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Organic Chemistry

Enzymatic dissymmetrization of *meso*-2,3-dimethylbutane-1,4-diol and its diacetate. Synthesis of scalemic (–)-lasiol

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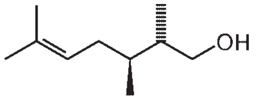
Acylation of *meso*-2,3-dimethylbutane-1,4-diol with vinyl acetate in the presence of porcine pancreatic lipase (PPL) leads to the dextrorotatory monoacetate of the above diol with enatiomeric excess (*ee*) 58—64%. Absolute configuration of this scalemic specimen was determined by its sequential transformation to levorotatory lasiol, a metabolite of the *Lasius* ants. Partial hydrolysis of the corresponding *meso*-diacetate, mediated by PPL or by the *Pseudomonas sp.* lipase affords the monoacetate of opposite configuration with *ee* 72—86%, a formal intermediate in the synthesis of (3*S*,4*R*)-faranal. Other microbial lipases used are distinctive in low chemoselectivity.

Key words: *meso*-2,3-dimethylbutane-1,4-diol; lipases; (+)- and (–)-*erythro*-4-acetoxy-2,3-dimethylbutan-1-ols; selenoacetals; (2*S*,3*S*)-2,3,6-trimethylhept-5-en-1-ol.

(2*R**,3*R**)-2,3,6-Trimethylhept-5-en-1-ol (lasiol, **1**), the major component of the mandibular gland secretion produced by males of the *Lasius meridionalis* ants,[1] has two vicinal methyl groups in the *erythro* configuration. For the introduction of this structural motif, suitably substituted bifunctional building blocks **2**[1—9] as well as substituent-directed *anti*-alkylation of 3-methylalkanolide enolates[10,11] have been employed.



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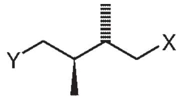

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Synthesis of non-racemic building blocks involves tedious application of chiral auxiliaries followed by the sepa-

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ration of diastereomers.[2—4] Although elegant, the ring opening of properly substituted epoxides using chiral agents is also not unproblematic.[5,6,12—14] In contrast, asymmetric hydrolysis of diethyl 3-methylglutarate catalysed by PLE appears to be a practical route to the required building blocks[10] if the remaining vicinal Me group could be readily introduced.

meso-2,3-Dimethylbutane-1,4-diol (**3**) can also be a good source of *erythro* configured compounds **2**. Previously[1,9] it was used only to prepare racemic forms of such compounds. However, the diol **3** may also be suitable for enantiotopic discrimination of 1,4-positioned functional groups, *e.g.*, by enzyme-catalysed partial acylation, or by enzymatic hydrolysis of its diacetate **4**. In theory, enantiopure products of such transformations can be obtained in quantitative yields.[15—17] If so, enantiomeric *meso*-4-acetoxy-2,3-dimethylbutan-1-ols (**5** or *ent*-**5**) could be processed to useful chirons in essentially the same manner as their racemic analogue.[9]

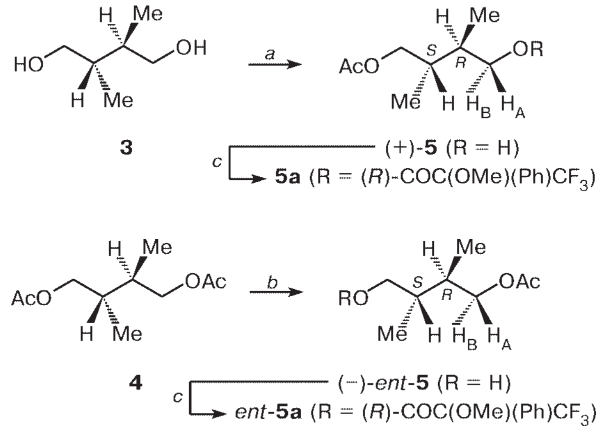
Results and Discussion

In order to find the best enzyme for dissymmetrisation of *meso* compounds **3** and **4**, screening experiments were performed employing the lipase from hog pancreas (PPL) and eight microbial lipases of various origin. Unfortunately, the ratio of **5** and *ent*-**5** (*er*) in the products (and thus the enantiomeric excess, *ee*) could not be determined by capillary gas chromatography on the available chiral phase since their retention times coincided. However, ^{1}H NMR analysis of the (*R*)-MTPA esters[18] derived from the above monoacetates (**5a** and *ent*-**5a**) allowed the determination of enantiomeric ratios, *er* to be made, since the geminal protons $H_A(1)$ and $H_B(1)$ in **5a** and *ent*-**5a** were clearly distinguishable.*

Except for PPL and the lipase from *Pseudomonas* sp. (PSL), all lipases tried showed poor chemoselectivity in acetylation of diol **3** and in hydrolysis of diester **4** (Table 1). Furthermore, the yields of the monoesters were less than 50%.

