Pheromones of Pine Sawflies: Synthesis of a Pure (2*S*,3*R*)-3-Methylalkan-2-ol Stereoisomer via an Asymmetric 1,3-Dipolar Cycloaddition; Preparation of a Pheromone Component of *Macrodiprion nemoralis*

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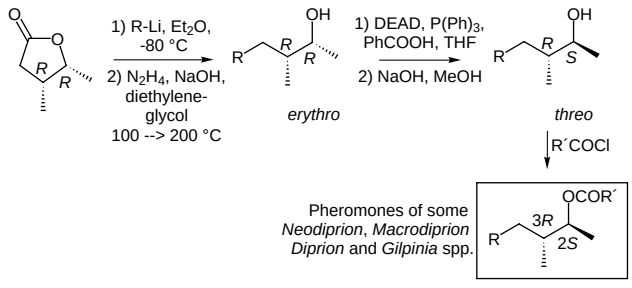
Abstract: This paper presents a new approach to the preparation of enantiomerically pure (2*S*,3*R*)-3-methylalkan-2-ols, the esters of which are sex pheromones of several pine sawflies. Thus, an asymmetric 1,3-dipolar cycloaddition between a sulfur containing 1,3-dipole and a dipolarophile attached to (1*R*)-camphorsultam containing a vinyl ether functionality furnished a 90:10 diastereomeric mixture of *trans*-3,4-disubstituted tetrahydrothiophene amides. The major one was converted to an enantiomerically pure tetrahydrothienylmethyl bromide, which was coupled with a monoalkylated dithiane unit. After Raney nickel reduction (2*S*,3*R*,7*R*,9*S*)-3,7,9-trimethyltridecan-2-ol was obtained, the acetate of which is the attractant sex pheromone component of *Macrodiprion nemoralis*. Because this new approach is quite efficient it can be valuable for the synthesis of similar compounds.

Key words: 1,3-dipolar cycloaddition, asymmetric synthesis, pine sawflies, dithiane, Raney nickel, lithiations, desulfurisations

Introduction

The pine sawflies belonging to the family Diprionidae are severe pests on conifers, in particular pine trees.[1,2] All of them contain a common structural unit, the 3-methyl-2-alkyl ester unit (see Scheme 1). Both *threo*- or the *erythro*-isomers are found among the active ones, almost all of them with (2*S*,3*R*)- or (2*S*,3*S*)-configuration, respectively.[2,3] We have a long standing interest in the synthesis of stereoisomerically pure sex pheromones from different species of pine sawflies.[4–13]



Previous approach to the *threo*-(2*S*,3*R*)-type of active pheromone components of certain species of pine sawflies

Scheme 1

Our previous strategy (Scheme 1) for the introduction of the enantiopure *threo*-unit into the carbon skeleton of the pheromones of various pine sawfly species initially involves synthesis of a stereoisomerically pure *erythro*-(2*R*,3*R*)-isomer, followed by inversion of the configuration around C-2 using a Mitsunobu reaction to give the corresponding *threo*-(2*S*,3*R*)-isomer. A desired single *erythro*-isomer is obtained via ring opening of either enantiopure (2*R*,3*R*)- or (2*S*,3*S*)-3,4-dimethyl-γ−butyrolactone by a suitable alkyllithium followed by Huang−Minlon reduction of the resulting keto alcohol. An example of this strategy is provided by the recent synthesis of all sixteen pure stereoisomers of the sex pheromone of *Macrodiprion nemoralis*.[5] Each lactone enantiomer is derived from the appropriate, pure butane-2,3-diol enantiomer. We felt that a more direct approach to the *threo*-pheromones, avoiding the Mitsunobu reaction and accompanying steps, would be desirable.

