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SYNTHESIS OF TWO STEREOISOMERS OF THE PROPANOATE ESTER OF 8-METHYL-2-DECANOL USING REMOTE ASYMMETRIC INDUCTION.

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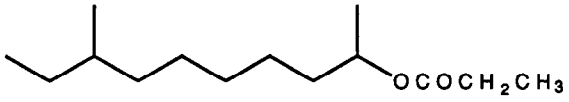
Abstract: A stereoselective synthesis of two isomers (2S,8R) and (2S,8S) of 8-methyl-2-decanol propanoate (the pheromone emitted by females of several *Diabrotica* species) has been accomplished using remote stereochemical relationships between carbons 3 and 9 of the 3,9-dimethyl decanolides **14** and **16**.

The sex pheromone emitted by the female Western corn rootworm (WCR), *Diabrotica virgifera virgifera* LeConte, was isolated and identified as 8-methyl-2-decanol propanoate **1** (figure 1).[1] Racemic 8-methyl-2-decanol has been synthesized previously (Guss et al.[1], **1982**; Abrams and Shaw[2], **1987**). The stereoisomers were also synthesized in high optical purity by the coupling of available enantiomerically pure starting material or from the resolution of intermediates (Mori and Watanabe[3], **1984**; Sonnet et al.[4], **1985**).



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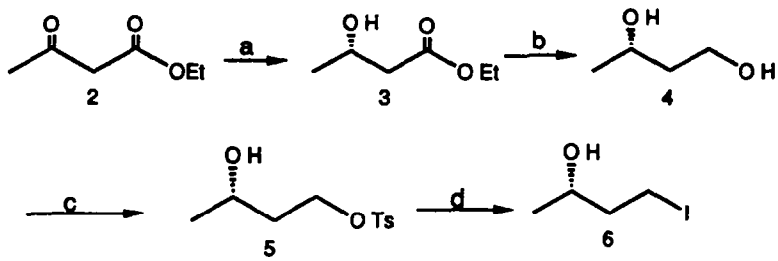
(figure 1)

In this paper we describe the asymmetric total synthesis of two diastereoisomers (2S,8S) **17** and (2S,8R) **18** of 8-methyl-2-decanol propanoate without the need for chiral auxiliaries or resolution.

Our synthesis features a diastereoselective process to produce the stereogenic centers of both isomers of 8-methyl-2-decanol, starting from one asymmetric center of (S)-(+)-4-iodo-2-butanol **6**.

The compound **6** ($[\alpha]_D$ = + 14.53, $CHCl_3$) was obtained in four steps from ethyl acetoacetate **2**. Ethyl acetoacetate was selectively reduced with baker's yeast[5] to the ethyl (S)-(+)-3-hydroxybutanoate **3** ($[\alpha]_D$ = + 31.60, $CHCl_3$). Conversion of **3** into the (S)-tosylate **5** was effected by reduction with LAH in tetrahydrofuran and subsequent tosylation of the primary alcohol. The iodide (S)- **6** was obtained in 37% overall yield by treating (S)-**5** with NaI in acetone (Scheme I).

From (S)-(+)- 4-iodo-1-butanol **6** the α,β–unsaturated lactone **13** was readily prepared in high yield, with Wakamatsu's methodology.[6]

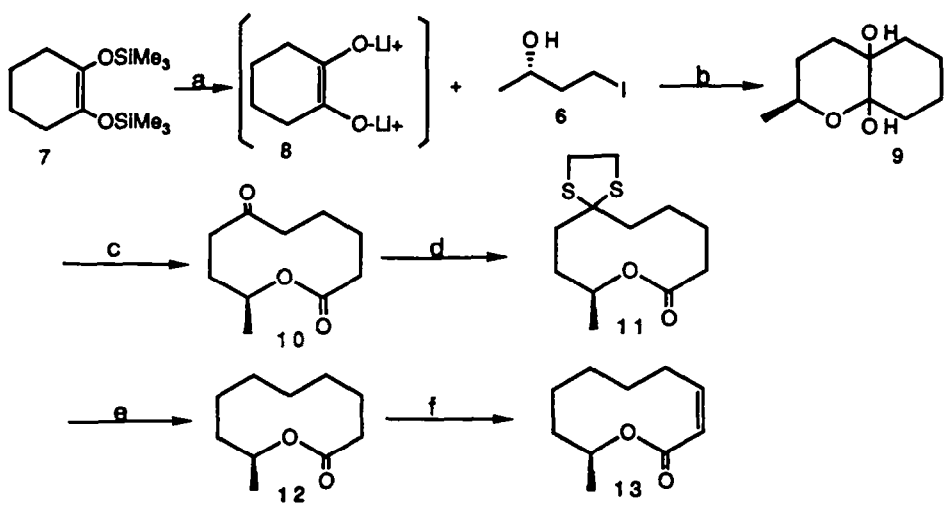


a) Baker's Yeast; b) LAH/THF; c) TsCl/Pyr; d) NaI/acetone

(Scheme I)

