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Transformation of Esters into 2-Substituted Allyl Halides via Tertiary Cyclopropanols: Application in the Stereoselective Synthesis of (2*S*,3*S*,7*S*)-3,7-Dimethyl-2-pentadecyl Acetate, the Sex Pheromone of the Pine Sawfly *Neodiprion sertifer*

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(2*S*,3*S*,7*S*)-3,7-Dimethyl-2-pentadecyl acetate (**ac-1**), the sex pheromone of the pine sawfly *Neodiprion sertifer*, has been newly synthesized by the transformation of the corresponding esters **8** and **12** into 2-oxyalkyl-substituted allyl bromides **4** and **5** via tertiary cyclopropanols **6** and **7**.

Introduction

Stereogenic methyl branches of carbon skeletons are characteristic structural elements of the pheromones of many insect species and their stereochemical configuration often exerts significant influence on their attractiveness.[1] One such substance is (2*S*,3*S*,7*S*)-3,7-dimethylpentadecan-2-ol (diprionol) (**1**), the acetate (**ac-1**) of which is the major component of the pine sawfly *Neodiprion sertifer* pheromone.[2] It has been established that pest attraction to the synthetic pheromone (2*S*,3*S*,7*S*)-**ac-1** is significantly reduced if the isomeric impurity content of (2*S*,3*R*,7*R*)-**ac-1** is more than 3%.[3] The stereoselective synthesis of compound **1** and its acylates has been described in several papers.[3–5] Alkylation reactions of chiral oxiranes,[3,4a,b,f] alkyl sulfonates,[4e,f,h] β-hydroxy acid esters,[4h] derivatives of alkanoic acids with oxazoline or prolinol chiral auxiliaries,[3,4c] as well as Claisen rearrangement of allyl vinyl ethers[4f] have been used in the creation of chiral centres at the C-3 and C-7 positions of this molecule. Resolution of diastereomeric mixtures of α-methyl-substituted secondary alcohols by crystallization[4d,4g] and functional group manipulations of (*R*)-citronellic acid[4a,b,d,g] are other methods that have also been used to create chiral centres at the C-3 and C-7 positions, respectively.

In this work, we report on the stereoselective synthesis of (2*S*,3*S*,7*S*)-3,7-dimethylpentadecan-2-ol (**1**) based on the creation of methyl branches in the carbon chain using the transformation of carboxylic esters into 2-substituted allyl halides via sulfonates of tertiary cyclopropanols.[6] Previously, we applied this methodology to the nonstereoselective construction of the methyl-branched skeleton of 3,7-dimethyl-2-tridecyl acetate and propionate,[7] the sex attractants of the pine sawfly *Diprion pini*,[8] and also to the stereoselective synthesis of the alkaloid (–)-heliotridane.[9]

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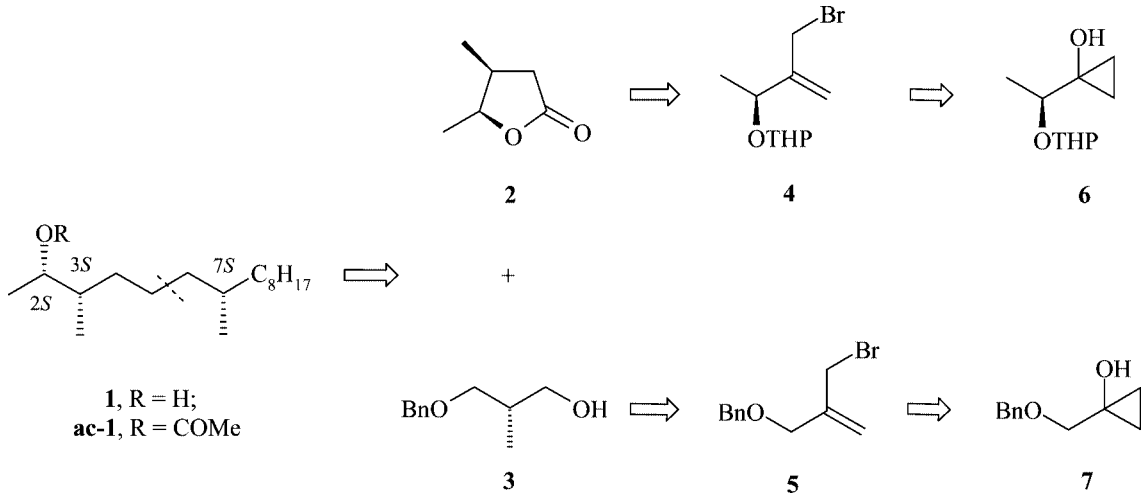
Results and Discussion

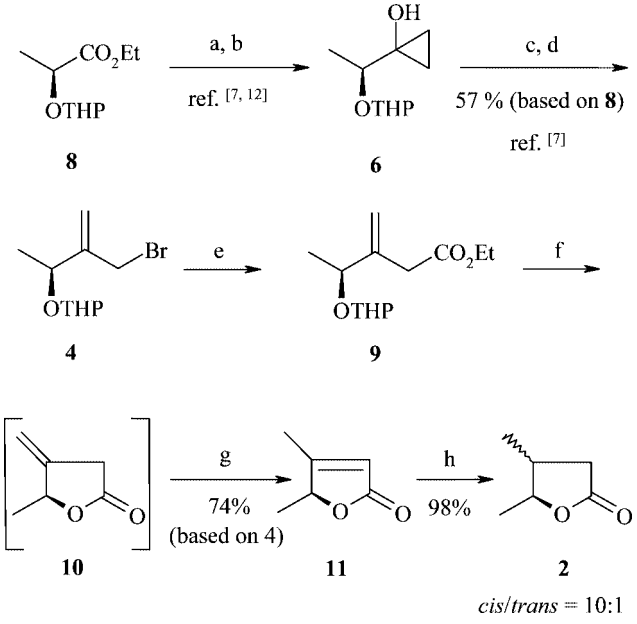
The key chiral building blocks **2** and **3** were synthesized from 2-oxyalkyl-substituted allyl halides **4** and **5**, which in turn were prepared starting from the readily accessible hydroxycyclopropane precursors **6** and **7** (Scheme 1).