After a relatively short time, small-scale acetylation of **3** in the presence of PPL (Table 1) afforded a crude material which, according to GC, consisted of a mixture of monoacetate **5** (~55%) and diacetate **4** (~45%). This material was subjected to chromatographic separation, and the monoacetate fraction was treated with (*S*)-(+)-MTPA-Cl. The ^{1}H NMR spectrum of the resulting pair of diastereomeric (*R*)-MTPA esters, **5a** and *ent*-**5a**, displayed two groups of signals belonging to the geminal protons $H_A(1)$ and $H_B(1)$ in each diastereomer: δ 4.15 dd + δ 4.36 dd and δ 4.23 dd + δ 4.28 dd, in a 77:23 ratio (corresponding to 54% *ee* in starting monoacetate). Similar results were obtained by enzyme mediated acetylation of diol **3** using PSL. When the lipase from *Humicola sp.* was used as the catalyst, the yield of monoacetate with the same ^{1}H NMR characteristics of its (*R*)-MTPA derivative was as high as 65%, but at the expense of *ee* (~20%).

Scheme 1



Reagents and conditions: *a*. pro-*S*-selective acylation, $H_2C=CHOAc$/toluene—PPL (or PSL), ~20 °C;
b. pro-*S*-selective hydrolysis, H_2O (0.1 *M* phosphate buffer, pH 6.8)/toluene—PPL, ~20 °C;
c. (*S*)-(+)-MTPA-Cl/Py, ~20 °C.

The PPL catalysed acetylation of diol **3** was performed also on a 0.5 mmol scale. An aliquot of the dextrorotatory monoester ($[\alpha]_D^{25}$ +12.6 ($CHCl_3$) at ~62% conversion (GLC)) was isolated and transformed to diastereomeric (*R*)-MTPA esters, and the ^{1}H NMR spectrum displayed the same diagnostic signals (δ 4.15 + δ 4.36 and δ 4.23 + δ 4.28) in a 82:18 ratio. Thus, the *ee* of the isolated (+)-monoacetate was 64%. In a preparative experiment (7.2 mmol of **3**) with a higher concentration of diol and less lipase, both the yield (29% at ~52% conversion) and optical purity (58% *ee*, $[\alpha]_D^{25}$ +11.0) of the (+)-monoacetate were somewhat lower. Subsequent transformations of this specimen (see below) showed that its major enantiomer **5** had the 2*R*,3*S* configuration, and hence the minor enantiomer, *ent*-**5**, was assigned the 2*S*,3*R* configuration.

PPL mediated hydrolysis of diacetate **4** to ~70% conversion gave a three-component mixture with the monoacetate fraction amounting to ~55%. The latter was converted to a mixture of diastereomeric (*R*)-MTPA esters. Its ^{1}H NMR spectrum displayed familiar diagnostic signals of protons $H_A(1)$ and $H_B(1)$: (δ 4.15 + δ 4.36 and δ 4.23 + δ 4.28), but in a 14:86 ratio. Thus, the isolated monoester consisted mainly of *ent*-**5** (*ee* 72%). Not surprisingly, it proved to be levorotatory ($[\alpha]_D^{25}$ −13.7 in an experiment with 0.25 mmol of diacetate **4**). In a preparative experiment using less solvent and PPL the optical

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* Unfortunately, the CF_3 groups of MTPA esters of **5a** + *ent*-**5a** were indistinguishable in the ^{19}F NMR spectra.

Table 1. Acetylation selectivity of diol **3** and hydrolysis selectivity of diacetate **4** in the presence of various lipases at 20—25 °C

