Bakers' Yeast Mediated Preparation of (*S*)-3-(2-Furyl)-2-methylpropan-1-ol, a Bifunctional Chiral C_5 Isoprenoid Synthon: Synthesis of (4*R*,8*R*)-4,8-Dimethyldecanal, a Pheromone of *Tribolium castaneum*

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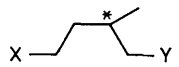
Bakers' yeast reduction of the α,β-unsaturated aldehyde (**4**), leads to the preparation of the bifunctional chiral synthon (**2**) in enantiomerically pure form and high chemical yield. The mechanism of the reduction is discussed. The usefulness of the chiral synthon (**2**) is exemplified by its transformation into optically pure (*S*)-3-methyl-γ-butyrolactone (**8**) and by the synthesis of (4*R*,8*R*)-4,8-dimethyldecanal, the pheromone of *Tribolium castaneum*.

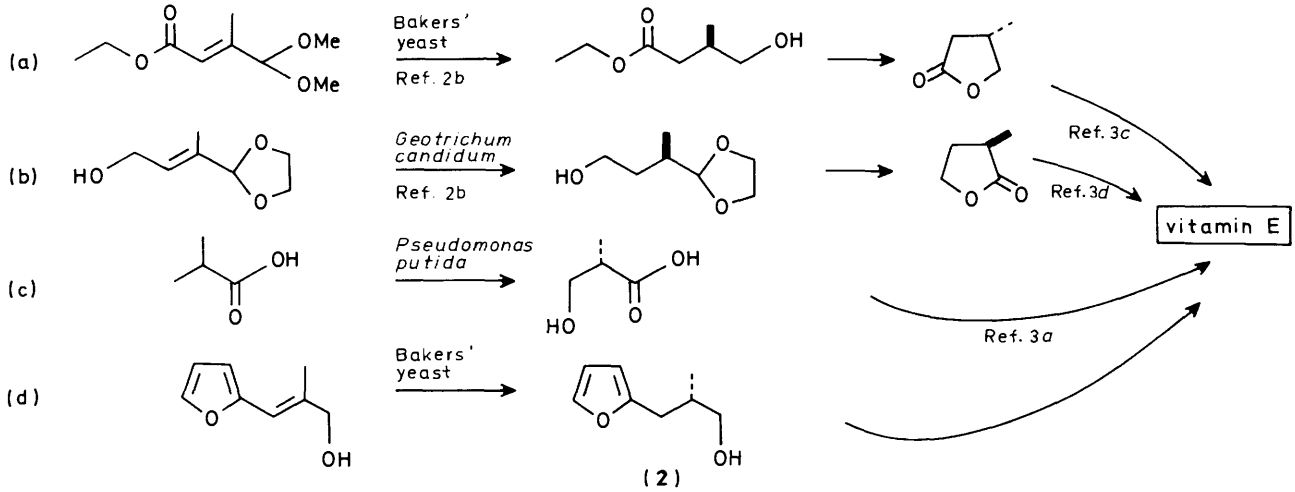
The chiral isoprenoid unit (**1**) is found in natural products of both synthetic and biological interest: *e.g.* tocopherol, phylloquinones, phytol, and insect pheromones.[1] Several synthetic equivalents for this unit (**1**) have, therefore, been developed[2] from different sources, generally advantage being taken of stereoselective transformations performed by micro-organisms on achiral or racemic substrates.



(**1**)

Many of these synthons have been used for the synthesis of the side chain of α-tocopherol and in Scheme 1 the key step microbial transformations which eventually led to optically active α-tocopherol are outlined.[3,4] Of the approaches shown in Scheme 1, three (a), (b), and (d) refer to stereospecific reduction of triply substituted double bonds and a fourth (c) to asymmetric oxidation of a prochiral substrate. Furthermore, there are some alternative approaches to the chiral C_5-unit (**1**) and chiral dimers of this using microbial transformations,[5a–d] resolution[5e] or carbohydrate starting materials.[5f]

Reaction (d) of Scheme 1, shows synthon (**2**) used by two of us some years ago in the total synthesis of α-tocopherol.[3e–4e] Preparation of (**2**) was then briefly described. Here we disclose full experimental details of the preparation of (**2**) and show how this compound can be considered an ideal chiron of type (**1**), following these observations. (i) The alcohol (**2**) can be prepared in excellent chemical yield from the readily available aldehyde (**4**) on a hundred gram scale. (ii) The optical purity of (**2**) and derived compounds is virtually 100%. (iii) Unlike the other synthons described in Scheme 1, (**2**) is a bifunctional chiral intermediate which does not need protective manipulation in that the furan ring can be seen as a carbonyl-protecting group and selectively removed; this permits chain elongation at both ends of the molecule. Indeed the synthetic utility of (*S*)-3-(2-furyl)-2-methylpropan-1-ol (**2**) rests on the fact that the functionalities can be used in a different order. Direct



Scheme 1.

ozonization with oxidative work-up should lead to the known lactone (**8**) which has previously been used in synthesis.[6] Alternatively, the alcohol functional group could be used to modify the side chain and the furan ring ozonized at a later stage.