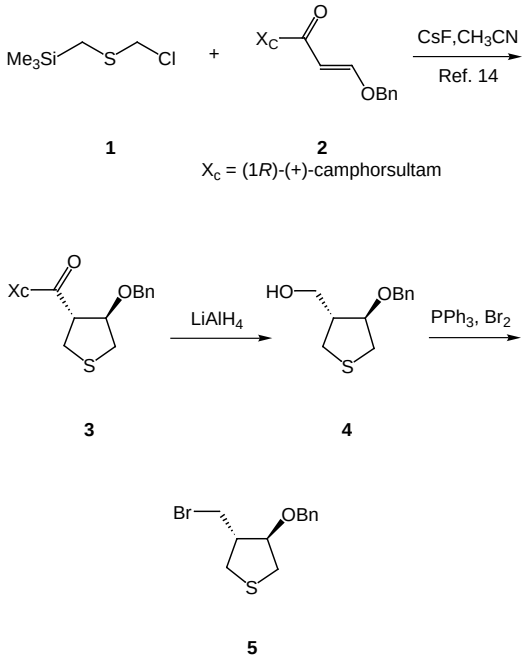
We have recently reported that the 1,3-dipolar cycloaddition of a thiocarbonyl ylide with various dipolarophiles can be performed in a diastereoselective fashion if the dipolarophile is attached to an enantiopure auxiliary and that camphorsultam is the best one in terms of yield and diastereoselectivity.[14] Thus *trans*-3,4-disubstituted tetrahydrothiophene derivatives are accessible as pure enantiomers via a simple sequence.[14] We have also demonstrated that an α,β-unsaturated dipolarophile containing a β-benzyloxy group functions well as the reactive partner in this cycloaddition sequence (cf. Scheme 2).[14] The resulting 3-tetrahydrothienylcarboxamide contains a *trans*-4-oxygen substituent. It occurred to us that such tetrahydrothiophenes could be used as building blocks for the construction of enantiopure *threo*-3-methylalkan-2-ols after desulfurisation and debenzylation via a simple synthetic sequence.

We now wish to present an alternative approach to (1*S*,2*R*,6*R*,8*S*)-1,2,6,8-tetramethyldodecyl acetate (acetate of **9**), the active sex pheromone component of *Macrodiprion nemoralis*. This involves the asymmetric 1,3-dipolar cycloaddition reaction discussed above in conjunction with two sequential dithiane alkylations as key steps.

Results and Discussion

The total synthesis of (2*S*,3*R*,7*R*,9*S*)-3,7,9-trimethyltridecan-2-ol (**9**) commenced with the construction of the

enantiopure tetrahydrothiophene building block **5** through a diastereoselective asymmetric 1,3-dipolar cycloaddition reaction between an enantiopure α,β-unsaturated dipolarophile, the camphorsultam amide **2,** and the dipole precursor, the thioether **1** (see Scheme 2). The cycloaddition product **3** was obtained in high diastereomeric purity (dr = 90:10) and in high yield.[14] Chromatographic removal of the minor diastereomer followed by reductive removal of the chiral auxiliary, camphorsultam, using $LiAlH_4$ furnished the corresponding alcohol **4**. This was transformed into the enantiopure building block, bromide **5**, using standard[15] conditions (PPh_3, Br_2).

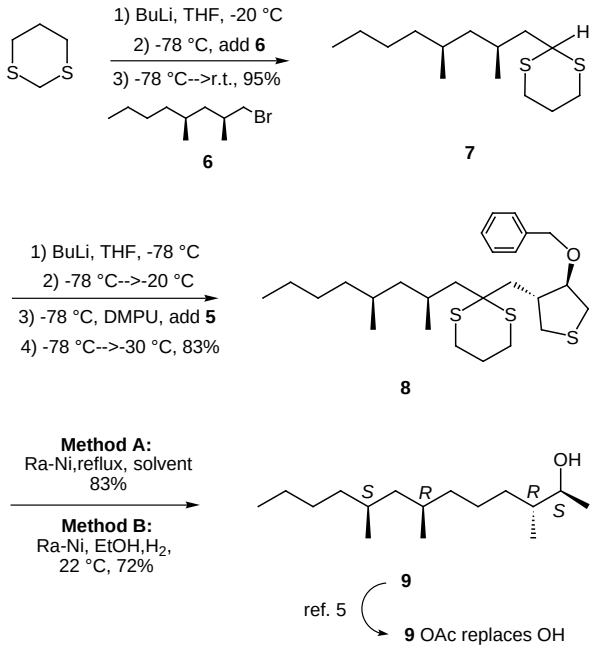


Synthesis of chiral building block **5** via an asymmetric 1,3-dipolar cycloaddition

Scheme 2

The second chiral building block, bromide **6** (Scheme 3), was obtained from the corresponding alcohol, (2*S*,4*S*)-2,4-dimethyloctan-1-ol prepared according to ref.[5] (stereoisomeric purity > 99.5%) using the same conditions as above (PPh_3, Br_2).

