

Total synthesis of glycinoclepin A

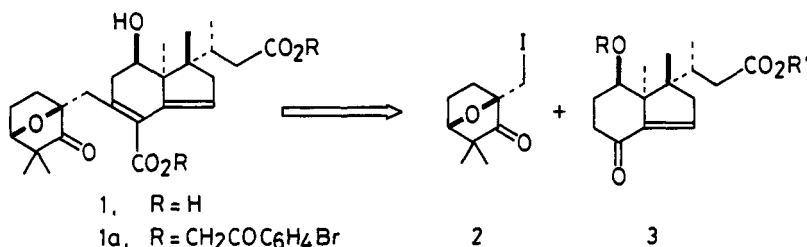
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Abstract - A total synthesis of glycinoclepin A, a natural hatching stimulus for the soybean cyst nematode, is described. The synthesis involves 32 steps and the overall yield is 0.4% from (R)-(-)-carvone. The hatch-stimulating activity of the synthetic sample was found to be indistinguishable from that of the natural sample.

INTRODUCTION

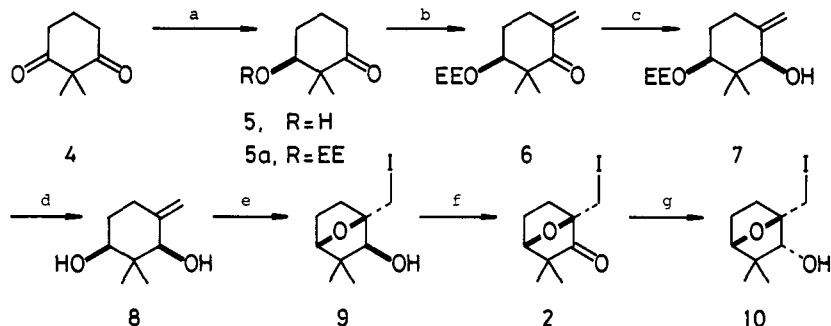
Glycinoclepin A, isolated from the aqueous extracts of dried roots of kidney bean (*Phaseolus vulgaris* L.), is a natural hatching stimulus for the soybean cyst nematode (*Heterodera glycines*) (ref. 1). This compound stimulates the hatching and emergence of larvae in vitro in highly diluted aqueous solutions. The molecular structure (1) of the compound has been confirmed by the X-ray diffraction analysis (ref. 2). The highly biological importance and the unusual skeletal array of 1 as well as the lack of a satisfactory natural amount have prompted us to investigate the chemical synthesis. The instability of 1 seemed to be attributed to the presence of a cross-conjugated moiety including in the C and D rings. Accordingly, we planned to disconnect the target molecule (1) into two fragments (2) and (3) as revealed below, reconnect them, and finally construct the cross-conjugated system in question. We describe herein the first total synthesis of the title target (ref. 3).



CHIRAL SYNTHESIS OF THE A RING FRAGMENT

The synthesis of the A ring part of 1 started with enzymatic reduction of 2,2-dimethylcyclohexane-1,3-dione (4) with baker's yeast (Scheme 1). The resulting (S)-2,2-dimethyl-3-hydroxycyclohexan-1-one (5) (ref. 4) (94.3% ee) was converted into the corresponding ethoxyethyl derivative (5a), which on successive treatment with Brederick's reagent (ref. 5) and with diisobutylaluminum hydride produced α,β -unsaturated ketone (6). The enone 6 was reduced with sodium trimethoxyborohydride, giving allyl alcohol (7) as a sole product which was transformed on acid hydrolysis into the (+)-olefinic cis-glycol (8). Treatment of 8 with N-iodosuccinimide in acetonitrile (MeCN) in the dark effected smooth cyclization to give iodomethyl oxabicycloheptane alcohol (9), which on simple recrystallization afforded an optically pure sample. Oxidation of 9 gave rise to (1R,4S)-3,3-dimethyl-1-iodomethyl-7-oxabicyclo-[2.2.1]heptan-2-one (2). This synthesis involves 8 steps from 4 in 27.6% overall yield. Compound 2 was further reduced with sodium borohydride to give exclusively the isomeric (2R)-alcohol (10).

