Synthesis of Optically Active Cyphenothrin-¹⁴C

—¹⁴C-Labeling at the carbonyl carbon —

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Optically active cyphenothrins, α -cyano-3-phenoxybenzyl (1R)-cis- and (1R)-trans-chrysanthemates¹ were labelled with ¹⁴C at the carbonyl carbon for use in metabolic studies. Ethyl glycinate-1-¹⁴C hydrochloride (6), prepared from potassium cyanide-¹⁴C (2) in the three steps, was condensed with 2,5-dimethyl-2,4-hexadiene via the diazo intermediate to give ethyl cis, trans-chrysanthemate-¹⁴C (7). Hydrolysis of the ester 7 followed by geometrical separation gave cis- and trans-chrysanthemic-¹⁴C acid (8a and 8b). Each geometrical isomer (8a or 8b), was optically resolved to afford (1R)-cis- or (1R)-trans-chrysanthemic-¹⁴C acid (8c or 8d). Esterification of 8c and 8d with α -cyano-3-phenoxybenzyl bromide (9) gave (1R)-cis- and (1R)-trans-cyphenothrin-(carbonyl-¹⁴C) (1a and 1b) in the yields of 4 and 6% from 2, respectively.

Key Words: carbon-14 labelling, cyphenothrin, optically active, carbonyl-labelled

1. Introduction

Cyphenothrin (α -cyano-3-phenoxybenzyl chrysanthemate) is a novel insecticide possessing a great potential for prevention of insect epidemics for domestic use due to its high insecticidal activity, moderate mammalian toxicity and adequate stability¹⁾. While cyphenothrin is a mixture of optical isomers, so-called cyphenothrin forte (1), which is the ester of (1R)-cis, trans-chrysanthemic acid and α -cyano-3-phenoxybenzyl alcohol (Table 1), has been revealed to be insecticidally more active than corresponding antipode²⁾. In this report we describe the synthesis of (1R)-cis- and (1R)-trans-cyphenothrin labelled with ¹⁴C at the carbonyl carbon for use in metabolic studies.

Table 1 Absolute configurations of cyphenothrins

Compound	Configuration	
	Acid	Alcohol
Cyphenothrin	1RS, 3RS	RS
<i>d</i> -cis Isomer	1R, 3S	RS
<i>d</i> -trans Isomer	1R, 3R	RS
Forte	1R, 3RS	RS

2. Results and Discussion

Figure 1 illustrates the procedure for the synthesis of (1R)-cis- and (1R)-trans-cyphenothrin-(carbonyl-¹⁴C) (1a, 1b). Glycine-1-¹⁴C hydrochloride (5) was prepared by the method of Sakami³⁾. ¹⁴C-Cyanation of *N*-chloromethylphthalimide (3) with potassium cyanide-¹⁴C (2), followed by acidic hydrolysis of resulting cyano-¹⁴C-methylphthalimide (4) gave 5 in 65% yield from 2. Esterification of 5 was carried out by the Bond's method⁴⁾ to give ethyl glycinate-1-¹⁴C hydrochloride (6) in 96% yield. *d*-l-cis,trans-Chrysanthemic-(carbonyl-¹⁴C) acid (8) was synthesized according to Nishizawa's method⁵⁾. Thus, condensation of ethyl diazoacetate-1-¹⁴C derived from 6 with 2,5-dimethyl-2,4-hexadiene in the presence of copper catalyst followed by basic hydrolysis to give 8 in 80% yield. Separation of geometrical isomers of the acid 8 was carried out efficiently by silica gel column chromatography eluting with a mixture of isopropyl acetate saturated with 10% aqueous ammonia and benzene (or methanol) to give *cis* and *trans* acids

Fig. 1 Scheme for the syntheses of (1R)-*cis*- and (1R)-*trans*-cyphenothrin-(carbonyl-¹⁴C).

