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A New Stereoselective Synthesis of (±)-Perhydrogephyrotoxin

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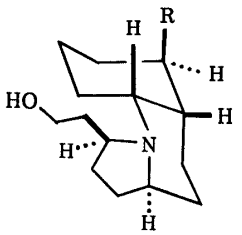
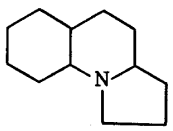
A stereoselective synthesis of (±)-perhydrogephyrotoxin (**3**) starting from 1,3-bis(trimethylsiloxy)-1,3-butadiene and ethyl *trans*-2-octenoate is described. A crucial step is reductive decarboxylation of the γ-carbamoyloxy-α,β-enoate (**6**) with lithium dibutylcuprate to yield the β,γ-enoate (**40**).

Keywords——*Dendrobates histrionicus*; poison-dart frog; alkaloid; gephyran; pyrrolo[1,2-*a*]quinoline; reductive decarboxylation; Diels–Alder reaction; perhydrogephyrotoxin; lithium dialkylcuprate

Many alkaloids which possess important pharmacological activities, such as nerve-muscle activities, have been isolated from skin extracts of brightly colored Neotropical poison-dart frogs belonging to the Dendrobatidae.[1] Such poison-dart alkaloids in the skin of these colored frogs act as a passive "defence" against predators.[2] These toxic alkaloids are classified into five major groups: pumiliotoxin C, pumiliotoxins A and B, batrachotoxins, and gephyrotoxins.[1] Synthetic studies of these toxic bases have been undertaken in many laboratories throughout the world, culminating in many brilliant syntheses.[3-9]

Gephyrotoxin (**1**) has been isolated, among other alkaloids, from *Dendrobates histrionicus* in 1974[10] and the constitution of the alkaloid was elucidated by chemical means and by X-ray analysis of gephyrotoxin hydrobromide.[11] A minor congener, dihydrogephyrotoxin (**2**), was also isolated and differs only in the presence of a *cis*-1,3-diene side chain.[11] On catalytic hydrogenation, both the bases (**1** and **2**) yielded the same reduction product, perhydrogephyrotoxin (**3**).[11]





4

1 : R = $CH_2CH\overset{Z}{=}CHC{\equiv}CH$

2 : R = $CH_2CH\overset{Z}{=}CHCH{=}CH_2$

3 : R = $(CH_2)_4CH_3$

Chart 1

The common novel framework of these toxins is perhydropyrrolo[1,2-*a*]quinoline (**4**). Although it has been reported that gephyrotoxins appeared to act as a weak muscarinic antagonist,[1,12] recent studies have revealed highly complex and interesting neurological activities of the toxins.[13] Structure–activity correlations for gephyrotoxin class alkaloids have

not been fully delineated because of the limited supplies available from natural sources. The scarcity of the toxins, together with their novel structures and interesting biological activities, make gephyrotoxin (**1**) and its perhydro derivative (**3**) attractive synthetic targets.

In this paper we describe a stereoselective synthesis of (±)-perhydrogephyrotoxin (**3**),[14] which illustrates the utility of the Diels–Alder reaction using 1,3-bis(trimethylsiloxy)-1,3-butadiene[15] and of the novel reductive decarboxylation of a γ-carbamoyloxy-α,β-enoate with lithium dialkylcuprate in solving some synthetic problems.[16]

Results and Discussion

The stereoselective synthetic route to the target (**3**) was based on the assumption that the key intermediates (**5** and **6**) would be formed from 1,3-bis(trimethylsiloxy)-1,3-butadiene and ethyl *trans*-2-octenoate as shown in the reaction sequence in Chart 2. On the basis of the above considerations, we synthesized **3** as follows.

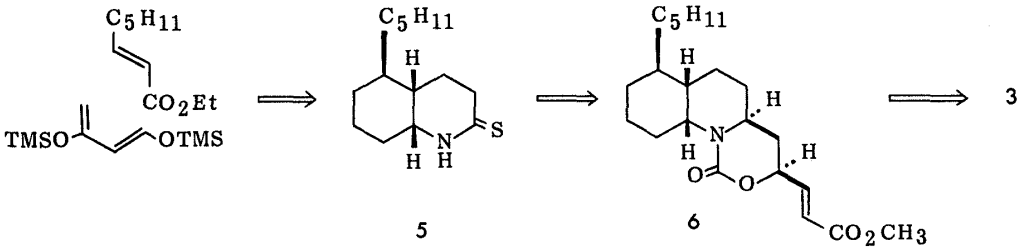


Chart 2

The Diels–Alder reaction of *trans*-1,3-bis(trimethylsiloxy)-1,3-butadiene[15] and ethyl *trans*-2-octenoate in dry xylene at 175 °C in a sealed glass tube gave a cycloadduct (**7**) as a single product in 95% yield and no regioisomeric adduct was detected in the reaction product. The adduct (**7**) was converted into the ketal-ester (**8**) by refluxing with ethylene glycol in benzene in the presence of *p*-toluenesulfonic acid with formation of the double bond in 84% yield. Although reduction of **8** with lithium aluminum hydride resulted in a substantial amount of an undesired saturated alcohol, treatment of **8** with diisobutylaluminum hydride yielded the allyl alcohol (**9**) as a single product. The allyl alcohol (**9**) was treated with butyllithium in a mixture of tetrahydrofuran–hexamethylphosphoric triamide at −78 °C in the presence of triphenylmethane, and subsequent reaction with *p*-toluenesulfonyl chloride[17] yielded the rather unstable allyl chloride (**10**). Cyanomethylenation of **10** with cyanomethyl-copper[18] furnished the γ,δ-unsaturated nitrile (**11**) in 78% yield.

Reaction of **11** with 30% hydrogen peroxide in methanolic sodium hydroxide gave the corresponding amide (**12**), which was treated with 5% hydrochloric acid to provide the γ,δ-unsaturated keto-amide (**13**) in 87% overall yield. No migration of the double bond to the α,β-position with respect to the keto-carbonyl group was observed under this acidic condition, as can be seen from the infrared (IR) spectrum [1708 cm^{-1} (saturated ketone) and 1680 cm^{-1} (amide carbonyl)] and the proton nuclear magnetic resonance (^{1}H-NMR) spectrum [δ: 5.46, 1H, t, J=3.5 Hz, olefinic proton)] of **13**. Although treatment of **13** with boron trifluoride etherate or concentrated hydrochloric acid at 0 °C afforded (4a*R**,5*S**,8a*S**)-5β-pentyl-*cis*-decahydroquinoline-2,7-dione (**15**) in low yield, reaction of **13** with sodium methoxide in refluxing methanol resulted in a more satisfactory yield (61%) of **15** as a single isolable product. Although we could not conclusively rule out the presence of three other possible stereoisomers of **15**, we were unable to detect them by chromatographic and spectroscopic methods. The *cis*-junction in **15** could be anticipated since the intramolecular Michael-type ring-closing reaction of compounds such as the presumed intermediate (**14**) usually gives the

