

Enzyme-Mediated Synthesis of (*S*)- and (*R*)-Verapamil

Elisabetta Brenna,^{*,[a]} Claudio Fuganti,^[a] Piero Grasselli,^[a] and Stefano Serra^[a]

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A lipase-mediated synthesis of (*S*)- and (*R*)-verapamil is described. The key steps of the synthetic sequence are the enantioselective acetylation, mediated by Lipase PS, of allylic alcohol (*Z*)-($\pm$)-**2**, affording the acetate derivative (*Z,R*)-($-$)-**3**

(*ee* 92%) and the Ireland–Claisen rearrangement of this latter and of its enantiomer (*Z,S*)-(+)-**3** (*ee* 92%) to afford acid derivatives (*E,R*)-($-$)-**4** (*ee* 94%) and (*E,S*)-(+)-**4** (*ee* 93%), precursors of (*S*)- and (*R*)-verapamil, respectively.

Introduction

Verapamil (**1**) belongs to the phenylalkylamine class of calcium channel blockers, characterized by a 5-amino-2-alkyl-2-phenylpentanenitrile moiety. It is widely used in racemic form for the treatment of vasospastic and classical angina pectoris and of supraventricular tachycardia. The two enantiomers of verapamil have different pharmacokinetic and pharmacodynamic properties.^[1] It has been shown that (*S*)-($-$)-**1** is more effective as a calcium channel blocker, while the *R* enantiomer is of potential interest for the treatment of multiple drug resistance during cancer therapy.^[2] Thus, the development of stereoselective strategies to both of the enantiopure forms of verapamil would be highly desirable.

Only two methods for the preparation of enantiopure ($-$)- and (+)-**1** have been reported in the literature. The first one^[3] was based on the classical resolution of diastereoisomeric salts of the key intermediate 3,4-dimethoxyphenyl-2-isopropyl-2-penten-4-oic acid by recrystallisation. A certain number of patents involving similar resolution procedures have also been registered.^[4]

The second synthetic pathway to the enantiopure forms of verapamil, adhering to the so-called strategy of the pool of chirality, employed optically active (2*S*)-(+)- and (2*R*)-($-$)-1,2-propanediol as starting materials.^[5] In 1996, a renewal of interest in the matter was witnessed after the appearance of a paper describing a quite general route for the synthesis of enantiomerically pure precursors of 5-amino-2-alkyl-2-phenylpentanenitrile, starting from commercially available chiral derivatives.^[6] Both enantiomers of noremapamil were prepared in 98% *ee*.

In the past we have been involved in the synthesis of optically active intermediates of verapamil by means of an approach mediated by bakers' yeast.^[7] Recently, we have successfully applied a lipase-catalysed stereoselective acetylation of allylic alcohols to the synthesis of chiral drugs^[8,9] and fragrances.^[10–13] We devised a possible means to exploit this kind of kinetic resolution for the preparation

of enantiopure (+)-**1** and ($-$)-**1**, and wish to report on the results of this research in this paper.

Results and Discussion

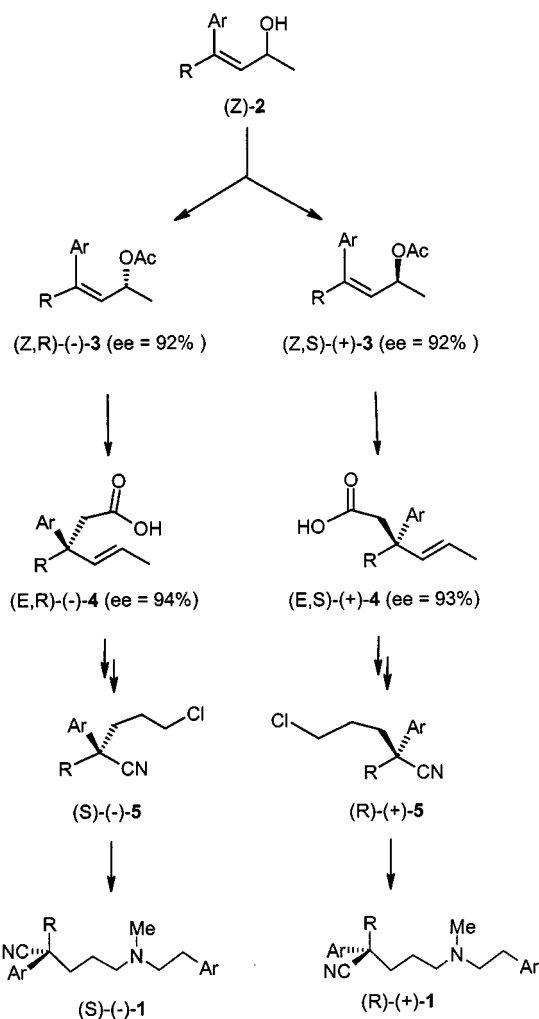
The first key step of our synthetic pathway (Scheme 1) is the enantioselective acetylation, mediated by Lipase PS, of allylic alcohol (*Z*)-($\pm$)-**2**, affording the acetate derivative (*Z,R*)-($-$)-**3**. The second is the Ireland–Claisen rearrangement of this latter, and of its enantiomer (*Z,S*)-(+)-**3**, to afford acid derivatives (*E,R*)-($-$)-**4** and (*E,S*)-(+)-**4**, respectively. By means of unexceptional but high-yielding organic reactions, we were able to homologate the CH₂COOR fragment into the CH₂CH₂CH₂Cl substituent, and to convert the propenyl unit into a CN group. Enantiomerically enriched chloro derivatives (*S*)-($-$)-**5** and (*R*)-(+)-**5** afforded (*S*)-($-$)-**1** and (*R*)-(+)-**1**, respectively, on treatment with *N*-methylhomoveratrylamine.^[3]

Racemic (*Z*)-**2** was prepared according to the synthetic procedure reported in Scheme 2. Condensation of 3,4-dimethoxyphenyl isopropyl ketone with acetonitrile in the presence of butyllithium afforded, after dehydration in toluene catalysed by 4-toluenesulfonic acid, a 1.5:1 mixture (¹H NMR) of (*Z*)- and (*E*)-**6**. DIBAL-H reduction to aldehydes (*Z*)- and (*E*)-**7** (1.4:1, GC-MS), followed by treatment with methylmagnesium bromide in THF, afforded a 1.5:1 mixture (GC-MS) of *Z* and *E* allylic alcohols **2**. Easy chromatographic separation of the corresponding acetate derivatives, followed by alcoholic potassium hydroxide saponification, allowed us to isolate racemic (*Z*)- and (*E*)-**2**.

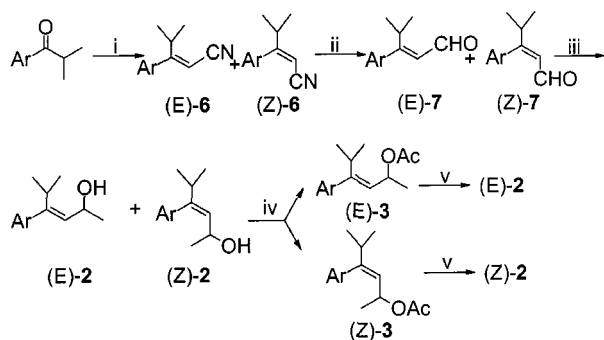
The stereochemistry of the double bond was defined by ¹H NMR spectra analysis: strong NOE effects were observed between H–C(5) and the vinylic hydrogen in derivative (*Z*)-**3**, and between H–C(5) and H–C(2) in derivative (*E*)-**3**.

Both the racemic allylic alcohols (*Z*)- and (*E*)-**2** were submitted to lipase-mediated acetylation. Biotransformation was observed only in the presence of Lipase PS as a catalyst, in diethyl ether solution, using vinyl acetate as an acyl donor. Other enzymes (such as *Candida rugosa* lipase and porcine pancreatic lipase) that had been active in the acetylation of disubstituted allylic alcohols^[10] did not con-

^[a] Dipartimento di Chimica del Politecnico, Centro CNR per la Chimica delle Sostanze Organiche Naturali, Via Mancinelli 7, 20131 Milano, Italy



Scheme 1. Ar = 3,4-dimethoxyphenyl; R = isopropyl.

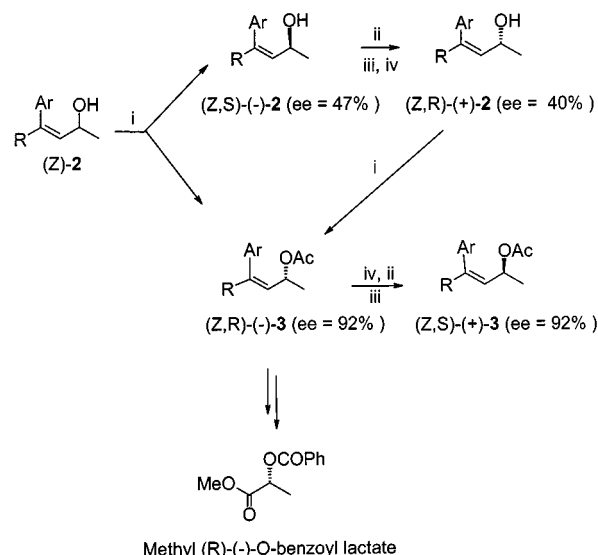


Ar = 3,4-dimethoxyphenyl

Scheme 2. i: acetonitrile, butyllithium, THF; 4-toluenesulfonic acid in toluene; ii: DIBAL-H in toluene; iii: methylmagnesium bromide in THF; iv: acetic anhydride in pyridine; column chromatography; v: KOH in methanol.

vert these trisubstituted allylic alcohol derivatives (Z)- and (E)-2 at all.

