Synthesis and stereostructure–activity relationship of a synthetic pyrethroid, 2-chloro-1-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether

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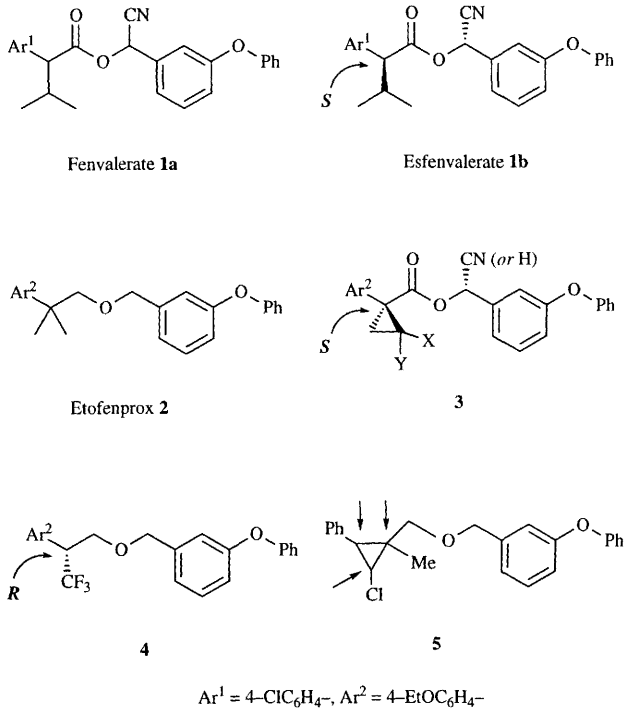
Of the four diastereoisomers of 2-chloro-1-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether 5, a new type of synthetic pyrethroid, which have been synthesized, only the (1*R,2*S**,3*S**)-isomer 5a showed significant insecticidal activity against the tobacco cutworm and the common mosquito. Two enantiomers (1*R*,2*S*,3*S*)-(−)-5a and (1*S*,2*R*,3*R*)-(+)-5a were prepared by the optical resolution process, and their absolute configurations were determined by chemical derivatization *via* predictable asymmetric cyclopropanation. Bioassay showed that the (1*R*,2*S*,3*S*)-(−)-5a was active, while (1*S*,2*R*,3*R*)-(+)-5a was not. The geometry around the asymmetric centre of the (1*R*,2*S*,3*S*)-enantiomer was correlated with that of representative pyrethroids which are both optically active and have insecticidal activity.**

Because there are marked differences in insecticidal activity for the various diastereoisomeric and enantioisomeric pyrethroid stereoisomers much attention has been focused on stereostructure–activity relationships in this area.[1] Such interest has become increasingly important as the search for bioactive, less toxic and readily degradable pesticides widens.

Synthetic pyrethroids with structures related to those of chrysanthemic acid from natural pyrethrins[2] include fenvalerate **1a**[3] and etofenprox **2**.[4] The former is representative of a non-cyclopropanecarboxylic acid-type pyrethroid whilst the latter has an ester structure not, earlier, associated with pyrethroids.

Ohno *et al.* who showed that esfenvalerate **1b**, the only active isomer of fenvalerate's **1a** four, possessed an *S*-acid component,[3] also described the correlation of **1b** with optically active chrysanthemic acid. The CSIRO group independently reported detailed studies of the stereostructure–activity relationship for the di- and mono-halogenocyclopropane ester and ether derivatives.[5] The structure of this insecticidally active *S*-stereoisomer **3**, for example, apparently was superimposable on esfenvalerate **1b**, *i.e.* the dimethyl group of **1b** corresponded to the dichloro group of **3**. Later, Tsushima *et al.* described an important finding, namely that the CF_3 substituted analogue **4**[6] derived from etofenprox **2** and having *R* stereochemistry, is insecticidally active.[7] In a separate paper, they account for this apparent contradiction by using computer-assisted methods, [semi-empirical MO conformational analysis (AM-1)], and showed that of each of the lower conformers of esfenvalerate **1b** and **4** were superimposable.[8] These results indicate the subtle nature of the relationship between insecticidal activity and geometry around the asymmetric centre of these pyrethroids.

In connection with our continuing interest in the reactions of *gem*-dihalogenocyclopropane,[9] we reported earlier a new class of synthetic pyrethroids **5** containing the halogenocyclopropane structure[10] and the related dihalogeno isosters, but which had very little activity; this result contrasts with that for the pyrethroid **3**. Moreover, we became interested in the stereostructure–activity relationship because the pyrethroid **5** possesses *three asymmetric centres* on the cyclopropane ring, in contrast to known pyrethroids, which have no more than two. We describe here: (i) the synthesis of all the four racemic diastereoisomers **5a–d** of the chlorocyclopropane-type pyrethroid **5**; (ii) the synthesis of two enantiomers of the insecticidally active diastereoisomer **5a**; (iii) the determination of the absolute configuration of these enantiomers; and (iv) provide a discussion of their stereostructure and insecticidal activity relationship by correlation of the representative synthetic pyrethroids.