(8a and 8b) in the yields of 30 and 57%, respectively. Optical resolutions of both of the racemic acids (8a, 8b) were achieved successfully by fractional recrystallization of their diastereomeric salts⁹⁻¹¹. Thus, *d*-1-phenyl-2-*p*-tolylethylamine was used for the *cis* acid (8a) according to the method of Matsui⁹, giving (1R)-*cis*-chrysanthemic-(carbonyl-¹⁴C) acid (8c) radiochemically in 28% yield. In the case of the *trans* acid (8b), after removing most of (1S)-*trans* acid as quinine salt⁹, repeated recrystallization of its *d*-1-phenyl-2-*p*-tolylethylamine salt¹¹ afforded (1R)-*trans*-chrysanthemic-(carbonyl-¹⁴C) acid (8d) radiochemically in 21% yield. Gas chromatography analysis⁹ of *d*-2-octyl esters of both (1R)-acids (8c, 8d) showed that their optical purities were over 98%. Each optically active acid (8c, 8d) was condensed with α -cyano-3-phenoxybenzyl bromide (9) in the presence of tetra-*n*-butylammonium bromide as a phase-transfer catalyst to afford (1R)-*cis*- or (1R)-*trans*-cyphenothrin-(carbonyl-¹⁴C) (1a or 1b) in a nearly quantitative yield. After purification by column chromatography, the overall yields of 1a and 1b were 4 and 6% from potassium cyanide-¹⁴C (2), respectively.

3. Experimental

Radio-thin layer chromatography (RTLTC) was carried out on Silica Gel 60 F₂₅₄ plates (Merck), and the radioactivity on the plate was determined by a Thin Layer Chromatogram Scanner (Aloka, Japan). Radio-gas chromatography (RGC) was conducted on a Yanaco G-80 gas chromatograph (Yanagimoto Co., Ltd., Japan) equipped with a RD-4 Gas-flow GM-counter (Aloka). Glass columns used were as follows: ① Silicone DC QF-1 WCOT (32 m $\times$ 0.25 mm ID) for the analysis of ethyl chrysanthemate-(carbonyl-¹⁴C) (7) (column temperature 120 $^{\circ}$ C, carrier gas He 0.70 ml/min; retention times: *cis* 8.2 min, *trans* 9.1 min); ② 3% Silicone OV-101 on Uniport HP (1.0 m $\times$ 3 mm ID) for the analyses of ¹⁴C-labelled cyphenothrins (1) (column temperature 190 $^{\circ}$ C, He 27 ml/min; retention times: *cis* 33.5 min, *trans* 35.5 min); ③ Silicone DC QF-1 WCOT (34 m $\times$ 0.25 mm ID) for the determination of diastereomeric ratios of 1 (column temperature 185 $^{\circ}$ C, carrier gas He 0.97 ml/min; retention times: *cis* 184.6 and 191.2 min, *trans* 202.7 and 211.4 min). Nuclear magnetic resonance (NMR), infrared (IR) and mass (MS) spectra of ¹⁴C-labelled cypheno-

thrins (1) were identical with those of unlabelled authentic samples. Optical purities of chrysanthemic-¹⁴C acids (8c, 8d) were determined according to the Murano's method⁹. Thus, a mixture of chrysanthemic-¹⁴C acid (1.5 mg), anhydrous pyridine (1.0 mg) in anhydrous toluene (50 μ l), thionyl chloride (4.2 mg) in anhydrous toluene (50 μ l), and *d*-2-octanol (11.5 mg) in anhydrous toluene (50 μ l) was heated at 95–100 °C with shaking for 20 min to yield *d*-2-octyl chrysanthemate-¹⁴C. The separation of four diastereomerized optical isomers was carried out on GC [Silicone DC QF-1 (32 m $\times$ 0.25 mm ID), column temperature 165 °C, carrier gas He 0.7 ml/min; retention times (min): (1*R*)-*cis* 9.2, (1*S*)-*cis* 9.7, (1*R*)-*trans* 10.3, (1*S*)-*trans* 10.8]. The optical purity of *d*-2-octanol was determined in the similar manner for correction by using (1*R*)-*trans*-chrysanthemic acid derived from natural pyrethrin on hydrolysis.

3.1 *N*-Cyano-¹⁴C-methylphthalimide (4)

To a solution of potassium cyanide-¹⁴C (2) (11.1 GBq, 781 mg, 12.0 mmol) in absolute methanol (30 ml) was added a solution of *N*-chloromethylphthalimide (3) (2.49 g, 12.3 mmol) in anhydrous dioxane (2.3 ml), and the mixture was stirred at room temperature for 1 h. After evaporation, the residue was diluted with water and extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate and evaporated to give a yellow solid, which was chromatographed on silica gel with benzene-methanol (100/0–95/5 v/v). Evaporation of the main fraction gave *N*-cyano-¹⁴C-methylphthalimide (4) (8.77 GBq, 1.59 g, 8.53 mmol); the purity 99% on RTLC (chloroform, *R_f* 0.14); IR ($\nu_{\max}$, cm⁻¹, chloroform): 1610 (aromatic), 1725 and 1775 (imido carbonyl); NMR (δ , ppm, CDCl₃): 4.46 (2H, s, -CH₂CN), 7.60–7.92 (4H, m, aromatic H).