Alcohol derivatives (Z)-(+)-2 and (E)-(+)-2 gave (Z,R)-(-)-3 ($[\alpha]_D^{20} = -16$, $c = 1.05$, CH_2Cl_2 ; $ee = 92\%$, HPLC; $c^{[14]} = 34\%$, $E^{[14]} = 35$ after 108 h reaction time), and (E,R)-(+)-3 ($[\alpha]_D^{20} = 95$, $c = 1.48$, CH_2Cl_2 ; $ee = 92\%$, HPLC of the corresponding alcohol; $c = 45\%$, $E = 67$ after 24 h reaction time), respectively. In both cases the R configuration was assigned to C(-2); indeed, acetate derivative (Z,R)-(-)-3 was correlated to methyl (R)-(-)-O-benzoyl-lactate ($[\alpha]_D^{20} = -13.5$, $c = 3.2$ CHCl_3) through a synthetic path we have already described (Scheme 3).^[10]



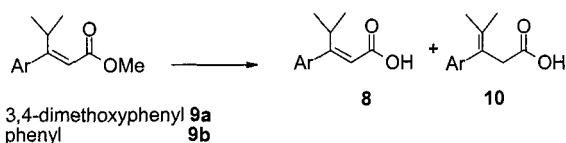
Scheme 3. i. Lipase PS, diethyl ether, vinyl acetate; column chromatography; ii. 4-toluenesulfonyl chloride, pyridine; iii. sodium acetate in dimethylformamide; iv. KOH in methanol.

Kinetic resolution of (Z)-(+)-2 was very slow: conversion had only reached 34% even after 108 h reaction time. Accordingly, access to (Z,S)-(+)-3 by chemical acetylation of the surviving alcohol (Z,S)-(-)-2 ($ee = 47\%$, HPLC) could not be satisfactorily achieved. Inversion of the configuration of the stereogenic carbon atom of the enzymically acetylated product was performed (Scheme 3): saponification of (Z,R)-(-)-3, followed firstly by treatment with 4-toluenesulfonyl chloride in pyridine and then by acetate displacement, gave (Z,S)-(+)-3 ($ee = 92\%$). In order to limit the quantity of waste material, and to enrich the starting alcoholic mixture in the enantiomer transformed effectively by Lipase PS, alcohol (Z,S)-(-)-2 ($ee = 47\%$, HPLC) was submitted to same procedure to yield (Z,R)-(+)-2 ($ee = 40\%$). Starting from 50 g of (Z)-(+)-2, nearly 30 g of (Z,R)-(-)-3 ($ee = 92\%$) were recovered: half of this quantity was used to prepare (Z,S)-(+)-3 ($ee = 92\%$, HPLC).

When derivative (E,R)-(+)-3 ($ee = 92\%$) was subjected to rearrangement conditions according to Ireland's procedure,^[15] racemic acid (E)-4 (identified by HPLC of the corresponding methyl ester) was obtained. The acetate derivative recovered unchanged from this reaction was found to be a 6:4 mixture (GC-MS) of (E,R)-(+)-3 ($ee = 92\%$, HPLC

of the corresponding alcohol) and (*Z,R*)-(-)-**3** (*ee* = 90%, HPLC). Thus, the racemisation occurring during the sigmatropic rearrangement could be attributed to the isomerisation of the double bond, probably promoted by the basic medium of the Ireland reaction. It is known^[16] that Claisen-type rearrangement of diastereoisomeric allylic alcohols that display the same configuration at the stereogenic carbon atom and opposite configuration at the double bond affords the two enantiomers of the corresponding γ,δ -unsaturated ester derivative.

We then found evidence of the peculiar mobility of this double bond towards the isopropyl unit while we were attempting the synthesis of acid **8** (to be used as a precursor of alcohol **2**) by saponification with alcoholic potassium hydroxide of ester **9a** (Scheme 4). A 6:4 mixture of the two regioisomer **8** and **10** was invariably obtained.



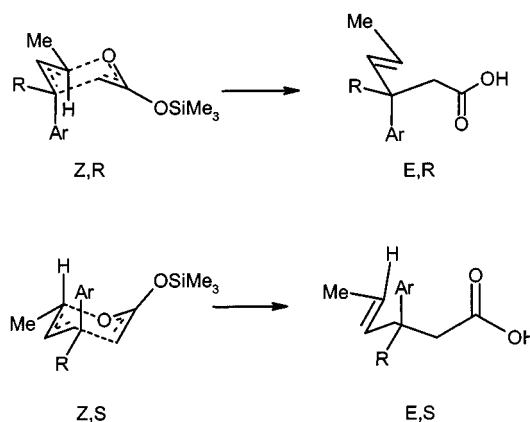
Scheme 4

Ester **9a** was obtained as a single diastereoisomer from 3,4-dimethoxyphenylisopropyl ketone, by means of a Reformatsky reaction followed by dehydration. This derivative was found to be the precursor of allylic alcohol (*Z*)-**2**: thus *cis* stereochemistry could be ascribed to its double bond. A search in the literature revealed that two contrasting ¹H NMR spectra of the unsubstituted derivative **9b** had been reported.^[17,18] One^[17] assigned the *trans* configuration to the substrate displaying H-C(4) at δ = 4.11 as a septet and H-C(2) at 5.70 as a singlet, and the *cis* configuration to the substrate with H-C(4) at δ = 2.65 as a double septet and H-C(2) at 5.87 as a doublet. In the other paper,^[18] the assignment was the exact opposite. The effect of the methoxy groups of the aromatic rings being quite negligible, our stereochemical assignment of compound **9a**, based on the chemical correlation to derivative (*Z*)-**2**, endorsed the NMR spectroscopic data reported in reference^[14] [**9a**, δ_{H} , *J* in Hz: 6.84 (d, 1 H, *J* = 8), 6.68 (dd, 1 H, *J* = 8, 2), 6.65 (d, 1 H, *J* = 2), 5.83 (d, 1 H, *J* = 0.7), 3.99 (q, 2 H, *J* = 7), 3.88 (s, 3 H), 3.86 (s, 3 H), 2.65 (1 H, d septet, *J* = 7, 0.7), 1.08 (m, 9 H)].

When derivative (*Z,R*)-(-)-**3** was submitted to Ireland reaction conditions, (*E,R*)-(-)-**4** (*ee* = 94%, HPLC of the corresponding ester) was obtained, bond formation occurring on the *si* face of the allylic double bond. The configurational assignment was based on the analysis of the chair-like transition states reported in Scheme 5, and was confirmed at the end of the synthetic sequence.

The Ireland rearrangement is a suprafacial, concerted, nonsynchronous pericyclic process that may be considered as an intramolecular $\text{S}_{\text{N}}2'$ process; as the stereochemistry of the resulting double bond is *E* [*J*(H-4/H-5) = 16 Hz], the *Z,R* acetate derivative can afford only the *R* enantiomer.

Having achieved optical activation by enzymatic kinetic resolution and constructed the tetrasubstituted stereocentre



R = Isopropyl, Ar = 3,4-dimethoxyphenyl

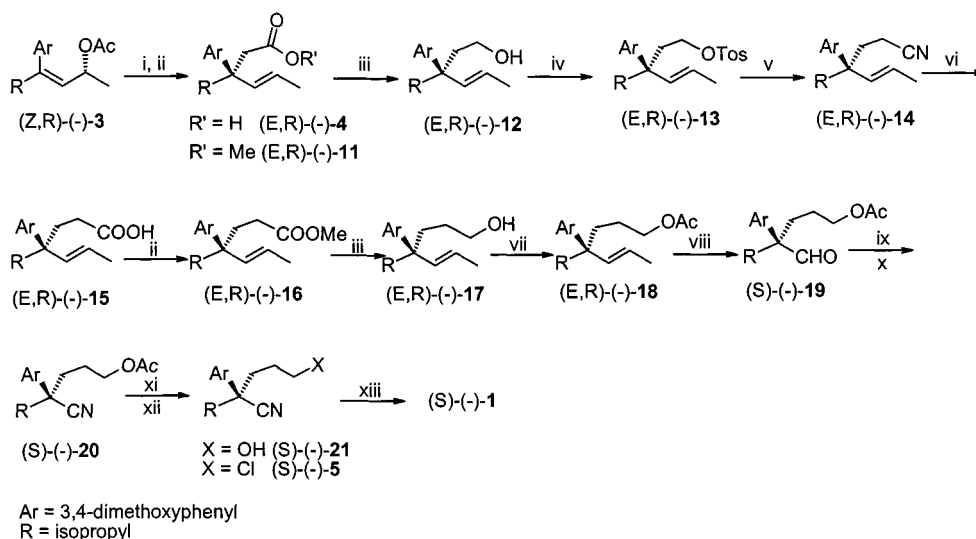
Scheme 5. Transition states and final products of Ireland–Claisen rearrangement of the two isomers of allylic alcohol (*Z*)-**2**

through a concerted rearrangement, we looked for simple high-yielding reactions with which to manipulate intermediates (+)- and (-)-**4** and prepare (+)- and (-)-**1** (Scheme 6).

