

SYNTHESIS OF TRITIUM-LABELLED FENOXYCARB AND S-31183, TWO PHENOXYPHENYL ETHER INSECT GROWTH REGULATORS

Marcus F. Boehm and Glenn D. Prestwich
Department of Chemistry
State University of New York
Stony Brook, NY 11794-3400

SUMMARY

Using 4-(*m*-bromophenoxy)phenol as an intermediate, two brominated phenoxyphenyl ether IGRs were prepared. Reductive tritiodibromination of the bromo IGRs furnished high specific activity tritium-labelled fenoxycarb and S-31183, which can be used to study the molecular action of these two potent juvenoid-type IGRs.

Key words: phenoxyphenyl ether, IGR, fenoxycarb, oxime ether, juvenoid, insect juvenile hormone, binding protein

INTRODUCTION

The phenoxyphenyl ether group occurs in a wide variety of insect growth regulators as the 4-phenoxyphenoxy regioisomer (1) and in a host of pyrethroid insecticides as the 3-phenoxyphenoxy regioisomer (2). In many cases, the molecular action of quite successful commercial pest control agrochemicals is still unknown. The phenoxyphenyl ethers (PPEs) are no exception, and we chose to prepare several of the most potent IGRs with specific activities exceeding 24 Ci/mmol in order to facilitate receptor binding assays.

Our target molecules are juvenoids (3,4), that is, compounds which bear little structural homology to the sesquiterpene juvenile hormone (JH) but which nonetheless produce physiological JH-like responses at extremely low doses. Figure 1 shows representatives of several classes of these juvenoid PPEs which have been reported recently, including the alkynyl PPEs of Ciba-Geigy (5), fenoxycarb and its analogs from Maag (6), and the unusual oxime ethers

from Sumitomo (7). For several insects, the most active juvenoid IGR known is Sumitomo's S-31183 (8), a 2-hydroxypyridyl ether analog of the Sumitomo oxime ether S-21149.

In connection with our studies on the use of radioligands to identify JH and JH analog binding proteins (9,10), we now describe the synthesis of fenoxycarb and S-31183 with a *meta*-tritium substituent in the terminal phenyl ether ring.

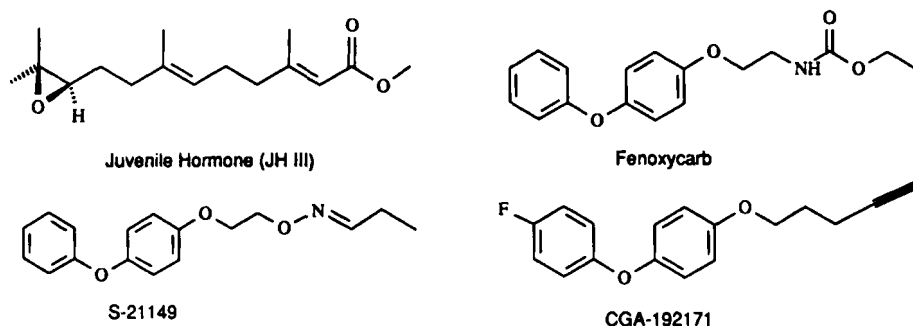


Figure 1. Juvenile hormone (JH III) and three PPE analogs

RESULTS AND DISCUSSION

The synthesis of ^3H -fenoxycarb is illustrated in Figure 2. *m*-Dibromobenzene and *p*-methoxyphenol were refluxed in collidine with a Cu_2O to give the 4-(3-bromophenoxy)phenyl methyl ether **3** (67% yield). Hydrolysis of **3** with refluxing 48% HBr in glacial acetic acid provided the *m*-bromophenoxyphenol **4** in 91% yield. Condensation of the phenolate anion of **4** with ethyl *N*-(2-chloroethyl)carbamate **5** gave *m*-bromofenoxycarb **6**. Catalytic tritiodermination of **6** was achieved in ethyl acetate solution using 10% Pd/C under carrier free tritium gas to give *m*-tritiofenoxycarb **7**, specific activity 24.9 Ci/mmol.