THP-protected ethyl (*S*)-lactate (**8**) was transformed into bromide **4** by titanium-catalyzed cyclopropanation of the ethoxycarbonyl group with ethylmagnesium bromide[10,11] and subsequent cationic cyclopropyl–allyl isomerization[6] of the methanesulfonate of the 1-substituted cyclopropanol **6** (Scheme 2).[7,12] Replacement of the bromine atom in compound **4** with an ethoxycarbonyl group upon treatment with zinc powder, activated by copper(I) chloride in the presence of ethyl chloroformate, resulted in the smooth formation of ester **9**. The latter, without further purification, was deprotected under acidic conditions to give, after concomitant lactonization, compound **10**.[13] The carbon–carbon double bond in lactone **10** was shifted under the action of triethylamine to form α,β-unsaturated lactone **11**, isolated by column chromatography on silica gel in 42% yield based on THP-protected ethyl (*S*)-lactate (**8**).[14]

The preferential formation of (3*S*,4*S*)-butanolide **2** was observed upon treatment of unsaturated lactone **11** with sodium borohydride in the presence of nickel chloride.[7,16] The diastereoselectivity of the reaction was unsatisfactory (*cis*-**2**/*trans*-**2** = 3–4:1) when methanol or ethanol was used as the solvent. However, it was substantially enhanced (*cis*-



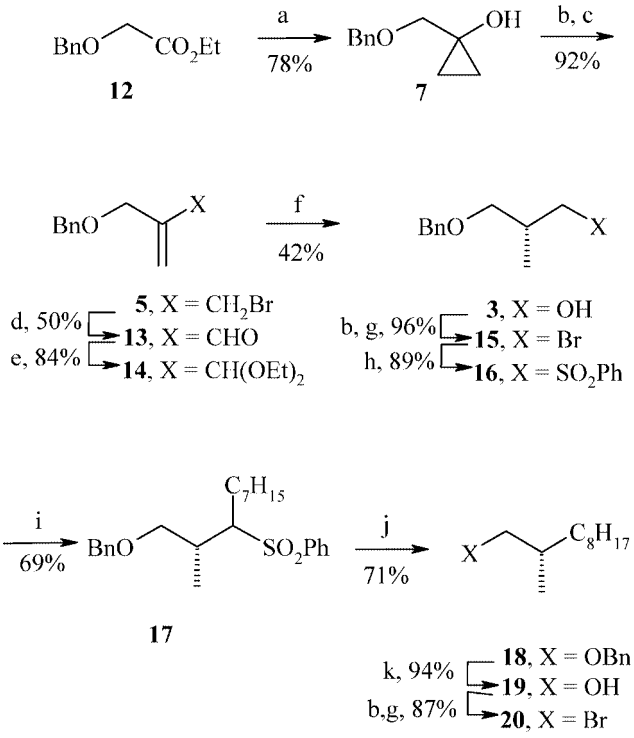
Scheme 1. Retrosynthetic analysis of **1** and **ac-1**.



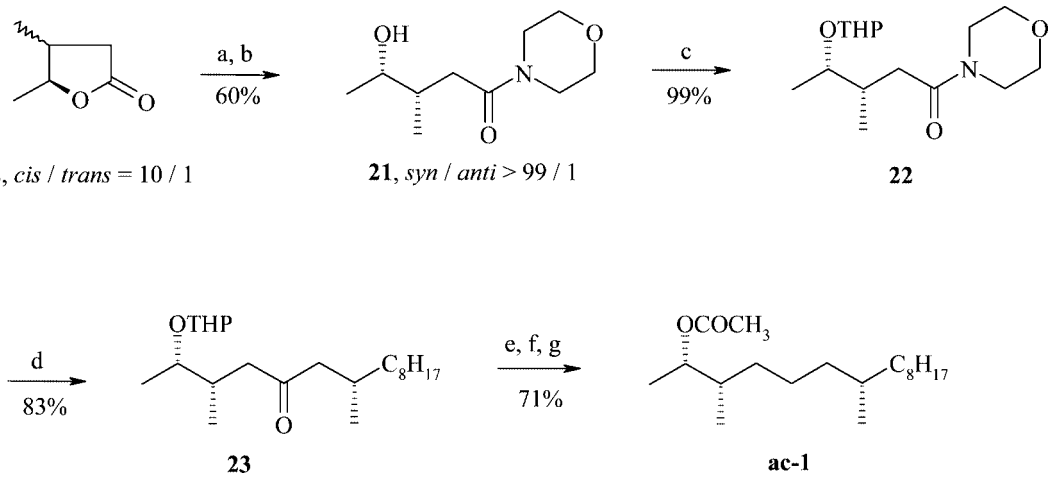
Scheme 2. Synthesis of lactone **2**. Reagents and conditions: (a) DHP, PPTS, CH_2Cl_2, reflux; (b) EtMgBr, Ti(O*i*Pr)$_4$, Et_2O/THF; (c) MsCl, Et_3N, Et_2O; (d) $MgBr_2$, $Et_2O/CHCl_3$, reflux; (e) Zn, CuCl, 1,2-dibromoethane, $ClCO_2Et$, reflux; (f) MeOH, THF, HCl, reflux; (g) Et_3N, reflux; (h) $NaBH_4$, $NiCl_2$, $B(OH)_3$, H_2O.

2/*trans*-**2** = 10:1) by carrying out the reduction in an aqueous medium. In this case, however, the reaction proceeded at a significantly lower rate, requiring more than 12 h for completion. We have found that lactone **11** could be reduced by this nickel reagent much faster in the presence of boric acid,[17] and the reaction was complete after 1 h without a reduction of the diastereoselectivity.