Acid derivative (*E,R*)-(-)-**4** was esterified by treatment with diazomethane in diethyl ether to afford the methyl ester derivative (*E,R*)-(-)-**11** (*ee* = 93%, HPLC). The introduction of an extra carbon atom into the $\text{CH}_2\text{COOCH}_3$ fragment was achieved by nucleophilic cyanide anion substitution on the tosylate derivative (*E,R*)-(-)-**13**. Hydrolysis of the nitrile group with KOH 20% in diethylene glycol, esterification with diazomethane, DIBAL-H reduction and acetylation with acetic anhydride in pyridine yielded compound (*E,R*)-(-)-**18**. This latter was subjected to ozonolysis under strictly controlled conditions: quenching of the reaction mixture with triphenylphosphane afforded aldehyde (*S*)-(-)-**19**. The formyl group was converted into a CN group by treatment with hydroxylamine hydrochloride and sodium acetate in ethanol, followed by acetic anhydride. Derivative (*S*)-(-)-**20** was hydrolysed, using potassium hydroxide in refluxing methanol, to alcohol derivative (*S*)-(-)-**21** ($[\alpha]_{\text{D}}^{20} = -11.5$, *c* = 2.75 CHCl_3 ; optical purity = 91% *ee*; ref.^[5] $[\alpha]_{\text{D}}^{20} = -12.6$, *c* = 3.84 CHCl_3).

Optically active (*S*)-(-)-**21** was quantitatively converted into chloro derivative (*S*)-(-)-**5** ($[\alpha]_{\text{D}}^{20} = -11.2$, *c* = 1.15, methanol; optical purity: 91% *ee*; ref.^[3] $[\alpha]_{\text{D}}^{20} = -12.3$, *c* = 1, methanol) by treatment with triphenylphosphane in carbon tetrachloride. Coupling of *S*-(-)-**5** with *N*-methylhomoveratrylamine at 130 °C afforded *S*-(-)-**1** (the specific rotatory power was determined on the corresponding HCl salt: $[\alpha]_{\text{D}}^{20} = -8.2$, *c* = 5.08, ethanol; optical purity 92% *ee*; ref.^[3]: $[\alpha]_{\text{D}}^{20} = -8.9$, *c* = 5.00, ethanol).

Enantiomer (*R*)-**1** was produced analogously (the specific rotatory power was determined on the corresponding hydrochloride: $[\alpha]_{\text{D}}^{20} = +8.3$, *c* = 5.05, ethanol; optical purity: 93% *ee*; ref. 3: $[\alpha]_{\text{D}}^{20} = +8.9$, *c* = 5.00, ethanol) from optically active (*Z,S*)-(+)-**3** by the same synthetic sequence.



Scheme 6. i: lithium diisopropylamide, trimethylchlorosilane, then room temp., MeOH; ii: diazomethane in diethyl ether; iii: DIBAL-H in toluene; iv: 4-toluenesulfonyl chloride in pyridine; v: NaCN in DMSO; vi: KOH 20% in diethylene glycol; vii: acetic anhydride in pyridine; viii: ozone, dichloromethane/ methanol 1:1; then triphenylphosphane; ix: hydroxylamine hydrochloride, sodium acetate in ethanol; x: acetic anhydride, sodium acetate, reflux; xi: KOH in methanol, reflux; xii: triphenylphosphane in carbon tetrachloride; xiii: *N*-methylhomoveratrylamine.

Conclusions

This is the first enzymatic synthesis of the enantiomeric forms of verapamil. The other two known approaches are based on the classical resolution of diastereoisomeric salts,^[3] and on the use of components from the pool of chirality.^[5] The starting racemic allylic alcohol could easily be obtained in a multigram scale synthesis from commercially available veratraldehyde, in good overall yield.

Both enantiomers [(*Z,R*)-**3** and (*Z,S*)-(+)-**3**] were obtained by combining Lipase PS-catalysed acetylation with inversion of the configuration of the stereocentre at certain stages of the synthetic sequence. Enrichment of the starting allylic alcohol mixture into the enantiomer preferentially converted by Lipase allowed us to obtain (*Z,R*)-(-)-**3** in 48% yield. The sluggishness of the kinetic resolution was overcome by performing two subsequent enzymatic acetylations: the first on racemic (*Z*)-**2**, the second on (*Z,R*)-(+)-**2**, showing *ee* = 40%. Compound (*Z,S*)-(+)-**3** was then prepared from (*Z,R*)-(-)-**3**.

Stereospecific Ireland–Claisen rearrangement allowed us to create the quaternary carbon atom characteristic of verapamil under the strict steric control of the enantiomerically enriched starting allylic acetate. Derivatives (*E,R*)-(-)-**4** and (*E,S*)-(+)-**4** were converted into (*S*)-(-)-**1** and (*R*)-(+)-**1**, respectively, through conventional organic reactions, characterised by high yields of conversion, and the use of very common reagents, under mild conditions.

The results of this work once again^[8–10] highlight the effectiveness of enzymes, and in particular of lipases,^[19,20] in resolution processes of racemic substrates, such as allylic alcohols,^[21,22] to which classical methods of crystallisation of diastereoisomeric salts are not easily applied. The structural pattern of (*Z*)-($\pm$)-**2**, characterised by a *cis*-trisubstituted double bond, makes the enzymatic acetylation very

slow and possible only in the presence of Lipase PS. The *trans* arrangement of the same substituents in diastereoisomer (*E*)-($\pm$)-**2** results in a very fast, enantiospecific, Lipase PS-mediated acetylation.

Experimental Section

Lipase PS *Burkholderia cepacia* (Amano Pharmaceuticals Co., Nagoya, Japan) was employed in this work. – Chiral HPLC analyses were performed on a Merck-Hitachi L-6200 apparatus: Chiralcel OD (Daicel-Japan) column, 0.6 mL/min, UV detector (254 nm). – ¹H NMR spectra were recorded in CDCl₃ solutions at room temperature unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz ¹H). The chemical shift scale was based on internal tetramethylsilane. *J* values are in Hz. Optical rotations were measured on a Jasco DIP 181 digital polarimeter. – Microanalyses were determined on a Carlo Erba Analyzer 1106. GC-MS analyses were performed on an HP 6890 gas chromatograph equipped with a 5973 mass detector, using an HP-5MS column (30m × 0.25 mm × 0.25 μm). The following temperature programs were employed: A) 60 °C (1 min)/ 6°/min/150° (1 min)/12°/min/280° (5 min); B) 100 °C (1 min)/ 10°/min/200° (1 min)/5°/min/280° (5 min). – TLC analyses were performed on Merck Kieselgel 60 F₂₅₄ plates. All the chromatographic separations were carried out on silica gel columns.

1-(3,4-Dimethoxyphenyl)-2-methylpropan-1-ol: A solution of isopropylmagnesium bromide (prepared from 334 g of isopropyl bromide and 62 g of magnesium) in THF (1000 mL) was added dropwise to a solution of 3,4-dimethoxybenzaldehyde (300 g, 1.81 mol) in THF (1000 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After the usual workup, the residue was purified by crystallisation from hexane to give the title compound in pure form (280 g, 74%); m.p. 56 °C. – ¹H NMR: δ_H = 6.87 (s, 1 H, aromatic hydrogen), 6.81 (m, 2 H, aromatic hydrogens), 4.26 [d, *J* = 7.2, 1 H, C(1)H], 3.87 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 1.92 [septet, *J* = 7, 1 H, C(2)H], 1.0 (d, *J* = 7, 3 H, CH₃CH), 0.78 (d,

$J = 7$, 3 H, CH_3CH). – $\text{C}_{12}\text{H}_{18}\text{O}_3$: calcd. C 68.55, H 8.63; found C 68.60, H 8.67).

3,4-Dimethoxyphenyl Isopropyl Ketone: Oxidation of 1-(3,4-dimethoxyphenyl)-2-methylpropan-1-ol (280 g, 1.33 mol) according to Jones's procedure gave, after purification by silica gel column chromatography using hexane/ethyl acetate (9:1) as eluent, the title compound in pure form (226 g, 82%). – ^1H NMR: $\delta_{\text{H}} = 7.59$ [dd, $J = 2.1$, 8.3, 1 H, aromatic hydrogen C(6)H], 7.55 (d, $J = 2.1$, 1 H, aromatic hydrogen C(2)H), 6.89 [d, $J = 8.3$, 1 H, aromatic hydrogen C(5)H], 3.94 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 3.54 [septet, $J = 6.7$, 1 H, $\text{CH}(\text{Me})_2$], 1.21 [d, $J = 6.7$, 6 H, $\text{CH}(\text{CH}_3)_2$]. – $\text{C}_{12}\text{H}_{16}\text{O}_3$: calcd. C 69.21, H 7.74; found C 69.26, H 7.78.

