Toward preparative resolution of chiral alcohols by an organic chemical method†

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Asymmetric alcohols were resolved as 1-α-*O*-alkyl-2,3-unsaturated hexosides. After separation of diastereoisomers, the auxiliary and the enantiomeric alcohol were recovered by transglycosidation. Potential applications include resolution of labile secondary and tertiary alcohols, difficult by existing techniques, and enhancement of ees of chiral alcohols produced enzymatically or by synthetic catalytic methods.

Organic chemical methods for resolving racemic mixtures of alcohols have proven difficult to develop, somewhat cumbersome to use and they appear to have limited scope.[1] Consequently, bio-organic approaches, commonly involving enantioselective enzymatic hydrolysis of racemic esters or stereoselective reduction of ketones, have gained favour.[2a,b] Their disadvantages, however, can include needs for high dilution, low throughputs of substrate, lengthy reaction times, low reactivity of sterically crowded molecules and difficulties with isolation.[2c–f] Encouragingly though, reports indicating early signs of progress in the resolution of sterically crowded molecules including tertiary alcohols, by enzymatic means, have appeared.[3]

With regard to synthetic approaches, a strategy involving thermal retro Diels–Alder reactions was recently disclosed.[4a] Most commonly, however, enantiospecific syntheses of asymmetric alcohols utilise precursor aldehydes, but such processes tend not to afford uniformly high ees with any one particular catalyst.[4b,c] Consequently, enantiomeric alcohols that are not readily accessible through the chiral pool[5] tend to be available in limited quantities and at premium prices.

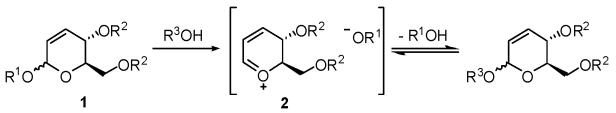
We now report preliminary studies toward a novel and green organic chemical approach for the preparative resolution of alcohols. It was considered that a chiral auxiliary could satisfy commercial requirements, including objectives of green chemistry,[6] if it had broad applicability and was effective, readily accessible, of relatively low molecular weight and low toxicity, and chemically stable, as well as easy to apply and to remove by reversible, efficient, non-hazardous methods.

Ferrier reaction[7] of glycals with racemic alcohols has already been employed to produce 2,3-unsaturated glycosides of optically active alcohols.[1j,k] Separation of the respective diastereoisomers and acid hydrolysis can afford individual enantiomers of the alcohol. A major drawback is that loss of the auxiliary sugar after successive chemical transformations renders the method wasteful and impractical for general use. Acid hydrolysis employed to cleave the glycosides also has the potential to affect the enantiomeric purity and to degrade some alcohols.

In this work, we have investigated a potential low-waste process that would not require strong acid and that involves the use and recycling of 2,3-unsaturated hexosides, *e.g.* **1** (Scheme 1) of low molecular weight alcohols such as MeOH and EtOH, as chiral auxiliaries. The aim was to attach and detach the chiral alcohol from such auxiliaries under mild conditions, by Lewis acid-catalysed transacetalisation processes that would afford optically enriched alcohols and enable the glycosidic moiety to be recycled.

It was hypothesised that attack by the chiral alcohol (*i.e.* that to be resolved) at the anomeric centre of the auxiliary would not proceed by nucleophilic substitution of **1**, but rather through a cationic intermediate such as **2** (Scheme 1), by a pathway analogous to that proposed for the Ferrier rearrangement and Ferrier glycosylation of 1,2-glycals.[8] If that premise were to hold, literature reports suggested that, owing to a strong anomeric effect, α-epimers would predominate.[9] Hence, racemic alcohols possessing one asymmetric centre would be expected to give essentially two major diastereoisomers instead of four. Somewhat surprisingly, literature precedents for transacetalisation of an *O*-glycoside of a 2,3-unsaturated hexose are rare.[10] Searches did not reveal any examples concerned with alcohol resolution.

The present process, outlined in Scheme 2 with racemic alcohol $R^3R^4R^5COH$, contains three key steps: (1) transacetalisation of resolving agents such as **1** by the racemic



Scheme 1 Pathway proposed for transacetalisation of 2,3-unsaturated hexosides.