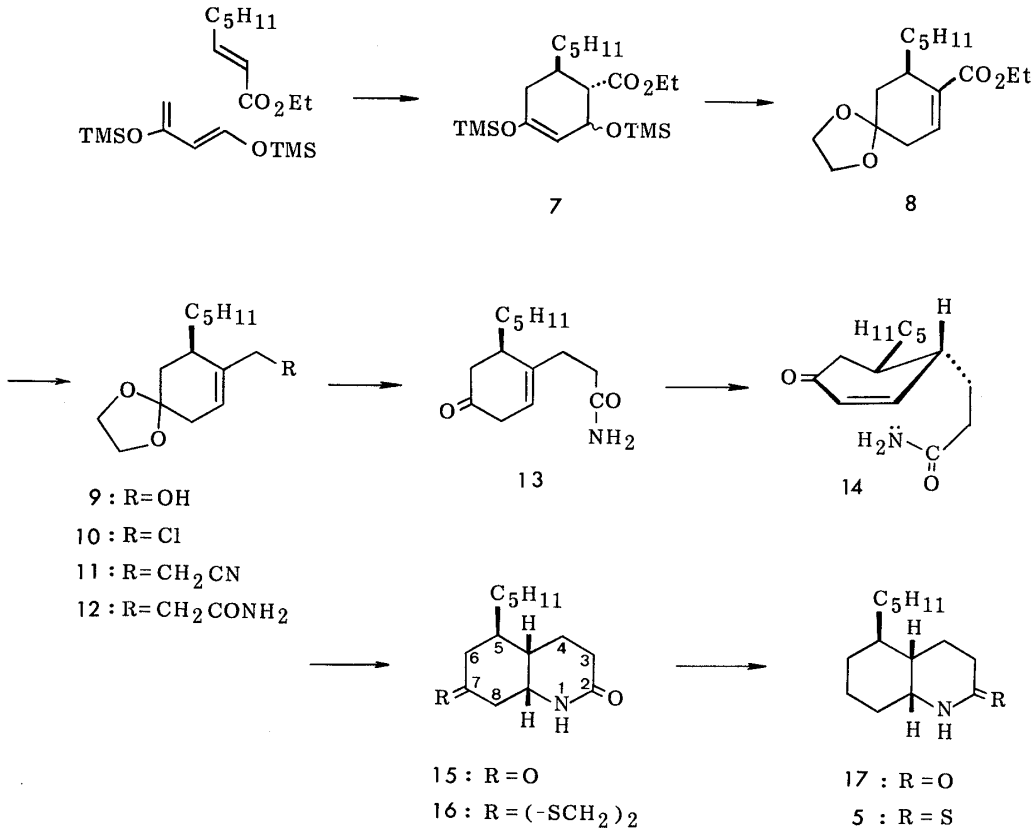


Chart 3

cis-isomer.[19] In fact, the ^{1}H-NMR spectrum of **15** exhibited a one-proton signal assignable to the C-8a position at δ 3.99 with a half-width ($W_{1/2}$) of 13 Hz, characteristic of a *cis*-fused perhydroquinoline.[20] Although the stereochemistry of the pentyl group at the C-5 position was not clarified at this stage, the β-configuration was inferred from a precedent.[15,21]

Thioacetalization of **15** followed by desulfurization with Raney nickel gave a lactam (**17**) which was transformed into a key intermediate (**5**) by treatment with Lawesson's reagent.[22]

The next step of the present synthesis was the addition of the C_5-moiety to the thiolactam carbon of **5**. This was effectively accomplished by the Eschenmoser procedure.[23] Thus, treatment of **5** with methyl 5-bromolevulinate in chloroform followed by bis(3-dimethylaminopropyl)phenylphosphine yielded the vinylogous amide (**18**) in 81% yield.

Although the keto-ester (**20**) was the desired intermediate for the present synthesis of **3**, stereoselective reduction of the double bond in **18** proved much more difficult than first envisioned. A number of standard reduction methods were attempted unsuccessfully on **18**. Of the two possible stereoisomers (**19** and **20**) which can result from reduction, the undesired isomer (**19**) was formed exclusively [*e.g.* sodium cyanoborohydride reduction at pH 4.0 (**19**, 99% yield); catalytic hydrogenation over platinum oxide in acetic acid followed by Jones oxidation (**19**, 78% yield)]. The keto-ester (**19**) [non-steroid form, ^{1}H-NMR δ: 2.90 (1H, m, $W_{1/2}$ 8 Hz, C-8a-H), 3.05 (1H, ddt, J=9.5, 6.5, 3.5 Hz, C-2-H)] was equilibrated with triethylamine in methanol to yield a *ca.* 3:1 mixture of **19** and an isomeric keto-ester (**20**) [steroid form, ^{1}H-NMR δ: 3.05 (1H, dt, J=11.7, 3.7 Hz, C-8a-H) and 3.32 (1H, ddt, J=9.5, 6.5, 3.5 Hz, C-2-H)]. All attempts to enhance the relative proportion of the desired **20** by equilibration with several Lewis acids as well as bases were of no avail. Although the yield of **20** was not high, the only other compound found in the product mixture was the starting material, and since the starting material can be recycled, the equilibration with triethylamine is in essence satisfactory.

