Partial separation of enantiomeric 1,2-diols *via* ketal formation with a polymer-supported chiral ketone

Ian D. Clarke and Philip Hodge*

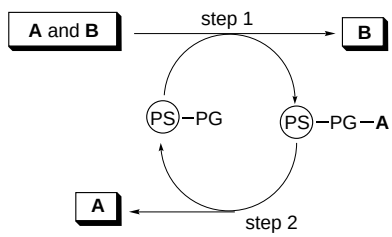
Department of Chemistry, University of Manchester, Oxford Road, Manchester, UK M13 9PL

Partial separations of the (*R*,*R*)- and (*S*,*S*)-enantiomers of butane-2,3-diol, *trans*-cyclohexane-1,2-diol and dimethyl tartrate were achieved *via* ketal formation with a polymer-supported 7-keto steroid; in each case one enantiomer reacted in higher yield than the other and release of the diols from the support gave diol fractions significantly enriched in one enantiomer

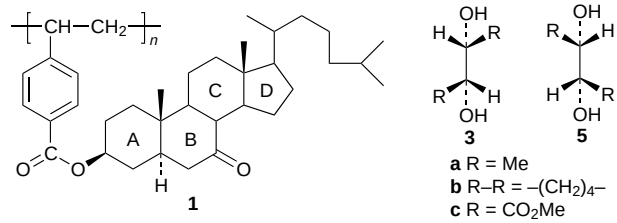
In recent years many organic reactions have been carried out which involve polymer-supported (PS) species.[1] The most well known examples are those involved in 'solid phase' peptide syntheses.[2] The latter can be viewed as examples of organic reactions using PS substrates and also as examples of the use of PS protecting groups (PS-PGs),[3] in this case for carboxylic acids. Reactions involving PS substrates are currently of great interest in combinatorial chemistry.[4,5] Organic reactions involving PS reagents and PS catalysts have also been studied extensively.[1]

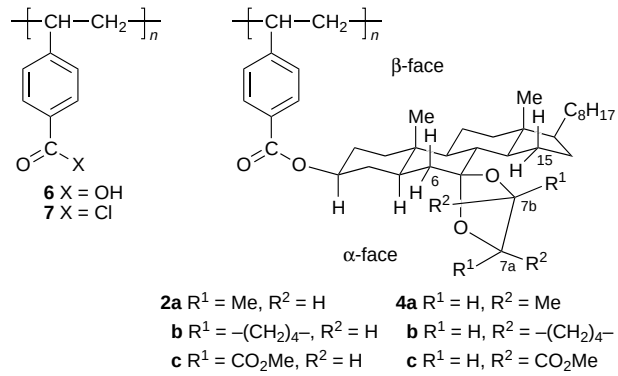
An application of PS species which has received little attention is the use of PS-PGs to achieve separations by the procedure summarised in Scheme 1. In step 1 the mixture of compounds to be separated, **A** and **B**, is treated with a PS-PG which selectively binds **A** to the support. Those components, **B**, of the mixture that fail to bind to the support are recovered. In step 2, the components of the original mixture, **A**, bound to the support are released by carrying out the appropriate 'deprotection' procedure. Thus, **A** is separated from **B** and the PS-PG is available for re-use. This method of achieving separations is less laborious than column chromatography and potentially it could be automated. Examples of this separation procedure being used in organic chemistry include the use of a PS-diol to separate 3-keto steroids from 17- and 20-keto steroids,[6] and of a PS-boronic acid to separate the *cis*- and *trans*-isomers of cyclohexane-1,2- and -1,3-diols.[7]

This communication is concerned with the separation of mixtures of *enantiomeric* diols *via* ketal formation with a PS chiral ketone. The PS chiral ketone selected for this initial study was an ester **1** of 3β-hydroxy-5α-cholestan-7-one. Inspection of Dreiding models of the ketals **2** derived from PS-ketone **1** and diols **3** indicates that the **R¹** groups at the 7b-position will experience significant steric interactions with the D-ring (especially the 15α-hydrogen) whilst the **R¹** groups at the 7a-position will not experience any significant non-bonding interactions with other parts of the steroid nucleus. In the ketals **4** derived from diols **5** the **R²** groups at the 7b-position may experience minor non-bonding interactions with the 6α-hydrogen whilst those at the 7a-position will again not experience any significant interactions. Thus, the PS ketone **1** is expected to bind diols **5** more readily than diols **3**. The presence of two **R** groups in each diol is necessary to ensure that one **R** group is present at the crucial 7b-position.



