Chemistry of Natural Compounds and Bioorganic Chemistry

Enantioselectivity of enzymatic acylation of some structurally various racemic alcohols in anhydrous aprotic media

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Partial acylation of (*R,S*)-3,7-dimethyloctan-1-ol (**1**) and (*R,S*)-7-methoxy-3,7-dimethyloctan-1-ol (**2**) with vinyl acetate catalyzed by the lipase from *Candida cylindracea* affords in good yields the corresponding *S*-configured acetates with 92—98% enantiomeric excess (*ee*). Under similar conditions, racemic α-cyclogeraniol (**3**), drim-7-en-11-ol, methyl 4-(3-hydroxy-2-methylpropyl)benzoate, and its η^6-chromium(tricarbonyl) complex (**6**) are acylated with rather poor (and, for the two latter, opposite) enantioselectivity, whereas (*R,S*)-2,4:3,5-di-*O*-benzylidenexylitol remains unaffected. Racemic isoborneol (**8**) and 2-nitro-1-phenylethanol also remain almost or completely unconverted. Attempts to perform enantioselective acylation of alcohols **3** and **8** with Ac_2O in the presence of porcine pancreatic lipase (PPL) proved equally unsuccessful. By contrast, the PPL-catalyzed acylation of alcohol **6** with vinyl acetate at 17% conversion affords the levorotatory acetate (*S*)-**6a** with *ca.* 100% *ee*. PPL-Mediated partial acylation of (*R,S*)-pantolactone with Ac_2O, followed by mild deacylation of the resulting *R* acetate, gives (*R*)-(−)-pantolactone of 97% enantiomeric purity in 60% overall yield.

Key words: chiral alcohols; *Candida cylindracea* lipase; porcine pancreatic lipase; partial acylation; racemates, kinetic resolution.

Lipase-mediated partial acylation of racemic alcohols in anhydrous solvents is one of the most effective ways of preparing chiral building blocks (CBB) in the organic synthesis of today.[1] A combination of anhydrous, nonpolar solvents with strong acylation agents, such as carboxylic acid anhydrides[2] or enol esters,[3] makes it possible to transform the reversible reaction of enzymatic acylation of alcohols (1) into an almost or completely irreversible one due to the low nucleophilicity of its product HX.

$$R^{*}OH + RCOX \xrightarrow{\text{Lipase}} R^{*}OCOR + HX \qquad (1)$$

$X = OCOR$ or $OC(R')=CH_2$,

$$\left(HOC(R')=CH_2 \rightleftharpoons MeC(=O)R' \right)$$

When HX is MeCOR′, reaction (1) becomes fully irreversible, which simplifies the analysis of the factors affecting its enantioselectivity.

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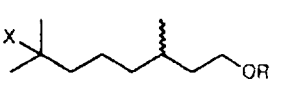
Here we report the results of our attempts to prepare a few CBBs of practical interest from ten racemic alcohols by way of their kinetic resolution upon partial acylation with vinyl acetate (catalyzed by the yeast lipase from *Candida cylindracea*, CCL*) and/or with acetic anhydride (catalyzed by porcine pancreatic lipase, PPL) in non-polar organic media.

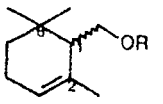
The following racemic substrates were tested for their ability to be resolved into optical antipodes: 3,7-dimethyloctan-1-ol (**1**), 7-methoxy-3,7-dimethyloctan-1-ol (**2**), α-cyclogeraniol (**3**), drim-7-en-11-ol (**4**), methyl 4-(3-hydroxy-2-methylpropyl)benzoate (**5**) and its η^6-chromium(tricarbonyl) complex (**6**), 2,4:3,5-di-*O*-benzylidenexylitol (**7**), isoborneol (**8**), 2-nitro-1-phenylethanol (**9**), and pantolactone (**10**). The *S* enantiomers of alcohols **1** and **2** are the key CBBs for the synthesis of the hormonal insecticides hydroprene and methoprene in their biologically most potent configuration, namely, (2*E*,4*E*,7*S*),[4,5] while the *R* enantiomer of alcohol **1**, (*R*)-**1**, is a convenient CBB for the synthesis of the pheromone of rice moth[6] as well as of phytol and vitamins E and K_1 which contain its moiety as side chains.[7] Enantiomers of racemic compounds **3** and **4** are used as fragrances or as intermediates in their production;[8,9] moreover, some derivatives of alcohol **4** are wasp repellents or their close precursors.[10] Both the *R* and *S* enantiomer of alcohol **5** are required as CBBs to obtain both enantiomers of 4-(2,6-dimethylheptyl)benzoic acid,[11,12] whose racemic form effectively inhibits the accumulation of cholesterol in the blood plasma and in the aortic cells. Enzymatic acylation of the racemic form of **6** was undertaken in connection with an earlier observation[12] that the opposite reaction, the enzymatic hydrolysis of the respective acetate **6a**, proceeded with considerably higher enantioselectivity than the hydrolysis of its precursor **5a**. Hence, it was anticipated that a similar trend might be observed for the partial acylation of parent alcohols **6** and **5**. The acylation of racemic alcohol **7** was attempted as a possible way of transforming xylitol into L-xylose, a carbohydrate of limited availability used as an antidiabetic food additive, and as an intermediate in the syntheses of some glutarimide and nucleoside antibiotics.[13]

(1*R*)-Isoborneol and its (1*S*)-enantiomer [(*R*)-**8** and (*S*)-**8**] are used as intermediates in the manufacturing of certain fragrances as well as of optically active camphor; they are also promising as chiral auxliaries. Enzymatic acylation of nitro alcohol **9** was studied as a model approach to pharmacologically active epinephrine analogs. Finally, partial acylation of (*R*,*S*)-pantolactone **10** mediated by the most available of all lipases, PPL, was tried as an alternative to the tedious procedure of optical resolution of **10** by fractional crystalization of diastereomeric salts formed by DL-pantoic acid with homochiral amines; this procedure is still used in the manufacture of calcium D-(+)-pantothenate.



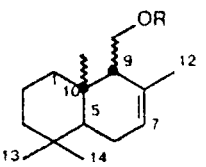
1, **1a**, **2**, **2a**

1: X = R = H
2: X = OMe, R = H
1a: X = H, R = Ac
2a: X = OMe, R = Ac



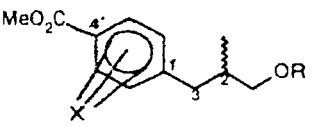
3, **3a**

3: R = H
3a: R = Ac



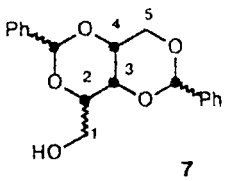
4, **4a**

4: R = H
4a: R = Ac



5, **5a**, **6**, **6a**

5: R = H, X is absent
5a: R = Ac, X is absent
6: R = H, X = η^6-Cr(CO)$_3$
6a: R = Ac, X = η^6-Cr(CO)$_3$



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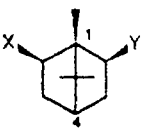
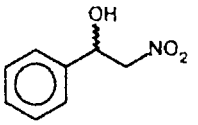


8

X = OH, Y = H
X = H, Y = OH (1 : 1)



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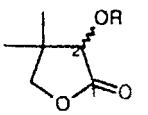


10, **10a**

10: R = H
10a: R = Ac

Kinetic resolution of racemic alcohols in the system vinyl acetate—CCL was carried out in diethyl ether. The conversion of the substrates (*C*) was estimated either on the basis of GC data or from the integral yields of an optically active acetate and of the respective optically active fraction of the residual alcohol after their quantitative chromatographic separation; in the case of alcohol **2** the value of *C* was additionally calculated from the equation $C = ee_s/(ee_s + ee_p)$, where ee_s is the enantiomeric excess in the residual fraction of the substrate, and ee_p is the enantiomeric excess in the acylation product.*

* Taxonomically, CCL is identical with the lipase of *Candida rugosa* (CRL).

* This expression for *C* forms a part of the Chen—Sih equation, which shows a measure of discrimination between the competing (+)- and (−)-components of a racemate by an enzyme, and reflects the ratio of the initial rates of an irreversible enzymatic reaction for the fast and slow enantiomers (*E* value, "enantiomeric ratio"), *cf.* Ref. 14.

Under standard conditions of acylation, the velocity of the process and enantioselectivity of enzymatic acylation depend quite markedly on the structure of the substrate. Among the seven primary alcohols tested, only 3-methyl-substituted alkanols **1** and **2** react fast and with high enantioselectivity (see Table 1, entries *1—3*). Alcohols of the general type $RCH(R')CH_2OH$, where R and R′ are substituents other than H, either react with poor enantioselectivity (*ee* ≤50%) or, as in the case of **7**, remain unaffected. Moreover, the acylation of the homoallylic alcohols **3** and **4** (see Table 1, entries *4* and *5*) is accompanied by the formation of isomeric allylic alcohols, that is, β-cyclogeraniol **11** and dextrorotatory (5*S*,10*S*)-drim-8-en-11-ol **12**, respectively (although no acetates corresponding to **11** or **12** could be found in the resulting acylation products!). The same admixtures appear in the blank experiment upon stirring the solution of **3** and **4** in Et_2O with an equal weight of CCL. Thence, for alcohol (*R*)-**3**, and even more so for its higher analog (*R*)-**4**, the values of *ee* found should be considered only as approximate (see below in the section considering the extent and the sense of enantioselectivity). Under selected standard conditions, secondary alcohols **8** and **9** are nearly or completely unreactive. Thus, in the case of (*R*,*S*)-isoborneol the yield of acetate (*R*)-**8a** amounted to only 1.3% after 11 days of exposition, while nitro alcohol **9** remained unaffected even after being exposed to a double amount of CCL (w/w) for 3 days.