Fenvalerate **1a** | Esfenvalerate **1b**

Etofenprox **2** | **3**

4 | **5**

Ar^1 = 4-ClC_6H_4–, Ar^2 = 4-$EtOC_6H_4$–

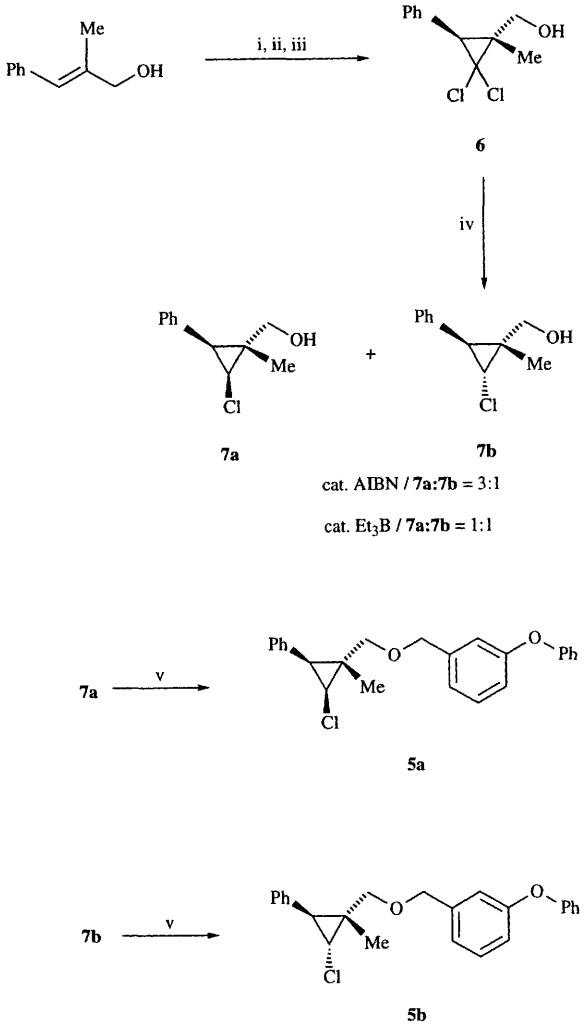
Results and discussion

Since, earlier, we described that the unsubstituted phenyl analogue, 2-chloro-1-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether **5**, was more active than variously substituted (2-F, 3-MeO, 4-Me, 4-MeO- and 4-Cl) analogues[10] we

selected it for a our study of stereostructure–insecticidal activity relationship. The synthesis of racemic (1*R**,2*S**,3*S**)-2-chloro-1-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether **5a** has been described in our previous report.

Synthesis of all four racemic diastereoisomers 5a–d of the chlorocyclopropane-type pyrethroid 5

First, we synthesized the racemic diastereoisomer (1*R**,2*R**,3*S**)-2-chloro-1-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether **5b** (see Scheme 1). The reported method



Scheme 1 *Reagents and conditions:* i, 2,3-dihydro-4*H*-pyran, cat. CSA; ii, $CHCCl_3$, 50% aq. NaOH, cat. BTEAC; iii, cat. PTS, MeOH; iv, Bu_3SnH, catalyst; v, $BrCH_2C_6H_4OPh$-*m*, NaH;

for the preparation of (1*R**,3*S**)-2,2-dichloro-3-phenylcyclopropylmethanol **6** from (*E*)-2-methyl-3-phenylprop-2-en-1-ol[10] was improved by protection and deprotection using the THP group (reported yield 19% increased to 63%). The key Bu_3SnH/catalytic azoisobutyronitrile (AIBN) reduction in refluxing toluene gave, predominantly, (1*R**,2*S**,3*S**)-2-chloro-1-methyl-3-phenylcyclopropylmethanol **7a** (**7a**:**7b** = *ca.* 3:1).[10] In subsequent work, we found that Ohshima and Utimoto's method using the Bu_3SnH/catalytic Et_3B system[11] increased the ratio of (1*R**,2*R**,3*S**)-diastereoisomer **7b** (**7a**:**7b** = *ca.* 1.2:1); the reason for the change in selectivity is as yet unclear. The diastereoisomer **7b** thus more readily available was coupled with 3-phenoxybenzyl bromide to produce the desired (1*R**,2*R**,3*S**)-diastereoisomer **5b**.

The racemic diastereoisomers **5c** and **5d** were next synthesized as shown in Scheme 2. The starting (*Z*-2-methyl-3-phenylprop-2-en-1-ol **8** was prepared using a *Z*-selective Horner–Emmons type reagent, *O*-ethyl *S*-ethoxycarbonylmethyl dithiocarbonate,[12] followed by a reduction with diisobutyl aluminum hydride (DIBAL).[13] The *Z*-allyl alcohol **8** was separated from the contaminated *E*-allyl alcohol by column chromatography on SiO_2. Dichlorocarbene addition to **8** gave (1*R**,3*R**)-2,2-dichloro-3-phenylcyclopropylmethanol **9**, which was transformed into (1*R**,2*R**,3*R**)- and (1*R**,2*S**,3*R**)-2-chloro-1-methyl-3-phenylcyclopropylmethanol **7c** and **7d**, respectively, by Bu_3SnH/catalytic AIBN reduction at 110 °C. This removal of chlorine proceeded with fair stereoselectivity (**7c**:**7d** = 1:1.7) for a total 77% yield. The independent coupling reaction of **7c** and **7d** with 3-phenoxybenzyl bromide gave the desired (1*R**,2*R**,3*R**)- and (1*R**,2*S**,3*R**)-diastereoisomers, **5c** and **5d**, respectively.

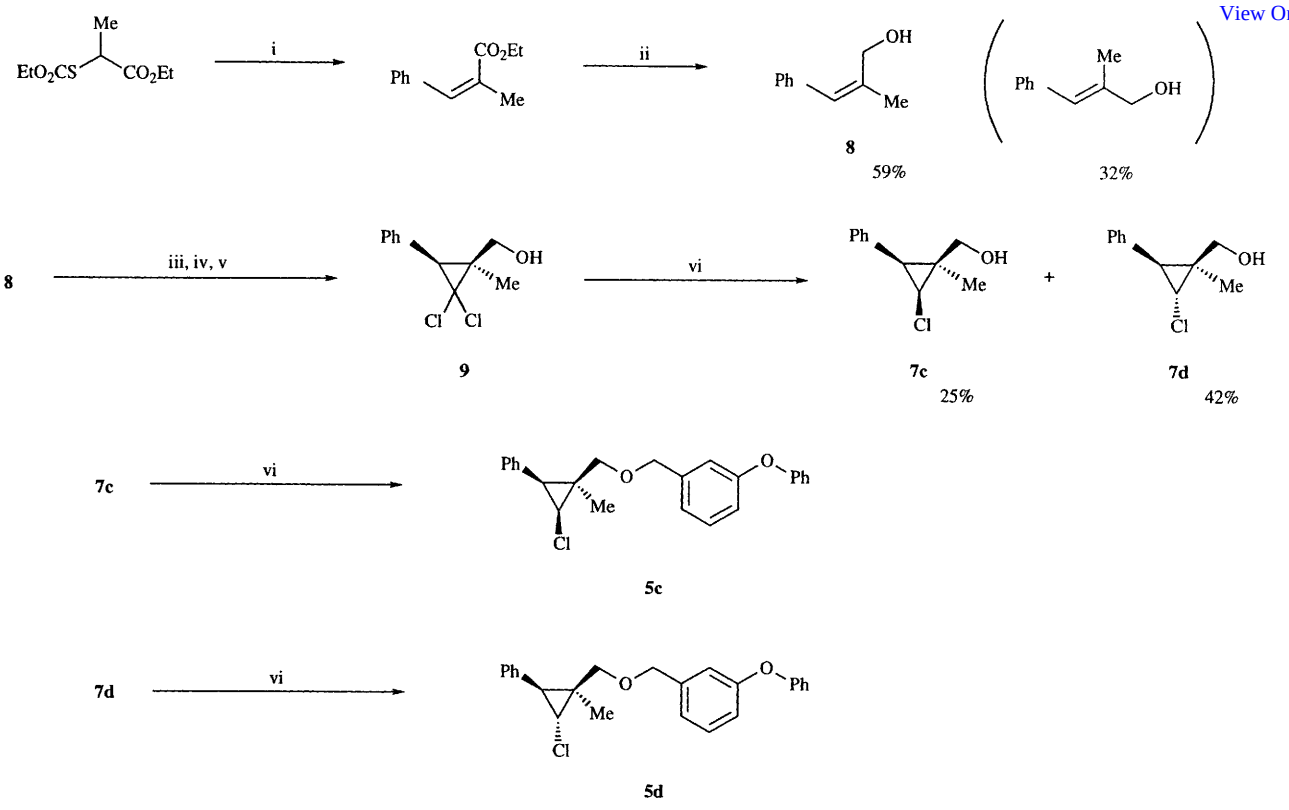
Synthesis of two of the enantiomers of the insecticidally active diastereoisomer 5a

