Stereodivergent synthesis of chiral low-molecular bioregulators using readily available lipases

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Kinetic resolution of racemic alcohols and esters or asymmetrization of prochiral *meso*-polyols and their esters mediated by the most readily available lipases (PPL, CCL) is a convenient method for stereodivergent synthesis of chiral biologically active molecules, particularly when the task is to determine which of the enantiomers is responsible for the biological activity. Examples of application of these enzymatic processes as key steps in the synthesis of all the possible stereoisomers of a given biomolecule and for the solution of related synthetic problems are considered.

Key words: pancreatic lipase (PPL); lipase *Candida cylindracea* (CCL); 4-(2,6-dimethlheptyl)benzoic acid, chiral η^6-complexes; 2,6-dimethyloct-1-yl carboxylates, diastereoselective hydrolysis; D-pantolactone, (*R*)-quadrilure; L-xylose, L-fucose, (*R*)-drim-7-en-15-ol; (*R*)-14α*H*-isoagat-12-en-15-ol.

Introduction

The first synthesis of an organic compound, urea,[1] became a sensation in science, and in his letter written on this occasion to a colleague, Wöhler expressed his pride in the fact that he did not need any tools of living nature for this synthesis. In the subsequent 150 years, the enthusiasm about this independence increased following the progress in the chemical organic synthesis and, especially, *catalysis by transition metals*. Later, however, in accordance with Hegelian dialectics laws, this enthusiasm switched to the realization of the new, broad opportunities opened up by integration of chemical and biotechnological methods for the preparation of organic substances and materials.[2] Nowadays, many people begin to worry about the depletion of the fossil resources and their scattering that involves environmental risk and expensive regeneration. This is why the today´s turn to natural biocatalysts ("a new wind of the ascending spiral of knowledge") has become a key point in the scientific and technical strategy based on the use of readily amended resources of living nature.

From the technological standpoint, biocatalysts can be represented by (1) cell cultures (isolated organs and tissues of animals and plants, yeast, and other living microorganisms); (2) cell-free biochemicals (enzymes and enzyme-containing complexes, cloned antibodies).

The former can be rather freakish in operation, even taking into account the self-provision of living cells by co-factors and the increase in their stability in "breathing" solid matrices. The latter can be classified as "shelf reagents", which only require delicate handling. They can be divided into those requiring and not requiring co-factors.

Hydrolytic enzymes, particularly, proteases and esterases and, among them, a specific sort of the latter, *lipases*, *i.e.,* enzymes that catalyze hydrolysis of triglycerides at the water—lipid interface, are the simplest of these materials. They are attractive from both technological and economical standpoints, so they have been widely used in laboratory and industrial syntheses in the last 15—20 years. Unlike most of metal enzymes (oxidoreductases, kinases, *etc.*), they need neither difficultly accessible co-factors (that require regular regeneration), nor thoroughly formulated media; conditions of their storage are rather simple.

A highly valuable feature of lipases is the ability to catalyze hydrolysis of esters in water—oil type heterogeneous media, while the reverse reaction (acylation of alcohols) and transesterification reactions are readily catalyzed in hydrophobic solvents. It comes as no surprise that the mechanism of action and the synthetic applications of lipases have been the subjects of several monographs[3] and reviews.[4]

In addition to their natural substrates, triglycerides, lipases can hydrolyze many other esters formed, as a rule, by alcohols with lower (C_1—C_6) fatty acids. The combination of this substrate tolerance with clear-cut chemo-, regio-, and stereospecificity makes lipases valuable tools in organic synthesis. Usually, they are utilized at auxiliary steps of target-directed syntheses, *e.g.*, to isolate the required enantiomer from a racemate or to increase the enantiomeric purity of chiral building blocks (CBB).

Meanwhile, there exists a field in target-directed synthesis where the use of lipases could be of strategic

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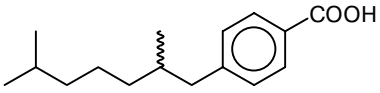
significance, namely, the identification of the active component in a biologically active racemate and other similar problems. If the racemate components have not yet been obtained as individual substances, stereodivergent synthesis *via* a common racemic intermediate would provide the shortest route to them. As *enantioselective catalysts,* lipases accomplish kinetic resolution of racemate components, which results in readily separable products, *i.e.*, an alcohol and an ester. If the reaction enantioselectivity is high and both components are produced with high *ee*, then, after "equalization" of their standings (by acylating or deacylating one of them), all the subsequent steps of the synthesis are carried out along the same pathway, resulting in optically active enantiomers of the target object. This strategy is much more efficient than the classical resolution of racemates *via* diasteromeric derivatives (salts, amides, urethanes, *etc.*) using chiral reagents, which is based on subtle differences between the physical properties of diastereomers and requires stoichiometric amounts of expensive chiral reagents. Strangely enough, until recently, this strategy has not found wide use in the target-directed synthesis.

To evaluate the opportunities provided by the use of lipases in the key step of stereodivergent syntheses, our research group was seeking chiral objects of different molecular complexity preferably among those whose biological activities have been reported only for the racemates. The work was carried out using two, most readily available lipases: the lipase from hog pancreas (PPL) and the lipase from *Candida cylindracea* yeast (CCL),* morphologically identical to the *C. rugosa* lipase.

Synthesis of 4-(2,6-dimethylheptyl)benzoic acid enantiomers. The effect of hapto-complexation on the enantioselectivity of the kinetic resolution of racemic substrates of the alkylarene type

The racemic form of 4-(2,6-dimethylheptyl)benzoic acid ((±)-**1**) suppresses cholesterol accumulation in the blood serum of rats (twice as efficiently as the reference Clofibrate®) and prevents the formation of cholesterol-containing lipoprotein plaques in the human aorta cell cultures.



(±)-**1**

Previously, nothing has been known of the biomedical properties of individual enantiomers of acid **1** because the enantiomers themselves have not been obtained. In order to synthesize pure enantiomers (*R*)-**1** and (*S*)-**1**, we studied the optical resolution of alcohol (±)-**3a** by means of partial enzymatic hydrolysis of acetate (±)-**3b**. The starting (±)-**3a** was prepared from methyl 4-formylbenzoate (a side product in the production of phthalate fiber) *via* enal **2**.

The hydrolysis of (±)-**3b** mediated by PPL in a phosphate buffer up to 43—50% conversion yielded dextrorotatory alcohol (*R*)-**3a** and levorotary acetate (*S*)-**3b**, which was then hydrolyzed to give alcohol (*S*)-**3a** (Scheme 1).[5] The configuration of the alcohols was determined by comparing the signs of their $[\alpha]_D$ with those of the closest analogs and by observing the direction of the Eu(fod)$_3$-induced shifts of the signals of the MeO and CF_3 groups in the ^1H and ^{19}F NMR spectra of the esters formed by (*S*)-**3a** with (*R*)- and (*S*)-Mosher acid (the Yasuhara—Yamaguchi method).

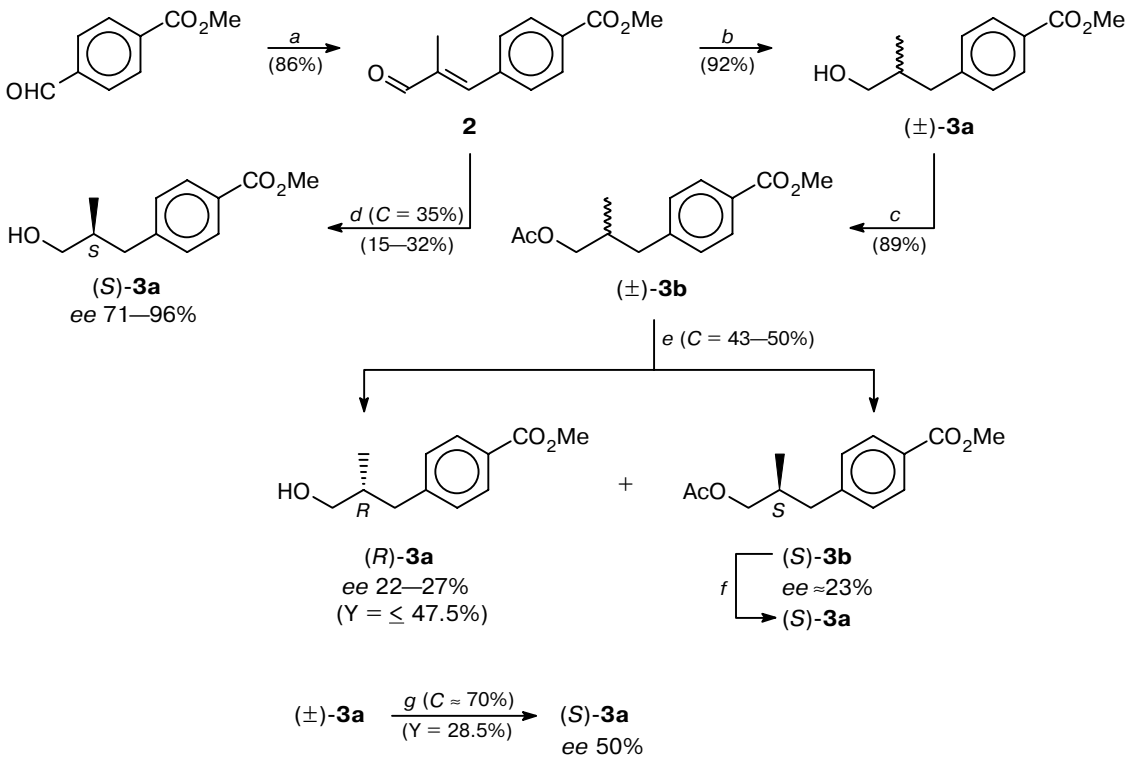
The resulting specimens of (*R*)-**3a** and (*S*)-**3a** proved to have low *ee* values (22—27%), and the attempts to increase the *ee* by repeated enzymatic hydrolysis of their acetates did not result in a substantial increase (*ee* $\leq$ 33%).[5] To obtain a speecimen of (*S*)-**3a** with a reasonable *ee*, enal **2** was converted into the corresponding allylic alcohol, which was subjected to the *S*-enantioselective biohydrogenation with the *Saccaromyces* yeast, in particular, with industrial bakers yeast (B.Y., GOST 171—81) up to a ~35% degree of conversion. This reaction is typical of 3-substituted 2-methylprop-2-en-1-ols.[6] The resulting samples of (*S*)-**3a** were characterized by *ee* 71—90% but this did not solve the problem of synthesis of *both enantiomers of* alcohol **3a** and, correspondingly, acid **1**.[5] An attempt to increase the *ee* for both alcohols by partial acylation of (±)-**3a** using CCL was not a success either.[7]