To synthesize the chiral building block **3** we used baker's yeast mediated biohydrogenation of the methylene-substituted acetal **14** as the key step.[18] The latter was readily obtained from ethyl (benzyloxy)acetate (**12**)[19] by reaction with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide[20] to form cyclopropanol **7**. Mesylation of compound **7** and subsequent treatment of the derivative obtained with magnesium bromide[6] led to bromide **5** in high yield. The latter was transformed, in a moderate yield, into α-methylene aldehyde **13** by Kornblum oxidation,[21] and then into the diethyl acetal **14** by a standard procedure. Biohydrogenation of the methylene moiety in compound **14** with baker's yeast led to chiral (*S*)-alcohol **3**, whose enantiomeric purity, as determined by Mosher's method, was more than 97%.[22] Alcohol **3** was converted into bromide **15** and then into sulfone **16** by standard procedures. Alkylation of sulfone **16** gave compound **17**, subse-



Scheme 3. Synthesis of bromide **20**. Reagents and conditions: (a) EtMgBr, Ti(O*i*Pr)$_4$; (b) MsCl, Et_3N; (c) $MgBr_2$; (d) DMSO, $NaHCO_3$; (e) $HC(OEt)_3$, H^+; (f) baker's yeast; (g) Bu_4NBr; (h) Bu_4NPhSO_2; (i) 1. BuLi; 2. $C_7H_{15}I$; (j) Na/Hg, EtOH; (k) H_2, Pd/C.



2, *cis* / *trans* = 10 / 1 **21**, *syn* / *anti* > 99 / 1 **22**

Scheme 4. Synthesis of **1** and **ac-1**. Reagents and conditions: (a) morpholine, 100 °C, 24 h; (b) recrystallization from diethyl ether; (c) DHP, PPTS, CH_2Cl_2; (d) (2*R*)-2-methyldecyllithium, Et_2O/THF, –78 °C; (e) N_2H_4, KOH, triethylene glycol, 180–210 °C; (f) MeOH, PPTS, reflux; (g) CH_3COCl, Et_3N, Et_2O.

quent reduction of which with sodium amalgam led to ether **18**. Catalytic debenzylation of the latter and replacement of the hydroxy group in alcohol **19**[23] by a bromine atom gave bromide **20** (Scheme 3),[23c] which was then used in the preparation of (2*R*)-2-methyldecyllithium. Use of this lithium compound in a coupling reaction with lactone **2** [obtained by a multistep synthesis from (2*R*,3*R*)-tartaric acid in an overall yield of less than 30%[3,4c]] followed by Kishner–Wolff reduction of the carbonyl group in the resulting product to form the target alcohol (2*S*,3*S*,7*S*)-**1** has been reported previously.[3,4c]

At the same time, lactone **2** was formed as a mixture of *cis*/*trans* isomers in a ratio of 10:1 and additional purification was required for the preparation of alcohol **1**. Since column chromatography was ineffective for this purpose, we transformed the crude lactone **2** into a crystalline morpholine **21**, single recrystallization of which from diethyl ether resulted in a *de* and *ee* of more than 98%. Tetrahydropyranylation of the hydroxy group in compound **21** and reaction of the resulting amide **22** with (2*R*)-2-methyldecyllithium (obtained from bromide **20**) gave ketone **23**. Kishner–Wolff reduction of the carbonyl group in **23**[3,4c] and removal of the THP protecting group led to the target (2*S*,3*S*,7*S*)-3,7-dimethylpentadecan-2-ol (**1**), which was then transformed into the acetate **ac-1**[24] containing less than 3% isomeric compounds as impurities (Scheme 4).

Conclusions

Acetate **ac-1**, the sex pheromone of the pine sawfly *Neodiprion sertifer*, was prepared in a stereoisomerically pure form in a total yield of 15%, starting from the THP-protected ethyl (*S*)-lactate **8**. For the stereospecific formation of the methyl branches at the C-3 and C-7 positions of compound **1**, the carbon–carbon double bonds in unsaturated lactone **11** and the acetal of α-methylene aldehyde **14** were reduced.

Experimental Section

General: Melting points were determined with a capillary apparatus. Optical rotations were measured at 20 ± 2 °C with a CM-3 polarimeter (scale factor: 0.05°). Column chromatography was performed on Merck 60 silica gel (70–230 mesh). IR spectra were recorded with a Specord IR-75 or Vertex 70 spectrometer. ^1H and ^{13}C NMR spectra were obtained with a Bruker AC 400 instrument at 400 and 100 MHz, respectively, in $CDCl_3$ (TMS at δ = 0.00 ppm or $CHCl_3$ at δ = 7.26 ppm for ^1H NMR and $CHCl_3$ at δ = 77.0 ppm for ^{13}C NMR as internal standard).

Ethyl 3-[(1*S*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]but-3-enoate (9): A vigorously stirred suspension of zinc powder (4.80 g, 73.4 mmol) and CuCl (0.30 g, 3.0 mmol) in THF (8 mL) was refluxed for 30 min under argon. Ethyl chloroformate (3.5 mL, 37 mmol) was added in one portion to the resulting mixture. Then a solution of allyl bromide **4**[7] (3.70 g, 14.9 mmol) and 1,2-dibromoethane (0.15 g, 0.80 mmol) in a mixture of THF (7 mL) and diethyl ether (7 mL) was added dropwise over 30 min to the stirred reaction mixture upon refluxing. The stirred reaction mixture was refluxed for an additional 30 min, cooled to room temperature and quenched with a saturated solution of $NaHCO_3$ (10 mL). The reaction mixture was filtered and the inorganic precipitate was additionally washed with diethyl ether (4 × 10 mL). The aqueous phase was separated and extracted with diethyl ether (4 × 5 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution, brine and dried with Na_2SO_4. Removal of the solvent under reduced pressure led to ester **9** (3.65 g), which was used in the next step without further purification. IR (CCl_4): $\tilde{\nu}$ = 3090, 1740, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.31 (m, 6 H, OCH_2CH_3 and CH_3CH), 1.44–1.90 (m, 6 H, $CH_2CH_2CH_2$), 2.96–3.23 (m, 2 H, 2-H), 3.37–3.54 (m, 1 H, OCH_2CH_2), 3.78–3.95 (m, 1 H, OCH_2CH_2), 4.13 (q, J = 7.3 Hz, 1 H, OCH_2CH_3), 4.14 (q, J = 7.3 Hz, 1 H, OCH_2CH_3), 4.28–4.38 (m, 1 H, CH_3CH), 4.52–4.60 (m, 0.5 H, OCHO), 4.69–4.76 (m, 0.5 H, OCHO), 5.02–5.04 (m, 0.5 H, 4-H), 5.06–5.08 (m, 0.5 H, 4-H), 5.16–5.19 (m, 0.5 H, 4-H), 5.22–5.24 (m, 0.5 H, 4-H) ppm. $C_{13}H_{22}O_4$ (242.3): calcd. C 64.44, H 9.15; found C 64.59, H 9.23.

