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SYNTHESIS AND GAS CHROMATOGRAPHIC SEPARATION OF THE EIGHT STEREOISOMERS OF DIPRIONOL AND THEIR ACETATES, COMPONENTS OF THE SEX PHEROMONE OF PINE SAWFLIES.

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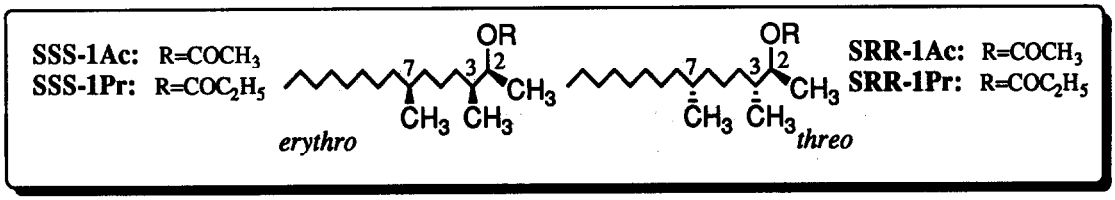
Abstract: The present report describes syntheses of the eight possible stereoisomers of 3,7-dimethyl-2-pentadecanol **1**, and the corresponding acetates. The latter are components of the sex pheromone of the *Neodiprion, Diprion and Gilpinia* genera *(Diprionidae)*. Synthetic intermediates were prepared from either chiral starting materials or by asymmetric syntheses. The stereochemical compositions of the isomeric diprionols were determined by using capillary gas chromatography on tandem column systems, some with chiral phase coatings.

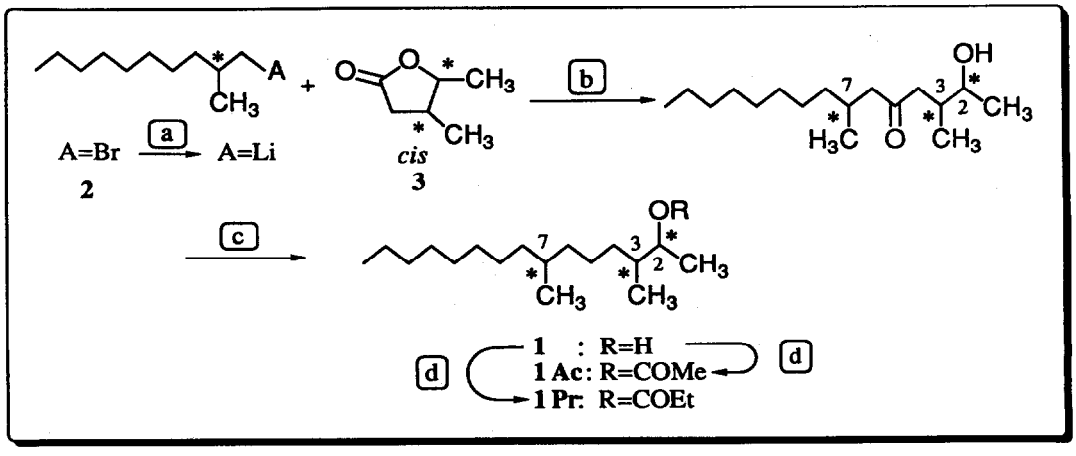
The pine sawfly *Neodiprion sertifer* (Geoffrey, *Diprionidae)* is a pest on Scots pine in the northern parts of Europe, Asia and North America.[1] A possible method for controlling and monitoring populations of this species could be to utilize synthetic pheromone blends. For several years we have been studying both a synthetic approach to, and biological activities of potential components of, the sex pheromone of this insect.[2-8] Olfactory communication in the diprionid sawflies was first noted by Coppel and coworkers, who, in 1960, reported that virgin females of *Diprion similis* (Hartig) strongly attract conspecific males.[9] They subsequently isolated and identified diprionol **1** (3,7-dimethyl-2-pentadecanol) from virgin females of three species of sawflies.[10,11] Based on the NMR-spectrum, the configurations of the carbons in the 2- and 3-positions of the isolated diprionol isomer were established as (2R*,3R*)-**1** (also called *erythro*-**1**). Field tests and electrophysiological experiments have shown that males of several *Neodiprion* species are strongly attracted to the acetate of **1**, whereas some species of this genus, and the genus *Diprion*, prefer the propionate.[6,11-23] Of the eight possible stereoisomers of diprionol **1**, the



esters of one *erythro*-isomer **SSS-1** are the preferred attractants for many *Neodiprion* species.[13-15,17,18] However, for some species of this genus, and for *Diprion similis* and *Gilpinia frutetorum*, one *threo*-isomer, **SRR-1Ac**(or **Pr**) has been found to be the attractant, either alone or in combination with other stereoisomers, especially **SSS-1Ac**(or **Pr**).[16,20-22] An intriguing composition-activity relationship has been found for *Neodiprion sertifer*. Males of this species are attracted to **SSS-1Ac**. Moreover, it has been found that, at concentrations below 0.3 %, the compound **SRR-1Ac** synergizes the attraction of compound **SSS-1Ac**, whereas at concentrations above 3 % it completely inhibits the attraction.[6,17,21,24] Whether other stereoisomers also can act as synergists or inhibitors is not yet established.