Lastly, we decided to find out whether the selectivity of the PPL-catalyzed kinetic resolution of (±)-**3a** and (±)-**3b** could be increased by a sharp increase in the size and polarity of the arene moiety in the substrate upon its transformation into the corresponding (η^6-arene)Cr(CO)$_3$ complex. It was assumed that the coordination of the Cr(CO)$_3$ species to the molecules of (±)-**3a** and (±)-**3b**, in which rotation of the benzene ring around the C(1′)—C(4′) axis is not sterically hampered, would not cause the formation of diastereomers, whereas the difference between the rates of enzymatic acylation and hydrolysis of (±)-**3a** and (±)-**3b** and the corresponding *hapto*-complexes (±)-**4a** and (±)-**4b** would be pronounced enough because the ligand environment of the asymmetric center would appreciably change.[8]

Indeed, the PPL-catalyzed acylation of the racemic η^6-complex (±)-**4a** to a degree of conversion of 50±3% resulted in smooth separation of the racemate into alcohol (*R*)-**4a** and acetate (*S*)-**4b**, whose oxidative decomplexation resulted in the regeneration of alcohol (*R*)-**3a** and acetate (*S*)-**3b**, which was subsequently

* In 2000, the price of hog pancreas lipase (PPL) with a specific activity within 20—100 u mg^{-1} was $20—50 per 100 g at the world market of biochemicals, the price of the lipase from the *Candida cylindracea* yeast (CCL) with a specific activity of 2 u mg^{-1} or higher was $30—70 per 10 g. Other microbial and plant lipases and their recombinant modifications are far more expensive.

Scheme 1



Reagents and conditions: *a*. EtCHO—KOH/DMF, 20 °C; *b*. H_2 (5 atm.)—Ni/Pr^{i}OH, 20 °C; *c*. Ac_2O—Py, 20 °C; *d*. (1) $NaBH_4$; (2) *Saccharomyces cerevisia* (PKM Y-337, Y-407 strains and GOST 171-81)—D-glucose/H_2O, 20 °C; *e*. (1) PPL—H_2O (pH 6.5), 20 °C, (2) chromatography (SiO_2); *f*. KOH—MeOH; *g*. H_2C=CHOAc—CCL/Et_2O, 20 °C.

hydrolyzed to give alcohol (*S*)-**3a**. The enantiomeric purity of alcohols (*R*)-**3a** and (*S*)-**3a** prepared in this way (89.5 and 96%)* was acceptable to pass from these compounds to the target acids.[9] Hydrolysis of acetate (±)-**4b** in the presence of PPL to 30% and 70% conversion furnished alcohol (*S*)-**4a** and acetate (*R*)-**4b**, respectively, whose oxidative decomplexation afforded specimens of (*S*)-**3a** and (*R*)-**3a** with *ee* ~100%;[8] however, the former protocol (acylation) proved to be preferable regarding the compromise between the factors of yield, the number of steps, and *ee* (Scheme 2).[9]

It is notable that the *hapto*-complexation with $Cr(CO)_6$ not only increases sharply the enantioselectivity of kinetic resolution of racemates **3a** and **3b** but also reverses the enantioselectivity in both cases.[5,7] The same trend was also observed in the case of acylation of (±)-**4b** in the presence of CCL, although the increase in *ee* in this case was not so pronounced.[7] Previously, this way of increasing the enantioselectivity of the enzymatic resolution of aliphatic-aromatic alcohols and esters has been unknown.

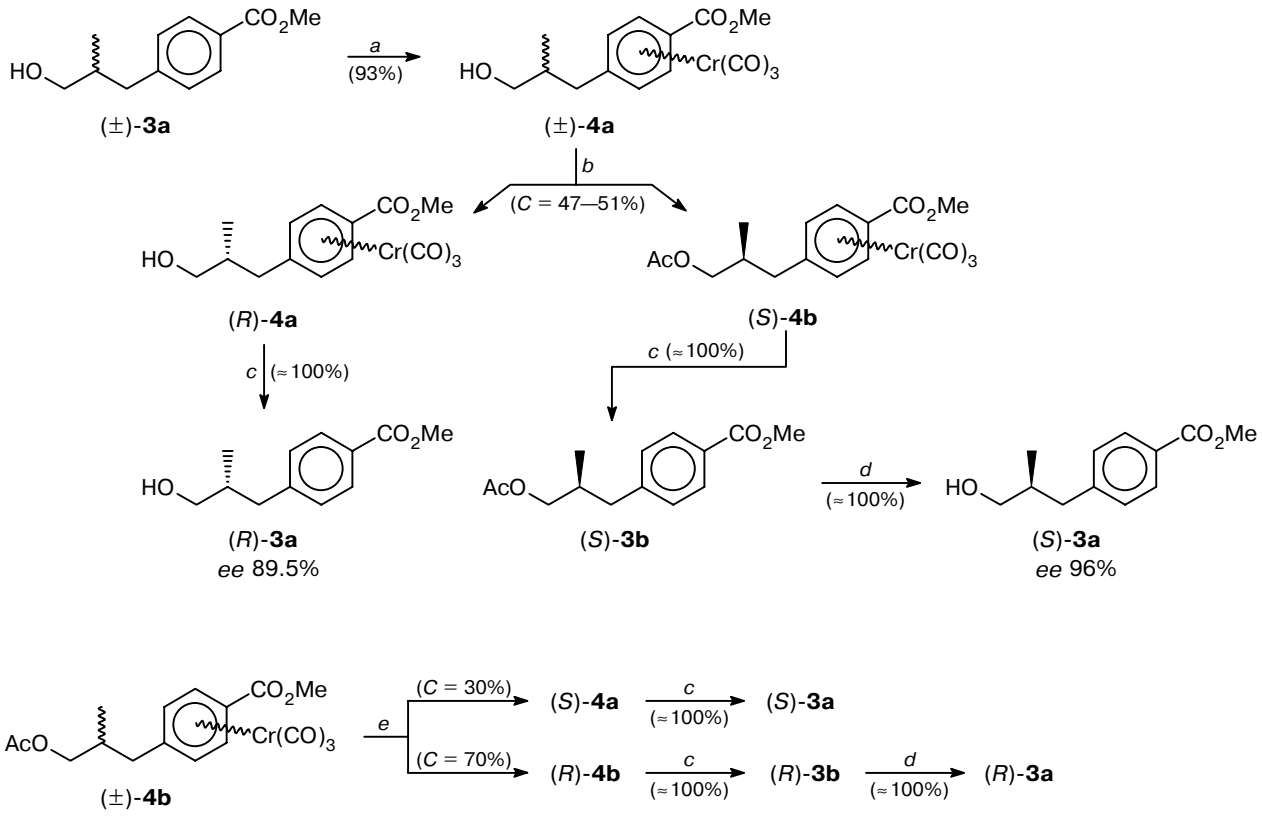
The transition from alcohols (*S*)-**3a** and (*R*)-**3a** *via* aldehydes (*S*)-**5** and (*R*)-**5** to acids (*R*)-**1** and (*S*)-**1**, respectively, was performed by the Wittig reaction under conditions that minimized racemization of the asymmetric center. After hydrogenation and alkaline hydrolysis, this gave two samples of the acid with identical absolute magnitudes of $[\alpha]_D$. The total yield of acids (*R*)-**1** and (*S*)-**1** from enal **2** was 12.5—14% (Scheme 3).[9]

The antihypercholesterolemic activities of acids (*R*)-**1** and (*S*)-**1** were determined by measuring their effect on the content of total cholesterol in the sclerotized human aortic cells cultured *in vitro* from an adipose band.[10] The decrease in the cholesterol level by acid (*S*)-**1** in concentrations of 10^{-4}—10^{-5} mol L^{-1} was statistically significant, while the results for (*R*)-**1** barely differed from the reference specimen.* Thus, we found which of the enantiomers in racemate (±)-**1** is responsible for the activity. Ozonolysis of the biologically inactive acid (*R*)-**1** followed by a two-step reduction of the ozonide (Zn/Et_2O(aq) and $NaBH_4$/MeOH) gave the known (*R*)-3,7-dimethyloctanol in 52% yield with *ee* 96%. This confirms the configuration assignment for alcohols (*R*)-**3a** and (*S*)-**3a** and, hence, for acids (*S*)-**1** and (*R*)-**1**.[10]

* Consistent data of polarimetry and the ^1H NMR spectra for diastereomeric (*S*)-MTPA esters prepared from (*R*)-**3a** and (*S*)-**3a**.

