) was added. The reaction mixture was stirred overnight, poured into saturated aqueous sodium bicarbonate solution, extracted with dichloromethane (3 × 3 ml), dried ($MgSO_4$), filtered and evaporated to give the *acetoxy bromide* **39** (28 mg, 99%; **39**:**38** 85:15) as a colourless oil; R_f 0.70 (20% EtOAc in petrol) (Found: $M^+ - HOAc - Br$, 199.1480; $C_{17}H_{23}BrO_2$ requires *M* − HOAc − Br, 1991486); ν_{max}/cm^{-1} (Nujol) 2931, 1730 (C=O) and 1454; δ_H (500 MHz, $CDCl_3$) 7.41–7.24 (5 H, m, Ph), 4.88 (1 H, dd, *J* 9.7 and 5.7, CHBr), 4.39 (1 H, ddd, *J* 12.3, 5.5 and 3.8, C*H*OAc), 2.50 (2 H, m), 1.96 (3 H, s, Me) and 1.7–0.9 (11 H, m); δ_C (500 MHz, $CDCl_3$) 169.5, 140.0, 127.8, 127.7, 126.4, 74.7, 49.8, 40.8, 40.3, 27.4, 26.8, 25.2, 25.0 and 20.0; *m*/*z* (EI) 278 ($M^+ - HOAc$, 2%), 199 (95), 117 (90) and 43 (100). The regioselectivity of the reaction was proved by the observation of an HMBC crosspeak between OAc and C*H*OAc.

(1*R**,3*R**)-Acetic acid 3-bromo-1-cyclohexyl-3-phenylpropyl ester 38

Trimethyl orthoacetate (40 µl, 0.33 mmol) and pyridinium toluene-*p*-sulfonate (1 mg) were added to a stirred solution of the diol *syn*-**25** (100 mg, 0.43 mmol) in dichloromethane (2 ml). The reaction mixture was stirred for 10 minutes at room temperature, cooled to −78 °C and acetyl bromide (58 µl, 0.75 mmol) was added dropwise. The reaction was stirred for 16 h, quenched with saturated sodium bicarbonate solution, extracted with dichloromethane (3 × 5 ml), dried ($MgSO_4$), filtered and evaporated to give the *acetoxy bromide* **38** (90 mg, 99%; **38**:**39** >98:2) as a colourless oil; R_f 0.70 (20% EtOAc in petrol) (Found: $M^+ - HOAc - Br$, 199.1483; $C_{17}H_{23}BrO_2$ requires *M* − HOAc − Br, 199.1486); ν_{max}/cm^{-1} (Nujol) 2931, 1732 (C=O) and 1454; δ_H (500 MHz, $CDCl_3$) 7.41–7.24 (5 H, m, Ph), 5.07 (1 H, ddd, *J* 10.4, 5.3 and 2.4, C*H*OAc), 4.88 (1 H, dd, *J* 9.7 and 5.7, CHBr), 2.49 (1 H, ddd, *J* 15.1, 9.2 and 2.4), 2.33 (1 H, ddd, *J* 15.1, 9.7 and 5.3), 1.88 (3 H, s, Me) and 1.8–0.9 (11 H, m); δ_C (500 MHz, $CDCl_3$) 170.6 (C=O), 142.0, 128.8, 128.4, 127.3, 76.1, 52.1 (CBr), 41.8, 41.3, 28.6, 28.1, 26.3, 26.03, 26.02 and 20.8; *m*/*z* (EI) 278 ($M^+ - HOAc$, 1%), 199 (85), 117 (100) and 43 (95). The regioselectivity of the reaction was proved by the observation of an HMBC crosspeak between OAc and C*H*OAc.