(5*S*)-4,5-Dimethylfuran-2(5*H*)-one (11): Concentrated aqueous HCl (4 drops) and MeOH (1.14 mL, 28.2 mmol) were added to a solution of ester **9** (3.65 g) in THF (20 mL). The reaction mixture was re-

fluxed for 40 min under argon. Then Et_3N (1.05 mL, 7.53 mmol) was added and boiling was continued for an additional 1 h. The greater part of the solvent was carefully removed at atmospheric pressure and the residue was diluted with diethyl ether (25 mL) and brine (40 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (6×15 mL). The combined organic extracts were dried with Na_2SO_4 and carefully concentrated. The residue was purified by chromatography on silica gel (eluent: light petroleum ether/diethyl ether, 3:1) to give lactone **11** (1.23 g, 74% based on bromide **4**) as a colourless oil. $[a]_D$ = +20.2 (*c* = 5.00, CH_2Cl_2). IR (CCl_4): $\tilde{\nu}$ = 1775, 1645 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.8 Hz, 3 H, 5-Me), 2.02 (d, *J* = 1.2 Hz, 3 H, 4-Me), 4.86 (m, 1 H, 5-H), 5.73 (m, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 17.9, 80.8, 116.1, 169.8, 172.9 ppm. $C_6H_8O_2$ (112.1): calcd. C 64.27, H 7.19; found C 64.35, H 7.13.

(4*S*,5*S*)-4,5-Dimethyldihydrofuran-2(3*H*)-one (2): $NaBH_4$ (3.50 g, 92.5 mmol) and then $B(OH)_3$ (4.85 g, 78.4 mmol) were added at 0 °C in small portions over 5 min each to a stirred and cooled emulsion of **11** (1.20 g, 10.7 mmol) in aqueous $NiCl_2$ (0.2 M, 55 mL). The reaction mixture was stirred at 0 °C for an additional 1 h, then saturated with NaCl at room temperature and extracted with diethyl ether (4×30 mL). The combined organic fractions were dried with Na_2SO_4 and carefully concentrated. The lactone **2** (*cis*/*trans* = 10:1, 1.20 g, 98%) obtained was used in the next step without further purification. The *trans*-isomer content was determined from the ^1H NMR spectrum of the reaction mixture on the basis of integral intensities of signals of methyl protons using data published in the literature for individual *cis* and *trans* isomeric lactones **2**.[25] $[a]_D$ = –35.5 (*c* = 6.67, Et_2O). The spectral data were similar to those reported in the literature.[25]

1-[(Benzyloxy)methyl]cyclopropanol (7): A solution of ethylmagnesium bromide obtained from magnesium (32.81 g, 1350 mmol) and ethyl bromide (152.6 g, 1400 mmol) in diethyl ether (550 mL) was slowly added dropwise with stirring and reflux to a solution of ethyl (benzyloxy)acetate (58.2 g, 300 mmol) and titanium tetraisopropoxide (85.2 g, 300 mmol) in diethyl ether (130 mL) and benzene (200 mL). At the end of the addition the reaction mixture was cooled and added through a dropping funnel with stirring and cooling to sulfuric acid (750 mL, 25% aqueous solution) at such a speed that the temperature did not exceed 10 °C. The aqueous phase was separated and extracted with diethyl ether (3×100 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution, brine, dried with $MgSO_4$ and concentrated under reduced pressure. Column chromatography on silica gel (eluent: from petroleum ether to petroleum ether/ethyl acetate, 5:1) gave compound **7** (41.7 g, 78%) as a colourless oil. IR (CCl_4): $\tilde{\nu}$ = 3593, 3453, 3093 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.55 (dd, *J* = 6.8, 5.6 Hz, 2 H, 2-H, 3-H), 0.83 (dd, *J* = 6.8, 5.6 Hz, 2 H, 2-H, 3-H), 2.94–3.00 (br. s, 1 H, O*H*), 3.52 [s, 2 H, O-CH_2-C(OH)], 4.60 (s, 2 H, PhCH_2O), 7.26–7.39 (m, 5 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.6, 54.5, 72.9, 76.0, 127.6, 127.7, 128.3, 137.9 ppm. $C_{11}H_{14}O_2$ (178.2): calcd. C 74.13, H 7.92; found C 74.20, H 7.95.

[2-(Bromomethyl)prop-2-en-1-yloxy]methylbenzene (5): Methanesulfonyl chloride (30.93 g, 270 mmol) was added dropwise with stirring at 0 °C to a solution of cyclopropanol **7** (39.0 g, 219 mmol) and triethylamine (45.5 g, 450 mmol) in diethyl ether (500 mL). The reaction mixture was kept at room temperature overnight and then treated with water (150 mL). The aqueous phase was extracted with diethyl ether (3×150 mL). The combined organic phases were washed with brine (100 mL), dried with $MgSO_4$ and concentrated under reduced pressure to give 1-[(benzyloxy)methyl]cyclopropyl methanesulfonate (55.44 g, 99%). For analytical purposes, a small portion was purified by chromatography on silica gel (eluent: from petroleum ether to petroleum ether/ethyl acetate, 5:1) to give 1-[(benzyloxy)methyl]cyclopropyl methanesulfonate as a colourless oil. IR (CCl_4): $\tilde{\nu}$ = 3093 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (dd, *J* = 7.8, 6.7 Hz, 2 H, 2-H, 3-H), 1.36 (t, *J* = 7.3 Hz, 2 H, 2-H, 3-H), 3.02 (s, 3 H, CH_3SO_3); 3.76 [s, 2 H, O-CH_2-C(OMs)], 4.61 (s, 2 H, PhCH_2), 7.27–7.37 (m, 5 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.6, 39.6, 64.5, 72.8, 72.9, 127.7, 127.8, 128.4, 137.5 ppm. $C_{12}H_{16}O_4S$ (256.3): calcd. C 56.23, H 6.29; found C 56.30, H 6.23.