Entry	Lipase	Acetylation of *meso*-diol **3**				Hydrolysis of *meso*-diacetate **4**			
		τ/h[a]	Composition of the reaction mixture (%)[b]			τ/h[a]	Composition of the reaction mixture (%)[b]		
			3	**4**	**5** + *ent*-**5**		**3**	**4**	**5** + *ent*-**5**
1	Hog pancreas (PPL)	2	0	45	55 (*er* = 77 : 23)[c]	6	<1	~34	66
		5	0	90	10	22	15	30	55 (*er* = 14 : 86)[c]
		8	0	100	0	46	21	24	55
2	*Pseudomonas* sp. (PSL)	2	20	15	65 (*er* = 77 : 23)[c]	6	0	80	20
		5	0	51	49	22	7	34	59 (*er* = 27 : 73)[c]
		8	0	79	21				
3	*Humicola* sp. (HSL)	2	Traces	35	65 (*er* = 60 : 40)[c]	6	<1	68	~32
		5	0	79	21	22	18	46	36
		8	0	94	6	46	70	9	21
4	*Rhizopus delemar* (RDL)	2	79	6	15	6	0	100	Traces
		5	65	8	27	22	0	92	8
		8	57	9	34	46	0	85	15
5	*Candida rugosa*	2	0	74	26	2.5	0	94	6
	≡ *C. cylindracea*	5	0	93	7	8	0	92	8
	(CRL, CCL)	8	0	100	0	22	33	53	14
6	*Candida antarctica*, type A	2	0	90	10	6	0	92	8
		5	0	100	0	22	4	79	17
						46	48	30	22
7	*Candida antarctica*, type B	2	0	100	0	2.5	47	17	36
						6	100	0	0
8	*Mucor miehei*	2	0	97	3	6	81	34	58
		5	0	100	0	22	70	0	30
9	*Pseudomonas cepacia*	2	0	100	Traces	2.5	13	55	32
						6	35	30	35
						18	39	40	21

[a] τ is time of reaction.

[b] Determined by capillary GLC of the reaction mixture samples.

[c] Ratios of intensities of diagnostic signals ($I_{(\delta\ 4.15\ +\ \delta\ 4.36)} : I_{(\delta\ 4.23\ +\ \delta\ 4.28)}$) from protons $H_A(1)$ and $H_B(1)$ in ^1H NMR spectra of the binary mixtures of MTPA esters. These *dr* values are assumed to correspond to *er* in scalemic specimens **5** + *ent*-**5**. The first figure in the ratio relates to the (+)-monoacetate **5**.

purity of the monoacetate *ent*-**5** (isolated yield 33%) was even higher (*er* = 7:93, *ee* 86%, $[\alpha]_D^{25}$ −15.2). Similar result was obtained upon the hydrolysis of diacetate **4** in the presence of PSL, but another lipases were less effective (see Table 1).

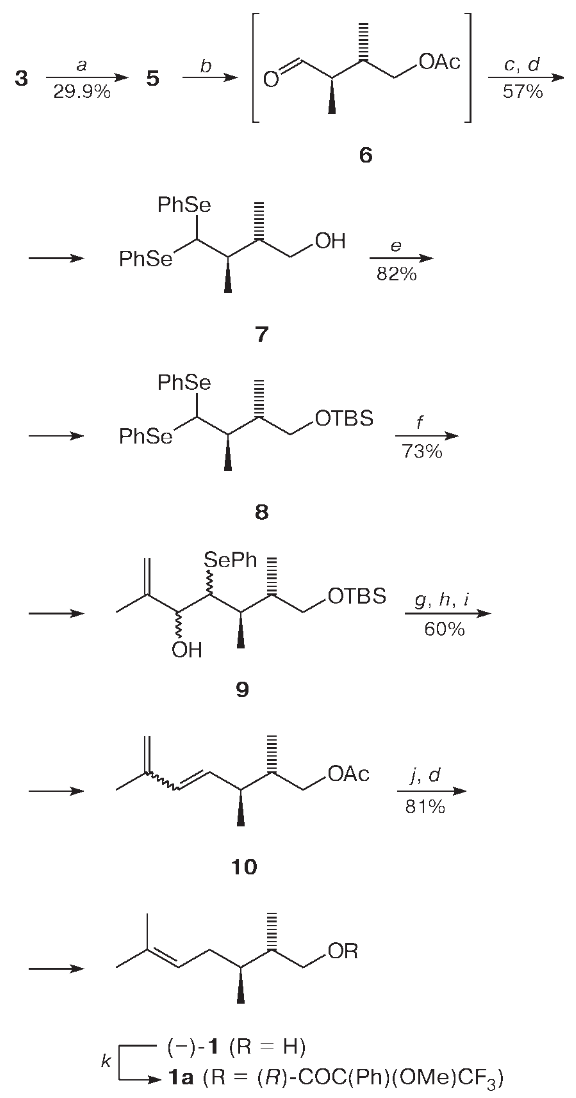
Both the formation of the 2*R*,3*S* monoacetate **5** upon acetylation of diol **3** and the formation of its 2*S*,3*R* counterpart *ent*-**5** upon the hydrolysis of diacetate **4** conform to the well-known tendency of PPL to direct the reactant towards the *S* configured (in the case of *meso* compounds — pro-*S* configured) part of the substrate.[15—17,19—21] However, numerous examples of the PPL mediated transformations of 1,4-bifunctional *meso* substrates pertain only to cyclic compounds,[15,19,20] and there can be exceptions to the above rule.[22—24]

