Simple Synthesis of Pyrethoid Metabolites

Minli Zhang and Jeffrey G. Scott*

Department of Entomology, Comstock Hall, Cornell University, Ithaca, New York 14853-0901

The primary metabolism of 3-phenoxybenzyl pyrethroids by microsomal P450 monooxygenases commonly results in hydroxylation at the 2'- or 4'-positions. This paper reports the synthesis of these types of metabolites directly from five pyrethroids: deltamethrin, permethrin, fenvalerate, acrinathrin, and bifenthrin. The reactions were electrophilic substitutions using organometallic reagents. When these pyrethroids were reacted with lead tetrakis(trifluoroacetate) in trifluoroacetic acid followed by hydrolysis in K_2CO_3, 2'- and 4'-hydroxy derivatives of the 3-phenoxybenzyl group were found as the major products. For bifenthrin, which is a 2-methylbiphenyl-3-yl pyrethroid, 5- and 4'-hydroxy products were formed. This simple synthetic procedure will be valuable for generating authentic standards for pyrethroid metabolism studies.

Keywords: *Pyrethroid insecticide metabolism; lead tetrakis(trifluoroacetate); hydroxylation; electrophilic substitution*

INTRODUCTION

Many economically important pyrethroid insecticides, such as deltamethrin, permethrin, cypermethrin, and fenvalerate, contain a 3-phenoxybenzyl substituent. Primary metabolism of these pyrethroids by mammals, insects and other organisms commonly results in hydroxylation at the 2'- or 4'-position (Casida et al., 1978; Casida and Ruzo, 1980). Identification of these metabolites, such as 2'-and 4'-hydroxydeltamethrins (**6 and 7**), has been based on cochromatography with synthetic standards (Ruzo et al., 1978, 1979, 1988; Shono et al., 1979; Akhtar, 1984; Akhtar et al., 1985; Baeza-Squiban et al., 1988; Wheelock and Scott, 1992). Reported syntheses of 2'- and 4'-hydroxydeltamethrins require many steps. For example, the acid moiety, bromo acid (Ruzo et al., 1977, 1978; Tessier, 1984), and the alcohol moieties, 2'- and 4'-hydroxycyanohydrin derivatives, were prepared from specific precursors (Unai and Casida, 1977; Ruzo et al., 1978). Esters of these acid and alcohol moieties were then synthesized (Ruzo et al., 1978). These synthetic processes require purification of the products in each step and may result in isomers that are difficult to separate.

Organometallic reagents such as lead and mercury acetate have been widely used to introduce hydroxy groups into aromatic rings. This type of reaction proceeds through an electrophilic substitution mechanism (Campbell et al., 1972). Hydroxylation of aromatic compounds in this way is a convenient synthesis procedure using mild conditions. It has been adopted for chemicals with aromatic structures such as estradiol (Santaniello and Ferraboshi, 1981; Kirk and Slade, 1982; Santaniello et al., 1983), estrone (Santaniello et al., 1983; Kirk and Slade, 1983; Berrier et al., 1984), vitamin B_6 (Parnell and Vollhardt, 1985), and quinol acetate derivatives (Hara et al., 1980; Begley et al., 1988).

Lead tetrakis(trifluoroacetate) (LTTFA) has been reported as a convenient reagent to hydroxylate aromatic groups (Partch, 1967; Kalman et al., 1972). This

* Author to whom correspondence should be addressed [telephone (607) 255-7340; fax (607) 255-0939; e-mail JGS5@postoffice.mail.cornell.edu].

reagent can be simply prepared from inexpensive commercial reagents or generated *in situ*. In this paper, we report the simple synthesis of monohydroxylated derivatives directly from five pyrethroids using lead tetraacetate (LTA) and LTTFA.