The high *S* selectivity of the CCL-mediated acylation of 3-methylalkan-1-ols **1** and **2** is in agreement with the results obtained earlier for the acylation of other alcohols of similar structural type in the presence of this enzyme.[16] It should also be noted that *the sense of*

Table 1. Enantioselectivity of the partial acylation of racemic alcohols **1—2** in the system vinyl acetate—CCL/Et_2O at 20—24 °C[a]

Entry	(*R*,*S*)-alcohol	Alcohol : CCL (w/w)	Time /h	*C* (%)	Products of partial acylation			
					Acetate		Alcohol	
					ee (%)	yield (%)	*ee* (%)	yield (%)
1	**1**	2 : 1	16	40	≥98 (*S*)	92	Not determined (*R*)	~100
2	**1**	2 : 1	26	70	Not determined (*S*)	~100	≥98 (*R*)	96
3	**2**	2 : 1	5	50[b] (51.6)	92 (*S*)	65	≥98 (*R*)	92
4	**3**	2 : 1	22	55	Not determined (*S*)	93	−9.3[c] (*R*)	98.5
5	**4**	1 : 1	20	75	Not determined (*S*)	88	≥13.9[d] (*R*)	92
6	**5**	1 : 1	19	70	Not determined (*S*)	70.4	50.0 (*R*)	95
7	**6**	2 : 1	6	25	18.5 (*R*)	~100	Not determined (*S*)	67
8	**6**	1 : 1	9	75	Not determined (*R*)	93.5	20.5 (*S*)	89
9	**7**	1 : 1	168	0	No reaction			
10	**8**	2 : 1	264	~1.5	−30[e] (*R*)	~96	Not determined (*S*)	91
11	**9**	1 : 2	72	0	No reaction			

[a] Reaction conditions: a solution of the substrate (in entry *9* — a fine suspension) and $H_2C{=}CHOAc$ (1.2—1.5 equiv.) in abs. Et_2O (3 mL per 1 mmol of the substrate) plus powdered lipase (a multiple to the weight of the substrate) are magnetically stirred in a hermetically stoppered flask. The yields relate to the isolated, apparently pure products. Their absolute configurations and values of *ee* are determined by comparing the found signs and magnitudes of $[\alpha]_D$ with the corresponding data reported in the literature for the specimens known to be of ~100% enantiomeric purity.

[b] Calculated from the equation: $C = ee_s/(ee_s + ee_p)$.

[c] Contaminated with achiral β-cyclogeraniol **11** (38—40%).

[d] Contaminated with isomeric dextrorotatory drim-8-en-11-ol **12** (~18—20%).

[e] $[\alpha]_D^{20}$ −16.7° (AcOEt). Ref. 15: $[\alpha]_D$ −50.2° (neat).

Table 2. Enantioselectivity of the PPL-mediated partial acylation of racemic alcohol **3**, **6**, **8**, and **10** with acetic anhydride (A) or vinyl acetate (B) at 20–24 °C[a]

Entry	Substrate (alcohol : : AcX, molar ratio)	Alcohol : : PPL (w/w)	Acylation agent /solvent	Time /h	*C* (%)	Reaction products			
						Acetate		Alcohol	
						ee (%)	yield (%)	*ee* (%)	yield (%)
1	**3** (1 : 1)	2 : 1	A/hexane	30	15	1.26 (*R*)	79	Not determined (*S*)	80
2	**6** (1 : 1.2)	2 : 1	B/Et_2O	21	17	~100[b] (*S*)	100	Not determined (*R*)	69
3	(*R*)-**6** (1 : 1.2)	1 : 1	B/Et_2O	21	34	99.8[b] (*S*)	100	~100[c] (*R*)	96
4	**8** (1 : 3)[d]	1 : 2	A[d]	30	30	~8.4 (*R*)	85	Not determined (*S*)	80
5	**8** (1 : 1.4)	1 : 1	B/$MeNO_2$	96	0	No reaction			
6	**10** (2 : 1)	2 : 1	A/hexane	48	40	25.3 (*R*)	27	50.1 (*S*)	77
7	**10** (1 : 1)	2 : 1	A/hexane	24	46	97.3 (*R*)	80	39.3 (*S*)	70
8	**10** (1 : 1)[e]	2 : 1	A/hexane	3.5[e]	30	28.3 (*R*)	48	8.8 (*S*)	76

[a] Acylation agents: Ac_2O (A) or H_2C=CHOAc (B). Starting amounts of the substrates: **3** and **6** — 1 mmol, **8** — 6.5 mmol, **10** — 10 mmol. The volume of the solvent used for substrates **3**, **6**, and **8** was 3 mL, and for **10**, 4.5 mL. The yields relate to the isolated, chromatographically and spectroscopically pure products. The values of *ee* are determined by comparing the found values of $[\alpha]_D$ obtained in this work with those reported earlier in the literature for the specimens of ~100% enantiomeric purity (in identical solvent for each pair).
[b] The value of *ee* of alcohol (*S*)-**5** obtained by oxidative decomplexing of acetate (*S*)-**6a** followed by saponification of the resulting acetate (*S*)-**5a**.
[c] The value of *ee* for a specimen of alcohol (*R*)-**5** obtained upon decomplexing alcohol (*R*)-**6**.
[d] Without solvent.
[e] At 40 °C.

enantioselectivity alters upon transition from alcohol **5** to the η^6-chromium(tricarbonyl) complex **6**: in the former, it is the *S* enantiomer that reacts faster, while in the latter the *R* enantiomer is more reactive, although in both cases the rate differences are not great.

Partial acylation of racemic alcohols mediated by porcine pancreatic lipase (PPL) was performed mainly with acetic anhydride as one of the most available acylation agents (Table 2). When treated with an equimolar amount of Ac_2O in hexane, α-cyclogeraniol **3** and pantolactone **10** are acylated to the extent of 15 and 46%, respectively, at comparable exposures (*cf.* entries *1* and *7*). In the case of isoborneol **8** a preparatively viable conversion is attained when the reaction is carried out in neat Ac_2O taken in 3–4 fold excess, but the enantioselectivity of acylation is negligible. An attempt to improve upon it by employing a polar solvent (a method recommended for the PPL-catalyzed acylation of a secondary alcoholic hydroxy group[17]) proved unsuccessful: no transformation of alcohol **8** took place in the recommended system vinyl acetate—PPL/$MeNO_2$ (see Table 2, entry *5*). On the other hand, the chromium(tricarbonyl) complex, alcohol **6**, is readily acylated in a similar system to give acetate (*S*)-**6a** with *ee* ~100% (entry *2*). Repeated partial acylation of the fraction of unconverted alcohol (enriched with the *R* enantiomer) affords a specimen of alcohol (*R*)-**6** of ~100% enantiomeric purity (entry *3*).

Enzymatic kinetic resolution of (*R,S*)-pantolactone was performed earlier in the system vinyl acetate—lipase from *Pseudomonas sp.* (PSL), but in order to obtain the products of high enantiomeric purity it required either a long exposure (~10 days),[18] or the immobilization of the enzyme onto an inert matrix.[19] As can be seen from Table 2 (entry *7*), the use of more available chemicals, Ac_2O and PPL, also permits one to attain high enantioselectivity, and in a much shorter time. Deceleration of the reaction due to deficiency of the acylation agent (entry *6*) or increasing reaction temperature (entry *8*) results in a lower stereoselectivity of the process. It should be mentioned that if the chromatographic separation of acetate (*S*)-**10a** and residual alcohol (*R*)-**10**

is performed on unbuffered silica gel, the enantiomeric purity of the alcohol fraction is markedly different from that of acetate (*S*)-**10a**. Apparently, this discrepancy is caused, at least partly, by the hydrolysis of the acetate in the column, which results in the contamination of the alcohol fraction with (*S*)-**10** thus formed.*

The sense and extent of the acylation enantioselectivity were determined by comparing the signs and magnitudes of specific rotations for the acetates formed (at ≤50% conversions) or for the fractions of unconverted alcohols (at ≥50% conversions) with the respective literature data. In the case of optically active complexes (*R*)-**6a**, (*S*)-**6a**, (*R*)-**6**, and (*S*)-**6** these measurements were preceded by the oxidative decomplexing of the above compounds to their respective precursors (*R*)-**5a**, (*S*)-**5a**, (*R*)-**5**, and (*S*)-**5**.

Thus (Scheme 1, *A*), a 40% conversion of alcohol **1** in the system vinyl acetate—CCL/hexane afforded a specimen of dextrorotatory acetate with $[\alpha]_D^{20}$ +6.0° ($CHCl_3$). Its saponification with 1 equiv. KOH in MeOH under mild conditions gave levorotatory alcohol with $[\alpha]_D^{20}$ −6.07° (MeOH). Its absolute configuration and enantiomeric purity were determined from a comparison of the found specific rotation with the $[\alpha]_D^{20}$ −6.10° (MeOH) reported earlier[20] for a specimen of alcohol (*S*)-**1** with *ee* ~100%. Hence, the specimen of dextrorotatory alcohol with $[\alpha]_D^{20}$ +6.15° (MeOH), isolated at a 70% conversion of racemic **1**, must be the *R* enantiomer. On treatment with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [prepared from (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, (*S*)-MTPA] alcohol (*R*)-**1** was transformed into the corresponding (*S*)-MTPA ester, (3*R*,2′*S*)-**13**. The ^{19}F NMR spectrum of the latter contained only one singlet signal. Hence, within the standard accuracy of the measurement, both the acetate (*S*)-**1a** obtained at *C* = 40% and the residual alcohol (*R*)-**1**, recovered at *C* = 70%, must possess *ee* ≥98%.