Next, a stereocontrolled synthesis was undertaken to correlate the absolute configuration of monoester **5** with that of known enantiomers of compound **1**.[6,11]

The transformation of monoester **5** into scalemic lasiol **1** (Scheme 2) was performed using a methodology developed earlier for the synthesis of (±)-faranal.[9] The preparative-scale acetylation of diol **3** in the presence of PPL afforded monoacetate **5** with $[\alpha]_D^{22}$ + 11.0 ($CHCl_3$), which was submitted to the Swern oxidation. The crude γ-acetoxyalkanal **6** without purification was converted to the corresponding acetoxy selenoacetal using earlier described procedure.[9] Deacetylation of this material gave alcohol **7**, the HO group of which was reprotected using *tert*-butyldimetylchlorosilane—imidazole. The overall yield of *O*-protected selenoacetal **8** from monoacetate **5** was 47%.

Lithium-selenium exchange in selenoacetal **8**, promoted by *n*-BuLi, gave a selenium-stabilised carbanion which reacted with α-methylacrolein to produce the β-hydroxy selenide **9** as a mixture of four diastereomers. On treating **9** with methanesulfonyl chloride and Et_3N

Scheme 2



Reagents and conditions: *a*. CH_2=CHOAc/toluene—PPL, ~22 °C, 18 h;
b. 1) $(COCl)_2$—DMSO/CH_2Cl_2, −50 °C, 2) Et_3N;
c. PhSeH—$ZnCl_2$/CCl_4, 0 → 20 °C;
d. MeOH/K_2CO_3, ~22°C; *e*. TBSCl—ImH/DMF;
f. 1) BuLi, THF, –78°C, 2) CH_2=CH(Me)CHO;
g. MsCl—Et_3N/CH_2Cl_2, 20 °C, 3 h; *h*. Bu_4NF/THF;
i. Ac_2O/DMAP, ~20 °C;
j. H_2 (50 atm.)—(η^6-naphthalene)·$Cr(CO)_3$/THF, 50°C, 3 h;
k. *(S)*-MTPA-Cl/Py.

elimination of vicinal PhSe and OH group occurred. Subsequent removal of the TBS group allowed us to isolate the conjugated diene **10** as a 3:2 mixture of 4*E* and 4*Z* stereoisomers. Mild 1,4-*cis*-hydrogenation of **10** using (η^6-naphthalene)chromium tricarbonyl as the catalyst followed by deacetylation of the resulting acetoxy monoolefin gave (−)-lasiol as the sole product. The ^{1}H and ^{13}C NMR spectra of the latter displayed practically the same δ_C, δ_H and *J* values as those reported in the literature for (±)-**1** [1] and for the two enantiomers of lasiol.[5,11]

The alcohol (−)-**1** thus obtained had $[\alpha]_D^{22}$ −6.6 (hexane), which corresponds to about 51—52% *ee*. This follows from the comparison of its specific rotation with that reported earlier (–12.9) for practically enantiopure (2*S*,3*S*)-lasiol[5,11] and from the diastereomer ratio of the mixture of (*R*)- and (*S*)-MTPA esters prepared from our specimen of (−)-**1** and both (*S*)-(+)- and (*R*)-(–)-MTPA-Cl, correspondingly. In the ^{1}H NMR spectrum of the resulting mixture of (*R*)-MTPA esters ((−)-**1a**) ratio of integral intensities of signals at δ_H 4.18 and 4.29 (both dd) to those of at δ_H 4.11 and 4.37 (both dd) (and *dr* value accordingly) was 79:21. The ^{1}H NMR spectrum of (*S*)-MTPA esters showed the opposite pattern of intensity of the same signals. Curiously enough, this pattern (δ 4.18 + δ 4.29) is similar to that reported for the (*S*)-MTPA ester of enantiopure (*S*,*S*)-(−)-**1**, while the former (δ 4.11 + δ 4.37) was observed in the spectrum of (*R*)-MTPA ester of (–)-**1**.[5,11] To avoid a mistake, for more certainty we confirmed the negative rotation of MTPA-Cl prepared from (*S*)-MTPA.[18]

Previously,[11] the levorotatory lasiol was prepared from the optically pure (*S*)-3-methylbutan-4-olide. We feel that the agreement of $[\alpha]_D$ signs (hexane) of enantiopure[11] and scalemic (*ee* > 50%, this work) lasiol is the strongest evidence for the absolute configuration. Moreover, a structural analogue of lasiol, (2*S*,3*S*,5*E*,9*Z*)-2,3,6,10-tetramethyldodeca-5,9-dien-1-ol, close precursor of "unnatural" (–)-*ent*-faranal, is also levorotatory.[4] It appears that the introduction of additional *erythro*-positioned methyl group at C(3) in the aliphatic chain would not affect the tendency of *(S)*-2-methylalkan-1-ols to be levorotatory in aprotic non-polar solvents.[25—29]

