Notes

Enzymatic Resolution of (*R*)- and (*S*)-2-(1-Hydroxyalkyl)thiazoles, Synthetic Equivalents of (*R*)- and (*S*)-2-Hydroxy Aldehydes

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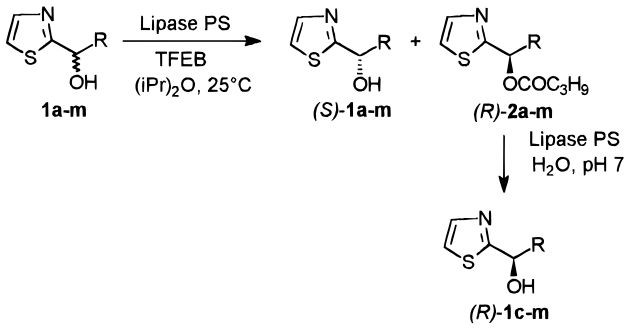
Introduction

In connection with our studies on the synthesis[1a−e] and biological evaluation[2a,b] of enantioenriched (*E*)-4-hydroxy- and (*E*)-4,5-dihydroxy-2-alkenals formed during lipid peroxidation, we confronted the problem of producing various (*R*)- and (*S*)-2-hydroxy aldehydes, convenient chiral building blocks[1c,d] for the synthesis of these physiologically active[3] hydroxylated 2-alkenals and of many other important natural products.[4a−d]

A literature survey showed that 2-hydroxy aldehydes of various structure can be obtained in high optical purity by general methods involving either the chemical elaboration of natural chiral precursors, like D-mannitol or monosaccharides,[1c,4b] or the use of chiral acyl anion equivalents.[5] Also some methods based on biocatalytic approaches have been reported, but these appear more limited since they permit the satisfactory preparation of only a restricted number of simple 2-hydroxy aldehydes or, often, of only the single (*S*)-enantiomer. Such methods include the stereoselective hydrolysis of α-acetoxy or α-butyroxy thioacetals by lipases[6] or the bioreduction of a small number of α-keto thioacetals by bakers' yeast,[7a−d] or of ketoacetals by other yeasts,[8] followed by the regeneration of the formyl group.

Scheme 1



Attempts directed at obtaining enantioenriched 2-(1-hydroxyalkyl)thiazoles, masked equivalents of chiral 2-hydroxy aldehyde, by a biological reduction of the corresponding 2-acylthiazoles gave poor results,[7b] apart from the case of 2-acetylthiazole which, with bakers' yeast, undergoes reduction affording only the enantiomer with the (*S*)-configuration.[9]

Considering that racemic 2-hydroxy aldehydes are conveniently obtained[10] *via* 2-(1-hydroxyalkyl)thiazoles, which are easily and efficiently prepared using 2-(trimethylsilyl)thiazole,[11] we decided to search for a simple method for the enzymatic resolution of 2-(1-hydroxyalkyl)thiazoles. The approach we adopted involved enantioselective esterification of the hydroxy group, using as catalysts enzymes in organic solvents. Dondoni et al. had already shown that thiazolyl to formyl deblocking occurs without epimerization of a stereogenic center adjacent to the formyl group;[10,12] thus the resolution of 2-(1-hydroxyalkyl)thiazoles *via* enzymes could provide a simple access to enantioenriched 2-hydroxy aldehydes.

We report the resolution of several (*R*)- and (*S*)-2-(1-hydroxyalkyl)thiazoles through the enantioselective acylation of the racemic mixture. This route gives the unreacted (*S*)-2-(1-hydroxyalkyl)thiazoles (*S*)-**1c**−**m** in high enantiomeric purity due to a transesterification reaction of the (*R*)-enantiomer with 2,2,2-trifluoroethyl butanoate (TFEB) in diisopropyl ether under immobilized Lipase PS catalysis.[13] Using the same enzyme in an aqueous medium, hydrolysis of the butanoates (**2c**−**m**; Scheme 1) afforded the (*R*)-enantiomers (*R*)-**1c**−**m** in similar satisfactory optical purity.