The enediol bis(trimethylsilyl)enol ether **7**, prepared by the modified acyloin condensation of diethyl adipate in the presence of chlorotrimethylsilane, was converted to the 1,2-enediolate **8**, which was immediately subjected to alkylation with (S)-**6** to give two diastereomeric bicyclic glycols **9**. Ring opening of **9** with lead tetraacetate in benzene afforded the keto lactone **10**, in 94% yield. Thioketalization of **10** with ethanedithiol gave the corresponding dithio lactone **11** in 95% yield, which upon desulfurization with Raney nickel provided (S)-(+)-decan-9-olide **12** ($[\alpha]_D$ = + 26.66, $CHCl_3$) in 92% yield.

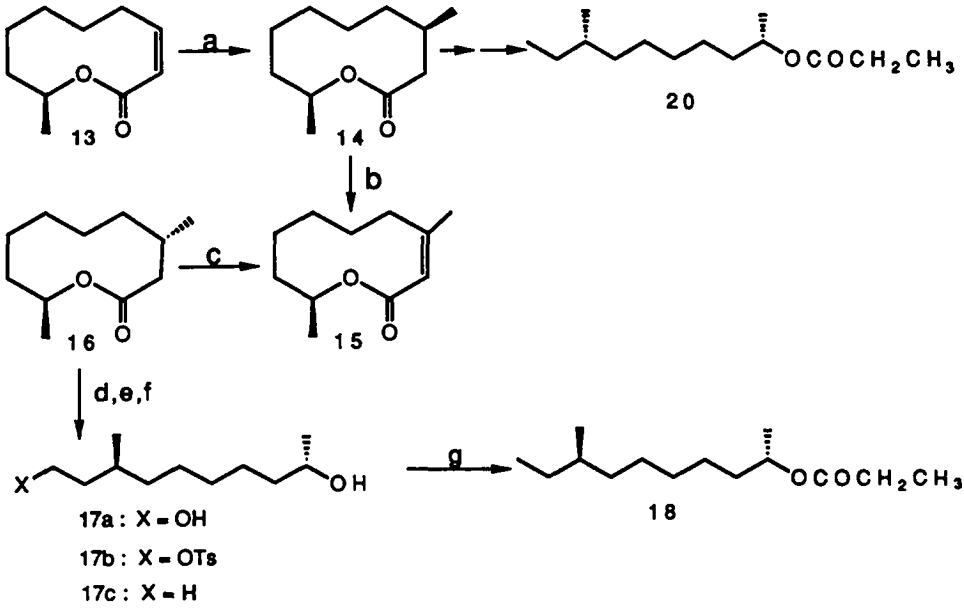
The α,β-unsaturated methyl lactone **13** ($[\alpha]_D$ = - 33.5, $CHCl_3$) was prepared from **12** via enolate selenation, oxidation and selenoxide elimination (Scheme II).



a) MeLi/DME; b) HMPA/THF (1:1) (60%); c) $Pb(OAc)_4$/Bz (94%); d) $HS(CH_2)_2SH/CH_2Cl_2$, $BF_3.Et_2O$ (95%); e) Ra(Ni) (92%); f) LDA/THF, PhSeCl, H_2O_2 (78%)

(Scheme II)

The chiral α-β-unsaturated methyl lactone **13** and the dimethyl lactone **15** , prepared from **13** (Scheme III), were subjected to the diastereoselective conjugate addition of dimethyl cuprate or catalytic hydrogenation to afford dimethyl lactones[7] **14** ($[\alpha]_D$ = + 16.04, $CHCl_3$) and **16** (*cis:trans* ratio of 77:23, determined by ^1H NMR), respectively (Scheme III).