Scheme 1





Gel-type polystyrene beads crosslinked with 2% of divinylbenzene and containing carboxylic acid residues **6** (1.10 mmol g^{-1}), were prepared from commercial blank crosslinked beads *via* lithiated polystyrene.[8,9] The carboxylic acid groups **6** were converted into acid chloride residues **7**, the latter reacted with 3β-hydroxy-5α-cholestan-7-one,† and the unreacted residues **7** capped with MeOH essentially as described before.[13] This gave polymer beads containing residues **1** with a loading (0.60 mmol g^{-1}), similar to that reported before.[13]

Ketal formation (step 1) was achieved by treating mixtures of enantiomeric diols in toluene at reflux temperature with PS ketone **1** in the presence of a catalytic amount of toluene-*p*-sulfonic acid (PTSA). The reaction was carried out for 56 h in an apparatus equipped with a Dean–Stark trap. At the end of the reaction period the beads were filtered off and unbound diol recovered. The ketalisation yield, *i.e.* the percentage of supported ketone converted into the ketals, was estimated from the amount of unbound diol. The bound diol was released (> 97% recovered) by treating the PS ketal at 20 °C for 22 h with wet dioxane containing a catalytic amount of PTSA. All diol fractions were shown to be > 98% pure by ^{1}H NMR spectroscopy. The percentage enantiomeric excesses of diol samples (ees) were estimated by polarimetry and/or chiral GC. The results are summarised in Table 1.

The separation of the (*R*,*R*)- and (*S*,*S*)-butane-2,3-diols was studied initially: see entries 1–7. It is evident that both diols

bound to the beads, but that, as expected, the (*S*,*S*)-diol **5a** bound in higher yields. The ketalisation yield was, however, only 57% even when equimolar amounts of (*S*,*S*)-diol **5a** and ketone **1** were used (entry 1). This may be due in part to some of the bound ketone being inaccessible due to steric crowding.[13] The diol recovered from the beads had a 42% ee of the (*S*,*S*)-diol **5a**. With an equimolar amount of racemate (*i.e.* 0% ee) as the starting material (entry 2) the diol recovered from the beads had a 39% ee of the (*S*,*S*)-diol **5a**. This rose to a 47% ee when the recovered diol was recycled (entry 3). The initial result (entry 2) indicates that 65% of the original (*S*,*S*)-diol **5a** bound to the beads whereas 29% of the (*R*,*R*)-diol **3a** bound, *i.e.* the yield ratio for the enantiomers was 2.2 : 1.

Apart from resolving racemates, other useful applications of the present type of system could involve raising the ee of reaction products from asymmetric syntheses. This might be achieved either by *concentrating* the major enantiomer or by *removing* the minor enantiomer. Starting with a mixture of butane-2,3-diol enantiomers having an 80% ee of the (*S*,*S*)-isomer **5a**, see entry 4, the diol recovered from the beads had a 90% ee. Similarly a starting material with 90% ee gave a product of 94% ee. This rose to a 97% ee when the recovered diol was recycled (entry 6). Thus through three cycles (entries 4–6) the ee of the (*S*,*S*)-diol **5a** was raised from 80 to 97%. Attempts to remove the (*S*,*S*)-enantiomer **5a** from a mixture having an 80 ee of the (*R*,*R*)-enantiomer **3a** was less successful (entry 7). After treating a five-fold excess of the mixture with the beads, the ee of recovered *unbound* diol had increased to only 82%. Evidently the binding of the preferred (*S*,*S*)-diol **5a** was almost entirely offset by the large proportion of the (*R*,*R*)-diol **3a** present.

