Dispiroketals: A new functional group for organic synthesis

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1 Introduction

Occasionally in science observations are made which open up whole new areas of research. In 1991 we were fortunate enough to recognise one of these opportunities which has led us into some fascinating and useful new chemistry. The work centres on 1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecanes, 'dispiroketals', as an easily decorated, well-defined and rigid skeletal motif which can be used for a wide range of synthetic applications (**Figure 1**).

In addition to this appealing architecture, the benefits of the dispiroketal unit include its relatively low molecular weight, the potential for a wide range of substitution patterns, and its easy preparation. The key feature, however, is the control that can be achieved at the two spiro centres during dispiroketal formation owing to the operation of multiple

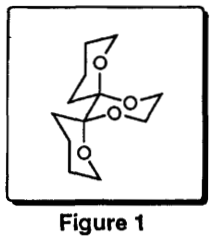
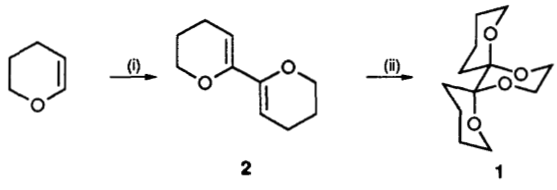


Figure 1

anomeric effects[1,2] favouring the formation of a single diastereoisomeric product.

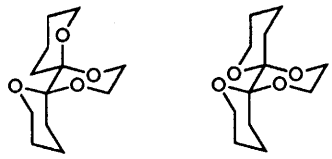
Of the several routes to these molecules that have been investigated the most convenient turns out to be the reaction of bis-dihydropyrans with vicinal diols. Preparation of the parent system **1**, for example, is achieved in good yield by reaction of bis-dihydropyran **2** with ethylene glycol in refluxing toluene containing catalytic camphorsulfonic acid (CSA) (**Scheme 1**).[3] Although compound **2** and a limited range of similar derivatives had in fact been prepared previously,[4] they had not been utilized as reagents for organic synthesis. We find that the bis-dihydropyran **2** can be conveniently obtained in excellent yield by oxidative homocoupling of dihydropyran itself using *tert*-butyllithium to form the anion followed by treatment with catalytic $PdCl_2(PPh_3)_2$ and $CuCl_2$ in THF at 0 °C (**Scheme 1**). This reaction can be scaled up easily and we routinely run reactions on a 100 g scale.

X-Ray crystal structure determination of **1** confirmed the identity of the product of this highly diastereoselective reaction; none of the alternative diastereoisomers **3** or **4**, where anomeric



Reagents: (i) Bu^tLi (1 eq.), THF, followed by addition of $PdCl_2(PPh_3)_2$ (cat.), $CuCl_2$ (1 eq.), 0 °C, 80%; (ii) Ethylene glycol (5 eq.), PhMe, CSA (cat.), reflux, 73%.

Scheme 1



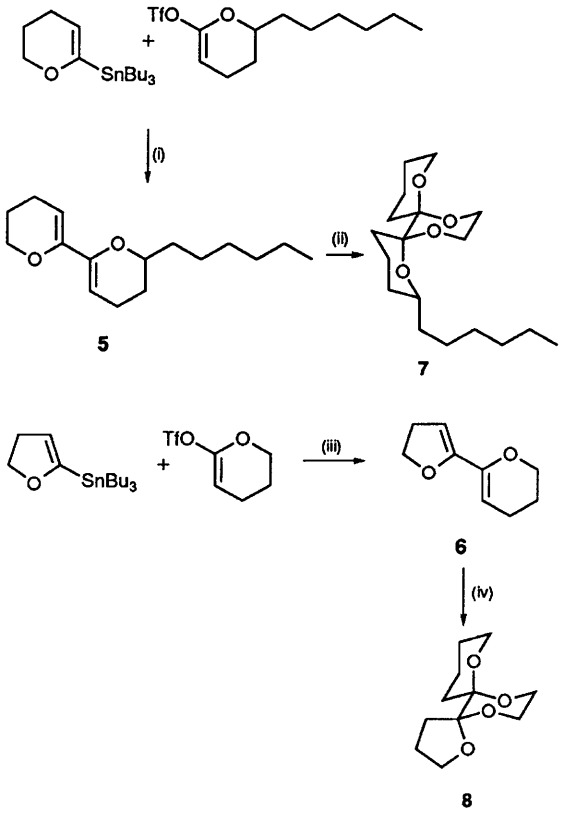
3 4

Figure 2

stabilization at the spiro centres is decreased, were observed in the reaction (**Figure 2**).

Pure bis-dihydropyran **2** is a white and relatively stable crystalline solid. It is, however, sensitive to hydrolysis as would be expected of an enol ether and is best stored in the long term under an inert atmosphere at −10 °C. It may also be stored in toluene solution containing trace amounts of galvinoxyl as a stabilizer for long periods of time at room temperature without noticeable decomposition.

In the above preparation of **2** we relied upon an oxidative homocoupling reaction of 2-lithio dihydropyran anions. However, we can also prepare unsymmetrical dienes by heterocoupling reactions using vinyl stannanes and enol triflates. For example, the dienes **5** and **6** are obtained using $Pd(TFP)_4$ to effect the coupling (**Scheme 2**).



Reagents: (i) $Pd_2(dba)_3$ (0.01 eq.), trifurylphosphine (0.04 eq.), LiCl (1 eq.), NMP, r.t., slow addition of triflate, 51%; (ii) ethylene glycol (10 eq.), CSA (cat.), PhMe, reflux, 75%; (iii) $Pd_2(dba)_3$ (0.01 eq.), trifurylphosphine (0.04 eq.), LiCl (1 eq.), NMP, r.t., slow addition of triflate, 40%; (iv) ethylene glycol (10 eq.), CSA (cat.), PhMe, reflux, 10%.

Scheme 2

The diene **5** was stable and reacts with ethylene glycol to give the corresponding dispiroketal **7** in 75% yield. On the other hand **6** was unstable and reacts only poorly with ethylene glycol to afford the spiroketal **8** (**Scheme 2**).

This review will encompass the applications of these dispiroketals in organic synthesis to date and discuss some new chemistry of these systems which has not been previously reported.

2 Vicinal diol protection

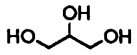
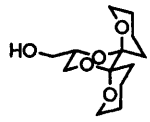
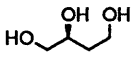
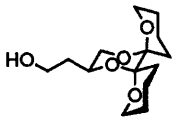
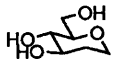
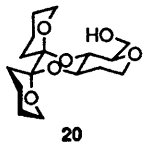
There are a number of useful ways of achieving 1,2-diol protection[5] but there is a need for new methods which afford higher levels of selectivity or stability. Armed with the basic dispiroketal formation described above we considered the more general use of **2** as an agent for protecting vicinal diols as dispiroketals. Indeed we found that the bis-dihydropyran **2** reacted with glycerol **9** in toluene containing catalytic acid to give **15** as essentially the only product of the reaction. Pleasingly, other diols and dithiols **10**–**14** were equally successful and gave the corresponding dispiroketal ('dispoke') protected products **16** to **20** (**Table 1**).

These results illustrate the potential of dispoke protection. **Entry 1** shows that bis-dihydropyran reacts with glycerol to give a single diastereoisomer. This product has full anomeric control at the spiro centres, but the selectivity does not stop there; additionally, the hydroxymethylene side-chain has adopted an equatorial orientation. As with the control of the anomeric centres, this presumably reflects the thermodynamic control that is operating in the reaction giving the most stable product rather than the alternative, where the side-chain would be in the more congested axial position.

Entries 1, 5 and 6 indicate that where the possibility of 1,2- and 1,3-protection patterns co-exist, the preference for six-membered ring formation enables dispoke to choose the former. Literature methods for the protection of the vicinal diol component in (*S*)-butane 1,2,4-triol **13** are less selective, giving for example a ratio of only 9:1 in favour of the 1,2 product when acetonide protection is employed.[10] Once again dispoke protection gives, in almost quantitative yield, a single diastereoisomer. This result represents an example of *chirality multiplication through the use of anomeric effects* since the starting material which contained one stereogenic centre has been transformed to a product which possesses three. When 1,3-diol protection is the only option, as with propane-1,3-diol itself, we find that the corresponding dispoke adduct is formed but in only 15% yield,[3] illustrating the instability of such a dispoke product.

The natural extension of these favourable results was to try dispoke protection on carbohydrates and **Entry 6** of **Table 1** begins to explore this; we see that dispoke meets the challenge since the 1,2-diequatorial diol has reacted, to give a stable dispoke product, in preference to substitution on the normally more reactive primary hydroxy group.

Table 1

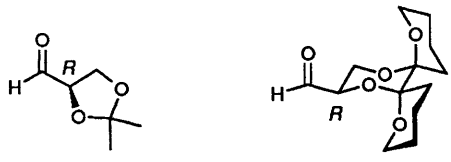
Entry	Diol	Dispoke Product	Yield (%)	Ref.
1			98	3
	9	**15**		
2			99	6
	10	**16**		
3			64	7
	11	**17**		
4			64	3
	12	**18**		
5			72	8
	13	**19**		
6			64	9
	14	**20**		

This was clearly a major growth area in the project and the ensuing work is described later (see Sections 9 and 10).

3 Use of glyceraldehyde dispiroketals

3.1 Preparation

D-Glyceraldehyde, especially as its isopropylidine derivative **21** (**Figure 3**), is an important and widely used three-carbon chiral building block for organic synthesis. It does, however, suffer some limitations as it is prone to racemization, polymerization, and hydrate formation. Moreover, the stereocontrolled addition of carbon nucleophiles, especially methyl groups, to **21** is disappointing. While good selectivity can be achieved using principles of chelation control to afford *syn* products, a new method is required to achieve an *anti* stereochemical relationship. We therefore sought to assess the reactivity towards carbon nucleophiles of our dispiroketal derivative, **22** (shown in **Figure 3**, where the wedging on the pyran ring indicates enantiomeric enrichment) against that of [2,3]-*O*-isopropylidene D-glyceraldehyde, **21**.[8]

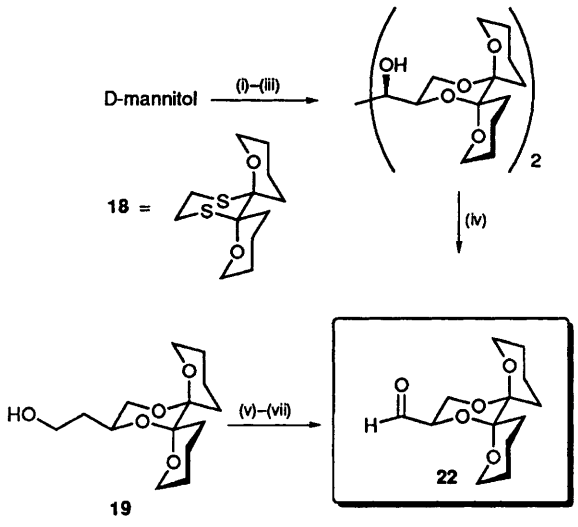


21 **22**

Figure 3

It was anticipated that **22** would be more configurationally stable than **21** owing to the locking of the aldehyde in an equatorial position. In addition **22** should be less prone to polymerization because of the bulk of the protecting group. We hoped that since **22** contains three stereogenic centres, compared with one in **21**, improved facial selectivity might be observed during carbonyl group addition reactions.

The preparation of **22** can be achieved by two routes. The first of these uses inexpensive mannitol as a starting material but involves an inelegant acylation step to facilitate purification (**Scheme 3**). This route is interesting because it demonstrates the use of the dithiadioxadispiroketal **18** (**Table 1**) to



Reagents: (i) Dithiadioxadispiroketal **18**, MeI, $NaHCO_3$, MeCN; (ii) Ac_2O, pyr; (iii) NaOMe, MeOH (40% over three steps); (iv) $NaIO_4$, H_2O, Et_2O, 99%; (v) TsCl (1 eq.), pyr, 92%; (vi) $KOBu^t$ (1.2 eq.), DMSO, 83%; (vii) O_3, PPh_3, 92%

Scheme 3

transfer the dispiro function to mannitol in the presence of methyl iodide under basic conditions. The second route utilized the dispoke-protected (*S*)-butane-1,2,4-triol derivative **19** discussed earlier. This was readily converted into **22** via tosylation, elimination, and ozonolysis (**Scheme 3**).

As expected, the dispiroketal aldehyde **22** formed in this way was far less volatile than **21** and was very much more stable. Indeed samples have been stored at 4 °C for over one year without noticeable decomposition. Compound **22** does show a tendency to hydrate, but the process may be reversed by Dean–Stark removal of water with toluene prior to use in synthesis.

3.2 Reactions with carbon nucleophiles

We then turned our attention to the addition of carbon nucleophiles to **22** to examine the selectivity for the preferential formation of the *anti versus* the *syn* product.[8] In **Table 2** we compare the results obtained for additions to **22** with corresponding literature results for additions to **21**.

The results demonstrate the ability of dispoke protection to influence the stereochemistry of the product. **Entries 1, 3, 4,** and **6** show a consistent *anti* selectivity for methylation, which seems to be independent of reagent choice. The titanium reagent (**Entry 7**) gives excellent *anti* selectivity, comparable to that achieved with dibenzyl or benzyl-*tert*-butyldimethylsilyl ethers of glyceraldehyde.[11,12] Addition of vinyl magnesium bromide (**Entry 8**) gives good *anti* selectivity in contrast to previous reported work.[13] Interestingly, ethynyl Grignard addition proceeds with opposite selectivity when glyceraldehyde is protected as the dispoke derivative **22** compared to isopropylidene glyceraldehyde **21** where a slight *syn* preference was observed.[14] It can be seen that the addition of most reagents to **22** leads to *anti* adducts as predicted by both Felkin's non-chelation controlled model[15,16] and the β or α, β coordination models proposed for **21**.[17] In the dispoke derivative **22** the rigidly defined geometry of the dioxane ring is likely to negate the possibility of β-coordination, due to greatly

Table 2

Entry	Reagent	Conditions (solvent, temp., time, method[g,h])	Yield (%)[a]	*anti/syn* Ratio	Lit. *anti/syn* Ratio[b]
1	MeLi	Et_2O/THF, −78 °C, 22 h, A	82	82:18[c]	60:40
2	MeLi	Et_2O/THF, 25 °C, 12 h, A	78	67:33[c]	—
3	MeMgCl	THF, −78 °C, 24 h, A	92	81:19[c]	—
4	MeMgBr	THF, −78 °C, 22 h, A	62	79:21[c]	73:27
5	$Me_2CuLiMe_2S$	Et_2O, −78 °C, 20 h, B	69	12:88[c]	18:82
6	$MeCuMgBrMe_2S$	Et_2O, −78 °C, 20 h, B	85	82:18[c]	65:35
7	$MeTi(OPr^i)_3$	Et_2O/C_6H_{14}, −40 °C, 20 h, B	87	93:7[c]	70:30
8	CH_2=CHMgBr	THF, −78 °C, 4 h, A	56	91:9[d]	60:40[f]
9	$(CH_2$=$CH)_2Zn$	THF, 25 °C, 48 h, A	84	67:33[d]	—
10	EthynylMgBr	THF, −78 °C, 5 h, A	65	89:11[d]	44:56
11	AllylMgBr	THF, −78 °C, 18 h, A	89	68:32[e]	60:40
12	EtMgBr	THF, −78 °C, 6 h, A	62	73:27[a]	—

[a]Yield corrected for unreacted starting material. [b]Literature ratio obtained for addition to 2,3-*O*-isopropylidene-D-glyceraldehyde. [c]Yield and ratio by gas chromatography of crude material. [d]Yield of isolated product, ratio by high field NMR. [e]Yield of isolated product, ratio by gas chromatography on acetylated product. [f]Vinyl magnesium chloride at 20–60 °C. [g]Method A: To a stirred solution of **22** (1 eq.), in the indicated solvent (Table 2), cooled to −78 °C, under argon, was added, dropwise, a solution of the organometallic reagent (10–20 eq.) and the resulting mixture was kept at −78 °C for 5–24 h. The reaction was quenched at −78 °C by addition of saturated aqueous ammonium chloride solution. Ether was added and the organic phase washed twice with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude compounds were purified by flash chromatography (eluent: ether/petroleum ether, 1:1). [h]Method B: To a stirred solution of the organometallic reagent (10–20 eq.) cooled to −78 °C under argon was added dropwise a solution of **22** (1 eq.), and the resulting mixture was stirred at −78 °C for 5–24 h. The isolation procedure was the same as that given above for Method A.

increased interatomic distances between the carbonyl oxygen and the β-oxygen.

