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Baker's yeast-induced asymmetric reduction of α-ketosulfides: synthesis of optically active 1-(benzothiazol-2-ylsulfanyl)-2-alkanols, 2-alkanols, and thiiranes

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Abstract

1-(Benzothiazol-2-ylsulfanyl)-2-alkanols **3** were prepared in very high enantiomeric excess by baker's yeast-induced asymmetric reduction of 1-(benzothiazol-2-ylsulfanyl)-2-alkanones **1**. Conversion of **3** into optically active simple 2-alkanols **4** and thiiranes **2** by reductive desulfurization and base treatment, respectively, is also described. The absolute configuration of the new compounds synthesized has been established by chemical correlation and specific rotation comparison.

1. Introduction

Thiiranes are suitable precursors for numerous products such as biologically active substances and polymers. New technical applications of thiiranes have been developed for the preparation of liquid crystals, photoresistors, components of paint and varnish coatings, antioxidant thermostable insulating materials, heat-resistant polymers, semiconductors, elastomers, etc.[1] The availability of a general methodology to prepare enantiomerically pure thiiranes could open the way to the synthesis of the above mentioned products with very high enantiomeric purity, which in the case of biologically active substances represents a very crucial target.

Of similar importance are chiral 2-alkanols, widely used as building blocks in the asymmetric synthesis of speciality chemicals.[2]

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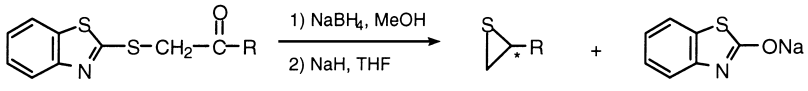
Thiiranes are usually prepared from the corresponding oxiranes or vicinally substituted ethane derivatives.[3–7] The synthesis of thiiranes generally involves the previous transformation of a diol into the corresponding epoxide and opening with thiocyanate ions or with thiourea, which are the most common reagents used for this transformation.[8–19] A recently described method for the synthesis of thiiranes involves a previous transformation of allylic alcohols into cyclic xanthates.[20–22] A new efficient and expeditious synthesis of thiiranes from cyclic sulfates of *vic*-diols is also described; opening of cyclic sulfates with potassium thioacetate or potassium thiocyanate followed by treatment with sodium methoxide lead to thiiranes.[23] Addition of organometallics to thioketones is an interesting route but low availability and inherent instability of thiocarbonyls have deterred this method from further development.[1] On the other hand, the synthesis of optically active alkyl substituted thiiranes with an enantiomeric excess ranging from 19% to 36% has already been published.[3–6]

Our previous studies on benzothiazole derivatives as versatile synthetic intermediates[24] led us to a simple synthesis of racemic thiiranes in high yield (Scheme 1)[25–28] by reduction to the corresponding alcohols (and subsequent transformation) of 1-(benzothiazol-2-ylsulfanyl)-2-alkanones **1**, which in turn were synthesized in 60–90% yield by reacting sodium (or potassium) benzothiazol-2-thiolate with the corresponding bromoketones (Table 1). Among these, 1-bromo-2-hexanone, 1-bromo-2-octanone, and 1-bromo-2-dodecanone, not commercially available, were prepared by bromination of the epoxide precursors (1,2-epoxyhexane, 1,2-epoxyoctane or 1,2-epoxydodecane, respectively), in CCl_4 under radical conditions,[29] affording the bromoketone (40–60% yield) and the bromohydrins, the latter possibly formed by interaction of the epoxide with hydrobromic acid produced during the reaction.



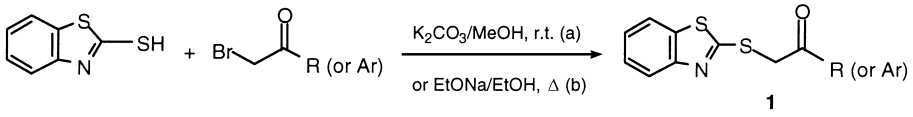
1 **2**

Scheme 1.

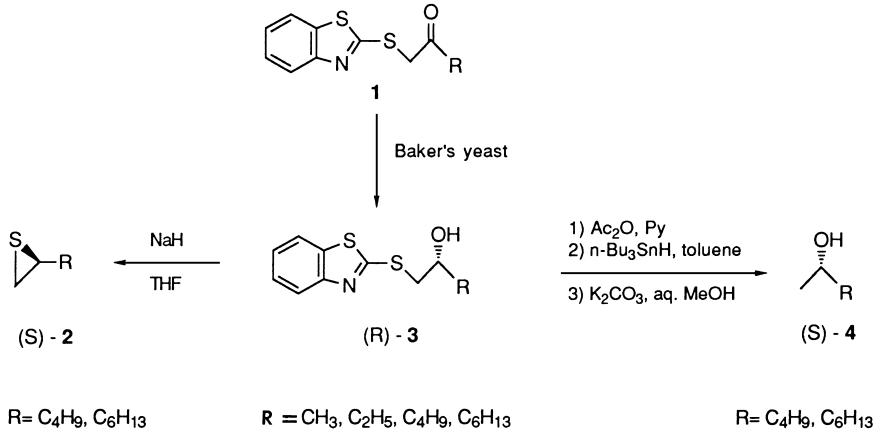
As for the reduction of the carbonyl function of **1**, baker's yeast-induced enantioselective reduction has now been investigated. It is known that baker's yeast can mediate the reduction of a wide variety of carbonyl compounds ranging from simple aldehydes and ketones to very complicated molecules such as steroids.[30,31] Though in some cases baker's yeast-induced asymmetric reduction of ketones gives alcohols with low enantiomeric excess (e.g. *ee*=23% starting from ethyl *n*-propyl ketone) in others, it proceeds with fair to high stereoselectivity. For instance, yeast-mediated stereoselective reduction of methyl and phenyl ketones (methyl ethyl ketone, methyl *n*-propyl ketone, methyl *n*-butyl ketone, methyl *t*-butyl ketone, acetophenone, valerophenone, etc.) has been accomplished by fermenting yeast affording alcohols with *ee*s ranging between 61% and 90%.[32] Baker's yeast-induced asymmetric reduction of some α-ketosulfides (1-phenylthio- and 1-benzylthio-2-alkanones) has also been reported,[33,34] but in this case, only the methyl derivatives showed any stereoselectivity. Thus, as is generally known, stereoselectivity is not predictable in advance in all cases, depending on various factors. Among these, an important role is exerted by the bulk (and nature) of the groups linked to the carbonyl. So, in this context, it seemed worth investigating the behaviour towards the same carbonyl function biotransformation of α-ketosulfides **1**, in which a new group (benzothiazol-2-ylsulfanylmethyl) having quite different features from the previously tested alkyl and aryl groups is present.

