Selective radical-chain epimerisation at electron-rich chiral tertiary C–H centres using thiols as protic polarity-reversal catalysts

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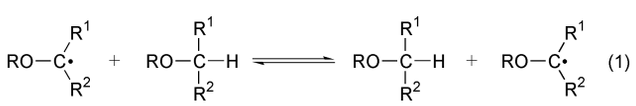
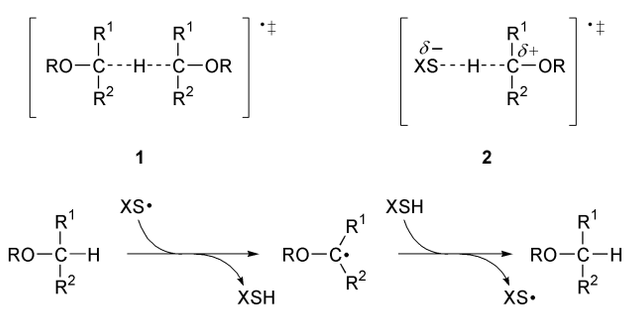
Radical-chain epimerisation at chiral tertiary CH centres adjacent to ethereal oxygen atoms can be brought about in the presence of thiols, the function of which is to act as protic polarity-reversal catalysts for hydrogen-atom transfer between pairs of nucleophilic α-alkoxyalkyl radicals. The viability of the method is demonstrated by epimerisation of a series of simple molecules that contain two chiral centres and then the procedure is applied to more complex carbohydrate-based systems, where it is possible to convert a readily available diastereoisomer into a rarer one in a straightforward manner. Of necessity, epimerisation always proceeds in the direction of thermodynamic equilibrium and, in general, the results obtained are in accord with the predictions of molecular mechanics calculations using the MMX force-field. When the required isomer is less stable than the starting diastereoisomer, thiol-catalysed epimerisation of a suitable derivative of the parent can provide a means to obtain the desired compound in satisfactory yield, after deprotection of the epimerised derivative. This strategy is demonstrated for the conversion of *trans*-cyclohexane-1,2-diol into the less stable *cis*-isomer and for related contra-thermodynamic isomerisation of some carbohydrates, as well as for the conversion of *meso*-1,2-diphenylethane-1,2-diol into the *dl*-form. Thiol-catalysed epimerisation at a CH centre adjacent to an ether-oxygen atom is much faster than at a similar centre adjacent to an amido-nitrogen atom, a result that can be understood in terms of the importance of polar effects on the rate of abstraction of hydrogen by electrophilic thiyl radicals.

Selective epimerisation of organic molecules that contain two or more chiral centres has significant potential as a simple method for the conversion of a readily accessible diastereoisomer into a more desirable one. In a preliminary communication,[1] we have reported that thiol-catalysed radical-chain epimerisation takes place selectively at a chiral tertiary CH centre that is activated by an attached ether-oxygen atom. The role of the thiol is to act as a protic polarity-reversal catalyst that mediates reversible hydrogen-atom abstraction at the CH centre.[2] In the present paper we report full details of these experiments and describe further applications of the methodology.

A thermoneutral hydrogen-atom exchange reaction of the type shown in eqn. (1) usually has a relatively high activation



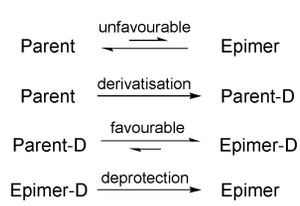
energy and is slow at moderate temperatures. This can be explained in terms of the importance of 'polar effects' in determining the rates of reaction of electrically neutral radicals, because of the absence of charge-transfer stabilisation of the symmetrical transition state **1**, in which the incoming and outgoing α-alkoxyalkyl radicals have the same electronegativity.[3] In the presence of a thiol catalyst, the direct hydrogen-abstraction process is replaced by the sequence of hydrogen-atom transfer reactions shown in Scheme 1. Each of these elementary reactions proceeds *via* the transition state **2**, which benefits from charge-transfer stabilisation because the electronegativities of



Scheme 1

the nucleophilic α-alkoxyalkyl radical and the electrophilic thiyl radical are significantly different.[3]

The thiol-catalysed epimerisation process is necessarily under thermodynamic control. However, it should prove possible to obtain an adequately high yield of the required epimer from its more stable or similarly stable parent by first converting the latter into a suitable derivative, such that the corresponding derivative of the desired epimer is now appreciably more stable. This strategy is outlined in Scheme 2 and a preliminary report of its realisation has been published.[4]



Scheme 2

† Correspondence concerning the X-ray crystallography should be directed to this Author.

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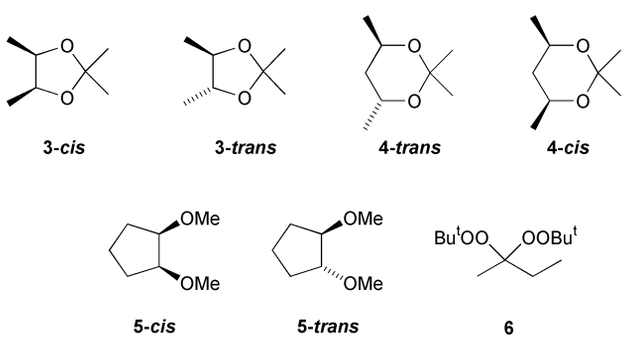
Results and discussion

1 Epimerisation of simple molecules

Epimerisation at the oxygen-activated tertiary CH centres in the cyclic ketals **3** and **4** and in 1,2-dimethoxycyclopentane **5** was examined initially in order to explore the viability of the approach. When a nonane solution containing **3-*cis*** (*ca.* 1 M) and 5 mol% of 2,2-bis(*tert*-butylperoxy)butane **6** (DBPB, present as an initiator) was heated under argon or nitrogen at 125 °C for 3 h, no conversion to the *trans*-isomer was observed by GLC analysis. The half-life for decomposition of DBPB to give alkoxyl radicals, which would go on to abstract hydrogen from **3**, is *ca.* 1 h at 125 °C; nonane was used as solvent in order to avoid interference with the GLC analysis. However, when the experiment was repeated in the presence of 5 mol% *tert*-dodecanethiol ‡ (TDT), slow epimerisation of **3-*cis*** to the more stable **3-*trans*** was observed and a final *cis* : *trans* ratio of 63 : 37 was achieved after 1 h. In the additional presence of 2,4,6-trimethylpyridine (collidine, 10 mol%), the function of which is probably to remove traces of acid formed from thiols under the reaction conditions, the *cis* : *trans* ratio was 46 : 54 after 1 h and reached a final value of 43 : 57 after 2 h. We have found previously[5,6] that silanethiols are often more effective protic polarity-reversal catalysts than are simple alkanethiols and when the TDT was replaced by triphenylsilanethiol (Ph_3SiSH; TPST), isomerisation of **3-*cis*** proceeded further and more rapidly (*cis* : *trans* = 24 : 76 after 1 h). However, when collidine was also present very little isomerisation took place, evidently because TPST reacts with collidine under the conditions used for epimerisation. Tri-*tert*-butoxysilanethiol [$(Bu^tO)_3SiSH$; TBST], which is much less sensitive to nucleophilic attack at silicon, proved to be a very efficient catalyst for the epimerisation of **3-*cis***, especially in the presence of 10 mol% of collidine. After 2.5 h at 125 °C a *cis* : *trans* ratio of 16 : 84 was reached and this corresponds to thermodynamic equilibrium, because the same isomer ratio was obtained when starting from pure **3-*trans***. Molecular mechanics calculations using the MMX force-field[7] indicate that the *trans*-isomer is 6.6 kJ mol^{-1} more stable than the *cis* and, assuming that this value corresponds approximately to the free-energy difference between the two isomers at 125 °C, the predicted *cis* : *trans* equilibrium ratio is 12 : 88.



Epimerisation of the 1,3-dioxanes **4**, obtained from pentane-2,4-diol, was carried out under similar conditions in octane solvent at 125 °C (bath temp.) in the presence of collidine and TBST as polarity-reversal catalyst. The pure *trans*-isomer was prepared from the (*R,R*)-diol and a 53 : 47 *cis* : *trans* mixture was prepared from a commercially available mixture of *meso*- and *dl*-diols. Whatever the isomeric composition of the starting dioxane, an equilibrium mixture consisting of 93% **4-*cis*** and 7% **4-*trans*** was obtained within 1 h. Molecular mechanics calculations predict the *cis*-isomer to be the more stable by 13.7 kJ mol^{-1}, which corresponds to an equilibrium ratio of 98 : 2 in favour of **4-*cis*** at 125 °C.

‡ Commercial mixture of isomers.

Table 1 Thiol-catalysed epimerisation of isosorbide dimethyl ether **7** in octane at 125 °C in the presence of DBPB initiator[a]

		Isomeric composition (%)		
Entry	Thiol catalyst	**7**	**8**	**9**
1	None	100	not detected	not detected
2	MeO_2CCH_2SH	89.1	1.1	10.0
3	TPST	62.4	1.2	36.4
4	$(4\text{-}FC_6H_4)_3SiSH$	58.4	1.2	40.4
5	TBST	40.0	1.5	52.5
6[b]	TBST	38.5	1.5	60.0

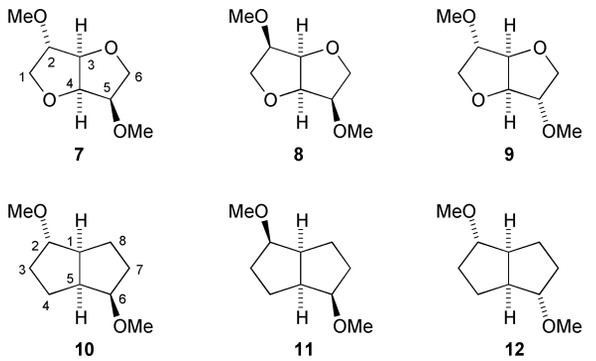
[a] The initiator and the thiol (5 mol% of each) were added initially and again after 1 h. The total reaction time was 4 h although, usually, no further change occurred after 3 h. [b] Collidine (10 mol%) was present initially.