MATERIALS AND METHODS

General. Organic solvents were purchased from Fisher Scientific (Springfield, NJ). All chemical reagents were from Sigma Chemical Co. (St. Louis, MO) except Pb_3O_4, which was from Fisher Scientific. LTTFA was prepared according to the method of Partch (1967). Preparative silica gel MK6F plates (250 μm, 20 × 20 cm) were from Whatman (Hillsboro, OR). Silica gel 60 (70–230-mesh ASTM) was from EM Science (Gibbstown, NJ). ^1H NMR 400 MHz spectra were obtained using a Varian VXR400S with $(CD_3)_2CO$ as solvent and acetone as the reference. Deltamethrin (**1**), authentic 2'-hydroxy- and 4'-hydroxydeltamethrins (**6, 7**), and acrinathrin (**3**) were from Roussel-Uclaf-Procida (Paris, France). Fenvalerate (**4**) was from DuPont (Wilmington, DE). Bifenthrin (**5**) was from FMC (Princeton, NJ). Permethrin was from ICI (Richmond, CA), and *cis*- and *trans*-isomers were separated by TLC using *n*-hexane/ethyl acetate (10:1). ^1H NMR of *cis*-permethrin [3-phenoxybenzyl (1*R,S*)-*cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (**2**)] [$(CD_3)_2CO$]: δ 7.40 (m, 3H), 7.16 (m, 2H), 7.05 (br, 1H), 7.03 (m, 2H), 6.96 (ddd, J = 8.0, 2.4, 0.8 Hz, 1H), 6.34 (d, J = 8.8 Hz, 1H), 5.25 (d, J = 12.4 Hz, 1H), 5.20 (d, J = 12.4 Hz, 1H), 2.12 (t, J = 8.8 Hz, 1H), 2.04 (d, J = 8.8 Hz, 1H), 1.27 (s, 1H), 1.23 (s, 3H).

(*S*)-α-Cyano-3-(2'-hydroxy)phenoxybenzyl (1*R,3R*)-3-(2,2-Dibromovinyl)-2,2-dimethylcyclopropanecarboxylate (2'-Hydroxydeltamethrin, 6) and (*S*)-α-Cyano-3-(4'-hydroxy)phenoxybenzyl (1*R,3R*)-3-(2,2-Dibromovinyl)-2,2-dimethylcyclopropanecarboxylate (4'-Hydroxydeltamethrin, 7). *(a) Reaction of Deltamethrin (1) with LTTFA Reagent.* At 4 °C, 1 (50 mg, 100 μmol) was added to 1 mL of 0.3 M LTTFA trifluoroacetic acid (TFA) solution. The solution was stirred for 2 h. The deltamethrin trifluoroacetate intermediates formed were not purified, but directly hydrolyzed to **6** and **7** by adding 25 mL of 10% K_2CO_3 and stirring for 15 min. The synthesis route is shown in **Figure 1**. Products (**6** and **7**) were purified as follows. Saturated NaCl (5 mL) was added, and the solution was extracted with 20 mL of ethyl acetate three times. After the ethyl acetate was evaporated, the products were dissolved in 1 mL of *n*-hexane/ethyl acetate (1:1), loaded onto a silica gel column (5 g of silica gel), and developed with 25 mL of *n*-hexane/ethyl acetate (1:1) to obtain a mixture of **1**, **6**, and **7** (25 mg). Further TLC separation (developed in benzene/ethyl acetate, 6:1) resulted in 12.1 mg

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Scheme 1:

1-4 → 6, 8, 10, 12 + 7, 9, 11, 13

Scheme 2:

5 → 14 + 15

1, 6, 7: R=

2, 8, 9: R=

4, 12, 13: R=

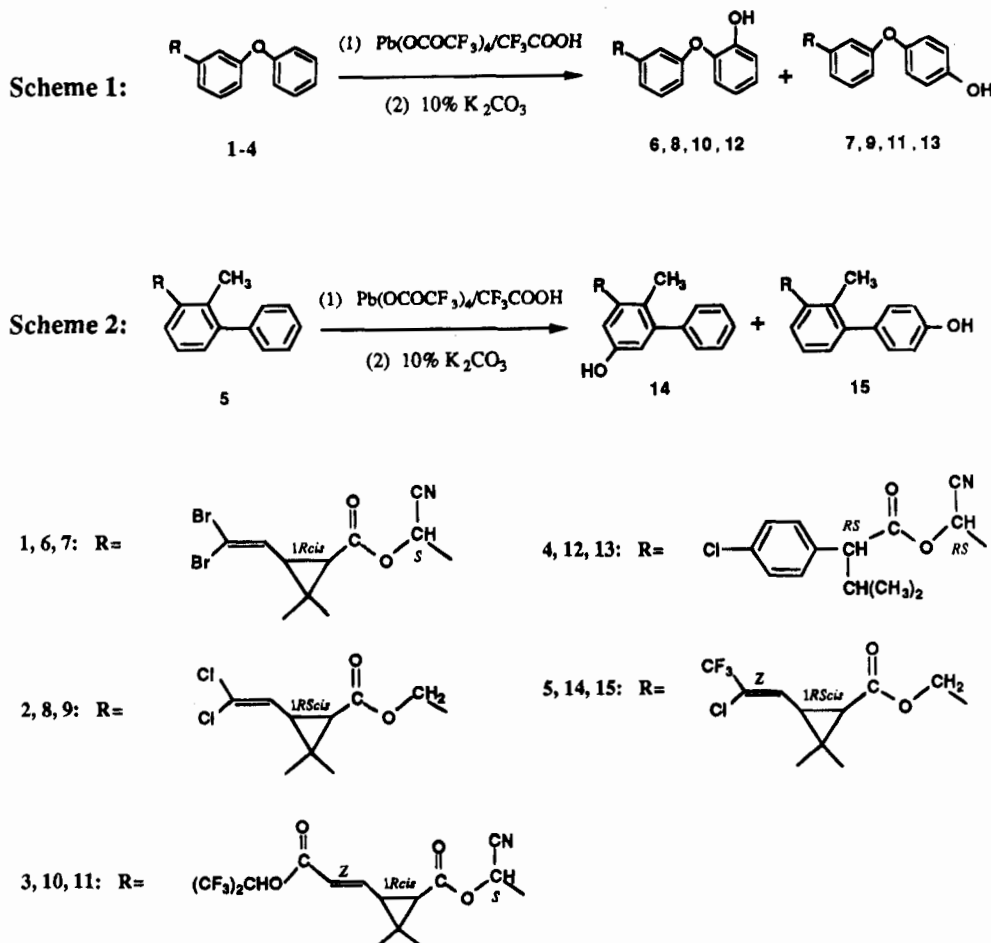5, 14, 15: R=

3, 10, 11: R=

Figure 1. Synthesis schemes for different hydroxylated pyrethroids.

of **1**, 5.3 mg of **6** (yield, 10%), and 2.1 mg of **7** (yield, 4%). Synthetic **6** and **7** have the same R_f values as their standards. Structures were confirmed with ^{1}H NMR and were also compared with those of the standards. ^{1}H NMR of **1** [(CD₃)₂CO]: δ 7.54 (t, J = 8.0 Hz, 1H), 7.44 (m, 2H), 7.40 (br d, J = 8.0 Hz, 1H), 7.25 (br, 1H), 7.21 (m, 1H), 7.12 (ddd, J = 8.0, 2.4, 1.2 Hz, 1H), 7.08 (m, 2H), 6.78 (dd, J = 6.4 Hz, 1H), 6.65 (s, 1H), 2.16 (m, 2H), 1.29 (s, 3H), 1.21 (s, 3H). ^{1}H NMR of **6** [(CD₃)₂CO]: δ 7.46 (t, J = 8.0 Hz, 1H), 7.29 (br d, J = 7.6 Hz, 1H), 7.15 (br, 1H), 7.13 (ddd, J = 8.0, 7.6, 1.6 Hz, 1H), 7.05 (dd, J = 8.0, 1.6 Hz, 1H), 7.03 (dd, J = 8.0, 1.6 Hz, 1H), 6.98 (br dd, J = 8.4, 2.6 Hz, 1H), 6.89 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 6.78 (dd, J = 7.2, 1.2 Hz, 1H), 6.63 (s, 1H), 2.15 (m, 2H), 1.28 (s, 3H), 1.21 (s, 3H). ^{1}H NMR of **7** [(CD₃)₂CO]: δ 7.47 (t, J = 8.0 Hz, 1H), 7.29 (br d, J = 7.6 Hz, 1H), 7.13 (t, J = 2.4 Hz, 1H), 7.02 (ddd, J = 8.4, 2.4, 1.2 Hz, 1H), 6.921 (m, 4H, AA′BB′), 6.77 (dd, J = 6.6, 1.2 Hz, 1H), 6.62 (s, 1H), 2.15 (m, 2H), 1.28 (s, 3H), 1.21 (s, 3H). This route and the purification procedure were used for the other pyrethroids.