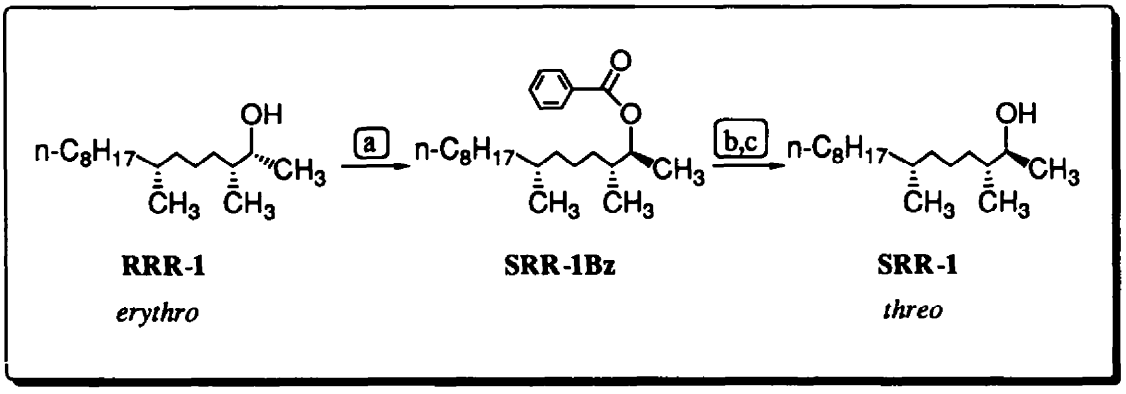
Stereoisomers other than the 2S,3S,7S- and 2S,3R,7R-diprionyl esters have also been reported as attractants in various other diprionid species.[16,19,23] It has been suggested that species specificity in diprionid sawflies is based on different combinations of the isomers of diprionyl acetate and/or the propionate.[6,11,14,20] The eight stereoisomers, in the form of either propionate or acetate, can be combined in 65 535 ways, not including variations in concentration. There are approximately 85 species of diprionid sawflies known today, so there is ample room for species specificity, which is expected to be based on unique combinations of two or more stereoisomers or esters in well defined proportions.

Several syntheses describing the preparation of racemic forms of diprionol have been reported.[12,25-33] However, it is evident from the facts discussed above, that diprionyl esters of high stereoisomeric purities and of known compositions are needed, if reliable results are to be obtained from biological tests with the diprionid sawflies. Several research groups have synthesized a few stereoisomers of diprionol and its esters, singly or as mixtures, and with



Scheme 1. **a**: Li, Et_2O -20°. **b**: 1) Et_2O, -80°. 2) H_2O. **c**: N_2H_4, KOH, +100° – +210°. **d**: Acylation of 1.

varying degrees of optical purity.[3,14,34-40] The total synthesis of the principal active component in the pheromone of the pine sawflies, the acetate of the *erythro*-isomer (2S,3S,7S)-diprionol (SSS-1) was described some years ago by, among others, some of the authors of the present paper.[3] Compound SSS-1 was obtained in a highly pure form in the 2- and 3-positions (*threo*-content less than 0.05 %).[41] However, in the 7-position a mixture of 86 % S and 14 % R was obtained, and this lower purity was, at the time, considered of little importance for the attraction of *Neodiprion* species.[13,14] The acetate of this material was used for field tests and electrophysiological studies.[6]



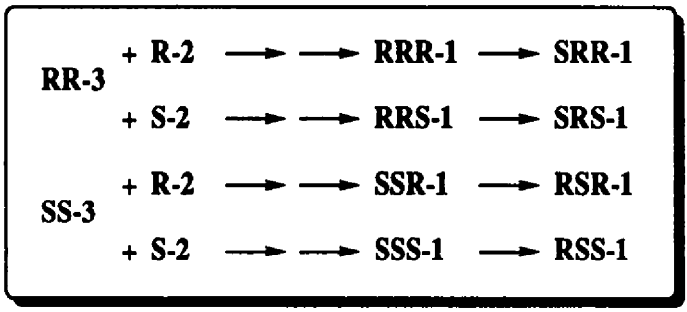
Scheme 2. Preparation of *threo*-1 from *erythro*-1. a: $P(Ph)_3$, $N_2(CO_2Et)_2$, $PhCO_2H$, THF. b: 1) $LiAlH_4$, Et_2O 2) H_3O^+.

As pointed out above, when studying the response of *Neodiprion sertifer* males to individual diprionyl acetate stereoisomers, 1Ac, even slight contamination by another stereoisomer, especially a *threo*-isomer, may have serious consequences. Therefore, it is very important to have complete stereochemical control over all the synthetic intermediates used in the preparation of the diprionol isomers. To achieve this, both highly stereospecific synthetic transformations and efficient analytical techniques are needed. The present investigation is an extension of our earlier work in this area and includes descriptions of the syntheses of each of the eight stereoisomers of diprionol 1 and the gas chromatographic methods used for establishing their purities.

Our approach to the synthesis of the eight diprionol isomers is shown in Scheme 1 (*cf.*, ref. 3). It is based on four chiral starting materials: the two enantiomers of 1-lithio-2-methyldecane, obtained from the bromide enantiomers R-2 and S-2; and the *cis*-lactone enantiomers SS-3 and RR-3. From these, the four 2,3-*erythro*-isomers of 1 are accessible. It should be noted that the chiral centers in the precursors are located in positions which do not take part in the transformations leading to the formation of the four isomers of *erythro*-diprionol. Therefore, if the isomeric purities of the precursors are known, the isomeric purities of the products should also be known.

A synthetic approach such as the one we used to acquire the two *cis*-lactone enantiomers 3 (Scheme 4 *cf.*, below) cannot be used to obtain the enantiomers of the corresponding *trans*-lactone. Therefore, our method is not suited for direct preparation of the four *threo*-isomers of diprionol 1.

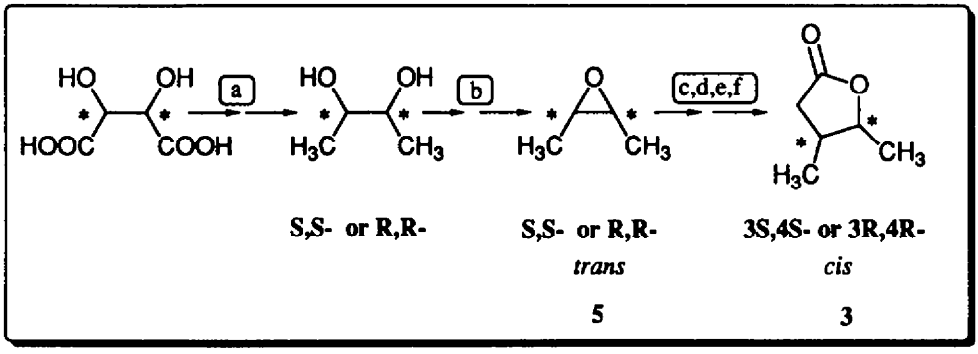
However, the Mitsunobu reaction,[42] which is known to proceed with complete inversion, provides a tool for stereospecific preparation of the *threo*-isomers from the *erythro*-isomers (Scheme 2). The analytical results



Scheme 3. Preparation of all eight stereoisomers of diprionol 1.