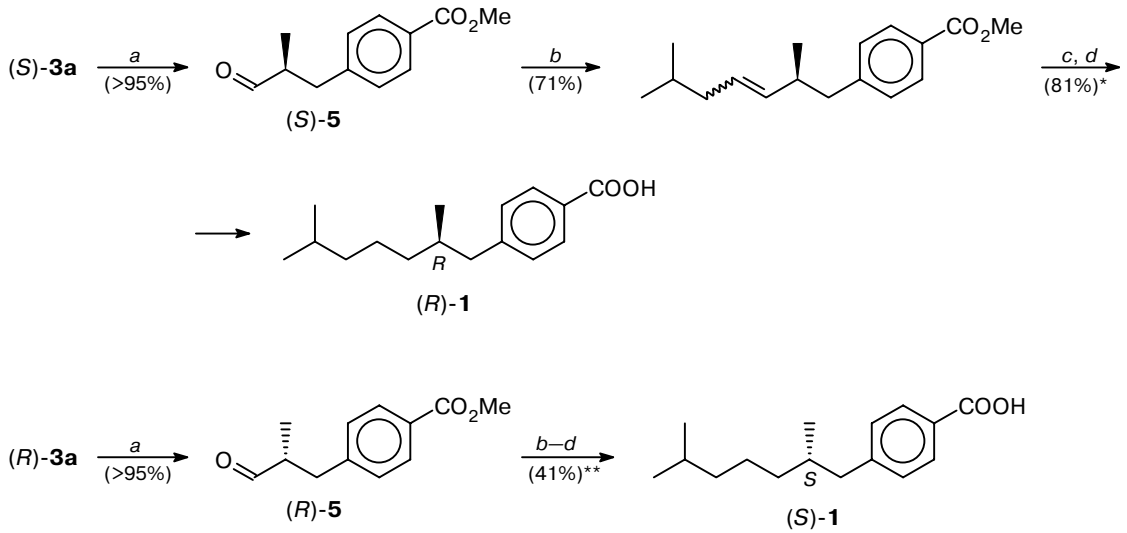
* The bioassays were carried out by A. N. Orekhov and V. V. Tertov in the Cardiological Scientific Center of the Russian Academy of Medical Sciences (Moscow) using a published procedure.[11]

Scheme 2



Reagents and conditions: *a*. $Cr(CO)_6/Bu_2^nO$, Δ; *b*. $H_2C{=}CHOAc$—PPL/Et_2O, 20 °C; *c*. I_2/THF, 20 °C; *d*. KOH—MeOH, 20 °C; *e*. PPL—H_2O (pH 6.5), 20 °C.

Scheme 3



Reagents and conditions: *a*. 1) $(COCl)_2$—DMSO/CH_2Cl_2, 2) NEt_3, −65→0 °C; *b*. $[Me_2C{=}CHCH_2PPh_3]I$—Bu^nLi/THF—hexane, −70 °C (Ar); *c*. H_2—Pd(C)/MeOH, 20 °C; *d*. 1) KOH/MeOH—H_2O (95 : 5), 65 °C, 2) recrystallization.

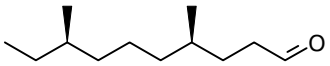
Some physicochemical characteristics: (*R*)-**1:** $[\alpha]_D$ +2.3 ($CHCl_3$), m.p. 76.5—77 °C; (*S*)-**1:** $[\alpha]_D$ −2.3 ($CHCl_3$), m.p. 76—77 °C.

* Overall yield over two steps.

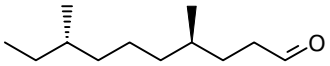
** Overall yield over three steps.

Stereodivergent synthesis of the four isomers of 2,6-dimethyloct-1-yl formate. Diastereoselective hydrolysis of quasi-racemic mixtures of diastereomeric alkyl carboxylates

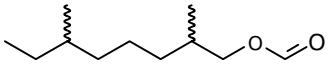
(*R*,*R*)-4,8-Dimethyldecanal is known to be the aggregation pheromone of *Tribolium confusum* and *T. castaneum* flour beetle, while its (4*R*,8*S*)-epimer is the synergist of the pheromone of the latter species. The *S*,*S*- and 4*S*,8*R*-isomers are inactive and (±)-4,8-dimethyloctanal (a mixture of two racemates formed by two pairs of possible stereoisomers) is an order of magnitude less active than the natural pheromone. All isomers are readily oxidized in air and lose their activity. A more stable isoster of (±)-4,8-dimethyldecanal, synthetic (±)-2,6-dimethyloct-1-yl formate ((±)-**6**), exhibits a comparable attractant activity.[12]



Pheromone (*R*,*R*)

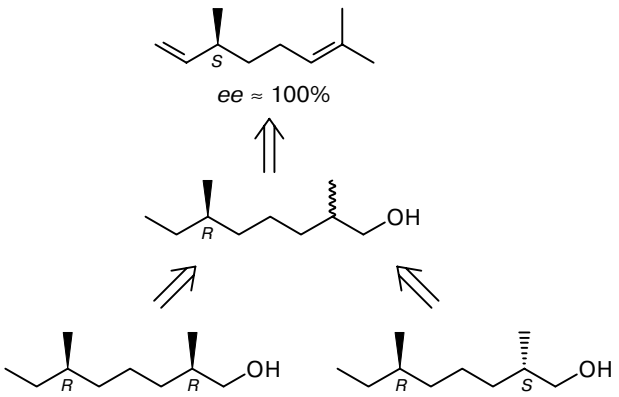


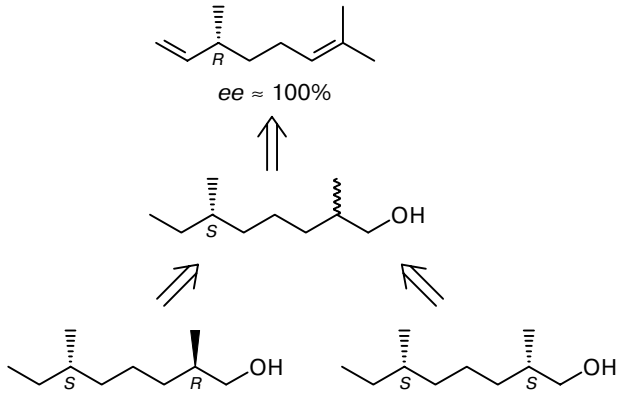
Synergist of the pheromone (4*R*,8*S*)



Mimic of the pheromone (±)-**6**

In order to elucidate the role of the absolute configuration of the molecule in the pheromone signal reception by meal worms, it was necessary to synthesize all the four possible stereoisomers with the skeleton of formate **6**. The first stride was to prepare the reference compound (±)-**6** from methyl ethyl ketone using the oxy-Cope rearrangement at the key step.[13] Subsequently, proceeding from optically pure (*S*)-(+)- and (*R*)-(−)-dihydromyrcenes (products of chemical processing of turpentine oil), the target formates were synthesized according to the following retrosynthetic plan:[14]