Scheme 1

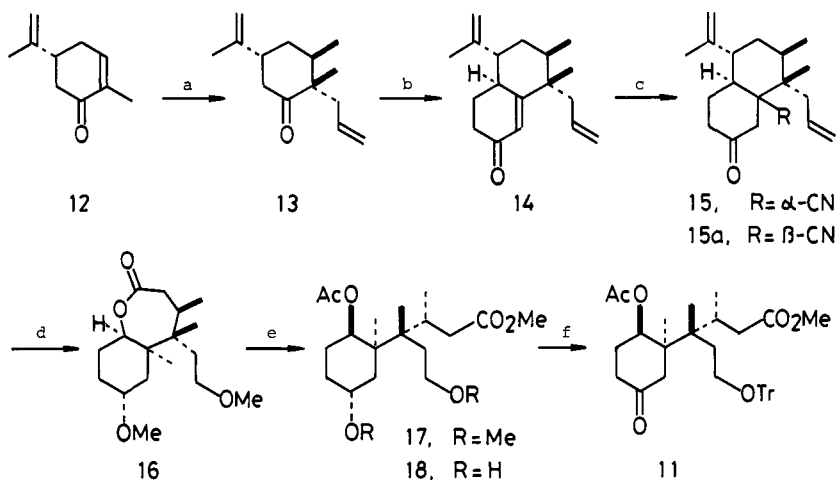


a) Baker's yeast, D -glucose, KH_2PO_4 , $MgSO_4$, aq DMF, 24 °C, 72 h; $EtOCH=CH_2$, PPTS (65% "94%"); b) DMF-dimethyl acetal, 110 °C, 2 d; DIBAH, THF, -78 → 23 °C, 1 h (63%); c) $NaBH(OMe)_2$ (87%); d) HCl (99%); e) NIS, MeCN, 20 °C, 16 h (79%); f) Jones oxid. (98%); g) $NaBH_4$ (94%).

STEREOSELECTIVE CONSTRUCTION OF THE C/D RING FRAGMENT

The synthesis of another fragment 11, corresponding to the C and D ring moiety of 1, commenced with (R)-(-)-carvone (12) and involved stereoselective construction of four successive chiral centers as the key steps (Scheme 2). Nucleophilic/electrophilic carba-condensation of 12 proceeded smoothly with high stereoselectivity, giving a dialkylated compound 13, which underwent annelation to yield an α,β -unsaturated octalone 14. Difficulty was encountered with introduction of the methyl group into an angular position of 14 by 1,4-conjugate addition with methylcuprate complexes under various conditions, owing to severe steric hindrance around the relevant reaction site, mainly due to the adjacent neopentyl group. This C-1 unit introduction was achieved by the hydrocyanation procedure as follows. Hydrocyanation of 14 under kinetic conditions (ref. 6) effected predominant formation (63%) of the desired *cis*-cyano ketone 15, accompanied by its *trans* isomer 15a (30%) (ref. 7). The configuration of these ketones was confirmed by the X-ray crystallographic analysis of 15 (ref. 8), indicating that stereoselective introduction of the four asymmetric centers has been completed as anticipated. Compound 15 was transformed by a usual several step sequence into decalone, which was oxidized with peroxytrifluoroacetic acid into ϵ -caprolactone 16 and then submitted to ring opening in a three-step process to give methoxycarbonyl acetate 17. Cleavage of the two methoxyl groups of 17 was effected according to the Fuji procedure (ref. 9) to yield triol monoacetate 18, which on tritylation and oxidation afforded acetoxy-cyclohexanone trityl ether 11.

