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

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Abstract — Glycinoeclepin A (**1**), a natural hatching stimulus for the soybean 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 avaiable 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.

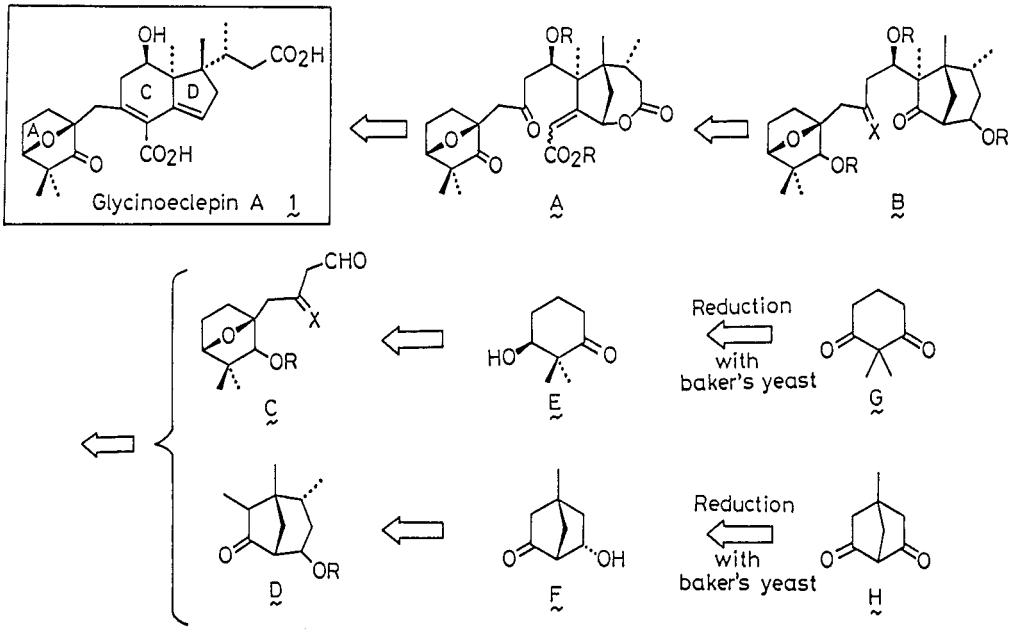

Fig.1. Synthetic plan.

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**(≡**6**), the (S)-hydroxy ketone **2**(≡**E**) 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 hydroxyl 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**(≡**15**) started from 3-methyl-2-cyclopentenone(**7**), which gave the prochiral diketone **8**(≡**H**) 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 Nozaki's method with small modification (ref.10). Reduction of **13** with sodium borohydride was followed by the removal of the acetal protectve group to give **14**. Our

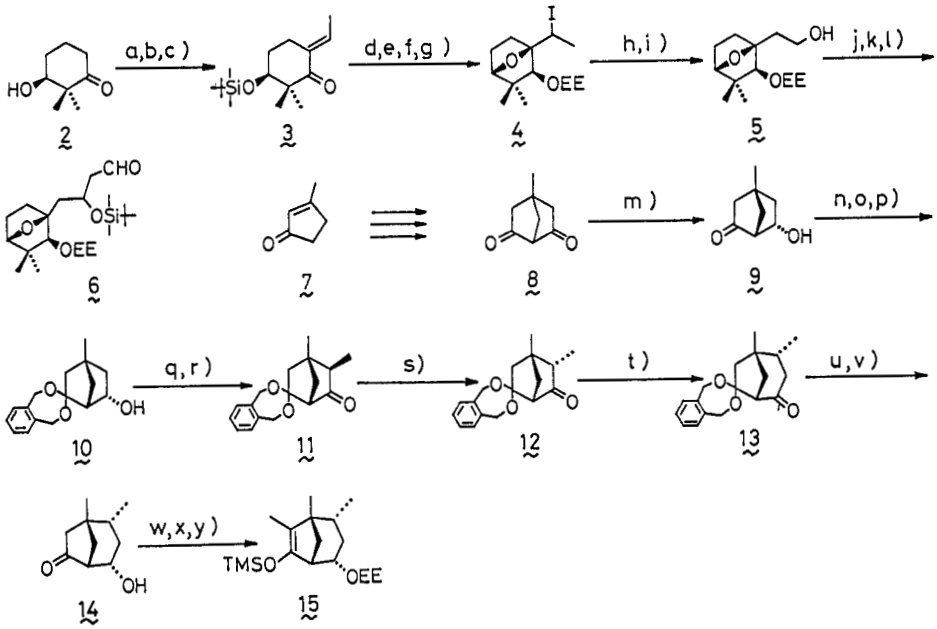

Fig.2. Preparation of the key intermediates C and D.
a) TBDMSCl,imidazole/DMF(quant.); b) LDA,CH_3CHO/THF(quant.); c) MsCl,Et_3N/CH_2Cl_2; DBU/THF(94%); d) $NaBH_4$/THF-EtOH(88%); e) CH_2=$CHOCH_2CH_3$,p-TsOH(98%); f) $(n\text{-}Bu)_4F$/THF(96%); g) NIS/CH_3CN(70%); h) DBU/toluene(95%); i) 9-BBN/THF;H_2O_2,NaOH (quant.); j) $(COCl)_2$,DMSO/CH_2Cl_2,Et_3N; CH_2=$CHCH_2MgBr$/THF(92%); k) TBDMSCl,imidazole/DMF(90%); l) OsO_4,$NaIO_4$/ether-H_2O(75%); m) baker's yeast, sucrose, pH 7 phosphate buffer(55%); n) Ac_2O,DMAP/Py(93%); o) o-xylene diol,p-TsOH/toluene(87%); p) NaOMe/MeOH(80%); q) PCC,NaOAc,MS-3A/CH_2Cl_2(97%); r) LDA,MeI/THF-HMPA(97%); s) LiHMDS/THF-HMPA;AcOH(98%); t) $LiCHBr_2$/THF; 1 eq MeLi-1 eq n-BuLi/THF(50%); u) $NaBH_4$/THF-EtOH(96%); v) H_2,Pd-C/EtOAc(99%); w) CH_2=$CHOCH_2CH_3$,p-TsOH(quant.); x) NaH,MeI/THF(97%); y) NaH,TMSCl,Et_3N/THF(99%)

