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Dispiroketals in Synthesis (Part 9)[1]: Resolution of 1,2-Diols Using a C_2-Symmetric Diphenyltetrahydrobipyran.

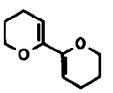
Paul J. Edwards, David A. Entwistle, Steven V. Ley*, Dafydd R. Owen† and Emily J. Perry.

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK.
† Department of Chemistry, Imperial College of Science, Technology and Medicine, London, SW7 2AY, UK.

Abstract: A series of 1,2-diols were resolved by the enantioselective formation of the thermodynamically most stable dispiroketal using (2*R*,2'*R*) and (2*S*,2'*S*) 2,2'-diphenyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran **2** and **3**. Deprotection was achieved using a metal ammonia reduction to liberate the resolved diols.

There are a number of common methods for the enantioselective synthesis of 1,2-diols.[2] These methods do, however, have some limitations. For example the Sharpless *cis*-dihydroxylation of terminal alkenes gives only relatively moderate enantiomeric excesses.[3] In these cases a resolution approach may be the most effective way of accessing chiral materials of high enantiomeric excess.[4]

Previous to this communication we have described the use of the dispiroketal (Dispoke)[1] protecting group as a protective agent in carbohydrate chemistry,[1a] in the synthesis of a stable glyceraldehyde equivalent[1b] and as a rigid lactate protecting group.[1c] The dispoke adducts are formed from the reaction of 3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran **1** with a 1,2-diol. More recently in these laboratories optically active 2,2'-disubstituted-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyrans, for example **2** and **3**, have been developed which take part in enantioselective reactions such as the 1,2-protection and concomitant desymmetrisation of glycerol, and in the regioselective protection of glucose derivatives.[5] We now wish to describe the resolution of 1,2-diols using (2*R*,2'*R*) and (2*S*,2'*S*) 2,2'-diphenyl-3,3',4,4'-tetrahydro-6,6'-bi-2*H*-pyran **2** and **3** ((*R*,*R*) and (*S*,*S*) PDHP).



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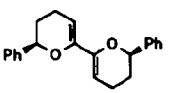

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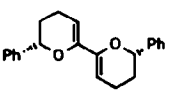
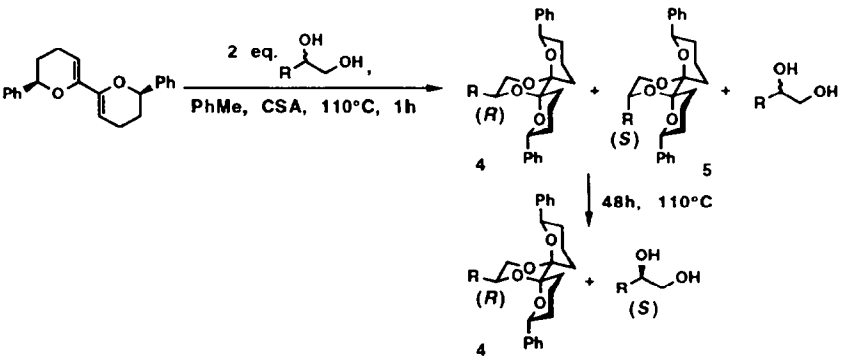


3

Studies have concentrated on the thermodynamically controlled enantioselective reactions of **2** and **3** with a series of vicinal diols, forming diastereomerically pure dispiroketals. The reaction of two equivalents of racemic 1,2-diol with **2** in the presence of camphorsulfonic acid (CSA) in boiling toluene initially gives two fully anomerically stabilised diastereomeric dispoke adducts (*Scheme 1*). The axial diastereomer **4** is formed by the reaction of (*R*,*R*) PDHP **2** with the (2*R*) 1,2-diol while the equatorial diastereomer **5** is formed by reaction of **2** with the opposite (2*S*) diol. On prolonged heating at 110°C equilibration occurs, leading to interconversion of dispoke adducts. This interconversion takes place by deketalisation of one diol enantiomer followed by ketalisation of the opposite enantiomer. Thus the thermodynamically more stable, equatorially substituted, dispiroketal **4** is ultimately formed in high yield. A similar equilibration process takes place with

the opposite (*S,S*) PDHP **3** to selectively protect the other diol enantiomer, forming the enantiomeric dispoke adduct.



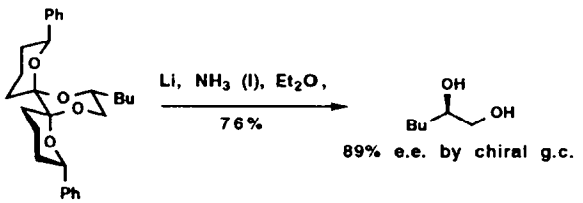
Scheme 1

This thermodynamic resolution procedure was applied to structurally varied 1,2-diols using both **2** and **3** (*Table*).