Thus, here we report our results on the preparation and baker's yeast-mediated stereoselective reduction of ketones **1** into the corresponding optically active β-hydroxysulfides **3**. In addition, the conversion of the latter into both optically active thiiranes and 2-alkanols is also described (Scheme 2).

Table 1
Yields of 1-(benzothiazol-2-ylsulfanyl)-2-alkanones isolated from the reaction of benzothiazol-2-thiolate and 1-bromo-2-ketones



R (or Ar)	Route (a) or (b)	Reaction time (h)	Yields(%)
CH_3 (**1a**)	(b)	1	90
C_2H_5 (**1b**)	(a)	24	73
n-C_4H_9 (**1c**)	(a)	24	81
n-C_6H_{13} (**1d**)	(a)	24	78
n-$C_{10}H_{21}$ (**1e**)	(a)	24	60
C_6H_5 (**1f**)	(b)	1	85



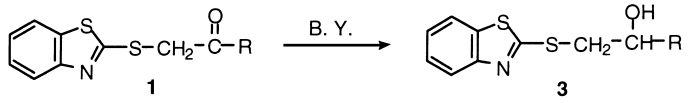
Scheme 2.

2. Results and discussion

Baker's yeast-catalyzed reduction of 1-(benzothiazol-2-ylsulfanyl)-2-alkanones **1a–f** was conducted in a variety of conditions to optimize the medium and the temperature, parameters that affect both the chemical yield and enantiomeric excess. So, the reduction was carried out by using several different procedures (A–G: see Experimental and footnote of Table 2).

From a careful analysis of the data obtained under the experimental conditions used it emerges that, for each substrate, the results [both different reaction times and different enantiomeric excesses (Table 2)] are

Table 2
Reduction of α-ketosulfides **1** by baker's yeast



1 **3**

			Alcohols 3	
R	**Procedure**[a]	**Reaction time**	**Yield %**[b]	**ee %**[c]
CH_3 (**1a**)	B	3 h	91	>99
"	A	23 h	80	83
C_2H_5 (**1b**)	A	5 days	74	68
"	B	"	89	74
"	C	"	89	64
"	D	6 days	79	67
n-C_4H_9 (**1c**)	A	10 days	78	81
"	B	4 days	74	70
"	C	"	56	86
"	E	3 days	72	84
"	D	"	80	>99
n-C_6H_{13} (**1d**)	D	6 days	80	91
"	E	7 days	72	72
"	F	8 days	80	87
"	G	"	80	91
n-$C_{10}H_{21}$ (**1e**), C_6H_5 (**1f**)		no reaction after 25 days		

a) Detailed description of the Procedure A, B, C, D, E, F and G is reported in the Experimental section.
b) The yields refer to the product isolated by flash chromatography.
c) Enantiomeric excesses were determined via HPLC (isocratic, flow rate= 1.0 ml/min, mobile phase: hexane/i-PrOH 98/2).

dependent upon the medium used to perform the reduction, and addition of a small amount of co-solvent (ca. 10%) such as ethanol or THF does not determine a remarkable change of the results. No effect on the enantioselectivity was observed by changing the temperature in the range 20–37°C.

The yeast-catalyzed reduction proceeded cleanly, usually giving either the alcohols (*R*)-**3** or a mixture of the desired alcohols **3** and unreduced starting material **1**. The crude products were routinely purified by column chromatography and then fully characterized. The enantiomeric excess of such chiral alcohols was determined via HPLC by using a chiral column (Chiralcel OD from Daicel).

The observed enantioselectivity was generally high, ranging between 64% and >99% (see Table 2).

In particular, the reduction of 1-(benzothiazol-2-ylsulfanyl)-propan-2-one **1a** and 1-(benzothiazol-2-ylsulfanyl)-hexan-2-one **1c** provided the corresponding chiral alcohols with *ee* >99%. 1-(Benzothiazol-2-ylsulfanyl)-butan-2-one **1b** and 1-(benzothiazol-2-ylsulfanyl)-octan-2-one **1d** gave alcohols with *ee*=74% and 91%, respectively. No reaction at all was observed instead for the less water-soluble substrates **1e** (R=$C_{10}H_{21}$) and **1f** (Ar=C_6H_5), even if they were incubated longer than **1a**–**d**, possibly because of both poor solubility and cell permeation, as well as for steric and (substrate **1f**) electronic effects.

Extension to a gram scale for **1c**–**d**, did not change the extent of conversion nor the enantiomeric excess compared to the reactions carried out on a smaller scale.

As for the assignment of the absolute configurations of **3**, it has been demonstrated to be *R* in the

cases of alkanols **3c** and **3d**. This was established by comparison of the specific rotations of the simple 2-alkanols obtained by them (2-hexanol **4c** and 2-octanol **4d**, respectively), with those of authentic samples commercially available [(*S*)-(+)-2-hexanol and (*S*)-(+)-2-octanol].[35–38] Thus, at least with reference to ketosulfides **1c** and **1d**, the stereochemical course during the baker's yeast-induced asymmetric reduction corresponds to a preferential hydrogen transfer on the *Si*-face of the prochiral ketone.

In the case of other previously examined α-ketosulfides (1-phenylthio- and 1-benzylthio-2-alkanones),[33,34] *S*-stereoselectivity (e.g. hydrogen attack on the *Re*-face) was instead observed for the methyl ketone, and no stereoselectivity at all was obtained in the case of a ketone with a larger alkyl group (C_5H_{11}), e.g. similar to those present in **1c** and **1d**.

