Formal total syntheses of (−)-oudemansins A, B and X based on a lipase-catalysed hydrolysis of an acetate

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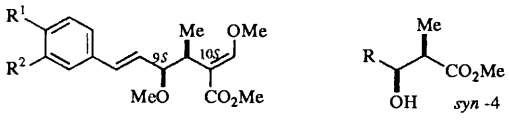
A highly stereoselective synthesis of versatile chiral synthons possessing two stereogenic centres and based on the enzymic hydrolysis of an acetate, has been achieved and an application of this to the formal total synthesis of (−)-oudemansins A (**1**), B (**2**) and X (**3**) is described.

Introduction

Three (−)-oudemansins A **1**,[1] B **2**[2] and X **3**[3] were first isolated by Anke and Steglich and their co-workers. Oudemansin A **1** was first isolated from mycelial cultures of *Oudemansiella mucida* in 1979. Oudemansins B **2** and X **3** were also isolated from submerged cultures of *Xerula melanotricha* in 1983 and from another basidiomycete fungus, *Oudemansiella radicata*, as recently as 1990, respectively. The fungicidal activity of the oudemansins arises from their ability to inhibit mitochondrial respiration in fungi. The oudemansins have (*E*)-styryl- and β-methoxyacrylate moieties and two contiguous stereogenic centres with the (9*S*,10*S*)-configuration, but differ in their functionalities in the aromatic portion of their molecules; these features focused considerable interest on them as target molecules for synthesis. Three different synthetic approaches to racemic oudemansins have been described[4] and several syntheses of homochiral oudemansins have been published.[5] The earliest homochiral synthesis of (−)-oudemansin A **1** was especially prominent for its determination of the absolute structure.[5a] The most intriguing point is how to construct common suitable intermediates with the required *syn*-stereochemistry as shown in the structure of *syn*-3-hydroxy-2-methyl ester **4** and with the desired absolute configuration.



syn-4

$R^1 = R^2 = H$	Oudemansin A	**1**
$R^1 = Cl, R^2 = OMe$	Oudemansin B	**2**
$R^1 = OMe, R^2 = H$	Oudemansin X	**3**

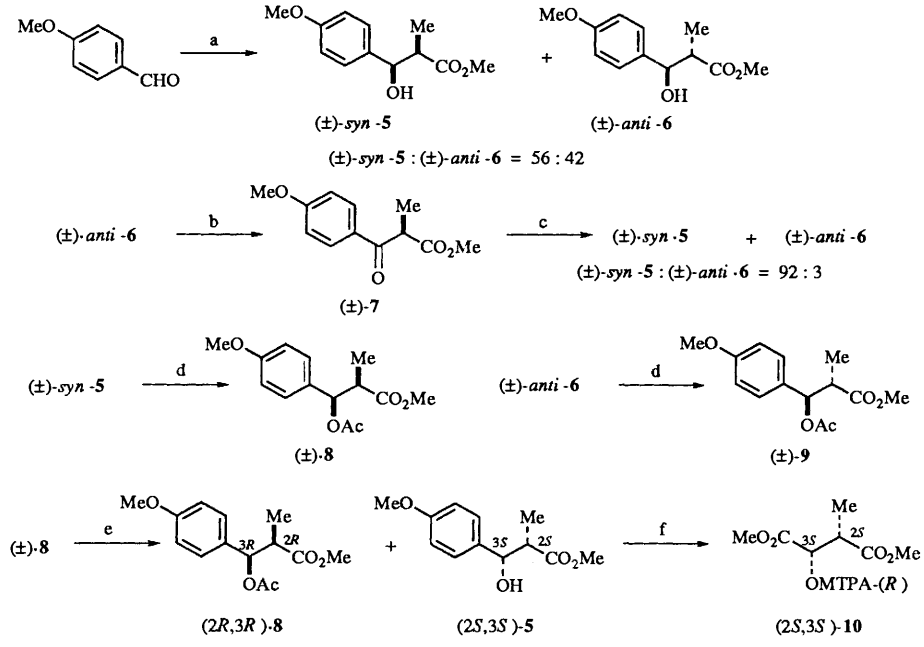
The optically active *syn*-3-hydroxy-3-(*p*-methoxyphenyl)-2-methylpropanoate **5** or its acetate **8** involving two stereogenic centres was selected as the target molecule because a *p*-methoxyphenyl group is convertible into a carboxylic acid or its congeners *via* ozonolytic cleavage. We now report the synthesis of two optically active building blocks, β-acetoxy esters (2*R*,3*R*)-**8** and (2*S*,3*S*)-**8** based on enzymic kinetic resolution (see Scheme 1), and the application of ester (2*R*,3*R*)-**8** to the formal total syntheses of the fungicide oudemansins A **1**, B **2** and X **3**.

Results and discussion

Reformatsky reaction of *p*-anisaldehyde and methyl α-bromopropionate gave the (±)-*syn*-β-hydroxy-α-methyl ester **5** (56% yield) and (±)-*anti*-β-hydroxy-α-methyl ester **6** (42% yield). Oxidation of compound (±)-**6** with Jones' reagent to afford the (±)-β-keto ester **7** (95% yield), which was reduced with $Zn(BH_4)_2$ to provide the (±)-*syn*-**5** (92% yield) along with a small amount of the (±)-*anti*-**6** (3% yield).