Molecular modelling studies (MM2)[18] indicate that although axially disposed δ oxygen atoms could theoretically form a chelated complex this would involve considerable strain. This suggests that the *anti* selectivity shown by the aldehyde **22** is mainly due to the large steric bulk of the dispiroketal group.

3.3 Miscellaneous reactions

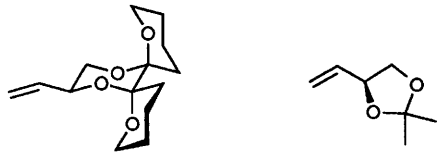
During the above studies we observed reactions which have not been previously published but which might be of some general interest. For example, reduction of **22** with sodium borohydride yields the corresponding alcohol **15** (**Figure 4**, see also **Table 1**).[19] This alcohol is synthetically equivalent to solketal **23** (isopropylidene glycerol) (**Figure 4**). However, whereas enantiopure solketal needs to be stored at low temperatures or used immediately, to prevent racemization through rapid acetonide migration, the spiroketal derivative **15** is stable (>1 year) at room temperature.

15 **23**

Figure 4

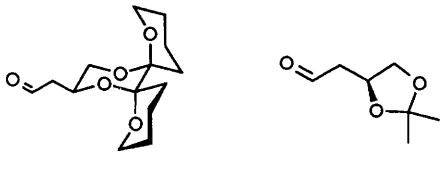
We also find that derivative **24** is stable and involatile whereas by contrast **25** is extremely volatile and difficult to handle (**Figure 5**).

Compound **26** shows superior stability towards β-elimination over the corresponding compound **27** (**Figure 6**); it is readily obtained from **19** (**Table 1**) by oxidation with tetra-n-propylammonium perruthenate (TPAP).[20]



24 **25**

Figure 5



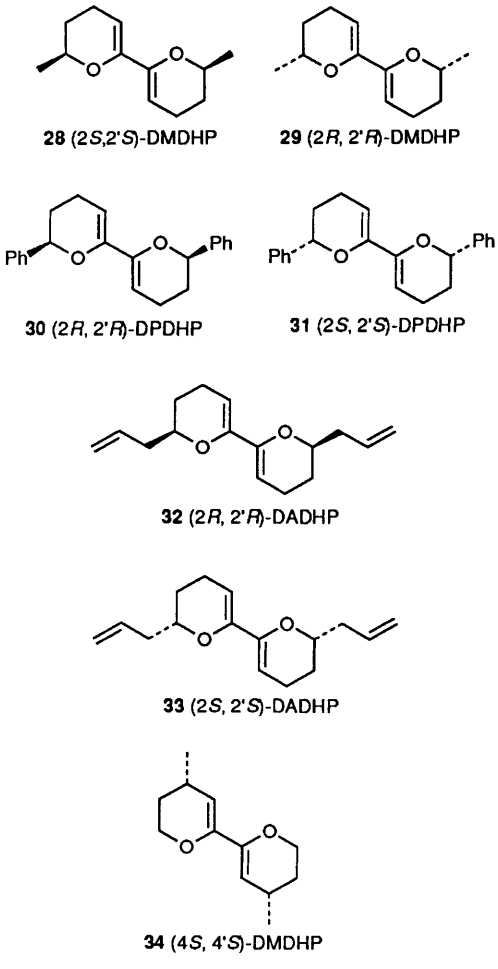
26 **27**

Figure 6

4 Preparation of chiral bis-dihydropyrans

In order to develop the chemistry of dispiroketals further we reasoned that the introduction of substituents on the diene would give us the opportunity to use chirality to achieve further control. During formation of dispiroketals, such substituents should have a preference for the equatorial orientation in the product; if these substituted centres were homochiral, this preference for the equatorial position should constrain the chirality at the two dispiroketal anomeric centres, leading to formation of a single diastereoisomeric product. An additional advantage is that the appended side-chains may facilitate alternative methods for removal of the dispiroketal protection which must be accomplished after the desired synthetic manipulations have been achieved. We therefore devised synthetic routes to homochiral bis-dihydropyrans such as **28–34** (**Figure 7**).

The shorthand notation which we use for these compounds relates to the configuration and substitution in the bis-dihydropyrans (DHPs). Thus for **28**, **29**, and **34**, 'DMDHP' refers to dimethyl bis-dihydropyran. The diphenyl substitution in **30** and **31** is indicated by 'DP' and diallyl substitution, as in **32** and **33**, by 'DA', *etc.* The phenyl group in **30** and



28 (2*S*,2'*S*)-DMDHP **29** (2*R*, 2'*R*)-DMDHP

30 (2*R*, 2'*R*)-DPDHP **31** (2*S*, 2'*S*)-DPDHP

32 (2*R*, 2'*R*)-DADHP

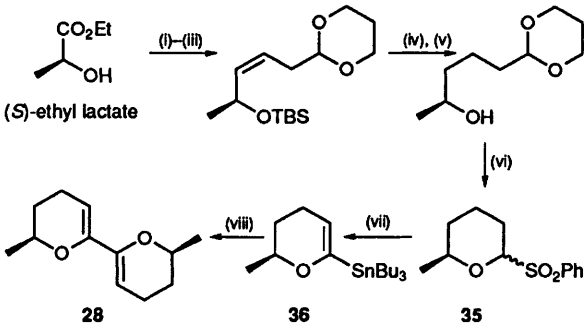
33 (2*S*, 2'*S*)-DADHP

34 (4*S*, 4'*S*)-DMDHP

Figure 7

31 was placed in this position to make possible later removal of the corresponding dispoke derivative by a hydrogenolysis or benzylic cleavage procedure. Likewise in 32 and 33 the allyl functional group was chosen as a chiral controlling substituent which could also facilitate removal of the dispoke adduct by an ozonolysis/β-elimination pathway (Section 9, **Scheme 40**).

Several routes to these homochiral bis-dihydropyrans have been developed. For example, compound **28** was synthesized starting from (*S*)-ethyl lactate as the initial source of chirality.[21] This was converted into an intermediate phenylsulfonyl-tetrahydropyran **35** (**Scheme 4**) since we had shown previously[22] that use of phenylsulfones of this type was an attractive way to stabilize anions at anomeric centres. Indeed anion formation and reaction with tributyltin chloride gave vinyl stannane **36** after spontaneous elimination of benzenesulfinic acid on warming. Transmetallation and oxidative cross-coupling produced the desired diene **28** (**Scheme 4**).



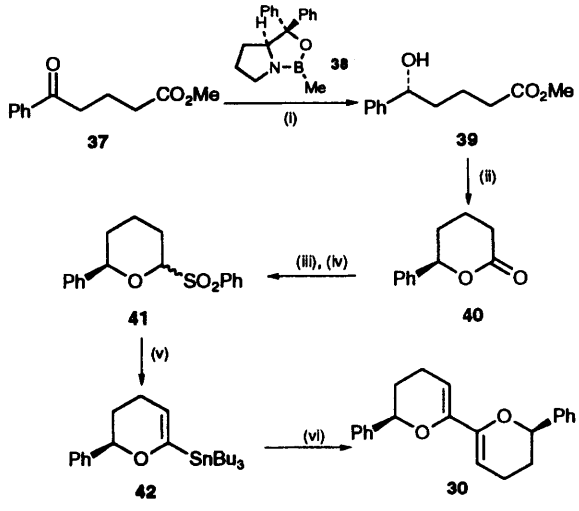
Reagents: (i) TBSCl, Imidazole, 98%; (ii) DIBAL-H, DCM, –78 °C; (iii) 2-(1,3-dioxan-2-yl)ethyltriphenylphosphonium bromide, KHMDS, THF, 0 °C, 79% over two steps; (iv) H_2/PtO_2, EtOAc, 98%; (v) TBAF, THF, 94%; (vi) $PhSO_2H$, $CaCl_2$, DCM, 89%; (vii) Bu^nLi, THF, –78 °C; then Bu_3SnCl, –20 °C to r.t.; then DIPEA, $CHCl_3$, 70 °C, 75%; (viii) Bu^nLi, THF, –78 °C; 6 mol% $PdCl_2(MeCN)_2$, $CuCl_2$, –78 to 0 °C; NH_4Cl/NH_3, 60%.

Scheme 4

The opposite enantiomer **29** was available by the equivalent route starting from (*R*)-methyl lactate.

The route to (2*R*, 2′*R*)-DPDHP[23] **30** starts from the known keto ester **37** (**Scheme 5**) which is obtained either by addition of phenylmagnesium bromide to glutaric anhydride[24] and subsequent esterification, or more conventionally by Friedel–Crafts acylation of benzene with glutaric anhydride,[25] again followed by esterification.

Asymmetric reduction of the prochiral carbonyl group in **37** was investigated using a variety of methods the best of which turned out to be the use of oxazaborolidines.[26] Application of the catalytic system consisting of borane methyl sulfide and the oxazaborolidine **38** gave the hydroxyester **39** in 83% e.e., which upon lactonization gave **40**. This was converted into the sulfone **41** by reduction with



Reagents: (i) 0.7 eq. BMS, 10 mol% **38**, THF, –15 °C; (ii) 10 mol% CSA, DCM, 90% over two steps; (iii) DIBAL-H, PhMe, –78 °C; (iv) $PhSO_2H$, $CaCl_2$, DCM, 75-88% over two steps; (v) Bu^nLi, THF, –78 °C; then Bu_3SnCl, –78 °C to r.t.; then DIPEA, $CHCl_3$, 70 °C, 2 h, 72%; (vi) Bu^nLi, THF, –78 °C then $PdCl_2(MeCN)_2$ (cat.), $CuCl_2$, –78 to 0 °C, NH_4Cl/NH_3, 60%.

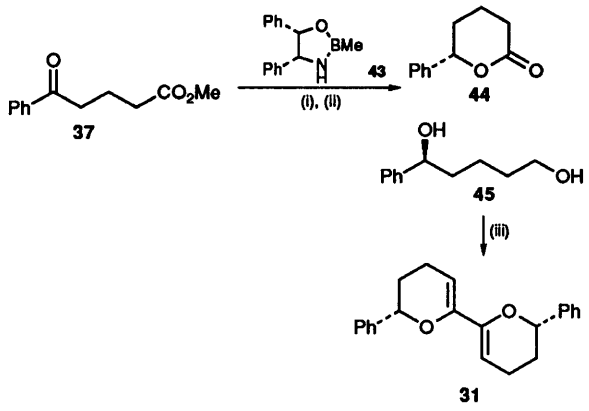
Scheme 5

DIBAL-H and treatment with benzenesulfinic acid in the presence of calcium chloride.[27] This material was then transformed into diene **30** via the vinyl stannane **42** and oxidative homocoupling route previously established (**Scheme 5**).

Based upon a statistical distribution of coupled products and having started from the 83% enantiomerically enriched compound **42**, the e.e. of **30** was estimated to be 98%, assuming equal rates of coupling of *R* to *R*, *S* to *S*, and *R* to *S*. The optical enhancement in the formation of **30** is at the cost of formation of some meso product which is produced by coupling of the major (*R*)-configured stannane with the minor epimeric (*S*)-configured material.

The prohibitive cost of the enantiomer of the catalyst **38** required for the synthesis of the enantiomeric (2*S*, 2′*S*)-DPDHP **31** caused us to investigate an alternative. It was found that the oxazaborolidine **43**[28] gave satisfactory results, affording **44** with an e.e. of 87%, although some over-reduction to the diol **45** was also observed. It was also found that the lactone **44** could be recrystallized to improve the e.e. to 99.1% as indicated by chiral phase GC analysis. This was converted into **31** following the usual strategy (**Scheme 6**).[23]

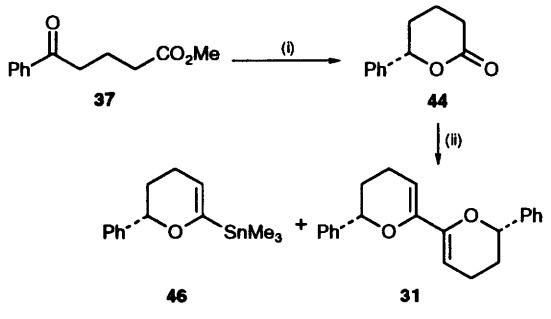
A second, shorter route to (2*S*, 2′*S*)-DPDHP **31** has been subsequently developed.[29] Reduction of ketoester **37** with (–)-*B*-chlorodiisopino-campheylborane (–)-DIP-Cl, a stoichiometric asymmetric reducing agent,[30] saponification to assist purification, and reacidification with concommitant lactonization[31] affords **44** directly, in 88% yield with an e.e. of 89%. Chromatographic purification is avoided, as the product is then recrystallized to



Reagents: (i) 0.7 eq. BMS, 10 mol% **43**, THF, r.t., 1 h. (ii) CSA, DCM, **44** 47%, **45** 11%. (iii) reagents and conditions as **Scheme 5**.

Scheme 6

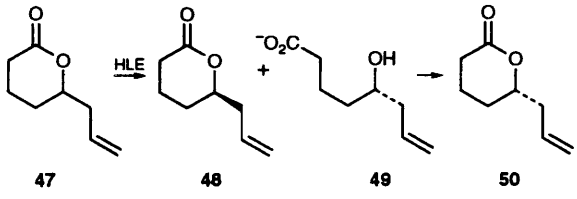
enhance its optical purity as before. The lactone is then converted into its enol triflate by deprotonation with lithium hexamethyldisilazide and treatment with *N*-phenyltriflimide. To the crude product is added hexamethylditin, lithium chloride, and catalytic tetrakis(triphenylphosphine) palladium(o), conditions employed by Kocienski to prepare vinyl stannanes from δ-lactones.[32] However, by employing only 0.5 equivalents of hexamethylditin we then have, theoretically, a 1:1 mixture of vinyl stannane **46** and unreacted enol triflate, which undergoes a Stille-type coupling[33] affording (2*S*, 2′*S*)-DPDHP **31** directly. In practice, enol triflate formation is not quantitative, hence **31** is obtained in 58% yield along with 19% of vinyl stannane **46** (**Scheme 7**).



Reagents: (i) (–)-DIP-Cl, THF, –15 °C; NaOH (aq.) then neutralise (conc. HCl); CSA (cat.), PhMe, 88%, 89% e.e.; (ii) LHMDS, DMPU, THF, –78 °C; then $PhN(Tf)_2$, –78 to 0 °C; then 3 mol% $Pd(PPh_3)_4$, Me_6Sn_2 (0.5 eq.), LiCl (6 eq.), reflux, 16 h, **31** 58%, **46** 19%.