On the other hand, the behaviour of 1-phenylthio- and 1-benzylthio-2-alkanones is in good agreement with the commonly accepted rationale[33,34] concerning the conditions for the stereoselectivity in the reductions of prochiral ketones by baker's yeast and based on the difference in steric requirements of the two groups attached to the carbonyl function as the important factor. Accordingly, when such a difference decreases, selectivity should in fact be reduced (or suppressed) correspondingly, as actually observed for 1-phenylthio- and 1-benzylthio-2-heptanone. In light of the same explanation, the behaviour observed by us for ketones **1c** and **1d** seems anomalous. In fact, in spite of a steric situation presumably not much different from 1-phenylthio- and 1-benzylthio-2-heptanone, selectivity not only is not suppressed, but, on the contrary, is high. Our results could therefore suggest that different factors can perhaps also be involved (e.g. some specific interaction between the benzothiazolyl moiety and the active site of an enzyme).

However, apart from the considerations concerning the more general question of the mechanism of enzyme action, our results seem appreciably interesting particularly from a synthetic point of view. In fact, the presence of the benzothiazol-2-yl moiety in the place of the previously tested phenyl or benzyl group in the α-ketosulfides allows the stereoselective reduction with high *ee*s not only of methyl ketones, but also of several more complex homologues.

This result is still more interesting when considering that the obtained optically active β-hydroxysulfides **3** are in turn, as mentioned above, further convertible into other important chiral products, some of which (e.g thiiranes) are obtainable just because of the presence, once again, of the benzothiazol-2-yl moiety.[1]

So, for instance, compounds (*R*)-**3c** and (*R*)-**3d**, previously converted into the corresponding acetates (quantitative yields), are easily transformed into (*S*)-**4c** and (*S*)-**4d** by reaction with tri-*n*-butyltin hydride in toluene under reflux and then with K_2CO_3 in MeOH–H_2O. Besides, (*R*)-**3c** and (*R*)-**3d** are allowed to react with NaH in THF at room temperature affording thiiranes (*S*)-**2c** and (*S*)-**2d** (Scheme 2 and Table 3).

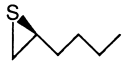
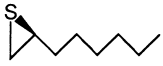
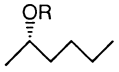
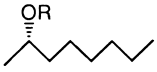
In all cases, the enantiomeric excesses for (*S*)-**4c**–**d**[35,38] and (*S*)-**2c**–**d**[37,38] did not change, compared to the starting alkanols (*R*)-**3c**–**d** (Scheme 2 and Table 3).

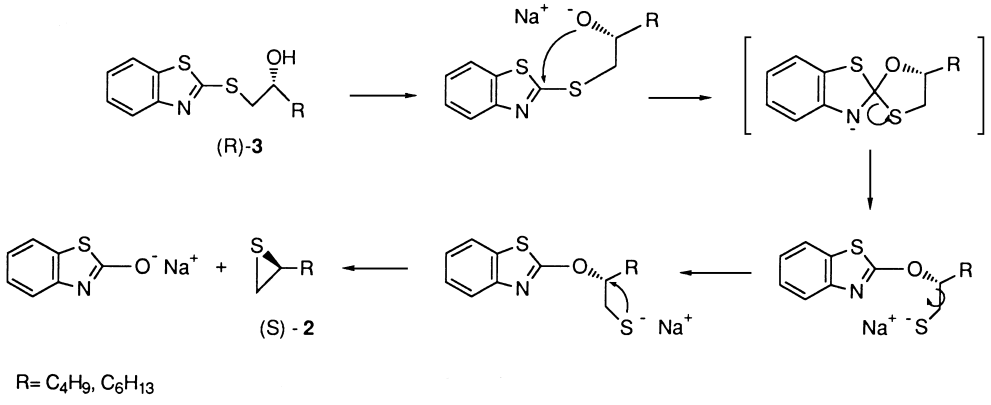
On the other hand, the absolute *S*-configuration of alcohols **4c** and **4d** was established, as described above, by direct comparison of optical rotations with those of the commercially available (*S*)-(+)-hexanol and (*S*)-(+)-octanol. From this, not only *R*-configuration of alkanols precursor **3c** and **3d**, but also, by considering that conversion of **3** into **2** occurs purely by inversion of configuration at the stereocentre,[1] *S*-configuration of both thiiranes **2c** and **2d** was finally deduced (Scheme 3).

3. Conclusion

The baker's yeast-induced asymmetric reduction of 1-(benzothiazol-2-ylsulfanyl)-2-alkanones was found to be a useful method for the preparation of the corresponding optically active β-hydroxysulfides.

Table 3
Enantiomeric excesses and yields of thiiranes **2** and alcohols **4**, obtained by treating alcohols **3** with NaH or tri-*n*-butyltin hydride and then with K_2CO_3

Product		Yield (%)	ee (%)
	(S)-**2c**	64	99
	(S)-**2d**	71	91
	R=$COCH_3$	72	99
	R=H, **4c**	80	"
	R=$COCH_3$	80	91
	R=H, **4d**	85	"



Scheme 3.

This transformation showed high selectivities with ketones bearing a small or medium-size alkyl group (C_1 to C_6), giving in these cases satisfactory enantiomeric excesses (64% to >99%; depending on the substrate features and the reaction medium). In contrast, ketones with a longer alkyl chain (C_{10}) or a phenyl group did not react at all, possibly due, however, to both lower water-solubility and cell permeation, besides electronic and/or steric effects. No change in enantiomeric excess was observed by converting the reduced products **3** into thiiranes **2** and 2-alkanols **4**.

Thus, in a large number of cases the present method not only constitutes a convenient way for the asymmetric reduction of the investigated ketosulfides into the corresponding alcohols but also provides a direct route to chiral thiiranes, as well as another efficient way to simple optically active 2-alkanols, which in turn are both valuable synthetic intermediates. In this context, new optically active compounds were also obtained and their absolute configuration established.

Further studies aimed at verifying the extension of this methodology to the asymmetric reduction of other not previously studied ketosulfides are in progress, in order to better define the behaviour of such systems towards the baker's yeast-induced asymmetric reduction of the carbonyl function, as well as to

synthesize new C_3 synthons containing other different groups. Such C_3 synthons will then be further elaborated to already existing biological active compounds or to new ones.

