Superacidic cyclisation–lipase-mediated kinetic resolution as a short route from achiral linear isoprenoid alcohols to scalemic cyclic isomers

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(±)-α-Cyclogeraniol and (±)-drim-7-en-11-ol acetates obtained *via* the FSO_3H-induced cyclisation of geraniol and (*E*)-farnesol and subsequent acetylation were hydrolysed in the presence of hog pancreas lipase (PPL) to afford (*R*)-(+)-α-cyclogeraniol (*ee* ~30% at the optimal conversion $C = 20\pm2\%$) and (5*R*,9*R*,10*R*)-(+)-drim-7-en-11-ol (*ee* 78.5% at $C = 30\%$), respectively; (±)-15-acetoxy-isoagath-12-ene, obtained similarly from all-*E*-geranylgeraniol, is resistant to PPL-mediated hydrolysis, but is hydrolysed in the presence of lipase from *Candida cylindracea* to afford (10*S*,14*R*)-(–)-isoagath-12-en-15-ol of 69–80% *ee* in ~3% yield.

Cyclic isoprenoids with a common structure and common relative configuration can occur in the nature in both enantiomeric forms. Typically, the species abundant in one or another enantiomer belong to rather remote taxons. To study the biomedical properties of enantiomeric terpenoids and, all the more so, to convert the latter into chiral building blocks, considerable amounts of both enanitomers are needed, but it is not always easy to obtain each of the two from natural sources or by chemical synthesis.

However, both enantiomers of certain cyclic isoprenoids could be obtained in only three steps *via* a stereodivergent protocol that includes (i) the stereospecific superacid-induced cyclisation of geometrically pure achiral alcohols of the type $H[CH_2C(Me)=CHCH_2]_nOH$ into racemic cyclic isomers, (ii) the acetylation of the latter to produce the corresponding (±)-acetates, and (iii) the subsequent lipase-mediated kinetic resolution of the acetates into differently functionalised (+)- and (–)-enantiomers by partial hydrolysis. Cyclisation of the lower members of the above type ($n = 2–4$) is well known,[1] while enzymatic optical resolution of chiral alcohols or esters is such an obvious solution,[2] that one can only wonder, (or just not wonder) why this protocol has not been actuated so far.†

This work demonstrates the feasibility of stereodivergent transformation of geraniol **1** and (*E*,*E*)-farnesol **2** into scalemic α-cyclogeraniols [(*R*)-**3**, (*S*)-**3**] and drim-7-en-11-ols [(all-*R*)-**4**, (all-*S*)-**4**]. Similar transformation of all-*E* geranylgeraniol **5** into (–)-isoagath-12-en-15-ol [(10*S*,14*R*)-**6**] is also reported. By means of superacidic cyclisation alcohols **1**, **2** and **5** were converted into corresponding cyclic isomers (±)-**3**, (±)-**4**, and (±)-**6**,‡ from which acetates (±)-**3a**, (±)-**4a** and (±)-**6a** were prepared§ and subjected to partial hydrolysis in the presence of hog pancreas lipase (PPL) or lipase from *Candida rugosa* (≡ *C. cylindracea*, CCL). In order to attain the highest possible *ee* of scalemic alcohols **3** and **4** without sacrificing too much the yield, conversions of (±)-**3a** and (±)-**4a** were arrested at $C \leq 30\%$. Acetate (±)-**6a** could not be hydrolysed in the presence of PPL even upon repetitive addition of the enzyme up to a twofold excess (w/w). The scalemic form of alcohol **6** was obtained only using CCL as the catalyst.¶

The PPL-mediated hydrolysis of (±)-**3a** proceeded with low enantioselectivity. In the best variant ($C = 20\%$ in 32 h), it afforded in a 20% yield a specimen of (+)-α-cyclogeraniol [(*R*)-**3**] with $[\alpha]_D^{20}$ +34.6° (*c* 0.96, EtOH), which corresponds to ~30% *ee*. For the specimens of **3** with *ee* ~100%, $[\alpha]_D^{25}$ +122° (EtOH)[4(a)] for the *R* enantiomer and –116° or –109.2° (EtOH) for its *S* antipode were reported.[4(b),(c)] Mild alkaline hydrolysis of the fraction of unconverted acetate gave a specimen of alcohol (*S*)-**3** with $[\alpha]_D^{20}$ –10.4% (*c* 1.05, EtOH), which corresponds to *ee* ~10%.