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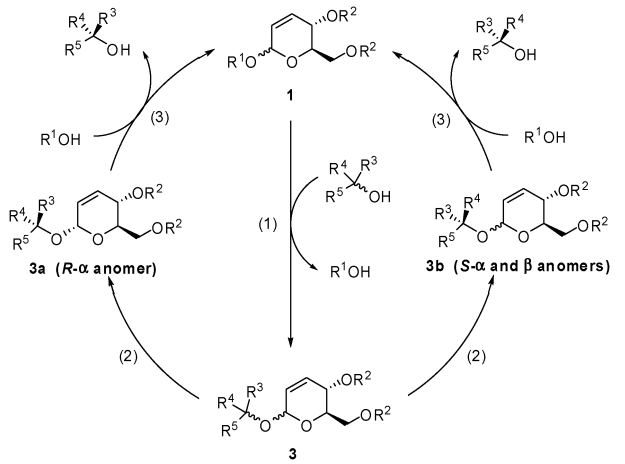
† Electronic supplementary information (ESI) available: Experimental methods, procedures and characterisation data of all new compounds. See DOI: 10.1039/b9nj00768g



Scheme 2 Cycle of alcohol resolution *via* transacetalisation.

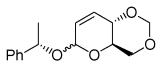
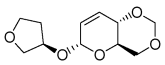
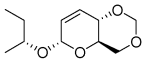
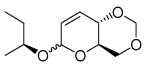
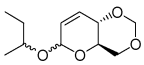
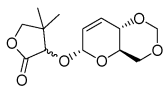
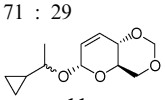
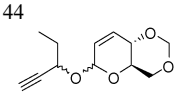
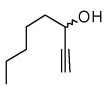
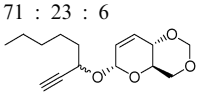
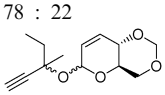
alcohol to afford a mixture of diastereoisomeric glycosides **3** of (*R*) and (*S*)-alcohols, with loss of R^1OH (typically MeOH or EtOH), (2) isolation and separation of diastereoisomeric glycosides **3a** and **3b** and (3) reverse transacetalisation of **3a** or **3b** with R^1OH to release the (*R*) or (*S*)-alcohol and to re-form the resolving agent **1**.

The relative stereochemistries about the asymmetric centres of auxiliaries **1** are depicted by way of illustration only, in Schemes 1 and 2. A wide array of auxiliaries analogous to **1** is possible, for example *via* *O*-derivatisation at the C4 and C6 positions as well as through the use of glycals obtained from various sugars or by total synthesis.[11] Such variations can influence properties such as polarity and crystallinity of the auxiliaries and their derivatives. Herein, the principle has been demonstrated through examples with novel auxiliary **4** derived from glucose. Auxiliary **4** was readily produced. It occurred predominantly as the α-anomer and was crystalline. This latter property was advantageous for preparative applications, but was somewhat offset by a tendency to sublime, behaviour that would militate against industrial applicability of **4**.

Regarding Step 1 (Scheme 2), glycosylation of racemic chiral alcohols was carried out in solvents of relatively low polarity. Toluene was preferred from the standpoint of green chemistry. K10 Montmorillonite clay or $BF_3{\cdot}OEt_2$ were employed as catalysts. Temperatures ranged from ambient to 80 °C depending upon the stability of the components under the conditions applied. The forward reaction was promoted by removal of MeOH or EtOH under partial vacuum (*ca.* 20 mmHg pressure) or, with MeOH, by 4 Å molecular sieves. The efficacy of K10 Montmorillonite as a catalyst appeared to vary with individual batches. Acid-treated clay gave higher conversions in shorter times. Significantly, during this step the isomeric ratio of products did not appear to be affected by reaction time or temperature.

As shown in Table 1, transacetalisation with different classes of alcohols was carried out with the methylene bridged auxiliary **4** and K10 Montmorillonite as catalyst, at temperatures of 50–80 °C. Alcohols including (*S*)-1-phenylethanol (**5**), (*R*)-3-hydroxytetrahydrofuran (**6**), (*R*), (*S*) and *rac*-2-butanols (**7**, **8** and **9**), *rac*-pantolactone (**10**), *rac*-α-methyl cyclopropanemethanol (**11**), *rac*-1-pentyn-3-ol (**12**), *rac*-1-octyn-3-ol (**13**) and *rac*-3-methyl-1-pentyn-3-ol (**14**) underwent substantial or complete conversion.