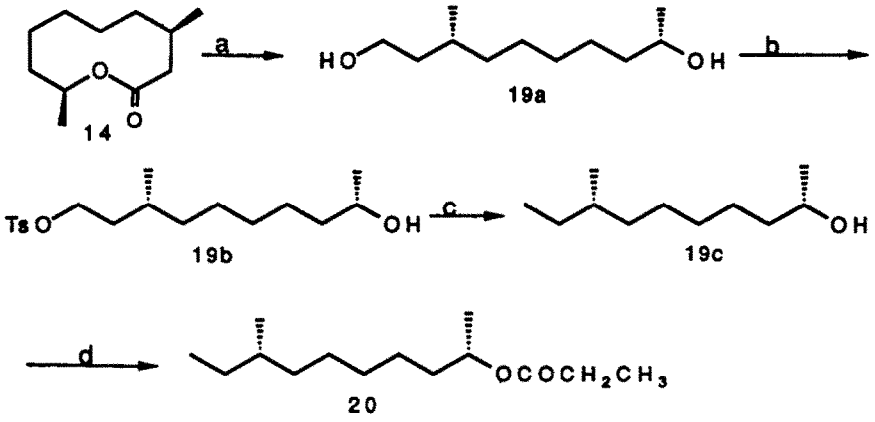
a) CuI/Et_2O, MeLi, $BF_3.Et_2O$, -70° (73.5%); b) LDA/THF, PhSeCl, H_2O_2 (82%);

c) H_2,Rh/C, MeOH (97%); d) LAH/THF (96%); e) TsCl/Pyr (100%);

f) LIB(C_2H_5)H/THF (75%); g) CH_3CH_2COCl/Pyr (80%)

(Scheme III)

Both isomers **20** and **18** were obtained by a series of straightforward transformations. Reductive cleavage of lactones **14** and **16** with lithium aluminum hydride afforded the corresponding 10-hydroxy- 8-methyl-2-decanol. Regioselective tosylation of the primary alcohol and subsequent reduction with lithium triethylborohydride[8] provided the 8-methyl- 2-decanol. Esterification of the alcohol was accomplished with propionyl chloride in pyridine to give 8-methyl-2-decanol propanoate stereoselectively. Scheme IV demonstrates the synthesis of the (2S,8S) isomer **20** from lactone **14**.



a) LAH/THF (96%); b) TsCl/Pyr (85%); c) LIB$(C_2H_5)_3$H/THF, O° (76%);

d) CH_3CH_2COCl/Pyr (81%)

(Scheme IV)

The optical rotation for the late intermediates and the final products was not obtained since the amount of material did not meet the technical specifications of our polarimeter. The reported[4] rotation angle for the propanoate **18** $[\alpha]_D$= -3.77° ($CHCl_3$, c = 15.0) and **20** $[\alpha]_D$= +8.5972° ($CHCl_3$, c = 12.7) was obtained using concentrated solutions of the products.

Experimental Section

NMR spectra were recorded on Varian FT-80, Perkin-Elmer Hitachi R-24A and Brucker AC 200 spectrometers. Mass spectra were recorded with an ionizing voltage of 70 eV on HP 5995 spectrometer. Optical rotations were measured as chloroform solutions on Bellingham + Stanley Limited polarimeter. IR spectra were recorded on Perkin-Elmer 735 spectrometer. Baker's Yeast was purchased locally (ITAYQUARA BRAND). All of the solvents used were previously distilled. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use.

Preparation of Iodoalcohol 6 from ethylacetoacetate 2.

Ethyl (S)-(+)-β-hydroxybutyrate 3. This microbiological reduction was performed using Seebach's procedure[5c]. The Ethyl (S)-(+)- β-hydroxybutyrate **3** was obtained after short path distillation, 57 °C (2,0 mmHg); lit[5c] 71-73 °C (21 mmHg),16.7 g (82 %), $[\alpha]_D$ = +31.6° ($CHCl_3$); lit[5c] $[\alpha]_D$=+37.2°($CHCl_3$, c=1.3):^{1}HNMR: 1.21-1.35 (m,6H), 2.45 (d,2H,J=6Hz), 3.84-4.34 (m,3H); IR:3430,2970,1725 cm^{-1}

(S)-1,3-Butanediol 4. A solution of **3** 16.6 g (126 mmol) in dry THF (30 ml) was carefully added to a suspension of LAH 4.05 g (106.8 mmol) in THF (300 ml) at O °C. The reaction mixture was stirred for 2.5 hr at room temperature, then cooled to 0 °C. Water (4 ml), 10% NaOH (4 ml) and H_2O (12 ml) were added in this order. After stirring for an additional hour at room temperature, the reaction mixture was filtered, dried over Na_2SO_4 and concentrated in vacuo. After short path distillation, 68-72 °C (0.5 mmHg), 7.5 g (66%) of **4** was obtained.^{1}HNMR: 1.23 (d,3H,J=6Hz), 1.6 (q,2H,J=6Hz), 3.73 (t,2H,J=6Hz), 3.75-4.35 (m,3H);IR: 3360, 2950 cm^{-1}