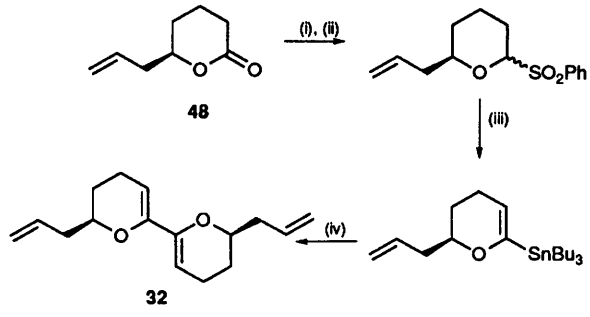
Scheme 7

The C_2-symmetric allyl substituted bis-dihydropyrans **32** and **33** were accessed by a different process, involving a lipase resolution, since the asymmetric reduction methods described above are not applicable to systems where there is relatively little differentiation in the substitution of the prochiral substrates. The racemic allyl lactone **47**, readily available from cyclopentanone,[34] was hydrolysed in pH 7.2 buffer with Hog Liver Esterase (HLE) by pH stat-controlled addition of 2M sodium hydroxide to give lactone **48** and the corresponding hydroxy acid salt **49**. The reaction was allowed to progress until hydrolysis was 60% complete. Extraction with ether afforded pure **48** while acidification of **49** and lactonisation gave the enantiomeric lactone **50** (**Scheme 8**).



Scheme 8

The lactones **48** and **50** obtained by this process were shown by chiral GC to have enantiomeric excesses of 90.3 and 51.2% respectively. The lactones were transformed into bis-dihydropyrans via what was by then our standard route, shown for diene **32** in **Scheme 9**.[35]

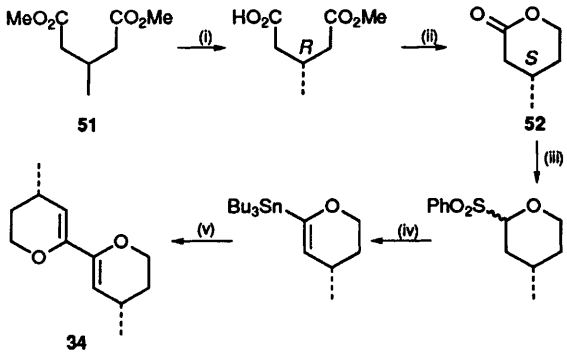


Reagents: (i) DIBAL-H, PhMe, –78 °C; (ii) $PhSO_2H$, $CaCl_2$, DCM, r.t., 83% over two steps; (iii) Bu^nLi, THF, –78 °C; then Bu_3SnCl, –78 to –10 °C; then DIPEA, $CHCl_3$, 70 °C, 55%; (iv) Bu^nLi, THF, –78 °C; then $PdCl_2(MeCN)_2$ (cat.), $CuCl_2$, NH_4Cl/NH_3, 30–75%.

Scheme 9

For the preparation of the C_2-symmetric (4*S*, 4′*S*)-DMDHP **34** we used another enzymatic procedure involving hydrolysis of meso diester **51** since this allows the preparation of material on a large-scale and in excellent optical purity. The process is outlined in **Scheme 10**.

This route provides the lactone **52** in 92% e.e. Conversion into **34** using the previously established chemistry gave material with an e.e. greater than 99%, the homocoupling process again enhancing the e.e. of the bis-dihydropyran with respect to the starting stannane at the cost of the production of 7% of the meso diene.[36]



Reagents: (i) PLE, phosphate buffer (10% MeOH), pH 7, 0 °C, 5 d, 90%; (ii) LiOH, MeOH, then $LiBH_4$, THF, 67%; (iii) DIBAL-H, PhMe, –78 °C, then $PhSO_2H$, $CaCl_2$, DCM, r.t., 88%; (iv) Bu^nLi, THF, –78 °C, then Bu_3SnCl, –78 to 0 °C, then DIPEA, $CHCl_3$, 70 °C, 70%; (v) Bu^nLi, THF, –78 °C; then $PdCl_2(MeCN)_2$, $CuCl_2$, NH_4Cl/NH_3, 50%.

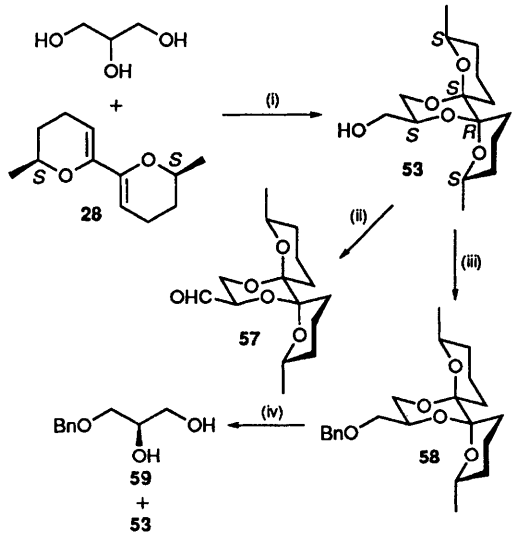
Scheme 10

5 Enantioselective protection of vicinal diols

The incorporation of chirality in the bis-dihydropyrans provides an additional control element over dispiroketal formation. We have made use of this in a new concept which accomplishes a simultaneous protection and enantioselective desymmetrization of meso polyols.

5.1 Reaction with glycerol

Reaction of glycerol with the C_2-symmetric homochiral bis-dihydropyran **28**, in the presence of catalytic camphorsulfonic acid in refluxing toluene, proceeded with complete diastereoselectivity to give the dispiroketal **53** in excellent yield (**Scheme 11**).[21(a)]



Reagents: (i) CSA (cat.), PhMe, reflux, 96%; (ii) DCM, 4 Å mol sieves, 30 min.; then PCC, DCM, 61%; (iii) NaH, BnBr, TBAI, THF, 85%; (iv) glycerol, CSA (cat.), PhMe, reflux, 83%.

Scheme 11

This enantioselective desymmetrization of glycerol is explained as follows. The absolute stereochemistry of the spiro centres (*S*,*R*) is controlled by a combination of multiple anomeric effects and the absolute configuration at the site of substitution of the methyl groups, which adopt a preferred equatorial orientation. Due to steric effects, the hydroxymethylene substituent on the dioxane ring also adopts an equatorial arrangement under thermodynamic control. These factors result in the exclusive formation of the glycerol dispoke derivative **53** with (*S*)-stereochemistry at the C-(2) position of the glycerol unit.

The alternative diastereoisomers **54**, **55** and **56** which could be theoretically formed and still possess full anomeric stabilization are not observed (**Figure 8**).

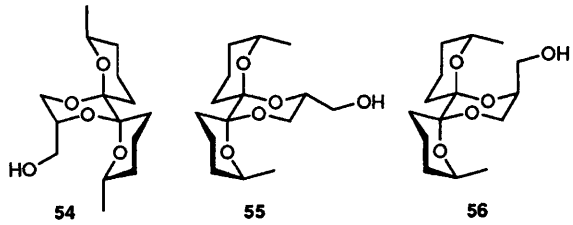
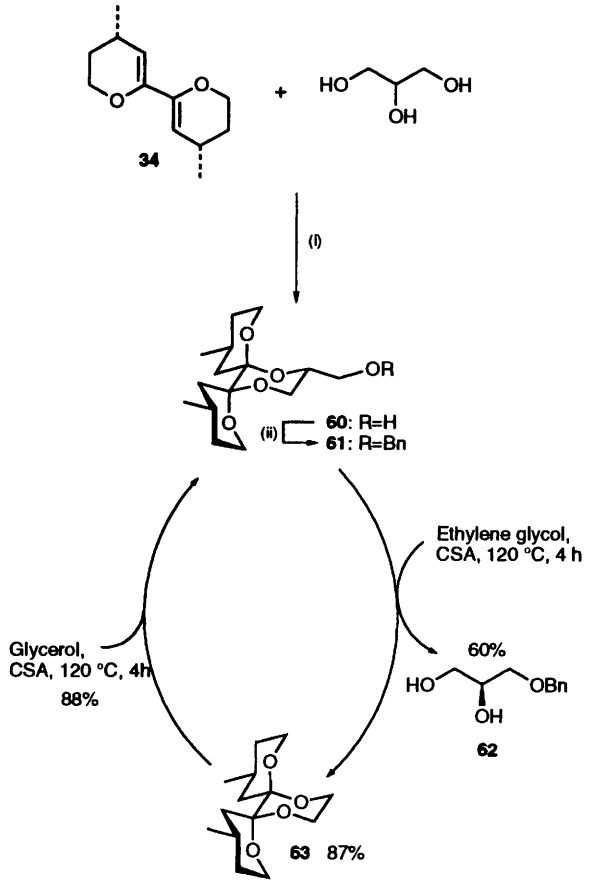


Figure 8

All these alternative products are obviously higher in energy relative to **53** owing to severe 1,3-interactions as a result of the axial substituents. The formation of compound **53** represents, therefore, an enantioselective vicinal diol protection of glycerol. Oxidation of **53** with pyridinium chlorochromate gives the enantiomerically pure aldehyde **57**.[21(a)]

The aldehyde **57** is synthetically equivalent to (*R*)-isopropylidene glyceraldehyde **21** as discussed earlier (Section 3.1). We therefore have a process for the preparation of useful three-carbon homochiral building blocks from a symmetrical starting material in just two synthetic steps.

Scheme 11 also shows the conversion of **53** into its corresponding benzyl ether **58**. We find that treatment of **58** with neat glycerol and catalytic CSA gives (*R*)-1-*O*-benzyl glycerol **59** in 83% yield, together with the returned dispiroketal adduct of glycerol **53** as a single diastereomer in high yield.[21(a)] Together these reactions constitute a very efficient recycling process. We believe this new method for the preparation of dissymmetric glycerol derivatives is potentially very useful, especially as the reaction appears to be general and is not restricted to glycerol (see Sections 5.2 and 5.3). Obviously should the enantiomeric materials be required for a particular synthesis the antipodal bis-dihydropyran **29** could be used in the above reactions; however, synthesis of **29** requires unnatural (*R*)-methyl lactate. An alternative enantiocomplimentary process involves the use of the (4*S*,4′*S*)-dimethyl bis-dihydropyran **34** which is much more readily available than **29** (see Section 4, **Scheme 10**).



Reagents: (i) PhMe, CSA (cat.), 110 °C, 15 h, 75%; (ii) NaH, BnBr, THF, 95%.

Scheme 12

Reaction of **34** with glycerol in refluxing toluene with catalytic CSA gave selectively **60** (**Scheme 12**), again as a result of combined anomeric and steric effects.[36]

The equatorial orientation of the hydroxymethylene substituent is the result of the thermodynamic conditions under which the reaction is run. Initially, a mixture of two isomers was formed, but after fifteen hours of reflux only a small amount (less than 5%) of the axial isomer still remained in the crude reaction mixture. A prolonged reaction time did not alter the ratio further. After purification by flash chromatography, **60** was isolated in 75% yield as a single diastereomer. Benzylation of **60** gave **61** which on treatment with neat ethylene glycol furnished (*S*)-1-*O*-benzyl glycerol **62**, identical to an authentic sample, together with **63**, in 60 and 87% yield respectively (**Scheme 12**).

With the aim of devising a recycling process, compound **63** was heated in glycerol with catalytic CSA. As expected **60** was obtained diastereomerically pure in 88% yield, after purification by flash chromatography. This recycling process, going via the ethylene glycol adduct **63**, was necessary as **61** reacted only very sluggishly with glycerol.

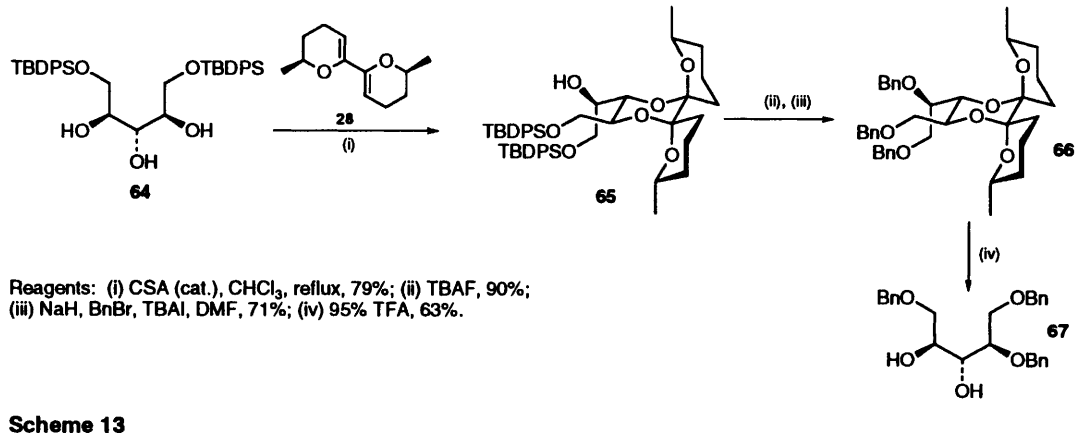
5.2 Reaction with other acyclic meso polyols

Several other acyclic polyols have been enantioselectively protected with chiral bis-dihydropyrans to give dissymmetric products.[37] For example, the symmetrical disilylated pentol **64** (**Scheme 13**) reacts with (2*S*,2′*S*)-DMDHP **28** in refluxing chloroform containing CSA to give the dispiroketal **65** in 79% yield as the only isolated product.

The dispiroketal is formed on only one of the enantiotopic diol pairs because only one has a chirality match with the diene, *i.e.*, the product which is formed is the thermodynamically most stable one in which the methyl substituents and the two dioxolane side-chains are equatorial and the spirocentres are fully anomerically stabilized (**Scheme 13**).

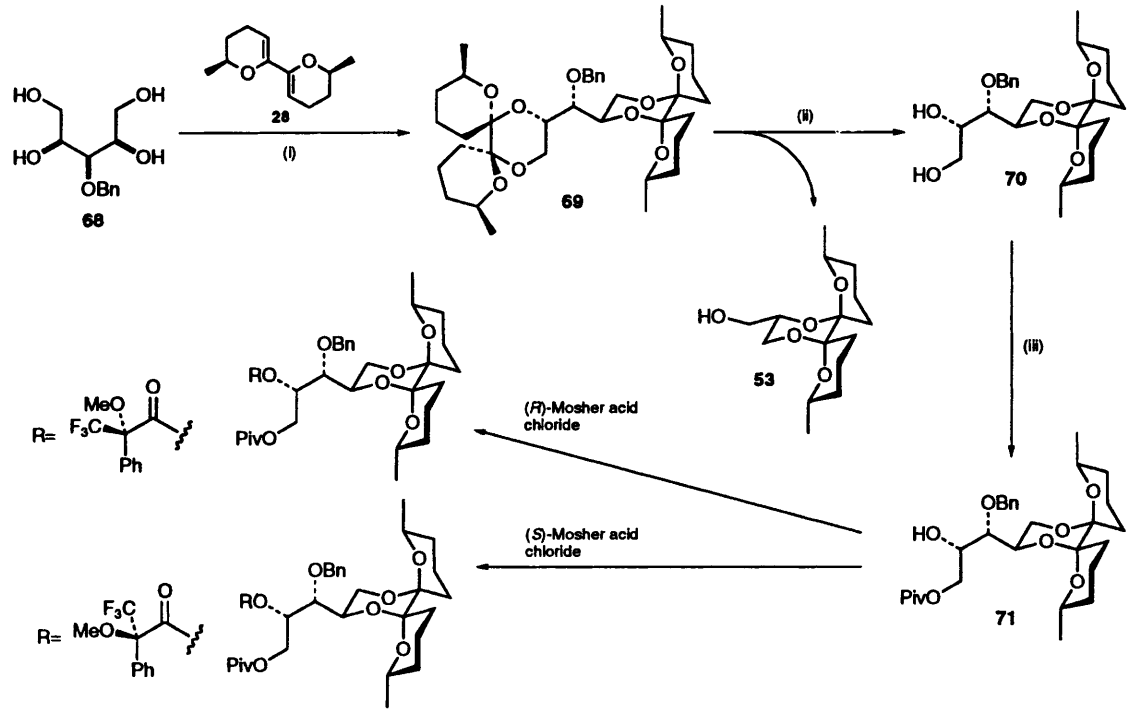
The dispiroketal **65** may be elaborated in a variety of ways. For example, deprotection with tetra-n-butylammonium fluoride followed by benzylation afforded **66** which upon treatment with trifluoroacetic acid then gave the polyol derivative **67** in enantiomerically pure form (**Scheme 13**).