(b) Reaction of Deltamethrin with LTTFA Reagent Generated in Situ. At 4 °C, **1** (50 mg) was added to 250 µL of TFA containing 63 mg (141 µmol) of LTA and stirred for 3 days. The reaction was stopped by adding 25 mL of 10% K₂CO₃. The mixture was then stirred for another 15 min. Products were extracted and purified as described in (a). After TLC purification, 20.0 mg of **1** was recovered and 2.5 mg of **6** (yield, 5%) and 2.1 mg of **7** (yield, 4%) were obtained.

3-(2′-Hydroxy)phenoxybenzyl (1R,S)-cis-3-(2,2-Dichlorovinyl)-2,3-dimethylcyclopropanecarboxylate (2′-Hydroxy-cis-permethrin, 8) and 3-(4′-Hydroxy)phenoxybenzyl (1R,S)-cis-3-(2,2-Dichlorovinyl)-2,3-dimethylcyclopropanecarboxylate (4′-Hydroxy-cis-permethrin, 9). After reaction and purification as described in (a), permethrin *cis*-isomer (**2**, 35 mg, 89 µmol) gave 1.8 mg (5%) of **8** and 1.2 mg (3%) of **9**. ^{1}H NMR of **8** [(CD₃)₂CO]: δ 7.32 (t, J = 8.0 Hz,

1H), 7.08 (m, 3H), 7.03 (dd, J = 8.0, 1.6 Hz, 1H), 6.96 (dd, J = 8.0, 1.6 Hz, 1H), 6.95 (br, 1H), 6.87 (ddd, J = 8.0, 6.8, 2 Hz, 1H), 6.84 (br dd, J = 8.4, 2.8 Hz, 1H), 6.34 (d, J = 8.8 Hz, 1H), 5.13 (d, J = 12.4 Hz, 1H), 5.08 (d, J = 12.4 Hz, 1H), 2.12 (t, J = 8.8 Hz, 1H), 2.03 (d, J = 8.8 Hz, 1H), 1.27 (s, 3H), 1.23 (s, 3H). ^{1}H NMR of **9** [(CD₃)₂CO]: δ 7.33 (dd, J = 8.0, 7.6 Hz, 1H), 7.07 (br d, J = 7.6, Hz, 1H), 6.95 (br, 1H), 6.90 (m, 4H, AA′BB′), 6.86 (br d, J = 8.0, 2.8 Hz, 1H), 6.34 (d, J = 8.8 Hz, 1H), 5.13 (d, J = 12.8 Hz, 1H), 5.07 (d, J = 12.8 Hz, 1H), 2.12 (dd, J = 8.8, 8.4 Hz, 1H), 2.03 (d, J = 8.4 Hz, 1H), 1.27 (s, 3H), 1.23 (s, 3H).