Table 1 Transacetalisation of auxiliary **4** with alcohols **5–14**

Entry	Alcohol	Product	Isolated yield (%)
1	 **5**	 (*S*)-α **5a** : (*S*)-β **5b** 85 : 15	45
2	 **6**	 **6a**	58
3	 **7**	 **7a**	72
4	 **8**	 **8a**	67
5	 **9**	 (*R*)-α **9a** : (*S*)-α **9b** : (*S*)-β **9c** 53 : 43 : 4	57
6	 **10**	 (*R*)-α **10a** : (*S*)-α **10b** 71 : 29	41 (**10a**) 4 (**10b**)
7	 **11**	 **11a** 56 : 44	40
8	 **12**	 (*R*)-α **12a** : (*S*)-α **12b** : (*S*)-β **12c** 71 : 23 : 6	61
9	 **13**	 (*R*)-α **13a** : (*S*)-α **13b** 78 : 22	39 (**13a**) 12 (**13b**)
10	 **14**	 **14a**[a] 57 : 43	15[b], 51[c]

[a] Stereochemistries were not determined. [b] Partially isolated as a single anomer. [c] Remainder of eluted adduct was a mixture of anomers.

The use of enantiomerically enriched alcohols (ee > 98%) in transacetalisations (entries 1–4, Table 1) established that epimerisation about the asymmetric centre was negligible under the conditions used. Furthermore, all of the (*R*)-alcohols investigated gave α-anomers exclusively. (*S*)-Alcohols tended to afford α-anomers predominantly, but unfortunately, not exclusively. Nonetheless, the stereoselectivity was usually around 4 : 1 and strongly favoured the α-anomer (see entries 1 and 5 in Table 1). This result was consistent with findings reported for Ferrier glycosylation of alkynols by Schreiber *et al.*[12] Significantly, in some cases, the transglycosylation step

itself displayed enantioselectivity. Indeed, more than 70% of the (*R*)-α adduct was obtained from *rac*-pantolactone (**10**), *rac*-1-pentyn-3-ol (**12**) and *rac*-1-octyn-3-ol (**13**) (entries 6, 8 and 9).

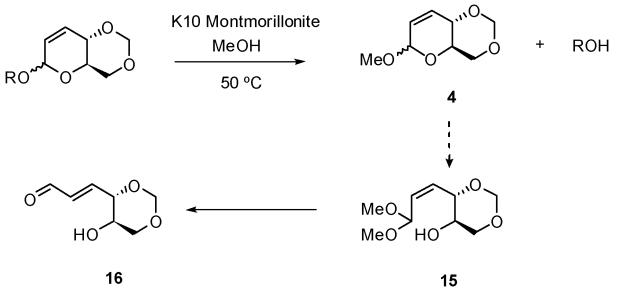
Of particular interest, the transacetalisation of a racemic tertiary alcohol, 3-methyl-1-pentyn-3-ol (**14**), also showed enantioselectivity. Analysis of the isolated adduct **14a** (Table 1, entry 10) by ^{13}C NMR and GC showed an enantiomeric ratio of 4 : 3 for derivatised alcohol **14**. Although the absolute stereochemistries were not determined, the enantiomeric ratio was preserved in the liberated alcohol **14** after reverse transacetalisation. This indicated that racemisation about the tertiary centre did not occur during the process and confirmed the applicability of the approach to tertiary alcohols, which otherwise can be reactive under acidic conditions.

Cyclopropylcarbinols also are acid labile, affording ring expansion and ring opening[13] and 1-phenylethanol (**5**) readily undergoes acid-catalysed dehydration which can lead to the formation of bis(α-methylbenzyl)ether.[14] In a literature example, the success of Ferrier glycosylation with acid-sensitive alcohols was dependent upon the Lewis acid catalyst used.[15] Herein, the stability of auxiliary **4**, together with the relatively mild conditions required for transacetalisation at C1, precluded decomposition of all labile alcohols investigated. Successful transacetalisation with *rac*-α-methylcyclopropanemethanol (**11**), *rac*-1-pentyn-3-ol (**12**), and *rac*-1-octyn-3-ol (**13**) demonstrated the feasibility of the process regarding that aspect.

Differences in polarity between the reactants and the products were exploited where possible, to facilitate isolation and separation of the components. In Step 1 (Scheme 2), a relatively non-polar auxiliary is attacked by a polar racemic alcohol to afford a relatively non-polar diastereoisomeric mixture of derivatised chiral alcohols. A volatile, polar alcohol of low MW is liberated. As mentioned, the leaving alcohol (shown as R^1OH) can be removed under reduced pressure or, in some cases, with molecular sieves, leaving a mixture of derivatised and underivatised chiral alcohols. In some cases the mixture could be class-separated by solvent partition with pentane and a mixture of MeOH–saturated aqueous $NaHCO_3$ (1 : 1). The glycosides were partitioned into the hydrocarbon solvent and the unreacted alcohol dissolved in the aqueous phase. The isolated glycosides may be separated chromatographically if necessary or, preferably, by crystallisation, as illustrated for **10a**.