A solution of $MgBr_2$ prepared from magnesium (14.6 g, 600 mmol) and 1,2-dibromethane (112.8 g, 600 mmol) in diethyl ether (300 mL) was added to a stirred and refluxed solution of 1-[(benzyloxy)methyl]cyclopropyl methanesulfonate (52.22 g, 204 mmol) in diethyl ether (150 mL). The reaction mixture was then refluxed for 2 days and then quenched with water (200 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (3×100 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. Compound **5** (45.30 g, 92%) was isolated by column chromatography on silica gel (eluent: from petroleum ether to petroleum ether/ethyl acetate, 5:1) as a colourless oil. The spectral data were similar to those reported in the literature.[26]

2-[(Benzyloxy)methyl]acrylaldehyde (13): A solution of allyl bromide **5** (32.0 g, 132.7 mmol) and $NaHCO_3$ (33.6 g, 400 mmol) in dry DMSO (250 mL) was stirred at room temperature for 48 h with regular removal of the resulting CO_2 and Me_2S in a 10 mbar vacuum. After completion of the reaction, the mixture was diluted with water (800 mL) and extracted with petroleum ether (5×400 mL). Removal of the solvent under reduced pressure and column chromatography of the residue on silica gel (eluent: from petroleum ether to petroleum ether/ethyl acetate, 5:1) gave aldehyde **13** (11.71 g, 50%). The spectral data were similar to those reported in the literature.[27]

[2-(Diethoxymethyl)allyloxymethyl]benzene (14): A solution of aldehyde **13** (11.1 g, 63.2 mmol), triethyl orthoformate (9.62 g, 65 mmol) and NH_4NO_3 (0.1 g) in dry ethanol (10 mL) was stirred at 50 °C for 8 h. Removal of the solvent under reduced pressure and column chromatography of the residue on silica gel (eluent: from petroleum ether to petroleum ether/ethyl acetate, 5:1) gave acetal **14** (13.3 g, 84%). IR (CCl_4): $\tilde{\nu}$ = 1453 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 6 H, CH_3), 3.49 (dq, *J* = 9.3, 7.2 Hz, 2 H, OCH_2Me), 3.62 (dq, *J* = 9.3, 7.2 Hz, 2 H, OCH_2Me), 4.09 (s, 2 H, 1′-H), 4.55 (s, 2 H, PhCH_2), 4.91 [s, 1 H, C*H*(OEt)$_2$], 5.36–5.38 (m, 1 H, 3′-H), 5.38–5.41 (m, 1 H, 3′-H), 7.26–7.39 (m, 5 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.1, 61.7, 69.3, 72.3, 101.4, 114.2, 127.4, 127.5, 128.3, 138.3, 142.9 ppm. $C_{15}H_{22}O_3$ (250.3): calcd. C 71.97, H 8.86; found C 71.95, H 8.83.

(2*S*)-3-Benzyloxy-2-methylpropan-1-ol (3): A known method for baker's yeast mediated reduction[18] was modified and adapted for the preparative-scale synthesis of compound **3**. A solution of acetal **14** (12.00 g, 48.0 mmol) in ethanol (60 mL) was added portionwise (in six portions over a period of 3 d) with stirring and at an internal temperature 34–38 °C to a suspension of pressed baker's yeast (1200 g) in a buffer solution (pH 5.25) of citric acid monohydrate (26.88 g, 128 mmol) and K_2CO_3 (15.46 g, 112 mmol) in water (2.4 L). For these 3 days and for a day afterwards, the reaction mixture was stirred and a sugar (3–6 g, 10–12 times a day) was added. Then the yeast suspension was carefully extracted with petroleum ether (6×2 L), dried with Na_2SO_4 and concentrated under reduced pressure. Column chromatography on silica gel (eluent: from petroleum ether to petroleum ether/ethyl acetate, 5:1) gave the title compound

(3.60 g, 42%) as a colourless oil. Enantiomeric excess of the alcohol **3** (*ee* > 97%) was determined by Mosher's method.[22] The spectral data were similar to those reported in the literature.[28]

(2*R*)-3-Bromo-2-[(methylpropyloxy)methyl]benzene (15): A solution of methanesulfonyl chloride (2.06 g, 18 mmol) in diethyl ether (15 mL) was added dropwise at 0 °C to a stirred solution of alcohol **3** (2.70 g, 15.0 mmol) and triethylamine (2.42 g, 24 mmol) in diethyl ether (50 mL). The reaction mixture was slowly warmed to room temperature and quenched with water (30 mL). The aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure to give (2*R*)-3-benzyloxy-2-methylpropyl methanesulfonate (3.74 g, 97%). $[\alpha]_D$ = –8.9 (*c* = 5.00, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 7.1 Hz, 3 H, 2-Me), 2.21 (m, 1 H, 2-H), 2.96 (s, 3 H, CH_3SO_3), 3.39 (dd, *J* = 9.2, 6.9 Hz, 1 H, 3-H), 3.45 (dd, *J* = 9.2, 5.1 Hz, 1 H, 3-H), 4.19 (dd, *J* = 9.6, 5.7 Hz, 1 H, 1-H), 4.25 (dd, *J* = 9.6, 5.6 Hz, 1 H, 1-H), 4.50 (s, 2 H, $PhCH_2$), 7.26–7.39 (m, 5 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.4, 33.5, 36.7, 70.8, 71.7, 72.9, 127.4, 127.5, 128.2, 138.0 ppm. $C_{12}H_{18}O_4S$ (258.3): calcd. C 55.79, H 7.02; found C 55.85, 7.00.

