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A Synthesis of (–)-(*R*)- and (+)-(*S*)-Lavandulol, (+)-Lavandulyl 2-Methylbutanoate, and (+)-Lavandulyl Senecioate through Orthoester Johnson–Claisen Rearrangement

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An efficient synthesis of (–)-(*R*)- and (+)-(*S*)-lavandulol, (+)-lavandulyl 2-methylbutanoate and (+)-lavandulyl senecioate is presented in this paper. The synthetic strategy features a chiral-pool approach to an allyl alcohol intermediate, and an orthoester Johnson–Claisen rearrangement as the key step.

Introduction

The monoterpene (–)-(*R*)-lavandulol (**1**; Figure 1) is an important additive in perfumes.[1] It also acts as a defensive pheromone in the red-lined carrion beetle, *Necrodes surinamensis*.[2] Its ester, lavandulyl 2-methylbutanoate (**2**), along with the cyclobutanoid monoterpene **3**, constitutes the female sex pheromone of the pink hibiscus mealy bug, *Maconellicoccus hirsutus* (Green) (Homoptera: Pseudococcidae), which is an insect pest for agricultural and vegetable crops, forest trees, and ornamental plants.[3] (–)-(*R*)-Lavandulyl acetate (**4**) has been identified as a male-produced aggregation pheromone of the western flower thrips *Frankliniella occidentalis*.[4] Lavandulol exists naturally in its (*R*) form in the essential oil of lavender, and the (*R*) and (*S*) forms of lavandulol (i.e., **1** and *ent*-**1**) have also been identified as constituents of insect hormones of the strawberry-blossom weevil, *Anthonomus rubi*,[5] and vine mealy bug, *Planococcus ficus*,[6] respectively. (*S*)-Lavandulyl senecioate (**5**) and (*S*)-lavandulyl isovalerate (**6**) have also been recently identified as sex pheromones of the vine mealy bug, which is a serious pest in vineyards.[6,7] Owing to their high commercial value as additives and potential markers in pest controls, considerable efforts have been put into the synthesis of these compounds, in both their racemic and homochiral forms.[8,9] A few methods have been based on biotransformations involving the resolution[10] of racemic lavandulol.

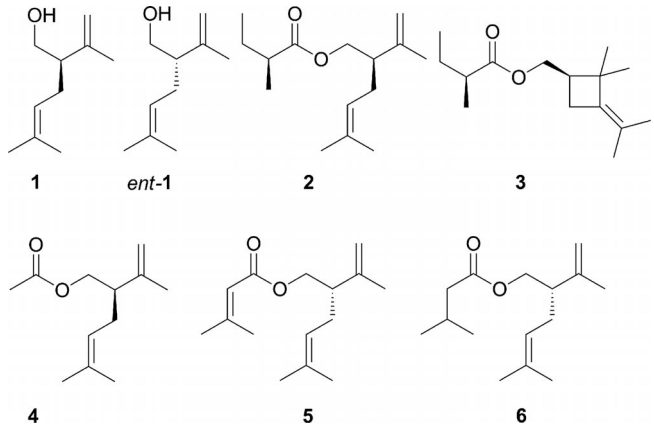

Figure 1. (–)-Lavandulol **1** and related compounds.

Results and Discussion

As part of our research program[11] into the total synthesis of biologically active natural products using the orthoester Johnson–Claisen rearrangement[12] of allyl alcohols with chiral vicinal diol functionality, we became interested in these volatile terpenoids. A retrosynthetic analysis of **1**, *ent*-**1**, **2**, and **5** is shown in Scheme 1. Ester **2** could be synthesized from alcohol **1** by esterification with (*S*)-2-methylbutanoic acid. Similarly, ester **5** could be obtained from alcohol *ent*-**1** by esterification with 3,3-dimethylacrylic acid. Alcohols **1** and *ent*-**1** could both be obtained from either diastereomer of **7**. γ,δ-Unsaturated ester **7** could be obtained from either **8** or **9** by orthoester Johnson–Claisen rearrangement. Alcohols **8** and **9** could both be synthesized from commercially available (*R*)-isopropylideneglyceraldehyde **10** by Wittig olefination.

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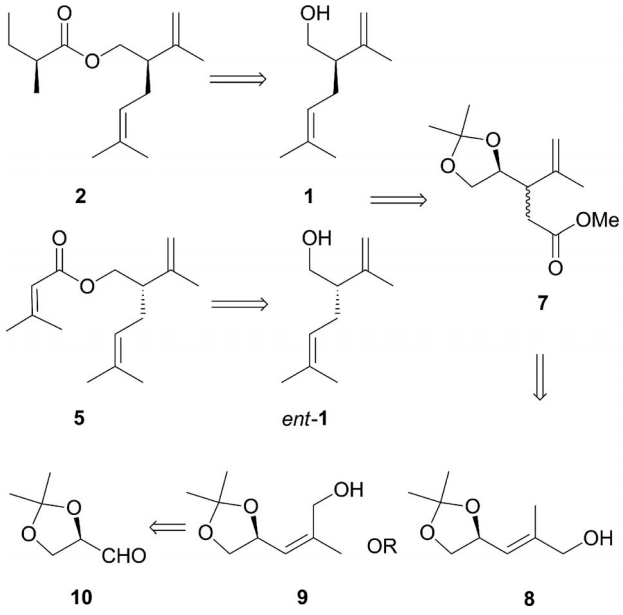
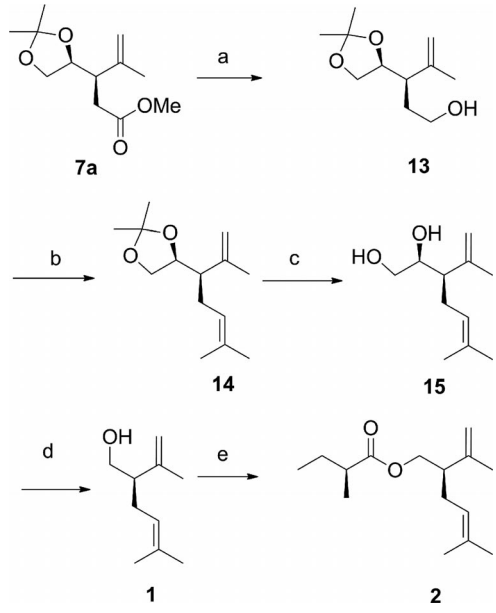


