Syntheses of the Sixteen Stereoisomers of 3,7,11-Trimethyl-2-tridecanol, Including the (2*S*,3*S*,7*S*,11*R*) and (2*S*,3*S*,7*S*,11*S*) Stereoisomers Identified as Pheromone Precursors in Females of the Pine Sawfly *Microdiprion pallipes* (Hymenoptera: Diprionidae)[‡]

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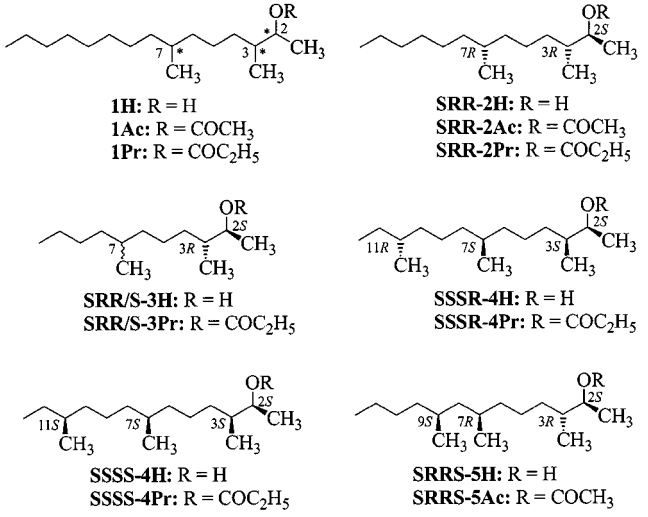
All sixteen stereoisomers of 3,7,11-trimethyl-2-tridecanol were synthesised in high stereoisomerical purities (> 95%), for use in the identification of the stereoisomers present in females of the pine sawfly *Microdiprion pallipes* (Fallén) (Hymenoptera: Diprionidae) as the precursor of the actual sex pheromone (which is the propionate), and also for investigation of the biological activities of the esters. The key step in the syntheses was the coupling of each of the enantiomers of *cis*-3,4-dimethyl-γ-butyrolactone with each of the four pure stereoisomers of 1-lithio-2,6-dimethyloctanes. The four corresponding alcohols were obtained by lipase-catalysed (Amano PS) kinetic separation, based on selective acylation of either (2*R*/*S*,6*S*)- or (2*R*/*S*,6*R*)-2,6-dimethyl-1-octanol (obtained from the optically pure enantiomers of citronellal). Additionally, a mixture of the 16 possible stereoisomers of 3,7,11-trimethyl-2-tridecanol was also prepared.

Introduction

Pine sawflies of the Diprionidae family are severe pests of conifers, particularly pine trees.[1] Until recently, all pine sawfly species were considered to use the acetates and/or propionates of the two stereoisomers of diprionol − either (2*S*,3*S*,7*S*)- or (2*S*,3*R*,7*R*)-3,7-dimethyl-2-pentadecanol (**1H**) − as their sex pheromone.[2] However, during the last five years, several pine sawfly species have been found to use sex pheromones representing structural types different from that of the diprionyl esters. Thus, the pheromone of *Diprion pini* was identified as either the propionate or the acetate of one stereoisomer of a chain-shortened diprionol, i.e., (2*S*,3*R*,7*R*)-3,7-dimethyl-2-tridecanol (***SRR*-2H**).[3,4] An even shorter homologue, the propionate of (2*S*,3*R*,7*R*/*S*)-3,7-dimethyl-2-undecanol (***SRR*/*S*-3Pr**), was identified as the pheromone of the Japanese pine sawfly *Diprion nipponica* by Tai et al.[5] Recently, the sex pheromone of *Microdiprion pallipes* was identified as the propionate of one or several stereoisomers of 3,7,11-trimethyl-2-tridecanol, and two *erythro* isomers of this alcohol − ***SSSR*-4H** and ***SSSS*-4H** − were found to be present in females of that species.[6,7] Yet another structural variation is found in the female of *Macrodiprion nemoralis*, which produces (2*S*,3*R*,7*R*,9*S*)-3,7,9-trimethyl-2-tridecanol (***SRRS*-5H**) as the precursor for the acetate that acts as the active sex pheromone.[8]



Several syntheses of sex pheromones of pine sawflies have been described during the last decade in papers from our laboratory, among them the syntheses of the acetates of the eight stereoisomers of 3,7-dimethyl-2-pentadecanol (**1Ac**),[9] the acetates and propionates of 3,7-dimethyl-2-tridecanol, including the biologically active compounds ***SRR*-2Ac** and ***SRR*-2Pr**,[4] and very recently the syntheses of the sixteen stereoisomers of acetylated 3,7,9-trimethyl-2-tridecanol were also published.[10] In this paper we wish to present the syntheses of all sixteen stereoisomers of 3,7,11-trimethyl-2-tridecanol, including the (2*S*,3*S*,7*S*,11*R*) and (2*S*,3*S*,7*S*,11*S*) stereoisomers (***SSSR*-4H** and ***SSSS*-4H**, respectively) found to be present[7] in the female of *M. pallipes*. The preparation of the two stereoisomers (2*S*,3*S*,7*S*,11*R*)- and (2*S*,3*R*,7*R*,11*R*)-3,7,11-trimethyl-2-tridecanol has recently been reported by others.[11] [Nakamura and Mori[11] claim that (2*S*,3*S*,7*S*,11*R*)- and (2*S*,3*R*,7*R*,11*R*)-3,7-dimethyl-2-

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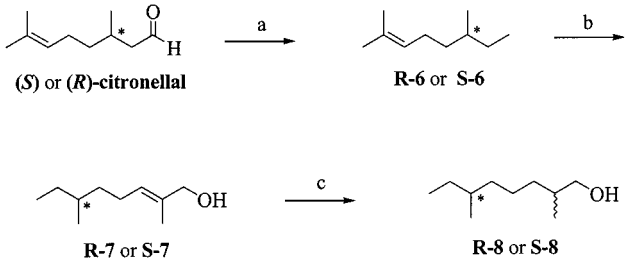
tridecanol, in the form of their propionate esters, are components of the sex pheromone of the pine sawfly *M. pallipes*. However, the latter isomer (in alcohol form) is not found in the female extract, whereas the former is.[7]] We also present the synthesis of the propionate ester of a sixteen isomer mixture of 3,7,11-trimethyl-2-tridecanol for field tests.[6]

Results and Discussion

All new compounds tested as potential pheromone components were prepared using essentially the same methodology as previously used in our laboratory for the syntheses of the stereoisomers of other diprionid pheromones and related compounds[4,9,10,12]. Accordingly, the propionates **4Pr** of the pure stereoisomers of 3,7,11-trimethyl-2-tridecanol were prepared as follows.

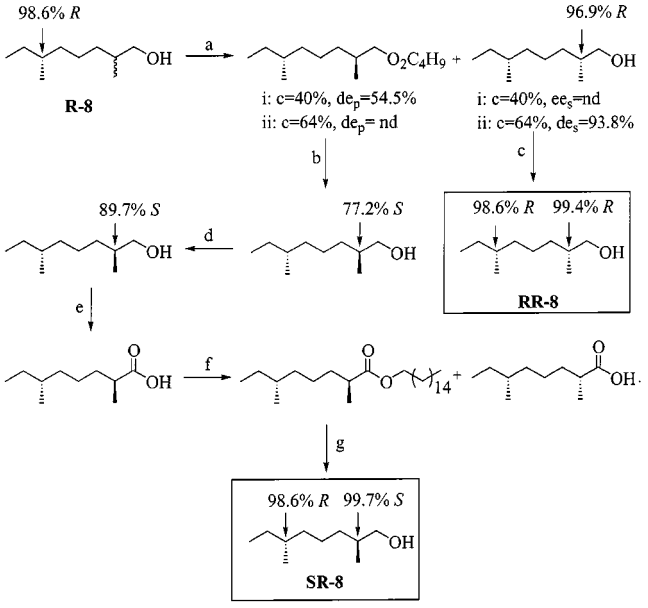
The individual isomers of (*S*)- and (*R*)-3,7-dimethyl-6-octenal were reduced to give ***R*-6** or ***S*-6**, respectively, under Huang−Minlon conditions similar to those in the literature procedure[13] (see Scheme 1). Selenium dioxide oxidation of these alkenes, followed by in situ reduction with $NaBH_4$, furnished the allylic oxidation products 2,6-dimethyl-2-octen-1-ol ***R*-7** or ***S*-7**, respectively. These allylic alcohols were subjected to catalytic hydrogenation with Raney nickel to give 2,6-dimethyl-1-octanol (***R*-8** or ***S*-8**, respectively), as mixtures of two diastereomers.

The optically pure stereoisomers of alcohol **8** were produced from the alcohols ***S*-8** (see Scheme 2) and ***R*-8** (see Scheme 3) by enzyme-catalysed reactions. Thus, the alcohol

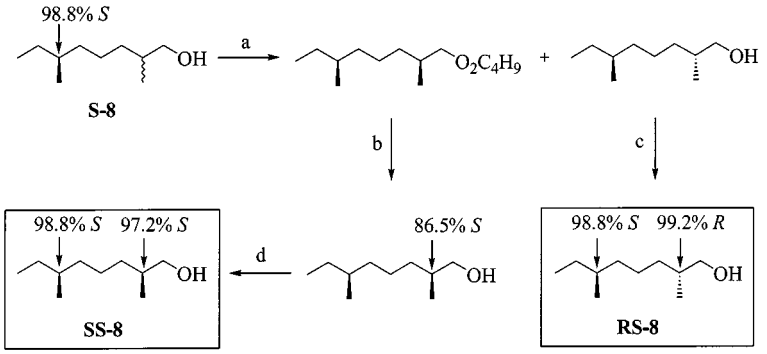


Scheme 1. a) $N_2H_4 \times H_2O$, KOH, diethylene glycol, 170 °C; b) 1. *t*BuOOH, SeO_2, CH_2Cl_2, 2. $NaBH_4$, NaOH, MeOH, 0−30 °C; c) Raney Ni, H_2, MeOH, 40 °C

***SS*-8** was obtained after two sequential, diastereoselective acylation reactions catalysed by Amano PS in chloroform at low water activity ($a_w \approx 0$) with vinyl butyrate as the acyl donor, resulting in a practically irreversible[14] reaction. For resolution of racemates under such conditions, the enantioselectivity (*E* value) can be calculated using the equations derived by Chen et al.[15] [$E = \{\ln[1 - c\cdot(1+ee_p)]\}/\{\ln[1 - c\cdot(1 - ee_p)]\}$ (where *E* is enantiomeric ratio), *c* (conversion) = $ee_s/(ee_s + ee_p)$, ee_s and ee_p are the enantiomeric excess of the substrate and product, respectively]. However, in the case of compounds ***R*-** or ***S*-8**, there were two stereogenic centres present in the starting alcohols, so use of the *E* value is not strictly appropriate. However, we did make use of the Chen formula to calculate the diastereose-



Scheme 3. a) Lipase-catalysed kinetic acylation; Amano PS, $CHCl_3$, vinyl butyrate, $a_w \approx 0$, $c = 40\%$ or 64% and then LC separation of the product and the substrate; b) KOH/MeOH; c) substrate ii, lipase-catalysed kinetic acylation; Amano PS, $CHCl_3$, vinyl butyrate, $a_w \approx 0$, $c = 40\%$ and then LC separation of the product and the substrate; d) 1. lipase-catalysed kinetic acylation; Amano PS, $CHCl_3$, vinyl butyrate, $a_w \approx 0$, $c = 70\%$ and then LC separation of the product and the substrate; 2. KOH/MeOH; e) CrO_3/H_2SO_4 acetone, 0 °C; f) lipase-catalysed kinetic acylation; Im-CRL, 1-hexadecanol, $a_w \approx 0.8$, cyclohexane, $c = 40\%$; g) $LiAlH_4$, Et_2O



Scheme 2. a) Lipase-catalysed kinetic acylation; Amano PS, $CHCl_3$, vinyl butyrate, $a_w \approx 0$, $c = 50\%$ and then LC separation of the product and the substrate; b) KOH/MeOH; c) lipase-catalysed kinetic acylation; Amano PS, $CHCl_3$, vinyl butyrate, $a_w \approx 0$, $c = 60\%$ and then LC separation of the product and the substrate; d) 1. lipase-catalysed kinetic acylation; Amano PS, $CHCl_3$, vinyl butyrate, $a_w \approx 0$, $c = 51\%$ and then LC separation of the product and the substrate; 2. KOH/MeOH

lectivity "*E*" of the lipase towards the stereogenic centre at C-2 in the alcohols ***R*-** or ***S*-8**. In this case, the ee_s and ee_p values are accordingly replaced by diastereomeric excess values (de_s and de_p, respectively).