The thiol-catalysed epimerisation of 1,2-dimethoxycyclopentane **5** required rather more forcing conditions to drive it to thermal equilibrium at 125 °C. In total, three additions of TBST and DBPB (3 mol% of each) were made, initially, after 30 min and after 1 h to **5-*cis*** in octane and the progress of the epimerisation was monitored by GLC. After heating for 3 h in all, the ratio **5-*cis*** : **5-*trans*** was 5 : 95 and this isomer ratio was also obtained when the pure *trans* isomer was subjected to the same treatment, showing that thermal equilibrium had been established. Molecular mechanics calculations predict that the *trans* isomer is more stable than the *cis* by 8.9 kJ mol^{-1}, which translates to a *trans* : *cis* ratio of *ca.* 6 : 94 at 125 °C if entropy differences are neglected.

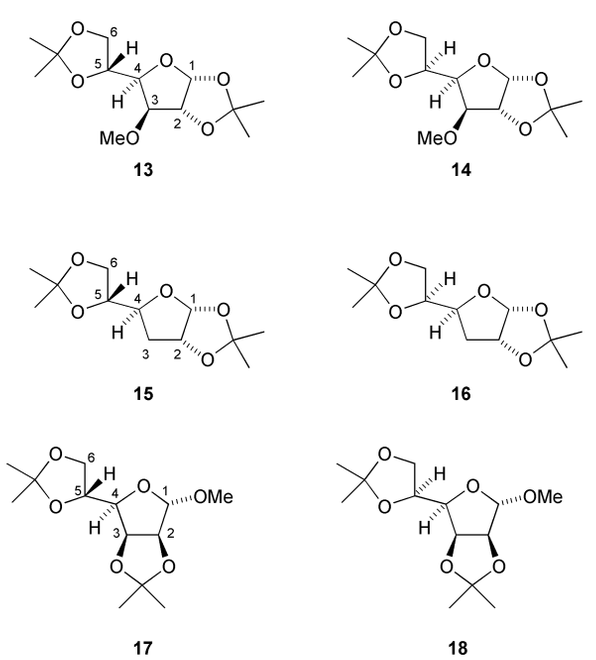
2 Epimerisation of more complex molecules

Di-*O*-methyl-1,4 : 3,6-dianhydro-D-glucitol (isosorbide dimethyl ether) **7** is readily available commercially. Assuming that the *cis* ring junction is preserved, epimerisation can take place either at C-2 to give the corresponding dianhydro-D-mannitol derivative **8** or at C-5 to give the dianhydro-L-iditol derivative **9**. While **8** is readily obtainable by methylation of commercial isomannide, the ether **9** is much less accessible. However, molecular mechanics calculations indicate that the order of stability is **9** (0) > **7** (+5.8 kJ mol^{-1}) > **8** (+15.0 kJ mol^{-1}). The epimerisation of **7** was investigated in octane solution at 125 °C, using DBPB as initiator and various thiols as catalysts. The progress of the reaction was monitored by GLC and the results are summarised in Table 1. The silanethiols TPST and TBST were much more effective catalysts than methyl thioglycolate (MeO_2CCH_2SH) and no epimerisation was detectable in the absence of a thiol. Tris(4-fluorophenyl)silanethiol, which was investigated on the basis that it should yield a more electrophilic thiyl radical than that from TPST, was no more effective than the latter. The presence of collidine improved the efficiency of the epimerisation somewhat (entries 5 and 6) and pure **9** was easily isolated in 56% yield from the latter run by flash chromatography on silica gel. When pure isomannide dimethyl ether **8** was subjected to the conditions of entry 6, the final epimeric proportions **7** : **8** : **9** were 41.5 : 45.5 : 13.0. Although **7** can be formed directly from **8**, compound **9** is presumably formed indirectly by epimerisation of **7**.

The carbocyclic analogue **11**[8a] of isomannide dimethyl ether was readily prepared by methylation of *endo,endo,cis*-bicyclo-[3.3.0]octane-2,6-diol[8b,c] and underwent epimerisation in a similar manner to **8** under the conditions of entry 6. Thus, after 4 h at 125 °C the epimeric proportions **10** : **11** : **12** determined by GLC were 42.0 : 51.5 : 6.5. According to molecular mechanics calculations, the relative energies (kJ mol^{-1}) of these molecules increase in the order **12** (0) < **10** (+1.2) < **11** (+7.0), following a trend qualitatively similar to that shown by **7**–**9** and as expected on steric grounds. Although the *exo,exo*-epimer **12** is the most stable, it cannot be formed directly from **11** and must arise from isomerisation of **10**.



The 3-*O*-methyl derivative **13**[9] of the readily available diacetone-D-glucose proved more resistant to epimerisation, which could, in principle, take place at C-3, C-4 or C-5. However, when **13** was heated under reflux in nonane in the presence of di-*tert*-butyl peroxide initiator and TBST as catalyst, partial conversion (32%) to another isomer was achieved; no other products were detected by NMR spectroscopy. The product was isolated in 25% yield by flash chromatography and shown to be the β-L-idofuranose **14**, on the basis that the only significant change in the ^{1}H NMR spectrum that accompanies epimerisation of **13** takes place for the lines assigned to the two protons attached to C-6. In **13** these protons give rise to the AB part of an ABX pattern (δ 4.01 and 4.08; J_{AB} = 8.6, J_{AX} = 5.4 and J_{BX} = 4.5 Hz), while in the product **14** the chemical-shift difference between the geminal protons increases substantially (δ 3.62 and 4.10; J_{AB} = 8.1, J_{AX} = 7.6 and J_{BX} = 6.6 Hz) such that the appearance becomes close to first-order. According to molecular mechanics calculations, the energies of the C-3, C-4 and C-5 epimers relative to **13** are +3.7, +3.2 and +2.3 kJ mol^{-1}, respectively, consistent with the observed partial epimerisation at C-5. Indeed, when a pure sample of **14** was subjected to the same conditions used to produce it from **13**, a 67 : 33 mixture of **13** and **14** was obtained, showing that this ratio corresponds essentially to thermodynamic equilibrium between these two epimers.



Deoxygenation of diacetone-D-glucose at C-3, *via* reaction of the corresponding xanthate with triphenylsilane in 1,4-dioxane at 60 °C,[10] afforded **15** in excellent yield. Compound **15** could potentially undergo epimerisation at C-4 or C-5 to give products with relative energies of +13.2 and +0.6 kJ mol^{-1}, respectively, according to molecular mechanics. The epimerisation of **15** proceeded more readily than that of **13** and could be carried out in octane at 125 °C with DBPB as initiator and TBST as catalyst, in the presence of collidine, to give 32% conversion to a single isomeric product which was identified as the C-5 epimer **16**; none of the C-4 epimer was detected in the reaction mixture. The L-*lyxo*-hexofuranose **16**, the D-antipode of which has been reported previously,[11] was isolated in 25% yield. When a pure sample of **16** was subjected to conditions used to epimerise **15**, GLC analysis showed that a mixture of **15** and **16** was obtained in the ratio 63 : 37, indicating that thermodynamic equilibrium is almost reached under the reaction conditions and implying that **15** is in fact slightly more stable than **16**, in agreement with the molecular mechanics calculations.

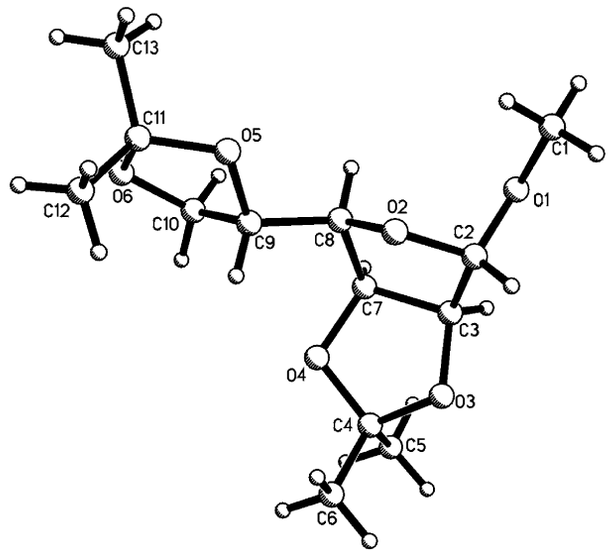


Fig. 1 Structure of methyl 2,3 : 5,6-di-*O*-isopropylidene-β-L-gulofuranoside **18** determined by X-ray crystallography. The crystallographic numbering system differs from the conventional system used in the text. Selected geometrical parameters (bond lengths in Å, bond angles in degrees): O(1)–C(2) 1.395(5), O(2)–C(2) 1.422(4), O(2)–C(8) 1.434(5), C(2)–C(3) 1.521(5), C(3)–C(7) 1.539(5), C(7)–C(8) 1.546(4), C(8)–C(9) 1.510(5), C(9)–C(10) 1.496(6); C(2)–O(1)–C(1) 113.3(4), C(2)–O(2)–C(8) 106.5, C(3)–C(7)–C(8) 103.7(3), O(2)–C(8)–C(7) 104.9(3), O(2)–C(8)–C(9) 110.0(3), C(8)–C(9)–C(10) 114.7(3).

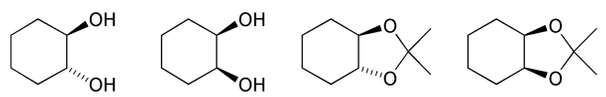
The α-D-mannofuranoside **17**[9,12] also underwent epimerisation at C-5 and the accompanying changes in the ^{1}H NMR spectrum were very similar to those described above for the epimerisation of **13** to **14**. Conversion to the β-L-gulofuranoside **18** was 30% (by GLC) in refluxing octane and the identity of the product was confirmed by single-crystal X-ray diffraction (see Fig. 1) after its isolation in 24% yield. According to molecular mechanics calculations, the C-5 (C-9 in Fig. 1) epimer **18** is marginally (by 1.1 kJ mol^{-1}) less stable than its parent **17**. In accord with this prediction, when pure **18** was subjected to the isomerisation conditions, the final ratio **17** : **18** was 65 : 35 in favour of the mannoside, showing that this is indeed the more stable epimer and that thermodynamic equilibrium is again almost achieved between these two epimers.