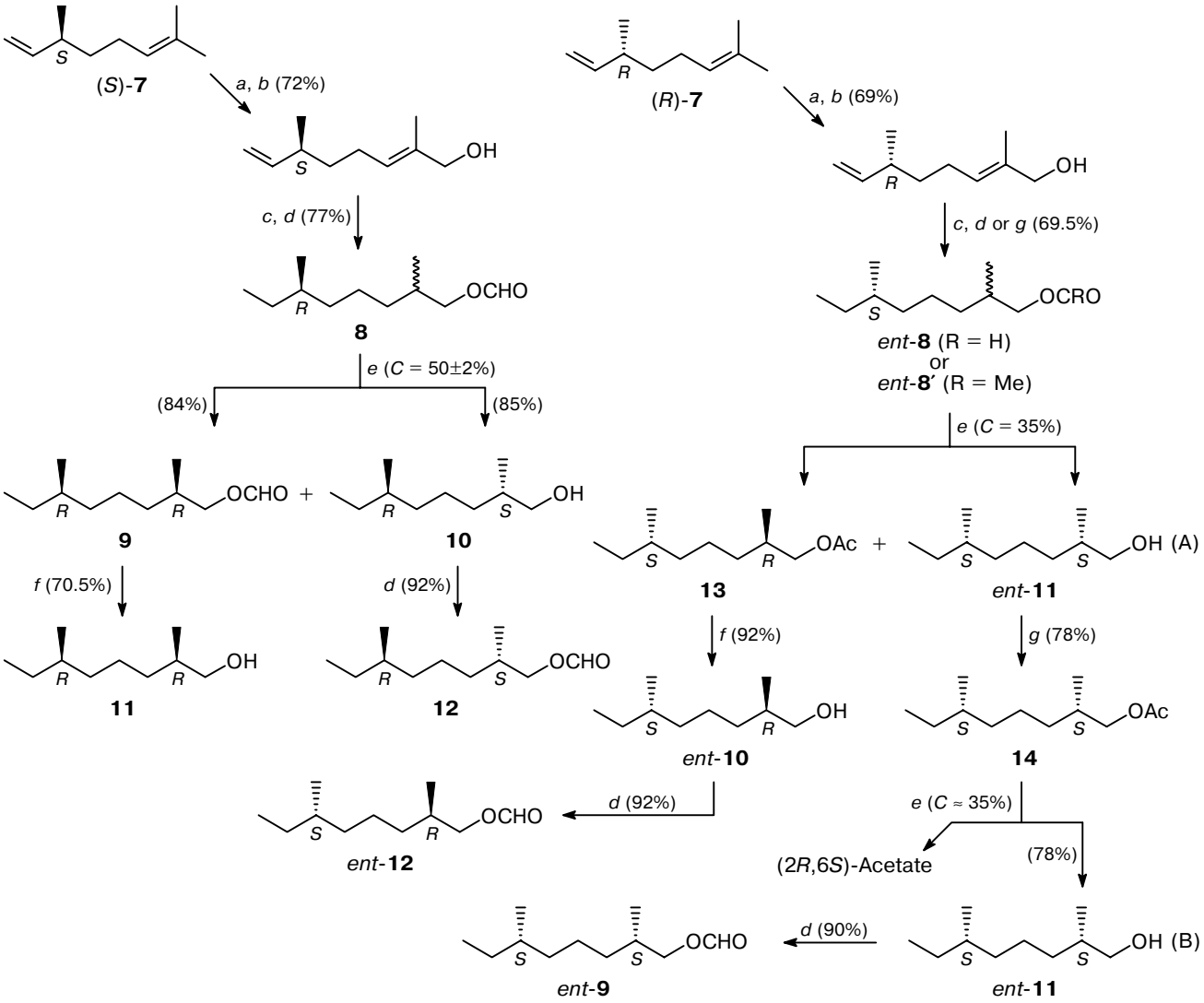


Both pairs of the target diastereomers were prepared by partial hydrolysis of the pseudo-racemates of two epimeric alcohols (as formates or acetates) in the presence of PPL. It was assumed that the configuration of the C(6) atom would not affect the enantioselectivity of the PPL-catalyzed reaction and, judging from the *S*-selectivity known for PPL,[4] the 2*S*-epimers would react faster in both pseudo-racemates.

Oxidation of diolefins (*S*)-**7** and (*R*)-**7** by the SeO_2(cat.)—*tert*-pentyl hydroperoxide (TPHP) system followed by hydride reduction gave enantiomeric allylic alcohols, whose hydrogenation resulted in the corresponding pseudo-racemic mixtures of saturated alcohols, which were converted into pseudo-racemic formates **8** and *ent*-**8**. Hydrolysis of formate **8** in the presence of PPL up to a ~50% conversion yielded (*R*,*R*)-formate **9** and 2*S*,6*R*-alcohol **10** with nearly equal diastereomeric excess (*de* 41±1%). By contrast, the PPL-catalyzed hydrolysis of formate *ent*-**8** proceeded with very low stereoselectivity (the *de* value for *S*,*S*-alcohol *ent*-**11** was only 1.2%). Therefore, in subsequent operations, pseudo-racemic acetate *ent*-**8′** was employed instead of *ent*-**8**, the degree of conversion being limited to 35%. The first enzymatic hydrolysis of *ent*-**8′** afforded *ent*-**11** with *de* 62% (sample A), and hydrolysis of the acetate of this sample furnished *ent*-**11** with *de* ≥ 96% (sample B). The acetate fraction recovered from enzymatic hydrolysis (acetate **13**) was subjected to saponification to give 2*R*,6*S*-alcohol *ent*-**10** with *de* ~41%. Formylation of alcohols **10**, *ent*-**10**, and *ent*-**11** (A and B) completed the synthesis of diastereomeric formates **9**, **12**, *ent*-**9**, and *ent*-**12** (Scheme 4).[14]

The configurations attributed to alcohols **10**, *ent*-**10**, **11**, and *ent*-**11** were proved by chemical correlation of an enantiomerically pure sample of alcohol *ent*-**11** (sample B, *de* and *ee* ≥ 96%) with known (*S*,*S*)-4,8-dimethyldecanal (**17**).[15] Diolefin (*R*)-**7** was converted into α,β-enal **15** in two steps, and the product was subjected to *S*-selective biohydrogenation in the presence of bakers yeast, which smoothly yielded alcohol **16**. Hydrogenation of this product gave a virtually pure sample of alcohol *ent*-**11**, whose transformation into the corresponding bromide and the Stork alkylation of the bromide did not affect the C(2) asymmetric center in the

Scheme 4



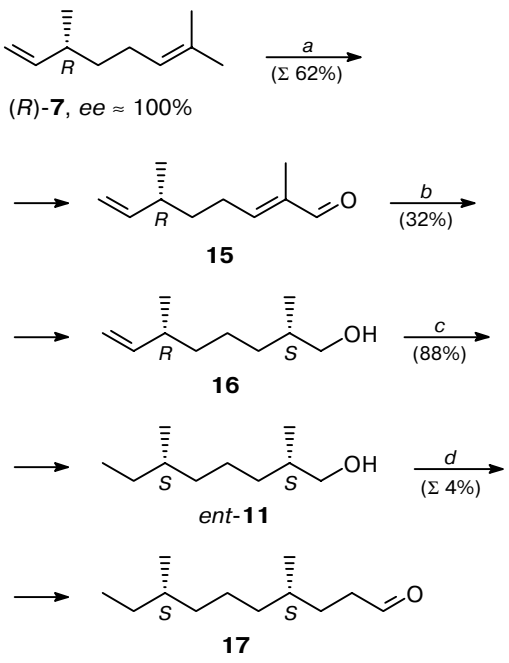
Reagents and conditions: *a*. SeO_2 (cat.)—TPHP/CH_2Cl_2, 20 °C; *b*. $NaBH_4$—MeOH; *c*. H_2—Pt(C)/MeOH, 20 °C; *d*. HCO_2H, 65 °C; *e*. PPL (cat.)—H_2O (pH 7.0), 37 °C; *f*. KOH—MeOH, 20 °C; *g*. Ac_2O—DMAP/Py, 20 °C.

electrophile. The final product of synthesis, which coincided in spectra and physicochemical parameters with (*S*,*S*)-alkanal **17** (the putative pheromone of *T. Freemani*),[16] had *ee* ~97% (Scheme 5)[14].

Unlike enzymatic hydrolysis of racemic esters, hydrolysis of pseudo-racemic pairs of epimers (**8**, *ent*-**8**, *ent*-**8′**) in the presence of PPL gives binary mixtures of products whose diastereomeric composition can be determined by polarimetry using the equation $[\alpha]_{D(obs)} = (1-x)\cdot[\alpha_1]_D + x\cdot[\alpha_2]_D$, where $[\alpha]_{D(obs)}$ is the $[\alpha]_D$ value for a binary mixture of epimers, $[\alpha_1]_D$ and $[\alpha_2]_D$ are the $[\alpha]_D$ values for the major and minor components of the mixture, respectively (in the same solvent), x is the mole fraction of the minor component. The composition of the ester fractions recovered after enzymatic hydrolysis was determined from the diastereomeric composition of the alcohols formed upon their saponification assuming that that it does not affect the asymmetric center. For *R*,*R*-alcohol **11** with *ee* ~100%, the $[\alpha]_D$ value was taken to be +7.3 ($CHCl_3$). In the case of 2*R*,6*S*-alcohol *ent*-**10** with a ~100% enantiomeric purity for both asymmetric centers, an $[\alpha]_D$ value of +15.7 ($CHCl_3$) has been found previously;[17] therefore, for pure 2*S*,6*R*-alcohol **10**, we took $[\alpha]_D$ −15.7 ($CHCl_3$). The composition of the four optically active epimeric pairs calculated in this way was confirmed by the data of the corresponding ^{13}C NMR spectra in which the ratio of the integral intensities of the identified signals of the Me groups coincided with calculated values to within the experimental error.[14]

The results indicate that in the case of PPL, hydrolysis of pseudo-racemic esters **8**, *ent*-**8**, and *ent*-**8′** involves

Scheme 5



Reagents and conditions: *a*. 1) SeO_2—TPHP, 2) PCC—AcONa; *b. Saccharomyces cerevisia* (B.Y.); *c*. H_2—Pt/C; *d*. 1) HBr aq, Δ, 2) $Li[CH_2CH{=}NBu^t]$;
Some physicochemical characteristics:
ent-**11:**— *de* ≈ 100%, $[\alpha]_D$ −7.3 ($CHCl_3$);
17: $[\alpha]_D$ −7.22 ($CHCl_3$), pheromone of the *Tribolium freemani* beetle (?), $[\alpha]_D$ −7.3 for *ee* 97%.[15]

predominantly, as expected, epimers with 2*S*-configurations. This implies that the use of a lipase at a key step of the stereodivergent synthesis has good prospects also for the resolution of *pseudo-racemic pairs of epimers*, although to attain high diastereoselectivity, the most selective lipase should be found in each particular case.