Microbial reductions of α- and/or β-substituted acroleins are well documented.[7] Substrates of type (**5**) have previously been

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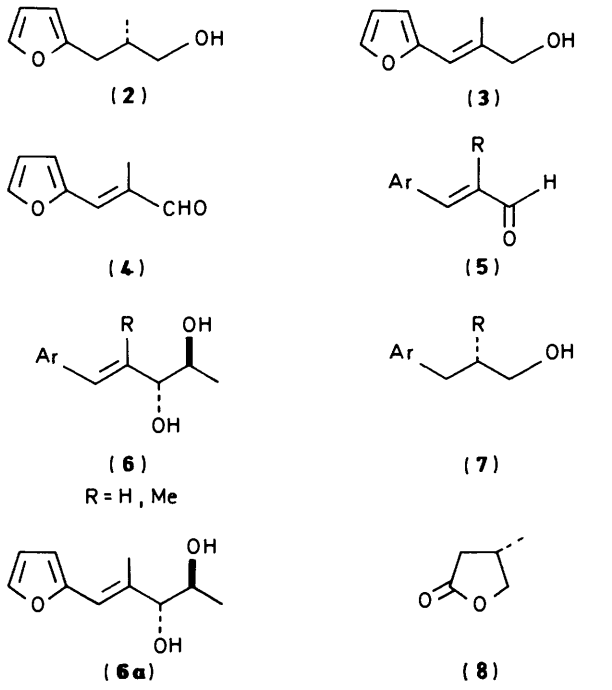


studied by some of us and were found to give chiral alcohols of type (7) along with chiral diols of type (6).[7b,c] Thus, as previously reported in the preliminary communication,[4e] α-methyl-β-(2-furyl)acrolein (4) gives (*S*)-3-(2-furyl)-2-methylpropan-1-ol (2) and the (2*S*,3*R*)-diol (6a); the latter was then used for the synthesis of the chiral C_{14} chromanyl-unit used on our tocopherol synthesis.[4e]

We have now extended the study of the formation of the furylmethylpropanol (2) and present a further application of its use as a synthetic equivalent for the unit (1) in a synthesis of (4*R*,8*R*)-4,8-dimethyldecanal (13) a pheromone component isolated from the red flour beetle, *Tribolium castaneum*.[8]

Results and Discussion

We found that (*S*)-3-(2-furyl)-2-methylpropan-1-ol (2) could be prepared in good yield (72%) and excellent optical purity (>99%) by reducing the furylmethylacrolein (4) with bakers' yeast at pH 5—5.5 rather than running the reaction in a phosphate buffer at pH approximately 7 as prescribed in the preliminary communication.[4e]

The chemical yield of the furylmethylpropanol (2) is slightly pH-dependent. Thus reactions at pH 3—3.5, 5—5.5, and 6.5—7.7 gives 40, 70, and 30% yield respectively when allowed to react for 4 days at room temperature. However, running these reactions to completion [<5% of unsaturated (3) left] leads to 60, 72, and 55% isolated yields of (2) respectively (reaction times 8, 5, and 8 days respectively).

The optical purities of the fermentation product (2) were high at all pH's investigated. Thus reactions at pH 3—3.5, 5—5.5, and 6.5—7.5 gave >98, >99, and 95% e.e. respectively as determined from the n.m.r. spectra of their esters with (−)-(*S*)-methoxy(trifluoromethyl)phenylacetic acid (MTPA) using the technique described previously for other 2-methylalkan-1-ols.[9]

The fermentation reaction was followed by gas chromatography. The furylacrolein (4) is almost completely transformed into the unsaturated alcohol (3) within 1 h (see Figure). The furylmethylpropanol (2) subsequently appears slowly and reaches a maximum after 4—6 days under the reaction conditions used. Extractive work up followed by distillation gives a 72% yield of virtually optically pure (2). The previously

