spectrum, calcd for $C_{14}H_{13}O_6F_3$ (M^+) 334.0664, found 334.0679. Anal. Calcd for $C_{14}H_{13}O_6F_3$: C, 50.31; H, 3.92. Found: C, 50.49; H, 3.75.

(2*R*,3*R*)-Methyl Trifluoroethyl Tartrate (15). A mixture of 14 (103 mg, 0.31 mmol) and 10% Pd-C (40.0 mg) in 1.5 mL of CF_3CH_2OH was thoroughly flushed with argon for 15 min. Then a balloon filled with H_2 was attached via a syringe needle to the top of the flask. The mixture was stirred for 12 h at room temperature, filtered through a plug of Celite, and rinsed with acetone. The solvents were removed in vacuo. The resulting liquid was filtered through silica gel using 1:1 EtOAc/hexane to give 70 mg (97% yield) of diol **15** a slightly yellow liquid. When stored in a -20 °C freezer it subsequently crystallized (low melting solid): R_f 0.22 (1:1 EtOAc/hexane); $[\alpha]^{25}_D$ -3.3° (*c* 7.5, CH_2Cl_2); ^{1}H NMR [$CDCl_3$, 300 MHz] δ 4.71-4.54 [m, 4 H], 3.89 [s, 3 H], 3.28 [d, J = 6.2 Hz, 1 H, OH], 3.23 [d, J = 8.2 Hz, 1 H, OH]; ^{13}C NMR [$CDCl_3$, 500 MHz] δ 176.56 [s], 170.12 [s], 122.50 [q], 72.04 [s], 71.94 [s], 61.37 [q], 53.21 [s]; IR (neat) 3610-3430 (br), 2980, 2960, 1765, 1750, 1440, 1410, 1235, 1170, 1120, 1090, 990, 975 cm^{-1}; high resolution mass spectrum, calcd for $C_7H_{10}O_6F_3$ (M^+ + 1) 247.0431, found 247.0440. Anal. Calcd for $C_7H_9O_6F_3$: C, 34.16; H, 3.69. Found: C, 34.43; H, 3.59.

Synthesis of 1,3,2-Dioxaborolane Derivatives 16 and 17. General. To a solution of **15** in anhydrous THF (0.5 mL) was added the boronic acid (1.0 equiv) as a solution in THF (0.5 mL). A small amount of $MgSO_4$ was added to the reaction mixture, which was subsequently stirred for 3 h. The mixture was then filtered and concentrated in vacuo. The products were stored under argon in a -20 °C freezer until the NMR analyses were performed.

Data for phenylboronate 16: ^{1}H NMR [$CDCl_3$, 300 MHz] δ 7.89 [d, J = 7.2 Hz, 2 H], 7.54-7.39 [m, 3 H], 5.20 and 5.08 [AB, J_{AB} = 5 .47 Hz, 2 H], 4.72-4.54 [m, 2 H], 3.87 [s, 3 H]; ^{11}B NMR ($CDCl_3$, 360 MHz] δ 32.0 (br), 29.2 (residual phenylboronic acid from hydrolysis of **16** in the NMR solvent).

Data for butylboronate 17: ^{1}H NMR [$CDCl_3$, 300 MHz; 23 °C] δ 4.98 and 4.87 [AB, J_{AB} = 5.2 Hz, 2 H], 4.67-4.53 [m, 2 H], 1.48-1.43 [m, 2 H], 1.37-1.32 [m, 2 H], 0.99 [t, J = 7.8 Hz, 2 H], 0.89 [t, J = 7.0 Hz, 3 H]; ^{1}H NMR (toluene-d_8, 500 MHz, 23 °C) δ 4.67 [AB, J_{AB} = 5.0 Hz, 1 H], 4.66 [AB, J_{AB} = 5.0 Hz, 1 H], 3.7-3.9 [m, 4 H], 3.20 [s, 3 H], 1.45-1.53 [m, 2 H], 1.25-1.4 [m, 4 H], 0.87 [t, J = 7 Hz, 3 H]; ^{13}C NMR ($CDCl_3$, 500 MHz) δ 169.46, 168.17, 120.22, 77.21, 76.95, 61.17 (q, due to ^{19}F splitting), 53.03, 29.67, 25.57, 25.09, 13.72; ^{11}B NMR ($CDCl_3$, 360 MHz) δ 35.7 (br), 32.9 (residual butylboronic acid from hydrolysis of **17** in the NMR solvent).

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Supplementary Material Available: X-ray crystallographic data and ORTEP drawings of benzylidene acetals **5-7** and ^{1}H NMR spectra of **12**, **16**, and **17** (19 pages). This material is contained in many 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.

Enantioselective Synthesis of (*S*)-2-Methyl-1-alkanols via Bakers' Yeast Mediated Reduction of α-Methyl-2-thiophenepropenals

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The bakers' yeast mediated enantioselective reductions of some α-methyl-5-(1-alkyl)-2-thiophenepropenals **3** are described. These furnished (*S*)-β-methyl-5-(1-alkyl)-2-thiophenepropanols **5** in good to high enantiomeric excesses (76-98% ee). An alternative approach to (*S*)-β-methyl-5-(1-alkyl)-2-thiophenepropanols **5d-f** (98% ee) is also described. Raney nickel reduction of their acetates, followed by hydrolysis, provided (*S*)-2-methyl-1-alkanols **2b-f** of unchanged optical purities.

The stereo-, chemo-, and regioselectivities of microbial systems have recently provided easy access to enantiomerically pure compounds for use in synthesis.[1] Bakers' yeast is a convenient reducing microbial system and has been used for the reduction of both carbon-oxygen and carbon-carbon double bonds.[2] Starting materials containing heterocycles has in some cases been used to improve selectivity of product formation[3] or as a means of masking a functional group.[4] In this context some of us recently participated in a study of the enantioselective bakers' yeast reduction of a carbon-carbon double bond in α-methyl-2-furanpropenal (**3a**) to give a high yield of (*S*)-β-methyl-2-furanpropanol (**5a**) in >99% ee where the furan ring served as a masked carboxyl group.[5]

Indeed, simple chiral methyl-branched compounds of high optical purities suitable as starting materials for syntheses are not readily available from the chiral pool. In connection with studies on the pheromone of pine sawflies, which are 3,7-dimethyl-2-pentadecyl esters, we required easy access to compounds of type **1** (* signifies a chiral center) as synthetic intermediates. Especially

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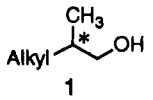

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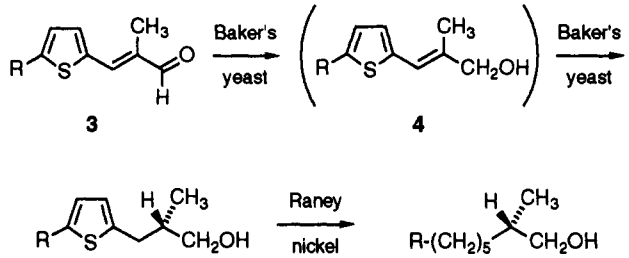
(*S*)-2-methyl-1-alkanols **2b–f** of high optical purities were needed.[6] Compounds of type **1** are widely used in synthesis, and many methods have recently been developed for their preparation, for example, asymmetric enolate alkylations,[6b,7] various bioorganic reactions, e.g., lipase-catalyzed,[8] and fermentations.[2,5,9] Previous work on bakers' yeast reduction of α- or β-substituted α,β-unsaturated aldehydes or alcohols[5,9] such as the reduction of the furan derivative **3a**,[5] mentioned above, suggested to us that an alternative route to nonracemic compounds of type **1** would be the enantioselective reduction of thiophenepropenals **3b–e** to give β-methyl-2-thiophenepropanols **5b–e** followed by Raney nickel (RaNi) reduction to furnish chiral, nonracemic 2-methyl-1-alkanols **2b–e**. Alternatively, the bifunctional nature of the chiral, nonracemic thiophenepropanol **5b** could be exploited in another synthesis of compounds of type **2**, namely via the introduction of an alkyl group in the free 5-position of the thiophene ring, followed by RaNi reduction. We shall now report the results of our study of these reaction sequences.