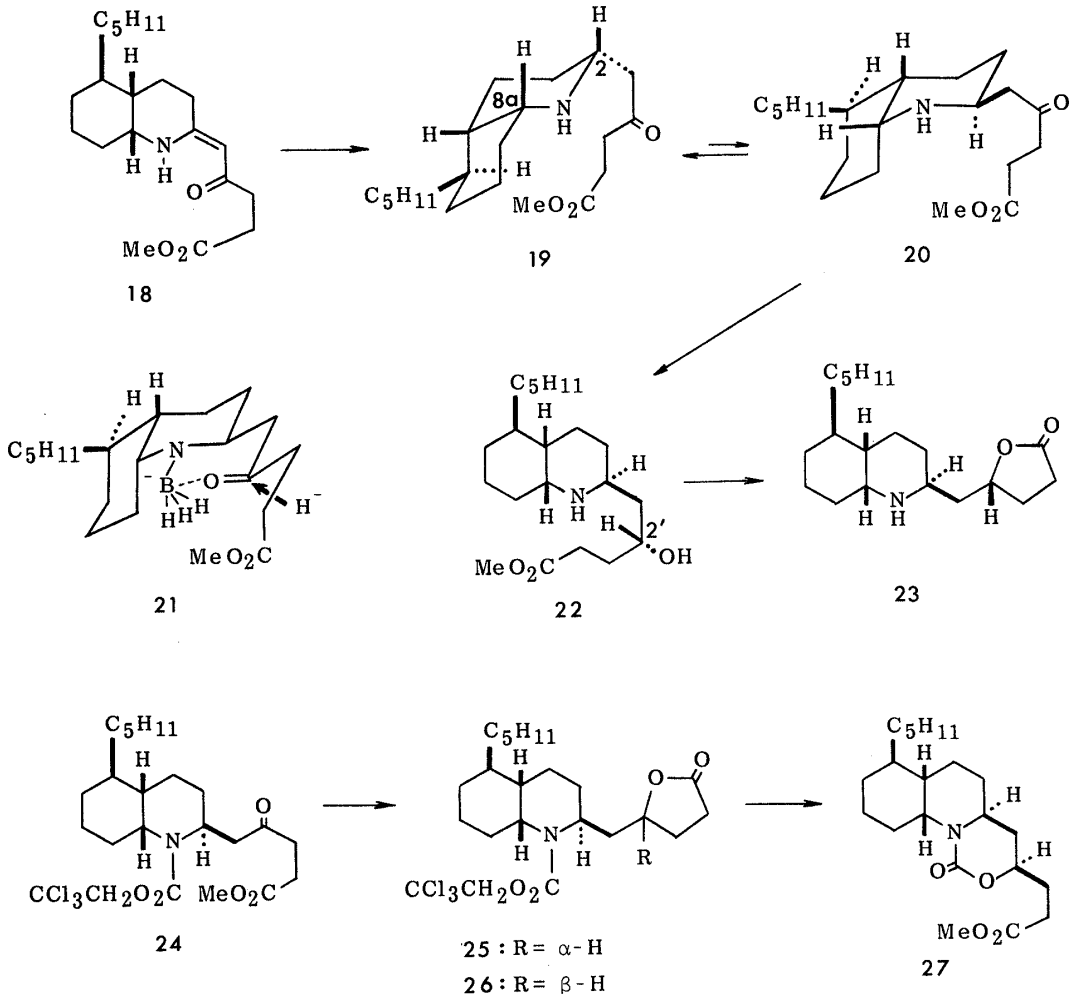


Chart 4

Reduction of **20** with sodium borohydride in methanol at −20 °C yielded the alcohol (**22**), which was treated with *p*-toluenesulfonic acid in refluxing benzene to yield the lactone (**23**) as a single product in 99% yield. Although the stereochemistry at the C-2′ position in **22** and **23** was not clarified at this stage, the (*R**)-stereochemistry at C-2′ in **22** and **23** was inferred from the nuclear Overhauser enhancement (*ca.* 9% enhancement) of the hydrogen at the C-2 position on irradiation of the hydrogen at the C-2′ position in **6** derived from **23** (*vide infra*). The remarkably high degree of stereoselectivity in the borohydride reduction of **20** should be due to initial reaction of the reducing agent with the secondary amino group and subsequent chelation to the carbonyl to yield the presumed cyclic intermediate (**21**). Attack of hydride could now occur from the least-hindered side, indicated by the arrow, to yield **22**.[24] On the other hand, treatment of the carbamate (**24**), which was derived from **20**, with sodium borohydride followed by treatment with *p*-toluenesulfonic acid in benzene under reflux yielded a mixture of the lactones (**25** and **26**). The stereochemistry at the C-2′ position of **26** was inferred from the ^{1}H-NMR spectral analysis of the cyclic carbamate (**27**) which was derived from **26**.

Protection of the secondary amino function in **23** with a phenoxycarbonyl group followed by phenylselenylation by a standard procedure gave the selenide (**29**) in 86% overall yield. Subsequent treatment of **29** with 30% hydrogen peroxide in the presence of pyridine yielded the α,β-unsaturated γ-lactone (**30**) in quantitative yield. Conversion of **30** to a cyclic γ-carbamoyloxy-α,β-enoate (**31**) by treatment with bases such as sodium methoxide and lithium

hydroxide followed by methylation with diazomethane proved to be much more difficult than first envisioned, and the only isolable product was found to be the rearranged keto-ester (**32**). Since our initial attempts to synthesize the requisite **31** from **30** were unsuccessful, the following reactions were undertaken.

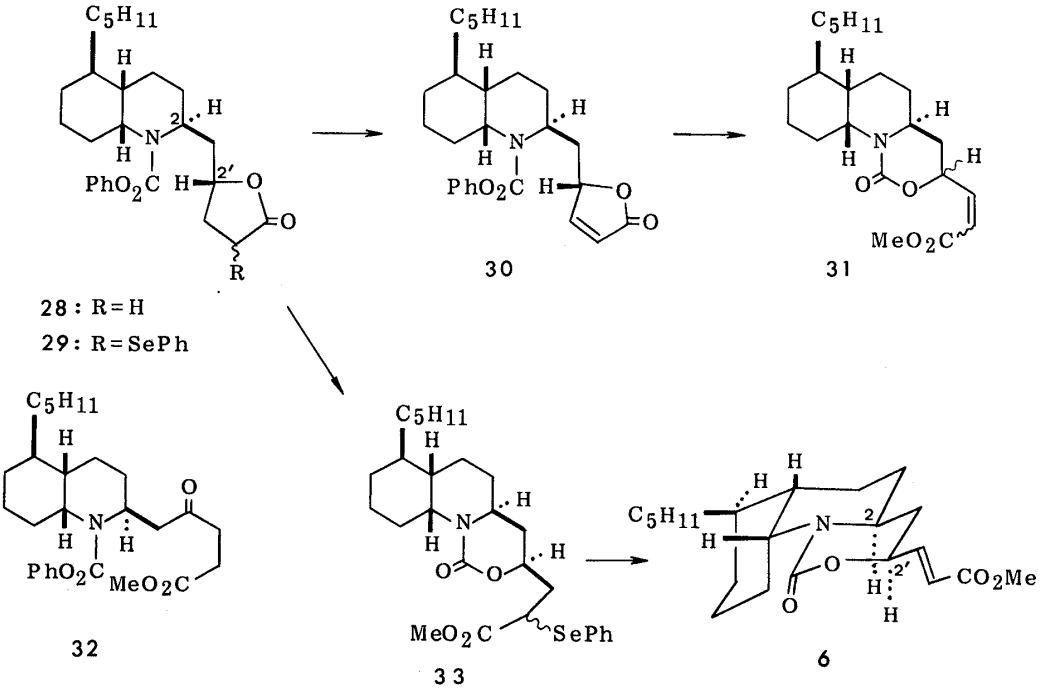


Chart 5

The selenide (**29**) was allowed to react with lithium hydroxide in aqueous methanol and, after acidification, the resulting carboxylic acid was treated with ethereal diazomethane to furnish the cyclic carbamate (**33**) in 80% yield. Oxidative elimination of the phenylselenyl group was effected by reaction of **33** with 30% hydrogen peroxide in the presence of pyridine to yield the γ-carbamoyloxy-α,β-enoate (**6**) in essentially quantitative yield. The (*E*)-configuration of the double bond in **6** was assigned on the basis of the large coupling constant ($J = 16$ Hz) between the two olefinic protons.