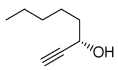
Forward reactions (Step 1, Scheme 2) usually proceeded readily. Not surprisingly then, the positions of equilibrium often disfavoured reverse reactions. In those cases, Step 3 required more forcing conditions than did Step 1. It was carried out with either MeOH or EtOH, depending upon the regenerated auxiliary desired, but typically with a higher loading of K10 Montmorillonite than for the forward process. Temperatures exceeding 50 °C tended to promote decomposition of the auxiliary, typically through ring opening of the pyran to afford an acetal, **15**, and/or an enal, **16**[16] (Scheme 3 and Table 2).

Reverse transacetalisation (depicted as Step 3, Scheme 2) was carried out on (*R*)-α-pantolactone adduct **10a** and (*R*)-α-1-octyn-3-ol adduct **13b** as shown in Table 2. Here also, release of (*R*)-α-1-octyn-3-ol required a substantially higher loading



Scheme 3 Decomposition of auxiliary **4** during transglycosylation.

Table 2 Release of chiral alcohols from adducts **10a** and **13b**

Entry	Adduct	Chiral alcohol	Isolated yield (%) 4 : alcohol : 15	% ee[a]
1	**10a**	 **10c**	18 : 35 : 13	>99
2	**13b**	 **13c**	23 : 38 : 22	>99

[a] Assessed by chiral GC.

of acid washed K10 Montmorillonite catalyst and a longer reaction time than did the forward reaction (Step 1, Scheme 2). Chiral alcohols **10c** and **13c** were recovered in reasonable yields and with high ee, as determined by chiral GC (Table 2). Auxiliary **4** was not fully recovered, owing to ring opening to the acetal **15**. The ultimate objective, establishment of industrially viable methodology, will depend upon the use of auxiliaries that are more stable under the conditions of transacetalisation.

To summarise, in this preliminary study, proof of principle has been demonstrated for a novel organic chemical approach toward resolution of chiral alcohols. A proposed reaction cycle involving three steps and the use of glycosides of 2,3-unsaturated hexoses has been validated experimentally, but yields and recoveries are not yet satisfactory. Non-enzymatic resolution of chiral tertiary alcohols has been addressed apparently for the first time. Although auxiliary **4** was the illustrative resolving agent employed herein, it could not be recovered quantitatively for future use, so its potential for industrial scale applications appears to be limited. However, given the wide array of naturally occurring sugars and scope for their derivatisation, there are ample opportunities for preparing robust auxiliaries. Apart from tertiary alcohols, the methodology was applied to secondary alcohols including those with additional reactive functionality. Such alcohols can be difficult to resolve by existing alternative techniques. After refinement of the technique, potential applications could include separation of racemic mixtures as well as enrichment of optically active alcohols produced enzymatically or by synthetic catalytic methods that do not afford high enantiomeric excesses in the reactive step. We acknowledge the ARC for funding this work.

Experimental

Full experimental details are provided as ESI.† Representative procedures for the preparation of auxiliary **4**, formation of the adducts of pantolactone (**10**) with this auxiliary and recovery of one enantiomer of the resolved alcohol and auxiliary follow.

Auxiliary preparation

Methyl-2,3-dideoxy-4,6-*O*-methylene-α-D-*erythro*-hex-2-enopyranoside (**4**) was prepared by a method adapted from the procedure of Lipták *et al.*[17] To a solution of methyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (1.00 g, 6.24 mmol) in DMSO (6 mL) was added NaOH (1.00 g, 24.96 mmol) as a powder. This mixture was stirred at 60 °C for 30 min under N_2 prior to the addition of CH_2Br_2 (1.14 g, 6.55 mmol). After 1.5 h at 60 °C the mixture was poured into water (20 mL) and extracted with diethyl ether (3 × 20 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil, which, after chromatographic purification (silica column eluting with diethyl ether–pentane = 7 : 2), yielded **4** as a white crystalline solid (0.46 g, 43%), mp 85.5–85.9 °C. IR (Nujol) ν cm^{-1} 2893, 2463, 1737, 1711, 1150, 1107, 1061, 1022, 998, 968, 940, 916, 893, 722, 670. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.07 (m, 1H), 5.71 (ddd, J = 2.3, 2.5, 10.3 Hz, 1H), 5.06 (d, J = 6.2 Hz, 1H), 4.85 (m, 1H), 4.67 (d, J = 6.2 Hz, 1H), 4.18 (m, 1H), 3.86 (m, 1H), 3.73 (m, 1H), 3.54 (t, J = 10.3, 1H), 3.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 130.7, 126.9, 96.1 (anomeric-C), 94.1, 75.3, 69.4, 64.2, 56.1. Mass spectrum (ESI^+, MeOH) m/z calculated for $[C_8H_{12}O_4Na]^+$ 195.0629, found 195.0633.