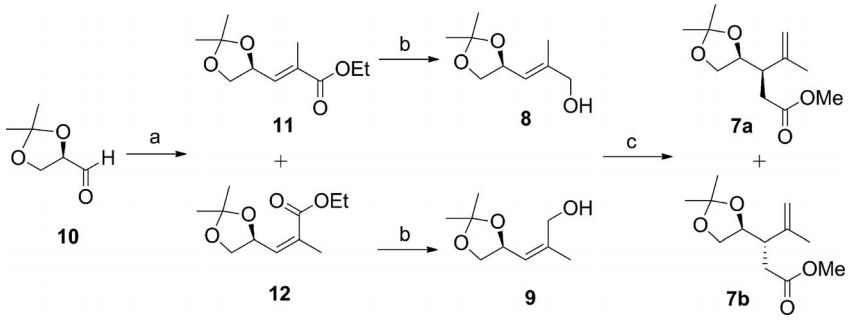
Scheme 1. Retrosynthetic analysis of lavandulol **1** and related compounds.

The synthesis of separable diastereomers **7a** and **7b** is shown in Scheme 2. Commercially available (*R*)-isopropylideneglyceraldehyde **10** underwent Wittig olefination with a stable phosphorane to give **11** stereoselectively in 93% yield.[13] However, when **10** reacted with $(EtO)_2P(O)CHMeCO_2Et$ and NaH at –78 °C, **12** was obtained as a mixture with **11** in a 1.1:1 ratio. The (*Z*)/(*E*) mixture could easily be separated by silica gel column chromatography to give **12** (46%) and **11** (43%). DIBAL-H (diisobutylaluminium hydride) reduction of olefin **11** provided allyl alcohol **8** (96%). Similarly, olefin **12** gave **9** in 95% yield. The orthoester Johnson–Claisen rearrangement of allyl alcohol **8** using trimethyl orthoacetate in the presence of a catalytic amount of propionic acid in toluene gave **7a** and **7b** in an optimum ratio of 1.2:1. Similarly, allyl alcohol **9** gave **7a** and **7b** in an optimum ratio of 1:1.5.[14] Although the diastereoselectivity was low, the mixtures of **7a** and **7b** could easily be separated by silica gel column chromatography. The separated diastereomers **7a** (44% from **8** or 32% from **9**) and **7b** (37% from **8** or 48% from **9**) were used to continue the synthesis.

The final transformations leading to the completion of the syntheses of **1** and **2** are shown in Scheme 3. The direct conversion of ester **7a** into the aldehyde (using DIBAL-H) and its subsequent Wittig olefination provided compound **14** in a low yield (25%). The low yield is attributed to the lack of selectivity in the reduction of **7a**, and the formation of a mixture of the corresponding aldehyde and alcohol **13** when 1 equiv. of DIBAL-H was used. The presence of alcohol **13** further diminished the yield of the subsequent Wittig product **14**. Hence, we attempted a stepwise sequence. Complete reduction of **7a** with DIBAL-H gave



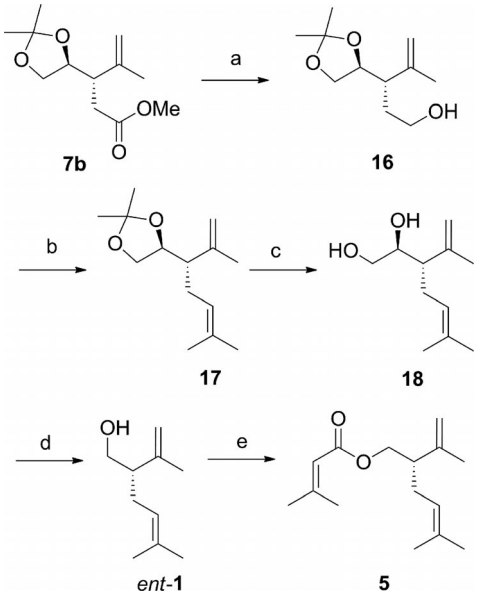
Scheme 3. Synthesis of **1** and **2**. Reagents and conditions: (a) DIBAL-H (2.4 equiv.), CH_2Cl_2, 0 °C, 3 h, 96%; (b) (i) DMSO (3.0 equiv.), $(COCl)_2$ (1.5 equiv.), CH_2Cl_2, –78 °C, 1 h, then Et_3N (4.5 equiv.), –78 °C, 0.5 h, (ii) $[Ph_3PCH(Me)_2]^+ Br^-$ (1.2 equiv.), *n*BuLi (1.2 equiv.), Et_2O, 0 °C, 3 h, 80%; (c) HCl (3 N), MeOH, room temperature, 2 h, 79%; (d) (i) $NaIO_4$/silica (3.0 equiv.), CH_2Cl_2, room temperature, 1 h, (ii) $NaBH_4$ (1.6 equiv.), MeOH, 0 °C, 1 h, 90%; (e) (*S*)-2-methylbutanoic acid (1.5 equiv.), Et_3N (3.0 equiv.), toluene, 0 °C, 30 min, then 2,4,6-trichlorobenzoyl chloride (2.0 equiv.), 0 °C to room temperature, 1.5 h, **1**, DMAP (3.0 equiv.), room temperature, 2.5 h, 69%.