The olfactometry tests using age- and sex-mixed populations of the *Tribolium castaneum* and *T.confusum* beetles showed the dependence of the attractant potency of 2,6-dimethyloctyl formates on the composition of binary epimer pairs.[18] Although the *de* values for almost all samples were 40—62% ([major] : [minor] ≈ (7 : 3)—(8 : 2)), the experiments on *T. castaneum* in the dose range of 10—100 μg/dispenser revealed a statistically reliable relationship between the configuration of the major epimer and the attractant activity:

ent-**12**/*ent*-**9** (*de* 41%) ≥ **9**/**12** (*de* 41%) ≥ (±)-**6** (double racemate) > **12**/*ent*-**9** (*de* 42%) > *ent*-**9**/*ent*-**12** (*de* ≥96%).

Binary mixtures with predominance of formates with *R* configuration at C(2), *i.e.*, the 2*R*,6*S*-isomer (*ent*-**12**) and *R*,*R*-isomer (**9**), are most attractive for *T. castaneum*. The same trend is observed in the experiments with *T. confusum* beetles, although the required doses are higher. Apparently, *R*-configuration of the asymmetric center adjacent to C=O group is required for the reception of not only the natural pheromone but also its isoster.[18]

Potentially waste-free stereodivergent protocols. PPL and CCL in the synthesis of D-pantolactone, (*R*)-quadrilure, and *S*-enantiomers of hydroprene and methoprene*

If one of the two products of enzymatic optical resolution is not utilized, but can readily undergo racemization, it is expedient to convert it again into the (±)-substrate and repeat the enzymatic resolution until the substrate is completely exhausted. If the racemization rate is higher than the rate of enzymatic reaction, the process can be performed in a continuous mode (see Refs. 2d and 4b). The situations in which both products of enzymatic resolution of the racemate find application in different but technologically similar processes are also promising.

D-Pantolactone. Lactone (*R*)-**18a**, an intermediate in the manufacture of calcium pantothenate, is prepared routinely by resolution of racemic lactone (±)-**18a** into the antipodes *via* diastereomeric salts of pantothenic acid with a stoichiometric amount of a chiral amine. The enantiomer (*S*)-**18a** is racemized in an acid medium, (±)-**18a** being recycled to the process. New routes are being developed to replace this technology; they are based either on the asymmetric reduction of the keto group in 2-didehydropantolactone (with the change of the whole production scheme) or on enzymatic resolutions of (±)-**18a** (without changing the rest of the scheme). Previously, a system comprising vinyl acetate and lipase from *Pseudomonas* sp. has been proposed for the resolution of (±)-**18a** into enantiomers; however, to prepare (*R*)-**18a** with *ee* ≥ 90%, either a long-term exposure (~10 days)[19] or enzyme immobilization in a matrix was required.[20]

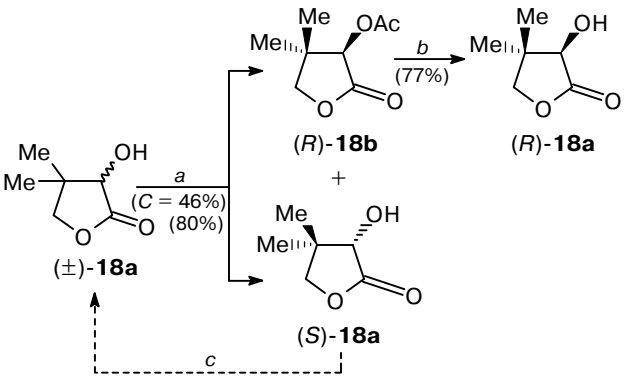
We have found that the use of PPL in the simple Ac_2O—hexane system makes it possible to reach high enantioselectivity of (±)-**18a** acylation over a period of only 24 h (~20 °C, [substrate] : [Ac_2O] = 1 : 1, [substrate] : [PPL] = 2 : 1 (w/w), degree of conversion *C* = 46—48%, the yield of acetate (*R*)-**18b** was 80%, *ee* ≥ 97%).

Smooth deacylation of acetate (*R*)-**18b** according to Zemplen's procedure gives D-pantolactone in good yield, the overall yield being 61% over two steps (Scheme 6).[7] The transition from (*S*)-**18a** to (±)-**18a** has long been a routine procedure.

(R)-Quadrilure. (3*R*,6*E*)-3-Acetoxy-7-methylnon-6-ene ((*R*)-**19**, (+)-quadrilure) is the aggregation phero-

* In this context, the term "waste-free" implies the highest (in theory, 100%) degree of transformation of the racemic or prochiral substrate into the final target product with high *ee*. The material balance of this process is not considered, although it can be estimated from the reactions used to avoid wastes relative to the key intermediate.

Scheme 6



Reagents and conditions: *a*. Ac_2O—PPL (cat.)/hexane, ~20 °C; *b*. NaOMe/MeOH, ~20 °C; *c*. H_3O^+.
Some physicochemical characteristics:
(*R*)-**18a**: $[\alpha]_D$ −27.3 (MeOH), *ee* 97.3%

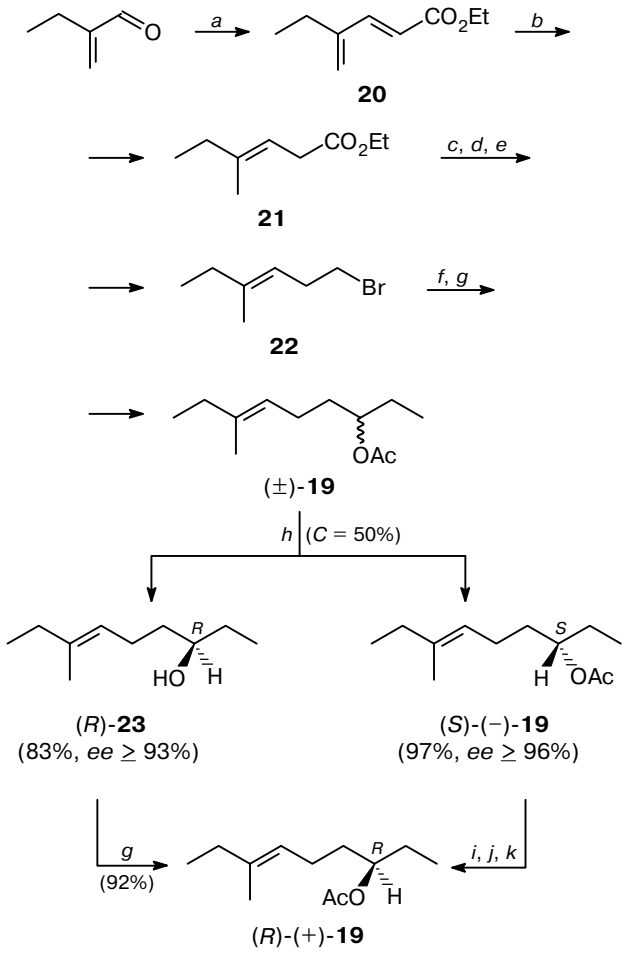
mone of a granary pest, the *Cathartus quadricollis* beetle. Efficient synthesis of racemate (±)-**19** was carried out by successive Horner—Emmons olefination of 2-ethylacrolein, 1,4-*cis*-hydrogenation of dienoate **20** catalyzed by (η^6-napthalene)$Cr(CO)_3$ and transformation of *E*-3-alkenoate **21** into *E*-homoallylic bromide **22** *via* three standard operations; bromide **22** was then converted into (±)-quadrilure ((±)-**19**) in two steps.*.

Hydrolysis of (±)-**19** in the presence of PPL up to a 50% degree of conversion proceeded with high enantioselectivity to give alcohol (*R*)-**23** and acetate (*S*)-**19** with *ee* > 96%. This allowed complete conversion of (±)-**19** into the "natural" (*R*)-(+)-form of the pheromone. A sample with *ee* 93.5% was prepared by acetylation of alcohol (*R*)-**23**, while the second-crop specimen with *ee* ~50% was synthesized from acetate (*S*)-**19** in three steps, which included the inversion at C(3) in an S_N2 reaction (Scheme 7).[21] This procedure is one of the most facile and efficient pathways to (*R*)-quadrilure.

Chiral C_{10}-aldehydes for the synthesis of juvenile hormone analogs. The environmentally benign larvicides hydroprene and methoprene are most active in the 2*E*,4*E*,7*S*-configuration;[22] therefore, their production requires enantiomerically pure C_{10}-aldehydes (*S*)-**24** and (*S*)-**25**. In a procedure developed previously,[23] aldehydes (*S*)-**24** and (*S*)-**25** were prepared after enantiomeric enrichment of their precursors, alcohols (*S*)-**26a** and (*S*)-**27a**, *via* the salts of the corresponding hydrogen phthalates with a chiral amine. This labor-consuming procedure is not quite practicable for industrial production. Therefore, we turned to enzymatic approach to alcohols (*S*)-**26a** and (*S*)-**27a** *via* readily available racemates (±)-**26a** (side product in the hydrogenation of citral into citronellol) and (±)-**27a** (prepared from citral in three steps with a thoroughly developed technology).

* Racemic quadrilure was synthesized by A. A. Vasil′ev.