The first enzymatic diastereoselective acylation of alcohol ***S*-8** was stopped at 50% conversion. The de_p of the faster reacting stereoisomer, of (*S*) configuration at C-2, was determined to be 73%, corresponding to an "*E*" value of 13.8. The intermediate ester product was hydrolysed, using KOH/MeOH, to give the (2*S*,6*S*)-alcohol ***SS*-8**, which was subsequently subjected to a second cycle of lipase-catalysed acylation (c = 51%), followed by base-promoted hydrolysis to yield ***SS*-8** (see Scheme 2) with a stereoisomeric purity at C-2 of 97.2% (*S*) and a diastereomeric purity of 96.0% (see Table 1).

Table 1. Stereoisomeric composition of the four individual stereoisomers (2*S*,6*S*)-, (2*S*,6*R*)-, (2*R*,6*S*)-, and (2*R*,6*R*)-2,6-dimethyl-1-octanol

Isomer	***SS*-8**	***SR*-8**	***RS*-8**	***RR*-8**	*ee*[a]	*dr*[b]
***SS*-8**	> 96.0%	1.2%	< 2.8%	< 0.1%	> 99.8%	> 96:4
***SR*-8**	1.3%	> 98.4%	< 0.1%	< 0.3%	> 99.8%	> 98.4:1.6
***RS*-8**	< 0.8%	< 0.1%	> 97.9%	1.2%	> 99.8%	> 98:2
***RR*-8**	< 0.1%	< 0.6%	1.3%	> 98.1%	> 99.8%	> 98.1:1.9

[a] Enantiomeric excess of the major isomer. – [b] Diastereomeric ratio [(***SS*-8** + ***RR*-8**)/(***SR*-8** + ***RS*-8**) or (***SR*-8** + ***RS*-8**)/(***SS*-8** + ***RR*-8**)].

In order to produce the diastereomerically pure ***RS*-8**, the remaining substrate from both reactions above, (2*R*,6*S*)-alcohol ***RS*-8**, was collected [68.5% (*R*) at C-2] and subjected to a new enzymatic diastereoselective acylation. At 60% conversion, ***RS*-8** was obtained with a stereoisomeric purity at C-2 of 99.2% (*R*) and with 97.9% diastereomeric purity (see Table 1).

The double kinetic, enzymatic, diastereoselective acylation technique described above for alcohol ***S*-8** was also applied to the alcohol ***R*-8**, which after the first (40% conversion) and second (70% conversion) enzymatic steps gave alcohol ***SR*-8** with 89.7% (*S*) configuration at C-2 (see Scheme 3). In this case, the "*E*" value was calculated to be 4.8 from the measured de_p and c (54.5% and 40%, respectively) At this stage, for our requirements, the diastereomeric purity at C-2 was unacceptably low. *Candida rugosa* lipase (CRL) had recently been used by two of us for successful catalysis of kinetic stereoselective separation by esterification of some dimethylcarboxylic acids, such as 2,6-dimethyloctanoic acid.[16] Therefore, we decided to apply this method to enhance the stereoisomeric purity of the obtained alcohol ***SR*-8**. Accordingly, this alcohol was oxidised to the carboxylic acid using Jones reagent (see Scheme 3) and then subjected to an esterification reaction, catalysed by immobilised CRL, with 1-hexadecanol in cyclohexane at a_w = 0.8. After reduction ($LiAlH_4$) of the (2*S*,6*R*)-ester (the faster reacting isomer), obtained at 40% conversion, the alcohol ***SR*-8** was obtained with > 99.5% (*S*) configuration at C-2 and a diastereomeric purity of 98.4% (See Table 1).

The remaining substrate obtained from the first Amano PS catalysed transesterification step mentioned above – (2*R*,6*R*)-dimethyl-1-octanol ***RR*-8**, with 96.9% (*R*) configuration at C-2 (see Scheme 3) – was subjected to a second enzymatic diastereoselective acylation catalysed by Amano PS. This resulted, after 70% conversion, in the alcohol ***RR*-8**, with 99.4% (*R*) configuration at C-2 (98.1% of the ***RR*-8** stereoisomer, see Table 1).

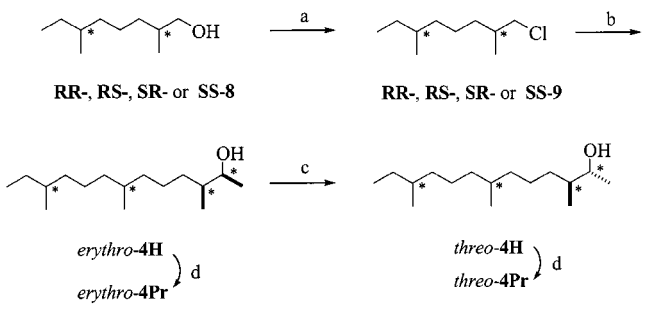
The observed difference in enzyme selectivity "*E*" for the two diastereomeric pairs ***R*-8** and ***S*-8** (4.8 and 13.8, respectively) in these lipase PS catalysed acylation reactions, is significant and intriguing, because the configuration at the remotely located, methyl-substituted C-6 obviously has a large influence on the selectivity of lipase PS. We are currently studying this phenomenon further. Similar observations have recently been made in cases of CRL-catalysed esterification of diastereomeric dimethyl-substituted acids.[16]

The optical rotations obtained by us for the alcohols ***SR*-8** ($[\alpha]_D^{25}$ = −21.4) and ***RS*-8** ($[\alpha]_D^{25}$ = +18.3) were much larger than those previously published.[17–20] Furthermore, the optical rotations for the alcohols ***SS*-8** ($[\alpha]_D^{25}$ = −2.41) and ***RR*-8** ($[\alpha]_D^{25}$ = +2.58) prepared by us were significantly smaller than those previously reported.[17–21] Most of the previously published syntheses[17–20] involved catalytic hydrogenation of an enantiomerically enriched unsaturated alcohol with the stereogenic centre located between the alcohol and the double bond. In many cases, reductions are known to give a certain degree of epimerisation,[13,22–26] leading to lower than expected stereoisomeric purity at C-6 in the final products.

In order to establish the optical rotation values for the individual isomers of **8**, we used an independent and unambiguous synthetic route to prepare two of the stereoisomers of 2,6-dimethyl-1-octanol: namely ***RS*-** and ***SS*-8** (see Exp. Sect. for details). Hence, enantiomerically pure (*S*)-2-methyl-1-butanol (> 99% *ee*) was converted into the bromide and then transformed into (*S*)-4-methylhexanoic acid (> 98% *ee*) by a malonic ester two-carbon chain-extension sequence. This acid was reduced ($LiAlH_4$) to the alcohol, which was converted into the iodide. When this was used in a diastereoselective alkylation of either one of the enolates obtained from the pure enantiomers of propionylated pseudoephedrine, according to the general procedure reported for such amide alkylations,[27] two diastereomeric 2,6-dimethyloctanoic amides were obtained. These were reduced (LiH_2NBH_3)[28] to give the target molecules ***RS*-8** and ***SS*-8**, with optical rotation values of $[\alpha]_D^{25}$ = +20.4, (c = 2.83, $CHCl_3$) and $[\alpha]_D^{25}$ = −2.71, (c = 2.65, $CHCl_3$), respectively.

The four individual stereoisomers of 2,6-dimethyl-1-octanol (***RR*-**, ***RS*-**, ***SR*-**, and ***SS*-8**) were converted into the chlorides (***RR*-**, ***RS*-**, ***SR*-**, or ***SS*-9**) (see Scheme 4). From these, the corresponding alkyllithium compounds were prepared and each was allowed to react with each of the enantiomers of *cis*-3,4-dimethyl-γ-butyrolactone. This gave in each case an oxo alcohol, which after Huang–Minlon reduction yielded one of the eight *erythro*-3,7,11-trimethyl-2-tridecanols (*erythro*-**4H**). Each one of the eight individual *erythro* isomers was obtained separately, with a diastereom-

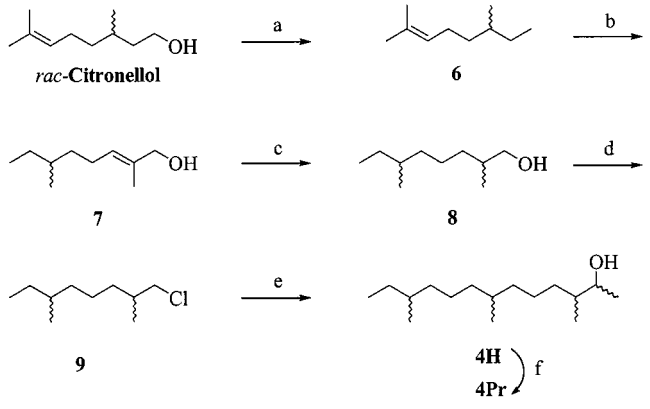
eric purity of > 97.6%, except for the (2*S*,3*S*,7*S*,11*S*) and (2*R*,3*R*,7*S*,11*S*) isomers, which had diastereomeric purities of 95.9% and 95.7%, respectively.