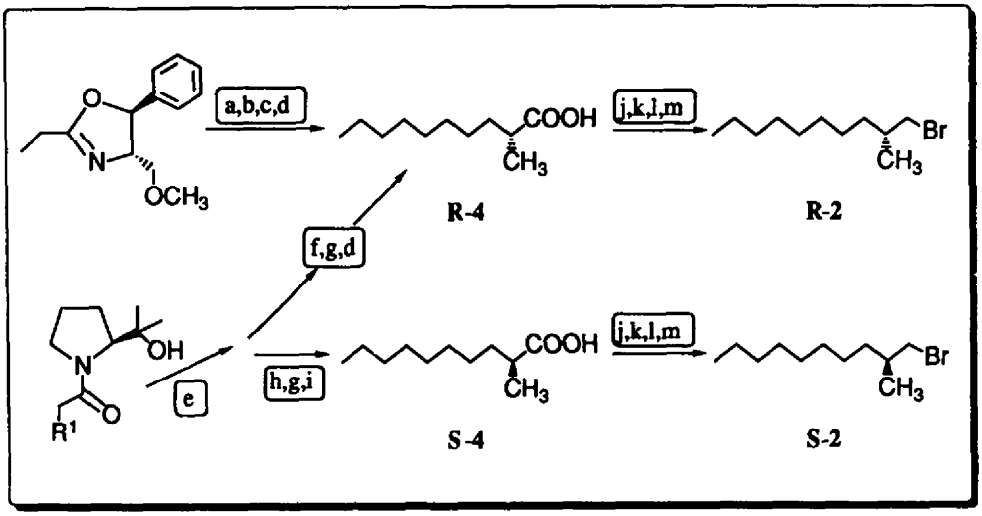
described below confirm that inversion was also complete in our experiments. Utilizing the synthetic procedures described above, all eight isomers of diprionol were prepared (Scheme 3).

The *cis*-lactone enantiomers were derived from the enantiomers of *trans*-epoxybutane **RR-5** and **SS-5**, which were prepared from the enantiomers of 2,3-butanediol (Scheme 4). The (2S,3S)-butanediol was obtained from commercial L-(+)-tartaric acid[3] and usually contained 0.05-0.5 % of the *meso*-diol, as determined by capillary gas chromatography. The concentration of the *meso*-form in the (2S,3S)-epoxide obtained from such a sample was always unchanged. No detectable amount of the (2R,3R)-epoxide was present, as judged from complexation[43]



Scheme 4. **a**, **b**: Prepared according to ref.[3] **c**: $Na^+ {}^-CH(COOCH_3)$, CH_3OH, Δx. **d**: KOH, CH_3OH/H_2O, Δx. **e** : H_3O^+. **f**: Pyridine, Δx.

capillary gas chromatography. Transformation to the lactone, as described,[3] gave **SS-3** containing no more than the expected amount of *trans*-lactone, considering the content of *meso*-epoxide in the starting epoxide (capillary GLC). It is not likely that both centers in the epoxide should simultaneously invert configuration during the reaction. Therefore, the optical purity of the lactone should be the same as that of the epoxide. Furthermore, the absence of detectable amounts of the enantiomer **RR-3** in **SS-3** was confirmed by GLC-analysis of the amide formed when the latter was allowed to react with (S)-(-)-1-phenyl-1-ethylamine. The (2R,3R)-epoxide **RR-5** was obtained either from D-(-)-tartaric acid or from commercially available (2R,3R)-butanediol. The **RR-5** obtained from commercial diol contained around 2 % *meso*-epoxide and <1 % (2S,3S)-epoxide, whereas material obtained



Scheme 5. Synthesis of the enantiomers of 1-bromo-2-methyldecane 2. **a**: LDA, THF, -80°. **b**: n-iodooctane, -95°. **c**: 4M H_2SO_4, Δx. **d**: cryst. from acetone with R-2-phenylethylamine. **e**: LDA (2 eq), THF -80°. **f**: (R^1 = n-octyl): MeI, -100°. **g**: 4M HCl (aq), dioxane (1:1), Δx. **h** (R^1 = methyl): n-iodooctane, -100°. **i**: cryst. from acetone with S-2-phenylethylamine. **j**: $LiAlH_4$, Et_2O. **k**: H_3O^+. **l**: TsCl, pyridine. **m**: LiBr, aceton, Δx

from tartaric acid was comparatively purer. Transformation to the (R,R)-lactone also gave a product which contained no more than the expected amount of *trans*-lactone. Analysis of the (S)-(-)-1-phenylethylamide derivative showed that the lactone **RR-3** contained less than 0.3 % **SS-3**.

Repeated chromatography on silica gel removed the small amount of *trans*-lactone present in the enantiomers of *cis*-lactone **3**, furnishing very pure lactones (**SS-3** usually contained less than 0.05 % *trans*-lactone and **RR-3** usually less than 0.4 % *trans*-lactone).