Table 1 Separation *via* ketal formation with PS keto steroid **1**

	Starting material[a]				Recovered diol[b]	
Entry	**3**,**5**	Ee (%)	Enantiomer in excess	Ketalisation yield (%)	Ee (%)[c]	Enantiomer in excess
1[d]	**a**	0	—	57	42	*S*,*S*
2	**a**	0	—	47	39	*S*,*S*
3	**a**	39	*S*,*S*	37	47[e]	*S*,*S*
4	**a**	80	*S*,*S*	43	90[f]	*S*,*S*
5	**a**	90	*S*,*S*	49	94	*S*,*S*
6	**a**	94	*S*,*S*	42	97[e]	*S*,*S*
7[g]	**a**	80	*R*,*R*	90[h]	82[i]	*R*,*R*[g]
8	**b**	0	—	11	55[f]	*S*,*S*
9	**b**	80	*S*,*S*	20	92	*S*,*S*
10	**c**	0	—	9	72[e]	*R*,*R*

[a] Except where indicated otherwise, ratio of diol to ketone was 1 : 1. [b] Except where indicated otherwise, the diol fraction examined was that obtained by deketalisation. The recoveries were > 97%. [c] Unless indicated otherwise, the ees were determined both by polarimetry and chiral GC. The results were in close agreement (±1%). Polarimetry was based literature values (ref. 14): $[\alpha]_D^{20}$ +13.0 (neat) for **5a**; $[\alpha]_D^{20}$ + 36.7 (*c* 0.45 in H_2O) for **5b**; $[\alpha]_D^{20}$ + 20.0 (*c* 20 in H_2O) for **5c**. Chiral GC was carried out using a CP-Chirosil-DEX CB stationary phase. [d] Ratio of diol to ketone was 2 : 1. [e] Ee determined by polarimetry only. [f] Ee determined by GC only. [g] This experiment used a five-fold excess of the diol and focused on the *unbound* diol. [h] Percentage of starting material *not* bound. [i] The *unbound* diol fraction was examined.

The ketalisation yields were lower starting with racemic mixtures of the (*R*,*R*)- and (*S*,*S*)-*trans*-cyclohexane-1,2-diols and dimethyl (*R*,*R*)- and (*S*,*S*)-tartrates (entries 8–10) but the recovered diols had higher ee, 55 and 72% respectively, than with butan-2,3-diol. Thus, the more significant the steric interactions the greater the discrimination between the enantiomers but the lower the chemical yield. It should be noted here that with a perfect discrimination between the enantiomers and all the ketone residues of **1** fully available, starting with racemates the ketalisation yields would be only 50%. As expected the enantiomers which bound in the higher yields were the (*S*,*S*)-enantiomer **5b** and (*R*,*R*)-enantiomer **5c**. The results using the racemates as starting materials indicate yield ratios of 6.9 : 1 with the enantiomeric diols **5b** and **3b** and 6.1 : 1 with the enantiomeric diols **5c** and **3c**.

The keto steroid had no tendency to detach from the beads under the reaction conditions used in this study. Thus, no steroid was detected by ^{1}H NMR spectroscopy in any of the diol fractions. Indeed, the FT–IR spectrum of the PS ketone **1** at the end of the experiments was indistinguisable from that when first prepared. All the above results were obtained with one batch of resin, thus demonstrating that the PS ketone **1** can be recycled.

This initial study shows that significant separations of enantiomers can be achieved using the procedure outlined in Scheme 1. The procedure could undoubtedly be automated. Future work is being directed towards identifying chiral molecules which are more discriminating between the enantiomers and which permit higher loadings to be achieved.

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Footnotes

* E-mail: philip.hodge@man.ac.uk

† 3β-Hydroxy-5α-cholestan-7-one, mp 168 °C (lit.,[10] 170.5–171.5) and $[\alpha]_D^{20}$ −33 (*c* 2 in chloroform) {lit.,[11] $[\alpha]_D^{20}$ −36 (*c* 1.6 in chloroform)}, was prepared by oxidising cholesteryl acetate with chromic acid,[12] hydrogenating (Pd–charcoal) the product, then hydrolysing the ester group.

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