The two chiral building blocks **5** and **6** were then linked to each other with an interlocking dithiane (Scheme 3). Seebach et al. have developed a stannylated dithiane derivative that can be used in two sequential one-pot alkylations.[16] This provides fast and efficient reactions due to facile relithiation of the dithiane unit after the first alkylation step. However, in our case, the alkylation with the stannylated dithiane proceeded in moderate yields and resulted in complex reaction mixtures probably due to steric hindrance in both building blocks **5** and **6** resulting in monoalkylation and homo-dialkylation products. Therefore, this approach was abandoned and instead unsubstituted dithiane was used. Thus, deprotonation of dithiane[16]



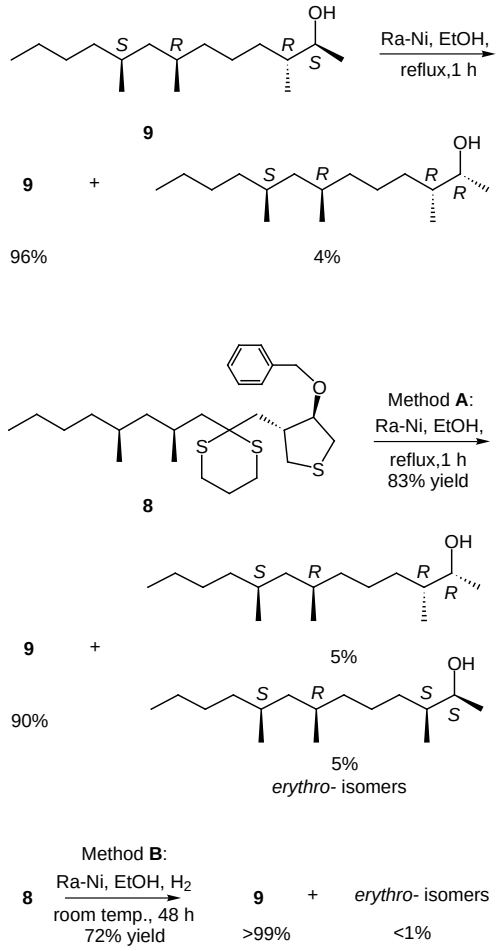
Total synthesis of the sex pheromone of *Macrodiprion nemoralis* through two sequential dithiane couplings

Scheme 3

with BuLi followed by the addition of bromide **6** furnished the alkylated product **7** in 95% yield. The second alkylation step was more problematic, probably due to steric hindrance coupled with decreased acidity of the remaining acidic proton of the dithiane unit. However, by using three equivalents of **7**, which was deprotonated by BuLi followed sequentially by addition of DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) as a cosolvent and addition of the bromide **5** at −78 °C, the desired product **8** was obtained in a satisfactory 83% yield, together with a quantitative recovery of unreacted **7**. In order to see if the overall yield in the alkylation sequence could be improved, the influence of various leaving groups in the electrophiles **5** and **6** were investigated. Whereas chlorides were unreactive, tosylates did give products, albeit in very low yields. On the other hand, iodides gave adequate results but they were clearly inferior to the bromides, which gave the cleanest reactions and furnished highest yield of the desired product **8**.

The projected final step in the synthetic sequence was the simultaneous desulfurisation of the dithiane and tetrahydrothiophene with concomitant removal of the benzyl protective group, which was planned to be accomplished by using Raney nickel. Thus treatment of compound **8** with Raney-Ni in EtOH under reflux for 10 minutes provided the target compound, (2*S*,3*R*,7*R*,9*S*)-3,7,9-trimethyltridecane-2-ol **(9)**, in 83% yield (Method **A**, Schemes 3 and 4.). Unfortunately, a certain degree of epimerisation around C-2 and C-3 was observed during the Raney-Ni reduction step. Thus, along with the desired (2*S*,3*R*,7*R*,9*S*)-*threo*-isomer **9**, two *erythro*-isomers were formed in a 1:1 ratio (total contaminating epimers sometimes amounted

to 10%). However, no (2*R*,3*S*)-*threo*-epimer was detected, nor any epimers around the 7 and 9 positions as judged from ^{13}C NMR and GC analyses. When the reaction was performed under milder conditions (Raney nickel, acetone, reflux) the benzyl group remained intact. The desulfurised compound isolated was debenzylated to yield **9** in a separate step using 10% Pd/C under hydrogen in EtOH. However, epimerisation around C-2 and C-3 was still a problem and the total degree of epimerisation was now approximately 5%. When the reaction was peformed in solvents such as MeOH, propan-2-ol, toluene, acetic acid and THF at reflux, complete desulfurisation and debenzylation were achieved but, again it gave a total of approximately 10% of unwanted epimers in the product **9**. Other desulfurisation methods (Na, NH_3 and Bu_3SnH, AIBN respectively)[25,26] were unsatisfactory giving only a trace of the desired product **9**.