The enantiomers of 1-bromo-2-methyldecane **2** were obtained from the tosylates derived from the enantiomers of 2-methyl-1-decanol, which were produced by lithium aluminiumhydride reduction of the corresponding 2-methyldecanoic acids (*cf.*, below), according to our previously used method.[3] Alternative methods for the asymmetric synthesis of the enantiomers of 2-methyl-1-decanol have been described.[47,48] The optical purities were determined by the NMR-spectra of the MTPA-esters of the alcohols, as described by some of us for various 2-methyl-1-alkanols.[3,44-46] Since the methyl group is isolated from the reacting center, no change in optical purity should take place when proceeding from the alcohol to diprionol **1**.

The enantiomers of acid **4** were obtained by carrying out asymmetric synthesis (Scheme 5). The acid **S-4** (60-75 % ee) was prepared using either a chiral oxazoline or a prolinol derivative as chiral auxiliary, as previously has been described.[3,5,44,45,49] The enantiomer **R-4** (80-87 % ee) was obtained using the latter chiral auxiliary.

Enhancement of the optical purity of either enantiomer of acid **4** was achieved by crystallization with the appropriate enantiomer of 1-phenyl-1-ethylamine (*cf.*, ref. 44). Thus, samples of both, with optical purities over 95 % ee, were obtained.

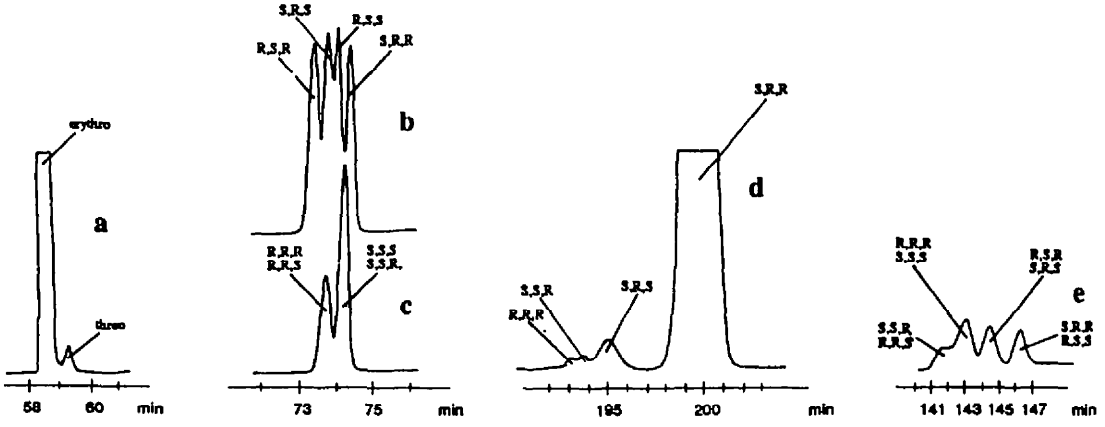


Figure 1. (a) Separation of diastereomeric *erythro/threo*- diprionols on tandem GLC. Carbowax (BP) (25 m, 0.26 mm I.D. d_f=0.4 μm) and CP-Sil-88, 25 m, 0.26 mm I.D. d_f= 0.21 μm). Conditions: isothermal at 120°C for 5 min and then programmed to 160° at a rate of 5°/min, carrier gas N_2 (10 psi), μ= 12.3 cm/s).

(b-c) Enantiomer separation of *threo* (b) and *erythro* (c) diprionols as isopropyl carbamate derivatives on a CP-XE-60-(S)-Valine-(S)-2-phenylethylamide column (30 m, 0.23 mm I.D. d_f= 0.24 μm). Conditions: isothermal at 130° for 5 min and then programmed to 190° at 2°/min, carrier gas N_2 (15 psi), μ= 14.5 cm/s.

(d) Enantiomer separation of 2S,3R,7R-diprionol as isopropyl carbamate derivative. Columns: CP-Sil-88 (25 m, 0.25 mm I.D. d_f= 0.21 μm) and DB-Wax (BP) (30 m, 0.25 mm I.D. d_f= 0.25) connected to the chiral column CP-XE-60-(S)-Valine-(S)-2-phenylethylamide (50 m, 0.23 mm I.D. d_f= 0.12 μm) with an universal Quick-seal splitter device. Conditions: isothermal at 130° for 10 min and programmed to 190°C at a rate of 2°/min, carrier gas N_2 (24.5 psi).

(e) Separation of the eight stereoisomers of diprionol as benzoates on tandem columns, CP-Sil-88 (30 m, 0.15 mm I.D. d_f= 0.24 μm) and CP-Sil-88 (25 m, 0,26 mm I.D. d_f=0.21 μm). Conditions: isothermal at 160°C, carrier gas N_2 (24.5 psi)

Table 1

Stereochemical composition in %.

Isomer analyzed	SSS	RSS	RRS	SRS	RRR	SRR	SSR	RSR
SSS	>97.5	<0.05[2)]	<0.05[1)]	<0.05[2)]	0[4)]	0[4)]	≈2.3[3)]	0[4)]
RSS	<0.05[2)]	>97.4	<0.05[2)]	0[4)]	0[4)]	0[4)]	0[4)]	≈2.5[1)]
RRS	<0.2[5)]	<0.1[2)1)]	>97.6	<0.1[2)1)]	≈2.0[5)]	0[4)]	0[4)]	0[4)]
SRS	<0.4[2)1)3)]	<0.2[1)]	<0.4[2)3)]	>97.0	0[4)]	≈2.0[1)]	0[4)]	0[4)]
RRR	0[4)]	0[4)]	≈1.5[5)3)]	0[4)]	>97.6	<0.4[2)1)3)]	<0.1[1)]	<0.4[2)3)]
SRR	0[4)]	<0.01[4)]	0[4)]	≈1.5[1)]	<0.3[3)2)1)]	>97.5	<0.3[2)3)1)]	<0.4[3)1)]
SSR	≈1.5[5)]	0[4)]	0[4)]	<0.01[5)]	0[4)]	≈0.1[2)3)]	>98.3	≈0.1[2)3)]
RSR	0[4)]	≈1.5[1)]	0[4)]	0[4)]	<0.2[2)]	0[4)]	<0.2[2)]	>98.1

1) As isopropyl carbamate derivatives on three columns in series, CP-Sil-88, Carbowax (BP) and CP-XE-60-(S)-Valine-(2)- phenylethylamide.
2) On tandem GC, Carbowax (BP) and CP-Sil-88.
3) As benzoates on two CP-Sil-88 in series.
4) Not detected <0.01%
5) Calculated from the related starting or product isomer from the Mitsunobu reaction (Scheme2)..