The (*S*,*S*)-configuration of scalemic (–)-**1** proves that both the PPL mediated acetylation of *meso*-2,3-dimethylbutane-1,4-diol and the hydrolysis of its diacetate are pro-(*S*)-selective. Scalemic monoacetates thus formed (**5** and *ent*-**5** correspondingly) are optical antipodes. Sequential transformation of monoacetate **5** into aldehyde **6** and further into selenoacetal **8** may be repeated starting from *ent*-**5**. The preparation of selenoacetal *ent*-**8** by this route is equivalent to the formal synthesis of (+)-faranal, the trail pheromone of the Pharaoh's ant, since the corresponding racemic seleno acetal (±)-**8** has been recently employed in the synthesis of the latter.[9]

Experimental

NMR spectra were recorded in $CDCl_3$ at 399.95 MHz (^{1}H), 100.57 MHz (^{13}C) and 57.21 MHz (^{77}Se) using a Varian Unity-400 spectrometer. NMR ^{77}Se spectra (working frequency

57.21 MHz) were measured using a Varian XL-300 instrument, the chemical shifts are given in ppm relative to neat Me_2Se. GC analysis was performed using a capillary column (15 m × 0.25 mm) with heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrine at 115 °C as the stationary phase and helium (40 kPa) as the carrier gas. Optical rotations were measured using a JASCO-DIP 360 instrument. Elemental analyses were performed by Analytical Laboratories, Lindlar, Germany. *meso*-2,3-Dimethylbutane-1,4-diol was prepared from *meso*-2,3-dimethylsuccinic acid (Aldrich) as described.[9] Syntheses of (η^6-naphthalene)chromium tricarbonyl and benzeneselenol were prepared according to known procedures cited in Ref. 9. Column chromatography was performed using silica gel MATREX LC 60/A/35-70 MY 80/25 85040 (GRACE Davison) using pentane—AcOEt mixtures as eluents.

***meso*-1,4-Diacetoxy-2,3-dimethylbutane (4)** was prepared by standard acetylation of diol 3 with excess Ac_2O (~20 °C) followed by column chromatography (pentane—AcOEt, 85 : 15), colourless oil. ^1H NMR, δ: 0.95 (d, 6 H, CH_3, $J = 6.9$ Hz), 1.87 (m, 2 H, CH), 2.03 (s, 6 H, CH_3), 3.95 (dd, 2 H, OCH_A, $J = 10.9$ Hz, $J = 3.9$ Hz), 4.05 (dd, 2 H, OCH_B, $J = 10.9$ Hz, $J = 4.05$ Hz). ^{13}C NMR, δ: 14.2 (CH_3), 20.9 (CH_3), 34.5 (CH), 67.0 (CH_2), 171.1 (C=O).

Screening of lipases efficiency. Microscale acetylation and hydrolysis (Table 1). ***Acetylation of diol* 3.** Mixtures of a lipase (Roche Diagnostics) (20 mg) with standard 0.01 *M* solution of diol **3** (1 mL) and vinyl acetate (150 mmol□L^{-1}) in toluene were vigorously stirred at 20—25 °C. The progress of acetylation was monitored by GC analysis of aliquots of the reaction mixture, which were diluted with an equal volume of toluene and centrifuged.

Hydrolysis of diacetate 4. A lipase (25 mg) was dispersed in 0.1 *M* phosphate buffer (pH 6.8) (1 mL) for 5 min. Then 0.01 *M* solution of diacetate **4** in toluene (0.8 mL) was added, and stirring was continued at 20—25 °C. Aliquots of a reaction mixture (0.25 mL) were homogenised, shaken with AcOEt (0.2 mL) and then centrifuged. The organic layers thus separated were analysed by GC.

