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Asymmetric Total Synthesis of Glycinoeclepin A: Generation of a Novel Bridgehead Anion Species

Yasuhiro Shiina,[1] Yoshihide Tomata,[1] Masaaki Miyashita,[2] and Keiji Tanino*[1]
[1]*Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Hokkaido 060-0810*
[2]*Department of Applied Chemistry, Faculty of Engineering, Kogakuin University, Hachioji, Tokyo 192-0015*

(Received June 18, 2010; CL-100570; E-mail: ktanino@sci.hokudai.ac.jp)

The asymmetric total synthesis of glycinoeclepin A, a hatch-stimulating agent of the soybean cyst nematode, was accomplished on the basis of a cyclopentene annulation for constructing the CD ring moiety having contiguous quaternary carbon atoms. Introduction of the A ring moiety was achieved by an alkylation reaction using a 7-oxabicyclo[2.2.1]hex-1-yl anion species.

The soybean cyst nematode (SCN) is a devastating pest of a small group of host plants including soybean, kidney bean, and adzuki. They have a limited host range and the specificity arises from response to specific stimuli secreted by the host plant.[1] Glycinoeclepin A (**1**) (Figure 1) was isolated from dried root of the kidney bean by Masamune et al. as a potent hatch-stimulating agent (10^{-12}–10^{-11} g mL^{-1}) of the SCN.[2] From a synthetic point of view, the structural features of **1**, namely, the contiguous quaternary carbon atoms on the CD ring system and the A ring with an oxygen bridge have attracted considerable attention from organic chemists, and three groups have reported the asymmetric total synthesis of **1**.[3]

Recently, we developed a stereoselective cyclopentene annulation method for preparing a CD ring segment of steroids from enone **3** on the basis of a conjugate addition reaction using nitrile **2a** (Scheme 1).[4]

Thus, the reaction of enone **3** with a carbanion species, which was generated from nitrile **2a** and potassium bis(trimethylsilyl)amide (KHMDS), followed by acetic anhydride afforded enol acetate **4** stereoselectively. Treatment of the adduct with aqueous hydrochloric acid resulted in formation of enone **5a** via hydrolysis of the enol ether moiety and intramolecular aldol condensation. Since the method was also effective for the stereoselective synthesis of enone **5b** with contiguous quaternary carbon atoms, we planned to develop a concise route for the asymmetric total synthesis of glycinoeclepin A (**1**) as shown in Scheme 2.

We chose optically active γ-silyloxy enone **7**[5] as the substrate of the cyclopentene annulation. Thus, bicyclic enone **6**, a monooxygenated analog of enone **5b**, would be obtained through attack of the anion species of nitrile **2b** on enone **7** from the opposite face of the TBSO group. The cyano group of **6** would be utilized for the stereoselective construction of the side chain through a hydroboration reaction of diene **III** followed by the Suzuki–Miyaura coupling. With a view to introducing the A ring moiety in a straightforward manner, we planned to develop a coupling reaction of anionic species **I** with the CD ring segment **II**.

The CD ring segment was synthesized as shown in Scheme 3. Enone **7**[5] was treated with the anion generated from nitrile **8**[6] followed by acetic anhydride to afford enol acetate **9** with high stereoselectivity (96:4). In order to avoid removal of the TBS group by hydrochloric acid, the cyclization reaction was

