Reliable chiral transfer through thermodynamic equilibrium of the intramolecular Meerwein–Ponndorf–Verley reduction and Oppenauer oxidation

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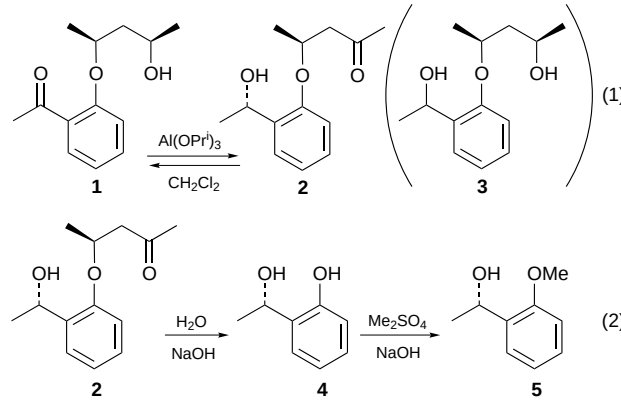
Forward and reverse hydride transfer with rigorous diastereodifferentiation is attained using intramolecular Meerwein–Ponndorf–Verley reduction and Oppenauer oxidation of a 2-acetylphenyl ether containing an optically active 3-hydroxy-1-methylbutyl group.

Meerwein–Ponndorf–Verley (MPV) reductions and Oppenauer oxidations have been revealed to proceed *via* reversible hydride transfer between carbonyl groups and alcohols.[1] Recently, intramolecular MPV reductions have been reported to proceed with high stereodifferentiation.[2–5] Reversible stereodifferentiating reactions, however, have the risk of lowering the stereochemical purity as well as chemical yield of products due to the reverse step, which does not always restore the formed product to the same stereoisomer as the initial reactant. Previous intramolecular stereocontrolled MPV reductions have succeeded as a result of the reaction being driven to completion under kinetic control.[2–5] In contrast, under thermodynamic equilibrium, both the forward and reverse steps must proceed with complete stereodifferentiation in order to prevent any decrease in optical purity of the reactant from the reverse step. Such stereodifferentiation reactions under thermodynamic equilibrium, however, have not yet been described for the intramolecular MPV–Oppenauer reaction.

We now report that the intramolecular hydride transfer of 2-acetylphenyl ether containing an optically active 3-hydroxy-1-methylbutyl group (**1**) proceeds with rigorous stereodifferentiation under thermodynamic equilibrium. The optically active 3-hydroxy-1-methylbutyl moiety acts as both the chiral auxiliary and hydride donor, and can easily be removed from the product **2** by alkaline hydrolysis as a result of the oxidation of the alcohol moiety to a ketone. Thus the multi-functional nature and simple structure of the optically active 3-hydroxy-1-methylbutyl moiety[4,6] provide an opportunity to construct a simple and reliable system for intramolecular chiral transfer *via* thermodynamic equilibration of the MPV–Oppenauer reaction.

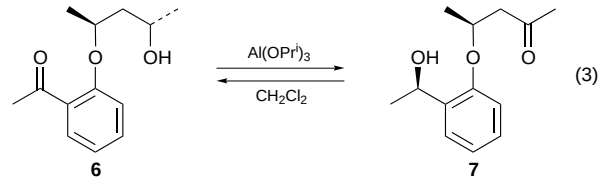
Evaluation of hydrogenation enthalpy data[1,7] for the conversion of ketones to the corresponding alcohols revealed that acetophenone is favorable to some extent as a hydride acceptor of intramolecular hydride transfer from the alcohol moiety, on the basis of the estimation that the enthalpy change (ΔH) for reduction of acetophenone by propan-2-ol is -3 kJ mol^{-1}, from which the quilibrium constant (K_{calc}) is calculated to be 3.0 at 313 K. The reactant, (1′*S*,3′*R*)-2-(3′-hydroxy-1′-methylbutoxy)acetophenone **1**, was prepared in 66% yield *via* the Mitsunobu reaction[8] of (2*R*,4*R*)-pentane-2,4-diol with 2′-hydroxyacetophenone. The epimer of **1**, (1′*S*,3′*S*-)-2-(3′-hydroxy-1′-methylbutoxy)acetophenone **6**, was also obtained by inversion of the alcohol moiety of **1** in 78% yield *via* the Mitsunobu reaction of **1** with benzoic acid followed by hydrolysis.

Treatment of **1** with $Al(OPr^i)_3$ (2.0 equiv.) in CH_2Cl_2 at reflux for 20 h caused the intramolecular hydride transfer from the alcohol to the aromatic ketone to yield **2** as a single isomer in 68% yield [eqn. (1)]. It should be noted that no diol **3**, produced by intermolecular hydride transfer from isopropoxide or **1**, was obtained. The remaining 32% was recovered as the reactant **1**, with no epimer **6**.‡ The product **2** was readily hydrolysed under alkaline conditions to give 1-(2-hydroxyphenyl)ethanol **4**, which was isolated after conversion to 1-(2-methoxyphenyl)ethanol **5** [eqn. (2)]. From the negative