3 4 5 2

For compounds 2 - 6:
a: O instead of S, R = H
b: R = H
c: R = CH_3
d: R = C_2H_5
e: R = n-C_3H_7
f: R = n-C_4H_9

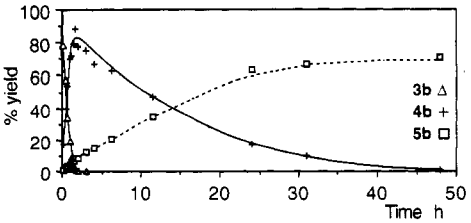
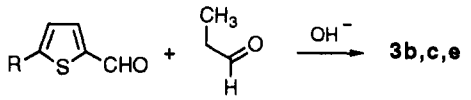


Figure 1. Reaction profile for a typical bakers' yeast mediated reduction of α-methyl-2-thiophenepropenal (**3b**).

It is well-known from previous studies that bakers' yeast will rapidly reduce substituted 3-aryl-2-propenals to the corresponding substituted 3-aryl-2-propen-1-ols. The 3-aryl-1-propanols are formed more slowly.[9b,c,f] A small amount of the propenal is always present during the fermentation. Experiments with deuterated 3-aryl-2-propen-1-ols indicate that they serve as a reservoir for the propenals and are continuously reoxidized to these, which are probably reduced to a 3-aryl-1-propanols via the 3-arylpropanals.[9b,c,f] If this hypothesis is correct the propenols are not true intermediates. Since the α,β-unsaturated aldehydes **3** are easily prepared we used these as starting materials rather than the equally suitable propenols **4**, thus avoiding an extra synthetic step.

The thiophenepropenals **3b,c,e** were prepared from the corresponding 2-thiophenecarboxaldehydes **6b,c,e** using



6b,c,e

a crossed aldol reaction with propanal, previously described only for the synthesis of **3b**.[10] The crystalline (*E*)-aldehydes **3b** and **3c** were highly pure with no indication of any (*Z*)-isomer present. The oily (*E*)-aldehyde **3e** might perhaps be contaminated by small amounts of the (*Z*)-form although no signs of that form were detected (NMR or GLC). The (*Z*)-form would probably yield the undesired (*R*)-propanol on bakers' yeast reduction.[9f] The aldehydes **6b** and **6c** were commercially available while 5-propyl-2-thiophenecarboxaldehyde (**6e**) was prepared via metalation of thiophene with butyllithium, followed by alkylation with 1-bromopropane (cf. ref 11). 2-Propylthiophene was then metalated and the product treated with DMF to furnish the desired aldehyde (cf. ref 12).

Initially, fermenting bakers' yeast at pH ≈6 (cf. ref 5b) was found to reduce α-methyl-2-thiophenepropenal (**3b**) very slowly, furnishing a mixture of β-methyl-2-thiophenepropenol (**4b**, prepared independently by borohydride reduction of compound **3b**) and (*S*)-β-methyl-2-thiophenepropanol (**5b**) with an isolated yield of the latter <30% after 10 days of fermentation in an open vessel.

Whereas anaerobic conditions completely inhibited the reaction (cf. ref 5b), we found that active aeration during the fermentation improved the yield of **5b** (≈40%) and shortened the reaction time (6 days). Since the presence of oxygen was crucial for obtaining good rates in this reaction, we passed oxygen through the reaction mixture. In this case the propenal **3b** was reduced, on a 1–6-g scale,

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within 2–3 days to give a 65% isolated yield of **5b**, and only minute amounts of the thiophenepropenol **4b** remained. The course of a typical reaction is depicted in Figure 1.

The (*S*)-configuration of **5b** was assigned based on conversion to compounds with known configuration (vide infra). The enantiomeric excesses (ee) of the thiophenepropanols **5** and other 2-methyl 1-alcohols were determined either by NMR spectrometry or by gas chromatography (GLC). Thus, the ee values were obtained either from the ^{1}H NMR spectra of the corresponding esters of (–)-methoxy(trifluoromethylphenyl)acetic acid [(–)-MTPA] as described by us for similar alcohols[5b,6a] (H-MTPA method) or from the ^{19}F NMR spectra of the esters of (+)- or (–)-MTPA (F-MTPA method). The alternative GLC analyses (amide method[13]) were performed on the amides formed from enantiomerically pure 1-phenylethylamine and the 2-methyl-substituted acids obtained from the alcohols **5** and other 2-methyl 1-alcohols on chromic acid oxidation, which is known to proceed without racemization in other cases.[13,14] Repeated analyses of amides formed from several chiral 2-methyl-substituted acids and enantiomerically pure (*R*)-(+)- or (*S*)-(–)-phenylethylamine gave the same results within ±0.2% ee. Both the NMR methods and the amide method generally gave reproducible and reliable results. However, the latter is probably the best, especially when the ee values are close to 100%. With **5b** the optical purity was found to be the same and ≈98% ee by both the NMR and GLC methods. The optical purity of the thiophenepropanol **5b** could be upgraded to ≥99.3% ee via recrystallization of its dinitrobenzoate **5bDNB** and subsequent alkaline hydrolysis.

As observed for the formation of the furan derivative **5a**,[5b] the optical purity of the corresponding fermentation product **5b** and its rate of formation were both pH-dependent (pH 4.5, 5, 5.7, 6.3, and 7 gave 93.7, 97.2, 97.5, 98.1, and 97.2% ee, respectively). The maximum reaction rate was reached at the same pH giving the highest ee, i.e., 6.3.

In order to obtain (*S*)-2-methylalkanols **2** of the highest possible optical purities from the (*S*)-β-methyl-2-thiophenepropanols **5**, these must be free of even trace impurities of the propenols **4**, since on RaNi reduction the latter would also yield 2-methylalkanols **2**, but in the undesired racemic forms. Product mixtures containing >2% **4b** in **5b** were neither separable by chromatography nor by distillation without an extensive loss in yield. However, it is well-known that allylic alcohols are easily oxidized to aldehydes by manganese dioxide whereas saturated alcohols are unaffected.[15] Thus, MnO_2 treatment of product mixtures of **5b** containing **4b** (>2%), led to selective oxidation of the latter to the aldehyde **3b** which was then easily separated by liquid chromatography leaving the pure (*S*)-propanol **5b**.

The two alkylated thiophenepropenals **3c** and **3e** were also subjected to the optimized fermentation conditions. The 5-methyl compound **5c** was isolated in 33% yield and 95% ee [F-MTPA method] after 3 days of fermentation (see Figure 2). An even lower yield (25%) and ee value [76% ee, F-MTPA method] were registered when the propylthiophenepropanol **5e** was obtained after 4 days of fermentation (Figure 2). Since both the yields and ee's were unsatisfactory, we sought for alternative methods for the preparation of **5c** and **5e**, which ultimately should furnish 2-methylalkanols **2c** and **2e**.

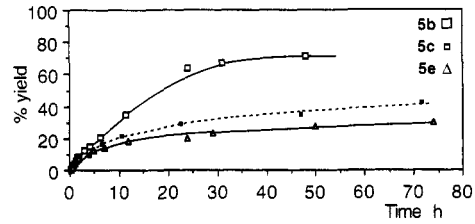
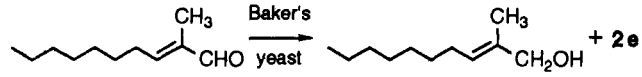


Figure 2. Rate of formation of (*S*)-β-methyl-2-thiophenepropenol (**5b**), (*S*)-β-methyl-5-methyl-2-thiophenepropanol (**5c**), and (*S*)-β-methyl-5-(1-propyl)-2-thiophenepropanol (**5e**) in the bakers' yeast mediated reduction under oxygen of the corresponding propenals **3b,c,e**.