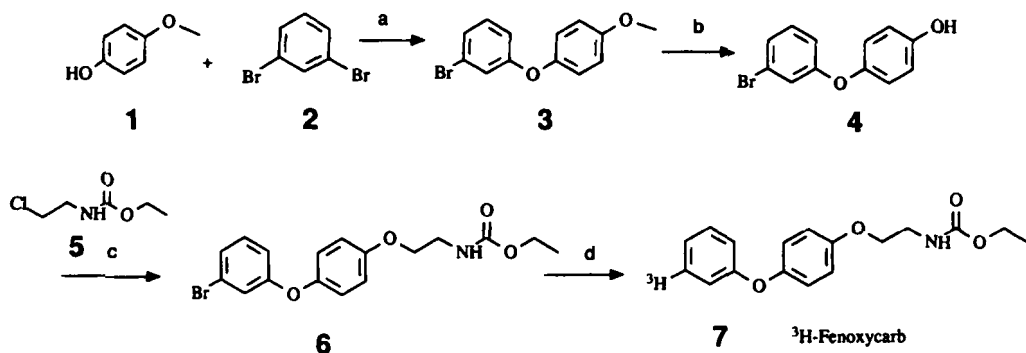


Figure 2. Synthesis of labelled fenoxycarb. Reagents: (a) collidine, Cu_2O ; (b) 48% HBr-HOAc; (c) NaH, DMSO-toluene; (d) $^3\text{H}_2$, 10% Pd/C.

The synthesis of S-31183 proceeded in an analogous fashion (Figure 3). Condensation of the phenolate anion of *m*-bromophenoxyphenol **4** with excess propylene oxide under phase-transfer conditions in a toluene - H₂O system gave 1-[4-(3-bromophenoxy)-phenoxy]propan-2-ol (**8**) in 60% yield. Heating of alcohol **8** with NaH in excess 2-chloropyridine (as solvent) gave *m*-bromo-S-31183 **9** in 81% yield after chromatography. Catalytic tritioderobromination of **9** as described above yielded *m*-tritio-S-31183 **10** with a specific activity of 24.4 Ci/mmol.

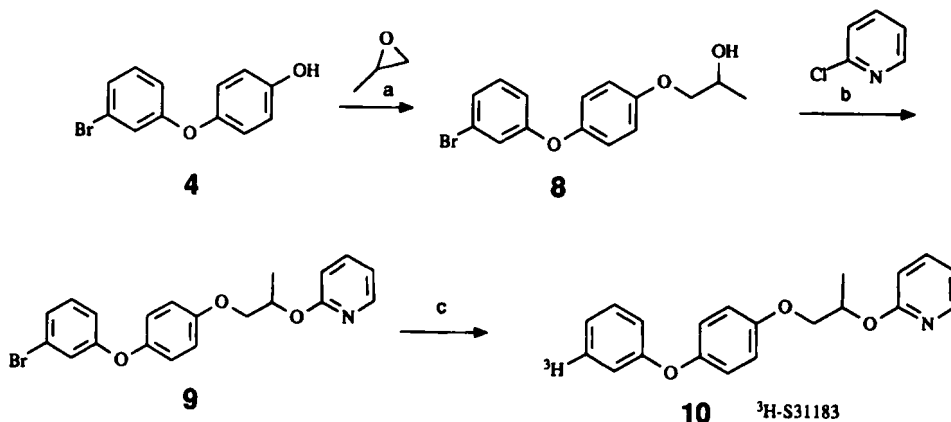


Figure 3. Synthesis of labelled S-31183. Reagents: (a) NaOH, NBu₄Br, toluene-water; (b) NaH; (c) ³H₂, 10% Pd/C.