(1*R**,3*R**)-Acetic acid 1-bromo-4-methyl-1-phenylpent-3-yl ester 47

The diol *syn*-**27** (340 mg, 1.75 mmol) was dissolved in dry dichloromethane (15 cm^3) and toluene-*p*-sulfonic acid (33 mg, 0.18 mmol) was added. Trimethyl orthoacetate (0.244 cm^3, 1.93 mmol) was added and the mixture stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The pressure was further reduced to 0.1 mm Hg and held for 2 min. The residue was redissolved in dichloromethane (15 cm^3) and acetyl bromide (0.155 cm^3, 2.10 mmol) was added at 0 °C and stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue purified by column chromatography (petrol–ether, 9:1) to give the *bromo ester* **47** (330 mg, 63%) as a colourless oil, R_f 0.24 (petrol–EtOAc, 2:3) (Found: M^+, 299.0659; $C_{12}H_{20}O_2{}^{79}Br$ requires MH^+, 299.0647); $\nu_{max}(CHCl_3)/cm^{-1}$ 1736 (C=O); δ_H (200 MHz, $CDCl_3$) 7.50 (5 H, m, Ph), 5.05–5.17 (1 H, m, C*H*CO_2Me), 5.02 (1 H, dd, *J* 7.5 and 5.0, C*H*Br), 2.60–2.22 (2 H, m, CH_2), 1.91 (3 H, s, COMe), 0.94 (3 H, d, *J* 7.2, Me) and 0.92 (3 H, d, *J* 7.3, Me); δ_C (54 MHz, $CDCl_3$) 170.1^- (CO), 140.2^- (Ph *ipso*-C), 129.1^+, 129.1^+, 127.2^+, 70.7^+ (CHOAc), 50.2^+ (CHBr), 40.1^- (CH_2), 32.0^+ (CO*Me*), 20.2^+ (*C*HMe_2), 18.1^+ (Me) and 18.0^+ (Me); *m*/*z* (+FAB) 299.1 (15, M^+).

(1*R**,3*R**)-Formic acid 3-bromo-1-cyclohexyl-3-phenylpropyl ester 49

By the same general method, trimethyl orthoformate (21 µl, 0.19 mmol), pyridinium toluene-*p*-sulfonate (1 mg), acetyl bromide (36 µl, 0.65 mmol) and the diol *anti*-**25** (31 mg, 0.13 mmol) gave a crude product which was purified by column chromatography, eluting with 15% EtOAc in petrol, to give the *formate* **49** (40 mg, >95%; **49**:**56** >90:10) as a colourless oil; R_f 0.75 (20% EtOAc in petrol) (Found: M^+-Br 245.1538; $C_{16}H_{21}BrO_2$ requires $M - Br$ 245.1542); ν_{max}/cm^{-1} ($CDCl_3$ solution) 3055, 2987, 1645, 1422 and 1266; δ_H (500 MHz, $CDCl_3$) 8.01 (1 H, s, CHO), 7.46–7.19 (5 H, m, Ph), 5.12 (1 H, ddd, *J* 9.6, 5.0 and 2.2, C*H*OCHO), 4.88 (1 H, dd, *J* 9.0 and 4.0, CHBr), 2.44 (1 H, ddd, *J* 15.0, 9.0 and 2.2), 2.23 (1 H, ddd, *J* 15.0, 9.6 and 4.0) and 1.7–0.8 (11 H, m); δ_C (500 MHz, $CDCl_3$) 159.8 (C=O), 140.8, 127.7, 127.5, 126.2, 75.6, 50.8 (CBr), 40.8, 40.3, 29.4, 28.7, 25.3 and 25.2 (1 peak missing); *m*/*z* (EI) 278 (M^+ − HOCHO, 1%), 245 (M − Br, 50), 199 (74), 117 (100) and 95 (61).

(1*R**,3*R**)-Acetic acid 3-bromo-1-cyclohexyl-3-phenylpropyl ester 38

Acetyl bromide (25 µl, 0.40 mmol) was added to a stirred solution of the diol *syn*-**25** (22 mg, 0.08 mmol) in dry dichloromethane at −78 °C. The reaction mixture was stirred overnight, poured into saturated aqueous sodium bicarbonate solution, extracted with dichloromethane (3 × 3 ml), dried ($MgSO_4$), filtered and evaporated to give the *acetoxy bromide* **38** (26 mg, >98%; **38**:**39** 91:9) as a colourless oil, spectroscopically identical to that obtained previously.

Treatment of *anti*-25 with acetyl bromide

By the same general method, the diol *anti*-**25** (33 mg, 0.12 mmol) gave *acetoxy bromides* **38** and **39** (37 mg, >98%; **38**:**39** 48:52) as a colourless oil, spectroscopically identical to that obtained previously.