(S)-3-Hydroxybutyl tosylate 5. To a solution of **4** 5.25 g (58.4 mmol) in pyridine (38 ml) at O °C was added *p*-toluenesulphonyl chloride 12.39 g (63.7 mmol). After 3 hr, the reaction mixture was diluted with water and extracted with ether. The organic phase was washed with saturated $CuSO_4$ and dried over Na_2SO_4. After solvent evaporation in vacuo, the crude product was purified by chromatography on silica gel with hexane-ether (3:2) to give 12 g (84%) of **5**.^{1}HNMR: 0.96-1.67 (m,3H), 1.5-1.83 (m,2H), 2.33 (s,3H), 3.67-4.17 (m,3H), 7.27 (d,2H,J=8Hz), 7.67 (d,2H,J=8HZ);IR: 3450, 2950, 1600, 1365, 1270 cm^{-1}

(S)-(+)-3-Hydroxybutyl iodide 6. A mixture of **5** 12 g (42 mmol), KI 23.9 g (144 mmol) and Na_2CO_3 6.35 g (75.6 mmol) in dry acetone (150 ml) was refluxed for 7 hr. After being concentrated in vacuo, the residue was diluted with water and extrated with benzene. The organic phase was washed respectivaly with water, 10% *meta*-sodiumbisulfite and water. After drying over Na_2SO_4 and solvent evaporation, the crude product was purified by short path distillation, 60-62 °C (0.5 mmHg) to give 7.8 g (79%) of pure iodoalcohol **6**, $[\alpha]_D$= +14.53° ($CHCL_3$).^{1}HNMR: 1.15 (d,3H,J=6Hz), 1.87 (q,2H,J=7Hz), 3.22 (t,2H,J=7Hz), 3.85 (m,1H); IR: 3370, 2950 cm^{-1}

Preparation of (S)-(-)-Dec-2-en-9-olide 13.

For the preparation of the unsaturated lactone **13** we used the exact procedure described by Wakamatsu[6] and co-workers, starting from the enediol bis(trimethylsilyl)enol ether **7** and the chiral iodoalcohol **6**. The overall yield was 38.5 %. The spectral data of the intermediates are given below.

(3S)-1,6-Dihydroxy-3-methyl-2-oxabyciclo(4.4.0) decane 9. ^{1}HNMR: 1.02 (d,3H,J=6.25Hz), 1.06-2.00 (m,12H), 3.47 (s,5H), 3.55 (s,5H), 3.80-4.25 (m,1H); 5.16 (s,5H), 5.20 (s,5H); IR: 3575, 3305, 2905, 1455cm^{-1}; mp=111-113°C (lit.[6] mp 110-111°C)

(S)-6-Oxodecan-9-olide 10. ^{1}HNMR: 1.24 (d,3H,J=6.25Hz), 1.40-2.67 (m,12H), 4.75-5.10 (m,1H);IR: 2930,1725, 1245, 1145 cm^{-1};mp= 43-44 °C (lit.[6] mp 44-44.5°C)

(S)-6,6-(Ethylenedithio)decan-9-olide11.^{1}HNMR:1.21(d,3H,J=6.25HZ), 1.4-2.5 (m,12H), 3.25 (s,4H), 4.66-5.16(m,1H); IR: 2940, 1710, 1450, 1205 cm^{-1}; mp= 71-72 °C (lit.[6] mp 71-72°C)

(S)-(+)-Decan-9-olide 12. ^{1}HNMR: 1.26 (d,3H,J=6.25HZ), 1.0-2.7 (m,14H), 4.8-5.47 (m,1H); ^{13}CNMR: 173.58, 72.39, 35.05, 31.50, 26.91, 24.23, 23.99, 23.32, 20.63, 19.35; IR: 2930, 1725, 1440, 1230 cm^{-1};$[\alpha]_D$= +26.66° ($CHCL_3$); lit[9] $[\alpha]_D$= +38.38° ($CHCl_3$,c= 0.68)

(S)-(-)-Dec-2-en-9-olide 13. ^{1}HNMR: 1.30 (d,3H,J=6.25Hz), 1.4-2.1 (m,8H), 2.4-3.1 (m,2H), 4.8-5.5 (m,1H), 5.77 (d,1H,J=10), 6.0-6.55 (m,1H);^{13}CNMR: 166.85, 144.57, 123.57, 71.01, 33.01, 26.90, 25.94, 25.53, 20.50, 19.83; IR: 2950,1715,1460,1280 cm^{-1}; $[\alpha]_D$= -33.50° ($CHCL_3$)

Preparation of (2S,8S)-8-methyl-2-decanol propanoate 20.