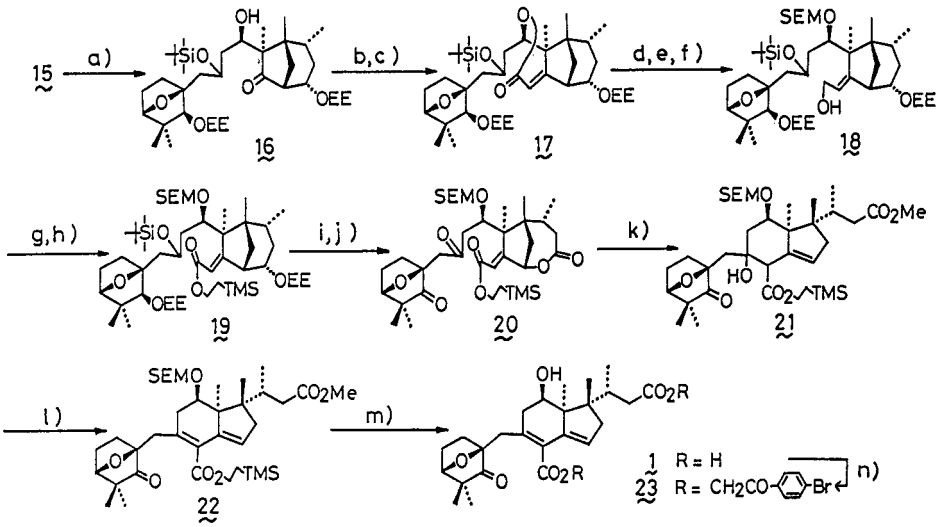

Fig.3. Synthethis of glycinoeclepin A.
a) MeLi,$ZnCl_2$,**6**/Et_2O; b) $(EtO)_2POCH_2CO_2H$,DCC/CH_2Cl_2(2 steps, 82%); c) NaH/THF(84%); d) $Ca(BH_4)_2$/EtOH; t-BuCOCl,Et_3N/CH_2Cl_2(95%); e) SEMCl,$(i\text{-}Pr)_2NEt$,$(n\text{-}Bu)_4NBr$/CH_2Cl_2(94%); f) MeLi/Et_2O(93%); g) $(COCl)_2$,DMSO/CH_2Cl_2,Et_3N(95%); h) $NaClO_2$,NaH_2PO_4,$(CH_3)_2C{=}CHCH_3$/t-BuOH-H_2O; $TMS(CH_2)_2OH$,DEAD,$(C_6H_6)_3P$/THF(80%); i) PPTS/aq.MeOH; $(COCl)_2$,DMSO/CH_2Cl_2,Et_3N(75%); j) MCPBA,$NaHCO_3$/CH_2Cl_2(88%); k) Me_2CuLi/THF; CH_2N_2/Et_2O(72%); l) $SOCl_2$/Py(82%); m) LiOH,$(n\text{-}Bu)_4NOH$/THF-H_2O; $(n\text{-}Bu)_4NF$/THF(58%); n) p-bromophenacyl bromide,$(i\text{-}Pr)_2NEt$/CH_3CN(95%)

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**(≡**D**) in 27% overall yield in 13 steps from **9**.

With two key-intermediates in hands, 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 diazometane. Dehydration of **21** gave **22**, whose deprotection yielded glycinoeclepin A (**1**). Its crystalline bis-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 enantiomercally pure compounds.

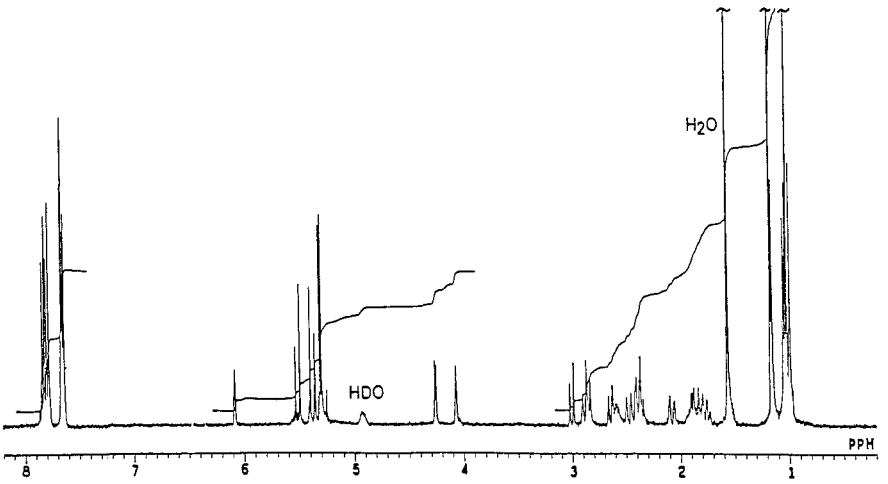

Fig.4. ^{1}H-NMR spectrum of glycinoeclepin A bis-p-bromophenacyl ester (23). (in $CDCl_3$-D_2O, 400 MHz)

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