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STEREOSELECTIVE SYNTHESIS OF HYDROXYLATED BIFENTHRIN ISOMERS[1]

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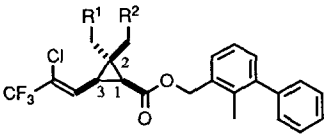
Abstract: Two isomeric, hydroxylated derivatives of the potent insecticide/acaricide bifenthrin were prepared from a common precursor. A high degree of control over the relative stereochemistry at all three stereogenic centers was achieved by closure of the C1-C3 bond of the cyclopropane ring using a judicious choice of ring closure substrates.

Bifenthrin **1** is a third generation pyrethroid[3] that is structurally and biologically unique:[4] structurally for the biphenyl alcohol fragment; biologically for the strong acaricidal (miticidal) activity that complements potent, broad spectrum insecticidal activity. As part of a metabolism study, authentic samples were needed of hydroxylated bifenthrin derivatives **2** and **3**.[5] Very little literature on the synthesis of these types of important metabolites. [6]

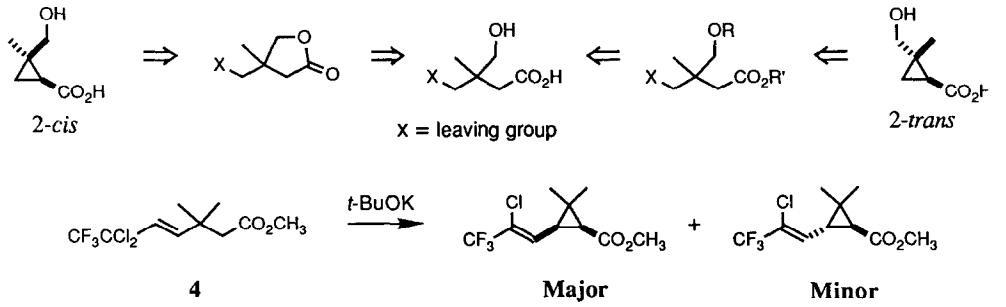


1 R^1=R^2=H **Bifenthrin**
2 R^1=H, R^2=OH
3 R^1=OH, R^2=H

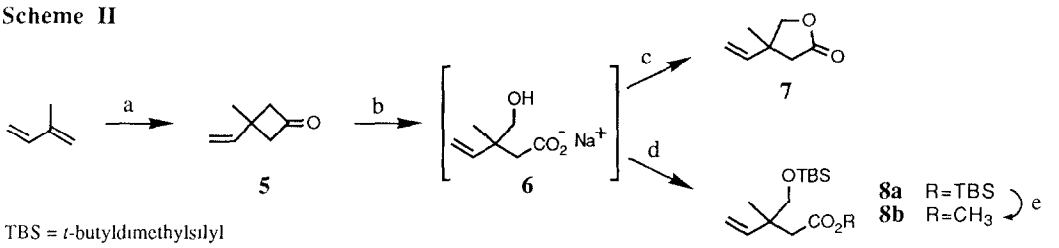
The acid portion of bifenthrin is 3-*cis* (>95%) and so the problem reduces to the preparation of two diastereomers of hydroxylated bifenthrin: 2-*cis*-3-*cis* **2** and 2-*trans*-3-*cis* **3**. A synthetic strategy to control the relative stereochemistry at all three stereogenic centers was adopted that involved the closure of the C1-C3 cyclopropane bond. Both isomers could then be formed from a common γ-hydroxyacid intermediate (Scheme I). The 2-*cis* isomer would be formed by closure of a γ-lactone and the 2-*trans* isomer would result from ring closure while the alcohol was protected with a suitably large, non-chelating group. Stereocontrol at C3 relied upon the observation that ring closure of **4** results in a predominantly 3-*cis* product.[7]

The sodium salt of the key intermediate 3-hydroxymethyl-3-methyl-4-pentenoic acid **6**[8] (Scheme II) was prepared using a basic peroxide ring cleavage of cyclobutanone **5**,[9] available in two steps from isoprene.[10] Acidification of **6** gave lactone **7** (60% from **5**). Alternatively, removal of solvent *in vacuo* and reaction of **6** with excess *tert*-butyldimethylsilyl (TBS) chloride in acetonitrile gave the silyl ether-silyl ester **8a**. This silyl

Scheme I



Scheme II



TBS = *t*-butyldimethylsilyl

a.) Ref. 9, 40%; b.) H_2O_2, NaOH c.) H^+, 60% d.) xs TBSCl e.) 1. CH_3OH, DBU, 2. CH_3I, 40%.

ester was then converted to the more stable methyl ester **8b** by treatment with DBU and methanol in acetonitrile, and alkylation of the DBU-carboxylate salt with iodomethane[11] (40% from **5**).