The enantiomers, (1*R*,2*S*,3*S*)- and (1*S*,2*R*,3*R*)-2-chloro-1-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ethers, (−)-**5a** and (+)-**5a**, respectively, were synthesized, since only racemic (1*R**,2*S**,3*S**)-**5a** was insecticidally active (the correlation between the absolute configuration and optical rotation, and the results of bioassay, are described *vide infra*); this sequence is illustrated in Scheme 3. Oxidation of the racemic alcohol, (1*R**,2*S**,3*S**)-2-chloro-1-methyl-3-phenylcyclopropylmethanol **7a**, by Jones' reagent gave the carboxylic acid (1*R**,2*S**,3*S**)-**10**, optical resolution of which was effected with optically active 1-(1-naphthyl)ethanamine (abbreviated NEA): *S*-(−)-NEA gave the (1*R*,2*S*,3*S*)-(−)-acid (−)-**10** {$[\alpha]_D^{24}$ −82.3, after four recrystallizations}, and *R*-(+)-NEA gave the (1*S*,2*R*,3*R*)-(+)-acid (+)-**10** {$[\alpha]_D^{26}$ +81.0, after four recrystallizations}. Use of optically active 1-(1-phenyl)ethanamine and quinine gave disappointing results, although quinine was known to be successful for the resolution of a similar *trans*-2-phenylcyclopropanecarboxylic acid.[14] The LAH reduction of the acids, (−)-**10** and (+)-**10**, gave the corresponding alcohols, (−)-(1*R*,2*S*,3*S*)-**7a** (96% ee by HPLC analysis) and (1*S*,2*R*,3*R*)-(+)-**7a** (98% ee by HPLC analysis), respectively. The desired enantiomers, (−)-(1*R*,2*S*,3*S*)-**5a** and (1*S*,2*R*,3*R*)-**5a**, were obtained by the same ether formation with (−)-**7a** and (+)-**7a**, respectively.

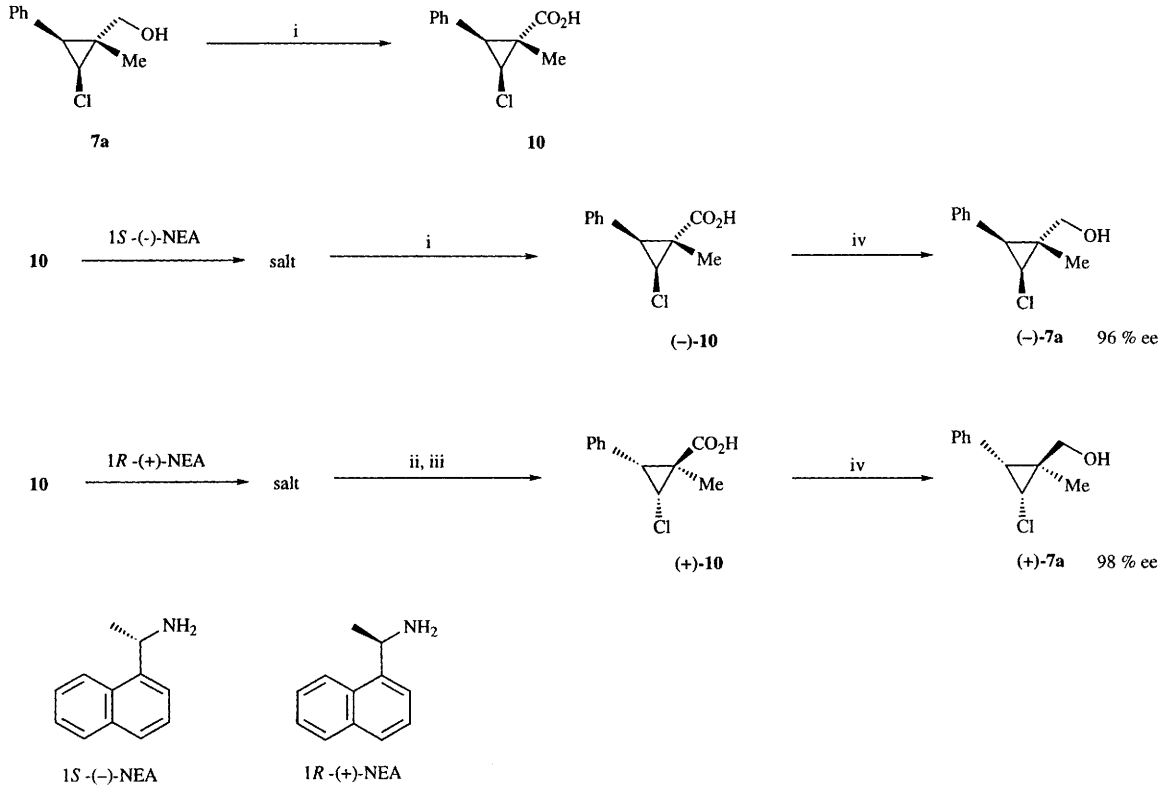
Determination of the absolute configuration of each enantiomer of (1*R**,2*S**,3*S**)-2-chloro-1-methyl-3-phenylcyclopropylmethanol 7a