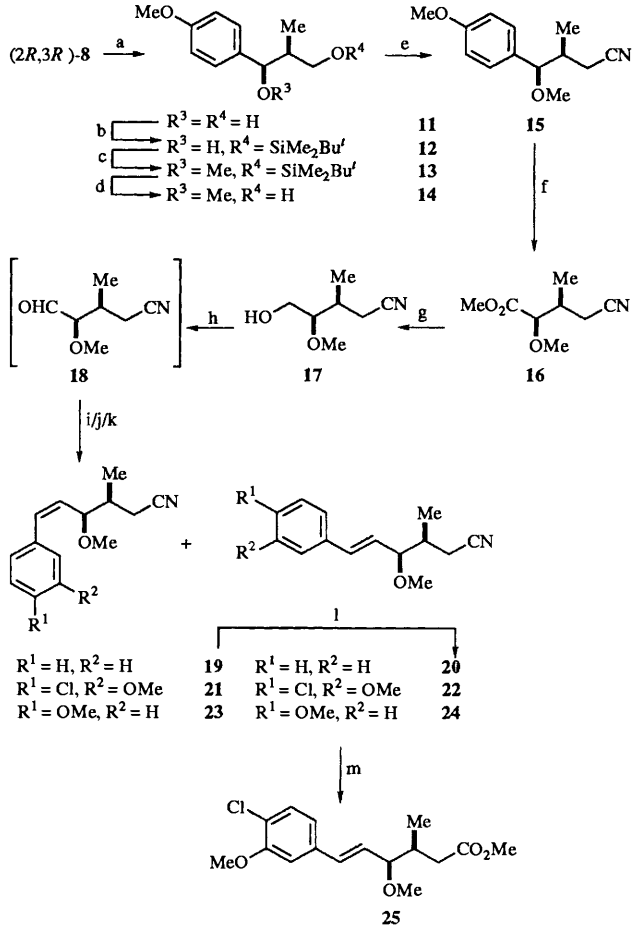
As $Zn(BH_4)_2$ reduction of the α-methyl-β-keto ester was reported to give predominantly the *syn*-α-methyl-β-hydroxy ester,[6] the relative structure of the present racemate (±)-**5** was assigned the *syn*-structure. The thus obtained racemates (±)-*syn*-**5** and (±)-*anti*-**6** were converted into the corresponding acetates (±)-*syn*-**8** and (±)-*anti*-**9** in 97 and 90% yield, respectively. The former was employed as a substrate for enzymic hydrolysis. At first, in order to determine the optical purity of the enzymic reaction products, two racemates [(±)-**5** and (±)-**8**] were subjected to HPLC analysis using a chiral column (CHIRALCEL OD, 4.6 × 250 mm) to give two well separated peaks. Details are given in the Experimental section. By taking account of our previously reported method,[7] racemate (±)-*syn*-**8** was found to be hydrolysed enantioselectively when using the lipase 'Amano A' from *Aspergillus niger* to afford alcohol **5** {$[\alpha]_D$ -16.4×10^{-1} deg cm^2 g^{-1} (*c* 4.7, $CHCl_3$), 51% yield} in high optical yield [94% enantiomeric excess (ee)] along with the unchanged acetate **8** {$[\alpha]_D$ +47.3 (*c* 4.6, $CHCl_3$), 48% yield, >99% ee}. When the lipase 'Amano A-6' from *A. niger* instead of the lipase 'Amano A' was employed, alcohol **5** (48% yield, 87% ee) and the unchanged acetate **8** (47% yield, >99% ee) were obtained. The optical purities of compounds (−)-**5** and (+)-**8** were calculated based on HPLC analysis after chromatographic separation. The absolute structure of compound (−)-**5** was determined as follows. The (−)-alcohol **5** (94% ee) was treated with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*R*)-MTPACl][8] to provide the (*R*)-MTPA ester [(−)-**5**-(*R*)-MTPA]. Ozonolysis of (−)-**5**-(*R*)-MTPA ester followed by oxidative treatment and subsequent esterification gave a diester **10**, whose NMR spectra were identical with those of authentic diester (2*S*,3*S*)-**10**.[9] Consequently, alcohol (−)-**5** should possess a 2*S*,3*S* configuration and thence the absolute configuration of acetate (+)-**8** is determined to be 2*R*,3*R*. For the purpose of enrichment of optical purity of alcohol (−)-**5**, this compound was converted into the (2*S*,3*S*)-acetate **8**, which was recrystallized to give an optically pure acetate (2*S*,3*S*)-**8** (>99% ee).

Reduction of acetate (2*R*,3*R*)-**8** with $LiAlH_4$ gave the (+)-1,3-diol **11** {$[\alpha]_D$ +58.1 (*c* 1.04, $CHCl_3$), 94% yield}, which was treated with *tert*-butyldimethylsilyl chloride (TBDMSCl) to give the (+)-monosilyl ether **12** {$[\alpha]_D$ +31.5 (*c* 1.52, $CHCl_3$), 97% yield} (Scheme 2). Methylation of the alcohol (+)-**12** yielded the (+)-methoxy silyl ether **13** {$[\alpha]_D$ +44.9 (*c* 1.48, $CHCl_3$), 99% yield}, which was treated with fluoride ion to afford the (+)-methoxy alcohol **14** {$[\alpha]_D$ +7.67 (*c* 0.99, $CHCl_3$), 91% yield}. Tosylation of alcohol (+)-**14** followed by treatment of NaCN afforded the (+)-methoxy nitrile **15** {$[\alpha]_D$



Scheme 1 *Reagents*: a, $MeCHBrCO_2Me$, Zn, PhH; b, CrO_3/H^+; c, $Zn(BH_4)_2/Et_2O$; d, Ac_2O–pyridine; e, lipase 'Amano A' in phosphate buffer (pH 7.25); f, (1) (*R*)-MTPACl/pyridine, (2) O_3, CCl_4, (3) 30% H_2O_2, (4) CH_2N_2