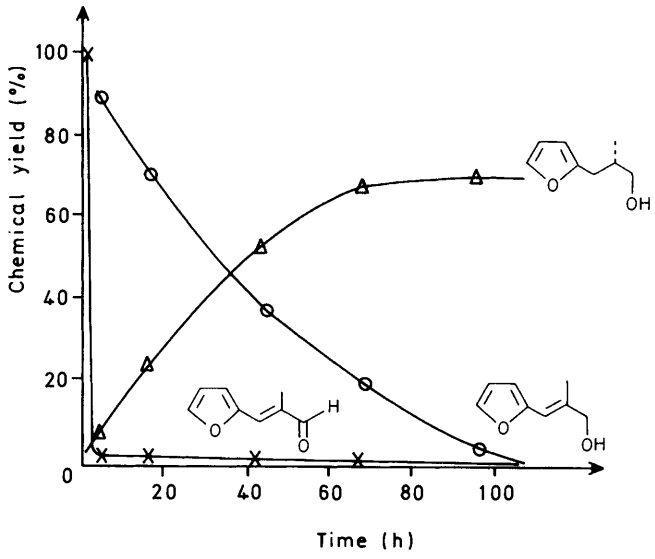
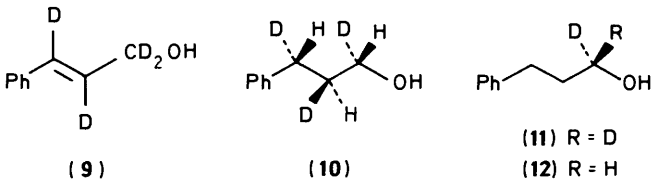
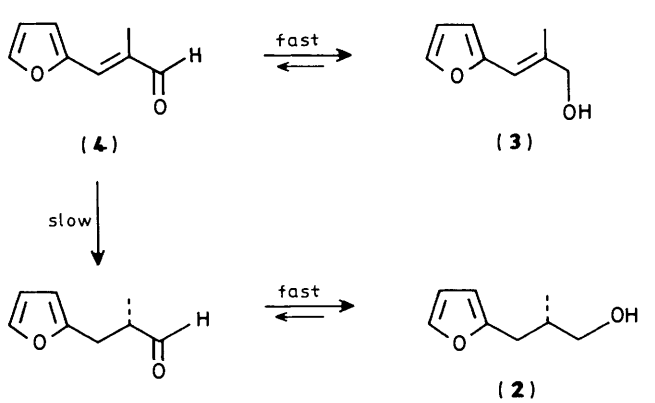


Figure.



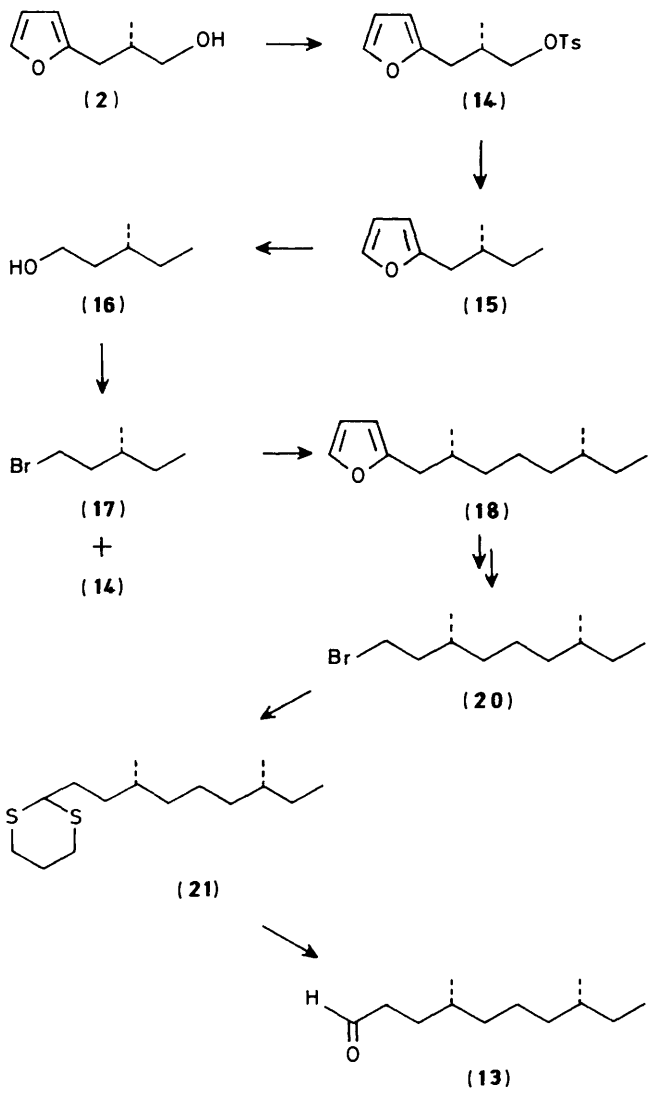
mentioned (2*S*,3*R*)-diol (6a) was isolated optically pure in 15% overall yield by chromatography of the distillation residue.

