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Efficient Opening of *trans*-2,3-Epoxybutane by a Higher Order Cuprate: Synthesis of *erythro*-3,7-Dimethylpentadecan-2-yl Acetate, Pheromone of Pine Sawflies.

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Abstract: A higher order cuprate reacted with *trans*-2,3-epoxybutane furnishing a mixture of the four erythro-isomers of diprionol (3,7-dimethyl-2-pentadecanol, **7**) in a high yield both counted on the epoxide (96%) and on the haloalkane (85%) used as the starting material for the cuprate. Acetylation furnished a mixture of erythro-acetates **8** suitable for mating disruption in the pine sawfly *Neodiprion sertifer*.

The pine sawfly *Neodiprion sertifer* (Geoffrey, Diprionidae) is a pest on Scots pine in the northern parts of Europe, Asia and North America. A possible method for controlling and monitoring populations of this species could be to utilise blends of synthetic pheromone components. For some years we and others have been studying both synthetic approaches to, and biological activities of potential components of the sex pheromone of this insect which uses *erythro*-(2*S*,3*S*,7*S*)-diprionyl acetate, (*SSS*-**1Ac**) (see Figure 1), as the main attractant.[1-13]

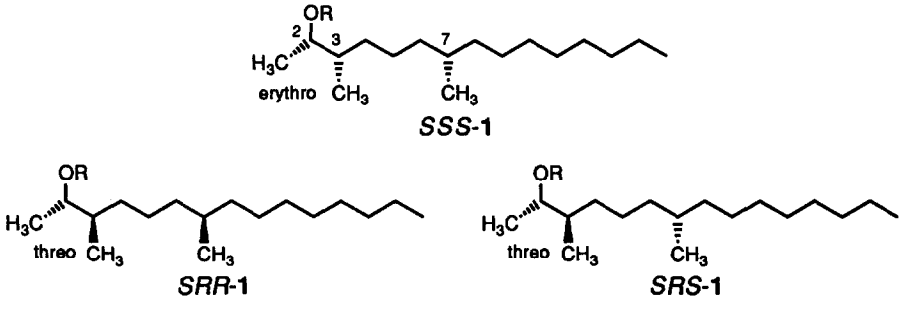


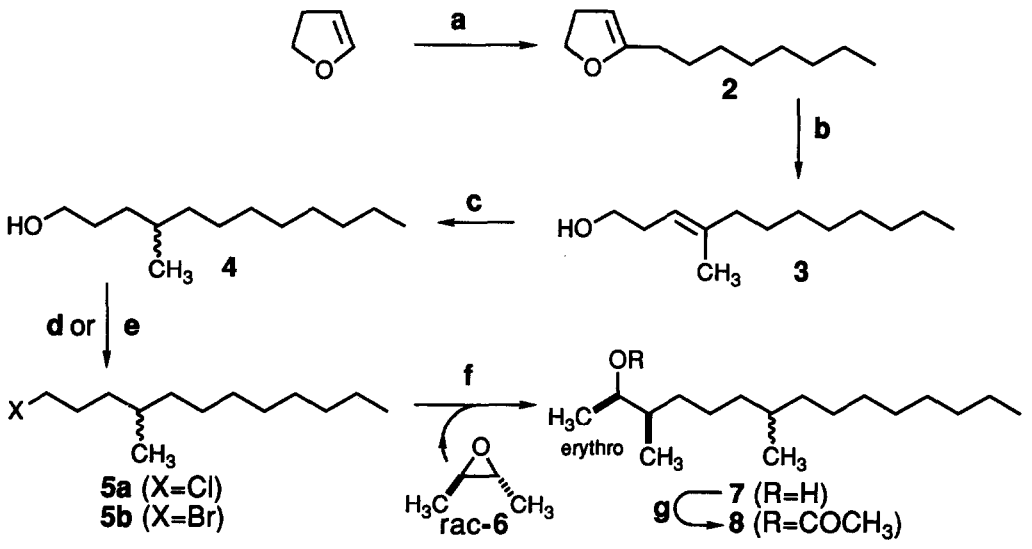
Figure 1. **1**: R = H; **1Ac**: R = $COCH_3$; **1Pr**: R = COC_2H_5