In the same reaction system, acylation of racemate **2** to the conversion depth *C* = 50±2% gave rise to an acetate with $[\alpha]_D^{20}$ +5.8° ($CHCl_3$) and the unreactive component of the substrate, an alcohol with $[\alpha]_D^{20}$ +6.07° (MeOH). As in the previous case, the latter was transformed into the corresponding (*S*)-MTPA ester, (3*R*,2′*S*)-**14**, which displayed only one singlet signal in its ^{19}F NMR spectrum. This permits one to assess the enantiomeric purity of the parent alcohol in about 100% (*ee* ≥98%). Since the saponificaton of the dextrorotatory acetate gave an alcohol with $[\alpha]_D^{20}$ −6.0° (MeOH), this alcohol has the same sign of optical rotation as those specimens which were used earlier in the synthesis of (*S*)-(+)-methoprene of high biological potency.[4,5] This fact implies that the residual alcohol has the *R* configuration. Comparison of the $[\alpha]_D$ values of the two enantiomeric alcohols shows that alcohol (*S*)-**2** and hence its acetate (*S*)-**2a** have *ee* ~92%.

The values of parameter *E* (the ratio of initial rates of transformation of each component of a racemate) were calculated by using the Chen—Sih equation[14] for the substrate (2) and product (3) of an irreversible reaction,

$$E = \ln[(1 - C)(1 - ee_s)]/\ln[(1 - C)(1 + ee_s)], \quad (2)$$

$$E = \ln[1 - C(1 + ee_p)]/\ln[1 - C(1 - ee_p)], \quad (3)$$

where *C*, ee_s, and ee_p represent the conversion, enantiomeric excess in the unconverted substrate, and enantiomeric excess in the product, respectively, expressed in decimal parts of a mole. The averaged values of *E* for alcohols **1** and **2** amount to ~103 and ~196, respectively. Thus, the enantioselectivity of formation of acetates (*S*)-**1a** and (*S*)-**2a** in the system vinyl acetate—CCL is quite high.

CCL-catalyzed acylation of homoallylic alcohols **3** and **4** proceded quite differently. Although racemates **3** and **4**, prepared by superacidic cyclization of geraniol and (2*E*,6*E*)-farnesol according to procedure,[21] were additionally purified by column chromatography on SiO_2 and contained no isomers (as followed from their ^1H and ^{13}C NMR spectra), in both cases residual alcohols recovered upon more than 50% conversions contained noticeable amounts of structural isomers, which were identified on the basis of ^1H and ^{13}C NMR spectra. Mixtures of similar composition were also obtained when the solutions of alcohol **3** or **4** in Et_2O were submitted to a prolonged contact with equal amounts of CCL (alcohol/enzyme = 1 : 1, w/w) in the absence of vinyl acetate. Thus, optically active alcohol with $[\alpha]_D^{20}$ +6.5° (EtOH), recovered upon 55% conversion of racemate **3** (Scheme 1, *B*), was identified as (*R*)-**3** in accordance with the sign of its optical rotation (*cf.* Refs. 8, 22, 23). However, ^1H NMR spectrum of this specimen contained additional signals attributable to an isomer of (*R*)-**3**, achiral β-cyclogeraniol **11**. The integral intensity of the signals specific to **11**, namely, of the allylic CH_2OH group (dd, δ 4.15) and *gem*-dimethyl group (s, δ 1.04),[24] contributes some 35—40% to the total integral intensity of the signals appearing in these parts of the spectrum. As the specimen in question contains no other admixtures besides alcohol **11** (GC, TLC, and ^1H NMR data), the actual value of $[\alpha]_D$ for alcohol (*R*)-**3** can be estimated using equation:

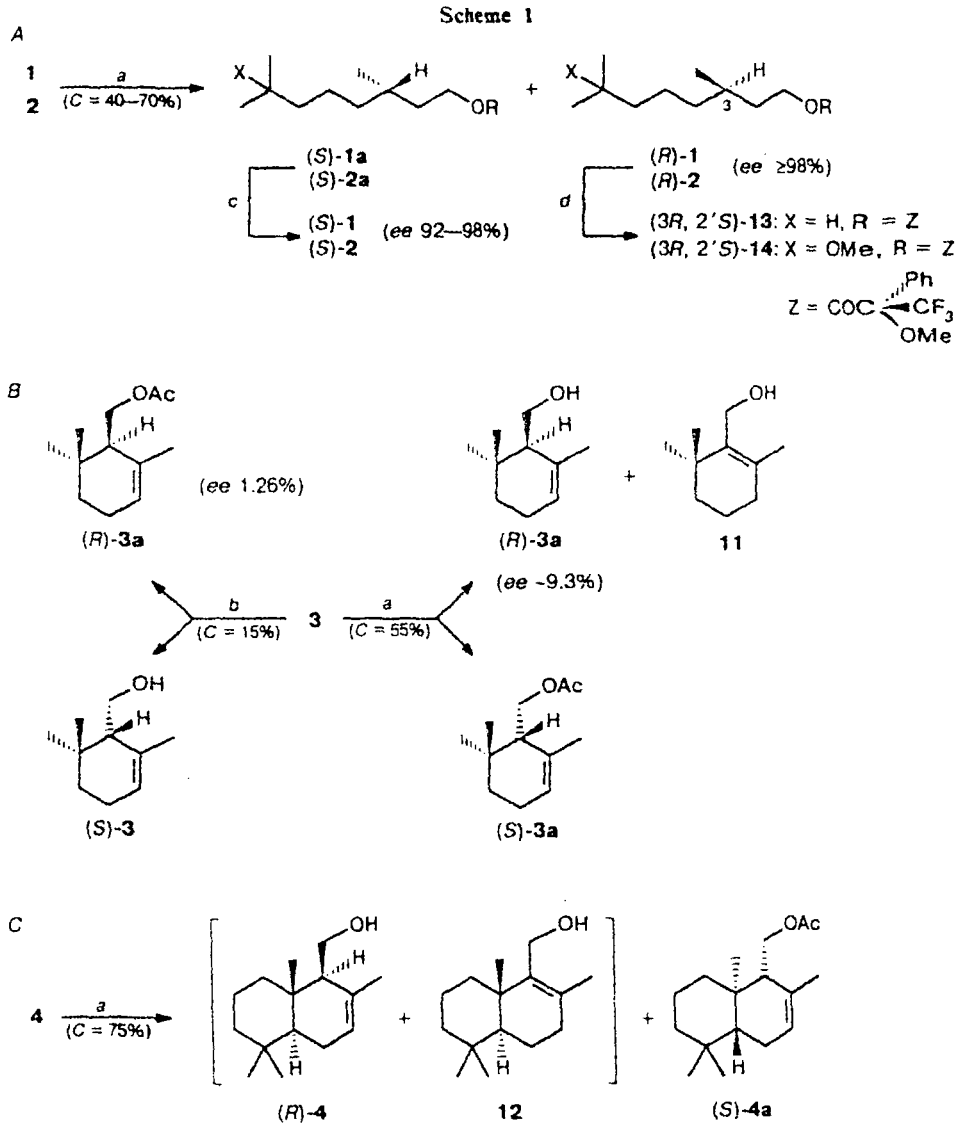
$$[\alpha]_{D(1)} \cdot (1 - x) + [\alpha]_{D(2)} \cdot x = [\alpha]_{D(obs)}, \quad (4)$$

where $(1 - x)$ and x are the molar parts of the major and minor isomer, respectively, $[\alpha]_{D(1)}$ and $[\alpha]_{D(2)}$ correspond to specific rotations of individual (*i.e.*, chemically and enantiomerically pure) components, and $[\alpha]_{D(obs)}$ is an experimentally found specific rotation of the specimen.

On the basis of the ^1H NMR spectrum, the value of x was assumed to be ~0.39. The value of $[\alpha]_D^{20}$ for

* When enantiomerically pure (*R*)-(−)-pantolactone was applied to the same adsorbent, no change of the $[\alpha]_D$ was observed after 24 h exposure.

Scheme 1



Reagents and conditions: *a*. H_2C=CHOAc–CCL/Et_2O; *b*. Ac_2O–PPL/hexane; *c*. KOH–MeOH; *d*. (*S*)-MTPA-Cl/Py–CCl_4.

enantiomerically pure (*R*)-**3** was assumed to be +114.8° (EtOH), which is an average from the reported values of $[\alpha]_D$ for its enantiomerically pure (*ee* ~100%) antipode (*S*)-**3** in the same solvents,[8,23] while for isomer **11** $[\alpha]_D$ is zero. By substituting these values for *x*, $[\alpha]_{D(1)}$ and $[\alpha]_{D(2)}$ in Eq. (4) we assessed the actual value of $[\alpha]_{D(obs)}$ to be +69.6° (EtOH). Thence, the enantiomeric purity of (*R*)-**3** in the specimen amounts to ~9.3%, so the enantioselectivity of partial acylation of alcohol **3** is rather low. It should be noted that the ^{1}H NMR spectrum of the respective acetate fraction displayed only the signals of acetate (*S*)-**3a**. This implies that the CCL-catalyzed processes of acylation and isomerization of alcohol **3** occur with comparable rates, whereas enzymatic acylation of the allylic alcohol **11** does not take place.

Partial acylation of drim-7-en-11-ol **4** (Scheme 1, *C*) represents a similar case, but its interpretation is more complicated. Here the residual alcohol, recovered upon 75% conversion, displayed $[\alpha]_D^{20}$ +2.3° (PhH). Since it had been found earlier that natural (5*S*,9*R*,10*S*)-drim-7-en-1-ol [(*R*)-**4**] displays $[\alpha]_D$ −18° (PhH)[25] or −20° ($CHCl_3$),[26] one might assume the recovered unreactive alcohol to be of opposite absolute configuration [(5*R*,9*S*,10*R*), (*S*)-**4**] and about 12–13% enantiomeric purity. However, the occurrence of irrelevant signals in the ^{1}H and ^{13}C NMR spectra of this specimen made this assignment doubtful. Unlike the ^{1}H NMR spectrum of the starting racemate **4**, that of the recovered alcohol contained a signal at 4.20 ppm (AB-system, J_{AB} ≈ 11 Hz) which accounted for 15–20% of the total integral intensity of the signals observ-

able in this part of the spectrum. This signal is characteristic of the allylic CH_2OH group of dextrorotatory (5*S*,10*S*)-drim-8-en-11-ol ["(+)-β-bicyclofarnesol," **12**][27] which is an isomer of the natural alcohol (*R*)-**4**. In addition to the signals of carbon atoms of the trisubstituted Δ^7 bond (δ 124.41 and 131.5) and the homoallylic CH_2OH group (δ 57.54) present in the ^{13}C NMR spectrum of the starting alcohol **4**, the ^{13}C NMR spectrum of the recovered alcohol fraction displays the signals of a tetrasubstituted Δ^8 bond (δ 128.25 and 139.90) and allylic CH_2OH group (δ 61.20) as well as an extra set of lines in the region of CH_3 and CH_2 groupings revealed by employing the INEPT technique. Therefore, this specimen of unconverted alcohol is a binary mixture of isomeric olefins (*R*)-**4** and **12**. Consequently, its specific rotation, $[\alpha]_D^{20}$ +2.3° (PhH), results from the superposition of specific rotations belonging to alcohol (*R*)-**4** and its isomer **12**.