Determination of optical purity of monoacetates 5 and *ent*-5. Diol **3** (59 mg, 0.5 mmol) and diacetate **4** (40.4 mg, 0.2 mmol) were reacted with vinyl acetate or aqueous buffer correspondingly (taken proportionally along with lipase) as described above. The reaction mixtures were treated as above and subjected to column chromatography. Elution with pentane—AcOEt (85 : 15, v/v) afforded diacetate **4.** Subsequent elution with a pentane—EtOAc gradient (7 : 3 → 6 : 4) gave scalemic monoacetates (**5** + *ent*-**5**), which on treatment with (*S*)-(+)-MTPA-Cl (Aldrich) in pyridine were converted into the corresponding mixtures of diastereomeric (*R*)-MTPA esters (**5a** + *ent*-**5a**). ^1H NMR (signals of geminal protons H_A and H_B of the $CF_3(Ph)(OMe)COO\underline{CH_2}$ moiety, δ_H: *diastereomer 1*, 4.15 (dd, ^2J = 11.1 Hz, ^3J = 6.8 Hz) and 4.36 (dd, ^2J = 11.1 Hz, ^3J = 5.4 Hz); *diastereomer 2,* 4.23 (dd, ^2J = 11.1 Hz, ^3J = 6.8 Hz) and 4.28 (dd, ^2J = 10.9 Hz, ^3J = 5.4 Hz). Ratios between integral intensities of these signals (*dr*) were assumed to reflect enantiomeric ratios of **5** and *ent*-**5** formed in the above experiments. The values thus determined are shown in Table 1.

(*2R,3S*)-4-Acetoxy-2,3-dimethylbutan-1-ol (5). ***A.*** To a stirred mixture of diol **3** (0.85 g, 7.2 mmol) and toluene (17 mL) vinyl acetate (1 mL, ~11 mmol) and PPL powder (0.35 g) were added and agitation was continued for 16 h at 22 °C. The reaction mixture was concentrated *in vacuo* and the remainder was subjected to column chromatography. Elution with pentane—AcOEt mixture (85 : 15) gave 0.233 g (16%) of diacetate **4**. Subsequent elution with pentane—AcOEt (6 : 4) afforded 0.329 g (29%) of scalemic monoacetate (**5** + *ent*-**5**) as a colourless oil with $[\alpha]_D^{22}$ +11.0 (*c* 2.6, $CHCl_3$). ^1H NMR and ^{13}C NMR data for the optically active monoacetate were in good agreement with those for the racemate (see Ref. 9). Ratio of integral intensities of H_A and H_B signals in ^1H NMR spectrum of its (*R*)-MTPA ester: $I_{(\delta\,4.15\,+\,\delta\,4.36)} : I_{(\delta\,4.23\,+\,\delta\,4.28)} = 79 : 21$ (*ee* 58%). Finally, unconverted diol **3** (0.408 g, 48%) was eluted with pentane—AcOEt (2 : 8 v/v) .

B. To the solution of diol **3** (59 mg, 0.5 mmol) in toluene (10 mL) vinyl acetate (0.28 mL) and PPL (0.2 g) were added, and stirring was continued for 8 h. A sample of monocetate (**5** + *ent*-**5**) with $[\alpha]_D^{22}$ +12.6 (*c* 1.0, $CHCl_3$) was isolated. Yield: 41 mg (52%). Ratio of integral intensities in ^1H NMR spectrum of corresponding (*R*)-MTPA ester: $I_{(\delta\,4.15\,+\,\delta\,4.36)} : I_{(\delta\,4.23\,+\,\delta\,4.28)} =$ 82 : 18 (*ee* 64%).

(2*S*,3*R*)-4-Acetoxy-2,3-dimethylbutan-1-ol (*ent*-5). ***A.*** A mixture of diacetate **4** (400 mg, 1.98 mmol), toluene (10 mL), 0.1 *M* phosphate buffer (12 mL) and PPL (200 mg) was vigorously stirred at 22±2 °C for 48 h with occasional addition of 2 *M* aqueous NaOH solution (1 mL in total) to maintain pH at 6.8. By that moment the concentrations of the three components (**4, 5** + *ent*-**5** and **3**) in homogenised aliquot related as 30 : 53 : 17 (GLC data). The organic layer was separated, the aqueous phase was extracted with ether. The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo*, and the remainder was subjected to column chromatography. Elution with pentane—AcOEt (85 : 15) gave diacetate **4** (88 mg, 22%). Subsequent elution with pentane—AcOEt (6 : 4) afforded scalemic levorotatory monoacetate (*ent*-**5** + **5**) with $[\alpha]_D^{25}$ −15.2 (*c* 1.0, $CHCl_3$), yield 103 mg (33%). ^1H NMR spectrum of the corresponding (*R*)-MTPA ester displays two groups of diagnostic signals from H_A and H_B in the ratio $I_{(\delta\,4.15\,+\,\delta\,4.36)} : I_{(\delta\,4.23\,+\,\delta\,4.28)} =$ 7 : 93. This corresponds to a 86% *ee* of scalemic monoacetate *ent*-**5** . Elution with pentane—AcOEt mixture (2 : 8) brought about 21 mg (9%) of diol **3**.