3 Contra-thermodynamic epimerisation

Clearly, it would be advantageous to circumvent the limitation on the yield of a desired epimer that is imposed by its thermodynamic stability relative to its parent. The viability of our strategy for achieving this, *via* indirect epimerisation as generalised in Scheme 2, was demonstrated for the cyclic acetonide derivatives of a number of 1,2-diols. For these diols the method relies on the different structural preferences of the acetonides and the ease with which acetonides may be prepared from, and converted back to, their parent diols.

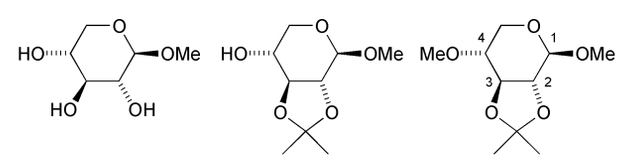
According to molecular mechanics calculations, the most stable conformation of *trans*-cyclohexane-1,2-diol **19** is more stable than that of the *cis*-isomer **20** by 2.2 kJ mol^{-1}. Both

isomers of the diol are readily converted to the corresponding acetonides **21** and **22** by treatment with an excess of 2,2-dimethoxypropane in the presence of an acidic ion-exchange resin (Amberlyst-15). The *trans*-diastereoisomer is destabilised with respect to the *cis*-form by the extra strain present when a five-membered dioxolane ring is *trans*-fused to the cyclohexane ring and molecular mechanics calculations indicate that the *trans*-acetonide is *less stable* than the *cis*-form by 3.8 kJ mol^{-1}. Heating either the *trans*- or the *cis*-acetonide in refluxing octane (bp 126 °C, bath temp. 140–145 °C, internal temp. *ca.* 130 °C) for 2.5 h in the presence of TBST (3 ×3 mol%), DBPB (3 × 3 mol%) and collidine (1 × 10 mol%) led to the same equilibrium mixture of isomers in which the *cis*-acetonide predominated to the extent of 95%. No detectable epimerisation takes place in the absence of the thiol. The acetonide **22** could be readily deprotected by treatment with an excess of methanol in the presence of Amberlyst-15 at room temperature to give the *cis*-diol in a pure state after one recrystallisation from ethyl acetate. The sequence of derivatisation, epimerisation and deprotection thus provides an efficient procedure for the conversion of *trans*-cyclohexane-1,2-diol into the less stable *cis*-isomer, based on the principle generalised in Scheme 2.

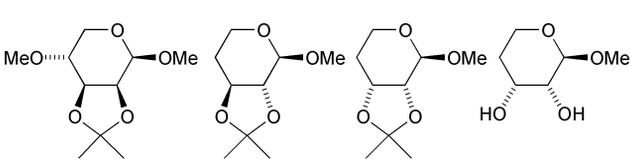


19 **20** **21** **22**

Methyl β-D-xylopyranoside **23** was converted into the acetonide **24** using the published method[13] and subsequent methylation afforded **25**, which is predicted by molecular mechanics calculations to be less stable than both its C-3 and C-2 epimers, by 6.9 and 8.2 kJ mol^{-1}, respectively. However, attempted isomerisation of **25** failed under the conditions used to epimerise **13** to **14**, and **25** remained unchanged. Under more forcing conditions, in refluxing nonane (bp 151 °C) with di-*tert*-butyl peroxide (20 mol%) as initiator and three additions of TBST (3 × 5 mol%) during 3 h, partial isomerisation of **25** took place to give **26** as the major product (30%), but the remainder of the starting material was unchanged. The structure of **26** was assigned on the basis of the nuclear Overhauser effects evident in its 2D NOESY spectrum. Thus, H-2 shows a strong correlation with both H-1 and H-3, indicating that all three protons are located on the same side of the pyranose ring. Assuming epimerisation at one site only, the configuration at C-1 must be the same as that in **25** and thus epimerisation must have taken place at C-2 to give **26**.

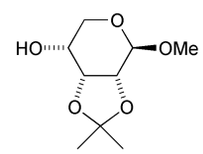


23 **24** **25**



26 **27** **28** **29**

In contrast to the sluggish isomerisation of **25**, its 4-deoxy analogue **27** underwent epimerisation readily in refluxing octane, essentially under the conditions used to isomerise **15**, and was converted almost quantitatively into the C-3 epimer **28**. The acetonide **27** is calculated to be less stable than **28** by 18.9 kJ mol^{-1} and less stable than its C-2 epimer by 12.0 kJ mol^{-1}. Deprotection of **28** (Amberlyst-15, excess of MeOH, room temperature) gave the free *cis*-diol, methyl 4-deoxy-β-D-*erythro*-pentopyranoside **29**. The structure of **28** was confirmed by its independent synthesis from D-ribose, which was first converted to a 1 : 3 mixture of the 2,3- and 3,4-*O*-isopropylidene-β-D-ribopyranosides **30** and **31**.[14] These isomers proved very difficult to separate completely and so a mixture enriched in **30** was converted to a mixture of the xanthates **32** and **33**, from which **32** could be readily obtained in a pure state and then reduced with triphenylsilane[10] to give **28**.



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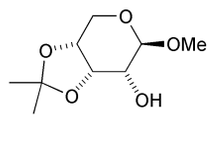

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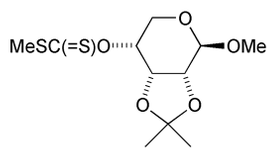

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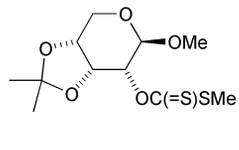

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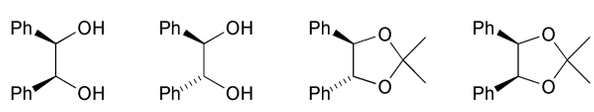
The large difference in reactivity of **25** and **27** towards thiol-catalysed epimerisation at C-3 is probably the result of steric shielding of H-3 by the 4-methoxy group in the former, coupled with the deactivating polar effect of this β-methoxy substituent on abstraction of H-3 by the electrophilic thiyl radical.[15]

According to molecular mechanics, the energies of the most stable conformations of the *dl*- and *meso*-forms of 1,2-diphenylethane-1,2-diol (hydrobenzoin) are almost the same. However, the *meso*-form **34** is appreciably easier to prepare than the *dl*-isomer **35** and the latter is much more costly to obtain commercially. On the other hand, the *trans*-acetonide **36** derived from the *dl*-diol is calculated to be more stable by 14.6 kJ mol^{-1} than the *cis*-acetonide **37** which can be obtained from the *meso*-diol, implying that radical-chain-epimerisation of **37** should provide an efficient means to convert the *meso*-diol to the *dl*-diol under mild neutral conditions.



34 **35** **36** **37**

In accord with this, treatment of **37** with 2,4,6-tris-(trifluoromethyl)thiophenol[16] as catalyst and DBPB as initiator in refluxing octane resulted in complete (≥98%) conversion to the *trans*-acetonide **36**, which could be deprotected (Amberlyst-15, excess of MeOH, reflux) to give the free *dl*-diol **35**. The choice of thiol catalyst for epimerisation of **37** proved to be critical and no significant conversion to **36** was observed when the arenethiol was replaced by TBST or *tert*-dodecanethiol, under otherwise identical conditions. The key point here is that epimerisation is taking place at a benzylic centre and involves an oxygen-stabilised secondary benzylic radical. For efficient radical-chain epimerisation, both abstraction of hydrogen from **37** by the thiyl radical *and* abstraction of hydrogen from the thiol by the resulting benzylic radical must be rapid, and it is likely that the latter reaction is significantly endothermic and thus relatively slow for alkane- or silane-thiols. The S–H bond in an arenethiol is appreciably weaker than that in an alkanethiol (366 kJ mol^{-1} in MeSH and 349 kJ mol^{-1} in PhSH)[17] and, in general, the choice of thiol catalyst needs to be made such that the strengths of the C–H and S–H bonds involved are fairly similar. A number of other arenethiols were investigated as catalysts for the epimerisation of **37** to **36** and the results are summarised in Table 2.

Table 2 Epimerisation of *cis*-2,2-dimethyl-4,5-diphenyl-1,3-dioxolane **37** in refluxing octane using DBPB as initiator and different arenethiols as catalysts[a]

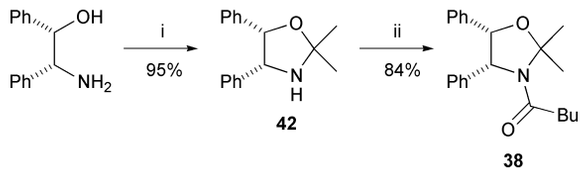
Arenethiol	Final ratio **36** : **37**
2,4,6-Tris(trifluoromethyl)thiophenol	≥98 : ≤2
4-(Trifluoromethyl)thiophenol	≥98 : ≤2
Pentafluorothiophenol	≥98 : ≤2
Pentachlorothiophenol	95 : 5
2,4-Dichlorothiophenol	81 : 19
4-Fluorothiophenol	68 : 32
4-Chlorothiophenol	66 : 34
Thiophenol	60 : 40
4-Methylthiophenol	36 : 64
4-Methoxythiophenol	14 : 86

[a] The thiol and DBPB initiator (3 mol% of each) were added initially, then again after 20 min and 40 min (9 mol% of each in all). The total reaction time was 2.5 h and the final ratio **36** : **37** was determined by ^{1}H NMR spectroscopy.