+34.4 (*c* 1.17, $CHCl_3$)} in 91% overall yield. Ozonolysis of aromatic compound (+)-**15** followed by oxidative treatment and subsequent esterification with CH_2N_2 provided the (+)-methyl ester **16** {$[\alpha]_D$ +44.5 (*c* 1.18, $CHCl_3$)} in 39% overall yield, which was reduced with $LiBH_4$ to give the alcohol **17** in 80% yield. Oxidation of alcohol **17** with pyridinum chlorochromate (PCC) followed by individual treatment of the benzylphosphonium salt in the presence of BuLi produced a mixture of double-bond-formation products **19**–**24**. That is to say, Wittig reaction of the aldehyde **18** and benzylphosphonium bromide gave a mixture of (*Z*)-**19** and (*E*)-**20** in a ratio of ~1:1 in 67% yield. This mixture was separated by silica gel column chromatography to compounds (+)-**19** {$[\alpha]_D$ +59.6 (*c* 0.305, $CHCl_3$), $J_{7,8}$ 12.2} and (−)-**20** {$[\alpha]_D$ −32.9 (*c* 0.455, $CHCl_3$), $J_{7,8}$ 16}. Isomerization of compound (*Z*)-**19** by using thiophenol in the presence of 2,2′-azoisobutyronitrile (AIBN) at reflux proceeded very efficiently to afford compound (*E*)-**20** (70% yield) and unchanged **19** (29% recovery). The physical data (IR and 400 MHz NMR) of the obtained isomer (*E*)-**20** were identical with those previously reported.[5a] Wittig alkenation of aldehyde **18** with 4-chloro-3-methoxyphenylmethylenephosphonium bromide afforded a ~1:1 mixture of isomers (*Z*)-**21** and (*E*)-**22** in 57% yield, which was separated into compounds (*Z*)-**21** {$[\alpha]_D$ +40.4 (*c* 0.91, $CHCl_3$), $J_{7,8}$ 12} and (*E*)-**22** {$[\alpha]_D$ −29.8 (*c* 1.05, $CHCl_3$), $J_{7,8}$ 16}. Conversion of nitrile (−)-**22** into the methyl ester **25** {$[\alpha]_D$ +10.1 (*c* 1.0, $CHCl_3$)} was achieved by the standard procedure (alkaline hydrolysis and then esterification) in 59% overall yield. The physical data (IR, NMR and $[\alpha]_D$) of the synthesized ester (+)-**25** were identical with those previously reported for isomer (+)-**25** {$[\alpha]_D$ +10.23 ($CHCl_3$)}.[5d,e] The third Wittig reaction of aldehyde **18** and 4-methoxyphenylmethylenephosphonium chloride yielded a ~1:1 mixture of isomers (*Z*)-**23** and (*E*)-**24** in 73% yield, which was separated into components (*Z*)-**23** {$[\alpha]_D$ +74.7 (*c* 1.08, $CHCl_3$), $J_{7,8}$ 11.7} and (*E*)-**24** {$[\alpha]_D$ −35.0 (*c* 1.1, $CHCl_3$), $J_{7,8}$ 15.6}. The physical data (IR, NMR and $[\alpha]_D$) of compound (−)-**24** were identical with those previously reported.[5f–h] Conversion of isomer (*Z*)-**23** into isomer (*E*)-**24** has already been reported.[5h] The obtained intermediates (−)-**20**, (−)-**22** and (−)-**24** have already been converted into the (−)-oudemansins A **1**,[5a] B **2**,[5d,e] and X **3**,[5f–h] respectively.



Scheme 2 *Reagents and conditions:* a, $LiAlH_4$–THF; b, Bu^tMe_2SiCl, imidazole, DMF; c, MeI, KH, THF; d, $Bu_4N^+F^-$/THF; e, (1) TsCl–pyridine; (2) NaCN–DMSO; f, (1) O_3–AcOEt, (2) 30% H_2O_2, (3) CH_2N_2; g, $LiBH_4$–THF; h, PCC–CH_2Cl_2; i, benzyltriphenylphosphonium bromide, BuLi; j, 4-chloro-3-methoxyphenylmethyl(triphenyl)-phosphonium bromide, BuLi; k, 4-methoxyphenylmethyl(triphenyl)-phosphonium chloride/BuLi; l, PhSH, AIBN, PhH, reflux; m (from **22**), (1) KOH, (2) H^+, (3) CH_2N_2

Experimental

All mps were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. IR spectra were measured on a JASCO FT/IR-300 instrument. NMR spectra were measured on a JEOL EX 4000 instrument. Spectra were taken for 5–10% (w/v) solutions in $CDCl_3$ with Me_4Si as internal reference, and J values are given in Hz. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D 300 or JEOL JMS-DX 303 spectrometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter, and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. The HPLC system was composed of two SSC instruments (UV detector 3000B and flow system 3100). All organic-solvent extracts were washed with saturated brine and dried over anhydrous magnesium sulfate ($MgSO_4$). All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

(±)-Methyl (2,3-*syn*)-3-hydroxy-3-(4-methoxyphenyl)-2-methylpropanoate 5 and (±)-methyl (2,3-*anti*)-3-hydroxy-3-(4-methoxyphenyl)-2-methylpropanoate 6

A stirred mixture of *p*-anisaldehyde (16 g), methyl α-bromopropanoate (21.6 g) and activated Zn dust [prepared from Zn (10 g)] in dry benzene (100 cm^3) was refluxed for 1 h. The reaction mixture was diluted with water, 10% hydrochloric acid was added and the mixture was extracted with diethyl ether. The organic layer was washed with saturated aq. $NaHCO_3$. Evaporation of the organic solvent provided a crude oily product, which was chromatographed on silica gel (300 g) to afford homogeneous oils (±)-**5** (14.8 g, 56%) and (±)-**6** (11.1 g, 42%) from the hexane–ethyl acetate (20:1) eluate in elution order. Racemate (±)-**5**: oil (Found: M$^+$, 224.1050. Calc. for $C_{12}H_{16}O_4$: M, 224.1049); $\nu_{max}(CCl_4)$/cm^{-1} 3520 and 1715; δ_H 1.15 (3 H, d, *J* 7, 2-Me), 2.76 (1 H, dq, *J* 4 and 7, 2-H), 2.84 (1 H, d, *J* 3.2, 3-OH), 3.66 (3 H, s, CO_2Me), 3.80 (3 H, s, OMe), 5.02 (1 H, dd, *J* 3.2 and 4, 3-H) and 6.87 and 7.25 (each 2 H, d, *J* 8.4, ArH). Compound (±)-**6**: oil, *m/z* 224 (M$^+$); ν_{max}(Nujol)/cm^{-1} 3452 and 1714; δ_H 0.98 (3 H, d, *J* 7.3, 2-Me), 2.79 (1 H, dq, *J* 7.3 and 8.8, 2-H), 2.85 (1 H, d, *J* 3.9, 3-OH), 3.73 (3 H, s, CO_2Me), 3.80 (3 H, s, OMe), 4.70 (1 H, *J* 3.9 and 8.8, 3-H) and 6.88 and 7.26 (each 2 H, d, *J* 8.8, ArH).