Introduction of the halogenated side chain was accomplished, for both **7** and **8b**, using a copper-catalyzed[12] addition of Freon-113a™ and gave a 1:1 mixture of diastereomers **9** and **13**, respectively (85%, Scheme III). The next step was to determine the level of stereogenic control engendered by the use of the TBS protecting group in **13**. Ester **13** was treated with potassium *t*-butoxide in heptane/N,N-dimethyl acetamide[6] followed by treatment with DBU to complete the dehydrohalogenation.[13] Gratifyingly, only the 2-*trans* isomers **16** were observed, indicating that the TBS group was sufficiently bulky to achieve the desired selectivity. In a similar fashion, lactone **9** cyclized to 2-*cis* cyclopropanes **12**.

The presence, in both **9** and **13**, of equivalent amounts of both chloride epimers at C3 resulted in the formation of a nearly equal mixture of 3-*cis* and 3-*trans* cyclopropane isomers. Removal of this stereogenic center by dehydrohalogenation to **10** and **14**, followed by S_n2' ring closure, was anticipated to result in predominantly 3-*cis* products.[6] Dehydrochlorination of **9** and **13** was therefore investigated.

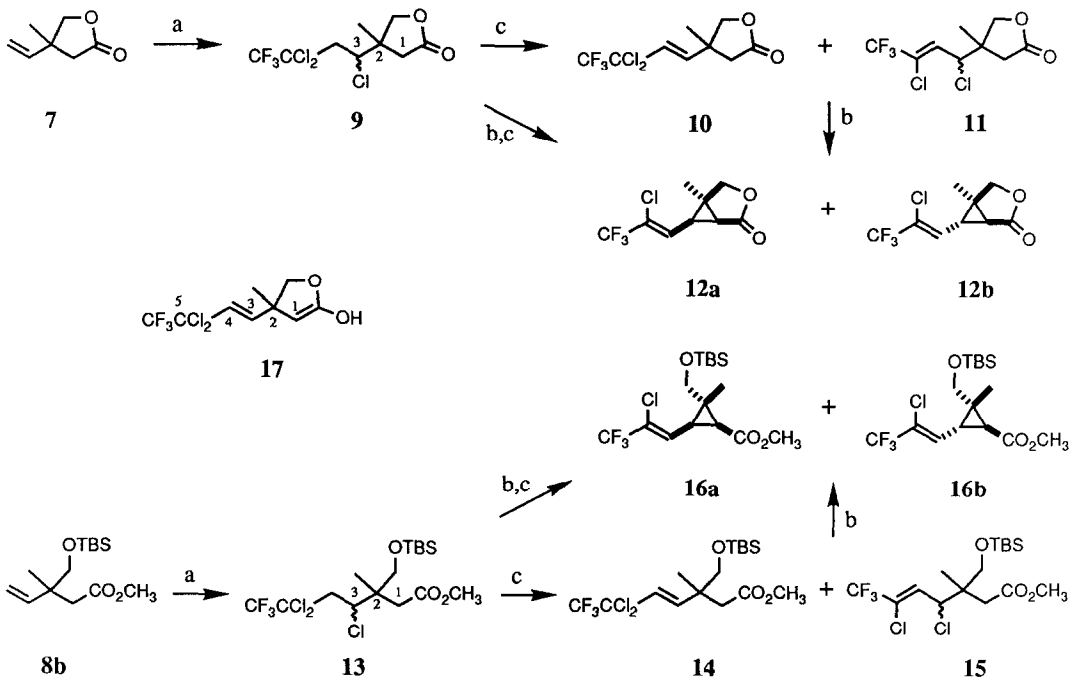
Dehydrochlorination of **9** (and **13**) can occur to give two isomeric products (**10** and **11**, or **14** and **15** respectively) and each case yielded very different olefin product ratios. In the case of lactone **9**, a 2:1 mixture of the desired 4-pentene **10** and a diastereomeric mixture of 5-pentenes **11** resulted (84%). In contrast, similar treatment of ester **13** with DBU gave only a small amount of the desired isomer **14**, with the diastereomeric mixture of **15** predominating by a factor of 1:10 (86%).