B. A mixture of diacetate **4** (40 mg), toluene (20 mL), phosphate buffer (pH 6.8, 26 mL) and PPL powder (625 mg) was stirred at 22 °C for 33 h (NaOH titration was omitted). Then the reaction mixture was treated as above to afford 14 mg (44%) of monoacetate (*ent*-**5** + **5**) with $[\alpha]_D^{25}$ −13.7 (*c* 1.0, $CHCl_3$). ^1H NMR spectrum of the corresponding (*R*)-MTPA ester: $I_{(\delta\,4.15\,+\,\delta\,4.36)} : I_{(\delta\,4.23\,+\,\delta\,4.28)} = 14 : 86$ (*ee* 72%).

(2*S*,3*R*)-2,3-Dimethyl-4,4-bis(phenylseleno)butan-1-ol (7) was obtained from 500 mg (3.12 mmol) of dextrorotatory 2*R*,3*S* monoester (**5** : *ent*-**5** = 79 : 21, *ee* 58%) using a three step protocol described earlier[9] for the corresponding racemic selenoacetal. Yield: 735 mg (57%), a colourless viscous oil with $[\alpha]_D^{25}$ +32.3 (*c* 1.0, $CHCl_3$). NMR ^1H and ^{13}C spectra of compound **7** and its racemic analogue were practically identical.

(2*R*,3*S*)-4-(*tert*-Butyldimethylsilyloxy)-2,3-dimethyl-1,1-bis(phenylseleno)butane (8) was prepared from selenoacetal **7** (700 mg, 1.70 mmol) as described earlier for the racemate.[9] Yield: 0.742 g (82%). Yellowish viscous oil with $[\alpha]_D^{27}$ +20.5 (*c* 2.0, $CHCl_3$).

(5*R*,6*S*)-7-(*tert*-Butyldimethylsilyloxy)-2,5,6-trimethyl-4-phenylselenohept-1-en-3-ol (9). To a stirred solution of selenoacetal **8** (655 mg, 1.24 mmol) in THF (7 mL) at –78 °C *n*-BuLi (0.5 mL of a 2.5 *M* solution in hexane, 1.24 mmol) was added. The mixture was stirred for 5 min, treated with a solution of 2-methylpropenal (87 mg, 1.24 mmol) in THF (1 mL), and the temperature was raised to 20 °C. The reaction mixture was quenched with $NaHCO_3$ (aq) and extracted with ether, the extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (gradient pentane — AcOEt 99 : 1 → 98 : 2) afforded 398 mg (73%) of a mixture of four diastereomers of selenide **9** as a yellowish oil. Found (%): C, 59.79; H, 8.64. $C_{22}H_{38}O_2SeSi$. Calculated (%): C, 59.84; H, 8.67. ^{77}Se NMR, δ: 235.8, 254.8, 269.8, 322.5.