Although it may seem that the unsaturated alcohol (3) is the immediate precursor for the saturated alcohol (2) this is not the case, since running the reaction under anaerobic conditions inhibits the formation of (2). Furthermore, some of us have earlier shown that the tetradeuteriated cinnamyl alcohol (9) on treatment with bakers' yeast gives the trideuteriated phenylpropanol (10)[7a] and that the dideuteriated phenylpropanol (11) is slowly converted[10] into the monodeuteriated alcohol (12) when treated with yeast alcohol dehydrogenase and NAD^+. Applied to the case at hand, these results are best explained by the reaction sequence depicted in Scheme 2. The unsaturated alcohol (3) is first oxidized to the aldehyde (4), after which the double bond is reduced by *trans* addition of hydrogen (the hydrogen atom in the 2-position is added *pro-R*). The resulting saturated aldehyde is then reduced by addition of a *pro-R* hydrogen atom. The aldehyde–alcohol equilibria are shifted strongly towards the alcohol under the reaction conditions.



Scheme 2.

Having established optimal conditions for the large-scale preparation of optically pure (*S*)-3-(2-furyl)-2-methylpropan-1-ol (**2**) this enabled us to use it as a chiral starting material. Direct ozonization of the furylmethylpropanol (**2**) followed by treatment with performic acid gave optically pure (*S*)-3-methyl-γ-butyrolactone (**8**) in 86% yield. Revealing of the hidden functionality of the furan ring at a later stage is exemplified by the synthesis of (4*R*,8*R*)-dimethyldecanal (**13**) mentioned above. Although there are some earlier syntheses of this compound,[11] the strategy used in this work, consists of the coupling of two furylmethylpropanol units and addition of two C_1-units at each end (Scheme 3).



(2) (14) (16) (15) (17) + (14) (18) (20) (21) (13)

Scheme 3.

The furylmethylpropanol (**2**) was converted into the tosylate (**14**) and this was used twice in the synthetic sequence. First it was treated with methylmagnesium bromide in the presence of dilithium tetrachlorocuprate to give (*R*)-1-(2-furyl)-2-methylbutane (**15**). Ozonization of this followed by reductive work-up furnished the known (*S*)-3-methylpentan-1-ol (**13**), $[\alpha]_D^{20}$ −8.2° (lit.,[12b] +7.94° for the antipode), which on treatment with *N*-bromosuccinimide and triphenylphosphine gave the corresponding known bromide (**17**), $[\alpha]_D^{20}$ −19.5° (lit.,[12a] −19.9°). The tosylate (**14**) was used for a second time when treated with the Grignard reagent from the bromide (**17**) in the presence of Li_2CuCl_4. The product, (2*R*,6*R*)-1-(2-furyl)-2,6-dimethyloctane (**18**) was ozonized and the ozonide reduced to afford an alcohol which was converted into the corresponding bromide (**20**). This was treated with 1,3-dithiane and the resulting dithioacetal (**21**) was cleaved by mercuric oxide and boron trifluoride–diethyl ether to afford the desired (4*R*,8*R*)-4,8-dimethyldecanal (**13**), $[\alpha]_D^{20}$ −7.0° (lit.,[11c] −7.3°).

Experimental

^{1}H N.m.r. spectra were recorded at 90 MHz unless otherwise stated. Chemical shifts are in p.p.m. (δ) relative to internal Me_4Si. Optical rotations were recorded on a Jasco DIP-181 digital polarimeter. Purification of products was performed by flash chromatography on silica gel (Merck 60, 0.040—0.063 mm) with mixtures of hexane and ethyl acetate. Analytical samples were prepared by bulb-to-bulb distillation under reduced pressure.

