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SYNTHESIS OF THE TWO ENANTIOMERS OF THE SEX PHEROMONE OF *DIABROTICA UNDECIMPUNCTATA HOWARDI* AND OF CHIRAL PRECURSORS OF OTHER PHEROMONES STARTING FROM ENANTIOMERICALLY PURE METHYL HYDROGEN (*R*)-3-METHYLGLUTARATE†

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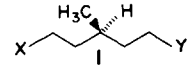
Abstract—Readily available methyl hydrogen (*R*)-3-methylglutarate (**2**) is a useful chiral building block for the synthesis of several biologically active compounds. Enantiomerically pure (*R*)-**2** has been employed to synthesize stereospecifically each of the two enantiomers, **1a** and **1b**, of 10-methyl-2-tridecanone, the sex pheromone of the southern corn rootworm, *Diabrotica undecimpunctata howardi* Barber. Compound (*R*)-**2** has been also used to prepare 99% optically pure (*R*)-3-methyl-1-pentanol (**6**) and enantiomerically pure (*R*)-5-methyl-i-tricosyne (**7**). These compounds are useful building blocks suitable for the further elaboration to other chiral insect pheromones.

Several acyclic chiral insect pheromones are characterized by the moiety **1**. Typical examples are the two enantiomers, **1a** and **1b**, of 10-methyl-2-tridecanone, the sex pheromone of the southern corn rootworm, *Diabrotica undecimpunctata howardi* Barber,[1,2] the propionates of (2*R*,8*R*) and (2*S*,8*R*)-8-methyl-2-decanol (**1c** and **1d**), respectively, which are attractants of the western corn rootworm, *D. virgifera virgifera* Le Conte,[3,4] (4*R*,8*R*)-4,8-dimethyldecanal (**1e**), the natural aggregation pheromone of *Tribolium castaneum*,[5] and (3*R*,11*R*) and (3*S*,11*R*)-3,11-dimethyl-2-nonacosanone (**1f** and **1g**), respectively, which are two stereoisomers of the pheromone of *Blattella germanica*.[6]



1

1a X = CH_3– ; Y = CH_3–CO–$(CH_2)_5$–

1b X = CH_3–CO–$(CH_2)_5$– ; Y = CH_3–$CH(CH_3)$–H

1c X = H ; Y = $-(CH_2)_5-C(H)(OCOEt)-CH_3$

1d X = H ; Y = $-(CH_2)_5-C(H)(CH_3)-OCOEt$

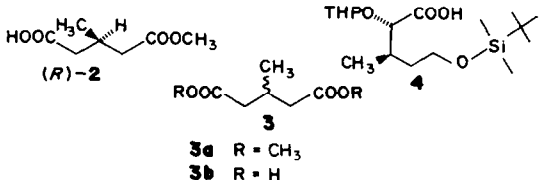
1e X = H ; Y = $-CH_2-C(H)(CH_3)-(CH_2)_2-CHO$

1f X = CH_3–$(CH_2)_{15}$– ; Y = $-(CH_2)_5-C(H)(CH_3)-COCH_3$

1g X = CH_3–$(CH_2)_{15}$– ; Y = $-(CH_2)_5-C(H)(CH_3)-COCH_3$

A useful chiral building block for the synthesis of such compounds may be represented by methyl hydrogen (*R*)-3-methylglutarate, (*R*)-**2**, which is easily available. In fact, 90% enantiomerically pure (*R*)-**2** has been recently prepared in 95% yield by enantioselective hydrolysis of dimethyl 3-methylglutarate (**3a**) by pig liver esterase.[7–9] This optically active compound has been employed to prepare the verrucarinic acid fragment (**4**)[10] and in synthetic studies of cytochalasanes.[11]

On the other hand, both the enantiomers of methyl hydrogen 3-methylglutarate with undefined *e.e.* may be



(*R*)-**2**

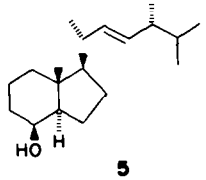
3

3a R = CH_3

3b R = H

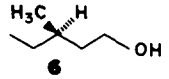
4

obtained by resolution of (±)-**2** cinchonidine.[12,13] Compound (*S*)-**2** has been used as starting material for the synthesis of the secondary alcohol **5**, which corresponds to Windaus and Grundmann's C_{19} ketone.[14]



5

In this paper we report that the resolution of (±)-**2** with cinchonidine allows to obtain enantiomerically pure (*R*)-**2**. We show also that this resolution process allows either to recycle the chiral auxiliary, or to reinsert into the resolution cycle (*S*)-**2** of low enantiomeric purity recovered from the mother liquors of the crystallizations. Moreover, we describe the use of enantiomerically pure (*R*)-**2** for the stereospecific synthesis of each of the two enantiomers of 10-methyl-2-tridecanone, **1a** and **1b**,[15] as well for the preparation of (*R*)-3-methyl-1-pentanol (**6**) and (*R*)-5-methyl-1-tricosyne (**7**). Compounds **6** and **7** represent useful chiral building blocks suitable for the further elaboration of other chiral insect pheromones such as **1c–1e** and **1f** and **1g**, respectively.