Scheme 4. a) PPh_3, CCl_4, reflux, b) 1. Li(s), reflux, *n*-hexane, 2. addition to one of the enantiomers of *cis*-3,4-dimethyl-γ-butyrolactone at −78 °C, 3. $N_2H_4 \times H_2O$, KOH, diethylene glycol, 170 °C, 1 h, then 210 °C, 3 h; c) 1. PPh_3, $PhCO_2H$, $N_2(CO_2Et)_2$, 2. NaOH, H_2O/MeOH/dioxane; d) 10 equiv. CH_3CH_2COCl, CH_2Cl_2

The eight individual *threo* isomers (*threo*-**4H**) were obtained from the *erythro* isomers by Mitsunobu inversion at C-2, followed by basic hydrolysis of the resulting benzoate. The eight *threo* isomers were all obtained with diastereomeric purities of > 97.4%, except for the (2*R*,3*S*,7*S*,11*S*) and (2*S*,3*R*,7*S*,11*S*) isomers, which had diastereomeric purities of 95.3 and 95.5%, respectively. Acylation of the individual *erythro* and *threo* isomers (*erythro*-**4H** and *threo*-**4H**) using propionyl chloride furnished the sixteen isomers of **4Pr**.

The propionate, **4Pr**, of 3,7,11-trimethyl-2-tridecanol was also prepared as a mixture of all 16 possible stereoisomers (*erythro*/*threo* ratio 58:42 mixture), by essentially the same method as that used for the syntheses of each of the sixteen individual stereoisomers in their pure forms. However, in this case the synthesis started from racemic citronellol, which was converted into a tosylate and reduced with $LiAlH_4$ to yield racemic 2,6-dimethyl-2-octene (**6**) (see Scheme 5).[6]



Scheme 5. a) 1. *p*TsCl, pyridine, 2. $LiAlH_4$, Et_2O; b) 1. *t*BuOOH, SeO_2, 2. $NaBH_4$; c) Raney Ni, H_2, MeOH, 40 °C; d) PPh_3, CCl_4, reflux; e) 1. Li(s), reflux, *n*-hexane, 2. addition to a *cis*/*trans* mixture (58:42) of *rac*-3,4-dimethyl-γ-butyrolactone at −78 °C, 3. $N_2H_4 \times H_2O$, KOH, diethylene glycol, 170 °C, 1 h, then 210 °C, 3 h; f) 10 equiv. CH_3CH_2COCl, CH_2Cl_2

Conclusion

In conclusion, we have synthesised the propionate esters, **4Pr**, of 3,7,11-trimethyl-2-tridecanol both as one mixture of all isomers, and as sixteen highly pure individual stereoisomers. The results from biological studies of the stereoisomers produced by female *M. pallipes*, from electrophysiological experiments and from field tests with *M. pallipes* will be published elsewhere.[7]

Experimental Section

Commercially available chemicals were used without further purification unless stated otherwise. Amano PS and *Candida rugosa* Lipase (CRL) were purchased from LABKEMI and Sigma Aldrich respectively, and stored at 4 °C over dry silica gel. Alkyl halides were distilled prior to use and stored under argon. The reactions involving lithium derivatives were carried out under anhydrous conditions and argon. Dry diethyl ether and tetrahydrofuran were distilled from $LiAlH_4$ and potassium/benzophenone, respectively. The (3*S*,4*S*)- and (3*R*,4*R*)-*cis*-dimethyl-γ-butyrolactones used were obtained from the same batches as those prepared by Bergström et al.:[4] (*SS*): > 99.9% *ee* and < 0.04% *trans*; (*RR*): > 99.7% *ee* and < 0.03% *trans*. (*R*)- and (*S*)-3,7-dimethyl-6-octenal were purchased from Fluka, checked by ^1H NMR and their optical rotations measured as +15.5 (neat) and −15.9 (neat), respectively. − The enantiomeric purity of these was determined by GC, 30 m × 0,25 mm I.D. capillary column coated with β-dex 225, d_f = 0.25 μm; carrier gas He 15 psi, split ratio 30:1 (GC programme: 90 °C/20 min, 1 °C/min, 120 °C); retention time (min): 37.4 [(*S*) enantiomer] and 37.9. [(*R*) enantiomer]. − (*S*)-(−)-2-Methyl-1-butanol was purchased from Fluka, checked by ^1H NMR and its enantiomeric purity determined by GC, 30 m × 0.25 mm I.D. capillary column coated with β-dex 325, d_f = 0.25 μm; carrier gas He 15 psi, split ratio 30:1 (GC programme: 40 °C/20 min, 0.5 °C/min, 50 °C); retention time (min): 33.5 [(*R*) enantiomer] and 34.9 [(*S*) enantiomer]. Preparative liquid chromatography (LC) was performed on straight-phase silica gel (Merck 60, 230−400 mesh, 0.040−0.063 mm) employing a gradient technique using an increasing concentration of distilled diethyl ether in distilled *n*-pentane or of distilled ethyl acetate in distilled cyclohexane (0 → 100%), as eluent. Progress was monitored by GC or thin layer chromatography, which was performed on silica gel plates (Merck 60 F_{254}, precoated aluminium foil) eluted with ethyl acetate (20−40%) in cyclohexane and developed by means of ultraviolet light and/or by spraying with vanillin/sulfuric acid in ethanol and heating at 120 °C. − NMR spectra were recorded with a Bruker DMX 250 (250 MHz ^1H and 62.9 MHz ^{13}C) spectrometer, using $CDCl_3$ as solvent and TMS as internal reference. − Optical rotations were measured with a Perkin−Elmer 241 polarimeter, using a 1-dm cell. − Mass spectra were recorded with a Saturn 2000 instrument, operating in the EI or CI (CH_3CN as chemical ionisation gas) mode, coupled to a Varian 3800 GC instrument. Exact masses (HRMS) were obtained using a VG-70E mass spectrometer. Unless otherwise stated, conversions and purities were monitored on a 30 m × 0.25 mm I.D. capillary column coated with CP-Sil 19CB, d_f = 0.25 μm; carrier gas N_2 100 kPa, split ratio 30:1 (flow 1 mL/min). − The *erythro*/*threo* ratio of **4H** and the individual isomers of *erythro*-**4H** and *threo*-**4H** were determined using a 30 m × 0.25 mm I.D., d_f = 0.25μm, capillary column coated with CP-WAX 52 CB, carrier gas He 16 psi, split ratio 30:1 (GC programme: 80 °C, 1 °C/min, 150 °C); retention time (min): 66.0 (*erythro*) and 67.2 (*threo*). − Unless otherwise stated, "extractive workup" consisted

of extraction with the given solvent followed by drying with anhydrous $MgSO_4$, filtering, and solvent removal in a rotary evaporator. Boiling points are uncorrected and given as air-bath temperatures (bath temp./mbar) in a bulb-to-bulb (Büchi-GKR-51) apparatus. − Elemental analysis was performed by Mikrokemi AB, SE-752 28 Uppsala, Sweden.

(*R*)-(−)-2,6-Dimethyl-2-octene (*R*-6): (*S*)-Citronellal (20.2 g, 0.13 mol) (> 97.3% *ee*) was added to a solution of freshly distilled diethylene glycol (277 mL, 2.92 mol) containing KOH (38.8 g, 0.69 mol) and hydrazine monohydrate (10.1 mL, 0.21 mol). The solution was slowly heated to 170 °C, at which temperature it was kept for 1 h before cooling and distillation. The product, together with some water, was collected between 105−110 °C. The water phase was extracted with 50 mL of *n*-pentane, the pooled organic phases were washed with 2 × 75 mL of H_2O and 75 mL of brine, dried, and concentrated to give the product (13.3 g, 73% after distillation, b.p. 155 °C/1 atm), > 99% pure by GC. − $[\alpha]_D^{25}$ = −11.0 (neat), ref.[29] $[\alpha]_D^{25}$ = −10.54 (neat). − ^{1}H NMR: δ = 0.86 (d, 3 H, *J* = 6.3 Hz), 0.86 (t, 3 H, *J* = 7.3 Hz), 1.08−1.19 (m, 2 H), 1.26−1.39 (m, 3 H), 1.60 (3 H, s), 1.68 (d, 3 H, *J* = 1.0 Hz), 1.91−1.99 (m, 2 H), 5.11 (1 H, tq, *J* = 1.3 and 7.1 Hz). ^{13}C NMR: δ 11.3, 17.6, 19.1, 25.6, 25.7, 29.4, 34.0, 36.7, 125.1, 130.9. − MS (EI); *m*/*z* (%): 140 (17) [M^+], 125 (10), 111 (24), 83 (18), 69 (100), 55 (70). − ^{1}H NMR and ^{13}C NMR spectral data correspond well with those reported in the literature.[30−33]

(*S*)-(−)-2,6-Dimethyl-2-octene (*S*-6): Similarly, (*R*)-citronellal (30.2 g, 0.20 mol) (97.5% *ee*) gave (*S*)-6 (22 g, 80%), > 99.5% pure by GC. B.p. 153−155 °C/1 atm. − $[\alpha]_D^{25}$ = +11.0 (neat), ref.[29] $[\alpha]_D^{25}$ = +10.54 (neat). − ^{1}H NMR, ^{13}C NMR, and MS (EI) spectral data match those of ***R*-6**.

2,6-Dimethyl-2-octene (6): Use of the tosylation method of Byström et al.,[34] but starting from citronellol (20 g, 0.13 mol), gave the tosylate, which was reduced with $LiAlH_4$ (5.3 g, 0.14 mol) according to the procedure of Rapoport and Bonner.[35] Compound **6** (13.2 g, 74%) was obtained after LC and distillation, (b.p. 82 °C/72 mbar), 98% pure by GC. ^{1}H NMR, ^{13}C NMR, and MS (EI) spectral data match those of ***R*-6**.

(*R*)-(−)-2,6-Dimethyl-2-octen-1-ol (*R*-7): Following the protocol of Umbreit and Sharpless,[36] ***R*-6** (13.2 g, 94.1 mmol) was added dropwise at 15 °C to a magnetically stirred suspension of 70% *tert*-butyl hydroperoxide (32.5 mL, 338 mmol), SeO_2 (0.21 g, 1.88 mmol), salicylic acid (1.30 g, 9.4 mmol), and CH_2Cl_2 (30 mL). The reaction mixture was kept at room temperature for 44 h and then quenched by addition of 70 mL of MeOH and a solution of $NaBH_4$ (5.7 g, 150 mmol) in 30 mL 0.2 M aq. NaOH at 0 °C. The solution was stirred at room temperature overnight and then treated with 150 mL of H_2O and 150 mL of *n*-pentane. The water phase was extracted with 2 × 50 mL of *n*-pentane and the pooled organic phases were washed with 100 mL brine. The mixture, containing the product and the starting material, was subjected to LC to give the title alcohol (11.5 g, 78% after distillation, b.p. 60 °C/5 mbar), > 99% pure by GC. − $[\alpha]_D^{25}$ = −10.4 (*c* = 4.84, EtOH), ref.[33] $[\alpha]_D^{25}$ = −9.7 (*c* = 0.6, EtOH). − ^{1}H NMR: δ = 0.86 (t, 3 H, *J* = 7.1 Hz), 0.87 (d, 3 H, *J* = 6.2 Hz), 1.08−1.25 (m, 2 H), 1.27−1.41 (m, 3 H), 1.43 (1 H, −OH, d, *J* = 0.3 Hz), 1.67 (d, 3 H, *J* = 0.3 Hz), 1.97−2.07 (m, 2 H), 4.00 (s, 2 H), 5.40 (1 H, tq, *J* = 1.2 and 7.1 Hz). − ^{13}C NMR: δ = 11.4, 13.6, 19.1, 25.2, 29.4, 34.0, 36.3, 69.1, 126.9, 134.4. − MS (EI); *m*/*z* (%): 156 (7) [M^+], 138 (10) [$M - H_2O]^+$, 123 (20), 109 (52), 96 (33), 83 (42), 67 (100), 55 (80). − The ^{1}H NMR and ^{13}C NMR spectral data are similar to those reported in the literature.[31,33]

(*S*)-(+)-2,6-Dimethyl-2-octen-1-ol (*S*-7): Similarly, ***S*-6** (21.5 g, 0.15 mol) gave ***S*-7** (20 g, 83%), 98.5% pure by GC. B.p. 60 °C/5 mbar. − $[\alpha]_D^{25}$ = +10.5. (*c* = 1.65, EtOH), ref.[37] $[\alpha]_D^{38}$ = +9.8 (*c* = 5.2, EtOH). − ^{1}H NMR, ^{13}C NMR, and MS (EI) spectral data match those of ***R*-7**.