The utility of the method was then demonstrated in the synthesis of (*R*)- and (*S*)-(*E*)-4-hydroxy-2-undecenals (**6**; Scheme 2), cytotoxic aldehydes formed in the peroxidation of (*n*-9)-polyunsaturated fatty acids bonded to membrane phospholipids.[3] However the method has a

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(13) Tested lipases were described as follows: lipase from *Pseudomonas sp.* (SAM-II, Amano), lipase from *Pseudomonas fluorescens* (Sam-2, Fluka), lipase from *Candida cylindracea* (CCL, type VII, Sigma), lipase from *Candida antarctica* SP 435 L (LCA, immobilized on a macroporous acrylic resin, Novo Nordisk, Denmark), lipase from porcine pancreas (PPL, type II, crude, Sigma), lipase from *Pseudomonas cepacia* (Lipase PS, Amano), Lipase PS was also immobilized on Hyflo Super Cell according to reference 14.

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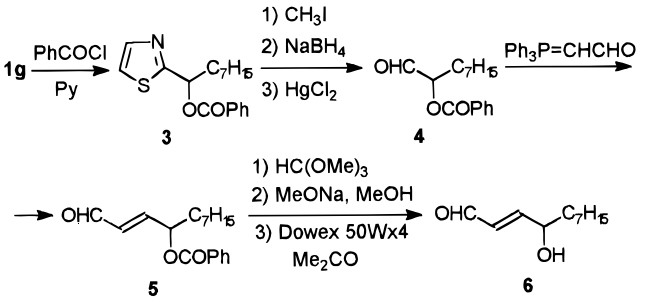
Scheme 2



more general relevance since 2-(1-hydroxyalkyl)thiazoles, versatile intermediates in organic chemistry,[12] are obtained in a high enough optical purity for the synthesis of natural compounds.

Results and Discussion

The 2-(1-hydroxyalkyl)thiazoles **1a**−**m** were prepared in good yields by reaction of an appropriate aldehyde with 2-(trimethylsilyl)thiazole.[11] Preliminary experiments for enzymatic resolution were then performed in order to screen enzymes, solvents, and acylating agents and to optimize the other reaction conditions.

For the enzyme screening, the transesterification between vinyl acetate and 2-(1-hydroxyoctyl)thiazole **1g** was checked in *tert*-butyl methyl ether, a solvent we found useful in some lipase-mediated acylations of racemic hydroxy acetals,[1e] in the presence of six commercial lipases.[13] One of these, Lipase PS, was tested both as a free enzyme and after immobilization onto Hyflo Super Cell.[14]

Of the screened enzymes, free and immobilized Lipase PS showed the highest enantioselectivity ($E > 16$) and activity, *Candida cylindracea* and immobilized *Candida antarctica* lipases were practically inactive, porcine pancreas lipase displayed extremely low activity and very poor selectivity ($E \cong 1$), lipases from *Pseudomonas sp.* and from *Pseudomonas fluorescens* catalyzed the reaction, showing low enantiospecificity ($E < 10$).

Immobilized Lipase PS was more active than the free enzyme and was thus selected for further studies to determine the possibility of improving the enzymatic enantioselectivity by choosing the most appropriate solvent and acyl donor. In these experiments the enantioselective acylation of **1g**, catalyzed by immobilized Lipase PS, was carried out using, as the acylating agents, vinyl acetate for the irreversibility of its reaction, and TFEB, because the very weak nucleophilicity of 2,2,2-trifluoroethanol makes the transesterification essentially irreversible. Each acylating agent was tested in the presence of eight solvents of different hydrophobicity (log *P*) and dielectric constant (ϵ), including *tert*-amyl alcohol which has been shown to have excellent enantioselectivity with immobilized Lipase PS[14] (Table 1).

Since the best reaction results, in terms of enantioselectivity, were with TFEB in diisopropyl ether, successive experiments were performed under the same conditions to determine the enantiomeric ratio (*E*) for all the substrates **1a**−**m**. These values are reported as the average of three values, calculated for conversions ranging from 10 to 50% (Table 2). It can be seen that the enantioselectivity of the enzyme is always good ($E \geq 20$) for all the substrates, except for **1a** and **1b** which have the shortest alkyl chains. In agreement with the good enantiomeric ratios, the lipase-catalyzed resolutions of the racemic 2-(1-hydroxyalkyl)thiazoles **1c**−**m** yielded the unreacted (*S*)-alcohols in high optical purity, driving the extent of the conversion to 53−57%, as suggested by the equations for the quantitative treatment of enzymatic kinetic resolution[15a,b] (Table 2).