3-(3,4-Dimethoxyphenyl)-3-hydroxy-4-methylpentanenitrile: A 10 M solution of butyllithium (162 mL, 1.62 mol) in ether/hexane was added dropwise to a solution of acetonitrile (66 g, 1.62 mol) in THF (1000 mL) at -50°C . After 30 min, a solution of 3,4-dimethoxyphenyl isopropyl ketone (226 g, 1.08 mol) in THF (300 mL) was added at -50°C . The reaction mixture was allowed to warm to room temperature and then stirred for 2 h. The reaction mixture was poured into 10% HCl, and extracted with diethyl ether. The organic phase was dried on sodium sulfate, and concentrated under reduced pressure, to give a residue (208 g, 77%) which was submitted to subsequent reaction without any further purification. – ^1H NMR: $\delta_{\text{H}} = 7.1$ – 6.88 (m, 3 H, aromatic hydrogens), 3.90 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 2.90 (s, 2 H, CH_2CN), 2.25 [septet, $J = 7$, 1 H, $\text{CH}(\text{Me})_2$], 0.96 (s, 3 H, CHCH_3), 0.82 (s, 3 H, CHCH_3). – GC-MS: progr. temp. A: $t_{\text{R}} = 23.23$ min, $m/z = 249$ [M^+], 231, 165. – $\text{C}_{14}\text{H}_{19}\text{NO}_3$: calcd. C 67.45, H 7.68, N 5.62; found C 67.41, H 7.63, N 5.67.

(E)- and (Z)-3-(3,4-Dimethoxyphenyl)-4-methylpent-2-enenitrile (6): A solution of 3-(3,4-dimethoxyphenyl)-3-hydroxy-4-methylpentanenitrile (208 g, 0.835 mol) in toluene (1000 mL) was refluxed for 2 h in the presence of a catalytic amount of 4-toluenesulfonic acid. After the usual workup, the residue was chromatographed on a silica gel column, eluting with hexane/ethyl acetate (7:3). The first eluted fractions gave a 1.6:1 mixture of (Z)- and (E)-6 (152 g, 79%). – ^1H NMR: $\delta_{\text{H}} = 7.05$ – 6.70 (m, 6 H, aromatic hydrogens of the two diastereoisomers), 5.29 (m, 2 H, $\text{CH}=\text{C}$ of the two diastereoisomers), 3.92 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 3.31 [septet, $J = 7$, $\text{CH}(\text{Me})_2$ of the minor diastereoisomer], 2.87 [d, septet, $J = 7$, 1.16, $\text{CH}(\text{Me})_2$ of the major diastereoisomer], 1.29 and 1.11 [2 d, $J = 7$, 6 H, $\text{CH}(\text{CH}_3)_2$ of the two diastereoisomers]. – GC-MS progr. temp. A: $t_{\text{R}} = 22.37$ min (E), 22.40 (Z); $m/z = 231$ [M^+], 216, 138. – $\text{C}_{14}\text{H}_{17}\text{NO}_2$: calcd. C, 72.70, H 7.41, N 6.06; found C 72.75, H 7.46, N 6.09.

(E)- and (Z)-3-(3,4-Dimethoxyphenyl)-4-methylpent-2-enal (7): A 1.5 M solution of DIBAL-H in toluene (660 mL, 0.990 mol) was added dropwise to a solution of (E)- and (Z)-6 (152 g, 0.660 mol) in toluene (1000 mL) at -20°C . The reaction mixture was stirred at -20°C for 2 h. After the usual workup, a 1.4:1 (GC-MS) mixture of (Z)- and (E)-7 was obtained (120 g, 78%), and used without any further purification. – ^1H NMR: $\delta_{\text{H}} = 9.44$ (d, $J = 8$, 1 H, CHO), 7.0– 6.6 (m, 3 H, aromatic hydrogens), 6.06 (d, $J = 8$, 1 H, $\text{CH}=\text{C}$), 3.92 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 2.80 [septet, $J = 7$, 1 H, $\text{CH}(\text{Me})_2$], 1.13 [s, 6 H, $\text{CH}(\text{CH}_3)_2$]. – GC-MS progr. temp. A: $t_{\text{R}} = 22.32$ min (Z), 22.45 min (E); $m/z = 234$ [M^+], 219, 203, 191. – $\text{C}_{14}\text{H}_{18}\text{O}_3$: calcd. C 71.77, H 7.74; found C 71.72, H 7.78.

(E)- and (Z)-3-(3,4-Dimethoxyphenyl)-1,4-dimethylpent-2-enol (2): A 3 M solution of methylmagnesium bromide in diethyl ether (258 mL, 0.772 mol) was added dropwise to a solution of (E)- and

(Z)-7 (120 g, 0.515 mol) in diethyl ether at 0°C . The reaction mixture was stirred at room temperature for 1 h. After the usual workup, the residue was chromatographed on a silica gel column, eluting with hexane/ethyl acetate 6:4. A 1.5:1 mixture of (Z)- and (E)-2 (GC-MS) was obtained (103 g, 80%). – GC-MS progr. temp. A: $t_{\text{R}} = 21.56$ min (Z), 22.25 min (E); $m/z = 250$ [M^+], 232, 217, 201, 189. – $\text{C}_{15}\text{H}_{22}\text{O}_3$: calcd. C 71.97, H 8.86; found C 71.93, H 8.82.

(E)-3-(3,4-Dimethoxyphenyl)-1,4-dimethylpent-2-enyl Acetate [(E)-($\pm$)-3] and (Z)-3-(3,4-Dimethoxyphenyl)-1,4-dimethylpent-2-enyl Acetate [(Z)-($\pm$)-3]: The 1.8:1 mixture of (Z)- and (E)-2 (above, 103 g, 0.412 mol) was acetylated with acetic anhydride in pyridine, and the corresponding diastereoisomeric acetates were separated by column chromatography, eluting with hexane/ethyl acetate (9:1). The fractions eluted first gave (E)-($\pm$)-3 (42.1 g, 35%). – ^1H NMR: $\delta_{\text{H}} = 6.85$ – 6.65 (m, 3 H, aromatic hydrogens), 5.82 (m, 1 H, CHOAc), 5.26 (d, $J = 8.9$, 1 H, $\text{CH}=\text{C}$), 3.88 (s, 6 H, 2OMe), 3.18 [septet, $J = 7$, 1 H, $\text{CH}(\text{Me})_2$], 2.06 (s, 3 H, CH_3CO), 1.36 (d, $J = 6.6$, 3 H, CH_3CH), 1.04 and 1.05 [2 overlapping d, $J = 7$, 6 H, $\text{CH}(\text{CH}_3)_2$]. – GC-MS progr. temp. A: $t_{\text{R}} = 23.11$ min, $m/z = 292$ [M^+], 232, 217, 207, 189. – $\text{C}_{17}\text{H}_{24}\text{O}_4$: calcd. C 69.84, H 8.27; found C 68.93, H 8.32.

The fractions eluted second gave (Z)-($\pm$)-3 (62.6 g, 52%). – ^1H NMR: $\delta_{\text{H}} = 6.90$ – 6.50 (m, 3 H, aromatic hydrogens), 5.38 (dd, 1 H, $J = 8.9$, 1.16, $\text{CH}=\text{C}$), 5.20 (m, 1 H, CHOAc), 3.89 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 2.52 [d, septet, $J = 7$, 1.16, 1 H, $\text{CH}(\text{Me})_2$], 1.99 (s, 3 H, CH_3CO), 1.20 (d, $J = 6.1$, 3 H, CH_3CH), 1.02 and 1.01 [2 overlapping d, $J = 7$, 6 H, $\text{CH}(\text{CH}_3)_2$]. – GC-MS progr. temp. A: $t_{\text{R}} = 22.25$ min, $m/z = 292$ [M^+], 232, 217, 207, 189. – $\text{C}_{17}\text{H}_{24}\text{O}_4$: calcd. C 69.84, H 8.27; found C 68.87, H 8.31.

(E)-($\pm$)-3-(3,4-Dimethoxyphenyl)-1,4-dimethylpent-2-enol (2): A solution of (E)-($\pm$)-3 (42.1 g, 0.144 mol) and potassium hydroxide (14.2 g, 0.216 mol) in methanol (250 mL) was refluxed for 1 h. After the usual workup, (E)-($\pm$)-3 (35.0 g, 97%) was recovered. – ^1H NMR: $\delta_{\text{H}} = 6.90$ – 6.60 (m, 3 H, aromatic hydrogens), 5.32 (d, 1 H, $J = 8.9$, $\text{CH}=\text{C}$), 4.82 (m, 1 H, CHOH), 3.88 (s, 6 H, 2OMe), 3.07 [1 Heptet, $J = 7$, $\text{CH}(\text{Me})_2$], 1.33 (d, $J = 7$, 3 H, CH_3CH), 1.09 and 1.05 [2 overlapping d, $J = 7$, 6 H, $\text{CH}(\text{CH}_3)_2$].