3.2 Glycine-1-¹⁴C hydrochloride (5)

N-Cyano-¹⁴C-methylphthalimide (4) (8.77 GBq, 1.59 g, 8.53 mmol) was dissolved in a mixture of water (12.6 ml), concentrated hydrochloric acid (11.7 ml) and acetic acid (10.8 ml). The mixture was refluxed for 15 h, and

then evaporated to dryness. The residue was washed with acetone, filtered and dried to give glycine-1-¹⁴C hydrochloride (5) (7.22 GBq, 782 mg, 7.01 mmol); the purity 99% on RTLC (*n*-butanol/acetic acid/water=4/1/1 v/v/v, *R_f* 0.14; 70% ethanol, *R_f* 0.33).

3.3 Ethyl glycinate-1-¹⁴C hydrochloride (6)

To a reaction flask equipped with a inlet tube of hydrogen chloride was added a mixture of glycine-1-¹⁴C hydrochloride (5) (7.22 GBq, 782 mg, 7.01 mmol) and absolute ethanol (32.3 ml). Dry hydrogen chloride was introduced into the vigorously stirred mixture at 70–80 °C for 2 h. After removal of insoluble materials by filtration at about 70 °C, the solution was concentrated to 10 ml. To the residual solution was added ether (100 ml) with stirring, then the precipitate formed was filtered, washed with ether and dried. The crude product was recrystallized from ethanol to give pure ethyl glycinate-1-¹⁴C hydrochloride (6) (6.96 GBq, 943 mg, 6.76 mmol) as a colorless crystal; the purity 99% on RTLC (*n*-butanol/acetic acid/water=4/1/1 v/v/v, *R_f* 0.36); IR ($\nu_{\max}$, cm⁻¹, nujol) 1740 (CO); NMR (δ , ppm, DMSO-*d*₆) 1.26 (3H, t, *J*=7 Hz, -CH₂-CH₃), 3.75 (2H, s, -N-CH₂-CO-), 4.20 (2H, q, *J*=7 Hz, -CH₂-CH₃), 8.03 (3H, bs, -NH₃).

3.4 Ethyl chrysanthemate-(carbonyl-¹⁴C) (7)

To a mixture of ethyl glycinate-1-¹⁴C hydrochloride (6) (6.96 GBq, 943 mg, 6.76 mmol), a solution of sodium acetate (7.9 mg) and sodium nitrite (698 mg, 10.1 mmol) in water (3.36 ml) and 2,5-dimethyl-2,4-hexadiene (1.68 ml) was added dropwise 10% sulfuric acid (0.168 ml) at 15 °C. The mixture was stirred at the same temperature for a few minutes, and the organic layer was separated. The aqueous layer was extracted with 2,5-dimethyl-2,4-hexadiene (2.2 ml $\times$ 3). The combined extracts were dried by passing through an anhydrous sodium sulfate column to afford a dry diazoacetate solution. To a vigorously stirring mixture of 2,5-dimethyl-2,4-hexadiene (2.41 ml) and copper powder (80.4 mg) was added dropwise this diazoacetate solution at 140 °C for 5 min, then the resultant mixture was stirred

at 140–150°C for further 20 min. After cooling, the reaction mixture was chromatographed on silica gel with a linear gradient of petroleum ether–ethyl ether (100/0–90/10 v/v). The main fraction was concentrated under atmospheric pressure to give ethyl chrysanthemate-(carbonyl- ^{14}C) (7) (5.65 GBq, 1.08 g, 5.49 mmol) as a yellow oil; the purity 99% on RTLC (*n*-hexane/benzene=1/1 v/v, R_f 0.30); *cis/trans*=34/66 on GC; IR (ν_{max} , cm^{-1} , liquid film) 1725 (CO).