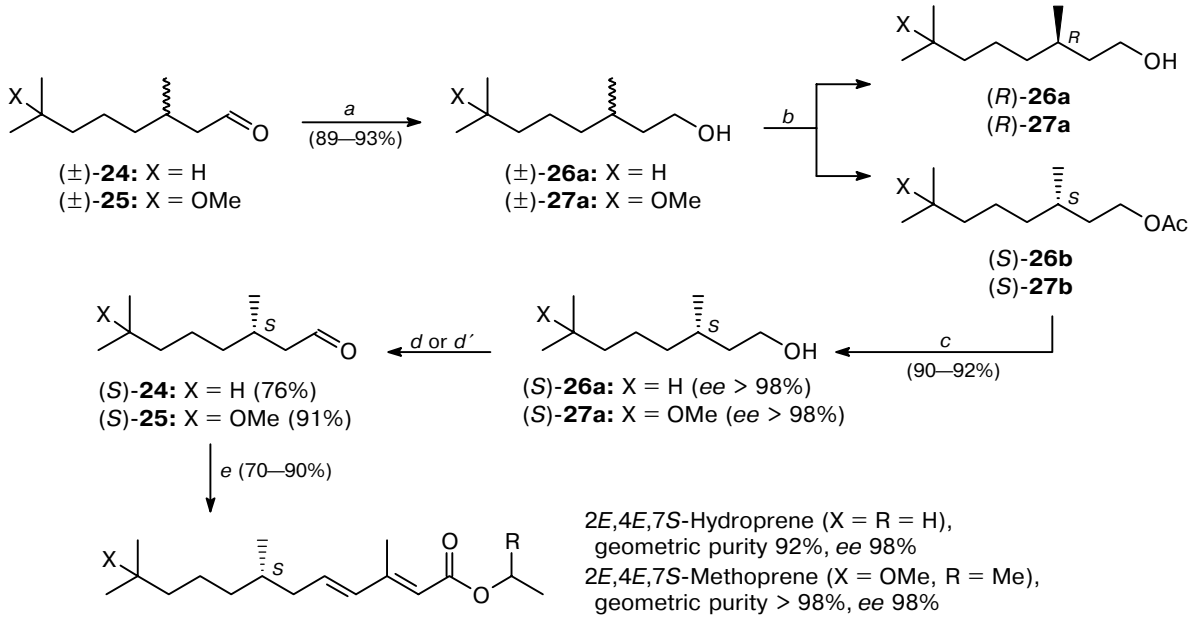
Scheme 7



Reagents and conditions: *a*. $(EtO)_2P(O)CH_2CO_2Et$—K_2CO_3 (aq), 20 °C; *b*. H_2 (1 atm.)—[η^6-$C_{10}H_8$]$Cr(CO)_3$/THF, 50 °C; *c*. $LiAlH_4/Et_2O$, 20 °C; *d*. TsCl/Py, 20 °C; *e*. NaBr/DMF, 60 °C; *f*. 1) Mg/THF (40 °C), 2) EtCHO, 20 °C; *g*. Ac_2O/Py; *h*. PPL— H_2O (pH 7); *i*. KOH/MeOH, 20 °C; *j*. MsCl—NEt_3/CH_2Cl_2, 0—5 °C; *k*. AcOK/DMF, ~100 °C.
Yields and some physicochemical characteristics:
(±)-**19**: Σ 19% over seven steps. (*R*)-(+)-**19**, 1st crop: *ee* ≥ 93%, Σ 4.7% based on ethylacrolein; 2nd crop (*i*—*k*): *ee* ≈ 50%, Σ 48% (2.5% based on ethylacrolein).

Incubation of alcohol (±)-**26a** with vinyl acetate in the presence of CCL to *C* = 50±2% resulted in acetate (*S*)-**26b**, whose mild alkaline hydrolysis gave alcohol (*S*)-**26a** with *ee* ≈ 100% (from the $[\alpha]_D$ value of the alcohol and the data of the ^{19}F NMR spectrum of its (*S*)-MTPA ester).[24] Two-phase electrochemical oxidation in an undivided cell in the presence of a NaBr—TEMPO-type nitroxyl couple gave aldehyde (*S*)-**24** in good yield with ~100% conversion. Using the Horner—Emmons reaction with the C_5-phosphonate component (R = H), this product was converted into a specimen of (+)-hydroprene of a very high geometric and enantiomeric purity. 7*S*-Hydroprene is twice as

Scheme 8



Reagents and conditions: *a*. H_2—Ni-Ra; *b*. H_2C=CHOAc—CCL (cat.)/Et_2O or hexane, 20 °C, *C* = 40—50%; *c*. KOH/MeOH, 20 °C; *d*. NaBr—$NaHCO_3$ (aq)/CH_2Cl_2/4-BzO-TEMPO, Pt-anode//Fe-cathode, 2.0 *F*, 10 °C (**26**→**24**); *d′*. Similarly to *d* but with 4-BzO-TEMPO (cat.) and C-anode//Fe-cathode, 2.5 *F* (**27**→**25**); *e*. $(Pr^iO)_2P(O)CH_2C(Me)$=$CHCO_2CHRMe$/KOH—Oct_4NBr (cat.)/PhH, 20 °C.

active as the racemate against the larvae of the plague flea and malarial mosquito.

Alcohol (*S*)-**27a**, aldehyde (*S*)-**25**, and (+)-methoprene were prepared *via* the same route (with slight modifications in the electrochemical oxidation step) (Scheme 8).[24]

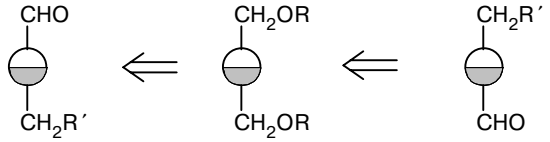
Alcohol (*R*)-**26a** recovered after enzymatic resolution is a promising CBB for the synthesis of α-tocopherol, vitamin K_1, the rice moth sex pheromone,[25] and other biomolecules. In the case of joint manufacture, this makes it possible to reduce the amount of process wastes with respect to the limiting raw material.

Potentially waste-free asymmetrization of prochiral substrates in the presence of lipases. Formal synthesis of L-aldoses from latently symmetrical D-aldoses *via* common *meso*-alditols

The chemo-enzymatic transformations of prochiral molecules open up interesting synthetic opportunities. Depending on the structure of the target object, a *meso*-type substrate can either be directly converted into a single enantiomer or chemically transformed into the racemic derivative, which is subjected to enzymatic resolution. Then the initial *meso*-structure is regenerated from the "waste" enantiomer, and the three-step process can be repeated again.

The interest in the biological properties of L-aldoses, in particular, L-fucose (L-**28**) and "unnatural" L-xylose (L-**29**) has markedly increased in the last two decades. The former compound participates in the cell surface recognition in mammalia and can be used as a marker or a remedy for several immune system defence pathologies, while the latter serves as a starting compound for the synthesis of anticancer, antiviral, and antidiabetic drugs or as an ingredient of pharmaceutical formulations.

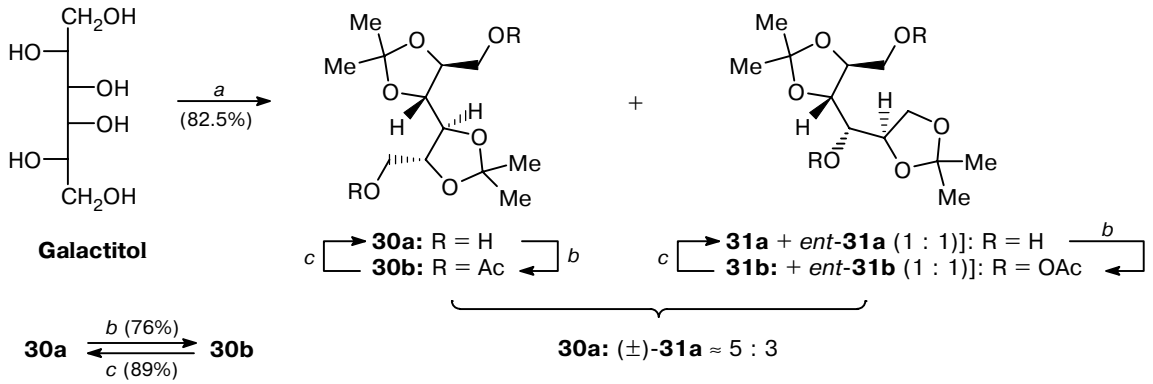
For the synthesis of aldose L-**28** from galactitol and aldose L-**29** from xylitol that would involve enzymatic asymmetrization of the substrate in the presence of readily available lipases as the key step,[26] our research group has developed two conceptually related methods for transforming *latently* symmetrical D-aldoses into less accessible L-aldoses *via meso*-alditols that are common alike to D- and L-aldoses. Since dulcitol and xylitol are manufactured from D-galactose and D-xylose in one step, the syntheses described below are equivalent to a chemo-enzymatic conversion of these D-aldoses into L-aldoses L-**28** and L-**29** by manipulating the end groups in the respective *meso*-alditols.