Tetrabutylammonium bromide (6.44 g, 20.0 mmol) was added to a solution of (2*R*)-3-benzyloxy-2-methylpropyl methanesulfonate (3.51 g, 13.6 mmol) in benzene (30 mL).[29] The reaction mixture was stirred at 70 °C for 2 h (progress was monitored by thin-layer chromatography on silica gel plates). After cooling to room temperature, water (30 mL) was added. The aqueous phase was extracted with benzene (2 × 30 mL). The combined organic phases were washed with water (20 mL), brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure to give bromide **15** (3.26 g, 99%) $[\alpha]_D$ = –9.6 (*c* = 12.2, MeOH). The spectral data were similar to those reported in the literature.[28e]

(2*R*)-1-Benzyloxy-2-methyl-3-(phenylsulfonyl)propane (16): Tetrabutylammonium benzenesulfinate[30] (7.66 g, 20.0 mmol) was added to a solution of bromide **15** (2.92 g, 12.0 mmol) in benzene (30 mL). The reaction mixture was stirred at 70 °C for 8 h and treated with water (30 mL). The aqueous phase was extracted with benzene (2 × 50 mL). The combined organic phases were washed with water (30 mL), brine (30 mL), dried with Na_2SO_4 and concentrated under reduced pressure. Column chromatography on silica gel (eluent: from petroleum ether to petroleum ether/ethyl acetate, 2:1) gave the title compound (3.26 g, 89%) as a colourless oil. $[\alpha]_D$ = +1.6 (*c* = 38.4, MeOH). The spectral data were similar to those reported in the literature.[31]

(2*R*)-1-Benzyloxy-2-methyl-3-(phenylsulfonyl)decane (17): A solution of BuLi in hexane (18 mL, 1 N, 18 mmol) was added dropwise at –78 °C to a stirred solution of sulfone **16** (3.04 g, 10.0 mmol) in a mixture of THF (26 mL) and HMPA (16 mL). The reaction mixture was heated to –30 °C over the course of 2 h and then again cooled to –78 °C. 1-Iodoheptane (4.52 g, 20.0 mmol) in hexane (7 mL) was added dropwise to the reaction mixture. The resulting solution was warmed to room temperature over 3 h and quenched with water (20 mL). The aqueous phase was extracted with diethyl ether (2 × 50 mL). The combined organic phases were washed with brine (20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (eluent: from petroleum ether to petroleum ether/ethyl acetate, 2:1) gave the title compound (2.78 g, 69%, *syn*/*anti* = 1:1) as a colourless oil. IR (CCl_4): $\tilde{\nu}$ = 3073, 3033 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.1 Hz, 1.5 H, 10-Me), 0.83 (t, *J* = 7.1 Hz, 1.5 H, 10-Me), 0.94 (d, *J* = 7.1 Hz, 1.5 H, 2-Me), 1.19 (d, *J* = 7.1 Hz, 1.5 H, 2-Me), 1.02–1.36 (m, 10 H, 5-, 6-, 7-, 8-, 9-H), 1.46–1.62 (m, 0.5 H, 4-H), 1.62–1.72 (m, 1 H, 4-H), 1.80–1.93 (m, 0.5 H, 4-H), 2.30–2.42 (m, 0.5 H, 2-H), 2.49–2.59 (m, 0.5 H, 2-H), 3.18–3.28 (m, 1.5 H, 1-H, 3-H), 3.31–3.37 (m, 0.5 H, 3-H), 3.47 (dd, *J* = 9.2, 6.7 Hz, 0.5 H, 1-H), 3.82 (dd, *J* = 9.2, 7.2 Hz, 0.5 H, 1-H), 4.29 (d, *J* = 11.9 Hz, 0.5 H, $PhCH_2$), 4.37 (d, *J* = 11.9 Hz, 0.5 H, $PhCH_2$), 4.47 (s, 0.5 H, $PhCH_2$), 4.48 (s, 0.5 H, $PhCH_2$), 7.16–7.34 (m, 5 H, $C_6H_5CH_2$), 7.44–7.51 (m, 2 H, $C_6H_5SO_2$), 7.54–7.61 (m, 1 H, $C_6H_5SO_2$), 7.81 (d, *J* = 6.9 Hz, 1 H, $C_6H_5SO_2$), 7.86 (d, *J* = 7.1 Hz, 1 H, $C_6H_5SO_2$) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.2, 13.85, 13.90, 13.95, 22.35, 22.40, 23.1, 26.1, 27.3, 28.6, 28.7, 28.8, 29.3, 31.45, 31.50, 31.6, 31.8, 34.1, 63.9, 65.1, 72.4, 72.5, 72.9, 127.25, 127.35, 127.40, 127.5, 128.1, 128.2, 128.4, 128.85, 128.90, 129.1, 133.2, 137.9, 138.4, 139.2, 139.9 ppm. $C_{24}H_{34}O_3S$ (402.6): calcd. C 71.60, H 8.51; found C 71.45, H 8.51.

(2*S*)-2-[(Methyldecyloxy)methyl]benzene (18): Powdered 3% sodium amalgam (57.5 g, 75.0 mmol) was added to a solution of sulfone **17** (2.46 g, 6.10 mmol) in absolute ethanol (50 mL).[32] The reaction mixture was stirred for 24 h. The organic phase was separated, diluted with water (250 mL) and extracted with petroleum ether (5 × 30 mL). The combined organic phases were concentrated under reduced pressure. Column chromatography of the residue on silica gel (eluent: from petroleum ether to petroleum ether/ethyl acetate, 10:1) gave the title compound (1.13 g, 71%) as a colourless oil. IR (CCl_4): $\tilde{\nu}$ = 3040 cm^{-1}. $[\alpha]_D$ = +3.9 (*c* = 12.8, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.5 Hz, 3 H, 10′-Me), 0.93 (d, *J* = 6.7 Hz, 3 H, 2′-Me), 1.03–1.50 (m, 14 H, 3′-, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-H), 1.75 (m, 1 H, 2′-H), 3.23 (dd, *J* = 9.1, 6.9 Hz, 1 H, 1′-H), 3.33 (dd, *J* = 9.1, 6.1 Hz, 1 H, 1′-H), 4.49 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 4.52 (d, *J* = 12.1 Hz, 1 H, $PhCH_2$), 7.24–7.41 (m, 5 H, C_6H_5) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 17.1, 22.7, 26.9, 29.3, 29.6, 29.9, 31.9, 33.4, 33.6, 72.9, 76.0, 127.3, 127.5, 128.3, 138.8 ppm. $C_{18}H_{30}O$ (262.4): calcd. C 82.38, H 11.52; found C 82.45, H 11.48.