In the Swedish *N. sertifer* population the threo-isomer *SRR*-**1Ac** acts as an inhibitor of the former even at a very low concentration (≥0.5%).[9,14,15] Another threo-isomer *SRS*-**1Ac** can also function as an inhibitor, but a much higher concentration (~50%) is required.[9] In related genera a threo-isomer functions as the attractant e.g. the propionate *SRR*-**1Pr** in *Diprion similis*.[16] We recently described the syntheses of all the eight stereoisomers

of diprionyl acetate[9] and of some diprionyl acetate homologues, probably identical with the minor components recently isolated from females of *N. sertifer*.[12]

In field experiments designed to cause mating disruption by massive release of the attractant component *SSS*-**1Ac**, we have established that using the erythro-diprionyl acetate mixture **8** (containing less than 0,2% of the four threo-isomers) is as efficient as using pure *SSS*-**1Ac**.[17]

Our previous syntheses have been based on the need for a rather limited amount (0,1 - 0,5 g) of all the eight individual stereoisomerically pure diprionyl esters. In order to be able to supply the much larger amounts of active compound needed for further mating disruption studies, we searched for alternative synthetic approaches, better suited for larger scale synthesis.



Scheme 1. **a**: 1) *t*-BuLi, THF, –40 °C. 2) 1-Iodooctane, –20 °C, 16 h at ambient temp. **b**: 1) $(Ph_3P)_2NiCl_2$, benzene. 2) MeMgBr. 3) Add 2-octyl-4,5-dihydrofuran (**2**), Δ_X 4.5 h. **c**: H_2, Pd/C, 24 h. **d**: Ph_3P, CCl_4, Δ_X. **e**: 1) Et_3N, MsCl, CH_2Cl_2, –5 °C, 1h. 2) LiBr, acetone, Δ_X, 4 h. **f**: 1) Compound **5a**, Li suspension with 2% Na, hexane, 30 °C, 5 h (or **5b**, Li with 2% Na, Et_2O, –10 - 0 °C, 2 h), 2) Add to lithium 2-thienyl(cyano)cuprate in Et_2O/THF at –78 °C. 3) Add racemic *trans*-2,3-epoxy-butane (rac-**6**), then 20 h at ambient temp. **g**: Ac_2O, pyridine.

The stereoselective ring opening of substituted epoxides by nucleophiles constitutes an attractive synthetic route to secondary alcohols.[18-25] Indeed, this method has been used by Mori and Tamada in their syntheses of the four individual erythro-isomers of diprionol *via* reaction of the pure enantiomers of *trans*-2,3-epoxybutane (**6**) with the appropriate enantiomer of a lithium di(4-methyldodecyl)cuprate.[19] We have recently prepared (2*S*,3*S*)-3-methyl-2-pentadecanol (a 7-desmethyl homologue of *SSS*-**1**), using (*S*,*S*)-2,3-epoxybutane and lithium didodecylcuprate.[12] However, in cases where both the reagent and the substrate, *i.e.* the haloalkane needed for the transferable alkyl group of the cuprate and the complimentary epoxide, are expensive, the yields counted on

both materials have to be considered simultaneously. In both reports mentioned above modest yields from both those materials were obtained (*vide infra*).

We now report a new procedure for the preparation of a mixture of the four erythro-isomers of diprionol **7** (most probably a 1:1:1:1-mixture of stereoisomers) using a modified cuprate–epoxide approach giving excellent yields both from the epoxide and the total amount of haloalkane used.

In order to obtain the appropriate cuprates racemic 1-halo-4-methyldodecanes were required (see Scheme 1). These were obtained using the methodology developed by Kociensky *et al.*[26] for the preparation of similar halides. Thus, 2-octyl-4,5-dihydrofuran (**2**) was obtained from 4,5-dihydrofuran in excellent yield, *via* lithiation with *t*-BuLi followed by treatment with 1-Iodoooctane. When subjected to a nickel(0) catalysed reaction with methyl magnesium bromide, compound **2** gave the unsaturated alcohol **3** in good yield. Catalytic hydrogenation of this gave racemic 4-methyldodecan-1-ol (**4**), which was converted to the chloride **5a** or bromide **5b**. The overall yield from 1-Iodooctane to 1-chloro-4-methyldodecane (**5a**) was 70%.

trans-2,3-Epoxybutane is an epoxide which should exhibit steric hindrance to nucleophilic attack, even when compared to the coresponding *cis*-isomer.[27] Therefore, it is not surprising that the cuprate - epoxide reactions discussed above do not give satisfactory yields of neither the diprionol isomers nor the desmethyl analogue.* Clearly better reaction alternatives are needed.