It is evident that electron-withdrawing substituents on the benzene ring increase the effectiveness of the arenethiol as a catalyst, relative to thiophenol itself, whilst electron-donating groups reduce the effectiveness of the thiol as a protic catalyst. It seems likely that there are two related reasons for this behaviour. First, the presence of electron-withdrawing substituents, particularly at *ortho*- and *para*-sites, leads to an increase in the strength of the S–H bond[18] and probably to better matching of the S–H and benzylic C–H bond strengths, while electron-donating groups weaken the S–H bond relative to that in thiophenol, leading to poorer matching. Second, electron-withdrawing substituents render the thiyl radical more electrophilic, resulting in increased charge-transfer stabilisation of the transition state (see structure **2**) for abstraction of the benzylic hydrogen atom to give the nucleophilic benzylic radical.[3] Electron-donating groups render the thiyl radical less electrophilic than that from thiophenol, resulting in a lower rate of hydrogen abstraction because of less favourable polar effects. Pentafluorothiophenol is particularly acidic with a pK_a of 2.6,[19] compared with 6.2 for thiophenol, and it seems likely that $C_6F_5S^{\bullet}$ will behave as an exceptionally electrophilic thiyl radical, in accord with the effectiveness of C_6F_5SH as a protic catalyst for the epimerisation of **37**.

Experiments were carried out to investigate the formal possibility that epimerisation of **37** might be brought about by a heterolytic ring-opening mechanism under the influence of simple acid catalysts. When **37** was heated in refluxing octane in the presence of toluene-*p*-sulfonic acid (5 mol%), with or without added DBPB, decomposition of the dioxolane was almost complete within 40 min to give unidentified products which did not include any of the *trans*-isomer **36**. When these runs were repeated, replacing the free sulfonic acid with its pyridine salt (5 mol%), no **36** was produced during 3 h and the *cis*-isomer **37** remained unchanged. In the absence of initiator, but under conditions otherwise identical to those used for radical-chain epimerisation, no conversion of **37** to **36** was observed in the presence of pentafluorothiophenol.

In order to compare the ease of epimerisation at CH groups adjacent to oxygen and adjacent to amido nitrogen, the *cis*–*trans* isomerisation of the enantiomeric oxazolidines **38** and **39** was examined. The oxazolidines were prepared from the commercially available (1*S*,2*R*) and (1*R*,2*S*) forms of 2-amino-1,2-diphenylethanol by treatment with acetone in the presence of an excess of aluminium powder, followed by acylation at nitrogen with valeryl chloride in the presence of triethylamine, as illustrated for **38** in Scheme 3. The parent oxazolidine **42** is very



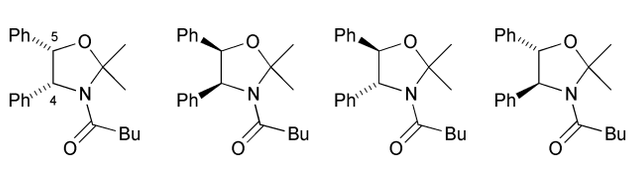
Scheme 3 *Reagents and conditions*: (i) Me_2CO, Al powder, cat. MeC(O)Cl in CH_2Cl_2, rt, 20 h; (ii) BuC(O)Cl, Et_3N in Et_2O, 0 °C to rt, 12 h.

sensitive to acid-catalysed hydrolysis and was converted directly to the stable crystalline derivative **38**. An authentic sample of the (4*R*,5*R*)-oxazolidine **40** was prepared in the same way from (1*R*,2*R*)-2-amino-1,2-diphenylethanol.[20]

Epimerisation of the *cis*-(4*R*,5*S*)-oxazolidine **38** was carried out in refluxing nonane using pentafluorothiophenol as catalyst (3 × 5 mol%) added initially, again after 20 min and again after 40 min; the total reaction time was 2.5 h. The initiator was di-*tert*-butyl peroxide (20 mol% present initially, followed by further additions of 5 mol% after 20 and 40 min). ^{1}H NMR analysis showed that the final *cis* : *trans* ratio of oxazolidines was 27 : 73 and the enantiomeric ratio **40** : **41** for the *trans*-isomer was found to be 95 : 5 by chiral stationary-phase HPLC analysis, using authentic **40** as a reference. Epimerisation thus takes place with high selectivity at the carbon centre adjacent to oxygen. The *trans*-oxazolidine was isolated in 72% yield and readily upgraded to >99% ee by a single recrystallisation from hexane. Similar reactions of the *cis*-(4*S*,5*R*)-oxazolidine **39** gave a final *cis* : *trans* ratio of 24 : 76 and the enantiomeric ratio **40** : **41** was 4 : 96; the *trans*-isomer was isolated in 71%.

The final *cis* : *trans* ratio of *ca.* 25 : 75 obtained in refluxing nonane is close to the value corresponding to thermodynamic equilibrium at *ca.* 155 °C (estimated internal temp.) for epimerisation at C-5 adjacent to oxygen, but far from equilibrium for epimerisation at C-4 adjacent to nitrogen. Thus, when a pure sample of the *trans*-(4*R*,5*R*)-oxazolidine **40** was subjected to the conditions used to epimerise **38** and **39**, the final *cis* : *trans* ratio was 20 : 80 as determined by ^{1}H NMR spectroscopy. However, the enantiomeric ratio **38** : **39** for the *cis*-isomer was *ca.* 97 : 3 (by HPLC), whereas thermodynamic equilibrium between these two enantiomers (established through epimerisation adjacent to nitrogen) would correspond to a racemic mixture of **38** and **39**. Consistent with this interpretation, no racemisation of recovered **40** (which would result from a double epimerisation *via* **39**) was detectable by HPLC analysis.

The relative ease of epimerisation at C-4 and C-5 in the oxazolidines **38** and **39** can be understood in terms of polar effects on the rates of benzylic hydrogen-atom abstraction by the electrophilic thiyl radical;[21] the strengths of the C5-H and C6-H bonds are likely to be very similar. The abilities of alkoxy and amido groups to stabilise positive charge on an attached carbon atom (*cf.* structure **2**) should be reflected in their Hammett σ or σ$^+$ substituent constants and for *p*-Me_2N, *p*-MeO and *p*-MeC(O)NH groups the values are −0.32 (−1.7), −0.27 (−0.78) and 0.0 (−0.6), respectively (σ$^+$-values in parentheses).[22] Thus, the rate of hydrogen-atom abstraction by electrophilic radicals from otherwise similar C–H bonds adjacent to amino,[23] alkoxy and amido substituents would be expected to decrease in this order.



Conclusions

In summary, it appears that thiol-catalysed selective epimerisation at tertiary CH centres adjacent to ether-type oxygen atoms can provide a useful method for the conversion of one

diastereoisomer into another, more valuable, diastereoisomer. The procedures used here are very straightforward, although sometimes careful choice of the thiol catalyst is essential for efficient epimerisation. When the required isomer is less stable than the starting diastereoisomer, thiol-catalysed epimerisation of a suitable derivative of the parent can provide a means to obtain the desired compound in satisfactory yield, after deprotection of the epimerised derivative.

Experimental

NMR spectra were recorded using a Bruker ADVANCE 500 instrument (500 MHz for ^{1}H, 125.7 MHz for ^{13}C). Unless stated otherwise, the solvent was $CDCl_3$ and chemical shifts are reported relative to Me_4Si; *J*-values are quoted in Hz and the use of [multiplet] indicates an apparent multiplet associated with an averaged coupling constant. Column chromatography and TLC were carried out using Merck Kieselgel 60 (230–400 mesh) and Kieselgel 60 F_{254} aluminium-backed pre-coated plates, respectively. Determination of enantiomeric excess by HPLC was carried out using Chiralcel-OD or Chiralpak-AD columns (4.6 mm × 250 mm; Daicel Chemical Industries Ltd.) in conjunction with hexane–isopropyl alcohol eluent (flow rate 1 cm^3 min^{-1}). The proportion of alcohol in the eluent is given in the text and UV detection was at 254 nm. Optical rotations were measured on an AA Series Polaar 2000 polarimeter (Optical Activity Ltd.) using a 1 dm cell and specific rotations are given in units of 10^{-1} deg cm^2 g^{-1}.

GLC analysis was carried out using an HP 6890 Series instrument in conjunction with capillary columns (25 m × 0.32 mm i.d.) coated with BPX5 (non-polar, 0.32 μm film) or BP20 (polar, 0.10 μm film) stationary phases, both obtained from SGE International Ltd. The carrier gas was helium and the flow rate was 1.2 cm^3 min^{-1}.

All manipulations and reactions of air-sensitive compounds were carried out under an atmosphere of dry argon or nitrogen and all extracts were dried over anhydrous $MgSO_4$, unless stated otherwise. Petroleum spirit refers to the fraction of distillation range 40–60 °C.

Materials

Anhydrous octane, nonane and 1,4-dioxane (Aldrich) were used as received. Di-*tert*-butyl peroxide (Aldrich) was distilled under reduced pressure and stored under argon in a refrigerator; 2,2-bis(*tert*-butylperoxy)butane **6** (50% w/w in mineral oil) was obtained commercially (Laporte Organics or Aldrich) and was used as received.

Tris(4-fluorophenyl)silanethiol. This thiol was prepared according to the method described in the literature for similar triarylsilanethiols.[24] A mixture of tris(4-fluorophenyl)silane[25] (5.0 g, 16.0 mmol) and powdered elemental sulfur (0.51 g, 16.0 mmol) in decalin (20 cm^3) was stirred and heated under reflux for 36 h. Decalin was removed by distillation under reduced pressure (12 mmHg) and the residue was distilled to give the *thiol* as an oil (3.8 g, 58%), bp 146–148 °C/0.02 mmHg, which slowly solidified on storage and was then recrystallised from hexane, mp 72–74 °C; δ_H 0.46 (1 H, s, SH), 7.11 (6 H, m, ArH), 7.57 (6 H, m, ArH); δ_C 115.5 (d, J_{CF} 20.2), 129.5 (d, J_{CF} 3.7), 137.4 (d, J_{CF} 7.9), 164.5 (d, J_{CF} 251.1) (Found: C, 62.4; H, 3.6; S, 9.2. $C_{18}H_{13}F_3SSi$ requires C, 62.4; H, 3.8; S, 9.3%).