We have also found that the symmetrical mono-protected polyol **68** reacts with two equivalents of the dimethyl bis-dihydropyran **28** to give the bis-dispiroketal **69**. In this compound we see that there



Reagents: (i) CSA (cat.), $CHCl_3$, reflux, 79%; (ii) TBAF, 90%; (iii) NaH, BnBr, TBAI, DMF, 71%; (iv) 95% TFA, 63%.

Scheme 13



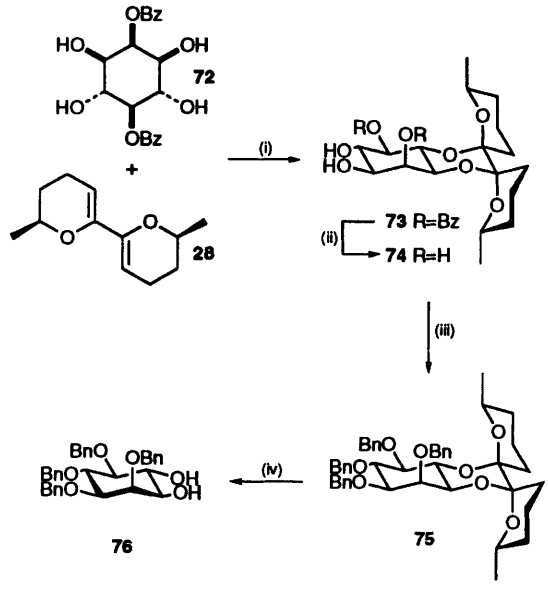
Reagents: (i) CSA (cat.), $CHCl_3$, reflux, 67%; (ii) CSA (cat.), $CHCl_3$, glycerol, reflux, **70** 75%, **53** 97%; (iii) PivCl, pyr, DCM, –20 °C, 82%.

Scheme 14

has been a good chirality match with one diol pair but that the other diol pair, which is relatively unhindered, also reacts. In order to accommodate the mismatched chirality the dioxane ring here must adopt a boat conformation meaning that this dispiroketal is less stable and can be selectively deprotected by adding glycerol and warming briefly to 61 °C in chloroform. This has the effect of removing the unstable spiroketal unit to give the dissymmetric diol **70** together with the glycerol adduct **53** (**Scheme 14**). The diol **70** can be selectively protected at the primary position by treatment with pivaloyl chloride at −20 °C to give the alcohol **71** in 82% yield. Application of the Mosher method has confirmed the stereochemistry of the secondary alcohol centre.

5.3 Reaction with cyclic meso polyols

Following the success of the enantioselective discrimination and protection procedure for acylic polyols we sought to apply the procedure to cyclic meso polyols in an effort to prepare enantiomerically pure inositols. These are extremely important materials in many biologically interesting systems. The conventional way of obtaining these compounds involves optical resolution of *myo*-inositol derivatives which requires tedious chromatographic separation or recrystallization procedures with generally low overall efficiency. Hence the known symmetrical 2,5-dibenzoyl-*myo*-inositol **72**[38] was reacted with the C_2-symmetric (2*S*,2′*S*)-dimethyl bis-dihydropyran **28** under



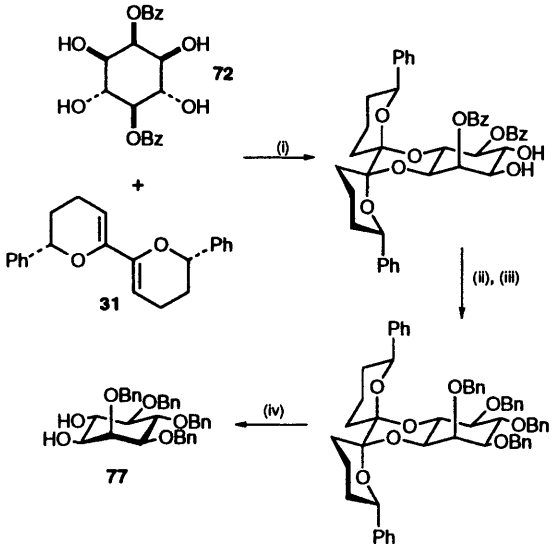
Reagents (i) CSA, $CHCl_3$, reflux, 70%; (ii) 1% NaOH, MeOH/Et_2O (9:1), 96%; (iii) NaH, BnBr, TBAI, DMF, 74%; (iv) 95% TFA, 63%.

Scheme 15

standard conditions to give the 3,4-protected dispoke adduct **73** (**Scheme 15**). This dispoke-protected compound **73** is fully anomerically stabilized with the oxygen substituents at the spiro centres adopting axial orientations. Regioselectivity is achieved via the use of the chiral bis-dihydropyran **28** which has the ability to protect one enantiotopic

pair of vicinal diols in the substrate **72** to give a 'matched' dispoke adduct, with the side-chain methyl substituents equatorial. Protection of the other enantiotopic vicinal diol pair would lead to a 'mismatched' adduct with axial methyl substituents if the structure possessed full anomeric stabilization, and this is therefore disfavoured. It is important to note that as the dibenzoyl inositol derivative **72** is a meso compound all the starting material is utilized in the step leading to the dissymmetric dispoke product **73**. Debenzoylation was achieved with sodium hydroxide to give the tetrol **74** in 96% yield. This compound **74** was then perbenzylated to give the fully protected dispoke adduct **75**. The diol was unmasked by treatment of **75** with 95% trifluoroacetic acid/water to give tetrabenzylated *myo*-inositol **76** in 63% yield[39] (**Scheme 15**), which was identical to an authentic sample prepared by alternative methods.

The enantiomeric tetrabenzylated-*myo*-inositol **77** could be prepared by the same sequence of reactions using either the (4*S*,4′*S*)-DMDHP **34** or the (2*S*,2′*S*)-DPDHP **31** as the desymmetrizing agent. The sequence of reactions for **31** is shown in **Scheme 16**.



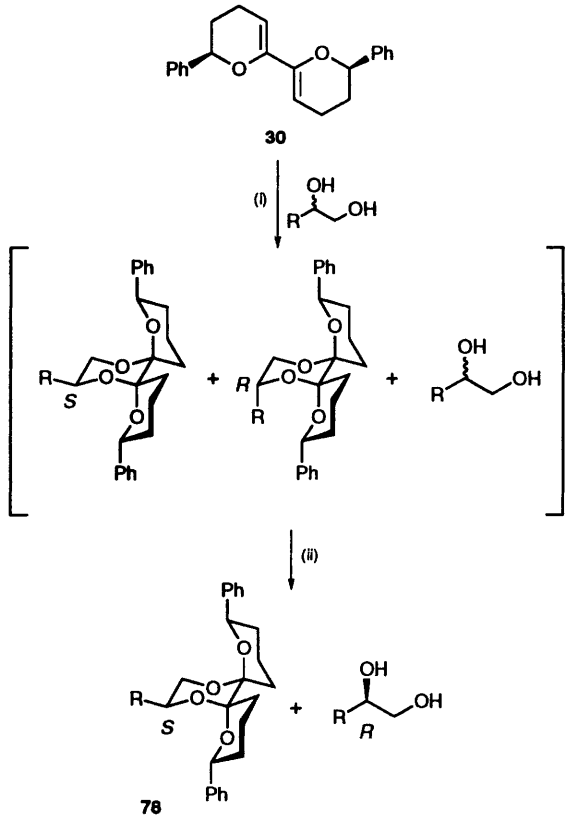
Reagents: (i) CSA, $CHCl_3$, reflux, 52%; (ii) 1% NaOH, MeOH/Et_2O (9:1), 99%; (iii) NaH, BnBr, TBAI, DMF, 98%; (iv) 95% TFA, 33%.

Scheme 16

6 Thermodynamic resolution of diols

Enantiopure 1,2-diols are useful building blocks for organic synthesis and their preparation on a large-scale is desirable. Even the brilliant enantioselective procedures of Sharpless and others suffer some limitations, particularly for terminal alkene oxidation. Resolution procedures can therefore be an effective way of accessing chiral materials, especially on a large scale. We have investigated the use of the C_2-symmetric bis-dihydropyrans as a route to chiral vicinal diols in which resolution occurs via a thermodynamically controlled enantioselective reaction forming diastereoisomerically pure dispiroketals.

The process involves reaction of two equivalents of racemic 1,2-diol with a chiral bis-dihydropyran such as **30** in the presence of CSA in boiling toluene. Initially, two products are formed, both with a fully anomerically stabilized dispoke core, but one with the side-chain equatorial and the other with it in axial orientation. On prolonged heating at 110 °C interconversion of the dispoke adducts is possible; deketalization of the less stable diol adduct followed by ketalization of the opposite diol enantiomer occurs, that is, thermodynamic equilibration takes place to favour the more stable, equatorially substituted, dispiroketal such as **78** which is formed in high yield (**Scheme 17**).



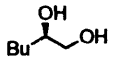
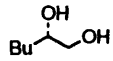
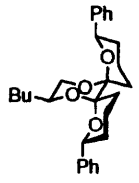
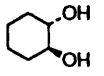
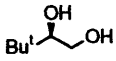
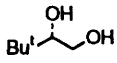
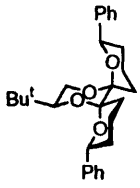
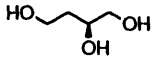
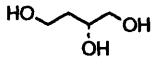
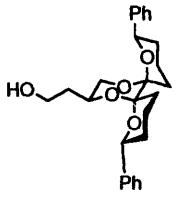
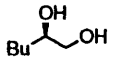
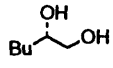
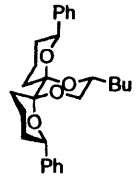
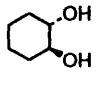
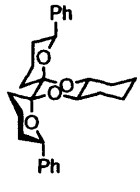
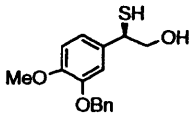
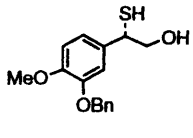
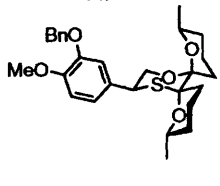
Reagents: (i) Diol (2 eq.), PhMe, CSA (cat.), 110 °C, 1 h; (ii) 110 °C, 48 h.

Scheme 17

This thermodynamic resolution procedure has been applied to a number of structurally different 1,2-diols using (2*R*,2′*R*)-DPDHP **30**, the enantiomeric bis-dihydropyran **31**, and the (2*S*,2′*S*)-DMDHP **28** (**Table 3**).

Theoretically, after reaction of exactly two equivalents of racemic diol with (2*R*,2′*R*) or (2*S*,2′*S*)-DPDHP **30** and **31**, one diol enantiomer should be ketalized and the other enantiomer left unreacted. In practice, however, a small amount of bis-dihydropyran decomposition occurs during the

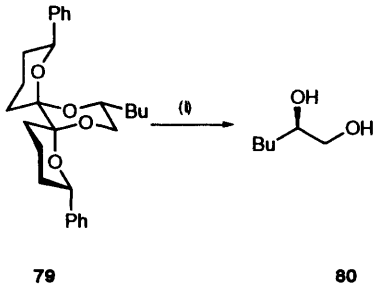
Table 3

Diene	Diol		Dispoke Adduct	Yield (%)[a]
30		+ 		93
30		+ 		80
30		+ 		90
30		+ 		91
30		+ 		62
31		+ 		90
31		+ 		82
31		+ 		96
28		+ 		66

[a] Yields based on bis-dihydropyran

reaction which lowers the optical purity of the unprotected diol and the yield, through not the optical purity, of the dispoke adduct. It was found that when two equivalents of diol were used complete reaction took up to forty-eight hours. This rather long reaction time could be decreased by using more equivalents of diol, but it should be noted that use of excess diol is inefficient as it naturally leads to a lower enantiomeric excess of the residual unprotected diol.

Liberation of the diol from the dispoke protected adducts can be achieved by treatment with lithium in liquid ammonia. For example, **79** gives the deprotected diol **80** in 76% yield (**Scheme 18**).[40]



79 **80**

Reagents: (i) Li, $NH_{3(l)}$, Et_2O, 76%, 89% e.e. by chiral g.c.

Scheme 18

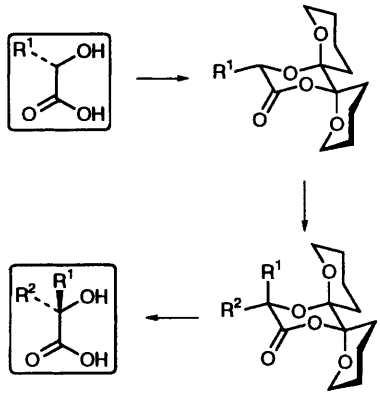
The fact that the optical purity of the released diol **80** is only 89% e.e., as opposed to >98% for the starting bis-dihydropyran **31**, indicates that partial racemization occurs during the extended reaction times needed for complete resolution, owing presumably to some benzylic cleavage and readdition. For this reason in any further study we would recommend the use of dimethyl bis-hydropyrans **28**, **29** or **34** which should not suffer from this problem.

We have also developed deketalization via ketal exchange as an alternative to the lithium ammonia reduction procedure which could find wider application with more sensitive substrates.[40] Alternatively, the use of DADHPs **32** or **33** where the chiral controller substituents are allyl groups can be used in these resolutions; removal is then effected by ozonolysis to give the aldehyde and treatment with base to give deprotection by a β-elimination mechanism.[41]

7 Protection of α-hydroxyacids and alkylation of the dispiroketal products

7.1 Introduction

In an effort to devise a new way to prepare enantiopure α,α-disubstituted α-hydroxyacids we envisaged that dispiroketals could be used to form a non-racemic equivalent of an enolate of lactic acid in a similar way to Seebach's elegant acetal work.[42] The formation of dispiroketals, however, brings further possibilities of using homochiral bis-dihydropyrans to prepare non-racemic enolate equivalents of prochiral α-hydroxy acids. We decided first of all to attempt the dispiroketalization of chiral α-hydroxyacids with simple bis-dihydropyran **2**. On the basis of previous work with diols it was hoped that such a reaction with a homochiral substrate would give one major diastereomer, with the substituent on the hydroxyacid preferentially adopting an equatorial position (**Scheme 19**). This tendency would, in conjunction with maximization of anomeric stabilization, control the configuration at the spiroketal centres. Having stored the chiral information in the dispiroketal, the original stereogenic centre could be destroyed by deprotonation to give the enolate which could then undergo a diastereoselective reaction with an electrophile. Finally, deprotection would afford the product of a useful overall enantioselective transformation (**Scheme 19**).