Chemical derivatization was used to determine the absolute configuration of each enantiomer of (1*R**,2*S**,3*S**)-2-chloro-1-methyl-3-phenylcyclopropylmethanol **7a**, the key alcohol intermediate for the synthesis of **5a** (see Scheme 4). The key step is use of asymmetric Simmons–Smith type cyclopropanation. Although, initially, we used the chiral disulfonamide-ligand controlled method for the Simmons–Smith cyclopropanation,[15] the trisubstituted allyl alcohol, (*E*)-2-methyl-3-phenylprop-2-en-1-ol as substrate gave poor results [*ca.* 10% ee compared with the optically pure authentic sample obtained by Bu_3SnH/cat. AIBN reduction of (−)-**7a**]. Next, we applied Yamamoto's method[16] using a C_2 chiral acetal derived from diisopropyl L-(+)-tartarate as substrate for this purpose, since a series of these cyclopropylacetals have a predictable configuration as a result of rational stereo-differentiating attack of CH_2I_2/Et_2Zn. Thus, the optically active acetal **11** derived from (*E*)-2-methyl-3-phenylprop-2-en-1-al and the diisopropyl L-(+)-tartarate obtained was converted into the chiral cyclopropyl acetal **12**, which was hydrolysed and reduced to give the desired (1*R*,2*S*)-(−)-2-phenylcyclopropylmethanol (−)-**13** {$[\alpha]_D^{26}$ −11.4}.

(−)-2-Chloro-3-phenylcyclopropylmethanol (−)-**7a** {$[\alpha]_D^{26}$ −81.7} prepared by the aforementioned optical resolution, was transformed into (−)-2-phenylcyclopropylmethanol (−)-**13** {$[\alpha]_D^{26}$ −15.1} by an excess of Bu_3SnH/cat. AIBN reduction. Accordingly, the absolute configurations were



Scheme 2 *Reagents and conditions:* i, LDA, PhCHO; ii, DIBAL; iii, 2,3-dihydro-4*H*-pyran, cat. CSA; iv, $CHCCl_3$, 50% aq. NaOH, cat. BTEAC; v, cat. PTS, MeOH; vi, $BrCH_2C_6H_4OPh$-*m*, NaH



Scheme 3 *Reagents and conditions:* i, Jones' oxidation; ii, 4 recrystallizations; iii, decomposition; iv, LAH

unambiguously determined by comparing each optical rotation; (−)-**7a** corresponds to 1*R*,2*S*,3*S* and (+)-**7a** corresponds to 1*S*,2*R*,3*R*.

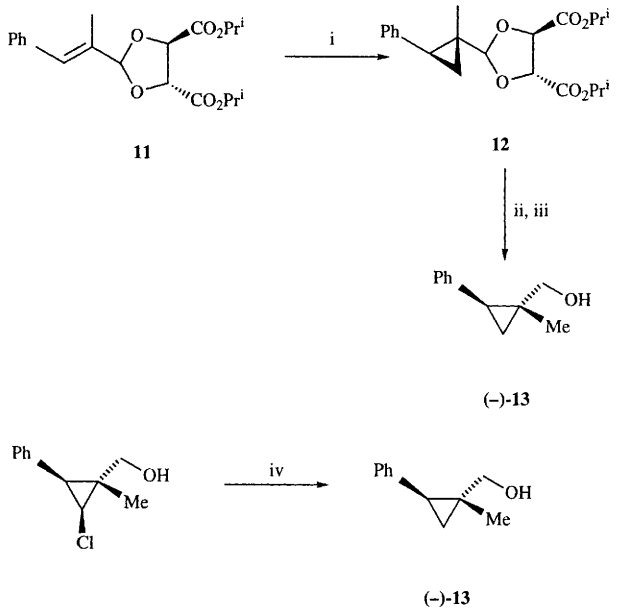
Stereostructure–activity relationship of all four racemic diastereoisomers 5a–d, and of a set of enantiomers of the diastereoisomer 5a

The insecticidal activity against the tobacco cutworm (*Spodoptera litura*) and the common mosquito (*Culex pipiens pallens*) was assessed for all four racemic diastereoisomers **5a**–**5d** and the results are listed in Table 1. The bioassay of racemic (1*R**,2*S**,3*S**)-**5a** showed that it had significant insecticidal activity, which has already been described in our previous report. In clear contrast, the other three racemic diastereoisomers (1*R**,2*R**,3*S**)-**5b**, (1*R**,2*R**,3*R**)-**5c** and (1*R**,2*S**,3*R**)-**5d** were quite inactive against both insects.

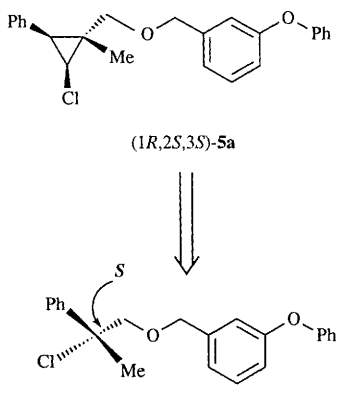
Table 1 Insecticidal activity of 2-chloro-1-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether[a]

Compound		Mortality (%)					
		Tobacco cutworm			Common mosquito[b]		
		50	25	5 (ppm)	100	50	25 (ppm)
1*R**,2*S**,3*S**	**5a**	100	55	10	B	B, C	C
1*R**,2*R**,3*S**	**5b**	0	0	0	C	C	C
1*R**,2*R**,3*R**	**5c**	0	0	0	C	C	C
1*R**,2*S**,3*R**	**5d**	0	0	0	C	C	C
1*R*,2*S*,3*S*	(−)-**5a**	100	85	70	A	A	B
1*S*,2*R*,3*R*	(+)-**5a**	0	0	0	C	C	C
Untreated	—	0	0	0	C	C	C

[a] Method of bioassay is described in the experimental section. [b] Criteria of the mortality are as follows: A, >90%; B, 10–90%; C, <10%.



Scheme 4 *Reagents and conditions:* i, CH_2I_2, $ZnEt_2$; ii, H_3O^+; iii, $NaBH_4$ iv, excess of Bu_3SnH, cat. AIBN



Scheme 5

Moreover, it is noteworthy that there was a distinct difference in the activities of the enantiomers **5a**; (1*R*,2*S*,3*S*)-(−)-**5a** was active while, in contrast, (1*S*,2*R*,3*R*)-(+)-**5a** was inactive. To our knowledge, this is the first example of the separation of activities of cyclopropane-type pyrethroids having three asymmetric centres in the cyclopropane ring. One interpretation of these results is that the total geometry around the three asymmetric centres of the enantiomer (1*R*,2*S*,3*S*)-(−)-**5a** is an exact fit for the 'pyrethroid receptor' compared with those for the other seven stereoisomers.