Purity of the various diprionols and their esters was determined by capillary gas chromatography. The *threo/erythro*-ratios were determined by chromatography on two tandem coupled columns [first Carbowax (BD) and then Silar 88; see fig 1a]. The four *threo*-isomers of diprionol were separated as isopropyl carbamates on a chiral column, CP-XE-60-(S)-valine-(S)-2-phenylethylamide (see fig.1b).[50] The isomeric purity of the 7-positions of the *threo*-isomers of diprionol could thus, for the first time, be assessed analytically. This system also separated **RRR-1** and **RRS-1** from **SSR-** and **SSS-1** as carbamates (see fig.1c). Unfortunately, when using this system, the *erythro*-isomers and some of the *threo*-isomers gave overlapping peaks. However, separation could be improved by first separating the *threo*- and *erythro*-isomers on a tandem system [first Silar 88 and then Carbowax (BD)] and then allowing them to pass through the CP-XE-60-(S)-valine-(S)-2-phenylethylamide column; analytical results for the natural inhibitor **SRR-1** obtained on this three column system are shown in fig. 1d. As a complement to the chiral column analysis, the four diastereomeric racemates of the benzoates **1Bz** were separated on a Silar 88 system (see fig. 1e), which allowed assessment of the purity in 7-position of the *erythro*-compounds. The combined analytical results are presented in Table 1.

Experimental

Moisture- and oxygen-sensitive reactions were carried out under argon. ^{1}H NMR spectra were recorded as $CDCl_3$ solutions, with TMS as internal standard. The standard GLC analyses were carried out using a 25 m x 0.32 mm I.D. capillary column coated with cross-linked SE-54, d_f= 0.52 μm; carrier gas N_2. Kiselgel 60, 230-400 mesh, was used for MPLC using hexane, with an increasing concentration of ethyl acetate as eluent. Boiling points are uncorrected and given as air bath temperatures in a bulb to bulb (Kugelrohr) apparatus.

Preparation of the isomeric 3,7-dimethyl-2-pentadecanyl acetates (Diprionyl acetates, **1Ac**). All eight stereoisomers of 3,7-dimethyl-2-pentadecanyl acetate were obtained from the corresponding 3,7-dimethyl-2-pentadecanol, using a previously described method.[3] Spectroscopic and physical data are summarized in Table 2.

(2S,3S,7S)-3,7-Dimethyl-2-pentadecanol (Diprionol, **SSS-1**). This compound was prepared from (3S,4S) -(-)-*cis*-dimethyl-(γ)-butyrolactone (**SS-3**) and (S)-1-bromo-2-methyldecane (**S-2**), as previously described.[3] *(2R,3R,7S)-, (2R,3R,7R)-, (2S,3S,7R)-3,7-dimethyl-2-pentadecanol* were obtained in a similar manner, starting from the appropriate combinations of **RR-3** or **SS-3** and **S-2** or **R-2**. Spectroscopic and physical data are presented in Table 3.

(2R,3S,7S)-3,7-Dimethyl-2-pentadecanyl benzoate (**RSS-1Bz**). (*2S,3S,7S*)-3,7-Dimethyl-2-pentadecanol (**SSS-1**) (1.09 g, 4.3 mmol), triphenylphosphine (2.37 g, 9.2 mmol), benzoic acid (1.06 g, 8.7 mmol) and 25 ml dry THF were stirred at -10°C under argon. Diethyl azodicarboxylate (1.56 g, 9.0 mmol) was added (1 min). The solution was stirred 2h and stored over night at +5° C, after which it was quenched with MeOH and poured into hexane. The hexane layer was separated from the solid, and the solid was then triturated with boiling hexane. The combined organic extracts were concentrated, leaving a residue (2 g), which was chromatographed and distilled (bulb to bulb, bath temp. 210°C/0.37 mm) to give **RSS-1Bz** (1.09 g, 3.01 mmol, 70 %). Preparation of *(2S,3R,7R)-, (2R,3S,7R)-, and (2S,3R,7S)-3,7-dimethyl-2-pentadecanyl benzoate* proceeded in the same manner, starting from (2R,3R,7R)-, (2S,3S,7R)- and (2R,3R,7S)-diprionol, respectively. Spectroscopic and physical data are shown in Table 4.