As seen from the tritium NMR of the two product PPEs, most of the tritium signal in both compounds is located in the *m*-position on the terminal phenoxy ring (Figure 4). The proton-decoupled tritium spectra (Figures 4a and 4c) show sharp singlets for the *meta*-tritons at δ 7.32 ppm for both compounds. Smaller singlets (< 5%) at δ 7.06 ppm might be attributed to exchange into *ortho* positions of the internal hydroquinone bisether ring, since no tritium-tritium coupling is observed. For ³H-S-31183 **10**, the singlet at δ 8.19 indicates about 20% exchange into the 6-position of the pyridinyl ring is also occurring. The proton-coupled tritium spectra in Figures 4b and 4d, shown with sine-bell window resolution enhancement, confirm these assignments. The aryl triton-proton couplings can be estimated to be J_{HT} *meta* = 2.1 Hz and J_{HT} *ortho* = 7.6 Hz for the phenoxy ring and J_{HT} *meta* = 1.6 Hz, J_{HT} *ortho* = 5.6 Hz for the pyridyloxy ring.

For each compound, the final specific activity decreased when the ratio of catalyst to substrate was increased. Thus, when 2 mg of 10% Pd/C was used per milligram of bromoaryl ether, the reaction was complete in 1 h and the specific activity was 18 Ci/mmol. On the other hand, when 0.2 mg of catalyst was per milligram of aryl bromide, the reaction was required 6 h and the specific activity was in excess of 24 Ci/mmol, close to the theoretical maximum of 29.6 Ci/mmol per site.