(S)-α-Cyano-3-(2′-hydroxy)phenoxybenzyl (Z)-(1R,3R)-3-[3-Oxo-3-(2,2,2-trifluoro-1-(trifluoromethyl)ethoxy)-1-propenyl]-2,2-dimethylcyclopropanecarboxylate (2′-Hydroxyacrinathrin, 10) and (S)-α-Cyano-3-(4′-hydroxy)phenoxybenzyl (Z)-(1R,3R)-3-[3-Oxo-3-(2,2,2-trifluoro-1-(trifluoromethyl)ethoxy)-1-propenyl]-2,2-dimethylcyclopropanecarboxylate (4′-Hydroxyacrinathrin, 11). From 60 mg (114 µmol) of acrinathrin (**3**) were produced 5.6 mg (9%) of **10** and 4.0 mg (7%) of **11** in the conditions given in (a). ^{1}H NMR of **3** [(CD₃)₂CO]: δ 7.54 (t, J = 8.0 Hz, 1H), 7.44 (m, 2 H), 7.40 (br d, J = 8.0 Hz, 1H), 7.27 (br, 1H), 7.20 (br t, J = 7.2 Hz, 1H), 7.12 (ddd, J = 8.40, 2.4, 1.2 Hz, 1H), 7.07 (m, 2H), 6.97 (dd, J = 11.2, 10.4 Hz, 1H), 6.40 (dq, J = 18.8, 6.4 Hz, 1H), 6.37 (s, 1H), 6.18 (dd, J = 11.6, 0.8 Hz, 1H), 3.24 (br dd, J = 10.4, 8.4 Hz, 1H), 2.32 (d, J = 8.4 Hz, 1H), 1.31 (s, 1H), 1.27 (s, 3H). ^{1}H NMR of **10** [(CD₃)₂CO]: δ 7.47(t, J = 8.0 Hz, 1H), 7.30 (br d, J = 7.6 Hz, 1H), 7.15 (br, 1H), 7.13 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 7.05 (dd, J = 8.0, 1.6 Hz, 1H), 7.04 (dd, J = 8.0, 1.6 Hz, 1H), 7.00 (br d, J = 8.0 Hz, 1H), 6.98 (dd, J = 11.6, 10.4 Hz, 1H), 6.90 (ddd, J = 8.0, 7.2, 2.0 Hz, 1H), 6.62 (s, 1H), 6.42 (dq, J = 18.8, 6.4 Hz, 1H), 6.19 (br d, J = 11.6 Hz, 1H), 3.25 (ddd, J = 10.4, 8.4, 0.8 Hz, 1H), 2.31 (d, J = 8.4 Hz, 1H), 1.32 (s, 3H), 1.27 (s, 3H). ^{1}H NMR of **11** [(CD₃)₂CO]: δ 7.48 (dd, J = 8.0, 7.6 Hz, 1H), 7.31 (br d, J = 7.6 Hz, 1H), 7.15 (t, J = 2.4 Hz, 1H), 7.03 (ddd, J = 8.0, 2.4, 0.8 Hz,

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Table 1. Observed R_f Values of Some Pyrethroids and Their Hydroxy Derivatives

compd	parent compd	position of introduced hydroxy group	R_f^a
1	deltamethrin		0.57
6	deltamethrin	2'-OH	0.37
7	deltamethrin	4'-OH	0.24
2	cis-permethrin		0.68
8	cis-permethrin	2'-OH	0.49
9	cis-permethrin	4'-OH	0.32
3	acrinathrin		0.54
10	acrinathrin	2'-OH	0.38
11	acrinathrin	4'-OH	0.26
4	fenvalerate		0.56
12	fenvalerate	2'-OH	0.38
13	fenvalerate	4'-OH	0.25
5	bifenthrin		0.71
14	bifenthrin	5-OH	0.38
15	bifenthrin	4'-OH	0.34

^{a} R_f values were measured using silica gel TLC plates developed in *n*-hexane/ethyl acetate (4:1).

1H), 6.98 (dd, $J = 11.6$, 10.4 Hz, 1H), 6.93 (m, 4H, AA'BB'), 6.62 (s, 1H), 6.42 (dq, $J = 18.8$, 6.2 Hz, 1H), 6.19 (dd, $J = 11.6$, 1.2 Hz, 1H), 3.25 (ddd, $J = 10.4$, 8.4, 0.8 Hz, 1H), 2.32 (d, $J = 8.4$ Hz, 1H), 1.32 (s, 3H), 1.27 (s, 3H).