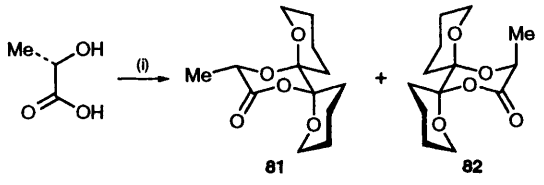


Scheme 19

This process has worked well and has allowed us to prepare a number of α-hydroxy acid derivatives, as described below.[21(b),43]

7.2 Protection of (*S*)-lactic acid

The best conditions for the reaction of (*S*)-lactic acid with the bis-dihydropyran **2** to give **81** and minimize formation of **82** were found to be the use of toluene as solvent with dry HCl (used as a 1.0 M solution in ether) as an acid catalyst at room temperature or below. These conditions gave an 85% yield of a 12:1 mixture of **81** to **82** (**Scheme 20**).



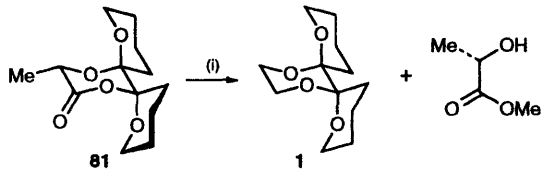
81 **82**

Reagents: (i) **2**, 10 mol% HCl, PhMe, r.t., 48 h, 85%.

Scheme 20

The major isomer could be obtained pure by a single recrystallization from 40–60 petroleum ether and X-ray crystallography showed, as expected, an all-chair conformation with the methyl group equatorial and the maximum anomeric stabilization at the spirocentres, that is, **81**. No crystal structure of the minor diastereoisomer could be obtained; however, its structure must represent a thermodynamically less stable compromise between an all-chair conformation having an unfavourable 1,3-diaxial interaction between the substituent and a carbon–oxygen bond, and a structure possessing a boat conformation of the 1,4-dioxane ring which relieves this steric interaction at the expense of eclipsing strain and reduced anomeric stabilization.

It was necessary to confirm that lactic acid did not racemize significantly under the conditions employed for dispiroketalization. The pure major diastereomer **81** was treated with a small excess of ethylene glycol and catalytic acid in methanol to afford the dispiroketal adduct **1** and methyl lactate (**Scheme 21**). It was demonstrated by gas chromatography on a Lipodex E chiral column that this possessed the *S*-configuration, with no trace of (*R*)-methyl lactate being detectable. This confirmed that **81** was of high enantiomeric excess and importantly that no racemization had occurred during deprotection.



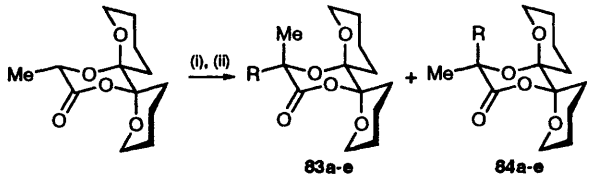
Reagents: (i) Ethylene glycol (1.1 eq.), CSA, MeOH, reflux, 16 h.

Scheme 21

7.3 Alkylation reactions of a non-racemic equivalent of a lactic acid enolate

Deprotonation of **81** occurred readily on treatment with strong bases in THF at −78 °C. The enolate was then alkylated with a range of alkyl halides to give the corresponding diastereoisomeric products **83a–e** and **84a–e** (**Scheme 22**, **Table 4**).

What is noticeable from the table is that alkylation with benzyl or allyl bromide is highly

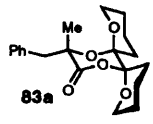
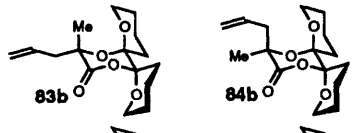
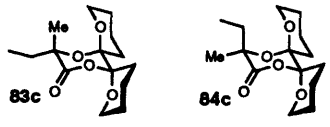


83a, 84a	R = benzyl
83b, 84b	R = allyl
83c, 84c	R = ethyl
83d, 84d	R = *n*-propyl
83e, 84e	R = *iso*-propyl

Reagents: (i) Base (see table), −78 °C. Method A, LDA, THF/DMPU; method B, LDA; Bu^{n}Li, THF/DMPU; method C, KHMDS, THF/PhMe; (ii) Electrophile R-X, −78 °C to r.t.

Scheme 22

Table 4

Entry	Electrophile	Product(s)	Method[a]	Ratio[b]	Yield (%)
1	Benzyl bromide	 **83a**	A B	>98:2 >98:2	72 86
2	Allyl bromide	 **83b** **84b**	A B	96:4 96:4	95 94
3	Ethyl iodide	 **83c** **84c**	A B C	81:19 82:18 89:11	83 84 75
4	*n*-Propyl iodide	 **83d** **84d**	A B C	77:23 83:17 92:8	73 79 67
5	*iso*-Propyl iodide	 **83e** **84e**	B	83:17	47[c]

[a] See scheme 22 for details. [b] See ref. 21b, 43 for methods employed. [c] 9% Starting material also recovered.

stereoselective, to the extent that it is difficult to detect the minor diastereoisomers. With smaller electrophiles such as ethyl and n-propyl iodide the selectivity is slightly lower. Alkylation with secondary halides such as iso-propyl iodide gave lower yields of alkylated product, presumably due to competing elimination, with no improvement in diastereoselectivity despite its greater size.

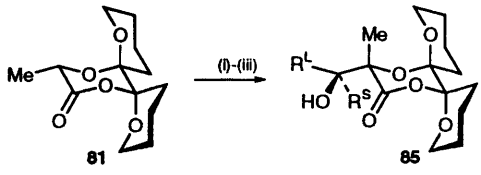
We found that use of *N,N'*-dimethylpropyleneurea (DMPU),[44] when added to the lithium enolate, gave enhanced reactivity during the alkylation reactions. In the cases where more moderate selectivity was observed this could be improved by the use of potassium hexamethyldisilazide (KHMDS) instead of LDA (**Entries 3** and **4**, **Table 4**). When LDA was used as the base increased yields were achieved when the diisopropylamine generated in the enolate formation was further deprotonated with a second equivalent of n-butyllithium prior to electrophile addition.[45]

The observed facial preference for alkylation of the enolate is as expected on steric grounds; the incoming electrophile approaches from the least hindered face such that there is no 1,3-interaction with the pseudoaxially disposed C–O bond of the spiroketal. The slightly lower selectivity observed for less reactive alkyl halides probably reflects the operation of a later transition state where the enolate has developed some pyramidal character, which reduces the energy differences between the competing alkylation pathways.

We have also investigated the reaction of the lactate dispiroketal enolate with a limited range of carbonyl compounds. Once again excellent diastereoselectivity was observed and in most examples only one of the four possible diastereomers was produced (**Scheme 23**, **Table 5**).

Only in the reaction with acetaldehyde (**Entry 3**), which we would expect to give the lowest level of stereoselectivity on account of the small size of the R^L group, were two diastereoisomeric products **85c** and **86** formed, in 93% and 4% yield respectively.

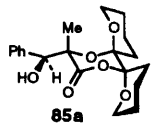
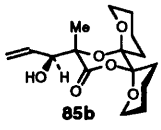
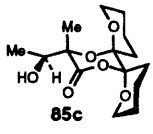
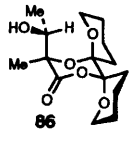
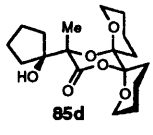
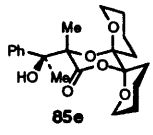
In the reactions with aldehydes yields were consistently high, but reactions with ketones gave lower yields with significant quantities of starting material being recovered, although the very high facial selectivity of alkylation was maintained. As retro-aldol reactions can occur in sterically hindered systems we suspect that this may have been occurring with the ketones although the reactions were quenched at −78 °C prior to product isolation in an attempt to minimize this pathway.



Reagents: (i) LDA, THF/DMPU, –78 °C; (ii) Bu^nLi; (iii) $R^LR^SC{=}O$.

Scheme 23

Table 5

Entry	Electrophile	Product(s)	Ratio	Yield (%)	Recovered SM (%)
1	Benzaldehyde	 **85a**	–[a]	96	–
2	Acrolein	 **85b**	–[a]	94	–
3	Acetaldehyde	 **85c**  **86**	93:4[b]	93[c]	–
4	Cyclopentanone	 **85d**	–[a]	35	46
5	Acetophenone	 **85e**	–[a]	29	56

[a] No minor diastereoisomer detectable. [b] Based on isolated amounts of **85c** and **86**. [c] Yield of major diastereoisomer **85c**.

The large preference for one diastereomer in these aldol coupling reactions can be rationalized by consideration of the two chair-like six membered transition states (**Figure 9**). In both, the larger substituent of the carbonyl component R^L is directed pseudoequatorially while the smaller group R^S, *i.e.* hydrogen for aldehydes, is axial and placed

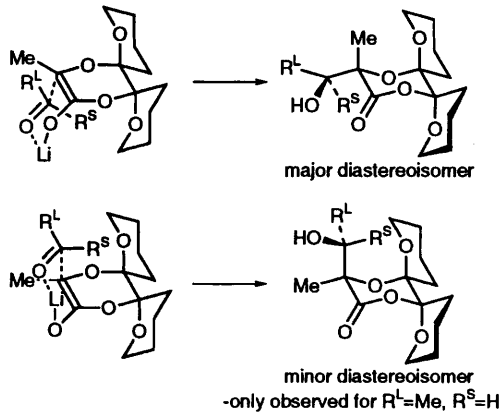


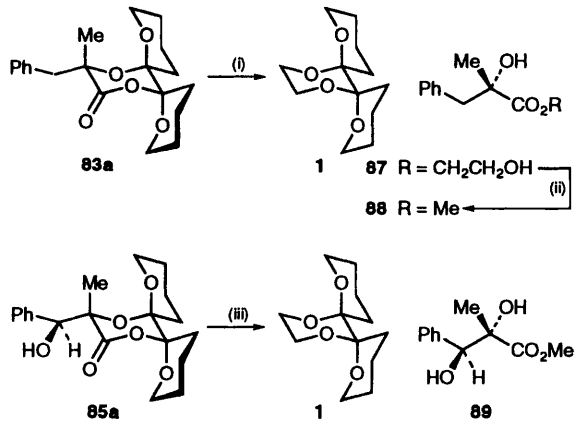
Figure 9

in the vicinity of the dioxane ring. The transition state which favours the formation of the major diastereoisomer is obviously much less sterically encumbered than that leading to the minor component.

As part of their structure elucidation, and because of the need to develop mild deprotections of these spiroketal products, ways to remove the spiroketal unit were investigated. For example, we found that the dialkylated adduct **83a** reacted with ethylene glycol in the presence of camphorsulfonic acid to give the parent spiroketal **1** and the ester **87** (**Scheme 24**). This ester could be further converted into the known[46] methyl ester **88** by treatment with MeOH and sodium carbonate giving an overall yield of 80% for the two steps. Alternatively, a more convenient procedure could be used to afford methyl esters directly whereby the aldol product **85a** was exposed to just 1.5 equivalents of ethylene glycol in methanol containing an acid catalyst to give **89**[47] in quantitative yield (**Scheme 24**).

7.4 A non-racemic equivalent of a glycolic acid enolate

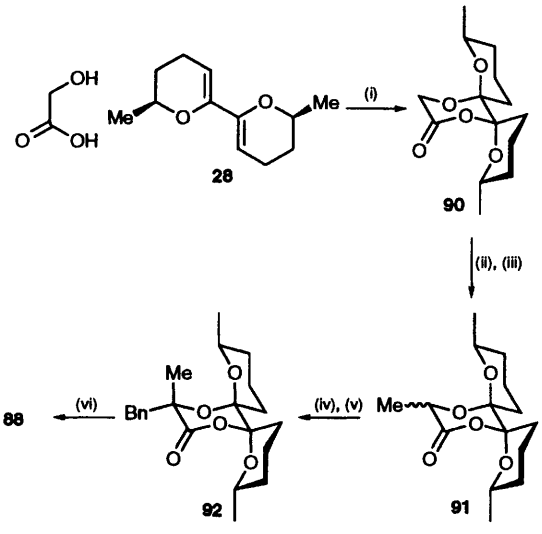
Although the above methods work well for the production of alkylated chiral α-hydroxy acids the process is restricted by the availability of enantiopure hydroxy acids as starting materials from the chiral pool. For this reason we sought to devise a method which would lead to a non-racemic glycolic acid enolate which could give access to a much wider range of α,α-disubstituted derivatives. This has been achieved using chiral bis-dihydropyrans both as a protecting group and as a chirality directing motif during alkylations.



Reagents: (i) Ethylene glycol (excess), CSA, 100 °C, 1 h; (ii) MeOH, Na_2CO_3, r.t., 48 h, 80% over 2 steps; (iii) Ethylene glycol (1.5 eq.), MeOH, CSA, reflux, 5 h, 100%.

Scheme 24

Reactions of glycolic acid with (2S, 2'S)-DMDHP **28** gave **90** as a single diastereoisomer in 75% yield (**Scheme 25**). The excellent control in the formation of the dispiroketal product is once again achieved as a result of the desire for methyl groups to adopt equatorial positions and the spiro centres to be fully anomerically stabilized. Compound **90** was then alkylated via its corresponding enolate, derived by treatment with LDA in THF, with methyl iodide to give **91** as a 10:1 mixture of diastereoisomers (**Scheme 25**).



Reagents: (i) PPTS, THF, r.t., 72 h, 75%; (ii) LDA, THF, –78 °C; (iii) MeI, 73%; (iv) LDA, THF/DMPU, –78 °C; (v) BnBr, 70%; (vi) ethylene glycol (3 eq.), MeOH, CSA, reflux, 5 d, 31%.

Scheme 25

These diastereomers could be isolated or simply treated as a mixture with LDA followed by alkylation with benzyl bromide as a second electrophile to give **92** as a single diastereoisomer.

On deprotection compound **92** afforded the methyl ester **88** which is identical to the previously obtained material (**Scheme 25**). Overall the process therefore constitutes a novel way of forming two new carbon–carbon bonds asymmetrically with control of the absolute stereochemistry from an achiral substrate such as glycolic acid. We believe this method has considerable promise for the asymmetric synthesis of unusually substituted α-hydroxy acids and compares favourably with, and is complementary to, existing literature procedures.[42] Currently we are investigating routes that might allow similar alkylation studies with thioglycolic acid, glycine, and other amino acid derivatives.

8 Preparation and use of dihydroxy dispiroketals as chiral auxiliaries

Another aspect of the dispiroketal chemistry which we have exploited makes use of the rigid architecture in these molecules for asymmetric synthesis. There is a consistent need for new cheap, low molecular weight chiral auxiliaries and chiral ligands for catalysts for asymmetric synthesis which are available in both enantiomeric forms.

It was envisaged that a wide range of such auxiliaries could be obtained by decorating further the dispiroketals to give bifunctional molecules such as those illustrated by the general structure types I, II and III below (**Figure 10**).

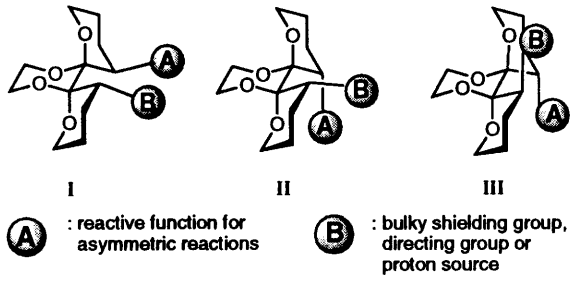
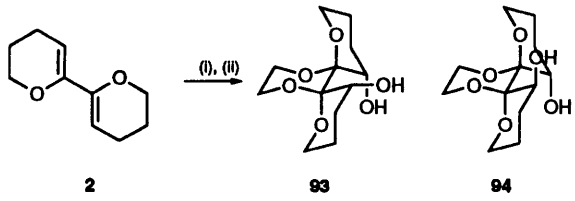


Figure 10

To obtain such compounds we had to introduce oxygen at the 5- and 12-positions of the dispiroketal framework (dispiroketal numbering). Extensive experiments showed that bis-dihydropyran **2** reacted under a variety of epoxidizing and hydroxylating conditions with subsequent trapping by ethylene glycol under thermodynamic acidic conditions to give two diastereoisomeric diols **93** and **94** which are readily separable by column chromatography (**Scheme 26, Table 6**).[48]

Proof of the structure of these compounds was obtained by X-ray crystallographic methods.[48] The majority of our early work has concentrated on the use of the enantiopure C_2-symmetrical diol **95** as a bifunctional auxiliary, obtained by classical resolution of the racemate **94** via dicamphanate ester formation. The dicamphanates were readily separated by flash chromatography and subsequent basic hydrolysis furnished enantiopure diols which could then be used for asymmetric synthesis.