Table 2

Compound 1Ac	Chemical purity by GLC (%)	$[\alpha]^{22}_{D}$ ° ±0.3 (hexane)	n^{20}_{D} ±0.0002	NMR 200 MHz
SSS	>99.9	-5.6 (c 1.0) lit.[37] -6.05 (c 4.3) lit.[35] -5.76 (neat) lit.[40] -6.3 (c 2.03)	1.4407	δ 0.83 (3H, d, *J* = 6.3 Hz), 0.87 (3H, t, *J* = 6.3 Hz), 0.88 (3H, d, *J* = 6.7 Hz), 1.15 (3H, d, *J* = 6.4 Hz), 1.25 (21H, broad), 1.56-1.72 (1H, m), 2.02 (3H, s), 4.82 (1H, q of d, *J* = 4.8 and 6.4Hz)
RRR	>99.2	+6.4 (c 1.5) lit.[35] +5.64 (neat)	1.4409	as (SSS)-1Ac
RSS	>99.9	-8.4 (c 1.1)	1.4411	δ 0.83(3H ,d,*J* = 6.3 Hz), 0.86 (3H, d, *J* = 6.6 Hz), 0.87 (3H, t, *J* = 6.2 Hz), 1.12 (3H, d,*J* = 6.4 Hz), 1.25 (21H, broad), 1.60-1.78 (1H ,m), 2.02 (3H, s), 4.80 (1H,q of d,*J* = 5.5 and 6.4 Hz)
SRR	>99.2	+7.8 (c 1.2) lit.[37] +6.97 (c 1.4) lit.[40] +6.3 (c 4.10)	1.4411	as (RSS)-1Ac
RRS	>99.5	+7.1 (c 0.8) lit.[35] +6.08 (neat)	1.4410	δ 0.83 (3H, d,*J* = 6.2 Hz), 0.87 (3H,t,*J* = 6.3 Hz), 0.88 (3H, d,*J* =6.6 Hz), 1.15 (3H, d, *J* = 6.4 Hz), 1.25 (21H, broad), 1.56-1.72 (1H, m), 2.02 (3H, s), 4.82 (1H, q of d, *J* = 4.9 and 6.4 Hz)
SSR	>99.6	-6.7 (c 1.4) lit.[35] -6.18 (neat)	1.4408	as (RRS)-1Ac
SRS	>99.8	+8.2 (c 1.4) lit.[37] +6.39 (c 4.9)		δ 0.83 (3H, d, *J* = 6.3 Hz), 0.86 (3H, d, *J* = 6.48 Hz), 0.87 (3H, t, *J* = 6.4 Hz), 1.12 (3H, d, *J* =6.4 Hz), 1.25 (21H ,broad), 1.60-1.78 (1H, m), 2.02 (3H, s), 4.79 (1H, q of d, *J* = 5.4 and = 6.4 Hz)
RSR	>99.8	-8.3 (c 1.4)	1.4410	as (SRS)-1Ac

(2R,3S,7S)-3,7-Dimethyl-2-pentadecanol (**RSS-1**). (2R,3S,7S)-3,7-Dimethyl-2-pentadecanyl benzoate (**RSS-1Bz**) (0.32 g, 0.88 mmol) was stirred with dry diethyl ether (7 ml) at room temperature and under argon. Lithium aluminiumhydride (4 ml, 3 M in diethyl ether) was added. After stirring (2h), the solution was carefully acidified with 2 M HCl and extracted with hexane. The organic layer was washed with $NaHCO_3$(sat.), dried ($MgSO_4$) and the solvent was evaporated off to give an oil (0.28 g), which was chromatographed and distilled (bulb to bulb, bath temp. 130 °C/0.12 mm) to give **RSS-1** (0.21 g 0.82 mmol, 93 %). Preparation of *(2R,3S,7R)-, (2S,3R,7S)- and (2S,3R,7R)-3,7-dimethyl-2-pentadecanol* was carried out in the same manner, starting from the (2R,3S,7R)-, (2S,3R,7S)- and (2S,3R,7R)-benzoate, respectively. Spectroscopic and physical data are shown in Table 3.

(3S,4S)-(-)-cis-Dimethyl-(γ)-butyrolactone (**SS-3**). This compound was synthesized from (2S,3S)-(+)-tartaric acid according to the method of Byström et al.[3] The synthesis yielded **SS-3** (5.7 g), which was shown to contain less then 0.07 % *trans*-isomers by GLC. $[\alpha]^{25}_{D}$ -54.8° ±0.3° (neat) [Lit.[3]: -54.9° (neat)]. n^{20}_{D}= 1.4376 ±0.0002. The ^{1}H NMR spectrum (200 MHz) was identical to that found in the literature.[3]

(3R,4R)-(+)-cis-Dimethyl-(γ)-butyrolactone (**RR-3**) This was synthesized from commercially available (2R,3R)-(+)-butane-2,3-diol *via* (2R,3R)-epoxybutane, in the same manner as that described for lactone **SS-3** .[3] The epoxide was of > 99 % ee and usually contained <2 % *meso*-epoxide by GLC (*cf.*, below). The lactone **RR-3** was made in two batches A and B. A contained less then 0.4 % *trans*-isomers by GLC and was used to prepare **RRR-1** and the **RRS-1** sample used for the preparation of **SRS-1**. $[\alpha]^{25}_{D}$+55.3° ±0.3° (neat). n^{20}_{D}= 1.4374±0.0002. Batch B contained less then 0.06 % *trans*-isomers by GLC, and was obtained from the first by flash chromatography (silica gel gradient elution with hexane/ethyl acetate) and used for the preparation of **RRS-1**. $[\alpha]^{25}_{D}$+52.6° ±0.3 (neat). n^{20}_{D}= 1.4372 ±0.0002. ^{1}H NMR spectra of A and B (200 MHz) were identical with that of the (3S,4S)-lactone (**SS-3**).