The efficiency of the nucleophilic ring–opening of epoxides by simple carbon nucleophiles such as Grignard reagents or alkyllithiums can be enhanced in different ways, either by increasing the nucleophilicity of the reagent by addition of a cosolvent such as hexamethylphosphortriamide (HMPA),[20] or by increasing the electrophilicity of the epoxide by adding a Lewis acid such as boron trifluoride etherate[21] or, alternatively, by using alkylaluminium reagents, which function both as carbon nucleophiles and Lewis acids.[28-29]

Grignard reagents are known to react with epoxides. However, with substituted epoxides side reactions may dominate. When opening such epoxides, a more selective reaction can be achieved by addition of a catalytic amount of cuprous iodide to the Grignard reagent prior to reaction with the epoxide.[24,28]

The lithium cuprate method discussed above provides yet another alternative. Low order (LO) homocuprates of the type (R_2CuLi) are uneconomic with respect to the R-groups since one of them is wasted in the reaction.[30-31] Therefore LO-mixed cuprates of the type R_TR_RCuLi (R_T=transferable, R_R=residual) have been developed.[32] However, these two types of cuprates frequently reacts with epoxides to give low yields of the desired product along with elimination and rearrangement products.[30-32] On the other hand, higher order (HO)-cyanocuprates such as $R_2Cu(CN)Li_2$[33] have been found to be more selective in the reactions with epoxides.[23,25] When valuable R-groups are to be transferred, a less reactive "dummy" ligand R_R can be used to give the cuprate $R_TR_RCu(CN)Li_2$.[22,25]

*Mori and Tamada[19] claim yields of **7** to be 43-92%. However, inspection of their experimental details reveals that the yields calculated from the epoxides are 20-47% and from the haloalkanes even lower.

Table 1. Nuclephilic Ring Opening of *trans*-2,3-epoxybutane.

Entry no.	Nucleophile R=4-methyl-dodecyl	Reaction conditions[a]	Yield[b] of 7 (%) from epoxide 6	from halide 5 (from RLi)
1	RLi^c	Bromide **5b** (1.5 mmol), Li (7.6 mmol) **B:** Cool to –78 °C, in Et_2O/THF/DMPU[d], (1.5:1.5:1) **C:** Add epoxybutane **6**, (1.4 mmol) –78 -> 20 °C 16 h.[20]	trace	trace
2	RLi^c	Bromide **5b** (4.2 mmol), Li (21 mmol) **B:** Cool to –78 °C, Et_2O/THF (1:1), BF_3OEt_2 (4.2 mmol) **C:** Add epoxybutane **6**, (1.4 mmol) at 0 °C 2h.[21]	5	2(3)
3	RMgBr	Bromide **5b** (2.1 mmol), Mg (2.1 mmol) ,THF, Δx **B:** Cool to –30 °C, THF, add to 0.21 mmol CuI, 0.12 h **C:** Add epoxybutane **6**, (1.14 mmol) at 0 °C 2h.[24]	9	5
4	R_2CuLi^c	Bromide **5b** (4.7 mmol), Li (23 mmol) **B:** –20 °C, add to CuI (0.7 mmol), Et_2O **C:** Cool to –50 °C, add epoxybutane **6** (1.4 mmol) , 2 h, then –20 °C over night.[19]	50	15(27)
5	$R_2Cu(CN)Li_2^c$	Bromide **5b** (3.1 mmol), Li (15 mmol) **B:** –78 °C, in Et_2O/THF (1:1), add to CuCN (1.54 mmol) **C:** Add epoxybutane **6** (1.4 mmol) at –20 °C 2h.[23]	55	25(45)
6	(2-Thienyl)-R $Cu(CN)Li_2^c$	Bromide **5b** (1.54 mmol), Li (7.6 mmol) **B:** –78 °C, in Et_2O/THF (1:1), add to Lithium 2-thienyl(cyano)cuprate (1.54 mmol) at 0 °C **C:** Add epoxybutane **6**, (1.4 mmol) at r.t. 4 h.[22]	35[e]	32[e](58)
7	$R_2Cu(CN)Li_2$	Bromide **5b** (96 mmol), Li (490 mmol), Et_2O, –10 - 0 °C, RLi: 41 %. **B:** Cool to –78 °C, in Et_2O:THF, 1:1, add to CuCN (39 mmol) **C:** Add epoxybutane **6**, (35 mmol) at -20 °C 4h.[23]	92[f]	34[f](83)
8	PhR-$Cu(CN)Li_2$	Bromide **5b** (29 mmol), Li (150 mmol) , Et_2O, –10 - 0 °C, RLi: 55 %. **B:** Cool to – 78 °C, add to lithium phenyl(cyano)cuprate (16 mmol) in Et_2O, **c** Add epoxy-butane **6** (16 mmol), at –20 °C 3 h.[25]	78[f]	43[f](78)
9	MeR-$Cu(CN)Li_2$	Bromide **5b** (29 mmol), Li (150 mmol), Et_2O, –10-0 °C, RLi: 56 %. **B:** Cool to –78 °C, add to lithium methyl(cyano)cuprate (16 mmol), in Et_2O, **C:** Add epoxy-butane **6** (16 mmol), at –20 °C 3 h.[25]	93[f]	51[f](91)
10	(2-Thienyl)-R $Cu(CN)Li_2$	Chloride **5a** (29 mmol), Li (87 mmol), hexane, 30 °C, RLi: 87% **B:** Cool to –78 °C, add to lithium 2-thienyl(cyano)cuprate (26 mmol) in Et_2O/THF, 1:1, **C:** Add epoxy-butane **6**, (26 mmol) at –78 °C , at r.t. 20h.[22]	96[f]	85[f](98)