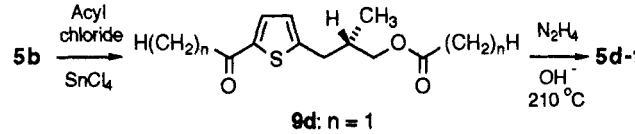
Initially we studied a more straightforward approach to alkanol **2e** than that described above, namely the fermentation of (*E*)-2-methyl-2-decenal **7**. This was obtained



7 **8**

via a crossed aldol reaction of octanol and propanal, which furnished a 25% yield of compound **7** after repeated fractional distillations. When this was subjected to bakers' yeast treatment, the 2-methyl-2-decenol **8** was first formed and then the 2-methyl-1-decanol **2e** slowly appeared. After three days a 1/1 mixture of **8**/**2e** had been formed. Workup furnished (*S*)-2-methyldecanol **2e** (34%, ≈95% ee, H-MTPA method). Neither the yield nor the enantiomeric excess obtained in this reaction were satisfactory. We therefore turned our attention to yet another approach leading to chiral long chain 2-methyl-1-alkanols **2**.

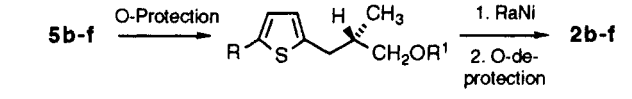
Friedel–Crafts acylation in the 5-position of 2-alkylthiophenes proceeds very efficiently (cf. ref 16). We therefore subjected the easily prepared fermentation product from above, (*S*)-β-methyl-2-thiophenepropanol **5b** (>98% ee) to Friedel–Crafts acylations with some acyl chlorides and tin tetrachloride, which furnished 90–94% yields of the keto esters **9**. As previously observed with



9d: n = 1
9e: n = 2
9f: n = 3

other acylthiophenes,[16] Huang–Minlon reductions of the keto esters **9d–f** gave the alkylated thiophenepropanols **5d–f** in good yields. The ee's of these products were the same as that of the starting material **5b** [F-MTPA method and amide method].

RaNi reductions under hydrogen of the chiral β-methyl-2-thiophenepropanols **5** produced the desired 2-methyl-1-alkanols **2**, unfortunately always accompanied by some racemization [**5** → **2**, **b**: 98 → 94, **c**: 95 → 88, and **d**: 76 → 71% ee (amide-, F-, and H-MTPA methods)].



5b - fR^1
R^1= DNB : 3,5-dinitrobenzoyl
R^1= TBDMS : *t*-butyldimethylsilyl
R^1= Ac : Acetyl
R^1= Pr : Propionyl

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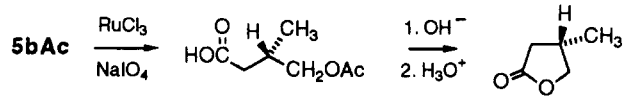
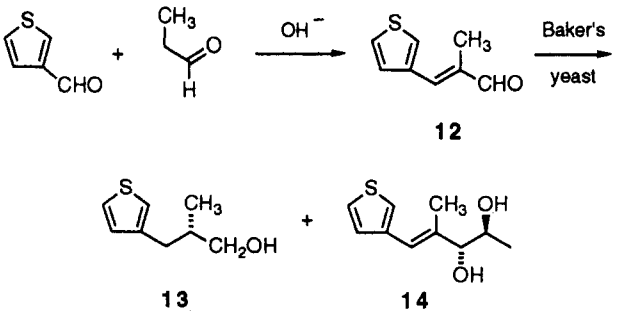
The losses in ee were not influenced by variation of the reaction temperature, hydrogen pressure, or the choice of solvent. Racemizations have previously been observed in similar RaNi and other transition metal catalyzed reductions.[17] With some transition metal catalysts, hydroxyl groups in the substrate are known to direct the hydrogenation of double bonds selectively, presumably via chelate formation.[18] Here, in analogy with other cases,[17] RaNi probably promoted a double-bond migration, which, helped by chelation to a certain extent, occurred toward the hydroxyl group in the molecules. A small but significant amount of an achiral allylic alcohol, a homologue of compound **8** (or an achiral enol), might have been formed transiently before final reduction to the racemic 2-methyl-1-alkanol **2** took place. In such case, protection of the hydroxyl group should prevent chelation and hence inhibit the double bond migration. Indeed, the *tert*-butyldimethylsilyl ether **5fTBDMS** and RaNi furnished **2f** with only 0.8% loss of optical purity after hydrolysis. Ultimately, the acetates **5Ac** and propionates **5Pr** were found to be superior giving no racemization at all. The well-known RaNi-catalyzed removal of an acyl group from an ester was, as judged by gas chromatography, much slower than desulfuration and double bond hydrogenation. Saponification of the product mixtures furnished 2-methylalkanols **2**.

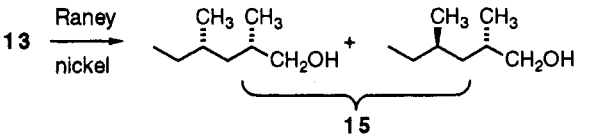
The reaction sequence **5b** → **9d–f** → **5d–f** → **2d–f** described above demonstrates one utilization of the bifunctional nature of the chiral thiophenepropanol **5b**. In this case the thiophene ring is exploited as a masked $-(CH_2)_4-$group. The thiophene ring can also serve as a masked carboxyl group, since ruthenium trichloride–sodium periodate is known to oxidize aromatics to acids.[19] Thus, we found that when the acetate **5bAc** was oxidized using this method, the acid **10** was obtained which furnished (*S*)-3-methyl-γ-butyrolactone (**11**) in unchanged ee after alkaline hydrolysis and subsequent acidic workup.



10 **11**

To widen the scope of the fermentation–RaNi reduction approach to methyl-substituted alkanols (*E*)-α-methyl-3-thiophenepropenal (**12**) was prepared from 3-thiophenecarboxaldehyde and propanal and subjected to bakers' yeast reduction to give (*S*)-β-methyl-3-thiophenepropanol **13** [74% yield, 94% ee (amide method)]. One byproduct was isolated and identified as the diol **14** (≈20%) which probably has the indicated stereochemistry because analogous diols of known configuration are frequently products from bakers' yeast treatment of substrates similar to **12**, e.g., **3a**.[5,20] This type of product was not produced in appreciable amounts in the fermentation of **3b**. The RaNi reduction of (*S*)-β-methyl-3-thiophenepropanol **13** proceeded smoothly, but it gave a poor diastereoselectivity. Thus, a 45/55 mixture of two diastereomeric 2,4-dimethylhexanols **15** was isolated. It is interesting to note that the RaNi reduction of the free alcohol **13** proceeded without racemization. Each of the two saturated diastereomers of **15** obtained showed the same ee (amide method) as the starting material **13**.





The results presented here provide a practical method for the preparation of (*S*)-2-methylalkanols of high enantiomeric purities. However, its use is limited by the enantioselectivity of the bakers' yeast. In theory the (*R*)-2-methylalkanols could probably be obtained from the (*Z*)-propenals.[9f] However, these are much more difficult to prepare and may partly rearrange to the (*E*)-propenals since these are expected to be thermodynamically more stable. Thus, if the corresponding (*R*)-2-methylalkanols are needed, they are probably more conveniently prepared using other routes. Strong competitors to the method described here are other enzymatic methods[8] or the widely used diastereoselective alkylations of chiral amide enolates.[7] However, the relatively few and simple synthetic steps and the cheap reagents and solvents used here should make our methodology competitive for the preparation of (*S*)-2-methyl-1-alkanols as well as some chiral thiophene derivatives.

Experimental Section

Unless otherwise stated, starting materials and solvents were used as received from commercial suppliers. Preparative liquid chromatography was performed on straight-phase silica gel (10–50 g/g of mixture) using the gradient elution technique described in ref 21 with an increasing concentration of distilled ethyl acetate in distilled hexane (0 → 100%). Thin-layer chromatography (TLC) was performed on silica gel plates (precoated aluminum foil) using ethyl acetate (20 or 40%) in hexane and developed by means of ultraviolet irradiation and/or by spraying with vanillin in sulfuric acid and heating at 120 °C. Unless otherwise stated, GLC analyses were carried out using a capillary column [crosslinked 5% phenylmethylsilicone, 22 m, 0.31-mm i.d., d_f = 0.52 μm, carrier gas N_2 (10 psi), split ratio 1/20]. Melting and boiling points are uncorrected, and the latter are, unless otherwise stated, given as air bath temperatures (bath temp/mmHg) in a bulb-to-bulb apparatus. Optical rotations were measured either neat in a 1-cm cell or in solution in a 1-dm cell. IR spectra were recorded neat between NaCl plates. Mass spectra were recorded using GLC–MS with an ion trap detector. Elemental analyses were carried out by Mikrokemi, Uppsala, Sweden. Unless otherwise stated below extractive workup consisted of extraction with the given solvent followed by drying with anhydrous $MgSO_4$, filtering, and the solvent being evaporated off on a rotary evaporator.