Finally, we considered a correlation between the stereostructure of (1*R*,2*S*,3*S*)-(−)-**5a** and the stereostructures of esfenvalerate **1b**, the cyclopropyl analogue **3**, and the CF_3 substituted analogue **4**. A simplifying assumption that all the three substituents (1*R*)-(3-phenoxybenzyloxymethyl)-, 2*S*-chloro- and 3*S*-phenyl- on the cyclopropane plane centred on the imaginary sp^3 carbon, by keeping these orientations, would lead to the conclusion that the absolute configuration of the tetrahedral sp^3 carbon is of the *S* configuration, which is the same as **1b** and **3** (Scheme 5). Computer-assisted molecular dynamics for this interpretation are now under investigation.

In conclusion, of the eight stereoisomers including the enantiomers of the synthetic pyrethroid, 2-chloro-1-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether **5**, which has been synthesized, only the (1*R*,2*S*,3*S*)-form showed significant insecticidal activity against the tobacco cutworm and the common mosquito. This suggests that total geometry around the three asymmetric centres of the (1*R*,2*S*,3*S*)-enantiomer are significant for the compound to be an active insecticide.

Experimental

Melting points were determined on a hot-stage microscope apparatus (Yanagimoto) and are uncorrected. NMR spectra were recorded on a JEOL EX-90 (90 MHz) and/or JEOL α (400 MHz) spectrometer in $CDCl_3$ using a TMS internal standard; *J* values are given in Hz. IR spectra were recorded on a Hitachi 270-30 spectrophotometer. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. HPLC analyses were performed using Shimadzu LC-10A system and columns (Sumichiral OA-4000 bearing a chiral stationary phase; 4.6 mm diam. × 25 cm) with UV (254 nm) detector. All of the reagents and solvents were purified prior to use. Silica-gel column chromatography was performed on a Merck Art. 7734 and 9385. Ether refers to diethyl ether.

(1*R**,3*S**)-2,2-Dichloro-3-phenylcyclopropylmethanol **6** and (1*R**,2*S**,3*S**)-2-chloro-1-methyl-3-phenylcyclopropylmethanol **7a** were prepared by a reported method.[10]

Improved method for preparing (1*R**,2*R**,3*S**)-2-chloro-1-methyl-3-phenylcyclopropylmethanol 7b

Bu_3SnH (629 mg, 21.6 mmol) and Et_3B (1 mol dm^{-3} hexane solution; 0.43 cm^3, 0.43 mmol) were added to a stirred solution of (1*R**,3*S**)-2,2-dichloro-3-phenylcyclopropylmethanol **6** (1.00 g, 4.3 mmol) in benzene (10.0 cm^3) at room temperature and the mixture was stirred for 20 h. After this it was treated with 10% aqueous KF (*ca.* 10 cm^3) and stirred for 1 h. Filtration of the mixture through Celite with ether, separated the organic phase, which was successively washed with water and brine, dried (Na_2SO_4) and concentrated. An NMR spectrum of the crude product showed a 1:1 ratio of **7a**:**7b**. The crude oil was subjected to flash column chromatography

on SiO_2 using C_6H_{14}–AcOEt (8:1) as eluent to give the products **7b** (332 mg, 39%) and **7a** (400 mg, 47%) as colourless liquids, the physical characteristics (^{1}H NMR and IR) of which agreed with reported values.[10]

(1*R,2*R**,3*S**)-2-chloro-1-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether 5b**

A mixture of (1*R**,2*R**,3*S**)-**7b** (75 mg, 0.38 mmol) and 3-phenoxybenzyl bromide (120 mg, 0.46 mmol) in DMF (1.0 cm^3) was added to a stirred suspension of NaH (60%; 20 mg, 0.50 mmol) in *N*,*N*-dimethylformamide (DMF; 0.7 cm^3) added at 0–5 °C, after which the mixture was stirred at room temperature for 10 h. It was then diluted with water and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4), and concentrated to give a crude oil which was subjected to flash column chromatography on SiO_2 with C_6H_{14}–AcOEt (50:1) as eluent. This gave the desired product (95 mg, 66%) as a colourless liquid (Found: C, 76.3; H, 6.4. $C_{24}H_{23}ClO_2$ requires C, 76.08; H, 6.12%); ν_{max}(neat)/cm^{-1} 1210 and 1250; δ_H(90 MHz) 0.95 (3 H, s), 2.30 (1 H, d, *J* 3.0), 3.40 (1 H, d, *J* 3.0), 3.70 (2 H, s), 4.60 (2 H, s) and 6.90–7.50 (14 H, m).

(1*R,3*R**)-2,2-Dichloro-3-phenylcyclopropylmethanol 9**

A mixture of (*Z*)-2-methyl-3-phenylprop-2-en-1-ol **8** (1.08 g, 7.3 mmol), 3.4-dihydro-2*H*-pyran (0.92 g, 11 mmol), and a little (+)-camphorsulfonic acid in ether (15 cm^3) was stored at room temperature for 10 h after which it was evaporated and treated with $CHCl_3$ (15 g) and benzyl(triethyl)ammonium chloride (83 mg, 0.36 mmol). 50% Aqueous NaOH solution (5.8 g) was then added to the vigorously stirred mixture at 35–40 °C. After being stirred for 2 h at the same temperature, the mixture was diluted with water (100 cm^3) and extracted with CH_2Cl_2 (50 cm^3 × 2). The combined extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. MeOH (15 cm^3) and a little toluene-*p*-sulfonic acid were added to the residue which, after being stored overnight, was treated with saturated aqueous $NaHCO_3$ (*ca.* 10 g) and then evaporated to give a residue. This was extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated to afford a crude oil which was subjected to flash column chromatography on SiO_2 with C_6H_{14}–EtOAc (12:1) as eluent to give the desired product (1.13 g, 69%) as colourless crystals, mp 76–77 °C (Found: C, 57.1; H, 5.1. $C_{11}H_{12}Cl_2O$ requires C, 57.17; H, 5.23%); ν_{max}(neat)/cm^{-1} 3300, 1450 and 1040; δ_H(90 MHz) 1.55 (1 H, br s, OH), 1.66 (3 H, s), 2.65 (1 H, s), 3.52 (1 H, d, *J* 12.5), 3.78 (1 H, d, *J* 12.5) and 7.20–7.40 (5 H, m).