2,6-Dimethyl-2-octen-1-ol (7): Similarly, **6** (12.5 g, 89.3 mmol) furnished **7** (11.5 g, 83%), > 99.0% pure by GC. ^{1}H NMR, ^{13}C NMR, and MS (EI) spectral data match those of (***R*)-7**.

(2*R*/*S*,6*R*)-(−)-2,6-Dimethyl-1-octanol (*R*-8): Compound ***R*-7** (11.4 g, 73.0 mmol) was stirred under H_2 in MeOH (100 mL) with a suspension of Raney Ni in water (ca. 5 g) at 40 °C for 24 h. The suspension was filtered and the collected solid was washed thoroughly with MeOH (5 × 15 mL). The MeOH was evaporated off and the crude product was subjected to LC followed by distillation (b.p. 55 °C/13 mbar) to give ***R*-8** (8.43 g, 73%), 99% pure by GC. − $[\alpha]_D^{25}$ = −7.19 (*c* = 23.6, $CHCl_3$), ref.[18] $[\alpha]_D^{20}$ = −7.40 (*c* = 2.16, $CHCl_3$). − ^{1}H NMR: δ = 0.85 (d, 3 H, *J* = 5.6 Hz), 0.86 (t, 3 H, *J* = 7.2 Hz), 0.92 (3 H, dd, *J* = 0.5 and 6.7 Hz), 1.02−1.66 (11 H, m), 3.42 (dd, 1 H, *J* = 6.5 and 10.5 Hz), 3.52 (1 H, ddd, *J* = 1.0, 5.8 and 10.5 Hz). − ^{13}C NMR: δ = 11.4 (2 C), 16.6 (2 C), 19.2 (2 C), 24.4 (2 C), 29.4, 29.6, 33.4, 33.5, 34.4 (2 C), 35.8 (2 C), 36.8, 36.9, 68.4, 68.5. − MS (EI); *m*/*z* (%) 125 (5), 111 (61), 97 (8), 83 (20), 85 (25), 69 (100), 55 (64). − The ^{1}H NMR and ^{13}C NMR spectral data are similar to those reported in the literature.[18]

(2*R*/*S*,6*S*)-(+)-2,6-Dimethyl-1-octanol (*S*-8): Similarly, ***S*-7** (19.5 g, 0.13 mol) gave ***S*-8** (15.5 g, 75%), 99% pure by GC. B.p. 52 °C/10 mbar. − $[\alpha]_D^{25}$ = +7.39 (*c* = 2.11, $CHCl_3$), ref.[18] $[\alpha]_D^{20}$ = +7.32 (*c* = 2.33, $CHCl_3$). − ^{1}H NMR, ^{13}C NMR, and MS (EI) spectral data coincid with those of ***R*-8**.

2,6-Dimethyl-1-octanol (8): Similarly, **7** (11.2 g, 71.7 mmol) furnished **8** (6.02 g, 53%), 95% pure by GC. B.p 110 °C/10 mbar. ^{1}H NMR, ^{13}C NMR, and MS (EI) spectral data matched those of ***R*-8** and the ^{1}H NMR spectrum is similar to that reported in the literature.[39]

Method A for Sequential Separation by Lipase PS Catalysed Kinetic Acylation of (2*S*/*R*,6*R*)-(−)-2,6-Dimethyl-1-octanol (*R*-8) and (2*R*/*S*,6*S*)-(+)-2,6-dimethyl-1-octanol (*S*-8): A chloroform solution (1 vol.) containing a given alcohol (0.57 M), tridecane (internal standard, 0.16 M), lipase PS (13.3 mg/mL solvent) and molecular sieves (4 Å) was stirred under argon at room temperature at 500 rpm. The reaction was started by addition of dry vinyl butyrate (2.17 M) to the flask. Conversion was followed by periodic withdrawal of samples. When the reaction had reached the desired degree of conversion, the mixture was filtered under argon and the solid washed with *n*-pentane (3 × 1 vol.). The mixture was concentrated and subjected to LC, the remaining alcohol was collected and the isolated ester was hydrolysed in 1 vol. of 2.4 M KOH/MeOH at reflux overnight. After cooling, water (1 vol.) and *n*-pentane (1 vol.) were added; this was followed by extractive workup with *n*-pentane (3 × 0.75 vol.) and a 3:2 mixture of Et_2O/*n*-pentane (3 × 0.75 vol.) to give the alcohol after drying ($MgSO_4$) and evaporation of the solvent. If necessary, the two alcohols were subjected to new cycles of the above reactions.

(2*S*,6*R*)-(−)-2,6-Dimethyl-1-octanol (*SR*-8): According to Method A, the reaction was performed from ***R*-8** (6.21 g, 39.2 mmol). However, although the reaction was run over two cycles that reached conversions of 40% and 70%, respectively, the diastereomeric purity at C-2 was unacceptably low (89.7% *S*). Therefore, the partially enriched (2*S*,6*R*)-alcohol (1.64 g, 10.4 mmol) was oxidised with Jones reagent (50 mL) at 0 °C as described in ref.[38] After 10 min

of stirring, Celite was added and the mixture was filtered and washed with Et_2O. The organic phase was extracted with sat. aq. Na_2CO_3 (3 × 50 mL), the combined water phases were acidified with HCl (15 mL, 6 M), the obtained acid was extracted into Et_2O (7 × 50 mL), dried ($MgSO_4$), and concentrated to give the acid, with a purity by GC of 98.7%. According to the methodology given by Nguyen and Hedenström,[16] the acid (1.67 g, 9.67 mmol) was mixed with cyclohexane (58 mL, 8.70 mmol), 1-hexadecanol (2.11 g, 8.70 mmol), tridecane (0.88 g, 4.78 mmol), Na_2SO_4 (1.66 g, 11.7 mmol), and $Na_2SO_4 \times 10\ H_2O$ (1.87 g, 5.81 mmol). The mixture was stirred for 1 h at 500 rpm at room temperature to allow equilibration to $a_w = 0.8$. Immobilised CRL (1.18 g) was added, and after 6.7 h (ca. 40% conversion) the CRL was filtered off, followed by extractive workup with Et_2O (150 mL) and Na_2CO_3 (3 × 40 mL, sat. aq.), and then the organic phase was dried and concentrated to give the ester, which was purified by LC. The ester was added to $LiAlH_4$ (150 mg, 3.96 mmol) in dry Et_2O (20 mL) and stirred for 1 h at ambient temperature followed by extractive workup and a bulb-to-bulb distillation (b.p. 90 °C/9 mbar) to give the alcohol ***SR*-8** (0.63 g, 20% based on the amount of ***SR*-8** present in ***R*-8**) > 99% pure by GC and 99.7% (*S*) configuration at C-2. − $[\alpha]_D^{25} = -21.4$ ($c = 3.18$, $CHCl_3$), ref.[18] $[\alpha]_D^{20} = -9.07$ ($c = 1.10$, $CHCl_3$). − ^{1}H NMR: δ = 0.84 (d, 3 H, $J = 6.1$ Hz), 0.86 (t, 3 H, $J = 7.2$ Hz), 0.92 (d, 3 H, $J = 6.7$ Hz), 1.05−1.65 (11 H, m), 3.42 (dd, 1 H, $J = 6.5$ and 10.5 Hz), 3.52 (dd, 1 H, $J = 5.8$ and 10.5 Hz). − ^{13}C NMR: δ = 11.4, 16.6, 19.2, 24.4, 29.6, 33.4, 34.4, 35.8, 36.8, 68.5. − MS (EI); *m*/*z* (%): 141 (2) $[M - OH]^+$, 125 (5), 111 (63), 97 (10), 83 (23), 69 (100), 55 (67).

(2*R*,6*R*)-(+)-2,6-Dimethyl-1-octanol (*RR*-8): The first lipase-catalysed acylation reaction of ***R*-8** was stopped at 64% conversion. The remaining substrate (2.12 g, 13.4 mmol) was subjected to a second lipase-catalysed acylation reaction, which was allowed to reach 40% conversion. After LC, the alcohol ***RR*-8** (0.51 g, 48% based on the amount of ***RR*-8** present in ***R*-8**) was isolated, > 98% pure by GC and with 99.4% (*S*) configuration at C-2. B.p. 100 °C/11 mbar. − $[\alpha]_D^{25} = +2.58$ ($c = 7.32$, $CHCl_3$), ref.[20] $[\alpha]_D^{20} = +6.9$ ($c = 5$, $CHCl_3$). − ^{1}H NMR: δ = 0.85 (d, 3 H, $J = 6.3$ Hz), 0.86 (t, 3 H, $J = 7.2$ Hz), 0.92 (d, 3 H, $J = 6.7$ Hz), 1.01−1.65 (11 H, m), 3.42 (dd, 1 H, $J = 6.5$ and 10.5 Hz), 3.52 (dd, 1 H, $J = 5.8$ and 10.5 Hz). − ^{13}C NMR: δ = 11.4, 16.6, 19.2, 24.4, 29.4, 33.5, 34.4, 35.8, 36.9, 68.4. − MS (EI); *m*/*z* (%): 140 (3) $[M - H_2O]^+$, 125 (5), 111 (63), 97 (10), 85 (40), 69 (100), 55 (50). − The ^{1}H NMR and ^{13}C NMR spectral data are similar to those reported in the literature.[21]

(2*S*,6*S*)-(−)-2,6-Dimethyl-1-octanol (*SS*-8): According to Method A, the title compound was prepared from 11.1 g (70.2 mmol) of ***S*-8**. The first reaction (conv. = 50%, $de_p = 73\%$) gave the ester, which was hydrolysed and subjected to a second reaction (conv. = 51%, $de_p = 94.4\%$). Workup followed by bulb-to-bulb distillation (b.p. 103 °C/11 mbar) furnished the title alcohol ***SS*-8** (2.55 g, 46% based on the amount of ***SS*-8** present in ***S*-8**), > 99% pure by GC and with 97.2% (*S*) configuration at C-2. − $[\alpha]_D^{25} = -2.41$ ($c = 2.24$, $CHCl_3$), ref.[18] $[\alpha]_D^{20} = -7.32$ ($c = 1.68$, $CHCl_3$). − ^{1}H NMR, ^{13}C NMR, and MS (EI) spectral data match those of ***RR*-8**.