Earlier,[27] for enantiomerically pure alcohol **12**, a value $[\alpha]_D^{20}$ +105.4° ($CHCl_3$) was reported. On the basis of the ^1H NMR spectrum of the recovered alcohol, that is, of the binary mixture of isomers (*R*)-**4** and **12**, their molar parts were assumed to be 0.825 and 0.175, respectively (averaged). By introducing these figures and the respective values of $[\alpha]_D$ in Eq. (4) one can calculate the value of $[\alpha]_D$ for the solution of the same mixture of enantiopure isomers in $CHCl_3$:

$$[\alpha]_{D(obs)} = (-20°) \cdot 0.825 + 105.4° \cdot 0.175 \approx 1.9°.$$

This is fairly close to the value of $[\alpha]_D^{20}$ +2.3° (PhH) found for the recovered alcohol. By substituting the values of $[\alpha]_{D(1)}$ and $[\alpha]_{D(2)}$ corresponding to 50, 25, and 10% enantiomeric purity of both components, one obtains $[\alpha]_{D(obs)}$ +0.97°, +0.49°, +0.19°. Thus, within the standard accuracy of the measurement and assuming the difference in *ee* values for (*R*)-**4** and **12** to be small, the above composition of their mixture will always be reflected in a slightly positive specific rotation. Were a mixture of the same proportion to consist of dextrorotatory alcohol (*S*)-**4** and, correspondingly, levorotatory alcohol *ent*-**12**, its specific rotation would be slightly negative.*

The *R* configuration of the major component in the binary mixture of isomeric alcohols is corroborated by the following facts. (*1*) Upon repeated incubation of the alcohol specimen with $[\alpha]_D^{20}$ +2.3° with a fresh portion of CCL, in the ^1H NMR of the recovered material the intensities of the signals attributable to the Δ^8 isomer became markedly increased, while $[\alpha]_D^{20}$ of this specimen was as high as +43.1° (PhH). This can be explained only by a strong positive rotation of accumulating isomer, which corresponds to stereoformula **12**. (*2*) Racemic α-cyclogeraniol **3** (*vide supra*) and nor-11-hydroxydriman-8-one,[28] two alcohols structurally related to racemate **4**, produce preferably *S*-acetates upon CCL-mediated partial acylation, while the alcohols accumulated in the unconverted part of the substrate possess *R* configuration at the asymmetric center nearest to the hydroxy group. Taken together, these data imply that upon partial acylation of substrate **4** in the system vinyl acetate—CCL/Et_2O it is the component (*S*)-**4** that reacts rapidly, whereas alcohol (*R*)-**4** is a slow-reacting component (conditionaly, *ee* is ≥13.9% at $C = 75\%$).

The acetate-containing fraction, obtained at a 75% conversion of **4** and consisting mainly of enantiomer (*S*)-**4a**, was free of the respective Δ^8 isomer (^1H NMR data); this is reminiscent of partial acylation of alcohol **3** mediated by the same enzyme.

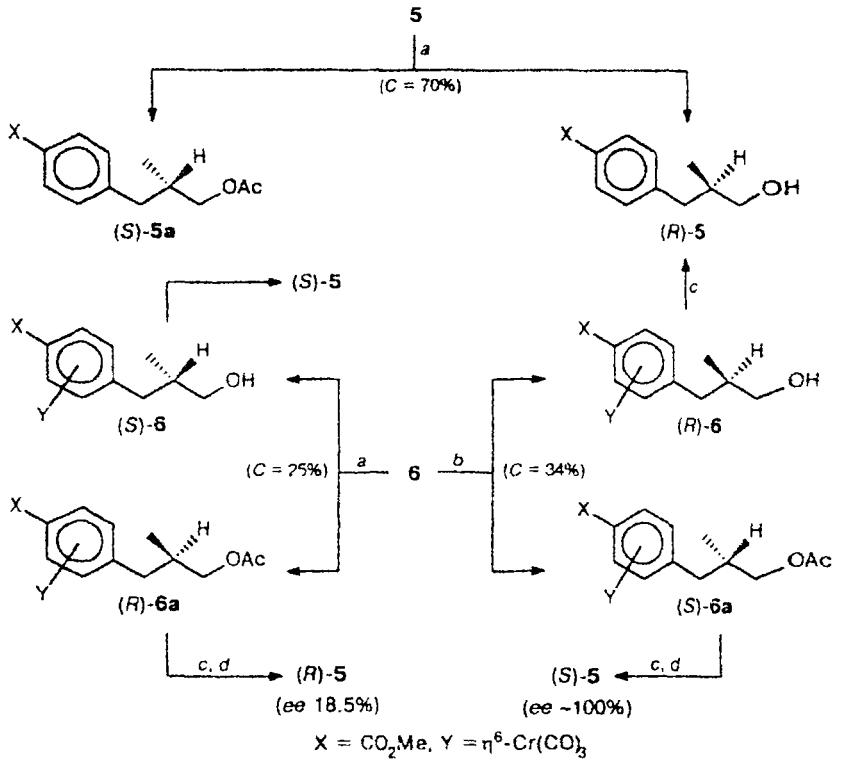
When α-cyclogeraniol **3** was acylated in the system Ac_2O—PPL/hexane to a 15% conversion depth, the isolated acetate had $[\alpha]_D^{20}$ +2.24° (EtOH). Since it was shown earlier[29] that the levorotatory (in EtOH) specimen of α-cyclogeranyl acetate has *S* configuration, our specimen must contain mainly acetate (*R*)-**3a**. Consequently, it is alcohol (*S*)-**3** that predominates in the unconverted substrate (see Scheme 1, *B*). However, the comparison of $[\alpha]_D$ of our specimen of (*R*)-**3a** with reported values of $[\alpha]_D$ for a few specimens of acetate (*S*)-**3a**, whose enantiomeric purity was determined after their mild saponification into alcohol (*S*)-**3**,[29] showed that the *ee* of (*R*)-**3a** obtained in the Ac_2O—PPL system was purely symbolic (~1.26%). In sum, acylation of alcohol **3** in the presence of either CCL or PPL proceeds with opposite enantioselectivities, but in both cases optical resolution of racemate **3** by this technique is not practical.

Acylation of alcohol **5** in the system vinyl acetate—CCL/Et_2O to 70% conversion gives a specimen of residual alcohol (*R*)-**5** with $[\alpha]_D^{20}$ +5.2° ($CHCl_3$) wich corresponds to its 50% enantiomeric purity; earlier,[12] for a specimen of (*R*)-**5** with ~100% *ee* $[\alpha]_D^{20}$ +10.4° ($CHCl_3$) was found. Apparently, in the system $H_2C{=}CHOAc$—CCL/Et_2O it is the *S* enantiomer of **5** that reacts faster.

In contrast with the enhancement of enantioselectivity of the PPL-catalyzed hydrolysis of the respective acetates,[12] the enantioselectivity of acylation in the system $H_2C{=}CHOAc$—CCL/Et_2O *decreases* upon the transition from **5** to its chromium(tricarbonyl) complex **6**. Even at a moderate conversion of racemate **6** (25%) the *ee* value of the resulting acetate was only 18.5%. This follows from comparing the $[\alpha]_D$ of alcohol (*R*)-**5**, obtained upon oxidative decomplexing of a specimen of acetate (*R*)-**6a** (formed in partial acylation of **6**) and subsequent saponification of the resulting acetate (*R*)-**5a**, with $[\alpha]_D$ of another specimen of (*R*)-**5** obtained earlier[12] with *ee* ~100% (+1.90° and +10.4°, respectively,

* As alcohol **12** was not isolated in the individual state from the fraction of unconverted substrate, one cannot exclude the possibility that under the conditions of partial acylation of racemate **4** the remaining alcohol (*R*)-**4** is accompanied by an admixture of racemic alcohol (*R,S*)-**12** (formed from **4** as an artefact). In such a case the *ee* of component (*R*)-**4** in the specimen with $[\alpha]_D^{20}$ +2.3° would be about 13.9%.

Scheme 2



Reagents and conditions: *a*. H_2C=CHOAc—CCL/Et_2O; *b*. H_2C=CHOAc—PPL/Et_2O; *c*. I_2/THF; *d*. NaOMe, 0 °C.

in $CHCl_3$). The enantiomeric excess of alcohol (*S*)-**5** resulting from oxidative decomplexing of the residual alcohol (*S*)-**6** recovered after a 75% conversion of racemate **6** (see Scheme 2 and Table 1, entry *8*) was nearly the same as above: the values of $[\alpha]_D^{20}$ for this specimen and for the already reported[12] specimen of (*S*)-**5** with *ee* ~100% were −2.14° and −10.33°, respectively (in $CHCl_3$). Hence, the *ee* of the former specimen is about 20.6%. The averaged parameter *E*, calculated for partial acylation of alcohol **6** in the system H_2C=CHOAc—CCL/Et_2O by using Eqs. (2) and (3), was as low as 1.46. On the other hand, the *enantioselectivity of acylation was reversed upon the transition from substrate* **5** *to substrate* **6**. This effect is analogous to that observed earlier[12] for the PPL-mediated hydrolysis of the corresponding acetates **5a** and **6a**.