With **6** in hand, the next step was reductive decarboxylation. It has been reported that a γ-oxygenated-α,β-enoate (**34**) is reduced with zinc-amalgam in the presence of hydrogen chloride[25] or zinc in acetic acid[8b] to yield the deconjugated β,γ-unsaturated ester (**35**). However, **34** react slowly and fail to give significant amounts of pure reductive decarboxylation product (**35**) even after extended periods at relatively high temperatures. The limitation we have encountered in the present study is the low conversion yield in zinc-mediated reductive decarboxylation.[26]

Although the conjugate addition and the substitution reaction of organocopper reagents are highly useful reactions for organic synthesis, we have recently reported a novel efficient reductive decarboxylation of γ-carbamoyloxy-α,β-enoates (**36** and **38**) with organocopper reagents under mild reaction conditions to afford the β,γ-enoates (**37** and **39**) in essentially quantitative yield.[14b] To the best of our knowledge, this type of reductive decarboxylation of γ-carbamoyloxy-α,β-enoates using organocuprates has no precedent in the literature. The organocopper-mediated electron transfer (reduction) is particularly interesting since, in living organisms, copper proteins are frequently involved in the electron transfer processes in membranes and mitochondria.[27]

The enoate (**6**) was allowed to react with lithium dibutylcuprate[28] in a mixture of ether

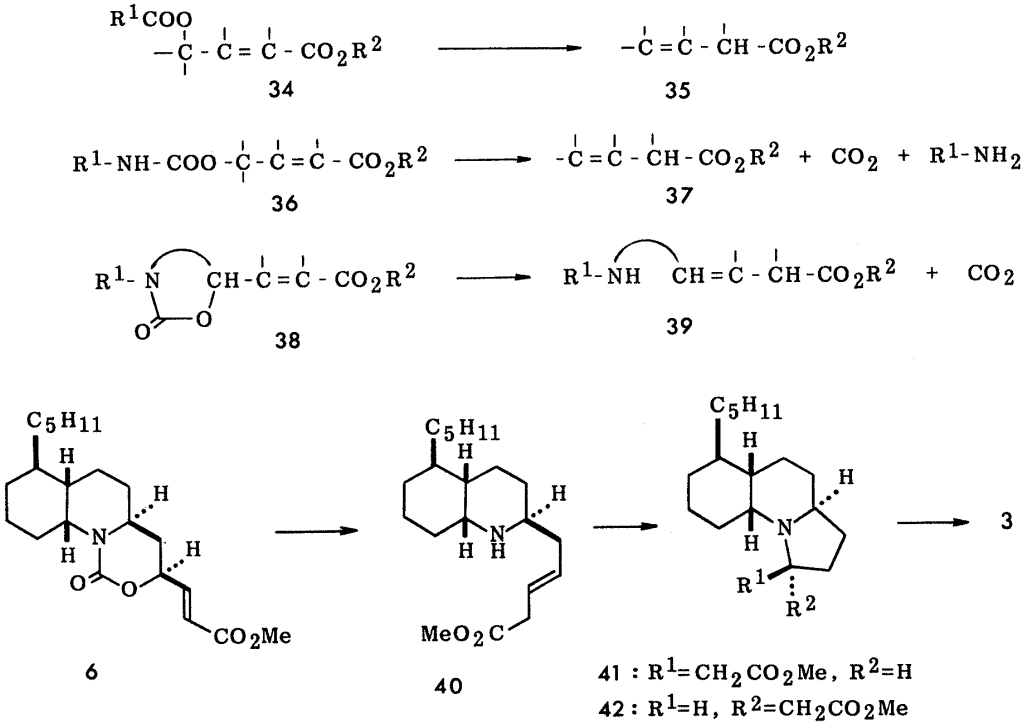


Chart 6

and tetrahydrofuran at −73 °C for 5 min to yield the β,γ-unsaturated ester (**40**) in almost quantitative yield. The (*E*)-stereochemistry of the double bond assigned to **40** is based on the identity with an authentic sample prepared from **6** by reduction with zinc in acetic acid[8b] at 90 °C for 12 h in 34% yield. Treatment of **40** with 1% sodium methoxide in dry methanol yielded the tricyclic compounds (**41**, 51% yield, and **42**, 9% yield) after chromatographic separation on an alumina column. Finally, reduction of the major product (**41**) with diisobutylaluminum hydride at −60 °C in toluene yielded (±)-perhydrogephyrotoxin (**3**) in 98% yield. The spectral data [IR ($CHCl_3$), ^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$)] of the synthesized compound were identical with authentic spectra.[8]

Experimental

General Methods——All reactions were performed under an atmosphere of argon. Tetrahydrofuran was freshly distilled from lithium aluminum hydride. All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. All IR spectra were recorded on a Shimadzu IR-400 spectrometer. Nominal and accurate mass spectra were recorded on a JEOL JMS-01SG-2 mass spectrometer equipped with a direct inlet system. All ^{1}H-NMR spectra were recorded on a JEOL FX-200 spectrometer. Chemical shifts are quoted in parts per million downfield from internal tetramethylsilane (s=singlet, d=doublet, dd=double doublet, t=triplet, q=quartet, m=multiplet). Elemental analyses were carried out by the Microanalytical Center of Kyoto University. For column chromatographies, silica gel (Mallinckrodt, 100 mesh) or alumina (Merck, Aluminum oxide 90, activity II—III) was employed.

The Diels–Alder Reaction of 1,3-Bis(trimethylsiloxy)-1,3-butadiene and Ethyl *trans*-2-Octenoate——A mixture of ethyl *trans*-2-octenoate (9.8 g, 57.6 mmol) and 1,3-bis(trimethylsiloxy)-1,3-butadiene (20 g, 86.4 mmol) in 30 ml of dry xylene was heated in a sealed glass tube at 175 °C for 48 h. After cooling of the mixture, the solvent was removed on a rotary evaporator (10 °C (20 Torr)) to leave a yellow residue. Distillation under reduced pressure gave 22 g (95% yield) of **7** as a slightly yellow oil. bp 150—153 °C (1 Torr). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1722, 1673. Mass spectrum (MS) *m/z* Calcd for $C_{20}H_{40}O_4Si_2$: 400.2474. Found: 400.2471.

Ethyleneacetalization of the Cycloadduct (7)——A mixture of **7** (11 g, 27.5 mmol), ethylene glycol (30 ml), benzene (100 ml), and *p*-TsOH (50 mg) was heated under reflux for 10 h. The solvent was removed under reduced pressure and the residue was extracted with ether after basification with 5% $NaHCO_3$. The extract was washed successively with 5% $NaHCO_3$ and water, dried over anhydrous $MgSO_4$, and concentrated to leave a yellow residue.

Distillation under reduced pressure gave 6.5 g (84% yield) of the acetal-ester (**8**) as a colorless oil. bp 140 °C (3 Torr). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (CO), 1644 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, tripletoid m, $CH_2C\underline{H}_3$), 1.26 (3H, t, J=6.9 Hz, $OCH_2C\underline{H}_3$), 3.96 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 4.16 (2H, m, $OC\underline{H}_2CH_3$), 6.71 (1H, t, J=4 Hz, olefinic proton). *Anal.* Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 67.78; H, 9.45.