(2*R*,6*S*)-(+)-2,6-Dimethyl-1-octanol (*RS*-8): The recovered remaining substrate alcohol ***RS*-8** [8.17 g, 51.7 mmol, 68.5% (*R*) configuration at C-2] obtained from both steps of the above lipase-catalysed kinetic acylation of ***S*-8** was subjected to Method A. The reaction was stopped at 60% conversion and worked up as described. Bulb-to-bulb distillation (b.p. 90 °C/9 mbar) gave the alcohol ***RS*-8** (2.94 g, 53% based on the amount of present ***RS*-8** in ***S*-8**) with a chemical purity of > 99% and with 99.1% (*S*) configuration at C-2. − $[\alpha]_D^{25} = +18.3$ ($c = 3.16$, $CHCl_3$), ref.[20] $[\alpha]_D^{25} = +15.7$ ($c = 2.8$, $CHCl_3$). − ^{1}H NMR, ^{13}C NMR, and MS (EI) spectral data match those of ***SR*-8**; the ^{1}H NMR is also similar to that reported in the literature.[19]

Determination of the Stereoisomeric Purity at C-2 of the Alcohols *SR*-8, *RS*-8, *RR*-8, and *SS*-8: The stereoisomeric purity at C-2 of the alcohols ***SR*-8**, ***RS*-8**, ***RR*-8**, ***SS*-8** was determined after oxidation of the alcohols to the acids using Jones reagent, followed by conversion into the corresponding phenylethylamides obtained from the enantiomerically pure (*S*)-1-phenylethylamine (for alcohols ***SR*-8** and ***RR*-8**) and (*R*)-1-phenylethylamine (for alcohols ***RS*-8** and ***SS*-8**) as described in the literature.[38] The diastereoisomeric ratios of the amides were determined using a Varian 3700 gas chromatograph equipped with a CP-WAX-52CB, 30 m × 0.25 mm, d_f = 0.25 μm, carrier gas He, 15 psi, split 1:30, isothermal 200 °C; retention time (min): 27.0 (***SR*-8** and ***RS*-8**) and 29.2 (***SS*-8** and ***RR*-8**) for the amide derivatives. Alternatively, the Varian 3700 gas chromatograph was equipped with an EC-WAX 30 m × 0.25 mm, d_f = 0.25 μm, carrier gas He, 16 psi, split 1:30, isothermal 200 °C; retention time (min): 36.3 (***RR*-8** and ***SS*-8**) and 33.0 (***RS*-8** and ***SR*-8**).

(2*R*,6*R*)-1-Chloro-2,6-dimethyloctane (*RR*-9): According to the protocol of Hedenström and Högberg[40] ***RR*-8** (0.40 g, 2.53 mmol) was mixed with triphenylphosphane (0.73 g, 2.80 mmol) and CCl_4 (1.5 mL, 16.0 mmol) and refluxed for 3 h. MeOH (0.5 mL) was poured into the crude product, which was immediately subjected to LC and bulb-to-bulb distillation, giving a colourless oil (0.42 g, 95%), > 98% pure by GC. B.p. 60 °C/1.3 mbar. − $[\alpha]_D^{25} = -5.47$ ($c = 0.85$, *n*-hexane). − ^{1}H NMR: δ = 0.85 (d, 3 H, $J = 6.3$ Hz), 0.86 (t, 3 H, $J = 7.0$ Hz), 1.00 (d, 3 H, $J = 6.7$ Hz), 1.05−1.52 (m, 9 H), 1.75−1.85 (m, 1 H), 3.41 (dd, 1 H, $J = 6.2$ and 10.6 Hz), 3.49 (dd, 1 H, $J = 5.2$ and 10.5 Hz). − ^{13}C NMR: δ = 11.4, 17.8, 19.2, 24.3, 29.4, 34.3 (2 C), 35.5, 36.7, 51.3. − MS (EI); *m*/*z* (%): 147 (2) $[M^{35}Cl - C_2H_5]^+$, 119 (29), 111 (53), 83 (42), 69 (100), 57 (46).

(2*S*,6*S*)-1-Chloro-2,6-dimethyloctane (*SS*-9): Similarly, ***SS*-8** (2.31 g, 14.6 mmol) gave ***SS*-9** (2.31 g, 90%), > 99% pure by GC. B.p. 115 °C/7.5 mbar. − $[\alpha]_D^{25} = +4.89$ ($c = 0.35$, *n*-hexane). − ^{1}H NMR, ^{13}C NMR, and MS (EI) spectral data match those of ***RR*-9**.

(2*S*,6*R*)-1-Chloro-2,6-dimethyloctane (*SR*-9): Similarly, ***SR*-8** (0.58 g, 3.65 mmol) gave ***SR*-9** (0.40 g, 62%), > 99% pure by GC. B.p 50 °C/1.1 mbar. − $[\alpha]_D^{25} = -12.5$ ($c = 2.79$, *n*-hexane). − ^{1}H NMR: δ = 0.85 (d, 3 H, $J = 6.0$ Hz), 0.86 (t, 3 H, $J = 7.1$ Hz), 1.00 (d, 3 H, $J = 6.7$ Hz), 1.07−1.46 (m, 9 H), 1.77−1.85 (m, 1 H), 3.40 (dd, 1 H, $J = 6.3$ and 10.6 Hz), 3.49 (dd, 1 H, $J = 5.2$ and 10.6 Hz). − ^{13}C NMR: δ = 11.4, 17.8, 19.2, 24.3, 29.5, 34.3 (2 C), 35.5, 36.6, 51.4. − MS (EI); *m*/*z* (%): 147 (3) $[M^{35}Cl - C_2H_5]^+$, 119 (34), 111 (49), 83 (76), 69 (100), 57 (73).

(2*R*,6*S*)-1-Chloro-2,6-dimethyloctane (*RS*-9): Similarly, ***RS*-8** (2.50 g, 15.8 mmol) gave ***RS*-9** (2.42 g, 87%), > 99% pure by GC. B.p 113 °C/7.5 mbar. − $[\alpha]_D^{25} = +12.3$ ($c = 1.49$, *n*-hexane). − ^{1}H NMR, ^{13}C NMR and MS (EI) spectral data match those of ***SR*-9**.

1-Chloro-2,6-dimethyloctane (9): Similarly, **8** (3.01 g, 19.0 mmol) gave **9** (2.80 g, 84%), > 99% pure by GC. B.p. 65 °C/0.3 mbar. − ^{1}H NMR: δ = 0.85 (d, 3 H, $J = 5.7$ Hz), 0.86 (t, 3 H, $J = 7.1$ Hz), 1.00 (d, 3 H, $J = 6.7$ Hz), 1.07−1.46 (m, 9 H), 1.75−1.87 (m, 1 H), 3.41 (dd, 1 H, $J = 6.3$ and 10.6 Hz), 3.49 (1 H, ddd, $J = 0.9$, 5.2 and 10.6 Hz). − ^{13}C NMR: δ = 11.4 (2 C), 17.8 (2 C), 19.2 (2 C), 24.3 (2 C), 29.4, 29.5, 34.3 (3 C), 35.5 (2 C), 36.6, 36.7, 51.3, 51.4. − MS (EI); *m*/*z* (%): 147 (2) $[M^{35}Cl - C_2H_5]^+$, 111 (72), 82

(32), 69 (100), 59 (73). − (HRMS, EI): $[M^{35}Cl - C_2H_5]^+$ 147.0961, $C_8H_{16}Cl$ requires 147.0941.

3,7,11-Trimethyl-2-tridecanol (4H): A known lithiation method[41] was modified to suit the preparation of 1-lithio-2,6-dimethyloctane. Accordingly, lithium (400 mg, 57.6 mmol) was washed with *n*-heptane, flattened to a thin sheet using a hammer, then, under argon, cut into very thin pieces directly into the reaction vessel and finally refluxed for 0.08 h in *n*-hexane (5 mL, freshly distilled and degassed by argon bubbling for 1 h). The solvent was removed, another 5 mL of freshly distilled and degassed *n*-hexane was added and heated to reflux. Distilled chloride **9** (0.50 g, 2.84 mmol) was added slowly (0.08 h) via syringe into the reaction flask. GC analysis indicated full conversion after 3 h. The suspension was cooled to −78 °C and taken up in a syringe (leaving the remaining lithium metal behind) and then added slowly (0.25 h) into a −78 °C solution of freshly distilled 3,4-dimethyl-γ-butyrolactone (*cis*/*trans* 62:38) (262 mg, 2.30 mmol) in Et_2O (5 mL, degassed by argon). The reaction mixture was kept for 10 h at −78 °C, after which it was quenched with NH_4Cl (3 mL, sat. aq.). The resulting mixture was extracted with Et_2O (5 × 10 mL), dried ($MgSO_4$) and concentrated. LC gave the oxo alcohol, which was immediately dissolved in distilled diethylene glycol (7 mL) containing KOH (0.62 g, 11.1 mmol) and hydrazine monohydrate (0.30 mL, 6.2 mmol). The solution was heated at 170 °C for 1 h and then at 210 °C for 3 h. After cooling, water (2 mL) was added. Extraction with Et_2O (5 × 10 mL), drying ($MgSO_4$) and concentration furnished a yellow oil, which after LC and distillation (b.p. 95 °C/0.85 mbar) gave the alcohol **4H** (0.17 g, 31% based on the lactone) > 98% pure and with a *erythro*/*threo* ratio of 58:42 by GC. − ^{1}H NMR: δ = 0.83−1.53 (33 H, m), 3.64−3.75 (m, 1 H). − ^{13}C NMR: δ = 11.4 (2 C), 14.1, 14.5, 19.2, 19.3, 19.4, 19.7, 20.3, 24.5 (2 C), 24.8, 29.5, 29.6, 32.8 (2 C), 32.9 (2 C), 33.0, 34.4, 36.9, 37.0, 37.3, 37.4, 37.5 (2 C), 39.8 (2 C), 71.4, 71.5, 71.8 (2 C). − MS (EI); *m*/*z* (%): 224 (6) $[M - H_2O]^+$, 140 (12), 125 (90), 111 (49), 97 (58), 85 (72), 71 (87), 57 (100). − (HRMS, EI): $[M - H_2O]^+$ 224.2464 and $[M - C_2H_5]^+$ 213.2186, $C_{16}H_{32}$ requires 224.2504 and 213.2218, respectively.

(2*S*,3*S*,7*S*,11*R*)-, (2*S*,3*S*,7*S*,11*S*)-, (2*S*,3*S*,7*R*,11*S*)-, (2*S*,3*S*,7*R*,11*R*)-, (2*R*,3*R*,7*S*,11*R*)-, (2*R*,3*R*,7*S*,11*S*)-, (2*R*,3*R*,7*R*11*S*)- and (2*R*,3*R*,7*R*,11*R*)-3,7,11-Trimethyl-2-tridecanol (*erythro*-4H): Similarly prepared: The appropriate enantiomer of *cis*-3,4-dimethyl-γ-butyrolactone and stereoisomerically pure alkyl chloride (***SS*-9**, ***RR*-9**, ***SR*-9**, or ***RS*-9**) gave 30−40% overall yields (based on the lactone) of the title compounds and with < 1.2% of *threo*-**4H** confirmed by GC analysis, except for the (2*S*,3*S*,7*S*,11*S*) and (2*R*,3*R*,7*S*,11*S*) isomers, which were found to contain 2% and 2.1% of *threo*-**4 H**, respectively. For spectral and physical data for the individual stereoisomers, see Table 2.