Scheme 2. Synthesis of separable diastereomers **7a** and **7b**. Reagents and conditions: (a) $Ph_3P{=}C(Me)CO_2Et$ (1.2 equiv.), CH_2Cl_2, 0 °C, 2 h, **11** (93%); or $(EtO)_2P(O)CHMeCO_2Et$ (1.1 equiv.), NaH (1.0 equiv.), THF, 0 °C, 0.5 h, –78 °C, **10**, 3 h, **12** (46%), **11** (43%); (b) DIBAL-H (2.3 equiv.), CH_2Cl_2, 0 °C, 3 h, **8** (96%), **9** (95%); (c) $(MeO)_3CMe$ (10.0 equiv.), toluene, $EtCO_2H$ (cat.), reflux, 48 h; **7a** (44%), **7b** (37%) from **8**; or **7a** (32%), **7b** (48%) from **9**.

alcohol **13** (96%). Further oxidation (Swern) to the aldehyde and subsequent Wittig olefination now provided **14** in 80% yield (77% from **7a** over two steps). Removal of the acetonide group from **14** using HCl (3 N)/MeOH gave diol **15** (79%). Oxidative cleavage of diol **15** to the aldehyde using $NaIO_4$ and then immediate reduction with $NaBH_4$ gave enantiopure (*R*)-lavandulol (**1**; 90%), $[\alpha]_D^{25}$ = –10.9 (*c* = 1.25, MeOH) {ref.[10d] $[\alpha]_D^{25}$ = –9.6 (*c* = 1.0, MeOH)}. Furthermore, Yamaguchi esterification of (*R*)-lavandulol (**1**) with (*S*)-2-methylbutanoic acid gave compound **2** in 69% yield, $[\alpha]_D^{25}$ = +4.8 (*c* = 0.24, MeOH) {ref.[9c] $[\alpha]_D^{24}$ = +5.0 (*c* = 0.1, MeOH)}. The spectroscopic data for **1** and **2** were in full agreement with the literature data.[9c,9h]

The synthesis of *ent*-**1** and **5** is shown in Scheme 4. DIBAL-H reduction of ester **7b** gave alcohol **16** (95%). Oxidation of alcohol **16** under Swern conditions and subsequent Wittig olefination gave diene **17** (81%). Removal of the acetonide group in **17** using HCl (3 N)/MeOH gave diol **18** in 81% yield. The oxidative cleavage of diol **18** to the aldehyde using $NaIO_4$ and then immediate reduction with $NaBH_4$ gave (*S*)-lavandulol (*ent*-**1**; 89%), $[\alpha]_D^{25}$ = +9.5 (*c* = 0.94, MeOH) {ref.[10d] $[\alpha]_D^{25}$ = +10.1 (*c* = 1.13, MeOH)}. (*S*)-Lavandulol (*ent*-**1**) was esterified with 3,3-dimethylacrylic acid using DCC (*N*,*N*′-dicyclohexylcarbodiimide) and DMAP [4-(dimethylamino)pyridine] to give (*S*)-lavandulyl senecioate (**5**) in 74% yield, $[\alpha]_D^{25}$ = +11.4 (*c* = 0.6, hexane) {ref.[9e] $[\alpha]_D^{22}$ = +8.55 (*c* = 0.703, hexane)}. The spectroscopic data for **5** were in full agreement with the literature data.[9e]



Scheme 4. Synthesis of *ent*-**1** and **5**. Reagents and conditions: (a) DIBAL-H (2.4 equiv.), CH_2Cl_2, 0 °C, 3 h, 95%; (b) (i) DMSO (3.0 equiv.), $(COCl)_2$ (1.5 equiv.), CH_2Cl_2, –78 °C, 1 h, then Et_3N (4.5 equiv.), –78 °C, 0.5 h, (ii) $[Ph_3PCH(Me)_2]^+$ Br^- (1.2 equiv.), *n*BuLi (1.2 equiv.), Et_2O, 0 °C, 3 h, 81%; (c) HCl (3 N), MeOH, room temperature, 2 h, 81%; (d) (i) $NaIO_4$/silica (3.0 equiv.), CH_2Cl_2, room temperature, 1 h, (ii) $NaBH_4$ (1.6 equiv.), MeOH, 0 °C, 1 h, 89%; (e) DCC (1.5 equiv.), DMAP (0.2 equiv.), 3,3-dimethylacrylic acid (1.5 equiv.), CH_2Cl_2, 0 °C to room temperature, 24 h, 74%.

Conclusions

We have achieved an efficient and concise synthesis of (–)-(*R*)- and (+)-(*S*)-lavandulol (**1** and *ent*-**1**), (+)-lavandulyl 2-methylbutanoate (**2**) and (+)-lavandulyl senecioate (**5**). The synthetic strategy is based on a chiral-pool approach to an intermediate allyl alcohol, and a subsequent orthoester Johnson–Claisen rearrangement as the key step. Both enantiomers of lavandulol were accessible from the common intermediate allyl alcohols **8** or **9**. Although the diastereoselectivity in the orthoester Johnson–Claisen rearrangement was low, the ready separation of the two diastereomers of the product (i.e., **7a** and **7b**) makes this an efficient strategy for the synthesis of both enantiomers of lavandulol and also their esters **2** and **5**. The synthesis was completed in seven steps from **10** and gave a 21.5% overall yield for **1**, and 18.3% for *ent*-**1**.