Conversion of compound (±)-*anti*-6 into isomer (±)-*syn*-5

To a stirred solution of racemate (±)-**6** (1.06 g) in acetone (150 cm^3) cooled in ice–water was added Jones' reagent (55 cm^3). After the mixture had been stirred for 1 h at the same temperature, isopropyl alcohol (50 cm^3) was added and the whole was stirred for 10 min. The reaction mixture was concentrated, diluted with water and extracted with diethyl ether. The organic layer was evaporated to give a residue, which was chromatographed on silica gel (300 g) to afford homogeneous, oily keto ester (±)-**7** (28.63 g, 95%) from the hexane–ethyl acetate (10:1) eluate. Compound (±)-**7**: oil (Found: C, 64.6; H, 6.3. Calc. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35%); ν_{max}(neat)/cm^{-1} 1743 and 1676; δ_H 1.48 (3 H, d, *J* 6.8, 2-Me), 3.68 (3 H, s, CO_2Me), 3.87 (3 H, s, OMe), 4.38 (1 H, q, *J* 6.8, 2-H) and 6.95 and 7.97 (each 2 H, d, *J* 9.3, ArH).

A $Zn(BH_4)_2$–diethyl ether solution (180 cm^3) [prepared from a 0.9 mol dm^{-3} solution of $ZnCl_2$ in diethyl ether (80 cm^3) and $NaBH_4$ (4 g) in diethyl ether (300 cm^3)] was added to a solution of racemate (±)-**7** (21.61 g) in dry CH_2Cl_2 (100 cm^3) under argon at −20 °C and the reaction mixture was stirred for 1 h at the same temperature. After the addition of 10% hydrochloric acid the whole was extracted with diethyl ether. The extract was washed with saturated aq. $NaHCO_3$. Removal of the solvent gave a residue, which was chromatographed on silica gel (200 g) to provide hydroxy ester (±)-**5** (20.14 g, 92%) and its isomer (±)-**6** (0.68 g, 3%) from the hexane–ethyl acetate (20:1) eluate in elution order.

(±)-Methyl (2,3-*syn*)-3-acetoxy-3-(4-methoxyphenyl)-2-methylpropanoate 8

A mixture of alcohol (±)-**5** (6.70 g), Ac_2O (10 cm^3) and pyridine (10 cm^3) was stirred for 4 h at room temperature. The reaction mixture was diluted with water and extracted with diethyl ether. The extract was washed successively with saturated aq. $NaHCO_3$ and saturated brine, and was dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (150 g) to provide homogeneous, oily acetate (±)-**8** (7.70 g, 97%) from the hexane–ethyl acetate (9:1) eluate. Compound (±)-**8**: oil (Found: M$^+$, 266.1154. Calc. for $C_{14}H_{18}O_5$: *M*, 266.1154); $\nu_{max}(CCl_4)$/cm^{-1} 1744; δ_H 1.23 (3 H, d, *J* 6.8, 2-Me), 2.08 (3 H, s, OAc), 2.94 (1 H, dq, *J* 6.8 and 7.6, 2-H), 3.56 (3 H, s, CO_2Me), 3.79 (3 H, s, OMe), 5.97 (1 H, d, *J* 7.6, 3-H) and 6.85 and 7.24 (each 2 H, d, *J* 8, ArH).

(±)-Methyl (2,3-*anti*)-3-acetoxy-3-(4-methoxyphenyl)-2-methylpropanoate 9

A mixture of alcohol (±)-**6** (7.034 g), Ac_2O (12 cm^3) and pyridine (25 cm^3) was stirred for 4 h at room temperature. The reaction mixture was worked up and purified in the same way as in the preparation of isomer (±)-**8** to give acetoxy ester (±)-**9** as a homogeneous oil (7.530 g, 90%), which was crystallized from hexane to afford needles, mp 80–81 °C (Found: C, 63.2; H, 6.9. Calc. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81%); ν_{max}(Nujol)/cm^{-1} 1732; δ_H 0.96 (3 H, d, *J* 6.8, 2-Me), 1.98 (3 H, s, OAc), 2.98 (1 H, dq, *J* 6.8 and 10.3, 2-H), 3.72 (3 H, s, CO_2Me), 3.79 (3 H, s, OMe), 5.80 (1 H, d, *J* 10.3, 3-H), 6.88 and 7.27 (each 2 H, d, *J* 8.8, ArH).

HPLC analysis of the racemic alcohol (±)-5 and acetate (±)-8 by using a chiral column

Two racemates [(±)-**5** and (±)-**8**] gave individually two well separated peaks [(±)-**5**; 32.1 and 39.9 min, (±)-**8**; 11.0 and 12.4 min] corresponding to each enantiomer under the following analytical conditions (eluent, hexane–EtOH (100:1); detection, UV at 254 nm; flow rate, 1.0 cm^3 min^{-1}).

Enantioselective hydrolysis of acetate

A mixture of racemate (±)-**8** (~100 mg) and lipase 'Amano A' (~50 mg) and 0.1 mol dm^{-3} phosphate buffer (pH 7.25; 20 cm^3) was incubated at 33 °C for 8 h. This reaction was carried out five times [total amount of (±)-**8** was 499 mg]. The reaction mixture was filtered and the filtrate was extracted with diethyl ether. The extract was evaporated to give a crude product, which was chromatographed on silica gel (20 g) to afford acetate (2*R*,3*R*)-**8** (241 mg, 48%) from the hexane–ethyl acetate (19:1) eluate and alcohol (2*S*,3*S*)-**5** (218 mg, 51%) from the hexane–ethyl acetate (9:1) eluate. Enantiomeric excess (ee) of acetate **8** and alcohol **5** was analysed by HPLC. Acetoxy ester (2*R*,3*R*)-**8**; crystallization from hexane gave needles, mp 58.5–59.5 °C (Found: C, 62.9; H, 6.9. Calc. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81%); $[\alpha]_D^{22}$ +47.3 (*c* 4.6, $CHCl_3$), corresponding to >99% ee. Alcohol (2*S*,3*S*)-**5**; oil (Found: C, 64.0; H, 7.3. Calc. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%); $[\alpha]_D^{22}$ −16.4 (*c* 4.7, $CHCl_3$), corresponding to 94% ee. In the case with lipase 'Amano A-6', the alcohol (2*S*,3*S*)-**5** (207 mg, 48%, 87% ee) and the unchanged acetate (2*R*,3*R*)-**8** (239 mg, 47%, >99% ee) were obtained from the starting substrate (±)-**8** (512 mg) in the same way as in the enantioselective hydrolysis using lipase 'Amano A'.