(S)-3-(2-*Furyl*)-2-*methylpropan*-1-*ol* (**2**).—A 40-l open cylindrical glass vessel equipped with a mechanical stirrer was charged with tap water (24 l) and the temperature was adjusted to 35 °C. Fresh bakers' yeast (2.5 kg) was parted in small pieces and added to the stirred water. Glucose (1.25 kg) was added and fermentation allowed to proceed for 3 h. After this the pH was adjusted to 5—5.5 by addition of saturated aqueous sodium carbonate and α-methyl-β-(2-furyl)acrolein (**4**)[13] (75 g) dissolved in ethanol (200 ml) was added from a dropping funnel during 15 min. A slow stream of air was passed through the vigorously stirred solution from this point on. Since the pH usually increased during the first few hours hydrochloric acid (1M) was used to adjust it to 5—5.5. After 1 h only a trace (*ca.* 2%) of the starting aldehyde was present and it remained at this level until the reduction was complete. The initial product formed 3-(2-furyl)-2-methylprop-2-en-1-ol (**3**) (which served equally well as starting material) was then slowly transformed into the final product (**2**) as judged by gas chromatography (see Figure). The following morning additional yeast (1.25 kg) and glucose (0.63 kg) was added and the pH adjusted to 5—5.5 as described above. Days 3 and 4 the same procedures were repeated (0.6 and 0.3 kg yeast and 0.3 and 0.15 kg glucose respectively and pH-control). Day 5 the reaction was checked by g.c. and if the compound (**2**):(**3**) ratio was higher than 95:5 the reaction was worked up; otherwise, the same procedure as day 4 was repeated each day until the reaction was complete. Diethyl ether (10 l) was added to the mixture which was then vigorously stirred for 10 min. The layers were allowed to separate and the water phase was decanted off by suction. The water phase was then extracted again with ether (2 × 5 l). The combined ether phases were dried (Na_2SO_4) and evaporated to an oil (70 g) which was distilled through a 10 cm Vigreux column to give the title compound (**2**) (56 g, 72%), b.p. 54—56 °C/0.8 mmHg, 101—103 °C/15 mmHg, $[\alpha]_D^{20}$ −17.0° (neat), −18.5° (*c* 8 in MeOH); δ(250 MHz, $CDCl_3$) 0.95 (d, 3 H, *J* 6.9 Hz), 2.02 (distorted octet, 1 H, *J ca.* 7 Hz), 2.55 (dd, 1 H, *J* 7.3 and 14.8 Hz), 2.73 (dd, 1 H, *J* 6.4 and 14.8 Hz), 3.50 (d, 2 H, *J* 6.0 Hz), 6.02 (dd, 1 H, *J* 0.7 and 3.2 Hz), 6.29 (dd, 1 H, *J* 1.8 and 3.2 Hz), and 7.31 (dd, 1 H, *J* 0.7 and 1.8 Hz) (Found: C, 68.45; H, 8.75. $C_8H_{12}O_3$ requires C, 68.54; H, 8.62%).

(2S,3R)-5-(2-*Furyl*)-3-*methylpent*-4-*ene*-2,3-*diol* (**6a**). The distillation residue from above was chromatographed on silica gel: 20—40% ethyl acetate in hexane eluted (**6a**) as an oil (15.2 g, 15%) (Found: C, 66.0; H, 7.71. $C_{10}H_{14}O_3$ requires C, 65.91; H, 7.74%), $[\alpha]_D^{20}$ −22.4° (*c* 2 in $CHCl_3$), $[\alpha]_D^{20}$ +14.2° (*c* 2.5 in MeOH); δ($CDCl_3$) 1.17 (d, 3 H, *J* 7 Hz), 2.0 (s, 3 H), 3.2 (br s, 2 H, –O*H*), 4.0 (m, 1 H), 4.2 (m, 1 H), 6.5 (m, 2 H), and 7.4 (d, 1 H).

Bakers' Yeast Reduction at Different pH *Values.*—These fermentations were performed as above but scaled down to 5 g of starting furylacrolein (**4**) and were run in wide beakers at room temperature without blowing air through. Work-up after 4 days as above gave 30% (pH 3—3.5), 70% (pH 5—5.5), and 30% (pH 6.5—7.5). Extended reaction times led to higher isolated yields as mentioned in the discussion.

