Enhancement and Reversal of Enantioselectivity of the Enzymatic Hydrolysis of (*RS*)-3-(4-Methoxycarbonyl)phenyl-2-methylprop-1-yl Acetate upon its Transformation into the η^6-Arene(tricarbonyl)chromium Complex

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Temporary introduction of the $Cr(CO)_3$ 'ligand' into the title substrate brings about a manifold increase in the enantioselectivity of its PPL-catalysed hydrolysis (characterised by the enantiomeric ratio parameter, *E*), and reverses the stereochemical result of the reaction.

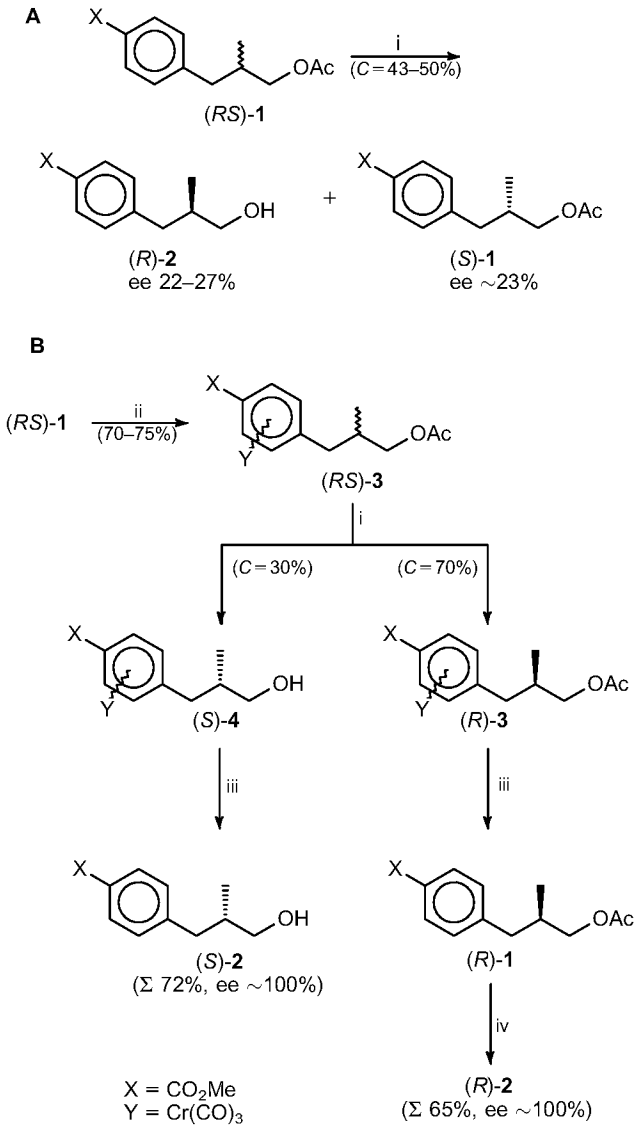
Recently,[1] it was found that the kinetic resolution of a racemic acetate, (*RS*)-**1**, attempted by hydrolysing it in the presence of porcine pancreatic lipase (PPL), preponderantly affected the *R* component of the racemate, the enantiomeric purity of both products of partial hydrolysis being rather modest (Scheme 1, A). The ratio of the specificity constants for the fast- and slow-reacting enantiomers, *E* (see ref. 2), was only 1.93, *i.e.*, very unpromising for synthetic purposes.

With a view to enhancing the effectiveness of the enzymatic kinetic resolution of (*RS*)-**1** we decided to employ, besides the well-known enantioselective lipase-catalysed acylation of racemic alcohols in non-aqueous media,[3] the effect of changing the size and polarity of the arene moiety in (*RS*)-**1** upon its transformation into the respective η^6-arene(tricarbonyl)chromium complex, (*RS*)-**3**.

Previously, the lipase-mediated optical resolution of racemic η^6-arene(tricarbonyl)chromium complexes was applied only to the *ortho*- and *meta*-substituted benzene derivatives containing no sp^3 hybridized asymmetric carbon atoms.[4] As regards (*RS*)-**3** and similar substrates where, because of the rotation of the benzene nucleus around the C(1′)-C(4′) axis, the complexing does not involve diastereoisomeric relationships, it could be anticipated that the rates of enzymatic hydrolysis of enantiomeric acetates would be markedly different because of the change of the ligand environment of the asymmetric C(2) atom in the side chain. In such a case, the $Cr(CO)_3$ 'ligand' could be employed as a removable, stereoselectivity-modulating auxiliary for the enzymatic transformation of aryl-containing substrates.