Treatment of **10**+**11** (2:1) with potassium *t*-butoxide gave a mixture of *cis* **12a** and *trans* **12b** in a ratio of 3.5:1, substantially more than the 1.5:1 mixture obtained from ring closure of **9** under the same conditions. Assuming that ring closure of **11** produces equal amounts of **12a** and **12b** (see below), the ratio derived from **10** is calculated to be >10:1! The reasons for this selectivity are unclear. Examination of the conformational energies of **17**, on rotation about the C2-C3 bond, revealed only a minor difference in the pro-*trans* and pro-*cis* conformations.[14]

A similar treatment of **14** and **15** (1:10) with potassium *t*-butoxide resulted in a 1:1 mixture of *cis* **16a** and *trans* **16b** (45%), identical with the results of ring closure of ester **13**, and consistent with a product diastereomer ratio determined by the C3 chloride configuration.

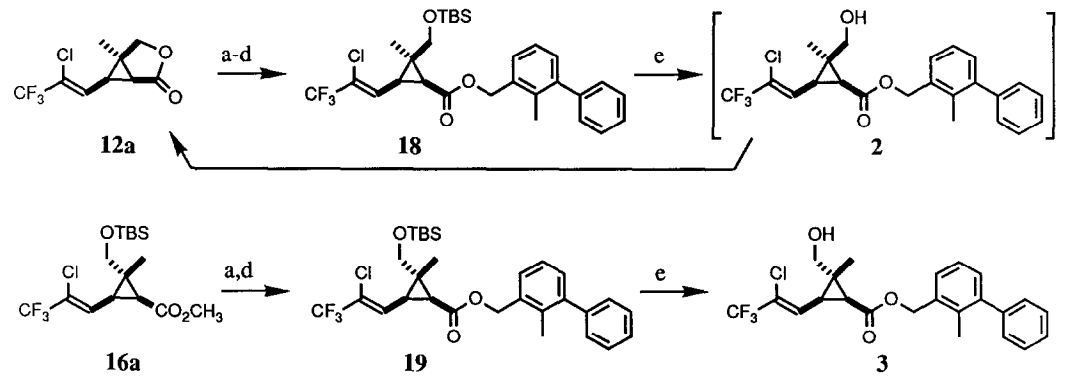
Esterification of lactone **12** with the bifenthrin alcohol was accomplished in a manner similar to the esterification of hydroxyacid **6**. Hydrolysis of lactone **12a** and isolation of the salt was followed by treatment with excess TBSCl. The resulting silyl ester was transformed to the DBU-carboxylate salt by methanolysis in the presence of DBU. Alkylation of the salt with 2-methyl-3-phenylbenzyl bromide in acetonitrile gave **18** (25% from **10**). Removal of the silyl protecting group of **18** to reveal proposed metabolite **2** resulted in the rapid spontaneous lactonization of the hydroxyester and recovery of only **12**. The apparent instability of **2** makes it unlikely to be more than a transitory metabolic entity. Transesterification of **16a** to 2-methyl-3-phenylbenzyl ester **19** under standard conditions, followed by deprotection, gave proposed metabolite **3** (20% from **16a**).

Scheme III



a.) CF_3CCl_3, CuCl, ethanolamine; b.) *t*-BuOK, THF; c.) DBU, THF.

Scheme IV



a.) KOH; b.) xs TBSCl; c.) CH_3OH, DBU d.) 2-methyl-3-phenylbenzyl bromide, CH_3CN; e.) HBF_4

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References and Notes

1 Presented at the Second International Symposium *Recent Advances in the Chemistry of Insect Control II*, Oxford, UK, July 17-19, 1989.

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3 Naumann, K. *Synthetic Pyrethroid Insecticides: Structures and Properties*; Springer-Verlag: New York, 1990. Davies, J. H. In *The Pyrethroid Insecticides*; Leahey, J. P., Ed.; Taylor & Francis: Philadelphia, 1985; pp. 1-41. Ruigt, G. S. F. In *Comprehensive Insect Physiology Biochemistry and Pharmacology*; Kerkut, G. A.; Gilbert, L. I., Eds.; Pergamon: New York, 1985; Vol. 12, Chapter 7, pp. 183-262.