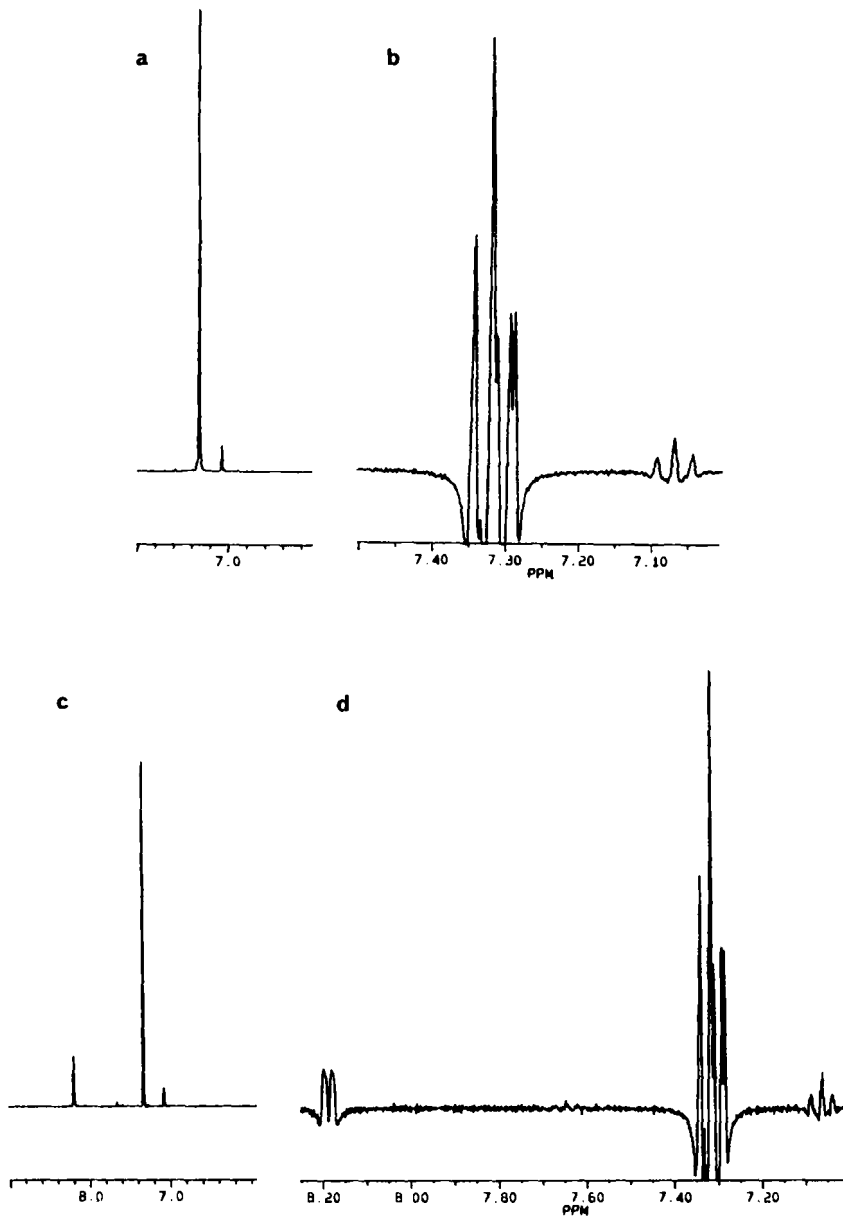


Figure 4. Tritium NMR spectra of tritium-labelled PPE IGRs: ^3H -fenoxycarb **7**, proton-decoupled (a) and coupled (b); ^3H -S-31183 **10**, proton-decoupled (c) and coupled (d).

The decreased specific activity seen with increasing quantities of catalyst can be attributed to the exchange of bound hydrogen present in the catalyst. Synthesis of the tritiated dodecadienoates ^3H -hydroprene (11) and ^3H -methoprene (12) gave compounds with specific activities greater than the theoretical maximum due to extensive tritium-hydrogen exchange (68 Ci/mmol for ^3H -hydroprene and 84 Ci/mmol for ^3H -methoprene). The absence of exchange in the phenoxyphenol compounds is a consequence of the lack of vinylic and allylic positions.

The two labelled PPE juvenoids are currently in use for the identification of cellular binding sites in insect tissues. The recent discovery that JH homologs and the dodecadienoate JHAs have different cellular receptors (13,14) adds special impetus for the characterization of PPE-binding proteins from JH target sites in insects.

MATERIALS AND METHODS

4-(3-Bromophenoxy)phenoxy-methyl ether (3). A solution of *p*-methoxyphenol **1** (5.1 g, 41.1 mmol) and 1,3-dibromobenzene **2** (9.5 g, 40.6 mmol) in 50 mL of collidine containing 2.93 g (20.6 mmol) of Cu_2O was refluxed at 170 °C for 2 days under nitrogen (15) and then poured into 2N HCl (200 mL). The crude phenoxyphenyl methyl ether **3** was extracted (20% EtOAc/hexane), washed (H_2O), concentrated and purified by flash chromatography (SiO_2 , 4% EtOAc/hexane) to give 4.65 g (16.7 mmol) of phenyl ether **3** (16) and 3.5 g (14.9 mmol) of starting material **1** (yield 67%); TLC (20% ethyl acetate-hexane): $R_f = 0.58$.

4-(3-Bromophenoxy)phenol (4). To 30 mL of a 1:1 mixture of 48% HBr-acetic acid was added 1.5 g (5.4 mmol) of methyl ether **3**. The reaction mixture was refluxed for 1 h, cooled, extracted (20% EtOAc-hexane) and chromatographed (15% EtOAc-hexane) to give 1.3 g (4.9 mmol) of the *m*-bromophenoxyphenol **4** (91% yield); TLC: $R_f = 0.43$.