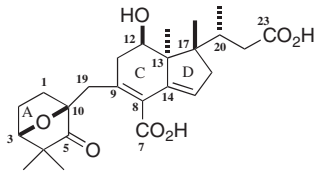
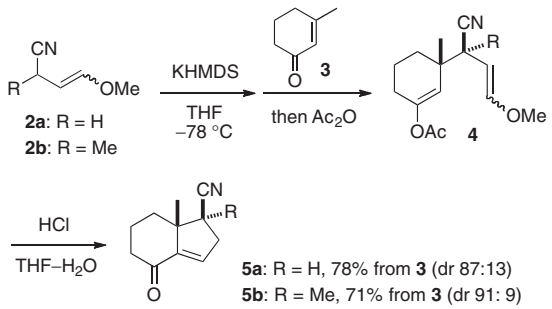
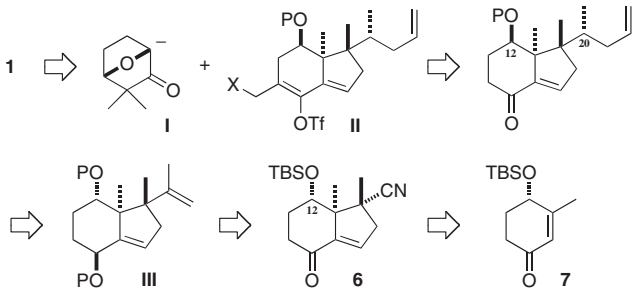


Figure 1. Structure of glycinoeclepin A (**1**).



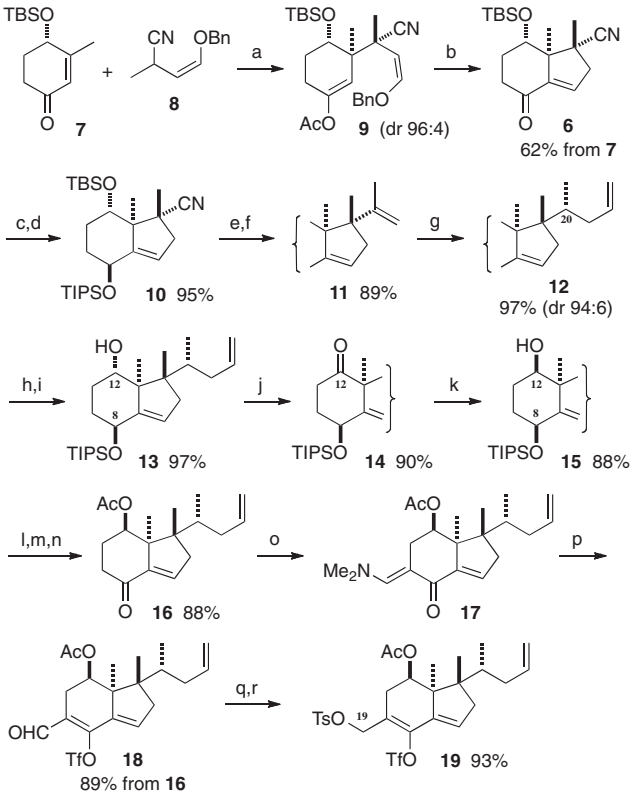
Scheme 1. Cyclopentene annulation for stereoselective synthesis of bicyclic enones.



Scheme 2. Retrosynthetic analysis of glycinoeclepin A (**1**).

performed by heating the crude product in aqueous acetic acid, and enone **6** was obtained in 62% yield after recrystallization. The trans relationship between the two methyl groups of enone **6** was established by NOE experiments. After reduction and protection of the ketone moiety, nitrile **10** was converted to diene **11** through an addition reaction with MeLi followed by a Wittig reaction. The stereocontrolled construction of the side chain was achieved through hydroboration of diene **11** using 9-borabicyclo[3.3.1]nonane (9-BBN) followed by palladium-catalyzed coupling with vinyl bromide,[7] while the configuration of the C20 position was not confirmed until the completion of the total synthesis.