Reduction of the Enoate (8) with Diisobutylaluminum Hydride——Diisobutylaluminum hydride (83.9 ml, 0.083 mol in hexane) was added dropwise to a solution of **8** (10.29 g, 0.036 mol) in a mixture of 35 ml of hexane–toluene (6 : 1, v/v) at −78 °C with stirring, and the whole was further stirred at 0 °C for 3 h. Then 70 ml of 10% NaOH was added at −30 °C with stirring, and the reaction mixture was stirred at ambient temperature for 40 min, then extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to leave a colorless oil, which was purified by alumina column chromatography with hexane–$CHCl_3$ (1 : 5, v/v) to yield 8.29 g (95% yield) of the allyl alcohol (**9**) as a colorless oil. bp 150 °C (3 Torr). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, tripletoid m, CH_3), 3.90 (4H, s, OCH_2CH_2O), 4.02 (2H, br s, $C\underline{H}_2OH$), 5.53 (1H, m, olefinic proton). *Anal.* Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.11; H, 10.16.

The Allyl Chloride (10)——Butyllithium (5.9 ml, 6 mmol in hexane) was added dropwise to a solution of **9** (1.2 g, 5 mmol), hexamethylphosphoric triamide (5 ml), and triphenylmethane (3 mg) in 10 ml of dry tetrahydrofuran (THF) at −70 °C with stirring. Then a solution of *p*-TsCl (1.14 g, 6 mmol) in THF (2 ml) was added to the mixture at −70 °C with stirring and the temperature was allowed to rise to 0 °C. The reaction mixture was poured into ice-water and extracted with a mixture of ether–pentane (1 : 2, v/v). The extract was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure at 0 °C to leave a colorless oil, which was purified by alumina column chromatography with pentane to yield 1.29 g (100% yield) of **10**. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, tripletoid m, CH_3), 3.90 (4H, s, OCH_2CH_2O), 3.88 and 4.16 (each 1H, d, J=11.0 Hz, CH_2Cl), 5.63 (1H, m, olefinic proton). The compound (**10**) was used immediately for the next step due to its instability.

The β,γ-Unsaturated Nitrile (11)——THF (100 ml) was added to semisolid butyllithium (0.2 mol) which was prepared from 118 ml of hexane solution of 1.7 M butyllithium by evaporating the solvent under reduced pressure. Acetonitrile (8.4 g, 0.2 mol) was added dropwise to the above solution at −73 °C with stirring and stirring was continued at the same temperature for 1 h. Then cuprous iodide (38.2 g, 0.2 mol) was added at −73 °C with vigorous stirring and the temperature was allowed to rise to −30 °C. The allyl chloride (**10**) (10.3 g, 0.04 mol) in 20 ml of THF was added to the above mixture at −73 °C with stirring and the temperature was allowed to rise to −30 °C. Saturated ammonium chloride solution (10 ml) was then added at −30 °C, and the mixture was extracted with ether. The usual work-up of the ethereal solution gave an oily residue, which was chromatographed on an alumina column. Elution with $CHCl_3$ gave the **11** (8.27 g, 78% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, tripletoid m, CH_3), 3.97 (4H, m, OCH_2CH_2O), 5.42 (1H, m, olefinic proton). MS *m/z* Calcd for $C_{16}H_{25}NO_2$: 263.1883. Found: 263.1880.

Hydrolysis of the Nitrile (11) with a Mixture of 30% Hydrogen Peroxide and 25% Potassium Hydroxide——Twenty-five percent KOH (20 ml) and 30% H_2O_2 (20 ml) were added to a solution of **11** (13.28 g, 50.5 mmol) in methanol (50 ml) with vigorous stirring at 0 °C, and the mixture was stirred at the same temperature for 12 h. After evaporation of the solvent, the residue was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated to leave a colorless oil, which was purified by alumina column chromatography with $CHCl_3$ to give the γ,δ-unsaturated carboxamide (**12**) (12.75 g, 90% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3485—3405 (NH_2), 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7 Hz, CH_3), 3.98 (4H, m, OCH_2CH_2O), 5.38 (1H, m, olefinic proton), 5.77 and 5.92 (each 1H, br s, NH_2). MS *m/z* Calcd for $C_{16}H_{27}NO_3$: 281.1990. Found: 281.1985.

The β,γ-Unsaturated Ketone (13)——A mixture of **12** (7.02 g, 25 mmol), 5% HCl (20 ml), and acetone (100 ml) was refluxed for 30 min. The major portion of the solvent was evaporated off under reduced pressure and the residual oil was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated to leave a colorless oil, which was purified by silica gel column chromatography with $CHCl_3$–acetone (9 : 1, v/v) to give **13** (5.74 g, 97% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500—3420 (NH_2), 1708 (ketone), 1680 (amide). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.5 Hz, CH_3), 5.46 (1H, t, J=3.5 Hz, olefinic proton), 5.52 and 5.66 (each 1H, br s, NH_2). MS *m/z* Calcd for $C_{14}H_{23}NO_2$: 237.1729. Found: 237.1709.

(4a*R,5*S**,8a*S**)-5β-Pentyl-*cis*-decahydroquinoline-2,7-dione (15)**——A mixture of **13** (82 mg, 0.346 mmol) in 2 ml of methanol and 3 ml of 5% sodium methoxide was heated under reflux for 20 min. The solution was cooled in an ice bath, then made acidic with 5% HCl. After removal of the solvent under reduced pressure, the residual aqueous solution was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated to leave a crystalline residue which was purified by silica gel column chromatography with $CHCl_3$ to give a crystalline mass. Recrystallization from acetone–ether (1 : 4, v/v) gave **15** (50 mg, 61% yield) as colorless crystals, mp 162 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3383—3200 (NH), 1714 (ketone), 1660 (lactam). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.4 Hz, CH_3), 3.99 (1H, m, $W_{1/2}$ 13 Hz, C-8a-H), 6.27 (1H, br s, NH). MS *m/z* Calcd for $C_{14}H_{23}NO_2$: 237.1729. Found: 237.1719.

The Thioacetal (16)——1,2-Ethanedithiol (40 mg, 0.424 mmol) and boron trifluoride etherate (35 mg, 0.246 mmol) were added to a solution of **15** (54 mg, 0.228 mmol) in $CHCl_3$ (2 ml) and the mixture was stirred for 1 h at ambient temperature. After removal of $CHCl_3$ under reduced pressure, the crystalline residue was purified by silica gel column chromatography with $CHCl_3$ to give a crystalline mass, which was recrystallized from acetone–ether (1 : 4,

v/v) to give **16** (70 mg, 98% yield) as colorless prisms, mp 125 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3359 (NH), 1656 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.6 Hz, CH_3), 3.28 (4H, m, SCH_2CH_2S), 3.79 (1H, m, C-8a-H), 5.76 (1H, s, NH). *Anal.* Calcd for $C_{16}H_{27}NOS_2$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.49; H, 8.79; N, 4.51.

Desulfurization of the Thioacetal (16) with Raney Nickel——Raney nickel (50 mg) was added to a solution of **16** (5 mg, 0.016 mmol) in ethanol (1 ml), and the mixture was stirred under reflux for 20 h. The mixture was acidified with 5% HCl under ice-cooling and then filtered. The filtrate was concentrated under reduced pressure and the residue was taken up in $CHCl_3$. The usual work-up of the $CHCl_3$ solution gave a crystalline residue, which was purified by silica gel column chromatography with $CHCl_3$. Recrystallization from acetone–ether (1 : 4, v/v) gave the lactam (**17**) (3.5 mg, 98% yield) as colorless plates, mp 117 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380—3180 (NH), 1645 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.8 Hz, CH_3), 3.62 (1H, m, C-8a-H), 5.72 (1H, br s, NH). *Anal.* Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28. Found: 75.11; H, 11.58.

