Recent results in the synthesis of semiochemicals:  
synthesis of glycinoeclepin A

Kenji Mori* and Hidenori Watanabe

Department of Agricultural Chemistry, The University of Tokyo,
Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

Abstract — Glycinoeclepin A 1, a natural hatching stimulus for the soy-
bean cyst nematode, was synthesized from two chiral building blocks (2 and
9) of microbial origin.

Importance of chirality in the perception of semiochemicals is now well recognized (ref.1). In order to supply a significant amount of an enantiomerically pure semiochemical, biological methods such as microbial and enzymatic transformations were proved to be very useful in providing chiral building blocks (ref.2). Readily available chiral building blocks like the enantiomer(s) of ethyl 3-hydroxybutanoate, methyl 3-hydroxypentanoate and 3-hydroxy-2,2-
dimethylcyclohexanone were extensively employed in the syntheses of various semiochemicals (ref.2). Herein we report an additional example to demonstrate the usefulness of the combined biochemical-organochemical approach in natural products synthesis.

Glycinoeclepin A 1 is a degraded triterpenoid isolated from kidney bean roots as a semiochemical effective on soybean nematode (ref.3 & 4). Its unusual structure as well as its strong hatch-stimulating activity for the soybean cyst nematode made it an attractive target for synthetic chemists (ref.3 & 5). Very recently Murai et al. announced the first total synthesis of 1 (ref.6). Two syntheses of simple model compounds were also reported (ref.7 & 8). We became interested in synthesizing 1 starting from two chiral building blocks of microbial origin.

![Fig.1. Synthetic plan.](image-url)
Our planned synthetic route to 1 is convergent as shown in Fig.1. The starting (S)-hydroxy ketone E can be prepared by reducing the corresponding 1,3-diketone G with baker's yeast (ref.9). Another bridged (S)-hydroxy ketone F can also be obtained by reducing the corresponding diketone H. These hydroxy ketones E and F yield two key-intermediates C and D, whose aldol condensation gives B. Introduction of a two-carbon unit to B gives A. The precursor A is thought to be convertible to the target molecule 1 by reductive fission of the lactone carbon-oxygen bond followed by the nucleophilic addition of the ester carbanion to the carbonyl group to generate the six-membered C-ring.

The two key-intermediates C and D were prepared as shown in Fig.2. For the synthesis of C(S6), the (S)-hydroxy ketone 2(S6) was first converted to a silyl ether, which was submitted to aldol reaction followed by dehydration to give 3. Reduction of 3 was followed by protection of the newly-formed hydroxy group and subsequent iodocyclization to afford 4. Treatment of 4 with DBU gave an olefin, whose hydroboration-oxidation furnished 5. Oxidation of 5 to the corresponding aldehyde was followed by three-carbon elongation with allylmagnesium chloride. Subsequent protection of a hydroxyl group and one-carbon shortening of the side-chain gave 6 in 32% overall yield in 14 steps from 2 (cf. ref.6).

Preparation of D((E)5) started from 3-methyl-2-cyclopentenone(7), which gave the prochiral diketone 8(E5) in 40% overall yield in 6 steps. Reduction of 8 with baker's yeast in the presence of phosphate buffer (pH 7) gave 3 of ca. 80% e.e., which could readily be purified to 100% e.e. by recrystallizing the corresponding acetal 10. Oxidation of 10 to the corresponding ketone was followed by methylation to give 11. In order to have the newly introduced methyl group in the correct configuration corresponding to the methyl group on the side-chain of 1, 11 was enolized and protonated to give the epimer 12. Ring expansion of 12 to 13 was achieved by Noyori's method with small modification (ref.10). Reduction of 13 with sodium borohydride was followed by the removal of the acetal protective group to give 14.

---

Fig.2. Preparation of the key intermediates C and D.

- a) TMSDCl, imidazole/DMF (quant.); b) LDA, CH₃CHO/THF (94%); c) NaH, Et₃N/CH₂Cl₂/
DBU/THF (94%); d) NaBH₄/THF/EtOH (88%); e) CH₂=CHOCH₂CH₃/p-TsOH (98%); f) (n-Bu)₃PF/THF (96%);
- g) NIS/CH₂CN (70%); h) DBU/toluene (95%); i) 9-BBN/THF/H₂O, NaOH (quant.); j) (CCl₂F₂)₂DMSO/
CH₂Cl₂, BBr₃; CH₂=CHCH₂Br/THF (92%); k) TBDMSCl, imidazole/DMF (90%); l) O₃, Na₂O₅/ether-
H₂O (75%); m) baker's yeast, sucrose, pH 7 phosphate buffer (55%); n) H₂O₂, DMAP/Pt (93%); o) o-xylene diol, p-TsOH/toluene (87%); p) NaOMe/MeOH (80%); q) PCC, NaOAc, MS-3A/CH₂Cl₂ (97%); r) LDA, MeI/THF/HMPA (97%); s) LiHMDS/THF/HMPA/AcOH (98%); t) LiCH₂Br₂/THF; 1 eq. MeLi-1 eq n-
BuLi/THF (50%); u) NaBH₄/THF/EtOH (96%); v) H₂, Pd-C/EtOAc (99%); w) CH₂=CHCH₂CH₃/p-
TsOH (quant.); x) NaH, MeI/THF (57%); y) NaH, TMSCl, Et₃N/THF (99%)
Synthesis of glycinoeclepin A

Novel acetal protective group proved to be a useful one, because it could be removed by hydrogenolysis under neutral condition. Protection of the hydroxyl group of 14 was followed by methylation and formation of the silyl enol ether to give 15 in 27% overall yield in 13 steps from 9.

With two key-intermediates in hand, we moved to the next stage as shown in Fig. 3. Aldol condensation of 15 with 6 was successful in the presence of zinc chloride (ref.11) to give unstable aldol 16, which was immediately converted to the corresponding diethyl phosphonoacetate. Treatment of the phosphonoacetate with sodium hydride gave a lactone 17 by the intramolecular olefination reaction. This was then reduced with calcium borohydride to give a diol, whose protection-deprotection transformation yielded allylic alcohol 18. To achieve the pivotal C-ring formation reaction (20 + 21), 18 was first converted to ester 19. It should be mentioned that the esterification of the carboxylic acid to 19 was only possible by the Mitsunobu procedure (ref.12). Removal of the EE- and TBDMS-protective groups of 19 was followed by oxidation of the resulting triol to the corresponding triketone. The Baeyer-Villiger oxidation of the triketone with MCPBA was surprisingly selective to give the desired diketo lactone 20 as the only isolable product. Reductive cyclization of 20 was tried under several conditions, and was successful when lithium dimethylcuprate in THF was used as the reducing agent (ref.13). Thus, without cleavage of its oxa-bicyclo ring, 20 furnished 21 after esterification with diazomethane. Dehydration of 21 gave 22, whose deprotection yielded glycinoeclepin A (1). Its crystalline big-p-bromophenacyl ester 23 showed 1H NMR spectrum (Fig. 4) identical to the published one (ref.5).

In summary, glycinoeclepin A (1) was synthesized by a combination of biochemical and chemical methods. The overall yield of 1 was 3.0% in 32 steps from 2 or 2.6% in 31 steps from 9. It is evident that biochemical methods are valuable tools for synthetic chemists to prepare enantiomerically pure compounds.
REFERENCES


Fig. 4. $^1$H-NMR spectrum of glycineclepin A; bis-p-bromophenacyl ester (23).
( in CDCl$_3$-D$_2$O, 400 MHz )