Theoretically, after reaction of exactly two equivalents of racemic diol with (*R,R*) or (*S,S*) PDHP, one diol enantiomer should be ketalised and the other enantiomer left unreacted. In practice, however, a small amount of diene decomposition occurs during reaction which lowers the optical purity of the unprotected diol and the yield, though not the optical purity, of the dispoke adduct. It was found that when two equivalents of diol were used complete resolution took up to 48h. This rather long reaction time could be decreased by using more equivalents of diol. However, 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. When diols and triols decomposed under the acidic reaction conditions lower yields of dispiroketals were obtained, but these could again be improved by the use of excess diol.

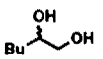
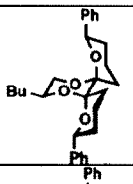
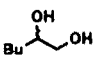
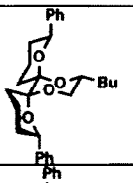
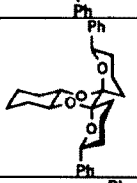
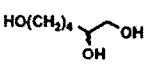
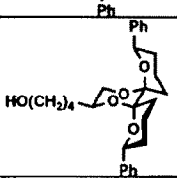
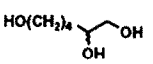
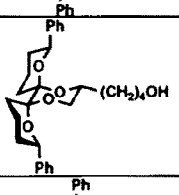
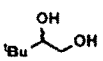
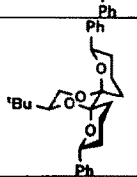
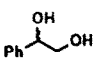
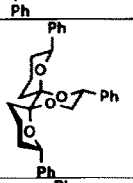
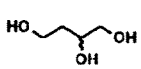
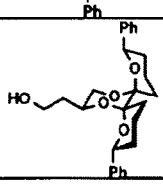
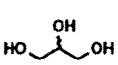
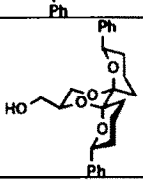
It is usually the case that in the synthesis of a particular natural product only one enantiomer is required as the two enantiomers may have different biological activity.[6] Since each diol enantiomer is "matched" to one of the PDHP enantiomers, for example, (*R,R*) PDHP selectively protects (*S*) hexane-1,2-diol, while (*S,S*) PDHP selects the (*R*) diol, correct choice of either (*R,R*) or (*S,S*) PDHP will facilitate ketalisation of the desired diol.

With a facile procedure for the formation of optically active dispoke adducts now available, we turned our attention to the liberation of the resolved, enantiomerically pure, diol. This can be achieved by treatment of the dispoke adduct with lithium in liquid ammonia (*Scheme 2*). The dissolving metal reduction affords a good yield and high enantiomeric excess of the resolved diol.



Scheme 2

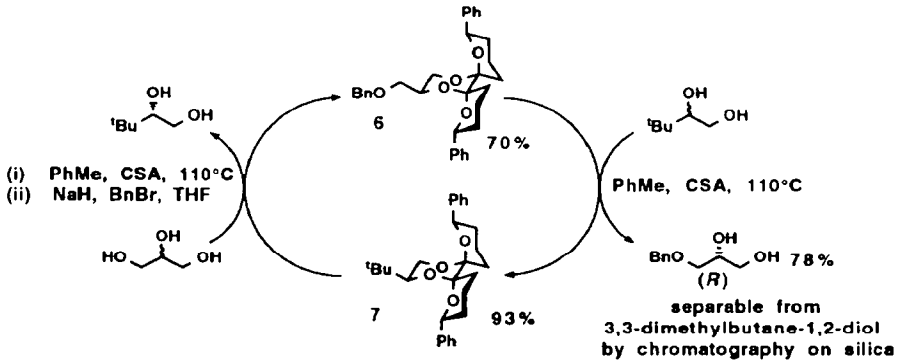
Table

PDHP	Diol	Dispoke Product	Yield[a] %	PDHP	Diol	Dispoke Product	Yield[a] %
2			93	3			90
2			80	3			82
2			47	3			46
2			90	3			35
2			91	3			96
2			62	2			72

(a) Yields based on PDHP

The lithium-ammonia deprotection functions well but involves destruction of the chiral auxiliary. It is apparent that since the homochiral (>98% e.e.) PDHP gives deprotected diol with an enantiomeric excess of less than 98%, there is a partial racemisation process occurring during ketalisation and/or deprotection. Studies are now in progress to ascertain whether this is due to the rather harsh equilibration conditions.

A more efficient approach to deketalisation is a ketal exchange (*Scheme 3*) where the diol, in this case benzyl-protected glycerol, is unmasked and a new dispiroketal **7** formed by equilibration of the dispoke adduct **6** with a new diol. Equilibration of **7** with a further portion of the diol to be resolved leads to a recycling of the optically active dispiroketal.



Scheme 3

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