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^{1}H- and ^{19}F-MTPA Ester Method (H- or F-MTPA Method) for Determination of Enantiomeric Excess. The 2-methoxy-2-(trifluoromethyl)-2-phenylacetates (MTPA esters) were prepared using the standard procedure[22] and purified by chromatography which was performed in such a way that no separation of diastereomers occurred. ^{1}H NMR spectra were recorded on the esters formed from (−)-MTPA, and the signals due to the methylene protons [(italicized) R-(CH_3)CH-CH_2OMTPA] were analyzed, after decoupling of the methine proton, as described earlier.[5b,6a] ^{19}F spectra gave one signal for each diastereomer. The ratio between these signals was calculated by cutting out the peaks and weighing them. Usually the ^{19}F spectra of esters formed from (+)-MTPA gave more reproducible and reliable results than those from (−)-MTPA.

Analyses of Diastereomeric Mixtures of Phenylethylamides (Amide Method) for Determination of Enantiomeric Excesses of 2-Methyl 1-Alcohols. A nonracemic 2-methyl 1-alcohol (10 μL) in acetone (0.5 mL) was shaken in a test tube with Jones' reagent[23] [10 μL (H_2CrO_3, 2.7 M in H_2SO_4/H_2O (1/3))] at 10 °C for 10 min. The mixture was filtered through Celite, the filtrate diluted with hexane (2 mL), and the solution extracted with saturated Na_2CO_3 solution (2 × 1 mL). Acidification to pH 1 with HCl (aqueous, 3 M) and extractive workup with diethyl ether (2 × 1 mL) gave a nonracemic acid. This was stirred in anhydrous diethyl ether (1 mL), and dry, distilled dimethylformamide (10 μL) was added followed by distilled $SOCl_2$ (10 μL) and enantiomerically pure (*S*)- or (*R*)-1-phenylethylamine (20 μL) while argon was passed through the solution to remove generated hydrogen chloride. After shaking at ambient temperature for 5 min, the mixture was partitioned between hexane (2 mL) and water (1 mL). The organic phase was washed with saturated Na_2CO_3 solution (2 × 1 mL) and brine (1 mL) and analyzed for % ee by GLC: column, crosslinked carbowax 20M, 30 m, 0.32-mm i.d., d_f = 0.25 μm; conditions isothermal 240 °C, carrier gas He (15 psi), split ratio 1/50. Retention times for the amide deriving indirectly from (*S*)-β-methyl-2-thiophenepropanol **5b** and (*R*)-phenylethylamine: *RR* (trace) 16.12 min; *SR* (major), 17.60 min.

Method A. General Procedure for the Aldol Condensation Reaction Giving the Thiophenepropenals 3 and 12. The appropriate thiophenecarboxaldehyde (*A* mol) and propanal (100 × *A* mL, 1.4 × *A* mol) were stirred in ethanol (200 × *A* mL) and cooled to −10 °C. A solution of NaOH (50 × *A* g, in ethanol, 250 × *A* mL, and water, 250 × *A* mL) was added at such a speed that the temperature never exceeded 0 °C. After completed addition, the mixture was allowed to reach room temperature. The mixture was neutralized with HCl (aqueous, 6 M, approximately 200 × *A* mL) and stored at −10 °C overnight after which it was filtered to give pale yellow crystals which were recrystallized from ethanol or ethanol/water. Alternatively, in case of an oily product, the product mixture was subjected to extractive workup with ether (2 × 200 mL), including washing with saturated $NaHCO_3$ solution, water, and brine. The resulting oil was subjected to flash chromatography and/or distilled.

Method B. General Procedure for the Bakers' Yeast Reduction of 3-Substituted Propenals 3, 7, and 12. Bakers' yeast (50 g/g substrate) was stirred with water (0.5 L/g substrate) and glucose (25 g/g substrate) in a 1-L round bottom, three-necked flask at room temperature. A constant flow of oxygen (40 mL/min/g substrate) was introduced at the bottom of the flask through a sintered tube end. After 1 h of fermentation the pH was adjusted to 6.0–6.5 with saturated Na_2CO_3 solution. The appropriate propenal 3, 7, or 12 from above (0.1–6 g) was dissolved in ethanol (6 mL/g substrate) and added to the vigorously stirred solution. The pH was adjusted occasionally by addition of saturated Na_2CO_3 solution or HCl (aqueous 6 M) and kept at 6.0–6.5 during the entire fermentation. Each day half the amount of yeast and glucose as compared with the day before was added. The fermentation was conveniently monitored by GLC on ether extracts obtained on shaking an aliquot withdrawn from the stirred reaction mixture. After the specified time the reaction mixture was exhaustively extracted with ether using continuous extraction. The ether extract was worked up to give an oil which was subjected to a rapid flash chromatography furnishing the desired propanol contaminated with various amounts of the propenol, and in some cases minor byproducts. If the propenol content was less than 2% at this stage, it could usually be completely removed by another flash chromatography using a larger column. If this was deemed unfeasible (usually >2–3% propenol), the product mixture was dissolved in 20% ethyl acetate in hexane (25 mL/g substrate) and stirred with manganese dioxide (20 g/g of estimated propenol content) until the propenol had disappeared (GLC: commonly within 24 h). The mixture was filtered and the filter cake thoroughly washed with 20% ethyl acetate in hexane and ether. The combined filtrates were concentrated to give an oil which was subjected to flash chromatography. The propenals formed were always eluted first and cleanly separated from the desired propanols.

GLC Analysis of Fermentation Reactions. A sample of the stirred reaction mixture (2.00 ± 0.01 mL) was extracted with ether (5 × 1 mL), and the combined organic phases were evaporated to dryness. An internal standard solution (1.00 ± 0.01 mL, 4.50 mM hexadecane in ether) was added to the residue, and the mixture was analyzed by GLC: standard SE54-type column described above. Conditions: isothermal 150 °C, carrier gas N_2 (10 psi), split ratio 1/20. Hexadecane: α = 1.00, retention time 9.97 min; α-methyl-2-thiophenepropenal (**3b**): α = 0.36, retention time 4.30 min; β-methyl-2-thiophenepropenol (**4b**): α = 0.41, retention time 4.73 min; (*S*)-β-methyl-2-thiophenepropanol (**5b**): α = 0.22, retention time 2.99 min.

Method C. General Procedure for the Preparation of (*S*)-β-Methyl-5-(1-alkylcarbonyl)-2-thiophenepropanol Alkanoates 9d–f. (*S*)-β-Methyl-2-thiophenepropanol (**5b**, >98% ee, 1.56 g, 10 mmol) in CH_2Cl_2 (30 mL, distilled from CaH_2 and stored over 4-Å molecular sieves) was stirred in an oven-dried two-necked flask under argon, and the appropriate acid chloride (21 mmol) in dry CH_2Cl_2 (15 mL) was added. Anhydrous $SnCl_4$ (7.97 g, 31 mmol) was then added dropwise at 0 °C. After 1 h, TLC showed that no starting material remained. HCl (aqueous, 6 M, 10 mL) was added dropwise at 0 °C and the aqueous phase extractively worked up with CH_2Cl_2 including washes with NaOH solution (aqueous, 4 M) and water to give an oil.

Method D. General Procedure for Huang-Minlon Reduction of Compounds 9d–f to the (*S*)-β-Methyl-5-(1-alkyl)-2-thiophenepropanols 5d–f. A (*S*)-β-methyl-5-(1-alkylcarbonyl)-2-thiophenepropanol alkanoate **9** (5 mmol) was dissolved in distilled diethylene glycol (12 mL) containing KOH (1.5 g, 28 mmol) and $N_2H_4{\cdot}H_2O$ (0.8 g, 16 mmol), and the solution was slowly heated to 170 °C where it was kept for 1 h and then at 210 °C for 3 h before cooling and pouring into water (50 mL). Extractive workup with ether including washing with water furnished an oil.