(*R,S*)-α-Cyano-3-(2'-hydroxy)phenoxybenzyl (*R,S*)-2-(4-chlorophenyl)-3-methylbutyrate (2'-Hydroxyfenvalerate, 12) and (*R,S*)-α-Cyano-3-(4'-hydroxy)phenoxybenzyl (*R,S*)-2-(4-Chlorophenyl)-3-methylbutyrate (4'-Hydroxyfenvalerate, 13). Fenvalerate (4) (42 mg, 123 μmol) reacting with LTTFA produced 2.7 mg (6%) of 12 and 2.6 mg (6%) of 13. ^{1}H NMR of 4 [(CD$_3$)$_2$CO]: δ 7.52 (t, $J = 8.0$ Hz, 1H), 7.48 (m, 2H), 7.39 (s, 4H), 7.36 (br d, $J = 7.6$ Hz, 1H), 7.21 (m, 2H), 7.10 (ddd, $J = 8.0$, 2.4, 1.2 Hz, 1H), 7.05 (m, 2H), 6.66 (s, 1H), 3.45 (d, $J = 10.4$ Hz, 1H), 2.32 (m, 1H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.71 (d, $J = 6.4$ Hz, 3H). ^{1}H NMR of 12 [(CD$_3$)$_2$CO]: δ 7.45 (t, $J = 8.0$ Hz, 1H), 7.40 (s, 4H), 7.26 (br d, $J = 7.6$ Hz, 1H), 7.13 (ddd, $J = 8.0$, 7.2, 1.6 Hz, 1H), 7.11 (br, 1H), 7.06 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.00 (ddd, $J = 8.4$, 2.4, 0.8 Hz, 1H), 6.90 (ddd, $J = 8.0$, 7.2, 1.6 Hz, 1H), 6.63 (s, 1H), 3.44 (d, $J = 10.4$ Hz, 1H), 2.32 (m, 1H), 0.97 (d, $J = 6.4$ Hz, 3H), 0.71 (d, $J = 6.4$ Hz, 3H). ^{1}H NMR of 13 [(CD$_3$)$_2$CO]: δ 7.46 (t, $J = 8.0$ Hz, 1H), 7.40 (s, 4H), 7.26 (br d, $J = 7.6$ Hz, 1H), 7.09 (br, 1H), 7.02 (ddd, $J = 8.0$, 2.4, 0.8 Hz, 1H), 6.92 (m, 4H, AA'BB'), 6.63 (s, 1H), 3.44 (d, $J = 10.4$ Hz, 1H), 2.32 (m, 1H), 0.97 (d, $J = 6.4$ Hz, 3H), 0.71 (d, $J = 6.8$ Hz, 3H).

2-Methyl-5-hydroxybiphenyl-3-ylmethyl (*Z*)-(*1R,S*)-*cis*-3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate (5-Hydroxybifenthrin, 14) and 2-Methyl-4'-hydroxybiphenyl-3-ylmethyl (*Z*)-(*1R,S*)-*cis*-3-(2-Chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate (4'-Hydroxybifenthrin, 15). From 42 mg (100 μmol) of bifenthrin (5) were formed 1.8 mg (4%) of 14 and 1.4 mg (3%) of 15. ^{1}H NMR of 5 [(CD$_3$)$_2$CO]: δ 7.46 (m, 2H), 7.39 (m, 2H), 7.31 (m, 2H), 7.27 (dd, $J = 8.0$, 7.6 Hz, 1H), 7.21 (dd, $J = 7.6$, 1.2 Hz, 1H), 7.06 (dd, $J = 8.8$, 0.8 Hz, 1H), 5.26 (d, $J = 12.8$ Hz, 1H), 5.22 (d, $J = 12.8$ Hz, 1H), 2.31 (ddd, $J = 8.8$, 8.4, 0.8 Hz, 1H), 2.27 (d, $J = 8.4$ Hz, 1H), 2.21 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H). ^{1}H NMR of 14 [(CD$_3$)$_2$CO]: δ 7.43 (m, 2H), 7.36 (m, 2H), 7.29 (m, 2H), 7.10 (dd, $J = 8.8$, 0.8 Hz, 1H), 6.90 (d, $J = 2.4$ Hz, 1H), 6.71 (d, $J = 2.4$ Hz, 1H), 5.19 (d, $J = 12.4$ Hz, 1H), 5.13 (d, $J = 12.4$ Hz, 1H), 2.31 (ddd, $J = 8.8$, 8.4, 0.8 Hz, 1H), 2.27 (d, $J = 8.4$ Hz, 1H), 2.09 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H). ^{1}H NMR of 15 [(CD$_3$)$_2$CO]: δ 7.33 (dd, $J = 7.2$, 1.6 Hz, 1H), 7.23 (t, $J = 7.6$ Hz, 1H), 7.19 (dd, $J = 7.6$, 1.6 Hz, 1H), 7.14 (m, 2H, part of AA'BB'), 7.09 (dd, $J = 8.4$, 1.0 Hz, 1H), 6.92 (m, 2H, part of AA'BB'), 5.24 (d, $J = 12.6$ Hz, 1H), 5.20 (d, $J = 12.6$ Hz, 1H), 2.31 (ddd, $J = 8.4$, 8.4, 1.2 Hz, 1H), 2.26 (d, $J = 8.4$ Hz, 1H), 2.22 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H).