4 Engel, J. F.; Plummer, E. L.; Stewart, R. R.; Van Saun, W. A.; Montgomery, R. E.; Cruickshank, P. A.; Harnish, W. N.; Nethery, A. A.; Crosby, G. A. In *Proceedings of the Fifth International Congress of Pesticide Chemistry*; Miyamoto, J.; Kearney, P. C., Eds.; Pergamon: New York, 1983; p. 101.

5 Hydroxylation of pyrethroid methyl groups is a common metabolism pathway, see: Kulkarni, A. P.; Hodgson, E. In *Ann. Rev. Pharmacol. Toxicol.*; Annual Reviews: Palo Alto, 1984.

6 For an example see: Unai, T.; Casida, J. E. *J. Agric. Food Chem.* **1977**, *25*, 979.

7 Patricia Levenberg, FMC Corporation, unpublished results.

8 All new compounds were characterized by NMR, IR, MS and combustion analysis and/or high resolution MS. Selected spectroscopic data: **3**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5-7.2 (m, 8H), 7.0 (dq, J=9, 0.8 Hz, 1H), 5.2 (s, 2H), 3.6 (s, 2H), 2.4 (tq, J=8.5, 0.8 Hz, 1H), 2.25 (d, J=8.5 Hz, 1H), 2.2 (s, 3H), 1.2 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 142.7, 141.5, 134.1, 133.8, 130.1, 129.0, 128.1, 127.8, 126.6, 125.3, 68.4, 65.3, 33.2, 28.4, 26.1, 15.9, 10.5. **7**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.8 (dd, J=16, 10 Hz, 1H), 5.08 (d, J=10 Hz, 1H), 5.05 (d, J=16 Hz, 1H), 4.1 (d, J=9 Hz, 1H), 3.9 (d, J=9 Hz, 1H), 2.5 (d, J=17 Hz, 1H), 2.25 (d, J=17 Hz, 1H), 1.2 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 140.7, 114.2, 77.6, 41.1, 22.8. **8b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.8 (dd, J=10, 16 Hz, 1H), 5.0 (d, J=10 Hz, 1H), 4.95 (d, J=16 Hz, 1H), 3.6 (s, 3H), 3.45 (d, J=11 Hz, 1H), 3.35 (d, J=11 Hz, 1H), 2.4 (d, 2H), 1.1 (s, 3H), 0.9 (s, 9H), 0.0 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 142.9, 112.9, 69.8, 50.9, 41.1, 41.2, 25.7, 25.7, 20.6, 18.1, -5.7. **12a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (m, 1H), 4.2 (dd, 2H), 2.4 (s, 2H), 1.5 (s, 3H). **12b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.1 (d, J=10 Hz, 1H), 4.35 (d, J=11 Hz, 1H), 4.15 (d, J=11 Hz, 1H), 2.3 (dd, J=10 Hz, 3H), 2.1 (d, J=3 Hz, 1H), 1.4 (s, 3H). **16a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.0 (d, J=11 Hz, 1H), 3.7 (s, 3H), 3.6 (d, 2H), 2.45 (t, J=10 Hz, 1H), 2.25 (d, J=9 Hz, 1H), 1.25 (s, 3H), 0.9 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 129.8, 129.7, 66.3, 51.5, 33.0, 27.2, 25.6, 25.2, 18.1, 10.6, -5.6. **18**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.2 (m, 8H), 7.0 (d, 1H), 5.2 (dd, 2H), 3.9 (dd, 2H), 2.2 (s+m, 4H), 2.1 (d, 1H), 1.3 (s, 3H), .9 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 142.9, 141.7, 134.4, 134.0, 130.3, 129.3, 128.4, 128.3, 128.0, 126.8, 125.6, 125.5, 65.5, 60.7, 34.2, 31.8, 25.7, 23.8, 18.0, 16.1.

9 Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321.

10 Mori, K.; Uematsu, T.; Minobe, M.; Yanagi, K. *Tetrahedron* **1983**, *39*, 1735.

11 Ono, N.; Yamada, T.; Saito, T.; Tanaka, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2401.

12 Bellus, D. *Pure Appl. Chem.* **1985**, *57*, 1827.

13 The size of the trifluoromethyl group, relative to chlorine, results in the exclusive formation of the (Z) alkene.

14 Modeled using the SYBYL software package (Tripos Associates, Inc. 1699 S. Hanley Drive, St. Louis, MO 63144)