R′ = H, OH (L-series aldoses), OH (D-series aldoses)
R = H (*meso*-alditols)

Lipase-mediated asymmetrization of acyclic derivatives of alditols[27] gives products with relatively low

Scheme 9



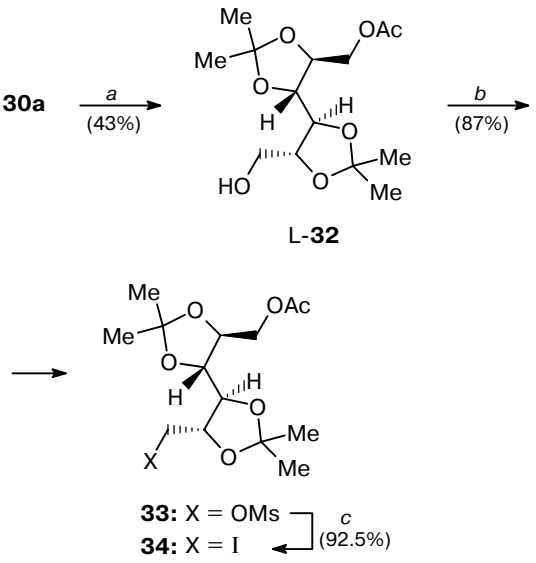
Reagents and conditions: *a*. $Me_2CO—H_2SO_4$ (cat.), $CuSO_4$, 20 °C; *b*. Ac_2O/Py; *c*. KOH/MeOH, 20 °C.

ee values. Conversely, PPL-catalyzed partial hydrolysis of 1-*O*-acetyl-2,4:3,5-di-*O*-methylene-DL-xylitol occurs with high enantioselectivity,[28] which prompts the idea of using bicyclic derivatives of alditols for enzymatic kinetic resolution. Two pathways were studied: (1) direct lipase-mediated asymmetrization of a cyclic *meso*-derivative and (2) transformation of *meso*-polyol into a cyclic monohydric (±)-alcohol (and/or its ester) with subsequent kinetic resolution of the racemate.[26]

The former pathway was used in the synthesis of L-fucose (L-**28**) from galactitol (Scheme 9). Using a known procedure,[29] galactitol was converted into a mixture of two diacetonides in which the symmetrical compound (**30a**) was the major product and the racemate (**31a**) was the minor one. *meso*-Diol **30a** was separated from racemate **31a**; to this end, the mixture of diols was converted into a mixture of diacetates **30b** and (±)-**31b**. Poorly soluble *meso*-diacetate **30b** was isolated by recrystallization, and pure diol **30a** was regenerated from it by saponification. At optimal exposure, the partial acylation of diol **30a** with vinyl acetate in the presence of CCL resulted in L-monoacetate (L-**32**) in 43% yield. The recovery of diol **30a** and the yield of diacetate **30b** amounted to 47 and 8%, respectively. After hydrolysis of **30b**, the initial *meso*-diol was used once again. Mesylation of monoacetate L-**32**, transformation of mesylate **33** into iodide **34**, and hydrogenolysis of the latter (with simultaneous deacylation) over Ni in the presence of K_2CO_3 furnished known 2,3:4,5-di-*O*-isopropylidenefucitol (**35**) (Schemes 10 and 11). Alcohol **35** was further subjected to Moffatt oxidation to give aldehyde **36**, which was immediately subjected to acid hydrolysis and thus transformed into L-aldose **28** (Scheme 11). All characteristics of this compound fully coincided with published data and with those of an authentic sample. Taking into account the content of *meso*-diol **30a** in the initial mixture of diacetonides, the yield of L-fucose (L-**28**) from galactitol was ~7% over nine steps, which is comparable with those attained in the best preceding syntheses.[29]

Acylation of diol **30a** catalyzed by PPL afforded monoacetate D-**32**.

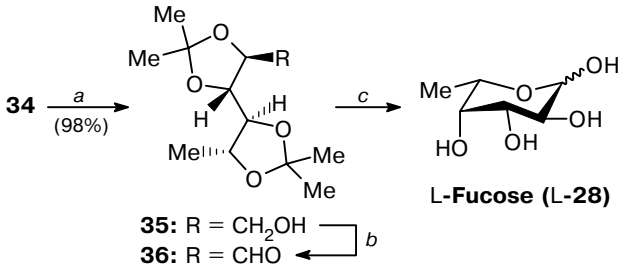
Scheme 10



Reagents and conditions: *a*. H_2C=CHOAc—CCL/Et_2O, 20 °C; *b*. MsCl/Py—$CHCl_3$; *c*. NaI/Me_2CO, 60 °C.

The first stage in the synthesis of L-xylose consisted in the transformation of xylitol into racemic diacetal (±)-**37a** and preparation of acetate (±)-**37b** from it. Partial hydrolysis of (±)-**37b** in the presence of PPL to degrees of conversion $C < 50\%$ showed that the D-enantiomer was hydrolyzed faster. However, already at $C = 55\%$, the unconverted part of the substrate proved to be the enantiomerically pure L-acetate (L-**37b**) because its alkaline hydrolysis to alcohol L-**37a** and esterification of this product by Mosher's *S*-acid afforded the (*S*)-MTPA ester with nearly 100% diastereomeric purity (^1H and ^{19}F NMR data). The Moffatt oxidation of

Scheme 11



Reagents and conditions: *a*. H_2—Ni (cat.)—K_2CO_3/MeOH, 20 °C, 1 atm.; *b*. DMSO—DCC—H_3PO_4 (cat.), 20 °C; *c*. AcOH—H_2O (6 : 4), 100 °C, Σ 48%, based on **34**.

alcohol L-**37a** yielded aldehyde L-**38**, whose transformation into chemically and enantiomerically pure L-xylose by acid hydrolysis completed this stereodivergent synthesis (Scheme 12).[26]

With allowance for the 55% degree of conversion in the enzymatic kinetic resolution of (±)-**37b**, the overall yield of L-**29** is equal to ~16% over the six steps of the synthesis; this is higher than the yields attained in the best purely chemical syntheses[30] of L-**29**.* The second asymmetrization product, D-**37a**, is converted into xylitol upon acid hydrolysis and can again be involved in the preparation of L-**29**.

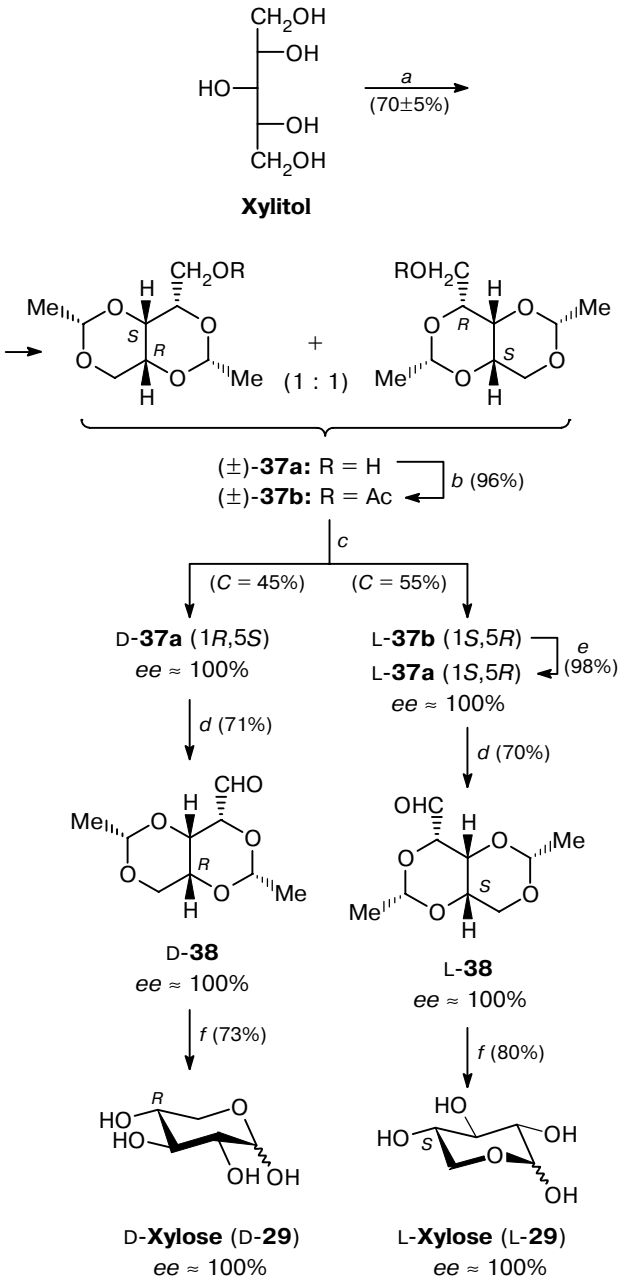
The success of the synthesis of L-**29** depends on the acetal protection chosen. If CH_2O is used instead of MeCHO, partial hydrolysis of the corresponding bicyclic (±)-acetate is enantioselective but the step of synthesis of L-**29** proceeds under harsh conditions and in a low yield. Hydrolysis of an analog of acetate (±)-**37b** with benzylidene protective groups in the presence of PPL occurs without any enantioselectivity.

A short pathway to scalemic cyclic terpenoids from achiral acyclic isomers

Stereodivergent synthesis in the presence of lipases could, in principle, be used for the transformation of geometrically (*E* or *Z*) pure isoprenoid alcohols with the general formula $H[CH_2C(Me)=CHCH_2]_nOH$ into optically active cyclic isoprenoids. The stereospecific superacid-induced cyclization of lower alcohols of this group (n = 2—5) into their cyclic isomers has been studied comprehensively,[32] and enzymatic separation of compounds into enantiomers is an evident choice, so it seems surprising that no attempts to implement this protocol have been undertaken so far. Recently, in a joint study of N. D. Zelinsky Institute of Organic Chemistry of the RAS and the Institute of Chemistry of the Academy of Sciences of the Republic of Moldova,[7,28]

* The conduction of highly impressive syntheses of aldoses L-**28** and L-**29** employing several enzymes[31] requires a deeper specialization in enzymology and better developed techniques.