(1*R,2*R**,3*R**)- and (1*R**,2*S**,3*R**)-2-chloro-1-methyl-3-phenylcyclopropylmethanols, 7c and 7d**

Bu_3SnH (1.38 g, 4.7 mmol) was added to a stirred solution of (1*R**,3*R**)-**9** (1.00 g, 4.3 mmol) and 2,2′-azoisobutyronitrile (AIBN; 71 mg, 0.43 mmol) in toluene (8.0 cm^3) at 60 °C under a nitrogen atmosphere and the mixture refluxed for 4 h. After cooling, the mixture was stirred with 10% aqueous KF (*ca.* 10 cm^3) for 30 min. Filtration of the mixture through Celite with ether separated the organic phase, which was successively washed with water and brine, dried (Na_2SO_4), and concentrated. The resulting crude oil was subjected to flash column chromatography on SiO_2 using C_6H_{14}–AcOEt (5:1) as eluent to give sequentially the *product* **7c** (130 mg, 15%), **7c** and **7d** mixtures (312 mg, 30%) and **7d** (190 mg, 22%) as colourless liquids (**7c**: Found: C, 66.9; H, 6.4; **7d**: Found: C, 67.0; H, 6.5. $C_{11}H_{13}ClO$ requires C, 67.18; H, 6.66%); **7c**, ν_{max}(neat)/cm^{-1} 3364, 1728, 1452 and 1028; δ_H(90 MHz) 1.44 (3 H, s), 2.30 (1 H, d, *J* 8.2), 3.20–3.50 (2 H, m), 3.56 (1 H, d, *J* 8.2) and 7.10–7.50 (5 H, m); **7d**, ν_{max}(neat)/cm^{-1} 3452, 1740, 1452 and 1030; δ_H(90 MHz) 1.51 (3 H, s), 2.31 (1 H, d, *J* 5.0), 3.20–3.50 (2 H, m), 3.56 (1 H, d, *J* 5.0) and 7.10–7.50 (5 H, m). The assignment of the **7c** and **7d** was determined according to the coupling constant between the *vicinal* protons on the cyclopropanes; J_{cis} is generally larger than J_{trans}.[17]

(1*R,2*R**,3*R**)-2-Chloro-1-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether 5c**

In a manner similar to that for the preparation of compound **5b**, the reaction of (1*R**,2*R**,3*R**)-**7c** with 3-phenoxybenzyl bromide gave the *title product* (74%) as a colourless liquid (Found: C, 76.2; H, 5.9. $C_{24}H_{23}ClO_2$ requires C, 76.08; H, 6.12%); ν_{max}(neat)/cm^{-1} 1585, 1490 and 1255; δ_H(90 MHz) 1.30 (3 H, s), 2.18 (1 H, d, *J* 10.5), 3.22 (1 H, d, *J* 10.5), 3.40 (2 H, s), 4.36 (2 H, s) and 6.70–7.50 (14 H, m).

(1*R,2*S**,3*R**)-2-Chloro-1-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether 5d**

In a manner similar to that for the preparation of compound **5b**, the reaction of (1*R**,2*S**,3*R**)-**7d** with 3-phenoxybenzyl bromide gave the *title product* (62%) as a colourless liquid (Found: C, 76.4; H, 6.0. $C_{24}H_{23}ClO_2$ requires C, 76.08; H, 6.12%); ν_{max}(neat)/cm^{-1} 1585, 1490 and 1255; δ_H(90 MHz) 1.42 (3 H, s), 2.22 (1 H, d, *J* 5.2), 3.07 (2 H, s), 3.40 (1 H, d, *J* 5.2), 4.12 (2 H, s) and 6.70–7.50 (14 H, m).

Optical resolution of (1*R,2*S**,3*S**)-2-chloro-1-methyl-3-phenylcyclopropanecarboxylic acid 10 with optically active 1-(1-naphthyl)ethanamine (NEA)**

A mixture of the racemic acid (1*R**,2*S**,3*S**)-**10** (1.00 g, 4.75 mmol), prepared by a reported procedure,[10] and *S*-(−)-NEA (0.81 g, 4.75 mmol) in EtOH (10 cm^3) was seeded with material from a small-scale resolution and stored at room temperature for 24 h. The first salt (407 mg, 22%) obtained was recrystallized from EtOH (2.3 cm^3) to give the second salt (250 mg, 14%), which was successively recrystallized from EtOH (3.3 cm^3) to give the third salt (143 mg, 8%). The third salt was recrystallized from EtOH (1.9 cm^3) to give the fourth salt (73 mg, 4%) which was decomposed with 1 mol dm^{-3} hydrochloric acid (5 cm^3) and extracted with ether (5 cm^3 × 2). The combined extracts were dried (Na_2SO_4) and concentrated to give (1*R*,2*S*,3*S*)-(−)-**10** (35 mg, 3.5%) as colourless crystals, mp 96.5–97.0 °C; $[\alpha]_D^{24}$ −93.3 (*c* 0.13, $CHCl_3$). In a procedure similar to that for the preparation of (1*R*,2*S*,3*S*)-(−)-**9**, (1*S*,2*R*,3*R*)-(−)-**10** was obtained using *R*-(+)-NEA as colourless crystals, mp 97–98 °C; $[\alpha]_D^{25}$ +93.0 (*c* 0.16, $CHCl_3$).