[a]The reaction conditions used were similar to those described in the references given at the end of each entry. [b]After aqueous work up, usually using NH_3/ NH_4Cl (aq); GC-yields; internal standard: *n*-$C_{20}H_{42}$. [c]Alkyllithium prepared in one batch. The amount used was withdrawn with a syringe (yield of alkyllithium: 55%). [d]DMPU used instead[34] of HMPA as cosolvent. [e]Low yield probably due to short reaction time. [f]Isolated yields.

Our attempts to improve the yields of the reaction between various 4-methyl-1-dodecyl nucleophiles and *trans*-2,3-epoxybutane (**6**) are described in Table 1. First we investigated the effect of adding the noncarcinogenic HMPA-substitute 1,3-dimethyl-2-oxo-hexahydropyrimidine (DMPU) to the alkyllithium before reacting it with the epoxide. This gave only a trace of the desired product (entry 1). Similarly the alkyllithium and the epoxide reacted in the presence of Lewis acid (BF_3Et_2O) to give a disappointing yield (entry 2) as did the copper catalyzed Grignard reaction (entry 3). Reaction of the LO-order homocuprate R_2CuLi with the epoxide according to Mori and Tamada was moderately successful in our hands (entry 4). When using HO-cuprates (entries 5-10) the yields were improved considerably both when calculated from the epoxide **6** and from 1-halo-4-methyldodecane (**5a** and **5b**). The most efficient cuprate of the type $R_TR_RCu(CN)Li_2$ was that with R_R=thienyl (entry 10), whereas those with R_R=2-methyl and R_R=phenyl were less satisfactory (entries 8 and 9).

The alkyllithium derived from 1-bromo-4-methyldodecane (**5b**) and used in entries 1-2 and 4-9 was formed in unsatisfactory yield (41-56%, by titration). In order to obtain a better yield of alkyllithium from a 1-halo-4-methyldodecane, we studied several alternative methods for the preparation of the former. The best results were

obtained when the alkyllithium was prepared from 1-iodo-4-methyldodecane by a metal-halogen exchange using *t*-BuLi[35] or alternatively from 1-chloro-4-methyldodecane using lithium dispersion in hexane containing 2% sodium.[36] Both methods gave acceptable yields (90% and 87%, respectively) of 1-lithio-4-methyldodecane. However, the latter method was the most attractive one, since the chloroalkane is easier to prepare in a high yield.