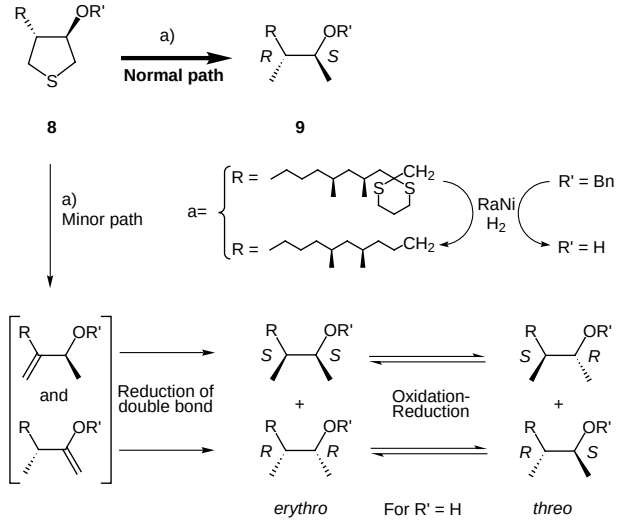


Raney nickel epimerisation of stereoisomerically pure (2*S*,3*R*,7*R*,9*S*)-**9** to the corresponding (2*R*,3*R*,7*R*,9*S*)-**9**-*erythro*-isomer.When **8** is reduced under the same conditions C-3 epimerisation is observed in addition to the "normal" C-2 epimerisation.

Scheme 4

The observed epimerisation is worth a short comment. It is well known that chiral secondary alcohols often suffer from epimerisation when subjected to Raney nickel.[17–22] A reversible oxidation-reduction of the secondary alcohol has been proposed to be responsible for this.[23] In fact, when subjected to Raney nickel under reflux in EtOH for 1 hour, stereoisomerically pure (2*S*,3*R*,7*R*,9*S*)-**9**[5] gave only the expected epimerisation around C-2 (4%) as judged by GC analysis leaving C-3 unaffected (Scheme 4).

On desulfurisation of **8**, the observed epimerisation of the 3-position in the product **9**, indicated that the Raney nickel mediated removal of the sulfur in the tetrahydrothiophene ring of **8** might be at least partly responsible (see Scheme 5). This C-3 epimerisation could tentatively occur via an elimination-addition process proceeding e.g. through reductive cleavage of the sulfide to thiol and subsequent elimination of H_2S from **8** to give intermediate alkenyl benzyl ethers or alkenols, the double bond of which then adds hydrogen to give **9** and epimers (Scheme 5). Because the *erythro*-epimers represent only 5−10% of the total amount in the product **9**, the probability that the (2*S*,3*S*)-*erythro*-isomer produced should form any detectable amount of the (2*R*,3*S*)-*threo*-epimer through C-2 epimerisation is very small explaining why the latter was not detected in the crude reaction mixture.



Proposed reaction pathway for the epimerisation around C-2 and C-3 in the presence of Raney nickel in refluxing EtOH in the reduction of **8** → **9**.The epimerisation may consist of an elimination of sulfur mechanism of the tetrahydrothiophene unit leaving (a) double bond(s) that in a later stage is reduced to the *erythro*-isomers. In addition, an oxidation-reduction mechanism of the secondary alcohol can occur giving C-2 epimerisation resulting in *threo*-isomers.

Scheme 5

It is known that the Raney-Ni induced epimerisation of secondary alcohols can be efficiently suppressed if a hydrogen source is added to the reaction mixture.[21,22,24] Thus, we found that when the reductive desulfurisation-debenzylation reaction was performed at room temperature under an atmosphere of hydrogen (Method **B,**

Scheme 4), the total amount of epimers in the product **9**, obtained in 72% yield, was reduced from 10% to less than 1%. Interestingly, complete epimerisation was achieved around C-2 and C-3 when the reaction was performed under hydrogen in the presence of a hydride source such as $NaBH_4$.