(1*R*,2*S*,3*S*)-(−)-2-Chloro-1-methyl-3-phenylcyclopropylmethanol (1*R*,2*S*,3*S*)-(−)-7a

(1*R*,2*S*,3*S*)-(−)-**10** {$[\alpha]_D^{25}$ −92.2 (*c* 1.00, $CHCl_3$), 158 mg, 0.71 mmol} in dry THF (0.7 cm^3) was added to a stirred suspension of LAH (32 mg, 0.85 mmol) in dry THF (0.7 cm^3) at 0–5 °C and the mixture was stirred at room temperature for 22 h. Saturated aqueous Na_2SO_4 was added to the mixture which was then extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated to give a crude oil which was subjected to flash column chromatography on SiO_2 with C_6H_{14}–EtOAc (6:1) as eluent to gave the *title compound* (131 mg, 89%); $[\alpha]_D^{24}$ −82.3 (*c* 1.31, $CHCl_3$), 96% ee. Determination of the ee was carried out as follows: a mixture of 1 mg of the sample alcohol **7a** and 3,5-dinitrophenyl isocyanate (1 mg) in pyridine–THF (1:1, 0.5 cm^3) was heated at 70 °C for 1 h. The mixture (1 mm^3) was analysed by HPLC (Sumichiral OA-4000; C_6H_{14}–EtOH, 98:2, 1 cm^3 min^{-1} as eluent). R_t for faster eluent of the 3,5-dinitrophenyl carbamate of (1*R*,2*S*,3*S*)-(−)-**7a** was 31.2 min, and that of the slower eluent of 3,5-dinitrophenylcarbamate of (1*S*,2*R*,3*S*)-(+)-**7a** was 37.6 min.

(1*S*,2*R*,3*R*)-(+)-2-Chloro-1-methyl-3-phenylcyclopropyl methanol (1*S*,2*R*,3*R*)-(+)-7a

In a manner similar to that for the preparation of (1*R*,2*S*,3*S*)-(−)-**7a**, (1*S*,2*R*,3*R*)-(+)-**7a** was obtained, $[\alpha]_D^{26}$ +81.0 (*c* 0.20, $CHCl_3$), 98% ee by HPLC analysis.

(1*R*,2*S*,3*S*)-(−)-2-Chloro-1-methyl-3-phenylcyclopropymethyl 3-phenoxybenzyl ether (1*R*,2*S*,3*S*)-(−)-5a

In a manner similar to that for the preparation of compound **7b**, the reaction of (1*R*,2*S*,3*S*)-(−)-**7a** {$[\alpha]_D^{24}$ −82.3 (*c* 1.31, $CHCl_3$)} with 3-phenoxybenzyl bromide gave the product (83%) as a colourless liquid, $[\alpha]_D^{24}$ −48.3 (*c* 1.55, $CHCl_3$).

(1*S*,2*R*,3*R*)-(+)-2-Chloro-1-methyl-3-phenylcyclopropylmethyl 3-phenoxybenzyl ether (1*S*,2*R*,3*R*)-(+)-5a

In a manner similar to that for the preparation of compound **7b**, the reaction of (1*S*,2*R*,3*R*)-(+)-**7a** {$[\alpha]_D^{24}$ +81.0 (*c* 0.20, $CHCl_3$)} with 3-phenoxybenzyl bromide gave the product (84%) as a colourless liquid, $[\alpha]_D^{24}$ +46.5 (*c* 1.04, $CHCl_3$).

(4*R*,5*R*)-Diisopropyl 2-(1-methyl-3-phenylvinyl)-1,3-dioxolane-4,5-dicarboxylate 11

A mixture of (*E*)-2-methyl-3-phenylprop-2-enal (2.00g, 13.7 mmol), (2*R*,3*R*)-diisopropyl L-tartarate (3.50 g, 15.1 mmol) and (+)-camphorsulfonic acid (20 mg) was refluxed in benzene (25 cm^3) with azeotropic removal of water by a Dean–Stark apparatus. When evolution of water had ceased the mixture was concentrated to give a crude oil which was subjected to flash column chromatography on SiO_2 with C_6H_{14}–ether (7:1) as eluent to afford the title compound (0.90 g, 18%) as a colourless liquid; ν_{max}(neat)/cm^{-1} 2980, 1730 and 1100; δ_H(90 MHz) 1.28 (6 H, d, *J* 2.3), 1.38 (6 H, d, *J* 2.3), 1.92 (3 H, s), 4.68 (1 H, d, *J* 5.0), 4.80 (1 H, d, *J* 5.0), 4.95–5.35 (2 H, m), 5.61 (1 H, s), 6.72 (1 H, s) and 7.10–7.60 (5 H, m).

(4*R*,5*R*)-Diisopropyl 2-[(1*R*,2*S*)-1-methyl-2-phenylcyclopropyl]-1,3-dioxolane-4,5-dicarboxylate 12

Diethylzinc (1 mol dm^{-3} hexane solution; 3.3 cm^3, 3.3 mmol) and diiodomethane (1.74 g, 6.5 mmol) were added successively to a stirred solution of diisopropyl dicarboxylate **11** (237 mg, 0.65 mmol) in hexane (7 cm^3) at −10 to 0 °C. The mixture was stirred at this temperature for 2 h, after which it was allowed to warm to room temperature at which it was kept for 1 h. Ice–saturated aqueous NH_4Cl was then added to the mixture after which it was extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and concentrated to give the crude oil, which was subjected to flash column chromatography on SiO_2 using C_6H_{14}–ether (7:1) as eluent to give the title compound (150 mg, 40%) as a colourless liquid; ν_{max}(neat)/cm^{-1} 1735, 1375 and 1105; δ_H(90 MHz) 0.89 (3 H, s), 1.00–1.40 (2 H, m), 1.30 (12 H, d, *J* 9.0), 2.20–2.50 (1 H, m), 4.60 (1 H, d, *J* 4.8), 4.73 (1 H, d, *J* 4.8), 4.96 (1 H, s), 4.90–5.30 (2 H, m) and 7.15–7.40 (5 H, m).

(1*R*,2*S*)-(−)-2-Phenylcyclopropylmethanol 13 by asymmetric cyclopropanation

A mixture of compound **12** (95 mg, 0.25 mmol) in THF (1 cm^3) and 10% aqueous $HClO_4$ (1 cm^3) was stirred at room temperature for 3 h after which it was diluted with water and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and evaporated under reduced pressure to give the crude aldehyde (65 mg). $NaBH_4$ (10 mg, 0.26 mmol) was added to a stirred solution in MeOH (0.5 cm^3) of the aldehyde at 0–5 °C and the mixture stirred at room temperature for 10 h. The mixture was then diluted with water and extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and concentrated to give the crude oil which, when subjected to flash column chromatography on SiO_2 with C_6H_{14}–EtOAc (6:1) as eluent, afforded the desired product (35 mg, 85%) as a colourless liquid; $[\alpha]_D^{26}$ −11.4 (*c* 0.17, $CHCl_3$). Other physical characteristics (^1H NMR and IR) agreed with the reported values.[10]

(1*R*,2*S*)-(−)-2-Phenylcyclopropylmethanol 13 by reduction with an excess of Bu_3SnH of (1*R*,2*S*,3*S*)-(−)-7a derived from (1*R*,2*S*,3*S*)-(−)-10a

A mixture of (−)-(1*R*,2*S*,3*S*)-**7a** {$[\alpha]_D^{24}$ −81.7 (*c* 0.36, $CHCl_3$), (36 mg, 0.18 mmol)} and AIBN (2 mg, 0.012 mmol) in Bu_3SnH (0.6 cm^3) was heated at 100 °C for 30 h under a nitrogen atmosphere. After cooling, the mixture was subjected to flash column chromatography on SiO_2 with C_6H_{14}–EtOAc (5:1) as eluent to give the desired product (12 mg, *ca.* 40%), containing a small amount of [(1*R*,2*S*,3*S*)-(−)-**7a**] as a colourless liquid, $[\alpha]_D^{26}$ −15.1 (*c* 0.12, $CHCl_3$).