On a preparative scale, the alkyllithium was generated from the chloride **5a** and added to the LO-cyanocuprate formed from 2-lithiothiophene and cuprous cyanide. Then *trans*-2,3-epoxybutane (**6**) was added at –78 °C and the resulting mixture was stirred for 20 h at ambient temperature and then quenched at this temperature (entry 10, Table 1). Acetylation[2] of the isolated diprionol **7** obtained furnished *erythro*-3,7-dimethylpentadecan-2-yl acetate (**8**), overall yield from epoxide **6**: 96%, from chloride **5a**: 85%.

Thus, we have shown, that HO-order mixed cuprates are very useful reagents if one has to employ expensive alkyl nucleophiles in the stereoselective ring opening of hindered epoxides such as *trans*-2,3-epoxybutane.

We are presently studying the possibility of separating the product mixture of the four *erythro*-3,7-dimethylpentadecan-2-ols (**7**) by using enzymatic methods, in order to obtain the (2*S*,3*S*,7*R*/*S*)-dimethylpentadecan-2-ol, in pure form. The HO-cuprate procedure used here should of course also be applicable in cases when enantiomerically pure *trans*-epoxybutane and/or 1-chloro-4-methyldodecane can be used as starting materials and should then furnish one of the eight stereoisomers of diprionol.

EXPERIMENTAL

Unless otherwise stated, starting materials and solvents were used as received from commercial suppliers. Dry solvents were obtained by distillation under argon (from the indicated drying agents): diethyl ether and hexane ($LiAlH_4$), THF (potassium, benzophenone), benzene and toluene (CaH_2) . The concentrations of the organolithium reagents were all determined by titration prior to use.[37] The *trans*-epoxybutane sample used here (Aldrich, dried with 3 Å mol. sieves) contained <0.02% of *cis*-epoxide (by GC: 60 m x 0.25 mm I.D. capillary column coated with DB-5, d_f = 0.25 μm; carrier gas N_2, isothermal 54 °C, 10 psi, split ratio 1 / 200, retention times: *trans*-isomer: 10.77 min: *cis*-isomer: 11.28 min.]. Preparative liquid chromatography (MPLC) was performed on straight phase silica gel (Merck 60, 230 - 400 mesh, 0.040 - 0.063 mm, 4 - 10 g / g of mixture) employing the gradient technique described[38] and using an increasing concentration of distilled ethyl acetate in distilled hexane (0 –> 100%) as eluent. Thin layer chromatography (TLC) was performed on silica gel plates (Merck 60, pre-coated aluminium foil) eluted with ethyl acetate (20%) in hexane, and developed in ultraviolet light and/or sprayed with vanillin in sulphuric acid and heated at 120 °C. ^1H NMR spectra were recorded with tetramethylsilane as internal standard and $CDCl_3$ as solvent, using a Jeol PMX60SI or a Jeol EX270 spectrometer. IR-spectra were recorded neat between NaCl plates using a Perkin Elmer 782 infrared spectrometer. Unless otherwise stated, GC analyses were carried out using a 30 m x 0.32 mm I.D. capillary column coated with DB-WAX d_f = 0.25 μm; carrier gas He, 15 psi, split ratio 1/30. Boiling points are uncorrected. Mass spectra were recorded using GC-MS (Varian 3300 and an ion trap detector, Finnigan ITD 800). Elemental analyses were carried out by Mikrokemi, Uppsala, Sweden.

2-Octyl-4,5-dihydrofuran (**2**). The title compound was prepared using a method analogous to that described for other substituted dihydrofurans.[26] To 4,5-dihydrofuran (26.1 g, 0.372 mol) in dry THF (200 ml) *t*-BuLi (200 ml of a 1.6 M solution in pentane, 0.320 mol) was added dropwise during 2 h, while maintaining the temperature below –40 °C. The mixture was allowed to reach –5 °C during 1h, cooled to –20 °C and then 1-Iodooctane (64 g, 0.266 mol, stored over anhydrous K_2CO_3 and 3Å mol. sieves) was added during 0.5 h. The reaction mixture was allowed to reach 20 °C during 16 h. After cooling to 0 °C it was poured into NH_4Cl (400 ml, satd. aq) and Et_2O (400 ml). The aqueous phase was extracted with Et_2O (200 ml), the combined organic extracts were washed with brine (400 ml) and dried 0.25 h ($MgSO_4$). Removal of the solvent and distillation (58-62 °C/0.1 mm Hg) afforded the product **2** (46.0 g, 95%) as an oil. n_D^{20} 1.4503, IR: 2955, 2925, 2855, 1667, 1642, 1466, 1175, 1162, 1006, 718 cm^{-1}. ^1H NMR (270 MHz): δ 0.88 (3 H, t, *J* = 6.8 Hz), 1.28 (10 H, bs), 1.48 (2H, apparent quintet, *J* = 7.2 Hz), 2.08 (2 H, t, J = 7.3 Hz), 2.59 (2 H, d of t, *J* ≈ 1.8 and *J* = 9.2 Hz),