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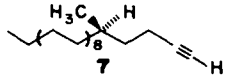

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(±)-Methyl hydrogen 3-methylglutarate, (*R*)(*S*)-**2**, which was prepared from 3-methylglutaric acid (**3b**) according to the literature,[12] was resolved by

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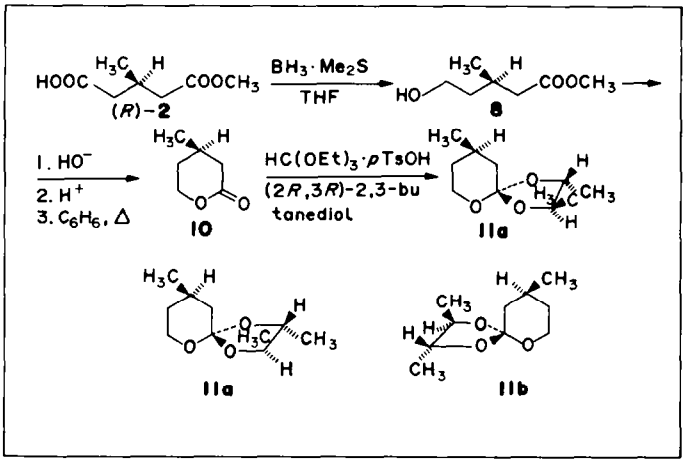


Scheme 1.

crystallization of the corresponding diastereomeric salts with cinchonidine from water.[12] After six crystallizations the obtained salt was decomposed by dissolution in dil HCl and the resolved acid (*R*)-**2**, which was recovered by extraction with ether followed by distillation, had $[\alpha]_D^{22}+0.58$ (neat). The mother liquors were concentrated, acidified and extracted with ether to afford (*S*)-**2** ($[\alpha]_D^{22}-0.18$ (neat)). Cinchonidine used in the resolution was recovered in almost quantitative yield in the following way. The acid aqueous solutions of the resolution were concentrated and treated with dil NaOH. The white solid so obtained was filtered, washed with water, and dried *in vacuo*.

Compound (*S*)-**2** was converted into (±)-**2** by the following reaction sequence. Saponification of (*S*)-**2** followed by acidification gave **3b** which was reacted with acetic anhydride to afford the corresponding crude anhydride. Treatment of such compound with 1 equivalent of sodium methoxide in methanol[12] afforded (±)-**2** in 95% overall yield.

In order to check the enantiomeric purity of (*R*)-**2**, this compound was reduced with borane-dimethylsulfide[14,16] and the resulting hydroxyester **8** was converted into the corresponding hydroxyacid **9** (Scheme 1). Dehydration of **9** in refluxing benzene afforded (*R*)-3-methylvalerolactone (**10**) in 75% overall yield. This lactone was then converted into (2*R*,3*R*,9*R*)-2,3,9-trimethyl-1,4,6-trioxaspiro[4,5]decane (**11a**) by reaction with (2*R*,3*R*)-2,3-butanediol and triethyl orthoformate in THF solution, in the presence of a catalytic amount of sulfuric acid[17] (Scheme 1). Capillary GLC analysis of **11a** and of a corresponding diastereomeric mixture **11a** + **11b**, which was similarly prepared from a sample of (±)-**10**, showed that (*R*)-**10** was *ca* 100% stereomerically pure. Therefore, the precursor (*R*)-**2** was enantiomerically pure.

Compound **8** was used as chiral starting material in the synthesis of **1a** and **1b** (Schemes 2 and 3). Thus, **8** was converted into the corresponding tosylate **12** which was reacted with lithium dimethylcuprate in ether at −35° to afford methyl (*R*)-3-methylhexanoate (**13**) in 70% overall yield. (*R*)-3-Methyl-1-hexanol (**14**),† which was obtained by reduction of this ester, was transformed into the corresponding mesylate (**15**). This compound was then reacted with a THF solution of 6-hepten-1-ylmagnesium bromide, in the presence of dilithium tetrachlorocuprate to afford (*R*)-10-methyl-1-tridecene (**16**) in 78.6% overall yield. Hydroxymercuriation of **16** followed by reduction with $NaBH_4$ gave (2*RS*,10*R*)-**17a** which by chromic oxidation was transformed into the target ketone (*R*)-**1a** ($[\alpha]_D^{24}-1.64\pm0.02$ ($CHCl_3$)) in 77% overall yield (Scheme 2).

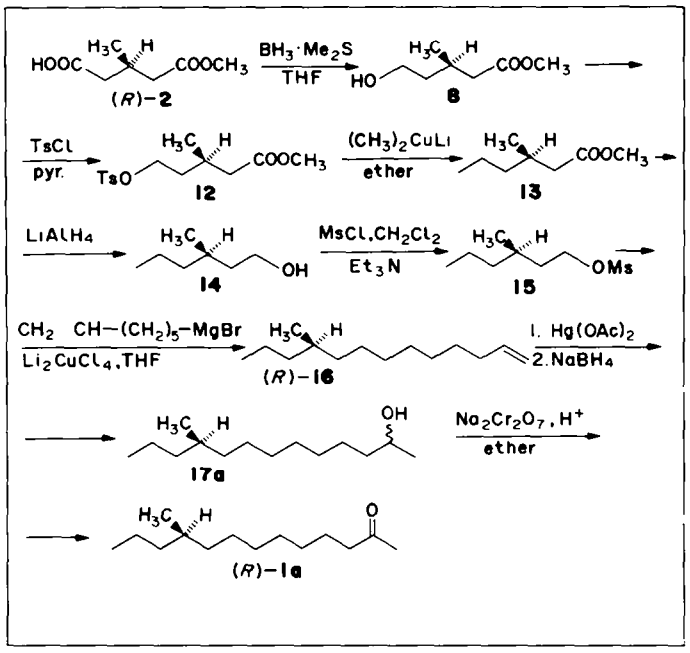
The synthesis of (*S*)-**1b** was carried out according to the reaction sequence depicted in Scheme 3. Compound **12** was reacted with lithium di(6-hepten-1-yl)cuprate in ether at −35° to give methyl (*R*)-3-methyl-11-dodecenoate (**18**) in 67% yield. Reduction of **18** with LAH followed by mesylation and treatment with lithium dimethylcuprate in ether at −35° gave (*R*)-**16** in 81% overall yield. This alkene was then converted into chemically pure (*S*)-**1b** ($[\alpha]_D^{24}+1.65\pm0.02$ ($CHCl_3$)) by a reaction sequence identical to that used for the preparation of the corresponding enantiomer.