Ester of (S)-3-(2-*Furyl*)-2-*methylpropan*-1-*ol with* (S)-(−)-*MTPA*).—(*S*)-3-(2-Furyl)-2-methylpropan-1-ol (**2**) (140 mg, 1 mmol), (S)-(−)-MTPA (468 mg, 2 mmol), and triphenylphosphine (524 mg, 2 mmol) were stirred in dry tetrahydrofuran (10 ml) under nitrogen at 0 °C. Diethyl azodicarboxylate (0.312 ml, 2.2 mmol) was added dropwise *via* a syringe. The mixture was warmed to 20 °C and stirred 2 h after which diethylene glycol (0.1 ml) was added to quench the excess of reagents. The THF solution was evaporated on silica gel (3 g) and chromatographed (silica gel, flash, 20 g). Ethyl acetate in hexane (0.5—1.5%) eluted an oil which was distilled bulb-to-bulb (bath temp. 130 °C/0.1 mmHg) to give the pure ester (330 mg, 95%); δ(250 MHz, $CDCl_3$) 0.95 (d, 3 H, *J* 6.9 Hz), 2.26 (distorted octet, 1 H, *J ca.* 7 Hz), 2.54 (dd, 1 H, *J* 6.9 and 14.7 Hz), 2.67 (dd, 1 H, *J* 6.5 and 14.7 Hz), 3.55—3.57 (m, 3 H), 4.12 (dd, 1 H, *J* 5.8 and 10.7 Hz), 4.24 (dd, 1 H, *J* 5.5 and 10.7 Hz), 5.99 (dd, 1 H, *J* 0.7 and 3.2 Hz), 6.28 (dd, 1 H, *J* 1.8 and 3.2 Hz), 7.31 (dd, 1 H, *J* 0.7 and 1.8 Hz), and 7.3—7.6 (m, 5 H). Irradiation at δ 2.26 p.p.m. [$CH_2CH(CH_3)CH_2$] gave two doublets (*J* 10.7 Hz) at δ 4.12 and 4.24 p.p.m. [$CH(CH_3)CH_aH_bOMTPA$]. The ester with *R*-(+)-MTPA had an identical spectrum except that the methyl doublet was at 0.96 p.p.m. and the CH_aH_b-OMTPA appeared at δ 4.180 (dd, 1 H, *J* 5.8 and 11.0 Hz) and 4.204 p.p.m. (dd, 1 H, *J* 6.0 and 11.0 Hz). When the spectrum of the *R*-ester was irradiated at δ 2.26 p.p.m. the two doublets of doublets around 4 p.p.m. were transformed into essentially two peaks at 4.184 and 4.196 p.p.m. with very small bands at 11 Hz distance on both sides (less than 10% of total intensity). The optical purity of each sample was determined by observing the peaks due to the $CH(CH_3)CH_aH_bOMTPA$ while irradiating at δ 2.26 p.p.m. The area under the peaks observed at δ 4.16—4.21 p.p.m. was compared with the area of the two doublets at δ 4.12 and the area under the peaks observed at δ 4.16—4.21 p.p.m. was compared with the area of the two doublets at δ 4.12 and 4.24 p.p.m. (*cf.* ref. 10. The optical purities were >98% (pH 3—3.5), >99% (pH 5—5.5), and around 95% (pH 6.5—7.5).

(S)-(−)-*Dihydro*-4-*methylfuran*-2(3H)-*one*, (S)-(−)-3-*Methyl*-γ-*butyrolactone* (**8**).—(*S*)-3-(2-Furyl)-2-methylpropan-1-ol (**2**) (10.0 g, 70.4 mmol) was dissolved in dichloromethane (10 ml) and the solution cooled to −60 °C. A stream of ozone was passed into the solution. When all the starting material had reacted (t.l.c.) the ozonization was stopped and the mixture was brought to −10 °C when formic acid (120 ml) was added and the ozonization was continued for a further hour at this temperature. The solution was then slowly heated to 90 °C whereupon the dichloromethane was evaporated off. After cooling and addition of hydrogen peroxide (30%; 4 ml) the mixture was slowly heated to 90 °C. After cooling Pd–C (10%; 40 mg) was added and the mixture again heated to 90 °C. After cooling the formic acid was evaporated off and the residue distilled to give the title compound (6.05 g, 86%), b.p. 87—89 °C/15 mmHg (lit.,[2b] 88—89 °C/14 mmHg). A sample of more than 99.5% purity (g.c.) showed $[\alpha]_D^{20}$ −24.60° (neat), $[\alpha]_D^{20}$ −24.8° (*c* 4 in MeOH) (lit. $[\alpha]_D^{20}$ −24.6° (*c* 4 in MeOH) [2b] $[\alpha]_D^{20}$ −24.96° (*c* 1.7 in MeOH).[2c] Spectral data were in accord with the literature.[2b,c]