4.29 (2 H, t, J = 9.2 Hz), 4.5 (1 H, t, $J \approx$ 1.4 Hz) ppm. ^{13}C NMR (67.8 MHz): δ 14.1, 22.7, 26.7, 27.9, 29.2, 29.3, 29.4, 30.0, 31.9, 69.7, 93.4, 159.1 ppm. Mass spectrum, m/e (relative intensity): 182 (M^+, 1%), 96 (100), 97 (7), 83 (55), 78 (3), 72 (6), 68 (9), 58 (7), 55 (22), 54 (92). Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.55; H, 12.30.

(3E)-4-Methyldodec-3-en-1-ol (**3**). MeMgBr (3.95 ml of a 3 M solution in dry Et_2O, 0.0111 mol) was added dropwise to $(PPh_3)_2NiCl_2$ (3.32 g, 0.0051 mol), which was stirred at 20 °C in dry benzene (200 ml). After 0.25 h additional MeMgBr (187.7 ml, 3M in Et_2O, 0.556 mol) was added, followed by 2-octyl-4,5-dihydrofuran (**2**) (46.4 g, 0.255 mol, stored over 4Å mol. sieves) in dry benzene (25 ml), (After these experiments were made it has been shown[39] that it is beneficial to concentrate the mixture containing the reduced nickel species to a fifth of the original volume to remove the Et_2O and then reconstitute the solvent volume with neat dry benzene prior to introduction of the alkyldihydrofuran). The mixture was then refluxed at 80 °C (bath temp) for 4.5 h (According to TLC no starting material remained after this time). After cooling to 0 °C the solution was carefully poured into a stirred solution of NH_4Cl (800 ml, satd. aq) at –20 °C. Stirring was continued until the colour of the solution was stable (0.25 h). The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 400 ml). The pooled organic extracts were dried ($MgSO_4$), filtered and the solvent removed. The residue was chromatographed to give the title alcohol **3** (44.4 g, 88%) as a colourless oil. n_D^{20} 1.4575, IR: 3320, 3052, 2955, 2925, 2852, 1667, 1466, 1378, 1048, 723 cm^{-1}. ^{1}H NMR (270 MHz): δ 0.88 (3 H, t, J = 6.8 Hz), 1.21-1.58 [13 H, m, (1 H disappeared on addition of D_2O)], 1.63 (3 H, s), 2.00 (2 H, t, J = 7.4 Hz), 2.28 (2 H, d of t, J = 7 and J = 6.6 Hz), 3.60 (2 H, t, J = 6.6 Hz), 5.12 (1 H, bt, J = 7.0 Hz) ppm. ^{13}C NMR (67.8 MHz): δ 14.1, 16.1, 22.7, 28.0, 29.3, 29.3, 29.5, 31.5, 31.9, 39.8, 62.4, 119.5 139.2 ppm. Mass spectrum, m/e (relative intensity): 198 (M^+, 1%), 84 (47), 82 (39), 69 (59), 68 (62), 66 (56), 57 (33), 56 (85), 55 (59), 54 (100). Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.95; H, 13.00.