The chiral building block (*R*)-**8** was also used to prepare in a simple way and in high yield (*R*)-3-methyl-1-pentanol (**6**) having high optical purity, which as previously mentioned is suitable for the further elaboration to some chiral acyclic insect pheromone components.[20] Compound **6** has been previously prepared starting from (*R*)-pulegone by lengthy reaction sequences[4,21] involving the conversion of (*R*)-pulegone into enantiomerically pure (*R*)-citronellol.[22] Thus, **8** was converted into the corresponding mesylate **21**, which was reacted with an excess of LAH in ether to afford (*R*)-**6**, $[\alpha]_D^{20}-8.67$ (neat) in 72% overall yield‡ (Scheme 4).‡ Since the maximum rotary power of (*S*)-**6** is $[\alpha]_D^{20}+8.77$,[23] the sample of (*R*)-**6** prepared resulted to be 99% optically pure.

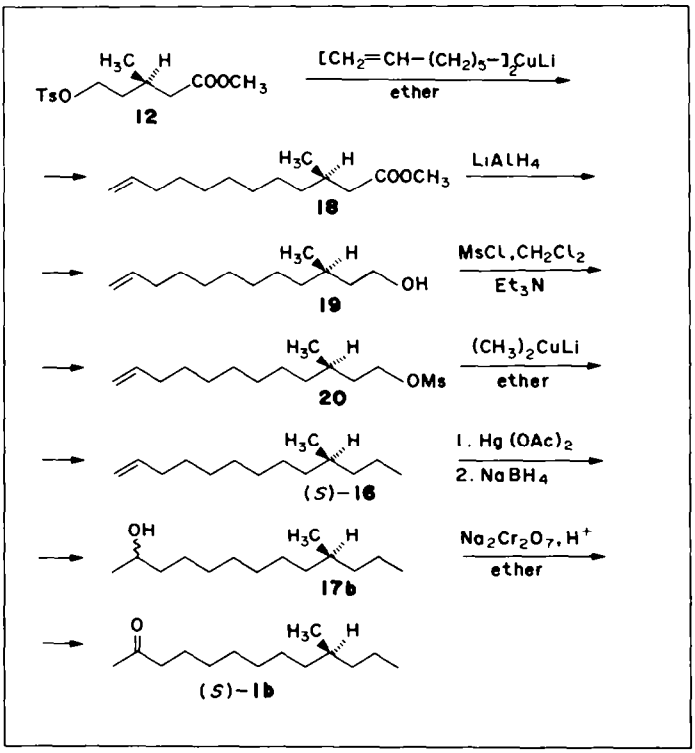
Finally, compound (*R*)-**2** was used as chiral starting material for the stereospecific synthesis of (*R*)-**7**

† The enantiomers of 3-methyl-1-hexanol were converted to the corresponding (*S*)-α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) esters to check their enantiomeric purity.[18] However, neither NMR nor GLC analyses of them yielded useful results. Analogously, HPLC analysis of the two diastereomeric (*R*)-1-(naphthyl)ethyl carbamates prepared from racemic 3-methyl-1-hexanol according to the literature[19] did not show difference in their Rv.

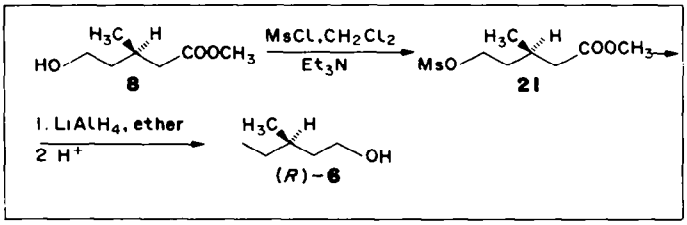
‡ It must be noted that this chemically pure sample of (*R*)-**6** had specific rotary power higher than that ($[\alpha]_D^{20}-8.5$ (neat)) of a corresponding sample obtained from 100% enantiomerically pure pulegone.[4]



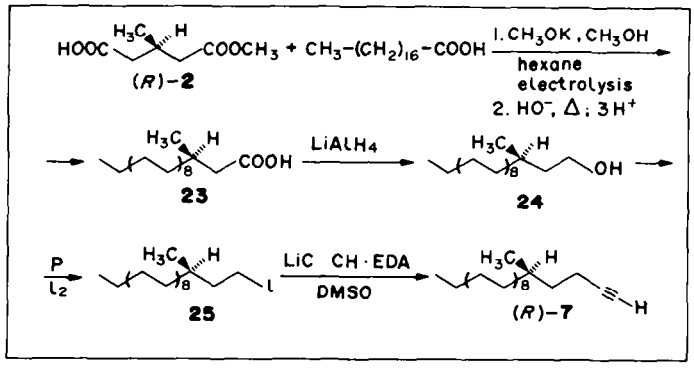
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

(Scheme 5). Thus, according to Bailey *et al.*[24] a mixture of (*R*)-**2** with stearic acid was electrolyzed. Hydrolysis of the resulting ester gave (*R*)-3-methylheneicosanoic acid (**23**) in 25% yield. The alcohol **24** which was obtained by LAH reduction of **23**, was converted into the corresponding iodide **25** which was treated with *lithium acetylide-EDA complex in DMSO* to afford (*R*)-5-methyl-1-tricosyne (**7**) in 51.6% overall yield based on **23**.