Table 3

Compound 1	Chemical purity by GLC (%)	$[\alpha]^{22}_D$ ° ±0.03 (neat)		n^{20}_D ±0.0002	NMR 200 MHz
SSS	>99.9	-11.80	lit.[37] -10.4 (c 3.7, hexane) lit.[35] -9.86 lit.[40] -11.5 (c 0.79, hexane)	1.4512	δ 0.85 (3H ,d, *J* = 6.3 Hz), 0.87 (3H, t, *J* = 6.5 Hz) 0.89 (3H, d, *J* = 6.5 Hz), 1.15 (3H, d, *J* = 6.4 Hz), 1.21 (1H, s), 1.26 (22H, broad), 3.71 (1H, q of d, *J* = 4.0 and ≈6.4 Hz)
RRR	>98.0	+11.50	lit.[35] +9.72	1.4513	as (SSS)-1
RRS	>99.3	+13.04	lit.[35] +10.77	1.4513	as (SSR)-1
SSR	>99.9	-13.05	lit.[35] -11.10	1.4513	δ 0.84 (3H, d, *J* = 6.3 Hz), 0.88 (3H, t, *J* = 6.4 Hz), 0.89 (3H, d, *J* = 6.6 Hz), 1.15 (3H, d, *J* = 6.4 Hz), 1.26 (22H ,broad), 1.31 (1H, s), 3.70(1H, q of d, *J* =4.0 and ≈ 6.4 Hz)
RSS	>99.9	-15.50		1.4513	δ 0.85 (3H, d, *J* = 5.5 Hz), 0.87 (3H, d, *J* = 6.2 Hz), 0.88 (3H ,t, *J* = 5.4 Hz), 1.12 (3H, d, *J* =6.3 Hz), 1.26 (22H, broad), 1.31 (1H ,s), 3.66 (1H, q of d, *J* =5.2 and ≈ 6.3 Hz)
SRR	>99.0	+15.11	lit.[37] +16.03 (c 5.2, hexane) lit.[40] +14.9 (c 3.33, hexane)	1.4512	as (RSS)-1
SRS	>99.7	+16.07	lit.[37] +16.36 (c 3.5, hexane)	1.4512	as (RSR)-1
RSR	>99.4	-16.33		1.4512	δ 0.84 (3H, d, *J* = 5.8 Hz), 0.87 (3H, d, *J* = 6.4 Hz), 0.88 (3H, t, *J* = 5.9 Hz), 1.12 (3H, d, *J* = 6.3 Hz), 1.26 (22H , broad), 1.32 (1H, s) 3.66 (1H, q of d, *J*=5.1 and ≈ 6.3 Hz)

(S,S)- and (R,R)-3,4-Dimethyl-4-hydroxybutyric 1-phenylethylamide. The (S)-(-)-1-phenylethylamine recovered after five recrystallization of the acid **R-4** (*cf.*, below) was further recrystallised as the acid salt of L-(+)-tartaric acid (*cf.*, ref. 51). The free amine thus obtained was optically pure $[\alpha]^{25}_D$-40.6° (neat). {Lit: $[\alpha]^{25}_D$ -40.6° (neat)}[51] This amine (50 mg) was mixed with the lactone **SS-3** (20 mg) and heated in a sealed tube under Ar for 24 h at 140°. The resulting oil was dissolved in ether. The solution was shaken with dilute hydrochloric acid to remove excess amine, dried and concentrated to give a colourless, viscous syrup. ^{1}H NMR (60MHz, $CDCl_3$): δ 0.85 (3H,

Table 4

Compound 1Bz	Chemical purity by GLC (%)	$[\alpha]^{22}_D$ °	n^{20}_D ±0.0002	NMR 200 MHz
RSS	>99.8	-29.3 ±0.1 (neat) -30.3 ±0.5 (c 0.2, hexane)	1.4830	δ 0.84 (3H, d, *J* = 6.3 Hz) 0.88 (3H, t, *J* = 6.3 Hz), 0.97 (3H, d, *J* = 6.8 Hz), 1.05-1.54 (24H, broad), 1.75-1.92 (1H, m), 5.08 (1H, q of d, *J* = 5.4 and ≈ 6.3 Hz), 7.40-7.55 (3H ,m), 8.02-8.07 (2H,m)
SRR	>97	+28.6 ±0.5 (c 0.3, hexane)	1.4832	as (RSS)-1Bz
RSR	>99.4	-27.7 ±0.5 (c 0.3, hexane)	1.4824	as (SRS)-1Bz
SRS	>96	+28.2 ±0.1 (neat)	1.4850	δ 0.84 (3H ,d, *J* = 6.2 Hz), 0.88 (3H, t, *J* = 6.2 Hz), 0.97 (3H, d, *J* =6.8 Hz), 1.08-1.50 (24H, m),1.75-1.93 (1H, m), 5.07 (3H, q of d, *J* =5.3 and ≈ 6.4 Hz), 7.33-7.54 (3H, m), 8.01-8.06 (2H, m)

d), 1.10 (3H. d), 1.42 (3H, d) 1.8-2.8 [4H (reduced to 3H on shaking with D_2O)] 3.3-3.8 (1H, m) 4.8-5.2 (1H, m) 5.8 (1H,broad) 7.15 (5H, s). When subjected to the same conditions, the lactone **RR-3** gave similar results. The amide from racemic lactone **3** gave rise to two GLC peaks (iso 200°, ret. time 16.2 min and 16.9 min, Crossl. SE54, d_f =0.52μm, I.D. 0.32 mm, 25 m, carrier gas N_2, 1.7 ml/min). The amide from lactone **SS-3** gave rise to a single peak at ret. time 16.2 min and was thus optically pure. The amide from the lactone enantiomer **RR-3** gave rise to two peaks in the ratio 0.3 / 99.7 and was thus of 99.4 % ee. After the present work was completed, a gas chromatographic method for the simultaneous separation of all four stereoisomers of the lactone **3** was published.[52]

(S)-1-Bromo-2-methyldecane.(**S-2**). This was synthesized according to the method of Byström et al.[3] from (S)-(-)-2-methyldecan-1-ol. (S)-1-Bromo-2-methyldecane was made in two batches A and B. A was shown to be at least 98 % pure by GLC and should be of >97 % ee (i.e. the same % ee as that of starting alcohol batch used) . $[\alpha]^{25}_D$+0.36° ±0.03° (neat), n^{20}_D= 1.4577 ±0.0002. This batch was used to prepare (2R,3R,7S)-dimethyl-2-pentadecanol (**RRS-1**). According to GLC the batch B was 98 % pure of >95 % ee (i.e. the % ee of the alcohol batch used) and was used for the preparation of **SSS-1**. $[\alpha]^{25}_D$ +0.27° ±0.03° (neat). n^{20}_D= 1.4580 ±0.0002. The ^{1}H NMR spectrum (60 MHz) was identical with that described in the literature.[3]