Preparation of (2*R*,3*S*,7*S*,11*R*)-, (2*R*,3*S*,7*S*,11*S*)-, (2*R*,3*S*,7*R*,11*S*)-, (2*R*,3*S*,7*R*,11*R*)-, (2*S*,3*R*,7*S*,11*R*)-, (2*S*,3*R*,7*S*,11*S*)-, (2*S*,3*R*,7*R*11*S*)-, and (2*S*,3*R*,7*R*,11*R*)-3,7,11-trimethyl-2-tridecanol (*threo*-4H): The title compounds were prepared using the Mitsunobu methodology described by Högberg et al.,[9] but starting from the appropriate *erythro*-3,7,11-trimethyl-2-tridecanols. This gave pure benzoate esters, which were directly hydrolysed to the corresponding alcohols (reflux overnight in a 1:1:1 mixture of 1.2 M NaOH in H_2O/MeOH/dioxane). The crude reaction mixtures were extracted with Et_2O (3 × 10 mL), dried ($MgSO_4$), and concentrated. After LC and bulb-to-bulb distillation, the desired products were obtained as colourless oils, with chemical purities of > 98% by GC. All *threo* isomers were obtained in 50−60% yield and with < 1.3% *erythro*-**4H** by GC analysis, except for the (2*S*,3*R*,7*S*,11*S*) and (2*R*,3*S*,7*S*,11*S*) isomers, which contained 2.2% and 2.3% of *erythro*-**4 H**, respectively. For spectral and physical data for the individual stereoisomers, see Table 2.

Preparation of the Propionate Ester of 3,7,11-Trimethyl-2-tridecanol (4Pr): Propionyl chloride (0.06 mL, 0.83 mmol) was added to a solution of the alcohol (**4H**) (19.4 mg, 0.08 mmol) in CH_2Cl_2 (0.5 mL) and the mixture was stirred for 12 h at room temperature. The crude product was concentrated, chromatographed and distilled (b.p. 130−150 °C/1.0 mbar). This furnished the sixteen-component mixture of stereoisomers of the product **4Pr** (22.1 mg, 92%) > 98% pure by GC. − ^{1}H NMR: δ = 0.83−1.60 (35 H, m), 2.31 (2 H, q, *J* = 7.6 Hz), 4.80−4.87 (m, 1 H). − ^{13}C NMR: δ = 9.31, 11.4, 17.0, 19.2, 19.3, 24.5, 28.0, 29.5, 29.6, 32.7, 32.8, 34.4, 36.9, 37.0, 37.3, 37.6, 37.7, 73.8, 73.9, 74.0, 174.1. − MS (EI); *m*/*z* (%): 224 (5) $[M - C_3H_6O_2]^+$, 140 (8), 125 (32), 111 (18), 97 (13), 86 (35), 70 (30), 57 (100). − (HRMS, EI): $[M - C_3H_6O_2]^+$ 224.2502, $C_{16}H_{32}$ requires 224.2504.

Preparation of the Sixteen Stereoisomerically Pure Propionates of 3,7,11-Trimethyl-2-tridecanols: Prepared as above for 4Pr. For spectral and physical data for the individual stereoisomers, see Table 3.

Alternative Method for the Preparation of SS-8 and SR-8

(*S*)-1-Bromo-2-methylbutane: Br_2 (3.64 mL, 68.1 mmol) was added to a solution of PPh_3 (17.9 g, 68.1 mmol) and imidazole (4.32 g, 63.5 mmol) in CH_2Cl_2 (50 mL) at 0 °C. (2*S*)-2-Methyl-1-butanol (4.0 g, 45.4 mmol) {> 99% ee, $[\alpha]_D^{25} = -5.65$ (*c* = 10.3, EtOH)} was added at that temperature and the reaction mixture was allowed to stand overnight. MeOH (1 mL) was poured into the reaction mixture, which was then subjected to LC and bulb-to-bulb distillation. The title compound was obtained as a colourless oil (3.95 g, 57%), > 98.3% pure by GC. B.p 75 °C/120 mbar. − $[\alpha]_D^{25} = +4.17$ (neat), ref. $[\alpha]_D^{25} = +3.98$ (neat),[42] $[\alpha]_D^{25} = +4.00$ (neat).[43] − ^{1}H NMR: δ = 0.91 (t, 3 H, *J* = 7.4 Hz), 1.01 (d, 3 H, *J* = 6.6 Hz), 1.19−1.78 (m, 3 H), 3.33 (dd, 1 H, *J* = 6.0 and 9.8 Hz), 3.40 (dd, 1 H, *J* = 5.2 and 9.8 Hz). − ^{13}C NMR: δ = 11.2, 18.4, 27.7, 36.9, 41.0. − MS (EI); *m*/*z* (%): 151 (0.2) $[M^{81}Br]^+$, 149 (0.2) $[M^{79}Br]^+$, 71 (100). − The ^{1}H NMR and ^{13}C NMR spectral data are similar to those reported in the literature.[44]

(*S*)-4-Methylhexanoic Acid: Diethyl malonate (5.39 mL, 35.7 mmol) was added to a sodium ethoxide solution [Na (s) 0.78 g, 33.4 mmol dissolved in 25 mL of EtOH] at room temperature and the solution was refluxed for 0.08 h. After cooling to room temperature, (*S*)-1-bromo-2-methylbutane (3.87 g, 25.6 mmol) was added. Overnight reflux, followed by evaporation of the EtOH (15 mL), gave the crude diethyl (*S*)-2-(2-methylbutyl)malonate. Hydrolysis with KOH/MeOH (19 mL, 4.0 M) at reflux overnight, concentration and treating with Et_2O (3 × 25 mL), HCl (5 mL, 6 M), Et_2O (5 × 25 mL) and brine (25 mL), drying ($MgSO_4$), and evaporation of the solvent furnished a crude diacid product, which was heated to 190 °C for 4 h. Extractive workup as above furnished the title acid. Bulb-to-bulb distillation gave a colourless oil (2.58 g, 77%), > 99% pure by GC. B.p 85 °C/0.7 mbar. − $[\alpha]_D^{25} = +10.1$ (*c* = 4.92, $CHCl_3$), ref. $[\alpha]_D^{22.5} = +10.3$ (*c* = 2.14, $CHCl_3$),[45] $[\alpha]_D^{25} = +10.8$ (*c* = 10.170, $CHCl_3$),[46] $[\alpha]_D^{25} = +10.89$ (*c* = 1, $CHCl_3$),[47] $[\alpha]_D^{25} = +10.3$ (*c* = 4.4, $CHCl_3$).[48] − ^{1}H NMR: δ = 0.88 (t, 3 H, *J* = 7.1 Hz), 0.88 (d, 3 H, *J* = 6.1 Hz), 1.03−1.76 (m, 5 H), 2.10−2.46 (m, 2 H), 11.6 (1 H, br. s). − ^{13}C NMR: δ = 11.3, 18.8, 29.1, 31.2, 32.0, 33.9, 181.0. − The ^{1}H NMR and ^{13}C NMR spectral data are similar to those reported in the literature.[49] MS spectral data matched those reported in the literature.[30] The enantiomeric purity of the acid (> 97.5% *ee*) was determined after derivatisation to the corresponding phenylethylamide, obtained as described in the literature[38] from (*S*)-1-phenylethylamine(> 99.5% *ee*). The diaster-

Table 2. Spectral and physical data for the sixteen individual 3,7,11-trimethyl-2-tridecanols **4H**