3.5 *d,l-cis,trans*-Chrysanthemic-(carbonyl- ^{14}C) acid (8)

To a solution of ethyl chrysanthemate-(carbonyl- ^{14}C) (7) (5.65 GBq, 1.08 g, 5.49 mmol) in ethanol (5.40 ml) was added a solution of sodium hydroxide (765 mg, 19.2 mmol) in water (1.47 ml), and the mixture was refluxed for 2 h. After evaporation of ethanol, the basic aqueous solution was diluted with water, washed with ether and acidified by careful addition of concentrated hydrochloric acid. The resultant mixture was extracted with ether. The ethereal extract was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate and evaporated to give *d,l-cis,trans*-chrysanthemic-(carbonyl- ^{14}C) acid (8) (5.55 GBq, 907 mg, 5.40 mmol): purity 99% and *cis/trans*=34/66 on RTLC (isopropyl acetate saturated with 10% aqueous ammonia/methanol=3/1 v/v; R_f : *cis*(8a) 0.24, *trans*(8b) 0.17).

3.6 Separation of geometrical isomers of chrysanthemic-(carbonyl- ^{14}C) acid (8a/8b)

cis,trans-Chrysanthemic-(carbonyl- ^{14}C) acid (8) (3.33 GBq, 544 mg, 3.24 mmol) was chromatographed on silica gel (Merck, 70–230 mesh, 40 cm $\times$ 3 cm ID). Elution with isopropyl acetate saturated with 10% aqueous ammonia–benzene (10:1 v/v) gave the fractions containing the *cis* isomer, and subsequent elution with isopropyl acetate saturated with 10% aqueous ammonia–methanol (10:3 v/v) afforded the fractions containing the *trans* isomer. The fractions containing each isomer were collected and concentrated to give a residue of the corresponding ammonium salt, which was acidified with 5%

hydrochloric acid and extracted with ether. Both extracts were individually washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate and evaporated to give *cis*-chrysanthemic-(carbonyl- ^{14}C) acid (8a) (1.01 GBq, 164 mg, 0.978 mmol) and *trans*-chrysanthemic-(carbonyl- ^{14}C) acid (8b) (1.90 GBq, 310 mg, 1.85 mmol), respectively; the purities 99% on RTLC. 8a: NMR (δ , ppm, CDCl_3) 1.21 (3H, s, $-\text{CH}_3$), 1.25 (3H, s, $-\text{CH}_3$), 1.56–2.10 (8H; 2s, d and d-d, $\text{C}=\text{C}(\text{CH}_3)_2$ and cyclopropyl H), 5.35 (1H, d-m, $J=7$ Hz, vinyl H), 10.90 (1H, bs, $-\text{COOH}$). 8b: NMR (δ , ppm, CDCl_3) 1.11 (3H, s, $-\text{CH}_3$), 1.30 (3H, s, $-\text{CH}_3$), 1.70 (6H, bs, $\text{C}=\text{C}(\text{CH}_3)_2$), 1.87–2.40 (2H, m, cyclopropyl H), 4.87 (1H, d-m, vinyl H), 12.40 (1H, bs, $-\text{COOH}$).

3.7 Optical resolution of *cis*-chrysanthemic- ^{14}C acid (8c from 8a)

To a stirred solution of *d,l-cis*-chrysanthemic- ^{14}C acid (8a) (1.01 GBq, 164 mg, 0.978 mmol) in acetone (1.0 ml) was added a solution of *d*-1-phenyl-2-*p*-tolylethyl amine (207 mg, 0.978 mmol) in acetone (0.7 ml). The mixture was refluxed with addition of acetone until the salt formed was dissolved completely. After cooling to room temperature, the mixture was stirred for 14 h. The colorless crystal formed was filtered, washed with a small amount of acetone and recrystallized twice in the above manner. The final crystal was decomposed in 5% sodium hydroxide (40 ml). The basic aqueous solution was washed with ether, acidified by addition of concentrated hydrochloric acid, and extracted with ether. The ethereal extract was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to give (1*R*)-*cis*-chrysanthemic-(carbonyl- ^{14}C) acid (8c) (281 MBq, 46 mg, 0.28 mmol): the optical purity 98.2% (*d*-2-octyl ester on GC).

3.8 Optical resolution of *trans*-chrysanthemic- ^{14}C acid (8d from 8b)

To a solution of *d,l-trans*-chrysanthemic- ^{14}C acid (8b) (1.90 GBq, 310 mg, 1.85 mmol) in absolute ethanol was added quinine (604 mg, 1.87 mmol) under dry nitrogen gas. The mix-

ture was heated at 60–70 °C until the salt was dissolved completely, cooled with gentle stirring for 6 h. The crystalline salt formed was filtered off and washed with ethanol (0.4 ml). The filtrate was evaporated to give a residue, which was decomposed in 5% hydrochloric acid and extracted with ether. The ethereal extract was evaporated to give (1*R*)-*trans*-enriched acid (1.24 GBq, 203 mg, 1.21 mmol).