5β-Pentyl-*cis*-decahydroquinoline-2-thione (5)——Lawesson's reagent[22] (4.6 g, 22.4 mmol) was added to a solution of **17** (5.0 g, 22.4 mmol) in xylene (80 ml) and the mixture was heated under reflux for 1 h, and then cooled. The mixture was made basic with 5% $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated to leave a semisolid, which was purified by silica gel column chromatography with $CHCl_3$. Recrystallization from acetone–ether (1 : 4, v/v) gave **5** (5.02 g, 94% yield) as colorless needles, mp 134 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340, 3170, 1520, 1320, 1103. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=6.8 Hz, CH_3), 3.63 (1H, m, C-8a-H), 8.03 (1H, br s, NH). *Anal.* Calcd for $C_{14}H_{25}NS$: C, 70.23; H, 10.52. Found: C, 70.32; H, 10.78.

The Vinylogous Amide (18)——A solution of methyl 5-bromolevulate (160 mg, 0.59 mmol) in $CHCl_3$ (5 ml) was added dropwise to a solution of **5** (100 mg, 0.42 mmol) in $CHCl_3$ (3 ml) and the mixture was stirred for 2 h. A solution of bis(3-dimethylaminopropyl)phenylphosphine (176 mg, 0.63 mmol) in $CHCl_3$ (3 ml) was added, and the whole was heated under reflux for 2 h. After removal of the solvent under reduced pressure at ambient temperature, the residue was purified by silica gel column chromatography with acetone–$CHCl_3$ (1 : 49, v/v) to give **18** (114 mg, 81% yield) as colorless needles, mp 52 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400—3180 (NH), 1730 (ester), 1600 (amide), 1555 (C=C), ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=6.8 Hz, CH_3), 2.59—2.62 (4H, m, $COCH_2CH_2CO$), 3.55 (1H, m, $W_{1/2}$ 10 Hz, C-8a-H), 3.69 (3H, s, CO_2CH_3), 4.90 (1H, s, olefinic proton). MS m/z Calcd for $C_{20}H_{33}NO_3$: 335.2461. Found: 335.2461.

Reduction of the Vinylogous Amide (18) with Sodium Cyanoborohydride——Sodium cyanoborohydride (170 mg, 2.7 mmol) in 3 ml of methanol was added portionwise to a solution of **18** (2.0 g, 5.97 mmol) in 5 ml of methanol with stirring. The solution was adjusted to pH 4.0 with 5% HCl using bromocresol green as an indicator, and the mixture was stirred at ambient temperature for 1 h. The major portion of the solvent was removed under reduced pressure and then the mixture was made basic with 5% $NaHCO_3$. Extraction with $CHCl_3$ and the usual work-up of the $CHCl_3$ extract gave the **19** (2.0 g, 99% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420—3340 (NH), 1731 (ester), 1715 (ketone). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.1 Hz, CH_3), 2.52—2.64 (4H, m, $COCH_2CH_2CO$), 2.68—2.84 (2H, m), 2.90 (1H, m, $W_{1/2}$ *ca.* 8 Hz, C-8a-H), 3.05 (1H, ddt, J=9.5, 6.5, 3.5 Hz, C-2-H). MS m/z Calcd for $C_{20}H_{35}NO_3$: 337.2616. Found: 337.2622.

The Keto-ester (19)——The vinylogous amide (**18**) (45 mg, 0.134 mmol) in 1 ml of acetic acid was catalytically hydrogenated over $PtO_2 \cdot 2H_2O$ (6 mg) at atmospheric pressure by a conventional procedure. The catalyst was filtered off and the filtrate was made basic with 5% $NaHCO_3$. Extraction with CH_2Cl_2 and the usual work-up of the extract gave a colorless oil (40 mg), which was dissolved in 1 ml of acetone. Oxidation of the above solution with Jones reagent gave **19** (35 mg, 78% yield) as a colorless oil. The keto-ester thus obtained was identical with an authentic sample prepared by reduction with sodium cyanoborohydride in terms of IR ($CHCl_3$), ^{1}H-NMR ($CDCl_3$), and thin layer chromatography (TLC).

Preparation of the Keto-ester (20)——A mixture of **19** (110 mg, 0.326 mmol), triethylamine (150 mg, 1.5 mmol), and methanol (5 ml) was heated under reflux for 5 h. After cooling of the mixture, the solvent was removed on a rotary evaporator to leave a colorless oil, which was chromatographed on an alumina column. Elution with $CHCl_3$ provided successively **19** (68 mg of the starting material, 62% yield) and the desired **20** (22 mg, 20% yield; 52% yield based on the consumed starting material). **20**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH), 1730 (ester), 1712 (ketone). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.6 Hz, CH_3), 2.48—2.64 (4H, m, $COCH_2CH_2CO$), 3.05 (1H, dt, J=11.7, 3.7 Hz, C-8a-H), 3.32 (1H, ddt, J=9.5, 6.5, 3.5 Hz, C-2-H), 3.67 (3H, s, CO_2CH_3). MS m/z Calcd for $C_{20}H_{35}NO_3$: 337.2616. Found: 337.2621.

Preparation of the γ-Lactone (23) from the Keto-ester (20)——A solution of 1 ml (1.0 mmol) of 1 M $NaBH_4$ in methanol was added dropwise to a solution of **20** (300 mg, 0.89 mmol) in 5 ml of methanol at −20 °C with stirring and the mixture was stirred for 1 h. After removal of the solvent under reduced pressure, the residue was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated to leave the alcohol **22** (302 mg, 100% yield) as a colorless oil, which was used for the next lactonization reaction without purification due to its instability. *p*-TsOH (190 mg, 1.0 mmol) was added to a solution of the alcohol (302 mg, 0.89 mmol) in 10 ml of benzene and the mixture was heated under reflux for 1 h, and then basified with 5% $NaHCO_3$. Extraction with ether and the usual work-up of the extract gave **23** (270 mg, 99% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (NH), 1767 (lactone). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, tripletoid m, CH_3), 3.05 (2H, m, C-2-H and C-8a-H), 4.62 (1H, m, C-2′-H). MS m/z Calcd for $C_{19}H_{33}NO_2$: 307.2511. Found: 307.2521.