4. Experimental

4.1. General methods

Melting points taken on an Electrothermal apparatus were uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian EM 390 or XL 200 spectrometer and chemical shifts were reported in parts per million (δ) from internal Me_4Si. Absolute values of the coupling constant were reported. IR spectra were recorded on a Perkin–Elmer 681 spectrometer. GC analyses were performed by using an HP1 column (methyl silicone gum; 5 m×0.53 mm×2.65 μm film thickness) on an HP 5890 model, series II. HPLC analyses for the determination of enantiomeric excesses were carried out using a Daicel Chiralcel OD column (tris-3,5-dimethylphenylcarbamate, derivatized cellulose film) on an HP series 1050 instrument. Optical rotations were measured on a Perkin–Elmer digital polarimeter, model 241 MC. Thin-layer chromatography (TLC) was performed on silica gel sheets with a fluorescent indicator (Statocrom SIF, Carlo Erba), the spots on the TLC were observed under ultraviolet light or were visualized with I_2 vapour. Flash chromatography was conducted using silica gel with an average particle size of 60 μm, a particle size distribution of 40–63 μm and 230–400 ASTM; GC–MS analyses were performed on an HP 5995C model and microanalyses on an elemental analyzer 1106 — Carlo Erba instrument.

4.2. Materials

Solvents used were commercial grade. All other chemicals were further purified by distillation or crystallization prior to use.

2-Bromoacetophenone, chloro-2-propanone, 1-bromo-2-butanone, 1,2-epoxyhexane, 1,2-epoxyoctane and 1,2-epoxydodecane were purchased from Aldrich Chemical Co. 1-Bromo-2-hexanone, 1-bromo-2-octanone and 1-bromo-2-dodecanone were not commercially available. They were prepared by the action of bromine on the epoxide precursors (1,2-epoxyhexane, 1,2-epoxyoctane or 1,2-epoxydodecane, respectively).[29]

4.3. Procedure for the synthesis of 1-bromo-2-hexanone (1-bromo-2-octanone or 1-bromo-2-dodecanone, respectively)

To a solution of 1,2-epoxyhexane (1,2-epoxyoctane or 1,2-epoxydodecane) (10 g, 0.10 mol in 50 ml of CCl_4), a solution of Br_2 (7.9 g, 0.05 mol) in 10 ml of CCl_4 was added at room temperature as follows: a few drops of the bromine were added, obtaining a red-brownish reaction mixture that was stirred at room temperature until it decolorized. Then, the bromine solution was slowly added. The reaction mixture was stirred until all the bromine disappeared (the red coloured mixture became colourless) and the epoxide was completely converted (6 h) into the two regioisomeric bromohydrins and bromoketone in the ratio 30:30:40 (both GC and GC–MS analysis). During the whole reaction time the mixture was irradiated. After 6 h the solution was washed with 10% sodium hydrogen carbonate, dried over anhydrous sodium sulfate and the solvent evaporated to give a residue (a mixture of products containing also the bromoketone) that was used in the reaction with the benzothiazol-2-thiolate, without any further purification. The products were identified by their mass spectra.

4.4. 1-(Benzothiazol-2-ylsulfanyl)-2-alkanones: general procedure

A suspension of benzothiazole-2-thiol (0.056 mol) and potassium carbonate (0.028 mol) in 100 ml of methanol was stirred at room temperature for 30 min. Then, the crude bromoketone (0.056 mol in 70 ml of methanol) was added. The reaction mixture was stirred at room temperature for a further 24 h, then cooled at 0°C and treated with cold water. [For compounds **1a** and **1f** the reaction was conducted by mixing an equimolar amount of benzothiazole-2-thiol (0.056 mol) and EtONa (0.056 mol, prepared in situ) in ethanol, then kept under reflux for one hour.] A yellow solid precipitated. The crude α-ketosulfides of benzothiazole-2-thiol were obtained by filtration. The product was separated from other impurities by flash chromatography [eluent, petroleum ether:ethyl ether (5:1)] and then recrystallized from methanol or as otherwise indicated. Yields of the ketosulfides ranged from between 60 and 90% (see Table 1). Melting points and other analytical data are reported below.

4.4.1. 1-(Benzothiazol-2-ylsulfanyl)-propan-2-one **1a**

Mp 64–65°C (ethanol) (lit.[39] 69°C, ethyl ether–pentane); IR (KBr): 3060, 2980, 2942, 1725, 1461, 1430, 1415, 1380, 1312, 1285, 1238, 1110, 1003, 760 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.86–7.71 (m, 2H, aromatic protons), 7.44–7.25 (m, 2H, aromatic protons), 4.24 (s, 2H, CH_2), 2.39 (s, 3H, CH_3); GC–MS (70 eV) m/z (rel. inten.) 223 (M^+, 37), 182 (16), 181 (100), 180 (69), 166 (11), 148 (60), 136 (37), 122 (13), 109 (12), 108 (30), 90 (10), 82 (11), 77 (10), 69 (23), 63(18), 45 (32), 43 (85), 42 (11). Anal. calcd for $C_{10}H_9NOS_2$: C, 53.81; H, 4.04; N, 6.28. Found: C, 53.89; H, 4.10; N, 6.24.

4.4.2. 1-(Benzothiazol-2-ylsulfanyl)-butan-2-one **1b**

Mp 88–90°C; IR (KBr): 3064, 2980, 2942, 1727, 1463, 1430, 1412, 1380, 1357, 1312, 1286, 1238, 1110, 1003, 761 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.84–7.71 (m, 2H, aromatic protons), 7.44–7.24 (m, 2H, aromatic protons), 4.23 (s, 2H, -CH_2-S-), 2.72 (q, J=7.3 Hz, 2H, -CO-CH_2-), 1.13 (t, J=7.3 Hz, 3H, CH_3); GC–MS (70 eV) m/z (rel. inten.) 237 (M^+, 32), 208 (29), 182 (13), 181 (100), 180 (38), 148 (35), 136 (21), 108 (18), 69 (11), 57 (49), 45 (16). Anal. calcd for $C_{11}H_{11}NOS_2$: C, 55.70; H, 4.64; N, 5.91. Found: C, 55.69; H, 4.65; N, 5.86.