Tri-*tert*-butoxysilanethiol (TBST) was prepared according to a modification of the method described in the literature.[26] Silicon disulfide (Alfa Aesar) was crushed to a fine powder using a dry stainless steel pestle and mortar enclosed in a polythene bag filled with nitrogen. Powdered silicon disulfide (95% pure; 20.2 g, 0.21 mol) was charged into a 100 cm^3 round-bottomed flask containing a robust stirrer bar and equipped with a reflux condenser. *tert*-Butyl alcohol (60.0 g, 0.81 mol) was added and the mixture was stirred and heated under reflux (stirring-heating mantle) under nitrogen for 72 h. The cooled reaction mixture was filtered through Celite to remove unchanged silicon disulfide and the filter cake was washed with diethyl ether. Excess of alcohol and diethyl ether were removed from the filtrate by rotary evaporation and the residual oil was distilled under reduced pressure to give the silanethiol (18.1 g, 31%) as a colourless liquid, bp 95 °C/15 mmHg (lit.,[26] 113–115 °C/35 mmHg); δ_H 0.18 (1 H, s, SH), 1.34 (27 H, s, Bu^t); δ_C 31.4, 74.4.

2,4,6-Tris(trifluoromethyl)thiophenol[16] was prepared as described previously and all other thiols were obtained commercially (Aldrich) and were used as received.

Preparation of starting isomers and standards

cis*-2,2,4,5-Tetramethyl-1,3-dioxolane 3-*cis*.** *meso*-Butane-2,3-diol (5.00 g, 56 mmol) in acetone (25 cm^3) was heated under gentle reflux for **4** h in the presence of 50% aq. sulfuric acid (*ca.* 30 mm^3). The acetone was removed by slow distillation at atmospheric pressure and the residue was dissolved in diethyl ether (50 cm^3), shaken with anhydrous K_2CO_3 (2 g), and dried. Distillation gave **3-*cis as a clear oil, bp 117–118 °C/755 mmHg (lit.,[27] 111–114 °C); δ_H 1.13 (6 H, d, *J* 5.9, Me), 1.32 (3 H, s, Me), 1.44 (3 H, s, Me), 4.22 (2 H, m, OCH); δ_C 15.5, 25.7, 28.5, 73.9, 107.2.

trans*-2,2,4,5-Tetramethyl-1,3-dioxolane 3-*trans*.** This was prepared by the procedure used for the *cis*-isomer, starting from *dl*-butane-2,3-diol, itself prepared by hydrolytic ring opening of *cis*-2,3-epoxybutane. Distillation gave **3-*trans as a clear oil, 109–111 °C/758 mmHg (lit.[27] 109–112 °C); δ_H 1.23 (6 H, d, *J* 5.8, Me), 1.39 (6 H, s, Me), 3.63 (2 H, m, OCH); δ_C 16.8, 27.3, 78.2, 107.5.

***trans*-2,2,4,6-Tetramethyl-1,3-dioxolane 4-*trans*.** This was prepared from (*R,R*)-pentane-2,4-diol according to the published method,[28] bp 135 °C/755 mmHg (lit.,[28] 135 °C); δ_H 1.19 (6 H, d, *J* 6.3, Me), 1.36 (6 H, s, Me), 1.59 (2 H, t, *J* 7.5, CH_2), 3.95 (2 H, m, OCH); δ_C 21.7, 25.2, 41.5, 62.7, 100.0. A 53 : 47 mixture of *cis*- and *trans*-**4** was prepared similarly from a commercially available mixture of *dl*- and *meso*-pentane-2,4-diol. The NMR spectrum of the *cis*-isomer showed δ_H 1.15 (6 H, d, *J* 6.3, Me), 1.40 (3 H, s, Me), 1.44 (3 H, s, Me), 1.46 (1 H, m, H^A-5), 1.50 (1 H, m, H^B-5), 3.94 (2 H, m, OCH); δ_C 19.8, 22.2, 30.3, 40.4, 65.0, 98.3.

***trans*-1,2-Dimethoxycyclopentane 5-*trans*.**[29] The published method[29b] was modified by the use of iodomethane as the methylating agent, instead of dimethyl sulfate, in order to facilitate isolation of the product. *trans*-Cyclopentane-1,2-diol (5.00 g, 49 mmol) in dry dimethylformamide (DMF, 20 cm^3) was added dropwise to a vigorously stirred suspension of sodium hydride (60% in mineral oil, 1.80 g, 125 mmol) in DMF (80 cm^3) cooled in an ice–water-bath. After the addition, the mixture was allowed to warm to room temperature and stirred vigorously until a homogeneous solution was obtained. The solution was cooled to 0 °C and iodomethane (21.3 g, 150 mmol) was added dropwise with stirring. The reaction mixture was then stirred at room temperature overnight before being quenched with water (100 cm^3) and extracted with diethyl ether (4 × 20 cm^3). The combined extracts were washed with saturated brine (2 × 20 cm^3) and dried; the diethyl ether and unchanged iodomethane were removed by careful rotary evaporation and the residue was distilled under reduced pressure to give the product as a clear oil (3.5 g, 55%). Further purification by chromatography on silica gel (petroleum spirit–diethyl ether, 5 : 1 v/v eluent) was necessary and re-distillation then afforded pure **5**-*trans*, bp 63–64 °C/35 mmHg (lit.,[29b] 45 °C/15 mmHg); δ_H 1.57 (2 H, m, CH_2), 1.65 (2 H, m, CH_2), 1.89

(2 H, m, CH_2), 3.34 (6 H, s, OMe), 3.64 (2 H, m, OCH); δ_C 21.3, 29.7, 56.8, 86.3.

***cis*-1,2-Dimethoxycyclopentane 5-*cis*.** This was prepared in 60% yield from the *cis*-diol by the method used for the *trans*-isomer; bp 70–72 °C/42 mmHg; δ_H 1.75 (6 H, m, CH_2), 3.38 (6 H, s, OMe), 3.66 (2 H, m, OCH); δ_C 19.0, 27.2, 57.1, 82.0 (Found: C, 64.4; H, 10.9. $C_7H_{14}O_2$ requires C, 64.6; H, 10.8%).

Isosorbide dimethyl ether 7. This was used as received from Aldrich. Isomannide dimethyl ether **8** was prepared by methylation of isomannide with dimethyl sulfate in the presence of potassium hydroxide, as described in the literature.[30]

***endo,endo-cis*-Bicyclo[3.3.0]octane-2,6-diol.** This was prepared according to the published method,[8b] bp 110–113 °C/0.02 mmHg (lit.,[8b] 130–144 °C/2.7 mmHg). The corresponding dimethyl ether **11**[8a] was prepared from the diol by methylation with dimethyl sulfate as described for isomannide dimethyl ether,[30] bp 45 °C/0.05 mmHg or 100–102 °C/15 mmHg; δ_H 1.40 (4 H, m, CH_2), 1.80 (4 H, m, CH_2), 2.55 (2 H, m, CH_2), 3.29 (6 H, s, OMe), 3.72 (2 H, m, OCH); δ_C 20.4, 31.0, 43.0, 57.2, 84.4.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranoside 13. This was prepared according to the literature procedure;[9] δ_H 1.32 (3 H, s, Me), 1.36 (3 H, s, Me), 1.43 (3 H, s, Me), 1.50 (3 H, s, Me), 3.45 (3 H, s, OMe), 3.77 (1 H, d, *J* 3.0, H-3), 4.01 (1 H, dd, *J* 8.6 and 5.4, H^A-6), 4.08 (1 H, dd, *J* 8.6 and 4.5, H^B-6), 4.11 (1 H, dd, *J* 7.9 and 3.0, H-4), 4.30 (1 H, d[t], *J* 7.9 and 5.0, H-5), 4.56 (1 H, d, *J* 3.8, H-2), 5.86 (1 H, d, *J* 3.8, H-1); δ_C 25.4, 26.2, 26.8, 26.9, 58.2, 67.2, 72.3, 81.0, 81.8, 83.6, 105.1, 109.0, 111.7.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose 15.[31] This was prepared by reduction with triphenylsilane of the xanthate derived from diacetone D-glucose,[10,32] bp 80–82 °C/0.5 mmHg (lit.,[31] 72–73 °C/0.2 mmHg); δ_H 1.32 (3 H, s, Me), 1.35 (3 H, s, Me), 1.42 (3 H, s, Me), 1.51 (3 H, s, Me), 1.77 (1 H, m, H^A-3), 2.18 (1 H, dd, *J* 13.7 and 4.1, H^B-3), 4.13 (4 H, m, H-4, -5 and -6), 4.75 (1 H, t, *J* 4.1), 5.82 (1 H, d, *J* 3.7, H-1); δ_C 25.1, 26.1, 26.4, 26.8, 35.2, 67.2, 76.7, 78.6, 80.4, 105.6, 109.6, 111.3.

Methyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside 17.[9,12] This was prepared according to the literature procedure; δ_H 1.32 (3 H, s, Me), 1.38 (3 H, s, Me), 1.45 (3 H, s, Me), 1.46 (3 H, s, Me), 3.31 (3 H, s, OMe), 3.90 (1 H, dd, *J* 7.7 and 3.6, H-4), 4.04 (1 H, dd, *J* 8.7 and 4.4, H^A-6), 4.11 (1 H, dd, *J* 8.7 and 6.3, H^B-6), 4.40 (1 H, ddd, *J* 7.7, 6.3 and 4.4, H-5), 4.56 (1 H, d, *J*, 5.9, H-2), 4.76 (1 H, dd, *J* 5.9 and 3.6, H-3), 4.87 (1 H, s, H-1); δ_C 24.6, 25.2, 25.9, 26.9, 54.6, 67.0, 73.2, 79.5, 80.3, 85.0, 107.4, 109.2, 112.6.

