Lipase-mediated stereodivergent synthesis of both enantiomers of 4-(2,6-dimethylheptyl)benzoic acid

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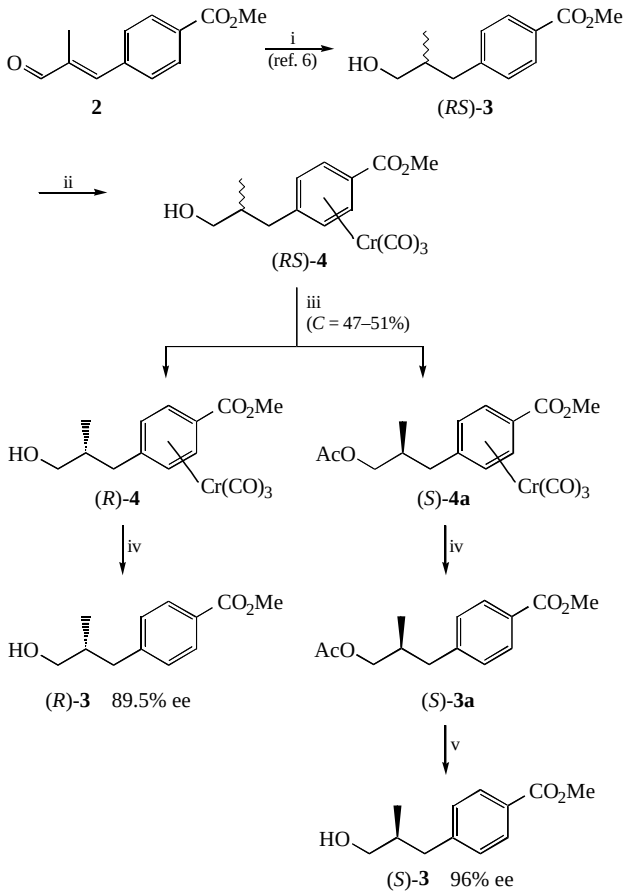
(*S*)- and (*R*)-Enantiomers of methyl 4-(3-hydroxy-2-methylpropyl)benzoate, obtained by enzymatic kinetic resolution of the related racemic arene(tricarbonyl)chromium complex in the vinyl acetate–PPL/Et_2O acylating system, have been converted in four steps into the (*R*)- and (*S*)-enantiomers of the title acid, respectively.

Racemic 4-(2,6-dimethylheptyl)benzoic acid, (*RS*)-**1** is known to effectively control the level of serum cholesterol *in vivo*,[1] to inhibit accumulation of intracellular cholesterol in the culture of sclerotized human aortic cells[2] and to activate cholesterol esterase *in vitro*.[3] Hence, it appears to be a promising drug for the treatment of hypercholesterolemia and atherosclerosis. However, the biomedical properties of its enantiomeric components, (*R*)-**1** and (*S*)-**1** have not been so far reported, since the latter have remained unknown themselves.

With a view to obtaining the hitherto unrecorded acids (*R*)-**1** and (*S*)-**1** we designed a stereodivergent scheme for their synthesis from a common precursor, enal **2** (see ref. 4), involving the stage of enzymatic kinetic resolution of the racemic alcohol (*RS*)-**3** (see refs. 5 and 6) with the aid of porcine pancreatic lipase (PPL).

Since neither partial enzymatic hydrolysis of the corresponding racemic acetate[6] nor partial acylation of (*RS*)-**3** using the vinyl acetate–PPL/Et_2O system[7] afforded the required products of high enantiomeric purity, we resorted to a hitherto unemployed device of sharply changing the size and polarity of the substrate upon its transformation into the respective arene(tricarbonyl)-chromium complex, (*RS*)-**4** (see ref. 7). Partial acylation of racemic metal complex (*RS*)-**4** using the vinyl acetate–PPL/Et_2O system (20 °C, 47–51% conversion)[†] followed by column chromatography on SiO_2 [hexane–Et_2O (1:1) → Et_2O] afforded optically active acetate (*S*)-**4a** and alcohol (*R*)-**4** in *ca.* 100% and 70% yield, respectively. Their decomplexing with an equimolar amount of I_2 in THF (20 °C, 2.5 h) resulted in quantitative recovery of acetate (*S*)-**3a** and alcohol (*R*)-**3**, isolated as colourless oils with $[\alpha]_D^{20}$ +7.28° ($CHCl_3$) and $[\alpha]_D^{20}$ +9.25° ($CHCl_3$), respectively. By means of the Zempleén deacylation acetate (*S*)-**3a** was converted into a specimen of alcohol (*S*)-**3** with $[\alpha]_D^{20}$ –9.80° ($CHCl_3$). From the values of $[\alpha]_D$ for alcohols (*R*)-**3** and (*S*)-**3** it followed that their enantiomeric purity was 89.5% and 96%, respectively. This seems to be a fair compromise between a short-path, good-yield approach to alcohols (*R*)-**3** and (*S*)-**3**, on the one hand, and high values of ee sufficient to serve the purpose, on the other.