In conclusion, a new approach was developed for the synthesis of enantiopure sex pheromone components having the *threo*-3-methylalkan-2-ol unit in its backbone and was exemplified by the preparation of **9** in 99% stereoisomeric purity. Acetylation of this gives[5] (1*S*,2*R*,6*R*,8*S*)-1,2,6,8-tetramethyldodecyl acetate (**9**, OAc instead of OH), which is an active sex pheromone component of the pine sawfly *Macrodiprion nemoralis*. This new strategy should constitute an efficient and useful method for the synthesis of similar compounds e.g. the numerous *threo*-3-methyl-2-alkyl esters shown to be pheromones of many pine sawflies.

All chemicals were used as received unless otherwise stated. THF (K, benzophenone), DMPU (CaH_2) and Et_2O ($LiAlH_4$) were distilled from the indicated drying agents. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker DMX 250 (250 MHz ^1H and 62.9 MHz ^{13}C) instrument. TLC was performed on silica gel plates (60 F_{254}, Merck) and preparative liquid chromatography on straight phase silica gel (Merck 60, 230−400 mesh, 0.040−0.063 mm) using an increasing concentration of distilled EtOAc or CH_2Cl_2 in distilled cyclohexane as eluent. Raney nickel (W-2 type) was obtained from Fluka and used as received. GC analyses were carried out using a capillary column EC-5, 30 m, 0.32 mm i.d., d_f = 0.25 μm, or a CP-Sil 19 CB, 30 m, 0.25 mm i.d., d_f = 0.25 μm, carrier gas N_2. The diastereomeric purity of compound **9** was determined using a capillary column EC-wax, 30 m, 0.25 mm i.d., d_f = 0.25 μm, carrier gas He. The elemental analyses (C, H, N) were performed by Mikro Kemi AB, SE-752 28 Uppsala, Sweden. Melting and boiling points are uncorrected and the latter are given as air bath temperatures (bath temp./mbar) in a bulb to bulb (Büchi GKR-51) distillation apparatus. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter in a 1 dm cell. Mass spectra were recorded on a Saturn 2000 instrument, coupled to a Varian 3800 GC instrument. Chloromethyl (trimehylsilyl)methyl sulfide (**1**) was obtained from the same batch as that used in ref. 14. Compounds **2**, **3** and **4** were prepared using the same procedure as reported by us previously[14] but using (1*R*)-camphorsultam as the chiral auxiliary. NMR, MS and GC analytical data for those intermediates were identical to those reported[14] for the enantiomers. Physical data: **2:** $[\alpha]_D^{25}$ +77.8 (*c* = 0.58, $CHCl_3$); mp 144−145 °C. {Lit.[14] for enantiomer: $[\alpha]_D^{25}$ −76.5 (*c* = 0.52, $CHCl_3$); mp 143−145 °C}. **3** $[\alpha]_D^{25}$ +140.9 (*c* = 0.42, $CHCl_3$). {Lit.[14] for enantiomer: $[\alpha]_D^{25}$ −137.3 (*c* = 0.66, $CHCl_3$)}. **4** $[\alpha]_D^{25}$ +112.1 (*c* = 0.67, $CHCl_3$); bp 185 °C/0.9 mbar. {Lit.[14] for enantiomer: $[\alpha]_D^{25}$ −107.7 (*c* = 0.34, $CHCl_3$); bp 180 °C/1.2 mbar}.

(3*R*,4*R*)-3-Benzyloxy-4-(bromomethyl)tetrahydrothiophene (5)
Compound **5** was prepared from the corresponding alcohol **4,** see above, (stereoisomeric purity > 99%) using PPh_3 and Br_2 under standard conditions.[15] Bp 160 °C/0.7 mbar; $[\alpha]_D^{25}$ +95.0 (*c* = 0.64, $CHCl_3$).

^1H NMR (250 MHz, $CDCl_3$): δ = 2.55-3.10 (m, 5 H), 3.44 (dd, 1 H, *J* = 6.5, 10.2 Hz), 3.50 (dd, 1 H, *J* = 5.2, 10.2 Hz), 4.01 (q, 1 H, *J* = 6.4 Hz), 4.54 (d, 1 H, *J* = 11.7 Hz), 4.63 (d, 1 H, *J* = 11.7 Hz), 7.28−7.40 (m, 5 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 31.2, 33.7 (2 C), 49.1, 72.0, 83.1, 127.8, 127.9, 128.5, 137.8.