***trans*- and *cis*-Acetonides 21 and 22.** These were prepared from *trans*- and *cis*-cyclohexane-1,2-diol, respectively, following the published procedure.[33]

Methyl 2,3-*O*-isopropylidene-4-*O*-methyl-β-D-xylopyranoside 25. This was prepared from **24**[13] by methylation with iodomethane, as described above for the preparation of **5**,[34] bp 70–72 °C/0.05 mmHg; $[\alpha]_D^{20}$ −32.9 (*c* 0.85, $CHCl_3$); δ_H 1.44 (3 H, s, Me), 1.45 (3 H, s, Me), 3.28 (1 H, dd, *J* 12.0 and 7.4, H^A-5), 3.33 (1 H, dd *J* 9.3 and 7.4, H-2), 3.47 (3 H, s, OMe), 3.52 (3 H, s, OMe), 3.56 (1 H, dd, *J* 8.7 and 6.3, H-3), 3.50 (1 H, m, H-4), 4.10 (1 H, dd, *J* 12.0 and 4.7, H^B-5), 4.53 (1 H, d, *J* 7.4, H-1); δ_C 26.6, 26.8, 56.4, 57.8, 65.2, 76.7, 77.9, 80.2, 102.6, 111.7 (Found: C, 55.1; H, 8.2. $C_{10}H_{18}O_5$ requires C, 55.0; H, 8.3%).

Methyl 4-deoxy-2,3-*O*-isopropylidene-α-L-*threo*-pentopyranoside 27.[35] This was prepared by deoxygenation of methyl 2,3-*O*-isopropylidene-β-D-xylopyranoside **24**[13] *via* the corresponding xanthate, mp 95–97 °C (lit.,[35] 93–97 °C). The ^1H NMR spectrum of **27** was identical to that described in the literature;[35] δ_C 26.5, 26.7, 56.5, 62.9, 64.2, 76.2, 79.2, 103.4, 110.3.

Methyl 4-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pentopyranoside 28. A 1 : 3 mixture of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside **30** and methyl 3,4-*O*-isopropylidene-β-D-ribofuranoside **31** was prepared according to the published procedure.[14] All attempts to isolate pure **30** by flash chromatography were unsuccessful and a mixture of the two compounds was converted to a mixture of the corresponding xanthates. Sodium hydride (60% in mineral oil; 0.55 g, 13.8 mmol) was added with stirring to a chromatographically enriched 45 : 55 mixture of **30** and **31** (2.57 g, 12.6 mmol) and imidazole (10 mg) in dry tetrahydrofuran (50 cm^3) under argon at 0 °C. The mixture was allowed to warm to room temperature and was stirred until liberation of hydrogen ceased (*ca.* 25 min). Carbon disulfide (2.51 g, 33 mmol) was added in one portion and the mixture was stirred for a further 30 min. Iodomethane (2.84 g, 20 mmol) was added dropwise and the mixture was then stirred at room temperature for 1 h. The reaction mixture was quenched with water (60 cm^3), the organic layer was separated, and the solvent was removed by rotary evaporation. The aqueous phase was extracted with diethyl ether (3 × 15 cm^3) and the combined extracts were added to the residue from the organic layer. The ethereal solution was washed with saturated brine (20 cm^3) and dried. The solvent was removed by rotary evaporation and the residue was purified by flash chromatography using petroleum spirit followed by petroleum spirit–diethyl ether (10 : 1 then 5 : 1 v/v) as eluent. The xanthate **32** (1.48 g, 89% based on **30**) was isolated from the earlier fractions as a pale yellow oil; δ_H 1.37 (3 H, s, Me), 1.57 (3 H, s, Me), 2.59 (3 H, s, SMe), 3.45 (3 H, s, OMe), 3.85 (1 H, dd, *J* 11.0 and 8.1, H^A-5), 3.95 (1 H, dd, *J* 11.0 and 5.0, H^B-5), 4.11 (1 H, dd, *J* 6.3 and 3.2, H-2), 4.60 (1 H, d, *J* 3.2, H-1), 4.63 (1 H, dd, *J* 6.3 and 4.0, H-3), 6.06 (1 H, ddd, *J* 8.1, 5.0 and 4.0, H-4); δ_C 25.5, 26.8, 56.2, 58.9, 67.9, 71.2, 74.0, 75.5, 100.6, 110.8, 215.9.

The xanthate **32** (294 mg, 1.0 mmol) was treated with triphenylsilane (310 mg, 1.2 mmol) and di-*tert*-butyl hyponitrite[36] (8.4 mg, 5 mol%) in 1,4-dioxane (2 cm^3) at 60 °C as described previously[10,32] to give **28** (155 mg, 82%) $[\alpha]_D^{20}$ −106.1 (*c* 3.8, $CHCl_3$); δ_H 1.36 (3 H, s, Me), 1.52 (3 H, s, Me), 1.89 (1 H, d[q], *J* 14.6 and 4.0, H^A-4), 2.01 (1 H, dd[t], *J* 14.9, 9.8 and 4.9, H^B-4), 3.46 (3 H, s, OMe), 3.66 (1 H, ddd, *J* 11.5, 9.8 and 3.7, H^A-5), 3.77 (1 H, d[t], *J* 11.5 and 4.7, H^B-5), 3.86 (1 H, [t], *J* 5.1, H-2), 4.38 (1 H, [q], *J* 4.8 H-3), 4.46 (1 H, d, *J* 4.7, H-1); δ_C 25.9, 27.3, 27.9, 56.2, 58.9, 71.5, 74.7, 101.8, 109.0 (Found: C, 57.2; H, 8.7. $C_9H_{16}O_4$ requires C, 57.4; H, 8.6%).

Compound **28** was also prepared by reduction of the xanthate **32** (2.94 g, 10.0 mmol) with tributyltin hydride to give **28** (1.77 g, 94%), bp 48–50 °C/0.05 mmHg.

***trans*-2,2-Dimethyl-4,5-diphenyl-1,3-dioxolane 36**[37b,c] **and the *cis*-isomer 37.**[37a] These were prepared from the corresponding diols as described in the literature.

(4*R*,5*S*)-2,2-Dimethyl-4,5-diphenyl-*N*-valeryloxazolidine 38. A mixture of (1*S*,2*R*)-2-amino-1,2-diphenylethanol (2.13 g, 10.0 mmol), aluminium powder (1.20 g, 44.4 mmol) and a catalytic amount of acetyl chloride (20 mm^3) in a mixture of dry acetone (10 cm^3) and dry dichloromethane (20 cm^3) was stirred under argon for 20 h at room temperature.[38] Excess of aluminium powder was removed by filtration and washed with dichloromethane. The solvent was removed from the filtrate by evaporation to give the essentially pure oxazolidine **42** as a viscous oil (2.40 g, 95%), which was partially hydrolysed during chromatography on silica gel; δ_H 1.58 (3 H, s, Me), 1.81 (3 H, s,

Me), 2.85 (1 H, br s, NH), 4.94 (1 H, d, *J* 7.7, H-5), 5.38 (1 H, d, *J* 7.7, H-4), 6.86 (1 H, m, Ph), 6.95 (1 H, m, Ph), 7.05 (8 H, m, Ph); δ_C 26.2, 27.9, 66.7, 81.8, 94.9, 126.4, 126.7, 127.0, 127.4(1), 127.4(2), 127.8, 137.4, 140.0.

Crude **42** (1.26 g, 5.0 mmol) was dissolved in dry diethyl ether (10 cm^3) containing triethylamine (0.70 g, 6.9 mmol) and the solution was stirred and cooled in an ice–water-bath while valeryl chloride (0.70 g, 5.8 mmol) was added dropwise from a syringe. The mixture was stirred at room temperature for 12 h, and the precipitated amine hydrochloride was removed by filtration and washed with diethyl ether. The solvent was removed from the filtrate by evaporation and the residue was purified by chromatography, eluting with petroleum spirit–diethyl ether (from 10 : 1 then 5 : 1 then 5 : 2 v/v), to give **38** as an *oil* (1.24 g, 74%) which was crystallised from hexane at −10 °C, mp 88–89 °C; $[\alpha]_D^{20}$ +114.3 (*c* 1.05, $CHCl_3$). The ee was determined by HPLC to be >99.5%, using the OD column with hexane–isopropyl alcohol (99 : 1) as eluent (t_R 11.9 min); δ_H 0.74 (3 H, t, *J* 7.3 CH_2*Me*), 1.14 (2 H, m, CH_2), 1.45 (2 H, m, CH_2), 1.80 (3 H, s, Me), 1.91 [1 H, ddd, *J* 15.5, 8.6 and 6.3, H^ACHC(O)], 2.06 (3 H, s, Me), 2.17 [1 H, ddd, *J* 15.5, 9.7 and 6.3, H^BCHC(O)], 5.05 (1 H, d, *J* 6.3, H-4 or -5), 5.54 (1 H, d, *J* 6.3, H-5 or -4), 6.90 (1 H, m, Ph), 6.99 (1 H, m, Ph), 7.11 (8 H, m, Ph); δ_C 13.7, 22.2, 23.4, 25.9, 26.7, 35.4, 66.4, 80.1, 95.1, 126.8, 127.3, 127.4, 127.7; (2-C), 127.9, 135.4, 137.6, 171.1 (Found: C, 78.1; H, 8.2; N, 4.1. $C_{22}H_{27}NO_2$ requires C, 78.3; H, 8.1; N, 4.2%).

(4*S*,5*R*)-2,2-Dimethyl-4,5-diphenyl-*N*-valeryloxazolidine 39. This was obtained in the same way from (1*R*,2*S*)-2-amino-1,2-diphenylethanol, mp 88–89 °C; $[\alpha]_D^{20}$ −113.7 (*c* 1.10, $CHCl_3$), ee > 99.5%, t_R 16.4 min (Found: C, 78.4; H, 8.2; N, 4.1. $C_{22}H_{27}NO_2$ requires C, 78.3; H, 8.1; N, 4.2%).

(4*R*,5*R*)-2,2-Dimethyl-4,5-diphenyl-*N*-valeryloxazolidine 40. This was prepared from (1*R*,2*R*)-2-amino-1,2-diphenylethanol, itself prepared in an overall yield of 70% from (1*S*,2*R*)-2-amino-1,2-diphenylethanol according to the published method.[20] The acetonide was obtained as described above for the *cis*-isomer; δ_H 1.64 (3 H, s, Me), 1.65 (3 H, s, Me), 2.80 (1 H, br s, NH), 4.24 (1 H, d, *J* 8.6, H-4 or -5), 4.80 (1 H, d, *J* 8.6, H-5 or -4), 7.28 (10 H, m, Ph); δ_C 28.4(5), 28.4(7), 70.0, 85.9, 95.4, 126.2, 127.2, 127.6, 127.9, 128.3, 128.7, 137.7, 139.7.