(Z)-($\pm$)-3-(3,4-Dimethoxyphenyl)-1,4-dimethylpent-2-enol (2): A solution of (Z)-($\pm$)-3 (62.6 g, 0.214 mol) and potassium hydroxide 85% (21.2 g, 0.322 mol) in methanol (300 mL) was refluxed for 1 h. After the usual workup, (Z)-($\pm$)-3 (52.1 g, 97%) was recovered. – ^1H NMR: $\delta_{\text{H}} = 6.90$ – 6.60 (m, 3 H, aromatic hydrogens), 5.42 (dd, $J = 8.9$ and 1.16, 1 H, $\text{CH}=\text{C}$), 4.18 (m, 1 H, CHOH), 3.89 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 2.52 [d, septet, $J = 7$ and 1.16, 1 H, $\text{CH}(\text{Me})_2$], 1.21 (d, $J = 6.1$, 3 H, CH_3CH), 1.02 and 1.01 [2 overlapping d, $J = 7$, 6 H, $\text{CH}(\text{CH}_3)_2$].

Enzyme-Catalysed Acetylations: A mixture of (Z)-($\pm$)-2 (50.0 g), lipase (50.0 g), and vinyl acetate (80 mL) in diethyl ether (400 mL) was stirred at room temperature for 18 h. The residue obtained upon evaporation of the filtered reaction mixture was chromatographed, eluting with hexane→hexane 1:ethyl acetate 1. The first eluted fractions provided the acetate derivative (Z,R)-(-)-3 (18.2 g, 30%): $[\alpha]_{\text{D}}^{20} = -16$, $c = 1.05$, CH_2Cl_2 ; ee 92% HPLC: hexane/2-propanol (95:5) t_{R} (Z,R)-(-)-3 = 9.4 min, t_{R} (Z,S)-(+)-3 = 11.4 min, ($E = 35$; $c = 34\%$). – ^1H NMR in accordance with that of the racemate. The last eluted fractions afforded the unchanged alcohol (Z,S)-(-)-2 (34.3 g, 68%) showing $ee = 47\%$ (HPLC hexane/2-propanol, 95:5; t_{R} (Z,R)-(+)-2 = 23.0 min, t_{R} (Z,S)-(-)-2 = 32 min). – ^1H NMR in accordance with that of the racemate.

According to the same procedure, (*E*)-($\pm$)-**2** (20.0 g) gave (*E,R*)-(+)-**3** (8.91 g, 38%) after 24 h reaction time: $[\alpha]_D^{20} = 95$, $c = 1.48$, CH_2Cl_2 ; $ee = 92\%$ HPLC of the corresponding alcohol: hexane/2-propanol, 95:5; t_R (*E,R*)-(+)-**2** = 27.1 min, t_R (*E,S*)-(-)-**2** = 22.4 min; $E = 67$; $c = 45\%$). – ^1H NMR in accordance with that of the racemate. The recovered alcohol (*Z,S*)-(-)-**2** (14.9 g, 51%) showed $ee = 76\%$ (HPLC); $[\alpha]_D^{20} = -19.4$, $c = 0.675$, CH_2Cl_2 . – ^1H NMR in accordance with that of the racemate.

By the same procedure, (*Z*)-**2** ($ee = 40\%$, 25.0 g, 0.10 mol) afforded (*Z,R*)-(-)-**3** (8.76 g, 30%).

General Procedure for Acetate Displacement: The appropriate allylic alcohol (10.0 g, 0.040 mol) was treated with 4-toluenesulfonyl chloride (11.4 g, 0.060 mol) in dichloromethane (100 mL) and pyridine (25 mL). After the usual workup, the tosylate derivative was subjected to acetate displacement in refluxing dimethylformamide solution (250 mL) in the presence of sodium acetate (4.92 g, 0.060 mol). The appropriate acetate derivative was recovered from the reaction mixture by column chromatography.

According to this procedure, (*Z,S*)-(-)-**2** ($ee = 47\%$, 34.0 g, 0.136 mol) gave (*Z,R*)-(+)-**2** ($ee = 40\%$, 25 g, 73%) after hydrolysis of the resulting acetate derivative by treatment with potassium hydroxide in refluxing methanol.

By this procedure, (*Z,R*)-(+)-**2** [4.9 g, 0.060 mol; $ee = 92\%$; $[\alpha]_D^{20} = 19.4$, $c = 0.40$, CH_2Cl_2 ; obtained from 18 g (*Z,R*)-(-)-**3** ($ee = 92\%$)] gave (*Z,S*)-(+)-**3** (13.3 g, 76%); $[\alpha]_D^{20} = 15$, $c = 1.13$, CH_2Cl_2 .

General Procedure for Ireland Rearrangement: A solution of 2 M lithium diisopropylamide (0.051 mol, 26 mL) was added dropwise to a solution of the appropriate allylic acetate (10.0 g, 0.034 mol) in THF at -78°C . After 5 min, trimethylchlorosilane (0.051 mol, 6.5 mL) was added in one batch. The cooling bath was removed; the reaction mixture was allowed to warm to room temperature over 30 min, then refluxed for 3 h. Methanol (10 mL) was added, the reaction mixture was stirred at room temperature for 10 min, then poured into a 5% aqueous sodium hydroxide solution (100 mL). This aqueous solution was washed with ethyl ether (washings discarded), and acidified with concentrated hydrochloric acid. The product acid was isolated by dichloromethane extraction.

By this procedure (*Z,R*)-(-)-**3** (10.0 g, 0.034 mol) gave (*E,R*)-(-)-3-(3,4-dimethoxyphenyl)-3-isopropylhex-4-enoic acid [(-)-**4**; 6.21 g, 63%]. – $[\alpha]_D^{20} = -9$, ($c = 0.90$, methanol); $ee = 95\%$ HPLC of the corresponding methyl ester hexane/2-propanol (99:1) t_R (*S*)-(+)-**11** = 21.8 min, t_R (*R*)-(-)-**11** = 24.8 min; E . – ^1H NMR: $\delta_{\text{H}} = 6.75\text{--}6.90$ (m, 3 H, aromatic hydrogens), 5.71 [dq, $J = 16$ and 1.6, 1 H, C(4)H], 5.56 [dq, $J = 16$ and 6, 1 H, C(5)H], 3.85 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 2.81 (d, $J = 14.5$, 1 H, CH–COOH), 2.73 (d, $J = 14.5$, 1 H, CH–COOH), 2.47 [septet, $J = 7$, 1 H, CH(Me)₂], 1.82 (dd, $J = 6$ and 1.6, 3 H, $\text{CH}_3\text{C}=\text{C}$), 0.85 (d, $J = 7$, 3 H, CH_3CH), 0.77 (d, $J = 7$, 3 H, CH_3CH). – GC-MS progr. temp. A: $t_R = 24.66$ min, $m/z = 292$ [M^+], 249, 203, 189. – $\text{C}_{17}\text{H}_{24}\text{O}_4$; calcd. C 69.84, H 8.27; found C 68.81, H 8.24.

By this procedure, (*Z,S*)-(+)-**3** (10.0 g, 0.034 mol) gave (*E,S*)-(+)-3-(3,4-dimethoxyphenyl)-3-isopropylhex-4-enoic acid [(+)-**4**; 6.42 g, 65%]. – $[\alpha]_D^{20} = 7$, ($c = 0.85$, methanol); $ee = 95\%$ HPLC of the corresponding methyl ester; the analytical data were in accordance with those of (-)-**4**.

By this procedure, (*E,R*)-(+)-**3** (10.0 g, 0.034 mol) gave (*E*)-($\pm$)-3-(3,4-dimethoxyphenyl)-3-isopropylhex-4-enoic acid [($\pm$)-**4**; 4.84 g, 48%] (HPLC of the corresponding methyl ester); m.p. 85°C ; the analytical data were in accordance with those of (-)-**4**.

Methyl (4*E*,3*R*)-(-)-3-(3,4-Dimethoxyphenyl)-3-isopropylhex-4-enoate [(-)-11**]:** Treatment of a solution of acid (-)-**4** (6.20 g, 0.021 mol) in ethyl ether with a solution of diazomethane in ethyl ether quantitatively gave methyl ester (-)-**11** (6.35 g, 97%). – $[\alpha]_D^{20} = -57$, ($c = 0.60$, CH_2Cl_2); $ee = 95\%$ HPLC hexane/2-propanol (99:1), t_R (*E,R*)-(-)-**11** = 24.8 min. – ^1H NMR: $\delta_{\text{H}} = 6.75\text{--}6.90$ (m, 3 H, aromatic hydrogens), 5.70 [dq, $J = 16$ and 1.1, 1 H, C(4)H], 5.56 [dq, $J = 16$ and 6, 1 H, C(5)H], 3.86 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 3.42 (s, 3 H, COOMe), 2.78 (d, $J = 14$, 1 H, CH–COOMe), 2.69 (d, $J = 14$, 1 H, CH–COOH), 2.51 [septet, $J = 7$, 1 H, CH(Me)₂], 1.83 (dd, $J = 6$ and 1.1, 3 H, $\text{CH}_3\text{C}=\text{C}$), 0.88 (d, $J = 7$, 3 H, CH_3CH), 0.78 (d, $J = 7$, 3 H, CH_3CH). – GC-MS progr. temp. A: $t_R = 23.88$ min (*E*), $m/z = 306$ [M^+], 263, 203, 189. – $\text{C}_{18}\text{H}_{26}\text{O}_4$; calcd. C 70.56, H 8.55; found C 70.60, H 8.51.