Determination of absolute structure of enzymic resolution product

(1) Pyridine (0.5 cm^3) was added to a mixture of alcohol **5** (53

mg) and (*R*)-MTPACl (72 mg) and the reaction mixture was stirred for 17 h at room temperature, diluted with water and extracted with diethyl ether. The extract was evaporated to give an oily product, which was subjected to preparative TLC [PLC; silica gel (20 × 20 cm); solvent, hexane–ethyl acetate (4:1)] to provide (2*S*,3*S*)-**5**-(*R*)-MTPA ester (88 mg) as a homogeneous oil.

(2) Ozone was passed through a solution of (2*S*,3*S*)-**5**-(*R*)-MTPA (88 mg) in CCl_4 (10 cm^3) at room temperature for 90 min, then 30% aq. H_2O_2 (5 cm^3) was added to the ozonolysed product and the reaction mixture was stirred for 15 min at room temperature before being diluted with water and extracted with diethyl ether. Removal of the solvent gave a residue, which was treated with a solution of CH_2N_2 in diethyl ether to provide an oily product. This was subjected to silica gel PLC [solvent, hexane–ethyl acetate (3:1)] to afford the dimethyl ester **10** (17 mg). The 400 MHz NMR spectrum of product **10** was identical with that of authentic (2*S*,3*S*)-(*R*)-MTPA ester **10**.[9]

(+)-(2,3-*syn*)-3-(4-Methoxyphenyl)-2-methylpropane-1,3-diol 11

To a stirred mixture of $LiAlH_4$ (1.54 g) in tetrahydrofuran (THF) (40 cm^3) was added a solution of acetate (2*R*,3*R*)-**8** (7.19 g) in THF (30 cm^3) at 0 °C and the mixture was stirred for 30 min at the same temperature. The reaction mixture was treated with water (1 cm^3), then was diluted with ethyl acetate, and filtered with the aid of Celite. The filtrate was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (160 g) to afford a homogeneous, oily compound **11** from the hexane–ethyl acetate (2:3) eluate. Crystallization of oily diol **11** from ethyl acetate–hexane gave needles (4.99 g, 94%). Diol (+)-**11**: mp 88–90 °C; $[\alpha]_D^{18}$ +58.1 (*c* 1.04, $CHCl_3$) (Found: C, 67.2; H, 8.3. Calc. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22%); ν_{max}(Nujol)/cm^{-1} 3305; δ_H 0.82 (3 H, d, *J* 7.3, 2-Me), 1.84 (1 H, s, OH), 1.97–2.08 (1 H, m, 2-H), 2.85 (1 H, br s, OH), 3.24 (1 H, br s, OH), 3.60 (2 H, d, *J* 4.9, 1-H_2), 3.79 (3 H, s, OMe), 4.84 (1 H, br s, 3-H) and 6.87 and 7.23 (each 2 H, d, *J* 8.3, ArH).

(+)-(1,2-*syn*)-3-(*tert*-Butyldimethylsiloxy)-1-(4-methoxyphenyl)-2-methylpropan-1-ol 12

To a stirred, ice–water-cooled solution of diol (+)-**11** (4.87 g) in dimethylformamide (DMF) (25 cm^3) were added TBDMSCl (4.87 g) and imidazole (4.4 g) over a period of 20 min. The reaction mixture was diluted with water and extracted with diethyl ether. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (280 g) to afford siloxy alcohol **12** as an oil (7.487 g, 97%) from the hexane–ethyl acetate (30:1). Compound (+)-**12**: *m/z* 293 (M^+ − OH); $[\alpha]_D^{18}$ +31.5 (*c* 1.52, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3465; δ_H 0.08 (6 H, s, $SiMe_2$), 0.83 (3 H, d, *J* 7.3, 2-Me), 0.94 (9 H, s, SiBu^t), 1.95–2.03 (1 H, m, 2-H), 3.55 (1 H, d, *J* 3.4, OH), 3.61 (1 H, dd, *J* 5.9 and 10, 3-H), 3.71 (1 H, dd, *J* 3.9 and 10, 3-H), 3.80 (3 H, s, OMe), 4.88 (1 H, t, *J* 3.4, 1-H) and 6.87 and 7.24 (each 2 H, d, *J* 8.3, ArH).

(+)-(1,2-*syn*)-3-(*tert*-Butyldimethylsiloxy)-1-methoxy-1-(4-methoxyphenyl)-2-methylpropane 13

To a mixture of KH (35% in mineral oil, 10 g) in THF (30 cm^3) was added a solution of siloxy alcohol (+)-**12** (7.49 g) in THF (20 cm^3) under argon at 0 °C and MeI (7 cm^3) was added to the above reaction mixture. The whole reaction mixture was stirred for 10 min at room temperature and was then quenched with Bu^{t}OH. The mixture was diluted with water and extracted with diethyl ether. Removal of the organic solvent gave an oily product, which was chromatographed on silica gel (160 g) to afford homogeneous, oily compound (+)-**13** (7.83 g, 99%) from the hexane–ethyl acetate (29:1) eluate. Compound (+)-**13**: (Found: C, 67.1; H, 10.1. Calc. for $C_{18}H_{32}O_3Si$: C, 66.67; H, 9.88%); $[\alpha]_D^{20}$ +44.9 (*c* 1.48, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1612; δ_H 0.005 and 0.018 (each 3 H, s, $SiMe_2$), 0.905 (9 H, s, SiBu^t), 0.915 (3 H, d, *J* 6.8, 2-Me), 1.76–1.82 (1 H, m, 2-H), 3.19 (3 H, s, 1-OMe), 3.28 (1 H, dd, *J* 9.8 and 5.4, 3-H), 3.50 (1 H, dd, *J* 9.8 and 5.4, 3-H), 3.81 (3 H, s, ArO*Me*), 4.16 (1 H, d, *J* 5.9, 1-H) and 6.87 and 7.17 (each 2 H, d, *J* 8.8, ArH).