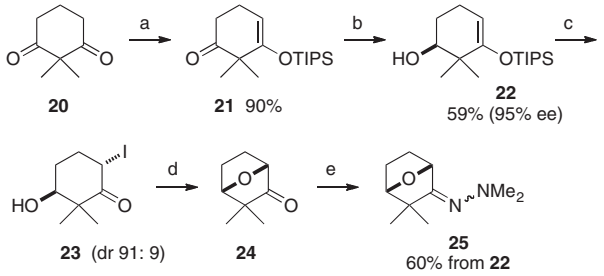
Since the bicyclic compounds derived from optically active enone **7** have *S*-configuration at the C12 position, which is opposite to that of glycinoeclepin A, inversion of the chiral



Scheme 3. Synthesis of the CD ring segment. Reagents and conditions: (a) nitrile **8** (1.5 equiv), KHMDS (1.3 equiv), THF, −78 °C, 1 h, then enone **7** (1 equiv), −78 °C, 1 h, then Ac_2O (2 equiv), −78–−50 °C; (b) AcOH–water (3:1), 100 °C, 9 h; (c) $NaBH_4$ (2.5 equiv), $CeCl_3 \cdot 7H_2O$ (2.5 equiv), MeOH, −78 °C–rt, 1 h; (d) TIPSOTf (1.3 equiv), 2,6-lutidine (2.6 equiv), CH_2Cl_2, 0 °C, 10 min; (e) MeLi (2 equiv), ether, rt, 6.5 h, then AcOH–water–THF (1:1:2), 40 °C, 1 h; (f) $Ph_3PCH_3 \cdot Br$ (3.3 equiv), *t*-BuOK (3 equiv), toluene–*t*-BuOH (1:1), 80 °C, 3 h; (g) 9-BBN (2 equiv), THF, 0 °C–rt, 7 h, then $Pd(PPh_3)_4$ (0.03 equiv), $BrCH{=}CH_2$ (excess), aq. NaOH, rt, 1.5 h; (h) TBAF (5 equiv), DMF, 80 °C, 6 h; (i) TIPSOTf (1.2 equiv), 2,6-lutidine (2.4 equiv), CH_2Cl_2, 0 °C, 20 min; (j) TPAP (0.05 equiv), NMO (2 equiv), MS 4A, CH_2Cl_2, rt, 1.5 h; (k) $LiEt_3BH$ (2 equiv), toluene, −78–−15 °C, 4 h; (l) Ac_2O (2 equiv), DMAP (0.2 equiv), pyridine, rt, 3 h; (m) TBAF (5 equiv), THF, rt, 1.5 h; (n) Swern oxidation; (o) *t*-$BuOCH(NMe_2)_2$ (3.5 equiv), benzene, 50 °C, 5.5 h; (p) Tf_2O (1.1 equiv), 2,6-di-*tert*-butylpyridine (2.2 equiv), CH_2Cl_2 −78 °C, 15 min, then aq. $NaHCO_3$, rt; (q) $NaBH_4$ (1.5 equiv), $CeCl_3 \cdot 7H_2O$ (1.5 equiv), MeOH, 0 °C–rt, 15 min; (r) *p*-TsCl (2 equiv), Et_3N (4 equiv), $Me_3N \cdot HCl$ (1 equiv), toluene, 0 °C, 2 h.

center was needed. To this end, compound **12** was transformed into alcohol **13** through removal of the two silyl groups by tetrabutylammonium fluoride (TBAF) followed by selective silylation of the less hindered C8 hydroxy group. Initial attempts to invert alcohol **13** under the Mitsunobu conditions[8] were not successful probably due to steric hindrance, which prompted us to explore stereoselective reduction of the corresponding ketone.

Alcohol **13** was treated with *N*-methylmorpholine *N*-oxide (NMO) and tetrapropylammonium perruthenate (TPAP)[9] to give ketone **14**. The reaction of the ketone with $LiAlH_4$ in THF at −78 °C afforded a 7:93 mixture of diastereomers **15** and **13**, but the ratio of the desired product **15** was dramatically increased to