This crude oxazolidine was acylated to give **40** as colourless needles, mp 75–76 °C; $[\alpha]_D^{20}$ +22.7 (*c* 1.78, $CHCl_3$), ee > 99.5%, determined by HPLC using the AD column and eluting with hexane–isopropyl alcohol (99 : 1, t_R 8.9 min); δ_H 0.70 (3 H, t, *J* 7.3, CH_2*Me*), 1.02 (2 H, m, CH_2), 1.26 (1 H, m, CH^AH), 1.45 (1 H, m, CH^BH), 1.61 [1 H, ddd, *J* 14.9, 8.7 and 5.8, H^ACHC(O)], 1.85 [1 H, ddd, *J* 14.9, 8.7 and 6.7, H^BCHC(O)], 1.89 (6 H, s, CMe_2), 4.59 (1 H, d, *J* 8.3, H-4), 4.85 (1 H, d, *J* 8.3, H-4), 7.10 (1 H, m, Ph), 7.20 (1 H, m, Ph), 7.33 (8 H, m, Ph); δ_C 13.7, 22.2, 24.7, 26.7 (2 C), 36.3, 70.2, 85.4, 96.7, 126.5, 126.7, 128.1, 128.5, 128.6, 129.1, 136.8, 138.9, 171.6 (Found: C, 78.0; H, 8.1; N, 4.1. $C_{22}H_{27}NO_2$ requires C, 78.3; H, 8.1; N, 4.2%).

Conditions for radical-chain epimerisation

Most reactions were carried out using one of the following three procedures.

Method A. A solution of the substrate (1.0 mmol) in dry octane (1.5 cm^3) containing collidine (7 mm^3, 0.10 mmol), DBPB (50% w/w in mineral oil; 34 mm^3, 0.05 mmol) and TBST (14 mm^3, 0.05 mmol) was stirred under argon and heated in an oil-bath, the temperature of which had been adjusted previously to 125 °C. The same amounts of DBPB and TBST were added after 1 h and the progress of the reaction was monitored by GLC for 2–3 h, until no further change occurred.

Method B. A solution of the substrate (1.0 mmol) in dry octane (1.5 cm^3) containing collidine (7 mm^3, 0.10 mmol), DBPB (50% w/w in mineral oil; 20 mm^3, 0.03 mmol) and TBST (9 mm^3, 0.03 mmol) was stirred under argon and heated under reflux in an oil-bath that had been pre-heated to 145–150 °C. The same amounts of DBPB and TBST were added after 30 min and again after 1 h; the total reaction time was 3 h. Before work-up, the reaction mixture was examined by NMR spectroscopy or GLC to determine the extent of isomerisation.

Method C. A solution of the substrate (1.0 mmol) in dry nonane (1.5 cm^3) containing collidine (7 mm^3, 0.10 mmol), di-*tert*-butyl peroxide (58 mm^3, 0.2 mmol) and TBST (9 mm^3, 0.03 mmol) was stirred under argon and heated under reflux in an oil-bath that had been pre-heated to 165–170 °C. The same amounts of DBPB and TBST were added after 30 min and again after 1 h; the total reaction time was 3 h. Before work-up, the reaction mixture was examined by NMR spectroscopy or GLC to determine the extent of isomerisation.

Results of epimerisation experiments

Epimerisation of the dioxolanes **3** was carried out under the conditions of method A, except that nonane was used as the solvent to avoid interference by octane in the GLC analysis. After 1 h, the *cis* : *trans* ratio reached 16 : 84 and this remained unchanged when further amounts of DBPB and TBST (5 mol% of each) were added and heating was continued. The epimerisation of **4** and of **5** was carried out using methods A and B, respectively.

Di-*O*-methyl-1,4 : 3,6-dianhydro-L-iditol 9 (isoidide dimethyl ether). An octane solution of di-*O*-methyl-1,4 : 3,6-dianhydro-D-glucitol **7** (174 mg, 1.0 mmol) was subjected to the conditions of method A. GLC analysis of the reaction mixture, using the BP20 column at 175 °C (t_R for **7**, **8** and **9** was 9.7, 10.9 and 8.7 min, respectively), showed the proportions of the ethers **7** : **8** : **9** to be 38.5 : 1.5 : 60.0. The *epimer* **9** was isolated as an oil by flash chromatography using petroleum spirit–diethyl ether (10 : 1) as eluent, $[\alpha]_D^{17}$ −8.0 (*c* 8.3, $CHCl_3$); δ_H 3.39 (6 H, s, 2 Me), 3.80–3.88 (6 H, m, H^{endo}-1,-6, H^{exo}-1,-6, H^{endo}-2,-5), 4.58 (2 H, s, H-3,-4); δ_C 57.2, 71.8, 84.8, 85.0 (Found: C, 54.9; H, 8.0. $C_8H_{14}O_4$ requires C, 55.2; H, 8.1%).

1,2 : 5,6-Di-*O*-isopropylidene-3-*O*-methyl-β-L-idofuranose 14. This was obtained in 32% conversion (NMR) by epimerisation of **13** (274 mg, 1.0 mol) under the conditions of method A. Isolation by flash chromatography using petroleum spirit–diethyl ether (10 : 1 then 5 : 1) as eluent gave **14** as a *clear oil* (70 mg, 25%), $[\alpha]_D^{20}$ −67.5 (*c* 0.85, $CHCl_3$); δ_H 1.32 (3 H, s, Me), 1.37 (3 H, s, Me), 1.45 (3 H, s, Me), 1.50 (3 H, s, Me), 3.36 (3 H, s, OMe), 3.62 (1 H, dd, *J* 8.1 and 7.6, H^A-6), 3.64 (1 H, d, *J* 3.9, H-3), 4.10 (1 H, dd, *J* 8.1 and 6.6, H^B-6), 4.17 (1 H, dd, *J* 8.1 and 3.9, H-4), 4.35 (1 H, ddd, *J* 8.1, 7.6 and 6.6, H-5), 4.57 (1 H, d, *J* 3.9, H-2), 5.97 (1H, d, *J* 3.9, H-1); δ_C 25.3, 26.3, 26.8, 26.9, 57.5, 65.8, 75.1, 81.3, 82.3, 84.9, 105.5, 109.9, 111.9 (Found: C, 57.1; H, 8.2. $C_{13}H_{22}O_6$ requires C, 56.9; H, 8.1%).

3-Deoxy-1,2 : 5,6-di-*O*-isopropylidene-β-L-*lyxo*-hexofuranose 16. Epimerisation of **15** (246 mg, 1.0 mmol) was carried out using method A, with the modification that further portions of TBST and DBPB (5 mol% of each) were added after 1 and 2 h. GLC analysis (BP20 column at 200 °C, t_R 10.6 min for **15** and 11.5 min for **16**) showed the final ratio **15** : **16** to be 68 : 32 and no evidence was found for the C-4 epimer. The *epimer* **16** (65 mg, 28%) was isolated by flash chromatography using petroleum spirit–diethyl ether (10 : 1 then 5 : 1) as eluent and then was recrystallised from hexane; mp 57–58 °C; $[\alpha]_D^{20}$ +22.5 (*c* 1.47, $CHCl_3$); δ_H 1.32 (3 H, s, Me), 1.37 (3 H, s, Me), 1.43 (3 H, s, Me), 1.52 (3 H, s, Me), 1.72 (1 H, ddd, *J* 13.3, 10.7 and

4.9, H^{exo}-3), 2.02 (1 H, dd, *J* 13.3 and 4.6, H^{endo}-3), 3.80 (1 H, dd, *J* 8.3 and 6.6, H-6), 4.02 (1 H, dd, *J* 8.3 and 6.9, H′-6), 4.13 (1 H, ddd, *J* 7.0, 6.6 and 5.3, H-5), 4.26 (1 H, ddd, *J* 10.7, 5.3 and 4.6, H-4), 4.73 (1 H, dd, *J* 4.9 and 3.7, H-2), 5.83 (1H, d, *J* 3.7, H-1); δ_C 25.5, 26.2, 26.3, 26.8, 34.6, 65.6, 76.8, 78.0, 80.3, 105.8, 109.8, 111.4 (Found: C, 59.0; H, 8.2. $C_{12}H_{20}O_5$ requires C, 59.0; H, 8.3%). For the D-enantiomer,[11b] mp 60–61 °C; $[\alpha]_D^{18}$ −24.7 (*c* 1.90, $CHCl_3$) have been reported.

Methyl 2,3 : 5,6-di-*O*-isopropylidene-β-L-gulofuranoside 18.[39] This was obtained from **17** using method B in 30% conversion (GLC, BPX5 column) at 170 °C, t_R11.4 min for **17** and 14.0 min for **18**. The epimer **18** was isolated by flash chromatography, using petroleum spirit–diethyl ether (10 : 1 then 5 : 1) as eluent, as a clear oil (66 mg, 24%) which was crystallised from hexane, mp 77–78.5 °C (lit.,[39] 76–77 °C); δ_H 1.28 (3 H, s, Me), 1.40 (3 H, s, Me), 1.45 (3 H, s, Me), 1.46 (3 H, s, Me), 3.37 (3 H, s, OMe), 3.71 (1 H, dd, *J* 8.4 and 7.1, H^A-6), 3.91 (1 H, dd, *J* 8.4 and 3.9, H-4), 4.20 (1 H, dd, *J* 8.4 and 6.5, H^B-6), 4.38 (1 H, ddd, *J* 8.4, 7.1 and 6.5, H-5), 4.57 (1 H, d, *J* 5.9, H-2), 4.64 (1 H, dd, *J* 5.9 and 3.9, H-3), 4.97 (1 H, s, H-1); δ_C 24.8, 25.3, 25.9, 26.8, 54.8, 66.0, 75.5, 79.8, 81.9, 85.1, 107.3, 109.7, 112.8. The structure was confirmed by single-crystal X-ray diffraction and is shown in Fig. 1.