(+)-(2,3-*syn*)-3-Methoxy-3-(4-methoxyphenyl)-2-methylpropan-1-ol 14

Tetrabutylammonium fluoride (TBAF, 12.88 g) was added to a stirred, ice–water-cooled solution of siloxy compound (+)-**13** (7.83 g) in THF (30 cm^3) and the reaction mixture was stirred for 2 h at room temperature before being diluted with water and extracted with diethyl ether. Evaporation of the extract gave an oily product, which was chromatographed on silica gel (250 g) to provide compound (+)-**14** as an oil (4.63 g, 91%) from the hexane–ethyl acetate (2:1) eluate. Compound (+)-**14**: (Found: M^+, 210.1225. Calc. for $C_{12}H_{18}O_3$: *M*, 210.1256); $[\alpha]_D^{19}$ +7.67 (*c* 0.99, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3417; δ_H 0.87 (3 H, d, *J* 7.3, 2-Me), 1.97–2.07 (1 H, m, 2-H), 2.77 (1 H, s, OH), 3.22 (3 H, s, 3-OMe), 3.43–3.49 (1 H, m, 1-H), 3.54–3.59 (1 H, m, 1-H), 3.80 (3 H, s, ArO*Me*), 4.25 (1 H, d, *J* 5.4, 3-H) and 6.90 and 7.19 (each 2 H, d, *J* 8.3, ArH).

(+)-(3,4-*syn*)-4-Methoxy-4-(4-methoxyphenyl)-3-methylbutanenitrile 15

To a solution of alcohol (+)-**14** (4.62 g) in ice–water-cooled pyridine (25 cm^3) was added *p*-tosyl chloride (16.28 g) and the whole was stirred for 12 h at room temperature before being diluted with 10% hydrochloric acid and extracted with diethyl ether. The extract was evaporated to give a crude product, which was used without further purification. To a stirred solution of the above crude product in dimethyl sulfoxide (DMSO) (20 cm^3) was added NaCN (1.34 g) and the whole was stirred for 12 h at 40 °C. The reaction mixture was then diluted with water and extracted with CH_2Cl_2. Evaporation of the organic solvent gave an oily product, which was chromatographed on silica gel (180 g) to afford oily nitrile (+)-**15** (4.37 g, 91%) from the hexane–ethyl acetate (20:1) eluate. Compound (+)-**15**: (Found: M^+, 219.1247. Calc. for $C_{13}H_{17}NO_2$: *M*, 219.1259); $[\alpha]_D^{19}$ +34.4 (*c* 1.17, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2247; δ_H 1.09 (3 H, d, *J* 6.8, 3-Me), 2.08–2.17 (1 H, m, 3-H), 2.05 (1 H, dd, *J* 16 and 7.3, 2-H), 2.38 (1 H, dd, *J* 16 and 4.9, 2-H), 3.21 (3 H, s, ArO*Me*), 3.81 (3 H, s, OMe), 4.05 (1 H, d, *J* 5.9, 4-H) and 6.91 and 7.18 (each 2 H, d, *J* 8.3, ArH).

(+)-Methyl (2,3-*syn*)-2,4-cyanomethoxy-3-methylbutanoate 16

Ozone was passed through a solution of aryl compound (+)-**15** (532 mg) in AcOEt (10 cm^3) at room temperature for 90 min, then 30% aq. H_2O_2 (2 cm^3) was added to the ozonolysed product and the reaction mixture was stirred for 10 min at room temperature. The reaction mixture was diluted with water and extracted with diethyl ether. Removal of the solvent gave a residue, which was treated with a solution of CH_2N_2 in diethyl ether to provide an oily product. This was subjected to silica gel (40 g) column chromatography to provide ester (+)-**16** as an oil (320 mg, 39%) from the hexane–ethyl acetate (10:1) eluate. Ester (+)-**16**: (FAB-MS) *m/z* 172 (M^+ + 1); $[\alpha]_D^{19}$ +44.5); (*c* 1.18, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2247 and 1751; δ_H 1.03 (3 H, d, *J* 6.8, 3-Me), 2.32–2.44 (2 H, m, 4-H_2), 2.50–2.60 (1 H, m, 3-H), 3.44 (3 H, s, 2-OMe), 3.79 (3 H, s, CO_2Me) and 3.86 (1 H, d, *J* 3.9, 2-H).

(3*S*,4*R*)-5-Hydroxy-4-methoxy-3-methylpentanenitrile 17

To a stirred mixture of $LiBH_4$ (0.32 g) in THF (5 cm^3) was added a solution of ester (+)-**16** (1.078 g) in ice–water cooled THF (5 cm^3) and the whole was then stirred for 12 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was evaporated

to give an oily product, which was chromatographed on silica gel (3 g) to afford oily compound (3*S*,4*R*)-**17** (718 mg, 80%) from the hexane–ethyl acetate (2:1) eluate. Compound (3*S*,4*R*)-**17**: *m/z* 126 ($M^+ - OH$) and 112 ($M^+ - OMe$); ν_{max}(neat)/cm^{-1} 3435 and 2247; δ_H 1.11 (3 H, d, *J* 6.8, 3-Me), 1.99 (1 H, br s, 5-OH), 2.19–2.28 (1 H, m, 3-H), 2.33 (1 H, dd, *J* 7.8 and 16.6, 2-H), 2.52 (1 H, dd, *J* 5.4 and 16.6, 2-H), 3.22–3.26 (1 H, m, 4-H), 3.46 (3 H, s, 4-OMe), 3.63 (1 H, dd, *J* 11.7 and 4.9, 5-H) and 3.73 (1 H, dd, *J* 11.7 and 4.0, 5-H).

(3*S*,4*R*,5*Z*)-4-Methoxy-3-methyl-6-phenylhex-5-enenitrile 19 and (3*S*,4*R*,5*E*)-4-methoxy-3-methyl-6-phenylhex-5-enenitrile 20

To a stirred mixture of PCC (760 mg) and powdered molecular sieves 4 Å (740 mg) in CH_2Cl_2 (5 cm^3) was added a solution of alcohol (3*S*,4*R*)-**17** (100 mg) in CH_2Cl_2 (5 cm^3) dropwise at room temperature. After being stirred for 30 min at the same temperature, the reaction mixture was filtered with the aid of Florisil (6 g), with diethyl ether as eluent. The filtrate was evaporated to give crude aldehyde **18** (99 mg, quantitative yield), which was used immediately in the next reaction without further purification.