4H	^{1}H NMR	^{13}C NMR	MS-EI	$[\alpha]_D^{25}$ (*c*) in hexane	B.p. °C/mbar
RRRR	0.84 (d, 3 H, *J* = 6.2 Hz), 0.85 (d, 3 H, *J* = 6.4 Hz), 0.86 (t, 3 H, *J* = 7.1 Hz), 0.89 (d, 3 H, *J* = 6.7 Hz), 1.15 (d, 3 H, *J* = 6.4 Hz), 0.93−1.50 (18 H, m), 3.71 (1 H, dq, *J* = 4.2 and 6.3 Hz)	11.4, 14.2, 19.3, 19.8, 20.3, 24.5, 24.8, 29.5, 32.8, 33.0, 34.4, 37.0, 37.3, 37.4, 39.8, 71.4	224 (2) [M − H_2O]$^+$, 140 (10), 125 (68), 111 (43), 97 (45), 85 (53), 71 (73), 57 (100)	+5.51 (0.89) +5.7 (0.98)[11]	150/1.6
SSSS	Same as *RRRR*	Same as *RRRR*	Same as *RRRR*	−5.78 (0.51)	Same as *RRRR*
SSSR	0.85 (6 H, d, *J* = 6.4 Hz), 0.86 (t, 3 H, *J* = 6.9 Hz), 0.89 (d, 3 H, *J* = 6.7 Hz), 1.15 (d, 3 H, *J* = 6.4 Hz), 0.96−1.50 (18 H, m), 3.71 (1 H, dq, *J* = 4.2 and 6.4 Hz)	11.5, 14.2, 19.2, 19.7, 20.3, 24.5, 24.8, 29.6, 32.8, 33.0, 34.4, 36.9, 37.3, 37.5, 39.8, 71.4	224 (5) [M − H_2O]$^+$, 140 (9), 125 (10), 111 (15), 97 (15), 85 (71), 71 (93), 57 (100)	−19.9 (0.82) −20.0 (1.02)[11]	100/0.65
RRRS	Same as *SSSR*	Same as *SSSR*	Same as *SSSR*	+19.4 (1.39)	Same as *SSSR*
SSRR	0.84 (d, 3 H, *J* = 6.2 Hz) 0.85 (d, 3 H, *J* = 6.4 Hz), 0.86 (t, 3 H, *J* = 6.9 Hz), 0.89 (d, 3 H, *J* = 6.7 Hz), 1.15 (d, 3 H, *J* = 6.3 Hz), 0.93−1.50 (18 H, m), 3.71 (1 H, dq, *J* = 4.3 and 6.3 Hz)	11.4, 14.1, 19.3, 19.7, 20.3, 24.5, 24.7, 29.5, 32.8, 32.9, 34.4, 37.0, 37.3, 37.5, 39.8, 71.5	224 (4) [M − H_2O]$^+$, 140 (7), 125 (53), 111 (32), 97 (33), 85 (57), 71 (73), 57 (80), 45 (100)	−18.9 (0.94)	120/1.5
RRSS	Same as *SSRR*	Same as *SSRR*	Same as *SSRR*	+17.7 (0.33)	Same as *SSRR*
SRRR	0.84 (d, 3 H, *J* = 6.2 Hz), 0.85 (d, 3 H, *J* = 6.3 Hz), 0.85 (t, 3 H, *J* = 7.2 Hz), 0.87 (d, 3 H, *J* = 6.7 Hz), 1.13 (d, 3 H, *J* = 6.3 Hz), 0.93−1.58 (18 H, m), 3.67 (1 H, dq, *J* = 5.4 and 6.3 Hz)	11.4, 14.5, 19.3 (2 C), 19.8, 24.5, 24.7, 29.5, 32.8, 32.9, 34.4, 37.0, 37.3, 37.4, 40.1, 71.8	224 (1) [M − H_2O]$^+$, 140 (109, 125 (62), 111 (34), 97 (40), 85 (52), 71 (66), 57 (97), 45 (100)	+10.4 (0.82) +10.5 (0.99)[11]	140/1.7
RSSS	Same as *SRRR*	Same as *SRRR*	Same as *SRRR*	−11.1 (1.30)	Same as *SRRR*
RSRR	0.84 (d, 3 H, *J* = 6.3 Hz), 0.85 (d, 3 H, *J* = 6.3 Hz), 0.86 (t, 3 H, *J* = 7.4 Hz), 0.87 (d, 3 H, *J* = 6.6 Hz), 1.13 (d, 3 H, *J* = 6.3 Hz), 0.90−1.55 (18 H, m), 3.66 (1 H, dq, *J* = 5.4 and 6.3 Hz)	11.4, 14.5, 19.3, 19.4, 19.7, 24.5, 24.6, 29.5, 32.8 (2 C), 34.4, 37.0, 37.3, 37.5, 40.0, 71.8	224 (3) [M − H_2O]$^+$, 140 (9), 125 (63), 111 (36), 97 (42), 85 (56), 71 (73), 57 (96), 45 (100)	−22.0 (0.93)	150/1.7
SRSS	Same as *RSRR*	Same as *RSRR*	Same as *RSRR*	+21.1 (1.47)	Same as *RSRR*
SRSR	0.84 (d, 3 H, *J* = 6.6 Hz), 0.85 (d, 3 H, *J* = 6.5 Hz), 0.86 (t, 3 H, *J* = 7.4 Hz), 0.87 (d, 3 H, *J* = 6.8 Hz), 1.13 (d, 3 H, *J* = 6.3 Hz), 0.99−1.55 (18 H, m), 3.66 (1 H, dq, *J* = 5.5 and 6.3 Hz)	11.4, 14.5, 19.2, 19.4, 19.6, 24.5, 24.7, 29.6, 32.7, 32.8, 34.4, 36.9, 37.4, 37.5, 40.0, 71.8	224 (2) [M − H_2O]$^+$, 140 (10), 125 (75), 111 (34), 97 (47), 85 (56), 71 (81), 57 (100)	+11.3 (1.14)	110/0.6
RSRS	Same as *SRSR*	Same as *SRSR*	Same as *SRSR*	−10.7 (1.37)	Same as *SRSR*
RSSR	0.84 (d, 3 H, *J* = 6.6 Hz), 0.85 (d, 3 H, *J* = 6.2 Hz), 0.85 (t, 3 H, *J* = 7.0 Hz), 0.87 (d, 3 H, *J* = 6.5 Hz), 1.13 (d, 3 H, *J* = 6.3 Hz), 1.00−1.55 (18 H, m), 3.67 (1 H, dq, *J* = 5.4 and 6.3 Hz)	11.4, 14.5, 19.2, 19.3, 19.7, 24.5, 24.7, 29.6, 32.8, 32.9, 34.4, 36.9, 37.3, 37.5, 40.1, 71.8	224 (1) [M − H_2O]$^+$, 140 (8), 125 (71), 111 (43), 97 (45), 85 (59), 71 (75), 57 (100)	−25.8 (0.90)	110/0.46
SRRS	Same as *RSSR*	Same as *RSSR*	Same as *RSSR*	+25.0 (1.47)	Same as *RSSR*
RRSR	0.84 (6 H, d, *J* = 6.5 Hz), 0.86 (t, 3 H, *J* = 6.4 Hz), 0.89 (d, 3 H, *J* = 6.7 Hz), 1.15 (d, 3 H, *J* = 6.3 Hz), 0.99−1.49 (18 H, m), 3.71 (1 H, dq, *J* = 4.3 and 6.4 Hz)	11.4, 14.1, 19.2, 19.6, 20.3, 24.5, 24.8, 29.6, 32.7, 32.9, 34.4, 36.9, 37.4, 37.5, 39.8, 71.5	224 (6) [M − H_2O]$^+$, 140 (7), 125 (75), 111 (45), 97 (47), 85 (63), 71 (85), 57 (100)	+6.94 (0.98)	120/1.3
SSRS	Same as *RRSR*	Same as *RRSR*	Same as *RRSR*	−6.60 (1.25)	Same as *RRSR*

eoisomeric ratio of the amide was determined using a 30 m × 0.25 mm I.D capillary column coated with β-dex 120, d_f = 0.25 µm, carrier gas He 15 psi, split ratio 30:1; retention time (min): 131.7 and 133.1 min for the amide diastereomers.

(*S*)-4-Methyl-1-hexanol: A solution of (*S*)-4-methylhexanoic acid (2.54 g, 19.5 mmol, 97.5% *ee*) in dry Et_2O (10 mL) was added dropwise to $LiAlH_4$ (0.74 g, 19.5 mmol) in dry Et_2O (15 mL) at room temperature. After stirring overnight, the reaction was quenched with HCl (5 mL, 2 M). Extractive workup with Et_2O (3 × 25 mL) and brine (1 × 20 mL), drying ($MgSO_4$), and concentration followed by LC and bulb-to-bulb distillation gave the title compound (1.94 g, 86%) > 99% pure by GC. B.p 45 °C/1.1 mbar. − $[\alpha]_D^{25}$ = +7.64 (*c* = 4.01, $CHCl_3$), ref. $[\alpha]_D^{23}$ = +8.62 (*c* = 3.65, $CHCl_3$),[50] $[\alpha]_D^{25}$ = +8.5 (*c* = 1.16, $CHCl_3$).[51] − ^{1}H NMR: δ = 0.87 (t, 3 H, *J* = 7.2 Hz), 0.87 (d, 3 H, *J* = 6.4 Hz), 1.09−1.65 (8 H, m), 3.63 (t, 2 H, *J* = 6.7 Hz). − ^{13}C NMR: δ = 11.4, 19.1, 29.4, 30.4, 32.5, 34.3, 63.5. − MS (EI); *m/z* (%): 115 (3) [M − 1]$^+$, 99 (32) [M − OH]$^+$, 98 (15) [M − OH_2]$^+$, 70 (64), 69 (54), 57 (100). − The ^{1}H NMR spectral data is similar to that reported in the literature.[52,53]

(*S*)-1-Iodo-4-methylhexane: According to the methodology of Smith et al.,[54] (*S*)-4-methyl-1-hexanol (1.94 g, 6.7 mmol) was added to a mixture of triphenylphosphane (6.13 g, 23.4 mmol) and

Table 3. Spectral data for the sixteen individual propionates **4Pr** obtained from the individual 3,7,11-trimethyl-2-tridecanols

4Pr	^{1}H NMR	^{13}C NMR	MS-EI
RRRR	0.84 (6 H, d, J = 6.3 Hz), 0.85 (t, 3 H, J = 6.7 Hz), 0.90 (d, 3 H, J = 6.8 Hz), 1.14 (t, 3 H, J = 7.6 Hz), 1.16 (d, 3 H, J = 6.4 Hz), 0.93−1.63 (17 H, m), 2.31 (2 H, q, J = 7.6 Hz), 4.85 (1 H, dq, J = 4.8 and 6.4 Hz)	9.3, 11.4, 14.8, 17.0, 19.3, 19.8, 24.5 (2 C), 28.0, 29.5, 32.7, 32.8, 34.4, 37.0, 37.3, 37.4, 37.6, 73.8, 174.2	224 (4) [M − $C_3H_6O_2$]$^+$, 140 (5), 125 (30), 111 (15), 97 (11), 86 (28), 69 (20), 57 (100)
SSSS	Same as *RRRR*	Same as *RRRR*	Same as *RRRR*
SSSR	0.84 (6 H, d, J = 6.5 Hz), 0.85 (t, 3 H, J = 6.8 Hz), 0.90 (d, 3 H, J = 6.8 Hz), 1.14 (t, 3 H, J = 7.6 Hz), 1.16 (d, 3 H, J = 6.4 Hz), 0.99−1.63 (17 H, m), 2.31 (2 H, q, J = 7.6 Hz), 4.85 (1 H, dq, J = 4.8 and 6.4 Hz)	9.3, 11.4, 14.8, 17.0, 19.2, 19.7, 24.5 (2 C), 28.0, 29.6, 32.7, 32.8, 34.4, 36.9, 37.3, 37.4, 37.7, 73.8, 174.2	224 (3) [M − $C_3H_6O_2$]$^+$, 140 (5), 125 (30), 111 (15), 97 (10), 86 (35), 69 (20), 57 (100)
RRRS	Same as *SSSR*	Same as *SSSR*	Same as *SSSR*
SSRR	0.84 (6 H, d, J = 6.4 Hz), 0.85 (t, 3 H, J = 6.1 Hz), 0.89 (d, 3 H, J = 6.8 Hz), 1.14 (t, 3 H, J = 7.6 Hz), 1.16 (d, 3 H, J = 6.4 Hz), 0.96−1.60 (17 H, m), 2.31 (2 H, q, J = 7.6 Hz), 4.84 (1 H, dq, J = 4.9 and 6.3 Hz)	9.31, 11.4, 14.8, 17.0, 19.3, 19.7, 24.5 (2 C), 28.0, 29.5, 32.7 (2 C), 34.4, 37.0, 37.2, 37.5, 37.6, 73.9, 174.1	224 (3) [M − $C_3H_6O_2$]$^+$, 140 (6), 125 (32), 111 (17), 97 (12), 86 (33), 69 (25), 57 (100)
RRSS	Same as *SSRR*	Same as *SSRR*	Same as *SSRR*
SRRR	0.84 (6 H, d, J = 6.0 Hz), 0.85 (t, 3 H, J = 7.0 Hz), 0.88 (d, 3 H, J = 6.8 Hz), 1.13 (d, 3 H, J = 6.4 Hz), 1.14 (t, 3 H, J = 7.6 Hz), 0.92−1.73 (17 H, m), 2.30 (2 H, q, J = 7.6 Hz), 4.82 (1 H, app. quint, J = 6.4 Hz)	9.28, 11.4, 14.6, 15.8, 19.3, 19.8, 24.5 (2 C), 28.0, 29.5, 32.8, 33.0, 34.4, 37.0, 37.3 (3 C), 74.0, 174.1	224 (5) [M − $C_3H_6O_2$]$^+$, 140 (9), 125 (30), 111 (13), 97 (11), 86 (33), 69 (25), 57 (100)
RSSS	Same as *SRRR*	Same as *SRRR*	Same as SRRR
RSRR	0.84 (6 H, d, J = 6.5 Hz), 0.85 (t, 3 H, J = 7.3 Hz), 0.88 (d, 3 H, J = 6.8 Hz), 1.13 (d, 3 H, J = 6.4 Hz), 1.14 (t, 3 H, J = 7.6 Hz), 0.93−1.71 (17 H, m), 2.31 (2 H, q, J = 7.6 Hz), 4.82 (1 H, app. quint, J = 6.4 Hz)	9.28, 11.4, 14.6, 15.9, 19.3, 19.7, 24.5 (2 C), 28.0, 29.5, 32.7, 32.9, 34.4, 37.0, 37.2, 37.3, 37.5, 74.1, 174.1	224 (5) [M − $C_3H_6O_2$]$^+$, 140 (7), 125 (32), 111 (18), 97 (12), 86 (37), 69 (20), 57 (100)
SRSS	Same as RSRR	Same as RSRR	Same as *RSRR*
SRSR	0.84 (6 H, d, J = 6.7 Hz), 0.85 (t, 3 H, J = 7.5 Hz), 0.88 (d, 3 H, J = 6.8 Hz), 1.13 (d, 3 H, J = 6.4 Hz), 1.14 (t, 3 H, J = 7.6 Hz), 0.92−1.70 (17 H, m), 2.31 (2 H, q, J = 7.6 Hz), 4.82 (1 H, app. quint, J = 6.2 Hz)	9.28, 11.4, 14.6, 15.9, 19.2, 19.6, 24.5 (2 C), 28.0, 29.6, 32.7, 32.9, 34.4, 36.9, 37.3 (2 C), 37.4, 74.1, 174.1	224 (4) [M − $C_3H_6O_2$]$^+$, 140 (6), 125 (30), 111 (15), 97 10), 86 (35), 70 (27), 57 (100)
RSRS	Same as *SRSR*	Same as *SRSR*	Same as *SRSR*
RSSR	0.84 (6 H, d, J = 6.4 Hz), 0.85 (t, 3 H, J = 7.1 Hz), 0.88 (d, 3 H, J = 6.8 Hz), 1.13 (d, 3 H, J = 6.4 Hz), 1.14 (t, 3 H, J = 7.6 Hz), 1.04−1.71 (17 H, m), 2.31 (2 H, q, J = 7.6 Hz), 4.82 (1 H, app. quint, J = 6.4 Hz)	9.28, 11.4, 14.6, 15.8, 19.2, 19.7, 24.5 (2 C), 28.0, 29.6, 32.7, 32.9, 34.4, 36.9, 37.3 (2 C), 37.4, 74.1, 174.1	224 (5) [M − $C_3H_6O_2$]$^+$, 140 (7), 125 (30), 111 (12), 97 (9), 86 (38), 69 (23), 57 (100)
SRRS	Same as *RSSR*	Same as *RSSR*	Same as RSSR
RRSR	0.84 (6 H, d, J = 6.5 Hz), 0.85 (t, 3 H, J = 6.5 Hz), 0.89 (d, 3 H, J = 6.8 Hz), 1.13 (t, 3 H, J = 7.6 Hz), 1.16 (d, 3 H, J = 6.4 Hz), 1.02−1.63 (17 H, m), 2.31 (2 H, q, J = 7.6 Hz), 4.84 (1 H, dq, J = 4.9 and 6.4 Hz)	9.31, 11.4, 14.8, 17.0, 19.2, 19.6, 24.5 (2 C), 28.0, 29.6, 32.6, 32.7, 34.4, 36.9, 37.3, 37.4, 37.6, 73.9, 174.2	224 (3) [M − $C_3H_6O_2$]$^+$, 140 (8), 125 (33), 111 (12), 97 (12), 86 (39), 69 (24), 57 (100)
SSRS	Same as *RRSR*	Same as *RRSR*	Same as *RRSR*