(3R,9S)-(+)-3-Methyl-decan-9-olide 14. Using Still's procedure[7] we were able to transform 363 mg of the unsaturated lactone **13** to 291 mg (74%) of the (3R,9S)-(+)-3-Methyl-decan-9-olide **14** , after chromatographic purification.^{1}HNMR: 0.985 (d,3H,J=6.25Hz), 1.245 (d,3H,J=6.25Hz), 1.28-1.88 (m,10H),1.88-2.0 (m,2H), 2.19-2.34 (m,1H), 4.59-5.16 (m,1H);^{13}CNMR: 173.945, 71.591, 42.915, 33.825, 31.799, 31.508, 26.547, 23.528, 22.903, 21.169, 20.539; IR: 2940, 1730, 1440 cm^{-1}; $[\alpha]_D$= +16.04° ($CHCL_3$)

(3R,9S)-3-methyl-9-Hydroxy decanol 19a. To a suspension of LAH 40.0 mg in dry THF, the dimethyl lactone **14** 40.0 mg (0.217 mmol) was added under nitrogen and the reaction was stirred at room temperature for 4 hr. After filtration and solvent evaporation in vacuo, the crude product was purified by chromatography on silica gel with EtOAc-hexane (10:1) to give 39 mg (95%) of **19a**.^{1}HNMR: 0.81 (d,3H,J=5Hz); 1.12 (d,3H,J=6.25Hz), 1.17-1.53 (m,13H), 3.25-3.86 (m,3H); ^{13}CNMR: 67.97, 61.01, 39.90, 39.24, 36.91, 29.72, 29.41, 26.73, 25.57, 23.35, 19.52; IR: 3350, 2940, 770 cm^{-1}

(3R,9S)-3-methyl-9-Hydroxy-decyl tosylate 19b. This was prepared in the same manner as described for **5**, 39 mg of **19a** gave 54 mg (77%) of **19b**.^{1}HNMR: 0.60-0.87 (m,3H), 1.00 (d,3H,J=6Hz), 1.05-1.67 (m,13H), 2.3 (s,3H), 3.0-4.0 (m,3H), 7.15 (d,2H,J=8Hz), 7.58 (d,2H,J=8Hz); IR: 3380, 2910, 1350, 1170 cm^{-1}

(2S,8S)-8-Methyl-2-decanol 19c. To an ice cooled solution of **19b** 107 mg (0.313 mmol) in THF (3 ml), 0.63 ml of 1.0 M solution of Super-hydride ^{R} was added under nitrogen. The reaction was allowed to stir at room temperature for 2 hr. Water (1.0 ml), 3M sodium hydroxyde (0.3 ml) and 30% hydrogen peroxyde were added, in this sequence. The product was extracted with ether and the combined organic phases washed with water and dried over Na_2SO_4. After solvent evaporation in vacuo, the crude product was purified by chromatography on silica gel with hexane-ether (1:1) to give 41 mg (76%) of **19c**.^{1}HNMR: 0.69-1.0 (m,6H), 1.17 (d,3H,J=6.25Hz), 1.18-1.72 (m,13H), 1.75 (s,1H), 3.5-3.97 (m,1H);^{13}CNMR: 68.08, 39.39, 36.58, 34.85, 29.89, 29.45, 27.06, 25.77, 23.4, 19.18,11.30; IR: 3385; 2935 cm^{-1}

(2S,8S)-8-Methyl-2-decanol Propanoate 20. A solution of **19c** (41 mg, 0.24 mmol) and propionyl choride (0.1 ml) in dry pyridine (1.5 ml) was stirred at room temperature overnight. After addition of 1M HCl solution (2 ml), the reaction mixture was extracted with ether. The organic phase was washed with water, saturated $NaHCO_3$ and saturated NaCl, then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel with ether-hexane (1:3) to give 44 mg (81%) of **20**.^{1}HNMR: 0.75-0.89 (m,6H), 1.10 (t,3H,J=7Hz), 1.16 (d,3H,J=6Hz), 1.2-1.6 (m,13H); 2.27 (q,2H,J=7Hz), 4.87 (m,1H); ^{13}CNMR: 174.188, 70.811, 36.498, 35.961, 34.350, 29.792, 29.464, 27.956, 26.963, 25.435, 19.989, 19.186, 11.387, 9.223, IR: 2920, 1735, 1460, 1180 cm^{-1}

Preparation of (2S,8R)-8-Methyl-2-decanol Propanoate 18.