Partial acylation of alcohol **6** proceeds with much higher enantioselectivity, if in the same acylating system porcine pancreatic lipase (PPL) is substituted for *Candida cylindracea* lipase (CCL). At the same time, the sense of enantioselectivity becomes reversed (see Scheme 2): in the presence of PPL the acetate isolated at 17% conversion had *S* configuration, and after oxidative decomplexing and subsequent saponification of the resulting acetate it afforded a specimen of alcohol (*S*)-**5** with $[\alpha]_D^{20}$ −10.38° ($CHCl_3$), which corresponds to ~100% *ee*. When the fraction of unconverted alcohol was resubmitted to partial enzymatic acylation (see Table 2, entry *3*), and the recovered slow-reacting alcohol was oxidatively decomplexed (see Scheme 2), this reaction sequence gave a specimen of alcohol (*R*)-**5** with $[\alpha]_D^{20}$ +10.42° ($CHCl_3$), *i.e.*, with ~100% *ee*. In agreement with the principle of microscopic reversibility, the fast-acetylated enantiomer of alcohol **6** and the fast-hydrolyzed enantiomer of acetate **6a** have the same configuration, which in the case of PPL-catalyzed reactions is *S* (*cf.* this work and Ref. 12).

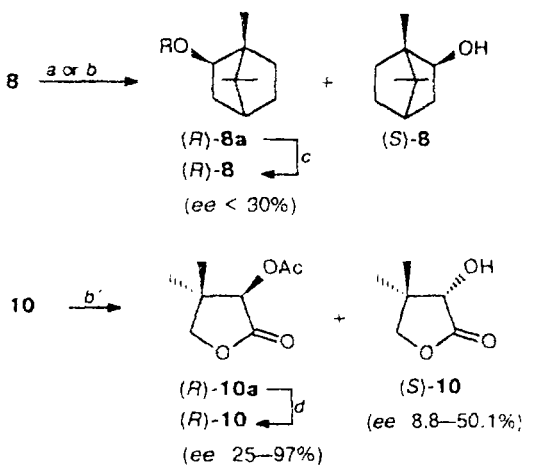
In the case of the β-branched primary alcohols **3** and **6** their CCL-catalyzed and PPL-catalyzed acylation display opposite enantioselectivities (*cf.* Table 1, entries *4*, *7*, and *8*, with Table 2, entries *1*—*3*, as well as Scheme 1, *B* and Scheme 2). By contrast, the acylation of isoborneol both in the system H_2C=CHOAc—CCL/Et_2O and in the system Ac_2O—PPL proceeds in the same stereochemical sense to give preponderantly acetate (*R*)-**8a**, although with poor enantiomeric excess and in low chemical yield (particularly when CCL is used). A specimen of (*R*)-**8a**, formed in the system H_2C=CHOAc—CCL/Et_2O and isolated in a less than 1.5% yield, showed $[\alpha]_D^{20}$ −16.7° (AcOEt), which corresponded to some 30—33% enantiomeric purity (*cf.* Ref. 15). Another specimen, obtained upon acylating **8** in the system Ac_2O—PPL (*C* = 25%, yield 8.5%) had $[\alpha]_D^{20}$ −3.5° (hexane). The configuration and *ee* of this acetate were

determined by saponifying it with 20% aqueous KOH, which gave the levorotatory (1*R*,2*R*,4*R*)-isoborneol, (*R*)-**8**, with $[\alpha]_D^{20}$ −2.7° (EtOH). Comparison with the $[\alpha]_D$ of configurationally homogeneous isoborneol in the same solvent (from −30.6 to −34.2°)[30] showed that for the above specimen of (*R*)-**8** and, consequently, for the respective specimen of acetate (*R*)-**8a** used as its precursor, the value of *ee* is within 7.9–8.9% (Scheme 3). As in the case of PPL-catalyzed acylation of alcohols **3** and **6**, the principle of microscopic reversibility is also valid for isoborneol **8**: its acylation gives preponderantly *R* enantiomer of the acetate, (*R*)-**8a**, which is somewhat more quickly hydrolyzed in the presence of PPL.[29]

In this context, partial acylation of (*R*,*S*)-pantolactone **10** in the system Ac_2O—PPL/hexane is interesting as a case of apparent violation of the principle of microscopic reversibility. PPL-catalyzed hydrolysis of racemic acetate **10a** is known to afford (*S*)-pantolactone, although with extremely low *ee* (only 1.26%).[29] When a polar reaction medium (a dispersion of acetate **10a** to be hydrolyzed in aqueous buffer) was replaced by a less polar one (a solution of alcohol **10** in Ac_2O—hexane) the resulting acetate had the *R* configuration [(*R*)-**10a**]. Under optimal conditions (see Table 2, entry 7) the hydroxylactone **10** afforded, in good yield, a specimen of acetate (*R*)-**10a** with $[\alpha]_D^{20}$ −12.75° (EtOH). Its deacetylation according to Zemplén's procedure proceeded smoothly to give (*R*)-pantolactone with m.p. 89–91 °C and $[\alpha]_D^{20}$ −27.3° (MeOH) (see Scheme 3). Earlier, for enantiomerically pure lactone (*R*)-**10** and its acetate (*R*)-**10a**, $[\alpha]_D^{20}$ −28.0° (MeOH)[31] and $[\alpha]_D^{20}$ −13.1° (EtOH),[32] respectively, were reported. Thus, the specimen of acetate (*R*)-**10a** obtained in the system Ac_2O—PPL/hexane has *ee* 97.3%, and its deacylation with NaOMe/MeOH does not involve racemization. The fraction of unconverted alcohol recovered after partial acylation of racemate **10** displayed positive optical rotation and therefore contained mainly the *S* enantiomer.

Recently,[29] the extremely low *S*-selectivity of the PPL-mediated hydrolysis of acetate **10a** was interpreted in terms of a conformational substrate model of PPL as the result of the energetic quasi-equivalence of the two planarized, W-shaped reaction conformations of the substrate wich are formed from the staggered and a low-energy *gauche* conformation, respectively. A change in the polarity and phase composition of the reaction medium can substantially affect the relative stability of starting and reaction conformations of the substrates like **10** and **10a** (where intramolecular dipole-dipole interactions are of great importance) and thus alter the stereochemical outcome of the reaction. For such substrates the enantioselectivity of lipase-catalyzed reactions of hydrolysis and acylation may be different in media of different polarity, and thus formally disobey the principle of microscopic reversibility.

Scheme 3



Reagents and conditions: *a*. $H_2C{=}CHOAc$—CCl/Et_2O; *b*. Ac_2O—PPL; *b'*. Ac_2O—PPL/hexane; *c*. KOH—H_2O, Δ; *d*. NaOMe/MeOH, ~20 °C.

Experimental

^1H NMR spectra were recorded with Bruker AC-200 and Bruker WM-250 spectrometers in $CDCl_3$ solution, ^{19}F NMR spectra were obtained using Bruker AC-200 spectrometer (188.3 MHz) in $CDCl_3$ solutions with $CFCl_3$ as the external reference. IR spectra were recorded with Carl Zeiss UR-20 spectrometer in CCl_4 solutions. GC analyses (for compounds **1**, **2**, **1a**, **2a**, **5**, **5a**, and **10**, **10a**) were carried out using an LKhM-8 MD instrument equipped with a flame ionization detector and a stainless steel column (1.5×0.003 m) packed with 5% SE-30 on Chromaton N-AW-DMCS as the stationary phase; the rate of N_2 was 60 mL min^{-1}, oven temperature was 190 °C (for **5** and **5a**) or 130 °C (for the others). TLC monitoring was performed on Silufol® plates with a fixed layer of SiO_2. Silica gel L (40–100 mm, Czech Republic) was used for column chromatography. The values of $[\alpha]_D$ were determined using a JASCO-DIP 360 polarimeter.

The starting racemic alcohols were obtained as follows: **1** (b.p. 137–138 °C (55 Torr), n_D^{20} 1.4370) — by rectifying *in vacuo* a fraction of saturated alcohols formed upon catalytic hydrogenation of (*R*,*S*)-citronellal (Moscow Experimental Plant of Fragrances); **2** (b.p. 115–118 °C (1.5 Torr), n_D^{20} 1.4460 — by hydrogenation of (*R*,*S*)-7-methoxy-3,7-dimethyloctanal prepared from (*R*,*S*)-citronellal according to a known procedure[33]; **3** and **4** — by the acid-catalyzed cyclization of geraniol and (2*E*,6*E*)-farnesol, respectively, in a superacidic medium according to Ref. 21, which was followed by additional purification on silica gel*; **5** and **6** — according to method[12]; **7** — according to method[34]; **9** — according to method[35]. (*R*,*S*)-Isoborneol **8**, m.p. 212–214 °C (Aldrich) and (*R*,*S*)-pantolactone

* Compounds **3** and **4** were kindly provided by P. F. Vlad (Institute of Chemistry, Academy of Sciences of Moldova, Kishinev) within the framework of a joint research project (P. F. Vlad, G. D. Gamalevich, V. N. Nikolsky, and E. P. Serebryakov, in preparation).

10, m.p. 89—91 °C (Experimental Plant of the Vitamin Research Institute, Moscow) were used without additional purification, as were vinyl acetate and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (both from Fluka). Diethyl ether, hexane, and Ac_2O were purified according to recommended procedures[36] and redistilled prior to use.

The specific activity of lipase from *Candida cylindracea* (type VII, ~30% lactose, Aldrich) was 1200 units per 1 mg of dry powder; that of porcine pancreatic lipase (Olainfarm, Latvia) was 47.8 mg per 1 mg of the protein.

