SEPTEMBER 1994
VOLUME 42, NUMBER 9

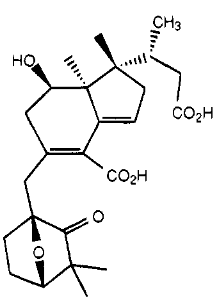
Journal of Agricultural and Food Chemistry

SHORT COMMUNICATIONS

Synthesis and Evaluation of Compounds That Affect Soybean Cyst Nematode Egg Hatch

Keywords: *Nematode; hatching stimulus; synthesis*

The soybean cyst nematode (SCN), *Heterodera glycines*, has been a serious national problem for over three decades. Although a number of strategies for the management of SCN have been tried, a solution that is consistent with both economics and sustainable agriculture has not yet been found (Niblack et al., 1992). Glycinoeclepin A is an incredibly effective hatching



Glycinoeclepin A

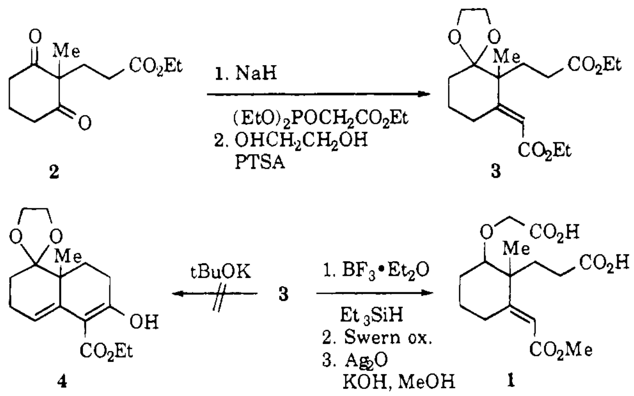
stimulus, capable of initiating hatching of SCN eggs at concentrations as low as 10^{-12} g/mL (Masamune et al., 1982). It is a natural product of low abundance whose structure suggests that it should be readily biodegradable. The synthesis of analogs of glycinoeclepin A that affect soybean hatch will be discussed herein.

The identification of the functionality sufficient for activity will play a key role in developing a useful nematicide. A useful control agent that emerges from our studies will be determined by the interplay between activity and ease of synthesis. The syntheses of glycinoeclepin A that have been reported are plagued by long pathways and low overall yields (Corey and Houpis, 1990). Our working hypothesis is that an effective analog must contain a secondary hydroxyl or alkoxy group and both carboxylic acid groups. This hypothesis is supported both by the analog studies of Murai et al. (1992) and by the results presented herein.

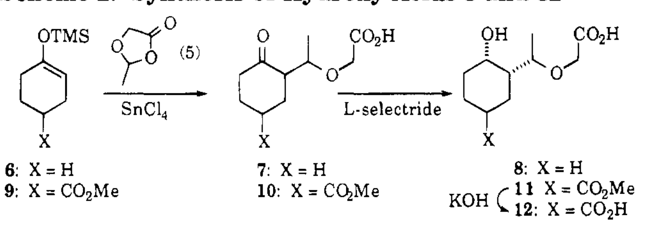
Scheme 1 depicts the synthesis of diacid **1**. The readily available diketone **2** (Peterse and de Groot, 1977) was treated with a phosphonate reagent followed by ketal formation with ethylene glycol to provide diester **3** as a single stereoisomer. We had intended to subject diester **3** to a base-induced cyclization reaction to form ester **4**. Although the desired cyclization failed, we eventually succeeded in converting diester **3** into diacid **1** by a sequence involving ketal opening ($BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, 0 °C), Swern oxidation, and aldehyde oxidation ($AgNO_3$, KOH, MeOH−H_2O). Diacid **1** was a mixture of isomers at the newly generated stereogenic center, as evidenced by the 300 MHz NMR spectrum. Biological evaluation of the mixture of isomers using an egg hatch test developed by Tylka et al. (1993) showed that diacid **1** stimulated soybean cyst nematode egg hatch at the parts per million level. However, there was substantial variation among experiments.

To develop a more flexible synthetic route, we tried the Lewis acid-catalyzed reaction of lactone **5** with enol silyl ether **6** (Scheme 2). Stannic chloride was the most effective catalyst for this reaction, which provided keto acid **7** in 67% yield. Keto acid **7** was reduced with L-Selectride to afford the axial alcohol **8** in 78% yield. Similarly, enol silyl ether **9** could be converted into diacid **12** in 54% overall yield. Evaluation using the egg hatch test showed that acid **8** exhibited no activity and that diacid **12** was a reproducible *inhibitor* of soybean cyst nematode egg hatch at the parts per million level. To the best of our knowledge this is the first glycinoeclepin A analog that acts as an inhibitor of egg hatch. Interestingly, compounds that inhibit soybean cyst nematode egg hatch could also be effective in managing the soybean cyst nematode if they were applied at the appropriate time. Moreover, such com-

Scheme 1. Synthesis of Diacid 1



Scheme 2. Synthesis of Hydroxy Acids 8 and 12



pounds could also play a key role in unraveling the complicated biochemistry of nematode egg hatch. The development of an enantioselective synthesis of **12** must now be addressed.

Despite the use of toxic nematicides, nematode infestation in the United States continues to be a major problem. The glycinoeclepin A analogs described herein are readily available and represent promising leads in the quest for safe and effective nematicides. The toxicity profile and soil compatibility issues of **1** and **12** will soon be studied. The synthesis and testing of the glycinoeclepin A analogs **1**, **8**, and **12** show the advantage of a multidisciplinary approach to the solution of agricultural problems.

ACKNOWLEDGMENT

We thank the Iowa Soybean Promotion Board for financial support of the research described in Scheme 2. We thank the Leopold Center for Sustainable Agriculture for support of the research described in Scheme 1.

LITERATURE CITED

Corey, E. J.; Houpis, I. N. Total synthesis of glycinoeclepin A. *J. Am. Chem. Soc.* **1990**, *112*, 8997–8999 and references cited therein.

Masamune, T.; Anetai, M.; Takasugi, M.; Katsui, N. Isolation of a natural hatching stimulus glycinoeclepin A for the soybean cyst nematode. *Nature* **1982**, *297*, 495–497.

Murai, A.; Ohkita, M.; Honma, T.; Hoshi, K.; Tanimoto, N.; Araki, S.; Fukuzawa A. Structure-activity relationship of glycinoeclepin A. *Chem. Lett.* **1992**, 2103–2104.

Niblack, T. L.; Baker, N. K.; Norton, D. C. Soybean Yield Losses due to Heterodera glycines in Iowa. *Plant Dis.* **1992**, *76*, 943–948.

Peterse, A. J. G. M.; de Groot, A. Dieckmann cyclizations in the synthesis of functionalized decalins. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 219.

Tylka, G. L.; Niblack, T. L.; Walk, T. C.; Harkins, K. R.; Barnett, L.; Baker, N. K. Flow cytometric analysis and sorting of Heterodera glycines eggs. *J. Nematol.* **1993**, *25*, 596–602.

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Received for review June 7, 1994. Accepted July 26, 1994.

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