Methyl (4*E*,3*S*)-(+)-3-(3,4-Dimethoxyphenyl)-3-isopropylhex-4-enoate [(+)-11**]:** Treatment of a solution of acid (+)-**4** (6.40 g, 0.022 mol) in ethyl ether with a solution of diazomethane in ethyl ether quantitatively gave methyl ester (+)-**11** (6.56 g, 97%); $[\alpha]_D^{20} = +55$, ($c = 0.54$, CH_2Cl_2); $ee = 95\%$ HPLC: hexane/2-propanol (99:1), t_R (*E,S*)-(+)-**11** = 21.8 min. The analytical data were in accordance with those of (-)-**11**.

(4*E*,3*R*)-(-)-3-(3,4-Dimethoxyphenyl)-3-isopropylhex-4-enol [(-)-12**]:** A 65wt.-% Red-Al solution in toluene (9.5 mL, 0.031 mol) was added to a solution of (-)-**11** (6.30 g, 0.021 mol) in toluene at 0°C . The solution was stirred at room temperature for 1 h; methanol was then added. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic phase, dried on sodium sulfate, was concentrated under reduced pressure to afford a residue which was chromatographed on a silica gel column, eluting with hexane-ethyl acetate (1:1). Compound (-)-**12** was obtained in a pure state (5.16 g, 89%); $[\alpha]_D^{20} = -37$, ($c = 0.41$, CH_2Cl_2). – ^1H NMR: $\delta_{\text{H}} = 6.90\text{--}6.75$ (m, 3 H, aromatic hydrogens), 5.70–5.50 [m, 2 H, C(4)H and C(5)H], 3.85 (s, 6 H, 2OMe), 3.43 (m, 1 H, CHOH), 3.25 (m, 1 H, CHOH), 2.12 (m, 2 H, $\text{CH}_2\text{CH}_2\text{OH}$), 1.94 [m, 1 H, CH(Me)₂], 1.83 (d, $J = 4.6$, 3 H, $\text{CH}_3\text{C}=\text{C}$), 0.85 (d, $J = 7$, 3 H, CH_3CH), 0.71 (d, $J = 7$, 3 H, CH_3CH). – GC-MS: temp. progr. B, $t_R = 15.23$ min, $m/z = 278$ [M^+], 235, 217, 202, 191. – $\text{C}_{17}\text{H}_{26}\text{O}_3$; calcd. C 73.35, H 9.41; found C 73.38, H 9.43.

(4*E*,3*S*)-(+)-3-(3,4-Dimethoxyphenyl)-3-isopropylhex-4-enol [(+)-12**]:** Compound (+)-**11** (6.50 g, 0.021 mol) was converted into the title compound by the same procedure as described for the preparation of its (*E,R*)-(-) enantiomer from (-)-**11** (5.45 g, 91%); $[\alpha]_D^{20} = 34$, ($c = 0.35$, CH_2Cl_2); the analytical data were in accordance with those of the corresponding enantiomer.

(4*E*,3*R*)-(-)-3-(3,4-Dimethoxyphenyl)-3-isopropylhex-4-enyl Tosylate [(-)-13**]:** A solution of derivative (-)-**12** (5.10 g, 0.018 mol) in pyridine (30 mL) was treated with 4-toluenesulfonyl chloride (5.12 g, mol). After the usual workup, purification of the residue by column chromatography gave tosylate (-)-**13** (7.17 g, 92%); m.p. 64°C . – $[\alpha]_D^{20} = -5$, ($c = 1.61$, CH_2Cl_2). – ^1H NMR: $\delta_{\text{H}} = 7.65$ (m, 2 H, aromatic hydrogens), 7.10–7.35 (m, 4 H, aromatic hydrogens), 6.80–6.60 (m, 3 H, aromatic hydrogens), 5.55 [dq, $J = 1.16$ and 16, 1 H, C(4)H], 5.39 [dq, $J = 6$ and 16, 1 H, C(5)H], 3.90–3.80 (2 s + m, 7 H, 2OMe + CHOTs), 3.53 (m, 1 H, CHOTs), 2.45 (s, 3 H, $\text{CH}_3\text{--C}_6\text{H}_4\text{--SO}_2$), 2.30–1.95 [m, 3 H, $\text{CH}_2\text{CH}_2\text{OTs}$ + CH(Me)₂], 1.77 (dd, $J = 1.16$ and 6, 3 H, $\text{CH}_3\text{C}=\text{C}$), 0.80 (d, $J = 7$, 3 H, CH_3CH), 0.65 (d, $J = 7$, 3 H, CH_3CH). – GC-MS: temp. progr. B, $t_R = 29.91$ min, $m/z = 432$ [M^+], 389, 217. – $\text{C}_{24}\text{H}_{32}\text{O}_5\text{S}$; calcd. C 66.64, H 7.46, S 7.41; found C 66.68, H 7.39, S 7.45.

(4E,3S)-(+)-3-(3,4-Dimethoxyphenyl)-3-isopropylhex-4-enyl Tosylate [(+)-13]: Tosylate (+)-13 (7.64 g, 90%) was obtained from derivative (+)-12 (5.40 g, 0.012 mol) by the same procedure as used for the preparation of (–)-13: $[\alpha]_D^{20} = 3$, ($c = 1.65$, CH_2Cl_2); the analytical data were in accordance with those of (–)-13.

(5E,4R)-(–)-4-(3,4-Dimethoxyphenyl)-4-isopropylhept-5-enenitrile [(–)-14]: A mixture of tosylate (–)-13 (7.10 g, 0.016 mol) and sodium cyanide (1.22 g, 0.024 mol) in dimethyl sulfoxide (39 mL) was stirred at 80 °C for 2 h. After the usual workup, purification of the residue by column chromatography, using hexane-ethyl acetate 7:3 as an eluent, gave the title compound in pure form (4.01 g, 85%). – $[\alpha]_D^{20} = -25$, ($c = 1.01$, CH_2Cl_2). – ^1H NMR: $\delta_{\text{H}} = 6.80$ – 6.60 (m, 3 H, aromatic hydrogens), 5.70–5.40 [m, 2 H, C(4)H and C(5)H], 3.87 (s, 6 H, 2OMe), 2.30–1.60 (m, 8 H, $\text{CH}_2\text{CH}_2\text{CN} + \text{CH}(\text{Me})_2 + \text{CH}_3\text{C}=\text{C}$), 0.86 (d, $J = 7$, 3 H, CH_3CH), 0.70 (d, $J = 7$, 3 H, CH_3CH). – GC-MS: temp. progr. B, $t_{\text{R}} = 16.48$ min, $m/z = 287$ [M^+], 272, 256, 244, 189. – $\text{C}_{18}\text{H}_{25}\text{NO}_2$: calcd. C 75.22, H 8.77, N 4.87; found C 68.81, H 8.24.

(5E,4S)-(+)-4-(3,4-Dimethoxyphenyl)-4-isopropylhept-5-enenitrile [(+)-14]: The title compound (4.37 g, 84%) was obtained from (+)-13 (7.60 g, 0.018 mol) by the same procedure as used to prepare its (–) enantiomer. $[\alpha]_D^{20} = 24$, ($c = 0.95$, CH_2Cl_2); the analytical data were in accordance with those of the corresponding enantiomer.

(5E,4R)-(–)-4-(3,4-Dimethoxyphenyl)-4-isopropylhept-5-enoic Acid [(–)-15]: A mixture of (–)-14 (4.00 g, 0.014 mol) and 20% KOH (10 mL) in diethylene glycol (20 mL) was refluxed for 1 h. After the usual workup, the title compound was recovered in pure form (3.43 g, 81%) $[\alpha]_D^{20} = -20.6$, ($c = 1.50$, methanol). – ^1H NMR: $\delta_{\text{H}} = 6.79$ (m, 3 H, aromatic hydrogens), 5.70–5.40 [m, 2 H, C(4)H and C(5)H], 3.86 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 2.20–1.70 (m, 8 H, $\text{CH}_2\text{CH}_2\text{COOH} + \text{CH}(\text{Me})_2 + \text{CH}_3\text{C}=\text{C}$), 0.85 (d, $J = 7$, 3 H, CH_3CH), 0.71 (d, $J = 7$, 3 H, CH_3CH). – GC-MS: temp. progr. B, $t_{\text{R}} = 17.47$ min, $m/z = 306$ [M^+], 289, 277, 263, 203. – $\text{C}_{18}\text{H}_{26}\text{O}_4$: calcd. C 70.56, H 8.55; found C 70.59, H 8.58.