To a stirred mixture of benzyltriphenylphosphonium bromide (430 mg) in THF (5 cm^3) at 0 °C under argon was added BuLi (1.6 mol dm^{-3} solution in hexane; 0.6 cm^3), and the resulting mixture was stirred for 1 h at the same temperature. To this reaction mixture at 0 °C was added a solution of the above crude aldehyde **18** (49 mg) in THF (2 cm^3). After being stirred at 0 °C for 1 h, the reaction mixture was quenched by the addition of saturated aq. NH_4Cl, and extracted with ethyl acetate. Removal of the organic solvent gave an oily product, which was chromatographed on silica gel (9 g) to afford the oily styrene (3*S*,4*R*,5*Z*)-**19** (25 mg, 33% from **17**) from the hexane–ethyl acetate (35:1) eluate, and the oily styrene (3*S*,4*R*,5*E*)-**20**: (25.5 mg, 34% from **17**) from the hexane–ethyl acetate (30:1) eluate. For compound (3*S*,4*R*,5*Z*)-**19**: (Found: M^+, 215.1374. Calc. for $C_{14}H_{17}NO$: *M*, 215.1310); $[\alpha]_D^{23}$ +59.6 (*c* 0.305, $CHCl_3$); ν_{max}(CCl_4)/cm^{-1} 2249; δ_H($CDCl_3$) 1.11 (3 H, d, *J* 6.8, 3-Me), 2.09–2.19 (1 H, m, 3-H), 2.27 (1 H, dd, *J* 7.8 and 16.6, 2-H), 2.54 (1 H, dd, *J* 6.4 and 16.6, 2-H), 3.21 (3 H, s, OMe), 4.16 (1 H, dd, *J* 4.4 and 9.3, 4-H), 5.55 (1 H, dd, *J* 9.3 and 12.2, 5-H), 6.82 (1 H, d, *J* 12.2, 6-H) and 7.22–7.38 (5 H, m, Ph). For compound (3*S*,4*R*,5*E*)-**20**: (Found: M^+, 215.1348. Calc. for $C_{14}H_{17}NO$: *M*, 215.1311); $[\alpha]_D^{23}$ −32.9 (*c* 0.455, $CHCl_3$); ν_{max}(CCl_4)/cm^{-1} 2248; δ_H($CDCl_3$) 1.14 (3 H, d, *J* 6.8, 3-Me), 2.07–2.17 (1 H, m, 3-H), 2.29 (1 H, dd, *J* 7.8 and 16.6, 2-H), 2.53 (1 H, dd, *J* 5.9 and 16.6, 2-H), 3.33 (3 H, s, OMe), 3.71 (1 H, dd, *J* 6 and 8, 4-H), 6.02 (1 H, dd, *J* 8 and 16, 5-H), 6.62 (1 H, d, *J* 16, 6-H) and 7.26–7.42 (5 H, m, Ph).

Conversion of (3*S*,4*R*,5*Z*)-19 into (3*S*,4*R*,5*E*)-20

A solution of compound (3*S*,4*R*,5*Z*)-**19** (20 mg), benzenethiol (1.4 mm^3) and AIBN (2 mg) in benzene (1 cm^3) was heated under reflux for 4 h. The reaction mixture was concentrated to give a residue, which was purified by the same way as in the previous case to provide starting material (3*S*,4*R*,5*Z*)-**19** (5.8 mg, 29% recovery) and the isomer (3*S*,4*R*,5*E*)-**20** (14 mg, 70%).

(3*S*,4*R*,5*Z*)-6-(4-Chloro-3-methoxyphenyl)-4-methoxy-3-methylhex-5-enenitrile 21 and (3*S*,4*R*,5*E*)-6-(4-chloro-3-methoxyphenyl)-4-methoxy-3-methylhex-5-enenitrile 22

To a stirred mixture of 4-chloro-3-methoxyphenylmethyl(triphenyl)phosphonium bromide (550 mg) in THF (5 cm^3) at 0 °C under argon was added BuLi (1.6 mol dm^{-3} solution in hexane; 0.8 cm^3), and the resulting mixture was stirred for 1 h at the same temperature. To this reaction mixture at 0 °C was added a solution of the above crude aldehyde **18** (49 mg) in THF (2 cm^3). After being stirred at 0 °C for 1 h, the reaction mixture was quenched by the addition of saturated aq. NH_4Cl, and extracted with ethyl acetate. Removal of the organic solvent gave an oily product, which was chromatographed on silica gel (9 g) to afford the oily styrene (3*S*,4*R*,5*Z*)-**21** (28.5 mg, 29% from **17**) from the hexane–ethyl acetate (22:1) eluate, and the oily isomer (3*S*,4*R*,5*E*)-**22** (27.5 mg, 28% from **17**) from the hexane–ethyl acetate (20:1) eluate. Compound (3*S*,4*R*,5*Z*)-**21**: (Found: M^+, 279.1015. Calc. for $C_{15}H_{18}ClNO_2$: *M*, 279.1026); $[\alpha]_D^{26}$ +40.4 (*c* 0.91, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2246; δ_H($CDCl_3$) 1.11 (3 H, d, *J* 6.8, 3-Me), 2.09–2.19 (1 H, m, 3-H), 2.29 (1 H, dd, *J* 7.8 and 16.6, 2-H), 2.54 (1 H, dd, *J* 6.8 and 16.6, 2-H), 3.22 (3 H, s, OMe), 3.92 (3 H, s, ArO*Me*), 4.17 (1 H, dd, *J* 3.7 and 9.5, 4-H), 5.57 (1 H, dd, *J* 9.5 and 12, 5-H), 6.76 (1 H, d, *J* 12, 6-H), 6.78 (2 H, br s, ArH) and 7.34 (1 H, d, *J* 7.8, ArH). Compound (3*S*,4*R*,5*E*)-**22**: (Found; M^+, 279.1011. Calc. for $C_{15}H_{18}ClNO_2$: *M*, 279.1025); $[\alpha]_D^{22}$ −29.8 (*c* 1.05, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2247; δ_H($CDCl_3$) 1.14 (3 H, d, *J* 6.8, 3-Me), 2.08–2.17 (1 H, m, 3-H), 2.32 (1 H, dd, *J* 7 and 16.6, 2-H), 2.52 (1 H, dd, *J* 5.9 and 16.6, 2-H), 3.34 (3 H, s, 4-OMe), 3.71 (1 H, dd, *J* 4.9 and 7.8, 4-H), 3.93 (3 H, s, ArO*Me*), 6.02 (1 H, dd, *J* 7.8 and 16, 5-H), 6.57 (1 H, d, *J* 16, 6-H), 6.93–6.95 (2 H, m, ArH) and 7.31 (1 H, d, *J* 8.8, ArH).