(2*S*,3*R*)-1-Acetoxy-2,3,6-trimethylhepta-4,6-diene (10). To a stirred solution of selenide **9** (360 mg, 0.815 mmol) and NEt_3 (0.57 mL, 3.3 mmol) in CH_2Cl_2 (4.3 mL) MsCl (0.20 mL) was added dropwise at 20 °C, and stirring was continued for 3 h. The reaction was quenched with $NaHCO_3$ (aq) and extracted with ether. The extract was dried ($CaCl_2$) and concentrated *in vacuo*, and the oily residue was subjected to column chromatography. Elution with gradient pentane — AcOEt (99 : 1 → 98 : 5) afforded 205 mg (93%) of (2*S*,3*R*)-1-(*tert*-butyldimethylsilyloxy)-2,3,6-trimethylhepta-4,6-diene, which was immediately desilylated by treating its solution in THF with 1 *M* solution of Bu_4NF in THF (0.84 mL) for 14 h at 20—22 °C. The alcohol thus formed was subjected to chromatography using pentane — AcOEt (9 : 1). However, it could not be separated from *tert*-butyldimethylsilanol that was formed as by-product. Therefore, the fraction containing this alcohol (along with Bu^tMe_2SiOH) was treated with a small excess Ac_2O in the presence of ~10 mg of DMAP (20 °C, 2 h) and concentrated *in vacuo*. Column chromatography with gradient pentane – AcOEt (99 : 1 → 97 : 3) afforded the title acetate **10** as a 3:2 mixture of *E/Z* isomers in a yield of 97 mg (64%). Found (%): C, 73.28; H, 10.26. $C_{12}H_{20}O_2$. Calculated (%): C, 73.43; H, 10.27. ^1H NMR, δ: *E-isomer*: 0.88 (d, 3 H, CH_3, J = 7.0 Hz), 1.04 (d, 3 H, CH_3, J = 7.0 Hz), 1.78 (m, 1 H, CH), 1.82 (s, 3 H, CH_3 allylic), 2.05 (s, 3 H, CH_3CO), 2.31 (sextet, 1 H, CH, J = 6.4 Hz), 3.88 (dd, 1 H, OCH_A, J = 10.9 Hz, J = 6.8 Hz), 3.98 (dd, 1 H, OCH_B, J = 10.9 Hz, J = 6.4 Hz), 4.88 (br. s, 2 H, $=CH_2$), 5.51 (dd, 1 H, C(4)H, J = 15.7 Hz, J = 8.5 Hz), 6.10 (d, 1 H, C(5)H, J = 15.7 Hz); *Z-isomer*: 0.89 (d, 3 H, CH_3, J = 6.9 Hz), 1.01 (d, 3 H, CH_3, J = 7.0 Hz), 1.71 (m, 1 H, CH), 1.85 (s, 3 H, allylic), 2.03 (s, 3 H, CH_3CO), 2.88 (m, 1 H, CH), 3.90 (dd, 1 H, OCH_A), 3.96 (dd, 1 H, OCH_B), 4.82 (br. s, 1 H, $C(7)H_A$), 4.91 (br s, 1 H, $C(7)H_B$), 5.23 (t, 1 H, C(4)H, J = 11.6 Hz), 5.85 (d, 1 H, C(5)H, J = 11.9 Hz). ^{13}C NMR, δ: *E*-isomer: 13.3 (CH_3), 18.0 (CH_3), 18.7 (CH_3), 20.9 (CH_3), 37.6 (CH), 38.5 (CH), 67.8 (CH_2), 114.9 ($=CH_2$), 132.7 (=CH), 132.9 (=CH), 141.9 (=C), 171.2 (C=O); *Z*-isomer: 13.3 (CH_3), 19.0 (CH_3), 21.0 (CH_3), 23.3 (CH_3), 33.4 (CH), 37.8 (CH), 67.8 (CH_2), 114.9 ($=CH_2$), 130.9 (=CH), 133.8 (=CH), 141.8 (=C), 171.2 (C=O).

(2*S*,3*S*)-2,3,6-Trimethylhept-5-en-1-ol ((–)-lasiol, (–)-1). A 250 mL stainless steel autoclave containing a solution of diene **10** (64 mg) in THF (17 mL) and (η^6-naphthalene)chromium tricarbonyl (0.3 g) was filled with hydrogen at 10 atm and then evacuated. After this operation has been repeated three times, the pressure of H_2 was adjusted to 40 atm, and the hydrogenation of the diene was carried out for 2 h at 40 atm. After decompression, the solvent was removed *in vacuo* and the remainder was subjected to column chromatography in pentane — AcOEt gradient (100 : 0 → 97 : 3). Without further purification (2*S*,3*S*)-1-acetoxy-2,3,6-trimethylhept-5-ene (acetate of (–)-lasiol) thus isolated was deacylated upon stirring with K_2CO_3 (10 mg) in MeOH (1.5 mL) for 5 h. The solvent was evaporated, and the residue during column chromatography was eluted with pentane—AcOEt (4 : 1) to afford chemically pure scalemic (–)-lasiol ((–)-**1**) as a colourless oil with $[\alpha]_D^{22}$ –6.6 (*c* 1.56, hexane) (yield 41 mg (81%)). The ^1H and ^{13}C NMR data were in good agreement with those previously reported for (±)-, (+)- and (–)-lasiol.[1,5,11]

(*R*)-MTPA ester of (–)-lasiol, (–)-**1a**, was prepared routinely from scalemic alcohol (–)-**1** and (*S*)-(+)-MTPA-Cl in pyridine.[18] NMR ^1H (ratio of intensities (I) of two groups from geminal protons H_A and H_B in the fragment $CF_3(Ph)(OMe)CCO_2\underline{CH_2}$ and corresponding δ_H (ppm) are indicated): $I_{(\delta\,4.18\,+\,\delta\,4.29)} : I_{(\delta\,4.11\,+\,\delta\,4.36)}$ = 79 : 21 (corresponds to 58% *ee* in the starting alcohol).

(*S*)-MTPA ester of (–)-lasiol, (–)-**1b**, was prepared from (–)-**1** and (–)-(*R*)-MTPA-Cl. ^1H NMR: $I_{(\delta\,4.18\,+\,\delta\,4.29)} : I_{(\delta\,4.11\,+\,\delta\,4.36)}$ = 21 : 79 (58% *ee* in the starting alcohol). ^{19}F NMR, δ_F: –71.93 for both diastereomers.

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