Method E. General Procedure for the Preparation of the Acetates 5Ac or Propionates 5Pr from 5. A (*S*)-β-methyl-5-(1-alkyl)-2-thiophenepropanol (**5**, >98% ee, 19 mmol) and the appropriate anhydride (290 mmol) in pyridine [100 mL, dried over NaOH (s) and distilled from CaH_2] was stirred under argon for 2 h. The solution was poured into an ice/water mixture, which was stirred until the ice had melted. Extractive workup with pentane, including washing with HCl (aqueous, 1 M), saturated $NaHCO_3$ solution, and brine gave an oil in almost quantitative yield. The esters were pure (>98% by GLC) enough for use without further purification and characterization in the RaNi reduction reactions.

Method F. General Procedure for the RaNi Reduction of the (*S*)-β-Methyl-5-(1-alkyl)-2-thiophenepropanols 5 or Their Derivatives 5R^1. A (*S*)-β-Methyl-5-(1-alkyl)-2-thiophenepropanol **5** or its derivative **5R^1** (10 mmol) was stirred under H_2 in CH_3OH (100 mL) with a suspension of RaNi in water (50%, 25 mL), usually for 2 h or else until according to GLC no starting material remained. When the starting material was an ester, a small amount of the free alcohol **2** had formed along with its ester.

When alcohols **5** were used as starting materials, the suspension was filtered and the RaNi washed thoroughly with CH_3OH. The CH_3OH was evaporated through a 30-cm vacuum-jacketed column containing glass helices. The residue was mixed with $NaHCO_3$ solution (5%, 15 mL) and extractively worked up with pentane (75 mL) to give a colorless oil.

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When esters such as **5Ac** or **5Pr** were used as starting materials, NaOH (1 g) was added to the reaction mixture after complete reduction. The mixture was stirred 1 additional h prior to filtration as above. If traces of the ester remained at this stage, the filtrate was heated under reflux until the ester was hydrolyzed completely (GLC) before CH_3OH was removed as described above.

(*E*)-α-Methyl-2-thiophenepropenal (3b). Method A: pale yellow crystals (ethanol); mp 33–34 °C (lit.[10] mp 27–30 °C). Other physical and spectral data were identical with those described previously.[10]

(*E*)-β-Methyl-2-thiophenepropenol (4b). $NaBH_4$ (7.1 g, 0.13 mmol) dissolved in KOH solution (0.2 M, 60 mL) was added to a stirred, cooled solution of α-methyl-2-thiophenepropenal (**3b**, 40 g, 0.26 mol) in ethanol (300 mL) at such a speed that the temperature did not exceed 30 °C. After 1 h the mixture was diluted with water and extractively worked up with ether to give 35 g (87%) of colorless crystals, mp 52–53 °C (ethanol/water). The product was unstable, decomposing when distilled under reduced pressure, stored in a desiccator or at −30 °C under inert gas. IR (neat): 3311, 1440 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 2.05 (3 H, bs), 4.25 (2 H, bs), 6.85 (1 H, m), 7.20 (1 H, d), 7.4–7.6 (2 H, m) ppm. MS *m/z* (relative intensity) 154 (M^+, 28), 135 (100), 121 (23), 111 (16), 97 (85), 91 (45), 84 (52), 77 (27), 69 (37). Anal. Calcd for $C_8H_{10}OS$: C, 62.30; H, 6.54. Found: C, 62.27; H, 6.57.

(*S*)-β-Methyl-2-thiophenepropanol (5b). Method B. Fermentation of α-methyl-2-thiophenepropenal (**3b**, 3 g, 19.4 mmol) for 48 h and workup followed by fractional distillation (bp 68 °C (0.2 mmHg)) gave a colorless oil (2.01 g, 65%), $[\alpha]^{20}_D$ −19.3° (neat). 98% ee (F-MTPA method and amide method), n^{20}_D 1.5356. IR (neat): 3350, 1454 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.97 (3 H, d, *J* = 6.6 Hz), 1.62 (1 H, s, OH), 1.96 (1 H, apparent octet, *J* ≈ 7 Hz), 2.69 (1 H, dd, *J* = 7.8 and 14.7 Hz), 2.96 (1 H, dd, *J* = 6.1 and 14.7 Hz), 3.52 (2 H, m), 6.79 (1 H, broad dd, *J* = 1.0 and 5.1 Hz), 6.92 (1 H, dd, *J* = 3.0 and 5.1 Hz), 7.12 (1 H, dd, *J* = 1.0 and 5.1 Hz) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 16.39, 33.41, 38.06, 67.21, 123.27, 125.21, 126.70, 143.09 ppm. MS *m/z* (relative intensity) 156 (M^+, 14) 138 (10), 123 (21), 97 (100), 84 (7). Anal. Calcd for $C_8H_{12}OS$: C, 61.50; H, 7.74. Found: C, 61.14; H, 7.63.

(*S*)-β-Methyl-2-thiophenepropanol Acetate (5bAc). Method E. (*S*)-β-Methyl-2-thiophenepropanol (**5b**, 3.0 g, 19 mmol) furnished after chromatography and distillation (bath temp 70 °C (0.2 mmHg)) an oil (3.7 g, 98%), $[\alpha]^{20}_D$ +2.5° (neat), n^{20}_D 1.5010. IR (neat): 1737, 1462, 1235 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.97 (3 H, d, *J* = 7.0 Hz), 2.06 (3 H, s), 2.14 (1 H, apparent octet, *J* ≈ 7 Hz), 2.71 (1 H, dd, *J* = 7.8 and 14.5 Hz), 2.93 (1 H, dd, *J* = 6.3 and 14.5 Hz), 3.94 (1 H, dd, *J* = 6.1 and 13.2 Hz), 3.98 (1 H, dd, *J* = 6.1 and 13.2 Hz), 6.77 (1 H, bdd, *J* = 1.0 and 3.3 Hz), 6.91 (1 H, dd, *J* = 3.3 and 5.1 Hz), 7.12 (1 H, dd, *J* = 1.0 and 5.1 Hz) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 16.62, 20.93, 33.62, 34.88, 68.32, 123.50, 125.44, 126.79, 142.33, 171.19 ppm. MS *m/z* (relative intensity) 198 (M^+, 0.1), 137 (5), 122 (7), 96 (100), 83 (5). Anal. Calcd for $C_{10}H_{14}O_2S$: C, 60.57; H, 7.12. Found: C, 60.72; H, 7.34.

(*S*)-2-Methyl-1-heptanol (2b). Method F. (*S*)-β-Methyl-2-thiophenepropanol acetate (**5bAc**, 98% ee, 1.6 g, 8.1 mmol) gave a colorless oil (**2b**, 0.81 g, 77%) after distillation [76 °C (13 mmHg), (lit.[24] 175 °C (760 mmHg))], $[\alpha]^{20}_D$ −13.4° (neat), 98% ee (H-MTPA method and amide method), n^{20}_D 1.5356. IR (neat): 3342, 1467 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 0.8 (3 H, broad t), 0.7–1.1 (6 H, m), 1.1–1.7 (9 H, m), 1.9 (1 H, broad s, OH), 3.5 (2 H, d, *J* = 6 Hz) ppm. RaNi reduction of the alcohol **5b** gave **2b** of 94% ee (F-MTPA, H-MTPA, and amide method).

(*E*)-α-Methyl-5-methyl-2-thiophenepropenal (3c). Method A. 6c (10 g, 79 mmol) gave colorless crystals (11 g, 84%), mp 70–70.5 °C (ethanol/water). IR (KBr): 1660, 1605, 1450 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 2.10 (3 H, broad s), 2.7 (3 H, broad s), 6.95 (1 H, broad d, *J* = 5 Hz), 7.3 (1 H, d, *J* = 5 Hz), 7.4 (1 H, broad s), 9.4 (1 H, s) ppm. Anal. Calcd for $C_9H_{10}OS$: C, 65.02; H, 6.06. Found: C, 65.08; H: 5.98.