To a solution of this acid in 70% aqueous methanol (0.4 ml) was added a solution of *d*-1-phenyl-2-*p*-tolylethyl amine (257 mg, 1.21 mmol) in 70% aqueous methanol (1.1 ml) under nitrogen. The mixture was heated at 80–85 °C with addition of 70% aqueous methanol to dissolve the diastereomeric salt formed, and cooled to room temperature for 2 h. The crystalline salt formed was filtered and washed with 70% aqueous methanol. Recrystallization of the salt was repeated twice in the above manner. The final salt was decomposed in 5% sodium hydroxide solution, and the free amine was removed by washing with ether. The resultant basic aqueous solution was acidified with concentrated hydrochloric acid, and extracted with ether. The extract was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated to give (1*R*)-*trans*-chrysanthemic-(carbonyl-¹⁴C) acid (8d) (390 MBq, 64 mg, 0.38 mmol): the optical purity 98.6% (*d*-2-octyl ester on GC).

3·9 (1*R*)-*cis*-Cyphenothrin-(carbonyl-¹⁴C) (1a)

To a solution of (1*R*)-*cis*-chrysanthemic-(carbonyl-¹⁴C) acid (8c) (178 MBq, 29 mg, 0.17 mmol) and α -cyano-3-phenoxybenzyl bromide (9) (50 mg, 0.17 mmol) in 1,1,1-trichloroethane (0.74 ml) was added a mixture of potassium carbonate (12 mg, 0.086 mmol) and tetra-*n*-butylammonium bromide (5 mg, 0.02 mmol) in water (0.49 ml). The mixture was stirred at 70 °C for 5 h. After cooling, the mixture was diluted with water and extracted with 1,1,1-trichloroethane. The extract was washed with

2% aqueous ammonia, water, 5% hydrochloric acid, water and saturated sodium chloride solution, successively, dried over sodium sulfate, and evaporated to give an oily residue, which was chromatographed on silica gel with *n*-hexane–benzene (1:3 v/v). Evaporation of the main fraction gave (1*R*)-*cis*-cyphenothrine-(carbonyl-¹⁴C) (1a) (174 MBq, 63.5 mg, 0.169 mmol): the purity over 99% on RGC, GC and RTLC (*n*-hexane/ethyl ether=1/1 v/v, R_f 0.54; benzene, R_f 0.39; chloroform, R_f 0.58).

3·10 (1*R*)-*trans*-Cyphenothrin-(carbonyl-¹⁴C) (1b)

Condensation of (1*R*)-*trans*-chrysanthemic-(carbonyl-¹⁴C) acid (8d) (296 MBq, 48 mg, 0.29 mmol) and α -cyano-3-phenoxybenzyl bromide (9) (79 mg, 0.29 mmol) was carried out in a similar manner described above to afford (1*R*)-*trans*-cyphenothrin-(carbonyl-¹⁴C) (1b) (292 MBq, 107 mg, 0.285 mmol): the purity over 99% on RGC and RTLC.

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要 旨

光学活性サイフェノトリン- ^{14}C の合成
——カルボニル炭素の ^{14}C 標識化——

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代謝研究に供するために, 光学活性サイフェノトリン [(1*R*)-シス-および(1*R*)-トランス-菊酸 α -シアノ-3-フェノキシベンジル] のカルボニル炭素を ^{14}C 標識化した。

シアニ化- ^{14}C カリウム(2)より3工程を経て合成したグリシン-1- ^{14}C エチル塩酸塩(6)をジアゾ化し, 2,5-ジメチル-2,4-ヘキサジエンと縮合してシス, トランス-菊酸- ^{14}C エチル(7)を得た。エステル7を加水分解後, 幾何異性体分離を行ってシス-およびトランス-菊酸- ^{14}C (8a, 8b)を調製, おのおのを光学分割して(1*R*)-シス-および(1*R*)-トランス-菊酸- ^{14}C (8c, 8d)を得た。光学活性菊酸 8c, 8d は α -シアノ-3-フェノキシベンジルブロミド(9)にてエステル化し, (1*R*)-シスおよび(1*R*)-トランス-サイフェノトリン-(カルボニル- ^{14}C)(1a, 1b)に誘導した。2からの通算収率は, おのおの4および6%であった。