Assay of the insecticidal activity against tobacco cutworm (*Spodoptera litura*) and common mosquito (*Culex pipiens pallens*)

(1) For the tobacco cutworm (*Spodoptera litura*), an artificial diet method was used. To an artificial diet (13 g, of Insecta-LF; Nippon Nousan Kogyo Co., Ltd.) in a plastic cup were added 2-cm^3 portions of a pre-determined concentration of test samples (50, 25 and 5 ppm). Ten fourth-instar larvae were released on the diet. Six days after the treatment at 25 °C, the mortality was observed (two replicants).

(2) For the common mosquito (*Culex pipiens pallens*), an immersion method was used. To a de-ionized water (100 cm^3) were applied 0.7-cm^3 portions of a pre-determined concentration of test samples (100, 50 and 25 ppm). Twenty last-instar larvae were released therein. Mortality was assessed after 24 h (two replicants).

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture (Japan). We thank Dr Noritada Matsuo for his helpful discussions throughout this study.

References

1 K. Naumann, *Chemistry of Plant Protection 5, Synthetic Pyrethroid Insecticides*, Springer-Verlag, Berlin, 1990.
2 (*a*) M. Matsui and I. Yamamoto, *Naturally Occurring Insecticides*, Marcel Dekker, New York, 1971; (*b*) M. Elliot and N. F. Janes, *Pyrethrum, The Natural Insecticides*, Academic Press, New York, 1973.
3 N. Ohno, K. Fujimoto, Y. Okuno, T. Mizutani, M. Hirano, N. Itaya, T. Honda and H. Yoshioka, *Pestic. Sci.*, 1976, **7**, 241; *Agric. Biol. Chem.*, 1974, **38**, 881.
4 T. Udagawa, S. Numata, K. Oda, S. Shiraishi, K. Kodaka and K. Nakatani, in *Recent Advances in the Chemistry of Insect Control*, ed. N. F. Janes, The Royal Society of Chemistry, London, 1985, vol. **53**, p. 192.
5 (*a*) G. Holan, D. F. O'Keefe, C. Vergona and R. Walser, *Nature*, 1978, **272**, 734; (*b*) G. Holan, W. M. P. Johnson, K. E. Jarvis, C. T. Virgona and R. A. Walser, *Pestic. Sci.*, 1976, **17**, 715.
6 (*a*) M. J. Bushell and R. A. E. Carr, GP 2199825/1988 (*Chem. Abstr.*, 1988, **109**, 210696b); (*b*) R. A. E. Carr and P. Lyn, EP 280383/1988 (*Chem. Abstr.*, 1989, **110**, 75025k); (*c*) M. J. Nicholds, D. H. G. David and I. Harvey, GP 2241953/1991 (*Chem. Abstr.*, 1992, **116**, 83362g).
7 (*a*) K. Tsushima, T. Yano, T. Takagaki, N. Matsuo, M. Hirano and N. Ohno, *Agric. Biol. Chem.*, 1988, **52**, 1323; (*b*) K. Tsushima, K. Yanagi, N. Matsuo, T. Takagaki and T. Yano, Jap P 8975437/1989; (*Chem. Abstr.*, 1989, **111**, 153344a); (*c*) K. Tsushima, K. Yanagi, N. Matsuo, T. Takagaki and T. Yano, Jap P 8975441/1989 (*Chem. Abstr.*, 1989, **111**, 153346c).
8 (*a*) D. G. Briggs, *Advances in the Chemistry of Insect Control III*, N. Matsuo, K. Tsushima, T. Takagaki, M. Hirano and N. Ohno, The Royal Society of Chemistry, London, 1993, p. 208; (*b*) Y. Kurita, K. Tsushima and C. Takayama, *ACS Symposium Series*, 1989, **413**, 183.
9 (*a*) S. Seko, Y. Tanabe and G. Suzukamo, *Tetrahedron Lett.*, 1990, **31**, 6883; (*b*) Y. Tanabe, Y. Nishii and K. Wakimura, *Chem. Lett.*, 1994, 1757; (*c*) Y. Nishii and Y. Tanabe, *Tetrahedron Lett.*, 1995, **36**, 8803; (*d*) Y. Tanabe, K. Wakimura, Y. Nishii and Y. Muroya, *Synthesis*, 1996, 388; (*e*) Y. Tanabe, K. Wakimura and Y. Nishii, *Tetrahedron Lett.*, 1996, **37**, 1837.
10 Y. Nishii, H. Matsumura, Y. Muroya, T. Tsuchiya and Y. Tanabe, *Biosci. Biotech. Biochem.*, 1995, **59**, 1355.
11 K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Ohshima and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 143.
12 K. Tanaka, R. Tanikaga and A. Kaji, *Chem. Lett.*, 1976, 917.

13 L. Hulskamper and P. Weyerstahl, *Chem. Ber.*, 1981, **114**, 746.
14 C. G. Overberger and Y. Shimokawa, *Macromolecules*, 1971, **4**, 718.
15 H. Takahashi, M. Yoshioka, M. Ohno and S. Kobayashi, *Tetrahedron Lett.*, 1992, **33**, 2575.
16 A. Mori, I. Arai and H. Yamamoto, *Tetrahedron*, 1986, **42**, 6447.
17 R. M. Silverstein, G. C. Bassler and T. C. Moril, *Spectrometric Identification of Organic Compounds*, 5th edn., John Wiley & Sons, New York, 1991.

Paper 5/06490B
Received 2nd *October* 1995
Accepted 8th *January* 1996