4.4.3. 1-(Benzothiazol-2-ylsulfanyl)-hexan-2-one **1c**

Mp 74–75°C; IR (KBr): 3035, 2978, 2960, 2942, 2880, 1730, 1472, 1448, 1363, 1320, 1300, 1245, 1140, 1130, 1056, 1039, 1012, 762 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.85–7.71 (m, 2H, aromatic protons), 7.44–7.25 (m, 2H, aromatic protons), 4.26 (s, 2H, -CH_2-S-), 2.68 (t, J=7.3 Hz, -CO-CH_2-), 1.67–1.56 (m, 2H, CH_2), 1.43–1.24 (m, 2H, CH_2), 0.90 (t, J=7.2 Hz, 2H, CH_3); GC–MS (70 eV) m/z (rel. inten.) 265 (M^+, 9), 208 (14), 182 (14), 181 (100), 180 (20), 149 (19), 148 (30), 136 (20), 108 (21), 85 (33), 77 (10), 69 (15), 57 (94), 45 (22), 41 (51), 39 (17). Anal. calcd for $C_{13}H_{15}NOS_2$: C, 58.87; H, 5.66; N, 5.28. Found: C, 58.82; H, 5.70; N, 5.25.

4.4.4. 1-(Benzothiazol-2-ylsulfanyl)-octan-2-one **1d**

Mp 65–68°C; IR (KBr): 3078, 2970, 2940, 2965, 1728, 1470, 1440, 1365, 1320, 1240, 1138, 1085, 1010, 762 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.83–7.72 (m, 2H, aromatic protons), 7.42–7.26 (m, 2H, aromatic protons), 4.24 (s, 2H, -CH_2-S-), 2.67 (t, J=7.3 Hz, 2H, -CO-CH_2-), 1.68–1.58 (m, 2H, CH_2), 1.40–1.15 (m, 6H, -$(CH_2)_3$-), 0.85 (m, 3H, CH_3); GC–MS (70 eV) m/z (rel. inten.) 293 (M^+, 18), 208 (17), 182 (12), 181 (100), 180 (14), 148 (15), 136 (11), 108 (10), 43 (52), 41 (17). Anal. calcd for $C_{15}H_{19}NOS_2$: C, 61.43; H, 6.48; N, 4.78. Found: C, 61.49; H, 6.44; N, 4.75.

*4.4.5. 1-(Benzothiazol-2-ylsulfanyl)-dodecan-2-one **1e***

Mp 58–61°C; IR (KBr): 3045, 2940, 2910, 2840, 1718, 1472, 1465, 1449, 1421, 1353, 1308, 1235, 998, 750 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.83–7.72 (m, 2H, aromatic protons), 7.42–7.24 (m, 2H, aromatic protons), 4.24 (s, 2H, -CH_2-S-), 2.66 (t, J=7.3 Hz, 2H, -CO-CH_2-), 1.90–1.70 (m, 2H, CH_2), 1.70–1.57 (m, 2H, CH_2), 1.38–1.13 (m, 12H, -$(CH_2)_6$-), 0.93–0.78 (m, 3H, CH_3); GC–MS (70 eV) m/z (rel. inten.) 349 (M^+, 18), 208 (17), 183 (10), 182 (13), 181 (100), 149 (30), 148 (12), 57 (12), 43 (22), 41 (16). Anal. calcd for $C_{19}H_{27}NOS_2$: C, 65.33; H, 7.74; N, 4.01. Found: C, 65.40; H, 7.75; N, 3.99.

*4.4.6. 2-(Benzothiazol-2-ylsulfanyl)-1-phenyl-ethanone **1f***

Mp 110–112°C; IR (CCl_4): 3035, 2958, 2900, 2840, 1680, 1590, 1450, 1438, 1419, 1260, 1182, 1001, 675 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 8.11–7.30 (m, 9H, aromatic protons), 4.98 (s, 2H, CH_2); GC–MS (70 eV) m/z (rel. inten.) 285 (M^+, 50), 253 (17), 252 (17), 225 (11), 180 (36), 105 (100), 77 (49), 51 (14), 45 (11). Anal. calcd for $C_{15}H_{11}NOS_2$: C, 63.16; H, 3.86; N, 4.91. Found: C, 63.20; H, 4.00; N, 4.86.

4.5. Reduction of 1-(benzothiazol-2-ylsulfanyl)-2-alkanones by $NaBH_4$/MeOH: general procedure

To a mixture of ketosulfides (4.2 mmol) in methyl alcohol (50 ml) kept in an ice-bath was added $NaBH_4$ (5 mmol). The reaction mixture was stirred at 0°C for 2 h. Then, the methyl alcohol was evaporated in vacuo. The residue was treated with 30 ml of H_2O and extracted three times with EtOAc (30 ml). The extracts were dried over Na_2SO_4 and the solvent evaporated. The products were obtained in quantitative yields.

These racemic alcohols were prepared for two main reasons, firstly to compare the analytical data of the corresponding products derived from the reduction of the ketosulfides performed in the presence of the baker's yeast, and secondly to set the conditions for the HPLC analysis to determine the enantiomeric excesses of the optically active alcohols **3**.

The HPLC retention time (t_R) and the separation factor (α) found for the (±)-alcohols **3** is shown below:

R	CH_3 (**3a**)	C_2H_5 (**3b**)	C_4H_9 (**3c**)	C_6H_{13} (**3d**)	$C_{10}H_{21}$ (**3e**)	C_6H_5 (**3f**)
t_R (±)	16.30/19.87	27.97/31.30	25.26/29.76	36.76/42.14	27.24/32.79	66.43/74.38
α	1.22	1.13	1.18	1.15	1.20	1.12

The HPLC analyses were executed in an isocratic manner, flow rate=1 ml/min, sparge=25 ml/min, mobile phase, hexane:*i*-PrOH (98:2).

4.6. Baker's yeast-mediated reduction of 1-(benzothiazole-2-ylsulphanyl)-2-alkanones

A typical procedure for the reduction of **1** is described below (Procedure A).

Fresh Golievit baker's yeast (140 g) was dispersed to give a smooth paste in tap water (1.4 l). Glucose (140 g) was added to the heterogeneous mixture which was stirred at 37°C and 250 rpm for 30 min. Then, ketosulfides **1** (1 g) were slowly added. The reaction was followed by TLC and stopped at the indicated time (see Table 2). The mixture was saturated with sodium chloride and centrifuged; the liquid phase was extracted with EtOAc several times. The combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the alcohol **3** was purified or separated from the remaining substrate **1** by flash chromatography on SiO_2 [eluent, petroleum ether:EtOAc (14:1)].