The 2,2,2-Trichloroethyl Carbamate (24)——2,2,2-Trichloroethyl chloroformate (320 mg, 1.5 mmol) was added to a solution of **20** (100 mg, 0.3 mmol) in 10.5 ml of a mixture of CCl_4–pyridine (20 : 1, v/v) at 0 °C with stirring, and the mixture was stirred for 30 min at ambient temperature, then extracted with $CHCl_3$–ether (1 : 5, v/v). The extract was successively washed with 5% $NaHCO_3$, water, 5% HCl, and water, dried over $MgSO_4$, and concentrated to leave a colorless oil. The oil was chromatographed on a silica gel column with hexane–$CHCl_3$ (1 : 4, v/v) to give **24** (130 mg, 85% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, tripletoid m, CH_3), 3.67 (3H, s, CO_2CH_3), 3.96—4.40 (2H, m, C-2-H and C-8a-H), 4.70 (2H, m, OCH_2CCl_3). MS *m/z* Calcd for $C_{23}H_{36}Cl_3NO_5$: 511.1658. Found: 511.1659.

Preparation of the γ-Lactones (25 and 26)——A solution of 0.3 ml (0.3 mmol) of 1 M $NaBH_4$ in methanol was added dropwise to a solution of **24** (100 mg, 0.195 mmol) in 10 ml of methanol at 0 °C with stirring, and the mixture was stirred for 30 min. The mixture was acidified with 5% HCl and the solvent was evaporated off under reduced pressure to leave an oily residue, which was extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, and concentrated to leave an oily residue. *p*-TsOH (56 mg) was added to a solution of the above oily residue in 10 ml of benzene and the mixture was heated under reflux for 30 min. The solvent was evaporated off under reduced pressure to leave an oily residue, which was chromatographed on a silica gel column. Elution with hexane–$CHCl_3$ (1 : 4, v/v) provided successively **25** and **26**. **25**: a colorless oil (12 mg, 13% yield). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1769 (lactone), 1695 (carbamate). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, tripletoid m, CH_3), 4.00 (2H, m, C-2-H and C-8a-H), 4.59 (1H, m, $COOCH\langle$), 4.70 and 4.79 (each 1H, d, J = 10 Hz, $CO_2CH_2CCl_3$). MS *m/z* Calcd for $C_{22}H_{34}Cl_3NO_4$: 481.1554. Found: 481.1563. **26**: a colorless oil (77 mg, 82% yield). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1768 (lactone), 1693 (carbamate). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, tripletoid m, CH_3), 4.08 (2H, m, C-2-H and C-8a-H), 4.61 (1H, m, $COOCH\langle$), 4.68 and 4.84 (each 1H, d, J = 12 Hz, $CO_2CH_2CCl_3$). MS *m/z* Calcd for $C_{22}H_{34}NO_4Cl_3$: 481.1554. Found: 481.1561.

The Cyclic Carbamate (27)——A mixture of **26** (20 mg, 0.0415 mmol), $LiOH \cdot H_2O$ (9 mg, 0.2 mmol), and methanol (3.5 ml) was stirred for 1 h at ambient temperature, then acidified with 5% HCl at 0 °C, and extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, and concentrated to leave a colorless oil. A mixture of NaH (20 mg), hexamethylphosphoramid (HMPA) (0.05 ml), and the above oil in 5 ml of THF was refluxed for 1 h, and then the mixture was acidified with 5% HCl at 0 °C and extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, and concentrated to leave an oily carboxylic acid, which was methylated with ethereal diazomethane. Silica gel column chromatographic purification with hexane–$CHCl_3$ (1 : 4, v/v) gave 14 mg (93% yield) of **27** as a crystalline mass. Recrystallization from ether gave colorless needles, mp 102 °C. **27**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1729 (ester), 1667 (carbamate). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, tripletoid m, CH_3), 2.54 (2H, t, J = 7 Hz, $CH_2CO_2CH_3$), 3.40 (1H, ddt, J = 11.2, 4.6, 2.7 Hz, C-2-H), 3.68 (3H, s, CO_2CH_3), 4.16 (1H, m, $NCO_2CH\langle$), 4.54 (1H, m, C-8a-H). Irradiation of the signal at δ 3.40 (C-2-H) showed a nuclear Overhauser effect (*ca.* 7% enhancement) of the signal at δ 4.16 (C-2′-H). MS *m/z* Calcd for $C_{21}H_{35}NO_4$: 365.2565. Found: 365.2559.

***N*-Phenoxycarbonylation of the γ-Lactone (23)**——Phenyl chloroformate (1.54 g, 10 mmol) was added dropwise to a solution of 4-dimethylaminopyridine (10 mg) and **23** (308 mg, 1 mmol) in 12 ml of pyridine at 0 °C with stirring, and the mixture was stirred for 48 h at ambient temperature, then acidified with 5% HCl at 0 °C and extracted with ether. The usual work-up of the ethereal extract gave an oily residue, which was purified by silica gel column chromatography with $CHCl_3$ to give **28** (425 mg, 99% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1768 (lactone), 1695 (carbamate). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, tripletoid m, CH_3), 4.11 (2H, m, C-2-H and C-8a-H), 4.66 (1H, m, C-2′-H), 7.05—7.45 (5H, m, Ph). MS *m/z* Calcd for $C_{26}H_{37}NO_4$: 427.2722. Found: 427.2736.

Phenylselenylation of the Lactone (28)——A solution of **28** (120 mg, 0.281 mmol) in 3 ml of THF was added dropwise to a solution of HMPA (0.5 ml) and lithium isopropylcyclohexylamide (2.8 mmol) in 1.65 ml of THF at −73 °C with stirring, and the temperature was allowed to rise to −40 °C. After cooling of the mixture to −73 °C, a solution of phenylselenyl chloride (130 mg, 0.67 mmol) in 1.35 ml of THF was added at −73 °C with stirring, and the whole was stirred at the same temperature for 10 min. The usual work-up of the reaction mixture gave an oily product, which was chromatographed on a silica gel column. Elution with $CHCl_3$ gave 76 mg (46% yield; 87% yield based on consumed starting material) of the selenide (**29**) and further elution gave 56 mg of unchanged starting material (**28**). **29**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1763 (lactone), 1697 (carbamate). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, tripletoid m, CH_3), 4.02 (2H, m, C-2-H and C-8a-H), 4.51 (1H, m, C-2′-H), 7.05—7.70 (10H, m, Ph × 2). MS *m/z* Calcd for $C_{32}H_{41}NO_4Se$: 583.2200. Found: 583.2207.

Oxidative Elimination of the Phenylselenyl Group in 29——A mixture of 30% H_2O_2 (0.5 ml), pyridine (0.15 ml), and **29** (53 mg, 0.091 mmol) in 3 ml of CH_2Cl_2 was stirred at 0 °C for 30 min, then acidified with 5% HCl at 0 °C. Extraction with CH_2Cl_2 and the usual work-up of the extract gave an oily residue, which was purified by silica gel column chromatography with hexane–$CHCl_3$ (1 : 4, v/v) to give **30** (39 mg, 100% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1751 (lactone), 1693 (carbamate). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, tripletoid m, CH_3), 4.08 (2H, m, C-2-H and C-8a-H), 5.19 (1H, tt, J = 6.0, 2.0 Hz, $COOCH\langle$), 6.09 (1H, dd, J = 6.0, 2.0 Hz, C-4′-H), 7.00—7.51 (5H, m, Ph), 7.67 (1H, d, J = 6 Hz, C-3′-H). MS *m/z* Calcd for $C_{26}H_{35}NO_4$: 425.2564. Found: 425.2556.