The R_f values of the original compounds and products are given in Table 1.

RESULTS AND DISCUSSION

In polar media, LTTFA reacts with aromatic substrates by an electrophilic substitution mechanism and the reaction is mainly monosubstitution (Campbell et al., 1972). When simple aromatic substitutents react with this reagent, the yield is about 60–90% (depending on type of substrates) and *para*-substitution is favored (Campbell et al., 1972). Probably due to the bulky structure of pyrethroids, the total yield was lower (the highest yield was about 10%) and more *ortho*-substituted product was produced than *para*-substituted products except in the case of fenvalerate, where about equal yields of both products were obtained. However, the low cost of reagents, simple steps, and mild reaction conditions make it possible to synthesize the hydroxy products directly from these pyrethroids with sufficient yields. Furthermore, most of these products can be easily separated by TLC.

Further studies using deltamethrin (1) indicated that 2'- and 4'-hydroxy products (6 and 7) were the major products when 1 was reacted with LTTFA reagent directly. This reaction was very clean. In the case of bifenthrin (5), no 2'-hydroxy product was produced in the reaction with LTTFA. Instead, a 5-hydroxy product (14) was formed. However, when 1 was reacted with the LTTFA generated *in situ* from LTA in TFA, the yield of hydroxy products (6 and 7) was lower and many side products were formed. When these reactions were run at room temperature, 6 and 7 could hardly be detected and many unidentified products were generated.

It was reported that when benzene or heptane was directly added to a mixture of TFA, trifluoroacetic anhydride, and Pb$_3$O$_4$, the same products and similar yield were obtained as for these compounds reacting directly with LTTFA (Partch, 1967). However, no 6 and 7 were obtained when 1 was added to this mixture. Deltamethrin may be unstable under conditions where LTTFA is generated *in situ*, probably due to many other reactive sites in the structure.

Synthetic standards of pyrethroid metabolites have been very critical in identifying these pyrethroid metabolites produced in different organisms. In some studies, the expected metabolites could not be confirmed due to the lack of standard samples (Bull and Pryor, 1990; Soderlund et al., 1987). Furthermore, studies have shown that hydroxylation of the benzyl group, with preference for the 4'-site, is prominent in the primary metabolism of pyrethroids such as fenothrin, deltamethrin, permethrin, cypermethrin, fenpropanate, fenvalerate, and bifenthrin (Casida et al., 1978; Hamed and Knowles, 1988; Ruzo et al., 1988), and 2'-hydroxylation occurs commonly in the phenoxybenzyl groups (Casida and Ruzo, 1980; Casida et al., 1978). Therefore, this simple synthetic procedure provides a potential means for the synthesis of these important pyrethroid metabolites as standards for metabolism studies.

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