The salt:substrate molar ratio was 1:1 when the reaction was carried out in the presence of a mineral supplement: procedures B, C, D, E, F and G.

Procedure B; the same as procedure A with $MgSO_4$. Procedure C; the same as procedure A with $ZnSO_4$. Procedure D; ketosulfides **1** (1 g), distilled water (250 ml), yeast (16 g), sucrose (4 g). Procedure E; the same as procedure D with KH_2PO_4, $MgSO_4$ and $CaCO_3$. Procedure F; the same as procedure D with $MgSO_4$. Procedure G; the same as procedure D with $ZnSO_4$. The workup and product isolation in the reaction performed following procedures B, C, D, E, F and G were carried out as described above for procedure A.

The same amount of baker's yeast and medium were added every two days for reactions with an incubation time longer than two days.

4.6.1. (+)-1-(Benzothiazol-2-ylsulfanyl)-propan-2-ol ***3a***

($[\alpha]_D^{20}$=+15.1, c=1 in $CHCl_3$, *ee*=99%); oil; IR (neat): 3650–3120, 3083, 2992, 2978, 2900, 1683, 1475, 1435, 1320, 1250, 1139, 1130, 1089, 1060, 1030, 1010, 765, 735 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.85–7.68 (m, 2H, aromatic protons), 7.46–7.25 (m, 2H, aromatic protons), 4.33–4.17 (m, 1H, -CH-), 3.80–3.58 (bs, 1H, OH: exchange with D_2O), 3.51 (dd, J=3.3 Hz and 14.3 Hz, 1H, -CH_2-S-), 3.35 (dd, J=6.9 Hz and 14.3 Hz, 1H, -CH_2-S-), 1.35 (d, J=6.3 Hz, 3H, CH_3); GC–MS (70 eV) m/z (rel. inten.) 225 (M^+, 11), 181 (44), 180 (21), 168 (19), 167 (100), 148 (54), 136 (18), 135 (11), 109 (11), 108 (23), 69 (18), 63 (11), 45 (41), 43 (13). Anal. calcd for $C_{10}H_{11}NOS_2$: C, 53.33; H, 4.89; N, 6.22. Found: C, 53.30; H, 4.65; N, 6.23.

4.6.2. (−)-1-(Benzothiazol-2-ylsulfanyl)-butan-2-ol ***3b***

($[\alpha]_D^{20}$=−15.5, c=1 in $CHCl_3$, *ee*=64%); oil; IR (neat): 3650–3120, 3085, 2990, 2980, 2900, 1685, 1470, 1438, 1320, 1250, 1138, 1129, 1089, 1060, 1030, 1010, 765, 735 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.84–7.67 (m, 2H, aromatic protons), 7.42–7.24 (m, 2H, aromatic protons), 4.30–3.98 (bs, 1H, OH: exchange with D_2O), 3.97–3.88 (m, 1H, -CH-), 3.51 (dd, J=2.8 Hz and 14.3 Hz, 1H, -CH_2-S-), 3.32 (dd, J=7.2 Hz and 14.3 Hz, 1H, -CH_2-S-), 1.74–1.58 (m, 2H, CH_2), 1.00 (t, J=7.4 Hz, 3H, CH_3); GC–MS (70 eV) m/z (rel. inten.) 239 (M^+, 7), 210 (30), 181 (46), 180 (20), 169 (10), 168 (27), 167 (100), 148 (53), 136 (17), 135 (11), 109 (11), 108 (24), 59 (12), 45 (21), 43 (11). Anal. calcd for $C_{11}H_{13}NOS_2$: C, 55.23; H, 5.44; N, 5.86. Found: C, 55.15; H, 5.38; N, 5.88.

*4.6.3. (*R*)-(−)-1-(Benzothiazol-2-ylsulfanyl)-hexan-2-ol* ***3c***

($[\alpha]_D^{20}$=−28.1, c=1 in $CHCl_3$, *ee*=99%); mp 28–30°C; IR (neat): 3700–3110, 3081, 2982, 2951, 2880, 1672, 1470, 1445, 1381, 1324, 1250, 1138, 1090, 1058, 1030, 1010, 765 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.84–7.69 (m, 2H, aromatic protons), 7.42–7.25 (m, 2H, aromatic protons), 4.40–4.10 (bs, 1H, OH: exchange with D_2O), 4.05–3.98 (m, 1H, -CH-), 3.53 (dd, J=3.1 Hz and 14.3 Hz, 1H, -CH_2-S-), 3.31 (dd, J=7.2 Hz and 14.3 Hz, 1H, -CH_2-S-), 1.70–1.55 (m, 2H, CH-*CH_2*-), 1.42–1.26 (m, 4H, -$(CH_2)_2$-), 0.90 (t, J=7.1 Hz, 3H, CH_3); GC–MS (70 eV) m/z (rel. inten.) 267 (M^+, 7), 210 (33), 181 (60), 180 (16), 169 (11), 168 (34), 167 (100), 148 (46), 136 (12), 108 (14), 69 (12), 45 (11), 41 (19). Anal. calcd for $C_{13}H_{17}NOS_2$: C, 58.43; H, 6.37; N, 5.24. Found: C, 58.40; H, 6.65; N, 5.23.

*4.6.4. (*R*)-(−)-1-(Benzothiazol-2-ylsulfanyl)-octan-2-ol* ***3d***

($[\alpha]_D^{20}$=−8.3, c=1 in $CHCl_3$, *ee*=91%); oil; IR (neat): 3700–3110, 3080, 2980, 2950, 2878, 1670, 1470, 1447, 1380, 1320, 1250, 1138, 1090, 1058, 1030, 1010, 765 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.86–7.67 (m, 2H, aromatic protons), 7.43–7.24 (m, 2H, aromatic protons), 4.50–4.20 (bs, 1H, OH: exchange with D_2O), 4.08–3.97 (m, 1H, CH), 3.52 (dd, J=2.8 Hz and 14.3 Hz, 1H, -CH_2-S-), 3.31 (dd, J=7.2 Hz and 14.3 Hz, 1H, -CH_2-S-), 1.70–1.15 (m, 10H, -$(CH_2)_5$-), 0.85 (m, 3H, CH_3); GC–MS (70 eV) m/z (rel. inten.) 295 (M^+, 4), 210 (33), 181 (65), 180 (16), 169 (12), 168 (41), 167 (100), 148 (38), 136 (12), 108

(13), 69 (10), 55 (18), 45 (11), 43 (28), 49 (31). Anal. calcd for $C_{15}H_{21}NOS_2$: C, 61.02; H, 7.12; N, 4.75. Found: C, 61.01; H, 7.09; N, 4.63.