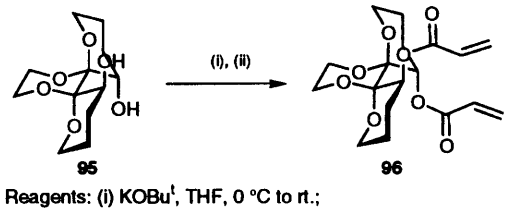
Reagents: (i) Epoxidation or dihydroxylation; (ii) Ethylene glycol, CSA, PhMe, reflux.

Scheme 26

Table 6

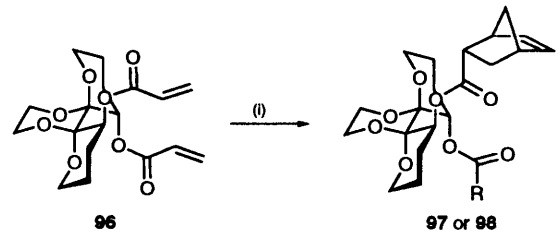
Epoxidation conditions	Overall yield (%)	**93:94**
Dimethyl dioxirane, −78 °C	83	2:1
Dimethyl dioxirane, 0 °C	92	1:1
*m*CPBA, DCM, 0 °C	48	1:4
Dihydroxylation conditions	**Overall yield (%)**	**93:94**
OsO_4.Bu^{t}OH, H_2O, $K_3Fe(CN)_6$, 0 °C	46	1:3

The first class of reactions to which we applied our auxiliary was Diels–Alder cycloadditions.[49] For example, the enantiopure diol **95** was converted into the diacrylate **96** (**Scheme 27**) and then reacted with cyclopentadiene in the presence of various Lewis acids to afford the corresponding Diels–Alder adducts **97** and **98** (**Scheme 28** and **Table 7**).



Reagents: (i) KOBu^t, THF, 0 °C to rt.; (ii) Acryloyl chloride, –78 °C, 82%.

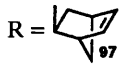
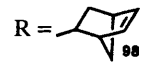
Scheme 27



Reagents: (i) Cyclopentadiene, Lewis acid, DCM, galvinoxyl (10 mol%), –78 °C to r.t.

Scheme 28

Table 7

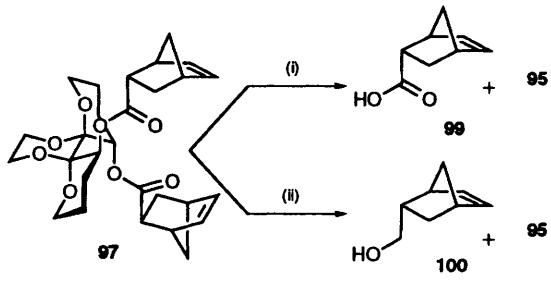
Entry	Lewis acid	Temp. (°C)	Time (hours)	Ratio of **97**:**98** Endo:Exo R =  **97** R =  **98**	Yield (%)
1	$EtAlCl_2$	−78	1	23.5:1	99
2	Et_2AlCl	−78	3	15.5:1	98
3	$AlCl_3$	−78	23	6.3:1	80
4	$ZnCl_2$	−78	18	2.6:1	84
5	$TiCl_4$	0	3.5	2.6:1	40
6	$SnCl_4$	0	3.5	1.4:1	12

During these reactions only one equivalent of the Lewis acid is required to give complete turnover to product. The acrylate side-chains are oriented in an *S-trans* configuration in the transition states leading to the major product being the bis-*endo* adduct **97**. Under the optimum conditions, using $EtAlCl_2$, the ratio of *endo, endo* isomer **97** to *endo, exo* isomer **98** was 23.5:1 in virtually quantitative chemical yield.

Cleavage of the Diels–Alder adduct in **97** from the auxiliary either hydrolytically (NaOH, MeOH, H_2O at reflux) or reductively ($LiAlH_4$ in Et_2O) gave **99** or **100** respectively (both identical in all respects to the literature). In neither case was any epimerization observed and the auxiliary **95** could be separated and recovered readily in high yield (**Scheme 29**).

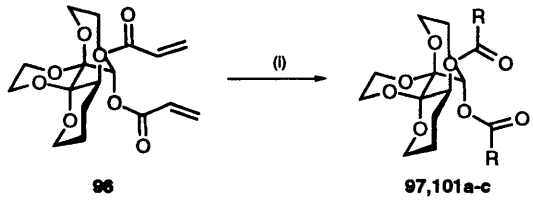
Using the optimized conditions for the formation of the bis-*endo* adduct **97** with cyclopentadiene, compound **96** was reacted with several other dienes to give the corresponding Diels–Alder products (**101a–c**) (**Scheme 30, Table 8**).

These Diels–Alder reactions represent a new opportunity for the use of dispiroketals, with the C_2-symmetrical dihydroxylated dispiroketal diol **95** acting as a chiral scaffold for acrylates in Lewis-



Reagents: (i) NaOH, H_2O:MeOH (1:2), reflux, 96% for **99** and 92% for **95**; (ii) $LiAlH_4$, Et_2O, −30 °C, 93% for **100** and 93% for **95**.

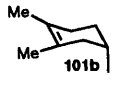
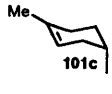
Scheme 29



Reagents: (i) Diene, $EtAlCl_2$, DCM, −78 °C to r.t.

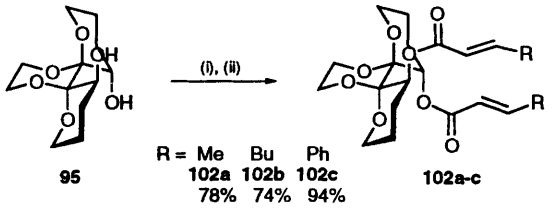
Scheme 30

Table 8

Entry	Diene	Temp. (°C)	Time (hours)	R	Yield (%)
1		−78 to 0	1	 **97**	96
2		−78 to 0	3	 **101a**	89
3		−78 to r.t.	14	 Me Me **101b**	83
4		−78 to 0	4	 Me **101c**	82

acid-catalysed cycloaddition processes. The C_2-symmetry and the bifunctional format of this auxiliary maximizes its effectiveness in that it is able to react two substrates per auxiliary unit.

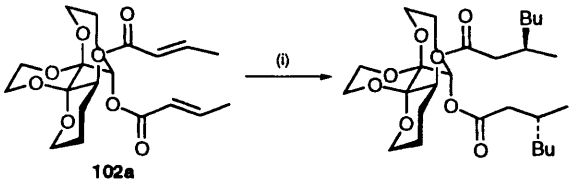
After achieving successful asymmetric induction in Diels–Alder reactions we turned our attention to the use of **95** to influence the stereochemistry of conjugate additions of various cuprate reagents to unsaturated systems such as compounds **102a–c** (**Scheme 31**).[50]



Reagents: (i) KOBu^t, THF, 0 °C to r.t.; (ii) Acid chloride, –78 °C.

Scheme 31

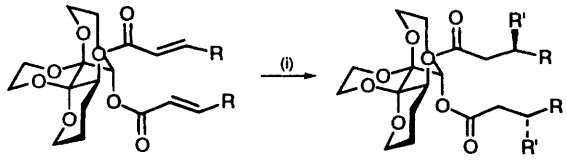
In order to determine the best reaction conditions for conjugate addition we centred our studies on the dicrotonate derivative **102a**. This compound was reacted with a variety of butyl organocuprate reagents which included homo- and hetero-cuprates and copper-catalysed Grignard reagents (**Scheme 32**, **Table 9**).



Reagents: (i) Butyl cuprate, Et_2O.

Scheme 32

In order to achieve the highest facial selectivity in the addition it was necessary to incorporate Lewis acids into the medium. Under these conditions reaction occurred with high yield and high *R*-selectivity. In the absence of a Lewis acid stereofacial selectivity was reversed. Once the most effective reaction conditions had been found (a modified version of conditions developed by Yamamoto[51]) these were applied to a variety of different systems (**Scheme 33**, **Table 10**).



Reagents: (i) R'-Li, CuI•PBu_3, BF_3•OEt_2, ether.

Scheme 33

In general the addition process proceeded with high yield and stereoselectivity. The addition of a phenyl organocuprate reagent (**Entry 2**), however, went with both reduced yield and selectivity; this was probably due to the low reactivity of this cuprate which necessitated an elevated reaction temperature. Additions of phenyldimethylsilyl cuprate[52] (**Entries 3** and **5**) to the dienoate system proceeded in high yield but with reduced stereofacial selectivity.

The high chemical and optical yields achieved with this novel C_2-symmetric bifunctional auxiliary in some of these Diels–Alder reactions and Michael additions are pleasing results *per se*; they also show the power of the dispiroketal framework as a chiral inductor. We are currently working on using the asymmetric unit more efficiently, as a chiral

Table 9

Entry	Butyl cuprate	Temp. (°C)	Time (hours)	Yield (%)	Config.	e.e. (%)
1	$BuCu{\cdot}BF_3{\cdot}PBu_3$	–60	16	88	*R*	96
2	$BuCu{\cdot}BF_3{\cdot}PBu_3$	–45	16	63	*R*	89
3	$Bu_2CuCNLi_2$, $ZnCl_2$	–60	16	80	*R*	63
4	BuMgCl, CuBr·DMS, $ZnCl_2$	–60	16	40	*R*	28
5	$Bu_2CuCNLi_2$	–60	16	82	*S*	35

Table 10

Entry	R	R'	Temp. (°C)	Time (hours)	Yield (%)	Config.	e.e. (%)
1	Me	Bu	–60	16	88	*R*	94
2	Me	Ph	–40	36	68[a]	*R*	81
3	Me	$SiMe_2Ph$	–70	12	92[b]	*R*	76
4	Ph	Me	–60	16	83	*S*	92
5	Ph	$SiMe_2Ph$	–60	16	91[b]	*R*	71
6	Ph	Bu	–60	16	87	*R*	92
7	Bu	Me	–60	16	79	*S*	93

[a]Yield based on recovered starting material. [b]Reaction carried out in 50:50 ether:THF.

modifier or as a basis for ligands to be used in asymmetric catalysis.

9 Protection of vicinal diols in carbohydrates

We are witnessing a resurgence of interest in carbohydrates owing to their involvement in an increasing array of important biological events ranging from cell-cell and viral recognition to cellular signalling and adhesion properties. In order to advance this area of glycoscience it will be necessary to have ready access to materials to probe their various biological functions. Although traditional methods of synthesis and the rapidly developing biological methods are proving useful, new techniques are going to be crucial to achieve success in the future.

Certain special properties associated with dispoke protection makes it an excellent candidate for achieving selective protection in carbohydrates; dispiroketalization leads to highly-stabilized fused six-membered ring systems which favours protection of diequatorial vicinal diols over axial-equatorial or diaxial systems. In addition, the use of homochiral bis-dihydropyrans should afford further possibilities for control. Therefore it was anticipated that use of dispiroketals could bestow considerable strategic advantages in the synthesis of carbohydrates.

In practice the reactions of bis-dihydropyrans with carbohydrates worked well and have led to a general method for the protection of diequatorial vicinal diols in a wide range of monosaccharides.[41,53] This result creates a new opportunity in selective carbohydrate protection; the protecting group pattern obtained in this way could normally only be achieved in a multistep protection/deprotection sequence. We find that bis-dihydropyran **2** reacts in toluene, or preferably boiling chloroform solution, in the presence of catalytic CSA, with the polyol to give diequatorial diol protection as the major outcome in all cases (**Table 11**).[53(a)] In order to fully characterize the products they were often acylated to aid NMR analysis. In a few cases some *cis* diol protection was noticed as a minor product when steric interactions were of lesser magnitude. At the C-1 carbon, *O*-methyl, *S*-ethyl or *O*-pentenyl groups are tolerated. From these data it was also noticed that the more lipophilic the groups at the anomeric centre, the higher were the yields of dispiroketals, reflecting the greater solubility of the compounds in $CHCl_3$. The use of more polar solvents such as DMF or acetonitrile failed to give any products probably due to competitive decomposition of the bis-dihydropyran. In a trial to assess the stability of dispiroketal-protected sugars, the galacto-derivatives **103** and **105** were shown to withstand benzylation and silylation to give **104** and **106** and then conversion back into **103** and **105** without loss of the protecting group (**Scheme 34**).[9] Of particular note is that *p*-methoxybenzyl substituents can be removed even in the presence of the -SEt group using DDQ oxidation. Dispiroketal protection also has a significant effect on reactivity of the carbohydrate in glycosylation reactions, which can be profitably harnessed in oligosaccharide coupling reactions. This key observation will be discussed in the next section.

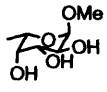
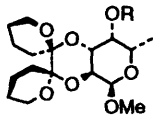
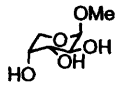
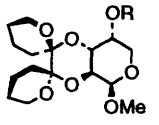
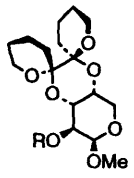
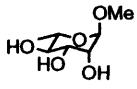
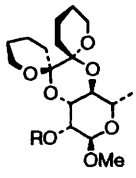
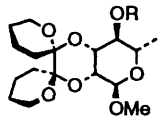
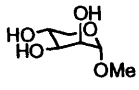
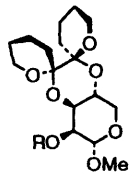
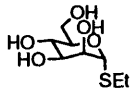
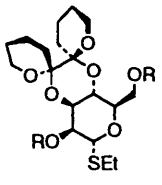
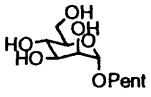
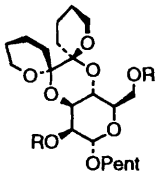
The regiocontrol in these reactions is as a result of the predictable stabilizing influence of multiple anomeric effects leading to the thermodynamically most stable isomers.