(5E,4S)-(+)-4-(3,4-Dimethoxyphenyl)-4-isopropylhept-5-enoic Acid [(+)-15]: The title compound (3.48 g, 79%) was obtained from derivative (+)-14 (4.30 g, 0.015) by the same procedure as used to prepare its (–) enantiomer: $[\alpha]_D^{20} = 19.3$, ($c = 1.20$, methanol); the analytical data were in accordance with those of the corresponding enantiomer.

Methyl (5E,4R)-(–)-4-(3,4-Dimethoxyphenyl)-4-isopropylhept-5-enoate [(–)-16]: The title compound was obtained (3.54 g, 98%) by treatment of the corresponding acid (–)-15 (3.40 g, 0.011 mol) with diazomethane in diethyl ether: $[\alpha]_D^{20} = -47$, ($c = 0.95$, CH_2Cl_2). – ^1H NMR: $\delta_{\text{H}} = 6.76$ (m, 3 H, aromatic hydrogens), 5.70–5.40 [m, 2 H, C(5)H and C(6)H], 3.87 (s, 6 H, 2OMe), 3.58 (s, 3 H, COOMe), 2.20–1.70 (m, 8 H, $\text{CH}_2\text{CH}_2\text{COOMe} + \text{CH}(\text{Me})_2 + \text{CH}_3\text{C}=\text{C}$), 0.85 (d, $J = 7$, 3 H, CH_3CH), 0.71 (d, $J = 7$, 3 H, CH_3CH). – GC-MS: temp. A: $t_{\text{R}} = 24.95$ min, $m/z = 320$ [M^+], 277, 245, 217, 203. – $\text{C}_{19}\text{H}_{28}\text{O}_4$: calcd. C 71.22, H 8.81; found C 71.27, H 8.86.

Methyl (5E,4S)-(+)-4-(3,4-Dimethoxyphenyl)-4-isopropylhept-5-enoate [(+)-16]: The title compound (3.41, 97%) was obtained from acid (+)-15 (3.40 g, 0.011 mol) by the same procedure as used to prepare its (–) enantiomer: $[\alpha]_D^{20} = 44$, ($c = 0.90$, CH_2Cl_2).

(5E,4R)-(–)-4-(3,4-Dimethoxyphenyl)-4-isopropylhept-5-en-1-ol [(–)-17]: A 65% wt. Red-Al solution in toluene (5 mL, 0.0165 mol) was added to a solution of ester (–)-16 (3.40 g, 0.011 mol) in toluene at 0 °C. The solution was stirred at room temperature for 1 h;

methanol was then added. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase, dried on sodium sulfate, was concentrated under reduced pressure, to afford a residue that was chromatographed on a silica gel column, eluting with hexane-ethyl acetate, 1:1. The compound (–)-17 was obtained in a pure state (2.76 g, 84%) $[\alpha]_D^{20} = -26$, ($c = 0.91$, CH_2Cl_2). – ^1H NMR: $\delta_{\text{H}} = 6.90$ – 6.70 (m, 3 H, aromatic hydrogens), 5.70–5.40 [m, 2 H, C(5)H and C(6)H], 3.87 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.50 (t, $J = 6.7$, 2 H, CH_2OH), 2.18 [septet, $J = 6.7$, 1 H, $\text{CH}(\text{Me})_2$], 1.83 (d, $J = 5$, 3 H, $\text{CH}_3\text{C}=\text{C}$), 1.1–1.80 (m, 4 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 0.84 (d, $J = 7$, 3 H, CH_3CH), 0.73 (d, $J = 7$, 3 H, CH_3CH). – GC-MS: temp. A: $t_{\text{R}} = 24.78$ min, $m/z = 292$ [M^+], 249, 231, 216, 203, 189. – $\text{C}_{18}\text{H}_{28}\text{O}_3$: calcd. C 73.93, H 9.65; found C 73.97, H 9.69.

(5E,4S)-(+)-4-(3,4-Dimethoxyphenyl)-4-isopropylhept-5-en-1-ol [(+)-17]: Ester derivative (+)-16 (3.40 g, 0.011 mol) was converted into the title compound by the same procedure as described for the preparation of its enantiomer (2.54 g, 80%): $[\alpha]_D^{20} = 24$, ($c = 0.85$, CH_2Cl_2). The analytical data were in accordance with those of the corresponding enantiomer.

(5E,4R)-(–)-4-(3,4-Dimethoxyphenyl)-4-isopropylhept-5-enyl Acetate [(–)-18]: Treatment of alcohol (–)-17 (2.78 g, 9.2 mmol) with acetic anhydride (5 mL) in pyridine (10 mL) gave the corresponding acetate (–)-18, which was purified by column chromatography, eluting with hexane/ethyl acetate 8:2 (3.01 g, 98%). – $[\alpha]_D^{20} = -28$, ($c = 0.92$, CH_2Cl_2). – ^1H NMR: $\delta_{\text{H}} = 6.80$ (m, 3 H, aromatic hydrogens), 5.70–5.40 [m, 2 H, C(4)H and C(5)H], 3.92 (t, $J = 6.7$, 2 H, CH_2OAc), 3.87 [s, 3 H, OMe], 3.86 [s, 3 H, OMe], 2.16 [septet, $J = 6.7$, 1 H, $\text{CH}(\text{Me})_2$], 2.01 (s, 3 H, CH_3COO), 1.83 (d, $J = 5.5$, 3 H, $\text{CH}_3\text{C}=\text{C}$), 1.1–1.80 (m, 4 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OAc}$), 0.83 (d, $J = 7$, 3 H, CH_3CH), 0.73 (d, $J = 7$, 3 H, CH_3CH); GC-MS: temp. B: $t_{\text{R}} = 17.47$ min, $m/z = 334$ [M^+], 291, 231, 189. – $\text{C}_{20}\text{H}_{30}\text{O}$: calcd. C 71.82, H 9.04; found C 71.87, H 9.09.

(5E,4S)-(+)-4-(3,4-Dimethoxyphenyl)-4-isopropylhept-5-enyl Acetate [(+)-18]: Treatment of alcohol (+)-17 (2.50 g, 9.2 mmol) with acetic anhydride (5 mL) in pyridine (10 mL) gave the corresponding acetate (+)-18, which was purified by column chromatography, eluting with hexane/ethyl acetate 8:2 (2.84 g, 98%). $[\alpha]_D^{20} = 26$, ($c = 0.85$, CH_2Cl_2); the analytical data were in accordance with those of the corresponding enantiomer.

(4S)-(–)-4-(3,4-Dimethoxyphenyl)-4-formyl-5-methylhexyl acetate [(–)-19]: Ozonolysis of derivative (–)-18 (3.00 g, 9.8 mmol) in dichloromethane/methanol 1:1 solution (30 mL) gave, after treatment with triphenylphosphane, aldehyde (–)-14 (1.97 g, 68%). – $[\alpha]_D^{20} = -43$, ($c = 0.42$, CH_2Cl_2). – ^1H NMR: $\delta_{\text{H}} = 9.81$ (s, 1 H, CHO), 6.88 [d, $J = 8$, 1 H, aromatic hydrogen C(5)H], 6.71 [dd, $J = 2$ and 8, 1 H, aromatic hydrogen C(6)H], 6.66 [d, $J = 2$, 1 H, aromatic hydrogen C(2)H], 4.00 (t, $J = 6$, 2 H, CH_2OAc), 3.89 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 2.38 [septet, $J = 7$, 1 H, $\text{CH}(\text{Me})_2$], 2.02 (s, 3 H, CH_3COO), 1.90 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OAc}$), 1.41 (m, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OAc}$), 0.94 (d, $J = 7$, 3 H, CH_3CH), 0.86 (d, $J = 7$, 3 H, CH_3CH). – GC-MS: temp. B: $t_{\text{R}} = 18.29$ min, $m/z = 322$ [M^+], 293, 233, 219, 191, 177, 165. – $\text{C}_{18}\text{H}_{26}\text{O}_5$: calcd. C 67.06, H 8.13; found C 67.01, H 8.16.

(4R)-(+)-4-(3,4-Dimethoxyphenyl)-4-formyl-5-methylhexyl Acetate [(+)-19]: Ozonolysis of derivative (+)-18 (2.50 g, 7.5 mmol) in dichloromethane/methanol 1:1 solution (30 mL) gave, after treatment with triphenylphosphane, aldehyde (+)-19 (1.66 g, 69%): $[\alpha]_D^{20} = 42$, ($c = 0.35$, CH_2Cl_2). The analytical data were in accordance with those of the corresponding enantiomer.