The hydrolysis of (±)-**4a** was quicker ($C = 30\%$ in 22 h) and more selective. The isolated drim-7-en-11-ol with all-*R* configuration [(*R*)-**4**] had $[\alpha]_D^{21}$ +13.1° (*c* 1.1, PhH), which corresponds to *ee* 78.5%. Lit., $[\alpha]_D^{25}$ +15.8° (PhH)[5(a)] for a specimen of (*R*)-**4** with *ee* 88% and $[\alpha]_D^{rt}$ –18° or –18.2° (PhH)[5(a),(b)] for the specimens of all-*S* drim-7-en-11-ol [(*S*)-**4**] of ~100% *ee*. The fraction of unconverted acetate upon alkaline hydrolysis gave alcohol (*S*)-**4** with $[\alpha]_D^{20}$ –5.81° (*c* 0.89, PhH), which corresponds to *ee* ~32% (Scheme 1). The enhanced hydrolysis enantioselectivity in the case of (±)-**4a** was considered earlier.[6]

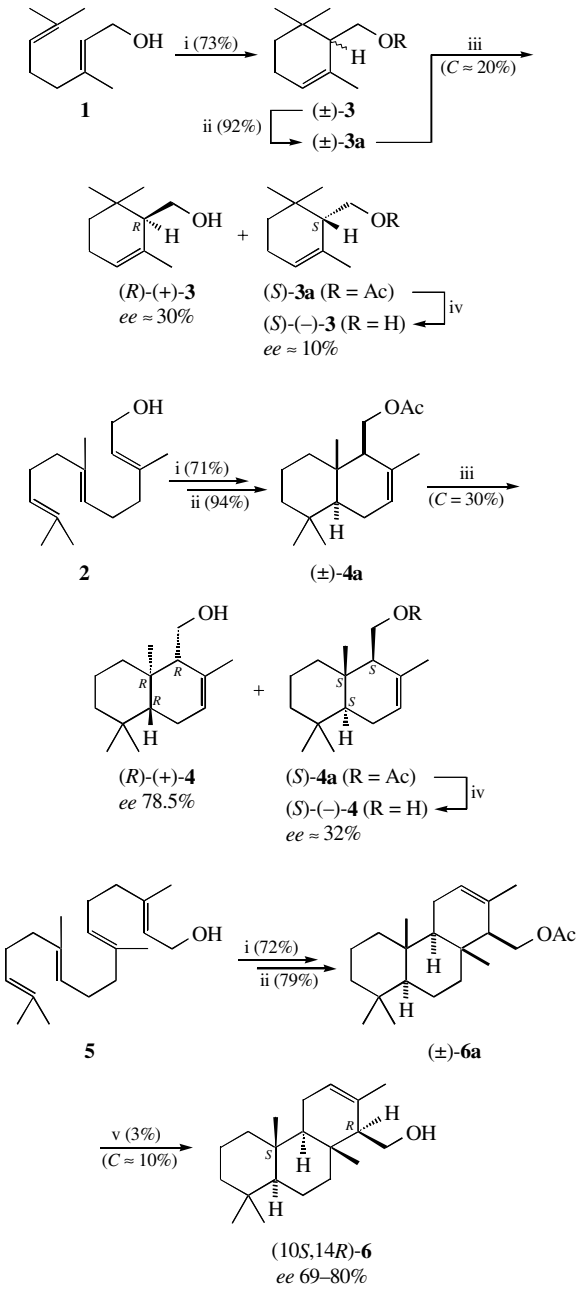
The transition from (±)-**4a** to (±)-**6a** resulted in a dramatical deceleration of the PPL-catalysed hydrolysis, the recovery of acetate (±)-**6a** after 96 h of incubation being almost quantitative. The hydrolysis of (±)-**6a** in the presence of CCL was also very slow (C ~10% after 148 h). The reaction mass was worked-up as usual and chromatographed twice, first on SiO_2 and then on Florisil®, to give an alcohol in 3% yield with $[\alpha]_D^{21}$ –7.2° (*c* 0.23, $CHCl_3$). It was identical to the (–)-enantiomer of **6** with the 10*S*,14*R* configuration in ^1H and ^{13}C NMR spectra, GC MS data[7(a),(b)] and the sign of $[\alpha]_D$. Specimens of the latter with ~100% *ee*, obtained earlier from natural sources[7(a),(b)] or by partial synthesis from grindellic acid[7(a)] and sclareol[7(c)], displayed $[\alpha]_D^{rt}$ –9 to –10.5° ($CHCl_3$).[7] Consequently, the *ee* of this speci-

† A conceptually similar approach to Ambrox®, from farnesyl acetate *via* lipase-mediated kinetic resolution of (±)-drimane-8,10-diol[3] is unsuitable for obtaining unsaturated cyclic alcohols with unambiguously positioned double bonds.