However, an even greater challenge to regiocontrol is posed by gluco-derived carbohydrates owing to the presence of *two* 1,2-*trans* diequatorial diol relationships. The other problem which we encountered in the gluco-series was that of poor chemical yield. Reaction of methyl α-D-glucopyranoside **107** under standard conditions gave two dispiroketals **108** and **109** (1:1.6) in only 39% yield (**Scheme 35**).[53(b)]

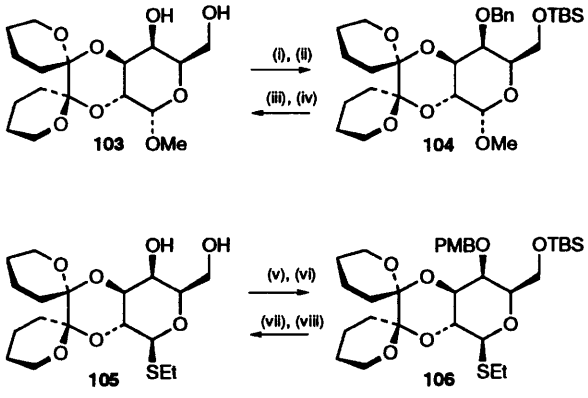
We first addressed the issue of improving the yield. The low conversion of **107** was attributed to its low solubility in chloroform and the instability of bis-dihydropyran under prolonged reaction conditions. We have found three alternative ways of surmounting this problem. Firstly, ultrasound is effective in assisting the dissolution process. Secondly, use of DMF as a solvent, although previously shown to be disadvantageous due to the greater rate of decomposition of bis-dihydropyran **2** relative to the rate of the desired dispiroketalization reaction, was found to be effective in the presence of a milder acid catalyst, triphenylphosphine/hydrogen bromide complex;[54] under these conditions methyl α-D-glucopyranoside **107** gave the regioisomeric dispiroketals **108** and **109** in a greatly improved combined yield of 68%, again as a 2:3 mixture. Separation and NMR analysis was aided by diacylation to give derivatives **110** and **111**, in 22% and 36% yield respectively from **107**. Thirdly, selective protection of the primary hydroxy group of **107** as its *tert*-butyldiphenylsilyl (TBDPS) ether **112**, with the aim of improving the solubility of the substrate, gave the two dispiroketals **113** and **114** in an excellent 82% yield (**Scheme 36**). A ratio of 1.4:1 for the 2,3- to the 3,4-protected products was obtained. Thus, once again even with a large group at C-6 there was little regiocontrol in the protection reaction.[53(b)]

To overcome this regiochemical challenge we devised an original solution using the concepts of chirality recognition previously established for *meso*-polyols (Section 5). Thus, chiral bis-dihydropyrans such as **30** and **31** were used to discriminate between the enantiomeric pairs of *trans*-1,2 diols in **112**.[41] The process once again exploits the preference of substituents (phenyl groups) to adopt equatorial positions while maintaining maximum anomeric stabilization at the spiro centres to give the most thermodynamically stable product. Pleasingly, reaction of (2*R*,2′*R*) DPDHP **30** with D-glucopyranoside derivative **112** under the usual conditions gave the dipiroketal adduct **115** as a single diastereomer in 88% yield (**Scheme 37**). Complete regioselectivity was observed as a result of chirality 'matching' of the C-2, C-3 diol pair with

Table 11

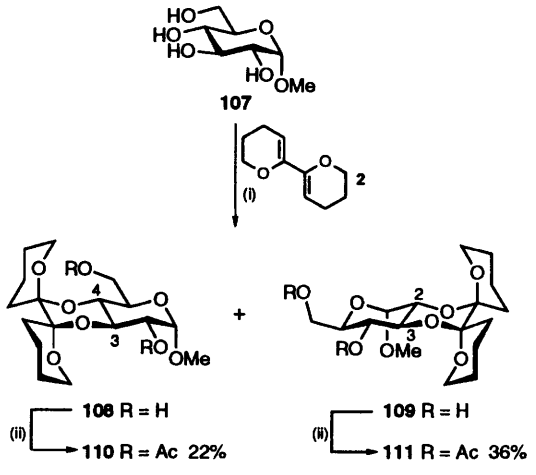
Entry	Substrate	Products	Yield (%)	*trans:cis*
1 Fuco-		 R = H, R = Ac	76	-
2 Arabino-		 R = H, R = Ac  R = H, R = Ac	98	3 : 2
3 Rhamno-		 R = H, R = Ac  R = H, R = Ac	79	3 : 2
4 Lyxo-		 R = H, R = Ac	62	-
5 Manno-		 R = H, R = Ac	36	[a]
6 Manno-		 R = H, R = Ac	45	[a]

[a] Other minor products were formed which were not readily identified.



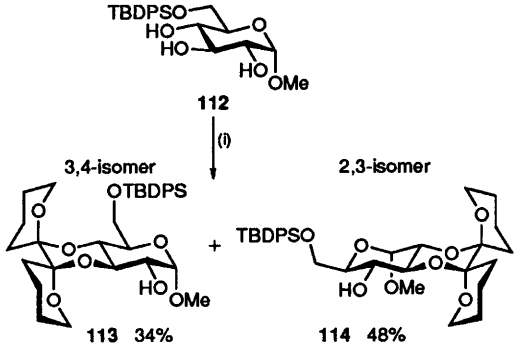
Reagents: (i) TBSCl, pyr, 86%; (ii) NaH, BnBr, 83%; (iii) TBAF, THF, 100%; (iv) H_2, Pd/C, 91%; (v) TBSCl, TEA, DMAP, 56%; (vi) NaH, 4-MeOBnCl, 84%; (vii) TBAF, THF, 100%; (viii) DDQ then $AcOH/H_2O$, 100%.

Scheme 34



Reagents: (i) **2** (2.1 eq.), CSA (cat.), $CHCl_3$, Δ, 1.5 h then ethylene glycol, Δ, 0.5 h, 39% or **2** (2.1 eq.), $Ph_3P{\cdot}HBr$ (cat.), DMF, 60 °C, 4 d, 68%; (ii) Ac_2O, pyr, **110** 22%, **111** 36%.

Scheme 35



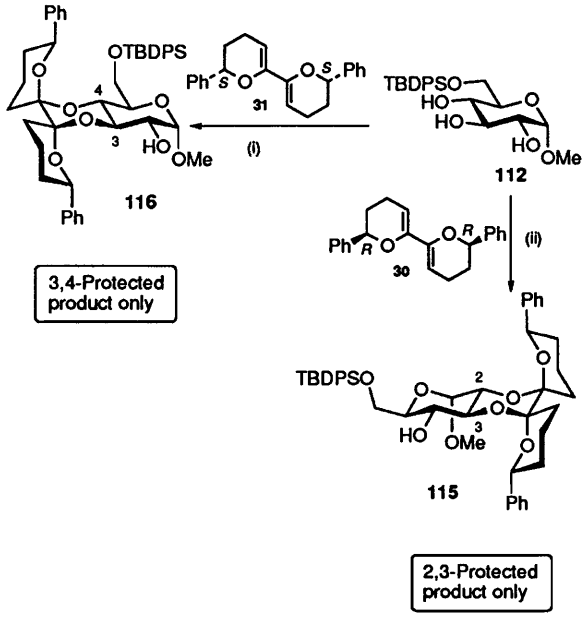
Reagents: (i) CSA (cat.), **2** (1.5 eq.), $CHCl_3$, reflux, overnight, 82%.

Scheme 36

that of the bis-dihydropyran leading to the most stable arrangement of the appended functionality. Mismatched products in this case would have led to severe steric crowding and placement of phenyl side-chains in axial positions.

The presence of phenyl groups in the dispiroketal at these positions also facilitates deprotection of the sugar with, for example, hydrogenolysis (Na/NH_3) or, in these monosaccharide examples and later derivatives, by treatment with $FeCl_3$.

Next we examined the *complementary* protection of the 3,4-diol pair in **112** using the enantiomeric (2*S*,2′*S*)-DPDHP **31** which was chosen to provide the correct chirality recognition leading to the matched product **116**. Once again this reaction proceeded extremely well and afforded **116** in 75% yield as the only isolated product (**Scheme 37**).



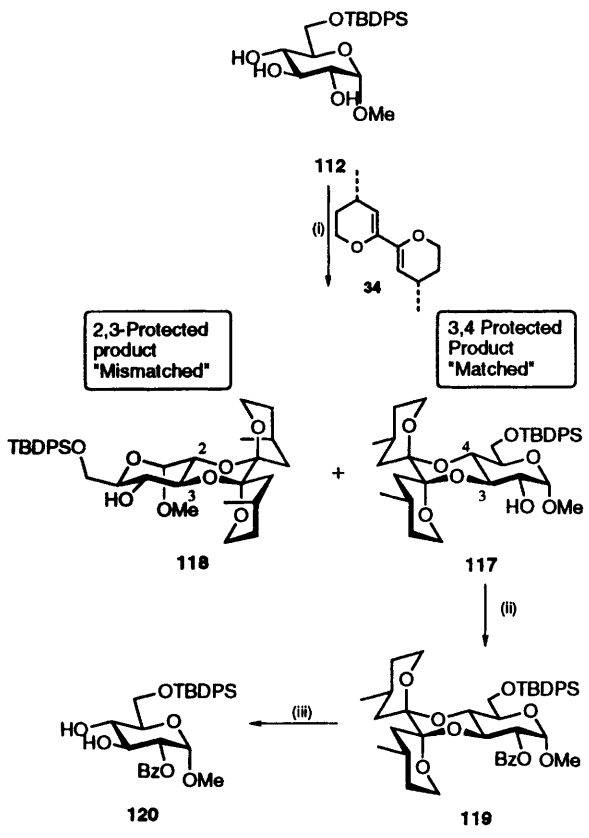
Reagents: (i) CSA (cat.), **31** (1.5 eq.), $CHCl_3$, reflux, overnight, 75%; (ii) CSA (cat.), **30** (1.5 eq.), $CHCl_3$, reflux, overnight, 88%.

Scheme 37

What we have established, therefore, is a new concept in vicinal diol protection whereby not only will these methods select *trans*-1,2 diequatorial pairs but they will also recognise the chirality associated with these units. These new enabling procedures should therefore considerably enhance the protecting group strategies available for oligosaccharide research. We went on to explore further the scope of these reactions.

In other experiments we have studied the use of different enantiopure bis-dihydropyrans such as (4*S*,4′*S*)-DMDHP **34** with the same glucopyranose derivative **112**.[53(c)] In this case, while we still see the 3,4-'matched' products **117** as the major isomer (58%) some of the 2,3-'mismatched' dispiroketal **118** becomes significant (11%), although the two are readily separable.

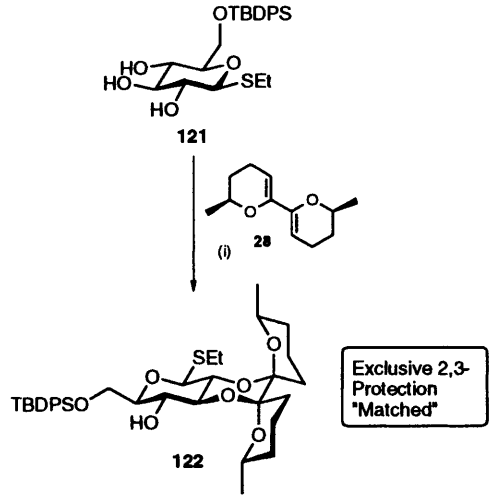
Further reaction of the major 3,4 adduct **117** with benzoyl chloride furnished the fully protected derivative **119**. The dispiroketal was then removed under acidic conditions with 95% trifluoroacetic acid/water giving methyl-2-*O*-benzoyl-α-D-glucopyranoside **120** (**Scheme 38**).



Reagents: (i) CSA (cat.), **34** (1.5 eq.), $CHCl_3$, reflux, overnight, **118** 11% + **117** 58%; (ii) BzCl, DMAP (cat.), pyr, $CHCl_3$, r.t., 2 d, 57%; (iii) 95% TFA, 4 h, r.t., 54%.

Scheme 38

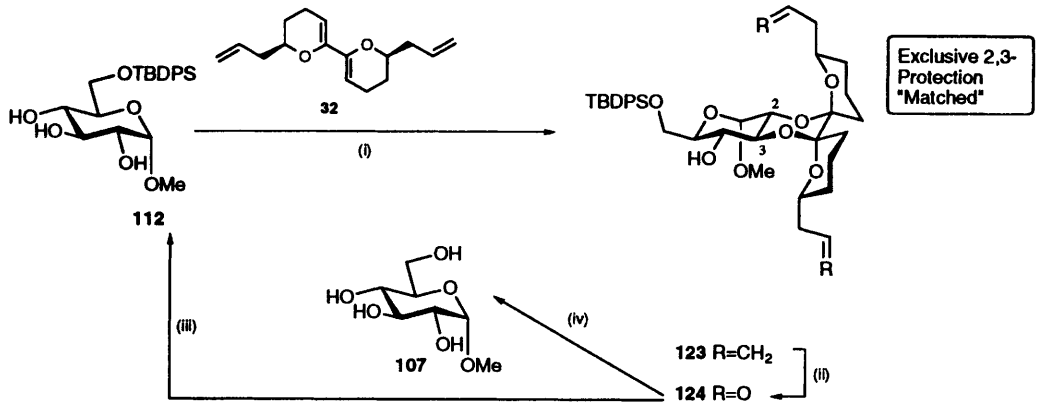
Alternatively, reaction of the glucopyranose derivative **121** with (2*S*,2′*S*)-DMDHP **28** under the usual reaction conditions gave the 2,3-adduct **122** as the exclusive product (**Scheme 39**).



Reagents: (i) CSA (cat.), **28** (1.72 eq.), $CHCl_3$, reflux, overnight, 64%.

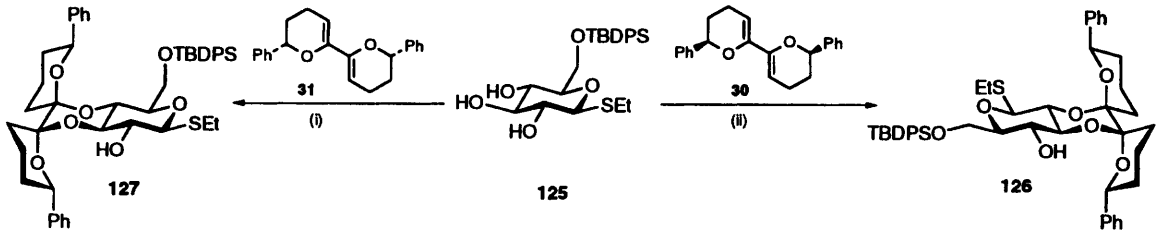
Scheme 39

In another series of experiments we have shown that the diallyl substituted bis-dihydropyran **32** also exhibits exclusive matched diol recognition to give **123** upon reaction with **112** (**Scheme 40**).[41] This is of particular interest because allyl groups can be used to effect an alternative method of deprotection in a two step process involving oxidative cleavage and base-catalysed β-elimination. Thus, ozonolysis to **124** and treatment with DBU leads to recovery of **112**. Use of the Schwesinger base[55] in the elimination step at 0 °C in THF gives not only rapid β-elimination but also removal of the silyl protection to give **107** in good yield (**Scheme 40**).



Reagents: (i) PPTS (cat.), **32** (1.16 eq.), $CHCl_3$, reflux, 2 d, 78%; (ii) O_3, CH_2Cl_2, −78 °C then Ph_3P (1.4 eq.), 7 h, r.t., 100%; (iii) DBU (1 eq.), PhMe, 80 °C, 21 h, 56%; (iv) P_4-*tert*-octyl (1 eq.), 0 °C, THF, 2 h, 73%.

Scheme 40

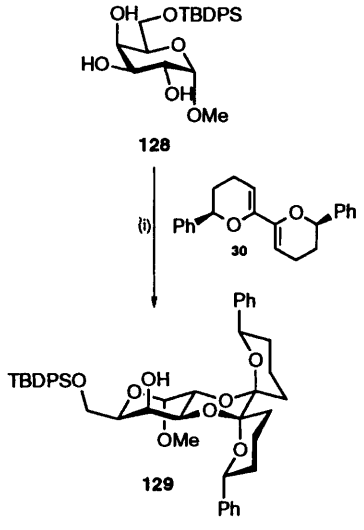


Reagents: (i) CSA (cat.), **31** (1.5 eq.), $CHCl_3$, reflux overnight, 76%; (ii) CSA (cat.), **30** (1.5 eq.), $CHCl_3$, reflux overnight, 82%.