(4S)-(-)-4-Cyano-4-(3,4-dimethoxyphenyl)-5-methylhexyl Acetate [(-)-20]: Derivative (-)-19 (1.97 g, 6.1 mmol) was treated with hydroxylamine chloride (0.64 g, 9.15 mmol) in ethanol (10 mL) in the presence of sodium acetate (0.75 g, 6.1 mmol). After the usual workup, the oxime derivative was refluxed in acetic anhydride to give, after purification on column chromatography eluting with hexane/ethyl acetate 1:1, nitrile (-)-15 (1.52 g, 75%). – $[\alpha]_D^{20} = -19.5$, ($c = 0.75$, CH_2Cl_2). – ^1H NMR: $\delta_{\text{H}} = 6.95\text{--}6.85$ (m, 3 H, aromatic hydrogens), 4.00 (t, $J = 6.4$, 2 H, CH_2OAc), 3.90 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 2.18 (m, 1 H, $\text{CHHCH}_2\text{CH}_2\text{OAc}$), 2.08 [septet, $J = 7$, 1 H, $\text{CH}(\text{Me})_2$], 2.02 (s, 3 H, CH_3COO), 1.85 (m, 1 H, $\text{CHHCH}_2\text{CH}_2\text{OAc}$), 1.71 (m, 1 H, $\text{CH}_2\text{CHHCH}_2\text{OAc}$), 1.41 (m, 1 H, $\text{CH}_2\text{CHHCH}_2\text{OAc}$), 1.20 (d, $J = 7$, 3 H, CH_3CH), 0.81 (d, $J = 7$, 3 H, CH_3CH). – GC-MS: temp. B: $t_{\text{R}} = 17.71$ min, $m/z = 319$ [M^+], 277, 235, 216, 207, 185. – $\text{C}_{18}\text{H}_{25}\text{NO}_4$: calcd. C 67.69, H 7.89, N 4.39; found C 67.63, H 7.83, N 4.43.

(4R)-(+)-4-Cyano-4-(3,4-dimethoxyphenyl)-5-methylhexyl Acetate [(+)-20]: Derivative (+)-19 (1.66 g, 5.2 mmol) was converted in derivative (+)-20 (1.19 g, 73%) by the same procedure as for the conversion of (-)-19 into (-)-20. The analytical data were in accordance with those of the corresponding enantiomer: $[\alpha]_D^{20} = 19.1$, ($c = 0.80$, CH_2Cl_2).

(2S)-(-)-2-(3,4-Dimethoxyphenyl)-5-hydroxy-2-isopropylpentanenitrile [(-)-21]: A solution of compound (-)-20 (1.50 g, 4.7 mmol), and potassium hydroxide 85% (0.47 g, 7.05 mmol) in methanol (20 mL) was refluxed for 2 h. After the usual workup, the residue was purified on a silica gel column chromatography, using hexane/acetate 3:7 as an eluent, to afford derivative (-)-21 (1.19 g, 92%); $[\alpha]_D^{20} = -11.5$, ($c = 2.75$ CHCl_3); optical purity = 91% *ee* ref.^[5]: $[\alpha]_D^{20} = -12.6$, ($c = 3.84$ CHCl_3). – ^1H NMR: $\delta_{\text{H}} = 6.93$ [dd, $J = 8$ and 2, 1 H, aromatic hydrogen C(6)H], 6.88 [d, $J = 2$, 1 H, aromatic hydrogen C(2)H], 6.86 [d, $J = 8$, 1 H, aromatic hydrogen C(5)H], 3.89 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.60 (m, 2 H, CH_2OH), 2.21 (ddd, $J = 13$, 11 and 4, 1 H, $\text{CHHCH}_2\text{CH}_2\text{OAc}$), 2.09 [septet, $J = 7$, 1 H, $\text{CH}(\text{Me})_2$], 1.93 (ddd, $J = 13$, 11 and 4, 1 H, $\text{CHHCH}_2\text{CH}_2\text{OAc}$), 1.62 (m, 1 H, $\text{CH}_2\text{CHHCH}_2\text{OAc}$), 1.28 (m, 1 H, $\text{CH}_2\text{CHHCH}_2\text{OAc}$), 1.19 (d, $J = 7$, 3 H, CH_3CH), 0.81 (d, $J = 7$, 3 H, CH_3CH). – GC-MS: temp. progr. B, $t_{\text{R}} = 16.61$ min, $m/z = 277$ [M^+], 234, 216, 185.

(2R)-(+)-2-(3,4-Dimethoxyphenyl)-5-hydroxy-2-isopropylpentanenitrile [(+)-21]: Derivative (+)-20 (1.19 g, 3.7 mmol) was converted into derivative (+)-21 (0.92 g, 90%) by the same procedure as for the conversion of (-)-20 into (-)-21: $[\alpha]_D^{20} = 10$, ($c = 2.90$ CHCl_3); the analytical data were in accordance with those of the enantiomer (-)-21.

(2S)-(-)-5-Chloro-2-(3,4-dimethoxyphenyl)-2-isopropylpentanenitrile [(-)-5]: A solution of alcohol derivative (-)-21 (1.19 g, 4.3 mmol) and triphenylphosphane (2.25 g, 8.6 mmol) in carbon tetrachloride (20 mL) was refluxed for 2 h. The title compound was recovered from the reaction mixture by column chromatography (1.20 g, 95%); $[\alpha]_D^{20} = -11.2$, ($c = 1.15$ methanol); optical purity = 91% *ee*; ref.^[3] $[\alpha]_D^{20} = -12.3$, $c = 1$ methanol. – ^1H NMR: $\delta_{\text{H}} = 6.94$ [dd, $J = 8$ and 2, 1 H, aromatic hydrogen C(6)H], 6.88–6.84 [two overlapping doublets $J = 2$ and 8, 2 H, aromatic hydrogens C(2)H and C(5)H], 3.90 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.49 (m, 2 H, CH_2Cl), 2.23 (ddd, $J = 13$, 12 and 4, 1 H, $\text{CHHCH}_2\text{CH}_2\text{Cl}$), 2.15–2.00 (m, 2 H, $\text{CH}(\text{Me})_2 + \text{CHHCH}_2\text{CH}_2\text{OCl}$), 1.87 (m, 1 H, $\text{CH}_2\text{CHHCH}_2\text{Cl}$), 1.47 (m, 1 H, $\text{CH}_2\text{CHHCH}_2\text{Cl}$), 1.20 (d, $J = 7$, 3 H, CH_3CH), 0.82 (d, $J = 7$, 3 H, CH_3CH). – GC-MS: temp. progr. B, $t_{\text{R}} = 16.05$ min, $m/z = 295$ [M^+], 252, 189.

(2R)-(+)-5-Chloro-2-(3,4-dimethoxyphenyl)-2-isopropylpentanenitrile [(+)-5]: Alcohol derivative (+)-21 (0.90 g, 3.2 mmol) was converted into (+)-5 (0.92 g, 96%) according to the same procedure for the conversion of (-)-21 into (-)-5: $[\alpha]_D^{20} = 11.0$, ($c = 1.22$ methanol); ref.^[3] $[\alpha]_D^{20} = 11.6$, ($c = 1$ methanol); the ^1H NMR was in accordance with that of the enantiomer.

(S)-(-)-Verapamil: A mixture of chloro derivative (-)-5 (1.20 g, 12.6 mmol) and *N*-methylhomoveratrylamine (5.01 g) was heated at 130 °C for 1 h. The reaction mixture was treated with a 1 N solution of sodium hydroxide and extracted with diethyl ether. The title compound was recovered by column chromatography, eluting with dichloromethane/methanol 97:3 (1.77 g, 91%). – $[\alpha]_D^{20} = -8.2$, ($c = 5.08$ ethanol); ref.^[4]: $[\alpha]_D^{20} = -8.9$, ($c = 5.00$ ethanol). – ^1H NMR: $\delta_{\text{H}} = 6.94$ (dd, $J = 8$ and 2, 1 H, aromatic hydrogen), 6.89 (d, $J = 2$, 1 H, aromatic hydrogen), 6.84 (d, $J = 8$, 1 H, aromatic hydrogen), 6.79 (d, $J = 8$, 1 H, aromatic hydrogen), 6.71 (d, $J = 2$, 1 H, aromatic hydrogen), 6.68 (dd, $J = 8$ and 2, 1 H, aromatic hydrogen), 3.90 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 2.68 (m, 2 H), 2.52 (m, 2 H), 2.36 (m, 2 H), 2.18 (s, 3 H, NMe), 2.11 (m, 1 H), 2.07 [septet, $J = 7$, 1 H, $\text{CH}(\text{Me})_2$], 1.83 (m, 1 H), 1.55 (m, 1 H), 1.19 (m + d, $J = 7$, 4 H), 0.80 (d, $J = 7$, 3 H, CH_3CH).

(R)-(+)-Verapamil: Chloro derivative (+)-5 (0.92 g, 3.12 mmol) was converted into the title compound by the same procedure as described for (S)-(-)-verapamil (1.36 g, 92%); the specific rotatory power was determined on the corresponding HCl salt: $[\alpha]_D^{20} = +8.3$, ($c = 5.05$ in ethanol); ref.^[4]: $[\alpha]_D^{20} = +8.8$, ($c = 5.00$ ethanol). The ^1H NMR spectrum was in accordance with that of the (-)-enantiomer.

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