Originally, it appeared that the safest route from alcohols (*R*)-**3** and (*S*)-**3** to acids (*S*)-**1** and (*R*)-**1** would be to transform the former successively into the corresponding tosylates, iodides and triphenylphosphonium salts, and then to extend the side chain by employing either organocopper reagents or Wittig olefination, either of which would proceed without affecting the stereogenic carbon atom in the chiral reactant. Unfortunately, the trial experiments, carried out starting from racemic alcohol (*RS*)-**3**, showed that neither the tosylate (*RS*)-**5** nor iodide (*RS*)-**6** gave satisfactory yields of the ester (*RS*)-**1** upon interaction with various organocopper reagents derived from $Me_2CHCH_2CH_2Br$. In all variants one observed the formation of alternative products and recovery of the racemic substrate.[‡] Attempts to obtain the olefinic ester (*RS*)-**8** by successively treating racemic phosphonium salt (*RS*)-**7** with base and 3-methylbutanal proved equally fruitless (Scheme 2).

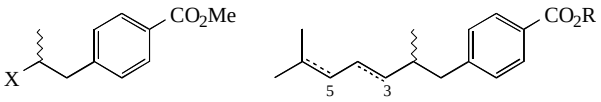


Scheme 1 *Reagents and conditions:* i, H_2–Ni/Pr^iOH, 95 °C, 80 atm H_2, 3 h (93%); ii, $Cr(CO)_6$/Bu_2O–THF (1:1, v/v), *ca.* 125 °C (Ar), 64 h (93%); iii, CH_2=CHOAc–PPL/Et_2O, room temperature, ~18 h [70% for (*R*)-**4**, ~100% for (*S*)-**4a**]; iv, I_2 (1 equiv.)/THF, room temperature, 2.5 h (*ca.* 100%); v, NaOMe/MeOH, room temperature, 40 min (*ca.* 100%).

Swern oxidation of alcohol (*RS*)-**3** turned out to be the best method among several tried for obtaining aldehyde (*RS*)-**9** (95% yield). This aldehyde was immediately made to react with the phosphorane generated from 3-methylbut-2-enyl(triphenyl)-phosphonium chloride (MBTPC) by treating its suspension in THF with a 0.6 M solution of Bu^nLi in hexane (–70 °C, 2 h, then 16 h at ~20 °C); the resulting diene ester (*RS*)-**10** was isolated in 76% yield. The latter was hydrogenated over Pd/C to give the required ester (*RS*)-**1a** (84.5% yield). Its saponification

[†] Porcine pancreatic lipase used in this work (14.7 U mg^{-1}) was purchased from 'Serva', Germany. Previously,[6] the specimens of alcohols (*R*)-**3** and (*S*)-**3** with *ca.* 100% ee [as shown by the ^1H and ^{19}F NMR spectra of the (*S*)-MTPA esters of (*R*)-**3** and (*S*)-**3**], were obtained by enzymatic hydrolysis of acetate (*RS*)-**4a** with 70% and 30% conversion, $[\alpha]_D^{20}$ +10.4° and –10.33°, respectively (both in $CHCl_3$).