(S)-3-Methyl-dec-2-en-9-olide 15. This was prepared in the same manner as described for **13** in 82% yield.^{1}HNMR: 1.15 (d,3H,J=6Hz), 1.33-1.70 (m,8H), 1.82 (s,3H), 2.50-3.17 (m,2H), 4.75-5.35 (m,1H); 5.63 (s,1H);^{13}CNMR: 167.340, 156.834, 118.639, 70.892, 33.094, 31.213, 26.956, 26.541, 26.291, 20.522, 20.109, IR: 2940, 1705, 1615, 1450, 1265 cm^{-1}

(3S,9S)-3-Methyl-decan-9-olide 16. To a suspension of 5% Rh/carbon (258 mg) in 10 ml of methanol was added **15** (175 mg, 0.96 mmol). The mixture was hydrogenated at 25 Kgf/cm^2 for 2 hr at 0 ^{o}C and then was allowed to warm to 25 ^{o}C. The catalyst was filtered off and the solvent was removed at reduced pressure to give 172 mg (97%) of **16** (contaminated with 23% of cis isomer (^{1}HNMR)).^{1}HNMR: 0.92 (d,3H,J=6.25Hz), 1.26 (d,3H,J=6.25Hz), 1.31-1.86 (m,10H), 1.88-2.14 (m,2H), 2.23-2.51 (m,1H), 4.86-5.14 (m,1H);^{13}CNMR: 172.847, 72.628, 42.924, 36.281, 31.468, 26.189, 24.803, 24.433, 23.646, 22.661, 19.204; IR: 2950, 1725, 1240 cm^{-1}

(3S,9S)-3-methyl-9-Hydroxy decanol 17a. This was prepared in the same manner as described for **19a** in 96% yield.^{1}HNMR: 0.88 (d,3H,J=6.25Hz), 1.16 (d,3H,J=6.25Hz), 1.19-1.72 (m,13H), 2.16 (s,2H), 3.44-3.94 (m,3H); ^{13}CNMR: 68.09, 61.04, 39.85, 39.26, 36.95, 29.83, 29.38, 26.82, 25.69, 23.42, 19.58; IR: 3350; 2935 cm^{-1}

(3S,9S)-3-methyl-9-Hydroxy-decyl tosylate 17b. This was prepared in the same manner as described for **19b** in 100% yield.^{1}HNMR: 0.65-0.96 (m,3H), 1.03 (d,3H,J=6Hz), 1.12-1.18 (m,13H) 2.38 (s,3H), 3.0-4.2 (m,3H), 7.3 (d,2H,J=8Hz), 7.73 (d,2H,J=8Hz); IR: 3355, 2910, 1355, 1165 cm^{-1}

(2S,8R)-8-Methyl-2-decanol 17c. This was prepared in the same manner as described for **19c** in 75% yield.^{1}HNMR: 0.69-1.0 (m,6H), 1.17 (d,3H,J=6.25Hz), 1.18-1.59 (m,13H), 3.44-3.95 (m,1H);^{13}CNMR: 68.17, 39.37, 36.54, 34.36, 29.99, 29.46, 27.05, 25.81, 23.45,19.19, 11.39, IR: 3370, 2950 cm^{-1}

(2S,8R)-8-Methyl-2-decanol Propanoate 18. This was prepared in the same manner as described for **20** in 80% yield.^{1}HNMR: 0.75-0.86 (m,6H), 1.10 (t,3H,J=7Hz), 1.16 (d,3H,J=6Hz), 1.2-1.6 (m,13H), 2.27 (q,2H,J=7Hz), 4.86 (m,1H); ^{13}CNMR: 174.191, 70.815, 36.499, 35.963, 34.349, 29.793, 29.463, 27.958, 26.962, 25.437, 19.987, 19.188, 11.385, 9.224; IR: 2920, 1735, 1460, 1180 cm^{-1}

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