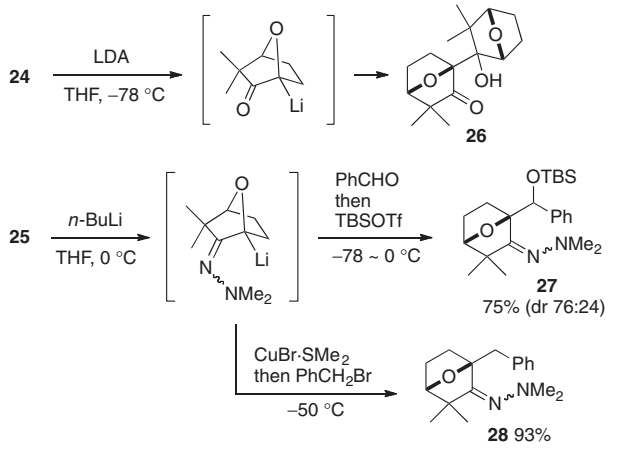


Scheme 4. Synthesis of the A ring segment. Reagents and conditions: (a) KHMDS (1.05 equiv), TIPSOTf (1.05 equiv), THF, −78–0 °C, 30 min; (b) (−)-DIPCl (1.1 equiv), rt, 24 h; (c) NIS (1.2 equiv), CH_2Cl_2, −40 °C–rt, 40 min; (d) AgOTf (1.5 equiv), 2,6-lutidine (1.1 equiv), CH_2Cl_2, 40 °C, 2 h; (e) Me_2NNH_2 (4.5 equiv), AcOH (0.3 equiv), ethanol, 70 °C, 12 h.

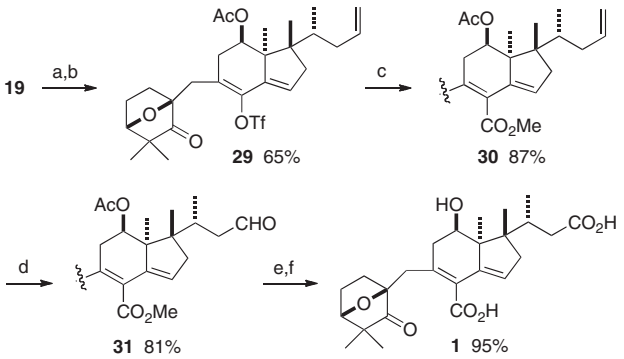
77:23 by using $LiEt_3BH$, a bulky reducing agent. Since the reaction with Li(*sec*-Bu)$_3$BH resulted in recovery of the substrate, we optimized the conditions of the $LiEt_3BH$ reduction. Fortunately, the stereoselectivity was improved to 92:8 by performing the reaction in toluene, and alcohol **15** was obtained in 88% yield after silica gel column chromatography. Then alcohol **15** was converted to ketone **16** through acetylation, desilylation, and the Swern oxidation. With the CD ring segment having the four contiguous stereogenic centers in hand, the stage was set for introduction of the A ring moiety. To this end, ketone **16** was converted to allyl tosylate **19** in four steps: (1) condensation with Bredereck's reagent,[10] (2) sulfonylation of aminovinyl ketone **17** with triflic anhydride followed by hydrolysis, (3) the Luche reduction of aldehyde **18**, and (4) tosylation of the allylic alcohol.[11]

On the other hand, the optically active A ring segment was synthesized as shown in Scheme 4. Diketone **20**[12] was treated with KHMDS followed by TIPSOTf to afford ketone **21** which was subjected to asymmetric reduction by Brown's protocol.[13] Thus, the reaction with (−)-*B*-chlorodiisopinocampheylborane (DIPCl) gave rise to optically active alcohol **22** in 95% ee.[14] Formation of the oxygen bridge was achieved through stereoselective iodination of enol silyl ether **22** with *N*-iodosuccinimide (NIS) and intramolecular cyclization of ketone **23** mediated by AgOTf.[15] The resulting ketone **24** was then converted to the corresponding hydrazone **25** which was obtained as a mixture of geometric isomers.[16]