(2*S*)-2-Methyldecan-1-ol (19): A solution of compound **18** (1.10 g, 4.20 mmol) in absolute EtOH (15 mL) was stirred under H_2 in the presence of 10% Pd/C (0.05 g) for 2 h. The mixture was filtered and the filtrate concentrated under reduced pressure. Column chromatography of the residue on silica gel (eluent: from petroleum ether to petroleum ether/ethyl acetate, 5:1) gave the title compound (0.68 g, 94%) as a colourless oil. The spectral data were similar to those reported in the literature.[23]

(2*S*)-1-Bromo-2-methyldecane (20): A known method[29] was modified to suit the preparation of the title compound. A solution of methanesulfonyl chloride (0.57 g, 5.0 mmol) in diethyl ether (5 mL) was added dropwise at 0 °C to a stirred solution of alcohol **19** (0.65 g, 3.8 mmol) and triethylamine (0.77 g, 7.6 mmol) in diethyl ether (15 mL). After stirring overnight, the reaction was quenched with water (15 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with brine (10 mL), dried with $MgSO_4$ and concentrated under reduced pressure to give a crude mesylate, which was immediately dissolved in benzene (10 mL) containing tetrabutylammonium bromide (1.61 g, 5.0 mmol). The solution was heated at 70 °C for 5 h. After cooling, water (5 mL) was added. Extraction with petroleum ether (5 × 15 mL), drying over $MgSO_4$ and concentration under reduced pressure furnished a yellow oil, which after column chromatography on silica gel (eluent: petroleum ether) gave the title bromide **20** (0.77 g, 87%). The spectral data were similar to those reported in the literature.[23c]

(2*S*,3*S*)-3-Methyl-5-morpholino-5-oxopentan-2-ol (21): A solution of lactone **2** (*cis*/*trans* = 10:1, 1.63 g, 14.3 mmol) in morpholine (15 mL) was heated at 100 °C for 24 h under argon. Morpholine was removed under reduced pressure. Column chromatography on

silica gel (eluent: from ethyl acetate/cyclohexane, 1:1 to ethyl acetate) gave crude **21** (2.45 g, 85%) as colourless crystals and lactone **2** (0.21 g, *cis*/*trans* = 3:1). Recrystallization from diethyl ether gave amide **21** (*syn*/*anti* > 99:1, 1.73 g, 60%). M.p. 79–81 °C. $[\alpha]_D$ = +3.5 (*c* = 6.67, CH_2Cl_2). IR ($CHCl_3$): $\tilde{\nu}$ = 3645, 3390, 1655 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 7.0 Hz, 3 H, 3-Me), 1.13 (d, *J* = 6.2 Hz, 3 H, 1-H), 2.09–2.19 (m, 1 H, 3-H), 2.23 (dd, *J* = 15.2, 6.2 Hz, 1 H, 4-H), 2.42 (br. s, 1 H, OH), 2.52 (dd, *J* = 15.2, 7.3 Hz, 1 H, 4-H), 3.47–3.55 (m, 2 H, NCH_2), 3.59–3.69 (m, 6 H, N-CH_2, O-CH_2), 3.84 (qd, *J* = 6.2, 3.1 Hz, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 19.2, 35.8, 36.2, 41.9, 46.2, 66.6, 66.8, 69.8, 171.7 ppm. $C_{10}H_{19}NO_3$ (201.3): calcd. C 59.68, H 9.52; found C 59.62, H 9.47. ^1H NMR (400 MHz, $CDCl_3$) of the isomeric (2*S*,3*R*)-3-methyl-5-morpholino-5-oxopentan-2-ol in the region δ = 1.0–1.5 ppm: δ = 0.97 (d, *J* = 7.1 Hz, 3 H, 3-Me), 1.23 (d, *J* = 6.1 Hz, 3 H, 1-H) ppm (these signals were used to determine the *syn*/*anti* ratio).

Determination of the Enantiomeric Purity of 21: The *ee* value of **21** was determined by Mosher's method[22a] from the integral intensities of the doublets of the methyl groups at δ = 0.92 and 0.98 ppm in the ^1H NMR spectra of the (*S*)- and (*R*/*S*)-MTPA esters. In this way the enantiomeric purity of compound **21** was determined to be more than 98%.

(1*S*,2*S*)-1,2-Dimethyl-4-morpholino-4-oxobutyl 3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate: ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.8 Hz, 1.5 H, 2-Me), 0.98 (d, *J* = 6.8 Hz, 1.5 H, 2-Me), 1.27 (d, *J* = 6.4 Hz, 1.5 H, 1-Me), 1.33 (d, *J* = 6.4 Hz, 1.5 H, 1-Me), 1.94–2.37 (m, 3 H, 2- and 3-H), 3.15–3.32 (m, 2 H, N-CH_2), 3.46 (s, 1.5 H, OMe), 3.55 (s, 1.5 H, OMe), 3.52–3.68 (m, 6 H, N-CH_2 and O-CH_2), 5.10–5.19 (m, 1 H, 1-H), 7.29–7.65 (m, 5 H, aromatic H) ppm.

(1*S*,2*S*)-1,2-Dimethyl-4-morpholino-4-oxobutyl (2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate: ^1H NMR (400 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.8 Hz, 3 H, 2-Me), 1.27 (d, *J* = 6.4 Hz, 3 H, 1-Me), 2.07 (dd, *J* = 16.4, 9.8 Hz, 1 H, 3-H), 2.27–2.37 (m, 2 H, 3-H and 2-H), 3.25–3.32 (m, 2 H, N-CH_2), 3.46 (s, 3 H, OMe), 3.52–3.66 (m, 6 H, N-CH_2 and O-CH_2), 5.12 (qd, *J* = 6.4, 2.9 Hz, 1 H, 1-H), 7.36–7.43 (m, 3 H, aromatic H), 7.47–7.55 (m, 2 H, aromatic H) ppm.