Scheme 2

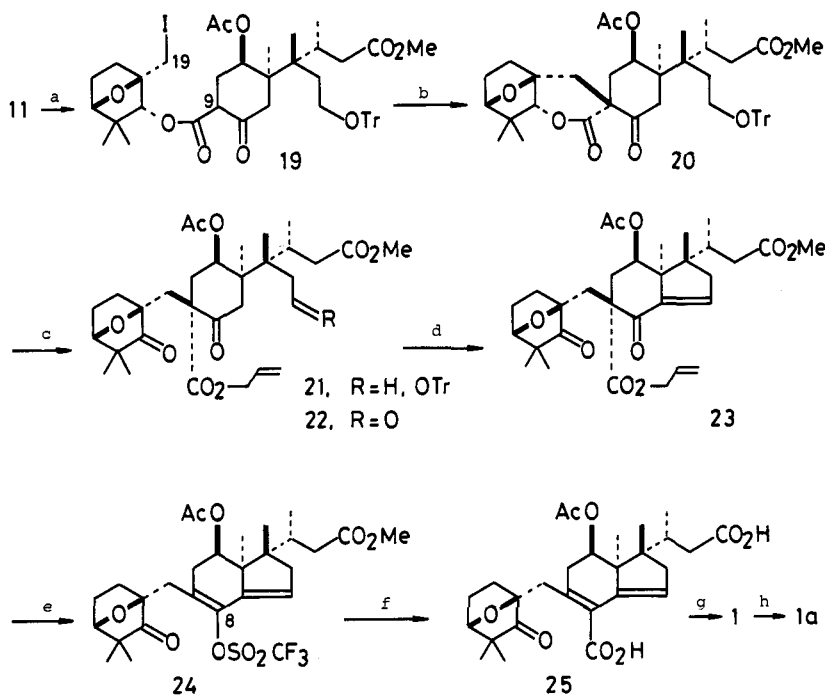


a) MeLi, CuI, Bu_3P , THF, -78 °C, 1 h and -40 °C, 4 h; HMPA, allyl bromide, -78 → 23 °C, 15 h (78%); b) LDA, $MeCOC(TMS)=CH_2$; NaOMe (74%); c) HCN, Et_3Al , THF, 23 °C, 30 h; d) OsO_4 , NMO; NaIO₄; $NaBH_4$; MeI, NaH; DIBAH; $NH_2NH_2 \cdot H_2O$, $NH_2NH_2 \cdot 2HCl$, triethylene glycol, 120 °C, 3.5 h; KOH, 200 °C, 6.5 h; O_3 ; Me_2S ; CF_3CO_2H ; $LiAlH_4$; Jones oxid.; CF_3CO_2H (15%); e) KOH; CH_2N_2 ; Ac_2O , DMAP, Et_3N ; $AlCl_3$, NaI, MeCN, 0 → 20 °C, 6 h; CH_2N_2 (49%); f) $TrCl$, DMAP, Et_3N ; PDC (91%).

**COUPLING OF THE A AND C/D RING FRAGMENTS LEADING TO
SYNTHESIS OF GLYCINOECLEPIN A**

The next phase of synthesis was the combination of the two fragments **10** and **11**, one of the most critical steps of the synthesis. After many fruitless attempts, we hoped to submit these compounds to an intramolecular coupling. Thus (Scheme 3), treatment of **11** with the bromomagnesium thioureide-carbon dioxide complex (ref. 10), resulted in α -carboxylation to yield β -ketocarboxylic acid, which was immediately reacted with **10** in the presence of dicyclohexyl carbodiimide to afford β -keto ester **19**. Further reaction of **19** with potassium fluoride in MeCN in the presence of 18-crown-6 at 65 °C effected the relevant coupling between C(9) and C(19), giving δ -lactone **20** in high yield (ref. 11). The lactone **20**, when treated with sodium allyloxide and then oxidized, was transformed into β -keto ester **21**, which was submitted to detritylation with acid and subsequent oxidation to afford **22**. Treatment of **22** with potassium *t*-butoxide in dimethoxyethane gave rise to the corresponding aldol, which was immediately dehydrated with 2-fluoropyridinium tosylate (ref. 12) to afford enone **23**. The allyloxycarbonyl group of **23** was then removed according to the procedure of Tsuji (ref. 13), giving the relevant dienol, which was treated immediately with sodium hydride and phenyl triflimide (ref. 14) to yield the corresponding dienyl triflate **24** in a high overall yield. The stage was now set to introduce the necessary one-carbon unit at the C(8) position of **24**. This was accomplished by a modification of the Ortner method (ref. 15). Compound **24**, when treated with tributylamine, palladium acetate, and 1,1'-bis(diphenylphosphino)ferrocene in a large excess of water in *N,N*-dimethylformamide under a carbon monoxide balloon at 95 °C for 3.5 h, was transformed into acetoxy dicarboxylic acid **25** in 42% yield (82% based on the recovered **24**). There is no experimental evidence available to detail how the compound **25** was produced under these conditions. Compound **25** was then saponified and esterified smoothly to give the corresponding bis(*p*-bromophenacyl) ester alcohol. The ester thus obtained was identical in every respect (¹H NMR, IR, MS, CD, HPLC) with **1a**, derived from the natural sample. The hatch-stimulating activity of the synthetic sample **1** was found to be indistinguishable from that of the natural sample (ref. 16).

Scheme 3



a) bromomagnesium thioureide-CO₂ complex, DMF, 20 °C, 20 h; **10**, DCC, DMAP, CH₂Cl₂, 0 + 20 °C, 20 h (84% "90%"); b) KF (3 equiv), 18-crown-6-ether (3 equiv), MeCN, 65 °C, 15 h (76% "94%"); c) sodium allyloxide; Swern oxid.; PTS; Swern oxid. (66% "82%"); d) *t*-BuOK, DME, -78 °C; 2-FC₅H₄NMe·OTs, Et₃N, CH₂Cl₂ (54%); e) Pd(OAc)₂, (C₆H₅)₂P, HCO₂H, Et₃N, THF; (CF₃SO₂)₂NC₆H₅, NaH (76%); f) CO, Bu₃N, Pd(OAc)₂, dppf, ac DMF, 95 °C, 3.5 h; g) NaOMe (66%); h) *p*-BrC₆H₄COCH₂Br, (*i*-Pr)₂NEt, MeCN (99%).

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