In the case of the acylated (*R*)-compounds the enantiomeric excesses was unsatisfactory. However, since only a drastic reduction in the extent of the conversion could bring about an acceptable improvement of their optical purity,[15b] we tested the possibility of obtaining (*R*)-2-(1-hydroxyalkyl)thiazoles (*R*)-**1c**−**m** by the hydrolysis of the enantiomerically enriched (*R*)-butanoates under catalysis of free Lipase PS. In fact, hydrolysis of the butanoates (*R*)-**2c**−**m**, mediated by free Lipase PS in phosphate buffer (pH 7), afforded the alcohols (*R*)-**1c**−**m** with high optical purity (Table 2).[16]

The enantiomeric excess and the absolute configuration of the (*R*)- and (*S*)-2-(1-hydroxyalkyl)thiazoles were determined by ^{1}H NMR analysis of their (*R*)- and (*S*)-Mosher esters,[17,18] while the enantiomeric excess of the butanoates (*R*)-**2a**−**m** was evaluated by ^{1}H NMR using tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III), [Eu(hfc)$_3$].[19]

The utility of the present method was demonstrated in the synthesis of (*R*)- and (*S*)-(*E*)-4-hydroxy-2-undecenal (**6**, Scheme 2), an important hydroxy 2-alkenal derived in LPO from (*n*-9) fatty acids. For this purpose (*R*)- and (*S*)-2-(1-hydroxyoctyl)thiazoles (**1g**) were separately esterified with benzoyl chloride in pyridine and successively converted, without racemization,[10,12] into the corresponding benzoyloxy aldehyde **4** [^{1}H NMR at 500 MHz; using Eu(hfc)$_3$].

A two-carbon homologation of the obtained 2-benzoyloxy aldehydes **4**, by Wittig reaction with (formylmethylene)triphenylphosphorane, and regeneration of the 4-hydroxy group accomplished the synthesis.

In conclusion 2-(1-hydroxyalkyl)thiazoles, important synthetic equivalents of 2-hydroxy aldehydes, have been efficiently resolved by biochemical kinetic resolution.

This method fills the gap that can be seen in the poor results (obtained until now) in the biocatalytic reduction of 2-acyl thiazoles and affords enantioenriched synthons which should find use in numerous organic syntheses.

Experimental Section

The ^{1}H NMR spectra (500.13 MHz) were recorded in $CDCl_3$ at 303 K and were referenced to $CHCl_3$ at 7.24 ppm. HPLC analyses were carried out on a Merck superspher 100 RP-18 column, 4 mm × 25 cm, the flow rate was 1 mL/min, and the detection was performed at 241 nm. Optical rotations were measured for 1% $CHCl_3$ solutions. TLC was carried out on silica gel 60 F_{254} microplates. Column chromatography refers to flash

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Table 1. Effects of the Nature of Organic Solvents on the Enantioselectivity and Activity of Immobilized Lipase PS in the Acylation of 2-(1-Hydroxyalkyl)thiazole (1g) with Vinyl Acetate and 2,2,2-Trifluoroethyl Butanoate

			$AcOCH{=}CH_2$		$Me(CH_2)_2CO_2CH_2CF_3$	
solvents	log *P*	ϵ	*E*[a]	relative rate %[b]	*E*[a]	relative rate %
hexane	3.50	8.10	6	100	10	95
chloroform	2.00	4.81	7	20	5	2
tert-butyl methyl ether	1.90	4.50	16	90	31	90
diisopropyl ether	1.90	3.88	21	85	50	100
2-methyl-2-butanol	1.45	5.80	6	35	–	<1
diethyl ether	0.85	4.20	9	40	–	<1
tetrahydrofuran	0.49	7.58	6	10	2	5
acetonitrile	−0.33	35.95	2	5	–	<1

[a] *E* (enantiomeric ratio) values were calculated from the degree of conversion and the ee of the product according to Chen, C.-S., *et al.*[15] Each value was the average of three values calculated for conversions ranging from 10 to 50%. [b] This parameter, average of three values, is based on 10% conversions and compares the activity of the enzyme in different solvents.