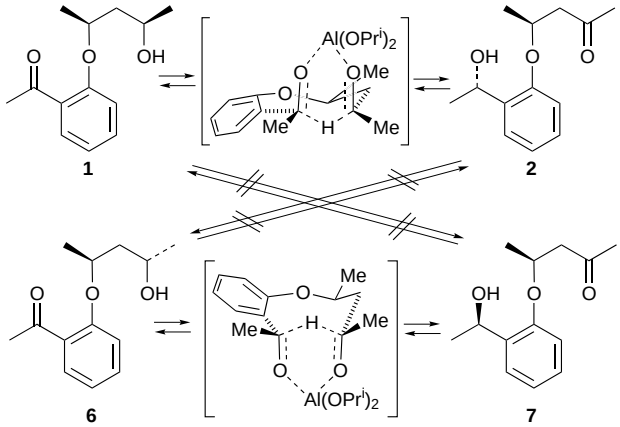
optical rotation of **5**, the absolute configuration of the α-position of **2** was determined to be *S*.[9]§

When **6** was treated with $Al(OPr^i)_3$ (2.0 equiv.) in CH_2Cl_2 at reflux for 20 h, the other diastereoisomer **7** was obtained at 67% yield [eqn. (3)] with the recovery of the reactant **6** in 33% yield.



These results indicate that the stereogenic centre at the hydroxy group, but at the ether, is responsible for that of the newly formed chiral centre.

The ratio of **1**:**2** remained constant at 1:2 and the epimerisation of **1** to **6** was also not observed even after extending the reaction period to 4 days. Increasing the quantity of $Al(OPr^i)_3$ to 4 equiv. also resulted in the same product distribution of **1**:**2**. The constant product ratio of **1**:**2** (1:2) which is independent of the reaction time and the amount of $Al(OPr^i)_3$ indicates that the intramolecular hydride transfer between **1** and **2** reaches an equilibrium with the equilibrium constant $K = 2.0$ The recovery of the initial reactant without empimerisation under the thermodynamic equilibrium implies the complete stereodifferentiation of the reverse step. Such rigorous stereodifferentiation in the reverse step as well as in the forward step may be a consequence of the restricted orientation of the carbonyl group and the alcohol in the transition state of



Scheme 1

the intramolecular MPV–Oppenauer reaction (Scheme 1). Preferential intramolecular coordination to aluminium also ensures from no formation of **3** generated by intermolecular MPV reduction is observed. Thus, the intramolecular hydride transfer proceeds without mixing the equilibrium between **1** and **2** with that between **6** and **7**.

In conclusion, a rigorous diastereodifferentiating hydride transfer has been achieved under a thermodynamic equilibrium, resulting from both the forward and reverse steps of the equilibrium proceeding diastereospecifically.

This work was partially supported by a Grant-in-Aid for Encouragement of Young Scientists No. 08750961 from the Ministry of Education, Science, Sports and Culture, Japan.

Footnotes and References

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‡ The epimers are distinguishable by use of ^{1}H NMR (400 MHz, $CDCl_3$) spectroscopy. *Selected data* for **1**: δ 7.68 (d, *J* 7.8, 1 H), 7.41 (t, *J* 7.8, 1 H), 7.00 (d, *J* 7.8, 1 H), 6.95 (t, *J* 7.8, 1 H), 4.77–4.69 (m, 1 H), 4.03–3.98 (m, 1 H), 2.58 (s, 3 H), 2.56 (s, 1 H), 2.06–1.98 (m, 1 H), 1.74–1.68 (m, 1 H), 1.35 (d, *J* 5.9, 3 H), 1.23 (d, *J* 6.4, 3 H). For **2**: δ 7.33 (d, *J* 7.8, 1 H), 7.20 (t, *J* 7.8, 1 H), 6.93 (t, *J* 7.8, 1 H), 6.89 (d, *J* 7.8, 1 H), 5.07–5.01 (m, 1 H), 4.98–4.91 (m, 1 H), 2.96 (dd, *J* 5.9, 16.6, 1 H), 2.67 (dd, *J* 6.3, 16.6, 1 H), 2.50 (d, *J* 4.9, 1 H), 2.17 (s, 3 H), 1.45 (d, *J* 6.3, 3 H), 1.36 (d, *J* 5.9, 3 H). For **6**: δ 7.68 (d, *J* 7.8, 1 H), 7.41 (t, *J* 7.8, 1 H), 7.01 (d, *J* 7.8, 1 H), 6.95 (t, *J* 7.8, 1 H), 4.86–4.79 (m, 1 H), 4.12–4.04 (m, 1 H), 2.58 (s, 3 H), 2.04 (d, *J* 4.4, 1 H), 1.91–1.85 (m, 1 H), 1.79–1.72 (m, 1 H), 1.34 (d, *J* 6.4, 3 H), 1.23 (d, *J* 5.9, 3 H). For **7**: δ 7.32 (d, *J* 7.8, 1 H), 7.20 (t, *J* 7.8, 1 H) 6.93 (t, *J* 7.8, 1 H), 6.89 (d, *J* 7.8, 1 H), 5.07–5.02 (m, 1 H), 4.95–4.90 (m, 1 H), 2.96 (dd, *J* 6.3, 16.6, 1 H), 2.68 (dd, *J* 5.9, 16.6, 1 H), 2.17 (s, 3 H), 1.46 (d, *J* 6.3, 3 H), 1.35 (d, *J* 5.9, 3 H).

§ The enantiomeric purity of **5** was determined to be over 99% ee by GC analysis using a CHROMPACK-Chirasil-DEX CB (i.d. 0.25 mm × 25 m) column. The column temperature was maintained at 120 °C. The retention time of the *S* isomer **5** was 16.9 min and that of the *R* isomer was 19.0 min.

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Received in Cambridge, UK, 20th June 1997; 7/04341D