Scheme 41

Since β-thioglucopyranosides represent an alternative and more versatile class of monosaccharide, useful in oligosaccharide synthesis, we have briefly examined the use of chiral bis dihydropyrans to achieve new regioselective protection of these substrates. Reaction of the thioethyl derivative **125** with (2*R*,2′*R*)-DPDHP **30** under standard spiroketalization conditions gave the 2,3-adduct **126** whereas upon reaction with the enantiomeric (2*S*,2′*S*)-DPDHP **31** gave the corresponding 3,4-dispiroketal **127** (**Scheme 41**). Both of these reactions once again proceeded in excellent yield with complete selectivity.[53(c)]

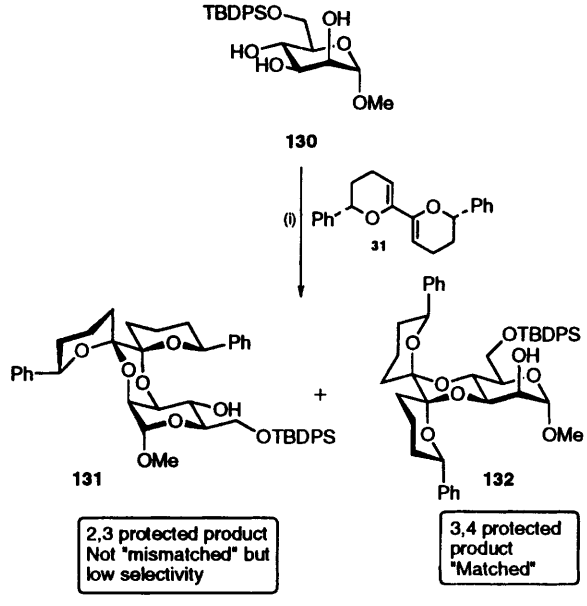
The reaction of these chiral bis-dihydropyrans are not restricted to coupling with gluco-configured substrates. In fact the corresponding galacto derivative **128** reacts with **30** to give the 2,3-matched adduct **129** in 88% yield (**Scheme 42**).



Reagents: (i) CSA (cat.), **30** (1.5 eq.), $CHCl_3$, reflux, overnight, 88%.

Scheme 42

On the other hand the reaction with manno-derivatives such as **130** was less selective. The reaction of **130** with **31** under standard conditions gave a separable mixture of dispoke adducts **131** and **132** in approximately equal amounts. These adducts arise from the protection of both the 2,3- and 3,4-vicinal diol moieties. The poor regioselectivity is disappointing but can be rationalized since both possess fully anomerically stabilized structures and have the phenyl substituents equatorial. The remaining steric interactions are obviously insufficient to discriminate between the formation of the two structures (**Scheme 43**).



Reagents: (i) CSA (cat.), **31** (1.8 eq.), $CHCl_3$, reflux, overnight, **131** 37% and **132** 43%.

Scheme 43

In spite of this one disappointing result we believe this new method of regioselective control in monosaccharide vicinal diol protection is a powerful tool for rapid achievement of protection patterns in carbohydrates which previously have required tedious multi-step procedures using conventional chemistry.

10 Use in oligosaccharide synthesis

In the previous section we described the development of a new enabling methodology for regioselective protection of *trans*-diequatorial 1,2-diols in monosaccharides. Our next step was to show that dispiroketals can also have an effect on the next level of carbohydrate architecture; dispiroketalization of sugar derivatives can have a

dramatic and controlling effect on the rate of coupling reactions in oligosaccharide synthesis.

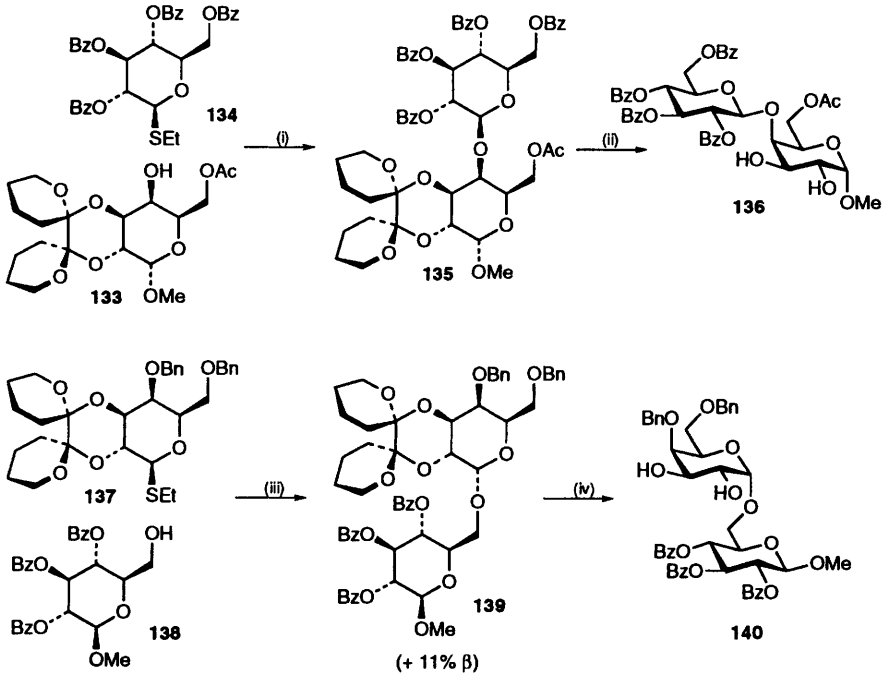
In the first experiments we investigated the steric effects that dispiroketalization might have on disaccharide formation. We therefore studied the coupling of the 2,3-dispiroketalized derivative of galactopyranoside **133**, in which the spiroketal is neighbouring the free hydroxyl group at C-4, with the thioethyl perbenzoylated glucosyl donor **134**. In the presence of *N*-iodosuccinimide (NIS) and triflic acid[56] disaccharide **135** was formed (**Scheme 44**).[9] The dispiroketal protecting group in **135** was removed by treatment with aqueous trifluoroacetic acid to give **136**.

We have also placed the dispiroketal function in the glycosyl donor as in **137** and successfully achieved coupling with the C-6 alcohol of the glucopyranoside derivative **138** to give the disaccharide **139**, again using NIS/triflic acid activation. Disaccharide **139** was formed in respectable yield and with $\alpha:\beta = 4:1$. This could also be selectively deprotected to **140** with TFA/H_2O as before (**Scheme 44**).

These results demonstrate that the dispiroketal group is compatible with glycosidic couplings whether present on the donor or the acceptor moiety. Importantly, we also note that the deprotection reaction proceeds without interfering with other protecting groups such as acetates or benzoates.

Next we considered the important armed/disarmed glycosylation concept introduced by Fraser-Reid[57] which has proven to be an extremely effective strategy for the concise preparation of complex oligosaccharides. The process relies upon the fact that reactivity of the anomeric centre can be regulated by the substitution of the hydroxy groups in the glycosyl donor[58] as ethers,[57(a)] esters[59] or cyclic acetals.[60] For example, a donor having an ether protecting group at C-2 would be highly reactive, and can be chemoselectively coupled to an acceptor bearing a C-2 ester group which would be relatively deactivated. Further glycosylation of the resulting oligosaccharide could be accomplished by using a more powerful activator of the anomeric leaving group or via functional group interconversion. Although this approach is useful there remains an exciting opportunity to tune the glycosyl donor still further and thus release a greater potential for more complex coupling reactions. We envisaged that dispiroketalization, because of the constraining effects of the fused chair ring systems, would inhibit the formation of the intermediate flattened oxonium ion species prior to glycosidic coupling and therefore slow down, that is, tune the rate of the coupling reaction. This tuning process would provide a new range of differentially reactive coupling substrates which would increase chances of achieving *multiple* saccharide coupling reactions.

Accordingly, we find that the highly reactive glycosyl galacto-donor **141** couples with the dispiroketal-detuned galacto-acceptor **142** in the presence of iodonium collidine perchlorate (IDCP) to give the disaccharide **143** in a convincing 82% yield. This undergoes a further coupling with a third manno-acceptor **144** which is deactivated by benzoyl



Reagents: (i) NIS, triflic acid, $ClCH_2CH_2Cl/Et_2O$, 53%; (ii) TFA/H_2O (19:1), 58%; (iii) NIS, triflic acid, $ClCH_2CH_2Cl/Et_2O$, 42%; (iv) TFA/H_2O (19:1), 59%.

Scheme 44

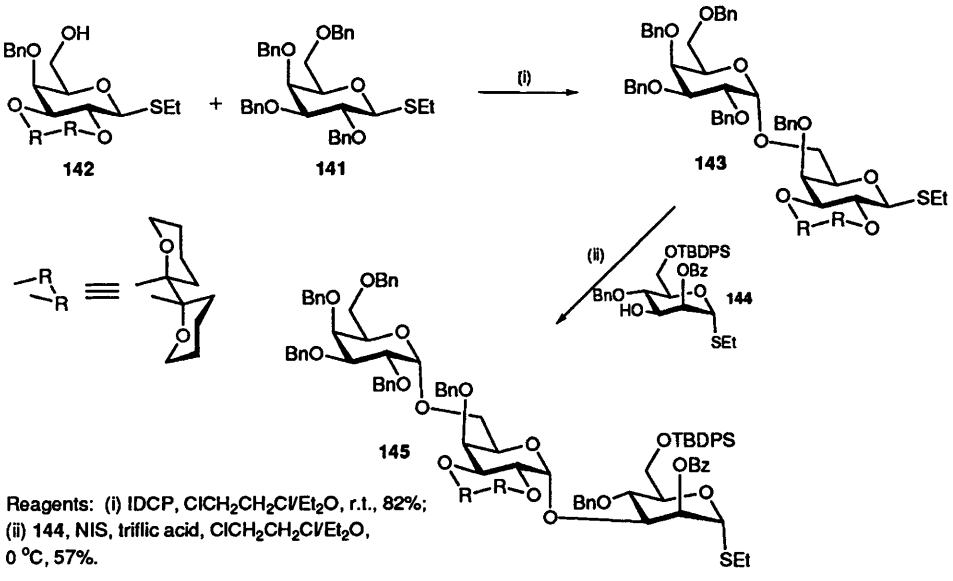
substitution at C-2, with the use of a more vigorous activating agent NIS/TfOH, to give **145** (**Scheme 45**).[61]

These observations have very important implications for the assembly of large carbohydrate molecules. It should be noticed that although the product **145** is deactivated by ester substitution in the manno-ring it is in principle still capable of further coupling with yet another monosaccharide to give a tetrasaccharide. It is conceivable that these reactions could also be performed in one pot and if so this would greatly simplify oligosaccharide synthesis. In connection with other work we have further coupled the trisaccharide **145** with a complex inositol substituted glucosyl derivative **146** to give **147**. This product was of interest in our work on the synthesis of the GPI anchor from *Trypanosoma brucei* (**Scheme 46**).

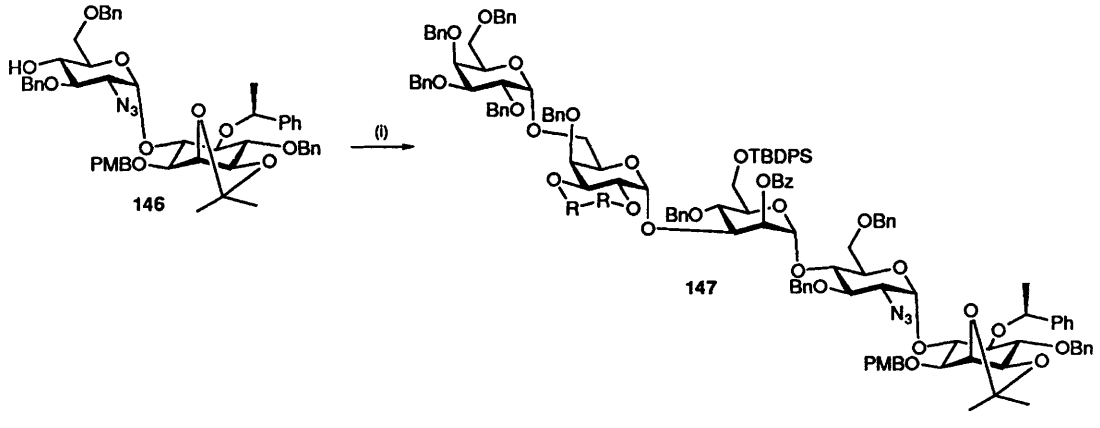
To demonstrate the usefulness of these new coupling ideas we have demonstrated an extremely rapid assembly of a tris-manno derivative. Thus, initial coupling is achieved between two thioethyl manno-derivatives **148** an **149**. The benzyl protected compound **148** was chosen as the reactive glycosyl donor while **149**, the coupling acceptor, was differentiated, detuned in its reactivity, by dispiroketalization. Coupling was effected in the presence of IDCP to give **150**. The third manno derivative **151**, which was fully deactivated by benzoylation at C-2, could then be coupled with **150** to afford **152** in the presence of NIS/triflic acid (**Scheme 47**).[61]

11 Summary and conclusions

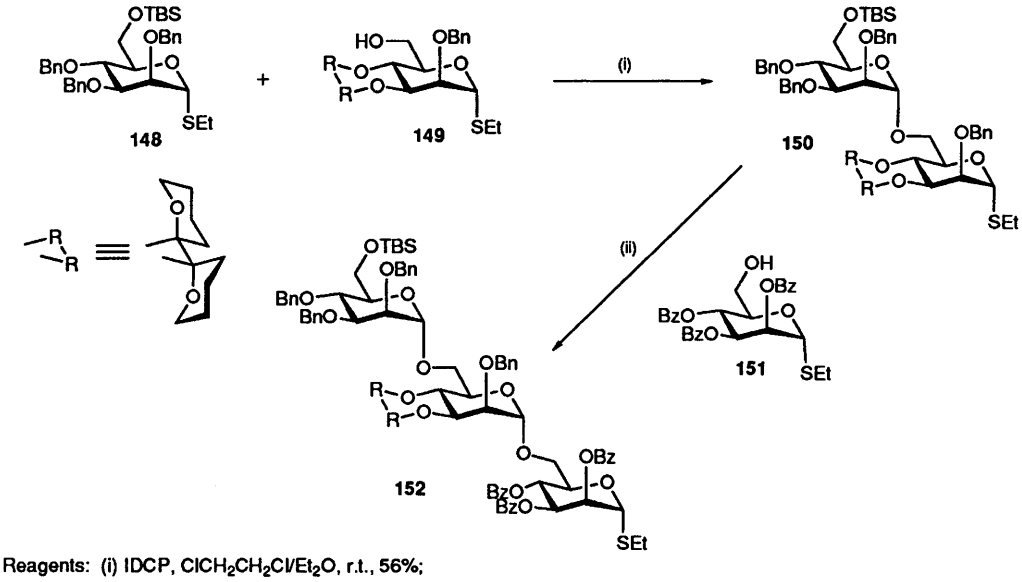
The concepts which we have delineated in the above discussion all harness the special control that can be achieved during the formation of two spiro centres owing to the four anomeric effects, especially when combined with the steric preference of a substituent



Scheme 45



Scheme 46



Reagents: (i) IDCP, $ClCH_2CH_2Cl/Et_2O$, r.t., 56%; (ii) **151**, NIS, triflic acid, $ClCH_2CH_2Cl/Et_2O$, 0 °C, 60%.

Scheme 47

to sit equatorially on a six-membered ring. These powerful principles have already led to the use of dispiroketals to achieve a surprisingly wide variety of synthetic objectives, as described in this review. We can anticipate many more such applications of these architecturally rigid motifs in the future as to date we have only exploited a small selection of the range of possible ring sizes and substitution patterns.

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