In conclusion, both the enantiomers of 10-methyl-2-tridecanone have been prepared starting from enantiomerically pure (*R*)-**2**. Since there was no synthetic step where significant racemization might be possible, such compounds have enantiomeric purity very similar to that of (*R*)-**2**.

On the other hand, the values of the specific rotatory power for **1a** and **1b**, $[\alpha]_D^{24} - 1.64 \pm 0.02$ ($CHCl_3$) and $[\alpha]_D^{24} + 1.65 \pm 0.02$ ($CHCl_3$), respectively, do not significantly differ from that one reported for a small sample of **1a**, $[\alpha]_D^{24} - 1.71$ ($CHCl_3$), with undefined chemical purity, which was purified by a simple bulb-to-bulb distillation.[15] It must also be noted that the synthetic schemes we followed to prepare **1a** and **1b** are more advantageous than those previously employed to prepare these compounds.[15] In fact, the key step of our synthesis which involves the resolution of (±)-**2** allows either to racemize enantiomerically impure (*S*)-**2** recovered from the crystallization of the diastereomeric salts with cinchonidine, or to recover the chiral auxiliary. These characteristics are not present in the resolution process previously employed to prepare **1a** and **1b**.[15]

Finally, this work demonstrates an efficient and convenient strategy to prepare the two chiral building blocks **6** and **7**. Compound **6** has been shown to be 99% optically pure and **7** is presumably enantiomerically pure. In fact, either the Kolbe reaction employed to transform (*R*)-**2** into **23**, or the reactions used to convert **23** into **7** do not involve racemization.[25]

Further work to complete the synthesis of the propionates of (2*R*,8*R*) and (2*S*,8*R*)-8-methyl-2-decanol (**1c** and **1d**), respectively, starting from **6** is in progress.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. IR spectra were determined on a Perkin–Elmer 225 spectrometer. ^{1}H-NMR spectra were recorded at 60 MHz on a Varian T 60 spectrometer using TMS as an internal standard. Mass spectra were recorded on a Hewlett–Packard 5995 A gas chromatograph/mass spectrometer. GLC analyses unless otherwise noted were performed on a DANI 3900 glass-capillary column dedicated gas chromatograph using a FFAP glass capillary column (25 m × 0.25 mm i.d.) and a FID detector. Purifications by preparative GLC were performed on a Perkin–Elmer F-21 preparative gas chromatograph. Purifications by liquid chromatography were performed on a Jobin–Yvon Chromatospac-Prep 10 liquid chromatograph using a Knauer differential refractometer as detector. Optical rotation were generally measured on a Perkin–Elmer 142 polarimeter. Optical rotations of **23**, **24**, **25** and **7** were however measured on a Schmidt–Haensch polarimeter. All reactions of air- and water-sensitive materials were performed in flame-dried glassware under N_2. (±)-Methyl hydrogen 3-methylglutarate was prepared starting from commercially available 3-methylglutaric acid according to the lit.[12]

Optical resolution of (±)-*methyl hydrogen 3-methylglutarate* (**2**). According to the lit.[12] cinchonidine (317 g) and (±)-methyl hydrogen 3-methylglutarate (182.2 g, 1.14 mol) were dissolved in a hot mixture of acetone (140 ml) and water (1550 ml). After cooling the separated crystals were collected and recrystallized 6 times from water to give 162 g of the cinchonidine salt. This salt was dissolved in N HCl and the soln was extracted with ether. The ether soln was washed with NaCl soln, dried, concentrated *in vacuo* and distilled to give (*R*)-**2** (46.7 g, 51% yield): b.p. 102°/0.3 torr; $[\alpha]_D^{22} + 0.58$ (neat). Lit.[12] $[\alpha]_D^{22} + 0.58$ (neat). The mother liquors of the resolution were concentrated *in vacuo*, treated with N HCl and extracted with ether. The ether soln was washed, dried, concentrated, and distilled to give (*S*)-**2** (125 g): b.p. 96–98°/0.15 torr; $[\alpha]_D^{22} - 0.18$ (neat).

Cinchonidine used in the resolution was recovered in the following way. The acid aq solns obtained after recovering (*R*)-**2** and (*S*)-**2** were concentrated and treated at 5% with dil NaOH aq. The white solid obtained was filtered, thoroughly washed with water and dried *in vacuo* to afford cinchonidine (302 g): m.p. 201–204°.

Compound (*S*)-**2** was converted into (±)-**2** by the following reaction sequence. A soln of (*S*)-**2** (125 g, 0.78 mol) in EtOH (200 ml) was added to a soln of KOH (175 g, 3.12 mol) in water (500 ml) and the resulting mixture was stirred overnight at room temp and then 3 hr at reflux. EtOH was removed *in vacuo* and the residue was acidified with 3N HCl. The acid soln was continuously extracted with ether and the ether soln was concentrated *in vacuo*. The residue was reacted with Ac_2O (250 ml) for 5 hr at reflux. AcOH and the excess of Ac_2O were accurately removed by distillation at 10 torr. The residue was then reacted for 1 hr at room temp with a soln prepared by reacting Na (17.94 g, 0.78 mol) with MeOH (300 ml). The excess MeOH was removed *in vacuo* and the residue was acidified with N HCl. The mixture was extracted with ether and the ether soln, which was washed with water and dried over Na_2SO_4, was distilled to give pure (±)-**2** (121.5 g, 97% yield): b.p. 114–116°/torr.