(S)-3-(2-*Furyl*)-2-*methylpropyl Toluene*-p-*sulphonate* (**14**).—Compound (**2**) (5.2 g, 37 mmol) was dissolved in anhydrous pyridine (25 ml) and treated under nitrogen at 0 °C whilst being stirred, with solid toluene-*p*-sulphonyl chloride (7.8 g, 41 mmol) in portions, during a period of 20 min; stirring was continued at room temperature for 3 h. The mixture was then poured into ice–water and extracted with diethyl ether (3 × 40 ml). The combined extracts were then thoroughly washed with saturated aqueous $KHSO_4$, dried (Na_2SO_4), and evaporated to give a slightly coloured oil. After flash chromatography compound (**14**) was obtained as an oil which solidified with time (9.9 g, 91%), m.p. 42—44 °C, $[\alpha]_D^{20}$ +6.97 (*c* 1 in $CHCl_3$) (Found: C, 61.25; H, 6.1. $C_{15}H_{18}O_4S$ requires C, 61.21; H, 6.17%); δ($CDCl_3$) 0.94 (d, 3 H), 2.2 (m, 1 H), 2.5 (s, 3 H), 2.6 (t, 2 H), 3.95 (d, 2 H), 5.95 and 6.3 (m, 2 H), and 7.3—7.9 (m, 5 H).

(R)-1-(2-*Furyl*)-2-*methylbutane* (**15**).—A stirred solution of compound (**14**) (6.8 g, 23 mmol) in dry THF (40 ml) was treated at −78 °C under nitrogen with a 3M solution of MeMgI in diethyl ether (16 ml, 46 mmol) and with a 0.1M solution of Li_2CuCl_4 in THF (10 ml, 1 mmol). The mixture obtained was allowed to reach room temperature and then stirred overnight. It was then poured into ice–water (200 ml) and extracted with ether (4 × 40 ml). The organic phase was washed with aqueous NH_4Cl and dried (Na_2SO_4). Flash-chromatography of the crude material obtained gave the title compound (**15**) (2.75 g, 68%), $[\alpha]_D^{20}$ −11.52 (*c* 2 in $CHCl_3$); δ($CDCl_3$) 0.9 (d, 3 H), 0.96 (t, 3 H), 1.3 (m, 2 H), 1.8 (m, 1 H), 2.55 (t, 2 H), 6 and 6.3 (m, 2 H), and 7.3 (m, 1 H) (Found: C, 78.05; H, 10.1. $C_9H_{14}O$ requires C, 78.21; H, 10.21%).

(R)-3-*Methylpentan*-1-*ol* (**16**).—Compound (**15**) (5.2 g, 37 mmol) dissolved in anhydrous methanol (45 ml) at −30 °C was treated with ozone until the starting material had disappeared (t.l.c.). Excess of ozone was eliminated with a stream of nitrogen. The solution evaporated to dryness, gave an oil which was dissolved in ethyl ether (30 ml) and added to a suspension of $LiAlH_4$ (2 g) in dry ethyl ether (40 ml) under nitrogen; the mixture was refluxed for 2 h. Excess of $LiAlH_4$ was quenched with ethyl acetate, ethanol, and a stoicheiometric quantity of water. The resulting solid was filtered off and washed with ether. Concentration of the dried extracts gave an oil (2.3 g, 60%) which was used in the subsequent steps without further purification. An analytical sample was distilled in a bulb-to-bulb apparatus: $[\alpha]_D^{20}$ −8.2° (*c* 1 in $CHCl_3$) {lit.,[12b] $[\alpha]_D^{20}$ +7.94 (neat antipode, rigorously dried}.

(R)-1-*Bromo*-3-*methylpentane* (**17**).—The alcohol (**16**) (2.1 g, 20.5 mmol) in dry CH_2Cl_2 (30 ml) was treated with PPh_3 (5.9 g, 22.6 mmol). *N*-Bromosuccinimide (4 g, 22.6 mmol) was then added portionwise in 20 min, while the temperature was kept within 15 and 20 °C. The mixture was stirred overnight at room temperature after which it was evaporated and the resulting solid triturated with hexane (5 × 20 ml). Evaporation of the solvent gave a residue which after bulb-to-bulb distillation yielded a colourless oil (2.9 g, 88%), $[\alpha]_D^{20}$ −19.43° (neat) {lit.,[12a] $[\alpha]_D^{20}$ −19.9° (*c* 1.7 in ether)}.