In fact, the PPL-catalysed hydrolysis of (*RS*)-**3**† in 0.1 M phosphate buffer (pH 6.5) at room temperature proved to be much more stereoselective than the respective transformation of (*RS*)-**1**. At the ratio (*RS*)-**3**/PPL = 2:1 (w/w, *ca.* 195 mg PPL per 1 mmol of the substrate)‡ and 30% conversion (*C*) of (*RS*)-**3** followed by a clean separation of the products of the partial hydrolysis by column chromatography on SiO_2 [hexane–Et_2O (1:1) → Et_2O] a pure specimen of alcohol (*S*)-**4** was isolated as a viscous yellow oil with $[\alpha]_D^{20}$ −14.1° ($CHCl_3$). Decomplexing with I_2 in THF afforded pure alcohol (*S*)-**2** with $[\alpha]_D^{20}$ −10.33° ($CHCl_3$); ref. 1: $[\alpha]_D^{20}$ −9.48° ($CHCl_3$) for a specimen of 90% ee. The ^{19}F NMR spectrum of the (*S*)-MTPA ester of (*S*)-**2** contained only the singlet of the CF_3 group.

Similarly, the 70% conversion of (*RS*)-**3** afforded pure acetate (*R*)-**3**, also a yellow oil, $[\alpha]_D^{20}$ +19.4° ($CHCl_3$), the decomplexing of which gave the acetate (*R*)-**1** with $[\alpha]_D^{20}$ −7.58° ($CHCl_3$).§ Deacetylation of (*R*)-**1** using NaOMe in MeOH smoothly produced a pure specimen of alcohol (*R*)-**2** with $[\alpha]_D^{20}$ +10.4° ($CHCl_3$), which was converted to another individual (*S*)-MTPA ester (as shown by the ^{19}F NMR spectrum). The overall yield of (*S*)-**2** and (*R*)-**2** from (*RS*)-**3** upon the 30% and 70% conversion, respectively,



Scheme 1 *Reagents and conditions*: i, PPL/H_2O (pH 6.5), room temperature; ii, $Cr(CO)_6$/Bu^n_2O–THF (10:1), 140 °C; iii, I_2/THF, room temperature, then $Na_2S_2O_3$ aq; iv, NaOMe–MeOH, 0 °C → room temperature, 30 min.

† Acetate (*RS*)-**3** was obtained in 70–75% yield by heating (*RS*)-**1** with $Cr(CO)_6$ (1.3 mol. equiv.) in Bu_2O–THF (10:1, v/v) at ~ 140 °C for 40–42 h and separating (*RS*)-**3** from the unreacted (*RS*)-**1** by column chromatography on SiO_2 (*cf.* ref. 5); the starting (*RS*)-**1** was prepared in 90–92% yield from 3-(4-methoxycarbonyl)phenyl-2-methylprop-2-enal[1] upon its hydrogenation over skeletal Ni in Pr^iOH (95 °C, 80 atm. H_2, 3 h) and subsequent conventional acetylation of the (*RS*)-**2** thus formed.

‡ Porcine pancreatic lipase used in this work (47.8 U mg^{-1}) was purchased from 'Olainfarm' (Latvia).

§ Ref. 1: $[\alpha]_D^{22}$ +7.87° ($CHCl_3$) for a sample of (*S*)-**1** with *ca.* 90% ee.

amounted to 21.6% (over two steps) and 19.5% (over three steps). These figures correspond to the 14–15.5% overall yield starting from (*RS*)-**1**.

The enantiodiscrimination parameter E was calculated using the Chen–Sih equations for the substrate and the product.[2] The depths of conversion of (*RS*)-**3** were 30 ± 2, 55 ± 3, 65 ± 2 and 70 ± 2, as estimated from the total weights of the fractions containing (*S*)-**4** or (*R*)-**3**. The enantiomeric purity of specimens of (*S*)-**4** and (*R*)-**3** was assumed to be identical with that of alcohols (*S*)-**2** and (*R*)-**2** received therefrom and correlated satisfactorily with the values of $[\alpha]_D^{20}$ of all these compounds at various depths of conversion. Due to systematic error inherent in this method of analysis, the discrepancy between the E values was rather large (5.6–31.8 for the substrate and 7.6–39.8 for the product), which contradicts the theory (*cf.* ref. 2); statistical treatment gave $E = 16.7$ as the most reliable value. Thus, temporary introduction of the $Cr(CO)_3$ 'ligand' in the molecule of (*RS*)-**1** made it possible to enhance the enantioselectivity of the hydrolysis by about 8–9 times.

Of particular interest is the reversal of enantioselectivity of the PPL-catalysed hydrolysis upon the transition from (*RS*)-**1** to (*RS*)-**3**. In our opinion, this effect (which may help to widen the scope of the stereocontrolled chemo-enzymatic synthesis) is mainly of conformational origin and implies the importance of conformational equilibria involved in the substrate-active site interactions.

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