Table 2. Immobilized Lipase PS-Catalyzed Resolution of 2-(1-Hydroxyalkyl)thiazoles

		acylation				hydrolysis
compd	R	*E*	convn[a] (%) (time, h)[b]	(*S*)-**1** ee (%)[c] (yield, %)[d]	(*R*)-**2** ee (%)[e] (yield, %)[d]	(*R*)-**1** ee (%)[c] (yield, %)[f]
1a	CH_3	5	53 (96)	55 (43)	49 (49)	– –
1b	C_2H_5	7	13 (260)	11 (83)	74 (10)	– –
1c	C_3H_7	27	55 (130)	94 (41)	77 (49)	98 (35)
1d	C_4H_9	20	56 (180)	93 (42)	72 (49)	96 (34)
1e	C_5H_{11}	29	55 (160)	95 (42)	78 (51)	98 (37)
1f	C_6H_{13}	32	55 (90)	96 (42)	78 (52)	98 (37)
1g	C_7H_{15}	50	55 (110)	>98 (41)	82 (50)	>98 (39)
1h	C_8H_{17}	34	55 (90)	96 (41)	79 (50)	98 (35)
1i	C_9H_{19}	27	57 (110)	97 (40)	73 (53)	97 (35)
1l	$C_{10}H_{21}$	25	56 (90)	95 (42)	75 (53)	97 (37)
1m	C_6H_5	58	53 (80)	97 (44)	86 (49)	>98 (37)

[a] Determined by HPLC. [b] Referred to enzymatic esterification. [c] Enantiomeric excesses were determined by ^{1}H NMR analysis of the Mosher esters. [d] After flash chromatography. [e] Enantiomeric excesses were determined by ^{1}H NMR using 0.1−0.2 equiv of Eu(hfc)$_3$. [f] After flash chromatography, referred to initial racemic mixture.

chromatography.[20] (*S*)- and (*R*)-α-Methoxy-α-(trifluoromethyl)-phenylacetate [(*S*)- and (*R*)-MTPA] derivatives were prepared from the appropriate (*R*)- and (*S*)-MTPA chlorides.[17,18] All organic solvents were dried before use.

Usual workup refers to washing the organic layer with water, drying it over Na_2SO_4, and evaporating the solvent under reduced pressure. The progress of all the reactions, the column chromatography, and compound purity were monitored by TLC and/or HPLC.

The 2-(1-hydroxyalkyl)thiazoles (**1a**−**m**) were synthesized on a 20 mmol scale using Dondoni's methodology[10] and showed the following yields and properties.

2-(1-Hydroxyethyl)thiazole (**1a**, 85% yield): oil. Anal. Calcd for C_5H_7NOS: C, 46.49; H, 5.46; N, 10.84. Found: C, 47.11; H, 5.30; N, 10.62.

2-(1-Hydroxypropyl)thiazole (**1b**, 87% yield): oil. Anal. Calcd for C_6H_9NOS: C, 50.32; H, 6.33; N, 9.78. Found: C, 50.57; H, 6.01; N, 9.84.

2-(1-Hydroxybutyl)thiazole (**1c**, 86% yield): oil. Anal. Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91. Found: C, 53.30; H, 7.19; N, 9.01.

2-(1-Hydroxypentyl)thiazole (**1d**, 90% yield): oil. Anal. Calcd for $C_8H_{13}NOS$: C, 56.11; H, 7.65; N, 8.18. Found: C, 56.20; H, 7.49; N, 8.09.

2-(1-Hydroxyhexyl)thiazole (**1e**, 89% yield): oil. Anal. Calcd for $C_9H_{15}NOS$: C, 58.34; H, 8.16; N, 7.56. Found: C, 58.50; H, 8.19; N, 7.47.

2-(1-Hydroxyheptyl)thiazole[11] (**1f**, 88% yield): oil. Anal. Calcd for $C_{10}H_{17}NOS$: C, 60.26; H, 8.60; N, 7.03. Found: C, 60.20; H, 8.74; N, 6.92.