Experimental Section

General Remarks: Flasks were oven- or flame-dried and allowed to cool in a desiccator. Dry reactions were carried out under Ar or N_2. Solvents and reagents were purified by standard methods. Thin-layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or with a UV lamp. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance III 400 spectrometer, and the chemical shifts are calibrated to the tetramethylsilane peak at δ = 0.00 ppm for ^1H NMR, and the $CDCl_3$ peak at δ = 77.00 ppm (t) for ^{13}C NMR spectra. IR spectra were obtained with a Perkin–Elmer Spectrum One FTIR spectrometer. Optical rotations were measured with a Jasco P-2000 digital polarimeter. HR mass spectra were recorded with a Micromass Q-Tof micro (YA-105) spectrometer.

Ethyl (*S*,*E*)-4,5-Isopropylidenedioxy-2-methylpent-2-enoate (11): The title compound was prepared stereoselectively according to a literature procedure.[13]

Ethyl (*S*,*E*)-4,5-Isopropylidenedioxy-2-methylpent-2-enoate (11) and Ethyl (*S*,*Z*)-4,5-Isopropylidenedioxy-2-methylpent-2-enoate (12): NaH (60% dispersion in mineral oil; 0.762 g, 19.06 mmol, 1.0 equiv.) was added to a solution of ethyl 2-(diethoxyphosphoryl) propanoate (5 g, 21.97 mmol, 1.1 equiv.) in dry THF (60 mL) at 0 °C. After stirring at 0 °C for 30 min, the resulting solution was stirred at –78 °C for 30 min. Then a solution of (*R*)-isopropylideneglyceraldehyde **10** (2.48 g, 19.06 mmol) in dry THF (20 mL) was added slowly, and the resulting mixture was stirred at –78 °C for 3 h. The reaction mixture was allowed to warm to 0 °C and quenched with water. The aqueous mixture was extracted with EtOAc (3× 75 mL), and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography (petroleum ether/EtOAc, 19:1) to give **12** (1.88 g, 46%) as a colorless oil. Further elution gave **11** (1.75 g, 43%) as a colorless oil.

Data for 11: $[\alpha]_D^{25}$ = +16.9 (*c* = 0.4, $CHCl_3$) {ref.[13b] $[\alpha]_D^{25}$ = +17.6 (*c* = 1.25, $CHCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2990, 2936, 1709, 1523, 1383, 1373, 1155, 1060, 928, 847, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3 H), 1.42 (s, 3 H), 1.45 (s, 3 H), 1.90 (d, *J* = 0.9 Hz, 3 H), 3.64 (dd, *J* = 7.9, 7.9 Hz, 1 H), 4.13–4.33 (m, 3 H), 4.82–4.90 (m, 1 H), 6.67–6.71 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 14.2, 25.8, 26.6, 60.9, 68.7, 72.7,

109.8, 131.1, 138.0, 167.3 ppm. HRMS (ESI^+): calcd. for $[C_{11}H_{18}O_4 + H]^+$ 215.1283; found 215.1281.

Data for 12: $[\alpha]_D^{25}$ = +74.24 (*c* = 0.48, $CHCl_3$) {ref.[13b] $[\alpha]_D^{25}$ = +66.3 (*c* = 1.02, $CHCl_3$)}. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2988, 2934, 1713, 1649, 1552, 1455, 1373, 1154, 1058, 1025, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H), 1.38 (s, 3 H), 1.45 (s, 3 H), 1.93 (dd, *J* = 1.1, 1.2 Hz, 3 H), 3.60 (dd, *J* = 8.2, 7.0 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.31 (dd, *J* = 8.2, 6.8 Hz, 1 H), 5.24–5.30 (m, 1 H), 6.07 (qd, *J* = 6.8, 1.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 20.0, 25.5, 26.6, 60.7, 69.6, 74.0, 109.4, 129.4, 142.2, 167.0 ppm. HRMS (ESI^+): calcd. for $[C_{11}H_{18}O_4 + H]^+$ 215.1283; found 215.1278.

(*S*,*E*)-4,5-Isopropylidenedioxy-2-methylpent-2-en-1-ol (8): Ester **11** (0.43 g, 2.01 mmol) was dissolved in CH_2Cl_2 (40 mL), and DIBAL-H (1.75 M in toluene; 2.7 mL, 4.63 mmol, 2.3 equiv.) was added dropwise at 0 °C. The reaction mixture was stirred for 3 h. The reaction was then quenched by the addition of potassium sodium tartrate (saturated aq.) at 0 °C, and the mixture was stirred vigorously at room temperature for 1 h. The aqueous mixture was extracted with CH_2Cl_2 (4× 30 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography (petroleum ether/EtOAc, 4:1) to give allyl alcohol **8** (0.332 g, 96%) as a colorless oil. $[\alpha]_D^{25}$ = +8.43 (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3437, 2988, 2935, 2875, 1638, 1456, 1373, 1157, 1059, 871, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.43 (s, 3 H), 1.74 (d, *J* = 1.2 Hz, 3 H), 1.81 (br. s, 1 H, OH), 3.56 (t, *J* = 8.1 Hz, 1 H), 4.04 (s, 2 H), 4.09 (dd, *J* = 8.1, 6.0 Hz, 1 H), 4.84 (ddd, *J* = 8.3, 8.3, 6.0 Hz, 1 H), 5.47–5.51 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 26.0, 26.7, 67.6, 69.3, 72.4, 109.0, 121.9, 140.9 ppm. HRMS (ESI^+): calcd. for $[C_9H_{16}O_3 + Na]^+$ 195.0997; found 195.0991.