(2R,6R)-1-(2-*Furyl*)-2,6-*dimethyloctane* (**18**).—The tosylate (**14**) (3.23 g, 11 mmol) in anhydrous THF (30 ml) at −78 °C under a nitrogen atmosphere was treated with a Grignard reagent obtained from the bromide (**17**) (2.4 g, 14.5 mmol) and magnesium (1.2 g) in dry diethyl ether (35 ml). The mixture was then treated with a solution of Li_2CuCl_4 in THF (10 ml, 1 mmol) and allowed to reach room temperature; stirring was continued for 5 h. The mixture, treated in the usual way, gave after flash-chromatography compound (**18**) (1.34 g, 59%) as a colourless oil, $[\alpha]_D^{20}$ −4.62° (neat); δ($CDCl_3$) 0.6—1.0 (m, 9 H), 1—1.5 (m, 9 H), 1.7—2 (m, 1 H), 2.6 (t, 2 H), 6 and 6.3 (m, 2 H), and 7.3 (m, 1 H).

(3R,7R)-3,7-*Dimethylnonan*-1-*ol* (**19**).—Compound (**18**) (4.6 g, 22 mmol) was ozonized and the intermediate ozonide reduced with the procedure indicated for the preparation of the product (**15**). After work-up and bulb-to-bulb distillation, compound (**19**) was obtained (2.6 g, 68%) as a colourless oil, $[\alpha]_D^{20}$ −3.2° (neat); δ($CDCl_3$) 0.8—10 (m, 9 H), 1.1—1.8 (m, 13 H), and 3.85 (t, 2 H) (Found: C, 76.8; H, 14.2. $C_{11}H_{24}O$ requires C, 76.67; H, 14.04%).

(3R,7R)-1-*Bromo*-3,7-*dimethylnonane* (**20**).—The above alcohol (**19**) (2.4 g, 14 mmol) was transformed into the corresponding bromide (**20**) using the procedure described in the preparation of compound (**17**). Thus, after bulb-to-bulb distillation, compound (**20**) was obtained as a slightly coloured oil (2.7 g, 84%), $[\alpha]_D^{20}$ −11.9 (neat); δ($CDCl_3$) 0.7—1.0 (m, 10 H), 1.0—1.5 (m, 8 H), 1.5—2.0 (m, 3 H), and 3.4 (t, 2 H).

(3R,7R)-1-(1,3-*Dithiane*-2-*yl*)-3,7-*dimethylnonane* (**21**).—A solution of 1,3-dithian-2-yl-lithium in THF was prepared at −40 °C under nitrogen atmosphere from 1,3-dithiane (1.2 g, 10 mmol) in dry THF (20 ml) and n-BuLi (1.5M solution in hexane; 7.3 ml, 11 mmol), the mixture being stirred at −40 °C during 6 h. The bromide (**20**) (2.2 g, 9.34 mmol) in dry THF (5 ml) was then added, and the mixture stirred at −30 °C overnight. The solution was then diluted with water (120 ml) and extracted with CH_2Cl_2 (4 × 30 ml). Flash-chromatography of the crude material afforded compound (**21**) (2.35 g, 92%), $[\alpha]_D^{20}$ −8.3° (*c* 1 in $CHCl_3$); δ($CDCl_3$) 0.8—1.1 (m, 12 H), 1.1—2.2 (m, 13 H), 2.9 (m, 4 H), and 4.1 (t, 1 H) (Found C, 65.5: H, 10.95. $C_{15}H_{30}S_2$ requires C, 65.65; H, 11.02%).

(4R,8R)-4,8-*Dimethyldecanal* (**13**).—The product (**21**) (1.9 g, 6.9 mmol) was dissolved in THF–water (7 : 3; 15 ml) and treated with solid HgO (3 g, 13.8 mmol) and $BF_3{\cdot}Et_2O$ (1.7 ml, 13.8 mmol). The mixture was stirred overnight at room temperature after which it was diluted with water (50 ml) and the reddish precipitate filtered off. The mixture was next extracted with ethyl ether (4 × 25 ml) and the combined extracts washed with 10% aqueous KOH and water. Evaporation of the dried organic phase gave a crude oil which yielded after distillation the title compound (**13**) (730 mg, 58%), $[\alpha]_D^{20}$ −7.0° (*c* 2 in $CHCl_3$) [lit.,[12c] −7.3° (*c* 2, in $CHCl_3$)]. Spectral data were in accord with literature values.[12]

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