(*S*)-β-Methyl-5-methyl-2-thiophenepropanol (5c). Method B. Fermentation of α-methyl-5-methyl-2-thiophenepropenal (**3c**, 1 g, 6.0 mmol) for 72 h gave an oil (0.75 g) containing a 25/75 mixture of propenol **4c** (a reference sample was prepared as described for **4b**) and propanol **5c** (according to GLC). MnO_2 treatment and workup furnished a colorless oil (0.36 g, 33%, >99% purity by GLC) after distillation (bath temperature 75 °C (3.5 mmHg)), $[\alpha]^{20}_D$ −17.4° (neat), 95% ee (F-MTPA method), n^{20}_D 1.5246. IR (neat): 3328, 1453 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.96 (3 H, d, *J* = 6.6 Hz), 1.47 (1 H, broad s, OH), 1.92 (1 H, apparent octet, *J* ≈ 7 Hz), 2.43 (3 H, s), 2.60 (1 H, dd, *J* = 7.6 and 14.8 Hz), 2.85 (1 H, dd, *J* = 6.4 and 14.8 Hz), 3.50 (1 H, dd, *J* = 6.1 and 13.5 Hz), 3.54 (1 H, dd, *J* = 6.1 and 13.5 Hz), 6.55 (2 H, s) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 15.29, 16.50, 33.76, 38.02, 67.37, 124.69, 124.99, 137.72, 140.88 ppm. MS *m/z* (relative intensity) 170 (M^+, 7), 141 (3), 123 (3), 110 (64), 96 (48), 76 (100). Anal. Calcd for $C_9H_{14}OS$: C, 63.49; H, 8.29. Found: C, 63.04; H, 8.42.

(*S*)-2-Methyl-1-octanol (2c). Method F. Reduction of (*S*)-β-Methyl-5-methyl-2-thiophenepropanol (**5c**) gave an oil (85%) after distillation (bath temperature 75 °C (4 mmHg) (lit.[25] 209–210 °C (760 mmHg))), n^{20}_D 1.4331 (lit.[25] n^{25}_D 1.4316), $[\alpha]^{20}_D$ −12.0° (*c* 1.0 MeOH), 87% ee (F- and H-MTPA method). IR (neat): 3331, 1467 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 0.95 (3 H, d), 0.95 (3 H, bt), 0.9–1.8 (11 H, broad m), 2.2 (1 H, broad s, OH), 3.4 (2 H, d) ppm.

(*S*)-β-Methyl-5-acetyl-2-thiophenepropanol Acetate (9d). Method C. 5b (>98% ee) furnished a colorless oil (90%) after distillation (bath temperature 160 °C (0.3 mmHg)), $[\alpha]^{20}_D$ +10.0° (*c* 1.5, MeOH), n^{20}_D 1.5289. IR (neat): 1739, 1661, 1455 cm^{-1}. NMR (60 MHz, $CDCl_3$): δ 1.0 (3 H, d, *J* = 6 Hz), 2.05 (3 H, s), 2.50 (3 H, s), 2.20 (1 H, m), 1.7–2.1 (2 H, m), 4.0 (2 H, d, *J* = 6 Hz), 6.90 (1 H, d, *J* = 4 Hz), 7.60 (1 H, d, *J* = 4 Hz) ppm. Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71. Found: C, 60.22, H: 6.57.

(*S*)-β-Methyl-5-ethyl-2-thiophenepropanol (5d). Method D. 9d (0.6 g, 2.5 mmol) afforded after chromatography and distillation (bath temperature 100 °C (0.4 mmHg)) a colorless oil (0.4 g, 87%), $[\alpha]^{20}_D$ −18.6° (*c* 1.2, MeOH), >98% ee (F-MTPA method), n^{20}_D 1.5214. IR (neat): 3336, 1455 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 0.95 (3 H, d, *J* = 8 Hz), 1.10 (3 H, t, *J* = 8 Hz), 1.6 (1 H, broad s, OH), 1.9 (1 H, apparent octet), 2.7–2.9 (4 H, m), 3.6 (2 H, d, *J* = 7 Hz), 6.7 (2 H, s) ppm. Anal. Calcd for $C_{10}H_{16}OS$: C, 65.17; H, 8.75. Found: C, 64.96; H, 8.56.

(*S*)-2-Methyl-1-nonanol (2d). Method F. Prepared from (*S*)-β-Methyl-5-ethyl-2-thiophenepropanol (**5d**, 98% ee). Distillation (bath temperature 90 °C (22 mmHg)) gave an oil (76%), $[\alpha]^{20}_D$ −12.1° (*c* 1, MeOH), 93.8% ee (F- and H-MTPA methods), n^{20}_D 1.4381. IR (neat): 3327, 1467 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 0.95 (3 H, d), 0.95 (3 H, bt), 0.9–1.8 (13 H, broad m), 1.6 (1 H, broad s, OH), 3.4 (2 H, d, *J* = 6 Hz) ppm. Anal. Calcd for $C_{10}H_{22}O$: C, 75.88; H, 14.01. Found: C, 76.08 H; 13.87.

2-(1-Propyl)thiophene. Metalation–alkylation of thiophene was performed in a way similar to that described in the literature.[11] Thus, thiophene (5.0 g, 59.4 mmol) was stirred under argon at ambient temperature. *n*-C_4H_9Li (1.6 M in hexane, 40.9 mL, 65.4 mmol) and *N,N,N,N*-tetramethylethylenediamine (TMEDA, 9.9 mL, 65.4 mmol, purified by distillation from CaH_2 and stored over 4-Å molecular sieves) was added. The solution was refluxed until the metalation was complete (GLC, 2 h). After the solution was cooled to −70 °C, 1-bromopropane (5.95 mL, 65.4 mmol, dried over 4-Å molecular sieves) was added dropwise, and the solution was stirred for 2 h at room temperature, after which it was poured into water and subjected to extractive workup with ether including washing with HCl (aqueous, 3 M), saturated $NaHCO_3$ solution. Fractional distillation of the extract gave the desired product (bp 70 °C (50 mmHg), 2.39 g, 32%) (lit.[26a] bp 158–9 °C (760 mmHg)). The physical and spectral properties were the same as those described previously.[26b]

5-(1-Propyl)-2-thiophenecarboxaldehyde (6e). A procedure similar to the method described for preparing other thiophenecarboxaldehydes[12] was used. Thus, 2-(1-propyl)thiophene (5.66 g, 45 mmol) and TMEDA (6.16 g, 53 mmol) were stirred under argon in hexane (35 mL, distilled from Na, stored over 4-Å molecular sieves). *n*-Butyllithium (0.8 M in hexane, 66 mL, 53 mmol) was added dropwise during 40 min while the reaction mixture

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was kept at <40 °C. The solution was then refluxed until metalation was complete (GLC, 2.5 h). After being cooled to −40 °C the reaction mixture was diluted with dry tetrahydrofuran (THF, 90 mL, distilled under argon from potassium–benzophenone). Dry dimethylformamide (7.60 mL, 98.6 mmol, distilled from CaH_2 and stored over 4-Å molecular sieves) was added, and the solution was stirred while being allowed to reach room temperature overnight and then poured into a HCl (aqueous, 6 M, 62 mL) ice–water (500 mL) mixture. Extractive workup including washing with saturated $NaHCO_3$ solution, chromatography, and fractional distillation (80 °C (1 mmHg)) gave an oil (5.81 g, 84%), n^{20}_D 1.5569 (lit.[27] bp 129 °C (15 mmHg); n^{20}_D 1.5555). IR (neat): 1667 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 1.05 (3 H, t, J = 7 Hz), 1.75 (2 H, sextet, $J \approx$ 7 Hz), 2.95 (2 H, t, J = 7 Hz), 7.05 (1 H, d, J = 4 Hz), 7.75 (1 H, d, J = 4 Hz), 10.0 (1 H, s) ppm.

(*E*)-α-Methyl-5-propyl-2-thiophenepropenal (3e). Method A. **6e** (1.75 g, 11.4 mmol) gave a light yellow oil (1.45 g, 66% of >97% purity by GLC) after flash chromatography and fractional distillation (bp 115–117 °C (0.8 mmHg)), n^{20}_D 1.6225. IR (neat): 1671, 1613, 1454 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 1.00 (3 H, t, J = 7 Hz), 1.3–2.1 (2 H, m), 2.05 (3 H, s), 2.85 (2 H, t, J = 7 Hz), 6.95 (1 H, d, J = 4 Hz), 7.30 (1 H, d, J = 4 Hz), 7.40 (1 H, bs), 9.55 (1 H, s) ppm. Anal. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.26. Found: C, 67.97; H, 7.08.