[‡] A detailed account of this part of the work will be given in a subsequent communication.[3]

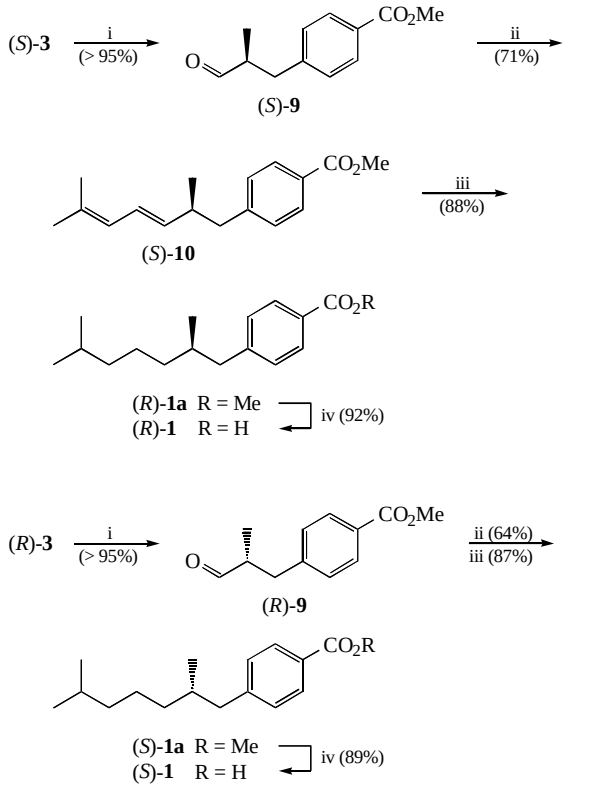


(*RS*)-**5** X = CH_2OTs (*RS*)-**1a** 3,4,5,6-tetrahydro (R = Me)
(*RS*)-**6** X = CH_2I (*RS*)-**8** 5,6-dihydro, Δ^3, (R = Me)
(*RS*)-**7** X = $CH_2P^+Ph_3I^-$ (*RS*)-**10** $\Delta^{3,5}$ (R = Me)
(*RS*)-**9** X = CHO (*RS*)-**1** 3,4,5,6-tetrahydro (R = H)

Scheme 2

in aqueous MeOH (*ca.* 65 °C, 8 h) afforded in 90% yield the racemic acid (*RS*)-**1** with mp 73–74 °C (from MeOH–H_2O).

Synthesis of the target acids (*R*)-**1** and (*S*)-**1** followed the same protocol, the only difference being that, in order to prevent the racemization of the stereogenic centre in aldehydes



Scheme 3 *Reagents and conditions:* i, (*a*) $COCl_2$–DMSO/CH_2Cl_2, –65 °C, (*b*) (*S*)-**3** or (*R*)-**3**, –65 °C, 20 min, (*c*) NEt_3, –65 → 0 °C; ii, (*a*) $[Me_2C{=}CHCH_2PPh_3]I$–Bu^nLi/THF–hexane, –70 °C, 2 h, (*b*) (*S*)-**9** or (*R*)-**9**, –70 °C, 3–5 h (Ar) → room temperature; iii, H_2–Pd(10%)/C–MeOH, room temperature; iv, KOH/MeOH–H_2O (95:5, v/v), 65 °C, 8 h.

(*R*)-**9** and (*S*)-**9**, the Wittig olefination was carried out using a small excess of MBTPC (1.2 equiv.) with respect to the aldehyde (1.0 equiv.) and Bu^nLi (1 equiv.) and the contact of the aldehyde with the phosphorane at –70 °C was extended to 3–5 h. Under these conditions the yield of dienes (*S*)-**10** and (*R*)-**10** remained preparatively attractive (64–71%). The yields of acids (*S*)-**1** and (*R*)-**1** over four steps were 50.9% and 54.9%, based on alcohols (*R*)-**3** and (*S*)-**3**, respectively. Accounting for *ca.* 50% conversion of racemic alcohol (*RS*)-**4** at the partial acylation stage and the yields of compounds (*S*)-**4a** and (*R*)-**4** thereof, the overall yields of acids (*R*)-**1** and (*S*)-**1** from the readily accessible enal **2** are within 12.5–14%.[§]

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[§] Acid (*R*)-**1**: mp 76.5–77 °C (from MeOH–H_2O), $[\alpha]_D^{20}$ +2.3° (*c* 1.0, $CHCl_3$); acid (*S*)-**1**: mp 76–77 °C (from MeOH–H_2O), $[\alpha]_D^{20}$ –2.3° (*c* 1.0, $CHCl_3$). EI MS: *m*/*z* 248 (M^+). All new compounds were characterised by their ^1H and ^{13}C NMR spectra.