*4.6.5. 1-(Benzothiazol-2-ylsulfanyl)-dodecan-2-ol **3e***

Oil; IR (neat): 3700–3110, 3080, 2980, 2950, 2878, 1670, 1470, 1447, 1380, 1320, 1250, 1138, 1090, 1058, 1030, 1010, 765 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.80–7.68 (m, 2H, aromatic protons), 7.60–7.19 (m, 2H, aromatic protons), 4.40–4.20 (bs, 1H, OH: exchange with D_2O), 4.15–3.90 (m, 1H, CH), 3.51 (dd, J=2.9 Hz and 14.3 Hz, 1H, -CH_2-S-), 3.32 (dd, J=7.2 Hz and 14.3 Hz, 1H, -CH_2-S-), 1.80–1.10 (m, 18H, -$(CH_2)_9$-), 0.89 (m, 3H, CH_3); GC–MS (70 eV) m/z (rel. inten.) 351 (M^+, 4), 210 (33), 181 (67), 180 (11), 169 (13), 168 (49), 167 (100), 148 (25), 55 (13), 43 (29), 41 (27). Anal. calcd for $C_{19}H_{29}NOS_2$: C, 64.96; H, 8.26; N, 3.99. Found: C, 64.89; H, 8.65; N, 4.01.

*4.6.6. 2-(Benzothiazol-2-ylsulfanyl)-1-phenylethanol **3f***

Oil; IR (CCl_4): 3605, 3580–3120, 3060, 3020, 2950, 2920, 1670, 1460, 1451, 1425, 1306, 1257, 1136, 1078, 1050, 1016, 1022, 755 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.96–7.70 (m, 2H, aromatic protons), 7.48–7.25 (m, 7H, aromatic protons), 5.19 (dd, J=7.9 Hz and 3.0 Hz, 1H, -C*H*OH-), 3.72 (dd, J=14.5 Hz and 3.0 Hz, 1H, -CH_2-S-), 3.45 (dd, J=14.5 Hz and 7.9 Hz, 1H, -CH_2-S-), 3.40–2.50 (bs, 1H, OH: exchange with D_2O); GC–MS (70 eV) m/z (rel. inten.) 287 (M^+, 3), 183 (10), 182 (12), 181 (100), 180 (17), 168 (17), 167 (38), 148 (40), 136 (12), 108 (12), 107 (12), 79 (25), 77 (29), 51 (11). Anal. calcd for $C_{15}H_{13}NOS_2$: C, 62.72; H, 4.53; N, 4.87. Found: C, 62.70; H, 4.65; N, 4.83.

*4.7. 1-(Benzothiazol-2-ylsulfanyl)-2-acetoxy derivatives of **3**: general procedure*

A solution of alcohol **5** (3 mmol) in pyridine (8 ml) and Ac_2O (6 ml) was stirred at room temperature until TLC analysis showed complete conversion of **5** into the acetoxyalkane (2 h). The reaction was quenched with H_2O, diluted with EtOAc (10 ml) and then washed with 5% HCl (2×10 ml). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The product was isolated in quantitative yield as an orange yellowish oil.

*4.7.1. (*R*)-(−)-1-(Benzothiazol-2-ylsulfanyl)-2-acetoxyhexane*

($[\alpha]_D^{20}$=−39.7, c=1 in $CHCl_3$, *ee*=99%); ^1H NMR ($CDCl_3$, δ): 7.87–7.72 (m, 2H, aromatic protons), 7.45–7.25 (m, 2H, aromatic protons), 5.26–5.14 (m, 1H, -CHOAc), 3.78 (dd, J=4.3 Hz and 13.8 Hz, 1H, -CH_2-S-), 3.42 (dd, J=6.9 Hz and 13.8 Hz, 1H, -CH_2-S-), 2.00 (s, 3H, -$OCOCH_3$), 1.89–1.62 (m, 2H, CH-*CH_2*-), 1.42–1.27 (m, 4H, -$(CH_2)_2$-), 0.95–0.85 (m, 3H, CH_3); GC–MS (70 eV) m/z (rel. inten.) 309 (M^+, 18), 249 (13), 216 (21), 193 (13), 192 (90), 181 (17), 180 (11), 169 (11), 168 (28), 167 (100), 166 (10), 148 (14), 136 (11), 108 (13), 55 (11), 43 (67), 41 (9). Anal. calcd for $C_{15}H_{19}NO_2S_2$: C, 58.25; H, 6.15; N, 4.53. Found: C, 58.30; H, 6.25; N, 4.23.

*4.7.2. (*R*)-(−)-1-(Benzothiazol-2-ylsulfanyl)-2-acetoxyoctane*

($[\alpha]_D^{20}$=−11.2, c=1 in $CHCl_3$, *ee*=91%); ^1H NMR ($CDCl_3$, δ): 7.86–7.70 (m, 2H, aromatic protons), 7.43–7.22 (m, 2H, aromatic protons), 5.28–5.13 (m, 1H, -CHOAc), 3.76 (dd, J=4.3 Hz, 13.8 Hz, 1H, -CH_2-S-), 3.42 (dd, J=6.9 Hz, 13.8 Hz, 1H, -CH_2-S-), 2.00 (s, 3H, -$OCOCH_3$), 1.83–1.63 (m, 2H, CH-*CH_2*-), 1.50–1.25 (m, 6H, -$(CH_2)_3$-), 1.00–0.85 (m, 3H, CH_3); GC–MS (70 eV) m/z (rel. inten.) 337 (M^+, 3), 192 (35), 168 (13), 167 (38), 69 (14), 55 (10), 43 (100), 41 (25). Anal. calcd for $C_{17}H_{23}NO_2S_2$: C, 60.53; H, 6.82; N, 4.15. Found: C, 60.25; H, 6.55; N, 4.13.