Methyl (R)-5-*hydroxy*-3-*methylpentanoate* (**8**). A 10 M soln of $BH_3 \cdot (CH_3)_2S$ (16.1 ml, 161 mmol) was added during 1.5 hr to a soln of (*R*)-**2** (20.2 g, 126 mmol) in dry THF (180 ml) cooled at −20°. After stirring at 20° for 16 hr, the mixture was cooled at 0°. Water (150 ml) was carefully added and the solvent removed *in vacuo*. The residue was extracted with ether, and the extract was washed with dil HCl and $NaHCO_3$ aq. It was then dried and evaporated at room temp to afford an oily product (17.5 g, 95% yield) which resulted homogeneous by GLC analysis. ^{1}H-NMR ($CDCl_3$): δ 0.95 (br d, 3H), 1.2–2.6 (m, 6H), 3.65 (s, 3H), 3.75 ppm (t, 2H). Compound **8** was used in the next step without any further purification.

Methyl (R)-5-*tosyloxy*-3-*methylpentanoate* (**12**). *p*-TsCl (23.35 g, 122 mmol) was added to a stirred and ice-cooled soln of **8** (14.17 g, 97 mmol) in dry C_5H_5N (57 ml). The stirring was continued for 5 hr at 0–5°. The mixture was poured into ice–dil HCl and extracted with ether. The ether soln was washed with dil HCl, water, sat $NaHCO_3$ aq and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give crude **12** (28.2 g, 97% yield). This was directly used for the next step.

(R)-3-*Methylvalerolactone* (**10**). A soln of **8** (2.16 g, 14.8 mmol) in Me_3OH (3 ml) was added to a soln of KOH (2.5 g, 44.5 mmol) in water (12 ml). The mixture was stirred for 18 hr at room temp and then for 2 hr at 50°. The solvent was removed *in vacuo* and the residue was acidified with dil HCl. The acid soln was continuously extracted with ether and the dried ether soln was concentrated *in vacuo*. The residue was dissolved in benzene (150 ml) and the mixture was refluxed using a Dean–Stark trap. After 4 hr the benzene soln was concentrated and the residue was fractionally distilled to give (*R*)-**10** (1.34 g, 79% yield): b.p. 105–106°/11 torr, $[\alpha]_D^{27}$ + 27.61 (*c* = 5.716, $CHCl_3$). Lit.[26] $[\alpha]_D^{27}$ −24.8 (*c* = 5.6, $CHCl_3$) for a sample with 90% e.e. GLC analysis showed that (*R*)-**10** was 100% chemically pure.

Determination of the enantiomeric purity of (R)-**10**. To (*R*)-**10** (0.46 g, 4.03 mmol) in dried THF (10 ml) was added, under N_2, D(−)-2,3-butanediol (0.546 g, $[\alpha]_D^{20}$ −13.1 (neat), triethyl orthoformate (0.90 g, 6.08 mmol) and 5 drops of conc H_2SO_4. The mixture was stirred at room temp for 48 hr and then treated with Et_3N (1 ml) and poured into sat $NaHCO_3$ aq. The mixture was then extracted with benzene and the extract was washed with $NaHCO_3$ aq, then with brine, and dried. The solvent was removed *in vacuo* to afford crude (2*R*,3*R*,9*R*)-**11a** which was analyzed by GLC on a SE 54 glass capillary column (25 m × 0.23 i.d.). A sample of a diastereomeric mixture of (2*R*,3*R*,9*S*)-**11b** and (2*R*,3*R*,9*R*)-**11a** was prepared in a similar way starting from racemic 3-methylvalerolactone.

GLC analysis of **11a** and of **11a** + **11b** revealed that the diastereomeric purity of **11a** was higher than 99.5% and that this diastereomer exhibited higher retention time than **11b**. Therefore, compound (*R*)-**10** resulted to be almost enantiomerically pure.

Methyl (R)-3-*methylhexanoate* (**13**). A soln of Me_2CuLi was prepared by adding a 2.2 N ether soln of MeLi (142 ml, 313 mmol) to a stirred suspension of CuI (30.2 g, 158.7 mmol) in dry ether (230 ml) at −25° under N_2. A soln of **12** (21.0 g, 70 mmol) in dry ether (120 ml) was added to the stirred and cooled Me_2CuLi at −40°. The mixture was stirred at −40° for 4.5 hr, then it was poured into sat NH_4Cl aq, stirred for 1 hr and extracted with ether. The ether extract was washed with water and brine, dried and concentrated. Fractional distillation of the residue gave **13** (7.86 g, 78% yield): b.p. 86°/65 torr; $[\alpha]_D^{23}$ 1.41 (neat). Lit.[27] b.p. 80°/60 torr; $[\alpha]_D^{23}$ 1.42 (neat). ^{1}H-NMR (CCl_4): δ 0.85–1.1 (m, 6H), 1.15–1.6 (m, 5H), 2–2.2 (br, 2H), 3.63 ppm (s, 3H). GLC analysis showed that **13** had *ca* 96% chemical purity.

(R)-3-*Methyl*-1-*hexanol* (**14**). A soln of **13** (7.1 g, 49.3 mmol) in dry ether (50 ml) was slowly added to a stirred suspension of LAH (1.92 g, 50.6 mmol) in ether (35 ml). The mixture was refluxed for 4 hr and then poured into ice-water. Dil H_2SO_4 was added and the mixture was extracted with ether. The ether extracts were washed with sat NaCl aq, water, dried and concentrated. Fractional distillation of the residue gave **14** (5.43 g, 95% yield): b.p. 85°/23 torr; $[\alpha]_D^{24}$ 1.68 (neat) (lit.[29] b.p. 161–162°, $[\alpha]_D^{24}$ + 1.58). ^{1}H-NMR (CCl_4): δ 0.91 (m, 6H), 1.1–1.8 (br m, 7H), 3.37 (s, 1H), 3.53 (t, 24). GLC analysis showed that **14** was chemically pure.