MS (EI): *m*/*z* (%) = 288 [32, (M^+, Br^{81})], 286 [32, (M^+, Br^{79})], 197 (12), 195 (12), 181 (10), 179 (10), 91 (100).

Anal. calcd for $C_{12}H_{15}BrOS$: C, 50.2; H, 5.3. Found: C, 50.1; H, 5.3.

(2*S*,4*S*)-1-Bromo-2,4-dimethyloctane (6)
Compound **6** was prepared from (2*S*,4*S*)-2,4-dimethyloctan-1-ol, which was obtained from the same batch prepared previously in our laboratory[5] (stereoisomeric purity >99.5%), using PPh_3 and Br_2 under standard conditions.[15] Bp 90 °C/7 mbar; $[\alpha]_D^{25}$ +2.8 (*c* = 1.2, $CHCl_3$).

^1H NMR (250 MHz, $CDCl_3$): δ = 0.87 (d, 3 H, *J* = 6.5 Hz), 0.89 (t, 3 H, *J* = 6.5 Hz), 1.01 (d, 3 H, *J* = 6.6 Hz), 1.03−1.51 (m, 9 H), 1.83−1.96 (m, 1 H), 3.30 (dd, 1 H, *J* = 6.2, 9.8 Hz), 3.42 (dd, 1 H, *J* = 4.3, 9.8 Hz).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.1, 19.4, 20.0, 23.0, 29.0, 30.0, 32.4, 36.5, 41.8, 42.5.

MS (EI): *m*/*z* (%) = 165 (100), 163 (90), 83 (75), 55 (62).

2-[(2*S*,4*S*)-2,4-Dimethyl-1-octyl]-1,3-dithiane (7)
A procedure similar to that reported by Page et al.[27] was used. BuLi (1.4 M in hexane, 2.4 mL, 3.4 mmol) was added dropwise to a stirred solution of 1,3-dithiane (0.41 g, 3.4 mmol) in THF (15 mL) at −20 °C. After 1 h, the solution was cooled to −78 °C and (2*S*,4*S*)-1-bromo-2,4-dimethyloctane (**6**; 0.50 g, 2.3 mmol) was added. The reaction was then allowed to reach 22 °C. After 1.5 h, the reaction was quenched by the addition of aq sat. NH_4Cl solution (25 mL) and extracted with Et_2O (75 + 25 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated. Flash column chromatography of the residue (EtOAc/cyclohexane, 0−5% as eluent) followed by distillation (bp 130 °C/1 mbar) furnished **7** (0.56 g, 95%) as a colourless oil in > 99% purity (GC); $[\alpha]_D^{25}$ +11.3 (*c* = 1.3, hexane).

^1H NMR (250 MHz, $CDCl_3$): δ = 0.85 (d, 3 H, *J* = 6.6 Hz), 0.88 (t, 3 H, *J* = 6.6 Hz), 0.90 (d, 3 H, *J* = 6.5 Hz), 0.93−1.53 (m, 10 H), 1.68−1.96 (m, 3 H), 2.07−2.19 (m, 1 H), 2.76−2.98 (m, 4 H), 4.10 (dd, 1 H, *J* = 5.4, 9.4 Hz).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.2, 20.1, 23.0, 26.2, 27.0, 29.1, 29.8, 30.3, 30.6, 36.4, 42.4, 45.0, 45.6.

MS (EI): *m*/*z* (%) = 260 (100, M^+), 185 (40), 119 (58).

Anal. calcd for $C_{14}H_{28}S_2$: C, 64.6; H, 10.8. Found: C, 64.5; H, 11.1.