(*S*,*Z*)-4,5-Isopropylidenedioxy-2-methylpent-2-en-1-ol (9): The title compound was prepared from **12** (0.57 g, 2.66 mmol) according to a procedure similar to that described for the conversion of **11** into **8** to give **9** (0.435 g, 95%) as a colorless oil. $[\alpha]_D^{25}$ = +9.87 (*c* = 0.22, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3437, 2987, 2938, 2878, 1635, 1455, 1373, 1244, 1157, 1058, 1013, 871, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.42 (s, 3 H), 1.85 (d, *J* = 1.4 Hz, 3 H), 1.97 (br. s, 1 H, OH), 3.55 (t, *J* = 8.0 Hz, 1 H), 4.07–4.12 (m, 2 H), 4.23 (d, *J* = 10.8 Hz, 1 H), 4.84–4.91 (m, 1 H), 5.34 (dd, *J* = 8.4, 0.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 25.9, 26.7, 61.7, 69.6, 71.9, 109.1, 124.9, 141.4 ppm. HRMS (ESI^+): calcd. for $[C_9H_{16}O_3 + Na]^+$ 195.0997; found 195.0990.

Methyl (3*R*,4*S*)-4,5-Isopropylidenedioxy-3-(prop-1-en-2-yl)pentanoate (7a) and Methyl (3*S*,4*S*)-4,5-Isopropylidenedioxy-3-(prop-1-en-2-yl)pentanoate (7b): Allyl alcohol **8** (0.37 g, 2.15 mmol) was dissolved in toluene (5 mL), and trimethyl orthoacetate (2.58 g, 21.5 mmol, 10.0 equiv.) and $EtCO_2H$ (cat.) were added. The solution was heated at reflux for 48 h. The mixture was allowed to cool to room temperature, the volatile material was removed under reduced pressure, and the residue was purified by silica gel flash column chromatography (petroleum ether/EtOAc, 19:1) to give **7a** (0.215 g, 44%) as a colorless oil. Further elution gave **7b** (0.181 g, 37%) as a colorless oil.

Data for 7a: $[\alpha]_D^{25}$ = +5.06 (*c* = 0.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3078, 2987, 2951, 2874, 1742, 1646, 1438, 1372, 1259, 1157, 1068, 972, 903, 862 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.41 (s, 3 H), 1.71 (d, *J* = 1.2 Hz, 3 H), 2.44 (dd, *J* = 14.8, 9.7 Hz, 1 H), 2.64–2.71 (m, 1 H), 2.77 (dd, *J* = 14.8, 4.8 Hz, 1 H), 3.64 (s, 3 H), 3.65 (dd, *J* = 8.2, 6.1 Hz, 1 H), 3.97 (dd, *J* = 8.2, 6.1 Hz, 1 H), 4.00–4.06 (m, 1 H), 4.81–4.85 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2, 25.6, 26.8, 36.1, 47.9, 51.5, 68.2, 77.2, 109.4, 114.0, 143.6, 172.9 ppm. HRMS (ESI^+): calcd. for $[C_{12}H_{20}O_4 + Na]^+$ 251.1259; found 251.1263.

Data for 7b: $[\alpha]_D^{25}$ = +9.63 (*c* = 0.16, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2930, 1735, 1437, 1374, 1158, 1062, 929, 850, 669, 628 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.41 (s, 3 H), 1.79 (s, 3 H), 2.45 (d, *J* = 8.1 Hz, 1 H), 2.46 (d, *J* = 6.9 Hz, 1 H), 2.85 (q, *J* = 7.2 Hz, 1 H), 3.62–3.67 (m, 1 H), 3.66 (s, 3 H), 3.95 (dd, *J* = 8.2, 6.2 Hz, 1 H), 4.15–4.22 (m, 1 H), 4.80 (s, 1 H), 4.89–4.91 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 25.3, 26.4, 34.4, 45.4, 51.6, 66.8, 76.6, 109.1, 113.2, 143.9, 172.5 ppm. HRMS (ESI^+): calcd. for $[C_{12}H_{20}O_4 + Na]^+$ 251.1259; found 251.1262.

Methyl (3*R*,4*S*)-4,5-Isopropylidenedioxy-3-(prop-1-en-2-yl)pentanoate (7a) and Methyl (3*S*,4*S*)-4,5-Isopropylidenedioxy-3-(prop-1-en-2-yl)pentanoate (7b): The title compounds were prepared from **9** (0.5 g, 2.91 mmol) according to a procedure similar to that described for the conversion of **8** into **7a** and **7b** to give **7a** (0.212 g, 32%) and **7b** (0.318 g, 48%) as colorless oils.

(2*S*,3*R*)-1,2-Isopropylidenedioxy-3-(prop-1-en-2-yl)pentan-5-ol (13): DIBAL-H (1.75 M in toluene; 4.8 mL, 8.40 mmol, 2.4 equiv.) was added dropwise to a solution of **7a** (0.8 g, 3.5 mmol) in CH_2Cl_2 (30 mL) at 0 °C, and the reaction mixture was stirred for 3 h. It was then quenched by the addition of a potassium sodium tartrate (saturated aq.), and the mixture was stirred vigorously at room temperature for 1 h. The aqueous solution was extracted with CH_2Cl_2 (4× 40 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography (petroleum ether/EtOAc, 4:1) to give alcohol **13** (0.674 g, 96%) as a colorless oil. $[\alpha]_D^{25}$ = –9.93 (*c* = 0.22, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3466, 3020, 2930, 1520, 1422, 1373, 1122, 1072, 1018, 929, 770, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.42 (s, 3 H), 1.68 (s, 3 H), 1.69–1.77 (m, 1 H), 1.90–2.01 (m, 1 H), 2.24–2.30 (m, 2 H), 3.54–3.65 (m, 2 H), 3.66–3.74 (m, 1 H), 3.91–4.00 (m, 1 H), 4.02–4.09 (m, 1 H), 4.80 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 25.8, 26.8, 34.5, 49.5, 61.5, 68.6, 76.7, 109.3, 113.4, 144.9 ppm. HRMS (ESI^+): calcd. for $[C_{11}H_{20}O_3 + H]^+$ 201.1491; found 201.1493.