4-Methyldodecan-1-ol (**4**). The unsaturated alcohol **3** (42.0 g, 0.212 mol) and Pd/C (5%, 3 g) in methanol (500 ml, predried over 3Å mol. sieves) was stirred under H_2 at ambient temp. and pressure for 24 h (GC: no starting material remained). The catalyst was filtered off and washed with dry methanol, the solvent was evaporated off to give the saturated alcohol **4** (41.2 g, 99%). n_D^{20} 1.4456, (Lit. [19] for (*R*)-4-methyldodecan-1-ol n_D^{20} 1.4433). IR: 3329, 2956, 2927, 2851,1466, 1377, 1342, 1057, 900, 723 cm^{-1}. The ^{1}H NMR (60 MHz): spectrum was identical with that of (*R*)-4-methyldodecan-1-ol in ref.[19]

1-Chloro-4-methyldodecane (**5a**). The saturated alcohol **4** (14.6 g, 0.073 mol), triphenyl phosphine (21.4 g, 0.082 mol) and CCl_4 (22.7 g, 0.148 mol) was heated to 110 °C with stirring, at which temperature a strong exothermic reaction occurred. After 1 h at 120 °C, ethanol (1.2 ml, 0.010 mol) and CCl_4 (4.7 g, 0.018 mol) was added and stirring was continued for an additional 0.25 h at that temperature. Cooling followed by addition of pentane (200 ml), filtration and washing of the solid collected (3 x 100 ml pentane) gave an oil after evaporation of the solvent. This oil was purified by chromatography and distilled (92-94 °C/0.7 mmHg) to give the pure chloride **5a** (13.5 g, 85%) as a colourless oil. n_D^{20} 1.4596, IR: 2953, 2922, 2851, 2868,1462, 1377, 1309, 723, 655, 602 cm^{-1}. ^{1}H NMR (270 MHz): δ 0.87 (3 H, d, J = 6.6 Hz), 0.88 (3 H, t, J = 6.6 Hz), 1.11-1.53 (17 H, m), 1.73-1.82 (2 H, m), 3.51 (2 H, t, J = 6.7 Hz) ppm. ^{13}C NMR (67.8 MHz): δ 14.1, 19.6, 22.7, 27.0, 29.4, 29.67, 30.0, 30.4, 32.0, 32.3, 34.2, 36.9, 45.5 ppm. Anal. Calcd for $C_{13}H_{27}Cl$: C, 71.36; H, 12.43. Found: C, 71.35; H, 12.15.

1-Bromo-4-methyldodecane (**5b**). The saturated alcohol **4** (41 g, 0.205 mol) and dry triethylamine (28.7 g, 0.287 mol) was stirred in dry CH_2Cl_2 (500 ml, stored over 3Å mol. sieves). Methanesulfonyl chloride (28.1 g, 0.246 mol) was added dropwise maintaining the temperature at –5 °C. After 1 h (TLC: no starting material remained) the mixture was poured into $NaHCO_3$ (700 ml, satd. aq.), the aqueous phase was extracted with CH_2Cl_2 (3x150 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent evaporated off to give the mesylate (60 g). Dry lithium bromide (71.2 g, 0.819 mol) dissolved in dry acetone (800 ml, dried over anhydrous K_2CO_3) was added to the mesylate and the mixture was stirred under reflux (4 h). The acetone was evaporated off and the residue mixed with water (700 ml), the mixture extracted with pentane (4 x 400 ml). The pooled organic phase was washed with HCl(aq) (400 ml, 2M), $NaHCO_3$ (400 ml, satd. aq.) and brine (2 x 400 ml) before drying ($MgSO_4$). After removal of the solvent the oil was chromatographed and

distilled (78-82 °C/0.05 mm Hg) to give the bromide **5b** (48.4 g, 90%) as a colourless oil. n_D^{20} 1.4596, (Lit. [19] for (*R*)-1-bromo-4-methyldodecane n_D^{20} 1.4575). IR: 2956, 2923, 2852, 1462,1378, 1256, 1208, 723, 645, 602 cm^{-1}. ^{1}H NMR (270 MHz): δ 0.87 (3 H, d, *J* = 7.0 Hz), 0.91 (3 H, t, *J* = 7.0 Hz), 1.05-1.37 (16 H, m), 1.36-1.53 (1 H, m), 1.76-1.96 (2 H, m), 3.39 (2 H, t, *J* = 7.0 Hz) ppm. The ^{1}H NMR (60 MHz): spectrum was identical with that of (*R*)-1-bromo-4-methyldodecane in ref.[19]