(*S*)-β-Methyl-5-propionyl-2-thiophenepropanol Propionate (9e). Method C. Compound **5b** (>98% ee, 0.80 g, 5.13 mmol) and propionyl chloride (0.97 g, 10.5 mmol) yielded a colorless oil (1.25 g, 91%) after distillation (bath temperature 170 °C (0.2 mmHg)). $[\alpha]^{20}_D$ +11.7° (*c* 1.5, MeOH), n^{20}_D 1.5194. IR (neat): 1739, 1663, 1460 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 1.00 (3 H, d, J = 6 Hz), 1.07 (3 H, t, J = 8 Hz), 1.11 (3 H, t, J = 8 Hz), 1.9–2.7 (3 H, m), 2.9–3.3 (4 H, m), 4.2 (2 H, d, J = 6 Hz), 7.05 (1 H, d, J = 4 Hz), 7.85 (1 H, d, J = 4 Hz) ppm. Anal. Calcd for $C_{14}H_{20}O_3S$: C, 62.66; H, 7.51. Found: C, 63.05; H, 7.45.

(*S*)-β-Methyl-5-(1-propyl)-2-thiophenepropanol (5e). Method B. Fermentation of **3e** (0.5 g, 2.6 mmol) for 75 h and workup gave an oil containing a mixture of the propenol **4e** and the desired propanol **5e** (according to GLC). After MnO_2 treatment and workup a colorless oil (0.13 g, 25%) was obtained (bath temperature 130 °C (0.1 mmHg)), $[\alpha]^{20}_D$ −14.3° (*c* 1.5, MeOH), 76% ee (F-MTPA method), n^{20}_D 1.5167. IR (neat): 3336, 1458 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 0.95 (3 H, t, $J \approx$ 6 Hz), 1.00 (3 H, d, J = 8 Hz), 1.4–2.2 (3 H, m), 1.6 (1 H, broad s, OH), 2.7–3.0 (4 H, m), 3.6 (2 H, d, J = 6 Hz), 6.7 (2 H, s) ppm. Anal. Calcd for $C_{11}H_{18}OS$: C, 66.61; H, 9.15. Found: C, 66.48; H, 9.12. **Method D.** Compound **9e** (1.15 g, 4.3 mmol) gave an oil (0.71 g, 84%) after chromatography and bulb-to-bulb distillation (125 °C (0.2 mmHg)). Purity: >99% (by GLC); $[\alpha]^{20}_D$ −17.4° (*c* 1.5, MeOH), >98% ee (F-MTPA method).

(*E*)-2-Methyl-2-decenal (7). Modified Method A. Octanal (500 mL, 3.2 mol) and propanal (500 mL, 7 mmol) were stirred in ethanol (2.5 L) and water (0.5 L) in a 4-L beaker in a water bath maintained at 20 °C. A solution of KOH (400 g in ethanol, 1 L, and water, 1 L) was added at such a speed that the temperature never exceeded 20 °C. When the addition was complete, the mixture was stirred for another 0.5 h, neutralized with HCl (aq, 6 M) and subjected to extractive workup with hexane (3 L) to give an oil. This was fractionally distilled through a 70-cm column, giving a mixture of low-boiling products (65 g, bp <65 °C (0.6 mmHg)) which was discarded. A fraction (120 g, bp 65–78 °C (0.6 mmHg)) contained mainly the title compound and a slightly more volatile component. Distillation of this fraction using a Teflon spinning band apparatus (60- × 0.5-cm i.d.) removed the more volatile component (bp <66 °C (0.6 mmHg)) and left the desired methyldecenal **7** in the residue. This was redistilled through a 30-cm column to remove high-boiling components. This procedure furnished a colorless oil (bp 68 °C (0.6 mmHg), 88 g, 24%). Purity ≈96% by GLC. The compound was unstable on storage at ambient temperature, n^{20}_D 1.4588. IR (neat): 1690, 1645, 1467 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.82 (3 H, t, J = 6.9 Hz), 1.1–1.4 (8 H, m), 1.43 (2 H, broad quintet), 1.67 (3 H, d, J = 1.3 Hz) 2.24–2.33 (2 H, m), 6.43 (1 H, dt, J = 1.3 and 7.4 Hz), 9.33 (1 H, s) ppm. Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 76.85; H, 11.93 (unsatisfactory result probably due to decomposition during transport).

(*S*)-2-Methyl-1-decanol (2e). Method B. The fermentation of (*E*)-2-methyl-2-decenal (**7**, 1 g) was stopped after 75 h. The brew was extracted continuously and dried ($MgSO_4$) and the solvent evaporated. MnO_2 treatment removed the decenol **8** (a reference sample was prepared as described for **4b**), and further workup furnished a colorless oil (0.35 g, 34%), $[\alpha]^{20}_D$ −9.62° (neat) (lit.[6b] $[\alpha]^{20}_D$ 10.11° (neat, mean value of (*S*)-(−)- and (*R*)-(+)-corrected to 100% ee)), 95% ee (F-MTPA method). The physical and spectral properties were in accordance with those described previously.[6a,7b] **Method F.** RaNi reduction of (*S*)-β-methyl-5-(1-propyl)-2-thiophenepropanol (**5e**) (98.1% ee) furnished **2e** (70%) of 91.8% ee and (F- and H-MTPA methods), $[\alpha]^{20}_D$ −8.9° (neat).

(*S*)-β-Methyl-5-butyryl-2-thiophenepropanol Butyrate (9f). Method C. Compound **5b** (98% ee) and butyryl chloride gave a colorless oil (94%, bath temperature 160 °C (0.15 mmHg)), $[\alpha]^{20}_D$ +12.2° (*c* 1.4, MeOH), n^{20}_D 1.5126. IR (neat): 1738, 1662, 1456 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 0.8–1.2 (9 H, m), 1.4–2.1 (4 H, m), 2.1–2.6 (3 H, m), 2.8–3.1 (4 H, m), 4.05 (2 H, d, J = 6 Hz), 7.0 (1 H, d, J = 4 Hz), 7.7 (1 H, J = 4 Hz) ppm. Anal. Calcd for $C_{16}H_{24}O_3S$: C, 64.83; H, 8.16. Found: C, 65.16; H, 8.13.

(*S*)-β-Methyl-5-(1-butyl)-2-thiophenepropanol (5f). Method D. Compound **9f** furnished an oil (91%, purity 99%) after distillation (bath temperature 100 °C (0.15 mmHg)), $[\alpha]^{20}_D$ −17.1° (*c* 1.8, MeOH), 99% ee (F-MTPA method), n^{20}_D 1.5125. IR (neat): 3337, 1459 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 0.90 (3 H, t, J = 6 Hz), 0.98 (3 H, d, J = 7 Hz), 1.1–2.1 (5 H, m), 2.7–2.9 (4 H, m), 3.4 (1 H, broad s, OH), 3.6 (2 H, d, J = 7 Hz), 6.7 (2 H, broad s) ppm. Anal. Calcd for $C_{12}H_{20}OS$: C, 67.87; H, 9.49. Found: C, 67.61; H, 9.28.

(*S*)-2-Methyl-1-undecanol (2f). Method F. Compound **5f** gave a colorless oil (77%) after bulb-to-bulb distillation (bath temperature 105 °C (1.5 mmHg)), $[\alpha]^{20}_D$ −10.3° (*c* 2, MeOH), 93% ee (F- and H-MTPA method), n^{20}_D 1.4423. IR (neat): 3327, 1466 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 0.86 (3 H, broad t, J = 6 Hz), 0.92 (3 H, d, J = 6 Hz), 1.1–1.7 (17 H, broad m), 1.6 (1 H, s, OH), 3.4 (2 H, d, J = 6 Hz) ppm. Anal. Calcd for $C_{12}H_{26}O$: C, 77.35; H, 14.06. Found: C, 77.68; H, 14.16. RaNi reductions of (*S*)-β-methyl-5-(1-butyl)-2-thiophenepropyl derivatives **5fAc**, **5fTBDMS**, and **5fMTPA** (all 98.1% ee) furnished, after hydrolysis, **2f** of 98.1, 97.3, and 95.7% ee, respectively (amide method).