(R)-3-*Methyl*-1-*hexyl mesylate* (**15**). MsCl (4.98 g, 43.4 mmol) was added to a stirred soln of **14** (4.59 g, 39.5 mmol) in dry CH_2Cl_2 (195 ml) containing Et_3N (6.0 g, 59.2 mmol) cooled at −15°. The stirring was continued for 5 hr at 0° ~ 5°. The mixture was poured into ice-dil HCl and extracted with CH_2Cl_2. The organic extract was washed with dil HCl, dil $NaHCO_3$ aq, water and dried. Concentration *in vacuo* afforded crude **15** (7.7 g, 100% yield) which was used in the next step without any further purification.

(R)-10-*Methyl*-1-*tridecene* (**16**). 1-Bromo-6-heptene (10.6 g, 60 mmol) (b.p. 63°/11 torr) was reacted with Mg (1.70 g, mmol) in THF (100 ml) to give the corresponding Grignard reagent. This soln was slowly added to a soln of **15** (7.7 g, 59.2 mmol) in THF (80 ml) cooled at −78°, which contained a catalytic amount of Li_2CuCl_4 (6 mmol). The mixture was stirred for 1.5 hr at −25° and for 12 hr at 0° ~ 5°. It was then poured into sat NH_4Cl aq, stirred for 1 hr and extracted with ether. The ether extract was washed with sat $NaHCO_3$ aq, water, dried and concentrated *in vacuo*. Fractional distillation of the residue gave (*R*)-**16** (6.1 g, 78.6% yield): b.p. 65°/0.3 torr; $[\alpha]_D^{25}$ −1.63 (*c* = 13.59, THF). IR (film): ν_{max} 3080, 2960, 2930, 2860, 2730, 1825, 1640, 1465, 1455, 1415, 1380, 1150, 990, 905, 735, and 725 cm^{-1}. ^{1}H-NMR (CCl_4): δ 0.9 (br n, 6H), 1.15–1.7 (br s, 17H), 2.04 (br m, 2H), 4.8–6.0 ppm (m, 3H). These spectral properties were very similar to those reported in the lit.[15] GLC analysis showed that (*R*)-**16** had chemical purity higher than 95%.

Methyl (R)-3-*methyl*-11-*dodecenoate* (**18**). A soln of 1-lithium-6-heptene was prepared by adding 1-bromo-6-heptene (73 g, 412 mmol) to a stirred suspension of powder of Li with 0.5% Na (14.5 g, 2.09 mol) in dry ether (400 ml) at −20° under N_2. The mixture was stirred for 2 hr at −20°. The alkyllithium so obtained was then added in 45 min to a stirred suspension of CuI (39.6 g, 208 mmol) in dry ether (150 ml) cooled at −30°. The dark mixture was stirred for 0.5 hr at −30°. A soln of **12** (28.2 g, 94 mmol) in (150 ml) was added to the stirred and cooled soln of lithium di(6-hepten-1-yl)cuprate and the resulting mixture was maintained at −35° for 2.5 hr. It was then poured into sat NH_4Cl aq, stirred for 1.5 hr and extracted with ether. The ether extract was washed with aq NH_4Cl, water and brine, dried and concentrated *in vacuo*. Fractional distillation afforded **18** (14.3 g, 67.3% yield): b.p. 88°/0.3 torr; IR (film): ν_{max} 3080, 2950, 2930, 2855, 1740, 1640, 1460, 1435, 1415, 1380, 1365, 1005, 990, 905, 830, 720 cm^{-1}. ^{1}H-NMR (CCl_4): δ 0.90 (br d, 3H), 1.27 (br s, 13H), 1.8–2.4 (br m, 4H), 3.58 (s, 3H), 4.7–6.0 ppm (m, 3H); $[\alpha]_D^{25}$ (l = 1) + 3.37 (neat). CIMS: *m/e* 226 GLC analysis showed that compound **18** was contaminated by *ca* 10% of 1,13-tetradecadiene. Compound **18** was used in the next step without any further purification.

(R)-3-*Methyl*-11-*dodecen*-1-*ol* (**19**). A soln of **16** (12.37 g, 54.7 mmol) in dry ether (80 ml) was slowly added to a stirred suspension of LAH (2.98 g, 78.5 mmol) in ether (50 ml). The mixture was refluxed for 5 hr and then poured into ice-water. Usual work-up gave **19** (10.0 g, 92% yield): b.p. 97°/0.3 torr; $[\alpha]_D^{25}$ + 4.63 (*c* = 10.33, hexane). IR (film): ν_{max} 3350, 3080, 2930, 2855, 1640, 1460, 1435, 1375, 1055, 990, 905, 840, 720 cm^{-1}. ^{1}H-NMR (CCl_4): δ 0.88 (br d, 3H), 1.1–1.7 (br m, 15H), 1.8–2.2 (br m, 3H), 3.55 (t, 2H), 4.7–6.1 (m, 3H). (Found: C, 78.95; H, 13.42. Calc for $C_{13}H_{26}O$: C, 78.72; H, 13.21%.) GLC analysis showed that **19** had chemical purity higher than 99%.