(1*R**,3*R**)- and (1*R**,3*S**)-Acetic acid 3-bromo-1-cyclohexyl-3-phenylpropyl esters 38 and 39

The diol *syn*-**25** (100 mg, 0.43 mmol) was dissolved in 45% hydrobromic acid in acetic acid (1 ml, 9.93 mmol). The reaction mixture was stirred for 40 minutes at room temperature. The reaction mixture was quenched with water (2 ml) and neutralised with saturated sodium bicarbonate solution. The reaction mixture was extracted with ether (3 × 30 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product which was purified by flash chromatography eluting with 1:4 ether–petrol to yield the *acetoxy bromides* **38** and **39** (0.14 g, 96%, **38**:**39** 25:75) as a brown oil, spectroscopically identical to that obtained previously.

(1*R**,3*R**)- and (1*R**, 3*S**)-Acetic acid 3-bromo-1-cyclohexyl-3-phenylpropyl esters 38 and 39

By the same general method, the diol *anti*-**25** (100 mg, 0.43 mmol) gave the *acetoxy bromides* (0.14 g, 96%, **38**:**39** 25:75) as a brown oil, spectroscopically identical to that obtianed previously.

(1*R**,3*R**)-3-Bromo-1-cyclohexyl-3-phenylpropan-1-ol 51

Diisobutylaluminium hydride (1.5 M in toluene, 0.65 ml, 0.98 mmol) was added to a stirred solution of the acetate **38** (70 mg, 0.22 mmol) in dry dichloromethane (3 ml). The reaction mixture was stirred for 1.5 hours at −78 °C, quenched with saturated ammonium chloride solution (3 ml), filtered through Celite with dichloromethane and the layers were separated. The aqueous fractions were extracted with dichloromethane (3 × 30 ml), and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to yield the *hydroxy bromide* **51** (65 mg, 99%) as a brown oil; R_f 0.30 (20% EtOAc in petrol) (Found: $M^+ - H_2O - Br$, 199.1482; $C_{17}H_{23}BrO_2$ requires $M - H_2O - Br$, 199.1486); ν_{max}/cm^{-1} (Nujol) 3418 (OH), 2931, 1495 and 1450; δ_H (500 MHz, $CDCl_3$) 7.42–7.24 (5 H, m, Ph), 5.30 (1 H, dd, *J* 11.5 and 2.7, CHBr), 3.80 (1 H, ddd, *J* 10.4, 5.6 and 2.0, C*H*OH), 2.51 (1 H, ddd, *J* 14.4, 10.4 and 2.7), 2.38 (1 H, ddd, *J* 14.4, 11.5 and 2.0) and 2.0–0.9 (11 H, m); δ_C (500 MHz, $CDCl_3$) 142.7, 128.6, 128.3, 127.3, 73.9, 54.0, 43.8, 43.9, 29.0, 28.0, 26.3, 26.2 and 26.0; *m*/*z* (EI) 278 ($M^+ - H_2O$, 1%), 199 (30), 105 (100) and 91 (55).