Adduct formation

rac-Pantolactone (**10**) (450 mg, 3.49 mmol) and methyl-2,3-dideoxy-4,6-*O*-methylene-α-D-*erythro*-hex-2-enopyranoside (**4**) (200 mg, 1.16 mmol) were dissolved in dry toluene (5 mL) and acid-treated K10 Montmorillonite (60 mg, 30 wt%) and 4 Å molecular sieves added. After heating at 75 °C for 20 h the clay and molecular sieves were removed by filtration and the solvent evaporated to give a yellow oil. GC analysis indicated 93% conversion to product with a ratio of (*R*)-α adduct **10a** : (*S*)-α adduct **10b** = 71 : 29. Upon trituration with methanol the (*R*)-α adduct **10a** crystallised as a white solid (126 mg, 41%), mp 192.4–194.6 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.12 (d, J = 10.8 Hz, 1H), 5.85 (m, 1H), 5.44 (br s, 1H), 5.07 (d, J = 6.2 Hz, 1H), 4.69 (d, J = 6.2 Hz, 1H), 4.16 (s, 1H), 4.12 (dd, J = 4.7, 10.3 Hz, 1H), 4.03 (d, J = 8.8 Hz, 1H), 3.94 (d, J = 8.9 Hz, 1H), 3.89 (br s, 1H), 3.77 (m, 1H), 3.56 (m, 1H), 1.20 (s, 3H), 1.11 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2, 130.9, 126.5, 94.1, 93.9, 78.6, 76.4, 75.1, 69.1, 64.5, 40.1, 22.9, 19.6. Mass spectrum (ESI^+, MeOH) m/z calculated for $[C_{13}H_{18}O_6Na]^+$ 293.1001, found 293.0997.

A small quantity of the (*S*)-α adduct **10b** was recovered as a yellow oil post column chromatography and partition (12 mg, 4%), ^1H NMR ($CDCl_3$, 300 MHz) δ 6.15 (d, J = 10.9 Hz, 1H), 5.77 (td, J = 2.5, 10.3 Hz, 1H), 5.06 (br d, 2H), 4.67 (d, J = 6.2 Hz, 1H), 4.28 (m, 1H), 4.08–3.88 (m, 5H), 3.48 (m, 1H), 1.20 (s, 3H), 1.11 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.5, 132.1, 125.6, 96.3, 94.2, 80.8, 75.9, 75.0, 69.1, 64.5, 40.5, 23.5, 19.5. Mass spectrum (ESI^+, MeOH) m/z calculated $[C_{13}H_{18}O_6Na]^+$ 293.1001, found 293.0990.

Resolved alcohol and auxiliary recovery: (*R*)-α adduct **10a** (160 mg, 0.59 mmol) was dissolved in dry methanol (20 mL) followed by the addition of acid-treated K10 Montmorillonite (1.28 g, 800 wt%). The reaction mixture was heated to 40 °C for 8 h, clay removed by filtration and the solvent evaporated to give a yellow oil containing no **10a**. GC analysis revealed auxiliary **4** and acetal **15** (ring-opened by-product) in a 60 : 40 ratio. After column chromatography on a silica column eluting with ethyl acetate–hexane (1 : 2), methyl-2,3-dideoxy-4,6-*O*-methylene-α-D-*erythro*-hex-2-enopyranoside (**4**) (31 mg, 18%), (*R*)-pantolactone (**10c**) (45 mg, 35%) and the acetal by-product **16** (26 mg, 13%) were recovered. The enantiomeric excess of recovered (*R*)-pantolactone was determined to be >99% by chiral GC (temperature program: initial column temperature was 110 °C for 10 min, then heated to 200 °C at 20 °C min^{-1} and maintained at 200 °C for 5 min).

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