Epimerisation of the *trans*-acetonide **21** to give the *cis*-isomer **22** (156 mg, 1.0 mmol) was carried out using method B; the *cis* : *trans* ratio at equilibrium was 95 : 5. Octane was removed by careful rotary evaporation, the residual oil was taken up in methanol (2 cm^3) and Amberlyst-15 acidic ion-exchange resin (15 mg) was added. The mixture was stirred overnight at room temperature, then filtered to remove the catalyst. Methanol was removed from the filtrate by evaporation, and recrystallisation of the residue from ethyl acetate gave *cis*-cyclohexane-1,2-diol **20** (98 mg, 85%), mp 100–101 °C, which showed ^1H and ^{13}C NMR spectra identical with those of the authentic compound.

Methyl 2,3-*O*-isopropylidene-4-*O*-methyl-β-D-lyxopyranoside 26. This was obtained in 30% conversion (NMR) by epimerisation of methyl 2,3-*O*-isopropylidene-4-*O*-methyl-β-D-xylopyranoside **25** (218 mg, 1.0 mmol) using method C. Isolation by flash chromatography using petroleum spirit–diethyl ether (10 : 1 then 5 : 1) as eluent gave **26** as a clear oil (55 mg, 25%) that still contained a small amount (2–3%) of **25**, δ_H 1.39 (3 H, s, Me), 1.56 (3 H, s, Me), 3.47 (3 H, s, OMe), 3.48 (3 H, s, OMe), 3.64 (1 H, [t], *J* 10.2, H^{ax}-5), 3.75 (1 H, ddd, *J* 10.0, 5.4 and 3.5, H-4), 3.90 (1 H, ddd, *J* 10.4, 5.4 and 0.9, H^{ax}-5), 3.99 (1 H, dd, *J* 6.0 and 4.6, H-2), 4.40 (1 H, d, *J* 4.6, H-1), 4.58 (1 H, ddd, *J* 6.0, 3.5 and 0.9, H-3); δ_C 25.7, 27.4, 56.6, 57.6, 60.7, 72.2, 73.3, 76.1, 102.0, 110.5 (Found: C, 55.2; H, 8.2. $C_{10}H_{18}O_5$ requires C, 55.0; H, 8.3%).

Methyl 4-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pentopyranoside 28. The epimerisation of **27** (188 mg, 1.0 mmol) was carried out using method B to give >98% conversion to **28** (by NMR). The latter was isolated as an oil (175 mg, 93%) by flash chromatography using petroleum spirit–diethyl ether (5 : 1 v/v) as eluent. It showed NMR spectra identical with those of the authentic compound, prepared as described above.

Methyl 4-deoxy-β-D-*erythro*-pentopyranoside 29. This was prepared by deprotection of **28**. Compound **28** (200 mg, 1.06 mmol) was stirred in methanol (3 cm^3) containing Amberlyst-15 (10 mg) for 20 h at room temperature. The resin was removed by filtration, and evaporation of the filtrate under reduced pressure gave essentially pure **29** (138 mg, 93%) as a viscous oil; $[\alpha]_D^{20}$ −95.5 (*c* 1.24, H_2O) {lit.,[40] $[\alpha]_D^{15}$ −95.9 (*c* 1.0, H_2O)}; δ_H (in CD_3OD) 1.25 (1 H, dq, *J* 13.0 and 4.7, H^A-4), 1.54 (1 H, ddd, *J* 13.0, 9.9 and 4.1, H^B-4), 3.02 (3 H, s, OMe), 3.20 (1 H, [t], *J* 3.2, H-2), 3.35 (2 H, m, H_2-5), 3.55 (1 H, ddd, *J* 9.9, 4.1 and 3.4, H-3), 4.22 (1 H, d, *J* 3.3, H-1); δ_C (in CD_3OD) 30.5, 55.6, 59.9, 67.1, 71.1, 103.4.

***trans*-2,2-Dimethyl-4,5-diphenyl-1,3-dioxolane 36.** This was obtained by epimerisation of the *cis*-isomer **37** (254 mg, 1.0 mmol) using method B, except that 2,4,6-tris(trifluoromethyl)thiophenol or pentafluorothiophenol was used as the catalyst and collidine was not used, because salt formation is essentially complete with these strongly acidic thiols. The solvent was removed by evaporation, and NMR analysis showed that conversion was complete (≥98%). The *trans*-isomer **36** (228 mg, 90%) was readily isolated by recrystallisation from petroleum spirit, mp 47–48 °C, (lit.,[37a] 46–48 °C); δ_H 1.69 (6 H, s, 2 Me), 4.76 (2 H, s, OCH), 7.20–7.33 (10 H, m, Ph); δ_C 27.2, 85.4, 109.4, 126.7, 128.2, 128.4, 136.8.

The *trans*-isomer **36** obtained from the above reaction was dissolved in methanol (5 cm^3) and Amberlyst-15 (10 mg) was added. The mixture was stirred under reflux for 6 h, the resin was removed by filtration, the solvent was removed from the filtrate under reduced pressure and the residue was recrystallised from dichloromethane–petroleum spirit to give *dl*-hydrobenzoin **35** as colourless crystals (180 mg, 84%). The mp (118–120 °C) and NMR spectra were identical with those of the commercially available (Aldrich) authentic compound.

(4*R*,5*R*)-2,2-Dimethyl-4,5-diphenyl-*N*-valeryloxazolidine 40. (4*R*,5*S*)-2,2-Dimethyl-4,5-diphenyl-*N*-valeryloxazolidine **38** (337 g, 1.0 mmol) was subjected to the conditions of method C, except that pentafluorothiophenol (6 mm^3, 0.05 mmol) was used as catalyst and collidine was absent; repeat additions of thiol were made after 20 and 40 min. After 2.5 h the ratio **38** : **40** was 27 : 73 (by NMR). Nonane was removed at room temperature under reduced pressure (0.02 mmHg) and **40** (235 mg, 70%) was isolated by flash chromatography, using petroleum spirit–diethyl ether (10 : 1 then 5 : 1 then 5 : 2) as eluent; the ee of the product was 91% [OD column, t_R 8.9 min using hexane–isopropyl alcohol (99 : 1) as eluent]. Recrystallisation from hexane gave enantiomerically pure **40** as *colourless needles*, mp 75–76 °C, $[\alpha]_D^{20}$ +22.5 (*c* 1.10, $CHCl_3$); δ_H 0.70 (3 H, t, *J* 7.3, Me), 1.02 (2 H, m, CH_2), 1.26 (1 H, m, CH^AH), 1.45 (1 H, m, CH^BH), 1.61 [1 H, ddd, *J* 14.9, 8.7 and 5.8, $H^ACHC(O)$], 1.85 [1 H, ddd, *J* 14.9, 8.7 and 6.7, $H^BCHC(O)$], 1.89 (6 H, s, CMe_2), 4.59 (1 H, d, *J* 8.3, H-4), 4.85 (1 H, d, *J* 8.3, H-4), 7.10 (1 H, m, Ph), 7.20 (1 H, m, Ph), 7.33 (8 H, m, Ph); δ_C 13.7, 22.2, 24.7, 26.7 (2-C), 36.3, 70.2, 85.4, 96.7, 126.5, 126.7, 128.1, 128.5, 128.6, 129.1, 136.8, 138.9, 171.6 (Found: C, 78.3; H, 8.1; N, 4.1. $C_{22}H_{27}NO_2$ requires C, 78.3; H, 8.1; N, 4.2%).

(4*S*,5*S*)-2,2-Dimethyl-4,5-diphenyl-*N*-valeryloxazolidine 41. This was produced by epimerisation of **39** following the procedure used to obtain **40**. Before recrystallisation, the product (240 mg, 71%) showed an ee of 92% [OD column, t_R 8.1 min using hexane–isopropyl alcohol (99 : 1) eluent]. The *enantiomerically pure product* showed mp 75–76 °C, $[\alpha]_D^{20}$ −22.7 (*c* 0.95, $CHCl_3$). The ^1H and ^{13}C NMR spectra were indistinguishable from those of **40** (Found: C, 78.2; H, 8.1; N, 4.1. $C_{22}H_{27}NO_2$ requires C, 78.3; H, 8.1; N, 4.2%).

X-Ray crystallography §

Data were collected on a Nicolet R3mV diffractometer at 20 °C using graphite-monochromated Mo-K_α radiation. Three standard reflections were monitored throughout the data collection and these showed no variation with time. The data were corrected for Lorentz and polarisation effects. The structures were solved by direct methods (SHELXS-86)[41] and developed using

§ CCDC reference number(s) 163544. See http://www.rsc.org/suppdata/p1/b1/b103558b/ for crystallographic files in .cif or other electronic format.

alternating cycles of least-squares refinement and difference-fourier synthesis (SHELXL-93).[42] Non-hydrogen atoms were refined anisotropically, while hydrogen atoms were placed in idealised positions and assigned a common isotropic thermal parameter.

Crystal data for methyl 2,3 : 5,6-di-*O*-isopropylidene-β-L-gulofuranoside 18. $C_{13}H_{22}O_6$, M = 274.3, orthorhombic, space group $P2_12_12_1$, a = 5.371(1), b = 10.704(2), c = 25.652(5) Å, V = 1474 Å^3 (by least-squares refinement of diffractometer angles for 28 reflections in the range $17 < 2\theta < 26°$, λ = 0.71073 Å), Z = 4, $F(000)$ = 592, D_c = 1.24 g cm^{-3}, μ(Mo-K$_\alpha$) = 0.9 cm^{-1}, colourless needle 0.76 × 0.22 × 0.16 mm. Full matrix least-squares refinement on 173 parameters gave R = 0.0483 (R_w = 0.1230) for 1154 independent reflections [$I > 2\sigma(I)$] and R = 0.0691 (R_w = 0.1468) for all 1534 independent reflections in the range $5 \leq 2\theta \leq 50°$. The final electron density map was featureless with the largest peak 0.21 e Å^{-3}.

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