Ethyl N-(2-chloroethyl)carbamate (5). The Maag patent procedure (17) was followed. Thus, to 20.1 g of 2-aminoethanol (330 mmol) in 50 mL of CH_2Cl_2 at 0 °C was added 17.78 g (165 mmol) of ethyl chloroformate and the reaction was stirred at room temperature for 1 h. The chloride salt of the aminoethanol that formed was filtered off and the desired product was concentrated in vacuo to give 18.8 g (141 mmol) of ethyl N-(2-hydroxyethyl)carbamate (85% yield). To 10 g (75.2 mmol) of the hydroxycarbamate was slowly added 17.9 g (152 mmol)

of thionyl chloride and the reaction stirred for 1.5 h to give the crude chlorocarbamate **5**.

Purification by distillation (reduced pressure) gave 8.7 g (57.6 mmol) of pure chloro carbamate reagent **5** (77% yield). This compound should be used soon after synthesis because it decomposes to a dark brown material within a few days.

Ethyl N-2-[4-(3-bromophenoxy)phenoxyethyl] carbamate (*m*-bromofenoxycarb) (6**)**.

The anion of 300 mg (1.14 mmol) of phenoxyphenol **4** was generated from the free phenol and 33 mg (1.34 mmol) of sodium hydride in 1 mL of 1:1 DMSO-toluene. After addition of 258 mg (1.71 mmol) of the chloroethyl carbamate **5** in 1 mL of toluene, the mixture was refluxed for 4 h and the product was isolated by addition of water and extraction with EtOAc. The crude *m*-bromofenoxycarb **6** was purified by column chromatography (SiO₂, 20% EtOAc-hexane) to give 285 mg (0.752 mmol) of bromofenoxycarb **6** which crystallized after standing for several days (66% yield); TLC: R_f = 0.30; ¹H-NMR: (CDCl₃) δ 1.25 (t, *J* = 6.5 Hz, CH₃CH₂O-), 3.59 (t, *J* = 5 Hz, -CH₂NH-), 4.03 (t, *J* = 5 Hz, -OCH₂-), 4.13 (q, *J* = 6.5 Hz, CH₃CH₂O-), 5.11 (br s, -NH-), 6.84-7.25 (m, aromatic region).

Ethyl N-2-(4-phenoxy)phenoxyethyl] carbamate (fenoxycarb). The aryl bromide **6** (20 mg, 0.052 mmol) was dissolved in 2 mL of ethyl acetate and 4 mg of 10% Pd/C was added. After removal of gas from the solution the mixture was stirred under 1 atm of H₂ for 3-4 h. The reaction was monitored by GC (DB-5 megabore column, 1500 for 1 min., 100/min) and the product co-eluted with an authentic sample of fenoxycarb. The reaction mixture was filtered to remove the catalyst and chromatographed (SiO₂, 20% EtOAc-hexane) to give 15 mg (0.050 mmol) of homogeneous fenoxycarb (96% yield); TLC: R_f = 0.30; ¹H-NMR: (CDCl₃) δ 1.25 (t, *J* = 6.5 Hz, CH₃CH₂O-), 3.59 (t, *J* = 5 Hz, -CH₂NH-), 4.03 (t, *J* = 5 Hz, -OCH₂-), 4.13 (q, *J* = 6.5 Hz, CH₃CH₂O-), 5.11 (br s, -NH-), 6.84-7.25 (m, aromatic region).

Ethyl N-2-[4-(3-tritlophenoxy)phenoxyethyl] carbamate (*m*-tritlofenoxycarb) (³H)-7****.

The aryl bromide **6** (20 mg, 0.052 mmol) was dissolved in 2 mL of ethyl acetate and 4 mg of 10% Pd/C was added. After a three cycles (freeze, thaw, degas), the mixture was stirred under 1 atm of T₂ for 4 h on the tritium gas line at the National Tritium Labeling Facility (NTLF), Berkeley, CA. The reaction mixture was filtered to remove the catalyst, lyophilized, and chromatographed (SiO₂, 20% EtOAc-hexane) to give 14 mg (0.047 mmol) of the pure [³H]-fenoxycarb **7** (90% yield). The radioactivity

comigrated on TLC with an authentic sample of fenoxycarb. The total radioactivity was 1.16 Ci giving a specific activity of 24.9 Ci/mmol. Decoupled $^3\text{H-NMR}$ (CDCl_3) δ 7.067 (s, 5% of total tritium), 7.316 (s, 95% of total tritium).