‡ Starting alcohols **1**–**3** were cyclised on treatment with fluorosulfonic acid (20 equiv.) in 2-nitropropane at –78°C, the reaction mass was neutralised with NEt_3, washed with water, extracted with Et_2O, dried (Na_2SO_4), and concentrated. The remainder was subjected to column chromatography on SiO_2 using hexane–Et_2O gradient elution (80:20 → 0:100) to give, in agreement with known procedures, (±)-α-cyclogeraniol [(±)-**3**, yield 73%],[1(a)] (±)-drim-7-en-15-ol [(±)-**4**, yield 71%][1(b)] and (±)-isoagath-12-en-15-ol [(±)-**6**, yield 72%].[1(c)]

§ The solutions of (±)-**4**, (±)-**5** and (±)-**6** (0.25 mmol in hexane) were treated with Ac_2O–Py (1:1, v/v; ~20 °C, 12–18 h) in the presence of 4-DMAP (4–5 mg). After standard work-up the acetates were purified by column chromatography on SiO_2 to give (±)-**3a**, (±)-**4a** and (±)-**6a** in 92, 94 and 79% yields, respectively.

¶ Powdered PPL (48 units per mg protein, Olainfarm, Latvia) or CCL (type VII with lactose, 1200 units per mg solid, Sigma) and a substrate (1:2, w/w) were suspended in a 0.1 M aqueous phosphate buffer solution [pH 6.5 for PPL or 7.0 for CCL, 1–3 ml per 0.25 mmol of (±)-acetate] and vigorously stirred at 20–22 °C. The duration of stirring for (±)-**3a**, (±)-**4a** and (±)-**6a** was 28–32 and 22 h (using PPL), or 148 h (using CCL), respectively. After standard work-up the only products of PPL-mediated hydrolysis, the required alcohol and acetate (TLC monitoring), were separated by column chromatography on SiO_2 [in the case of CCL-mediated hydrolysis of (±)-**6a** this was followed by additional chromatography on Florisil®] and identified spectroscopically. The enantioselectivity of hydrolysis was estimated by comparing the signs and magnitudes of $[\alpha]_D$ of chromatographically pure alcohols obtained at $C \leq 30\%$ with those reported in the literature for the same alcohols of ~100% *ee*. The fractions of unconverted acetates left after the hydrolysis of (±)-**3a** or (±)-**4a** were saponified (1 N NaOH/MeOH–H_2O, ~20 °C, 2–4 h) to give alcohols with the opposite signs of $[\alpha]_D$.



Scheme 1 *Reagents and conditions*: i, FSO_3H (20 equiv.)/Me_2CHNO_2, –75 °C; ii, Ac_2O–Py (1:1, v/v)/4-DMAP (cat.), room temperature; iii, H_2O (pH 6.5)/PPL (substrate:enzyme = 2:1, w/w), room temperature; iv, KOH–MeOH (aqueous), room temperature; v, H_2O (pH 7.0)/CCL (substrate: enzyme = 2:1, w/w), room temperature, 148 h.

men of (*R*)-**6** is 69–80%. The unconverted acetate afforded '*ent*-isoagath-7-en-11-ol' [(10*R*,14*S*)-**6**] with only ~1.5% *ee* {$[\alpha]_D^{21}$ +0.13° (*c* 0.4, $CHCl_3$)} upon alkaline hydrolysis.

Attempts to enhance the enantioselectivity of enzymatic resolution of alcohols (±)-**3** and (±)-**4** by acylating them in the Ac_2O–PPL/hexane or vinyl acetate–CCL/Et_2O systems were unsuccessful. The PPL-mediated acylation of alcohol (±)-**3** to 15% conversion gave acetate (*R*)-**3a** with only ~1.3% *ee*. When CCL was used, the fractions of unconverted alcohols recovered at *C* 55–75% [predominantly (*S*)-**3** and (*S*)-**4**] were contaminated by β-cyclogeraniol and drim-8-en-12-ol, respectively, and had ~9–13% *ee* (as estimated by correlating the observed $[\alpha]_D$ values with the respective ^1H and ^{13}C NMR data).[8]

Our results suggest that the superacidic cyclisation–acetylation–enzymatic hydrolysis protocol is synthetically useful. Its optimisation by lipase screening and/or by other known biocatalytic methods[2,9] seems to be a feasible task.

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