erythro-*3,7-Dimethylpentadecan-2-ol* (**7**), (Table 1 entry 10). 2-Lithiothiophene (24.3 ml, 1.05 M solution in THF, 0.026 mol) was added dropwise to CuCN [2.288 g, 0.026 mol, predried at 105 °C and then dried by azeotropic evaporation of toluene (30 ml, dry) at 20 °C under reduced pressure] and dry Et_2O (20 ml) at –78 °C. The solution was allowed to reach 0 °C, then recooled to –78 °C followed by dropwise addition of 4-methyldodecyllithium (0.026 mol). The alkyllithium was prepared from 1-chloro-4-methyldodecane (6.32 g, 0.029 mol) in dry hexane (10 ml) which was slowly added (2 h) to lithium [5.6 ml of a lithium suspension, 0.081 mol (sodium content 2%) in hexane] diluted with dry hexane (10 ml) at 30 °C under argon. After stirring for 5 h the solution was filtered and the amount of resulting alkyllithium was determined to be 26 mmol (87%) by titration.[37] After the addition of the alkyllithium was complete, *trans*-2,3-epoxybutane (**6**) (1.85 g, 2.14 ml, 0.026 mol) was injected at –78 °C. The temperature was allowed to slowly reach 20 °C. After 20 h NH_4OH / NH_4Cl (200 ml, 10% in water) was added. After 0.5 h of vigorous stirring the organic phase was separated and the blue aqueous layer was extracted with Et_2O (2 x 150 ml). The combined extracts were washed with water (100 ml), brine (100 ml) and dried ($MgSO_4$). The solvent was evaporated off which gave an oil which was chromatographed and distilled (108-110 °C/0.05 mmHg) to give the erythro-mixture of the alcohol **7** (6.82 g, 0.0266 mol, 96% from the epoxide and 85% from the chloride). n_D^{20} 1.4493, IR: 3359, 2955, 2922, 2852, 1463, 1377, 1094, 1090, 1053, 927 cm^{-1}. ^{1}H NMR (270 MHz): δ 0.84 (3H, d, *J* = 6.3 Hz), 0.89 (3H, t, *J* = 6.6 Hz), 0.92 (3H, d, *J* = 6.6 Hz), 1.14 (3H, d, *J* = 6.3 Hz), 1.0-1.5 (23H, m), 4..82 (1H, b (q of d), *J* = 5.0 and *J* = 6.3 Hz). ^{13}C NMR (67.8 MHz): δ 14.1, 19.6, 19.8, 20.3, 22.7, 24.7, 27.1, 29.3, 29.7, 30.0, 31.9, 32.7, 33.0, 37.1, 37.3, 39.8, 71.4 ppm. Spectroscopic and physical data for the title compound are identical with those previously described.[40]

erythro-*3,7-Dimethylpentadecan-2-yl acetate* (**8**). This compound was prepared as described in ref.[2] from the alcohol **7** in quantitative yield. Analysis of the erythro-/threo-ratio by GC: Column: J&W DB-WAX (equivalent to carbowax 20 M, 30 m x 0.32 mm I.D., d_f = 0.25 μm). Conditions: carrier gas He (15 psi), isothermal 120 °C for 10 min., and programmed to 170 °C at a rate of 1 °C/min., split ratio 1/30, retention times: erythro 33.75 min: threo 34.25 min. Result: <0.02% threo. n_D^{20} 1.4392, IR: 2956, 2925, 2855, 1738, 1462, 1372, 1245, 1045, 1021, 947 cm^{-1}. ^{1}H NMR (270 MHz): δ 0.84 (3H, d, *J* = 6.3 Hz), 0.89 (3H, t, *J* = 6.6 Hz), 0.92 (3H, d, *J* = 6.6 Hz), 1.15 (3H, d, *J* = 6.3 Hz), 1.02-1.38 (22H, m), 1.54-1.60 (1H, m), 2.02 (3H, s), 4.82 [1H, d of q, *J* = 5.0 and *J* = 6.3 Hz]. ^{13}C NMR (67.8 MHz): δ 14.1, 14.8, 17.0, 19.6, 21.3, 22.7, 24.5 27.1, 29.3, 29.7, 30.0, 31.9, 32.7, 32.7, 37.1, 37.3, 37.6, 74.1, 170.8 ppm. Spectroscopic and physical data for the title compound are comparable with those previously described.[41]

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