The Keto-ester (32) from the Unsaturated Lactone (30)——A mixture of 5% sodium methoxide (0.2 ml, 0.19 mmol) and **30** (8 mg, 0.019 mmol) in 3 ml of methanol was stirred at 0 °C for 30 min, then acidified with 5% HCl, and treated with ethereal diazomethane. The reaction mixture was extracted with ether and the extract was washed

with brine, dried over $MgSO_4$, and concentrated to leave a colorless oil, which was purified by silica gel column chromatography with hexane–$CHCl_3$ (1 : 4, v/v) to give 5 mg (58% yield) of **32** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730—1680 (overlapped broad absorption). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, tripletoid m, CH_3), 2.40—3.18 (6H, m, $COCH_2 \times 3$), 3.65 (3H, s, CO_2CH_3), 4.14 (1H, m, NH–C<u>H</u>), 4.32 (1H, m, NH–C<u>H</u>), 7.05—7.40 (5H, m, Ph). MS *m/z* Calcd for $C_{27}H_{39}NO_5$: 457.2827. Found: 457.2809.

Preparation of the Cyclic Carbamate (33)——A solution of $LiOH \cdot H_2O$ (133 mg, 0.32 mmol) in 2 ml of 50% aqueous methanol was added to a solution of **29** (190 mg, 0.323 mmol) in 15 ml of methanol and the mixture was heated under reflux for 12 h. The mixture was acidified with 5% HCl, then treated with ethereal diazomethane, and extracted with $CHCl_3$. The usual work-up of the extract gave an oily residue, which was purified by preparative TLC (Silica gel PF_{254}, Merck) with acetone–$CHCl_3$ (1 : 19, v/v) to give **33** (135 mg, 80% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (ester), 1677 (carbamate). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, tripletoid m, CH_3), 3.36 (1H, m, C-2-H), 3.64 (3H, s, CO_2CH_3), 4.01 (1H, m, C-8a-H), 4.46 (1H, m, C-2′-H), 7.20—7.61 (5H, m, Ph). MS *m/z* Calcd for $C_{37}H_{39}NO_4Se$: 521.2042. Found: 521. 2035.

The γ-Carbamoyloxy-α,β-enoate (6)——Pyridine (1 ml) and 30% H_2O_2 (4 ml) were added to a stirred solution of **33** (135 mg, 0.259 mmol) in 5 ml of CH_2Cl_2 at 0 °C. The mixture was stirred for 30 min, then acidified with 5% HCl, and extracted with CH_2Cl_2. The usual work-up of the extract led to a crystalline residue, which was recrystallized from ether to give **6** (94 mg, 100% yield) as colorless needles, mp 113 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (ester), 1678 (carbamate). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, tripletoid m, CH_3), 3.48 (1H, qt, J = 10.5, 5.0, 3.0 Hz, C-2-H), 3.75 (3H, s, CO_2CH_3), 4.58 (1H, m, C-8a-H), 4.70 (1H, m, C-2′-H), 6.19 (1H, dd, J = 16.0, 1.8 Hz, –CH = C<u>H</u>–CO_2CH_3), 6.85 (1H, dd, J = 16.0, 4.6 Hz, –C<u>H</u> = CH–CO_2CH_3). MS *m/z* Calcd for $C_{21}H_{33}NO_4$: 363.2409. Found: 363.2417.

The β,γ-Unsaturated Enoate (40)——A solution of **6** (20 mg, 0.055 mmol) in THF (0.5 ml) was added dropwise to a solution of lithium dibutylcuprate (0.5 mmol) in ether (2 ml) at −73 °C with stirring and the mixture was stirred for 5 min. Aqueous 5% NH_4Cl (1 ml) was added dropwise to the above mixture at −73 °C with stirring. The whole was extracted with $CHCl_3$ and the usual work-up of the extract gave **40** (18 mg, 100% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300—3100 (NH), 1732 (ester). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, tripletoid m, CH_3), 2.84 (1H, m, C-2-H), 3.04—3.14 (3H, m, CH = CH–$CH_2CO_2CH_3$ and C-8a-H), 3.68 (3H, s, CO_2CH_3), 5.42—5.74 (2H, m, olefinic protons). MS *m/z* Calcd for $C_{20}H_{35}NO_2$: 321.2667. Found: 321.2661.

Reaction of the β,γ-Unsaturated Ester (40) with Sodium Methoxide——A mixture of **40** (35 mg, 0.11 mmol) in methanol (5 ml) and 1% sodium methoxide (5.3 ml, 0.98 mmol) was heated under reflux for 1.5 h. After cooling, the mixture was acidified with 5% HCl at −20 °C, and then treated with ethereal diazomethane. The mixture was made basic with 10% ammonia and extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, and concentrated to leave an oily residue. Preparative thin layer chromatographic separation (Aluminum oxide, 150 PF_{254}, Merck) of the residue with hexane–$CHCl_3$ (1 : 3, v/v) gave the desired tricyclic compound (**41**) and its isomer (**42**). **41**: a colorless oil (18 mg, 51% yield). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1729. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, tripletoid m, CH_3), 3.09 (2H, m, HN–C<u>H</u> × 2), 3.67 (3H, s, CO_2CH_3). MS *m/z* Calcd for $C_{20}H_{35}NO_2$: 321.2668. Found: 321.2659. **42**: a colorless oil (3 mg, 9% yield). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1729. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, tripletoid m, CH_3), 2.79, 3.27, and 3.42 (each 1H, m, –N–CH × 3), 3.67 (3H, s, CO_2CH_3). MS *m/z* Calcd for $C_{20}H_{35}NO_2$: 321.2668. Found: 321.2671.

(±)-Perhydrogephyrotoxin (3)——Diisobutylaluminum hydride (0.56 ml, 0.56 mmol) was added dropwise to a solution of **41** (18 mg, 0.056 mmol) in toluene (0.56 ml) at −60 °C with stirring and the mixture was stirred for 30 min. Saturated aqueous ammonium chloride (1 ml) and 10% NaOH (1 ml) were added with stirring at −30 °C and the whole was stirred at ambient temperature for 30 min, then extracted with $CHCl_3$. The usual work-up of the extract gave **3** (16 mg, 98% yield) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3180 (OH). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, tripletoid m, CH_3), 1.05—1.98 (28H, m), 2.07 (1H, m, CH(<u>H</u>)CH_2OH), 2.54 (1H, m, –N–C<u>H</u>), 3.26 (2H, m, –N–C<u>H</u> × 2), 3.65 (1H, dt, J = 11.0, 4.0 Hz, C<u>H</u>(H)OH), 4.02 (1H, td, J = 11.0, 3.0 Hz, CH(<u>H</u>)OH). MS *m/z* Calcd for $C_{19}H_{35}NO$: 293.2718. Found: 293.2719. The spectral data of **3** were identical with authentic spectra[8] [IR ($CHCl_3$), ^{1}H-NMR ($CDCl_3$), ^{13}C-NMR ($CDCl_3$)].

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