(R)-3-*Methyl*-11-*dodecen*-1-*ylmesylate* (**20**). MsCl (6.30 g, 54.95 mmol) was added to a stirred soln of **19** (9.91 g, 50 mmol) in dry CH_2Cl_2 (250 ml) containing Et_3N (10.44 ml, 75 mmol) cooled at −15°. The stirring was continued for 6.5 hr at 0° ~ 5°. The mixture was poured into ice–dil HCl and extracted with CH_2Cl_2. The extract was washed with dil HCl, dil $NaHCO_3$ aq, water, and dried. Concentration *in vacuo* afforded crude **20** (13.69 g, quantitative yield) which was used in the next step without any further purification.

(S)-10-*Methyl*-1-*tridecene* (**16**). A soln of Me_2CuLi was prepared by adding a 1.8 N ether soln of MeLi (123.8 ml, 221 mmol) to a stirred suspension of CuI (21.59 g, 111.6 mmol) in

dry ether (170 ml) at −25° under N_2. A soln of **20** (13.69 g, 50 mmol) in dry ether (80 ml) was added to the stirred and cooled soln of $(CH_3)_2CuLi$ at −40°. The mixture was stirred at −40° for 4 hr, then the temp was slowly raised to −10°. The mixture was poured into sat NH_4Cl aq, stirred for 1 hr and extracted with ether. The ether extract was washed with NH_4Cl aq and water, dried and concentrated. Fractional distillation of the residue gave (*S*)-**16** (8.65 g, 88% yield): b.p. 74–75°/0.6 torr; $[\alpha]_D^{25}+1.77$ (c = 13.69, THF). The IR and ^{1}H-NMR spectra resulted identical to those of (*R*)**16**. GLC analysis showed that (*S*)-**16** had chemical purity higher than 99%.

(2RS, 10R)- *and* (2RS, 10S)-10-*Methyl-2-tridecanol*, (**17a**) *and* (**17b**), *respectively*. A soln of (*S*)-**16** (6.15 g, 31.4 mmol) in THF (57 ml) was added dropwise to a stirred soln of $Hg(OAc)_2$ (12.0 g, 37.6 mmol) in water (57 ml) cooled at 0°. The resulting mixture was stirred under N_2 for 2 hr at room temp. To the mixture cooled at 0° was added 3N NaOH (108 ml) and then a soln of $NaBH_4$ (1.70 g, 44.9 mmol) in 3N NaOH (45 ml). The final mixture was stirred for 20 min at room temp, diluted with water, and extracted with hexane. The extract was dried and concentrated. The residue was chromatographed on a Merck H 60 silica gel column, using a mixture of hexane/ether (4 : 1) as eluant to give (2*RS*, 10*S*)-**17b** (4.55 g, 68% yield): b.p. 116°/1.5 torr; $[\alpha]_D^{25}+1.76$ (c = 12.76, hexane). Lit.[15] b.p. 63–65°/0.04 torr. IR (film): ν_{max} 3350, 2960, 2920, 2850, 1460, 1375, 1300, 1235, 1215, 1090, 935, 840, 735, 720 cm^{-1}. ^{1}H-NMR (CCl_4): δ 0.8–1.0 (br m, 9H), 1.1–2.1 (br, 19H), 3.75 ppm (br m, 1H).

In a similar way (*R*)-**16** (5.30 g, 27.1 mmol) was converted into (2*RS*, 10*R*)-**17a** (65% yield): b.p. 96–97°/0.2 torr; $[\alpha]_D^{25}$ −1.76 (c = 12.49, hexane). GLC analysis showed that (2*RS*, 10*R*)-**17a** had 98.7% chemical purity and that (2*RS*, 10*S*)-**17b** was chemically pure.

(R)- *and* (S)-10-*Methyl-2-tridecanone*, (**1a** *and* **1b**), *respectively*. A soln of $Na_2Cr_2O_7$ (3.29 g, 11.04 mmol) in water (17 ml) and conc H_2SO_4 (4.44 ml) was added in 30 min to a soln of (2*RS*, 10*S*)-**17b** (3.80 g, 17.76 mmol) in ether (44 ml). The resulting mixture was stirred for 4 hr, then diluted with water, and extracted with ether. The ether extract was washed with aq $NaHCO_3$ soln, and water, dried, and concentrated. Fractional distillation gave (*S*)-**1b** (3.55 g, 94.3% yield): b.p. 98–99%/0.5 torr; $[\alpha]_D^{24}+1.65\pm0.02$ (c = 9.360, $CHCl_3$). IR (film): ν_{max} 2960, 2930, 2860, 1720, 1465, 1455, 1375, 1355, 1160, 1120, 940, 735, 715 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.9 (br m, 6H), 1.1–2.0 (br, 17H), 2.12 (s, 3H), 2.43 (t, 2H). The IR and ^{1}H-NMR spectra resulted identical to those of an authentic sample of (*S*)-**1b**.[15] GLC analysis showed that (*S*)-**1b** was 100% chemically pure.

In a similar way (2*RS*, 10*R*)-**17a** was converted in 96% yield into (*R*)-**1a**: b.p. 93°/0.3 torr. GLC analysis showed that (*R*)-**1a** had 98% chemical purity. Therefore it was purified by preparative GLC using a 7% Carbowax 20 M + 2% KOH column (3 m). A sample of (*R*)-**1a** so purified (100% chemical purity) had: $[\alpha]_D^{24}-1.64\pm0.02$ (c = 9.390, $CHCl_3$). Lit.[15] $[\alpha]_D^{24}-1.71$ (c = 9.35, $CHCl_3$).

