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Enantioselective Synthesis of a Simple Benzenoid Analogue of Glycinoeclepin A

Simon Giroux and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

corey@chemistry.harvard.edu

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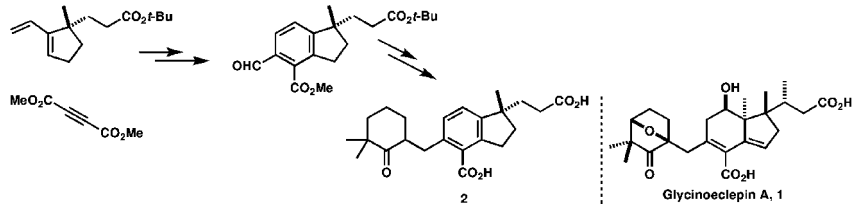
ABSTRACT



A synthesis of the readily accessible glycinoeclepin A analogue 2 is reported.

Glycinoeclepin A (**1**), a biosynthetic product of the soybean plant, diffuses from the plant roots into the soil where, at concentration as low as 10^{-12} g/mL, it stimulates hatching of eggs of the predatory nematode *Heterodera glycines*.[1] In the absence of a nearby growing plant, the eggs of the nematode can remain unhatched and viable for many months, emerging only when a plant becomes available. The agricultural strategy of crop rotation is based on the disruption of this natural battle by spacing soybean crops over a period of time larger than the survival time of the eggs of *H. glycines*.

In principle, if the eggs of *H. glycines* could be induced to hatch well in advance of the planting of new soybean plants, destruction of the crop should be prevented, since the lifetime of the hatched nematode itself is only a matter of weeks. Thus, glycinoeclepin A (**1**) might be a useful agrochemical. Unfortunately, **1** is produced only in trace amounts by the soybean plant, and so naturally biosynthesized glycinoeclepin A is essentially unavailable, even in subgram amounts. Although glycinoeclepin A has been obtained by total synthesis,[2] the known synthetic processes are too complex and costly to provide an unlimited and inexpensive supply. We have, therefore, embarked on research to develop a biologically active mimic of glycinoeclepin A that would be relatively simple to synthesize and also sufficiently potent to be useful. Such a synthetic mimic could be effective and practical even at levels of intrinsic activity orders of magnitude below that of **1**. Our initial studies have focused on the tricyclic benzenoid analogue **2** of glycinoeclepin A. The selection of this analogue was guided by the aim of trading off potency for synthetic accessibility. Reported herein is a simple and potentially practical synthesis of **2**.

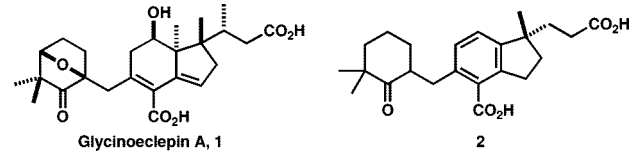


Figure 1. Structure of glycinoeclepin A.

The synthesis of analogue **2** commenced with the condensation of 2-methylcyclopentanone and (*R*)-α-methylbenzylamine and subsequent Michael reaction with *tert*-butyl acrylate to provide the (*S*)-keto ester **3** (73% yield) after acidic hydrolysis of the resulting imine.[3] Conversion of **3** to the corresponding vinyl triflate (NaHMDS, $PhN(Tf)_2$, THF,

(1) (a) Fukuzawa, A.; Furusaki, A.; Ikura, M.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1985**, 221–222. (b) Masamune, T.; Anetai, M.; Takasugi, M.; Katsui, N. *Nature* **1982**, *297*, 495–496.