(2*S*,3*R*)-1,2-Isopropylidenedioxy-6-methyl-3-(prop-1-en-2-yl)hept-5-ene (14): Oxalyl chloride (0.16 mL, 1.875 mmol, 1.5 equiv.) was gradually added to a solution of DMSO (0.27 mL, 3.75 mmol, 3 equiv.) in CH_2Cl_2 (25 mL) at –78 °C over a period of 5 min. After stirring for 10 min, a solution of **13** (0.25 g, 1.25 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred for 1 h. Et_3N (0.78 mL, 5.63 mmol, 4.5 equiv.) was added, and the mixture was stirred for 30 min. The mixture was gradually warmed to room temperature, and then it was diluted with CH_2Cl_2 (20 mL). Water (20 mL) was added, and then the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 40 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated to give the crude aldehyde (0.28 g), which was used directly in the next reaction.

*n*BuLi (1.6 M in hexane; 0.94 mL, 1.5 mmol, 1.2 equiv.) was added to a suspension of isopropyltriphenylphosphonium bromide (0.578 g, 1.5 mmol, 1.2 equiv.) in dry Et_2O (15 mL) at 0 °C. After stirring at 0 °C for 30 min, a solution of the crude aldehyde in dry Et_2O (5 mL) was added, and the resulting mixture was stirred at 0 °C for 3 h. The reaction was then quenched with a few drops of water, and the organic phase was filtered through a cotton plug. The residue was washed with Et_2O (2× 15 mL). The filtrate was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (pe-

troleum ether/EtOAc, 50:1) to give olefin **14** (0.224 g, 80%) as a colorless oil. $[\alpha]_D^{25}$ = –4.5 (*c* = 0.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3074, 3019, 2988, 2932, 1645, 1515, 1453, 1381, 1157, 1067, 900, 861, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (s, 3 H), 1.41 (s, 3 H), 1.61 (s, 3 H), 1.63 (s, 3 H), 1.67 (d, *J* = 0.6 Hz, 3 H), 2.00–2.18 (m, 2 H), 2.43–2.48 (m, 1 H), 3.60 (dd, *J* = 8.2, 7.0 Hz, 1 H), 3.92 (dd, *J* = 8.2, 6.0 Hz, 1 H), 3.99–4.05 (m, 1 H), 4.72 (s, 1 H), 4.80 (s, 1 H), 5.01–5.05 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 20.0, 25.7, 25.8, 26.9, 28.5, 51.7, 68.4, 77.8, 109.0, 113.4, 121.8, 132.2, 144.4 ppm. HRMS (ESI^+): calcd. for $[C_{14}H_{24}O_2 + H]^+$ 225.1855; found 225.1860.

(2*S*,3*R*)-6-Methyl-3-(prop-1-en-2-yl)hept-5-ene-1,2-diol (15): HCl (3 N; 0.5 mL) was added to a solution of **14** (0.204 g, 0.91 mmol) in MeOH (6 mL), and the mixture was stirred at room temperature for 2 h. The reaction was then quenched by the addition of powdered $NaHCO_3$ (1.0 g). The whole mixture was concentrated, and the residue was purified by silica gel flash column chromatography (petroleum ether/EtOAc, 3:2) to give **15** (0.132 g, 79%) as a colorless oil. $[\alpha]_D^{25}$ = +5.7 (*c* = 0.2, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3393, 3075, 2968, 2926, 1646, 1452, 1377, 1098, 1053, 897, 669 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.64 (s, 3 H), 1.66 (d, *J* = 0.4 Hz, 3 H), 1.67 (d, *J* = 1.1 Hz, 3 H), 1.85–2.00 (br. s, 1 H, OH), 2.00–2.20 (m, 2 H), 2.20–2.32 (br. s, 1 H, OH), 2.41–2.54 (m, 1 H), 3.41–3.52 (m, 1 H), 3.60–3.71 (m, 2 H), 4.75 (s, 1 H), 4.81–4.86 (m, 1 H), 5.03–5.11 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 19.9, 25.7, 28.1, 50.6, 65.4, 73.8, 113.4, 122.3, 132.4, 144.7 ppm. HRMS (ESI^+): calcd. for $[C_{11}H_{20}O_2 + H]^+$ 185.1542; found 185.1541.

(*R*)-5-Methyl-2-(prop-1-en-2-yl)hex-4-en-1-ol [(*R*)-Lavandulol, 1]: $NaIO_4$ (supported on silica gel; 0.417 g, 1.95 mmol, 3.0 equiv.) was added portionwise to a solution of diol **15** (0.120 g, 0.65 mmol) in CH_2Cl_2 (15 mL) at room temperature, and the reaction mixture was stirred for 1 h. The mixture was then filtered through a cotton plug, and the residue was washed with CH_2Cl_2 (3× 20 mL). The filtrate was concentrated to give the crude aldehyde (0.130 g), which was used for the next reaction without further purification.