Methyl (R)-5-*mesyloxy*-3-*methylpentanoate* (**21**). MsCl (12.93 g, 113 mmol) was added to a stirred soln of **8** (15.0 g, 102.7 mmol) in dry CH_2Cl_2 (500 ml) containing Et_3N (21.43 ml, 154 mmol) cooled at −15°. The mixture was stirred for 5.5 hr at 0° ~ 5°, poured into ice–dil HCl, and extracted with CH_2Cl_2. The extract was washed with dil HCl, dil $NaHCO_3$ aq, water, and dried. Concentration at 20 torr and room temp afforded crude **21** (22.96 g, quantitative yield) as an oily substance which was used in the next step without any further purification.

(R)-3-*Methyl*-1-*pentanol* (**6**). A soln of (*R*)-**21** (22.96 g, 102 mmol) in dry ether (150 ml) was added during 1 hr to a stirred suspension of LAH (10.13 g, 267 mmol) in ether (250 ml) under N_2. The mixture was refluxed overnight, then carefully poured into ice-water, acidified with 10% H_2SO_4, and extracted with ether. The ether extract was washed with $NaHCO_3$ aq, and water, dried, and concentrated. Fractional distillation of the residue afforded (*R*)-**6** (7.48 g, 71.9 yield): b.p. 99°/97 torr, $[\alpha]_D^{20}$ −8.67 ± 0.02 (neat). Lit.[23] b.p. 152–153°; $[\alpha]_D^{20}+8.77$ (neat) for the (*S*)-enantiomer; $[\alpha]_D^{20}-8.5$ (neat) for (*R*)-**6**.[4] GLC analysis showed that (*R*)-**6** was chemically pure.

(R)-3-*Methylheneicosanoic acid* (**23**). According to the procedure employed to prepare (*S*)-**23**, stearic acid (40 g, 0.14 mmol) was electrolysed with (*R*)-**2** (10.66 g, 66 mmol) in MeOH (230 ml) and hexane (200 ml), in the presence of KOMe (prepared from 0.7 of K) at about 2 amp for 3 hr. The mixture was then cooled and filtered, and the filtrate diluted with water. The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with dil K_2CO_3 aq, and water, and concentrated *in vacuo*. Water (35 ml), ethanol (420 ml) and KOH (42.2 g) were added to the residue and the resulting mixture was refluxed for 5 hr. Water (250 ml) was then added and the mixture was extracted with ether. The aqueous EtOH soln was acidified with dil HCl and extracted with ether. Concentration of the dried ether extract afforded crude (*R*)-**23** which was crystallized from acetic acid (5.64 g, 25% yield): m.p. 56.5–57.5°; $[\alpha]_D^{10}+3.66\div4.00$ (c = 3.00, $CHCl_3$). Found: C, 77.90; H, 13.32. Calc for $C_{22}H_{44}O_2$: C, 77.58; H, 13.02%. Lit.[24] m.p. 56.9°; $[\alpha]_D^{10}-3.8$ (c = 3.00, $CHCl_3$) for (*S*)-**23**.

(R)-3-*Methyl*-1-*heneicosanol* (**24**). A soln of (*R*)-**23** (4.23 g, 12.4 mmol) in dry ether (100 ml) was slowly added to a stirred suspension of LAH (0.68 g, 15.5 mmol) in ether (30 ml). The mixture was refluxed for 9 hr. Usual work-up afforded crude (*R*)-**24** as a solid which was crystallized from hexane (3.76 g, 93% yield): m.p. 50.5–51.5°; $[\alpha]_D^{25}+2.2\div2.4$ (c = 5.00, $CHCl_3$). Found: C, 80.59; H, 14.37. Calc for $C_{22}H_{46}O$: C, 80.90; H, 14.20%. MS: *m/e* 326 (M^+).

(R)-1-*Iodo*-3-*methylheneicosane* (**25**). A mixture of (*R*)-**24** (7.45 g, 22.8 mmol), I_2 (3.36 g) and red P (238 mg) was maintained at 145° for 6 hr in the dark, and then for 12 hr at room temp. The mixture was extracted with ether and the extract was washed with water, 5% NaOH aq, water, aq $NaHSO_3$, and water, then dried and concentrated *in vacuo*. The solid residue was crystallized from acetone to give (*R*)-**25** (9.07 g, 91.2 yield): m.p. 31.5–32°; $[\alpha]_D^{25}-6.6\div-6.8$ (c = 5.00, $CHCl_3$). MS: *m/e* 436 (M^+). Found: C, 60.29; H, 10.62; I, 29.30. Calc for $C_{22}H_{45}I$: C, 60.53; H, 10.39, I, 29.07%.

(R)-5-*Methyl*-1-*tricosyne* (**7**). A soln of LiC≡CH · EDA in dry DMSO (15 ml) was added to a suspension of (*R*)-**25** (8.86 g, 20.3 mmol) in DMSO (100 ml) cooled at 0°. The mixture was stirred for 0.5 hr at 0° and then at room temp for 22 hr. Water (100 ml) was then added and the resulting mixture was extracted with ether. The ether extract was washed with sat HaCl aq, and water, dried, and concentrated *in vacuo* to afford a solid. This was recrystallized from EtOH to give (*R*)-**7** (5.9 g, 68.9% yield): m.p. 28.5–29.5°; $[\alpha]_D^{25}+2.66$ (c = 6.00, hexane). MS: *m/e* 334 (M^+). IR (film) ν_{max} 3300, 2950, 2840, 2100 cm^{-1}. (Found: C, 85.96; H, 13.68. Calc for $C_{24}H_{46}$: C, 86.14; H, 13.86%.)

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