The conversion of substrates **1**, **2**, **5**, and **10** was followed using GC (as an average from 3—5 measurement, standard deviation ±2%). In the other cases the conversion was inferred from the integral weight of the unconverted alcohol recovered after careful chromatographic separation on a silica gel column in a hexane→Et_2O gradient.

Partial acylation of alcohol 1—9 with vinyl acetate—CCL (general procedure). A substrate (1 mmol) was dissolved in abs. Et_2O (3 mL), and vinyl acetate (110—130 mL, 1.2—1.5 mmol) was added to the solution. This was followed by the addition of powdered CCL taken as a multiple to the weight of the substrate (0.5, 1.0 or, in the case of alcohol **9**, 2.0 parts per one part of the substrate). The mixture was stirred magnetically in a sterilized and hermetically stoppered two-neck flask; the course of the reaction was monitored by GC and/or TLC. After a period indicated in Table 1, the reaction mass was filtered through a thin pad of Celite on a porous glass funnel, the cake on the filter was washed with dry Et_2O, and the combined organic solution was concentrated *in vacuo* (25—30 Torr) at bath temperature ≤40 °C. The remainder, a mixture of an acetate with unconverted alcohol, was chromatographed on a column filled with SiO_2 (neutral Al_2O_3, Brockmann grade II, was used to separate acetate (*S*)-**2a** and alcohol (*R*)-**2**) at an adsorbent: adsorbate ratio *ca.* 40 : 1 using a hexane→Et_2O gradient to elute final and starting products. The chemical yields in Table 1 correspond to the theoretically possible amount of optically active material at the indicated conversion of a racemic substrate.

(*S*)-(−)-3,7-Dimethyloctan-1-ol, (*S*)-1. The products resulting from the acylation of alcohol **1** to 40% conversion (see Table 1, entry *1*) were separated by eluting the column with hexane—Et_2O (9 : 1, v/v) to give pure (*S*)-3,7-dimethyloctyl acetate [(*S*)-**1a**] as a colorless oil with R_f 9.3 min and $[\alpha]_D^{20}$ +6.00° (*c* 0.60, $CHCl_3$). Yield 92%. ^1H NMR, δ: 0.94 (d, 6 H, 8-H_3 and 7-Me, J = 7 Hz); 0.98 (d, 3 H, 3-Me, J = 6.5 Hz); 1.07—1.66 (m, 10 H, CH_2 and CH); 2.01 (s, 3 H, COMe); 4.11 (t, 2 H, 1-H_2, J = 7 Hz). Elution of the column with hexane—Et_2O (1 : 1, v/v) afforded in quantitative yield the fraction of unconverted alcohol **1** containing mainly the *R* enantiomer, (*R*)-**1**.

Acetate (*S*)-**1a** (140 mg, 0.7 mmol) was added to a solution of KOH (40 mg, 0.71 mmol) in abs. MeOH (4 mL), and the mixture was stirred for 90 min at 20—22 °C until the starting acetate was fully consumed (TLC, GC). The reaction mixture was concentrated at 50 Torr, and the remainder was diluted with water (0.5 mL) and extracted with Et_2O (3×1 mL). The extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* (25—30 Torr) to leave chromatographically pure (TLC, GC) alcohol (*S*)-**1**, a colorless oil with n_D^{20} 1.4352, R_f 7.1 min, and $[\alpha]_D^{20}$ −6.07° (*c* 0.50, MeOH). Ref. 20: $[\alpha]_D^{20}$ −6.10° (MeOH). Yield 100 mg (91%). ^1H NMR, δ: 0.94 (d, 6 H, 8-H_3 and 7-Me, J = 7 Hz); 0.98 (d, 3 H, 3-Me, J = 6.5 Hz); 1.06—1.66 (m, 10 H); 1.70 (br.s, 1 H, OH); 3.67 (m, 2 H, 1-H_2).

(*R*)-(+)-3,7-Dimethyloctan-1-ol, (*R*)-1. The products formed upon acylating alcohol **1** to 70% conversion (see Table 1, entry *2*) were eluted from the column first with hexane—Et_2O (9 : 1), which gave an acetate fraction containing mainly the *S* enantiomer, and then with hexane—Et_2O (1 : 1), which afforded pure alcohol (*R*)-**1** with n_D^{20} 1.4354 and the same ^1H NMR spectrum as that of (*S*)-**1**, but with $[\alpha]_D^{20}$ +6.15° (*c* 0.50, MeOH). Yield 96%.

A solution of the acyl chloride, prepared according to Ref. 37 from (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (35 mg, 0.15 mmol) and $SOCl_2$ in dry pyridine (0.15 mL), was added to a solution of alcohol (*R*)-**1** (16 mg) is dry CCl_4 (30 mL). After a 15 min exposure the reaction mass was worked up according to a known procedure,[38] and the (*S*)-MTPA ester of alcohol (*R*)-**1** [(3*R*,2'*S*)-**13**] was isolated as a viscous, colorless oil free of visible contaminants (TLC). ^1H NMR, δ: 0.92 (d, 6 H, 8-H_3 and 7-Me, J = 7 Hz); 0.95 (d, 3 H, 3-Me, J = 6.6 Hz); 1.05—1.68 (m, 10 H, CH_2 and CH); 3.56 (s, 3 H, 2'-OMe); 4.14 (br.t, 2 H, 1-H_2); 7.18 (m, 5 H, Ph). ^{19}F NMR, δ: 70.83 (s, the only signal).

(*S*)-(−)-7-Methoxy-3,7-dimethyloctan-1-ol, (*S*)-2. The products formed upon acylating alcohol **2** to 50% conversion (see Table 1, entry *3*) were separated on a column with Al_2O_3. Elution with hexane—Et_2O (9 : 1) gave pure acetate (*S*)-**2a** as a colorless oil with R_f 11.2 min and $[\alpha]_D^{20}$ +6.80° (*c* 0.50, $CHCl_3$). Yield 96%. ^1H NMR, δ: 0.74 (d, 3 H, 3-Me, J = 7 Hz); 0.97 (s, 6 H, 8-H_3 and 7-Me); 1.06—1.33 (m, 6 H, H_2); 1.35—1.52 (m, 3 H, 2-H_2 and 3-H); 2.15 (s, 3 H, COMe); 3.06 (s, 3 H, OMe); 4.14 (br.t, 2 H, 1-H_2). Further elution with hexane—Et_2O (1 : 1) afforded pure alcohol (*R*)-**2** as a colorless oil with $[\alpha]_D^{20}$ +6.52° (*c* 0.70, MeOH). ^1H NMR spectrum was practically identical with that recorded for alcohol (*S*)-**2** (*vide infra*).

Acetate (*S*)-**2a** was saponified in exactly the same manner as described for the preparation of alcohol (*S*)-**1** to give chromatographically pure (GC, TLC) alcohol (*S*)-**2** as a colorless oil with $[\alpha]_D^{20}$ −6.00° (*c* 0.50, MeOH). Yield 91%. ^1H NMR, δ: 0.74 (d, 3 H, 3-Me, J = 7 Hz); 0.97 (s, 6 H, 8-H_3 and 7-Me); 1.06—1.33 (m, 6 H, CH_2 groups); 1.35—1.52 (m, 3 H, 2-H_2 and 3-H); 3.02 (s, 3 H, OMe); 3.35 (br.s, 1 H, OH); 3.54 (m, 2 H, 1-H_2).

Determination of enantiomeric purity of alcohol (*R*)-2. The specimen of alcohol (*R*)-**2** with $[\alpha]_D^{20}$ +6.52° (*vide supra*) was transformed into the corresponding oily (*S*)-MTPA ester [(3*R*,2'*S*)-**14**] in the same manner as described for the preparation of its analog, (3*R*,2'*S*)-**13**. ^1H NMR, δ: 0.81 (d, 3 H, 3-Me, J = 7 Hz); 0.95 (s, 6 H, 8-H_3 and 7-Me); 1.06—1.40 (m, 6 H, 4-H_2, 5-H_2, and 6-H_2); 1.43—1.57 (m, 3 H, 2-H_2 and 3-H); 3.04 (s, 3 H, 7-OMe); 3.55 (s, 3 H, 2'-OMe); 4.12 (m, 2 H, 1-H_2); 7.17—7.29 (m, 5 H, Ph). ^{19}F NMR, δ: 70.85 (s, the only signal).

(*R*)-(+)-α-Cyclogeraniol, (*R*)-3. The products formed upon acylating alcohol **3** to 55% conversion (see Table 1, entry *4*) were separated by column chromatography on SiO_2 which was washed first with hexane—Et_2O (9 : 1) to give a fraction of the acetate enriched with the *S* enantiomer (yield 93%). Further elution with hexane—Et_2O (6 : 4 and 1 : 1) afforded the apparently homogeneous (TLC) alcohol fraction as a colorless oil with $[\alpha]_D^{20}$ +6.5° (*c* 0.65, EtOH). According to its ^1H NMR spectrum, this material was a mixture of the dextrorotatory (*R*)-α-cyclogeraniol, (*R*)-**3**, with β-cyclogeraniol **11** in a proportion ~62.5 : 37.5 (averaged from the ratios of integral intensities ranging from 65 : 35 to 60 : 40). Yield 98.5%. ^1H NMR, δ: 0.89, 0.95, and 1.04 (all s, 6 H, intensity ratio *ca.* 3 : 3 : 4, 6-Me_2 in isomeric alcohols **3** and **11**); 1.08—1.65 (m, 5 H, CH_2 and CH); 1.45 (c, 1 H, OH); 1.70 and 1.73 (both *S*, 3 H, intensity ratio *ca.* 1.9 : 1.1, 2-Me in isomers **3** and **11**); 3.63 and 3.67 (AB-part of an ABX system,

integral intensity ~1.2 H, CH_2OH in isomer 3, J_{AB} ≈ 11 Hz); 4.15 (dd, ~0.8 H, CH_2OH in isomer **11**, $J \approx J' \approx 1.5$ Hz); 5.54 (br.s, 0.65 H, 3-H in the preponderant isomer 3).