$NaBH_4$ (40 mg, 1.04 mmol, 1.6 equiv.) was added portionwise to a solution of crude aldehyde in MeOH (2 mL) at 0 °C, and the reaction mixture was stirred for 1 h. The reaction was then quenched by the addition of NH_4Cl (saturated aq.). The mixture was extracted with Et_2O (3× 20 mL), and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography (petroleum ether/CH_2Cl_2, 4:1) to give **1** (0.09 g, 90%) as a volatile colorless oil. $[\alpha]_D^{25}$ = –10.9 (*c* = 1.25, MeOH) {ref.[10d] $[\alpha]_D^{25}$ = –9.6 (*c* = 1.0, MeOH)}. IR ($CHCl_3$): $\tilde{\nu}$ = 3398, 3075, 2968, 2928, 1646, 1450, 1377, 1038, 892, 838, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.61 (s, 3 H), 1.70 (s, 3 H), 1.71 (s, 3 H), 1.97–2.16 (m, 2 H), 2.23–2.34 (m, 1 H), 3.50 (dd, *J* = 10.7, 8.2 Hz, 1 H), 3.57 (dd, *J* = 10.7, 5.1 Hz, 1 H), 4.79–4.85 (m, 1 H), 4.90–4.96 (m, 1 H), 5.05–5.12 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 19.4, 25.7, 28.3, 49.9, 63.6, 113.1, 122.0, 132.7, 145.4 ppm. HRMS (ESI^+): calcd. for $[C_{10}H_{18}O + H]^+$ 155.1436; found 155.1431.

(*R*)-5-Methyl-2-(prop-1-en-2-yl)hex-4-enyl (*S*)-2-Methylbutanoate (2): Dry Et_3N (0.325 mL, 2.33 mmol, 3 equiv.) was added to a solution of (*S*)-2-methylbutanoic acid (0.120 g, 1.166 mmol, 1.5 equiv.) in dry toluene (4 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, and then 2,4,6-trichlorobenzoyl chloride (0.16 mL, 1.04 mmol, 2.0 equiv.) was added at the same temperature. The resulting solution was stirred at room temperature for 1.5 h, and a solution of alcohol **1** (0.120 g, 0.778 mmol) in toluene (4 mL) and DMAP (0.131 g, 1.07 mmol, 3 equiv.) were added, and the stirring was continued for a further 2.5 h. The reaction was then quenched with water, and the solution was extracted with CH_2Cl_2 (3× 25 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography (petroleum ether/EtOAc, 19:1) to give ester **2** (0.128 g, 69%) as a colorless oil. $[\alpha]_D^{24}$ = +4.8 (*c* = 0.24, MeOH) {ref.[9c] $[\alpha]_D^{24}$ = +5.0 (*c* = 0.1, MeOH)}. IR ($CHCl_3$): $\tilde{\nu}$ = 2971, 2934, 1737, 1649, 1461, 1384, 1265, 1186, 1154, 1122, 1017, 897 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.4 Hz, 3 H), 1.13 (d, *J* = 7.0 Hz, 3 H), 1.41–1.49 (m, 1 H), 1.60 (s, 3 H), 1.61–1.74 (m, 1 H), 1.69 (s, 3 H), 1.70 (s, 3 H), 2.02–2.10 (m, 1 H), 2.10–2.20 (m, 1 H), 2.30–2.45 (m, 2 H), 4.01–4.15 (m, 2 H), 4.74 (s, 1 H), 4.82 (d, *J* = 1.4 Hz, 1 H), 5.04–5.09 (m, 1 H) ppm. ^1H NMR (400 MHz, C_6D_6): δ = 0.84 (t, *J* = 7.4 Hz, 3 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 1.31–1.40 (m, 1 H), 1.50 (s, 3 H), 1.60 (d, *J* = 0.32 Hz, 3 H), 1.61 (s, 3 H), 1.63–1.74 (m, 1 H), 1.97–2.16 (m, 2 H), 2.29 (sext, *J* = 6.9 Hz, 1 H), 2.43 (quint, *J* = 7.1 Hz, 1 H), 4.07–4.19 (m, 2 H), 4.77–4.81 (m, 1 H), 4.81–4.86 (m, 1 H), 5.08–5.17 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.6, 16.6, 17.8, 19.8, 25.7, 26.7, 28.6, 41.1, 46.2, 65.4, 112.4, 121.6, 132.9, 144.8, 176.7 ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 12.2, 17.3, 18.2, 20.2, 26.2, 27.5, 29.3, 41.7, 47.2, 65.8, 113.1, 122.7, 133.0, 145.6, 176.2 ppm. HRMS (ESI^+): calcd. for $[C_{15}H_{26}O_2 + H]^+$ 239.2011; found 239.2017.

(2*S*,3*S*)-1,2-Isopropylidenedioxy-3-(prop-1-en-2-yl)pentan-5-ol (16): The title compound was prepared from **7b** (0.218 g, 0.955 mmol) according to a procedure similar to that described for the conversion of **7a** into **13** to give **16** (181 mg, 95%) as a colorless oil. $[\alpha]_D^{25}$ = +33.7 (*c* = 0.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3364, 3020, 2930, 1525, 1436, 1311, 1093, 1021, 928, 772, 670, 627 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.41 (s, 3 H), 1.53–1.59 (m, 1 H), 1.59–1.71 (m, 2 H), 1.76 (d, *J* = 0.6 Hz, 3 H), 2.38–2.45 (m, 1 H), 3.54–3.62 (m, 1 H), 3.64–3.70 (m, 2 H), 4.02–4.13 (m, 2 H), 4.83 (s, 1 H), 4.93 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 25.5, 26.7, 31.6, 47.4, 60.8, 67.9, 76.7, 108.9, 113.8, 144.5 ppm. HRMS (ESI^+): calcd. for $[C_{11}H_{20}O_3 + H]^+$ 201.1491; found 201.1496.