4-[(3*S*,4*S*)-3-Methyl-4-(tetrahydro-2*H*-pyran-2-yloxy)pentanoyl]-morpholine (22): A solution of amide **21** (1.87 g, 9.29 mmol), 3,4-dihydro-2*H*-pyran (1.56 g, 18.6 mmol) and PPTS (0.05 g, 0.2 mmol) in chloroform (20 mL) was refluxed for 3 h. The reaction mixture was washed with a saturated $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted with chloroform (3 × 10 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. Compound **22** (2.63 g, 99%) was isolated by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 2:1) as a colourless oil. $[\alpha]_D$ = –3.9 (*c* = 9.67, Et_2O). IR (CCl_4): $\tilde{\nu}$ = 1665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.9 Hz, 1.5 H, 3′-Me), 0.96 (d, *J* = 6.9 Hz, 1.5 H, 3′-Me), 1.07 (d, *J* = 6.5 Hz, 1.5 H, 5-H), 1.17 (d, *J* = 6.5 Hz, 1.5 H, 5-H), 1.42–1.86 (m, 6 H, $CH_2CH_2CH_2$), 2.05 (dd, *J* = 10.5, 9.1 Hz, 0.5 H, 2′-H), 2.09 (dd, *J* = 10.5, 9.1 Hz, 0.5 H, 2′-H), 2.15–2.28 (m, 1 H, 3′-H), 2.53 (dd, *J* = 14.6, 4.2 Hz, 0.5 H, 2′-H), 2.67 (dd, *J* = 14.6, 4.5 Hz, 0.5 H, 2′-H), 3.42–3.97 (m, 11 H, 2-, 3-, 5-, 6-, 4′-H, $CH_2CH_2CH_2O$), 4.59–4.64 (m, 1 H, OCHO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 15.1, 15.5, 17.0, 20.0, 20.1, 25.28, 25.34, 31.1, 31.2, 34.35, 34.42, 35.46, 35.51, 41.72, 41.75, 45.9, 62.8, 63.1, 66.5, 66.6, 66.80, 66.82, 74.0, 76.6, 96.6, 98.8, 171.2, 171.5 ppm. $C_{15}H_{27}NO_4$ (285.4): calcd. C 63.13, H 9.54; found C 63.27, H 9.64.

(2*S*,3*S*,7*S*)-3,7-Dimethyl-2-(tetrahydro-2*H*-pyran-2-yloxy)pentadecan-5-one (23): A solution of (2*R*)-2-methyldecyllithium was prepared from (2*S*)-2-methyl-1-bromodecane (**20**) (0.70 g, 3.0 mmol) and lithium (0.05 g, 7.2 mmol) in diethyl ether (3 mL) at –20 °C under argon. The solution obtained (with small unreacted lithium shards) was cooled to –78 °C. A solution of amide **22** (0.33 g, 1.2 mmol) in THF (3 mL) was added dropwise over 5–10 min to the stirred solution of (2*R*)-2-methyldecyllithium. The reaction mixture was stirred for 2 h at –78 °C and then quenched at the same temperature first with MeOH (0.05 mL), and then with a saturated NH_4Cl solution. The organic layer was separated and the aqueous layer extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Compound **23** (0.34 g, 83%) was isolated by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 15:1) as a colourless oil. IR (CCl_4): $\tilde{\nu}$ = 1735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.90 (m, 9 H, 3-Me, 7-Me, 15-H), 1.04 (d, *J* = 6.1 Hz, 1.5 H, 1-H), 1.13 (d, *J* = 6.4 Hz, 1.5 H, 1-H), 1.18–2.04 (m, 22 H, 3-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-H, $CH_2CH_2CH_2$ in tetrahydropyran), 2.11–2.29 (m, 2 H, 4-H or 6-H), 2.33–2.43 (m, 1 H, 4-H or 6-H), 2.51–2.59 (m, 0.5 H, 4-H or 6-H), 2.61–2.70 (m, 0.5 H, 4-H or 6-H), 3.42–3.51 (m, 1 H, CHO or CH_2O), 3.64–3.75 (m, 1 H, CHO or CH_2O), 3.80–3.93 (m, 1 H, CHO or CH_2O), 4.56–4.64 (m, 1 H, OCHO) ppm. $C_{22}H_{42}O_3$ (354.6): calcd. C 74.52, H 11.94; found C 74.68, H 11.96.

(2*S*,3*S*,7*S*)-3,7-Dimethylpentadecan-2-ol (1): Powdered KOH (0.30 g, 5.4 mmol) was added to a solution of ketone **23** (0.33 g, 0.9 mmol) and hydrazine hydrate (0.2 mL) in triethylene glycol (4.5 mL). The reaction mixture was slowly (30 min) heated to 180 °C. Starting from 120 °C, a very weak flow of argon was periodically passed through the solution in order to remove gaseous byproducts. The stirred reaction mixture was heated at 180 °C for 1 h and then at 210 °C for 1.5 h. Then it was cooled to room temperature, diluted with water (5 mL) and extracted with diethyl ether (3 × 7 mL). The combined organic extracts were washed with a saturated $NaHCO_3$ solution, brine, dried with Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in methanol (10 mL) and refluxed in the presence of PPTS (0.02 g, 0.1 mmol) for 1 h. The solvent was removed under reduced pressure. The target alcohol **1** (0.19 g, 80% based on ketone **23**) was isolated by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 15:1) as a colourless oil. $[\alpha]_D$ = –9.7 (*c* = 1.2, hexane). The spectral data were similar to those reported in the literature.[3,4]

(1*S*,2*S*,6*S*)-3,7-Dimethyl-2-pentadecyl Acetate (ac-1): CH_3COCl (0.15 mL, 2.1 mmol) was added in one portion at 0 °C to a stirred solution of alcohol **1** (0.180 g, 0.70 mmol) and Et_3N (0.59 mL, 4.2 mmol) in diethyl ether (3 mL). The reaction mixture was stirred for 10 h at room temperature and then quenched with water (3 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (4 × 2 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The product (0.184 g, 88%) was isolated by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 25:1) as a colourless oil. $[\alpha]_D$ = –5.6 (*c* = 1.2, hexane). The spectral data were similar to those reported in the literature.[3,4]

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