(*S*)-(−)-α-Cyclogeranyl acetate, (*S*)-3a, isolated as indicated above, is a clear, chemically individual oil (TLC, ^{1}H NMR). ^{1}H NMR, δ: 0.93 and 0.96 (both s, 6 H, 6-Me_2); 1.1—1.6 (m, 5 H, 1-H, 4-H_2, 5-H_2); 1.72 (s, 3 H, 2-Me); 2.04 (s, 3 H, COMe); 4.10 and 4.18 (dq, 2 H, CH_2OAc, J_{AB} = 12 Hz, J_{vic} = 6 Hz); 5.46 (br.s, 1 H, 3-H).

(*R*)-(−)-Drim-7-en-11-ol, (*R*)-4. The separation of the products resulting from the acylation of racemate **4** to 75% conversion (see Table 1, entry *5*) was carried out exactly as described in the above case of alcohol **3**. The fraction of the acetate, a colorless oil containing mainly the *S* enantiomer [(*S*)-**4a**], was found to be chemically pure (TLC and ^{1}H NMR data). Yield 88%. ^{1}H NMR, δ: 0.85, 0.90, and 0.94 (all s, 13-H_3, 14-H_3, 15-H_3); 1.15—1.95 (m, 10 H, 1-H_2, 2-H_2, 3-H_2, 5-H, 6-H_2, 9-H); 1.73 (s, 3 H, 12-H_3); 2.06 (s, 3 H, COMe); 4.08 and 4.13 (dq, 2 H, CH_2OAc, J_{AB} ≈ 11 Hz, J_{vic} = 6 Hz); 5.46 (br.s, 1 H, 7-H). Elution with more polar eluents gave a binary mixture of isomeric alcohols (*R*)-**4** and **12**, a clear oil with $[\alpha]_D^{20}$ +2.3° (*c* 0.70, PhH). Yield 92%. ^{1}H NMR, δ: 0.85, 0.89, and 0.95 (s + s + s, 2.6 H, 3.2 H, and 3.2 H, 13-H_3, 14-H_3, and 15-H_3); 1.15—2.10 (m, 10 H, 4 CH_2 + 5-H + 9-H); 1.46 (br.s, 1 H, OH); 1.73 (br.s, 3 H, 12-H_3); 3.69 and 3.72 (AB-part of the ABC system, ~1.65 H, 11-H_2, J_{AB} = 12 Hz); 4.20 (dq, ~0.35 H, CH_2OH group of alcohol **12**, J_{AB} = 11 Hz, $J_{allylic}$ ≈ 1.3 Hz); 5.46 (br.s, ~0.67 H, 7-H). ^{13}C NMR, δ (INEPT): 19.40 (C-12); 21.67 (C-15); 22.13 (C-13); 22.96 (C-14); 23.60 (C-1); 24.55 (C-9); 25.01 (C-6); 29.2 (C-2); 33.12 (C-4); 33.14 (C-3); 42.34 (C-5); 46.04 (C-10); 57.54 (C-11); 124.41 (C-7); 131.35 (C-8); the signals of isomer **12** were identified at δ 18.70 (C-12); 23.96 (C-15); 28.70 (C-7); 36.70 (C-4); 42.62 (C-5); 61.20 (C-11); 128.25 (w, C-8), and 139.90 (w, C-9).

Methyl (*R*)-4-(3-hydroxy-2-methylpropyl)benzoate, (*R*)-5. The products of partial acylation of alcohol **5** (see Table 1, entry *6*) were separated by column chromatography to give first (elution with hexane—Et_2O, 1 : 1) a fraction of the acetate enriched with enantiomer (*S*)-**5a**, a clear oil with R_f 8.5 min, the ^{1}H NMR spectrum of which was identical with that reported earlier.[11] Further elution with hexane—Et_2O (4 : 1 and 9 : 1) afforded a specimen of alcohol (*R*)-**5**, a colorless oil with R_f 6.0 min and $[\alpha]_D^{20}$ +5.20° (*c* 0.80, $CHCl_3$). Yield 95%. ^{1}H NMR spectrum coincided with that of Ref. 11.

Chromium(tricarbonyl) complex of alcohol (*S*)-5 [(*S*)-6]. The products formed upon acylating racemate **6** to 75% conversion (see Table 1, entry *8*) were separated using hexane—Et_2O gradient (from 0 to 50% Et_2O) to afford an acetate fraction containing mainly acetate (*R*)-**6a** (a viscous yellow oil, coinciding with the specimen of (*R*)-**6a** described in the following section by R_f and ^{1}H NMR spectrum, yield 93.5%), and a chemically pure fraction (TLC and ^{1}H NMR data) of unconverted alcohol. This specimen (yield 89%), a viscous yellow oil with $[\alpha]_D^{20}$ −2.96° (*c* 0.70, $CHCl_3$) was shown to be alcohol (*S*)-**6** with a 20.5% *ee*. Ref. 12: $[\alpha]_D^{20}$ −14.10° (*c* 0.75, $CHCl_3$) for a specimen of (*S*)-**6** with *ee* ~100%. ^{1}H NMR (DMSO-d_6), δ: 0.90 (d, 3 H, 2-Me, J = 6.5 Hz); 1.85 (m, 1 H, 2-H); 2.15 and 2.52 (both dd, 2 H, 3-H_2, J_{AB} = 14 Hz, J_{vic} = 6.5 Hz); ~2.7 (br.s, ~0.5 H, OH); 3.40 (s, ~0.5 H, OH, partly overlaps with the nearest downfield signal); 3.46 (t, degenerate AB system, 2 H, 1-H_2, J_{AB} = 12 Hz); 3.85 (s, 3 H, CO_2Me); 5.15 and 6.10 (A_2B_2 system, 2 H + 2 H, X—C_6H_4—Y, J = 8 Hz). ^{13}C NMR (DMSO-d_6), δ: 15.84 (2-Me); 37.31 (C-2); 37.85 (C-3); 52.54 (C-1); 127.0 (C-4′); 128.99 (C-3′); 129.29 (C-2′); 146.00 (C-1′); 167.71 (—OC=O); 210.25 (Cr...C≡O).

A solution of this specimen of (*S*)-**6** (172 mg, 0.5 mmol) in THF (10 mL) was treated with a solution of I_2 (15 mg) in THF (10 mL) at 20—22 °C, and the mixture was left for 24 h. The volatile products were stripped off at 40 °C (bath temperature, 15 Torr), and the remainder was washed with saturated aqueous $Na_2S_2O_3$ (5 mL) and extracted with Et_2O (4×3 mL). The extract was successively washed with saturated aqueous $Na_2S_2O_3$, $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated *in vacuo* at ~40 °C. The specimen of alcohol (*S*)-**5** thus obtained had practically the same ^{1}H NMR spectrum, R_t, and R_f as the above specimen of alcohol (*R*)-**5**. The $[\alpha]_D^{20}$ of the former was −2.14° (*c* 0.45, $CHCl_3$), which corresponded to ~20.7% *ee*. Ref. 12: $[\alpha]_D^{20}$ −10.33° ($CHCl_3$) for a specimen of (*S*)-**5** with ~100% *ee*. Yield 81 mg (80%).

Chromium(tricarbonyl) complex of acetate (*R*)-5a [(*R*)-6a]. The products formed upon acylating alcohol **6** to 25% conversion (see Table 1, entry *7*) were chromatographed as above, and a specimen of chemically pure (TLC, ^{1}H NMR) acetate (*R*)-**6a** was isolated as a viscous yellow oil with $[\alpha]_D^{20}$ +3.59° (*c* 0.70, $CHCl_3$). This rotation corresponded to ~18.5% *ee*. Ref. 12: $[\alpha]_D^{20}$ +19.40° ($CHCl_3$) for a specimen of (*R*)-**6a** with ~100% enantiomeric purity. Yield ~100%. ^{1}H NMR, δ: 1.01 (d, 3 H, 2-Me, J = 6.5 Hz); 2.01 (m, 1 H, 2-H); 2.09 (s, 3 H, COMe); 2.30 and 2.55 (AB-part of an ABM system, 2 H, 3-H_2, J_{AB} = 13 Hz, J_{vic} = 6.5 Hz); 3.87 (s, 3 H, CO_2Me); 3.96 and 4.02 (AB-quartet, 2 H, 1-H_2, J_{AB} ≈ 12 Hz); 5.12 and 6.15 (A_2B_2 system, 2 H + 2 H, X—C_6H_4—Y, J_{AB} = 8 Hz).

A solution of acetate (*R*)-**6a** (154 mg, 0.4 mmol) in THF (5 mL) was mixed at room temperature with that of I_2 (15 mg) in THF (3 mL) and left for 24 h. Then the reaction mass was worked up as described above for decomplexing (*S*)-**6** to give a specimen of acetate (*R*)-**5a** which without further purification was deacetylated at 20—22 °C by a solution of NaOMe in abs. MeOH (prepared from 12 mg of Na and 2 mL of MeOH). After a 40 min exposure the reaction mixture was neutralized with a solution of 2—3 drops of glacial AcOH in MeOH (1 mL), and the volatile products were removed *in vacuo*. The remainder was dissolved in Et_2O (5 mL), and the ethereal extract was washed with water, dried (Na_2SO_4), and evaporated to leave a specimen of alcohol (*R*)-**5** as a chemically pure (GC, TLC, ^{1}H NMR), colorless oil with $[\alpha]_D^{20}$ +1.90° (*c* 0.62, $CHCl_3$); this value corresponds to an 18.3% *ee*. Ref. 12: $[\alpha]_D^{20}$ +10.40° ($CHCl_3$) for a specimen of alcohol (*R*)-**5** with *ee* ~100%.