1-[4-(3-Bromophenoxy)phenoxy]propan-2-ol (8). A solution of 2 g (7.58 mmol) of *m*-bromophenoxyphenol **4**, 1.2 g (30.3 mmol) of NaOH, 200 mg (0.62 mmol) of *n*Bu₄NBr and excess propylene oxide was stirred in 10 mL of toluene-H₂O (5:2) for 2-3 days until the reaction was complete by GC. The reaction mixture was poured into 100 mL of H₂O, extracted (20% EtOAc-hexane), dried (MgSO₄), and concentrated to give 1.7 g (5.28 mmol) of the crude bromophenoxypropanol **8** (70% yield); TLC R_f = 0.25. The product was used without further purification in the next step.

2-(1-Methyl-2-(4-(3-bromophenoxy)phenoxy)ethoxy)pyridine (m-bromo-S-31183, 9).

To 1.7 g (5.28 mmol) of alcohol **8** in 2 mL (21.15 mmol) of 2-chloropyridine was added 127 mg (5.28 mmol) of NaH at 0 °C. The mixture was stirred at 90 °C for 10 h; excess 2-chloro pyridine was distilled off and the product was purified by chromatography (SiO₂, 10% EtOAc-hexane) to give 1 g of **9** (2.51 mmol) and 700 mg (2.17 mmol) of starting material **8** (81 % yield of **9**); TLC: R_f = 0.53; $^1\text{H-NMR}$ (CDCl_3) δ 1.48 (d, J = 6.5 Hz, CH₃-), 4.14 (dd+dd, J = 23 Hz and J = 6.0 Hz, -CH₂-), 5.58 (ddt, J = 6.0 and J = 6.5 Hz, -CH-), 6.72-8.17 (m, aromatic regions).

2-[1-Methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine (S-31183). Aryl bromide **9**

(20 mg, 0.050 mmol) was dissolved in 2 mL of ethyl acetate and 4 mg of 10% Pd/C was added. After removal of gas from the solution the mixture was stirred under 1 atm of H₂ for 3-4 h. The reaction was monitored by GC (DB-5 megabore column, 150° for 1 min., 100°/min) and the product co-eluted with an authentic sample of S-31183. The reaction mixture was filtered to remove the catalyst and chromatographed (SiO₂, 10% EtOAc-hexane) to give 14.5 mg (0.045 mmol) of the pure S-31183 (90% yield); TLC: R_f = 0.50; $^1\text{HNMR}$ (CDCl_3) δ 1.48 (d, J = 6.5 Hz, CH₃-), 4.14 (dd+dd, J = 23 Hz and J = 6.0 Hz, -CH₂-), 5.58 (ddt, J = 6.0 and J = 6.5 Hz, -CH-), 6.72-8.17 (m, aromatic regions).

[*m*- ^3H]-S-31183 (10). Aryl bromide **9** (20 mg, 0.050 mmol) was dissolved in 2 mL of ethyl acetate and 4 mg of 10% Pd/C was added. Following the tritium gas reduction above

(4 h at 1 atm $^3\text{H}_2$), the catalyst was removed and the residue was chromatographed (SiO_2 , 10% EtOAc-hexane) to give 14 mg (0.044 mmol) of the pure $[\text{^3H}]\text{-S-31183 10}$ (88% yield). The radioactivity comigrated on TLC with an authentic sample of S-31183. The total radioactivity was 1.07 Ci giving a specific activity of 24.4 Ci/mmol. Decoupled $^3\text{H-NMR}$ (CDCl_3) δ 7.063 (s, 4% of total tritium), 7.315 (s, 80% of total tritium), 8.186 (s, 16% of total tritium).