2-(1-Hydroxyoctyl)thiazole (**1g**, 90% yield): oil; IR (film) 3230, 2920, 1500 cm^{-1}; ^{1}H NMR δ 7.56 (1H, d, J = 3.5 Hz), 7.17 (1H, d, J = 3.5 Hz), 4.90 (1H, dd, J = 7.7, 4.9 Hz), 1.86 (1H, dddd, J = 13.3, 9.4, 5.6, 4.9 Hz), 1.78 (1H, dddd, J = 13.3, 9.8, 7.7, 4.9 Hz), 1.46−1.16 (10H, m), 0.80 (3H, t, J = 7.0 Hz); MS *m/z* 213 (2), 170 (9), 114 (100), 86 (24), 59 (11). Anal. Calcd for $C_{11}H_{19}NOS$: C, 61.93; H, 8.98; N, 6.57; S, 15.03. Found: C, 62.01; H, 8.81; N, 6.60, S, 14.94.

2-(1-Hydroxynonyl)thiazole (**1h**, 85% yield): mp 44−46 °C (from diethyl ether−hexane). Anal. Calcd for $C_{12}H_{21}NOS$: C, 63.39; H, 9.31; N, 6.16. Found: C, 63.42; H, 9.24; N, 6.27.

2-(1-Hydroxydecyl)thiazole (**1i**, 87% yield): mp 52−54 °C (from diethyl ether−hexane). Anal. Calcd for $C_{13}H_{23}NOS$: C, 64.68; H, 9.60; N, 5.80. Found: C, 64.50; H, 9.43; N, 5.61.

2-(1-Hydroxyundecyl)thiazole (**1l**, 90% yield): mp 60−62 °C (from diethyl ether−hexane). Anal. Calcd for $C_{14}H_{25}NOS$: C, 65.83; H, 9.87; N, 5.48. Found: C, 65.90; H, 9.77; N, 5.30.

2-(1-Hydroxy-1-phenylmethyl)thiazole[11] (**1m**, 90% yield): mp 107−109 °C (from diethyl ether−hexane). Anal. Calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.74; H, 4.91; N, 7.20.

Lipase-Mediated Acylation of Racemic 2-(1-hydroxyalkyl)thiazoles (1a−m) in Organic Solvents. General Procedure. 2,2,2-Trifluoroethyl butanoate (2 mmol) and immobilized Lipase PS (400 mg; 30% on Hyflo Super Cell) were added to a solution of each of the racemic 2-(1-hydroxyalkyl)-thiazoles (**1a**−**m**, 1 mmol) in diisopropyl ether (10 mL).

The resulting suspension was shaken at 25 °C and monitored by HPLC (LiChroCART 250-4, Superspher 100 RP-18, 4 × 244 mm, Merck, 1 mL/min, λ 241 nm; the different thiazoles were eluted with aqueous methanol ranging from 70 to 90%). When the desired conversion was reached, the enzyme was recovered by filtration and the solvent evaporated under reduced pressure. Flash chromatography (hexane−AcOEt, 80:20 v/v) of the residue afforded the unreacted alcohols (*S*)-**1a**−**m** and the butanoates (*R*)-**2a**−**m**, with the yields and enantiomeric excess shown in Table 2.

In particular, the unreacted (*S*)-2-(1-hydroxyalkyl)thiazoles (*S*)-**1a**−**m** (purity > 97% by HPLC) showed correct physicochemical properties, identical to those observed for their racemates, and the following optical rotations, $[\alpha]^{25}_D$: −3.5 for (*S*)-**1a**, −7.4 for (*S*)-**1b**, −32.4, for (*S*)-**1c**, −26.0 for (*S*)-**1d**, −18.5 for (*S*)-**1e**, −16.3 for (*S*)-**1f**, −18.1 for (*S*)-**1g**, −15.3 for (*S*)-**1h**, −13.9 for (*S*)-**1i**, −13.8 for (*S*)-**1l**, and −29.0 for (*S*)-**1m**.

The butanoates (*R*)-**2a**−**m** showed ^{1}H NMR spectra with appropriate proton signals and the following optical rotations, $[\alpha]^{25}_D$: +35.1 for (*R*)-**2a**, +29.4 for (*R*)-**2b**, +56.7 for (*R*)-**2c**, +58.1 for (*R*)-**2d**, +39.1 for (*R*)-**2e**, +42.1 for (*R*)-**2f**, +36.6 for (*R*)-**2g**, +40.5 for (*R*)-**2h**, +40.0 for (*R*)-**2i**, +33.9 for (*R*)-**2l**, and +76.8 for (*R*)-**2m**. They were normally used directly in the next hydrolysis.