imidazole (1.71 g, 25.1 mmol) in CH_2Cl_2 (25 mL) at 0 °C. Iodine (6.79 g, 26.7 mmol) was added and after 5 h of stirring the reaction was quenched with methanol (1 mL). Extractive workup with $Na_2S_2O_3$ (aq. sat., 10 mL), Et_2O (3 × 25 mL) and brine (20 mL), followed by concentration and LC, gave the product (3.09 g, 82%), > 99% pure by GC. B.p. 40 °C/0.8 mbar. − $[\alpha]_D^{25}$ = +10.2 (c = 2.47, hexane), ref.[55] $[\alpha]_D^{25}$ = +3.63 (neat). − ^{1}H NMR: δ = 0.87 (t, 3 H, J = 7.1 Hz), 0.87 (d, 3 H, J = 6.1 Hz), 1.10−1.47 (m, 5 H), 1.73−1.90 (m, 2 H), 3.18 (t, 2 H, J = 7.0 Hz). − ^{13}C NMR: δ = 7.65, 11.3, 19.1, 29.3, 31.3, 33.7, 37.4. − MS (EI); *m*/*z* (%): 197 (1), 169 (4), 155 (3), 141 (2), 99 (8), 57 (100).

(*2S*,*6S*)-*N*-[(1*R*,2*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl]-*N*,2,6-trimethyloctanamide: A solution of *n*-butyllithium in hexane (16.6 mL, 26.6 mmol, 1.6 M) was added to a suspension of lithium chloride (dried under vacuum at 150 °C for 14 h in the reaction flask, 3.94 g, 93.0 mmol) and dry diisopropylamine (4.00 mL, 28.6 mmol) in dry THF (25 mL) at −78 °C. The solution

was warmed to room temperature for 0.08 h and then cooled to −78 °C. (*R*,*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methylpropionamide {$[\alpha]_D^{25}$ = −100.4 (*c* = 0.57, MeOH), 3.08 g, 13.9 mmol} in dry THF (50 mL) at 0 °C was added via cannula at such a speed that the temperature did not exceed −60 °C. The mixture was kept at −78 °C for 1 h and then allowed to reach +16 °C for 0.17 h, followed by lowering the temperature to −40 °C. To this mixture, (4*S*)-1-iodo-4-methylhexane (1.5 g, 6.64 mmol) was added neat and the reaction mixture was left stirring overnight. The reaction was quenched with NH_4Cl (aq. sat., 20 mL) and the resulting mixture was extracted with EtOAc (6 × 70 mL), dried with Na_2SO_4, and concentrated. The crude product was diluted with 50 mL of *n*-hexane and the crystalline starting material was filtered off. The product was isolated by LC, which yielded the octylamide as a viscous, yellow oil (1.83 g, 86%) > 98% pure by GC. − $[\alpha]_D^{25}$ = −46.0 (*c* = 2.61, MeOH). − ^{1}H NMR (asterisk denotes minor rotamer peaks): δ = 0.83 (d, 3 H, *J* = 6.0 Hz), 0.85 (t, 3 H, *J* = 7.2 Hz), 1.01−1.63 (m, 9 H), 1.09 (d, 3 H, *J* = 6.8 Hz), 1.14 (d, 3 H, *J* = 6.9 Hz), 2.6 0 (sext, 1 H, *J* = 6.6 Hz), 2.85 (s, 2 H), 2.92* (s, 1 H), 3.74 (1 H, br. s), 4.00−4.18* (0.3 H, m), 4.33−4.49 (0.7 H, m), 4.58−4.63 (m, 1 H), 7.23−7.35 (m, 5 H). − ^{13}C NMR (asterisk denotes minor rotamer peaks): δ = 11.4, 14.5, 15.5*, 17.4, 18.0*, 19.2, 19.3*, 24.9, 25.1*, 29.3*, 29.5, 33.3, 34.2, 34.3, 35.9*, 36.6, 36.7, 36.8*, 58.0*, 59.3, 75.5*, 76.6, 126.3, 126.9*, 127.5, 128.3, 128.7*, 141.1*, 142.6, 178.1*, 179.3. − MS (CI, CH_3CN); *m*/*z* (%): 320 (100) $[M + H]^+$, 303 (3), 302 (8), 148 (24). − $C_{20}H_{33}NO_2$: C 75.2; H 10.4; N 4.4; found C 74.8; H 10.5; N 4.4.

(2*R*,6*S*)-*N*-[(1*S*,2*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl]-*N*,2,6-trimethyloctanamide: Similarly, the (*S*,*S*) enantiomer of the pseudoephedrine propionamide {$[\alpha]_D^{25}$ = +103.6 (*c* = 1.20, MeOH), 2.69 g, 12.2 mmol} gave the title compound (1.60 g, 86%), > 98% pure by GC. − $[\alpha]_D^{25}$ = +57.6 (*c* = 3.08, MeOH). − ^{1}H NMR (asterisk denotes minor rotamer peaks): δ = 0.82−0.88 (m, 6 H), 1.01.63 (m, 9 H), 1.09 (d, 3 H, *J* = 6.7 Hz), 1.14 (d, 3 H, *J* = 6.9 Hz), 2.59 (sext, 1 H, *J* = 6.6 Hz), 2.85 (s, 2 H), 2.92* (s, 1 H), 4.00−4.17* (0.3 H, m), 4.33−4.49 (0.7 H, m), 4.58−4.63 (m, 1 H), 7.24−7.42 (m, 5 H). − ^{13}C NMR (asterisk denotes minor rotamer peaks): δ = 11.4, 14.5, 15.5*, 17.3, 17.9*, 19.2, 24.9, 25.1*, 29.4, 29.6*, 33.3, 34.2, 34.3, 34.4*, 35.9*, 36.5, 36.6, 36.8*, 57.9*, 59.2, 75.5*, 76.5, 126.3, 126.9*, 127.5, 128.3, 128.7*, 141.2*, 142.6, 177.9*, 179.3. − MS (CI, CH_3CN); *m*/*z* (%): 320 (100) $[M + H]^+$, 303 (10), 302 (75), 148 (12).

(2*S*,6*S*)-(−)-2,6-Dimethyl-1-octanol (*SS*-8): LiH_2NBH_3 reduction according to the procedure given by Smith and Roush,[28] starting from (2*S*,6*S*)-*N*-[(1*R*,2*R*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl]-*N*,2,6-trimethyloctanamide (1.71 g, 5.35 mmol), gave a crude product. After LC and bulb-to-bulb distillation, a colourless oil was obtained (0.62 g, 73%), > 99.5% pure by GC and with 99% (*S*) configuration at C-2. B.p 100 °C/10 mbar. − $[\alpha]_D^{25}$ = −2.71 (*c* = 2.65, $CHCl_3$), ref.[18] $[\alpha]_D^{20}$ = −7.32 (*c* = 1.68, $CHCl_3$). − ^{1}H NMR, ^{13}C NMR, and MS (EI) spectral data match those of ***RR*-8**.

(2*R*,6*S*)-(+)-2,6-Dimethyl-1-octanol (*RS*-8): Prepared similarly to the above, but from (2*R*,6*S*)-*N*-[(1*S*,2*S*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl]-*N*,2,6-trimethyloctanamide (0.88 g, 2.76 mmol), giving ***RS*-8** (0.37 g, 85%), 98.8% pure by GC and with 99.2% (*R*) configuration at C-2. B.p 65 °C/1.1 mbar. − $[\alpha]_D^{25}$ = +20.4 (*c* = 2.83, $CHCl_3$). − Ref.[20] $[\alpha]_D^{25}$ = +15.7 (*c* = 2.8, $CHCl_3$). ^{1}H NMR, ^{13}C NMR, and MS (EI) spectral data coincide with those of ***SR*-8**.[19]

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