(2*R**,4*S**)-2-Cyclohexyl-4-phenyloxetane 52

Trimethyl orthoacetate (140 µl, 1.10 mmol) and pyridinium toluene-*p*-sulfonate (2 mg) were added to a stirred solution of the diol *syn*-**25** (218 mg, 0.98 mmol) in dichloromethane (7 ml). The reaction mixture was stirred for 5 minutes at room temperature, cooled to −78 °C and acetyl bromide (185 µl, 2.50 mmol) was added dropwise. The reaction was stirred for 16 h, quenched with saturated sodium bicarbonate solution, extracted with dichloromethane (3 × 5 ml), dried ($MgSO_4$), filtered and evaporated to give a crude product. The crude product was dissolved in dry dichloromethane (6 ml), cooled to −78 °C and diisobutylaluminium hydride (2.0 ml of a 1.5 M solution in dichloromethane, 3.0 mmol) was added. The reaction was stirred for 1.5 h, saturated aqueous ammonium chloride added and the reaction mixture filtered through Celite, eluting with dichloromethane (100 ml). The layers were separated, the aqueous layer extracted with dichloromethane (3 × 50 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a crude product. Analysis of the crude product by 300 MHz ^1H NMR spectroscopy showed that the hydroxy bromide **51** was present as a >98:2 mixture of diastereoisomers. The crude product was dissolved in dry THF (10 ml), sodium hydride (80 mg, 60% dispersion in oil, 2.00 mmol) was added and the reaction was refluxed overnight. The reaction was quenched with saturated aqueous ammonium chloride solution, the layers were separated, the aqueous layer was extracted with dichloromethane (3 × 50 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a crude product which was purified by flash chromatography, eluting with 10% EtOAc in petrol, to give the *oxetane* **52** (55 mg, 26%) as a colourless oil; R_f 0.70 (20% EtOAc in petrol) (Found: $M^+ - H$, 215.1435; $C_{15}H_{20}O$ requires $M -$ H, 215.1435); ν_{max}/cm^{-1} ($CDCl_3$ solution) 2924, 2856, 1451 and 1097; δ_H (500 MHz, $CDCl_3$) 7.43–7.25 (5 H, m, Ph), 5.66 (1 H, app t, *J* 7.8, PhC*H*), 4.47 (1 H, app q, *J* 7.9), 2.88 (1 H, dt, *J* 10.8 and 6.9), 2.31 (1 H, dt, *J* 10.8 and 8.1), 2.01 (1 H, m) and 1.8–0.8 (10 H, m); δ_C (500 MHz, $CDCl_3$) 143.9, 128.8, 128.0, 125.8, 82.1, 78.5, 45.4, 35.1, 28.3, 26.8, 26.5, 26.0 and 25.8; *m*/*z* (EI) 215 ($M^+ - H$, 25%), 105 (100) and 77 (45). The relative stereochemistry was confirmed by the observation of a mutual NOE between 1-H and 3-H.

Analysis of the crude reaction mixture by 300 MHz ^1H NMR spectroscopy showed the oxetane **52** to be present as a >98:2 mixture of diastereoisomers.

(2*R**,4*R**)-2-Cyclohexyl-4-phenyloxetane 54

By the same general method, the diol *syn*-**25** (218 mg, 0.98 mmol gave the *oxetane* **54** (110 mg, 52%) as a colourless oil; R_f 0.80 (20% EtOAc in petrol) (Found: $M^+ - H$, 215.1434; $C_{15}H_{20}O$ requires $M - H$, 215.1435); ν_{max}/cm^{-1} ($CDCl_3$ solution) 2925, 2856, 1451 and 1266; δ_H (500 MHz, $CDCl_3$) 7.43–7.25 (5 H, m, Ph), 5.58 (1 H, dd, *J* 8.5 and 6.2, PhC*H*), 4.49 (1 H, app q, *J* 6.2), 2.75 (1 H, ddd, *J* 14.5, 8.5 and 6.2), 2.56 (1 H, ddd, *J* 14.5, 8.5 and 6.2), 2.02 (1 H, m) and 1.9–0.8 (10 H, m); δ_C (500 MHz, $CDCl_3$) 144.2, 128.8, 127.9, 125.7, 84.2, 80.1, 44.6, 34.4, 28.5, 27.1, 27.0, 25.8 and 25.7; *m*/*z* (EI) 215 ($M^+ - H$, 20%), 105 (100) and 77 (50).

Analysis of the crude reaction mixture by 300 MHz ^1H NMR showed that the oxetanes **54** and **52** were present as an 88:12 mixture of diastereoisomers.

(2*R**,4*S**)-2-Cyclohexyl-4-phenyloxetane 52

Trimethyl orthoformate (280 µl, 2.56 mmol) and pyridinium toluene-*p*-sulfonate (2 mg) were added to a stirred solution of the diol *syn*-**25** (500 mg, 2.14 mmol) in dichloromethane (15 ml). The reaction mixture was stirred for 1.5 h at room temperature, cooled to −78 °C and acetyl bromide (385 µl, 5.34 mmol) was added. The reaction was stirred for 16 h, quenched with saturated sodium bicarbonate solution, extracted with dichloromethane (3 × 15 ml), dried ($MgSO_4$), filtered and evaporated to give a crude product. The crude product was dissolved in dry THF (10 ml), and methanol (95 µl, 2.35 mmol) and sodium hydride (256 mg, 60% dispersion in oil, 6.41 mmol) were added. The reaction was stirred for 48 h at 60 °C, quenched with water and extracted with EtOAc (3 × 15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a crude product which was purified by flash chromatography, eluting with 10% ether in petrol, to give the *oxetane* **52** (69 mg, 15%) as a colourless oil spectroscopically identical to that obtained previously.