ACKNOWLEDGMENTS

We thank the National Science Foundation (DCB-8509629) for financial support of this project, the Camille and Henry Dreyfus Foundation and the Rohm and Haas Company for unrestricted awards, and Dr. H. Morimoto (NTLF) for assistance in tritium gas reductions and Dr. P.G. Williams for recording tritium NMR spectra. We also thank Drs. R. Zurlüh and F. Dorn (Socar) and Drs. G. Hüppi and S. Dorn (Maag) for gifts of fenoxycarb, substituted analogs, and unpublished procedures; Dr. Y. Kosuge (Sumitomo) provided samples of S-21149 and S-31183 and valuable advice and unpublished procedures; and Drs. G. Voss and U. Burckhardt (Ciba-Geigy) for several alkynyl PPEs.

REFERENCES

1. Retnakaran, A., Grannet, J. and Ennis, T. -- In *Comprehensive Insect Physiology, Biochemistry, and Pharmacology* (Kerkut, G.A. and Gilbert, L.I., eds.), Pergamon, Oxford, Vol. 12 pp. 529-601 (1985)
2. Henrick, C.A., Anderson, R.J., Carney, R.L., Garcia, B.A. and Staal, G.B. -- In *Recent Advances in Chemistry of Insect Control* (Janes, N.F., ed.), Royal Society of Chemistry, pp. 133-161 (1985)
3. Henrick, C.A. -- In *Insecticide Mode of Action* (Coats, J.R., ed.), Academic Press, NY, pp. 315-402 (1982)
4. Slama, K. -- In *Comprehensive Insect Physiology, Biochemistry, and Pharmacology* (Kerkut, G.A. and Gilbert, L.I., eds.), Pergamon, Oxford, Vol. 11 pp. 357-394 (1985)
5. Karrer, F. and Farooq, S. -- In *Regulation of Insect Development and Behavior* (Sehnal, F., Zabza, A., and Cymborowski, R., eds.), Technical University of Wrocław Press, pp. 289-302 (1981)
6. Fisher, U., Schneider, F. and Zurlüh, R. *Eur. Pat. Appl.* 4,334 (3 Oct 1978); U.S. Patent 4,215,139 (29 June 1980)
7. Ohsumi, T., Hatakoshi, H., Kisida, H. and Itaya, N. -- In *Recent Advances in Chemistry of Insect Control* (Janes, N.F., ed.), Royal Society of Chemistry, pp. 103-113 (1985)
8. Nishida, S., Hatakoshi, M., Matsuo, N., and Kisida, H. -- *Eur. Pat. Appl.* 84302685.7 (19 April 1984)

9. Prestwich, G.D. -- *Science*, 237:999 (1987)
10. Prestwich, G.D., Eng, W.-s. and Boehm, M.F. -- In *Molecular Biology of Invertebrate Development* (O'Connor, J.D., ed.), pp. 279-288 (1987)
11. Boehm, M.F. and Prestwich, G.D. -- *J. Org. Chem.*, 52:1349 (1987)
12. Boehm, M.F. and Prestwich, G.D. -- *J. Labelled Compnd. Radiopharm.*, in press (1987)
13. Osir, E.O., Boehm, M.F., Eng, W.-s., Edwards, M., Kulcsár, P., Prestwich, G.D. and Riddiford, L.M. -- unpublished results.
14. Riddiford, L.M., Osir, E.O., Fittinghoff, C.M. and Green, J.M. -- *Insect Biochem.*, 17:1049 (1987)
15. Bacon, R.G.R. and Stewart, O.J. -- *J. Chem. Soc.*, 4953 (1965)
16. Long, L., Jr. and Burger, A. -- *J. Org. Chem.* 6:852 (1941)
17. Zurlüh, R. and Dom, S. -- Poster No. 4334, IUPAC Pesticide Chemistry Symposium, Ontario, Canada (1979)