Prior to the coupling with the CD ring segment, experiments to generate an anion species from the A ring segment were carried out (Scheme 5). It should be noted that ketone **24** with a bridged bicyclic framework cannot form a stable enolate anion because of Bredt's rule.[17] Indeed, treatment of **24** with LDA in THF resulted in formation of dimer **26** even at −78 °C. This indicates that the hydrogen atom at the bridgehead position is acidic enough to be abstracted with LDA, but the resulting anion immediately attacks the remaining ketone. We therefore decided to protect the carbonyl group of ketone **24**, and promising results were obtained by using hydrazone **25**.[16] Thus, treatment of **25** with *n*-BuLi at 0 °C afforded a stable bridgehead anion species that underwent an addition reaction with benzaldehyde giving rise to **27**.[18] While the alkylation reaction with benzyl bromide suffered from formation of 1,2-diphenylethane through a Br–Li exchange pathway, the corresponding cuprate was found to give ketone **28** in high yield.



Scheme 5. Generation and reactions of the bridgehead anion species.



Scheme 6. Total synthesis of glycinoeclepin A. Reagents and conditions: (a) hydrazone **25** (4.8 equiv), *n*-BuLi (4 equiv), THF, 0 °C, 1 h, then $CuBr{\cdot}SMe_2$ (2.1 equiv), −40 °C, 30 min, then tosylate **19** (1 equiv), −40 °C, 5 h; (b) AcOH–H_2O (3:1), 130 °C, 5 h; (c) CO (1 atm), $Pd(OAc)_2$ (0.1 equiv), 1,1′-bis(diphenylphosphino)ferrocene (0.11 equiv), Bu_3N (1.5 equiv), DMF–MeOH (2:1), 80 °C, 45 min; (d) OsO_4 (0.1 equiv), NMO (3 equiv), *t*-BuOH–H_2O–THF (2:2:1), 0 °C, 1.5 h, then $NaIO_4$ (5 equiv), rt, 2 h; (e) $NaClO_2$ (2 equiv), NaH_2PO_4 (3 equiv), 2-methyl-2-butene (6 equiv), *t*-BuOH–H_2O (3:1), 0 °C, 1 h; (f) LiI (5 equiv), 2,4,6-collidine, 120 °C, 2 h, then LiOH (20 equiv), THF–H_2O (1:1), 60 °C, 2 h, then dil. H_2SO_4.

The reaction conditions were applied to the coupling reaction with allyl tosylate **19**, and ketone **29** was obtained after hydrolysis of the hydrazone moiety (Scheme 6). The palladium-catalyzed carbonylation reaction[3a] of enol triflate **29** afforded ester **30**, and glycinoeclepin A (**1**) was obtained through oxidative cleavage of the terminal olefin followed by deprotection of the ester groups. The synthetic **1** gave spectral and physical data in full agreement with those reported by Mori[3d] ($[\alpha]_D^{29}$ −11.5 ($c = 0.67$, MeOH), lit. $[\alpha]_D^{24}$ −10.2 ($c = 0.63$, MeOH), mp 120–123 °C (lit. 120–121.5 °C)).

In conclusion, the asymmetric total synthesis of glycinoeclepin A (**1**) was accomplished on the basis of a cyclopentene annulation for constructing the CD ring moiety with contiguous quaternary carbon atoms. The A ring moiety was introduced by an alkylation reaction using a novel bridgehead anion. Application of these methods to total synthesis of related compounds are under investigation.

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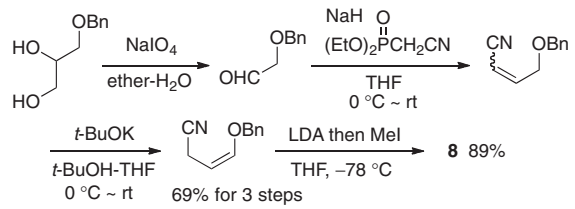
6 Since nitrile **2b** proved to be unsuitable for large scale synthesis due to its high volatility, nitrile **8** was used for the cyclopentene annulation method instead of **2b**. Nitrile **8** was prepared from glycerol monobenzyl ether as shown bellow.



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18 Since it was difficult to separate the adduct from hydrazone **25**, it was converted to the corresponding silyl ether **27**.