(2*R**,4*R**)-2-Cyclohexyl-4-phenyloxetane 54

By the same general method, trimethyl orthoformate (59 µl, 0.54 mmol), pyridinium toluene-*p*-sulfonate (2 mg), acetyl bromide (81 µl, 1.12 mmol), *anti*-**25** (105 mg, 0.45 mmol), methanol (20 µl, 0.49 mmol) and sodium hydride (54 mg, 60% dispersion in oil, 1.35 mmol) gave a crude product which was purified by flash chromatography, eluting with 5% ether in petrol to give the *oxetane* **54** (47 mg, 47%) as a colourless oil, spectroscopically identical to that obtained previously.

(2*R**,4*S**)-2-Cyclohexyl-4-phenyloxetane 52

Trimethyl orthoacetate (132 µl, 1.04 mmol) and pyridinium toluene-*p*-sulfonate (2 mg) were added to a stirred solution of the diol *syn*-**25** (202 mg, 0.84 mmol) in dichloromethane (4 ml). The reaction mixture was stirred for 10 minutes at room temperature, cooled to −78 °C and acetyl bromide (156 µl, 2.158 mmol) was added. The reaction was stirred for 1.5 h, quenched with saturated sodium bicarbonate solution, extracted with dichloromethane (3 × 5 ml), dried ($MgSO_4$), filtered and evaporated to give a crude product. The crude product was dissolved in dry THF (5 ml), and methanol (39 µl, 0.95 mmol) and sodium hydride (104 mg, 60% dispersion in oil, 2.59 mmol) were added. The vessel was wrapped in foil and the reaction stirred for 24 h at 60 °C, quenched with water and extracted with EtOAc (3 × 15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give a crude product which was purified by flash chromatography, eluting with 10% ether in petrol, to give the *oxetane* **52** (39 mg, 21%) as a colourless oil spectroscopically identical to that obtained previously.

(2*R**,4*R**)-2-Cyclohexyl-4-phenyloxetane 54

By the same general method, trimethyl orthoacetate (93 µl, 0.73 mmol), pyridinium toluene-*p*-sulfonate (2 mg), acetyl bromide (112 µl, 1.52 mmol), the diol *anti*-**25** (142 mg, 0.61 mmol), methanol (27 µl, 0.67 mmol) and sodium hydride (73 mg, 60% dispersion in oil, 1.82 mmol) gave a crude product which was purified by flash chromatography, eluting with 5% ether in petrol to give the *oxetane* **54** (80 mg, 51%) as a colourless oil, spectroscopically identical to that obtained previously.

(2*R**,3*S**,4*S**)-2-Cyclohexyl-3-methyl-4-phenyloxetane 57

By the same general method, trimethyl orthoacetate (123 µl, 0.98 mmol), the diol **29** (200 mg, 0.81 mmol), pyridinium toluene-*p*-sulfonate (2 mg), acetyl bromide (149 µl, 2.02 mmol), methanol (36 µl, 0.89 mmol) and sodium hydride (97 mg, 60% dispersion in oil, 2.419 mmol) gave a crude product which was purified by flash chromatography, eluting with 10% EtOAc in petrol to give the *oxetane* **57** (26 mg, 13%) as a colourless oil; R_f 0.70 (20% EtOAc in petrol) (Found: $M^+ - H$, 229.1590; $C_{16}H_{22}O$ requires $M - H$, 229.1593); ν_{max}/cm^{-1} ($CDCl_3$ solution) 2925, 2856, 1451 and 1267; δ_H (500 MHz, $CDCl_3$) 7.43–7.26 (5 H, m, Ph), 5.08 (1 H, d, *J* 6.0, PhCH), 4.43 (1 H, dd, *J* 10.2, 8.0, CHChex), 2.92 (1 H, app. sextet, *J* 7.2, CHMe), 2.07–0.71 (11 H, m, Chex) and 1.30 (3 H, d, *J* 7.2, Me); δ_H (500 MHz, $CDCl_3$) 143.3, 128.5, 127.6, 125.3 (Ph), 87.2 (PhCH), 85.2 (CHChex), 40.6 (CHMe), 39.0, 28.3, 26.6, 25.6, 25.5 (Chex) and 14.1 (Me); *m*/*z* 229 ($M^+ - H$, 30%) and 77 (100).

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