(3*S*,4*R*,5*Z*)-4-Methoxy-6-(4-methoxyphenyl)-3-methylhex-5-enenitrile 23 and (3*S*,4*R*,5*E*)-4-methoxy-6-(4-methoxyphenyl)-3-methylhex-5-enenitrile 24

To a stirred mixture of 4-methoxyphenylmethyl(triphenyl)-phosphonium chloride (1.01 g) in THF (10 cm^3) at 0 °C under argon was added BuLi (1.6 mol dm^{-3} solution in hexane; 1.4 cm^3), and the resulting mixture was stirred for 1 h at the same temperature. To this reaction mixture at 0 °C was added a solution of the above crude aldehyde **18** (112 mg) in THF (4 cm^3). After being stirred at 0 °C for 1 h, the reaction mixture was quenched by the addition of saturated aq. NH_4Cl, and extracted with ethyl acetate. Removal of the organic solvent gave an oily product, which was chromatographed on silica gel (11 g) to afford oily compound (3*S*,4*R*,5*Z*)-**23** (70 mg, 36% from **17**) from the hexane–ethyl acetate (25:1) eluate, and oily compound (3*S*,4*R*,5*E*)-**24** (73 mg, 37% from **17**) from the hexane–ethyl acetate (20:1) eluate. Compound (3*S*,4*R*,5*Z*)-**23**: (Found: M^+, 245.1417. Calc. for $C_{15}H_{19}NO_2$: *M*, 245.1415); $[\alpha]_D^{26}$ +74.7 (*c* 1.08, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2246; δ_H($CDCl_3$) 1.11 (3 H, d, *J* 6.8, 3-Me), 2.10–2.22 (1 H, m, 3-H), 2.28 (1 H, dd, *J* 7.8 and 16.6, 2-H), 2.55 (1 H, dd, *J* 6.4 and 16.6, 2-H), 3.21 (3 H, s, 4-OMe), 3.81 (3 H, s, OMe), 4.21 (1 H, dd, *J* 3.9 and 9.3, 4-H), 5.45 (1 H, dd, *J* 9.3 and 11.7, 5-H), 6.73 (1 H, d, *J* 11.7, 6-H) and 6.89 and 7.18 (each 2 H, d, *J* 8.8, ArH). Compound (3*S*,4*R*,5*E*)-**24**: (Found: M^+, 245.1419. Calc. for $C_{15}H_{19}NO_2$: *M*, 245.1416); $[\alpha]_D^{19}$ −35.0 (*c* 1.10, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2248; δ_H($CDCl_3$) 1.13 (3 H, d, *J* 7.3, 3-Me), 2.05–2.17 (1 H, m, 3-H), 2.28 (1 H, dd, *J* 7.3 and 16.6, 2-H), 2.52 (1 H dd, *J* 5.9 and 16.6, 2-H), 3.31 (3 H, s, 4-OMe), 3.66 (1 H, dd, *J* 5.4 and 7.8, 4-H), 3.81 (3 H, s, Ar-O*Me*), 5.87 (1 H, dd, *J* 7.8 and 15.6, 5-H), 6.55 (1 H, d, *J* 15.6, 6-H) and 6.88 and 7.34 (each 2 H, d, *J* 8.3, ArH).

Methyl (3*S*,4*R*,5*E*)-6-(4-chloro-3-methoxyphenyl)-4-methoxy-3-methylhex-5-enoate 25

A stirred mixture of chloride (3*S*,4*R*,5*E*)-**22** (44 mg), KOH (540 mg), water (0.1 cm^3) and ethanol (2.2 cm^3) was refluxed for 16 h. The reaction mixture was diluted with water, acidified with 10% hydrochloric acid and extracted with diethyl ether. The organic layer was evaporated to provide crude acid, which was treated with an ethereal solution of CH_2N_2 to give crude product. This was chromatographed on silica gel (15 g) to give oily ester (3*S*,4*R*,5*E*)-**25** (29 mg, 59% from **22**) from the hexane–ethyl acetate (10:1) eluate. Compound (3*S*,4*R*,5*E*)-**25**: (Found: M, 312.1138. Calc. for $C_{16}H_{21}ClO_4$: *M*, 312.1128);

$[\alpha]_D^{25}$ +10.1 (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1736; δ_H($CDCl_3$) 1.00 (3 H, d, *J* 6.8, 3-Me), 2.16 (1 H, dd, *J* 8.3 and 15, 2-H), 2.24–2.35 (1 H, m, 3-H), 2.53 (1 H, dd, *J* 5.4 and 15, 2-H), 3.32 (3 H, s, 4-OMe), 3.60 (1 H, dd, *J* 5.4 and 8.7, 4-H), 3.64 (3 H, s, CO_2Me), 3.93 (3 H, s, Ar-O*Me*), 6.04 (1 H, dd, *J* 7.8 and 16, 5-H), 6.49 (1 H, d, *J* 16, 6-H), 6.91–6.94 (2 H, m, ArH) and 7.30 (1 H, d, *J* 7.8, ArH).

Acknowledgements

This work was supported by a grant for the Biodesign Research Program from The Institute of Physical and Chemical Research (RIKEN) to H. A. and a Grant-in-Aid for Scientific Research (No. 06672115) from the Ministry of Education, Science and Culture of Japan to H. A.

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Paper 5/01734C
Received 20*th March* 1995
Accepted 28*th April* 1995