Lipase-Mediated Hydrolysis of the Butanoate (*R*)-2c−m. General Procedure. Lipase PS (75 mg) was added to a solution of the butanoates **2c**−**m** (derived from the previous acylation), in phosphate buffer (5 mL, 0.1 M, pH 7, kept constant at the starting value by controlled addition of 0.1 M sodium hydroxide) and acetone (0.5 mL). The hydrolysis was followed by HPLC, and when the desired conversion was reached the mixture was extracted with CH_2Cl_2. Usual workup afforded a residue which was purified by flash chromatography (hexane−AcOEt, 80:20 v/v) to give the (*R*)-2-(1-hydroxyalkyl)thiazoles (*R*)-**1c**−**m** (purity > 97% by HPLC), which showed appropriate

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physicochemical properties identical to those observed for (*S*)-enantiomers, apart from optical rotations, $[\alpha]^{25}_D$, which were: +32.6 for (*R*)-**1c**, +26.9 for (*R*)-**1d**, +18.7 for (*R*)-**1e**, +16.6 for (*R*)-**1f**, +18.3 for (*R*)-**1g**, +15.7 for (*R*)-**1h**, +14.2 for (*R*)-**1i**, +14.0 for (*R*)-**1l**, and +29.4 for (*R*)-**1m**.

Synthesis of (*R*)-(*E*)-4-Hydroxy-2-undecenal (*R*)-6. (i) Benzoylation of (*R*)-2-(1-hydroxyoctyl)thiazole (1g). To a solution of thiazole (*R*)-**1g** (250 mg, 1.2 mmol) in pyridine (10 mL) was added benzoyl chloride (210 mg, 1.5 mmol) at 0 °C, and the mixture was stirred at 25 °C for 1 h. After usual workup, the resulting oil was purified by flash chromatography (CH_2Cl_2) to give the ester (*R*)-**4** (362 mg, 95% yield) as an oil: $[\alpha]^{25}_D$ −18.4; ^{1}H NMR δ 8.09 (2H, d, J = 7.7 Hz), 7.75 (1H, d, J = 3.5 Hz), 7.55 (1H, dd, J = 7.7, 7.7 Hz), 7.43 (2H, dd, J = 7.7, 7.7 Hz), 7.27 (1H, d, J = 3.5 Hz), 6.35 (1H, t, J = 6.3), 2.17 (2H, dt, J = 9.1, 6.3 Hz), 1.47−1.16 (10H, m), 0.83 (3H, t, J = 7.0 Hz); MS *m*/*z* 317 (2), 212 (100), 114 (18), 105 (63), 77 (27). Anal. Calcd for $C_{18}H_{23}NO_2S$: C, 68.10; H, 7.30; N, 4.41. Found: C, 68.27; H, 7.24; N, 4.53.

(ii) Thiazolyl-to-Formyl Deblocking. To a solution of ester **3** (320 mg, 1.5 mmol) in acetonitrile (10 mL) was added methyl iodide (3.2 g, 22.5 mmol), and the resulting mixture was refluxed for 15 h. The solvent was then removed under reduced pressure and the residue dissolved in methanol (10 mL) and cooled to 0 °C. Sodium borohydride (85 mg, 2.25 mmol) was then added under vigorous stirring. After 30 min acetone (0.5 mL) was added and the solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2, and the combined extracts were worked up to afford an oil which was dissolved in acetonitrile (1.5 mL) and slowly added to a vigorously stirred solution of $HgCl_2$ (488 mg, 1.8 mmol) in a mixture of acetonitrile−water (5 mL, 4:1 v/v). After 15 min, the reaction mixture was filtered on a pad of Celite, and the inorganic residue was washed with diethyl ether. The ethereal extracts were added to the filtered solution, and the mixture was concentrated under reduced pressure. The residue was diluted with brine (5.0 mL) and extracted with CH_2Cl_2. Usual workup afforded a residue which was purified by flash chromatography (hexane−AcOEt, 80:20 v/v) to give (*R*)-2-(benzoyloxy)nonanal (*R*)-**4** (244 mg, 62% yield) as an oil: $[\alpha]^{23}_D$ +32.6; ^{1}H NMR δ 9.62 (1H, d, J < 1), 8.08 (2H, d, J = 7.7 Hz), 7.59 (1H, dd, J = 7.7, 7.7 Hz), 7.46 (2H, dd, J = 7.7, 7.7 Hz), 5.20 (1H, dd, J = 8.4, 4.9 Hz), 1.99−1.83 (2H, m), 1.53−1.20 (10H, m), 0.86 (3H, t, J = 7.7 Hz); MS *m*/*z* 212 (14), 105 (100), 77 (23). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.42; H, 8.50.