(1*R*,2*R*)-Isobornyl acetate, (*R*)-8a. The products of partial acylation of alcohol **8** (see Table 1, entry *10*) were chromatographed to give a specimen of acetate (*R*)-**8a** as a colorless oil with $[\alpha]_D^{20}$ −16.7° (*c* 1.0, AcOEt). In total, only 17 mg of acetate (*R*)-**8a** was obtained from 1.95 g of starting racemate. The rest (1.93 g) consisted of practically unconverted alcohol **8**. Taking into account the degree of conversion attained (*C* ~1.5%), the yield of (*R*)-**8a** amounts to ~96%. ^{1}H NMR, δ: 0.72, 0.93, 1.08 (all s, 9 H, 1-Me and 7-Me_2); 1.10—1.22 (m, 7 H, 3-H_2, 4-H, 5-H_2, and 6-H_2); 2.03 (s, 3 H, COMe); 3.60 (br.s, 1 H, 2-H).

Attempted acylation of 2,4:3,5-di-*O*-benzylidenexylitol (7). Finely ground powder of alcohol **7** (304 mg, 1 mmol) and powdered CCL (300 mg) were suspended in a mixture of vinyl acetate and hexane by vigorous magnetic stirring. Subsequent standard work-up was carried out using chloroform instead of Et_2O. The recovery of the starting material (m.p. 183—186 °C, $[\alpha]_D^{20}$ 0°) after 7 days of stirring was 300 mg.

Attempted acylation of 2-nitro-1-phenylethanol (9). Standard work-up of the reaction mixture (see Table 1, entry *11*) gave 12 mg of a chromatographically mobile, non-polar prod-

uct (R_f 0.90 upon development with hexane—Et_2O 9 : 1, intense coloring of the spot with iodine vapors) which contained no acetyl group (the data of IR and ^1H NMR spectra). The recovery of nitro alcohol **9** (a brown-reddish oil with the same appearance, R_f, and ^1H NMR spectrum as the starting material) was 315 mg after 3 days of exposure.

Partial PPL-mediated acylation of alcohols 3, 8, and 10 with Ac_2O (general procedure). The reaction conditions are indicated in Table 2. The course of acylation reactions was monitored by TLC (for **3** and **8**) or by GC (for hydroxylactone **10**). After a given period the reaction mass was filtered through a thin pad of Celite on a porous glass funnel, the cake on the filter was washed with five portions of dry Et_2O (the volume of each portion being 1.5 mL per 1 mmol of substrate), the combined organic filtrate was concentrated at 35—40 °C (bath temperature) and 25—30 Torr to *ca.* one third of its volume, and the concentrate was washed with cold aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The remainder, a mixture of the corresponding acetate with unconverted part of the substrate, was chromatographed on SiO_2 using a hexane—Et_2O gradient to elute the column.

(*R*)-α-Cyclogeranyl acetate, (*R*)-3a, was isolated by eluting the column with hexane—Et_2O (9 : 1). A colorless oil with $[\alpha]_D^{20}$ +2.24° (*c* 0.60, EtOH). ^1H NMR spectrum: exactly the same as reported for acetate (*S*)-**3a** (*cf.* Table 1, entry *3*).

(*R*)-Isobornyl acetate, (*R*)-8a, was isolated by eluting the column with hexane—Et_2O (95 : 5) as a colorless oil with $[\alpha]_D^{20}$ −3.5° (*c* 1.0, hexane). Its ^1H NMR spectrum was practically indistinguishable from that described above (*cf.* Table 1, entry *10*). Yield 0.35 g (84.7%, taking into account the 30% conversion of the substrate).

The emulsion of acetate (*R*)-**8a** (300 mg, 1.53 mmol) in 20% aqueous KOH (5 mL) was refluxed for 120 h until the disappearance of the starting acetate (TLC monitoring). The resulting alcohol was extracted with Et_2O (2×1 mL), and the extract was washed with water, dried (Na_2SO_4), and slowly evaporated in the air. The remainder was sublimed at 150—170 °C (bath temperature) and 12 Torr to afford a specimen of alcohol (*R*)-**8** with m.p. 209—213 °C and $[\alpha]_D^{20}$ −2.70° (*c* 0.85, EtOH). Yield 186 mg (79%). Ref. 30: m.p. 214°, $[\alpha]_D^{20}$ −30.6° to −34.2° (EtOH).

Acetate of (*R*)-pantolactone, (*R*)-10a. The products resulting from the acylation of (*R,S*)-pantolactone **10** with an equimolar amount of Ac_2O to 46% conversion (see Table 2, entry *7*) were successively eluted from the column with hexane—Et_2O (from 25 to 100% Et_2O). The fractions of low polarity were evaporated to give a chromatographically and spectroscopically (IR, ^1H NMR) pure specimen of acetate (*R*)-**10a** as a colorless, quickly solidifying oil with R_t 5.2 min and $[\alpha]_D^{20}$ −12.75° (*c* 1.0, EtOH). Ref. 32: $[\alpha]_D^{20}$ −13.10° (EtOH). After recrystallization from Et_2O the yield of the product with m.p. 43—44 °C (Ref. 32: m.p. 44—45 °C) was 80%, or 40% reckoned from the whole mass of the starting racemate. ^1H NMR, δ: 1.08 (s, 3 H, 3-Me); 1.18 (s, 3 H, 3-Me); 2.17 (s, 3 H, COMe); 4.01 (br.s, 2 H, 4-H_2); 5.32 (s, 1 H, 2-H).

This specimen (200 mg, 1.16 mmol) was added to a solution of NaOMe, prepared from metallic sodium (3 mg) and abs. MeOH (1.5 mL). The reaction mixture was stirred for 30 min at room temperature until the starting acetate disappeared (GC, TLC), and neutralized to pH 7 with one or two drops of glacial AcOH. The volatile components were removed *in vacuo* at 40 °C (bath temperature) and 15—20 Torr. The residue was diluted with Et_2O (10 mL), and the ethereal solution was successively washed with saturated aqueous solution of $NaHCO_3$ (2 mL) and NaCl (2 mL), dried (Na_2SO_4), and evaporated to give an oil which soon solidified. Recrystallization from pentane afforded pure (*R*)-pantolactone [(*R*)-**10**] with R_t 2.5 min, m.p. 89—90 °C, and $[\alpha]_D^{21}$ −27.3° (*c* 1.0, MeOH). Yield 115 mg (76.6%). Ref. 31: m.p. 89—91 °C, $[\alpha]_D^{20}$ −28.0° (MeOH).

Fractions eluted from the column with pure Et_2O produced upon evaporation a crystalline specimen of lactone (*S*)-**10** with m.p. 86—89 °C and $[\alpha]_D^{20}$ +11.0° (*c* 1.2, MeOH). ^1H NMR, δ: 1.08 (s, 3 H), 1.21 (s, 3 H); 3.75 (br.s, 1 H); 3.92 and 4.02 (AB quartet, 2 H); 4.19 (s, 1 H).

Acylation of alcohol 6 in the system vinyl acetate—PPL/Et_2O. The work-up of the reaction mixture and the isolation of the products were carried out analogously to the processing described for the system H_2C=CHOAc—CCL/Et_2O. Thus (see Table 2, entry *2*), a mixture of alcohol **6** (344 mg, 1 mmol), vinyl acetate (110 mL, 1.2 mmol), and powdered PPL (172 mg) in dry Et_2O (3 mL) was stirred at 20—22 °C, worked up as described above, and the products were chromatographed on a column with SiO_2. Elution with hexane—Et_2O (1 : 1) afforded acetate (*S*)-**6a** as a chemically distinct (TLC and ^1H NMR data), viscous yellow oil with $[\alpha]_D^{20}$ −19.38° (*c* 1.10, $CHCl_3$); this value corresponds to ~100% enantiomeric purity[12]. Yield 65.5 mg (100% at a 17% conversion depth). The ^1H NMR spectrum of (*S*)-**6a** was practically identical with that of acetate (*R*)-**6a** obtained from alcohol **6**.

The above specimen of acetate (*S*)-**6a** (60 mg) was oxidized with a saturated solution of I_2 in THF, and the resulting acetate (*S*)-**5a** was saponified in the same way as was described above for (*R*)-**6a**. This time, the intermediate acetate (*S*)-**5a** (35 mg, yield 90%) had $[\alpha]_D^{20}$ +7.56° (*c* 0.45, $CHCl_3$), and the product of its saponification, alcohol (*S*)-**5** (26.8 mg, yield 90%), had $[\alpha]_D^{20}$ −10.35° (*c* 0.25, $CHCl_3$). The coincidence of the values of $[\alpha]_D$ found for the specimens of compounds (*R*)-**6**, (*S*)-**5a**, and (*S*)-**5** in this work with those found earlier[12] for the same products proven to have *ee* ~100% indicates that the former are also of practically the same enantiomeric purity.

The fraction of unconverted substrate, isolated at 17% conversion of the complexed alcohol **6** (see Table 2, entry *2*), was recycled in order to obtain enantiomerically pure alcohol (*R*)-**6**. A mixture of unconverted alcohol (190 mg, 0.55 mmol), vinyl acetate (60.5 mL, *ca.* 0.66 mmol), and powdered PPL (190 mg) in dry Et_2O (3 mL) was stirred at 20—22 °C for 21 h, and the resulting compounds were separated on a column of SiO_2 (see Table 2, entry *3*). First, the acetate fraction was collected (yield 34%), while further elution with pure Et_2O afforded a specimen of alcohol (*R*)-**6** with $[\alpha]_D^{20}$ +14.40° (*c* 0.95, $CHCl_3$); yield 120 mg (96%). This alcohol (86 mg, 0.25 mmol) was dissolved in THF (5 mL) and oxidized with a saturated solution of I_2 in THF (2.5 mL). After 24 h of exposure at 20—22 °C, followed by the standard work-up, it was transformed into alcohol (*R*)-**5** with $[\alpha]_D^{20}$ +10.42° (*c* 0.58, $CHCl_3$); yield 48.5 g (92%). The values of $[\alpha]_D$ found for these specimens of (*R*)-**6** and (*R*)-**5** correspond to about 100% enantiomeric purity of both alcohols (*cf.* Refs. 11, 12).

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