2-[(3*R*,4*R*)-(4-Benzyloxy-3-tetrahydrothienyl)methyl]-2-[(2′*S*,4′*S*)-2′,4′-dimethyl-1′-octyl]-1,3-dithiane (8)
For the synthesis of compound **8**, a procedure similar to that reported by Rokach et al.[28] was used. To a solution of **7** (96.5 mg, 0.37 mmol) in THF (2 mL) was added BuLi (1.6 M hexane, 0.23 mL, 0.37 mmol) at −78 °C. After 1 h the solution was slowly allowed to reach −20 °C (1 h). After 2 h at −20 °C, the solution was recooled to −78 °C and DMPU (0.2 mL) was added followed by the addition of compound **5** (34.4 mg, 0.12 mmol). The reaction mixture was slowly allowed to reach −30 °C (1 h) and then quenched by the addition of aq sat. NH_4Cl solution (4 mL). The aqueous phase was extracted with EtOAc (4 × 5 mL) and the combined organic phases were dried (Na_2SO_4). Concentration followed by flash column chromatography (EtOAc/cyclohexane, 0−5%) afforded recovered **7** (distilled, 64.0 mg, nearly 100%) in nearly 100% purity (GC) and the desired product **8** (46.8 mg, 83%) as a colourless oil; purity >99% (GC); $[\alpha]_D^{25}$ +51.1 (*c* = 0.65, $CHCl_3$).

^1H NMR (250 MHz, $CDCl_3$): δ = 0.87 (d, 3 H, *J* = 6.5 Hz), 0.87−1.05 (m, 5 H), 1.01 (d, 3 H, *J* = 6.5 Hz), 1.14−1.52 (m, 7 H), 1.69 (dd, 1 H, *J* = 6.7, 14.9 Hz), 1.76−1.97 (m, 5 H), 2.04 (dd, 1 H, *J* = 2.5, 14.8 Hz), 2.58−2.90 (m, 7 H), 2.98 (dd, 1 H, *J* = 5.2, 10.9 Hz),

3.22−3.32 (m, 1 H), 3.83 (q, 1 H, *J* = 5.2 Hz), 4.55 (d, 1 H, *J* = 12.0 Hz), 4.64 (d, 1 H, *J* = 12.0 Hz), 7.27−7.37 (m, 5 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.2, 20.5, 22.9, 23.0, 24.9, 26.3, 26.6, 27.1, 29.1, 30.1, 33.5, 34.8, 36.0, 41.5, 43.9, 47.3, 47.7, 54.3, 71.4, 85.8, 127.7, 128.4, 138.2.

MS (EI): *m*/*z* (%) = 467 (20, $[M+1]^+$), 359 (18), 255 (75), 91 (100).

Anal. Calcd for $C_{26}H_{42}OS_3$: C, 66.9; H, 9.1. Found: C, 66.9; H, 9.3.

(2*S*,3*R*,7*R*,9*S*)-3,7,9-Trimethyltridecan-2-ol (9)

Method A: A suspension of a large excess of Raney Ni (W-2) in the solvent specified in the discussion part above was added dropwise to a refluxing solution of **8** in the same solvent. Typical reaction time was 5 to 30 min. Workup as described below furnished **9** in a yield ranging between 20 to 83% (alcoholic solvents gave the highest yields). ^{13}C NMR and GC analyses showed that the two *erythro*-epimers (2*S*,3*S*,7*R*,9*S*)-**9** and (2*R*,3*R*,7*R*,9*S*)-**9** had been formed in a 1:1 ratio in a total amount ranging between 5 to 10%. No other stereoisomers could be detected.

Method B: A solution of **8** (18.0 mg, 0.0039 mmol) in absolute EtOH (5 mL, saturated with H_2) was added via syringe to a suspension of a large excess of Raney-Ni (W-2) in EtOH (4 mL, saturated with H_2). The reaction was then allowed to stir for 48 h under an atmosphere of H_2. The Raney-Ni was filtered off through a pad of Celite-silica gel and the solids were rinsed with CH_2Cl_2. The filtrate was concentrated and purified through flash column chromatography (EtOAc/cyclohexane, 0−5% as eluent) and distilled (bp 110 °C/1 mbar) to give **9** (6.7 mg, 72%) as a colourless oil; purity >99% (GC); $[\alpha]_{546}^{25}$ +23.6 (*c* = 0.31, hexane). {Lit.[5] $[\alpha]_{546}^{25}$ +23.3 (*c* = 1.0, hexane); bp 110 °C/0.4 mbar. NMR and MS data were identical to those previously reported.[5] No contaminating stereoisomers could be detected according to ^{13}C NMR analyses and GC confirmed the stereoisomeric purity to be > 99%.

Acetylation of **9** as described[5] gave the corresponding acetate. The physical data of the acetate were identical in all respects with that previously described.[5]

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