(iii) Wittig Reaction with (Formylmethylene)triphenylphosphorane. To a solution of the benzoyloxy aldehyde (*R*)-**4** (200 mg, 0.76 mmol) in toluene (20 mL) was added (formylmethylene)triphenylphosphorane (277 mg, 0.91 mmol), and the resulting mixture was refluxed for 6 h. Then the mixture was diluted with diethyl ether (30 mL), and the triphenylphosphine oxide was filtered.

Usual workup and column chromatography (hexane/AcOEt, 80:20 v/v) afforded the (*R*)-(*E*)-4-(benzoyloxy)-2-undecenal [(*R*)-**5**, 188 mg, 86% yield] as an oil: $[\alpha]^{20}_D$ −53.6; ^{1}H NMR ($CDCl_3$) δ 9.57 (1H, d, J = 7.7 Hz), 8.05 (2H, d, J = 7.7 Hz), 7.57 (1H, dd, J = 7.7, 7.7 Hz), 7.45 (2H, dd, J = 7.7, 7.7 Hz), 6.83 (1H, dd, J = 15.4, 4.9 Hz), 6.27 (1H, ddd, J = 15.4, 7.7, 1.4 Hz), 5.75 (1H, ddt, J = 6.3, 4.9, 1.4 Hz), 1.90−1.79 (2H, m), 1.48−1.19 (10H, m), 0.85 (3H, t, J = 7.7 Hz); MS *m*/*z* 167 (3), 122 (10), 105 (100), 77 (21). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.09; H, 8.47.

(iv) Regeneration of the Hydroxyl Group. The benzoyloxy aldehyde (*R*)-**5** (173 mg, 0.6 mmol), dissolved in CH_2Cl_2 (8 mL), was stirred with montmorillonite clay K-10 (200 mg) in trimethyl orthoformiate (0.22 mL, 2 mmol) for 2 h. At this time the reaction mixture was filtered, washed with saturated aqueous $NaHCO_3$, and worked up to give the crude benzoyloxy acetal which was equilibrated with a methanolic solution of sodium methoxide (5 mL, 0.1 M) at room temperature for 8 h. Then the reaction mixture was diluted with water (15 mL) and extracted with AcOEt (20 mL). Usual workup afforded a crude hydroxy acetal which was dissolved in moist acetone (5 mL) and treated with an acidic ion exchange resin (Dowex-50 W-hydrogen, 125 mg), for 1 h at room temperature. After filtration of the resin, the solvent was evaporated and the crude residue purified by flash chromatography (hexane−AcOEt, 70:30 v/v) to give the (*R*)-(*E*)-4-hydroxy-2-undecenal [(*R*)-**6**, 82 mg, 74% yield) as an oil: $[\alpha]^{20}_D$ −44.2. This compound showed appropriate physicochemical properties identical to those reported.[1e]

Synthesis of (*S*)-(*E*)-4-Hydroxy-2-undecenal [(*S*)-6]. This aldehyde was obtained by a reaction sequence identical to that described for the (*R*)-enantiomer. The final and intermediate compounds showed appropriate physicochemical properties, identical to those observed for (*R*)-enantiomers, but differing in optical rotation. In fact compounds (*S*)-**3**, (*S*)-**4**, (*S*)-**5**, and (*S*)-**6** showed, respectively: $[\alpha]^{21}_D$ +18.2; $[\alpha]^{23}_D$ −32.4; $[\alpha]^{21}_D$ +53.4; $[\alpha]^{22}_D$ +44.0.

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Supporting Information Available: IR, ^{1}H NMR (500 MHz), and mass spectra of 2-(1-hydroxyalkyl)thiazoles (**1a**−**m**) (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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