(R)-1-Bromo-2-methyldecane (**R-2**). This was prepared according to the literature[3] from (R)-(+)-2-methyl-1-decanol and gave **R-2** of ≥97 % ee (the same % ee as that of starting alcohol batch used) and shown to be chemically pure by GLC. $[\alpha]^{25}_D$-0.31° ±0.03° (neat). n^{20}_D= 1.4574 ±0.0002. The ^{1}H NMR spectrum (60 MHz) was identical with that described in the literature.[3]

(S)-(-)-2-Methyl-1-decanol. This was prepared from (S)-2-methyldecanoic acid (**S-4**) using a method previously described.[3] (S)-2-Methyl-1-decanol was made in two batches A and B. Batch A (4.40 g) was ≥99.8 % chemically pure by GLC and of ≥97 % ee [judging from the ^{1}H NMR spectrum (200 MHz) of its ester with (-)-MTPA],[3] $[\alpha]^{25}_D$-9.64° ±0.03° (neat) [Lit.[47] (R-alc) +10.0° (c 4 CH_2CL_2)]. n^{20}_D= 1.4389 ±0.0002. Batch A was used in the preparation of (2R,3R,7S)-methyl-2-pentadecanol, **RRS-1**. Batch B, used for the preparation of **SSS-1**, was at least 99.9 % pure by GLC and of ≥95 % ee [judging from ^{1}H NMR-spectrum (200 MHz) of the ester from (+)-MTPA-Cl and (S)-methyldecan-1-ol], $[\alpha]^{20}_D$-9.54° ±0.03° (neat). n^{20}_D= 1.4391 ±0.0002. The ^{1}H NMR spectrum (60 MHz) was identical with that described in the literature.[3]

(R)-(+)-2-Methyl-1-decanol. This was prepared from (R)-2-methyldecanoic acid (**R-4**) using the previously described method.[3] (R)-2-Methyldecan-1-ol 7.7 g was at least 99.9 % pure by GLC and of ≥ 97 % ee [judging from the ^{1}H NMR spectrum (200 MHz) of its ester with (+)-MTPA]. $[\alpha]^{25}_D$+9.88° ±0.03° (neat). n^{20}_D= 1.4392 ±0.0002. The ^{1}H NMR spectrum (60 MHz) was identical with that described in the literature.[3]

(S)-2-Methyldecanoic acid (**S-4**). This was synthesized as described,[44] and crystallized with (R)-(+)-1-phenylethylamine. (S)-2-Methyldecanoic acid **S-4** was made in two batches A and B. A was pure (GLC). $[\alpha]^{25}_D$+15.2° ±0.3° (neat), corresponding to approximately 98 % ee [Lit.:[3] +15.5°(neat)]. n^{20}_D= 1.4373 ±0.0002 and the other batch B was pure by GLC $[\alpha]^{25}_D$+14.50° ±0.03° (neat), corresponding to approximately 94 % ee n^{20}_D= 1.4371 ±0.0002. ^{1}H NMR (200 MHz) : δ 0.88 (3H, t, J=6.4 Hz), 1.18 (3H, d, J=6.9 Hz), 1.27 (12H, broad), 1.38-1.54 (1H, m), 1.58-1.89(1H, m), 2.37-2.58 (1H, m), 11.50 (1H, s).

(R)-2-Methyldecanoic acid (R-4). This was synthesized as described by Guoqiang et al.[44] and further purified by crystallization with (S)-(-)-α-phenylethylamine as described.[44] The (R)-2-methyldecanoic acid obtained was pure judging by GLC. $[\alpha]^{25}_{D}$-15.60° ±0.03° (neat), corresponding to approximately 100 % ee n^{20}_{D}= 1.4365 ±0.0002. The ^{1}H NMR-spectrum (200 MHz) was identical with that for (S)-2-methyldecanoic acid (*cf.*, above).

Formation of derivatives for Capillary Gas Chromatography. The isopropyl carbamates of the diprionol isomers were prepared from diprionol (500 ng) dissolved in dichloromethane (100 µl). Isopropyl isocyanate (30 µl) was added, and the mixture heated (1 h, 100°C). The solvent was evaporated by purging with dry nitrogen. The residue was dissolved dichloromethane (200 µl). Aliquots from his solution (1 µl) were injected.[53] The benzoates of diprionol isomers were prepared, in dry pyridine (1 ml), from diprionol (10 mg) and benzoyl chloride (5 drops). After heating to the boiling point, methanol (5 drops) was added, the pyridine was evaporated off, and the residue chromatographed. The benzoate obtained after evaporation of the solvent was dissolved in dichloromethane (5ng/µl) and analyzed.

Analysis of diprionyl derivatives using Capillary Gas Chromatography. Gas chromatographic analyses were performed on a Hewlett Packard 5880 gas chromatograph, equipped with a FID detector and a N/P detector. The separation of diastereomeric *erythro/threo*-diprionols was performed without derivatization, using tandem columns. Carbowax column [(BP), 25 m , 0.25 mm I.D., d_f=0.4µm] and CP-Sil-88 column [25 m, 0.26 mm I.D., d_f=0.21 µm] were joined together with a Quick-seal column connector. For enantiomeric separation of the eight isopropyl carbamate derivatives, three columns were connected in series. First a CP-Sil-88 column [25 m, 0.26 mm I.D., d_f=0.21 µm] was coupled to a DB-Wax column [(BP), 30 m, 0.25 mm I.D., d_f=0.25µm] with a Quick-seal column connector. This tandem system was then coupled to a chiral CP-XE-60-(S)-Valine-(S)-2-phenylethylamide[50] [50 m, 0.23 mm I.D., d_f=0.12 µm (Chrompack)], with a universal Quick-seal splitter device (Chrompack). This Y-shaped glass splitter makes it possible to increase the gas pressure so as to obtain a correct gas flow through the last column. The diprionyl benzoates were analyzed on a tandem system, with a CP-Sil-88 column [30 m, 0.15 mm I.D., d_f=0.24 µm] connected to another CP-Sil-88 column [25 m, 0.26 mm I.D., d_f=0.21 µm] with a Quick-seal connector. All results are summarized in Table 1.

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