(*S*)-3-Methyl-γ-butyrolactone [or (*S*)-4,5-Dihydro-4-methyl-2(3*H*)-furanone] (11). (*S*)-β-Methyl-2-thiophenepropanol acetate (**5bAc**, 396 mg, 2 mmol) in CCl_4 (8 mL) and CH_3CN (8 mL) was stirred with sodium periodate (6.21 g, 29 mmol) in water (12 mL). $RuCl_3 \times 3H_2O$ (20 mg) was added to the mixture. After 6 h the starting material had disappeared as judged by TLC. The mixture was diluted with HCl (aqueous, 2 M, saturated with NaCl) and subjected to extractive workup with ethyl acetate which gave 4-acetoxy acid **10** (≈300 mg). ^1H NMR (60 MHz, $CDCl_3$): δ 1.0 (3 H, d), 2.05 (3 H, s), 1.7–2.3 (1 H, m), 2.3 m (2 H, m), 3.95 (2 H, m) 10.5 (1 H, bs, OH) ppm. IR: 1660, 2500–3400 cm^{-1}. The acetoxy acid **10** was treated with NaOH (1 mL, 15% in water) at 100 °C for 15 min. The solution was carefully acidified to pH <0 with H_2SO_4 (aqueous, 3 M) and reheated to 100 °C for 5 min. After being cooled the mixture was extracted with ether (5 mL) and the ether phase was washed with saturated $NaHCO_3$ solution (3 mL). The same extraction procedure was repeated 10 times while always checking that the pH of the saturated $NaHCO_3$ solution was over 6 after each extraction. After the tenth extraction cycle only a trace of the desired hydrophilic lactone **11** could be detected in the extract from the water phases. After drying ($MgSO_4$) and filtration of the combined ether extracts, the solvent was removed by distillation through a column and finally by drying in a vacuum to give an oil (149 mg, 80%, 97% pure by GLC). Distillation (bath temperature 100 °C (10 mm)) gave the pure lactone (>99.5% by GLC), $[\alpha]^{20}_D$ −24.9° (*c* 2.1, MeOH) [lit.[28] −24.96° (*c* 1.7, MeOH)]. The spectral and

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physical data were in accord with the those described previously.[9d,28]

(*E*)-α-Methyl-3-thiophenepropenal (12). Method A. 3-Thiophenecarboxaldehyde (29 g, 0.26 mol) gave an oil, which after fractional distillation (80–85 °C (0.5 mmHg)) solidified to 29 g (74%) of pale yellow crystals, mp 25.5–27 °C (98.5% pure by GLC). The compound was unstable on storage. IR (neat): 1678, 1622, 1446 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 2.1 (3 H, d), 7.1–7.7 (4 H, m), 9.6 (1 H, s) ppm. Anal. Calcd for C_8H_8OS: C, 63.13; H, 5.30. Found: C, 62.54; H, 5.27. Repeated unsatisfactory elemental analyses were probably due to partial decomposition of the sample.

(*S*)-β-Methyl-3-thiophenepropanol (13). Method B. The fermentation of compound **12** (1.0 g, 6.5 mmol) was stopped after 72 h. The crude ether extract consisted of a mixture of the desired product **13** and a small amount of the corresponding propenol (according to GLC, a reference sample was prepared as described for **4b**) plus the byproduct, the diol **14**, which was eluted in the last fractions in the first chromatography. The fractions containing mainly compound **13** and a small amount of the corresponding propenol were combined and concentrated. The remaining product after MnO_2 treatment and workup furnished a colorless oil (bath temp 60 °C (1 mmHg), 0.75 g, 74%), $[\alpha]^{20}_D$ −29.7° (*c* 0.9, CH_3OH), 96% ee (F-MTPA method), 94.3% ee (amide method), n^{20}_D 1.5341. IR (neat): 3350, 1454 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.97 (3 H, d, *J* = 6.9 Hz), 1.42 (1 H, s, OH), 1.95 (1 H, apparent octet, *J* ≈ 7 Hz), 2.50 (1 H, dd, *J* = 7.9 and 14.2 Hz), 2.74 (1 H, dd, *J* = 6.4 and 14.2 Hz), 3.47 (1 H, dd, *J* = 6.0 and 10.6 Hz), 3.52 (1 H, dd, *J* = 6.0 and 10.6 Hz), 6.93 (1 H, d, *J* = 3.2 Hz), 6.93 (1 H, d, *J* = 1.5 Hz), 7.25 (1 H, dd, *J* = 1.5, 3.2 Hz) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): 16.57, 33.93, 37.07, 67.60, 121.00, 125.25, 128.63, 140.81 ppm. MS *m/z* (relative intensity) 156 (M^+, 0.3), 97 (100). Anal. Calcd for $C_8H_{12}OS$: C, 61.50; H, 7.74. Found: C, 61.57; H, 7.94.

(2*S*,3*S*)-4-Methyl-5-(3-thienyl)-4-pentene-2,3-diol (14). The late fractions from the chromatography described in the preparation of compound **13** above were concentrated to give an oil which solidified on standing to colorless needles (0.15 g, 13%), mp 77.0–77.5 °C (C_2H_5OH), $[\alpha]^{20}_D$ +32.3° (*c* 1.5, MeOH). IR (KBr): 3729, 1446 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 1.19 (3 H, d, *J* = 6.3 Hz), 1.85 (1 H, s, OH), 1.94 (3 H, d, *J* = 1.3 Hz), 2.15 (1 H, s, OH), 3.96 (1 H, m transformed into an apparent quintet after shaking with D_2O, *J* ≈ 6 Hz), 4.12 (1 H, m transformed into a d after shaking with D_2O, *J* = 4.6 Hz), 6.55 (1 H, broad s), 7.10 [1 H, dd, *J* = 5.0 and 1.3 Hz (the latter is due to coupling to the vinylic proton at δ 6.55 ppm)], 7.18 (1 H, d, *J* = 2.8 Hz), 7.28 (1 H, d, *J* = 2.8 and 5.0 Hz) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 15.11, 17.43, 68.91, 80.54, 121.42, 122.97, 124.94, 128.70, 135.94, 138.28 ppm. MS *m/z* (relative intensity) (M^+, not found), 151 (8), 122 (5), 96 (100), 90 (64), 83 (70). Anal. Calcd for $C_{10}H_{14}O_2S$: C, 60.57; H, 7.12. Found: C, 60.30; H, 7.15.

(2*S*,4*RS*)-Dimethyl-1-hexanol (15). Method F. Compound **13** gave after distillation (bath temperature 100 °C (10 mmHg) (lit.[29] bp 172–175 °C (760 mmHg)) a 45/55 mixture of diastereomers (GLC) as an oil (62%), 95% ee (2-position, amide method), n^{20}_D 1.4279. IR (neat): 3347, 2959, 1462, 1379 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 0.9–1.0 (9 H, m), 1.0–1.5 (5 H, m), 1.65 (1 H, b s, OH), 1.71 (1 H, m), 3.3–3.6 (2 H, m) ppm. Irradiation at δ 1.71 ppm formed two doublets of doublets [δ 3.37 (corresponds to ≈0.5 H, d, *J* = 10.2 Hz) and 3.52 (≈0.5 H, d, *J* = 10.2 Hz) for one diastereomer and 3.40 (≈0.5 H, d, *J* = 10.2 Hz) and 3.48 (≈0.5 H, d, *J* = 10.2 Hz) for the other]. ^{13}C NMR (67.8 MHz, $CDCl_3$): 11.43, 16.37, 19.82, 64.82, 31.63, 61.3, 67.13, 61.98 (for one diastereomer) and 11.16, 17.34, 18.92, 29.07, 31.63, 33.17, 40.65, 68.41 (for the second diastereomer) ppm. The isomer ratio based on the ^{13}C NMR spectrum was calculated to be 46/54.

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Supplementary Material Available: The preparations of and analytical and spectral data for compounds **4c**, **8**, and (*E*)-β-methyl-3-thiophenepropenol as well as the upgrading of the optical purity of **5b** via its dinitrobenzoate **5bDNB** (3 pages). Ordering information is given on any current masthead page.

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