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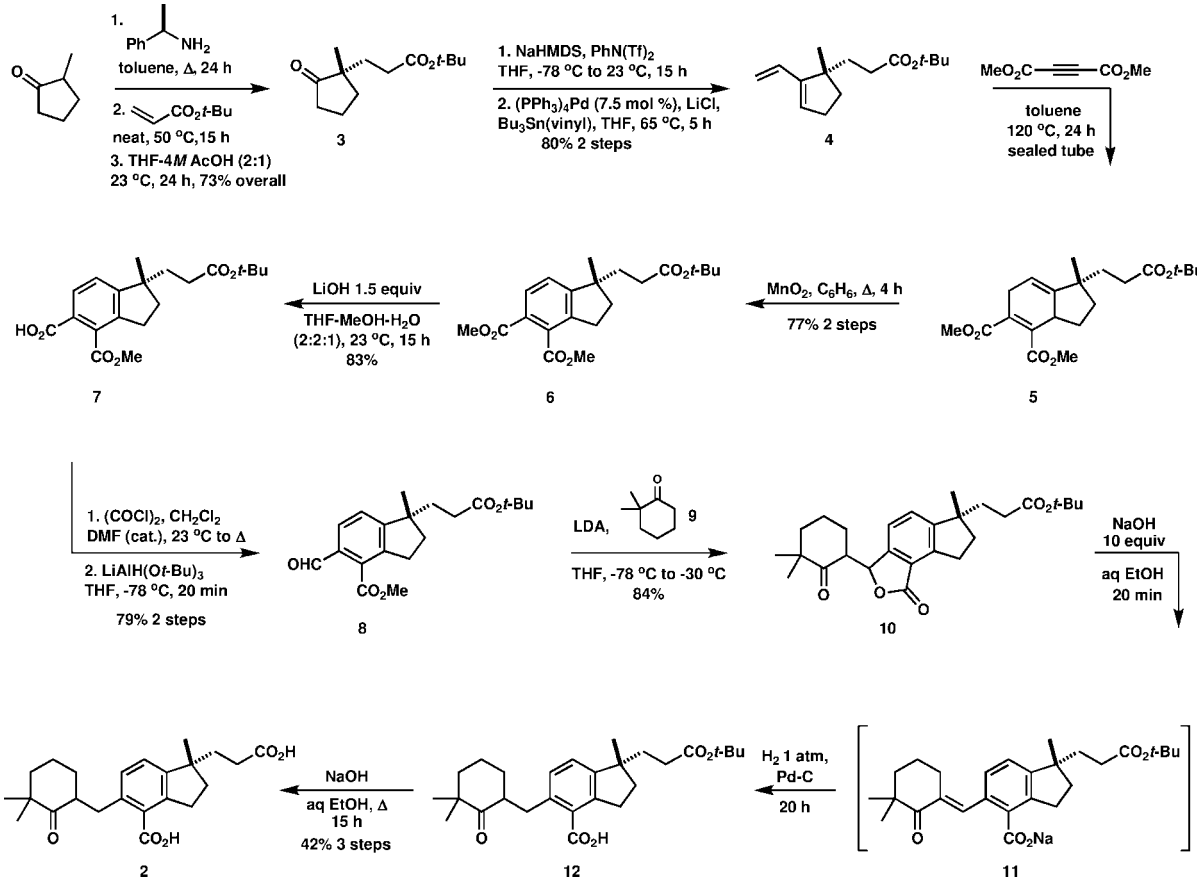
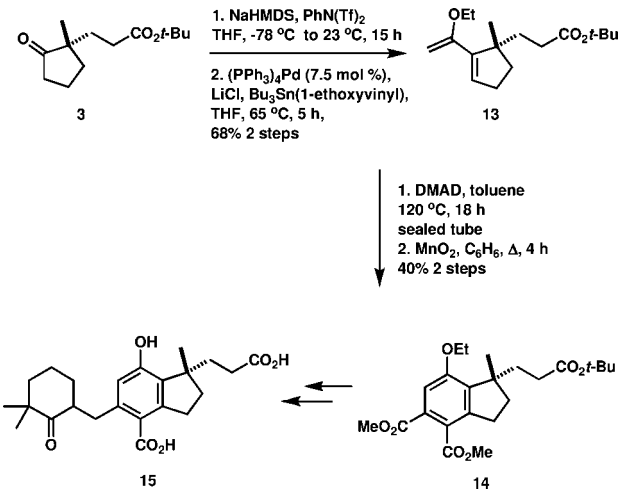
Scheme 1. Synthesis of the Glycinoeclepin A Analogue **2**



−78 °C) and subsequent palladium-catalyzed vinylation [(Pd(PPh$_3$)$_4$ 7.5 mol %, tributyl(vinyl)tin, LiCl, THF, 65 °C)] afforded the diene **4** in 80% yield for the two-step sequence. Heating **4** with dimethyl acetylenedicarboxylate (DMAD) in toluene (sealed tube, 120 °C) led to a 1:1 mixture of diastereomeric Diels−Alder adducts **5** which was oxidized with MnO_2 in refluxing benzene to provide benzenoid triester **6** (77%, two steps). Selective hydrolysis of the least hindered methoxycarbonyl group was achieved using LiOH (1.5 equiv) in THF−MeOH−H_2O (2:2:1) to provide the monoacid **7** in 83% yield. The reduction of acid **7** to aldehyde **8** was effected by a two-step procedure involving the formation of the corresponding acid chloride [$(COCl)_2$, DMF cat., CH_2Cl_2] followed by reduction using freshly prepared LiAlH(O-*t*-Bu)$_3$ in THF. The intermolecular aldol coupling between ketone **9**[4] and aldehyde **8**, with concomitant cyclization to the adjacent ester, proceeded smoothly using LDA as base (THF, −78 to −30 °C) to give a mixture of diastereomeric lactones **10** in 84% yield. The diastereomeric mixture of lactones **10** proved to be resistant to reduction using hydrogenation over Pd−C, PtO_2, or Pd(OH)$_2$ as catalysts or using ionic reduction (TFA, Et_3SiH). Eventually, this difficulty was overcome by using NaOH (10 equiv) in aqueous EtOH to generate the bright yellow enone **11** in situ and exposure to Pd−C and H_2 (1 atm) for 20 h, which

Scheme 2. Synthesis of Benzenoid Derivative **14**



(2) (a) Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *J. Am. Chem. Soc.* **1988**, *110*, 1985–1986. (b) Mori, K.; Watanabe, H. *Pure Appl. Chem.* **1989**, *61*, 543–546. (c) Corey, E. J.; Houpis, I. N. *J. Am. Chem. Soc.* **1990**, *112*, 8997–8998.

(3) Corey, E. J.; Wood, H. B. *J. Am. Chem. Soc.* **1996**, *118*, 11982–11983, and references therein.

(4) Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391–5396.

resulted in the required product **12**. Saponification of the *tert*-butyl ester with NaOH in refluxing EtOH provided analogue **2** in 43% yield (over the last three steps).

We have also shown the feasibility of using the synthetic strategy exemplified in Scheme 1 to access the tricyclic phenolic diacid **15**, which is an even closer analogue to glycinoeclepin A than **2**. The key steps are outlined in Scheme 2.

Preliminary evaluation of glycinoeclepin analogue **2** has revealed that it is capable of stimulating the hatching of *H. glycines* at subnanomolar concentrations. More detailed studies are underway to confirm this activity and to determine the minimum concentration for effective hatching under a range of conditions. Very extensive studies are required because the larvae of *H. glycines* are encased in the bodies of dead female nematodes and not free in soil. It is gratifying that our initial research appears promising because *H. glycines* has been estimated to reduce yields of soybean crops by about 10%.[5]

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) We are indebted to Dr. Gregory Tylka of Iowa State University for conducting the biological evaluation.