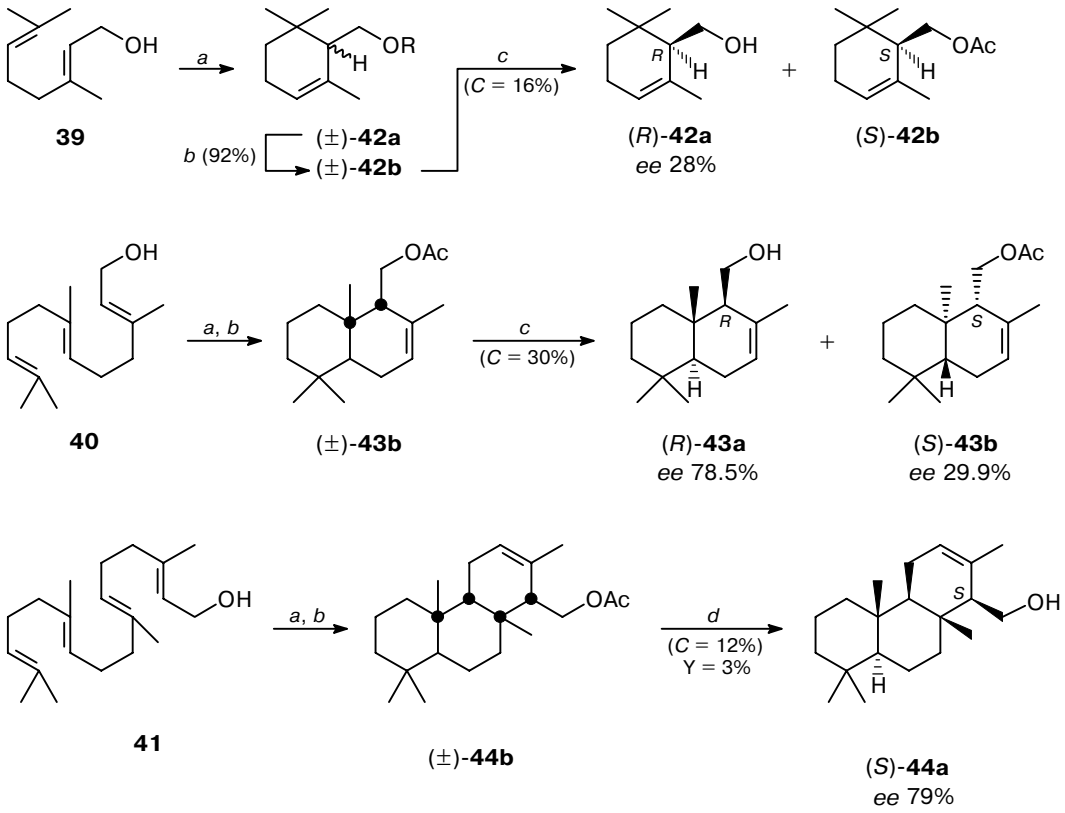
Scheme 12



Reagents and conditions: *a*. MeCHO/conc. HCl, 50 °C; *b*. Ac_2O—DMAP/Py; *c*. H_2O/PPL (pH 7), 20 °C; *d*. DMSO—DCC—H_3PO_4 (cat.), 20 °C; *e*. KOH/MeOH, 20 °C; *f*. H_2O—H_2SO_4 (cat.)/Me_2CO, 60 °C.

an attempt was made to convert geraniol (**39**), (3*E*,7*E*)-farnesol (**40**), and (*all-E*)-geranylgeraniol (**41**) into optically active α-cyclogeraniol (**42a**), drim-7-en-12-ol (**43a**), and 14α*H*-isoagat-12-en-15-ol (**44a**) *via* the corresponding racemates ((±)-**42a**, (±)-**43**, (±)-**44a**) using PPL and CCL. Alcohols **42a** and **43a** are fragrance compounds, while derivatives of alcohols **43a**

Scheme 13



Reagents and conditions: *a*. FSO_3H/Pr^iNO_2, −78 °C; *b*. Ac_2O—DMAP/Py, 20 °C; *c*. PPL (cat.)—H_2O (pH 7), 20 °C; *d*. CCL (cat.)—H_2O (pH 7).

Note. Y is chemical yield, *C* is degree of conversion.

and **44a** are insect and fish antifeedants;[33] derivatives of alcohol **44a** are specific metabolites of sea organisms not found among the land flora or fauna.

Racemic alcohols (±)-**42a**, (±)-**43a**, and (±)-**44a** obtained by superacid-induced cyclization were acetylated, and the acetates were thoroughly purified by chromatography on SiO_2. The enantioselectivity of hydrolysis of acetate (±)-**42b** in the presence of PPL was low: even for a degree of conversion of 16%, the *ee* value in the resulting alcohol (*R*)-**42a** was only 28%. The hydrolysis of acetate (±)-**43b** was more selective: alcohol (*R*)-**43a** isolated at a 30% conversion had *ee* of 78.5%, while alkaline hydrolysis of "residual" acetate (*S*)-**43b** gave alcohol (*S*)-**43a** with *ee* ~30%. The increase in the enantioselectivity of the PPL-catalyzed hydrolysis on passing from acetate (±)-**42b** to its bicyclic isoprenolog (±)-**43b** might be related to the steric factor.[28] Further increase in the molecular size of the substrate decreases the rate of the PPL-catalyzed hydrolysis to nearly zero, and acetate (±)-**44b** was recovered almost entirely. The attempts to increase the selectivity of the separation by acylating alcohols (±)-**42a** and (±)-**43a** in the Ac_2O—PPL/hexane or vinyl acetate—CCL/Et_2O system failed: in the former case, the *ee* value of the acetate (*R*)-**42b** obtained at a 15% degree of conversion of (±)-**42a** was 1.3%, while in the latter system, the "residual" alcohols (*R*)-**42a** and (*R*)-**43a** with *ee* 9—13% obtained at a 55—75% degree of conversion were contaminated with isomers formed as by-products, achiral β-cyclogeraniol and dextrorotatory drim-8-en-12-ol.[7]

Hydrolysis of acetate (±)-**44b** in the presence of CCL proceeded very slowly (a 12% degree of conversion of the substrate was attained only over a period of 148 h) but gave rise to alcohol (*R*)-**44a** with *ee* ~79%, which was isolated from the reaction mixture in a yield of only 3% (Scheme 13).* The fraction of the residual acetate (*S*)-**44b** was converted by alkaline hydrolysis into alcohol (*R*)-**39** with *ee* of only 1.5%. The acylation of alcohol (±)-**44a** in the vinyl acetate—CCL/Et_2O system resulted in a mixture of starting (±)-**44a** with its Δ^{13}-isomer, according to ^1H and ^{13}C NMR spectra; the yield of the acetate fraction was close to zero.

Although fairly modest, the results obtained demonstrate that the protocol comprising superacid-in-

* P. F. Vlad, G. D. Gamalevich, V. N. Kul′chitskii, and E. P. Serebryakov, private communication.

duced cyclization of polyprenol/acetylation of racemic cyclenol/enzymatic kinetic resolution of the (±)-acetate is not devoid of synthetic prospects. Even evidently non-optimal lipases (PPL, CCL) make it possible to transform commercially available C_{15}—C_{20} isoprenoid alcohols into optically active bi- and tricyclic isomers with acceptable *ee* values (78—79%). The overall yields of compounds of type **43a**, **44a** are relatively low but the yields of the same compounds with the same *ee* values would not necessarily be higher upon multistep chemical syntheses. Optimization of this strategy through screening of microbial lipases appears quite practicable.

Conclusion

The results outlined above demonstrate the expediency of developing protocols for chemo-enzymatic synthesis of chiral molecules in which a lipase is used as the asymmetrizing tool in the key step of the stereodivergent synthesis. These protocols provide the possibility of targeted optimization of proper enzymatic reactions (selection and immobilization of the enzyme, medium parameters, temperatures, concentration ratio, process control, *etc.*). Development of the proper technological aspects of chemo-enzymatic synthesis of chiral bioregulators would be a necessary continuation of the first stage of investigations, whose goal was identify rational schemes and the scope of application of this synthetic strategy.

The main bulk of the review is represented by the results of studies initiated and performed over the last seven years. Here, it is pertinent to mention the researchers whose efforts embodied these results. The author would like to thank, first of all, his many-year collaborator Mrs. G. D. Gamalevich, whose active involvement and great synthetic experience made this work possible. She worked with the assistance of students of the Higher Chemical College of the RAS B. N. Morozov and A. L. Vlasyuk, who obtained a number of valuable results. The author is grateful to researchers of the N. D. Zelinsky Institute of Organic Chemistry of the RAS A. A. Vasil′ev, N. E. Voishvillo, A. V. Ignatenko, G. I. Nikishin, Yu. N. Ogibin, and M. I. Struchkova, who contributed to the development of this research at different stages.

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