4.8. Synthesis of thiiranes: general procedure

The alcohol was dissolved in dry THF containing a stoichiometric amount of sodium hydride. The suspension was stirred at room temperature for 5 h. After evaporation of the solvent, the residue was washed with 5% aq. NaOH to remove 2-hydroxybenzothiazole, then with water and finally dried. The solvent was evaporated and the thiirane was obtained in almost pure form.

4.8.1. (S)-(+)-2-Butylthiirane **2c**

($[\alpha]_D^{20}$=+17.8, c=13 in hexane, *ee*=99%) (lit.[4,40,41] $[\alpha]_D^{25}$=−4.51, c=13.3 in hexane, *ee*=25%, *R*-configuration); IR (neat): 2998, 1445, 1372, 1264, 1105, 1030, 905, 715 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.95–2.80 (m, 1H, -CH-S-), 2.47 (d, J=6.0 Hz, 1H, -CH_2-S-), 2.13 (d, J=6.0 Hz, 1H, -CH_2-S-), 1.90–0.60 (m, 9H); GC–MS (70 eV) m/z (rel. inten.) 116 (M^+, 70), 115 (18), 87 (26), 83 (35), 82 (17), 75 (22), 74 (76), 73 (18), 69 (18), 67 (54), 60 (26), 59 (24), 55 (53), 47 (20), 45 (49), 42 (17), 41 (100), 39 (43). IR and ^1H NMR data were consistent with the reported values.[4]

4.8.2. (S)-(+)-2-Hexylthiirane **2d**

($[\alpha]_D^{20}$=+14.9, c=13 in hexane, *ee*=91%) (lit.[4,42] $[\alpha]_D^{25}$=−3.45, c=13.3 in hexane, *ee*=21%, *R*-configuration); IR (neat): 2995, 1445, 1370, 1265, 1107, 1030, 905, 715 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 2.70–3.16 (m, 1H, -CH-S-), 2.50 (d, J=6.0 Hz, 1H, -CH_2-S-), 2.17 (d, J=6.0 Hz, 1H, -CH_2-S-), 2.00–0.60 (m, 13H); GC–MS (70 eV) m/z (rel. inten.) 144 (M^+, 20), 115 (18), 110 (12), 101 (10), 97 (10), 87 (26), 81 (35), 74 (64), 73 (14), 69 (55), 68 (20), 67 (30), 60 (19), 59 (16), 55 (75), 54 (22), 47 (18), 45 (35), 43 (29), 42 (17), 41 (100), 39 (40). IR and ^1H NMR data were consistent with the reported values.[4]

4.9. Conversion of 1-(benzothiazol-2-ylsulfanyl)-2-acetoxyhexane and 1-(benzothiazol-2-ylsulfanyl)-2-acetoxyoctane into the corresponding acetoxyalkanes by tri-n-butyltin hydride

Bu_3SnH (378 mg, 1.3 mol) was added under a nitrogen atmosphere to a mixture containing 1-(benzothiazole-2-ylsulfanyl)-2-acetoxyhexane (200 mg, 0.65 mol), 2,2′-azobis(2-methylpropionitrile) (1%) in 3 ml anhydrous toluene, using a nitrogen-flushed three necked flask equipped with a magnetic stirrer, nitrogen inlet and reflux condenser. The reaction was kept at 110°C overnight, then the toluene was distilled and the residue chromatographed on silica gel [eluent, petroleum ether:ethyl acetate (14:1)]. The product was obtained in 72% yield (67 mg).

(*S*)-(+)-2-Acetoxyhexane and (*S*)-(+)-2-acetoxyoctane were prepared by reacting the commercially available 2-hexanol and 2-octanol, respectively, and acetic anhydride in pyridine for direct comparison of the sign and specific rotation of the products isolated from the reaction of the 1-(benzothiazol-2-ylsulfanyl)-2-acetoxyalkanes and Bu_3SnH. In addition, (*S*)-(+)-2-acetoxyhexane and (*S*)-(+)-2-acetoxyoctane from the reaction of (*R*)-(−)-1-(benzothiazol-2-ylsulfanyl)-2-acetoxyhexane and (*R*)-(−)-1-(benzothiazol-2-ylsulfanyl)-2-acetoxyoctane were saponified to (*S*)-(+)-2-hexanol **4c** and (*S*)-(+)-2-octanol **4d** by treatment with 1.2 M K_2CO_3/MeOH–H_2O, room temperature 1 h, 80% and 85% yields, respectively.

4.9.1. (S)-(+)-Acetoxyhexane

($[\alpha]_D^{20}$=+4.8, c=1 in $CHCl_3$, *ee*=99%); ^1H NMR ($CDCl_3$, δ): 4.90–4.80 (m, 1H, -CHOAc-), 1.99 (s, 3H, CH_3CO-), 1.63–1.20 (m, 6H, -$(CH_2)_3$-), 1.16 (d, J=6.14 Hz, 3H, CH_3-CH-), 0.95 (m, 3H, CH_3-); GC–MS (70 eV) m/z (rel. inten.) 129 (M^+−15, 5), 113 (10), 112 (6), 87 (20), 70 (9), 57 (6), 56 (75), 55

(12), 43 (100), 41 (22). All the analytical data were consistent with the values obtained on the sample prepared from commercial (*S*)-(+)-2-hexanol.

4.9.2. (S)-(+)-2-Acetoxyoctane

($[\alpha]_D^{20}$=+5.1, c=1 in $CHCl_3$, *ee*=91%); ^{1}H NMR ($CDCl_3$, δ): 4.91–4.83 (m, 1H, -CHOAc-), 2.00 (s, 3H, CH_3CO-), 1.61–1.23 (m, 10H, -$(CH_2)_5$-), 1.19 (d, J=6.32 Hz, 3H, CH_3-CH-), 0.85 (m, 3H, CH_3-); GC–MS (70 eV) m/z (rel. inten.) 172 (M^+, 0.2), 112 (17), 87 (37), 70 (16), 58 (12), 57 (8), 56 (11), 55 (14), 43 (100), 41 (12). All the analytical data were consistent with the values obtained on the sample prepared from commercial (*S*)-(+)-2-octanol.

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