(2*S*,3*S*)-1,2-Isopropylidenedioxy-3-(prop-1-en-2-yl)-6-methylhept-5-ene (17): The title compound was prepared from **16** (0.12 g, 0.6 mmol) according to a procedure similar to that described for the conversion of **13** into **14** to give **17** (109 mg, 81%) as a colorless oil. $[\alpha]_D^{25}$ = +23.9 (*c* = 0.22, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2985, 2930, 1454, 1378, 1254, 1159, 1062, 892, 864, 518 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.40 (s, 3 H), 1.59 (s, 3 H), 1.72 (s, 3 H), 1.73 (s, 3 H), 2.03 (t, *J* = 7.1 Hz, 2 H), 2.20 (q, *J* = 7.5 Hz, 1 H), 3.63 (t, *J* = 7.5 Hz, 1 H), 3.95–4.10 (m, 2 H), 4.75–4.77 (m, 1 H), 4.86–4.90 (m, 1 H), 5.00–5.05 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 20.0, 25.6, 25.7, 26.7, 28.2, 50.7, 68.1, 77.5, 108.6, 113.1, 121.7, 132.5, 144.8 ppm. HRMS (ESI^+): calcd. for $[C_{14}H_{24}O_2 + H]^+$ 225.1855; found 225.1862.

(2*S*,3*S*)-6-Methyl-3-(prop-1-en-2-yl)hept-5-ene-1,2-diol (18): The title compound was prepared from **17** (0.12 g, 0.534 mmol) according to a procedure similar to that described for the conversion of **14** into **15** to give **18** (0.08 g, 81%) as a colorless oil. $[\alpha]_D^{25}$ = +14.0 (*c* = 0.4, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3403, 3074, 2969, 2927, 1644, 1451, 1377, 1157, 1096, 1055, 896, 668, 581 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.61 (s, 3 H), 1.68 (s, 3 H), 1.70 (s, 3 H), 1.97–2.10 (m, 1 H), 2.11–2.27 (m, 3 H, OH), 2.41 (br. s, 1 H, OH), 3.50–3.65 (m, 2 H), 3.77 (d, *J* = 10.7 Hz, 1 H), 4.83 (s, 1 H), 4.96 (s, 1 H), 4.97–5.03 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 19.4, 25.7, 27.6, 50.2, 64.7, 72.2, 114.8, 121.6, 132.7, 145.0 ppm. HRMS (ESI^+): calcd. for $[C_{11}H_{20}O_2 + H]^+$ 185.1542; found 185.1538.

(*S*)-5-Methyl-2-(prop-1-en-2-yl)hex-4-en-1-ol [(*S*)-Lavandulol, *ent*-1]: The title compound was prepared from **18** (0.08 g, 0.434 mmol) according to a procedure similar to that described for the conversion of **15** into **1** to give *ent*-**1** (0.06 g, 89%) as a volatile colorless oil. $[\alpha]_D^{25}$ = +9.5 (*c* = 0.94, MeOH) {ref.[10d] $[\alpha]_D^{25}$ = +10.1 (*c* = 1.13, MeOH)}. Other spectroscopic data, i.e., IR, and ^{1}H and ^{13}C NMR data were the same as for (*R*)-lavandulol (**1**).

(*S*)-5-Methyl-2-(prop-1-en-2-yl)hex-4-enyl 3-Methylbut-2-enoate (5): 3,3-Dimethylacrylic acid (39 mg, 0.389 mmol, 1.5 equiv.), DCC (80.3 mg, 0.389 mmol, 1.5 equiv.), and DMAP (6.3 mg, 0.052 mmol, 0.2 equiv.) were added to a solution of *ent*-**1** (40 mg, 0.259 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 24 h. After the reaction was complete, it was quenched by the addition of HCl (1 N; 3 drops), and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography (petroleum ether/EtOAc, 19:1) to give ester **5** (45.4 mg, 74%) as a colorless oil. $[\alpha]_D^{22}$ = +11.4 (*c* = 0.6, hexane) {ref.[9e] $[\alpha]_D^{22}$ = +8.55 (*c* = 0.703, hexane)}. IR ($CHCl_3$): $\tilde{\nu}$ = 3076, 2962, 2925, 2856, 1721, 1650, 1448, 1378, 1347, 1265, 1227, 1147, 1078, 1029, 1006, 893, 851 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58 (s, 3 H), 1.68 (d, *J* = 1.1 Hz, 3 H), 1.70–1.71 (m, 3 H), 1.88 (d, *J* = 1.4 Hz, 3 H), 2.02–2.22 (m, 2 H), 2.15 (d, *J* = 1.2 Hz, 3 H), 2.35–2.50 (m, 1 H), 4.00–4.12 (m, 2 H), 4.72–4.76 (m, 1 H), 4.81–4.85 (m, 1 H), 5.01–5.11 (m, 1 H), 5.64–5.68 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 19.9, 20.2, 25.7, 27.4, 28.7, 46.1, 65.1, 112.2, 116.1, 121.7, 132.8, 145.1, 156.4, 166.7 ppm. HRMS (ESI$^+$): calcd. for $[C_{15}H_{24}O_2 + H]^+$ 237.1855; found 237.1857.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds **11**, **12**, **8**, **9**, **7a**, **7b**, **13**, **14**, **15**, **1**, **2**, **16**, **17**, **18**, and **5**; GC analysis of racemic lavandulol, (−)-(*R*)- and (+)-(*S*)-lavandulols.

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